Genetics
& Cell biology

◉ Sheet ○ Slides

Number

4

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Last time we talked about chromosomal abnormality and associated human disorder specifically the autosomal aneuploidy (Down syndrome, Edward syndrome and Patau syndrome) also we talked about special case of Down syndrome (partial trisomy 21)

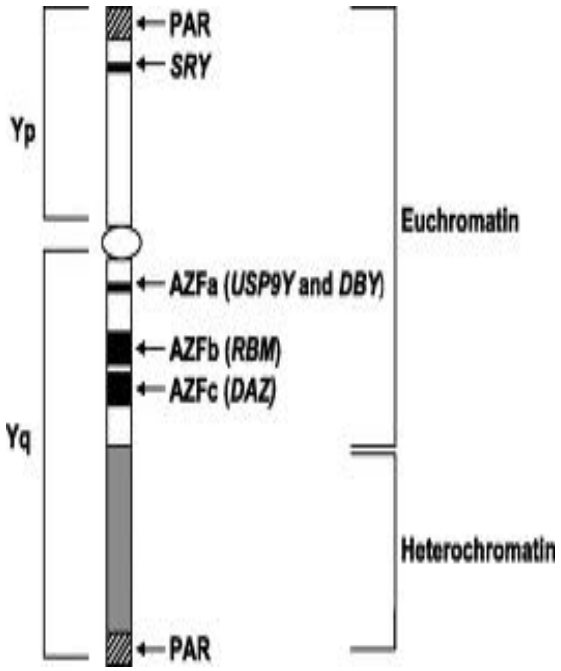
Today we will continue talking about human disorder associated with sex chromosomal abnormality.

The Chromosomal Basis of Sex

- In humans and other mammals, there are two varieties of sex chromosomes: a larger X chromosome and a smaller Y chromosome , they differ in size , number of genes on each chromosome, X chromosome contain 900-1400 genes while Y chromosome contain 70-200 genes and this reflected in the size (X chromosome larger than Y chromosome)
- There are some region that are comparable between X and Y chromosome (i.e. they have 2 alleles) but most of the genes are unique to X chromosome (Therefore, in male we cannot called these genes homozygous or heterozygous instead we call them hemizygous), and some of genes are present only on Y chromosome.

Hemizygous: Having only a single copy of a gene instead of the customary two copies. All the genes on the single X chromosome in the male are hemizygous.)

- On the P arm of the Y chromosome there is region called SRY region (**Sex-determining region Y**)
- During embryonic development , the embryo Will develop to female (by default), but when the SRY region present on the Y chromosome the embryo will develop to male , that is why some cases are 46, XY but sexually they are female due to abnormal deletion in the SRY region.
- On the q arm of the male Y chromosome there is regions called (AZFa, AZFb, AZFc) , deletion in these region are associated with inability to produce sperm (infertility).

