Medical Genetics

Sheet: 4 — Aneuploidy of Sex Chromosomes

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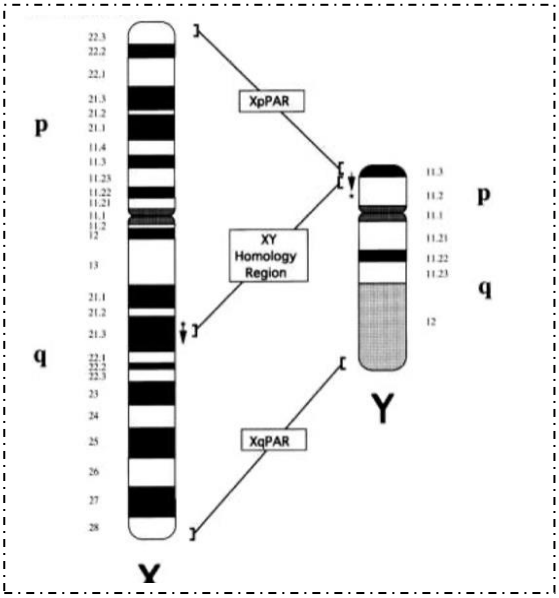
Aneuploidy of Sex Chromosomes

✓ In this sheet we are going to discuss sexual aneuploidies—that is; what happens if non-disjunction occurs with X or Y chromosomes.

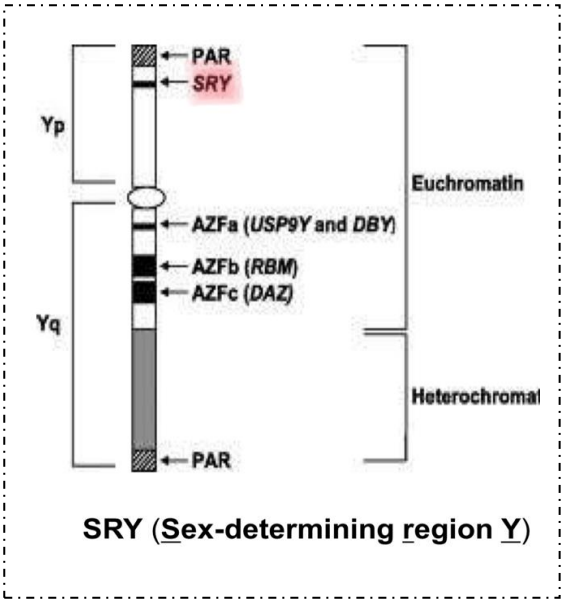
✓ Let us start off with **an overview of sex chromosomes**. Notice the figure.



- Left: X chromosome. Right: Y chromosome.
- If you look, even physically, you notice that the **Y chromosome** is much smaller than the **X chromosome,** which means that there are genes in the **X chromosome** that are <u>absent</u> in the **Y chromosome**. Therefore, this is one of the scenarios where there is <u>one allele</u> for those genes. So, the terms (homozygous, heterozygous genes) don't apply here, and instead we call them: **<u>Hemizygous genes.</u>** (Hemizygous means that there's only one allele for a certain gene).

- Some regions on the **X chromosome** are shared on the **Y chromosome**. Those regions are called **<u>pseudoautosomal regions</u>** (they look like autosomal regions where there are 2 versions of the same gene (2 alleles)).

➢ Now if you zoom in on the **Y chromosome**, you get the adjacent figure.



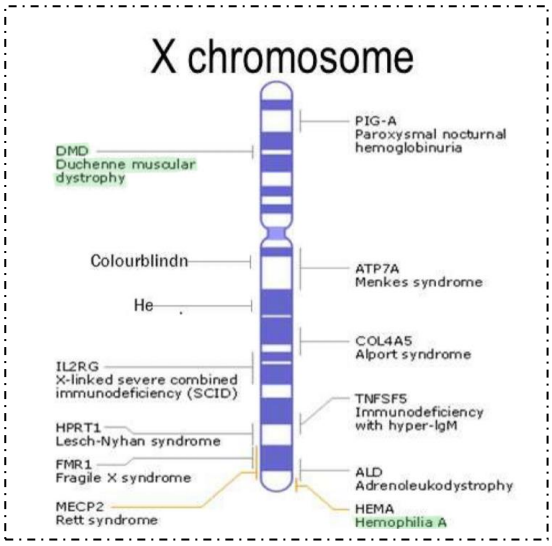
SRY (Sex-determining region Y)

- The highlighted region is the **<u>SRY</u> (<u>S</u>ex-determining <u>R</u>egion <u>Y</u>).** From the name, you can see that this region plays a role in determining the sex during embryonic development. By default, the embryonic development is FEMALE. If there's the **Y chromosome** and the **SRY region**, this embryo is destined not to develop to the default but to MALE.
- It's of importance to glance at one of the rare cases in which the karyotype is: 46, XY but the primary sexual organs indicate a FEMALE (ovaries, not testes). How would you explain that?
  There's a deletion in the SRY region.
  So, the SRY region is responsible for the development of MALE anatomical features.

