Intellectual impairment (II, ID, MR, learning/intellectual disability/difficulties)

Krzysztof Szczałuba MD PhD

18.03.2016

Definition

According to AAMR*:

A. Full-scale Wechsler Intelligence Quotient (IQ) of less than 70 (based on individual psychological assessment)

B. Abnormalities in at least three areas: communicating skills, self-dependence, social/interpersonal skills, public goods usage, life attitudes, education, rest/relaxation, health and safety

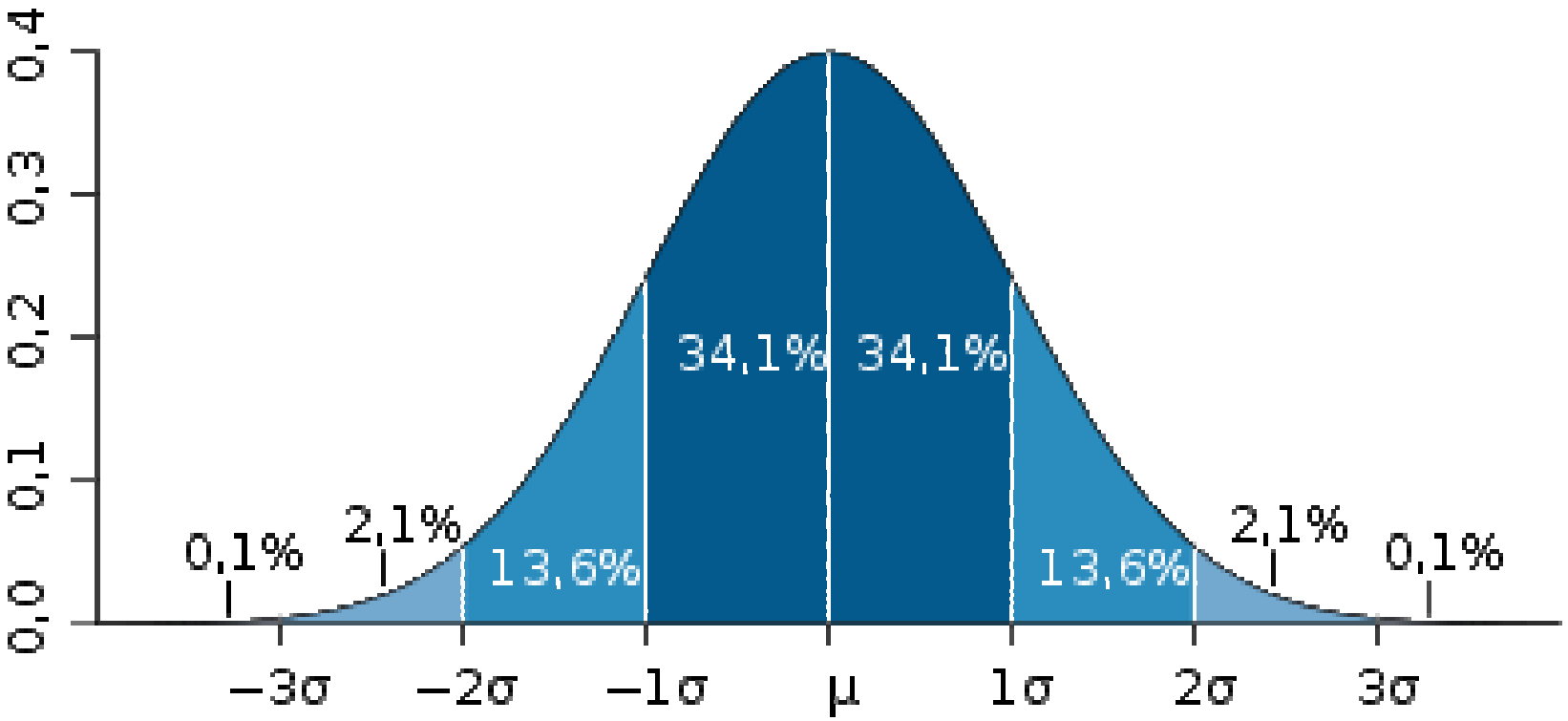
C. Childhood onset

1. only A

2. A and B

3. A, B and C

American Association on Mental Retardation. Mental Retardation: Definition, Classification and Systems of Supports, 10th ed, Washington, 2002


0,0
0,1
0,2
0,3
0,4
0,1%
2,1%
13,6%
34,1%
34,1%
13,6%
2,1%
0,1%
−3σ
−2σ
−1σ
μ
1σ
2σ
3σ

Adult individuals with ID?

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 145C:232–240 (2007)

ARTICLE

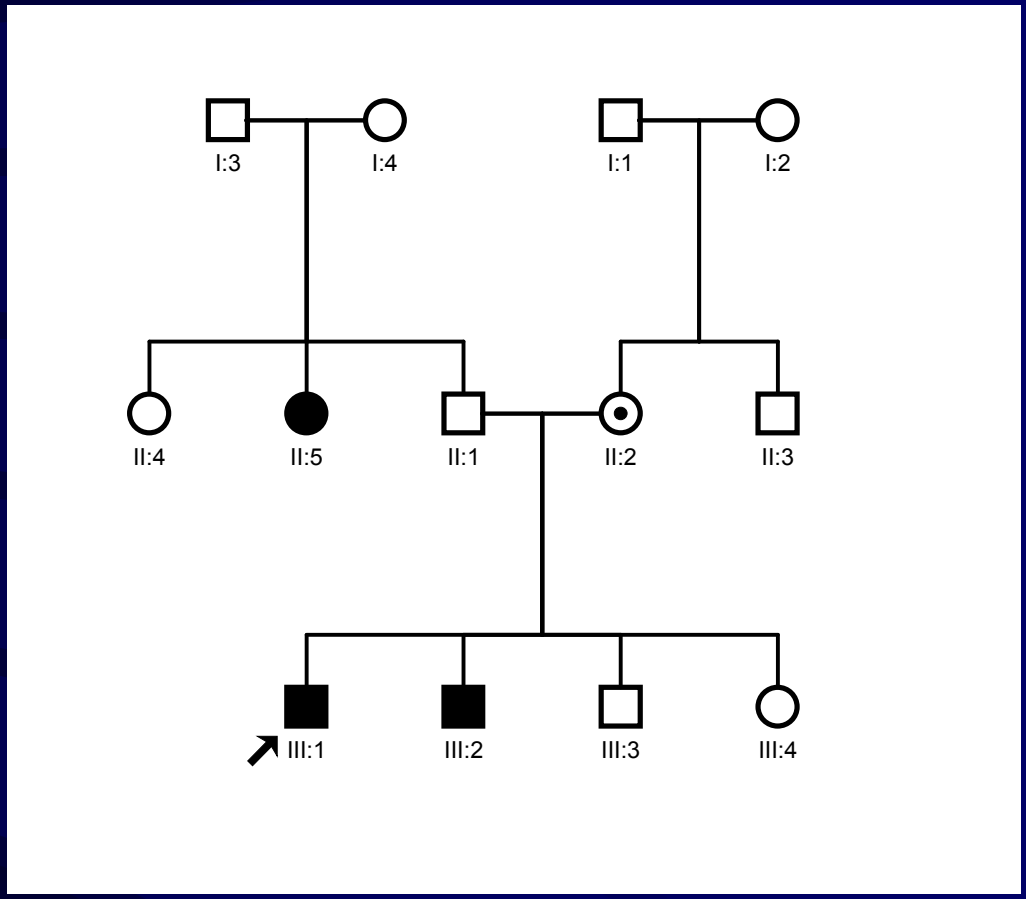
Analysis of 88 Adult Patients Referred for Genetics Evaluation

STEPHANIE N. MAVES, MARC S. WILLIAMS,* JANET L. WILLIAMS, PETER J. LEVONIAN, AND KEVIN D. JOSEPHSON

1.	Congenital anomalies syndromes + ID	n=26
2.	Collagenopathies/Connective tissue disorders	n=18
3.	Chromosome aberrations	n=12
4.	ID only	n=12
5.	Endocrine/Metabolic disorders	n=8
6.	Bone dysplasias/dysostoses/dysgeneses	n=6
7.	Others	n=6

ID at least 50 of 88

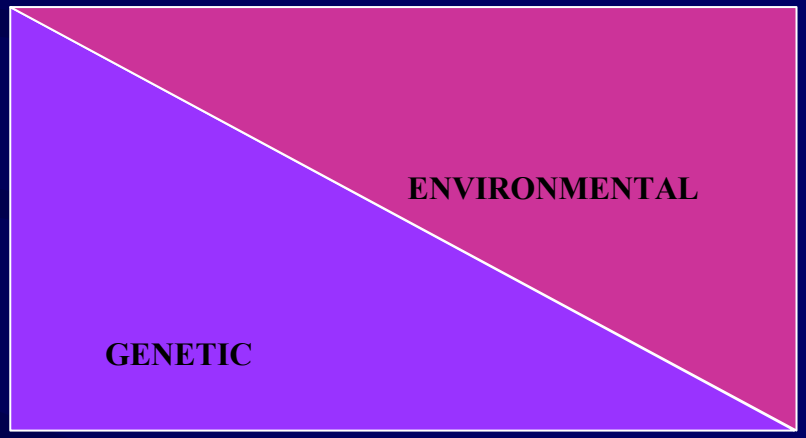
Adults with ID?



