Genetics
& Cell biology

◉ Sheet ○ Slides

Number

3

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Recap:

As we knew the chromosome has 2 important structures:

1- Centromeres
2- Telomeres

1- Centromere: A tandem repeat of 171 nucleotides, they are the site of chromosome where spindle fibers get attached to, (DNA sequence + protein).

Function: the proper binding of spindle fibers with chromosome 1, and it has no function in gene coding (heterochromatin) so it plays an important role in DNA segregation in anaphase.

2- Telomere: is a structural region which plays an important role in the integrity of chromosomes and it s a tandem repeat of (TTAGGG).

Function: linear DNA polymerase can t replicate the telomere part of the DNA, so a special enzyme called telomerase replicate this region in S phase. Telomerase works since the formation of the zygote (one cell) until the adulthood *16-18years (billions of cells), the formation of those billions of cells from one cell needs a massive number of cell divisions and telomerase aids in this. On the other hand, after the age of 18 cells replicate and with every mitotic division the telomere gets shorter (The chromosome of a 40 years old person is shorter than the chromosome of a 20 years old one) and shortening continue until there s no telomere and erosion of other genes will happen so the cell will die. So we can say that the function of the telomere is a double-edged sword through which:

A- If there s a cell with massive divisions in adulthood (a candidate for cancer), telomere ends, erosion starts, and eventually the cell dies before transforming into cancer.
B- In cancer cells telomerase is reactivated and is the reason for cells immortality.

We have to say also that telomere has the same sequence in all cells (TTAAGGG) because if we have a probe that is complementary to the telomere and added it to the chromosomes it will bind to all of them at both ends.

***Subtelomeric region:* its sequence isn t as universal as the telomere but it s sometimes common between chromosomes.

Aneuploidy: we can define it that it s a condition associated with not having the exact number of (n), in which (n) equals 23 chromosomes and (2n) equals 46 chromosomes.

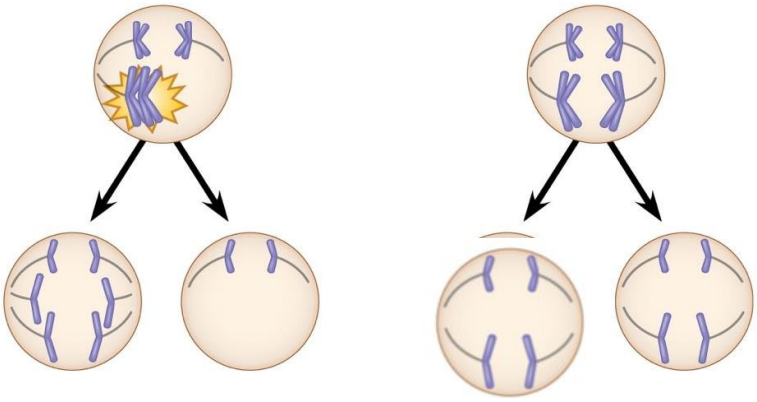
So if the number of chromosomes was for example 47 which is abnormal, then the problem is in the ***nondisjunction.***

Nondisjunction:

Normally when forming an egg or a sperm the cell goes on meiosis, as disjunction happens between homologous chromosomes as in figure (A), but what happens abnormally is that homologous chromosomes go to one end and nondisjunction happens, as in figure (B).

A B

Now let s assume that every cell carries 4 chromosomes, when normal disjunction happens in meiosis 1, each new daughter cell must carry 2 chromosomes, but if nondisjunction happens abnormally during this phase, one new daughter cell will carry 1 chromosome and the other will carry 3 chromosomes as in the figure.



Daughter cells don t know they carry an extra or missing chromosome so they proceed into meiosis 2 and what really happens in meiosis 2 is:

1- Each chromosome will align to the metaphase plate.
2- Sister chromatids will be separated giving 2 chromosomes.

