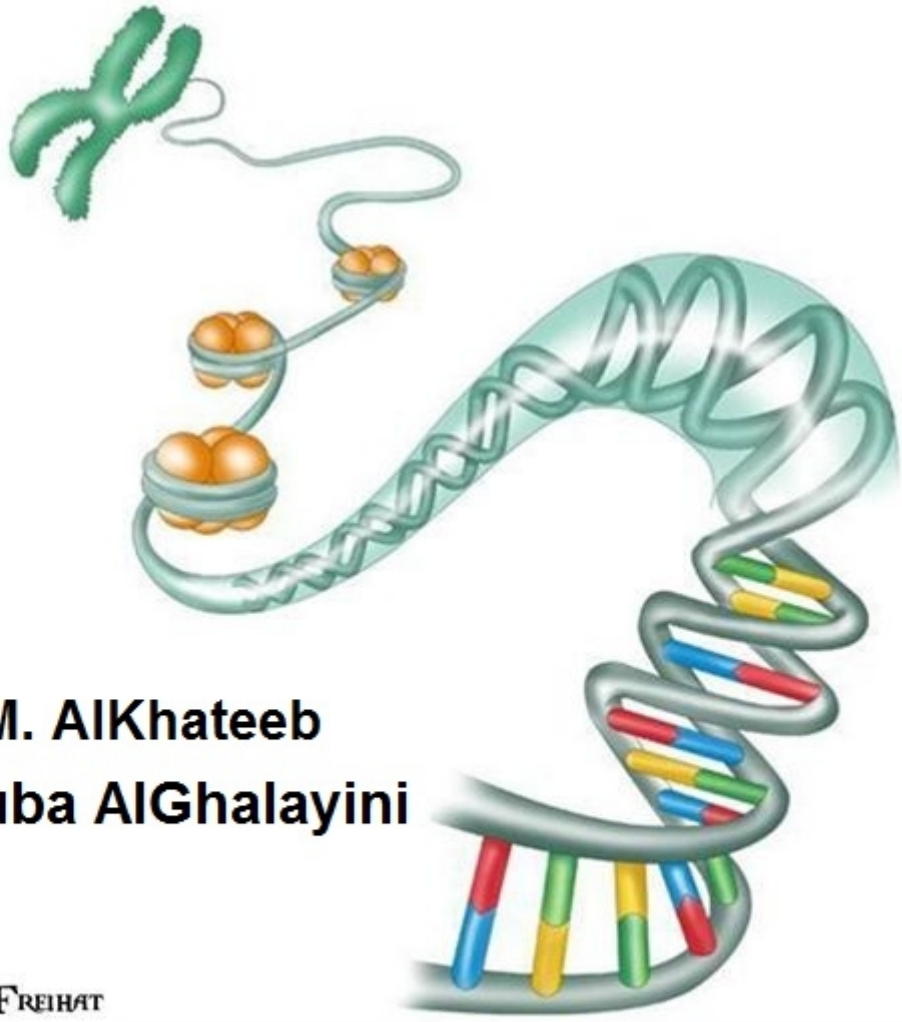
University of Jordan
Faculty of Medicine
Batch 2013-2019

Medical Committee
The University of Jordan

Genetics & Molecular Biology

○ Slides ✣ Sheet ○ Handout ○ other.....



Sheet#: 3

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Chromosomal abnormalities

- Last time we talked about "how we can examine the chromosomes" today we'll see the abnormalities we can find in the chromosomes.

Generally, we can classify the abnormalities into 2 different groups:

1) **Numerical abnormalities**: The number of chromosomes is not right; it's either more or less than normal, or it's duplicated.

2) **Structural changes** within the same chromosome; deletion, traslocation, inversion….

Let's start with numerical abnormalities.

Polyploidy: the number of all chromosomes is increased. You know that the normal number of chromosomes in a human cell should be 2n (n=23) so it should be 46, in case of polyploidy it could be 3n (69) or 4n (92) and so on depending on where is the abnormality we're talking about.

Aneuploidy: here we are talking about abnormality in one chromosome, it could be 2n+1, 2n-1, 2n+2, 2n+3... It depends on the number of chromosomes we are interested in.

Now why does this happen?