- There are 3 other regions on the **Y chromosome** that we need to know, those are: **AZFa, AZFb, AZFc regions**. These regions are responsible for the formation of sperm. If the sex is destined to be MALE and the **AZF regions** are mutated, this mutation influences the formation of sperm, so this male is infertile because he is making no sperms, only Sertoli cells exist. So, if someone in the clinic comes to you with infertility; low or ZERO sperm count (*azoospermic* individual = ZERO sperm count), you have to look at those 3 **AZF regions** on the **Y chromosome.**

➢ **Fact: not all the genes carried on sex chromosomes are necessarily sex-related (some genes are not related to a sex trait).** Notice the highlighted regions in the figure.

- For example, at the bottom of the (q arm) of **X chromosome**, you will find the gene that has to do with Hemophilia; a clotting disorder that has nothing to do with sex. If a mutation happens in it, bleeding occurs.
- Another example is DMD (Duchenne Muscular Dystrophy) gene, a mutation which results in muscle weakness and the patient becomes wheelchair-bound or they might eventually die. This gene is carried on a sex chromosome yet is not sex-related.



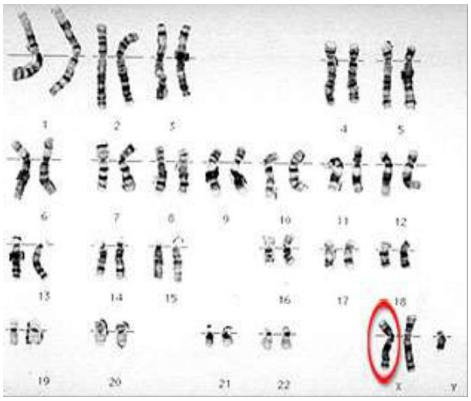
Note: overall, we have 900-1600 genes on **X chromosome**, 70-200 genes on **Y chromosome**.

This was a quick overview of sex chromosomes. Now let's move on to Sex Disorders.

➢ Before that, let's agree upon the fact that chromosomal disorders occur because of **numerical abnormalities (a missing or an extra chromosome)** or **structural abnormalities (i.e. deletion, duplication, inversion or translocation)**. The sex-related abnormalities that are going to be discussed in this lecture are:

- **Numerical abnormalities**: *Kleinfelter Syndrome (KS)*, *Turner Syndrome.*
- **Structural abnormalities**: *Cri-du-chat (cry of the cat) Syndrome*, certain cancers such as *Chronic Myelogenous Leukemia (CML).*

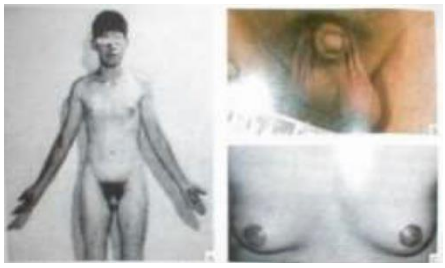
Klinefelter Syndrome (also spelled Kleinfelter)

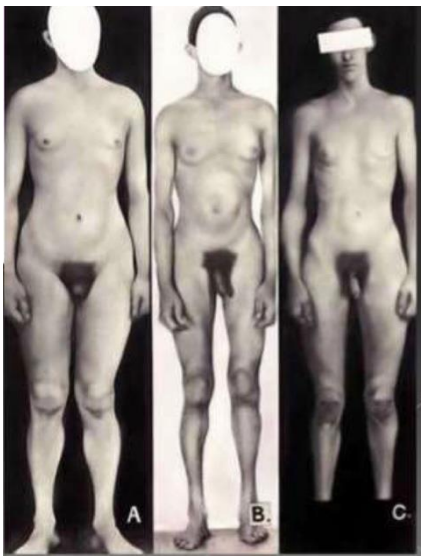


- Notice the karyogram. You can see that there's an extra **X chromosome**. The karyotype is **47, XXY**. **Klinefelter Syndrome** is a syndrome in which MALES* (why?) have an extra **X chromosome**. (so it's a trisomy)
  *Individuals with this syndrome develop MALE primary sexual organs because, regardless of how many **X chromosomes** they have, there's still a **Y chromosome** and an **SRY region**.

