Medical genetics III

Duplications, marker chromozomes, other CHAs

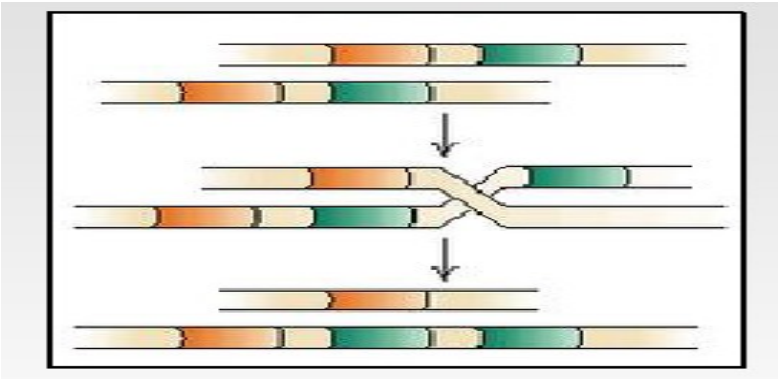
Duplications (dup)

Origin:

a) **NAHR**

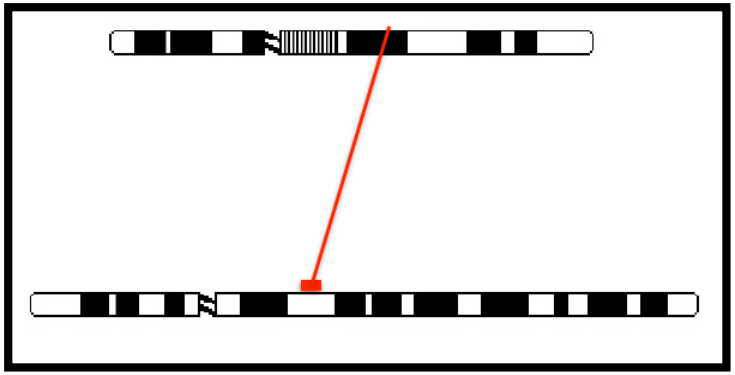
b) **abnormal segregation (carriers of inversion or translocation)**

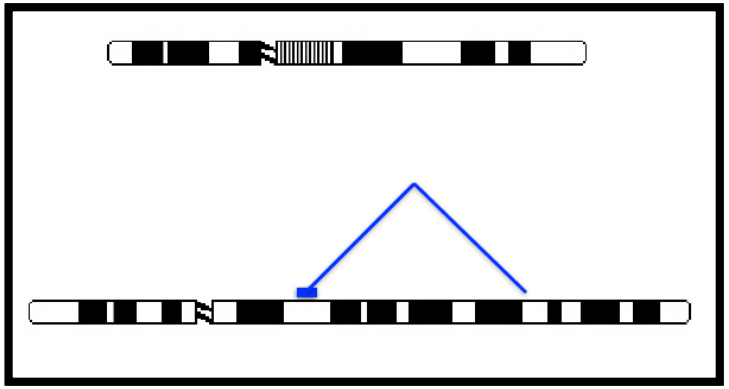
c) **Errors in replication**

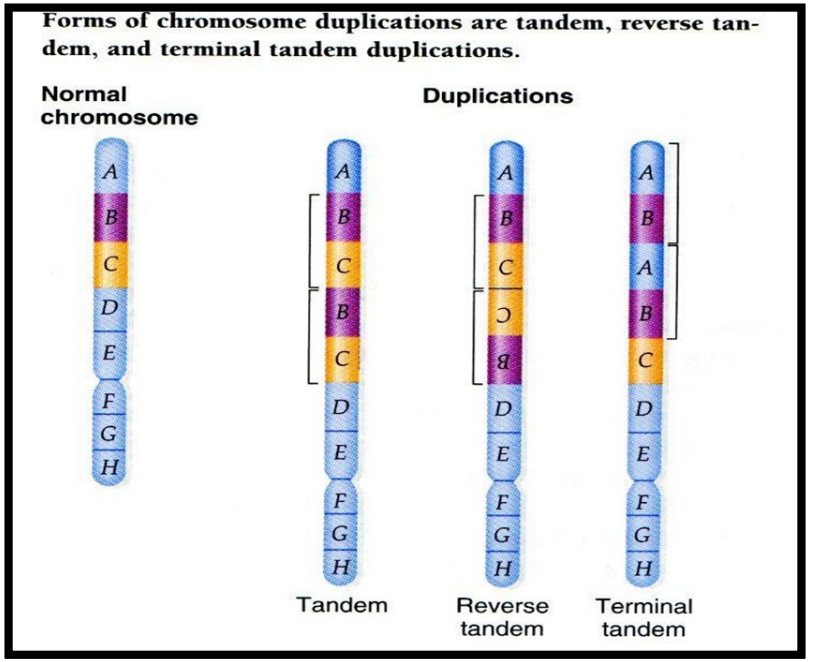


Inter- a intrachromozomal duplication
Tandem and reverse tandem duplication

Size: hunderds pb till Mbs

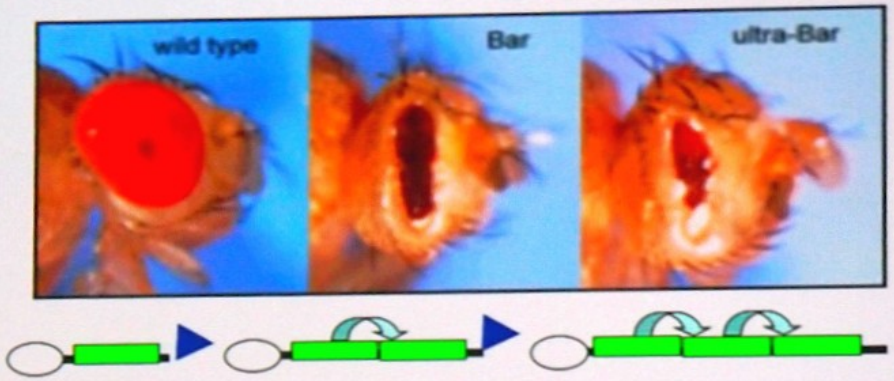






Unequal crossing-over, duplication and muation of *Bar gene* in Drosophila

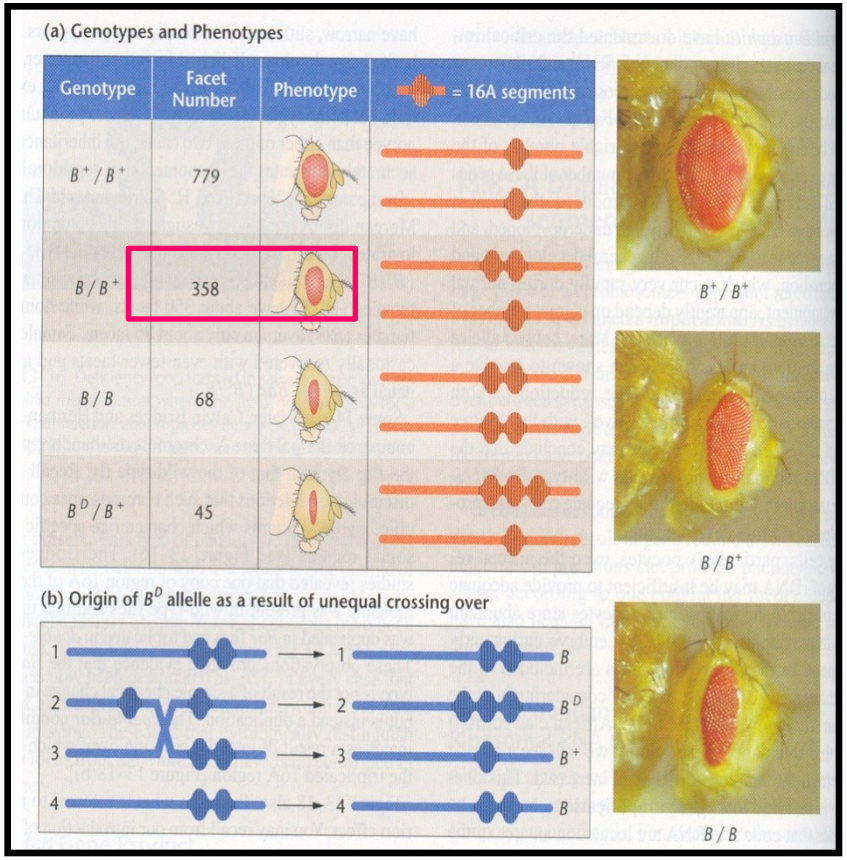
Alfred Sturtevant

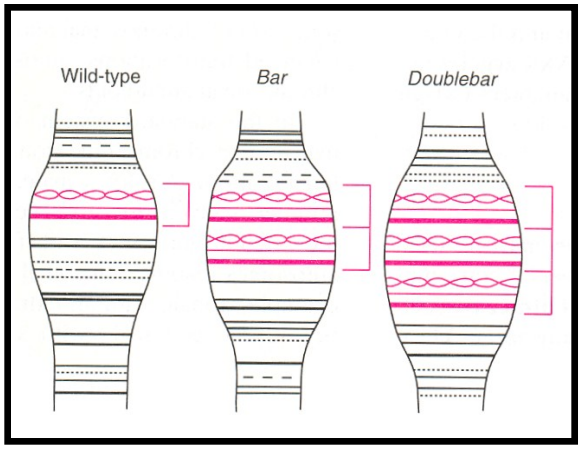


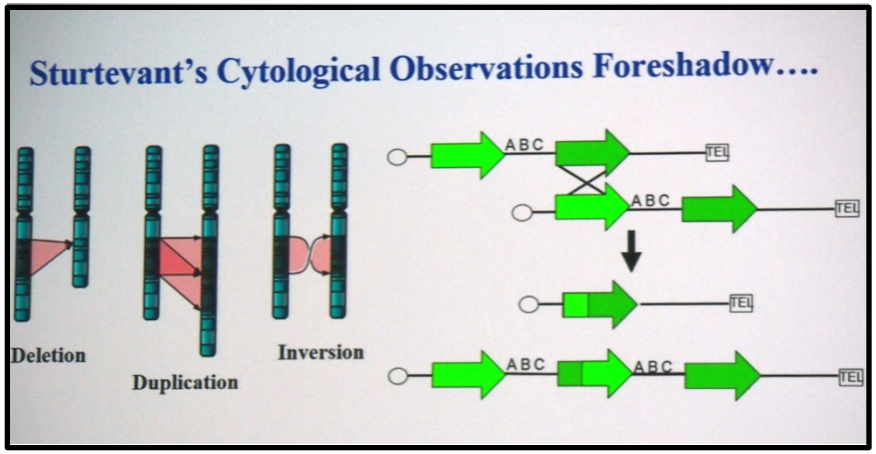
"Crossing over has proved to be the key to the mutation behavior of bar……The case appears not to be, strictly speaking, a point-mutation after all, but a new kind **of section-mutation**……in which **unequal crossing over furnishes the mechanism** for bringing about the new types"

Sturtevant , *Genetics*, 1925

Bar duplication in *Drosophila* B+,B affects facet number in compound eyes







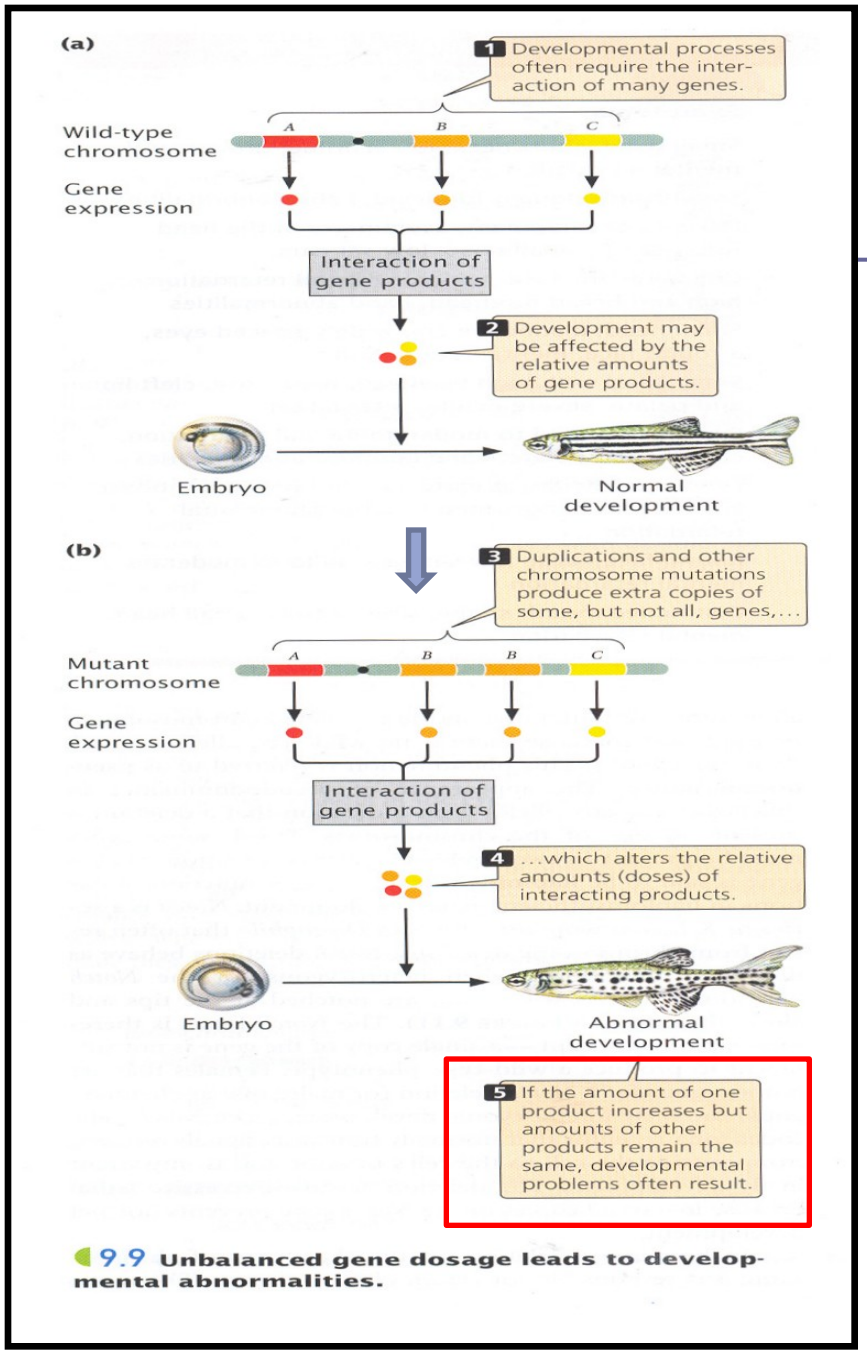
Microduplications

- Duplications of a megabase or so of DNA that are most often too small to be seen under the microscope
- Produce well defined *gene duplication syndromes* such as Charcot-Marie-Tooth 1A
- CMT-1A is a peripheral neuropathy resulting from a 1.5 Mb tandem duplication which includes the peripheral myelin protein (PMP-22) gene

- there are about **80 microduplication** syndromes
- Microduplications - **milder influence** on phenotype, variable expressivity, can often be inherited from healthy parents

Duplications – effect of gene dosage!

