Lec(2)

Classifications of genetic disorders

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Objectives:

To Define and classify genetic diseases

To Describe Mendelian disorders

Human diseases in general can roughly be classified in to:

1-Those that are genetically determined.

2-Those that are almost entirely environmentally determined.

3- Diseases with multifactorial (polygenic inheritance) implies that both genetic and environmental had a role in the expression of diseases such as hypertension and diabetes mellitus

Classifications of genetic disorders

:Classical Genetic Diseases -1

A. Single gene (or unifactorial) disorders (Mandelian .disorders)

.B. Chromosomal (cytogenetic) disorders

.C. Multifactorial disorders

Non - Classical diseases (or the single gene disorders with -2 atypical pattern of inheritance)

.A. Diseases caused by mutation in mitochondrial genes

.B. Triplet repeat mutations

.C. Genomic imprinting

.D. Gonadal mosaism

Autosomal: the gene responsible for the phenotype is located on one of the 22 pairs of .autosomes (non-sex determining chromosomes)

X-linked: the gene that encodes for the trait is .located on the X chromosome

Dominant: conditions that are manifest in heterozygotes (individuals with just one copy of .the mutant allele)

Recessive: conditions are only manifest in individuals who have two copies of the mutant .allele (are homozygous)

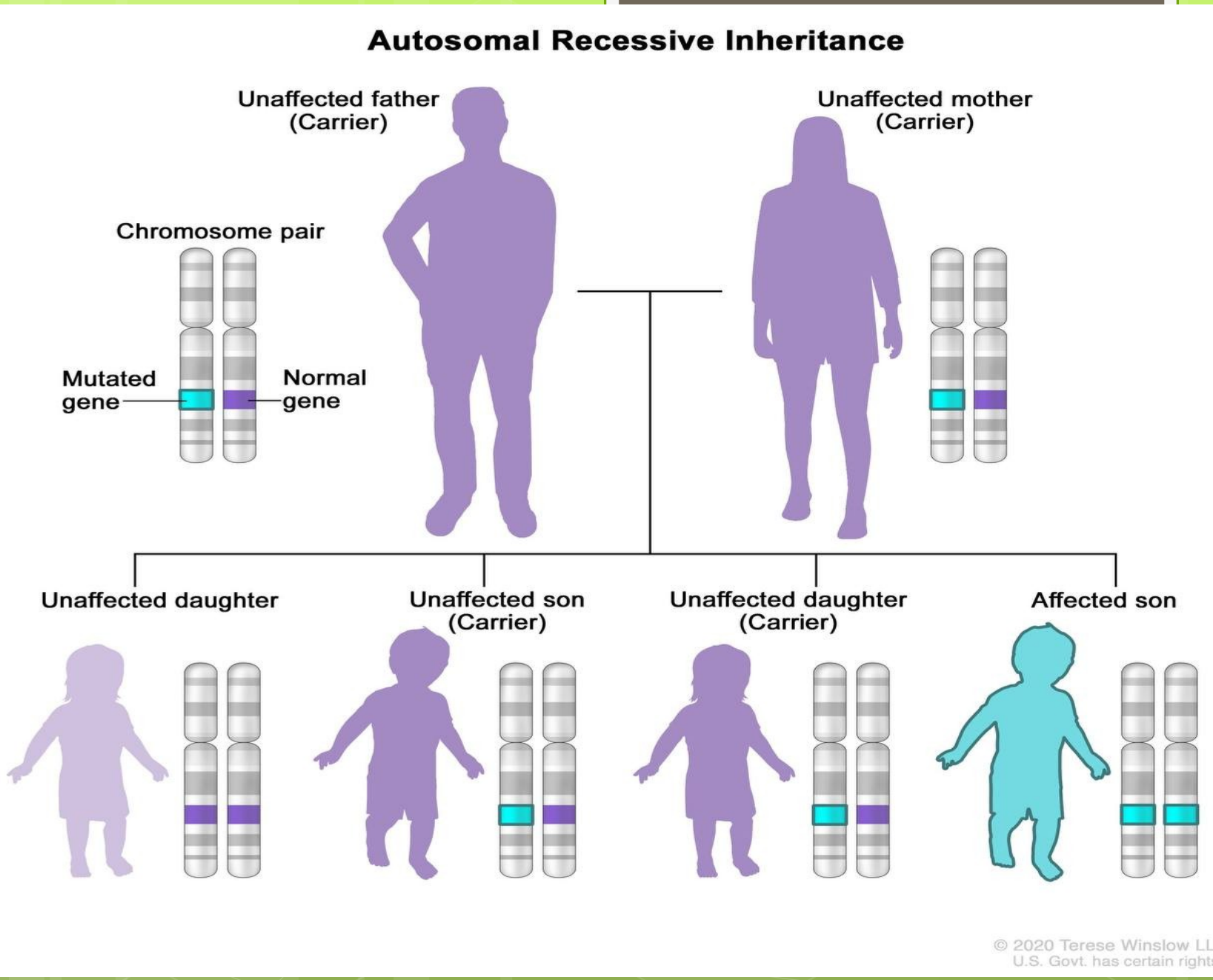
Single gene (or unifactorial) .disorders (Mandelian disorders)

