

## Educational Item Section

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# How human chromosome aberrations are formed

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### I- Introduction

#### Characteristics of the species homo sapiens:

- Many!
- Among others: excessively high incidence of reproductive failure and chromosome aberrations.
- Determination of origin and mechanisms of formation of chromosome aberrations: Each newly developed technique, from Q banding over FISH and microsatellite marker analysis to CGH, has brought additional information as to the origin of chromosomal imbalance in man.

### II- Origin and mechanisms of formation of chromosome aberrations

#### Origin may be:

- maternal
- paternal
- combined

#### Formation:

- Nondisjunction: meiotic, pre-meiotic, post-meiotic
- Rearrangement: meiotic, pre-meiotic, post-meiotic

#### Any combination:

Incorporation of 2 sperms or of a polar body into the oocyte.

### III- Chromosome aberrations, classification

#### Numerical aberrations:

- Monosomy (X/Y)
- Trisomy
- Sex chromosome aneuploidy
- Double/triple aneuploidy
- Uniparental disomy

#### Ploidy aberrations:

- Haploidy
- Triploidy

- Tetraploidy

**Structural aberrations:**

- Deletions
- Rings
- Duplications
- Balanced rearrangements
- Combined duplication-deletion
- Complex rearrangements

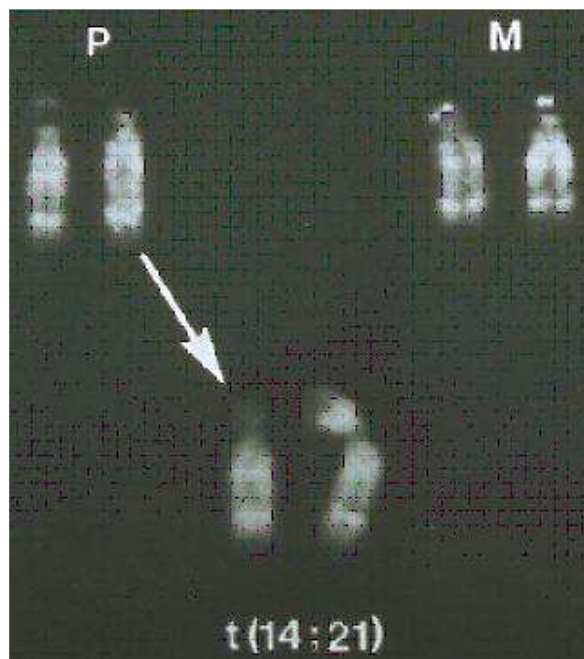
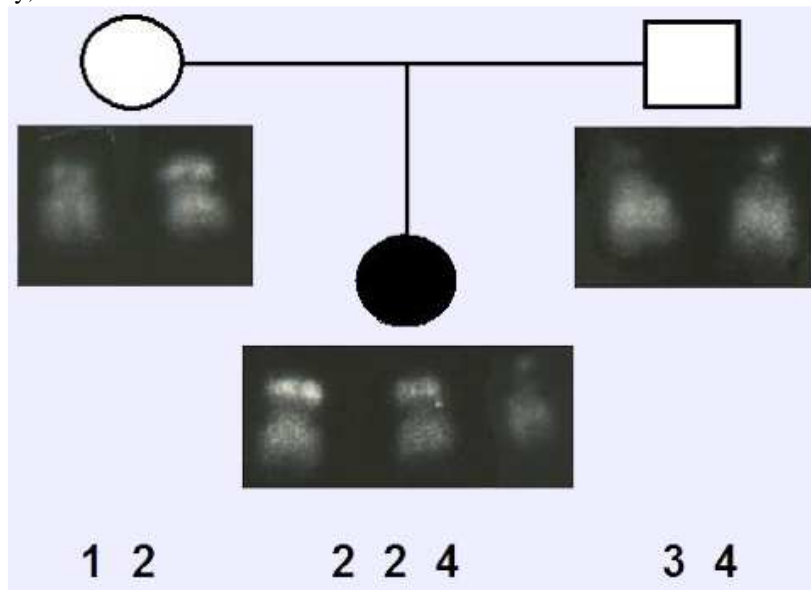
**Mosaic and chimeras**

Combinations:

- Numerical and structural
- Numerical and ploidy, etc...

