Medical Genetics

Sheet: 3, Aneuploidy

Writer: Mothana Al-Olimat

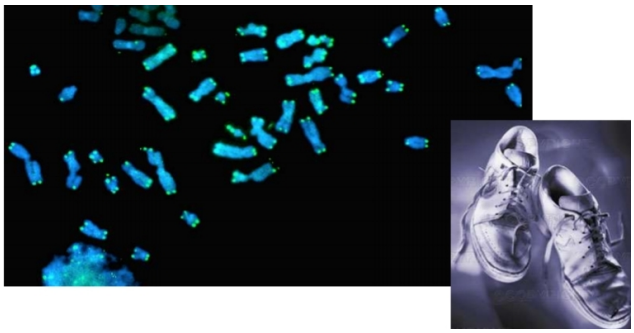
Scientific: Leen Attar

Final: Omar Ismail

Doctor: Bilal Azab

Telomere (TTAGGG)n

• Telomeres are repetitive sequences that exist at the end of the chromosomes and do not encode for genes.



• All of our 46 chromosomes carry the same telomeric sequence (TTAGGG) repeated many times.
↳ At certain age during adulthood the enzyme that replicates telomeres becomes inactive (telomerase).

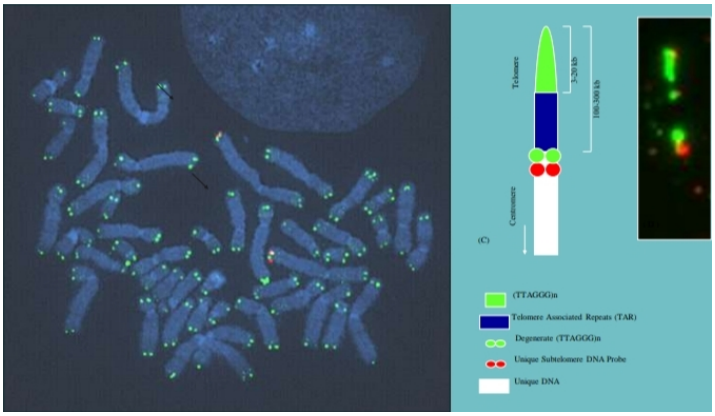
Every time there is a cell cycle (DNA replication in the S phase) the chromosome loses some of its telomeric region and becomes shorter, with time there is more and more erosion of the DNA at the ends.

◯ During embryonic development and until the age of 16 to 18, massive rounds of mitotic divisions are needed for growth and that's when the telomerase is working and keeps the DNA from eroding.

◯ When you become an adult, there's no need for all this mitosis so our telomerase is switched off because our cells divide slowly.
With each division DNA is lost from the telomere, this is the main reason for aging, on the other hand this protects from the possibility of transformation into cancer as rapidly dividing cells will eventually lose their genes and die.
↳ If a cell manages to become cancerous then it turns on the telomerase and becomes immortal.

Human Sub-telomeric Regions

• **The sub-telomeric region is also a repetitive sequence but it's not shared by all of our chromosomes.**
(shown in red color)



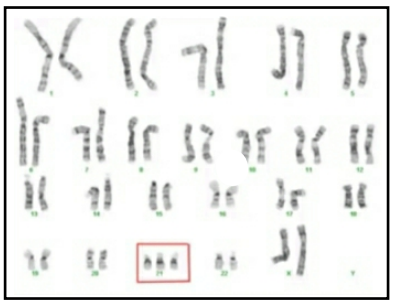
There is some sequence homology between subtelomeres

Aneuploidy

▪ Is defined as any chromosome number that is not an exact multiple of haploid number (n = 23 chromosomes, 2n = 46 chromosomes).

↳ For example trisomy or monosomy.

- **Trisomy → is the presence of an extra chromosome.**
- **Monosomy → is the absence of a single chromosome.**



◇ This karyotype shows a number of chromosomes not being the exact multiple of n.
(47 chromosomes instead of 46 as there's an extra copy of chromosome 21)

▪ This change in the number of chromosomes is due to ⇒ **Nondisjunction**

This cell taken from the testis or the ovary is assumed to have 2 pairs of homologous chromosome (4 chromosome) & will undergo meiosis :

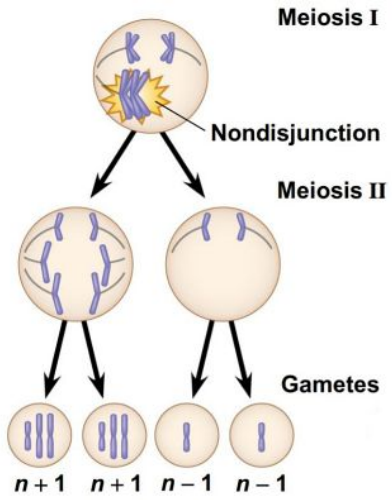
Scenario A:

