Clinical Cytogenetics

Disorders of the Autosomes

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Pr I.Maystadt

10/01/2020

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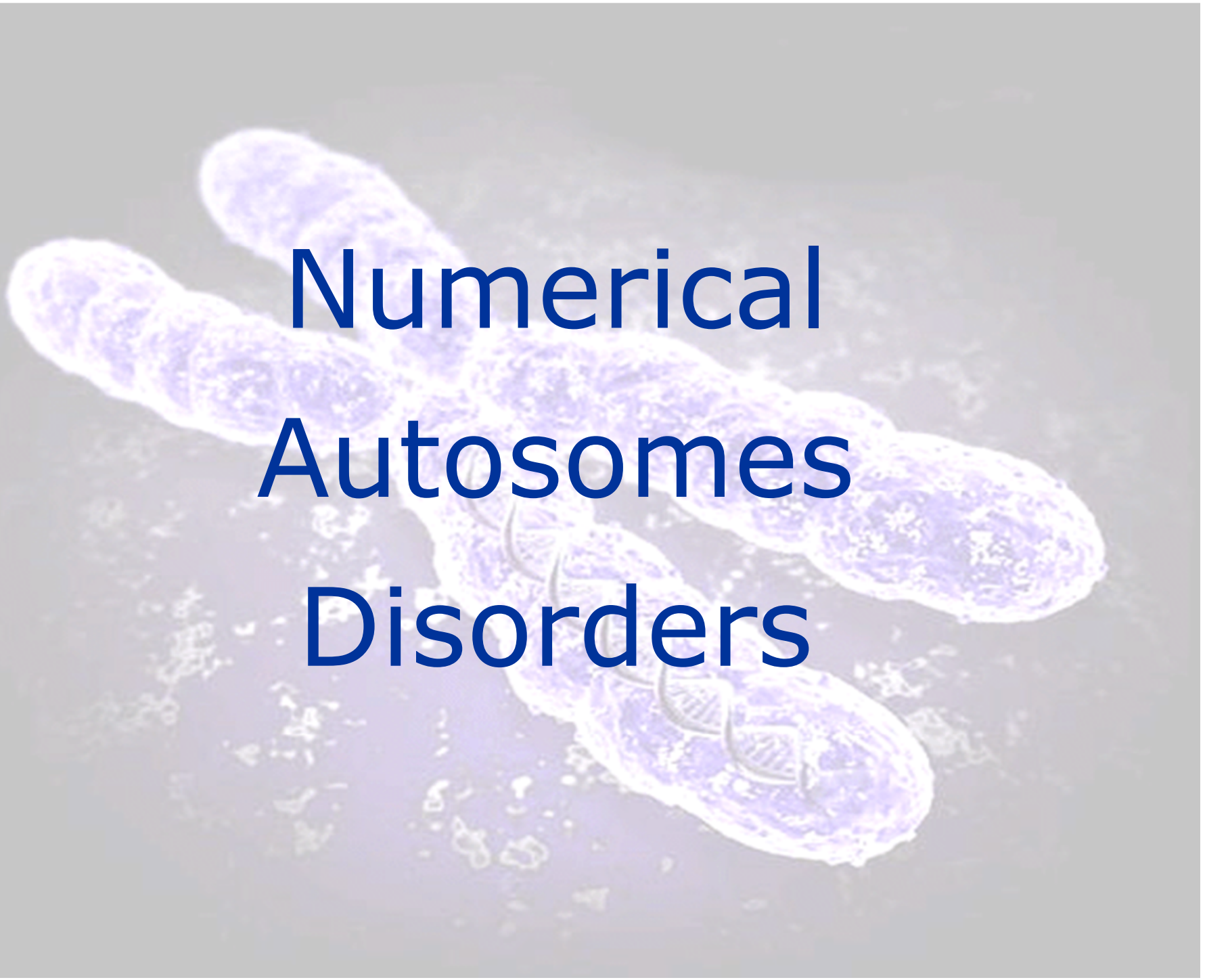
Chapter 6

1. Autosomal Disorders

   - Numerical disorders
   - Structural disorders

2. The sex chromosomes and their abnormalities (Pr I. Maystadt)


Numerical
Autosomes
Disorders

Numerical autosomes abnormalities

- Most of them are spontaneously aborted (94%)
- Incidence in newborns: 1/160 births (0.5-0.7%)

	Pregnancies (incidence)	% Spontaneous abortions	% Live births
Total	**10000**	**1500 (15%)**	**8500 (85%)**
Abnormal chromosomes	**800 (8%)**	**750 (94%)**	**50 (6%)**
Triploid/tetraploid	**170 (1.7%)**	**170 (100%)**	**0**
Trisomy 16	**112 (1.1%)**	**112 (100%)**	**0**
Trisomy 18	**20 (0.2%)**	**19 (95%)**	**1 (5%)**
Trisomy 21	**45 (0.4%)**	**35 (78%)**	**10 (22%)**
Other trisomy	**209 (2%)**	**208 (99.5%)**	**1 (0.5%)**

Incidence of autosomal aneuploidies in 10000 pregnancies (Table 5-5)

- ! Except for mosaic forms

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Numerical autosomes abnormalities

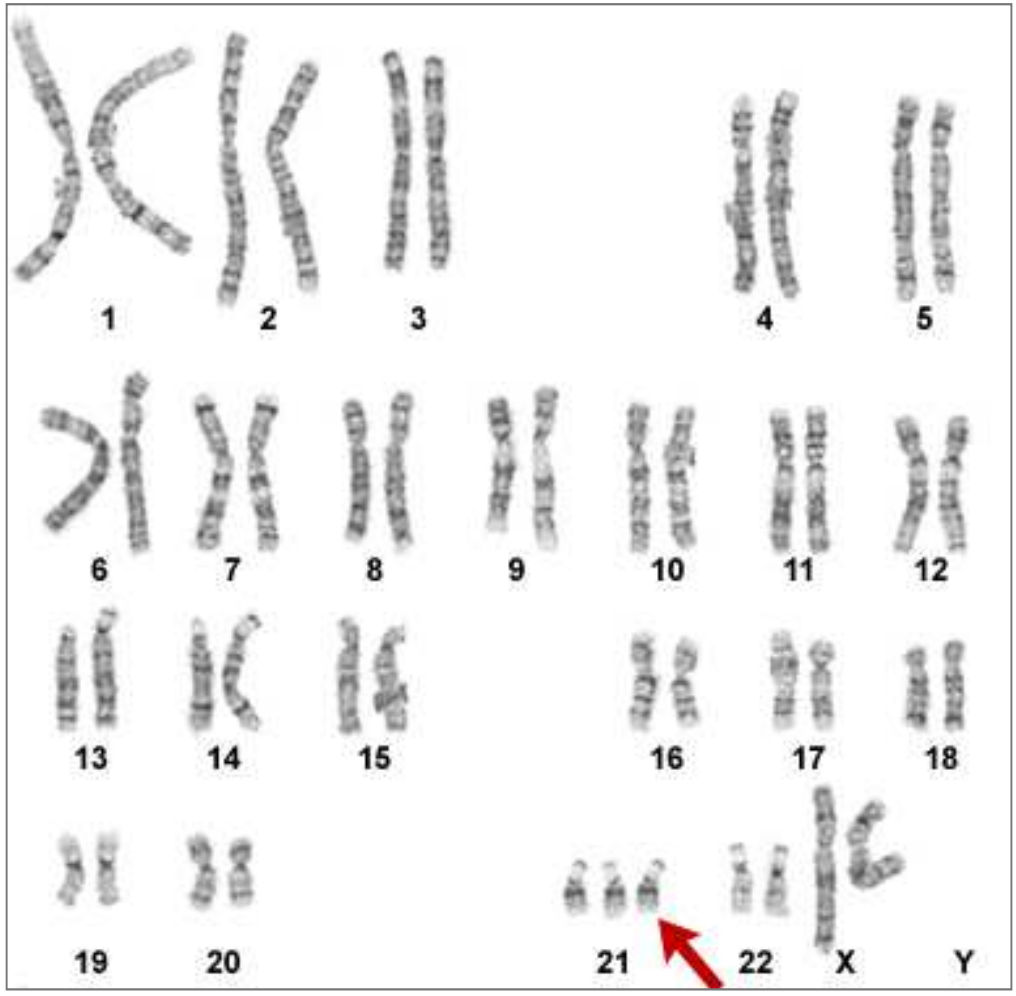
- 3 well-defined non mosaic chromosome numerical disorders compatible with postnatal survival:
  - Trisomy 21 (Down syndrome)
  - Trisomy 18
  - Trisomy 13

	Number	Approximate incidence
Total	**68.159**	
Trisomy 21	**82**	**1/830**
Trisomy 18	**9**	**1/7500**
Trisomy 13	**3**	**1/22700**
Other aneuploidy	**2**	**1/34000**
All aneuploidies	**96**	**1/700**

Incidence of autosomal aneuploidies in newborn surveys (Table 5-3)

Down syndrome (Trisomy 21)

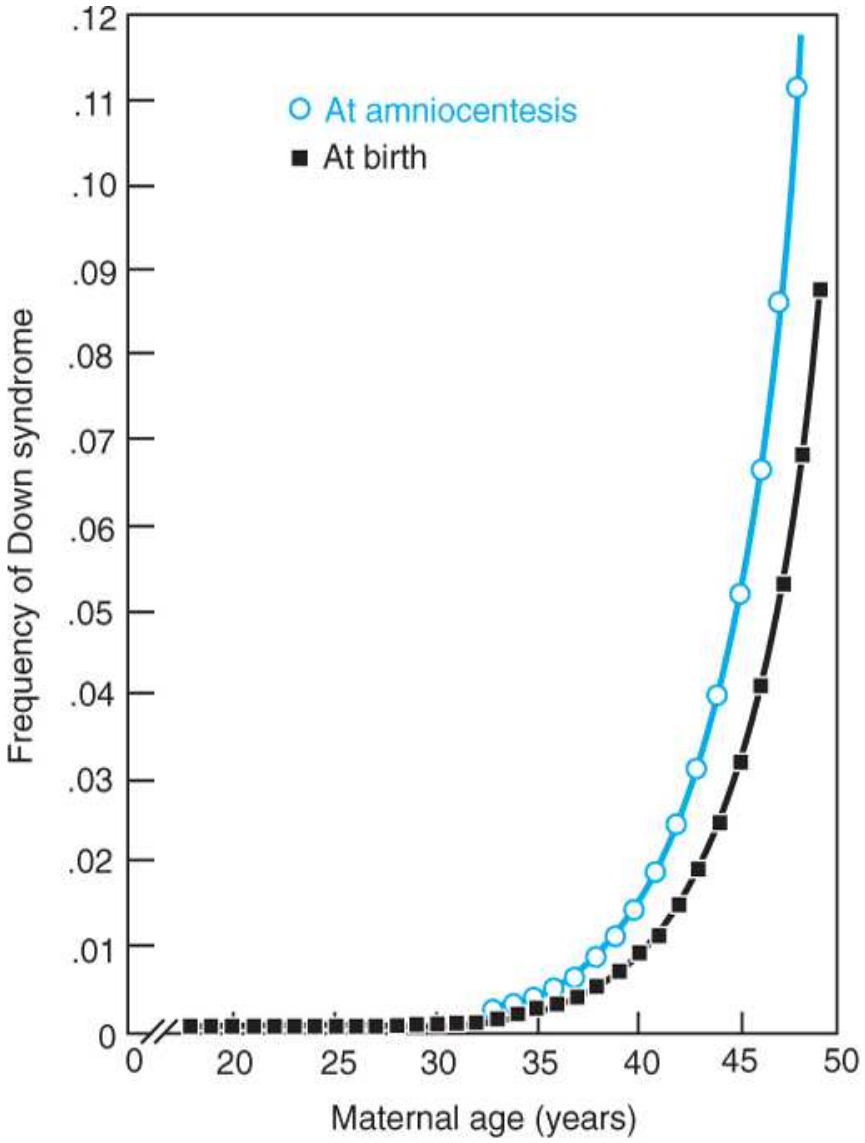
- First clinically described in 1866 by Langdon Down
  genetically explained in 1959
- 1/800 live births



47,XX,+21

Down syndrome (Trisomy 21)

- increased risk with higher maternal age

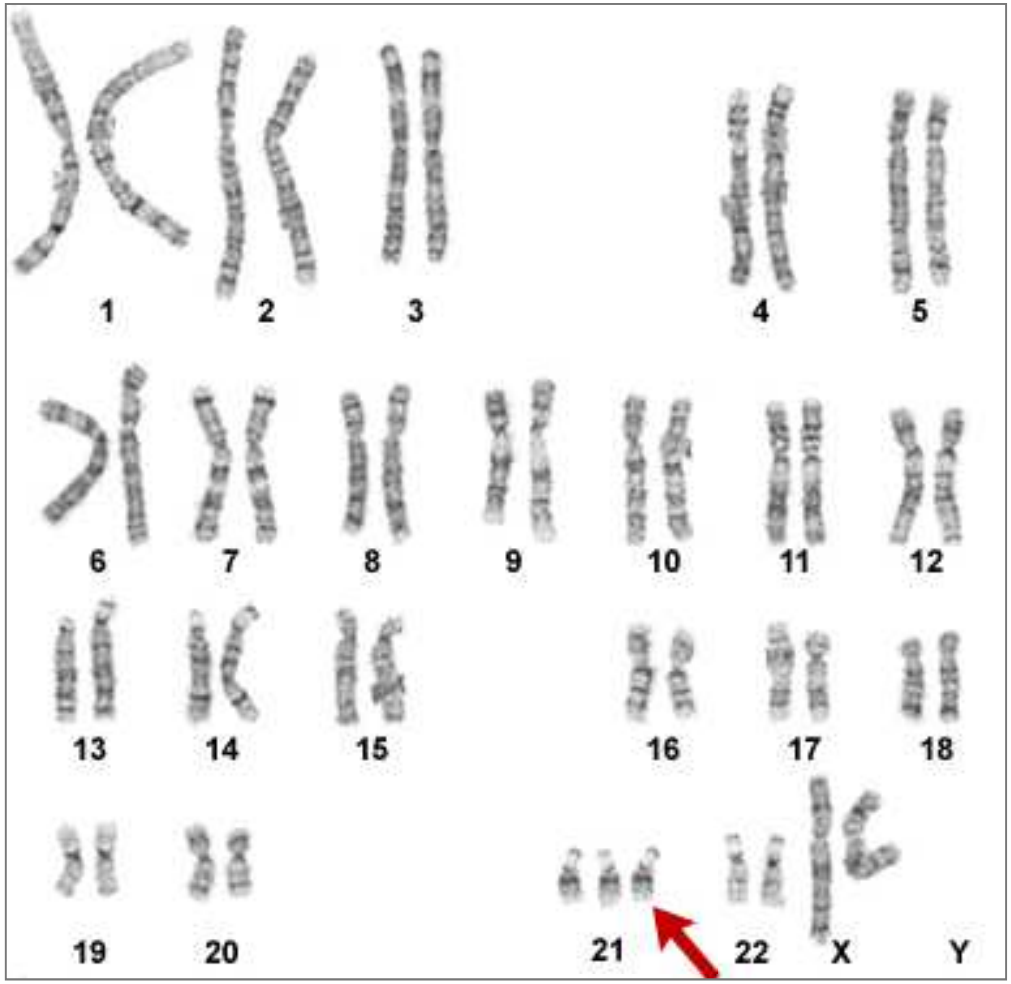


Mat age (years)	At birth	Amn Liq (16w)	CVS (9-11w)
15-19	1/1250	-	-
20-24	1/1400	-	-
25-29	1/1100	-	-
33	1/625	1/420	1/370
35	1/385	1/250	1/250
38	1/175	1/115	1/115
40	1/100	1/70	1/80
42	1/65	1/40	1/30
≥50	1/25	1/20	1/15

Table 15-1
(chapter 15)

Down syndrome (Trisomy 21)

- 95% = meiotic nondisjunction of the chromosome 21 pair
  - ↳ 90% maternal meiosis I, 10% paternal meiosis II
  - ↳ « old egg » model



STANDARD TRISOMY 21

Recurrence risk: 1%

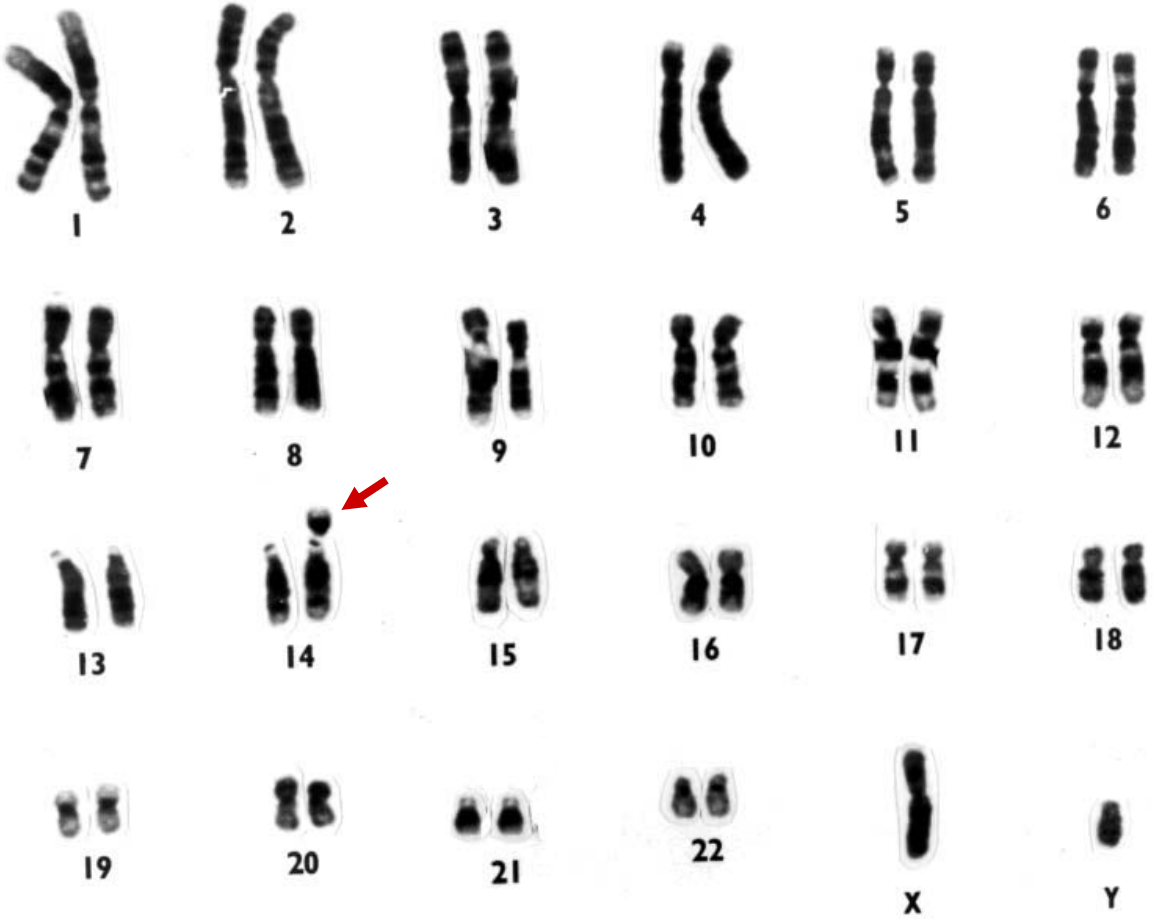
→ 1.4% <30y

→ age-related risk >30y

47,XX,+21

Down syndrome (Trisomy 21)

- 4% = Robertsonian Translocation
  der(14;21), der(21;22), der(21;21)