- increased gene expression
- disorders of gene regulation and function
- emergence of fusion genes
- gene disruption (breaks)



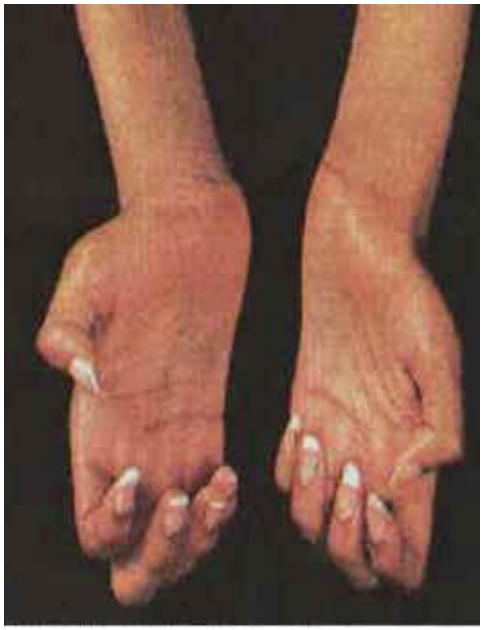
9.9 **Unbalanced gene dosage leads to developmental abnormalities.**

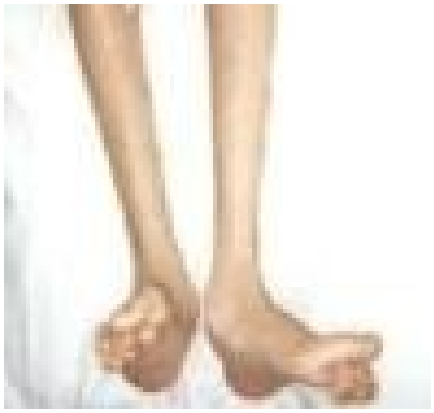
Charcot-Marie-Tooth (*CMT1A*) – duplication of cca 1,5 Mb

- **AD neurological disorder**
- **incidence: 1 : 2500**
- **gene dose effect** - duplication of the myelin protein gene symptoms: muscle atrophy

Clinical features

- Weakness in your legs, ankles and feet
- Loss of muscle bulk in your legs and feet
- High foot arches, curled toes (hammertoes)
- Decreased sensation or a loss of feeling in your legs and feet
- 90% arise in male meiosis (recombination between repetitive sequences)



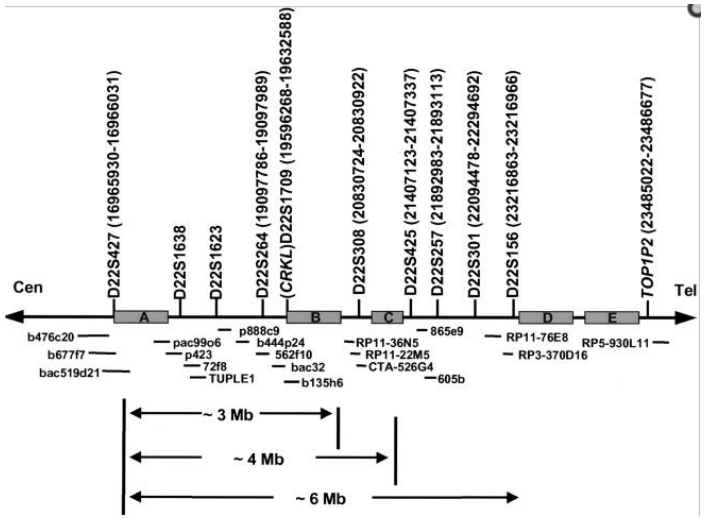


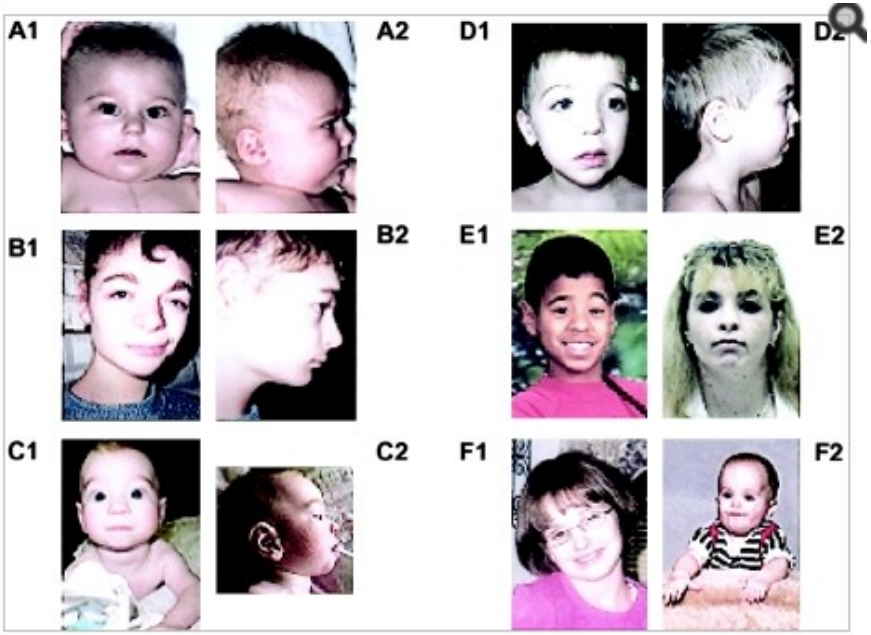
Microduplication syndrome 22q11

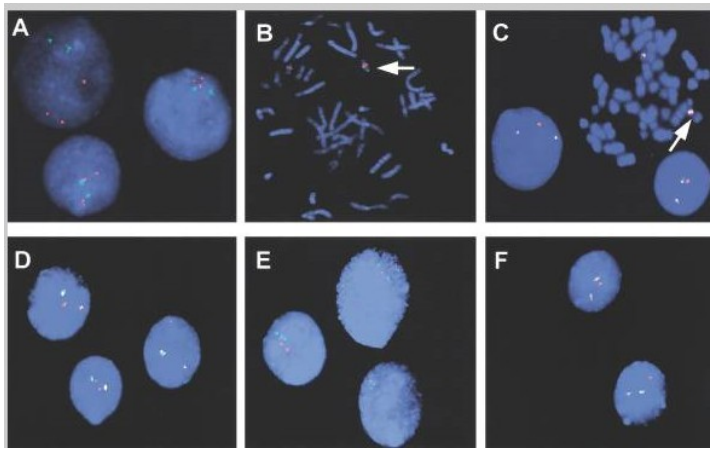
Am J Hum Genet. 2003 Nov; 73(5): 1027–1040.
Published online 2003 Oct 2. doi: 10.1086/378818
PMCID: PMC1180483

Microduplication 22q11.2, an Emerging Syndrome: Clinical, Cytogenetic, and Molecular Analysis of Thirteen Patients

Regina E. Ensenauer,[1] Adewale Adeyinka,[2] Heather C. Flynn,[2] Virginia V. Michels,[1] Noralane M. Lindor,[1] D. Brian Dawson,[3] Erik C. Thorland,[3] Cindy Pham Lorentz,[2] Jennifer L. Goldstein,[4] Marie T. McDonald,[4] Wendy E. Smith,[5] Elba Simon-Fayard,[6] Alan A. Alexander,[8] Anita S. Kulharya,[9] Rhett P. Ketterling,[2] Robin D. Clark,[7] and Syed M. Jalal[2]

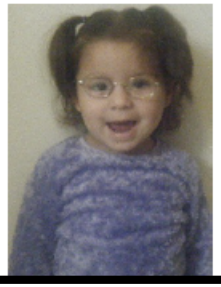






Main features

- Differences in heart structure or function
- A problem with the roof of the mouth known as velopharyngeal insufficiency, with or without a cleft (split) in the palate
- Hearing loss
- Growth delay
- Developmental delay
- Need for support with learning
- Behaviour issues
- Some unusual facial features

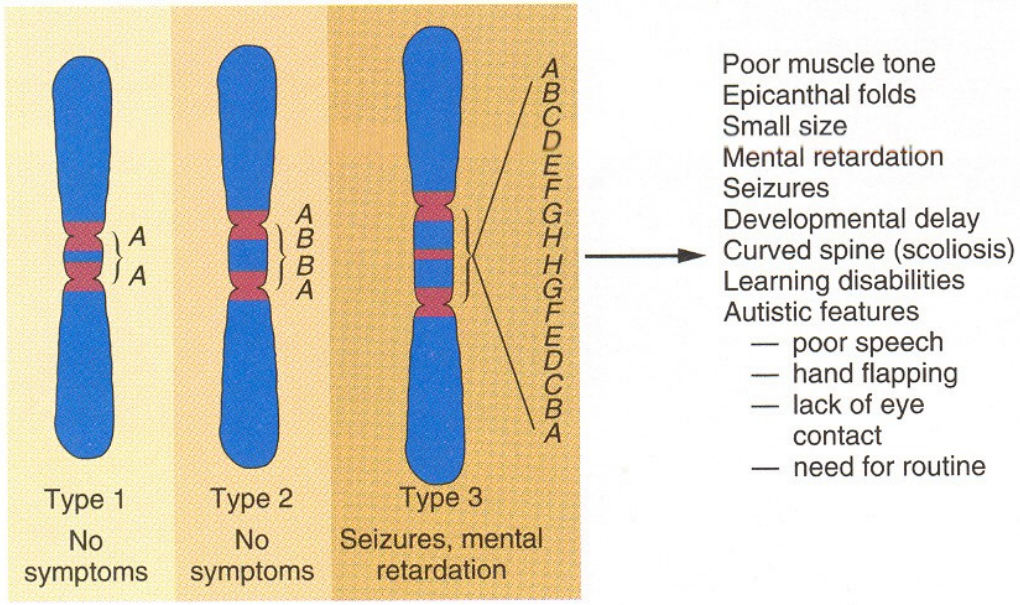


Comparison of clinical features in deletion/duplication 22q11.2 - milder involvement, incomplete penetrance, high variable expressivity

Comparison of 22q11.2 Deletion and Duplication Disorders

	% (FRACTION) WITH SYMPTOM IN			
SYMPTOM	Microduplication22q11.2	Large InterstitialDuplication 22q11[a]	Cat-EyeSyndrome[b]	Microdeletion22q11.2[c]
Cognitive deficits	100 (11/11)	100 (7/7)	56 (38/68)	90–100
Downslanting palpebral fissures	75 (9/12)	71 (5/7)	69 (48/70)	Not characteristic
Urogenital malformations	46 (5/11)	57 (4/7)	71 (55/77)	37 (25/67)
Hearing loss	42 (5/12)	33 (1/3)[d]	16 (11/68)	39 (19/49)
Cleft palate or absent uvula	39 (5/13)	0 (0/7)	31 (15/48)	32 (75/234)
Conotruncal heart defects[e]	17 (2/12)[f]	0 (0/7)	9 (7/80)	38 (116/305)
Other heart defects	8 (1/12)[f]	50 (3/6)[d]	88 (70/80)	37 (113/305)
Preauricular malformations	8 (1/12)	71 (5/7)	87 (78/90)	Not characteristic
Immunodeficiency	8 (1/12)	Not characteristic	Not characteristic	77 (46/60)
Anorectal malformations	0 (0/13)	14 (1/7)	81 (71/88)	Rarely reported[g]
Ocular coloboma	0 (0/13)	43 (3/7)	61 (54/88)	Rarely reported[h]
Hypocalcemia	Not detected	Not detected	Not detected	49 (77/158)

Syndrome inv dup(15) – ofen as marker chromosome !!!



a.

Poor muscle tone
Epicanthal folds
Small size
Mental retardation
Seizures
Developmental delay
Curved spine (scoliosis)
Learning disabilities
Autistic features
- poor speech
- hand flapping
- lack of eye contact
- need for routine

b.

Small supernumerary marker chromosomes (sSMC)

- it is a small redundant chromosome that cannot be analyzed by cytogenetic banding method

> Crolla et al. 1997: „Small structurally abnormal chromosomes that occurr in addition to the normal 46 chromosomes"

Characterization of sSMCs

- **chromosome** - carries functional kinetochores, mostly regular inheritance
- **small** - size usually smaller than G chromosomes;
- **redundant** - exceptions are markers derived from gonosomes;
- **absence of banding pattern** - cannot be analysed by conventional cytogenetic methods !!!
- markers sometimes do not contain centromeric DNA sequences - yet they are stable - **neocentromeres**
- often without telomeres - circular chromosomes

Frequency of "marker" chromosomes

	cases	marker chromosomes	
newborn	153701	70 (0.046%)	1:2195
unselected prenatal	688030	514 (0.075%)	1:1339
suspicious prenatal ultrasound	4409	9 (0.204%)	1:490
patients with mental retardation	69332	200 (0.288%)	1:347
males with fertility problems	21841	36 (0.165%)	1:607
females with fertility problems	9165	2 (0,022%)	1:4582

Classification of sSMCs

1) Satellite marker chromosomes (up to 80%)

- *Distamycin A/DAPI positive* - most often from **chromosome 15**
  idic(15) - "*inverted duplication 15 syndrome*"
- *Distamycin A/DAPI - negative* - **frequent 13, 14, 21, 22**
  idic(22) - "cat eye syndrome„

