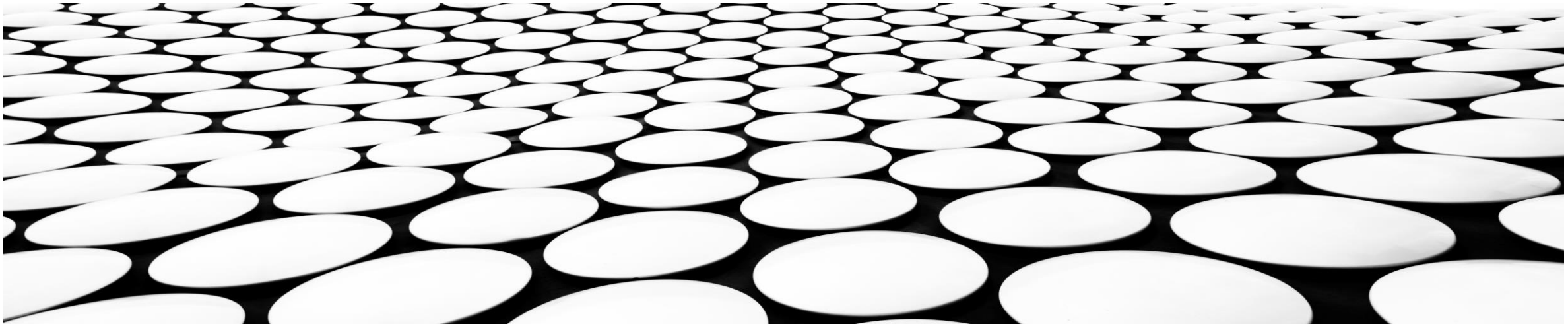
DEVELOPMENTAL DELAYS IN CHILDREN SYMPTOMS, GENETIC EVALUATIONS, AND INTERVENTIONS

DR YU PUI TAK , ASSOCIATE CONSULTANT

DEPARTMENT OF PAEDIATRICS, QUEEN MARY HOSPITAL

CLINICAL GENETICIST, HONG KONG GENOME PROJECT (QMH CENTER)



OBJECTIVE

- Definition of developmental delay
- Clinical approach to developmental delay (history , physical examination , assessment, investigation)
- Causes of developmental delay
- Genetic etiology of developmental delay
- Chromosomal abnormalities, microdeletion, microduplication syndrome, monogenic disorder, imprinting disorder
- Other consideration: developmental regression, autism spectrum disorder, isolated motor delay
- Management of global developmental delay

Developmental delay

- Incidence in preschool children (<5 years old) : 3% for GLOBAL developmental delay

Global developmental delay (GDD) -defined as a delay in two or more developmental domains of gross/fine motor, speech/language, cognition, social/personal and activities of daily living, affecting children under the age of 5 years.

mild (functional age<33% below chronological age)

moderate (functional age 34%–66% of chronological age)

severe (functional age>66% of chronological age)

- A significant delay is defined as performance that is 2 SD below the mean on age-appropriate standardised norm-referenced testing

Heterogeneous underlying causes

Global delay- causes

Table 2. Causes of global developmental delay/intellectual disability

Broad category	Possible causes	Proportion of diagnostic yield*
Prenatal intrinsic	Genetic	Up to 47%
	Central nervous system malformations	Up to 28%
	Metabolic	
Prenatal extrinsic	Teratogens/toxins (drugs of abuse, medications, etc.)	Up to 21%
	Infections	
Perinatal	Asphyxia	Up to 55%
	Prematurity	
	Neonatal complications	
Postnatal	Neglect/psychosocial environment	Up to 11%
	Infections	
	Trauma	
	Toxins	

Data taken from ref. (3).

*Percentage of total cases of GDD/ID with an identified etiologic diagnosis who fall into this specific category.

Bélanger, S. A., & Caron, J. (2018). Evaluation of the child with global developmental delay and intellectual disability. Paediatrics & child health, 23(6), 403–419.

AAN Guideline Summary for CLINICIANS

EVALUATION OF THE CHILD WITH GLOBAL DEVELOPMENTAL DELAY

This is a summary of the American Academy of Neurology (AAN) and Child Neurology Society (CNS) guideline on diagnosis of the child with global developmental delay. Global developmental delay is a subset of developmental disabilities defined as significant delay in two or more of the following developmental domains: gross/fine motor, speech/language, cognition, social/personal, and activities of daily living. Those deficits are evident in comparison with the skills attainment of chronological peers. Significant delay is defined as performance two standard deviations or more below the mean on age-appropriate, standardized norm-referenced testing.

This practice parameter reviewed available evidence concerning the value of diagnostic testing in the initial evaluation of a young child with a global developmental delay that is static, nonprogressive, and has no clear etiology. Based on this evidence, below are specific recommendations for each testing modality.

EVIDENCE FOR EVALUATIONS OF THE CHILD WITH GLOBAL DEVELOPMENTAL DELAY

Paediatrics & Child Health, 2018, 403–410
doi: 10.1093/pch/pxy093
Position Statement

Canadian Paediatric Society

OXFORD

Position Statement

Evaluation of the child with global developmental delay and intellectual disability

Stacey A. Bélanger, Joannie Caron

Canadian Paediatric Society, Mental Health and Developmental Disabilities Committee, Ottawa, Ontario

Correspondence: Canadian Paediatric Society, 100–2305 St. Laurent Blvd., Ottawa, Ontario K1G 4J8. E-mail info@cps.ca,
cps.ca

Paediatric Society position statements and practice points are reviewed regularly and revised as needed. Consult the ements section of the CPS website www.cps.ca/en/documents for the most current version. Retired statements are n the website.

American Academy of Pediatrics

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FROM THE AMERICAN ACADEMY OF PEDIATRICS

Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

Comprehensive Evaluation of the Child With Intellectual Disability or Global Developmental Delays

John B. Moeschler, MD, MS, FAAP, FACMG, Michael Shevell, MDCM, FRCP, and COMMITTEE ON GENETICS

ABBREVIATIONS
AAP—American Academy of Pediatrics
CMA—chromosome microarray
CNS—central nervous system
CNV—copy number variant
CT—computed tomography
FISH—fluorescent in situ hybridization
GAA—guanidinoacetate
GDD—global developmental delay
ID—intellectual disability
XLID—X-linked intellectual disability

abstract

FREE

Global developmental delay and intellectual disability are relatively common pediatric conditions. This report describes the recommended clinical genetics diagnostic approach. The report is based on a review of published reports, most consisting of medium to large case series of diagnostic tests used, and the proportion of those that led to a diagnosis in such patients. Chromosome microarray is designated as a first-line test and replaces the standard karyotype and fluorescent in situ hybridization subtelomere tests for the child with intellectual disability of unknown etiology. Fragile X testing remains an important

Clinical approach- History

Antenatal history

-Maternal history e.g. recurrent miscarriage suggestive of chromosomal balanced translocation carrier predisposed to an offspring with unbalanced chromosomal abnormalies

-Previous stillbirth / early death (genetic disorder, IEM disorder)

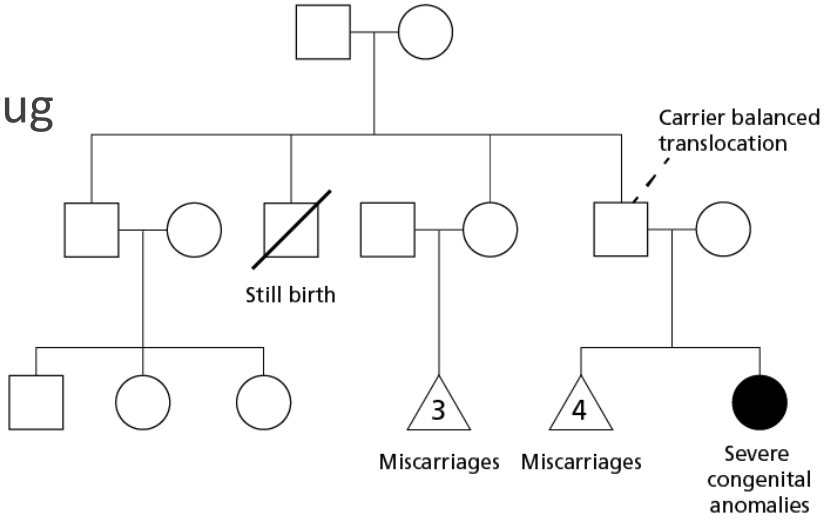
-Consanguinity

-Potential teratogens , e.g. antiepileptics, alcohol, psychiatric drug

- Antenatal infection (TORCH infection)

Perinatal history

- such as asphyxia, prematurity, HIE



Clinical approach- History

Postnatal history

- General medical history (e.g. seizure)

- Social history ,e.g. neglect

- Developmental history (gross motor, fine motor, verbal expression, verbal comprehension, cognitive, social behavioural)

- Hearing (conductive , sensorineural hearing loss)

- Vision (anterior segment, coloboma, glaucoma, retinopathy, optic atropy, maculopathy etc)

- Features of autism

- Family history of developmental delay / neurodevelopmental disorder

Clinical Approach- P/E

- Growth parameter (microcephaly, macrocephaly, Failure to thrive, overgrowth, short stature, obese)

- General observation (poor eye contact, repetitive behavior , hand wringing)

- Dysmorphism , neurocutaneous stigmata , skin bruises

- CNS exam (e.g. hypotonia, gait)

- CVS exam (e.g. heart murmur)

- Abdominal exam (e.g: hepatosplenomegaly)

- Skeletal abnormalities (e.g. vertebral anomalies, bradydactyly, clinodactyly, kyphoscoliosis)

Investigation

Table 1 Table demonstrating recommendations for first-line investigations for global developmental delay from four guidelines and our proposed recommendations

Tests category	UK current McDonald *et al*[8]	UK proposed	USA Moeschler and Shevell[4]	Irish O'Byrne *et al*[10]	Australian Silove *et al*[9]
Genetic	Karyotype Frag X	Microarray Frag X (selected)	Microarray Frag X	Microarray Frag X (selected) Chromosomal: banded analysis (selected)	Microarray Frag X
Biochemical and metabolic					
Blood tests	U&E CK TFT Lead Urate FBC Ferritin Biotinidase	U&E CK TFT Lead (If PICA) FBC Ferritin (dietary restriction) AA Homocysteine Acylcarnitine profile	TFT Lead (selected) AA Homocysteine Acylcarnitine profile	U&E CK TFT LFT FBC Bone profile Urate Glucose, lactate Venous blood gas AA Homocysteine (selected if raised methionine)	U&E CK TFT FBC Lead AA
Urine tests		OA GAG Oligosaccharides Creatine/GAA Purine and pyramidines	OA GAG Oligosaccharides Creatine/GAA Purine and pyramidines	OA GAG Paired urate +Urate/creatinine	OA GAG

AA, amino acids; ASD, autistic spectrum disorder; CK, creatine kinase; FBC, full blood count; Frag X, fragile X; GAG, glycosaminoglycans; LFT, liver function test; OA, organic acids; TFT, thyroid function tests; U&E, urea and electrolytes.

Mithyantha R, Kneen R, McCann E, et al. Current evidence-based recommendations on investigating children with global developmental delay. Archives of Disease in Childhood 2017;102:1071-1076.

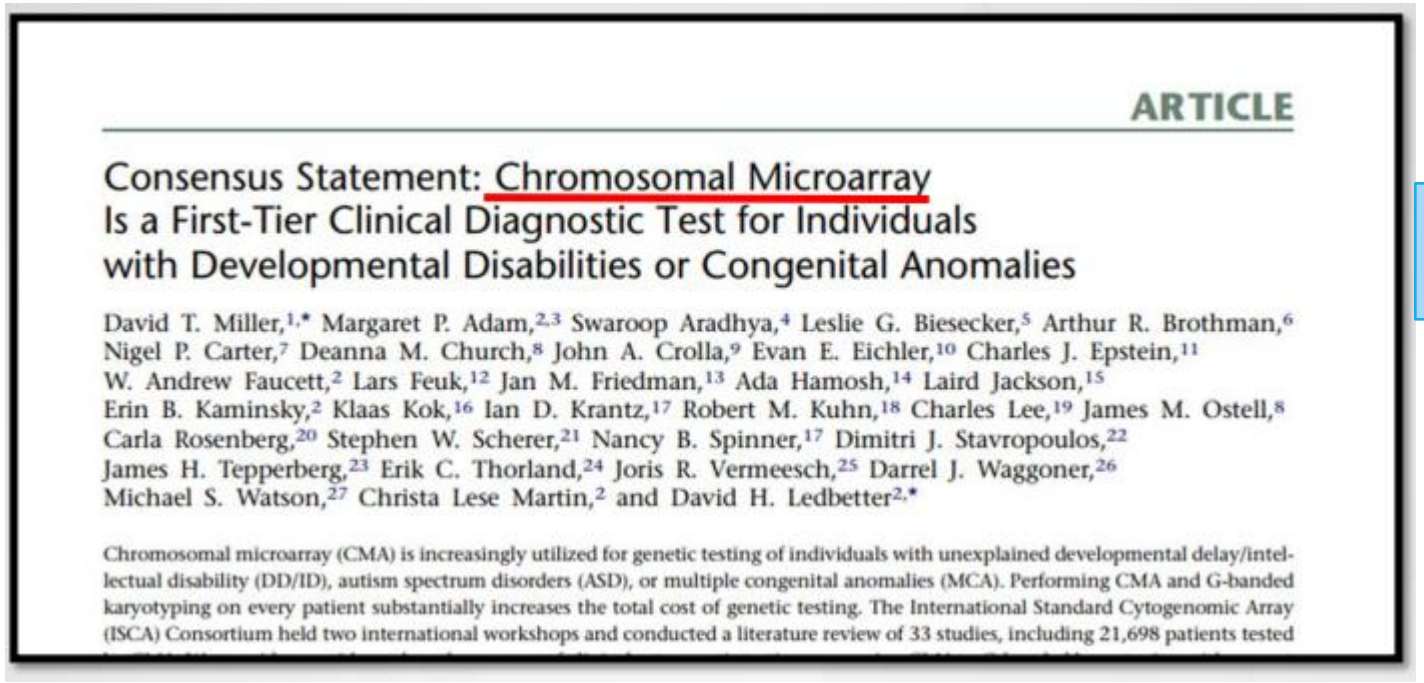
Investigation

-Blood for CBC, LFT , CK, TFT, bone profile, blood gas, glucose , lactate, homocysteinuria, acylcarnitine profile

-Urine for OA, GAG

-Genetic test: microarray, Fragile X (first line) , WES (consider WGS, methylation study based on clinical suspicion)

-Brain imaging: MRI brain (can be considered , esp in the presence of micro/macrocephaly, epilepsy), EEG (if suspected seizure)



ARTICLE

Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

David T. Miller,[1,*] Margaret P. Adam,[2,3] Swaroop Aradhya,[4] Leslie G. Biesecker,[5] Arthur R. Brothman,[6] Nigel P. Carter,[7] Deanna M. Church,[8] John A. Crolla,[9] Evan E. Eichler,[10] Charles J. Epstein,[11] W. Andrew Faucett,[2] Lars Feuk,[12] Jan M. Friedman,[13] Ada Hamosh,[14] Laird Jackson,[15] Erin B. Kaminsky,[2] Klaas Kok,[16] Ian D. Krantz,[17] Robert M. Kuhn,[18] Charles Lee,[19] James M. Ostell,[8] Carla Rosenberg,[20] Stephen W. Scherer,[21] Nancy B. Spinner,[17] Dimitri J. Stavropoulos,[22] James H. Tepperberg,[23] Erik C. Thorland,[24] Joris R. Vermeesch,[25] Darrel J. Waggoner,[26] Michael S. Watson,[27] Christa Lese Martin,[2] and David H. Ledbetter[2,*]

Chromosomal microarray (CMA) is increasingly utilized for genetic testing of individuals with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD), or multiple congenital anomalies (MCA). Performing CMA and G-banded karyotyping on every patient substantially increases the total cost of genetic testing. The International Standard Cytogenomic Array (ISCA) Consortium held two international workshops and conducted a literature review of 33 studies, including 21,698 patients tested

Am J Hum Genet. 2010 May 14;86(5):749-64

SYSTEMATIC REVIEW | Genetics inMedicine

Open

Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders

Siddharth Srivastava, MD[1], Jamie A. Love-Nichols, MS, MPH[1], Kira A. Dies, ScM[1], David H. Ledbetter, PhD[2], Christa L. Martin, PhD[2], Wendy K. Chung, MD, PhD[3,4], Helen V. Firth, DM, FRCP[5,6], Thomas Frazier, PhD[7], Robin L. Hansen, MD[8], Lisa Prock, MD, MPH[1,9],

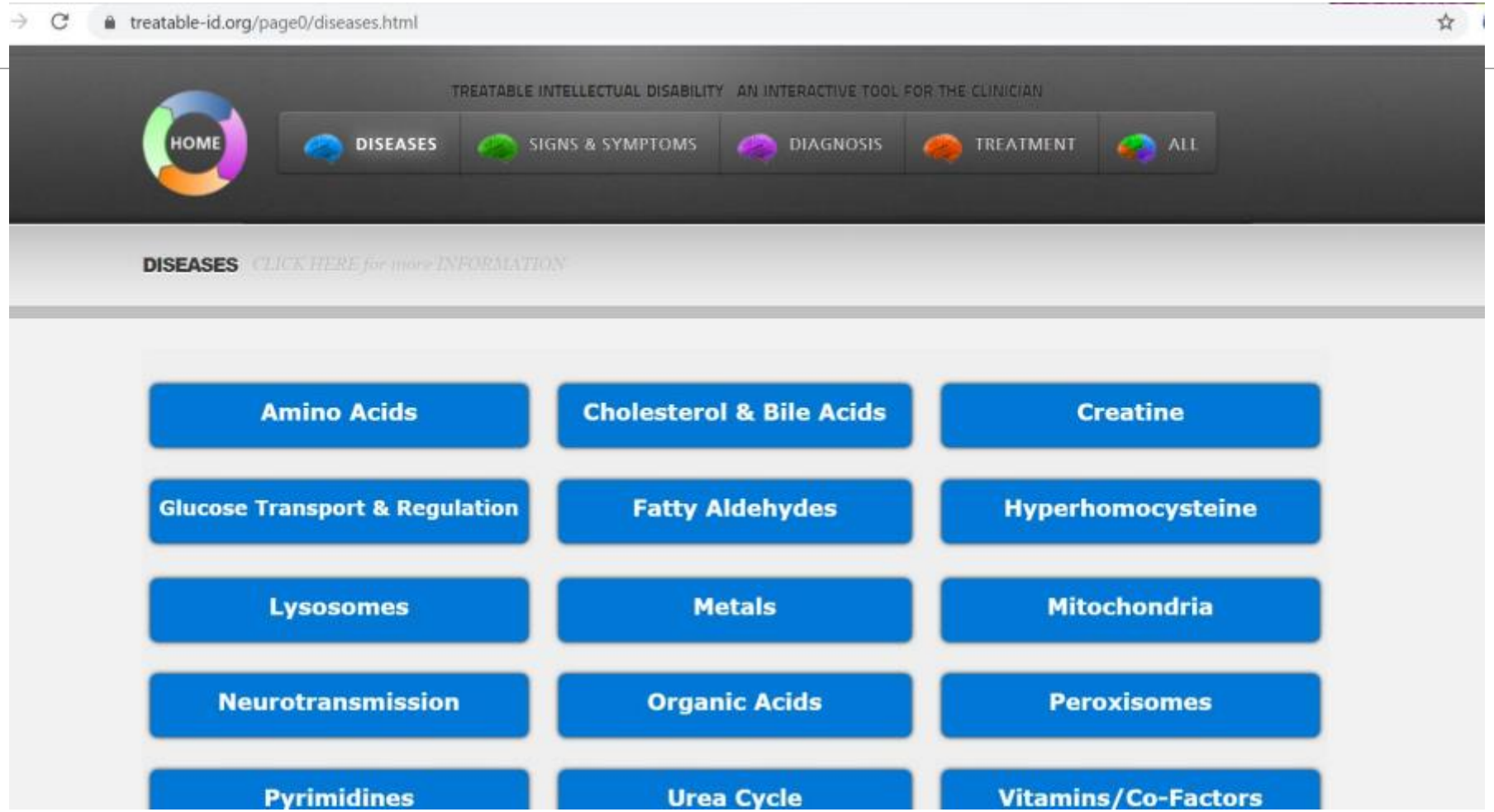
Genetics in Medicine volume 21, pages2 413–2421(2019)

Why early diagnosis is important?