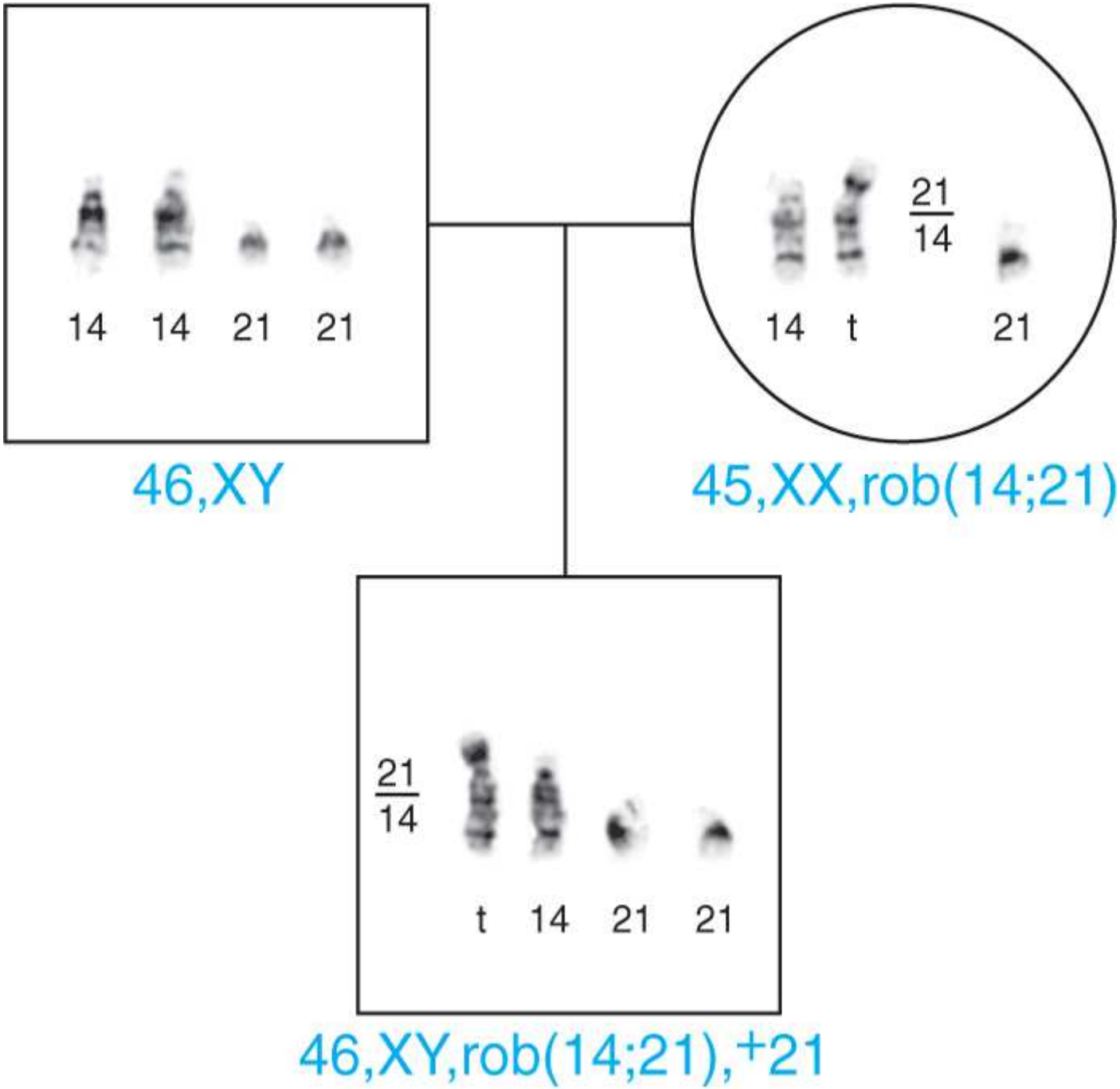


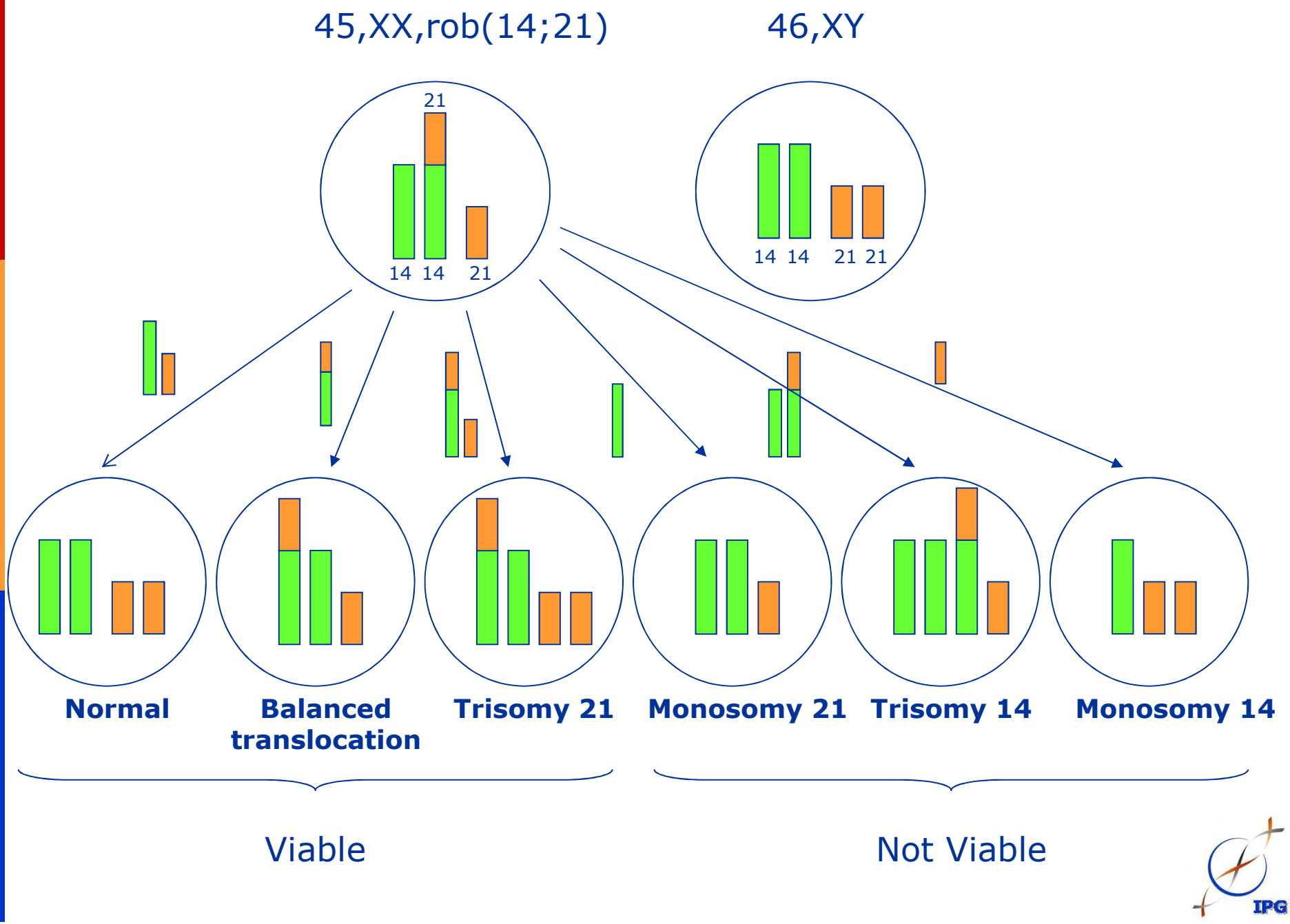
46,XY,rob(14;21)(q10;q10),+21

TRISOMY 21

by translocation

Recurrence risk: ↑↑

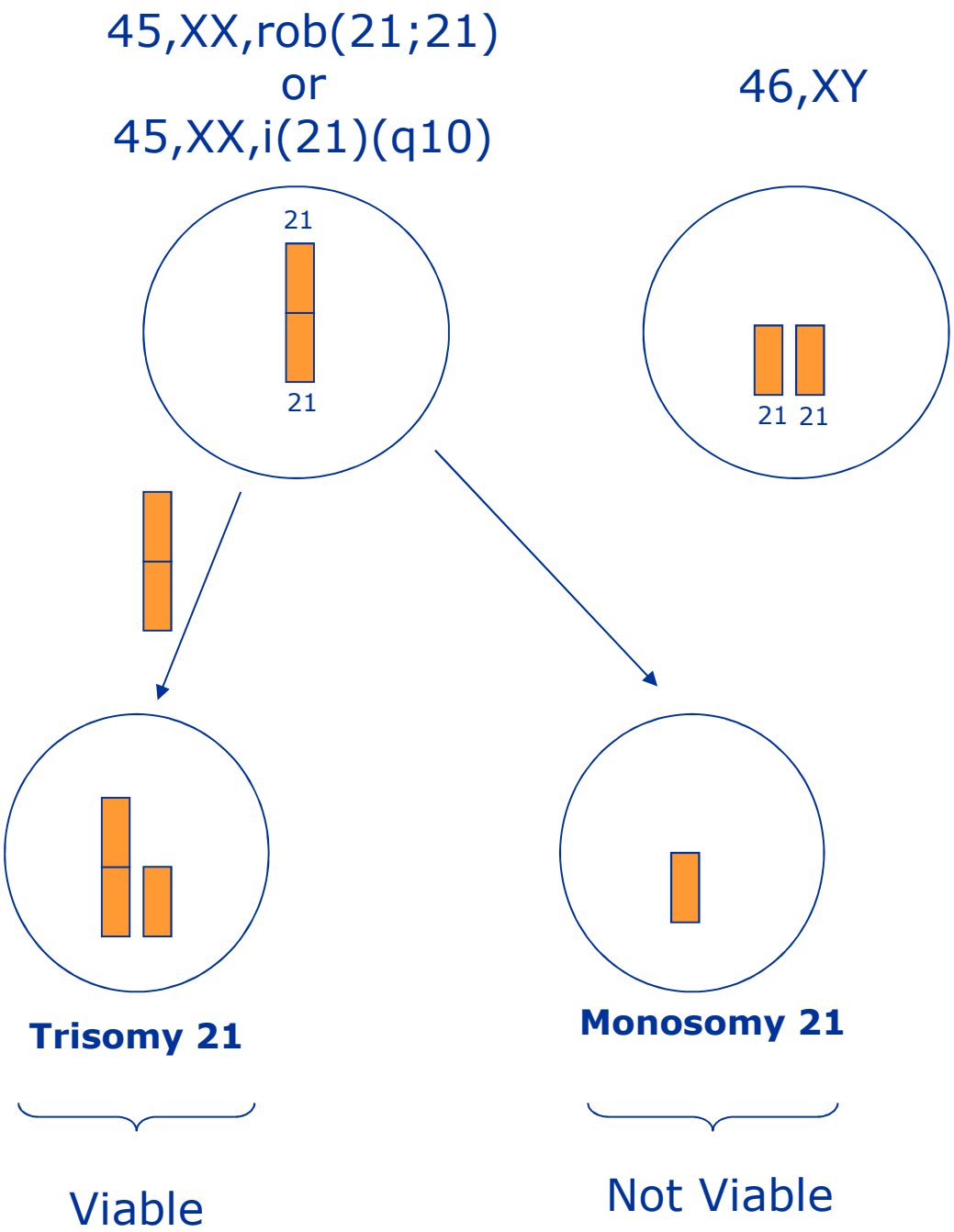



45,XX,rob(14;21)
46,XY
21
14 14 21
14 14 21 21
Normal
Balanced translocation
Trisomy 21
Monosomy 21
Trisomy 14
Monosomy 14
Viable
Not Viable

Down syndrome (Trisomy 21)

46,XY,rob(21;21)(q10;q10),+21

Or 46,XY,i(21)(q10)

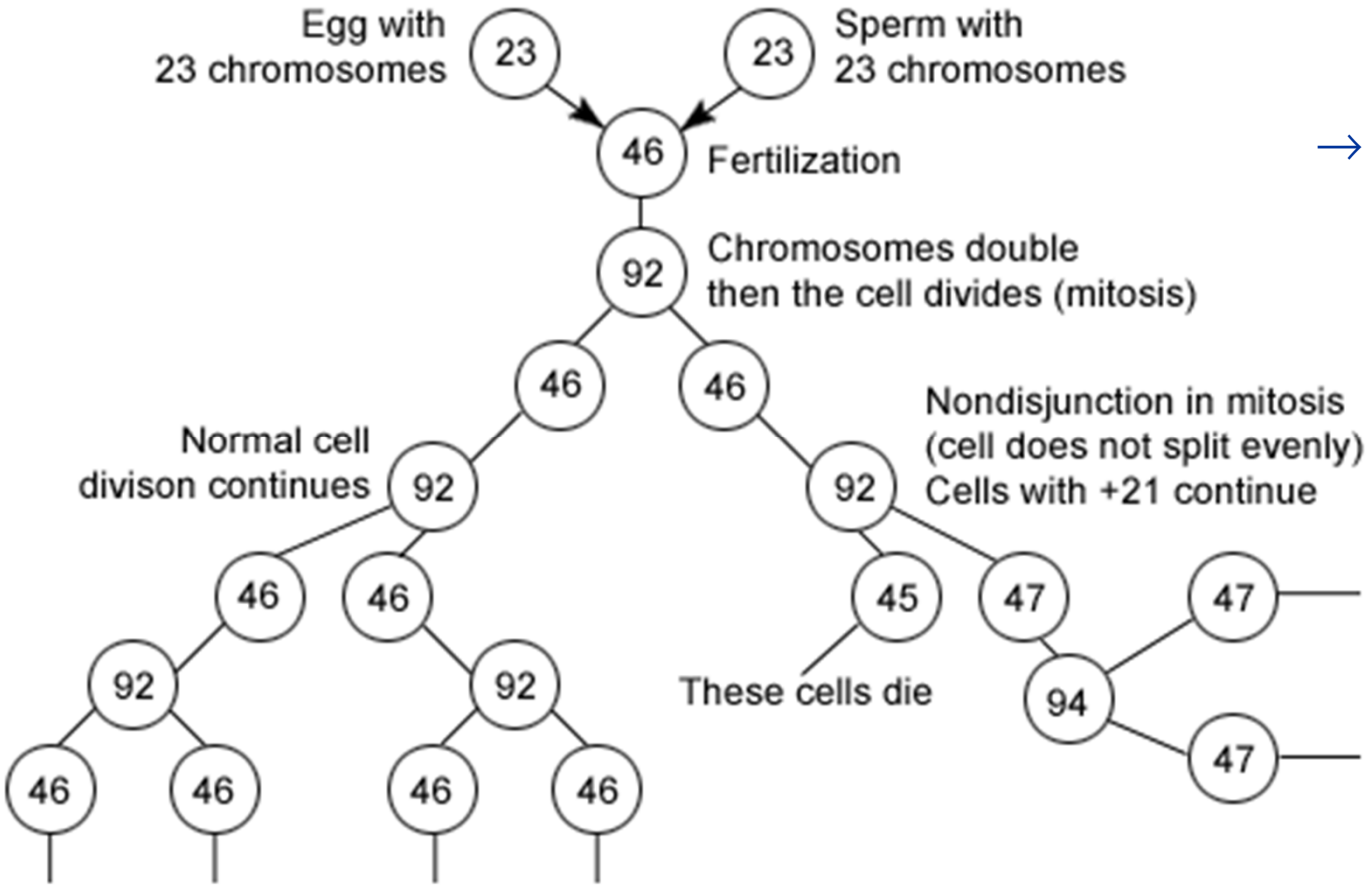

45,XX,rob(21;21)
or
45,XX,i(21)(q10)
46,XY
21
21
21 21
Trisomy 21
Monosomy 21
Viable
Not Viable

TRISOMY 21 by translocation : recurrence risk

	Maternal carrier 45,XX,rob	Paternal carrier 45,XY,rob
Rob (14;21)	10-15%	2.5%
Rob (21;22)	10-15%	2.5%
Rob (21;21) or i(21)	100%	100%

Down syndrome (Trisomy 21)

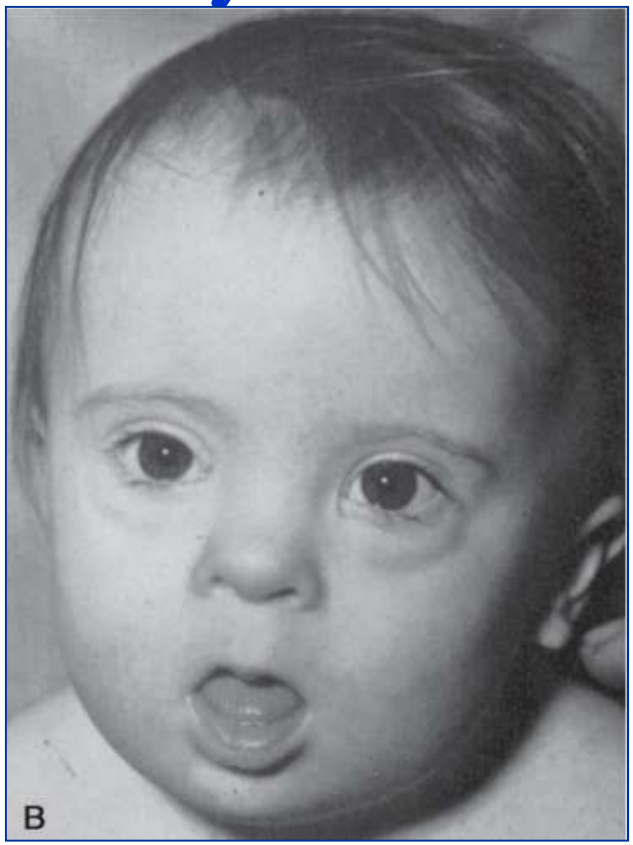
- 2%: mosaic Down syndrome

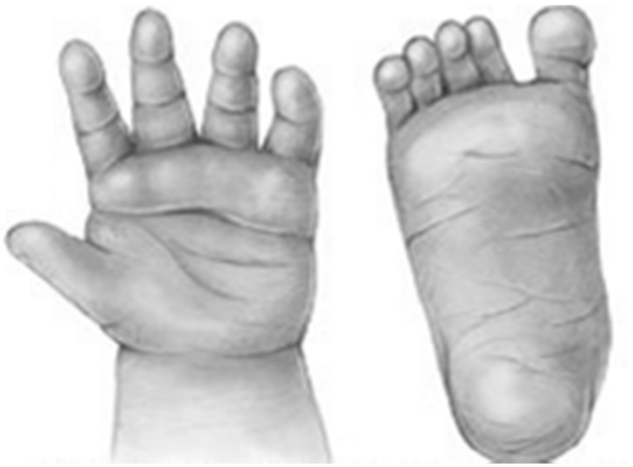


→ No recurrence risk

- <1%: Partial trisomy 21

Down syndrome: postnatal diagnosis





- Dysmorphic features
  - **Short stature**
  - Flattened face
  - Brachycephaly, flat occiput
  - Bilateral epicanthus
  - Upslanting palpebral fissures
  - Brushfield spots
  - Protruding tongue
  - Low-set-ears
  - **Short neck, with loose skin**
  - Short and broad hands
  - Single transverse palmar crease
  - Clinodactyly
  - « sandal » gap

Down syndrome (Trisomy 21)

- Hypotonia
- Mental retardation (IQ 30-60): 100%
- Congenital heart disease: 33%

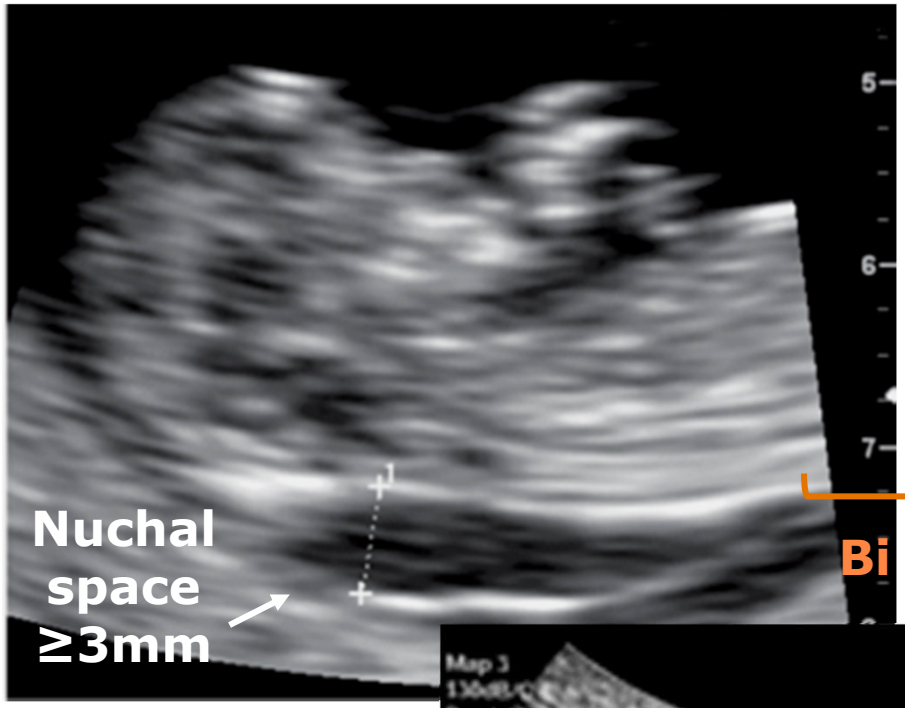
  (complete atrioventricular canal, …)
- Other congenital malformations

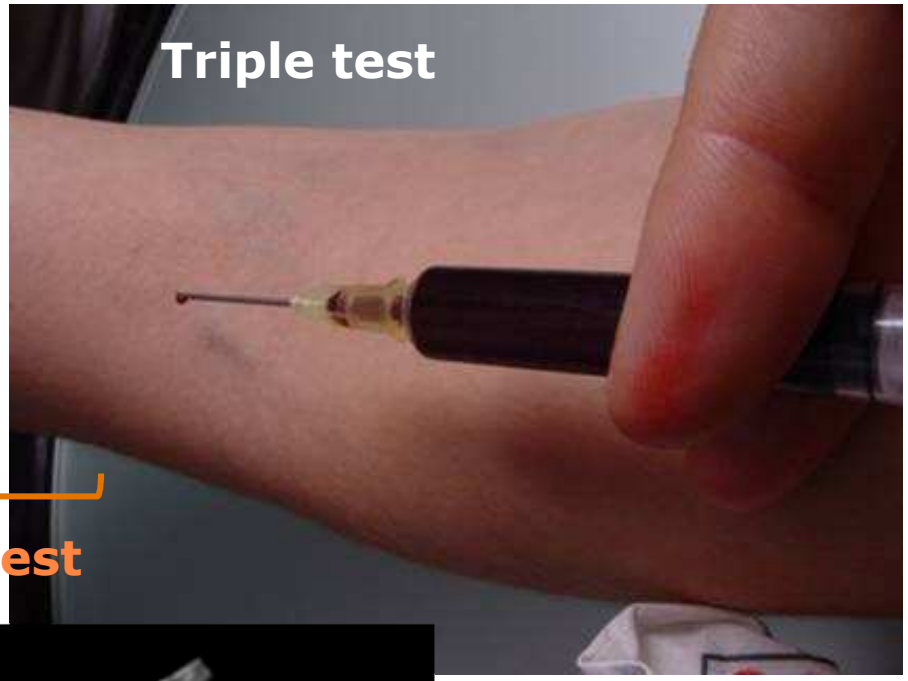
  (duodenal atresia, tracheoesophageal fistula,

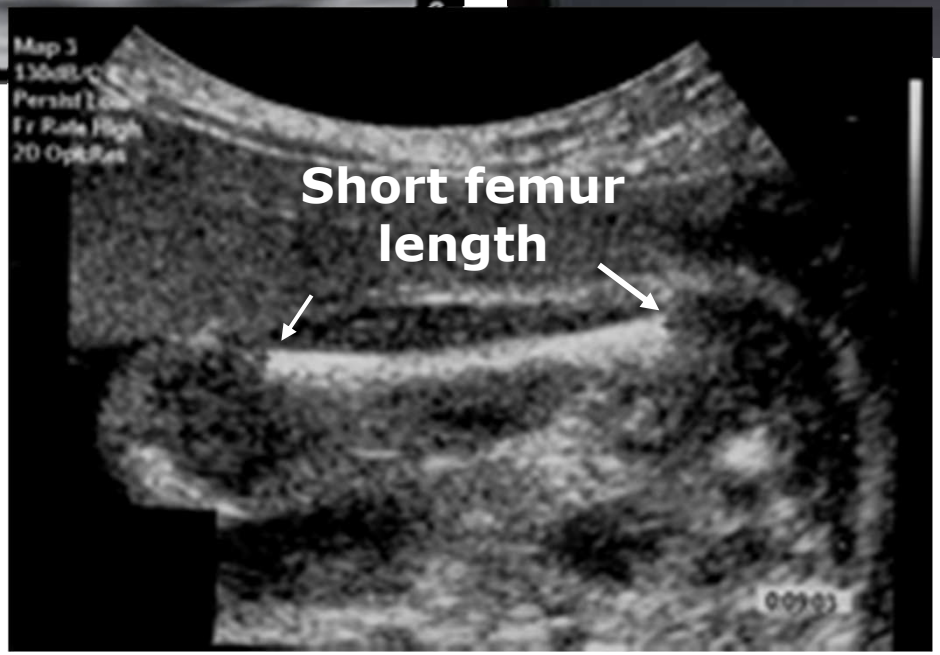
  congenital cataract, Hirshprung disease, …)
- Other increased risk

  (hypothyroidism, diabetes, leukemia, Alzheimer,…)

Down syndrome: prenatal diagnosis

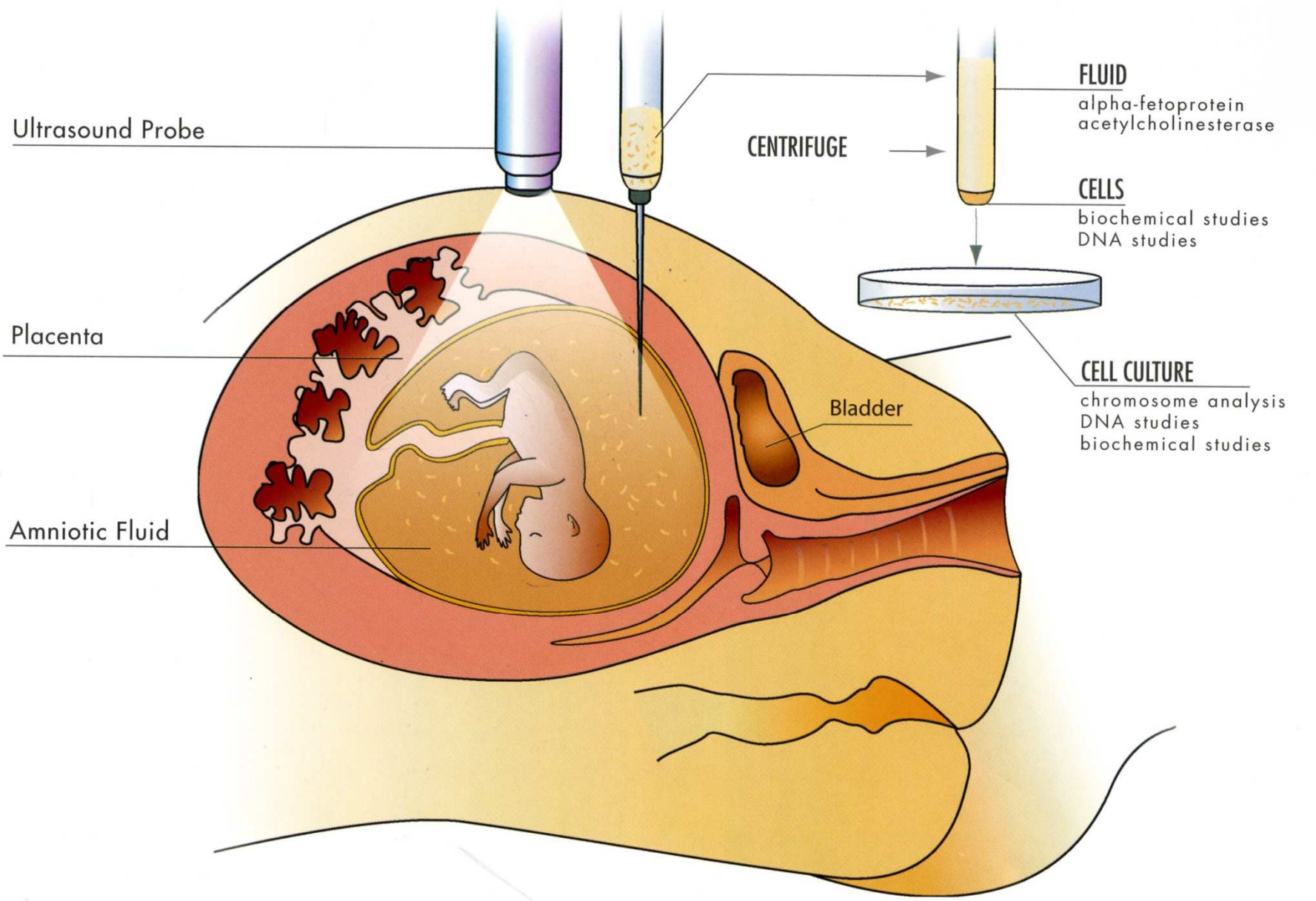




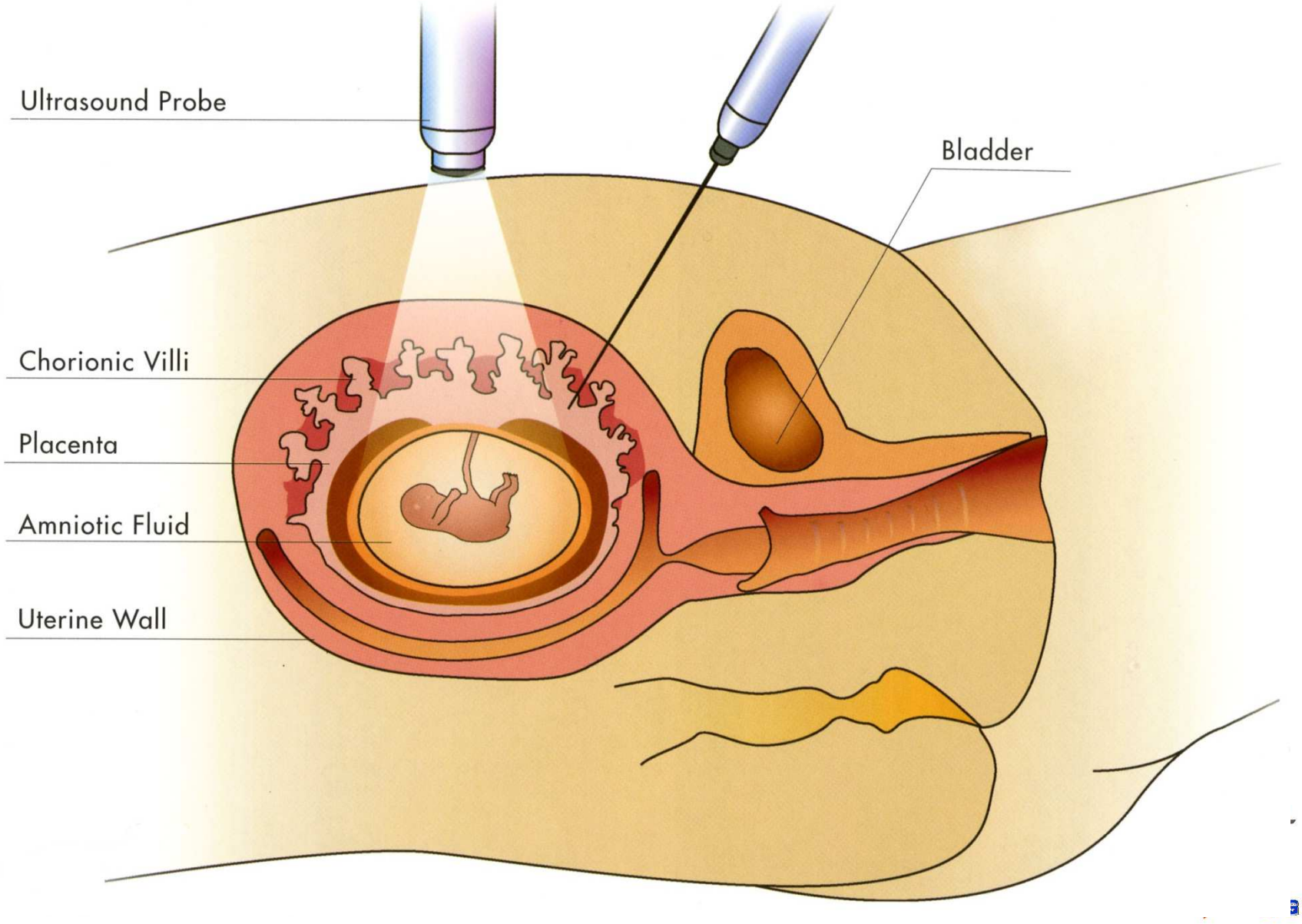


See chapter 15

Amniocentesis (15-16 gestational weeks)