Last lecture we talked about chromosomal segregation in meiosis and mitosis stages, during the segregation of these chromosomes nondisjunction might happen; that is, the two chromatids did not separate and they both went to one cell rather than each one going to two different cells.

Nondisjunction: the failure of chromosome pairs to separate properly generally during the first stage of meiosis, or sister chromatids during mitosis or the second stage of meiosis.

Haploid: 23 chromosomes, one from each.
Diploid: 2 chromosomes from each.
Triploid: 3 chromosomes from each.
Tetraploid: 4 chromsomes from each.

Polyploidy could be triploidy 69 XXY or could be tetraploidy 92 XXY. Aneuploidy might be monosmy such as 45 X in females (only one x), or trisomy like 47 XY (as we'll see in Down syndrome), or tetrasomy (4 copies of a particular chromosome).

We'll talk about all of these.

Why does this happen?

If we have a normal ovum which contains 23 chromosomes and one of them is fertilized with two sperms at the same times (each sperm having 23 chromosomes), thus the zygote will have 69 chromosomes (23*3).

Or the ovum itself has 46,xx chromosomes because no segregation occurred in meiosis. When this ovum fertilizes with a normal sperm (23,x or 23,y) it will also have 69 chromosomes and we could female or male.

Another case is the fertilization of a normal ovum (23,x chromosomes) with a sperm that has 46,xy chromosomes (because the chromosomes did not segregate) and this will also lead to a zygote with 69 chromosomes and here we will get a male.

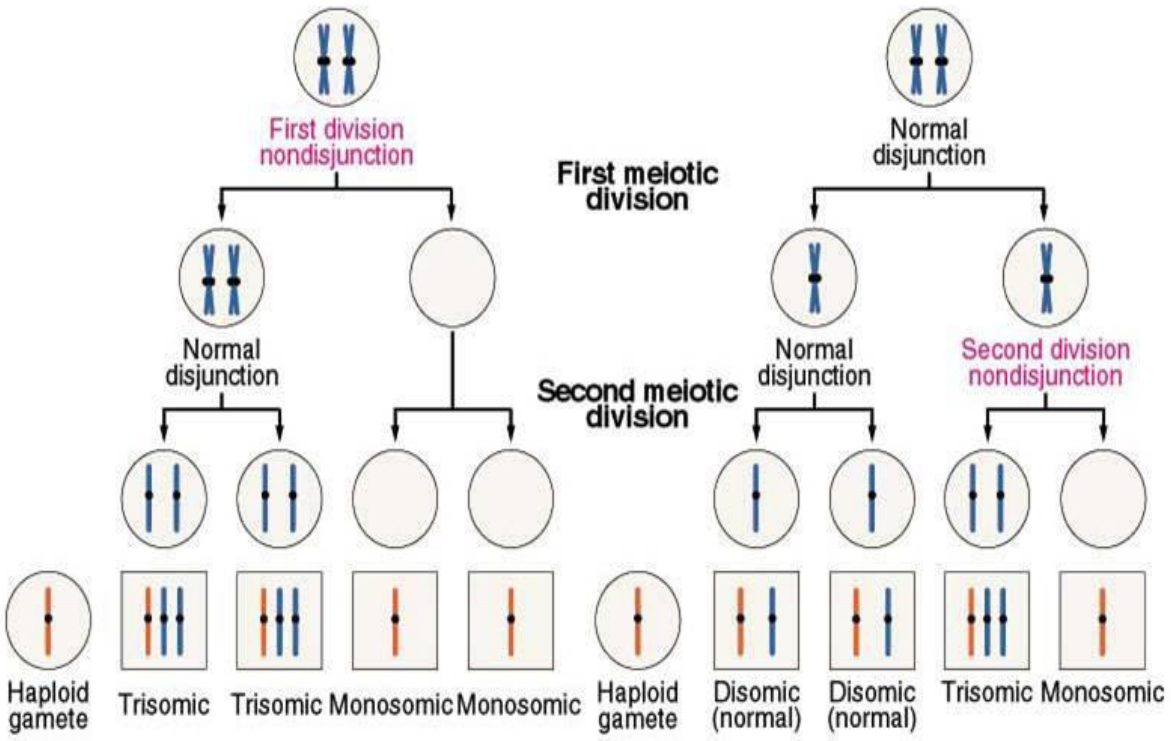
If both the ovum and the sperm have 2n (46 chromosomes) each, this will lead to a zygote with 92 chromosomes.

