Manchester ESHG Syndromology and Dysmorphology Course 2026

Metabolic Dysmorphic Syndromes

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What is an IEM?

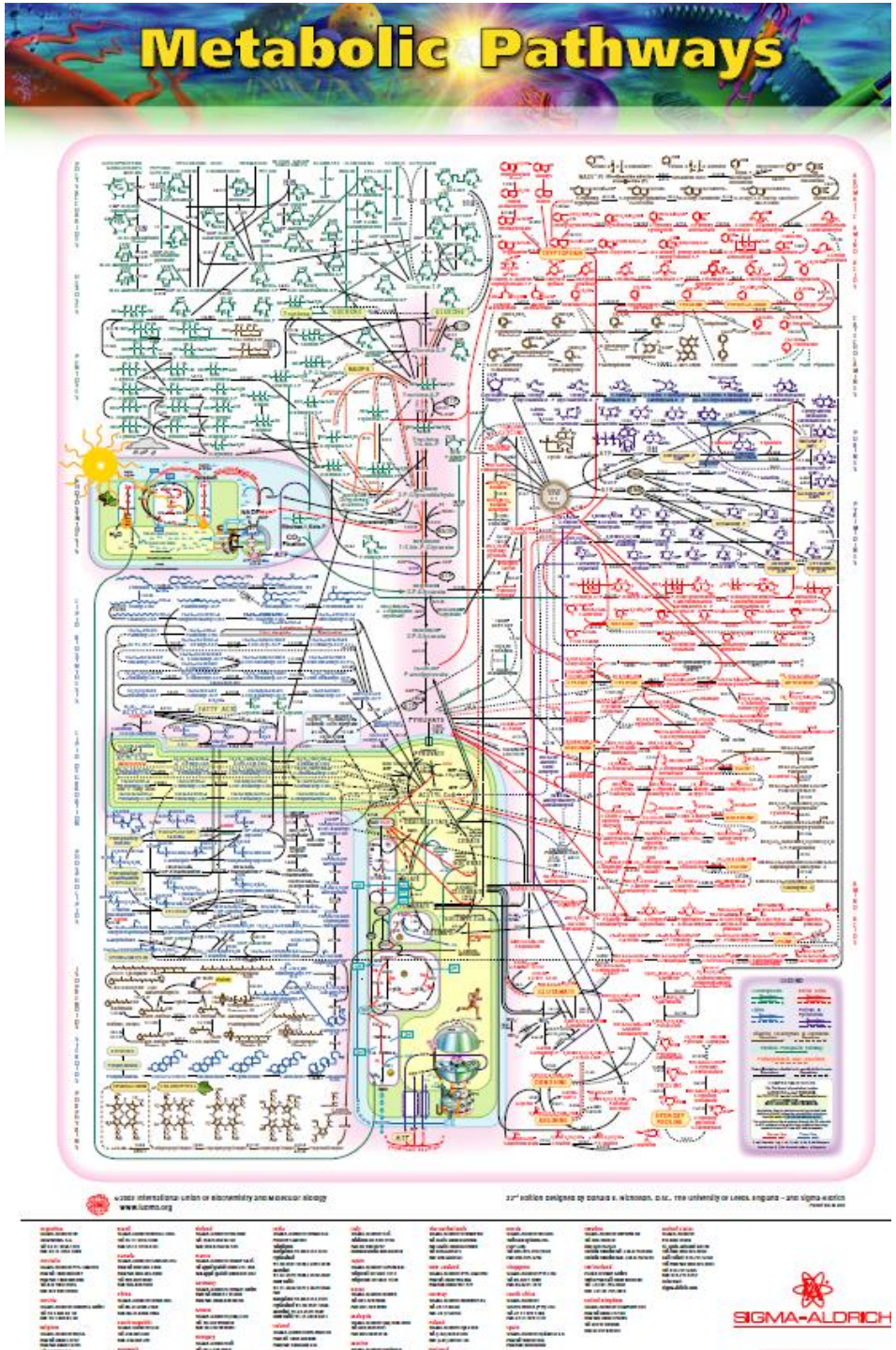
Any condition that leads to a disruption of a metabolic pathway, irrespective of whether it is associated with abnormalities in biochemical laboratory tests

Enzyme deficiency

Cofactor deficiency

Transporter/chaperone deficiency

Transcription deficiency



First IEM described in 1902 by Garrod

"classification of a disorder as an IMD requires only that impairment of specific enzymes or biochemical pathways is intrinsic to the pathomechanism"

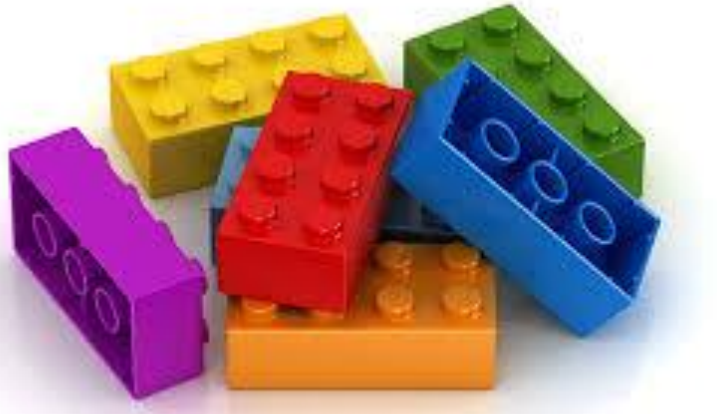
2019 – 1100 IEM divided into 130 groups

(Ferreira 2019)

- 232 mitochondrial disorders
- 188 Errors in metabolism of Nitrogen containing compounds
- 123 Congenital disorders of glycosylation
- 79 disorders of vitamin metabolism
- 67 storage disorders
- 47 errors of sterol metabolism
- 27 peroxisomal disorders
- 25 errors of metal metabolism







SMALL MOLECULES

COMPLEX MOLECULES



Simplified classification: Based on clinical phenotypes and mechanism of disease

- the core mechanism of each disease that correlates the most with clinical signs and biomarker

Small molecules

Complex molecules

Energy Defects

Small molecules

Can be measured easily in plasma or urine - amino acids, organic acids, acylcarnitines, pophyrins, fatty acid, purines, pyrimidine, metals

- <u>Accumulation of small molecules (1)</u>

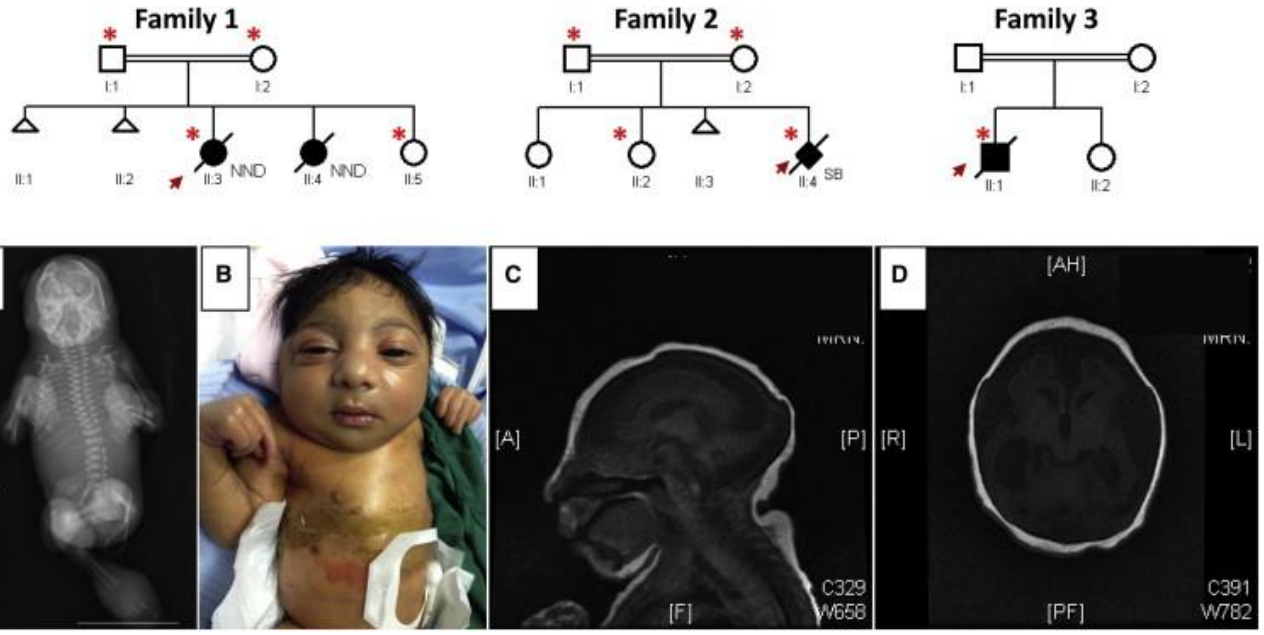
 - Postnatal intoxication – acute or progressive after symptom free interval

- Precipitated by food intake or acute metabolic crisis
- Do not generally interfere with embryo development

Small molecules (2)

- Deficiency
- Defective synthesis of essential compounds or defective transport through cellular organelles
- Includes neurotransmitter disorders
- Predominantly neurodevelopmental phenotype

