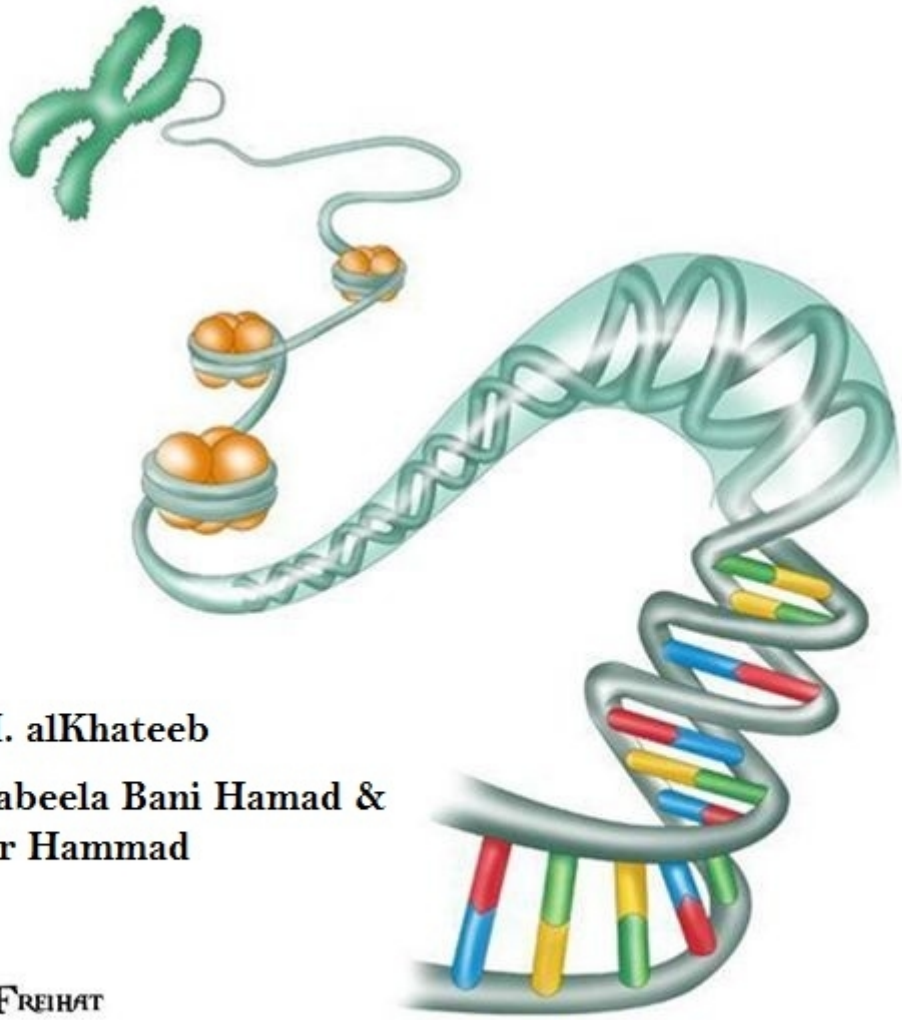
University of Jordan
Faculty of Medicine
Batch 2013-2019

Medical Committee
The University of Jordan

Genetics & Molecular Biology

○ Slides ✥ Sheet ○ Handout ○ other.....



Sheet#: 4

Dr. Name: M. alKhateeb

Done By: Salsabeela Bani Hamad & Noor Hammad

Designed by Nadeen Al-Freihat

Chromosomal abnormalities (2)

Today we will talk about chromosomal abnormalities related to structural changes.

- Human chromosomal disorders:

In general , chromosome's structure changes are rare , and we see them most commonly in infancy or before birth and most of them are associated with abortion because these diseases most of the time are incompatible with life . And the cases that live normally are almost of small ages and the number of cases subsides with age, so usually we don't see these abnormalities late in life.

So keep in mind that most embryos that have such abnormality are spontaneously aborted. Also alterations in chromosomes cause many disastrous things and can lead to develop mental problems result from biochemical imbalance.

Certain conditions can be correlated and can be seen compatible with life, they can survive for a certain period.

So individuals who live normally and are under the risk , in general they have what we call a **balance rearrangement** that doesn't cause a genetic disease ; which means if there is structural abnormality in the chromosome but all the genetic material is within the person , he will live a normal life . But if we talk about his children, here we will see abnormalities, because he will inherit the balance to his offspring.

The chromosomes can't line up evenly during meiosis; because there will be some problems, during this we may have some chromosomes with some missing segments, some with extra segments and most commonly are chromosomes with a combination of both, missing segments in a part and extra segments in the other part.

When we talk about **balance**, this means there is no loss of DNA, all the needed genetics material is found within the chromosomes, so the individuals will have all the genes needed for life and rarely produce disorders, disorders will be produced when there is breakage.

Unbalanced DNA:

Here there is breakage and part of the DNA is lost , the individuals are missing one or more genes , this often leads to genetics' disorders and the severity of the disease depend on how much of the genetic material is lost or how much is gained .

