



GENETIC DISORDERS AND HEREDITARY DISORDERS

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Genetic disorders are either hereditary disorders or a result of mutations. Some disorders may confer an advantage, at least in certain environments. There are a number of pathways to genetic defects, the simplest of which are summarized below.

- There are genetic disorders caused by the abnormal chromosome number, as in Down syndrome (three instead of two “number 21” chromosomes, therefore a total of 47).
- Triplet expansion repeat mutations can cause fragile X syndrome or Huntington's disease, by modification of gene expression or gain of function, respectively.
- Defective genes are often inherited from the parents. In this case, the genetic disorder is known as a hereditary disease. This can often happen unexpectedly when two healthy carriers of a defective recessive gene reproduce, but can also happen when the defective gene is dominant.

Currently around 4,000 genetic disorders are known, with more being discovered. Most disorders are quite rare and affect one person in every several thousands or millions. Cystic fibrosis is one of the most common genetic disorders; around 5% of the population of the United States carry at least one copy of the defective gene.

Terms you should know:

GENE: A small segment of DNA that codes for the synthesis of a specific protein. Genes are located on the chromosomes. Examples: ABO blood group gene, Rh blood group gene.

CHROMOSOMES: genes for the same traits, in the same order.

LOCUS: Position or location of a gene on a chromosome.

ALLELE: Refers to the different forms of a gene at one locus.

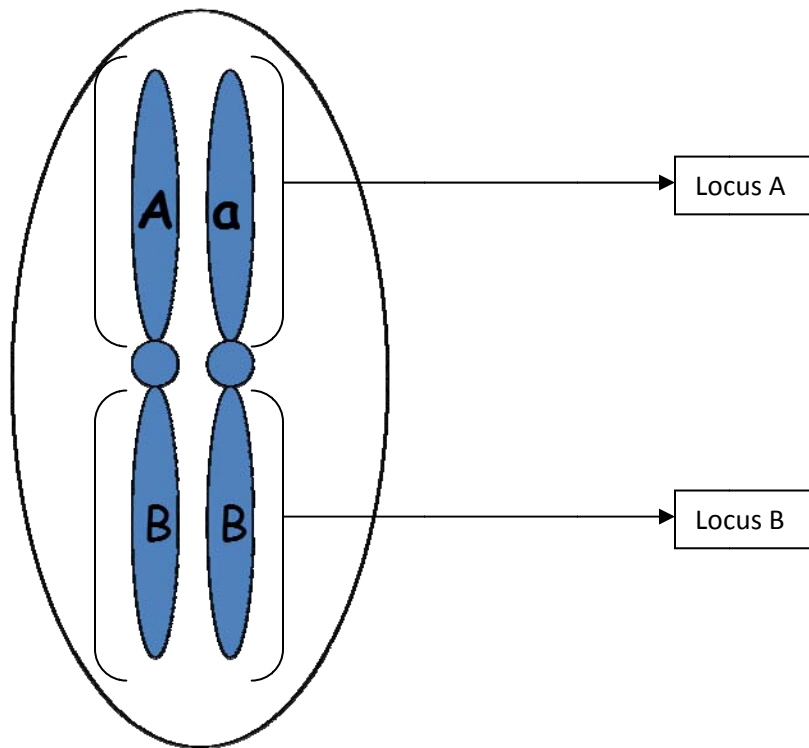
GENOTYPE: The specific pair of alleles present at a single locus. These are features seen genetically but may or may not have phenotypic (observable) characteristics.

PHENOTYPE: The clinical features or the observable characteristics of an individual determined by a pair of genes at a given locus (or genotype). The phenotype can vary following interaction with modifying genes or the environment.

PENETRANCE: The frequency with which individuals carrying a given gene will show the clinical manifestations associated with the gene.

DOMINANT: A gene (allele) which is expressed clinically in the heterozygous state. In a dominant disorder only one mutant allele need be present as it covers up, or masks, the normal allele.

