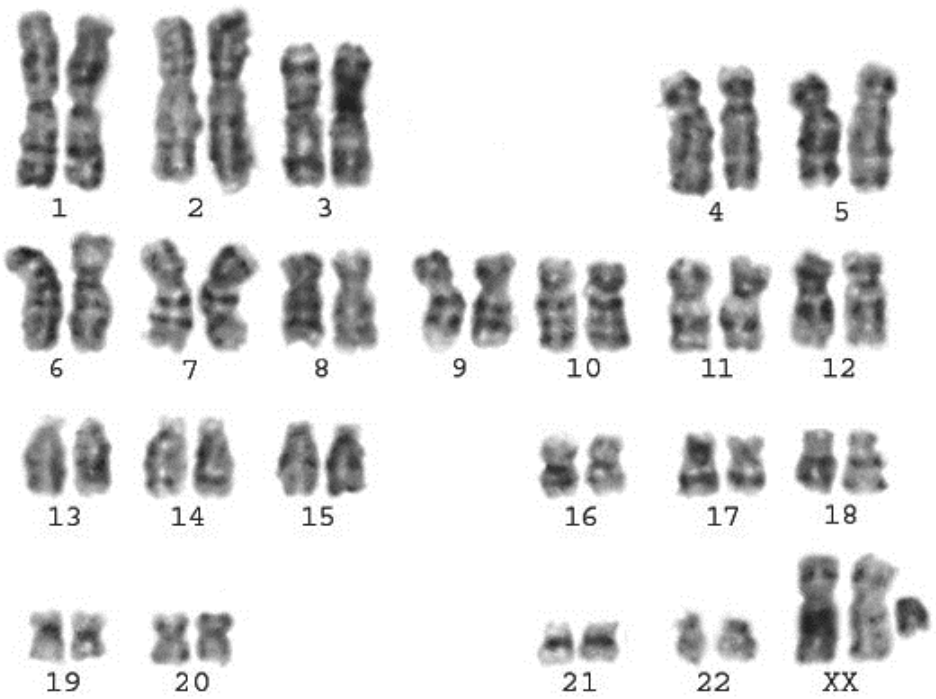
LEARNING OBJECTIVES

What are the single gene disorders with abnormal Mendelian inheritance?

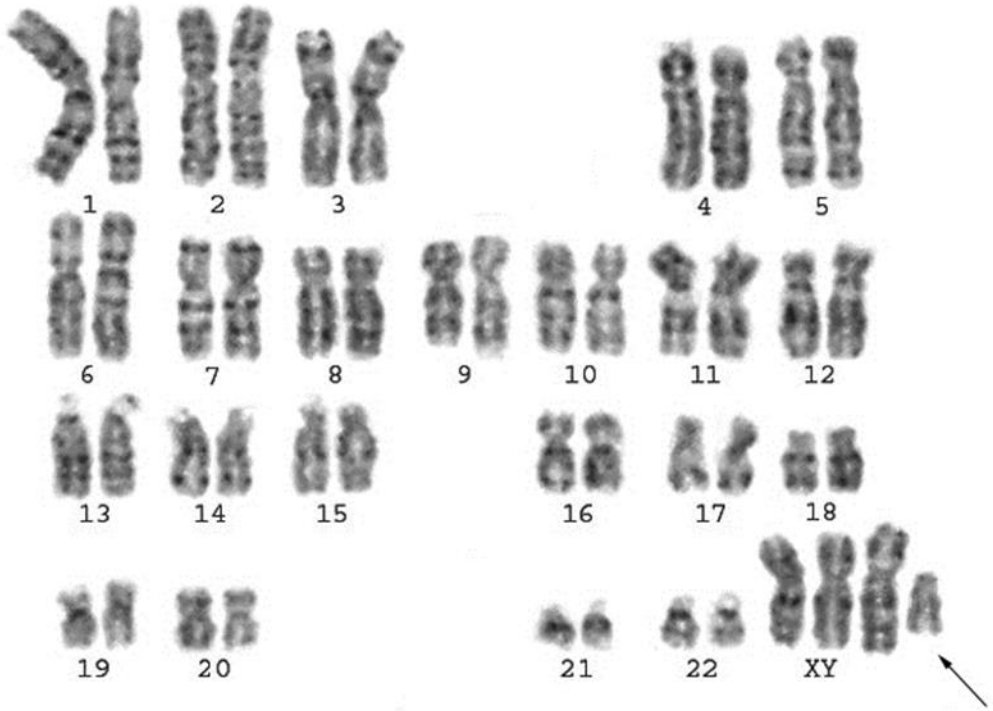
Klinefelter Syndrome

- Klinefelter syndrome is a chromosomal condition that affects male physical and cognitive development.
- Affected individuals typically have small testes that do not produce as much testosterone as usual which can lead to delayed or incomplete puberty, breast enlargement (gynecomastia), reduced facial and body hair, and infertility.
- Older children and adults with Klinefelter syndrome tend to be taller than their peers.
- Children with Klinefelter syndrome may have learning disabilities and delayed speech and language development.

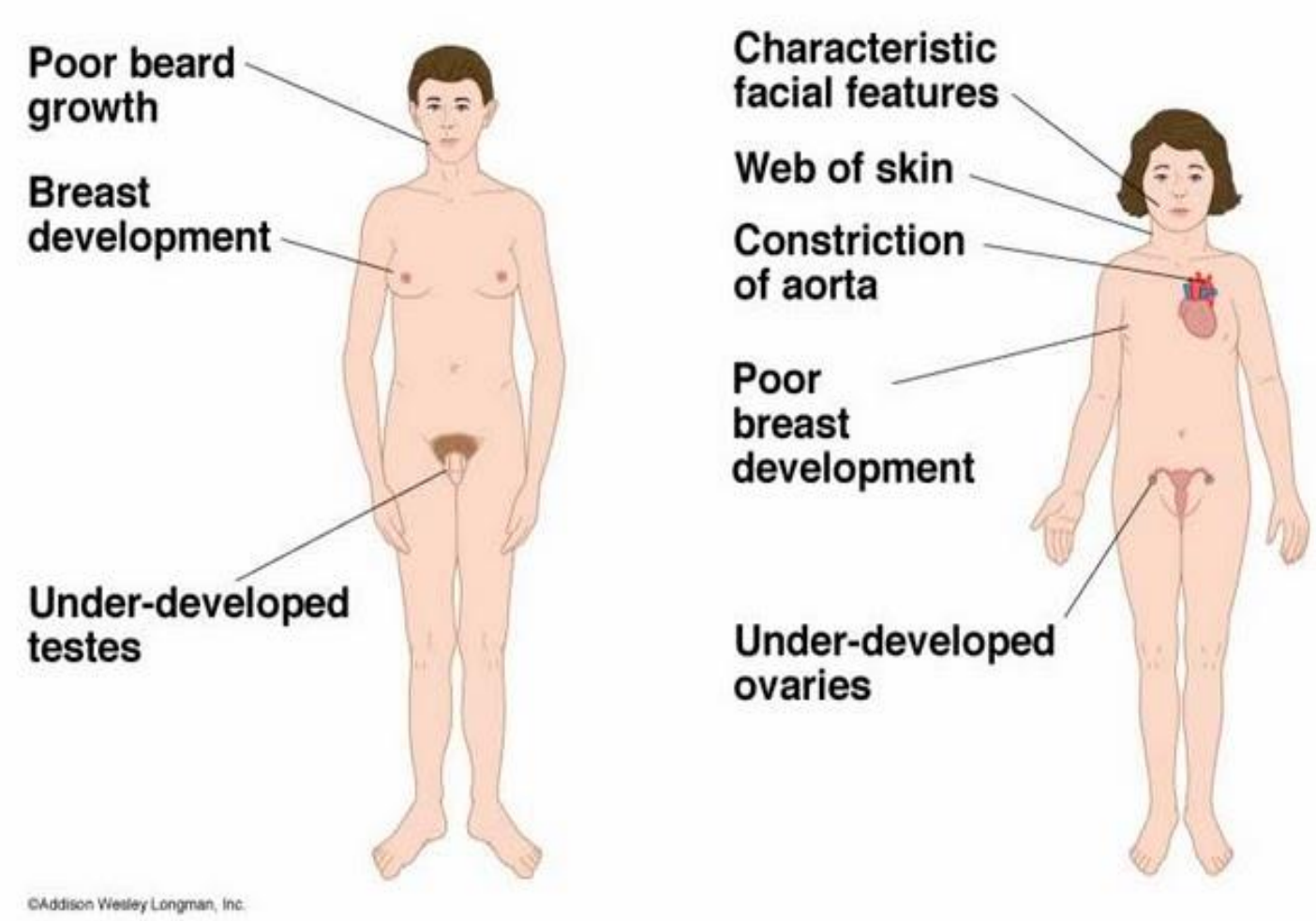
- Klinefelter syndrome affects 1 in 500 to 1,000 newborn males.
- Klinefelter syndrome results from the presence of one extra copy of the X chromosome in each cell (47,XXY).



