MOLECULAR BASIS OF DISEASE

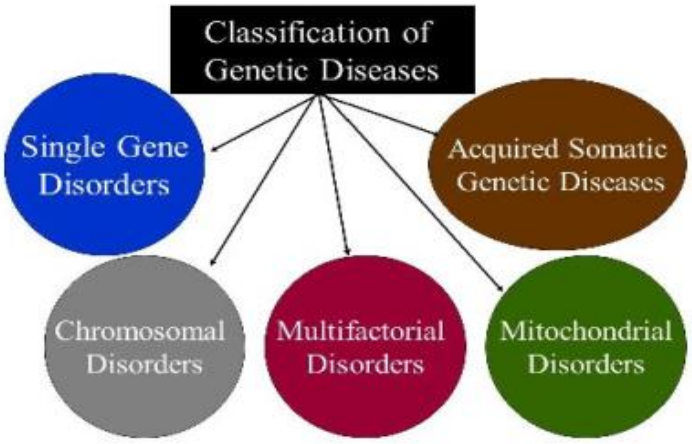
GENETIC DISORDERS

What are genetic disorders?

- A genetic disorder is a disease caused in whole or in part by a change in the DNA sequence away from the normal sequence.
- Genetic disorders can be caused by a mutation in one gene (monogenic disorder), by mutations in multiple genes (multifactorial inheritance disorder), by a combination of gene mutations and environmental factors, or by damage to chromosomes (changes in the number or structure of entire chromosomes, the structures that carry genes).
- As we unlock the secrets of the human genome (the complete set of human genes), we are learning that nearly all diseases have a genetic component.
- Some diseases are caused by mutations that are inherited from the parents and are present in an individual at birth, like sickle cell disease.
- Other diseases are caused by acquired mutations in a gene or group of genes that occur during a person's life. Such mutations are not inherited from a parent, but occur either randomly or due to some environmental exposure (such as cigarette smoke). These include many cancers.

Classification

- **3 groups of genetic diseases**
- **Disorders with multifactorial inheritance (polygenic)**
- **Monogenic (mendelian) disorders**
- **Chromosomal aberrations**



Monogenetic disorders

Monogenetic disorders are caused by a mutation in a single gene.

- The mutation may be present on one or both chromosomes (one chromosome inherited from each parent). Examples of monogenic disorders are: sickle cell disease, cystic fibrosis.
- A major distinction among monogenic disorders is between "dominant" and "recessive" diseases.
- Dominant diseases are caused by the presence of the disease gene on just one of the two inherited parental chromosomes.
- In dominant diseases, the chance of a child inheriting the disease is 50 percent. In a family situation, for example, if the parents have four children, it may be possible that two of those children inherit the disease gene.
- Examples of dominant diseases are : **Huntington disease.**
- Recessive diseases require the presence of the disease gene on both of the inherited parental chromosomes.
- In this case, the chance of a child inheriting a recessive disease is 25 percent. In the family example, if the parents have four children, it may be more likely that only one child will develop the disease. Examples of recessive diseases include **cystic fibrosis, sickle cell anemia.**

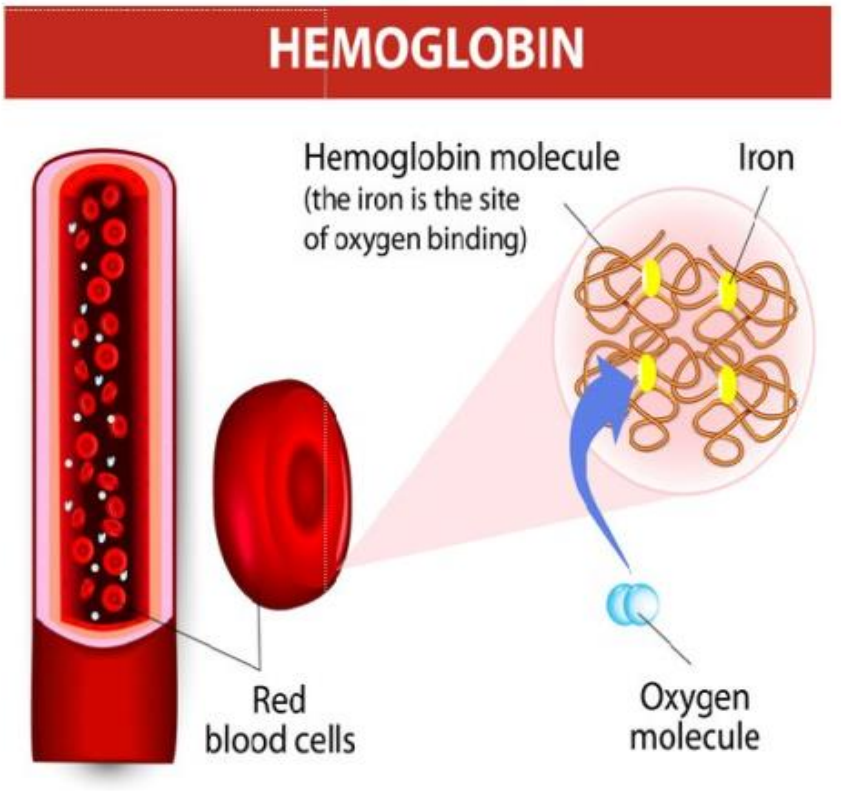
mutation of 1 gene, mendelian type of inheritance

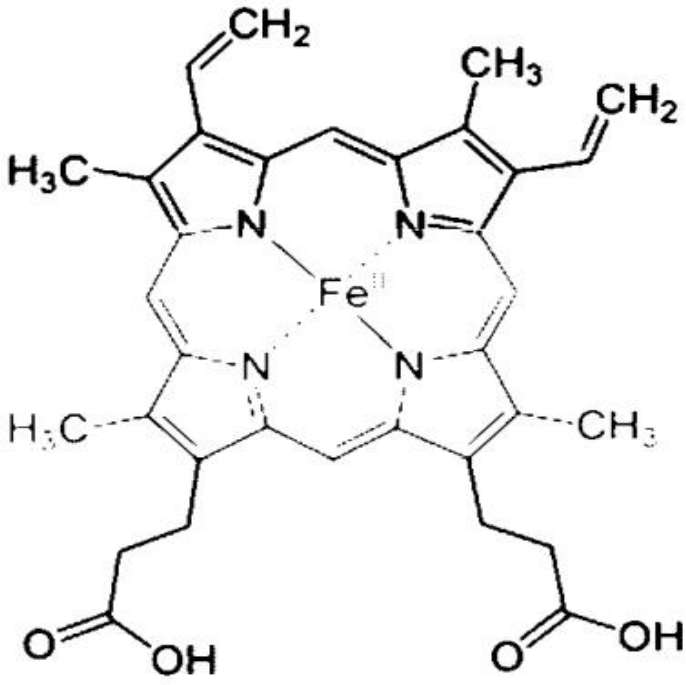
- today about 5000 diseases
- Autosomal dominant
- Autosomal recessive
- X-linked

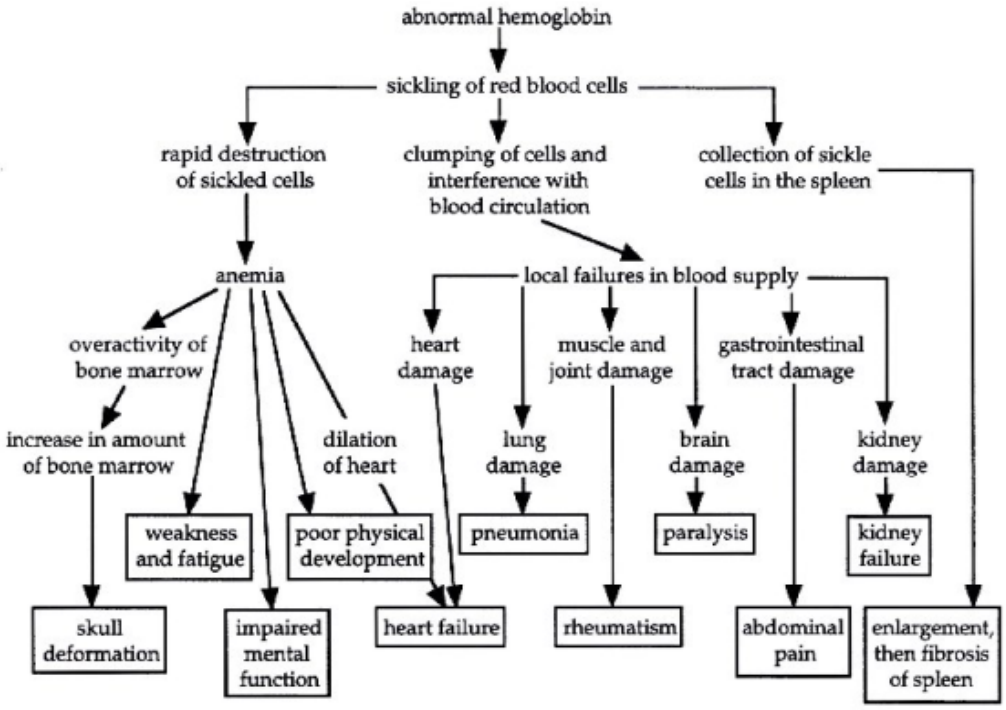
Example: **HAEMOGLOBIN DISORDERS**

- Hemoglobin is the protein molecule in red blood cellsthat carries oxygen from the lungs to the body's tissues and returns carbon dioxide from the tissues back to the lungs.
- Hemoglobin is made up of four protein molecules (globulin chains) that are connected together. The normal adult hemoglobin (abbreviated Hgb or Hb) molecule contains two alpha-globulin chains and two beta-globulin chains.