Autosomal Recessive Disease

.affected equally ♀ & ♂

The affected individual should be homozygous for-
.the affected gene

If both parents are heterozygous the chance of-
.having affected child is 25%


Autosomal Recessive Inheritance
Unaffected father
(Carrier)
Unaffected mother
(Carrier)
Chromosome pair
Mutated
gene
Normal
gene
Unaffected daughter
Unaffected son
(Carrier)
Unaffected daughter
(Carrier)
Affected son
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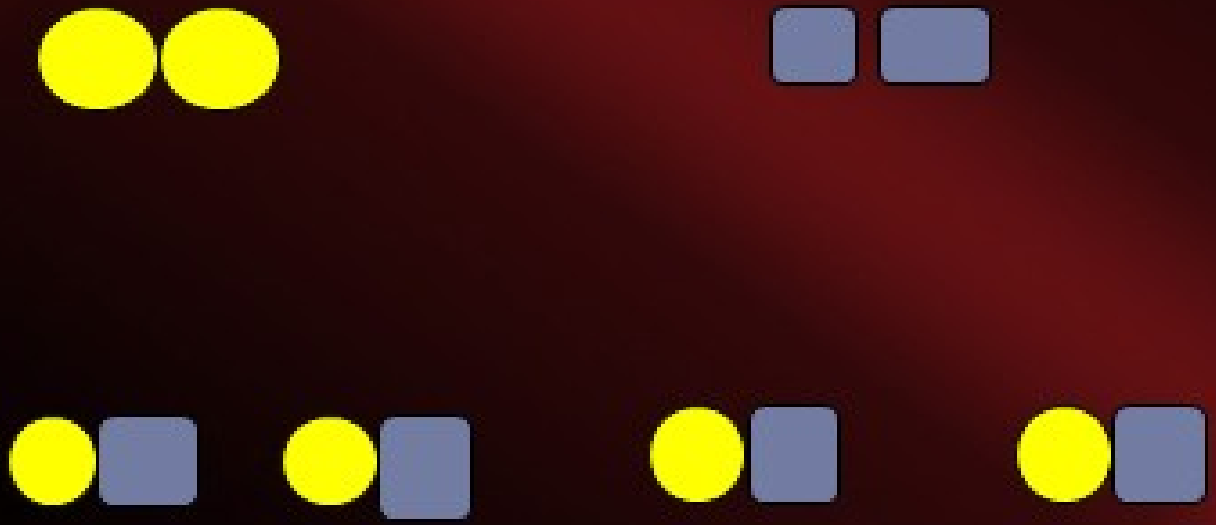
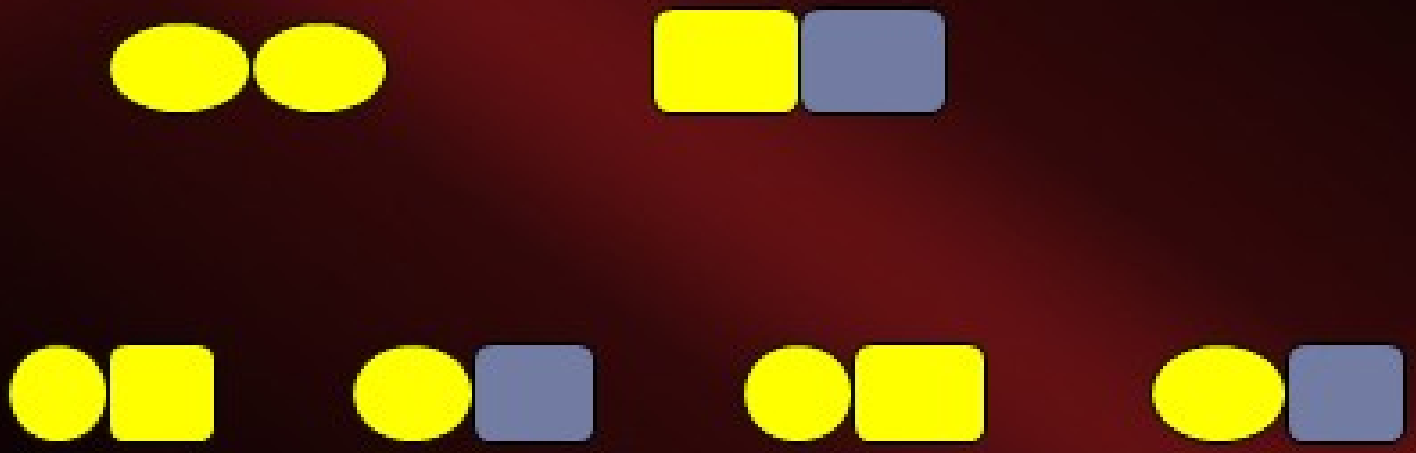
If the affected person married from normal person, all the children will be heterozygous.



