What is genetic diseases/disorders?

The human body is composed up of cells , each one specializing a particular function like sensing light, smelling etc, So the chromosomes which are the sub cellular structure that exist in the nucleus of each cell that makes a human body .There are 23 pairs of chromosomes in human, these chromosomes are responsible for transferring genetic information from one generation to another.

Most people have the concept that genetic disease must be the one which is transmitted from one generation to next. Actually this is not totally correct. In medicine genetic disease refers to one that is caused by abnormalities of the genetic material at the stage of germ cells or early embryo.

CATEGORIES OF GENETIC DISORDERS

a) Chromosomal Disorder: Abnormalities in chromosome structure such as missing or extra copies.

b) Single Gene Disorder: Disorders caused by abnormality or mutation in the sequence of a single gene. The pure genetic diseases are caused by a single gene in the human DNA. These are classified as Dominant, Recessive and X-linked diseases.

c) Multifactorial Disorders: That are caused by the result of the combined effect of genetic and environmental factors.

d) Mitochondrial Disorders: Caused by mutation in the non chromosomal DNA of mitochondria

Mutations

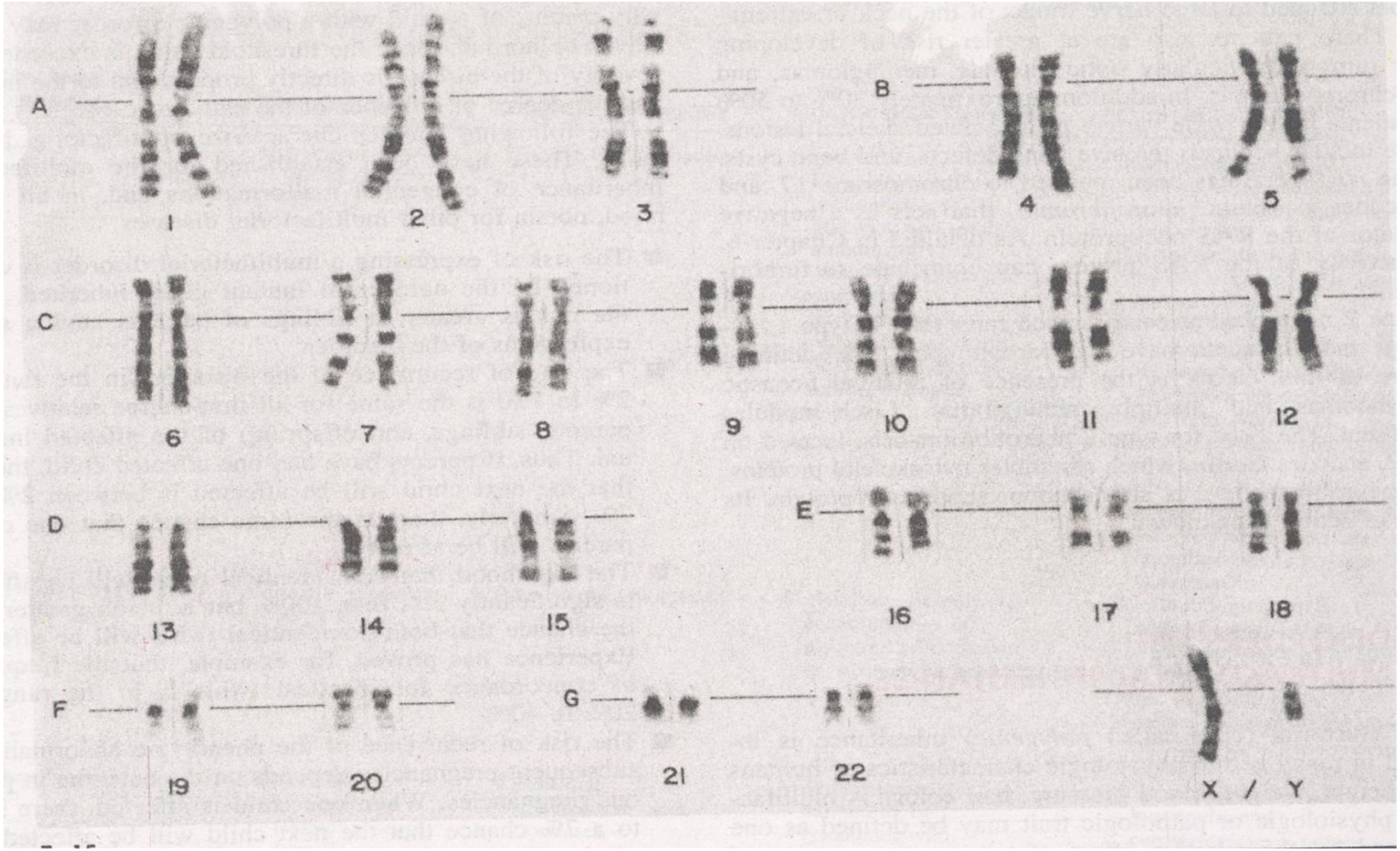
Gene mutations can be either inherited from a parent or acquired. A hereditary mutation is a mistake that is present in the DNA of virtually all body cells. Hereditary mutations are also called germ line mutations because the gene change exists in the reproductive cells and can be passed from generation to generation, from parent to newborn. Moreover, the mutation is copied every time body cells divide

Mutations occur all the time in every cell in the body. Each cell, however, has the remarkable ability to recognize mistakes and fix them before it passes them along to its descendants. But a cell's DNA repair mechanisms can fail, or be overwhelmed, or become less efficient with age. Over time, mistakes can accumulate

Cytogenetic Disorders

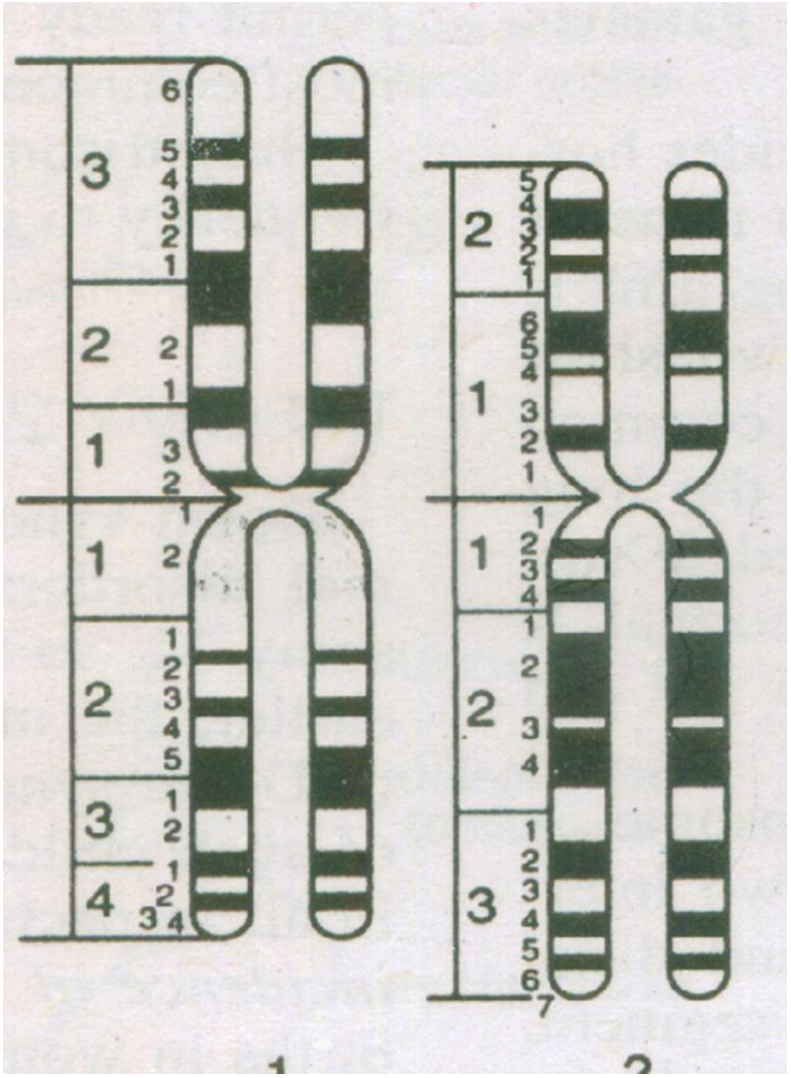
- Basic tool of cytogeneticist
- Karyotype is a photographic representation in which chromosomes are arranged in order of decreasing length
- Giemsa stain (G banding) technique—each chromosome can be seen to possess a distinctive pattern of alternating light and dark bands of variable widths
- Cytogenetic disorders may result from structural or numeric abnormalities of chromosomes
- It may affect autosomes or sex chromosomes