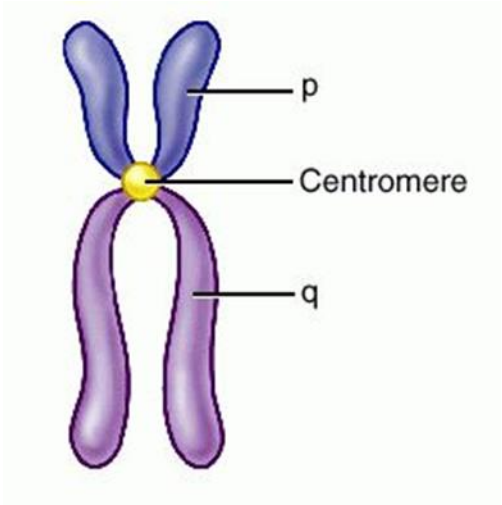
47,XXY



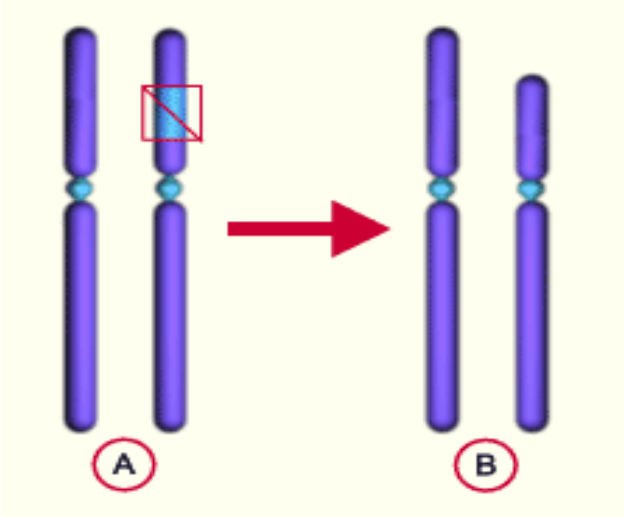
48,XXXY

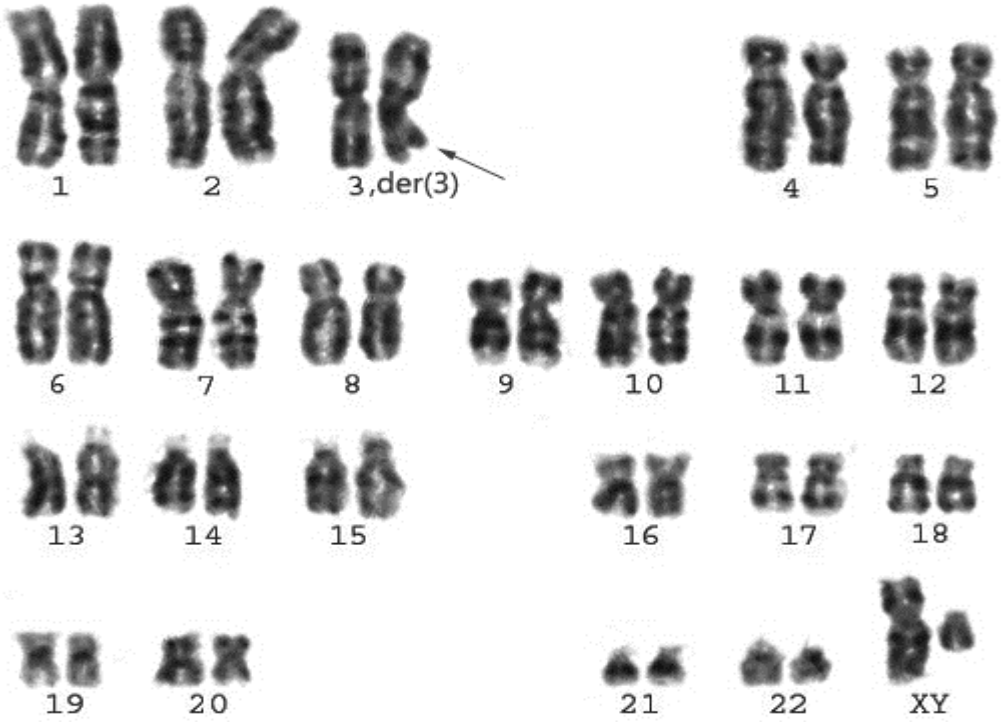

Poor beard growth
Breast development
Under-developed testes
©Addison Wesley Longman, Inc.
Characteristic facial features
Web of skin
Constriction of aorta
Poor breast development
Under-developed ovaries

Structural Abnormalities



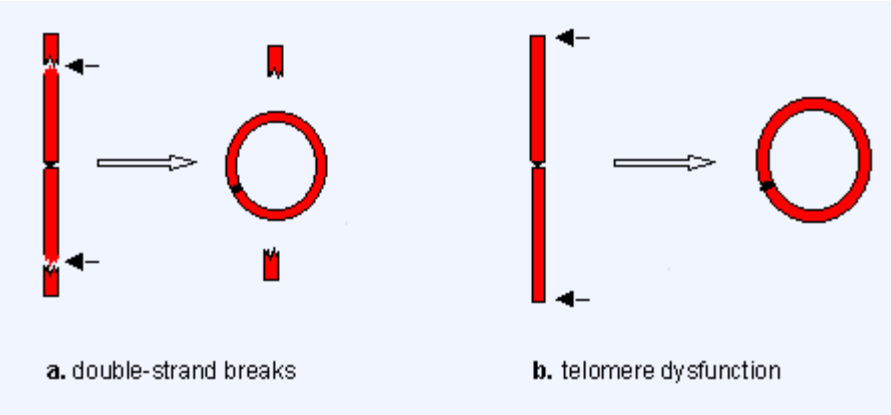
- Deletion: It means loss of a portion of chromosomes.



