Updates on phenotypes in CDG

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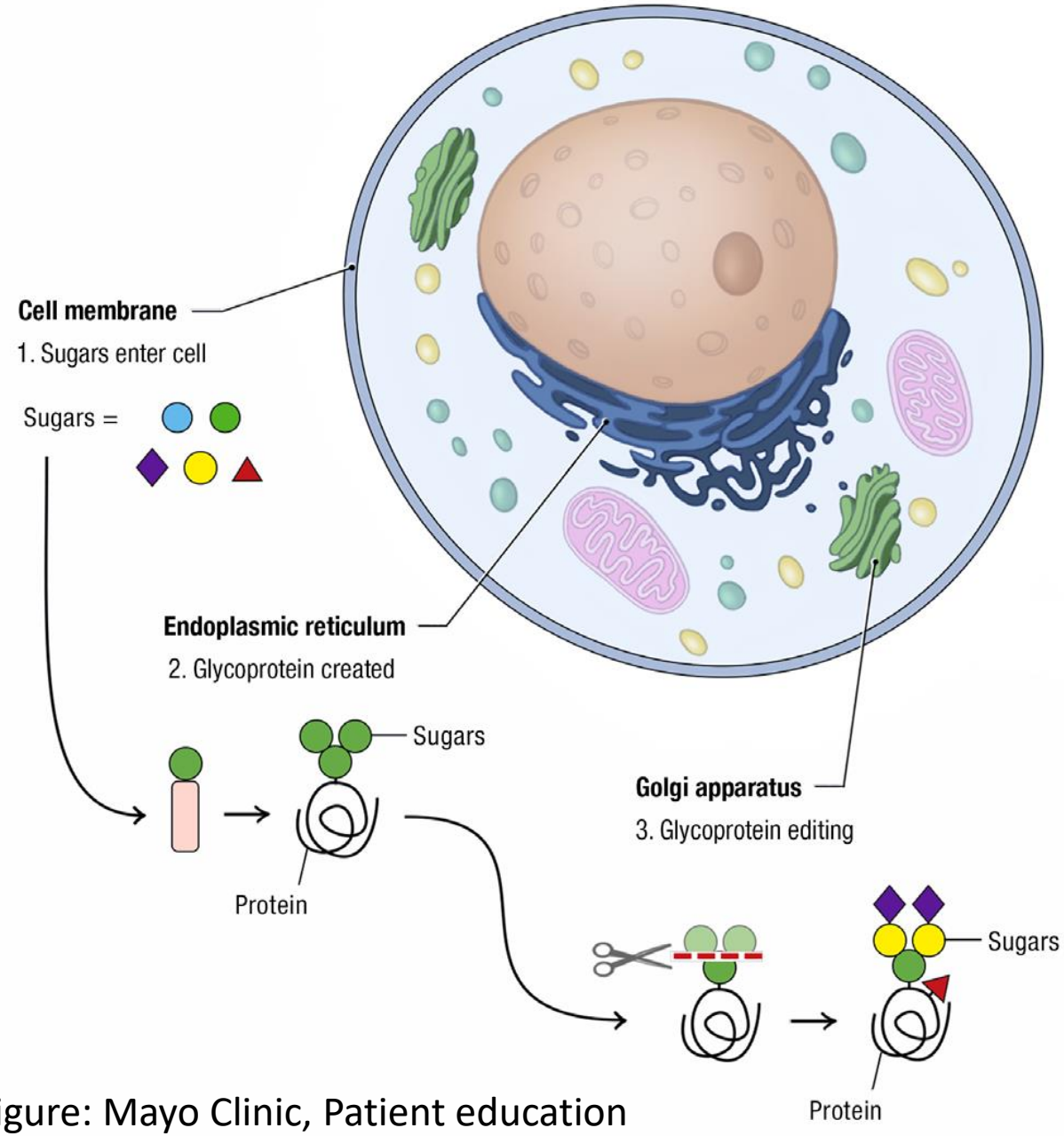
Normal glycosylation in the cell

Most of our functional proteins are glycosylated

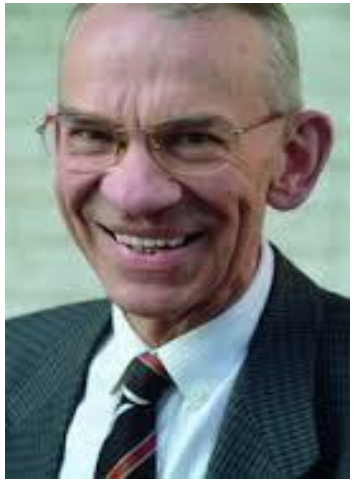
-N-linked glycosylation
-O-Linked glycosylation
-Combined glycosylation pathways
-Lipid glycosylation and other pathways



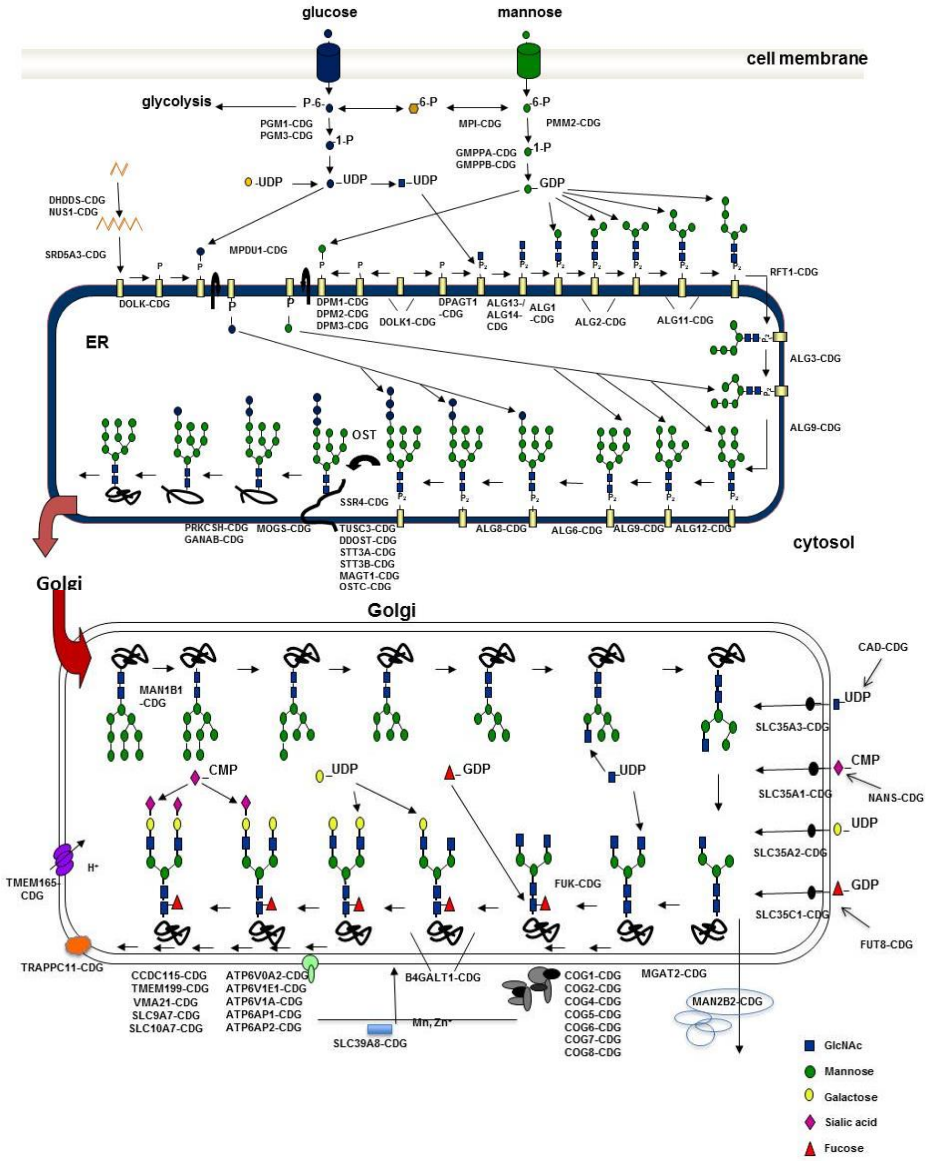
Schematic figure: Mayo Clinic, Patient education