- In fetuses and infants, beta chains are not common and the hemoglobin molecule is made up of two alpha chains and two gamma chains. As the infant grows, the gamma chains are gradually replaced by beta chains, forming the adult hemoglobin structure.







SICKLE CELL DISEASE

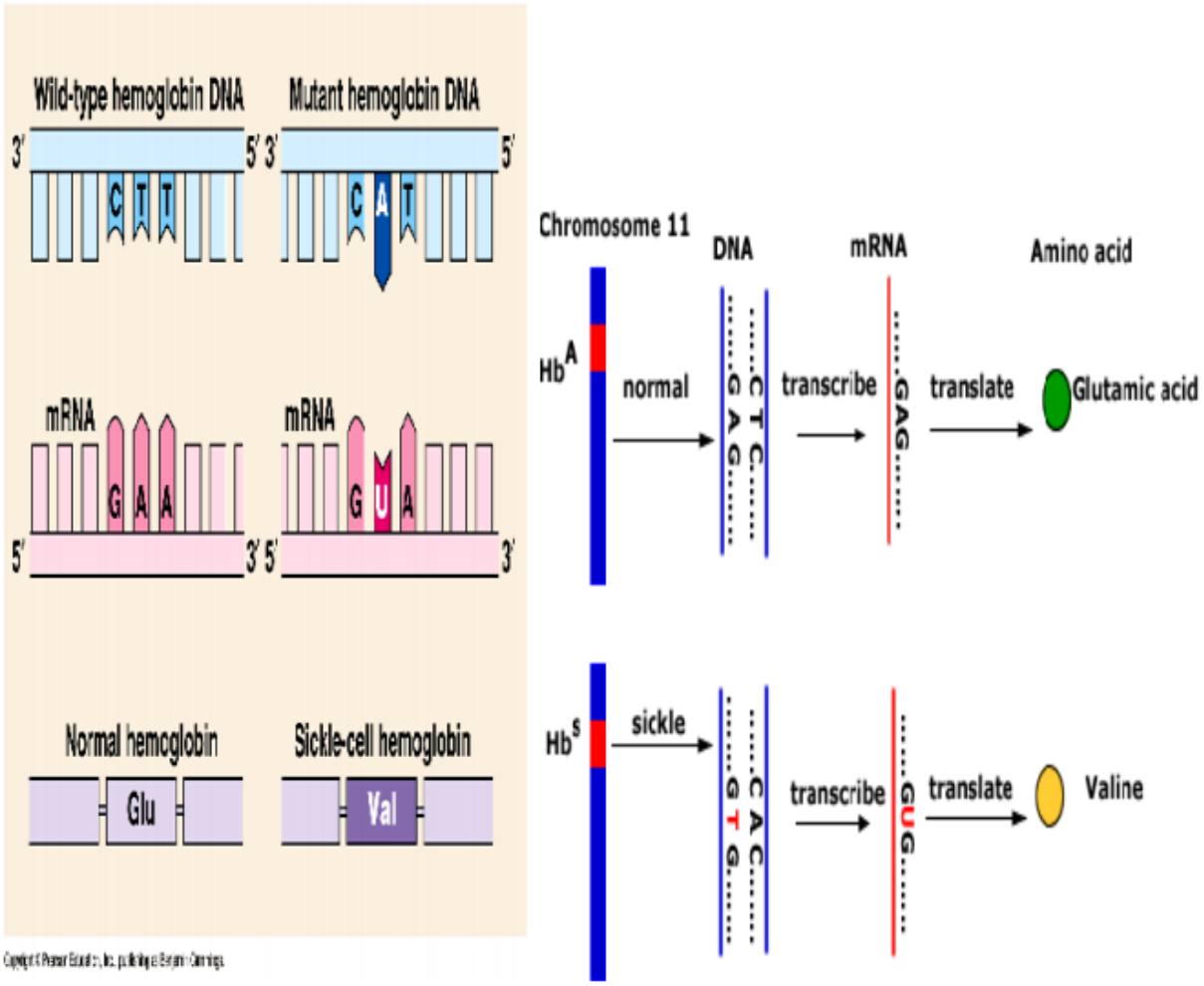
- Sickle cell disease is a group of disorders that affects hemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body. People with this disorder have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle, or crescent, shape.
- Signs and symptoms of sickle cell disease usually begin in early childhood. Characteristic features of this disorder include a **low number of red blood cells** (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.

Frequency

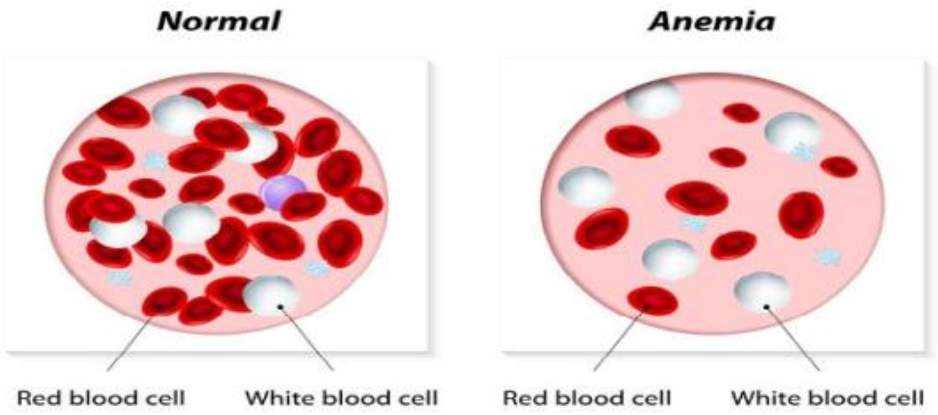
- Sickle cell disease affects millions of people worldwide.
- It is most common among people whose ancestors come from Africa; Mediterranean countries such as **Greece, Turkey, and Italy; the Arabian Peninsula; India; and Spanish-speaking regions in South America, Central America, and parts of the Caribbean.**
- Sickle cell disease is the most common inherited blood disorder in the United States, affecting 70,000 to 80,000 Americans. The disease is estimated to occur in 1 in 500 African Americans and 1 in 1,000 to 1,400 Hispanic Americans

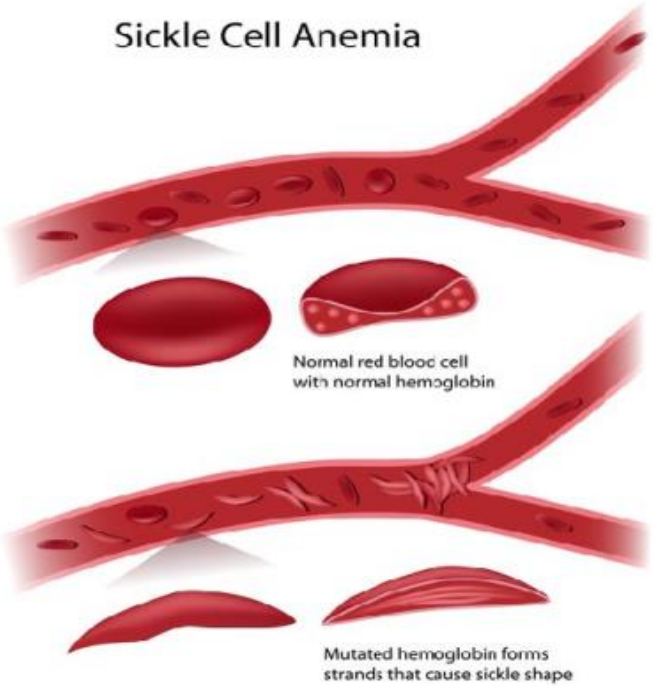
Genetic Changes



- Mutations in the *HBB* gene cause sickle cell disease.
- Hemoglobin consists of four protein subunits, typically, two subunits called alpha-globin and two subunits called beta-globin.
- **The *HBB* gene provides instructions for making beta-globin.**
- **Various versions of beta-globin result from different mutations in the *HBB* gene.**
- One particular *HBB* gene mutation produces an abnormal version of beta-globin known as **hemoglobin S (HbS).**
- Other mutations in the *HBB* gene lead to additional abnormal versions of beta-globin such as **hemoglobin C (HbC)** and **hemoglobin E (HbE).**

- *HBB* gene mutations can also result in an **unusually low level of beta-globin;** this abnormality is **called beta thalassemia**.
- The *HBB* gene provides instructions for making a protein called **beta-globin.**
- Beta-globin is a component (subunit) of a larger protein called hemoglobin, which is located inside red blood cells.
- In adults, hemoglobin normally consists of four protein subunits: two subunits of beta-globin and two subunits of another protein called alpha-globin, which is produced from another gene called*HBA*.
- Each of these protein subunits is attached (bound) to an iron-containing molecule called heme; each heme contains an iron molecule in its center that can bind to one oxygen molecule.
- Hemoglobin within red blood cells binds to oxygen molecules in the lungs. These cells then travel through the bloodstream and deliver oxygen to tissues throughout the body.
- In people with sickle cell disease, at least **one of the beta-globin subunits in hemoglobin is replaced with hemoglobin S.**
- In sickle cell anemia, which is a common form of sickle cell disease, **hemoglobin S replaces both beta-globin subunits in hemoglobin.**
- In other types of sickle cell disease, just one beta-globin subunit in hemoglobin is replaced with hemoglobin S.
- The other beta-globin subunit is replaced with a different abnormal variant, such as hemoglobin C.
- For example, **people with sickle-hemoglobin C (HbSC) disease have hemoglobin molecules with hemoglobin S and hemoglobin C instead of beta-globin.**
- If mutations that produce hemoglobin S and beta thalassemia occur together, individuals have hemoglobin S-beta thalassemia (HbSBetaThal) disease.
- Abnormal versions of **beta-globin can distort red blood cells into a sickle shape**.
- The sickle-shaped red blood cells die prematurely, which can lead to anemia.
- Sometimes the inflexible, sickle-shaped cells get stuck in small blood vessels and can cause serious medical complications.