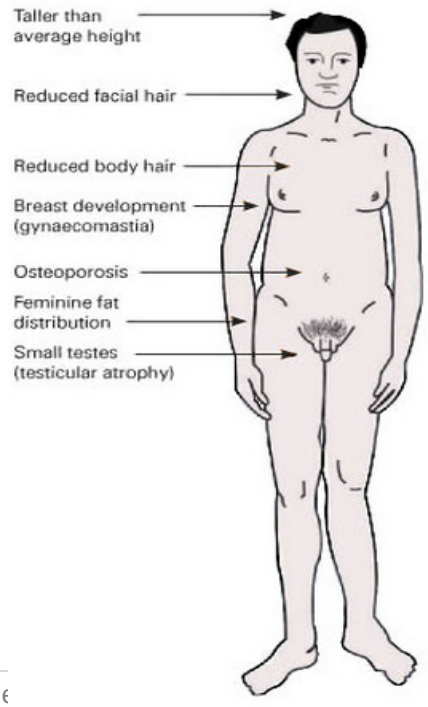


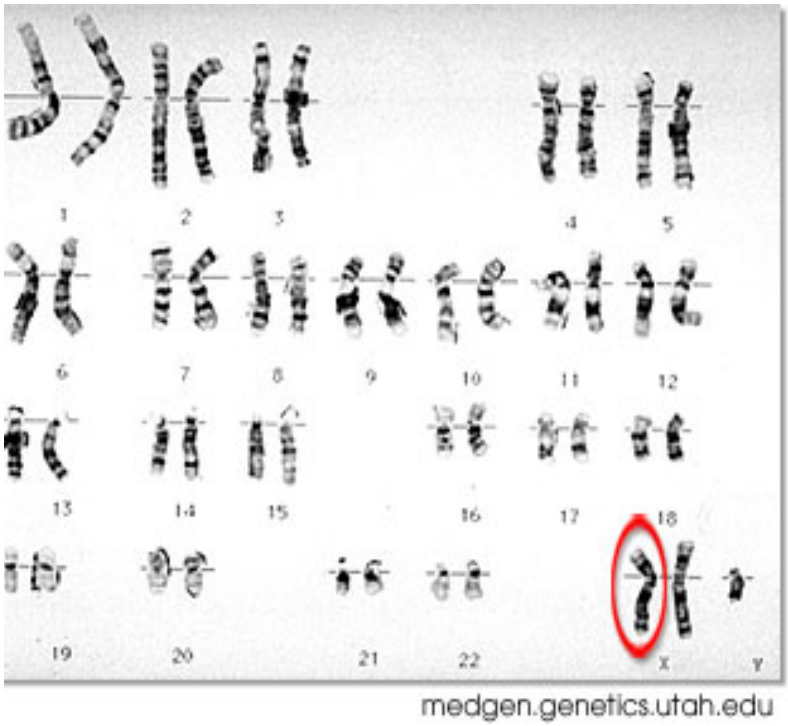
- Not all genes on X chromosome are sex related genes; some of them have nothing to do with sex, e.g. DMD gene , mutation in this gene result in duchenne muscular dystrophy (weakness in the peripheral muscles), HEMA (hemophilia A)gene has nothing to do with sex but it present on the X chromosome, also colourblindin gene , that cause red green blind, is present on X chromosome even it is not a sexual trait.

❖ Sex chromosome aneuploidy and associated disorders :

1) Kleinfelter syndrome :

- **47, XXY**, Y chromosome with SRY region present, so the primary sexual organ is male but some female characteristic also exist.
- General characteristic of klreinfelter patient :
  - a- Enlarge breast
  - b- Reduced body hair
  - c- Infertility result from testicular atrophy and absent sperm.
  - d- Evidence of mental retardation may or may not be present
  - e- Taller than average height
  - f- feminine fat distribution
  - g- Osteoporosis (a condition characterized by a decrease in the density of bone, decreasing its strength and resulting in fragile bones).





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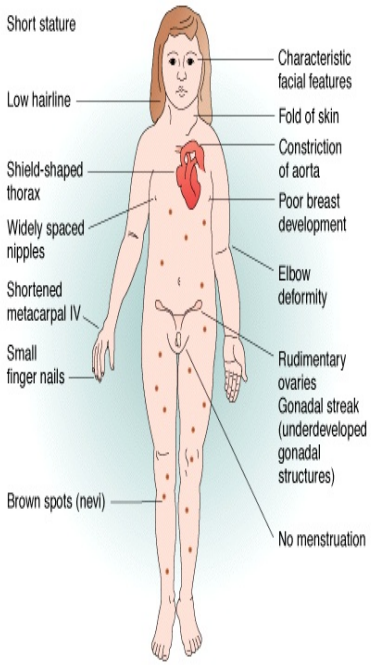
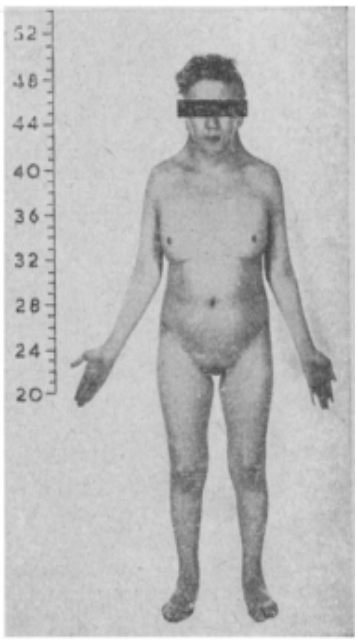
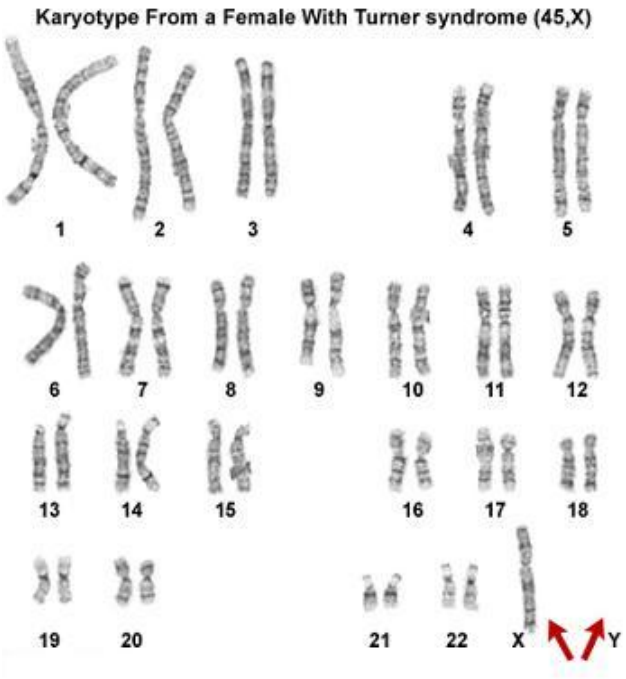
2) turner syndrome:

