

# Neurocristopathies

Neurocristopathies are a class of pathologies, or disorders, in vertebrates, including humans, that result from abnormal expression, migration, differentiation, or death of neural crest cells (NCCs) during embryonic development. NCCs are cells derived from the embryonic cellular structure called the neural crest. Abnormal NCCs can cause a neurocristopathy by chemically affecting the development of the non-NCC tissues around them. They can also affect the development of NCC tissues, causing defective migration or proliferation of the NCCs. There are many neurocristopathies that affect many different types of systems. Some neurocristopathies result in albinism (piebaldism) and cleft palate in humans. Various pigment, skin, thyroid, and hearing disorders, craniofacial and heart abnormalities, malfunctions of the digestive tract, and tumors can be classified as neurocristopathies. This classification ties a variety of disorders to one embryonic origin.

A neural crest is a cellular structure that arises early in the development of a vertebrate embryo. It becomes visually distinct from other germ layers during the neurula stage of the embryo, when the neural plate folds and becomes the neural tube. Subsequently, the cells derived from the neural crest, NCCs, migrate down several different paths as the embryo develops. As they migrate, they differentiate into diverse cell types that contribute to a wide range of organs and tissues including the eyes, ears, face, heart, digestive system, and skin. There are three categories of NCCs based on their shared paths of migration and contribution to organs: trunk (tNCCs), sacral and vagal, cardiac (CarNCCs), and cranial (CNCCs). The diversity of NCCs contribution to different biological systems explains why neurocristopathies encompass such a wide range of disorders.

Robert Bolande, a physician at McGill University in Montreal, Canada, coined the term neurocristopathy in his 1974 article "The Neurocristopathies: A Unifying Concept of Disease Arising in Neural Crest Maldevelopment." He argued that the classification of neurocristopathy helped unify multiple disorders under one concept. This classification traced the disorder to a common origin. The disorders' neural crest origins explained why many of these disorders often occur together in an individual. Bolande divided neurocristopathies into four categories: tumors, tumor syndromes, malformations, and all other neurocristopathies.

Due to the rediscovery of cranium cells derived from neural crest cells in the latter half of the twentieth century, the cataloged number and variety of neurocristopathic disorders has increased since Bolande's 1974 publication. Following Bolande's publication, researchers studied how NCCs contribute to craniofacial skeleton abnormalities. Researchers, including Gillian Morris-Kay working in 1987 at the University of Oxford in Oxford, UK, found that many craniofacial abnormalities resulted from the defective development of NCCs, therefore making them neurocristopathies. One example of a neurocristopathic craniofacial abnormality is the cleft palate, which occurs in approximately five in every 2,000 US births.

Decades before researchers classified craniofacial abnormalities as neurocristopathies, several biologists proposed that the craniofacial skeleton developed from NCCs. The first was Julia Platt, working in Woods Hole, Massachusetts, who discovered in 1893 that NCCs contribute to structures in the cranium of mudpuppies. Many researchers rejected Platt's research because it contradicted the germ layer theory, which described the mesoderm as the germ layer that was the only progenitor of the craniofacial skeleton. Throughout the first half of the nineteenth century, several independent experiments done by Francis Leroy Landacre at Ohio State University in Columbus, Ohio, and Leon Stone at Yale University in New Haven, Connecticut, illustrated problems with the germ layer theory by demonstrating the NCC contribution to craniofacial structures.

Doctors in the early twenty-first century continued to classify neurocristopathies using Bolande's

four categories of tumors, tumor syndromes, malformations, and all other neurocristopathies. Neurocristopathic tumors are tumors that affect only one type of tissue, and they all arise from abnormal tNCCs. Neuroblastomas, also called malignant embryomas, are the most common tumors found in small children. They are neuroendocrine adrenal gland tumors and arise from abnormal tNCC neurons. Another type of neurocristopathic tumor, in the bowel and gastrointestinal tract, doctors call carcinoid. These tumors arise from tNCC originated adrenal medulla cells. A related disorder, due to its tNCC origin and effects on the digestive tract, is Hirschsprung disease, which doctors characterize by a lack of ganglia in the colon. However, it is not a tumor.

