Sex Determination in Humans

In humans, sex determination is the process that determines the biological sex of an offspring and, as a result, the sexual characteristics that they will develop. Humans typically develop as either male or female, primarily depending on the combination of sex chromosomes that they inherit from their parents. The human sex chromosomes, called X and Y, are structures in human cells made up of tightly bound deoxyribonucleic acid, or DNA, and proteins. Those are molecules that contain the instructions for the development and functioning of all life forms, including the development of physical traits and body parts that correspond with each biological sex. Humans who inherit two X chromosomes typically develop as females, while humans with one X and one Y chromosome typically develop as males. Sex determination is the beginning of the development of many characteristics that influence how a human looks and functions as well as the societal expectations that other humans have for each other.

The process of sex determination begins after fertilization, a process where male and female germ cells fuse to form a zygote, or a single-celled, fertilized egg. Germ cells are those that carry genetic information from parents to offspring during fertilization. Male germ cells are sperm cells and female germ cells are egg cells. When the egg and sperm cells fuse, the zygote divides into multiple cells and later forms an embryo. The embryo includes a combination of part of each parent's genetic information, including one sex chromosome from each parent. The combination of sex chromosomes that an embryo inherits from germ cells determines what biological sex it will later develop as.

A process called meiosis determines the sex chromosome that the parents' germ cells pass on to their offspring. Meiosis occurs inside of the testes and ovaries, the organs in males and females, respectively, that produce germ cells. During meiosis, each cell divides twice, which results in four cells. When the germ cells fuse during fertilization, the resulting embryo will have the normal amount of genetic material, including two sex chromosomes, because it receives one from each parent. Because females tend to only have X chromosomes, the egg cells that they produce typically carry an X chromosome, while the male sperm cell can carry either an X or Y. Therefore, the sex chromosome that a male sperm carries determines whether the offspring will develop into a male or a female.

Typical males and females differ in a variety of physical traits. The main parts of the male reproductive system include the penis, testicles that appear outside the body on the groin, and accessory glands. The penis is the male external sex organ. The testicles produce sperm and a hormone called testosterone, which causes males to develop deeper voices, bigger muscles, and body and facial hair during puberty. Male accessory glands, including the seminal vesicles and the prostate gland, produce fluids. Those glands are near the bladder of the body and connect to the penis and testicles through a tube called the vas deferens.

The main parts of the female reproductive system include the vagina, uterus, ovaries, and fallopian tubes. The vagina is a female organ that connects the internal reproductive organs to the outside of the body. The uterus is an internal reproductive organ in the lower abdominal region and houses an embryo during pregnancy. The female body typically has two ovaries, placed on the right and left sides of the uterus, that produce egg cells and a hormone called estrogen. Estrogen tells the female body to release egg cells during a process called ovulation. There are also two fallopian tubes that connect each ovary to the uterus.

Discussions about why males and females possess different physical characteristics date back to some of the earliest texts. Aristotle, an ancient Greek philosopher who lived from 384 BCE to 322 BCE, suggested that embryos arose from the mixture of male semen and female blood that

comes from the uterus. Aristotle also wrote that the amount of heat present during an embryo's development determines its biological sex. Specifically, Aristotle proposed that all embryos are meant to develop into males, but embryos that did not have enough heat would stop development early and grow into females. According to historian Maryanne Horowitz, Aristotle's theories on sex determination lent credibility to the idea that females are a biologically inferior sex because, according to those theories, females were simply underdeveloped males.

Scientists continued to accept Aristotle's ideas about sex determination for centuries after his time. For example, Aristotle's ideas partly influenced Galen, a Greek physician and philosopher who lived between 129 CE to 216 CE. Around 200 CE, Galen documented male and female anatomy in a series of texts and depicted the female reproductive system as an identical but inverted version of the male reproductive system. Following Aristotle's teachings, Galen argued that reproductive organs remain inside of the female body, as the embryo did not develop to the point where it could push those organs outside of the body due to a lack of heat.

It was not until the seventeenth century that scientists began to question Aristotle's teachings. During that time, scientists began to discover germ cells, although the roles of sperm and egg cells during sex determination remained unclear. In 1651, William Harvey, a physician in the United Kingdom, demonstrated that Aristotle and Galen's ideas were not completely accurate when he observed an empty uterus of an animal that recently mated. That observation implied that the mixture of fluids alone did not always give rise to an embryo. Rather, Harvey wrote that all mammals arise from egg cells, although he did not observe egg cells within the female body. Later, Antonie van Leeuwenhoek, who studied microorganisms in the Netherlands, was one of the first people to observe sperm cells. He described sperm cells in a letter to the Royal Society of London in London, United Kingdom, in 1676 as small eel-like animals, which he referred to as spermatic animalcules, in the semen of men and male dogs. Leeuwenhoek proposed that the spermatic animalcules provide substance vital to forming embryos, while female egg cells provide nutrients to the embryo.