Disorder of serine metabolism- defective synthesis



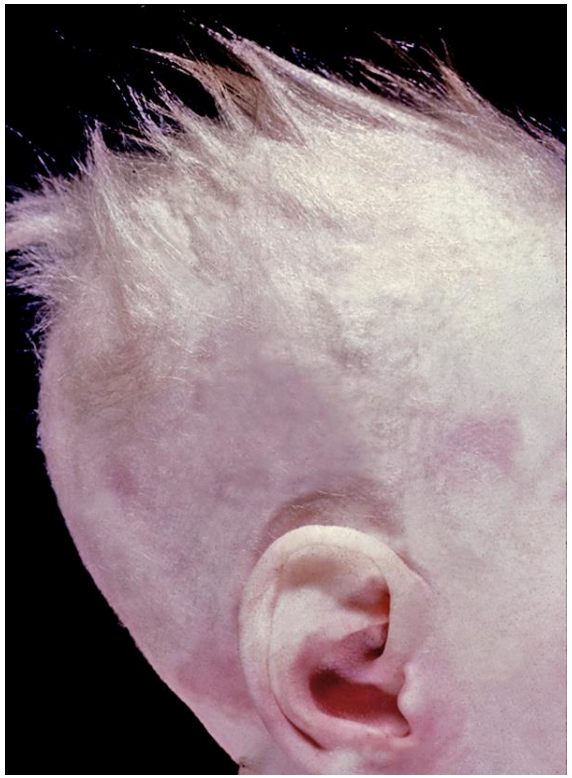
Am J Hum Genet 94:6, 898 - 904

Variable age of onset

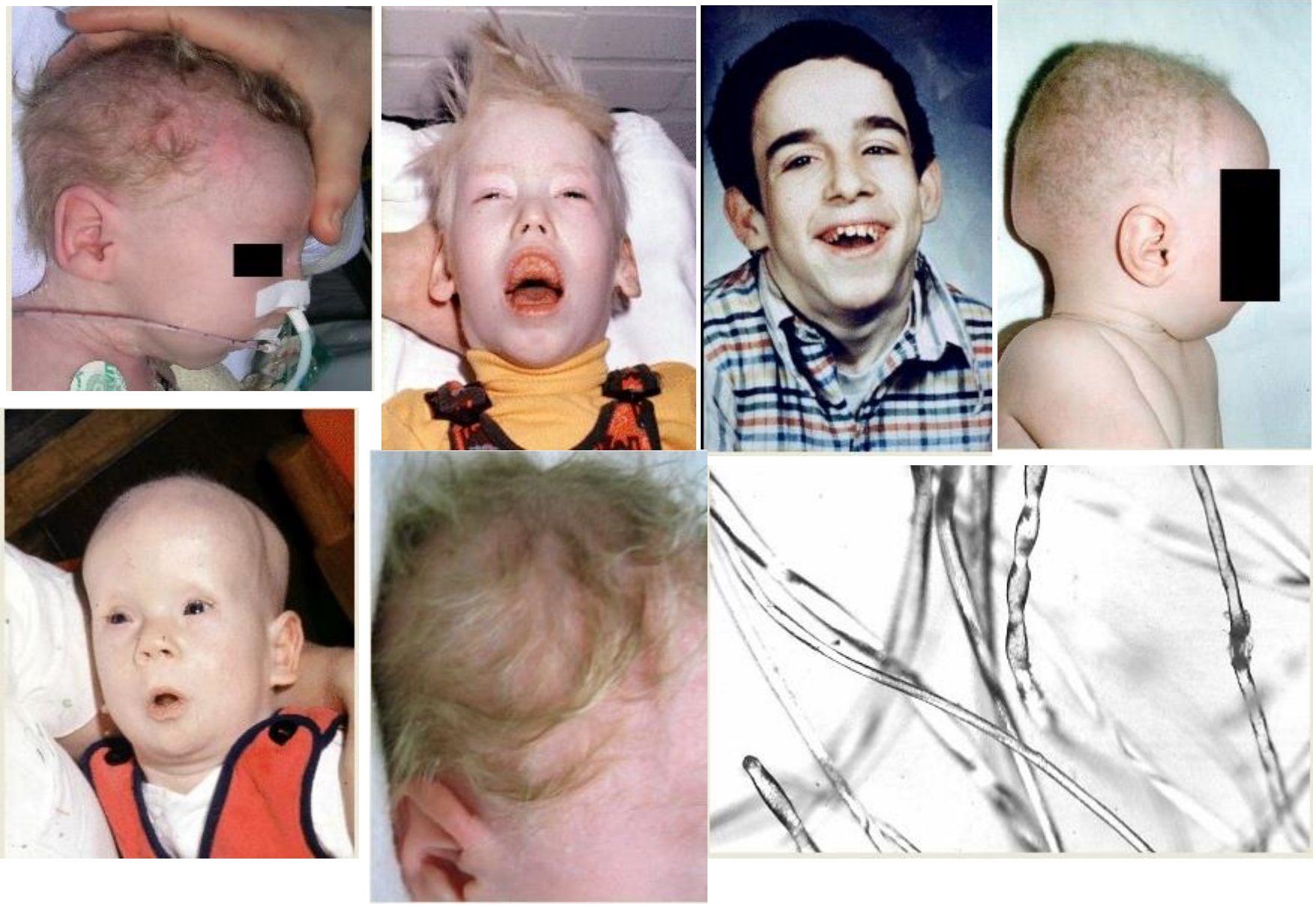
<u>Infantile</u>
IUGR
Microcephaly
Congenital cataracts
Colloidion like skin appearance
Perinatal lethal

Juvenile onset – seizures, spastic quadriplegi
Adult onset - polyneuropathy

Small molecules - Disorders of Metal Metabolism







Courtesy Dr K Metcalfe



hypotension
Vascular abnormalities
Chronic diarrhoea
Bladder diverticulae
Normal or mildly decreased IQ


F
G
R
H
R
L
I

Disorders of Complex molecules

- Complex molecules that are neither water soluble nor diffusible.
- glycogen, triglycerides, sphingolipids (SPL), phospholipids(PL), bile acids, glycosaminoglycans, oligosaccharides, glycoproteins, glycolipids and nucleic acids.
- Very long chain fatty acids and cholesterol included
- Disorders of synthesis and recycling of complex molecules
- Disorders are typically non progressive

Disorders of complex molecules

- Accumulation
- Sphingolipidoses
- Lysosomal storage disorders

- Disorders of autophagy

- Deficiency
- Defects in synthesis of sphingolipids, glycosphingolipids
- Peroxisomal disorders -number of molecular defects affecting either the peroxisome biogenesis or a specific matrix enzyme involving the catabolism of very long chain, and branched chain fatty acids (phytanic acid), or complex molecule synthesis like bile acids or plasmalogen
- Cholesterol and Bile aid synthesis defects

Lysosomal storage disorders

Disorder	Region or population	Incidence (per 100,000 individuals)
Gaucher disease type I	Ashkenazi Jews	100 (REF.[9])
Tay–Sachs disease (infantile)	Ashkenazi Jews	25 (REF.[114])
Niemann–Pick disease type A	Ashkenazi Jews	2.5 (REF.[9])
GM1 gangliosidosis	Rudari isolate	10 (REF.[198])
Metachromatic leukodystrophy	Western Navajo Nation	40 (REF.[199])
Pompe disease	The Netherlands	2.5 (REF.[200])
Cystinosis	Brittany	3.8 (REF.[201])
Salla disease	Finland or Sweden	2.5 (REF.[202])
Aspartylglucosaminuria	Finland	54 (REF.[12])
Niemann–Pick disease type C	Nova Scotia (French Acadian)	100 (REF.[203])
Fabry disease	Nova Scotia	9.3[a]
Hermansky–Pudlak (types 1 and 3)	Puerto Rico	56 (REFS[13,14])

70 monogenic disorders

Present as visceromegaly and neurodegeneration

Prevalence 1 /5000 although individually rare

Sphingolipidoses

Mucopolysaccharidoses

Glycogen storage diseases

Glycoproteinoses

Lipid storage disorders

Neuronal Ceroid Lipofuscinoses

Sphingolipidoses



1/7000-8000 live births

Defective lysosomal degradation of sphingolipids

Autosomal recessive (except Fabrys)

