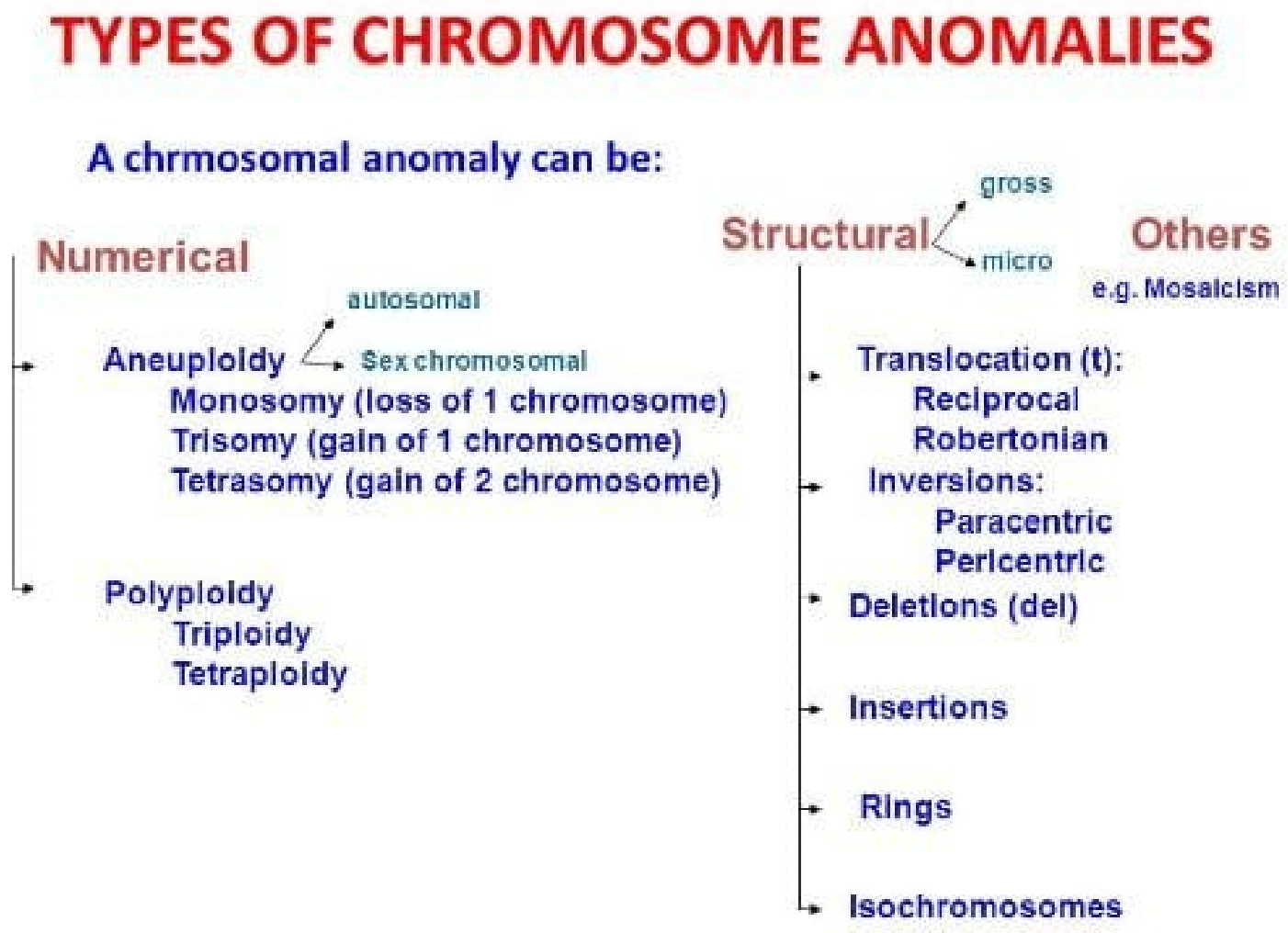
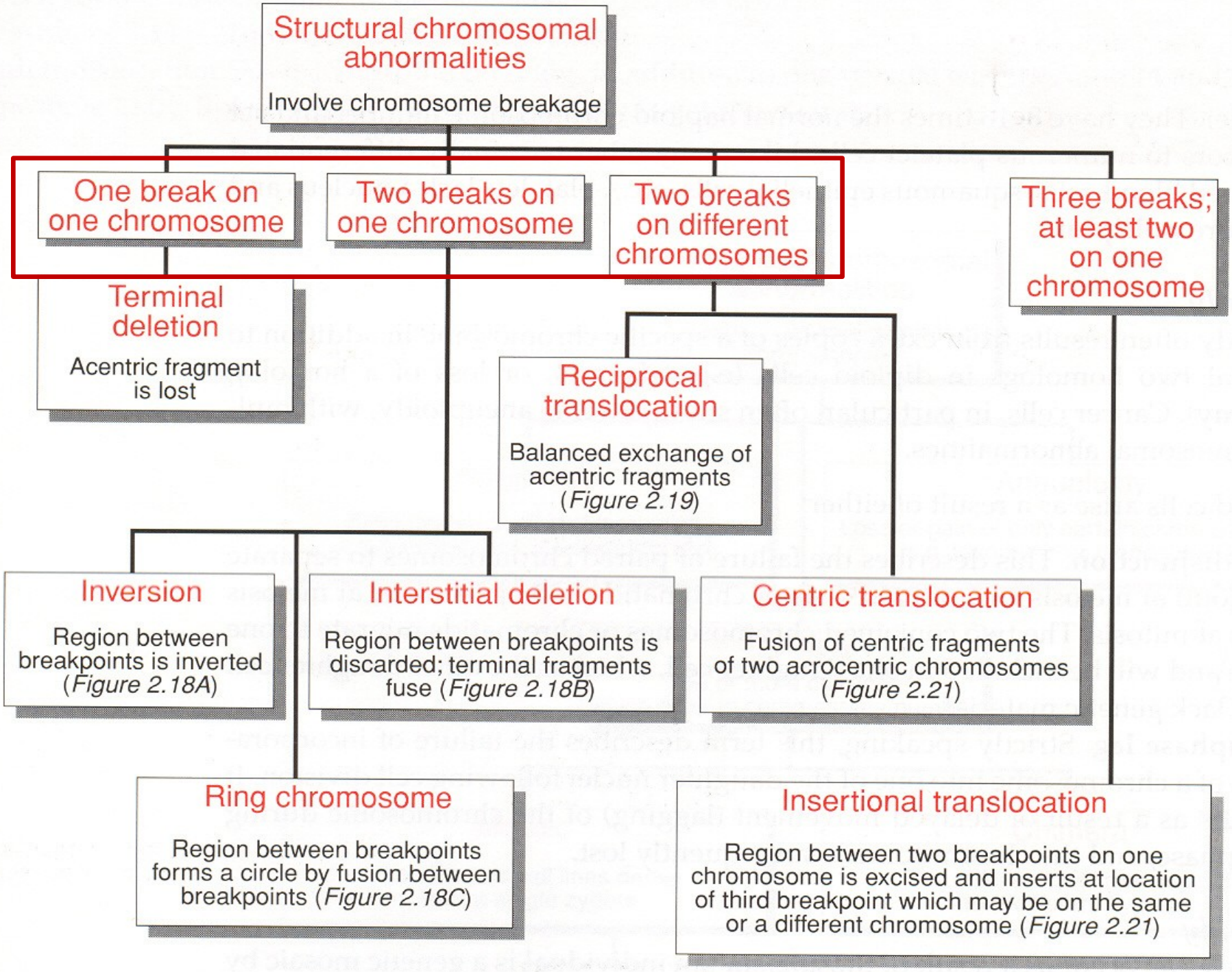
Medical genetics II

Microdeletion syndromes

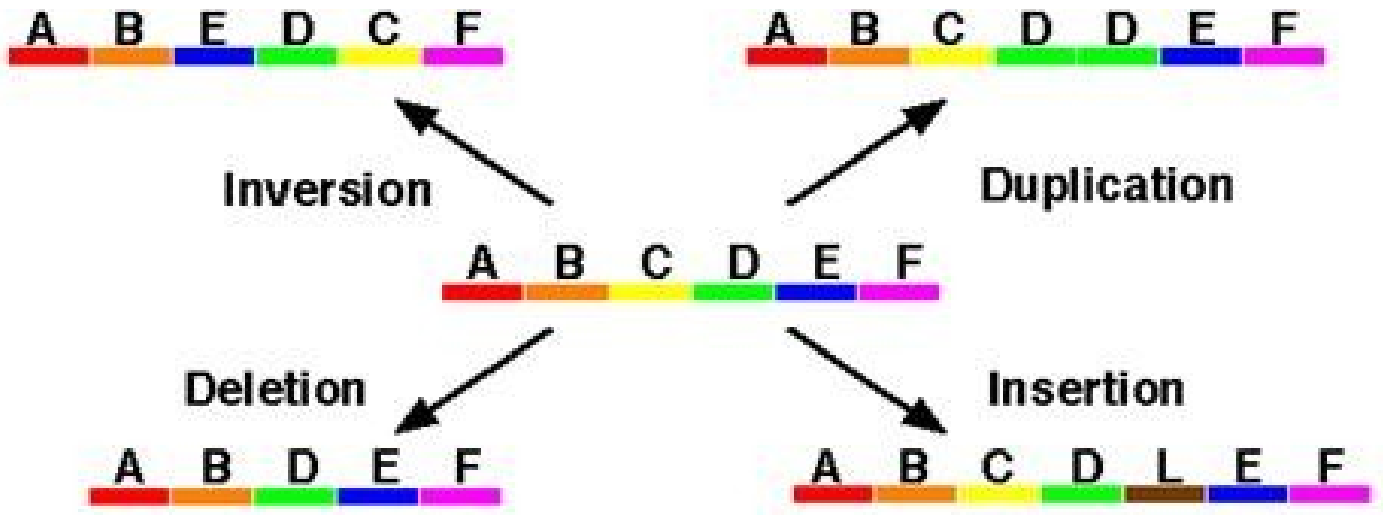
Standard karyotype 46,XX or 46, XY

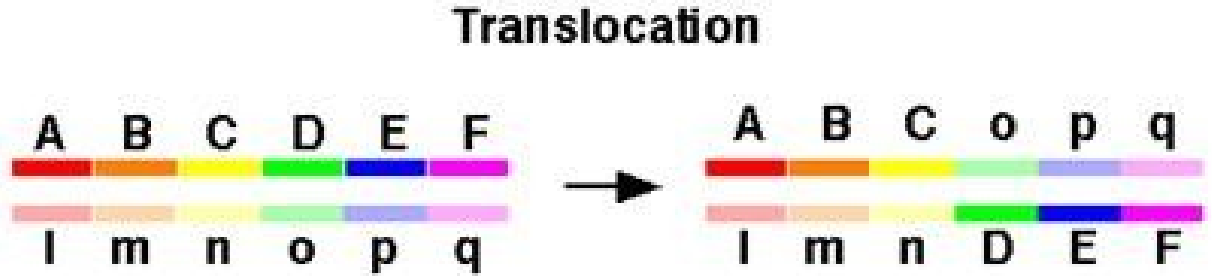


https://readbiology.com/wp-content/uploads/2020/04/aberration.jpg


Structural chromosomal abnormalities
Involve chromosome breakage
One break on one chromosome
Two breaks on one chromosome
Two breaks on different chromosomes
Three breaks; at least two on one chromosome
Terminal deletion
Acentric fragment is lost
Reciprocal translocation
Balanced exchange of acentric fragments (Figure 2.19)
Inversion
Region between breakpoints is inverted (Figure 2.18A)
Interstitial deletion
Region between breakpoints is discarded; terminal fragments fuse (Figure 2.18B)
Centric translocation
Fusion of centric fragments of two acrocentric chromosomes (Figure 2.21)
Ring chromosome
Region between breakpoints forms a circle by fusion between breakpoints (Figure 2.18C)
Insertional translocation
Region between two breakpoints on one chromosome is excised and inserts at location of third breakpoint which may be on the same or a different chromosome (Figure 2.21)

Structural chromosomal abnormalitites





Weckselblatt et Rudd, 2015

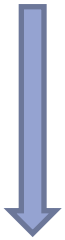
Structural variability of chromosomes

- **Changes in genome greater than 1000 bases (1 kb**)
  = submicroscopic changes, microscopic changes, changes in the number of individual chromosomes, changes in genomes...

a) **Quantitative** - copy number variation (CNVs) - deletion, duplication, insertion

b) **Positional** - translocations

c) **Orientation** - inversion



*Copy number variation **(CNVs)** - segments of DNA greater than 1 kb present in a variable copy number compared to the reference genome*

Congenital chromozomal abberations (CHAs)

For every child conceived, there is a general genetic risk of 3 - 5% of being born with a congential disorder !!!

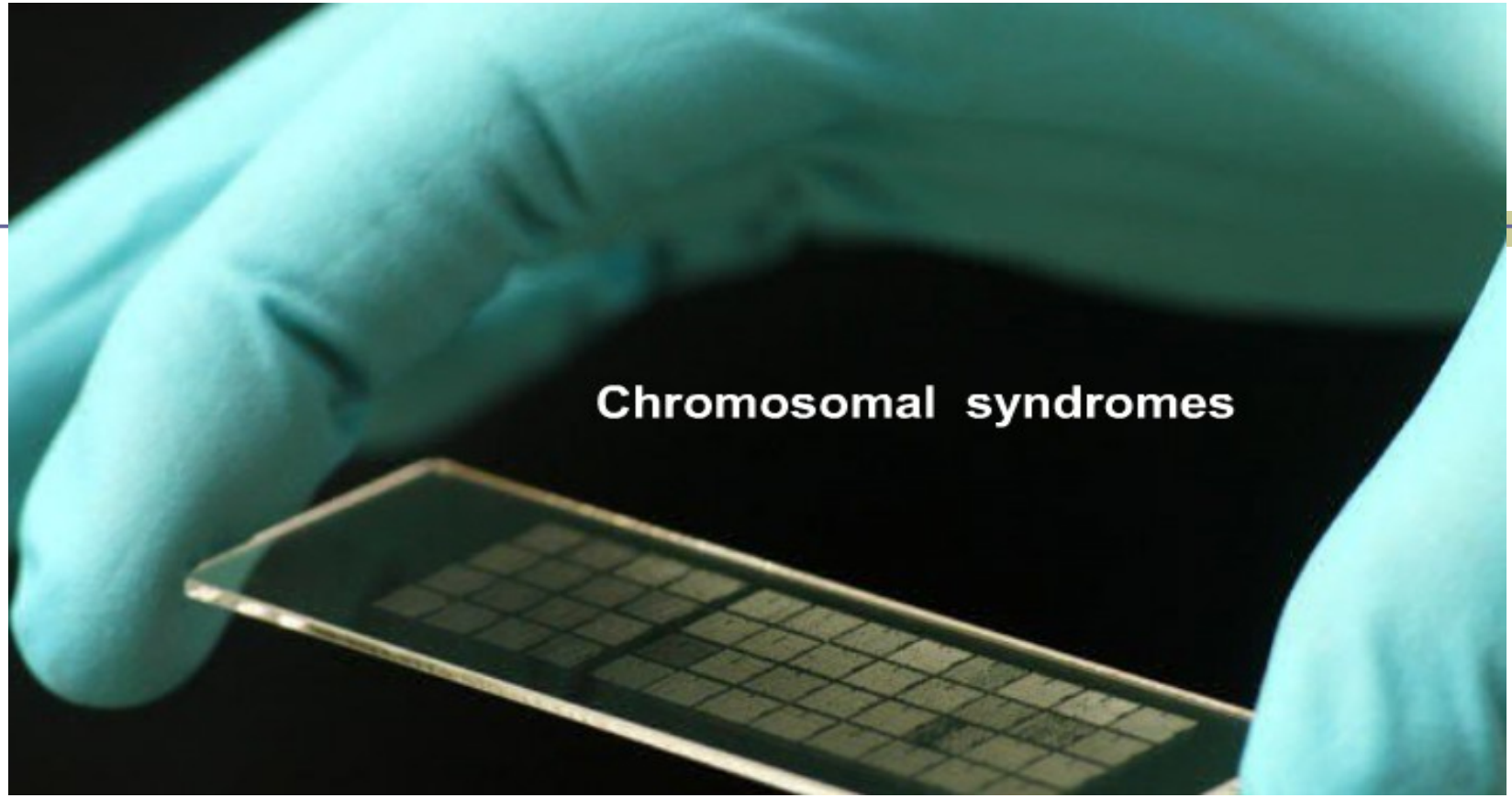
Congenital CHA: 50 - 60% of first trimester abortions

0.56% of live births have CHA

of which 0.1% trisomy 21, 0.1% Robertsonian translocation or other balanced translocation, 0.1% XXX,XXY, or XYY, 0.05% unbalanced change, 0.01% trisomy 18 or 13

NDD, psychomotor retardation, sterility, testicular hypoplasia, amenorrhea, obesity, autism, etc.