RECESSIVE A gene (allele) which is only expressed clinically in the homozygous state i.e. it can be suppressed if present with a dominant gene and will not show it's character in presence of a dominant gene. In a recessive disorder, both genes at a given locus must be abnormal to manifest the disorder



'A' and 'B' are loci, as are 'a' and 'B'
A or a is an allele of locus A. While B is an allele of locus B
Locus A is heterozygous but
locus B is homozygous

Types of Genetic Disorders

1 Single gene disorders including Mendelian Disorders (i.e, follow mendelian order of inheritance i.e. Autosomal and X-linked and Y-linked) and Non-Mendelian disorders (i.e, do not follow mendelian order of inheritance e.g. mitochondrial inheritance)

2 Multifactorial and polygenic disorders

3 Disorders with variable modes of transmission

4 Cytogenetic disorder: including autosomal disorders and sex chromosome disorders.

1] Single gene disorders

Where genetic disorders are the result of a single mutated gene they can be passed on to subsequent generations in the ways outlined in the table below. Genomic imprinting and uniparental disomy, however, may affect inheritance patterns. The divisions between recessive and dominant are not "hard and fast" although the divisions between autosomal and X-linked are (related to the position of the gene). For example, achondroplasia is typically considered a dominant disorder, but young goats or children with two genes for achondroplasia have a severe skeletal disorder that achondroplasics could be viewed as carriers of. Sickle-cell anemia is also considered a recessive condition, but carriers that have it by half along with the normal gene have increased immunity to malaria in early childhood, which could be described as a related dominant condition.

Subclasses of single gene disorders are as follows:

Name of Inheritance pattern Description Examples are below followed by their explanatory charts:

Autosomal dominant Only one mutated copy of the gene is needed for a person to be affected by an autosomal dominant disorder. Each affected person usually has one affected parent. There is a 50% chance that a child will inherit the mutated gene. Conditions that are autosomal dominant have low penetrance, which means that, although only one mutated copy is needed, a relatively small proportion of those who inherit that mutation go on to develop the disease, often later in life.
E.g. Huntingtons disease, Neurofibromatosis 1, Marfan Syndrome.

Autosomal recessive Two copies of the gene must be mutated for a person to be affected by an autosomal recessive disorder. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers). Two unaffected people who each carry one copy of the mutated gene have a 25% chance with each pregnancy of having a child affected by the disorder. E.g. Cystic fibrosis, Sickle cell anemia, Tay-Sachs disease, Spinal muscular atrophy.

X-linked dominant X-linked dominant disorders are caused by mutations in genes on the X chromosome. Only a few disorders have this inheritance pattern. Males are more frequently affected

than females, and the chance of passing on an X-linked dominant disorder differs between men and women. The sons of a man with an X-linked dominant disorder will not be affected, and his daughters will all inherit the condition. A woman with an X-linked dominant disorder has a 50% chance of having an affected daughter or son with each pregnancy. Some X-linked dominant conditions, such as Aicardi Syndrome, are fatal to boys, therefore only girls have them (and boys with Klinefelter Syndrome).

E.g Hypophosphatemia, Aicardi Syndrome,

X-linked recessive X-linked recessive disorders are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females, and the chance of passing on the disorder differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene. With each pregnancy, a woman who carries an X-linked recessive disorder has a 50% chance of having sons who are affected and a 50% chance of having daughters who carry one copy of the mutated gene.

E.g Hemophilia A, Duchenne muscular dystrophy, Color blindness, Muscular dystrophy, Androgenetic alopecia and also includes G-6-PD (Glucose-6-phosphate dehydrogenase) deficiency.

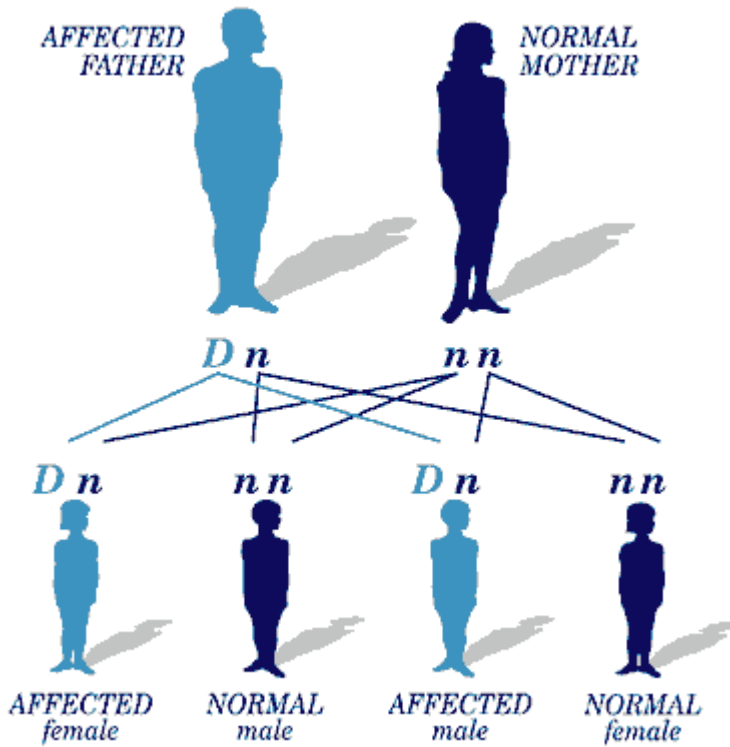
Y-linked Y-linked disorders are caused by mutations on the Y chromosome. Only males can get them, and all of the sons of an affected father are affected. Since the Y chromosome is very small, Y-linked disorders only cause infertility, and may be circumvented with the help of some fertility treatments.