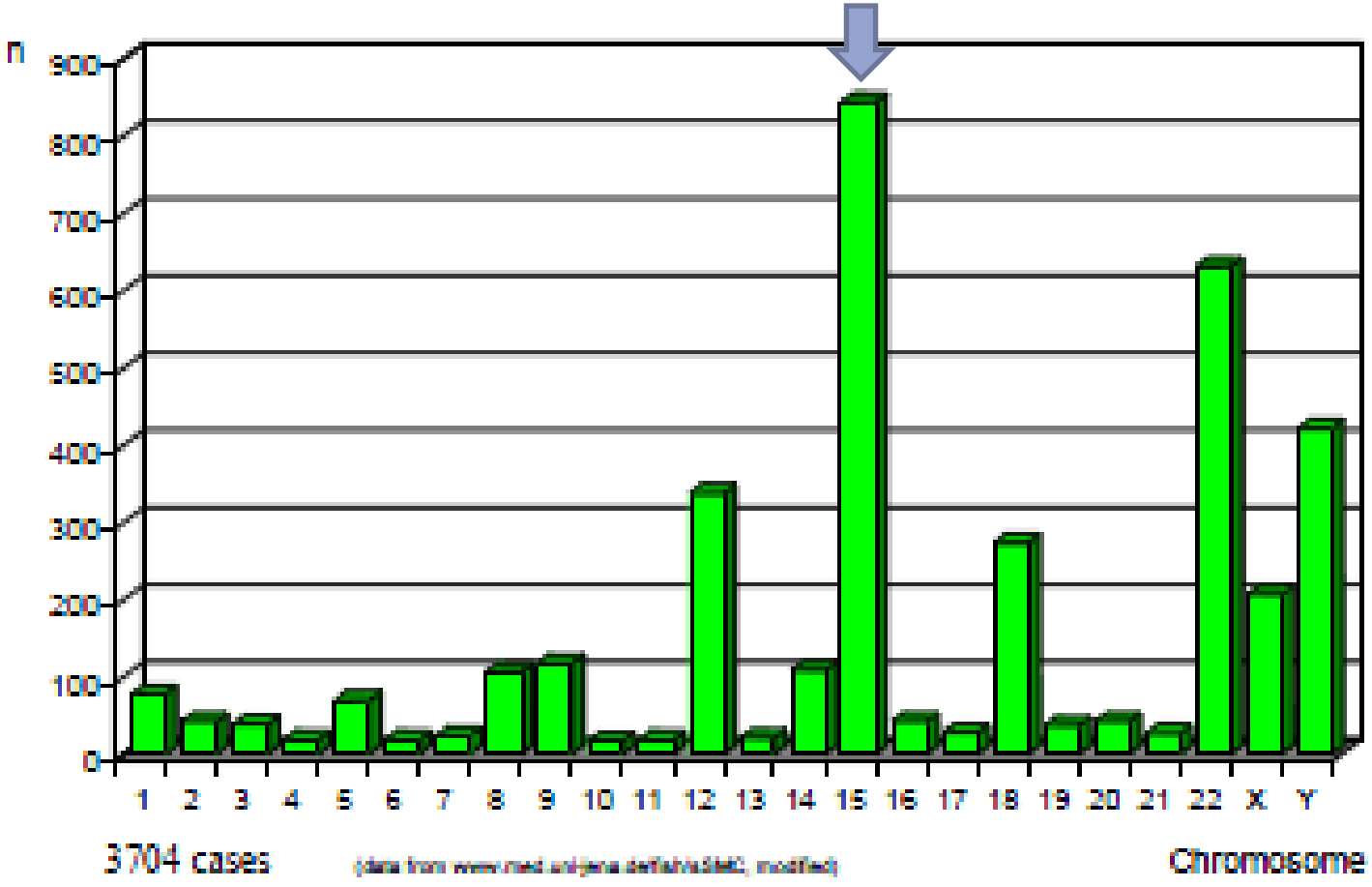
2) Non-satellite marker chromosomes (often ring-ring chromosomes)

- Distamycin A/DAPI - positive – **frequent chr. 1, 9, 16**
- Distamycin A/DAPI - negative **chr. 5, 8, 9, 12, 18**

3) Marker chromosomes derived from gonosomes

frequent r(X)

Origin of "marker" chromosomes



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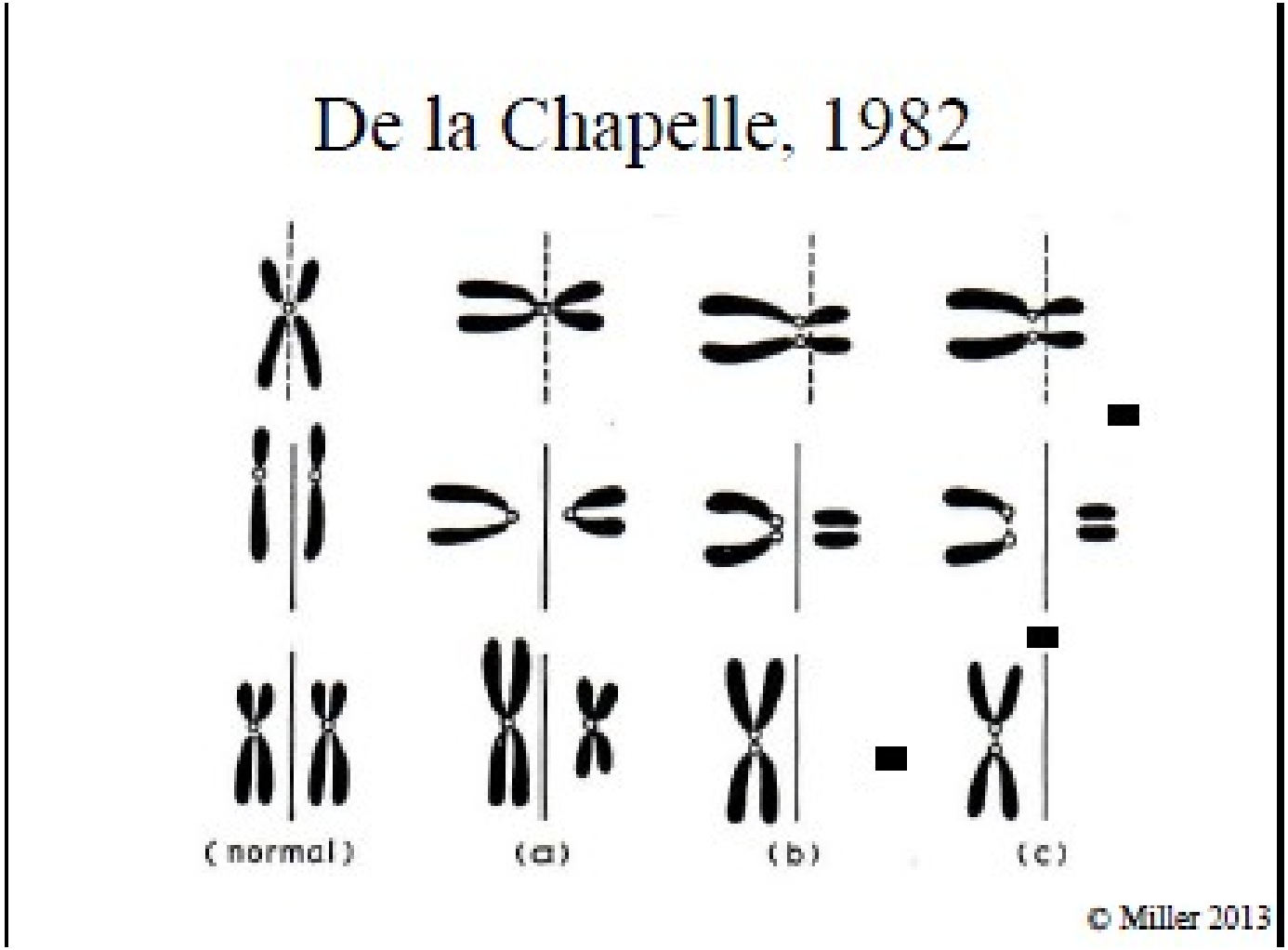
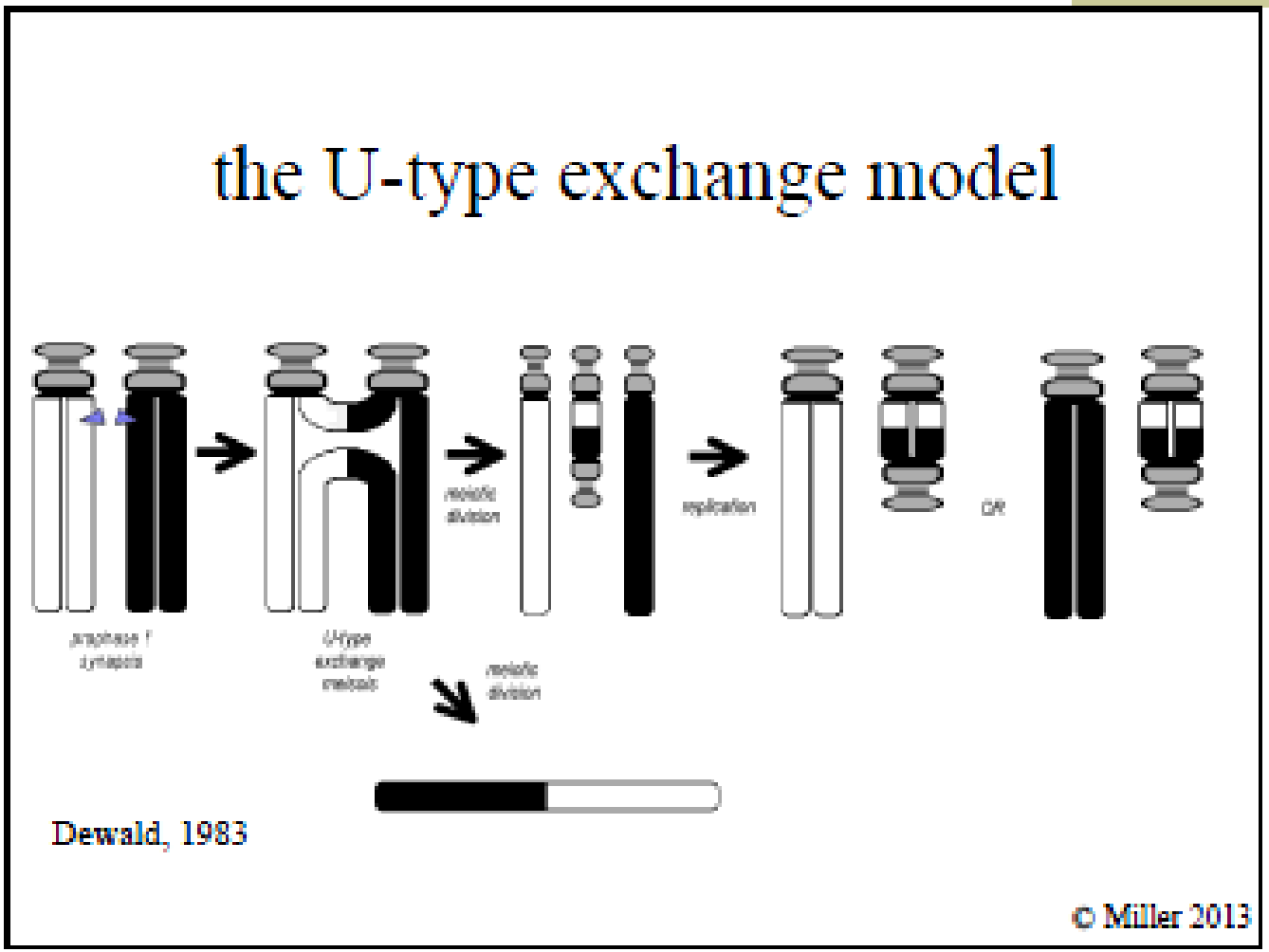
Origin of sSMCs



Origin of sSMCs



Techniques used for identification of marker chromosomes

Marker chromosomes:

- **without euchromatin** - may not affect the phenotype
- **with euchromatin - partial trisomy !!!**
- banding (C-, Ag-NOR banding)
- FISH (CEP, WCP)
- SKY, M-FISH, M-BAND
- **Mikrodisection – reverse FISH**

- **array-CGH (the most effective)**

sSMCs and genetic counselling

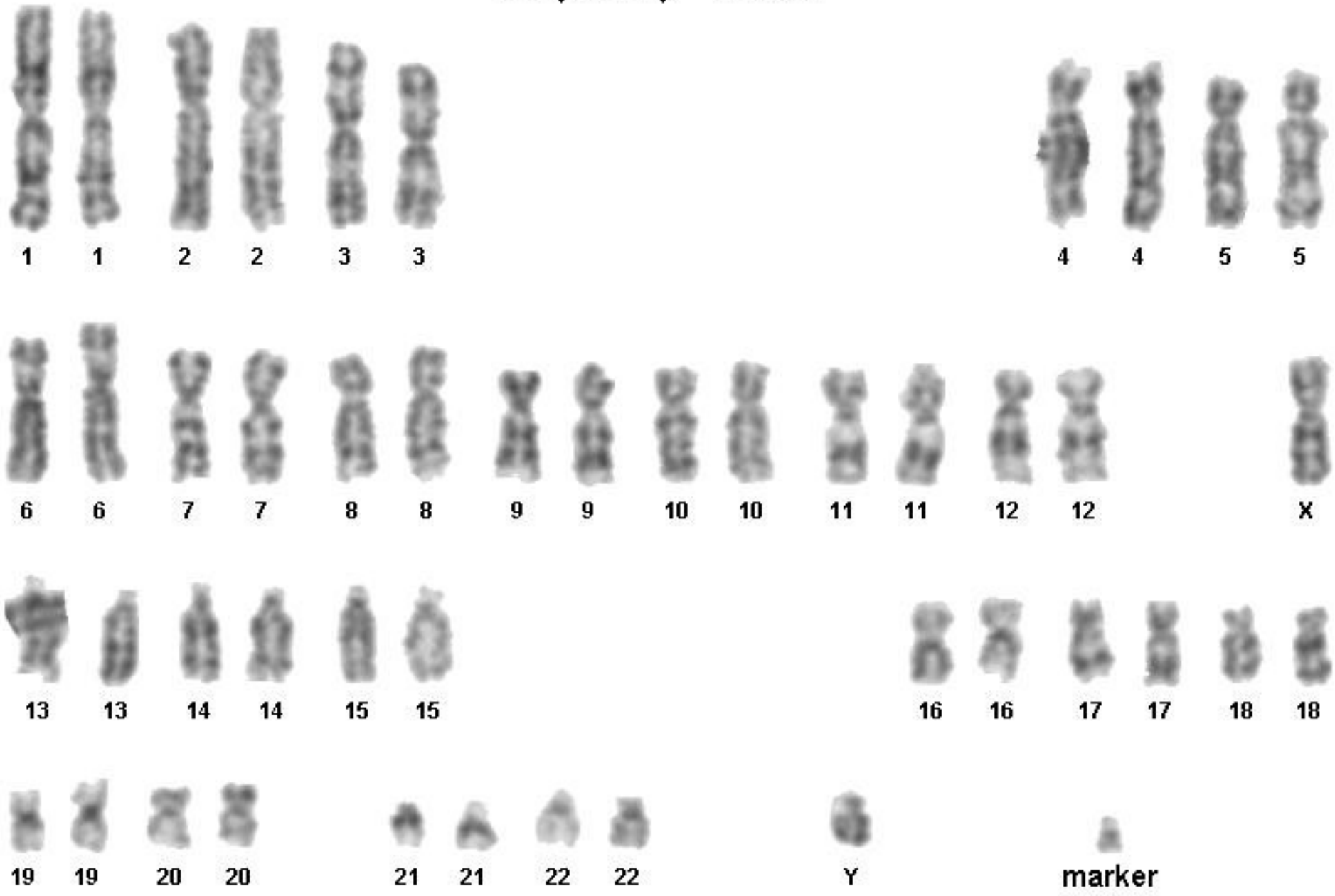
Finding of a marker chromosome in the fetal karyotype is always a **serious problem** for prognosis estimation and further genetic counselling !!!It is necessary to **determine the origin** !!!