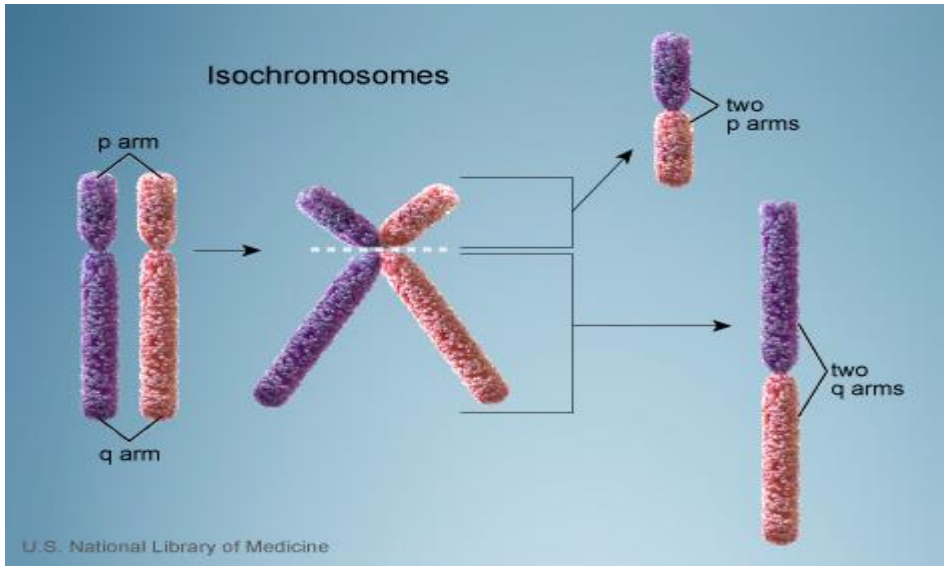


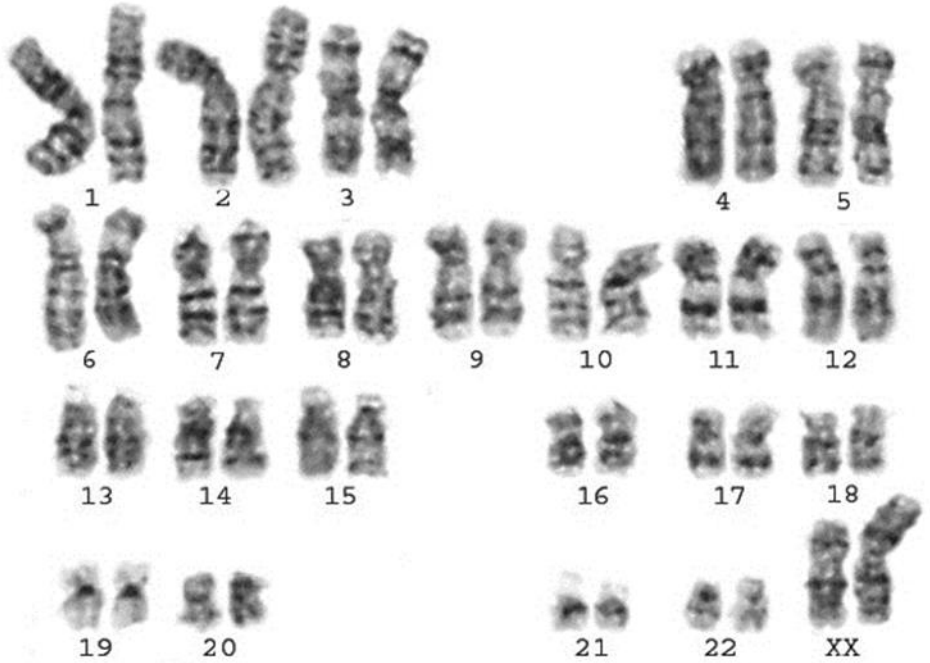
46,XY,del(3)(q26q27.2)

Ring chromosome: It means deletion of both ends of chromosomes with fusion of damaged ends.



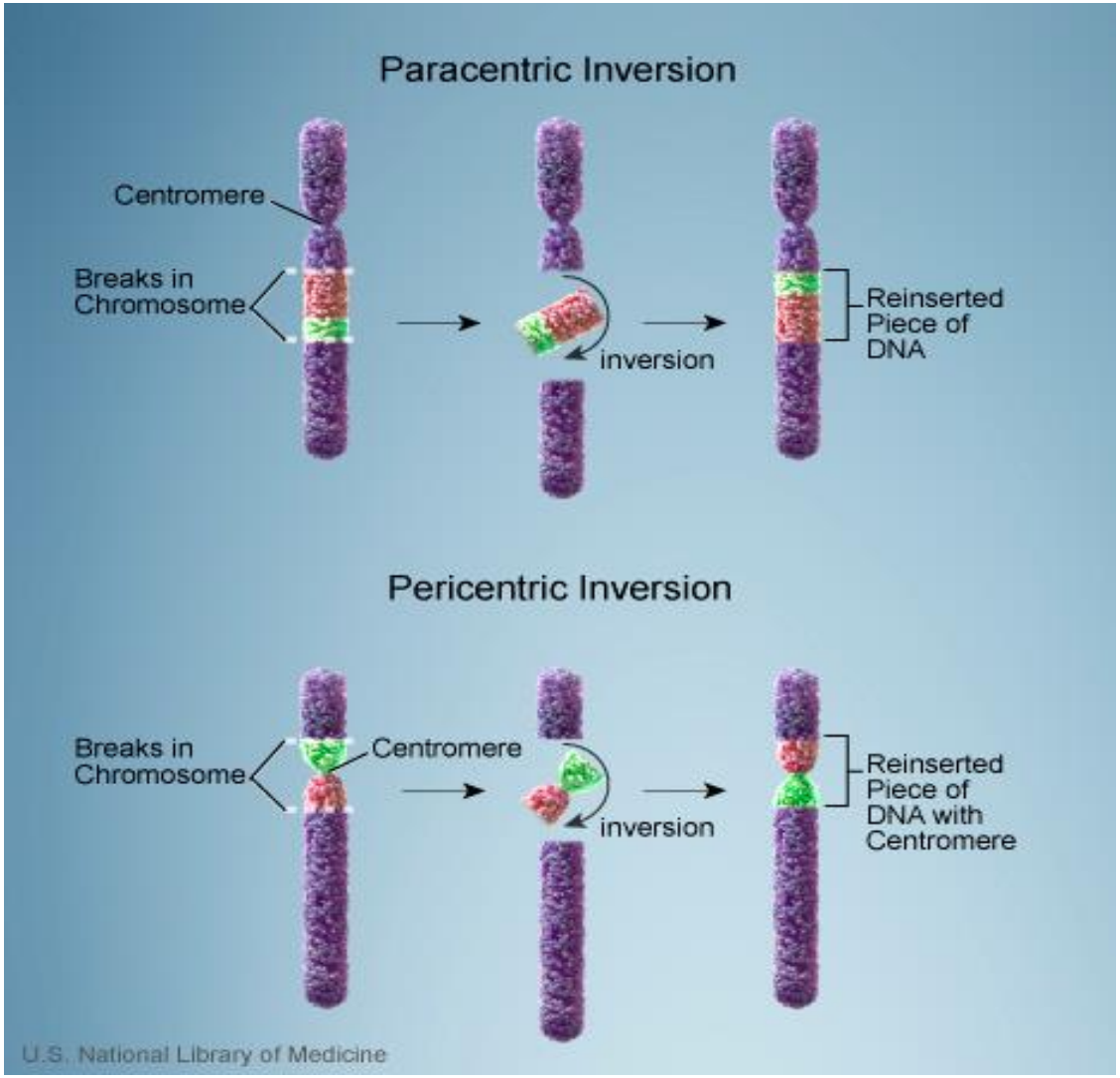
- **Isochromosome:** A chromosome produced by transverse splitting of the centromere so that both arms are from the same side of the centromere, are of equal length, and possess identical genes.