E.g. Male Infertility

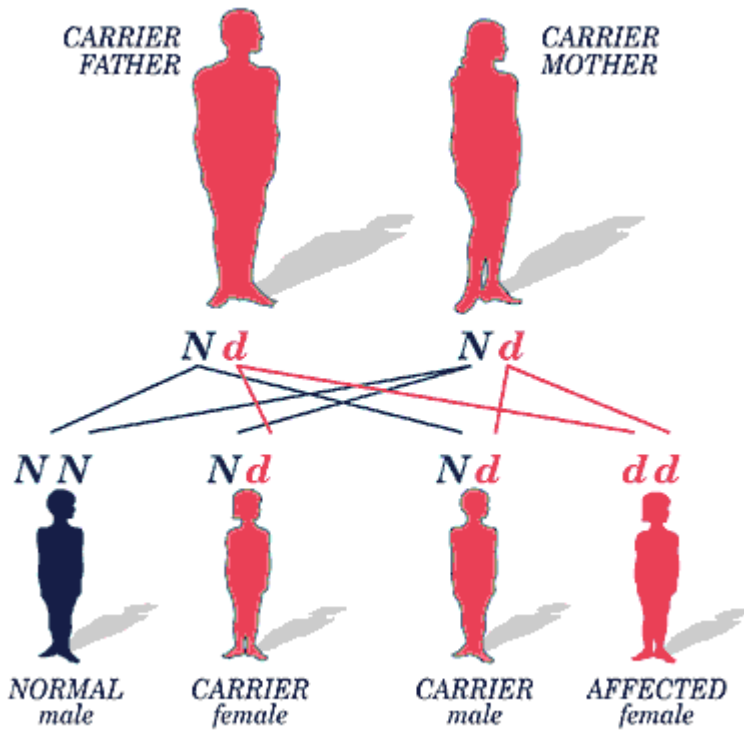
Mitochondrial This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial conditions to their children.

E.g. Leber's Hereditary Optic Neuropathy (LHON)

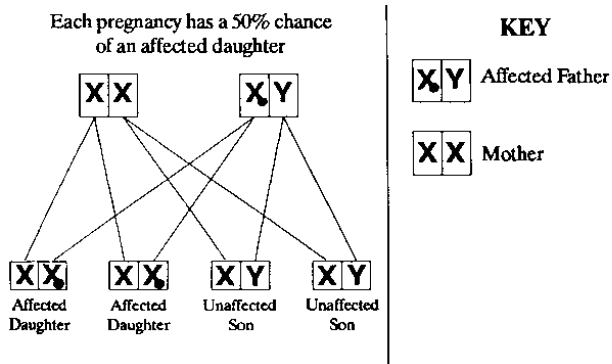
Autosomal dominant inheritance pattern: (Either parent can be dominant “D”, and normal gene is “n”, here just for the example, the father is dominant I.e. affected, It is possible to construct a pattern with the mother to be dominant too but it’s not shown here)



