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North American Metabolic Academy

Congenital Disorders of Glycosylation

Adapted from SIMD

Peter Witters, UZLeuven

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>1200 defects

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1

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Classification

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2

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IEMbase®
Inborn Errors of Metabolism Knowledgebase

Home About Disorders Resources Classification Gamuts Contact

Search

Disorders + Search

IEMBASE Search

Using IEMBASE

The IEMBASE accepts an array of biochemical and clinical symptoms from a user and returns a ranked list of possible IEM disorders that match the input profile. In addition, the system can explain the rationale of its results, suggest possible tests that would assist in narrowing down the differential diagnosis, and provide access to its database of biochemical, molecular, and clinical information if more evidence is desired.

Disease-characterizing profiles of clinical (n=1179) and biochemical (n=902) symptoms from an expert generated database of 500+ IEM disorders were used. These profiles were mapped to the Human Phenotype Ontology (HPO) and Logical Observation Identifiers Names and Codes (LOINC) in order to exploit the semantic relationships of symptoms from the profiles. This, in turn, allows the expert system to determine a tiered list of possible IEMs which match the user-provided symptoms.

<http://www.iembase.org/>

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Classification

FROM
130 categories
9 groups

TO
3 categories
8 groups

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What is glycosylation?

Glycosylation is the synthesis of fully functional glycans, and their covalent enzymatic attachment to other molecules including proteins, lipids, and small RNA.

(Congenital) glycosylation disorders are caused by (inborn) pathogenic variants in the genes encoding proteins involved anywhere in the different glycosylation pathways.

These are mostly disorders of assembly and modification of bound glycans, but may include their disassembly when it also affects their assembly.

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5

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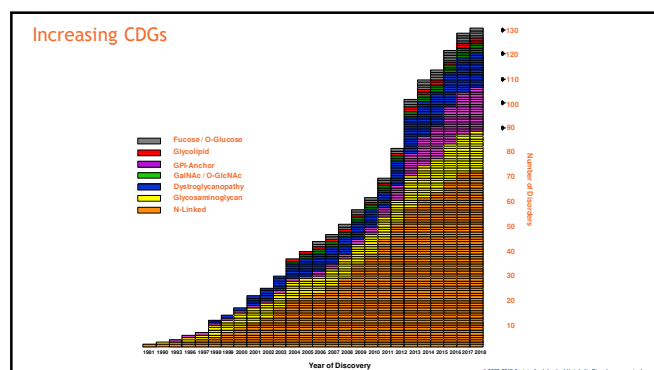
> 70% of the proteome is glycosylated

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6



7

>160 CDGs

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PMM2 MPI DPAGT1 ALG13 ALG14 ALG1 ALG2 ALG11 RFT1 ALG3 ALG9 ALG12 ALG6 ALG8 TUSC3 DDOST STT3A STT3B OSTC MAGT1 SSR3 SSR4 MOGS GANAB PRKCSH MAN1B1 MAN2B2 MGAT2 B4GALT1 FUT8 FUK POMT1 POMT2 POMGNT1 POMGNT2 B3GALT2 POMK CRPPA EKTN FKRP RXYLT1 B4GAT1 LARGE1 FAM20B XYL1 XYL2 B4GALT7 B3GALT6 B3GAT3 EXT1 EXT2 EXT13 NDST1 HS6ST1 HS6ST2 CHSY1 CHST3 CHST14 DSE CSGALNACT1 CHST6 CANTI GALNT3 GALNT4 C1GALTIC1 OGT EOGT ST3GAL3 POGUT1 POFUT1 LFNG B3GLCT PIGA PIGC PIGP PIGY PIGH PIGL PIGW PIGM PIGV PIGN PIGB PIGO PIGG PIGT PIGS PIGU PIGK PGAP1 PGAP3 PGAP2 ST3GAL5 B4GALNT1 A4GALT GFPT1 GNE NANS NPL PGMI GNPAT1 PGM3 G6PC3 DHDDS NUS1 SRD5A3 DOLK DPM1 DPM2 DPM3 MPDU1 CAD GMPPA GMPBP UGP2 UGDH SLC10A7 SLC35A1 SLC35A2 SLC35A3 SLC35C1 SLC35D1 SLC39A8 COG1 COG2 COG4 COG5 COG6 COG7 COG8 COPA COPB2 ARCN1 SEC23A SEC23B SEC24D SAR1B TRIP11 TRAPPC2 TRAPPC2L TRAPPC4 TRAPPC6B TRAPPC9 TRAPPC11 TRAPPC12 GOSR2 ATP6V0A2 ATP6AP1 ATP6AP2 ATP6V1A ATP6V1E TMEM199 CCDC115 YMA21 TMEM165 SLC9A7 TGD8 GFUS PIGF SLC37A4

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8

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LETTER TO THE EDITOR

CDG or not CDG

To the Editor,
Congenital disorders of glycosylation (CDG) are an exponentially growing group of genetic diseases. The first patients were reported in 1980 by Jaak Jaeken, and subsequently found to have PMM2-CDG.^{1,2} The actual number of CDG is over 160 and several others are in the pipeline.³ It is not always clear whether a certain disease belongs to this group. Therefore, one of us (H.H.F.) took the initiative for a discussion about this matter on occasion of the Scientific CDG Symposium 2021 (virtual symposium June 23–24, 2021) organized by Gert Matthijs. This discussion was attended by some 45 clinicians, biochemists, geneticists, researchers, and representatives of patient organizations. The discussion was moderated by Gert Matthijs and introduced by Hudson H. Freeze. Jaak Jaeken presented a brief history of the CDG nomenclature.