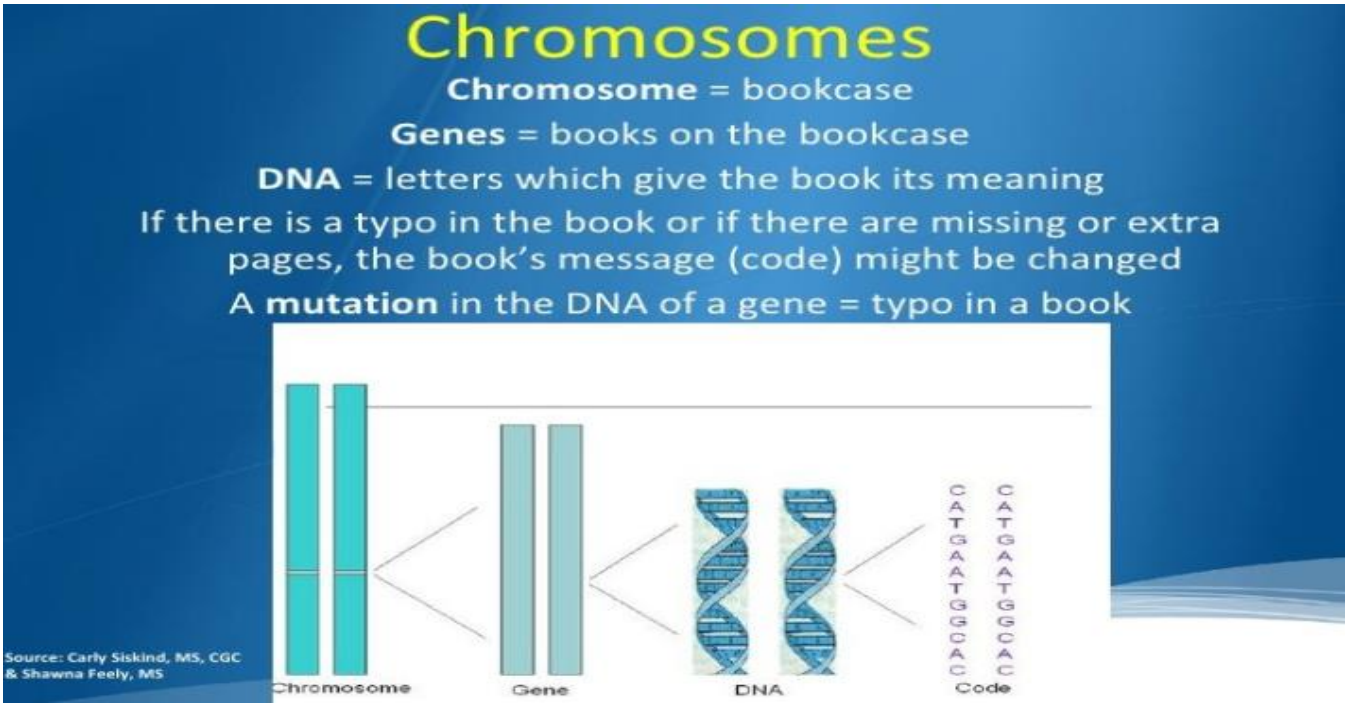
- The **signs and symptoms of sickle cell disease** are caused by the sickling of red blood cells.
- When **red blood cells sickle**, they break down prematurely, which can lead to anemia.
- **Anemia can cause shortness of breath, fatigue, and delayed growth and development in children.**
- The rapid breakdown of red blood cells may also cause **yellowing of the eyes and skin, which are signs of jaundice.**

- **Painful episodes** can occur when **sickled red blood cells, 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 sickle cell disease and can lead to heart failure.**

Inheritance Pattern

- This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations.
- The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Chromosome disorders



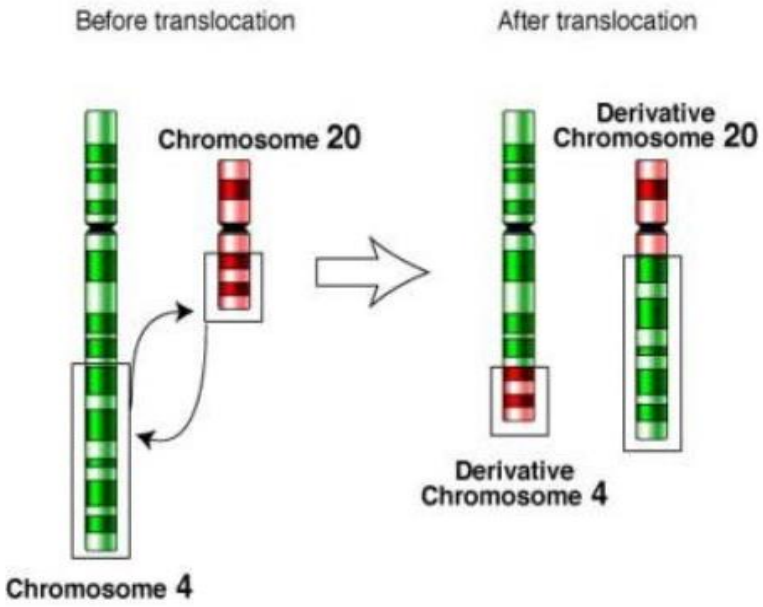
- ***Chromosome disorders*** are caused by an excess or deficiency of the genes that are located on chromosomes, or by structural changes within chromosomes.

Chromosomal aberrations (cytogenetic disorders)

- Alternations in the number or structure of chromosomes
- Autosomes or sex chromosomes
- Studied by cytogenetics
- Cell cycle arrested in metaphase (colchicin) - staining by giemsa method (g-bands) - photographing - karyotype
- 2 sets of 23 chromosomes
- 22 pairs of autosomes, 2 sex chromosomes (xx or xy)
- Cytogenetic disorders are relatively frequent! (1:160 newborns; 50% of spontaneous abortions)

Numerical abnormalities

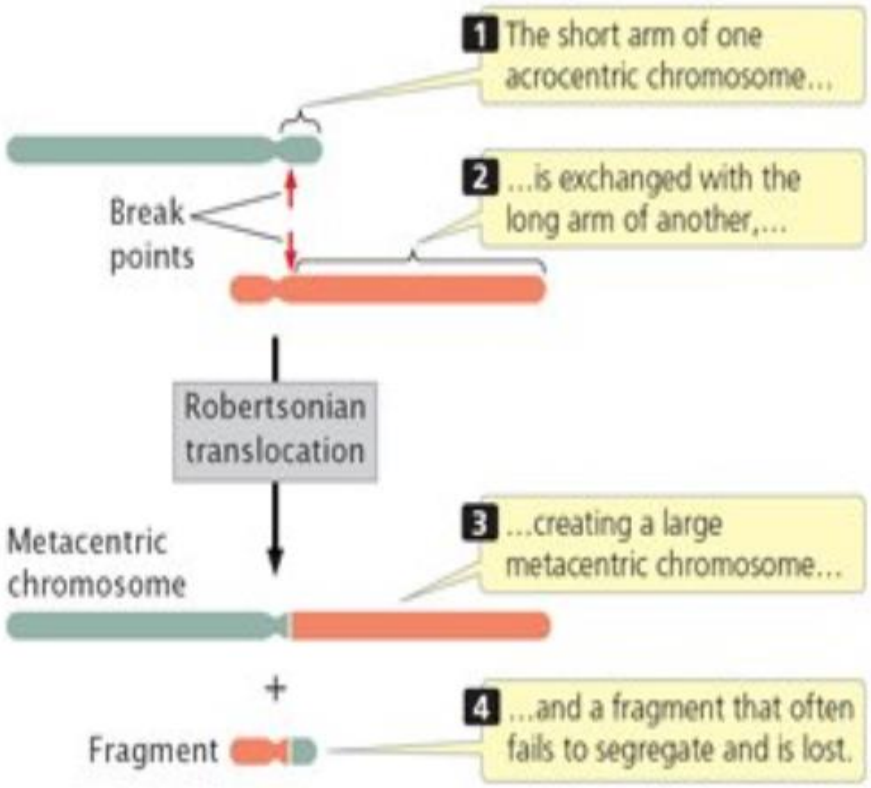
- Such translocations are usually harmless and may be found through prenatal diagnosis.
- However, **carriers of balanced reciprocal translocations have increased risks of creating gametes** with **unbalanced chromosome translocations,** leading to **miscarriages or children with abnormalities**



Robertsonian translocation

- Robertsonian translocation is a type of translocation caused by breaks at or near the centromeres of two acrocentric chromosomes.
- The reciprocal exchange of parts gives rise to one large metacentric chromosome and one extremely small chromosome that may be lost from the organism with little effect because it contains so few genes.

The resulting karyotype in humans leaves only 45 chromosomes, since two chromosomes have fused together.



Robertsonian translocation-DISEASES

- A Robertsonian translocation in **balanced form results in no excess or deficit of genetic** material and causes no health difficulties.
- If, for example, the long arms of **chromosomes 13 and 14 fuse**, no significant genetic material is lost - and the person is completely normal in spite of the translocation.
- Common Robertsonian translocations are confined to the acrocentric chromosomes **13, 14, 15, 21 and 22, because the short arms of these chromosomes encode for rRNA** which is present in multiple copies.
- In **unbalanced forms, Robertsonian translocations cause chromosomal deletions or addition** and result in syndromes of multiple malformations, including trisomy 13 (Patau syndrome) and trisomy 21 (Down syndrome).

