# Characterization of Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT)

by

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A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Approved July 2014 by the
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ARIZONA STATE UNIVERSITY

August 2014

ABSTRACT

Small Cell Carcinoma of the Ovary Hypercalcemic Type (SCCOHT) is a rare and highly aggressive ovarian cancer that affects children and young women at a mean age of 24 years. Most SCCOHT patients are diagnosed at an advanced stage and do not respond to chemotherapy. As a result, more than 75% of patients succumb to their disease within 1-2 years. To provide insights into the biological, diagnostic, and therapeutic vulnerabilities of this deadly cancer, a comprehensive characterization of 22 SCCOHT cases and 2 SCCOHT cell lines using microarray and next-generation sequencing technologies was performed. Following histological examination, tumor DNA and RNA were extracted and used for array comparative genomic hybridization and gene expression microarray analyses. In agreement with previous reports, SCCOHT presented consistently diploid profiles with few copy number aberrations. Gene expression analysis showed SCCOHT tumors have a unique gene expression profile unlike that of most common epithelial ovarian carcinomas. Dysregulated cell cycle control, DNA repair, DNA damage-response, nucleosome assembly, neurogenesis and nervous system development were all characteristic of SCCOHT tumors. Sequencing of DNA from SCCOHT patients and cell lines revealed germline and somatic inactivating mutations in the SWI/SNF chromatin-remodeling gene SMARCA4 in 79% (19/24) of SCCOHT patients in addition to SMARCA4 protein loss in 84% (16/19) of SCCOHT tumors, but in only 0.4% (2/485) of other primary ovarian tumors. Ongoing studies are now focusing on identifying treatments for SCCOHT based on therapeutic vulnerabilities conferred by ubiquitous inactivating mutations in SMARCA4 in addition to gene and protein expression data. Our characterization of the molecular landscape of SCCOHT and the breakthrough identification of inactivating SMARCA4 mutations in almost all cases of SCCOHT offers the first significant insight into the molecular pathogenesis of this

disease. The loss of SMARCA4 protein is a highly sensitive and specific marker of the disease, highlighting its potential role as a diagnostic marker, and offers the opportunity for genetic testing of family members at risk. Outstanding questions remain about the role of SMARCA4 loss in the biology, histogenesis, diagnosis, and treatment of SCCOHT.

DEDICATION

This dissertation is dedicated to my dear parents, Pilar Altamira and Francisco Ramos, my sister, Luz, and my brothers Javier, Ignacio, Alvaro and Borja. I would also like to dedicate this work to my karate family, especially my Sensei, and to all the good friends who have supported me through the good times and the bad.

ACKNOWLEDGMENTS

Sample procurement: I particularly thank the SCCOHT families and patients for their contributions. Thanks to the faculty and staff of TGen's Macromolecular Analysis & Processing Center (Dr. Hostetter), and the Office of Research Compliance (Lora Nordstrom, Stephanie Althoff, and Stephanie Buchholtz). Thanks also to all the physicians of the Children's Oncology Group who assisted in the collection of biospecimens. Additional thanks are given to Drs. Robert Haas and Barbara Vanderhyden for providing us with the SCCOHT-1 and BIN67 cells, respectively.

Technical support and mentoring: The author appreciates all the technical assistance and bioinformatics guidance that was provided by various members of TGen, including Megan Russell, Dr. David Craig, Dr. Jeff Kiefer, Dr. Christophe Legendre, Dr. Amol Tembe, Dr. Michael Barrett, Victoria Zissmann, Catherine Mancini, Dr. Winnie Liang, Dr. Michael Bittner and Sonsoles Shack. A special thank you to our collaborators at the British Columbia Cancer Agency, Dr. David Huntsman, Dr. Anthony Karnezis, and Dr. Yemin Yang, and various members of their bioinformatics and pathology teams. The author is truly grateful for the mentoring, experimental planning, career guidance and support provided by the graduate committee members, Dr. Jeffrey Trent, Dr. Karen Anderson, Dr. Kenro Kusumi, Dr. Douglas Lake, and the previous committee members Dr. Heather Cunliffe and Dr. Jeff Touchman. Moreover, the author is extremely thankful for the support, advice, opportunities, and scientific guidance that were provided by the most amazing mentors Dr. Aleksandar Sekulic, Dr. William Hendricks and Dr. Jeffrey Trent.

Funding support: This study was supported by grants from The Marsha Rivkin Center for Ovarian Cancer Research, The Anne Rita Monahan Foundation, The Ovarian Cancer Alliance of Arizona, The Small Cell Ovarian Cancer Foundation, and philanthropic support to the TGen Foundation.

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LIST OF GENE SYMBOLS

| **Symbol** | **Gene Name** |
|---|---|
| *ACTL6A* | Actin-like protein 6A |
| *ACTL6B* | Actin-like protein 6B |
| *AE-1/AE-3* | Cytokeratin AE1/AE3 |
| *AFP* | Alpha-fetoprotein |
| *AGMO* | Alkylglycerol monooxygenase |
| *AP1M2* | Adaptor-related protein complex 1, mu 2 subunit |
| *ARID1A* | AT-rich interactive domain-containing protein 1A |
| *ARID1B* | AT-rich interactive domain-containing protein 1B |
| *ASGR1* | Asialoglycoprotein receptor 1 |
| *ASXL1* | Putative Polycomb group protein |
| *AURKA* | Aurora kinase a |
| *AURKB* | Aurora kinase B |
| *B72.3* | Tumor associated glycoprotein |
| *Bcl-6* | B-cell lymphoma 6 protein |
| *BMP4* | Bone morphogenic protein 4 |
| *BRAF* | Proto-oncogene B-raf |
| *BRCA1* | Breast cancer 1, early onset |
| *BRCA2* | Breast cancer 2, early onset |
| *C-kit* | Human proto-oncogene c-kit |
| *CD10* | Cluster of differentiation 10 (Neprilysin) |
| *CD20* | B-lymphocyte antigen |
| *CD3* | Cluster of differentiation 3 |
| *CD30* | Cluster of differentiation 30 (TNFRSF8) |
| *CD34* | Cluster of differentiation 34 |
| *CD4* | Cluster of differentiation 4 |
| *CD43* | Cluster of differentiation 43 |
| *CD56* | Neural cell adhesion molecule (NCAM) |
| *CD68* | Cluster of differentiation 68 |
| *CD8* | Cluster of differentiation 8 |
| *CD99* | Cluster of differentiation 99 (MIC2) |
| *CDH10* | Cadherin 10 |
| *CDK2* | Cyclin-dependent kinase 2 |
| *CDX2* | Caudal type homeobox 2 |

| Symbol | Gene Name |
|---|---|
| *CEA* | Carcinoembryonic antigen |
| *CEND1* | Cell cycle exit and neuronal differentiation 1 |
| *CHD5* | Chromodomain helicase DNA binding gene |
| *CK/AE-1* | Cytokeratin AE1 |
| *CK20* | Cytokeratin 20 |
| *CK7* | Cytokeratin 7 |
| *CRB3* | Crumbs family member 3 |
| *CRMP1* | Collapsin response mediator protein 1 |
| *CTNNB1* | Beta-catenin |
| *DHFR* | Dihydrofolate reductase |
| *DNMT1* | DNA-methyltransferase 1 |
| *DNMT3A* | DNA-methyltransferase 3 alpha |
| *DNMT3B* | DNA-methyltransferase 3 beta |
| *DPF1* | Double PHD fingers family 1 |
| *DPF2* | Double PHD fingers family 2 |
| *DPF3* | Double PHD fingers family 3 |
| *EFNB2* | Ephrin B2 |
| *EMA* | Epithelial marker antigen |
| *ER* | Estrogen receptor |
| *ERBB3* | Receptor tyrosine-protein kinase 3 |
| *ERBB4* | Receptor tyrosine-protein kinase 3 |
| *FAK* | Focal adhesion kinase |
| *FANCA* | Fanconi anemia, complementation group A |
| *FANCD2* | Fanconi anemia group D2 |
| *FASL* | Fas ligand |
| *FGF11* | Fibroblast growth factor 11 |
| *FGFR1* | Fibroblast growth factor receptor 1 |
| *FGFR3* | Fibroblast growth factor receptor 3 |
| *Fli-1* | Friend leukemia integration 1 transcription factor |
| *FLT3* | Fms-related tyrosine kinase 3 |
| *FYN* | Proto-oncogene tyrosine-protein kinase |
| *GATA4* | GATA binding protein 4 |
| *GFAP* | Glial fibrillary acidic protein |
| *H2A* | Histone 2A |
| *HCG* | Human chorionic gonadotropin |
| *HGF* | Human growth factor |
| *HMB-45* | Human melanoma black 45 |

| Symbol | Gene Name |
|---|---|
| *INHA* | Inhibin A |
| *INPP1* | Inositol polyphosphate-1-phosphatase |
| *JAK3* | Janus kinase 3 |
| *JNK* | c-Jun N-terminal kinase |
| *Ki-67* | Antigen KI-67 |
| *KRAS* | V-Ki- ras 2 Kirsten rat sarcoma viral oncogene homolog |
| *KRT* | Keratin |
| *LCA (CD45)* | Leukocyte-common antigen |
| *LRRTM4* | Leucine rich repeat transmembrane neuronal 4 |
| *MAK6* | Serine/threonine-protein kinase MAK 6 |
| *MEOX2* | Mesenchyme homeobox |
| *MET* | Hepatocyte growth factor receptor |
| *MFSD6* | Major facilitator superfamily domain containing 6 |
| *MLLT10* | Mixed-lineage leukemia |
| *MyoD1* | Myogenic differentiation 1 |
| *NCAM1* | Neural cell adhesion molecule |
| *NCL* | Nucleolin |
| *NLGN1* | NEUROLIGIN-1 |
| *NmU* | Neuromedin U |
| *NOTCH2* | Notch homolog 2 |
| *NSE* | Neuron specific enolase |
| *NTN1* | Netrin 1 |
| *NTS* | Neurotensin |
| *NXPH1* | Neurexophilin-1 |
| *OCT3/4* | Octamer-binding transcription factor 3/4 |
| *p16* | Cyclin-dependent kinase inhibitor 2A |
| *p53* | Tumor protein p53 |
| *PAX 8* | Paired box gene 8 |
| *PBRM1* | Protein polybromo-1 |
| *PCDH9* | Protocadherin 9 |
| *PCNA* | Proliferating cell nuclear antigen |
| *PHF10* | PHD finger protein 10 |
| *PIK3CA* | Phosphatidylinositol-4,5-biphosphate 3-kinase |
| *PKP3* | Plakophilin 3 |
| *PLAP* | Placental alkaline phosphatase |
| *PLEKHG* | Pleckstrin homology domain containing |
| *PR* | Progesterone receptor |

| Symbol | Gene Name |
|---|---|
| *PTEN* | Phosphatase and tensin homolog |
| *PTH* | Parathyroid hormone |
| *PTHRP* | Parathyroid related protein |
| *RAB25* | Ras-related protein 25 |
| *RANK* | Receptor activator of nuclear factor kappa-B |
| *RANKL* | Receptor activator of nuclear factor kappa-B ligand |
| *RAP-GEF* | Rap guanine nucleotide exchange factor |
| *ROBO1* | Roundabout homolog 1 |
| *S100* | Neural crest cells |
| *SEMA3A* | Semaphorin-3A |
| *SEMA3F* | Semaphorin-3F |
| *SMA* | Smooth muscle acting |
| *SMARCA2/BRM* | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 2 |
| *SMARCA4/BRG1* | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4 |
| *SMARCB1/SNF5* | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 |
| *SMARCC1* | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily C member 1 |
| *SMARCC2* | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily C member 2 |
| *SMARCD1* | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily D member 1 |
| *SMARCD2* | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily D member 2 |
| *SMARCE1* | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1 |
| *SRCAP* | Snf2-related CREBBP activator protein |
| *TGF-beta* | Transforming growth factor beta |
| *TK* | Tyhimidine kinase |
| *TOP1* | Topoisomerase 1 |
| *TOP2A* | DNA topoisomerase 2-alpha |
| *TP53* | Tumor protein p53 |
| *TPX2* | Microtubule-associated |
| *TTF-1* | Thyroid transcription factor-1 |
| *TUBB3* | Tubulin beta-3 |

| Symbol | Gene Name |
|---|---|
| *UBBs1* | Ubiquitin B |
| *WNT3* | Wingless-type MMTV integration site family, member 3 |
| *WT1* | Wilms' tumor suppressor 1 |
| *ZNF726* | Zinc finger protein 26 |

CHAPTER 1

# SMALL CELL CARCINOMA OF THE OVARY, HYPERCALCEMIC TYPE (SCCOHT): A RARE, LETHAL AND COMPLEX CANCER

## Introduction

Each year, nearly 204,000 women are diagnosed with ovarian cancer worldwide (Rauh-Hain et al. 2011). The fifth most common cause of cancer in women in the United States, ovarian cancer takes an estimated 14,270 lives per year in this country (Howlader N 2014). Ovarian carcinomas are highly heterogeneous tumors. Based on morphological, immunophenotypic, and ultrastructural features, primary ovarian tumors are classified into three main groups: epithelial ovarian tumors derived from the mesothelial cells on the surface of the ovary, germ cell ovarian tumors which arise from the egg-producing cells within the ovarian parenchyma, and tumors that develop from the sex-cord stroma. Epithelial carcinomas are the most common, accounting for 90% of all ovarian tumors while germ cell, sex-cord stromal and other rare neoplasms account for only 5-10% of cases of ovarian cancer (Society 2014). Within each group, neoplasms are further divided based on histopathological characteristics and molecular genetic alterations. Epithelial ovarian carcinomas exhibit the greatest tumor diversity and are classified into type I and type II tumors (Kurman and Shih 2011). Type I tumors, which include low-grade serous, endometrioid, clear cell, and mucinous tumors, are indolent and relatively chemotherapy resistant. They typically harbor somatic mutations in BRAF, KRAS, PIK3CA, PTEN, CTNNB1, and ARID1A genes (Kuo et al 2009, Kurman and Shih 2011). In contrast, Type II tumors are aggressive, highly proliferative and relatively chemotherapy sensitive. They include high-grade serous, high-grade endometrioid, carcinosarcomas, and undifferentiated tumors. These tumors display high levels of genomic instability, TP53 mutations in over 90% of

cases, and germline (10-20% of cases) and somatic (50% of cases) alterations in the homologous recombination (HR) DNA damage repair genes BRCA1 and BRCA2 (Kurman and Shih 2011; Landen, Birrer, and Sood 2008; TCGA 2011 Pal et al. 2005). Yet another recent paradigm shift in our understanding of epithelial ovarian tumors occurred when it was demonstrated that the majority of serous, endometrioid, and clear cell carcinomas arise in the fallopian tube and the endometrium (Kim et al. 2012; Kindelberger et al. 2007; Veras et al. 2009). Clearly, there are substantial differences in the tumor behavior, underlying genetic alterations, and clinical outcome between each histologic subtype of ovarian cancer which have motivated characterization of each entity to facilitate accurate diagnosis and treatment selection.

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare and deadly ovarian cancer that afflicts young women. Classified by the World Health Organization (WHO) within the group of "miscellaneous tumors of the ovary" (F.A. Tavassoéli 2003), it accounts for less than 1% of all ovarian cancer diagnoses (Clement 2005; Richard Dickersin, Kline, and Scully 1982; Scully 1979; Siegel, Naishadham, and Jemal 2013; Young, Oliva, and Scully 1994). Since it was first characterized in 1979 (Scully 1979), less than 500 cases have been described. The majority of cases reported occurred in patients of European descent, but Asian, Hispanic and African American patients have also been documented (Cheng et al. 2008; Krishnansu Tewari 1997; McCormick et al. 2009; Niimi et al. 2006; Seidman 1995; Yuka Idei 1996). While the average age of diagnosis for most ovarian cancers is 63 years, SCCOHT affects young women in their second or third decade of life (mean age of 24), and is also found in pediatric patients as young as 14 months of age(Florell et al. 1999). In addition, cases of familial SCCOHT have also been noted (Estel et al. 2011; Florell et al. 1999; Lamovec, Bracko, and Cerar 1995; Longy et al.

1996; Martinez-Borges et al. 2009; Young, Oliva, and Scully 1994), strongly suggesting a genetic etiology for this disease.

Symptoms associated with SCCOHT are similar to more common forms of ovarian cancer (abdominal pain, bloating, difficulty eating and urinary symptoms). However, 60% of cases also present with elevated levels of serum calcium, and thus, this tumor type is denoted "hypercalcemic type." Hypercalcemia is relatively common in other cancer types, occurring in approximately 20% of all cancer cases (Grill and Martin 2000). It is mainly observed in patients with breast cancer, lung cancer, and myeloma (Strewler 1998), but it is unusual in pediatric cancers. In the absence of bone metastases, secretion of parathyroid hormone-related protein (PTHrP) by the tumor cells is the most frequent cause of hypercalcemia of malignancy (Grill and Martin 2000; Strewler 1998). PTHrP leads to increased levels of extracellular ionized calcium concentrations by binding to its receptor, parathyroid hormone receptor 1 (PTH1R), found on the surface of osteoblasts. This in turn induces the expression of receptor activator of nuclear factor kappa B ligand (RANKL); and RANKL interaction with receptor activator of nuclear factor kappa B (RANK) in osteoclasts leads to activation of bone resorption (Lumachi et al. 2009). Positive immunostaining for PTHrP has been observed in several SCCOHT tumors, but not all cases presented with paraneoplastic hypercalcemia (Abeler, Kjorstad, and Nesland 1988; Chen, Dinh, and Haque 2005; Xavier Matias-Guiu 1993; Young, Oliva, and Scully 1994). For SCCOHT patients with hypercalcemia, the levels of serum calcium return to normal following tumor resection, and can be used to monitor disease recurrence (Xavier Matias-Guiu 1993). A better understanding of the mechanisms leading to SCCOHT associated hypercalcemia and the role of calcium in SCCOHT pathogenesis might reveal fundamental molecular properties of this cancer.

Ovarian neoplasms are diagnosed intraoperatively with subsequent pathologic confirmation. Differential diagnosis of SCCOHT is challenging due to the lack of specific morphologic and immunohistochemical features. Many neoplasms that involve the ovary can be confused with SCCOHT including endometrioid stromal sarcoma, desmoplastic small round cell tumor, primitive neuroectodermal tumor, and neuroblastoma (McCluggage et al. 2004). Histologically, SCCOHT tumors are characterized by poorly differentiated small tumor cells with scant cytoplasm, hyperchromatic nuclei, and the presence of follicle-like structures contained within sheets of cells (Robert H. Young 1994). Despite SCCOHT's name, about half of tumors have populations of large cells with a luteinized or rhabdoid appearance (Clement 2005; McCluggage et al. 2004; Young, Oliva, and Scully 1994). Recently, two cases of SCCOHT were shown to have arisen in the setting of an immature teratoma, one of which also had a component of yolk sac tumor (YST) (Kupryjanczyk et al. 2013), consistent with the proposal that SCCOHT may be a germ cell tumor (Ulbright et al. 1987). Immunohistochemical analysis of SCCOHT reveals an assorted immunoprofile that is not consistent with any one particular ovarian cell type. SCCOHTs consistently express WT1, CD10, EMA and vimentin, and lack expression of inhibin, chromogranin, TTF1, S100, desmin and AFP (McCluggage et al. 2004; Young, Oliva, and Scully 1994). Future studies are necessary to fully understand SCCOHT's histogenesis and facilitate its differential diagnosis.

Treatment for SCCOHT includes surgical debulking followed by chemotherapy and/or radiation, with autologous stem cell transplantation if indicated (Distelmaier et al. 2006; Estel et al. 2011; G. Richard Dickersin 1982; Robert H. Young 1994). Primary disease is typically identified as a large unilateral tumor (averaging 14.7 cm in diameter), with regional tumor spread (Robert H. Young 1994). In a study of 150 cases diagnosed greater than stage IA, improved outcomes correlated with (i)

normal preoperative serum calcium, (ii) age at diagnosis >30 years, (iii) tumor size <10 cm, and (iv) absence of large-cell variants (Robert H. Young 1994). The most successful chemotherapeutic regimens reported for SCCOHT are the dose-intense combinations PAVEP (cisplatin, adriamycin, vepeside, cyclophosphamide) and VPCBAE (vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, etoposide) (Elizabeth K. Senekjian 1989; Estel et al. 2011; Robert H. Young 1994). However, these regimens have not been evaluated in additional studies and were not derived from controlled studies. The rarity of this tumor type, the heterogeneity in clinical reports, and the relative dearth of molecular studies of SCCOHT have hindered progress in determining effective treatment approaches.

SCCOHTs lack the mutational spectrum characteristic of the major histopathological subtypes of ovarian cancer. The absence of *KRAS* and *BRAF* mutations distinguishes SCCOHTs from low-grade ovarian serous carcinomas and mucinous cancers (Cuatrecasas et al. 1997; Schuyer et al. 1999). And the low level of chromosomal aberrations and lack of *TP53* mutations differentiates SCCOHT tumors from high-grade ovarian serous carcinomas (Integrated genomic analyses of ovarian carcinoma  2011; Singer et al. 2005). Finally, although several familial cases of SCCOHT have been previously reported (Distelmaier et al. 2006; Lamovec, Bracko, and Cerar 1995; Longy et al. 1996; McDonald et al. 2012; Schuyer et al. 1999; Ulbright et al. 1987) no association with BRCA1/BRCA2 mutations has been established.

The clinicopathological characteristics of SCCOHT were comprehensively described in Young and Scully's 1994 seminal study of 150 cases (Young, Oliva, and Scully 1994). In this chapter, an examination of 22 SCCOHT cases that recapitulates most of the previously reported clinical, histological, and cytogenetic features of SCCOHT is presented (Eichhorn et al. 1992; Hauptmann S. 2006; Young, Oliva, and

Scully 1994). In addition, we performed gene expression analysis of 4 SCCOHT tumors compared to normal ovary and to a pool of 15 epithelial ovarian carcinomas, in order to identify genes and molecular pathways that contribute to SCCOHT.

## Materials and Methods

### Clinical samples

A web-based IRB-approved HIPAA-compliant protocol was established to facilitate collection of biospecimens from consenting SCCOHT patients, their legal proxy if under 18 years of age, or the loved ones of deceased patients (www.tgen.org/scco) (Protocol No. hcunliffe10-032). Consented participants donated tumor (fresh frozen or FFPE) and a blood sample when possible. Pathology reports, and self-reported demographic and medical history data were also collected. Two tumor samples were obtained through collaboration with Dr. Richard Roden, Department of Pathology, The Johns Hopkins University, Baltimore MD. Patient and sample information is provided in Tables 1 and 2. In addition, fifteen fresh-frozen non-SCCOHT ovarian tumors used for transcriptomic comparison with SCCOHT cases were obtained from an annotated biorepository also established and maintained at TGen.

### Tissue microarray (TMA) and immunohistochemistry (IHC)

A TMA representing nine SCCOHT patient cases was generated for this study as previously described (Kononen et al. 1998). Each case included at least two representative core punches of 0.6 mm in diameter. While no patient-matched normal ovary was available, two cases had uninvolved fallopian tube and were included in the TMA. IHC biomarker data were extracted from available medical and pathology reports, and additional immunoassays were performed on our cases.

Table 1.

SCCOHT Biospecimens.

| Sample ID | Age | Ethnicity | FIGO stage | Hypercalcemia | Tumor sample | Blood sample |
|---|---|---|---|---|---|---|
| SCCO-001 | 22 | E | Unkn. | Yes | FFPE | N/A |
| SCCO-002 | 26 | E | IA | Yes | FF/FFPE | Y |
| SCCO-003 | 33 | E | IIIA | No | N/A | N/A |
| SCCO-004 | 32 | E | IB | Unkn. | FFPE | Y |
| SCCO-005 | 18 | E | IA | No | FFPE | Y |
| SCCO-006 | 32 | E | IIB | Unkn. | FFPE | Y |
| SCCO-007 | 25 | E | IC | Yes | FFPE | N/A |
| SCCO-008 | 9 | E | IA | Yes | FFPE | Y |
| SCCO-009 | 27 | E | IIIC | No | FFPE | N/A |
| SCCO-010 | 6 | E | IC | Yes | FFPE | Y |
| SCCO-011 | 30 | E | IA | No | FFPE | N/A |
| SCCO-012 | 21 | E | IIIC | Yes | FF/FFPE | N/A |
| SCCO-013 | 42 | E | IIB | No | N/A | Y |
| SCCO-014 | 33 | AA | IIIC | Yes | FF | N/A |
| SCCO-015 | 27 | AA | IIIA | Unkn. | FF | N/A |
| SCCO-016 | 12 | Unkn. | IA | Yes | FFPE | N/A |
| SCCO-017 | 10 | E | IIIC | Yes | FFPE | Y |
| SCCO-018 | 5 | E | IIIC | Yes | FFPE | N/A |
| SCCO-019 | 27 | E | IIIC | Unkn. | FFPE | N/A |
| SCCO-020 | 28 | E | IA | Unkn. | FFPE | N/A |
| SCCO-021 | 30 | E | Unkn. | Yes | N/A | Y |
| SCCO-022 | 29 | E | IC | Yes | N/A | Y |

E =European; AA = African American; Unkn. = Unknown; FF = Fresh Frozen; FFPE = Formalin Fixed Paraffin-Embedded; N/A = Not Available.

Additional IHC stains were performed by PhenoPath Laboratories (Seattle, WA; TOP2A, CD56, AFP, p53, Calretinin and Oct-3/4) or the TGen TMA Core Facility (CD4, CD8, CD20, CD68). Antibodies: TOP2A, Millipore, Darmstadt, Germany; Calretinin, Leica Microsystems, Buffalo Grove, IL; CD56, Thermo Scientific; Lafayette, CO; AFP, p53 and CD20cy, Dako, Carpinteria, CA; OCT 3/4, Biocare Medical, Concorde, CA. IHC scoring was performed by board certified pathologists from TGen (Phoenix, AZ) and the Mayo Clinic (Scottsdale, AZ).

**RNA isolation and gene expression microarrays**

Frozen tissue was disrupted in RLT buffer (Qiagen, Valencia, CA) by sonication using the Covaris S-2 system (Covaris; Woburn, MA) and stabilized by addition of equal volume of Trizol (Life Technologies; Grand Island, NY). Total RNA was isolated from 4 SCCOHT and 15 epithelial ovarian tumors (obtained at TGen) using the Qiagen RNeasy micro kit. Total RNA from two premenopausal normal ovary donors (ages 32 and 37) was obtained from OriGene (Rockville, MD), pooled (100 ng each RNA) and used as a reference for SCCOHT vs. normal. For analysis of SCCOHT vs. non-SCCOHT epithelial ovarian tumors, a pool of 200 ng of total RNA from each of 19 ovarian tumors (15 epithelial tumors (6 serous, 6 endometrioid, 2 clear cell, 1 mucinous) and 4 SCCOHT tumors) was used as a common reference against all 19 tumors. RNA integrity and purity was measured using a 2100 Bioanalyzer (Agilent Technologies; Palo Alto, CA) and a Nanodrop ND-1000 Spectrophotometer (Nanodrop; Wilmington, DE). Labeled cRNA probes were prepared and hybridized to Agilent 4x44K (v2) oligonucleotide microarrays following manufacturer protocols (Agilent). Slides were washed and scanned at 5 μm using an Agilent Microarray Scanner (model G2505B) in an ozone-controlled environment, and data extracted, processed and normalized using Agilent Feature Extraction (FE) software (v10.5).

Genes were considered significantly up or down regulated relative to reference if the LogRatio p-value calculated during feature extraction was <0.001. Raw and processed data files have been deposited in GEO at accessions GSE49887 and GSE49888.

**Multi-dimensional scaling (MDS) analysis**

Level 1 expression array data was obtained from twelve randomly selected ovarian serous cystadenocarcinoma samples profiled on Agilent 244K expression arrays (Custom platform G4502A-07-2) by The Cancer Genome Atlas (TCGA) Network. We extracted data for array features in common with Agilent 44K v2 that we had used to profile six serous and four SCCOHT tumors. To allow for comparison across arrays, the background subtracted signal for only the sample channel was used for analysis. The raw intensity data from both TCGA samples and SCCOHT samples were subset by the 3,174 genes that were found discriminatory between SCCOHT and non-SCCOHT ovarian cancers (see Methods: Microarray data filtering and visualization). The average of the intensities across each probe for samples SCCO-002, SCCO-014, and SCCO-015 was calculated and then subtracted from the intensity of each corresponding probe from sample SCCO-012 to give the difference. The absolute value of the difference was then used to rank the probes in decreasing order. Duplicates of the same probe were removed from the analysis. The top 300 most differentiating probes between SCCO-012 and the other 3 SCCOHT cases were removed from the analysis (see Results: Gene Expression Analysis of SCCOHT tumors vs. normal ovary for details). This left a total of 2,280 probes. The combined dataset was normalized using the normalize quantiles function (normalize.quantiles) in the preprocessCore package of the R statistical application (v2.15.2; http://www.r-project.org). MDS coordinates were generated using the classical

multidimensional scaling function (cmdscale) of the R statistical application (v2.15.2) based on sample-to-sample distances calculated using Euclidean distance (usual square distance between the two vectors).

**Pathway enrichment analysis**

Log2Ratios filtered for consistent significance among the four SCCOHT tumors were averaged for analyses. Functional pathway enrichment was performed using MetaCore™ (Thomson Reuters), including GO (gene ontology), network processes and canonical pathway maps. Due to the preponderance of GO categories associated with the cell cycle, we selectively removed genes associated with cell cycle. To accomplish this we selected 213 genes mapped to cell cycle (GO:0007039) gene ontology category within MetaCore™ and removed them from the gene expression matrix discussed above. Functional pathway enrichment was then repeated. Single sample Gene Set Enrichment Analysis (ssGSEA) (http://bit.ly/1g2nVqc) was used to identify biological functions differentially enriched in SCCOHT vs. non-SCCOHT tumors, using only the c5 gene set library (GSEA | MSigDB). ssGSEA is an extension of GSEA that calculates separate enrichment scores for each pairing of a sample and gene set (Verhaak et al. 2013). Each ssGSEA enrichment score represents the degree to which the genes in a particular gene set are coordinately up or downregulated within a sample. The resulting dataset was then used for comparative marker selection (http://bit.ly/1g2oBvJ).

**Purification of tumor cell nuclei for cell cycle analysis and array-comparative genomics hybridization (aCGH)**

Tumor cell nuclei were isolated and purified from 50 µm FFPE scrolls or microscope slides using DNA content-based flow cytometry as previously described

(Holley et al. 2012). Cell cycle analysis was performed using MultiCycle software (Phoenix Flow Systems; San Diego, CA). DNA was purified from 50,000 flow-sorted nuclei from the 2N (G1) and 4N (G2/M) populations and profiled by aCGH following linear amplification(Holley et al. 2012). Amplified DNA samples were labeled and co-hybridized to 400K oligonucleotide CGH arrays (Agilent), using 46, XX, genomic DNA (Promega; Madison, WI) as the comparative reference. Data was extracted, processed and normalized using Agilent Feature Extraction Software (v10.7). Genomic Identification of Significant Targets in Cancer (GISTIC) analysis was performed using Nexus Copy Number Software (BioDiscovery; Hawthorne, CA) to identify recurrent copy number aberrations (Beroukhim et al. 2007).

## Results

### SCCOHT patient cohort

Between November 2010 and June 2013, twenty-two cases of SCCOHT were consented for this study, twenty of which were able to provide a tumor sample. A blood sample was donated by 10 of the patients (Materials and Methods, Table 1). A summary of demographic, diagnostic and clinical features of all patients is shown in Table 2.

Consistent with previous reports, the average age at diagnosis for our cohort was 23.8 years (range of 5 - 42 years), with five pediatric and 17 adult cases enrolled. All adult cases, including the oldest patient of 42 years, were premenopausal and reported using oral contraceptives. About half (55%) of cases, both adult and pediatric, reported having paraneoplastic hypercalcemia (Young, Oliva, and Scully 1994).

Table 2.

Demographic and Clinicopathological Characteristics of SCCOHT Cases.

| Sample ID | Age | FIGO stage | Hyper-calcemia | Tumor size (cm) | Surgical procedure | Adjuvant therapy (No. of cycles) | Recurrence interval (months) | Salvage treatment after relapse (No. of cycles) | Follow up (months to publication) |
|---|---|---|---|---|---|---|---|---|---|
| SCCO-001 | 22 | Unkn. | Yes | 13 | XLAP/RO | P/CDDP/B/E/I(6); Radiation | - | NED | Alive (83) |
| SCCO-002 | 26 | IA | Yes | 17 | XLAP/RSO/PaLNS/OM | P/Cb/E(6) | 52 | SD, Radiation & Chemo: Cddp/Ir(3) | Alive (96) |
| SCCO-003* | 33 | IIIA | No | 16 | XLAP/LSO/PLAD/PaLAD/OM | P/CDDP/E(6) | 19 | Unkn. | DOD (23) |
| SCCO-004 | 32 | IB | Unkn. | 10 | XLAP/TAH/BSO/PPaLNS/OM | Tt/Cb(6) | 10 | SD & Chemo:VP-16/Av/P(6); G/Cddp; G/Cb(3); G/Cddp(1) | Alive (55) |
| SCCO-005 | 18 | IA | No | 18.6 | XLAP/LSO/OM/PPaLNS | P/CDDP/E(6); Radiation | - | NED | Alive (29) |
| SCCO-006 | 32 | IIB | Unkn. | 20 | XLAP/RSO/PPaLNS/OM | CDDP/E(4); Radiation | - | NED | Alive (29) |
| SCCO-007 | 25 | IC | Yes | 9 | XLAP/RO/OM/PPaLNS/Appy | CDDP/E(4); Am(2); Av/P/Cb(2) Radiation | - | - | DOD (13) |
| SCCO-008 | 9 | IA | Yes | 12 | XLAP/RO/OM | V/CDDP/Cy/B/Db/E(5); Cb/Th(1); StemCT | - | NED | Alive (34) |
| SCCO-009 | 27 | IIIC | No | 17.5 | XLAP/LSO/PPaLNS/OM | CDDP/B/Db/E(6) Cy/V(4) | - | NED | Alive (54) |
| SCCO-010 | 6 | IC | Yes | 8 | XLAP/RO | V/CDDP/Cy/B/Db/E(6); Cb/E/M(1);Rad/ StemCT | - | NED | Alive (41) |
| SCCO-011 | 30 | IA | No | 9.5 | XLAP/RO | V/CDDP/Cy/Db/E | 5 | SD | DOD (13) |
| SCCO-012 | 21 | IIIC | Yes | 12 | XLAP/LSO/OM/PPaLNS/Appy | CDDP/Cy/B/Db/E(8) | 7 | SD: TAH/RSO/AB/PLNS. G(2); Rad; Ir/Av(2); Tt | DOD (12) |
| SCCO-013* | 42 | IIB | No | 9.5 | XLAP/TAH/BSO/OM/SigRsxn | P/E(6)/CDDP(4)/Cb(2) | - | NED | Alive (24) |
| SCCO-014 | 33 | IIIC | Yes | Unkn. | XLAP/TAH/BSO/PPaLNS/Appy | Unkn. | Unkn. | Unkn. | Unkn. |
| SCCO-015 | 27 | IIIA | Unkn. | 20 | XLAP/TAH/BSO/OM/PLNS | Unkn. | Unkn. | Unkn. | Unkn. |
| SCCO-016 | 12 | IA | Yes | 13 | XLAP/RSO; XLAP/TAH/LSO/Appy | Unkn. | Unkn. | Unkn. | Unkn. |
| SCCO-017 | 10 | IIIC | Yes | 15.5 | XLAP/RO/OM/PaLNS | V/CDDP/Cy/B/Db/E(6) | - | NED | Alive (99) |
| SCCO-018* | 5 | IIIC | Yes | 5 | XLAP/RSO/Appy/PPaLNS/OM | CDDP/Cy/Db/E | - | - | DOD (3) |
| SCCO-019* | 27 | IIIC | Unkn. | 20 | XLAP/TAH/BSO/OM/PPaLNS | Unkn. | Unkn. | Unkn. | Unkn. |
| SCCO-020* | 28 | IA | Unkn. | 6 | XLAP/RSO/Appy/PaLNS; TAH/LSO | Unkn. | - | - | Alive (253) |
| SCCO-021* | 30 | Unkn. | Yes | Unkn. | Unkn. | Unkn. | - | - | Alive (23) |
| SCCO-022* | 29 | IC | Yes | 19 | Unkn. | Unkn. | - | - | Alive (7) |

Cases marked * were not able to provide a tumor sample for microarray the analyses, but are included in analyses described in subsequent chapters. Abbreviations: E=European; AA=African American; P=Paclitaxel; Tt=Taxotere; Cddp=Cisplatin; Cb=Carboplatin; Cy=Cyclophosphamide; B=Bleomycin; Db=Doxorubicin; E=Etoposide; V=Vinblastine; I=Ifosfamide; Av=Avastin; G=Gemcitabine; Am=Amrubicin; Ir=Irinotecan, Th=Thiotepa; M=Melphalan; AB=Abdominal mass excision; ABL=Aortic bifurcation lymphadenectomy; AL=Aortic lymphadenectomy; Appy=Appendectomy; BSO=Bilateral salpingo-oophorectomy; CIL=Common iliac lymphadenectomy; EIL=External iliac lymphadenectomy; HPeriAL=High peri-aortic lymphadenectomy; IIL=Internal iliac lymphadenectomy; IR=Infrarenal lymphadenectomy; JRVCL=Juxta renal, vena caval lymphadenectomy; LAD=Lymphadenectomy; LSO=Left salpingo-oophorectomy; MesenAL=Mesenteric lymphadenectomy; O=Oophorectomy; OL=Obturator lymphadenectomy; OM=Omentectomy; PaLNS=Para-aortic lymph node sampling; ParaAL=Para-aortic lymphadenectomy; PCL=Precaval lymphadenectomy; PelvL=Pelvic lymphadenectomy; PeriAL=Periaortic lymphadenectomy; PerientAL=Perienteric lymphadenectomy; PLNS=Pelvic lymph node sampling; RSO=Right salpingo-oophorectomy; SigRsxn=Sigmoid colon implant excision; SrpaoAL=Supra renal para-aortic lymphadenectomy; TAH=Total abdominal hysterectomy; Unkn. = Unknown; USO=Unilateral salpingo-oophorectomy; XLAP=Exploratory laparotomy; StemCT=Stem Cell Transplant; SD=Secondary debulking; NED=No evidence of disease.

Self-reported symptoms were available for 17 cases, and where consistently similar to the typical symptoms of ovarian cancer (Olson et al. 2001): pressure or pain in the abdomen or pelvis, difficulty eating or feeling full quickly, and urinary symptoms. The average duration that symptoms were experienced was 4.7 weeks (range 0.5 – 8 weeks). The average primary tumor size was 13 cm (range 8-20 cm). Tumor size did not vary by age at diagnosis, however tumors were smaller (by 2 cm on average) in hypercalcemic patients. Like in most published cases (Estel et al. 2011; Young, Oliva, and Scully 1994), all tumors were unilateral with 70% involving the right ovary.

One case of familial SCCOHT was found within our cohort, patient SCCO-020, who reported having an older sister who previously succumbed to SCCOHT. A tumor sample from the sister was not available. Only one other case reported a family history of gynecologic malignancy (SCCO-018), with a first-degree relative affected by an ovarian cancer of unknown histotype. No significant variance was observed with age at menarche, BMI, alcohol, tobacco use or vaccination history. Five patients of reproductive age reported having either a miscarriage or an abortion, but detailed information about the clinical circumstances was not available. Morbidities included HPV+ (4 cases), hypothyroidism (2 cases), medulloblastoma, juvenile arthritis, asthma, left ventricular aneurism and temporomandibular joint disorder. Two cases reported their fathers being exposed to Agent Orange prior to their conception.

Follow-up data was obtained for 18 patients and showed an average time to recurrence of 18.6 months. Long-term survival for SCCOHT patients is extremely rare, and most patients die within 2 years of diagnosis (Clement 2005; Estel et al. 2011; Young, Oliva, and Scully 1994). Strikingly, 13 of 20 cases in study cohort were alive at the last follow-up. Moreover, most of them were alive well beyond 2 years post diagnosis (range of 6 months to 21 years after diagnosis). The youngest patient

in our study, a 5-year old girl diagnosed stage IIIC with hypercalcemia, had the worst overall survival and lived only 3 months from the time of diagnosis. The four other pediatric cases were all alive at last follow up.

For cases providing surgical information, no significant correlation was found between procedure performed and outcome. Of the 15 cases with treatment data, all received multi-agent chemotherapy that included a platinum agent and 14/15 received etoposide. Multimodal therapy was used in the treatment of 6/15 patients, who additionally received radiation and/or stem cell transplantation. Five of these patients were alive at follow-up (average 43.2 months).

**Histological review of SCCOHT cases**

Histologic evaluation of all FFPE cases was conducted by a board-certified pathologist from TGen's Macromolecular Analysis & Processing Center (MAPC). Representative images of hematoxylin and eosin (H&E) stained SCCOHT tumors are shown in Figure 1. Tissue architecture was consistent with previous observations (Robert H. Young 1994). Large-cell variants with pleiomorphic nuclei were focally apparent in four cases (SCCO-009, SCCO-010, SCCO-017 and SCCO-019). IHC results were abstracted from pathology reports with additional analyses performed to enhance information for TOP2A, p53, calretinin, AFP, Oct3/4, NCAM1, CD4, CD8, B-lymphocyte antigen (CD20) and, CD68, as described in the materials and methods. A summary of these findings for each tumor case is provided in Table 3, and representative images are shown in Figure 2. Data for markers of the 3 main cell types of the ovary was as follows: the majority of tumors showed expression of the epithelial marker EMA (8/13), which agrees with previous reports (McCluggage et al. 2004; Young, Oliva, and Scully 1994); all cases were consistently positive for the germ cell

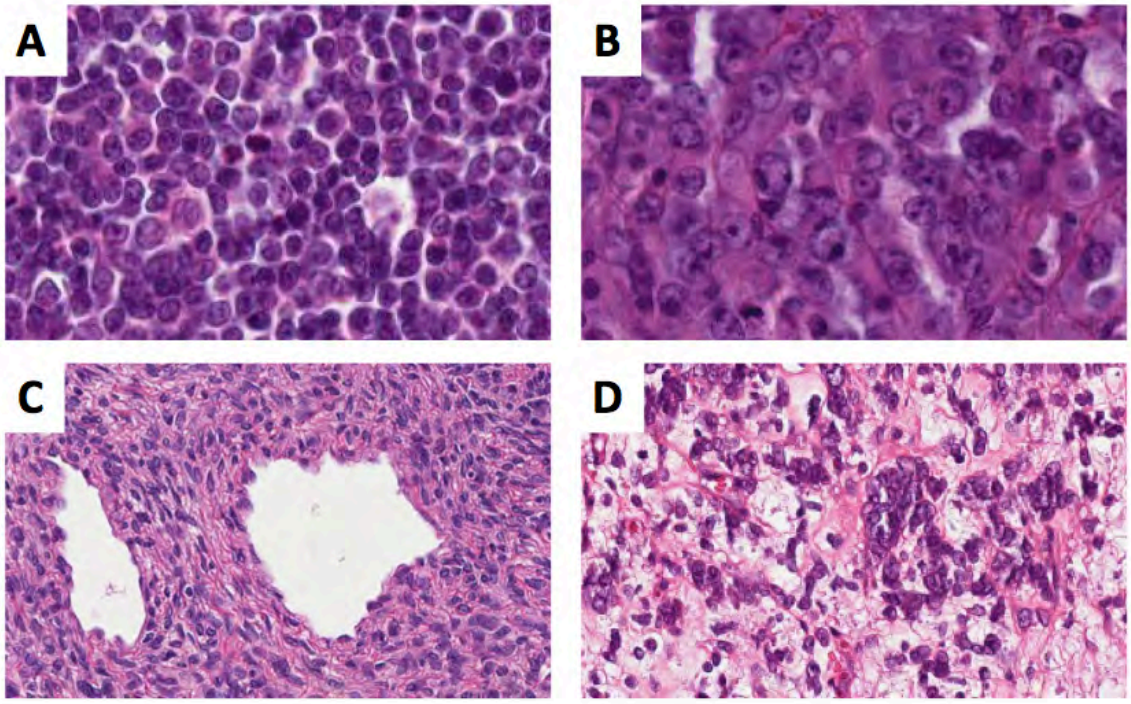


*Figure 1.* Representative H&E staining of SCCOHT tumors. Tumors are characterized by broad sheets of tightly packed tumor cells with uniform and round hyperchromatic nuclei, scant cytoplasm, extensive mitotic figures and few areas of necrosis. Tumors are often highly vascularized and show a trabecular configuration. Frequent areas of acellular hyalinization and fibrinoid organization were observed. **A.** Regions of tightly packed tumor cells with hyperchromatic nuclei and scant cytoplasm. **B.** Large cell variant of SCCOHT. **C.** Follicle-like structures. **D.** Areas of acellular hyalinization, fibrinoid organization and tumor scar tissue with large areas of scantly stroma (e.g. loose eosinophilic areas). Additional common features included leaky capillaries and vessels (hemorrhage), perivascular cuffing and early stages of organizing hyalinization (not shown). Images acquired with 20X objective and represented at 200X magnification.

Table 3.

Molecular Markers Assessed in SCCOHT Tumors.

| Molecular Marker | No. Cases Stained | No. Cases Positive | % Cases Positive | No. Cases Negative | % Cases Negative |
|---|---|---|---|---|---|
| **Vimentin** | 8 | 8 | 100% | 0 | 0% |
| **Pan cytokeratin** | 6 | 6 | 100% | 0 | 0% |
| **NSE** | 2 | 2 | 100% | 0 | 0% |
| **p53** | 12 | 11 | 92% | 1 | 8% |
| **WT-1** | 8 | 7 | 88% | 1 | 13% |
| **AE-1/AE-3** | 8 | 6 | 75% | 2 | 25% |
| **NCAM1** | 15 | 11 | 73% | 4 | 27% |
| **CD99** | 9 | 6 | 67% | 3 | 33% |
| **Cam5.2** | 3 | 2 | 67% | 1 | 33% |
| **EMA** | 13 | 8 | 62% | 5 | 38% |
| **CD20** | 5 | 3 | 60% | 2 | 40% |
| **CD10** | 2 | 1 | 50% | 1 | 50% |
| **Calcitonin** | 2 | 1 | 50% | 1 | 50% |
| **Calretinin** | 15 | 7 | 47% | 8 | 53% |
| **Synaptophysin** | 9 | 4 | 44% | 5 | 56% |
| **PTH** | 3 | 1 | 33% | 2 | 67% |
| **CD117 (C-kit)** | 4 | 1 | 25% | 3 | 75% |
| **CD30** | 4 | 1 | 25% | 3 | 75% |
| **Chromogranin** | 10 | 2 | 20% | 8 | 80% |
| **PLAP** | 6 | 1 | 17% | 5 | 83% |
| **AFP** | 16 | 0 | 0% | 16 | 100% |
| **Inhibin alpha** | 13 | 0 | 0% | 13 | 100% |
| **OCT3/4** | 11 | 0 | 0% | 11 | 100% |
| **S100** | 10 | 0 | 0% | 10 | 100% |
| **Desmin** | 6 | 0 | 0% | 6 | 100% |
| **ER** | 5 | 0 | 0% | 5 | 100% |
| **Myogenin** | 5 | 0 | 0% | 5 | 100% |
| **LCA (CD45)** | 5 | 0 | 0% | 5 | 100% |
| **HCG** | 5 | 0 | 0% | 5 | 100% |
| **PR** | 4 | 0 | 0% | 4 | 100% |
| **CK7** | 4 | 0 | 0% | 4 | 100% |
| **4-Oct** | 3 | 0 | 0% | 3 | 100% |
| **TTF-1** | 3 | 0 | 0% | 3 | 100% |
| **Alpha-1-antitrypsin** | 2 | 0 | 0% | 2 | 100% |

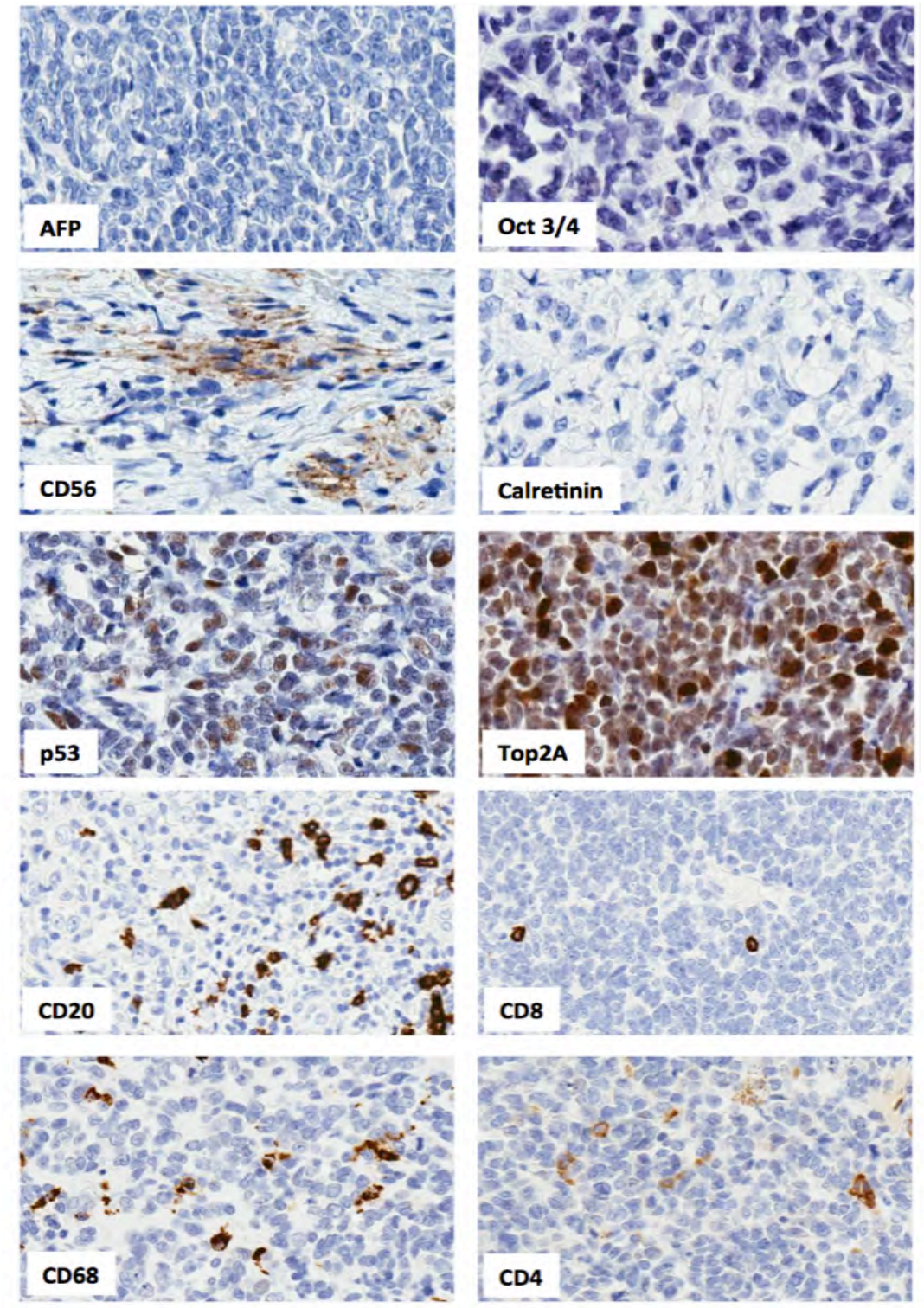


*Figure 2.* Representative immunohistochemical (IHC) staining of SCCOHT tumors. Panels showing representative staining patterns for the markers indicated. Images acquired at 20X magnification. IHC was performed as described in the Materials and Methods.

markers AFP (16/16) and placental alkaline phosphatase PLAP (5/6); a mixed profile of markers of sex-cord stroma was observed, with all tested tumors lacking inhibin alpha (INHA) (13/13), but showing positive staining for Wilms' tumor suppressor protein 1 WT1 (7/8), and about 50% positivity for Calretinin (7/15). In addition, tumors were consistently negative for the stem cell marker OCT3/4 (11/11), and predominantly negative for markers of neuroendocrine differentiation, chromogranin (8/10) and synaptophysin (5/9), and neural crest cells, S100 (10/10). Our additional analysis of lymphocytic markers, showed scattered positive staining for CD4, CD8, CD20 and CD68 in all SCCOHT cases (Figure 2). Positive p53 staining was observed in the majority of cases (11/12 cases).

**Gene expression profiling of SCCOHT tumors relative to normal ovary**

To gain insight into what genes and/or networks operate in SCCOHT, we performed gene expression profiling on 4 cases relative to age-matched normal ovary. We identified 5,104 genes as significantly up- or down-regulated in all cases (see Appendix A for gene list and expression ratio data); with 4,128 of these genes (81%) consistently deregulated in 4/4 tumors (2,197 up- and 1,931 down-regulated). Unsupervised, 2-dimensional hierarchical clustering of these genes revealed two clusters of genes uniquely divergent for case SCCO-012 (Figure 3). Gene Ontology (GO) analysis of the upregulated genes indicated significant enrichment for lymphoid and immune response processes, consistent with this sample being from a lymph node resection. IHC analysis showed a significant immune infiltrate in the specimen (Figure 3). Meanwhile, downregulated genes unique to SCCO-012 were associated with cardiac development (data not shown).

Pathway analysis for the remaining 4,128 genes consistently expressed in all cases showed strong enrichment for processes associated with cell cycle progression,

response to steroid hormones and sex organ development (Appendix B). This result was not unexpected given the biologic comparison of highly proliferative ovarian tumors relative to normal ovary. To identify functional processes that may be masked by the strong proliferative signal, we selectively subtracted genes mapped to the cell cycle GO network (see Materials and Methods) and repeated the enrichment analysis. This time, the most prevalent cellular processes were DNA repair, DNA damage-response, nucleosome assembly, neurogenesis, and nervous system development (Appendix C). Upon inspection of significantly up-regulated genes in all SCCOHT tumors, we discovered several whose expression is predominantly observed in (and even restricted to) neural tissue. Examples include *CDH10* (263.8 average fold ratio), a brain-specific cadherin involved in synaptic adhesion and axon guidance, *LRRTM4* (78.6 average fold ratio) required in nervous system development, and *CEND1* (6.4 average fold), a neuron specific protein required for neuronal cell differentiation.

**Expression of ligand genes in SCCOHT**

Approximately 60% of SCCOHT patients present with paraneoplastic hypercalcemia (Young, Oliva, and Scully 1994). The mechanism of development of this condition remains unclear, but it is thought to involve secretion of PTHrP by the tumors cells, which can act through PTH receptors to mediate the calcium release (Grill and Martin 2000; Strewler 1998). Immunoreactivity for PTHrP (also known as PTHLH) has been detected in some SCCOHT tumors (Abeler, Kjorstad, and Nesland 1988; Chen, Dinh, and Haque 2005; Xavier Matias-Guiu 1993; Young, Oliva, and Scully 1994); however, the presence and strength of immunoreactivity does not appear to correlate with the presence or degree of hypercalcemia (Xavier Matias-Guiu 1993).

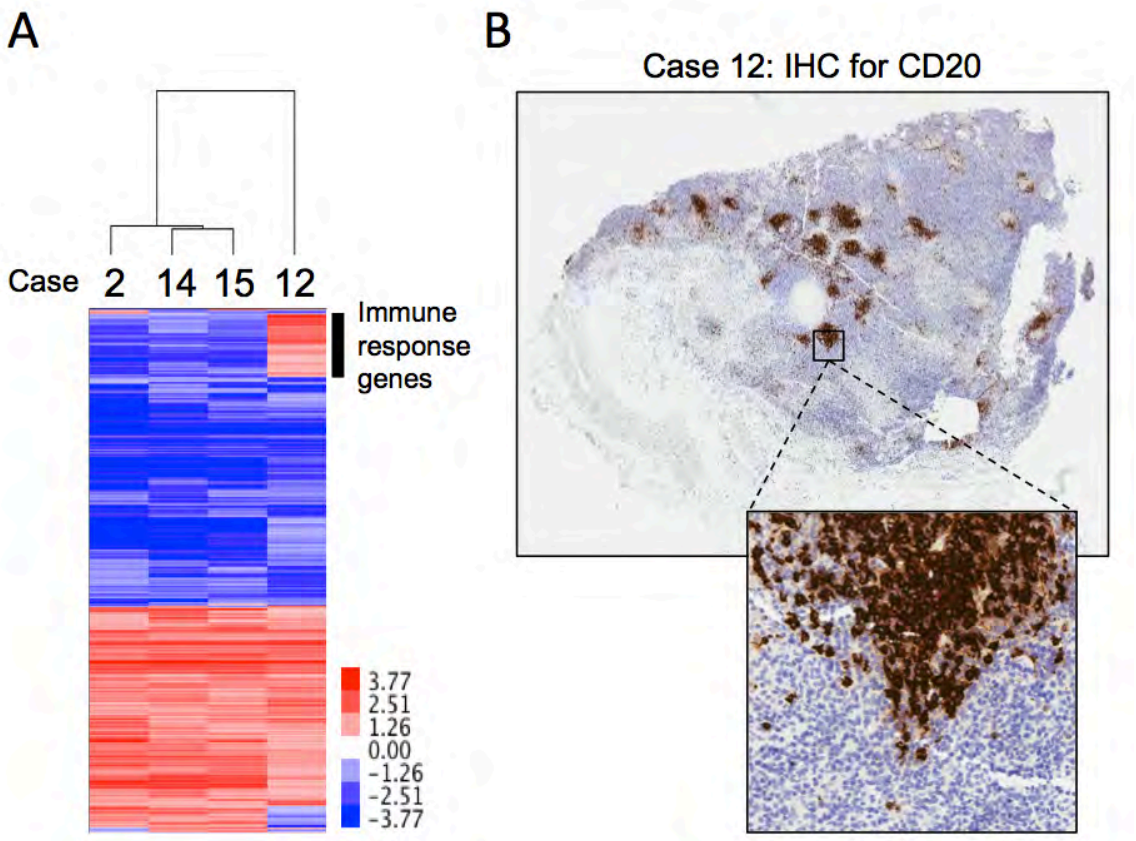


*Figure 3.* Gene expression microarray analysis of 4 SCCOHT tumors vs. normal ovary. **A.** Unsupervised, 2-dimensional hierarchical clustering of 5,104 genes significantly expressed in 4/4 fresh-frozen SCCOHT tumors relative to age-matched normal ovary. Genes divergently expressed in SCCO-012 were strongly enriched for immune response processes. Clustered genes in the dendogram are provided in Appendix A. **B.** CD20 IHC for case SCCO-012 shows significant infiltration of immune cells, consistent with the expression data for this tumor.

To investigate the expression of PTHrP and other genes encoding secreted ligands in SCCOHT, we extracted genes linked to the GO category 'Receptor Ligand Object Types' from our expression data of 4 tumors compared to normal ovary. The top overexpressed ligand genes are shown on Table 4. Expression of PTHrP was highly elevated in 3 of 4 patients (SCCO-002, SCCO-014, and SCCO-015), two of them diagnosed with hypercalcemia (information for SCCO-015 was not available).

Interestingly, we found that the majority of overexpressed ligand genes encoded for neuropeptides, including *NXPH1*, *NTS* and *NmU*. *NTS* is known to promote adhesion between dendrites and axons, and is a potent mitogen in colorectal cancer (Wang et al. 2006). Additional highly expressed genes included *FGF11*, *NTN1*, *EFNB2*, *HGF, WNT3*, and several members of the TGF-beta superfamily. These genes encode powerful morphogenic signaling ligands involved in regulation of axon guidance, neuronal migration, neuronal differentiation as well as embryo, bone and organ morphogenesis. While the potential pro-malignant role of these secreted morphogens is not clear, their consistently high expression may prove useful as translational biomarkers for SCCOHT.

**SCCOHT genomes are overtly diploid with subtle aberrations in DNA content**

Unlike most poorly differentiated, highly malignant tumors, SCCOHT tumors are characteristically diploid (Eichhorn et al. 1992; Hauptmann S. 2006; Heinrich Walt 2001; Lamovec, Bracko, and Cerar 1995; Robert H. Young 1994). We performed a flow cytometric analysis on 13 SCCOHT tumor samples, yielding evaluable data for 9 cases (Table 5). A diploid (2N) and tetraploid (4N) peak was identified in 9/9 tumors consistent with previous studies. No aneuploid peaks were identified. Array CGH (aCGH) analysis of flow-sorted nuclei from 15 SCCOHT tumors was performed as described in the Materials and Methods. While the DNA landscape

Table 4.

