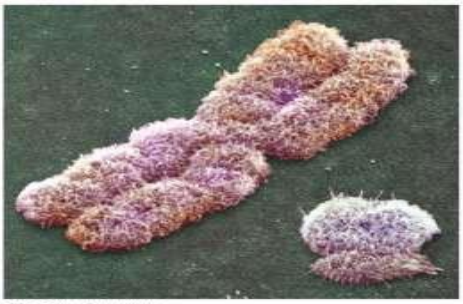
Genetics & molecular biology

◉ Sheet ○ Slide

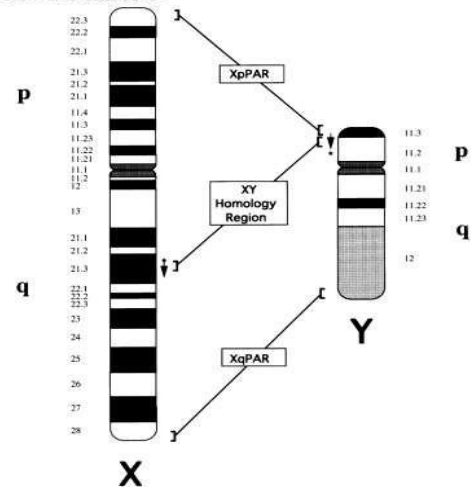
Number:	19
Done by:	Farah Almudallal
Corrected by:	Lujain Hamdan
Doctor:	Belal

The chromosomal bases for sex



In sexual aneuploidies we will talk about diseases that considered what happens if non disjunction happens with X,Y chromosomes.

First of all let's talk about sex chromosomes (X,Y):

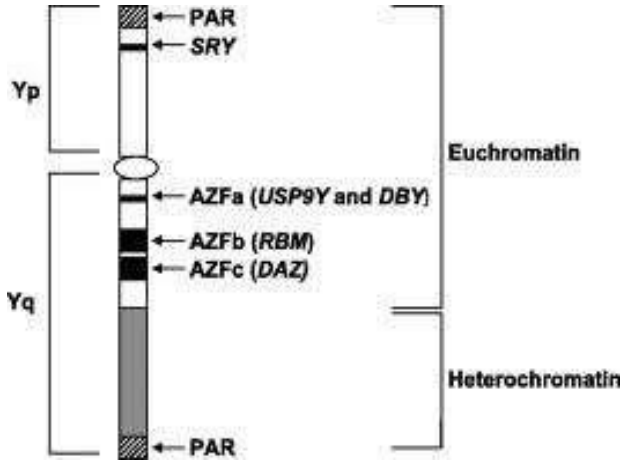


If you look even physically→ **Y chromosome** is much smaller than **X chromosome** which means that there are genes exist in X chromosome but absent in Y chromosome (this one of the scenarios where there is only **ONE allele** for those genes, so I can't call it homozygous or heterozygous, instead, I call it **HEMIZYGOUS**.

Hemizygous: there is only one allele for the f gene.

-Some regions on the X chromosome are shared on Y chromosome and those regions are called **PSEUDOAUTOSOMAL regions** because they look like autosomal regions where there is **TWO versions for the same gene (TWO alleles).**

If you zoom in on Y chromosome this is what you get (the picture below)**:**



1) SRY region→ (Sex-determining region Y), the name is implying that this region is playing a role in determining the **sex** during the embryonic development.

*By **default** the embryonic development is **FEMALE***. This is a default embryonic development.

If there is the **Y chromosome** and there is the ***SRY region***, this embryo is distinct not to develop to the default (not to the female, but to the ***MALE***).

⇨ There are some rare cases where the karyotype is **46XY** but the primary sexual organ is **FEMALE**. How would you explain that? (a person with 46XY with **ovaries** not testes)

Answer → there is a ***deletion in the SRY region***.

2)AZFa (USP9Y and DBY)

3) AZFb (RBM)

4) AZFc (DAZ)

If the sex is distinct to be male and the **AZF a,b,c** are mutated, they influence **the formation of the sperms**. For example, if a male has a mutation in the AZF genes, this male become **infertile** because this male is making **no sperms**. *Only **Sertoli cells** (somatic **cells** of the testis that are essential for testis formation and spermatogenesis) exist but sperms are absent.*

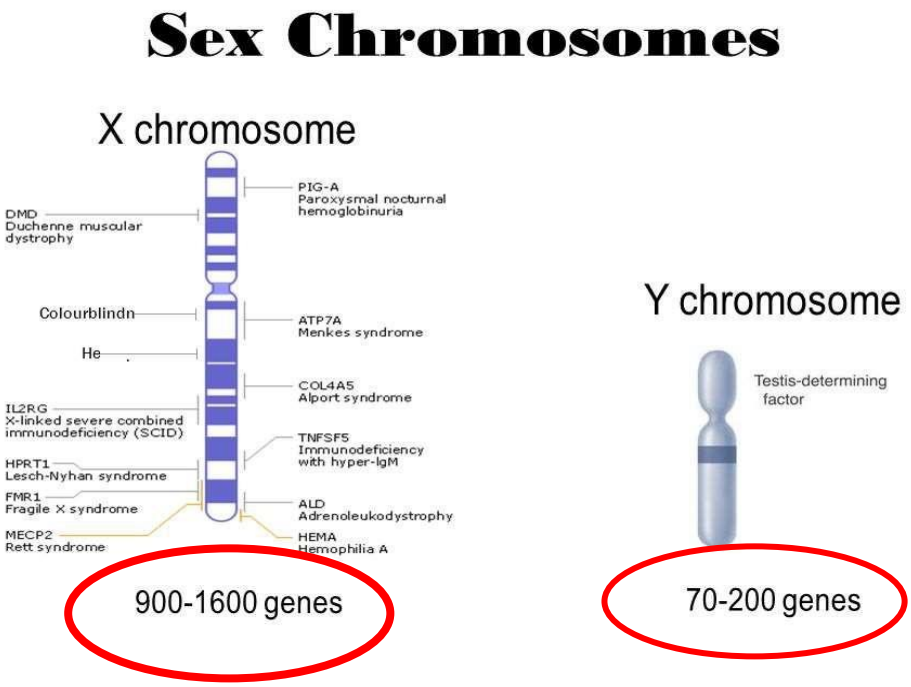
So if someone comes to you in the clinic with 1) infertility, 2) sperm count is low or nothing (**azoospermia**), you are supposed to look for those 3 regions in y chromosome.