Normale Karyotype



Banding

- Short arm denoted as p, long arm denoted q.
- Each arm divided into numbered regions from the centromere onwards.
- Each region numerically arranged into bands.
- For e.g., 5p24 would denote chromosome 5, short arm, region 2 and band 4



- Normal Chromosomal number is 46. (2n=46). This is called **euploid** state. (Exact multiple of haploid number).
- **Polyploidy**: posession of more than two sets of homologous chromosomes. Chromosomal numbers like 3n or 4n. (Incompatible with life); generally results in spontaneous abortion
- **Aneuploidy**: Any Chromosomal number that is not an exact multiple of haploid number . E.g 47 or 45

Aneuploidy

- Most common cause is nondisjunction of either a pair of homologous chromosomes during meiosis I or failure of sister chromatids to separate during meiosis II.
- The resultant gamete will have either one less chromosome or one extra chromosome
- Fertilization of such gamete will result in zygote being either trisomic (2n+1) or monosomic (2n-1).
- Monosomy in autosomes is incompatible with life. Trisomy of certain autosomes and monosomy of sex chromosomes is compatible with life

- **Mosaicism**
- The presence of two or more types of cell populations in the same individual.
- Postzygotic mitotic nondisjunction will result in one trisomic and one monosomic daughter cell.
- The descendants of these cells will produce a mosaic

- **Structural Abnormalities**
- Usually result from chromosomal breakage, resulting in loss or rearrangement of genetic material.
- Patterns of breakage:
  - Translocation.
  - Isochromosomes.
  - Deletion.
  - Inversions.
  - Ring Chromosomes

TRANSLOCATION

- Transfer of a part of one chromosome to another chromosome
- Translocations are indicated by t
- E.g. 46,XX,t(2;5)(q31;p14)
- Balanced reciprocal translocation is not harmful to the carrier, however during gametogenesis, abnormal gametes are formed, resulting in abnormal zygotes

- Centric fusion type or robertsonian translocation:
- The breaks occur close to the centromere, affecting the short arms of both choromosomes
- Transfer of the chromosome leads to one very large and one extremely small chromosome
- The short fragments are lost, and the carrier has 45 chromosomes
- Such loss is compatible with survival
- However, during gametogenesis difficulties arise

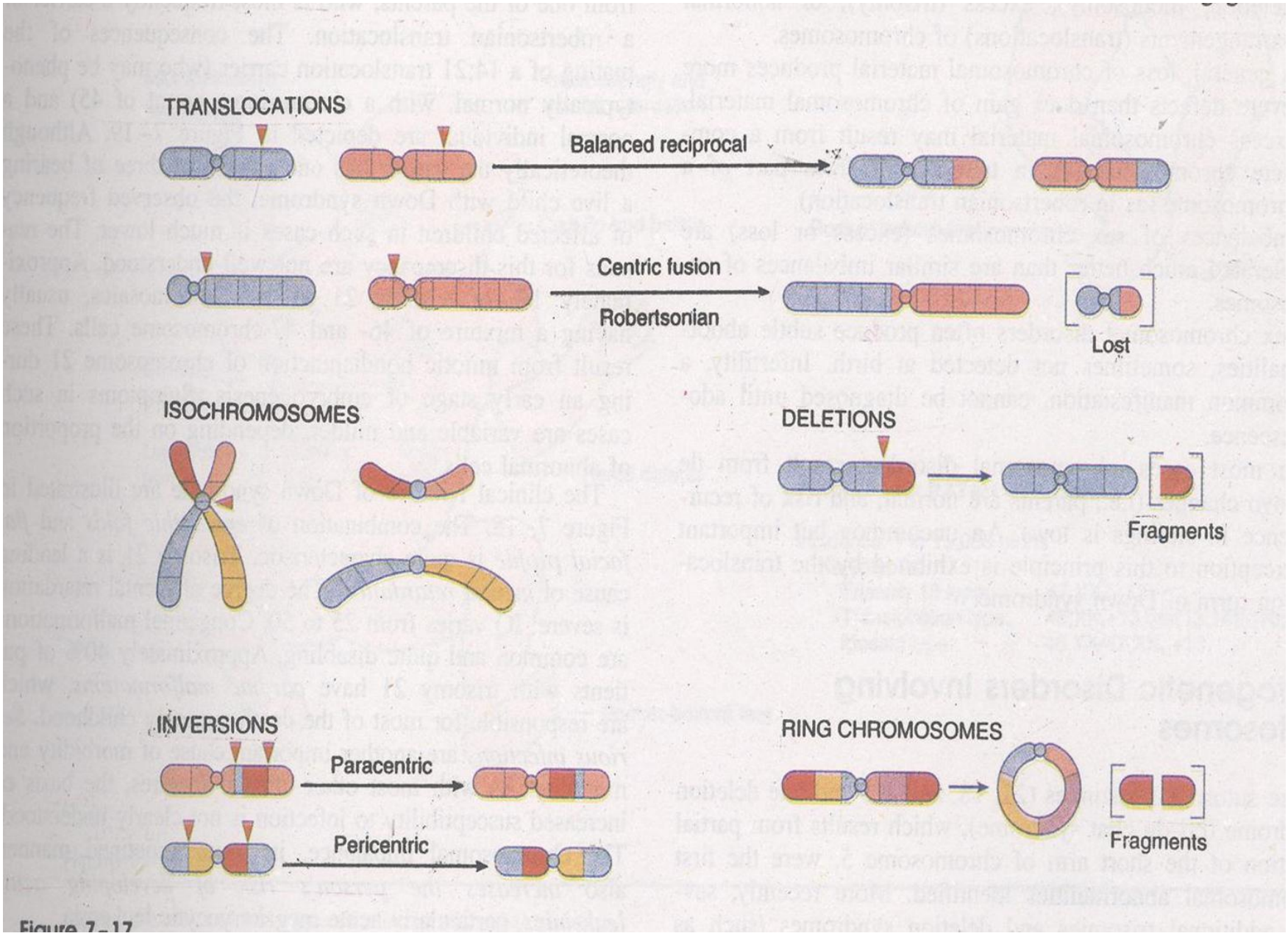

TRANSLOCATIONS
Balanced reciprocal
Centric fusion
Robertsonian
Lost
ISOCHROMOSOMES
DELETIONS
Fragments
INVERSIONS
Paracentric
Pericentric
RING CHROMOSOMES
Fragments

Figure 7-17

Others

- **ISOCHROMOSOMES**
- Result when one arm of a chromosome is lost and the remaining arm is duplicated, resulting in a chromosome consisting of two short arms only or of two long arms.

- **DELETION**
- Loss of a portion of chromosome
- This can be terminal (close to the end of the chromosome on the long arm or the short arm), or it can be interstitial (within the long arm or the short arm).
- A ring chromosome is a variant of deletion.It occurs when break occurs at both the ends of chromosome with fusion of the damaged ends
- **INVERSIONS**
- Occur when there are two breaks within a single chromosome with inverted reincorporation of the segment.
- Since there is no loss or gain of chromosomal material, inversion carriers are normal.
- An inversion is paracentric if the inverted segment is on the long arm or the short arm .
- The inversion is pericentric if breaks occur on both the short arm and the long arm

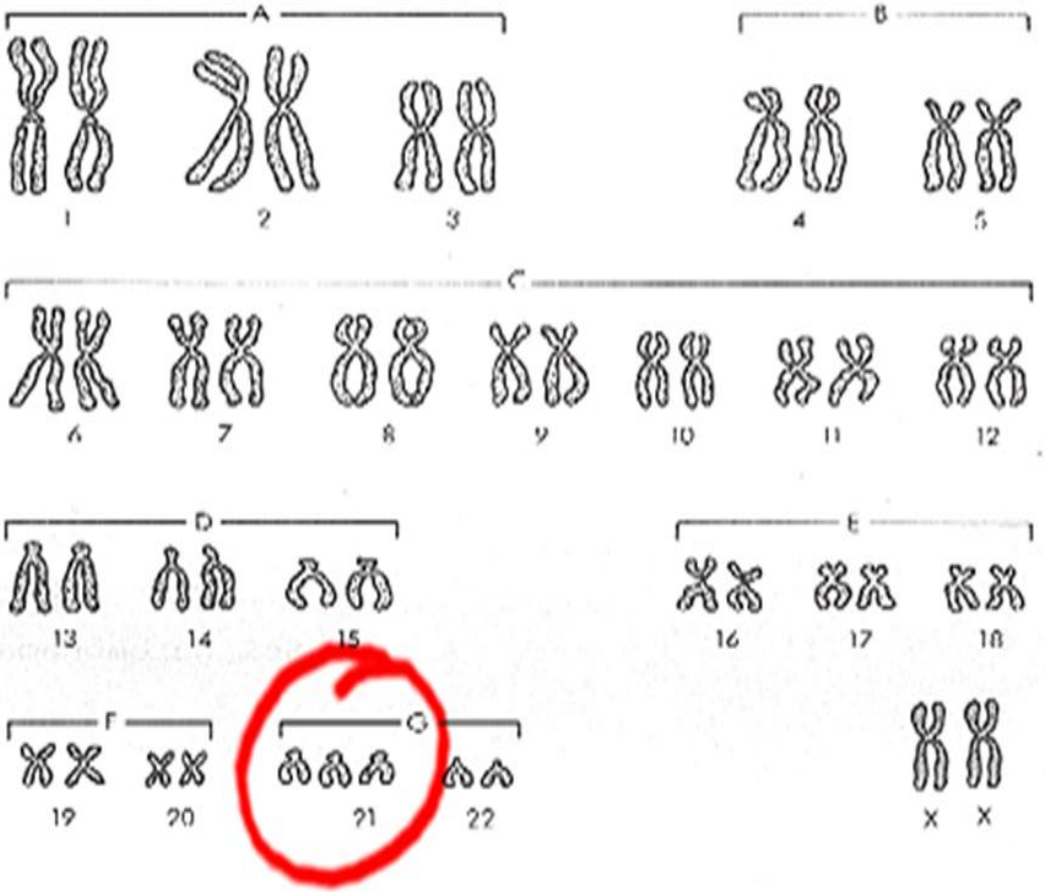
General Features of Cytogenetic Disorders

