

Lecture 7: Human heritable diseases: principles of classification, forms of manifestation, and patterns of inheritance.

Plan of the lecture

1. Notion of Medical Genetics.
2. Genetic classification of hereditary diseases.
3. Gene diseases and their patterns of inheritance.
4. Multifactorial diseases.

The goals of this lecture are to review the genetic essentials, features of manifestation and patterns of inheritance of hereditary diseases in man.

1. Notion of Medical Genetics

The 46 human chromosomes consist of almost 3 billion base pairs of DNA that contains about 30,000 - 40,000 protein-coding genes. The coding regions make up less than 5% of the genome (the function of the remaining DNA is not clear). Changes of hereditary material can result in obvious physical defects or progressive deterioration in individuals with inborn errors of metabolism.

The branch of **Human Genetics** applied to the etiology, pathogenesis, diagnosis, prognosis, management, and prevention of genetic diseases is called **Medical Genetics**. It is a relatively new field of study. The chromosomal basis of many recognizable syndromes, for instance, was not known until 1958 when the underlying cause of Down syndrome (trisomy 21) was discovered. Way back in the seventies of last century it was possible to catalog what was known about single gene disorders in a single text. Further, knowledge about genes and genetic disorders is expanding at high a rate. The integration of basic research and clinical application has spawned a new specialty in medicine, Medical Genetics, which was officially recognized as a medical subspecialty at the first of the nineties.

2. Genetic classification of hereditary diseases

Genetic disease - a disease caused by an abnormality in an individual's genome.

According to the type of mutation and character of gene . environment interaction genetic disorders can be classified into six categories.

1. **Single gene inheritance, or gene disorders** (also called Mendelian or monogenic inheritance) caused by changes or mutations that occur in the DNA sequence of a single gene. There are more than 6000 known single-gene disorders, which occur in about 1 out of every 200 births. Single-gene disorders are inherited in recognizable patterns: autosomal dominant, autosomal recessive, and X-linked.
2. **Chromosome diseases** caused by chromosomal and genomic mutations, i.e., structural and numerical abnormalities of chromosomes, respectively.
3. **Multifactorial diseases** (also called complex or polygenic diseases) caused by a combination of environmental factors and mutations in multiple genes (i.e., both genetic and non-genetic or environmental factors are involved in determining the trait). For example, different genes that influence breast cancer susceptibility have been found on chromosomes 6, 11, 13, 14, 15, 17, and 22. Some common chronic diseases are multifactorial disorders (e.g., atherosclerosis, hypertension, ulcer disease, Alzheimer disease, arthritis, diabetes, cancer, and obesity).
4. **Genetic diseases of somatic cells**. Examples are cancer, autoimmune diseases.
5. **Diseases due to incompatibility of genes**. Example is haemolytic disease of newborns, in which fetal red blood cells die earlier due to the action of antibodies formed by the mother against fetal Rh-antigen.
6. **Mitochondrial inheritance**. This type of genetic disorder is caused by mutations in the nonchromosomal DNA of mitochondria. Each mitochondrion may contain 5 to 10 circular pieces of DNA. Examples of mitochondrial disease include an eye disease called Leber's hereditary optic atrophy; a type of epilepsy called MERRF which stands for Myoclonus Epilepsy with Ragged Red Fibers; and a form of dementia called MELAS for Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes.

There is also a **clinical classification of hereditary diseases** which is based on the system and organ principle. In this case, hereditary diseases are divided into some groups in concordance with the affected organ or organ system. For examples, hereditary diseases of nervous system, immune system, respiratory system, muscle and bone diseases, etc.

3. Gene diseases and their patterns of inheritance

Gene diseases . hereditary disorders caused by an alteration (mutation) in a single gene. Errors that occur within a gene can result in absent, deficient or abnormal protein products. The chromosomes, or karyotype, of a patient with a single gene disorder are expected to be normal, 46,XX or 46,XY. Therefore, chromosome analysis (cytogenetic analysis) is not recommended for patients who are thought to have a single gene disorder.

It is known nearly 3000 such conditions, most of which are serious, none are curable and relatively few are treatable or manageable.