CHAs - responsible for about 100 clinically defined syndromes



Designation

According to: discoverer.....Down Syndrome

by symptoms .....cat cry syndrome

by location..... del 1p36 syndrome

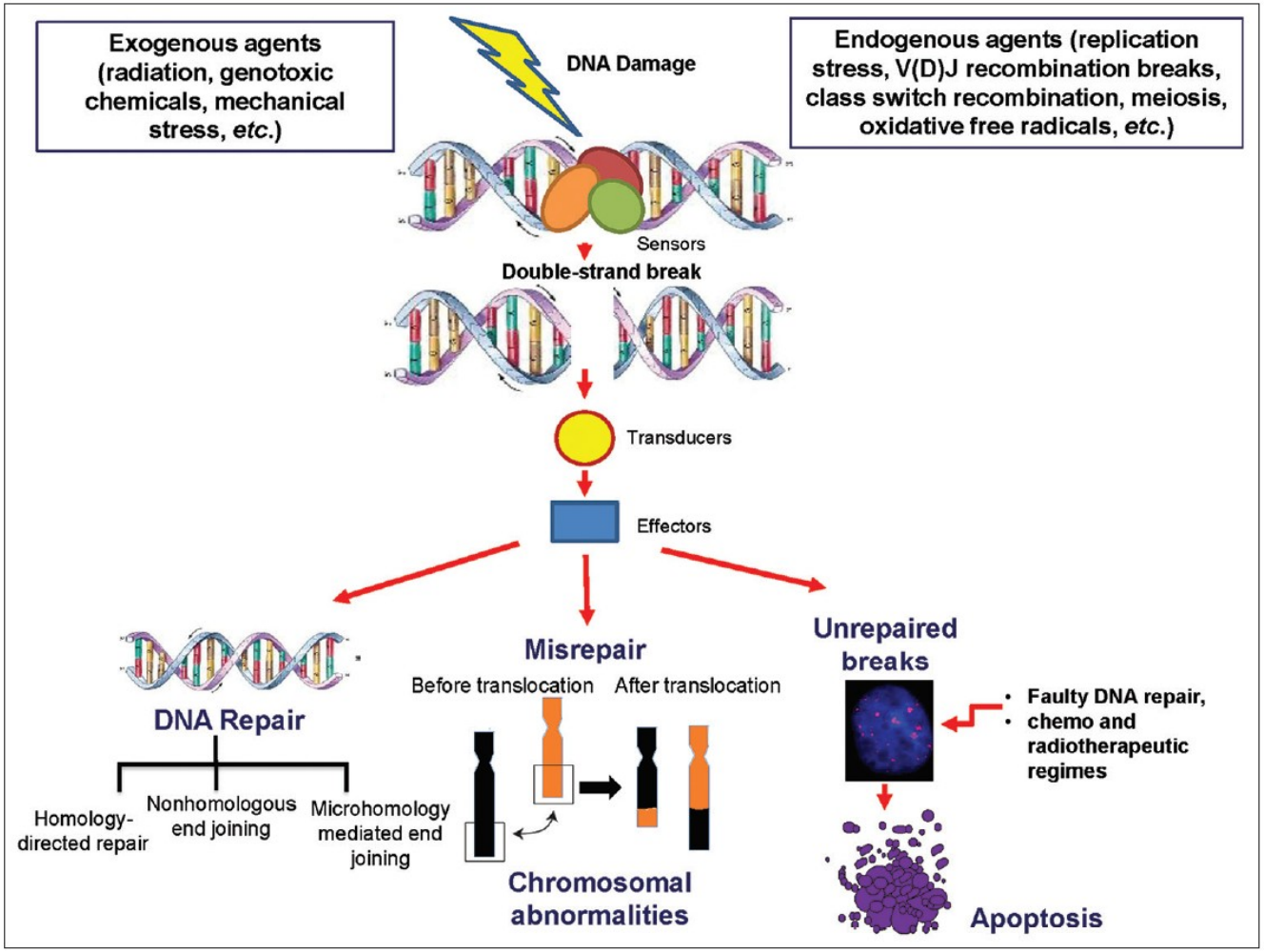
General origin of chromosomal aberations

- A) **spontaneous** (DNA damage + replication, replication, recombination, segregation defects...)
- B) **induced by clastogens** (ionizing radiation, UV radiation, chemicals, viruses...DNA damage)

- **Congenital aberrations**
- **Acquired aberrations**

Structural aberration - the crucial lesion is a double-stranded DNA break (DSB)!
unrepaired = lethal
incorrectly repaired = aberration

DSB effects on DNA



Pandey and Raghavan 2018

Molecular mechanisms of creation of structural chromosomal aberrations

DNA damage and lack of repair

- formation of a double-strand break (DSB) + new telomeric sequences - terminal deletion
- DSB + telomere loss - breakage-fusion-bridge cycle

DNA damage and repair failures:

- DSBs and repair defects via homologous recombination **(HR)**
- DSB and non-homologous end joining **(NHEJ**) and microhomology mediated end joining (**MMEJ**)

Replication disorders:

- Replication fork stalling and jumping to a different template **(FoSTeS)**
- Replication induced by DNA microhomology breaks **(MMBIR)**

Recombination disorders:

- non-allelic homologous recombination (NAHR) - unequal crossing over

Reparation of DSBs – mechanism of homologous / non-homomologous repairs (NHEJ, MMEJ)

Nonhomologous DNA end joining (NHEJ)

Ku70/86, DNA-PKcs, Artemis, pol μ & λ, XRCC4, ligase I V, XLF/Cernunnos

«Error prone»

Entire cell cycle

Whatever the DNA end

Generate diversity

Homology-directed repair (HR & SSA)

RAD50, MRE 11, Nbs1 (MRN); RAD51(B,C,D), XRCC2, XRCC3, RAD52, RAD54B, BRCA2, and other proteins

Restricted to S-G2

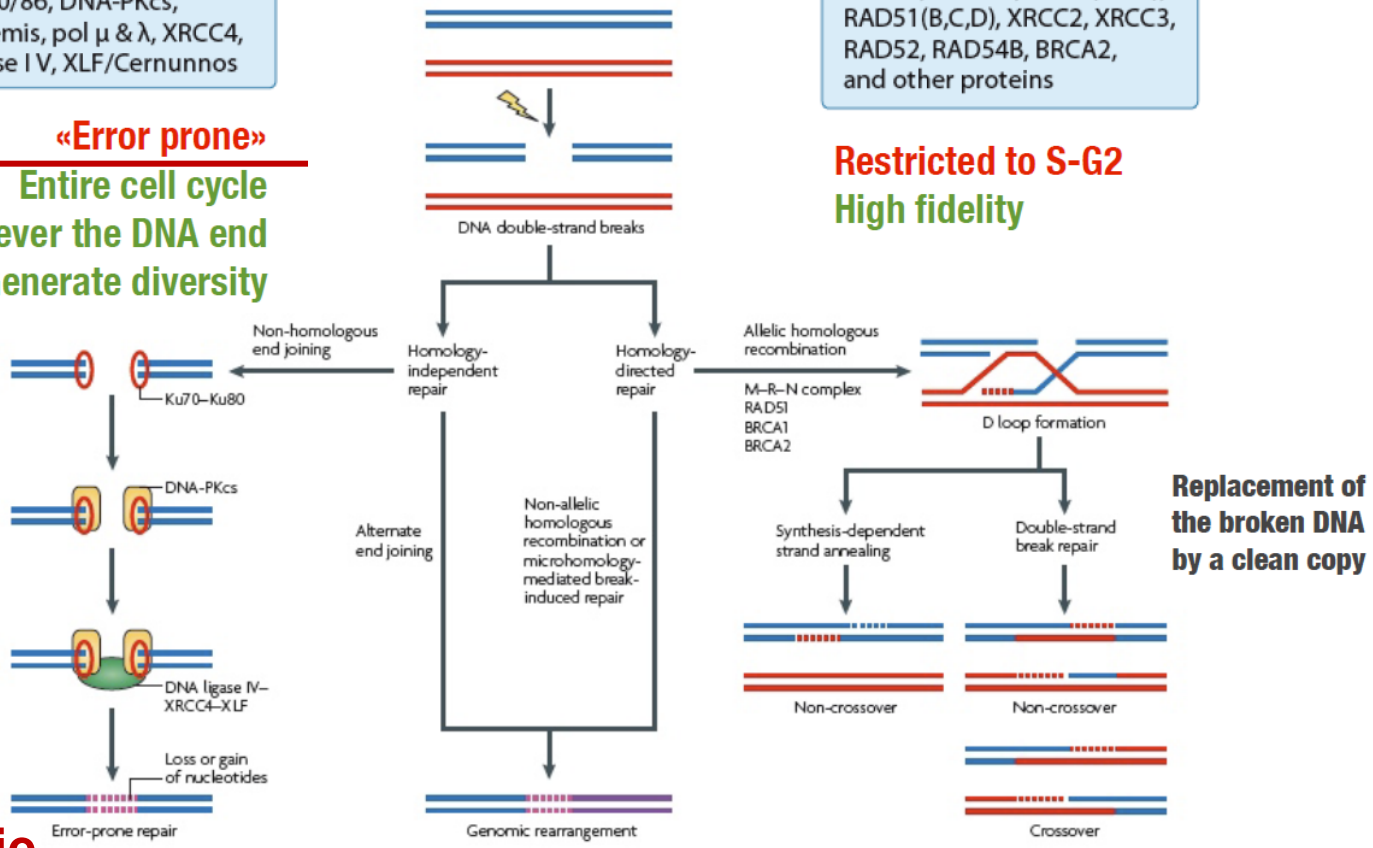
High fidelity

NHEJ

Modification of the ends and ligation

MMEJ

5-25 bp homologie



Replacement of the broken DNA by a clean copy

R-S Mani & A M Chnnaiyan., Nature Rev Genetics 2010-11;819

Examples of CHAs created by by non-homologous end joining (NHEJ)

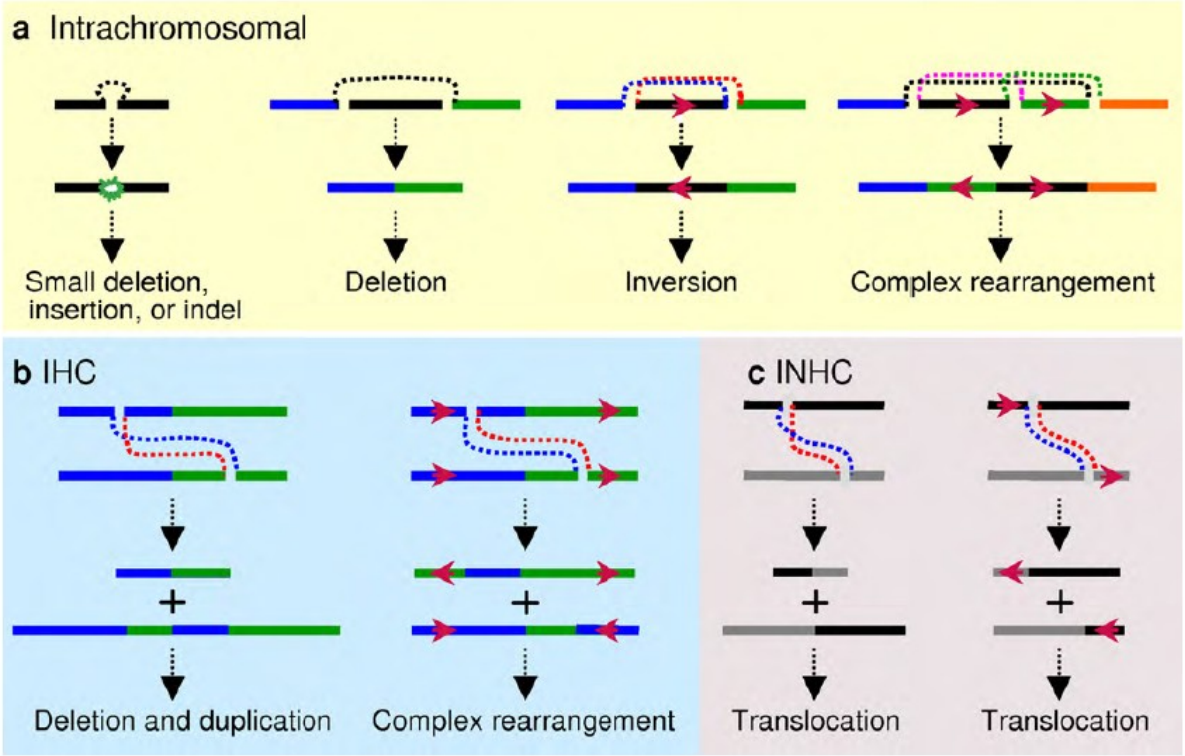
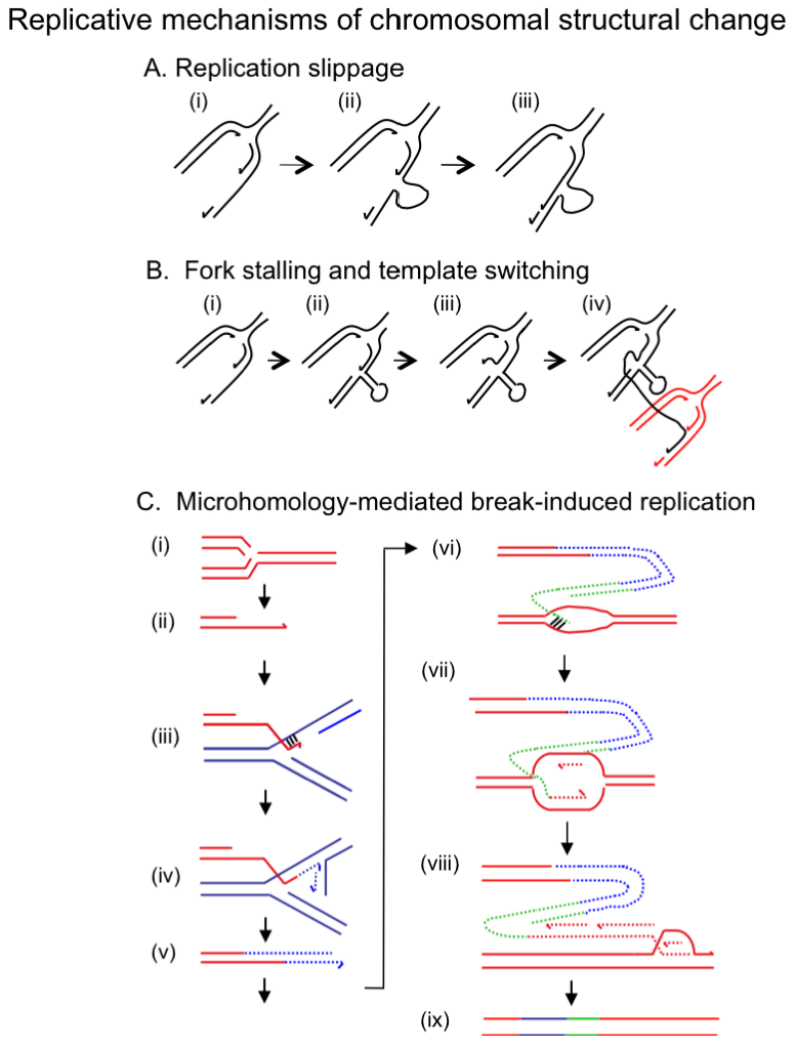


Fig. 4. Examples of genomic rearrangements resulting from non-homologous end joining (NHEJ). Ends ligated are indicated by dotted lines. In b and c, the final outcome, unlike non-allelic homologous recombination (NAHR), is not necessarily reciprocal. In theory, the flexibility of NHEJ implies an unlimited number of different types of genomic rearrangement. IHC, inter-homologous chromosomes. INHC, inter-nonhomologous chromosomes.