Nondisjunction of homologous chromosomes in meiosis I

◇ Meiosis I ⇒ Homologous chromosomes do not separate from each other so one of the daughter cells will have one extra chromosome (total of 3 in this example) and the other will have one less chromosome (only one chromosome in this example)

◇ Meiosis II ⇒ Each single chromosome will align on the metaphase plate and the sister chromatids are separated from each other normally

◇ Result ⇒ Half of the gametes will be carrying an extra chromosome (n+1) and the other half will be missing a chromosome (n-1)



(a) Nondisjunction of homologous chromosomes in meiosis I

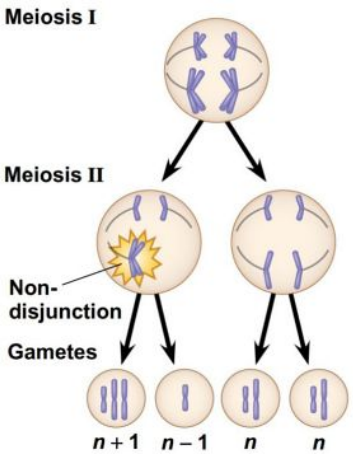
Scenario B:

Nondisjunction of sister chromatids in meiosis II

Meiosis I ⇒ The homologous chromosomes are separated from each other correctly and each goes to a different daughter cell.

Meiosis II ⇒ The sister chromatids for one of the chromosomes fail to disjoin.

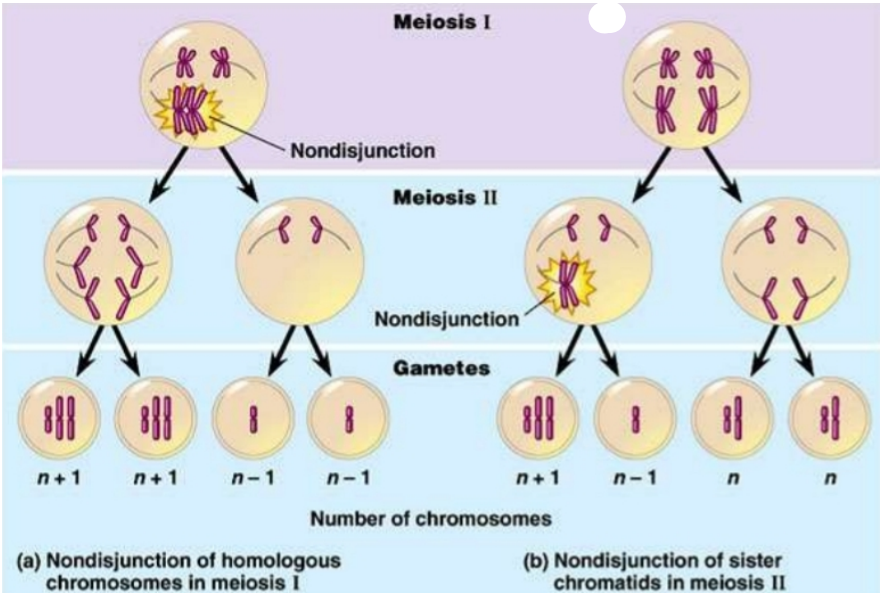
Result ⇒ Half of the cells will be carrying the correct number of chromosomes (n), 1/4 will have an extra chromosome (n+1) and 1/4 will have a missing chromosome (n-1).



(b) Nondisjunction of sister chromatids in meiosis II

♧ **Note: nondisjunction can happen during mitosis in the same way it happens in meiosis II**

Aneuploidy results from the fertilization of gametes in which the nondisjunction occurred, an offspring with this condition will have an abnormal number of a particular chromosome (trisomy if they have three copies of that chromosome and monosomy if they have only one copy of that chromosome)



Polyploidy/Euploid

● **Is when an organism has more than two complete sets of chromosomes (extra but exact multiples of n).**

- Most of our somatic cells are diploid (2n), our gametes are haploid (n).

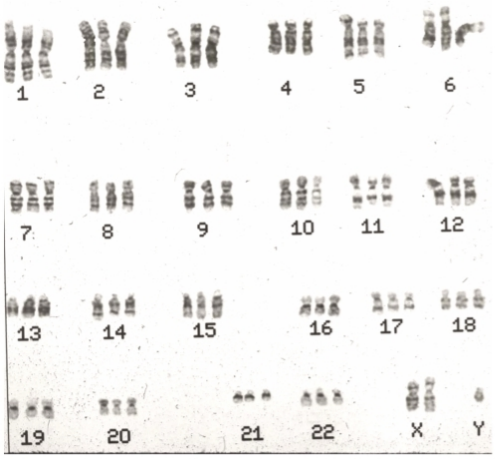
》 Triploidy (3n) is three sets of chromosomes (3 copies per chromosome).