Congenital Disorders of Glycosylation

The first CDG was discovered by Prof Jaeken, 1980

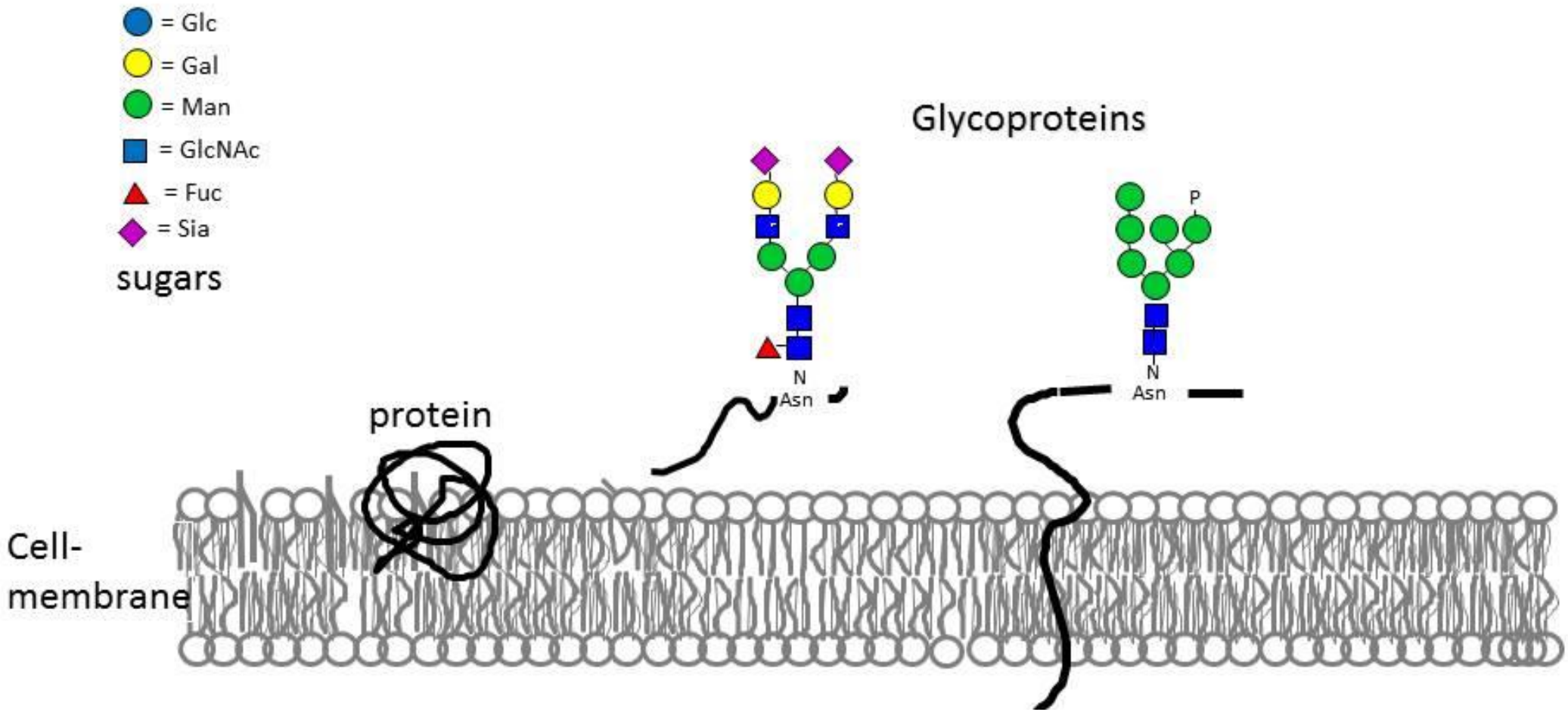


More than 160 types are known (Ferreira et al, JIMD, 2019)



N-linked glycosylation

Glycans and the glyco-code



Kliegman; Nelson Textbook of Pediatrics, 21th edition, Morava and Witters, Chapter on CDG