- **45, X OR 45, X0** , sex is female
- General characteristic of turner patient :
  a- Short stature (about 20 cm below the average)
  b- Low hair line
  c- Characteristic facial features
  d- Webbed neck (fold of skin along the sides of the neck)
  e- Widely spaced nipple
  f- Abnormal size of digit (shortened metacarpal IV)
  g- Small finger nails
  h- Poor breast development
  i- Elbow deformity
  j- No menstruation , underdeveloped primary sexual organ, so ovaries do not produce egg
  k- Nevi (brown spot): abnormal growth of cells but do not reach the level of cancer.







❖ Structurally altered chromosome and associated disorders:

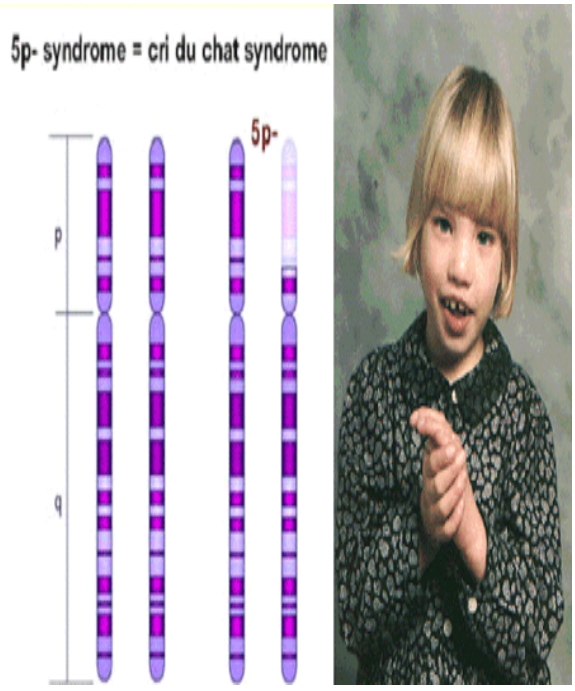
So far we talked about syndromes caused by complete addition or missing of chromosomes , but some time you may find individuals with 46 chromosome even that they have disorders due to change in the structure of chromosome itself.

1) **Cri du chat syndrome (cry of cat):**

- Patient with 46 chromosome and deletion in part of the P arm of chromosome 5.

-approximately 75% of the patient die within first few months of life and about 90 % before they are aged 1 year, but nowadays there is more survive due to more clinical support like help in respiration because these patients have problem in respiration…etc.

- General characteristic of cri du chat syndrome:



a- small head (microcephaly)
b- Unusually round face
c- Small chin
d- Eyes that are very far apart
e- Folds of skin over their eyes
f- Small nose bridge
h- Heart defect
i- Muscular /skeletal problem/ poor muscle tone are also possible
j- Hearing and sight problem
k- Difficulty walking and talking correctly
l- They might have behavior problem like hyperactivity and aggression
m- Some of them may have mental retardation

- Pneumonia, aspiration pneumonia, heart defect and respiratory distress are the most common cause of death.