- Not all the genes that are carried on the sex chromosome are necessarily related to sexual traits. For example, on the X chromosome

1) On the bottom, this gene is related to **haemophilia** (if a mutation happens in it, a patient will develop blood bleeding).

2) **Duchenne muscular dystrophy** gene (**DMD)** → is a muscle weakness. Patients might eventually die.

3) Red green color blindness gene. (it is not written).



Sex disorders

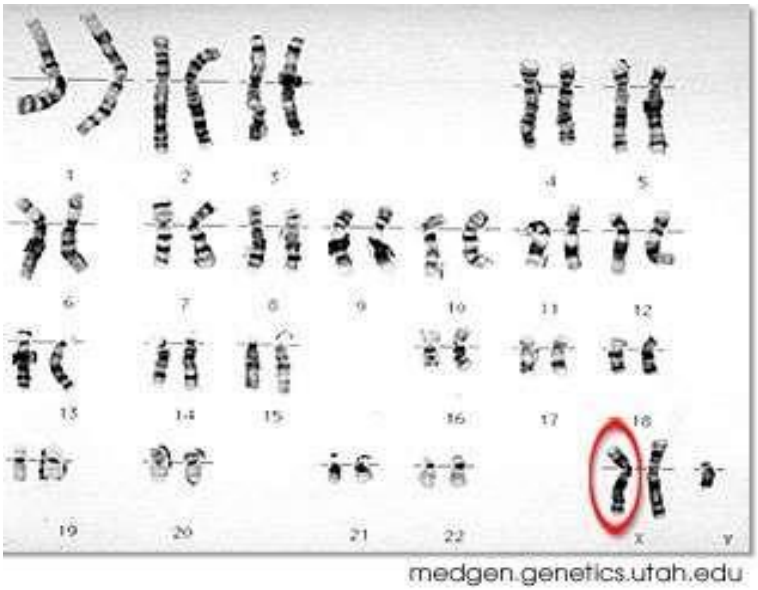
1st sexual disorder →

-This is a **47, XXY, +X** or just **47, XXY** karyotype.

-There is an *extra X Chromosome.*

→ Kleinfelter's syndrome.

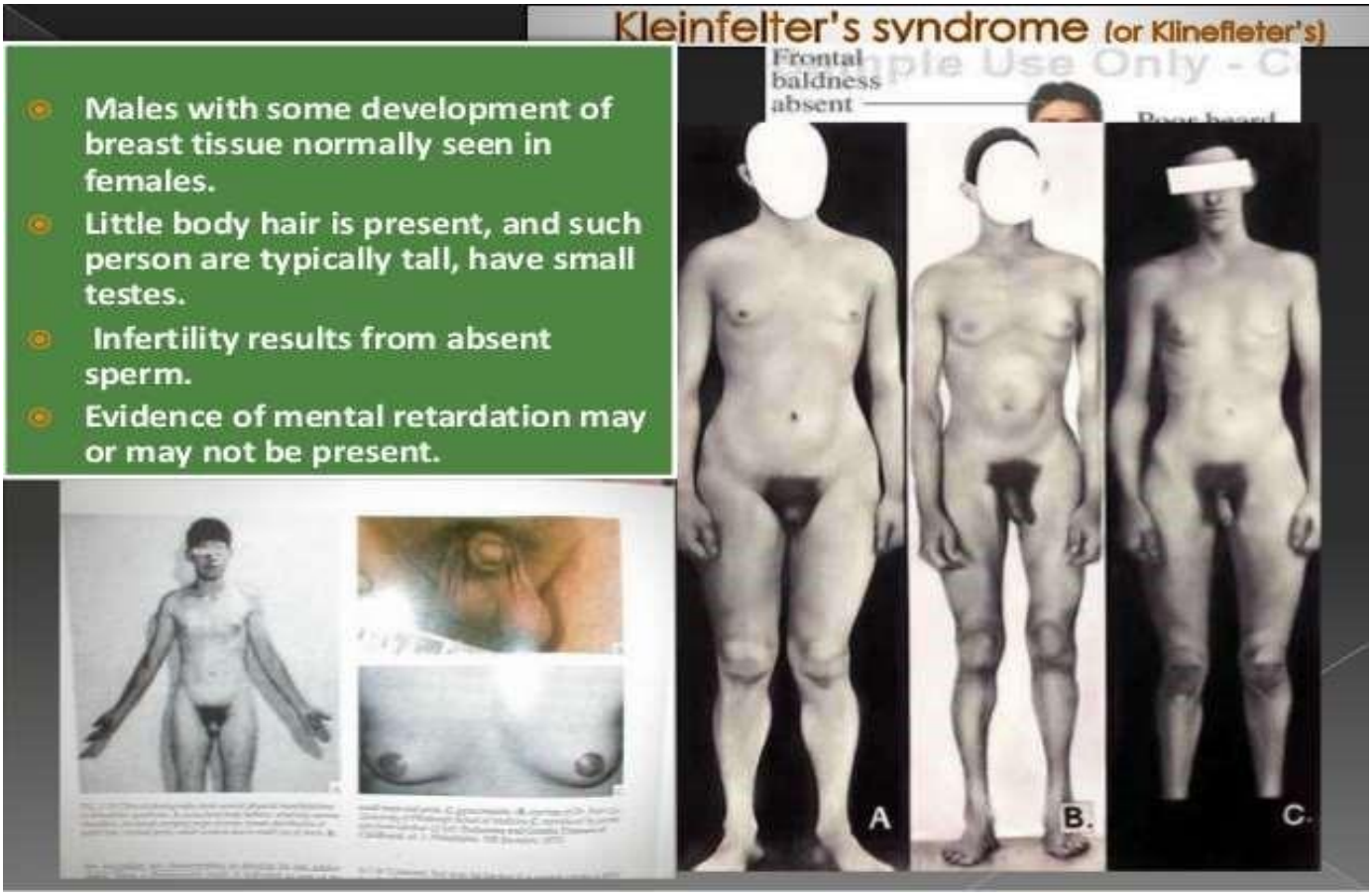
-Male developed *primary Sexual organs because there Is a Y (there is SRY region).*