Chen at al. 2010

Failures of replication and chromosomal aberrations



FoSTeS - stopping the replication fork and jumping to a different template -
during replication, the replication fork is blocked (single strand break or secondary structure formation), the lagging DNA strand is released and jumps to another replication fork that shares the microhomology region - deletion, duplication

MMBIR - replication induced by DNA microhomology breaks -
initiated by a break in a template strand, skipping and restarting replication on another template - temporary replication fork on another chromosome or sister chromatid - complex changes - deletion, duplication

Hastings et al. 2010

Duplications in genome – „hot spots“ for chromosomal aberrations

- **more than 5.4%** of the human genome is covered **by duplications** (>1 kb with >90% sequence homology), average 18.5 kb

- **1%-14% of each chromosome contains SDs (segmental duplications)**
- 3.4% to 10.7% of genes may be duplicated

The human genome consists

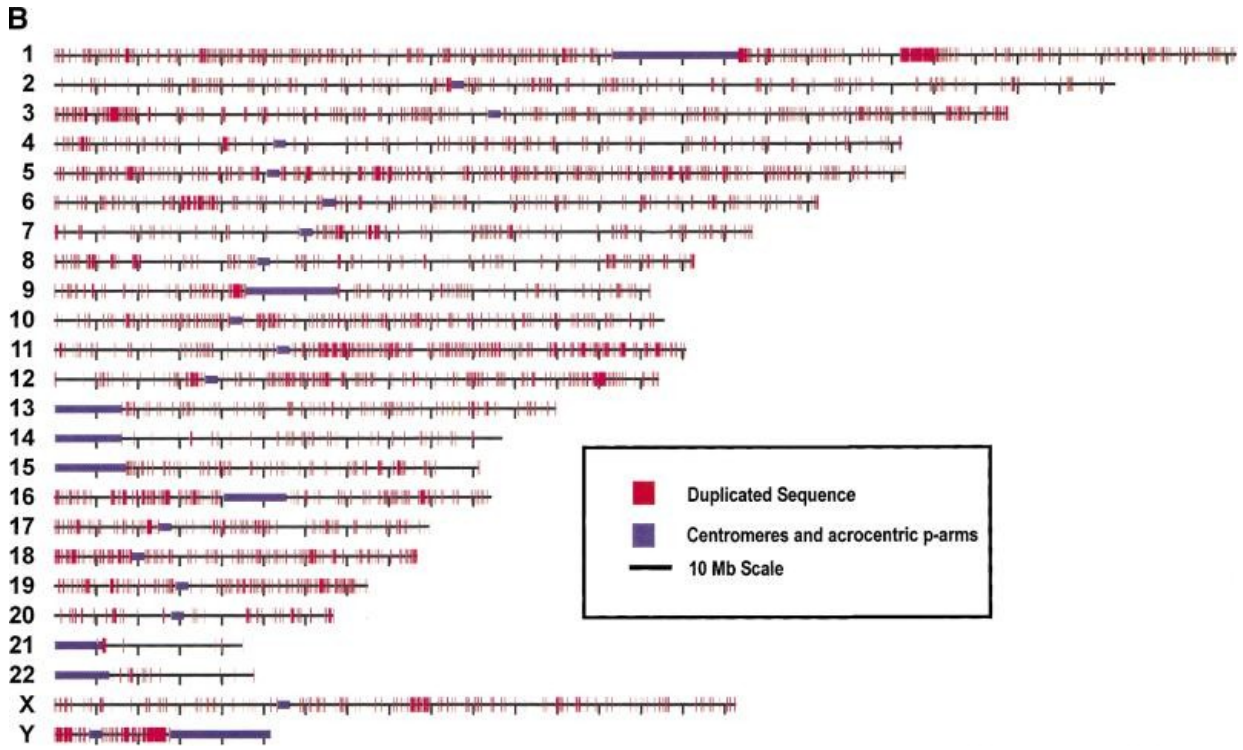
- *low copy number repetitive sequences (LCRs)* - intrachromosomal duplications of >10 kb with >97% sequence identity

- segmental duplications (SDs) - segments >1 kb in size with >90% sequence identity

- *retrotransposons LINE sequences* (L1 6 kb - 516,000 copies), SINE (Alu sequences - 300 bp - 1 to 1.5 million copies)

Zhang et al. 2004

Intrachromozomové oblasti SDs v lidském genomu



duplications (90%-98%; ≥1 kb) cover 3.6% of all sequences

Accumulation in pericentric and subtelomeric regions of chromosomes
interstitial regions chromosomes

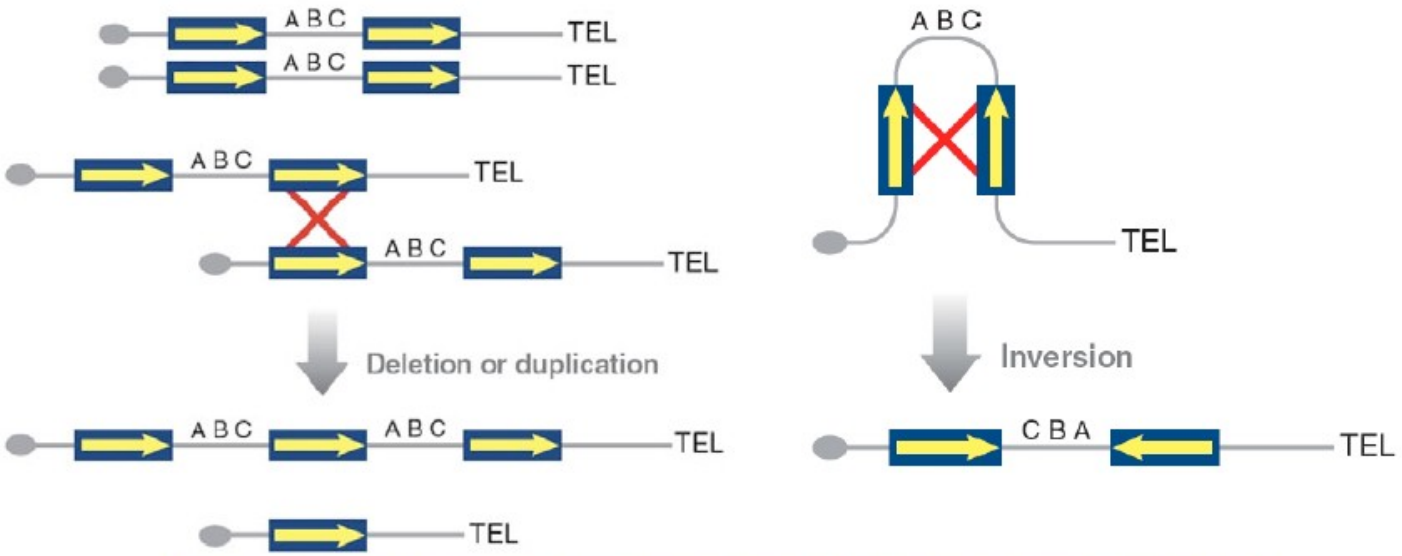
"hot-spot" for NAHR (169 ?)

Genome-wide view of **segmental duplications**. The positions of alignments are depicted in red for each of the 24 chromosomes. Panels separate alignments on the basis of similarity: (**B) 98%–100% identity**. Purple bars depict centromeric gaps as well as the p-arms of acrocentric chromosomes (13, 14, 15, 21, and 22).Because of scale constraints, only alignments >5 kb are visible. Views were generated with the program PARASIGHT (J.A. Bailey, unpubl.), a graphical pairwise alignment viewer.

Bailey et al 2001

Non-allelic homologous recombination (NAHR) recurent deletions / duplications / inversions

- defective meiotic recombination between repetitive sequences (SDs or LCRs)



Genomic disorders

Genomic disorders

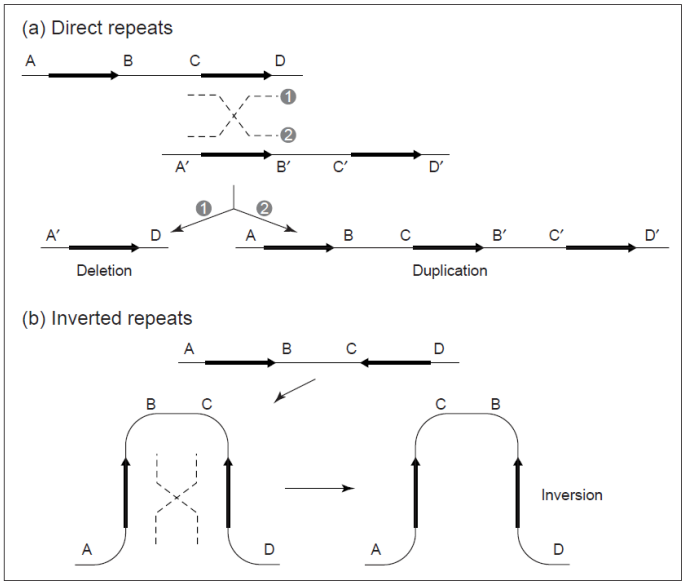
Trends in Genetics

Cell PRESS

Volume 14, Issue 10, 1 October 1998, Pages 417–422

Genomic disorders: structural features of the genome can lead to DNA rearrangements and human disease traits

James R Lupski



Genomic rearrangements resulting from **recombination between repeated sequences.**

Genomic disorders - diseases resulting from genomic rearrangements causing **gene gain or loss (CNVs)**

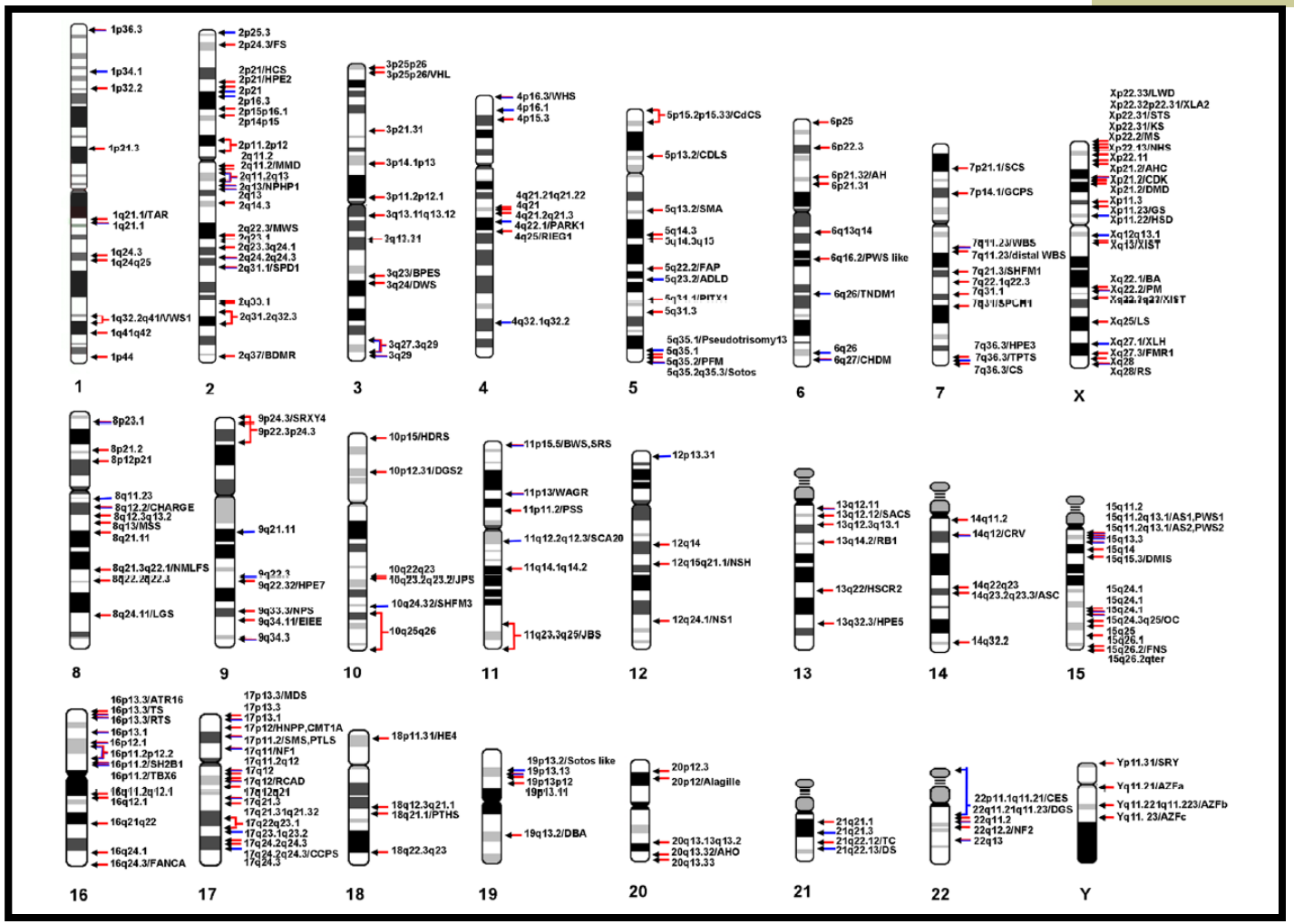
The genome architecture creates suitable conditions for **non-allelic homologous recombination**, which can result in chromosomal rearrangements (NAHR)

Microdeletion/duplication syndromes

Mikrodeletion syndromes - pathological CNVs

- a group of genetically determined diseases caused by small microdeletions of **DNA segments (2-4 Mb)** that are not detectable by classical cytogenetic methods
- patients share ***specific clinical symptoms***...previously described by phenotype ("*phenotype first*"...)
- now "*genotype first*" approach ...first finding, size comparison, genes - influence on phenotype
- **subset of CNVs....pathogenic CNVs** !
- **recurrent** - *arise repeatedly at the same location on the chromosome ...e.g. del 22q11....areas with LCR*s...
- **non-recurrent** - *can arise anywhere in the genome* ...