Frontiers of CDG Consortium Sites

FCDGC

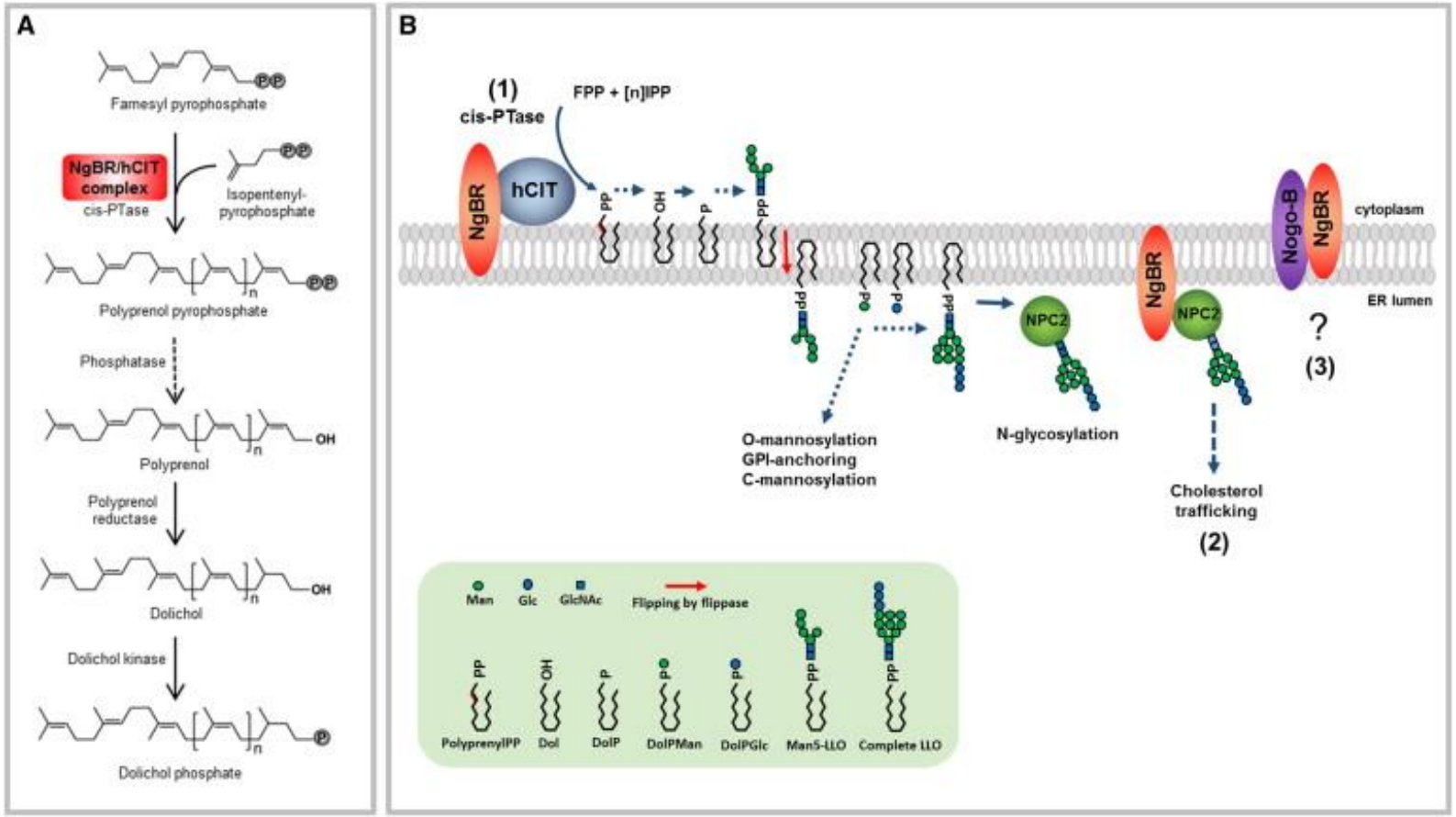
- Mayo Clinic Rochester
- Baylor College of Medicine
- Boston Children's Hospital
- Children's Hospital of Colorado
- Children's Hospital of Pittsburgh
- Children's Hospital of Philadelphia
- National Human Genome Institute
- Seattle Children's Hospital
- Tulane University Medical School
- University of Alabama
- University of Minnesota Masonic Children's Hospital
- University of Utah
- Sanford Burnham Institute

CDG Centers of Excellence
Work together with the patient associations

Diagnostics, biomarker and therapy development

Old genes –new phenotypes

DHDDS-CDG



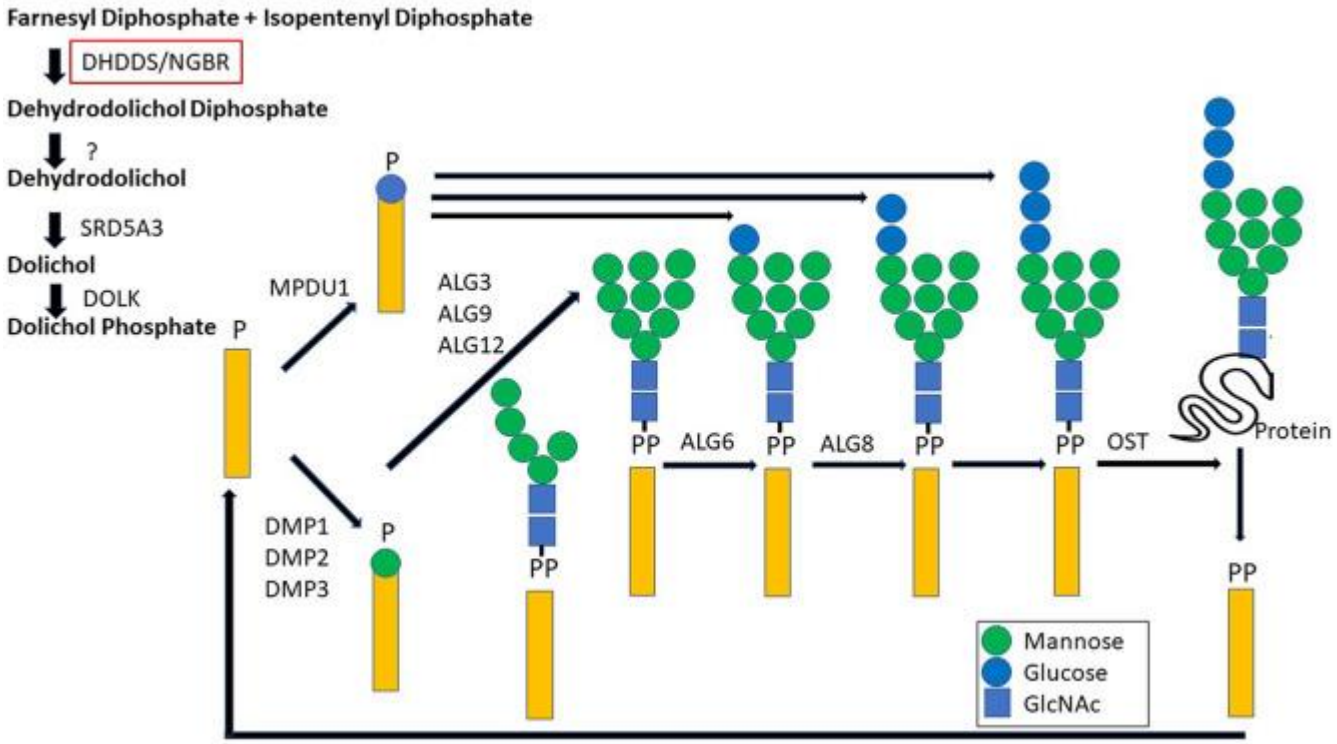
-*DHDDS* encodes for the catalytic subunit (DHDDS) of the enzyme *cis*-prenyltransferase

-It's involved in dolichol biosynthesis and protein glycosylation in the ER

-It forms a complex with NUS1 (NUS1 is stabilizing NPC2 for ER cholesterol transport)

DHDDS-CDG

Hypotonia
Hepatomegaly
Micropenis
Renal Failure
Epilepsy
Visual loss
Sensorineural deafness
FTT
Died at 8 months