- Timely initiation of causal treatment or supportive management
- Prevention of complications
- Improved prognostication
- Accurate genetic counselling regarding recurrence risk and prenatal/preimplantation genetic diagnosis
- Better access to services in the community
- Resolution of a diagnostic odyssey

Treatable causes

http://www.treatable-id.org/



Genetic testing- diagnostic yield

- FRAXA (1-5%)
- microarray (15-20%)
- WES (30-40%)
- WGS (30-57%)

Depends on

- Clinical phenotype (severity , associated syndromal features, dysmorphism, presence of other morbidities like epilepsy etc)
- Sample (Singleton vs Trio)

-Miller DT et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. AmJ Hum Genet. 2010;86:749–764
-van Slobbe et al. Reanalysis of whole-exome sequencing (WES) data of children with neurodevelopmental disorders in a standard patient care context. Eur J Pediatr 183, 345–355 (2024).
-Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. NPJ Genom Med 2018; 3: 16
-Lee et al., Diagnostic yield and treatment impact of whole-genome sequencing in paediatric neurological disorders. Dev Med Child Neurol, 63: 934-938 (2021)

Limitation of genetic tests

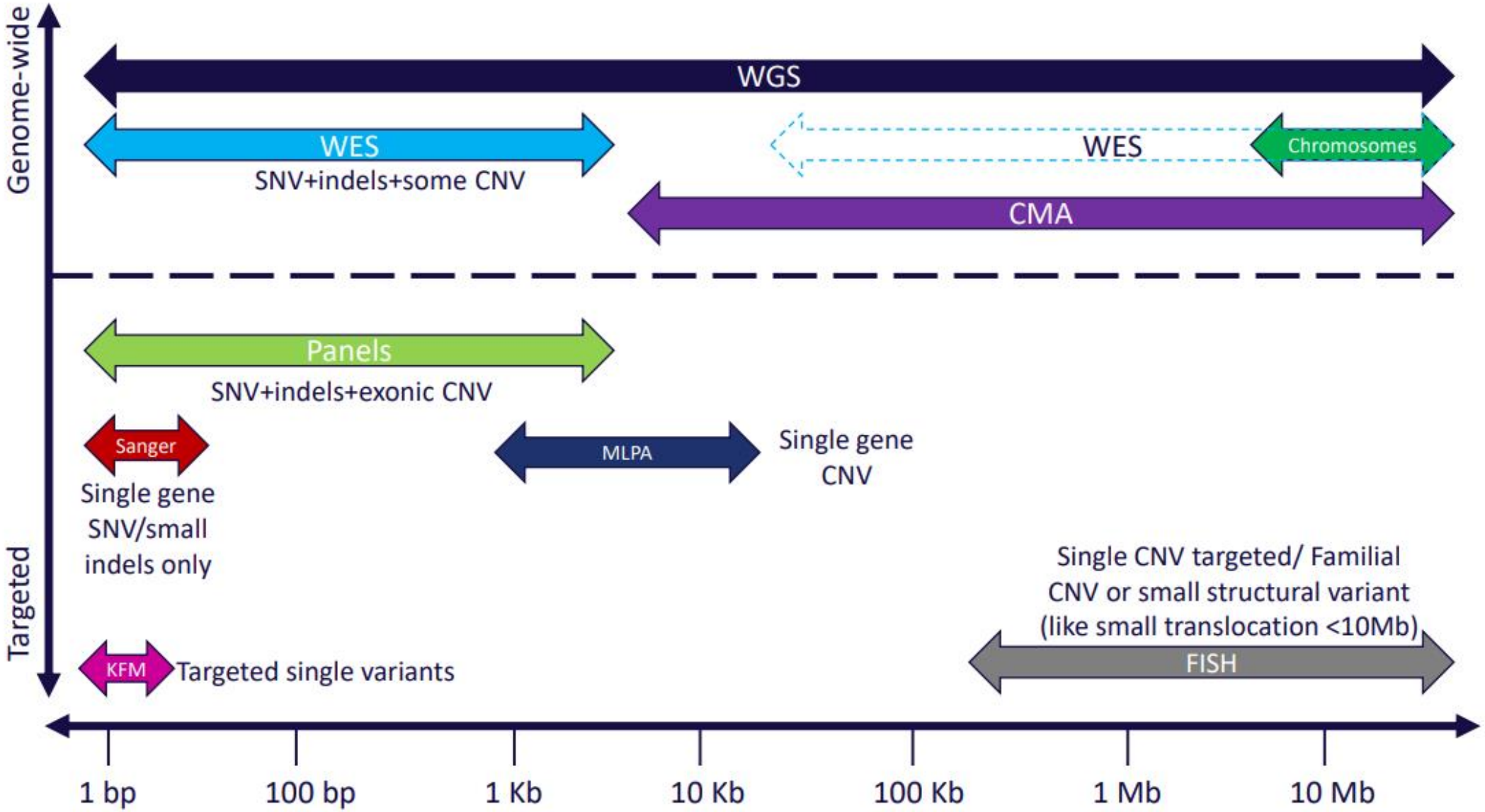
Cytogenetics

- Karyotype
- FISH
- Microarray

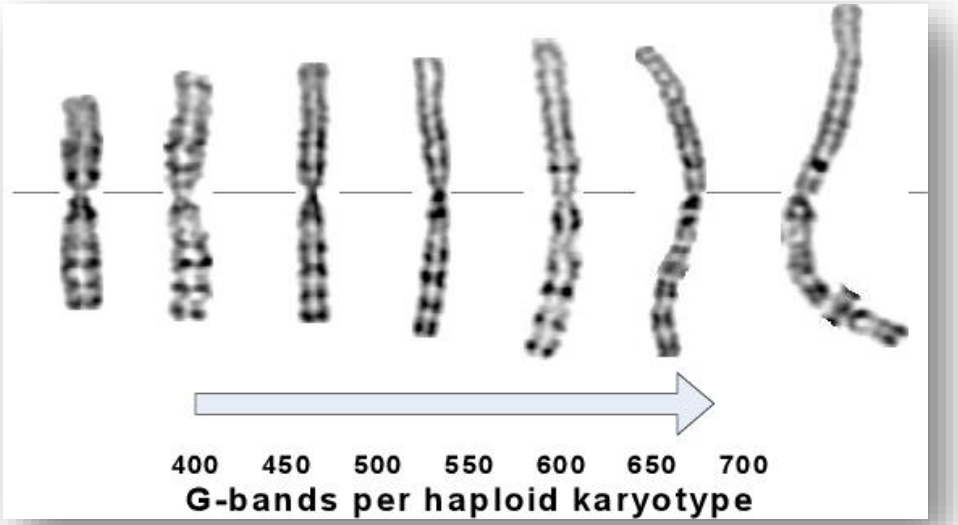
There is no one perfect test!

Molecular

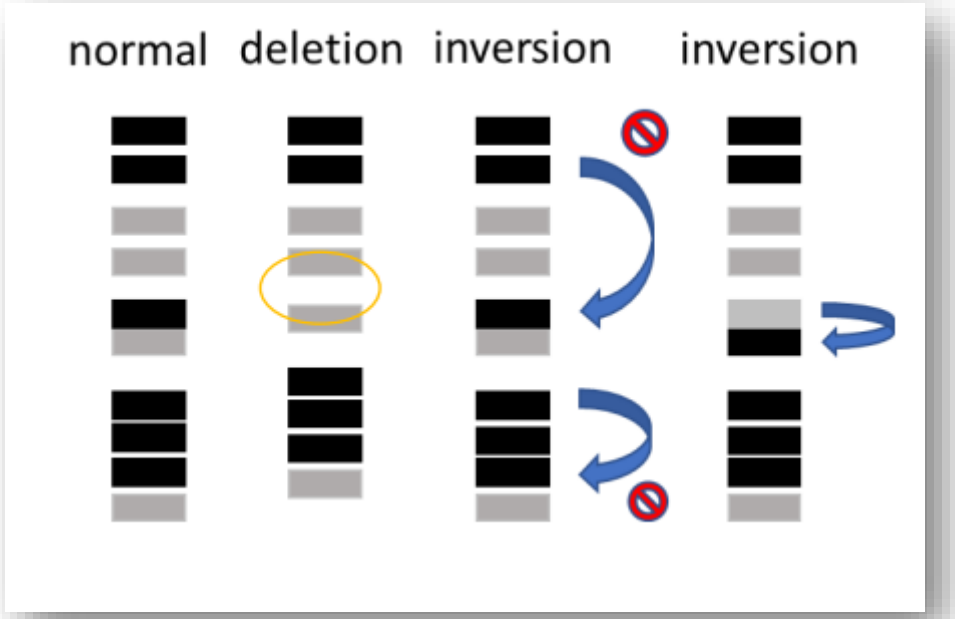
- Sanger sequencing
- NGS panel
- WES
- WGS
- New technology : Long read sequencing, optical mapping


Genome-wide
WGS
WES
SNV+indels+some CNV
WES
Chromosomes
CMA
Panels
SNV+indels+exonic CNV
Sanger
Single gene
SNV/small
indels only
MLPA
Single gene
CNV
Targeted
Single CNV targeted/ Familial
CNV or small structural variant
(like small translocation <10Mb)
FISH
KFM
Targeted single variants
1 bp
100 bp
1 Kb
10 Kb
100 Kb
1 Mb
10 Mb

Karyotype



Chromosomes are limited by resolution and resolution varies by the tissue type and preparation Resolution is ~4-5 Mb*** for high resolution blood



The resolution also depends on the type of abnormality and the region of the genome

Microarray

to detect copy number change in genome wide approach

ADVANTAGE	LIMITATIONS
- Resolution much higher than FISH/chromosomes - Can assess the entire genome at once - Useful to identify markers, rings, "chromatin of unknown origin" and other ambiguous cytogenetic findings	- Copy number analysis only-no information on location of gained material or complex rearrangements - Cannot detect balanced structural rearrangements - Gene and exon level coverage is dependent on genome architecture and repetitive sequences - Can pick up mosaicism down to (~15%)

NGS panel

Collection of genes related to a common phenotype or pathway

ADVANTAGE	LIMITATIONS
- Cost efficient for disorders with multiple genes of interest - Deeper sequencing in panels vs exome -Can detect mosaicism - Targeted sequencing→ specific genes or gene regions are selectively amplified using gene panels meaning genes of interest will be covered >99%	- Library must be kept up to date with recently identified genes or variants locations - NGS can call copy number changes if multi-exon changes. Single exon losses are difficult if heterozygous and duplications are even more difficult - if concerned about CNV → send additional copy number test such as MLPA or CMA - Panels with the same name may have very different gene content at different labs

Whole Exome Sequencing

2-3% of the genome
• Majority of exons (not all), +/- 5-20 intronic
• Average coverage ~100-200X (>95% 20X coverage)

ADVANTAGE

- For phenotype with significant genetic heterogeneity , and differential diagnosis are VERY BROAD

- Covers most genes related to Mendelian disease→ replaces need for multiple separate panels

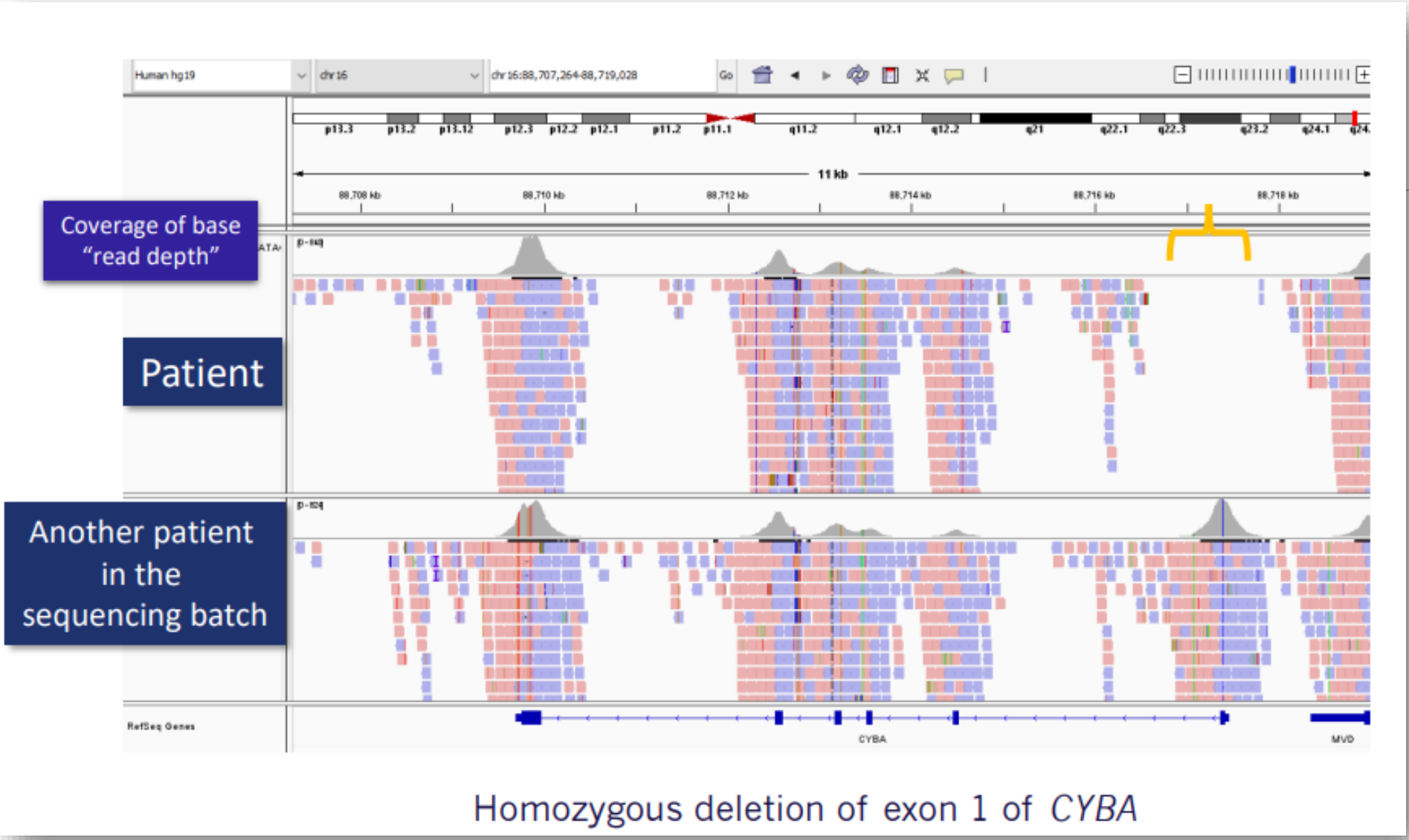
LIMITATIONS

• Cannot cover every gene at >99%

• Complex regions will not be covered

• Difficult to call CNVs confidently -usually limited to homozygous or multiple exon deletions

• possibility of VUS

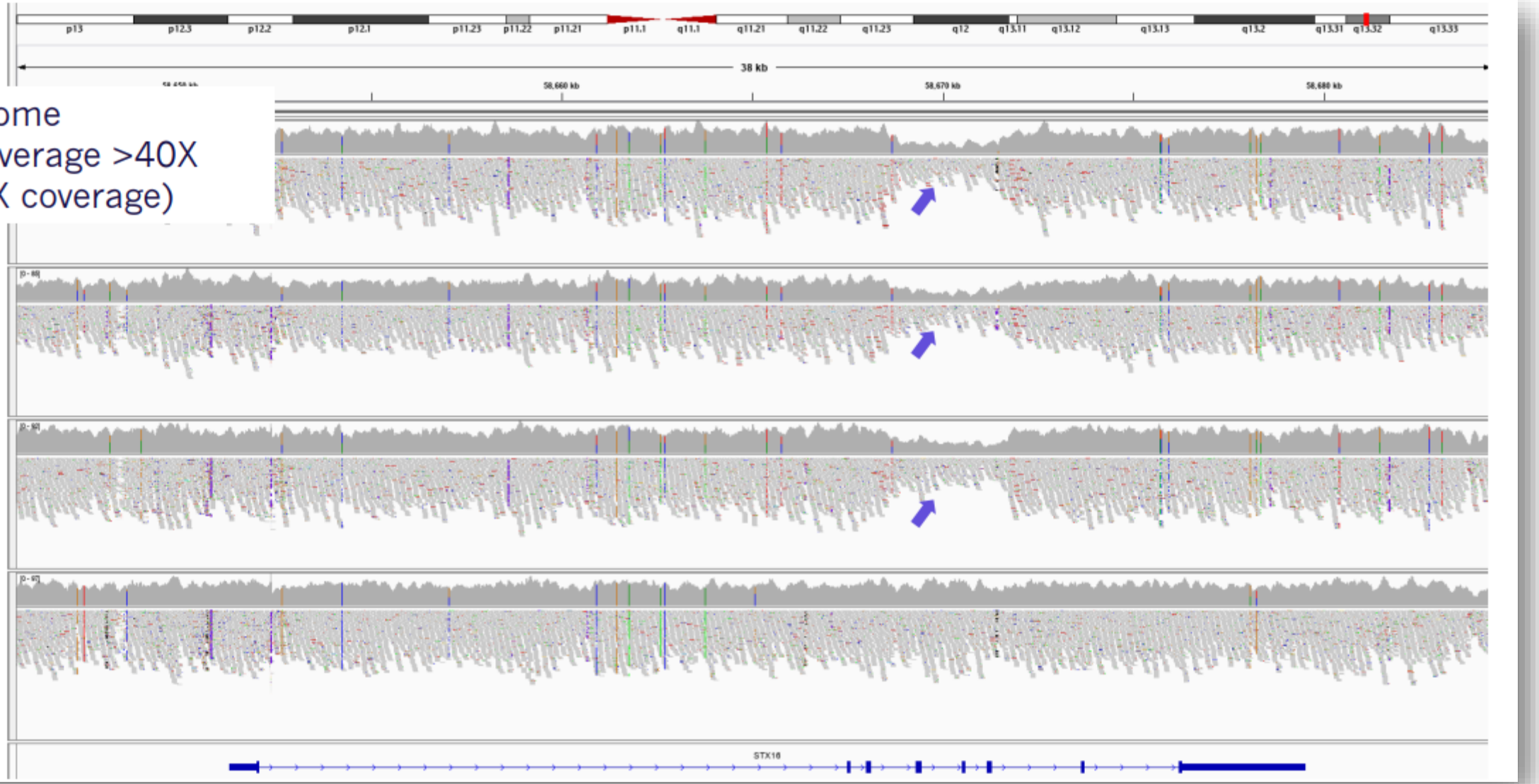


Homozygous deletion of exon 1 of *CYBA*

Whole Genome Sequencing

ADVANTAGE	LIMITATIONS
- When differential is VERY BROAD - Covers the entire genome - Heavily reliant on bioinformatics pipelines to extract AOH, CNV, SNV data , trinucleotide repeat disorder, mitochondrial genome	- Not ideal to detect low level mosaicism (SNVs or CNVs) -Generate more VUSs

- Whole genome
- Average coverage >40X (>95% 20X coverage)



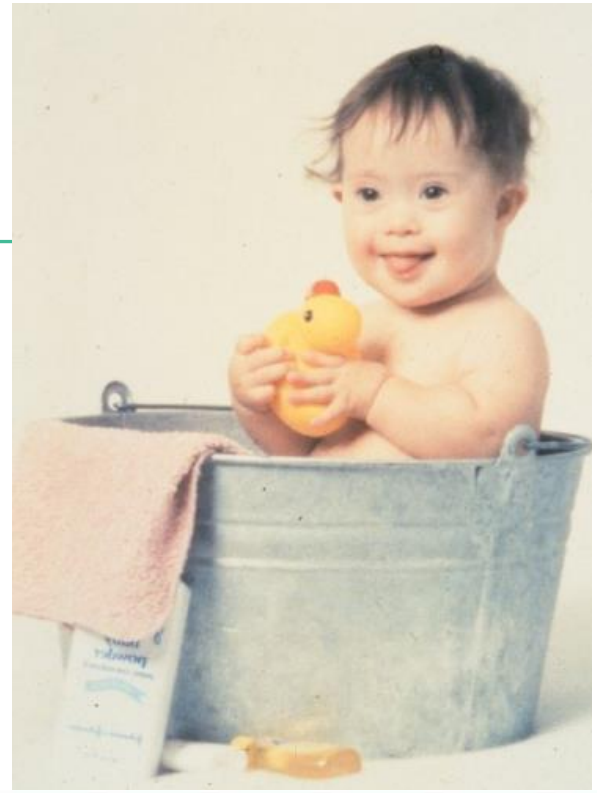
Genetic disorders and GDD

Chromosomal disorder

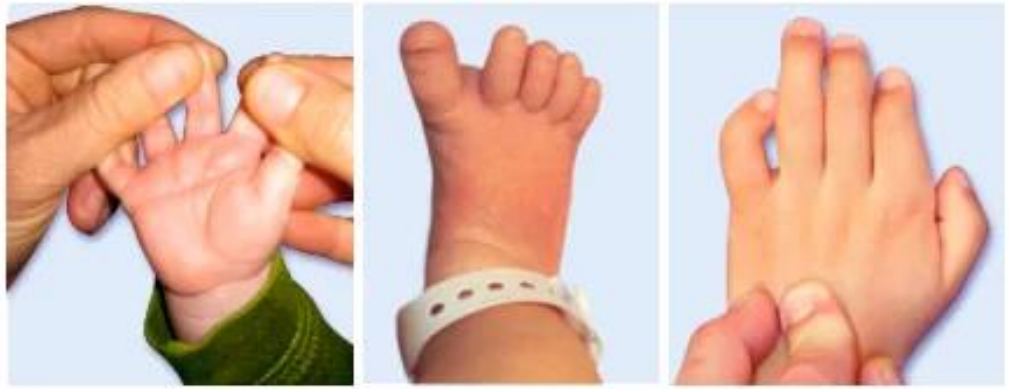
- Chromosomal aneuploidy
- Trisomy 21, 13, 18
- Unbalanced chromosomal rearrangement
- Marker chromosome/ ring chromosome

Karyotypes	No. children (n=34)	%
Numerical abnormalities		
49,XXXXY	2	5.9
47,XYY	1	2.9
47,XXY	1	2.9
47,XXX	1	2.9
45,X/46,XY	1	2.9
47,XXY/46,XY	1	2.9
Structural abnormalities		
46,XY,rob(13;14) (q10;q10) or 46,XX,rob(13;14)(q10;q10)	2	5.9
45,XX,rob(13;14) (q12.1;q11.2)	2	5.9
46,XX,del(5)(p15.2pter)	3	8.8
46,XX,der(5)add(8)(q13)del(5)(p13) pat	1	2.9
46,XX,der(22)t(5;22)(p12;q11.2) (06)/46,XX(10)	1	2.9
46,XY,der(18)t(8;18)mat	1	2.9
46,XX,del(18)(p11.2pter)	1	2.9
46,XX,del(18)(q21.31qter)	1	2.9
46,XY(6)/47,XY,+mar(18)	1	2.9
46,XX/46,XX,del(14)(q11.2q13)	1	2.9
46,XX,inv(22)(p11.2q12.3)pat	1	2.9
45,XX,t(19;22)/46,XX/47,XX,+21	1	2.9
46,XX,+inv dup(12)(p11.2pter)	1	2.9
46,XX,der(15)t(3;15)(p24;q26)mat	1	2.9
46,XY,del(9)(q13q21)	1	2.9
46,XY,del(9)(p22pter)(37)/47,XY, del(9) (p22pter),+mar(63)	1	2.9
46,XY,del(11)(q23.2qter)	1	2.9
46,X,del(Y)(q11)	1	2.9
46,XX,?del (12)(q23)	1	2.9
46,XX,dup(17)(q24q25)	1	2.9
46,XY,del (15)(q11.2q12)	1	2.9
46,XX,del(4)(p15.3pter)	1	2.9
47,XX,+mar	1	2.9
Total	34	100

Down syndrome (Trisomy 21)