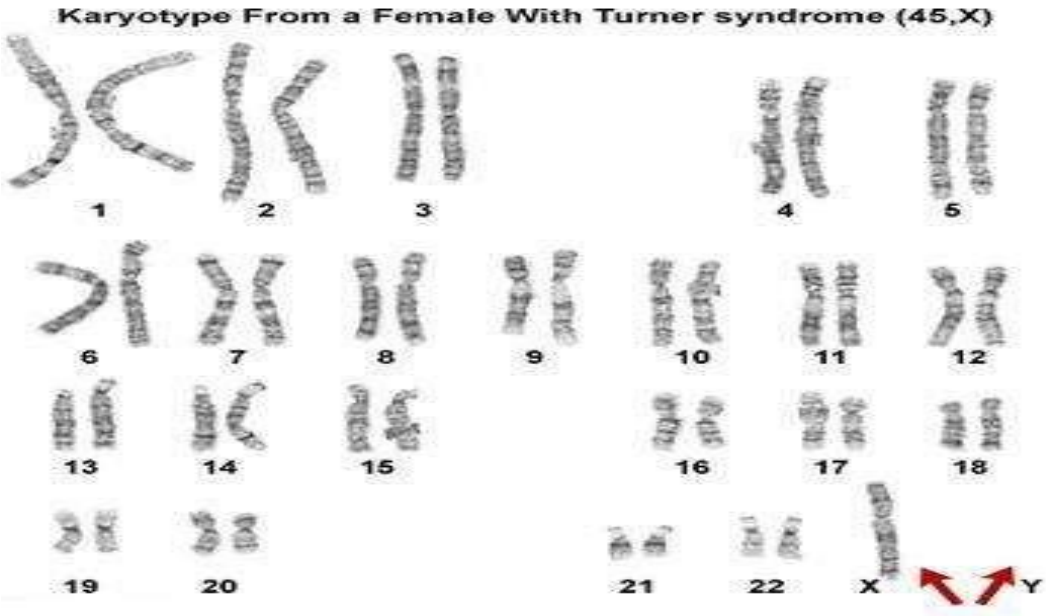


-Those males *have some 2ry Females characters:*

1. Female fat distribution "the curve" in the hip (1st picture from the left).

2. Enlargement of the breast.
3. Body hair is curse.
4. They are taller than average.
5. Sexually, they are males but their primary male sexual organs are under developed.
6. They are infertile.
7. There is some evidence of mental retardation that some patients might harvest and other might not.





2nd sexual disorder →

Turner syndrome (45,X or 45,XO)

-There is a missing sex chromosome (only one X chromosome).

-She is a **FEMALE** because there is no Y chromosome (no SRY region).

➔ They have **characteristic features →**

1) They have *brown spots (nevi)*. There is more than one type of them.

2) Their *breast is typically under developed* and there is a wide distance between breast nipples.

3) They have something called **web neck** (*there is an extra skin*).

4) They are *20 cm shorter than the average in height*.

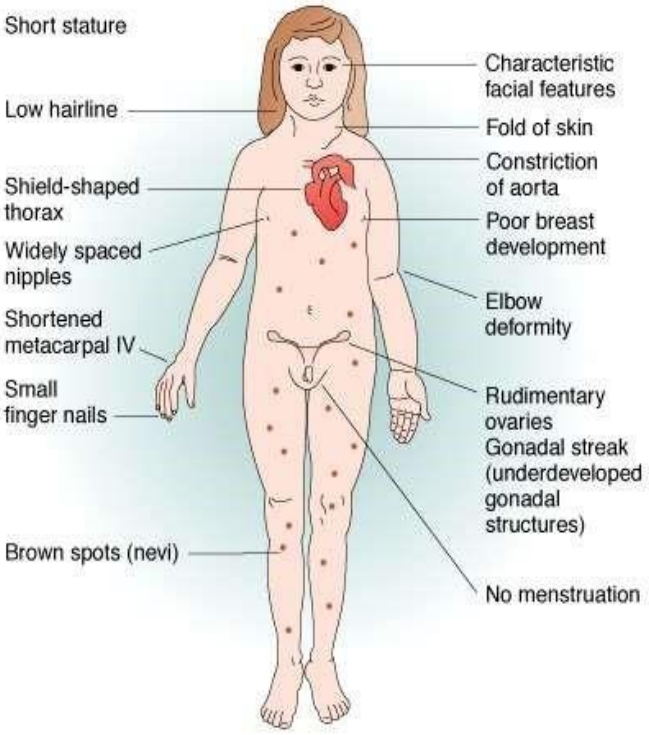
5) If you look at their primary sexual organs, you will see that the *ovaries are rudimentary and the gonads are under developed which as indication of infertility.*