So the abnormalities that we can see during these conditions could be:

- Translocation
- Inversion
- Deletion
- Insertion
- Rings formation
- Duplication
- Isochromosomes

These are the interstitial characteristics that we can see in these chromosomes.

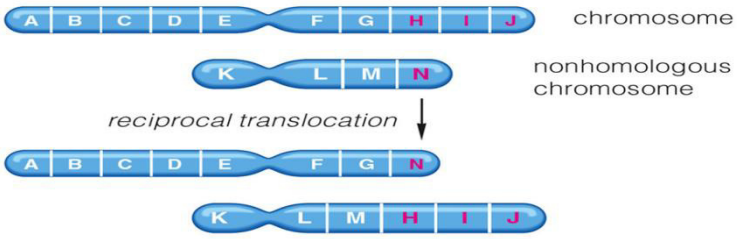
A) Translocation:

We have two types:

1) Reciprocal Translocation:

Caused by rearrangement of parts between **non homologous** chromosomes.

Look at the figure below , the pair of non homologous chromosomes above are normal , compare it with the lower pair , you will notice that segments (H , I , J) in the first chromosome were substituted with segment (N) in the second chromosome .



Here we have two **non homologous** chromosomes have **different** structures; if the cut result in no change (no loss) we call it **balanced translocation.**

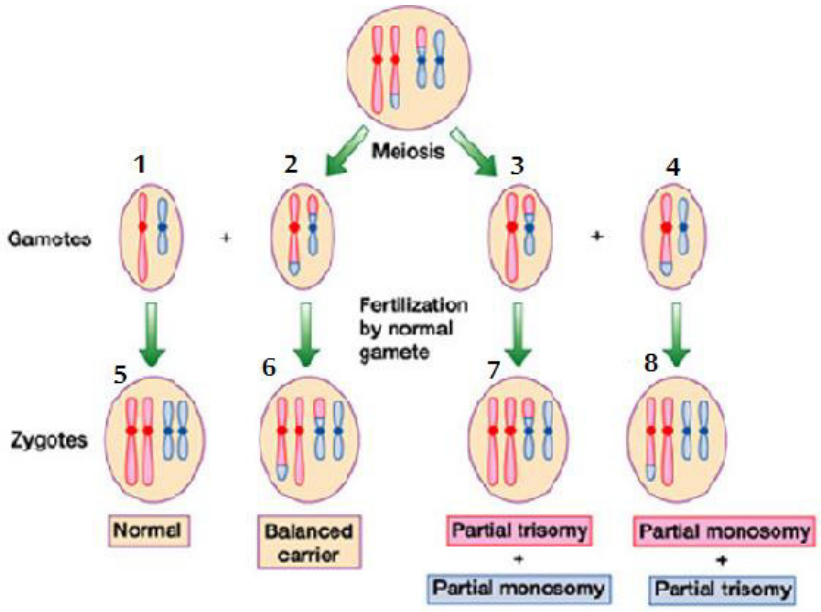
- What will be the end result of the reciprocal translocation?

If there is a translocation between the two chromosomes and there is no loss of genetic material, the person is completely normal. **But** during meiosis, at the level of segregation of genetic material and producing of two daughter cells there will be many possibilities.

- ✓ Some daughter cells will be normal with **complete** genetic material (like cell 1, in the figure below).
- ✓ Some daughter cells will have Translocation between the two chromosomes but the there is no loss of the total genetic material (like cell 2, in the figure below).
- ✓ Some daughter cells will have **missing segments** (like cells 3, 4).

When these gametes are fertilized with **Normal** sperms/ovums there will be 4 possibilities:

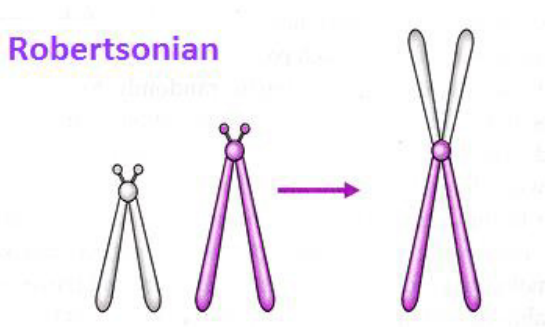
1. Normal zygote (like number 5).
2. Balanced carrier (like 6).
3. Partial Trisomy + Partial monosomy (like 7).
4. Partial monosomy + partial trisomy (like 8) .



2)Robertsonian Translocation:

This involves **Acrocenteric chromosomes** that **don't have P-arm**, if you count the chromosomes in a person with this abnormality you will find them **45**.