Upregulated Ligand Genes Expressed in SCCOHT Tumors.

| Gene Name | Description | Average Log2Ratio in 4 SCCO tumors vs. normal ovary |
|---|---|---|
| **NXPH1** | Neurexophilin-1 | 7.162 |
| **NTS** | Neurotensin/neuromedin N | 7.081 |
| **NMU** | Neuromedin-U | 4.655 |
| **BMP5** | Bone morphogenetic protein 5 | 4.520 |
| **ULBP1** | NKG2D ligand 1 | 4.443 |
| **MST1** | Hepatocyte growth factor-like protein | 3.917 |
| **DLL3** | Delta-like protein 3 | 3.539 |
| **BMP4** | Bone morphogenetic protein 4 | 3.226 |
| **HGF** | Hepatocyte growth factor | 3.143 |
| **VGF** | Neurosecretory protein VGF | 3.121 |
| **FGF11** | Fibroblast growth factor 11 | 3.038 |
| **PTHLH** | Parathyroid hormone-related protein | 2.468 |
| **NTN1** | Netrin-1 | 2.384 |
| **EFNB2** | Ephrin-B2 | 2.267 |
| **TGFB2** | Transforming growth factor beta-2 | 2.116 |
| **WNT3** | Proto-oncogene Wnt-3 | 2.089 |
| **BMP3** | Bone morphogenetic protein 3 | 2.079 |
| **CD70** | CD70 antigen | 1.875 |

of individual tumors appears unremarkable, the cumulative aberration plot indicated some focal areas of recurrent aberration (Figure 4). Genomic Identification of Significant Targets in Cancer (GISTIC) analysis on these data identified 37 CNVs (32 gain, 5 loss) distributed across all but one chromosome, totaling 8.52 Mb (0.27% of the genome), encompassing 67 RefSeq genes (Appendix D). Of the 55 RefSeq genes in CNV gains, 26 (47%) were also significantly overexpressed in three or four SCCOHT tumors relative to normal ovary (Appendix D). Several of these genes play important roles in neurobiology and neuropathology, including neuroligin-1 (*NLGN1*), roundabout homolog 1 (*ROBO1*), protocadherin 9 (*PCDH9*), alkylglycerol monooxygenase (*AGMO)*, mesenchyme homeobox (*MEOX2*), inositol polyphosphate-1-phosphatase (*INPP1*) and major facilitator superfamily domain containing 6 (*MFSD6)*. We noted several genes frequently aberrant and dysregulated in malignancies of the ovary, lung, colon, breast and brain. For example, *NLGN1* is frequently amplified in ovarian and lung cancers; *MEOX2* and *AGMO* are frequently amplified in glioblastoma, colon and lung cancer; and *INPP1* is highly expressed in colon cancer resulting in deregulated phosphatidylinositol signaling (Benjamin et al. 2014; Cerami et al. 2012; Gao et al. 2013). Also, several genes frequently deleted in ovarian cancer show CNV gains and expression upregulation in SCCOHT. These include *RAPGEF* and *PLEKHG*, both guanine nucleotide exchange factors of the RAS GTPase superfamily, asialoglycoprotein receptor 1 (*ASGR1*), GATA binding protein 4 (*GATA4*) and Wilms tumor 1 (*WT1*), the latter 3 important in embryo and organogenesis (Cerami et al. 2012; Gao et al. 2013). Lastly, GISTIC analysis identified Myeloid/lymphoid or mixed-lineage leukemia (*MLLT10*) and zinc finger protein 26 (*ZNF726*), important in leukemogenesis, and deregulation of histone acetylation function.

**Identification of pathways enriched in SCCOHT compared to epithelial ovarian tumors**

We performed single-sample Gene Set Enrichment Analysis (ssGSEA) to define the cellular processes enriched by the 3,174 most highly differentiating genes between SCCOHT and non-SCCOHT tumors (2 classes), and used comparative marker selection to display the most salient differences in terms of biological processes between the two classes (Figure 7 and Appendix F). This analysis demonstrated a characteristic upregulation of molecular signals associated with development of the nervous system in SCCOHT tumors, including neurogenesis and synaptogenesis. These findings were consistent with our earlier observations, with distinct differences revealed by the tumor-derived reference. Cellular processes downregulated in SCCOHT compared to EOCs, were largely associated with enzyme activity and protein transport.

Table 5.

Flow Cytometry Analysis of SCCOHT Tumor Cells.

| Sample ID | FACS peaks | % G1 | % G2 | % S |
|---|---|---|---|---|
| **SCCO-001** | 2N 4N | 86.25 | 7.385 | 6.365 |
| **SCCO-002** | 2N 4N | 52.681 | 5.986 | 41.333 |
| **SCCO-004** | 2N 4N | 82.832 | 10.179 | 6.989 |
| **SCCO-005** | 2N 4N | ND | ND | ND |
| **SCCO-006** | 2N 4N | 75.914 | 24.086 | 0 |
| **SCCO-007** | 2N 4N | 75.719 | 16.45 | 7.831 |
| **SCCO-008** | ND | ND | ND | ND |
| **SCCO-009** | 2N 4N | 80.59 | 9.7 | 9.683 |
| **SCCO-010** | 2N 4N | ND | ND | ND |
| **SCCO-011** | 2N 4N | 88 | 4.513 | 7.473 |
| **SCCO-012** | 2N 4N | 88.015 | 4.513 | 7.473 |
| **SCCO-016** | 2N 4N | 74.43 | 14.5 | 11.07 |
| **SCCO-017** | ND | ND | ND | ND |
| | | Mean % G1 = 78.3 | Mean % G2 = 10.8 | |

ND = Not determined due to cellular debri. Unk. = Unknown.

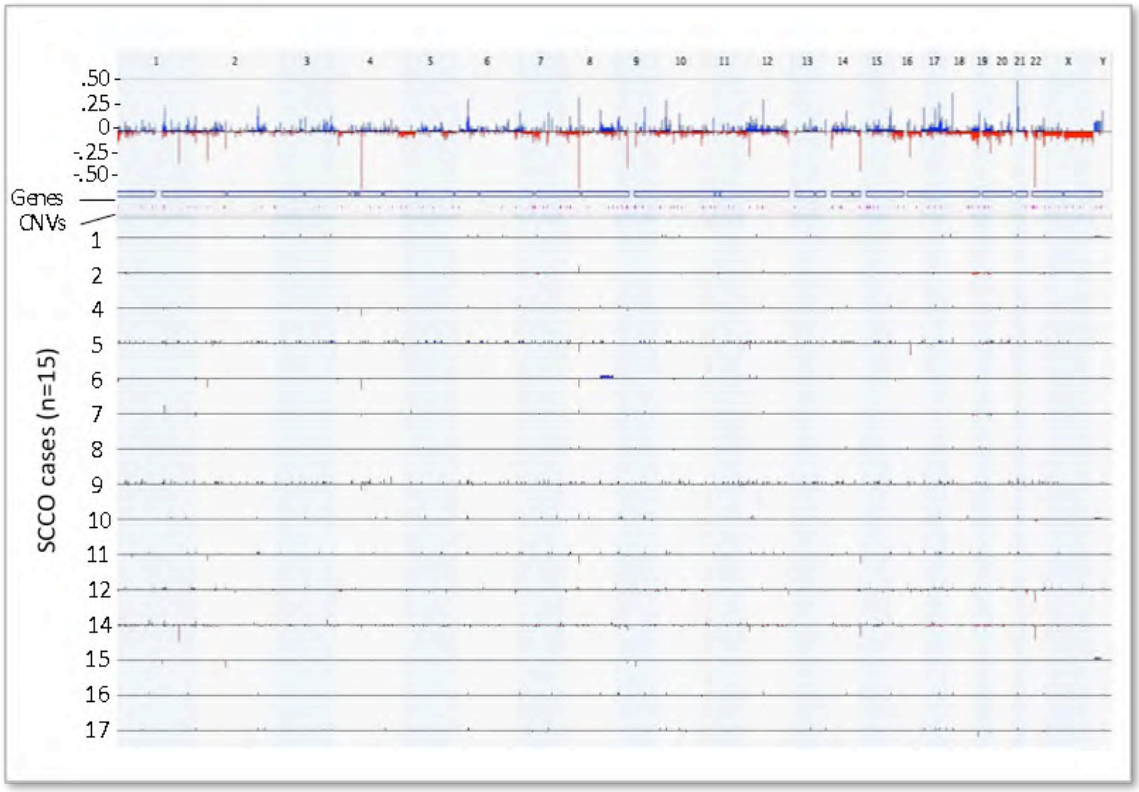


*Figure 4.* Landscape of copy number alterations in SCCOHT. Individual (bottom panel) and aggregate genome-wide frequency plots of copy number gains (blue) and copy number losses (red) identified in the DNA of 4N cell populations isolated from 15 SCCOHT FFPE tumors. Sample plots were generated using Nexus software (Biodiscovery). Threshold for gain or loss = 0.35 < x > 0.4.

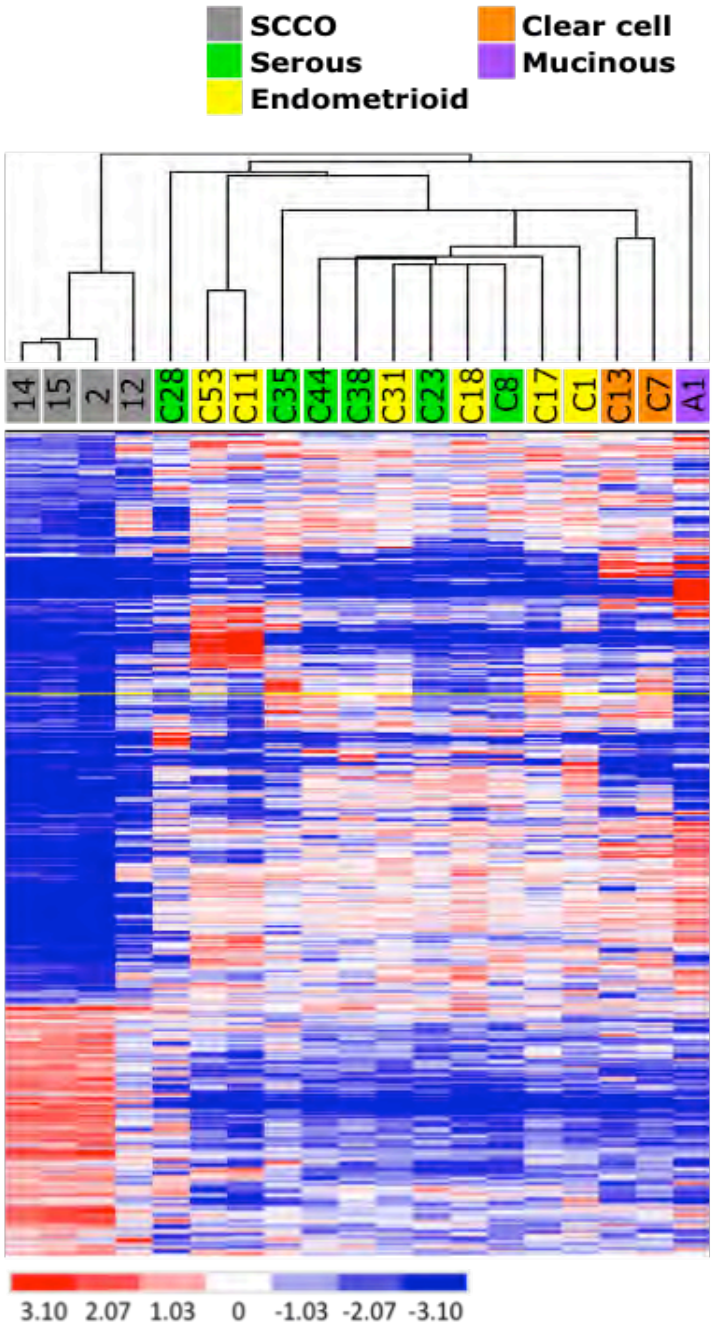


*Figure 5.* Expression profiling of SCCOHT and epithelial ovarian tumors. Two-dimensional hierarchical clustering dendogram of 3,175 genes most differentially expressed between 4 SCCOHT and 15 epithelial ovarian tumors samples of different histological subtypes. Gene list and Log2Ratio expression data for SCCOHT tumors is provided in Appendix E.

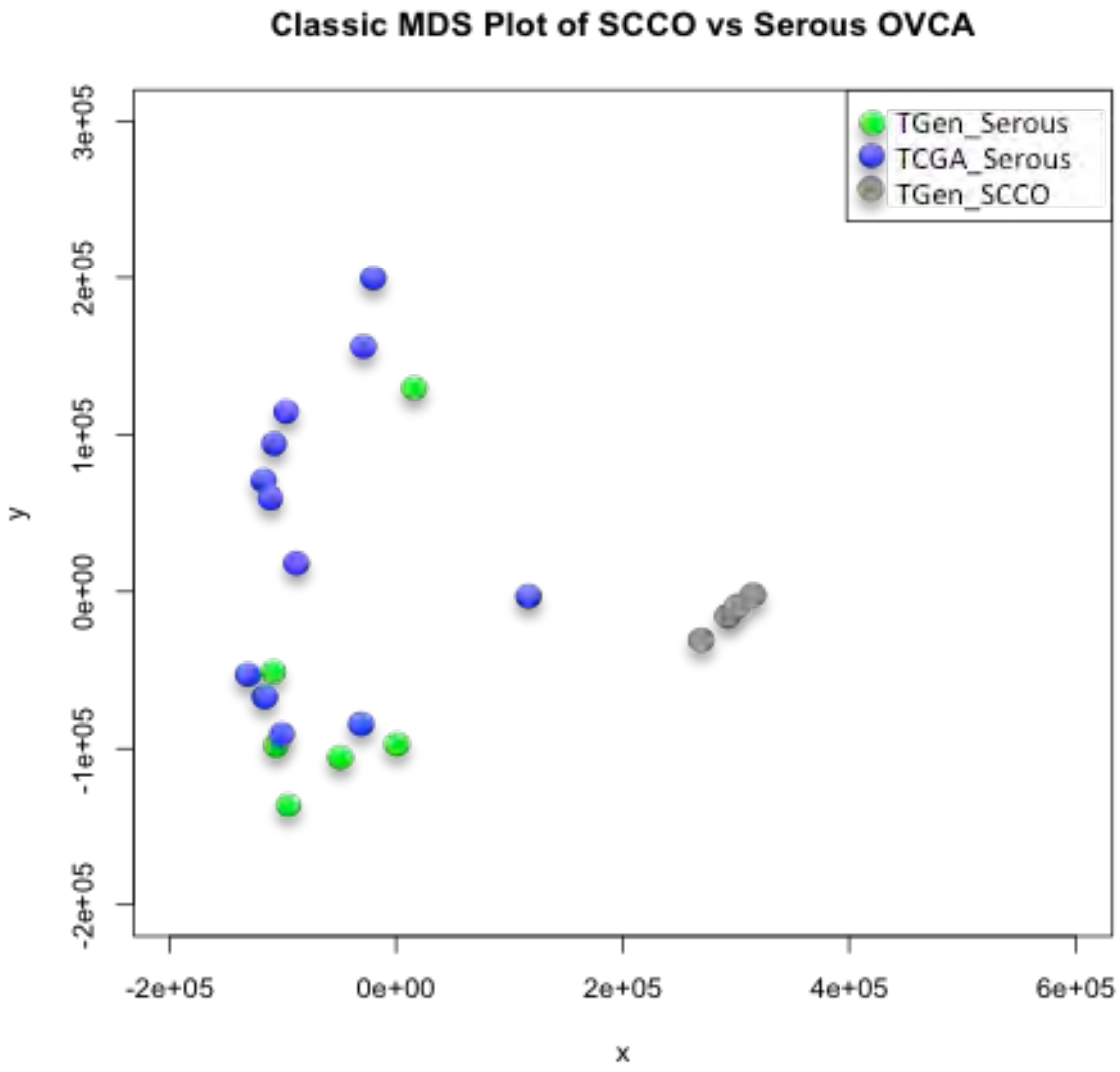


*Figure 6.* Multidimensional Scaling (MDS) analysis of SCCOHT and serous ovarian carcinomas. Two-dimensional MDS plot of 4 SCCOHT and 6 ovarian serous tumors (this study) and 12 serous ovarian tumors (TCGA) color-coded for distinction. Each plotted point represents one tumor sample and the Euclidean distances between samples (see Materials and Methods).


*Figure 7.* Single sample gene set enrichment analysis (ssGSEA) of SCCOHTs compared to epithelial ovarian tumors (EOC). Muc = Mucinous, End = Endometrioid, Cle = Clear cell, Ser = Serous. See Appendix F for enrichment scores.

**Discussion**

First described by the renowned pathologist Robert E. Scully in 1979, SCCOHT is a rare and extremely aggressive type of ovarian cancer (Scully 1979). It is most often diagnosed in women of reproductive age (15-44 years) but it also affects children as young as 14 months old (Florell et al. 1999; Young, Oliva, and Scully 1994). Although the pathological and clinical characteristics of SCCOHT have been defined, very little progress has been achieved in elucidating the molecular biology underlying the disease. Its differential diagnosis remains a challenge even for expert pathologists, and treatment options are limited and unpredictable. It is imperative that we investigate the biology of SCCOHT and determine how to better diagnose and treat this deadly tumor.

To facilitate this study, we developed a HIPPA-compliant and IRB-approved SCCOHT biospecimen collection protocol. Consented participants enrolled in this study donated tumor tissue and a peripheral blood sample where possible. Clinical data including operative, pathology and cytology reports, and treatment regimens were also obtained when available. Between November 2010 and June 2013, 22 cases of SCCOHT were consented. Twenty tumors (4 frozen, 16 FFPE) from 18 cases and 10 blood samples were obtained. Considering that there are likely less than 100 cases of SCCOHT diagnosed each year in the United States (SCCOHT is estimated to account for less than 1% of the 21,900 cases of ovarian cancer diagnosed per year), our cohort represents a significant resource for the study of this cancer.

A review of the clinicopathological and histological characteristics of the 22 SCCOHT cases in our cohort recapitulated the previously described features of this aggressive and poorly differentiated tumor. The age distribution of our cases (5 - 42 years old) reflected the broad range of ages of SCCOHT patients, with the majority of diagnoses being in the 20s and 30s, and more rarely in children under 18 and

women over 40. Treatment of patients in our study was similar to those previously reported, and relied on multiagent chemotherapy including etoposide, paclitaxel, and cisplatin or carboplatin. As mentioned in the results section, it is striking that 13 of 20 (65%) cases in our study remained alive well beyond 2 years after diagnosis since the 2-year survival for SCCOHT is less than 35% (Clement 2005; Estel et al. 2011; Young, Oliva, and Scully 1994). It is possible that our sample acquisition process introduced a bias towards long-term survivors.

The immunoprofile of SCCOHT tumors in our cohort showed the usual intense staining for vimentin, cytokeratins, WT-1 and p53, and lack of inhibin a (INHA). Expression data for these genes was consistent with the levels of protein expression (see Appendix A). SCCOHTs are reported to have strong p53 IHC staining in 80-100% of cases (McCluggage 2004), suggesting that TP53 mutations might be involved in SCCOHT pathogenesis (Navone et al. 1993); however, all SCCOHT tumors analyzed to date lacked TP53 mutations (Gamwell et al. 2013; McDonald et al. 2012).

Cytogenetic analysis of SCCOHT tumors revealed a stable diploid genome with few copy number variations. Using GISTIC analysis we identified 37 recurrent alterations across the 15 SCCOHT tumors that were profiled by aCGH (Table 8). A number of genes located within regions exhibiting copy number gains were found to be overexpressed in at least 3 of the 4 SCCOHT tumors analyzed by gene expression microarray. Some of these genes have been shown to play a role in neurobiology and neuropathology, such as *NLGN1* and *ROBO1*. However, we did not identify any copy number anomalies consistent with previous reports (Eichhorn et al. 1992; Hauptmann S. 2006; Heinrich Walt 2001; Lamovec, Bracko, and Cerar 1995; Robert H. Young 1994).

SCCOHT tumors have a distinct expression profile when compared to

epithelial ovarian tumors. Their immunohistochemical and expression profiles suggest that they are driven by genetic aberrations different than those found in epithelial ovarian carcinomas. SCCOHT tumors show enrichment of genes involved in cell cycle control, DNA damage response and repair mechanisms, and inhibition of apoptosis. G1/S cyclin genes and their corresponding cyclin-dependent kinases (cdks) were highly elevated, particularly cyclin D2, a known biomarker of ovarian and testicular tumors (Bartkova et al. 1999; Choi et al. 2000). A characteristic of G1/S deregulation is the enrichment of E2F-target genes. Indeed, we observed abundant transcripts encoding Cyclin E, cyclin-dependent kinase 2 (CDK2), tyhimidine kinase (TK), Dihydrofolate reductase (DHFR), Proliferating cell nuclear antigen (PCNA), and Histone 2A (H2A), a key component in nucleosome formation. Interestingly, rather than canonical H2A, SCCOHT tumors show significantly elevated expression of selected alternative H2A family members previously linked to tumor progression (Bosch and Suau 1995). Variant H2A proteins alter specificity of nucleosome composition during chromatin remodeling, the dynamic process whereupon chromatin architecture is modified to facilitate transcription, DNA replication/repair, chromosome segregation and apoptosis. Expression of histone deacetylase, histone acetyltransferase, polycomb group and trithorax group genes important in chromatin remodeling is also significantly deregulated in our cases. In addition, DNA methyltransferases *DNMT1, DNMT3A* and *DNMT3B* are upregulated in SCCOHT. It is tempting to speculate that the neuronal-like expression profile in SCCOHT may be the result of altered epigenetic control, resulting in transcriptional reprogramming towards a neuronal lineage.

Analysis of cell morphologic and signaling mechanisms in SCCOHT transcriptomes provides insight into possible etiology and drivers of SCCOHT progression. First, we observed large numbers of genes associated with embryonal

and mesenchymal features. SCCOHT tumors uniformly lack expression of cell polarity and cell junction markers (including *RAB25, CRB3, PKP3, AP1M2*, and numerous claudins, cadherins, integrins, and adhesion molecules). However, calcium-dependent cadherins and neuronal catenins were shown to be highly upregulated. Interestingly, neurotrophin receptors and their ligands were not expressed in SCCOHT.

Among the most highly overexpressed transcripts in SCCOHT were *CRMP1* and Class 3 semaphorins *SEMA3A* and *SEMA3F,* which regulate axonal growth cone guidance/collapse (Yazdani and Terman 2006). A secreted morphogen highly expressed in SCCOHT is bone morphogenic protein 4 (*BMP4)*, a TGF-beta family member regulated in early embryonic development of the dorsal-ventral axis. BMP4 regulates osteoblast commitment, differentiation of stem cells, early ovarian follicle development, and is proposed to aid in oocyte survival (Nilsson and Skinner 2003). BMP4 receptors are moderately expressed in SCCOHT. Another very highly expressed gene in SCCOHT encoding a secreted ligand is hepatocyte growth factor (*HGF)*, the cognate ligand for the proto-oncogene MET (hepatocyte growth factor receptor). While SCCOHT tumors do not express appreciable *MET*, an oncogenic mechanism of MET-independent HGF-signaling has been described, leading to downregulation of FAS and FAS ligand (FASL) in prostate cancer (Tate et al. 2006). Furthermore, the cell surface response mediator for HGF in this mechanism is nucleolin (*NCL*), which is highly expressed in SCCOHT. It is therefore plausible the observed lack of *FAS* and *FASL* expression in SCCOHT may be mediated by HGF/NCL signaling.

We successfully established a fully annotated SCCOHT biospecimen cohort and leveraged various array-based technologies to gain understanding of the molecular processes accounting for the pathobiology of SCCOHT. Collectively, the information presented in this chapter compliments the subsequent sequencing

analyses performed on these same samples by providing important patient and molecular characteristics to contextualize the genetic aberrations identified in SCCOHT.

CHAPTER 2

# INACTIVATING SMARCA4 MUTATIONS DRIVE SCCOHT

## Introduction

Although IHC and microarray studies have identified important clues to the pathobiology of SCCOHT, it remains a major task to define the mutation spectrum of these tumors. Rapid advances in cancer genome sequencing have empowered us to characterize cancer genomes and quickly translate genomic information to the clinical care of cancer patients. We therefore aimed to perform exome or whole-genome sequencing of a series of SCCOHT tumors and germline samples to search for consistent genetic variations potentially involved in the development and/or predisposition to SCCOHT carcinogenesis.

A discovery cohort of 12 SCCOHT patients and 1 SCCOHT cell line (BIN-67) (Gamwell et al. 2013) was analyzed using next-generation sequencing techniques. An expanded sample cohort of 12 additional tumors, 3 matched germline samples, and the cell line SCCOHT-1 (Otte et al. 2012) were subsequently examined using targeted sequencing approaches. Our analysis revealed frequent inactivating mutations in the Switch/Sucrose NonFermentable (SWI/SNF) chromatin-remodeling gene *SMARCA4*. No other recurrent mutations were identified. Immunohistochemical assessment showed that SMARCA4 (BRG1) protein was absent in the majority of SCCOHT tumors. Moreover, we found that among ovarian tumors, loss of SMARCA4 was highly specific to SCCOHT, as only 2 of 485 (0.4%) other primary ovarian tumors were negative for SMARCA4 staining. Moreover, *SMARCA4* mutations were present in the germline DNA of 2 SCCOHT patients and therefore established a heritable component in the genesis of this disease.

In non-neoplastic cells, SMARCA4 serves as critical member of the SWI/SNF complex. Using the energy of adenosine triphosphate (ATP) hydrolysis, the SWI/SNF

complex functions to destabilize histone-DNA interactions and move, eject or restructure nucleosomes, thereby regulating accessibility of transcriptional and DNA replication/repair machinery (Hargreaves and Crabtree 2011; Roberts and Orkin 2004). SWI/SNF complexes are thus critical regulators of transcription and have been shown to influence multiple biological processes including skin development, limb morphogenesis, erythropoiesis, vasculature, gliogenesis, neural stem/progenitor cells, and T-cell development (Shen et al. 2008). Conserved in yeast and humans, the SWI/SNF complex is composed of 10-15 subunits. Two mutually exclusive ATPases – SMARCA4 or SMARCA2 carry the enzymatic activity of the complex (Hargreaves and Crabtree 2011); three mutually exclusive "core" subunits confer functional specificity and have scaffolding functions: SMARCB1 (BAF47/SNF5), SMARCC1 (BAF155), SMARCC2 (BAF170); and several "accessory" subunits associated with the complex in various combinations that afford variable roles: ARIDA1A (BAF250A), ARID1B (BAF250B), PBRM1 (BAF180), SMARCE1 (BAF57), SMARCD1 (BAF60A), SMARCD2 (BAF60B), SMARCD3 (BAF60C), PHF10 (BAF45A), DPF1 (BAF45B), DPF2 (BAF45D), DPF3 (BAF45C), ACTL6A (BAF53A) and ACTL6B (BAF53B) (Shain and Pollack 2013; Weissman and Knudsen 2009). Specificity of SWI/SNF function is dictated by subunit composition, and imbalances in subunit expression can lead to malignant transformation, often in a tissue-specific manner (Kadam and Emerson 2003; Moshkin et al. 2007; Trotter and Archer 2008; Wang et al. 2006).

Recent studies suggest that mutations in genes comprising the SWI/SNF complex may be ubiquitous across diverse cancer types, with *SMARCA4* being the most commonly mutated SWI/SNF subunit (Integrated genomic analyses of ovarian carcinoma 2011; Shain and Pollack 2013). Mutations in *SMARCA4* have been reported in a variety of cancers including melanoma, pancreatic, lung and ovarian

carcinomas (Integrated genomic analyses of ovarian carcinoma 2011; Shain and Pollack 2013). Studies in genetically engineered mice models strongly indicate a tumor suppressor role of SMARCA4, as 10% of *SMARCA4* heterozygous animals develop germline mammary tumors due to haploinsufficiency (Bultman et al. 2000; Bultman et al. 2008). Further, a recent study showed that conditional inactivation of *SMARCA4* in the ovaries and the uterus of mice leads to the development of ovarian cysts and uterine tumors (Serber et al. 2012). Moreover, SMARCA4 is essential for mammalian development as demonstrated by the early embryonic lethality of *SMARCA4* null homozygous mice (Bultman et al. 2000; Bultman et al. 2008). We now have showed that in SCCOHT, SMARCA4 behaves as a classical tumor suppressor, and its mutational inactivation leads to protein loss in most cases. The functional consequences of SMARCA4 loss on SWI/SNF activity and its downstream effects remain to be elucidated.

## Materials and Methods

### Clinical samples

Samples at TGen were obtained as described in Chapter 1. At the University of British Columbia, B.C., Canada, we collected biospecimens from the Ovarian Cancer Research Program (OvCaRe) tissue bank in Vancouver, British Columbia, Canada; the University of Toronto in Toronto, Canada; the Children's Oncology Group at Nationwide Children's Hospital in Columbus, Ohio, USA; and the Hospital de la Santa Creu i Sant Pau at Autonomous University of Barcelona, Spain, via an IRB-approved protocol. All of the specimens were small cell carcinoma of hypercalcemic type, with 4 cases (SCCO-009, SCCO-017, and SCCO-019) classified as large cell variant of SCCOHT in their pathology reports. Cases of small cell carcinoma of pulmonary type were excluded from the study.

**Genomic DNA isolation**

Fresh-frozen tissue was disrupted and homogenized in Buffer RLT plus (Qiagen), using the Bullet BlenderTM, Next Advance (Next Advance Inc; Averill Park, NY), and transferred to a microcentrifuge tube containing Buffer RLT plus and 1.6 mm stainless steel beads. Blood leukocytes (buffy coat) were isolated from whole blood by centrifugation at room temperature and resuspended in Buffer RLT plus. All samples were homogenized, centrifuged at full speed, and lysates were transferred to the Gentra Puregene Kit (Qiagen; Valencia, CA) or AllPrep Kit (Qiagen) for DNA isolation. Genomic DNA was purified following the manufacturer's protocol.

FFPE DNA was extracted using Qiagen's All Prep DNA/RNA FFPE kit (Qiagen; Valencia, CA). Saliva samples from consented relatives of SCCOHT patients were obtained using Oragene Saliva Collection kit OGR-500 (DNA Genotek; Ottawa, ON, Canada). DNA was then extracted using prepIT-L2P (DNA Genotek) following the manufacturer's instructions.

All DNAs were quantified using the Nanodrop spectrophotometer (Nanodrop; Wilmington, DE) based on 260/280nm and 260/230nm absorbance ratios, and by Qubit Assay (Life Technologies).

**Exome library preparation**

Briefly, ~3 µg of high quality genomic DNA were fragmented to a target size of 150 to 200 bp on the Covaris E210 system (Covaris; Woburn, MA). Fragmentation was verified on a 2% TAE gel and fragmented samples were end repaired using New England Biolab's NEBNext kit (New England Biolab; Ipswich, MA). Repaired samples were purified using Ampure XP beads, adenylated at the 3' end using the NEBNext kit, and purified again with Ampure XP beads. Illumina index adapters were next ligated onto A-tailed products and purified with Ampure XP beads. Samples were

next PCR amplified using Herculase II polymerase (Agilent). Samples were then run on the Agilent Bioanalyzer to verify amplification and to quantify samples. Samples were adjusted to 147 ng/μL for a 16 hour hybridization to exonic probes using Agilent's SureSelect All Exon 50Mb Plus kit. Captured products were then selected for, purified, and PCR amplified. Final libraries were verified and quantified using the Agilent Bioanalyzer.

**PCR free whole genome library preparation**

3 μg of genomic DNA from each sample was fragmented to a target size of 300–350 base pairs (bp). Overhangs in the fragmented samples were repaired and adenine bases were ligated. Diluted paired-end Illumina adapters were then ligated onto the A-tailed products. Following ligation, samples were run on a 3% TAE gel to separate products. Ligation products at 300 bp and 350 bp were selected for each sample, isolated from gel punches, and purified. Products were quantified using Agilent's High Sensitivity DNA chip on the Agilent 2100 Bioanalyzer.

**Paired-end next generation sequencing**

Tumor and normal libraries were prepared for 100 bp paired-end sequencing. Clusters were generated using Illumina's cBot and HiSeq Paired End Cluster Generation Kits and sequenced on Illumina's HiSeq 2000 using Illumina's HiSeq Sequencing Kit.

**Mapping and variant analysis**

For whole genome and exome sequencing fastq files were aligned with BWA 0.7.5a to hs37d5 and the SAM output were converted to a sorted BAM file using samtools 0.1.19. BAM files went through indel realignment, mark duplicates, and

recalibration steps in this order with GATK 2.8-1 where dpsnp137 was used for known SNPs and Mills_and_1000G_gold_standard.indels.b37.vcf was used for known indels. Lane level sample BAMs were then merged with Picard 1.91 if they were sequenced across multiple lanes. Variant calling was done with Unified Genotyper and the output VCF files were recalibrated with VariantRecalibrator from GATK 2.8-1. SnpEff 3.2 and SnpSift 1.9c was then used to annotate these VCF files with database version GRCh37.70. Only variants with a minimum quality score of 20 were extracted. Thereafter, we excluded somatic coding variants (SNVs) that either appeared in the 1000 Genomes database, the dbSNP database, or the NHLBI Exome Sequencing Project database, assuming that these SNVs might be of less importance for tumorigenesis. All *SMARCA4* mutations were validated by Sanger sequencing.

**PCR amplification and Sanger sequencing analysis.**

PCR amplification of *SMARCA4* was performed using previously published primers (Witkowski et al. 2014) targeting 34 coding exons (the alternative exon 29 was not sequenced). All amplification reactions were performed using Platinum Taq DNA Polymerase #10966-034 (Life Technologies; Carlsbad, CA). Each primer pair was mixed with 10 ng of genomic DNA and subjected to the following cycling parameters: 94°C for 2 min., 3 cycles at each temperature: 30 sec. at 94°C, 30 sec. at 60-57°C, 45 sec. at 72°C; 25 cycles: 30 sec. at 94°C, 30 sec. at 62°C, 45 sec. at 72°C; final extension of 5 min. at 72°C. PCR amplicons were sequenced using M13 forward and reverse primers at the Arizona State University's DNA Lab (Tempe, AZ). Sequencing data was analyzed with Mutation Surveyor (State College, PA).

**Immunohistochemistry**

A tissue microarray (TMA) representing nine SCCOHT patient cases was generated at TGen as described in Chapter 1. Whole slide sections from 6 additional SCCOHT tumor cases were used for an immunohistochemical validation cohort. Paraffin blocks were also prepared from formalin fixed A549 and BIN-67 cells. TMAs of ovarian epithelial, sex cord-stromal and germ cell tumors were constructed and stained at the Genetic Pathology Evaluation Centre in British Columbia. Each case included at least two representative core punches of 0.6 mm in diameter. Histologic sections of normal premenopausal ovaries and fallopian tubes were obtained from the Vancouver General Hospital Pathology archives. The unstained slides were processed using a Ventana Discovery Ultra system (Ventana Medical Systems; Tucson, AZ) using a rabbit monoclonal SMARCA4/BRG1 antibody (Clone EPNCIR111A, catalogue number ab110641, 1:25 dilution. Abcam; Cambridge, MA) and mouse monoclonal SMARCB1/INI1 antibody (clone 25/BAF47, catalogue number 612110, 1:50 dilution. BD Transduction Laboratories; San Jose, CA). The SMARCB1 antibody was used to confirm antigenic reactivity of tumor cells and cell lines that were negative for SMARCA4. Tumors were scored positive if any tumor cell nuclei showed moderate to strong (definite) positive nuclear staining. Tumors were scored negative when tumor cells showed no nuclear staining only if there was adequate nuclear staining of an internal positive control (endothelial cells, fibroblasts or lymphocytes). No cytoplasmic staining was seen for SMARCA4.

**Western Blot Analysis**

Whole cell extracts were prepared in RIPA buffer containing protease and phosphatase inhibitors. Lysates were electrophoresed on 8% SDS-PAGE gels, blotted to nitrocellulose, probed overnight with primary antibodies to SMARCA4 (see above)

and vinculin (Sigma-Aldrich; St. Louis, MO), then incubated for 1 hour with HRP-conjugated secondary antibodies (Sigma-Aldrich), and visualized using ECL-Plus (GE Life Sciences; Pittsburgh, PA). The lung cancer cell line A549, previously shown to lack SMARCA4 protein (Oike et al. 2013), was used as a negative control. All cell lines were confirmed negative for mycoplasma contamination.

**Loss of Heterozygosity Analysis (LOH)**

We used VCFtools v0.1.11 to extract only singlenucleotide variants with minimum depth of 15X and minimum mapping quality of 20 to create a ped file. SNPs with a call rate of 0.2 were plotted from the ped file in R version 3.0.2 using the pheatmap version 0.7.7 package.

**DNA methylation analysis**

Global DNA methylation was evaluated using the Infinium HumanMethylation450 BeadChip Array. Briefly, 1 μg of each sample DNA underwent bisulfite conversion using the EZ DNA methylation kit according to the manufacturer's recommendation for the Illumina Infinium Assay. Bisulfite-treated DNA was then hybridized to arrays according to the manufacturer's protocol. We used GenomeStudio V2011.1 (Illumina) for methylation data assembly and acquisition as well as background correction and normalization. Methylation levels for each CpG residue are presented as β values, estimating the ratio of the methylated signal intensity over the sum of the methylated and unmethylated intensities at each locus. The average β value reports a methylation signal ranging from 0 to 1 representing completely unmethylated to completely methylated values, respectively. All probes with detection p-values >0.01 were removed. Differential methylation was performed in GenomeStudio by comparing 8 SCCOHT samples to

two individual pools of normal fallopian tissue. Resultant β values were assigned a DiffScore to measure statistical significance. All p-values were corrected by calculating a false discovery rate. Probes with DiffScores ≥13 or ≤-13 and delta β values ≥0.2 or ≤-0.2 were considered statistically significant and differentially methylated.

## Results

### Next-generation Sequencing Analysis of SCCOHT

To analyze the genetic etiology of SCCOHT, we performed next-generation sequencing on a series of tumors and germline samples from 12 SCCOHT patients (9 tumors with 4 matched germlines and 3 additional germlines), and on the SCCOHT cell line BIN-67 (Gamwell et al. 2013) (Table 6). DNA from tumor and blood specimens were analyzed using whole-genome sequencing (2 matched tumor/normal pairs and the BIN-67 cell line) and exome sequencing (remaining samples). Stringent variant-calling methods were used to identify single-base substitutions and insertions/deletions (see Tables 7 and 8 for a summary of sequencing metrics). *SMARCA4*, a gene previously implicated in SCCOHT (Kupryjanczyk et al. 2013), was the only recurrently-mutated gene, bearing inactivating mutations in 6 of 9 tumors and in BIN-67 cells (Appendix G). Two tumors harbored 2 mutations each, suggesting biallelic inactivation. The majority of these mutations mapped to the ATPase domain and are expected to result in truncated proteins (Figure 8). Given that SCCOHT has been reported to occur in families (Martinez-Borges et al. 2009; McDonald et al. 2012; Young, Oliva, and Scully 1994) and also that germline mutations of SWI/SNF genes have been previously reported in highly malignant pediatric cancers (Eaton et al. 2011), we evaluated SCCOHT germline DNA for *SMARCA4* mutations. We discovered truncating mutations in 2 of the 7 patients

examined (APPENDIX E and Figure 8), diagnosed at ages 9 and 10. The 9-year-old patient bore the germline heterozygous nonsense mutation c.C2935T (p.R979*), which truncates SMARCA4 upstream of the helicase and bromo domains. Similarly, germline DNA of the 10-year-old patient contained a frameshift mutation in exon 4, c.722-735delGTCCCGGCCCGGCA (p.G241fs), removing all essential SMARCA4 functional domains. Since we did not have matching germline DNA for 5 of the sequenced tumors, 4 of which had *SMARCA4* mutations, we cannot exclude the possibility that some of the detected tumor mutations may also be present in the patients' germlines.

The total number of somatic non-silent mutations detected by paired exome or whole-genome sequencing analysis in SCCOHT tumors and matched normal DNAs ranged from 2 to 19 (see Appendix H) reflecting the mutation rate of other pediatric tumors and tumors of non-self-renewing tissues (Jelinic et al. 2014; Ramos et al. 2014; Vogelstein et al. 2013; Witkowski et al. 2014). No secondary mutations in cancer driver genes were noted.

Table 6.

SCCOHT Patient Samples Analyzed by Next-Generation Sequencing.

| Sample | Age at diagnosis (years) | FIGO Stage | Ethnicity | SCCOHT DNA source | Hypercalcemia |
|---|---|---|---|---|---|
| SCCO-002* | 26 | IA | European | Tumor recurrence/Blood | Yes |
| SCCO-008 | 9 | IA | European | Blood | Yes |
| SCCO-010 | 6 | IC | European | Blood | Yes |
| SCCO-017 | 10 | IIIC | European | Blood | Yes |
| SCCO-012 | 21 | IIIC | African American | Tumor recurrence | Yes |
| SCCO-014 | 33 | IIIA | African American | Primary tumor | Yes |
| SCCO-015 | 27 | IIIC | European | Primary tumor | N/A |
| DAH23 | 30 | IA | N/A | Primary tumor | Yes |
| DAH456* | 39 | IIIC | Hispanic | Primary tumor/Blood | N/A |
| DAH457 | 23 | IV | European | Primary tumor | N/A |
| DG1006* | 34 | N/A | N/A | Primary tumor/Blood | Yes |
| DG1219* | 37 | I | European | Tumor recurrence/Blood | Yes |

*Cases with sequenced Tumor/Normal pair.
N/A = Information not available.

Table 7.

Summary of Metrics of Whole-Genome and Exome Sequencing Analysis Performed on SCCOHT Tumors.

| | SCCOHT tumor Samples | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Whole-genome metrics** | **SCCO-002*** | **SCCO-012** | **SCCO-014** | **SCCO-015** | **DAH23** | **DAH456*** | **DAH457** | **DG1006*** | **DG1219*** | **BIN-67** |
| Total number of reads | - | - | - | - | - | - | - | 1512074555 | 1502778278 | 1504328893 |
| Total number of PF pair reads | - | - | - | - | - | - | - | 1449151450 | 1429246797 | 1448453288 |
| Total number of PF aligned pair reads | - | - | - | - | - | - | - | 1509925840 | 1499491346 | 1502605294 |
| Mean target coverage depth | - | - | - | - | - | - | - | 46.0 | 45.3 | 46.1 |
| **Exome metrics** | | | | | | | | | | |
| Total number of reads | 232025862 | 195375482 | 230238937 | 261197872 | 172202460 | 149547353 | 85303940 | - | - | - |
| Total number of PF pair reads | 230583799 | 194239332 | 229025887 | 259852392 | 164325868 | 142415523 | 82778121 | - | - | - |
| Total number of PF aligned pair reads | 231919894 | 195274958 | 230144200 | 261088816 | 172161320 | 149506468 | 85283208 | - | - | - |
| Mean target coverage depth | 121.5 | 105.1 | 122.6 | 140.6 | 37.6 | 19.0 | 30.1 | - | - | - |

*Paired tumor/normal sample. 'PF' stands for 'pass filter' and refers to the total number of reads that are of high quality (this value is separate form the Q30 score) as analyzed by Illumina HiSeq software.

Table 8.

Summary of Metrics of Whole-Genome and Exome Sequencing Analysis Performed on SCCOHT Germline Samples.

| | Normal DNA Samples from SCCOHT patients | | | | | | |
|---|---|---|---|---|---|---|---|
| **Whole-genome metrics** | **SCCO-002*** | **SCCO-008** | **SCCO-010** | **SCCO-017** | **DAH456*** | **DG1006*** | **DG1219*** |
| Total number of reads | - | - | - | - | - | 1518719316 | 1557386424 |
| Total number of PF pair reads | - | - | - | - | - | 1471379481 | 1481449223 |
| Total number of PF aligned pair reads | - | - | - | - | - | 1516504726 | 1555451266 |
| Mean target coverage depth | - | - | - | - | - | 46.8 | 46.9 |
| **Exome metrics** | | | | | | | |
| Total number of reads | 266077494 | 199438593 | 163447895 | 175232115 | 157107856 | - | - |
| Total number of PF pair reads | 264600968 | 198601744 | 162738215 | 174470126 | 149603213 | - | - |
| Total number of PF aligned pair reads | 265865946 | 199353890 | 163361760 | 175154980 | 157054184 | - | - |
| Mean target coverage depth | 121.3 | 90.6 | 74.7 | 81.1 | 29.6 | - | - |

*Paired tumor/normal sample. 'PF' stands for 'pass filter' and refers to the total number of reads that are of high quality (this value is separate form the Q30 score) as analyzed by Illumina HiSeq software.

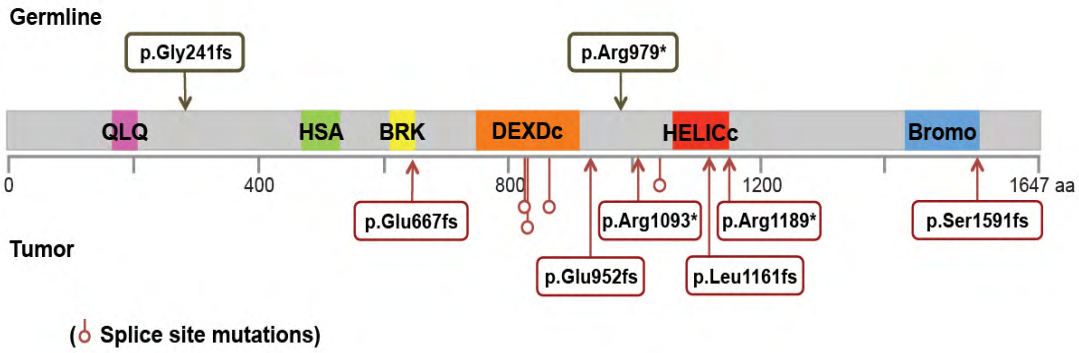


*Figure 8.* Inactivating germline and somatic *SMARCA4* mutations identified in small cell carcinoma of the ovary, hypercalcemic type. Schematic representation of the SMARCA4 protein, showing the location of mutations identified in SCCOHT germline and tumor DNA samples. Gln, Leu, Gln (QLQ) motif, helicase/SANT-associated (HSA) domain, Brahma and Kismet (BRK) domain, DEAD-like helicase superfamily (DEXDc) and helicase superfamily c-terminal (HELICc) domains and bromodomain (Bromo).

**SMARCA4 Targeted Sequencing Analysis of Additional SCCOHT cases**

To validate the *SMARCA4* mutations identified by next-generation sequencing and further examine the prevalence of *SMARCA4* mutations in SCCOHT, we performed targeted *SMARCA4* sequencing analysis of an additional 12 SCCOHT cases, 3 matched germline samples, and the cell line SCCOHT-1 (Otte et al. 2012) (Appendix E). All of these samples were previously described in Chapter 1 (Table 2). This analysis was performed by PCR amplification of all coding exons of the *SMARCA4* gene followed by Sanger sequencing. DNA samples were extracted from formalin-fixed paraffin-embedded (FFPE) blocks and from saliva samples of SCCOHT patients. In total, using both next-generation and targeted sequencing we found 19 of 24 sequenced tumors with *SMARCA4* mutations (Appendix E).

**Immunohistochemical Analysis of SCCOHT Tumors**

To evaluate possible functional effects of mutations on the *SMARCA4* gene product, we assessed SMARCA4 protein expression in 19 SCCOHT tumors. IHC analysis revealed that 16 of 19 (84%) cases lacked SMARCA4 protein (Appendix E and Figure 9).

We found only 3 tumors that were positive for SMARCA4 protein, all of which had no SMARCA4 somatic mutations. Interestingly, IHC analysis for the SWI/SNF family member SMARCB1 revealed that two of these cases were negative, suggesting that inactivation of SMARCB1 can also promote the development of SCCOHT. The third case, DAH456, retained both SMARCA4 and SMARCB1 protein expression. On the other hand, of the 5 tumors with no identified mutation in *SMARCA4*, two lacked SMARCA4 protein by IHC, indicating either an unidentified mutation or epigenetic inactivation.

Overall, all tumors in our study with *SMARCA4* mutations contained no SMARCA4 protein by IHC. Further, SMARCA4 loss is specific to tumor cells, as normal cells within the same sections show robust SMARCA4 staining (Figure 9). The SMARCA4 antibody recognizes an epitope containing amino acids 240 to 277. Excepting the p.G241fs mutation in the germline of SCCO-002, all mutants are predicted to yield proteins detectable by this antibody. Thus, the complete loss of SMARCA4 protein may be consistent with nonsense-mediated decay of the mutant transcript.

Although loss of SMARCA4 protein in *SMARCA4* wild-type tumors and in tumors without multiple *SMARCA4* mutations suggests that other mechanisms lead to SMARCA4 loss, neither DNA methylation nor LOH contribute to inactivation in these cases (Figures 10 and 11).

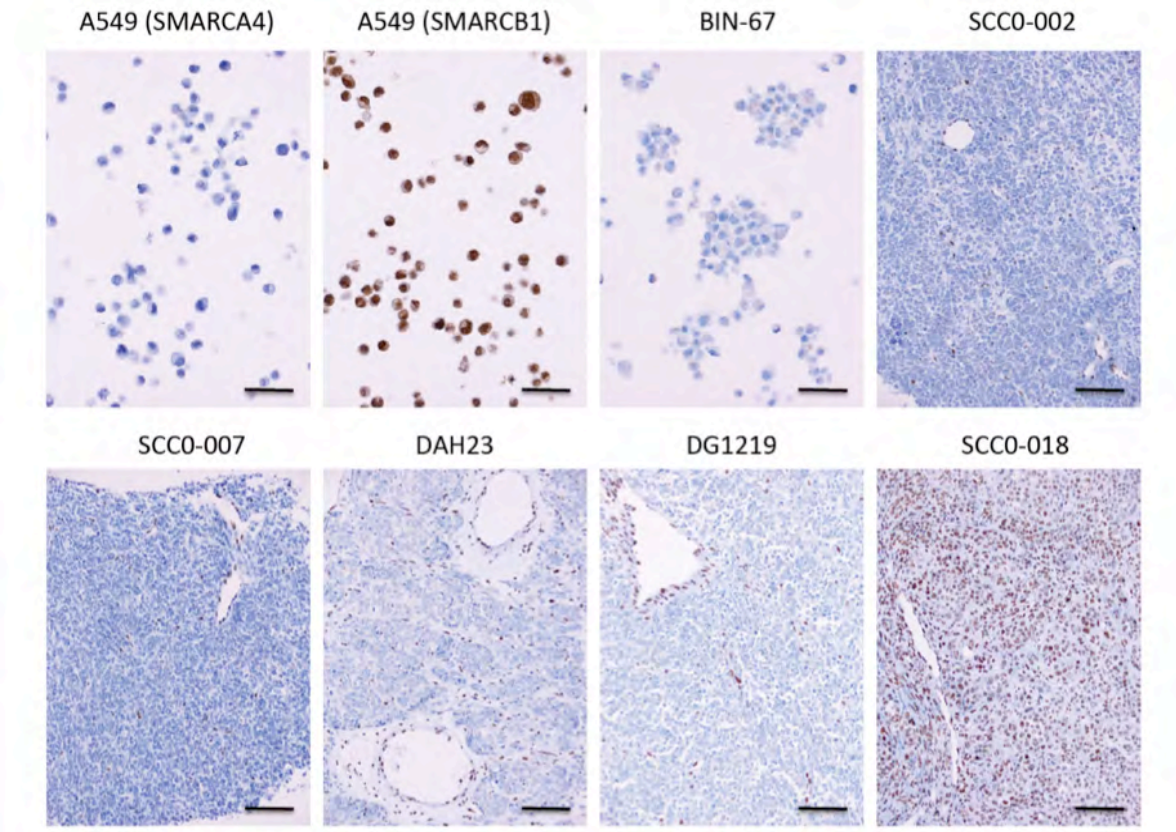


*Figure 9.* SMARCA4 immunohistochemistry (IHC) analysis. Representative images of SMARCA4 negative SCCOHT tumors. Only 2 tumor cases showed positive nuclear staining for SMARCA4 (SCCO-018 shown). 200x magnification. Scale bars 100 μm. IHC of A549 cells for SMARCA4 and SMARCB1 was used as a negative and antibody specificity control. 400x magnification. Scale bars 50 μm.

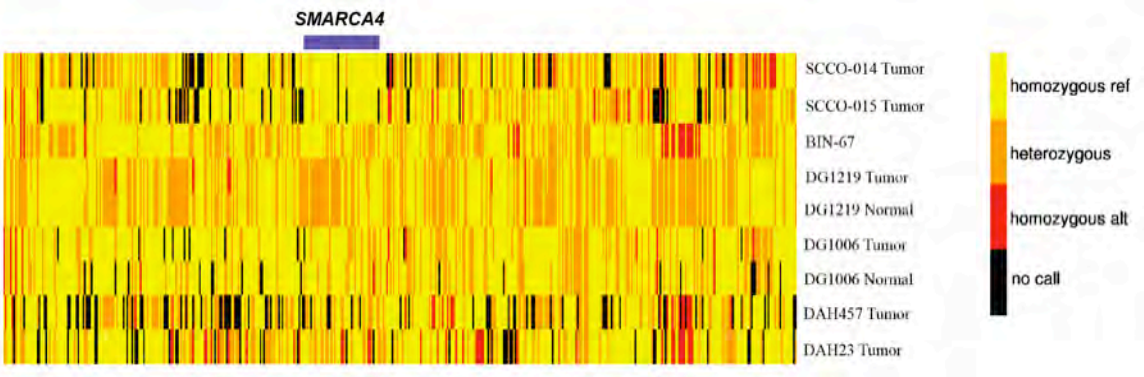


*Figure 10.* Loss of heterozygosity (LOH) analysis in SCCOHT tumors with *SMARCA4* mutations. LOH analysis was performed using a bcbio-nextgen 0.7.7a-e91123c to map reads with bwa 0.7.5a to GRCh37 and freebayes v0.9.10-11 for joint variant calling restricted to chr19:10667750-11554548. Heatmap shows SNPs with a call rate of 0.2. No evidence of LOH was observed.

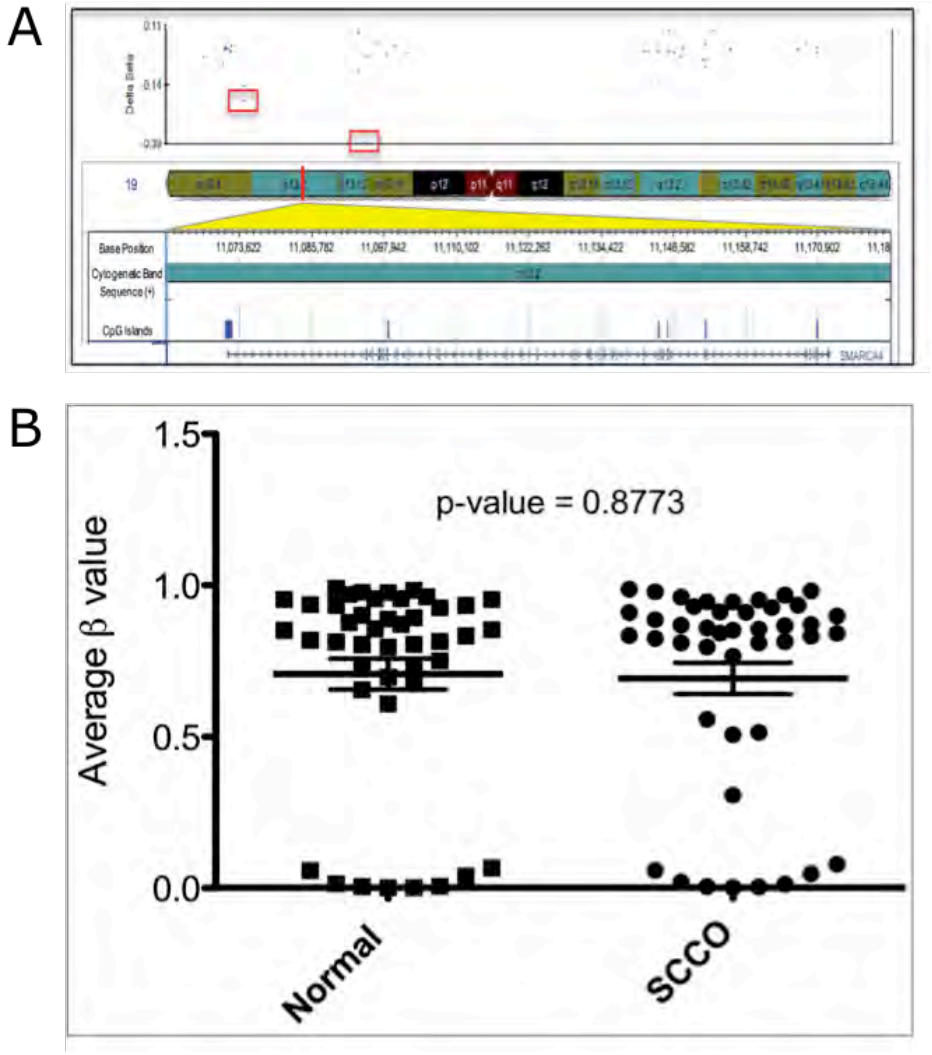


*Figure 11.* Methylation analysis. **A.** Genome view of SMARCA4 450K methylation data. The top panel is a scatter plot displaying delta beta values of all 44 SMARCA4 CpG probes in 8 SCCOHT samples. Only two probes demonstrate differential hypomethylation (indicated by a red box). The upper limit of the y axis does not exceed 0.11, indicative of a lack of differential hypermethylation for any probe. **B.** SMARCA4 methylation status in SCCOHT tumors and normal fallopian tube tissues. Vertical scatter plot of the average β values of 44 SMARCA4 450K CpG methylation probes in 8 SCCOHT and 2 pools of normal fallopian tissue. There is no significant SMARCA4 methylation difference between normal tissue and SCCOHT.

**Immunohistochemical Analysis of SMARCA4 in Primary Ovarian Tumors and Cell Lines of Different Histologic Subtypes**

To determine the specificity of SMARCA4 loss for SCCOHT, we performed IHC for SMARCA4 on 485 primary ovarian epithelial, sex cord-stromal and germ cell tumors (Table 9) as well as normal premenopausal ovary and fallopian tube (Figure 12). Only two tumors (0.4%)—both clear cell carcinomas—were negative for SMARCA4. Notably, tumors most closely resembling SCCOHT histologically, including all granulosa cell tumors of juvenile (n=8) and adult (n=36) types, maintained SMARCA4 expression. In addition, representative cell lines from 4 ovarian carcinoma subtypes as well as immortalized granulosa cells (SVOG) and adult granulosa tumor cells (KGN) all maintained SMARCA4 expression by Western blot (Figure 13). In contrast, the SCCOHT cell lines BIN-67 and SCCOHT-1, both of which harbor mutations in *SMARCA4*, showed complete absence of SMARCA4 protein (Figure 13). These results demonstrate that SMARCA4 loss is highly specific for SCCOHT.

Table 9.