II-5 oligophrenia, encephalopathy, embriopathy, microcephaly → **5p-**

ID – a clinical symptom

DIVISION	BASIS
Borderline	IQ 70-85
Mild	IQ 50-70
Moderate	IQ 35-50
Severe	IQ 20-35
Profound	IQ<20



INCIDENCE IN PL:

Wald, Zaremba: 0,34% (for more profound ID – incidence measured for age 7-14yrs)

WORLD: 0,3% for more severe end – 7% for milder end

ID – classification (chosen)

- Constitutional ID: 3%, IQ usually >50, ‘school type’, no CNS changes, important socioeconomic status
- Pathological ID: 0,3%, IQ usually <50, ‘preschool type’, CNS changes, no family influence

- According to the causative factor timing:
- prenatal (genetic [1/3], mother’s illness, infections, malnutrition, dystrophy);
- perinatal (SGA, infections, hypoxia, intracranial hemorrhage);
- postnatal (trauma, infections)

Mild ID– causes (n=439, *Bundey JMG 1989*)

DS	5,7%
FRAX	4,6%
Other chromosome aberrations	0,6%*
CP, other neonatal disorders, sequelae of intrauterine infections	2,7%
Postnatal trauma	3,2%
Congenital anomaly and genetic syndromes	3,4%**
Unknown	80%

* currently likely +5-17% for the whole ID group (telomere *screening*, CGH, arrayCGH)

** +10-20% after Whole-exome or Whole-genome techniques are applied

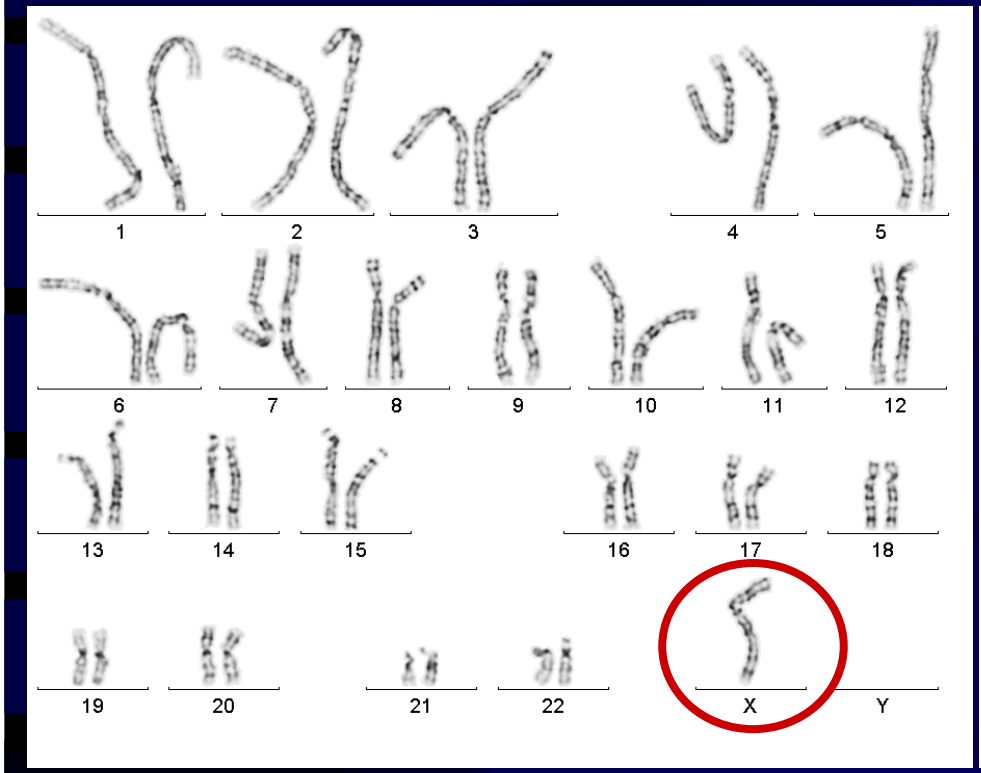
Severe ID – causes (*Curry AJMG 1997*)

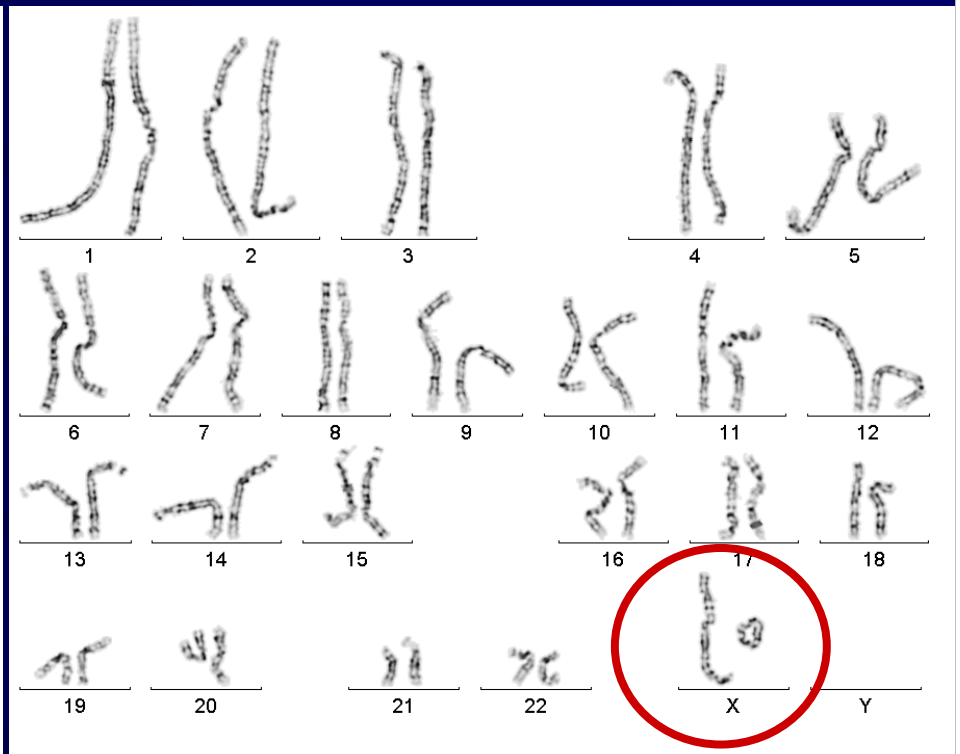
Chromosome aberrations	4-28%*
FRAX	2-6%
CNS anomalies	7-17%
Environmental factors, prematurity	5-13%
Congenital anomaly and genetic syndromes	10-20%**
Unknown	30-50%

* currently likely +5-17% for the whole ID group (telomere *screening*, CGH, arrayCGH)

** +10-20% after Whole-exome or Whole-genome techniques are applied

ID – chromosome aberrations





mos 45,X/46,X,r(X)

likely clinical picture with ID of variable degree

Down syndrome

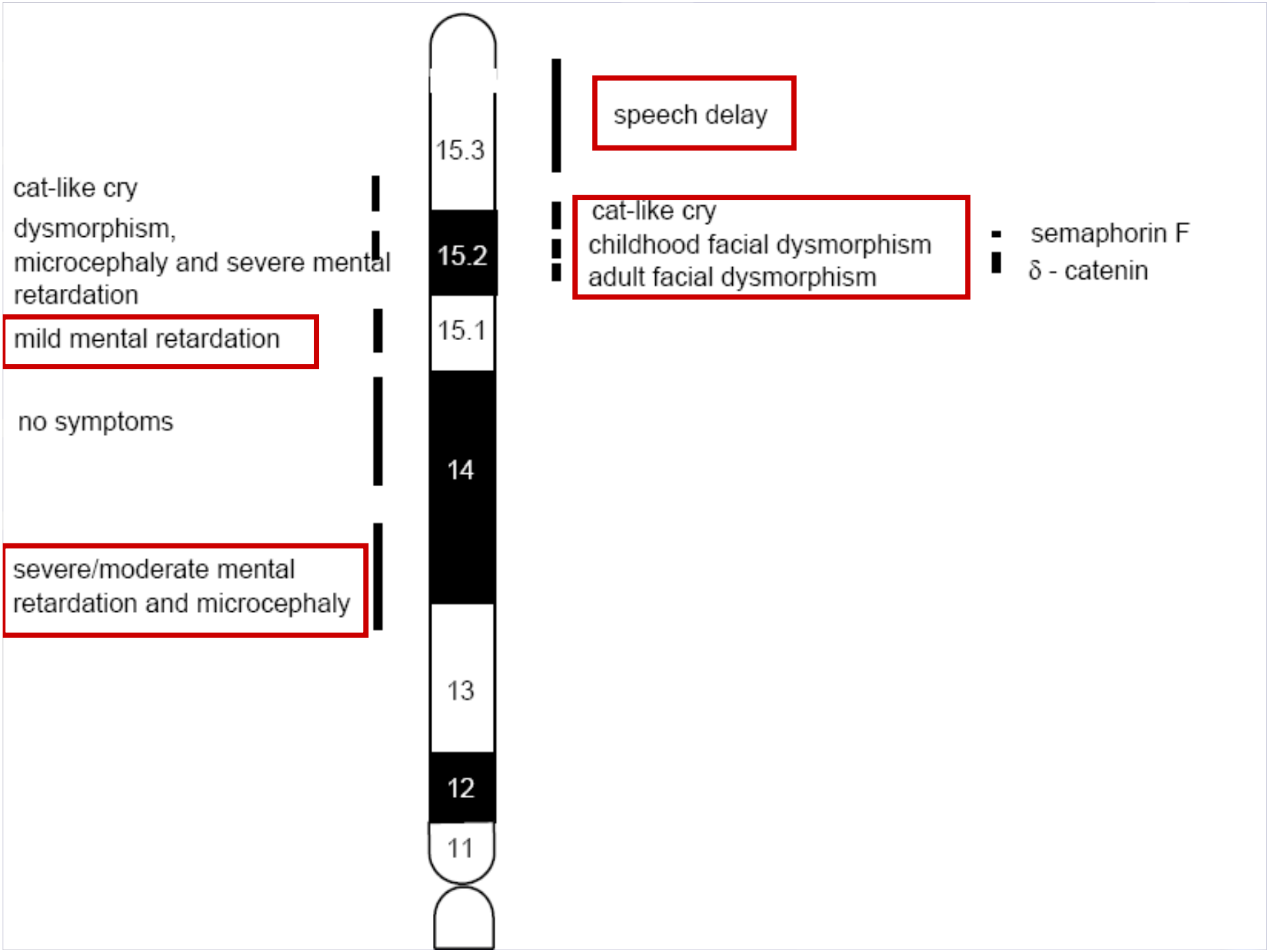
- ***Locus* (*loci*)**: 21q22.1-q22.2
- **Inheritance**: 95% *de novo*, 2% translocation event (50% familial)
- **Clinics**: moderate ID, hypotonia, physical delay, strabismus, cataracts in adulthood, myopia, conductive HL, large tongue, weak dentition, joint laxity, hypogenitalism, heart defect, duodenal atresia, Hirschsprung disease, thyroid disorders, early-onset Alzheimer, ALL
- **Diagnostics: PRENATAL**: US: NT + NB 80-85%, *screening*: ↑ free βHCG, ↓PAPP-A, karyotype from amniocytes, cell-free fetal DNA 99,7% **POSTNATAL**: karyotype

Patau syndrome

- **Inheritance**: 90% *de novo*, 5-20% translocation event
- **Clinics**: rarest trisomy in liveborn, holoprosencephaly, polydactyly, seizures, HL, maicrocephaly, cleft lip and/or palate, *omphalocele*, heart and kidney anomalies, ID. In mosaics: clinial heterogeneity: from typical to milder ID degree and longer survival
- **Diagnostics:** PRENATAL: US+biochemical screening, amnio- karyotype, cell-free fetal DNA 80%, POSTNATAL: MRI, EEG, audiogram, echocardiogram, kidney US, karyotype
- 44% does not survive to 1mth, >70% die in the first year. In others severe ID.

