

Genetic syndromes affecting sex determination; Sex and behavior

Genetic syndromes

There are many genetic syndromes that affect sex determination in people. We considered three: 5-alpha-reductase deficiency, Androgen Insensitivity Syndrome and Congenital Adrenal Hyperplasia. Each of these syndromes results in sex organs that are ambiguous or differ from the karyotypic sex of the individual.

5-alpha-reductase deficiency: As the name indicates, this trait results from mutations in the gene that encodes the enzyme responsible for converting testosterone into dihydroxytestosterone (DHT). XX females with this deficiency are unaffected. XY individuals have testes that produce anti-Mullerian Hormone and testosterone, but the testosterone does not get converted to DHT. Because testosterone is responsible for the development of internal male sex structures and anti-Mullerian hormone causes the Mullerian ducts to degenerate, internal structures develop normally. But DHT is largely responsible for the development of the external genitalia of the male during fetal development, and because DHT is not produced in 5-alpha-reductase deficient XY individuals, they are born with feminized external sex organs. The phenotype can vary from ambiguous sex organs with both male and female characteristics to sex organs that appear female. The latter individuals are raised as girls. When they reach puberty, the individuals' testes produce large amounts, and the androgens result in virilization of the sex organs and secondary male characteristics such as the development of facial hair.

Androgen Insensitivity Syndrome: The lack of a functional androgen receptor results in this syndrome. The androgen receptor gene is on the X chromosome, and the trait is passed from mothers, who are carriers (heterozygous), to their XY progeny. (What do you think is the probability of these mothers generating XY offspring that have the trait-- i.e., are female?) XY progeny lacking the androgen receptor have testes that produce anti-Mullerian hormone and testosterone. The testosterone is converted to DHT. But the testosterone and DHT do not do anything because the receptor that mediates their effects is missing. Because the testes produce anti-Mullerian hormone, the Mullerian ducts degenerate, and because testosterone cannot be utilized, the Wolffian ducts degenerate. Consequently, no internal sex structures are produced. Because DHT cannot be sensed, the external structures are female. There is no indication that these girls have any problem until they reach puberty and fail to menstruate. It is important to remove their testes because the higher temperatures in the body cavity increase the risk of testicular cancer.

Congenital Adrenal Hyperplasia: The adrenal glands produce aldosterone and cortisol, which regulate mineral homeostasis and responses to stress. One enzyme is shared in the production of these steroid hormones. A mutation in the gene for this enzyme results in a failure to produce these hormones, and individuals that are homozygous for the mutation have medical problems that require hormone therapy to supplement the missing steroids.

The precursors that build up in the absence of the enzyme are now used to produce androgens. XX individuals with this enzyme deficiency are born with genitalia that are masculinized.

XY individuals with a deficiency of 5-alpha-reductase and XX individuals with Congenital Adrenal Hyperplasia are often born with ambiguous genitalia. Whether to raise the children as boys or girls and whether to make the genitalia male or female by surgical intervention are difficult decisions that parents face. Our understanding of how humans acquire their sexual identity shapes those decisions. Sexual or gender identity is defined as a person's sense of whether the person identifies as being male or female. Usually, but not always, a person identifies with their biological sex. With intersexual children, it would be ideal to know with which sex the individual is likely to identify before any intervention is attempted. Some psychologists believe that social interactions control gender identity, and the sexual identity of children is malleable. They argue that raising a child as a girl or a boy with hormone and surgical intervention can be used to assign gender identity. Others believe that genetics and hormones largely shape gender identity and orientation.

Sex and behavior

How much of our behavior is controlled by our sex? Do women tend to be better communicators? Are men more likely to be analytical? If behavior differences between men and women do exist, are they controlled by social constraints, by our biology or by both? We will consider two aspects of sexual behavior: sexual identity, which is defined above, and sexual orientation, which is defined as the sex to which a person is sexually attracted. We will start with sexual orientation and focus first on experimental animals. Then we will consider sexual identity and orientation in humans.