Scientists began to better understand the role of sperm and egg cells in the creation of embryos during the 1800s, although the mechanisms behind sex determination remained unclear. Karl von Baer, who studied comparative embryology and anatomy in Estonia in 1827, supported Harvey's theory after discovering mammalian egg cells while observing dog ovaries under a microscope. Then, in 1841, Rudolf Albert von Kölliker, who studied embryos in Switzerland, concluded that rather than being independent animals present in semen, the male testes create sperm cells. Kölliker further suggested that sperm cells need to come into contact with the female egg cell for successful reproduction. Also, in 1876, Oskar Hertwig, who studied embryos and cells in Germany, observed the fusion of nuclei between sperm and egg cells during fertilization. Nuclei are the most central parts of the sperm and egg cells, which control the cell's activities.

Even after learning how embryos formed, it was not until the late nineteenth century that scientists discovered chromosomes and began to understand the mechanisms of sex determination. Hermann Henking, who studied cells in Germany, was one of the first people to observe the X chromosome in 1891. Observing the process of cell division in wasp sperm cells, Henking noticed that some of those cells had twelve chromosomes and others only had eleven. He called the twelfth chromosome the X element but never fully explained its role in sex differentiation. However, in 1899, Clarence Erwin McClung, who researched heredity at the University of Kansas in Lawrence, Kansas, also observed the X chromosome while studying grasshopper sperm cells. McClung hypothesized that the X chromosome helps determine what sex an organism develops as.

In 1905, Edmund Beecher Wilson, who studied genetics at Columbia University in New York City, New York, was one of the first people to observe and study the Y chromosome in the sperm cells of male beetles. Wilson observed equal numbers of chromosomes in several species of insects but noticed that the chromosomes of one pair were different sizes. He hypothesized that the larger chromosome was the X element that Henking previously observed. That same year, Nettie Maria Stevens, who studied genetics at Bryn Mawr College in Bryn Mawr, Pennsylvania, was one of the first people to discuss the role of the Y chromosome in sex differentiation. After noticing that female mealworm egg cells consistently had twenty large chromosomes, while male cells had nineteen large chromosomes and one small one, Stevens hypothesized that the small chromosome paired with the X chromosome. Stevens deduced that the small chromosome determined an organism's

biological sex, depending on its presence. That hypothesis conflicted with other scientists' beliefs that the X chromosome determined sex. Drawing upon Stevens's findings, Wilson later named the small chromosome Y, following Henking's X.

Researchers began to better understand how cells read and carry out the instructions that sex chromosomes carry to determine biological sex during the mid-twentieth century. In 1949, Murray Barr, a medical researcher in Canada, discovered dense masses of chromatin, or condensed material that contain genetic information, in female nerve cells but not male nerve cells. Barr hypothesized that those chromatin masses represent inactivated X chromosomes, or X chromosomes that do not work. Then in 1961, geneticist Mary Lyon proposed that egg cells inactivate one X chromosome. Lyon explained that because X chromosomes carry copies of the same sets of genes, egg cells have to inactivate one of the X chromosomes so those genes do not doubly express.

After the discovery of inactivated X chromosomes in 1949, scientists began to determine an organism's biological sex by detecting whether dense chromatin masses were present in the organism's cells. If a chromatin mass was present, that meant that there was an inactive X chromosome within the cell. In that case, scientists could assume that the cell belonged to a female. However, in 1959, two experiments changed that perception. Patricia Jacobs and John Strong, who researched genetics in the United Kingdom, discussed the chromosomal basis of Klinefelter syndrome, a condition that causes males to be born with an extra X chromosome. The extra X chromosome influences the development of features that are more typically associated with female development, such as more prominent breasts and less facial hair and muscle tone. The males that Jacobs and Strong studied had chromatin present in their cells, which usually would have led the researchers to think that they had two X chromosomes and were female. However, Jacobs and Strong realized that the males actually had two X chromosomes in addition to a Y chromosome, or an XXY chromosome combination.

Later, during the 1950s, Charles Ford, who researched the genetics of sex determination in the United Kingdom, led a team of scientists that showed that the presence of chromatin masses should not be an indicator of a person's biological sex. Ford and his colleagues found that Turner syndrome, a condition that causes females to have delayed sexual development and experience infertility, results from females having a missing X chromosome, or a X0 chromosome combination. Together, the Jacobs and Strong and Ford studies showed that the presence of chromatin cannot itself determine biological sex, and that people can have chromosome combinations beyond those of typical males and females.

Around that same time, researchers began discovering and studying instances of males and females born with chromosome combinations typical of the opposite sex. In 1955, Gim Swyer, an obstetrician in London, United Kingdom, observed and described two of his female patients who had XY chromosome combinations, a condition that is now referred to as Swyer syndrome. People who have Swyer syndrome usually develop female body parts but do not have functional ovaries that produce the hormones necessary to experience puberty. Later, in 1964, Albert de la Chapelle, who worked as a genetics researcher in Finland, became one of the first people to identify a human male who had a XX chromosome combination, a condition that is now known as de la Chapelle syndrome. People who have de la Chapelle syndrome have male body parts but do not have functional testes and experience testosterone deficiency.