Edwards syndrome

- **Inheritance**: <1% translocation event
- **Clinics**: clenched hand, fingers 2&5 overlap 3&4, IUGR, rocker-bottom feet, micrognathia, prominent occiput, microphthalmia, VSD, ASD, PDA, kidney anomalies, ID. In mosaics usually milder picture (to normal IQ !!)
- **Diagnostics**: echocardiogram, abdominal US.
  PRENATAL *screening*: ↓ AFP, free βhCG and uE_3, amnio- karyotype, cell-free fetal DNA >99%
  POSTNATAL: karyotype
- 50% does not survive to 1mth, 90% die before first birthday


15.3
15.2
15.1
14
13
12
11
speech delay
cat-like cry
childhood facial dysmorphism
adult facial dysmorphism
semaphorin F
δ - catenin
cat-like cry
dysmorphism,
microcephaly and severe mental
retardation
mild mental retardation
no symptoms
severe/moderate mental
retardation and microcephaly

Wolf-Hirschhorn syndrome (4p-)

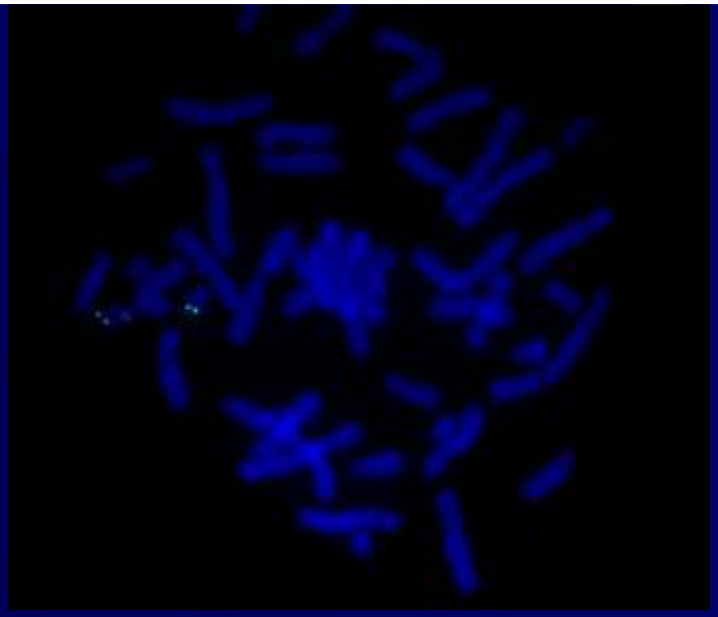
- **Genes**: WHSCR: *WHSC1* and *WHSC2* (unknown function)
- ***Locus***: 4p; critical region165kb
- **Inheritance**: 87% *de novo*, 13% translocation event
- **Clinics**: „Greek helmet" face, microcephaly, pre- and postnatal short stature, variable degree ID, seizures, facial asymmetry, ptosis, CNS anomalies, cleft lip and/or palate, heart defect, renal anomalies
- **Diagnostics**: EEG, brain MRI, echocardiogram, IgA level, karyotype HRT 4p16.3 (60-70%), MLPA/FISH/CGH (>95%)
- **Treatment**: in 2/3 absence seizures responsive to valproic acid

ID – chromosome aberrations

What is the most likely diagnosis in a 6yo with CL/P, TOF, height at 3rd centile for age and ID?

A. Down syndrome
B. Trisomies 13 or 18
C. Velocardiofacial syndrome
D. Otopalatodigital syndrome
E. Cardiofaciocutaneous syndrome

ID in submicroscopic aberrations – del22q11.2



- **Genes**: *UFDIL, TBX1, VEGF*
- ***Locus***: 22q11.2
- **Inheritance**: 93% *de novo*
- **Clinics**: CHD (74%) (esp. TOF, interrupted aortic arch, conotruncal defects), immunological deficits, palatal abnormalities (69%), feeing dufficulties, psychomotor retardation, learning difficulties (70-90%), hypocalcemia (50%), renal abnormalities (37%), psychiatric issues
- **Diagnostics**: Ca, PTH, lymphocytes T/B , Igs, renal US videolaryngoscopy, MLPA/FISH/CGH DGSCR (95%)(3 Mb /1,5 Mb)
- **Mechanism**: branchial arches 3&4 defect
- **Treatment**: heart defect correction, palatal surgery, Ca supplementation, in case of an immunological deficit do not administer live vaccinations

ID in submicroscopic aberrations– del7q11.23 (Williams syndrome)

- **Genes**: *ELN* , *LIMK*
- ***Locus***: 7q11.23
- **Inheritance:** mostly *de novo*
- **Clinics**: arterial stenosis, supravalvular aortic stenosis (75%), facial dysmorphism, snorring, hernias, joint movement constriction or joint laxity, ID, specific behaviour, hypercalcemia, hypercalciuria, hypothyroidism, abnormal growth in infancy
- **Diagnostics**: calcium, creatinine, thyroid hormones, audilogic and ophthalmologic assessment, renal US, echocardiogram, MLPA/FISH/CGH WBSCR (~99%)
- **Mechanism**: *ELN* deletion causes vascular problems, *LIMK* deletion causes visuo-spatial coordination and cognitive deficits
- **Treatment:** adults with bicuspid valve problems, heart insufficiency, HL, hypothyroidism, diabetes

ID in submicroscopic aberrations – Angelman syndrome

- **Gene**: *UBE3A*
- **Protein:** ubiquitin E3A ligase
- ***Locus***: 15q11-q13
- **Inheritance**: functional or total lack of maternally inherited imprinted allele 15q11.2-q13 AS/PWSCR
- **Clinics**: severe ID, severe speech delay, ataxia, specific behaviour, microcephaly, seizures
- **Diagnostics**: secondary microcephaly, seizures before 4th birthday, abnormal EEG (high amplitude, slow 2-3Mhz waves), MS-PCR, methylation MLPA, maternal allele deletion (4-6 Mb) (65-75%), *UBE3A* mutations (10-20%), imprinting center defect (2,5%), paternal UPD (<5%), unknown

ID in submicroscopic aberrations –Prader-Willi syndrome

- **Genes**: *SNURF-SNRPN, MKRN3, MAGEL2, NDN*
- ***Locus***: 15q11-13
- **Inheritance**: functional or total lack of paternally inherited imprinted allele 15q11.2-q13 AS/PWSCR
- **Clinics**: hypothalamic dysfunction, neonatal hypotonia, psychomotor delay, hyperphagia and obesity, short stature, small feet and hands, hypogonadism, ID
- **Diagnostics**: MS-PCR, methylation MLPA, paternal deletion 3-5 Mb (~70%), maternal UPD (~30%), imprinting center defect (2%)
- **Treatment**: GH+diet, beware of feeding problems in infancy, obesity, OCD, psychoses, scoliosis, diabetes, osteopenia

ID in submicroscopic aberrations –Rubinstein-Taybi syndrome

- **Genes**: *CREBBP, EP300*
- ***Locus***: 16p13.3, 22q13
- **Inheritance**: *de novo*
- **Clinics**: microcephaly, beaked nose, wide thumbs and big toes, cryptorchidism, growth delay, severe ID, heart defect, strabismus, ptosis, tumours (meningioma, pilomatrixoma, leukemia), behaviour problems
- **Diagnostics**: echocardiogram, MLPA/FISH/CGH *CREBBP* (~10%), *CREBBP* seq (40-60%), *EP300* seq (~3%)
- **Mechanism**: defective histone acetylation
- **Treatment**: eyesight, hearing, heart defect

Examples of ID in monogenic syndromes

Inborn errors of metabolism: untreated/maltreated phenylketonuria, galactosemia (speech delay), glutaric acidemia type I, biotinidase deficit, creatine deficits, homocystinuria, storage disorders

Can ID be a symptom of monogenic disorders typically not showing any cognitive problems?

