Genetic Disorders

A **genetic disorder** is a health problem caused by one or more abnormalities in the genome.

It can occur due to **Mutations** which are defined as a permanent change in the DNA

- Origin
  - germ cells – transmitted to progeny
  - somatic cells – cancer and some congenital malformations
- Types of mutation
  - Chromosomal mutation – structural changes within the chromosome – translocations, deletions, etc
  - Genome mutation – loss or gain of whole chromosomes: monosomy and trisomy
  - Gene mutation – alterations at the level of the gene

The mutation can occur –

- spontaneously before embryonic development (a *de novo* mutation)
- Inherited from two parents who are carriers of a faulty gene (autosomal recessive) or from a parent with the disorder (autosomal dominant).
- through X chromosome
- Few disorders on the Y chromosome or mitochondrial DNA.

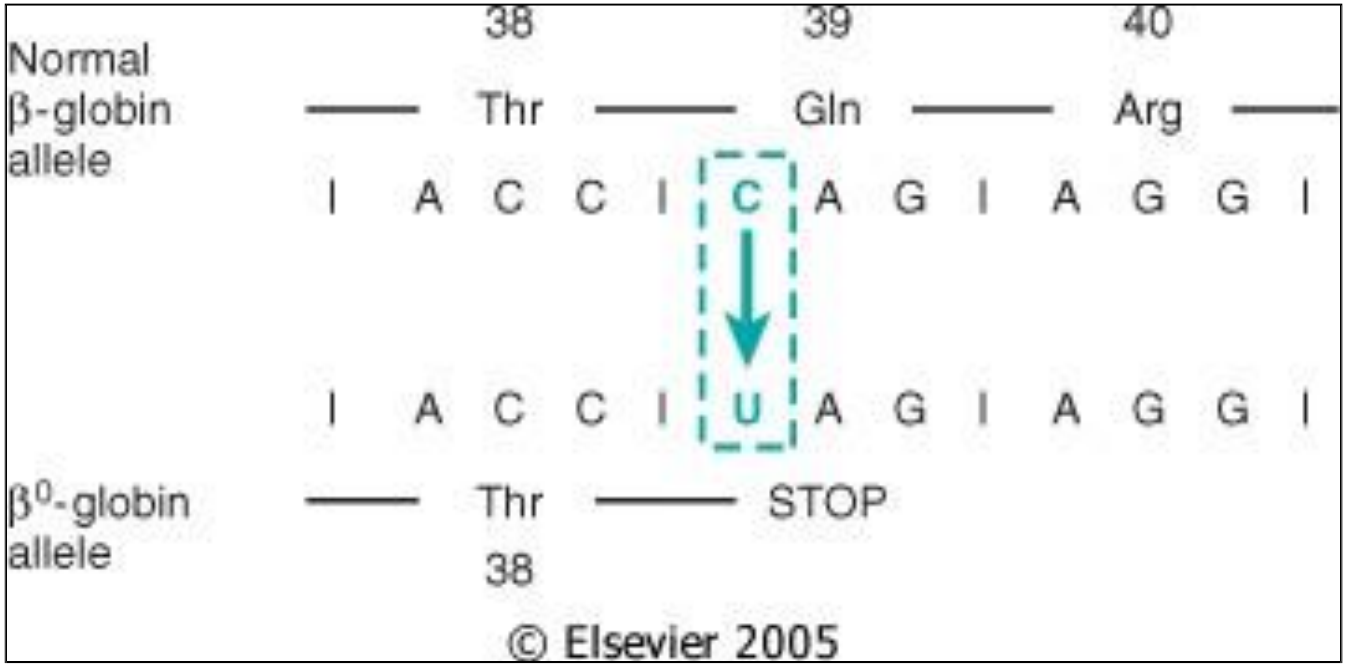
Types of Mutations

1. Point Mutations
2. Deletions
3. Insertions

Point mutation

- Result from substitution of a single base in the DNA
- **Coding portion of gene**
  - **Missense-** result in substitution of one amino acid for another in the coded protein
    - conservative – function not affected
    - nonconservative – function altered
  - **Nonsense**
    - stop codon – results in truncated protein
- **Noncoding portion of gene**
  - promoter and enhancer regions
  - posttranslational processing – defective splicing