Single-gene diseases typically describe classic simple Mendelian patterns of inheritance. There are 1364 disorders, where the mode of inheritance has been firmly established. These include 736 **autosomal dominant**, 521 **autosomal recessive** and 107 **X-linked disorders**. There are further 1447 disorders where **unifactorial inheritance** is suspected, but not yet proven.

The patterns followed by single-gene traits within families over a number of generations are determined by the following factors:

1. Whether a trait is dominant or recessive.
2. Whether a gene determining a trait is autosomal or X-linked.
3. Chance distribution of genes from parents to children through their gametes.
4. Factors affecting the expression of a gene, which include
 - a. heterogeneity
 - b. pleiotropy
 - c. reduced penetrance
 - d. variable expressivity
 - e. variability of age of onset
 - f. sex limitation, complete or partial
 - g. interaction of two or more gene pairs
 - h. environmental effects

Classical methods applied to study of single gene disorders are pedigree analysis (genealogical method), twins method, population method. Modern methods include biochemical method and DNA molecular diagnosis.

The traditional method used to study an inherited disease is to observe the pattern of its distribution in families through examination of a pedigree, the construction of which begins with the individual first known to have the disease. The pedigree pattern allows one to judge whether or not the distribution conforms to Mendelian principles of segregation and assortment, and thus represents single-factor inheritance. Patterns that do not conform to Mendelian principles may represent polygenic traits, which represent the cumulative effects of a number of different genes. These complex patterns underlie the vast majority of human diseases.

Disorders caused by single mutant genes show one of four simple (Mendelian) patterns of inheritance: (1) autosomal dominant, (2) autosomal recessive, (3) X-linked dominant, or (4) X-linked recessive.

Autosomal dominant inheritance

Features of autosomal dominant inheritance are

1. Among children, whose parents both have a dominant inherited trait i.e., both are heterozygous for the gene responsible for the trait, the genotypic expectations follow Mendel's ratio 1:2:1. One-fourth of the children are homozygous affected and one-fourth homozygous normal.
2. The trait appears in every generation. Normally, there is no skipping of generation.
3. The trait is transmitted by an affected person (heterozygous) to half his children on an average.
4. Unaffected persons do not transmit the trait to their children.
5. The occurrence and transmission of the trait are not influenced by sex. Males and females have equal chances of having the trait and transmitting it.

Autosomal dominant disorders often show two additional characteristics that are rarely seen in recessive disorders: (1) marked variable expressivity (severity) of the disorder and (2) delayed age of onset. In heterozygotes, the expression of the abnormal gene can be so weak that a generation appears to be skipped because the carrier of the abnormal gene is clinically normal. In such fortunate individuals, the trait is said to be "non-penetrant." In some diseases, such as Huntington's disease and adult polycystic kidney disease, the disorder may not become manifest clinically until adult life even though the mutant gene has been present since conception.

In every autosomal dominant disease, some affected persons owe their disorder to a new mutation rather than to an inherited allele. A reasonable estimate of the frequency of mutation is on the order of 5×10^{-6} mutations per allele per generation. Because a dominant trait requires a mutation in only one of the parental gametes, the expected frequency for a new autosomal dominant disease in any given gene is one in 100,000 newborns.

Examples of dominant traits in humans:

1. Huntington's Disease
2. Marfan's Syndrome
3. Ehlers Danlos Syndrome
4. Neurofibromatosis
5. Tuberous Sclerosis
6. Familial hypercholesterolemia
7. Achondroplasia
8. Retinoblastoma

1. Huntington's Disease is a fatal hereditary disease that destroys neurons in areas of the brain involved in the emotions, intellect, and movement. Lethal dominant allele on chromosome 4 and has no obvious phenotypic effect until the individual is about 35 to 45 years old (but can develop in younger and older people). The gene encodes a protein known as *huntingtin*. Gradually, this protein accumulates within brain cells. The course of the disease is characterized by jerking uncontrollable movement of the limbs, trunk, and face (chorea); progressive loss of mental abilities; and the development of psychiatric problems (some people stop recognizing family members; others are aware of their environment and are able to express emotions).