So the numerical abnormalities are several defects in chromosome material, imbalance in sex chromosomes, and autosomal chromosomes, sometimes manifested in adolescence and sometimes it is de novo.

We can see the abnormality in females more than males especially if she was above 35 years, because the ovums age is equal to the mother's (the female's) age because they are produced at birth. But that does not mean that we can't see the abnormality in males, we can see it.

So it's either that in meiosis I the chromosome pairs did not separate from each other or in meiosis II the sister chromatids did not separate.

Below is an example of Meiotic nondisjunction generating aneuploidy:



The first two cells are the parent cells which contain all the genetic material (46 chromosomes).

Regarding the first cell; in the first meiotic division the chromosomes did not segregate so the result is a cell that has a pair of chromosomes and a cell that has none. In the second meiotic division the cell will divide normally but the abnormality will still be there with 2 cells having 2 chromosomes each, and 2 cells having none. When this cell fertilizes with a sperm or an ovum (a haploid gamete) we get a trisomy, trisomy, monosomy, monosomy.

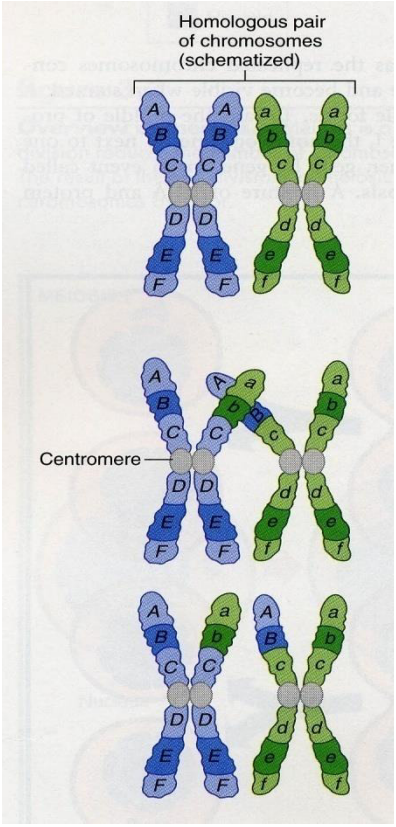
This was in case the nondisjunction happened in the first meiosis.

If nondisjunction happened in the second mieosis (the parent cell on the right side), the first meiotic division is normal, but in the second meiosis the cell that normally divided will have the right number of chromosomes but the second the chromosomes did not separate and we'll have a cell with 2 chromosomes and a cell with none. And after fertilization we'll have normal, normal, trisomy, monosomy.

Below is the distribution of the most common chromosomes in Paternal and Maternal cells where non-disjunction (the abnormality) generally occurs: (The professor mentioned them all).

	Meiosis I	Meiosis II	Mitosis
Maternal	21, 15, 16	18	15, 18, 21, 8
Paternal	-	18, 21	18, 21

Now we will talk about the genetic diversity; the cross over between maternal and paternal chromosomes. That's why brothers and sisters don't have exactly the same chromosomes from the mother and father so if we take chromosome from the child and compare it to the mother's or father's we'll find a difference because of this type of arrangement that happened during the first stage of meiosis.



What about these abnormalities?

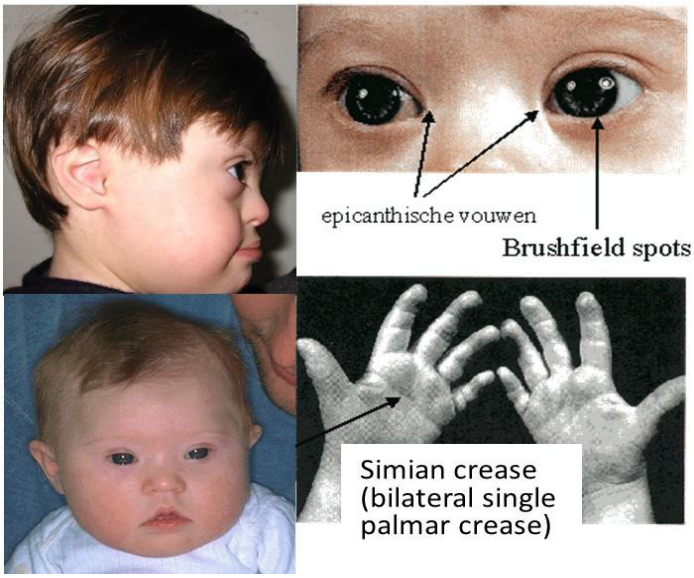
-When we talk about numerical abnormalities, the most common is trisomy 21, trisomy 18, trisomy 13. These three are compatible with life; this means that the affected child is born, the other autosomal trisomies in general are not compatible with life and there will be abortion at an early time of pregnancy.