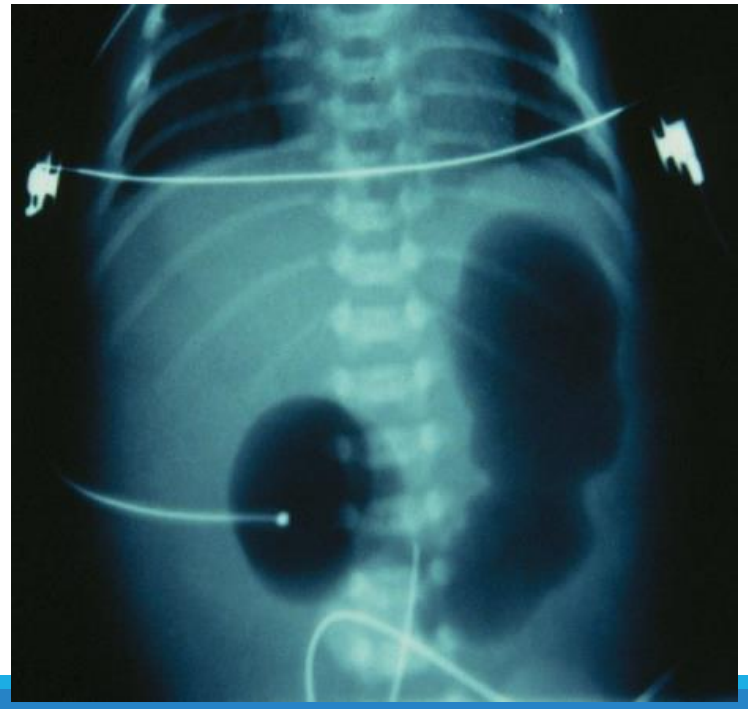


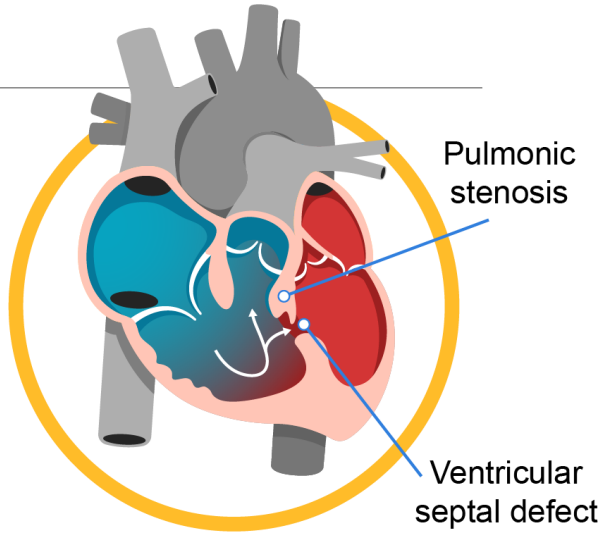
- Incidence 1/800
- Generalized hypotonia
- Microcephaly, brachycephaly
- Small and round ears, upslanting palpebral fissures, epicanthal folds, midface hypoplasia, tongue protrusion
- Intellectual Disability: IQ average is 40-60
- Broad and short neck, redundant skin
- Brachydactyly, single transverse palmar creases, 5th finger clinodactyly
- Sandal gap deformity
- Recurrence risk 1% for free trisomy 21



Down syndrome (Trisomy 21)

- 40-50 % Congenital heart defect (AV canal)
  - Gastrointestinal anomalies: duodenal atresia, Hirschprung disease, celiac disease
- Hematologic: AML => megakaryoblastic leukemia
- Hypothyroidism
- Increase incidence of Alzheimer disease





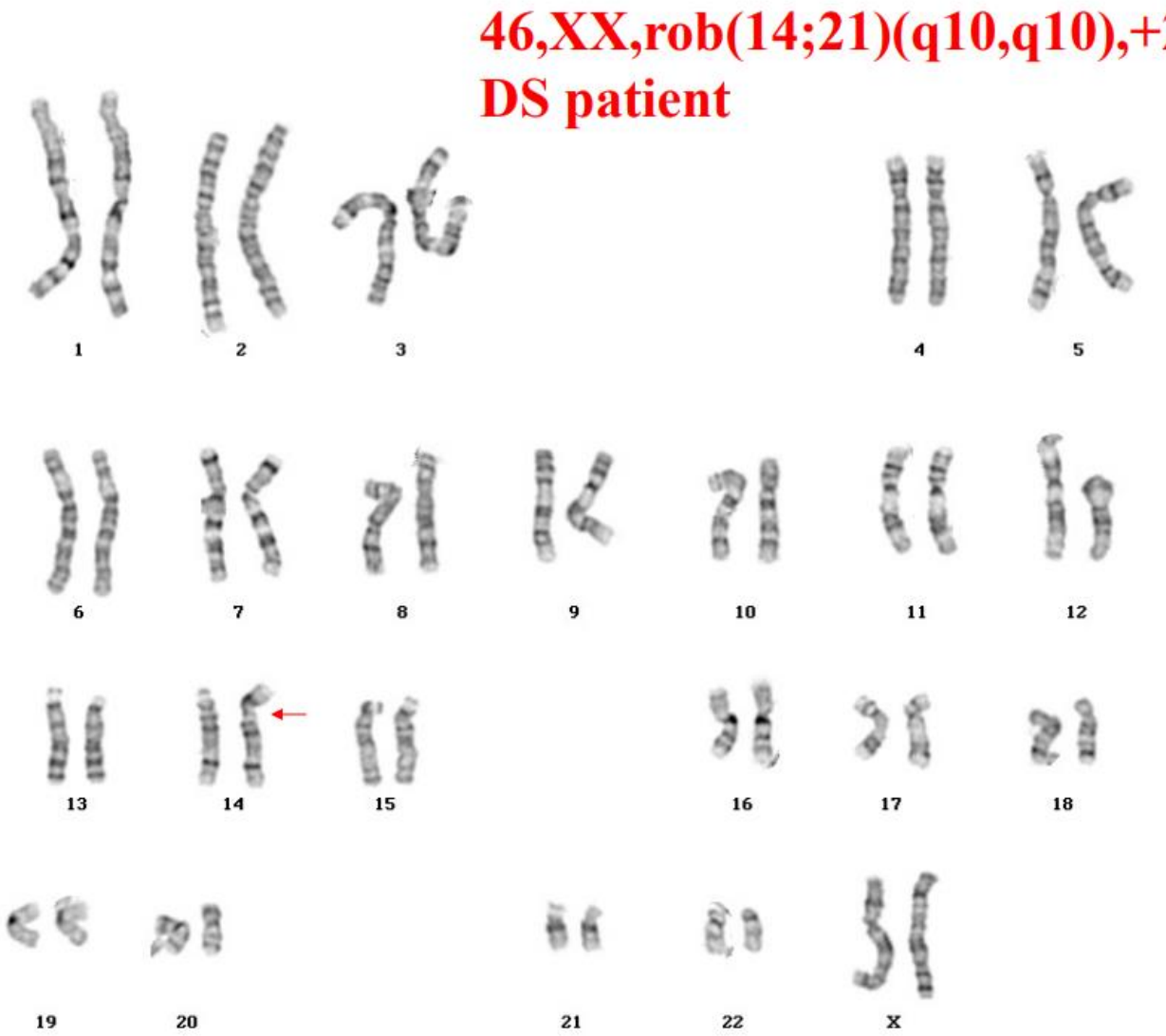
Down Syndrome- Genetic etiologies

Majority Trisomy 21 (95%) due to non-disjunction

Recurrence risk : 1% (maternal age dependent)

2-4% due to Robertsonian translocation

Remainin Mosaic Trisomy 21



Parental study showed tat 45,XX,rob(15;21)(q10q10) - Carrier DS translocation

Recurrence risk 13;21, 14;21 or

15;21 (for carrier parents)

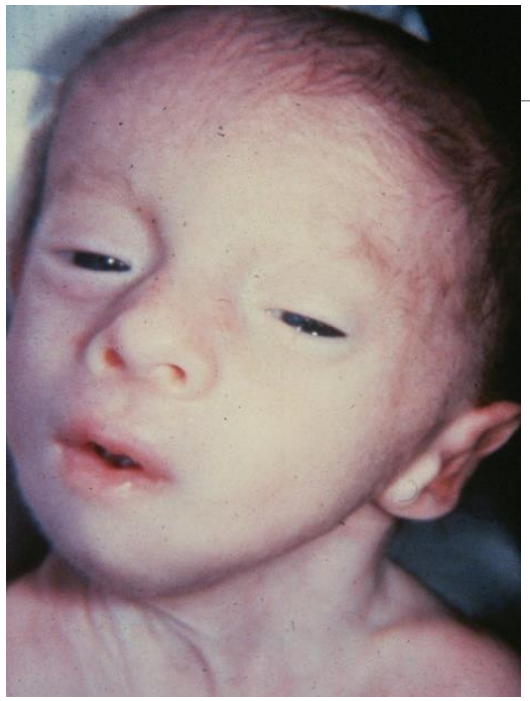
- Mother 5-7%

- Father 0%

For 21;21 translocation

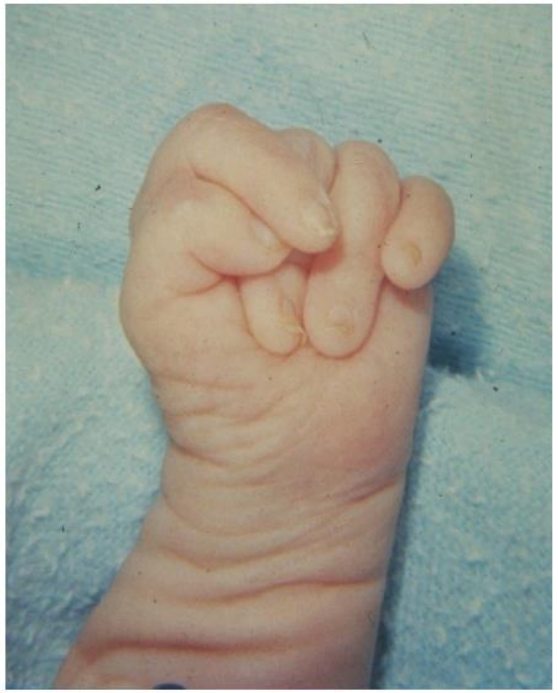
- 100%

Trisomy 18

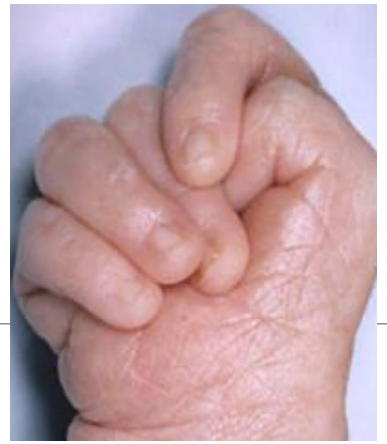


Microcephaly
- Microphthalmia
- Low set and malformed ears
- Micrognathia
- Small mouth
- Triangular face

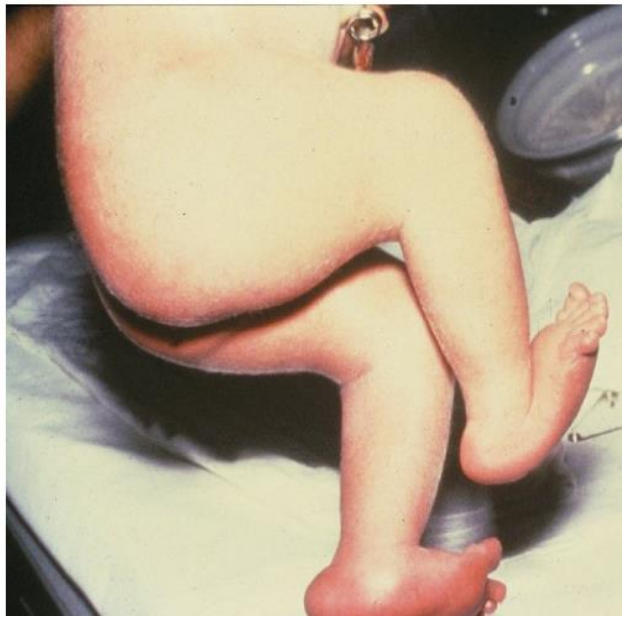
-Clenching hand
-Severe intellectual disability
- CNS anomalies, hypertonia, seizures



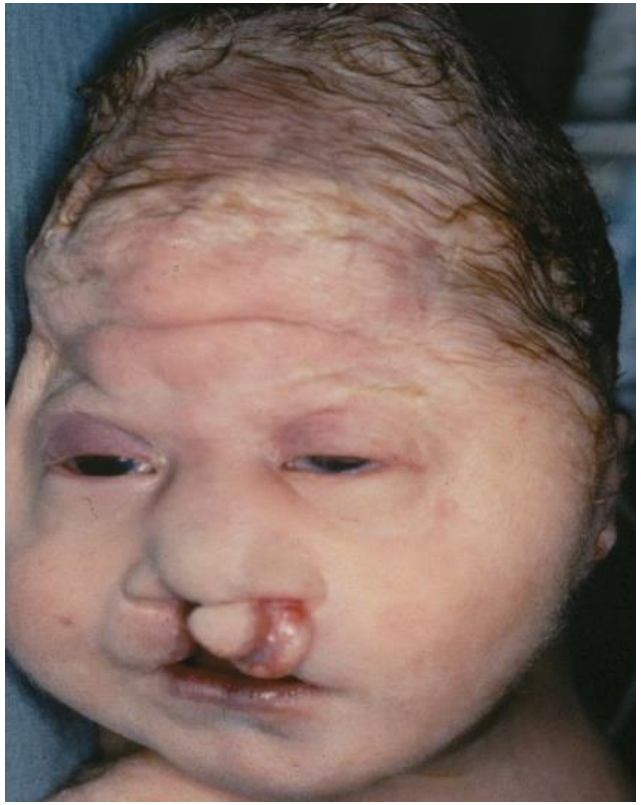
overlapping of fingers

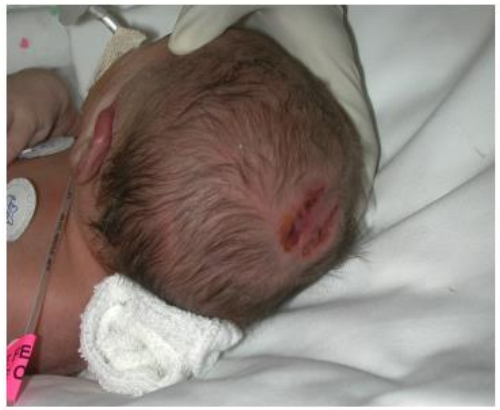


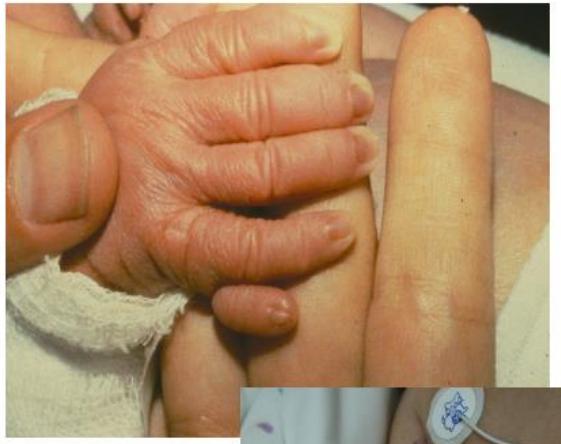
rockerbottom feet

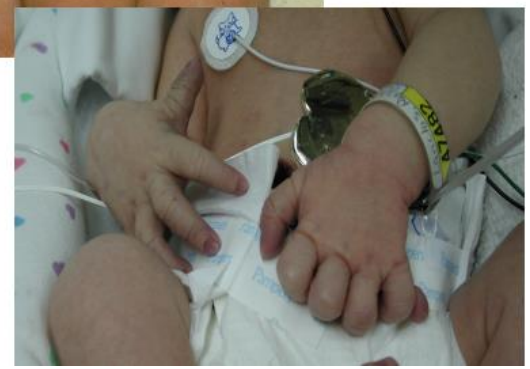


Trisomy 13









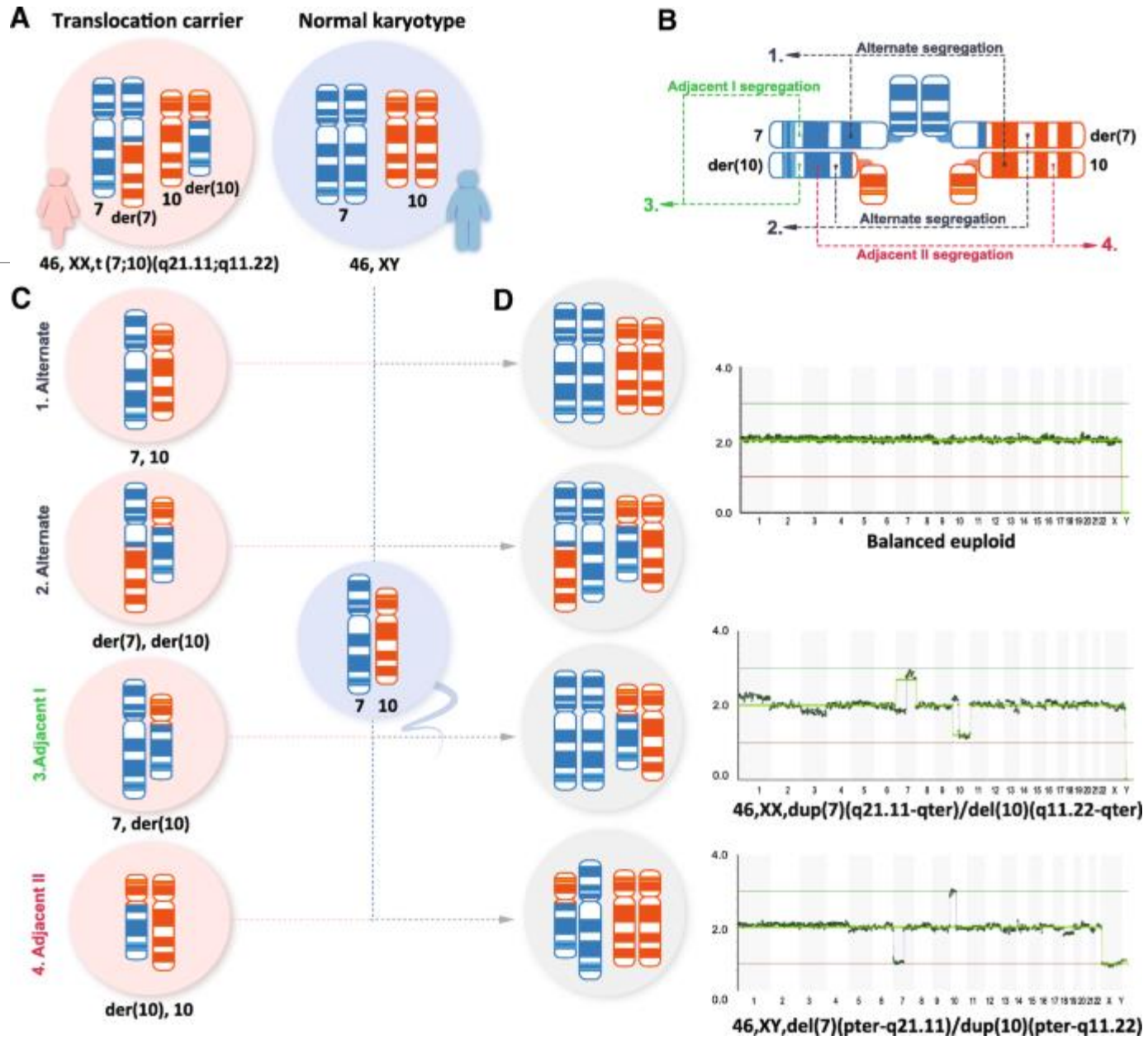
- Growth deficiency
- Limb: postaxial polydactyly
- Heart defects: VSD, ASD
- Scalp defects

Cleft lip and palate
Microphthalmia
Abnormal ears
seizures
Holoprosencephaly
Severe developmental delay

Chromosomal rearrangement

Parental balanced translocation carrier, inversion carrier

-predispose to recurrent miscarriage
-Viable affected offspring



Microdeletion/ microduplication syndrome

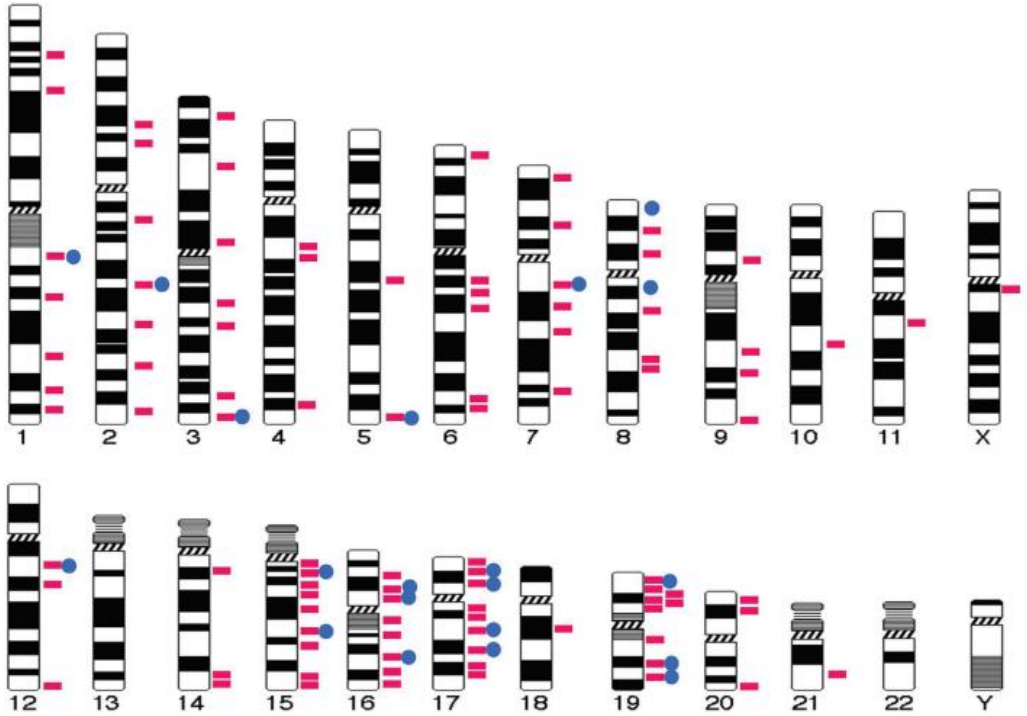


Figure 3 - New microdeletion and microduplication syndromes discovered over the last three to five years. Red squares indicate reported microdeletions; blue circles indicate reported microduplications.