Some human diseases caused by translocations are:

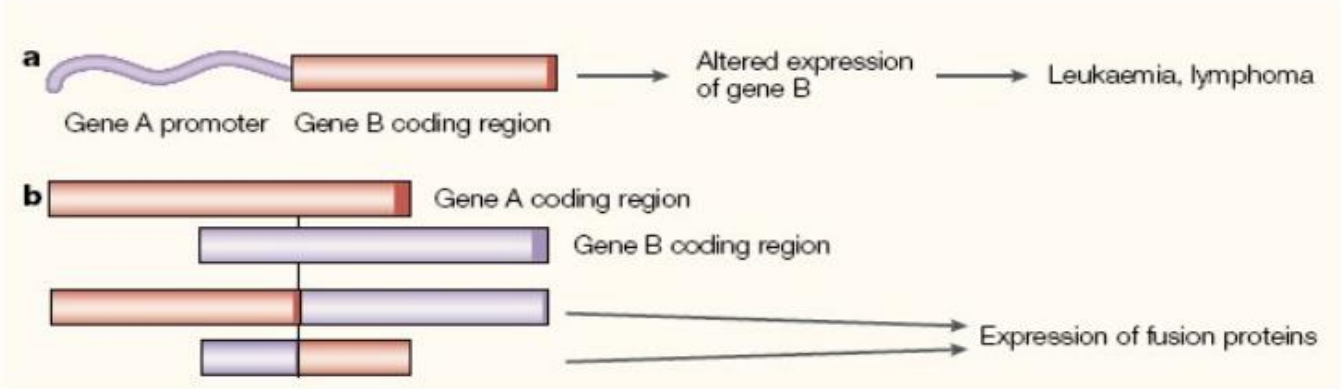
1. Cancer: Several forms of cancer are caused by acquired translocations (as opposed to those present from conception); this has been described mainly in leukemia (acute myelogenous leukemia and chronic myelogenous leukemia). Translocations have also been described in solid malignancies such as Ewing's sarcoma.
2. Infertility: One of the would-be parents carries a *balanced translocation*, where the parent is asymptomatic but conceived fetuses are not viable.
3. Down syndrome is caused in a minority (5% or less) of cases by a Robertsonian translocation of the chromosome 21 long arm onto the long arm of chromosome 14.

Chromosomal translocations between the sex chromosomes can also result in a number of genetic conditions, such as

1. XX male syndrome: caused by a translocation of the SRY gene from the Y to the X chromosome

Translocations-RELATED DISEASES -CANCER

- Translocations involving human chromosomes are of great clinical interest because they have been linked to a number of disorders, including mental retardation, infertility, and cancer.

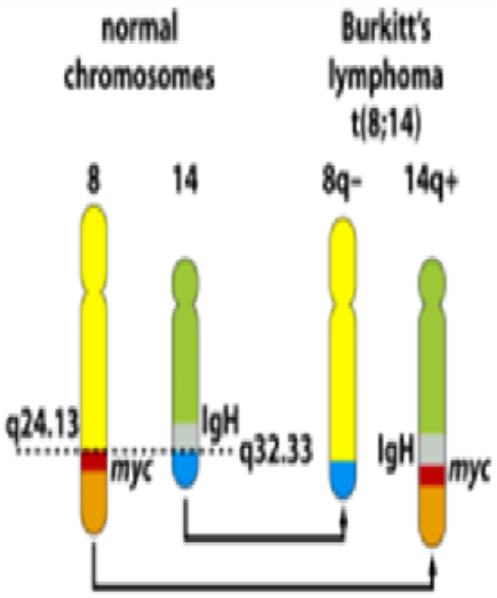


a) In some lymphomas and leukemias, chromosome translocations lead to the juxtaposition of promoter/enhancer elements from one gene (gene A, purple) with the intact coding region of another gene (gene B, red). **Example: Burkitt's lymphoma**

b) b) By contrast, translocations seen in CML and many of the acute leukemias result in recombination of the coding regions of two different genes. This results in a fusion protein that might have a new function. This is the case for the BCR-ABL fusion protein that is encoded by the Philadelphia chromosome. **Example:Cronic Myeloid Lymphoma.**

Burkitt's lymphoma

- The translocation places the coding sequence of one gene (Gene B) in proximity to the regulatory sequence for a different gene (Gene A).
- The first translocation of this kind to be described was a translocation involving chromosomes 8 and 14 in patients with Burkitt's lymphoma.
- This particular translocation places the ***MYC*** **proto-oncogene** from **chromosome 8** under the **control of the powerful immunoglobin heavy chain gene (*IGH*) promoter on chromosome 14**.
- The **MYC protein normally signals for cell proliferation, and the translocation causes high levels of *MYC* overexpression in lymphoid cells, where the *IGH* promoter is normally active.**



Chronic Myeloid Lymphoma:

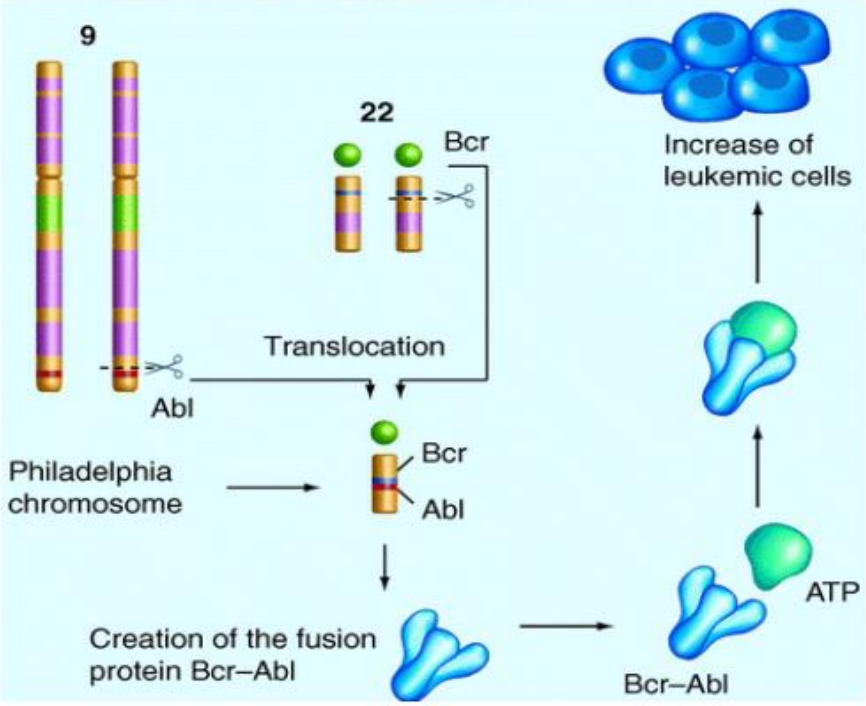
The Philadelphia chromosome, discovered in 1960 in the Philadelphia laboratories of Peter Nowell and David Hungerford, is the best-known example of an oncogenic chromosomal translocation.

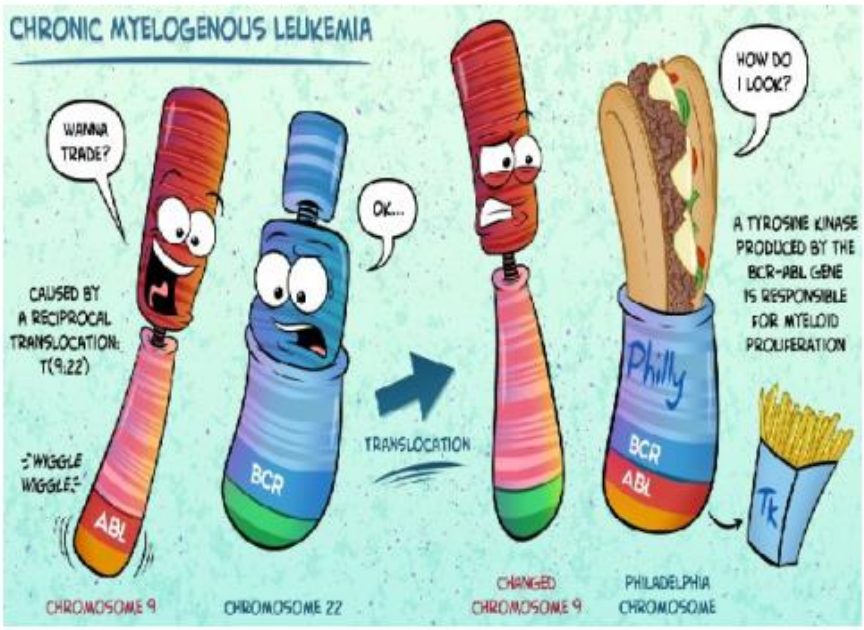
- In this case, one end of chromosome 9 is exchanged with one end of chromosome 22. At the broken end of chromosome 22 lies **the *BCR*(**"breakpoint cluster region") **gene,** which fuses with a fragment of chromosome 9 that carries the ***ABL1*** **(**"Abelson"-name of leukemia virus carry same gene) **gene**; this fused **chromosome is called the**

Philadelphia chromosome. When the **chromosome ends fuse, the two genes also fuse with each other to become *BCR-ABL*.**

Molecular basis of CML

1. ***ABL1*** **-** expresses a membrane-associated protein, a tyrosine kinase.
2. **BCR:**Displays serine/threonine kinase activity.
3. **BCR-Abl transcript-fusion protein** is also **translated into a tyrosine kinase.** The activity of tyrosine kinases is typically controlled by other molecules, but the **mutant tyrosine kinase of the BCR-Abl transcript codes for a protein that is "always on" or continuously activated, which results in unregulated cell division (i.e. cancer).**
4. The unregulated expression of this protein activates a repertoire of other proteins that are involved in cell cycle regulation and stimulation of cell division. As a result, the **Philadelphia chromosome is associated with chronic myelogenous leukemia (CML) and several other forms of leukemia**.