What about defects in glycan modifying enzymes/transporters and modifications with sulfate, phosphate, selenate, selenite, fucose, acetyl? Some were in favor of including them as CDG, others not. The patient advocacy groups would not be happy with “dropping” defects that are already settled as CDG. Anyway, defects in soluble or membrane-associated trafficking molecules (alone or in complexes) can only be considered as CDG if they have a proven effect on glycosylation. Another puzzle is *ALG13*. In yeast, it is essential for the synthesis of the lipid bound N-glycan precursor. Humans have a single X-linked *ALG13* gene, and recurrent de novo mutations in the catalytic domain cause a neurological phenotype. Homologous patient mutations impair N-glycosylation in yeast, but they do not impair N-glycosylation of serum glycoproteins in patients.⁴ Evolution and phylogenetics would say that defective *ALG13* indeed causes a CDG.

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Gene, function, or activity	Examples	CDG?
Gene known to be involved in any glycosylation pathway	PMM2, ALG1, PIGA, EXT1/2, OGT, MOGS, STT3A, MPI, DPM1, SLC35A2, POM1, PIGL, POMT1, FKRP, PAPSS1, B3GLCT, B4GALT7, SRD5A3	YES
Glycosylation gene conserved in evolution	ALG13	YES
Gene in ER, Golgi, post-Golgi trafficking that alters glycan synthesis	COG4, COG7, SEC23B, TRAPPC11, GET4	YES
Gene involved in pH or metal ion homeostasis that alters glycan synthesis	ATP6V0A2, TMEM199, ATP6AP2, SLC38A8	YES
Subunit of a glycosylation-altering molecular complex, but lacking evidence of altered glycans	TRAPPC12, TRAPPC6B	NO
Status debated without consensus	GALT, GALE, ALDOB	Yes/No?

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10

CDG nomenclature

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- Introduced in 2008
- The new CDG nomenclature uses the official gene symbol (not in italics) followed by “-CDG”
- Descriptive names such as hereditary multiple exostoses and familial tumoral calcinosis may continue to be used alongside the novel designations

Enzyme deficiency	Glycosylation designation
Phosphomannomutase-2 deficiency	PMM2-CDG (CDG-1a)
Mannosephosphate isomerase deficiency	MPI-CDG (CDG-1b)

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11

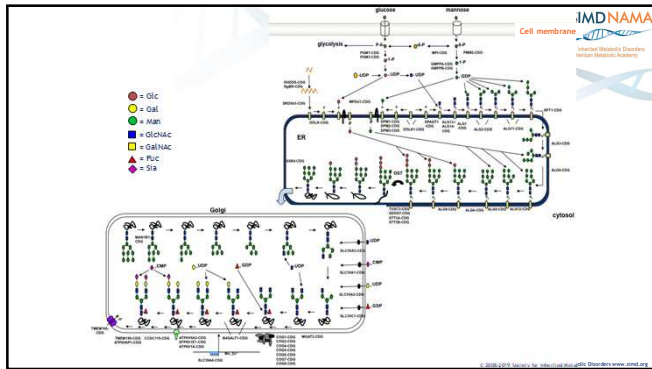
Genetics of CDGs

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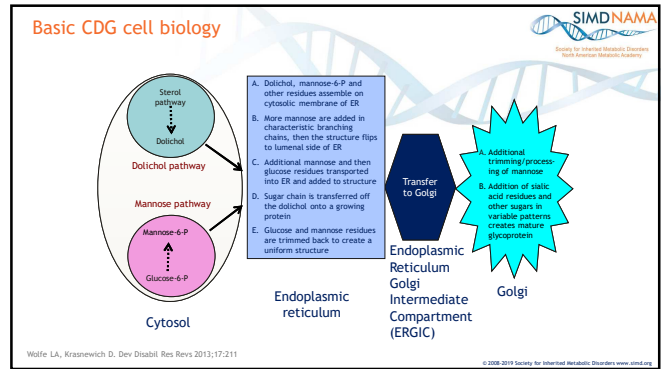
- Most CDGs are autosomal recessive (PMM2-CDG prevalence may be as high as 1 in 20,000)
- X-linked disorders include MAGT1-CDG, SSR4-CDG, PIGA-CDG and SLC35A2-CDG
- Autosomal dominant disorders due to loss-of-function mutations cause haploinsufficiency
 - EXT1-CDG
 - EXT2-CDG
- De novo mutations cause X-linked ALG13-CDG and SLC35A2-CDG