2. Marfan's Syndrome is a connective tissue disorder that has been linked to the *FBN1* gene on chromosome 15. The gene encodes the glycoprotein fibrillin, a major building block of microfibrils. The disease so affects many structures, including the *skeleton* (the patient's limbs are long compared with the trunk; arachnodactyly, pectus deformities (scoliosis / kyphosis) and mild joint laxity and high arched palate), *lungs, eyes* (lens subluxation, angle anomaly, glaucoma, hypoplasia of dilator muscle, axial myopia and retinal detachment), *heart and blood vessels* (aneurysms of the ascending aorta and aortic regurgitation), *muscular underdevelopment*, leading to a high incidence of hernias. The disease is believed to have affected the US president Abraham Lincoln.

3. Ehlers Danlos Syndrome is a heterogeneous group of inherited connective-tissue disorders. It is characterized by joint hypermobility, cutaneous fragility, and hyper-extensibility. According to the modern classification there are 6 main types of the disease. Symptoms of classic type: joint and cardiac effects, hypermobility. Infants with hypermobile joints often appear to have weak muscle tone, which can delay the development of motor skills such as sitting, standing, and walking. Soft, highly elastic, velvety skin which may tear, bruise, or scar easily and/or be slow to heal, and which has a tendency to develop benign fatty growths as well as benign fibrous growths on pressure areas.

4. Neurofibromatosis (NF) is a genetic neurological disorder that affects cell growth in nerve tissue. NF produces tumors of the skin, internal organs, and nerves that may become cancerous (malignant). It also can affect bones, causing severe pain and debilitation and may result in learning disabilities, behavioral dysfunction, and hearing and vision loss. There are two types: NF-1 & NF-2.

NF-1 neurofibromatosis, also called von Recklinghausen NF, is transmitted on chromosome 17 is the most common subtype and is referred to as peripheral NF. This type causes multiple areas of hyperpigmentation (i.e., birthmarks) that appear shortly after birth. In late childhood, a few to thousands of tumors appear on the skin (cutaneous lesions) and under the skin (subcutaneous lesions). These tumors may become cancerous.

NF-2 neurofibromatosis results from mutation (or rarely, deletion) of the *NF2* gene and is transmitted on chromosome 22, this type is referred to as central NF. In this type, tumors form in the nervous system. This type causes hearing loss and loss of sense of balance (equilibrium), usually during the late teens or early 20s. These tumors may become cancerous. There is no cure for NF.

5. Tuberous Sclerosis is a rare, multi-system disease characterized by the growth of numerous benign (noncancerous) tumors in many parts of the body (skin, brain, heart, lungs, kidneys, eyes and other organs), in some cases leading to significant medical problems. A combination of symptoms

may include seizures, developmental delay, behavioural problems, skin abnormalities, lung and kidney disease. Tumors on the face (facial angiofibromas) are also common, beginning in childhood.

6. Familial hypercholesterolemia, disorder characterized by elevation of serum cholesterol bound to low-density lipoprotein (LDL). Cause of disease is mutations in the LDL receptor (LDLR) gene on chromosome 19. Heterozygotes develop fatty collections on their tendons, a corneal arc, and, of greatest concern, coronary artery disease, which typically presents in the fourth or fifth decade of life. Homozygotes develop these features at an accelerated rate. However, among patients with a history of myocardial infarction (heart attacks), the heterozygote frequency is about one in twenty.

7. Achondroplasia is one of a group of disorders called *chondrodystrophies* or osteochondrodysplasias. Cause of disease is mutation in the fibroblast growth factor receptor gene 3 (*FGFR3*), which causes an abnormality of cartilage formation. In achondroplasia, the mutated form of the receptor is constitutively active and this leads to severely shortened bones. The disorder causes the most common type of dwarfism. Clinical features of achondroplasia: nonproportional short stature with an average adult height of 131 cm (4 feet 3.8 inches) for males and 123 cm (4 feet 0.6 inches) for females; shortening of the proximal limbs, short fingers and toes, a large head with prominent forehead, small midface with a flattened nasal bridge, spinal kyphosis (convex curvature) or lordosis (concave curvature), frequent ear infections (due to Eustachian tube blockages), and hydrocephalus.

8. Retinoblastoma is a cancer of the retina. It occurs mostly in children younger than 5 years and accounts for about 3% of the cancers occurring in children younger than 15 years. Adult cases have also been clinically recorded. The tumor may begin in one or both eyes. Retinoblastoma is usually confined to the eye but can spread to the brain via the optic nerve.

As the retina is the light-sensitive part of the eye necessary for vision, loss of vision occurs.