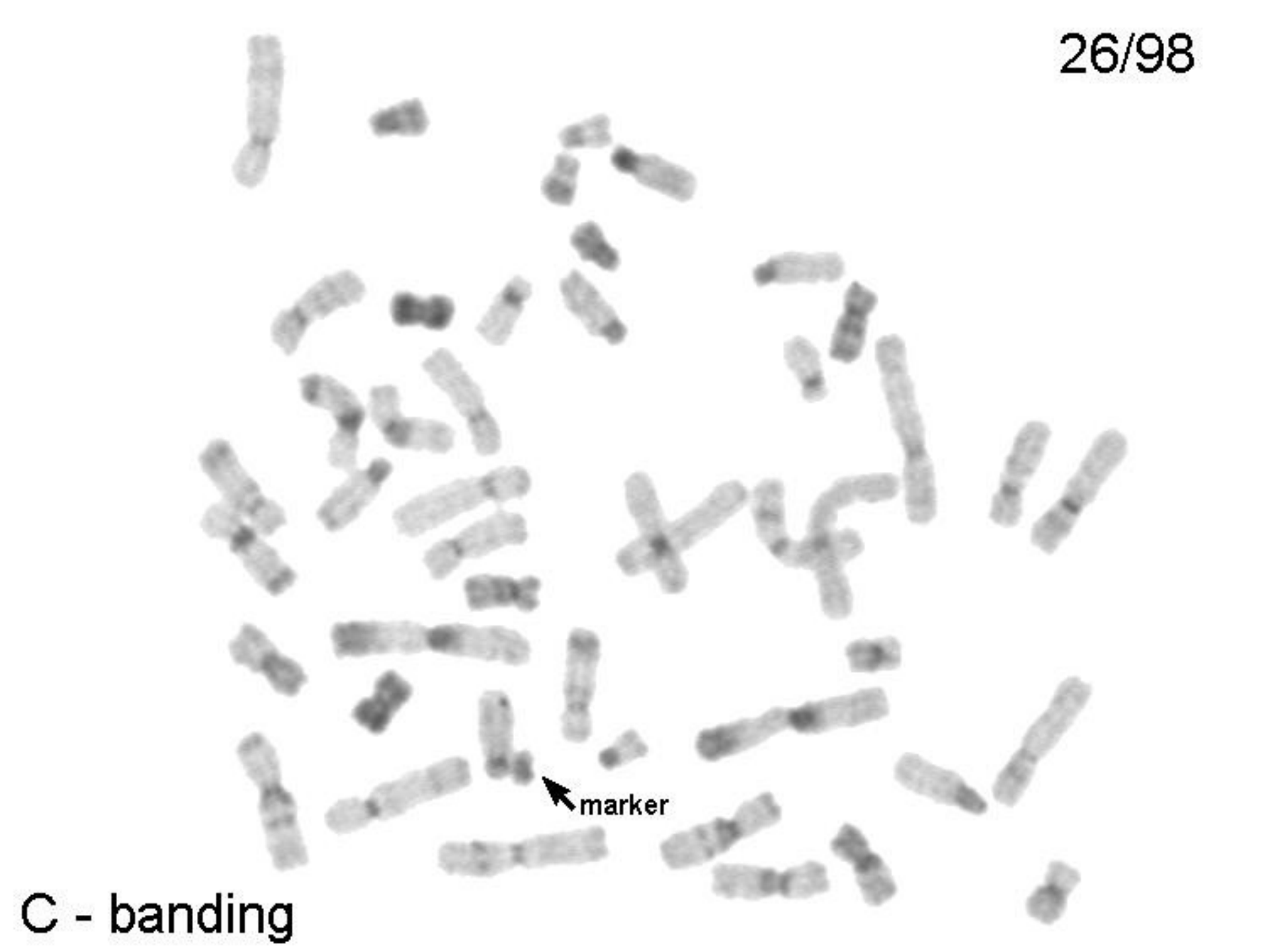
sSMC - case report PATIENT 1 - reason for cytogenetic examination and its result

- boy (born 1984) - indicated due to mild psychomotor retardation and short stature;
- karyotype determined 47,XY,+mar;
- marker origin: *de novo*, contains centromere and satellites;