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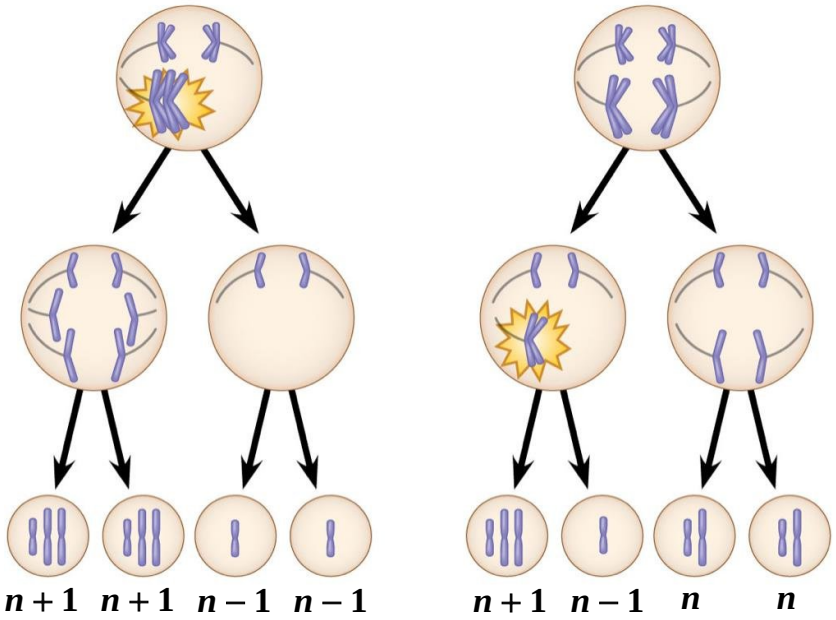
Actually nondisjunction may happen at meiosis 1 or meiosis 2, through which meiosis 1 happens correctly but sister chromatids fail to disjoin and nondisjunction happens. So mathematically we ll see that if nondisjunction happens in:

1-meiosis 1: (nondisjunction of homologous chromosomes): we ll have half of the daughter cells with an extra chromosome (n+1) and the other half with a missing one (n-1).

2-meiosis 2: (nondisjunction of sister chromatids): we ll have half of the daughter cells with the normal number of chromosomes (n), one fourth with an extra chromosome (n+1) and one fourth with a missing chromosome (n-1).



But do you think that nondisjunction may happen in mitosis? Actually the answer is yes since it happens in meiosis 2. And meiosis 2 and mitosis have the same mechanism so it may happen in mitosis; resulting by nondisjunction of sister chromatids. So, each one of us may have cells with extra chromosomes, but the small number of such cells prevents the manifestation of clinical symptoms.

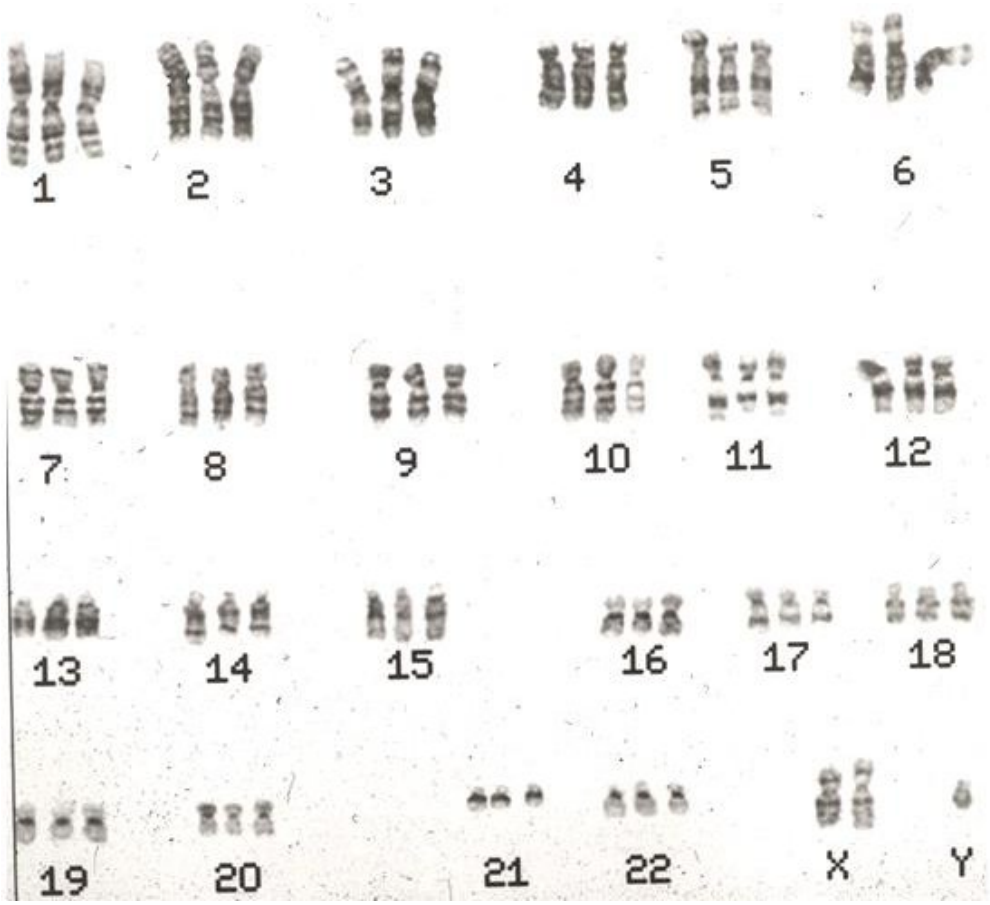
TERMS:

Trisomy: having an extra chromosome, like in Down syndrome which is trisomy 21.

Monosomy: having a missing chromosome; i.e. a chromosome loses its homologous one.

***Polyploidy: having the exact multiple of (n), it s like having (3n) or (4n); it s more common in plants rather than animals.*

Euploidy: is the same as polyploidy and an example of it is when 2 sperms fertilize one egg, we ll have (3n) and it s lethal and the fetus dies.

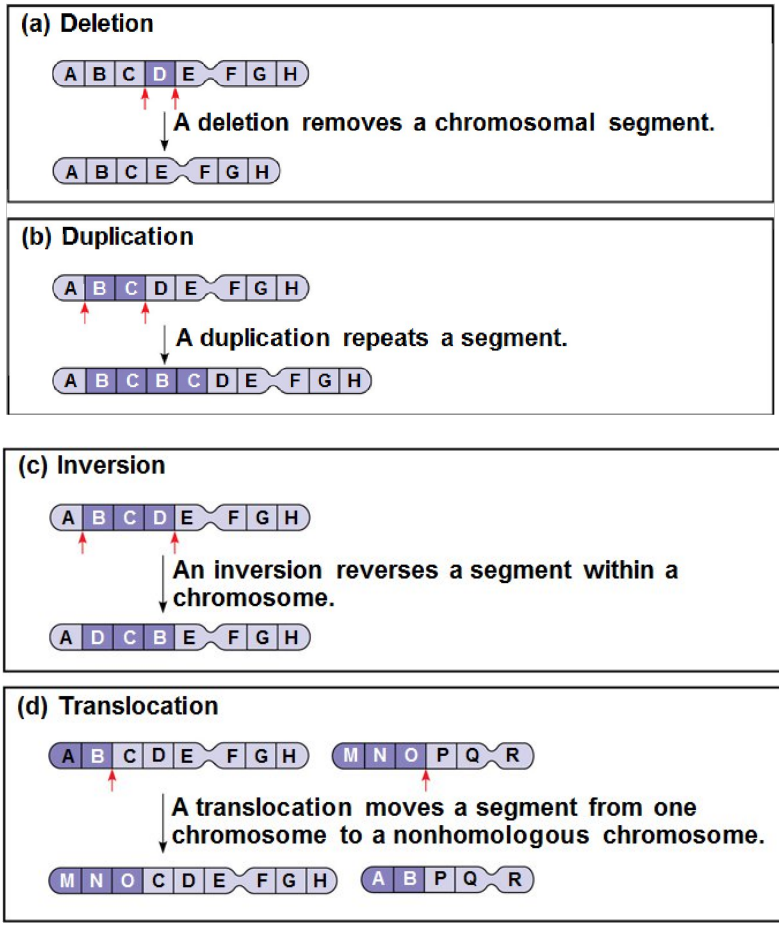


Triploidy
69,XXY

Note that, if a gamete with (n-1) "lacks a chromosome" fertilizes another gamete the resulting zygote will be (45, XX or XY; -21). This case is it is incompatible with life. In other words, having extra genetic material may not be lethal (but obviously abnormal), but lacking genetic material is lethal.

Alteration of chromosome structure:

We have in the next figures the normal number of chromosomes; which means that there s no euploidy or aneuploidy, but some other errors happen:



Note: in deletion and duplication, a change in the quantity of the genetic material occurs, whereas in inversion and translocation, no net change occurs on the amount of the genetic material (only change in arrangement).

Translocation vs. recombination

Remember that recombination is an exchange of genetic material between non sister chromatids of homologous chromosomes during meiosis (during crossing-over).

Translocation: an exchange of genetic material between non homologous chromosomes.

