# SEX AND INHERITANCE

## Key Notes

Recessive alleles of genes mapping to the X chromosome are not expressed in heterozygous female mammals but will be expressed in males because males have only one X chromosome. Males transmit the recessive allele to their daughters, where it is not expressed. They are referred to as carrier females. The daughters, in turn, transmit the allele to half of their sons, where it is re-expressed. Some genes are on the Y chromosome and are passed directly from father to son. This is known as holandric inheritance. A small region of homology exists between the X and Y chromosomes. Genes in this region, the pseudoautosomal region, do not show sex-linked inheritance.

Sex-limited traits are inherited traits caused by a single gene which are expressed only in one sex. Sex-influenced traits **are** those which are observed more frequently in one sex than in the other. This can be caused by dominance relationships being different in the two sexes.
Sex determination (C8)

**Sex-linked Inheritance** Due to the fact that. in mammals, the X chromosome is present in only one copy in males and in two copies in females, genes which map to this chromosome show a particular pattern of inheritance that differs from the normal expectations for Mendelian inheritance (see Topics Bl and B2). This is known as **sex** linkage.

Recessive alleles are not expressed in heterozygous females. The male has only one copy of the X chromosome (hemizygous), and hence recessive alleles present are expressed. A useful example is colorblindness in humans. This is due to a recessive allele of a gene which maps to the X chromosome. The normal allele is denoted CB and the mutant allele responsible for colorblindness *cb.* The possible genotypes are shown in *Table* 1.

The *cb* allele is relatively rare in human populations, with approximately one male in 40 being affected. Colorblind females must have two *cb* alleles and thus occur at a much lower frequency, approximately 1 / 1600 (the square of the frequency in males).

A color blind man must have inherited the cb allele with his X chromosome from his mother. If she had normal vision then she must have been a heterozygote CB */cb.* A colorblind man cannot transmit his *cb* allele to his son as, by definition, his son must inherit a Y chromosome from his father. By the same rule he must pass *cb to* all of his daughters. Any daughter that inherits the *cb* allele from her father and a normal allele from her mother will be a carrier and transmit the syndrome to, on average, half of her sons. A daughter of a carrier and a colorblind father will have a 50% chance of inheriting the syndrome *(Fig. 1).*
Hence a phenotype present in a male disappears in the next generation, and then reappears in his grandsons. All affected males except for new mutants, must have inherited the allele in question from their mother. These are the hallmarks of sex-linked inheritance.

*Table 1. Possible genotypes at the colorblind locus*

| | |
|---|---|
| Normal male | CB/Y |
| Colorblind male | cb/Y |
| Colorblind female | *cb/cb* |

Normal female CB/CB or CB/cfc

Y denotes the Y chromosome. The CB/cb female is a carrier for the syndrome.

Duchenne muscular dystrophy and hemophilia are other examples of sex-linked conditions in humans. In the case of hemophilia, family records show that Queen Victoria had a mutant allele for hemophilia and transmitted the disease to some of her sons and many of the European royal houses through marriage of her daughters. As there is no evidence of hemophilia in her ancestors. Queen Victoria must have inherited a mutation that arose in the germ cells of one of her parents.
Sex linkage is complicated to some extent by the process of X-inactivation (see Topic Bl) in female mammals. This means that approximately half of the cells of a carrier female will express the allele responsible for the syndrome. This can easily be shown, in examples such as glucose-6-phosphate deficiency or Lesch-Nyhan syndrome, by the analysis of single cells. However this is insufficient to affect the overall phenotype.

Sex linkage is not displayed by genes which map to a small segment of the X chromosome, the **pseudoautosomal region,** the part of the X chromosome which pairs with the Y chromosome at meiosis. In humans this is found at the tip of the short arm of the X chromosome. Because there is homology between the X and Y chromosomes in this region, crossing-over can occur and alleles can switch between X and Y- Genes mapping to this region show the same inheritance pattern as genes on autosomes.

Any genes resident on the Y chromosome are obviously passed directly from father to son. There have been some controversial examples of this including traits The carrier mother passes her chromosome carrying the The colorblind father passes his recessive cb allele to all mutant altete for colorblindness on to half of her sons of his daughters making them carriers, but with normal and half of her daughters, sight.