》 Tetraploidy (4n) is four sets of chromosomes.

● **Polyploidy is common in plants but not animals**

● **Polyploids are more normal in appearance than aneuploids**

◇ This karyotype shows triploidy (3n) with 69 chromosomes, one of the reasons for this is ⇒ when two sperms fertilize an egg by mistake and this is lethal to the fetus (we call the karyotype 69, XXY)

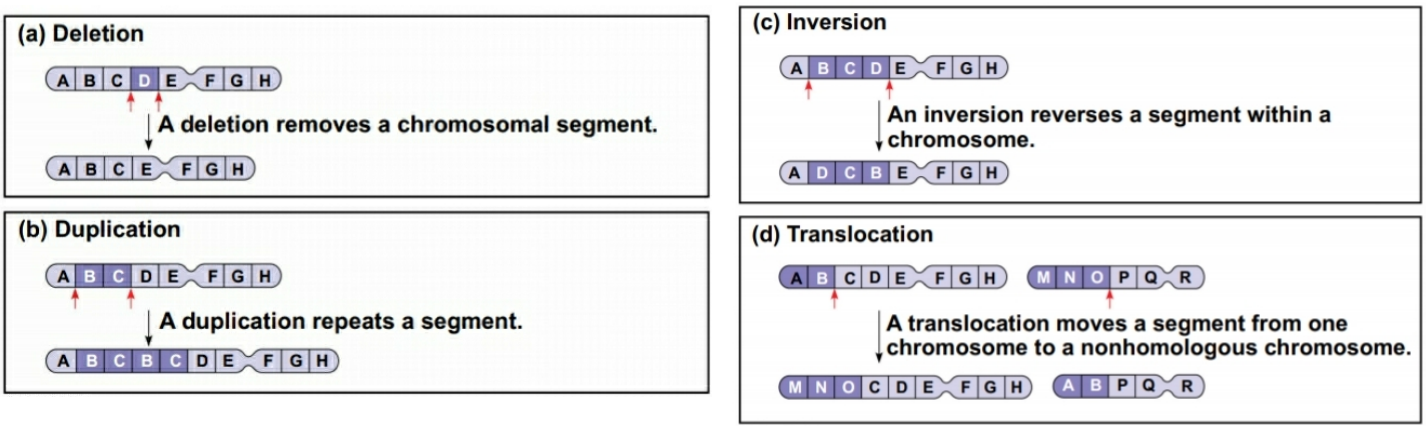


Triploidy 69,XXY

Alterations of Chromosome Structure

Breakage of chromosomes can change their structures in four different ways :

- Deletion: removes a chromosomal segment
- Duplication: repeats a segment
- Inversion: reverses the orientation of a segment within a chromosome
- Translocation: moves a segment from one chromosome to another



Recombination vs translocation

》 Recombination is the exchange of DNA between non-sister chromatids of homologous chromosomes (happens in meiosis to give diversity).

》 Translocation is the exchange of genetic material between non-homologous chromosomes.

- Alterations of chromosome number and structure are associated with some serious disorders.
- Some types of aneuploidy disrupt the genetic balance less than others, resulting in individuals surviving to birth and beyond
- These surviving individuals will suffer from a set of symptoms (syndrome) which is characteristic to that type of aneuploidy

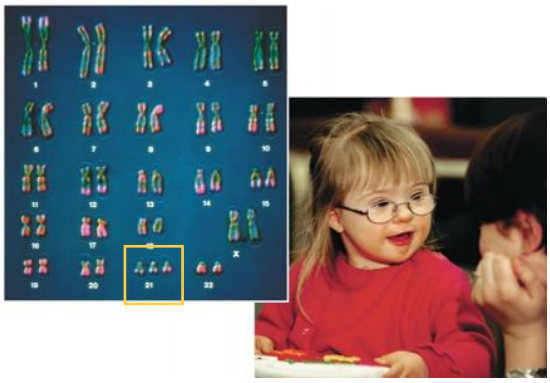
↳ Abnormalities can be aneuploidy of sex chromosomes, autosomal aneuploidy or structural abnormalities. We will focus on autosomal aneuploidy for the rest of this lecture.