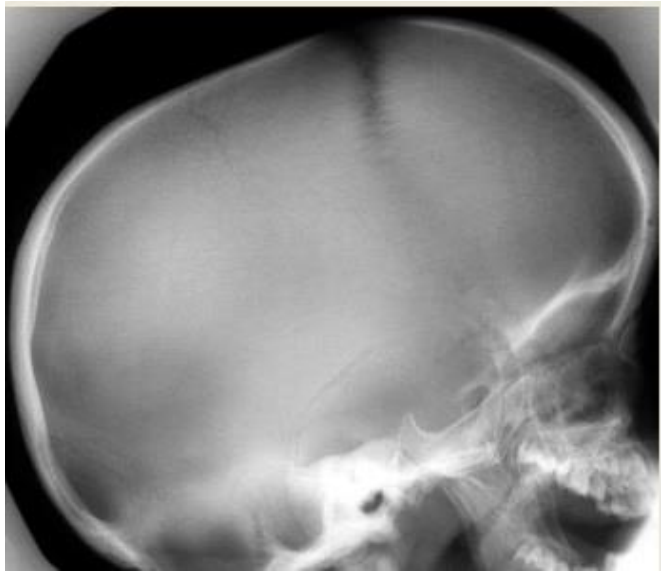
GM1 gangliosidosis

Sandhoff, Tay Sachs, Gaucher, Niemann-Pick, Metachromatic leukodystrophy

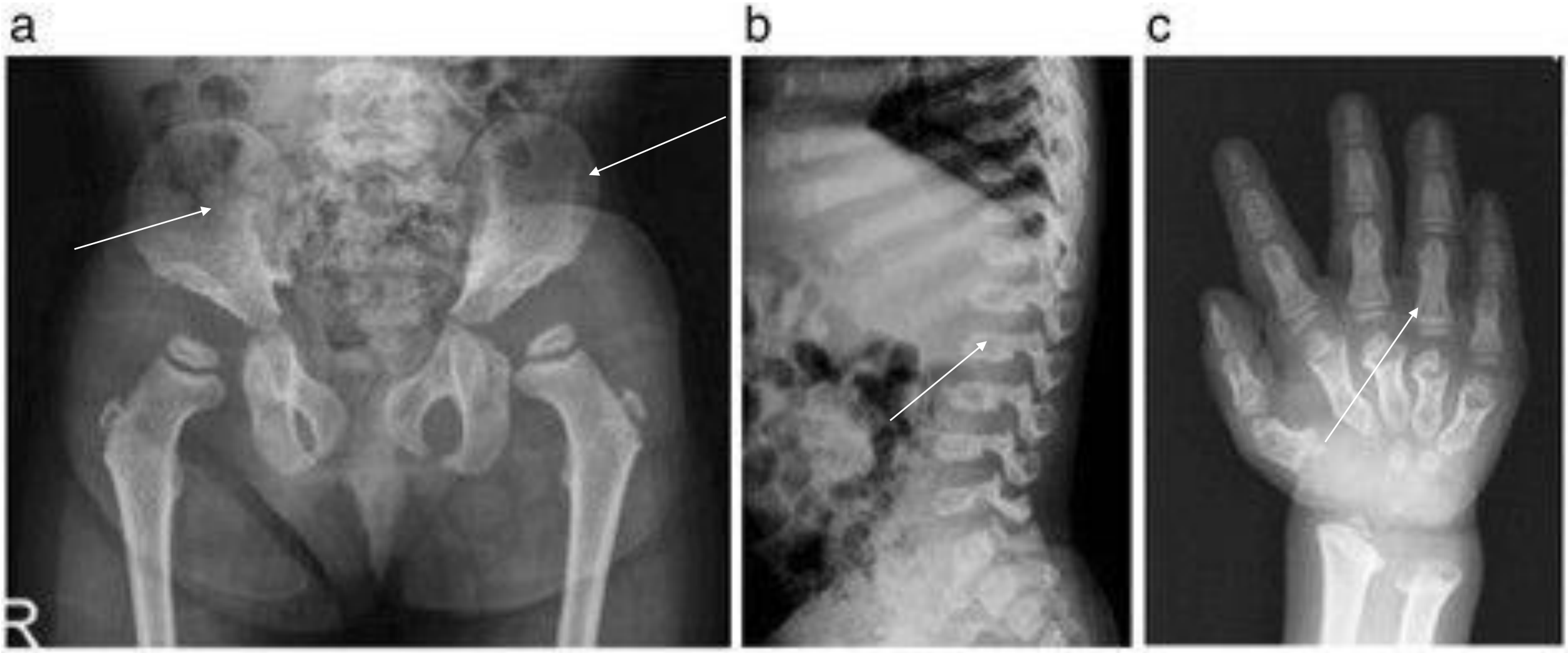
Neonatal/ Infantile/ Juvenile/Adult

Progressive neurological deterioration





Relative macrocephaly
Prominence of forehead and brow
Some puffiness of eyelids
Broadening and flattening of nasal bridge
Anteverted nares, chronic nasal discharge
Thick upper lip
Fleshy ears
Thickened tongue, gum hypertrophy
Coarse hair
+- corneal clouding



*Orphanet Journal of Rare Diseases*2014**9**:192

MPS I (Hurler)



Enlarged sella





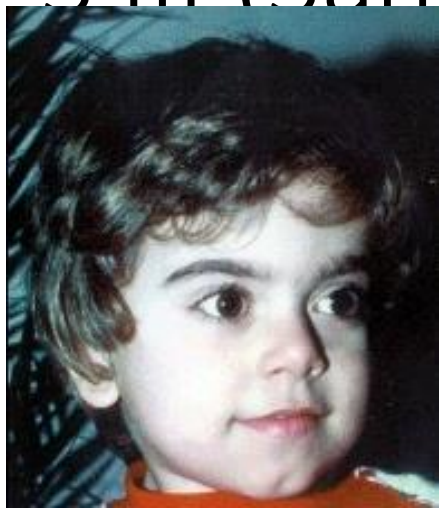






Prox.pointing of MCPs 2-5

MPS III (San Filippo)









Milder somatic phenotype
Mildly coarse facial features in older children
Coarse abundant hair
Ht normal or sl reduced
Very mild dysostosis- normal hands
Behavioural problems especially aggressive hyperactivity



MPS IV (Morquio)

Hyperetension of neck
Teeth in IVA- dull grey, pitted enamel
Corneal clouding
Adult ht 80-120cm I IVa
Unstable waddling gait
Joint hyperextensibility
Absent/ hypoplastic odontoid
Platyspondyly, short neck

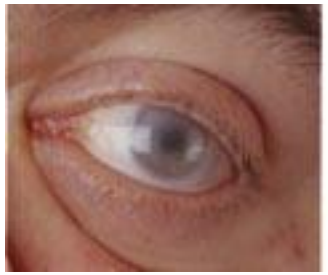




MPS VI (Maroteaux-Lamy)

- Mild-intermediate-severe
- Coarse features
- Corneal clouding
- Perthes like hips
- Joint contractures
- Aortic stenosis
- Reduced hearing
- Adult ht 110-168cm
- Normal mentation







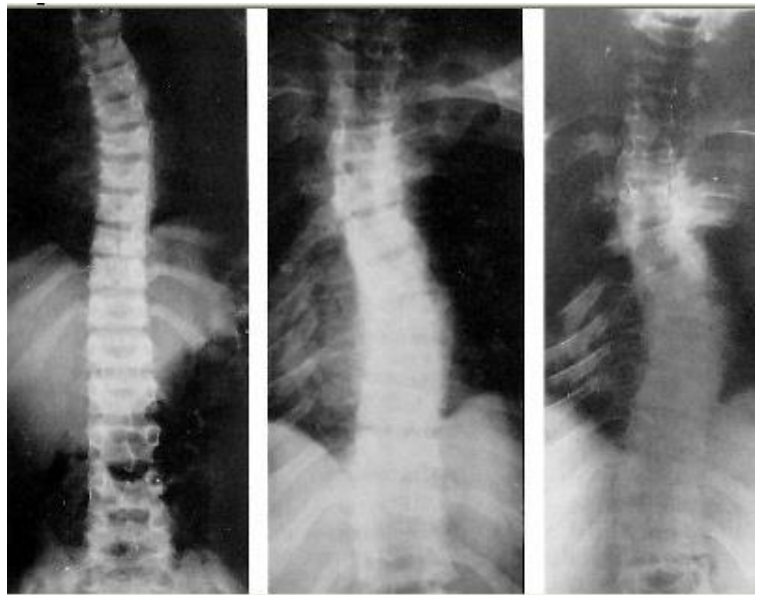




MPS VII (beta glucuronidase deficiency)









Very rare
Severe-mild
Can have prenatal onset with hydrops
Short stature from 2nd year
Progressive MR after 2y in severe type
Mod-severe dysostosis multiplex
No corneal clouding
Hepatosplenomegaly

Mucopolysacharidoses







ARCH NEUROL / VOL 64 (NO. 11), NOV 2007



J Indian Soc Pedod Prev Dent 2012;30:66-9



Am J Med Genet 164A(6):1443-53

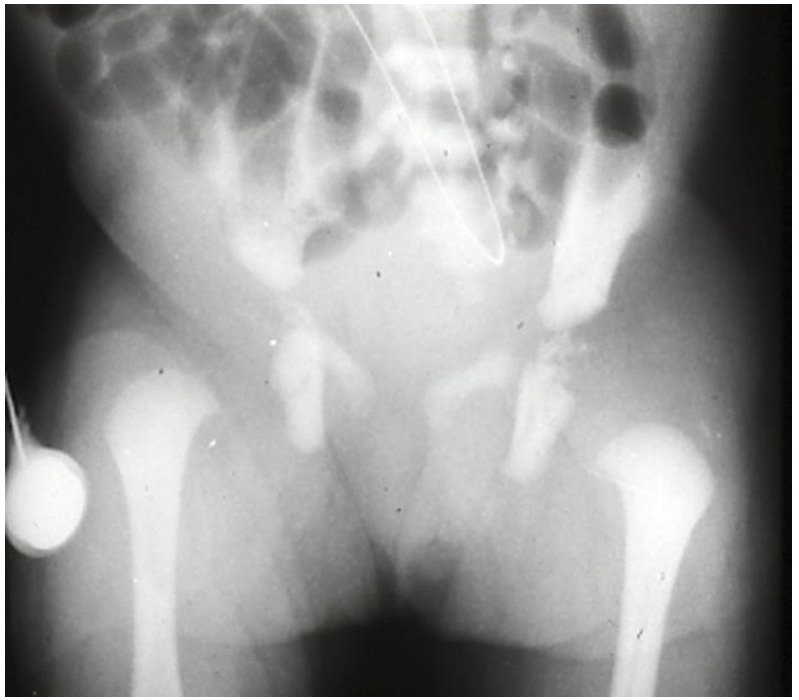
MPS I	MPS II	MPS III	MPS VI	MPS VII
IDUA	*IDA*	*SGSH*	*ARSB*	*GUSB*

All autosomal recessive except MPS II









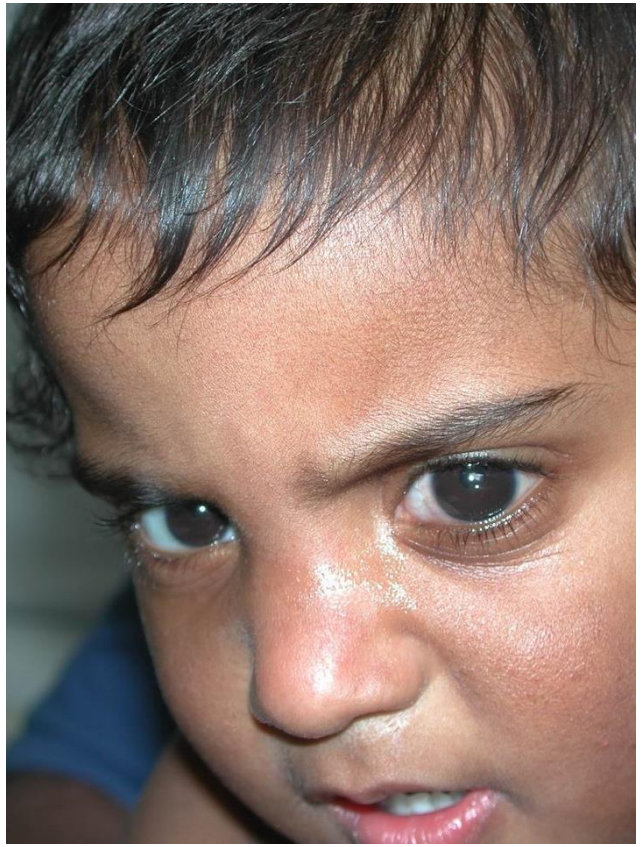
Peroxisomal biogenesis disorder



- Classical ZSD
- Intermediate ZSD – mainly neurological presentation- ataxia, liver dysfunction, visual and hearing impairment, hypotonia and delayed development
- Biochemical – elevated C26:C22, increased phytanate, pristanate, reduced plasmalogens
- At least 13 *PEX* genes