- **Characteristics**: notice the figures.
  - Secondary FEMALE characters:

FEMALE fat distribution (notice the hips) with breast development (gynecomastia)

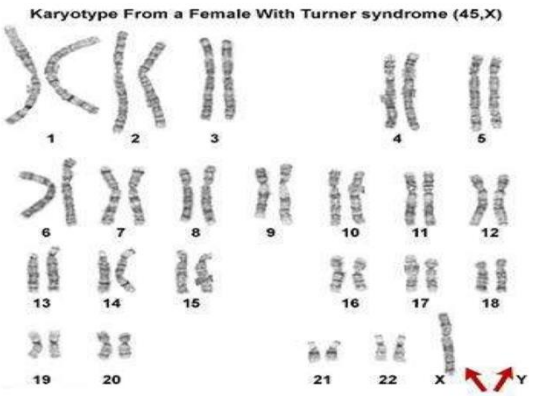




- Underdeveloped primary MALE sexual organs (testicular atrophy/small testes) which means they're infertile MALES.
  Infertility results from absent sperm.
- Coarse/reduced body hair
- Taller than average
- Evidence of mental retardation that may or may not be present
- Evidence of osteoporosis

Turner Syndrome

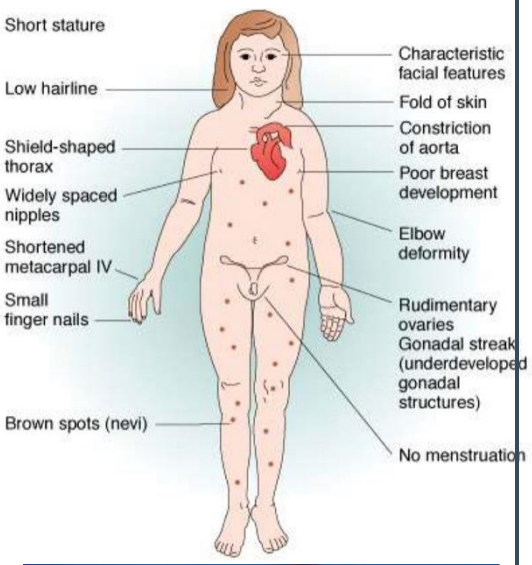
- ✓ Notice the karyogram. You can see that there's a missing **X chromosome**. The karyotype is **45, XO**. Turner syndrome produces females who are sterile.
- ✓ **Note: Turner Syndrome is the ONLY VIABLE monosomy.**
- ✓ **Turner Syndrome** is a syndrome in which FEMALES* (why?) have a missing **X chromosome**. (so, it's a monosomy)

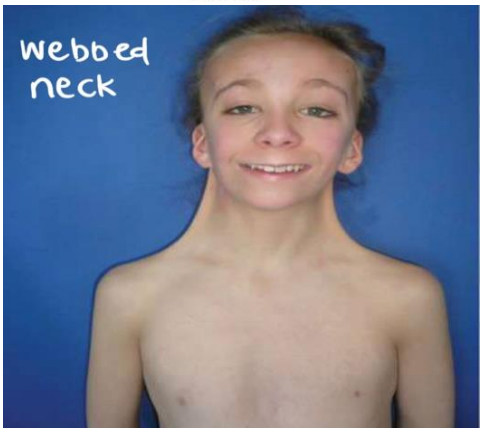


*Individuals with this syndrome are FEMALES because there's neither a **Y chromosome** nor an **SRY region.**

➢ **Characteristics**:

- Skin brown spots (nevi)
- Underdeveloped breasts with a wide distance between the nipples
- Webbed neck: an extra fold of the skin along the sides of the neck (notice the figure below)
- 20 cm shorter than average
- Rudimentary ovaries and underdeveloped gonads which is an indication of infertility
- No menstrual cycle
- Abnormal elbow position
- Secondary non-significant features: small fingernails and shortened metacarpals

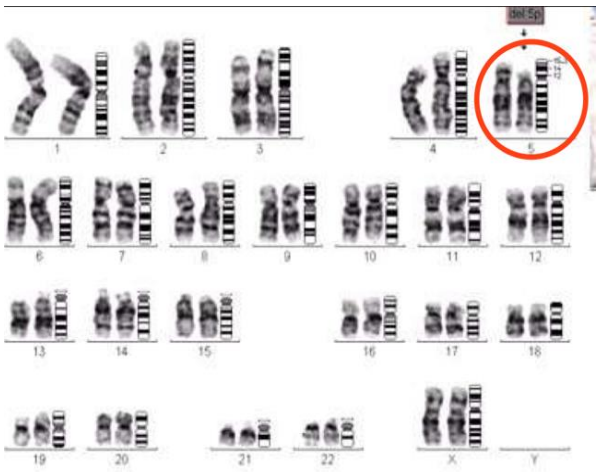




Take home message: Monosomy is not compatible with life— it's lethal. It is true that extra genetic material (trisomy) is less deleterious than missing genetic material (monosomy). Extra genetic material will have clinical impacts but at least the individual is alive. As mentioned above, TURNER SYNDROME is the ONLY VIABLE monosomy.