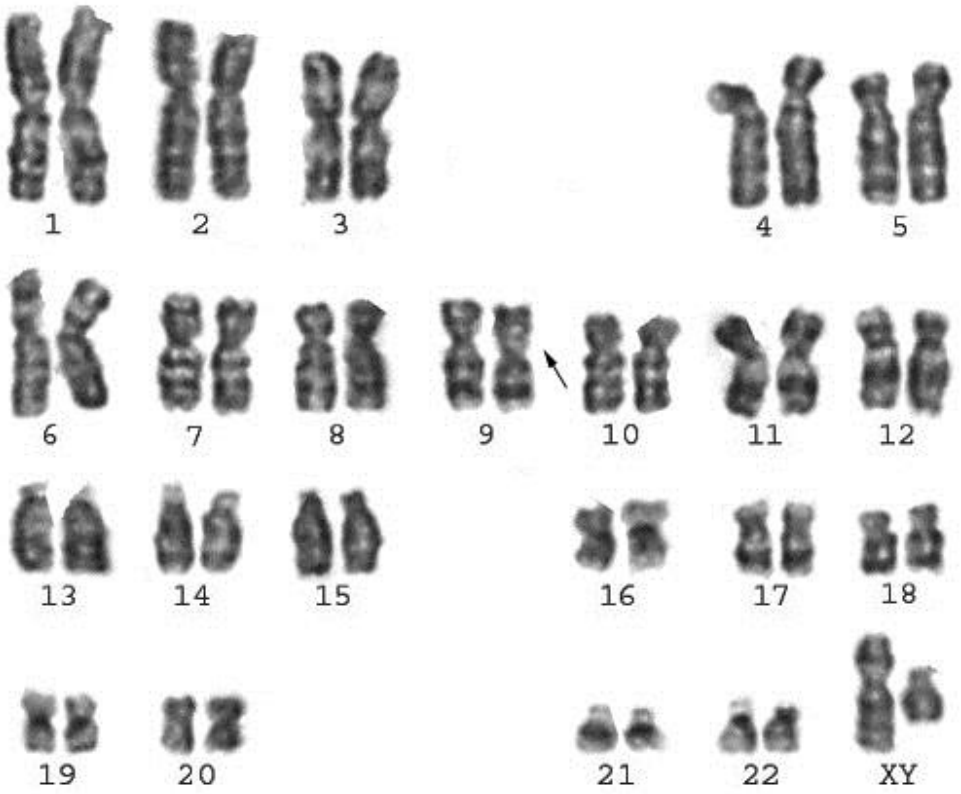




46,X,i(Xq)

- Inversion: A chromosomal rearrangement in which a segment of genetic material is broken away from the chromosome, inverted from end to end, and re-inserted into the chromosome at the same breakage site.


Paracentric Inversion
Centromere
Breaks in Chromosome
inversion
Reinserted Piece of DNA
Pericentric Inversion
Breaks in Chromosome
Centromere
inversion
Reinserted Piece of DNA with Centromere
U.S. National Library of Medicine



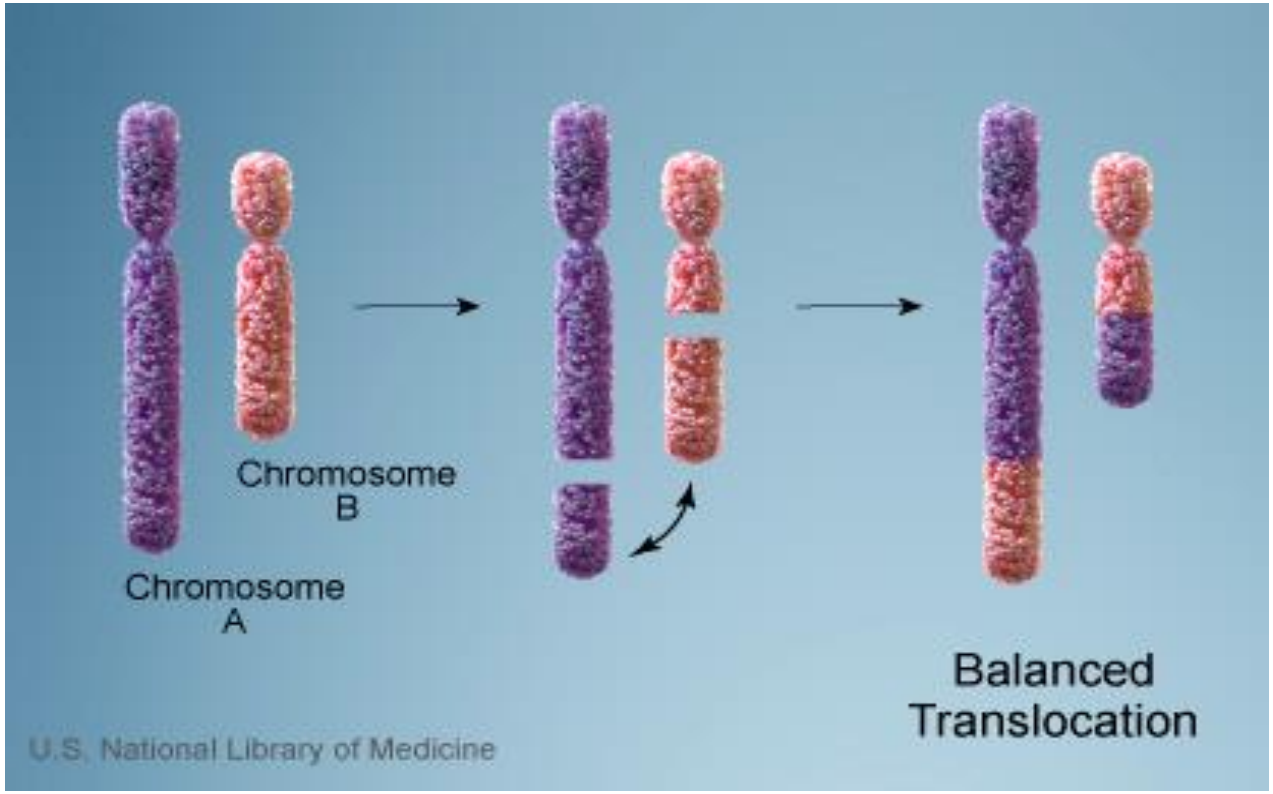
46,XY,inv(9)(p11q13)