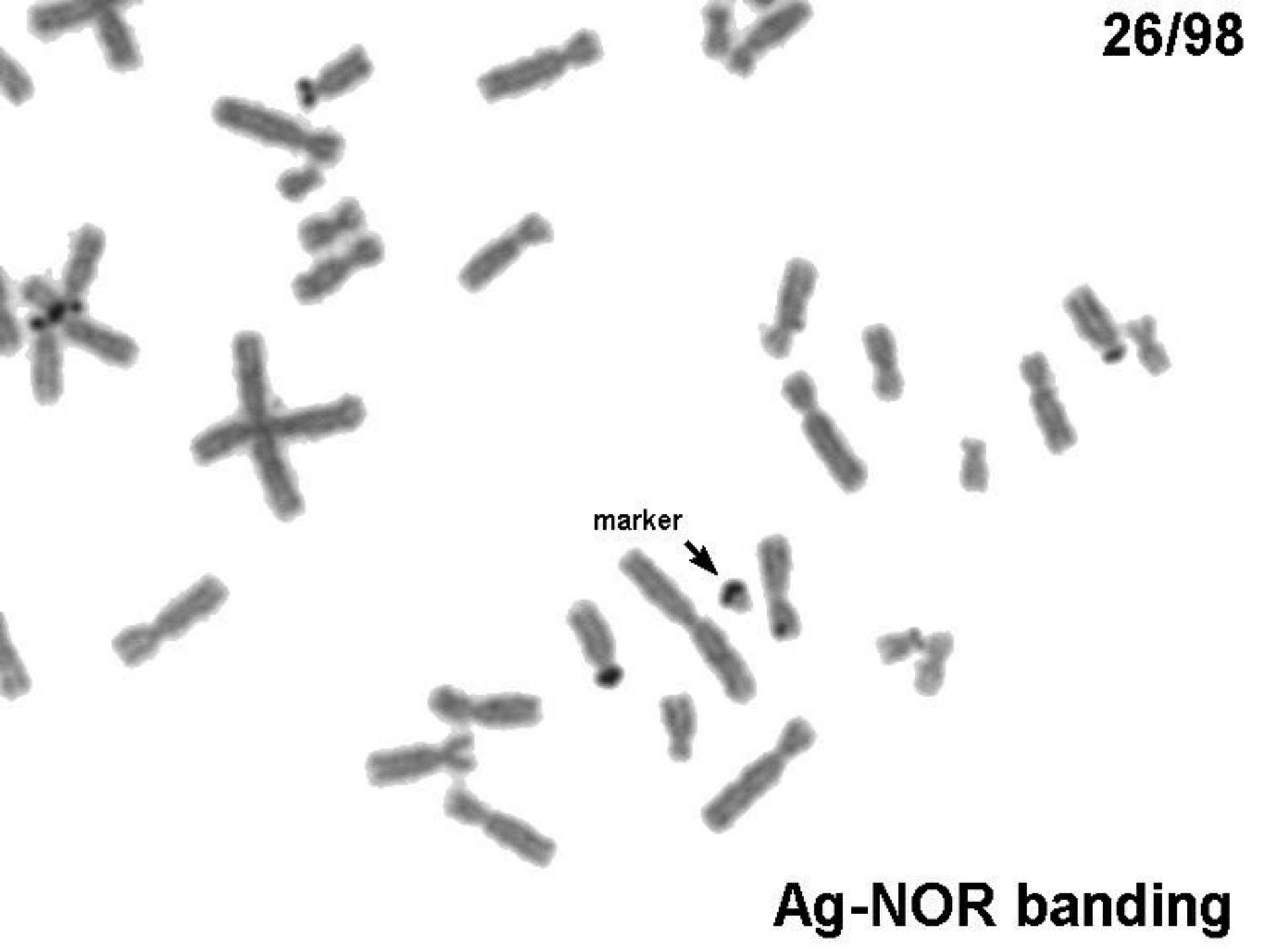
47,XY,+mar

26/98





C - banding

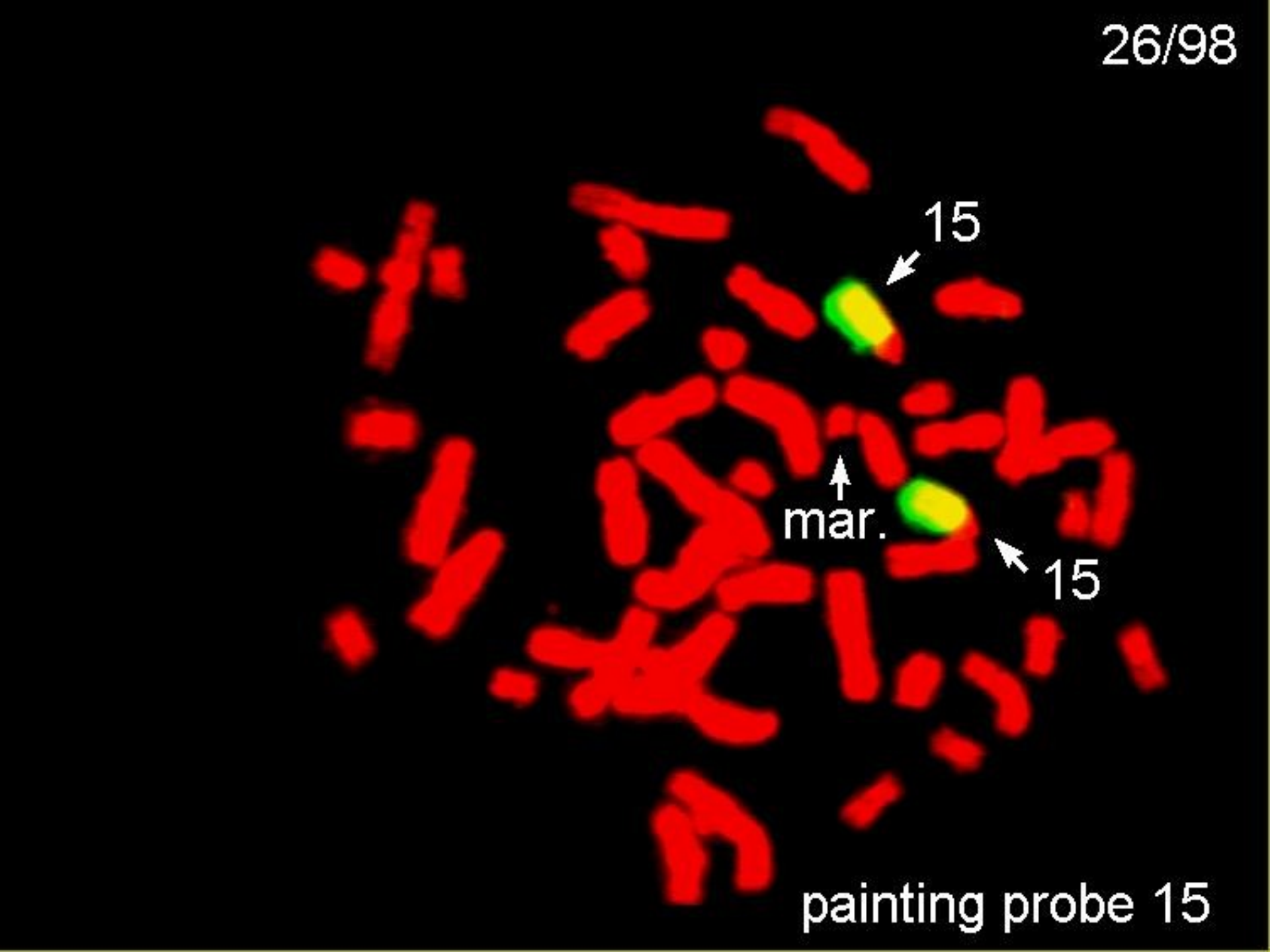


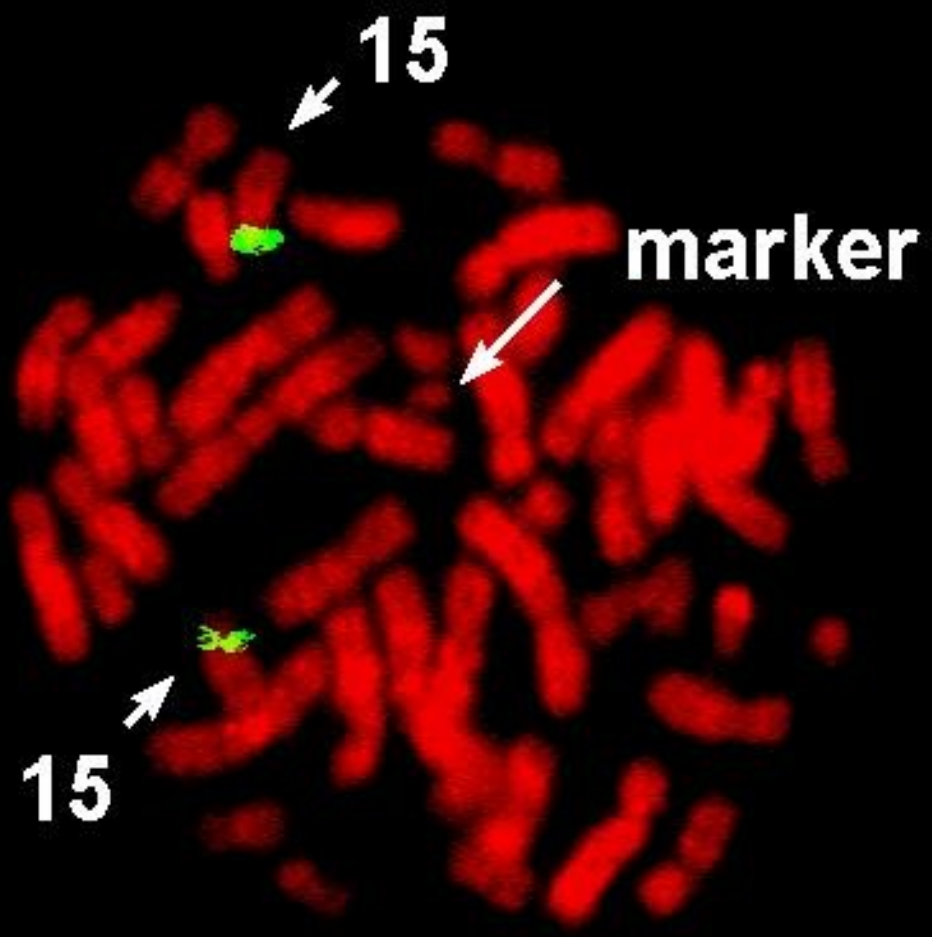
Ag-NOR banding

PATIENT 1 - FISH investigation

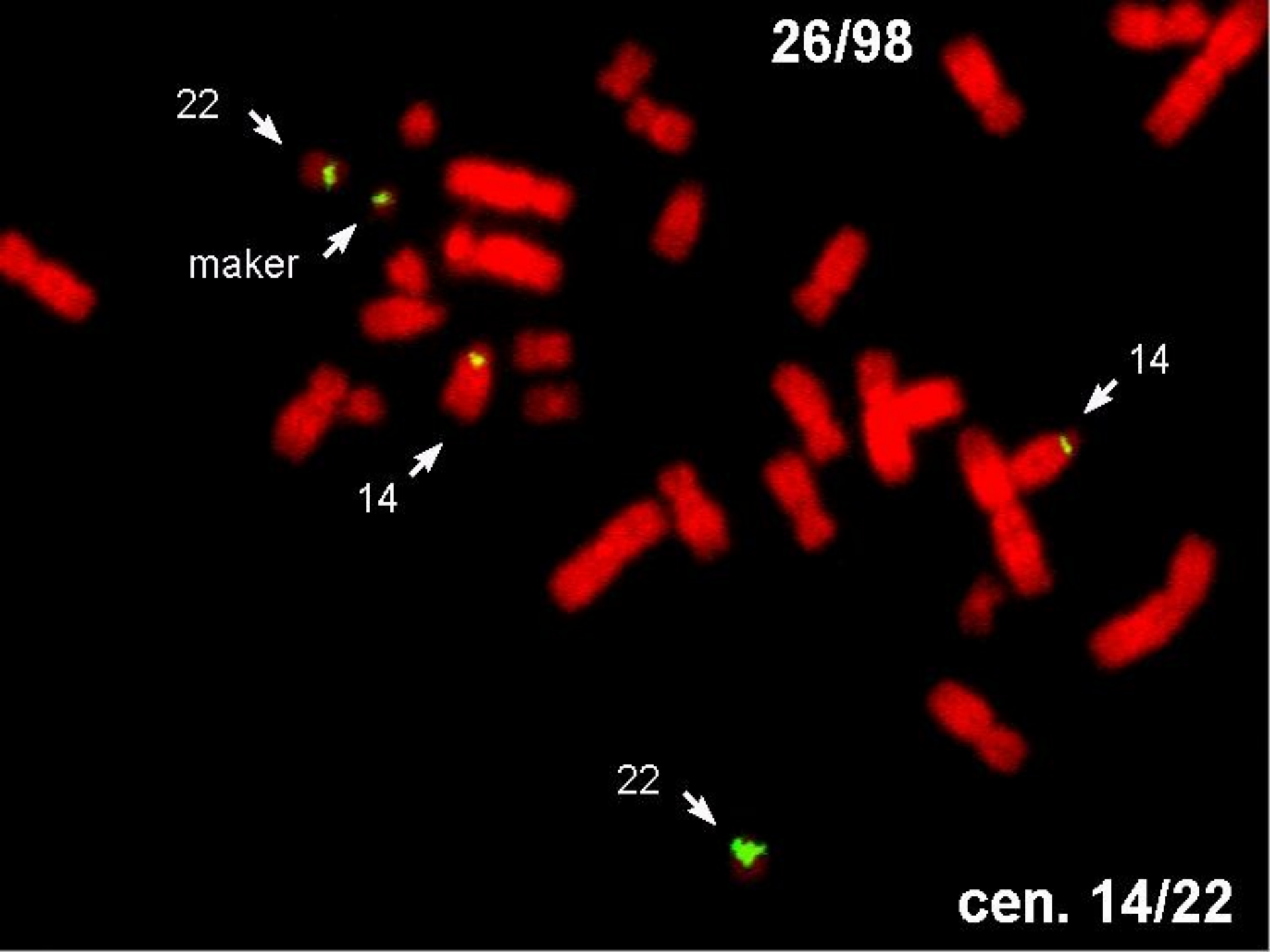
- centromeric probe and whole chromosome probe 15 both negative;
- centromeric probe: 14/22 positive;
- whole-chromosome probe: 22 negative;
- **whole-chromosome probe: 14 positive**;

- **We've determined the origin, but we don't know what genes the marker contains...**


15
mar.
15
painting probe 15



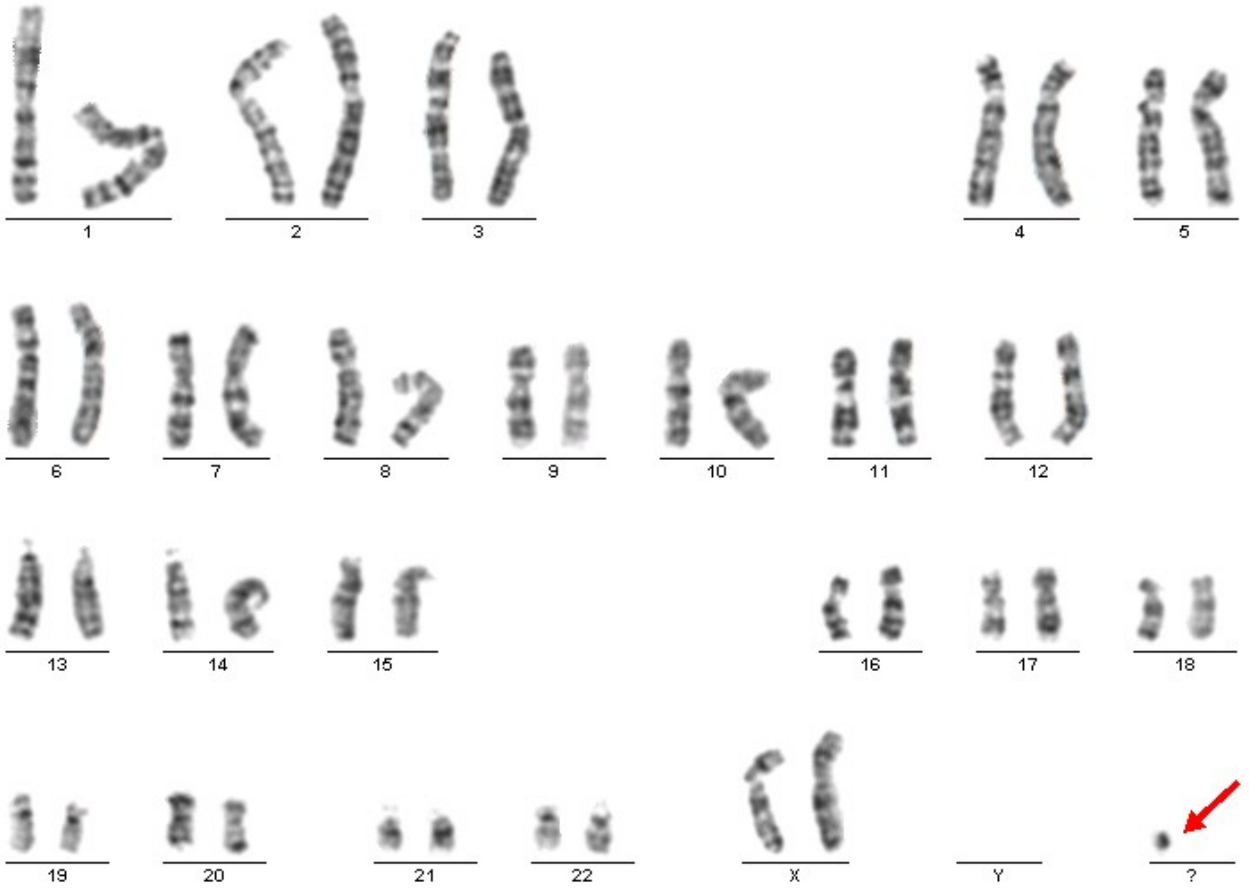
cen. 15


26/98
22
maker
14
14
22
cen. 14/22

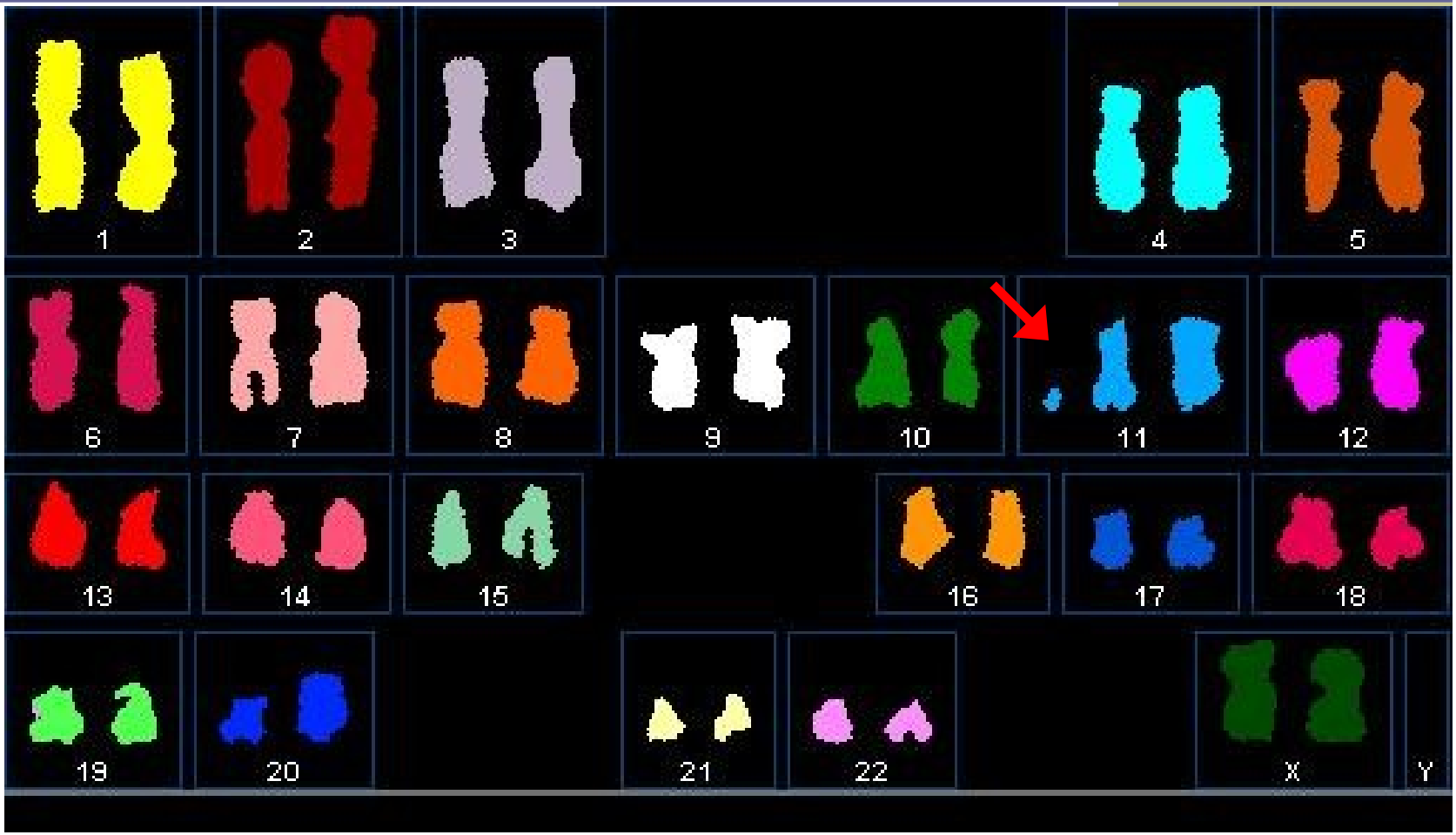
sSMC PACIENT 2

- Child from first pregnancy
- findings: hearing loss in the P ear, complete deafness in the L ear
- born 2001
- both parents and younger sister healthy

Karyotype:
47, XX, + mar [18] / 46, XX [12]
Origin of sSMC unknown

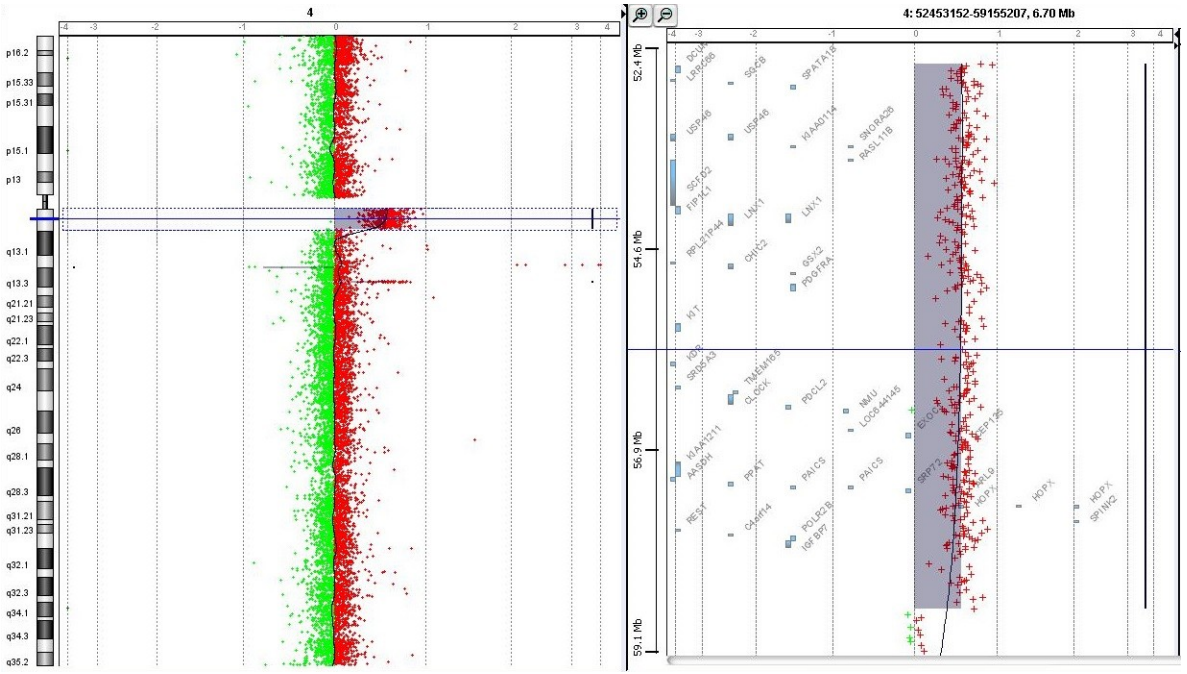


SKY: 47, XX, + mar(11)



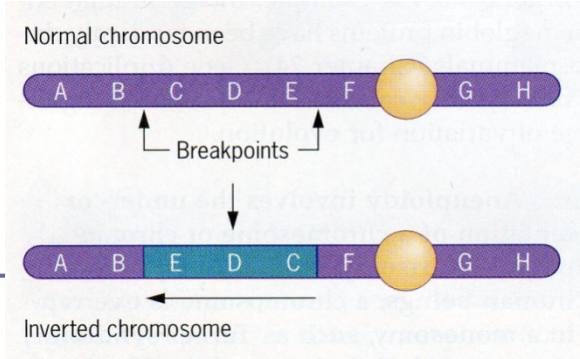
Identification of sSMCs nowadays array CGH + karyotype