If affected person married from a heterozygous person the children will be:
50% affected.
50% heterozygous (carrier).
(Pseudodominant)



- The affected cases are almost always born in only one generation (sister, brother or cousins…), this is called horizontal .inheritance

- Increased frequency of consanguinity, particularly for rare traits. The risk of a genetic disorder for the offspring of a first-cousin marriage (6-8%) is about double the risk in general population (3-4%)

Examples of autosomal recessive disorder:

Haemopoitic : sickle cells anaemia and thalassemias.-

Metabolic : cystic fibrosis , phenyle ketonuria, galactosemia,homocystenuria,lysosomal storage disease, Wilson disease, haemochromatosis, glycogen storage disease.-

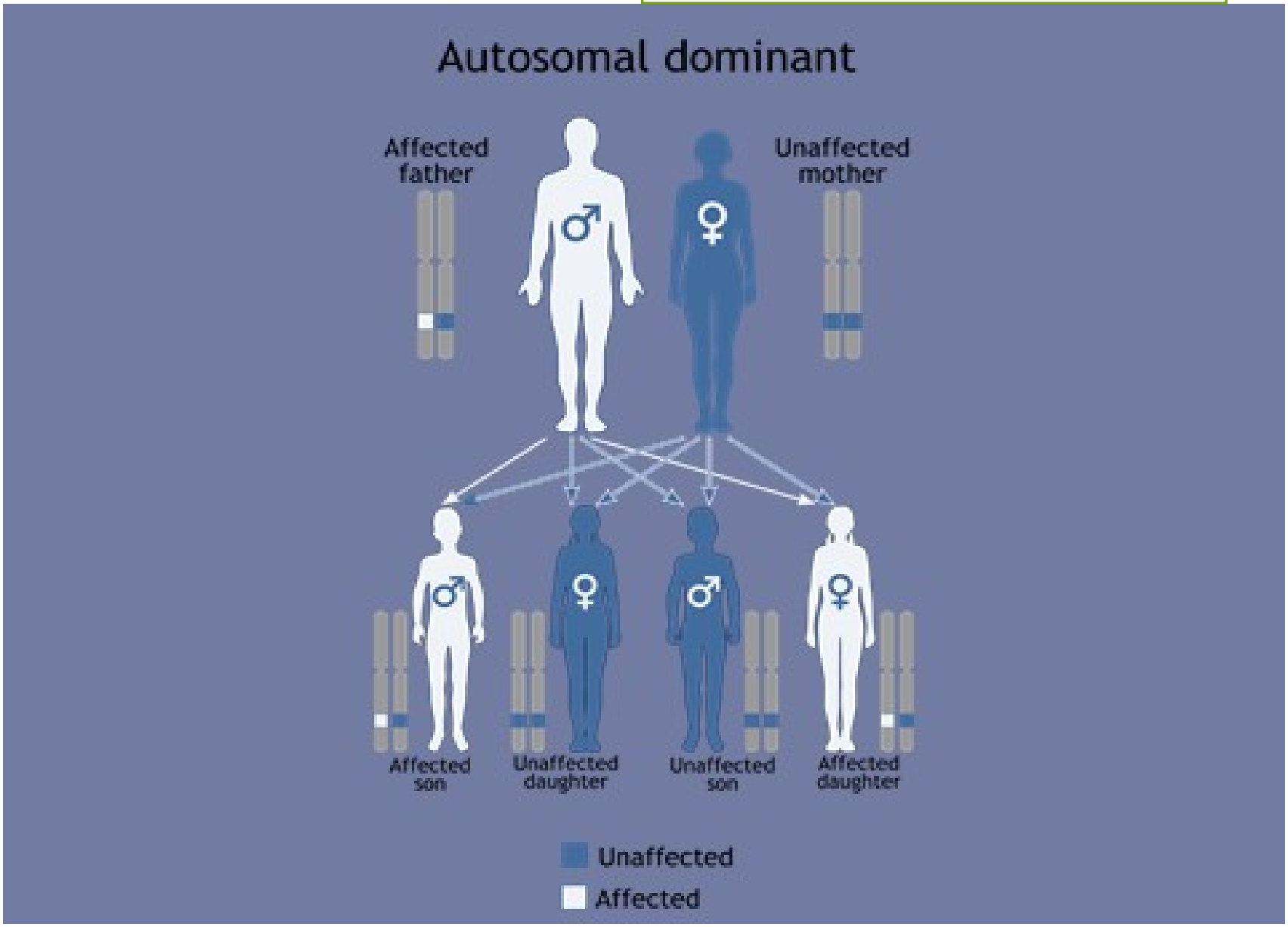
Endocrine : congenital adrenal hyperplasia.-