SMARCA4 Immunohistochemical Analysis in Primary Ovarian and Adnexal Epithelial, Sex Cord-Stromal and Germ Cell Tumors.

| **EPITHELIAL TUMORS** | **n** | **SMARCA4 negative** | **Percent** |
|---|---|---|---|
| High grade serous carcinoma | 204 | 0 | 0 |
| Clear cell carcinoma | 93 | 2 | 2.2 |
| Endometrioid adenocarcinoma | 28 | 0 | 0 |
| Mixed endometrioid adenocarcinoma | 6 | 0 | 0 |
| Endometrioid borderline tumor | 2 | 0 | 0 |
| Low grade serous carcinoma | 9 | 0 | 0 |
| Serous borderline tumor | 17 | 0 | 0 |
| Mucinous tumors (borderline and carcinoma) | 14 | 0 | 0 |
| Undifferentiated carcinoma | 7 | 0 | 0 |
| Benign Brenner tumor | 3 | 0 | 0 |
| Borderline Brenner tumor | 1 | 0 | 0 |
| **SUBTOTAL** | **384** | **2** | **0.5** |

| **SEX CORD-STROMAL TUMORS** | **n** | **SMARCA4 negative** | **Percent** |
|---|---|---|---|
| Adult granulosa cell tumor | 36 | 0 | 0 |
| Juvenile granulosa cell tumor | 8 | 0 | 0 |
| Fibroma/fibrosarcoma | 9 | 0 | 0 |
| Thecoma | 1 | 0 | 0 |
| Sertoli-Leydig cell tumor | 20 | 0 | 0 |
| Leydig cell tumor | 4 | 0 | 0 |
| Sex cord tumor with annular tubules | 2 | 0 | 0 |
| Steroid cell tumor | 1 | 0 | 0 |
| Stromal luteoma | 1 | 0 | 0 |
| Sclerosing stromal tumor | 6 | 0 | 0 |
| Gynandroblastoma | 1 | 0 | 0 |
| Sex cord tumor, not otherwise specified | 4 | 0 | 0 |
| Female adnexal tumor of Wolffian origin | 2 | 0 | 0 |
| **SUBTOTAL** | **95** | **0** | **0** |

| **GERM CELL TUMORS** | **n** | **SMARCA4 negative** | **Percent** |
|---|---|---|---|
| Dysgerminoma | 3 | 0 | 0 |
| Yolk sac tumor | 3 | 0 | 0 |
| **SUBTOTAL** | **6** | **0** | **0** |

| | | | |
|---|---|---|---|
| **TOTAL** | **485** | **2** | **0.5** |

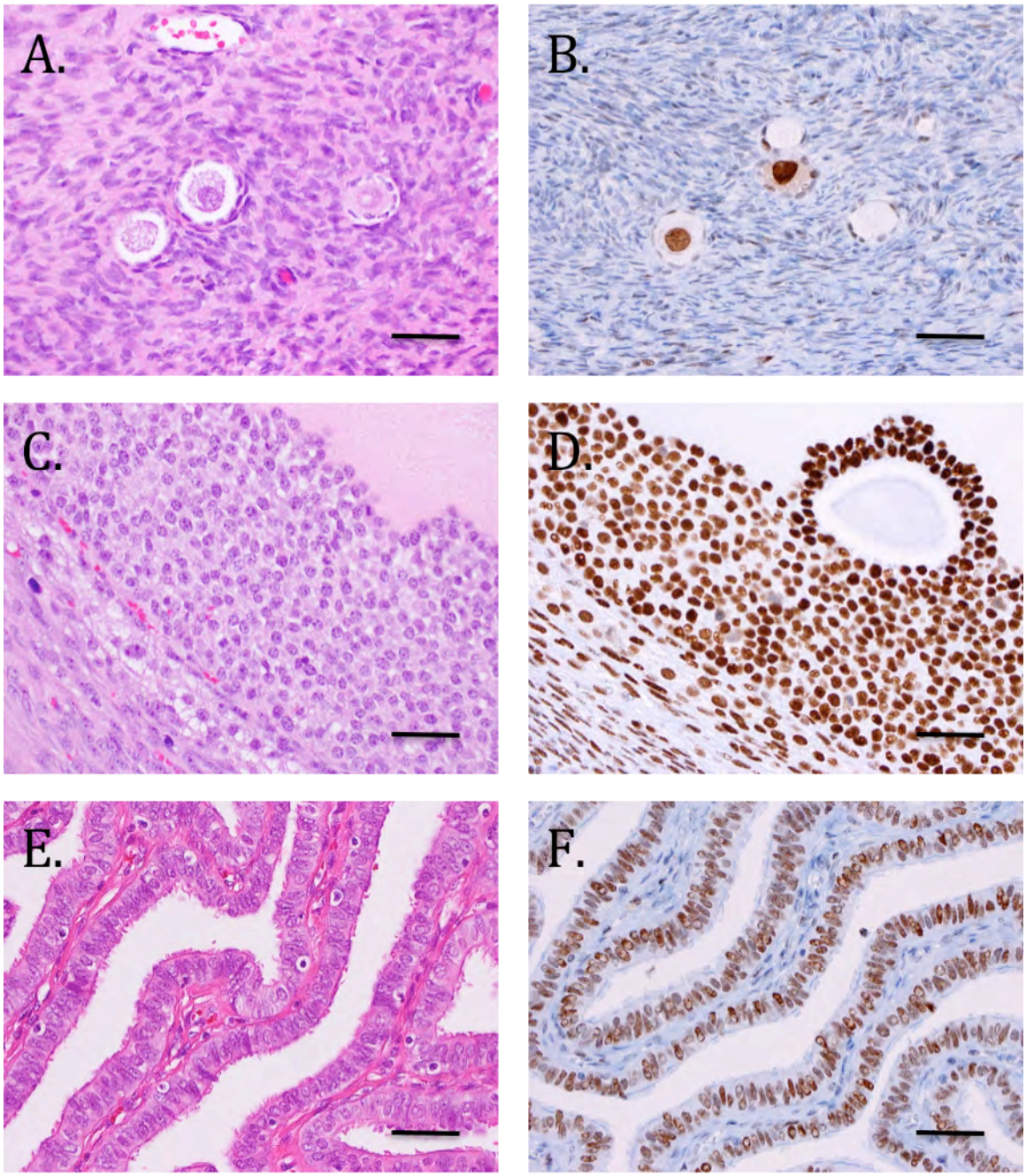


*Figure 12.* SMARCA4 immunohistochemistry in normal pre-menopausal ovary and fallopian tube. H&E stained sections (**A, C, E**) and SMARCA4 immunohistochemistry (**B, D, F**) demonstrating strong, uniform positive nuclear staining in oocytes (**B**), granulosa cells of primordial (**B**) and secondary follicles (**D**), theca cells (**D**), and in secretory and ciliated cells throughout the fallopian tube ampulla (**F**) and fimbria (not shown). In contrast, the ovarian stroma stains weakly (**B**) or is negative (not shown). 400x magnification. Scale bars 50 μm.

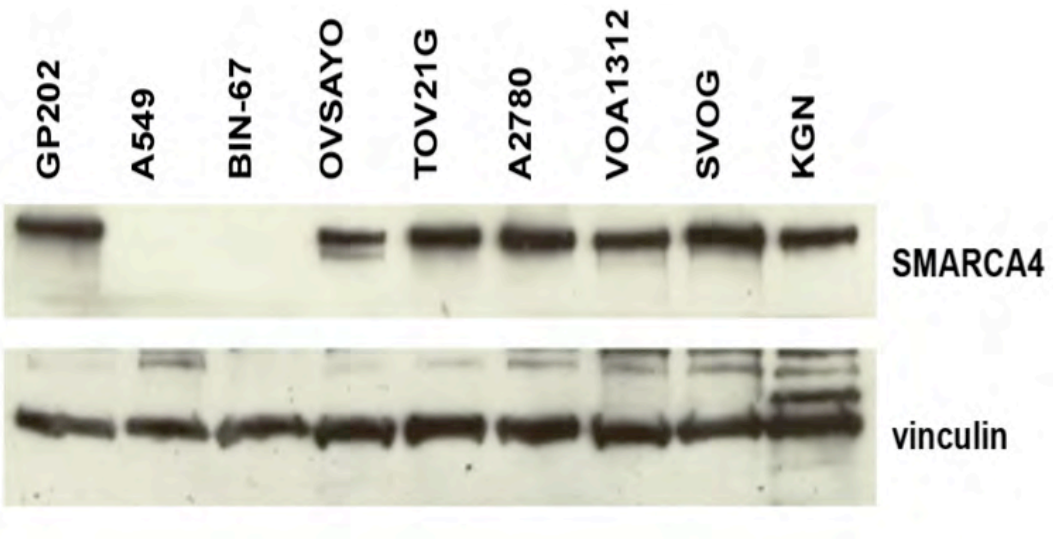


*Figure 13.* SMARCA4 protein expression in representative cell lines from 5 major ovarian carcinoma subtypes (small cell, BIN-67; high-grade serous, OVSAYO; clear cell, TOV21G; endometrioid, A2780; low-grade serous, VOA1312), immortalized granulosa cells (SVOG), and an adult granulosa cell tumor cell line (KGN). Lung (A549) and gastric (GP202) carcinoma cell lines were included as negative and positive SMARCA4 expression controls. The SCCOHT cell line SCCOHT-1 also did not show any SMARCA4 protein by Western (data not shown).

**Discussion**

We have framed the biological understanding of SCCOHT by revealing that nearly all tumors harbor inactivating, often bi-allelic, mutations in the chromatin-remodeling tumor suppressor gene *SMARCA4* (Ramos et al. 2014). Our analysis identified 19 of 24 (79%) sequenced tumors with *SMARCA4* mutations and 16 of 19 (84%) stained tumors with loss of SMARCA4 protein. Together with sequencing analyses from independent laboratories, we have now confirmed the presence of *SMARCA4* mutations and concomitant protein loss in ~90% of nearly 70 evaluated SCCOHT cases (Jelinic et al. 2014; Kupryjanczyk et al. 2013; Witkowski et al. 2014).

Across all published studies to date and including the data reported here, 64 of 69 SCCOHT cases (including 2 cell lines) have been shown to bear *SMARCA4* mutations (Figure 14 and Appendix I) (Jelinic et al. 2014; Kupryjanczyk et al. 2013; Ramos et al. 2014; Witkowski et al. 2014). With the exception of 3 missense mutations all other *SMARCA4* mutations identified in SCCOHT are truncating, frameshift, deletion, or splice-site mutations. The 3 missense mutations, 2 of which are identical (p.Gly1080Asp) and occur in the germlines of two related family members, are predicted to be damaging by Polyphen-2 (Adzhubei et al. 2010; Witkowski et al. 2014). Bi-allelic inactivation of SMARCA4 in SCCOHT is common either through the presence of two mutations or loss of heterozygosity (LOH) at the *SMARCA4* locus (Jelinic et al. 2014; Witkowski et al. 2014). In keeping with these findings, immunohistochemistry has revealed loss of SMARCA4 protein in 54 of 61 SCCOHT tumors and cell lines (Jelinic et al. 2014; Kupryjanczyk et al. 2013; Ramos et al. 2014; Witkowski et al. 2014). Loss of SMARCA4 protein expression is associated with *SMARCA4* mutation in all but 2 of the cases for which *SMARCA4* has been sequenced (Jelinic et al. 2014; Kupryjanczyk et al. 2013; Ramos et al. 2014; Witkowski et al. 2014). Conversely, all but 4 *SMARCA4*-mutant SCCOHTs for which

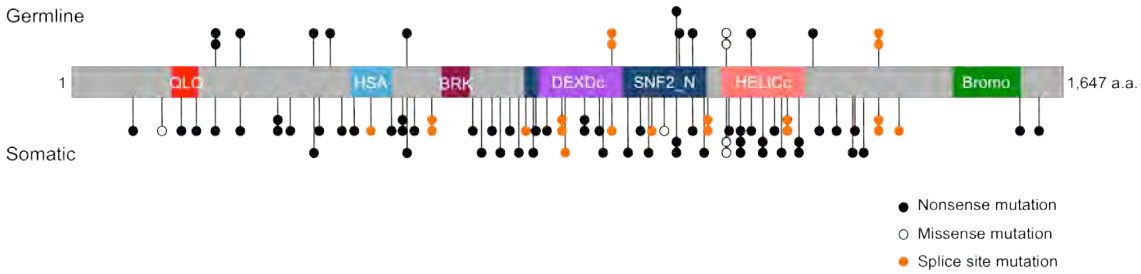


*Figure 14.* Schematic of the location of SMARCA4 mutations identified in germline and tumor DNA from SCCOHT patients, and in two SCCOHT cell lines (Case 103 from Jelinic et al. with exon deletion is not shown) (Jelinic et al. 2014; Kupryjanczyk et al. 2013; Ramos et al. 2014; Witkowski et al. 2014).

IHC has also been performed lack expression of SMARCA4 protein (Jelinic et al. 2014; Kupryjanczyk et al. 2013; Ramos et al. 2014; Witkowski et al. 2014). These 4 *SMARCA4*-mutant, positive-staining tumors harbored either splice site or missense mutations or, in one case, an in-frame homozygous deletion of exons 25 and 26 that resulted in expression of an inactive protein product (Jelinic et al. 2014; Witkowski et al. 2014). In our cohort, we also found 3 tumors that had no *SMARCA4* mutations and showed retention of protein expression by IHC. Interestingly, two of these cases lacked the protein SMARCB1, a SWI/SNF-associated tumor suppressor gene mutated in rhabdoid tumors, supporting the hypothesis that SCCOHT may share an etiological link with rhabdoid tumors and that SMARCB1 inactivation can also promote the development of SCCOHT (Foulkes et al. 2014; Ramos et al. 2014). The third case retained both SMARCA4 and SMARCB1 protein expression and may bear either an alternative driver mutation or may simply be a misdiagnosis (Ramos et al. 2014). SMARCA4 is clearly a tumor suppressor inactivated by "two hits" in the majority of SCCOHTs, but several of the above exceptional cases provide clues to a more complex disease etiology.

Further supporting the prominence of SMARCA4's tumor suppressor role in SCCOHT, germline mutations have been identified in 17 SCCOHT cases, predominantly in younger patients (Jelinic et al. 2014; Ramos et al. 2014; Witkowski et al. 2014). Such mutations have been found to segregate in 4 families in which all affected members whose tumors could be tested developed either a second inactivating mutation or LOH in the remaining wild-type allele (Witkowski et al. 2014). Alongside previous clinical descriptions of SCCOHT families, these mutations elucidate a heritable component to the disease and suggest that the broad age distribution of SCCOHT could reflect inherited versus acquired *SMARCA4* mutations (Distelmaier et al. 2006; Longy et al. 1996; Martinez-Borges et al. 2009; McDonald

et al. 2012; Peccatori et al. 1993; Ulbright et al. 1987). *SMARCA4* mutation also occurs in the absence of recurrent secondary genomic alterations and amidst relative karyotypic stability and therefore appears to be the primary driving event in SCCOHT tumorigenesis. *SMARCA4* mutations appear to be the primary driving event in SCCOHT tumorigenesis. They occur in the absence of recurrent secondary genomic alterations and amidst relative karyotypic stability. The total number of somatic non-silent mutations detected by paired exome or whole-genome sequencing analysis in SCCOHT tumors and matched normal DNAs ranges from 2 to 19. Among these whole genome or exome-sequenced paired cases, few secondary mutations in cancer driver genes were discovered and each driver gene mutation (those in JAK3, ASXL1, NOTCH2, and WT1) occurred in only a single case (Jelinic et al. 2014; Ramos et al. 2014; Witkowski et al. 2014). Overall, the low SCCOHT mutation rate, the nearly universal presence of inactivating *SMARCA4* mutations in SCCOHT, the presence of these mutations in patient germlines and families, and the lack of recurrent secondary alterations in these tumors all strongly suggest that loss of SMARCA4 is necessary and sufficient for SCCOHT initiation.

Given SCCOHT's complex histological appearance and the absence of known precursor lesions, the cellular origin of SCCOHT and its relationship to other tumor types remains unclear. SCCOHTs are characterized by poorly differentiated small tumor cells with scant cytoplasm and hyperchromatic nuclei, and the presence of follicle-like structures contained within sheets of cells (Robert H. Young 1994). Despite SCCOHT's name, about half of tumors have populations of large cells with rhabdoid features (Robert H. Young 1994). Indeed, there are many similarities between SCCOHT and atypical teratoid/rhabdoid tumors of the brain (AT/RTs) and MRTs of the kidney (MRTK). All three tumor types are linked to mutations in the SWI/SNF genes *SMARCB1* (AT/RT and MRT) or *SMARCA4* (SCCOHT and AT/RT), all

have diploid genomes and they occur in young or pediatric patients (McKenna et al. 2008; Robert H. Young 1994). Shared morphology and mutational spectra make a compelling case that SCCOHT may be a type of malignant rhabdoid tumor (MRT). The strikingly similar morphology and genetics of rhabdoid tumors in 3 very different organs suggests either a common cell of origin or convergent morphologic evolution upon SMARCA4 loss (or both) although no MRT cell of origin has yet been identified (Foulkes et al. 2014; Kupryjanczyk et al. 2013; Ulbright et al. 1987). On the other hand, there is some histological evidence for a germ cell etiology for SCCOHT. In particular, a recent report identified immature teratoma in two SCCOHTs, one of which also contained foci of yolk-sac tumor (Kupryjanczyk et al. 2013). This finding agrees with Ulbright et al. who, in one of the earliest publications on SCCOHT (1987) (Ulbright et al. 1987), also suggested SCCOHTs might be related to yolk-sac tumors, based on presence of shared histopathological and ultrastructural features. Engineered *SMARCA4* knockouts in putative precursor cells *in vitro* and *in vivo* are needed to shed light on SCCOHT histogenesis.

Among ovarian tumors, the loss of SMARCA4 protein appears to be highly specific for SCCOHT. Our assessment of 485 primary ovarian epithelial, sex cord-stromal, and germ cell tumors showed only 2 tumors (0.4%), both clear cell carcinomas, with negative SMARCA4 staining (Ramos et al. 2014). Other ovarian tumors in the differential diagnosis of SCCOHT – undifferentiated carcinomas, adult and juvenile granulosa cell tumor, and germ cell tumors – all expressed SMARCA4 or were wild type for *SMARCA4* (Ramos et al. 2014; Witkowski et al. 2013). The expression status of SMARCA4 remains to be determined in several other primary and metastatic ovarian tumors in the differential diagnosis of SCCOHT including endometrioid stromal sarcoma, desmoplastic small round cell tumor, primitive neuroectodermal tumor, neuroblastoma and others. However to date, the absence of

SMARCA4 protein is highly sensitive and specific for SCCOHT and can be used to distinguish it from other ovarian tumors with similar histology to facilitate diagnosis. Nonetheless, future studies are necessary to fully understand SCCOHT's histogenesis.

Our recent discovery of inactivating mutations in *SMARCA4* alongside SMARCA4 protein loss in the majority of SCCOHTs sets the stage for dramatic progress in the biological understanding and clinical management of this disease. SMARCA4 is one of two mutually-exclusive ATPase subunits of the chromatin-remodeling SWI/SNF complex (the other one being SMARCA2), a regulator of cell cycle arrest, DNA repair, apoptosis and differentiation. While several subunits of this complex are tumor suppressors in 20% of human cancers, their role in tumorigenesis remains unclear. SMARCA4 is one of the most commonly mutated subunits of the SWI/SNF complex across cancer types, occurring at a frequency of about 4% and arising regularly in cancers such as non-small-cell lung cancer, Burkitt's lymphoma, and medulloblastoma while also occurring occasionally in melanoma, pancreatic adenocarcinoma and ovarian clear cell carcinoma (Shain and Pollack 2013). Elucidation of the impact of such mutations on SWI/SNF composition and the downstream effect on expression programs will be vital for our broader biological understanding of cancers driven by inactivating *SMARCA4* mutations and dysregulation of the SWI/SNF complex.

The breakthrough identification of inactivating *SMARCA4* mutations as the in almost all cases of SCCOHT is the first significant insight into the molecular pathogenesis of the disease. The loss of SMARCA4 protein is a highly sensitive and specific marker of the disease, highlighting its potential role as a diagnostic marker. Studies are currently in progress to elucidate the cell of origin and identify therapeutic vulnerabilities and to further understand the pathogenesis of SCCOHT.

CHAPTER 3

# THERAPEUTIC IMPLICATIONS OF SMARCA4 LOSS IN SCCOHT

## Introduction

Our finding that the majority of SCCOHTs are driven by *SMARCA4* mutations amidst simple genomic backgrounds provides an opportunity to empirically develop effective treatment strategies with a high probability of impact for many of these patients. Supported by knowledge acquired from immunohistochemical, aCGH and RNA expression analysis of SCCOHT tumors (Chapter 1), we will seek to develop rational treatment approaches for SCCOHT.

Typically, SCCOHT patients undergo surgery followed by aggressive multi-agent chemotherapy regimens most commonly administered in the setting of epithelial ovarian or small cell lung carcinoma(Estel et al. 2011; Pressey 2011). Combinations including cisplatin or carboplatin, etoposide and vinca alkaloids may be associated with improved survival, yet relapse occurs in 65% of cases within 2 years (Clement 2005; Estel et al. 2011; Young, Oliva, and Scully 1994). The rarity of SCCOHT and the lack of logical treatment options have limited clinical study.

Given that this disease is driven in virtually all cases by the loss of a tumor suppressor, the path to an effective small molecule will likely be dependent on identification of a synthetic lethal target. To this end, a synthetic lethal dependence of SMARCA4-deficient cancers cells on SMARCA2 has recently been described in non-small cell lung cancer, ovarian and liver cancer cell lines(Oike et al. 2013; Wilson et al. 2014). This dependence is likely due to SMARCA2's status as the only other known ATPase subunit of the SWI/SNF complex. However, our preliminary IHC staining of 3 SCCOHT cases showed lack of SMARCA2 protein in all 3 cases (data not shown), suggesting that SCCOHT may lack the expression of both SMARCA2 and SMARCA4. Although further analysis of SMARCA2 expression status in SCCOHT is

needed, it suggests that investigation of other synthetic lethal partners is warranted. For example, although it has been shown in other tumor types such as non-small cell lung cancer cell lines that the SWI/SNF core complex still forms in the absence of both SMARCA4 and SMARCA2(Hoffman et al. 2014), it remains to be determined whether this complex retains chromatin remodeling activity and whether targeting the residual SWI/SNF complex can selectively kill SCCOHT cells. Further, future studies to investigate the mechanism underlying SMARCA4 loss-driven tumorigenesis in SCCOHTs will help identify treatment options. Such efforts will require *in vitro* models of SCCOHT such as the cell lines BIN-67 and SCCOHT-1, and the establishment of *in vivo* models of SCCOHT to facilitate drug efficacy studies.

Described here, is the creation of two patient-derived xenograft models of SCCOHT and preliminary high-throughput (HT) compound and siRNA screenings to undertake empirical development of treatment strategies for SCCOHT. These efforts will be focused both on rapid identification of current clinically-approved agents in addition to novel compounds and synthetic lethal targets. We hope that these studies will make a meaningful impact in the clinical course of this disease.

## Materials and Methods

### Tissue Culture

The BIN-67 cell line was maintained in DMEM enriched with 20% Ham's F12 medium (Life Sciences), and supplemented with 20% fetal bovine serum and antibiotics, as previously described (Upchurch et al. 1986).

### siRNA Transfection Optimization and Assay Development

The optimal seeding density for BIN-67 cells was determined to be 750 cells per well. Transfection efficiency was determined using a universally lethal positive-

control siRNA directed against ubiquitin B (UBBs1) and negative control siRNAs, including a nonsilencing scrambled siRNA or a siRNA directed against green fluorescent protein (GFP) (Qiagen). The best transfection conditions were those that produced the least reduction in cell viability with negative controls and greatest reduction with lethal UBBs1 siRNA, 96 hours post transfection. For BIN-67 cells, RNAiMAX 1:3 ratio (0.067 µL/well) gave the best results, reaching a transfection efficiency of 95-98%.

**High-throughput (HT) siRNA Screening**

siRNAs (4 siRNA oligos per gene) (Qiagen) alongside negative and positive control siRNAs were preprinted on flat-bottom, white solid-bottom 384-well plates (Corning; NY, USA) at 1 µL volume for a final assay concentration of 13 nM. A total of 25 µL of diluted RNAi Max transfection reagent solution was added to each well. Plates were then incubated for 30 minutes at room temperature to allow the formation of transfection reagent-nucleic acid complexes. BIN-67 cells were trypsinized, quantified and resuspended in 10% DMEM/F12 assay medium (no antibiotic) and dispensed into the plates (25 µL per well) containing the siRNA (750 cells per well). Cells were then incubated at 37°C for 4 days (96 hours). Cell viability was determined using CellTiter-Glo luminescence assay (Promega; Madison, WI) and an Analyst GT Multimode Microplate Reader (Molecular Devices; Sunnyvale, CA).

**Compound/Drug Library Screen**

Two libraries of pharmacological compounds were used for this screening and further described in the Results section. BIN67 cells were plated at 750 cells/well in assay plates. After the addition of the compounds at a final concentration of 5 µM and 10 µM [final 0.05% and 0.1% DMSO (v/v)], plates were incubated for 72 hours

at 37°C. A control plate was also dosed as a 12pt 1:2 serial dilution from 100 μM. Cell viability was then measured using CellTiter-Glo. We completed 2 runs of these libraries in BIN-67 run in duplicate. Counter-screens were performed against the liver cancer cell line HepG2.

## Results

### Identification of Molecular Targets from Gene Expression Microarray Data

Gene expression microarray data of SCCOHT tumors compared to normal ovary and to epithelial ovarian carcinomas was interrogated for expression of known clinically actionable targets. Genes significantly altered in at least 3 of the 4 tumors with a potential clinical association are presented in Table 10.

With respect to cytotoxic agents, elevated *TOP2A* is consistent with reported responses to topoisomerase II inhibitors, although elevated *TOP1* also suggests sensitivity to camptothecin derivatives. We conducted a further evaluation of TOP2A protein expression in 12 tumors and found that, on average, 21.6% of SCCOHT tumor cells showed strong nuclear staining (3+) (Figure 15). This finding is consistent with the high proliferative index for SCCOHT.

The typical resistance of SCCOHT to platinum agents could potentially be explained by a strong upregulation of a cascade of DNA damage repair (DDR) genes, and members of the Fanconi anemia gene family such as *FANCA*, *FANCD2* and *BRCA1/2* (Wiedemeyer, Beach, and Karlan 2014). We also observed dysregulation of genes associated with resistance to taxanes, including highly elevated levels of *TUBB3*, a biomarker of very poor prognosis in ovarian cancer (Gao et al. 2012).

With respect to targeted agents, our data strongly suggests a lack of potential benefit from antihormonal therapies. While the majority of well-known receptor tyrosine kinase genes are not expressed or not elevated in SCCOHT, a few were

identified as consistently overexpressed including *FLT3*, *ERBB3*, *ERBB4*, *AURKA* and *AURKB.*

**High-throughput (HT) siRNA Screening**

As a first step towards assessing druggable and synthetic lethal targets in SCCOHT, we designed a customized HT-siRNA screen. This screen consisted of a library of siRNA targeting the human kinome and a custom siRNA library targeting 80 genes including putative drug targets, SWI/SNF genes, ATPases of the DEAD/H helicase family (in addition to *SMARCA4* and *SMARCA2*), and other candidate synthetic lethal targets derived from the literature or gene expression data of SCCOHT tumors compared to normal ovary (Figure 16).

We performed the screen using optimized conditions in BIN-67 with a surrogate measure of cell viability as the end point measured by CellTiter-Glo reagent. The screen was deemed high quality with a covariance <7.3%, transfection efficiency of >99% and Z'-factor >0.77. A multivariate hit selection methodology was employed. Hits were identified with at least 2 siRNAs per target, 40% or less viability remaining after siRNA knockdown, and Redundant siRNA Activity (RSA) (Konig et al. 2007) score of ≥ 0.2.

Seventy-three gene targets were selected (see APPENDIX G) from the kinome library, including the clinical drug targets *FGFR1* and *FGFR3*, 3 glycolytic enzymes, 3 enzymes involved in cytidine generation, the Src family kinase *FYN* as well as *FAK*, and 3 kinases in the JNK pathway.

Hits identified in the custom list of siRNAs are shown in Table 11. Knockdown of six members of the SWI/SNF complex showed an effect on BIN67 cell viability, including the SMARCA4, mutually exclusive ATPase, SMARCA2; suggesting that SMARCA2 is expressed in BIN-67. Four DEAD/H helicase ATPases were identified as

Table 10.

Therapeutic Vulnerabilities in SCCOHT Derived from Gene Expression Profiling of 4 SCCOHT Tumors (Chapter 1).

| Drug Type | Target | Fold change vs. normal reference | Clinical association |
|---|---|---|---|
| **Chemotherapies** | | | |
| Topoisomerase I inhibitors | TOP1 | **2.93** | Sensitivity |
| | SLC2A3 | **10.01** | Sensitivity |
| Topoisomerase II inhibitors | TOP2A | **40.12** | Sensitivity |
| | SLC2A3 | **10.01** | Sensitivity |
| Antimicrotubule agents | TUBB3 | **14.95** | Resistance |
| | SPARC | **-12.50** | Resistance |
| | BCL2 | **-45.45** | Resistance |
| | JUN | **-17.86** | Resistance |
| Alkylating agents | BRIP1 | **25.25** | Resistance |
| | FANCA | **21.65** | Resistance |
| | FANCD2 | **5.32** | Resistance |
| | RAD51 | **14.08** | Resistance |
| | ATM | **4.43** | Resistance |
| | BRCA2 | **6.10** | Resistance |
| | BRCA1 | **4.89** | Resistance |
| | TUBB3 | **14.95** | Resistance |
| | BCL2 | **-45.45** | Resistance |
| **Hormonal agents** | | | |
| | AR | **-7.04** | Resistance |
| | ESR1 | **-55.56** | Resistance |
| | PGR | **-250.00** | Resistance |
| **Therapeutic antibodies** | | | |
| | ERBB3 | **10.82** | Sensitivity |
| | HGF | **31.06** | Sensitivity |
| **Kinase / enzyme inhibitors** | | | |
| | ERBB4 | **23.45** | Sensitivity |
| | ERBB3 | **10.82** | Sensitivity |
| | AURKA | **5.40** | Sensitivity |
| | AURKB | **18.53** | Sensitivity |
| | FLT3 | **8.23** | Sensitivity |
| | CHEK2 | **14.57** | Sensitivity |
| | CHEK1 | **4.05** | Sensitivity |
| | CDK1 | **25.26** | Sensitivity |
| | CDK2 | **5.57** | Sensitivity |
| | CDK6 | **5.53** | Sensitivity |
| | ABL1 | **4.10** | Sensitivity |
| | PRKCG | **32.00** | Sensitivity |
| | PTCH1 | **8.20** | Sensitivity |
| | GLI1 | **7.00** | Sensitivity |

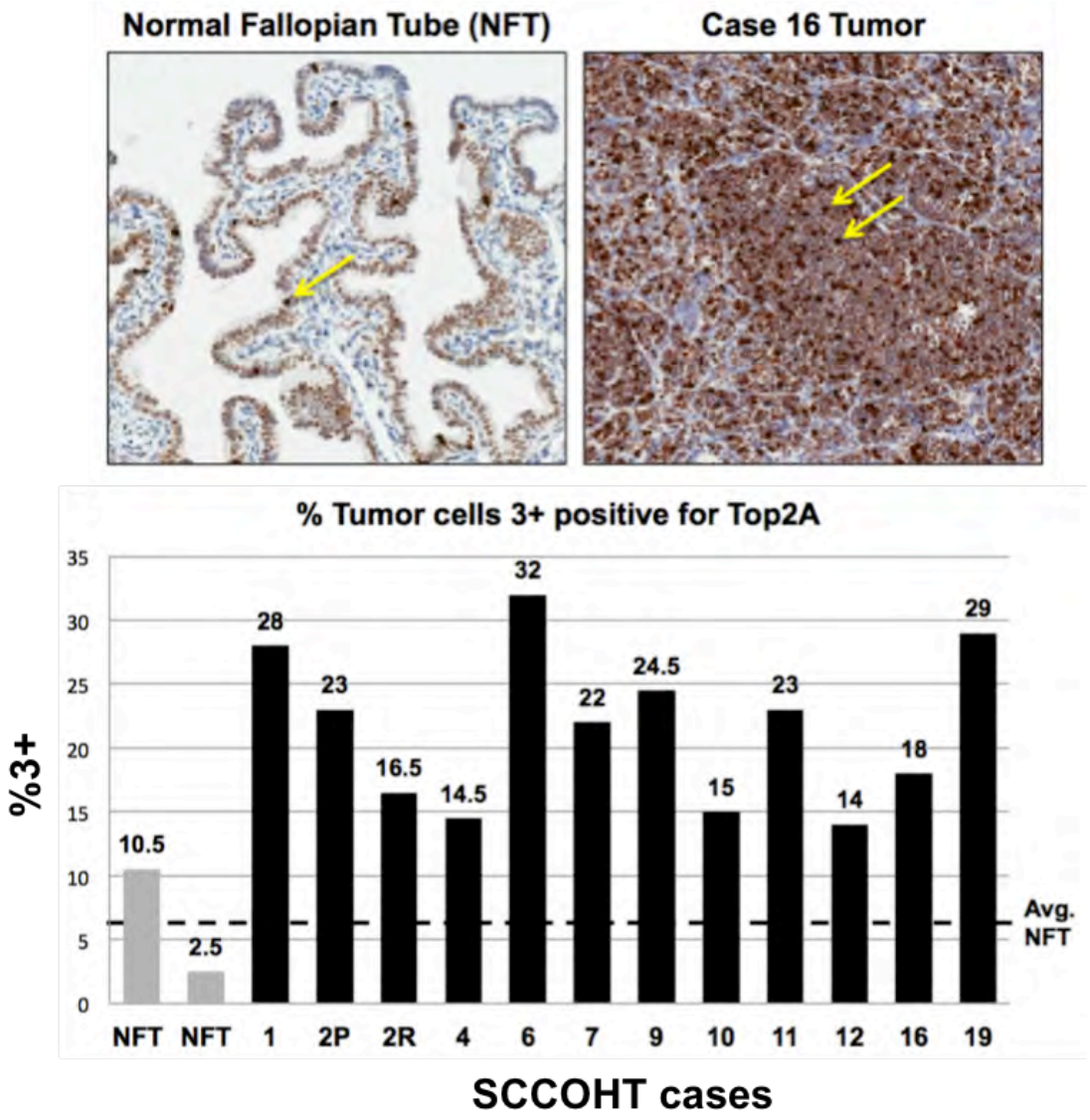


*Figure 15.* IHC evaluation of TOP2A in SCCOHT tumors. Scoring criteria: 3+, very dark nuclear intensity (see arrows in upper panel); 2+, moderate nuclear intensity; 1+, light nuclear intensity; 0, no nuclear staining. A minimum of 200 nuclei were scored per tumor (or normal fallopian tubal epithelium). No stromal elements were evaluated. **A**. Representative staining for TOP2A in SCCOHT tumor case 16 and normal fallopian tube. **B**. Histogram of cell nuclei staining 3+ for TOP2A across 12 SCCOHT cases, and sections of normal fallopian tube from 2 separate SCCO patients. Average SCCOHT tumor cells scoring 3+ was 21.6% compared with 6.5% in normal tubal epithelium.

required for BIN-67 cell growth. Among these was the snf2-related CREBBP activator protein, *SRCAP*, an ATPase of the SWR1 remodeling complex that besides regulating transcriptional processes, plays crucial roles in maintenance of genome stability (Morrison and Shen 2009). *CHD5*, which belongs to the chromodomain helicase DNA-binding (CHD) family of enzymes (Hargreaves and Crabtree 2011), was also prioritized while the other 2 selected ATPases have less well-understood functions.

Dependency on clinically actionable targets from our custom list included the genes *TUBB3* and *TPX2*. These targets were corroborated by our expression analyses of recurrent tumors (SCCO-002 and SCCO-013), drug sensitivities in the screen outlined below, and clinical responses to these agents.

**Pilot Compound Screening**

We developed a high-throughput assay to evaluate sensitivity of the BIN67 cell line to pharmacologically active compounds from the Prestwick and LOPAC drug libraries. In combination, these libraries contain 2,400 drugs with about 20% overlap, of FDA-approved small molecules, encompassing all major classes of targets including G protein coupled receptors, neurotransmitters, nuclear receptors, and ion channels, all with good bioavailability and toxicity profiles.

We completed 2 runs of these libraries in BIN-67 with duplicates, at final screening concentrations of 5 μM and 10 μM, and measured cell viability at 72 hours post-treatment with CellTiter-Glo. NIH screening standards require achieving covariance <10% and a Z'-factor >0.5. In this case, the screen was of high quality with covariance <5% and Z'-factor 0.83-0.91. After filtering shared hits from a counterscreen in the cell line HepG2, which is routinely used to generically filter out broadly cytotoxic hits due to its parenchymal morphology and expression of drug-metabolizing enzymes, BIN67 displayed hypersensitivity to 68 compounds

representing a hit rate of about 3%. Notable classes of lead compounds were enriched in these hits including 9 cardiac glycosides, 6 tubulin polymerization inhibitors, 2 topoisomerase II inhibitors, and 2 Src family kinase inhibitors.

### *In vivo* validation: Establishment and Characterization of 2 SCCOHT patient-derived xenograft (PDX) models

As SCCOHT is an extremely rare disease, few models exist by which to evaluate its biology or therapeutic vulnerability. Therefore, we set out to establish two patient-derived xenograft (PDX) models of SCCOHT. All mouse work was performed with the assistance of a subcontractor (TD2; Scottsdale, AZ) under TGen IACUC approval using standard protocols for tumor implantation, mouse monitoring, and tumor measurement.

Tumor samples were provided by Molecular Response (San Diego, CA), and were obtained from 3 patients diagnosed with SCCOHT at 19, 20 and 24 years of age. PDXs were developed in immune-deficient NOG mice by subcutaneous injection of $4x10^5$ – $3x10^6$ viable tumor cells mixed with Matrigel. Five NOG mice per tumor line were inoculated. We chose the highly immunodeficient mouse strain NOG (NOD/Shi-scid/IL-2R$\gamma^{null}$) in order to increase the chances of tumor formation and progression. These mice lack T cell, B cell and NK cell activity, have defective complement activity as well as dysfunctional macrophages and dendritic cells (Ito, NOD/SCID 2002).

Successful xenografting was achieved for two of the three SCCOHT samples: SCCO-040 (19-year old patient) and SCCO-065 (20-year old patient). Tumor growth and mouse weight were measured and recorded weekly. Tumor volume was calculated with an external caliper using the modified ellipsoid formula: ½ (length x width$^2$) (Tomayko and Reynolds 1989). As shown in Figure 17, the pattern of tumor

growth was consistent throughout all passages with tumors taking an average of 11 weeks to reach 800-1000 $mm^3$, at which point mice were sacrificed. The 2 PDX lines were passed 3 times (P0-P3) with decreasing number of mice on each passage. In total, 50 mice were used, of which 2 did not develop any tumor growth. During P0 and P1, seven total mice with small tumors were lost before reaching the sample collection endpoint. Two of these mice were Nude mice that were used when NOG mice were not available for passing one SCCO-040 tumor sample from P0 to P1. When tumors reached between 800-1,000 $mm^3$, mice were sacrifice and tumor samples were collected for cryopreservation, formalin fixed paraffin-embedded (FFPE) processing, and passaging into new mice. Additionally, fresh tumor specimens were collected for the establishment of primary cell lines. Efforts to grow primary cells *in vitro* are currently ongoing.

Established SCCOHT PDX models were confirmed by histologic analysis, demonstrating the typical histological and morphological characteristics of SCCOHT tumors (Figure 18). In addition, DNA and RNA was extracted from each model and subjected to Agilent gene expression microarray analysis (data not shown) and *SMARCA4* targeted sequencing (see Chapter 2 for targeted sequencing methods). Both xenograft models harbored *SMARCA4* heterozygous mutations predicted to result in truncation of SMARCA4 protein: p.Pro679fs (SCCO-040) and p.Val1171fs (SCCO-065). Functional inactivation of SMARCA4 was confirmed for both models by IHC analysis, which showed complete absence of SMARCA4 protein (Figure 18).

**Known Drug Targets**

| Gene Name | GENE ID | siRNA Library | Gene Name | GENE ID | siRNA Library |
|---|---|---|---|---|---|
| **AKT1S1** | 84335 | WHGv1 | **MUC1** | 4582 | DGv3 |
| **APH1A** | 51107 | DGv3 | **NPTX1** | 4884 | WHGv1 |
| **ASNS** | 440 | DGv3 | **PPAT** | 5471 | DGv3 |
| **BRCA1** | 672 | DGv3 | **PTCH1** | 5727 | DGv3 |
| **BRCA2** | 675 | DGv3 | **RAD51** | 5888 | DGv3 |
| **BRIP1** | 83990 | DGv3 | **RRM2** | 6241 | DGv3 |
| **CACNA1A** | 773 | DGv3 | **SCN8A** | 6334 | DGv3 |
| **DHFR** | 1719 | DGv3 | **SLC2A3** | 6515 | WHGv1 |
| **DNMT3A** | 1788 | DGv3 | **SSTR2** | 6752 | DGv3 |
| **DPYD** | 1806 | DGv3 | **TGFB2** | 7042 | DGv3 |
| **FANCA** | 2175 | DGv3 | **TOP1** | 7150 | DGv3 |
| **FANCD2** | 2177 | DGv3 | **TOP2A** | 7153 | DGv3 |
| **GLI1** | 2735 | DGv3 | **TUBB3** | 10381 | DGv3 |
| **HGF** | 3082 | DGv3 | **TYMS** | 7298 | DGv3 |
| **IL1B** | 3553 | DGv3 | **ZNF217** | 7764 | WHGv1 |

**SWI/SNF Genes**

| Gene Name | GENE ID | siRNA Library |
|---|---|---|
| **DPF1** | 8193 | DGv3 |
| **ARID1A** | 8289 | DGv3 |
| **SMARCC1** | 6599 | WHGv1 |
| **SMARCB1** | 6598 | WHGv1 |
| **SMARCD1** | 6602 | WHGv1 |
| **BRD7** | 29117 | WHGv1 |
| **ACTL6A** | 86 | DGv3 |
| **BRD9** | 65980 | WHGv1 |
| **PBRM1** | 55193 | DGv3 |
| **SMARCE1** | 6605 | WHGv1 |
| **SMARCAL1** | 50485 | DGv3 |
| **ARID2** | 196528 | WHGv1 |
| **ARID1B** | 57492 | WHGv1 |
| **ACTB** | 60 | WHGv1 |
| **SMARCD3** | 6604 | DGv3 |
| **ACTL6B** | 51412 | DGv3 |
| **SMARCC2** | 6601 | WHGv1 |
| **EP400** | 57634 | WHGv1 |
| **SMARCA3** | 6596 | DGv3 |
| **SMARCA4** | 6597 | DGv3 |
| **SMARCD2** | 6603 | WHGv1 |
| **DPF2** | 5977 | DGv3 |
| **PHF10** | 55274 | DGv3 |
| **SMARCA2** | 6595 | DGv3 |
| **DPF3** | 8110 | WHGv1 |

**ATPases of the DEAD/H helicase family**

| Gene Name | GENE ID | siRNA Library |
|---|---|---|
| **SMARCA1** | 6594 | WHGv1 |
| **SMARCA5** | 8467 | WHGv1 |
| **CHD1** | 1105 | DGv3 |
| **CHD2** | 1106 | WHGv1 |
| **CHD3** | 1107 | DGv3 |
| **CHD4** | 1108 | DGv3 |
| **CHD5** | 26038 | WHGv1 |
| **CHD6** | 84181 | WHGv1 |
| **CHD7** | 55636 | WHGv1 |
| **CHD8** | 57680 | WHGv1 |
| **CHD9** | 80205 | WHGv1 |
| **HELLS** | 3070 | WHGv1 |
| **SMARCAD1** | 56916 | DGv3 |
| **INO80** | 54617 | WHGv1 |
| **BTAF1** | 9044 | WHGv1 |
| **ERCC6** | 2074 | DGv3 |
| **RAD54B** | 25788 | DGv3 |
| **ATRX** | 546 | DGv3 |
| **TTF2** | 8458 | WHGv1 |
| **PTN** | 5764 | DGv3 |
| **SRCAP** | 10847 | WHGv1 |
| **SRISNF2L** | 23132 | WHGv1 |

**Other**

| Gene Name | GENE ID | siRNA Library |
|---|---|---|
| **MAX** | 4149 | DGv3 |
| **RAN** | 5901 | DGv3 |
| **TPX2** | 22974 | DGv3 |

*Figure 16.* List of 80 Custom-Selected Targets for siRNA Screen in SCCOHT.

Table 11.

siRNA Hits from Custom-Selected Targets.

| SWI/SNF subunits |
| --- |
| ARID1A |
| DPF1 |
| SMARCA2 |
| SMARCAL1 |
| SMARCB1 |
| SMARCD3 |

| Clinically Actionable Targets Upregulated in SCCOHT tumors |
| --- |
| AKT1S1 |
| BRCA1 |
| GLI1 |
| PTCH1 |
| TGFB2 |
| TUBB3 |
| ZNF217 |

| DEAD/H helicase ATPases |
| --- |
| CHD5 |
| PTN |
| SRCAP |
| TTF2 |

| SMARCA4 synthetic lethal partners in SCLC |
| --- |
| TPX2 |

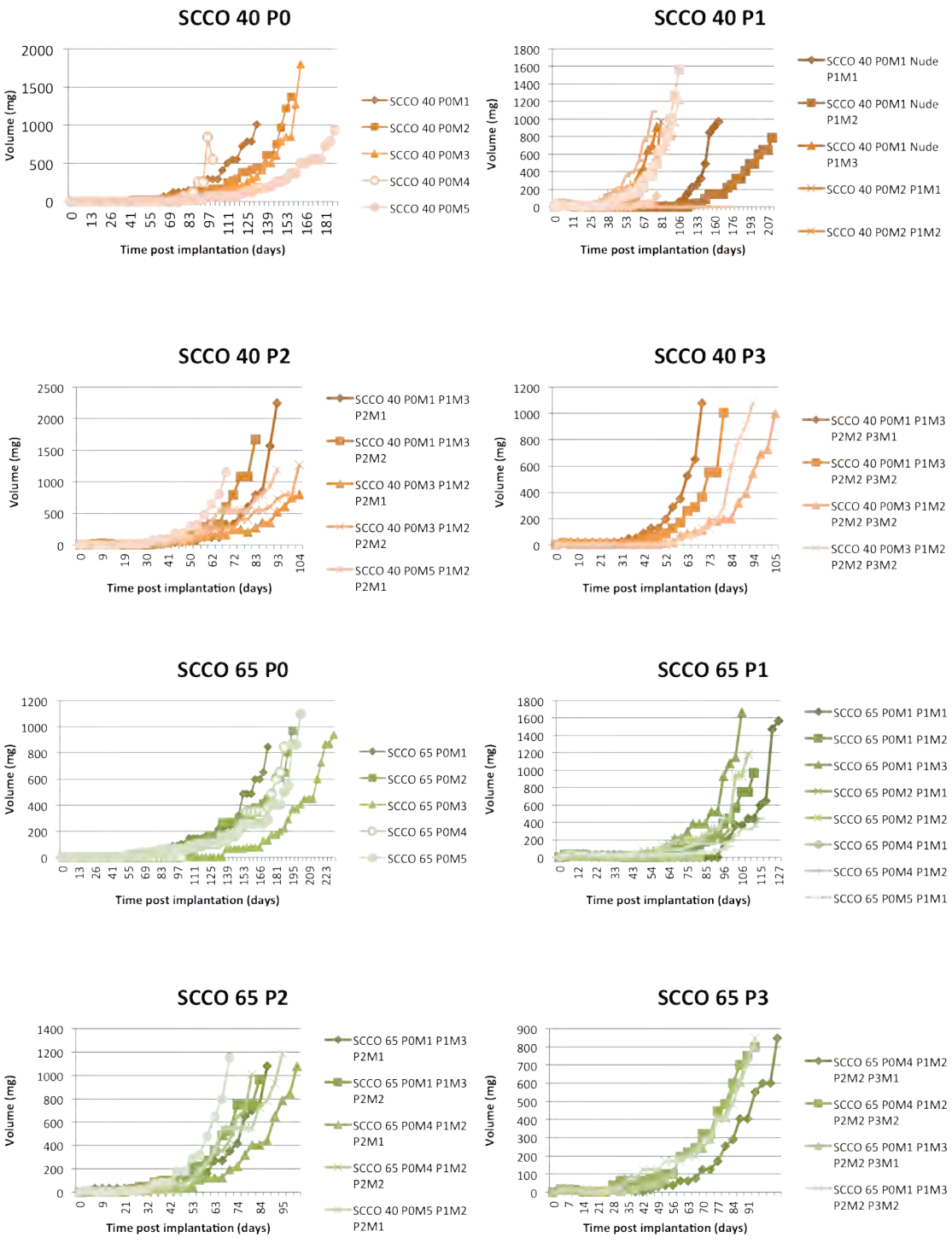


*Figure 17.* Tumor growth curves of SCCOHT patient-derived xenografts in NOG mice (2 tumors from SCCO-040 passage P0 mice were passed into Nude mice during P1).

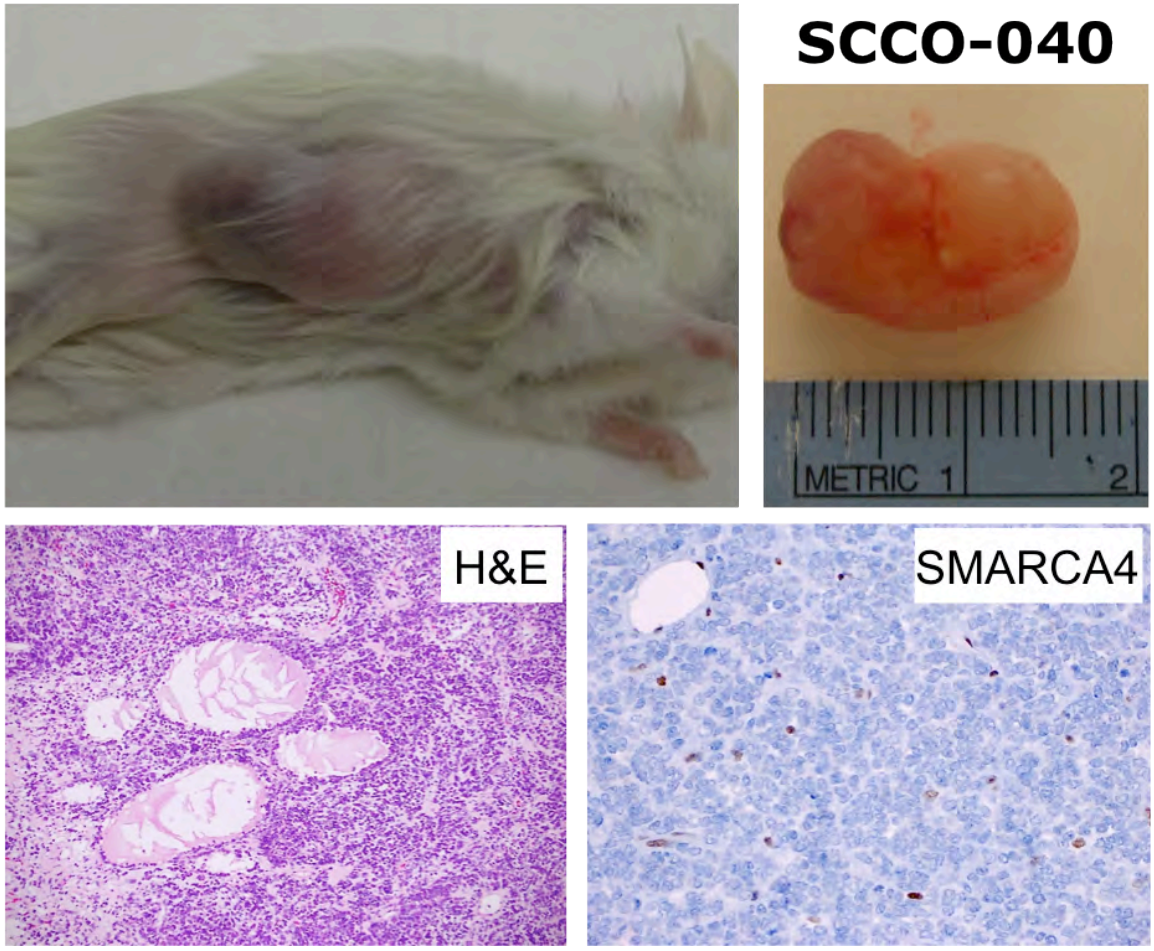


*Figure 18.* SCCOHT tumor cells were subcutaneously injected into NOG mice (top left image). Tumors of 800-1000 $mm^3$ (tope right image) were collected and processed for cryopreservation, FFPE, and passing into new mice. H&E of xenograft tumors showed typical histological and morphological characteristics of SCCHOT tumors (bottom left). Both SCCO-040 and SCCO-065 were negative for SMARCA4 protein by IHC (bottom right).

**Discussion**

The current SCCOHT clinical standard of care is based on limited data due in large part to the rarity of this cancer. SCCOHT patients are sorely in need of individual molecularly-guided treatment regimens that are capable of increasing responses to chemotherapy and extend survival. The recurring and highly specific nature of the *SMARCA4* mutation in SCCOHT presents a unique opportunity for

This study leveraged array-based and sequencing technologies to gain molecular insight into the pathobiology of SCCOHT and empower development of new evidence-based treatment rationales. Our evaluation of molecular targets to predict potential drug efficacy in SCCOHT revealed abundant evidence consistent the refractory nature of SCCO to platinum and taxane drugs. Importantly however, the presence of consistently and highly deregulated mechanisms such as the Fanconia anemia/BRCA pathway, cell cycle checkpoint control, microtubule motor protein function and *de novo* epigenetic modification processes suggests opportunities to resensitize SCCOHT tumors to a variety of cytotoxic agents.

Our preliminary HT siRNA and compound screens suggested several novel vulnerabilities, some of which clearly derive from mutations in *SMARCA4* (such as dependence on other components of the SWI/SNF complex) in addition to wholly novel findings such as sensitivity to cardiac glycosides and dependence on ATPases of the DEAD/H helicase family. We will continue to work to exploit SCCOHT's vulnerability by rational design of treatment regimens according to HT screening of combinations of frontline agents suggested by *SMARCA4* mutations and molecular profiling as well as by HT siRNA sensitization screening in combination with these agents.

Finally, we have been able to establish two *in vivo* models of SCCOHT. To our knowledge, these are the only existing SCCOHT PDX models available. Along with the

SCCOHT cell lines BIN67 and SCCOHT1, we have a unique collection of SCCOHT models that will facilitate rapid development of treatment strategies for SCCOHT. Candidate therapeutic agents suggested by siRNA and compound screenings will be validated in these PDXs in mice.

Information obtained from these studies will not only reveal therapeutic vulnerabilities in SCCOHTs by identifying current clinical agents that can be immediately evaluated in these patients in addition to discovering novel targets and compounds for further development, but will also potentially reveal synthetic lethal dependencies. Moreover, great potential also exists for this work to more broadly impact ovarian cancer research and drug design given the high frequency of SWI/SNF mutations across cancer types.