Peroxisomal disorders

- Peroxisomes are intracellular organelles involved in b-oxidation of VLCFA, production of cholesterol, bile acids ad plasmalogens





Rhizomelic Chondrodysplasia Punctata



Congenital cataracts

Profound Growth retardation

Severe Intellectual disability

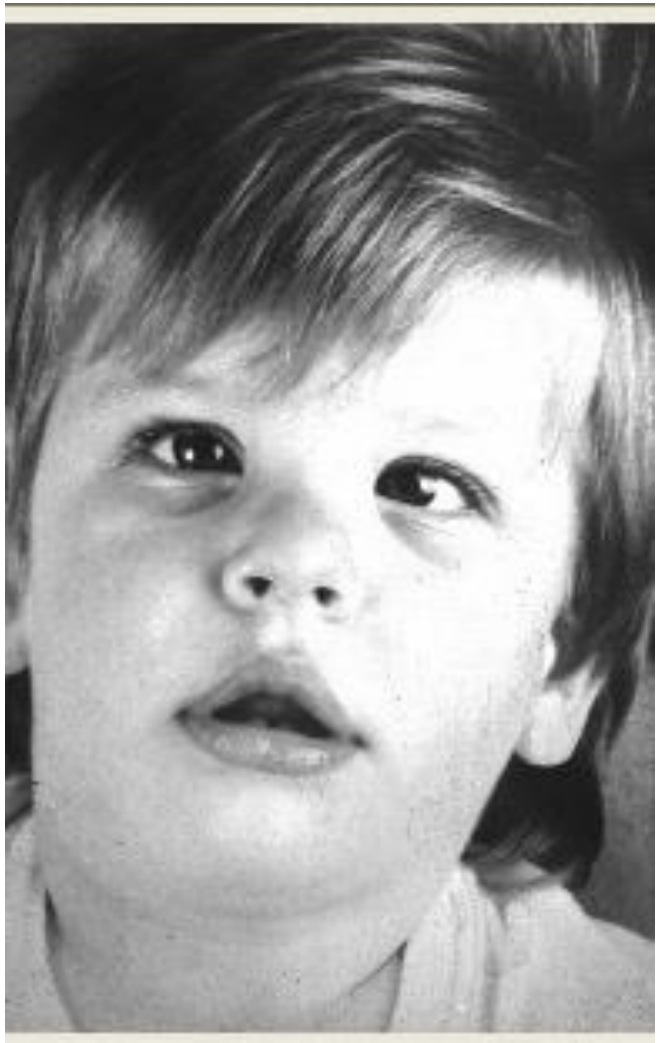
Majority develop seizures

1/3 ichthyotic skin changes

5-10% cleft palate

PEX7

51% p.Leu292Ter





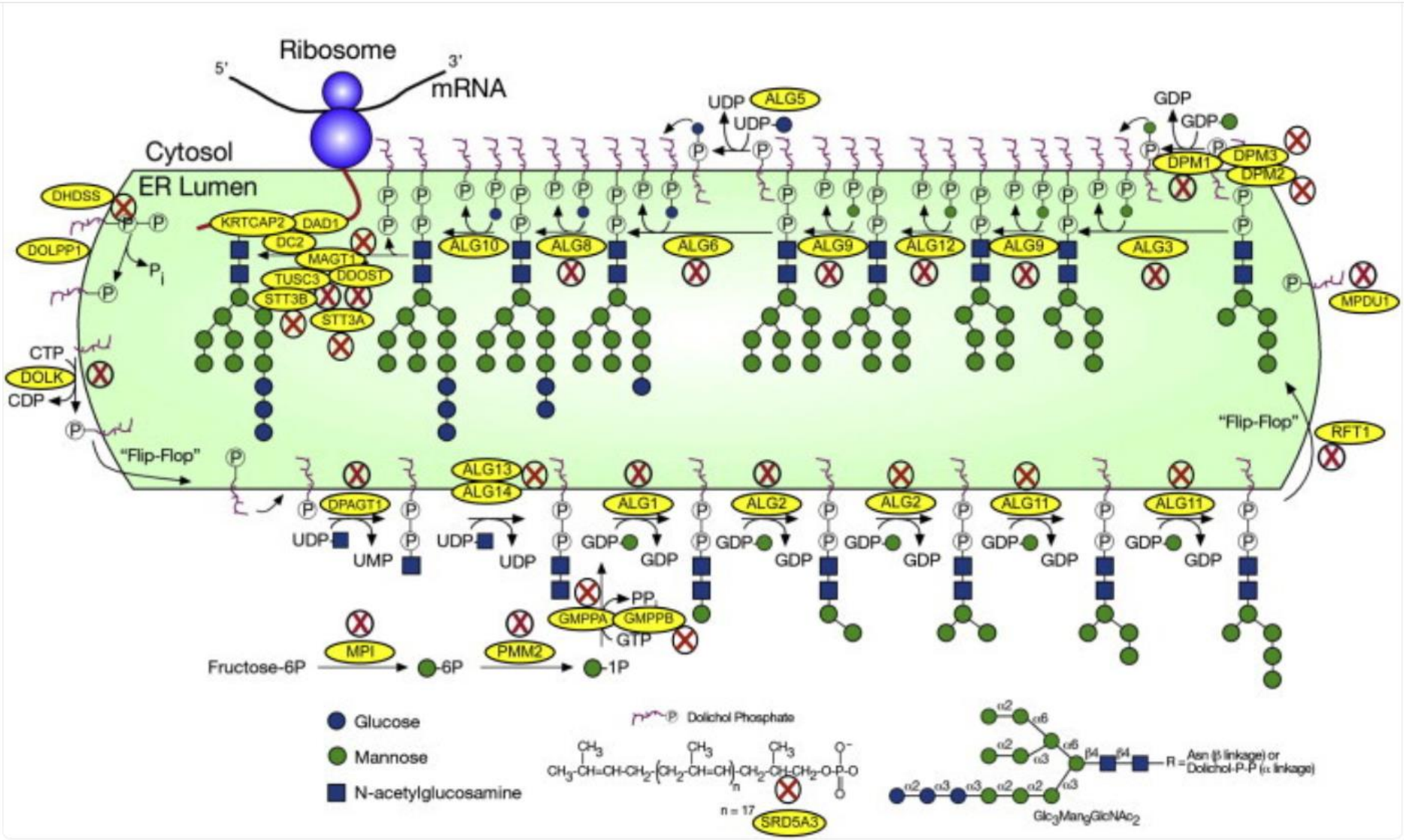




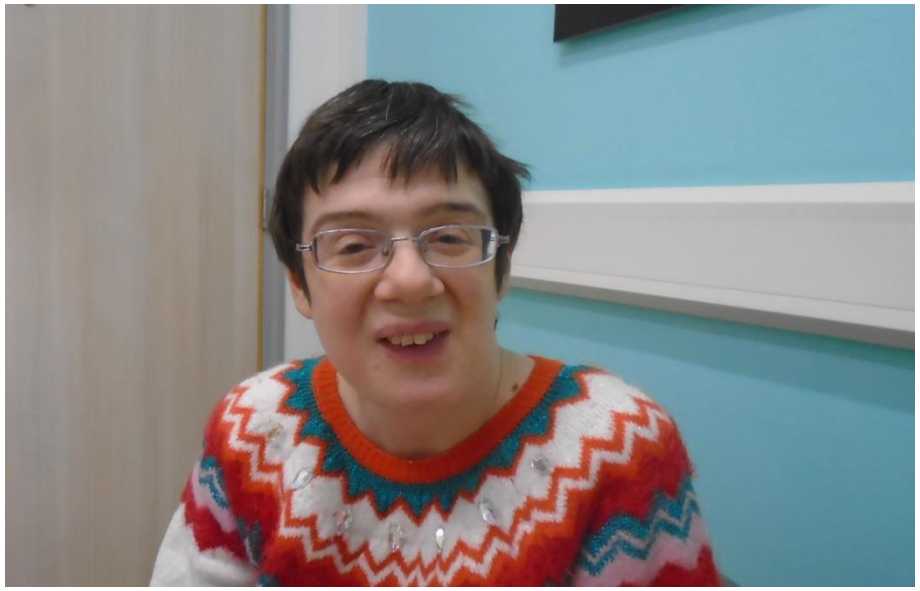
PMM2-CDG (Type Ia)