We'll talk about these three trisomies.

1) Trisomy 21 (Down Syndrome): (1 in 800 live births)

The features of Down syndrome are very obvious so any person can tell whether it's Down syndrome or not.

- The main characteristics are:
  1. Severe mental retardation.
  2. Abnormality in the heart, congenital heart diseases, aorta problems.
  3. Sometimes they have increased risk for leukemias and lymphomas.
  4. Atypical type of simian line in the hand, normal people have two or three while they have only one simian line.
  5. Their mouth, eyes (epicanthal folds) and ears are atypical; there is a folding around the eye.
  6. A space between the first toe and the rest of the toes.
  7. The tongue is abnormal; long and protruded outside.



-This is not an inherited disease, it will not be inherited from the father or mother, both could be normal. This is an abnormality happening after fertilization during the nondisjunction between these chromosomes. The other thing is that the risk increases with increasing mother's age, the incidence is really high if the mother is above 35 years.That does not mean that if she was younger

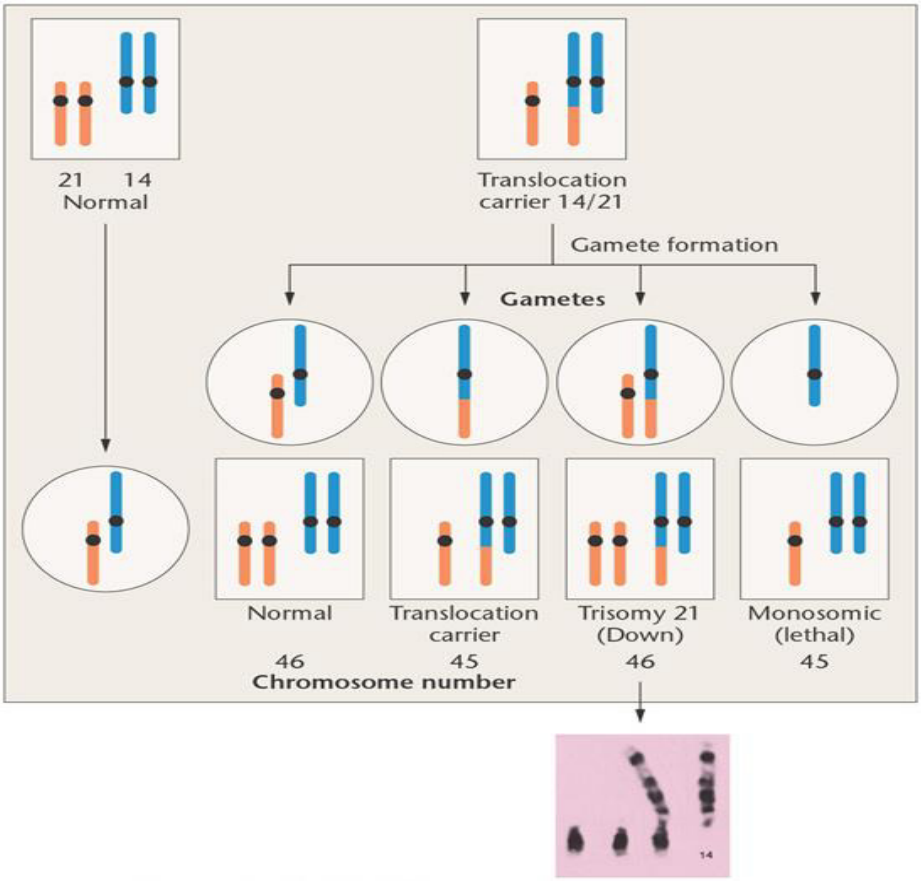
there is no probability that her child would have Down syndrome, for instance there is a woman who was pregnant at the age of 23 and her first child had this trisomy. So it does not only depend on mother's age.