Cri-du-chat Syndrome

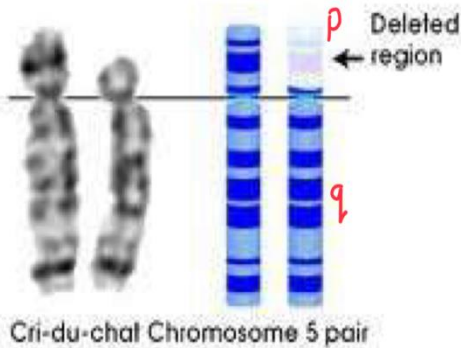
- ✓ It is a French sentence, which means (the cry of the cat).
- ✓ As the name indicates, people with this syndrome have a cat-like cry.
- ✓ Notice the karyogram. The chromosomes are normal in number; **46 chromosomes**. But if you zoom in on **chromosome 5** and look at the (p arm) of the homologue, you see that it's **missing** some genetic material (part of the p arm is **deleted**). What is the consequence of that?



A deletion mutation in the (p arm) of chromosome 5 results in <u>Cri-du-chat Syndrome</u>.

➢ **Characteristics**:

- Small head (microcephaly)
- Small chin
- Small nasal bridge
- Unusually round face
- Eyes are far from each other with a fold of skin over them



Cri-du-chat Chromosome 5 pair

➢ **Clinical symptoms also include**:

- Heart defects
- Hearing or sight problems
- Motor problems: muscular/skeletal defects, poor muscle tone. One of the indications of Cri-du-chat, on top of the facial clinical features, are walking difficulties. As a clinician, when you ask the patient to walk, you'll notice they have motor problems
- Hyperactivity and aggression (some of the cases)
- Severe mental retardation (some of the cases)

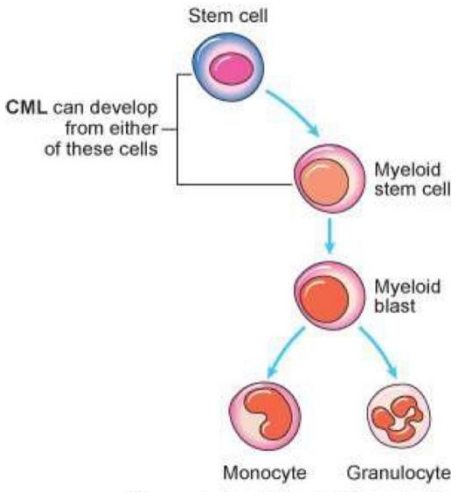
Most Cri-du-chat patients die within the 1st year of age but nowadays, with the advanced healthcare system and management, they make it to older ages.

Most common causes of death: pneumonia, aspiration pneumonia, RDS and CHD.

Chronic Myelogenous Leukaemia (CML) (blood cancer)

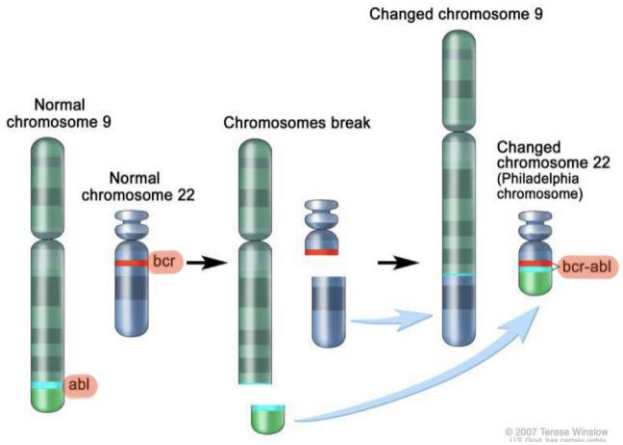
Remember, in hematology, a <u>stem cell</u> differentiates into a <u>myeloid stem cell</u> in the bone marrow and the myeloid stem cell becomes a <u>myeloid blast</u> which further differentiates into <u>monocytes</u> and <u>granulocytes</u>.

✓ **CML** can either develop from the stem cell or the myeloid stem cell (which is the precursor for WBCs)



- **Quick idea about leukemia**: it is of 4 types (acute or chronic, mylogenous or lymphoblastic)
- Acute mylogenous leukemia, acute lymphoblastic leukemia, chronic mylogenous leukemia, chronic lymphoblastic leukemia.