Congenital Disorders of Glycosylation

- More than 100 CDGs reported
- Defect in post trainslation addition of glycans of other molecules, mainly proteins and lipids
- Multisystem disorders
- Classification based on the gene – eg PMM2-CDG
- Most AR
- No clear biochemical signature and most diagnosed via NGS



Hudson et al.Am J Hum Genet 94(2):161–175





Developmental delay
Hypotonia in infancy
Myopia
Seizures





Widely spaced eyes
Micrognathia
Low set ears

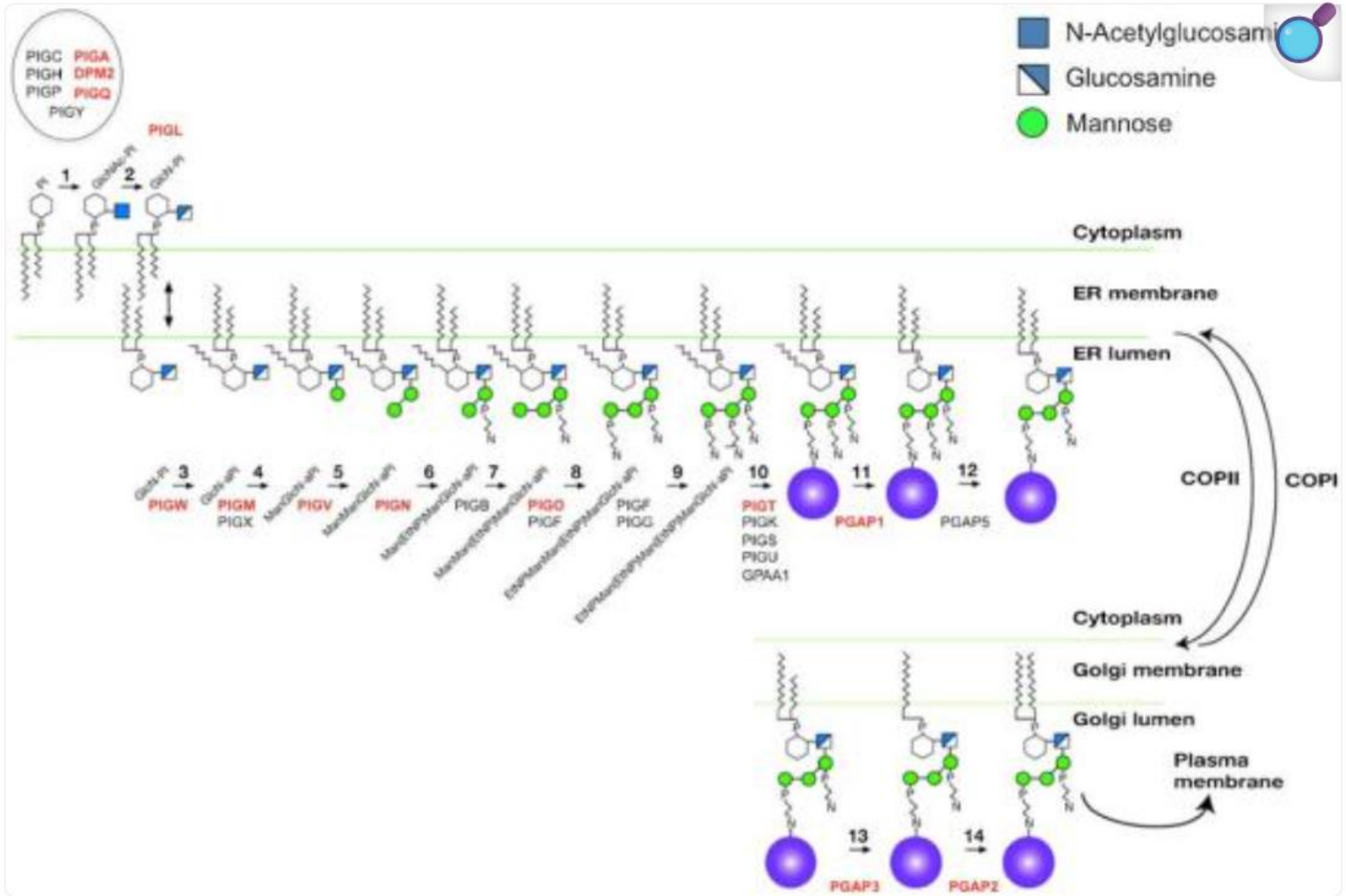
ALG6-CDG







ATP6V0A2-CDG



J Inherit Metab Dis. 2014 Aug 28;38(1):171–178

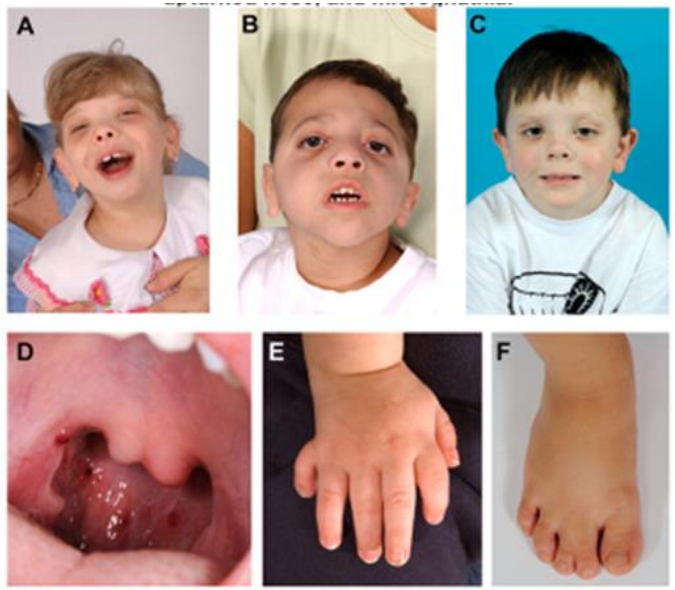


Second child of consanguineous parents
Older sibling deceased with similar

Decreased fetal movements
Hyoptonic

Elevated alkaline phosphatase

PIGN



Forbes D. Porter, and Gail E. Herman J. Lipid Res.
2010;52:6-34

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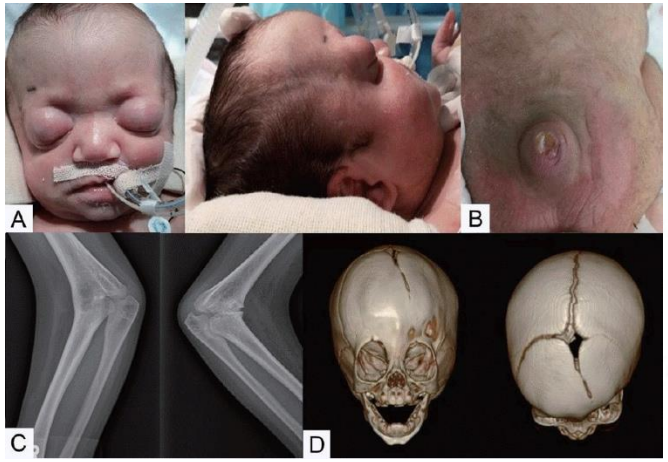
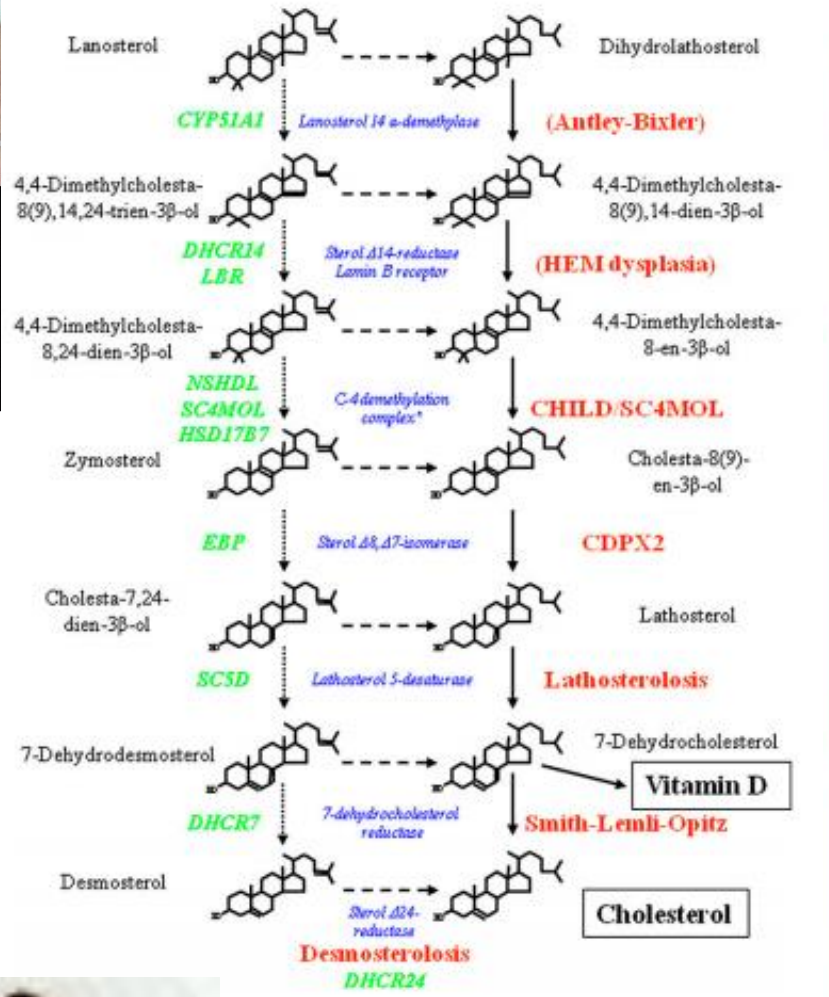