Incidence of microdeletions / microduplications in human genome



Weise et al. 2012

Recurent microdeletions

TABLE 1 Selected chromosomal rearrangements in humans

Chromosome anomaly	Syndrome/disorder	Estimated frequency[a]
INTERSTITIAL DELETIONS		
del(7)(q11.23q11.23)	Williams	1 in 20,000–50,000
del(8)(q24.1q24.1)	Langer-Giedion	—[b]
del(11)(p13p13)	WAGR	1 in 60,000–100,000
del(15)(q12q12)	Prader-Willi or Angelman	1 in 20,000
del(17)(p11.2p11.2)	Smith-Magenis	1 in 25,000
del(17)(p12p12)	HNPP[c]	—
del(20)(p11.23p11.23)	Alagille	1 in 70,000
del(22)(q11.2q11.2)	DiGeorge/velocardiofacial	1 in 4,000
TERMINAL DELETIONS		
del(1)(p36.3)	Monosomy 1p	1 in 10,000
del(4)(p16)	Wolf-Hirschhorn	1 in 50,000
del(5)(p15)	Cri-du-chat	1 in 50,000
del(16)(p13.3)	Rubinstein-Taybi	1 in 125,000
del(17)(p13.3)	Miller-Dieker	—
INTERSTITIAL DUPLICATIONS		
dup(7)(p12p13)	Russell-Silver	—
dup(15)(q12q12)	Variable features with autism	—
dup(17)(p11.2p11.2)	Mild developmental delay	—
dup(17)(p12p12)	Charcot-Marie-Tooth disease type 1A	1 in 2,500
dup(X)(q22q22)	Pelizaeus-Merzbacher disease	—

[a]Wilms tumor, aniridia, genitourinary dysplasia, mental retardation.
[b]Dash denotes incidence is not known, either due to rarity of anomaly or under recognition/ascertainment.
[c]Hereditary neuropathy with liability to pressure palsies.

Examples of LCRs in known syndromes

TABLE 3 Known characteristics of low copy, region-specific repeat sequences (LCRs) in the human genome

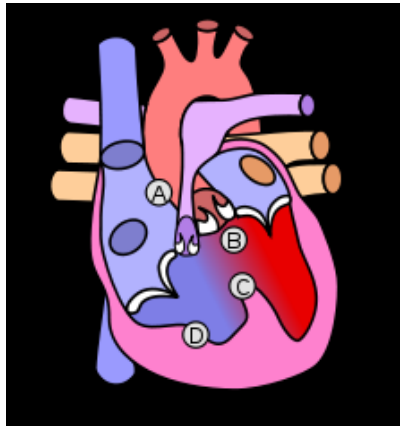
Rearrangement	Syndrome	Size of repeats (kb)	Distance between repeats (Mb)
del(7)(q11.23q11.23)	Williams	320	1.6
del(15)(q12q12)	Prader-Willi/Angelman	400	3.5
del or dup(17)(p11.2p11.2)	Smith-Magenis	250–400	5.0
del or dup(17)(p12p12)	CMT1A/HNPP	24	1.5
del(17)(q11.2q11.2)	Neurofibromatosis I	15–100	1.5
del(22)(q11.2q11.2)	DiGeorge/velocardiofacial	200	3.0

Genetic effects of microdeletions

- **AD heritability - haploinsufficiency** - inability of one copy of the genetic material to maintain the functions that are provided by both copies
- **heterozygote** - monosomy for that part of the genetic information that is located on the corresponding segment of the normal chromosome
- **loss of heterozygosity** - LOH (loss of the dominant allele.....)
- deletion of multiple genes - „***contiguous gene syndromes“***
- Pathological effects of the patient are connected to the size of the microdeletion.....
- incomplete penetrance and variable expressivity.....

Mikrodeletion 22q11
DiGeorge (VCFS) syndrome

- **autosomal dominant with variable expressivity**
- discovered in 1965 by pediatric endocrinologist Angelo DiGeorge
- frequency **1:4000 to 1:6000** live births
- also referred to as Velo-Cardio-Facial Syndrome (VCFS) or CATCH 22
- typical congenital heart defects (also detected prenatally !)
- **Facial dysmorphia**
- hypoplasia - thymus aplasia (***Tbx1*** gene) or parathyroid glands -
- calcium deficiency, cramps
- immunodefects
- (absence of T-lymphocytes)



Fallotova tetralogie: **A**: stenóza plicnice **B**: dextropozice aorty **C**: defekt komorového septa **D**: hypertrofie pravé komory

Cri-du-chat (cat's cry) syndrome

Figure 1
Clinical features of a patient with Cri du Chat syndrome at age of 8 months (A), 2 years (B), 4 years (C) and 9 years 6/12 (D).

Comparison of sizes of 5p deletions - phenotypy - candidate genes

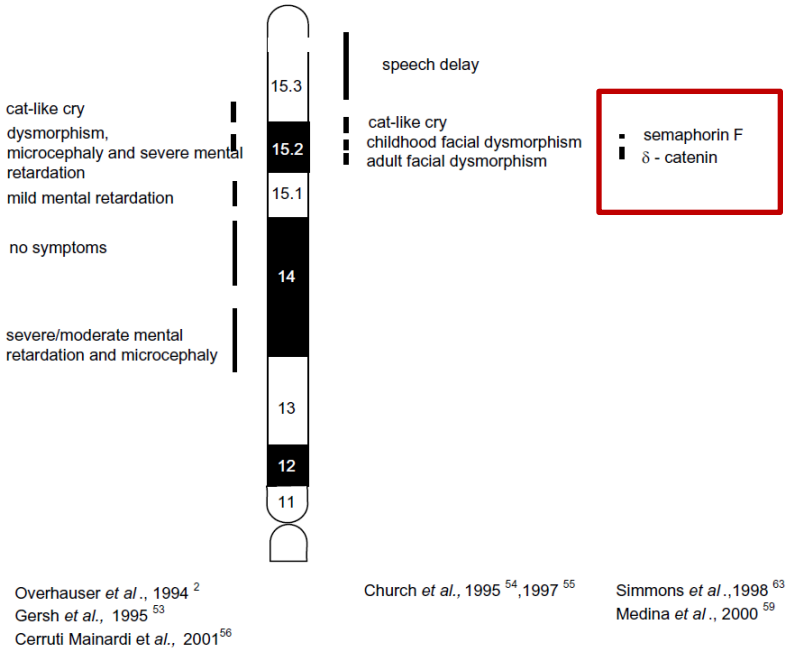


Figure 2
Phenotypic map of 5p. Vertical lines indicate the critical regions for the cry in p15.3, and for the other signs of Cri du Chat syndrome in p15.2. Vertical lines in p15.1, p14 and p13 refer to clinical symptoms reported in individual families with interstitial deletions.

Mainardi CP, 2006

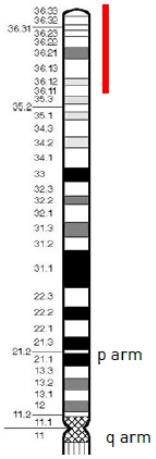
1p36 deletion syndrome

1: 5000

What is 1p36 deletion syndrome?

1p36 deletion syndrome is a chromosome disorder. A chromosome disorder is a change in chromosome number or structure which results in a set of features or symptoms. People with 1p36 deletion syndrome have lost a small but variable amount of genetic material from one of their two chromosome 1s.

Chromosome 1 is the largest chromosome and represents about eight per cent of the total DNA in cells. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. People with 1p36 deletion syndrome have one intact chromosome 1, but the other is missing a tiny piece which affects their learning and physical development in relatively predictable ways. Most of the clinical difficulties are probably caused by the presence of only one copy (instead of the usual two) of a number of genes. However, a child's other genes and personality also help to determine future development, needs and achievements.



Chromosome 1

Most people have, as babies:

- Delay in development
- Feeding difficulties
- Muscles that feel floppy (hypotonia)
- Very large fontanelle (soft spot)
- Eyesight and hearing problems
- Heart conditions, usually mild.

Medical Concerns

Feeding At least two babies out of three need feeding support as they suck too weakly or have difficulty co-ordinating sucking, swallowing and breathing. Many babies also have difficulty keeping their feeds down. This condition is called gastro-oesophageal reflux - GO or GE reflux. In young babies, giving small feeds, adding prescribed thickeners to formula milk and careful positioning may be all that's needed. Babies with severe reflux can have surgery to make a valve that allows food into the stomach but stops the stomach contents returning up the food pipe. Another approach is to insert a feeding tube (G-tube, gastrostomy) direct into the stomach.

Seizures Between half and three quarters of children have seizures. Some children outgrow them or the seizures become less frequent, but many need to take anti-epileptic medicines.

Heart conditions More than 40 per cent of children are born with a heart condition. However, this is often minor and heals naturally. A small number of children need surgery. One child in three has a condition where the activity of the heart muscle is abnormal, called dilated cardiomyopathy. In some children this too improves with time.

Eyesight problems affect four children in five. Most commonly, children are long-sighted. Other problems (such as strabismus/squints) are also treatable but a sizeable number of children have long-lasting problems which mean that they are registered partially sighted or blind.

Hearing Most children have at least a mild sensori-neural (permanent) hearing loss and glue ear (usually temporary) may increase their difficulties.

Infections Vulnerability to infection has not been formally reported as a feature of 1p36 deletion syndrome, but in Unique's experience it affects 2 in 3.

Thyroid One child in five has a low thyroid level. As this can be corrected, thyroid function should be checked at birth, at 6 months and then every year.

Constipation affects more than half of children and occasionally is severe.

Development

- Physical development

Children are slow to sit and walk. Hypotonia (floppiness) makes it hard for them to stay upright and as babies they prefer to move by rolling or wriggling. Typically children sit between the ages of 2 and 3 and walk between three and eight, but some children never walk. All children benefit from physiotherapy and swimming is a popular and valuable form of exercise.

- Learning

Children need very considerable support with their learning. A few learn to use some words and understand clear spoken directions, but most rely on a signing system. Some children do not communicate at this level. Controlling seizures is believed to strongly influence children's ability.

- Behaviour

Children can be a delight.
They are often finely emotionally attuned and show and receive affection. The Unique experience suggests that they are sensitive to music. As they mature, children may become more demanding.

- Growth

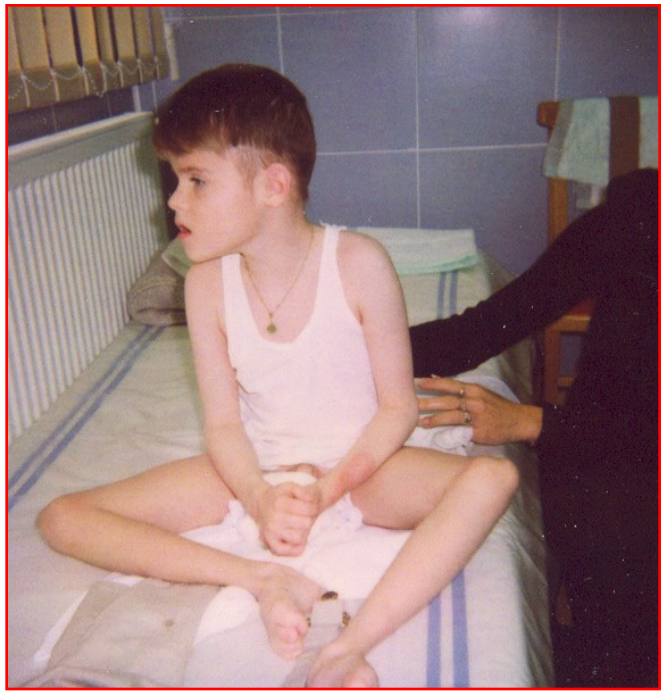
Some babies are born very tiny and remain short.
However, a good number catch up and grow to average height.
Some children even put on too much weight from middle childhood.

Microdeletion syndrome 1p36 - patient OLG FN Brno

- Proband - 4 year old boy

- severe PMR
- facial dysmorphia
- Autism
- tendency to self-harm
- karyotype normal

- **microdeletion 1p36 - 3.2 Mb**



Microdeletion 22q11
DiGeorge (VCFS) syndrome

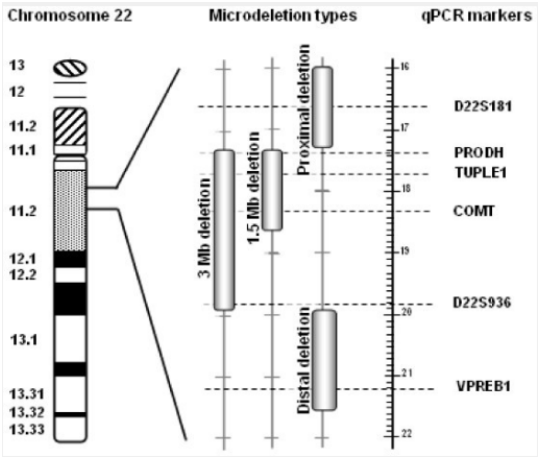
- **autosomal dominant with variable expressivity**
- discovered in 1965 by pediatric endocrinologist Angelo DiGeorge
- frequency **1:4000 to 1:6000** live births
- also referred to as Velo-Cardio-Facial Syndrome **(VCFS)** or **CATCH 22**
- typical congenital heart defects (also detected

  prenatally !)
- **Facial dysmorphia**
- hypoplasia - thymus aplasia (***Tbx1*** gene)

  or parathyroid glands -
- calcium deficiency, cramps
- immunodefects
- (absence of T-lymphocytes)

CATCH 22 - del(22)(q11)

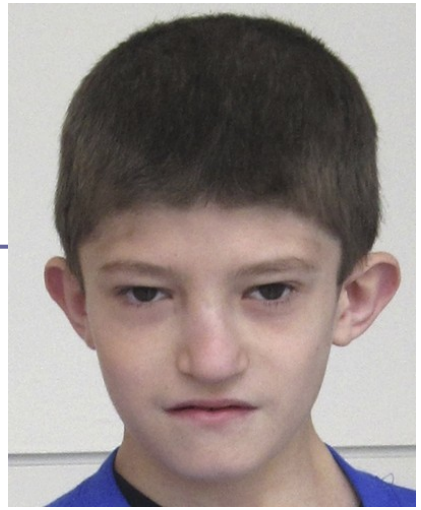
- **C**ardiac defect - typical heart defects
- **A**bnormal faces - chin
- **T**hymic hypoplasia - immune disorders
- **C**left palate - cleft palate
- **H**ypocalcemia - convulsions

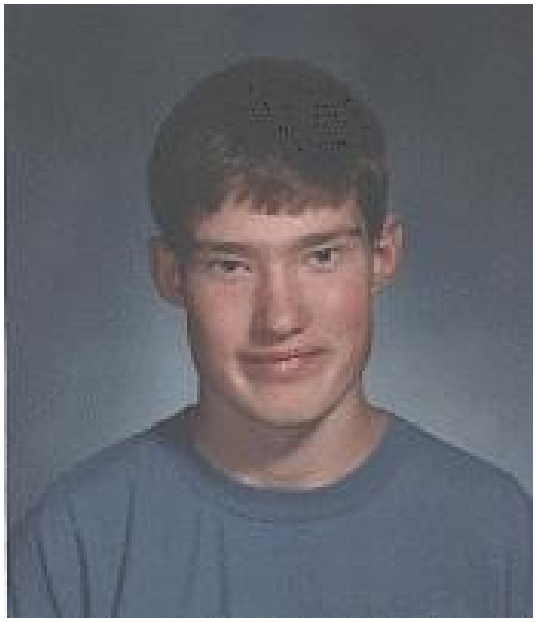


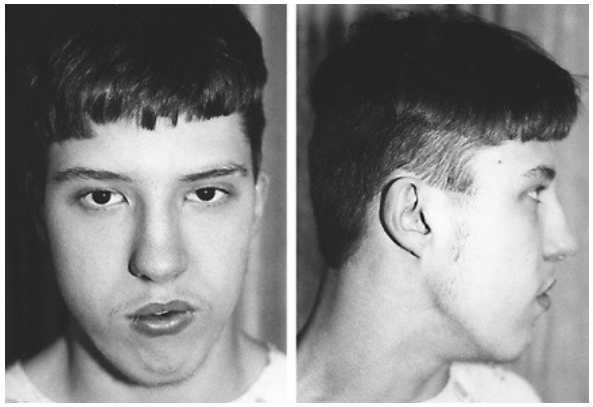
- microdeletion size 22q11 **1,5 - 3 Mb**
- rarely - deletion 10p 10 %
- (DiGeorge II) 80% of patients

Photos of DG/VCFS patients

prominent chin, low set ears, prominent nose....