Genetics and Molecular Biology, 37, 1 (suppl), 210-219 (2014)

www.sbg.org.br

Review Article

New microdeletion and microduplication syndromes: A comprehensive review

Julián Nevado[1,2]*, Rafaella Mergener[3]*, María Palomares-Bralo[1,2], Karen Regina Souza[3], Elena Vallespín[1,2], Rocío Mena[1,2], Víctor Martínez-Glez[1,2], María Ángeles Mori[1,2], Fernando Santos[1,4], Sixto García-Miñaur[1,4], Fé García-Santiago[1,5], Elena Mansilla[1,5], Luis Fernández[1,6], María Luisa de Torres[1,5], Mariluce Riegel[3,7$] and Pablo Lapunzina[1,4,8$]

Some commonly reported microdeletion syndromes asso with developmental delay

22q11.2 microdeletion/DiGeorge syndrome

22q13 microdeletion/Phelan-McDermid syndrome

7q11.23 deletion/Williams-Beuren syndrome

15q11.2 (BP1-BP2) deletion

16p11.2 deletion syndrome

16p13.11 microduplication

22q11.2 microduplication

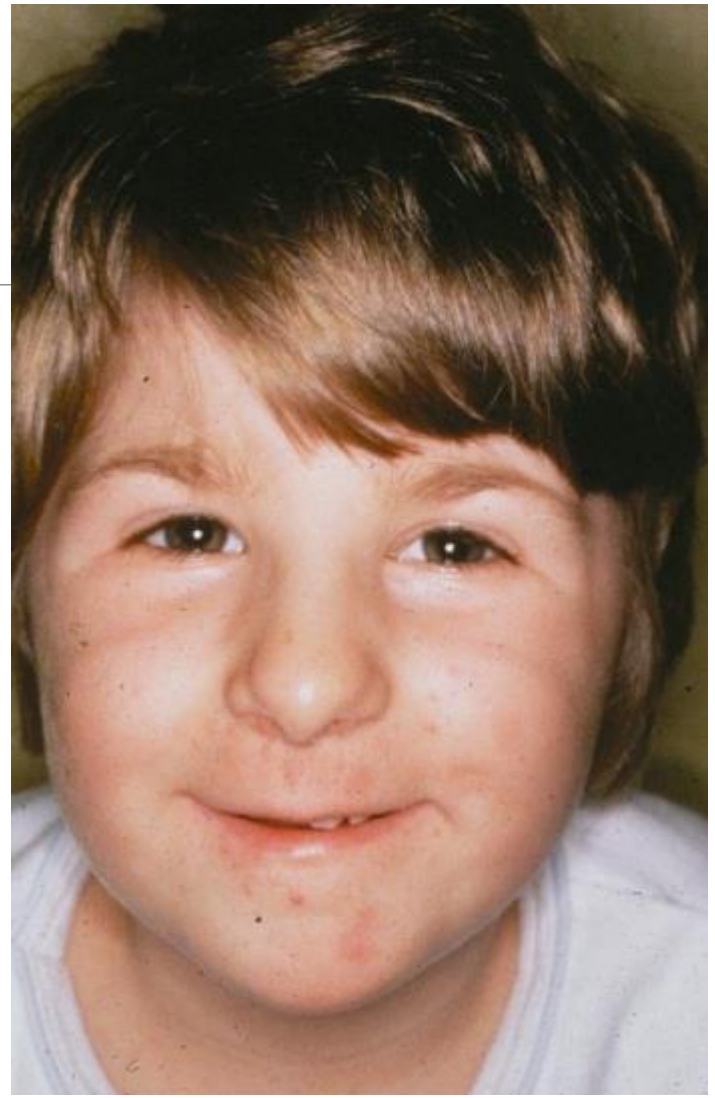
The 15q11-q13 deletion/Prader-Willi syndrome/Angelman syndrome (OMIM# 176270/105830; n = 9) variant size ranged from 4.9 to 5.69 Mb.

22q11.2 deletion syndrome

Velocardiofacial Syndrome/DiGeorge Syndrome

Submicroscopic deletions at 22q11.2 detected by molecular techniques (classic: 3Mb)

- Heart disease (conotruncal) : tetralogy of Fallot, interrupted aortic arch type B, truncus arteriosus, ventricular septal and atrial septal defects (TBX1 gene)
- Cleft palate (overt or submucous), velo-pharyngeal incompetence (VPI), bifid uvula.
- Hypocalcemia (parathyroid hypoplasia)
- Cellular immunodeficiency (thymus related)
- Mild intellectual disability



Dysmorphic features: hypoplastic alae nasi
Bulbous nose, low set ear

22q11.2 deletion syndrome

- Learning problems, mild Intellectual Disability (IQ ~ 80)
- Psychiatric illnesses (>40 %): schizophrenia, bipolar disorder
- Renal abnormalities (>30%)

William Beuren syndrome 7q11.23 deletion

-Mild intellectual disability

with IQ's up to 80

-Typical behaviors:

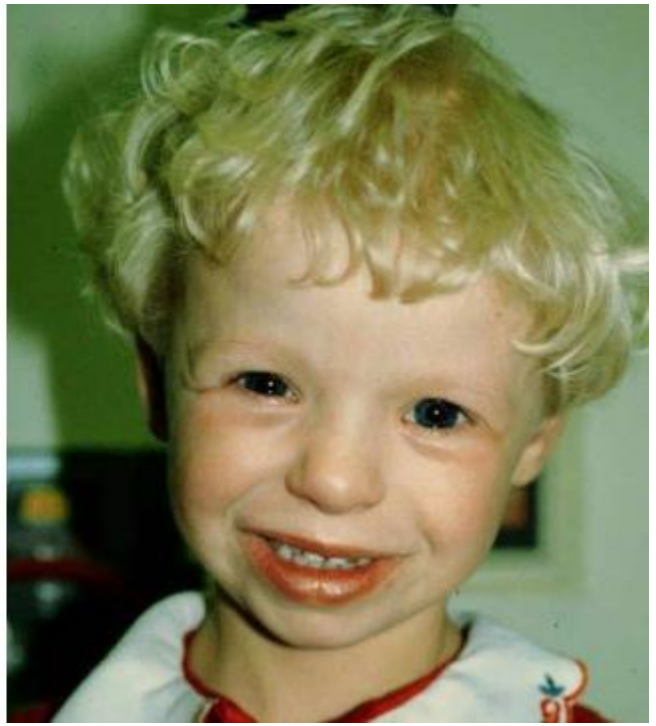
overfriendliness, attention

deficit disorder

- Hypercalcemia (15%)

- constipation, and muscle cramps

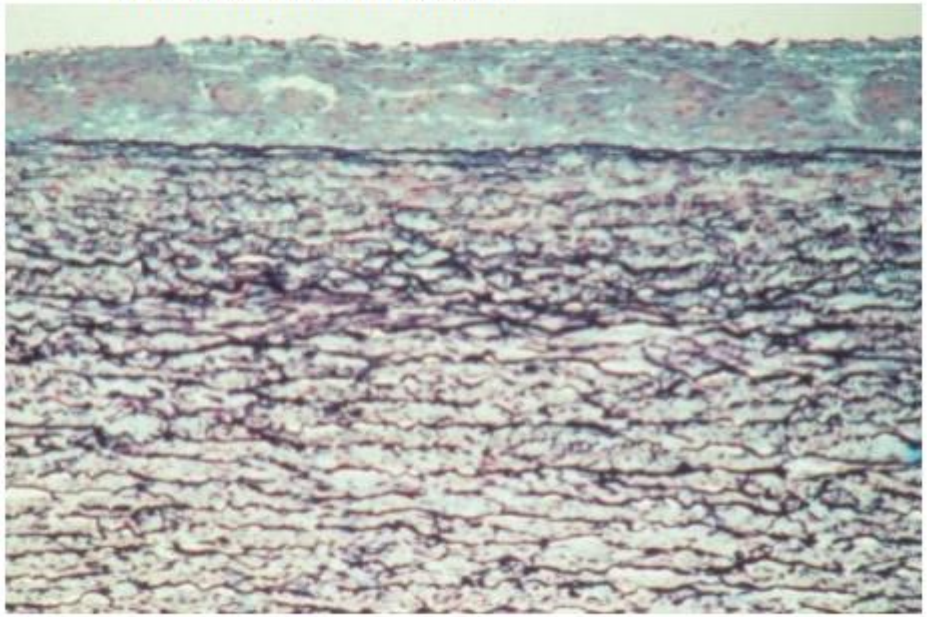
-Renal anomalies, nephrocalcinosis



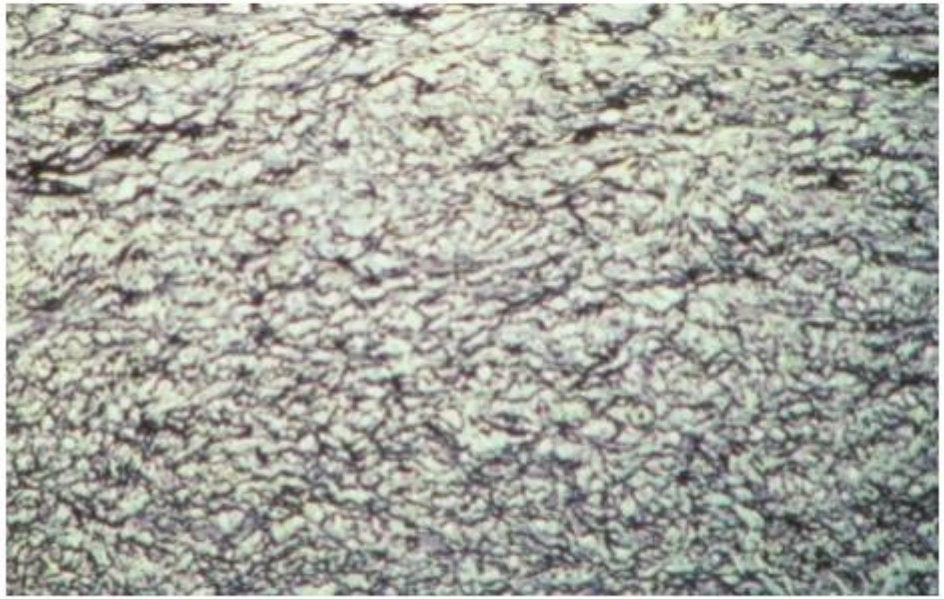
-Periorbital fullness
-Long philtrum
-Thick lip, wide mouth
-Happy disposition

The elastin gene is disrupted by a translocation associated with supravalvular aortic stenosis. Curran ME, et al., *Cell* 1993 Apr 9;73(1):159-68

Normal elastin stain

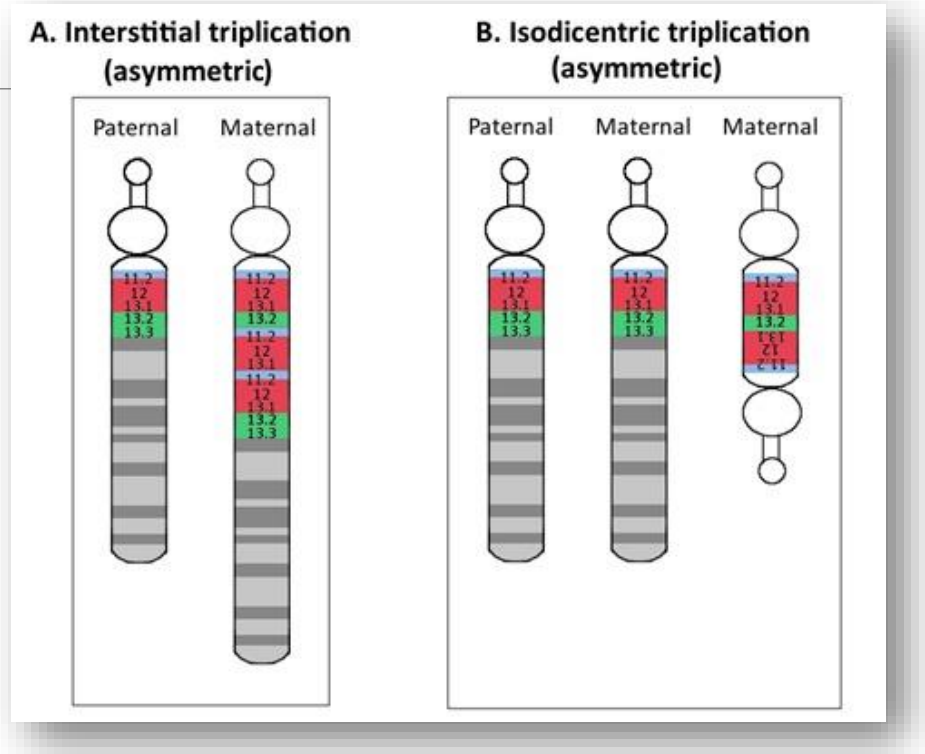


Elastin stain in a patient with WS



- Coronary artery stenosis has been implicated in some cases of SIDS
- Renal artery stenosis (hypertension)

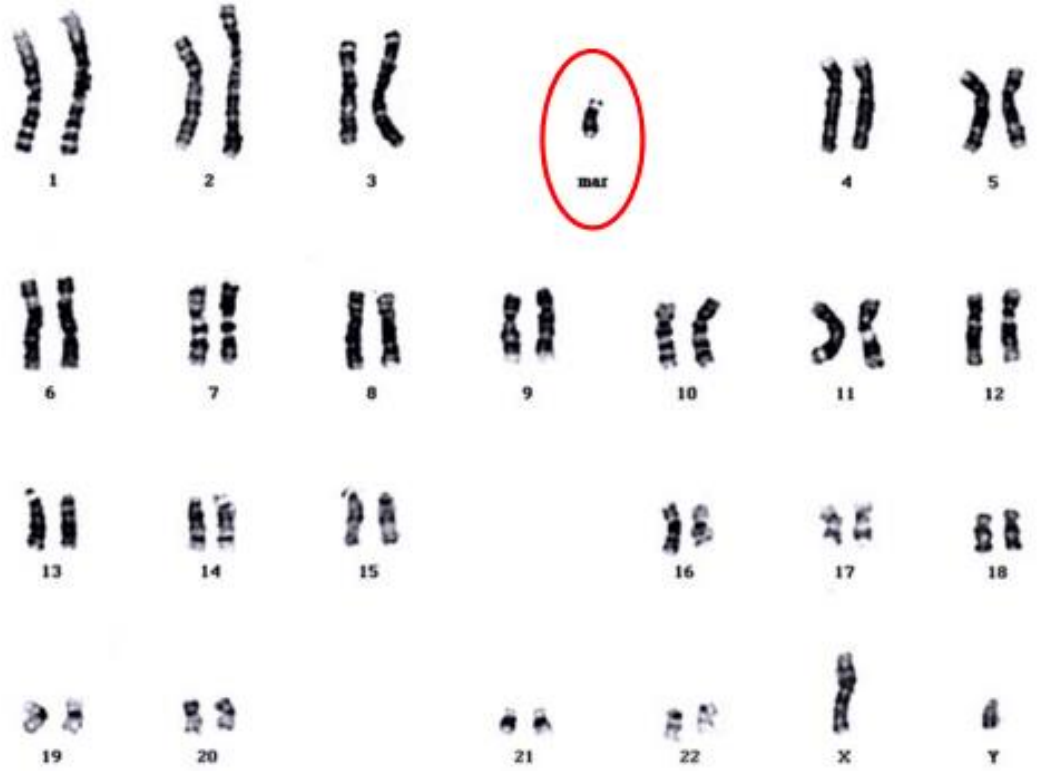
15q11q13 microduplication syndrome



Variable & non-specific clinical features

- Non-specific dysmorphic features
- Microcephaly
- Motor delay, hypotonia, unsteady gait
- Absent speech
- Global delay, MR
- Autistic features
- Hyperactive, aggressive, self-mutilation, short attention span
- Seizure

Maternally inherited 15q11-q13 duplication/triplication



Supernumerary marker chromosomes (SMC)

Severity depends on

- Extent of the duplicated region

-Small SMC(15) (no euchromatin)

-Familial or de novo

-Not associated with abnormal phenotype

- Dosage of PWS/AS region

- 4 copies in inv dic(15)

- 3 copies in heterozygous tandem duplication

- Parent of origin effect

- All maternally derived

- No paternal large SMC(15)s– lethal or selection against during spermatogenesis

Single gene disorders

-More than 1000 genes are linked to developmental disorder

-Fragile X syndrome is the most common monogenic defect associated with GDD/ID, being responsible for about 5% of the cases of intellectual disability

Moeschler JB, Shevell M Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global and developmental delays. Pediatrics. 2014;134(3):e903–918

Genes linked to GDD

Genes implicated in **metabolic pathways** (organic acid metabolism - ALDH5A1, L2HGDH genes; polysaccharide metabolism – NAGLU, SGSH genes; purine metabolism - ADSL gene; protein glycosylation- PMM1 gene; monocarboxylate transporter - SLC16A2 gene; creatine transporter - SLC6A8 gene)

Genes implicated in **neurogenesis** (mitotic spindle regulation in neuroblast – ASPM, CDK5RAP2, CENPJ genes; DNA repair and mitotic arrest in neuroblast - MCPH1 gene)

Genes implicated in **neuronal migration** (protein glycosylation - POMGNT1, POMT1, POMT2, FKTN, FKRP, LARGE genes; microtubule subunits - TUBA1A, TUBB2B genes; microtubule regulation – DCX gene; microtubule associated proteins - PAFAH1B1; transcription factors implicated in neuronal migration - ARX)

Genes implicated in **presynaptic function** (adhesion between pre and postsynaptic membranes - NRXN1, CDH15 genes; vesicle traffic - RAB3GAP1, STXBP1, GDI1, RAB39B genes; exocytosis inhibition - IL1RAPL1, CASK genes)

Miclea D et al., Genetic testing in patients with global developmental delay / intellectual disabilities. A review. Clujul Med. 2015;88(3):288-92. doi: 10.15386/cjmed-461. Epub 2015 Jul 1. PMID: 26609258

Genes linked to GDD

Genes implicated in **postsynaptic density organization** (adhesion between pre and postsynaptic membranes - CNTNAP2, NLGN3, NLGN4 genes; neurotransmitter receptor interaction with membrane proteins - SHANK2, SHANK3 genes; subunits of NMDA receptor - GRIN2A, GRIN2B genes)

Genes implicated in the **regulation of postsynaptic proteins** (ubiquitin ligase of UPS proteolysis - UBE3A, UBE2A, UBR1; HUWE1, CUL4B genes; transport of mRNA from the nucleus to the cytoplasm - FMR1 gene)

Genes implicated in **cytoskeletal dynamics of dendritic cells** (activation in Rho-GTPase pathway - MEGAP, OCRL1, OPHN1, FGD1, ARHGEF6, ARHGEF9 genes; regulation of actin polymerization and vesicles endocytosis- LIMK1, AP1S2, IQSEC2 genes; Rho-GTPase and cytoskeleton interaction - PAK3 gene)

Genes implicated in **intracellular signalization** (Ras-MAPK-ERK pathway - SOS1, RAF1, BRAF, SHOC2, HRAS, KRAS, PTPN11, SPRED1, MAP2K1, MAP2K2, NF1, DYRK1A, RPS6KA3 genes; PI3K-AKTmTOR pathway - TSC1, TSC2, PTEN genes)

Genes implicated in **epigenetic regulation of transcription** (histone deacetylase - HDAC4 gene; histone acetyl-transferase – CREBBP, EP300 genes; histone methyltransferase – NSD1, EHMT1, MLL2 genes; histone demethylase - KDM5C gene; subunits of Mediator complex (transcription pre-initiation) MED12, MED17 and MED23 genes; transcription factors - TCF4, RAI1, ZNF711, ZNF41, ZNF674, ZNF81, PHF6, PHF8 genes; DNA replication - SETBP1 gene; DNA methyltransferase - DNMT3B gene; repression of transcription factors – BCOR, MECP2 genes; chromatin modification – ATRX, BRWD3 genes)

Fragile X syndrome

Long face

Prominent forehead and Jaw

Large ears

Mild to profound intellectual disability; autistic-like w/hand-flapping; repetitive, explosive, stuttering, stammering speech; seizures

Macroorchidism-post-pubertal

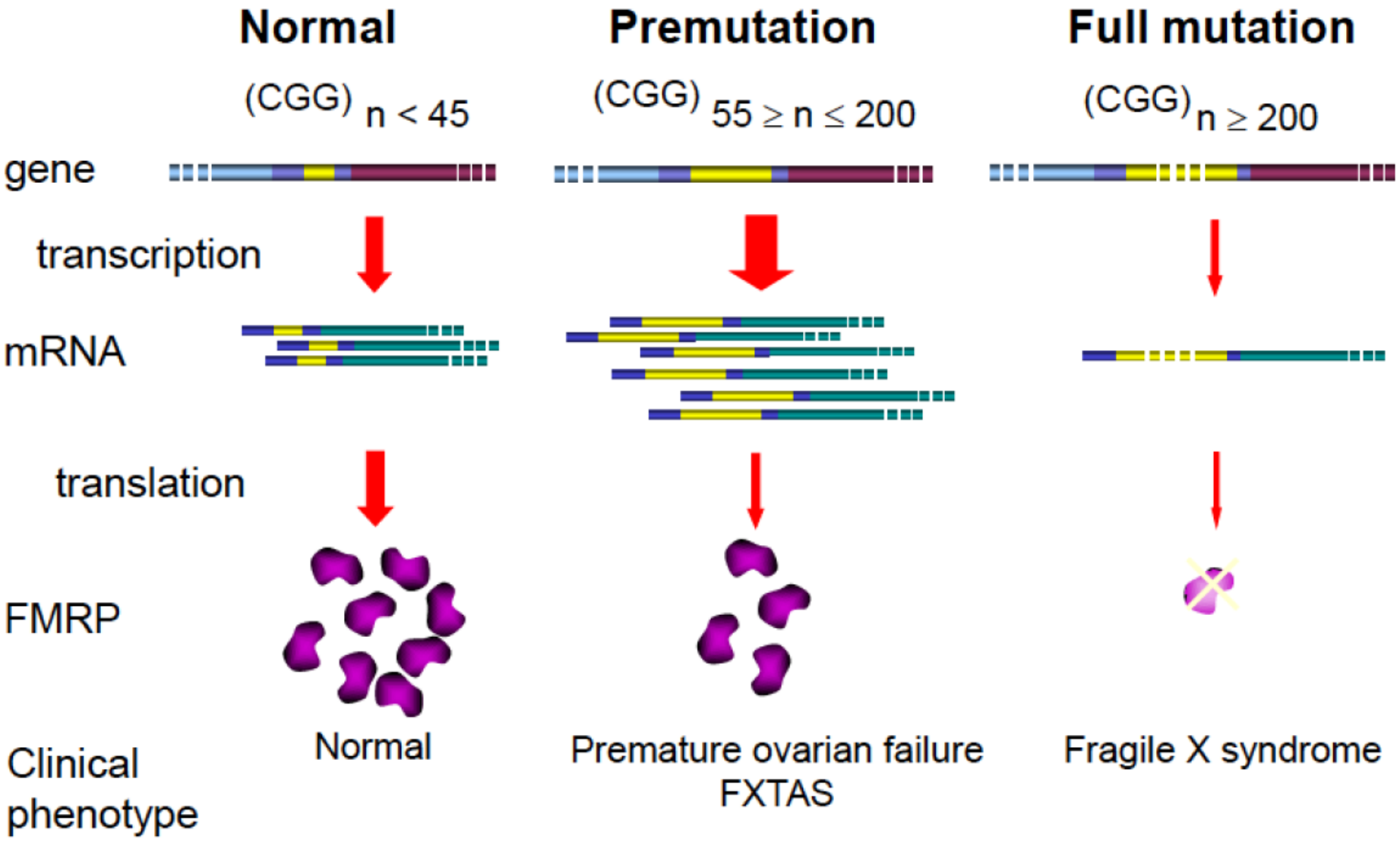
Mild connective tissue dysplasia-joint laxity