- on the array-CGH profile, the marker chromosome appears as a gain of genetic material
- it is **necessar**y to know the **karyotype** - differentiation of the marker from tandem duplication
- Determination of which genes the marker contains

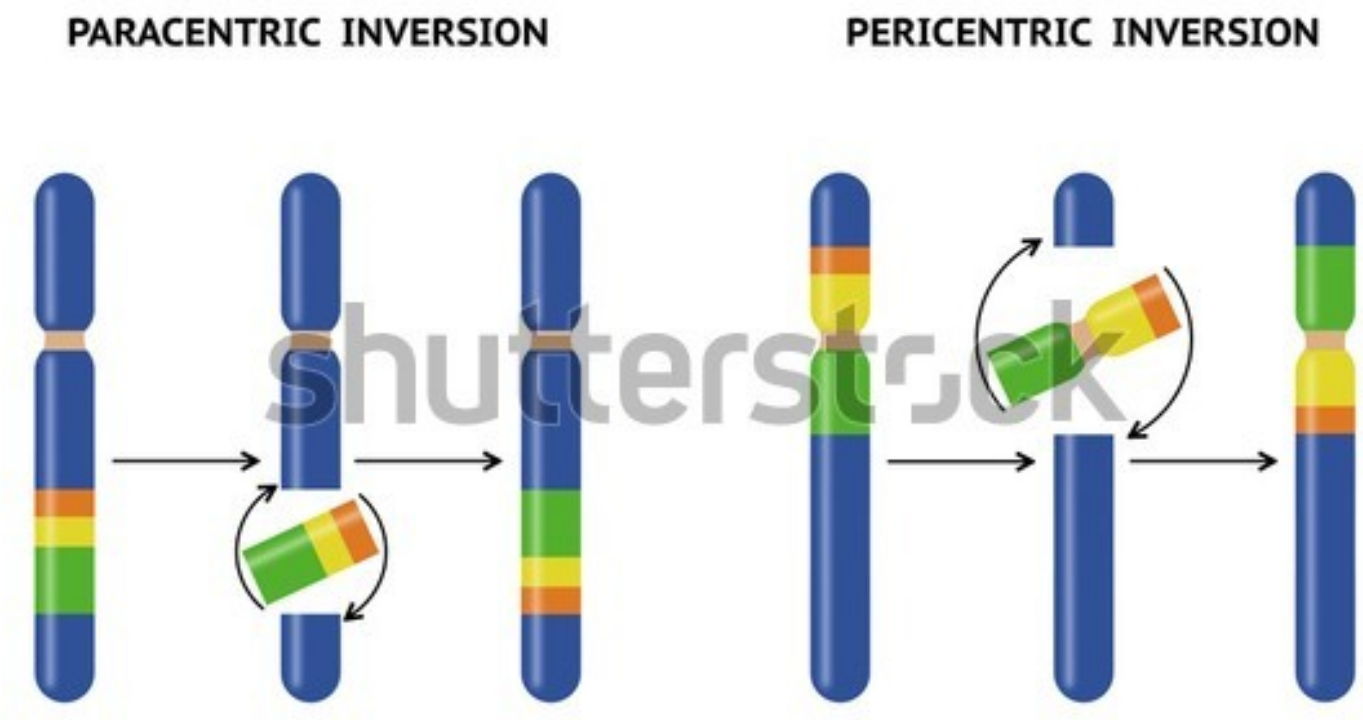


Profile of array-CGH with sSMC orginated from 11q12 area (5,96 Mb)

Inversions (i)



Origin: breaks on chromsosme
2 possible types



Genetic significance of inversions

- **Inversions** does not cause an abnormal phenotype in its carriers....but creates problems in **heterozygotes....**

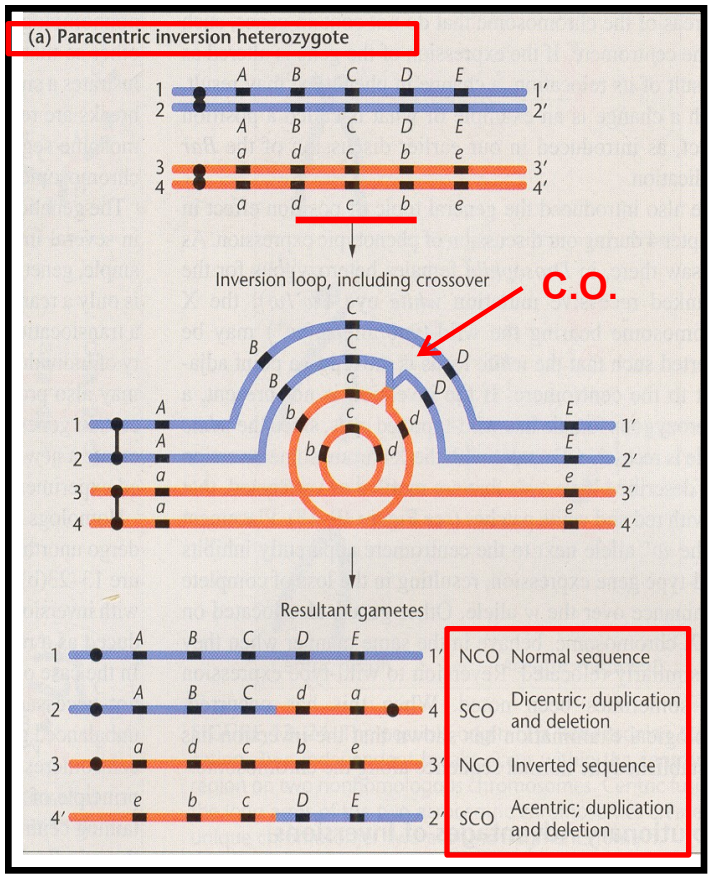
  an inversion loop is created in meiosis!

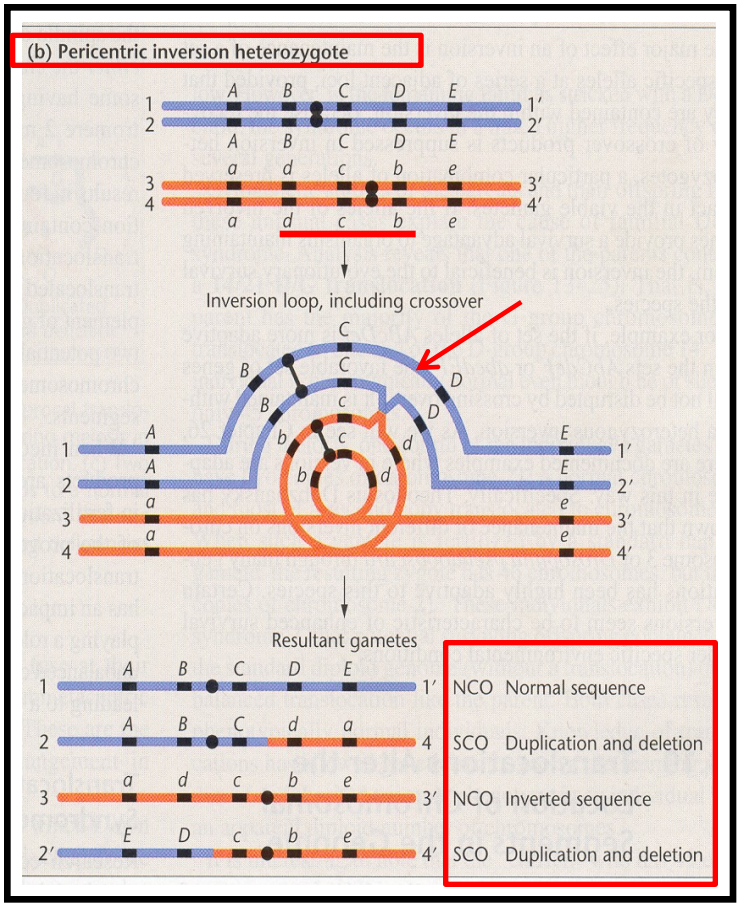
- **reduction of crossing-over frequency** - reduction of contact sites within the loop - **blockage of crossing-over** - evolutionary significance of inversions (genes do not separate by c.o. and are transmitted together...)

- In humans - clinical significance for offspring - **carrier of any inversion has increased risk** of abnormal gametes arising **after c.o. - unbalanced CHA in offspring** (dicentric chromosomes, acentric chromosomes, duplications, deletions)....**abortions, affected children.... STERILITY !**

Inversion and consequence of crossing-over in inverted heterozygotes

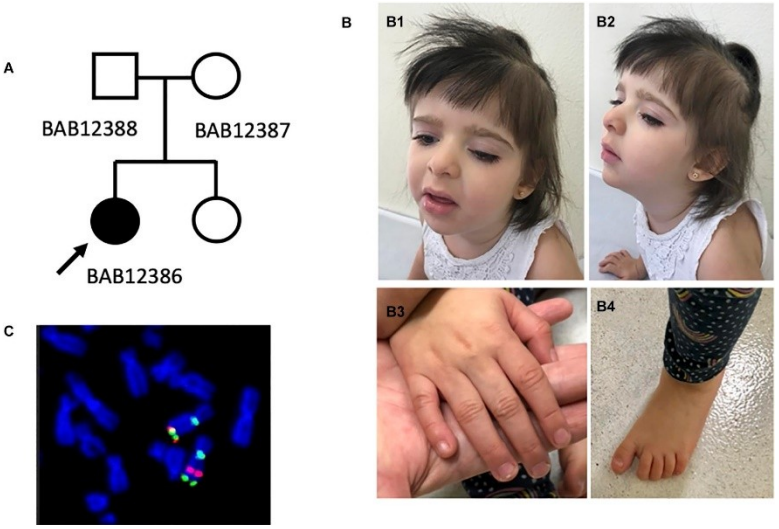
unbalanced chromosome aberrations in gametes after crossing-over - duplication - deletion (peric.) or dicentric - acentric fragment (parac.) - gametes unviable !