Researchers continued to study the mechanisms that cause people to develop Swyer and de la Chapelle syndromes during the 1980s. In 1984, de la Chapelle found that males who had XX chromosome combinations also had a small piece of the Y chromosome attached to one of their X chromosomes, resulting from an error in the separation of chromosomes during meiosis. At that same time, according to geneticist Jennifer Graves, other researchers identified that females who had XY chromosome combinations lacked a small piece of the Y chromosome. Graves explains that during the 1980s, researchers suspected that those added and deleted regions of the Y chromosome contained a gene responsible for allowing an embryo to develop testes and fully develop as a biological male. Scientists referred to that gene as the testes-determining factor, or TDF.

During the 1980s, researchers searched for the TDF along the Y chromosome to understand why its presence pushed embryos to develop as males. It was not until 1990 that Andrew Sinclair, who

studied molecular biology in the United Kingdom, identified the location of the TDF on the Y chromosome. Sinclair led a team that used technology that allowed them to read a cell's DNA and search for the TDF. They read stretches of DNA along the bits of the Y chromosome of males who had XX chromosome combinations to approximate the location of the TDF. They named the region of the Y chromosome that contains the TDF the sex-determining region Y, or the SRY gene, because the presence of that specific region of the Y chromosome determines an embryo's biological sex. The SRY gene contains instructions for making the SRY protein, which causes the embryo to develop as male. If the SRY gene is present, then the embryo will begin to develop testes around its seventh week of development. Then, during the eighth week, the testes will begin to produce testosterone, which allows male external genitalia to develop. However, if no SRY gene is present, then the undifferentiated embryo will not develop testes and will instead proceed to develop as female.

The SRY does not contain all the genetic information necessary for the development of all sexual characteristics, though. For that reason, people with Swyer syndrome, who have XY chromosomes without an SRY, or de la Chappelle syndrome, who have XX chromosomes with an SRY, do not fully develop the characteristics typical of either biological sex. Such conditions where a person's body does not fully conform with expectations of male or female bodies are often considered intersex. Intersex is not a singular condition or a distinct biological sex. It is an umbrella term encompassing a variety of phenotypes, such as people with Swyer syndrome, de la Chappelle syndrome, Klinefelter syndrome, or Turner syndrome.

It was not until the 1990s that people began to publicly acknowledge that others could be born intersex. Throughout the twentieth century, when doctors encountered a child born intersex who had some characteristics less typical of their apparent biological sex, the doctors surgically altered the child so that their body fit the expectations of typical males or females. During the 1950s, scientists at Johns Hopkins University in Baltimore, Maryland, created a model to forcibly alter children at birth and to help intersex children fit into society, claiming that doing so would maintain their psychological health in the long run. Then, during the 1960s, John Money, a controversial psychologist who researched sex identity in humans, provided support for the Johns Hopkins University model, stating that biological sex was changeable early in life. Money further stated that the manner in which parents raised their child mattered more to a child's psychological health than their biological sex at birth. However, as intersex children who underwent forcible surgical alterations grew older, many of them were uncomfortable with their assigned biological sex, according to the Intersex Society of North America, or ISNA.

During the 1990s, feminists and intersex activists began to speak out against forcible surgical alterations and raise awareness about the intersex experience. In 1993, Anne Fausto-Sterling, a biologist and feminist activist, wrote articles for The New York Times and The Sciences. In the latter article, Fausto-Sterling explores what the world would be like if society accepted the existence of five genders aligned with being male, female, and three common types of intersex. In response to Fausto-Sterling's articles, Cheryl Chase, an activist born intersex whose body was surgically altered to conform to a typical female's, founded the ISNA to mobilize intersex people who had never felt comfortable with their altered bodies. The work of the ISNA, as well as scientists like Fausto-Sterling, helped raise awareness about intersexuality and that intersex people can grow up psychologically healthy without receiving surgical alteration.

The work of intersex advocates helped spread the knowledge that not all bodies strictly conform to typical male and female categories. In line with that, various scholars have called for reconceptualizing biological sex as a spectrum rather than a binary, as human bodies themselves do not consistently develop into two clearly delineated options, and can develop into many varieties beyond what is typically expected of males and females. However, such calls are met with continuous resistance, and those ideas have not been able to spread socially. As of 2021, many countries continue the practice of surgically altering intersex children at an age where the child is not able to give consent. Intersex people continue to fight to end such unconsensual practices that are founded on societal beliefs about how bodies should appear rather than on genuine medical need. Some organizations have amplified intersex people's concerns, such as Human Rights Watch, which released an article in 2017 that called for an end to forcible surgical alterations on intersex children, deeming such alterations to be medically unnecessary. Nonetheless, social expectations of bodies to conform to

male and female categories persist.

The slowly increasing understanding and acceptance of intersex people exemplifies how scientists and society still have a lot to learn about biological sex and the ways sex determination occurs in humans. Though biologists have an understanding that chromosome combinations influence the biological sex that an embryo develops as, biologists still know very little about the specific genes and mechanisms that control the sexual development pathway. Additionally, there are many factors beyond chromosomes that influence the sexual characteristics a person develops, and scientists are continually uncovering more intricacies in the development process. Finally, the events that lead to atypical sexual development have to be further explored.

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