- Associated with absence, excess, or abnormal rearrangements of chromosomes.
- Loss of genetic material produces more severe defects than does gain.
- Abormalities of sex chromosomes generally tolerated better than those of autosomes
- Sex chromosomal abnormalities are usually subtle and are not detected at birth.
- Most cases are due to de novo changes (i.e. parents are normal and recurrence in siblings is low).

Chromosomal abnormalities Autosomes

- Trisomy
- Down syndrome is caused by an extra chromosome present on chromosome 21
- Down syndrome is caused by mutations
- Caused by non-disjunction of the 21st chromosome.
- This means that the individual has a trisomy (3 – 2lst chromosomes).

Down's Syndrome or Trisomy 21



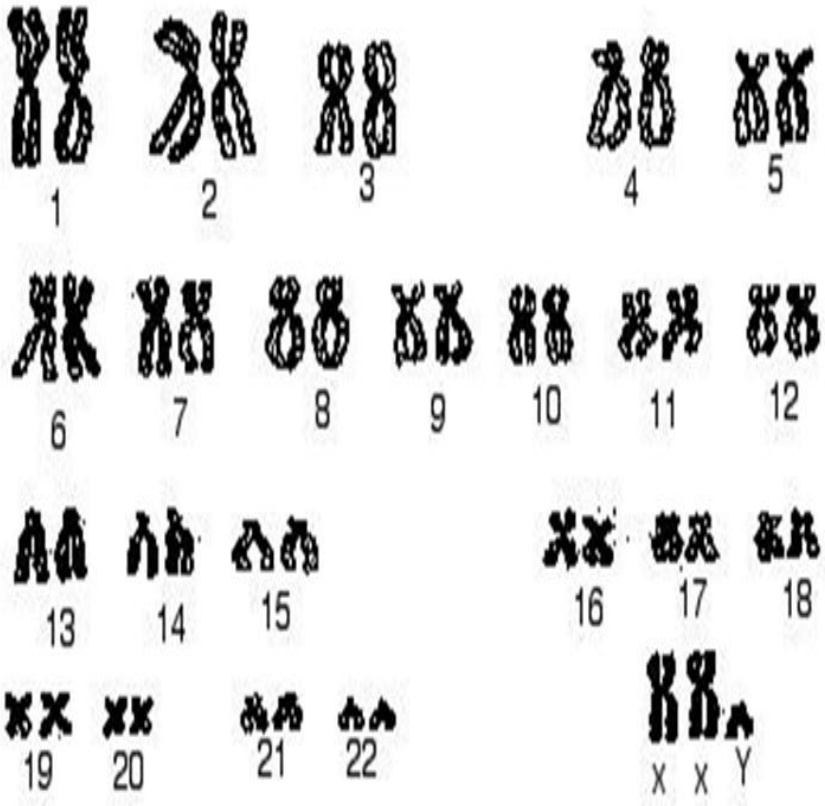
Symptoms of Down Syndrome

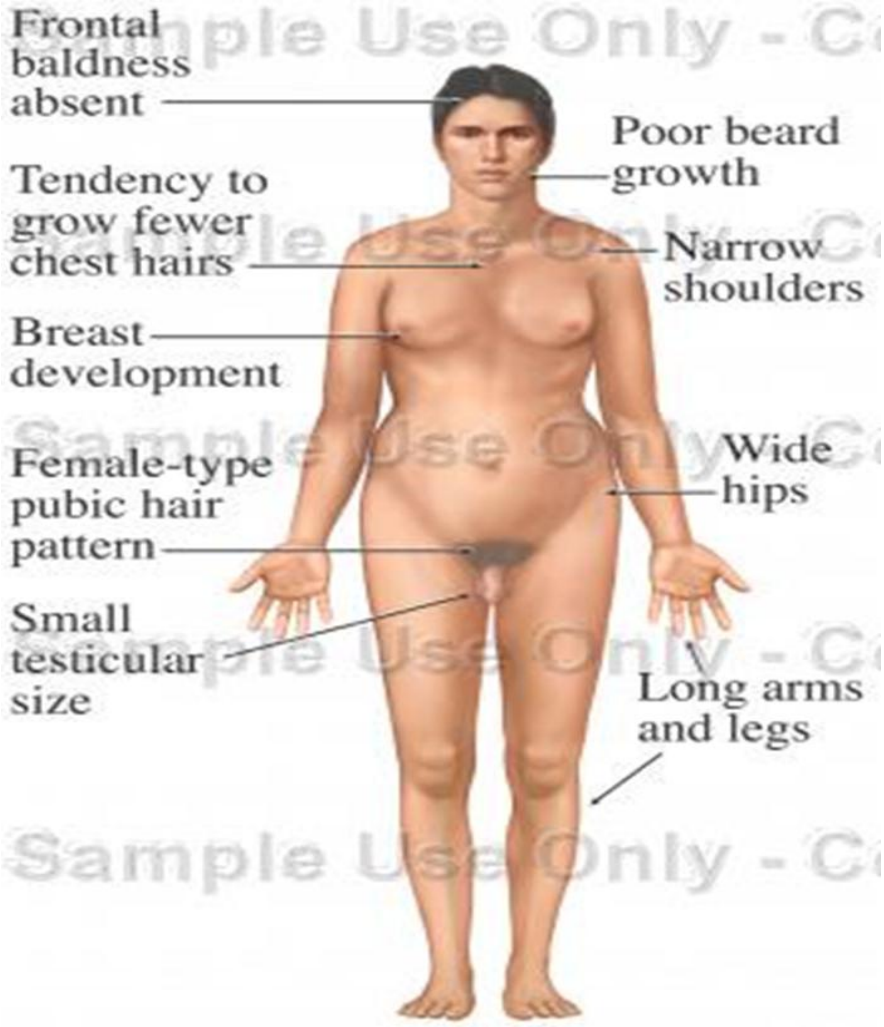
- Upward slant to eyes.
- Small ears that fold over at the top.
- Small, flattened nose.
- Small mouth, making tongue appear large.
- Short neck.
- Small hands with short fingers.
- Low muscle tone.
- Single deep crease across center of palm.
- Looseness of joints.
- Small skin folds at the inner corners of the eyes.
- Excessive space between first and second toe.
- In addition, down syndrome always involves some degree of mental retardation, from mild to severe. In most cases, the mental retardation is mild to moderate.
- Trisomy 18 :Edwards Syndrome.
- Trisomy 13 :Patau Syndrome

Kleinfelter's syndrome (or Klinefleter's)

- disease(Klinefelter syndrome, also known as the XXY condition, is a term used to describe males who have an extra X hromosome in most of their cells
- Disorder occurring due to nondisjunction of the X chromosome.
- The Sperm containing both X and Y combines with an egg containing the X, results in a male child.
- The egg may contribute the extra X chromosome
- Males with some development of breast tissue normally seen in females.
- Little body hair is present, and such person are typically tall, have small testes.
- Infertility results from absent sperm.
- Evidence of mental retardation may or may not be present.