Nervous: spinal muscular atrophy.-

Autosomal Dominant Disease

- The transmission occurs from one parent to the child.
- The responsible mutant gene can arise by- spontaneous mutant gene.
- The affected cases in multiple generation,- which is called vertical or perpendicular inheritance. (grand parent-parent-child)

- affected equally ♀ & ♂ -
- The recurrence risk is 50%-


Autosomal dominant
Affected father
Unaffected mother
Affected son
Unaffected daughter
Unaffected son
Affected daughter
Unaffected
Affected

The finding of male-to-male transmission essentially confirms AD inheritance.

For many patients with AD disorder there is no history of an affected family member, which could be explained by:

A-New mutation.

B-Incomplete penetrance:- not all the individuals who carry the mutation have phenotypic manifestations.

C-Variable expression: manifestations of the disorder in different degrees.

D-Somatic mutations: the mutation occur not in the egg or sperm that forms a child but in the cell of an developing embryo

Examples of autosomal dominant : disease

. Nervous: tuberous sclerosis-

. Urinary : polycystic kidney-

. Gastrointestinal : familial polyposis-

Haemopoitic : hereditary spherocytosis,-
.von willebrand disease

Skeletal : marfan-
.syndrome ,achondroplasia

Metabolic : familial hypercholestrolemia-

X-Linked Recessive Disease

Males are more commonly and more severely- .1
.affected than females

Female carriers are generally unaffected, or if- .2
affected, they are affected more mildly than
.males .3