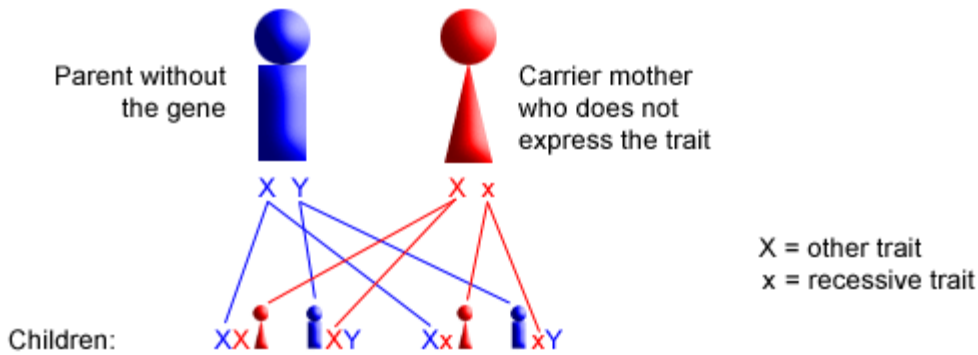
Autosomal recessive inheritance pattern: (recessive gene is "d" and normal gene is "N")



X-linked dominant inheritance pattern: (note that either parent can be the one who is affected)



X-Linked recessive inheritance pattern:

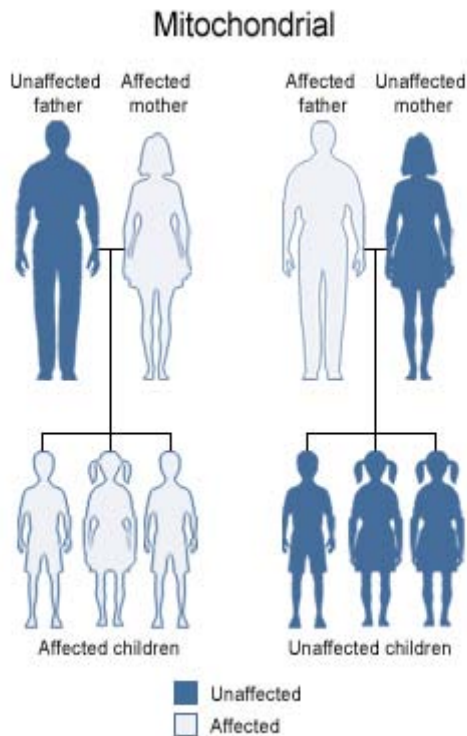


Daughter who is a carrier but does not express the trait = Xx

Daughter and son who do **not** carry the gene **nor** express the trait = XX XY

Son who has the gene and expresses the trait or condition = xY

Mitochondrial Inheritance pattern:



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Some Diseases discussed:

Huntington's disease (autosomal dominant)

Huntington's disease (HD), also known as Huntington disease and previously as Huntington's chorea and chorea maior, is a rare inherited neurological disorder affecting up to 8 people per 100,000. It affects 1 out of 20,000 people of Western European descent and 1 out of one million in people of Asian and African descent. It takes its name from the Ohio physician George Huntington who described it precisely in 1872 in his first medical paper. HD has been heavily researched in the last few decades and it was one of the first inherited genetic disorders for which an accurate test could be performed. Huntington's disease is caused by a trinucleotide repeat expansion in the Huntingtin (Htt) gene and is one of several polyglutamine (or PolyQ) diseases. This expansion produces an altered form of the Htt protein, mutant Huntingtin (mHtt), which results in neuronal cell death in select areas of the brain and is a terminal illness.

Huntington's disease's most obvious symptoms are abnormal body movements called chorea and a lack of coordination, but it also affects a number of mental abilities and some aspects of personality. These physical symptoms commonly become noticeable in a person's forties[citation needed], but can occur at any age. If the age of onset is below 20 years then it is known as Juvenile HD. There is currently no cure, but the symptoms are managed with medication and appropriate care.

Inheritance: HD is inherited in an autosomal dominant fashion. Huntington's disease is autosomal dominant, needing only one affected allele from either parent to inherit the disease. Although this generally means there is a one in two chance of inheriting the disorder from an affected parent, the inheritance of HD and other trinucleotide repeat disorders is more complex. When the gene has more than 36 copies of the repeated trinucleotide sequence, the DNA replication process becomes unstable and the number of repeats can change in successive generations. If the gene is inherited from the mother, the count is usually similar. Paternal inheritance tends to increase the number of repeats. Because of the progressive increase in length of the repeats, the disease tends to increase in severity and have an earlier onset in successive generations. This is known as anticipation.