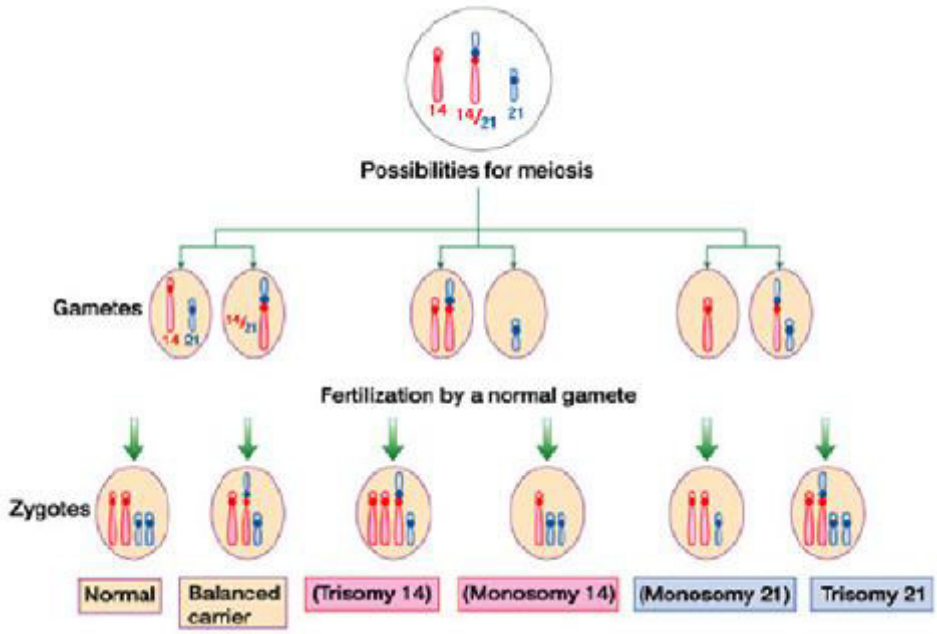
Explanation: when translocation occurs the two involved chromosomes will join each other and will make one chromosome, that's why the number of chromosomes in the affected person will be 45.



This type of translocation could occur in **Acrocenteric** chromosomes which are 5 in human genome **(chromosomes; 13, 14, 15, 21, 22)**.

- What will be the end result of the Robertsonian translocation?

The doctor didn't answer, but you can take a look to the figure below.



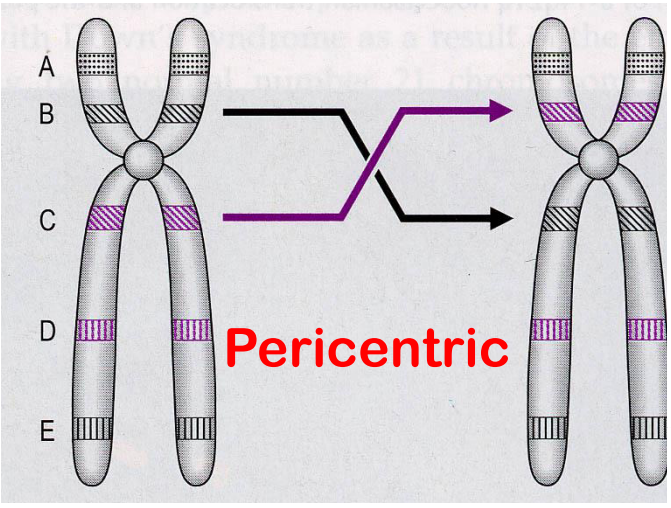
B) Inversion:

The DNA segment or chromosomal segment will change its location in the sequence.
We have two type of inversion:

1) Pericentric inversion :

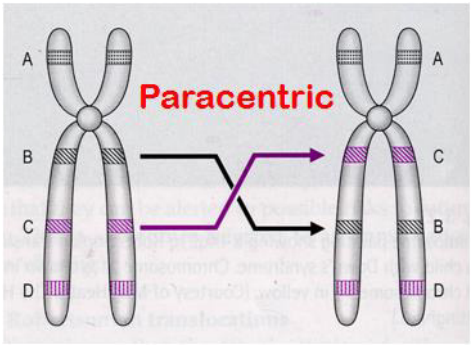
Notice the figure below , the chromosome in the left has a sequence of 5 segments (A ,B , C , D , E) , now look at the chromosome in the right , you will notice that sequence is different , it is (A ,C ,B ,D ,E).
Here, a segment from P-arm inverted to be located in the q-arm.
This is called Pericentric inversion.

Result: In Pericentric inversion a segment of genetic material will be inverted from P-arm to q-arm or vice versa.



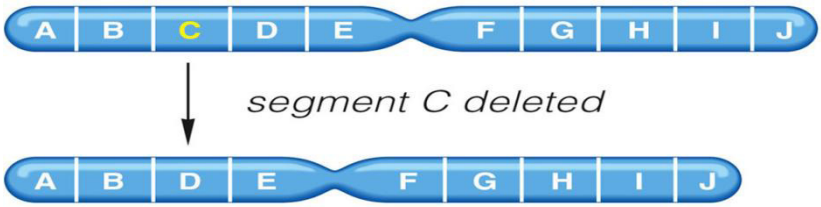
2) Paracentric Inversion:

The two segments that are, involved in the inversion, **are in the same arm,** could be p-arm or q-arm. Look at the figure below.