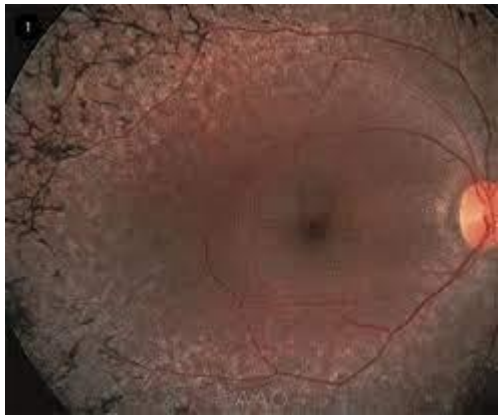


DHDDS	c.192G > A (p.W64X)	Stop
	c.441-24A > G (p.C148EfsX11)	Intron (splice)

Abnormal transferrin

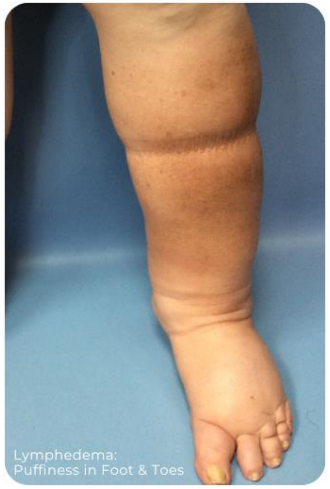
DHDDS(-CDG?)

Recurrent K42E *DHDDS* variants lead to an AR form of retinitis pigmentosa (RP 59)



Recent reports show multisystem presentation in some of the K42E homozygous patients

Ataxia, seizures, edema, hypothyroidism, hepatopathy



Mousa J et al, MGM, 2022

De novo DHDDS variants cluster around the active site of the DHDDS subunit cause a neurodevelopmental and neurodegenerative disorder with myoclonus

Galos et al, 2022

Generalized epilepsy

Action myoclonus

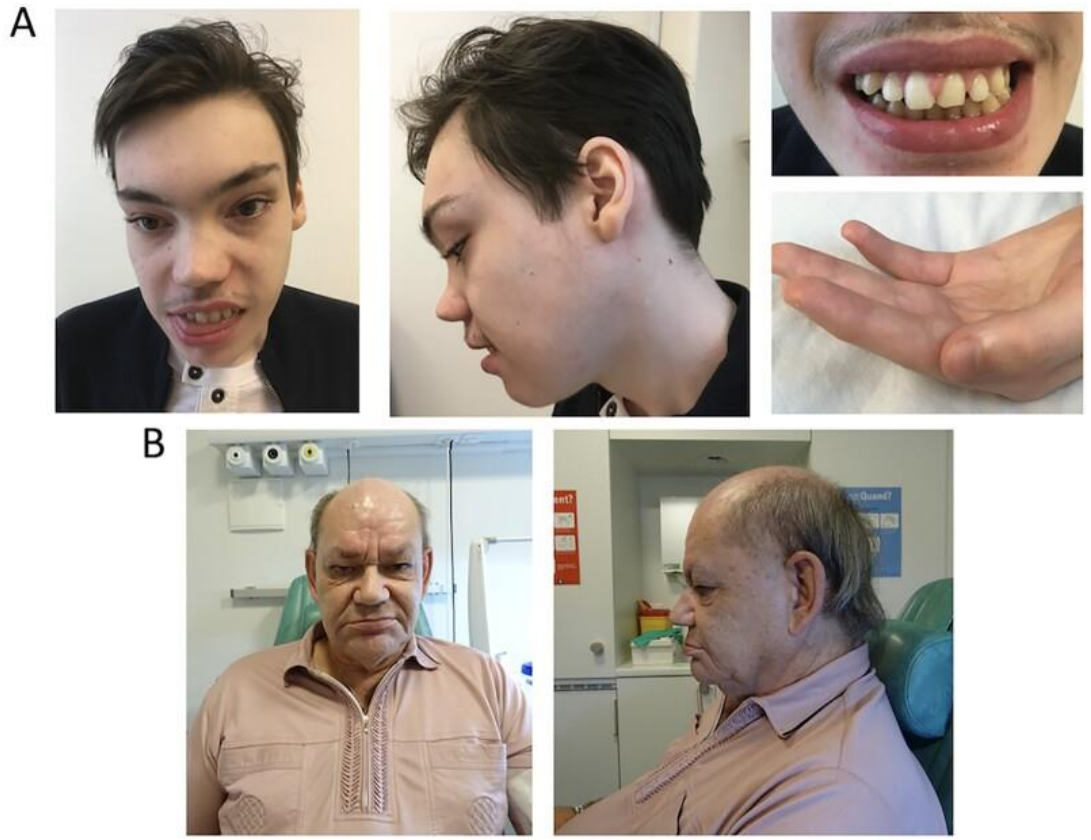
Cortical tremor and ataxia.

