Genetic disorders

A **genetic disorder** is a genetic problem caused by one or moreabnormalities in the genome, especially a condition that is present from birth (congenital). Most genetic disorders are quite rare and affect one person in every several thousands or millions. A congenital defect is any biochemical, functional, or structural abnormality that originates prior to or shortly after birth. It must be emphasized that birth defects do not all have the same basis, and it is even possible for apparently identical defects in different individuals to reflect different underlying causes. Though the genetic and biochemical bases for most recognized defects are still uncertain, it is evident that many of these disorders result from a combination of genetic and environmental factors.

The single-gene or monogenic diseases can be classified into three main categories:

- Dominant
- Recessive
- X-linked

All human beings have two sets or copies of each gene called “allele”; one copy on each side of the chromosome pair. Recessive diseases are monogenic disorders that occur due to damages in both copies or allele. Dominant diseases are monogenic disorders that involve damage to only one gene copy. X linked diseases are monogenic disorders that are linked to defective genes on the X chromosome which is the sex chromosome. The X linked alleles can also be dominant or recessive. These alleles are expressed equally in men and women, more so in men as they carry only one copy of X chromosome (XY) whereas women carry two (XX).

If a person has a change in a dominant gene that is associated with a particular condition, he or she will usually have features of that condition. And, each of the person's children will have a 1 in 2 (50%) chance of inheriting the gene and developing the same features. Diseases and conditions caused by a dominant gene include achondroplasia (pronounced: ay-kon-druh-PLAY-zhuh, a form of dwarfism), Marfan syndrome (a connective tissue disorder), and Huntington disease (a degenerative disease of the nervous system).

People who have a change in just one copy of a recessive gene are called "carriers." They don't usually have the disease because they have a normal gene copy of that pair that can do the job. When two carriers have a child together, however, the child has a 1 in 4 (25%) chance of getting a gene with a mutation from both parents, which would result in the child having the disease. Cystic fibrosis (a lung disease), sickle cell anemia (a blood disorder), and Tay-Sachs disease (which causes nervous system problems) are caused by recessive mutations from both parents coming together in a child.

With recessive gene mutations on the X chromosome, usually only guys can develop the disease because they have only one X chromosome. Girls have two X chromosomes — since they have a back-up copy of another X chromosome, they don't always show features of X-linked conditions. These include the bleeding disorder hemophilia (pronounced: hee-muh-FIL-ee-uh) and color blindness.

NUMERICAL ABNORMALITIES

Numerical abnormalities, involving either the autosomes or sex chromosomes, are believed generally to result from meiotic nondisjunction—that is, the unequal division of chromosomes between daughter cells—that can occur during either maternal or paternal gamete formation. Meiotic nondisjunction leads to eggs or sperm with additional or missing chromosomes. Although the biochemical basis of numerical chromosome abnormalities remains unknown, maternal age clearly has an effect, such that older women are at significantly increased risk to conceive and give birth to a chromosomally abnormal child. The risk increases with age in an almost exponential manner, especially after age 35, so that a pregnant woman age 45 or older has between a 1 in 20 and 1 in 50 chance that her child will have trisomy 21 (Down syndrome), while the risk is only 1 in 400 for a 35-year-old woman and less than 1 in 1,000 for a woman under the age of 30. There is no clear effect of paternal age on numerical chromosome abnormalities.

Although Down syndrome is probably the best-known and most commonly observed of the autosomal trisomies, being found in about 1 out of 800 live births, both trisomy 13 andtrisomy 18 are also seen in the population, albeit at greatly reduced rates (1 out of 10,000 live births and 1 out of 6,000 live births, respectively). The vast majority of conceptions involving trisomy for any of these three autosomes are nonetheless lost to miscarriage, as are all conceptions involving trisomy for any of the other autosomes. Similarly, monosomy for any of the autosomes is lethal in utero and therefore is not seen in the population. Because numerical chromosomal abnormalities generally result from independent meiotic events, parents who have one pregnancy with a numerical chromosomal abnormality are generally not at markedly increased risk above the general population to repeat the experience. Nonetheless, a small increased risk is generally cited for these couples to account for unusual situations, such as chromosomal translocations or gonadal mosaicism, described below.