**IV- Modes of determination of the mechanisms of formation of chromosome aberrations**

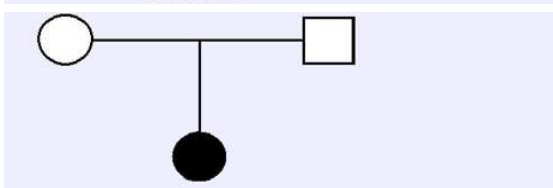
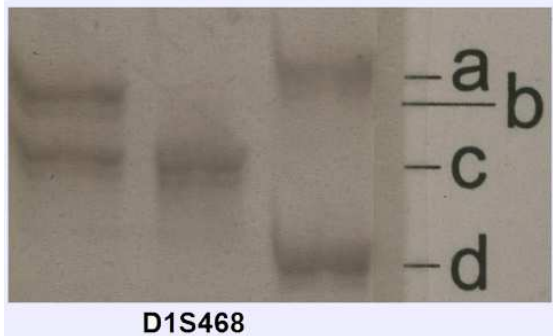
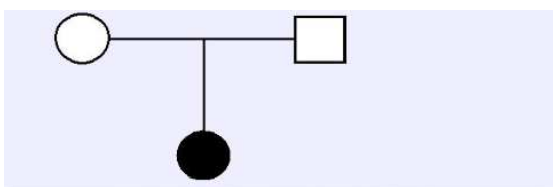
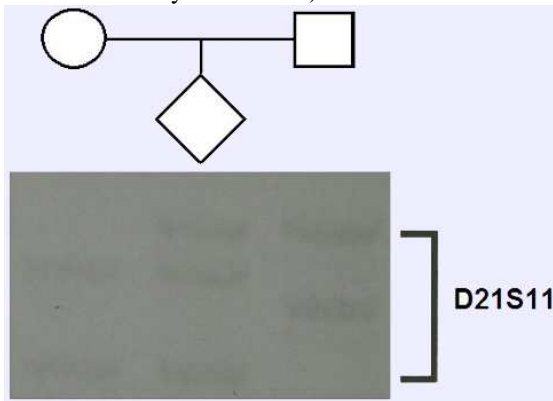
1. Aberration per se:
  - free trisomy: nondisjunction
  - mosaicism: either postzygotic origin or two steps
  - triploidy
2. Cytogenetic markers.
3. Molecular marker analysis in proband and parents.
4. Molecular marker analysis in grandparents of proband.
5. CGH.



Legend: Paternal (P) and maternal (M) chromosomes 14, the free 14 and the 14/21 translocation from the Down's offspring, Q-banded. The free 14 is of paternal origin, therefore the 14/21 is of maternal origin (from Chamberlin 1980; Hum Genet 53: 343).

**V- Microsatellite marker analysis**

- Almost always able to determine the origin of deletions.
- Often not successful for duplications, especially direct or inverted duplications stemming from chromatid interchanges (no third allele, often no clear intensity differences).



**VI- Summary of parental origin of chromosome aberrations**

- Numerical, autosomes: predominantly mat.
- Numerical, X chromosomes: idem.
- Numerical, X and Y: overwhelming paternal origin.

- Structural, terminal deletions and rings: predominantly pat.
- Structural, extra rearranged chromosomes isochromosomes, inv dup chromosomes: predominantly mat from initial nondisjunction.
- Structural, intrachromosomal rearrangements: equal distribution.
- Structural, interchromosomal rearrangements: idem.
- Uniparental disomy:
  - o Heterodisomy: predominantly mat from initial trisomy.
  - o Isodisomy: predominantly pat.
- Mosaics: mostly starting with maternal trisomy
  - o Triploidy: predominantly (80%) mat, incorporation of a polar body into the oocyte;
  - o rarer (20%) fertilization of the oocyte by 2 different sperms.

**VII- Origin of Ullrich-Turner syndrome 45,X**

Xg studies: predominant maternal origin of the remaining X-chromosome.

Expected distribution (as 45,Y is none-viable) if mat = pat: 66 vs 33%.

Distribution found: 80 vs 20% (statistically significant).

Parental Xg information about 306 females with 45,X Ullrich-Turner syndrome (Sanger et al., 1971).