C) Deletion:

There is a deleted segment from the chromosome. Look at the figure below, notice that (segment C) at the first chromosome is **deleted** in the second one.



Ex 1: 46, XY, del (5) P (13).
This means there is a deletion in the genome of a male at the third segment/band of the first region of the short arm of chromosome number 5.

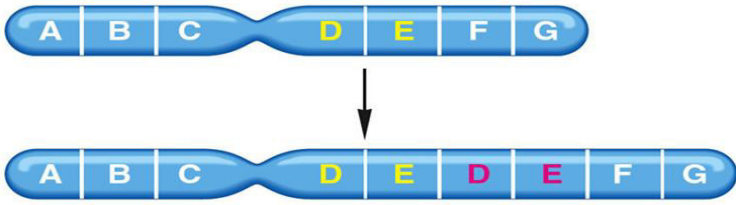
Ex 2: 46, XY, del (13)(q12q21) .
This means there is a deletion in the genome of a male from q12 to q21 of the long arm of chromosome number 13.

In (Ex.2) there is a little difference in the way of writing, that's because the deletion in Ex2 is **within the chromosome** while deletion in Ex1 is at the end **of the chromosome**.

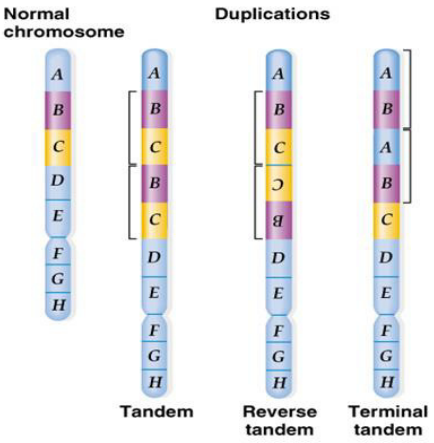
D) Duplication:

One segment will be duplicated; this is commonly seen in **Tumors;** as some oncogenes increases this type of abnormality (Duplication).

Look at the figure below, the first chromosome is the normal one (notice segments D, E), now look at the second chromosome; you will notice that the segments (D, E) are duplicated.



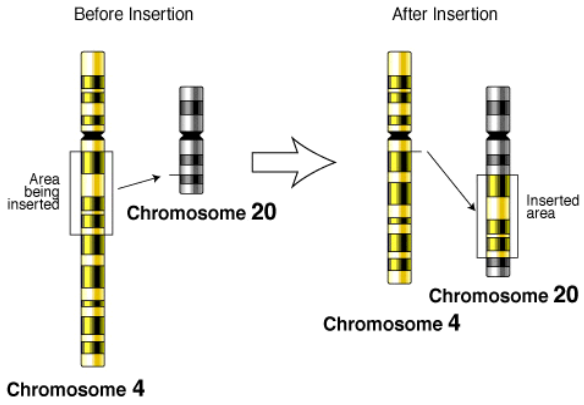
- Keep in mind that duplication can be reversed, the figure below illustrates this.



E) Insertion:

Specific segment from one chromosome will be cut an **inserted** into another chromosome (Not Exchange).

In the figure below, you can see that a segment from chromosome 4 is cut and be inserted in chromosome 20.



Keep in mind that Insertion has two types:

1. **Direct:** the cut segment will be inserted in the second chromosome with its original orientation/sequence (its orientation in the first chromosome).
2. **Inverted:** The orientation of the inserted segment will be inverted (opposite to its original orientation).

What is the end result of duplication?

One of the result is something called **pseudodominance**.

Remember, in autosomal dominant one affected allele is enough to get the disease, while in autosomal recessive both alleles must be affected to get a disease.

In translocation, as there is new (added) segment, both alleles will work as dominant (actually they are not dominant but because of the added segment was duplicated they will work as dominant).

Pseudodominance: An autosomal recessive condition present in individuals in two or more generations of a family, thereby appearing to follow a dominant inheritance pattern. ~ Internet

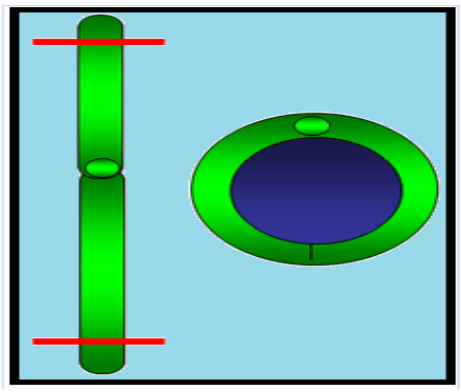
Another result might be **haploinsufficiency** :

If the deleted segment is responsible for production of heavy chain for example, assume that one allele can produce 10 ng (nano gram), two can produce 20 ng and so on. If you get duplication in that allele you will get production of double of the previous amount but if you get deletion of the allele you will get half of the amount , this is what we mean by haploinsifficiency ; the amount of proteins synthesized are not enough to do the function or it is increased and do over-function.