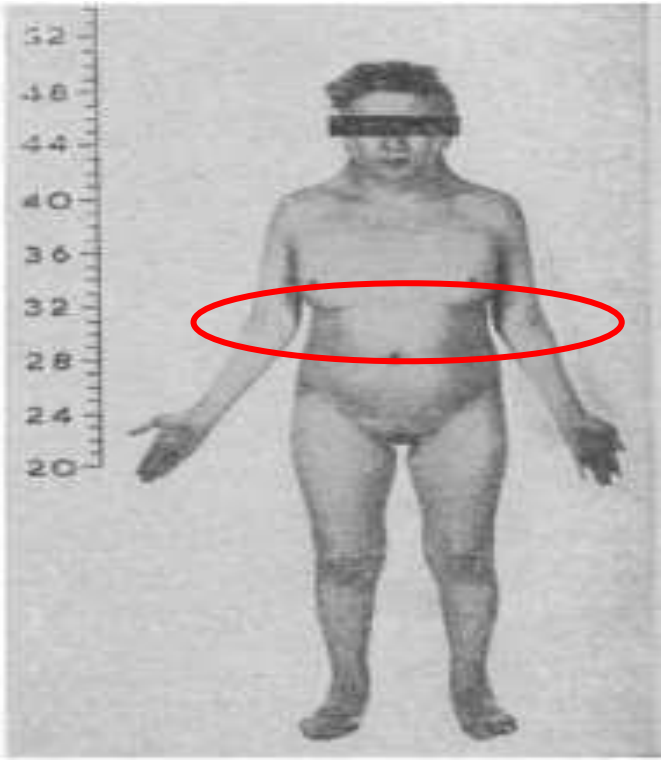
6) There is *no menstrual cycle.*

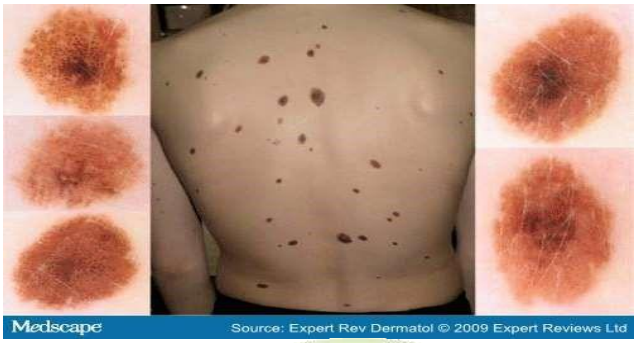
7) Their *nails are very small.*

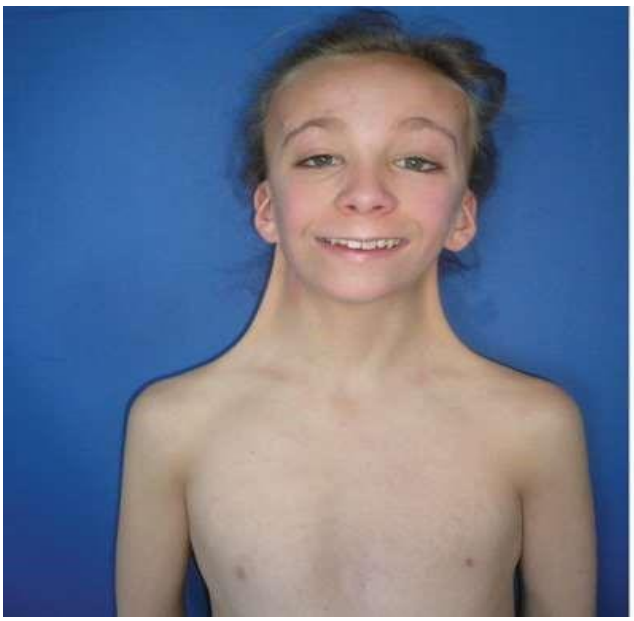
8) The size of their *metacarpals (especially metacarpal IV) are shortened.*

9) If you ask them to talk this position (in the picture below) you can see the *elbows are having an abnormal position*.









*We talked about trisomy 21, trisomy 18 and trisomy 13 which are all characterized as extra 21 chromosome, extra 18 chromosome and extra 13 chromosome but we didn't talk about monosomy 21, monosomy 18 and monosomy 13 because it is not viable (They die before their life begin). → **CONCLUSION:**

¤ **An extra genetic material is less deleterious than missing genetic material**. It is true that when you have extra genetic material, you will develop *clinical feature but at least you are alive*. If you are missing a genetic material, the consequence is more devastating to a point that it is lethal.

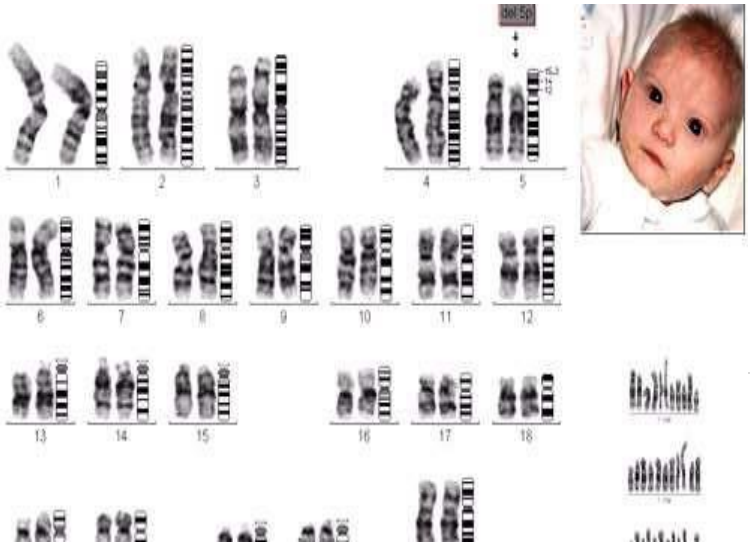
So far we talked about nondisjunction of chromosomes which happens in meiosis where there is an extra or missing chromosome rather than having a normal 46 chromosomes. We also took 3 examples for autosomes (extra chromosome) and we took couple of examples for sex chromosomes. As a matter of fact, the only viable monosomy is **turner syndrome** (missing one chromosome but still alive).