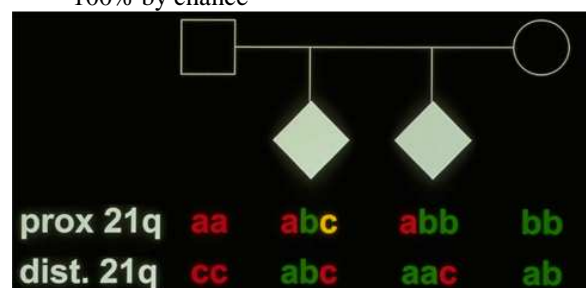
Xg groups of			Source of normal X	Number
Father	Mother	T		
+	+	+	unknown	150
+	+	-	maternal	31
+	-	+	paternal	5
+	-	-	maternal	10
-	+	+	maternal	60
-	+	-	unknown	35
-	-	-	unknown	15
Total				306

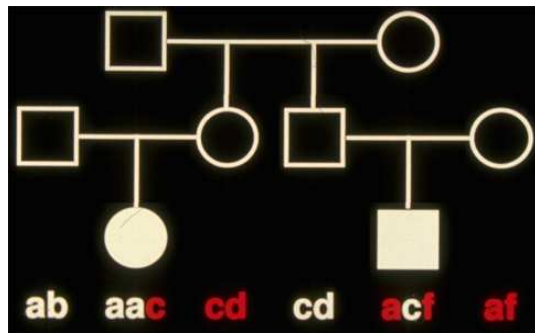
+ = Xg(a+); - = Xg(a-)

**VIII- Origin of recurrent free trisomy 21**

Results of molecular marker studies:

- 1. In siblings:
  - 60% by chance
  - 40% parental gonadal mosaicism
- 2. In more remote relatives:
  - 100% by chance





**IX- Interchromosomal effect (ICE)**

**- Definition:**

A balanced chromosome aberration increases the risk of non-disjunction for other chromosomes.

**- Consequence:**

Prenatal cytogenetic diagnosis is indicated if one parent carries a balanced rearrangement even if unbalanced segregation cannot lead to viable offspring.

**- Evidence for ICE:**

More familial balanced translocations found in Down syndrome patients than expected by chance.

**- Evidence against an ICE:**

In haploid sperms of male carriers of balanced translocations there is no increase of disomies over controls.

	Number of families	Origin of the supernumerary 21	
		mat	pat
mat. rearrangement	2	2	0
pat. rearrangement	11	11	0

**X- Origin of mosaic trisomy**

- Mostly first trisomy: secondary somatic loss of the third homologue.
- Not infrequently: mosaicism between (maternal) trisomy and (maternal) uniparental disomy.

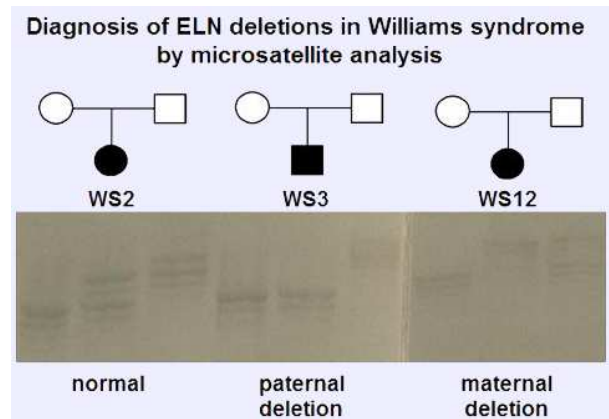
**XI- Origin of interstitial (micro-)deletions, interchromosomal versus intrachromosomal**

**Principle**

Investigation of grandparents of the side of origin with markers flanking the deleted segment.