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12



13



14

CDG classification

- Each CDG type is defined by a specific enzyme defect and the mutation in its underlying gene
- Most CDG mutations are hypomorphic and allow some glycan synthesis
- There are more than 160 types of CDGs
- PMM2-CDG is the most frequent one: 1500+ cases worldwide
- New disorders continue to be identified mostly by exome or genome sequencing now

15

Functions of N-glycans proteins

- N-linked glycans are attached to asparagine on the amide motif
- Protein folding & stability
- Protein-protein complex formation
- Imparting protease resistance
- Signaling
- Cell-cell recognition

N-linked (ER)

Key:
 ◆ NeuAc ● Gal ● Glc ● Man ▲ Fuc ■ GalNAc ■ GlcNAc

16

Functions of O-glycans proteins

- O-linked glycans attach to the protein at the OH motif of serine or threonine
- Antibacterial agent in saliva
- Defines ABO blood groups
- Involved in sperm motility, sperm-egg binding, preventing polyspermia
- Cell adhesion & migration
- Lymphocyte targeting & inflammatory response

O-linked (Golgi)

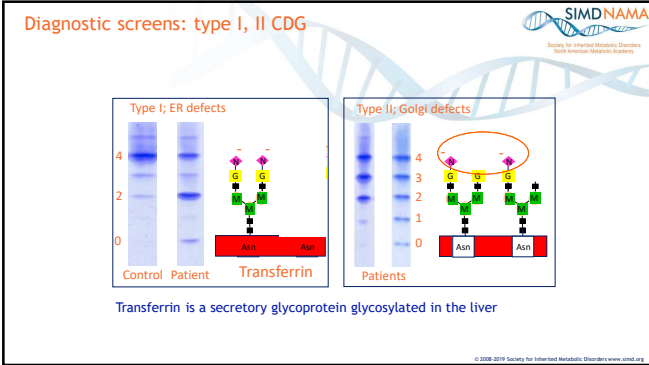
Key:
 ◆ NeuAc ● Gal ● Glc ● Man ▲ Fuc ■ GalNAc ■ GlcNAc

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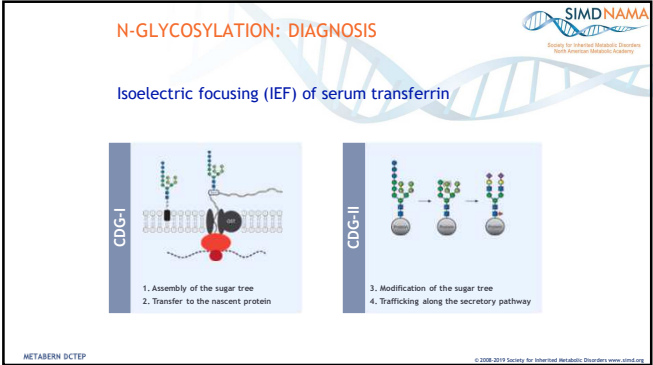
Perinatal/natal CDG presentations

Disorders represented	Died	Symptoms by frequency
ATP6V0A2	16	Liver involvement 52/57
SRD5A3	12 1	Hypotonia 51/58
PMM2	10 3	Eye abnormalities 47/58
ALG6	6 2	Dysmorphic features 44/58
ALG1	3 2	Feeding problems 30/58
MPI	3	Abnormal coagulation 15/58
COG7	3 3	Increased TSH 5/58
ALG8	1	Cardiomyopathy 3/58
DPM3	1	
B4GALT	1	
COG8	1	
SCL35A	1 1	