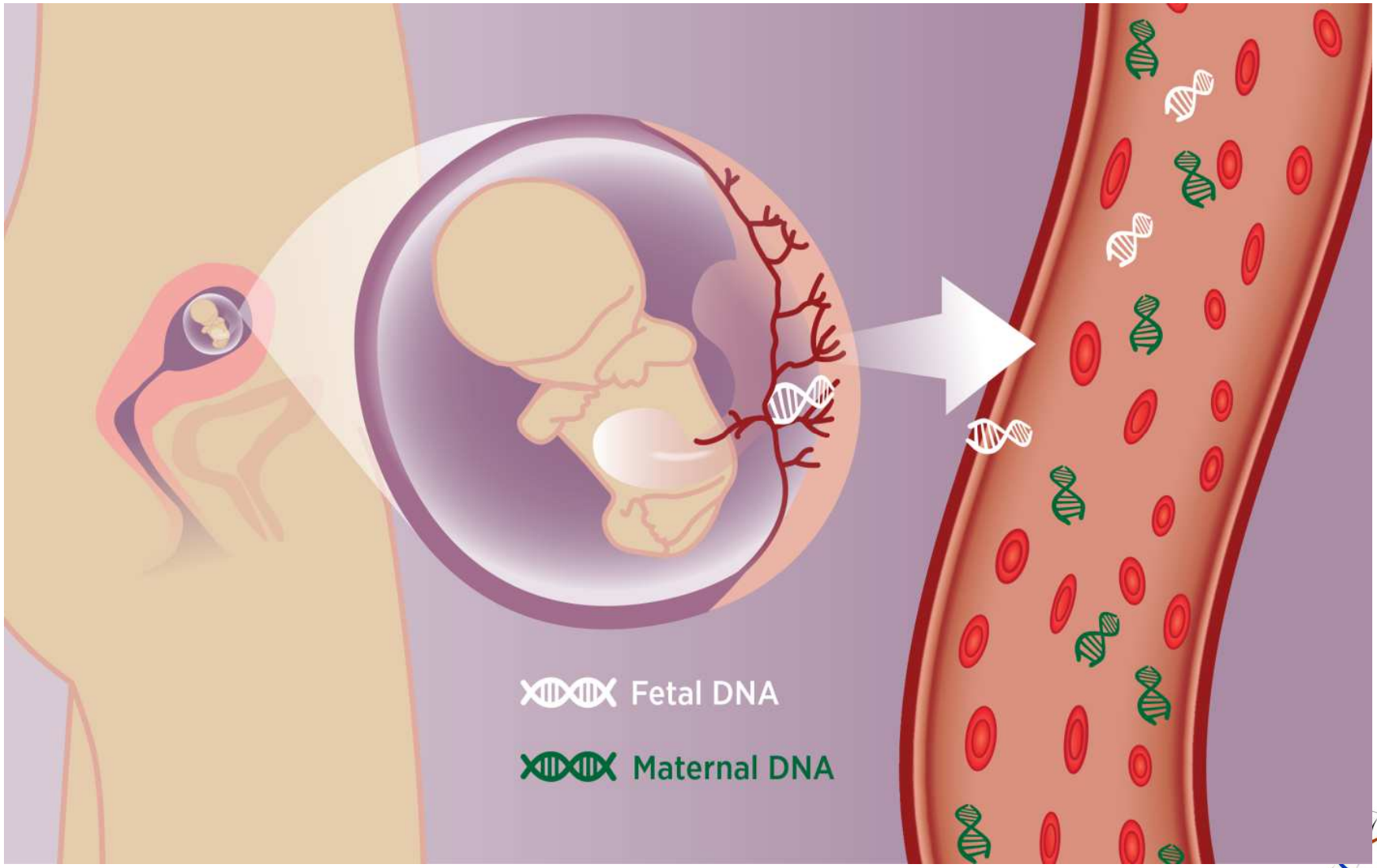


Chorious Villous Sample
(10 - 12 gestational weeks)

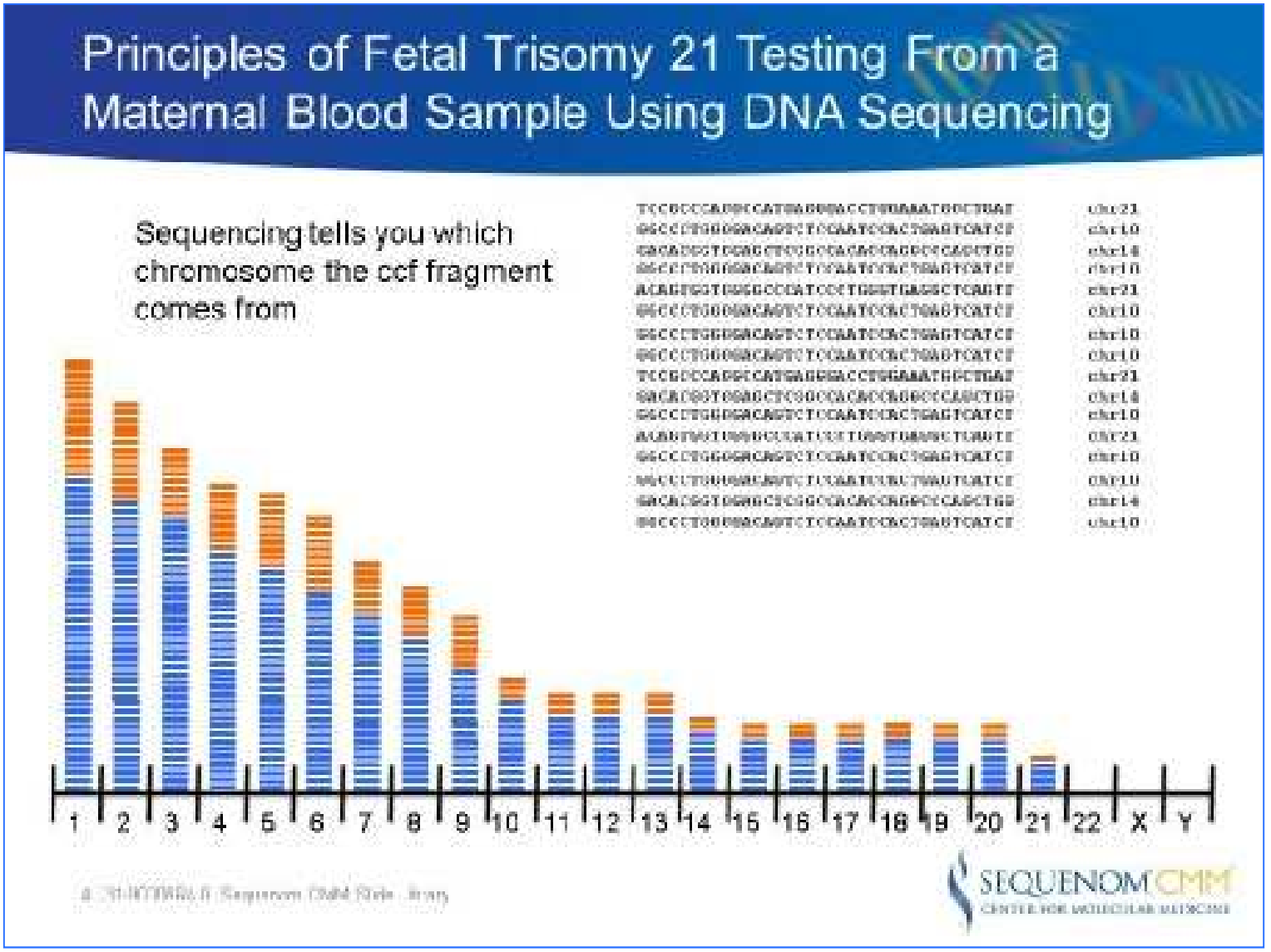


Down syndrome: NIPT

(non invasive prenatal testing, > 10w)



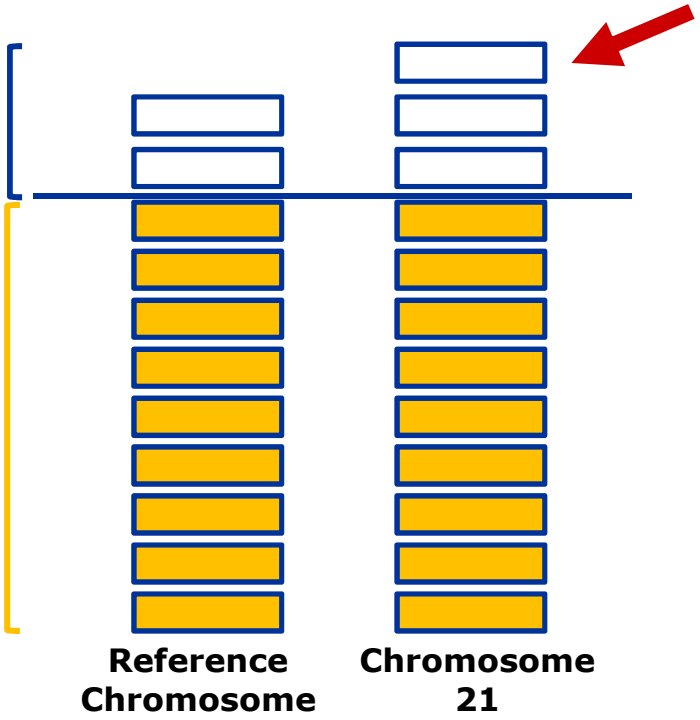
Next-generation sequencing techniques (Illumina, ion Proton)



NIPT

Foetal cffDNA

Maternel cfDNA

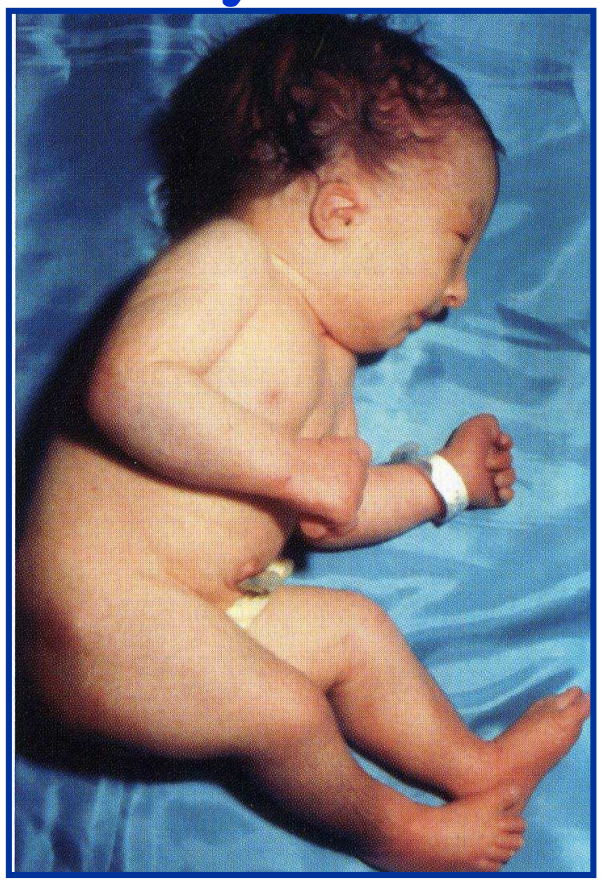


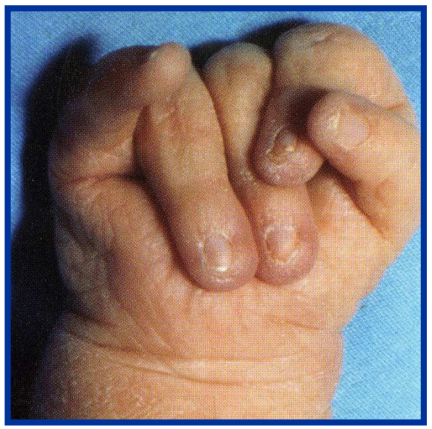
NIPT

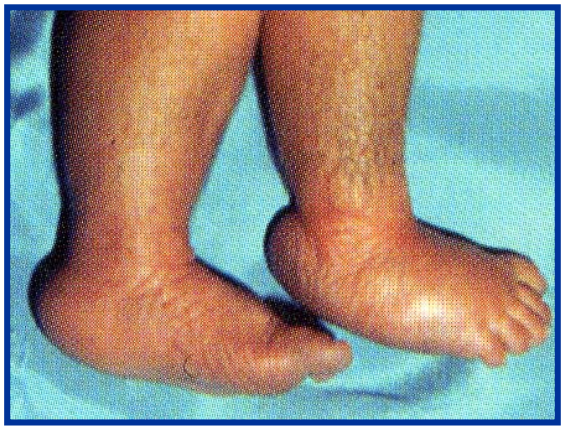
	Detection rate (Sensitivity)	FPR (Specificity)
Trisomy 21	> 99.5%	0.1%
Trisomy 18	98 %	0.1-0.4%
Trisomy 13	80-90 %	0.1-0.2%

Chiu et al, 2011;Chen et al, 2011; Ehrich et al, 2011; Palomaki et al, 2011; Bianchi et al, 2012; Sparks et al, 2012; Ashoor et al, 2012; Norton et al, 2012

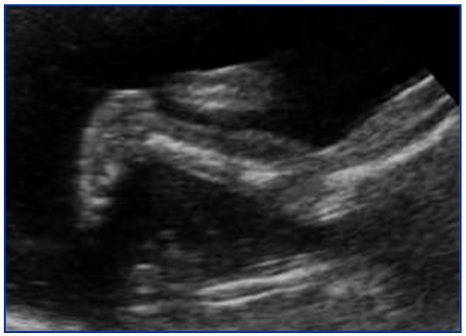
Trisomy 18

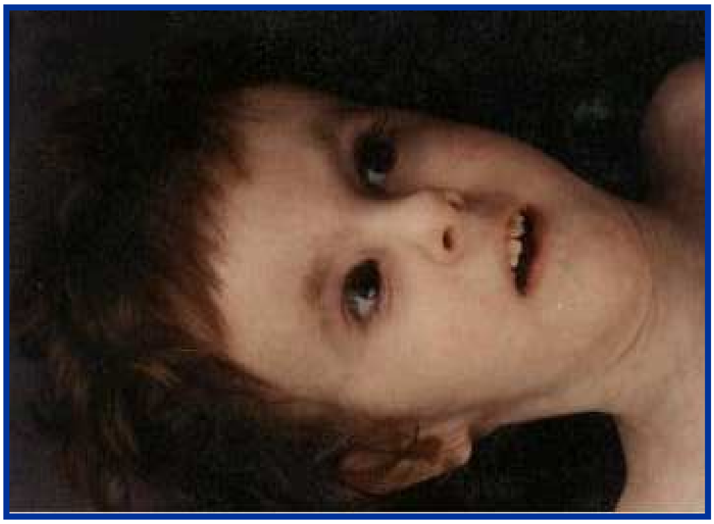


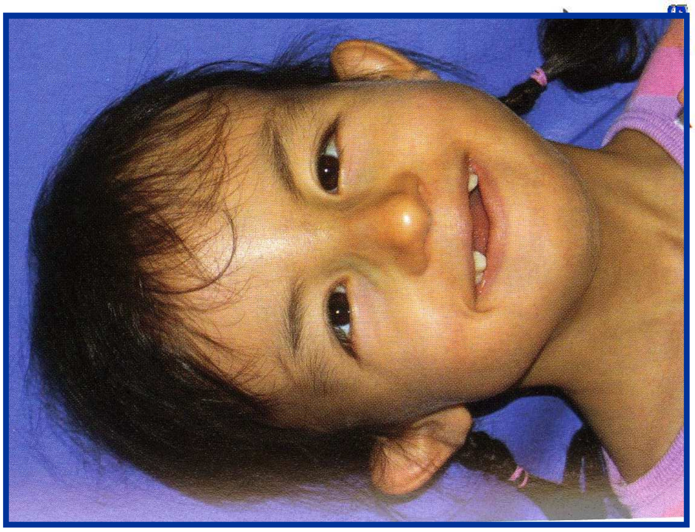




- Mental retardation
- **Failure to thrive**
- **Cardiac malformation**
- Hypotonia, then hypertonia
- Dysmorphic features
  - **-Prominent occiput**
  - -Retrognathia
  - -Low-set and malformed ears
  - -Short sternum
  - -Clenched hands
  - -Hypoplastic nails
  - **-Rocker-bottom feet**

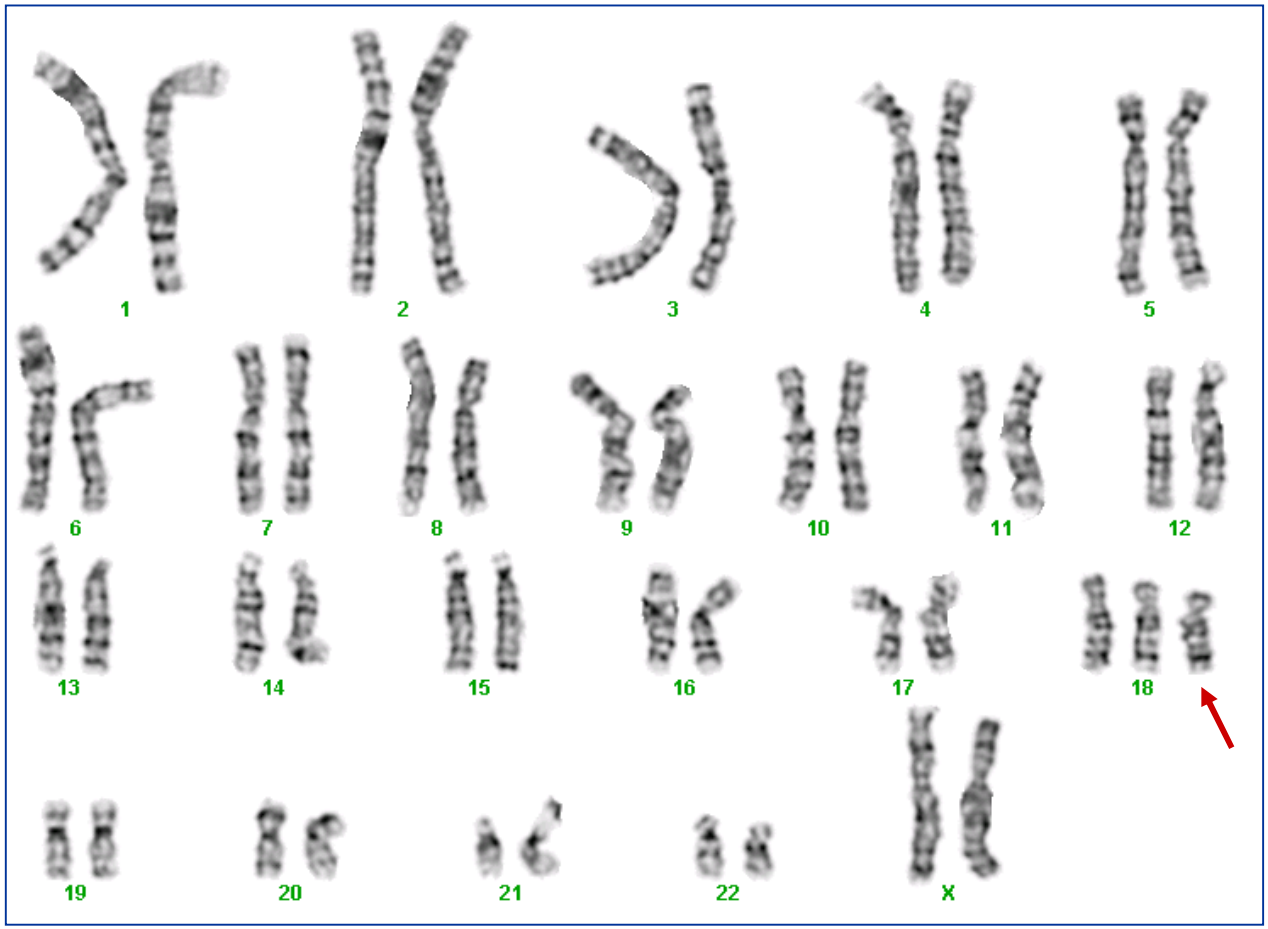






Trisomy 18

- 95% sponteaneously aborded
- 1 / 7500 live births
- increased risk with higher maternal age



80%: standard trisomy 18

20%: translocation (de novo or inherited)

47,XX,+18

Trisomy 13

- Mental retardation
- Growth retardation
- **CNS malformation** (holoprosencephaly,…)
- Congenital heart defect
- Urogenital anomalies
- Dysmorphic features

  -Microcephaly

  -Sloping forehead

  -Scalp defect

  -**Cleft lip/palate**

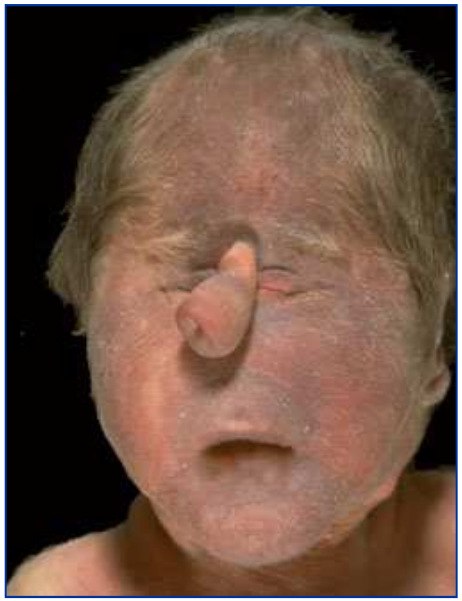
  -**Eye anomalies**

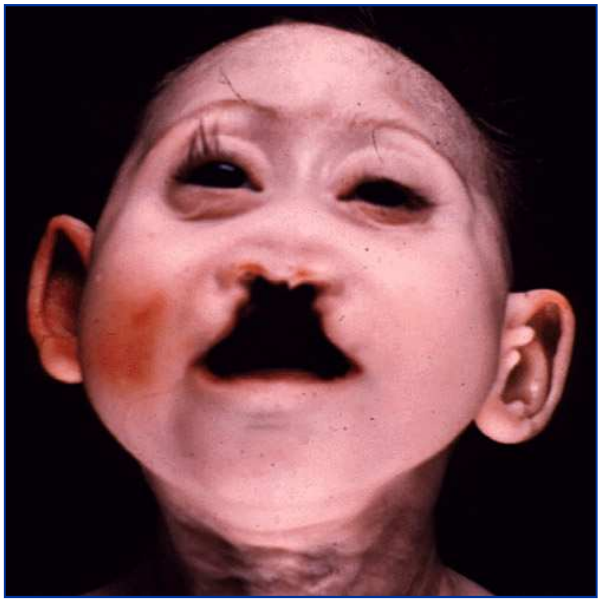
  (microphtalmia, iris coloboma,…)