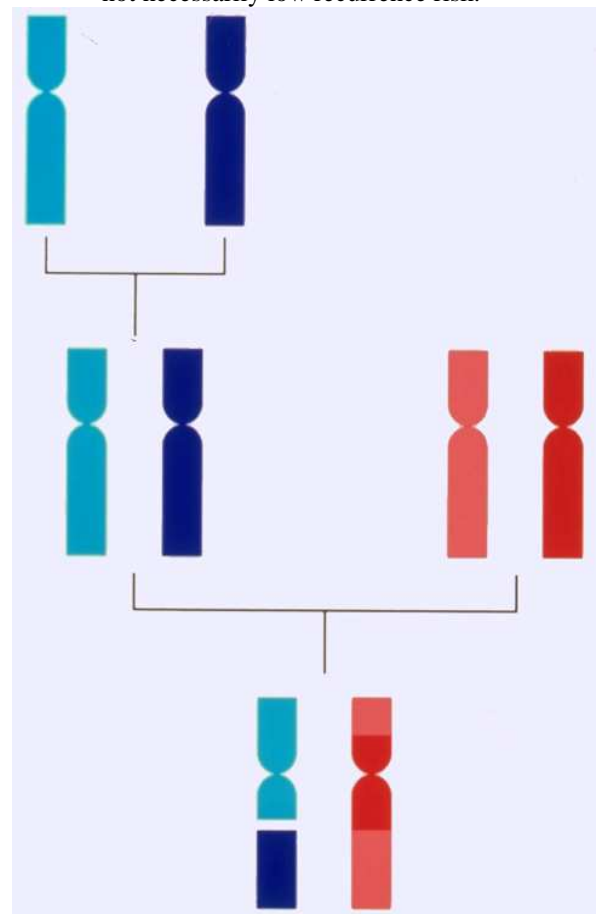
**Williams-Beuren syndrome:**

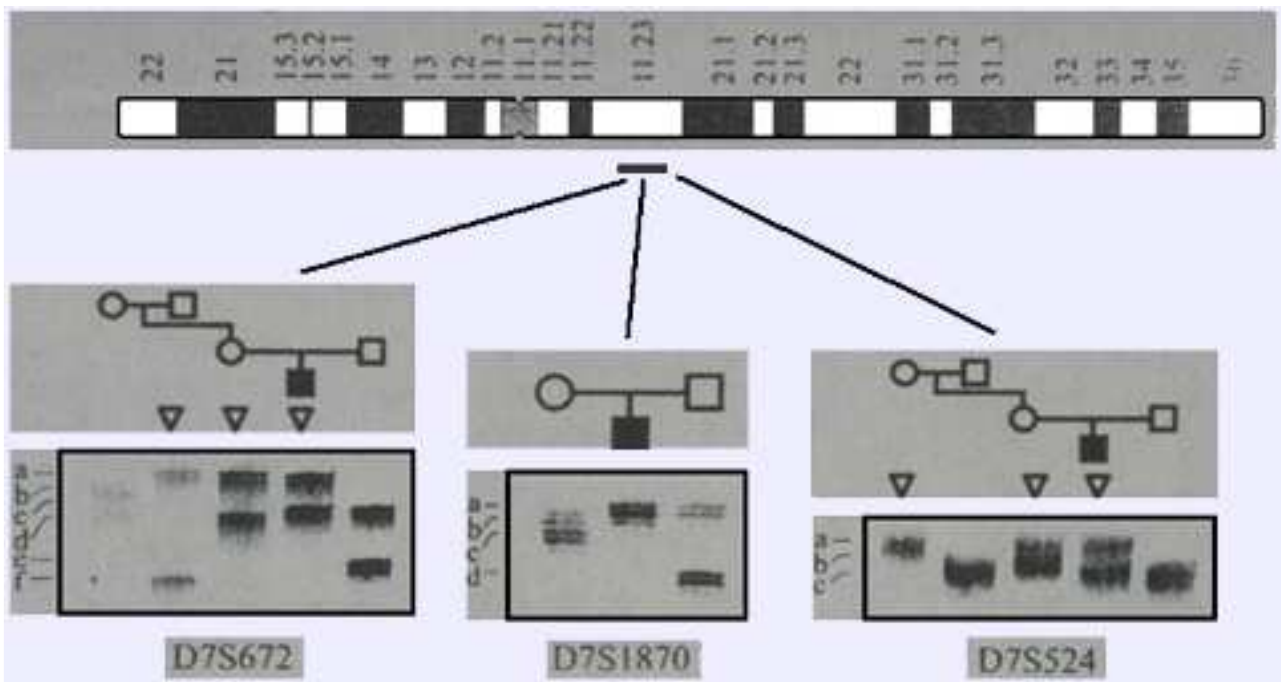
- Deletion of 7q11.22 including the Elastin locus.
- Supravalvular aortic stenosis.
- Peripheral pulmonary stenosis.
- Growth retardation.
- Moderate mental retardation.
- Outgoing pleasant personality.
- Full lips, cheeks and lids.
- Deep voice



**Result:**

- Switch from grandpaternal to grandmaternal origin on either side:
  - interchromosomal rearrangement.
  - meiotic origin.
  - low recurrence risk.
- No switch, markers on either side from grandparent:
  - intrachromosomal rearrangement (between 2 chromatids).
  - meiotic or pre- or post-meiotic origin.
  - not necessarily low recurrence risk.