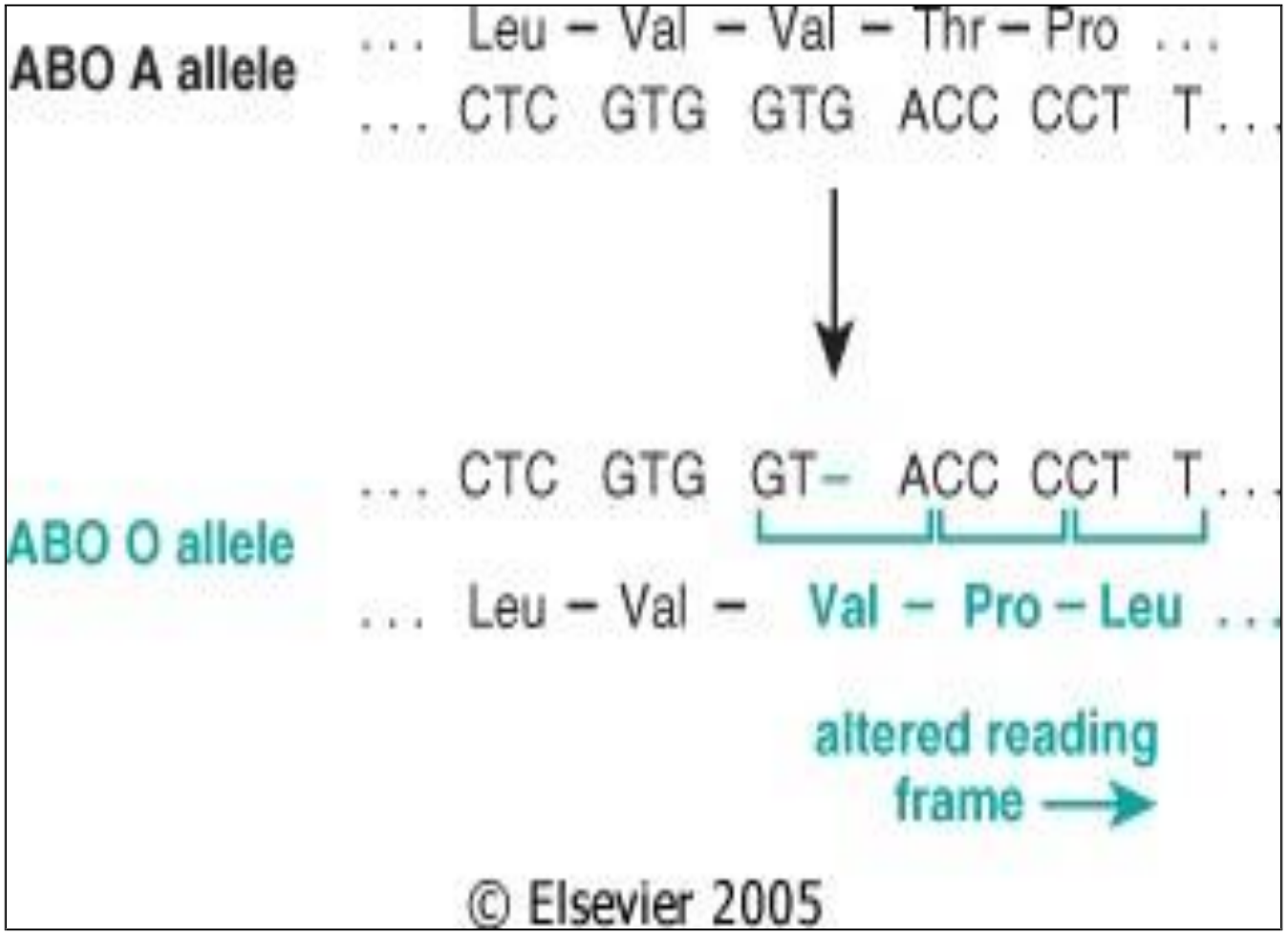
β^0 Thalassemia: Point Mutation Leading To Premature Chain Termination



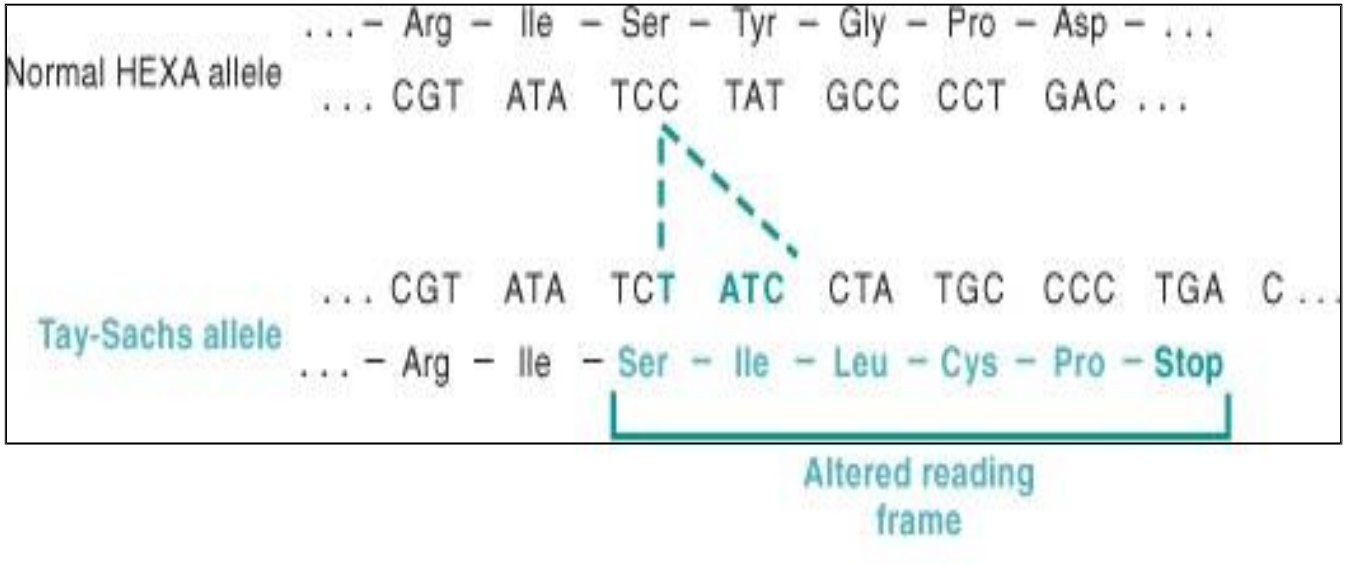
Deletions and Insertions

- Deletion of single or multiple of 3 bases
- Frameshift mutation
  - genetic code is altered distal to the mutation
  - usually leads to stop codon