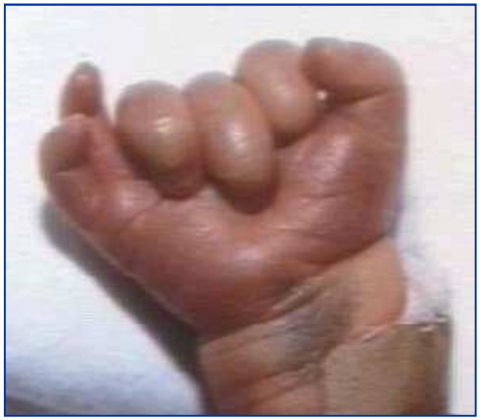
  -Post-axial **polydactyly**

  -Clenched hands

  -Rocker-bottom feet

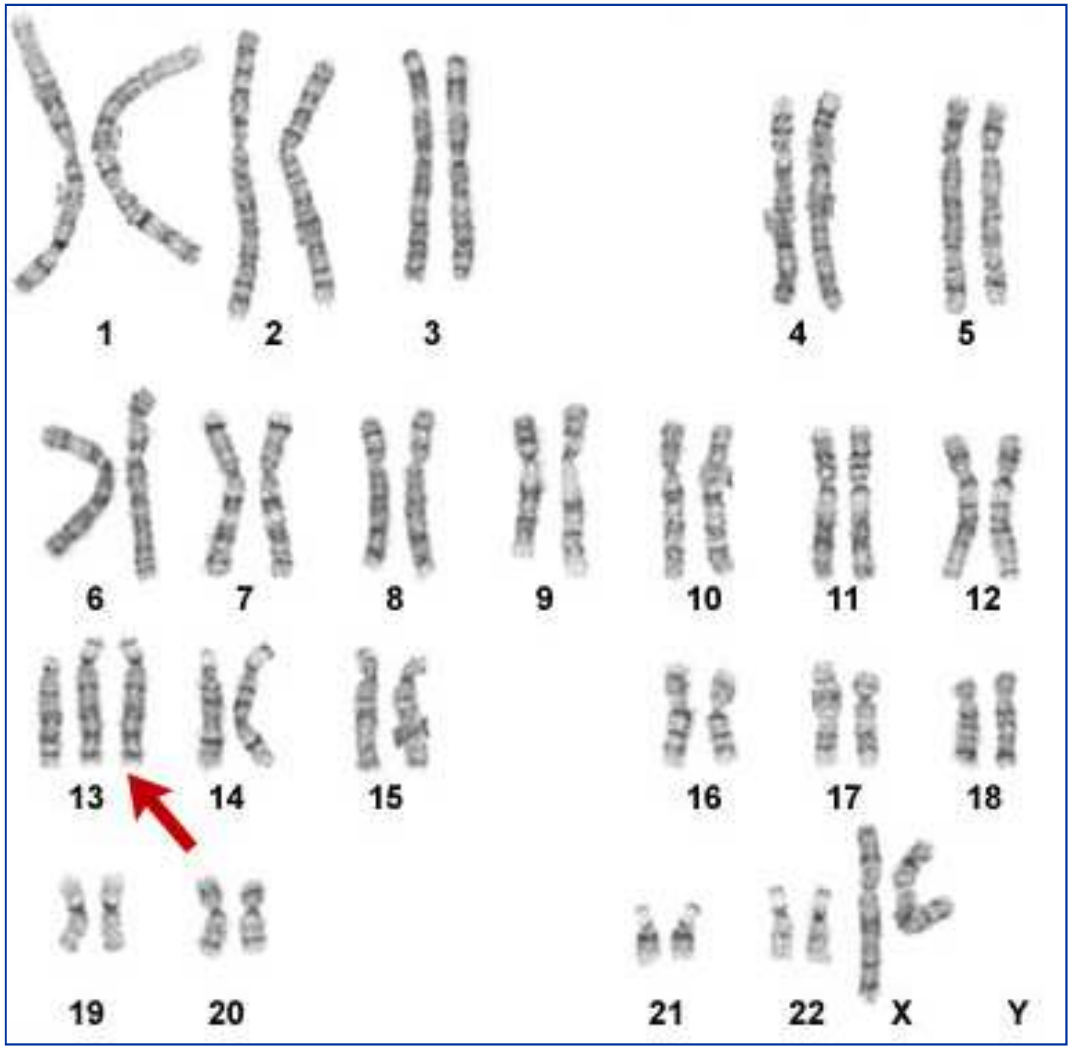






Trisomy 13

- 95% sponteaneously aborded
- 1 / 15000 – 1 / 25000 live births
- increased risk with higher maternal age



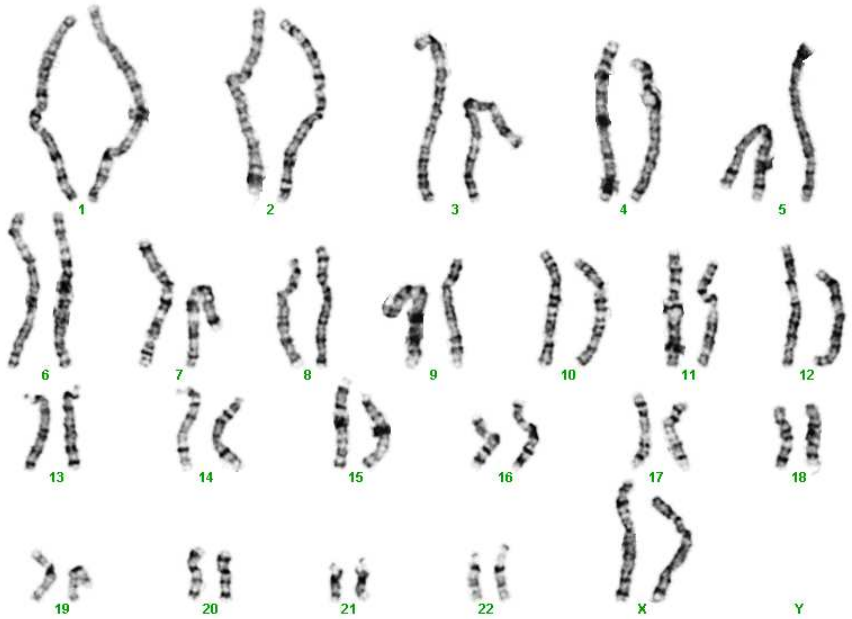
80%: standard trisomy 13

20%: unbalanced translocation

→ Low recurrence risk (<2%)

47,XX,+13

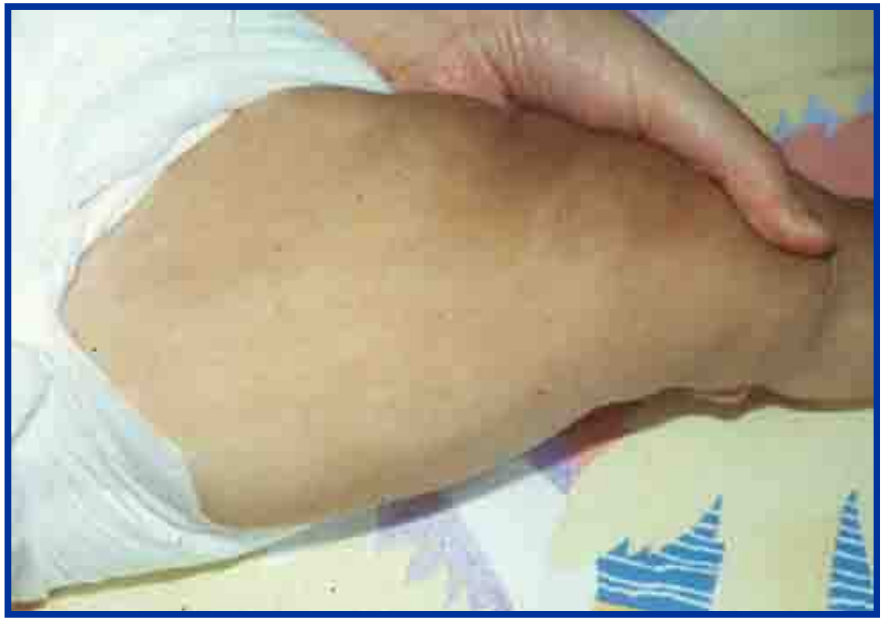
Other autosomes numerical anomalies

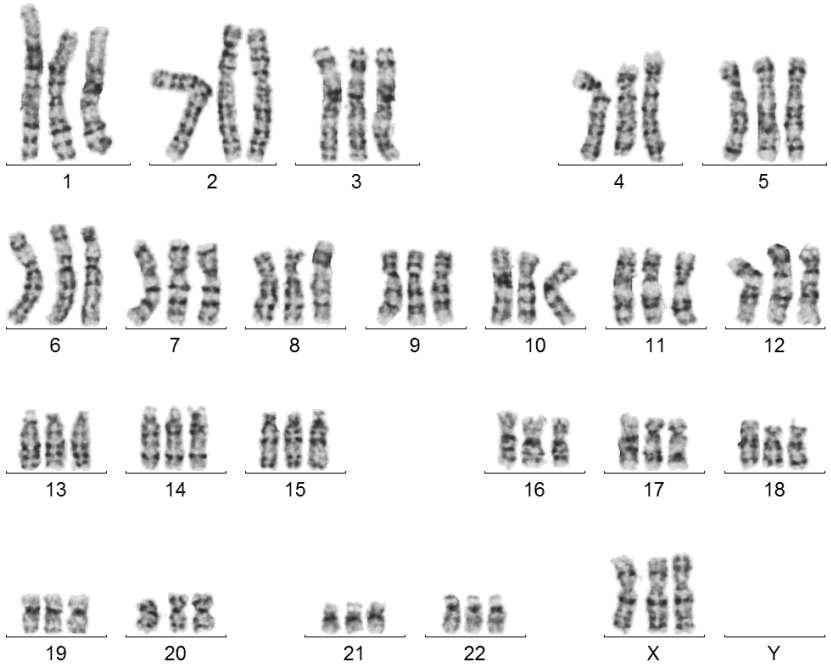


blood (leukocytes):

46,XX

Other autosomes numerical anomalies





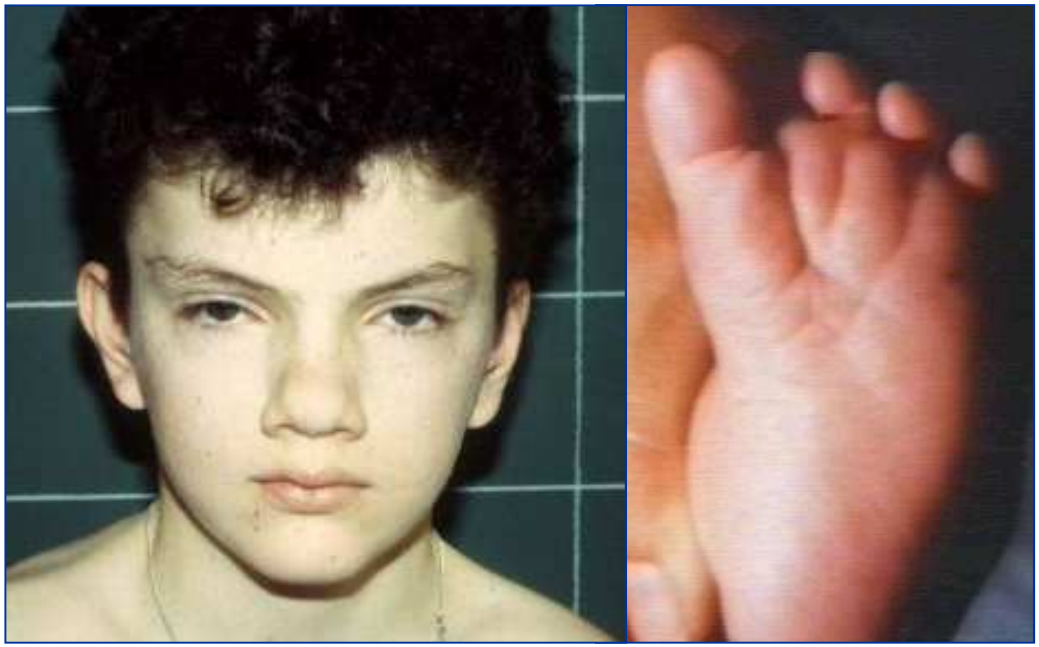
Skin biopsy (fibroblasts):

69,XXX

⇓

Mosaic Triploidy

Other autosomes numerical anomalies



Mosaic Trisomy 8

Mosaic Trisomy 9

Structural Autosomes Disorders

Structural autosomes abnormalities

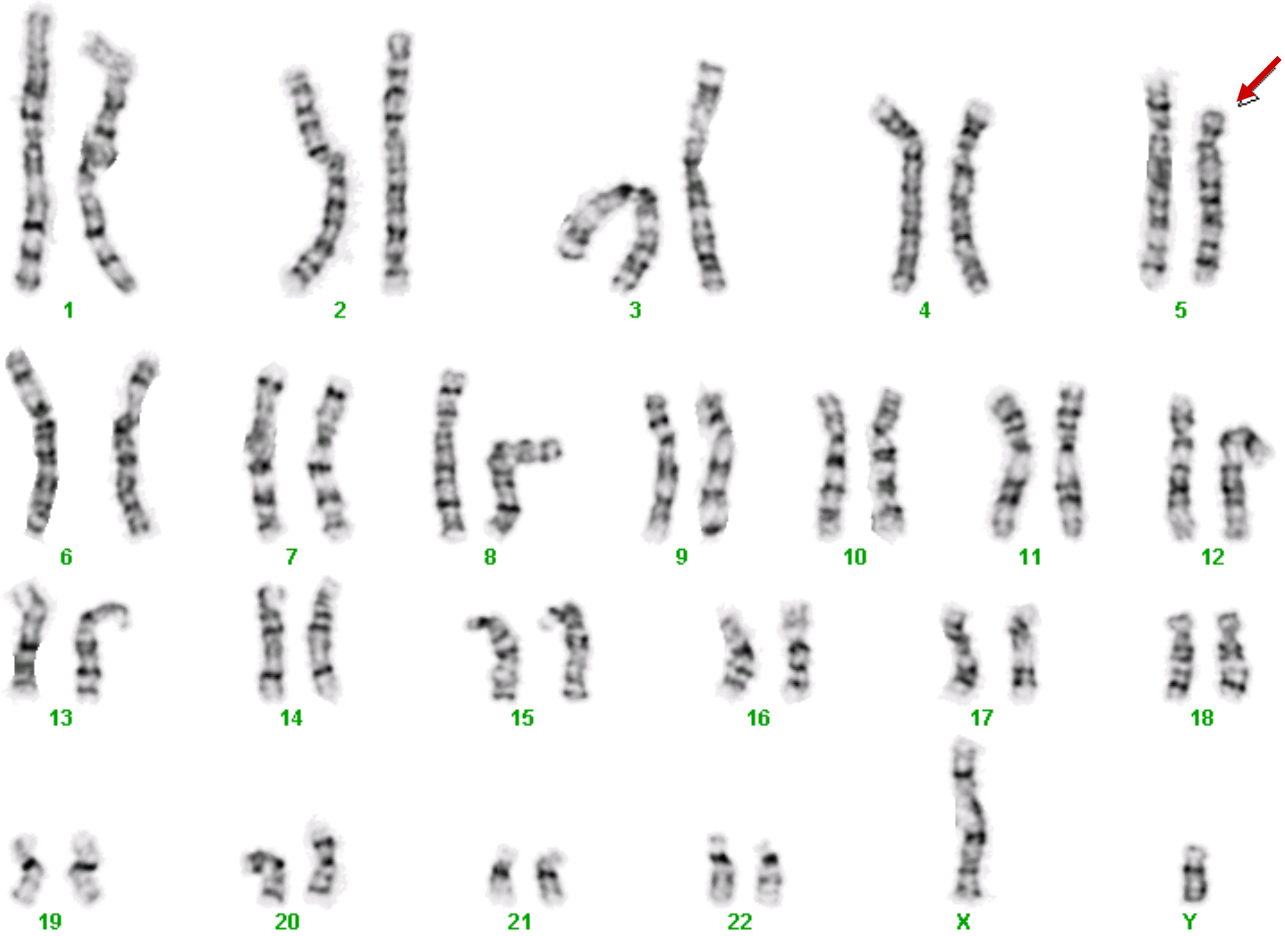
- Most of unbalanced rearrangements are spontaneously aborted (85%) – *see table 5-5*
- But some of them are viable

	Number	Approximate incidence
Total	**68.159**	
Balanced rearrangement	**139**	**1/490**
Unbalanced rearrangement	**43**	**1/1585**
All structural rearrangements	**182**	**1/375**

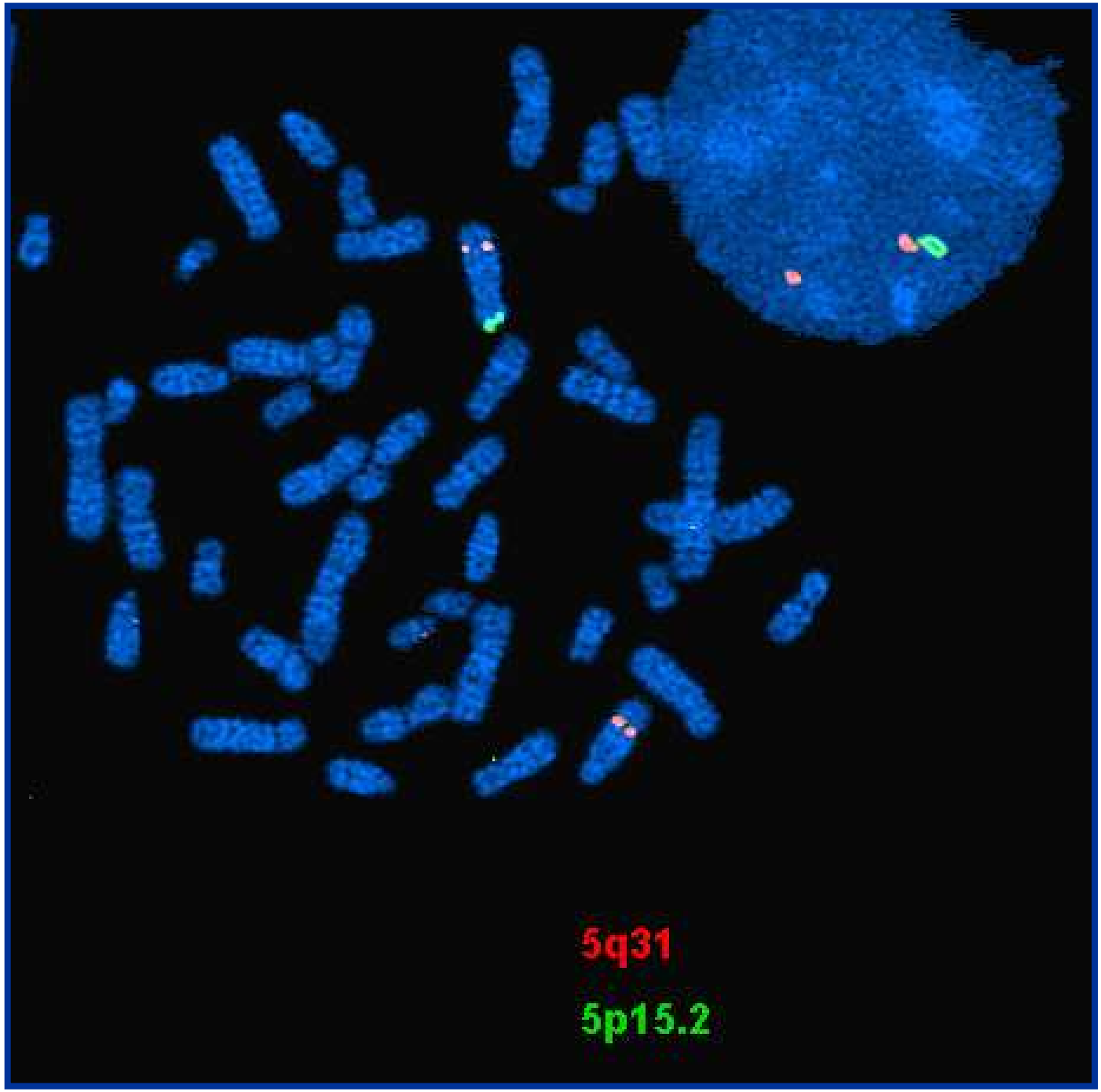
Incidence of structural abormalies in newborn surveys (Table 5-3)

Autosomal deletion syndromes

- cytogenetically visible autosomal deletion: 1/7000 live births
- some clearly recognizable syndromes
  (5p-, 4p-, 9p-, 9q-, 18p-, …)



example: 46,XY, del(5)(pter→p14.2)


5q31
5p15.2

Cri du Chat syndrome (5p-)

- Mental retardation
- Cry like a mewing cat
- Heart defect
- Dysmorphic features

  -Microcephaly

  -Hypertelorism

  -Epicanthal folds

  -Low-set ears

  -Preauricular tags

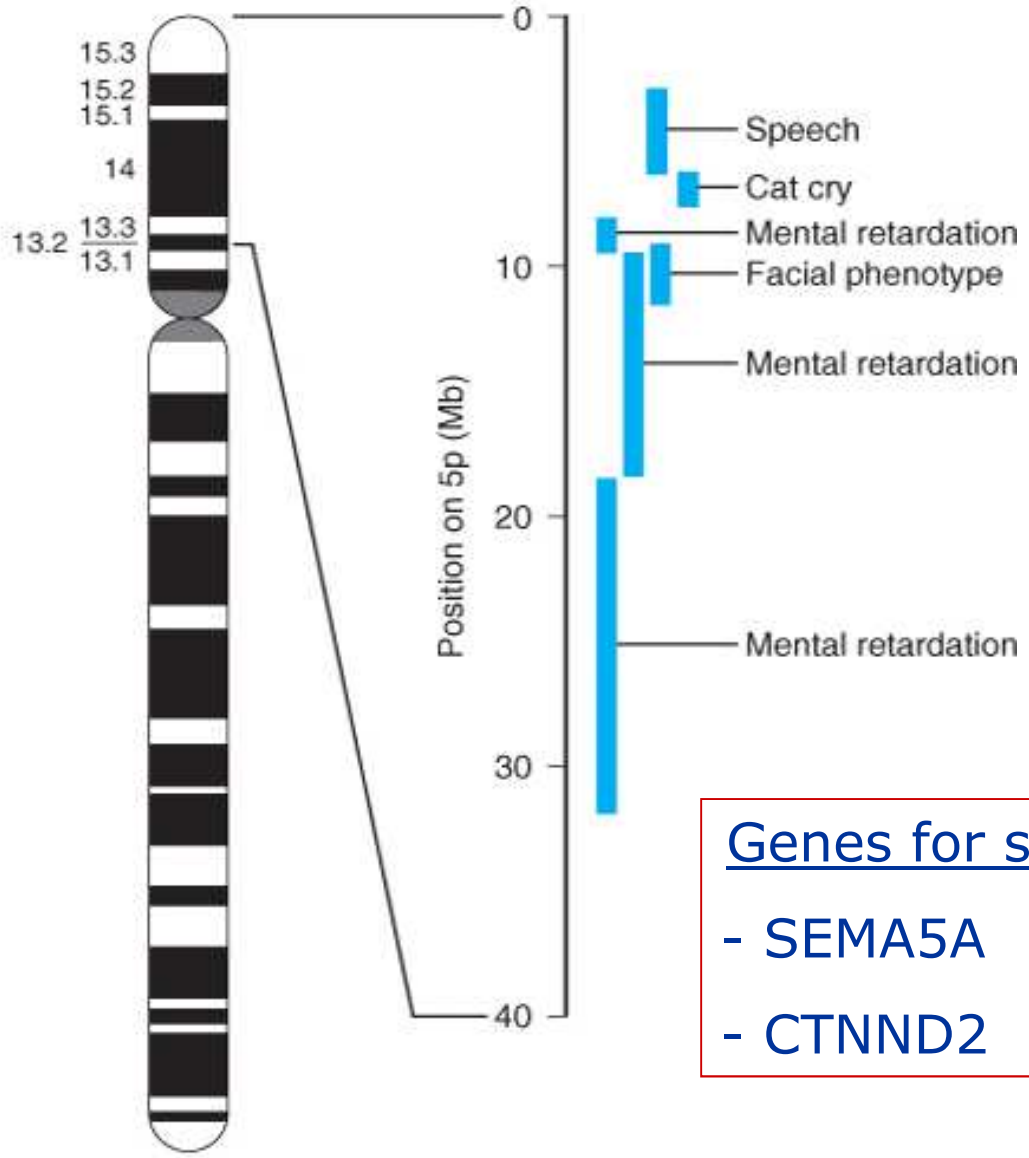
  -Micrognathia

85-90%: de novo (sporadic)

10-15%: parental translocation

Cri du Chat syndrome (5p-)

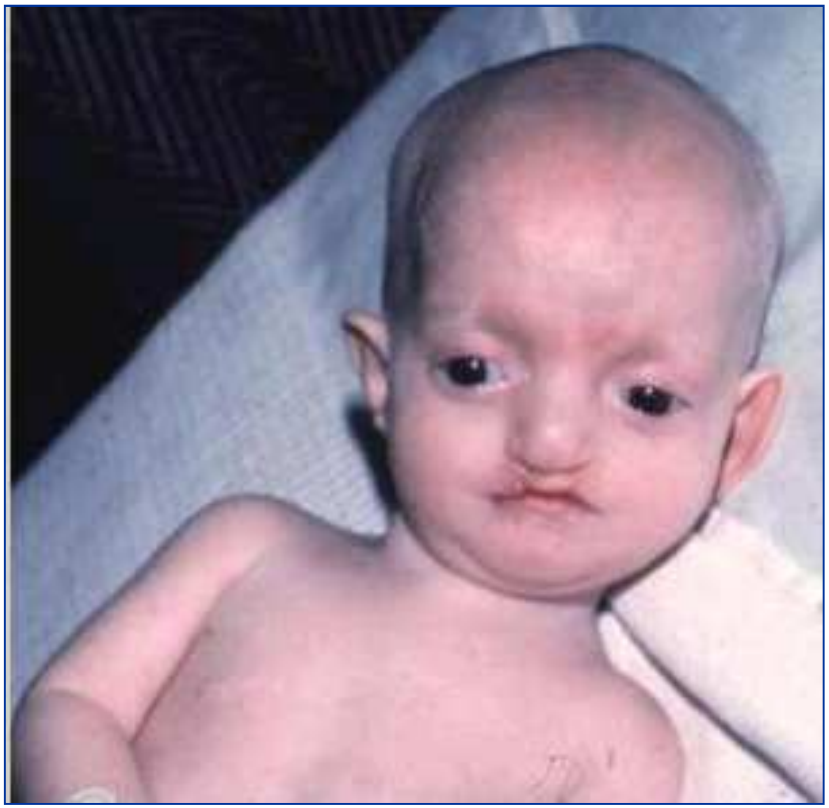
- Genotype-Phenotype correlations



Genes for severe MR

- SEMA5A
- CTNND2

Autosomal deletion syndromes: other examples



4p deletion (Wolf-Hirshhorn)

9p deletion

Genomic disorders:

Microdeletion and microduplication syndromes

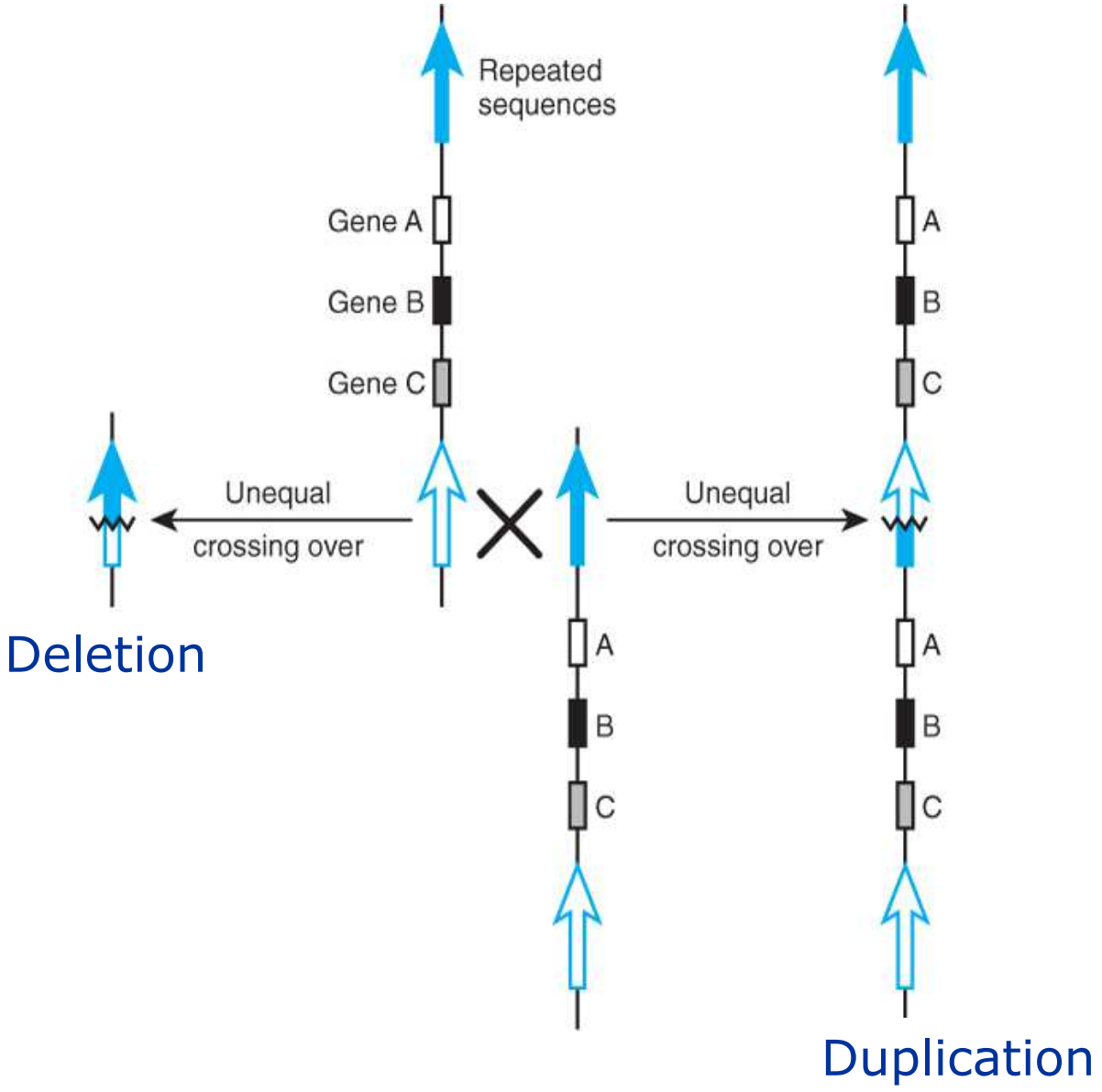
- small deletions or duplications, most often cryptic

  ⇒ - high-resolution karyotype
  - FISH analysis
  - MLPA (multiple ligation-dependant probe assay)
  - array-CGH

- several clinically recognizable syndromes
  including « contigous gene syndromes »

Genomic disorders:

Microdeletion and microduplication syndromes



Genomic disorders:

Microdeletion syndromes

Disorder	Location	Rearrangement Type	Rearrangement Size (kb)
Smith-Magenis	17p11.2	Deletion	4000
HNLPP	17p12	Deletion	1400
Velo-cardio-facial	22q11.2	Deletion	3000,1500
Prader Willi/ Angelman	15q11-q13	Deletion	3500
Williams	7q11.23	Deletion	1600
Neurofibromatosis	17q11.2	Deletion	1400
Sotos	5q35	Deletion	2000
Azoospermia (AZFc)	Yq11.2	Deletion	3500

Examples of genomic disorders due to recombination between low-copy repeat sequences (Table 6-1)

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Genomic disorders:

microduplication syndromes

Disorder	Location	Rearrangement Type	Rearrangement Size (kb)
Charcot-Marie-Tooth1A	17p12	Duplication	1400
Cat-eye syndrome	22q11.2	Triplication	3000,1500

Examples of genomic disorders due to recombination between low-copy repeat sequences (Table 6-1)

Genomic disorders:

new microduplication syndromes

Disorder	Location	Rearrangement Type	Rearrangement Size (kb)
Charcot-Marie-Tooth1A	17p12	Duplication	1400
Cat-eye syndrome	22q11.2	Triplication	3000,1500
(Smith-Magenis)	17p11.2	Dup 17p11.2	4000
(Velo-cardio-facial)	22q11.2	Dup 22q11.2	3000,1500
(Prader Willi/ Angelman)	15q11-q13	Dup 15q11-q13	3500
(Williams)	7q11.23	Dup 7p11.23	1600
(Neurofibromatosis)	17q11.2	Dup 17q11.2	1400

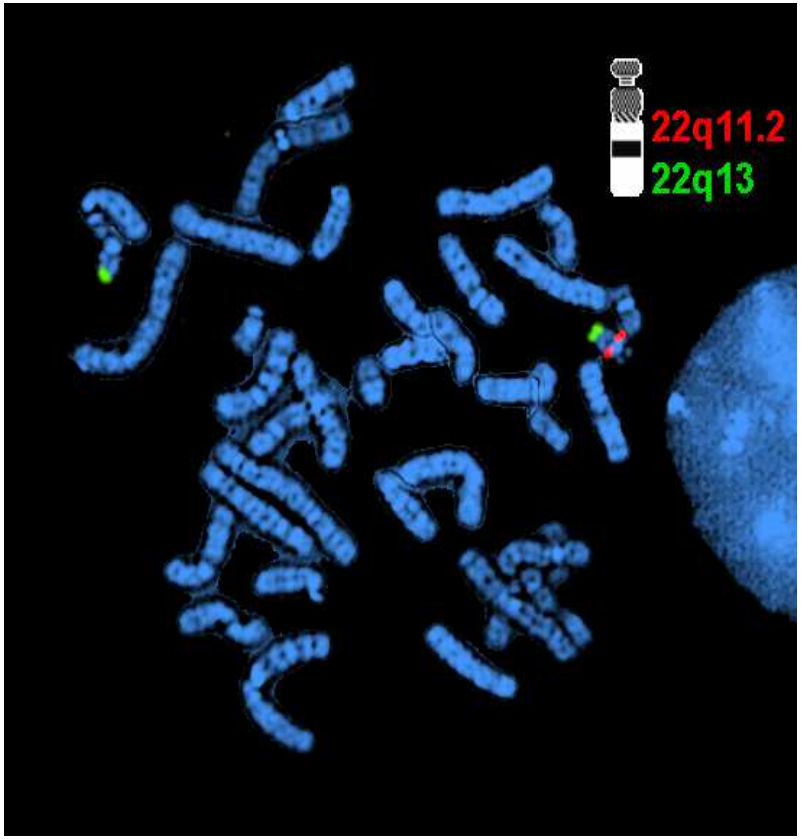
Examples of genomic disorders due to recombination between low-copy repeat sequences (Table 6-1)

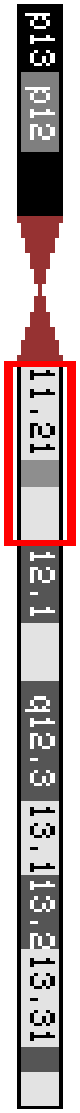
IPG

Region 22q11

Deletion

Velo-cardio-facial syndrome



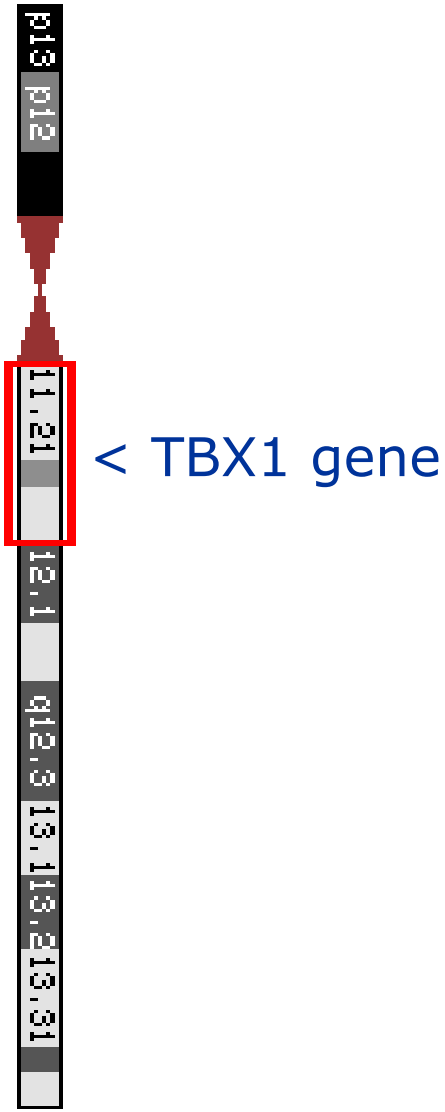


Region 22q11

Deletion

Velo-cardio-facial syndrome

- 1/2000-1/4000 live births
- Learning difficulties (60%)
- Psychiatric disorders (10%)
- Heart defects (65%)
- Velar incompetence (95%)
- Facial dysmorphy



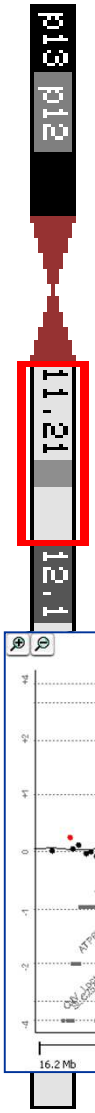
Region 22q11

Deletion

Velo-cardio-facial syndrome

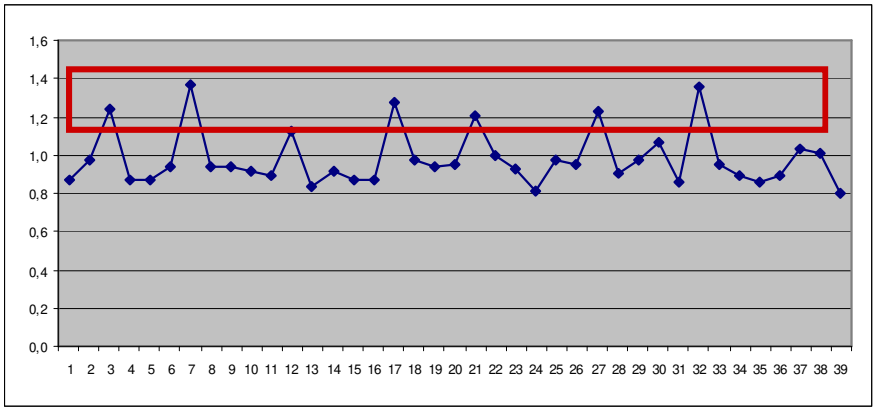
- 1/2000-1/4000 live births
- Learning difficulties (60%)
- Psychiatric disorders (10%)
- Heart defects (65%)
- Velar incompetence (95%)
- Facial dysmorphy

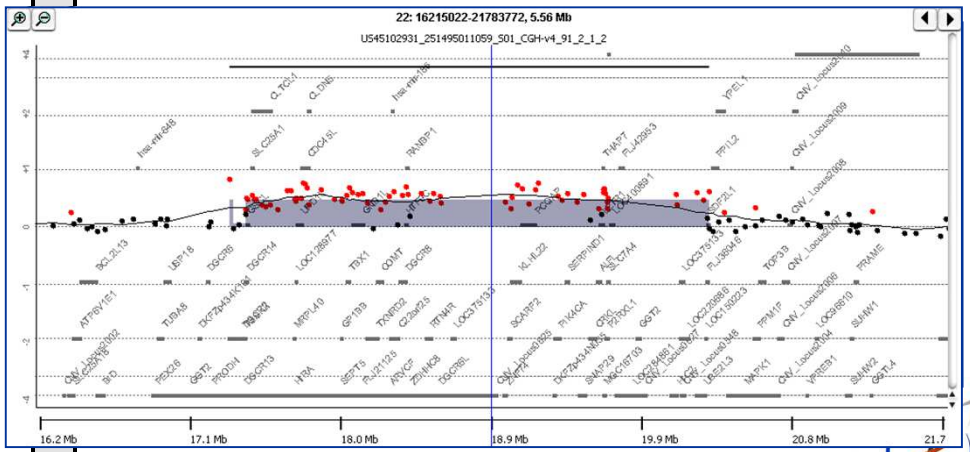
Ch 22



Duplication

Dup (22)(q11.2)





IPG

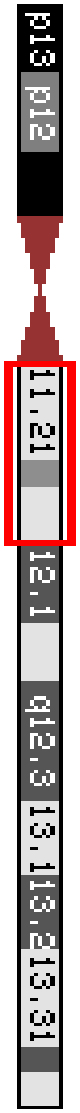
Region 22q11

Deletion

Velo-cardio-facial syndrome

- 1/2000-1/4000 live births
- Learning difficulties (60%)
- Psychiatric disorders (10%)
- Heart defects (65%)
- Velar incompetence (95%)
- Facial dysmorphy

Ch 22



Duplication

Dup (22)(q11.2)

- Learning difficulties (100%)
- Behavioral problems (50%)
- Heart defects(15-20%)
- Velar incompetence (70%)

IPG

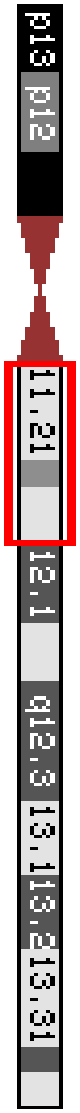
Region 22q11

Deletion

Velo-cardio-facial syndrome

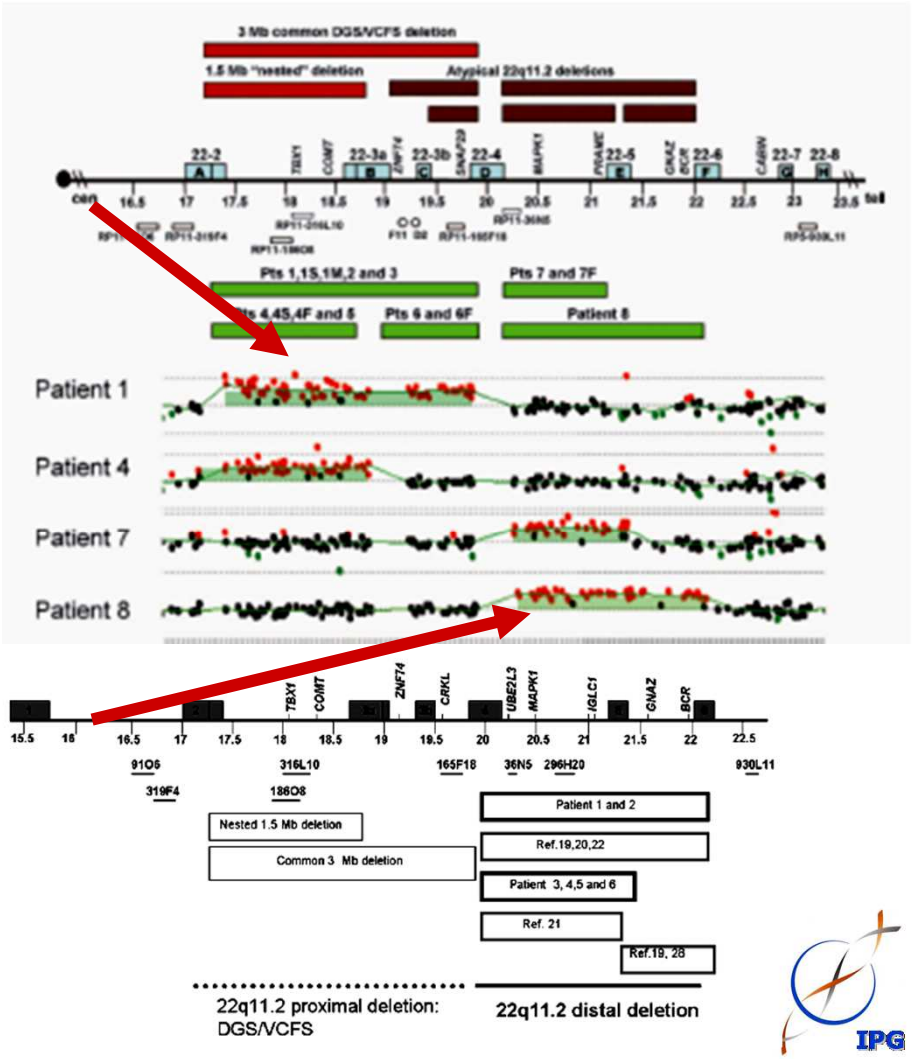
- 1/2000-1/4000 live births
- Learning difficulties (60%)
- Psychiatric disorders (10%)
- Heart defects (65%)
- Velar incompetence (95%)
- Facial dysmorphy

Ch 22



Duplication

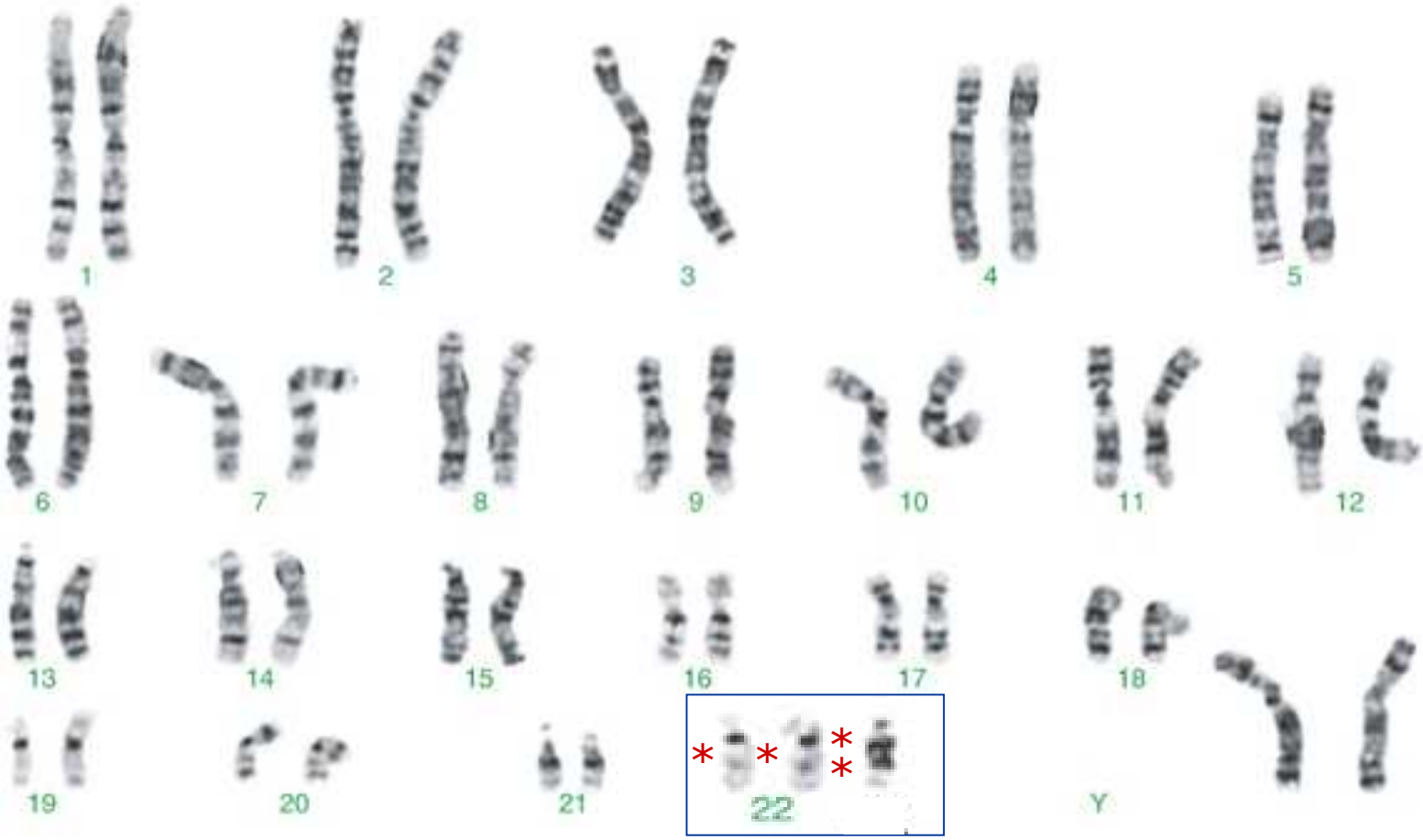
Dup (22)(q11.2)



IPG

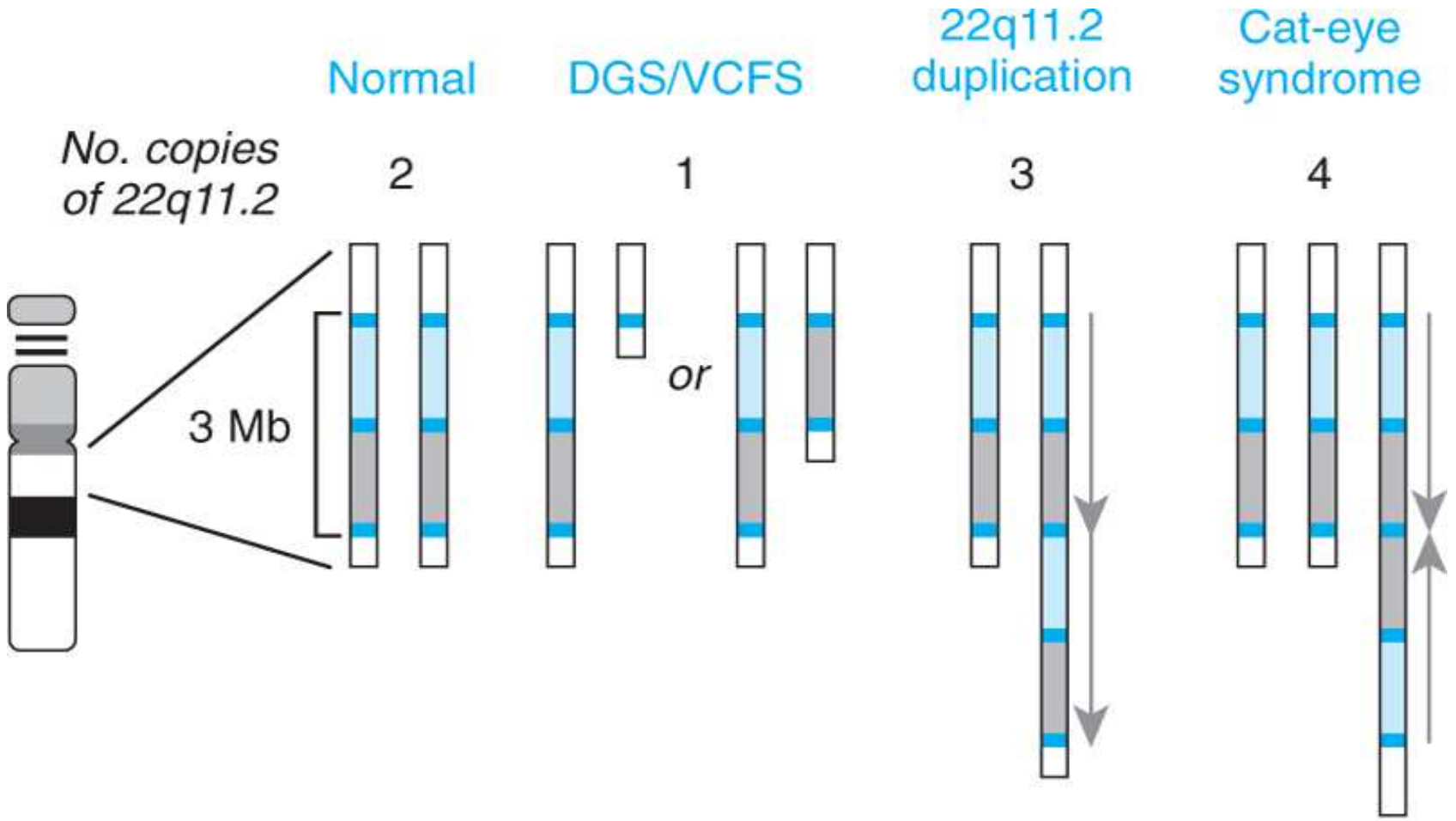
Region 22q11

Tetrasomy 22q11→ Cat-eye syndrome



47,XX,+inv dup(22)(pter→q11.2)

Region 22q11

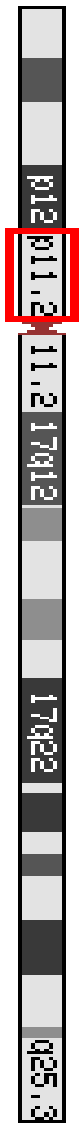


Region 17p11.2

Deletion

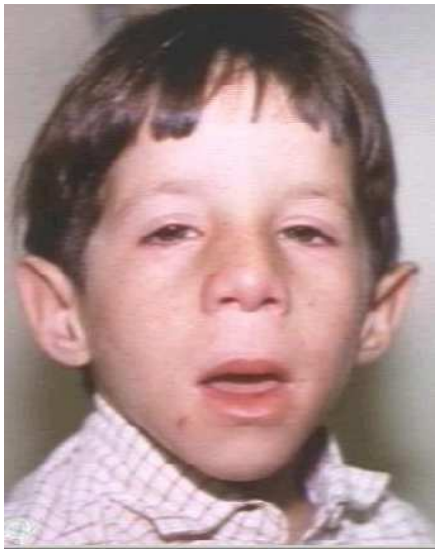
Smith-Magenis syndrome

- Mental retardation, speech delay
- Self-destructive behavior
- Sleep disorders
- Flat midface, brachycephaly
- Brachydactyly
- Congenital anomalies