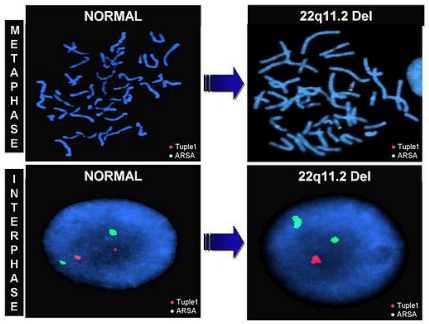


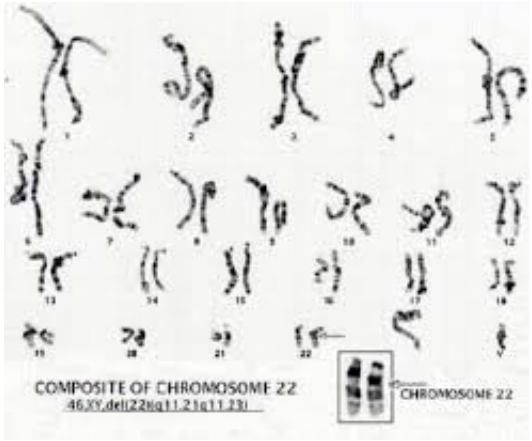
...developmental delay - mild mental retardation, schizophrenia, autism....

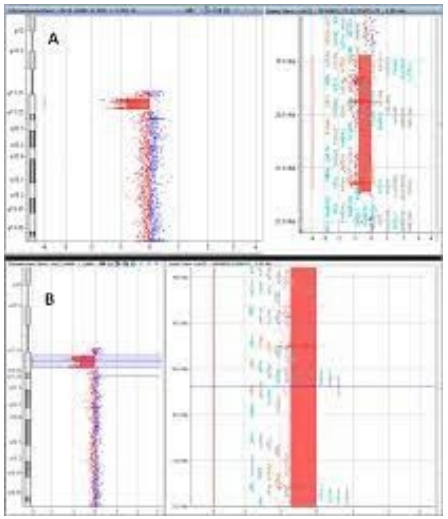
...speech disorders, especially slurring of speech, articulation disorders, speech fluency....

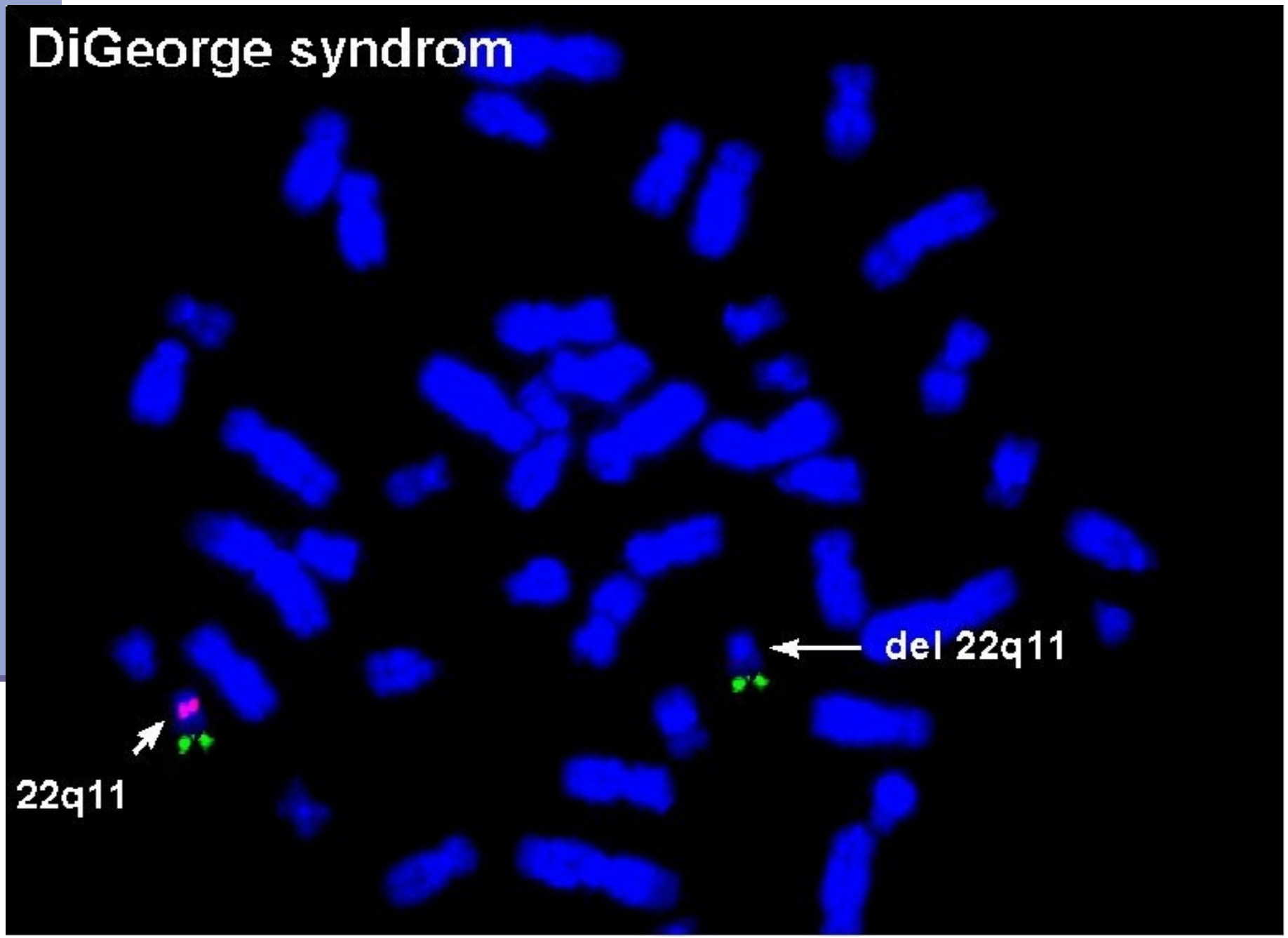
DG/VCFS and detection techniques
(general approach foe all microeletion syndromes)

- Approximately **90% of probands** have ***de novo*** deletion of 22q11, about **6%** have familial transmission
- cytogenetic analysis of karyotype detects only 10-20% of 22q11 microdeletions
- a small percentage of patients may have a translocation or monosomy of chromosome 22
- microdeletion testing is performed by **FISH, MLPA or aCGH**
- **always starting with the karyotype !**

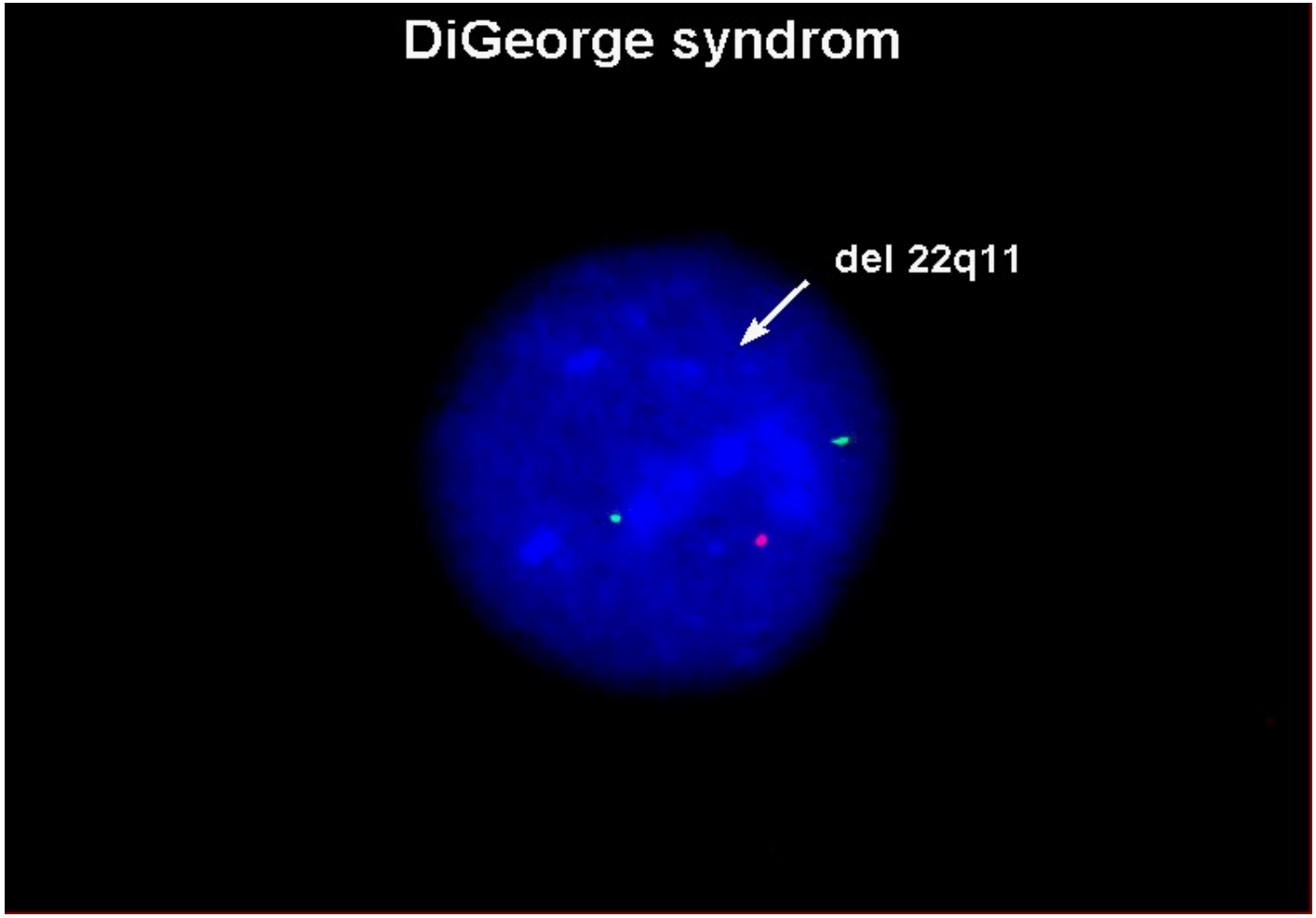




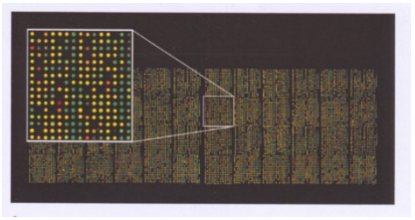


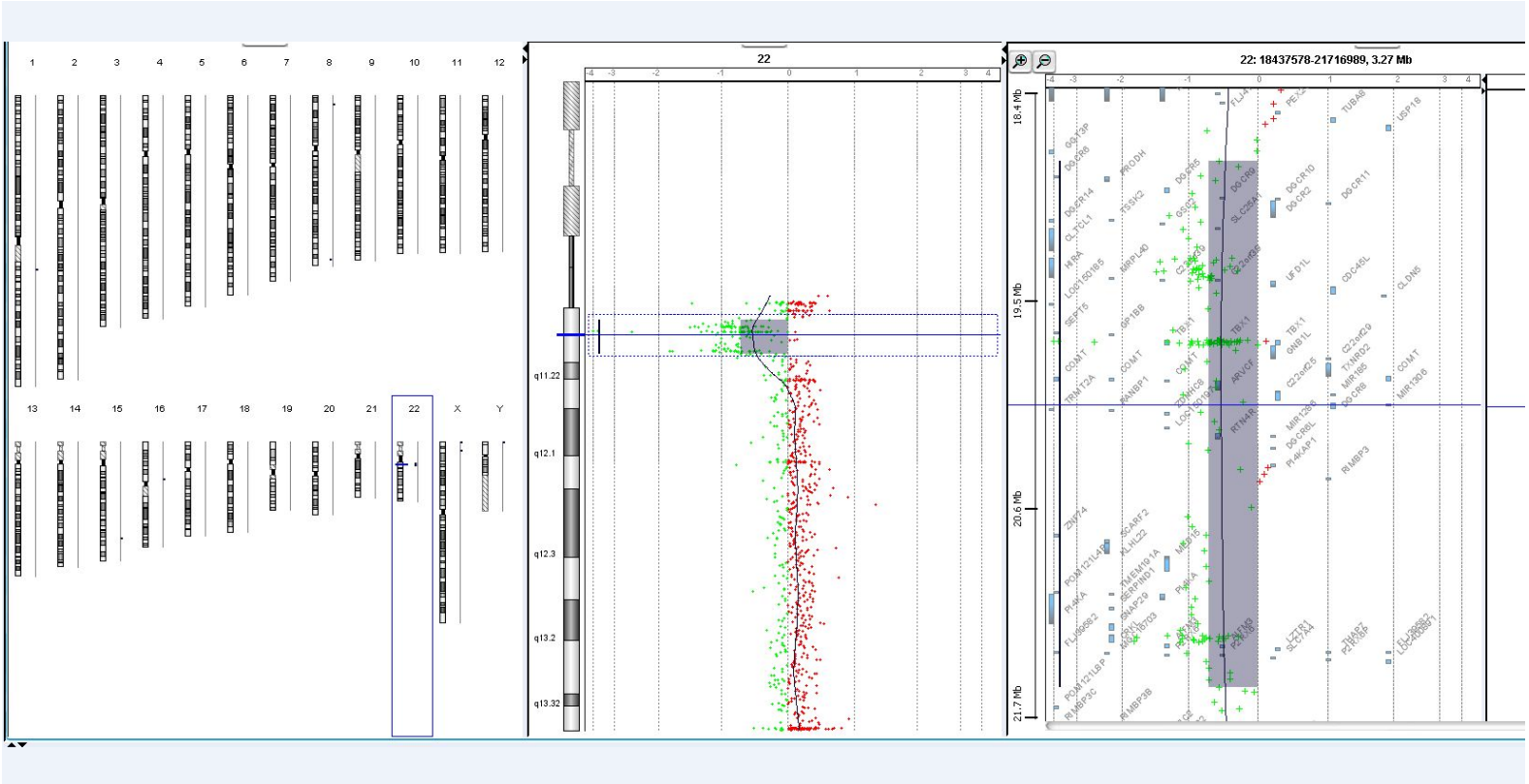

DiGeorge syndrom
del 22q11
22q11

I-FISH



Array –CGH – size of microdeletion





Array-CGH profile of patient with microdeletion 22q11 of size **2,72 Mb**

ISCN: arr[GRCh37] 22q11.21(18818376_21540347)x1

Case report - child with DG/VCFS

- microdeletions can also arise secondarily

- result of abnormal chromosome segregation with balanced translocations or inversions