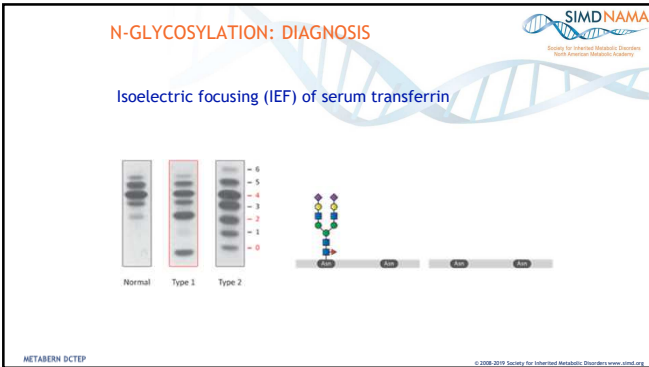
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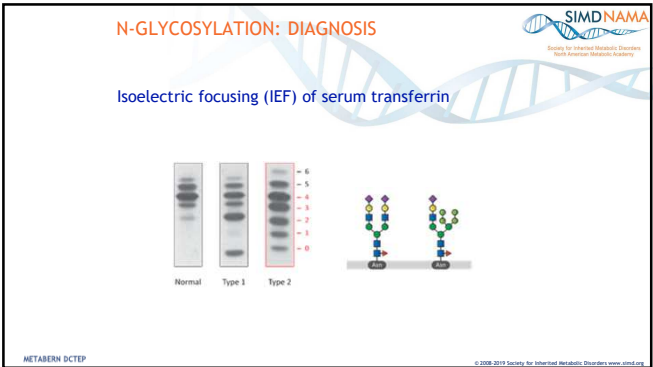
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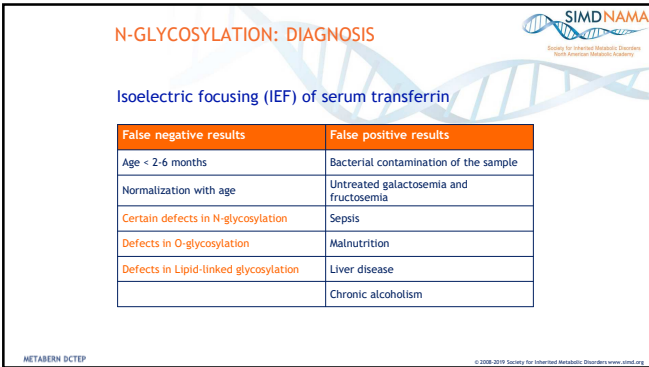
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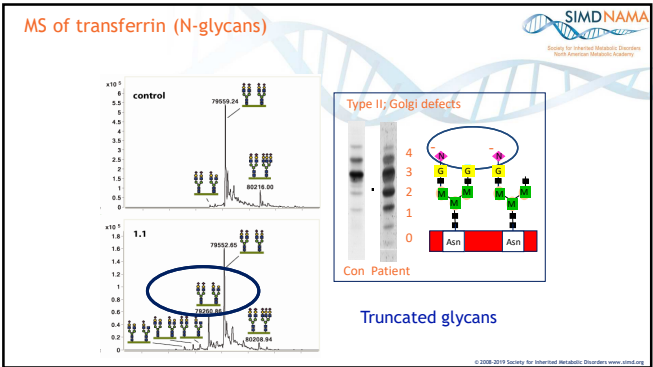
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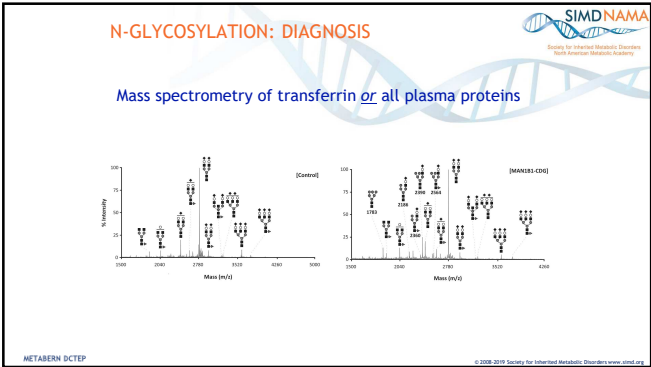
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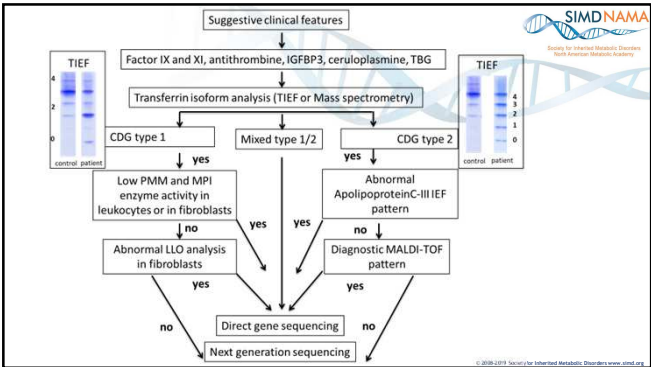
N-GLYCOSYLATION: DIAGNOSIS

Additional biochemical findings

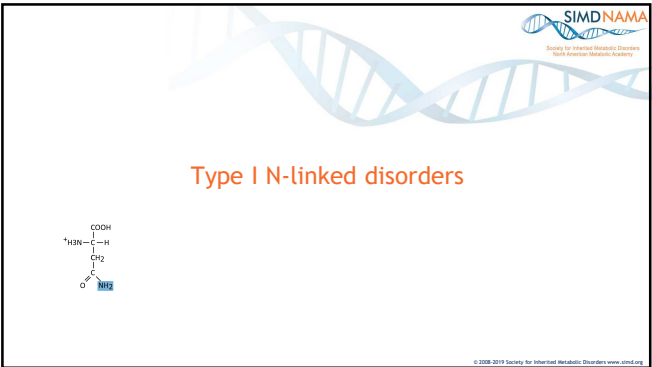
Liver transaminases ↑ (AST > ALT)	Protein C ↓
Cholesterol ↓	Protein S ↓
Albumin ↓	Antithrombin III ↓
Arylsulfatase A ↑	Factor IX ↓
TSH ↑ with normal or slight T4 ↓	Factor XI ↓