Autosomal recessive inheritance

Autosomal recessive conditions are clinically apparent only in the homozygous state . when both alleles at a particular genetic locus are deleterious. In most autosomal recessive disorders the clinical presentation tends to be more uniform than in dominant diseases, and the onset is often early in life. Consanguinity increases the likelihood of a child presenting with a recessive disease because the likelihood of inheriting the same rare mutation from a distant common ancestor, or "founder" increases. First cousins share, on the average, 1/8 of their genes. When two first cousins marry, an offspring has, on average, 1/16 of the loci homozygous for a gene derived from a common ancestor. In general, offspring of first cousins are slightly more likely to have congenital malformations, as well as mental defects and metabolic diseases, than are children born to unrelated parents.

Increased frequency of consanguinity is not observed if the recessive disease is common.

Features of autosomal recessive inheritance

1. An autosomal recessive trait characteristically is seen only in sibs - brothers and sisters. It is not seen in their parents, offsprings or other relatives.

2. On an average the ratio of affected, carrier and non-affected is 1:2:1 in sibs; the recurrence risk in such a family is 1 in 4 for each birth.

3. The parents of the affected child may be closely related consanguineously.

4. Males and females are affected equally and transmit the trait equally.

Examples of autosomal recessive traits are

1. Phenylketonuria
2. Albinism
3. Galactosemia
4. Cystic fibrosis
5. Sickle-cell Anemia
6. Lysosomal Storage Diseases
 - a. Gauchers Disease
 - b. Niemann . Pick Disease
 - c. Tay . Sachs Disease
7. Wilson's Disease

1. Phenylketonuria (PKU) is metabolic disorder characterized by a deficiency in the enzyme phenylalanine hydroxylase (PAH) which is necessary to metabolize the amino acid *phenylalanine* (Phe) to the amino acid tyrosine. When PAH is deficient, Phe accumulates and is converted into

phenylketones, which are detected in the urine. Left untreated, this condition can cause problems with brain development, leading to progressive mental retardation and seizures. However, PKU is one of the few genetic diseases that can be controlled by diet. A diet low in phenylalanine and high in tyrosine can bring about a nearly total cure.

2. Albinism is a form of hypopigmentary disorder, caused by mutations in genes that regulate the melanin synthesis, distribution of pigment by the melanocyte, and/or melanosome biogenesis are the basis for these diseases. There are 2 main categories of albinism in humans:

- a. oculocutaneous albinism
- b. ocular albinism, only the eyes lack pigment. People with ocular albinism have generally normal skin and hair color, and many even have a normal eye appearance.
- c.

3. Galactosemia is a rare metabolic disorder which affects an individual's ability to properly metabolize the sugar galactose. Cause: Inability of the body to metabolize the simple sugar galactose, causing the accumulation of galactose-1-phosphate in the body. This causes damage to the liver, CNS, and other body systems. After drinking milk for a few days, a newborn with disease refuses to eat and develop such symptoms: jaundice (yellowish discoloration of the skin and the whites of the eyes), vomiting, poor feeding (baby refusing to drink milk-containing formula), poor weight gain, lethargy, irritability, convulsions. The only treatment for classic galactosemia is eliminating lactose and galactose from the diet.

4. Cystic fibrosis (CF) is a disease of the mucus and sweat glands. It affects mostly lungs, pancreas, liver, intestines, sinuses and sex organs. CF causes mucus to be thick and sticky. Disorder leads to the disruption of pancreatic exocrine function and chronic bronchitis with emphysema (The mucus clogs the lungs, causing breathing problems and making it easy for bacteria to grow), as well as biliary cirrhosis, meconium ileus, and an enhanced loss of salt through the skin, which is the basis of the "sweat test" used for screening purposes.

The symptoms and severity of CF vary widely. Disease is common among individuals of Northern European descent. In the United States, an estimated 1 in 29 Caucasian Americans have the CF gene. The frequency of individuals affected with cystic fibrosis is one in 2,500, and typically the parents are unrelated.

5. Sickle cell disease is a group of disorders that affects hemoglobin of RBCs. Sick people have atypical hemoglobin molecules called hemoglobin S, which can distort RBCs into a sickle, or crescent, shape.