- E.g. healthy parent with balanced translocation - affected child with deletion or duplication

Unique Combination of 22q11 and 14qter Microdeletion Syndromes Detected Using Oligonucleotide Array-CGH

E. Zrnová[a, b] V. Vranová[a, b] J. Šoukalová[b] I. Slámová[a, b] M. Vilémová[b]
R. Gaillyová[b] P. Kuglík[a, b]

[a]Department of Genetics and Molecular Biology, Institute of Experimental Biology, Faculty of Science, Masaryk University, and [b]Department of Medical Genetics, University Hospital, Brno, Czech Republic

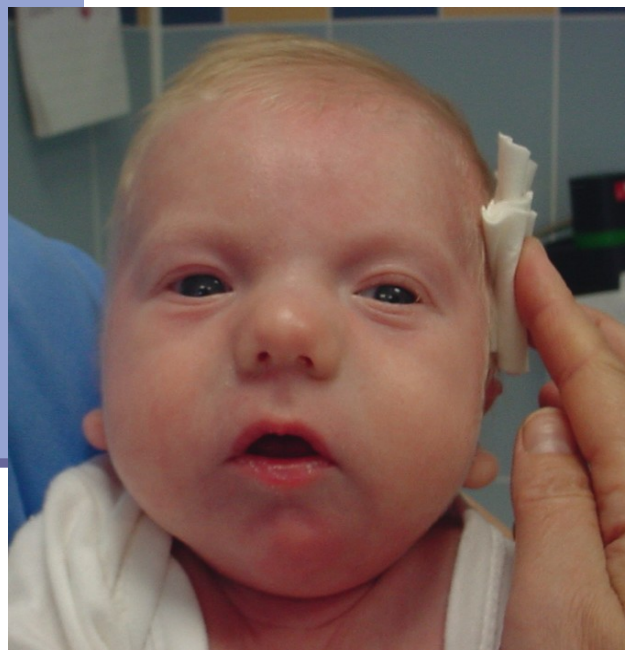
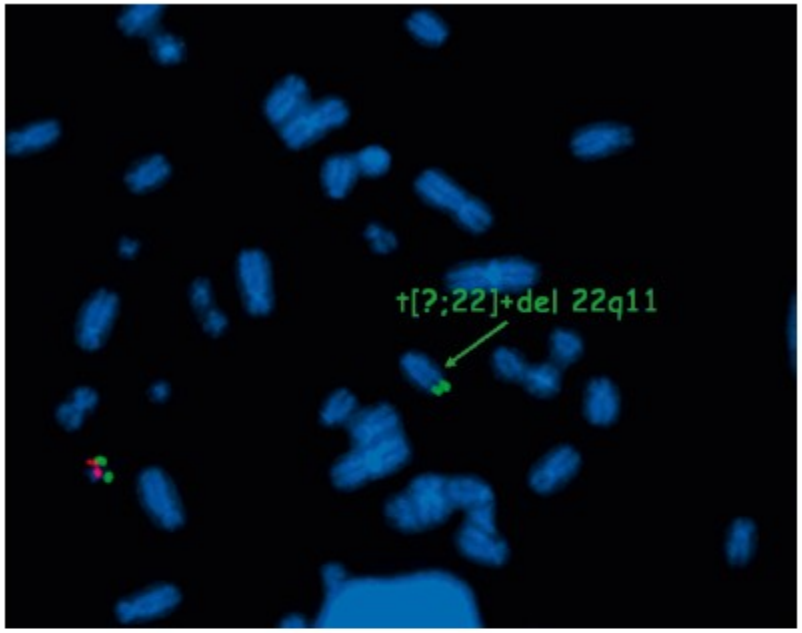
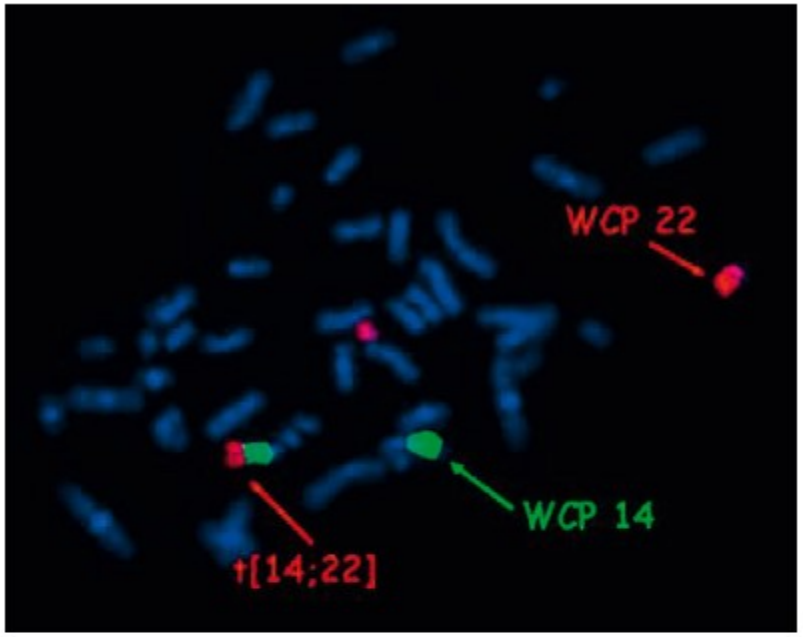


Photo of the proband at 2 months of age showing micrognathia, hypertelorism, prominent tubular nose, dysplastic lowset ears, thin lips, carp-shaped mouth, and a short neck.

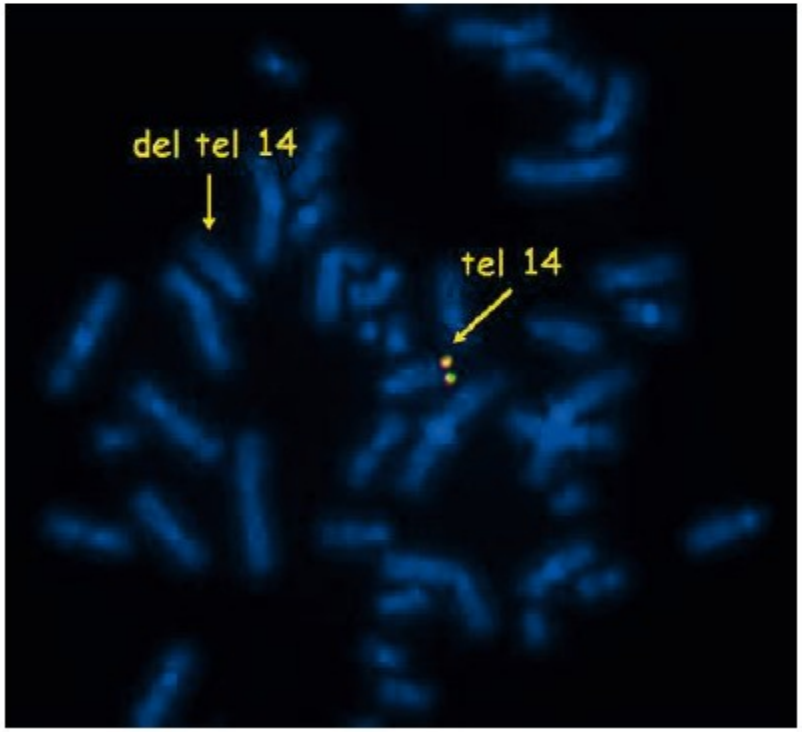
Translocation and two different microdeletions in one patient!



2



4



3

Moleclary-cytogenetic investigation of proband

- Translocation t(14;22)
- Deletion 22q11
- Deletion 14q

Fig. 2. FISH analysis using LSI N25 SR/ARSA SG probe proving the deletion of the 22q11 region (missing red signal at 22q11) with translocation of the remaining chromosome 22 to an unknown acrocentric chromosome (green signal for the gene *ARSA* at 22q13) in the proband.

Fig. 3. FISH analysis using a subtelomeric probe of chromosome 14q. The missing yellow signal at one chromosome 14 indicates a deletion of telomeric region 14q.

Fig. 4. FISH whole chromosome painting (WCP) probes (red for chromosome 22 and green for chromosome 14) show t(14;22) and eliminate the possibility of a 3-chromosome translocation.

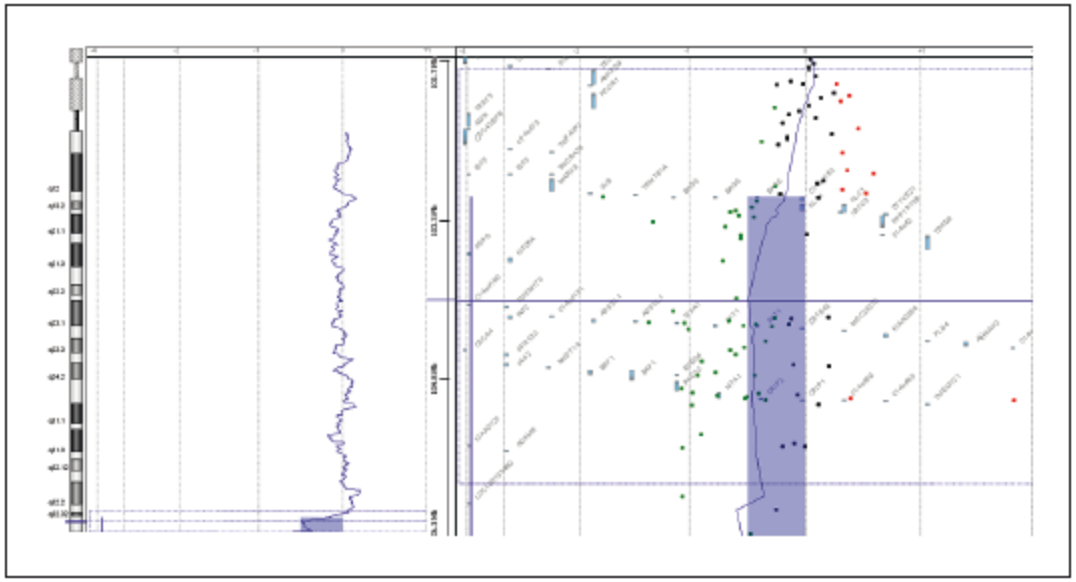


Fig. 5. Array-CGH profile confirmed a 3.24 Mb deletion of 14q32.33 in the proband. The same deletion was also revealed in the mother.

..but mother was healthy..?

Penetrance ?

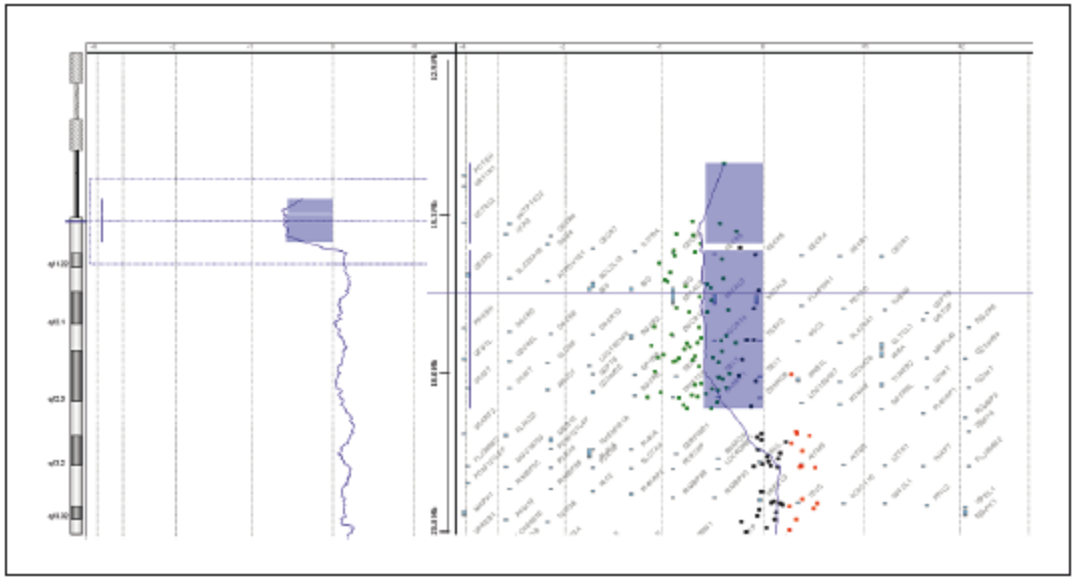
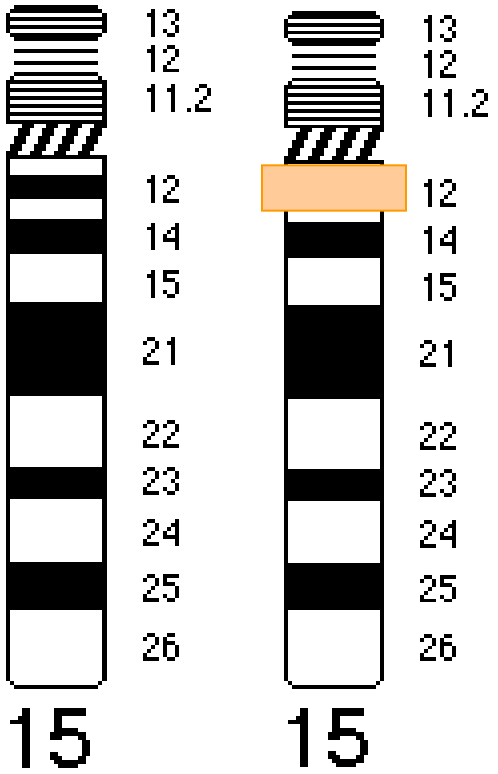


Fig. 6. Array-CGH profile confirmed a 4.25 Mb deletion of 22q11.21 in the proband.

Prader-Willi Angelman syndrome
(microdeletion + uniparental disomy)



- abnormalities in ***chromozome 15*** in 15***q11-q13***
- ***clinically different*** **syndromes!!**

Juan Carreño de Miranda (1680)
„The nude monster“
PW syndrome?