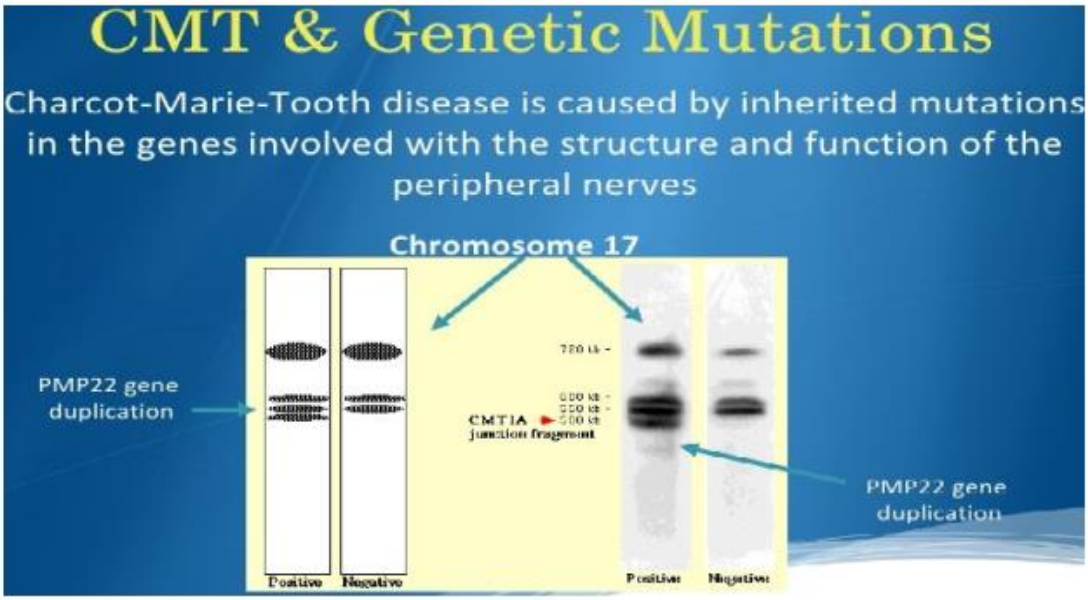


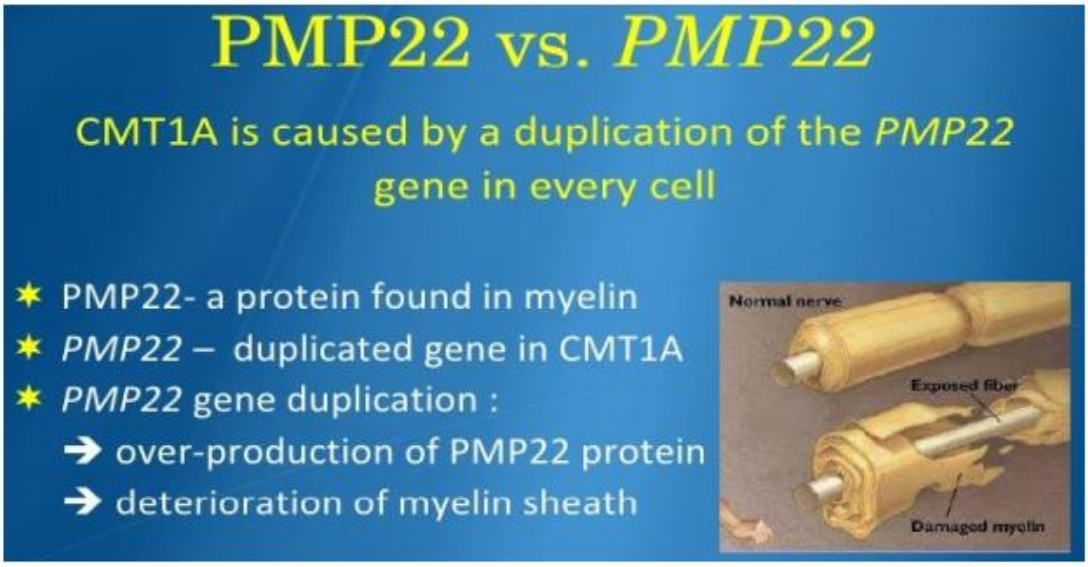


- Evidence that cells expressing the BCR-ABL fusion protein suffer from oncogene addiction .
- **Thus imatinib**, an ABL kinase inhibitor, to treat CML patients. This drug, which **targets the tyrosine kinase activity of ABL**.
- However, more long-**term clinical studies using imatinib to treat CML patients are showing that some patients may begin to show signs of drug resistance over time.**

Chromosomal Duplications

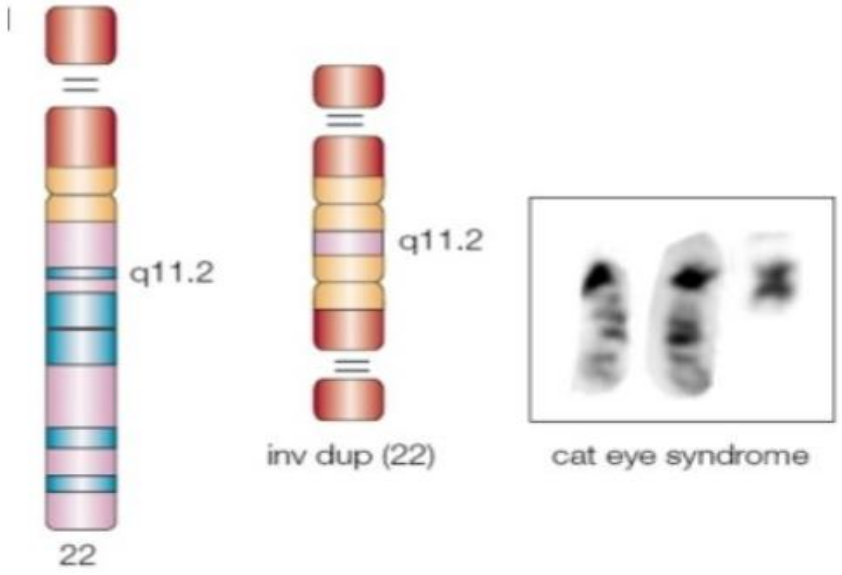
- In chromosomal duplications**, extra copies of a chromosomal region are formed, resulting in different copy numbers of genes** within that area of the chromosome.
- If the **duplicated sections are adjacent to the original**, the process is known as **tandem duplication,** whereas if they are **separated by nonduplicated regions**, the duplication is said to be **displaced**.
- Duplications may affect phenotype by **altering gene dosage.**



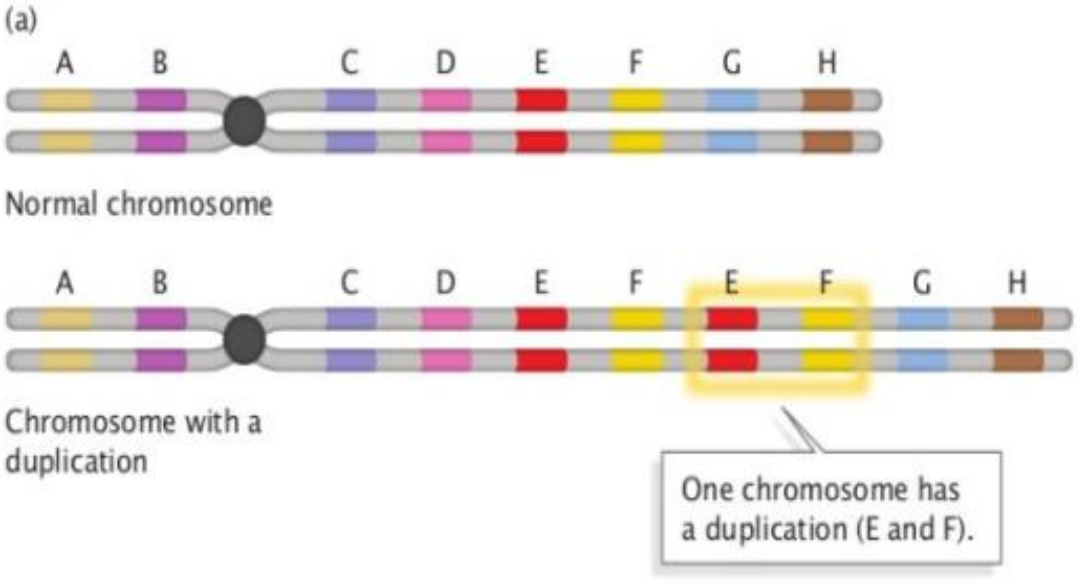


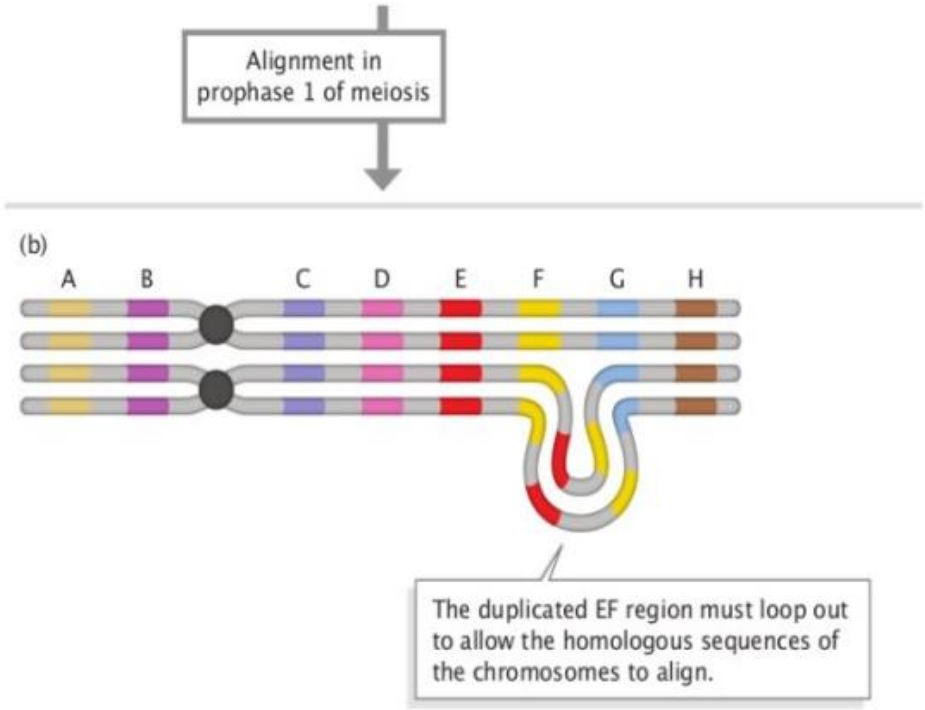
Cat eye syndrome is a rare chromosomal disorder that may be evident at birth.