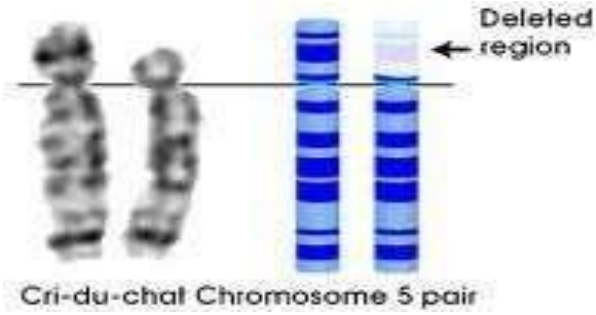
Let's now talk about **chromosomal aberration** → you count the chromosomes and they are 46 chromosomes but not necessarily the 46 chromosomes are normal, so *the chromosomal count is normal but there is something wrong with the structure of chromosomes.*

[1] Cri-du-chat disease (cat's cry disease)

-Those patients when they cry, their crying is exactly a cat voice.

-The chromosomes are 46, but if you look at **pair of chromosome 5** there is something wrong! → **the p arm of the homolog is missing genetic material** (part of the p arm is deleted).





Memorize every single detail in this picture.

-They *die within the first year of age*, but *nowadays with the advanced health care system and the management, they make it to older ages.*

To sum up, there is no extra or less chromosomes, instead, there is a ***deletion in a genetic material from one of the homologous chromosomes***.

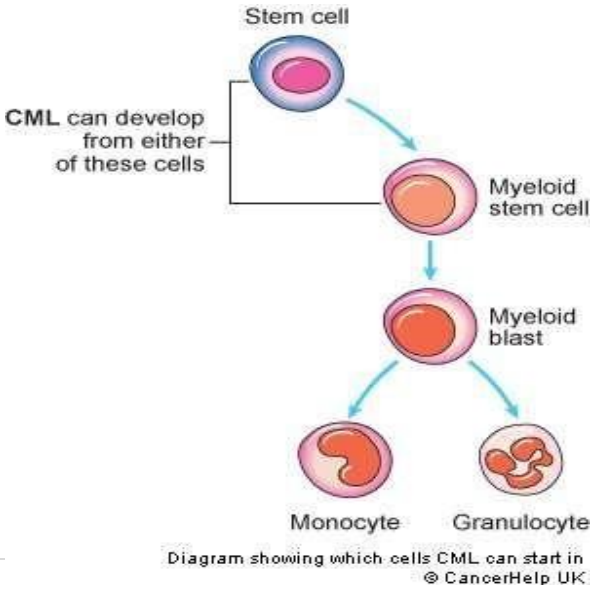
---

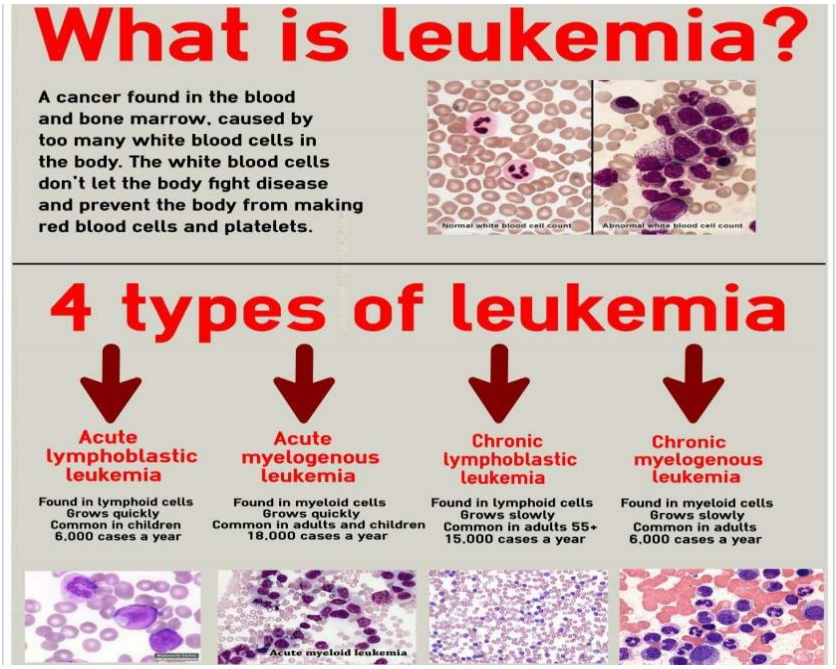
[2] Chronic myelogenous leukemia (CML)

-Stem cell is differentiated to myeloid stem cell in the bone morrow, then the myeloid stem cell becomes myeloid blast which is further differentiated to *monocytes and granulocytes*.

*CML can either develop from the stem cell or from the myeloid stem cell which is the Precursor for WBC (monocyte & Granulocyte).

*Quick idea about leukemia: the doctor just said that there are 4 types of leukemia