Sometimes the abnormality could be a translocation of the chromosome rather than an extra chromosome. For example chromosome 21 could be translocated to another chromosome; we might have a translocation between chromosome 14 and 21. In case of translocation, the number of chromosomes would be 45 chromosomes not 46 because two chromosomes are bound to each other. This is an inherited disease, because if one of the parents carries this type of translocation it can be transmitted to their offspring. So translocation trisomies are inherited, but extra chromosome trisomies are not.

-How can we diagnose these abnormalities prenatally (during pregnancy)?

By taking amnion fluid or CVS (Chorion villi sampling) and look for the chromosomes. We can do FISH for these chromosome (we talked about it last lecture) and we'll see that there is an extra chromosome in 21, for example because the chrome we used is specific for chromosome 21.

In the translocated Down syndrome, the segregation or inheritance will be like this: a normal chromosome should be 21, 14 (the Normal box in figure below), a translocation 14/21 results in Down syndrome, both chromosomes bound to each other, so when these segregate these are the possibilities: normal 21 and 14, translocated 14/21, or the translocated one plus 21, or you might get only 14.



When these fertilize with a normal sperm or a normal ovum you will get: a normal person with 46 chromosomes, another 45 but he's normal; he has two 21 and two 14(carrier of the disease), trisomy three of chromosome 21 and two 14 (Down), monosomy one 21 and two 14 (this is not compatible with life).

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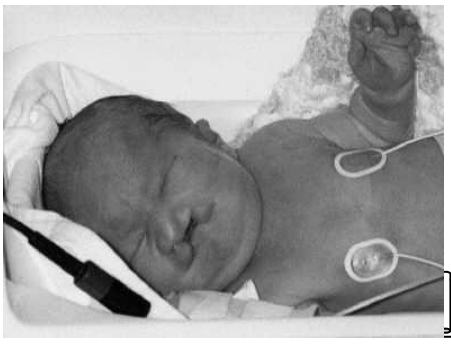
2) Trisomy 13 (Patau syndrome):

Here we have extra chromosome 13 in males or females. Incidence is much less than Down syndrome; it's (1 in 15-25000 births).

Characteristics:

1) Mental retardation.

2) Low birth weight.



3) Abnormal development.

4) Congenital heart disease.

5) renal abnormalities.

6) microphthalmia, often blind there are almost no eyes.

7) Absence of corpus callosum, the stem of the brain is not there.

8) Bilateral cleft lip/ palate, abnormal ears and fist.

9) They are polydactyl; having extra fingers and toes.

10) atypical ear and fist closure.

	Karyotype	Incidence
Trisomy 13	47,XX,+13	>75%
R. Translocation	46,XX,der(13;14)+13)	20%
Mosaicism	47,XX,+13/46,XX	5%

From the table, the incidence in trisomy 13 where the karyotype is having an extrachromosome is above 75%

In translocation it's 20%

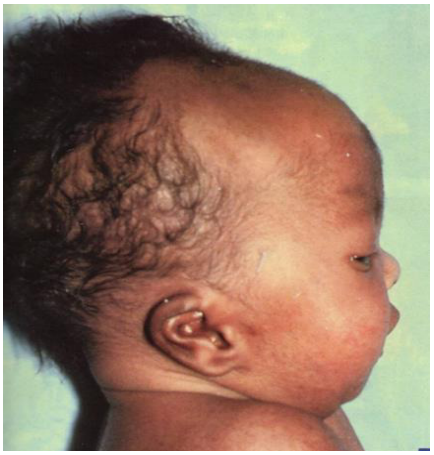
In Mosaicism it's 5%, we can also see mosaicism in Down syndrome which is having cells that are normal and others that are abnormal.

3) Trisomy 18 (Edward's syndrome):

Characeristics:

1) Mental and growth retardation.

2) webbed neck (short and thick) with a short sternum



3) micrognathia (undersize of jaw).

4) renal abnormalities.

5) abnormal fist, and feet are like rocket.

6) ears are abnormal.

-Cytogenetically: 90% we have extra chromosome, translocation is rare, and 10% mosaicism.

-Maximally they can survive for a couple of years not more.

-Trisomy 13 (Patau syndrome), the survival rate was 7 years for one patient but others dies very early in life.