Klinefleter's(XXY)

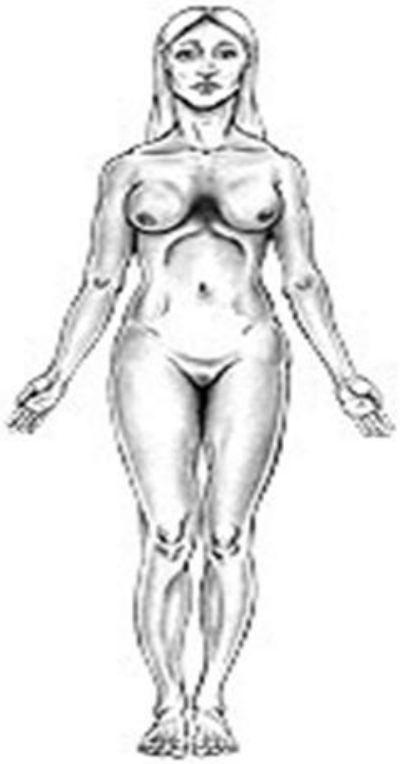


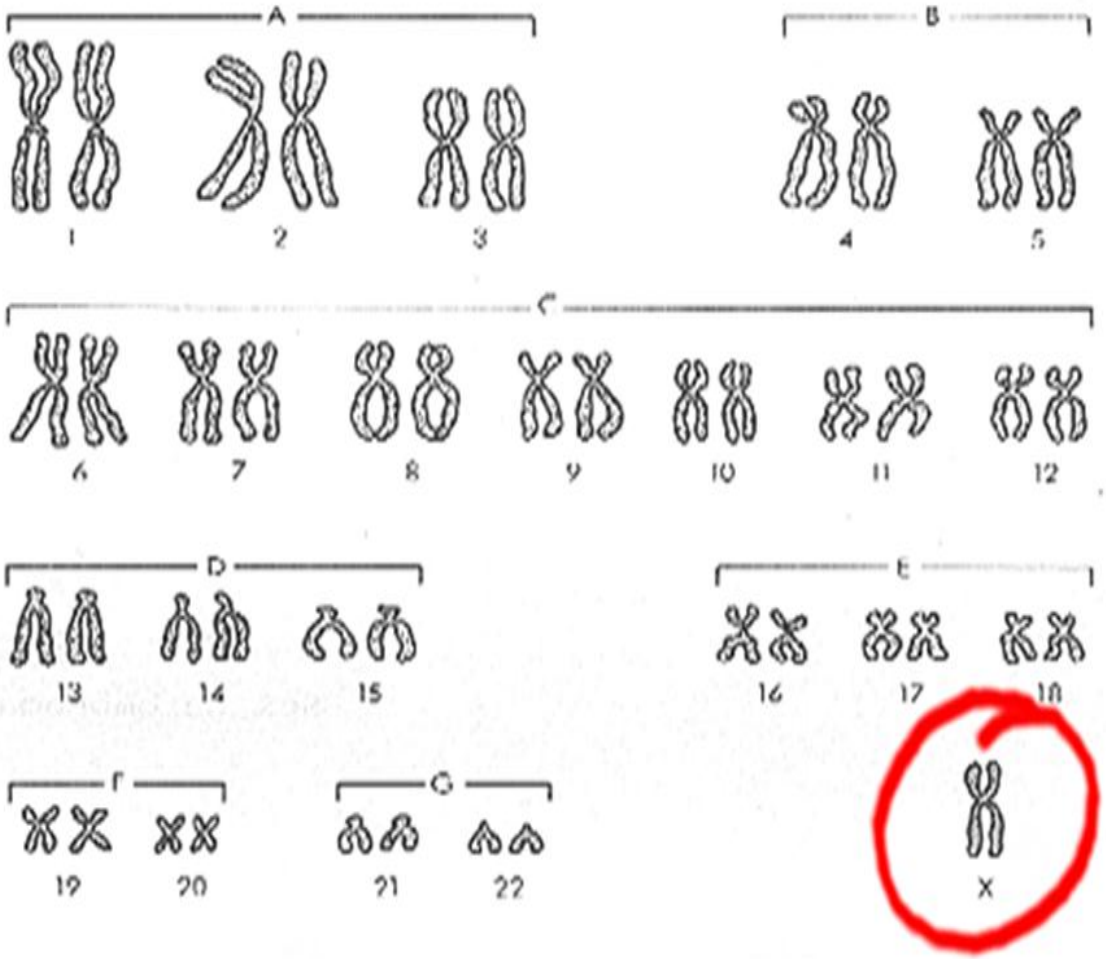


Turner’s syndrome

- Turner syndrome is a chromosomal condition related to the X chromosome that alters development in females.It leads to infertility,
- lymphedema, skeletal abnormalities, heart defects and kidney problems.
- Turner syndrome is associated with underdeveloped ovaries, short stature, webbed, and is only in women.
- Bull neck, and broad chest. Individuals are sterile, and lack expected secondary sexual characteristics.
- Mental retardation typically not evident.
- ?

Turner's Syndrome





maternal age effect

- Advanced maternal age, in a broad sense, is the instance of a woman being of an older age at a stage of reproduction, although there are various definitions of specific age and stage of reproduction.[1] The variability in definitions regarding age is in part explained by the effects of increasing age occurring as a continuum rather than as a threshold effect.[1]

- In Western, Northern, and Southern Europe, first-time mothers are on average 26 to 29 years old, up from 23 to 25 years at the start of the 1970s. In a number of European countries (Spain), the mean age of women at first childbirth has now even crossed the 30 year threshold.[2]

- This process is not restricted to Europe. Asia, Japan and the United States are all seeing average age at first birth on the rise, and increasingly the process is spreading to countries in the developing world like China, Turkey and Iran. In the U.S., the average age of first childbirth was 26 in 2013.[3]

- In present generations it is more common to have children at an older age. Several factors may influence the decisions of mothers when having their first baby. Such factors include educational, social and (probably the most important) economic status.
- De novo = new

Decreased fertility

- Main article: Age and female fertility
- A woman's fertility peaks in the early and mid twenties, after which it starts to decline, with advanced maternal age causing an increased risk of female infertility.

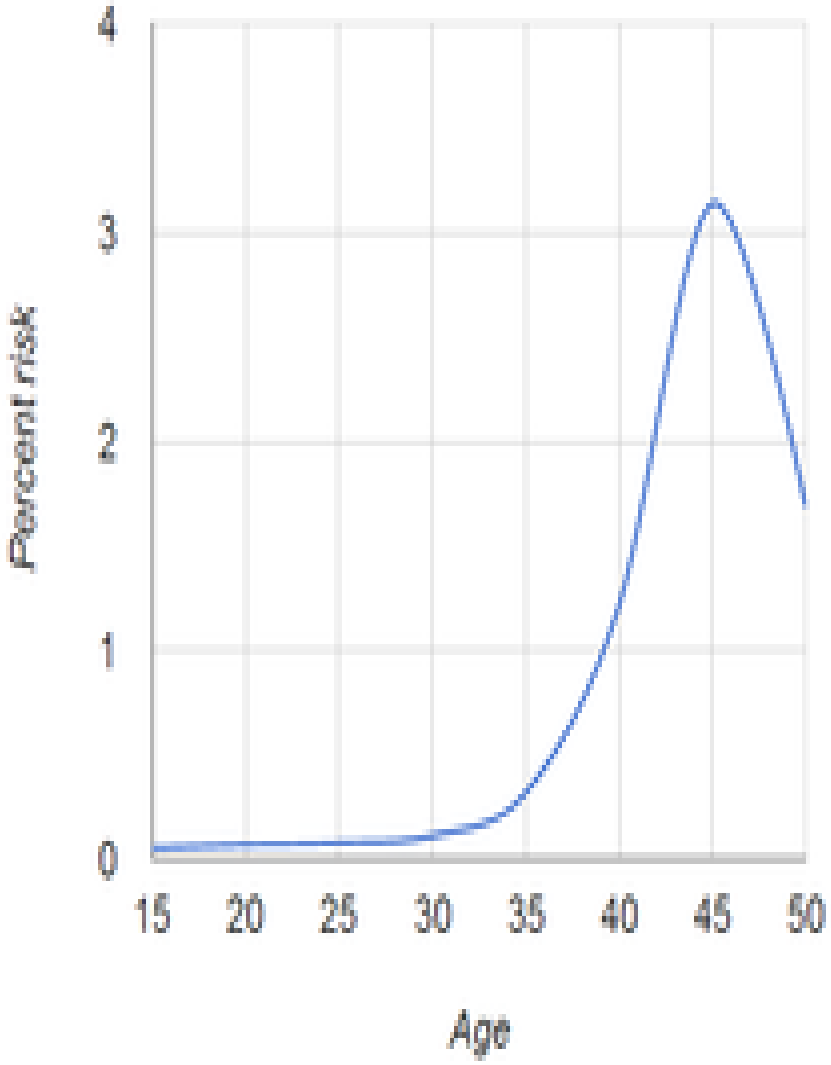
- According to Henri Leridon, PhD, an epidemiologist with the French Institute of Health and Medical Research, of women trying to get pregnant, without using fertility drugs or in vitro fertilization: [6]

- At age 30
- 75% will have a conception ending in a live birth within one year
- 91% will have a conception ending in a live birth within four years.
- At age 35
- 66% will have a conception ending in a live birth within one year
- 84% will have a conception ending in a live birth within four years.
- At age 40
- 44% will have a conception ending in a live birth within one year
- 64% will have a conception ending in a live birth within four years

Risk of birth defects

- A woman's risk of having a baby with chromosomal abnormalities increases with her age. Down syndrome is the most common chromosomal birth defect, and a woman's risk of having a baby with Down syndrome is:[7]

- At age 20, 1 in 1,441
- At age 25, 1 in 1,383
- At age 30, 1 in 959
- At age 35, 1 in 338
- At age 40, 1 in 84
- At age 45, 1 in 32
- At age 50, 1 in 44
- Figure The risk of having a Down syndrome pregnancy in relation to a mother's age.