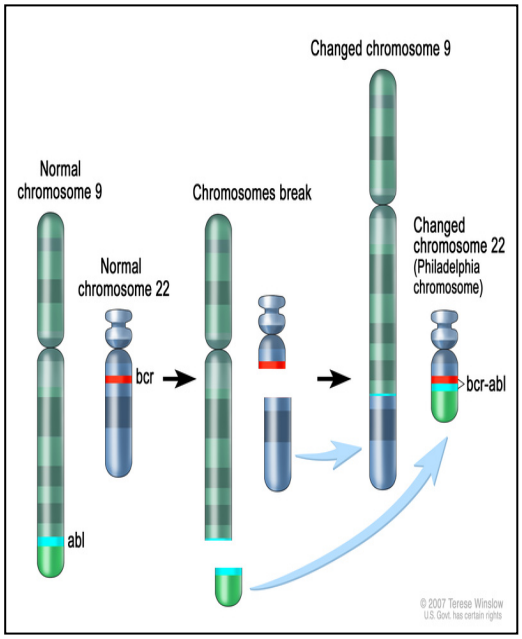
Student question:

If the deletion is in part of one chromosome only and the other homologous chromosome is normal, why there are such clinical features?

Answer : same reason why dominant disorder happen , because some time one copy is not enough (haploinsufficiency) for complete normal phenotype , some time we need both allele to be normal .

2) Chronic myelogenous leukemia

- Normally, Stem cells in bone marrow become myeloid stem cells , then myeloid stem cells make myeloid blast , after that myeloid blast differentiate to monocyte and granulocyte
- Leukemia divided into myelogenous leukemia or lymphoblastic leukemia , each one of them are categorized as acute or chronic , so we have 4 types of leukemia : acute lymphoblastic leukemia, acute myelogenous leukemia, chronic lymphoblastic leukemia and chronic myelogenous leukemia.
- CML (common in adult) can develop from either stem cells or myeloid stem cells.
- Pathogenesis: translocation between chromosome 22 and chromosome 9 results in Philadelphia chromosome (also called derivative 22, because part of it is not from chromosome 22). So there no loss or gain in the DNA, instead the DNA is abnormally rearranged.
- Why this translocation cause CML?
  Because the chromosome contain genes that transcribed into RNA by the RNA polymerase and transcription factors that bind to promoter region of that gene , any change in the promoter region means you lose controlling expression of the gene (increase or decrease its expression).
  In CML the translocation result in moving of the APL gene in chromosome 9 under different promoter, PCR promoter, because PCR promoter is stronger than the original one ,this result in more expression of APL gene → faster cell division → transformation and cancer.



Student question:

Why the cell does not recognize the problem and try to fix it?

Answer: if the mutation passes the repair mechanism, it becomes permanent. On the level of DNA , DNA polymerase make proofreading and make sure that complementary nucleotide was added during DNA replication , each of us on average have in our entire DNA 60 mutation , hopefully , abnormal of those mutation are in agenic region , because gene represent less than 2 %.

Types of translocation:

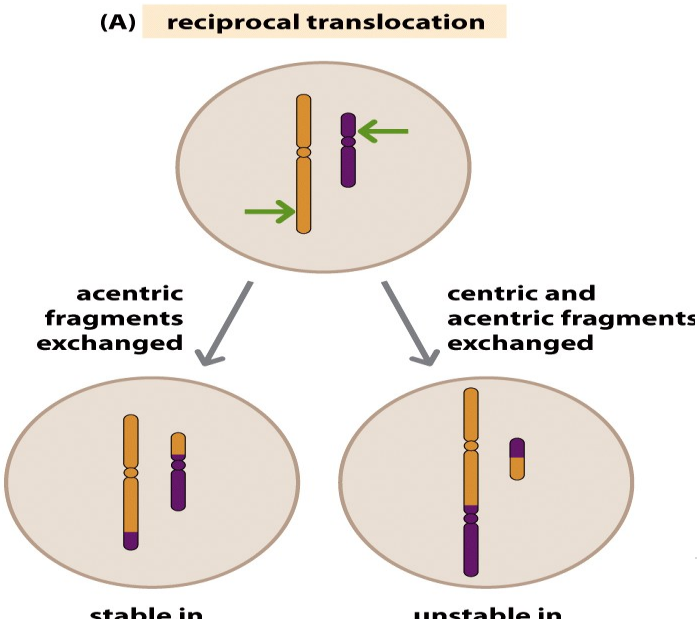
We can classify the translocation mutations into 2 types: reciprocal and robertsonian translocation, we will talk about each of them in details.