Representative examples of microsatellite analysis at 7q11.2 carried out. The deleted region of chromosome 7 is indicated with a black bar beside the chromosome 7 ideogram. Marker D7S1870, located within the deleted region, illustrates the maternal origin of the deletion. Grandparental origin of the regions flanking the deletion are shown with markers D7S672 (proximal region) and D7S524 (distal region).

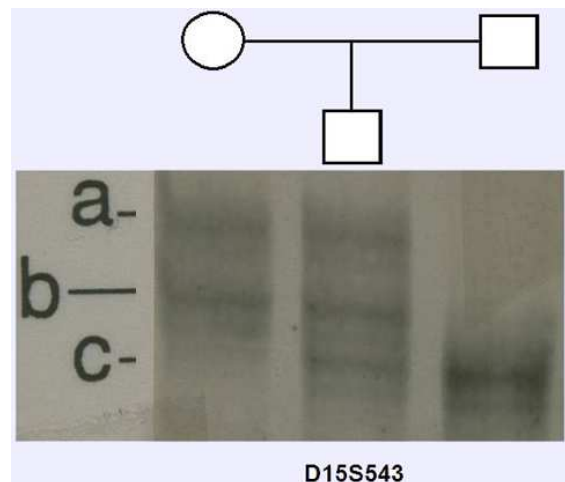
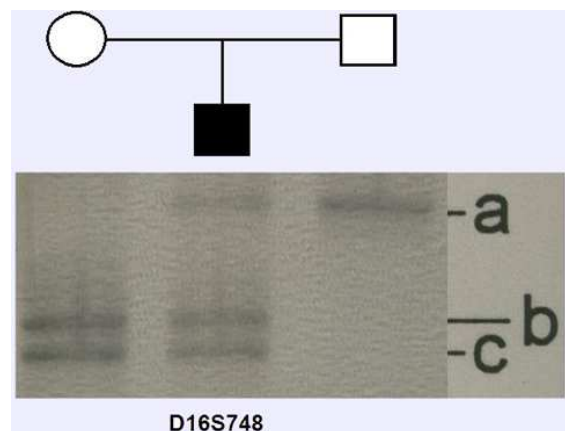
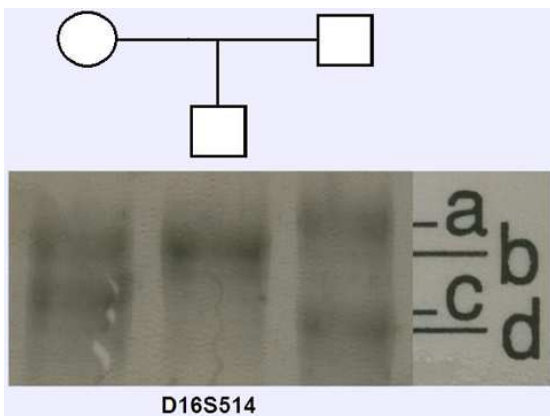
**XII- Frequent interstitial microdeletions (15q12, 7q11.23, 22q11.2)**