Other effect

- Advanced maternal age is associated with adverse outcomes in the perinatal period, which may be caused by detrimental effects on decidual and placental development.[8]
- The risk of the mother dying before the child becomes an adult increases by more advanced maternal age, such as can be demonstrated by the following data from France in 2007:-

Maternal age at childbirth	25	30	35	40	45
Risk of mother not surviving until child's 18th birthday (in %)	1.0	1.6	2.6	3.8	5.5

Advanced maternal age continues to be associated with a range of adverse pregnancy outcomes including low birth weight, pre-term birth, stillbirth, unexplained fetal death, and increased rates of Caesarean section.

On the other hand, advanced maternal age is associated with a more stable family environment, higher socio-economic position, higher income and better living conditions, as well as better parenting practices,[9] but it is more or less uncertain whether these entities are effects of advanced maternal age, are contributors to advanced maternal age, or common effects of a certain state such as personality type.

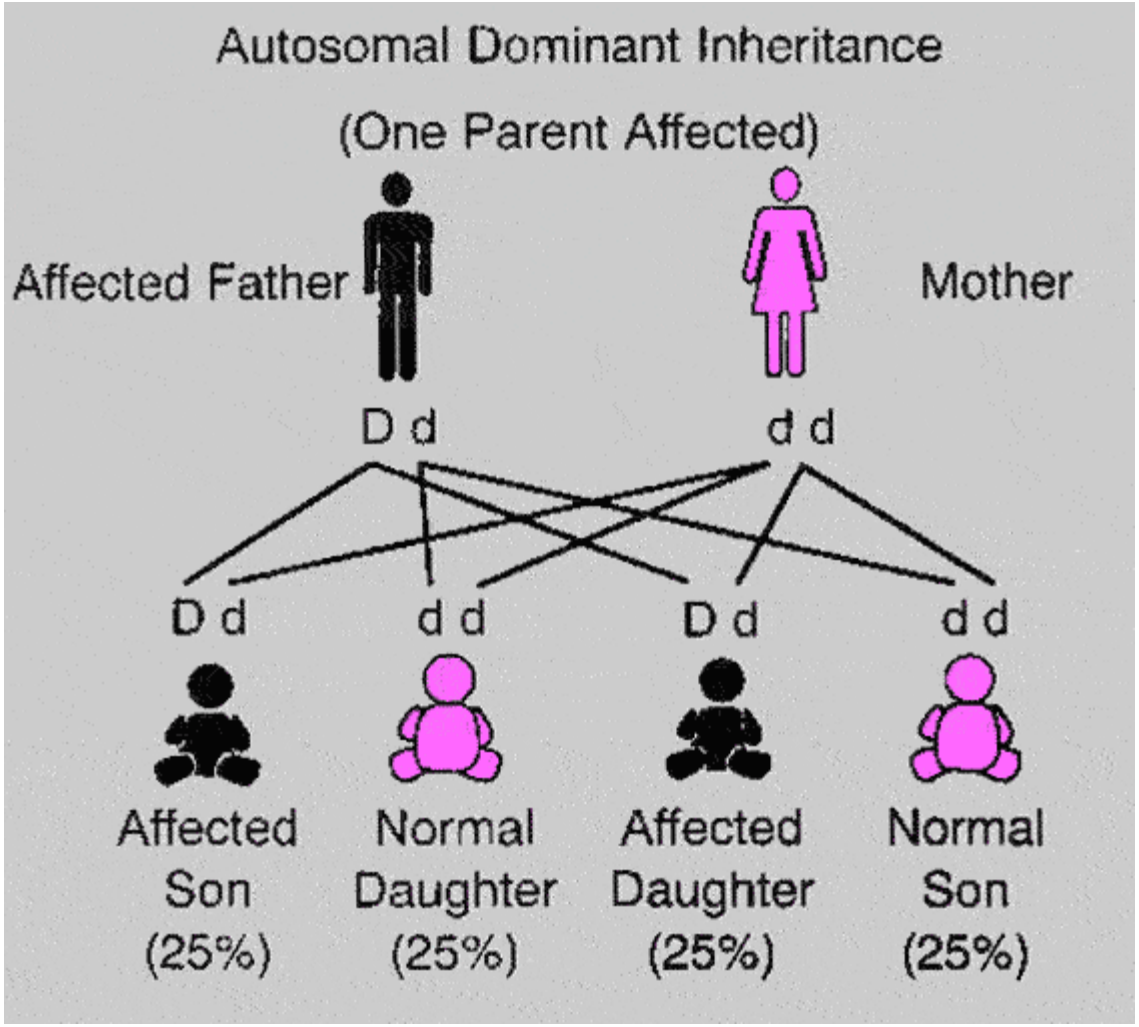
Mendelian Single Gene Disorder Transmission : (Monogenic)

Transmission Patterns of Single Gene Disorders

1. **Autosomal Dominant**
2. **Autosomal Recessive**
3. **X-linked**

Autosomal Dominant Disorders

- Manifested in heterozygous state
- One parent usually (NEW mut.)
- Males and females equal ratio and both can transmit the disease
- Affected person marries unaffected one, every child has 1 chance in 2 or 50% chance
- Because Mutation :- It PERMANENT change in DNA
- GENE MUTATION : (may, and often, result in a single base error)
- CHROMOSOME MUTATION: (visible chromosome change)
- GENOME MUTATION: (whole chromosome)
- Base pair ➡ triplet ➡ gene ⟶ chromosome segment whole chromosome ⟶ genome


Autosomal Dominant Inheritance
(One Parent Affected)
Affected Father
Mother
D d
d d
D d
d d
D d
d d
Affected Son (25%)
Normal Daughter (25%)
Affected Daughter (25%)
Normal Son (25%)

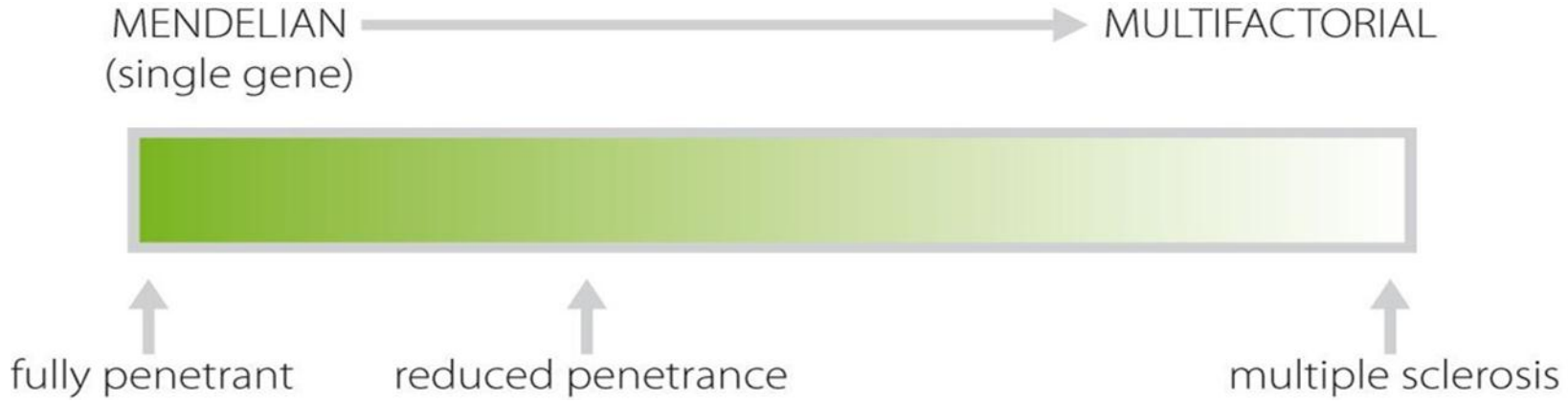
GENE MUTATION

- DELETION OF A SINGLE BASE
- SUBSTITUTION OF A SINGLE BASE
- POINT MUTATION within a coding sequence: VAL-GLU
- MUTATIONS in NON-coding sequences defective transcription, regulation, apop.
- DELETIONS/INSERTIONS “frameshift” mutation, involvement is NOT a multiple of 3, In a “frameshift mutaton”, NON-multiple of three mutations “shift” the whole DNA “frame”!
- A frameshift mutation (also called a framing error or a reading frame shift) is a genetic mutation caused by indels (insertions or deletions) of a number of nucleotides in a DNA sequence that is NOT divisible by three!
- Tri-nucleotide REPEATS, e.g., CGG repeats many times in fragile X syndrome, CAG in others
- INTERFERE with protein synthesis
- SUPPRESS transcription, DNA RNA
- PRODUCE abnormal mRNA
- DEFECTS carried over into TRANSLATION
- ABNORMAL proteins WITHOUT impairing syntheses
- Note :- In the classical one-gene, one-protein model, abnormal (i.e., mutated) genes mean abnormal proteins
- SINGLE gene mutations, following classical MENDELIAN inheritance patterns the most