Symptoms of the disease usually begin in early childhood. Characteristic features include anemia, repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person. Some people have mild symptoms, while others are frequently hospitalized for more serious complications. Anemia can cause shortness of breath, fatigue, and delayed growth and development in children. The rapid breakdown of RBCs may also cause yellowing of the eyes and skin, which are signs of jaundice. Painful episodes can occur when sickled RBCs, which are stiff and inflexible, get stuck in small blood vessels. These episodes deprive tissues and organs of oxygen-rich blood and can lead to organ damage, especially in the lungs, kidneys, spleen, and brain. A particularly serious complication of sickle cell disease is high blood pressure in the blood vessels that supply the lungs (pulmonary hypertension). Pulmonary hypertension occurs in about one-third of adults with disease and can lead to heart failure.

6. Lysosomal storage diseases (LSD) are caused by a lack of enzymes that normally eliminate unwanted substances in the cells of the body. The enzymes are found in lysosomes. The lack of certain enzymes causes a buildup of the substance that the enzyme would normally eliminate, and deposits accumulate in many cells of the body. Abnormal storage causes inefficient functioning and damage of the body's cells, which can lead to serious health problems.

There are more than 40 known LSDs, including:

- a. **Tay-Sachs disease** - a LSD that occurs more commonly in people of Eastern European Ashkenazi descent and causes degeneration of the brain in infants.
The most common form of Tay-Sachs disease becomes apparent in infancy. Infants with this disorder typically appear normal until the age of 3 to 6 months, when their development slows and muscles used for movement weaken. Affected infants lose motor skills such as turning over, sitting, and crawling. They also develop an exaggerated startle reaction to loud noises. As the disease progresses, children with Tay-Sachs disease experience seizures, vision and hearing loss, intellectual disability, and paralysis. An eye abnormality called a *cherry-red spot*,

which can be identified with an eye examination, is characteristic of this disorder. Children with this severe infantile form of Tay-Sachs disease usually live only into early childhood. Even with the best of care, children with Tay-Sachs disease usually die by age 4.

- b. **Gaucher disease** causes the spleen to enlarge, anemia and bone lesions if untreated
- c. **Niemann-Pick** disease leads to enlargement of the spleen and liver, as well as lung disease

Disease	Deficiency of enzyme	Accumulated substance	Affected organs & Symptoms	Notes
Tay-Sachs disease	hexosaminidase	gangliosides, (ganglioside GM2)	Brain (neurological deterioration), blindness	Child usually dies by the age of 4 or 5 years.
Gaucher disease	glucocerebrosidase	glucocerebroside	Enlargement of liver, spleen, anemia and bone lesions if untreated	There are 3 clinical subtypes
Niemann-Pick disease	sphingomyelinase	sphingomyelin, cholesterol, and other kinds of lipids	Enlargement of the spleen and liver, as well as lung disease	There are 3 clinical subtypes that may or may not involve the CNS or respiratory system

7. Wilson's disease, or hepatolenticular degeneration - excessive deposition of copper in the body's tissues (liver, brain, kidneys, and the eyes). A cause of disease is a mutation, localized on chromosome 13q, affects the Cu-transporting ATPase gene (*ATP7B*) in the liver. Frequency ranges worldwide from 1:30,000 in Japan to 1:100,000 in Australia; is more common in females than in males (4:1).

It causes tissue damage, death of the tissues, and scarring, which causes the affected organs to stop working correctly. Liver failure and damage to the CNS (brain, spinal cord) are the most predominant, and the most dangerous, effects of the disorder. If not caught and treated early, Wilson's disease is fatal.

In diagnosis an eye examination may show Kayser-Fleischer rings (rusty or brown-colored ring around the iris). Eye movement may be restricted.

X-Linked Inheritance

Diseases or traits that result from genes located on the X chromosome are termed "X-LINKED." Because the female has two X chromosomes, she may be either heterozygous or homozygous for the mutant gene, and the trait may exhibit recessive or dominant expression. The terms "X-LINKED dominant" and "X-LINKED recessive" refer only to expression of the trait in females. The male has only one X chromosome and therefore is hemizygous for X-linked traits. Males can be expected to express X-linked traits regardless of their recessive or dominant behavior in the female. This accounts for the large numbers of X-linked diseases. Affected males do not transmit an X chromosome to their sons; thus an important feature of X-linked inheritance is the absence of male-to-male transmission. In contrast, since all females inherit their fathers' single X chromosomes, their daughters are all obligate carriers.