F) Ring Chromosome:

Remember when we talked about telomeres, at each end of each chromosome there is telomere that are important to keep the integrity of the chromosome.
What will happen here is that specific enzyme will chop the two ends of the chromosome and remember that these two ends are complementary to each other so what will occur now? Actually the two ends will turn and join each other and form a ring.

Look at the figure below.



If you do chromosomal analysis you will see segments of chromosome that you don't know their origin, these are the cut segments. Ex of this: 46, XY , r(5)(p15q23) . r:ring.

This occurs mainly in the **anaphase** stage of cell division.

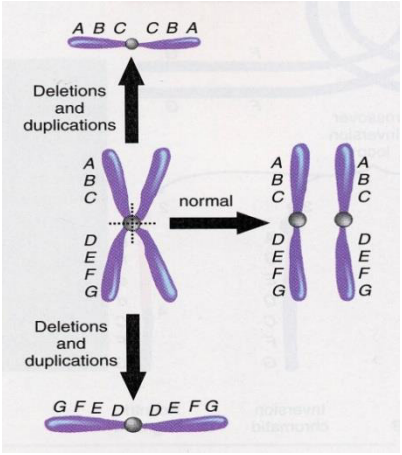
G) Isochromosome:

Normally , when the two sister chromatids segregate from each other , the centromere is cut **vertically** , the result will be p-arm with q-arm together in one pole and p-arm with q-arm together in the another pole .

When we talk about **Isochromosomes**, the cut will be **horizontally**, the result will be two p-arms together in one pole and two q-arms in the other pole.

- ✓ This can be seen in **Turner's syndrome**.
- ✓ Ex: 46, XY, i(12)(p10).

I: means isochromosomes.



- We talked about structural abnormalities of chromosomes and now we will talk about the corresponding diseases (that occur due to them).

Chromosomal Deletion Syndromes:

Two types:

1. **Large deletion:** where large segment of chromosome is deleted , Ex:
   - Cri du Chat Syndrome
   - Wolf-Hirschorn Syndrome
   - DiGeorge Syndrome (DGS)

2. **Micro deletion:** where small segment is deleted , Ex:
   - Deletion 1p36
   - Williams
   - Langer Giedion
   - Neurofibromatosis NF-1
   - Prader-Willi Syndrome (PWS)
   - Angelman Syndrome (AS)
   - Rubinstein – Taybi
   - Miller – Dieker
   - Smith-Magenis
   - 22q11.2 deletion (DiGeorge/VCFS)

{Large Deletion abnormalities}

1) Cri du Chat Syndrome:

Abnormality: Large deletion in chromosome 5 at the distal part of the p-arm; many genes are deleted.

Main characteristics: The face will be similar to kitten (Young cat).
Diagnosis: we can do chromosomal analysis and will notice that there is a large deletion in chromosome (5).

2) Wolf – Hirschorn Syndrome:

The deletion is in chromosome (4), and the deleted segment has many genes .The critical region is 4p (16.3-16.5) kilobase segment, located at the short arm of chromosome (4)

Characteristics: the patient has (greek helmet) face.
Incidence: 1/50,000 live birth.

Clinical features:

- ✓ Distinctive "greek helmet" facies (as we mentioned) .
- ✓ Cardiac defects and problems in 50%.
- ✓ Mental retardation, because they have Microcephaly.
- ✓ Most are stillborn or die in infancy.
- ✓ Frequent seizures.
- ✓ Around 90% are de novo deletions; not inherited (the defect occurred during development).
- ✓ Abnormal faces. Cardiac, renal, and genital abnormalities.

Diagnosis: we can detect the abnormal chromosome in the lab by doing normal chromosomal analysis or by FISH (Florescence in situ hybridization) technique.

3) DiGeorge Syndrome:

- Normally characterized by chip and palate cleft.
- It occurs due to deletion in chromosome 22 (so it is called as 22q11 deletion syndrome).
- And also called Velocardiofacial Syndrome (VCFS).

Characteristics:

- ✓ Congenital heart disease (75%).
- ✓ Palatal abnormalities.
- ✓ Characteristic facial features.
- ✓ Learning difficulties; which means they have mental retardation.

Diagnosis: again, either by normal chromosomal analysis or by FISH technique.

{Micro Deletion abnormalities}

- ✓ Deletion 1p36**:** occurs at chromosome (1).
- ✓ Williams : 7q deletion of elastin gene (1-4 mega base)
- ✓ Langer Giedion Syndrome; 8q23.3-q24.13, as you can see deletion here occur at chromosome (8). Here also we can see Trichorhinophalangeal syndrome type 2 (TRPS).
- ✓ Neurofibromatosis NF-1, TSG chromosome 17.
- ✓ Prader-Willi Syndrome (PWS) / Angelman Syndrome (AS), in chromosome (15).
- ✓ Rubinstein – Taybi , in chromosome 16
- ✓ Miller – Dieker , in chromosome 17 .
- ✓ 22q11.2deletion (DiGeorge/VCFS), 95% of it is due to deletion in chromosome (22).