- Individuals with a normal chromosomal make-up have two 22nd chromosomes, both of which have a short arm, known as 22p, and a long arm, called 22q.
- However, in individuals with cat eye syndrome, **the short arm and a small region of the long arm of chromosome 22 (i.e., 22pter-22q11)** are present three or four times (trisomy or tetrasomy) rather than twice in cells of the body.



The name **"cat eye syndrome"** is derived from a distinctive eye (ocular) abnormality that is present in some affected individuals. This feature consists of partial absence of ocular tissue (coloboma), often affecting both eyes (bilateral). Affected ocular tissues may include the colored region (iris), the middle layer (choroid), and/or the nerve-rich innermost membrane (retina) of the eye.





(a) This normal chromosome has eight genes, designated by letters A through H. A chromosome with a duplicated region has two copies of the E and F genes, for a total of ten genes.

(b) The two extra regions cause a loop to appear when homologous chromosomes align during prophase.

Chromosomal Deletions

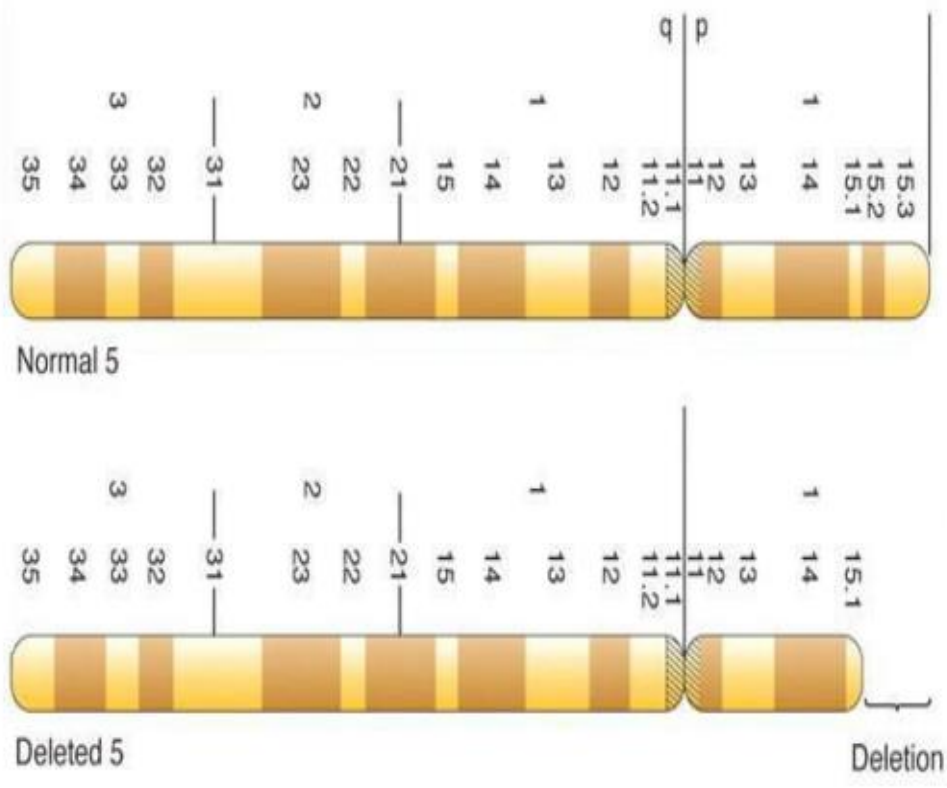
- Deletions involve the loss of DNA sequences. Phenotypic effects of deletions depend on the size and location of deleted sequences on the genome.

- The term "deletion" simply means that a part of a chromosome is missing or "deleted." A very small piece of a chromosome can contain many different genes. When genes are missing, there may be errors in the development of a baby, since some of the "instructions" are missing.

- One example of a genetic syndrome caused by a **deletion is called "Cri du Chat," where part of the #5 chromosome is missing or deleted.**

Cri du Chat or "Cat Cry syndrome" caused by a deletion of **chromosome 5p, which is written "5p-.", (11p and 13p also reported)**

- Babies with Cri du Chat have a **high-pitched cry, poor muscle tone, a small head size, and low birthweight.**
- They also have problems with **language, and may express themselves by using a small number of words or sign language.**
- Other health problems can be present. These include **delays in walking, problems with feeding, hyperactivity, scoliosis, and severe intellectual disability.**
- Most people **with Cri du Chat may have a normal lifespan, unless they are born with other serious organ defects.**
- Educational **intervention at an early age, in addition to physical and language therapy,** is important for children with Cri du Chat to reach their full potential



Deletions and Duplications-cancer

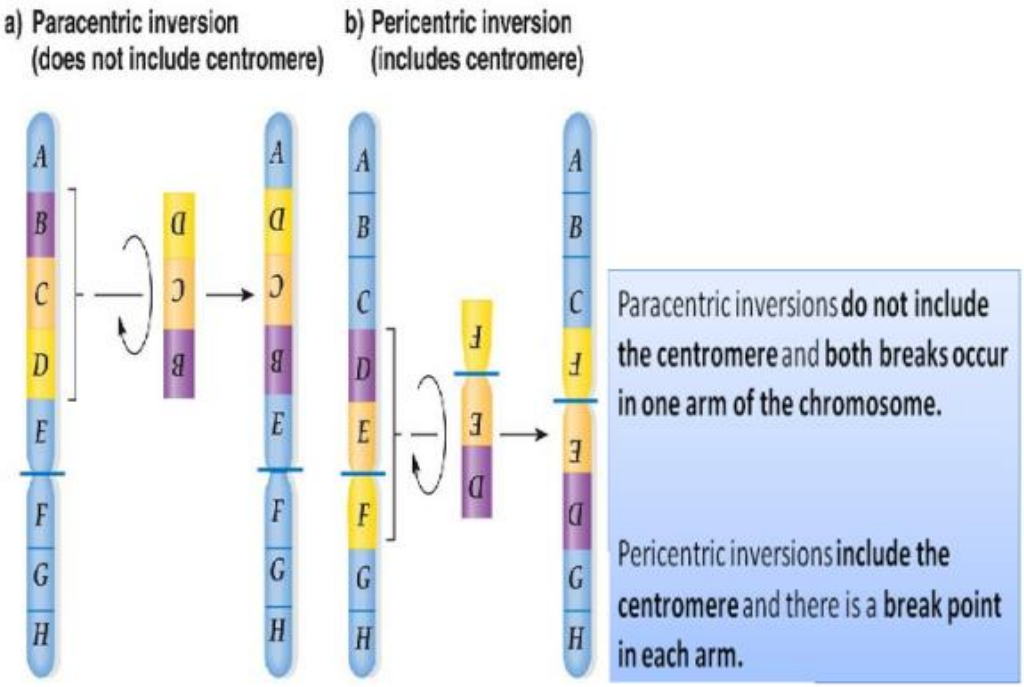
- In cancers such as **Wilms' tumor** and **retinoblastoma, gene deletions or inactivations** are responsible for initiating cancer progression .
- In fact, inactivation of tumor suppressor genes is associated with many types of cancer, as chromosomal regions associated with tumor suppressors are commonly deleted or mutated.
- For example, **deletions, inversions, and translocations are commonly detected in chromosome region 9p21 in gliomas, non-small-cell lung cancers, leukemias, and melanomas** .
- These chromosomal changes inactivate a tumor suppressor **called cyclin-dependent kinase inhibitor 2A.**
- Along with these deletions of specific genes, large portions of chromosomes can also be lost.
- For instance, **chromosomes 1p and 16q are commonly lost in solid tumor cells .**

Gene duplications

- Gene duplications and increases in gene copy numbers can also contribute to cancer and can be detected with transcriptional analysis or copy number variation arrays.
- For example, the chromosomal region 12q13-q14 is strikingly amplified in many sarcomas.
- This chromosomal region encodes a binding protein called MDM2, which is known to bind to a tumor suppressor called p53. When MDM2 is amplified, it prevents p53 from regulating cell growth, which can result in tumor formation.
- Breast cancers are associated with overexpression and increases in copy number of the *ERBB2* gene, which codes for human epidermal growth factor receptor 2.
- Measuring the *ERBB2* copy number can provide a diagnostic tool for breast cancer and other cancers.