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# APPENDIX A

# GENES SIGNIFICANTLY DYSREGULATED IN 4 SCCOHT TUMORS COMPARED TO NORMAL OVARY

| GENE SYMBOL | Log2Ratio SCCO-002 vs. Normal Ovary | Log2Ratio SCCO-014 vs. Normal Ovary | Log2Ratio SCCO-015 vs. Normal Ovary | Log2Ratio SCCO-012 vs. Normal Ovary |
|---|---|---|---|---|
| AREG | -5.165301 | -3.592656 | 1.22625 | 1.187075 |
| EPCAM | -3.794671 | -1.944194 | 0.953031 | 1.905747 |
| FAAH2 | -1.64327 | -1.014734 | 0.748609 | 0.963515 |
| HCAR3 | -4.118101 | -1.360223 | 3.677633 | 1.610293 |
| LOC338620 | -1.586405 | -0.793923 | 1.022345 | 0.853565 |
| HOXA9 | -1.360286 | -2.58642 | 1.370565 | 1.293341 |
| NEFL | -2.42843 | -3.80569 | 4.649602 | 2.03558 |
| NEFM | -3.757131 | -3.89108 | 4.317223 | 3.264227 |
| GLDC | -1.146193 | -1.614812 | 0.905182 | 3.548445 |
| MYO10 | -1.200757 | -1.031425 | 0.909733 | 1.489434 |
| STMN2 | -1.698642 | -2.184149 | 1.660764 | 2.887088 |
| GJA1 | 1.358758 | -1.281716 | 1.086661 | -2.074462 |
| CYP2U1 | 1.484761 | -2.243187 | 0.961605 | -2.116768 |
| LOC391322 | 1.804105 | -3.395642 | 2.091529 | -3.449043 |
| LOC284244 | 1.552135 | -2.753897 | 0.875695 | -1.239366 |
| FGF20 | 3.079955 | -1.905304 | 4.519815 | -1.76154 |
| POU6F2 | 3.018361 | -1.617386 | 2.394944 | -2.619191 |
| ABCC9 | 1.694696 | -4.335101 | -3.017322 | -1.262036 |
| KITLG | 0.739371 | -3.691574 | -3.274425 | -1.914975 |
| FGF12 | 2.13199 | -1.955164 | -3.254607 | -3.586511 |
| BAMBI | 1.812627 | -3.380173 | -4.020133 | -4.273889 |
| CPE | 0.974113 | -1.358003 | -2.087425 | -2.118994 |
| REEP6 | 0.751788 | -1.034447 | -1.462915 | -1.679681 |
| LOC388588 | 0.726757 | -0.997944 | -1.516139 | -2.03836 |
| ID4 | 0.940363 | -1.176871 | -3.464189 | -3.988583 |
| CASC1 | 1.856716 | -2.160745 | -1.554919 | -3.274043 |
| DUOX1 | 1.66286 | -1.230099 | -1.1428 | -2.961212 |
| IGSF1 | 2.200173 | -3.272408 | -1.249508 | -5.167086 |
| DUOX2 | 1.046877 | -1.041081 | -1.344872 | -2.932995 |
| MTTP | 1.440278 | -1.731694 | -2.09208 | -4.724144 |
| PSORS1C1 | 0.757039 | -0.960654 | -1.025538 | -2.002166 |
| CNTN1 | 1.064879 | -2.260467 | -2.022356 | -2.272528 |
| AMPH | 1.58268 | -3.122495 | -1.946196 | -2.4604 |
| ESR2 | 0.988914 | -3.252671 | -1.755684 | -2.979064 |
| FAM189A2 | 0.925719 | -3.528494 | -2.378415 | -2.908714 |
| SOHLH2 | 3.290076 | -3.932987 | -2.606722 | -3.874063 |
| TXLNB | 1.296173 | -2.055989 | -0.967382 | -2.105391 |

| | | | | |
|---|---|---|---|---|
| GATA2 | 2.455606 | -1.579164 | -2.870704 | -2.005473 |
| LOC254057 | 2.854741 | -1.374096 | -2.25031 | -2.085987 |
| RAB40B | 1.326999 | -0.74965 | -1.032207 | -1.276302 |
| SC4MOL | 2.347087 | -1.175188 | -1.353578 | -1.58261 |
| FAM84B | 3.475838 | -3.400307 | -4.087395 | -1.566469 |
| TMEM192 | 2.416814 | -2.243391 | -3.052995 | -1.756737 |
| SPECC1 | 2.918688 | -2.25364 | -1.75392 | -1.243809 |
| LPHN2 | 2.735349 | 1.371043 | -2.196652 | -0.907973 |
| COX1 | 1.06221 | 1.030704 | -1.982273 | -2.29378 |
| GRM7 | 2.010367 | 1.083411 | -2.13685 | -2.41164 |
| TRIM16L | 0.70655 | 0.838032 | -0.764822 | -1.354849 |
| LOC100144602 | 4.082205 | 3.617391 | -2.433403 | -3.315121 |
| TMC4 | 1.300091 | 0.812944 | -0.873681 | -1.171553 |
| DNMT3A | 0.026507 | -0.135764 | -0.265188 | 1.025442 |
| CXCR2P1 | -4.617514 | -1.515484 | -2.039704 | 5.150734 |
| ARHGAP9 | -2.053792 | -0.853805 | -1.595406 | 3.031006 |
| PREX1 | -1.885579 | -0.707043 | -1.323242 | 2.741438 |
| MMP10 | -3.288766 | -1.328525 | -2.92434 | 5.355713 |
| KLHDC7B | -2.122066 | -1.028222 | -1.403746 | 3.074214 |
| GHRL | -1.520993 | -0.905912 | -1.200512 | 2.517575 |
| SAMSN1 | -1.74787 | -0.979253 | -1.310071 | 3.062643 |
| CLEC4G | -1.944425 | -1.225804 | -1.033004 | 4.008002 |
| BIRC3 | -2.41932 | -1.439722 | -1.456473 | 4.598705 |
| STAT4 | -1.40563 | -0.863334 | -0.828968 | 2.747052 |
| FAM26F | -2.167372 | -1.212768 | -0.88873 | 3.062652 |
| CD3G | -2.999664 | -2.252434 | -1.942333 | 5.190368 |
| SLC6A2 | -1.140217 | -0.89078 | -0.865108 | 1.918886 |
| FCRL3 | -3.048315 | -2.805163 | -1.57843 | 4.799712 |
| RASGRP1 | -1.727101 | -1.604619 | -1.062341 | 3.233969 |
| TXNDC3 | -2.078796 | -2.024051 | -1.374766 | 3.762788 |
| CD36 | -0.730363 | -1.993813 | -2.065604 | 3.081572 |
| EMB | -1.017717 | -1.828311 | -1.948952 | 3.170501 |
| HMHA1 | -0.974839 | -1.821125 | -1.783761 | 2.543749 |
| PIK3IP1 | -0.778259 | -1.903775 | -1.523341 | 2.435483 |
| CD27 | -0.796784 | -1.611199 | -2.223176 | 3.155748 |
| GPR171 | -1.136452 | -1.677533 | -2.644232 | 4.028095 |
| NCR3 | -0.838403 | -1.249021 | -1.635822 | 2.730565 |
| PDE6G | -0.881762 | -1.208854 | -1.693661 | 2.3585 |
| GNLY | -1.460715 | -1.131001 | -2.068373 | 4.78259 |
| GZMB | -1.440874 | -1.283438 | -2.307343 | 5.587629 |

| | | | | |
|---|---|---|---|---|
| TCL1A | -1.175975 | -1.375573 | -2.218361 | 5.805066 |
| CA2 | -1.41001 | -1.755572 | -2.045225 | 3.796191 |
| ITGA4 | -1.066765 | -1.380638 | -1.152283 | 2.785405 |
| PTCRA | -1.14825 | -1.428626 | -1.189882 | 3.045818 |
| SH2D2A | -1.218879 | -1.269718 | -1.413998 | 3.338986 |
| LTB | -1.831544 | -1.623071 | -2.56938 | 4.995139 |
| SELPLG | -0.86344 | -0.801018 | -1.335355 | 2.386054 |
| TRIM14 | -1.411919 | -1.128878 | -1.366697 | 2.648614 |
| CYP2J2 | -1.198778 | -3.380872 | -1.145644 | 2.557619 |
| LEF1 | -1.429956 | -4.428352 | -0.941648 | 2.942604 |
| GAP43 | -0.755387 | -3.98798 | -1.564599 | 3.050852 |
| KLRD1 | -1.069075 | -3.890036 | -1.81605 | 3.393979 |
| ELOVL7 | -0.998931 | -1.718974 | -1.033188 | 1.441162 |
| LOC100129399 | -0.879769 | -1.533624 | -0.812969 | 1.214736 |
| NR5A2 | -2.197769 | -3.447057 | -1.167304 | 2.234434 |
| RAPGEF5 | -1.789694 | -3.006699 | -1.164174 | 1.612179 |
| CCR7 | -2.620398 | -2.307025 | -4.408659 | 5.416086 |
| IL2RG | -1.997162 | -1.065366 | -2.394233 | 3.57436 |
| PDCD1 | -1.315987 | -0.910164 | -1.572171 | 2.462244 |
| CANX | -0.996041 | -0.816657 | -0.730168 | 1.093383 |
| CYSLTR1 | -2.043525 | -1.699016 | -1.626075 | 2.396821 |
| PRF1 | -2.212677 | -1.729761 | -1.795243 | 2.717185 |
| BATF | -2.945678 | -1.865148 | -2.444994 | 3.403992 |
| AOAH | -2.590959 | -1.481984 | -1.94732 | 2.758729 |
| RGS18 | -2.595669 | -1.503146 | -2.11874 | 2.798966 |
| GMFG | -2.466736 | -1.533343 | -1.82807 | 2.895578 |
| LCP2 | -1.781423 | -1.012686 | -1.280091 | 2.025214 |
| IKZF1 | -2.572134 | -1.780383 | -2.147376 | 3.202351 |
| CD300A | -2.100234 | -1.245939 | -1.490933 | 2.117503 |
| FYB | -3.131059 | -1.882373 | -2.230584 | 3.160949 |
| PVRIG | -2.633239 | -1.6 | -1.956732 | 2.56689 |
| GPR18 | -3.298727 | -2.193351 | -2.525985 | 3.342941 |
| RASSF5 | -2.674597 | -1.820723 | -1.946483 | 2.768507 |
| IL2RB | -2.449757 | -1.741035 | -2.055108 | 3.418091 |
| SLC31A2 | -1.502891 | -1.101977 | -0.956337 | 2.086519 |
| MARCH1 | -1.910205 | -0.902943 | -1.395402 | 2.196468 |
| ARHGDIB | -2.530699 | -1.323198 | -1.823168 | 2.953733 |
| IL18 | -2.198947 | -1.126801 | -1.618471 | 2.533312 |
| RAC2 | -2.16082 | -1.130861 | -1.852956 | 2.826688 |
| TMC8 | -2.405219 | -1.30101 | -2.149691 | 3.093137 |

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|---|---|---|---|---|
| LCP1 | -2.966849 | -1.15833 | -2.376317 | 3.295326 |
| PLEK | -2.552867 | -0.746089 | -1.877921 | 2.873287 |
| GBP5 | -2.848268 | -1.249343 | -3.21143 | 3.902761 |
| CD38 | -3.069462 | -1.514777 | -3.317279 | 3.668023 |
| EPSTI1 | -2.542463 | -1.334926 | -2.550865 | 3.215232 |
| LCK | -2.823611 | -1.764437 | -3.194634 | 3.879911 |
| SIRPG | -2.582189 | -1.510665 | -2.977891 | 3.489562 |
| ICAM3 | -1.403297 | -0.926236 | -1.560585 | 2.145777 |
| CD6 | -3.018245 | -1.912458 | -2.978047 | 3.26432 |
| PSTPIP1 | -1.961794 | -1.301494 | -2.187982 | 2.1022 |
| ABI3 | -1.382798 | -0.960581 | -1.675654 | 1.932541 |
| BCL11B | -2.780257 | -2.109051 | -3.338207 | 3.817177 |
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| A23747 | -2.652225 | -1.800228 | -2.874161 | 3.396668 |
| HPDL | -1.637497 | -1.017095 | -1.548548 | 2.012972 |
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| PARP14 | -1.409631 | -1.14067 | -1.627742 | 1.809871 |
| CD8B | -2.521256 | -2.087483 | -2.885443 | 3.559467 |
| DENND1C | -2.058422 | -1.601185 | -2.102478 | 2.797873 |
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| KLRC3 | -2.038928 | -2.007208 | -1.934929 | 3.084277 |
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| ISG20 | -1.883368 | -2.127454 | -2.045628 | 3.39055 |
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| ICOS | -1.844628 | -2.312548 | -2.454564 | 4.063127 |
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| TIGIT | -2.702376 | -3.183899 | -2.319992 | 4.679474 |
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| AMICA1 | -3.223287 | -1.703524 | -2.529087 | 2.294877 |
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| LAPTM5 | -2.627044 | -1.233994 | -2.198872 | 1.680253 |
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| FLJ32255 | -3.068607 | -1.993177 | -2.912609 | 2.179158 |
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| MPP1 | -1.310768 | -0.916632 | -1.184034 | 0.865473 |
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| SIGLEC7 | -1.715845 | -0.908211 | -1.570004 | 1.389996 |
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| SMPD3 | -2.31133 | -0.923927 | -1.478242 | 2.075272 |
| BATF2 | -2.442254 | -0.812906 | -1.592327 | 1.689251 |
| GPR65 | -2.844015 | -0.917032 | -1.681947 | 2.073029 |
| NLRC4 | -2.763437 | -0.906639 | -1.794854 | 2.161312 |
| HLA-J | -2.645266 | -0.861426 | -1.977634 | 2.162005 |
| LSP1 | -2.860018 | -0.836317 | -2.052408 | 2.268702 |
| CSF2RA | -2.880367 | -1.749202 | -2.163217 | 2.616097 |
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| NCKAP1L | -2.491625 | -1.151299 | -1.802776 | 2.141309 |
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| HLA-E | -1.681307 | -0.745459 | -1.385033 | 1.560677 |
| KMO | -2.723633 | -1.199313 | -2.380555 | 2.481279 |
| PARVG | -2.065689 | -1.094721 | -1.969421 | 1.974727 |
| HCST | -2.492958 | -1.114264 | -2.207544 | 2.577642 |
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| LRRC25 | -2.460516 | -0.9763 | -2.372698 | 1.638985 |
| NCF1 | -2.210937 | -0.767331 | -2.05788 | 1.47359 |
| TARP | -3.263792 | -1.078303 | -3.578912 | 2.12185 |
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| ARL4C | -3.353256 | -2.58242 | -2.068426 | 2.19276 |

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| IRF8 | -3.523561 | -2.742757 | -2.444234 | 2.720262 |
| PTPRE | -2.617715 | -1.970008 | -1.840547 | 1.793681 |
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| INPP5D | -3.062469 | -2.008547 | -2.221985 | 1.982318 |
| HLA-B | -3.533635 | -2.49857 | -2.591838 | 2.217316 |
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| CD40LG | -4.241724 | -4.547853 | -3.46818 | 3.022131 |
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| APLNR | -1.608586 | -2.088702 | -1.481034 | 1.72552 |
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| PVT1 | -1.175361 | -1.716094 | -1.088917 | 1.176806 |
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| GPR182 | -3.361896 | -3.947198 | -2.530141 | 1.980227 |
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| FAM78A | -1.377781 | -1.486478 | -1.408771 | 1.742294 |
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| ITK | -4.103226 | -3.752886 | -3.8385 | 5.136071 |
| CLEC4M | -2.645473 | -2.390874 | -2.398309 | 2.939886 |
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| OSTF1 | -1.746168 | -1.57933 | -1.300057 | 1.57649 |
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| KLRC4 | -2.613306 | -3.206481 | -3.758051 | 2.818047 |
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| FAM49A | -2.785323 | -2.483362 | -2.314656 | 2.061131 |
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| MGAT4A | -1.586158 | -1.285173 | -1.240679 | 1.116124 |
| KLRK1 | -3.807922 | -3.019448 | -3.327399 | 3.251746 |
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| TUBA4A | -2.254819 | -2.187398 | -2.118557 | 1.83078 |
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| FGD3 | -2.364 | -1.906147 | -2.409463 | 2.3656 |
| SCML4 | -3.796043 | -3.189139 | -3.777483 | 3.632831 |
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| TRAF3IP3 | -3.414791 | -2.671745 | -3.184479 | 3.099923 |
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| SH2D1A | -3.025825 | -2.773165 | -3.435731 | 3.582143 |
| MARCH6 | -1.702922 | -1.255925 | -0.706046 | 1.892499 |
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| CYTIP | -3.608812 | -2.247981 | -1.098211 | 3.57565 |
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| ADAM12 | -1.981064 | -1.829885 | -1.031695 | 1.516568 |
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| DHX58 | -1.141107 | -2.036954 | -2.458355 | 1.244724 |
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| TNIK | -0.977018 | -3.868877 | -4.539841 | 2.042652 |
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| BTNL8 | -4.29991 | -1.784733 | -3.713046 | 1.458854 |

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| DUSP2 | -2.689515 | -1.063156 | -2.791494 | 1.053791 |
| CCL4 | -3.252181 | -0.903284 | -2.03906 | 1.117204 |
| ARHGAP22 | -2.611389 | -0.844267 | -1.807511 | 0.972199 |
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| HLA-DRB4 | -3.078458 | -1.122244 | -2.344944 | 1.107084 |
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| FCGR1B | -3.129366 | -0.845873 | -1.535107 | 0.769502 |
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| ASGR2 | -2.676146 | -2.423578 | -2.129054 | 1.084802 |
| ANK3 | -4.749916 | -3.894123 | -3.46584 | 1.618937 |
| DOCK10 | -3.77905 | -3.11551 | -2.792863 | 1.410047 |
| HOXB4 | -2.145365 | -1.82611 | -1.609435 | 0.782141 |
| DENND3 | -2.287414 | -1.991866 | -1.577102 | 0.949665 |
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| AB306238 | -4.024518 | -3.270549 | -2.732478 | 2.025344 |
| MAML2 | -1.879668 | -1.668343 | -1.369661 | 0.996116 |
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| HLA-DQB1 | -4.221203 | -2.945049 | -2.668799 | 1.786832 |
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| GIMAP8 | -3.381876 | -2.659357 | -2.777826 | 1.422143 |
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| CASP1 | -3.318843 | -2.615918 | -2.530806 | 1.7916 |
| GIMAP2 | -3.609711 | -2.875648 | -2.881235 | 1.819731 |
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| TYROBP | -2.899539 | -1.950141 | -2.345642 | 1.572766 |
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| GBP4 | -3.070511 | -2.897864 | -2.754609 | 1.752692 |
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| TSPAN32 | -3.005675 | -2.922986 | -3.101634 | 2.037384 |
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| ALOX5 | -2.521312 | -1.859808 | -2.569706 | 1.273333 |
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| OAS1 | -2.43196 | -2.170085 | -2.61325 | 1.608064 |
| HLA-DPA1 | -2.755223 | -2.138336 | -2.904372 | 1.879829 |
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| ELMO1 | -2.77533 | -2.669679 | -2.479134 | 1.206235 |
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| RTP4 | -3.925881 | -3.880797 | -3.891278 | 1.796396 |
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| MST4 | -3.68801 | -3.927125 | -4.382478 | 1.411498 |
| HAVCR2 | -1.863665 | -2.06258 | -2.256412 | 0.923095 |
| OAS2 | -2.621249 | -3.137067 | -3.335983 | 1.236248 |
| TMEM229B | -1.876106 | -2.185634 | -2.265495 | 0.804872 |
| HERPUD1 | -2.001673 | -2.149611 | -1.633534 | 0.785674 |
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| BCL2L11 | -2.171278 | -2.37012 | -2.092222 | 0.770232 |
| PLCG2 | -2.579914 | -2.592047 | -2.314064 | 0.856378 |
| PTPN18 | -1.944466 | -2.015457 | -1.804354 | 0.714785 |
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| HTATIP2 | -3.805255 | -3.085953 | -2.676377 | 0.988534 |
| FGD4 | -4.984274 | -3.58783 | -3.457697 | 1.244022 |
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| LOC388242 | -3.090732 | -2.347764 | -2.22563 | 0.85278 |
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| IL15RA | -3.131932 | -2.316215 | -2.214534 | 1.044624 |
| CXCR6 | -5.093635 | -3.663429 | -3.753007 | 0.746738 |
| SGK223 | -3.97773 | -2.858786 | -2.909207 | 0.838257 |
| ATP10A | -4.391063 | -3.355367 | -3.632575 | 0.949076 |
| IFITM1 | -4.015676 | -3.118863 | -3.532711 | 0.928268 |
| FASLG | -3.989732 | -3.359371 | -3.402665 | 0.887813 |
| APH1B | -3.027138 | -2.470393 | -2.495562 | 0.797526 |
| TRIM38 | -3.65317 | -2.940575 | -3.072593 | 0.937289 |
| DENND1B | -4.219392 | -3.779327 | -3.767422 | 0.763559 |
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| GIMAP6 | -3.204918 | -2.723088 | -2.918702 | 0.739952 |
| CCRL2 | -3.446355 | -3.138894 | -3.298375 | 0.795068 |
| PLXNA3 | -2.828885 | -2.548762 | -2.687662 | 0.768197 |
| SP100 | -4.03624 | -3.655837 | -3.302332 | 0.713497 |
| KLRB1 | -4.356933 | -4.112794 | -4.062482 | 1.488037 |
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| FAM113B | -3.23429 | -1.878945 | -2.405516 | 0.740374 |
| GBP1 | -5.125296 | -3.372578 | -4.072022 | 0.928799 |
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| SH3TC1 | -2.001489 | -1.375001 | -1.627288 | 0.49458 |
| CD83 | -3.618622 | -2.508798 | -3.029542 | 1.256784 |
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| ICAM4 | -3.153578 | -2.22063 | -2.592091 | 1.248462 |
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| PFKFB3 | -2.767308 | -1.857413 | -2.062451 | 0.800509 |
| HLA-DRB3 | -2.665037 | -1.67636 | -2.2043 | 0.852166 |
| HLA-DQA2 | -3.437346 | -2.254742 | -3.044753 | 1.215875 |
| ZNF385D | -2.858298 | -1.881968 | -2.580095 | 0.942663 |
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| TNFAIP3 | -3.802148 | -3.08628 | -4.029128 | 0.813834 |
| DPEP2 | -2.812117 | -2.360606 | -2.863671 | 0.795062 |
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| HLA-DRB5 | -3.40774 | -1.984474 | -4.25566 | 2.309811 |
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| PRINS | -1.526161 | -0.882561 | -1.778091 | 0.858807 |
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| IFI30 | -3.434198 | -2.154171 | -3.669164 | 2.133847 |
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| PLCB2 | -2.478875 | -1.515747 | -2.310481 | 1.569197 |
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| RIPK3 | -3.357179 | -1.991477 | -3.106674 | 1.382022 |
| CSF3R | -2.538402 | -1.622363 | -2.593145 | 1.235997 |
| FGR | -3.745887 | -2.383805 | -3.642761 | 1.965904 |
| HLA-DMA | -2.429734 | -1.621326 | -2.400132 | 1.23738 |
| SLAMF7 | -4.382699 | -2.995118 | -4.385349 | 2.346658 |
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| MAFB | -3.07078 | -2.242467 | -2.955979 | 1.17725 |
| PECAM1 | -1.938464 | -1.25282 | -1.969603 | 0.715791 |
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| CCL5 | -3.94563 | -2.29338 | -3.969488 | 1.060092 |
| TCERG1L | -3.062275 | -1.734453 | -3.319736 | 0.765288 |
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| MATL2963 | -2.218426 | -2.606934 | -3.202158 | 1.368467 |
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| PARP9 | -1.50596 | -1.380337 | -2.073041 | 0.910153 |
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| CCR1 | -3.53195 | -2.146102 | -2.484572 | 1.279611 |
| GALNT6 | -2.595352 | -1.587943 | -1.721483 | 0.882082 |
| GZMA | -5.068328 | -3.062269 | -3.365599 | 1.746195 |
| PIK3CG | -3.46922 | -1.884099 | -2.43049 | 1.27545 |
| PLB1 | -2.162933 | -1.272847 | -1.650614 | 0.862353 |
| TBXAS1 | -2.153855 | -1.26713 | -1.603491 | 0.756926 |
| SLFN13 | -4.254018 | -2.750192 | -2.65488 | 1.284366 |
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| TLR1 | -3.059273 | -1.511663 | -1.283158 | 1.145915 |
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| SAT1 | -2.564405 | -1.453521 | -1.271109 | 1.081182 |
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| VDR | -4.281508 | -2.457521 | -1.639517 | 0.879619 |
| ADORA3 | -1.989594 | -1.943331 | -1.136056 | 0.774786 |
| CYP1B1 | -4.866491 | -3.969388 | -3.005347 | 0.903509 |
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| ST6GALNAC3 | -2.632801 | -3.407198 | -2.156147 | 0.771149 |
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| TSC22D3 | -3.789857 | -3.960106 | -1.49337 | 0.850816 |
| MGC16275 | -1.962124 | -1.062755 | -2.621305 | 0.995967 |
| HS3ST3B1 | -5.209339 | -3.817616 | -1.490738 | 2.469903 |
| GLIPR2 | -1.85293 | -1.485476 | -0.762082 | 1.150914 |
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| RGS1 | -4.311271 | -2.992024 | -2.010307 | 2.331182 |
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| ERAP1 | -1.448742 | -0.825011 | -0.087617 | 0.444191 |
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| QPCT | -3.665779 | -1.384542 | -1.068809 | 0.992361 |
| TTC39C | -2.225326 | -0.912058 | -0.842028 | 0.76331 |
| HLA-A | -2.646499 | -0.939202 | -0.898928 | 1.614726 |
| PRKCB | -4.23525 | -1.500724 | -1.742903 | 3.11884 |
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| AIM2 | -4.49311 | -1.960417 | -1.914776 | 3.824826 |
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| VAV1 | -2.494933 | -1.044076 | -0.790504 | 2.019959 |
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| RUNX2 | -3.285242 | -1.030331 | -1.224217 | 1.490556 |
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| TLR2 | -3.003207 | -1.205569 | -1.767112 | 1.801286 |
| CXCL14 | -6.079125 | -1.814519 | -2.975336 | 2.919085 |
| TRPM2 | -2.240242 | -0.819025 | -1.120256 | 1.302228 |
| VNN2 | -3.421934 | -1.063677 | -1.713766 | 1.899989 |
| DDX43 | -2.971646 | -7.479033 | -5.623103 | 0.765158 |

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| EBF3 | -2.661407 | -5.708088 | -4.956989 | 1.135166 |
| HEY2 | -2.854517 | -4.970886 | -4.557001 | 0.935587 |
| B3GNT3 | -1.00741 | -2.025286 | -1.425729 | 1.095058 |
| CHST2 | -0.754925 | -1.969588 | -1.485728 | 0.990704 |
| LOC100507055 | -1.850548 | -3.969867 | -2.677116 | 1.412587 |
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| PDE4D | -2.419691 | -4.102349 | -3.248414 | 1.725097 |
| POPDC2 | -1.592181 | -2.887856 | -2.440621 | 1.423646 |
| FAM107B | -1.271629 | -2.257367 | -2.085825 | 1.553505 |
| IGSF6 | -1.989707 | -3.008159 | -2.548624 | 2.008254 |
| LOC440149 | -1.334735 | -2.05782 | -1.938819 | 1.226932 |
| NAAA | -0.990962 | -1.513421 | -1.484284 | 0.924079 |
| HERC6 | -1.759504 | -2.448753 | -2.839259 | 1.397533 |
| LAX1 | -2.534249 | -3.698481 | -3.783533 | 1.974367 |
| FAM125A | -1.147047 | -1.92601 | -1.95959 | 0.913547 |
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| DLX6 | -2.379759 | -3.774905 | -3.247788 | 1.14699 |
| GPR155 | -1.803868 | -2.899387 | -2.386209 | 0.9934 |
| TRGV7 | -2.234749 | -3.410771 | -2.950367 | 1.217077 |
| LAMC2 | -2.413232 | -3.380664 | -2.793602 | 0.921799 |
| PLA2G7 | -3.693994 | -5.191063 | -4.41473 | 1.520697 |
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| TNFRSF17 | -2.926036 | -4.121935 | -4.412909 | 1.260471 |
| CCL18 | -3.470792 | -3.890933 | -4.519326 | 0.704736 |
| TNFRSF14 | -1.97838 | -1.916487 | -1.993935 | 0.031938 |
| HERC5 | -1.343189 | -3.795555 | -1.965738 | 0.794706 |
| SYT1 | -2.070754 | -4.731179 | -2.114581 | 1.308148 |
| ZNF815 | -1.554178 | -3.095724 | -1.449462 | 1.19137 |
| CADM1 | -3.05537 | 0.985627 | -0.865068 | -1.789388 |
| DMD | -2.481311 | 1.901982 | -3.552075 | -2.791181 |
| LRRC10B | -1.837101 | 0.791369 | -1.900208 | -2.605448 |
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| HFM1 | -0.851238 | -2.594393 | -1.985601 | -4.821043 |
| FLRT3 | -0.740293 | -2.664923 | -1.256308 | -4.168894 |
| CORIN | -2.427761 | -1.441806 | -2.173728 | -5.411355 |
| CYP2B6 | -1.41721 | -1.104238 | -1.059286 | -2.847574 |
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| MRC2 | -1.576903 | -1.261831 | -1.252978 | -3.088738 |
| CMYA5 | -2.460037 | -2.398717 | -2.437184 | -5.741761 |
| MYL2 | -0.97012 | -0.864361 | -0.921306 | -2.409146 |
| OR2A20P | -1.121635 | -0.944081 | -1.025081 | -2.063794 |
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| MAPK10 | -1.601528 | -1.989815 | -1.507983 | -3.840012 |
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| MAGED2 | -0.973173 | -1.284715 | -0.950057 | -2.675621 |
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| KCNQ1OT1 | -1.223097 | -1.567389 | -0.977304 | -3.183257 |
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| KIAA0368 | -1.18609 | -1.097002 | -0.809012 | -2.873538 |
| DFNA5 | -1.087642 | -1.070853 | -0.72902 | -2.393588 |
| SNX21 | -1.20436 | -1.265787 | -0.74367 | -2.573238 |
| MAGI2 | -1.560835 | -1.966026 | -1.050672 | -3.436027 |
| DAAM2 | -0.749643 | -0.949093 | -1.214447 | -2.429351 |
| CHRNB1 | -0.742529 | -0.89511 | -1.090819 | -2.008298 |
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| NUDT4 | -0.807194 | -1.322305 | -1.424188 | -2.892137 |
| SEMA3C | -0.798587 | -1.640464 | -1.71793 | -3.477278 |
| CHURC1 | -0.99049 | -1.514898 | -1.405051 | -3.898668 |
| ZAK | -1.015094 | -1.338046 | -1.443417 | -3.832098 |
| SLC47A1 | -0.72262 | -0.717457 | -0.849194 | -2.349801 |
| GPRC5C | -0.796663 | -0.713477 | -1.371758 | -2.909266 |
| INHA | -1.180367 | -1.032763 | -2.238253 | -4.42881 |
| NOXA1 | -0.934591 | -0.811696 | -1.36244 | -2.665026 |
| RPL22 | -0.825134 | -0.772177 | -1.209015 | -2.409789 |
| NUDT10 | -1.21783 | -1.319358 | -1.510139 | -5.598182 |
| SLC25A27 | -0.81905 | -2.11243 | -0.825245 | -4.848773 |
| CCL23 | -1.232124 | -2.766446 | -4.027321 | 0.770852 |
| GREM1 | -1.440408 | -3.550456 | -5.730007 | 0.893719 |

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| ITM2A | -0.826521 | -4.701496 | -4.086771 | -1.467766 |
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| CPA3 | -1.517992 | -6.404132 | -6.216414 | -2.179649 |
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| LOC100134937 | -0.951428 | -2.464172 | -2.178817 | -0.808541 |
| LOC339290 | -1.647721 | -4.63712 | -3.810285 | -1.259482 |
| NLRX1 | -1.089643 | -2.15929 | -2.685589 | -0.846826 |
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| SNTG2 | -2.018343 | -5.029723 | -5.008088 | -1.497026 |
| KLHL29 | -1.202014 | -2.885638 | -3.264629 | -0.957083 |
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| AQP7P3 | -1.093637 | -1.302036 | -3.788219 | -0.976335 |
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| CHI3L1 | -3.207492 | -0.989805 | -2.39856 | -1.988858 |
| EHD2 | -3.303219 | -0.987578 | -2.082398 | -1.768984 |
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| FOS | -5.453727 | -2.003394 | -3.922221 | -4.317654 |
| MIRLET7BHG | -2.531447 | -0.897316 | -1.841817 | -1.91789 |
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| KRT19 | -5.379099 | -2.338309 | -5.222941 | -5.889293 |
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| HIC1 | -1.533096 | -0.887847 | -1.557124 | -1.698693 |
| FGL1 | -2.620135 | -0.981948 | -1.626025 | -2.592522 |
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| KRT19P2 | -6.792731 | -2.181063 | -5.802415 | -6.555854 |
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| FHL2 | -5.362783 | -3.224431 | -1.138691 | -4.396923 |
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| ENPP5 | -3.820013 | -1.285826 | -2.326345 | -4.341965 |
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| CDK14 | -2.306381 | -1.120282 | -0.923901 | -2.207405 |
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| RBP1 | -3.860967 | -2.274169 | -1.631713 | -3.772826 |
| PLA2R1 | -2.627585 | -1.211195 | -1.119151 | -2.839499 |
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| NAF1 | -2.529807 | -0.903117 | -0.946503 | -1.672926 |
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| THRA | -2.24537 | -1.309455 | -1.120137 | -3.638706 |
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| MMP19 | -2.449987 | -2.312766 | -3.161294 | -1.443002 |
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| NMT2 | -2.409153 | -2.469436 | -3.83821 | -1.376866 |
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| HPR | -5.518806 | -2.592302 | -5.215267 | -2.403309 |
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| RASL11A | -2.479655 | -1.008808 | -2.079537 | -1.053934 |
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| TNFSF14 | -4.773809 | -3.010053 | -5.356077 | -0.719342 |
| GSTT2 | -3.197281 | -1.918925 | -2.92816 | -0.749215 |
| MAN1A1 | -4.083285 | -1.986207 | -3.373772 | -0.922372 |
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| CD177 | -3.504896 | -3.295407 | -2.953377 | -3.725225 |
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| RPL41 | -1.299935 | -1.252779 | -1.140477 | -1.336631 |
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| TRH | -5.689908 | -5.075307 | -4.779907 | -3.514565 |
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| IRS2 | -3.537241 | -3.687132 | -3.406878 | -1.89891 |
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| FOXP1 | -1.547478 | -1.813858 | -1.56515 | -0.870894 |
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| PPP1R12B | -3.152048 | -3.694548 | -3.299257 | -1.930625 |
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| MYO15B | -3.100328 | -1.43696 | -1.803283 | -1.588721 |
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| APOD | -5.079258 | -3.339104 | -3.773924 | -3.147435 |
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| LGR4 | -3.18192 | -3.72962 | -2.713643 | -2.428934 |
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| D4S234E | -3.22425 | -4.286537 | -2.259633 | -2.2925 |
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| EPS15 | -0.977373 | -1.461988 | -0.704661 | -0.742534 |
| ITGB8 | -2.082652 | -3.144721 | -1.323627 | -1.501442 |
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| FGF13 | -4.542945 | -5.025168 | -5.060659 | -0.776709 |
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| LPL | -3.512585 | -4.197777 | -4.037364 | -0.913738 |
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| TIE1 | -2.945834 | -2.336581 | -2.385827 | -0.70694 |
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| PLXDC2 | -3.530998 | -2.603122 | -2.768306 | -1.207704 |
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| ATP8A2 | -3.543771 | -3.334489 | -2.681567 | -0.962416 |
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| EMILIN1 | -3.474889 | -2.99346 | -2.398989 | -0.910331 |
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| MYLIP | -3.853333 | -4.526414 | -3.557427 | -0.714774 |
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| THSD7A | -4.092526 | -5.755896 | -3.88446 | -1.49187 |
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| EMCN | -3.324343 | -4.201968 | -3.566486 | -1.243449 |
| UTS2D | -3.061384 | -3.950267 | -3.584374 | -1.150003 |
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| LIFR | -4.485724 | -5.646939 | -3.971101 | -1.538708 |
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| SHE | -3.226907 | -3.972046 | -3.005341 | -1.045216 |
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| HOXD3 | -3.912606 | -4.676231 | -3.382429 | -1.853836 |
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| PGRMC1 | -1.927957 | -2.052925 | -1.873789 | -0.760434 |
| GRB10 | -3.697016 | -4.194788 | -3.540354 | -1.593036 |
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| RPLP1 | -1.388643 | -2.476151 | -2.082071 | -0.845455 |
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| MYO19 | 0.881397 | 1.715247 | 1.096768 | 1.344878 |
| NFKBID | 0.779341 | 2.441694 | 1.522584 | 1.58934 |
| CAPN12 | 1.090101 | 1.642289 | 0.905428 | 1.671751 |
| HMGA1 | 1.221219 | 2.073002 | 1.132999 | 1.819384 |
| NDE1 | 1.997964 | 3.518814 | 1.722288 | 2.798203 |
| COX8A | 0.913795 | 1.427934 | 1.082756 | 1.389644 |
| FAM57B | 1.010798 | 1.585021 | 1.155669 | 1.498619 |
| ECE2 | 1.506852 | 2.238917 | 1.718221 | 2.184682 |
| BAK1 | 0.928171 | 1.569731 | 1.0658 | 1.537278 |
| CDR2L | 1.704703 | 2.582846 | 1.74506 | 2.388615 |
| TAF8 | 0.956202 | 1.474728 | 0.975051 | 1.376959 |
| TECPR1 | 0.779886 | 1.294175 | 0.795792 | 1.109937 |
| TTYH3 | 1.107812 | 1.881814 | 1.208772 | 1.612565 |
| MRPS12 | 0.770497 | 1.795569 | 1.023033 | 1.545446 |
| PML | 1.219124 | 2.746512 | 1.425204 | 2.422975 |
| EXOSC6 | 1.437903 | 1.823925 | 0.876256 | 1.429016 |
| LOC100130009 | 2.802852 | 3.501706 | 1.758979 | 2.865709 |
| VAC14 | 1.209756 | 1.71304 | 0.853095 | 1.393434 |
| RNF126 | 1.259687 | 1.580364 | 0.862389 | 1.499263 |

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| RAP1GAP2 | 2.247393 | 3.343151 | 1.096543 | 2.177999 |
| AQP4 | 1.788783 | 3.836401 | 1.024163 | 1.527402 |
| CLPTM1L | 0.925987 | 1.889691 | 0.991099 | 0.946064 |
| FBXW5 | 0.777747 | 1.531348 | 0.75311 | 0.828123 |
| CCL15 | 1.115035 | 1.833141 | 0.951852 | 1.021994 |
| MDM1 | 1.217268 | 2.142556 | 1.072045 | 1.181194 |
| ZC3H18 | 1.021773 | 1.600994 | 0.863153 | 0.98297 |
| SNX17 | 0.794001 | 1.354707 | 0.80737 | 0.757978 |
| MRPL37 | 0.967342 | 1.745487 | 0.755875 | 0.755624 |
| PSME3 | 1.155466 | 2.270188 | 0.920593 | 1.025868 |
| SEPN1 | 0.88989 | 1.951768 | 0.867836 | 0.858084 |
| DNAJC11 | 0.744497 | 2.688455 | 2.365142 | 1.945936 |
| DPF1 | 1.280893 | 3.495693 | 2.905795 | 2.665327 |
| PARD6B | 1.171384 | 3.339966 | 2.566467 | 2.85398 |
| TMEM160 | 0.773229 | 1.69602 | 1.299635 | 1.570947 |
| AMOTL1 | 0.805188 | 1.090992 | 1.393205 | 1.178219 |
| AP1S3 | 1.650453 | 2.074588 | 2.599699 | 2.274415 |
| ASPHD2 | 1.516245 | 1.843858 | 2.212421 | 1.890018 |
| DHFR | 1.25616 | 1.576881 | 1.845769 | 1.465742 |
| ARHGEF2 | 1.113228 | 1.532216 | 1.856666 | 1.431874 |
| RRM1 | 0.735966 | 1.002219 | 1.210215 | 0.944178 |
| CTSL2 | 4.057615 | 4.552857 | 5.269371 | 4.739817 |
| ENTPD4 | 0.808694 | 0.958332 | 1.071261 | 1.006891 |
| DGCR11 | 0.992547 | 1.090066 | 1.38542 | 1.269568 |
| HMGB1 | 0.816264 | 0.89618 | 1.068926 | 1.024636 |
| BZW1 | 0.802355 | 1.053949 | 1.237454 | 1.208889 |
| POLR3G | 1.152235 | 1.44046 | 1.660066 | 1.668365 |
| HS1BP3 | 1.823988 | 2.359866 | 2.664732 | 2.464449 |
| PDLIM7 | 0.75739 | 1.022721 | 1.081254 | 0.98552 |
| ALG10 | 0.797032 | 0.907646 | 1.302129 | 1.18512 |
| LHX1 | 1.904947 | 1.894174 | 2.871732 | 2.503553 |
| RPRML | 2.793962 | 2.745113 | 4.260672 | 3.758763 |
| PRPS1L1 | 0.849351 | 0.827054 | 1.368375 | 1.200237 |
| JHDM1D | 0.747009 | 0.8236 | 1.162374 | 0.9313 |
| DIAPH1 | 2.000343 | 1.913432 | 2.883914 | 2.303174 |
| LOC153811 | 0.941823 | 0.945903 | 1.406093 | 1.070936 |
| MAML3 | 1.588836 | 1.499044 | 2.1517 | 1.752342 |
| SLC39A9 | 0.882705 | 0.890111 | 1.208256 | 0.983585 |
| BAG6 | 0.778895 | 0.776006 | 1.147364 | 0.832168 |
| NRF1 | 0.808606 | 0.822944 | 1.157702 | 0.836261 |

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| NUDT5 | 1.352534 | 1.241249 | 1.796238 | 1.388262 |
| ZNF695 | 4.106152 | 3.675489 | 5.355855 | 3.926539 |
| HMGB3 | 1.660467 | 1.983161 | 2.693196 | 1.843742 |
| PAK4 | 0.908306 | 0.997547 | 1.376854 | 0.954432 |
| DLX2 | 3.225001 | 3.517765 | 5.440762 | 3.632571 |
| XRCC4 | 1.034183 | 1.037671 | 1.632418 | 1.017128 |
| ELOVL4 | 0.892832 | 1.062468 | 1.816016 | 1.079844 |
| MFSD6 | 1.475605 | 1.665897 | 2.909701 | 1.650898 |
| DUSP6 | 1.415514 | 2.026853 | 3.108498 | 2.138042 |
| POLG | 0.758278 | 1.043568 | 1.826879 | 1.263953 |
| TRAF4 | 0.939883 | 1.614938 | 2.168131 | 1.501516 |
| LRRC8D | 0.775595 | 0.758334 | 1.585203 | 1.118957 |
| MYL12A | 1.05839 | 1.124994 | 1.95892 | 1.439657 |
| BU963192 | 2.467836 | 3.925011 | 3.977574 | 2.488128 |
| ERF | 1.090966 | 1.600266 | 1.636151 | 1.103326 |
| MPHOSPH9 | 1.246976 | 1.831054 | 1.835321 | 1.184822 |
| FBXO5 | 1.349479 | 1.791017 | 1.90021 | 1.130762 |
| GEN1 | 1.288789 | 1.744354 | 1.857504 | 1.178326 |
| MCM6 | 1.220984 | 1.644975 | 1.731224 | 1.083626 |
| INTS6 | 1.104398 | 1.903401 | 1.768792 | 1.103866 |
| HSPA8 | 1.455195 | 2.496142 | 2.526359 | 1.713705 |
| SLC29A4 | 1.120563 | 2.038145 | 2.103076 | 1.307487 |
| CCNYL1 | 1.034069 | 1.440263 | 1.839725 | 1.207423 |
| EIF4E2 | 0.740665 | 0.975189 | 1.27103 | 0.87676 |
| APBA2 | 1.507762 | 2.518352 | 2.773577 | 1.928072 |
| INA | 3.957469 | 6.167879 | 7.156875 | 4.825051 |
| MAP7D2 | 2.404341 | 3.564381 | 4.375058 | 2.779991 |
| ZNF154 | 1.450033 | 2.266868 | 2.896845 | 1.890186 |
| NETO2 | 2.983575 | 4.412993 | 5.330754 | 3.04389 |
| TMEM106C | 0.795513 | 1.177319 | 1.321282 | 0.816605 |
| UBB | 0.791521 | 1.236156 | 1.387086 | 0.836823 |
| UXS1 | 1.182027 | 1.68337 | 1.864429 | 1.102732 |
| LOC729737 | 1.300467 | 1.752557 | 2.86551 | 1.342368 |
| NPAS1 | 1.881415 | 2.451863 | 3.725171 | 1.494243 |
| CBFB | 0.763603 | 1.04618 | 1.39859 | 0.724783 |
| SGK494 | 0.985107 | 1.450637 | 1.951026 | 0.923804 |
| SYCP2 | 1.858573 | 3.418942 | 4.504592 | 2.168995 |
| TMEM180 | 0.766507 | 1.201642 | 1.736534 | 0.760573 |
| ZNF260 | 1.097836 | 1.790242 | 2.41674 | 1.387276 |
| FZD8 | 0.859643 | 3.163298 | 3.652983 | 2.876471 |

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| MMP14 | 0.955093 | 2.365278 | 3.055518 | 1.75848 |
| TGFB2 | 0.925122 | 1.850273 | 3.457008 | 2.233038 |
| CDC42SE1 | 0.768699 | 1.302074 | 1.723334 | 1.614232 |
| SLC22A23 | 0.81597 | 1.398936 | 1.911848 | 1.751944 |
| TPM3 | 1.242906 | 1.873853 | 2.621842 | 2.170401 |
| SLC4A11 | 1.240496 | 2.428904 | 3.173947 | 3.456626 |
| CTAG2 | 4.419884 | 4.227623 | 3.933281 | 3.961536 |
| GPRIN1 | 3.808018 | 3.614205 | 3.41376 | 3.314581 |
| CDC23 | 1.697636 | 1.54717 | 1.505753 | 1.467852 |
| HIST1H2AM | 2.84088 | 2.568491 | 2.486181 | 2.48337 |
| APC2 | 4.250757 | 3.911481 | 3.735418 | 3.845603 |
| HCRP1 | 2.171363 | 1.987379 | 1.869857 | 1.932976 |
| KCNN1 | 4.082386 | 3.645808 | 3.491926 | 3.562511 |
| SMC1A | 1.680092 | 1.52352 | 1.422728 | 1.46069 |
| CELSR3 | 4.357431 | 4.004193 | 3.97173 | 3.738697 |
| NCRNA00306 | 4.229269 | 3.897797 | 3.869407 | 3.588999 |
| MAD2L1 | 3.486282 | 3.146325 | 3.091739 | 2.896363 |
| B4GALNT1 | 4.265462 | 3.765163 | 3.715715 | 3.579643 |
| EIF4G3 | 2.112315 | 1.804968 | 1.853088 | 1.72108 |
| HIST1H2AK | 2.483583 | 2.140114 | 2.162652 | 2.00042 |
| TRAIP | 2.396658 | 2.081239 | 2.129688 | 1.952788 |
| PBX2 | 2.138895 | 1.840601 | 1.906604 | 1.782959 |
| ATCAY | 3.733422 | 3.31501 | 3.419035 | 3.48153 |
| CRMP1 | 4.440754 | 3.801275 | 3.967118 | 4.168868 |
| CDK8 | 1.452743 | 1.190341 | 1.265837 | 1.344204 |
| MGA | 0.918506 | 0.765376 | 0.794535 | 0.855775 |
| HIST1H2AI | 4.534172 | 3.756908 | 3.974829 | 4.142684 |
| SRRM2 | 1.670332 | 1.383331 | 1.401983 | 1.552185 |
| BRI3BP | 2.815925 | 2.414594 | 2.582482 | 2.46888 |
| MBTPS2 | 0.918885 | 0.76857 | 0.827736 | 0.803207 |
| MDN1 | 1.568328 | 1.330359 | 1.378045 | 1.366827 |
| PSMD11 | 1.978171 | 1.63244 | 1.719445 | 1.743362 |
| SNORD15A | 3.481221 | 2.850111 | 2.96488 | 2.932933 |
| HES6 | 2.182408 | 1.681539 | 1.773432 | 1.694383 |
| HIST1H2AH | 2.683069 | 2.141005 | 2.269767 | 2.157146 |
| HSF5 | 3.380598 | 2.668954 | 2.900299 | 2.709185 |
| BRIP1 | 5.348893 | 4.281789 | 4.40903 | 4.289937 |
| HIST1H2AJ | 2.278221 | 1.875355 | 1.895477 | 1.784979 |
| VGF | 3.579804 | 2.980606 | 3.01679 | 2.907084 |
| CHEK2 | 2.305673 | 1.949442 | 2.005844 | 1.753422 |

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| HIST1H2BF | 3.518883 | 2.861474 | 3.0527 | 2.67509 |
| NYNRIN | 2.033695 | 1.66942 | 1.843764 | 1.506845 |
| DIDO1 | 1.069166 | 0.800743 | 0.92072 | 0.842968 |
| LRWD1 | 1.786478 | 1.439048 | 1.605323 | 1.432675 |
| NUP88 | 1.630134 | 1.2993 | 1.450086 | 1.265864 |
| LYPD6 | 2.605493 | 2.020909 | 2.246946 | 1.953998 |
| TAOK1 | 1.080051 | 0.817394 | 0.917217 | 0.823078 |
| ZFAND3 | 1.432083 | 1.106118 | 1.236374 | 1.024295 |
| CELF1 | 2.218851 | 1.822036 | 1.731579 | 2.034189 |
| CACNA1B | 4.791566 | 3.766339 | 3.851339 | 4.335287 |
| HSPA4 | 1.506144 | 1.1796 | 1.209477 | 1.40072 |
| RCC1 | 2.407506 | 1.823963 | 1.828819 | 2.169495 |
| COG4 | 1.7458 | 1.339563 | 1.14045 | 1.451087 |
| FAM192A | 1.152627 | 0.814503 | 0.754152 | 0.938439 |
| CNOT1 | 1.816168 | 1.418056 | 1.28722 | 1.559324 |
| NCRNA00292 | 2.518571 | 1.97329 | 1.819638 | 2.120312 |
| KIF5A | 5.369296 | 4.016049 | 3.819041 | 4.46 |
| TLK2 | 1.227679 | 0.94561 | 0.92237 | 1.052671 |
| NR6A1 | 3.123558 | 2.475059 | 2.359988 | 2.58356 |
| RAPGEF6 | 2.100077 | 1.503702 | 1.522418 | 1.722093 |
| EFTUD2 | 2.281719 | 1.682018 | 1.529659 | 1.656017 |
| COQ4 | 2.166494 | 1.605215 | 1.41038 | 1.680497 |
| LRPPRC | 2.024306 | 1.509879 | 1.357909 | 1.551168 |
| SNORA73A | 3.114258 | 2.329699 | 1.993735 | 2.329594 |
| CDK13 | 1.22832 | 0.939983 | 0.869525 | 0.891728 |
| LOC652586 | 1.449354 | 1.095504 | 1.035046 | 1.013821 |
| HSP90AA1 | 1.061825 | 0.805142 | 0.815641 | 0.763244 |
| MLLT4 | 1.355091 | 0.930788 | 1.004684 | 0.982244 |
| MSL1 | 2.155544 | 1.551359 | 1.579851 | 1.572446 |
| RDM1 | 4.683771 | 3.411155 | 3.411368 | 3.431712 |
| STH | 4.75897 | 3.173036 | 3.259578 | 3.51458 |
| WHSC1L1 | 1.847036 | 1.260238 | 1.237495 | 1.407037 |
| CACNG7 | 3.210043 | 2.791078 | 2.318973 | 2.527188 |
| CDK12 | 1.897422 | 1.709363 | 1.349173 | 1.579698 |
| PRR7 | 2.468588 | 2.197088 | 1.778481 | 2.099537 |
| HUWE1 | 1.421624 | 1.213434 | 0.980287 | 1.198338 |
| NOL9 | 1.095074 | 0.936993 | 0.71744 | 0.920123 |
| CK825926 | 1.473303 | 1.249099 | 1.097875 | 1.11695 |
| HIST1H2AC | 3.499343 | 2.847918 | 2.661659 | 2.609438 |
| MAP3K9 | 2.545952 | 2.105566 | 1.92275 | 1.950346 |

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| MZT1 | 1.492404 | 1.19545 | 1.091124 | 1.149698 |
| PPME1 | 1.240696 | 0.982425 | 0.922689 | 0.966674 |
| CLSTN3 | 2.095179 | 1.940365 | 1.680294 | 1.644017 |
| NCAPD3 | 1.480151 | 1.288597 | 1.204885 | 1.118414 |
| EIF5B | 0.910999 | 0.788994 | 0.74002 | 0.708874 |
| SECISBP2L | 1.05455 | 0.92267 | 0.854075 | 0.82368 |
| RAN | 1.227922 | 1.084333 | 1.003101 | 0.951602 |
| DLGAP3 | 2.628634 | 2.434986 | 2.114313 | 2.290796 |
| RPL36A-HNRNPH2 | 1.73241 | 1.527941 | 1.370647 | 1.49826 |
| SF3B3 | 1.950628 | 1.740677 | 1.587417 | 1.660532 |
| KREMEN2 | 5.515251 | 4.893763 | 4.30738 | 4.539984 |
| SERBP1 | 1.264803 | 1.142479 | 1.022669 | 1.02694 |
| CIRH1A | 1.155796 | 0.929512 | 0.726415 | 0.758906 |
| ANUBL1 | 1.577066 | 1.266693 | 1.116818 | 1.101202 |
| PTPRS | 1.597823 | 1.348059 | 1.159422 | 1.095036 |
| TAF5 | 1.615882 | 1.346487 | 1.177706 | 1.091845 |
| AGFG1 | 1.488156 | 1.239538 | 1.013814 | 1.036708 |
| LSM12 | 1.907963 | 1.661277 | 1.28262 | 1.368799 |
| USP37 | 1.402132 | 1.193497 | 0.933116 | 1.002241 |
| ODF2 | 1.269411 | 1.053353 | 0.878399 | 0.944454 |
| TUBG1 | 2.019073 | 1.639604 | 1.356712 | 1.484661 |
| BCL2L10 | 1.479932 | 1.414635 | 1.380509 | 1.742433 |
| INCENP | 2.972362 | 2.875375 | 2.657556 | 3.479617 |
| PIKFYVE | 1.355654 | 1.219181 | 1.219011 | 1.577892 |
| HPCA | 1.905054 | 1.823068 | 1.593026 | 2.216203 |
| ARNTL2 | 2.857635 | 3.128631 | 3.31926 | 3.885844 |
| CDK1 | 4.089279 | 4.211971 | 4.321029 | 5.389404 |
| BLM | 3.0188 | 3.012455 | 3.148275 | 3.485095 |
| NAT15 | 2.035089 | 2.096836 | 2.176214 | 2.435867 |
| KIF14 | 4.722315 | 4.895732 | 4.88617 | 5.514556 |
| BAX | 2.078869 | 2.155683 | 2.272625 | 2.594951 |
| SNRPG | 1.294986 | 1.262807 | 1.335722 | 1.580499 |
| TSTD2 | 1.490318 | 1.528435 | 1.51712 | 1.818417 |
| CCDC18 | 1.90643 | 2.099989 | 2.029687 | 2.413211 |
| GSPT1 | 1.156304 | 1.260859 | 1.200154 | 1.434628 |
| ALDH4A1 | 3.054317 | 3.515086 | 3.328178 | 4.00098 |
| NIPAL3 | 1.527227 | 1.715058 | 1.690994 | 1.976451 |
| FOXA3 | 1.316858 | 1.505059 | 1.285346 | 1.638768 |
| NKAIN1 | 3.70353 | 4.288472 | 3.708978 | 4.768172 |
| RASGRP2 | 1.765818 | 2.030878 | 1.836674 | 2.276297 |

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| PSMA2 | 0.709213 | 0.875543 | 0.750842 | 0.960039 |
| BUB1 | 4.435297 | 4.60646 | 4.813198 | 4.913734 |
| FBN3 | 3.846847 | 4.114398 | 4.402526 | 4.437413 |
| CDC45 | 4.396595 | 4.617811 | 4.417138 | 4.795356 |
| CDCA2 | 4.555484 | 4.71107 | 4.582453 | 4.861692 |
| CASC5 | 4.899601 | 5.243059 | 5.188162 | 5.385652 |
| DIAPH3 | 3.249707 | 3.447576 | 3.421691 | 3.581443 |
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| MAP4 | 2.22931 | 2.462015 | 2.299408 | 2.406922 |
| NUP205 | 1.015723 | 1.11419 | 1.036301 | 1.129453 |
| SPC25 | 4.371876 | 4.834031 | 4.463282 | 4.862196 |
| SLC39A3 | 1.365383 | 1.512993 | 1.365031 | 1.499184 |
| LPCAT1 | 1.373158 | 1.498972 | 1.436089 | 1.618154 |
| CCNA2 | 3.691192 | 4.212589 | 3.974459 | 4.010875 |
| MAN1B1 | 2.857053 | 3.270884 | 2.995698 | 3.058447 |
| KIF20B | 1.291788 | 1.442979 | 1.401098 | 1.37328 |
| OTUD5 | 2.318479 | 2.552027 | 2.550474 | 2.426103 |
| CDCA8 | 3.735686 | 4.215989 | 4.180041 | 4.240089 |
| PTTG1 | 3.094042 | 3.41333 | 3.401685 | 3.463609 |
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| RAB1B | 3.177104 | 3.797275 | 3.708494 | 3.748195 |
| ACYP1 | 0.908964 | 0.963899 | 0.871627 | 0.90591 |
| CENPM | 3.49758 | 3.644811 | 3.28311 | 3.468971 |
| CDT1 | 3.239508 | 3.434726 | 3.146157 | 3.377685 |
| CTAG1A | 5.664017 | 5.288809 | 5.281115 | 5.342732 |
| E2F2 | 4.10359 | 3.881551 | 3.84226 | 3.842409 |
| PANK2 | 0.938349 | 0.891401 | 0.90117 | 0.879875 |
| KIAA0101 | 5.62983 | 5.441498 | 5.234522 | 5.524203 |
| CDC25C | 5.094482 | 5.13122 | 4.876106 | 4.991802 |
| DLGAP5 | 4.612542 | 4.691834 | 4.432862 | 4.557112 |
| GINS4 | 2.258555 | 2.258879 | 2.271525 | 2.243643 |
| HJURP | 4.934833 | 5.006027 | 4.882535 | 4.924847 |
| TCF19 | 2.037642 | 1.990497 | 2.024328 | 2.03901 |
| CDKN2AIPNL | 2.326835 | 2.243866 | 1.999891 | 2.199826 |
| SON | 1.221299 | 1.174527 | 1.039884 | 1.122383 |
| STK35 | 1.93232 | 1.804974 | 1.64137 | 1.786032 |
| ECHDC1 | 1.298927 | 1.17201 | 1.353716 | 1.270568 |
| ICA1 | 1.757769 | 1.620492 | 1.785803 | 1.7469 |
| ATAD5 | 2.432925 | 2.283826 | 2.582647 | 2.515677 |
| CHEK1 | 3.773821 | 3.669491 | 4.039998 | 3.946252 |

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| LOC100131257 | 0.899183 | 0.882599 | 1.00603 | 0.968291 |
| NR2C2 | 0.914773 | 0.866722 | 1.005014 | 0.967916 |
| KIF2A | 1.48757 | 1.382958 | 1.595488 | 1.605484 |
| EEF1A2 | 3.571661 | 3.459139 | 3.586951 | 3.738054 |
| BCAS4 | 3.723128 | 3.540952 | 3.730884 | 3.782257 |
| PSMB6 | 1.148826 | 1.074201 | 1.144843 | 1.174506 |
| RNASEH1 | 1.071494 | 1.005463 | 1.073297 | 1.113943 |
| SBK1 | 3.468048 | 3.408091 | 3.576821 | 3.616024 |
| CCNB2 | 3.928081 | 3.858409 | 3.817302 | 4.146841 |
| MELK | 5.158414 | 4.957009 | 5.031396 | 5.411084 |
| PDSS1 | 1.083691 | 1.059766 | 1.106993 | 1.186972 |
| SNRPD1 | 1.533327 | 1.543271 | 1.539408 | 1.657346 |
| ZC3H7B | 1.93434 | 1.938056 | 1.971392 | 2.107762 |
| CCDC65 | 1.908406 | 1.949935 | 1.806628 | 2.072268 |
| ENO3 | 1.146797 | 1.165519 | 1.129848 | 1.2742 |
| PASK | 1.942161 | 2.039862 | 1.922656 | 2.153102 |
| E2F1 | 2.768638 | 2.876105 | 2.550836 | 2.982576 |
| TRIP13 | 2.970181 | 3.088464 | 2.725294 | 3.302564 |
| GNB1 | 1.022468 | 1.095961 | 0.980078 | 1.116692 |
| SURF4 | 1.612274 | 1.753061 | 1.565317 | 1.818218 |
| NLRP2 | 4.000657 | 4.484357 | 3.91835 | 4.633126 |
| SEPHS1 | 1.024767 | 1.134389 | 1.024072 | 1.202907 |
| CDCA5 | 3.91472 | 4.001959 | 3.728207 | 4.481138 |
| TUBGCP3 | 0.929188 | 0.97905 | 0.919457 | 1.120354 |
| DENND1A | 2.11932 | 1.86613 | 1.853566 | 2.171189 |
| KLHL12 | 1.779389 | 1.500865 | 1.515334 | 1.792723 |
| HIST1H1D | 3.156294 | 2.78292 | 2.700097 | 3.094233 |
| DDX21 | 1.401481 | 1.319203 | 1.227231 | 1.434198 |
| HIST2H3A | 5.07719 | 4.853464 | 4.667787 | 5.288944 |
| RANBP1 | 0.93347 | 0.874865 | 0.873203 | 0.95699 |
| TK1 | 3.997647 | 3.850102 | 3.654428 | 4.349017 |
| CTDP1 | 1.553593 | 1.421347 | 1.42126 | 1.697807 |
| OIP5 | 3.001156 | 2.704585 | 2.773367 | 3.157287 |
| UCK2 | 1.817503 | 1.713544 | 1.730921 | 1.952981 |
| ATF6B | 2.254206 | 1.805121 | 2.019582 | 2.312513 |
| NHP2 | 0.947159 | 0.811406 | 0.842438 | 0.949686 |
| UBAP2L | 2.077505 | 1.721456 | 1.871349 | 2.058212 |
| WDR67 | 2.20495 | 1.945419 | 2.045189 | 2.219487 |
| SUFU | 1.934068 | 1.596489 | 1.80888 | 1.957969 |
| HIST1H4C | 1.641107 | 2.188521 | 1.845727 | 2.019422 |

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|---|---|---|---|---|
| DDX39A | 1.708127 | 2.033848 | 1.697371 | 1.98877 |
| ARHGAP11A | 3.516368 | 4.337312 | 3.800445 | 4.193092 |
| TXNL4A | 1.248595 | 1.571144 | 1.395826 | 1.511309 |
| ROBO1 | 2.160826 | 2.70155 | 2.307194 | 2.622102 |
| NF2 | 1.322298 | 1.585897 | 1.382463 | 1.60265 |
| PSMD2 | 0.993132 | 1.170599 | 1.064087 | 1.151327 |
| DRAP1 | 1.492872 | 1.842272 | 1.51287 | 1.649147 |
| PKMYT1 | 2.73013 | 3.374004 | 2.927055 | 3.081802 |
| T53825 | 0.746013 | 0.914441 | 0.824156 | 0.818364 |
| CHAF1B | 1.563664 | 1.947735 | 1.772698 | 1.98952 |
| PAFAH1B1 | 1.453359 | 1.838245 | 1.675179 | 1.814022 |
| WDR62 | 2.243419 | 2.863983 | 2.670737 | 2.880056 |
| PRDM15 | 1.671357 | 2.205801 | 2.062914 | 2.171727 |
| NXPH1 | 5.919124 | 7.50244 | 7.531724 | 7.695502 |
| KDM1B | 1.403397 | 1.625253 | 1.610843 | 1.786183 |
| PPIAL4A | 0.912218 | 1.069211 | 1.095684 | 1.159787 |
| RAD51 | 3.334065 | 3.791226 | 3.926565 | 4.101872 |
| CCDC109B | 1.142791 | 0.997836 | 1.081976 | 1.331067 |
| HIST1H4F | 2.12946 | 1.921155 | 2.084169 | 2.404954 |
| NAA16 | 1.069372 | 0.991094 | 1.078532 | 1.245519 |
| RAB39B | 2.662956 | 2.28537 | 2.548604 | 2.921204 |
| HIST1H4I | 1.266472 | 1.170701 | 1.387834 | 1.568999 |
| FOXN4 | 5.133927 | 4.325175 | 5.364681 | 6.138451 |
| HIST2H4B | 1.641032 | 1.399224 | 1.640131 | 2.015152 |
| PHF8 | 1.465943 | 1.253547 | 1.449218 | 1.733558 |
| ATP5G3 | 1.239054 | 1.030691 | 1.324214 | 1.414469 |
| RIMKLA | 3.024474 | 2.585466 | 3.219603 | 3.404972 |
| MFSD8 | 0.993922 | 0.883625 | 1.045876 | 1.120924 |
| SMC6 | 0.84173 | 0.780943 | 0.89603 | 0.987227 |
| EIF4E | 0.885622 | 0.868486 | 0.997232 | 1.057089 |
| HNRNPUL2 | 1.811236 | 1.718937 | 2.083934 | 2.018592 |
| PSMD14 | 0.988296 | 0.972352 | 1.152169 | 1.128151 |
| SGOL1 | 3.284323 | 3.264274 | 3.74927 | 3.794396 |
| ANLN | 3.033827 | 3.717369 | 3.993719 | 2.89298 |
| CSNK1E | 1.401106 | 1.714801 | 1.834857 | 1.316052 |
| CIT | 3.058946 | 3.728911 | 3.848612 | 2.81206 |
| ATP4A | 3.280504 | 4.2809 | 4.441138 | 3.180887 |
| NDUFS6 | 0.742952 | 0.974007 | 1.038733 | 0.764638 |
| RFC4 | 1.429935 | 1.921168 | 2.00326 | 1.457881 |
| E2F8 | 2.707652 | 3.506223 | 3.710877 | 2.877078 |

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|---|---|---|---|---|
| PTTG3P | 2.969943 | 3.706683 | 4.073475 | 2.974191 |
| BARD1 | 1.331646 | 1.618058 | 1.638368 | 1.313871 |
| ERCC6L | 4.215873 | 5.024185 | 5.09133 | 4.009704 |
| CENPF | 3.80337 | 4.178256 | 4.411071 | 3.696913 |
| GPC2 | 2.683217 | 2.971379 | 3.055407 | 2.488162 |
| HYOU1 | 0.939822 | 1.018504 | 1.033411 | 0.85246 |
| CENPK | 3.736762 | 4.235803 | 4.653054 | 3.696453 |
| CTNND1 | 2.218621 | 2.573388 | 2.835151 | 2.215623 |
| KIAA0087 | 1.749764 | 2.034604 | 2.321827 | 1.75981 |
| CDC123 | 1.03977 | 1.085722 | 1.172686 | 0.872526 |
| FBXO43 | 2.791687 | 2.873426 | 3.208172 | 2.294317 |
| NEK2 | 5.489061 | 5.798934 | 6.438763 | 4.84584 |
| G6PD | 1.086967 | 1.143894 | 1.187437 | 0.940103 |
| TROAP | 2.984993 | 3.045624 | 3.275046 | 2.571383 |
| NCAPD2 | 1.8033 | 1.930924 | 2.018548 | 1.485621 |
| DSCC1 | 1.557769 | 1.697172 | 2.076791 | 1.452207 |
| AKIRIN1 | 1.60469 | 1.871307 | 2.348907 | 1.642856 |
| ETV5 | 2.250039 | 2.635304 | 3.217307 | 2.310123 |
| SYNCRIP | 1.447885 | 1.777353 | 2.086151 | 1.526906 |
| ASPM | 3.705656 | 4.371138 | 4.276332 | 3.893897 |
| DNA2 | 2.458859 | 2.912142 | 2.842588 | 2.572974 |
| CHMP7 | 0.963378 | 1.143271 | 1.136264 | 1.000398 |
| GINS3 | 1.429381 | 1.737552 | 1.632523 | 1.534089 |
| CCT6A | 1.092844 | 1.337432 | 1.27882 | 1.133083 |
| PSMC1 | 0.815463 | 1.013423 | 0.937127 | 0.827449 |
| GPSM2 | 1.124759 | 1.412559 | 1.360246 | 1.267201 |
| MGAT5B | 3.338344 | 4.226739 | 4.000994 | 3.84677 |
| DEPDC1B | 3.061362 | 3.845784 | 3.983301 | 3.471714 |
| PRO0471 | 1.807493 | 2.278247 | 2.390272 | 2.147128 |
| ESCO2 | 3.912611 | 4.421046 | 4.751298 | 4.130018 |
| RACGAP1 | 2.279689 | 2.580883 | 2.78399 | 2.471437 |
| NCAPG | 4.702082 | 5.619428 | 5.946212 | 5.047198 |
| CKAP2L | 4.294134 | 5.825287 | 5.843007 | 5.125687 |
| G2E3 | 0.903785 | 1.19919 | 1.197482 | 1.060257 |
| ARPC4 | 1.333998 | 1.887708 | 1.85861 | 1.592819 |
| MECP2 | 1.042445 | 1.483328 | 1.424566 | 1.265833 |
| HNRNPAB | 1.40557 | 1.838136 | 1.779019 | 1.527021 |
| HDGF | 1.681188 | 2.391548 | 2.197619 | 1.930676 |
| YKT6 | 0.866312 | 1.208477 | 1.095338 | 0.978606 |
| SF3A3 | 0.704098 | 1.010362 | 0.934538 | 0.79498 |