Neurocristopathic tumor syndromes affect multiple tissues, as opposed to the neurocristopathic tumors, which only affect one. An example of these syndromes is neurofibromatosis. Neurofibromatosis occurs when abnormal Schwann cells arise from tNCCs and cNCCs. This syndrome results in neuroid tumors, discoloration of the skin, and possible scoliosis or other abnormalities of the bones. Another example is Sipple syndrome, which results from abnormal calcitonin producing cells that originate from vagal NCCs. Sipple syndrome is associated with the appearance of several types of tumors throughout the neuroendocrine system including thyroid and adrenal carcinomas.

Neurocristopathic malformations affect the configuration of body structures. Abnormal mesenchymal cells derived from cNCCs cause these types of malformations. One example is a disorder that consists of several malformations that often occur together. These disorders are abbreviated as the CHARGE association and include an abnormal iris (Coloboma of the iris), Heart defects, abnormal tissue blockage of the nasal pathway (Atresia of choanae), Retardation of physical and mental development, Genital anomalies, and deafness. Neurocristopathic malformations of the eyes, ears, and jaw are called Mandibulofacial dysostosis and Otocephaly. A cleft palate is classified in this group of disorders.

Researchers use the miscellaneous group for neurocristopathic disorders that do not fit into the previous classifications. These disorders affect pigment of skin cells by abnormal pigment cells derived from vagal NCCs. The most recognizable neurocristopathic pigment disorder is albinism.

Some researchers characterize neurocristopathies by the type of NCC that caused the abnormality. For instance, one type of NCCs, the cranial neural crest cells (cNCCs), migrate away from the neural crest during development, eventually contributing to the cartilage and bone of the skull. Therefore, neurocristopathies derived from abnormal cNCCs will affect regions of the skull. While other types of NCCs, vagal and sacral, cardiac, and trunk (tNCCs), develop into other structures such as skin pigment, neurons and ganglia form other structures of the head, neck, gut, and certain structures of the heart. Therefore, neurocristopathies derived from these NCCs may affect the nervous system, the digestive tract, color of skin, or the heart.

Researchers also classify neurocristopathies by discerning whether the disorder results from defective migration of NCCs or from defective proliferation of NCCs. Defects in the migration of NCCs during development result in malformation disorders such as CHARGE association, Mandibulofacial dysostosis, and Otocephaly. Proliferation defects, on the other hand, result in dysplasias such as neuroblastomas, carcinoid tumors, and neurofibromatosis.

Researchers have traced some neurocristopathies to abnormal functioning of the Hox genes, a set of genes responsible for body patterning. For instance in 1993, Maureen Gendron-Maguire and colleagues at the Roche Institute of Molecular Biology Roche Research Center in Nutley, New Jersey, found that an increase of products made from the Hox 1.1 gene induces a cleft palate in mice. And in 1995, Nancy Manley and Mario Capecchi working at the University of Utah School of Medicine in Salt Lake City, Utah, discovered that, by deleting Hox 1.6 in a mouse embryo, they could induce development of the embryo without a cranial ganglia.

Researchers have shown that teratogens, substances that produce defects to an embryo or fetus, also contribute to neurocristopathies by disrupting the growth and migration of NCCs. Ethanol has been shown to induce craniofacial neurocristopathies, such as cleft palate. Thus, there is a connection between abnormal NCCs and the facial abnormalities that occur in newborns with fetal alcohol syndrome.

After 2009, neurocristopathic research focused on the molecular basis of NCC cell proliferation

and migration. Researchers examined the chemical outputs of specific NCCs related to particular disorders during development. They also manipulated the environments of embryos during development to induce a disorder to pinpoint the cause of the NCCs abnormalities. Also, researchers described specific genes that may contribute to the disorder, such as the Hox genes previously mentioned. Scientists have identified other types of genes that contribute to neurocristopathies such as Hirschsprung disease, which is a mutation in the gene Sox10.

## Sources

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