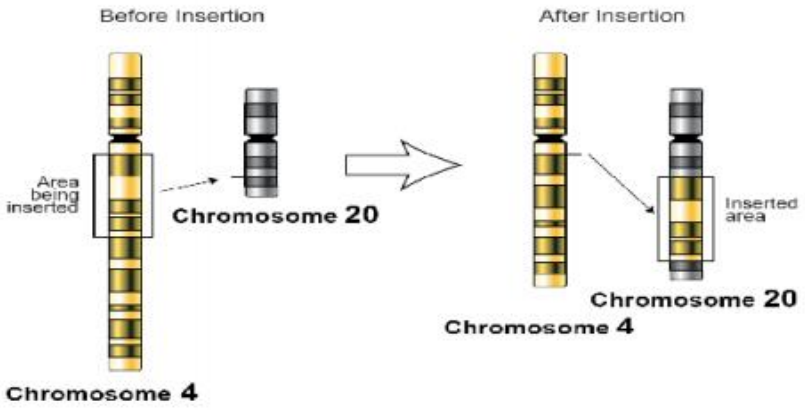
Chromosomal inversion

- Inversions: A portion of the chromosome has broken off, turned upside down, and reattached, therefore the genetic material is inverted.
- An inversion occurs when a single chromosome undergoes breakage and rearrangement within itself. Inversions are of two types: **paracentric** and **pericentric**.



- The most common inversion seen in humans is on chromosome 9, at inv(9)(p12q13).
- This inversion is generally considered to have no harmful effects, but there is some suspicion it could lead to an increased risk for miscarriage or infertility for some affected individuals

Insertions: A portion of one chromosome has been deleted from its normal place and inserted into another chromosome.



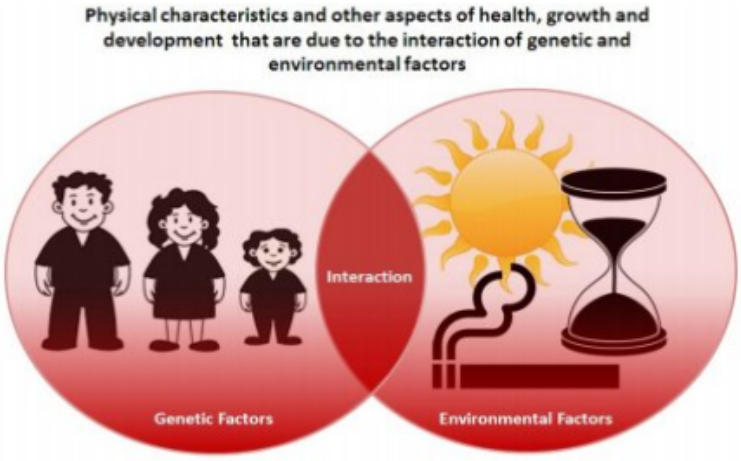
- Rings: A portion of a chromosome has broken off and formed a circle or ring. This can happen with or without loss of genetic material.
- Isochromosome: Formed by the mirror image copy of a chromosome segment including the centromere.

Multifactorial disorders

Disorders with multifactorial inheritance (polygenic)

- Influence of multiple genes + environmental factors
- Relatively frequent
- Diabetes mellitus
- Hypertension
- Gout
- Schizophrenia
- Congenital heart disease - certain forms
- Some types of cancer (ovarian, breast, colon)
- Often familial occurrence - probability of disease is in 1st degree relatives about 5-10%; 2nd degree relatives - 0,5-1%

- ***Multifactorial inheritance*** refers to the pattern of inheritance of certain health problems caused by a **combination of both genetic and other factors.**
- Multifactorial inheritance refers to the pattern of inheritance of certain conditions **due to a combination of both genetic and other factors that may include internal factors such as ageing, and exposure to external environmental factors such as diet, lifestyle, and exposure to chemicals or other toxins.**
- Multifactorial conditions **do not always develop despite the presence of a genetic mutation which increases the person's risk.**
- For example, not all women who have a hereditary breast and ovarian cancer gene mutation will develop breast or ovarian cancer. The mutation alone is not **completely penetrant**.
- The reason for **this incomplete penetrance** of the condition is most likely due to the interaction between the information in the gene mutation with the information in one or more other genes and with other environmental factors.



Examples of Multifactorial Diseases

Birth Defects: cleft palate/lip, neural tube defects such as spina bifida	**Cancer**: bowel, breast, ovarian, bowel, melanoma and prostate
Cardiovascular conditions: high blood pressure, some causes of heart disease, high cholesterol	**Metabolic**: diabetes
Neurological/psychiatric conditions: Alzheimer disease in later life, schizophrenia, bipolar disorder	**Muscular/skeletal**: arthritis, rheumatic disorders, osteoporosis
Skin conditions: psoriasis, moles, eczema	**Respiratory**: asthma, allergies, emphysema

ARE MULTIFACTORIAL GENETIC CONDITIONS PASSED DOWN THROUGH THE FAMILY?

It may be possible to determine if you or other members of your family are at risk for developing a particular multifactorial condition by documenting your family health history in detail.

Some of the clues that there may be a multifactorial genetic condition in your family include you and/or one or more blood relatives who have been affected by a condition, particularly at a younger than expected age.

Documenting the health history of family members (blood relatives) over several generations is important in determining if a condition is running in the family. Ask about the family history of on both your mother's and father's side of the family.

It is important to note:

· How the individual is related to you
· The type condition they have or had
· The age of the individual when they were first diagnosed with the condition.

Pattern of Inheritance-Genetic Disorders

Modes of Inheritance-genetic disorder

- ❑ Inheritance patterns describe how a disease is transmitted in families.
- ❑ These patterns help to predict the recurrence risk for relatives.
- ❑ In general, inheritance patterns for single gene disorders are classified based on whether they are autosomal or X-linked and whether they have a dominant or

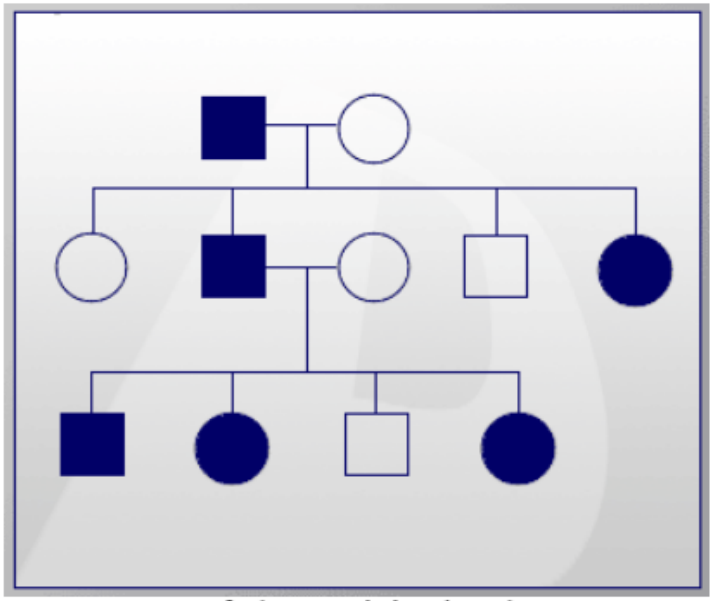
recessive pattern of inheritance. These disorders are called ***Mendelian disorders***, after the geneticist Gregor Mendel.

Autosomal Dominant Inheritance

- ✓ In **autosomal dominant inheritance**, **only one copy of a disease allele** is **necessary for an individual to be susceptible to expressing the phenotype.**
- ✓ With each pregnancy, **there is a one in two (50%) chance the offspring will inherit the disease allele.**
- ✓ Unless a new mutation has occurred, all affected individuals will have at least one parent who carries the disease allele.
- ✓ Autosomal dominant inheritance is often **called vertical inheritance** because of the transmission from parent to offspring.
- ✓ Across a population, **the proportion of affected males should be equal to the proportion of affected females**.
- ✓ **Male-to-male transmission can be observed.**

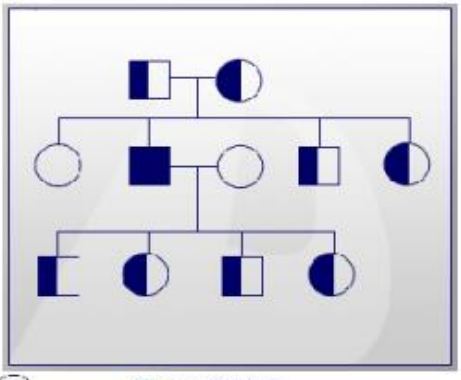
Examples :**Myotonic muscular dystrophy**

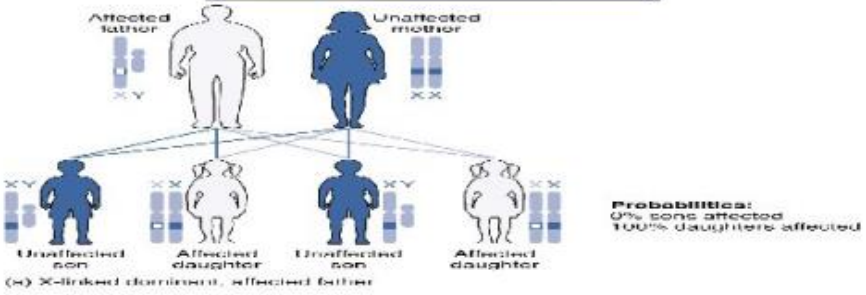
Huntington disease.

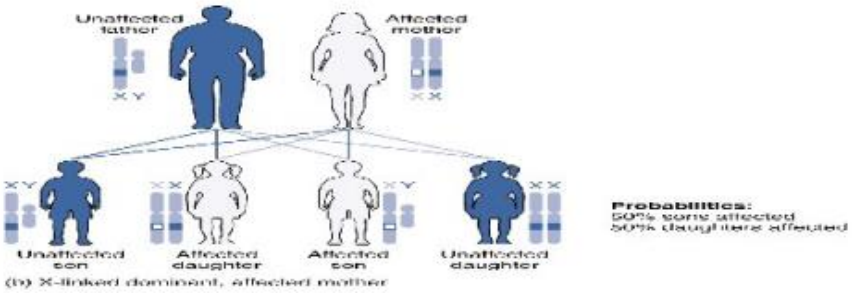


Autosomal Recessive Inheritance

- ✓ In autosomal recessive inheritance, **two copies of a disease allele** are required for an individual to be susceptible to expressing the phenotype.
- ✓ Typically, **the parents of an affected individual are not affected but are gene carriers.**
- ✓ With each pregnancy of carrier parents:
  - ✓ There is a one in four (25%) chance the offspring will inherit two copies of the disease allele and will therefore have the phenotype.
  - ✓ There is a one in two (50%) chance the offspring will inherit one copy of the disease allele and will be a carrier.
  - ✓ **There is a one in four (25%) chance the offspring will inherit no copies of the disease allele and will not express the phenotype or be a carrier. This individual would not be at risk for passing the disorder on to his/her offspring.**
- ✓ As with autosomal dominant inheritance, **the proportion of affected males should be equal to the proportion of affected females in a given population**.
- ✓ **Examples : sickle cell anemia**
  cystic fibrosis.