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|---|---|---|---|---|
| SLC4A8 | 1.115781 | 1.483116 | 1.33911 | 1.19656 |
| GPRIN2 | 1.469217 | 2.284864 | 2.340216 | 1.92842 |
| SNX22 | 1.903949 | 2.919305 | 2.983439 | 2.405224 |
| RNFT2 | 1.862072 | 2.55225 | 2.791687 | 2.195082 |
| TRIM59 | 1.292024 | 1.861257 | 1.914907 | 1.515893 |
| RACGAP1P | 2.332074 | 3.428539 | 3.114524 | 2.447367 |
| EHMT1 | 2.632838 | 2.69303 | 2.439952 | 2.45395 |
| ASF1B | 3.768383 | 3.756824 | 3.341359 | 3.357143 |
| MLF1IP | 3.908498 | 4.027866 | 3.447446 | 3.464086 |
| MYBL2 | 2.904675 | 2.969442 | 2.48731 | 2.566593 |
| CHTF18 | 1.264122 | 1.447411 | 1.149718 | 1.101604 |
| PAM16 | 1.780515 | 1.970796 | 1.562655 | 1.497131 |
| AGAP7 | 0.831673 | 0.933433 | 0.735832 | 0.764923 |
| CSTF2 | 1.035757 | 1.190015 | 0.978355 | 0.99383 |
| NUP43 | 1.338292 | 1.510797 | 1.221307 | 1.260149 |
| RQCD1 | 1.360365 | 1.459631 | 1.176078 | 1.219463 |
| ESPL1 | 3.578044 | 3.857964 | 3.282906 | 3.062558 |
| IQGAP3 | 2.584862 | 2.654563 | 2.235325 | 2.168184 |
| SLC35E3 | 1.231286 | 1.309287 | 1.079287 | 1.033391 |
| HELLS | 2.996789 | 3.221969 | 2.732388 | 2.72017 |
| RFWD3 | 1.899941 | 2.081822 | 1.78098 | 1.704329 |
| CC2D1A | 1.788587 | 2.050313 | 1.831095 | 1.854565 |
| FOXM1 | 4.490964 | 5.157797 | 4.520505 | 4.605251 |
| CINP | 0.894748 | 1.038748 | 0.950231 | 0.927547 |
| CADM2 | 6.29756 | 6.935144 | 6.414176 | 6.358259 |
| EIF5A | 3.073176 | 3.498324 | 3.148735 | 3.092844 |
| TYMS | 4.406924 | 4.934481 | 4.568613 | 4.363715 |
| AURKA | 2.406867 | 2.605184 | 2.374901 | 2.325087 |
| MKI67 | 4.812218 | 5.321222 | 4.784521 | 4.625136 |
| FANCI | 2.377838 | 2.59442 | 2.348911 | 2.235812 |
| TPX2 | 4.507455 | 4.881177 | 4.417536 | 4.23378 |
| PCDHAC2 | 3.551308 | 3.758751 | 3.395238 | 3.275713 |
| SPC24 | 4.276587 | 4.514845 | 4.105304 | 3.922686 |
| CENPA | 5.077619 | 5.584706 | 5.372245 | 5.108609 |
| BUB1B | 5.245542 | 5.859683 | 5.635675 | 5.301961 |
| MRE11A | 1.079679 | 1.211631 | 1.162881 | 1.093788 |
| CENPE | 3.202111 | 3.381308 | 3.248059 | 3.022579 |
| TTK | 4.779119 | 5.131872 | 5.049048 | 4.646557 |
| DTL | 3.547186 | 3.858869 | 3.846538 | 3.383128 |
| SMARCC1 | 1.459964 | 1.648983 | 1.605321 | 1.438396 |

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|---|---|---|---|---|
| GINS2 | 3.702255 | 3.924309 | 3.661504 | 3.633314 |
| NDC80 | 2.028036 | 2.13518 | 2.062231 | 2.010566 |
| AURKB | 4.240895 | 4.293727 | 4.257477 | 4.0402 |
| UBE2T | 3.578836 | 3.658421 | 3.61219 | 3.396739 |
| SLX4 | 1.379617 | 1.43358 | 1.460215 | 1.351383 |
| CDCA3 | 3.504443 | 3.523368 | 3.291427 | 3.112653 |
| FANCA | 4.423769 | 4.355277 | 4.095108 | 3.952829 |
| GTSE1 | 4.558163 | 4.462963 | 4.325931 | 4.039461 |
| LHX2 | 6.62096 | 6.478988 | 6.243672 | 5.91338 |
| KIF2C | 4.141542 | 4.030465 | 3.976529 | 3.713162 |
| CENPO | 3.243888 | 3.462891 | 3.19621 | 2.809402 |
| HNRNPA2B1 | 1.515553 | 1.654006 | 1.505341 | 1.367659 |
| LMNB2 | 1.939131 | 2.047525 | 1.860273 | 1.733278 |
| POC1A | 3.628031 | 3.772401 | 3.506103 | 3.202272 |
| CDC7 | 2.700601 | 2.865803 | 2.725606 | 2.433898 |
| KIFC1 | 3.794485 | 3.934921 | 3.830444 | 3.390777 |
| PBK | 5.408034 | 5.57545 | 5.397429 | 4.72737 |
| KRTAP19-5 | 1.656399 | 1.733577 | 1.710049 | 1.51376 |
| NCAPG2 | 2.335072 | 2.37064 | 2.270164 | 2.083826 |
| POLQ | 4.043098 | 4.122639 | 4.001844 | 3.715017 |
| ZWINT | 4.10122 | 4.156684 | 4.061519 | 3.708221 |
| GTPBP4 | 1.673653 | 1.697723 | 1.784839 | 1.503897 |
| KIF11 | 3.630784 | 3.719121 | 3.75927 | 3.255586 |
| TIMELESS | 2.853025 | 2.921818 | 3.003846 | 2.571516 |
| EWSR1 | 1.586299 | 1.876757 | 1.61971 | 1.434926 |
| BRD4 | 1.870834 | 2.076151 | 1.857072 | 1.62817 |
| PRC1 | 2.586774 | 2.937649 | 2.612475 | 2.320861 |
| AP3M1 | 0.888629 | 1.030203 | 0.970878 | 0.846194 |
| PVRL1 | 1.685228 | 2.023909 | 1.858899 | 1.63811 |
| DEPDC1 | 3.330836 | 3.76808 | 3.463513 | 3.206154 |
| CCNB1 | 3.119336 | 3.480282 | 3.268706 | 2.891432 |
| UBE2C | 5.513566 | 6.0659 | 5.76653 | 5.130971 |
| SPAG5 | 3.546434 | 3.942921 | 3.716536 | 3.176802 |
| STRN3 | 1.708372 | 1.896333 | 1.790101 | 1.538445 |
| FAM72D | 4.255641 | 4.284707 | 4.019902 | 3.258208 |
| FBXO18 | 1.755657 | 1.772747 | 1.631742 | 1.31012 |
| FAM83D | 3.674042 | 3.846244 | 3.52849 | 2.692584 |
| GON4L | 1.984441 | 2.066331 | 1.880391 | 1.502962 |
| RFXANK | 1.825279 | 1.929121 | 1.764408 | 1.381822 |
| ERH | 0.838734 | 0.933068 | 0.887003 | 0.725638 |

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|---|---|---|---|---|
| KIF23 | 3.444524 | 3.810045 | 3.610817 | 2.973771 |
| CHD2 | 1.717453 | 1.846111 | 1.76146 | 1.415379 |
| NUSAP1 | 2.533188 | 2.746782 | 2.639788 | 2.115906 |
| RTN3 | 3.378364 | 3.659913 | 3.627653 | 2.813363 |
| ARHGAP19 | 1.904071 | 1.951159 | 1.951826 | 1.5498 |
| KIF20A | 4.531727 | 4.72614 | 4.667954 | 3.816765 |
| TNNT1 | 4.31341 | 4.470492 | 4.25862 | 3.534818 |
| TOP2A | 5.331768 | 5.638899 | 5.317842 | 4.396849 |
| CKAP2 | 2.488199 | 2.80569 | 2.596111 | 2.063699 |
| TCF20 | 1.383796 | 1.572874 | 1.395437 | 1.139946 |
| ANKMY1 | 1.309952 | 1.422401 | 1.339332 | 1.012996 |
| SUGP1 | 2.150346 | 2.33709 | 2.150155 | 1.624964 |
| WHSC1 | 2.212389 | 2.377425 | 2.269423 | 1.657695 |
| RFT1 | 1.118113 | 1.217186 | 1.174531 | 0.889588 |
| C1QL4 | 4.290316 | 4.112855 | 4.117283 | 3.412141 |
| DEPDC5 | 1.709004 | 1.650967 | 1.702851 | 1.410726 |
| EPHA10 | 5.882219 | 5.480436 | 5.587692 | 4.40544 |
| DMXL2 | 2.311975 | 2.115862 | 2.059903 | 1.757715 |
| EZH2 | 3.53925 | 3.179255 | 3.235521 | 2.66145 |
| FAM72A | 4.46848 | 4.071631 | 4.091215 | 3.440362 |
| TP53TG3 | 5.109429 | 4.715864 | 4.665247 | 4.06406 |
| TARDBP | 1.856269 | 1.607901 | 1.679048 | 1.388776 |
| BTBD9 | 1.449204 | 1.358448 | 1.3883 | 1.20111 |
| EXO1 | 4.36672 | 4.169685 | 4.059742 | 3.652822 |
| PCDHA11 | 2.263618 | 2.140193 | 2.120969 | 1.904743 |
| RAD54L | 4.368785 | 4.148977 | 3.966412 | 3.503075 |
| NSUN2 | 1.340738 | 1.25084 | 1.18667 | 1.078379 |
| ZDHHC22 | 5.922499 | 5.623778 | 5.265535 | 4.795281 |
| RECQL4 | 3.045391 | 2.806016 | 2.630498 | 2.493338 |
| SPECC1L | 1.818576 | 1.718074 | 1.550461 | 1.512287 |
| ENTPD5 | 1.50622 | 1.529002 | 1.38589 | 1.282081 |
| GINS1 | 2.915631 | 3.009247 | 2.731692 | 2.44678 |
| PCNA | 1.909629 | 1.903949 | 1.817214 | 1.571725 |
| SNRPC | 1.395403 | 1.391985 | 1.323174 | 1.132701 |
| PYCR1 | 4.20367 | 4.302523 | 4.019502 | 3.438972 |
| ZNF259P1 | 1.412274 | 1.447214 | 1.353299 | 1.182929 |
| PPAP2C | 2.65229 | 2.565104 | 2.388623 | 2.042533 |
| CPSF3 | 1.206337 | 1.207124 | 1.041867 | 0.938233 |
| SMG5 | 1.866176 | 1.853656 | 1.621818 | 1.472024 |
| ZNF192 | 1.623551 | 1.643806 | 1.446172 | 1.272562 |

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|---|---|---|---|---|
| RNU1-5 | 2.803987 | 2.712833 | 2.402553 | 2.245723 |
| ENHO | 2.755535 | 2.584216 | 2.698539 | 2.501755 |
| CLSPN | 5.625232 | 5.03202 | 5.590198 | 5.128205 |
| MLLT11 | 2.73729 | 2.489186 | 2.697073 | 2.439383 |
| HMGB3P22 | 2.706827 | 2.463624 | 2.57399 | 2.49124 |
| HMMR | 4.929767 | 4.360644 | 4.7219 | 4.552252 |
| NOP56 | 1.06687 | 0.945746 | 1.044924 | 1.008325 |
| DDX31 | 1.658923 | 1.563756 | 1.589698 | 1.435232 |
| FAM98B | 2.040596 | 1.875252 | 1.995072 | 1.742705 |
| ZBED4 | 1.26229 | 1.19518 | 1.263552 | 1.103488 |
| HNRNPA3 | 0.891146 | 0.835624 | 0.93438 | 0.733622 |
| IGF2BP3 | 6.266605 | 5.643317 | 6.316466 | 5.41863 |
| METTL21A | 2.13944 | 1.8877 | 2.207999 | 1.854828 |
| FBXO22 | 1.778076 | 1.658339 | 1.846994 | 1.513742 |
| SLC35A2 | 1.27173 | 1.199498 | 1.32838 | 1.112531 |
| ZWILCH | 2.149599 | 2.013773 | 2.323862 | 1.894925 |
| ANP32D | 2.160169 | 1.797906 | 2.181219 | 1.83134 |
| ZNF808 | 1.10981 | 0.940174 | 1.124173 | 0.940731 |
| NIPA1 | 2.252932 | 1.905095 | 2.335388 | 1.930781 |
| DLL3 | 3.564496 | 3.35972 | 3.840027 | 3.392892 |
| KIRREL2 | 7.227038 | 7.429472 | 7.878087 | 6.959589 |
| HIST1H4L | 2.105843 | 2.03872 | 2.162841 | 1.998357 |
| KIF4A | 3.75308 | 3.675111 | 3.937348 | 3.526264 |
| RRM2 | 3.398465 | 3.3526 | 3.602828 | 3.269586 |
| GSG2 | 4.376736 | 4.427558 | 5.000023 | 4.290785 |
| WDR76 | 2.326987 | 2.406262 | 2.662203 | 2.274652 |
| RNF44 | 1.09407 | 1.127386 | 1.270917 | 1.022565 |
| ISLR2 | 1.737009 | 1.873371 | 2.012673 | 1.865112 |
| PTTG2 | 3.243148 | 3.530922 | 3.666577 | 3.41884 |
| E2F7 | 3.735946 | 3.821191 | 4.103568 | 3.89652 |
| ZNF682 | 1.954397 | 1.986942 | 2.11061 | 1.949518 |
| NFATC2 | 1.75527 | 1.560571 | 1.987884 | 1.817832 |
| MCM10 | 3.771118 | 3.734607 | 4.538282 | 3.843445 |
| REST | 1.206798 | 1.211456 | 1.448057 | 1.289409 |
| PSME4 | 0.889452 | 0.768227 | 1.000225 | 0.846159 |
| STIL | 3.26236 | 3.002678 | 3.793593 | 3.111542 |
| BAGE | 1.630544 | 0.984461 | 1.57166 | 1.097678 |
| ABCC5 | 1.384154 | 0.871602 | 1.414689 | 0.908379 |
| DNAL1 | 1.853023 | 1.214402 | 1.876929 | 1.212922 |
| CHGA | 2.821995 | 1.870985 | 2.935584 | 1.992315 |

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|---|---|---|---|---|
| CAMKMT | 1.518787 | 1.053136 | 1.40668 | 1.023247 |
| ADK | 1.475345 | 1.07036 | 1.49149 | 1.150545 |
| MTOR | 1.043671 | 0.741654 | 1.006733 | 0.816112 |
| LOC100132077 | 1.695787 | 1.162591 | 1.673883 | 1.224173 |
| LOC729082 | 1.339744 | 0.822554 | 1.217088 | 0.955863 |
| MTX3 | 1.393176 | 0.893201 | 1.241093 | 0.985415 |
| ANO8 | 1.564202 | 1.008174 | 1.617225 | 0.893599 |
| DBN1 | 1.531318 | 1.038466 | 1.707145 | 0.932231 |
| MTL5 | 3.04786 | 2.199773 | 3.205369 | 1.908748 |
| CBL | 1.011277 | 0.717696 | 1.152025 | 0.784636 |
| BRWD3 | 1.15679 | 0.793954 | 1.317912 | 0.901913 |
| HENMT1 | 1.927711 | 1.33144 | 2.201511 | 1.488417 |
| LOC100335030 | 1.817699 | 1.436626 | 2.093114 | 1.458334 |
| VPS13B | 1.540392 | 1.206873 | 1.909476 | 1.237381 |
| EXOC6 | 1.459487 | 1.393823 | 1.923367 | 1.276944 |
| CCNE2 | 3.473826 | 2.9913 | 4.403759 | 2.694945 |
| XIAP | 1.072273 | 0.967444 | 1.44424 | 0.887635 |
| ZNF737 | 1.140928 | 1.036614 | 1.483554 | 0.857219 |
| ANKRD36 | 1.04321 | 0.97995 | 1.20548 | 0.922068 |
| FANCB | 1.368203 | 1.239008 | 1.540091 | 1.197204 |
| PFDN6 | 0.826766 | 0.716634 | 0.933026 | 0.725537 |
| DNMT3B | 2.20642 | 1.986602 | 2.577696 | 1.874693 |
| UBR5 | 0.870532 | 0.780031 | 1.001064 | 0.726325 |
| CEP170 | 1.692528 | 1.467236 | 1.999791 | 1.266657 |
| C8G | 1.268554 | 1.109643 | 1.375634 | 0.958494 |
| POLR2H | 0.977965 | 0.873309 | 1.079011 | 0.733454 |
| NELL2 | 4.919299 | 4.493315 | 5.67038 | 3.914922 |
| TBC1D7 | 1.477179 | 1.354439 | 1.742013 | 1.163875 |
| ABHD15 | 1.943255 | 1.582867 | 1.840231 | 1.522107 |
| ANP32A | 1.991919 | 1.63573 | 1.954951 | 1.544776 |
| WDHD1 | 2.796761 | 2.419781 | 2.672335 | 2.214761 |
| MUC5AC | 2.71069 | 2.339456 | 2.798942 | 2.151619 |
| SMC2 | 3.01491 | 2.588203 | 3.140934 | 2.332091 |
| TLE3 | 1.333504 | 1.113535 | 1.357843 | 0.98365 |
| SLC2A14 | 3.115041 | 2.522172 | 3.156484 | 2.395286 |
| SLC2A3 | 3.572978 | 3.172864 | 3.524488 | 2.713677 |
| POLE2 | 3.166816 | 2.720891 | 3.164144 | 2.30913 |
| ZNF257 | 1.312907 | 1.176227 | 1.340256 | 0.954703 |
| KGFLP1 | 2.357815 | 1.842995 | 2.44966 | 1.575931 |
| SCO1 | 1.310545 | 1.055171 | 1.442583 | 0.951745 |

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| CLASP1 | 1.315156 | 0.836937 | 1.199282 | 1.089452 |
| CSTF3 | 1.869651 | 1.199437 | 1.775808 | 1.547483 |
| SNORA81 | 2.237322 | 1.428628 | 2.068227 | 1.941966 |
| HIST1H3J | 1.423729 | 0.991544 | 1.372526 | 1.320041 |
| EPT1 | 2.142297 | 1.655686 | 2.12109 | 2.111277 |
| TMEM151B | 4.782396 | 3.63641 | 4.670454 | 4.907568 |
| MAGEA2B | 3.806916 | 2.819457 | 3.496714 | 3.577004 |
| SBNO1 | 1.90084 | 1.497606 | 1.701077 | 1.750318 |
| DPYSL5 | 4.774107 | 4.079808 | 4.878107 | 4.840138 |
| MRPL17 | 0.969389 | 0.797174 | 0.997751 | 0.920958 |
| RABEP1 | 1.131497 | 0.916212 | 1.139 | 1.101355 |
| LOC399815 | 4.019596 | 3.243277 | 3.86637 | 3.624313 |
| MAGEA4 | 5.860689 | 4.797765 | 5.717086 | 5.430164 |
| MASTL | 1.628519 | 1.330743 | 1.60943 | 1.462484 |
| SLC35D1 | 1.434264 | 1.120924 | 1.439065 | 1.301019 |
| STX16 | 1.812423 | 1.350216 | 1.725956 | 1.614132 |
| ATR | 1.320479 | 0.934906 | 1.108357 | 1.126602 |
| DCPS | 1.528376 | 1.07967 | 1.300652 | 1.347672 |
| TRIM37 | 2.257908 | 1.509753 | 1.814252 | 1.875627 |
| MCCC2 | 1.424646 | 1.024171 | 1.189582 | 1.176497 |
| SEPHS2 | 1.222445 | 0.938321 | 1.046791 | 1.028192 |
| TSC2 | 1.481044 | 1.137503 | 1.205217 | 1.260826 |
| LOC645676 | 1.311902 | 0.955143 | 1.198658 | 1.056188 |
| SNORA23 | 3.000456 | 2.275824 | 2.757329 | 2.433517 |
| COX7A2 | 0.956758 | 0.735516 | 1.216831 | 1.119437 |
| RBM8A | 1.060532 | 0.791635 | 1.370977 | 1.234832 |
| ASNS | 1.575176 | 1.312419 | 1.929266 | 1.657965 |
| PSMB3 | 1.089898 | 0.932275 | 1.411735 | 1.253609 |
| TMEM206 | 1.637414 | 1.333245 | 2.186724 | 1.766908 |
| ELMO2 | 1.252484 | 0.876153 | 1.413996 | 1.285016 |
| PBRM1 | 1.308722 | 0.924922 | 1.473005 | 1.329785 |
| MFN2 | 3.289749 | 2.50438 | 3.676498 | 3.327693 |
| KIAA1432 | 1.337807 | 1.048397 | 1.432851 | 1.281679 |
| RNF145 | 1.981904 | 1.573439 | 2.186336 | 1.986207 |
| SCARNA10 | 1.949678 | 1.408025 | 2.046944 | 1.786751 |
| RFX5 | 1.321414 | 0.85845 | 1.338275 | 1.299153 |
| NT5C2 | 1.37261 | 1.071705 | 1.521366 | 1.21395 |
| DPPA3 | 3.863249 | 4.927978 | 3.712288 | 4.046712 |
| FAM64A | 3.386843 | 4.359669 | 3.415421 | 3.522815 |
| NDUFAB1 | 1.067926 | 1.293991 | 0.981508 | 1.039301 |

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| COMMD4 | 0.764759 | 1.008536 | 0.741399 | 0.751578 |
| COPS7B | 1.191349 | 1.616022 | 1.212726 | 1.187807 |
| MAZ | 1.693653 | 2.30528 | 1.773893 | 1.755958 |
| ORC1 | 3.52589 | 4.90275 | 3.66589 | 3.777523 |
| TMEM222 | 1.473883 | 2.054935 | 1.569387 | 1.474886 |
| BUB3 | 0.931016 | 1.252421 | 1.029999 | 1.002571 |
| RCC2 | 1.579502 | 2.066538 | 1.707522 | 1.637104 |
| MAGEC1 | 2.100761 | 2.721576 | 2.273532 | 2.296217 |
| ATG4D | 0.855188 | 1.233718 | 1.029838 | 0.993186 |
| MAPK1IP1L | 0.740099 | 1.020751 | 0.86611 | 0.842119 |
| FMNL1 | 2.266886 | 3.067969 | 2.523417 | 2.622682 |
| LYPLA2 | 1.545453 | 2.155655 | 1.744437 | 1.808984 |
| TOMM40 | 2.682335 | 3.722844 | 2.959742 | 3.190127 |
| CDC20 | 2.505027 | 3.339518 | 2.63953 | 2.304932 |
| NOC2L | 1.460962 | 1.919705 | 1.459787 | 1.278971 |
| RANBP3 | 1.34276 | 1.797464 | 1.36415 | 1.236753 |
| EIF2B2 | 0.895495 | 1.115777 | 0.876238 | 0.8443 |
| LOC389906 | 1.817501 | 2.309752 | 1.742924 | 1.666415 |
| SNRPB | 2.180345 | 2.749853 | 2.068939 | 1.974843 |
| RAB3D | 1.235299 | 1.717729 | 1.195652 | 1.200729 |
| CFL1 | 2.659245 | 3.34537 | 2.811453 | 2.35596 |
| FLJ45340 | 2.108987 | 2.51712 | 2.210853 | 1.846992 |
| MCM7 | 2.324544 | 2.862835 | 2.485119 | 1.948183 |
| CPT1C | 1.950435 | 2.594097 | 2.167009 | 1.798005 |
| USP12 | 1.826971 | 2.434271 | 2.070439 | 1.616782 |
| MAP7D1 | 1.140107 | 1.525009 | 1.239061 | 0.964123 |
| SRSF7 | 0.894785 | 1.211639 | 0.976877 | 0.799178 |
| YRDC | 0.845204 | 1.164693 | 0.917573 | 0.747009 |
| FEN1 | 2.503819 | 3.001142 | 2.656835 | 2.476081 |
| SMC4 | 2.052676 | 2.481338 | 2.158431 | 2.038575 |
| AGAP1 | 1.102363 | 1.430359 | 1.177829 | 1.050514 |
| MND1 | 3.548565 | 4.430935 | 3.956074 | 3.393299 |
| ZNF746 | 1.375863 | 1.747553 | 1.534928 | 1.341335 |
| SHCBP1 | 3.042129 | 3.915323 | 3.418446 | 3.063447 |
| KIAA1598 | 0.870271 | 1.454667 | 1.089288 | 1.108965 |
| MCM5 | 1.218907 | 2.039881 | 1.320136 | 1.443717 |
| PFN1 | 1.608636 | 2.470679 | 1.699341 | 1.7938 |
| H1FX | 1.428466 | 2.342593 | 1.766674 | 1.566435 |
| FBXO22OS | 1.56287 | 2.380449 | 1.873994 | 1.655254 |
| MED22 | 0.723049 | 1.089405 | 0.814522 | 0.761291 |

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| SPINLW1 | 3.115793 | 4.740062 | 3.555781 | 3.21758 |
| SCAND1 | 0.996668 | 1.474802 | 1.107059 | 1.05803 |
| VHLL | 2.086354 | 3.110404 | 2.305269 | 2.251037 |
| CCNE1 | 2.302948 | 1.905078 | 1.576043 | 2.72331 |
| CDH10 | 8.407965 | 6.792045 | 5.497199 | 9.128197 |
| MGAT1 | 1.8162 | 1.482136 | 1.105548 | 1.962365 |
| GLT1D1 | 2.305186 | 1.800989 | 1.310095 | 2.507192 |
| ARPC5L | 1.428141 | 1.106431 | 0.86162 | 1.408848 |
| RLTPR | 2.729645 | 2.191731 | 1.665874 | 2.786083 |
| KDM2B | 1.93302 | 1.598316 | 1.208958 | 1.889638 |
| HEATR3 | 2.022766 | 1.708676 | 1.390028 | 2.07071 |
| TCEB3 | 1.900076 | 1.502704 | 1.285327 | 1.841109 |
| CYCS | 1.274023 | 1.049807 | 0.946437 | 1.348946 |
| FSD1 | 2.716148 | 2.248413 | 1.945892 | 2.956189 |
| HIST1H3D | 2.18147 | 1.834096 | 1.611962 | 2.392785 |
| MANEAL | 2.777933 | 2.398695 | 2.096718 | 3.139016 |
| HAS3 | 2.422883 | 2.006063 | 1.893261 | 2.689539 |
| DGKA | 1.918219 | 1.532918 | 1.546858 | 2.269042 |
| DAZAP1 | 1.056233 | 0.90966 | 0.835768 | 1.329015 |
| SRGAP2 | 1.794906 | 1.598653 | 1.482355 | 2.285893 |
| OPA1 | 1.121272 | 1.010044 | 0.895684 | 1.342585 |
| RMRP | 1.902579 | 1.664361 | 1.471716 | 2.277095 |
| HN1L | 1.692566 | 1.545579 | 1.178217 | 2.00588 |
| PA2G4 | 1.289658 | 1.201553 | 0.938141 | 1.473738 |
| SRPK1 | 1.059254 | 0.74091 | 0.721262 | 1.078525 |
| ATP1A3 | 1.56632 | 1.544759 | 0.980322 | 1.948516 |
| NOP16 | 1.519752 | 1.629055 | 0.894921 | 1.923404 |
| ATAD3C | 1.48561 | 1.629667 | 1.11167 | 1.967342 |
| ZDHHC24 | 1.168498 | 1.268735 | 0.789494 | 1.564512 |
| FITM2 | 1.719036 | 1.69573 | 1.088828 | 1.816611 |
| FLJ36000 | 2.51997 | 2.280712 | 1.479683 | 2.666005 |
| DDHD1 | 2.271442 | 2.319665 | 1.537647 | 2.705701 |
| SUV39H1 | 1.872194 | 1.989926 | 1.272179 | 2.172417 |
| NPRL3 | 1.089729 | 1.169834 | 0.835395 | 1.295715 |
| RAD23B | 1.364427 | 1.310463 | 0.962681 | 1.483386 |
| GART | 1.461483 | 1.389707 | 1.234248 | 1.436161 |
| ANKLE2 | 1.418445 | 1.260045 | 1.147195 | 1.400989 |
| CKS2 | 2.908294 | 2.660707 | 2.395083 | 2.868371 |
| HIST1H3B | 4.171456 | 3.838395 | 3.313369 | 4.113417 |
| TSSC1 | 1.13593 | 1.078676 | 0.920543 | 1.165386 |

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| CENPI | 2.974573 | 2.925012 | 2.452781 | 2.974625 |
| PRR11 | 3.704633 | 3.597628 | 2.984456 | 3.592311 |
| FAM166A | 2.161969 | 2.061595 | 1.658021 | 2.096163 |
| USP10 | 1.080949 | 1.031013 | 0.838056 | 1.045691 |
| NAP1L4 | 1.926912 | 1.940953 | 1.518173 | 1.929452 |
| HIST1H1E | 2.373634 | 2.111097 | 1.696576 | 2.218221 |
| DDA1 | 1.565716 | 1.428374 | 1.232658 | 1.477371 |
| SKA3 | 3.837022 | 3.474836 | 2.903888 | 3.507629 |
| GDPD1 | 3.119395 | 2.534799 | 2.406346 | 3.201118 |
| GOLGA7B | 3.349995 | 2.700963 | 2.608439 | 3.402442 |
| RBM33 | 1.758836 | 1.497369 | 1.37323 | 1.810634 |
| HIST1H3F | 3.049211 | 2.613671 | 2.313496 | 3.032669 |
| INPP4A | 1.600768 | 1.369286 | 1.176878 | 1.595351 |
| BCAR1 | 1.753813 | 1.50437 | 1.282617 | 1.697179 |
| LOC284939 | 1.696963 | 1.487173 | 1.225614 | 1.647927 |
| RMI2 | 2.137264 | 1.84992 | 1.545046 | 2.027842 |
| PWP2 | 1.229466 | 0.977826 | 0.87896 | 1.135109 |
| BCL2L13 | 1.152508 | 1.045894 | 0.770209 | 1.036291 |
| CAMTA2 | 1.788616 | 1.584794 | 1.090863 | 1.601303 |
| TMPO | 1.491641 | 1.304817 | 0.928018 | 1.367922 |
| NUP133 | 1.412431 | 1.165599 | 0.915436 | 1.299985 |
| RPS4X | 1.731512 | 1.479794 | 1.131033 | 1.62607 |
| FAM189B | 1.161379 | 1.117997 | 0.810952 | 1.108887 |
| ATP6V1C2 | 1.744175 | 1.686303 | 1.146582 | 1.704071 |
| ZDHHC12 | 1.84811 | 1.786235 | 1.237656 | 1.811264 |
| DGKZ | 1.568515 | 1.503535 | 0.997878 | 1.404286 |
| PYCR2 | 2.172802 | 2.05404 | 1.272197 | 1.933129 |
| RTEL1 | 1.508908 | 1.476856 | 0.931658 | 1.42689 |
| ATP5J2 | 1.358955 | 1.640328 | 0.971392 | 1.276699 |
| ELAC2 | 2.043598 | 2.396249 | 1.538996 | 1.856057 |
| PSMG3 | 0.903063 | 1.119278 | 0.715817 | 0.824597 |
| IFRD2 | 1.513638 | 1.634015 | 1.015284 | 1.203851 |
| ARHGAP11B | 4.334166 | 4.680256 | 3.175144 | 3.776283 |
| LRFN1 | 1.370523 | 1.461315 | 0.969771 | 1.170645 |
| MOV10 | 2.310314 | 2.503611 | 1.621309 | 2.024118 |
| MUM1 | 3.086887 | 3.357177 | 2.099377 | 2.670033 |
| SAC3D1 | 1.596689 | 1.769448 | 1.001037 | 1.399605 |
| TUFM | 1.451885 | 1.596778 | 0.882571 | 1.217101 |
| CTDSP2 | 1.262554 | 1.522425 | 0.964233 | 1.261891 |
| RREB1 | 1.701112 | 2.092624 | 1.281866 | 1.795433 |

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| EIF2C2 | 0.973392 | 1.112196 | 0.719032 | 1.026184 |
| NOP14 | 1.930312 | 2.120476 | 1.368552 | 1.939728 |
| MSTO1 | 1.440463 | 1.573856 | 1.07789 | 1.411364 |
| CHAC1 | 1.220801 | 1.236019 | 0.872096 | 1.145852 |
| SLC25A15 | 2.042711 | 2.107323 | 1.385782 | 1.931035 |
| PLK1 | 3.493709 | 3.740733 | 2.232927 | 3.304971 |
| DAXX | 1.224455 | 1.381261 | 0.95159 | 1.141606 |
| DOT1L | 1.747841 | 1.953208 | 1.47096 | 1.610089 |
| HIST1H4B | 1.678711 | 1.916161 | 1.384914 | 1.587878 |
| SEMA6C | 1.669152 | 1.959364 | 1.445473 | 1.586455 |
| GAK | 1.625227 | 1.715156 | 1.272363 | 1.572455 |
| COG8 | 1.655821 | 1.875774 | 1.401008 | 1.660438 |
| TERT | 3.085084 | 3.368593 | 2.500185 | 2.919684 |
| DKKL1 | 2.856474 | 3.165686 | 2.526278 | 2.802418 |
| EIF4A1 | 1.036816 | 1.210352 | 0.934381 | 1.040411 |
| PTGES2 | 1.833912 | 2.135212 | 1.650004 | 1.878559 |
| MAPKAP1 | 1.044525 | 1.191064 | 0.952553 | 1.067835 |
| MARK2 | 1.595317 | 1.839137 | 1.516133 | 1.61894 |
| WBP11 | 1.016603 | 1.202945 | 0.997511 | 1.040027 |
| TMEM93 | 1.353174 | 1.581453 | 1.285173 | 1.442233 |
| CDC37 | 2.286568 | 2.352306 | 1.886631 | 2.143764 |
| HIST1H4D | 1.704055 | 1.696302 | 1.394283 | 1.594943 |
| HAUS8 | 1.735893 | 1.756526 | 1.362804 | 1.600056 |
| PGLS | 0.934409 | 0.956984 | 0.806451 | 0.907436 |
| RC3H2 | 1.38629 | 1.478566 | 1.194683 | 1.404537 |
| TACC3 | 2.902 | 3.127915 | 2.43463 | 3.008468 |
| SLC5A6 | 1.760249 | 1.82734 | 1.510308 | 1.852505 |
| FLJ35409 | 4.762514 | 5.686028 | 4.19088 | 5.23617 |
| CHMP1A | 2.478547 | 2.6614 | 1.916075 | 2.60913 |
| PIF1 | 1.796085 | 1.978241 | 1.472827 | 1.94113 |
| TNFRSF13C | 2.213208 | 2.516873 | 1.877732 | 2.394956 |
| PGAM5 | 2.043671 | 2.331557 | 1.586677 | 2.255051 |
| POLR2D | 1.014847 | 1.164299 | 0.842602 | 1.17605 |
| CDKN2A | 2.330522 | 2.795732 | 1.963289 | 3.114243 |
| BOP1 | 1.538058 | 2.010042 | 1.234981 | 2.061084 |
| UBE3C | 2.041234 | 2.402764 | 1.551284 | 2.428259 |
| MPDU1 | 1.361073 | 1.846232 | 1.378355 | 1.791138 |
| DCTPP1 | 1.291063 | 1.800483 | 1.193643 | 1.637701 |
| SKA1 | 3.784411 | 5.169357 | 3.585376 | 4.840592 |
| MTFP1 | 1.549369 | 2.110377 | 1.408063 | 1.999618 |

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| NUP210 | 2.04481 | 2.657746 | 1.831487 | 2.6769 |
| PNPLA6 | 1.048319 | 1.334989 | 0.969399 | 1.315365 |
| SLC27A4 | 1.458208 | 1.84505 | 1.244563 | 1.723148 |
| BYSL | 1.916818 | 2.080041 | 1.658418 | 2.592953 |
| SH3KBP1 | 1.286902 | 1.421238 | 1.199008 | 1.777712 |
| CEP128 | 1.487821 | 1.909089 | 1.40646 | 2.205604 |
| NBEAL2 | 1.44891 | 1.804806 | 1.353669 | 2.115588 |
| CLPB | 0.840331 | 1.104791 | 0.859636 | 1.214136 |
| LPPR3 | 3.989357 | 4.91138 | 3.867552 | 5.396981 |
| NUDT1 | 1.342917 | 1.715321 | 1.313224 | 1.857077 |
| RAB5C | 1.199949 | 1.563911 | 1.121126 | 1.680265 |
| LOC100132966 | 1.237221 | 1.512095 | 1.269972 | 1.752909 |
| PPP1R14B | 1.304241 | 1.623392 | 1.418877 | 1.925302 |
| WWTR1 | 1.332173 | 1.731203 | 1.383601 | 2.023952 |
| CENPN | 1.834147 | 1.947901 | 1.611607 | 2.056073 |
| GATC | 2.231636 | 2.52882 | 2.009173 | 2.754973 |
| P2RX5 | 2.977003 | 3.230923 | 2.518033 | 3.510646 |
| HIST1H1B | 5.049279 | 5.502036 | 4.674822 | 6.125458 |
| PDAP1 | 0.939701 | 0.974839 | 0.828975 | 1.10624 |
| SNRPF | 1.172578 | 1.229122 | 1.085619 | 1.451737 |
| LOC642345 | 5.86185 | 6.865968 | 5.257826 | 7.064052 |
| IKBKB | 1.558849 | 1.871968 | 1.4834 | 1.997613 |
| OLFM1 | 0.952468 | 1.183878 | 0.906443 | 1.217464 |
| RAPGEF1 | 2.486046 | 3.051366 | 2.407327 | 3.131927 |
| KCTD5 | 1.574574 | 1.52762 | 1.276626 | 1.69739 |
| SMG1 | 1.739557 | 1.738482 | 1.372587 | 1.886729 |
| UHRF1 | 3.265214 | 3.33643 | 2.675028 | 3.630052 |
| CHAC2 | 0.815577 | 1.500477 | 1.43886 | 2.34233 |
| C1GALT1 | 0.761806 | 1.071695 | 0.995692 | 1.857198 |
| NUP50 | 0.966231 | 1.501252 | 1.219639 | 2.360779 |
| IL17RA | 1.011307 | 1.374962 | 1.052383 | 2.037344 |
| ELK4 | 0.892382 | 1.123529 | 0.807246 | 1.440878 |
| CDC25A | 1.252496 | 1.464903 | 1.187394 | 2.093565 |
| CSNK1G2 | 1.305827 | 1.443596 | 1.102685 | 2.144468 |
| NUS1 | 1.074665 | 1.207829 | 0.954138 | 1.788929 |
| DTYMK | 1.061735 | 1.047325 | 0.841512 | 1.591972 |
| SACS | 1.075643 | 1.16103 | 0.916713 | 1.620506 |
| TMEM63C | 1.920344 | 2.033033 | 1.657742 | 2.895451 |
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| CCDC134 | 0.963673 | 1.317248 | 1.334959 | 1.933186 |

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| CYB561D2 | 0.753159 | 0.997376 | 0.936027 | 1.492332 |
| GMNN | 0.706103 | 0.964298 | 0.848116 | 1.314845 |
| MLLT6 | 1.033202 | 1.613778 | 1.479855 | 2.389892 |
| ADM2 | 1.162906 | 1.877721 | 1.556638 | 2.507886 |
| SP9 | 0.797322 | 1.324449 | 1.029699 | 1.705528 |
| TCAM1P | 2.822011 | 4.509041 | 3.724452 | 5.664179 |
| GCGR | 1.89403 | 3.272574 | 2.254103 | 4.054368 |
| AP1B1 | 1.098437 | 1.754427 | 1.306382 | 2.018589 |
| TSPAN17 | 1.300351 | 2.143862 | 1.541028 | 2.457405 |
| NCLN | 0.841422 | 1.16847 | 0.770808 | 1.378723 |
| NCRNA00273 | 1.257741 | 1.840682 | 1.192038 | 2.077488 |
| PHF7 | 1.597633 | 2.287643 | 1.669795 | 2.587858 |
| H2AFZ | 0.783859 | 0.913494 | 0.905783 | 1.241816 |
| BRCA2 | 1.929822 | 2.360967 | 2.26014 | 2.884019 |
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| PSMA4 | 0.709597 | 0.849635 | 0.888508 | 1.110327 |
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| RANGAP1 | 0.989513 | 1.257787 | 1.065598 | 1.680936 |
| NPTX1 | 4.080861 | 4.872269 | 4.313364 | 6.266919 |
| WDR4 | 1.167275 | 1.339886 | 1.231625 | 1.790243 |
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| CYP26A1 | 2.486582 | 2.073693 | 3.647824 | 3.8062 |
| LOC440896 | 2.301951 | 1.999426 | 3.147608 | 3.37578 |
| PRDX1 | 0.879859 | 0.716723 | 1.17294 | 1.272689 |
| EZR | 0.704703 | 0.80661 | 1.030813 | 1.300303 |
| PICALM | 0.756152 | 0.916272 | 1.074248 | 1.322016 |
| FOXD4 | 1.638935 | 1.727042 | 2.255721 | 3.160333 |
| STAC3 | 1.367305 | 1.516554 | 1.792966 | 2.474145 |
| PTPN2 | 0.79723 | 0.735971 | 1.196916 | 1.58166 |
| CAPN10 | 0.997675 | 1.244835 | 1.235724 | 1.3874 |
| FAM111B | 1.789674 | 2.120756 | 2.153542 | 2.446564 |
| CSAG1 | 2.352014 | 2.940038 | 3.13042 | 3.276547 |
| PPIA | 0.894682 | 1.142751 | 1.207545 | 1.319671 |
| CEP55 | 3.658457 | 4.236128 | 4.663386 | 5.144384 |
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| HIST1H4A | 2.154208 | 2.34818 | 2.783548 | 3.05451 |
| PRRC2B | 0.748465 | 0.860466 | 0.984528 | 1.129128 |

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| ELOVL6 | 1.853106 | 2.048473 | 2.323888 | 2.418701 |
| TIMM8B | 1.207009 | 1.356152 | 1.490045 | 1.562197 |
| DLGAP4 | 1.012869 | 0.856679 | 1.142109 | 1.271377 |
| DNAJC9 | 0.92921 | 0.870104 | 1.130823 | 1.28243 |
| KIAA0317 | 1.303044 | 1.180298 | 1.492627 | 1.716433 |
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| RAPH1 | 0.919568 | 0.80055 | 1.122185 | 1.238421 |
| KLHL7 | 0.831853 | 0.841195 | 1.020475 | 1.214543 |
| NCOA3 | 0.930973 | 0.983076 | 1.196547 | 1.430081 |
| PANK3 | 0.884365 | 0.898277 | 1.049057 | 1.311582 |
| GTF3C6 | 0.766397 | 0.707566 | 1.030198 | 1.059795 |
| KLHL17 | 1.399543 | 1.489297 | 2.019572 | 2.158882 |
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| CDKN1A | 1.452581 | 1.490165 | 1.905436 | 1.882027 |
| MDM2 | 0.974979 | 0.985232 | 1.314878 | 1.297338 |
| TNPO3 | 0.906548 | 0.904416 | 1.189108 | 1.250451 |
| MGAT5 | 1.704982 | 1.937017 | 2.451251 | 2.555345 |
| RBL1 | 1.184456 | 1.419355 | 1.823988 | 1.988704 |
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| FOXN2 | 0.996429 | 0.851931 | 1.001525 | 1.269178 |
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| CHFR | 1.476702 | 1.225899 | 1.525831 | 1.955202 |
| UBE2K | 0.883719 | 0.74478 | 0.930984 | 1.17309 |
| BOLA2B | 1.578187 | 1.315744 | 1.391048 | 1.991911 |
| SLIRP | 1.087322 | 0.867057 | 0.960864 | 1.363587 |
| AVL9 | 1.102635 | 0.915449 | 1.024253 | 1.47308 |
| UBE2NL | 1.34313 | 1.096164 | 1.183373 | 1.751448 |
| ASXL1 | 1.338861 | 1.053377 | 1.228849 | 1.660038 |
| TMEM48 | 2.096264 | 1.692046 | 1.961993 | 2.673355 |
| DUSP18 | 1.614547 | 1.355832 | 1.494721 | 2.059826 |
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| MDM4 | 1.265495 | 0.994781 | 1.10692 | 1.516946 |
| MYCBP | 1.47556 | 1.280367 | 1.335522 | 1.803423 |
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| MRPL14 | 1.162145 | 1.133185 | 1.006848 | 1.647864 |
| APH1A | 1.500286 | 1.516644 | 1.464052 | 2.24071 |
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| SSH1 | 1.288719 | 1.232561 | 1.188196 | 1.862402 |
| HIST1H4K | 0.866292 | 0.890829 | 0.806602 | 1.308563 |
| TOR3A | 0.905265 | 0.885838 | 0.81711 | 1.359736 |
| YARS2 | 1.06012 | 1.024049 | 0.993106 | 1.639117 |
| PAFAH1B2 | 0.931324 | 0.970235 | 1.08763 | 1.562315 |
| KPNA2 | 2.931678 | 2.928609 | 3.241964 | 4.870535 |
| ZBTB8OS | 0.85767 | 0.847241 | 0.899567 | 1.426147 |
| USP49 | 1.305209 | 1.110941 | 1.336828 | 1.999032 |
| TOP1 | 1.409914 | 1.182086 | 1.290893 | 2.121861 |
| TRAF2 | 2.450513 | 1.975577 | 2.118468 | 3.35324 |
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| DPP3 | 1.323333 | 1.926909 | 1.799331 | 1.910473 |
| CAPZA1 | 0.909412 | 1.443529 | 1.323357 | 1.431962 |
| NEBL | 2.160954 | 3.505949 | 3.153323 | 3.306098 |
| HIST1H2BE | 1.658032 | 2.535722 | 2.162366 | 2.265338 |
| ITPA | 0.975736 | 1.459118 | 1.216704 | 1.329837 |
| SEH1L | 1.031721 | 1.513576 | 1.309081 | 1.394185 |
| SLC44A2 | 0.83494 | 1.359289 | 1.164837 | 1.199656 |
| MRPL51 | 0.851317 | 1.307466 | 1.1389 | 1.066931 |
| CCDC167 | 1.226737 | 1.826058 | 1.853684 | 1.95672 |
| LYPLA1 | 0.907033 | 1.372279 | 1.288124 | 1.447943 |
| CRIP1 | 0.774495 | 1.242954 | 1.25195 | 1.369144 |
| UBE2S | 1.411314 | 2.367634 | 2.392062 | 2.53706 |
| DDX3Y | 1.159372 | 1.681121 | 1.577428 | 1.92519 |
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| POLD1 | 1.111309 | 1.724492 | 1.856415 | 2.132134 |
| TUBA1B | 0.995986 | 1.380943 | 1.491804 | 1.71045 |
| TUBB3 | 2.737925 | 3.802831 | 3.902548 | 4.597006 |
| GLT25D1 | 1.619268 | 2.266382 | 1.917156 | 2.594475 |
| FKBP1A | 1.223714 | 1.625674 | 1.40307 | 1.744599 |
| SKP2 | 1.236048 | 1.832573 | 1.586641 | 1.851117 |
| WDR1 | 1.306035 | 1.813747 | 1.653789 | 1.934906 |
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| MGC23284 | 1.303132 | 0.735919 | 1.238454 | 0.925823 |
| HIP1R | 1.350818 | 0.908664 | 0.986081 | 0.889215 |
| FAM155B | 3.187577 | 2.260532 | 2.56828 | 2.430808 |
| ADAMTS7 | 3.429624 | 2.420303 | 2.754537 | 2.376025 |

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| THOC2 | 1.533143 | 1.09431 | 1.200604 | 1.098004 |
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| DSCR3 | 1.908532 | 0.937594 | 1.316194 | 1.201367 |
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| FAM117B | 2.068497 | 1.157672 | 1.652243 | 1.462352 |
| PPM1N | 3.220334 | 1.77242 | 2.534547 | 2.177729 |
| PHF6 | 1.29985 | 0.733566 | 1.081551 | 0.946854 |
| SNORA28 | 2.601548 | 1.35012 | 2.148678 | 1.835855 |
| MEF2BNB | 2.79922 | 1.613011 | 2.107402 | 1.785833 |
| RMI1 | 1.303217 | 0.728106 | 1.038069 | 0.817383 |
| ATF7IP | 1.902292 | 1.094806 | 1.385621 | 1.338888 |
| STX2 | 1.536691 | 0.838336 | 1.056348 | 1.070264 |
| ANKRD2 | 2.612561 | 1.598041 | 1.889112 | 1.83953 |
| HESX1 | 2.773377 | 1.719068 | 1.92228 | 1.934623 |
| ZNF81 | 1.648606 | 1.054538 | 1.195757 | 1.133851 |
| PRKRIP1 | 1.20928 | 0.744978 | 0.842976 | 0.787219 |
| GUCY1B2 | 3.751087 | 2.205683 | 2.931431 | 2.805757 |
| VCP | 1.249934 | 0.733915 | 0.942009 | 0.973389 |
| AEN | 1.948384 | 1.319645 | 1.542107 | 1.767049 |
| HMBS | 2.187338 | 1.459253 | 1.731181 | 2.036661 |
| NAA25 | 1.23637 | 0.779387 | 0.981721 | 1.124311 |
| ARID3A | 2.54218 | 1.895844 | 2.102257 | 2.422018 |
| HIST1H2AL | 3.24348 | 2.395053 | 2.71329 | 3.202933 |
| MLL | 2.166834 | 1.543378 | 1.670922 | 1.941547 |
| RSC1A1 | 1.534131 | 1.140984 | 1.177551 | 1.462693 |
| HIST1H4H | 1.359547 | 0.872608 | 1.015583 | 1.131016 |
| HELB | 2.200975 | 1.427661 | 1.520168 | 1.855869 |
| KHSRP | 2.40199 | 1.584935 | 1.549261 | 2.014335 |
| CHRNB2 | 3.380115 | 1.868781 | 2.732506 | 3.245674 |
| DSCR6 | 7.186458 | 3.974065 | 5.689581 | 7.101288 |
| NIN | 1.439918 | 0.781428 | 1.128621 | 1.388258 |
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| MBD2 | 2.714202 | 1.563015 | 1.900683 | 2.586228 |
| PBX4 | 1.921421 | 1.088564 | 1.25134 | 1.810976 |
| TIMM8A | 1.429164 | 0.843355 | 0.95112 | 1.349129 |
| LOC286109 | 1.436765 | 0.913791 | 1.201841 | 1.266747 |
| DDT | 1.513676 | 0.882586 | 1.150115 | 1.28673 |
| BAGE4 | 1.664684 | 0.965077 | 1.226561 | 1.421053 |
| ULBP1 | 5.529347 | 3.23504 | 4.168365 | 4.842767 |

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| SNORA74B | 1.313255 | 0.755793 | 0.99156 | 1.200003 |
| TMEM26 | 5.284569 | 2.833845 | 4.182124 | 4.51724 |
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| DDI2 | 1.79191 | 1.322282 | 1.628283 | 2.008404 |
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| YWHAZ | 1.195473 | 0.776715 | 1.027595 | 1.220577 |
| ITSN2 | 1.240095 | 0.782349 | 0.986715 | 1.350914 |
| CYFIP2 | 2.317022 | 1.63623 | 1.897609 | 2.590207 |
| PSMA5 | 1.069993 | 0.786306 | 0.857776 | 1.251818 |
| TIPIN | 1.169338 | 0.792318 | 0.882666 | 1.319706 |
| KIF5B | 1.332375 | 0.941221 | 1.316195 | 1.572661 |
| PIGL | 1.153555 | 0.795737 | 1.058161 | 1.312361 |
| RELL2 | 2.080359 | 1.363707 | 1.912454 | 2.395885 |
| BRSK2 | 3.710519 | 1.561414 | 3.632902 | 4.402752 |
| NAT8L | 2.074601 | 1.001948 | 1.814652 | 2.532056 |
| NFE2L3 | 2.306004 | 1.384213 | 2.680423 | 2.554397 |
| NLN | 1.891555 | 1.140426 | 1.970966 | 2.177659 |
| SCYL2 | 1.25615 | 0.784113 | 1.314841 | 1.52752 |
| RALBP1 | 1.385757 | 0.797122 | 1.32121 | 1.488165 |
| DOLPP1 | 1.613528 | 0.718331 | 1.11699 | 1.42353 |
| MAB21L2 | 3.372866 | 1.360936 | 2.459946 | 2.911287 |
| RTKN2 | 4.812082 | 2.111102 | 3.459499 | 4.08541 |
| LSM14B | 1.994605 | 0.972133 | 1.260622 | 1.559559 |
| MAGEA1 | 10.004759 | 3.369358 | 5.321831 | 7.934848 |
| FBXO41 | 1.276887 | 0.848704 | 0.708228 | 0.91087 |
| HPS1 | 1.756327 | 1.168093 | 0.995389 | 1.302425 |
| FAM169A | 2.616844 | 1.537873 | 1.446937 | 2.050515 |
| MED20 | 3.366176 | 1.998387 | 1.899109 | 2.506681 |
| NME2 | 1.254177 | 0.764263 | 0.720769 | 0.908039 |
| MADCAM1 | 3.127083 | 2.11666 | 1.73121 | 2.731664 |
| MGRN1 | 2.172497 | 1.507727 | 1.254561 | 1.804022 |
| NCAPH2 | 1.500171 | 1.077027 | 0.872162 | 1.269421 |
| ACACA | 1.721611 | 0.972616 | 1.083807 | 1.266367 |
| DYRK1A | 1.337945 | 0.758984 | 0.852934 | 0.948843 |
| TMEM107 | 1.891222 | 0.948253 | 1.11802 | 1.284141 |
| PCDHA12 | 3.606992 | 1.947351 | 1.950545 | 2.295297 |
| ATXN7L1 | 1.373855 | 0.874718 | 0.815906 | 0.901536 |
| CKMT1A | 4.589483 | 2.944414 | 2.879169 | 3.198979 |

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| PSPC1 | 1.639938 | 0.965335 | 0.948619 | 1.026497 |
| SNORD3B-1 | 4.408108 | 2.799142 | 2.766526 | 2.765268 |
| STRADA | 2.558437 | 1.535654 | 1.60773 | 1.644941 |
| DNAJA1 | 1.437591 | 0.991061 | 0.87357 | 0.896781 |
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| RUVBL1 | 1.886433 | 1.323839 | 1.045984 | 1.172377 |
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| HDHD1 | 1.49286 | 1.108261 | 0.833766 | 1.038794 |
| MIAT | 3.573173 | 2.600673 | 2.129451 | 2.597195 |
| SH2B2 | 2.222042 | 1.591042 | 1.30476 | 1.502545 |
| UPF2 | 1.470355 | 1.032213 | 0.893111 | 1.004456 |
| FOXK2 | 2.173819 | 1.759536 | 1.286145 | 1.642815 |
| RNU105A | 2.64374 | 2.128633 | 1.568248 | 1.941246 |
| NACC1 | 1.469708 | 1.250873 | 0.8955 | 1.203508 |
| AKAP5 | 2.416636 | 1.484186 | 0.948858 | 1.651461 |
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| ELOVL3 | 4.255695 | 2.740808 | 1.904565 | 2.617216 |
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| NPLOC4 | 1.832497 | 1.146876 | 0.978676 | 1.137611 |
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| B3GAT1 | 5.648894 | 2.975171 | 2.52874 | 4.16919 |
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| FKBP4 | 2.439388 | 1.927016 | 1.190256 | 1.459794 |
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| LOC100128184 | 2.079562 | 1.705367 | 1.008556 | 1.120832 |
| PCDHA4 | 3.752047 | 2.977182 | 1.696729 | 2.091379 |
| LOC100131929 | 1.891063 | 1.731981 | 1.104044 | 0.928493 |
| MRPS23 | 1.876886 | 1.521038 | 1.032542 | 0.833638 |
| SLC25A10 | 2.834984 | 2.206981 | 1.434255 | 1.308476 |
| KRTAP5-7 | 2.363694 | 1.94289 | 1.407002 | 1.199218 |
| ZMYND19 | 1.714678 | 1.367467 | 0.967993 | 0.893914 |
| DAGLB | 1.143036 | 1.128353 | 0.721945 | 0.964044 |
| DNM2 | 1.321119 | 1.314968 | 0.832103 | 1.034931 |
| PAQR4 | 3.973079 | 3.980215 | 2.61607 | 3.064434 |

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| ANKRD27 | 1.673594 | 1.637742 | 1.110481 | 1.329707 |
| SPPL2B | 1.359712 | 1.290314 | 0.859014 | 1.042123 |
| KIFC2 | 3.90271 | 3.705884 | 2.590895 | 3.164735 |
| CD320 | 1.433682 | 1.332199 | 1.067533 | 1.075613 |
| ATIC | 1.063541 | 1.00292 | 0.720764 | 0.728667 |
| CCT3 | 2.017742 | 1.944606 | 1.449757 | 1.437175 |
| GAS2L2 | 3.77377 | 3.602569 | 2.641932 | 2.686948 |
| CBLN2 | 5.59954 | 5.437878 | 3.916305 | 4.187711 |
| GLYR1 | 2.193304 | 2.156726 | 1.63366 | 1.659892 |
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| SET | 1.753543 | 1.671365 | 1.292822 | 1.333378 |
| RPAIN | 1.067705 | 1.130389 | 0.831875 | 0.813163 |
| MACROD2 | 1.241072 | 1.182396 | 0.938894 | 1.025075 |
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| WDR77 | 1.459604 | 1.528569 | 1.158537 | 1.283812 |
| MAP3K14 | 1.936633 | 1.974186 | 1.507096 | 1.544576 |
| ZNF259 | 1.210535 | 1.251324 | 0.916843 | 0.989366 |
| FAM108A1 | 2.147568 | 2.238901 | 1.23366 | 1.606975 |
| MFSD10 | 1.213739 | 1.267486 | 0.754565 | 0.901075 |
| SLC35E1 | 1.146596 | 1.173731 | 0.741746 | 0.762533 |
| TARS2 | 1.275367 | 1.24562 | 0.775677 | 0.804844 |
| AIMP2 | 1.580177 | 1.435958 | 0.938332 | 1.102499 |
| DNM1P46 | 3.374559 | 2.928997 | 1.97496 | 2.341843 |
| EXOSC4 | 1.322635 | 1.18271 | 0.725854 | 0.860707 |
| NME1 | 1.706772 | 1.408843 | 0.975152 | 1.074518 |
| PTCD3 | 1.452516 | 1.161942 | 0.885496 | 0.854744 |
| NFATC2IP | 1.583228 | 1.41487 | 0.980095 | 1.025931 |
| SCARNA12 | 2.669894 | 2.339528 | 1.697014 | 1.694541 |
| MAPK8IP2 | 2.013814 | 1.712672 | 1.281369 | 1.179762 |
| THOC4 | 2.268612 | 1.920255 | 1.387676 | 1.373849 |
| SPATA21 | 1.812979 | 1.626986 | 1.171424 | 1.099225 |
| CDCA7 | 3.670104 | 3.412366 | 1.918359 | 2.669334 |
| MRM1 | 1.523118 | 1.379595 | 0.830969 | 1.107811 |
| SEMA3A | 5.466143 | 4.914944 | 2.905446 | 4.269238 |
| CCDC137 | 1.991453 | 1.576407 | 0.900807 | 1.590249 |
| LARP4B | 2.358802 | 1.852183 | 1.171798 | 1.824438 |
| PDPR | 1.814072 | 1.501848 | 0.956118 | 1.489099 |
| TLCD1 | 2.666283 | 1.914664 | 1.229069 | 1.765638 |
| UQCC | 1.819902 | 1.371754 | 0.852317 | 1.290435 |