1) **Reciprocal translocation:**

- Exchange of genetic material between 2 nonhomologous chromosomes.
- Possibilities :
  - a- First chromosome with part from the second chromosome and second chromosome with part from the first chromosome (one acentric fragment is exchanged for another acentric fragment), and both translocated chromosome carrying its original centromere (centromere for each chromosome is intact) and these 2 translocated chromosome are called derivative 1 or derivative 2 according to the centromere, and the derivative chromosome are stable in mitosis. (left side in the figure)

Or

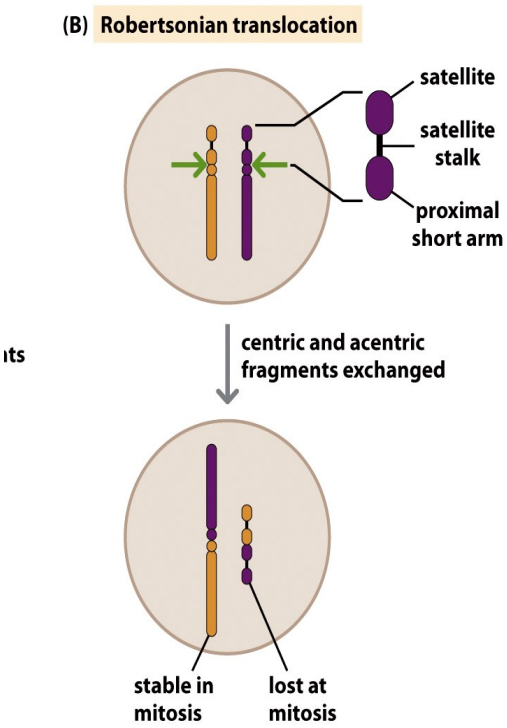
  - b- Acentric fragment is exchanged for centric fragment , which result in dicentric and acentric chromosome , both of them are unstable in mitosis and the acentric chromosome will be lost during cell division .(right side of the figure)



2) Robertsonian translocation

- This is a highly specialized reciprocal translocation in which exchange of centric and acentric fragments produces a dicentric chromosome that is nevertheless stable in mitosis, plus an acentric chromosome that is lost in mitosis (because they are not carrying centromere) without any effect on the phenotype.

- this type occur only on acrocentric chromosomes (13, 14, 15, 21, 22) in which their P arm is very small and very similar in DNA content, each consists of three regions: a proximal heterochromatic region (composed of highly repetitive noncoding DNA), a distal heterochromatic region (called a chromosome satellite), and a thin connecting region of euchromatin (the satellite stalk) composed of tandem rRNA genes (1-2 Mb), so losing these region is not a big deal.



- Breaks that occur close to the centromere can result in a dicentric chromosome in which the two centromeres are so close that they can function as a single centromere. The loss of the small acentric fragment has no phenotypic consequences because the only genes lost are rRNA genes that are also present in large copy number on the other acrocentric chromosomes.

But why we study this?

because not all translocation are necessarily disease causing , for example if I have translocation between 2 chromosomes and the translocation (cut) happen in a heterochromatin region this typically will not cause a disease.

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Possible outcomes of meiosis in a carrier of a balanced reciprocal translocation