Slow neurological decline

Hyper- or hypokinetic movements

Cognitive deterioration

Psychiatric disturbances



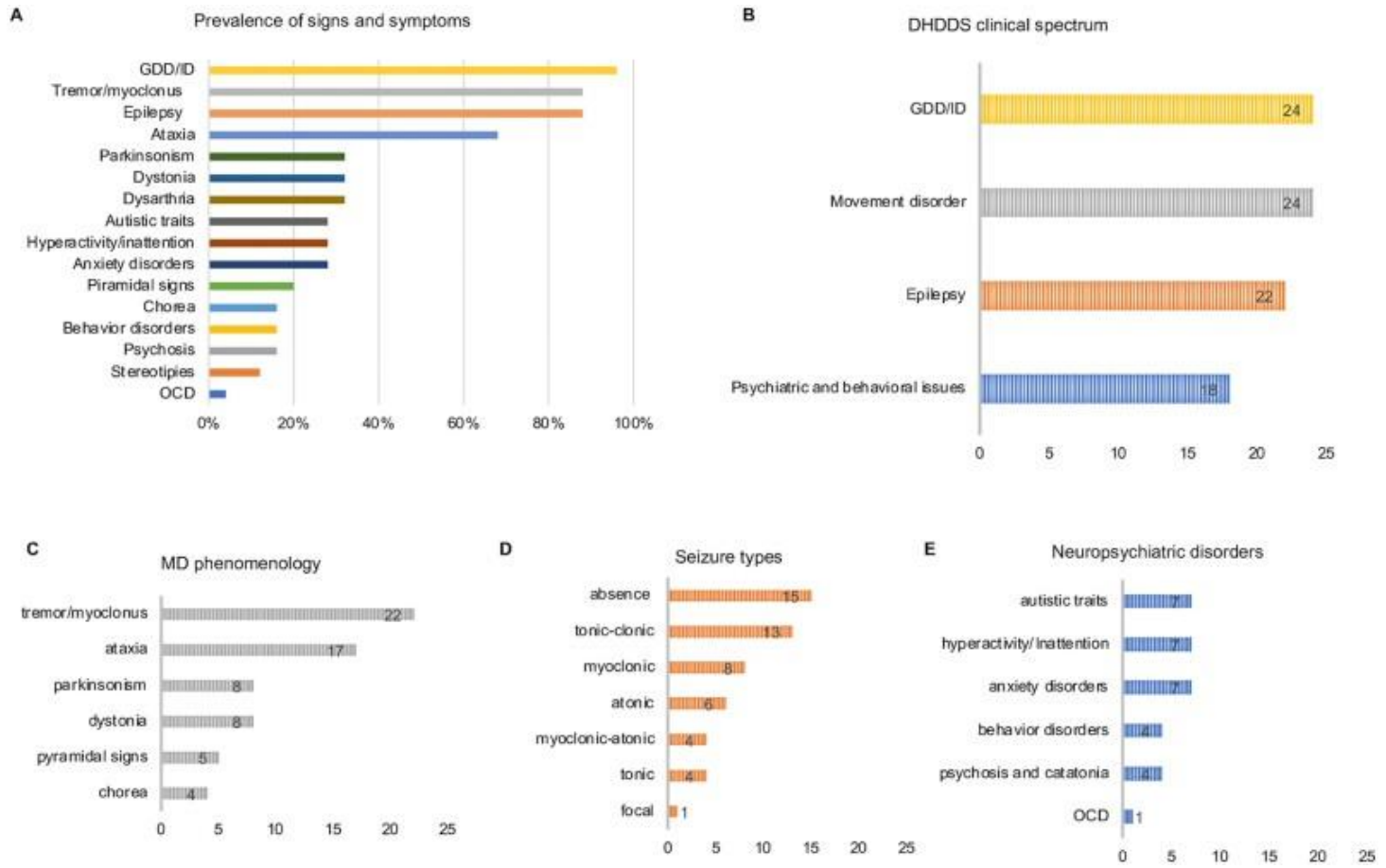
Two recurring *de novo* substitutions

c.632G>A (p.Arg211Gln)

c.110G>A (p.Arg37His)

De novo DHDDS variants cause a neurodevelopmental and neurodegenerative disorder with myoclonus

Galos et al, 2022

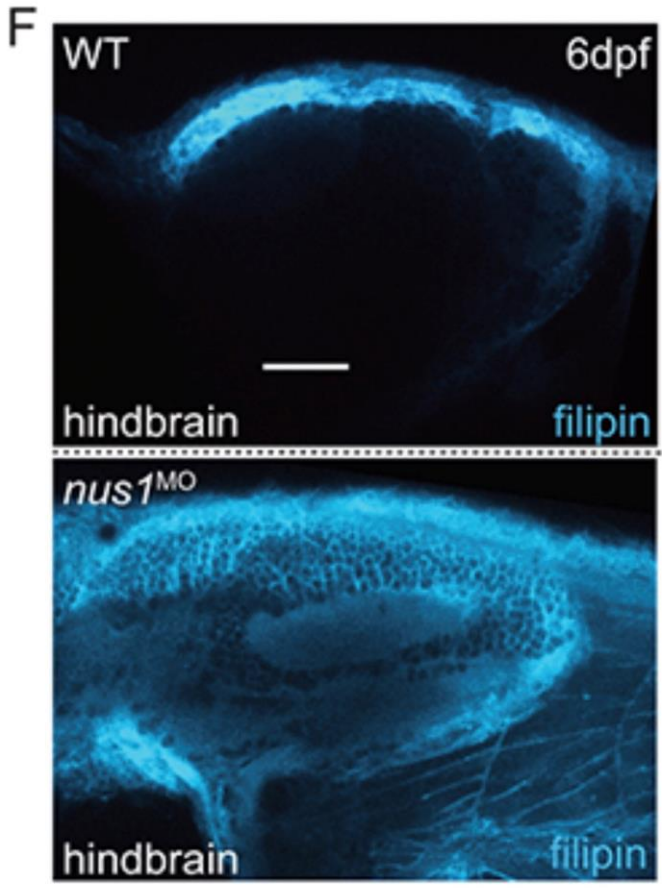


Disorder on the intersection of CDG and inherited storage diseases with several features akin to of progressive myoclonus epilepsy such as neuronal ceroid lipofuscinosis and other lysosomal disorders.

De novo DHDDS variants cause myoclonic epilepsy and Parkinsonism

- storage of lipidic material and altered lysosomes in myelinated fibres and fibroblasts
- dysfunction of the lysosomal enzymatic scavenger machinery.
- Serum glycoprotein hypoglycosylation is not detected
- the urinary dolichol D18/D19 ratio is normal.

De novo NUS1 variants cause myoclonic epilepsy and Parkinsonism



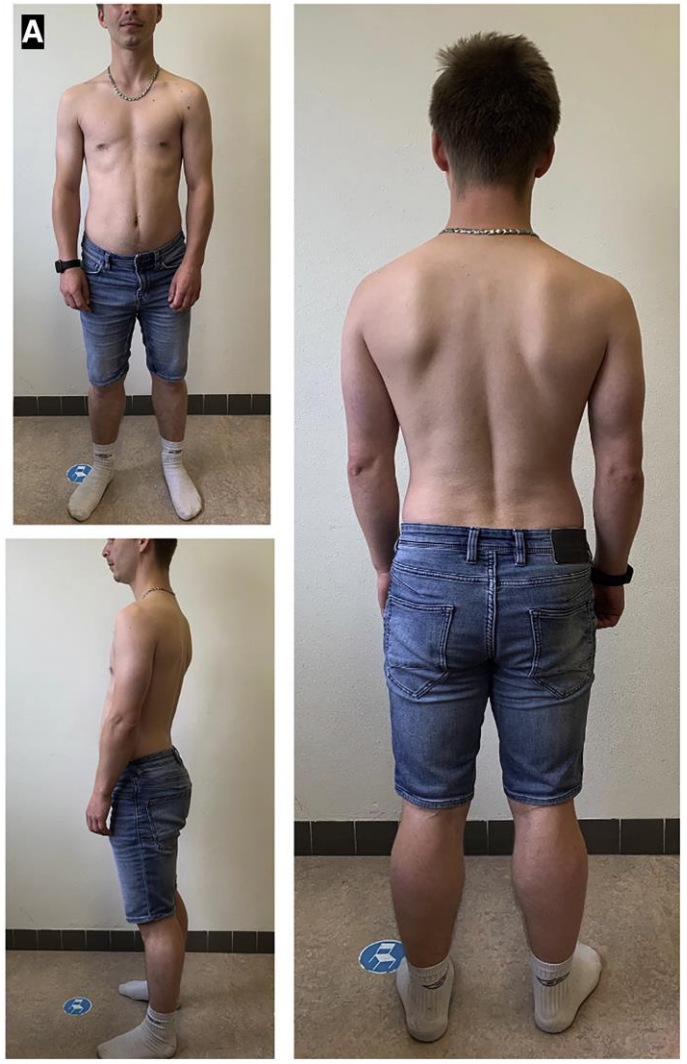
New disorders: the STT3A story

Family 1

17 year old male with increased muscle tone, muscle pain, joint pain and short stature