Autosomal Dominant Disorders : Other Characteristics:

In some, parents not affected → new mutations in egg or sperm → siblings no increased risk

- New mutation directly proportional to in reproductive fitness → older father germ cells more new mutations
- Reduced Penetrance: Mutant gene but phenotype normal, *e.g., 50 % penetrance → 50% of gene carriers will express the trait*
- *Note: - Continuum of penetrance.*
- *There is a continuum of penetrance from fully penetrant conditions, where other genes and environmental factors have no effect, through to low-penetrance genes that simply play a small part, along with other genetic and environmental factors, in determining a person's susceptibility to a disease*



Autosomal Dominant Disorders : Other Characteristics:

Variable Expressivity: Trait in all gene carriers but different expression among individuals, e.g., NF 1 mere brownish spots --- multiple skin tumors and skeletal deformities

- *Mechanisms of RP and VE not known but most likely effect of other genes or modifying environmental factors*
- *E.g., Sickle Cell anemia → mutation at β-globin (quality) locus → influenced by genotype at α-globin (quantity) locus*
- *Hypercholesterolemia → expression of ATH is different according to dietary lipid intake*
- May have a DELAYED ONSET occurs later in life In some conditions like Huntington's Disease, S & S are delayed until adulthood.

Autosomal Dominant Disorders

- Biochemical Mechanisms of Disease:
- Dependant on nature of mutation and type of protein affected
- Loss of Function Mutations: gene product or inactive protein, depends upon nature of protein affected
- Enzyme proteins not usually AD inheritance → heterozygotes usually normal → 50% in enzyme activity can be compensated by compensatory mechanisms.
- Proteins affected in AD disorders:
- Proteins involved in complex metabolic pathways, feedback inhibition e.g., membrane receptors of LDL □ 50% loss □ elevated cholesterol □ ATH in heterozygotes
- Structural proteins like collagen, RBC cytoskeleton Spectrin □ 50% abnormal phenotype
- One subunit of multimeric protein affected □ faulty assembly of normal multimers e.g., collagen trimer, Dominant negative

Autosomal Dominant Disorders (AD)

- Biochemical Mechanisms of Disease:

- Gain of Function Mutations: Less commonly,

  mutant protein product gains properties not shown by Wild-type protein (normal protein with toxic properties)

  Always AD disorder, *e.g., Huntington's Disease → abnormal protein → toxic to neurons → hence even heterozygotes affected*

- Summary: Two types of mutations and two types of proteins affected in AD disorders

Types of Autosomal Dominant Disorders

1- Nervous :

HUNTINGTON DISEASE ,
NEUROFIBROMATOSIS
MYOTONIC DYSTROPHY
TUBEROUS SCLEROSIS

2- Urinary :-POLYCYSTIC KIDNEY

3- Gastrointestinal: polyposis coli

4-Hematopoitiec:-

HEREDITARY SPHEROCYTOSIS
VON WILLEBRAND DISEASE

5- Skeletal :- MARFAN SYNDROME

EHLERS-DANLOS SYNDROMES (some)

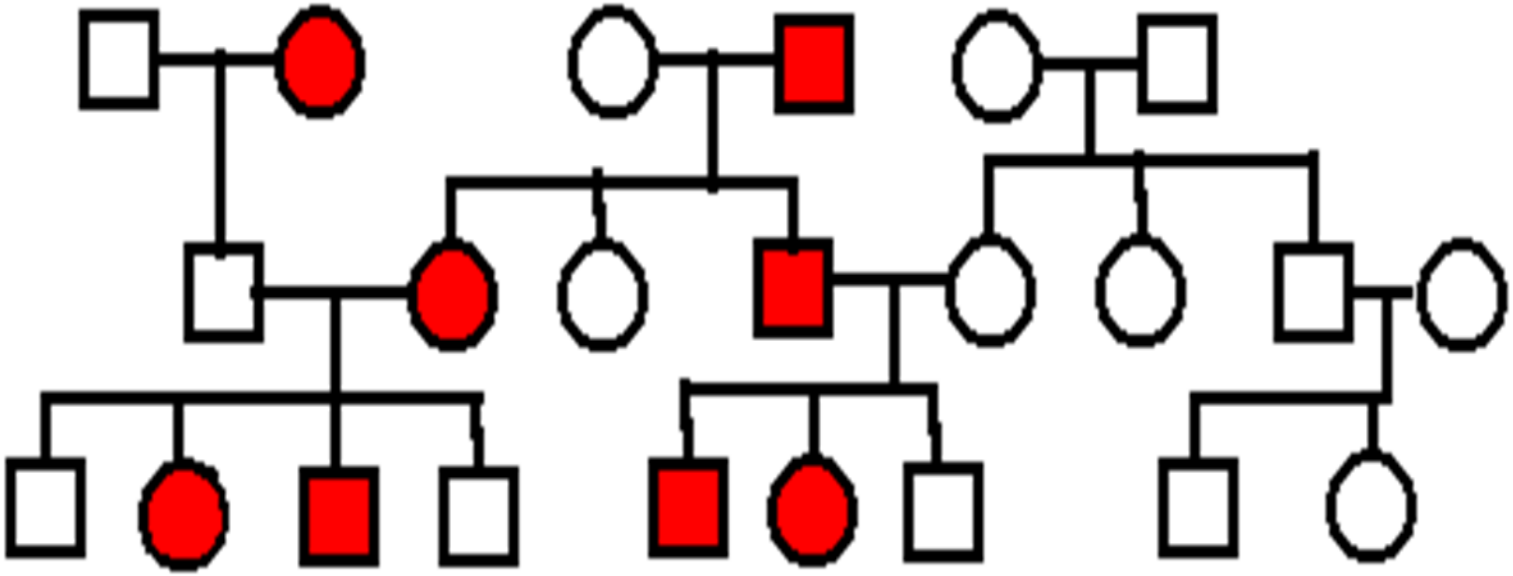
OSTEOGENESIS IMPERFECTA
ACHONDROPLASIA

6- Metabolic :-

ACUTE INTERMITTENT PORPHYRIA.