Practically in all cases where microdeletion or less frequently microduplication of that particular region is present

ID in monogenic conditions – Tuberous Sclerosis (TS)

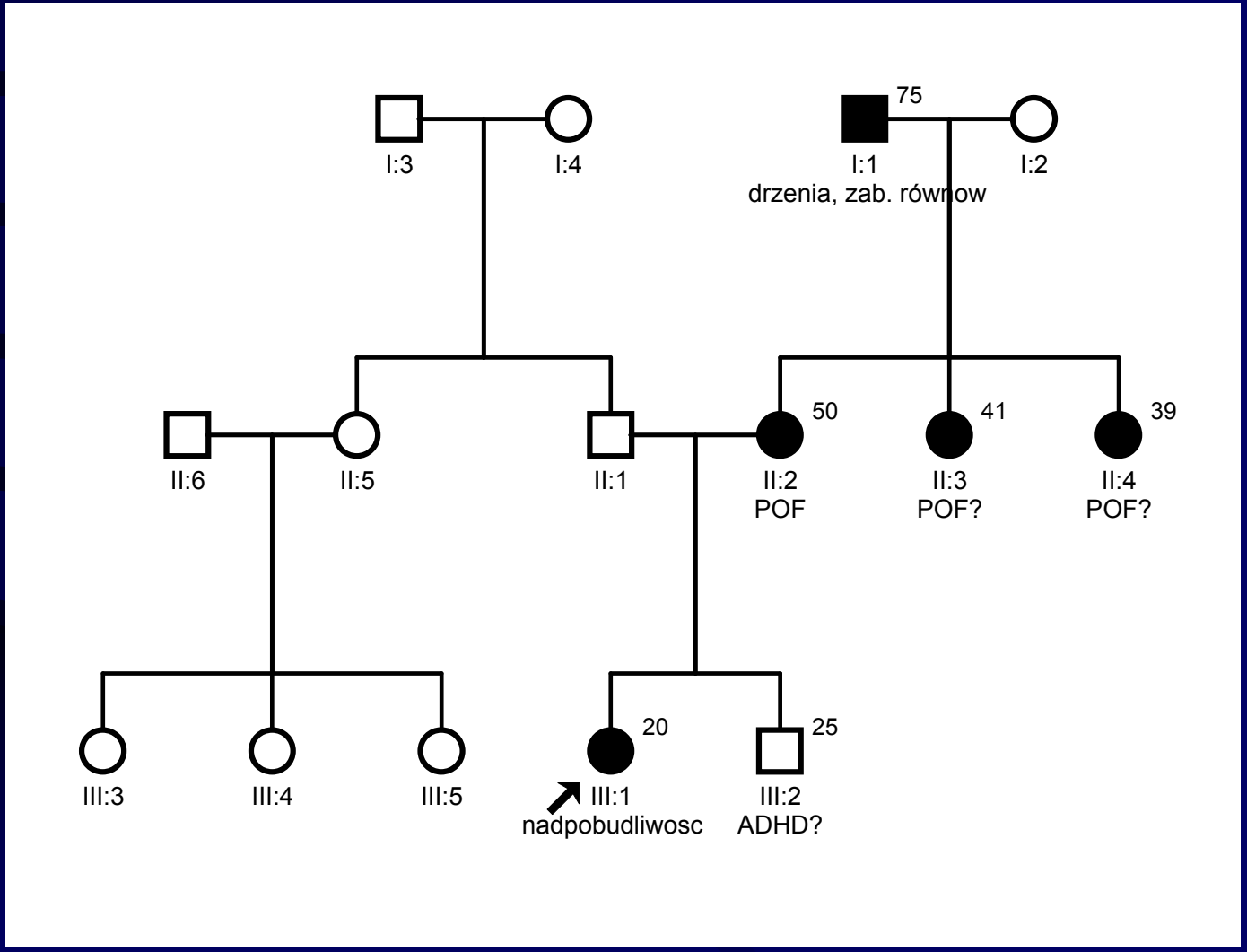
- **Genes**: *TSC1* and *TSC2*
- **Proteins:** Hamartin and Tuberin
- ***Loci***: 9q34, 16p13
- **Inheritance**: 2/3 *de novo*
- **Clinics**: hypomelanotic foci, facial angiofibroma, shagreen patches, periungual fibromas, subependymal tumours, cortical tubers, astrocytoma, seizures, renal angiomyolipoma, renal epithelial cysts, <1% cancer risk, cardiac rhabdomyoma (tendency to regress), lung lymphangiomatosis (*TSC2*, women 20-40yo), ocular hamartomas; microdeletion syndrome *TSC2/ADPKD1*
- **Diagnostics**: MRI, echocardiogram, renal US, Wood's lamp, EEG, *TSC1* seq (30% familial) and *TSC2* seq (50% familial)
- **Mechanism**: abnormal activity of tumour suppressor protein
- **Treatment**: renal US every 1-3yrs, may use CT/MRI (prophylactic renal artery embolization), thoracic CT if lung symptoms

Seizures and learning difficulties in TS

Dev Child Neurol 1996; 38: 146

	ID	normal
Seizure onset		
<6 mths	41	7
6-24 mths	20	6
2-5 yrs	6	6
>5 yrs	0	13
Seizure type		
infantile	33	2
tonic-clonic, absence, partial	18	17
febrile	2	5
Seizure control		
insufficient	41	11
good	11	11

ID in monogenic conditions – what disorder is it?



POF – premature ovarian failure

Fragile X syndrome (FRAX)

- **Gene**: *FMR-1*
- **Protein:** FMRP
- ***Locus***: Xq27.3
- **Inheritance**: trinucleotide repeat expansion
- **Clinics**: developmental delay, ID (moderate/severe in boys, milder degree in girls), hyperactivity, autistic traits, premutation female carriers: OCD, depression, 20% POF, premutation male carriers: intention tremour, ataxia, parkinsonism, autonomic dysfunction (=FXTAS: >30% male carriers and <5% female carriers; 1,5% ♂ and 3%♀ late-onset ataxia;
  1/3000 ♂ two other *loci*: FraXE: only ID, FraXF: lack of phenotype
- **Diagnostics**: CGG triplet detection PCR: fast testing, small premutations; Southern: all mutation classes + normal alleles, mosaics, costly. Normal allele: 5-44 repeats, median: 45-58 repeats (grey zone), premutation: 59-200 repeats, mutation: >200 repeats
- **Mechanism**: >200 repeats = methylation = inactivation = lack of FMRP. POF and FXTAS (59-200 repeats) gain of function mutation (?)

ID – Fragile X syndrome

The best diagnostic test is:

1. quantitative PCR
2. ASO
3. Southern → **large expansions + methylation status**

The likelihood that the healthy mother of an affected son has normal number of triplet repeats in both alleles is:

1. 50%
2. 25%
3. 10%
4. 5%
5. 0%

Genetic basis of ID

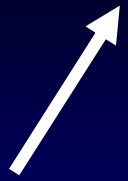
1. Chromosomal aberrations (the most frequent?)
2. Single gene defects

Hypothesis 1

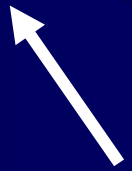
Genes coding for various aspects of cognitive functions are common within the genome

Hypothesis 2

More such genes are localized on X chromosome than on any other comparable segment of an autosome



affected males/ affected females = 1,3/1



easier identification of hemizygous genes

X-linked ID (XLMR)

1. XLMR in syndromes (**MRXS**: *Syndromic X-linked Mental Retardation*)
2. XLMR non-specific (**MRX** or NS-XLMR: *Non-Specific X-linked Mental Retardation*)

?

syndromic association of clinical features including ID and specific symptoms on clinical exam

ID is the only characteristic sign

Syndromic XLMR - Coffin-Lowry syndrome

- **Gene**: *RPS6KA3*
- **Locus**: Xp22.2-p22.1
- **Clinics**: severe.profound ID, short soft hands, small fingertips, short stature, microcephaly, characteristic facial dysmorphism, normal IQ to severe ID in female carriers
- **Diagnostics**: X-ray: bone enlargement, abnormal vertebra, metacarpal pseudoepiphyses, *RPS6KA3* seq (35-40%)
- **Mechanism**: RPS6KA3 is a RAS-MAPK cascade protein
- **Treatment**: Risperidone in behavioural abnormalities, echocardiogram

Syndromic XLMR – other phenotypes

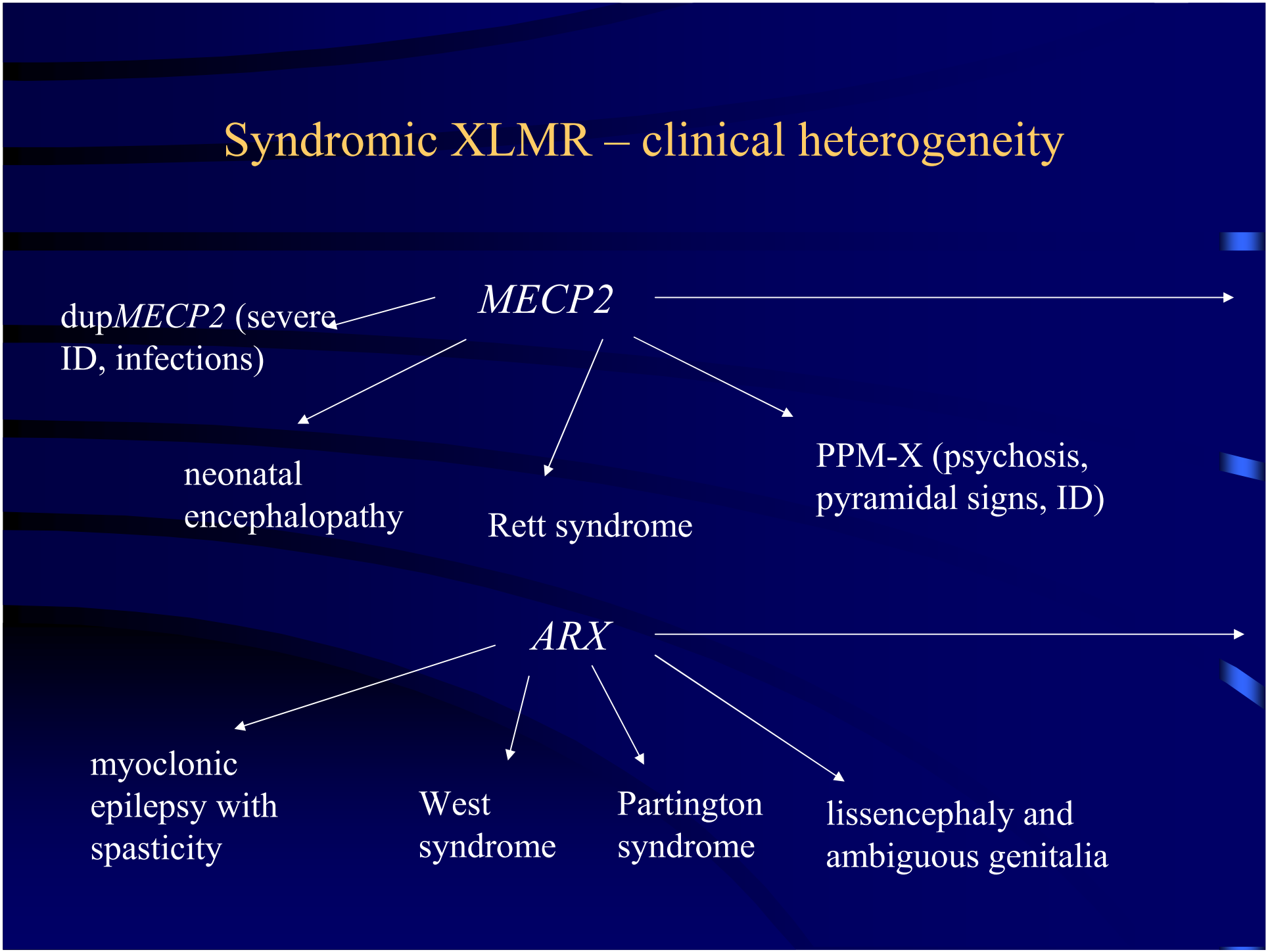
1. Autism - *NLGN3/4* mutations
2. Cerebellar ataxia – oligophrenin gene mutations
3. High T3- *SLC16A2* mutations
4. Dystonia - *ARX*