His brother has similar features and some learning difficulties

Mother has multiple joint arthritis, fibromyalgia, short stature and macrocephaly



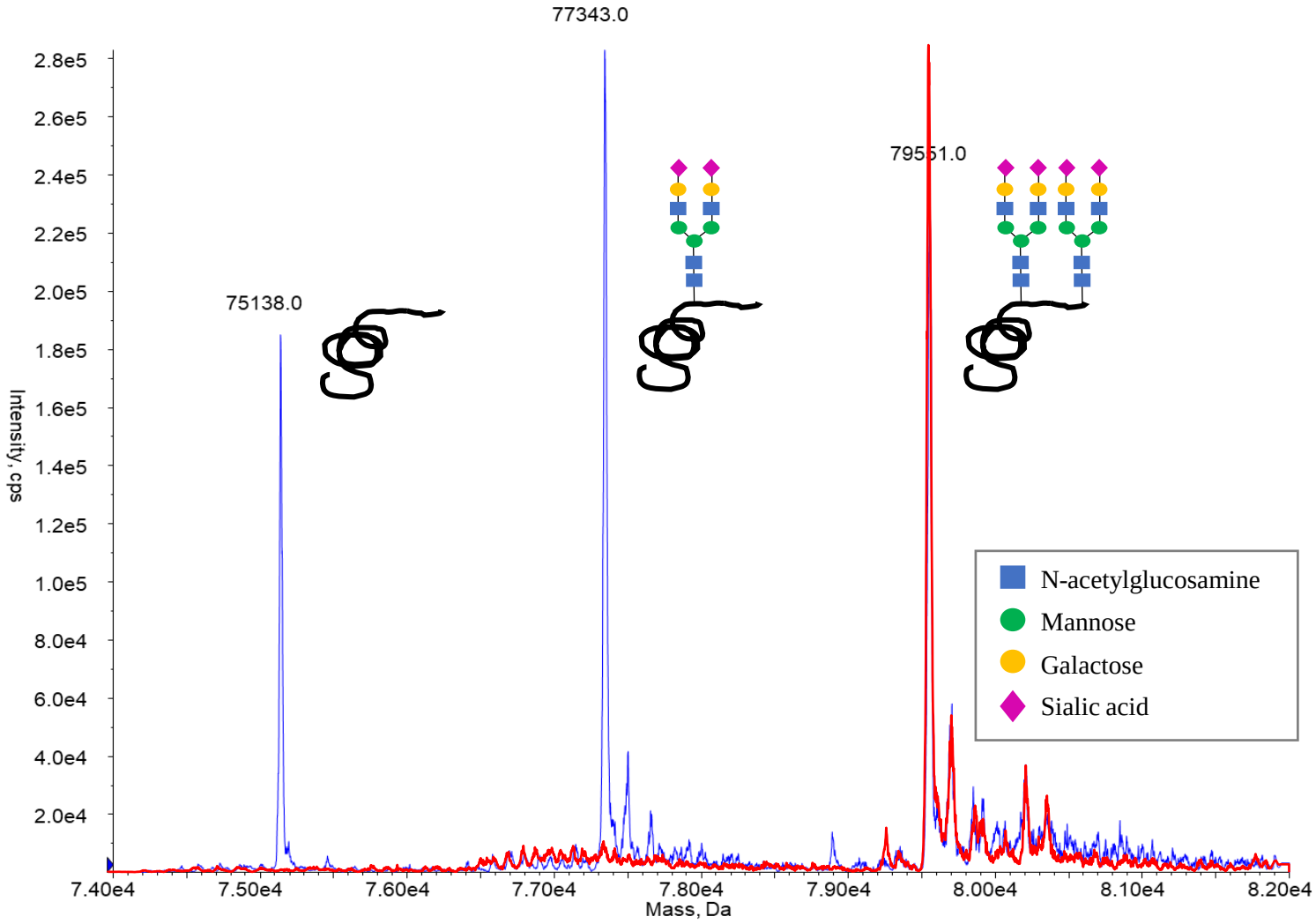
Biochemical serendipity during metabolic screening

***1. Transferrin glycosylation** (ESI-MS):*

* ↑ Mono−oligosaccharide/Di−oligosaccharide
* ↑ A−oligosaccharide/Di−oligosaccharide