X-linked dominant inheritance

Features of X-linked dominant inheritance

1. In rare X-linked dominant disorders, affected females are twice as common as affected males.
2. Affected males pass on the trait to all their daughters, but to none of their sons. Thus, X-linked dominant inheritance can be distinguished from autosomal dominant inheritance only by the progeny of affected males.
3. Transmission by affected females follows the same pattern as autosomal dominant. Affected heterozygous females transmit the condition to half their children of both sexes. Affected homozygous females transmit the trait to all their children.

Examples of X-linked dominant inheritance are

1. Familial Hypophosphatemia
2. Vitamin D resistant rickets, or Familial Hypophosphatemia
3. Incontinentia pigmenti (also known as naevus pigmentosus systematicus)

1. Familial Hypophosphatemia

In familial hypophosphatemia, disorder of bone mineralization, the kidneys fail to reabsorb sufficient phosphate, leading to low levels of serum phosphate. This usually begins after age 6-10 months. Prior to this occurrence, the glomerular filtration rate is low, which sustains an adequate phosphate level. Mutations in the *PHEX* gene are the cause of X-linked hypophosphatemic rickets (XLHR). *PHEX* codes for a protease, which is an enzyme that catalyzes the hydrolysis of a protein. However, such a protein has not yet been identified.

2. Vitamin D resistant rickets, or Familial Hypophosphatemia is a form of rickets characterized by high concentrations of phosphate in the blood due to defective renal tubular reabsorption of phosphate and subnormal absorption of dietary calcium.

Cause is the disorder is the mutation in the *PHEX* gene (Xp.22) and subsequent inactivity of the *PHEX* protein. Frequency: 1:20000.

Symptoms include musculoskeletal and dental manifestations.

Musculoskeletal manifestations: smooth bowing of lower extremities when begin to weight bear, waddling gait, bow leggedness, short stature, dolichocephaly (long head).

Dental Manifestations: pulp deformities, "intraglobular dentin" tooth anomaly, occasional enamel defects, periapical infections.

3. Incontinentia Pigmenti (IP) is a disorder that affects the skin, hair, teeth, and nails. Cause: mutations in the *IKBKG* gene coding for the protein that normally helps protect cells from self-destructing (undergoing apoptosis). IP is lethal in most, but not all, males. A female with IP may have inherited the mutant gene from either parent or have a new gene mutation. Symptoms: blistering and wart-like skin growths in early childhood followed by changes in skin pigmentation. The condition may also affect the teeth, hair, eyes, and central nervous system (the brain and spinal cord).

X-linked recessive inheritance

Features of X-linked recessive inheritance

1. An X-linked recessive trait is mostly seen in males. It is uncommon in females.
2. The trait is transmitted from an affected man through all his daughters half of his grandsons.
3. The trait can be transmitted through a series of carrier females.

Examples of X-linked recessive inheritance are

1. Haemophilia
2. Colour blindness
3. Duchenne muscular dystrophy
4. Glucose-6-phosphate dehydrogenase deficiency (favism).

1. Hemophilia is a hereditary bleeding disorder. Hemophilia is a hereditary blood disorder, characterized by a deficiency of the blood clotting protein that results in abnormal bleeding. Babylonian Jews first described hemophilia more than 1700 years ago.

There are three types; Type A, Type B, and Type C. Haemophilia A is a genetic disorder characterised by deficiency of Factor VIII in the blood, which is synthesized mainly in the liver, and is one of many factors involved in blood coagulation. The factor VIII gene is located on the X chromosome. Since males have only a single copy of most of genes located on the X chromosome, they cannot offset damage to that genes with an additional copy as can females. Consequently, X-linked disorders such as hemophilia are far more common in males. Type A is the most common. One in 10,000 males is born with deficiency or dysfunction of the factor VIII molecule. Although normal hemostasis requires at least 25% factor VIII activity, symptomatic patients usually have factor VIII levels below 5 percent. Patients with <1% factor VIII activity have severe disease.

Hemophilia B is caused by the deficiency of Factor IX. It is also known as Christmas disease. It occurs in 1 in 100,000 male births. Antenatal diagnosis can be done in females having high degree of probability of being a carrier. This is done by doing chorion villus sampling at 8-9 weeks of gestation.