Incidence of Chromosomal Abnormalities in Newborns

Type of Abnormality	Prevalence at Birth
Sex Chromosome Aneuploidy	
Males (43,612 newborns)	
47,XXY	1/1000
47,XYY	1/1000
Females (24,547 newborns)	
45,X	1/5000
47,XXX	1/1000
Autosomal Aneuploidy (68,159 newborns)	
Trisomy 21	1/800
Trisomy 18	1/6000
Trisomy 13	1/10,000
Structural Abnormalities (68,159 newborns)	
(Sex chromosomes and autosomes)	
Balanced rearrangements	
Robertsonian	1/1000
Other (reciprocal and others)	1/885
Unbalanced rearrangements	1/17,000
All Chromosome Abnormalities	
Autosomal disorders and unbalanced rearrangements	1/230
Balanced rearrangements	1/500
Total	1/154

Data from Hsu LYF (1998) Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A (ed.), *Genetic Disorders and the Fetus*, 4th edition, Johns Hopkins University Press, Baltimore, pp. 179-248.

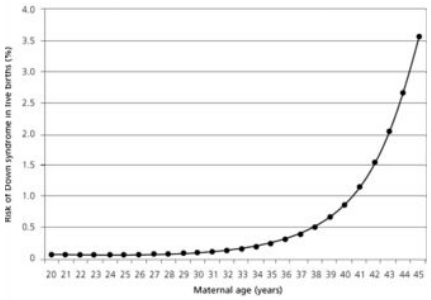
A- Down Syndrome (Trisomy 21)



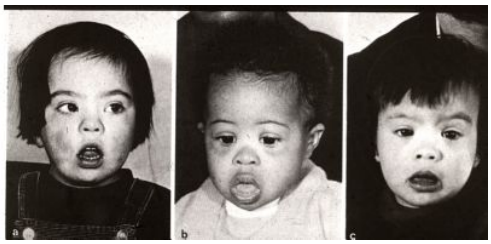
》 Down syndrome is an aneuploid condition that results from having three copies of chromosome 21.

》 It affects about one out of every 700 children born in the United States.

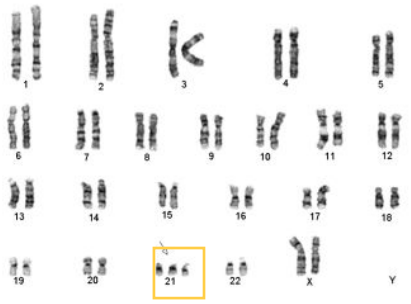
》 A correlation between maternal age and the risk of down syndrome is noticed but has not been explained (we don't know why they're related)



- we recommend for a mother who is having pregnancy at an advanced age to do karyotyping for the amniotic fluid or chorionic villi to check for trisomy 21 in the fetus.



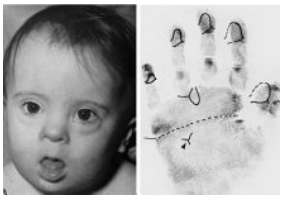
Male:Female ratio is 3:2

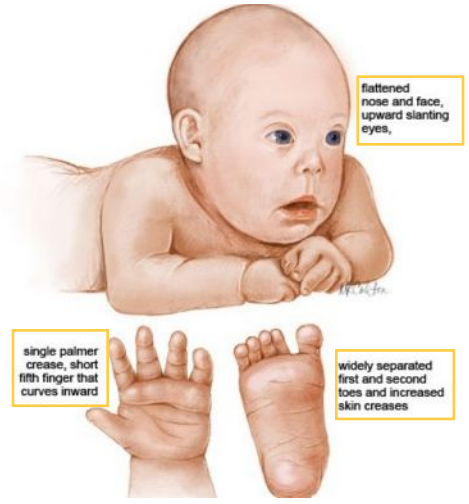


The karyotype shows 3 copies of chromosome 21 instead of two

》 **Clinically**, down syndrome is characterized by:

- Mental retardation (IQ 25-50) [IQ is obtained by dividing a person's mental age by the person's chronological age and multiply the resulting fraction by 100]
- Low nasal bridge (90%)
- Hypotonia (80%) ~ muscles are loose
- Up slanting palpebral fissures (80%)
- Small, low-set ears (60%) ~ a classical clinical abnormality for chromosomal aneuploidy
- Congenital heart disease (30%-50%)
- Epicanthic folds in the eye
- Protruding tongue
- Intestinal problems
- Gap between first and second toes
- 15-fold increase in risk for leukemia
- Simian line (transverse crease) (45%) ~ one line in their hand
- Distinct facial features