Genetické příčiny vzniku PWS a AS

Prader-Willi syndrome

1. Deletion on paternal chromosome 15 (70%)
2. Maternal uniparental disomy on chromosome 15 (20-25%)
3. Change in imprinting (2 - 4 %)
4. Different chromosomal rearrangements (less than 5%)

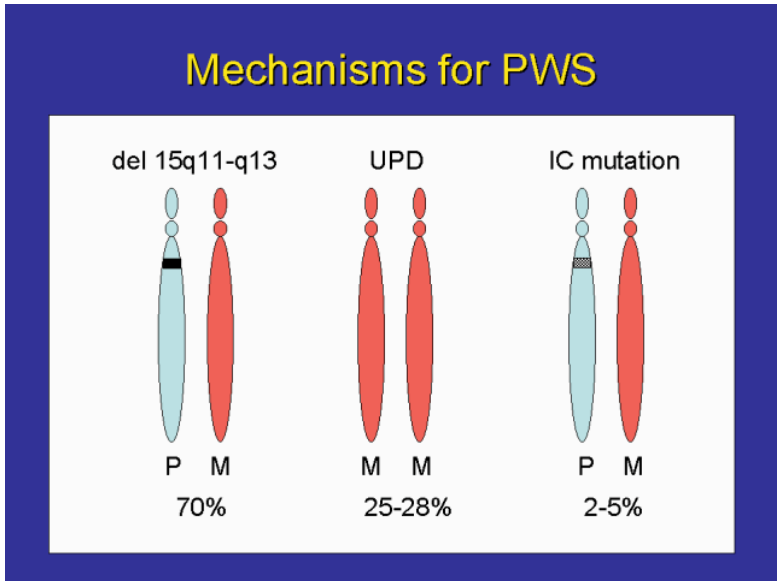
Angelman syndrome

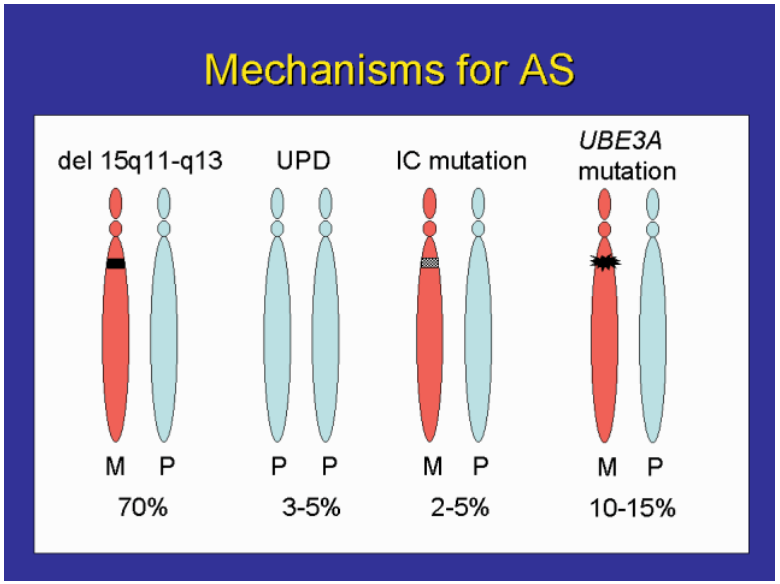
1. Deletion on the maternal chromosome 15 (70 %)
2. Paternal uniparental disomy on chromosome 15 (4 %)
3. Change in imprinting 1 %)
4. Various chromosomal rearrangements (2 %)
5. Mutations in the *UBE3A* gene (3-5 %)

GENOMIC IMPRINTING

Prader –Willi/Angelman syndrome

- **a reversible process whereby sex-specific modification of genes in the parental generation leads to functional differences between the paternal and maternal genomes (alleles) in the offspring**
  - **epigenetic form of gene regulation that leads to functional haploidy:**
    parent-specific monoallelic expression of !
  - **loss of expression of paternal (PWS) or maternal (AS) genes causes disease**





Critical region for PW / AS in chromozome 15

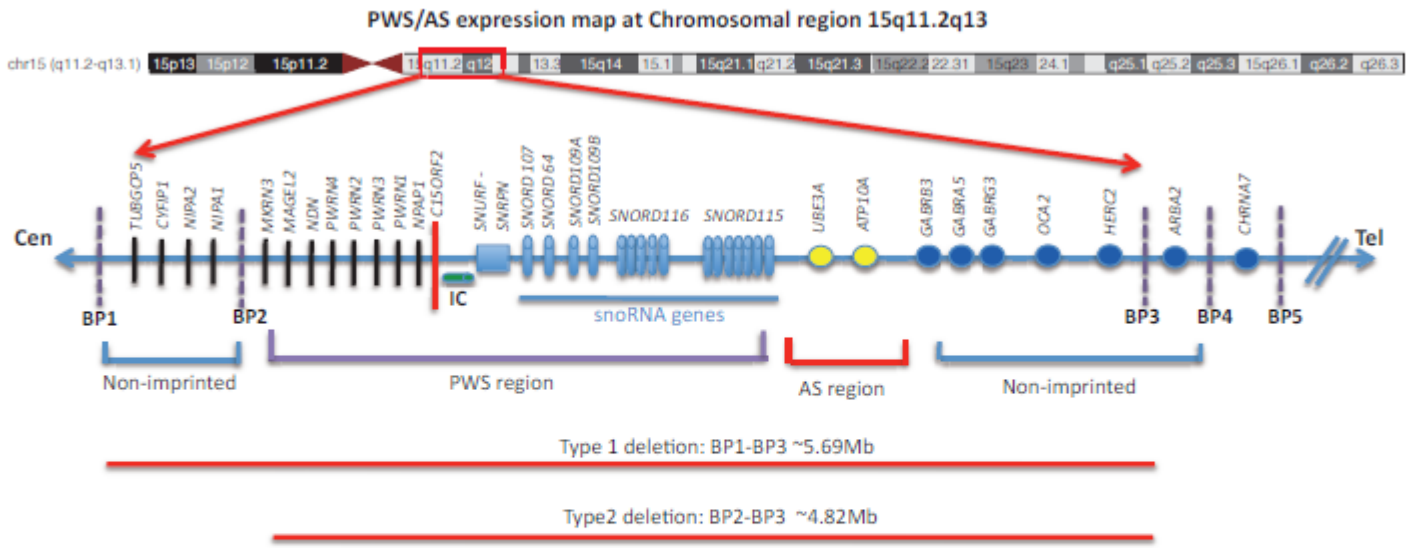


Figure 1 The critical region for PWS on chromosome 15, with the main genes indicated. MKRN3 (or ZNF127) is a zinc finger protein, expressed only from the paternal chromosome; MAGEL2 is expressed only from the paternal chromosome mainly in the brain; NECDIN encodes a DNA binding protein; C15ORF2 is the open reading frame of the *SNURF/SNRPN* gene; *MAGEL2*, *NDN* and *MKRN3* are all small intronless genes. Black lines and light blue ovals between BP2 and BP3 indicate imprinted genes in PWS, Black lines between BP1 and BP2 indicate non-imprinted genes and the 2 yellow circles are the maternally imprinted genes in Angelman syndrome. Exons 1-10 are within SNRPN; snoRNAs are here depicted pictorially. IPW, an RNA transcript lies within the snoRNA region, does not encode a protein but is paternally expressed only; SNORD116 also lies within the snoRNA region and is paternally expressed only. BP, breakpoint; Cen, centromere; tel, telomere.

Smith and Hung, 2016

Paternal UPD and AS

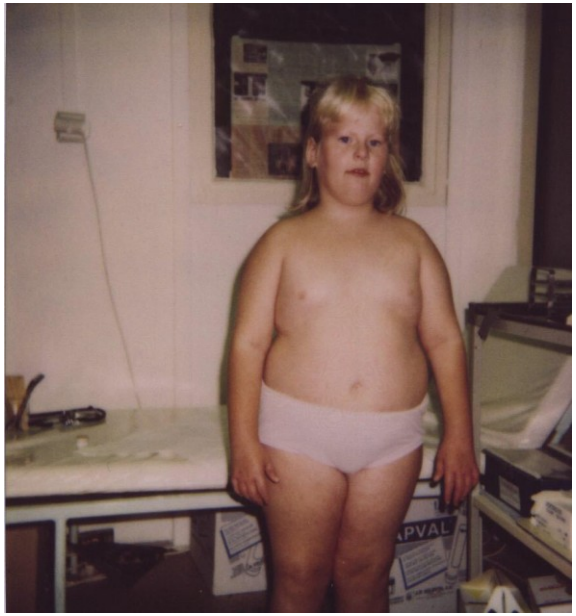
Maternal UPD accounts for 25-28% of PWS whereas paternal UPD accounts for only 3-5% of AS.

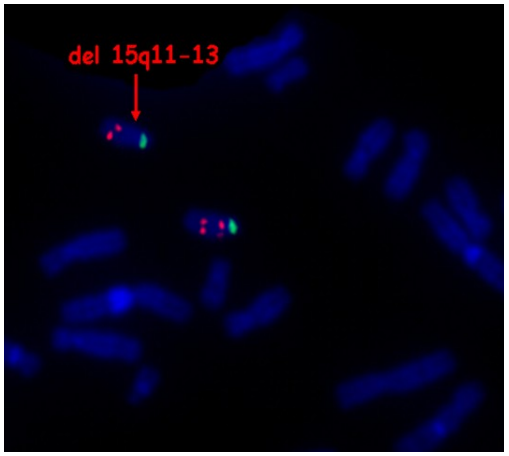
Why?

Because non-disjunction is much more common during maternal meiosis than paternal

Prader-Willi syndrome (del 15q11-q13)

- paternal deletion
- low fetal activity
- hypotonia
- excessive weight gain, hyperphagia
- short stature
- hypogonadism
- mental retardation
- hypopigmentation
- skeletal development delay (acromicria)





Angelman syndrom
(happy puppet syndrome)

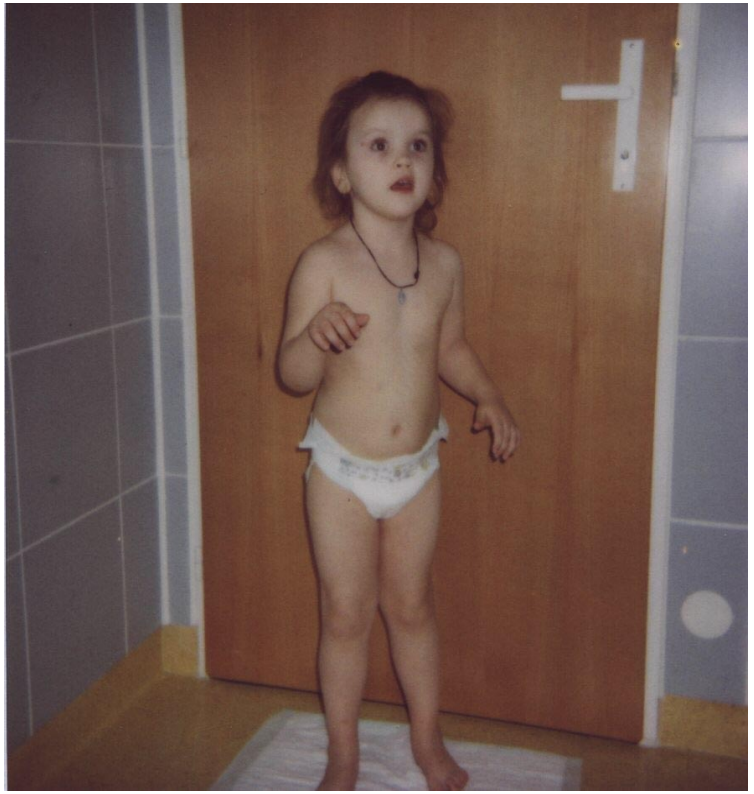
Harry Angelman (1965) – first description

Occurrence: frequency not exactly known

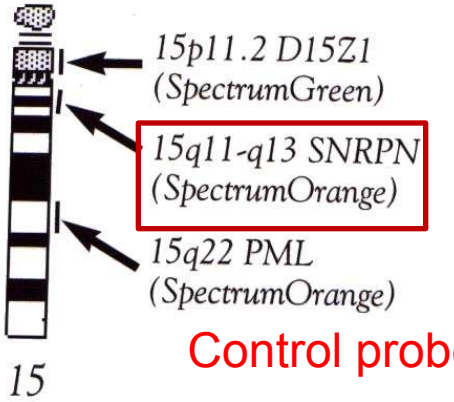
- estimate about 1:15,000- 1:30,000
- in both sexes and all races

Angelman syndrome (del 15q11-q13) „Happy Puppet“

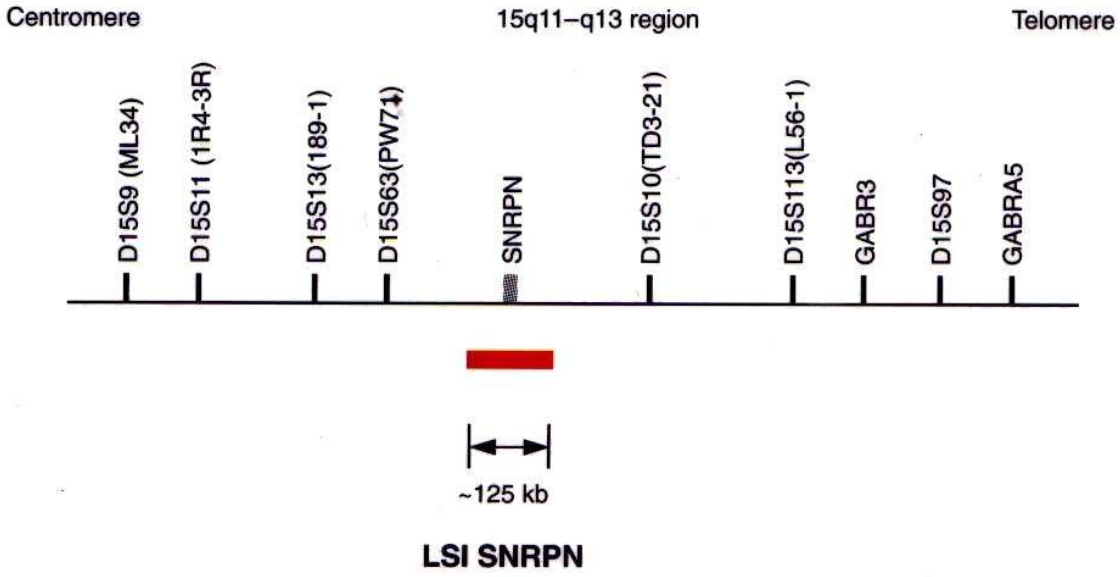
- maternal deletion
- hard mental retardation
- hypotonia
- epilepsia, seizures
- hypopigmentation
- hyperactivity
- speech absence
- prominent scull shape (mandibul, microcephaly, flat back of head..)
- „happy character“
- movement or balance disorder