Syndromic XLMR – *locus* heterogeneity

5. Microcephaly - *ATRX, MECP2, PQBP1, SMCX*
6. Short stature - *PQBP1, SMCX*
7. Spastic paraplegia - *SLC16A2, ATRX, SMCX, MECP2*
8. Epilepsy - *AGTR2, SYN1, ATRX, SLC6A8, ARX, SMCX*

and others

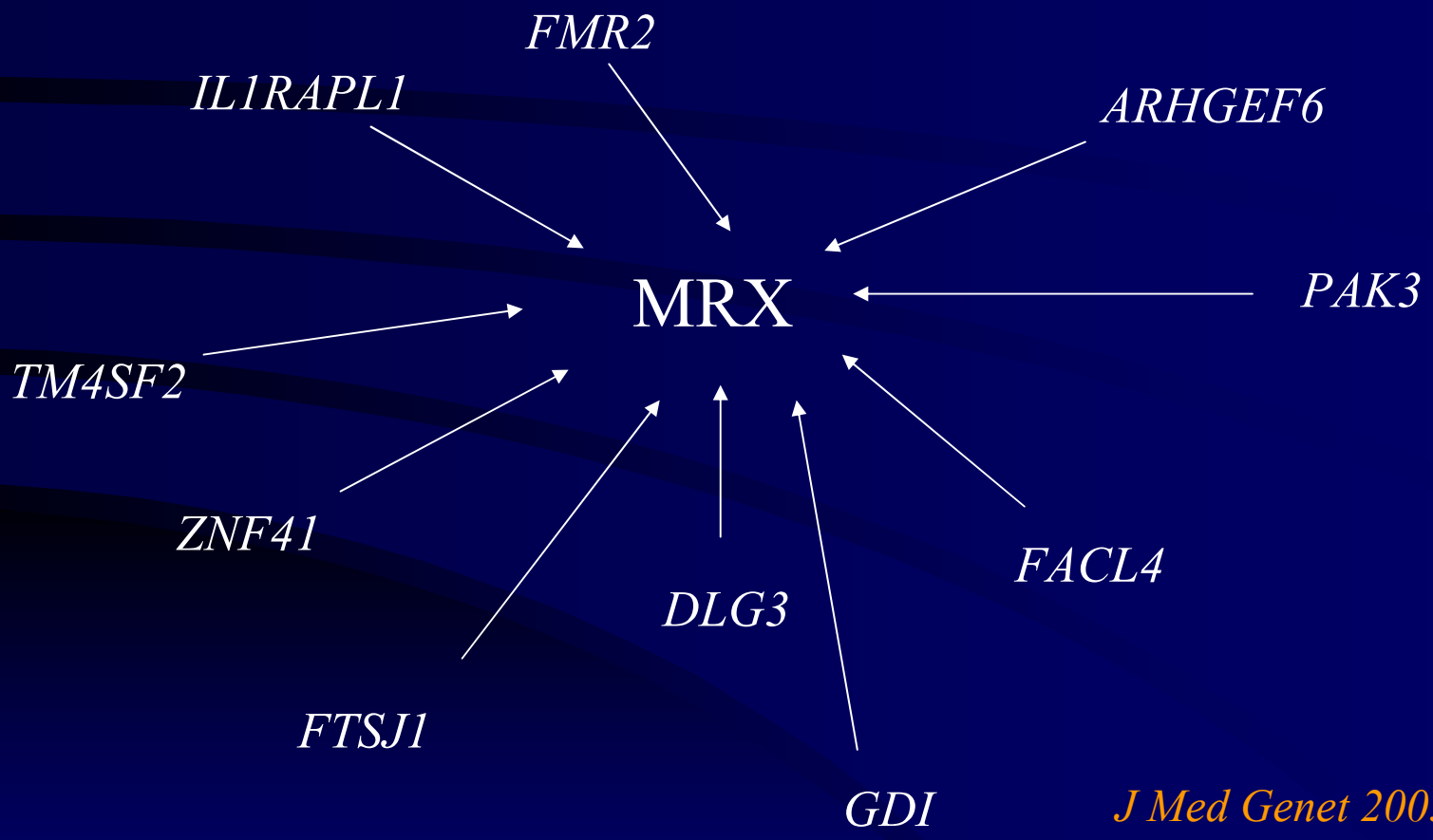
Syndromic XLMR – clinical heterogeneity



MRX

Same single gene defects lead both to MRXS and MRX phenotypes

Genetic basis of non-specific X-linked ID (MRX)

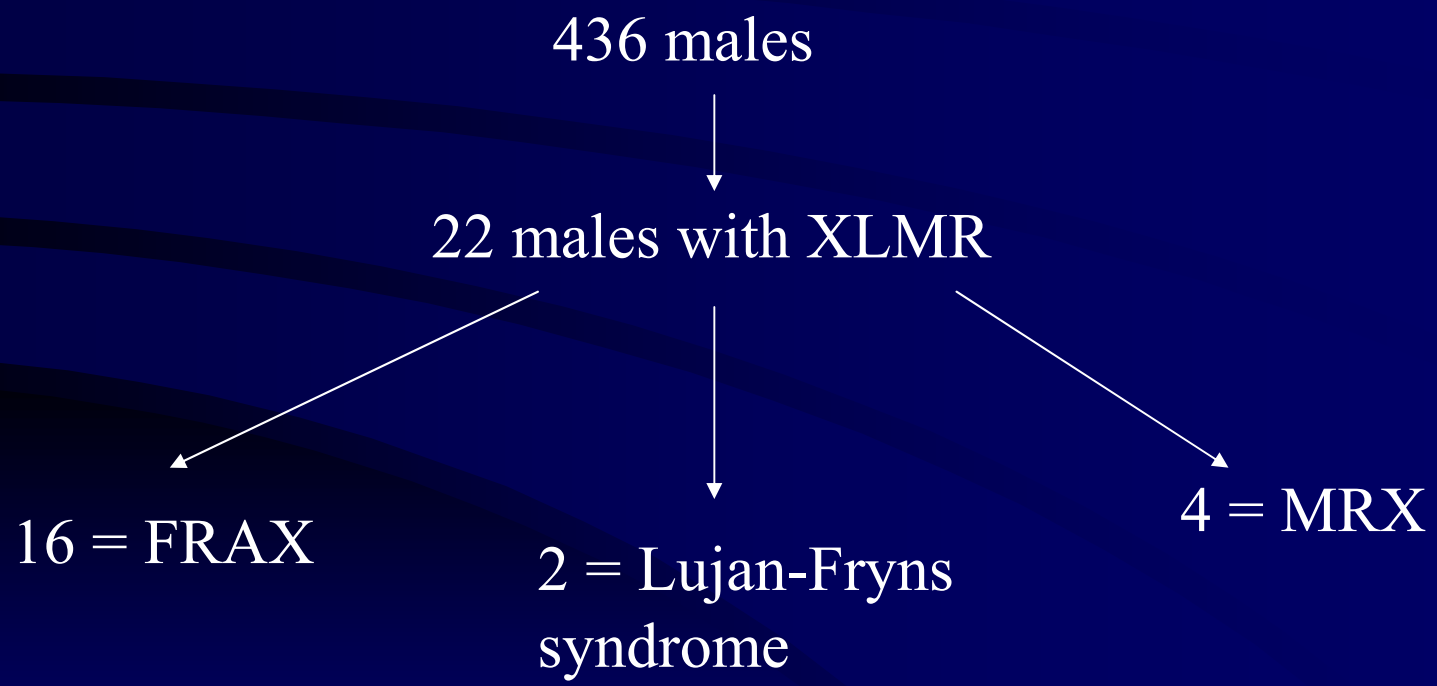


J Med Genet 2005

XLMR – diagnostic dilemma

The clinical phenotype in institutionalised adult males with X-linked mental retardation (XLMR)