.4

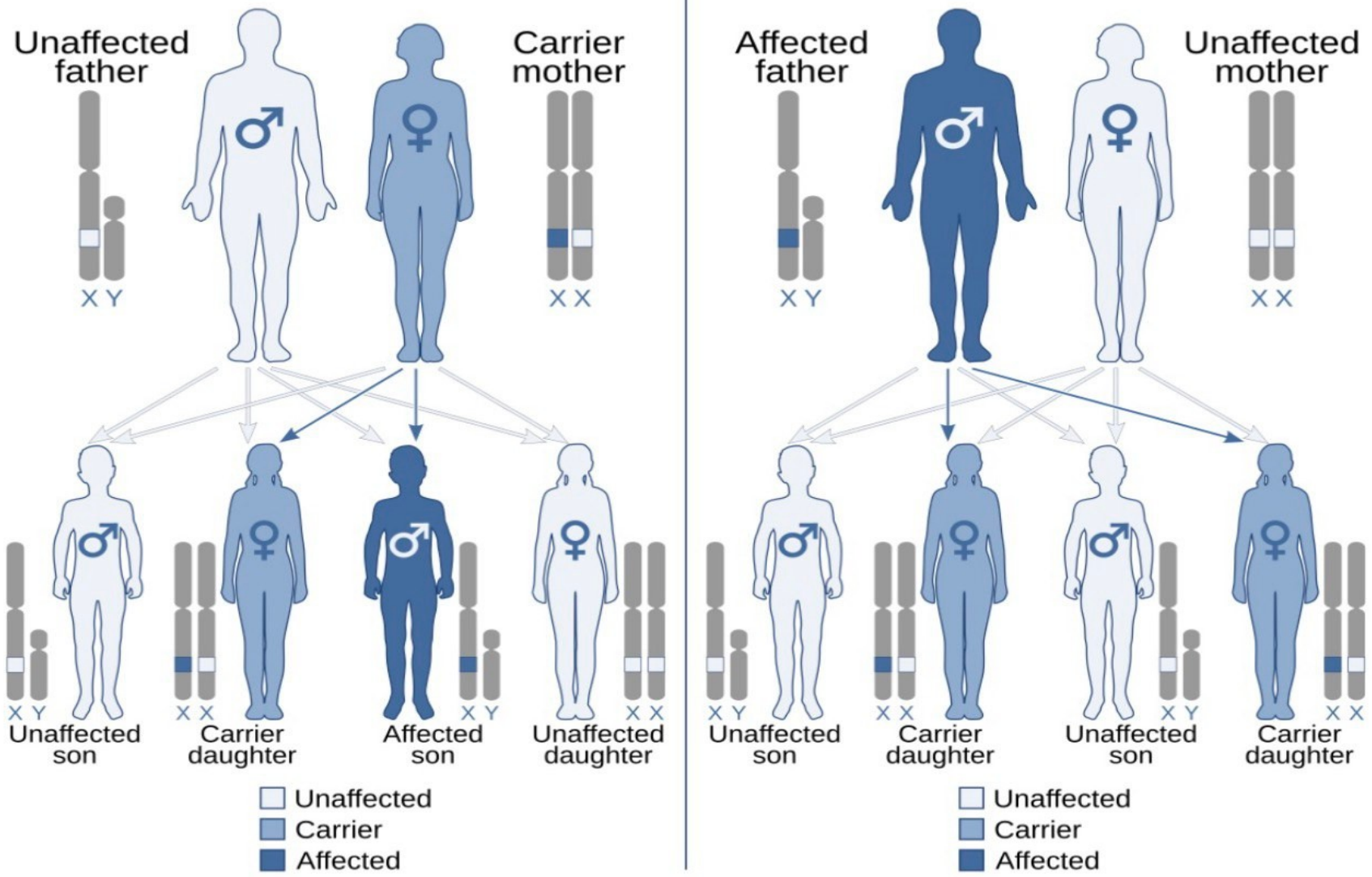
.♀ Only the ♂ is clinically affected via carrier - .5

♂ If the carrier ♀ married from normal- .6
.of sons affected **50%** .7

.of daughters are carrier **50%** .8

.So the chance of affected son is 25% .9

X-linked recessive



Note: a few carriers may be mildly affected due to skewed X-inactivation.

♀ If affected ♂ married from normal-

.All daughters will be carriers

.All sons will be normal

So no ♂ to ♂ transmission but grand son can be-
.♀ affected by carrier

Don't forget to ask about affected uncles from-
mother side or affected sons of sisters because the
.disease is transmitted in indirect vertical descent

- :The ♀ can be affected in .1

- .♂ If she is a product of carrier ♀ & affected -
- .Turner syndrome (XO) -
- Lionization (Lion hypothesis, X chromosome - inactivation): in which only one X chromosome is .active in each cell