Don't panic, we are required to memorize only the numbers related to disorders that we will talk about in details.☺

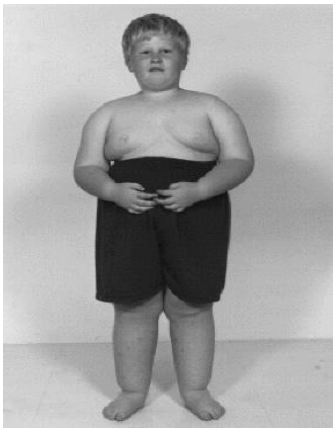
1) Prader-Willi and Angelman syndromes:

Both disorders can result from micro deletion in 15q11-q13, (Both syndromes are linked to the same imprinted region of chromosome 15 and the only difference between them is either the copy from mom or the copy from dad is epigenetically silenced.)

The abnormality is on the paternally derived chromosome 15 for **Prader-Willi (PW)** and the maternally derived 15 for **Angelman (AS)** because of genomic imprinting.

Parder-Willi :

Phenotype:



- ✓ Short stature, small hands, feet and eyes.
- ✓ Hyperphagia (compulsive overeating), obesity.
- ✓ Hypotonia, poor feeding in infancy.
- ✓ Dysmorphic face.

Angelman syndrome:

Phenotype:

- ✓ Jerky movements and typical standing
- ✓ Inappropriate laughter
- ✓ Developmental delay
- ✓ Mental retardation
- ✓ Happy and puppet syndrome
- ✓ Easily provoked laughter
- ✓ Severe MR(mental retardation), absence of speech

Prevalence and Incidence statistics:

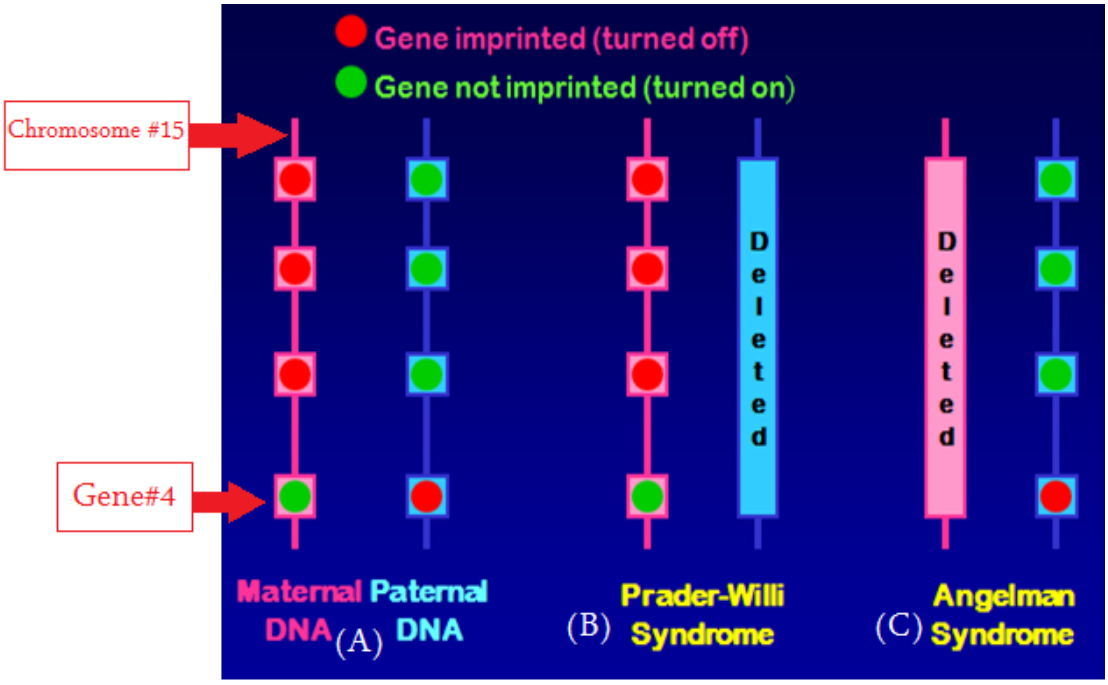
- The incidence rate of both disorders is one to ten per thousand.
- The high incidence rate in the newborn.
- The risk factor is paternal or maternal chromosomal damage.

Pathophysiology :

You receive your genes from your parents, one copy from your mother (maternal copy) and another one from your father (paternal copy). Your cells typically use information from both copies, but in a small number of genes, only one copy is active.

Now look at the figure below.

- Case (A) represents a normal individual, the maternal allele of the certain gene (gene number 4) of chromosome 15 is expressed (turned on) and the paternal allele is specifically silenced (turned off). The maternal allele is almost exclusively the active one.
- If the maternal is lost or mutated, the result is Angelman syndrome (case C in the figure).
- Some other genes on chromosome 15 are maternally imprinted (turn off), and when the paternal contribution is lost, by deletion, the result is Prader-Willi syndrome (case B in the figure).