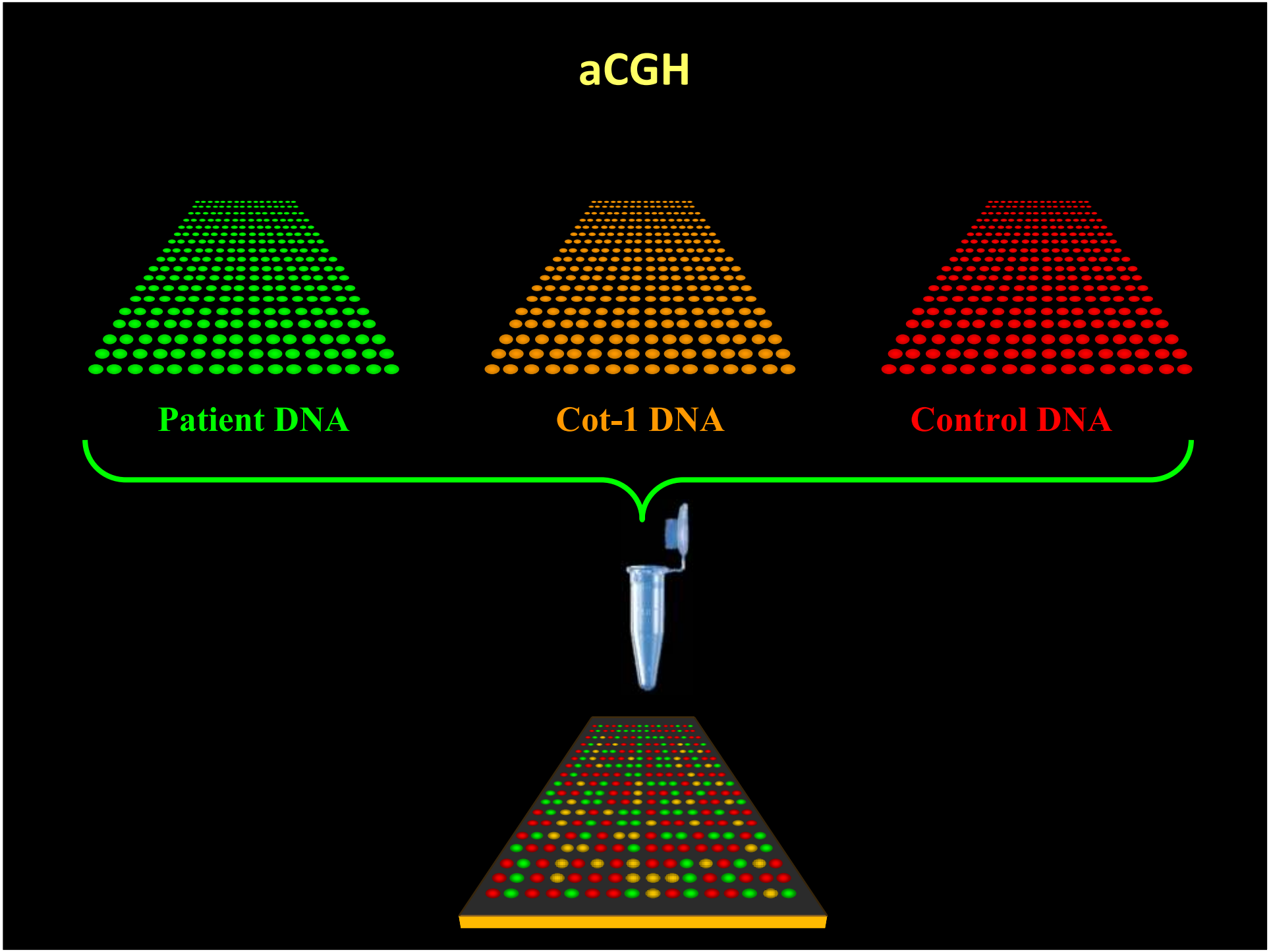
Annales de Genetique 44, 2001



Modern diagnostic techniques

Technique	Sensitivity
• FISH	>0.04-0.25Mb
• MLPA	about 0.04Mb
• HR-CGH	>3Mb
• aCGH with BAC probes	>1Mb
• aCGH with oligo- probes	>0.001Mb
• New Generation Technology /Next Generation Technology (NGS, WGS/WES)	unlimited!

Mb – one milion base pairs

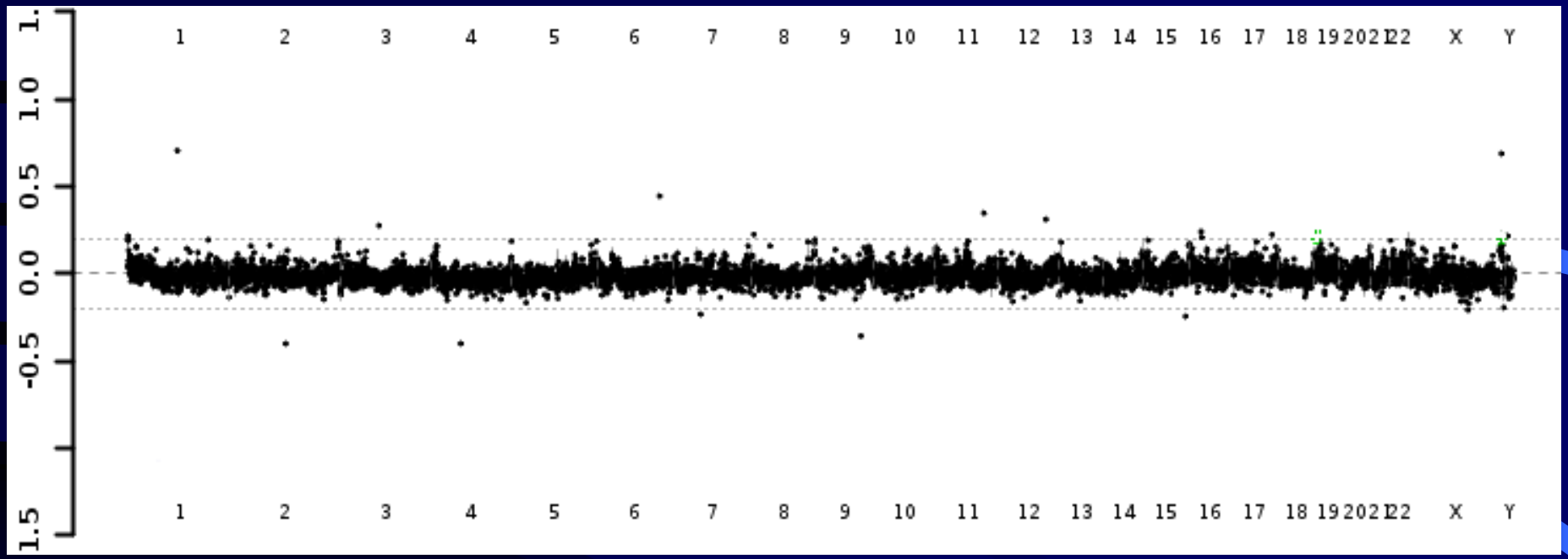

aCGH
Patient DNA
Cot-1 DNA
Control DNA

CGH technique

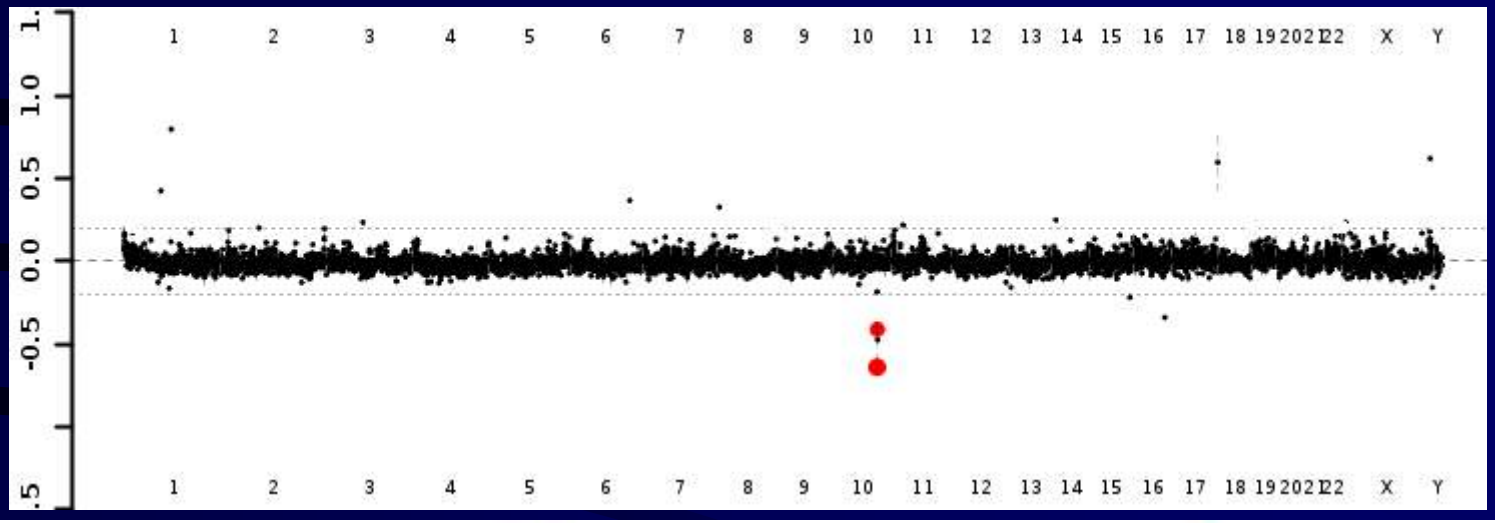
- Hybridization of two genomic DNAs, reference and patient's, fluorescein-stained and mixed 1:1, to normal chormosomes