2. Color blindness, or color vision deficiency, is the inability to perceive differences between some or all colors that other people can distinguish. The English chemist John Dalton in 1798 published the first paper on the subject, "Extraordinary facts relating to the vision of colours", after the realization of his own color blindness; because of Dalton's work, the condition is sometimes called *daltonism*.

Color blindness is usually classed as disability; however, in selected situations color blind people may have advantages over people with normal color vision. There are many types of color blindness. The most common are red-green hereditary (genetic) photoreceptor disorders.

3. Duchenne muscular dystrophy (DMD) and the milder Becker muscular dystrophy (BMD) are the product of mutations in the dystrophin gene on the X chromosome. The most distinctive feature of DMD is a progressive proximal muscular dystrophy with characteristic pseudohypertrophy of the calves. On average, a typical patient with DMD is diagnosed around the age of five, is wheelchair dependent at twelve years of age, and is dead before the age of twenty. One-third of cases represent new mutations.

4. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is disease featuring abnormally low levels of the G6PD enzyme, which plays an important role in red blood cell function. Individuals with the disease may exhibit nonimmune hemolytic anemia in response to a number of causes. It is closely linked to favism, a disorder characterized by a hemolytic reaction to consumption of broad beans, with a name derived from the Italian name of the broad bean (fava). Sometimes the name, favism, is alternatively used to refer to the enzyme deficiency as a whole.

Y Æ linked inheritance (holandric inheritance):

Features of Y-linked inheritance

Males alone get affected and an affected male transmits the trait to all his sons but to none of his daughters. As the Y chromosome is single, genes on Y chromosome are always expressed phenotypically.

Examples of Y-linked inheritance are

1. Hypertrichosis pinnae auris (hairy ears)
2. Azoospermia - complete inability to produce sperm, caused by a deletion of the azoospermia factor (AZF) region,
3. Abnormal or Absent Testicular Development (gonadal dysgenesis), caused by a deletion SRY gene.
4. Retinitis Pigmentosa is a eye disease caused by mutations in the RPY gene. Symptoms: a progressive loss of sight starting with decreased night vision, followed by loss of peripheral or side vision and finally blindness.

Mitochondrial inheritance

Features of mitochondrial inheritance

The diseases caused by mutations in mitochondrial genome are inherited only through the egg, sperm mitochondria never contribute to the zygote population of mitochondria. All the children of an affected female but none of the children of an affected male will inherit the disease.

Examples of mitochondrial inheritance are

1. Pearson marrow-pancreas syndrome
2. MELAS syndrome (Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes)
3. MERRF syndrome (Myoclonic Epilepsy with Ragged-Red Fibers)
4. Leber's hereditary optic neuropathy (LHON)

4. Polygenic Traits and Multifactorial Genetic Diseases

Most phenotypic traits are determined by many genes collaborating at different loci (polygenic) rather than by single gene effects. Parents and offspring, and usually siblings, have 50% of their genes in common. Second-degree relatives share, on average, one-fourth of all genes, and third-degree relatives (cousins) share 1/8. As the degree of relation becomes more distant, the probability of inheriting the same combination of genes is reduced, and the degree of resemblance is likely to be less.

Many common chronic diseases (e.g., essential hypertension, coronary artery disease, and schizophrenia) and the common birth defects of children (e.g., cleft palate, cleft lip, and neural tube defects) that tend to run in families fit best into the category of multifactorial genetic diseases. Multifactorial genetic diseases have both a polygenic component and an environmental component of causative factors. Susceptibility, or risk, genes are present in low frequency in the population at large. However, if any one individual has a particularly large number of such genes, the disease may mani-

fest. When an individual is unfortunate enough to have inherited just the right (or wrong) combination of risk genes, he or she passes beyond a "risk threshold" at which environmental factors may determine the expression and severity of disease. In order for another family member to develop the same disease, that individual would have to inherit the same, or a very similar, combination of genes. The likelihood of such an occurrence is clearly greater in first-degree than in more distant relatives. The chances of another relative inheriting the right combination of risk genes decreases as the number of genes required to express a given trait increases. For example, the recurrence risk for siblings in neural tube defects is almost 4%, or ten times greater than the risk in the population as a whole.