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| SATB1 | 1.674089 | 1.582755 | 0.747145 | 1.487004 |
| CCNG2 | 1.756986 | 0.89861 | 1.209684 | 0.812606 |
| CCDC34 | 1.920379 | 0.895352 | 1.316649 | 0.919854 |
| PIDD | 1.472057 | 0.709228 | 1.006198 | 0.766721 |
| PITPNC1 | 4.33932 | 2.588721 | 3.502427 | 2.271629 |
| BCAS3 | 2.512592 | 1.736276 | 1.912451 | 1.237801 |
| BF346224 | 2.481479 | 1.686734 | 1.814175 | 1.246545 |
| CCDC43 | 2.054532 | 1.455786 | 1.493031 | 1.053106 |
| ACAD10 | 2.666135 | 1.871499 | 1.878651 | 1.192548 |
| DNASE1 | 3.221471 | 2.212831 | 2.202538 | 1.465272 |
| CYP27B1 | 3.858148 | 2.70123 | 2.726842 | 1.858786 |
| APTX | 2.366607 | 1.653402 | 1.566749 | 1.220576 |
| GLMN | 1.716788 | 1.210528 | 1.150615 | 0.892811 |
| RIMBP3 | 2.800916 | 1.964716 | 1.841508 | 1.359933 |
| E2F5 | 3.123931 | 2.317234 | 2.401138 | 1.662752 |
| DDX17 | 1.492818 | 1.116904 | 1.159495 | 0.828258 |
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| BMP5 | 6.053687 | 4.150572 | 4.562387 | 3.315194 |
| BCL7A | 1.607674 | 1.137617 | 1.18837 | 0.869983 |
| TRIM46 | 4.580473 | 3.221565 | 3.462648 | 2.427686 |
| SCARNA16 | 3.614346 | 2.547956 | 2.77813 | 2.072062 |
| HIST1H3H | 4.696345 | 3.437616 | 3.566637 | 2.758949 |
| LOC100506398 | 2.174321 | 1.590418 | 1.596507 | 1.302366 |
| SUZ12 | 1.264555 | 0.878897 | 0.920737 | 0.727554 |
| ATF2 | 1.601031 | 0.953078 | 1.047907 | 0.750697 |
| HIST1H2BN | 1.815972 | 1.146452 | 1.221582 | 0.882132 |
| METTL2A | 2.402466 | 1.496829 | 1.802587 | 1.226462 |
| ZNF736 | 2.034728 | 1.274529 | 1.462519 | 1.01592 |
| ALS2 | 1.594576 | 0.988211 | 1.188456 | 0.958249 |
| GDF11 | 1.413801 | 0.916574 | 1.063414 | 0.877995 |
| HIST1H2BJ | 2.431826 | 1.583623 | 1.848309 | 1.441431 |
| HIST2H2AB | 1.318463 | 0.830582 | 0.930954 | 0.796021 |
| ATRX | 1.675988 | 1.038325 | 1.304671 | 0.980656 |
| LOC100133089 | 1.629535 | 1.013404 | 1.261 | 0.908059 |
| PSIP1 | 2.123411 | 1.20372 | 1.401233 | 1.131038 |
| UBXN7 | 1.599183 | 1.003124 | 1.056629 | 0.914321 |
| ABR | 3.202199 | 2.292173 | 2.24829 | 1.921683 |
| GFRA2 | 3.609493 | 2.639625 | 2.577539 | 2.287903 |
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| DARS2 | 1.78047 | 1.385006 | 1.291373 | 1.128868 |
| PARG | 1.338093 | 1.049702 | 0.950111 | 0.857969 |
| ZNF625 | 1.25798 | 0.949049 | 0.828189 | 0.789352 |
| DHX8 | 1.257766 | 0.988481 | 0.879404 | 0.708894 |
| KCNC3 | 3.774936 | 2.808082 | 2.457401 | 2.125925 |
| LRP2 | 1.474642 | 1.123005 | 0.922617 | 0.725885 |
| ZNF121 | 2.085294 | 1.654129 | 1.336197 | 1.131758 |
| ARL10 | 1.784412 | 1.157243 | 1.022119 | 1.036147 |
| NDOR1 | 1.583801 | 0.984379 | 0.918666 | 0.950439 |
| KCTD19 | 2.925218 | 1.914382 | 1.764121 | 1.570145 |
| PPRC1 | 1.511758 | 1.044845 | 0.916836 | 0.84188 |
| PALM3 | 2.872095 | 1.947483 | 1.613564 | 1.570284 |
| BAI1 | 4.417153 | 2.849904 | 2.342445 | 1.826917 |
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| DLEU1 | 3.376557 | 1.585734 | 1.805531 | 1.531105 |
| IGLON5 | 2.326513 | 1.213996 | 1.422443 | 0.909165 |
| ROCK1 | 3.507195 | 1.966904 | 2.105578 | 1.294924 |
| TRIM27 | 2.352184 | 1.393179 | 1.385295 | 0.916499 |
| HIST1H2BI | 2.429215 | 1.560771 | 1.698265 | 0.758181 |
| ATP6V1E2 | 2.56586 | 1.657793 | 1.615383 | 0.771077 |
| CLGN | 5.077277 | 3.358724 | 3.24296 | 1.705714 |
| TMEM194A | 3.20484 | 2.272942 | 2.094619 | 0.95271 |
| CES4A | 3.340927 | 2.570496 | 2.145627 | 1.121135 |
| LRRC46 | 3.115438 | 2.193313 | 1.757462 | 1.004218 |
| RPS6KB1 | 3.505035 | 2.425711 | 2.088331 | 1.212168 |
| GFI1 | 4.146796 | 2.878922 | 2.763021 | 1.654348 |
| SULT4A1 | 2.46226 | 1.838346 | 1.674876 | 1.047713 |
| CBX2 | 2.918354 | 1.799096 | 2.201931 | 0.977416 |
| MARCH9 | 1.977425 | 1.20521 | 1.53584 | 0.758922 |
| HIST1H2BC | 3.002975 | 1.87149 | 2.324569 | 1.142896 |
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| HIST1H2BG | 3.103015 | 1.922091 | 2.43653 | 1.245079 |
| ASMTL-AS1 | 3.782396 | 2.522869 | 3.055158 | 1.435955 |
| HIST1H2BK | 2.935235 | 1.951115 | 2.454492 | 1.172195 |
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| RDX | 3.011574 | 2.021074 | 2.624349 | 1.069542 |

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| HIST2H2AA4 | 2.76167 | 1.827513 | 2.210953 | 1.318928 |
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| TBL1X | 2.871616 | 1.683415 | 2.122557 | 1.182698 |
| TBL1Y | 2.949541 | 1.696906 | 2.223759 | 1.252074 |
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| PIK3R3 | 2.436418 | 1.287188 | 1.748821 | 0.779984 |
| SPAG17 | 4.635017 | 2.498061 | 3.546045 | 1.199917 |
| SPAG6 | 7.907896 | 4.006277 | 6.85718 | 2.497739 |
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| HOXC13 | 7.386046 | 3.056979 | 6.15801 | 3.255546 |
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| TRNT1 | 1.546678 | 0.75216 | 1.359654 | 0.826664 |
| OR3A1 | 6.008844 | 3.450893 | 6.110916 | 2.90878 |
| HRK | 4.129436 | 1.532028 | 2.765351 | 1.308609 |
| NBR2 | 3.252638 | 1.436527 | 2.309715 | 0.963082 |
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| CEP72 | 1.557555 | 1.225385 | 1.059102 | 0.759237 |
| AGPAT1 | 2.022355 | 1.667899 | 1.401883 | 0.933504 |
| NARF | 1.581121 | 1.351464 | 1.065808 | 0.712372 |
| ATP7B | 1.520953 | 1.320021 | 1.090955 | 0.806467 |
| FBXO44 | 1.77921 | 1.516063 | 1.250937 | 0.931881 |
| FCHO1 | 2.533665 | 2.260295 | 1.70059 | 1.295013 |
| INTS4 | 1.903656 | 1.678543 | 1.262419 | 1.018118 |
| PRY2 | 3.394369 | 3.145048 | 2.308443 | 1.801772 |
| KCTD17 | 1.920945 | 1.727077 | 1.340951 | 0.88955 |
| COL23A1 | 1.647569 | 1.55839 | 1.179742 | 0.754897 |
| KIAA1967 | 2.076772 | 1.910044 | 1.436056 | 0.93633 |
| TEAD4 | 2.189756 | 2.058769 | 1.571279 | 1.059555 |
| LRRC4B | 4.147159 | 4.114369 | 2.949814 | 1.846896 |
| GUSBP11 | 1.610143 | 1.589641 | 1.159872 | 0.772699 |
| PMS2L2 | 1.929711 | 1.962074 | 1.395504 | 0.953 |
| MSH5 | 2.144471 | 2.11325 | 1.461116 | 1.028264 |
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| TONSL | 3.310427 | 3.363307 | 2.608139 | 1.583686 |
| KDM5C | 1.903865 | 2.051369 | 1.72205 | 1.213859 |
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| KCTD13 | 1.880355 | 1.99129 | 1.619668 | 1.199627 |
| LHPP | 3.11975 | 3.257244 | 2.660631 | 1.841424 |

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| FOXRED1 | 1.338062 | 1.38154 | 1.143947 | 0.83201 |
| UBE2Z | 2.855751 | 2.926652 | 2.437836 | 1.712 |
| CC2D1B | 1.372147 | 1.366808 | 1.118311 | 0.869216 |
| ABCD1 | 2.03912 | 1.962335 | 1.725176 | 1.237035 |
| XR_110956 | 2.619715 | 2.469679 | 2.167378 | 1.650777 |
| TRMU | 1.837751 | 1.713204 | 1.470633 | 1.085158 |
| ACIN1 | 1.454524 | 1.61244 | 1.184438 | 0.813645 |
| CPSF3L | 1.880669 | 2.070737 | 1.536281 | 1.042813 |
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| SYCE2 | 3.034713 | 3.123929 | 2.424089 | 1.702198 |
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| CDK5 | 2.240312 | 1.982615 | 1.741935 | 1.106351 |
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| MUS81 | 1.810469 | 1.792127 | 1.526169 | 0.943021 |
| ASB7 | 1.962601 | 1.866233 | 1.630795 | 1.083948 |
| NCRNA00265 | 1.819543 | 1.708445 | 1.507444 | 1.033158 |
| MED18 | 3.133151 | 3.043703 | 2.489187 | 1.638395 |
| EME2 | 2.842831 | 2.640165 | 2.205809 | 1.530895 |
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| TBC1D3B | 3.067784 | 2.891165 | 2.368519 | 1.641033 |
| QSOX2 | 1.379969 | 1.298025 | 1.129724 | 0.717488 |
| TMEM177 | 1.911998 | 1.809997 | 1.547019 | 0.985825 |
| EDC4 | 1.773508 | 1.902232 | 1.271464 | 1.052424 |
| POLE | 2.209905 | 2.305117 | 1.587899 | 1.269156 |
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| FAM158A | 2.246563 | 2.283298 | 1.653185 | 1.246707 |
| GTPBP6 | 1.775202 | 1.790355 | 1.288424 | 0.964511 |
| TOPBP1 | 1.498283 | 1.564716 | 1.134189 | 0.84295 |
| G6PC3 | 1.693713 | 1.64828 | 1.108396 | 0.976235 |
| QKI | 1.651611 | 1.620788 | 1.118397 | 0.963268 |
| ABCF3 | 1.378397 | 1.5693 | 0.911388 | 0.854315 |
| GPSM1 | 0.90774 | 1.041224 | 0.600901 | 0.51235 |
| GNB2 | 1.334964 | 1.56082 | 0.916421 | 0.776822 |
| PUF60 | 1.247172 | 1.477429 | 0.867569 | 0.711297 |
| SH3GL1P2 | 1.975924 | 2.325153 | 1.453435 | 1.185067 |
| MFAP3L | 3.580279 | 3.859882 | 2.362228 | 2.033737 |
| ZMAT5 | 1.525631 | 1.613706 | 0.996449 | 0.794186 |
| ATXN7L3 | 1.810408 | 1.906204 | 1.512954 | 1.231936 |
| KRT25 | 4.028081 | 4.086748 | 3.283094 | 2.717421 |
| FANCD2 | 2.401223 | 2.562438 | 2.05877 | 1.718368 |

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| ADD1 | 1.422512 | 1.4428 | 1.254481 | 1.011185 |
| CCT7 | 1.287214 | 1.283973 | 1.105454 | 0.886564 |
| CEP164 | 2.988407 | 2.998218 | 2.548063 | 2.114089 |
| EIF4EBP1 | 1.297113 | 1.359948 | 1.128181 | 0.95535 |
| KIF18A | 4.758213 | 4.885414 | 4.081284 | 3.454138 |
| PIP4K2B | 2.20961 | 2.265303 | 1.987828 | 1.628829 |
| IPO7 | 1.180991 | 1.153987 | 0.988647 | 0.841614 |
| DEM1 | 1.214973 | 1.266481 | 1.100047 | 0.947199 |
| GPR137 | 2.655995 | 2.816981 | 2.368289 | 2.053198 |
| CCDC71 | 2.618926 | 2.791536 | 2.42341 | 2.1544 |
| ZNF382 | 1.398747 | 1.491022 | 1.289739 | 1.125242 |
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| FLAD1 | 1.732099 | 2.112916 | 1.66171 | 1.350186 |
| HNRNPK | 1.396325 | 1.689115 | 1.302579 | 1.046557 |
| RNF40 | 1.759681 | 2.061026 | 1.58445 | 1.310189 |
| MED1 | 1.714909 | 1.933666 | 1.55684 | 1.239603 |
| SLITRK5 | 4.607851 | 5.18323 | 4.148662 | 3.547259 |
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| KIF22 | 3.04793 | 3.466532 | 2.647384 | 2.380221 |
| POLA2 | 1.571568 | 1.820771 | 1.336388 | 1.238085 |
| SYNGAP1 | 2.987613 | 3.162823 | 2.519603 | 2.244277 |
| VARS | 1.510268 | 1.657722 | 1.247333 | 1.127143 |
| ANK1 | 3.078665 | 2.853843 | 2.361181 | 1.978057 |
| AP3D1 | 1.211518 | 1.093548 | 0.915485 | 0.812697 |
| MCM4 | 3.703882 | 3.278385 | 2.711956 | 2.360724 |
| DDX11 | 2.395689 | 2.163105 | 1.786725 | 1.400925 |
| WNK1 | 2.272931 | 1.998128 | 1.746564 | 1.387569 |
| FUBP3 | 1.989686 | 1.807606 | 1.430487 | 1.358483 |
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| CANT1 | 2.344805 | 2.254748 | 1.691568 | 1.479512 |
| XRCC3 | 1.790728 | 1.781107 | 1.3096 | 1.086817 |
| PARP1 | 1.209075 | 1.187254 | 0.94223 | 0.805812 |
| CCNL2 | 1.699849 | 1.364005 | 1.475688 | 1.121305 |
| BRCA1 | 2.658644 | 2.142217 | 2.204909 | 1.797848 |
| EME1 | 3.210173 | 2.549804 | 2.692546 | 2.227113 |
| ORC2 | 1.304338 | 1.082235 | 1.119703 | 0.941387 |
| FLJ33996 | 3.565993 | 2.933274 | 2.91438 | 2.372744 |
| CDKN3 | 5.434212 | 4.425846 | 4.52423 | 3.496809 |
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| LOC100128881 | 2.314028 | 1.87055 | 1.862817 | 1.470153 |

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| HERC2 | 2.179385 | 1.745171 | 1.704497 | 1.350934 |
| TBC1D10B | 2.190304 | 1.735055 | 1.717049 | 1.34809 |
| SORD | 1.447016 | 1.18869 | 1.130292 | 0.901679 |
| AP1S1 | 3.122149 | 2.721338 | 2.637017 | 2.116324 |
| AMBRA1 | 1.865719 | 1.584789 | 1.509953 | 1.239985 |
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| COL9A2 | 2.219326 | 1.907865 | 1.832887 | 1.610949 |
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| CBX5 | 1.912805 | 1.724757 | 1.576871 | 1.397878 |
| RHOT1 | 1.412966 | 1.251234 | 1.1241 | 0.987008 |
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| ATAD2 | 1.816713 | 1.657231 | 1.544227 | 1.267697 |
| NOLC1 | 1.79341 | 1.678705 | 1.521695 | 1.286632 |
| GTPBP2 | 1.542596 | 1.367032 | 1.22387 | 1.017374 |
| PRAME | 4.469027 | 3.965688 | 3.582657 | 2.944929 |
| MNT | 3.336845 | 3.049246 | 2.769204 | 2.198574 |
| ORC6 | 3.671223 | 3.350613 | 3.060772 | 2.366165 |
| TM9SF4 | 1.094825 | 1.018468 | 0.899678 | 0.743198 |
| SMG7 | 1.862033 | 1.716709 | 1.450282 | 1.28035 |
| XPO5 | 1.997489 | 1.879619 | 1.599048 | 1.405821 |
| COX15 | 1.664024 | 1.46389 | 1.327187 | 0.893462 |
| CSNK2A1 | 1.674717 | 1.489567 | 1.318083 | 0.945304 |
| ABCC10 | 1.991614 | 1.692315 | 1.566189 | 1.158353 |
| SCNN1D | 5.57911 | 4.736356 | 4.458856 | 3.30522 |
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| ZACN | 2.418657 | 2.055258 | 1.965788 | 1.406971 |
| UBQLN4 | 2.62269 | 2.285168 | 2.135724 | 1.583257 |
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| ZNF239 | 1.44128 | 1.199718 | 1.268459 | 0.833922 |
| ATF7IP2 | 2.072113 | 2.017906 | 1.962524 | 1.104545 |
| LMNB1 | 5.185164 | 4.920513 | 4.768905 | 2.643879 |
| PCCB | 1.957264 | 1.842277 | 1.822576 | 0.94994 |
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| DLG4 | 2.865323 | 2.595012 | 2.68569 | 1.449691 |
| SEC61A2 | 1.825456 | 1.695865 | 1.743534 | 0.949826 |
| HERC2P4 | 2.834279 | 2.754197 | 2.51061 | 1.48318 |
| MYCL1 | 6.698841 | 6.55418 | 6.076851 | 3.577772 |
| TMEFF2 | 5.271231 | 5.124704 | 4.710247 | 2.627842 |

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| PRSS30P | 3.720242 | 3.473195 | 3.160089 | 1.9037 |
| C2CD4C | 2.635225 | 2.839465 | 2.568283 | 1.615671 |
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| CCDC22 | 1.160842 | 1.220421 | 1.077337 | 0.778506 |
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| PIN1P1 | 1.786299 | 1.988478 | 1.77025 | 1.198332 |
| TMEM63B | 1.356383 | 1.514655 | 1.353927 | 0.89164 |
| ACTR3B | 1.483657 | 1.551083 | 1.378399 | 0.915523 |
| ATXN2L | 1.971416 | 1.956692 | 1.793446 | 1.19687 |
| WIPF2 | 1.938405 | 1.954029 | 1.777271 | 1.143751 |
| SLC6A8 | 2.25234 | 2.184547 | 2.004066 | 1.272796 |
| CENPH | 2.343396 | 2.19099 | 2.134696 | 1.348987 |
| RBM15 | 1.798835 | 1.658377 | 1.608989 | 0.999575 |
| TRIM11 | 2.139481 | 1.951542 | 1.873627 | 1.225835 |
| APLP1 | 4.739557 | 4.658081 | 4.699851 | 3.066677 |
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| NFIB | 2.657103 | 2.757388 | 2.641617 | 1.610695 |
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| RBM28 | 1.607459 | 1.690904 | 1.624345 | 1.055633 |
| MARS | 1.244251 | 1.290041 | 1.219733 | 0.807161 |
| ZDHHC21 | 1.378704 | 1.40399 | 1.338409 | 0.89381 |
| COPZ1 | 1.453755 | 1.386274 | 1.346312 | 0.932143 |
| HOXC10 | 5.197952 | 4.925716 | 4.821876 | 3.340861 |
| ZNF562 | 1.937498 | 1.799145 | 1.748465 | 1.236983 |
| FAM5C | 4.523746 | 4.508909 | 4.279576 | 3.000871 |
| SCN8A | 5.201022 | 5.122233 | 4.770471 | 3.30934 |
| PABPC1L | 3.136114 | 3.191123 | 2.91112 | 2.163203 |
| FKBP1B | 2.715801 | 2.92018 | 2.916847 | 1.682999 |
| AGSK1 | 2.97852 | 3.049782 | 3.101969 | 1.803942 |
| YEATS4 | 1.385152 | 1.40039 | 1.410652 | 0.79027 |
| PPAPDC1B | 1.626295 | 1.67858 | 1.793796 | 0.969832 |
| R3HDM1 | 2.144888 | 2.141732 | 2.286394 | 1.274195 |
| HSD17B10 | 1.37439 | 1.456649 | 1.419771 | 0.783016 |
| RFX3 | 1.741922 | 1.842951 | 1.739293 | 0.981358 |
| CKS1B | 2.209094 | 2.092592 | 2.33385 | 1.657969 |
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| AGAP2 | 5.036078 | 5.059977 | 5.207964 | 3.558875 |
| CENPL | 2.011888 | 1.947619 | 2.065622 | 1.38415 |

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| PLOD1 | 2.128098 | 2.05054 | 2.127875 | 1.447656 |
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| PPP2R5B | 1.215482 | 1.197456 | 1.215785 | 0.861321 |
| VBP1 | 1.026544 | 0.997936 | 1.003699 | 0.716664 |
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| GRIP1 | 2.058331 | 1.813371 | 2.058395 | 1.385808 |
| PREP | 1.324455 | 1.119858 | 1.268804 | 0.865604 |
| CLOCK | 1.448723 | 1.308528 | 1.389131 | 1.032093 |
| HCN4 | 3.857744 | 3.322751 | 3.484132 | 2.56386 |
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| NCBP1 | 1.638948 | 1.464222 | 1.436563 | 1.091492 |
| LHFPL4 | 5.961173 | 5.566082 | 5.464149 | 4.202015 |
| DNAJC14 | 1.611799 | 1.485712 | 1.482518 | 1.106245 |
| PSMD5 | 1.40148 | 1.293083 | 1.304302 | 0.97333 |
| TMEM145 | 3.737276 | 3.395627 | 3.366433 | 2.585647 |
| SUV39H2 | 1.528789 | 1.449964 | 1.384782 | 1.040346 |
| RAD51AP1 | 2.743619 | 2.56005 | 2.626744 | 1.856533 |
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| GFOD2 | 1.761018 | 1.546625 | 1.652456 | 1.091426 |
| ZNF280A | 2.558336 | 2.164245 | 2.343309 | 1.554577 |
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| GCFC1 | 1.693634 | 1.549437 | 1.779225 | 1.127251 |
| OLFM2 | 2.249877 | 2.058105 | 2.350985 | 1.462791 |
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| RHPN1 | 3.320837 | 3.19817 | 3.542854 | 2.268211 |
| CSNK1G3 | 1.607005 | 1.327977 | 1.463719 | 0.759552 |
| MESP1 | 3.278896 | 2.609576 | 2.7462 | 1.391909 |
| HIST1H2AE | 3.688948 | 2.665157 | 2.964311 | 1.722145 |
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| FKBP3 | 1.522565 | 1.154697 | 1.308687 | 0.799691 |
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| DCAF13 | 1.863406 | 1.474983 | 1.554121 | 0.843228 |

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| ZFHX2 | 2.538389 | 1.991929 | 2.098794 | 1.187869 |
| ATP2B4 | 2.127771 | 1.680096 | 1.744085 | 1.046196 |
| ZNF26 | 1.835273 | 1.435156 | 1.57752 | 0.91702 |
| ZNF850 | 3.654425 | 2.96938 | 3.137448 | 1.842718 |
| DLX4 | 5.225141 | 4.262097 | 3.997756 | 2.368819 |
| CAMSAP1 | 2.010962 | 1.68995 | 1.59933 | 0.904759 |
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| GLRX2 | 1.983111 | 1.621129 | 1.54486 | 0.990761 |
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| HIST1H2AB | 2.47798 | 1.851204 | 2.202531 | 1.60115 |
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| DNAJB5 | 1.587443 | 1.23655 | 1.349584 | 0.966531 |
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| FAM108C1 | 2.124707 | 1.574746 | 1.956074 | 1.207813 |
| SPRN | 1.767558 | 1.343699 | 1.606028 | 1.052777 |
| PLCXD1 | 2.278002 | 1.704275 | 1.998893 | 1.267324 |
| CDCA7L | 3.615492 | 3.203439 | 3.966459 | 2.286799 |
| HDAC6 | 2.278791 | 2.022214 | 2.511642 | 1.376277 |
| QPCTL | 2.411123 | 2.178913 | 2.696983 | 1.62556 |
| PEX13 | 1.538127 | 1.257996 | 1.682446 | 0.947233 |
| BSDC1 | 1.73502 | 1.564068 | 1.777106 | 0.994913 |
| PPAT | 2.927731 | 2.576949 | 3.040882 | 1.589236 |
| RNGTT | 1.434584 | 1.229992 | 1.441966 | 0.780433 |
| NUP155 | 1.778746 | 1.560243 | 1.791035 | 1.080887 |
| SIPA1L1 | 1.531589 | 1.322515 | 1.576214 | 0.908065 |
| KIAA1539 | 1.658595 | 1.346057 | 1.739091 | 0.862585 |
| TDRKH | 2.827794 | 2.399175 | 3.016012 | 1.548798 |
| GMFB | 2.413013 | 1.703827 | 2.408408 | 1.318863 |
| PCDHGB1 | 3.196949 | 2.366946 | 3.207619 | 1.756338 |
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| TP53BP1 | 1.553103 | 1.167863 | 1.451043 | 0.797809 |

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| CCZ1 | 1.498186 | 1.288023 | 1.767804 | 0.80984 |
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| MARCH7 | 1.167539 | 1.029846 | 1.454875 | 0.726015 |
| TTL | 1.694378 | 1.511837 | 2.051296 | 1.03471 |
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| PTP4A2 | 1.148574 | 1.102215 | 1.616168 | 0.755354 |
| CCDC99 | 1.119782 | 1.148507 | 1.409699 | 0.73725 |
| CHST10 | 2.341875 | 2.259665 | 2.763891 | 1.647324 |
| HSPA4L | 2.371668 | 2.38587 | 2.891385 | 1.718964 |
| CATSPERG | 2.757125 | 2.781175 | 3.355159 | 1.898223 |
| MEMO1 | 1.367518 | 1.407572 | 1.732985 | 0.976662 |
| MYL12B | 1.405398 | 1.378291 | 1.760405 | 0.990048 |
| TET2 | 1.123556 | 1.092136 | 1.367243 | 0.755721 |
| DDX25 | 2.659505 | 2.873945 | 3.25183 | 1.810192 |
| PPP4R2 | 1.198515 | 1.272301 | 1.373339 | 0.755052 |
| PITPNM1 | 2.543527 | 2.74656 | 3.141005 | 1.517031 |
| CABYR | 2.02808 | 2.196976 | 3.219626 | 1.635134 |
| ILF2 | 1.054561 | 1.06513 | 1.587366 | 0.820889 |
| RBBP8 | 1.172747 | 1.23785 | 1.762116 | 1.039262 |
| XPR1 | 0.984262 | 0.998579 | 1.394905 | 0.813205 |
| ABL1 | 1.680904 | 2.007725 | 2.629438 | 1.479693 |
| NAB1 | 1.843972 | 2.244577 | 2.846666 | 1.710518 |
| TDG | 1.450478 | 1.602131 | 2.0185 | 1.094336 |
| ZNF730 | 1.899568 | 2.192168 | 2.693293 | 1.513714 |
| ECT2 | 3.070312 | 3.744852 | 4.299016 | 1.978764 |
| LOC730202 | 1.950373 | 2.231832 | 2.625162 | 1.133 |
| ANKRD20A2 | 2.497365 | 2.741876 | 3.38153 | 1.593806 |
| ZSCAN16 | 1.864417 | 2.08859 | 2.538138 | 1.144023 |
| COX2 | 1.48381 | 1.760165 | 1.900878 | 1.077131 |
| CTSC | 2.778366 | 3.547358 | 3.766678 | 2.055364 |
| ZNF699 | 1.301219 | 1.584599 | 1.830799 | 0.944323 |
| MSH2 | 1.129364 | 1.652099 | 1.897008 | 0.782341 |
| MTRF1L | 1.106661 | 1.535218 | 1.768437 | 0.836465 |
| PSMA1 | 1.15925 | 1.708599 | 1.866516 | 0.857546 |
| PPM1J | 2.055407 | 2.507566 | 3.195627 | 1.363088 |

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| SLAIN1 | 1.185153 | 1.503296 | 1.976848 | 0.93245 |
| CDCA4 | 2.40903 | 3.395758 | 2.897142 | 1.659292 |
| ARHGAP35 | 1.790571 | 2.740502 | 2.140031 | 1.283577 |
| ZNF587 | 1.713241 | 2.539321 | 2.006214 | 1.191738 |
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| MYPOP | 1.733581 | 2.557185 | 2.122664 | 1.354087 |
| HEATR1 | 1.386652 | 1.851278 | 1.525054 | 0.973856 |
| RAD54L2 | 1.062086 | 1.464561 | 1.184839 | 0.801318 |
| TMEM44 | 1.808068 | 2.461433 | 1.940717 | 1.329133 |
| MCM3 | 1.129983 | 1.501818 | 1.269544 | 0.902515 |
| HNRPLL | 1.191397 | 1.611705 | 1.55694 | 0.856026 |
| CITED1 | 2.530775 | 3.54961 | 3.337187 | 2.021442 |
| SALL4 | 3.273008 | 4.450658 | 4.167104 | 2.519862 |
| FLJ41327 | 1.722713 | 2.34259 | 2.141484 | 1.264952 |
| TMEM185B | 1.025987 | 1.361692 | 1.219884 | 0.723636 |
| PPP1R14C | 3.590264 | 4.637634 | 4.34109 | 2.529004 |
| BBS5 | 1.492439 | 1.820215 | 1.606938 | 0.911683 |
| KNTC1 | 2.069253 | 2.447581 | 2.174947 | 1.297876 |
| ODC1 | 1.232916 | 1.594571 | 1.322517 | 0.753758 |
| PRR19 | 1.682943 | 2.080262 | 1.81398 | 0.92686 |
| ADAMTS6 | 3.369721 | 4.09662 | 3.812912 | 1.80609 |
| SYCE1 | 4.195311 | 5.27534 | 5.086864 | 2.300113 |
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| LEPRE1 | 1.731466 | 2.001663 | 1.841544 | 0.847285 |
| FUBP1 | 1.620475 | 1.869844 | 1.841233 | 1.000308 |
| SGK196 | 2.210889 | 2.597361 | 2.50336 | 1.362257 |
| NTS | 7.296605 | 8.504088 | 8.381744 | 4.14182 |
| RAB38 | 2.091169 | 2.404438 | 2.509373 | 1.334615 |
| MYBL1 | 3.884765 | 5.796716 | 5.539411 | 2.422988 |
| PLSCR3 | 1.423851 | 1.935724 | 1.851171 | 0.922416 |
| CDK2 | 2.362678 | 2.840179 | 2.470204 | 1.808059 |
| MCM2 | 2.167752 | 2.71947 | 2.380092 | 1.705726 |
| KIAA0100 | 1.064011 | 1.280057 | 1.185807 | 0.833924 |
| DAB2IP | 2.708815 | 3.222077 | 2.811138 | 1.944641 |
| LIPG | 3.630082 | 4.395983 | 3.910904 | 2.570876 |
| MCM3AP | 1.009735 | 1.263927 | 1.041929 | 0.722085 |
| RNF167 | 1.491619 | 1.762644 | 1.47576 | 1.065569 |
| DPP9 | 1.657555 | 2.014607 | 1.880441 | 1.52043 |
| KIF15 | 4.198079 | 5.097316 | 4.825958 | 3.739925 |

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| NUF2 | 3.689086 | 4.270294 | 4.192201 | 3.067698 |
| REXO1L1 | 3.178007 | 3.747352 | 3.544042 | 2.58304 |
| GPBP1L1 | 0.834004 | 1.159865 | 1.116247 | 0.772462 |
| FLJ35424 | 2.00438 | 2.737024 | 2.507189 | 1.85047 |
| KLC2 | 1.981837 | 2.518134 | 2.386123 | 1.747843 |
| E2F3 | 2.314414 | 3.034309 | 2.877447 | 1.856671 |
| RTN2 | 2.038867 | 2.668384 | 2.500881 | 1.667646 |
| WIBG | 0.909644 | 1.163357 | 1.080459 | 0.733073 |
| GABBR2 | 5.319125 | 6.304063 | 6.141139 | 4.133717 |
| DHX30 | 2.316775 | 2.668409 | 2.626363 | 1.657877 |
| ACOT7 | 2.041989 | 2.461048 | 2.431041 | 1.522021 |
| ROMO1 | 1.126376 | 1.319512 | 1.312181 | 0.835396 |
| PCDH9 | 5.228373 | 5.578346 | 5.75476 | 3.756039 |
| SNORA62 | 2.432944 | 2.62656 | 2.742127 | 1.690365 |
| TMEM194B | 1.54716 | 1.665719 | 1.818321 | 1.118864 |
| RPL39L | 1.918796 | 2.107557 | 2.134015 | 1.301922 |
| XKR6 | 3.195773 | 3.558359 | 3.54116 | 2.15389 |
| ETV4 | 4.039069 | 4.889938 | 5.151083 | 3.564919 |
| FAM173A | 1.375055 | 1.62129 | 1.721025 | 1.16487 |
| CASC2 | 1.701522 | 2.085784 | 2.089759 | 1.429609 |
| PLK4 | 2.753866 | 3.334019 | 3.488179 | 2.263079 |
| INTS7 | 1.122718 | 1.236199 | 1.355987 | 0.916475 |
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| TNK2 | 2.257788 | 2.558147 | 2.700752 | 1.756435 |
| SFMBT1 | 2.67259 | 3.007273 | 3.44411 | 2.077725 |
| STMN1 | 2.27804 | 2.630692 | 2.886348 | 1.840678 |
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| AGMO | 6.865838 | 6.832437 | 6.595399 | 1.407124 |
| PCDHB2 | 4.274878 | 4.240973 | 4.200286 | 0.765443 |
| FLJ39632 | 2.895407 | 3.725552 | 2.751255 | 0.800419 |
| FOXF1 | 4.509095 | 5.180525 | 4.308959 | 1.185803 |
| WDR54 | 2.578373 | 2.827607 | 2.333743 | 0.73381 |
| PAQR6 | 2.778339 | 3.002028 | 2.479503 | 0.962794 |
| PARD6A | 2.307633 | 2.501521 | 2.061481 | 0.815181 |
| CBX8 | 3.465064 | 3.172431 | 2.684055 | 0.887092 |
| CTNNBIP1 | 2.277707 | 2.113961 | 1.877097 | 0.852943 |
| LRRTM4 | 9.767971 | 9.061311 | 8.120997 | 3.907266 |
| FAM113A | 2.028347 | 2.074761 | 1.762749 | 0.954526 |
| FGF11 | 3.725478 | 3.591671 | 3.126418 | 1.710604 |
| TMEM191B | 2.709615 | 2.699004 | 2.274677 | 1.128853 |

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| PLEKHG1 | 3.319294 | 3.002445 | 2.637303 | 1.480032 |
| SCAMP5 | 2.198797 | 1.923041 | 1.830541 | 0.954888 |
| PLEKHB1 | 2.915812 | 2.638609 | 2.214372 | 1.169261 |
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| DNASE1L2 | 3.304604 | 2.685221 | 2.377012 | 1.202706 |
| ZDHHC23 | 4.097792 | 3.321976 | 2.884374 | 1.421578 |
| SLC25A35 | 2.864262 | 2.370205 | 2.139198 | 1.079682 |
| ZNF492 | 2.493515 | 2.131181 | 1.964355 | 0.968394 |
| YBX2 | 2.516768 | 2.114483 | 1.721138 | 0.815648 |
| PCSK4 | 3.407983 | 2.605595 | 2.435171 | 0.938204 |
| GLI1 | 3.227765 | 3.063505 | 3.043858 | 0.988372 |
| VSTM2A | 3.793937 | 3.556832 | 3.28685 | 1.197736 |
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| ZNF608 | 3.673546 | 3.397265 | 3.352851 | 0.889061 |
| FLJ22184 | 3.15439 | 2.742173 | 2.737107 | 1.206455 |
| SPAG7 | 1.984826 | 1.754499 | 1.757495 | 0.82358 |
| TRIM49 | 6.870447 | 5.977158 | 6.468517 | 2.47829 |
| PTPN3 | 3.608638 | 3.3177 | 3.776302 | 1.260283 |
| CXADR | 5.543526 | 4.047612 | 5.293639 | 1.220893 |
| ITPKA | 2.811123 | 2.194814 | 2.403039 | 0.874115 |
| VPS13A | 2.96656 | 2.243152 | 2.336358 | 0.802923 |
| RNF212 | 3.413399 | 2.419033 | 2.817218 | 0.955405 |
| TBCC | 2.948492 | 1.946413 | 2.257274 | 0.747149 |
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| FANCC | 2.27999 | 2.54918 | 2.670644 | 1.023629 |
| NPHS1 | 3.725958 | 4.181692 | 4.247812 | 1.639756 |
| XKR4 | 3.677303 | 4.27631 | 4.612308 | 1.555308 |
| KCNK12 | 2.626329 | 3.212523 | 2.85227 | 1.001805 |
| NQO1 | 2.299042 | 2.857378 | 2.758064 | 0.929814 |
| LOC388152 | 2.648343 | 3.088026 | 3.237085 | 0.710215 |
| YPEL1 | 2.238128 | 2.703814 | 2.911007 | 0.770122 |
| BX114012 | 3.032375 | 2.583781 | 2.947239 | 1.411526 |
| CCDC138 | 2.51954 | 2.288394 | 2.611325 | 1.287691 |
| TNKS2 | 1.686922 | 1.512281 | 1.708647 | 0.842449 |
| CELSR2 | 1.763509 | 1.812865 | 1.960697 | 0.891586 |
| MYEF2 | 3.950539 | 3.927866 | 4.345713 | 1.992123 |
| CELF4 | 1.632361 | 1.598391 | 1.662955 | 0.841751 |

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| ARGLU1 | 2.04699 | 2.401824 | 1.719484 | 0.998295 |
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| MMP15 | 1.783331 | 2.093407 | 1.730513 | 0.959783 |
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| TBRG4 | 1.548103 | 1.923185 | 1.229258 | 1.212424 |
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| SNAR-C4 | 2.583535 | 3.155922 | 1.917691 | 1.716369 |
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| RRP7A | 1.980205 | 2.364614 | 1.499289 | 1.605155 |
| SNRNP40 | 1.013353 | 1.104348 | 0.736223 | 0.720722 |
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| SNRPA1 | 0.920314 | 1.240595 | 0.957045 | 0.741043 |
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| RAP2B | 1.107456 | 0.818166 | 2.70836 | 1.004619 |
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| SLC30A7 | 1.034805 | 0.724326 | 0.721746 | 1.858611 |
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| IL1RAPL1 | 4.4933 | 3.841827 | 3.988216 | -1.138105 |
| RMND5A | 1.772509 | 1.249755 | 0.947776 | -0.085307 |
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| SOSTDC1 | 6.204701 | 5.758579 | 4.618943 | -3.152818 |
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| SLITRK6 | 3.442881 | 4.477034 | 3.183959 | -1.390703 |
| TBX2 | 2.743857 | 3.376742 | 2.24677 | -0.873442 |
| AGBL5 | 1.039037 | 1.611048 | 0.945837 | -0.962121 |
| FAM193A | 0.776519 | 1.077748 | 0.779419 | -0.750739 |
| FGD1 | 1.390978 | 2.034264 | 1.320029 | -0.773381 |
| IRX5 | 2.82796 | 4.180965 | 2.213627 | -1.807894 |
| AS3MT | 1.854441 | 2.339922 | 1.13359 | -1.563374 |
| ATP6AP1L | 1.249057 | 1.350513 | 0.714561 | -0.752019 |
| NAB2 | 1.486531 | 1.643354 | 0.971752 | -0.899758 |
| ISYNA1 | 2.564749 | 2.875162 | 1.920465 | -1.652416 |
| ADCY6 | 1.391433 | 1.336875 | 0.835195 | -0.933915 |
| SCARNA23 | 1.979635 | 1.992794 | 1.24686 | -1.324844 |
| IFT140 | 1.308954 | 1.420731 | 0.890649 | -1.019722 |
| ROBO2 | 2.871189 | 3.095591 | 2.434788 | -2.294914 |
| ALDH7A1 | 1.649678 | 1.619728 | 1.200569 | -1.505371 |
| HAND2 | 3.037494 | 3.162575 | 1.720859 | -2.828554 |

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|---|---|---|---|---|
| PFN2 | 1.457526 | 1.451701 | 0.904444 | -1.266197 |
| LOC650293 | 2.251498 | 2.060868 | 1.008009 | -1.701555 |
| DCLK2 | 0.987475 | 1.535351 | 1.023799 | -1.644996 |
| BAI3 | 3.160693 | 4.40601 | 2.997943 | -3.910397 |
| MDGA2 | 2.280456 | 3.666488 | 2.277633 | -3.006919 |
| CNNM2 | 0.801908 | 0.788591 | 0.716717 | -1.177363 |
| ARHGEF25 | 0.914359 | 1.178019 | 0.879378 | -1.31278 |
| SOX12 | 1.24203 | 1.527303 | 1.366593 | -1.82563 |
| LANCL1 | 0.825597 | 0.913367 | 0.834273 | -1.016349 |
| WNT6 | 1.290394 | 1.259405 | 1.083577 | -1.482073 |
| LIN52 | 1.088014 | 1.108092 | 0.730628 | -1.202973 |
| NR4A2 | 2.274112 | 2.608871 | 1.536845 | -3.114506 |
| SPTBN4 | 1.524508 | 1.776962 | 1.043539 | -1.882316 |
| CAPRIN2 | 0.764751 | 0.83512 | 0.962688 | -1.110659 |
| RPRM | 3.66889 | 3.346411 | 4.430274 | -5.326301 |
| EFHC1 | 0.987182 | 1.144375 | 1.398719 | -1.892319 |
| TRO | 1.091817 | 1.04574 | 1.335106 | -1.854779 |
| PCDHB10 | 1.92867 | 1.788701 | 2.255045 | -2.255753 |
| BMP3 | 5.38537 | 3.843003 | 4.156197 | -5.065911 |
| LOC100289333 | 0.939004 | 0.828159 | 0.903297 | -1.225955 |
| PCLO | 2.057036 | 1.740645 | 2.012852 | -2.417821 |
| PPP1R9A | 1.375934 | 1.052352 | 1.186475 | -1.442923 |
| SGK2 | 1.580384 | 1.137576 | 1.404624 | -1.740861 |
| LOC155060 | 1.236773 | 0.743718 | 0.750085 | -1.316612 |
| DNAH7 | 3.597084 | 2.173969 | 2.299663 | -3.439679 |
| SSBP2 | 1.38763 | 0.848435 | 0.938947 | -1.427591 |
| PCDHB9 | 2.556998 | 1.951713 | 1.425854 | -2.453459 |
| SMN2 | 1.163338 | 0.975908 | 0.782076 | -1.214734 |
| FGF9 | 1.763133 | 0.981807 | 1.832406 | -1.916947 |
| SEZ6L2 | 1.462658 | 1.033611 | 1.633126 | -1.589868 |
| KIAA1549 | 1.290173 | 0.792991 | 1.673203 | -1.186656 |
| SIX4 | 2.229032 | 1.393851 | 2.396334 | -1.878259 |
| FBXO36 | 1.340833 | 0.900487 | 1.058542 | -0.895424 |
| ASPHD1 | 2.269642 | 1.652207 | 1.894333 | -1.599982 |
| FAM66C | 1.372557 | 0.978736 | 1.188647 | -0.952183 |
| WSB1 | 1.266312 | 0.906151 | 1.105238 | -0.90497 |
| GPLD1 | 2.339039 | 1.901403 | 1.860114 | -1.942118 |
| GREB1L | 3.209729 | 2.486451 | 2.572837 | -2.358593 |
| LOC100130950 | 1.318012 | 1.055809 | 1.051842 | -0.999332 |
| SCG5 | 1.414462 | 1.213282 | 1.28081 | -1.244667 |

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|---|---|---|---|---|
| ERBB3 | 3.12071 | 2.448325 | 2.191426 | -2.075069 |
| ARPM1 | 1.43758 | 1.151573 | 1.090214 | -0.901905 |
| MDGA1 | 1.993658 | 1.656763 | 1.479383 | -1.283076 |
| FAM106A | 3.11929 | 2.454231 | 1.982227 | -2.19758 |
| PCDHGA12 | 1.567147 | 1.205484 | 1.00618 | -1.107903 |
| SPEF1 | 1.879953 | 1.568722 | 1.090796 | -1.305844 |
| USP11 | 1.377776 | 0.981889 | 0.772022 | -0.868932 |
| CACNB3 | 1.533339 | 0.954646 | 1.060412 | -1.081427 |
| FLJ42289 | 3.091912 | 1.892169 | 1.881613 | -2.022967 |
| LRRC1 | 1.425197 | 0.920897 | 0.874508 | -1.002338 |
| TM7SF2 | 1.28633 | 0.716108 | 0.802254 | -0.815201 |
| MYOM1 | 1.878357 | 1.084843 | 1.201388 | -1.43507 |
| ENAH | 2.006223 | 1.116053 | 1.726426 | -1.281959 |
| LRTOMT | 1.657135 | 0.900326 | 1.431035 | -1.055712 |
| INTU | 1.673013 | 1.138277 | 1.180509 | -0.964707 |
| L3MBTL1 | 2.000723 | 1.137913 | 1.275544 | -1.068378 |
| LOC646903 | 2.08147 | 1.470355 | 1.61059 | -1.030729 |
| SAMD5 | 4.473391 | 2.707513 | 3.44902 | -2.247294 |
| STXBP4 | 1.341627 | 0.776915 | 0.984008 | -0.722138 |
| MLF1 | 1.77488 | 0.79769 | 1.282872 | -0.766906 |
| SLC2A11 | 1.759418 | 0.829684 | 1.224891 | -0.828386 |
| SPATA17 | 2.86316 | 1.311769 | 2.039262 | -2.15445 |
| SASH1 | 1.966362 | 1.070158 | 2.1333 | -1.054566 |
| SPINK5 | 4.721143 | 2.513289 | 4.635295 | -2.402501 |
| COPG2IT1 | 1.232929 | 2.892702 | 3.511029 | -2.355887 |
| CTNND2 | 1.732133 | 2.618151 | 3.455835 | -2.726167 |
| LOC389834 | 0.816446 | 1.339709 | 1.700603 | -1.255377 |
| RASSF9 | 1.129896 | 2.043409 | 2.349822 | -1.848307 |
| PNMAL1 | 0.840294 | 1.406511 | 1.700401 | -1.660383 |
| RNF182 | 1.173738 | 2.169218 | 3.674853 | -2.822858 |
| ARHGEF10 | 1.067388 | 1.168338 | 1.573741 | -0.869134 |
| CRHR1 | 1.229202 | 1.717104 | 2.674983 | -1.108763 |
| HOXC4 | 1.20568 | 1.971087 | 2.240568 | -1.321572 |
| OXR1 | 1.059863 | 1.881227 | 2.36053 | -1.139389 |
| LOC100506930 | 1.073827 | 1.544371 | 1.321165 | -1.165648 |
| RAB6B | 0.985984 | 1.411807 | 1.317765 | -1.095472 |
| HSF4 | 1.272241 | 1.544455 | 1.661801 | -1.408916 |
| LPHN3 | 2.908249 | 3.36965 | 3.696081 | -3.065229 |
| NLGN1 | 2.433433 | 3.019309 | 3.143522 | -2.516244 |
| STXBP1 | 1.016493 | 1.269095 | 1.289667 | -1.1458 |

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|---|---|---|---|---|
| RSPH3 | 0.896693 | 1.164862 | 1.269268 | -1.099739 |
| PCDHB14 | 1.911744 | 2.275351 | 2.26269 | -1.765322 |
| PTHLH | 3.681636 | 4.640454 | 4.986216 | -3.436168 |
| ZNF667 | 1.240923 | 1.19345 | 1.30662 | -1.101134 |
| NR2F2 | 1.381143 | 1.230762 | 1.853699 | -1.349553 |
| RCOR2 | 1.062391 | 1.20665 | 1.561834 | -1.199997 |
| TET1 | 1.212706 | 1.281596 | 1.647729 | -1.271526 |
| FST | 1.423213 | 5.128318 | 5.100541 | -2.277769 |
| NPNT | 0.872176 | 4.002031 | 3.656909 | -1.910401 |
| NTN5 | 1.337762 | 3.59533 | 3.40273 | -1.415938 |
| MEST | 1.325554 | 4.30678 | 4.688699 | -0.743623 |
| LOC100128361 | 0.733651 | 1.962334 | 1.090202 | -0.84196 |
| CDHR3 | 1.192995 | 2.339653 | 2.031047 | -1.464404 |
| TNKS1BP1 | 1.317541 | 2.22459 | 1.721042 | -1.101111 |
| CYP4B1 | 1.041814 | 3.01541 | 2.062699 | -2.019174 |
| PKD1 | 0.765909 | 1.6433 | 1.032175 | -0.984497 |
| ZNF248 | 0.828179 | 1.604026 | 1.108235 | -1.045454 |
| PLCD4 | 0.774745 | 2.894115 | 1.211503 | -2.063086 |
| SGCG | 1.296005 | 4.103683 | 2.805493 | -3.621988 |
| CAV2 | 0.897297 | 2.112536 | 2.340915 | -3.03281 |
| RAB34 | 0.736848 | 1.64601 | 0.921513 | -2.135137 |
| CAND2 | 1.800761 | 0.81237 | 1.617614 | -2.959265 |
| KATNAL2 | 1.960975 | 0.832907 | 1.435524 | -2.329979 |
| AGR2 | 2.282879 | 1.293638 | 0.893736 | -3.64299 |
| NBLA00301 | 3.499471 | 2.845103 | 1.179124 | -5.810321 |
| CCDC89 | 2.242922 | 1.376237 | 1.210514 | -2.983728 |
| RFPL1-AS1 | 1.649285 | 1.095907 | 1.181571 | -2.218624 |
| IQCA1 | 1.861475 | 1.428755 | 0.911831 | -2.476299 |
| WARS2 | 1.37538 | 1.140921 | 0.855774 | -1.800479 |
| NEDD4L | 1.501841 | 0.937687 | 1.120835 | -2.557997 |
| SPTB | 1.55041 | 1.199736 | 1.043746 | -2.695862 |
| NCRNA00245 | 1.683168 | 0.730694 | 0.929995 | -2.995593 |
| CNTNAP2 | 1.756681 | 2.430037 | 2.198965 | -5.103864 |
| GATA4 | 1.28525 | 2.234983 | 1.810625 | -4.641358 |
| MKX | 1.452006 | 3.167756 | 3.017691 | -7.000669 |
| MDH1B | 1.5048 | 0.98919 | 1.275094 | -3.670963 |
| BNC2 | 1.489851 | 1.379108 | 1.083568 | -3.477577 |
| WT1-AS | 2.382595 | 2.411025 | 1.986042 | -6.44465 |
| WT1 | 2.851654 | 2.910365 | 2.791783 | -6.900506 |
| SLITRK3 | 1.586048 | 1.990137 | 2.666675 | -7.046425 |

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|---|---|---|---|---|
| WDR16 | 0.854707 | 1.177546 | 0.760844 | -3.42137 |
| HOXC6 | 0.855586 | 1.052631 | 1.259976 | -2.460992 |
| PDZRN4 | 2.401165 | 2.436876 | 3.428547 | -5.904812 |
| ZC3H12B | 1.08123 | 0.985052 | 1.423637 | -2.385363 |
| SMARCD3 | 0.763648 | 1.014884 | 0.976912 | -1.752381 |
| ZNF528 | 0.828542 | 0.897565 | 0.920016 | -1.562258 |
| EPHA7 | -1.941764 | 1.357333 | 1.169889 | 0.991359 |
| FARP1 | -2.384035 | 1.453314 | 1.576416 | 0.972711 |
| RNF207 | -2.958497 | 1.444997 | 1.198466 | 1.460318 |
| FBN2 | -0.791564 | 1.835608 | 3.602771 | 0.752972 |
| EGLN3 | -1.23202 | 2.472142 | 3.602337 | 0.810591 |
| TMEM100 | -1.032576 | 2.532812 | 3.150539 | 0.942946 |
| ARL4A | -1.430391 | 2.637891 | 2.399817 | 1.624159 |
| PDE3B | -3.165529 | 4.421743 | 4.719927 | 3.575149 |
| ARHGEF26 | -1.120629 | 1.229991 | 1.726203 | 1.706926 |
| PHLDA1 | -0.92948 | 1.227071 | 1.81243 | 1.278427 |
| PTPRJ | -0.766543 | 1.320103 | 2.138266 | 1.706398 |
| MSN | -1.325494 | 1.097949 | 1.461407 | 1.152906 |
| FSCN1 | -0.921237 | 0.733891 | 0.893611 | 1.534056 |
| RELB | -0.83124 | 1.12367 | 1.279399 | 2.235741 |
| SH2D3A | -2.360523 | 0.824077 | 3.172165 | 2.591805 |
| FABP5 | -0.727244 | 3.111495 | 0.861241 | 1.150106 |
| VIPR1 | -2.672031 | 5.856202 | 2.220007 | 3.236846 |
| BTBD16 | -1.646596 | 1.208132 | 0.867686 | -2.13947 |
| DMKN | -1.656211 | 1.546347 | 0.976986 | -2.696019 |
| PMP22 | -1.375309 | 1.471786 | 0.770286 | -1.837997 |
| BAHCC1 | -1.747003 | 1.483748 | 1.02044 | -1.449865 |
| NOS1AP | -1.661993 | 1.281721 | 1.019823 | -1.579463 |
| APLN | -0.833418 | 1.412763 | 1.01525 | -3.283422 |
| KRTDAP | -0.978005 | 1.937138 | 1.426811 | -3.575207 |
| EPHA4 | -0.898086 | 0.744852 | 1.163361 | -1.429251 |
| ZBTB10 | -1.134186 | 0.922663 | 1.6732 | -2.556409 |
| LOC100127909 | -1.516562 | 2.261666 | 2.446754 | -4.215686 |
| ZBTB7C | -1.597562 | 2.242535 | 2.130999 | -2.948833 |
| EYA2 | -0.956403 | 1.006978 | 2.617574 | -2.227937 |
| KALRN | -0.41155 | -0.049263 | 0.730023 | -0.201992 |
| EMP1 | -2.27274 | 1.051507 | 3.451727 | -1.278062 |
| SH3RF1 | -1.689224 | 0.873788 | 1.744597 | -1.329007 |
| FUT1 | -1.102232 | 2.918328 | 2.459409 | -0.732876 |
| CYP4F12 | -1.106558 | 1.643347 | 1.723176 | -1.134122 |

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|---|---|---|---|---|
| FRAS1 | -2.125577 | 3.317302 | 3.036376 | -2.085458 |
| FLNB | -0.782226 | 1.063268 | 0.821381 | -0.86855 |
| TFPI2 | -2.310583 | 2.547354 | 3.831866 | -2.161177 |
| SYNE1 | -1.758684 | 1.914929 | 2.126616 | -0.902122 |
| GPC4 | -1.206689 | 2.952063 | 1.805532 | -1.627192 |
| CRABP2 | -1.342762 | 3.442619 | 3.070671 | -1.841178 |
| NGEF | -0.81479 | 3.950809 | 3.579599 | -2.461302 |
| SEMA6A | -0.76884 | 2.903424 | 3.401364 | -2.06632 |
| PPL | -1.00268 | 2.406241 | 2.776102 | -2.583437 |
| ST3GAL4 | -0.272354 | 0.961445 | 0.262971 | -0.521545 |
| S100A10 | -4.354639 | 0.990263 | 1.53658 | -1.021321 |
| SOX6 | -3.708115 | 1.60598 | 1.111075 | -1.688651 |
| KIF5C | 1.735526 | -1.122559 | 1.102977 | 1.348262 |
| GPR64 | 3.579795 | -1.498476 | 1.369706 | 2.764912 |
| NNAT | 2.544889 | -1.429364 | 1.060307 | 2.12966 |
| MICB | 1.210014 | -1.680964 | 1.194435 | 1.40632 |
| XCL1 | 2.135817 | -2.077481 | 1.744307 | 2.32466 |
| KLF12 | 0.732131 | -3.79874 | -0.853628 | 0.760583 |
| LRMP | 0.720804 | -3.139128 | -3.083513 | 1.512046 |
| CXCR4 | 0.716801 | -1.397978 | -0.892737 | 2.603895 |
| UCHL1 | 0.99774 | -2.049729 | -1.221566 | 2.04697 |
| NOS2 | 0.851942 | -1.00304 | -1.543534 | 1.381317 |
| RPS2 | 0.427108 | -0.115332 | -0.322239 | 0.569246 |
| LRRD1 | 2.071655 | -1.258415 | -1.247121 | 0.889076 |
| KRTAP19-2 | 2.119902 | -1.166729 | -1.437067 | 1.442246 |
| PRSS36 | 1.980103 | -1.141228 | -1.308538 | 1.394983 |
| ZFHX4 | 3.738277 | -2.874626 | -3.738858 | 1.409562 |

# APPENDIX B

# GENE ONTOLOGY PROCESSES ASSOCIATED WITH SCCOHT TUMORS RELATIVE TO NORMAL OVARY

| Rank | GO Processes | pValue | FDR | Ratio | |
|---|---|---|---|---|---|
| 1 | Response to estradiol stimulus | 1.81E-17 | 8.27E-14 | 114 | 208 |
| 2 | Mitotic cell cycle | 2.35E-17 | 8.27E-14 | 211 | 654 |
| 3 | Interferon-gamma-mediated signaling pathway | 9.72E-15 | 2.28E-11 | 63 | 93 |
| 4 | Male gonad development | 3.31E-13 | 5.82E-10 | 80 | 166 |
| 5 | Mitotic prometaphase | 8.42E-13 | 1.18E-09 | 71 | 117 |
| 6 | Cell division | 1.32E-12 | 1.35E-09 | 179 | 498 |
| 7 | Cell adhesion | 1.34E-12 | 1.35E-09 | 290 | 927 |
| 8 | Response to organic cyclic compound | 1.60E-12 | 1.41E-09 | 149 | 1181 |
| 9 | M phase of mitotic cell cycle | 3.79E-12 | 2.97E-09 | 115 | 227 |
| 10 | Cell surface receptor signaling pathway | 1.11E-11 | 7.80E-09 | 144 | 3169 |
| 11 | Response to drug | 2.44E-11 | 1.56E-08 | 259 | 707 |
| 12 | Mitosis | 5.43E-11 | 3.18E-08 | 142 | 464 |
| 13 | Immune response | 7.76E-11 | 3.87E-08 | 204 | 1340 |
| 14 | Positive regulation of apoptotic process | 7.81E-11 | 3.87E-08 | 165 | 660 |
| 15 | Aging | 8.26E-11 | 3.87E-08 | 137 | 394 |
| 16 | Regulation of muscle contraction | 3.10E-10 | 1.31E-07 | 32 | 180 |
| 17 | Blood coagulation | 3.15E-10 | 1.31E-07 | 253 | 654 |
| 18 | Negative regulation of cell proliferation | 3.42E-10 | 1.34E-07 | 226 | 767 |
| 19 | Nervous system development | 4.27E-10 | 1.58E-07 | 237 | 2397 |
| 20 | Positive regulation of angiogenesis | 4.64E-10 | 1.63E-07 | 71 | 137 |
| 21 | Cell cycle | 6.15E-10 | 2.06E-07 | 285 | 1424 |
| 22 | Cytokine-mediated signaling pathway | 8.06E-10 | 2.57E-07 | 149 | 425 |
| 23 | Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II | 8.40E-10 | 2.57E-07 | 19 | 128 |
| 24 | Antigen processing and presentation | 1.33E-09 | 3.90E-07 | 51 | 287 |
| 25 | Detection of bacterium | 1.54E-09 | 4.32E-07 | 27 | 37 |
| 26 | Cellular response to follicle-stimulating hormone stimulus | 3.72E-09 | 9.68E-07 | 21 | 24 |
| 27 | Antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-independent | 3.72E-09 | 9.68E-07 | 21 | 24 |
| 28 | Positive regulation of epidermal growth factor receptor signaling pathway | 6.40E-09 | 1.61E-06 | 19 | 35 |
| 29 | Organ regeneration | 7.52E-09 | 1.82E-06 | 66 | 125 |
| 30 | Antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent | 1.01E-08 | 2.36E-06 | 60 | 109 |
| 31 | Smooth muscle contraction | 1.29E-08 | 2.89E-06 | 33 | 82 |
| 32 | Axon guidance | 1.31E-08 | 2.89E-06 | 178 | 477 |
| 33 | Antigen processing and presentation of exogenous peptide antigen via MHC class I | 1.67E-08 | 3.56E-06 | 62 | 115 |