Abnormalities:

Aneuploidy can happen between autosomal chromosomes or between sex chromosomes. Also we may have the exact normal number of chromosomes but with structural abnormality

1- Autosomal aneuploidy:

A. Down syndrome:

There s a relation between the maternal age and the risk of down syndrome, so pregnant women at advanced age (>35yrs) are advised to test amniotic or chronic villi and check for trisomy 21 for her fetus. NIFTY is a non-invasive procedure to check for the trisomy in the cells that leak from the embryo to the maternal blood circulation. If NIFTY shows negative results, invasive procedures must be applied. (In karyotyping you ll find 3 chromosomes at chromosome 21 s site).

The male to female ratio in Down syndrome is 3:2.

Clinical features of Down syndrome include:

1- Mental retardation (IQ 25-50)
2- Low nasal bridge
3- Hypotonia (weakness of the muscles)
4- Up slanting palpebral fissures, small low set of ears (present in other chromosomal abnormalities)
5- Congenital heart diseases
6- Epicanthic folds
7- Protruding tongues
8- Intestinal problems
9- Gap between first and second toes
10- 15 - fold increase in risk for leukemia
11- simian line (transverse crease)

The incidence of Down syndrome is 1 in 770 and it s calculated by dividing Down syndrome births over all births.

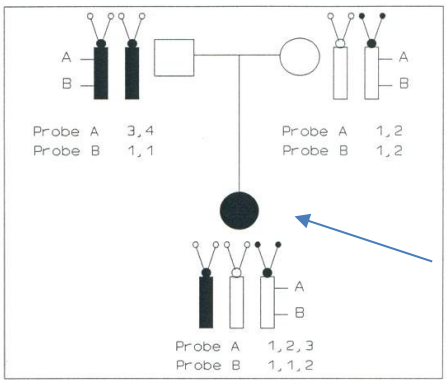
Down syndrome happens due to nondisjunction leading to trisomy 21, around 95% of the cases is due to maternal errors (nondisjunction in forming the ovum and more in meiosis 1) and 4.5% is due to paternal errors.

Down syndrome risk is not related to the paternal age. But the nondisjunction can be of paternal or maternal origin.

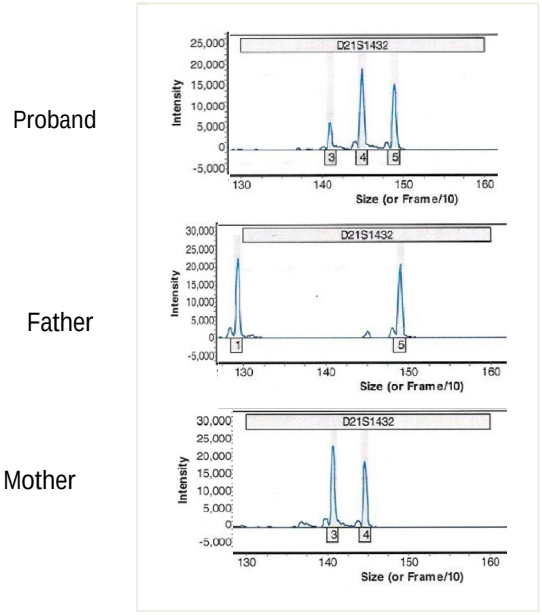
10-20 minutes

**But how do we know if the extra chromosome is coming from the father or the mother? We can do it by looking at polymorphic markers, we have many DNA regions on all chromosomes, those regions are noncoding regions and they have repetitive sequence, for the same location the number of repeats between individuals at certain

regions of chromosomes, and we can use this marker to know from where this DNA came from.



Now let s look at the figure above and see the down fetus or child, we ll see that probe B has (#1,#1,#2) repetitions, #2 officially came from the mother (the circle) but we can t figure out from where the #1's came from, because both parents have this (#1) repetition in their probe B (so, probe B is non-informative. So let s try with probe A which has (#1,#2,#3) repetitions, #3 came from the father (square), 1 and 2 came from the mother, so the extra chromosome is from the mother.