Other: macrocephaly, prognathism, pale blue irises, mitral prolapse

CGG repeat expansion

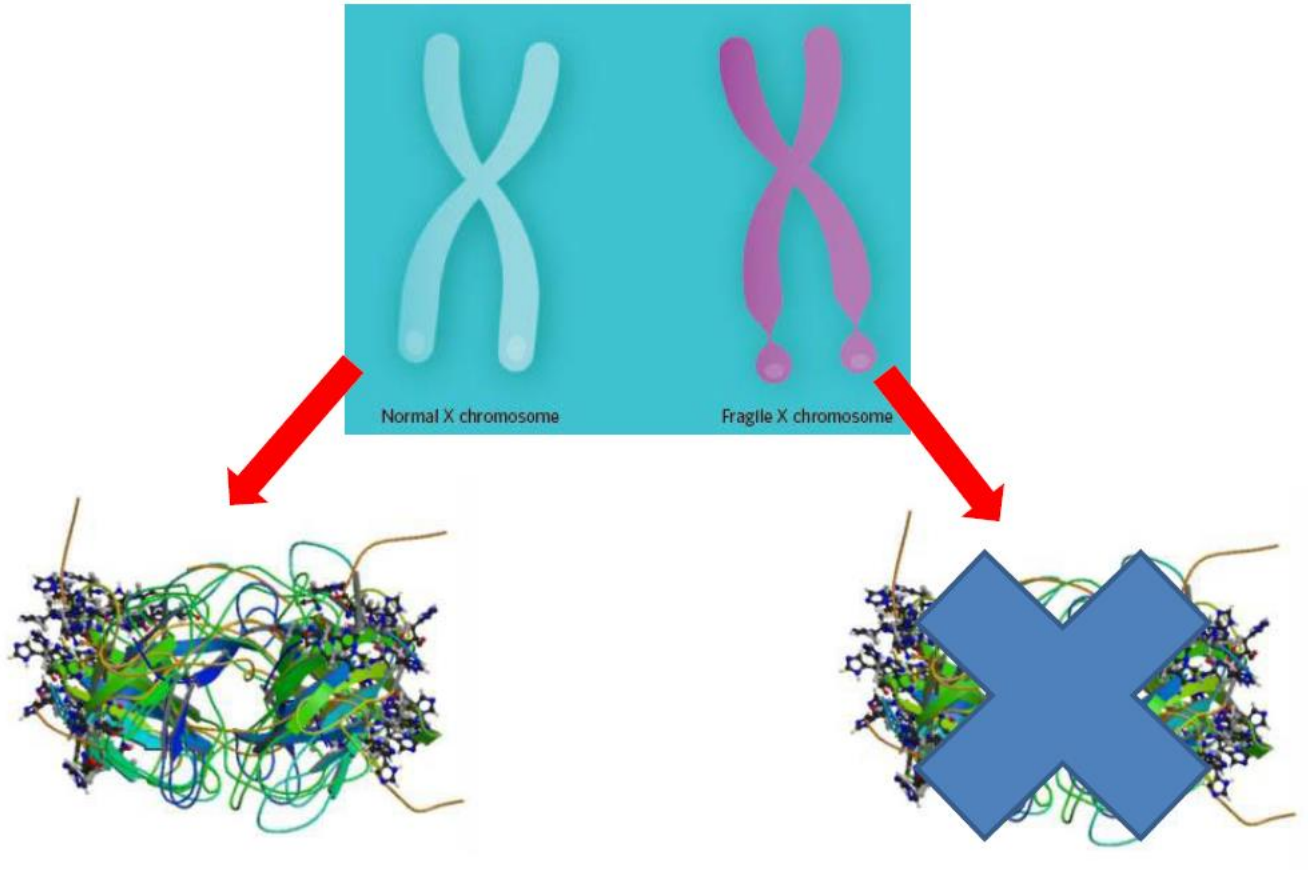
caused by CGG expansion of 5’ UTR in the FMR1 gene

- 5-44 repeats normal (29-31 average)
- 45-54 gray zone or borderline:14% of these individuals may become unstable and expand.
- 55-200 repeats: premutation alleles: not associated with FXS but risk for POI, FXTAS
- >200 full-mutation alleles associated with aberrant hypermethylationof the FMR1 gene promoter



Pediatrics, 2009; 123:378-390

Fragile X Syndrome - Female



Depends on the X inactivation, the level of FMR1 protein production is different

Risk of expansion to full mutation

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

AGG interruptions within the maternal *FMR1* gene reduce the risk of offspring with fragile X syndrome

Carolyn M. Yrigollen BSc[1], Blythe Durbin-Johnson PhD[2], Louise Gane MS[3], David L. Nelson PhD[4], Randi Hagerman MD[3,5], Paul J. Hagerman PhD, MD[1,3] and Flora Tassone PhD[1,3]

Purpose: The ability to accurately predict the likelihood of expansion of the CGG repeats in the *FMR1* gene to a full mutation is of critical importance for genetic counseling of women who are carriers of premutation alleles (55–200 CGG repeats) and who are weighing the risk of having a child with fragile X syndrome. The presence of AGG interruptions within the CGG repeat tract is thought to decrease the likelihood of expansion to a full mutation during transmission, thereby reducing risk, although their contribution has not been quantified.

Results: We found that the presence of AGG interruptions significantly increased genetic stability, whereas specific haplotypes had a marginal association with transmission instability.

Conclusion: The presence of AGG interruptions reduced the risk of transmission of a full mutation for all maternal (premutation) repeat lengths below ~100 CGG repeats, with a differential risk (0 vs. 2 AGG) exceeding 60% for alleles in the 70- to 80-CGG repeat range.

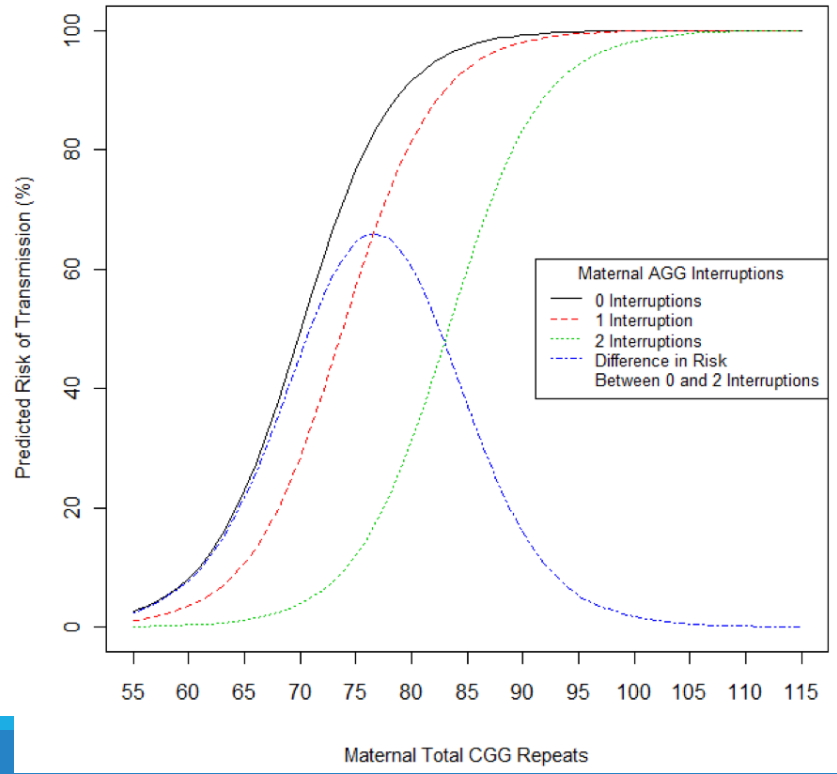
Genet Med 2012:14(8):729–736

Table 1

Transmission of FMR1 Premutation Repeats from Females, with Correction for Ascertainment

Repeat Size of Maternal Allele	No. of Mothers	No. of Offspring with		% Expanded to Full Mutation
		Premutation	Full Mutation	
55–59	21	26	1	3.7
60–69	80	107	6	5.3
70–79	76	62	28	31.1
80–89	133	59	81	57.8
90–99	118	22	89	80.1
100–109	84	0	70	100
110–119	72	1	53	98.1
120–129	33	1	35	97.2
130–139	23	1	17	94.4
140–149	5	0	1	100
150–159	6	0	2	100
160–169	9	0	10	100
170–199	4	0	6	100
Total	664	279	399	58.8

Predicted Risk of Transmission By Maternal Total CGG Repeats and AGG Interruptions



Molecular testing

Molecular Genetic Testing Used in *FMR1*-Related Disorders

Gene [1]	Test Method	Pathogenic Variants Detected [2]	Variant Detection Frequency by Test Method [3]
FMR1	Targeted analysis for pathogenic variants	**PCR**. CGG expansion in *FMR1* (allele sizes in the normal and lower premutation range) [4, 5]	>99%
		Southern blot. CGG expansion in *FMR1* (all repeat ranges); methylation status [4, 6]	
		AGG trinucleotide repeat genotyping. Number and position of AGG trinucleotide repeats that may interrupt the CGG repeats of *FMR1* [7]	100% of alleles of this structure [7]
	Methylation analysis	Methylation of *FMR1* promoter region [8]	100% of alleles with this modification
	FISH	Large (partial- or whole-gene) *FMR1* deletions	<1%
	Deletion/duplication analysis [9]	Large (partial- or whole-gene) *FMR1* deletions/duplications	<1%
	Sequence analysis [10]	*FMR1* sequence variants [4, 5]	<1%

Cornelia de Lange syndrome

- ***NIPBL*** **(5p13.2)**

Cohesin loading

- ***SMC1A*** **(Xp11.22)**

Core cohesin subunit

- ***SMC3*** **(10q25.2)**

Core cohesin subunit

- ***RAD21*** **(8q24.11)**

Core cohesin subunit

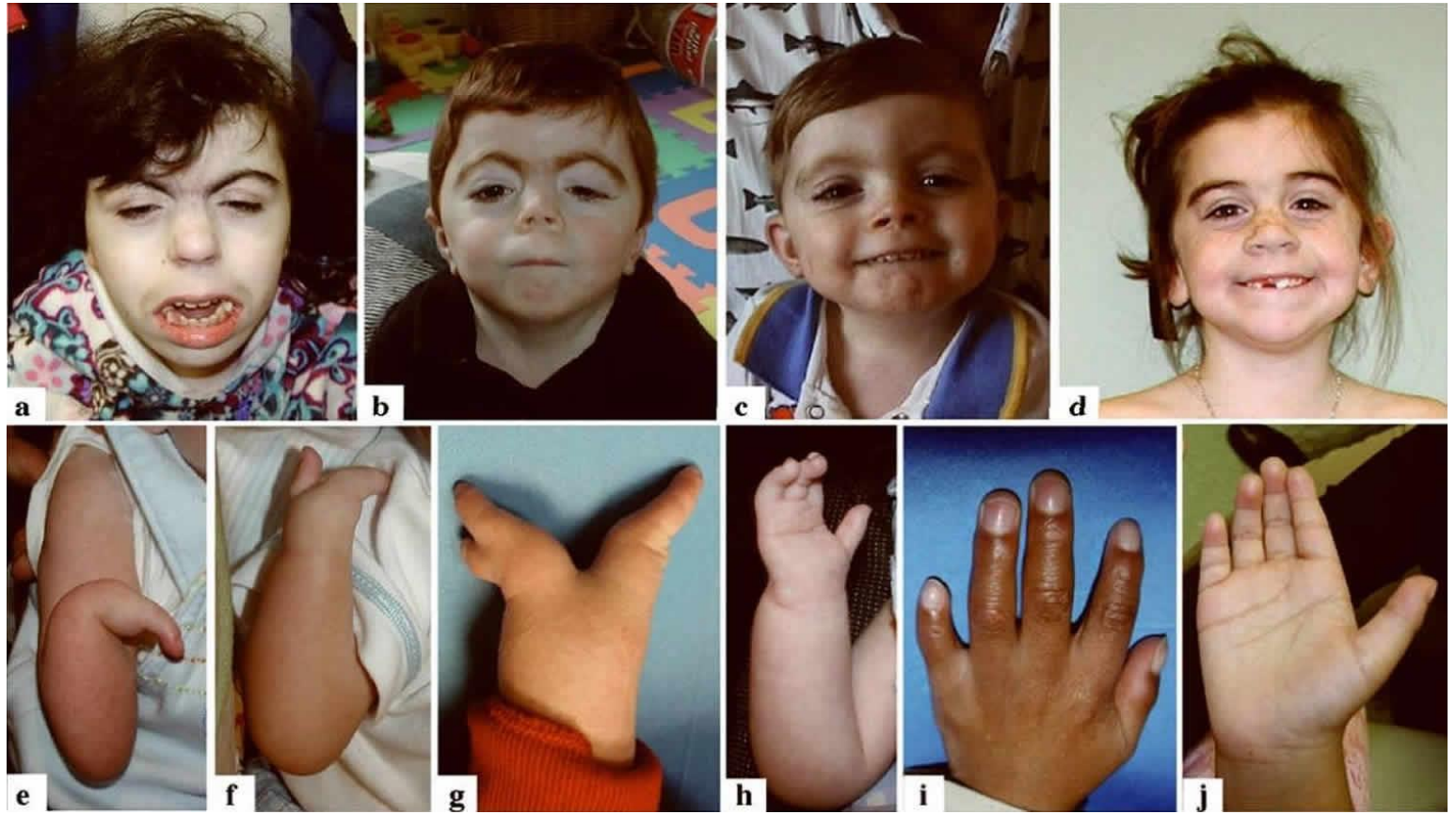
- ***HDAC8*** **(Xq13.1)**

Cohesin recycling

- ***BRD4*** **(19p13.12)**

BET family of nuclear proteins

Co-precipitate with NIPBL



Rett syndrome

Progressive neurodevelopmental disorder primarily affecting girls

Apparently normal psychomotor development during the first six to 18 months of life

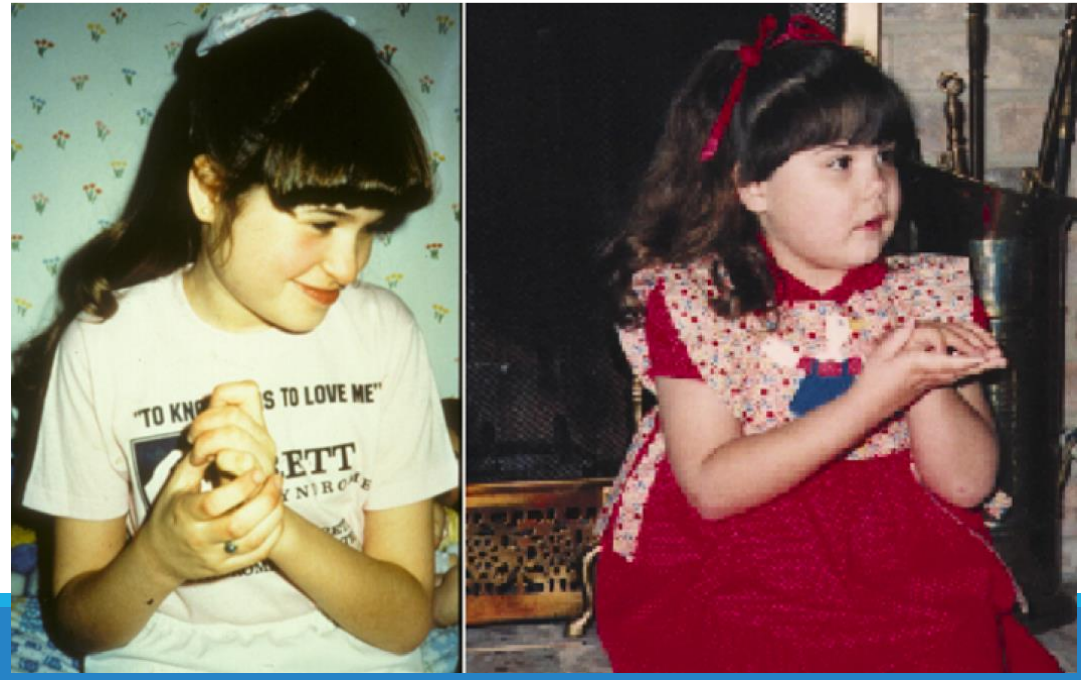
Followed by a short period of developmental **stagnation, then rapid regression in language and motor skills then long-term stability.**

Loss of purposeful hand movements

- Acquired microcephaly
- Dystonia, spasticity, seizures
- Typically sporadic (99%):

~1:10,000

MECP2 pathogenic variant



Rett syndrome

***MECP2* variant in a male is presumed to most often be lethal; phenotypes in rare surviving males are**

primarily:

- Severe neonatal encephalopathy
- Manic-depressive psychosis
- Pyramidal signs Parkinsonian, and macro-orchidism (PPM-X syndrome) => affected males usually have

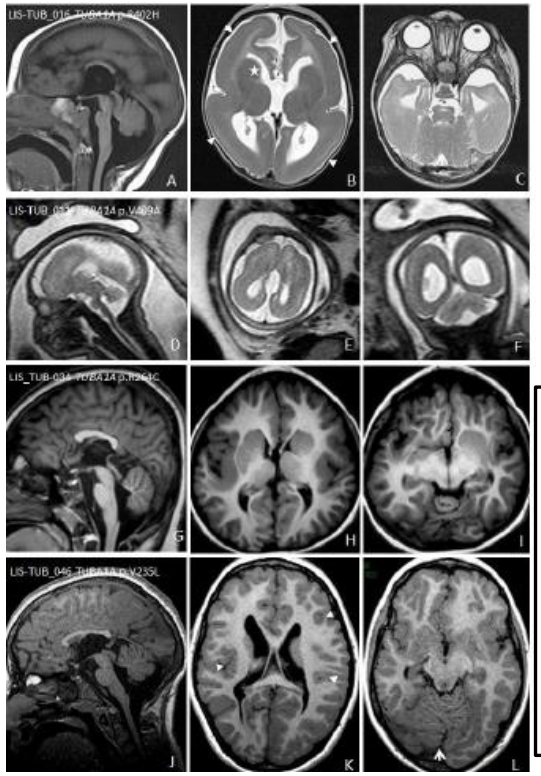
severe intellectual disability, a resting tremor, and

slowness of movements and ataxia, but no seizures or microcephaly.

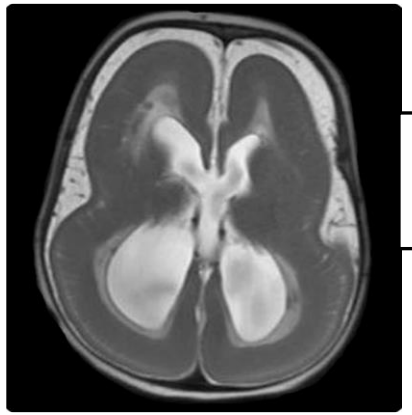
- Rett Males: sex chromosome mosaics 46,XY with 47,XXY
- Males with 46,XY = neonatalencephalopathy

Neuronal migration defects

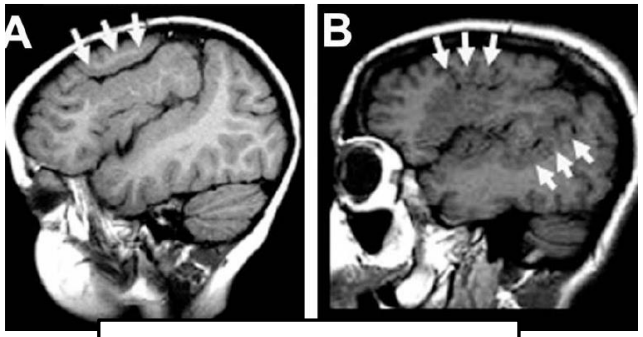
clinically heterogeneous with brain malformations, microcephaly, developmental delay and epilepsy being the main clinical features



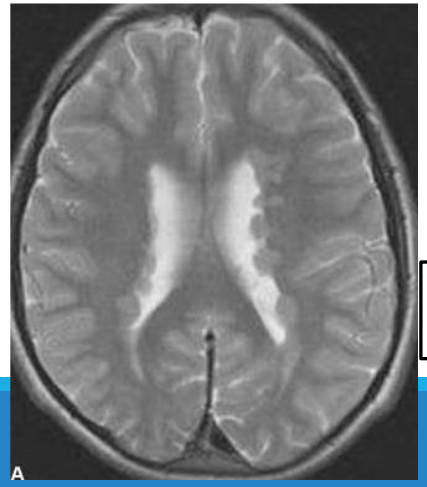
Tubulinopathies
-genes encoding different isotypes of α tubulin TUBA1A or TUBA8) β tubulin (TUBB2A, TUBB2B TUBB3 T UBB TUBB5]), and γ tubulin (TUBG1)