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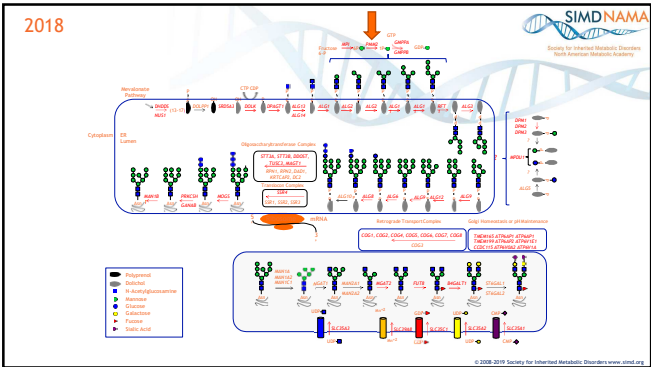
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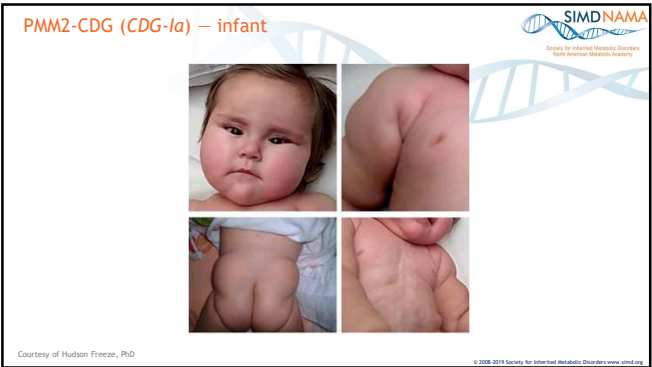
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28



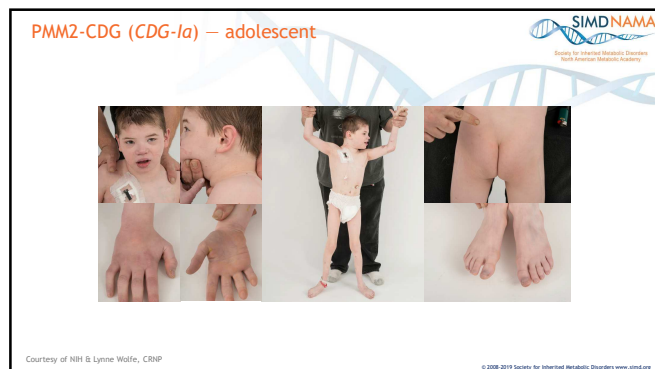
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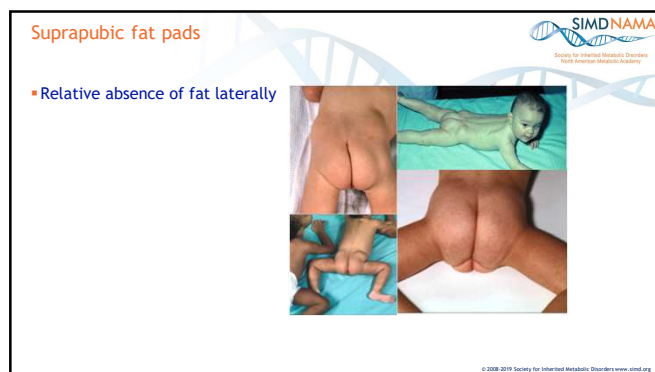
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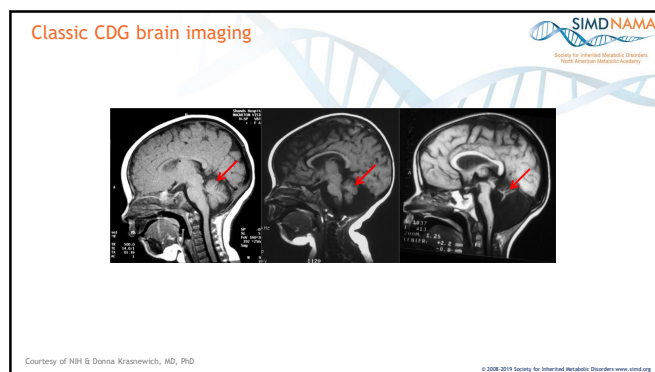
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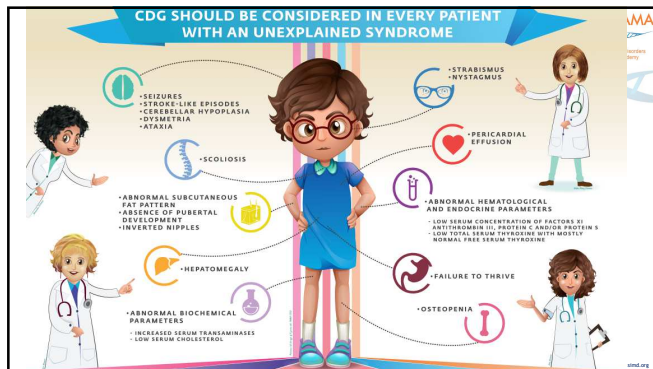
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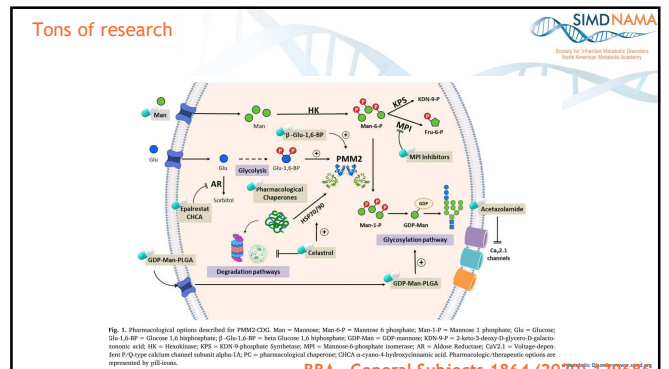
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36