Causes: The gene involved in Huntington's disease, called the HD gene, is located on the short arm of chromosome 4 (4p16.3). The end of the HD gene has a sequence of three DNA bases, cytosine-adenine-guanine (CAG), that is repeated multiple times (i.e. ...CAGCAGCAG...); this is called a trinucleotide repeat. CAG is the codon for the amino acid glutamine, thus a CAG repeat may be termed a polyglutamine (polyQ) expansion. A sequence of fewer than 36 glutamine amino acid residues is the normal form, producing a 348 kDa cytoplasmic protein called huntingtin (Htt). A sequence of 40 or more CAG repeats produces a mutated form of Htt, mHtt. The greater the number of CAG repeats, the earlier the onset of symptoms. In genetically altered "knockin" mice, the mutant CAG repeat portion of the gene (which codes for the N-terminal end of mHtt) is all that is needed to cause disease. Aggregates of mHtt are present in the brains of both HD patients and HD mice, specifically in striatal neurons. These aggregates consist mainly of the amino terminal end of mHtt (CAG repeat), and are found in both the

cytoplasm and nucleus of neurons. The presence of these aggregates however does not correlate with cell death. Thus mHtt acts in the nucleus but does not cause apoptosis through aggregation.

Marfan syndrome (autosomal dominant)

Marfan syndrome is an autosomal dominant genetic disorder of the connective tissue characterized by disproportionately long limbs, long thin fingers, a relatively tall stature and a predisposition to cardiovascular abnormalities, specifically affecting the heart valves and aorta. The disease may also affect numerous other structures and organs — including the lungs, eyes, dural sac surrounding the spinal cord, and hard palate. It is named after Antoine Marfan, the French pediatrician who first described it in 1899.

Pathogenesis: Marfan syndrome has been linked to a defect in the FBN1 gene on chromosome 15,[6] which encodes a glycoprotein called fibrillin-1. Fibrillin is essential for the formation of the elastic fibers found in connective tissue, as it provides the scaffolding for tropoelastin.[3] Elastic fibers are found throughout the body but are particularly abundant in the aorta, ligaments and the ciliary zonules of the eye, consequently these areas are among the worst affected. Without the structural support provided by fibrillin many connective tissues are weakened, which can have severe consequences for support and stability.

Sickle-cell disease (autosomal recessive)

Sickle-cell disease is a group of genetic disorders caused by sickle hemoglobin (Hgb S or Hb S). In many forms of the disease, the red blood cells change shape, usually looking much like that of a banana, upon deoxygenation because of polymerization of the abnormal sickle haemoglobin (haemoglobin precipitates into long crystals inside the cell making it sickle shaped rather than the normal biconcave disc). This process damages the red blood cell membrane (making it fragile leading to anemia), and can cause the cells to become stuck in blood vessels. This deprives the downstream tissues of oxygen and causes ischemia and infarction, which may cause organ damage, such as stroke. The disease is chronic and lifelong. Individuals are most often well, but their lives are punctuated by periodic painful attacks. The mutated allele is recessive, meaning it must be inherited from each parent for the individual to have the disease.

Cystic fibrosis (autosomal recessive)

Cystic fibrosis (CF), also called mucoviscidosis, is a hereditary disease that affects the entire body, causing progressive disability and early death. Formerly known as cystic fibrosis of the pancreas, this entity has increasingly been labeled simply 'cystic fibrosis.'

Difficulty breathing and insufficient enzyme production in the pancreas are the most common symptoms. Thick mucous production as well as a low immune system results in frequent lung infections, which are treated, though not always cured, by oral and intravenous antibiotics and other medications. A multitude of other symptoms, including sinus infections, poor growth, diarrhea, and potential infertility (mostly in males, due to the condition Congenital bilateral absence of the vas Deferens) result from the effects of CF on other parts of the body. Often, symptoms of CF appear in infancy and childhood; these include meconium ileus, failure to thrive, and recurrent lung infections.

Cystic fibrosis is one of the most common life-shortening, childhood-onset inherited diseases. In the United States, 1 in 3900 children are born with CF. It is most common among Europeans and Ashkenazi Jews; one in twenty-two people of European descent carry one gene for CF, making it the most common genetic disease among them.