Duplication

Dup (17)(p11.2)

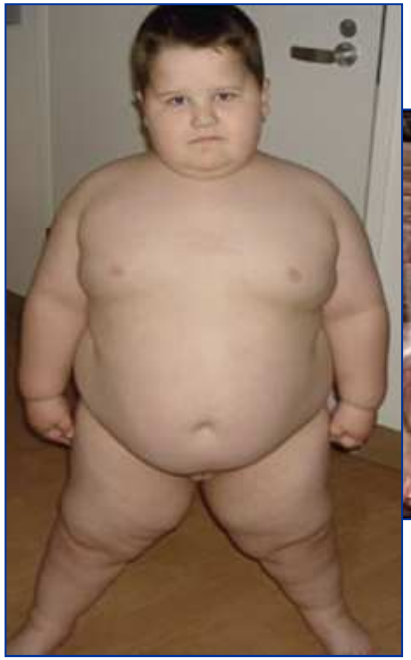


- Dvpt delay, speech delay
- Poor feeding, growth retardation
- Autistic features
- Cardiac defect

Region 15q11-q13

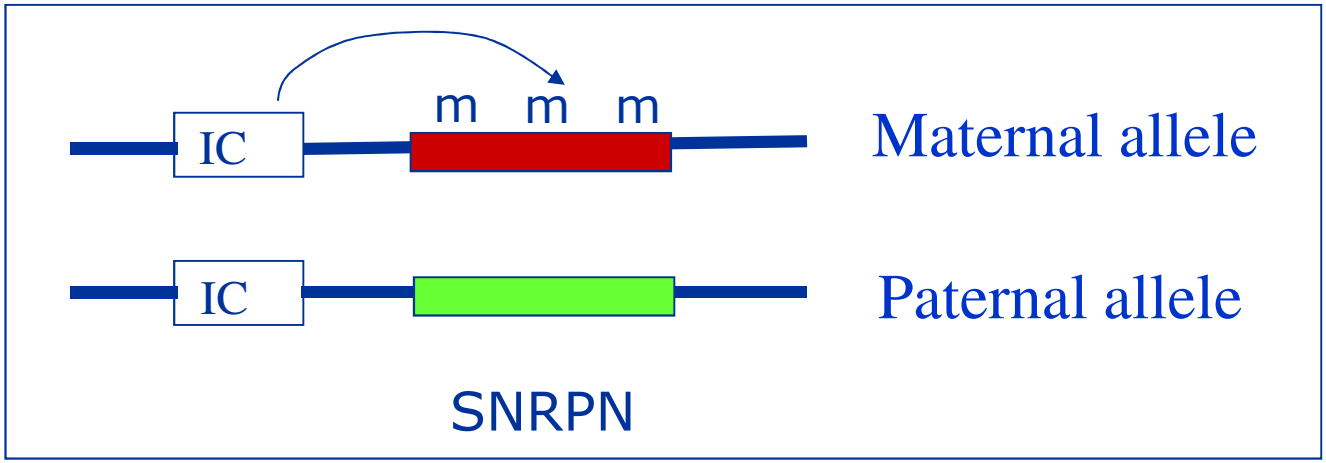
Paternal Deletion Ch 15

Prader-Willi syndrome

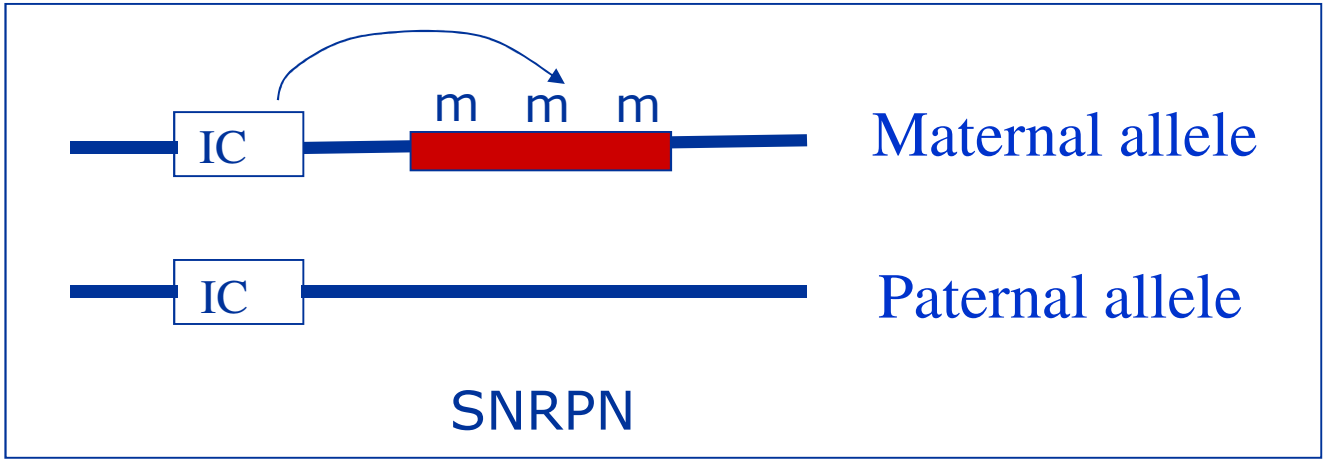


- Mental retardation
- Behavior problems
- Neonatal hypotonia
- Hyperphagia, morbid obesity
- Hypogonadism