- ✓ **In CML**, myeloid cells grow slowly, and it is more common in adults than in children.
- ✓ **CML** happens because of reciprocal **translocation**. Notice the figure.
- ✓ A translocation is the exchange of genetic material between non-homologous chromosomes. In this case, there's an exchange of genetic material between **chromosome 9** and **chromosome 22**. We call the translocated chromosome 22 **Philadelphia chromosome**.



  - The exact mechanism: When the translocation occurs, the ABL gene that induces the cell cycle becomes under a stronger promoter which is the BCR promoter. The BCR-ABL transcript is translated into a mutant tyrosine kinase that results in a protein that is continuously activated (always on - its activity is elevated relative to wild-type ABL). Therefore, there are many more unregulated cell divisions and, thus, a higher chance of developing cancer.

- ✓ CML is an example of the first type of translocations which is **reciprocal translocation**. The figure shows the possible scenarios (1,2) of reciprocal translocation.

  - ***Scenario no. 1:*** acentric fragment is exchanged with another acentric fragment → both centromeres are preserved → **mitotically stable chromosomes**
  - ***Scenario no. 2:*** centric fragment is exchanged with an acentric fragment → acentric + dicentric chromosomes → **mitotically unstable chromosomes**

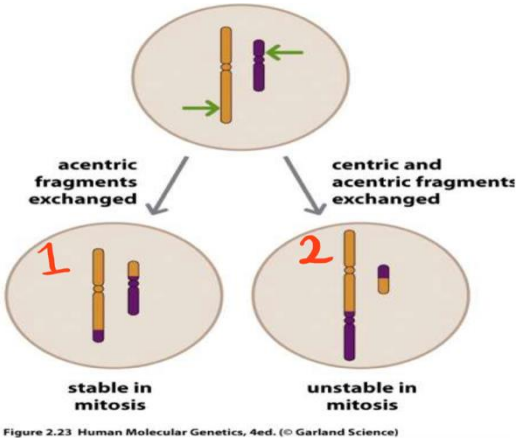


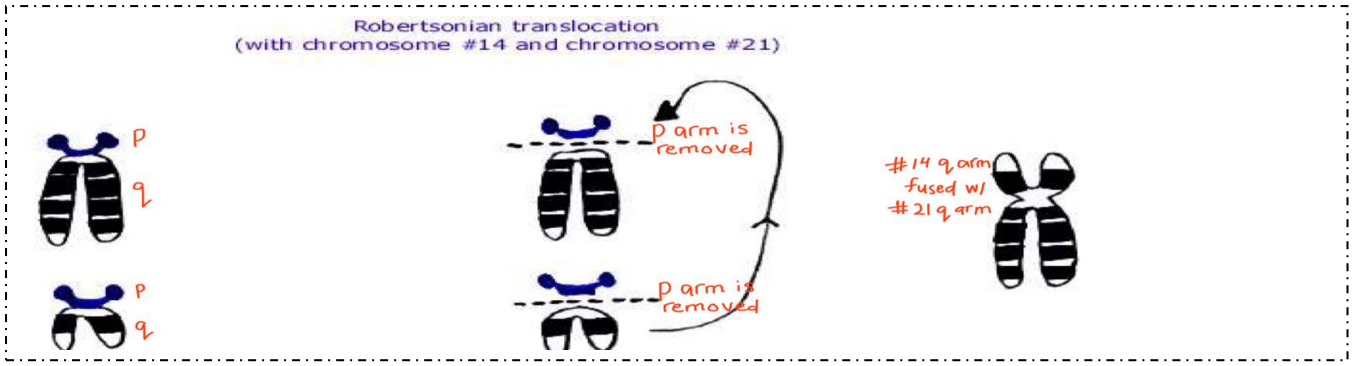
Figure 2.23 Human Molecular Genetics, 4ed. (© Garland Science)

(*Centric vs Acentric:* A break in the chromosome generates two fragments. One will contain the centromere, hence called a *centric* fragment, while the other won't contain a centromere, hence called an *acentric* fragment)

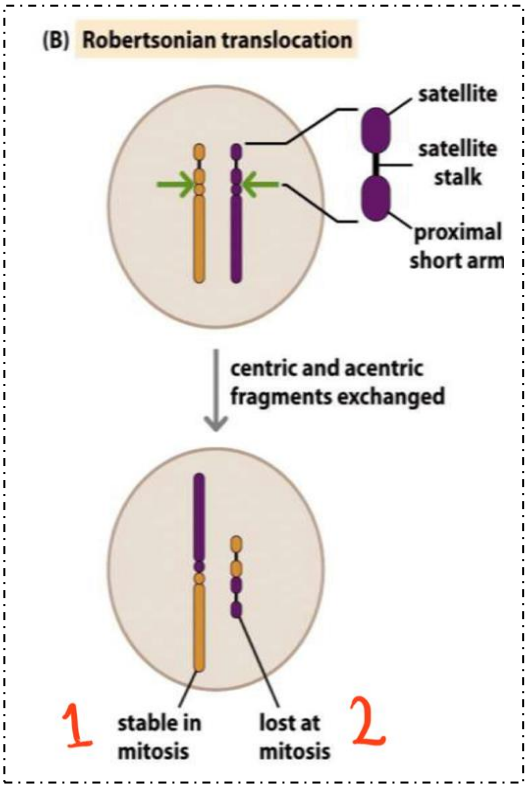
- ✓ The second type of translocation is **Robertsonian translocation**.