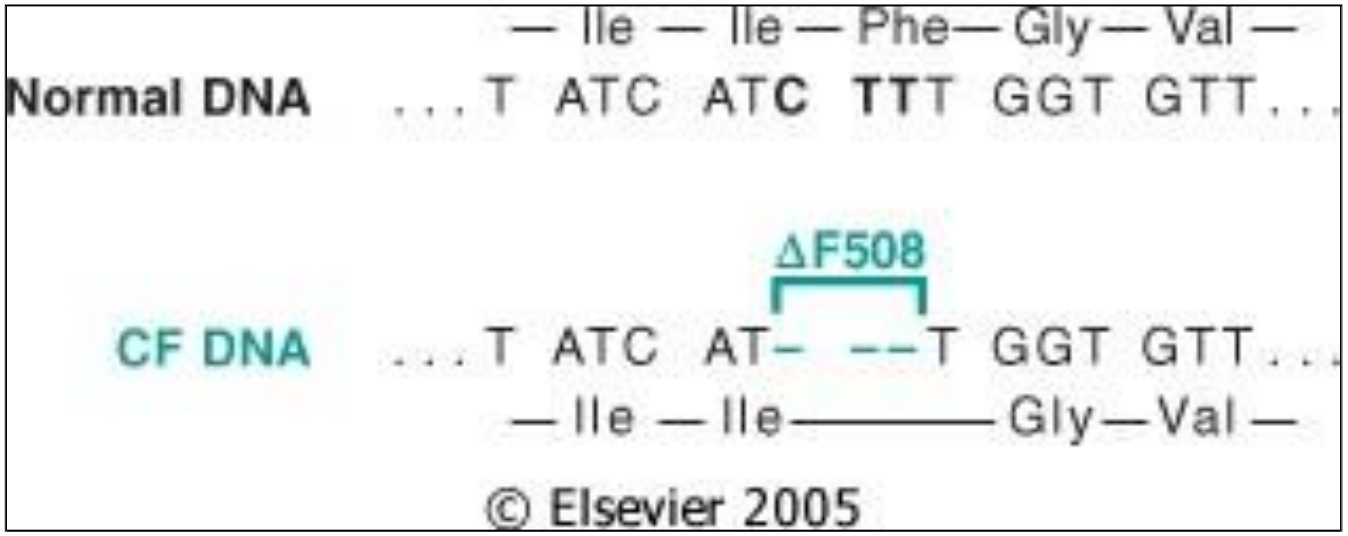
Blood Group O: Single-base deletion at the ABO locus



Tay-Sachs Disease: Four-base Insertion In The Hexosaminidase A Gene



Three-base Deletion In The Common Cystic Fibrosis (CF) Allele



Classification of genetic disorders

1. Single-gene disorders, where a mutation affects one gene for eg. Sickle cell anemia

2. Chromosomal disorders- where chromosomes (or parts of chromosomes) are missing or changed. Down syndrome is a chromosomal disorder.

3. Complex disorders or multifactorial disorders- where there are mutations in two or more genes. Often our lifestyle and environment play a role. Colon cancer is an example.

Single gene disorders

Single gene inheritance is also called Mendelian or monogenetic inheritance. Changes or mutations that occur in the DNA sequence of a single gene cause this type of inheritance. There are thousands of known single-gene disorders. These disorders are known as monogenetic disorders (disorders of a single gene).

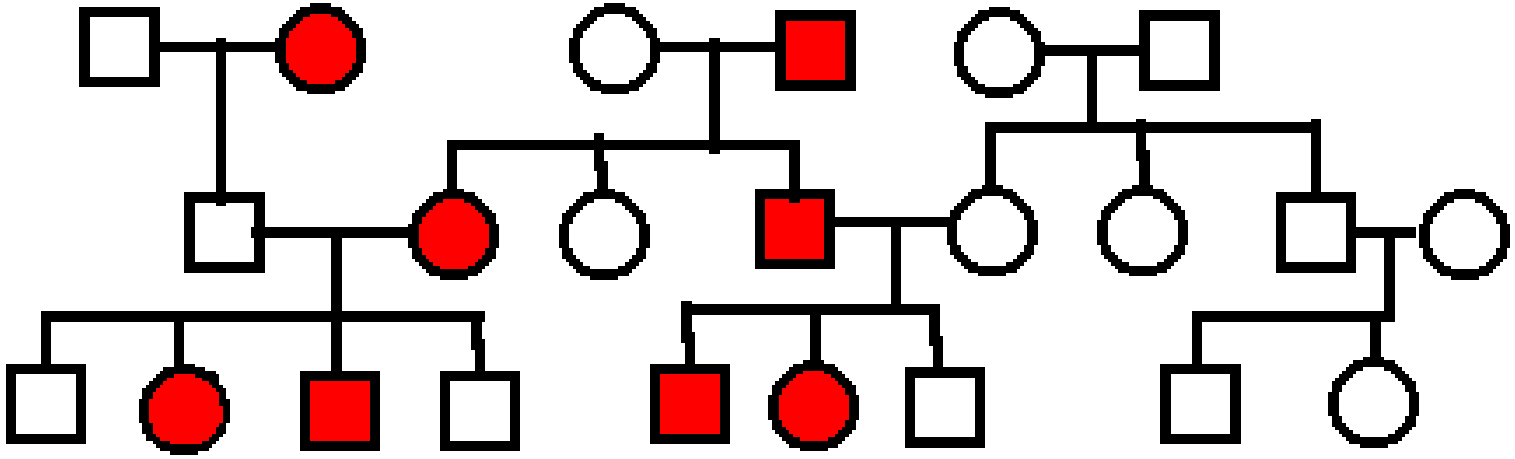
Single-gene disorders have different patterns of genetic inheritance, including

- **autosomal dominant** inheritance, in which only one copy of a defective gene (from either parent) is necessary to cause the condition;
- **autosomal recessive** inheritance, in which two copies of a defective gene (one from each parent) are necessary to cause the condition; and
- **X-linked inheritance**, in which the defective gene is present on the female, or X-chromosome. X-linked inheritance may be dominant or recessive.