CDG type I

The CDG test was positive in Both brothers and mother

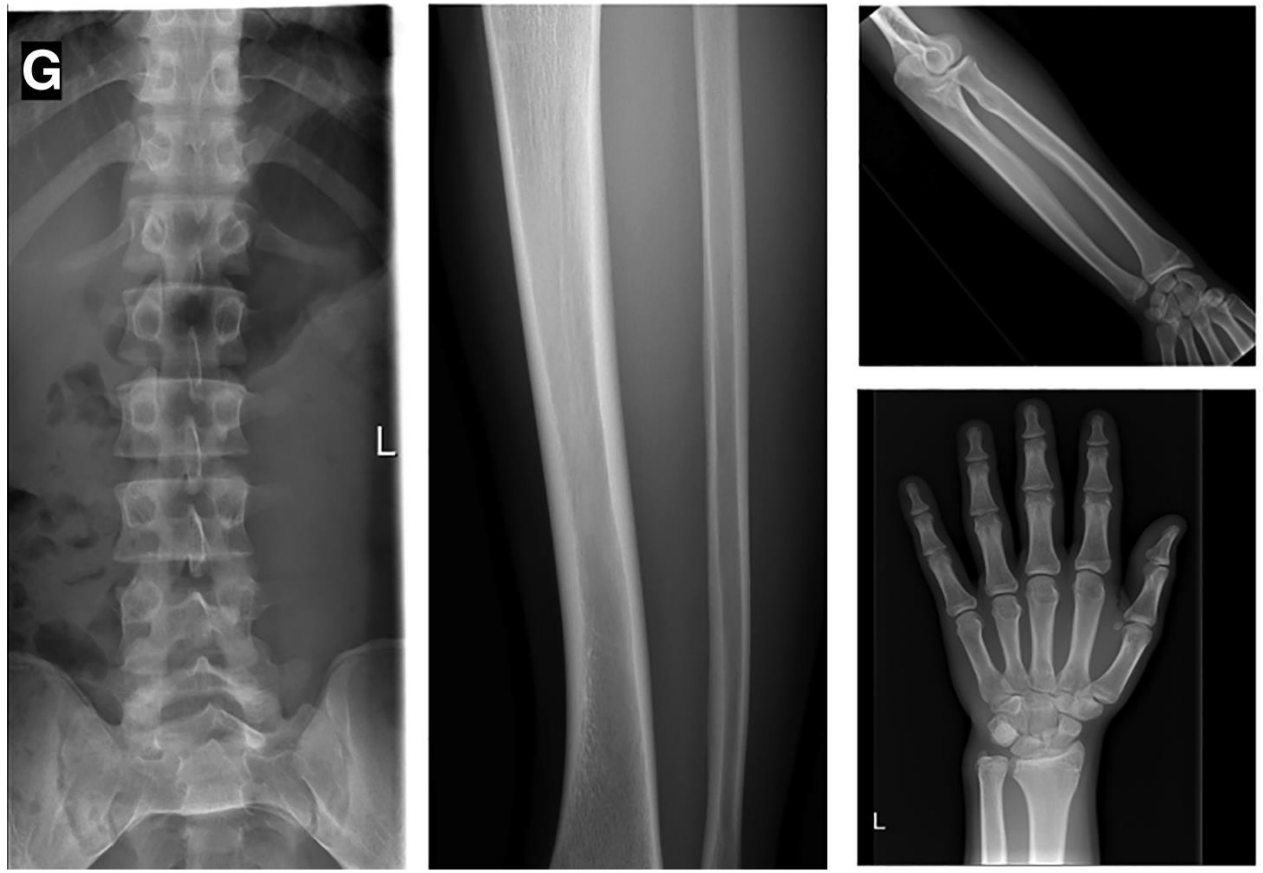


Is this an autosomal dominant CDG?….

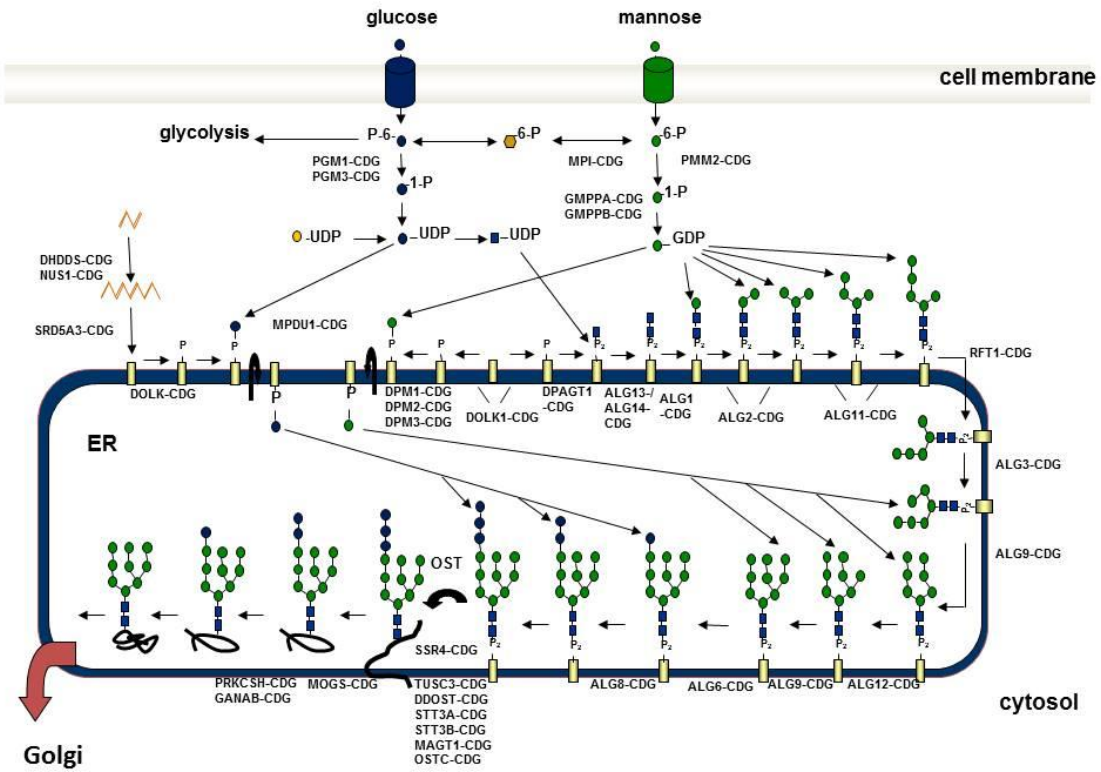
Exome sequencing (three times during 8 years…)

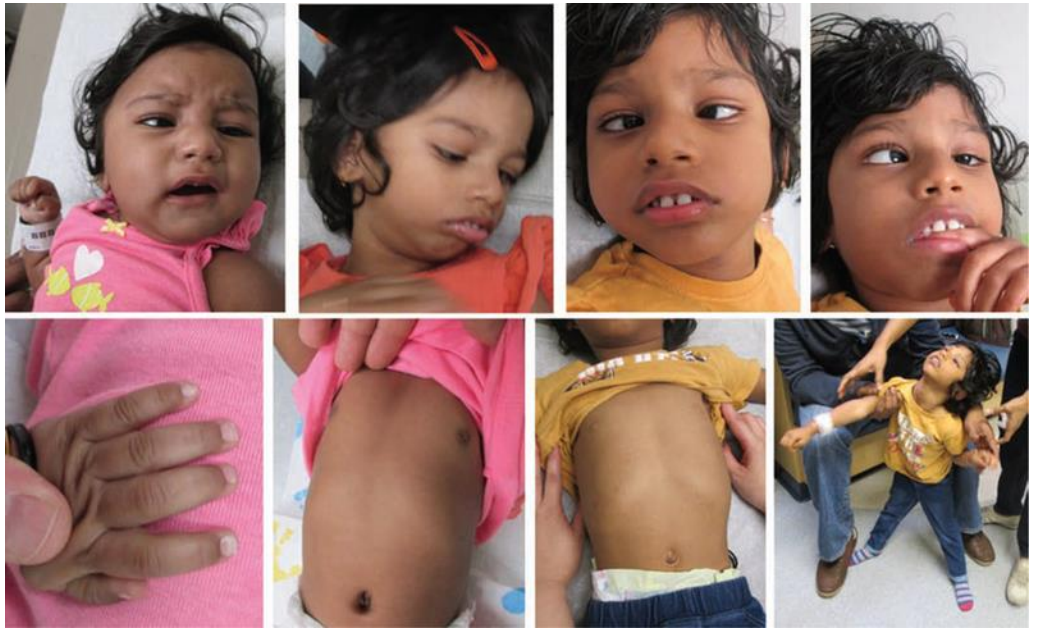
Negative, but carrier for STT3A (coming from mother)