Remember: **acrocentric chromosomes** in humans are chromosomes (13, 14, 15, 21 and 22). These 5 chromosomes have the same (**p arm**) that contains 1) the proximal heterochromatic region (highly repetitive non-coding DNA), 2) a satellite region (non-coding distal heterochromatic region), and 3) a thin connecting region of euchromatin (the stalk) composed of tandem rRNA genes. Having said that these 5 chromosomes have very similar (p arms), we can conclude that it is of **no problem** if a (p arm) is missing from one of the 5 chromosomes because the other 4 chromosomes carry the same/similar DNA sequences in their (p arms)

- ✓ **Robertsonian translocation**: the exchange of genetic material between non-homologous acrocentric chromosomes. It is simply removing the (p arms) of both chromosomes then fusing the (q arms) of both chromosomes together to get one chromosome carrying two (q arms) of two acrocentric chromosomes. Notice the figure



- ✓ **Robertsonian translocation** 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 without any effect on the phenotype. It occurs exclusively after breaks in the short arms of the human acrocentric chromosomes.
(**Note**: Although listed as a separate type, it is considered a special form of reciprocal translocations. The reason why Robertsonian translocation is listed separately is because it has many unique features that distinguish it from other translocations). The figure shows the outcomes (1,2) of Robertsonian translocation.



- ✓ **In Robertsonian translocation**:

  1. centric fragments fuse with each other → dicentric chromosome → ***nevertheless mitotically stable**.

  2. acentric fragments fuse with each other → acentric chromosome → **mitotically unstable** (lost in mitosis) **without any effect on the phenotype**.

  As we said, there's no effect on the phenotype because the only genes lost are rRNA genes of the (p arm) that are also present in large copy number on the other acrocentric chromosomes.

Note: In scenario 2 of reciprocal translocation, we mentioned that one chromosome will end up with 2 centromeres (dicentric), while the other will have no centromeres. In general, chromosomes with multiple OR no centromeres are mitotically unstable because each chromosome should only have one centromere. **Now you're probably wondering, how come the dicentric chromosome in Robertsonian translocation is mitotically stable if it has 2 centromeres? This is because in this particular case, the break occurs close to the centromere, and the two fused centromeres are so close to each other that they can function as a single centromere, hence mitotically stable).**

- Lastly, we are going to talk about the **possible outcomes of meiosis in individuals that CARRY reciprocal / Robertsonian translocations**.

Note: These individuals are usually phenotypically NORMAL (asymptomatic balanced carriers) but often produce gametes that are unbalanced resulting in monosomy or trisomy in the zygote. (Refer to the "Extra Notes" section at the end of the sheet for details regarding the definition of "balanced")