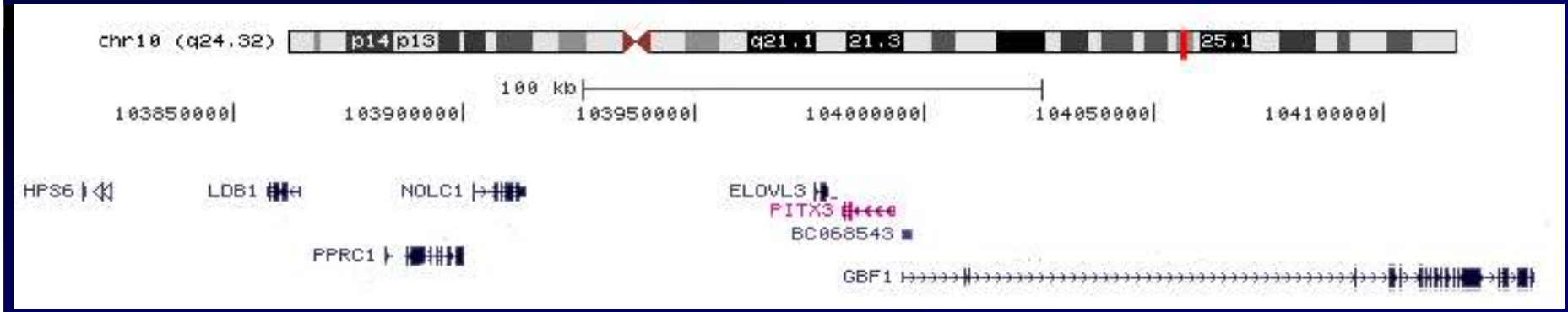
Science 1992; 258: 818-821

aCGH normal Agilent180K



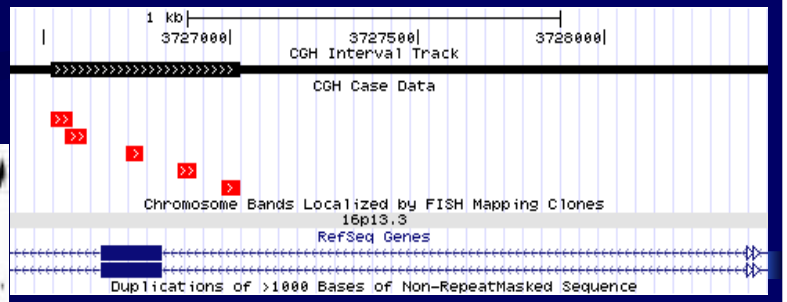
aCGH abnormal
del 10q24.32 ≈317kb





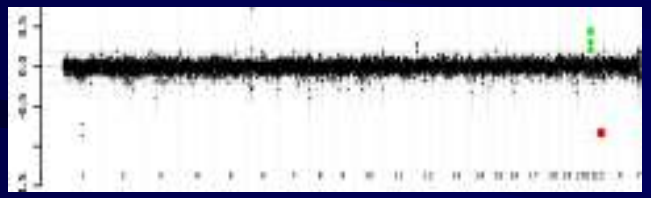
Rubinstein-Taybi syndrome (RTS)

CREBBP

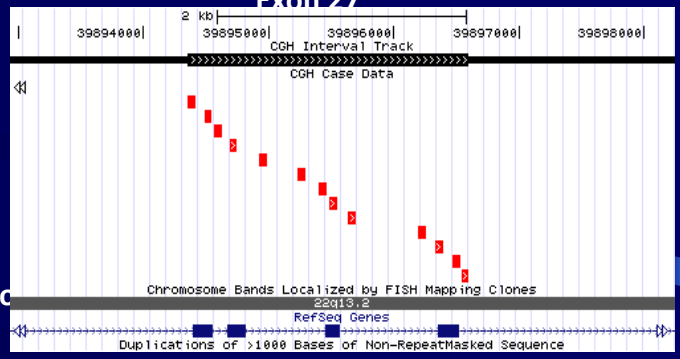


dev delay, RTS-like

EP300

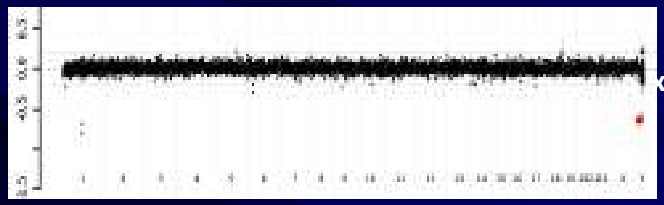


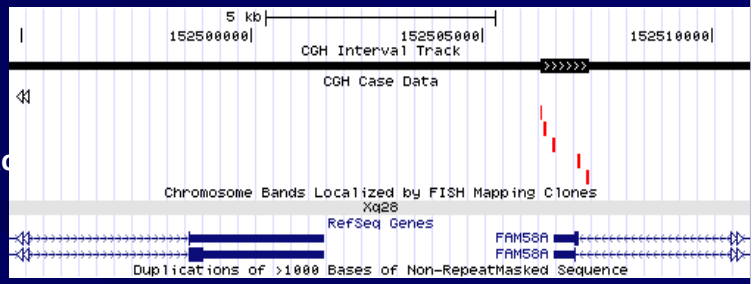
Exon 27



multiple congenital anomalies (STAR syndrome)

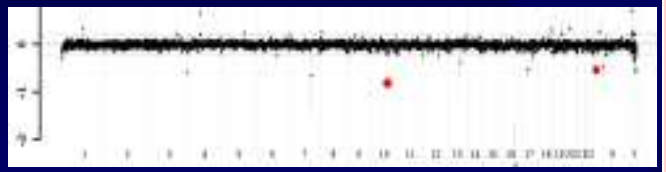
FAM58A

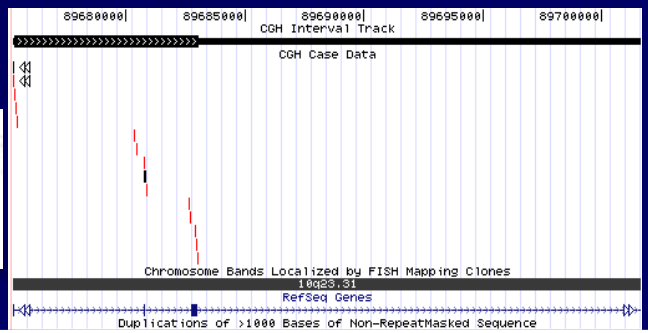




Cowden syndrome

PTEN





Advantages of CGH

- enables identification of genomic copy-number variants without prior knowledge (suspicion) of their existence
- analyses the genome in a single run
- array CGH (aCGH): identification of variants not seen in a standard cytogenetic analysis (submicroscopic aberrations) with an unprecedented resolution!

aCGH – clinical validation

- Metaanalysis of 14,000 pts with ID, congenital anomalies and normal karyotype results: **10%**
- (IMiD) in 116 pts with ID and dysmorphism: **11.8%**

- aCGH with subtelomeric probes:

1. normal karyotype: 3%
2. abnormal karyotype: 43%

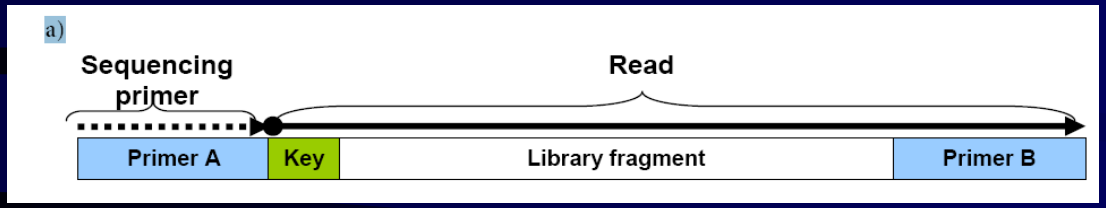
Genet Med 2009; 11: 139-146
Am J Med. Genet 2008; 146: 2361-2369
Am J Med Genet 2008; 146: 2242-2251

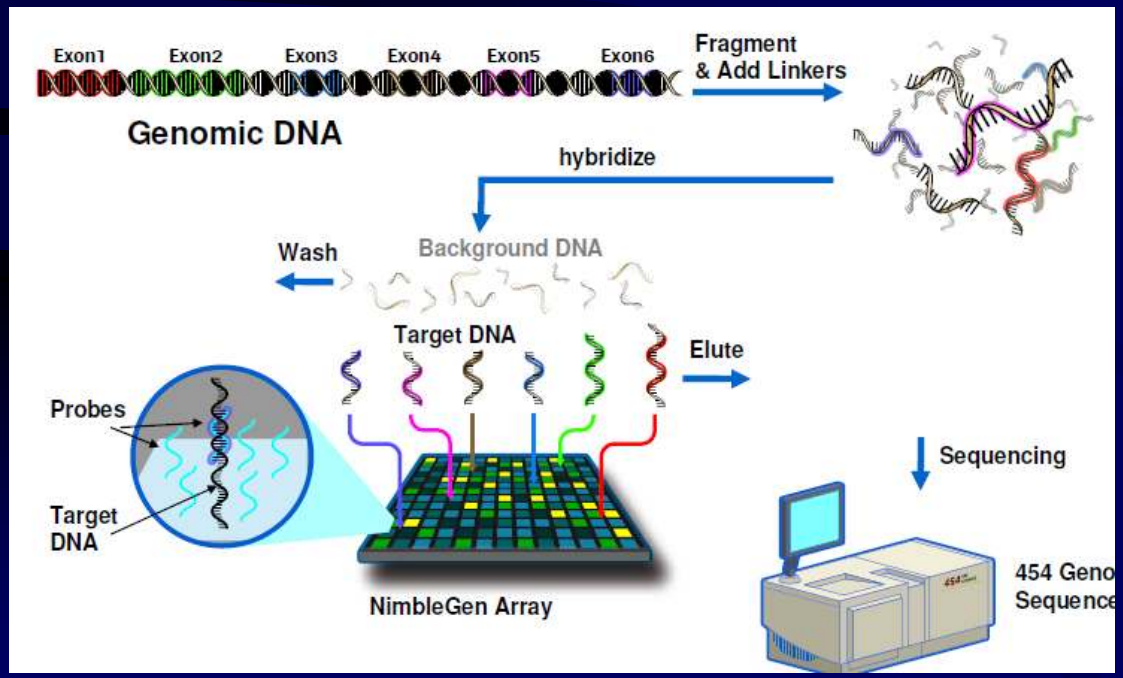
Modern diagnostic techniques

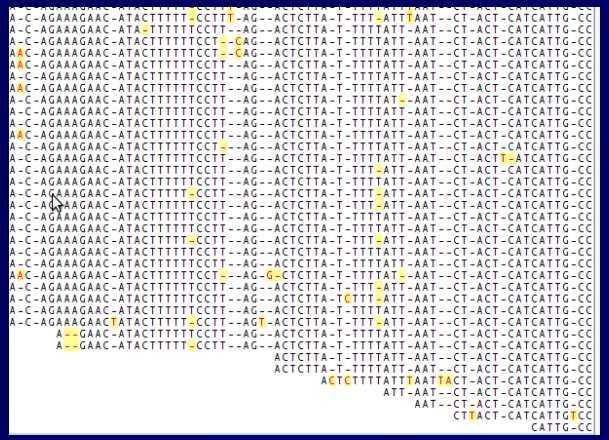
Technique	Sensitivity
• FISH	>0.04-0.25Mb
• MLPA	about 0.04Mb
• HR-CGH	>3Mb
• aCGH with BAC probes	>1Mb
• aCGH with oligo- probes	>0.001Mb
• New Generation Technology /Next Generation Technology (NGS, WGS/WES)	unlimited!