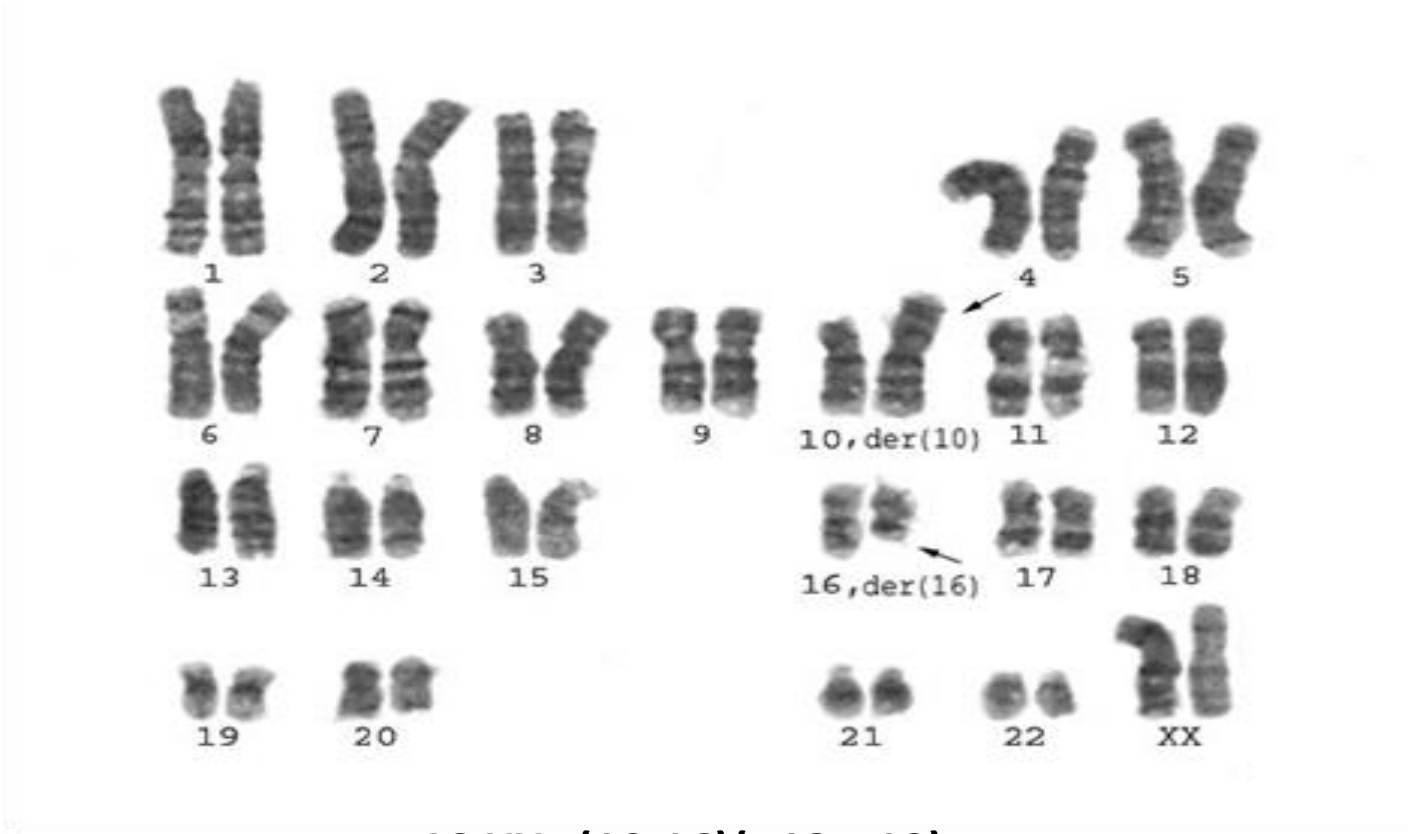
- Translocation:

A chromosome alteration in which a whole chromosome or segment of a chromosome becomes attached to or interchanged with another whole chromosome or segment.

- **Balanced translocation:**

There is no net loss or gain of chromosome material, usually not associated with phenotypic abnormalities, although gene disruptions at the breakpoints of the translocation can, in some cases, cause adverse effects, including some known genetic disorders

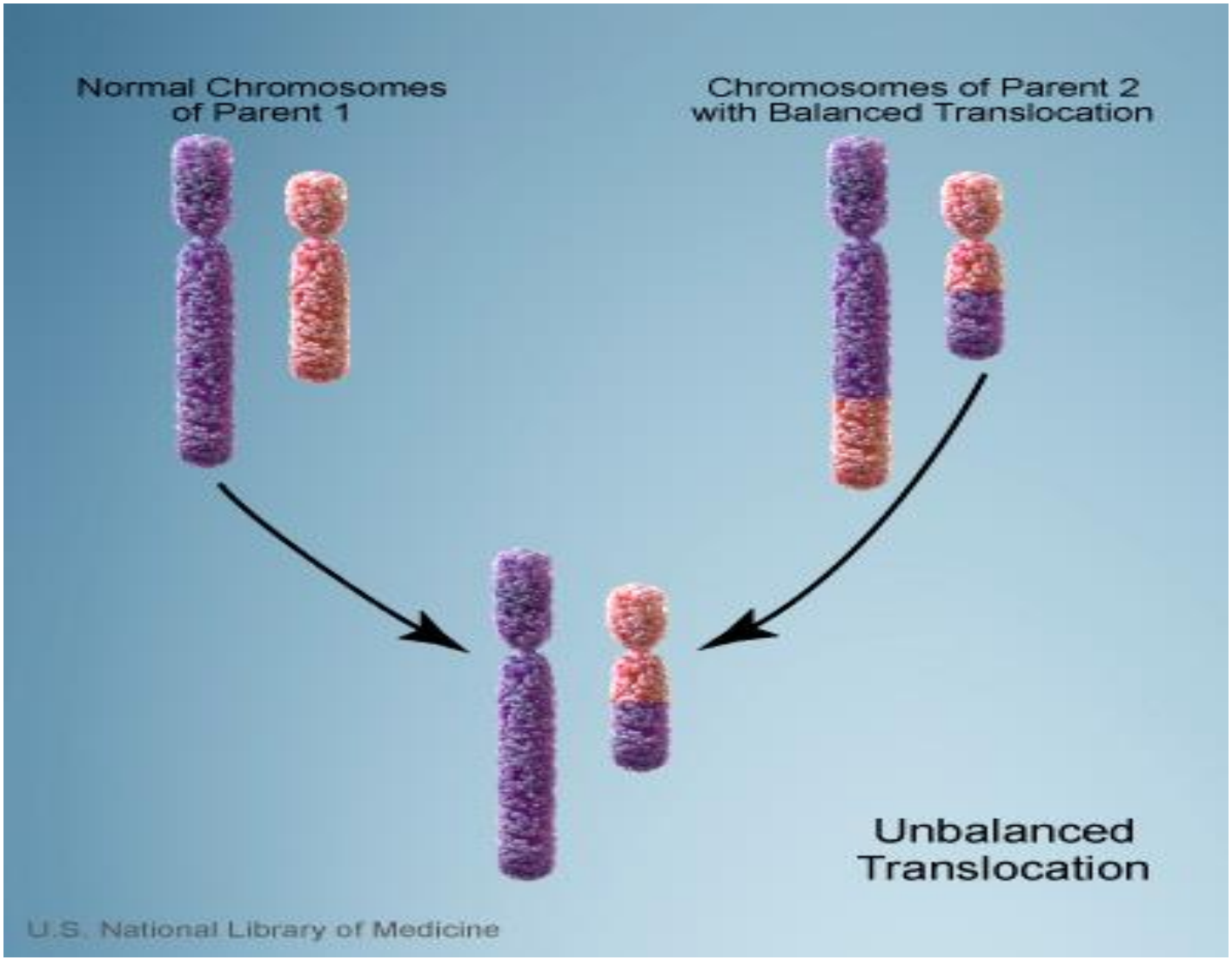

Chromosome
B
Chromosome
A
Balanced
Translocation
U.S. National Library of Medicine