Flies: A lot is known about sexual behavior in *Drosophila melanogaster*. During mating, the male fly receives visual and olfactory pheromone cues from the female. The male goes through a courtship dance that involved tapping the female and a courtship song that is played by extending and vibrating his wing. These events culminate in copulation and sperm transfer. *Drosophila* sex determination is understood molecularly and at the top of the genetic hierarchy is the Sex lethal gene, which is directly regulated by the X:autosome ratio. Sex lethal is active in XX (ratio is 1.0) and inactive in XY (ratio is 0.5) animals. Sex lethal controls gonad development, sexual traits and sexual development. The *fruitless* gene plays the major role in sexual behavior but not in other aspects of sexual development. XY flies that lack *Fruitless* are males that produce sperm but rarely attempt to mate with females.

The *fruitless* gene is transcribed in both males and females to generate a precursor RNA that is spliced differently in males and females. RNA splicing is essential to remove the introns in the precursor RNA, splicing together the exons to generate an mRNA that can be translated into a protein. Most animal genes have introns that have to be removed from precursor RNAs, but often only one type of splicing occurs. For some genes, however, there can be alternate splicing, which then results in different mRNAs that can code for different proteins. The *fruitless* precursor is spliced differently in males and females.

Most of the male or female Fruitless protein is the same, but because splicing of one of the exons is different in males and females, this difference results in male and female proteins that have distinct functions. Because Fruitless is a transcription factor, the two proteins can presumably regulate genes differently to result in male and female sexual behavior.

By replacing the *fruitless* gene by a transgene that can express only the female protein or only the male protein, investigators have been able to address how these two forms of the protein control sexual behavior. Remarkably, expressing male Fruitless in XX females causes them to adopt male mating behavior: tapping, singing and attempting to copulate. The mutant male phenotype and the phenotype of these transgenic animals show that male Fruitless is both necessary and sufficient for male mating behavior.

Males and females also fight differently. When forced to compete for food, males hit each other with their legs, a behavior that is violent and referred to as “boxing.” Females push each other. The different sexes also adopt different dominance patterns in these fights. Although the probability of one fly winning a fight is 50% for either male or female fights (to win one fly chases the other fly after a boxing match), males establish dominance patterns more readily. Dominance is defined by the likelihood that a winner will win the next fight. In males, 88% of the time a winner will win the next bout. This dominance is less pronounced in females, with female winners only winning 61% of the next bouts. The form of Fruitless expressed determines how flies fight. For example, transgenic males expressing only female fruitless push instead of box. They also establish dominance patterns that are more similar to those of females.

The Fruitless proteins are expressed in neurons of the fly brain. Understanding how these proteins regulate neural circuitry will reveal the neural mechanisms that define sexual behavior.

Rats: Experiments in rats suggest that certain aspects of mating behavior is under the control of testosterone. Males attempt to mount females and females arch their back during mating, a behavior called lordosis. The critical period where these behaviors can be modified is soon after birth. If females are treated with testosterone at this time, they try to mount females when they reach sexual maturity. If males are castrated they exhibit lordosis behavior.

The brains of rats are sexually dimorphic. There are regions of the rat brain that are larger in males, and other regions that are larger in females. One such region, the SDN, is larger in males, and its size is determined by androgens.

Sheep: Sheep have become a model for studying homosexuality. About 8% of domestic rams are less interested in ewes and attempt to mate with other rams. It is interesting that this is roughly the same frequency of human males that are gay. Like rats, the brains of sheep are sexually dimorphic, and the region in sheep that is thought to be the equivalent of the SDN in rats is also larger in rams than in ewes. But in the “gay” rams, this brain region is similar in size to the region of females and smaller than the same region in rams.

that mate with ewes. The important question to address is whether the differences in the brain regions are responsible for the different behaviors in the two types of rams.