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|---|---|---|---|---|---|
| 34 | Negative regulation of angiogenesis | 2.57E-08 | 5.19E-06 | 47 | 90 |
| 35 | Locomotory behavior | 2.58E-08 | 5.19E-06 | 62 | 217 |
| 36 | Apoptotic process | 2.76E-08 | 5.40E-06 | 348 | 1196 |
| 37 | Nucleosome assembly | 5.98E-08 | 1.14E-05 | 62 | 121 |
| 38 | Muscle contraction | 6.26E-08 | 1.14E-05 | 73 | 279 |
| 39 | Memory | 6.30E-08 | 1.14E-05 | 53 | 132 |
| 40 | G1/S transition of mitotic cell cycle | 9.53E-08 | 1.68E-05 | 103 | 234 |
| 41 | Sensory perception of pain | 1.57E-07 | 2.69E-05 | 53 | 115 |
| 42 | Steroid hormone mediated signaling pathway | 1.67E-07 | 2.79E-05 | 48 | 87 |
| 43 | Angiogenesis | 1.85E-07 | 3.03E-05 | 123 | 376 |
| 44 | Positive regulation of cell proliferation | 1.95E-07 | 3.11E-05 | 241 | 977 |
| 45 | Positive regulation of nitric oxide biosynthetic process | 2.13E-07 | 3.33E-05 | 34 | 54 |
| 46 | Cell cycle checkpoint | 2.67E-07 | 4.09E-05 | 79 | 300 |
| 47 | Mitotic anaphase | 3.51E-07 | 5.26E-05 | 88 | 191 |
| 48 | Positive regulation of ERK1 and ERK2 cascade | 3.98E-07 | 5.84E-05 | 64 | 130 |
| 49 | Skeletal system development | 4.29E-07 | 6.16E-05 | 87 | 495 |
| 50 | Cellular response to drug | 4.69E-07 | 6.60E-05 | 33 | 53 |

# APPENDIX C

## GENE ONTOLOGY PROCESSES ASSOCIATED WITH SCCOHT TUMORS RELATIVE TO NORMAL OVARY, MINUS CELL CYCLE CATEGORY GENES

| Rank | GO Processes | pValue | FDR | Ratio | |
|---|---|---|---|---|---|
| 1 | DNA repair | 1.24E-08 | 5.45E-05 | 84 | 466 |
| 2 | DNA replication | 4.52E-08 | 9.05E-05 | 48 | 243 |
| 3 | Mitotic cell cycle | 8.15E-08 | 9.05E-05 | 85 | 654 |
| 4 | DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest | 8.25E-08 | 9.05E-05 | 26 | 78 |
| 5 | Nervous system development | 2.74E-07 | 2.35E-04 | 103 | 2397 |
| 6 | RNA metabolic process | 3.21E-07 | 2.35E-04 | 62 | 3402 |
| 7 | Regulation of hair follicle cell proliferation | 1.59E-06 | 9.97E-04 | 6 | 8 |
| 8 | Myeloid progenitor cell differentiation | 2.26E-06 | 1.24E-03 | 8 | 11 |
| 9 | DNA metabolic process | 4.02E-06 | 1.80E-03 | 17 | 917 |
| 10 | S phase of mitotic cell cycle | 4.18E-06 | 1.80E-03 | 37 | 162 |
| 11 | Response to DNA damage stimulus | 4.52E-06 | 1.80E-03 | 80 | 712 |
| 12 | mRNA export from nucleus | 5.93E-06 | 2.17E-03 | 20 | 66 |
| 13 | Positive regulation of progesterone secretion | 1.01E-05 | 3.07E-03 | 6 | 7 |
| 14 | mRNA metabolic process | 1.02E-05 | 3.07E-03 | 51 | 665 |
| 15 | Regulation of cellular amino acid metabolic process | 1.07E-05 | 3.07E-03 | 18 | 65 |
| 16 | Peripheral nervous system neuron development | 1.12E-05 | 3.07E-03 | 9 | 19 |
| 17 | Gene expression | 1.31E-05 | 3.39E-03 | 124 | 3676 |
| 18 | Nucleosome assembly | 1.68E-05 | 4.05E-03 | 29 | 121 |
| 19 | RNA splicing | 1.76E-05 | 4.05E-03 | 59 | 339 |
| 20 | Microtubule-based process | 1.86E-05 | 4.08E-03 | 18 | 479 |
| 21 | mRNA transport | 2.08E-05 | 4.34E-03 | 24 | 123 |
| 22 | Hair follicle morphogenesis | 2.23E-05 | 4.45E-03 | 14 | 38 |
| 23 | mRNA processing | 2.58E-05 | 4.79E-03 | 60 | 427 |
| 24 | ATP catabolic process | 2.62E-05 | 4.79E-03 | 45 | 223 |
| 25 | 'De novo' posttranslational protein folding | 3.38E-05 | 5.93E-03 | 16 | 67 |
| 26 | Apoptotic process | 4.68E-05 | 7.83E-03 | 140 | 1196 |
| 27 | Telomere maintenance via recombination | 4.87E-05 | 7.83E-03 | 12 | 31 |
| 28 | Nucleobase-containing small molecule metabolic process | 5.00E-05 | 7.83E-03 | 22 | 947 |
| 29 | Telomere maintenance via semi-conservative replication | 5.78E-05 | 8.74E-03 | 11 | 27 |
| 30 | Protein polyubiquitination | 6.63E-05 | 9.38E-03 | 31 | 197 |
| 31 | Axonogenesis | 6.63E-05 | 9.38E-03 | 31 | 661 |
| 32 | Telomere maintenance | 7.38E-05 | 1.01E-02 | 19 | 76 |
| 33 | G1/S transition of mitotic cell cycle | 8.69E-05 | 1.16E-02 | 44 | 234 |
| 34 | Regulation of transcription, DNA-dependent | 1.00E-04 | 1.29E-02 | 343 | 3549 |
| 35 | Neural tube closure | 1.08E-04 | 1.35E-02 | 22 | 91 |

| | | | | | |
|---|---|---|---|---|---|
| 36 | Ubiquitin homeostasis | 1.37E-04 | 1.66E-02 | 4 | 4 |
| 37 | Regulation of translation | 1.56E-04 | 1.85E-02 | 28 | 288 |
| 38 | Actin cytoskeleton organization | 1.71E-04 | 1.98E-02 | 40 | 449 |
| 39 | Somatic stem cell division | 1.83E-04 | 2.05E-02 | 8 | 29 |
| 40 | Negative regulation of cAMP-mediated signaling | 2.27E-04 | 2.49E-02 | 6 | 10 |
| 41 | Protein folding | 2.37E-04 | 2.52E-02 | 41 | 248 |
| 42 | Membrane to membrane docking | 2.56E-04 | 2.52E-02 | 5 | 7 |
| 43 | Aggresome assembly | 2.56E-04 | 2.52E-02 | 5 | 7 |
| 44 | Cardiac right ventricle formation | 2.56E-04 | 2.52E-02 | 5 | 7 |
| 45 | DNA strand elongation involved in DNA replication | 2.58E-04 | 2.52E-02 | 12 | 39 |
| 46 | Brain development | 2.87E-04 | 2.74E-02 | 56 | 763 |
| 47 | Transmission of nerve impulse | 3.19E-04 | 2.97E-02 | 10 | 918 |
| 48 | Negative regulation of transcription from RNA polymerase II promoter | 3.82E-04 | 3.49E-02 | 109 | 740 |
| 49 | Epithelial to mesenchymal transition | 4.29E-04 | 3.78E-02 | 13 | 65 |
| 50 | Neuron migration | 4.31E-04 | 3.78E-02 | 27 | 127 |

# APPENDIX D

## COPY NUMBER ABERRATIONS IDENTIFIED IN SCCOHT TUMORS

| Chromosome band | Interval | Size (bp) | CNV | Q-Bound[a] | G-Score[b] | RefSeq genes in interval | Expression elevated in SCCOHT (p <0.001)[c] |
|---|---|---|---|---|---|---|---|
| 1p31.1 | 1:81,904,969-82,210,805 | 305,837 | Gain | 4.80E-02 | 1.833 | - | n/a |
| 1q21.3 | 1:150,821,505-150,854,987 | 33,483 | Gain | 8.78E-05 | 3.488 | ARNT | - |
| 2q32.2 | 2:191,028,210-191,513,892 | 485,683 | Gain | 2.72E-05 | 3.745 | C2orf88, HIBCH, INPP1, MFSD6, TMEM194B | HIBCH, **INPP1, MFSD6, TMEM194B** |
| 3p12.3 | 3:78,963,346-79,145,860 | 182,515 | Gain | 3.60E-02 | 1.927 | ROBO1 | **ROBO1** |
| 3q26.31 | 3:172,908,698-173,570,950 | 662,253 | Gain | 5.07E-03 | 2.473 | NLGN1 | NLGN1 |
| 4q13.2 | 4:69,072,425-69,404,572 | 332,148 | Loss | 3.91E-07 | 8.899 | FTLP10, TMPRSS11B, YTHDC1, TMPRSS11E | No expression |
| 4q32.1 | 4:160,133,935-160,325,584 | 191,650 | Gain | 4.39E-02 | 1.869 | RAPGEF2 | **RAPGEF2** |
| 6p22.2 | 6:26,226,800-26,367,230 | 140,431 | Gain | 9.54E-08 | 4.881 | HIST1H1D, HIST1H4F, HIST1H4G, HIST1H3F, HIST1H2BH, HIST1H3G, HIST1H2BI, HIST1H4H | **HIST1H1D, HIST1H4F, HIST1H3F, HIST1H2BH, HIST1H2BI, HIST1H4H** |
| 6q25.1 | 6:150,944,725-151,180,594 | 235,870 | Gain | 4.16E-02 | 1.887 | PLEKHG1 | **PLEKHG1** |
| 7p21.2 | 7:15,597,038-15,697,375 | 100,338 | Gain | 3.48E-04 | 3.114 | AGMO, MEOX2 | **AGMO,** MEOX2 |
| 7q22.2 | 7:104,374,103-104,459,023 | 84,921 | Gain | 1.13E-03 | 2.900 | LHFPL3 | - |
| 8p11.22 | 8:39,355,401-39,485,162 | 129,762 | Gain | 2.84E-08 | 5.234 | ADAM3A, LOC100130964, ADAM18 | - |
| 8p11.22 | 8:39,355,401-39,508,473 | 153,073 | Loss | 3.91E-07 | 8.797 | ADAM3A, LOC100130964, ADAM18 | n/a |
| 8p23.1 | 8:11,564,955-11,658,574 | 93,620 | Gain | 1.46E-02 | 2.292 | GATA4, NEIL2 | GATA4, NEIL2 |
| 8q23.1 | 8:106,391,657-106,696,351 | 304,695 | Gain | 1.23E-04 | 3.356 | ZFPM2 | - |
| 9p22.3-9p22.2 | 9:16,503,403-16,772,775 | 269,373 | Gain | 1.30E-02 | 2.303 | BNC2 | BNC2 |
| 9p12-9p11.3 | 9:43,445,839-44,199,460 | 753,622 | Loss | 8.51E-04 | 5.753 | SPATA31A6, CNTNAP3B | No change |
| 9q22.32 | 9:96,811,422-96,865,087 | 53,666 | Gain | 2.91E-05 | 3.727 | PTPDC1 | - |
| 10p12.31 | 10:21,867,808-21,872,548 | 4,741 | Gain | 2.05E-07 | 4.759 | MLLT10 | MLLT10 |
| 10q21.2 | 10:63,324,600-63,513,214 | 188,615 | Gain | 1.94E-03 | 2.740 | C10orf107 | C10orf107 |
| 11p13 | 11:32,381,037-32,582,094 | 201,058 | Gain | 2.71E-02 | 1.991 | WT1 | WT1 |
| 12q13.13 | 12:52,674,727-52,716,578 | 41,852 | Gain | 8.60E-08 | 4.931 | KRT81, KRT86, KRT83 | - |
| 13q21.32 | 13:66,455,933-66,901,722 | 445,790 | Gain | 2.52E-02 | 2.036 | PCDH9 | **PCDH9** |
| 14q23.2 | 14:63,394,815-63,494,021 | 99,207 | Gain | 3.08E-04 | 3.1457 | KCNH5 | - |
| 14q32.33 | 14:105,604,542-105,651,652 | 47,111 | Loss | 2.43E-04 | 6.207 | JAG2, NUDT14 | No change |
| 15q26.2 | 15:94,399,414- | 261,039 | Gain | 1.06E-04 | 3.423 | - | n/a |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 94,660,452 | | | | | | |
| 16q12.1 | 16:51,639,455-51,926,232 | 286,778 | Gain | 4.16E-02 | 1.884 | - | n/a |
| 17p13.1 | 17:7,056,916-7,089,725 | 32,810 | Gain | 8.16E-05 | 3.531 | ASGR1 | **ASGR1** |
| 17q22 | 17:55,199,726-55,283,335 | 83,610 | Gain | 2.16E-06 | 4.284 | - | n/a |
| 18p Cent | 18:16,100,000-16,950,216 | 850,217 | Gain | 5.10E-10 | 5.944 | - | n/a |
| 19q13.2 | 19:41,666,634-42,079,770 | 413,137 | Gain | 2.52E-02 | 2.020 | CYP2S1, AXL, HNRNPUL, CCDC97, TGFB1, B9D2, TMEM91, EXOSC5, BCKDHA, B3GNT8, ATP5SL, LOC100505495 | CYP2S1, HNRNPUL, |
| 19p12 | 19:24,024,178-24,157,914 | 133,737 | Gain | 3.48E-04 | 3.110 | ZNF726 | Feature not on array |
| 20q13.2 | 20:51,621,454-51,926,985 | 305,532 | Gain | 2.24E-03 | 2.698 | TSHZ2 | - |
| 21q21.1 | 21:16,705,311-16,902,517 | 197,207 | Gain | 1.60E-14 | 7.855 | - | n/a |
| 22q11.22 | 22:22,672,813-22,730,297 | 57,485 | Loss | 1.90E-06 | 8.580 | LOC96610 | No expression |
| Xp22.33 | X:1,376,310-1,477,273 | 100,964 | Gain | 2.27E-02 | 2.088 | CSF2RA, IL3RA | - |
| Yq11.23 | Y:26,870,361-27,126,444 | 256,084 | Gain | 2.26E-04 | 3.219 | DAZ1, DAZ2, DAZ3, DAZ4 | - |

GISTIC analysis of 15 SCCOHT cases. The threshold for significance in the GISTIC analysis was determined by the false discovery rate q-values (Q-bound <0.1). Expression of genes included within each CNV region were investigated in our microarray data for 4 SCCOHT vs. normal ovary. Genes significantly overexpressed in 3 or 4 SCCOHT are listed (bold if overexpressed in 4/4 SCCOHT).

# APPENDIX E

## GENES SIGNIFICANTLY DYSREGULATED IN 4 SCCOHT TUMORS COMPARED TO EPITHELIAL OVARIAN CARCINOMAS

| Gene Name | Log2Ratio SCCO-014 vs. EOCs | Log2Ratio SCCO-015 vs. EOCs | Log2Ratio SCCO-002 vs. EOCs | Log2Ratio SCCO-012 vs. EOCs |
|---|---|---|---|---|
| ARL4D | 1.289551 | 1.205097 | -0.465573 | -2.694382 |
| IQCD | -1.123695 | -0.456245 | -0.933453 | -3.124651 |
| FAM183B | 0.724361 | 1.237432 | 0.631214 | -2.731334 |
| TMEM190 | 0.377126 | -0.546273 | -1.204489 | -2.285315 |
| SERTAD4 | 0.563842 | -0.697325 | -0.896021 | -3.136518 |
| CHDH | -0.765539 | -1.575802 | -0.046344 | -2.342041 |
| IL17RB | -1.451059 | -2.7654 | -0.904501 | -3.044697 |
| ITLN2 | -0.42847 | -0.638378 | -1.809072 | -1.178978 |
| OBSL1 | 0.165337 | -1.005392 | 0.275877 | -3.125654 |
| AQP7P1 | -0.755027 | -2.63653 | -1.13339 | -0.360354 |
| GJA3 | -1.313634 | -1.366794 | -2.406379 | -2.289315 |
| ALDOC | -1.206993 | -1.482926 | -2.283869 | -0.462815 |
| KCNS1 | -2.344386 | -0.794161 | -2.161818 | -1.399362 |
| CALB2 | -0.068027 | -1.464004 | 0.834153 | -1.281077 |
| CHRDL2 | -0.729185 | -0.743196 | -0.469465 | -1.312111 |
| RSPO1 | -0.722884 | -3.321018 | -3.726441 | -2.651022 |
| SCN2B | -0.829778 | -1.297256 | -0.555857 | -2.211119 |
| APOBEC3C | 1.196453 | -0.884281 | -3.462179 | 1.30485 |
| ANO7 | -0.474057 | -1.023155 | -2.108883 | -0.710128 |
| CAPN12 | -0.180455 | -0.831937 | -0.746459 | -0.314917 |
| LOC100129617 | -2.219031 | -1.571019 | -0.529337 | -0.129626 |
| PCSK5 | -0.945687 | 0.1465 | -0.841908 | -0.487664 |
| CCRL1 | -2.353084 | -1.583505 | -1.786353 | 0.855172 |
| AGMAT | -1.977317 | -3.151856 | -1.613133 | 1.45052 |
| CCRL2 | -1.764116 | -2.088069 | -2.197091 | 1.935117 |
| LOC115110 | -2.514977 | -1.638943 | -1.970926 | 1.247342 |
| LFNG | -2.137508 | -1.320778 | -2.747964 | 0.786796 |
| PDE4D | -2.005332 | -1.628483 | -2.118676 | 2.128912 |
| BANK1 | -3.692192 | -3.058681 | -4.00255 | 0.507734 |
| NR3C2 | -2.983647 | -0.713246 | -3.435587 | 0.161368 |
| PARM1 | -3.394849 | -2.272833 | -1.696953 | 1.878146 |
| MCF2L | -1.581663 | -0.84028 | -1.57293 | 0.466309 |
| HPGDS | -1.195417 | -0.74414 | -0.649261 | -1.152401 |
| IGSF22 | -2.151939 | -0.71619 | -1.716532 | 0.628323 |
| CAPS | -1.853279 | -2.382049 | -1.550295 | -1.920001 |
| EDA | -2.235482 | -1.835705 | -0.551387 | -1.399771 |
| ARAP3 | -1.85122 | -1.291696 | -2.003148 | -0.040633 |

| | | | | |
|---|---|---|---|---|
| AQP3 | -1.134947 | -1.785555 | -2.459777 | 1.521006 |
| SPATA13 | -2.031524 | -2.272426 | -1.485932 | 0.754507 |
| CCND1 | -1.993806 | -0.903298 | -1.984145 | -1.239087 |
| SYBU | -1.20354 | -1.294699 | -3.103698 | -1.697544 |
| AQP5 | -0.973843 | -1.328275 | -1.177362 | -1.411785 |
| SPDEF | -2.217386 | -1.846583 | -2.252777 | -2.748545 |
| SH3RF2 | -1.581763 | -1.302826 | -1.421505 | -1.733902 |
| LOC284276 | -2.88559 | -3.316099 | -2.860506 | -2.493236 |
| TSHZ2 | 0.536377 | -2.22202 | -2.925266 | -0.185288 |
| PGM5 | -3.694163 | -0.696969 | -2.399974 | 0.603115 |
| RGS7BP | -2.496119 | -3.004687 | -3.182607 | -0.876528 |
| CARD6 | -2.080132 | -2.074557 | -2.774395 | 0.88099 |
| ADCY4 | -1.170525 | -1.360409 | -1.427664 | 1.342222 |
| LOC153684 | -2.262216 | -1.816523 | -1.273254 | 1.493087 |
| PPM1K | -2.589812 | -1.752801 | -1.295184 | 1.707467 |
| BCL2 | -1.447175 | -1.761501 | -2.20356 | 1.820972 |
| NUDT9P1 | -3.920039 | -2.800229 | -2.150904 | 1.277035 |
| ASCL2 | -1.375217 | -2.544166 | -2.444411 | 1.323547 |
| CYP4V2 | -1.257111 | -1.993545 | -3.709891 | 0.412272 |
| SIGLEC11 | -1.280746 | -1.561244 | -2.906624 | 1.197492 |
| KLKB1 | -1.393349 | -0.579091 | -2.332653 | 1.087417 |
| PCSK6 | -2.161906 | -1.687527 | -1.52528 | 0.59079 |
| TNFRSF18 | -2.075305 | -2.536583 | -2.098421 | 1.857546 |
| ANO9 | -1.463338 | -1.649834 | -1.326656 | 1.464641 |
| ANK3 | -2.117573 | -2.170347 | -2.225097 | 1.75263 |
| TNFSF15 | -1.997833 | -1.416608 | -2.811022 | 0.937767 |
| ATHL1 | -1.393479 | -2.196522 | -2.315769 | 1.561262 |
| FGD4 | -2.375171 | -2.645192 | -3.358917 | 1.86791 |
| HLA-DPB2 | -1.384775 | -1.54122 | -1.685292 | 2.212818 |
| HCP5 | -1.768791 | -2.101766 | -2.484272 | 2.183318 |
| STAT5A | -0.978458 | -1.613886 | -2.689197 | 1.964266 |
| MILR1 | -1.004345 | -1.010993 | -1.770816 | 2.188231 |
| VAV1 | -1.002182 | -0.685731 | -2.164941 | 2.272774 |
| SEMA7A | -0.555497 | -1.596711 | -3.193035 | 1.21645 |
| APOL4 | -1.697335 | -1.659968 | -1.628163 | 1.220563 |
| IL6R | -0.47482 | -0.223322 | -2.576674 | 2.062391 |
| ZC3HAV1 | -1.311713 | -1.673577 | -0.558017 | 2.088769 |
| GSDMD | -1.449619 | -2.51761 | -1.834359 | 1.060196 |
| ST3GAL1 | -1.65473 | -1.740715 | -2.454208 | 1.138468 |
| VWA1 | -1.071606 | -1.811751 | -1.185285 | 0.811877 |
| PSMB9 | -1.309131 | -2.061166 | -1.260057 | 2.147668 |

| | | | | |
|---|---|---|---|---|
| ME3 | -2.437493 | -0.680677 | -2.570434 | -0.551528 |
| GAS6 | -1.77213 | -0.933421 | -1.541552 | -0.220214 |
| TRIB2 | -1.605609 | -0.730915 | -2.291107 | 0.603359 |
| GUCY1A3 | -0.688496 | -1.931939 | -2.491179 | 1.039488 |
| LOC100131262 | -1.811762 | -0.89461 | -2.128237 | -0.065455 |
| SARDH | -0.969523 | -1.488046 | -1.918529 | 1.321922 |
| ADAM12 | -1.299058 | -0.729942 | -1.606051 | 1.654133 |
| DCN | 1.070527 | -0.328493 | -4.150699 | -0.934871 |
| FN1 | -0.861649 | -1.169911 | -1.778981 | -0.619814 |
| GUCA2B | -1.039541 | -0.372209 | -0.994271 | -1.106898 |
| COL6A3 | -1.431603 | -1.218942 | -2.897816 | 1.201282 |
| CRISPLD2 | -1.708857 | -1.038335 | -1.272541 | 0.180383 |
| OLFML3 | -1.722829 | -0.240151 | -1.881895 | -0.099202 |
| COL6A2 | -1.447592 | -0.485312 | -2.029603 | 0.619095 |
| WISP1 | -1.235304 | -0.940157 | -2.389996 | 0.917617 |
| MXRA8 | -0.969367 | -0.796188 | -1.339875 | -0.118436 |
| RGS16 | -1.725983 | -1.131658 | -3.071607 | -0.711331 |
| SLC12A8 | -1.373074 | -1.76518 | -2.018231 | -0.675683 |
| CD86 | -1.177565 | -1.268123 | -2.19635 | -1.197671 |
| PPP6R1 | -0.894109 | -0.661968 | -3.287024 | -0.066107 |
| LRRC2 | -1.389767 | -1.351027 | -2.979349 | -2.788804 |
| DIO3 | -0.961338 | -1.38056 | -2.789847 | 0.624254 |
| ITIH5 | -1.031496 | -1.728631 | -1.552288 | 0.324173 |
| THC2672097 | -1.593668 | -2.439562 | -1.771282 | 1.073168 |
| PTN | -3.087276 | -1.062051 | -1.477844 | -0.090546 |
| SOX5 | -2.381317 | -1.431267 | -1.70448 | 1.480907 |
| GRIK3 | -2.865849 | -3.767413 | -1.48222 | -7.119744 |
| C1QTNF3 | -0.709952 | -0.467804 | -1.395721 | -1.970136 |
| KCTD1 | -0.756382 | -1.215923 | -0.99241 | -3.206725 |
| ACTL8 | -2.523614 | -1.494376 | -1.840102 | -2.797693 |
| SLC12A1 | -2.305218 | -2.374217 | -2.571775 | -2.576568 |
| JSRP1 | -1.617063 | -2.334434 | -2.596182 | -1.054851 |
| MEOX1 | -1.650774 | -0.811592 | -3.70778 | 1.135505 |
| ADAM32 | -0.380969 | 0.110378 | -4.236222 | -1.708173 |
| DSEL | 0.933107 | -3.019351 | -3.410838 | -1.352828 |
| HMCN1 | 0.694161 | -0.750795 | -4.158042 | -3.341136 |
| PYGO1 | -0.226123 | -0.278183 | -4.004095 | -0.951745 |
| XYLT1 | -1.251188 | -2.164122 | -2.544481 | 0.29526 |
| CADM1 | 0.586538 | -1.425904 | -3.479351 | -2.215995 |
| FGF18 | -0.198752 | 0.381588 | -1.979409 | -3.351701 |
| DMKN | 0.712711 | 0.566284 | -2.407375 | -3.77527 |

| | | | | |
|---|---|---|---|---|
| AR | -3.09869 | 0.695247 | -0.728173 | -3.655532 |
| EYA2 | -1.539805 | 0.302949 | -3.384014 | -4.150185 |
| MAMDC2 | -3.203375 | -2.015211 | -4.061862 | -2.019473 |
| VWCE | -1.580669 | -0.946285 | -0.870237 | -0.962972 |
| CCL7 | -2.369036 | -1.279361 | -2.452759 | -0.297534 |
| FONG | -1.093213 | -0.091336 | -1.711681 | 0.03025 |
| BQ888653 | -1.240668 | -1.039787 | -1.592261 | -1.642563 |
| LRP8 | -1.775134 | -1.259521 | -0.776876 | 0.396203 |
| PDE4DIP | -1.435917 | -1.526369 | -1.548721 | -0.249847 |
| TAP2 | -1.324612 | -1.82168 | -2.263291 | 0.113863 |
| NXNL2 | -0.546155 | -0.780436 | -2.592942 | -3.370797 |
| ALB | -3.340865 | -4.349431 | -0.762643 | -3.258848 |
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| GPR143 | -0.365429 | -2.084034 | -1.722193 | -2.823508 |
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| NIPAL4 | -2.275535 | -3.064732 | -2.925394 | 0.519819 |
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| PRSS21 | -3.060662 | -2.788472 | -2.636888 | -0.725611 |
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| MOBKL2B | -0.616389 | -2.625078 | -4.159099 | -0.717894 |
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| SH3BP4 | -1.174658 | -0.341224 | -1.929617 | -2.417186 |
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| FXYD4 | -1.494891 | -2.174284 | -0.959712 | -2.574853 |
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| SLC6A13 | -2.85689 | -2.03697 | -1.699693 | -2.185455 |
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| CXCR2 | -1.530957 | -1.752973 | -3.424508 | 1.962176 |
| FLVCR2 | -0.953189 | -0.907931 | -2.709198 | 1.724836 |
| CRTAC1 | -3.088667 | -2.620983 | -3.645295 | -3.39876 |
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| CDH15 | -0.471267 | -2.273068 | -2.321173 | -2.130227 |
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| LOXL4 | -1.57092 | -1.542237 | -3.256243 | -1.638886 |
| TDO2 | -2.415841 | -1.872862 | -3.127747 | 0.350079 |
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| CARD16 | -1.89038 | -1.909245 | -2.904905 | 2.209267 |
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| ALOX5AP | -2.990957 | -2.696346 | -3.778759 | 1.408717 |
| CXCL1 | -1.316577 | -3.301762 | -3.221764 | 0.540804 |
| CXCL2 | -1.038312 | -3.185042 | -3.367971 | -0.309061 |
| CXCL3 | -1.949023 | -4.119782 | -4.632634 | -1.350583 |
| APOBR | -2.147067 | -2.554202 | -2.043605 | 2.007405 |
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| CD74 | -2.128436 | -2.492179 | -3.001614 | 1.573307 |
| HLA-DRB3 | -1.810345 | -1.938448 | -2.399047 | 1.277254 |
| HLA-DRB4 | -1.905445 | -2.547409 | -3.160303 | 0.883127 |
| HLA-DMA | -2.329053 | -2.581482 | -2.715578 | 0.944462 |
| HLA-DMB | -2.102276 | -2.525973 | -2.686295 | 1.071024 |
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| HLA-DRA | -2.21635 | -2.894467 | -3.743725 | 0.380167 |
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| HLA-DQA2 | -2.688324 | -3.353536 | -3.254249 | 0.668306 |
| TLR2 | -1.550869 | -2.40832 | -3.576101 | 1.210169 |
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| APOC1 | -2.411986 | -2.31123 | -2.85421 | 1.402056 |
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| CH25H | -1.801529 | -3.034515 | -0.66737 | 0.75215 |
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| FAM20A | -1.59792 | -2.790256 | -1.079783 | -1.312993 |
| CCL3 | 0.01066 | -1.75162 | -3.002637 | 0.40777 |
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| OSM | -1.136958 | -2.324651 | -2.850209 | 0.123854 |
| ICAM1 | -1.715285 | -2.727197 | -3.534342 | 0.962133 |
| GPR84 | -1.567806 | -2.810376 | -3.415651 | 0.288964 |
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| TREM1 | -0.763349 | -2.759187 | -3.017315 | 0.106403 |
| FCGR1B | -0.494131 | -0.861753 | -2.821964 | 1.149995 |
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| LRRK1 | -2.140453 | -2.348919 | -2.743018 | 0.871606 |
| SLCO3A1 | -2.149379 | -2.094211 | -3.580039 | 0.153205 |
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| FAM46C | -3.233185 | -3.069134 | -2.370509 | -0.681109 |
| ALOX5 | -2.18703 | -3.221113 | -3.022495 | 0.582308 |
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| ZNF683 | -1.838792 | -2.801527 | -2.105594 | 0.196998 |
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| CTSS | -0.904007 | -2.821894 | -2.947237 | 1.859036 |
| MLKL | -1.907076 | -2.428424 | -2.497448 | 1.513585 |
| PLCG2 | -2.422559 | -2.285138 | -2.466583 | 1.167137 |
| TMEM176A | -2.531754 | -3.321163 | -3.278945 | 1.296503 |
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| RASGRP1 | -2.0431 | -2.115893 | -2.729109 | 1.902807 |
| AQP9 | -1.718616 | -3.671302 | -4.00165 | 0.731586 |
| ACSS3 | -1.039647 | -4.572327 | -4.565345 | -0.928785 |
| SLC39A8 | -2.728347 | -4.001933 | -4.712401 | -0.883617 |
| CPXM2 | -3.38105 | -2.799011 | -4.208108 | -1.2456 |
| TNFSF14 | -2.303095 | -4.368989 | -3.453905 | 0.074712 |
| CKM | -1.138153 | -1.936724 | -2.607583 | 2.181737 |
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| ENTPD1 | -2.573724 | -1.191049 | -2.664297 | 0.979566 |
| CLCN4 | -4.26344 | -2.562066 | -4.514417 | 0.284252 |
| MDFIC | -2.292634 | -2.355099 | -3.824718 | 1.53123 |
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| NLGN4Y | -1.619404 | -1.707302 | -2.254573 | -0.08744 |
| PITPNM2 | -1.502352 | -2.147131 | -3.61484 | 1.083139 |
| MID1 | -1.18693 | -1.805755 | -2.077575 | 0.324481 |
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| CAMK2N1 | -1.726695 | -2.407968 | -1.881665 | -2.30654 |
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| FOXL2 | -3.146328 | -0.991696 | 1.124758 | -4.165952 |
| HSD17B3 | -2.318389 | -0.688797 | -3.134777 | -2.948741 |
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| HEATR8 | 0.077126 | -1.307405 | -0.353453 | -2.205524 |
| THSD7B | -3.448034 | -0.966549 | -1.819116 | -0.250486 |
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| ADAMTS16 | -3.473382 | -2.455585 | -3.440144 | -2.29883 |
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| RASD1 | -3.524575 | -2.357474 | -3.780878 | -0.581692 |
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| PLLP | -1.064503 | -1.380348 | -1.299197 | -1.296374 |
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| OR51E1 | -1.418938 | -2.071538 | -1.109609 | -1.875464 |
| TBC1D8B | -2.891487 | -2.230016 | -2.619934 | -0.815456 |
| IGFBP4 | -1.072881 | -1.336985 | -2.4277 | 0.223095 |
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| ITIH3 | -1.557632 | -0.753909 | -2.204032 | 0.681417 |
| TMEM200A | -1.707947 | -1.336658 | -2.594759 | -0.856255 |
| PID1 | -1.840036 | -1.749513 | -2.420679 | 0.543317 |
| CNTN3 | -2.32582 | -2.805507 | -3.029397 | -2.887539 |
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| CACNB2 | -2.197181 | -2.871672 | -2.584018 | -1.687407 |

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| ATP1A2 | -3.176652 | -2.266152 | -5.771158 | -2.966976 |
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| CYYR1 | -3.507635 | -2.508762 | -2.379152 | -0.314296 |
| GHR | -2.835932 | -2.691638 | -3.836545 | -0.448517 |
| JAM2 | -3.624979 | -1.973714 | -1.604271 | 0.546927 |
| FRZB | -3.205731 | -2.917237 | -1.816022 | 0.689356 |
| OXCT1 | -4.44637 | -4.253424 | -3.643368 | 0.118584 |
| PTPRZ1 | -2.304818 | -2.933245 | -0.993906 | -1.912023 |
| SPRR2A | -0.940602 | -3.165109 | -1.826958 | -2.468684 |
| BMP6 | -2.856147 | -1.59328 | -2.674365 | -1.453843 |
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| TMEM163 | -3.889975 | -1.947621 | -2.473808 | 0.54249 |
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| GNG4 | -2.381237 | -1.681001 | -1.584214 | -1.047723 |
| PDE7B | -2.182155 | -0.687094 | -1.607806 | -0.35033 |
| THSD7A | -3.061106 | -1.640145 | -2.036088 | 0.76506 |
| S100Z | -1.607261 | -2.788032 | -2.969289 | 1.989463 |
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| ADORA2A | -0.468462 | -0.354972 | -2.856342 | 1.097804 |
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| HAPLN1 | 1.648068 | -0.978299 | -2.041789 | 2.929282 |
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| LOC388630 | 0.392734 | -0.600255 | -3.034544 | -2.258926 |
| RBFOX3 | -0.172875 | -1.012222 | 0.842467 | 0.480212 |
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| LRRK2 | 0.865874 | 1.034887 | 1.058768 | 0.698797 |
| KCNK10 | -1.307797 | -0.005575 | -2.010352 | 2.379631 |
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| LOC389332 | 1.119759 | -1.298273 | -2.251874 | -3.157596 |
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| ITGA2 | -2.610355 | -2.707685 | -2.305082 | -1.921945 |
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| ARL14 | -3.33583 | -3.576086 | -3.989611 | -4.100664 |
| POF1B | -3.690639 | -3.737652 | -3.77995 | -3.910678 |
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| DLX6 | -6.649004 | -6.787916 | -5.593235 | -2.545727 |
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| DLX5 | -6.77976 | -5.633541 | -5.452437 | -3.188844 |
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| FOXF2 | -3.275125 | -3.058399 | -4.05116 | -1.109898 |
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| NKX3-2 | -4.123871 | -3.317626 | -4.387718 | -0.131432 |
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| COL4A3 | -3.449759 | -3.717996 | -2.20913 | -1.583813 |
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| KCP | -1.084975 | -1.288371 | -1.507987 | -2.260202 |
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| CYP2C18 | -3.006354 | -3.108419 | -3.209063 | -3.656432 |
| CYP2C19 | -4.129172 | -4.754074 | -4.835992 | -5.556195 |
| CYP2C9 | -6.926938 | -6.779935 | -6.114217 | -7.240998 |
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| ONECUT2 | -3.166747 | -2.606629 | -3.213249 | -4.01639 |
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| MOGAT1 | -4.802156 | -5.11502 | -3.062153 | -4.358924 |
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| AK125006 | -2.82042 | -2.755919 | -3.068392 | -2.523659 |
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| SERPINA1 | -3.057703 | -4.189619 | -4.148966 | -0.886031 |
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| NPC1L1 | -1.716105 | -1.923505 | -1.478332 | -1.975645 |
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| CYP3A5 | -5.800012 | -5.887793 | -5.476067 | -5.482877 |
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| SLC4A4 | -4.249279 | -4.240541 | -3.360672 | -5.32695 |
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| AXDND1 | -3.951647 | -4.195525 | -0.963634 | -4.325015 |
| FAM3D | -3.927453 | -4.464338 | -3.929438 | -3.498892 |
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| UGT1A6 | -2.47446 | -2.758154 | -3.232764 | -2.921891 |
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| SPINK4 | -4.716396 | -4.58152 | -3.618032 | -4.725588 |
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| ABP1 | -2.05312 | -1.85619 | -2.009036 | -1.284794 |
| ONECUT3 | -1.184077 | -0.957923 | -0.582591 | -2.06762 |
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| GGT3P | -0.671812 | -0.618397 | -0.898341 | -0.831395 |
| SCIN | -1.154767 | -0.049616 | -2.295765 | -2.2054 |
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| GBA3 | -4.523107 | -4.182994 | -0.139575 | -2.059345 |
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| MET | -3.65554 | -0.200922 | -3.902248 | -3.47237 |

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| LRRN1 | -3.168604 | -3.700639 | -3.548161 | -4.099248 |
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| GATA5 | -2.167191 | -2.408681 | -2.984122 | -2.812129 |
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| NOSTRIN | -2.368048 | -1.788329 | -2.961117 | -0.213853 |
| OTC | -3.337902 | -3.627313 | -3.73111 | -2.492067 |
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| FAS | -1.145961 | -2.60747 | -1.322611 | 0.072074 |
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| LRRC48 | -0.491658 | -2.718901 | -0.302375 | -2.863103 |
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| KLHL29 | -1.647655 | -2.317311 | -0.423547 | -0.42943 |
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| CAMP | -3.085682 | -4.510105 | -4.558154 | 0.181887 |
| LPCAT2 | -2.418471 | -2.329272 | -2.774443 | -0.348968 |
| SULT2B1 | -1.283944 | -2.034642 | -1.857876 | -0.801937 |
| KCNN4 | -2.572553 | -3.004494 | -3.507637 | 0.019657 |
| SLC7A8 | -1.598961 | -1.452988 | -2.690302 | -0.743688 |
| BDKRB1 | -0.571003 | -1.865942 | -2.846788 | -2.767051 |
| FUT3 | -0.301154 | -1.358935 | -0.975595 | -5.003175 |
| ATP10B | -4.945182 | -5.010423 | -1.943666 | -5.651615 |
| SLC9A4 | -3.049898 | -3.500826 | -3.544156 | -3.167085 |
| ALDH3A1 | -1.430242 | -0.903094 | -2.02125 | -1.787378 |
| ATP2C2 | -4.865565 | -3.849789 | -2.801122 | -4.320044 |
| CAPN8 | -3.409163 | -3.958388 | -3.368292 | -4.072405 |
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| ARSJ | -2.40762 | -2.660111 | -2.845365 | -0.974128 |
| IRS2 | -2.598692 | -2.625446 | -2.594511 | -0.996814 |
| TPPP | -3.593666 | -1.498531 | -4.132321 | -1.262041 |
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| CA3 | -4.422658 | -2.005095 | -3.38949 | -1.078989 |
| RLN2 | -3.706835 | -1.743101 | -1.590101 | -0.06131 |
| MARK1 | -2.940901 | -1.774196 | -1.689025 | -0.946726 |
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| ATP6V0A4 | -4.555081 | -3.307176 | -5.405569 | -5.335753 |
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| AMOT | -1.304523 | -0.512179 | -1.984825 | -2.892568 |
| CHRM2 | -1.978719 | -1.652967 | -0.849613 | -1.963105 |
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| ABCA8 | -2.916384 | -1.274006 | -3.390511 | -0.875774 |
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| CCDC85A | -3.136084 | -3.946087 | -1.487317 | -3.425504 |
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| KLKP1 | -1.877623 | -1.82503 | -1.823757 | -4.105409 |
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| C8B | -2.72487 | -2.322869 | -2.559749 | -3.062273 |
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| DBH | -3.330765 | -3.534223 | -2.569429 | -3.235655 |
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| RAB27B | -3.284782 | -2.949458 | -2.057092 | -2.498106 |
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| IL20RA | -5.573919 | -5.798296 | -5.989883 | -4.841762 |
| LOC440925 | -4.014933 | -4.097048 | -4.130222 | -4.01197 |
| SEC14L4 | -3.123278 | -4.416335 | -3.922347 | -3.517294 |
| LRRC17 | -1.189035 | -1.047421 | -0.92237 | -0.507707 |
| LHX6 | -1.707638 | -1.75976 | -1.83367 | 0.291102 |

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| CYTL1 | -2.026176 | -3.244506 | -3.596659 | 0.858445 |
| GRASP | -2.317328 | -2.444047 | -1.389418 | 0.981854 |
| CDH11 | -2.402365 | -1.070005 | -4.727851 | -1.224193 |
| ECM2 | -1.271542 | -1.502288 | -3.568284 | -1.502545 |
| SORCS2 | -1.639721 | -2.7564 | -4.2809 | -1.921545 |
| FAM198B | -2.247894 | -3.016297 | -2.653372 | -0.164255 |
| TWIST2 | -1.696113 | -2.9676 | -3.876077 | -0.688654 |
| NRK | -4.343571 | -2.357413 | -4.235213 | -4.792781 |
| SMOC2 | -0.78766 | -2.274559 | -4.505154 | -0.718639 |
| ADAMTSL2 | -3.138856 | -2.961785 | -3.265141 | -0.020618 |
| ITGA1 | -2.239484 | -1.49473 | -3.075363 | -0.174641 |
| TMEM204 | -2.282655 | -0.967021 | -2.133497 | 0.75978 |
| DYNC1I1 | -4.175475 | -3.510034 | -2.759104 | -2.482822 |
| PLCB4 | -2.197523 | -0.762002 | -3.642889 | -2.167381 |
| TSPAN5 | -2.56603 | -0.620137 | -2.113964 | -0.366196 |
| CYP27A1 | -1.072865 | -2.645009 | -3.352148 | -0.073382 |
| GPC6 | -2.341184 | -3.753426 | -2.570644 | -2.098914 |
| MOXD1 | -4.391639 | -2.943583 | -3.898268 | -1.291706 |
| LOC100505806 | -3.646829 | -1.691084 | -4.312373 | -1.135991 |
| SLC24A3 | -5.242793 | -4.412616 | -4.353349 | -2.131244 |
| GDNF | -2.510384 | -1.827546 | -1.954703 | -1.312345 |
| TWIST1 | -1.586557 | -1.34603 | -1.76669 | -0.938395 |
| RUNX2 | -1.801348 | -2.344305 | -4.070419 | 0.439183 |
| IL10 | -1.270987 | -2.205105 | -2.131143 | 0.63505 |
| RAB7B | -0.992767 | -1.79927 | -2.614508 | 0.708564 |
| PTGS2 | -1.067576 | -3.065597 | -4.116827 | -0.657827 |
| PTPRO | -1.665173 | -2.159316 | -3.464926 | 0.747575 |
| SPATA9 | -2.941267 | -3.120065 | -3.183068 | 0.85129 |
| VGLL3 | -1.371327 | -1.553181 | -1.190438 | 0.440461 |
| DCLK1 | -2.80855 | -3.18648 | -3.145162 | 1.415215 |
| PLA2G4A | -2.394759 | -1.71705 | -3.678154 | 0.398069 |
| OSBPL6 | -2.406976 | -2.610541 | -1.01367 | 0.820582 |
| SLC25A18 | -2.862877 | -2.828149 | -3.542858 | 1.10176 |
| TTLL7 | -2.847925 | -2.837023 | -2.932514 | 0.0822 |
| RUNDC3B | -2.727141 | -2.146336 | -3.074582 | -0.127287 |
| TOX | -3.473718 | -3.653555 | -2.541009 | 0.690619 |
| NRXN3 | -1.190738 | -2.419429 | -3.23287 | -2.025565 |
| PPARGC1A | -3.473171 | -3.947382 | -4.262572 | -1.843592 |
| HP | -3.484954 | -5.76711 | -6.281753 | -3.102079 |
| HPR | -3.888337 | -6.320197 | -6.545438 | -3.433176 |
| SUSD2 | -2.207551 | -1.623388 | -3.875303 | -1.322317 |

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| PIP | -4.719873 | -4.301354 | -4.244449 | -4.825015 |
| PKHD1L1 | -4.709751 | -4.933321 | -4.936826 | -2.367257 |
| NXF3 | -2.283579 | -2.431383 | -2.793153 | -2.795763 |
| MBD3L1 | -1.991166 | -1.60446 | -2.418968 | -1.82259 |
| STRA6 | -2.81889 | -2.406095 | -2.679184 | -1.453646 |
| WNT11 | -3.395016 | -2.158432 | -5.219594 | -3.185163 |
| RMST | -1.917221 | -2.467562 | -3.499418 | -3.391785 |
| ZNF474 | -1.627511 | -1.453383 | -1.709517 | -2.356613 |
| DUOX1 | -1.82446 | -2.085169 | 0.230996 | -3.018593 |
| SORBS1 | -1.262716 | -0.95965 | -1.920674 | -2.067737 |
| VWA2 | -2.100895 | -2.318719 | -2.006343 | -2.05535 |
| TRAF3IP2 | -1.70932 | -0.350907 | -1.445692 | -1.419366 |
| THC2670340 | -3.477533 | -2.702938 | -4.103214 | -1.420596 |
| AQP7P3 | -2.29913 | -4.29777 | -2.387025 | -2.643861 |
| PITX2 | -3.776213 | -4.641225 | -1.985718 | -1.857764 |
| PAX6 | -4.288647 | -4.205677 | -3.847883 | -4.964342 |
| CDKN2A | -2.511216 | -3.220097 | -3.106229 | -1.713576 |
| SYNPR | -1.974697 | -2.638497 | -2.848079 | -2.618337 |
| GPR87 | -1.90194 | -2.084128 | -2.745534 | -3.006514 |
| SH3GL3 | -0.854045 | -2.334988 | -1.06175 | -1.902169 |
| FCRL6 | -2.083772 | -1.676223 | -2.309655 | -0.302718 |
| FIGF | -3.863192 | -1.765361 | -4.386188 | -0.978128 |
| CXCL17 | -2.068469 | -2.37162 | -2.019083 | -2.378314 |
| BTG2 | -1.915619 | -2.692348 | -1.888541 | -0.510781 |
| GNAO1 | -2.951653 | -3.314824 | -1.64488 | 0.671692 |
| TIMP4 | -3.02688 | -3.552684 | -2.248729 | 0.360996 |
| PLXNA4 | -2.356445 | -2.026859 | -2.775356 | 0.855964 |
| DIO2 | -6.083287 | -3.529681 | -2.499505 | -1.65449 |
| CHRD | -1.57486 | -1.043285 | -1.163511 | -0.870135 |
| FBLN1 | -1.915355 | -2.289764 | -2.320011 | -1.280586 |
| SCGB2A2 | -4.340923 | -4.524076 | -4.60766 | -4.562996 |
| CCL11 | -3.749966 | -1.123358 | -4.564133 | -4.144356 |
| COL6A5 | -3.106174 | -3.257735 | -3.649499 | -1.72279 |
| COL6A6 | -2.083424 | -3.965234 | -4.333537 | -4.340803 |
| EPYC | -2.731033 | -2.938289 | -3.906703 | -4.016625 |
| CLEC1B | -2.762995 | -2.467707 | -2.89614 | -2.348174 |
| MMP13 | -2.782127 | -2.886046 | -2.837527 | -2.480203 |
| GRP | -1.41421 | -1.920658 | -1.821875 | -2.308028 |
| MMP11 | -1.154342 | -0.497845 | -1.836527 | -1.923261 |
| C4BPA | -4.19511 | -4.189151 | -5.49821 | -4.083655 |
| MATN3 | -1.925921 | -2.702292 | -1.950494 | -2.801682 |

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|---|---|---|---|---|
| COMP | -3.91441 | -1.436351 | -4.870275 | -3.459095 |
| NKAIN4 | -1.519587 | -1.869137 | -2.348704 | -2.329828 |
| KBTBD12 | -3.804348 | -4.068768 | -4.426477 | -4.486339 |
| ASB2 | -1.970216 | -2.756562 | -2.017416 | 1.985071 |
| FAM49A | -1.956011 | -2.147851 | -2.388595 | 2.309053 |
| LIN7A | -2.774666 | -2.510929 | -2.268756 | 1.246443 |
| ADCY7 | -1.357059 | -2.375067 | -2.960071 | 1.612637 |
| GLRX | -2.859558 | -3.409102 | -3.606504 | 1.22228 |
| SLC8A1 | -2.304413 | -3.247291 | -2.444764 | 1.093567 |
| KLHDC7B | -2.336343 | -2.977788 | -2.840104 | 1.764192 |
| FAM198A | -2.706801 | -4.013604 | -5.14187 | -1.316668 |
| JUN | -2.213928 | -1.720994 | -2.722159 | -2.46583 |
| KCNIP3 | -1.596423 | -2.513066 | -2.67079 | -1.677321 |
| ANKH | -3.927494 | -1.520781 | -2.712498 | -0.685566 |
| ASTN1 | -2.729088 | -1.29611 | -4.012289 | -1.907897 |
| MUM1L1 | -5.91455 | -3.756057 | -6.45714 | -6.575651 |
| C1QTNF7 | -2.157925 | -0.899619 | -3.650019 | -2.10812 |
| COL16A1 | -1.659853 | -1.419009 | -3.515138 | -1.333894 |
| CPZ | -2.255933 | -2.255755 | -3.005487 | -2.024224 |
| SRPX2 | -2.708882 | -0.497816 | -3.632486 | -0.539088 |
| LEPREL1 | -1.848914 | -0.592234 | -3.270495 | -0.275776 |
| BHMT2 | -2.698295 | -2.831207 | -2.833993 | 0.424842 |
| ENPP1 | -3.567612 | -2.32718 | -3.248859 | -0.56211 |
| ZNF521 | -2.701885 | -2.910199 | -3.049282 | 0.31451 |
| LRRN4CL | -1.807222 | -0.587464 | -1.879855 | -0.702631 |
| RCAN2 | -1.880423 | -1.168026 | -2.429865 | -0.902748 |
| ANXA8L2 | -1.064202 | -3.92456 | -3.625555 | -4.369613 |
| AGTR1 | -3.301322 | -3.741151 | -3.22389 | -0.170736 |
| ACTG2 | -3.120468 | -2.789007 | -3.064741 | -1.500964 |
| ANGPTL1 | -3.533448 | -3.253483 | -3.436087 | -0.41891 |
| GPR133 | -1.514203 | -4.009802 | -3.805606 | -0.363559 |
| MFAP4 | -3.352828 | -1.273834 | -4.482129 | -0.189954 |
| TDRD10 | -2.924895 | -1.693274 | -2.016646 | -0.949562 |
| AGT | -4.720939 | -4.436306 | -3.65559 | 0.030003 |
| CNR1 | -4.284251 | -3.601219 | -2.483186 | 0.392762 |
| TSPAN2 | -3.840779 | -3.933403 | -3.343188 | -0.310288 |
| HOXA11 | -3.160874 | -3.141897 | -3.457406 | -3.338708 |
| SRPX | -2.259757 | -0.900228 | -3.751997 | 0.261803 |
| FMOD | -3.421742 | -3.04742 | -5.367444 | 0.18304 |
| ARHGAP24 | -2.127347 | -2.385137 | -3.36926 | 1.022452 |
| ANKRD35 | -2.999505 | -2.504175 | -3.257949 | 0.318003 |

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| COX7A1 | -2.292493 | -1.661359 | -2.0976 | 1.424004 |
| BEND6 | -1.99603 | -1.898036 | -2.492307 | 0.538071 |
| DDR2 | -3.226662 | -2.495154 | -4.002554 | -0.218847 |
| FILIP1L | -2.894498 | -1.679454 | -3.160522 | 0.189825 |
| PALLD | -2.215469 | -1.466207 | -2.61506 | 0.203617 |
| LMOD1 | -2.723855 | -3.221718 | -3.495249 | -0.11259 |
| MRGPRF | -1.790847 | -1.630793 | -2.639476 | 0.743726 |
| MRVI1 | -2.950235 | -2.175115 | -1.238166 | -1.078511 |
| DIO3OS | -3.66528 | -2.488767 | -3.986552 | -0.401081 |
| SPARCL1 | -2.643013 | -1.652102 | -3.121518 | -0.493172 |
| NCAM1 | -3.238928 | -3.358101 | -3.299975 | -3.707593 |
| PLA2G5 | -1.321795 | -2.0093 | -1.767124 | -0.600939 |
| SFRP1 | -1.995984 | -2.604647 | -2.881531 | -0.46094 |
| PDZRN3 | -4.407197 | -2.903549 | -4.064163 | -1.469824 |
| SFRP4 | -5.82077 | -4.652681 | -4.51615 | -1.65018 |
| COLEC12 | -1.400999 | 0.064299 | -3.163598 | -0.218475 |
| FMO1 | -1.876188 | -1.128348 | -3.506906 | -1.009682 |
| FIBIN | -4.660349 | -2.736682 | -4.162932 | -1.890804 |
| CCDC80 | -1.128232 | -0.931708 | -4.581247 | -0.400804 |
| IGF1 | -2.371604 | -0.757294 | -3.26309 | -0.604665 |
| OMD | -1.830096 | -3.233153 | -3.655985 | -0.989959 |
| ITGBL1 | -3.599933 | -2.231123 | -3.734031 | -0.863016 |
| ACTA2 | -2.320029 | -2.304574 | -2.523639 | -0.298918 |
| EFEMP1 | -1.199436 | -2.474998 | -4.908522 | 0.669499 |
| PTGDS | -2.685285 | -2.934644 | -3.59796 | 0.385324 |
| FNDC1 | -2.772288 | -2.685094 | -5.150588 | -0.548371 |
| COL8A1 | -3.069794 | -2.653513 | -4.667556 | -4.737817 |
| CERCAM | -1.20447 | -1.694521 | -2.090137 | -2.47324 |
| FV367791 | -0.971384 | -1.593121 | -2.041 | -2.226944 |
| COL10A1 | -4.426283 | -2.583443 | -4.33401 | -3.765644 |
| LRRC15 | -3.950275 | -3.240917 | -4.505408 | -3.1449 |
| INHBA | -2.270749 | -1.932035 | -2.810531 | -2.31436 |
| ITGA11 | -1.842841 | -0.68847 | -1.866283 | -1.745173 |
| THBS2 | -2.146192 | -1.008689 | -3.674266 | -1.518155 |
| PLAU | -0.923887 | -0.760652 | -2.839217 | -1.393861 |
| ISLR | -3.218358 | -1.438756 | -3.84191 | -1.468277 |
| LUM | -2.827939 | -1.558285 | -4.997249 | -0.933568 |
| COL5A1 | -1.277171 | -1.012354 | -2.272199 | -1.064483 |
| SSC5D | -0.970342 | -0.743541 | -2.352777 | -0.412761 |
| MMP19 | -1.757944 | -1.768105 | -3.11392 | 1.155494 |
| PDLIM3 | -2.90449 | -2.945404 | -3.966806 | -0.327746 |

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| CTSK | -2.377086 | -2.257102 | -2.449832 | -0.098613 |
| SFRP2 | -4.042399 | -3.333095 | -2.383668 | -0.621257 |
| CTHRC1 | -3.082425 | -2.440918 | -3.384844 | -2.347155 |
| FAP | -2.585149 | -1.37116 | -4.523683 | -1.417844 |
| MMP2 | -2.488252 | -1.926526 | -3.885905 | -2.067996 |
| ZNF469 | -1.547025 | -1.907739 | -2.325598 | -0.73282 |
| SPON2 | -1.953538 | -1.410876 | -3.869088 | -1.105162 |
| NKD2 | -2.628596 | -2.153475 | -4.144789 | -0.377642 |
| MYLK | -2.809976 | -2.675872 | -2.948503 | -0.477698 |
| PRKCDBP | -1.588527 | -3.392688 | -3.004419 | 0.452065 |
| KCNE4 | -3.398066 | -2.412834 | -3.354856 | 0.686222 |
| TMEM119 | -2.760199 | -3.021124 | -2.600543 | 1.203634 |
| SERPINF1 | -1.993024 | -1.477491 | -3.85214 | 0.139729 |
| NALCN | -4.451636 | -3.443292 | -4.775048 | -1.705784 |
| ALPK2 | -1.625534 | -3.224225 | -2.491036 | 1.009705 |
| THC2767512 | -1.855568 | -2.995725 | -3.501713 | -0.719561 |
| NTM | -4.32222 | -3.791591 | -4.596872 | -0.563224 |
| TNFSF4 | -1.440614 | -1.784195 | -2.424087 | -0.442234 |
| PTGER3 | -1.142285 | -3.439261 | -4.266858 | -0.744421 |
| HOPX | -3.663184 | -1.246924 | -4.643609 | -1.731068 |
| RAI14 | -2.147446 | -0.430387 | -3.207053 | -0.715878 |
| RARRES2 | -2.03712 | -0.554044 | -4.457003 | -0.726645 |
| TMEM47 | -3.171724 | -3.307227 | -2.752771 | -1.137033 |
| HSD11B1 | -1.886381 | -1.327097 | -4.69111 | 0.889204 |
| MMP23B | -1.908344 | -1.316583 | -2.466345 | -0.209869 |
| HSPB2 | -2.163014 | -1.87639 | -2.5772 | -0.741017 |
| TAGLN | -1.69257 | -1.313315 | -2.29421 | -0.050795 |
| PLIN2 | -1.298518 | -2.224597 | -2.983087 | -0.292054 |
| PF4 | -1.282078 | -1.875932 | -3.369086 | -0.19376 |
| PPBP | -1.906422 | -2.189904 | -2.419738 | -0.69852 |
| LOC100287221 | -1.91532 | -2.327083 | -2.881462 | -0.044535 |
| PAMR1 | -1.918675 | -1.634986 | -1.999132 | -2.255319 |
| FOS | -0.577139 | -2.107677 | -3.623086 | -1.953958 |
| LIF | -2.209439 | -2.654507 | -2.728969 | -1.735607 |
| GJB2 | -2.58951 | -5.288488 | -5.214387 | -5.506476 |
| PODNL1 | -1.319989 | -2.201934 | -1.673822 | -2.034862 |
| ATF3 | -2.705629 | -2.896415 | -3.503984 | -1.208728 |
| DUSP1 | -2.209919 | -3.156711 | -3.583936 | -1.124647 |
| GLDC | -5.849738 | -4.564372 | -5.997182 | -1.820169 |
| ODF3L1 | -1.935051 | -1.545252 | -2.761662 | -1.26892 |
| CRYAB | -3.80784 | -1.618786 | -4.801124 | -3.269545 |