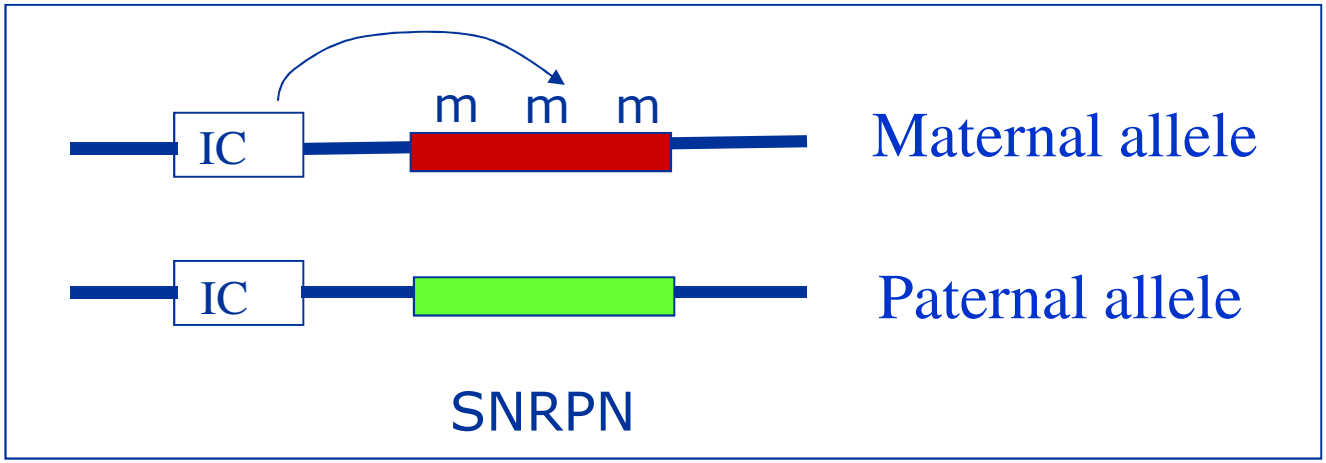
Region 15q11-q13



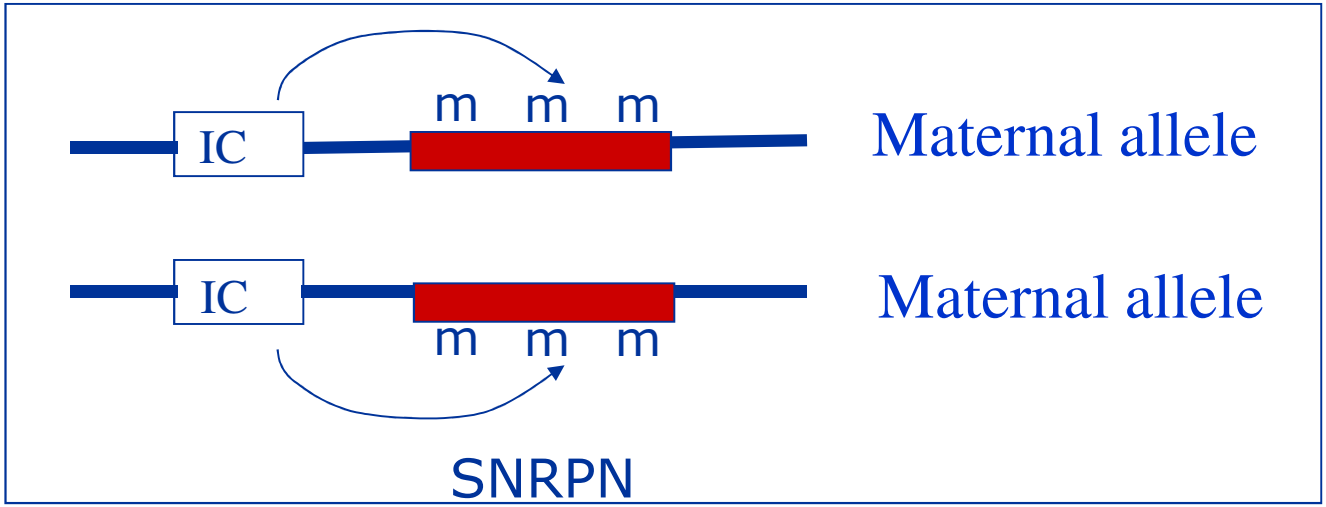
70% *paternal allele deletion*



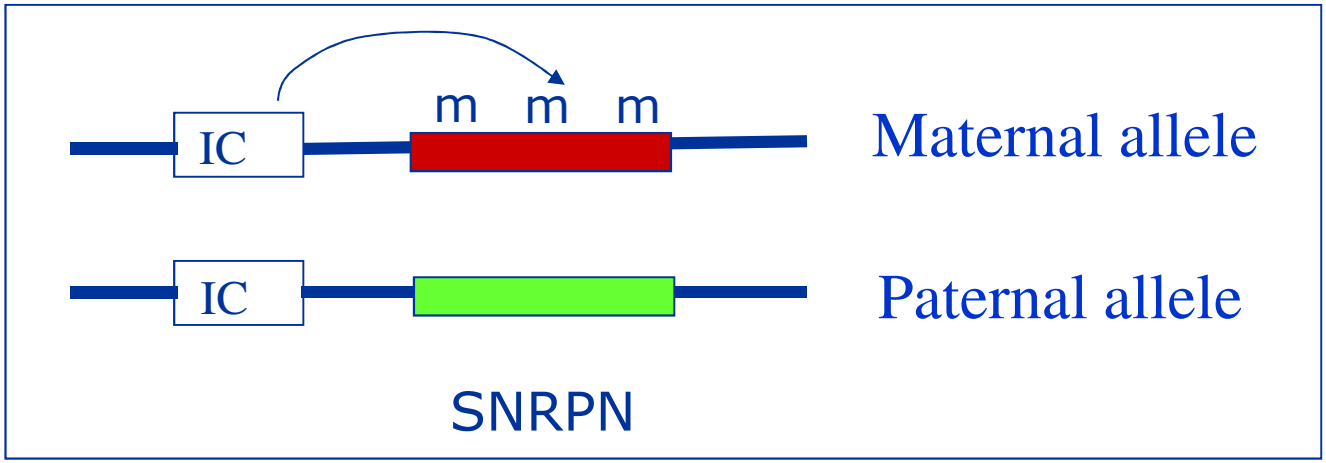
Region 15q11-q13



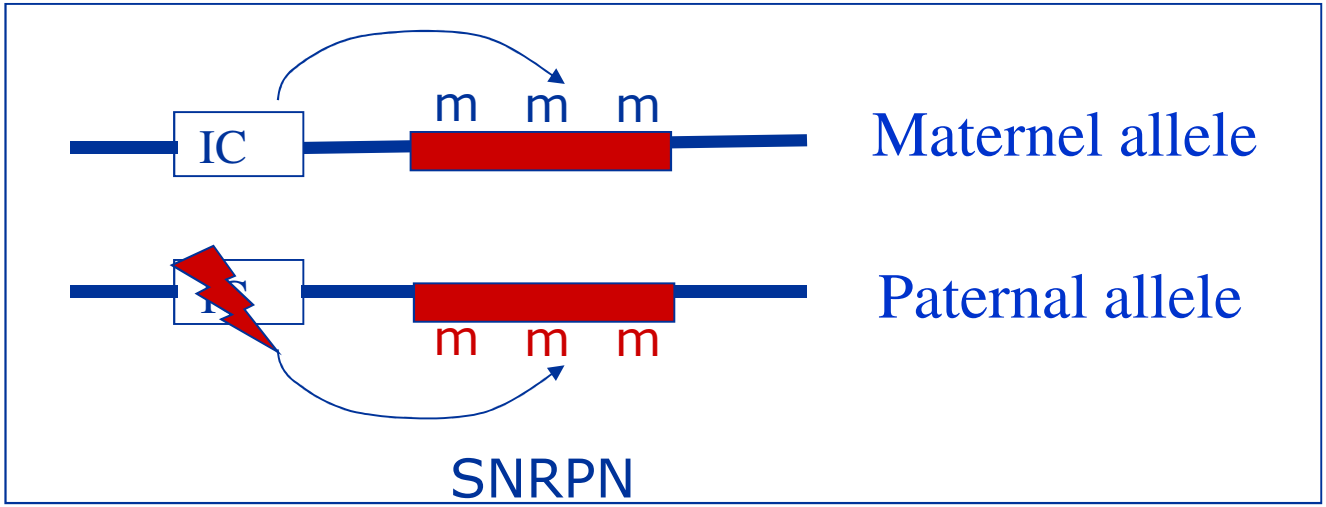
25-30% *maternal uniparental disomy*



Region 15q11-q13



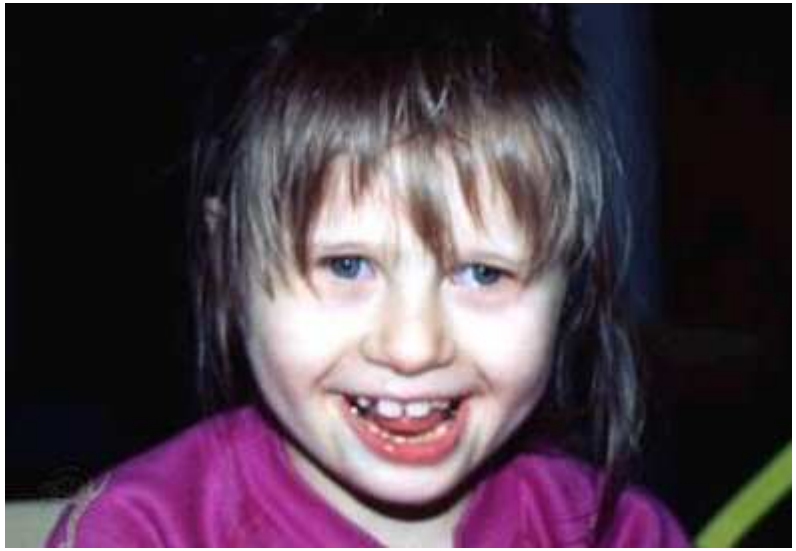
<5% *defect in the imprinting center*

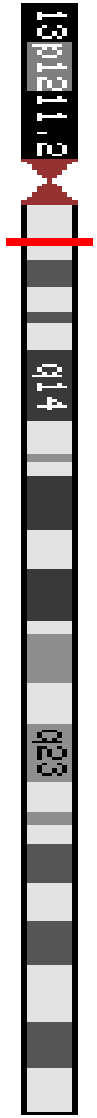


Region 15q11-q13

Maternal Deletion Ch 15

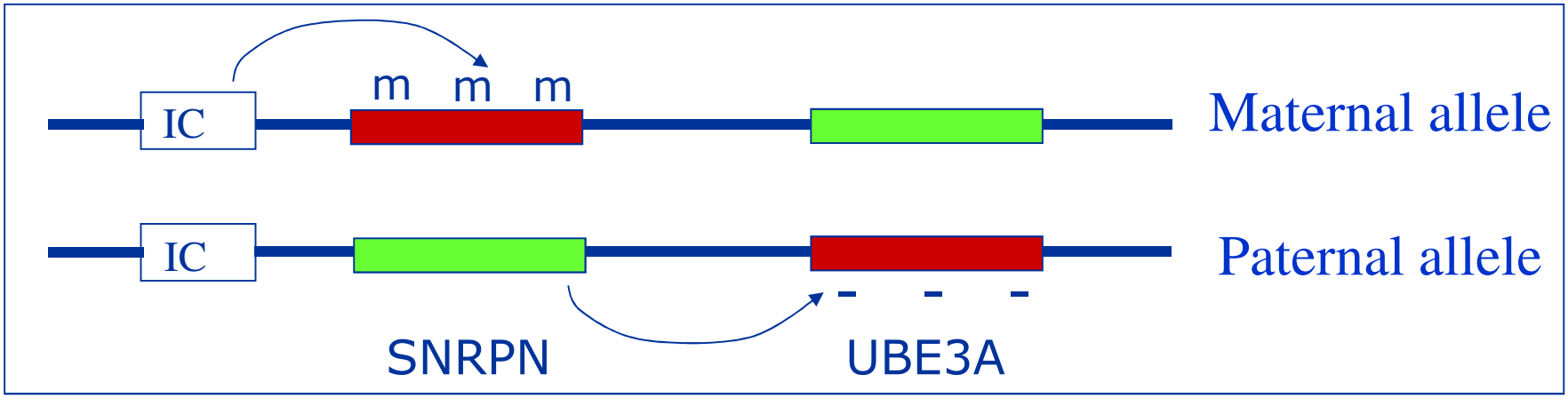
Angelman syndrome



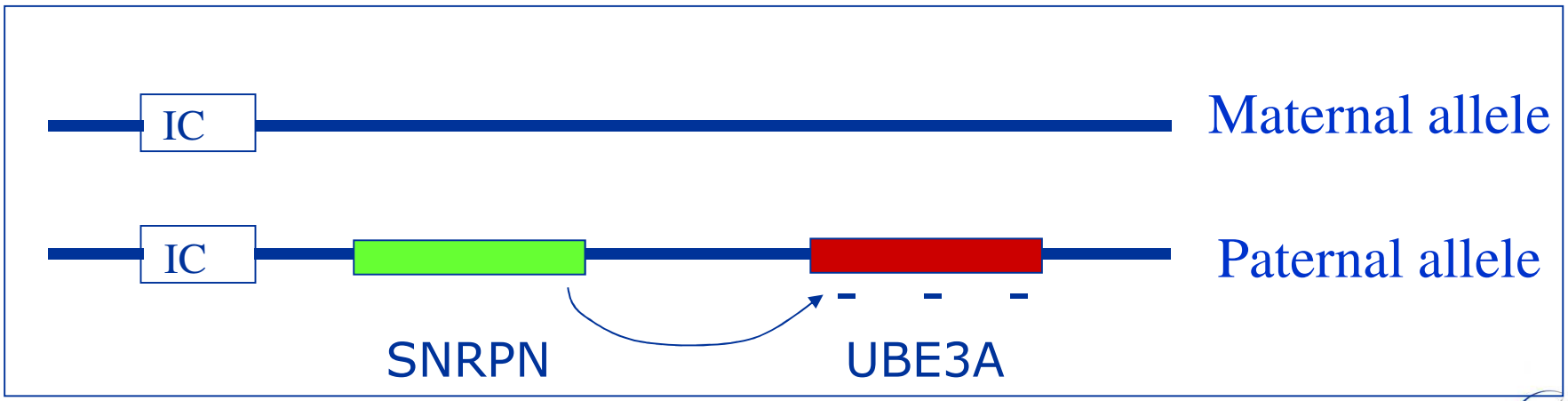


- Severe mental retardation
- Ataxia
- Epilepsy
- Happy behavior

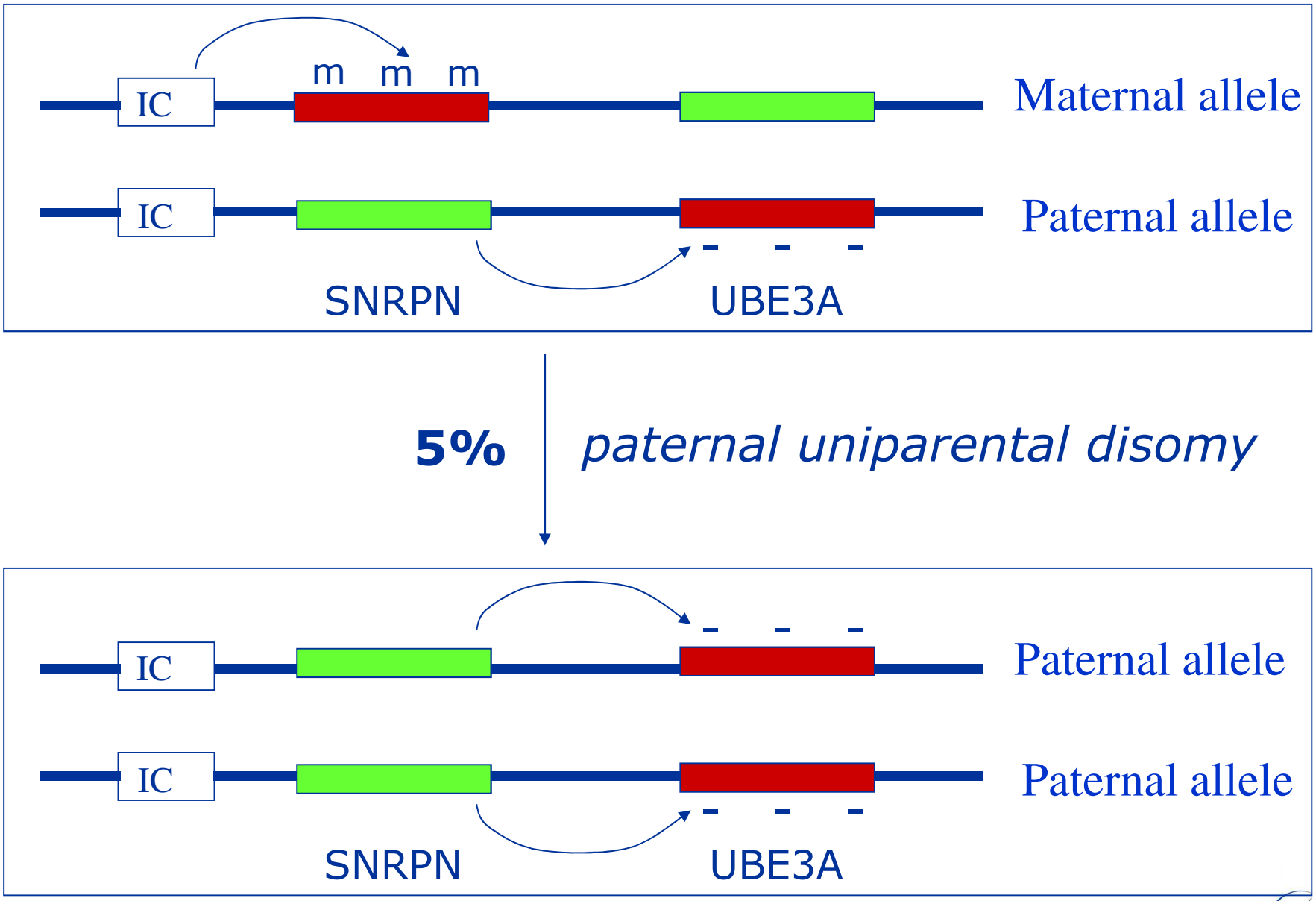
Region 15q11-q13



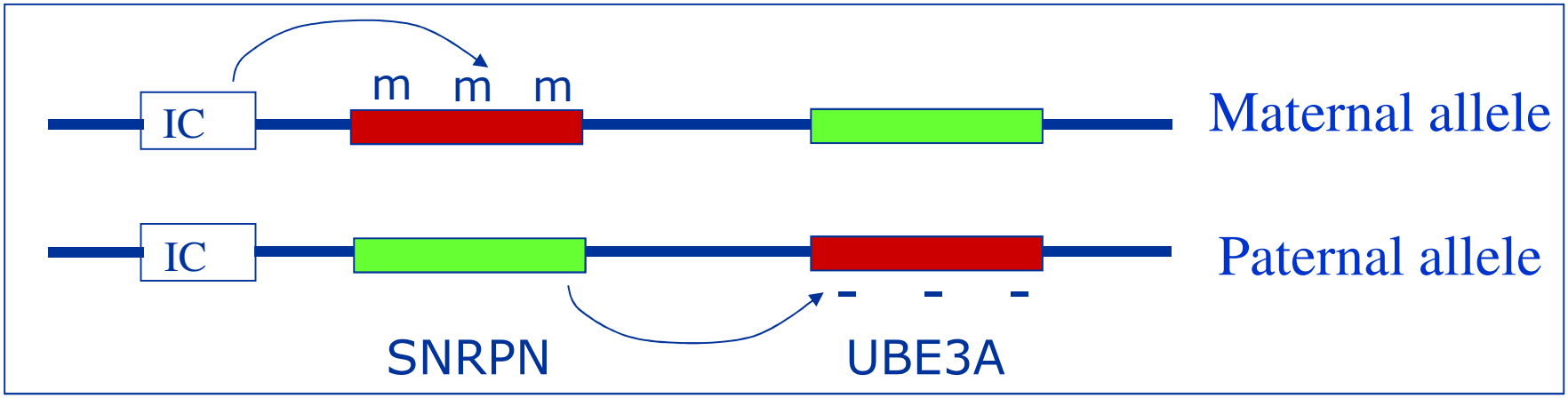
70% *maternal allele deletion*



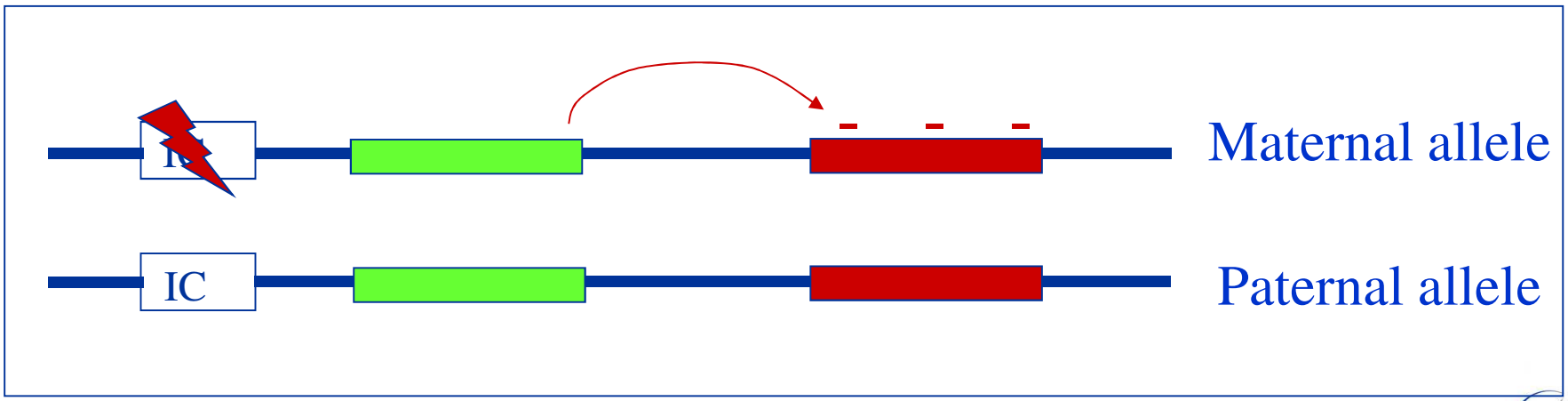
Region 15q11-q13



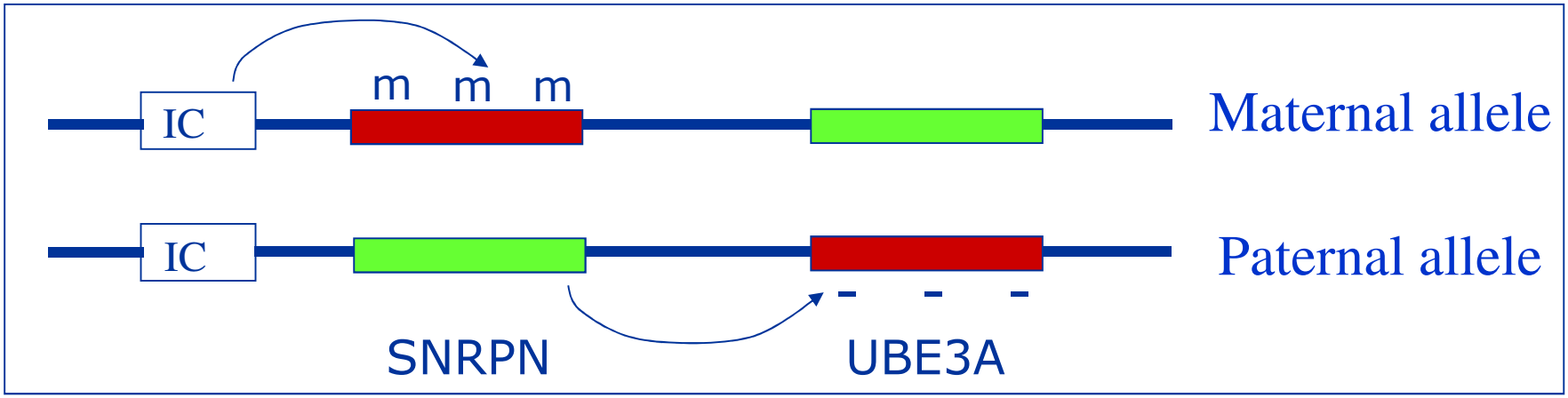
Region 15q11-q13



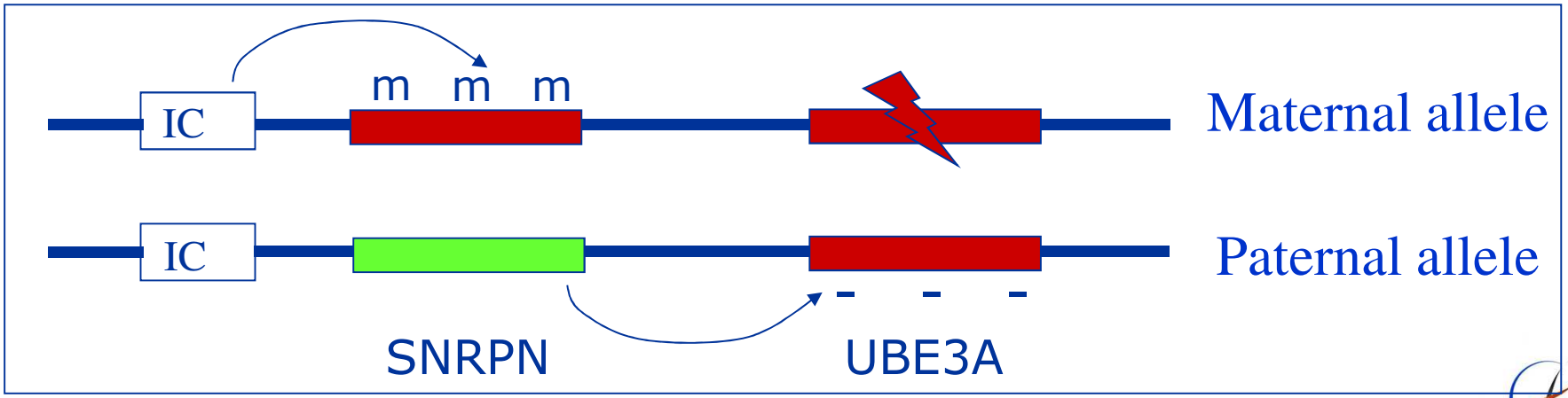
5% *defect in the imprinting center*



Region 15q11-q13



10% *mutation in UBE3A gene*



	PW	Angelman
Deletion	**70% (pat)**	**70% (mat)**
Uniparental Disomy (UPD)	**25-30% (mat)**	**5% (pat)**
Single gene mutation	**None detected**	**10% Familial cases**
Imprinting Center Mutation	**<5%**	**5%**
Unidentified	**<1%**	**10-15%**

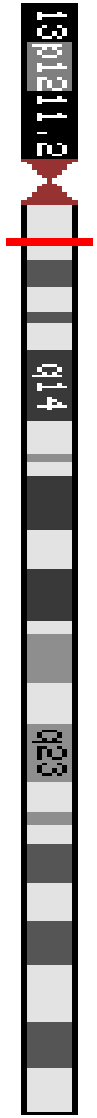
Table 5-6: Molecular mechanisms causing Prader-Willi and Angelman syndromes

Region 15q11-q13

Paternal Deletion

Prader-Willi syndrome

Ch 15



Duplication

Dup (15)(q11-q13)

- Mental retardation
- Autism

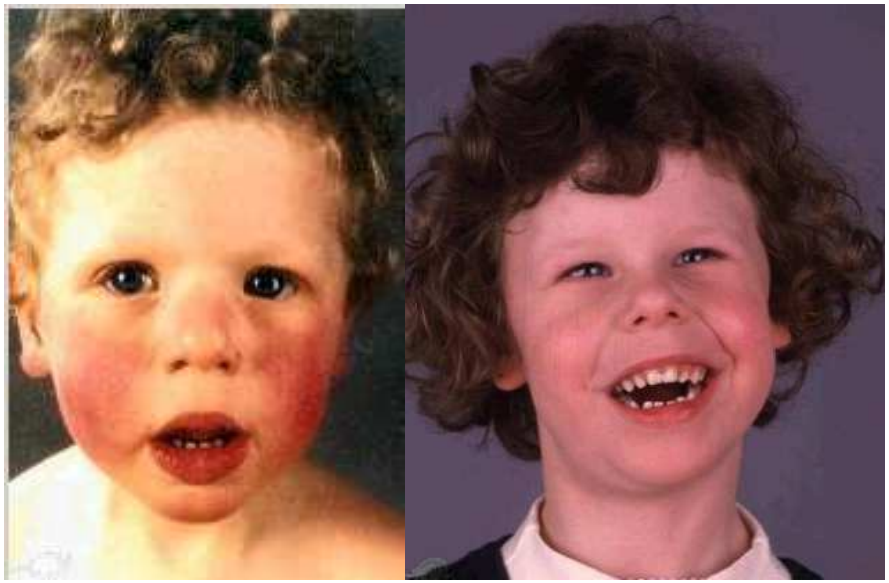
Maternal Deletion

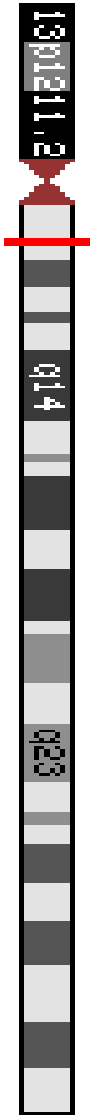
Angelman syndrome

Region 7q11

Deletion

Williams syndrome



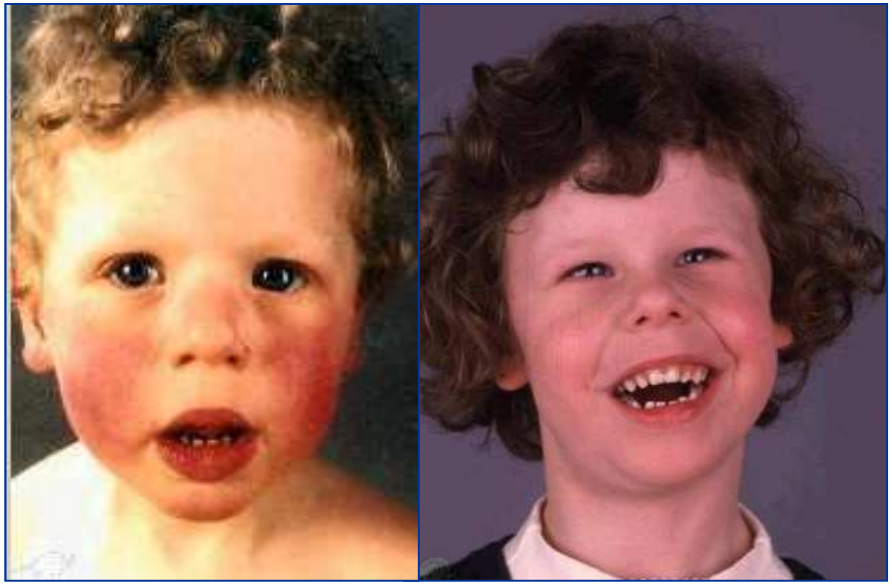


- Cardiovascular anomalies
- Distinctive facies
- Mental retardation
- Friendly personality

Region 7q11

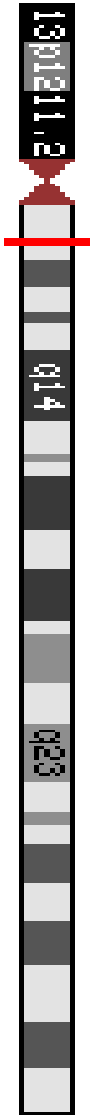
Deletion

Williams syndrome



- Cardiovascular anomalies
- Mental retardation
- Friendly personality

Ch 7



Duplication

Dup (7)(q11)

- Mental retardation
- Speech delay
- Behavioral problems

New microdeletions/microduplications syndromes:

susceptibility factors for mental retardation/autism/epilepsy/psychiatric disorders

- 1q21.1 del/dup
- 3q29 del
- 15q11.2 del/dup
- 15q13.3 del
- 16p11.2 del/dup
- 16p13.11 del/dup
- 17q 21.31 del
- etc…..

1q21 dup

16p11 del

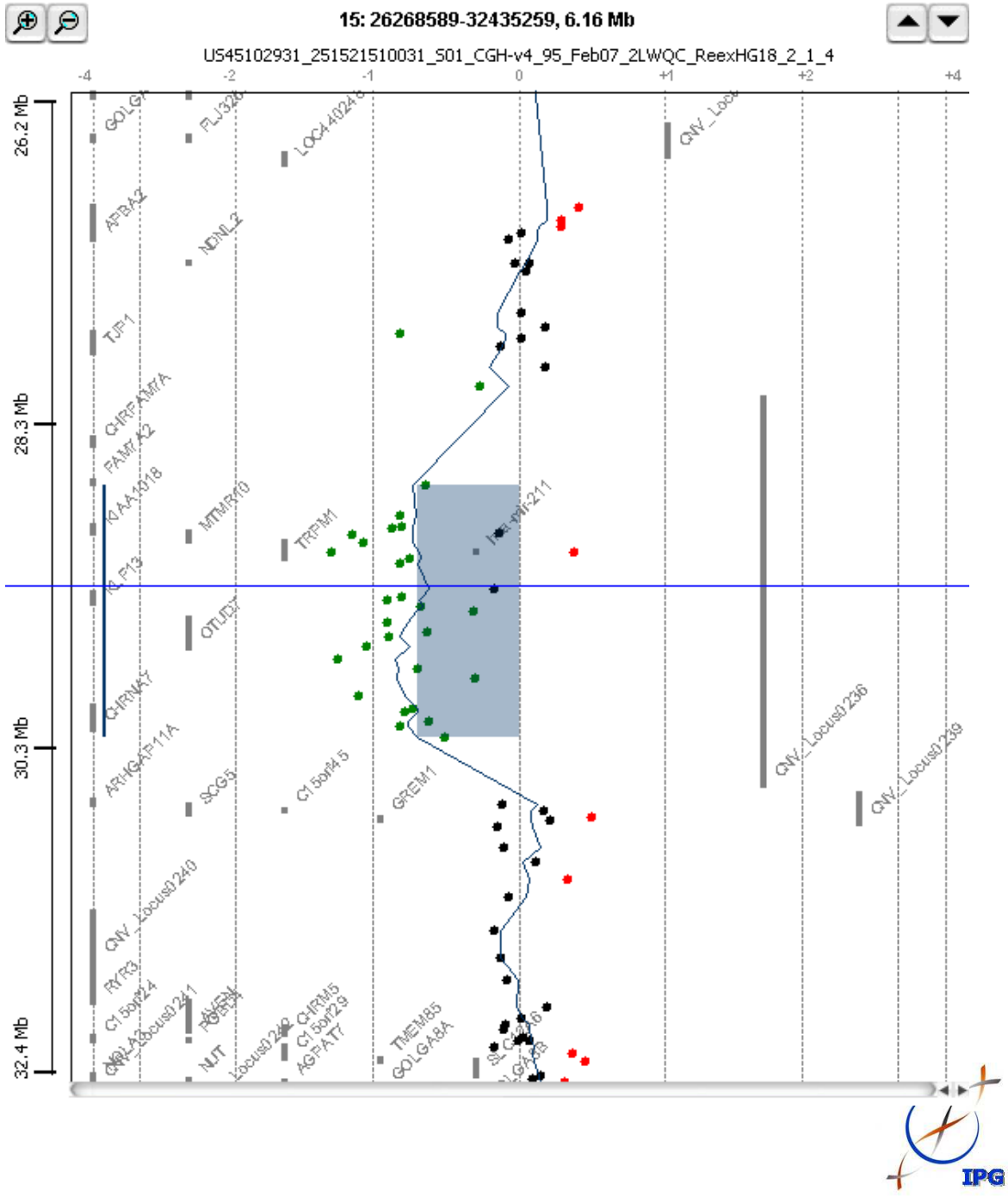
15q13.3 del

> Highly variable expressivity

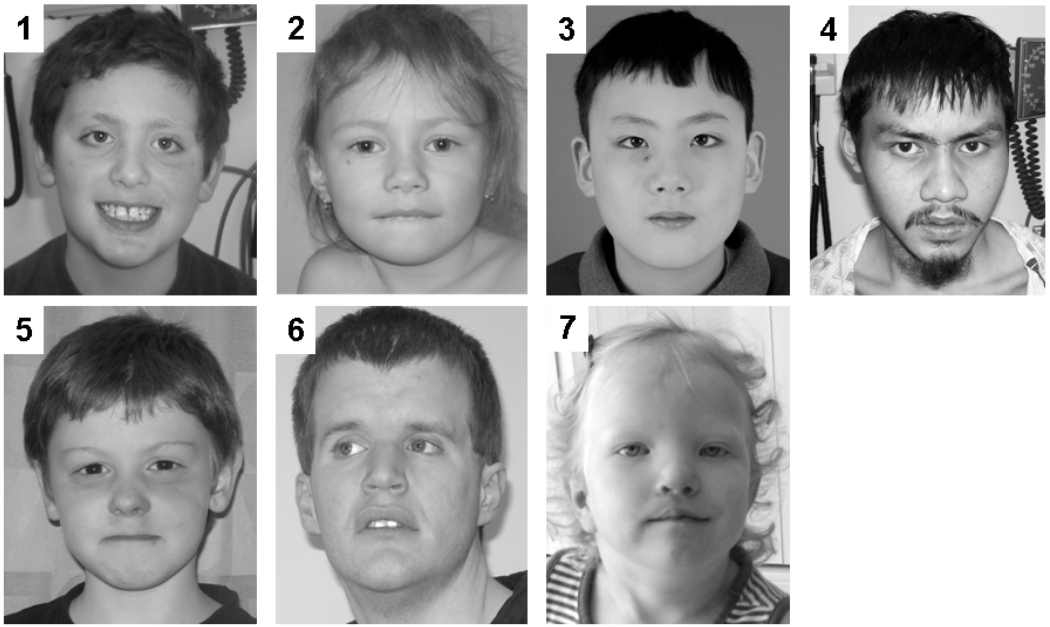
Exemple: 2 brothers

- Developmental delay
  - Walk > 18 months
  - Speech delay
- Learning difficulties
- Epilepsy
- Behavioral problems

15q13.3 deletion (1,5 Mb)

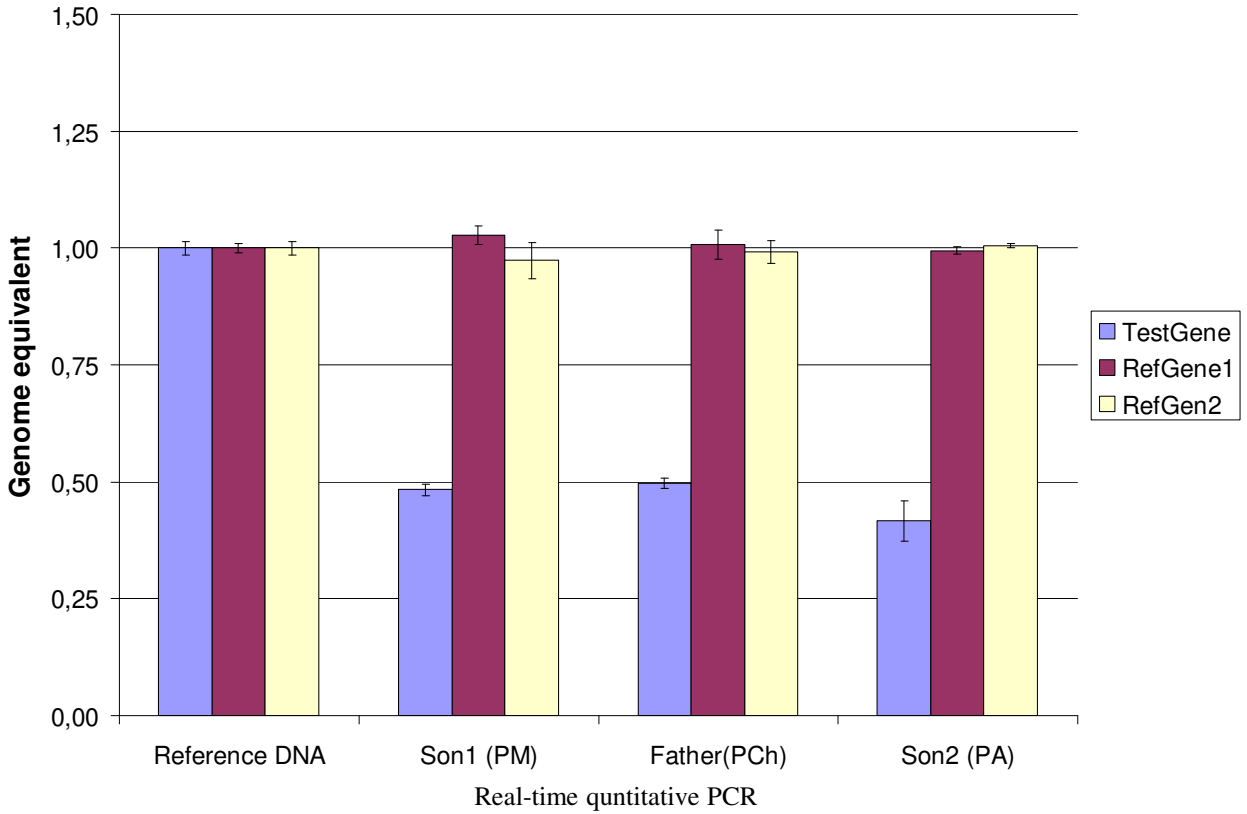


Sharp et Al (Nat Genet 2008)



Miller et Al (J Med Genet 2008)

Familial screening (Q-PCR)



2 brothers : 15q13.3 délétion
Father : 15q13.3 délétion

→ inherited rearrangement from an asymptomatic father

A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures

Andrew J Sharp[1,15], Heather C Mefford[1], Kelly Li[2], Carl Baker[1], Cindy Skinner[3], Roger E Stevenson[3], Richard J Schroer[3], Francesca Novara[4], Manuela De Gregori[4], Roberto Ciccone[4], Adam Broomer[2], Iris Casuga[2], Yu Wang[2], Chunlin Xiao[2], Catalin Barbacioru[2], Giorgio Gimelli[5], Bernardo Dalla Bernardina[6], Claudia Torniero[6], Roberto Giorda[7], Regina Regan[8], Victoria Murday[9], Sahar Mansour[10], Marco Fichera[11], Lucia Castiglia[11], Pinella Failla[11], Mario Ventura[12], Zhaoshi Jiang[1], Gregory M Cooper[1], Samantha J L Knight[8], Corrado Romano[11], Orsetta Zuffardi[4,13], Caifu Chen[2], Charles E Schwartz[3] & Evan E Eichler[1,14]

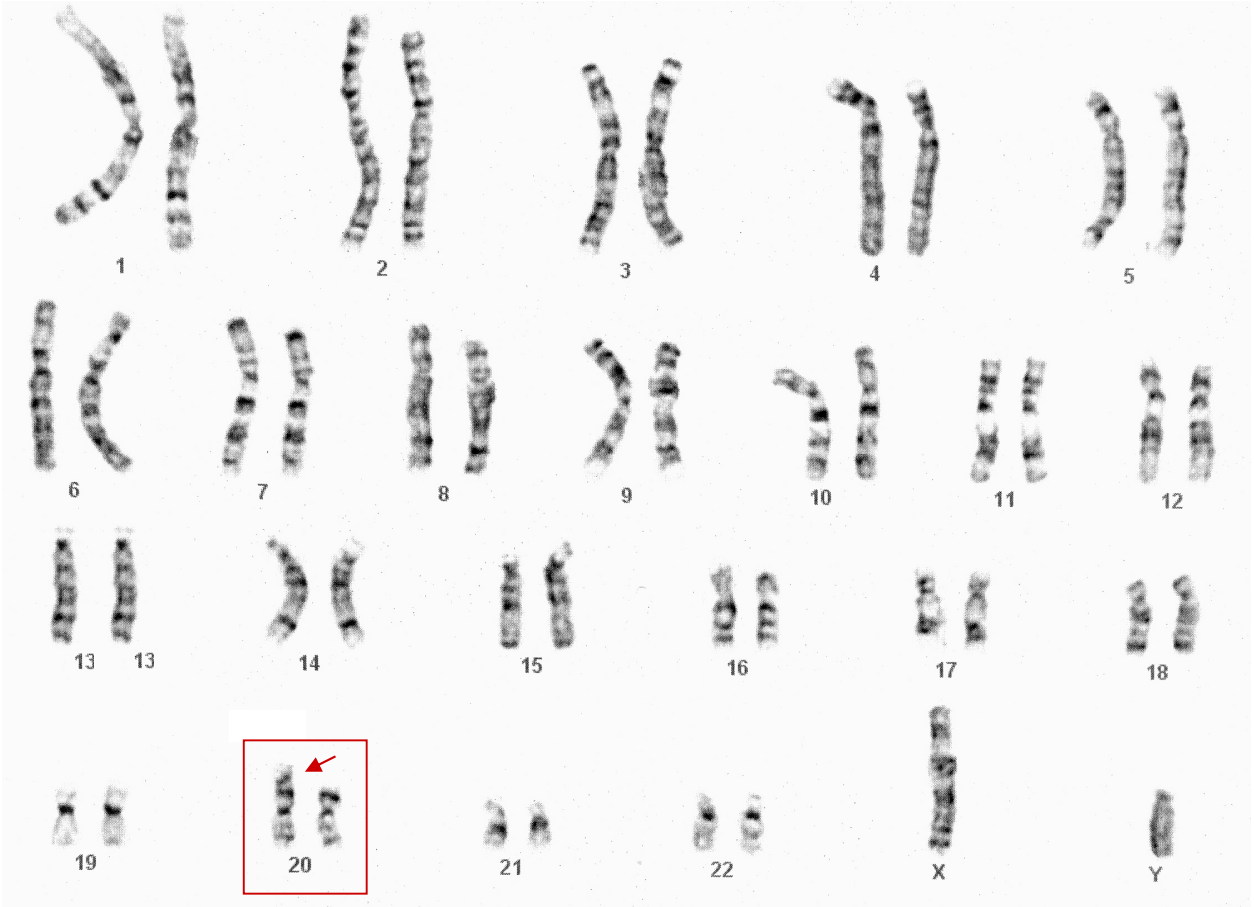
Nat Genet, 2008 : 40(3), 322-328

Incomplete penetrance

Variable Expressivity

IPG

Autosomes structural anomalies: particular examples (non recurrent)