Chromosomal Duplication Syndromes:

- Beckwith-Wiedemann : Duplication-11p15 (Paternal)
- Duplication 17p11.2p12
- Cat-Eye Syndrome : Duplication of 22q
- - Velo-cardio-facial syndrome – features (VCF) Duplication – 22q11.21-q11.22
- 5-PWS/AS Duplication – 15q11-q13

❖ Note: here we present a patient with typical **15q11-q13** deletion who also carried a familial duplication of centromerically located in **15q11-q13.**

Marker Chromosomes:

- A marker chromosome is defined as a structurally abnormal chromosome that cannot be identified by routine cytogenetics.
- Occasionally occur as supernumerary (**they are extra**) chromosomes with or without phenotypic effect (**range from NORMAL to SEVERELY ABNORMAL**).
- Parental chromosomes should be analyzed to understand the karyotype-phenotype relationship of supernumerary marker chromosomes.

OTHER ABNORMALITIES:

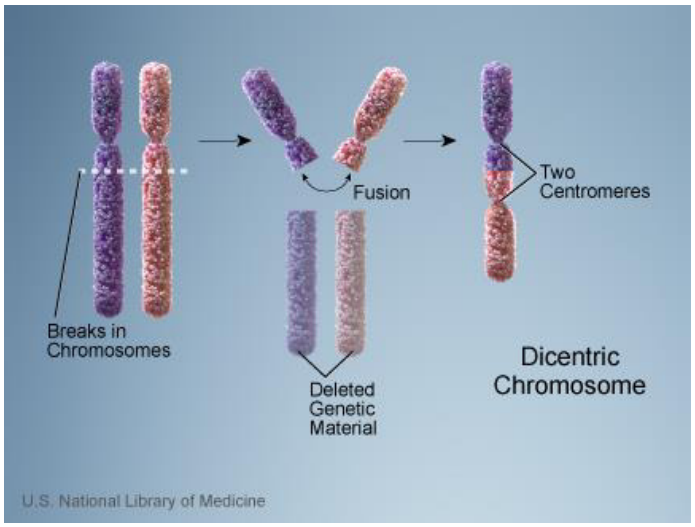
1- Chromosome breaks:

- Once chromosome broken by some means
- Unstable situation as telomeres not at end
- Usually join up to other piece

Chromosome breakage syndrome: are a group of inherited conditions associated with chromosomal instability and breakage .leading to chromosomal rearrangements encompassing several different classes of events: deletions, duplications, inversions; and translocations. Each of these events can be caused by breakage of DNA double helices in the genome at two different locations, followed by a rejoining of the broken ends to produce a new chromosomal arrangement of genes, different from the gene order of the chromosomes before they were broken.

2-Dicentric Chromosomes:

Chromosomes with two centromeres from different chromosome or from the two chromatids of a single chromosome (centromere is duplicated without segregation).



From different chromosomes

3- Double minutes:

Are small fragments of extrachromosomal DNA.

- A minute is an acentric fragment smaller than the width of a chromatid
- Double Double minutes (dmin) are seen in tumor cells as **double dots.**

*These abnormalities are associated with many diseases, for example:

1. 2.5 % unexplained infertility in males mainly that could be due to chromosomal abnormality.
2. 60% recurrent miscarriages

Chromosomal findings in early miscarriages:

- ❖ The chromosomal abnormalities are increased with mother's age
- ❖ 40% apparently normal and 60% abnormal

- ✓ Trisomy (47 chromosomes – one extra chromosome), 30%.
- ✓ 45, X "turner syndrome" (45 chromosomes – one missing), 10%.
- ✓ Triploidy (69 chromosomes – three sets), 10%.
- ✓ Tetraploidy (92 chromosomes – four sets), 5%.
- ✓ Other chromosome anomalies (e.g. structural anomalies), 5%.

Indications for postnatal chromosomal analysis:

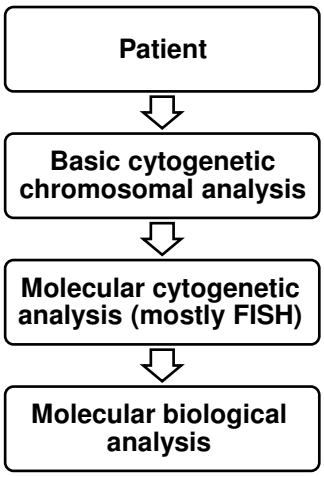
When do we use the chromosomal analysis?

- Suspicion to concrete chromosomal abnormality (concrete syndrome)
- Multiple congenital anomalies or developmental delay
- Mental retardation
- Gonadal dysgenesis

- Infertility
- Miscarriages
- Delivery of dead fetus or death of a newborn child
- Occurrence of certain malignancies

The sequence of events in diagnosis of chromosomal abnormalities:

If the results of the basic cytogenetic chromosomal analysis does not satisfy you, you use the FISH and the same thing applied to FISH (if the results of the FISH does not satisfy you, you use the molecular biological analysis).