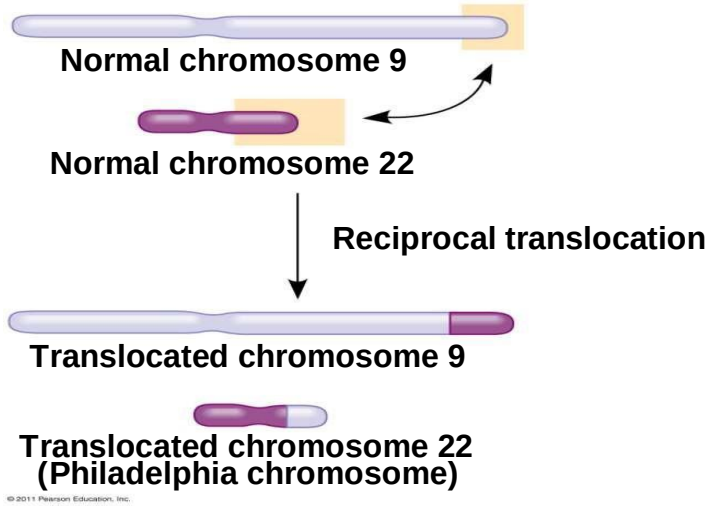


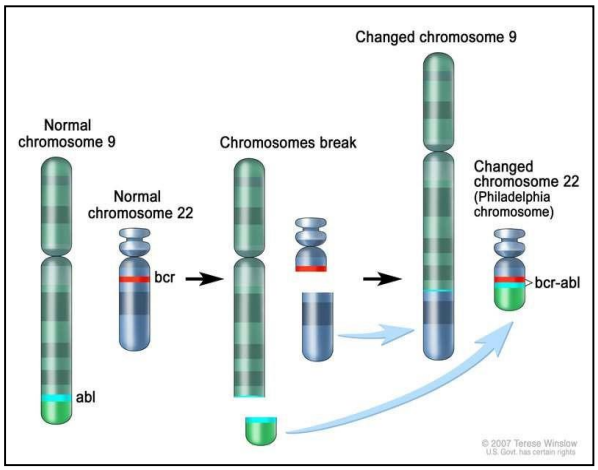


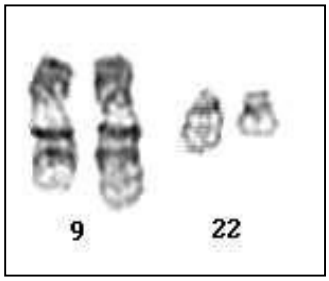
1)Acute lymphoblastic 2) acute myelogenous 3) chronic lymphoblastic 4) chronic myelogenous (2 acute, 2 chronic, 2 lymphoblastic, 2 myelogenous) and we are going to discuss the 4th part which is ***chronic myelogenous leukemia*** which is found in myeloid tissue, grows slowly and common in adults than children.

-It happens due to ***translocation*** (exchange of genetic material between non homologous chromosomes) *between chromosome 9 and 22 and we call this Philadelphia chromosome.*

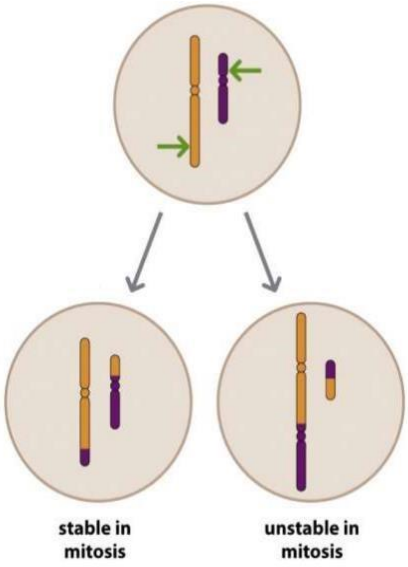
→ This happens due to the fact that the *gene which induces the cell cycle* ***(ABL)*** becomes under a stronger promoter when translocation happens which is the **BCR promoter**. ***The BCR promoter*** *induces more expression of* ***ABL (downstream gene)*** and therefore there is *much more cell cycle* and a higher chance for transforming into a cancer.







1st type of translocation → Reciprocal translocation



As we know the translocation is the exchange of genetic material between non-homologous chromosomes, we have two scenarios for the translocation: -

For example, we have in the figure chromosome 1 and 4. As you see, the cuts happened where the arrows are placed.

The first scenario is that the two small parts will exchange between the two chromosomes, this cell will be **stable in mitosis** (both chromosomes have the centromere), which will give us identical daughter cells because every chromosome has its own centromere that the spindle fibers can attach to.

In **the second scenario**, we have the same cuts as in scenario one but the long parts and the small parts will connect to each other, this cell will be **unstable in mitosis** because: -

1. There will be no identical daughter cells after mitosis.

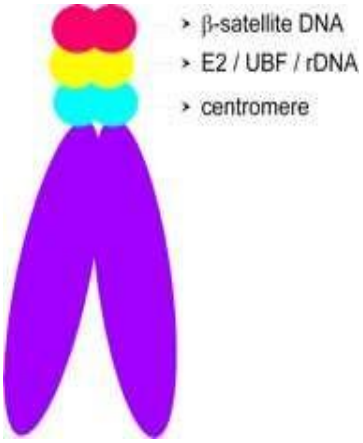
2. The chromosome that produced from the small parts doesn't have centromere which will be lost in mitosis because the spindle fiber

can't attach to it (the genetic material will be lost the daughter cells).

3. The chromosome that produced from the long parts has two centromeres and that will confuse the cell in the metaphase and the anaphase, so the spindle fibers will attach to two centromeres for the same chromosome, which will cause instability in the number of chromosomes in the daughter cells.

2nd type of translocation → Robertsonian translocation

Revision for acrocentric chromosomes:



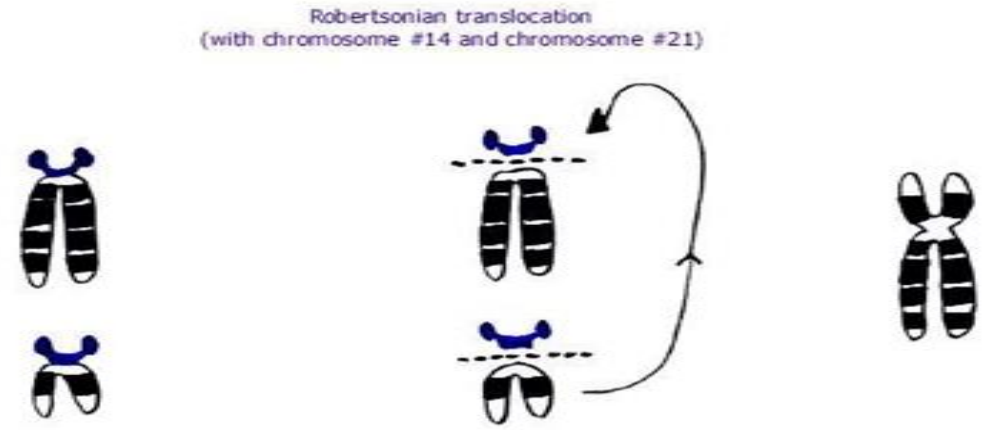
- (13,14,15,21, and 22) are chromosomes.