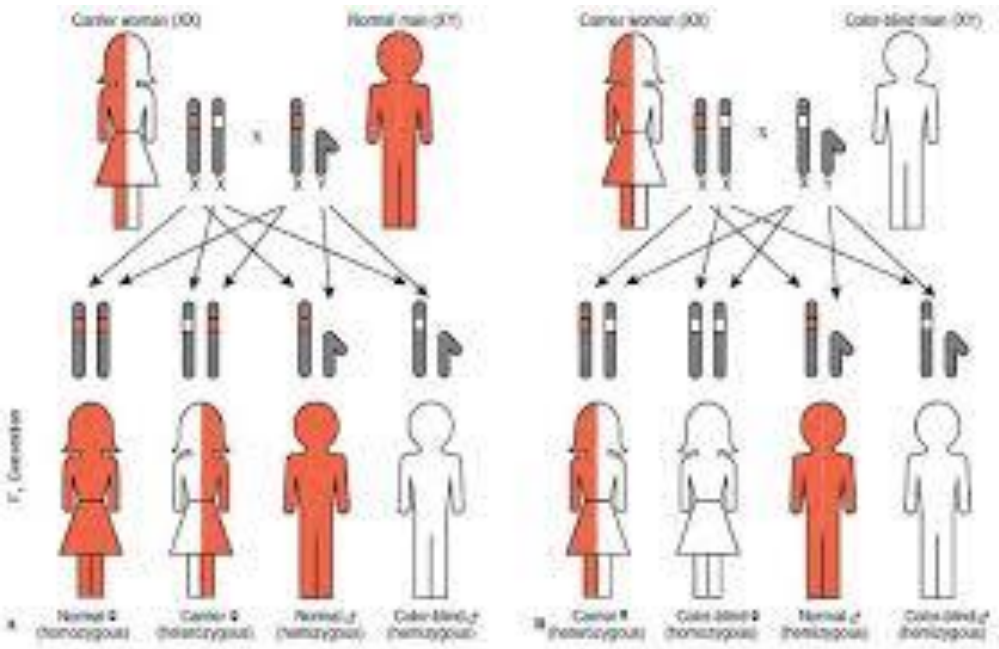

*Fig. 1. The inheritance of colorblindness. X chromosomes are depicted as the long vertical lines, Y chromosomes as the short vertical lines.*

such as 'porcupine man' and webbing *of toes. A* gene lor hairs on the outer rim of the ear appears to show this pattern of **holandric inheritance.** Recently it has been shown that the sex-determining gene *SRY* and a gene for a minor histocompatibility antigen, H-Y, map to the Y chromosome, and hence are passed directly from father to son.

**Sex-limited and** These terms relate to situations where the phenotype produced by a specific **sex-influenced** genotype is altered because of the sex of an individual. The two terms are easily **traits** confused, and care must be taken to differentiate between them.

AIleles of sex-limited genes will be expressed only in one sex. One example of this concerns mutant alleles of the breast cancer susceptibility gene *BRCA1*, which are dominant and cause breast cancer in females but not in males. In contrast to this, a second breast cancer susceptibility gene, *BRCA2*, causes breast cancer in both males and females, and is thus clearly not sex limited.

The difference between sex-limited and sex-influenced genes is subtle but

important. In the former a phenotype is restricted to one sex, but in the latter the same phenotype will occur in both sexes but is more common in one. A good example of this is inherited pattern baldness. This is the form of baldness where hair loss spreads out from the crown of the head, and is controlled by a single gene with two alleles *B* and *b*. Homozygous *BB* individuals show premature pattern baldness, and *bb* homozygotes do not. The phenotype of the heterozygote, *Bb*, differs between males and females. In males the B allele is dominant and heterozygotes are bald, but in females it is recessive and no hair loss occurs. This is set out in *Table 2*. The dominance of such an altele is clearly influenced by the hormone balance of the individual. In this context it is interesting to note that this gene is also associated with polycystic ovarian disease in females.

Sex-limited and sex-influenced genes are autosomal and the genotypes follow normal Mendelian patterns of inheritance, but the phenotypes are altered by the hormonal environment. In contrast, the pattern of inheritance of sex-linked genes is due to the inheritance of genotypes caused by the genes being located on sex chromosomes.

*Table 2. The expression of pattern baldness genotypes in male and female humans*

| Genotype | Female phenotype | Male phenotype |
|---|---|---|
| *Bb* | Pattern baldness | Pattern baldness |
| *Bb* | Normal hair | Pattern baldness |
| *bb* | Normal hair | "formal hair |