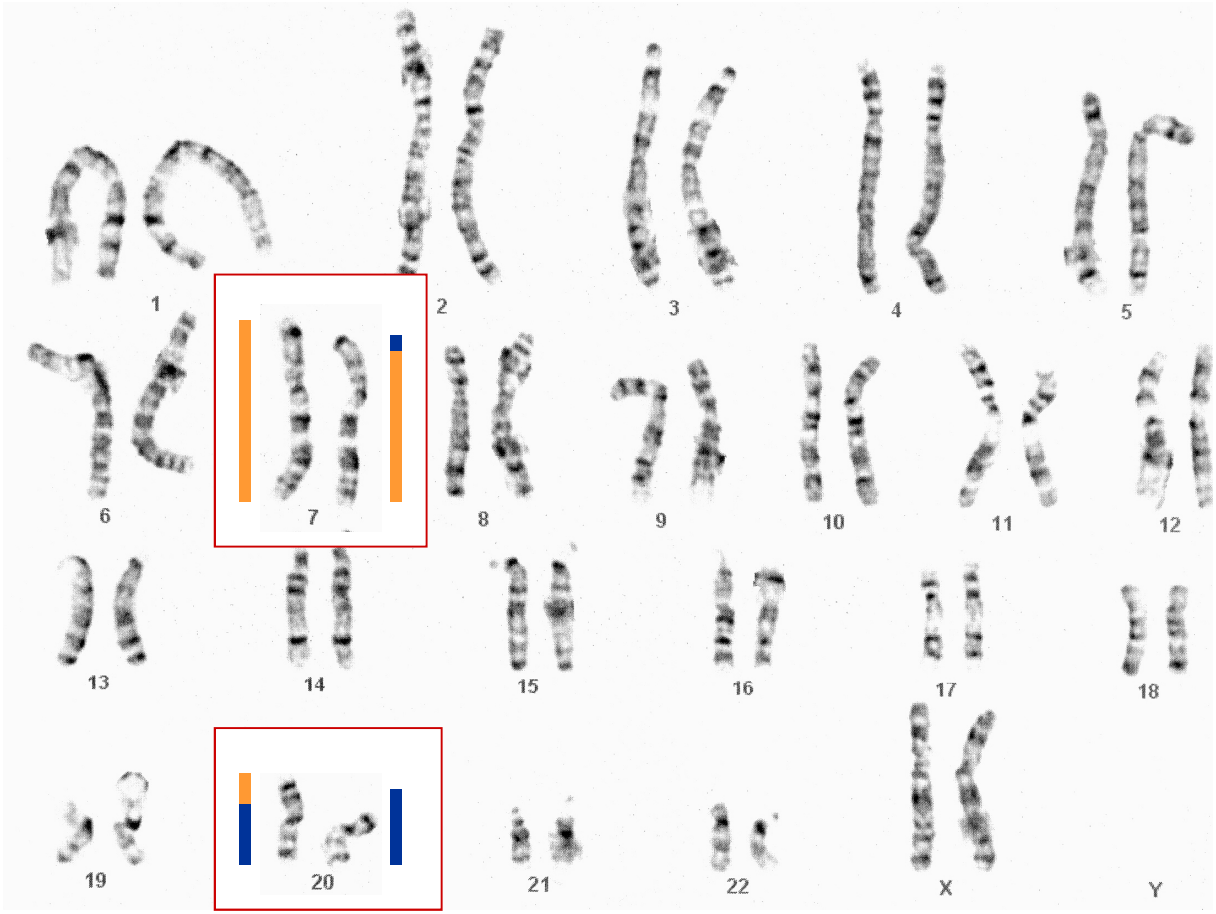


- **Mental retardation**
- **Autistic features**
- **Facial dysmorphy**

46,XY,der(20)

Autosomes structural anomalies: particular examples

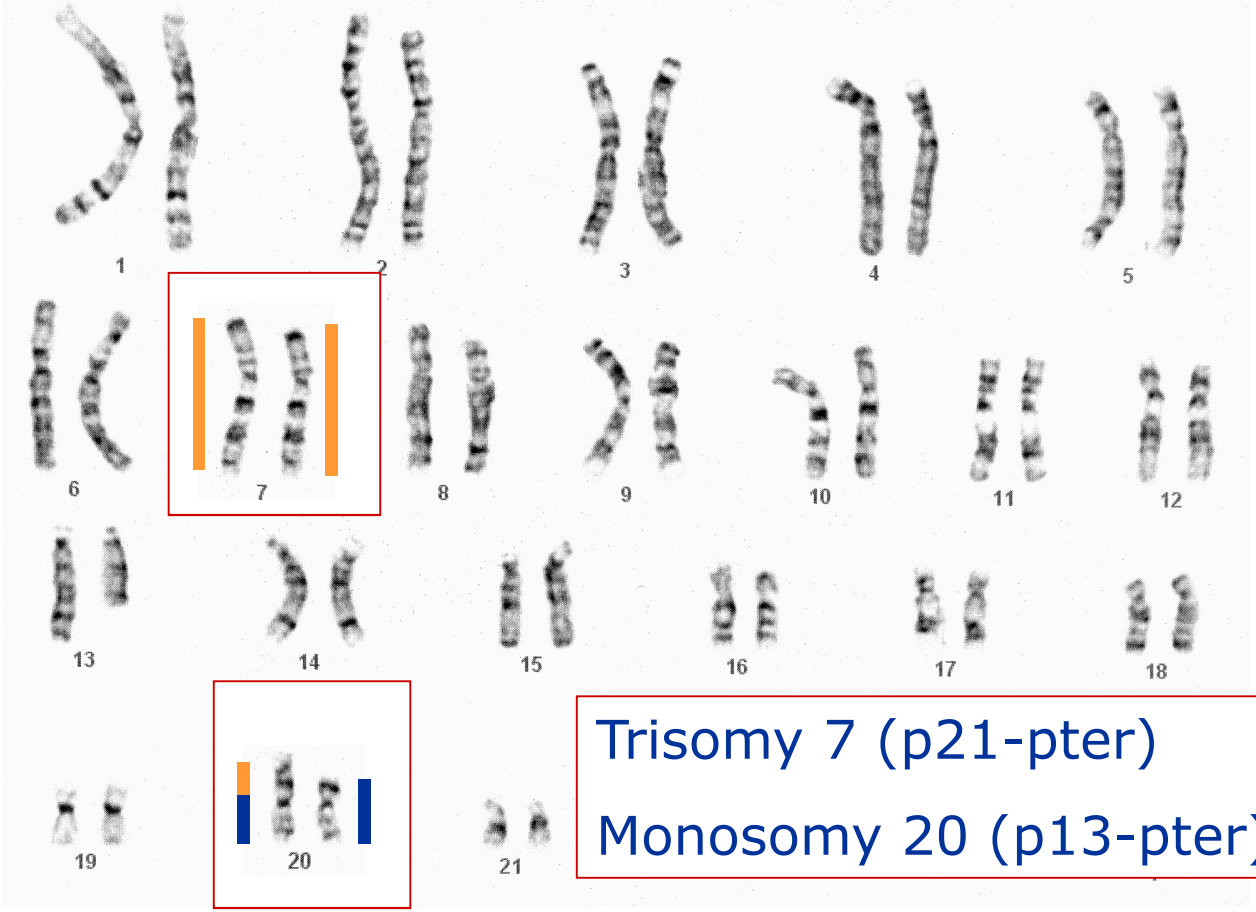
Mother's karyotype:



46,XX,t(7;20)(p21;p13)

Autosomes structural anomalies: particular examples

⇒ patient's karyotype:

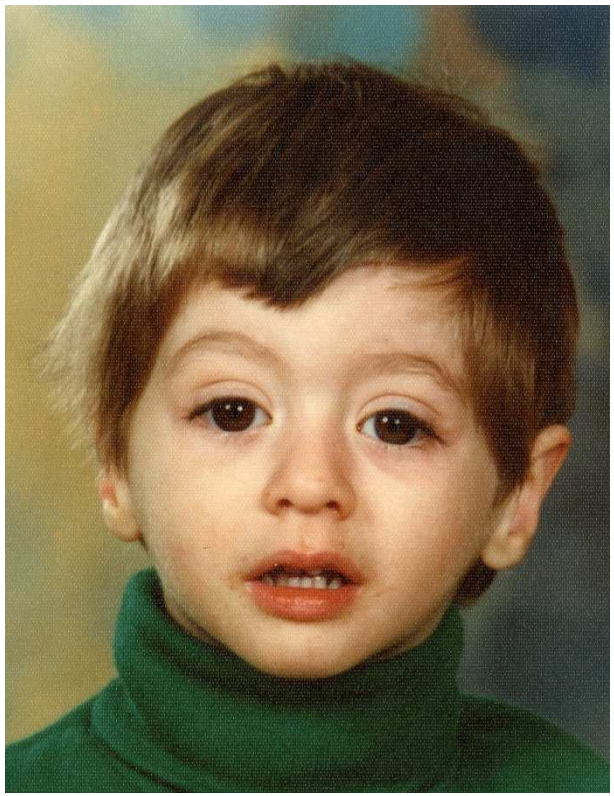


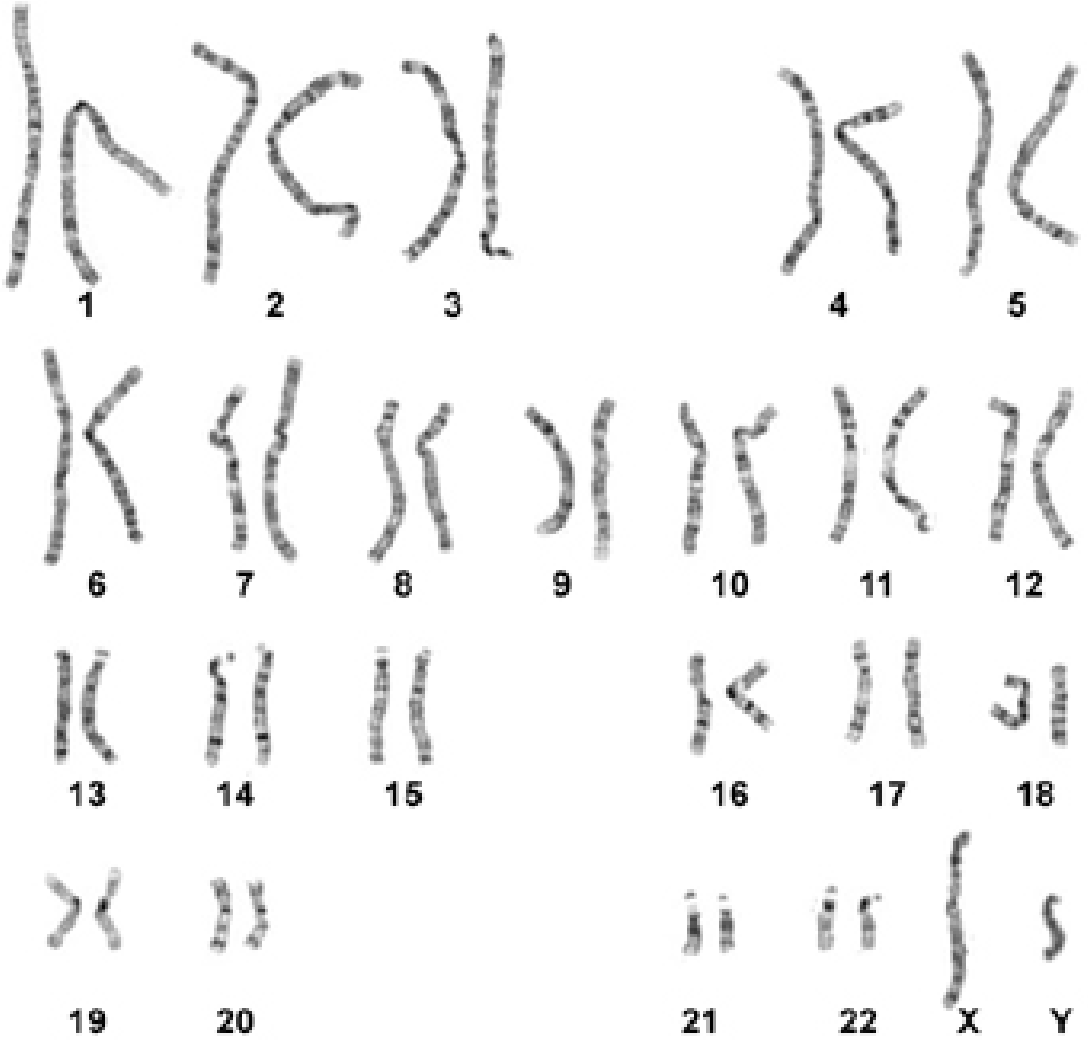
Trisomy 7 (p21-pter)

Monosomy 20 (p13-pter)

46,XY,der(20)t(7;20)(p21;p13)mat

Autosomes structural anomalies: particular examples

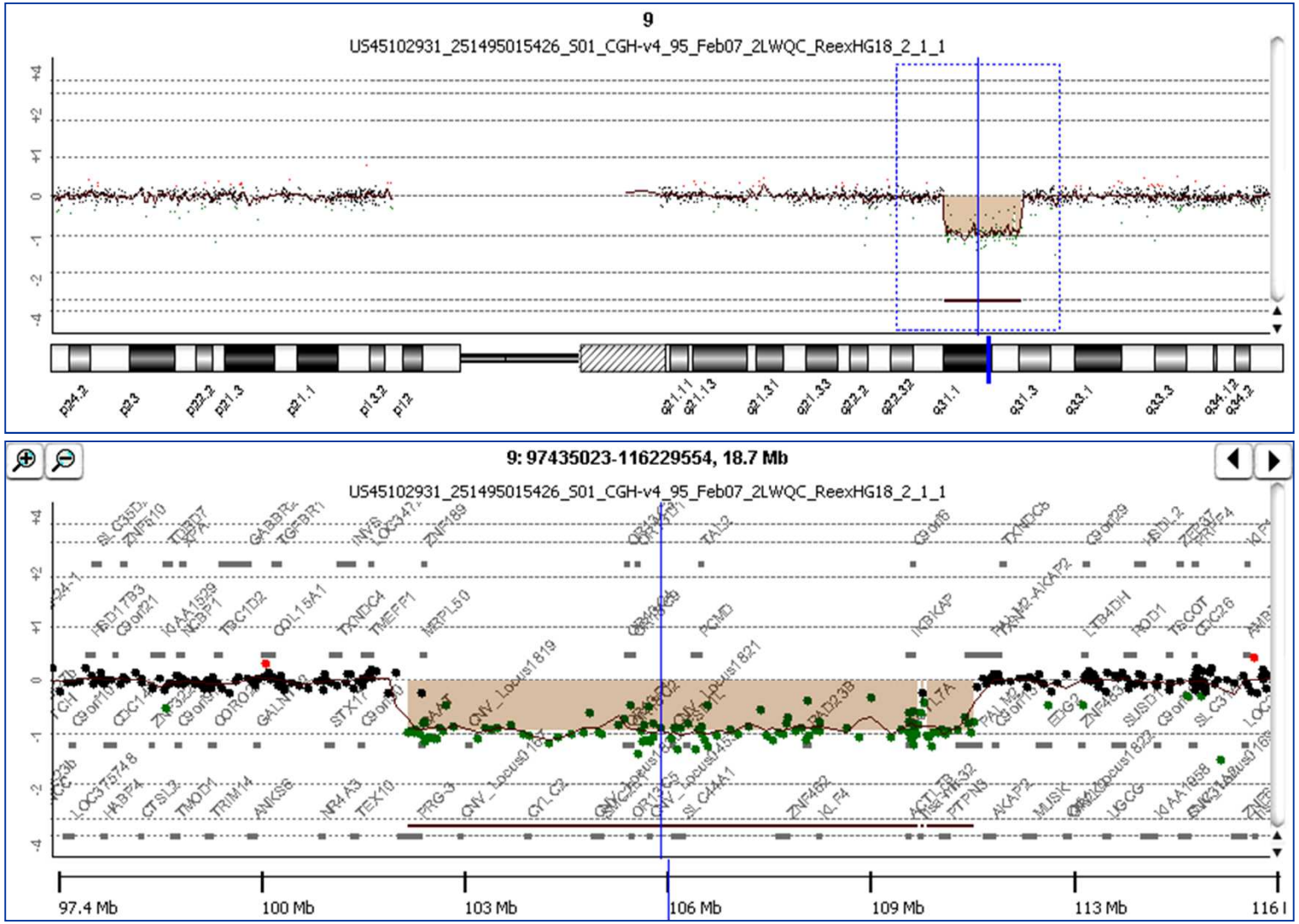




- Mental retardation
- Autistic features
- Facial dysmorphy

46,XY

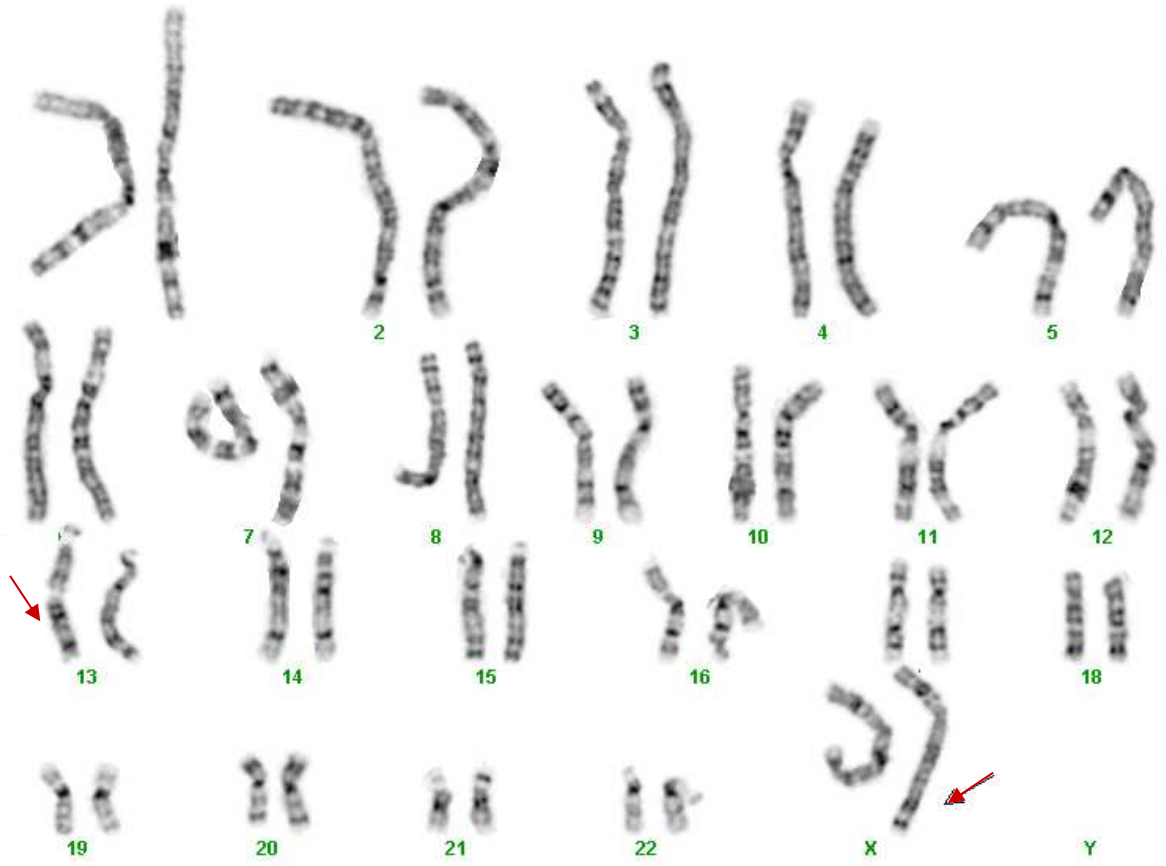
Autosomes structural anomalies: particular examples



De novo 8.7 Mb deletion on 9q31.1-q31.3

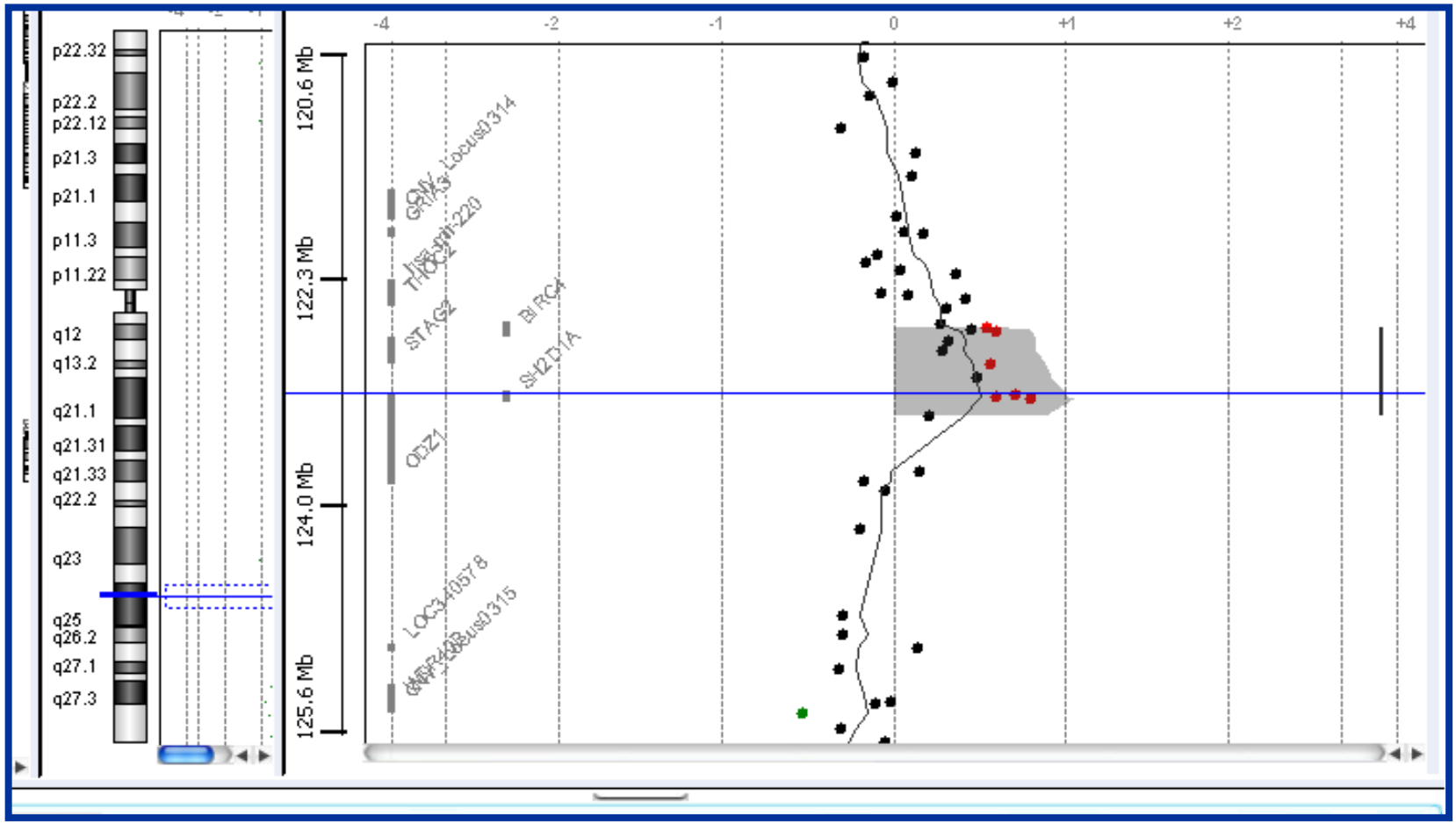
Autosomes structural anomalies: particular examples

- **Mental retardation**
- **Facial dysmorphy**
- **Supernumerary nipple**



46,X,t(X;13)(q24;q22),inv(9)(p12q13)

Microarrays: Microduplication Xq25



Microrearrangement at the breakpoint on chromosome X

CONCLUSIONS

- ***Numerical autosomes abnormalities:***
  - frequent spontaneous abortions
  - Trisomy 13, trisomy 18, trisomy 21
    - *low recurrence risk if no parental rearrangement*
  - pigmentary changes, corporal asymmetry
    - *skin biopsy (mosaicism)*
    - *low recurrence risk*
  - supernumerary marker chromosomes
    - *low recurrence risk*

CONCLUSIONS

- ***Structural autosomes abnormalities:***

  - cytogenetically detectable (karyotype)

    ↳ *autosomal deletion syndromes*

  or genomic disorders (FISH, MLPA, arrays,…)

    ↳ *microdeletion and microduplication syndromes*

  - well-defined syndromes

    ↳ *sporadic or inherited (! variable expressivity)*

  or particular cases

    ↳ *low recurrence risk if no parental rearrangement*

  - apparently balanced translocations

    ↳ *microarrays if abnormal phenotype*

THANK YOU FOR YOUR ATTENTION