Mb – one milion base pairs

Next (new) Generation Sequencing (NGS) = Massive Parallel Sequencing (MPS)

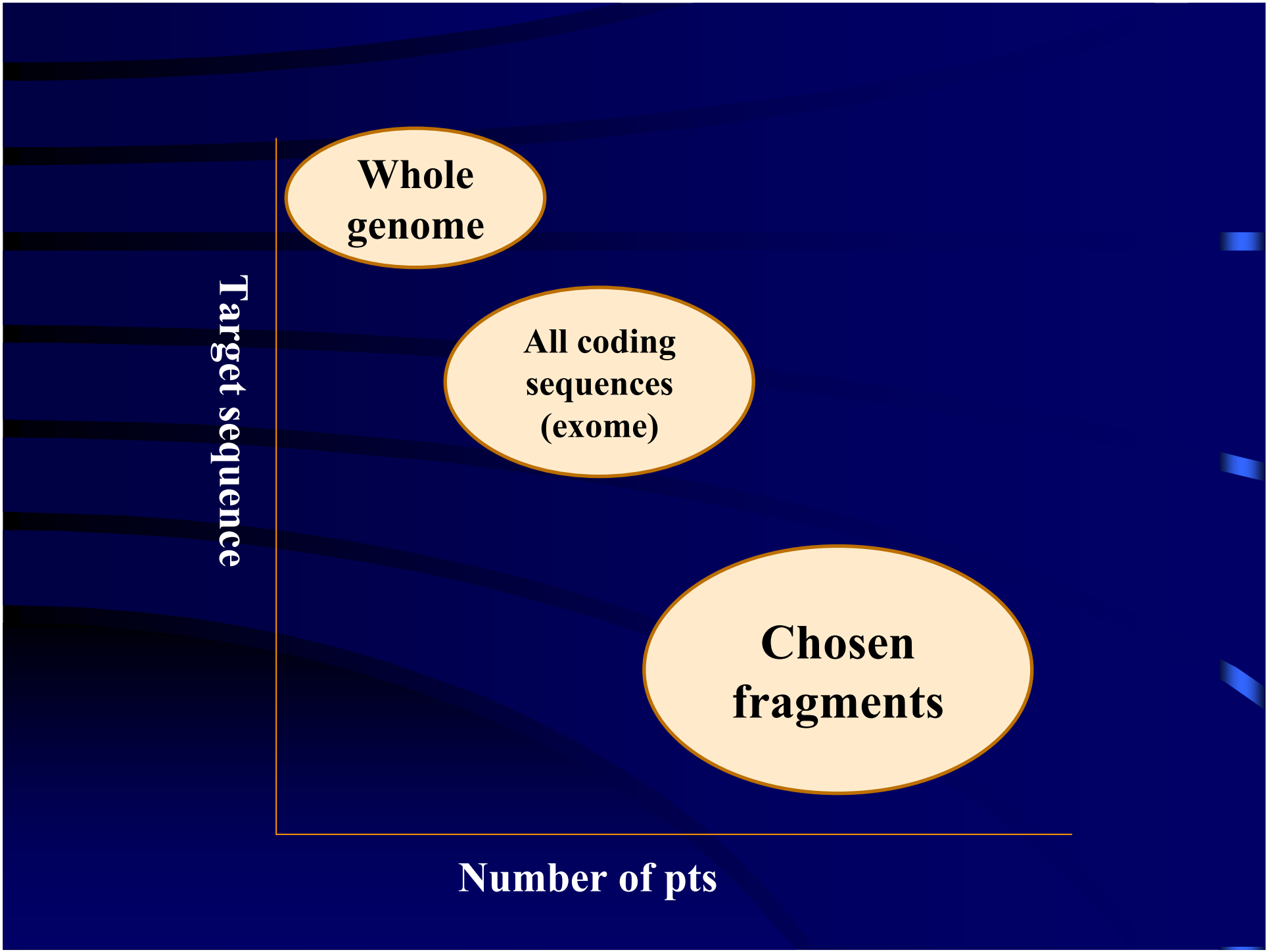






NGS = Massive Parallel Sequencing

1. Library creation – random DNA fragmentation, ligation with linkers
2. Library amplification
3. Direct step-by-step detection of each nucleotide added to seq reaction
4. Hundreds to hudreds of milions reactions in a single run – massive parallel seq
   - shorter-fragment reads compared to Sanger seq
   - digital reads
   - paired-end seq, from both ends in parallel reactions


Whole genome
All coding sequences (exome)
Chosen fragments
Target sequence
Number of pts

NGS in medical genetics

Target gene sequencing

- **Known regions/genes responsible for the disorders**
- Candidate genes chosen based on their putative role in disease pathomechanism

Exome sequencing

- **All exons – (only coding sequences) – unknown genetic basis**
- Monogenic disorders - (dominant and recessive)
- Multifactorial diseases
- Mitochondrial disorders

NGS in medical genetics

Target gene sequencing

- Requires selective „enrichment”
- Relatively easy interpretation
- Identification of larger structural variants – if present in the genome
- Good value for money

Exome sequencing

- Commercially available „enrichment kits”
- Much more challenging interpretation
- Structural variants – suboptimal detection
- Still relatively expensive

NGS – clinical validation

- deLigt et al.: 21,000 genes (exome seq) in 100 pts with severe ID + so called confirmation series of 765 pts with ID (high-throughput reseq): **16%**
- all the muts: *de novo*, incl: 10 in AD genes, 3 in XLR genes and 3 in novel genes
- + 19 muts in genes functionally associated with ID

N Engl J Med 2012

Exome sequencing in ID

- ID and WES [Topper, 2010]: in syndromes, sporadic nonsyndromic, familial
- Rabbani, 2014: review of WES in syndromic ID (30 studies in 20 syndromes)
- Genotype-first: Classen, 2013; Rauch, 2012 (51 trios with IQ<60): 1.41 *de novo* mutations/patient
- Schuurs, 2013: familial cases (recessive variants?) – 19 families of 2-5 individuals with ID: 9 pathogenic mutations

Genome sequencing in ID

- Gilissen, 2013: 21/50 patients with IQ<50 (20 dominant *de novo* variants and one compound heterozygote
- What was the selection process like?

1. aCGH: 12%
2. WES: 27%
3. WGS: 60%

NGS panels in ID

Greenwood Genetic Center XLID	GeneDx XLID
114 genes >20x	Clinician's decision
$5500	From $3000
Lack of promoter and 3'UTR assessment	Lack of assessment of del/dup
Lack of assessment of trinucleotide expansions	Lack of assessment of trinucleotide expansions
What is the coding sequence coverage with median coverage min. 20x?	Exome slice possible
TAT	TAT

Exome slice –exome seq + analysis of genes linked with phenotype only (choice of genes on customer's wish)

Diagnostic algorithm in ID

- Careful analysis of three-generation pedigree with detailed developmental analysis of all the relatives
- Maternal health status assessment from pre-pregnancy era
- Pregnancy-stage assessment
- Birth physical parameters
- Developmental milestones (incl physical development)
- Exclusion of phenylketonuria and hypothyroidism
- IQ and psychological assessment + school progress
- Physical exam with careful assessment of dysmorphism and neurological symptoms
- Karyotype and/or Fragile X where necessary
- Array CGH / NGS for the rest
- Head MRI (when neurological symptoms/abnormal head circumference)
- EEG (when seizures)
- Metabolic screen

Neurology 2003; 60: 367-380 and further works of Shevell et al.

Treatment of ID

„A child with ID requires a constant and frequently multidisciplinary care. The choice of therapy depends on etiological factors causative of cognitive problems as well as an individual developmental progress of the child.”

1. **Optimal development and prevention of developmental regression (stimulation level depending on the kid’s skills)**
2. **Medical, psychological and schooling interventions**
3. **Social care (incl financial issues)**
4. **Pharmacotherapy only as a supportive tool**
5. **Early intervention centers, integrative pre-schooling, special groups in mass and special schools, mass schools with individual therapeutic programs, integrative classes, special classes in mass schools, classes for kids with severe ID**

ID – genetic counselling

ID risk in sibs of the affecteds:
- relative to the level of ID (aberrtion?, monogenic syndrome?)
- when unknown cause, careful estimates: 1-25%

(multifactorial ⇔ AR) – beware of MRX families!
- a child with unknown-cause ID = ↑10x risk for sibs

Greenwood Genetic Center:
- 452 pts with mean IQ=41 and mean head circumference 43c with idiopathic ID
- next sib: 502 ♂ and 468 ♀
- 21% brothers and 14% sisters with ID
- the higher the IQ, the higher risk in sibs

Taking the Challenge: Finding Recurrence Risks in Idiopathic Mental Retardation. J.S. Collins, A.F. Nave, G.A. Satten, R.E. Stevenson. Greenwood Genetic Center, Greenwood, S.C., 2002

ID - summary

- A clinical symptom , of genetic disease as well, which can be the only trait or be part of a syndrome of congenital anomalies
- The most frequent genetic causes of ID are chromosome aberrations (at various levels of detection) and single gene defects. Gene dosage effect.
- Care for individuals with ID is constant and multidisciplinary