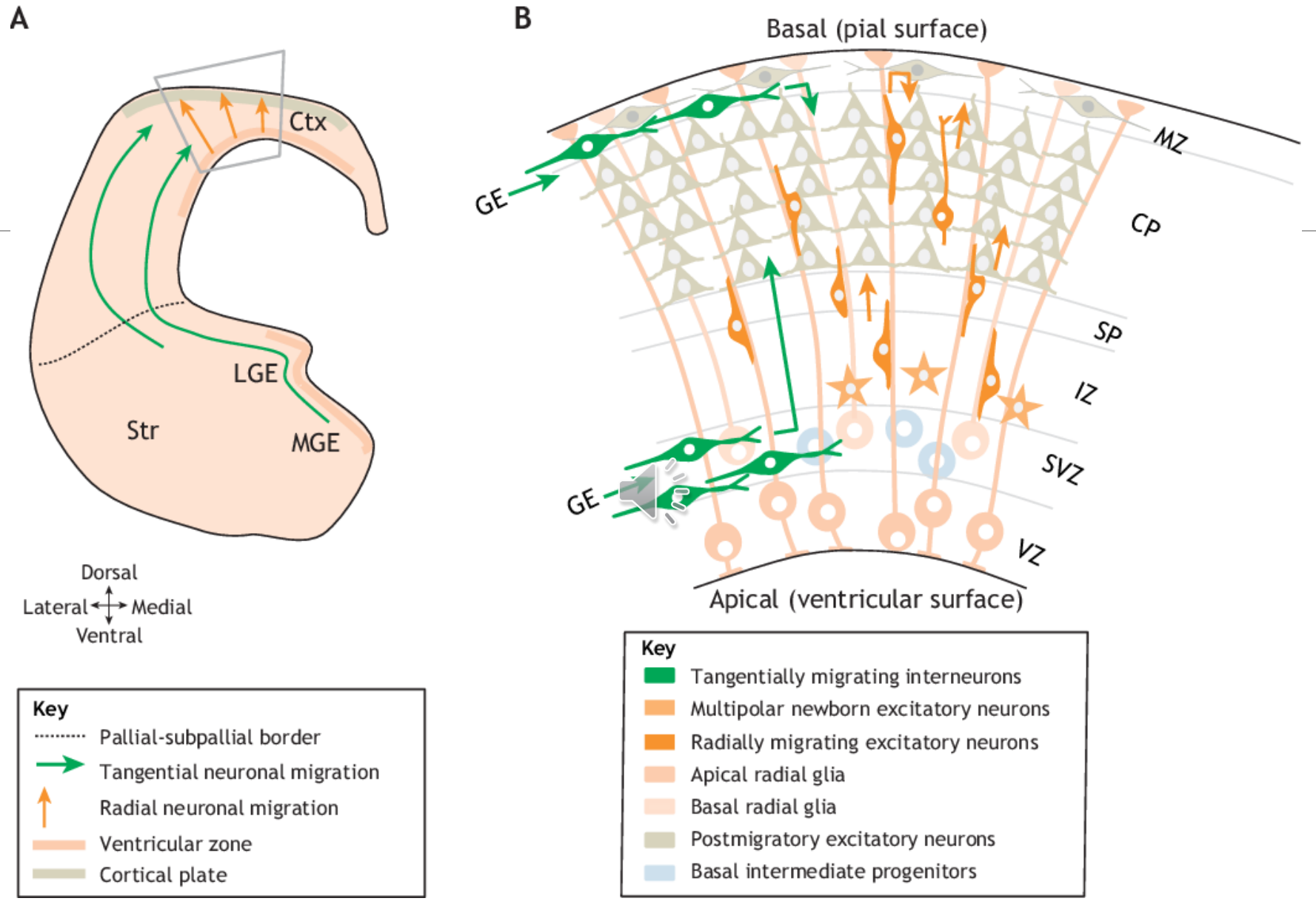
Lissencephaly
LIS1 pathogenic variants



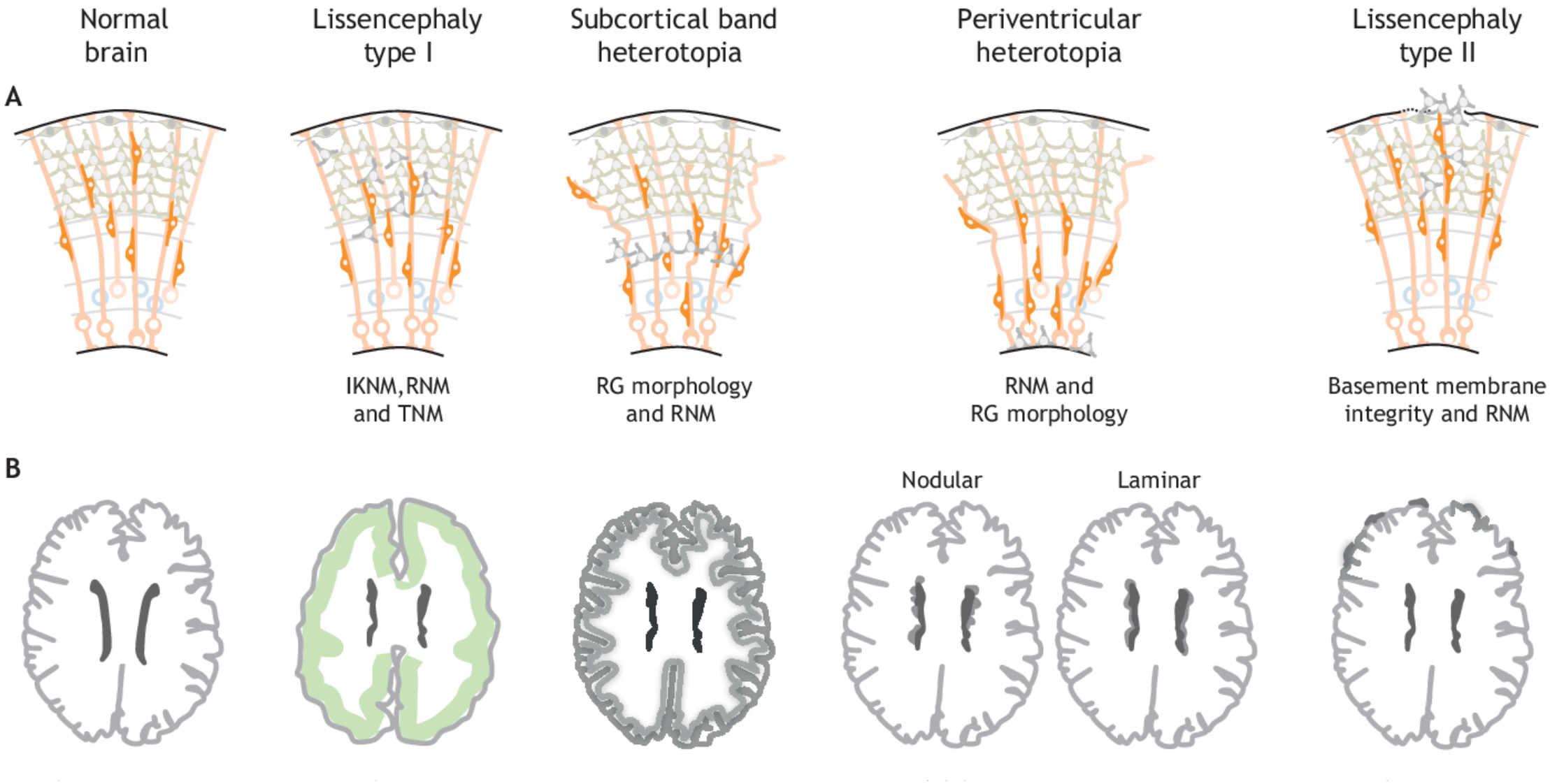
Polymicrogyria
e.g. muscle eye brain disease



FLNA related periventricular nodular heterotopia (PVNH)



Buchsbaum, Isabel Y and Silvia Cappello. "Neuronal migration in the CNS during development and disease: insights from in vivo and in vitro models." Development 146 (2019): n. pag.



Buchsbaum, Isabel Y and Silvia Cappello. "Neuronal migration in the CNS during development and disease: insights from in vivo and in vitro models." Development 146 (2019): n. pag.

Gene	Cortical malformation	Main protein function	References
Lissencephaly type I and subcortical band heterotopia			
LIS1 (*PAFAH1B1*)	Lissencephaly type I; subcortical band heterotopia; (microcephaly)	Cytoskeleton (microtubules, dynein)	des Portes et al., 1998; Faulkner et al., 2000; Reiner et al., 1993; Sheen et al., 2006
DCX	Lissencephaly type I; subcortical band heterotopia; periventricular heterotopia; (microcephaly)	Cytoskeleton (microtubule stability), dynein binding, nucleokinesis	Bahi-Buisson et al., 2013; des Portes et al., 1998; Francis et al., 1999; Gleeson et al., 1998; Horesh et al., 1999; Sicca et al., 2003
14-3-3e (*YWHAE*)	Lissencephaly type I	Cytoskeleton (microtubules), intracellular signalling	Reiner et al., 1993
TUBA1A	Lissencephaly type I; subcortical band heterotopia; polymicrogyria (with microcephaly, corpus callosum agenesis, and cerebellar hypoplasia)	Cytoskeleton (microtubule component)	Bahi-Buisson et al., 2008; Bahi-Buisson et al., 2013; Keays et al., 2007; Poirier et al., 2007
RELN	Lissencephaly type I with cerebellar hypoplasia; (microcephaly)	Secreted ECM protein; Cytoskeleton (microtubules and actin), cell adhesion	Dulabon et al., 2000; Hirota and Nakajima, 2017; Hong et al., 2000
ARX	Lissencephaly type I with corpus callosum agenesis	Transcription factor	Colombo et al., 2007; Kato et al., 2004; Kitamura et al., 2002
VLDLR	Lissencephaly type I with cerebellar hypoplasia	Reelin receptor: RELN to microtubule signalling	Schlotawa et al., 2013; Trommsdorff et al., 1999
NDE1	Extreme microcephaly with lissencephaly type I	Cytoskeleton (microtubules/ centrosome): nuclear migration, centrosome duplication, mitotic spindle assembly	Alkuraya et al., 2011
ACTG1	Lissencephaly type I	Cytoskeleton (actin component)	Verloes et al., 2015
ACTB	Lissencephaly type I	Cytoskeleton (actin component)	Verloes et al., 2015
Periventricular heterotopia			
FLNA	Periventricular nodular heterotopia; polymicrogyria	Cytoskeleton (actin binding and crosslinking protein), junction formation	Fox et al., 1998; Lu et al., 2006; Parrini et al., 2006; Sheen et al., 2004b
KIF2A	Heterotopia; subcortical band heterotopia; agyria, pachygyria; (thin corpus callosum, congenital microcephaly)	Kinesin: microtubule-associated motor	Poirier et al., 2013
TUBG1	Laminar heterotopia; agyria, pachygyria; (microcephaly, dysmorphic corpus callosum)	Cytoskeleton (microtubule component)	Poirier et al., 2013
ARFGEF2	Periventricular nodular heterotopia with microcephaly	Golgi vesicle formation and trafficking; cell-cell adhesion; interaction with FLNA; Rac/Rho signalling	Bardón-Cancho et al., 2014; Lu and Sheen, 2005; Lu et al., 2006; Sheen, 2014; Sheen et al., 2004a; Shin et al., 2005
EML1	Periventricular heterotopia; ribbon-like subcortical band heterotopia; lissencephaly type I; (macrocephaly)	Cytoskeleton (microtubules), mitotic spindle orientation, cell adhesion	Bizzotto et al., 2017; Kielar et al., 2014
FAT4	Periventricular nodular heterotopia	Protocadherin: cell-cell and apical adhesion	Badouel et al., 2015; Cappello et al., 2013
DCHS1	Periventricular nodular heterotopia	Protocadherin: cell-cell and apical adhesion	Cappello et al., 2013
ERMARD (*C6orf70*)	Periventricular nodular heterotopia with polymicrogyria and corpus callosum agenesis	ER membrane-associated RNA degradation; trafficking; cell-cell adhesion	Conti et al., 2013
NEDD4L	Periventricular nodular heterotopia; polymicrogyria	Ubiquitin ligation and protein degradation, mTOR and (PI3K) AKT pathway	Broix et al., 2016
AKT3	Periventricular heterotopia with megalencephaly; polymicrogyria	(PI3K) AKT pathway	Alcantara et al., 2017
MAP1B	Periventricular heterotopia; (polymicrogyria)	Cytoskeleton (microtubules)	Heinzen et al., 2018
MCPH1	Microcephaly with periventricular nodular heterotopia and pachygyria	DNA damage response (G2/M checkpoint)	Trimborn et al., 2004
INTS8	Periventricular nodular heterotopia	RNA processing and transcription regulation	Oegema et al., 2017
Cobblestone lissencephaly (lissencephaly type II)			
TMTC3	Cobblestone lissencephaly; periventricular heterotopia; lissencephaly type I	Protein degradation in the endoplasmic reticulum; regulation of GABAergic inhibitory synapses	Farhan et al., 2017; Jerber et al., 2016
POMT1	Cobblestone lissencephaly; pachygyria	O-glycosylase: basement membrane integrity	Beltrán-Valero de Bernabé et al., 2002; Mercuri et al., 2009
POMT2	Cobblestone lissencephaly; (microcephaly)	O-glycosylase: basement membrane integrity	Mercuri et al., 2009; van Reeuwijk et al., 2005
FKRP	Cobblestone lissencephaly	O-glycosylase: basement membrane integrity	Mercuri et al., 2009

Continued

DEVELOPMENT

Buchsbaum, Isabel Y and Silvia Cappello. "Neuronal migration in the CNS during development and disease: insights from in vivo and in vitro models." Development 146 (2019): n. pag.

IEM disorder

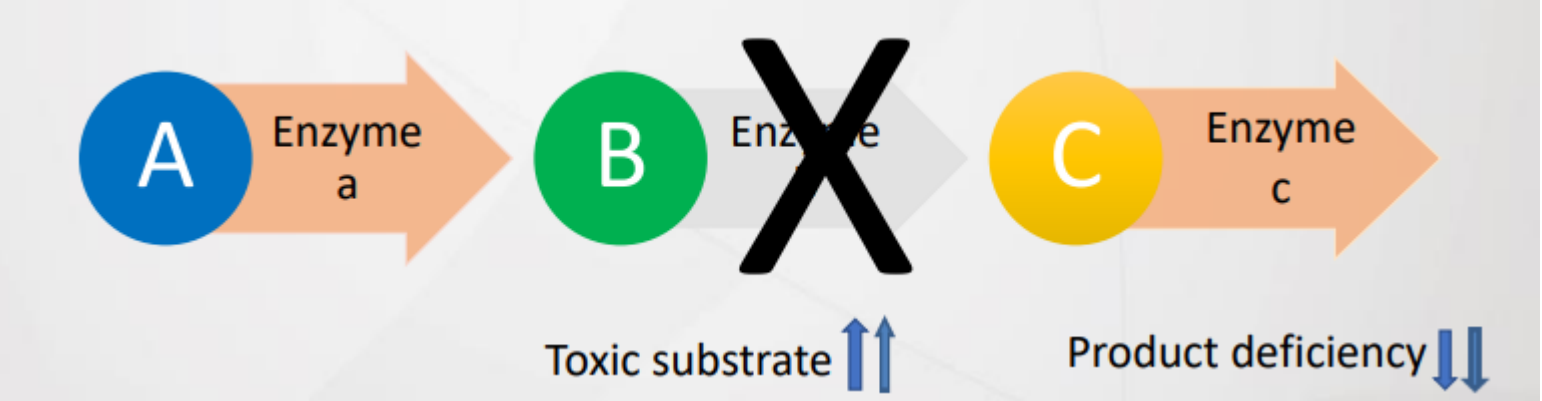
Individually rare, Collective incidence: 1/500

- Amino acid
- Acylcarnitine
- Organic acids
- Urea cycle
- Metals
- Glucose
- Lysosome
- Vitamins
- Mitochondria
- neurotransmitter
- Creatine
- Cholesterol
- Bile acids
- Homocysteine
- Pyrimidine
- Purine
- Peroxisome
- Fatty aldehydes

Most are covered in newborn metabolic screening programme

IEM

single gene defects resulting in defective function of particular enzymes that are essential for conversion of substrates into products



IEM disorders cause inadequate essential metabolites or accumulation of toxic intermediary metabolites for the body

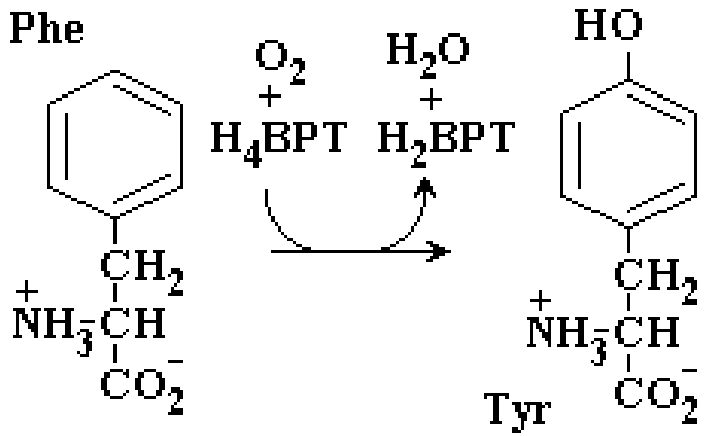
Examples of IEM disorders

Amino acid disorders	Phenylketonuria, Maple syrup urine disease, Citrullinemia type 1, Argininosuccinic aciduria, Homocystinuria
Organic acid disorder	Propionic acidemia, Isovaleric acidemia , Glutaric acidemia type 1 , Methylmalonic aciduria , Betaketothiolase deficiency, Multiple carboxylase deficiency
Fatty acid oxidative disorder	Carnitine uptake defect, Medium-chain acyl-CoA dehydrogenase deficiency, Very long-chain acyl-CoA dehydrogenase deficiency, Carnitine Acylcarnitine translocase deficiency, Carnitine palmitoyltransferase I /II deficiency

Examples of IEM disorders

Storage diseases	Lysozymal storage disease Glycogen storage disease
Disorder of purine and pyrimidine biosynthesis	Adenylosuccinase deficiency HPRT1 related disorders
Disorder of cholesterol and bile acid metabolism	Smith Lemli Opitz syndrome
Neurometabolic and neurotransmitter disorders	GABA transaminase deficiency Aromatic L-amino acid decarboxylase deficiency Creatine Deficiency Syndromes (GAMT deficiency) X linked creatine transporter (CRTR)(SLC6A8) deficiency Glucose transporter defect (GLUT1)

Phenylketonuria



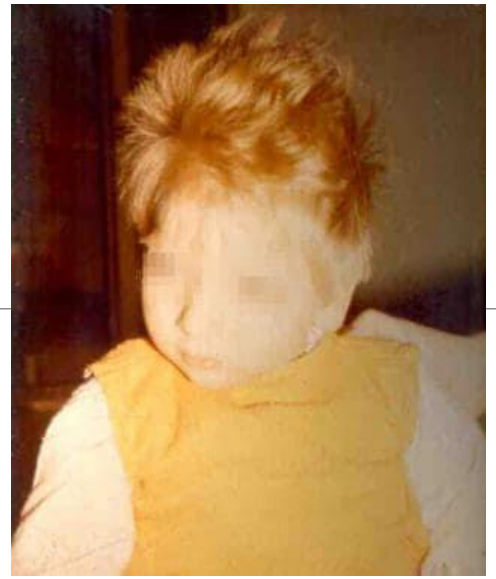
Genetic deficiency of phenylalanine hydroxylase

PAH converts phenylalanine to tyrosine expressed in liver

- Autosomal recessive
- Most common amino acid disorder
- Prevalence of PKU shows considerable geographic variation
- Estimated to be 1/10,000 live births in Europe with higher rate in some countries (Ireland, Italy). Prevalence is particularly high in Turkey: 1/4,000 live births. PKU is far rarer in Finnish, African and Japanese populations.

PKU

- Normal at birth
- Developmental delay
- Irritability, vomiting, rash, musty odor
- Lighter pigmentation (hair and skin)
- Poor growth, seizures, microcephaly
- Severe to profound intellectual disability



- Confirmation by serum phenylalanine level
- Treatment is DIETARY, starts if phe > 6mg/dl
  - –low phenylalanine (low protein, 200 g of natural protein/day)
  - –Special formula
  - –Sapropterin
  - –Pegvaliase
- Monitor phenylalanine/tyrosine levels
- Monitor development

Lysozymal storage disease-classification

1) Mucopolysaccharidoses- Failure to degrade glycosaminoglycans

MPSI, II, III, IV, VI, VII, IX

2) Sphingolipidoses- Failure to degrade glycosphingolipids

Fabry disease, Gaucher disease, Krabbe disease, Niemann Pick disease, Metachromatic leukodystrophy, GM1/2 gangliosidosis

3) Oligosaccharidoses (Galactosidosis, Fucosidosis, Mannosidosis)

4) Mucolipidosis

Mucolipidosis Type I (Sialiodosis), Mucolipidosis Type II (I Cell disease), Mucolipidosis Type III (Pseudo Hurler), Mucolipidosis Type IV (Sialolipidosis)

Type of MPS

MPS type	Common name(s)	Associated gene	Enzyme deficiency
I	Hurler Hurler-Scheie Scheie	*IDUA*	α-L-iduronidase
II	Hunter	*IDS*	Iduronate sulfatase
III	Sanfilippo A Sanfilippo B Sanfilippo C Sanfilippo D	*SGSH* *NAGLU* *HGSNAT* *GNS*	Heparan N-sulfatase α-N-acetylglucosaminidase Acetyl CoA: α-glycosaminide N-acetylglucosamine-6-sulfatase
IV	Morquio A Morquio B	*GALNS* *GLB1*	Galactose 6-sulfatase β-galactosidase
VI	Maroteaux-Lamy	*ARSB*	N-acetylgalactosamine 4-sulfatase (arylsulphatase B)
VII	Sly	*GUSB*	β-glucuronidase
IX	Natowicz	*HYAL1*	Hyaluronidase

Some common phenotypes in MPS

Coarse facial features, Macrocephaly, prominent eye, swollen gum

Developmental delay

Corneal clouding or related ocular abnormalities

Umbilical / inguinal hernias

Short stature

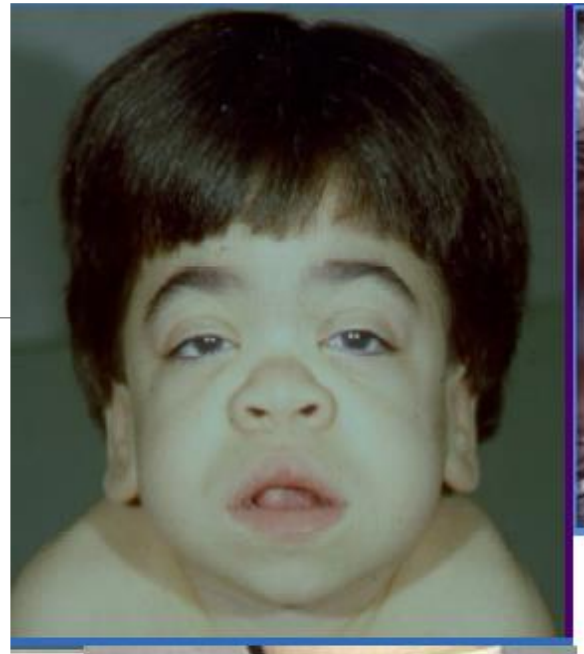
Organs dysfunction (such as valvular heart disease, OSA)

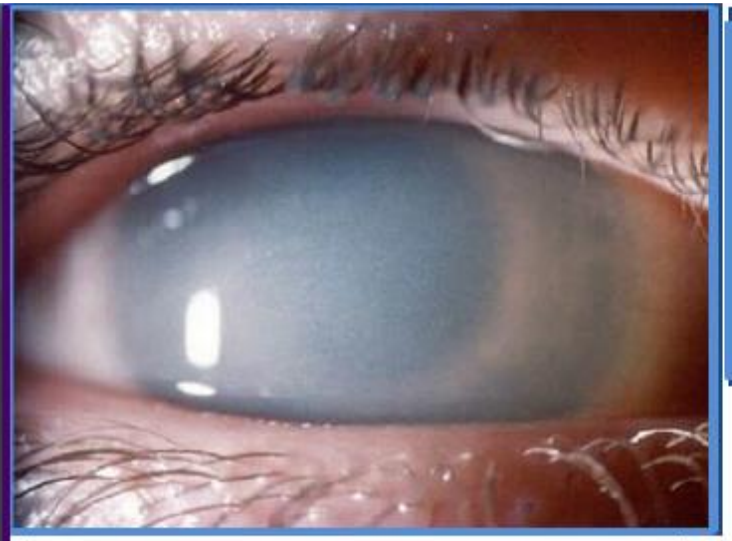
Joint or skeletal deformities

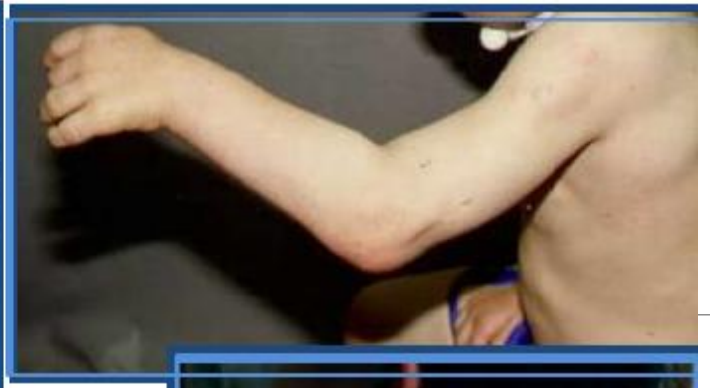
Visceromegaly(especially liver and spleen)

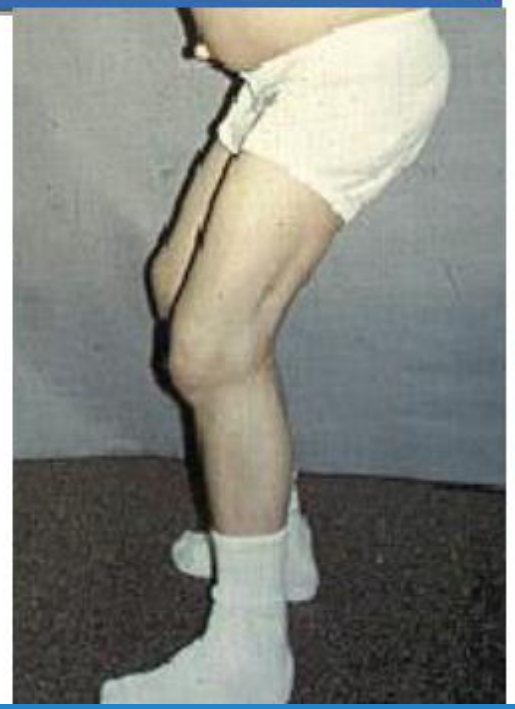
Muscle weakness or lack of control (ataxia, seizures, etc.)