STRUCTURAL ABNORMALITIES

Structural abnormalities of the autosomes are even more common in the population than are numerical abnormalities and include translocations of large pieces of chromosomes, as well as smaller deletions, insertions, or rearrangements. Indeed, about 5 percent of all cases of Down syndrome result not from classic trisomy 21 but from the presence of excess chromosome 21 material attached to the end of another chromosome as the result of a translocation event. If balanced, structural chromosomal abnormalities may be compatible with a normal phenotype, although unbalanced chromosome structural abnormalities can be every bit as devastating as numerical abnormalities. Furthermore, because many structural defects are inherited from a parent who is a balanced carrier, couples who have one pregnancy with a structural chromosomal abnormality generally are at significantly increased risk above the general population to repeat the experience. Clearly, the likelihood of a recurrence would depend on whether a balanced form of the structural defect occurs in one of the parents.

Even a small deletion or addition of autosomal material—too small to be seen by normal karyotyping methods—can produce serious malformations and mental retardation. One example is *cri du chat* (French: “cry of the cat”) syndrome, which is associated with the loss of a small segment of the short arm of chromosome 5. Newborns with this disorder have a “mewing” cry like that of a cat. Mental retardation is usually severe.

Down syndrome, also called **Down's syndrome, trisomy 21,** or (formerly) **mongolism**, congenital disorder caused by an extra chromosome on the chromosome 21 pair, giving the person a total of 47 chromosomes rather than the normal 46. British physician John Langdon Down first described the physical features of the disorder in 1866, and thus the disorder was later named for him. The physical and mental impacts of Down syndrome range from mild to severe. Some common physical signs of the disorder include a small head, flattened face, short neck, up-slanted eyes, low-set ears, enlarged tongue and lips, and sloping underchin. Other characteristics of the disorder may include poor muscle tone, heart or kidney malformations (or both), and abnormal dermal ridge patterns on the palms of the hands and soles of the feet. Intellectual disability occurs in all persons with Down syndrome and usually ranges from mild to moderate. Congenital heart disease is found in about 40 to 60 percent of people with Down syndrome.

ABNORMALITIES OF THE SEX CHROMOSOMES

About 1 in 400 male and 1 in 650 female live births demonstrate some form of sex chromosome abnormality, although the symptoms of these conditions are generally much less severe than are those associated with autosomal abnormalities. Turner syndrome is a condition of females who, in the classic form, carry only a single X chromosome (45,X). Turner syndrome is characterized by a collection of symptoms, including short stature, webbed neck, and incomplete or absent development of secondary sex characteristics, leading to infertility. Although Turner syndrome is seen in about 1 in 2,500 to 1 in 5,000 female live births, the 45,X karyotype accounts for 10 to 20 percent of the chromosomal abnormalities seen in spontaneously aborted fetuses, demonstrating that almost all 45,X conceptions are lost to miscarriage. Indeed, the majority of liveborn females with Turner syndrome are diagnosed as mosaics, meaning that some proportion of their cells are 45,X while the rest are either 46,XX or 46,XY. The degree of clinical severity generally correlates inversely with the degree of mosaicism, so that females with a higher proportion of normal cells will tend to have a milder clinical outcome.

In contrast to Turner syndrome, which results from the absence of a sex chromosome, three alternative conditions result from the presence of an extra sex chromosome: Klinefelter syndrome, trisomy X, and 47,XYY syndrome. These conditions, each of which occurs in about 1 in 1,000 live births, are clinically mild, perhaps reflecting the fact that the Y chromosome carries relatively few genes, and, although the X chromosome is gene-rich, most of these genes become transcriptionally silent in all but one X chromosome in each somatic cell (i.e., all cells except eggs and sperm) via a process called X inactivation. The phenomenon of X inactivation prevents a female who carries two copies of the X chromosome in every cell from expressing twice the amount of gene products encoded exclusively on the X chromosome, in comparison with males, who carry a single X. In brief, at some point in early development one X chromosome in each somatic cell of a female embryo undergoes chemical modification and is inactivated so that gene expression no longer occurs from that template. This process is apparently random in most embryonic tissues, so that roughly half of the cells in each somatic tissue will inactivate the maternal X while the other half will inactivate the paternal X. Cells destined to give rise to eggs do not undergo X inactivation, and cells of the extra-embryonic tissues preferentially inactivate the paternal X, although the rationale for this preference is unclear. The inactivated X chromosome typically replicates later than other chromosomes, and it physically condenses to form a Barr body, a small structure found at the rim of the nucleus in female somatic cells

between divisions. The discovery of X inactivation is generally attributed to British geneticist Mary Lyon, and it is therefore often called "lyonization."