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

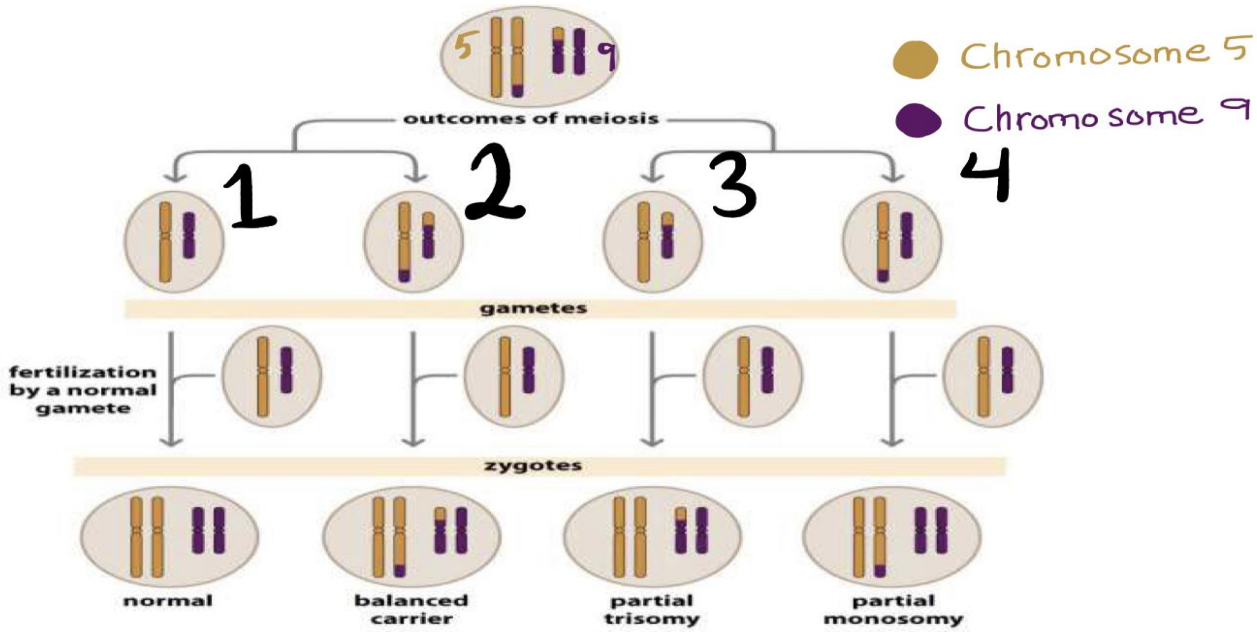


Figure 2.24 Human Molecular Genetics, 4ed. (© Garland Science)

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

Notice the figure. A *normal balanced carrier* has the correct quantity of DNA but REARRANGED. The problem arises when this carrier starts producing gametes (egg, sperm). During meiosis, each chromosome is going to be in the daughter cell (gamete) without its homologue (i.e., separated). Here are the possible gametes: (Refer to image as you read)

1. **Gamete 1** carries chromosome 5 (normal) and chromosome 9 (normal). *This is a normal gamete.*
2. **Gamete 2** contains both of the translocated chromosomes. So, each chromosome contains part of chr. 5 and part of chr. 9. However, overall, both chromosomes collectively contain all the genes of chromosomes 5 and 9 (No missing genes, they are just distributed differently. *So, this gamete can actually give rise to a normal balanced individual if fertilisation occurs with another normal gamete)*
3. **Gamete 3** contains chromosome 5 (normal) but only has part of chromosome 9. So some genes of chromosome 9 are missing, and there are some extra chromosome 5 genes in this gamete. *This gamete will NOT give rise to normal balanced individuals when fertilised.*
4. **Gamete 4** contains chromosome 9 (normal) but only part of chromosome 5. So, some genes of chromosome 5 are missing, and there are some extra chromosome 9 genes in their place. *This gamete will NOT give rise to normal balanced individuals when fertilised.*

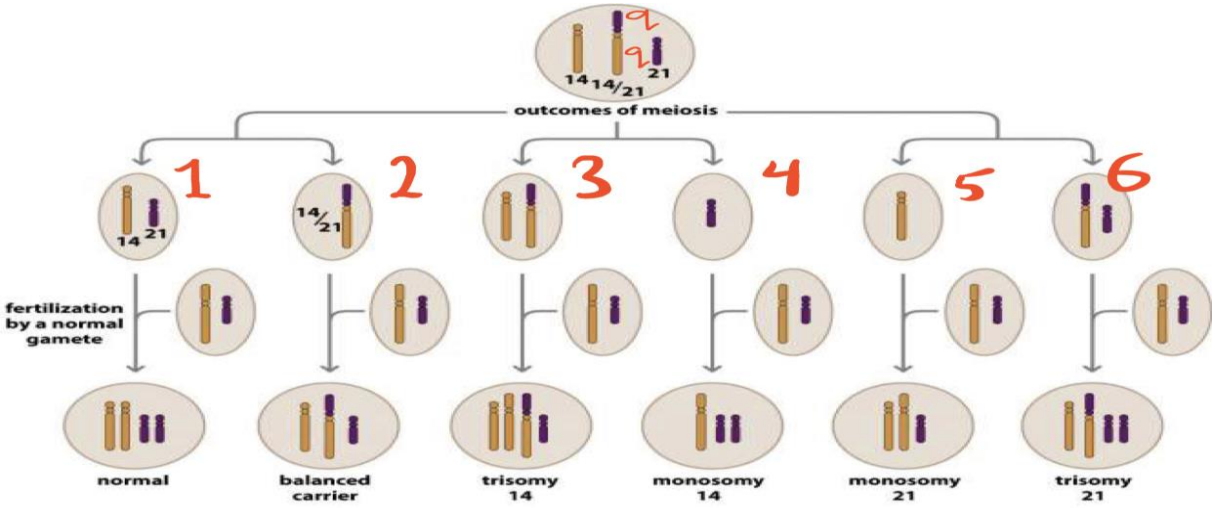
Now, let's see what happens to those gametes when fertilised: (Refer to image as you read)