Examples

HYPOPHOSPHATEMIC RICKETS:

Dominant mutations in the phosphate-regulating endopeptidase gene (*PHEX*), which resides on the X chromosome, are associated with x-linked dominant .

RETTSYNDROME:

A neurodevelopmental disease, is associated with dominant mutations in the methyl-cpg-binding protein 2 gene (*MECP2*).

Rett syndrome almost exclusively affects females, because male embryos with a dominant mutation in the *MECP2* gene rarely survive.

Oral-Facial-Digital syndrome type I

- **A disorder characterized by oral, facial, digital, brain, and kidney manifestations.**
- **The clinical features include oral (lobed tongue, cleft palate, hypodontia and other dental abnormalities), facial (hypertelorism, hypoplasia of alae nasi, cleft lip, micrognathia), digital (brachydactyly, syndactyly, clinodactyly, duplicated hallux, polydactyly), brain (atrophy, agenesis of corpus callosum, Dandy-Walker malformation), and kidney (polycystic kidney disease) manifestations.**
- **Affected males are usually miscarried.**
- **The incidence of OFDI is approximately 1 in 50,000.**
- **The disorder is X-linked dominant. The gene is called OFD1 and is located at Xp22.3-p22.2.**
- **Approximately 75% of cases are sporadic and males are usually miscarried.**
- **Therefore, when the mother is affected, 1/3 of the female offspring will be unaffected, 1/3 of females will be affected, and 1/3 of males will be unaffected.**
- **When the mother of an affected child does not carry the gene mutation, there is a 1% chance female offspring will be affected due to either a second new mutation or germline mosaicism.**

X-Linked Recessive Inheritance

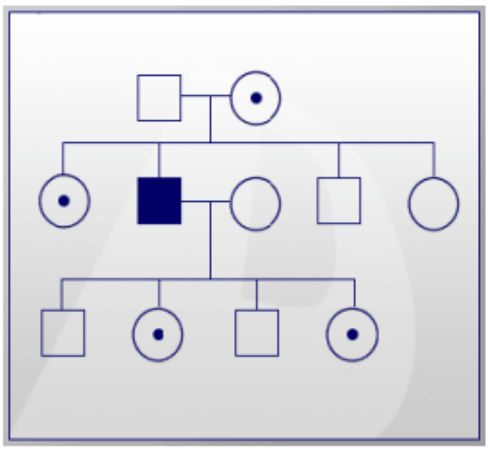
- As in autosomal recessive inheritance, **two copies of a disease allele on the X chromosome** are required for an individual **with two X chromosomes (a female) to be affected with an X-linked recessive disease.**

- Since males are ***hemizygous* for X-linked genes** (they have only one X chromosome), any **male with one copy of an X-linked recessive disease allele is affected**.
- Females are **usually carriers** because they only **have one copy of the disease allele**. **Affected males are related through carrier females.**
- For a **carrier female, with each pregnancy there is a one in two (50%) chance her sons will inherit the disease allele and a one in two (50%) chance her daughters will be carriers.**
- **Affected males transmit the disease allele to all of their daughters, who are then carriers, but to none of their sons**.
- **Women are affected** when they have two copies of the disease allele. **All of their sons will be affected, and all of their daughters will be unaffected carriers.**
- Examples :Duchenne muscular dystrophy,

  hemophilia A

  hypohidrotic or anhidrotic ectodermal

  dysplasia.



Examples

- Males who have a mutant copy of **the factor VIII gene (*F8*)** will always have hemophilia.
- In contrast, women are rarely affected by this disease, although they are most often carries of the mutated gene.
- Duchenne muscular dystrophy is another example of a single-gene disease that exhibits an X chromosome-linked recessive inheritance pattern. This condition is associated with **mutations in the dystrophin gene (*DMD*).**

Hypohidrotic or anhidrotic ectodermal dysplasia

This condition is characterized by three cardinal features that become apparent in childhood: hypotrichosis (sparse or brittle hair), hypohidrosis (reduced ability to sweat and problems with heat regulation), and hypodontia (missing teeth, conical teeth).

Other clinical features include facial dysmorphism (including saddle nose), occasional mental retardation, increased susceptibility to infection, and raspy voice.

Hypohidrotic ectodermal dysplasia occurs in approximately 1 in 17,000 newborns.

There are **three clinically similar forms with different genetic causes:**

1. X-linked recessive (most common), caused by mutations in the **ED1 gene at Xq12-q13.1.**
2. The **molecular abnormality is in the protein ectodysplasin**, which is important in the development of hair, teeth, and sweat glands.
3. Autosomal dominant and autosomal recessive forms caused by mutations in **the EDAR at 2q11-q13 and EDARADD at 1q42.2-q43 genes.**

- ✓ Females who **are carriers for the X-linked** form may **have partial expression, such as missing teeth and inability to sweat in parts of body.**

Y Chromosome–Linked Single-Gene Disease

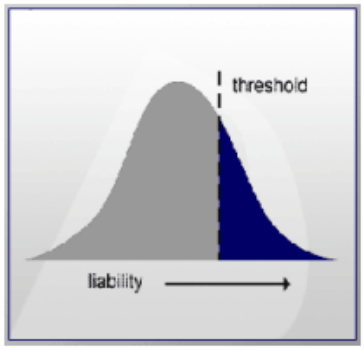
- ❑ Y chromosome-linked diseases are also extremely rare. Because **only males have a Y chromosome and they always receive their Y chromosome from their father, Y-linked single-gene diseases are always passed on from affected fathers to their sons**. It **makes no difference whether the Y chromosome-linked mutation is dominant or recessive**, because **only one copy of the mutated gene is ever present; thus, the disease-associated phenotype always shows.**
- ❑ Example :**Nonobstructive spermatogenic failure**, a condition that leads to infertility problems in males.

This disorder is associated with mutations in **the ubiquitin-specific protease 9Y gene (*USP9Y*)** on the Y chromosome.

Complex Inheritance

- ➢ Complex disorders (**once known as multifactorial disorders**) are caused by the **interactions of variations in multiple genes and environmental factors**.

- The genes involved **may make a person susceptible to the disorder, and the environmental factors may trigger this susceptibility.**
- The **liability to exhibit the phenotype of the complex disorder is determined by both genetic and environmental factors**.
- Only individuals with enough genetic liability (multiple genes) who are in the presence of certain environmental factors will exhibit the phenotype. **The threshold is the point at which these factors combine sufficiently for the individuals to exhibit the phenotype.**
- Complex disorders are often common disorders in the population and **include heart disease, diabetes, asthma, and many birth defects, such as cleft lip +/- cleft palate.**



Cleft Lip +/- Cleft Palate

- **Cleft lip with or without cleft palate** (CL/P) occurs **when the frontal maxillary process fails to fuse at 35 days gestation.** Cleft lip can **be unilateral or bilateral.**
- The clinical features differ depending on the cause of the CL/P, with some cases being syndromic. In isolated cases, bilateral cleft lip is more severe than unilateral cleft lip.
- CL/P is relatively common, with an incidence of 1-2 per 1,000 births. There is a male to female ratio of 3:2. The rates differ in different ethnic backgrounds, with CL/P occurring 1/1000 Caucasians, 1.7/1000 Japanese, 0.4/1000 American Blacks.
- CL/P is very heterogenous. **Approximately 75-80% cases are sporadic**. Syndromic cases may be monogenic, due to a chromosome abnormality (trisomy 13), or environmental factors (maternal rubella). Other cases are familial.
- **All inheritance patterns have been described and depend on the specific cause. However, the majority of cases are of complex inheritance, resulting from multiple genes and environmental factors.**

- Recently, a gene for van der Woude syndrome (VWS), which includes lip pits and CL/P, was identified; the **gene is the interferon regulatory factor 6** (IRF6). **VWS is the most common clefting syndrome**.
- The recurrence risks for CL/P caused by complex inheritance are higher in families with more than one affected and in cases with a more severe presentation (bilateral vs. unilateral, isolated cleft lip vs. cleft lip and cleft palate. For example, the risk to sibs are shown below:

➢ Genetic testing for the nonsyndromic cases is only available under a research basis. With improved technology, CL/P can sometimes be visualized on ultrasound. Clinical and/or research testing is available for some of the clefting syndromes.

Autosomal and Sex-linked Inheritance Patterns

Inheritance Patter	Description	Example
Autosomal Dominant	Only one mutated allele is needed for a person to be affected by anautosomal dominant disorder. Each affected person usually has one affected parent. There is a 50% chance that a child will inherit the mutated gene.	Huntingtons disease, Achondroplasia, Neurofibromatosis 1, Marfan Syndrome, Hereditary nonpolyposis colorectal cancer
Autosomal Recessive	Both copies of the gene must be mutated for a person to be affected by anautosomal 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).	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.	

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. 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. A woman who carries an Xlinked 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.	Hemophilia A, Duchenne muscular dystrophy, Color blindness
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. Y-linked disorders only cause infertility, and may be circumvented with the help of some fertility treatments.	Male Infertility