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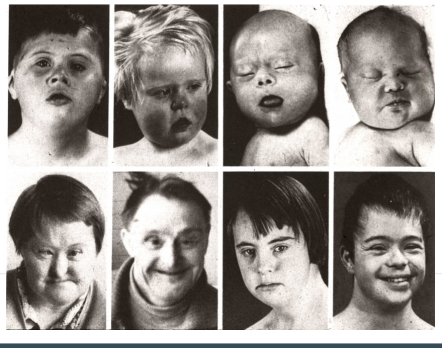
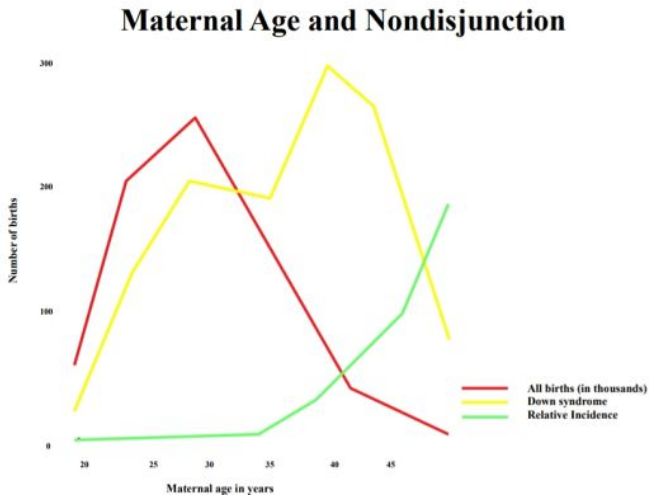


*These features are easily recognized at birth.

**The congenital heart problems noted in people having Down syndrome include ventricular septal defect (VSD) & atrioventricular canal defects (AV). Approximately 40% with congenital heart disease die during the first year.

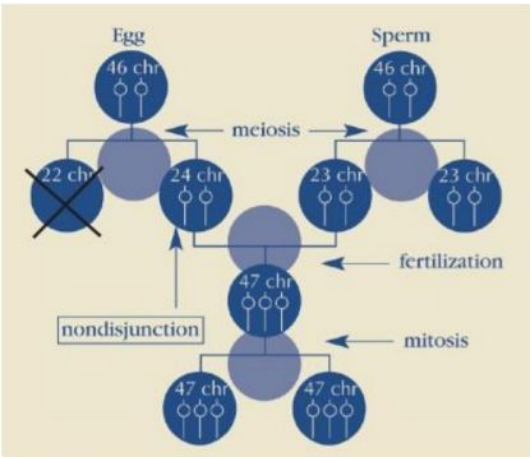
- To calculate the probability of down syndrome in relation to the maternal age we divide the number of down syndrome patients (shown in yellow) by the number of births (shown in red). And that gives us the curve of correlation that we studied before.

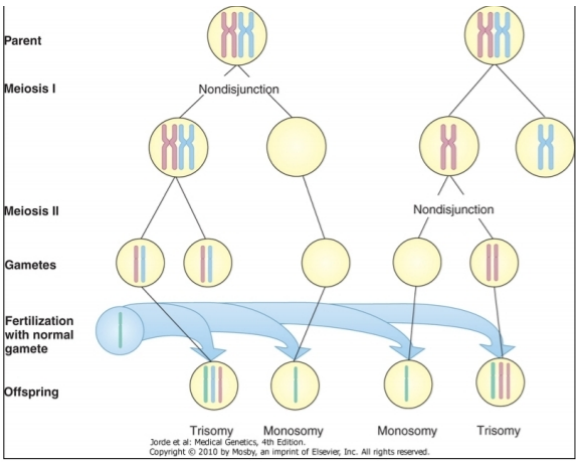


Trisomy 21 happens due to a nondisjunction that could happen either in meiosis I or meiosis II

⊙ 94% of down patients are due to a maternal error (nondisjunction in the egg)
- 64% of these nondisjunctions happen in meiosis I
- 19% of these nondisjunctions happen in meiosis II
- 11% are intermediate

⊙ 4.5% of down patients are due to a paternal error (nondisjunction in the sperm)
- 1% of these nondisjunctions happen in meiosis I
- 3.5% of these nondisjunctions happen in meiosis II
- 1.5% of down patients are due to an unknown error