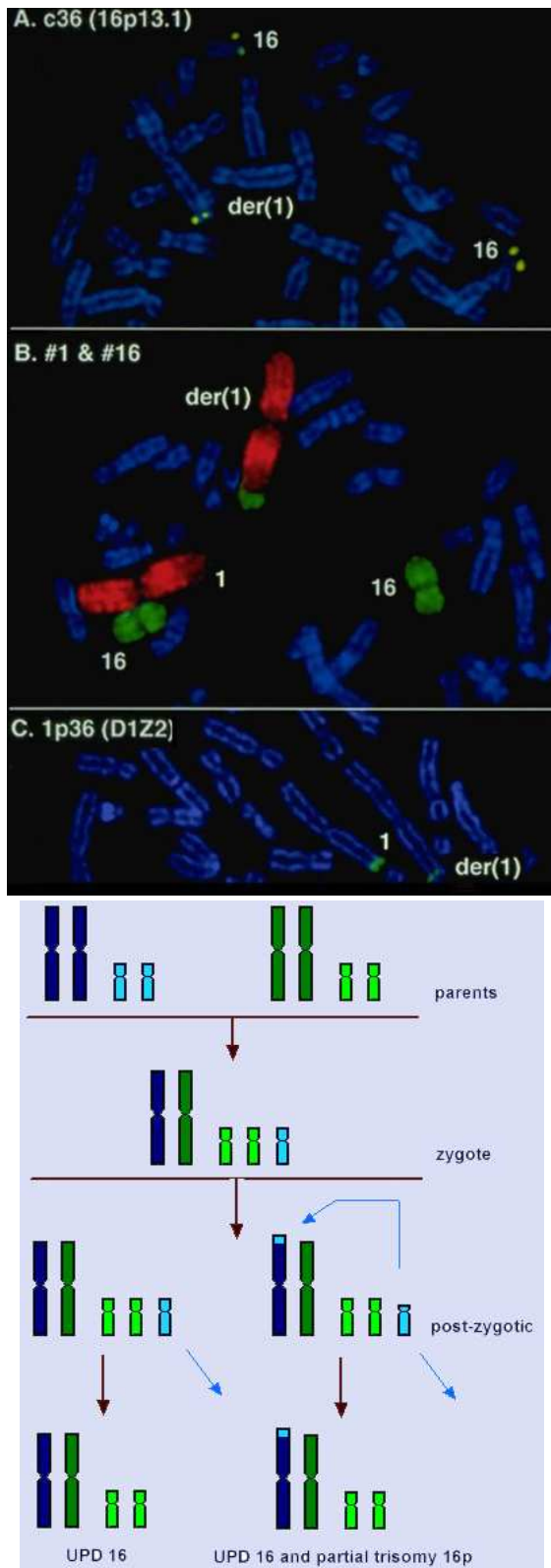
- Reason for their high incidence: similar short tandem repeats.
- Frequent paracentric inversions of this segment.
- Tend to pair at meiosis.
- Cutting out of the segment forming an inversion loop.

**XIII- Origin of mosaic duplications (de novo)**

Not infrequently:

- First trisomy;
- Second rearrangement;
- Third uniparental disomy.





**XIV- Origin of additional isochromosomes and isodicentric chromosomes**

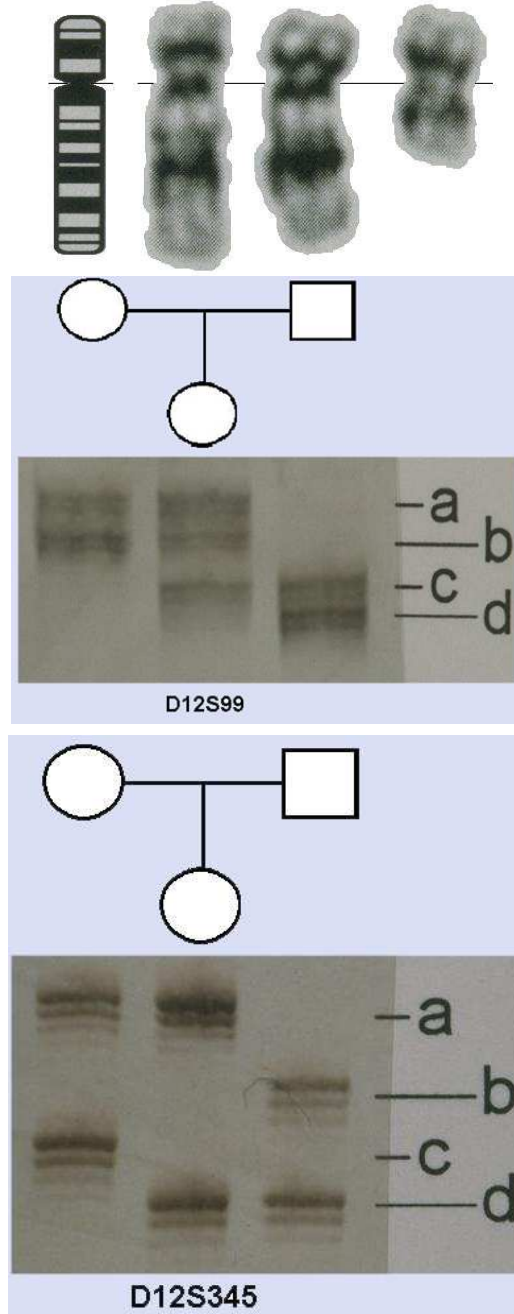
**Molecular marker analysis:**

- Postmeiotic: one normal, one strong allele.