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*Monosomy: when we have only one chromosome and its homologous counterpart is missing (only one representative of a chromosome).

-Monosomies are not compatible with life. We're talking about somatic chromosomes.

Nondisjunction: which means the failure of chromosomes to separate, so one cell ends up with one copy (monosomic) and the other has 3 (trisomic).

There is Anaphase lag: which means anaphase segregation will not be completed; chromosome fails to move into the new daughter cell.

-All complete monosomic abnormalities are lethal, not compatible with life. But people can survive with mosaic forms.

Sex chromosomes abnormalities: (x, y)

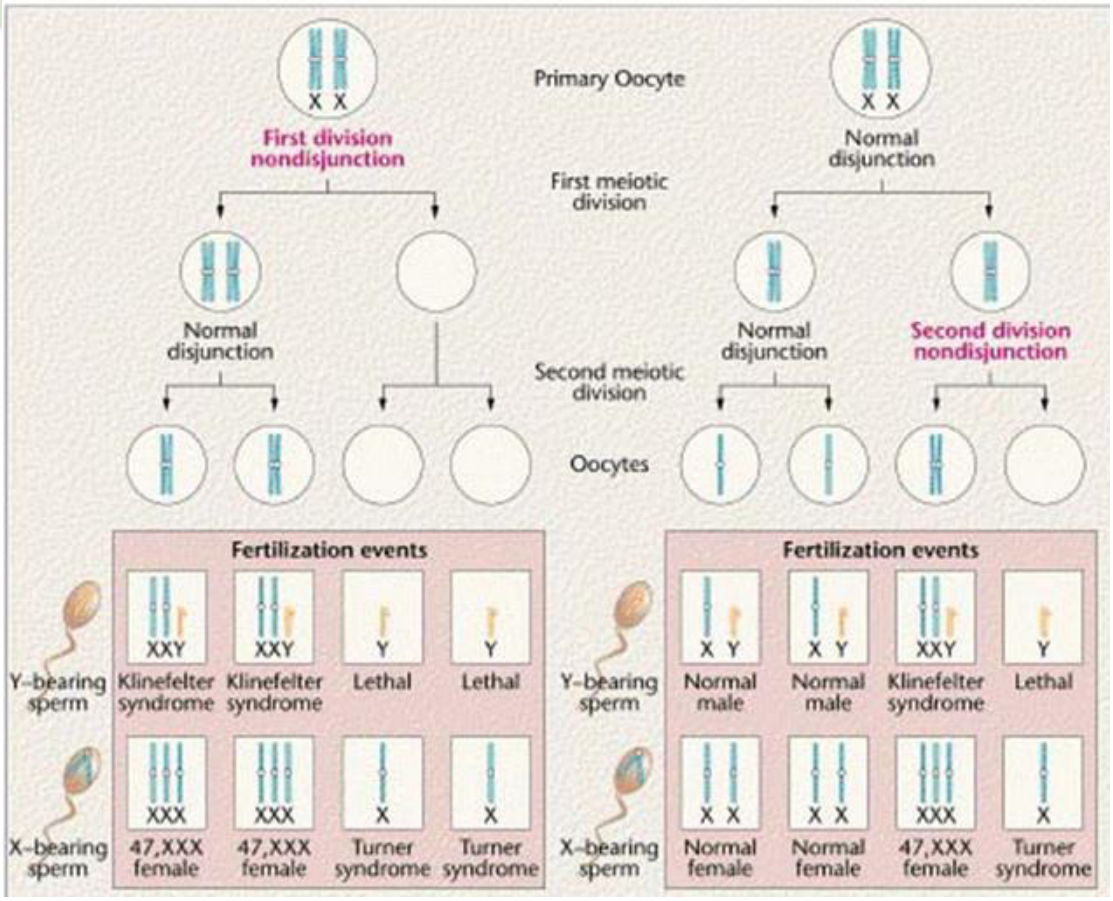
- Imbalances of X-chromosomes are better tolerated than those of the somatic chromosomes; one X can survive, and three X can survive.

- We have what is called "Lyonization" which means that some of these chromosomes will be functional while others will not be functional in females (we'll talk about this in detail).