The result of X inactivation is that all normal females are mosaics with regard to this chromosome, meaning that they are composed of some cells that express genes only from the maternal X chromosome and others that express genes only from the paternal X chromosome. Although the process is apparently random, not every female has an exact 1:1 ratio of maternal to paternal X inactivation. Indeed, studies suggest that ratios of X inactivation can vary. Furthermore, not all genes on the X chromosome are inactivated; a small number escape modification and remain actively expressed from both X chromosomes in the cell. Although this class of genes has not yet been fully characterized, aberrant expression of these genes has been raised as one possible explanation for the phenotypic abnormalities experienced by individuals with too few or too many X chromosomes.

Klinefelter syndrome (47,XXY) occurs in males and is associated with increased stature and infertility. Gynecomastia (i.e., partial breast development in a male) is sometimes also seen. Males with Klinefelter syndrome, like normal females, inactivate one of their two X chromosomes in each cell, perhaps explaining, at least in part, the relatively mild clinical outcome.

Trisomy X (47,XXX) is seen in females and is generally also considered clinically benign, although menstrual irregularities or sterility have been noted in some cases. Females with trisomy X inactivate two of the three X chromosomes in each of their cells, again perhaps explaining the clinically benign outcome.

47,XYY syndrome also occurs in males and is associated with tall stature but few, if any, other clinical manifestations. There is some evidence of mild learning disability associated with each of the sex chromosome trisomies, although there is no evidence of mental retardation in these persons.

Persons with karyotypes of 48,XXXY or 49,XXXXY have been reported but are extremely rare. These individuals show clinical outcomes similar to those seen in males with Klinefelter syndrome but with slightly increased severity. In these persons the "$n - 1$ rule" for X inactivation still holds, so that all but one of the X chromosomes present in each somatic cell is inactivated.

Table 1: Examples of Human Diseases, Modes of Inheritance, and Associated Genes

Disease	**Type of Inheritance**	Gene **Responsible**
Phenylketonuria (PKU)	Autosomal recessive	Phenylalanine hydroxylase (*PAH*)
Cystic fibrosis	Autosomal recessive	Cystic fibrosis conductance transmembrane regulator (*CFTR*)
Sickle-cell anemia	Autosomal recessive	Beta hemoglobin (*HBB*)
Albinism, oculocutaneous, type II	Autosomal recessive	Oculocutaneous albinism II (*OCA2*)
Huntington's disease	Autosomal dominant	Huntingtin (*HTT*)
Myotonic dystrophy type 1	Autosomal dominant	Dystrophia myotonica-protein kinase (*DMPK*)
Hypercholesterolemia, autosomal dominant, type B	Autosomal dominant	Low-density lipoprotein receptor (*LDLR*);apolipoprotein B (*APOB*)
Neurofibromatosis, type 1	Autosomal dominant	Neurofibromin 1 (NF1)
Polycystic kidney disease 1 and 2	Autosomal dominant	Polycystic kidney disease 1 (*PKD1*) andpolycystic kidney disease 2 (*PKD2*), respectively
Hemophilia A	X-linked recessive	Coagulation factor VIII (*F8*)
Muscular dystrophy, Duchenne type	X-linked recessive	Dystrophin (*DMD*)
Hypophosphatemic rickets, X-linked dominant	X-linked dominant	Phosphate-regulating endopeptidase homologue, X-linked (*PHEX*)
Rett's syndrome	X-linked dominant	Methyl-CpG-binding protein 2 (*MECP2*)
Spermatogenic failure, nonobstructive, Y-linked	Y-linked	Ubiquitin-specific peptidase 9Y, Y-linked(*USP9Y*)