- In the p arm there is rDNA that is transcribed into rRNA. There is also a **satellite region** which is heterochromatin non-coding region.

-**The p arm in all these 5 chromosomes is the same** which means if my p arm of any of the acrocentric chromosomes is missing, I don't care because *the other 4 acrocentric chromosomes they are carrying the same exact genetic material.*

Now let's discuss the **Robertsonian translocation →** the translocation or exchange of genetic material between non-homologous acrocentric chromosomes.

For example, if we have 2 acrocentric chromosomes (14 and 21 in this example) and we remove the p arm of both chromosomes, then the q arms will be fused together to get one chromosome carrying 2 q arms for 2 acrocentric chromosomes.



VERY IMPORTANT!!!! The doctor said he will bring questions from these 2 pictures and their explanation so try to concentrate and understand every single detail.

*If I have a translocation **(reciprocal translocation),** it is not necessarily that it will have a clinical outcome especially if the cut region (where the translocation happens) is a non-coding region which is usually the case because 99% of the DNA doesn't encode for a protein. **I have chromosomal rearrangement but I don't have a net gain or loss in the DNA (I have the same quantity of DNA. It is rearranged but the same).** I call this individual → **a normal balanced carrier** (I'm carrying translocation without gain or loss in the DNA). But isn't there any problem?

ANSWER → off course there is problem but where?

It happens ***when I start making gametes*** (when I make eggs or sperms) because *I'm carrying a reciprocal translocation* where **one chromosome will be in a daughter cell in the gamete without the homolog**. So it could be that one of the daughter cells is carrying chromosome 5 for ex and part of chromosome 9.

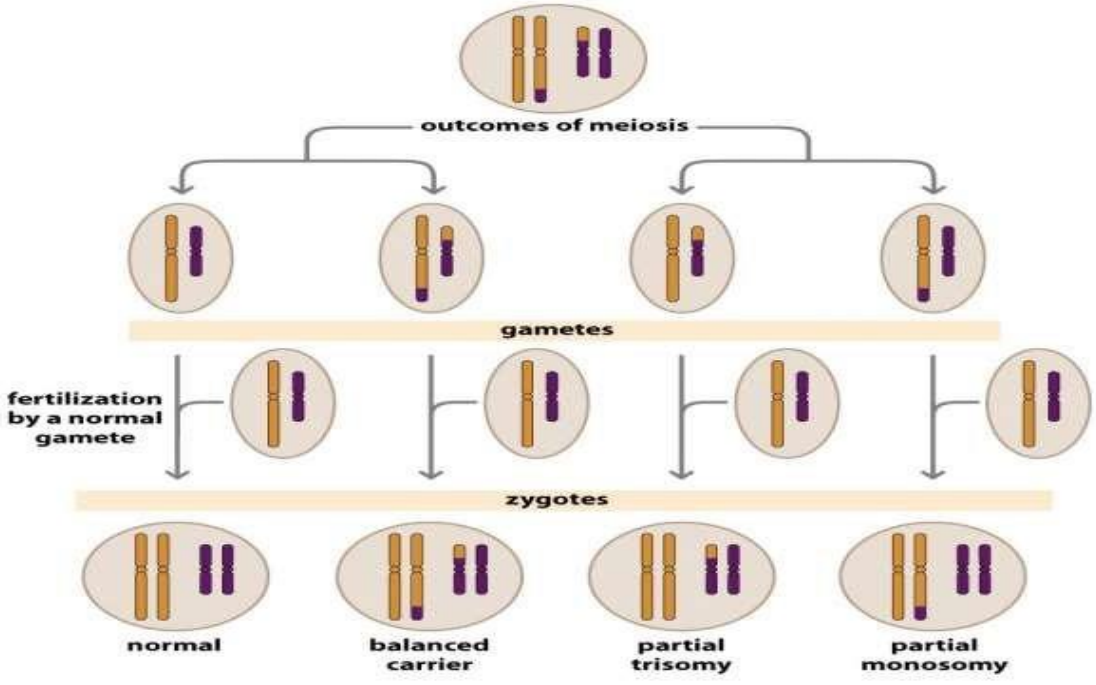


Figure 2.24 Human Molecular Genetics, 4ed. (© Garland Science)

Further explanation → assume that the 5 chromosome is the brown one and the 9 chromosome is the purple one.

When you make gametes, one of the gametes might take the chromosomes that are not translocated and this is **normal**. The other gamete will have the 2 other translocated chromosomes. But what might also happen that gamete has 1 not translocated chromosome and 1 translocated chromosome. One of these gametes has the translocated purple so it is carrying an **extra genetic material from the brown and missing genetic material from the purple** and the other gamete has the opposite, **the extra genetic material is from the purple and the missing genetic material is from the brown**.

Assume that **normal** partners are fertilizing through their other gamete, what will be produced one of the following:

1) Normal zygote → if both gametes are not translocated.

2) Balanced carrier → there is a translocation but there is no gain or loss of genetic material.

3) Partial trisomy → 2 brown chromosomes and a 3rd part of the brown so there is a partial trisomy for the brown and a **partial monosomy** of the purple.

4) Partial monosomy → 2 purple chromosomes and a 3rd part of the purple so there is a partial trisomy for the purple and a partial monosomy for the brown.