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| IL6 | -1.067533 | -3.940497 | -5.665579 | -1.299301 |
| RBP4 | -2.123024 | -2.320838 | -2.49594 | -1.452266 |
| CLDN16 | -4.065768 | -4.44198 | -4.483709 | -4.60561 |
| LOC730020 | -4.488803 | -6.878737 | -5.277389 | -2.901293 |
| WNT3A | -2.303562 | -3.867154 | -3.292799 | -3.400057 |
| IL1RAP | -3.077896 | -2.745862 | -3.462219 | -2.066797 |
| WNT2 | -4.714074 | -1.213439 | -4.111012 | -3.957756 |
| FOSB | -1.295271 | -3.177489 | -4.16534 | -1.861126 |
| CBLN4 | -0.989366 | -1.053182 | -2.728593 | -3.402648 |
| WNT4 | -0.671671 | -1.607308 | -1.566693 | -3.728914 |
| MYOC | -2.357318 | 0.01936 | -3.149099 | -2.940394 |
| DEFA3 | -2.394752 | -2.09889 | -2.361781 | 0.555881 |
| CYP1B1 | -2.506681 | -1.665964 | -3.435854 | 1.857146 |
| RNASE2 | -1.682336 | -2.982892 | -3.408598 | 1.265833 |
| S100A12 | -1.803101 | -2.089231 | -2.83865 | 1.57855 |
| RARRES1 | -1.426182 | -2.422513 | -2.545456 | -0.780304 |
| HOXA10 | -3.821704 | -3.947424 | -3.445449 | -0.212587 |
| HOXA11-AS1 | -4.703947 | -3.262921 | -2.692548 | -1.783109 |
| HOXA3 | -3.886388 | -4.672748 | -4.411147 | -1.877521 |
| HOXA4 | -2.619192 | -2.257251 | -2.010364 | -0.917868 |
| HOXA5 | -2.624357 | -2.607209 | -2.299061 | -0.479652 |
| LOC285943 | -2.637464 | -3.056127 | -2.572663 | -1.396177 |
| NT5E | -2.609519 | -2.69712 | -3.437371 | -0.486552 |
| MMP3 | -2.831078 | -3.155838 | -3.190083 | -3.190076 |
| HOXD10 | -2.128755 | -2.043787 | -1.653427 | 0.139023 |
| SKAP2 | -2.482286 | -1.955649 | -2.825723 | 0.414227 |
| IL20RB | -1.504596 | -1.067533 | -2.083866 | -0.920358 |
| FLJ13744 | -4.830353 | -4.149243 | -4.796836 | -4.679575 |
| DCAF12L1 | -4.183354 | -4.345718 | -4.009171 | -4.343721 |
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| CD109 | -1.439021 | -1.274139 | -0.906223 | -2.370495 |
| TMTC1 | -1.662134 | -0.344505 | -1.081273 | -1.940372 |
| HOXD3 | -4.323229 | -3.741646 | -4.158908 | -2.407252 |
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| LYPD6B | -5.020396 | -5.117122 | -5.312442 | -5.459676 |
| TMPRSS3 | -6.380432 | -5.862886 | -5.772058 | -3.512191 |
| KRT14 | -4.884757 | -5.636112 | -6.205726 | -4.407594 |
| KRT17 | -3.200731 | -3.880544 | -4.363475 | -3.251872 |
| KRT16P2 | -3.015088 | -3.634124 | -2.893644 | -3.175615 |
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| S100A1 | -4.236141 | -4.938887 | -4.563892 | -5.153902 |
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| KLK13 | -3.192159 | -4.560241 | -3.729163 | -3.878167 |
| ESRG | -5.521497 | -5.857209 | -6.161524 | -6.389917 |
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| BBOX1 | -7.204571 | -7.310379 | -5.725719 | -8.13669 |
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| DOK7 | -3.781618 | -4.412549 | -4.226135 | -4.207435 |
| KLK6 | -6.493885 | -6.826721 | -6.817846 | -6.816211 |
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| SYNDIG1 | -5.379305 | -6.227256 | -5.203182 | -1.924072 |
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| WISP3 | -5.134571 | -4.945335 | -5.695285 | -5.872712 |
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| IFI16 | -2.869787 | -3.279824 | -3.858057 | 0.80483 |
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| ITGAV | -2.625569 | -2.391419 | -2.808422 | -0.65981 |
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| OLR1 | -3.602577 | -4.051089 | -4.019403 | -0.502517 |
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| BST2 | -3.336548 | -3.856033 | -3.759307 | -0.119149 |
| TNFAIP2 | -3.494346 | -4.309493 | -4.386543 | -0.330961 |
| RARRES3 | -2.935724 | -3.42928 | -3.885432 | -0.151903 |
| S100A4 | -2.849236 | -4.513933 | -4.120604 | 0.035308 |
| SUSD3 | -3.75881 | -4.653884 | -4.717111 | -0.010172 |
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| SPP1 | -1.783016 | -2.307714 | -4.980711 | -3.310427 |
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| G0S2 | -3.065608 | -3.520998 | -5.601705 | -0.733468 |
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| ASS1 | -1.801941 | -2.870713 | -3.984049 | -3.173891 |
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| SLC28A3 | -1.089408 | -4.258949 | -4.262381 | -3.750494 |
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| EGFL6 | -1.429145 | -5.701774 | -4.894652 | -3.940883 |
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| MT1F | -3.282801 | -3.608965 | -4.572845 | -1.692411 |
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| ANKRD43 | -3.282133 | -5.707454 | -3.849587 | -2.586871 |
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| SAMD13 | -2.478704 | -1.01946 | -1.2488 | -2.617527 |
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| WNT5A | -1.136127 | -1.211194 | -0.16401 | -2.583816 |
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| LHX1 | -5.717549 | -5.867024 | -6.241368 | -6.377416 |
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| CYP4F11 | -3.28025 | -1.390992 | -3.229291 | -2.33336 |
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| SDCBP2 | -1.018829 | -0.520708 | -0.919974 | -1.543528 |
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| CASZ1 | -2.139209 | -2.579918 | -2.561798 | -1.564271 |
| GJB1 | -3.004788 | -3.778321 | -3.799779 | -3.580111 |
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| ITPR3 | -1.115085 | -0.549319 | -4.924528 | -1.425319 |
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| MAST4 | -2.241346 | -2.180368 | -2.739654 | 0.14048 |
| ACOX2 | -2.77641 | -2.430323 | -3.319051 | -1.606763 |
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| FAM3B | -5.508575 | -5.137749 | -5.645754 | -3.581214 |
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| GJB3 | -2.612265 | -2.979841 | -2.978709 | -3.208344 |
| GJB4 | -3.994364 | -4.318081 | -4.086247 | -4.026933 |
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| CDS1 | -4.938623 | -4.559313 | -4.04511 | -3.700675 |
| ABHD11 | -2.765303 | -2.598712 | -2.124116 | -2.690649 |
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| KRT7 | -2.463701 | -2.504042 | -2.720702 | -2.871115 |
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| TMEM125 | -6.624696 | -7.226534 | -6.814322 | -6.936103 |
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| NFIL3 | -2.931776 | -2.779342 | -1.921667 | -0.074326 |
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| RAPGEF3 | -2.302916 | -2.249145 | -2.367733 | -1.271012 |
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| MAP1B | 0.239032 | 0.609488 | 0.853515 | 1.314 |
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| DLX4 | 1.203808 | -0.291483 | 3.154676 | -1.193322 |
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| INSL5 | 0.030014 | 1.118967 | 1.445696 | -2.874942 |
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| ARHGEF25 | 1.341107 | 1.695253 | 1.715958 | -1.383296 |
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| FOLH1 | 2.32666 | 0.777741 | 0.939052 | -1.694265 |
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| IGF2BP3 | 0.772207 | 1.358144 | 0.966402 | -0.174682 |
| ATP1B2 | 0.958471 | 0.974676 | 2.898807 | -0.473203 |
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| MYCL1 | 2.082702 | 1.418676 | 2.083749 | -1.183334 |
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| ZNF560 | 1.940925 | 2.856366 | 1.550276 | 1.700176 |
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| KIAA2022 | 1.605228 | 1.888861 | 1.772031 | -0.9075 |
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| EFNB2 | 1.785115 | 0.899911 | 1.530586 | -2.698262 |
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| ASGR1 | 1.559002 | 1.831071 | 1.282408 | 0.525091 |
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| BMP5 | 2.30696 | 0.739811 | 2.954863 | 0.182179 |
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| ENOX1 | 0.958616 | 0.834002 | 1.833487 | -0.724792 |
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| GFI1 | 1.423742 | 1.453086 | 3.026209 | 1.493101 |
| NHEDC1 | 1.815168 | 1.441806 | 2.150559 | 1.096187 |
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| ELOVL4 | 1.223271 | 1.916044 | 0.928402 | 0.978734 |
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| TEK | 0.848425 | -1.824423 | -2.678854 | 2.07175 |
| PROCR | 1.707264 | -0.142794 | -1.146397 | -3.25E-04 |
| PCDH11Y | -1.063862 | 1.167604 | -1.896014 | -0.458719 |
| PKIA | -2.027442 | 0.388406 | 2.165371 | 0.081818 |

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| UCHL1 | -2.217774 | -1.559746 | 0.439096 | 0.795204 |
| ST6GAL2 | -0.371728 | 1.250206 | -2.356689 | -2.437663 |
| BEX1 | 1.021025 | 0.555214 | 1.080042 | 1.504802 |
| NRXN1 | 0.894827 | 2.363376 | 2.451626 | -0.284029 |
| RBP7 | 0.914982 | 0.699055 | 1.523829 | 0.532214 |
| SRSF12 | 0.910584 | 0.956793 | 1.871406 | -0.388263 |
| ARL4A | 1.730507 | 1.555128 | -2.487902 | 0.819703 |
| FOXS1 | 1.936075 | 2.064196 | -1.966025 | 0.030109 |
| SYNE1 | 2.157937 | 2.123045 | -1.523378 | -0.270427 |
| DENND2C | 1.244405 | 0.82806 | 1.698918 | -0.548999 |
| BG216262 | 0.82905 | -0.552708 | 1.614554 | -0.801393 |
| LOC389634 | 1.621715 | -0.554554 | 1.943401 | 0.460339 |
| FAM169A | 0.867715 | 0.497404 | 1.780342 | 1.01385 |
| ABCC8 | 1.073346 | 0.600865 | 2.804013 | -1.355695 |
| BMP4 | 2.580109 | 1.303176 | 2.731799 | 0.212776 |
| DEPDC7 | 0.796627 | 1.559909 | 0.925967 | -1.164866 |
| CRISPLD1 | 1.105461 | 1.550972 | 1.929023 | -1.094481 |
| SLC36A4 | 1.061761 | 0.953037 | 1.318012 | 0.43019 |
| FLJ13197 | 1.24742 | 1.720478 | 0.578418 | -0.681855 |
| SLC25A35 | 0.874677 | 0.864613 | 1.546779 | -0.095665 |
| GSTM3 | 0.732088 | 0.568063 | 0.160232 | -1.405605 |
| JPH4 | 0.095926 | 0.021627 | 2.397303 | -0.799486 |
| B3GAT1 | -0.465138 | -1.719062 | 1.922831 | 0.740222 |
| VSTM2L | -0.157882 | -1.075618 | -1.923856 | -1.39132 |
| SMAD9 | -0.526556 | -1.992085 | 0.870072 | -1.915662 |
| SPOCK1 | 1.281354 | -2.515466 | -0.455813 | -2.700738 |
| MIAT | 1.300697 | 0.661869 | 2.104471 | 1.037342 |
| LIPG | 2.867758 | 0.52882 | 0.014185 | -0.906604 |
| PDE4A | 1.153633 | 0.46871 | 1.427559 | -0.669134 |
| MAP6 | 1.01467 | 2.177593 | 0.458469 | -0.698304 |
| CES4A | 1.447869 | 1.418551 | 2.508425 | -0.121365 |
| ZSWIM5 | 1.20015 | 1.498537 | 1.265397 | 0.15397 |
| OLFM1 | 1.565267 | 1.009598 | 1.172943 | 1.440188 |
| SOCS2 | 1.570569 | 1.789637 | 0.326458 | 0.567158 |
| RUNX1 | 0.661907 | -0.511689 | 2.275723 | -3.097941 |
| HSPA4L | 1.21618 | 1.369051 | 1.266219 | 0.460469 |
| EFHA2 | -0.120526 | 1.242215 | 0.827255 | -0.760036 |
| TMEM22 | 1.008626 | 0.965067 | 1.234526 | -0.144522 |
| FLJ39051 | 0.876127 | 1.045228 | 1.424677 | -0.241268 |
| DNAH6 | 1.37048 | 1.709129 | 1.929246 | -2.199776 |
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| FAM66C | 1.308132 | 1.244739 | 1.556628 | -0.734677 |
| ALDH7A1 | 1.797349 | 1.389591 | 2.237573 | -2.615689 |
| CTNND2 | 1.122036 | 1.933777 | 0.191477 | -3.074359 |
| ZDHHC2 | 0.358099 | 1.485392 | 1.200887 | -1.332589 |
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| RIC3 | 1.370653 | 1.012453 | 1.511759 | -1.050913 |
| PDE8B | 1.151515 | 1.365257 | -0.048541 | -1.648877 |
| ERC2 | 0.726534 | 1.654288 | 2.159575 | -1.115031 |
| HOMER1 | 1.417744 | 1.516551 | 2.07926 | -0.81114 |
| MLLT3 | 1.205449 | 1.172284 | 1.918271 | -0.381172 |
| PAR1 | 1.21751 | 1.341985 | 0.838594 | 0.493102 |
| SNORD116-19 | 1.256387 | 1.990103 | 1.386722 | 0.073556 |
| PLCB1 | 0.029491 | 1.493167 | 0.650799 | -2.462057 |
| SPAG17 | -0.113535 | 0.631105 | 1.993386 | -1.767013 |
| ULK2 | 1.088008 | 0.849084 | 1.767332 | 0.6179 |
| ZCCHC18 | 0.374302 | 0.869832 | 0.494806 | 1.012382 |
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| LOC647946 | 0.847461 | 1.368047 | 0.302948 | -1.714278 |
| PRAMEF6 | 0.043564 | 1.752454 | 2.116882 | -1.157662 |
| SPINK5 | 0.268065 | 2.252261 | 1.837733 | -2.126172 |
| TRERF1 | 1.101325 | 1.584025 | 1.776034 | 2.172054 |
| CCDC153 | -0.863533 | 1.530655 | 1.276549 | -2.022359 |
| CDHR3 | 1.379163 | 1.675309 | 1.293124 | -1.286347 |
| PLCXD1 | 0.788914 | 1.306167 | 1.242195 | 0.829067 |
| LY6H | 2.371552 | 2.131992 | 1.994025 | 0.709383 |
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| SH3BGRL2 | 1.020553 | 1.358543 | -0.295672 | -1.773351 |
| TSIX | 0.97206 | 0.829786 | 0.602791 | -0.148483 |
| CACNA2D2 | 1.522678 | 1.506002 | 1.740298 | -0.727858 |
| CUZD1 | 1.832418 | 0.997605 | 0.7653 | 0.21485 |
| HENMT1 | 0.982783 | 1.516036 | 1.208031 | 0.761713 |
| LOC100288428 | 0.935151 | 1.087121 | 2.378303 | -1.948367 |
| A1BG | 1.671626 | 1.390356 | 1.123566 | 0.214978 |
| A1BG-AS1 | 1.117054 | 1.216765 | 0.767562 | 0.405021 |
| AKAP12 | 0.769532 | 1.420547 | 0.790363 | -0.575571 |
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| E2F2 | 0.97814 | 0.477511 | 0.334248 | 0.721476 |
| BRIP1 | 1.26015 | 0.544818 | 1.89988 | 0.700907 |
| CCDC150 | 0.902335 | 2.57089 | -0.423528 | -0.508546 |
| ARHGAP11A | 1.151247 | 1.286173 | 0.800171 | 0.662933 |
| BUB1B | 1.085269 | 0.81043 | 0.672243 | 0.484348 |
| CASC5 | 1.486125 | 1.104795 | 0.960131 | 1.1057 |
| CLSPN | 1.843296 | 1.570106 | 1.503787 | 1.479707 |
| SPC24 | 1.61718 | 0.671174 | 0.913106 | 0.607351 |
| FAM64A | 1.393067 | 0.64243 | 0.820167 | 0.598566 |
| GSG2 | 1.232875 | 1.121099 | 0.370459 | 0.971712 |
| CENPI | 0.708935 | 0.842937 | 0.929115 | 1.031908 |
| SHCBP1 | 1.407744 | 1.296665 | 0.824849 | 1.28308 |
| NEK2 | 0.775113 | 0.805739 | 0.318869 | -0.588053 |
| BRCA2 | 1.190932 | 0.617338 | 0.615157 | 0.849713 |
| CENPK | 1.070087 | 1.029017 | 0.694655 | 0.243134 |
| NEIL3 | 1.269419 | 0.420296 | 1.182264 | 0.863132 |
| CDKN3 | 0.668812 | 0.893546 | 2.288437 | -0.380033 |
| FAM72A | 0.895099 | 0.718937 | 0.992661 | 0.366141 |
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| TOP2A | 1.198198 | 0.722168 | 0.414248 | -0.26511 |
| NCAPG | 1.145012 | 1.108167 | 0.584045 | -0.047709 |
| MKI67 | 1.702564 | 0.820652 | 0.164633 | 0.152988 |
| UBE2C | -0.296551 | -0.534471 | -0.88001 | -1.07819 |
| RTKN2 | 0.257525 | 0.892613 | 2.851641 | 0.88132 |
| COL11A2 | 0.317701 | 0.849201 | 0.262829 | -1.693229 |
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| CDCA7L | 1.241648 | 1.821065 | 1.971161 | 0.443419 |
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| DCLK2 | 2.447188 | 2.073871 | 1.976465 | -0.477377 |
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| ZNF208 | 1.807334 | 1.978796 | 2.324781 | 0.334522 |
| VAMP1 | 1.214418 | 2.334786 | 1.341892 | 1.467241 |
| ZNF454 | 1.843912 | 1.724974 | 3.746193 | 1.047143 |
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| KREMEN2 | 1.072436 | -0.602033 | 0.965229 | -0.619693 |
| EFNB3 | 1.3793 | 0.176118 | 2.125828 | -1.763882 |
| TNNT1 | 0.675889 | 0.256888 | -1.8433 | -3.16547 |
| CACNA1B | 0.447982 | 0.29844 | 1.86719 | 0.998947 |
| BEX2 | 0.08873 | 0.567641 | 0.705774 | -0.992404 |
| GABBR2 | -0.715201 | -2.021203 | -2.26671 | -3.288549 |
| GRM4 | 1.608028 | 1.112469 | 0.487727 | -1.563116 |
| TMEM100 | 0.417798 | 0.765958 | -3.375867 | -1.647689 |
| MYEF2 | 0.883037 | 1.178345 | 0.677388 | -1.120886 |
| GLDN | 1.852611 | -1.028265 | 1.162092 | -1.146988 |
| TRIM58 | 1.55982 | 0.248361 | -0.773163 | -1.921434 |
| SALL4 | 1.659553 | 0.982739 | -1.345472 | -2.022364 |
| RAB39B | 0.787786 | 1.013063 | 1.022589 | 1.172065 |
| SLC7A10 | 0.131899 | 1.41141 | -0.938417 | 2.849627 |
| OLFML2A | 2.122882 | 0.693919 | -0.344527 | -1.58532 |
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| RAB6B | 1.154666 | 1.044965 | 0.742032 | -0.623324 |
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| ERBB4 | -0.944763 | 0.034714 | -0.737458 | 1.070556 |
| TCAM1P | 0.960435 | -0.201825 | -0.584291 | 1.946157 |
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| MFAP3L | 1.806718 | 0.98213 | 1.127518 | -0.55613 |
| PRSS30P | 1.520331 | 1.485692 | 2.015263 | 0.308662 |
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| FLJ39095 | -0.020695 | -0.237106 | 2.666586 | -2.453649 |
| TMEM130 | 0.707895 | -0.943241 | 1.358917 | -1.586303 |
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| GDPD1 | 1.518274 | 1.555886 | 1.731283 | 1.053791 |
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| KCTD16 | 2.308533 | 1.921066 | 1.767883 | -1.388802 |
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| GNAZ | 1.753825 | 1.744986 | 2.27917 | -0.18558 |
| RPS6KA6 | 1.54693 | 1.915426 | 1.701509 | 0.396608 |
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| CACNA2D1 | 1.953792 | 1.953833 | 4.209016 | -0.220759 |
| APBA2 | 1.696265 | 2.311443 | 0.80728 | 1.809918 |
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| GUSBP10 | 2.668292 | 1.653869 | 3.803112 | 1.170925 |
| LRRC4B | 3.206499 | 3.303629 | 4.115186 | 1.754172 |
| SPTBN4 | 2.852734 | 2.793353 | 2.892865 | 0.442965 |
| LPPR3 | 2.840209 | 1.238426 | 3.075961 | 3.377108 |
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| H2AFJ | 0.970331 | 2.217522 | 2.570859 | 0.809397 |
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| TMEM38A | 1.690465 | 1.615043 | 1.980485 | -0.734968 |
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| RFPL3-AS1 | 1.628706 | 1.665076 | 1.60836 | -0.290422 |
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| GATA4 | 2.70591 | 3.234806 | 2.594805 | -1.771753 |
| PTCH1 | 1.764617 | 1.89545 | 2.687597 | -0.440817 |
| NLGN3 | 2.373318 | 2.314176 | 3.042149 | -0.062603 |
| INPP1 | 2.19026 | 2.856175 | 1.849305 | 1.307312 |
| NHEDC2 | 1.463568 | 1.834223 | 1.696031 | 1.315607 |
| SCARNA9 | 1.640706 | 2.101316 | 1.304165 | 1.118503 |
| SHC2 | 1.753954 | 2.338258 | 2.238997 | 0.308661 |
| SERP2 | 1.490393 | 1.610671 | 1.99656 | -0.443082 |
| PRDM5 | 1.967086 | 1.902765 | 2.611513 | -0.382976 |
| SLC38A10 | 1.696907 | 2.323858 | 2.663983 | 1.02843 |
| FAM98B | 1.895204 | 1.773862 | 2.306084 | 1.304042 |
| PHF7 | 2.508551 | 1.557791 | 1.796629 | 2.173158 |
| ZNF167 | 2.200507 | 1.427091 | 2.22289 | -0.131118 |
| CHST10 | 2.085333 | 2.374378 | 2.354593 | 1.122115 |
| KDELC2 | 1.32337 | 1.512281 | 1.566737 | 0.924326 |
| WNT3 | 2.076318 | 1.601668 | 1.822734 | 0.401959 |

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| CABP1 | 3.009296 | 3.187867 | 1.953604 | 0.225956 |
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| ELAVL2 | 2.445441 | 4.147039 | 2.797917 | -0.690943 |
| AK123308 | 1.415378 | 2.36299 | 2.008284 | 0.645567 |
| PCDHGA3 | 0.603183 | 2.684061 | 1.813609 | -0.617484 |
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| JPX | 2.948052 | 2.079826 | 2.220782 | -0.155256 |
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| SEMA4F | 1.662692 | 1.958827 | 1.683962 | 0.899122 |
| DOC2A | 1.71799 | 2.089969 | 2.983999 | -0.356364 |
| TRIM71 | 1.925971 | 1.280091 | 3.648882 | -0.990904 |
| PTPRG | 1.889805 | 1.60076 | 3.504381 | -1.646846 |
| RNPC3 | 1.34307 | 1.857948 | 2.32262 | -0.840195 |
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| XKR6 | 1.682719 | 1.460777 | 1.796926 | -0.108198 |
| DPYD | 2.295813 | 1.139726 | 1.859691 | 1.569242 |
| PCDHA10 | 1.349964 | 0.693354 | 2.182716 | 0.016197 |
| GRAMD1B | 1.055763 | 2.617256 | -0.275347 | 1.113841 |
| NQO1 | 1.442373 | 1.314388 | 0.827284 | -0.149834 |
| GSPT2 | 0.962394 | 1.524113 | 1.420418 | 0.642537 |
| RAP2B | 0.703766 | 2.371921 | 0.790368 | 0.56989 |
| IPO9 | 0.742657 | 1.071459 | 0.508672 | -0.52124 |
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| VWA5B2 | 0.657405 | 0.464038 | 1.948161 | -1.505795 |
| MED12L | 1.677339 | 1.075321 | 2.041312 | -1.122426 |
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| NEBL | 1.206726 | 1.357847 | -0.532652 | 1.466833 |
| THBS4 | -1.059022 | 1.916312 | -1.617328 | -0.191578 |
| NEURL | -0.830377 | -0.503185 | 0.972369 | 0.473482 |
| NR0B1 | 0.581529 | 0.998345 | 1.318022 | -2.870836 |
| SORCS1 | -0.310041 | -0.575092 | -1.385432 | 1.416228 |
| TUSC3 | 0.963704 | 1.11918 | 0.880485 | -0.594875 |
| ZNF676 | 1.360147 | 1.273431 | 0.011593 | -0.311235 |
| CCDC102B | -0.199163 | 1.233183 | -0.069954 | 2.45187 |
| COL5A3 | 0.081013 | 1.873604 | 0.157521 | 0.957173 |
| CCNB3 | -0.021747 | 1.769374 | -0.316843 | -1.458666 |
| PPEF1 | -0.153565 | -0.163201 | 2.619294 | -2.556726 |
| EXTL1 | 2.584936 | 1.610467 | 1.145788 | -0.022111 |
| SCRN1 | 1.122605 | 1.517646 | 0.838538 | -0.578171 |
| BNC1 | -1.920484 | -3.258182 | -1.125756 | -3.001611 |
| SMC1B | 1.034971 | 0.803541 | 1.032405 | -1.969535 |
| ZIK1 | 0.758873 | 1.20113 | 0.22236 | 0.674251 |
| LPHN2 | 0.945809 | -2.12689 | 2.460646 | -0.574304 |
| SHC4 | -0.450454 | -0.057029 | 1.150143 | -1.285125 |
| BSN | 0.630305 | 0.975431 | 1.088655 | -0.3788 |
| ZYG11A | 0.807904 | 2.639704 | -1.544287 | 1.02648 |
| KLF4 | 1.86244 | 1.803777 | -1.396352 | 1.562517 |
| KLF2 | 1.058538 | 1.759965 | 1.082909 | 1.357158 |
| PIGZ | 1.010271 | 0.867835 | 0.837825 | -0.283276 |
| NGFR | 1.825536 | 2.424589 | 0.25306 | 2.103641 |
| CLMP | 1.607838 | 2.175485 | -2.137046 | 0.654226 |
| LOC338817 | 1.330762 | 1.46203 | -0.464018 | 0.487226 |
| PABPC5 | 0.450344 | 2.827634 | -1.69213 | 1.179254 |
| ZNF540 | -0.040643 | 1.221808 | -1.101053 | 1.070229 |
| ITM2A | -1.603797 | -0.877705 | 2.282595 | 1.711807 |
| HBG1 | -1.944583 | -0.121761 | -1.980793 | 2.988451 |
| CD28 | -0.273984 | -0.151422 | -1.297362 | 3.095292 |
| CLEC10A | -0.086031 | -1.453194 | -1.887141 | 3.072891 |
| MRC1 | -0.620431 | -1.003797 | -1.437427 | 2.3958 |
| MPEG1 | -0.888613 | -0.551119 | -1.363122 | 2.749321 |

| | | | | |
|---|---|---|---|---|
| TTN | -0.397115 | -0.513868 | -2.061049 | 3.194563 |
| FGFR1 | 1.284593 | 1.030842 | 0.47406 | 2.732277 |
| P2RX5 | 1.957615 | 0.899563 | 1.38502 | 2.311625 |
| TSKS | 1.132431 | 0.818572 | -0.28815 | 3.441784 |
| LILRA3 | 0.829722 | -0.226672 | -1.460738 | 3.59276 |
| TLR10 | 0.811355 | 2.023506 | -1.324795 | 4.004095 |
| LAG3 | 1.434311 | 1.104125 | -1.550278 | 2.325248 |
| TNFRSF8 | 1.341241 | 1.045118 | -1.342072 | 1.023216 |
| RTN1 | -1.167063 | 1.204781 | 1.321162 | 1.457335 |
| P2RX7 | 2.687366 | 2.997539 | -1.550337 | 1.340595 |
| MYOM1 | 0.386606 | 0.69238 | 1.404779 | -1.974527 |
| SPIB | -0.107672 | -0.942363 | -1.955099 | 2.754247 |
| SYN2 | -2.097427 | 0.111951 | 1.575597 | -0.457145 |
| HAS3 | 0.573485 | 0.86564 | 0.152893 | 2.649548 |
| SNX10 | 0.421257 | 1.108814 | 0.214527 | 0.996166 |
| PCDHAC2 | 0.987891 | 1.370786 | 1.44675 | 1.604978 |
| CHN1 | -1.217468 | -1.57883 | -0.576441 | 2.828002 |
| XCL1 | -3.20565 | 0.598193 | 1.278139 | 1.355059 |
| MEGF11 | 1.155789 | 0.339363 | 0.935939 | -1.410652 |
| MYLK4 | -0.251101 | 0.336865 | 1.800611 | -1.689872 |
| HIST1H3H | 0.432929 | 0.88147 | 2.28925 | -0.189443 |
| MBD2 | -0.28876 | -1.409489 | 1.36233 | 1.595236 |
| AMH | 0.639637 | 1.113494 | 1.671838 | -1.344207 |
| PRAME | 1.662102 | 1.384826 | 2.257878 | 0.493487 |
| LOC100131347 | 1.917741 | 1.539194 | 2.585283 | 0.642483 |
| SERTAD2 | 1.112989 | 1.518399 | 1.626217 | 0.441439 |
| RNF112 | 1.342209 | 0.911329 | 0.494625 | 0.613614 |
| ZNF549 | 2.562708 | 2.261364 | 1.62482 | 1.334464 |
| ZNF667 | 1.853982 | 2.085654 | 1.841979 | -0.086369 |
| OCLN | 0.66868 | 1.717274 | -0.110888 | -1.882674 |
| PCDHA6 | 0.043179 | 0.866984 | 1.7443 | -0.429168 |
| PCDHA9 | 0.646875 | 1.068991 | 1.638255 | -0.752487 |
| SLC2A12 | -1.399439 | -1.793904 | -0.195038 | -2.272623 |
| TRIM63 | -1.04128 | -2.042517 | -0.283018 | -3.889502 |
| AK124971 | 0.994359 | -0.349734 | 0.894829 | -0.236381 |
| ANK1 | 1.351029 | 0.770295 | 1.529645 | 0.683609 |
| CNTNAP3 | -1.312912 | 0.672075 | 0.993903 | 1.909924 |
| TRIM7 | -0.957149 | 1.129492 | 1.688318 | 0.070335 |
| FAM153A | 0.351687 | 1.563233 | 2.145673 | 0.782057 |
| FAM153B | 0.149309 | 1.201275 | 1.887879 | 0.603227 |
| ADHFE1 | 1.000902 | 0.924615 | 1.294437 | -0.42886 |

| | | | | |
|---|---|---|---|---|
| HIST2H2BE | 0.510945 | 1.834684 | 1.455005 | -0.942391 |
| LOC283861 | 0.078587 | 1.402544 | 1.788556 | -0.282677 |
| THC2680609 | 0.745217 | 0.847596 | 1.682786 | 0.131254 |
| NF1P1 | 1.287905 | 1.386176 | 1.390873 | 0.418244 |
| TRAF1 | 0.281232 | 0.077395 | 0.713407 | 2.146268 |
| EDA2R | -0.67023 | 1.46791 | 1.171856 | -0.824774 |
| LOC100128348 | 1.251969 | 1.16054 | 1.355532 | -0.538804 |
| THC2723408 | 1.317246 | 0.953574 | 1.207036 | -0.084412 |
| LYPLAL1 | 0.803287 | 0.663406 | 0.650259 | -0.347134 |
| DTX1 | 0.810262 | 0.860398 | 2.325917 | 1.368488 |
| GNA14 | 0.205405 | 0.677794 | 2.336509 | 1.792526 |
| GSTM1 | 1.147696 | 0.877416 | 1.031285 | -0.270041 |
| LOC100507421 | 2.329891 | 2.369813 | 2.884711 | 0.883234 |
| SULT4A1 | 0.989177 | 1.568653 | 1.648088 | 0.636829 |
| PARD6A | 2.00183 | 2.000677 | 2.065531 | 1.03466 |
| LOC100128668 | 1.422618 | 3.321206 | 2.464268 | -1.138818 |
| TMEM150C | 1.184617 | 1.902622 | 0.063408 | 1.3631 |
| WNT5B | 0.735685 | 1.783297 | 0.857412 | 2.304179 |
| ANKRD20A8P | 1.67824 | 1.794155 | 1.801052 | -0.424143 |
| ZMAT1 | 1.434433 | 1.650088 | 1.890346 | 0.222919 |
| SRRM3 | 2.132787 | 2.871602 | 1.554137 | -0.627579 |
| SPDYA | 0.81038 | 1.14196 | 1.486854 | -1.946925 |

# APPENDIX F

# SCCOHT TUMORS vs. EPITHELIAL OVARIAN CARCINOMAS ssGSEA ENRICHMENT SCORES

| ID | Rank | p-value | FDR | SCCO-002 | SCCO-012 | SCCO-014 | SCCO-015 |
|---|---|---|---|---|---|---|---|
| Sample Type | | | | SCCO | SCCO | SCCO | SCCO |
| GTPASE ACTIVITY | 1 | 0.001996 | 0.0147 | 771.9349 | 583.2598 | 665.3749 | 786.0159 |
| NEUROGENESIS | 2 | 0.001996 | 0.0147 | 710.2548 | 338.2216 | 710.3406 | 790.9142 |
| GENERATION OF NEURONS | 3 | 0.001996 | 0.0147 | 686.8301 | 345.6315 | 690.2432 | 793.5269 |
| NEURON DIFFERENTIATION | 4 | 0.001996 | 0.0147 | 737.1888 | 328.0484 | 691.6592 | 800.0927 |
| NUCLEOSIDE TRIPHOSPHATASE ACTIVITY | 5 | 0.001996 | 0.0147 | 564.6907 | 518.9498 | 632.1911 | 685.9863 |
| AXON GUIDANCE | 6 | 0.001996 | 0.0147 | 826.927 | 509.3356 | 907.141 | 1042.7775 |
| CELLULAR MORPHOGENESIS DURING DIFFERENTIATION | 7 | 0.001996 | 0.0147 | 704.2968 | 269.5277 | 696.6626 | 777.7568 |
| AXONOGENESIS | 8 | 0.001996 | 0.0147 | 704.2968 | 269.5277 | 696.6626 | 777.7568 |
| NEURITEDEVELOPMENT | 9 | 0.001996 | 0.0147 | 697.2829 | 265.5372 | 666.5981 | 771.3181 |
| NEURON DEVELOPMENT | 10 | 0.001996 | 0.0147 | 650.4121 | 290.0594 | 644.452 | 764.9664 |
| NERVOUS SYSTEM DEVELOPMENT | 11 | 0.001996 | 0.0147 | 522.2457 | 151.9929 | 502.777 | 491.6122 |
| PYROPHOSPHATASE ACTIVITY | 12 | 0.001996 | 0.0147 | 537.0847 | 412.9899 | 547.2112 | 632.8636 |
| HYDROLASE ACTIVITY ACTING ON ACID ANHYDRIDES | 13 | 0.001996 | 0.0147 | 537.0847 | 412.9899 | 547.2112 | 632.8636 |
| SEQUENCE SPECIFIC DNA BINDING | 14 | 0.001996 | 0.0147 | 790.9737 | 522.4899 | 842.4286 | 803.6003 |
| M PHASE OF MITOTIC CELL CYCLE | 15 | 0.001996 | 0.0147 | 670.0147 | 983.4147 | 758.3572 | 722.3364 |
| MITOSIS | 16 | 0.001996 | 0.0147 | 670.0147 | 983.4147 | 758.3572 | 722.3364 |
| CHROMOSOME ORGANIZATION AND BIOGENESIS | 17 | 0.003992 | 0.0210 | 637.344 | 582.5443 | 538.5919 | 481.1779 |
| INTRACELLULAR ORGANELLE PART | 18 | 0.001996 | 0.0147 | 143.9742 | 161.4615 | 176.2847 | 183.0013 |
| ORGANELLE PART | 19 | 0.001996 | 0.0147 | 143.9742 | 161.4615 | 176.2847 | 183.0013 |
| PATTERN SPECIFICATION PROCESS | 20 | 0.003992 | 0.0210 | 445.8036 | 246.1957 | 202.478 | 271.6404 |
| CAMP MEDIATED SIGNALING | 21 | 0.003992 | 0.0210 | 425.1986 | 52.4493 | 726.1094 | 378.0503 |
| G PROTEIN SIGNALING COUPLED TO CAMP NUCLEOTIDE SECOND MESSENGER | 22 | 0.003992 | 0.0210 | 425.1986 | 52.4493 | 726.1094 | 378.0503 |
| REGULATION OF CELL DIFFERENTIATION | 23 | 0.001996 | 0.0147 | 690.9872 | 147.5777 | 909.91 | 709.1957 |
| CYCLIC NUCLEOTIDE MEDIATED SIGNALING | 24 | 0.007984 | 0.0323 | 375.2209 | 201.2277 | 592.0203 | 245.9402 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| G PROTEIN SIGNALING COUPLED TO CYCLIC NUCLEOTIDE SECOND MESSENGER | 25 | 0.007984 | 0.0323 | 375.2209 | 201.2277 | 592.0203 | 245.9402 |
| SYNAPTIC TRANSMISSION | 26 | 0.01796 | 0.0625 | 563.1757 | -221.2022 | 531.1635 | 550.085 |
| RNA POLYMERASE II TRANSCRIPTION FACTOR ACTIVITY | 27 | 0.001996 | 0.0147 | 94.7546 | 310.2815 | 220.0892 | 437.0663 |
| PROTEIN PROCESSING | 28 | 0.007984 | 0.0323 | 633.2747 | 148.3031 | 753.9393 | 607.9616 |
| CATION CHANNEL ACTIVITY | 29 | 0.007984 | 0.0323 | 250.0394 | 75.0674 | 443.7844 | 484.3365 |
| REGULATION OF CELL CYCLE | 30 | 0.001996 | 0.0147 | 446.4481 | 693.1426 | 332.1025 | 304.6489 |
| CENTRAL NERVOUS SYSTEM DEVELOPMENT | 31 | 0.003992 | 0.0210 | 342.8981 | 50.7179 | 360.8685 | 270.924 |
| METAL ION TRANSMEMBRANE TRANSPORTER ACTIVITY | 32 | 0.02395 | 0.0784 | 163.4294 | 81.5075 | 318.5092 | 336.3756 |
| ATPASE ACTIVITY | 33 | 0.003992 | 0.0210 | 293.5123 | 424.3022 | 579.4186 | 545.0493 |
| ATPASE ACTIVITY COUPLED | 34 | 0.003992 | 0.0210 | 293.5123 | 424.3022 | 579.4186 | 545.0493 |
| HEMOPOIETIC OR LYMPHOID ORGAN DEVELOPMENT | 35 | 0.04591 | 0.114 | 528.6393 | 431.5878 | 623.3032 | 741.8558 |
| IMMUNE SYSTEM DEVELOPMENT | 36 | 0.04591 | 0.114 | 528.6393 | 431.5878 | 623.3032 | 741.8558 |
| HEMOPOIESIS | 37 | 0.04591 | 0.114 | 528.6393 | 431.5878 | 623.3032 | 741.8558 |
| SYNAPTOGENESIS | 38 | 0.02794 | 0.0863 | 990.2471 | -675.3848 | 1029.4548 | 1056.8962 |
| TRANSMISSION OF NERVE IMPULSE | 39 | 0.01996 | 0.0673 | 561.0675 | -235.0623 | 531.4042 | 547.9159 |
| CELL SURFACE | 40 | 0.01198 | 0.0444 | 84.4465 | 271.0054 | 404.2405 | 444.3256 |
| BRAIN DEVELOPMENT | 41 | 0.03593 | 0.0962 | 614.0378 | -134.459 | 640.1589 | 580.5057 |
| VOLTAGE GATED CATION CHANNEL ACTIVITY | 42 | 0.01796 | 0.0625 | 453.2144 | -408.5424 | 467.252 | 565.7113 |
| EXTRACELLULAR STRUCTURE ORGANIZATION AND BIOGENESIS | 43 | 0.02994 | 0.0888 | 732.8448 | -623.3364 | 633.0256 | 687.5338 |
| SYNAPSE ORGANIZATION AND BIOGENESIS | 44 | 0.03593 | 0.0962 | 688.5699 | -818.6898 | 744.9666 | 723.3106 |
| VOLTAGE GATED CHANNEL ACTIVITY | 45 | 0.02994 | 0.0888 | 329.786 | -307.295 | 326.9486 | 529.2955 |
| REGULATION OF CELLULAR METABOLIC PROCESS | 46 | 0.06188 | 0.1328 | 18.048 | 242.4978 | 270.2726 | 152.3833 |
| MITOTIC CELL CYCLE | 47 | 0.02395 | 0.0784 | 498.6461 | 610.7933 | 386.6638 | 289.9799 |
| NUCLEAR PART | 48 | 0.003992 | 0.0210 | 223.3564 | 580.2588 | 415.3607 | 299.6281 |
| NEUROLOGICAL SYSTEM PROCESS | 49 | 0.03393 | 0.0961 | 161.7056 | -366.7457 | 271.1746 | 205.1427 |
| REGULATION OF METABOLIC PROCESS | 50 | 0.06387 | 0.1357 | 18.7505 | 229.9949 | 273.2888 | 152.0275 |
| EXTRACELLULAR | 393 | 0.003992 | 0.0210 | -533.3955 | -434.9046 | -350.1783 | -531.6147 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SPACE | | | | | | | |
| OXIDOREDUCTASE ACTIVITY | 394 | 0.01198 | 0.0444 | -556.2234 | 116.5838 | -496.6693 | -589.7682 |
| INTRACELLULAR PROTEIN TRANSPORT | 395 | 0.001996 | 0.0147 | -49.8983 | 111.6669 | 11.4957 | -255.0942 |
| SMALL GTPASE MEDIATED SIGNAL TRANSDUCTION | 396 | 0.005988 | 0.0264 | -364.1205 | 379.4459 | -374.951 | -223.2679 |
| CALCIUM ION BINDING | 397 | 0.005988 | 0.0264 | -586.6292 | -257.5257 | -505.6845 | -424.3741 |
| PROTEIN KINASE REGULATOR ACTIVITY | 398 | 0.003992 | 0.0210 | -398.6812 | -397.3839 | -699.1248 | -557.9597 |
| KINASE REGULATOR ACTIVITY | 399 | 0.003992 | 0.0210 | -398.6812 | -397.3839 | -699.1248 | -557.9597 |
| GAMETE GENERATION | 400 | 0.003992 | 0.0210 | -531.151 | -835.9851 | -806.4949 | -658.144 |
| REGULATION OF BIOLOGICAL QUALITY | 401 | 0.001996 | 0.0147 | -507.2691 | -110.3124 | -328.45 | -405.9878 |
| CYTOSKELETON | 402 | 0.003992 | 0.0210 | -115.2292 | -105.5998 | -49.0366 | -35.4249 |
| ENZYME ACTIVATOR ACTIVITY | 403 | 0.003992 | 0.0210 | -349.3511 | 319.2023 | -487.4375 | -428.6584 |
| SERINE TYPE ENDOPEPTIDASE INHIBITOR ACTIVITY | 404 | 0.003992 | 0.0210 | -555.6916 | -352.1396 | -696.0656 | -273.0508 |
| SERINE TYPE ENDOPEPTIDASE ACTIVITY | 405 | 0.001996 | 0.0147 | -898.8819 | -500.6642 | -923.8177 | -881.0483 |
| SERINE HYDROLASE ACTIVITY | 406 | 0.001996 | 0.0147 | -898.8819 | -500.6642 | -923.8177 | -881.0483 |
| SERINE TYPE PEPTIDASE ACTIVITY | 407 | 0.001996 | 0.0147 | -898.8819 | -500.6642 | -923.8177 | -881.0483 |
| EPIDERMIS DEVELOPMENT | 408 | 0.001996 | 0.0147 | -728.2922 | -953.2261 | -775.0378 | -714.2462 |
| MULTI ORGANISM PROCESS | 409 | 0.005988 | 0.0264 | -687.3802 | -161.797 | -698.1433 | -778.1232 |
| AMINE METABOLIC PROCESS | 410 | 0.001996 | 0.0147 | -797.6571 | -514.3273 | -853.1907 | -700.8266 |
| LIPID METABOLIC PROCESS | 411 | 0.003992 | 0.0210 | -464.6909 | -56.3503 | -499.1738 | -474.5736 |
| PROTEASE INHIBITOR ACTIVITY | 412 | 0.003992 | 0.0210 | -836.2816 | -713.2341 | -893.3275 | -655.5845 |
| ORGANIC ACID METABOLIC PROCESS | 413 | 0.001996 | 0.0147 | -615.3661 | -129.6967 | -733.8336 | -583.9717 |
| CARBOXYLIC ACID METABOLIC PROCESS | 414 | 0.001996 | 0.0147 | -615.3661 | -129.6967 | -733.8336 | -583.9717 |
| HOMEOSTATIC PROCESS | 415 | 0.001996 | 0.0147 | -722.0543 | -384.4078 | -548.962 | -676.7865 |
| ENZYME REGULATOR ACTIVITY | 416 | 0.001996 | 0.0147 | -343.1852 | -81.4577 | -441.5355 | -375.9703 |
| TRANSPORT | 417 | 0.001996 | 0.0147 | -218.9341 | -43.6067 | -168.7363 | -178.4467 |
| RECEPTOR COMPLEX | 418 | 0.001996 | 0.0147 | -259.4996 | -116.2824 | -590.4314 | -338.3235 |
| ESTABLISHMENT OF LOCALIZATION | 419 | 0.001996 | 0.0147 | -240.1724 | -84.2888 | -146.1154 | -180.7207 |
| STEROID METABOLIC PROCESS | 420 | 0.001996 | 0.0147 | -683.6624 | -807.7336 | -783.7552 | -769.508 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ENZYME INHIBITOR ACTIVITY | 421 | 0.001996 | 0.0147 | -388.8479 | -430.6704 | -433.6656 | -396.9168 |
| CELLULAR CATION HOMEOSTASIS | 422 | 0.001996 | 0.0147 | -807.5004 | -357.8847 | -641.4784 | -636.3035 |
| SEXUAL REPRODUCTION | 423 | 0.003992 | 0.0210 | -591.7082 | -835.8108 | -805.8743 | -636.2712 |
| CELLULAR HOMEOSTASIS | 424 | 0.001996 | 0.0147 | -832.8239 | -330.0287 | -685.893 | -704.5195 |
| CATION HOMEOSTASIS | 425 | 0.001996 | 0.0147 | -787.0532 | -403.5824 | -636.7249 | -660.5696 |
| NITROGEN COMPOUND METABOLIC PROCESS | 426 | 0.001996 | 0.0147 | -735.6963 | -494.9637 | -709.7031 | -599.9429 |
| CHEMICAL HOMEOSTASIS | 427 | 0.001996 | 0.0147 | -768.8953 | -435.6961 | -630.0493 | -686.239 |
| ECTODERM DEVELOPMENT | 428 | 0.001996 | 0.0147 | -724.1939 | -847.3606 | -806.9662 | -761.7172 |
| ION HOMEOSTASIS | 429 | 0.001996 | 0.0147 | -817.7072 | -367.6243 | -685.8494 | -727.3134 |
| REPRODUCTION | 430 | 0.003992 | 0.0210 | -326.5291 | -530.2076 | -509.6114 | -389.1745 |
| PROTEIN TRANSPORT | 431 | 0.001996 | 0.0147 | -251.149 | -54.7231 | -194.9001 | -382.8925 |
| PROTEIN TARGETING | 432 | 0.001996 | 0.0147 | -189.1389 | -290.3859 | -211.5203 | -450.8821 |
| MACROMOLECULE LOCALIZATION | 433 | 0.001996 | 0.0147 | -270.8893 | -68.9022 | 11.0974 | -179.7686 |
| IDENTICAL PROTEIN BINDING | 434 | 0.001996 | 0.0147 | -361.2807 | -117.8349 | -208.3356 | -238.8636 |
| ESTABLISHMENT OF PROTEIN LOCALIZATION | 435 | 0.001996 | 0.0147 | -335.6292 | -188.6457 | -24.4066 | -349.4225 |
| APICOLATERAL PLASMA MEMBRANE | 436 | 0.001996 | 0.0147 | -952.5406 | -1027.0845 | -883.0633 | -874.291 |
| APICAL JUNCTION COMPLEX | 437 | 0.001996 | 0.0147 | -952.5406 | -1027.0845 | -883.0633 | -874.291 |
| INTERCELLULAR JUNCTION | 438 | 0.001996 | 0.0147 | -768.0267 | -935.444 | -751.1049 | -838.53 |
| ANION TRANSMEMBRANE TRANSPORTER ACTIVITY | 439 | 0.001996 | 0.0147 | -958.8814 | -867.2037 | -1144.2427 | -1028.7422 |
| PROTEIN LOCALIZATION | 440 | 0.001996 | 0.0147 | -374.6898 | -188.0299 | -114.1904 | -346.6974 |
| REGULATION OF TRANSPORT | 441 | 0.001996 | 0.0147 | -579.9343 | -535.5339 | -635.5785 | -786.3221 |
| CELL JUNCTION | 442 | 0.001996 | 0.0147 | -690.9211 | -821.545 | -707.6072 | -752.2447 |

# APPENDIX G

# *SMARCA4* MUTATIONS IDENTIFIED IN DNA FROM SCCOHT PATIENTS AND CELL LINE

| Sample ID | Sequencing analysis performed | Age at diagnosis (years) | *SMARCA4* mutations | | IHC | |
|---|---|---|---|---|---|---|
| | | | Germline | Tumor | SMARCA4 | SMARCB1 |
| SCCO-001 | Sanger | 22 | N/A | p.Ala161Val<br>p.Ala532fs | Negative | Positive |
| SCCO-002 | Whole Genome | 26 | None | None | Negative | Positive |
| SCCO-004 | Sanger | 32 | None | p.Val204fs | Negative | Positive |
| SCCO-005 | Sanger | 18 | None | p.Asp1299fs | N/A | N/A |
| SCCO-006 | Sanger | 32 | None | p.Trp764fs<br>p.Gly836 | Negative | Positive |
| SCCO-007 | Sanger | 25 | N/A | p.Gln331<br>p.Ile542fs | Negative | Positive |
| SCCO-008 | Exome | 9 | p.Arg979 | N/A | N/A | N/A |
| SCCO-009 | Sanger | 27 | N/A | p.Tyr1050fs | Negative | Positive |
| SCCO-010 | Exome/Sanger | 6 | None | None* | Positive | Negative |
| SCCO-011 | Sanger | 30 | N/A | p.Arg1189 | Negative | Positive |
| SCCO-012 | Exome | 21 | N/A | None | Negative | Positive |
| SCCO-014 | Exome | 33 | N/A | p.Glu667fs<br>p.Leu1161fs | N/A | N/A |
| SCCO-015 | Exome | 27 | N/A | p.Arg1189 | N/A | N/A |
| SCCO-016 | Sanger | 12 | N/A | p.Arg1329fs | Negative | Positive |
| SCCO-017 | Exome/Sanger | 10 | p.Gly241fs | p.Gly241fs* | Negative | Positive |
| SCCO-018 | Sanger | 5 | N/A | None | Positive | Negative |
| SCCO-019 | Sanger | 27 | N/A | p.Phe844fs | Negative | Positive |
| DAH23 | Exome | 30 | N/A | c.2438+1_2438+2insTGA | Negative | N/A |
| DAH456 | Exome | 39 | None | None | Positive | Positive |
| DAH457 | Exome | 23 | N/A | p.Arg1093 | N/A | Positive |
| DG1006 | Whole Genome | 34 | None | p.Glu952fs<br>p.Ser1591fs | Negative | N/A |
| DG1219 | Whole Genome | 37 | None | c.3168+1>A | Negative | N/A |
| BIN-67 | Whole Genome | Tumor cell line | N/A | c.2438+1G>A<br>c.2439-2A>T | Negative | Positive |
| SCCOHT-1 | New case | Tumor cell line | N/A | p.Pro1180fs | Negative | N/A |

*Germline DNA was analyzed by Exome sequencing and tumor DNA was analyzed by Sanger sequencing.

# APPENDIX H

# SOMATIC MUTATIONS IDENTIFIED IN SCCOHT TUMORS BY NEXT-GENERATION SEQUENCING

| Sample | Gene | Chr | hg19 Pos | Ref | Alt | Aberration Value |
|---|---|---|---|---|---|---|
| SCCO-002 | HLA-DRB1 | chr6 | 32551957 | G | C | A100G |
| SCCO-002 | KRTAP10-12 | chr21 | 46117768 | A | C | T218P |
| DAH456 | CD163L1 | chr12 | 7551176 | C | A | K481N |
| DAH456 | CDC7 | chr1 | 91973956 | T | G | SPLICE SITE DONOR |
| DAH456 | FAM3C | chr7 | 120991309 | G | A | A161V |
| DAH456 | PCDHB8 | chr5 | 140558522 | C | T | R303* |
| DAH456 | RHBDL2 | chr1 | 39384898 | C | G | G76A |
| DG1006 | ADAMTS8 | chr11 | 130298117 | G | GGCA | CODON INSERTION |
| DG1006 | CCDC164 | chr2 | 26667147 | T | A | F362L |
| DG1006 | COL12A1 | chr6 | 75799829 | G | A | R618* |
| DG1006 | COQ9 | chr16 | 57493577 | G | A | R275H |
| DG1006 | EPG5 | chr18 | 43523146 | G | A | R642* |
| DG1006 | FAM184A | chr6 | 119295631 | G | T | N959K |
| DG1006 | KNDC1 | chr10 | 135027224 | A | G | I1509V |
| DG1006 | NDNF | chr4 | 121958405 | G | A | P241S |
| DG1006 | PPP1R12B | chr1 | 202409853 | A | G | Y493C |
| DG1006 | SMARCA4 | chr19 | 11170467 | CAGCG | C | FRAME SHIFT |
| DG1006 | SMARCA4 | chr19 | 11132638 | GA | G | FRAME SHIFT |
| DG1006 | TBP | chr6 | 170871012 | A | G | Q63R |
| DG1219 | AC096644.1 | chr1 | 220603312 | T | G | T43P |
| DG1219 | AP000552.1 | chr22 | 21646812 | G | C | V184L |
| DG1219 | C1orf220 | chr1 | 178514560 | A | T | *107C |
| DG1219 | CABP1 | chr12 | 121093633 | C | G | A7G |
| DG1219 | FRMPD2 | chr10 | 49400889 | G | A | A668V |
| DG1219 | LRRTM1 | chr2 | 80530223 | C | A | R241L |
| DG1219 | MT-ATP6 | chrMT | 9048 | TGGAA | T | FRAME SHIFT |
| DG1219 | RPGRIP1 | chr14 | 21778748 | C | G | Y304* |
| DG1219 | SCIN | chr7 | 12666383 | G | A | A386T |
| DG1219 | SELPLG | chr12 | 109017671 | GGCA | G | CODON CHANGE PLUS CODON DELETION |
| DG1219 | SMARCA4 | chr19 | 11136185 | G | A | SPLICE SITE DONOR |
| DG1219 | SYNE3 | chr14 | 95912298 | C | T | R527K |

# APPENDIX I

# SMARCA4 MUTATIONS AND SMARCA4/SMARCB1 PROTEIN STATUS IN SCCOHT CASES PUBLISHED IN 3 OTHER STUDIES

| Sample ID | Publication | Age at diagnosis (years) | *SMARCA4* mutations | | IHC | |
|---|---|---|---|---|---|---|
| | | | Germline | Tumor | SMARCA4 | SMARCB1 |
| FA1a | Witkowski et al. | 23 | c.4071+1G>A | c.4071+1G>A<br>p.Val343fs | Negative | N/A |
| FA1b | Witkowski et al. | 11 | c.4071+1G>A | c.4071+1G>A<br>LOH | Negative | N/A |
| FA2a | Witkowski et al. | 16 | p.Gln215* | N/A | Negative | N/A |
| FA2b | Witkowski et al. | 16 | p.Gln215* | p.Gln215*<br>p.Asn563fs | Negative | N/A |
| FA3a | Witkowski et al. | U | c.2617–3C>G | N/A | Negative | N/A |
| FA3b | Witkowski et al. | 11 | c.2617–3C>G | c.2617–3C>G<br>LOH | Negative | N/A |
| FA4a | Witkowski et al. | 40 | p.Gly1080Asp | p.Gly1080Asp<br>LOH | Positive | N/A |
| FA4b | Witkowski et al. | 13 | p.Gly1080Asp | p.Gly1080Asp<br>p.Ser442fs* | Negative | N/A |
| NF1 | Witkowski et al. | 41 | p.Leu409fs | N/A | Negative | N/A |
| NF2 | Witkowski et al. | 19 | p.Gln555* | p.Gln555*<br>LOH | Negative | N/A |
| NF3 | Witkowski et al. | 29 | None | p.Gln1166*<br>LOH | Negative | N/A |
| NF4 | Witkowski et al. | 22 | p.Lys1213fs | N/A | Negative | N/A |
| NF5 | Witkowski et al. | 26 | p.Leu1161fs | N/A | Negative | N/A |
| NF6 | Witkowski et al. | 18 | None | p.Lys711fs<br>p.Gln460* | Negative | N/A |
| NF7 | Witkowski et al. | 25 | None | p.Met749fs | Negative | N/A |
| UN1 | Witkowski et al. | 35 | N/A | p.Thr187*<br>p.Gln788* | Negative | N/A |

| | | | | | | |
|---|---|---|---|---|---|---|
| UN2 | Witkowski et al. | 30 | N/A | p.Gln1226* | Negative | N/A |
| UN3 | Witkowski et al. | 18 | p.Arg978* | p.Arg978*<br>LOH | Negative | N/A |
| UN4 | Witkowski et al. | 47 | None | p.Trp1178fs<br>p.Ile1564fs | Negative | N/A |
| UN5 | Witkowski et al. | 42 | None | c.2275–1G>T<br>LOH | Negative | N/A |
| UN6 | Witkowski et al. | 25 | N/A | p.Phe947fs<br>LOH | Negative | N/A |
| UN7 | Witkowski et al. | 7 | p.Arg381* | p.Arg381*<br>LOH | Negative | N/A |
| UN8 | Witkowski et al. | 15 | N/A | p.Tyr731fs<br>LOH | Negative | N/A |
| UN9 | Witkowski et al. | 26 | N/A | c.1420+1G>T | Positive | N/A |
| UN10 | Witkowski et al. | 27 | N/A | p.Val684fs | Negative | N/A |
| UN11 | Witkowski et al. | 24 | N/A | p. Phe1082fs | Negative | N/A |
| UN12 | Witkowski et al. | 13 | N/A | p.Trp922* | Negative | N/A |
| UN13 | Witkowski et al. | 30 | N/A | c.3546+1G>T<br>LOH | Negative | N/A |
| UN14 | Witkowski et al. | 18 | N/A | p.Leu972Pro<br>c.3168+1G>C | Negative | N/A |
| UN15 | Witkowski et al. | 20 | N/A | c.1761+2T>A<br>LOH | Negative | N/A |
| UN16 | Witkowski et al. | 25 | N/A | p.Ser78fs<br>LOH | Negative | N/A |
| BIN-67 | Witkowski et al. | Tumor cell line | N/A | c.2438+1G>A<br>c.2439-2A>T | Negative | N/A |
| 101 | Jelinic et al. | 40 | N/A | c.3546+1G>A | Negative | N/A |
| 102 | Jelinic et al. | 22 | N/A | c.4170+1G>A | Negative | N/A |
| 103 | Jelinic et al. | 19 | N/A | Homozygous deletion | Positive | N/A |

| | | | | | | |
|---|---|---|---|---|---|---|
| 104 | Jelinic et al. | 21 | N/A | c.1761+1G>A<br>p.Arg978* | N/A | N/A |
| 105 | Jelinic et al. | 25 | N/A | p.Gln331*<br>p.Ile542fs | N/A | N/A |
| 106 | Jelinic et al. | 40 | N/A | p.Arg1093*<br>p.Leu388fs | Negative | N/A |
| 107 | Jelinic et al. | 18 | N/A | p.ETVN1300del | N/A | N/A |
| 108 | Jelinic et al. | 22 | N/A | p.Gln847* | Negative | N/A |
| 109 | Jelinic et al. | 32 | N/A | p.Leu762fs<br>p.Gly836* | Negative | N/A |
| 110 | Jelinic et al. | 42 | N/A | p.Gln1166* | Negative | N/A |
| 111 | Jelinic et al. | 35 | p.Arg1005* | p.Arg1005*<br>LOH | Negative | N/A |
| 112 | Jelinic et al. | 28 | N/A | c.2859+1G>A | Equivocal | N/A |
| PJK1182 | Kupryjanczyk et al. | 35 | N/A | p.Glu1254* | Negative | Positive |
| PJK1233 | Kupryjanczyk et al. | 27 | N/A | p.Gln729fs<br>p.Arg1093* | Negative | Positive |

# APPENDIX J

## BIN67 siRNA SCREEN: HIT KINASE siRNAs

| Hit Kinases |
| --- |
| AAK1 |
| ADCK5 |
| AKAP8 |
| AKT1 |
| AKT2 |
| AURKA |
| BAIAP2L1 |
| BRD4 |
| BRSK2 |
| CALM3 |
| CAMK2B |
| CASK |
| CDC2L1 |
| CDC42SE2 |
| CDK5R2 |
| CSNK1E |
| DGKA |
| DGKQ |
| DYRK1B |
| EPHB2 |
| FGFR4 |
| ILK |
| IP6K3 |
| ITPK1 |
| ITPKA |
| LIMK1 |
| MAP2K3 |
| MAP3K10 |
| MAP3K14 |
| MAP3K3 |
| MAP3K6 |
| MAP4K5 |
| MAPK6 |
| MAST1 |
| MERTK |
| NEK8 |
| NEK9 |
| PAK3 |
| PAK6 |

| |
|---|
| PFKL |
| PFKP |
| PFTK2 |
| PIK3CD |
| PIK3R2 |
| PIP4K2B |
| PIP5K1C |
| PKN1 |
| PLK1 |
| PRKAB1 |
| PRSS7 |
| RIOK2 |
| RIPK1 |
| RPS6KA3 |
| RPS6KA5 |
| RPS6KA6 |
| SBK1 |
| SORCS3 |
| SPHK1 |
| SPRYD3 |
| STK10 |
| STK17B |
| STK38L |
| TK1 |
| TNIK |
| TRAF3IP3 |
| TYRO3 |
| UCK1 |
| ULK1 |
| ULK2 |
| VRK3 |
| WEE1 |
| WNK4 |
| YSK4 |