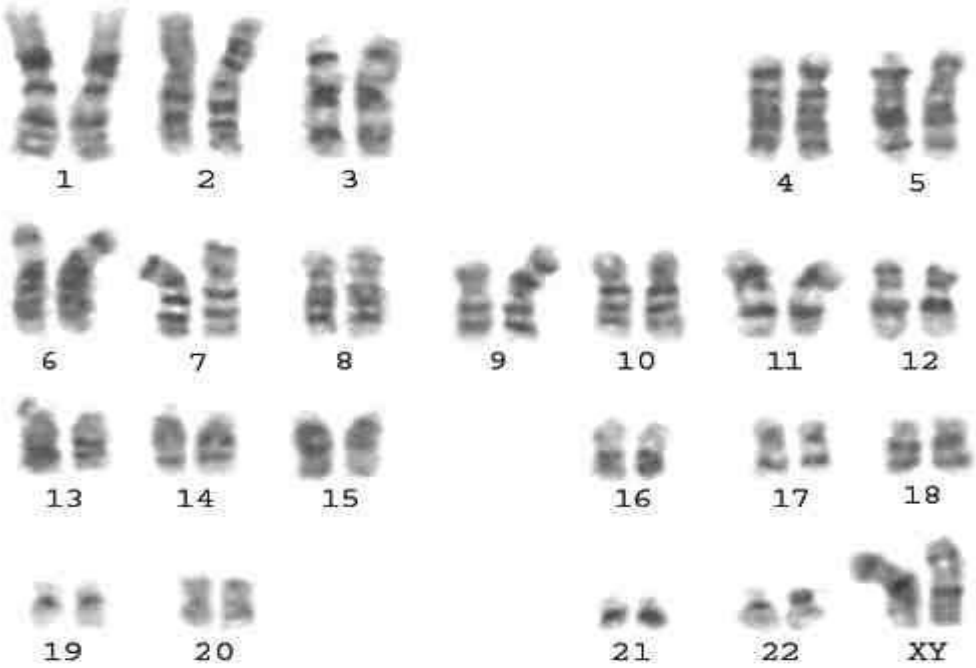


46,XX,t(10;16)(p13;q12)

- **Unbalanced translocation:**

There is loss or gain of chromosome material nearly always yield an abnormal phenotype.

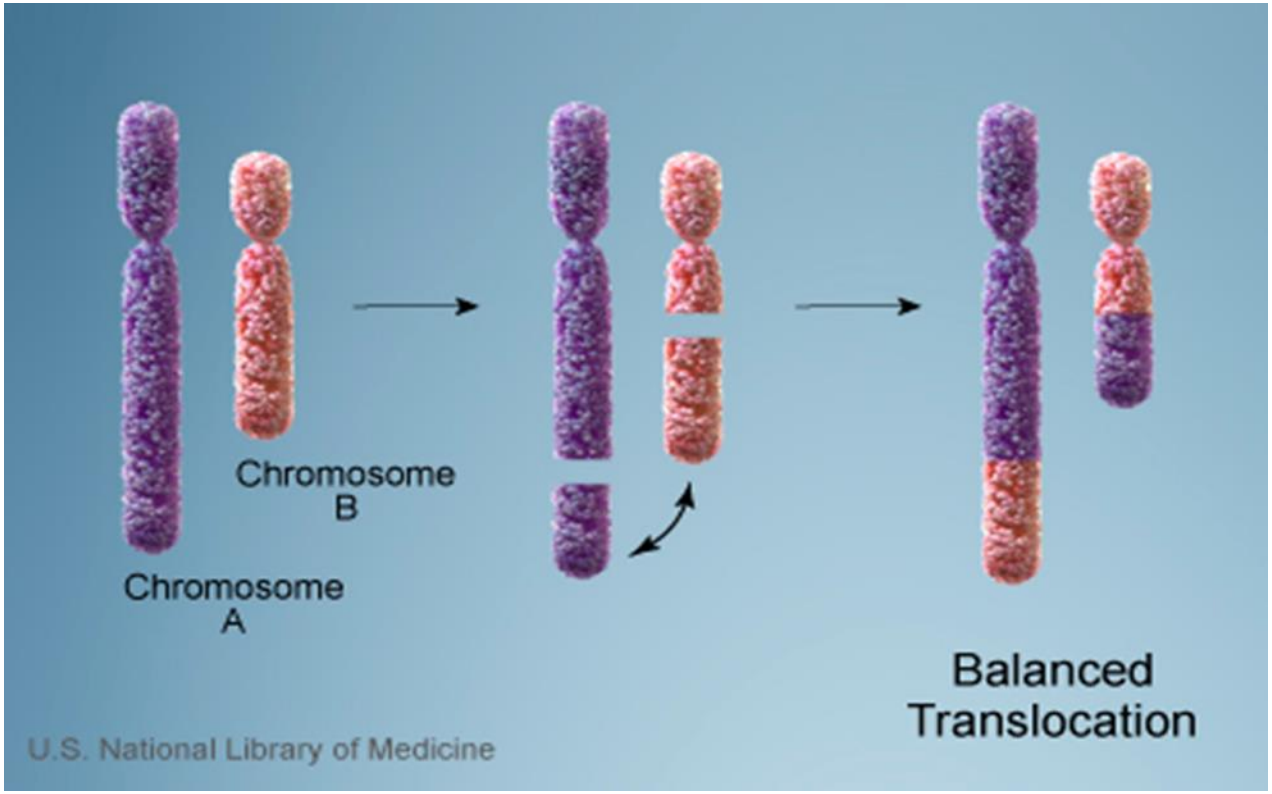

Normal Chromosomes of Parent 1
Chromosomes of Parent 2 with Balanced Translocation
Unbalanced Translocation
U.S. National Library of Medicine



46, XX,add(9)(p22)