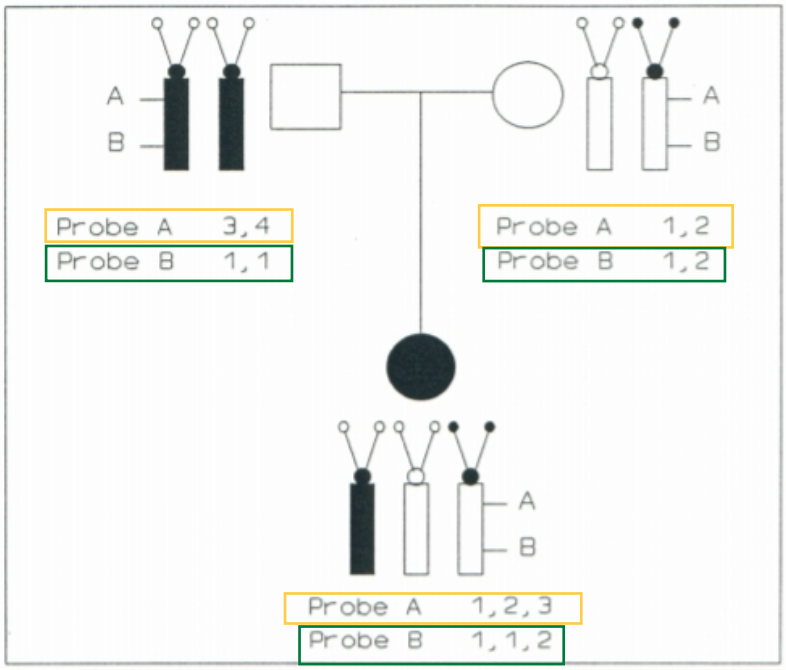
How to know wether the extra chromosome for a down patient is coming form their mother or father?

We have many DNA regions on all our chromosomes that do not encode for protein or RNA (non-coding regions), these non-coding regions are repetitive (e.g. GGC GGC GGC). For the same location on the same chromosome the number of repeats differ from person to person and we can use this as a polymorphic marker to know where this DNA came from.

Example 1 Causal Factors in Nondisjunction

We have a down syndrome patient and we want to know where the extra chromosome came from ⇒ by looking at two regions on chromosome 21 known to have different numbers of repeats in different individuals and comparing them with their parents.

♡ Starting with region B, first we notice the number of repeats in the three chromosomes is (1,1,2) so two of the chromosomes carry one repeat in their region and the third chromosome carries two repeats on its region.



》 In the father, both chromosomes carry one repeat in region B (father is represented by a square).

》 In the mother, region B on one chromosome carries one repeat and on the other it carries two repeats .

↳ So, we conclude that the chromosome in the patient which carries 2 repeats on its region B is coming from the mother but we can't know for sure whether the remaining two chromosomes which carry only 1 repeat are coming both from the father or one per parent so we look at the region A to become sure.

♡ Looking at region A for the patient we noticed that one chromosome carries one repeat on its region, the second chromosome carries two repeats and the third chromosome carries three.

》 In the father region A on one chromosome carries three repeats and on the other chromosome it carries four repeats.

》 In the mother region A on one chromosome carries one repeat and on the other chromosome it carries two repeats

↳ So we conclude that the two chromosomes carrying 1,2 repeats on their region A are coming from the mother and the third chromosome carrying 3 repeats on its region A is coming from the father.

So, the extra chromosome comes from the mother.

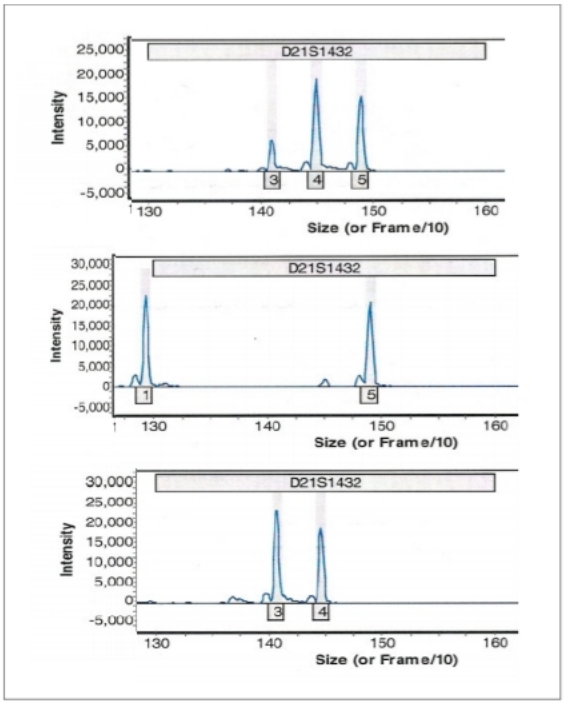
Example 2 — Evaluate the Origin of the Extra Chromosome Using Polymorphic Markers

Here we are studying a region on chromosome 21 called D21S1432

- Proband (the affected individual) has three copies of chromosome 21 and these copies have the following numbers of repeats (143,144,145)