FAMILIAL HYPERCHOLESTEROLEMIA

AUTOSOMAL DOMINANT PEDIGREE

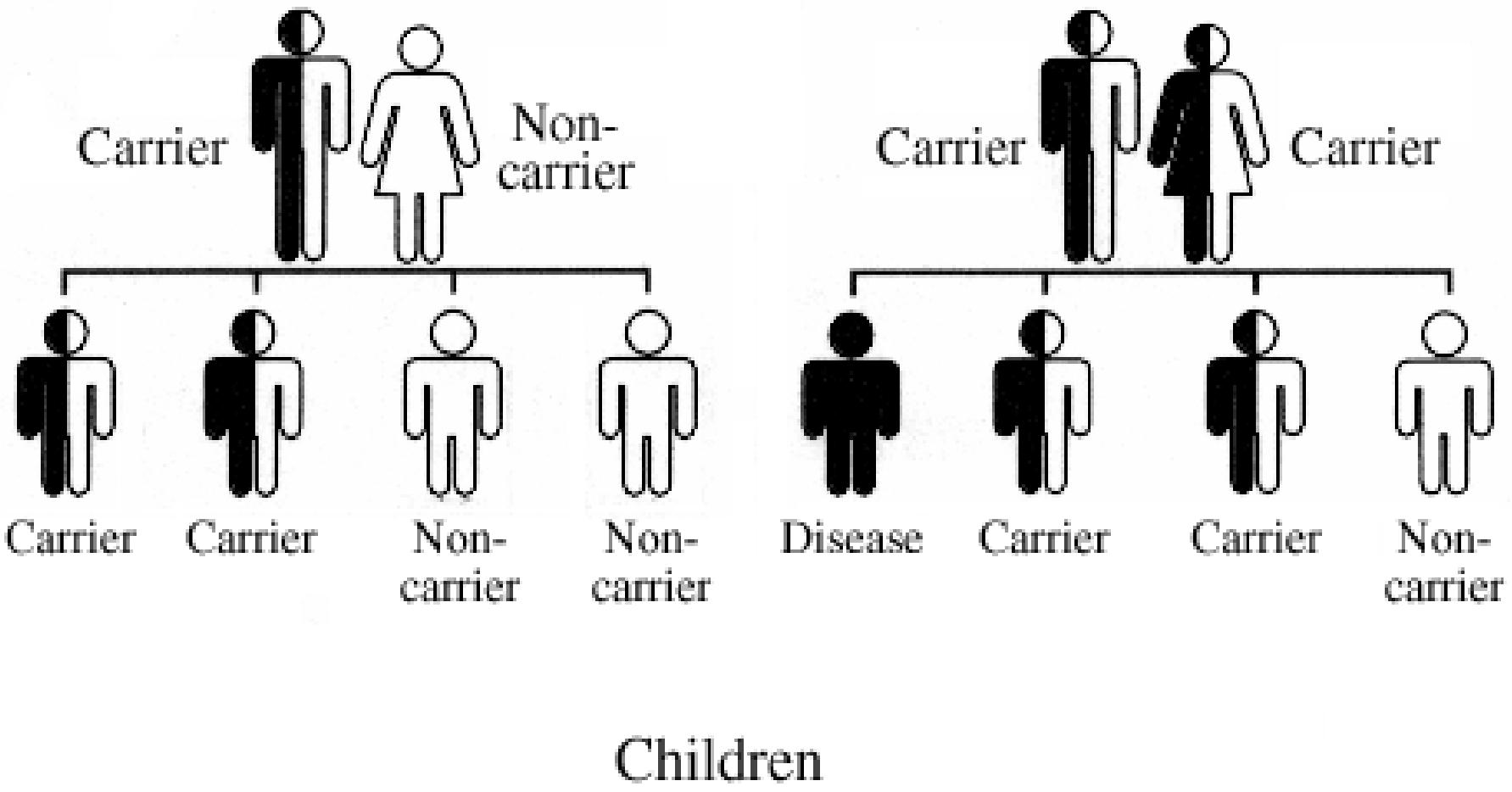


1) BOTH SEXES INVOLVED
2) GENERATIONS NOT SKIPPED

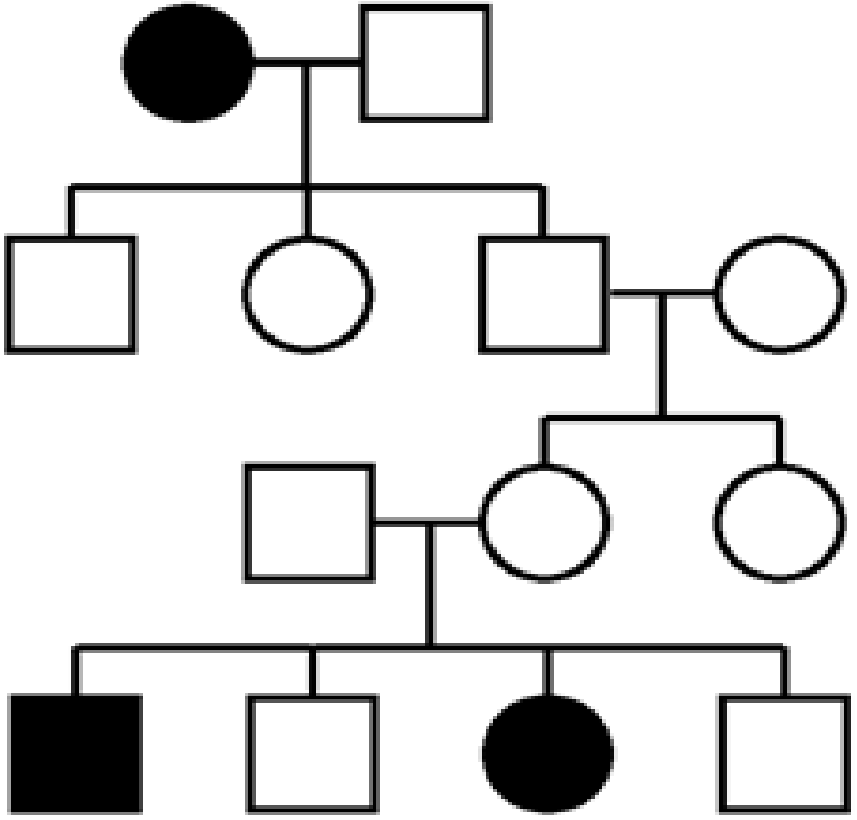
Autosomal Recessive Disorders

- Single largest category of Mendelian disorders
- Affected when homozygous i.e., both alleles affected

1. Parents not necessarily affected (carriers) but siblings may be affected
2. Siblings 1 in 4 chance of being affected (25%)
3. If mutant gene low freq. in population → strong likelihood that diseased offspring result of consanguineous marriage


Parents
Carrier
Non-carrier
Carrier
Carrier
Carrier
Carrier
Non-carrier
Non-carrier
Children
Carrier
Carrier
Disease
Carrier
Carrier
Non-carrier

AUTOSOMAL RECESSIVE PEDIGREE



1) BOTH SEXES INVOLVED

2) GENERATIONS **SKIPPED**

Autosomal Recessive Disorders

Distinguishing Features from AD disorders:

- **Expression of defect more uniform than AD**
- **Complete penetrance common**
- **Onset frequently early in life**
- New mutations occur but rarely detected → asymptomatic heterozygote → many generations pass to mate with other carrier to produce homozygous offsprings
- **Enzyme proteins affected** by Loss of Function →
  in heterozygotes → normal enz. = defective enz. → compensation
- ***Almost all inborn errors of metabolism included***
- ***MUCH more common that autosomal dominant***

Table 7–3. AUTOSOMAL RECESSIVE DISORDERS

System	Disorder
Metabolic*	Cystic fibrosis*
	Phenylketonuria*
	Galactosemia*
	Homocystinuria
	Lysosomal storage diseases*
	α_1-Antitrypsin deficiency
	Wilson disease
	Hemochromatosis
	Glycogen storage diseases*
Hematopoietic	Sickle cell anemia
	Thalassemias
Endocrine	Congenital adrenal hyperplasia
Skeletal	Ehlers-Danlos syndrome (some variants)*
	Alkaptonuria
Nervous	Neurogenic muscular atrophies
	Friedreich ataxia
	Spinal muscular atrophy

X-Linked Disorders

- All sex linked disorders are x-linked
- Almost all X-linked are recessive
- Several genes on “Y” → all related to spermatogenesis
- Male mutations in “Y” are infertile, hence no Y-linked inheritance
- Some X CH genes homologues mapped on Y CH but no mutational disorders described

X-Linked Disorders

- X-Linked Recessive Inheritance:
- Small number of well-defined clinical conditions
- Most part of “Y” not homologous with “X”, so mutant genes unpaired
- So male is called Hemizygous for X-linked mutant genes
- Disorders mostly expressed in males

X-Linked Disorders

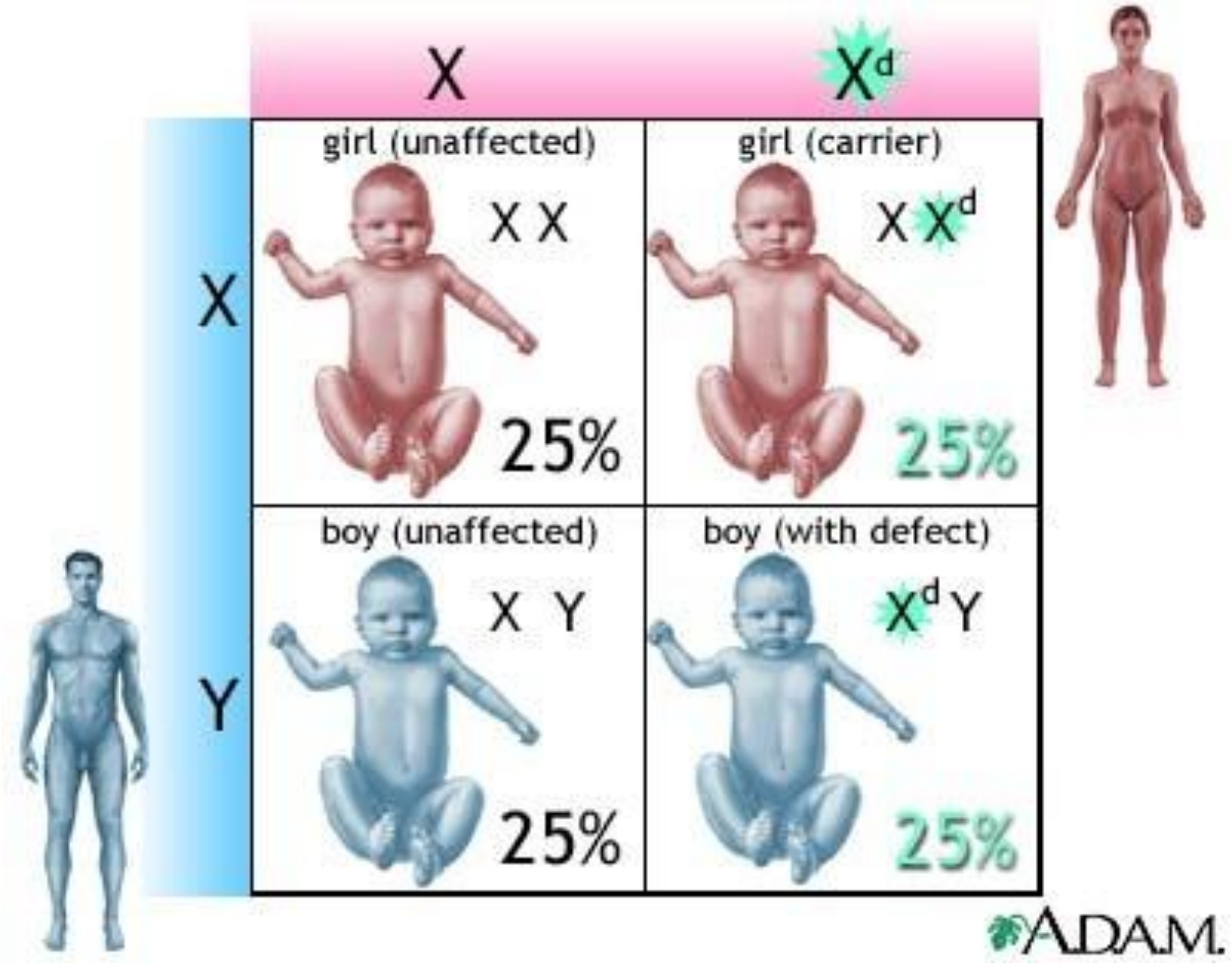
- X-Linked Recessive Inheritance:
- Characteristic Features:

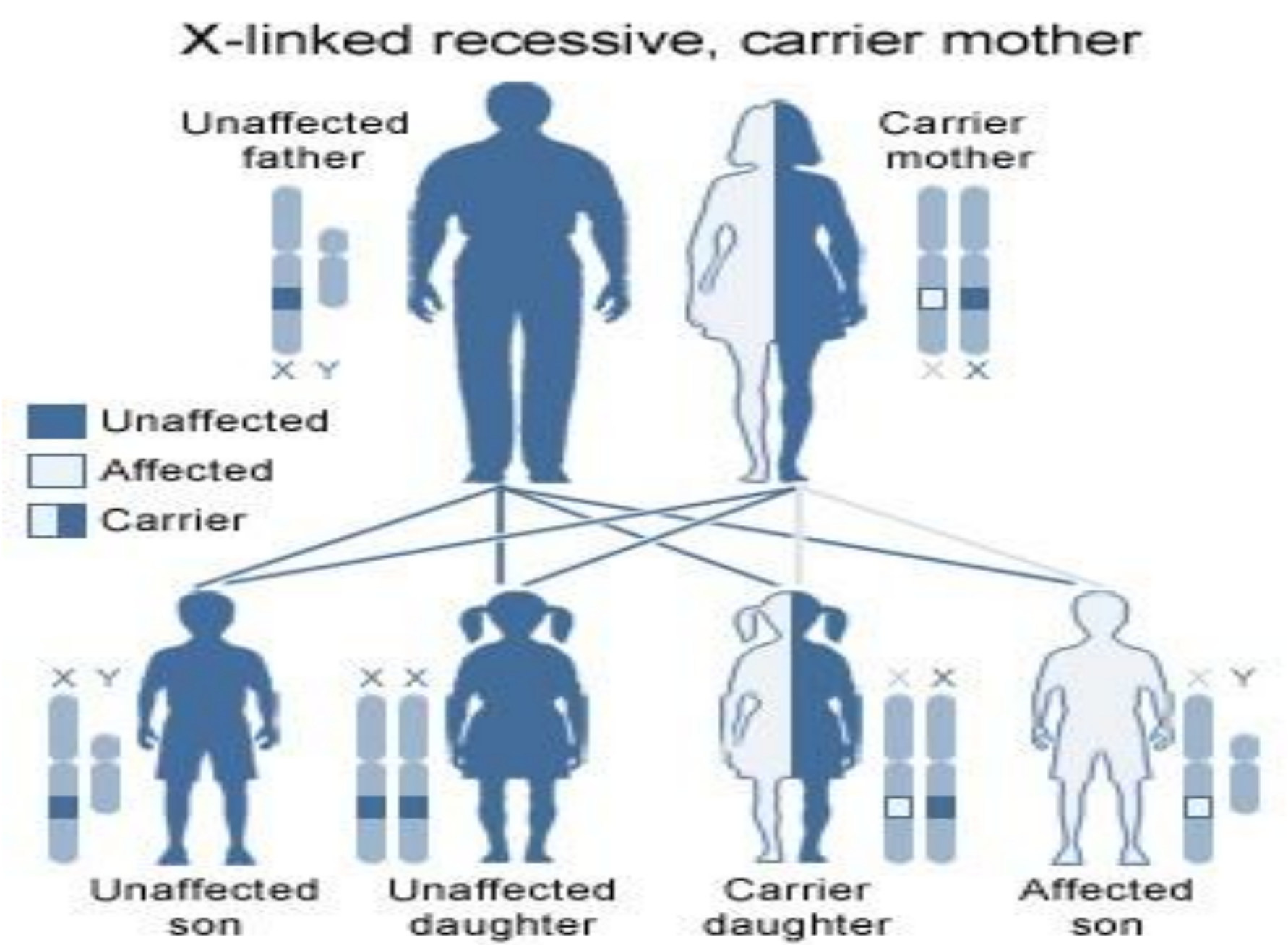
- Affected male → Sons unaffected, daughters are carriers

  XY + XX → XX XX XY XY

- Heterozygous women → Sons 1 chance in 2 of disease

  XY + XX → XX XX XY XY


X
X^d
X
Y
girl (unaffected)
X X
25%
girl (carrier)
X X^d
25%
boy (unaffected)
X Y
25%
boy (with defect)
X^d Y
25%
A.D.A.M.


X-linked recessive, carrier mother
Unaffected father
Carrier mother
X Y
X X
Unaffected
Affected
Carrier
X Y
X X
X X
X Y
Unaffected son
Unaffected daughter
Carrier daughter
Affected son
U.S. National Library of Medicine

X-Linked Disorders

- X-Linked Recessive Inheritance:

- Heterozygous female → no full phenotypic disease → paired normal allele

- THEORETICALY POSSIBLE????

  XY + XX → XX XX XY XY ?????

Above almost impossible bcz of the Random Inactivation of one X CH in females

Moreover the % itself is 1 in 2 daughter and 1 daughter in 4 children

Moreover it's remotely possible that a diseased male always marries a carrier female and always a female is born???? Increasing the chances of homozygous female

X-Linked Disorders

- X-Linked Recessive Inheritance:
- X Inactivation or Lyonization:
- One of 2 copies of X Ch inactivated in female mammals
- Inactive X Ch → silenced → packaging into inactive heterochromatin → Barr Body in female cell nucleus
- Reason? So that no duplication of gene products bcz of double X Ch as compared to males (dosage compensation)
- Inactivation is Random but once inactivated will remain for lifetime
- Applied to both homozygous and heterozygous recessive females
- In heterozygotes, it's almost always the mutant or abnormal allele that is inactivated
- Remotely possible for normal allele to be deactivated in most cells to express the disease
- Variable proportion of cells in which mutant X Ch is active

X-Linked Disorders

- X-Linked Recessive Inheritance:
- E.g., G6PD deficiency → Favism → drug induced hemolysis
- Males hemizygous so all RBC can be hemolyzed
- But in females, bcz of X-inactivation, some RBCs from BM may be with erroneous normal allele inactivation
- So hemolysis can be present in females carriers too, but less severe than males

Table 7–4. X-LINKED RECESSIVE DISORDERS

System	Disease
Musculoskeletal	Duchenne muscular dystrophy
Blood	Hemophilia A and B Chronic granulomatous disease Glucose-6-phosphate dehydrogenase deficiency
Immune	Agammaglobulinemia Wiskott-Aldrich syndrome
Metabolic	Diabetes insipidus Lesch-Nyhan syndrome
Nervous	Fragile X syndrome*

X-Linked Disorders

- X-Linked Dominant Inheritance:
- Fewer

- Caused by dominant disease alleles on X Ch

- Affected heterozygote female → half sons, half daughters
- xy + Xx → xX xx Xy xy

- Affected father → no son but all daughters affected if mother unaffected
- Xy + xx → Xx Xx xy xy

- E.g., Vitamin D – resistant rickets

X-Linked Dominant Inheritance