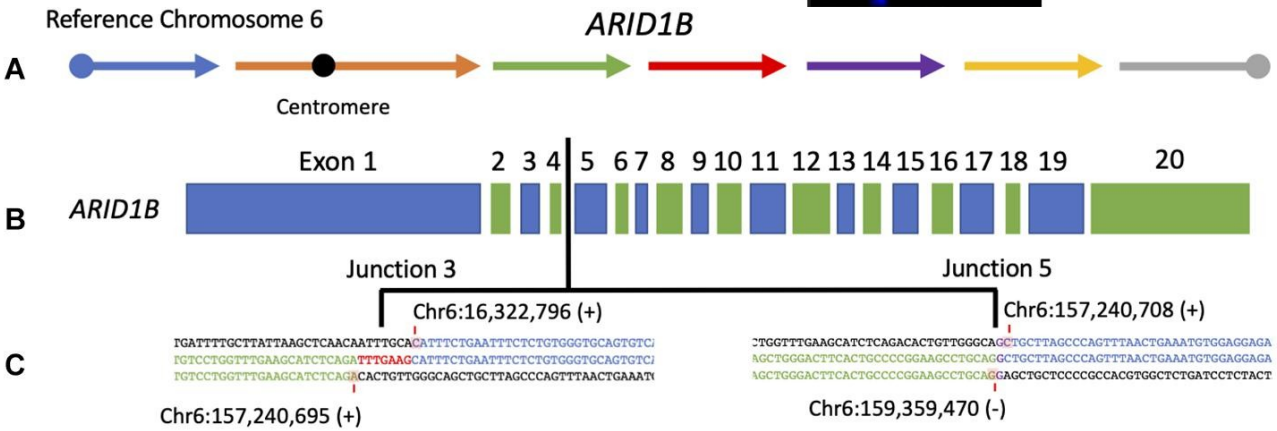


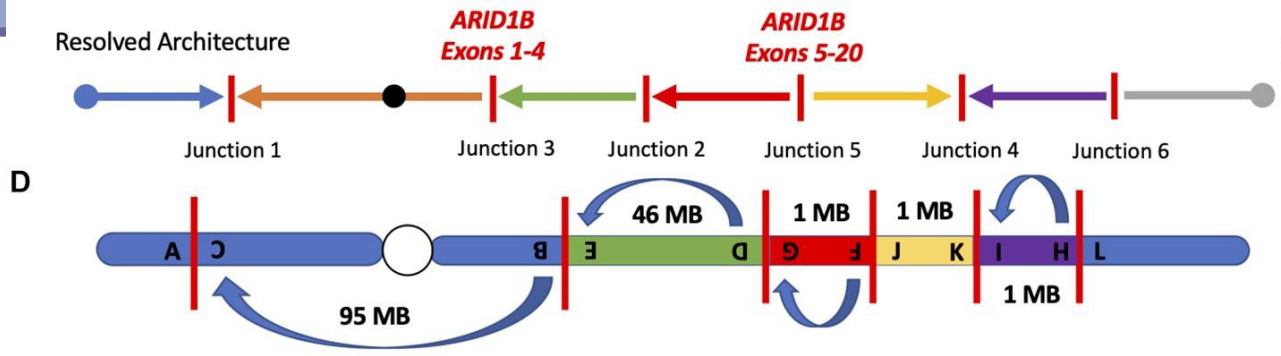


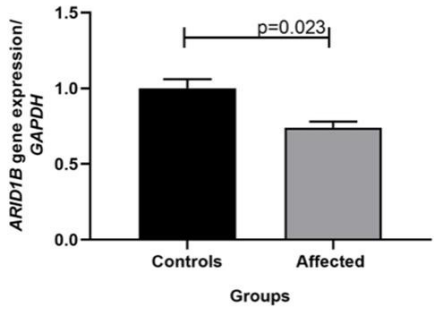
Inversions – case report

- Disruption of chr. 6









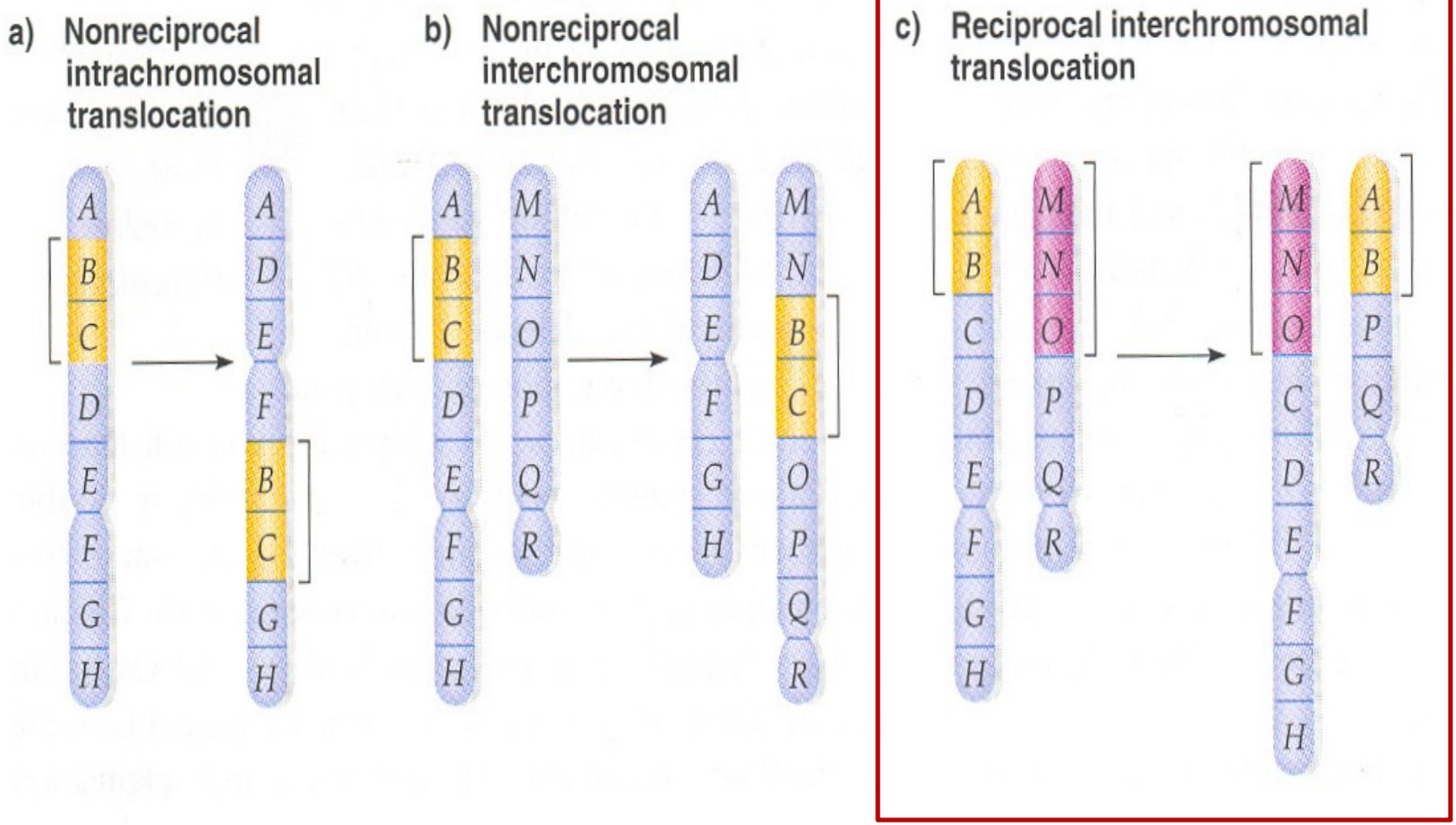
Chromoanagenesis Event Underlies a *de novo* Pericentric and Multiple Paracentric Inversions in a Single Chromosome Causing Coffin–Siris Syndrome" . *Grochowski et, Front. genetics*

Translocations

- exchange of chromosome segments between two or more chromosomes

- reciprocal x simple
- Robertsonian translocations - acrocentric chromosomes
- complex translocations (affecting three or more chromosomes)

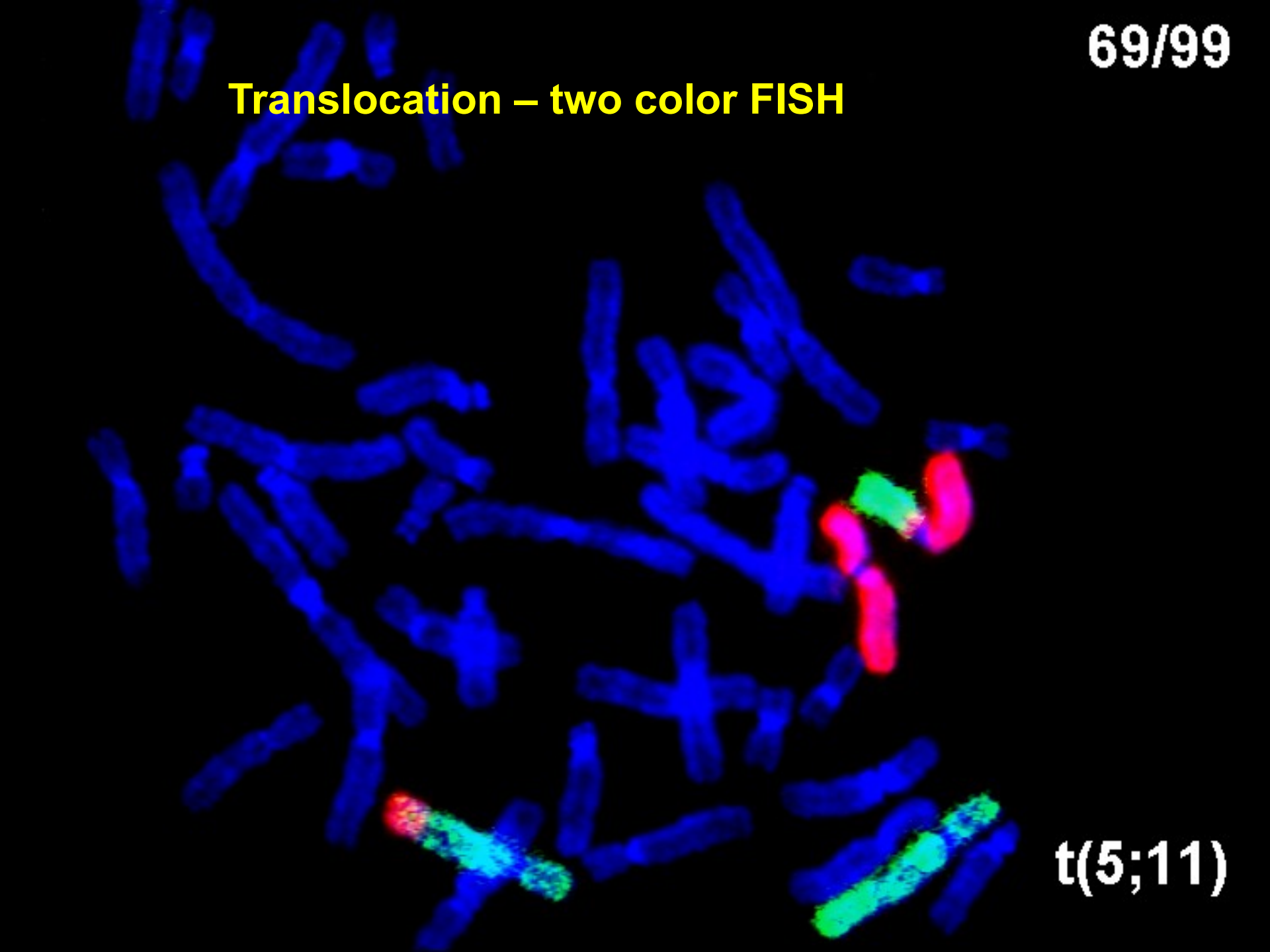
Types of chromosomal translocations



Congentital reciprocal translocations in humans

- **occurrence** in the population with a frequency of **about 1 : 500**
- do not clearly affect the carrier phenotype (5 times higher incidence in the mentally retarded population)
- **significant cause of sterility in carriers**
  - *due to aberrant meiotic segregation*
  - formation of gametes with **unbalanced rearrangements** (duplication, deletion)
- **acquired translocations** - positional effect in tumors - activation of oncogenes, deregulation of gene expression !
- **fusion genes** (e.g. Ph chromosome)

Translocation – two color FISH



Reciprocal translocations - problems in meiosis - formation of cross structures at synapsis

Segregation in translocation heterozygotes - possible formation of gametes with unbalanced assemblies - with duplication, deletion...

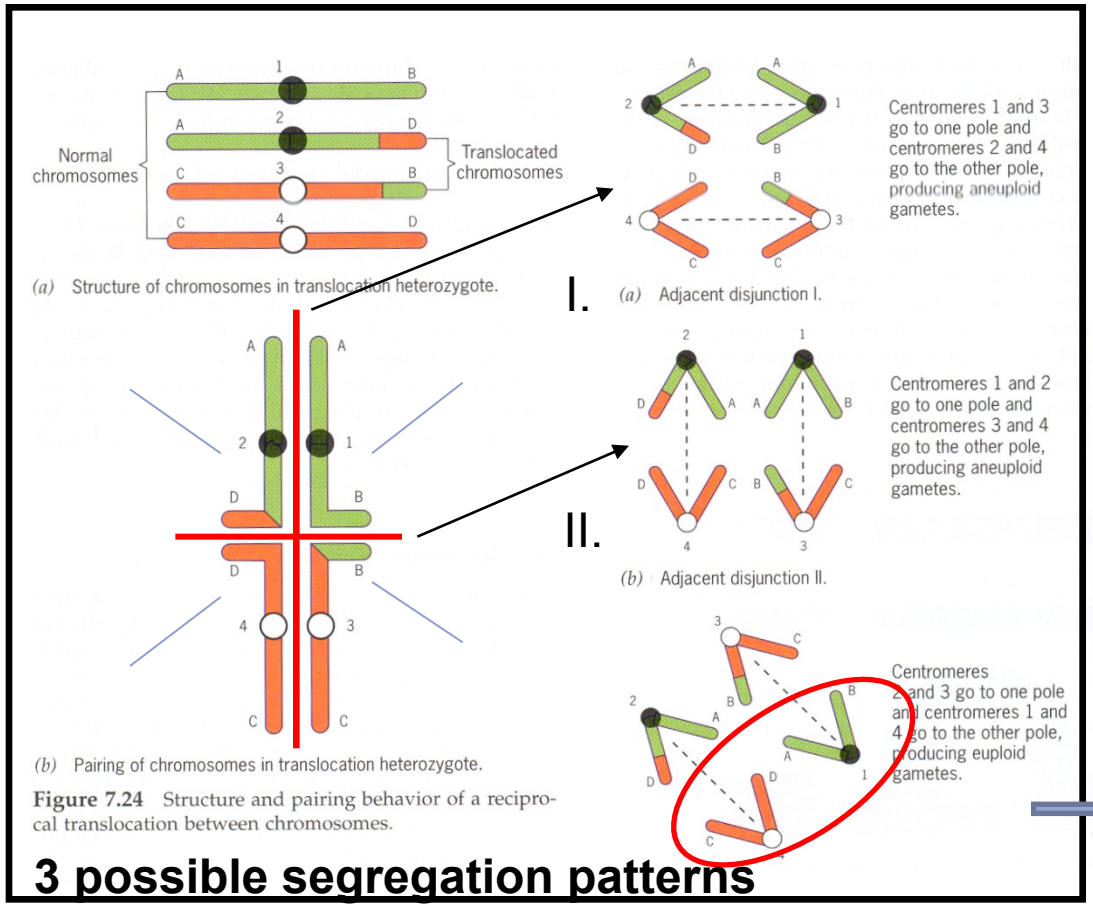


Figure 7.24 Structure and pairing behavior of a reciprocal translocation between chromosomes.

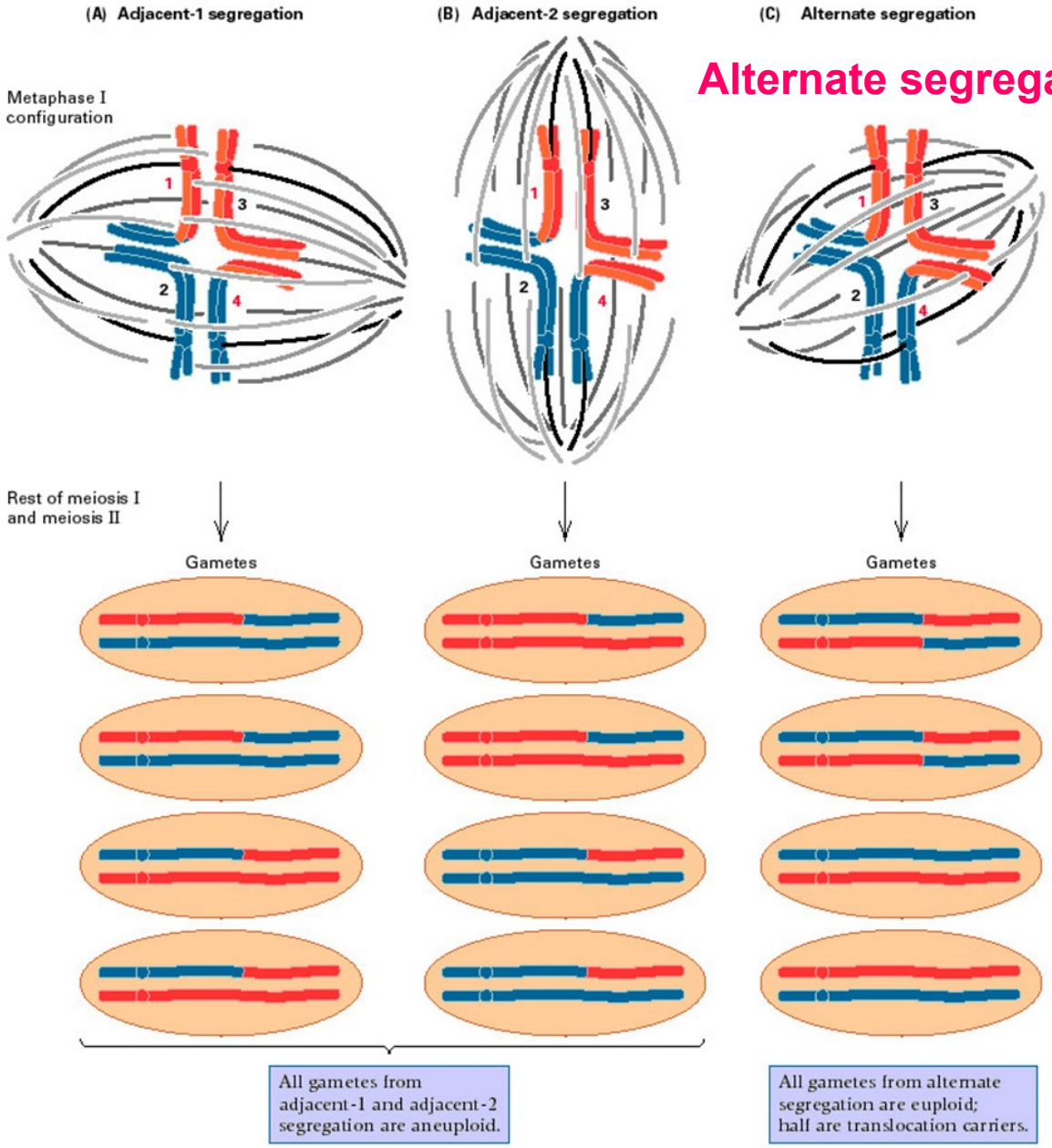
3 possible segregation patterns

Segregation of adjacent chromosomes type I
*(homologous centromeres diverge into **different daughter cells**)*