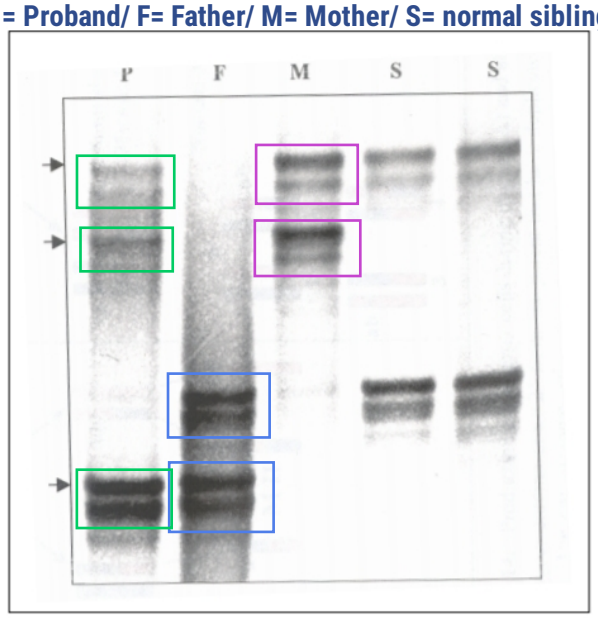
The chromosome with (145) repeats on its region is obviously coming from the father and the other two chromosomes with (143,144) repeats are coming from the mother

So, the mother contributed two 21 chromosomes instead of one.



Example 3 — DNA markers can be used to determine the parental origin of the extra chromosome in trisomic individuals

P = Proband/ F= Father/ M= Mother/ S= normal siblings.



Here we have some samples of gel electrophoresis.

The patient has three bands (pointed with the arrows) and stain a little bit darker, The father, mother and the siblings each have two bands.

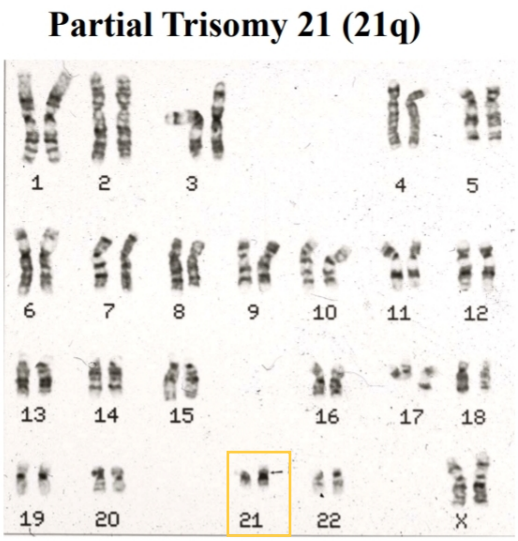
↳ These bands represent a region which has different number of repeats which means different DNA sizes and that shows on the gel as different locations for these bands.

The first two bands in the patient (upper two) come from the mother and the last band comes from the father, so the case is due to maternal nondisjunction.

Partial Trisomy 21 (21q)

- This picture shows phenotypically a down syndrome patient, but the karyotype shows 46 chromosomes (there's no extra chromosome 21)

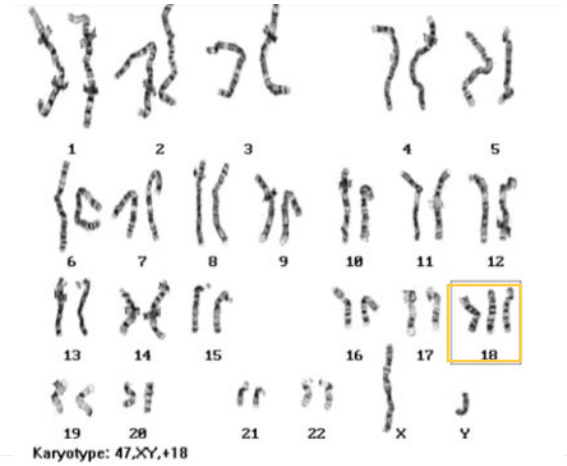
↳ When we take a deeper look at one of the chromosomes 21 we notice that it has 2 fused q arms instead of 1 and that is represented as (46,XX,21 q+)



** Remember that chromosome 21 is one of the five acrocentric chromosomes {13,14,15,21,22} in which the p arm is carrying nothing but ribosomal DNA and some repetitive sequence; so we only need an extra q arm for this case to happen (a total of 3q arms) and this is called partial trisomy 21

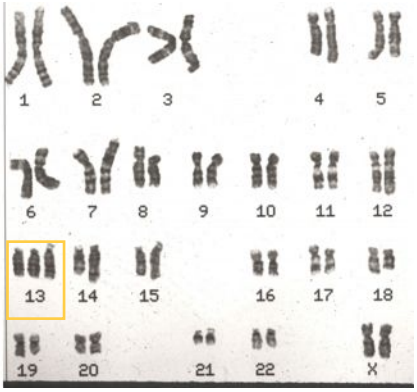
B–Edward syndrome (Trisomy 18)