Autosomal Dominant

- Disease occurs when only one allele at given gene locus is present
- Penetrance
  - proportion of patients who have the gene who express the trait (expressed as %)
- Expressivity
  - degree to which trait is expressed- e.g neurofibromatosis cases

AUTOSOMAL DOMINANT PEDIGREE



AUTOSOMAL DOMINANT

S.No.	Disease	Pathogenesis	Pathology, Cardinal Symptoms
1.	**POLYCYSTIC KIDNEY**		Numerous, disparate, heterogenous renal cysts occurring bilaterally. Onset in adult life. Associated with liver cysts.
2.	**Von Hippel-Lindau Syndrome**	Short arm of chromosome 3. Same genetic region is associated with incidence of **renal cell carcinoma**.	Hemangioblastomas of cerebellum, medulla, or retina, adenomas, cysts in visceral organs. High risk for renal cell carcinoma.
3	**FAMILIAL HYPERCHOLESTEROLEMIA**	**LDL-Receptor** defect	Heterozygous: accelerated atherosclerosis. Homozygous: accelerated atherosclerosis, MI by age 35, **xanthomas**.
4	**HUNTINGTON DISEASE**	Genetic defect on Chrom 4 ------> atrophy of caudate nuclei, putamen, frontal cortex.	Progressive dementia with onset in adulthood, choreiform movements, athetosis.
5	**HEREDITARY SPHEROCYTOSIS**	**Band-3** deficiency in RBC membrane ------> spherical shape to cells. Other RBC structural enzyme deficiencies can cause it, too.	Sequestration of spherocytes in spleen ------> hemolytic anemia.
6	**MARFAN SYNDROME**	**Fibrillin** deficiency ------> faulty scaffolding in connective tissue (elastin has no anchor).	Arachnodactyly, dissecting aortic aneurysms, **ectopia lentis** (subluxation of lens), mitral valve prolapse.
7	**NEUROFIBROMATOSIS**	**NF1 gene** defect (no GTPase protein) ------> dysregulation of *Ras* tumor-suppressor protein.	Multiple neurofibromas (Café au Lait spots) which may become malignant, **Lisch nodules** (pigmented hamartomas of the iris).Increased risk for tumors: pheochromocytoma, Wilms tumor, Rhabdomyosarcoma, leukemias.
8	**TUBEROUS SCLEROSIS**		**Tubers** (glial nodules), seizures, mental retardation. Associated with adenoma sebaceum (facial lesion), myocardial rhabdomyomas, **renal angiomyolipomas**.
9	**Von Willebrand Disease**	Defect in initial formation of platelet plugs, and shorter half-life of Factor VIII in blood.	Hemorrhage, similar to hemophilia.**Type-I**: Most mild. **Type-II**: Intermediate. **Type-III**: most severe, with recessive inheritance (complete absence).
10.	**Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)**		**Telangiectasias** of skin and mucous membranes.

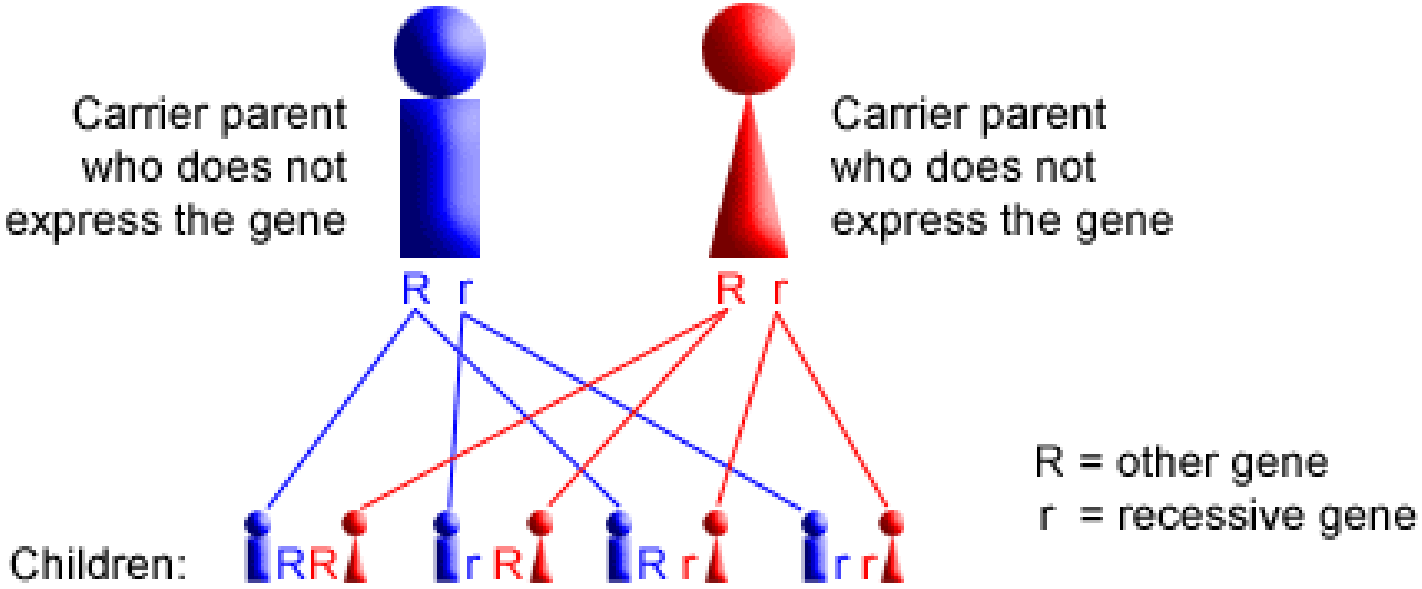
Autosomal Recessive

- Disease occurs only when both alleles at given gene locus are present
- Parents are usually normal
- Nearly all inborn errors of metabolism are recessive