Gametes with unbalanced changes – dels, dups

Segregation of adjacent chromosomes type II
*(homologous centromeres diverge into the **same daughter cell**)*

Alternate segregation
(gametes with a normal chromosome set or with two chromosomes with a reciprocal translocation)



Alternate segregation

balanced

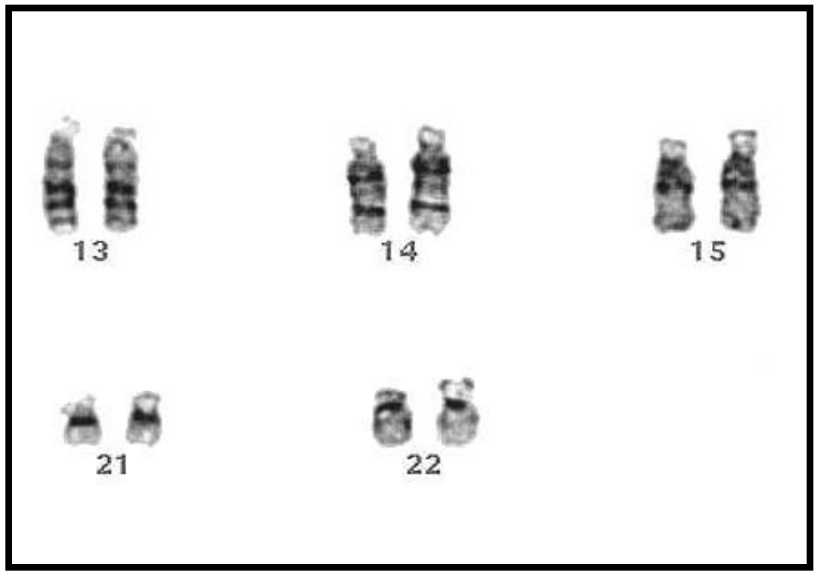
normal

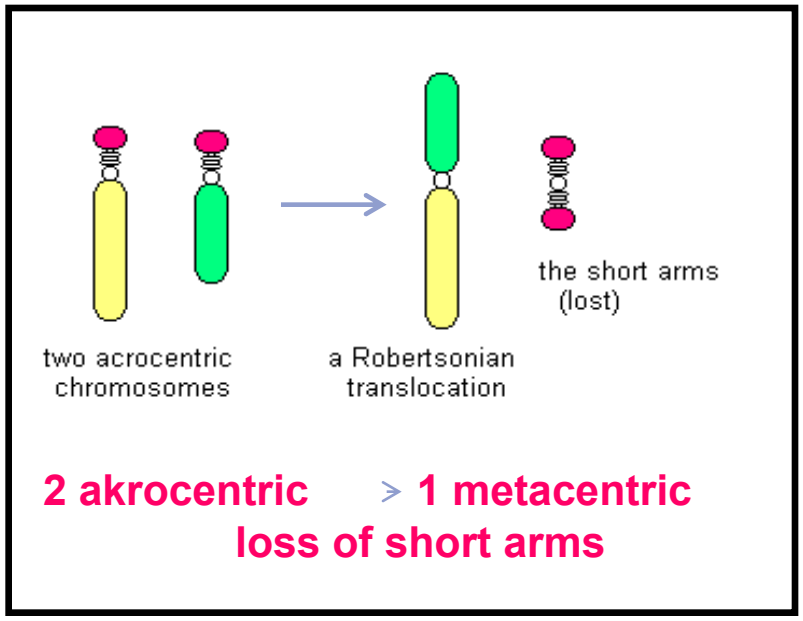
Unbalanced gametes

Robertsonian translocations are connected with acrocentric chromosomes in human

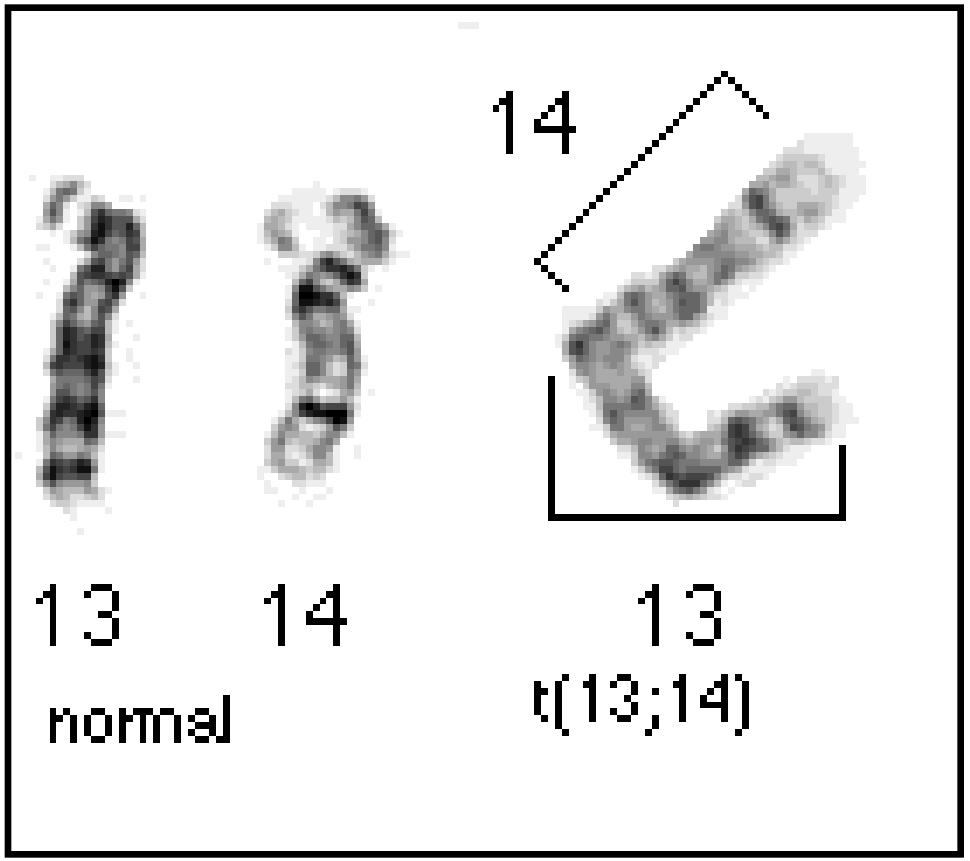
45,XX,der(13;21)(q10;q10) or 45,XX,rob(13;21)(q10;q10)

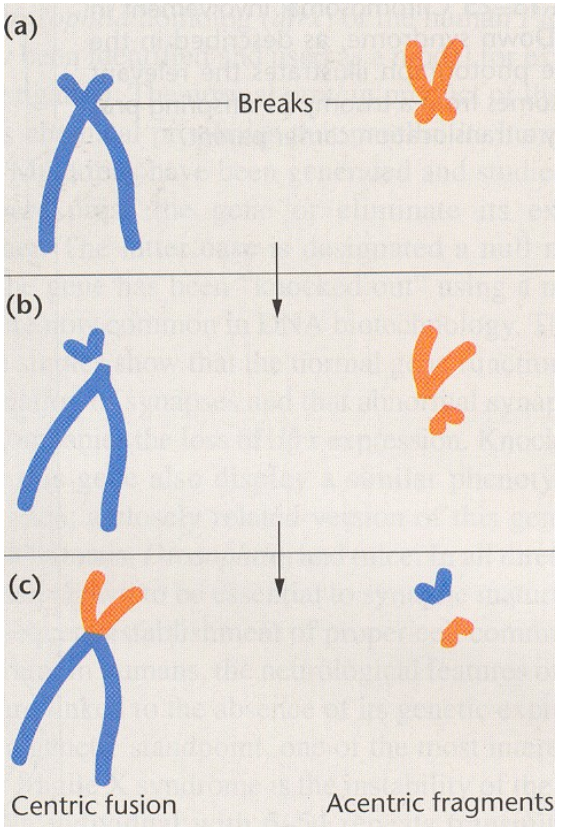
–ISCN description 45 chromozomes in karyotype !





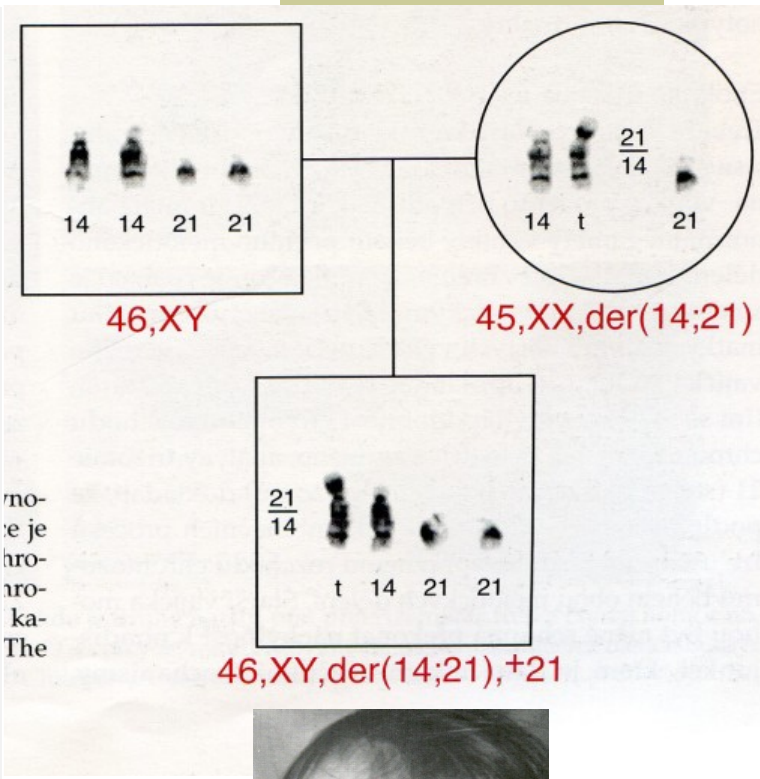
der(13;14) – the most common Robertsonian translocation in humans 1 / 1300 individuals

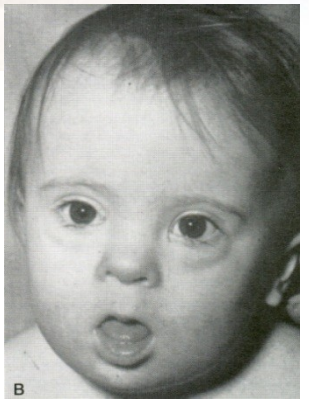




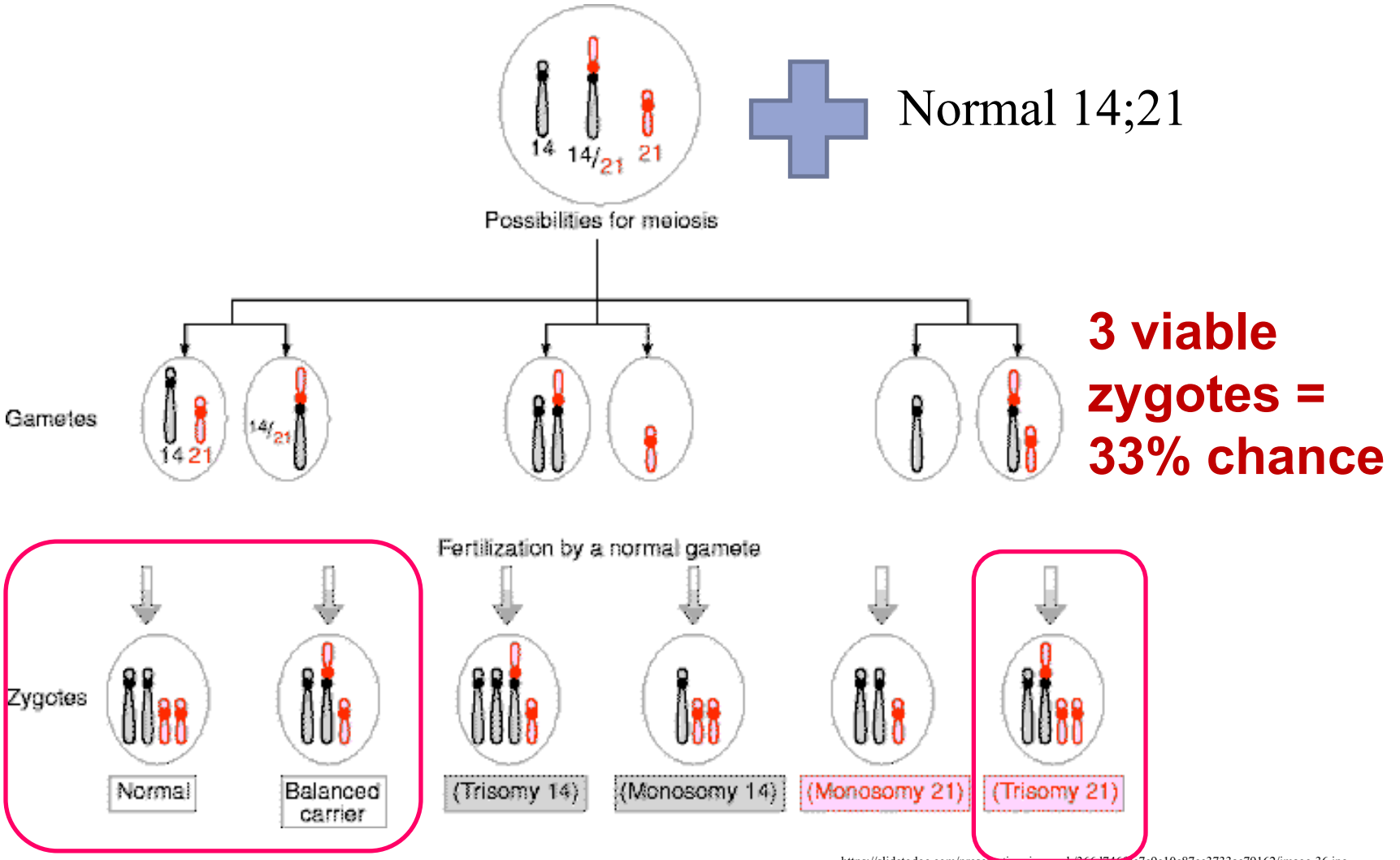
Robertsonina translocations and Down syndrome

- **about 4% of Down syndrome cases - a consequence of Robertsonian translocations affecting chromosome 21**
- the parent carrier der(14;21) is normal ! **but the child inherits chromosome 14 with 21**!
- the theoretical risk of the child being affected by **D.S. is 33% !**
- population studies - **10 to 15% in carrier mothers**





Karyotype of male with Down syndome casused by translocation t(14;21)



https://slidetodoc.com/presentation_image_h/366d74618c7c9e10c87cc3733ac79162/image-36.jpg

45,XX,der(21;21)

100% cases of Down syndrome in offsprings