Individuals with cystic fibrosis can be diagnosed prior to birth by genetic testing (See also Dor Yeshorim) or in early childhood by a sweat test. Newborn screening tests are increasingly common and effective. There is no cure for CF, and most individuals with cystic fibrosis die young — many in their 20s and 30s from lung failure although with many new treatments being introduced the life expectancy of a person with CF is increasing. Ultimately, lung transplantation is often necessary as CF worsens.

CF is caused by a mutation in a gene called the cystic fibrosis transmembrane conductance regulator (CFTR). The product of this gene helps create sweat, digestive juices, and mucus. Although most people without CF have two working copies of the CFTR gene, only one is needed to prevent cystic fibrosis. CF develops when neither gene works normally. Therefore, CF is considered an autosomal recessive disease. The name cystic fibrosis refers to the characteristic 'fibrosis' (tissue scarring) and cyst formation within the pancreas, first recognized in the 1930s.

Aicardi syndrome (X-linked dominant)

Aicardi syndrome is a rare congenital disorder thought to result from an abnormality of the X chromosome and characterized by (partial or complete) agenesis of the corpus callosum, retinal abnormalities, and seizures (often infantile spasms). It is X-linked dominant. Only 500 reported cases in the world.

Color blindness (X-linked recessive)

Color blindness, (also known as Dyschromatopsia) or color vision deficiency, in humans is the inability to perceive differences between some or all colors that other people can distinguish. It is most often of genetic nature, but may also occur because of eye, nerve, or brain damage, or due to exposure to certain chemicals. The English chemist John Dalton in 1798 published the first scientific paper on after the realization of his own color blindness; because of Dalton's work, the condition is sometimes called

Daltonism, although this term is now used for a type of color blindness called deuteranopia. Color blindness is usually classed as disability; however, in selected situations color blind people may have advantages over people with normal color vision. It is a X-linked Recessive genetic disorder.

Male Infertility (Y-Linked)

It is believed to have a genetic predisposition. There are other causes however. It can be treated using fertility treatments

Leber's hereditary optic neuropathy (Mitochondrial inheritance)

Leber's hereditary optic neuropathy (LHON) or Leber optic atrophy is a mitochondrially inherited (mother to all offspring) degeneration of retinal ganglion cells (RGCs) and their axons that leads to an acute or subacute loss of central vision; this affects predominantly young adult males. However, LHON is only transmitted through the mother as it is primarily due to mutations in the mitochondrial (not nuclear) genome and only the egg contributes mitochondria to the embryo. LHON is usually due to one of three pathogenic mitochondrial DNA (mtDNA) point mutations. These mutations affect nucleotide positions 11778, 3460 and 14484, respectively in the ND4, ND1 and ND6 subunit genes of complex I of the oxidative phosphorylation chain in mitochondria. Men cannot pass on the disease to their offspring.

Genetics:

Leber hereditary optic neuropathy is a condition related to changes in mitochondrial DNA. Although most DNA is packaged in chromosomes within the nucleus, mitochondria have a distinct mitochondrial genome composed of mtDNA. Mutations in the MT-ND1, MT-ND4, MT-ND4L, and MT-ND6 genes cause Leber hereditary optic neuropathy. These genes code for the NADH dehydrogenase protein involved in the normal mitochondrial function of oxidative phosphorylation. Oxidative phosphorylation uses a large multienzyme complex to convert oxygen and simple sugars to energy. Mutations in any of the genes disrupt this process to cause a variety of syndromes depending on the type of mutation and other factors. It remains unclear how these genetic changes cause the death of cells in the optic nerve and lead to the specific features of Leber hereditary optic neuropathy.

A significant percentage of people with a mutation that causes Leber hereditary optic neuropathy do not develop any features of the disorder. Specifically, more than 50 percent of males with a mutation and more than 85 percent of females with a mutation never experience vision loss or related medical problems. Additional factors may determine whether a person develops the signs and symptoms of this disorder. Environmental factors such as smoking and alcohol use may be involved, although studies of these factors have produced conflicting results. Researchers are also investigating whether changes in additional genes, particularly genes on the X chromosome, contribute to the development of signs and symptoms.

A note on Mitochondrial Inheritance:

Mitochondrias come from ancestor anaerobic bacteria ;---> they have their own DNA. We then have extranuclear DNA in our cells.