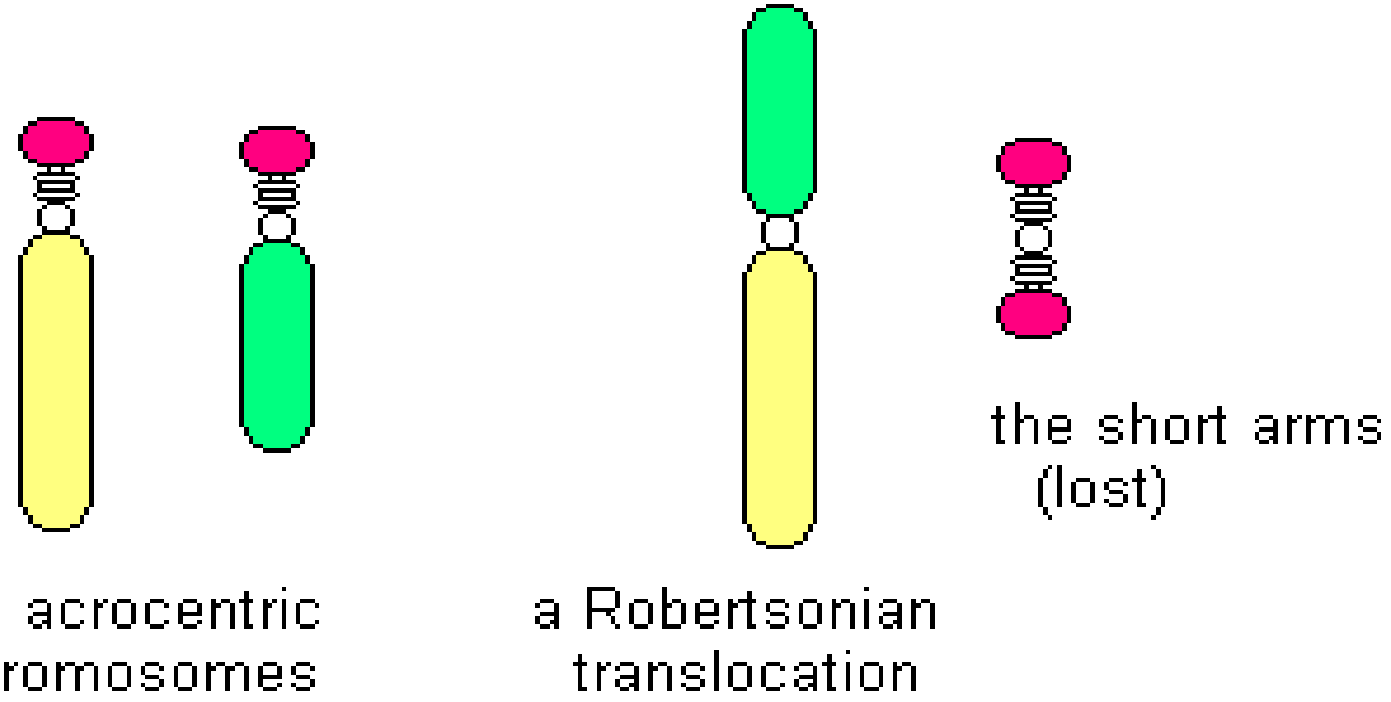
- **Reciprocal translocation:**

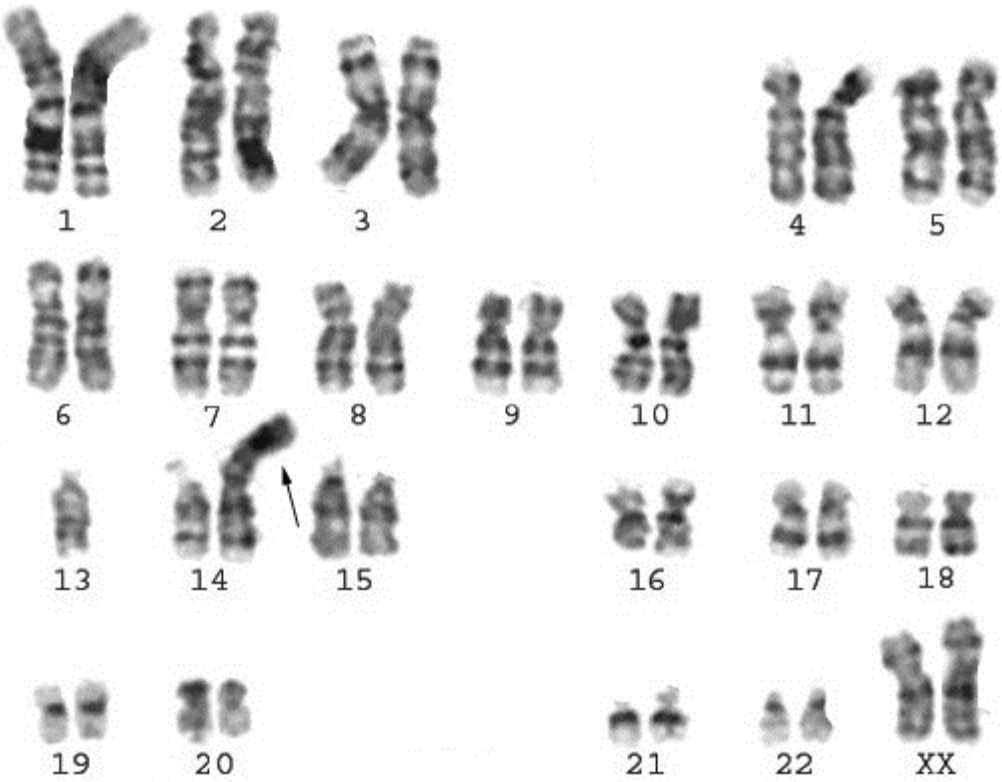
A segment of one chromosome is exchanged with a segment of another chromosome of a different pair


Chromosome
B
Chromosome
A
Balanced
Translocation
U.S. National Library of Medicine

- **Robertsonian translocation:**

The joining of two acrocentric chromosomes at the centromeres with loss of their short arms to form a single abnormal chromosome; acrocentric chromosomes are the Y chromosome and chromosome numbers 13, 14, 15, 21, and 22


two acrocentric chromosomes
a Robertsonian translocation
the short arms (lost)



45,XX,der(13;14)(q10;q10)

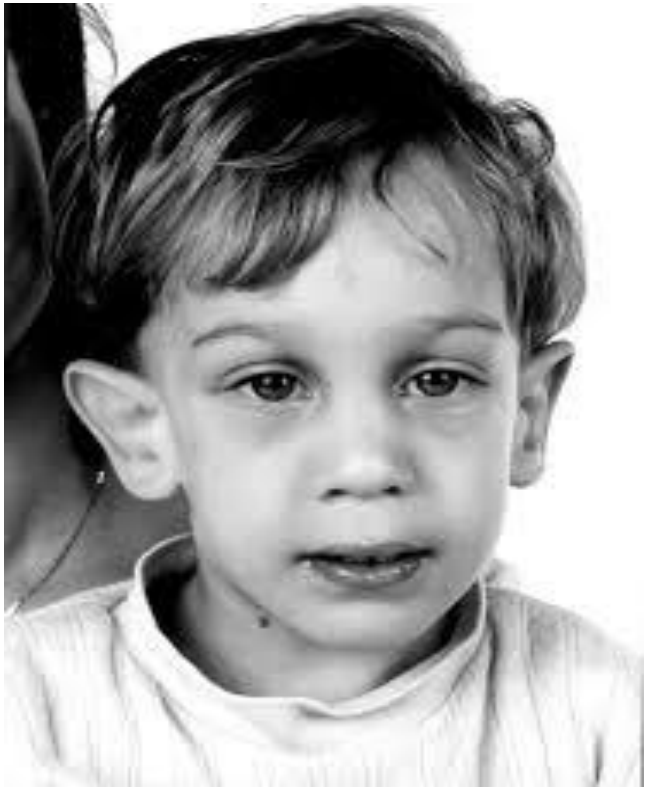
Single gene disorder with non classic inheritance:

- **Fragile X syndrome:**

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment. Usually, males are more severely affected by this disorder than females.

Affected individuals usually have delayed development of speech and language by age 2. Most males with fragile X syndrome have mild to moderate intellectual disability, while about one-third of affected females are intellectually disabled. Seizures occur in about 15 percent of males and about 5 percent of females with fragile X syndrome.