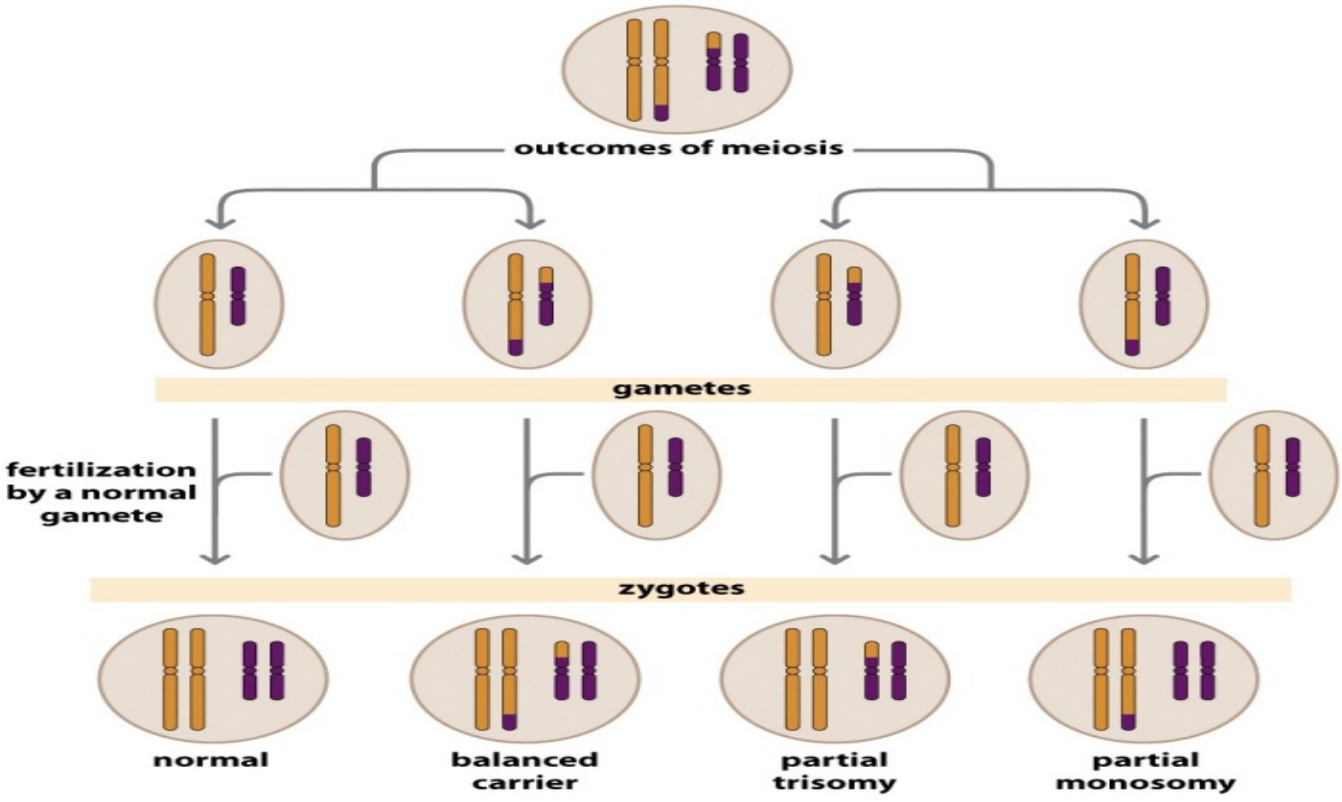
- Assume we want to produce a gamete in a carrier with balanced reciprocal translocation (remember: during meiosis, the homologous chromosome will separate and each daughter cell will receive one copy of each chromosome).

Possibilities:

1) First gamete receive 2 untranslocated (normal) chromosome , result in normal gamete→ fertilization → normal individual
   And Second gamete receives 2 translocated chromosomes (balanced), no gain or loss in DNA → fertilization→ normal individual (balanced carrier).

2) First gamete receive translocated chromosome (purple colour) and untranslocated chromosome (brown colour), so there is a missing part of purple chromosome and extra part of brown chromosome → fertilization→ individual with partial trisomy of brown chromosome and partial monosomy of purple chromosome .

Second gamete is similar to the first one and after fertilization the individual will result with partial trisomy of purple chromosome and partial monosomy of brown chromosome.