: Examples of X-linked recessive

. Haemopoitic : G6PD , Hemophilia A, B

Muscloskeletal: Duchene muscular-
. dystrophy

Immune : wiskott –alderich syndrome-

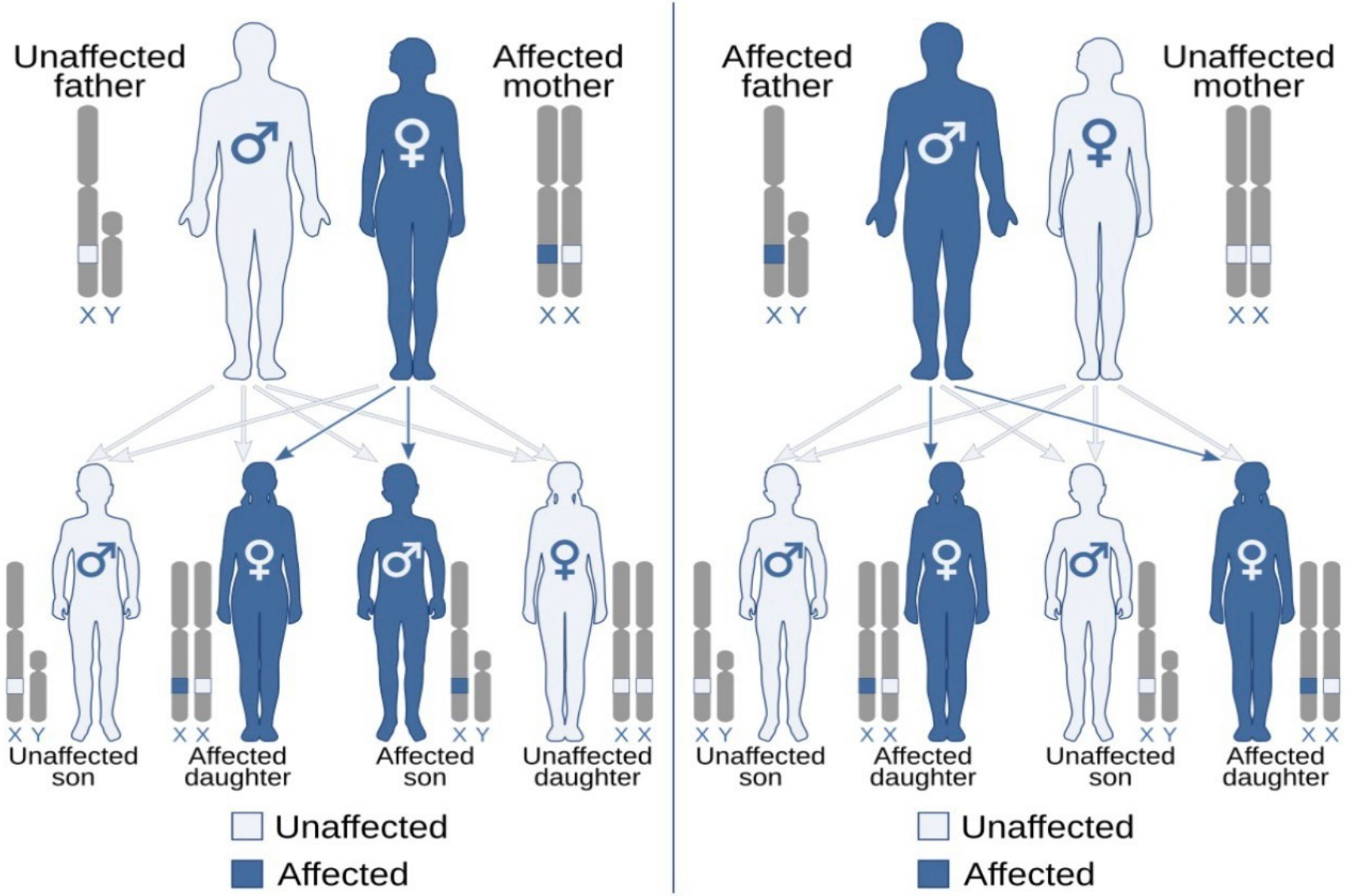
.Metabolic : diabetes insipidus-

.Nervous : fragile X syndrome-

X-Linked Dominant Disease

- .♂ Both ♂ & ♀ affected, but the disease is more severe in-
- .The disease transmitted from one generation to another-
- The affected ♀ transmit the disease to 50% of her-
  .daughters & 50% of her sons
- The affected ♂ transmit the disease to all his daughters-
  but to non of his sons, so the disease appears more
  .♀ common in
- .The pedigree shows only affected females -
- .Vit.D resistant Ricket's, incontinentia pigmenti (.e.g)

X-linked dominant



Note: some X-linked dominant disorders are embryonic lethal in males, and most affect females less severely.

Thanks