Basic cytogenetic chromosomal analysis:

To identify chromosome abnormalities detectable by routine cytogenetic analysis (culturing and banding)...If we want to be more specific, we should use **FISH technology** which is used in the detection of chromosomal abnormalities and it has high sensitivity and specificity.

Methods available for identifying contiguous gene deletions:

- **FISH :**
  - ✓ commercially available probes for most deletion
  - ✓ may have difficulties detecting small deletions
  - ✓ May be difficult to characterise the deletion for syndromes associated with variable deletions.

- **MLPA Analysis**
  - ✓ commercially available
  - ✓ 'microdeletion syndrome' and 'mental retardation' available to test for >1 syndrome
  - ✓ can be confirmed using FISH probes

- **CGH Analysis** (Comparative genomic hybridization): important in diagnosing cases with unknown genetic etiology

- **qPCR analysis**: Copy number of individual genes .

Summary about the chromosomal abnormalities:

Note: you only need to know about the syndromes that the doctor explained during the lecture.

Diagnostic Potential For Karyotype, FISH, and Chromosomal Micro- array Analysis (CMA) For Selected Disorders

Condition	Locus studied	Karyotype	Disease specific FISH	Telomere FISH	CMA
Aneuploidy	various	~100%	Not detected	Detected by karyotype	~100%
Large deletions, large dupllications, translocation of large segments	various	~100%	Not detected	Detected by karyotype	Karyotype better for present
Cryptic Rearrangements of telomeres	various	Not detected	Not detected	~100%	~100% for unbalanced
1p36 deletion	1p36.3	Few	~99%	>95%	~99%
Wolf-Hirschhorn	4p16.3	Most	~99%	>95%	~99%
Cri-du-chat	5p15.2	Most	~99%	>95%	~99%
Williams-Beuren	7q11.2	Almost none	~99%	Not detected	~99%
Prader-Willi	15q11-q13	Unreliable	~70%	Not detected	~70%
Angelman	15q11-q13	Unreliable	~70%	Not detected	~70%
Miller-Dieker lissencephaly	17p13.3	Few	>90%	Some detected	>90%
Smith-Magenis	17p11.2	Some	>95%	Not detected	>95%
Velocardiofacial/DiGeorage 1	22q11.2	Rarely	>95%	Not detected	>95%

Introduction about the next lecture {single gene disorder} :

A single-gene disorder:

- Is the result of a single mutated gene.
- Types of Genetic Diseases :
  - ✓ Chromosomal Abnormalities
  - ✓ Single Gene Defects
  - ✓ Non- Traditional Inheritance
  - ✓ Multifactorial Disorders

- ✓ Cancer Genetics

- There is three ways for a single gene to be inherited :
  1) Autosomal recessive
  2) Autosomal dominant
  3) Factors complicating Mendelian inheritance:
     - ✓ X-linked recessive
     - ✓ X-linked dominant
     - ✓ Y-linked

1,2 are the most common X-linked recessive, X-linked dominant and Y-linked are sex-linked

❖ Autosomal recessive inheritance

Used to describe a characteristic or condition that appears only in individuals who have received two copies of an altered gene, once copy from each parent.

❖ Autosomal Dominant :

Dominant conditions are expressed in individuals who have just one copy of the mutant allele.

- **Characteristics of autosomal dominant inheritance :**
  - ✓ A gene is dominant if it is expressed when heterozygous.
  - ✓ An affected individual has a 50% chance of having an affected child.
  - ✓ An affected child will have one affected parent.
  - ✓ The affected parent can be either the mother or the father.
  - ✓ Autosomal dominant traits have low frequencies in the population.
  - ✓ Autosomal dominant traits are usually lethal when homozygous.

- ✓ Appears in both sexes with equal frequency (Both sexes transmit the trait to their offspring).
- ✓ No skipping of generations (We can find the disease in each generation).

- **Characteristics of Autosomal Recessive :**
  - ✓ Appears in both sexes with equal frequency.
  - ✓ Traits tend to skip generations.
  - ✓ Affected offspring are usually born to unaffected parents.
  - ✓ When both parents are hetzyg. ~1/4 of the progeny will be affected.
  - ✓ Appears more frequently among the children.
  - ✓ Of consanguine marriages.

❖ **Example:**

Sickle-cell disease occurs when a person inherits two abnormal copies of the haemoglobin gene, one from each parent .If one allele is defected the person will be physically normal **(A person with a single abnormal copy does not experience symptoms)**.But when the two alleles are defected, the symptoms are developed.

Sometimes We have to see for ourselves... We have to make our own mistakes... We have to learn our own lessons...until we finally understand for ourselves.. that knowing is better than wondering... That waking is better than sleeping... And even the BIGGEST FAILURE is better than never trying ☺

Best of Luck

Done by: Salsabeela Bani Hamad and Noor Hammad