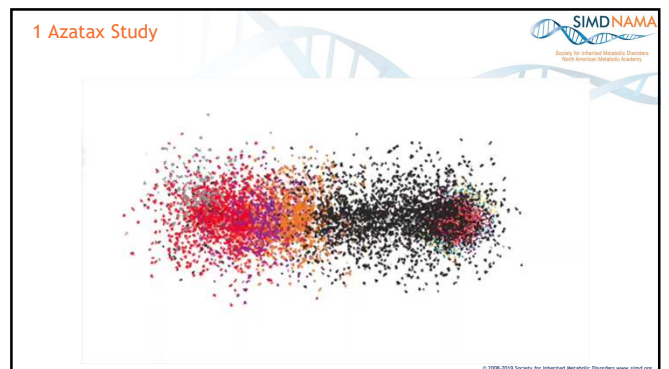
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38



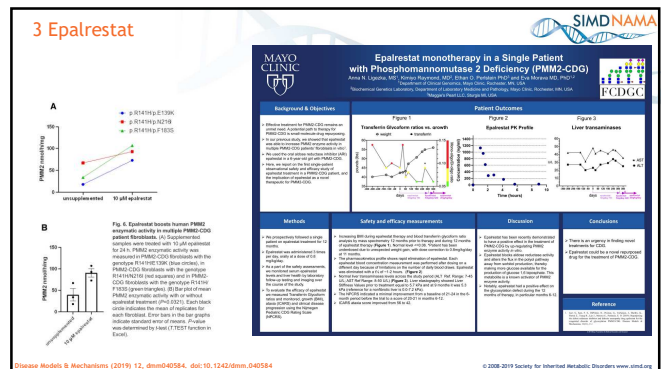
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40



41



42

MPI-CDG (CDG-Ib)

Loss of function of mannose-phosphate isomerase (MPI)

- Prevents synthesis of mannose from fructose-6-phosphate

Unique hepato-intestinal disease

- Recurrent vomiting, abdominal pain, protein-losing enteropathy, gastrointestinal bleeding
- Recurrent thrombosis, coagulopathy, liver disease/hepatic fibrosis, cirrhosis
- Hyperinsulinemic hypoglycemia when young
- No dysmorphism, no – or only minor – neurological involvement

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43

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NORMAL GLYCOPROTEIN
NO CDG

INCOMPLETE SUGAR ANTENNAS
CDG

ABSENCE OF SUGAR ANTENNAS
CDG

GASTROINTESTINAL SYSTEM
Vomiting | Diarrhea | Villous atrophy | Lymphangiectasia | Failure to thrive | Protein-losing enteropathy | Malabsorption

ENDOCRINE SYSTEM
Hyperinsulinemic hypoglycemia

LIVER
Hepatomegaly | Hepatic fibrosis | Cirrhosis | Hepatic failure | Thrombosis/bleeding

LABORATORY TEST
Hypoalbuminemia | Antithrombin, protein C, factor XI deficiency | Serum transferrin isoelectrofocusing type 1 pattern | Phosphomannose isomerase deficiency in leukocytes and fibroblasts

OTHER SYMPTOMS
Prolonged bleeding | Easy bruising

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MPI-CDG (CDG-Ib)

CDG-Ib is the “classic” treatable type, so diagnosis is important

Treatment is oral mannose, 1 g/kg/day divided into 5 doses (www.saccharides.net)

Treated children should be followed carefully for progressive liver disease

- Symptoms that improve include diarrhea, coagulopathy, and hypoglycemia
- After several months, transferrin isoelectric focusing normalizes