J Genet Med 2016;13(1):31-35







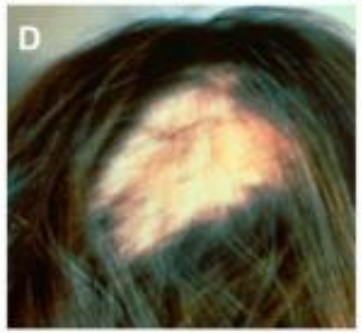


SLOS illustrates patients ha



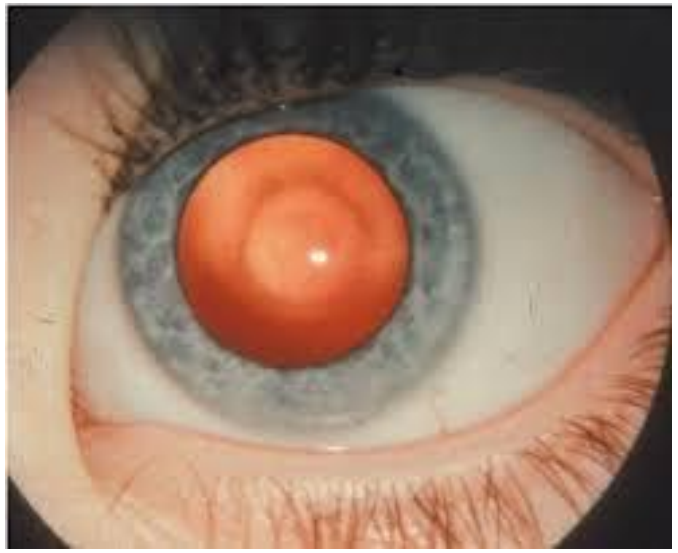












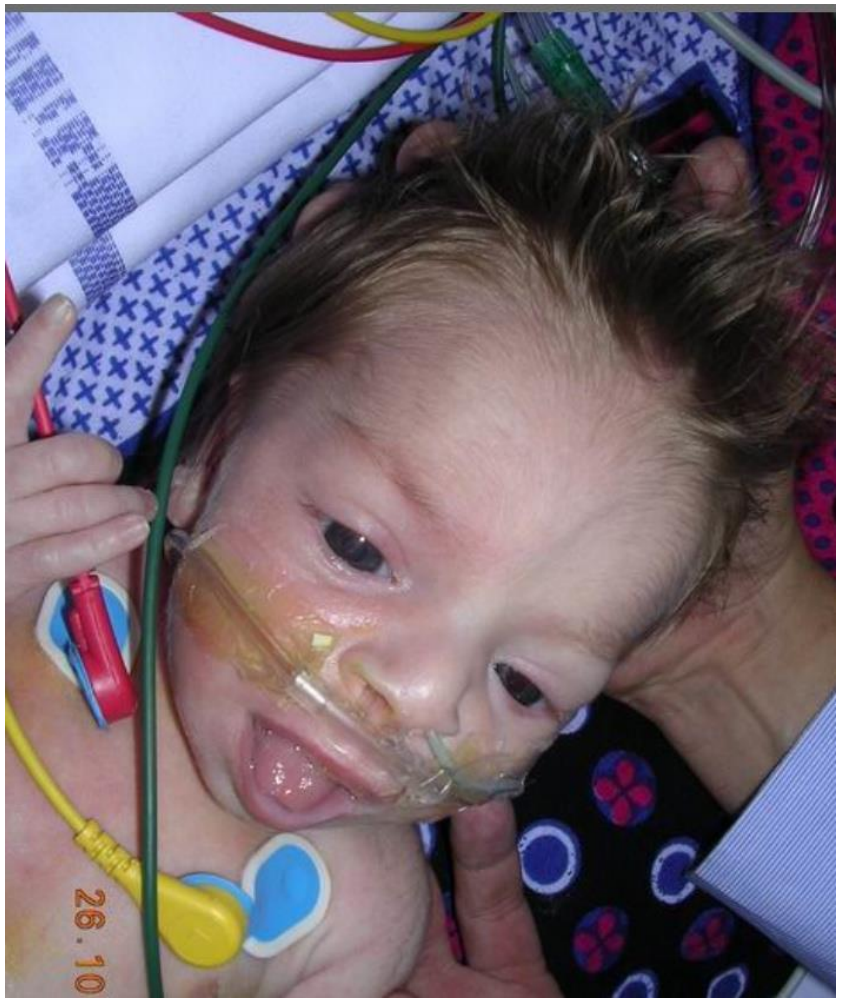
Clinical Ophthalmology 9:77-79

Conjugated hyperbilirubinemia
Liver dysfunction

Cataracts also seen in

Wilsons disease
Arginosuccinicaciduria
Homocystinuria
MPSI
Mannosidosis
Refsum Disease
SLO (20%)

Congenital disorders of autophagy



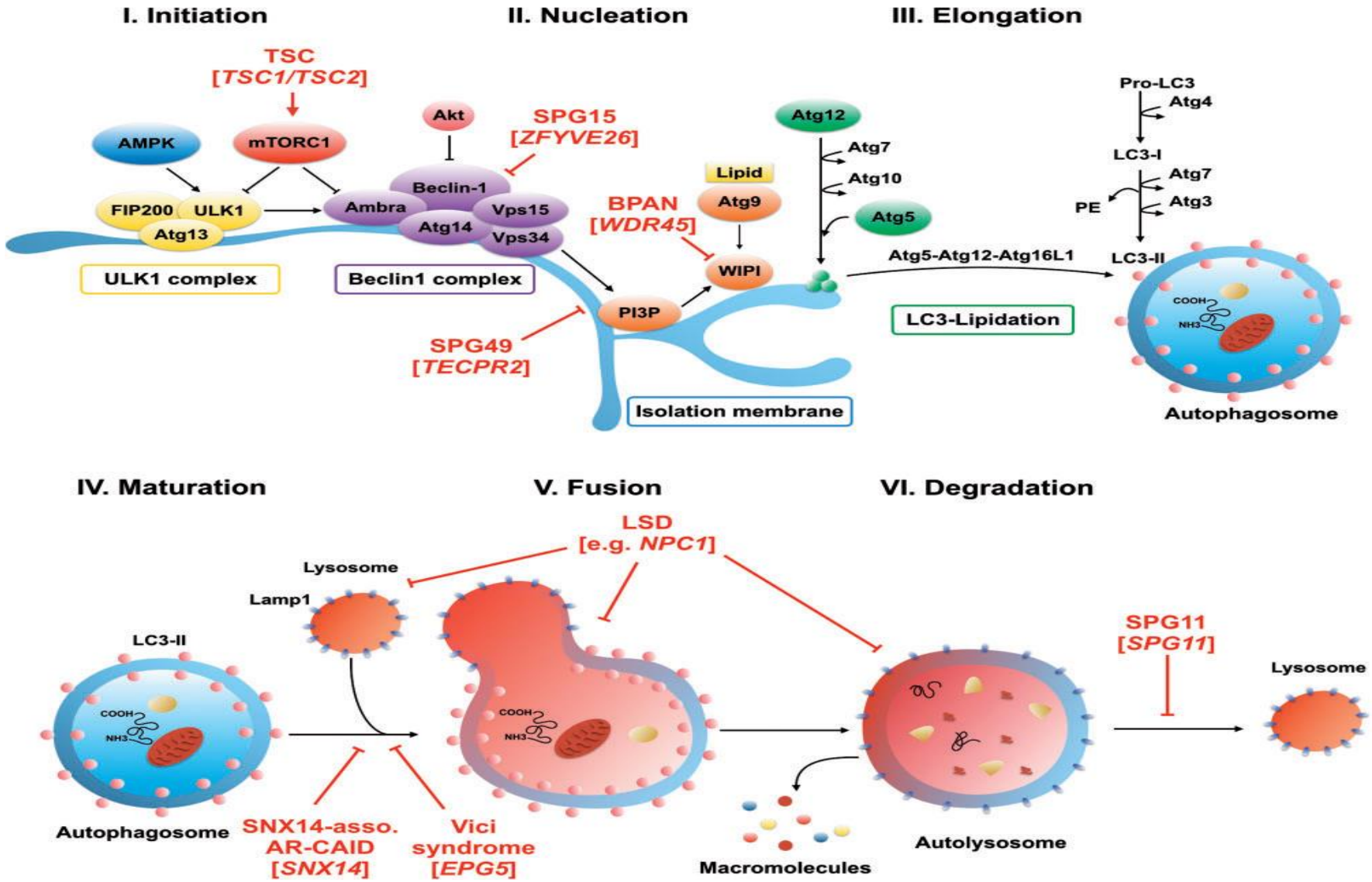
Progressive multisystem disorders

Failure to thrive
Progressive microcephaly
Hypotonia
Cataracts
Sensorineural deafness
Immune deficiency
Visceral organomegaly
Developmental regression
Seizures