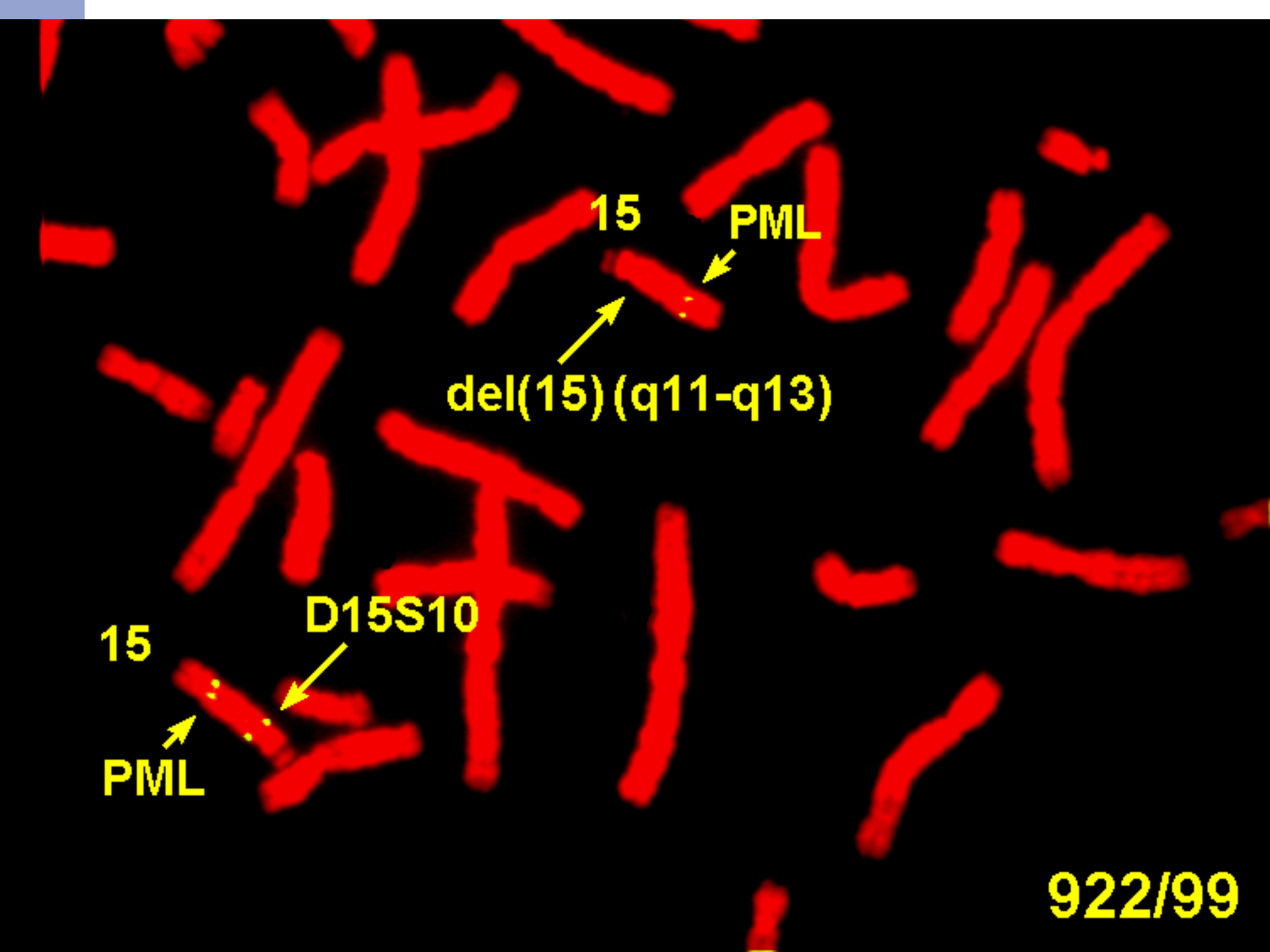


FISH probe - Vysis
Locus SNRPN
PW syndrom



Control probe




15
PML
del(15)(q11-q13)
D15S10
15
PML
922/99

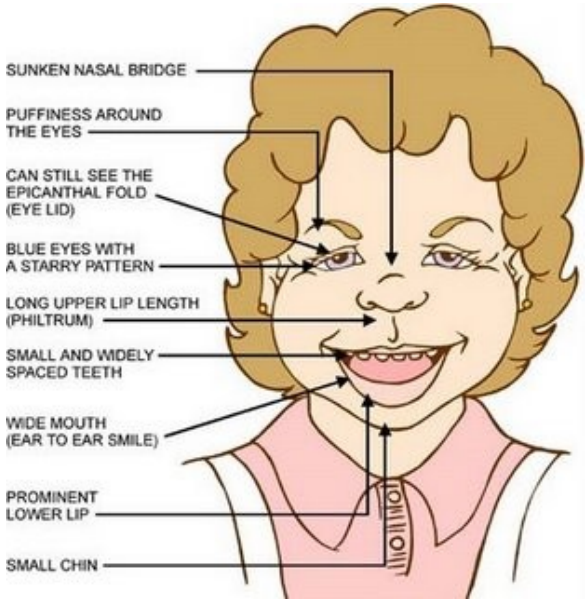
William-Beuren syndrome

- autosomal dominant disease with variable expressivity, usually *de novo*
- risk of the same disability is 50% for children of probands
- incidence 1:20 000 live births
- cause: **del (7)(q11.23),** the deletion region of about **1.5 Mb** includes at **least 17 genes**, the most important being the ***ELN*** gene encoding **elastin**
- detekce: FISH sonda Vysis – LSI Elastin gene 7q11.23 Spectrum Orange/ 7q31 Spectrum Green control probe DNA
- MLPA, aCGH

Williams Beuren syndrome (del 7q11)

- developmental delay
- mental disability
- failure to thrive
- heart defects (heart murmur, narrowing of main blood vessels)
- flattened nasal bridge
- widely spaced teeth
- hypercalcemia
- gastrointestinal problems
- urinary difficulties

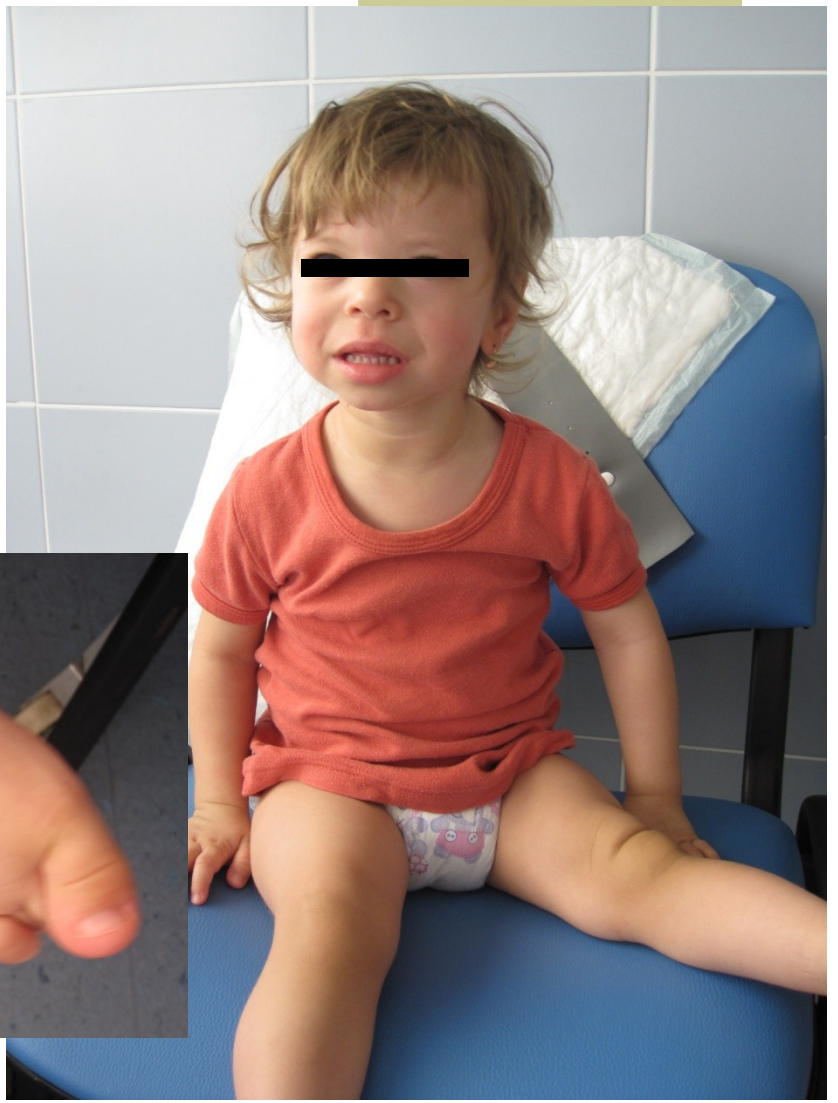
https://www.google.cz/search?q=williams+beuren+syndrome&source=lnms&tbm=isch&sa=X&ei=MimGUvDpC4GctQaJhYGwCg&ved=0CAcQ_AUoAQ&biw=1920&bih=989#facrc=_&imgdii=_&imgrc=MdTDkcoWBwg-WM%3A%3BTKKZzTKDfniYIM%3Bhttp%253A%252F%252Fwww.thespeciallife.com%252Fimages%252F

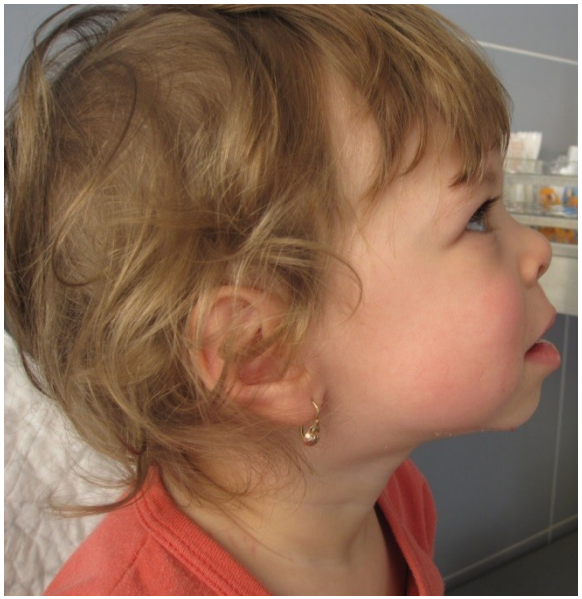


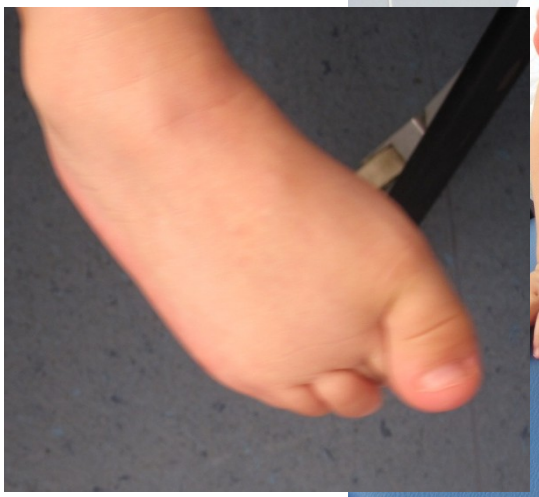
https://www.google.cz/search?q=williams+beuren+syndrome&source=lnms&tbm=isch&sa=X&ei=MimGUvDpC4GctQaJhYGwCg&ved=0CAcQ_AUoAQ&biw=1920&bih=989#facrc=_&imgdii=_&imgrc=HTjyFEuSnZo4JM%3A%3BkqK81uaGRtKPIM%3Bhttp%253A%252F%252Fgeneticsf.laba

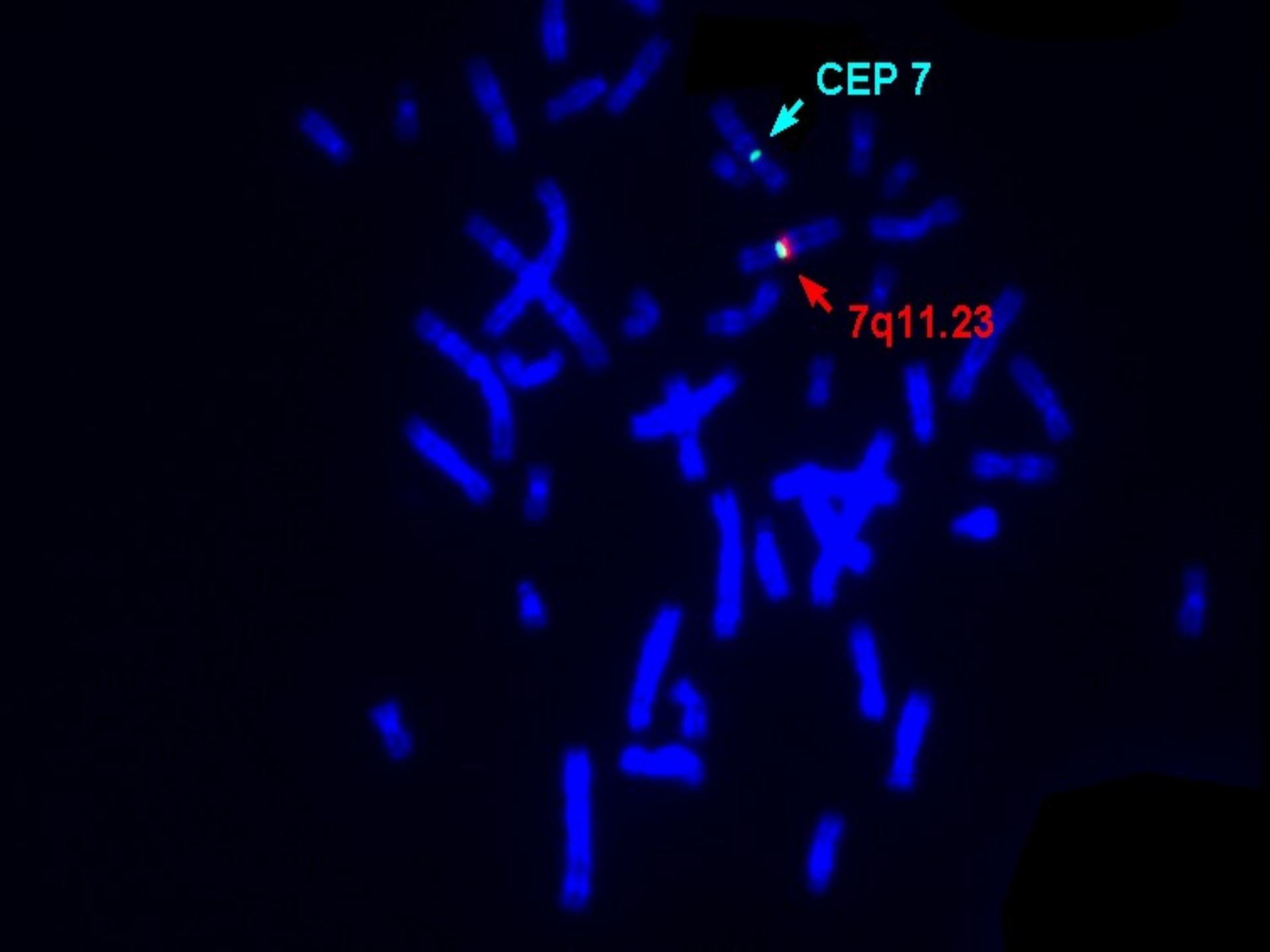
Williams – Beurenův syndrome: case report

- Birth: 2010
- Phenotype: NDD, stigmatizatio
- Cause: **del 7q11.23 (1,4 Mb)**








CEP 7
7q11.23

Výsledek vyšetření – profil array-CGH s mikrodelecí 7q11.23