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Type II N-linked disorders

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46

PGM1-CDG

Pierre Robin, bifid uvula, hypoglycemia, liver disease, endocrine

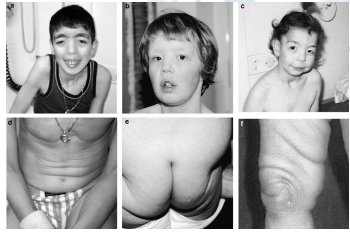
Coagulation disorder, muscle disease, cardiomyopathy



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47

ATP6V0A2-CDG



Autosomal recessive cutis laxa

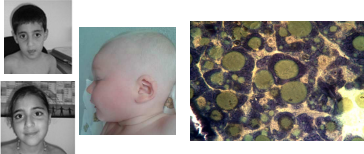
Morava et al. EJM, 2006

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48

Defects of Golgi with liver disease

- No significant dysmorphic features
- "Wilson like" phenotype
- Progressive liver disease: steatosis
- Liver transplantation for treatment



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49

Defects of Golgi with liver disease

Presentation	CCDC115-CDG	TMEM199-CDG	ATP6AP1-CDG
Liver involvement	+	+	+
Developmental delay	+	-	+/-
Low ceruloplasmin and copper	+	+	+
High cholesterol	+	+	+/-
High AST, ALT, ALP	+	+	+/-

Janssen et al, Am J H Gen, 2016, Janssen et al, Nature Rev, 2016

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Mixed N + O-linked disorders



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51

COG7-CDG

- Adducted thumbs
- Microcephaly
- Severe growth delay
- VSD
- Hyperthermia



Morava, (2009), Eur J Hum Genet, 17: 1099.

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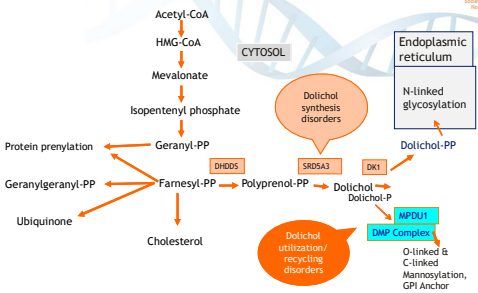
52

Dolichol disorders

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53

Dolichol synthesis pathway



Wille- LA et al, Am J Med Genet Part C Semin Med Genet 2012 Nov 15;161(4):322

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SRD5A3-CDG (CDG-1q)

Morava et al., Brain, 2011 and Wolfe LA et al., Am J Med Genet Part C Semin Med Genet 2012 Nov 15;164(4):322

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Dolichol disorder presentations

Dysmorphic Acquired microcephaly Cortical atrophy Cerebellar atrophy Developmental delay/intellectual disability Seizures Ichthyosis Stroke-like episodes Hypotonia Ataxia/spasticity Cortical visual impairment	Pigmentary retinopathy Nystagmus/optic atrophy Coloboma Cataracts/glaucoma Microphthalmia Dilated cardiomyopathy Congenital heart defect Cardiac dysrhythmias FTT/feeding problems Liver dysfunction Coagulopathy Microcytic anemia Muscular dystrophy phenotype/elevated CK
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GPI anchor disorders

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57

GPI anchor synthesis

Ng and Freeze, (2015) J Inher Metab Dis, 38:171

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58

Faces of GPI Anchor patients

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59

LIPID-GLYCOSYLATION: DIAGNOSIS

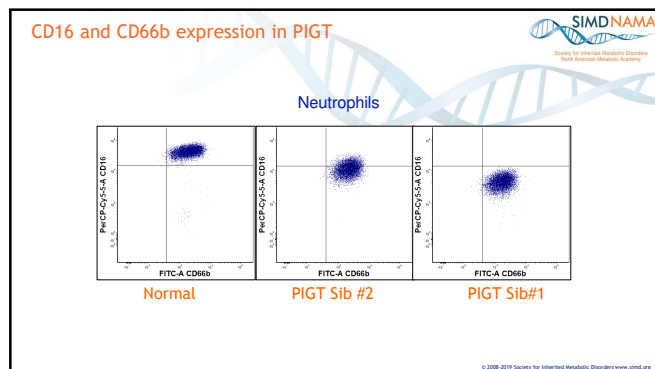
GPI anchor

- FACS analysis of GPI bound factors (e.g. CD59, CD16, CD24 ↓)
- Alkaline phosphatase ↑↑