-The female has XX, and the male has XY (one X). So if we take X-linked problems such as G6PD deficiency (glucose 6-phosphate dehydrogenase) found on X chromosome, and we measure the G6PD in males and females the concentration is exactly the same despite the fact that females have two X, i.e. G6PD is not doubled. Why is that? Because some X chromosomes are not functioning in females, they are inactivated (Lyonization).

-The other thing is that we look for X numbers normally before doing cytogenetics, because before cytogenetics the only test was to look for what is called " Barr body". The inactivated X chromosome has a certain inclusion body which can be seen inside the cell and this body is called "Barr body". So males have one X and no Barr body, females have two X and only one Barr body, if we have XXX there should be two Barr bodies. So at that time they used to look for the Barr body to know whether it's a male or a female, and this can be done by a normal histological examination.

-Nondisjunction could also occur here in X chromosomes:



- If nondisjunction happens in the first meiotic division, the result is a cell that has a pair of chromosomes and a cell that has none, so this abnormality will be carried to the second meiotic division despite the normal disjunction of the cells, so two cells will have XX and two cells with no x chromosomes (the normal division would give a cell with only one X)

*Fertilization with Y-bearing sperm: the result is a trisomy of XXY (Klinefelter syndrome), another trisomy XXY, monosomy Y which is lethal, another monosomy (these monosomies are a result of the fertilization of the cells which have no sex chromosomes with Y-bearing sperm).

*Fertilization with X-bearing sperm: the result is a trisomy of XXX female, another trisomy XXX, monosomy X (Turner syndrome), another monosomy X, Turner syndrome is compatible with life.

On the right side of the figure above the nondisjunction happened in the second meiotic division, the result is two normal cells with one X each but the other cell in which the nondisjunction happened, resulted in a cell that has XX and another that has none.

*Fertilization with Y-bearing sperm: the result is 2 normal males XY, trisomy XXY (Klinefelter syndrome), monosomy Y(lethal)

*Fertilization with X-bearing sperm: the result will be 2 normal females XX, trisomy XXX female, monosomy X (turner).

*If the abnormality was in the sperm as a result of nondisjucntion, we will get sperm with XX chromosomes and a sperm without sex chromosomes, fertilizing with a normal ovum we will get a zygote 47, XXX, and another zygote with 45,X (turner syndrome),

or we will get as a result of the abnormality in disjunction a sperm with YY chromosomes and another sperm without sex chromosomes, fertilizing with a normal ovum, we will get a zygote 47, XYY and another zygote 45,X (Turner syndrome).

We'll start with **Turner syndrome**:

Monosomy one X, so the female has 45 XO (45 chromosomes only because the other X is missing).

The incidence is 1 in 5000 births, most common is 1 in 1000 births.

The typical characteristics of this female:

Eyes are very small, Problems in the aorta, pigmentation all over the body, short stature, thick neck we called webbed neck, widely-spaced nipples, sterile because the ovaries are not functioning.

Karyotyping: we can see more than one type of chromosomal abnormalities:

Classical 45,X

46, X, i(Xq) we'll talk about it next lecture. (i: isochromosome)

46 XXq-

46 XXp-

46, X r(X)

45, X/46, XX (mosaic)

Cytogenetics:

45,X (57%)

mosaics (29%)

Other conditions, structural abnormalities of X chromosome (14%)

*Klinefelter syndrome: male with 47 XXY

The male has two X, the characteristics:

Very tall stature, extremities are long, gynecomastia- excessive development of the male mammary glands, infertile, testicular atrophy, high FSH, LH, we can see a Barr body in cells, female-like distribution of hair.

Karyotyping:

47, XXY (60%)

Mosaics XY/XXY

XXXY, XXYY,XXXXY

Incidence is about 1 in 500 male births

* Jacobs syndrome 47 XYY:

This syndrome was associated with having a criminal mind; that the male that has an extra Y chromosome has a criminal mind but this was proved to be not true.

He is more aggressive, hyperactive, impulsive, attention deficit.

How does this result? From the nondisjunction in the sperm thus producing a cell that has 2 Y, and then this cell is fertilized with a normal ovum (having X).

*Males with 48 XXXY:

Here we have mental retardation more than Klinefelter syndrome

- As a rule: additional X chromosomes cause a more abnormal phenotype- more mental impairment.

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* Note: percentages are **not** for memorizing.

By: Ruba AlGhalayini