- Meiotic: M1: proximal heterozygosity / M2 : vice versa.
- Results: mostly M2 maternal.

**Mechanism:**

- first meiotic nondisjunction,
  - second isochromosome formation.
- Examples: i(8p), i(9p), i(12p), i(18p).



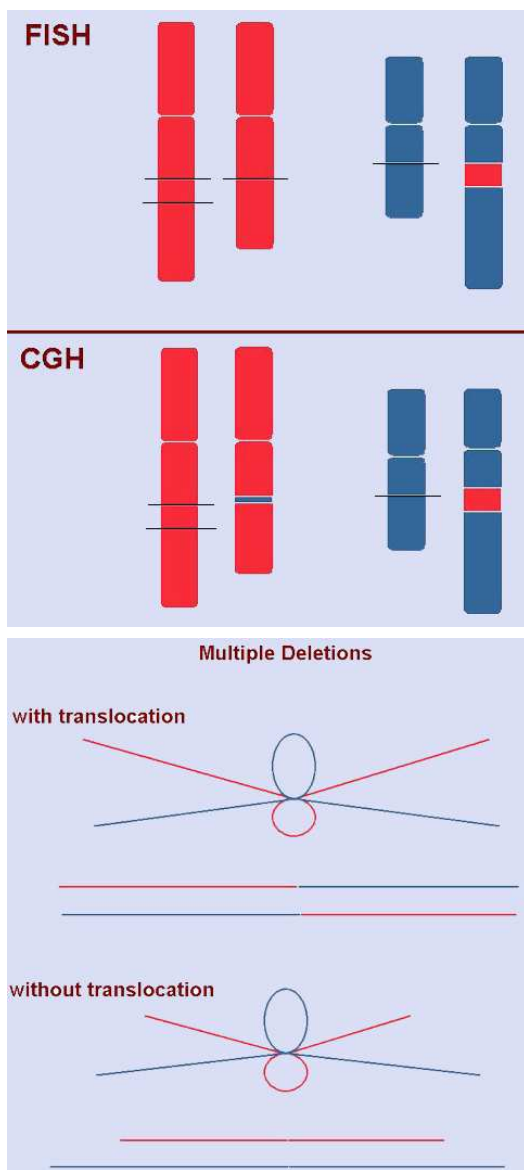
**XV- Chaotic chromosome aberrations**

- Found especially at investigation of early spontaneous abortions.
- Multiple deletions, combined deletions and duplications, etc...

- Complex balanced and unbalanced aberrations often following irradiation.

**XVI- Origin of multiple structural chromosome aberrations**

CGH re-investigations of visible structural chromosome aberrations not infrequently detect further submicroscopic imbalances, mostly small deletions, rarer duplications. These point towards a much more complex mechanism of origin of structural aberrations than seen on the first glance and parallels the complex origin of mosaics, especially for structural and combined numerical - structural chromosome aberrations.



**XVII- Primary and secondary chromosome aberrations**

Secondary aberrations may enable survival of an otherwise lethal unbalanced product.

**Examples:**

- Additional isochromosomes deriving from a trisomy.
- Correction of trisomy through uniparental disomy.
- Secondary structural aberrations with loss of a chromosomal segment following a trisomy.
- Reduction of a complex rearrangement with multiple breaks to a simpler one through recombination - balanced and unbalanced.

**XVIII- Conclusion**

A distinct feature of homo sapiens is the excessively high incidence of unbalanced chromosome aberrations, especially trisomy and triploidy.

Nature has an incredible phantasy and many different mechanisms to correct such unbalanced aberrations.

This may happen because of a high proneness to early postzygotic numerical and structural aberrations combined with a high selection pressure.

It is unknown whether primary aberrations may lead with preference to secondary imbalance.

Anyway, these visible aberrations constitute the tip of an iceberg, and under the water surface are the many spontaneous miscarriages due to chromosomal imbalance.

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