Brain – ACC, cortical or cerebellar vermis dysplasia, reduced white matter bulk

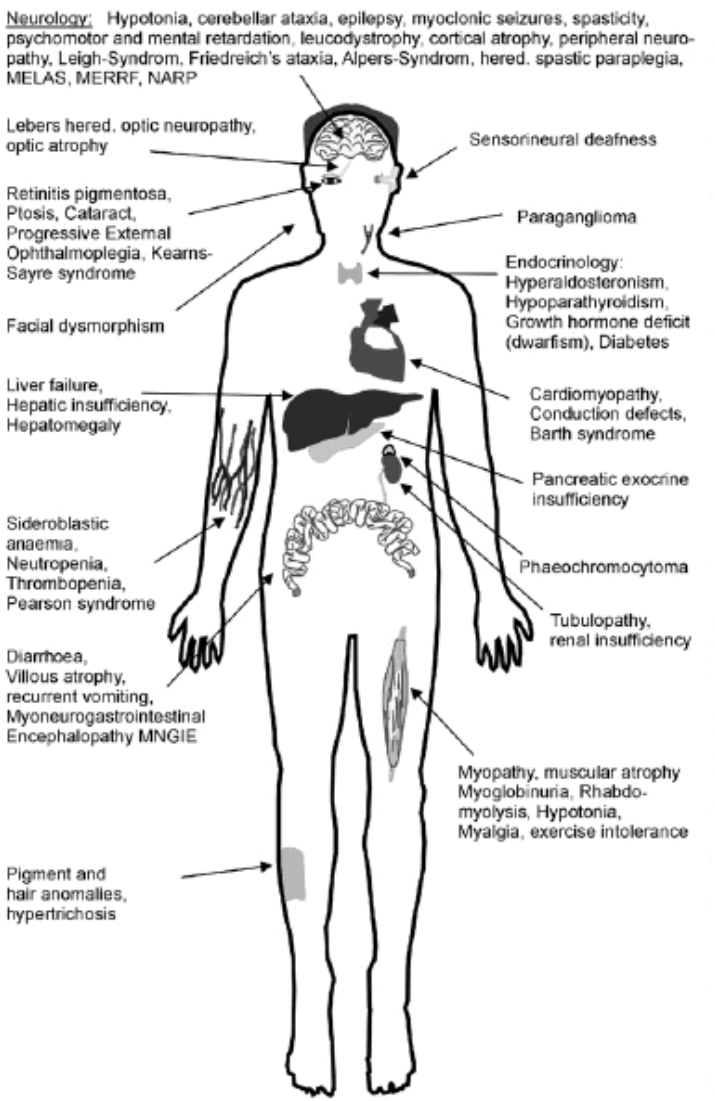
Neurodegeneration with **B**rain **I**ron **A**ccumulation
Beta-propeller **P**rotein **A**ssociated **N**eurodegeneration X –linked