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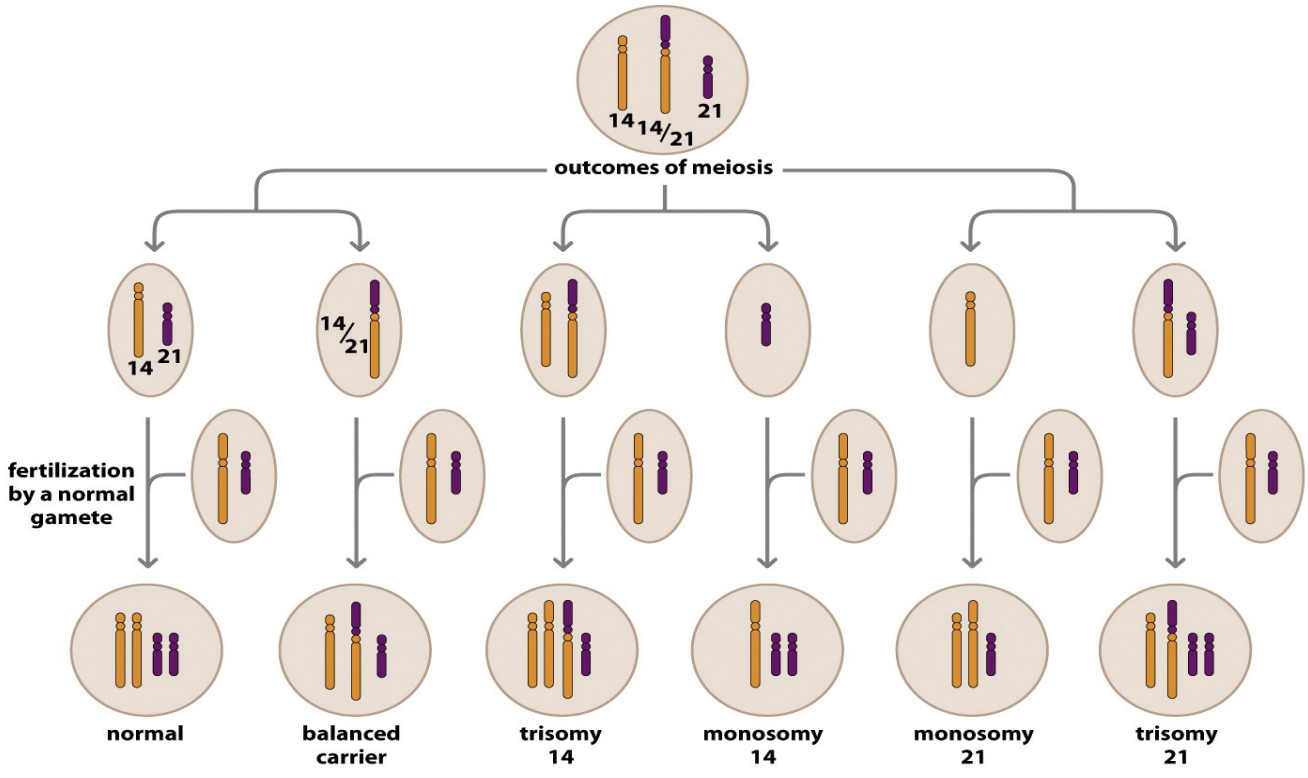
Possible outcomes of meiosis in a carrier of a Robertsonian translocation

- Assume we have a carrier with robertsonian translocation (q arms of chromosome 14 and 21 are fused together), this individual is normal without any clinical feature, but the problem is when gamete produce, because this individual often produce unbalanced gametes that can result in a monosomic or trisomic zygotes.
- **<u>Possibilities</u>** :
  1) First gamete receive chromosome 14 and 22 (normal) → fertilization → normal individual
     And second gamete receive fused chromosome 14 and 22 (balanced carrier) → fertilization → normal (balanced) individual
  2) First gamete receive chromosome 14 and fused chromosome → fertilization→ trisomy 14
     And the second gamete receive only chromosome 21 → fertilization → monosomy 14
  3) First gamete receive chromosome 14 only → fertilization → monosomy 21
     And second gamete receive chromosome 21 and fused chromosome → fertilization → trisomy 21**.**



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Student question:
Why we consider individual with fused chromosome 14 and 21 normal?
Answer : because we have nothing in the P arm of acrocentric chromosme except ribosomal DNA and this part is also present in large copy number on the other acrocentric chromosomes, so losing p arm is not an issue, all what we care about is q arm .
Student question:
Is fused chromosome 14 and 21 moncentric or dicentric ?
Answer : dicentric , but the 2 centromere are very closed to each other , that is why some time is treated as homologous for chromosome 14 and sometime as homologous for chromosome 21 during metaphase and anaphase.

Do not confuse between recombination and translocation

- Recombination: exchange of genetic material between non sister chromatid of homologous chromosomes.
- Translocation: exchange of genetic material between non homologous chromosomes.