Features of Autosomal Recessive Disorders

- Expression of the disorder more uniform than with dominant diseases
- Complete penetrance is common
- Onset is frequently early in life
- New mutations may occur but are rarely detected

Autosomal Recessive Inheritance pattern



Children with the disease = r r
(one in four, or 25%)

Children who are carriers of the gene like their parents = r R R r
(two in four, or 50%)

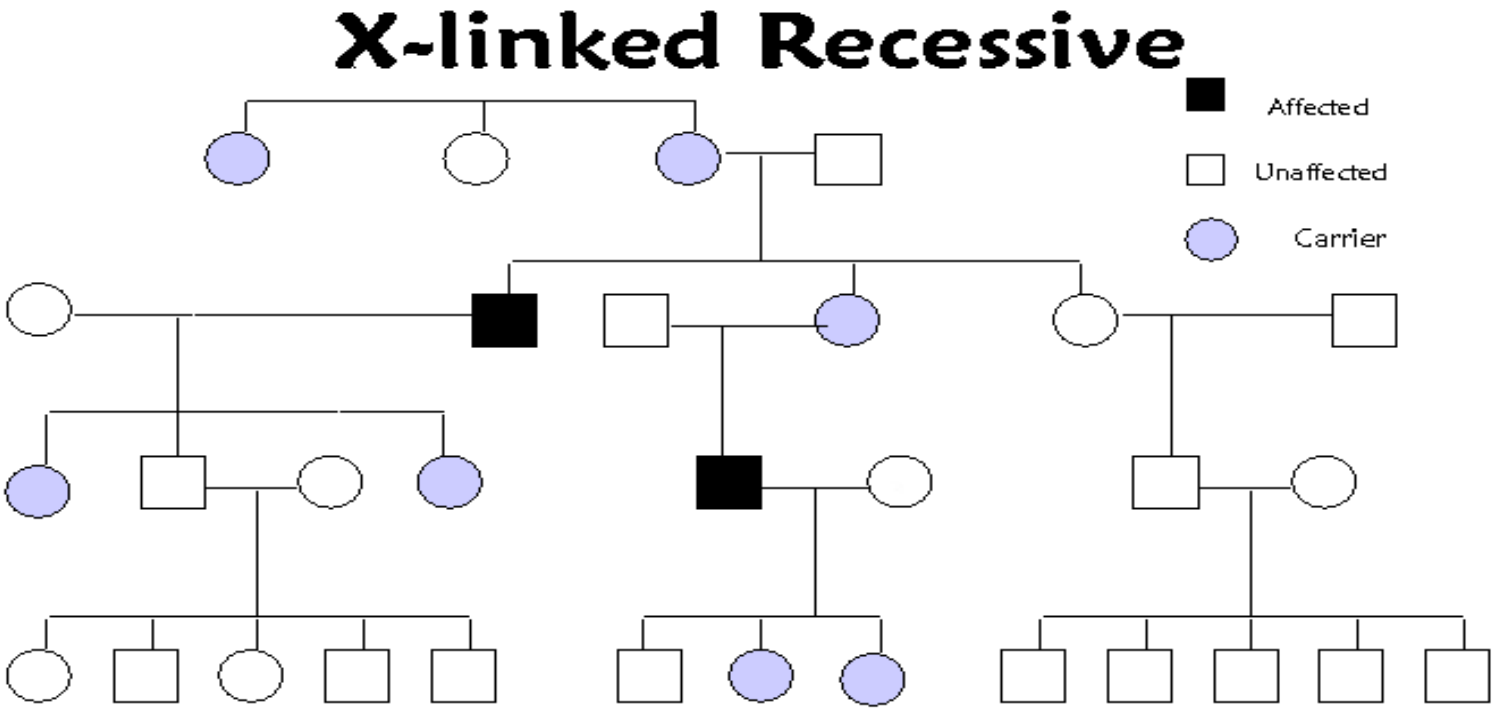
Children who do not get the gene from either parent = RR
(one in four, or 25%)