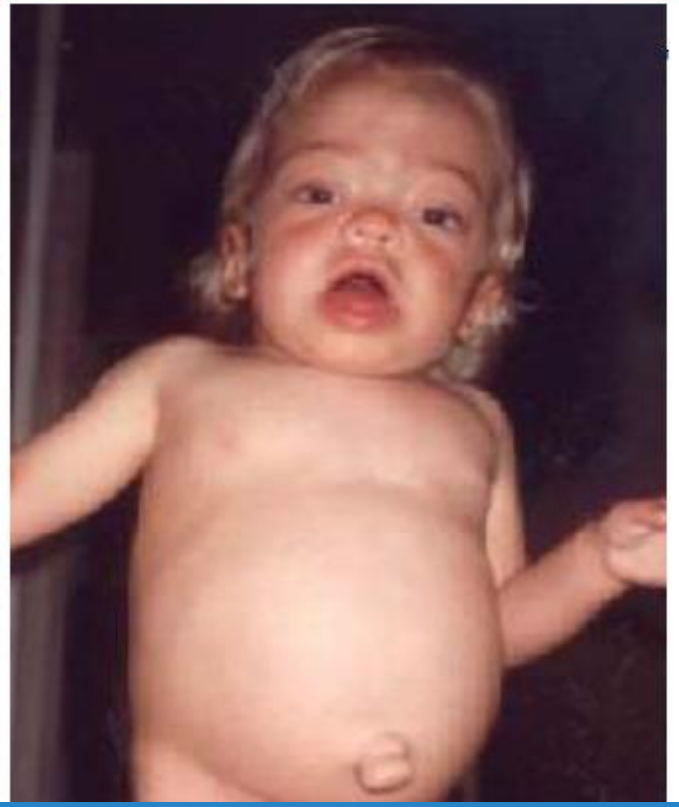
Neurologic failure/ decline or loss of gained development

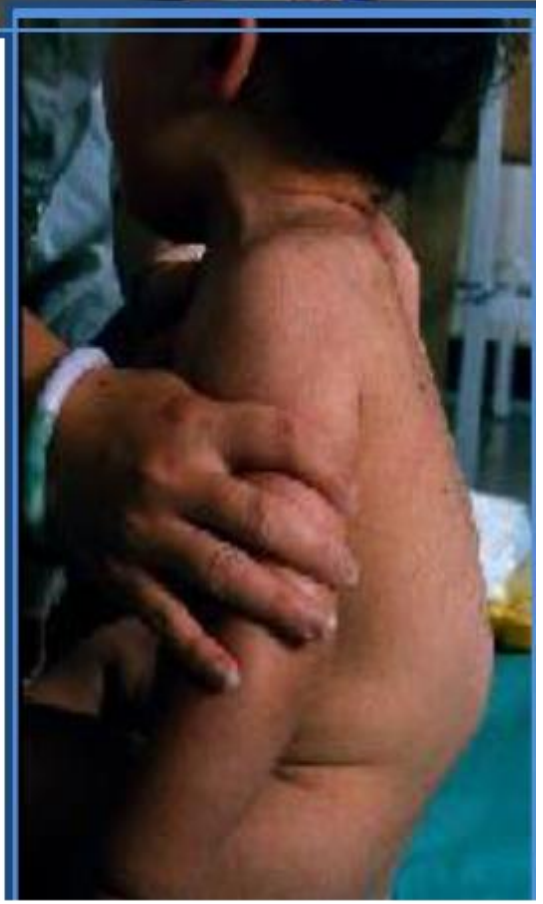












Treatment for MPS

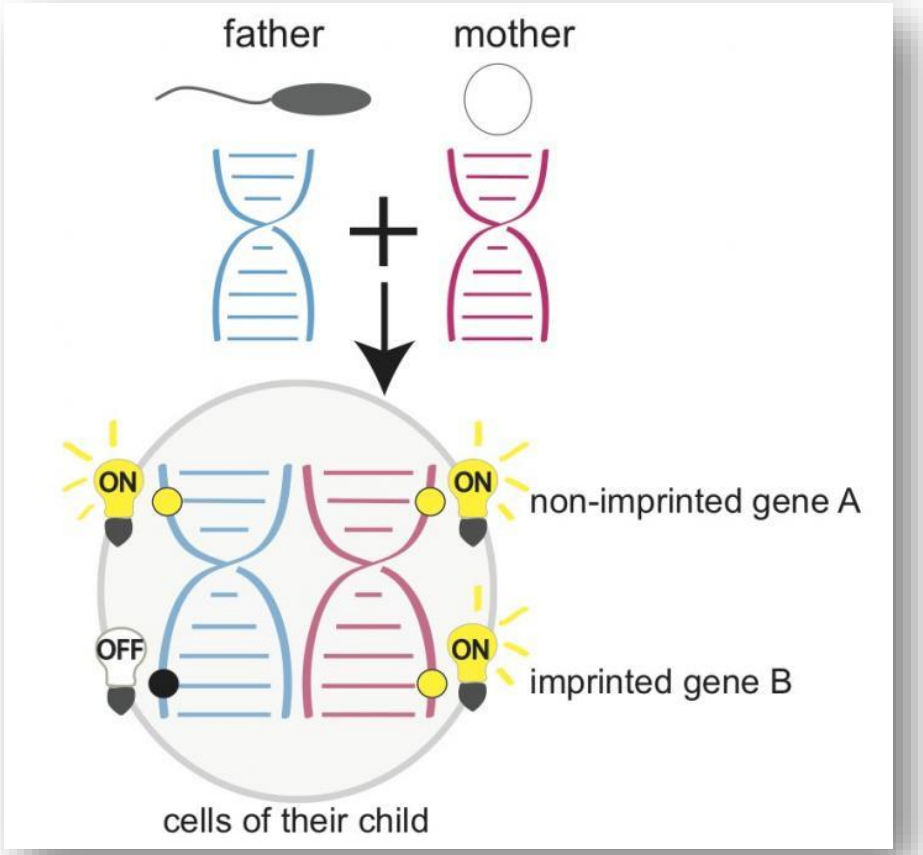
Available treatment options for some MPS include:

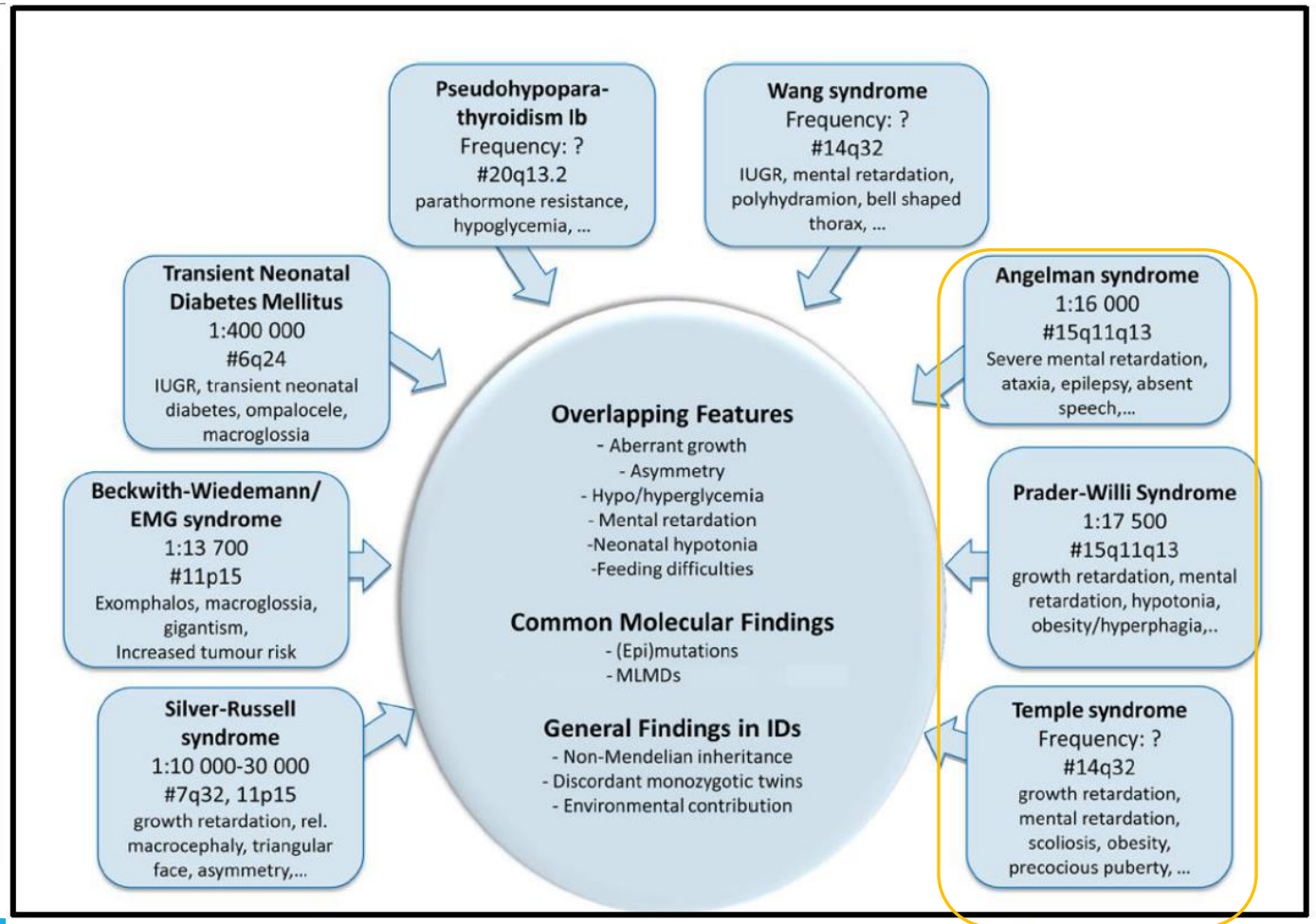
1.Supportive treatment (multidisciplinary)

2.Hematopoietic stem cell transplant (HSCT)

3.Enzyme Replacement Therapy (ERT)

Imprinting disorder





Prader Willi Syndrome

almond-shaped eyes

a thin upper lip and a downturned mouth.

unusually fair hair, skin and eyes

small hands and feet

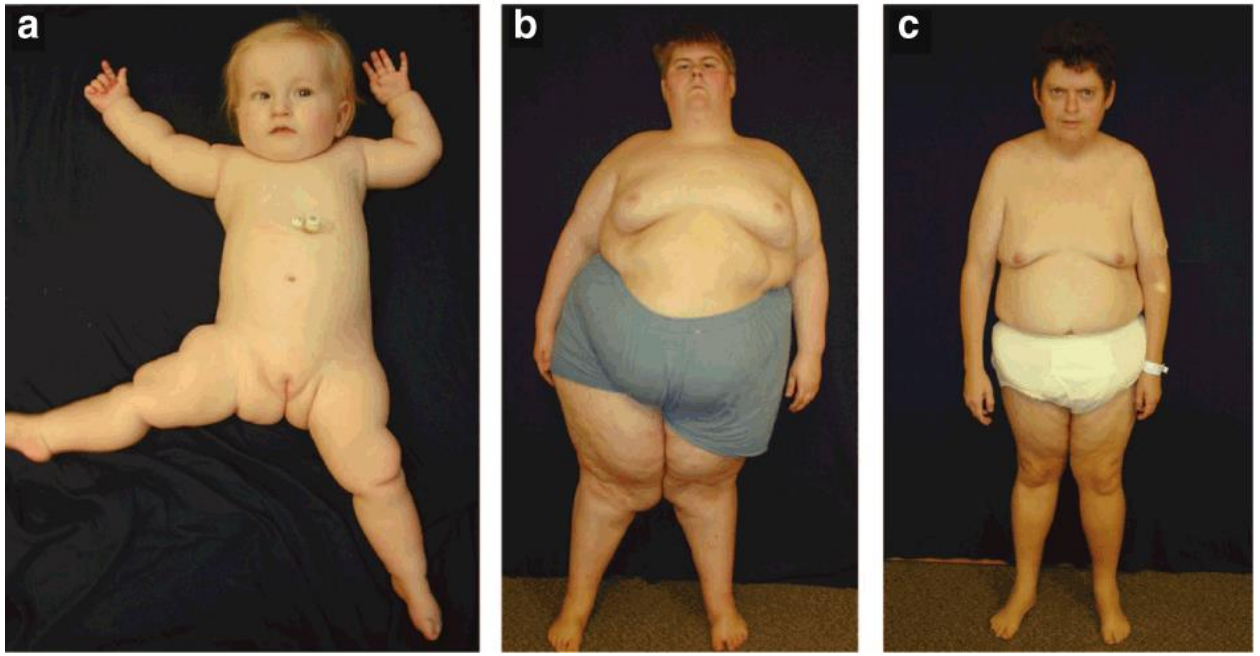
Hypotonia

Poor feeding , failure to thrive

Obesity

Developmental delay

Behavioural problem likes autism



Cassidy, S., Schwartz, S., Miller, J. et al. Prader-Willi syndrome. Genet Med 14, 10–26 (2012).

Angelman syndrome

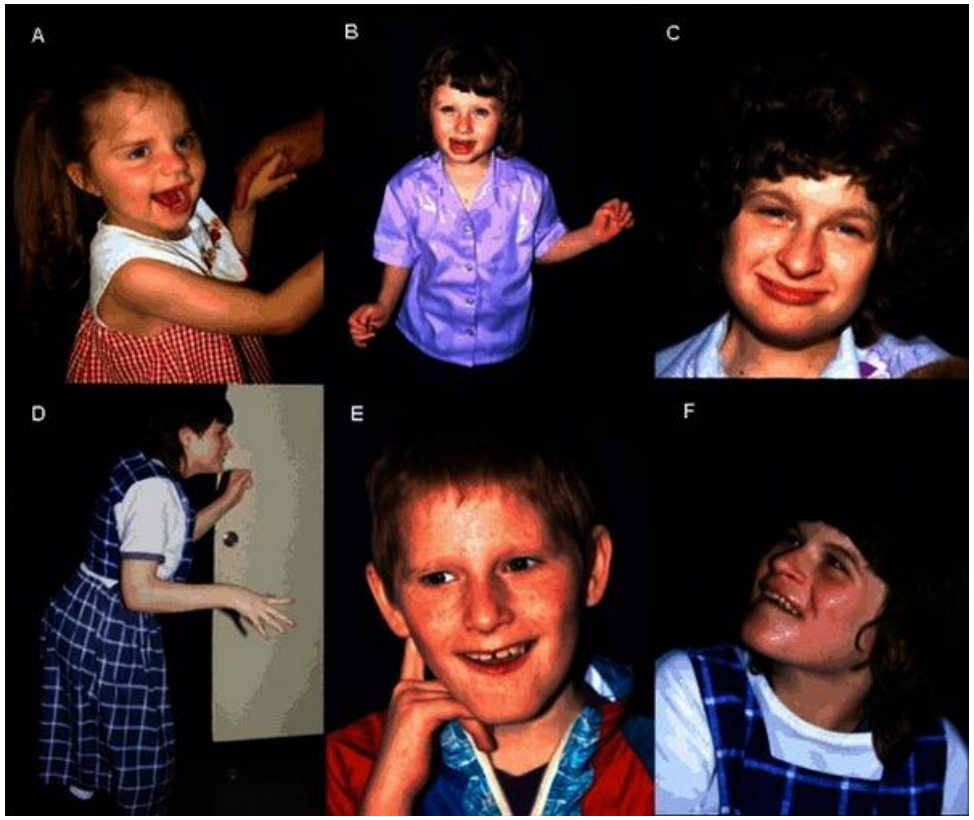


Photo from MedlinePlus

Table 2
Features of AS

Consistent (100%)	Frequent (80%)	Associated (20%–80%)
Developmental delay	Seizures	Hypotonia
Ataxia and/or tremors	Microcephaly	Strabismus
Absent speech	—	Frequent drooling, mouthing behaviors
Happy demeanor, including hand flapping, frequent laughter/smiling	—	Protruding tongue, tongue thrusting
—	—	Wide mouth, wide spaced teeth sleep disturbances
—	—	Sleep disturbances
—	—	Fascination with water
—	—	Anxiety

Pediatr Clin N Am 62 (2015) 587–606

Expression in PWS/AS region: 15q11-13

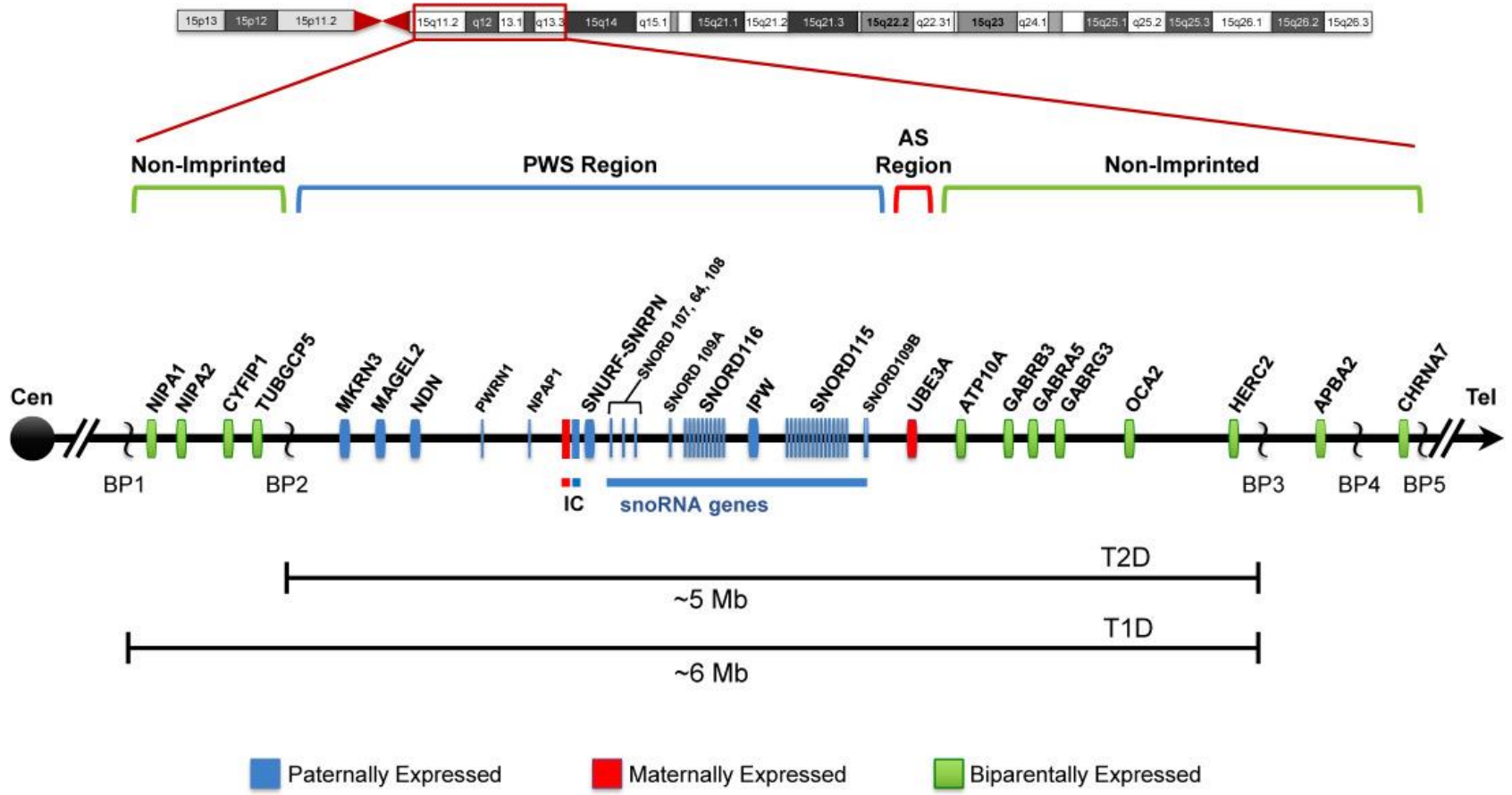
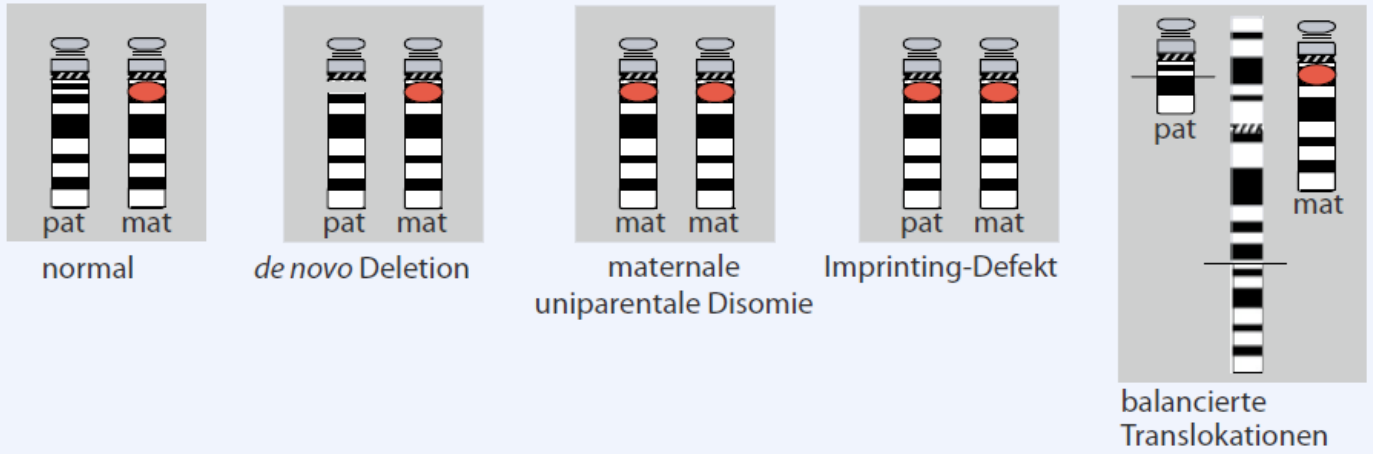