》 Clinical features
- CHD (95%) ~ Congenital heart disease
- Failure to thrive
- Mental retardation
- Growth retardation
- Hypertonia ~ muscles are tight
- Prominent occiput ~ occipital bone
- Low-set, malformed ears
- Short sternum
- Intestinal problems
- Clenched fist (unusual hand opposition)
- Rocker bottom feet

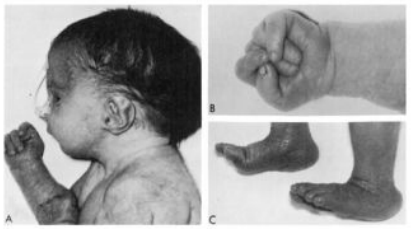


C– Patau syndrome (Trisomy 13)

》 Clinical features
- CHD (85%)
- Mental retardation
- Hyper- or hypotonic
- Scalp defects
- Microcephaly ~ Head size smaller than average
- Small eyes
- Low-set malformed ears
- Cleft lip/palate
- Polydactyly (extra digit) & Syndactyly (digits fused together)
- Polycystic kidneys
- Rocker bottom feet



Trisomy 18 (Edward syndrome)



CHD (95%)
Failure to thrive (FTT)
Mental retardation
Growth retardation
Hypertonia
Prominent Occiput

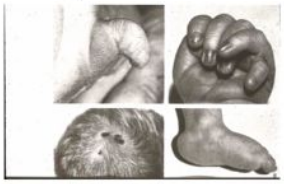
Findings:

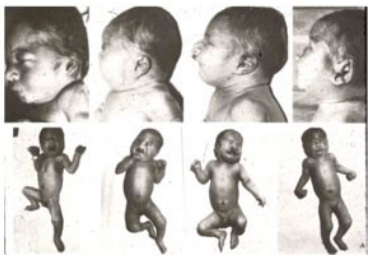
Low-set, malformed ears
Short sternum
Intestinal Abnormalities
Unusual hand position
Rocker bottom feet

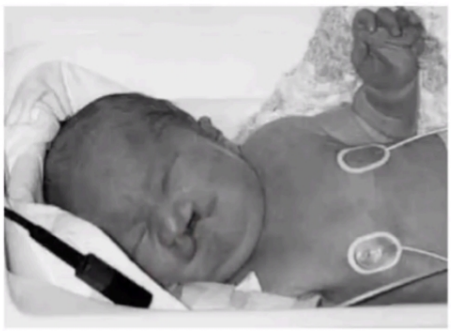
Findings:

CHD (85%)
Mental retardation
Hyper- or hypotonia
Scalp defects
Microcephaly
Small eyes
Low-set, malformed ears
Cleft lip/palate
Polydactyly and syndactyly
Polycystic kidneys
Rocker-bottom feet

Trisomy 13
(Patau syndrome)

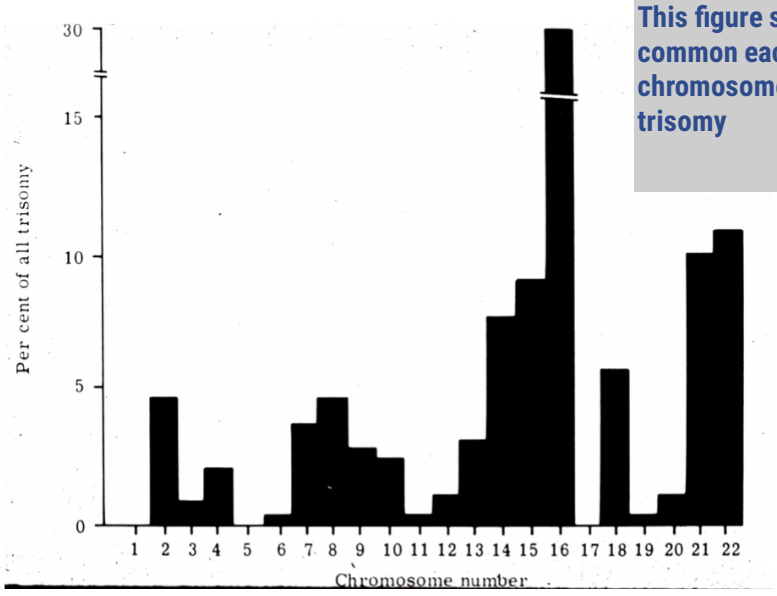






A newborn male with full trisomy 13 (Patau syndrome). this baby has a cleft palate, atrial septal defect, inguinal hernia, and postaxial polydactyly of the left hand.

An individual with full trisomy 13 at age 7 years (survival beyond the first year is uncommon). He is deaf and legally blind.



This figure shows how common each chromosome gets trisomy