AUTOSOMAL RECESSIVE DISEASES

S.No.	Disease	Pathogenesis	Pathology, Cardinal Symptoms
1.	**Cystic Fibrosis**	**CFTR gene** defect on Chrom 7 ------> No Cl^- transport and failure to hydrate mucous secretions (no NaCl transport) ------> excessively viscous mucoid exocrine secretions	Meconium ileus (caused by thick, mucoid meconium), respiratory bronchiectasis, *Pseudomonas* pneumonia, pancreatic insufficiency, hypertonic (high Cl^- concentration) sweat..
2.	**Fanconi Anemia**	**congenital pancytopenia**	Short stature, microcephaly, hypogenitalism, strabismus, anomalies of the thumbs, radii, and kidneys, mental retardation, and microphthalmia.
3	**Hartnup's Disease**	Defect in GI uptake of neutral amino acids ------> malabsorption of **tryptophan** (niacin precursor) ------> **niacin deficiency** among other things.	**Pellagra**-like syndrome (diarrhea, dementia, dermatitis), light-sensitive skin rash, temporary cerebellar ataxia..
4	**Kartagener's Syndrome**	Genetic defect on Chrom 4 ------> atrophy of caudate nuclei, putamen, frontal cortex.	**Recurrent sinopulmonary infections** (due to impaired ciliary tract). ***Situs inversus***, due to impaired ciliary motion during embryogenesis: lateral transposition of lungs, abdominal and thoracic viscera are on opposite sides of the body as normal. Possible dextrocardia, male sterility.
5	**Pyruvate Dehydrogenase Deficiency**	**Pyruvate Dehydrogenase** deficiency ------> buildup of lactate and pyruvate ------> **lactic acidosis.**	Neurologic defects.
6	**Xeroderma Pigmentosum**	Defect in DNA repair, inability to repair **thymine dimers** resulting from **UV-light** exposure ------> excessive skin damage and skin cancer.	Dry skin, melanomas, pre-malignant lesions, other cancers. Ophthalmic and neurologic abnormalities..
7	**Congenital Fructose Intolerance**	**Aldolase B** deficiency ------> buildup of **Fructose-1-Phosphate** in tissues ------> inhibit glycogenolysis and gluconeogenesis.	Severe **hypoglycemia**
8	**Galactosemia**	Inability to convert galactose to glucose ------> accumulation of galactose in many tissues	Failure to thrive, infantile cataracts, mental retardation. Progressive hepatic failure, **cirrhosis**, death..
9	**Severe Combined Immunodeficiency (SCID)**	**Adenosine Deaminase** deficiency ------> accumulation of **dATP** ------> inhibit ribonucleotide reductase ------> decrease in DNA precursors	Severe deficiency in both humoral and cellular immunity, due to impaired DNA synthesis. Bone marrow transplant may be helpful in treatment.
10.	**Gaucher's Disease**	**Glucocerebrosidase** deficiency ------> accumulation of glucocerebrosides (gangliosides, sphingolipids) in lysosomes throughout the body.	• **Type-I**: Adult form. 80% of cases, retain partial activity. Hepatosplenomegaly, erosion of femoral head, mild anemia. Normal lifespan with treatment. • **Type-II**: Infantile form. Severe CNS involvement. Death before age 1. • **Type-III**: Juvenile form. Onset in early childhood, involving both CNS and viscera, but less severe than Type II.
11	**Niemann-Pick Lipidosis**	**Sphingomyelinase** deficiency ------> accumulation of sphingomyelin in phagocytes.	•Sphingomyelin-containing **foamy histiocytes** in reticuloendo-thelial system and spleen. Hepatosplenomegaly, anemia, fever, sometimes CNS deterioration. Death by age 3
12	**Tay-Sachs Disease**	**Hexosaminidase A** deficiency ------> accumulation of G_{M2} ganglioside in neurons.	•CNS degeneration, retardation, **cherry red-spot** of macula, blindness (amaurosis). Death before age 4.
13	**Alkaptonuria**	**Homogentisic Oxidase** deficiency (inability to metabolize Phe and Tyr) ------> buildup and urinary excretion of **homogentisic acid**.	•Urine turns dark and black on standing, **ochronosis** (dark pigmentation of fibrous and cartilage tissues), ochronotic arthritis, cardiac valve involvement. Disease is generally *benign*.
14	**Albinism**	**Tyrosinase** deficiency ------> inability to synthesize melanin from tyrosine. Can result from a lack of migration of neural crest cells.	•Depigmentation, pink eyes, increased risk of skin cancer.

X-Linked Disorders

- Nearly all X-linked disorders are recessive
- Dominant and recessive apply only to the female – males are hemizygous
- Absence of father-son transmission
- All daughters of affected male are obligate carriers