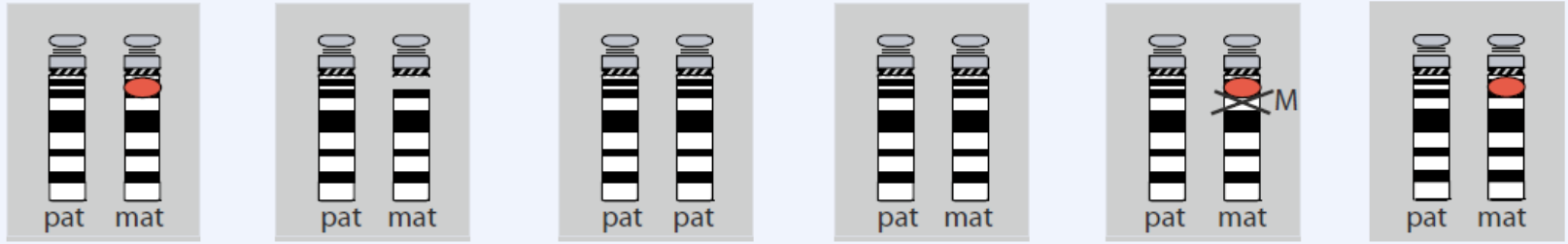
Diagram from gene review

Prader-Willi-Syndrom



	normal	*de novo* Deletion	maternale uniparentale Disomie	Imprinting-Defekt	balancierte Translokationen
Frequenz		~ 70%	25 - 30%	~ 1-3%	sehr selten
Wiederholungsrisiko		< 1%*	< 1%*	< 1% keine IC-Deletion 50% familiäre IC-Deletion	< 1%

Angelman-Syndrom

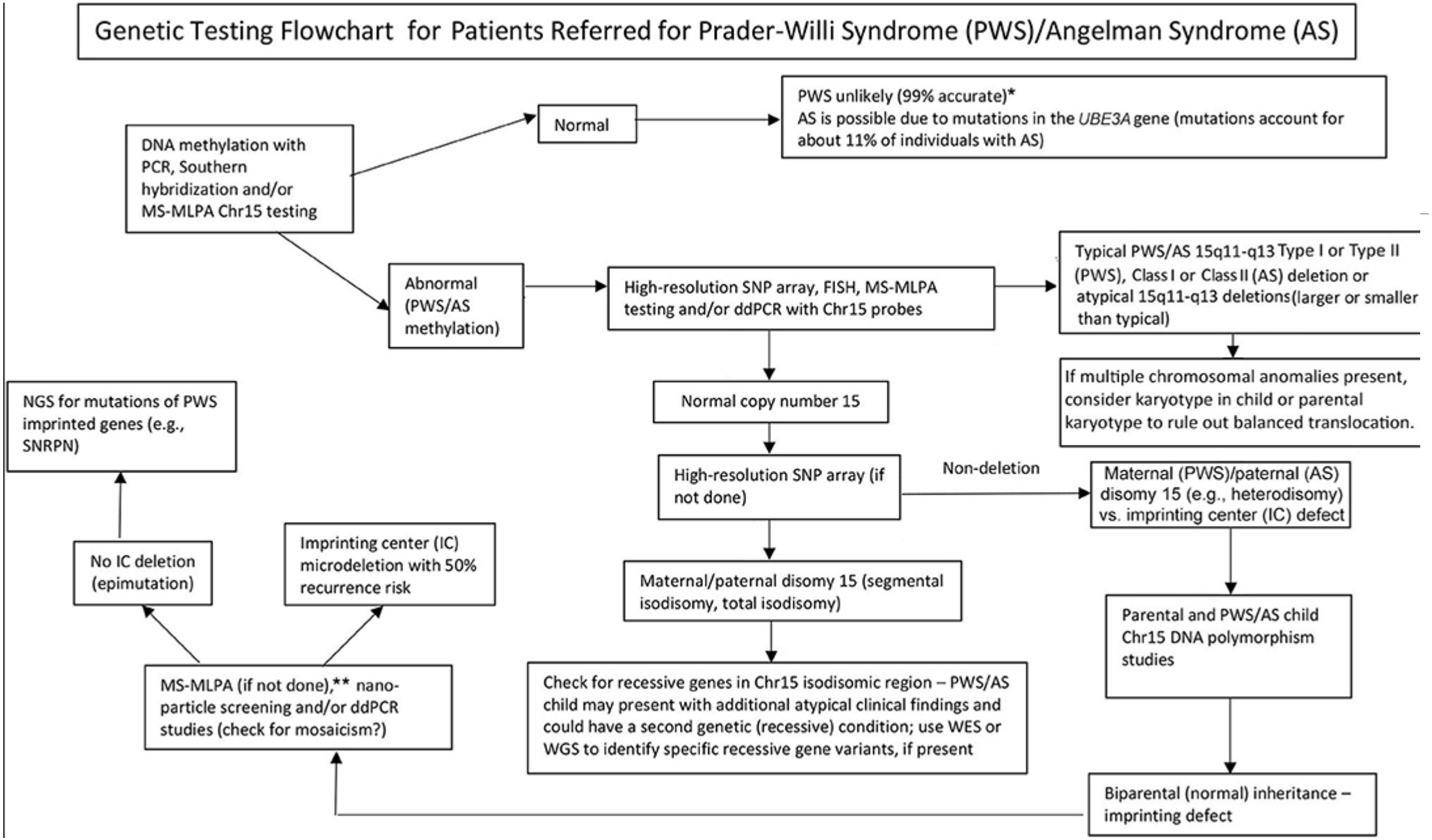


	normal	*de novo* Deletion	paternale uniparentale Disomie	Imprinting-Defekt	*UBE3A* Mutation	unbekannte Ursache
Frequenz		~ 70%	~ 1 - 2%	~ 2-4%	~ 5-10%	10-15%
Wiederholungsrisiko		< 1%*	< 1%*	< 1% keine IC-Deletion 50% familiäre IC-Deletion	< 1% *de novo* Mutation 50% familiäre Mutation	

* bei normalen elterlichen Chromosomen

Table 3.2 Genetic mechanisms in Angelman syndrome (AS) and Prader–Willi syndrome (PWS) and risk of recurrence in the siblings of an affected child

Genetic mechanism	Percentage of families	Recurrence risk
Deletion of 15q11-q13	70 (both AS and PW)	<1%
UPD of chromosome 15	~25 (PWS) 3–7 (AS)	<1%
Mutation in UBE3A	~10 (AS)	50% if present in mother
No identifiable molecular abnormality	~10 (AS)	Unknown
Imprinting center defect without mutation in the imprinting center	1–3 (both)	<1%
Imprinting center defect with mutation in the imprinting center	<1 (both)	50% if present in father (PWS) or mother (AS)
De novo unbalanced rearrangement of 15q11-q13	<1 (both)	<1%
Inherited unbalanced rearrangement of 15q11-q13	<1 (both)	≤50%
UPD due to parental rearrangement involving chromosome 15	<1 (both)	Depends on translocation; if parent has 15;15 Robertsonian translocation, risk would approach 100%; for most others, risk is <0.75%



Butler, M. G., & Duis, J. (2020). Chromosome 15 Imprinting Disorders: Genetic Laboratory Methodology and Approaches. Frontiers in pediatrics, 8, 154.

Special consideration

Developmental regression

Autism spectrum disorder

Isolated Gross motor delay

Developmental regression

- Loss of previously acquired developmental milestones

- other signs, such as behavioural changes, epilepsy

- Age of onset and mode of presentation

- gender: females: Rett , male: X linked conditions such as XL adrenoleukodystrophy (X-ALD) and Pelizaeus-Merzbacher disease (PMD)

-Ethnic groups: e.g. Tay-Sachs in the Ashkenazi jewish

-Fluctuation with intercurrent illness may indicate an underlying metabolic disturbance, such as mitochondrial disorders, MSUD etc

- Refractory epilepsy

- Coarse facial features

- eye problems (deepset eye in Cockayne syndrome,. Conjunctival telangiectasia in AT, KF ring in Wilson disease, supranuclear gaze palsy in Niemann Pick C)

Some diagnoses to consider

- Autism

- Rett syndrome

- Metabolic and storage disease

Neuronal ceroid lipofuscinoses , Sanfilippo syndrome (MPS III)

- Neurological

Landau Kleffner syndrome, leukodystrophy (X-Linked adrenoleukodystrophy)

-Mitochondrial disease

Management and treatment

-Physiotherapy

-Occupational therapy

-Speech therapy

-Developmental paediatrician

-Clinical geneticist

-Paediatric neurologist

-Surgical Team

-Dietician (IEM, ketogenic diet)

-Preschool training and support

-Patient support group

-Clinical psychologist

Gene therapy

Modulate downstream pathway from the genetic defect

Replace the missing genetic material

Gene therapy

Gene editing

Gene product replacement

- mRNA therapy
- Enzyme replacement therapy

Stabilize aberrant proteins

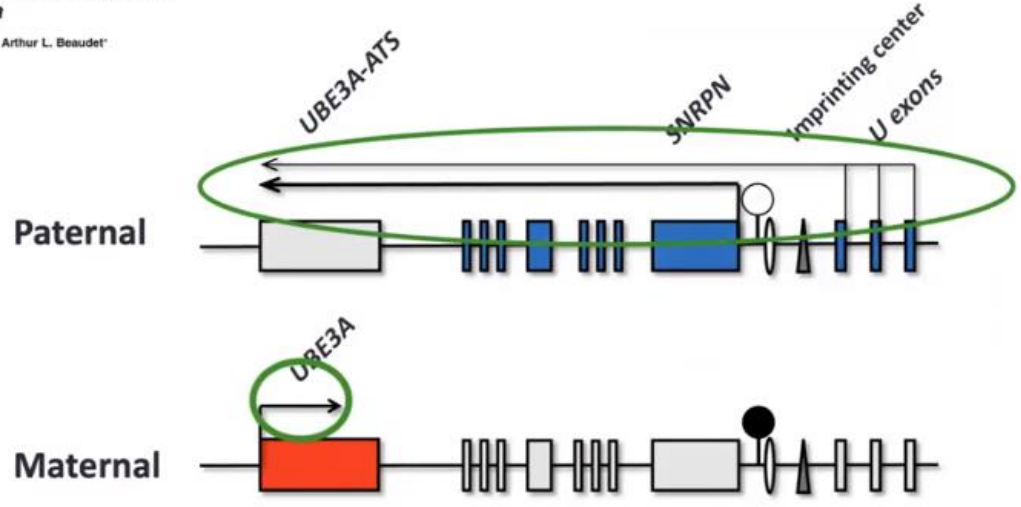
Splicing modulators

Oligonucleotide therapies

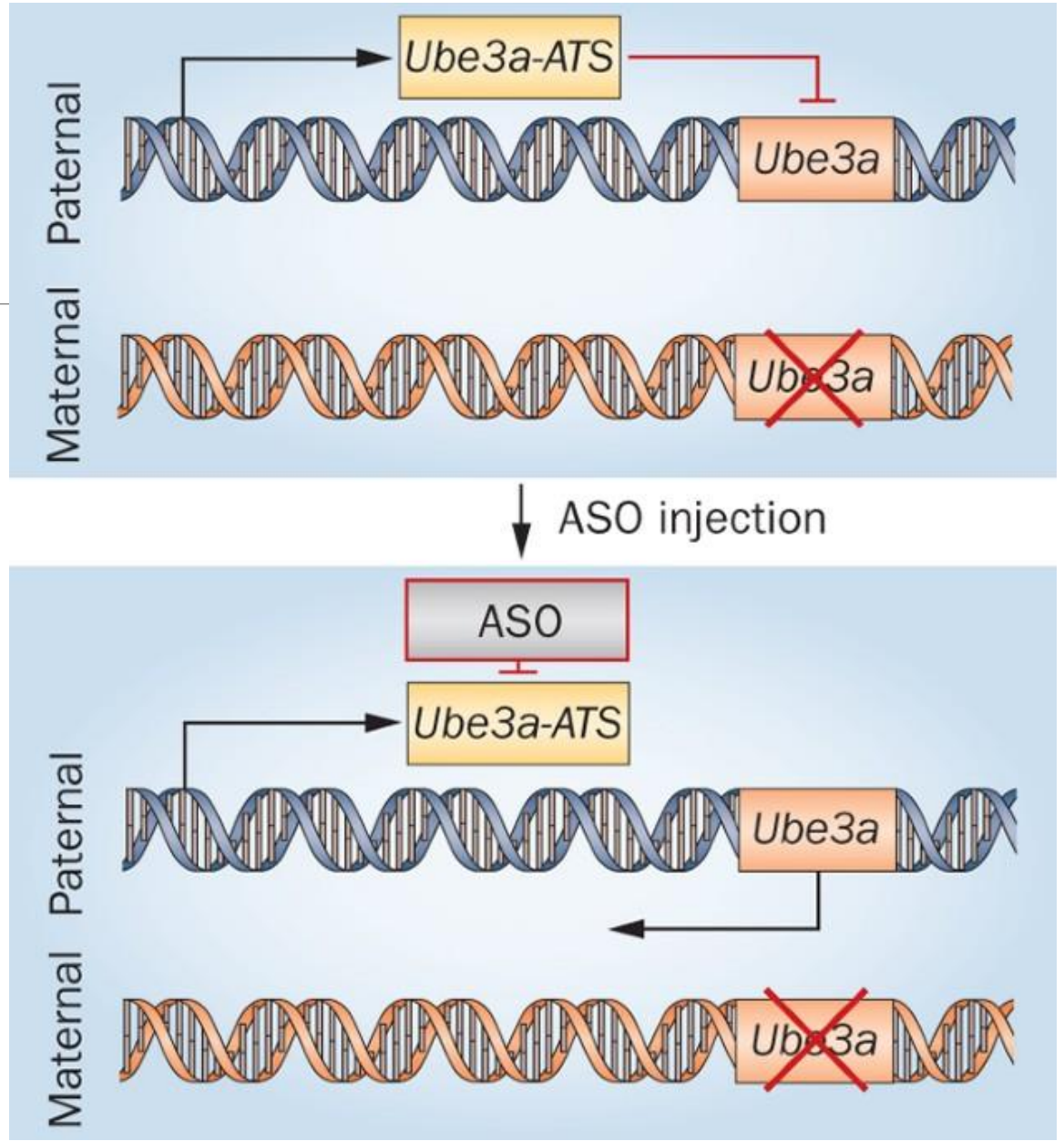
Example
Angelman syndrome

Ube3a-ATS **is an atypical RNA polymerase II transcript that represses the paternal expression of *Ube3a***

Linyan Meng, Richard E. Person and Arthur L. Beaudet*



Genomic structure of 15q11-13



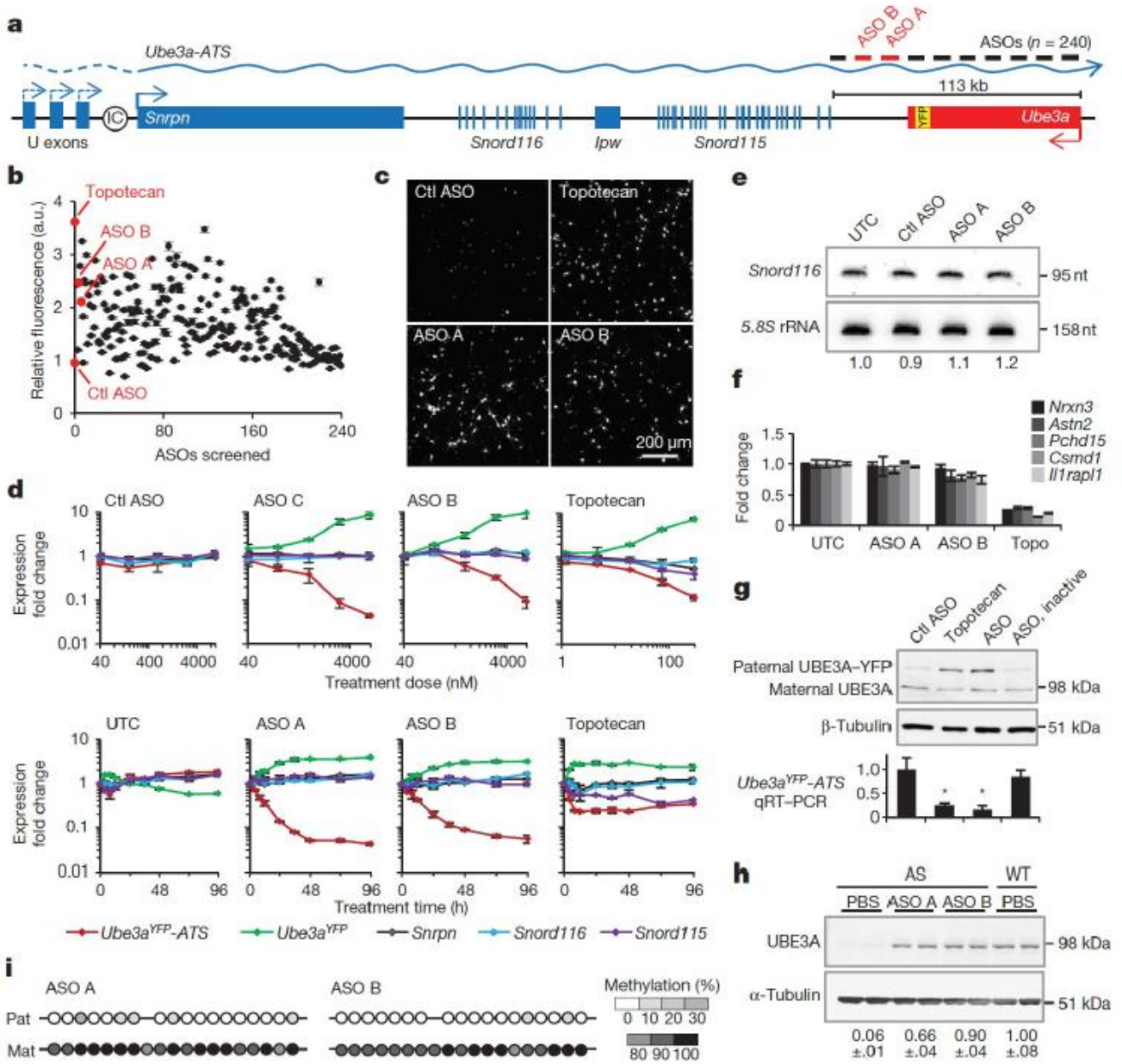


Figure 1 | Unsilencing of the *Ube3a* paternal allele by *Ube3a-ATS*-targeted ASOs in cultured mouse neurons. **a**, Schematic mouse *Ube3a* genomic locus. IC, imprinting centre. **b**, UBE3A–YFP fluorescence (arbitrary units (a.u.)) in ASO-treated primary neurons relative to untreated control (UTC). **c**, YFP fluorescent imaging of treated Pat^{YFP} neurons. **d**, Normalized mRNA levels in Pat^{YFP} neurons treated with increasing doses (top) or for increasing times (bottom). **e**, Northern blot of *Snord116* expression. *Snord116* intensity relative to *5.8S* ribosomal RNA is quantified. nt, nucleotides. **f**, Normalized mRNA levels of long genes. Topo, topotecan. **g**, Western blot (top) and reverse transcription with quantitative polymerase chain reaction (qRT–PCR) (bottom) from Pat^{YFP} neurons. 'ASO, inactive' is a sequence-matched RNase H inactive ASO. $^*P < 0.05$, two-tailed *t*-test, $n = 2$ per group, mean ± absolute deviation. **h**, Western blot from wild-type (WT) or Angelman syndrome (AS) primary neurons. UBE3A signal intensity was quantified relative to α-tubulin. **i**, DNA methylation analysis of the PWS imprinting centre. The paternal allele was distinguished by the conversion of a CpG dinucleotide (CG > AA) in CAST.Chr7 mice.

Conclusion

- Global developmental delay can be caused by genetic and non-genetic etiologies

- Genetically heterogeneous

- Clinical approach with latest clinical guidelines and recommendation

- Early diagnosis is beneficial in disease management and reproductive aspects

- Understand the categories of genetic disorders leading to GDD

- Understand the advantages and limitation of different genetic tests , can help in disease diagnosis

- Gene therapy is an evolving aspects , with currently about >100 FDA approved drugs for rare disease

Thank you