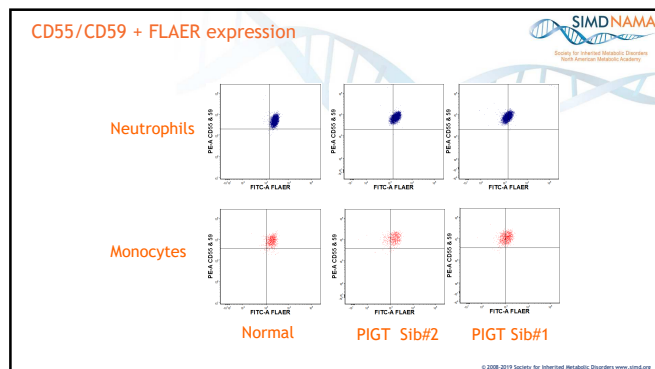
MATERN DCTP

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60



61



62

GPI anchor presentations

Multiple congenital anomalies	Macrocephaly
Seizures	Nephrocalcinosis
Hypoplastic nails	FTT/feeding problems
Skeletal abnormalities	Thrombosis
Hyperphosphatasia	Hemolytic anemia
Hypophosphatasia	Frequent infections
GU anomalies/renal cysts	Ichthyosis
Abnormal MRI	Restrictive cardiomyopathy/
Coloboma	congenital heart defects
Down gaze ophthalmoplegia	Abnormal lung anatomy
Hearing impairment	Inverted nipples
Developmental delay/	Hypotonia
Intellectual disability	

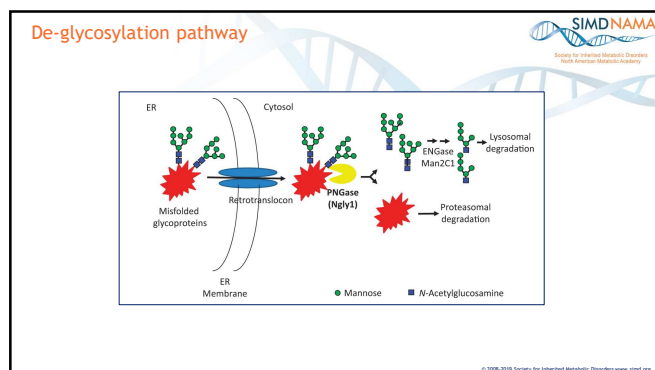
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63

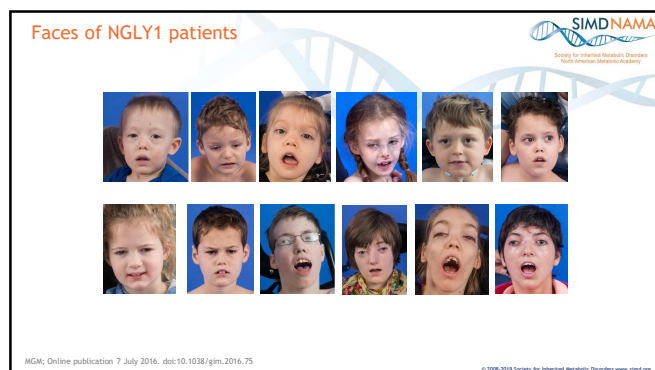
De-glycosylation
CDDG

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64



65



66

New NGYL1 clinical findings

- Low CSF protein and albumin levels
- Abnormal neurotransmitter levels
- MRI white matter disease
- Optic atrophy & retinal degeneration
- Dyssynchronous 8th cranial nerve transmission on ABR
- Abnormal liver texture & size on fibroscan & ultrasound
- Demyelinating peripheral neuropathy
- Decreased sweat response on autonomic testing
- Consistently affectionate and happy demeanor



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Treating CDGs



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Treatments for CDGs

Dietary

- MPI-CDG: Mannose
- Galactose
 - PGM1-CDG
 - SLC35A2-CDG
 - SCL35C1-CDG (+/- Fucose)
- GNE-CDG: ManNAc
- Triacetyluridine (Xuriden)
 - CAD-CDG
 - SLC35A2-CDG
- MAGT1-CDG (aka XMEN syndrome): Magnesium
- SLC39A8-CDG (+/- Galactose): Manganese

Organ Transplantation

- MPI-CDG: liver
- DOLK1-CDG: heart
- TMEM199-CDG: liver
- ATP6AP1-CDG: liver
- PGM3-CDG: bone marrow



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69

Limitations

- No controlled trials
 - SUGAR Trial for PGM3-CDG failed
- Families starting treatment on their own
 - Limits naïve participants for future study
- Lack of understanding about glycan turnover
- Lack of knowledge about how fast oligosaccharides are incorporated into glycans
- Current Biomarkers
 - Normalizing of Carbohydrate Deficient Transferrin
 - Correcting glycosylated proteins
 - Use of other clinical endpoints
 - Dosing limited by osmotic diarrhea
- Has been difficult to obtain special sugars
- Lack of insurance coverage
 - It is "just a sugar"
 - Xuriden is an off-label without research to support its use in these disorders



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70

When to think of CDGs?

- Concern may occur in any age group
- Any time you are seeing dysmorphic patients
- Any single symptom unexplained by another diagnosis such as anemia or immune deficiency (SEC23B, LADII)
- Any time you are considering testing for mitochondrial disorders or sterol defects
- Any time a patient presents with a static or progressive neurodegenerative disorder
- Any time multiple systems are involved
- Secondary glycosylation abnormalities can be seen in mitochondrial disorders



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71