X linked disorders

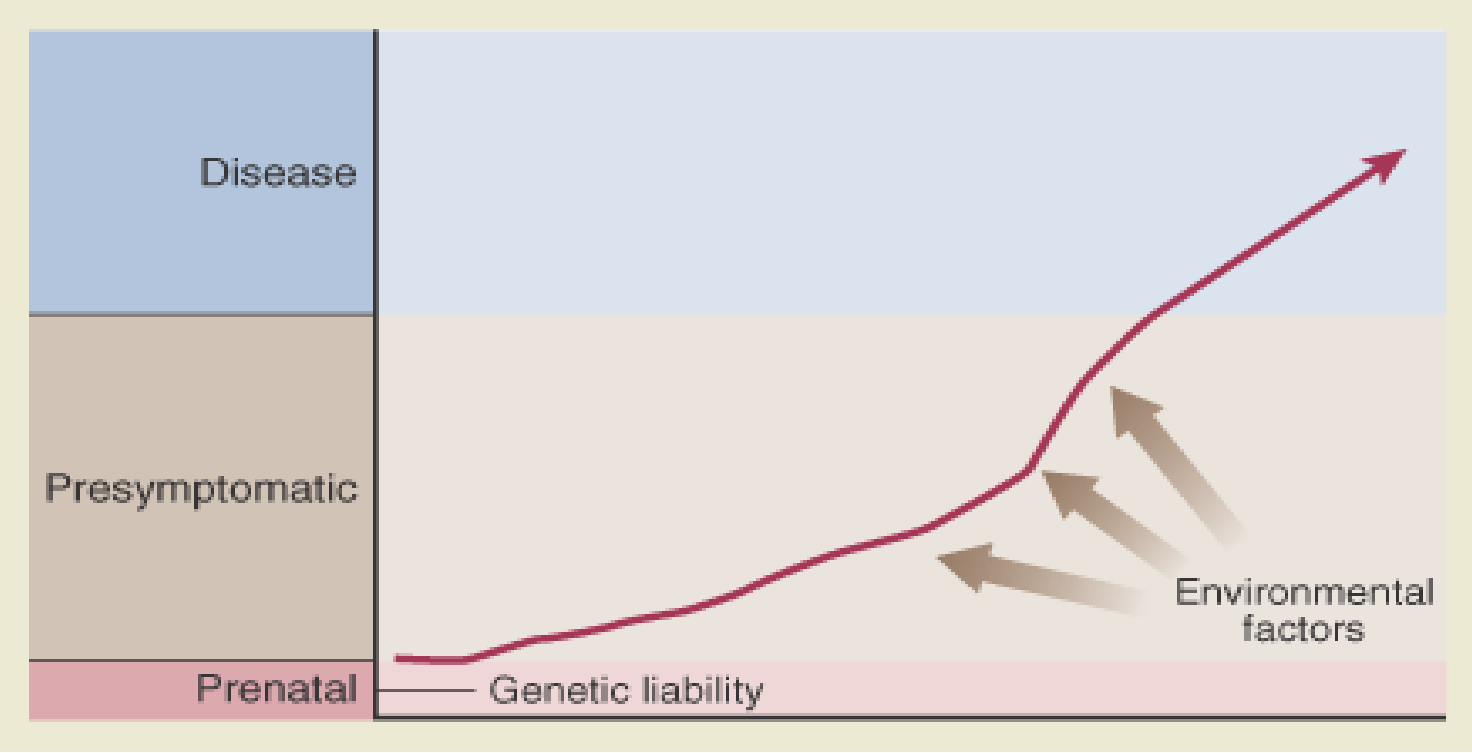
S.No.	Disease	Pathogenesis	Pathology, Cardinal Symptoms
1.	**Fragile-X Syndrome**	Progressively longer **tandem repeats** on the long arm of the X-chromosome. The longer the number of repeats, the worse the syndrome. Tandem repeats tend to accumulate through generations.	Second most common cause of **mental retardation** next to Down Syndrome. Macro-orchidism (enlarged testes) in males.
2.	**Klinefelter's Syndrome (XXY)**	SNon-disjunction of the sex chromosome during Anaphase I of meiosis ------> **Trisomy (47,XXY)**.	Hypogonadism, tall stature, gynecomastia. Mild mental retardation. Usually not diagnosed until after puberty. One Barr body seen on buccal smear..
3	**Turner's Syndrome (XO)**	Non-disjunction of the sex chromosome during Anaphase I of meiosis ------> **Monosomy (45,X)**	Streak gonads, primary amenorrhea, webbed neck, short stature, **coarctation of Aorta**, infantile genitalia. *No mental retardation.* No Barr bodies visible on buccal smear..
4	**XXX Syndrome**	**Trisomy (47,XXX)** and other multiple X-chromosome abnormalities.	Usually phenotypically normal. May see menstrual abnormalities or mild mental retardation in some cases..
5	**Hemophilia A (Factor VIII Deficiency)**	X-Linked Recessive. **Factor VIII** deficiency	Hemorrhage, hematuria, hemarthroses. Prolonged PTT.
6	**Hemophilia B (Factor IX Deficiency)**	X-Linked Recessive. **Factor IX** deficiency.	Milder than Hemophilia A. Hemorrhage, hematuria, hemarthroses. Prolonged PTT..
7	**Chronic Granulomatous Disease**	X-Linked (usually) **NADPH Oxidase** deficiency ------> no formation of peroxides and superoxides ------> no oxidative burst in phagocytes.	Failure of phagocytes leads to susceptibility to infections, especially *Staph Aureus* and *Aspergillus* spp. B and T cells usually remain normal.
8	**X-Linked Agammaglobulinemia (Bruton's Disease)**	Mutation in gene coding for **tyrosine kinase** causes failure of Pre-B cells to differentiate into B-Cells.	Recurrent pyogenic infections after 6 months (when maternal antibodies wear off). Can treat with polyspecific gamma globulin preparations..
9	**Fabry's Disease**	**Alpha-Galactosidase A** deficiency ------> buildup of **ceramide trihexoside** in body tissues.	**Angiokeratomas** (skin lesions) over lower trunk, fever, severe burning pain in extremities, cardiovascular and cerebrovascular involvement.
10.	**Hunter's Syndrome**	**L-iduronosulfate sulfatase** deficiency ------> buildup of **mucopolysaccharides** (heparan sulfate and dermatan sulfate)	Hepatosplenomegaly, micrognathia, retinal degeneration, joint stiffness, mild retardation, cardiac lesions.

MULTIFACTORIAL INHERITANCE

- Multi-"FACTORIAL", not just multi-GENIC "SOIL" theory
- Common phenotypic expressions governed by "multifactorial" inheritance
  - Hair color
  - Eye color
  - Skin color
  - Height
  - Intelligence
  - Diabetes, type II

Features of Multifactorial Inheritance

- Expression determined by NUMBER of genes
- Overall 5% chance of 1st degree relatives having it
- Identical twins >>>5%, but WAY less than 100%