- Fertilisation of gamete #1 by another normal gamete gives a **normal zygote**.
- Fertilisation of gamete #2 by another normal gamete gives a normal **balanced carrier** (both translocated chromosomes in the daughter cell with balanced DNA quantity)
- Fertilisation of gamete #3 by another normal gamete gives an individual with **partial trisomy for chromosome 5** (unbalanced DNA quantity as the quantity of chromosome 5 > chromosome 9). In other words, this individual has **partial monosomy for chromosome 9**.
- Fertilisation of gamete #4 by another normal gamete gives an individual with **partial monosomy for chromosome 5** = **partial trisomy for chromosome 9**.

Note: Partial trisomy: We have more than 2 but less than 3 chromosomes, hence a partial trisomy.
Partial monosomy: we have less than 2 but more than 1 chromosome, hence a partial monosomy.

✓ Notes from the slides: The relative frequency of each possible gamete is not readily predicted. The risk of a carrier having a child with each of the possible outcomes depends on its frequency on the gametes and also on the likelihood of a conceptus with that abnormality developing to term.

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



Note: assuming this individual is a MALE, the karyotype is: **45*, XY, t(21q:14q)**.

***45 chromosomes** because in Robertsonian translocation the (q arms) of both acrocentric chromosomes fuse together resulting in one viable dicentric chromosome, the other acentric chromosome is lost; so instead of 46 chromosomes the individual has 45 choromosomes.

Notice the (6) possible combinations of gametes a balanced carrier of Robertsonian translocation can produce. The **outcome** is based on these combinations.

- Fertilisation of gamete #1 by another normal gamete gives a **normal zygote**.
- Fertilisation of gamete #2 by another normal gamete gives a **balanced carrier** (phenotypically normal) (identical to the parent cell)
- Fertilisation of gamete #3 by another normal gamete gives a **full trisomy 14**. (lethal)
- Fertilisation of gamete #4 by another normal gamete gives a **full monosomy 14**. (lethal)
- Fertilisation of gamete #5 by another normal gamete gives a **full monosomy 21**. (lethal)
- Fertilisation of gamete #6 by another normal gamete gives a **full trisomy 21**. (viable)

- ✓ So, we can conclude that a carrier of a balanced Robertsonian translocation can produce gametes that after fertilisation can give rise to an entirely normal child, a phenotypically normal balanced carrier, or a conceptus with full trisomy or full monosomy for one of the chromosomes involved.

Note: the two monosomic zygotes (monosomy 14 and monosomy 21) in addition to trisomy 14 zygote -in this example- are not expected to develop to term. On the contrary, trisomy 21 zygote is expected to make it to life with Down Syndrome.

Relevant note:

- The only viable **TRISOMIES** are: trisomy 21 (Down Syndrome), trisomy 18 (Edward Syndrome) and trisomy 13 (Patau Syndrome).
- The only viable **MONOSOMY** is Turner Syndrome.

Always be curious!

Extra Notes – Not Required (not mentioned in slides or lecture video)

- ✓ ***Definition of "balanced" and unbalanced in genetics***: Chromosomal changes can be described as: 1) balanced if the overall amount of DNA does not change (e.g., a reciprocal translocation can be balanced, because the chromosomes exchange DNA but the total amount of DNA is normal), and 2) unbalanced if the chromosomal change results in an overall change in the amount of DNA.
  Usually, individuals who have balanced translocations are phenotypically normal because they do not have missing DNA (that is, all genes are present, they are just rearranged differently). So, these ***phenotypically normal*** individuals, who ***carry*** the ***balanced*** translocation are called: **Normal balanced carriers**.

  You might have noticed that in page 9, we said: "a *balanced* carrier of Robertsonian translocation". But don't we lose DNA (the p arms) in this translocation? So, there is less DNA. Then why did we use the term "balanced" here? Strictly speaking, we cannot use the term "balanced". Nevertheless, since the missing DNA here is actually redundant, we can neglect it, as if no DNA is missing. So, sometimes, we use the term "balanced" to refer to phenotypically normal individuals, even if they have missing (but redundant) DNA. (Most "balanced" translocations cause a normal phenotype, so we can say "balanced" = normal phenotype, although this is not correct strictly speaking, but it explains why some people say that Robertsonian translocations can be balanced").

- ✓ Note that in page 9 (at the bottom), we used the term *full* trisomy. Strictly speaking, they are not actually full trisomies, because they have two complete copies (each containing p + q arms) and one incomplete copy of the same chromosome (q arm only). But since the p arm is not very important in acrocentric chromosomes (redundant), we can neglect its absence.