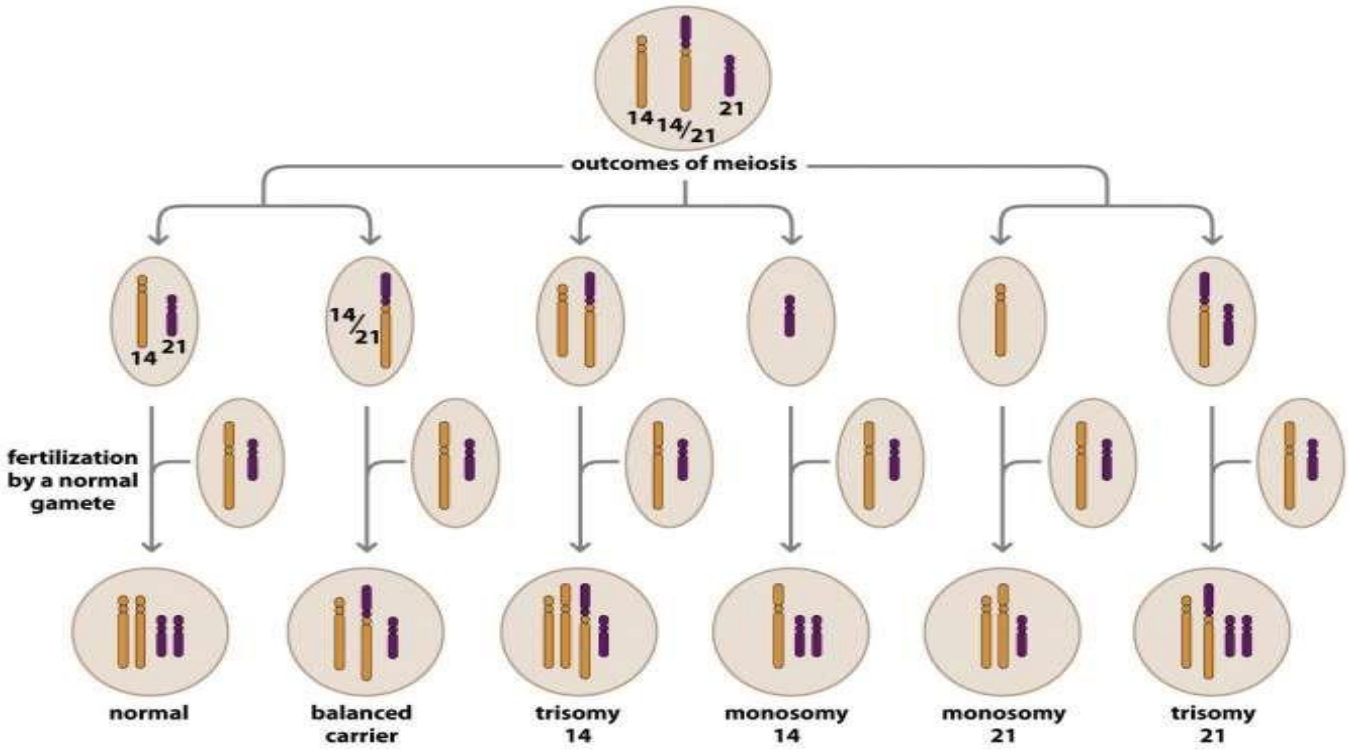


Figure 2.25 Human Molecular Genetics, 4ed. (© Garland Science)

Now let's discuss a situation of someone carries **Robertsonian translocation** → it is an acrocentric chromosome carrying **2 Q arms** together. (p arm doesn't matter/count)

Explanation of the picture →

This individual has chromosome 14, chromosome 21 and a translocated chromosome carrying the Q arm of 14 and the Q arm of 21.

Can anyone guess what is the karyotype?

ANSWER→ 45, XY, t (21q:14q) t → translocation.

*If someone clinically is normal and he has translocation in acrocentric chromosomes, I assume his chromosomal complement is 45.

When this individual makes gametes, there are many scenarios that might happen →

In meiosis 1, specifically in metaphase 1 or anaphase 1, homologous chromosomes are aligned together then they are separated and daughter cells are produced which might distribute as this:

A) One of them might have the normal 14 and the normal 21 so the other will have only the translocated (14:21) chromosome.

B) The normal 14 and the translocated (14:21) will be in the same gamete and the other will have only the normal 21.

C) The normal 21 and the translocated (14:21) will be in the same gamete and the other will have only the normal 14.

What is the consequence of these 3 scenarios? "This is very important!!!"

The resultant gametes from **"A" scenario →**

1) Normal zygote→ the gamete that has 21 and 14 chromosomes is fertilized by the homologous chromosomes from other normal gamete (carries the correct number of chromosomes).

2) Balanced carrier→ the gamete that has 14:21 translocated chromosome is fertilized by a normal gamete. **This one is identical to its parent.**

The resultant gametes from **"B" scenario →**

3) Trisomy 14→ two 14 chromosomes, the Q arm of 14, 21 chromosome and the Q arm of 21 "Also, this zygote will have the normal number of chromosome 21 that's why it is called **trisomy 14**". **It's not viable**, this zygote will die. (**The only viable autosomal trisomies are 21, 13, and 18**).

QUESTION: why is there viable autosomal trisomy of 21 for ex and at the same time there is no viable autosomal trisomy of 14?

ANSWER → *genes are different on those 2 different chromosomes. Genes on 21, 13 and 18 chromosomes you can cope with more of them but the other genes you can't cope of more of them as an organism.*

IMPORTANT NOTE: trisomies happen only in **late chromosomes** so there is no trisomy 1 because it is a very big chromosome (early number of chromosomes are the larger which means more genetic material, more extra genes when they are trisomies and therefore that means more difficulty in coping with those extra genes).

4) Monosomy 14 zygote: Daughter cell have chromosome 21 got fertilized with normal gamete, so there will be one chromosome 14 missing.

The resultant gametes from scenario **"C" scenario** →

5) Trisomy 21 zygote: the same as in **trisomy 14** but the extra chromosome is chromosome 21 instead of chromosome 14.

6) Monosomy 21 zygote: the same as in **monosomy 14** but the missing chromosome is chromosome 21 instead of chromosome 14.

I wish you understand everything I explained. If you have any question don't hesitate.

THE END 💙