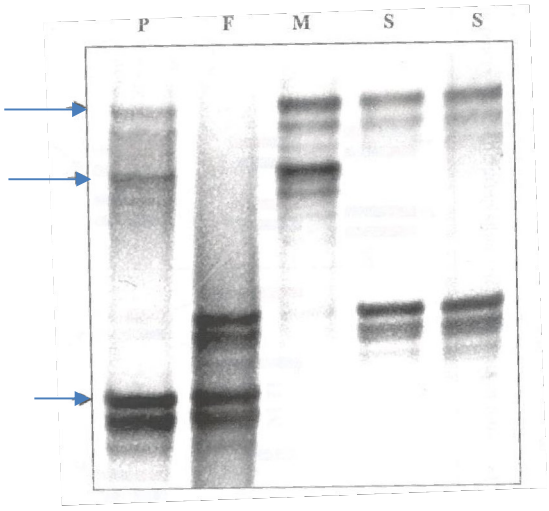
From this figure you ll see that 3 and 4 are from the mother, and 5 is from the father, so the extra chromosome is from the mother. (proband: the individual who brings the family for clinical attention (in contact with the physician). Here, the proband is the affected individual. But that is not always the case! D21S1432 is the tested region on chromosome 21.)

P: proband

F: father

M: mother

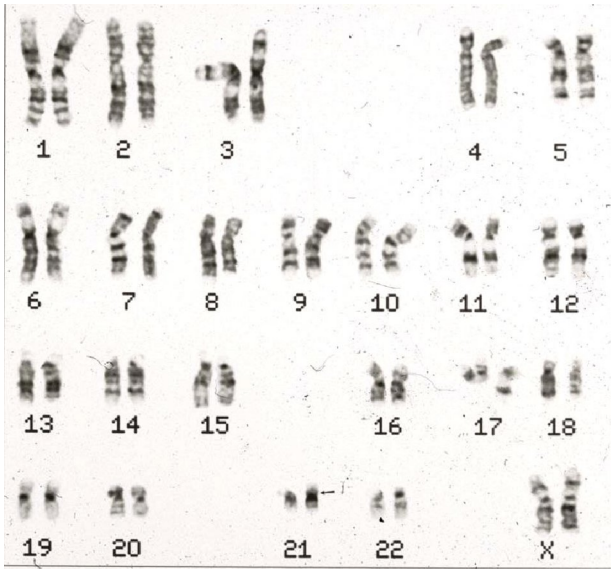
S: normal siblings



From the figure above, which is made by gel electrophoresis, you ll see also that 2 bands are from the mother and one band is from the father, so it s a maternal error.

20-30 minutes

Partial trisomy 21:



Partial trisomy clinically looks like Down syndrome but in its karyotype we ll see 46 chromosomes, which means there s no extra chromosome 21. But if we zoom in at one of the two chromosomes 21 we ll see that something wrong is happening here, (remember that chromosomes 13, 14, 15, 21, 22 are acrocentric chromosomes, which have Q arm, centromere then a very small P arm which carry nothing but ribosomal DNA and some repetitive sequence) what s wrong is that one of the two chromosomes

21 is carrying 2 fused Q arms together so this individual is 46, XX (or XY),+21q, with a total of 3 Q arms.

We don t care about the P arm if it exists or not because P arms of the 5 acrocentric chromosomes have the same exact DNA, and when losing one of those P arms, nothing happens, since the others can compensate.

*now we finished talking about Down syndrome so let s move on to a new autosomal aneuploidy which is Edward syndrome.

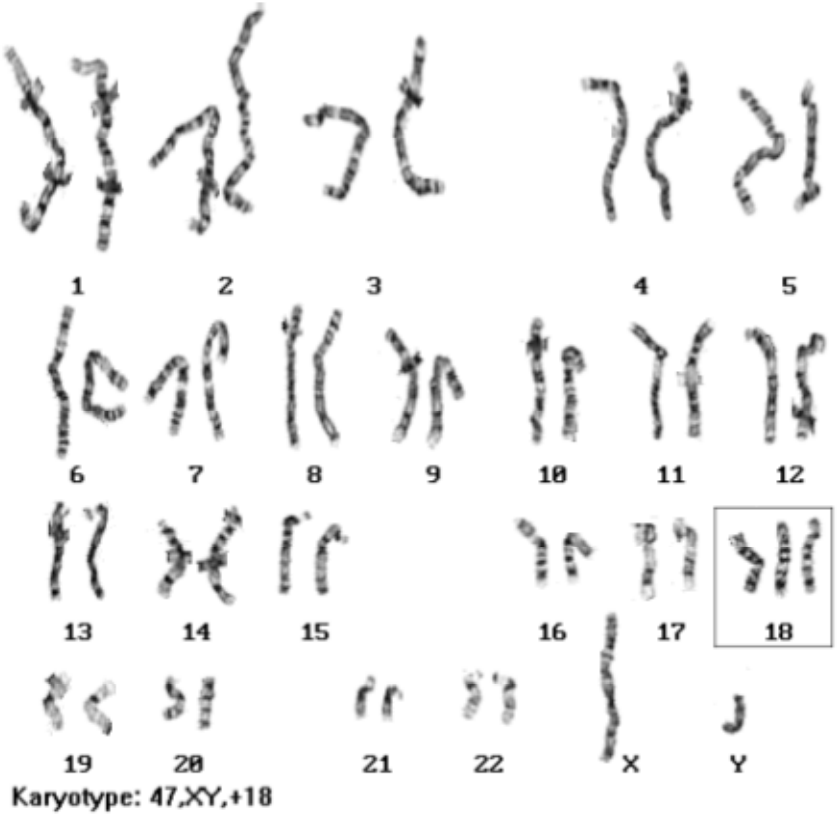
<u>What if a patient had a karyotype of 45, XY, +21q, -21?</u>