Most males and about half of females with fragile X syndrome have characteristic physical features that become more apparent with age. These features include a long and narrow face, large ears, a prominent jaw and forehead, unusually flexible fingers, flat feet, and in males, enlarged testicles (macroorchidism) after puberty.

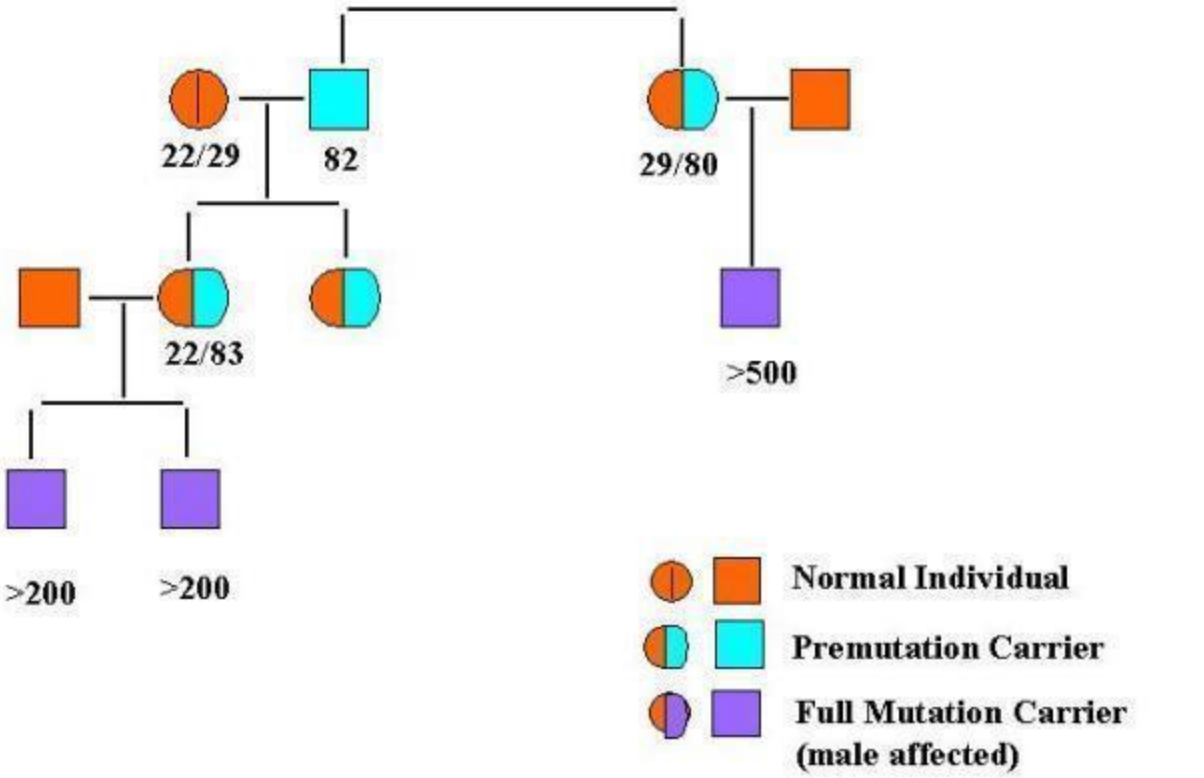


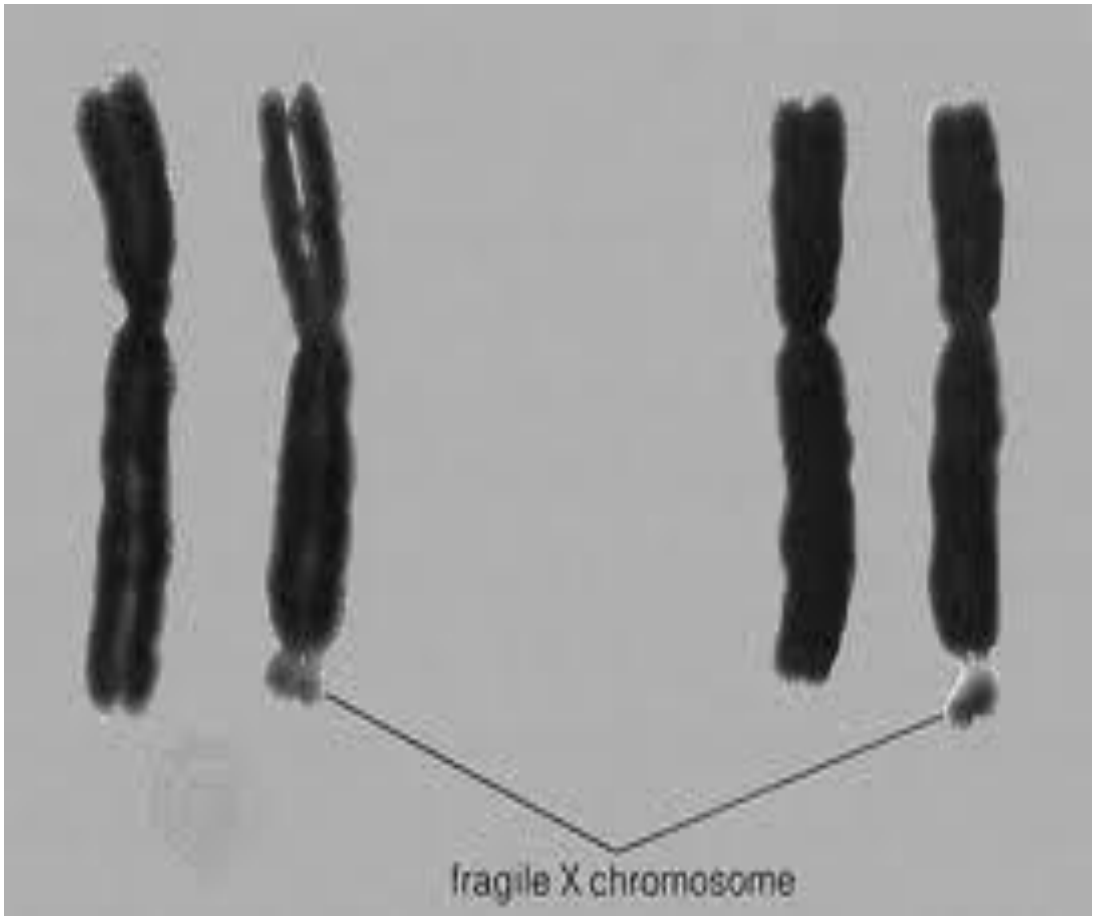
Mutations in the FMR1 gene cause fragile X syndrome. The FMR1 gene provides instructions for making a protein called fragile X mental retardation 1 protein, or FMRP. This protein helps regulate neural functions.

Nearly all cases of fragile X syndrome are caused by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the FMR1 gene. Normally, this DNA segment is repeated from 5 to about 40 times. In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times. The abnormally expanded CGG segment turns off (silences) the FMR1 gene, which prevents the gene from producing FMRP. Loss or a shortage (deficiency) of this protein disrupts nervous system functions and leads to the signs and symptoms of fragile X syndrome.

Males and females with 55 to 200 repeats of the CGG segment are said to have an FMR1 gene premutation. Most people with a premutation are intellectually normal.

Fragile X Syndrome Pedigree




fragile X chromosome