MITOCHONDRIAL DNA :

- 1.Circular DNA of 16 kb for which the sequence is entirely known.
- 2.37 genes code for 13 proteins, ribosomal RNA and transfer RNA.
- 3.The genetic code is different from the universal code (1): Mito Univ UGA Trp STOP AUA Met Ile AGA/AGG STOP Arg.
- 4.Mitochondria are present in the ovocyte (in large number).
5. Results in ---> non mendelian inheritance: strictly maternal inheritance.
- 6.There are hereditary diseases due to mutant mitochondrial genes.

Mitochondrial cytopathies are often deleterious with a pleiotropic symptomatology (multiple), since the deficit involves several organs: Pearson syndrome: exocrine pancreatic insufficiency, medullar insufficiency/ myelodysplasia, muscular deficit, hepatic, renal and gastro intestinal diseases.

A mitochondrial gene disease is transmitted :

- solely by women.
- to all her descents.
- Often the genetic defect is not present in all-but in a fraction only of mitochondria transmitted to the next generation; then according to the number of gene mutations in mitochondria.
- variable expressivity.

The term mitochondrial cytopathy may be ambiguous : the mitochondrial cytopathies include not only the pathologies due to mitochondrial gene mutations but also those due to nuclear genes coding for proteins invoved in the mitochondrial metabolism (enzymes of the respiratoiry chain).

Examples of of mitochondrial hereditary diseases : Leber optic atrophy, Mitochondrial myopathies

II] Multifactorial and polygenic disorders

Genetic disorders may also be complex, multifactorial or polygenic, this means that they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. Multifactorial disorders include heart disease and diabetes. Although complex disorders often cluster in families, they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified.

On a pedigree, polygenic diseases do tend to "run in families", but the inheritance does not fit simple patterns as with Mendelian diseases. But this does not mean that the genes cannot eventually be

located and studied. There is also a strong environmental component to many of them (e.g., blood pressure).

E.g Gout: It is a genetic/acquired disorder of uric acid metabolism that leads to hyperuricemia and consequent acute and chronic arthritis. The recurrent but transient attacks of acute arthritis are triggered by the precipitation of monosodium urate crystals into joints from supersaturated body fluids which accumulate in and around the joints and other tissues causing inflammation.

Cause of gout: Unknown enzyme defects or known enzyme defects leading to overproduction of uric acid like partial deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT) enzyme (as person lacks the genes to produce this enzyme). Also high dietary intake of purines as in pulses, as purines are metabolized to uric acid. Thus it has both a genetic (due to enzyme malfunction) and environmental predisposition (such as diet) and hence multifactorial.

Other examples are

heart disease, hypertension, diabetes, obesity, cancers.

III] Disorders With Variable Modes of Transmission:

Heredity malformations are congenital malformations which may be familial and genetic or may be acquired by exposure to teratogenic agents in the uterus. Heredity malformations are associated with several modes of transmission. Some multifactorial defects are cleft lip, congenital heart defects, pyloric stenosis etc. Certain congenital malformations are either multifactorial or by a single mutant gene (thus a different class of their own).

E.g. Ehlers-Danlos Syndrome: It is characterized by defects in collagen synthesis and structure. These abnormal collagen fibres lack adequate tensile strength and hence the skin is hyperextensible and the joints are hypermobile. Causes include either of the following- deficiency of the enzyme lysyl hydroxylase, deficient synthesis of type 3 collagen due to mutations in their coding genes, and deficient conversion of procollagen type 1 to collagen due to mutation in the type 1 collagen gene.

IV] Cytogenetic Disorders:

These may be from alterations in the number or structure of the chromosomes and may affect autosomes or sex chromosomes.

E.g. Fragile X chromosome. It is characterized by mental retardation and an inducible cytogenetic abnormality in the X chromosome. It is one of the most common causes of mental retardation. The cytogenetic alteration is induced by certain culture conditions and is seen as a discontinuity of staining or constriction of in the long arm of the X-chromosome.

Other disorders include Down's Syndrome in which the number of chromosomes is increased by a third "21st chromosome" and hence a total of 47 chromosomes occur.

References

- 1) Wikipedia - http://en.wikipedia.org/wiki/Hereditary_disease
- 2) Answers.com - <http://www.answers.com/topic/genetic-disorder?cat=health>
- 3) http://www.ornl.gov/sci/techresources/Human_Genome/medicine/assist.shtml
- 4) Genetic Interest Group - <http://www.gig.org.uk/education2.htm>