Clinically, the individual is normal, but its gametes will either have fused q arms of 21 chromosome (predisposing to offspring with partial Down syndrome) or lack a 21 chromosome.

B. Edward syndrome:

If we look at the karyotype of Edward syndrome karyotype, we ll see that it has one extra chromosome at chromosome 18 (trisomy 18).

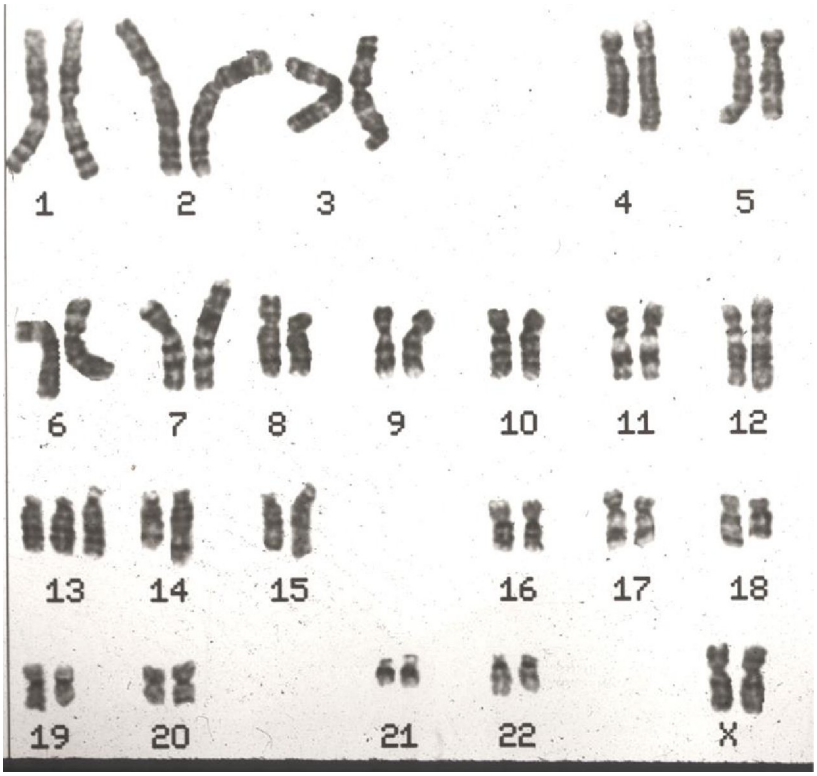
The karyotype is (47, XY, +18).



Clinical features:

1- Congenital heart diseases.
2- Failure to thrive: growth beyond average.
3- Mental retardation.
4- Growth retardation.
5- Hypertonia (remember that down was hypotonic).
6- Prominent occiput.
7- Low-set ears.
8- Short sternum.
9- Intestinal problems.
10- Unusual hand position (clinched fest).
11- Rocker bottom feet.

Patau syndrome:



It s a trisomy 13. The survival beyond first year is minimal. If they are old, they are usually blind and deaf

Clinical features:

1- Congenital heart diseases.
2- Mental retardations.
3- Hyper- or hypotonic.

4- Scalp defects.
5- Microcephaly.
6- Small eyes.
7- Low-set malformed wars.
8- Cleft lip\ palate.
9- Polydactyly (extra digit) and syndactyly (fused digit).
10- Kidney diseases.
11- Rocker bottom feet.

As we see, trisomies of other chromosomes like 15, 16, 17 for example are not common, and that is due to the lethality of such trisomies (not compatible with life).

People who are hungry to success do things that others don t do to have things others won t have