We talked about 2 different scenarios

1) Aneuploidy : not the exact multible of n , gain or loss of chromosomes ,e.g. individual with 45 or 47 chromosomes
2) Structurally altered chromosome: individual with 46 chromosomes but the chromosome itself is abnormal.

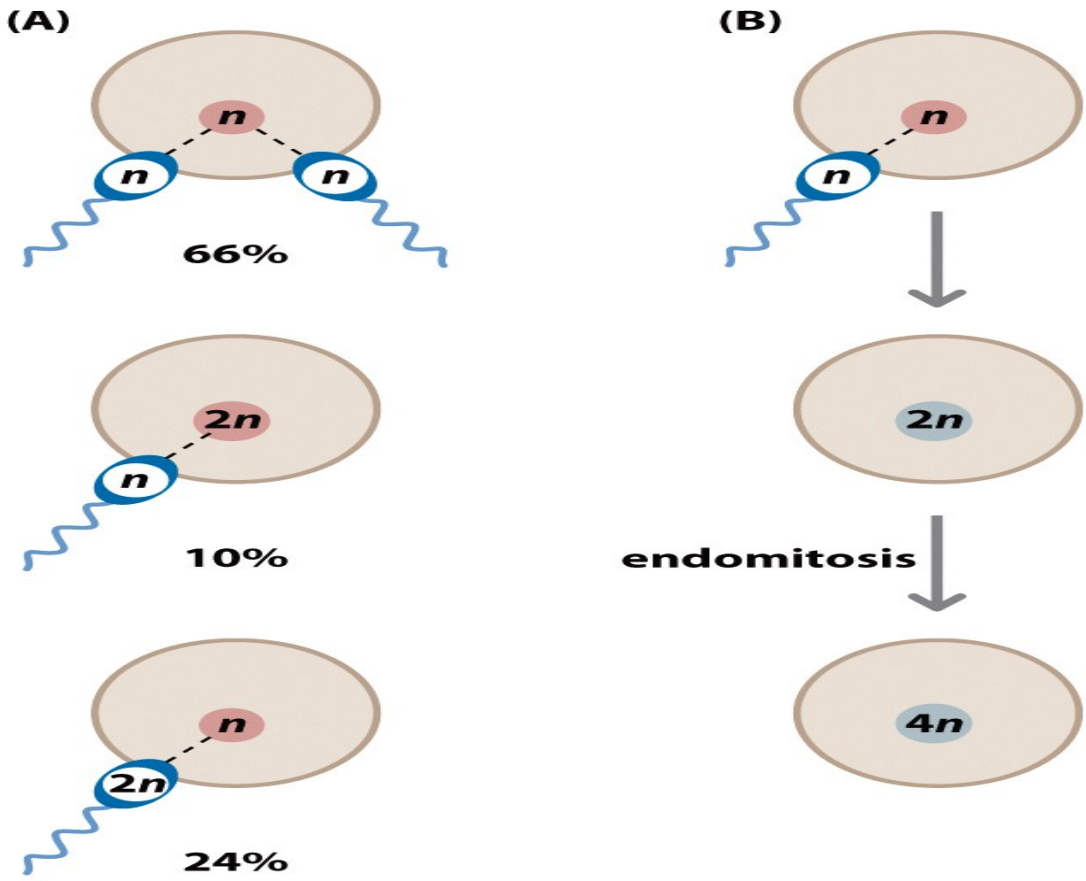
Now we will talk about 3rd scenario which is polypoidy.

Polypoidy: exact multiple of n → 3n, 4n…etc.
Origins of human triploidy:
1) **Dispermy** is the principal cause, accounting for 66% of cases.
2) **Diploid gametes** that arise by occasional faults in meiosis; fertilization of a diploid ovum and fertilization by a diploid sperm account for 10% and 24% of cases, respectively.

Dispermy: Entrance of two sperms into one oocyte.

Diploid gametes result because of failure of cytokinesis (division of cytoplasm) which result in daughter cell receives 2 n and the other daughter cell receives only cytoplasm.

Tetraploidy involves normal fertilization and fusion of gametes to give a normal zygote. Subsequently, however, tetraploidy arises by endomitosis when DNA replicates without subsequent cell division.



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