Congenital disorders of autophagy



BRAIN 2016: 139; 317–337

Mitochondrial disorders



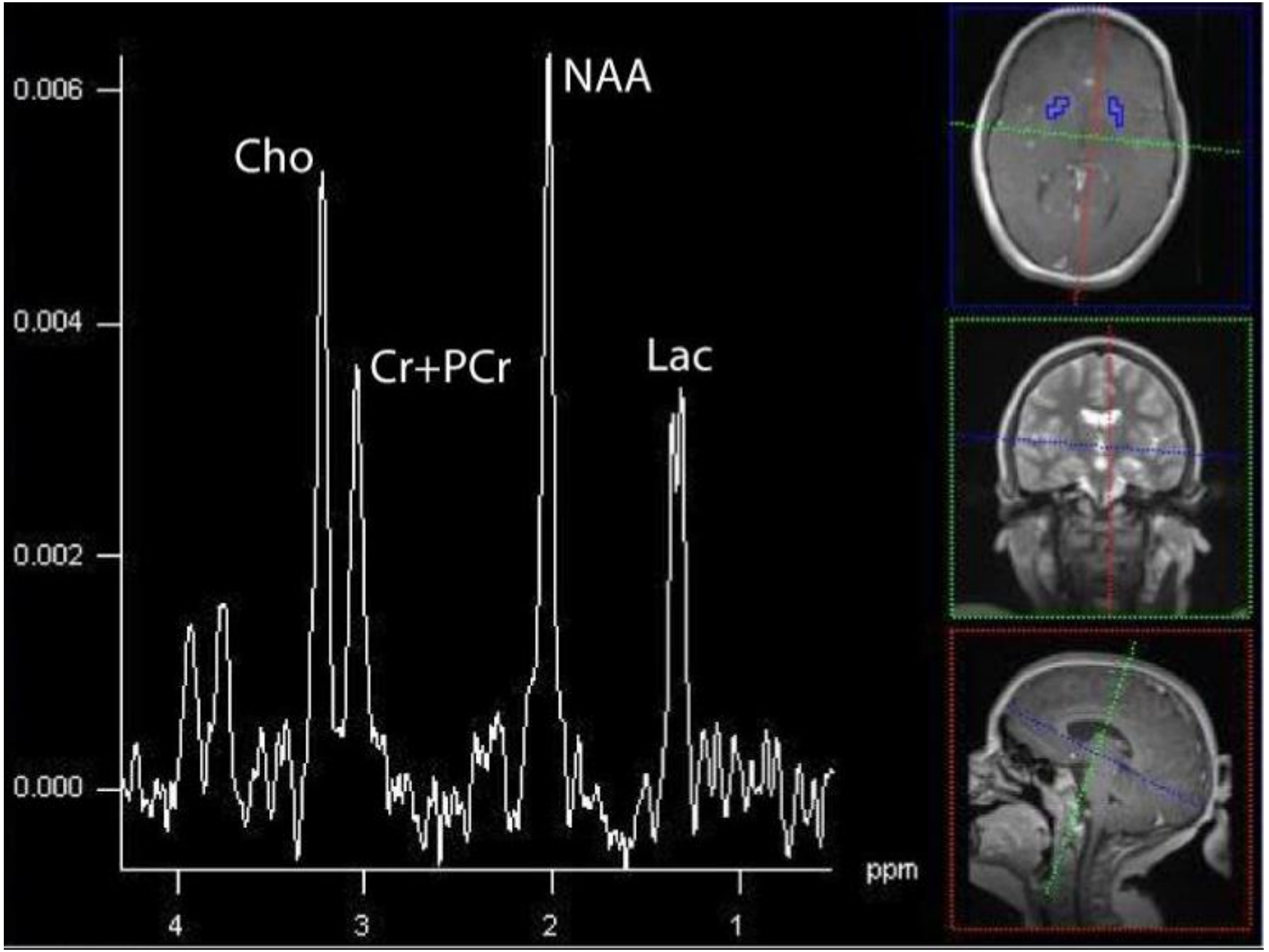
Multisystem disorders

Present at any age/any system involvement

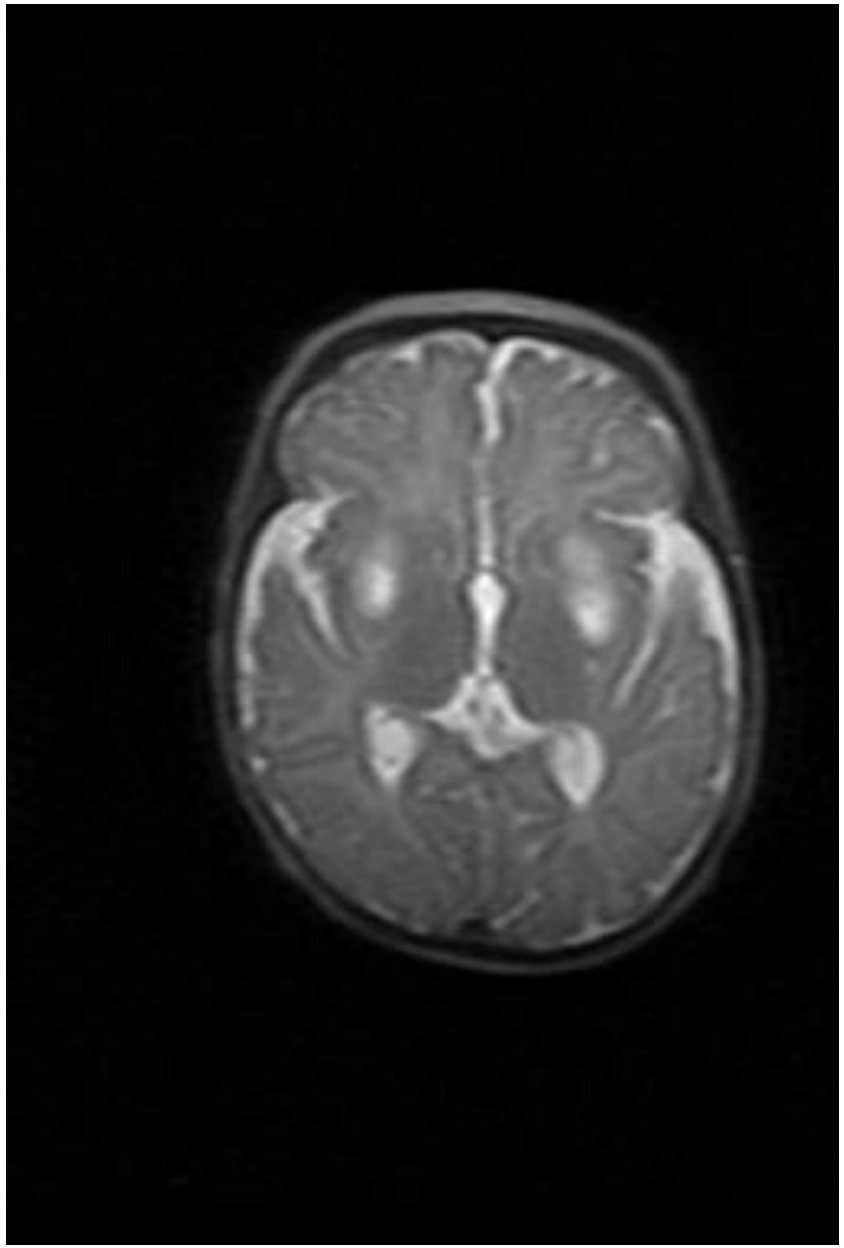
Common clinical presentation

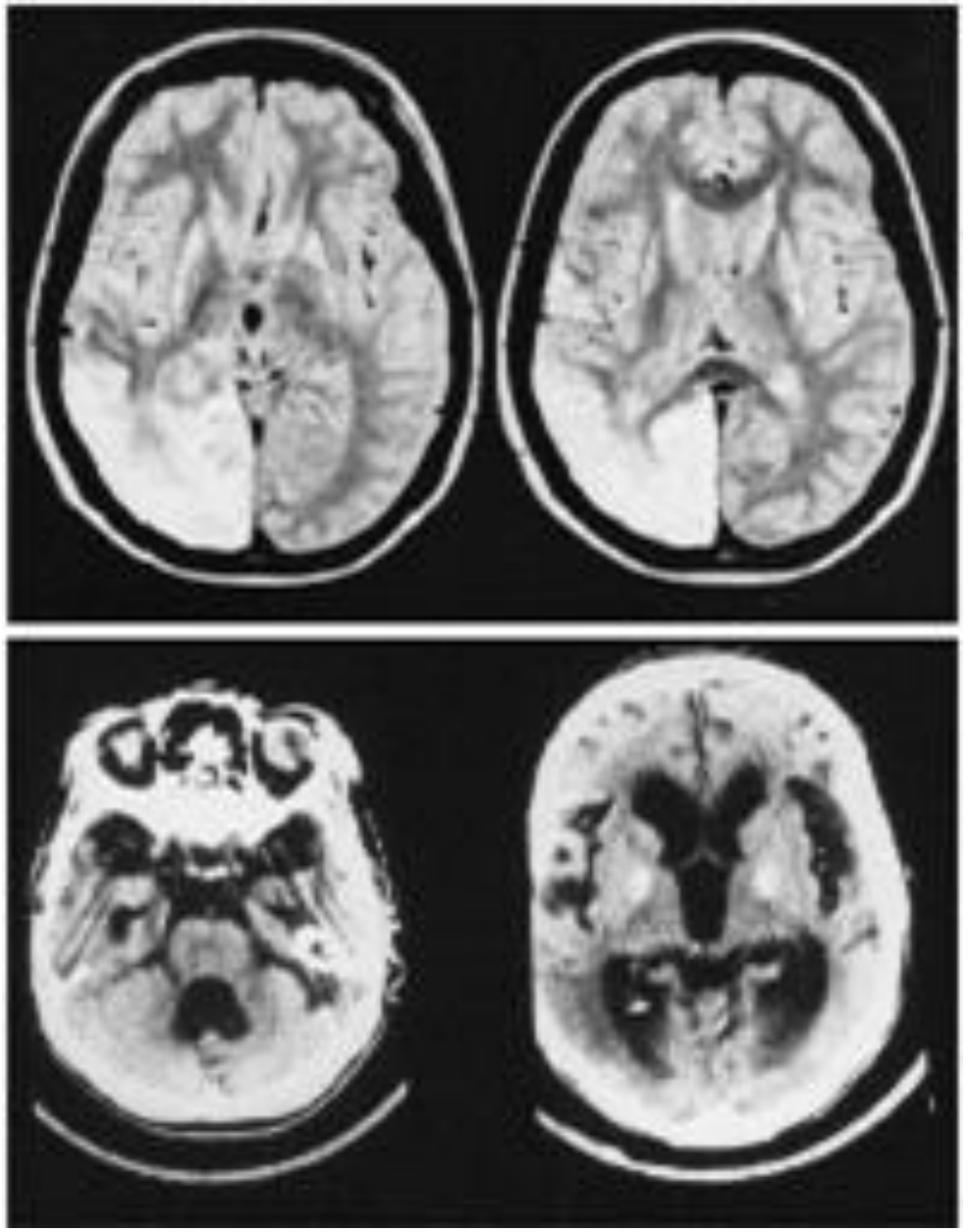
- seizures
- movement disorders
- cardiomyopathy
- liver dysfunction
- myopathy
- gut dysmotility

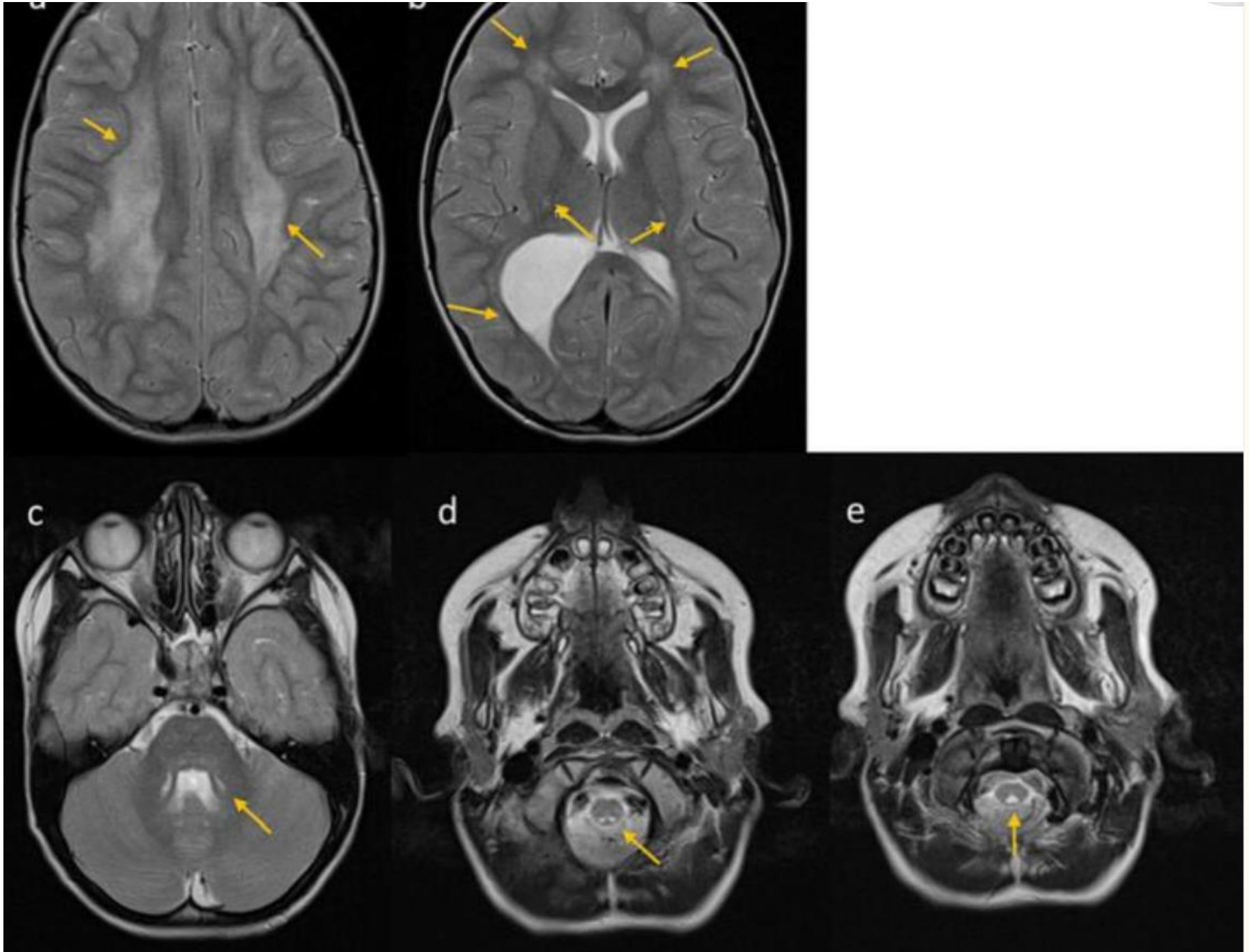
MRS



Saneto RP.*Mitochondrion* 2008. 8:396-413







Mol Genet Metab Rep
. 2023 Dec 2;38:101025

Prenatal presentation of Metabolic Disorders

FETAL HYDROPS

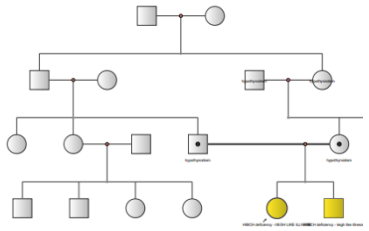
Mucopolysaccharidoses type VII
Gaucher
Galactosialidosis
Mucolipidosis
GM1 gangliosidosis
Sialic acid storage disease

The newer disorders- are they recognisable?



Sudden onset of dystonia following febrile illness
Progressed to bulbar palsy

bilateral basal ganglia changes noted with diffusion restriction.



Trio whole genome sequencing – metabolic and childhood onset dystonia panels negative

Reanalysis: HIBCH c.140G>T, p.Gly47Val

VUS!

3-hydroxyisobutyryl-coenzyme A hydrolase deficiency

CELLULAR TRANSPORT AND TRAFFICKING

SIMPLE MOLECULES

Accumulation

Progressive accumulation
Toxicity
Acute/intermittent/ chronic

Urea cycle
Galactosemia
Vitamin deficiency
Purine/pyrimidine

Deficiency

Failure to synthesize complex molecules

Fatty acid transport defect
Amino acid transport/synthesis
Metal deficiency
Neurotransmitter defects

CDGs
Disorders of autophagy
synaptic vescicle
synthesis and cycling

Defects of Energy Production

Glycolysis
Creatine
Metabolism
Mitochondrial

COMPLEX MOLECULES

Accumulation

Lysosomal Storage Disorders
GSDs
CDGs
Peroxisomal

Deficiency

Glycogen deficiency
Complex lipid deficiency
Cholesterol

Take Home Messages:

- Inborn errors of metabolism are multisystem disorders
- Simple molecule disorders present with accumulation of metabolites after a symptom free period
- Complex molecule disorders present with congenital malformations, ‘storage disorder’
- Investigations – biochemical, genetic testing
- Treatments- supportive, specific diet modification, co-factor provision, enzyme replacement