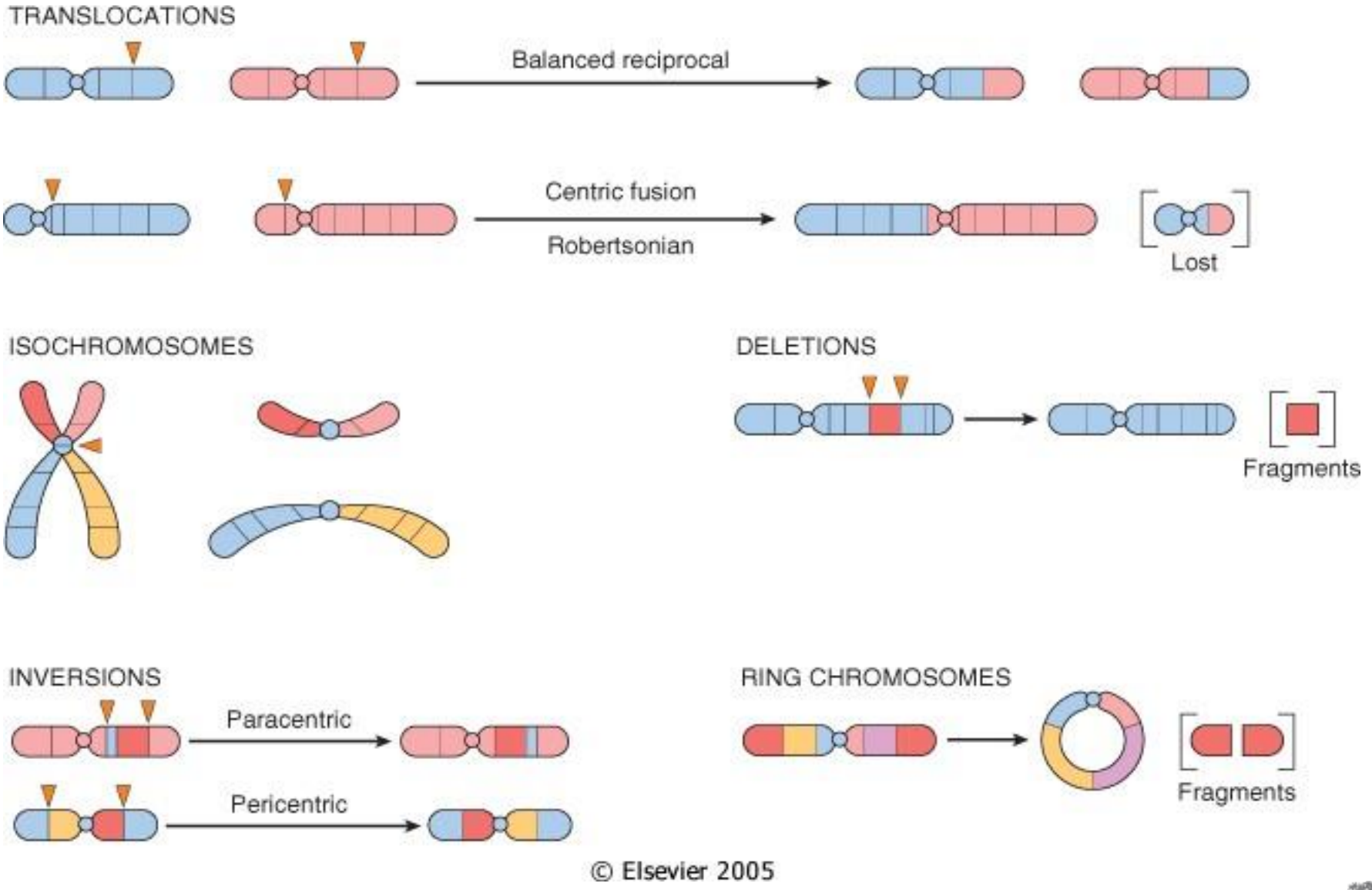
MULTIFACTORIAL DISORDERS

- Cleft lip, palate
- Congenital heart disease
- Coronary heart disease
- Hypertension
- Gout
- Diabetes
- Pyloric stenosis

CHROMOSOMAL DISORDERS

- Chromosome mutation – structural changes within the chromosome
  - deletion
  - inversion
  - translocation
- Genome mutation – loss or gain of whole chromosomes: monosomy and trisomy
  - sex chromosomes
  - autosomes

Types Of Chromosomal Rearrangements.



Diseases caused by Chromosomal Disorders

S.No.	Disease	Pathogenesis	Pathology, Cardinal Symptoms
1.	Angelman Syndrome	Deletion of part of short arm of chromosome 15, maternal copy. An example of genomic imprinting.	Mental retardation, ataxic gait, seizures. Inappropriate laughter.
2.	Cri du Chat Syndrome	5p-, deletion of the long arm of chromosome 5.	"Cry of the cat." Severe mental retardation, microcephaly, cat-like cry. Low birth-weight, round-face, hypertelorism (wide-set eyes), low-set ears, epicanthal folds.
3	Down Syndrome	Trisomy 21, with risk increasing with maternal age. Familial form (no age-associated risk) is translocation t(21,x) in a minority of cases.	Most common cause of mental retardation. Will see epicanthal folds, simian crease, brushfield spots in eyes. Associated syndromes: congenital heart disease, leukemia, premature Alzheimer's disease
4	Edward's Syndrome	Trisomy 18	Mental retardation, micrognathia, rocker-bottom feet, congenital heart disease, flexion deformities of fingers. Death by 1 year old.
5	Patau's Syndrome	Trisomy 13	Mental retardation, microphthalmia, cleft lip and palate, polydactyly, rocker-bottom feet, congenital heart disease. Similar to and more severe than Edward's Syndrome. Death by 1 year old.
6	Prader-Willi Syndrome	Deletion of part of short arm of chromosome 15, paternal copy. An example of genomic imprinting.	Mental retardation, short stature, hypotonia, obesity and huge appetite after infancy. Small hands and feet, hypogonadism.
7	DiGeorge Syndrome	Chromosome 22q11 deletion syndrome	Conotruncal anomaly face syndrome, Congenital Thymic Aplasia, Cardiac Abnormality, Abnormal facies Thymic aplasia Cleft palate Hypocalcemia

Thank You