No known association between STT3A and musculo-skeletal findings



STT3A-CDG



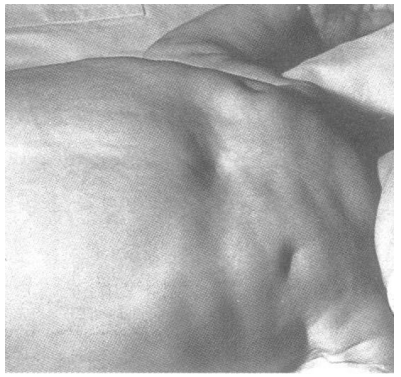


Autosomal recessive CDG:
Severe developmental delay
Microcephaly
Seizures
Visual loss
Failure to thrive

No clinical overlap

Family 2

3 months old baby with delayed motor development and inverted nipples



Father with severe hip arthritis, hip replacement at 40 years, increased muscle tone, and short stature

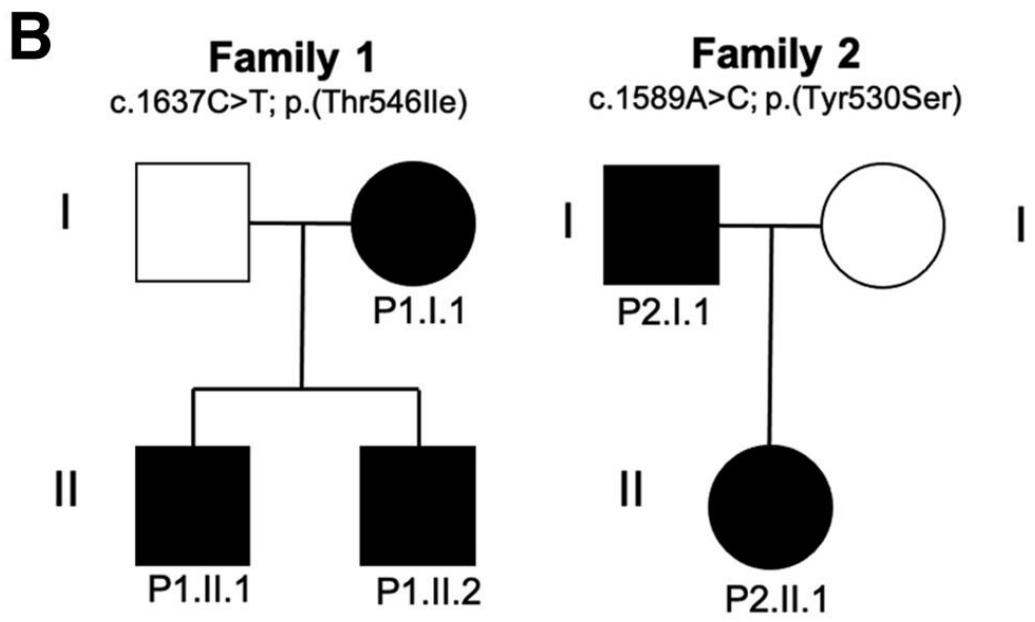
***1. Transferrin glycosylation** (ESI-MS):*

* Mono−oligosaccharide/Di−oligosaccharide ↑
* A−oligosaccharide/Di−oligosaccharide ↑

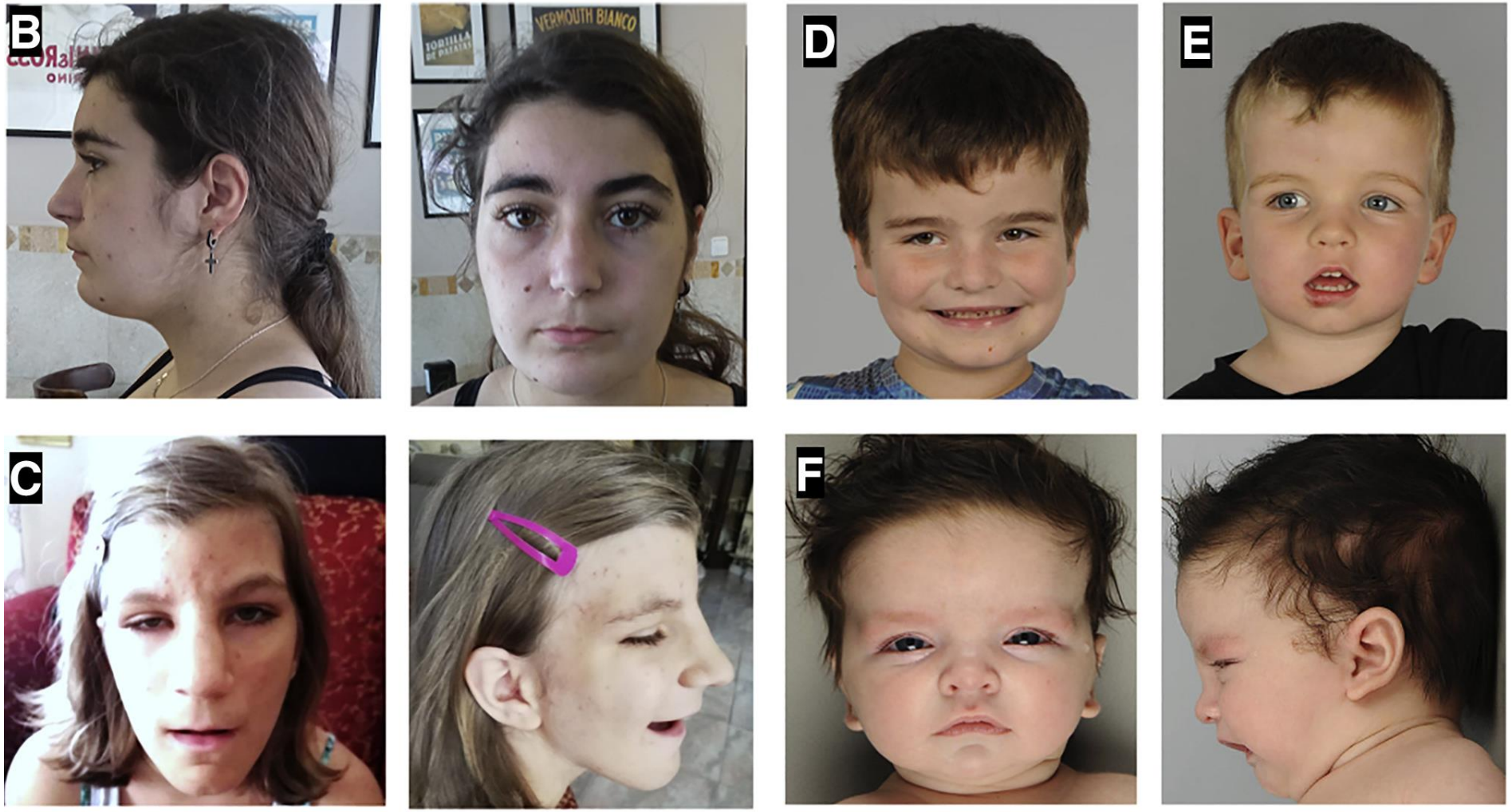
Exome sequencing (two times during 4 years…)

Negative, but carrier for STT3A (coming from Father)

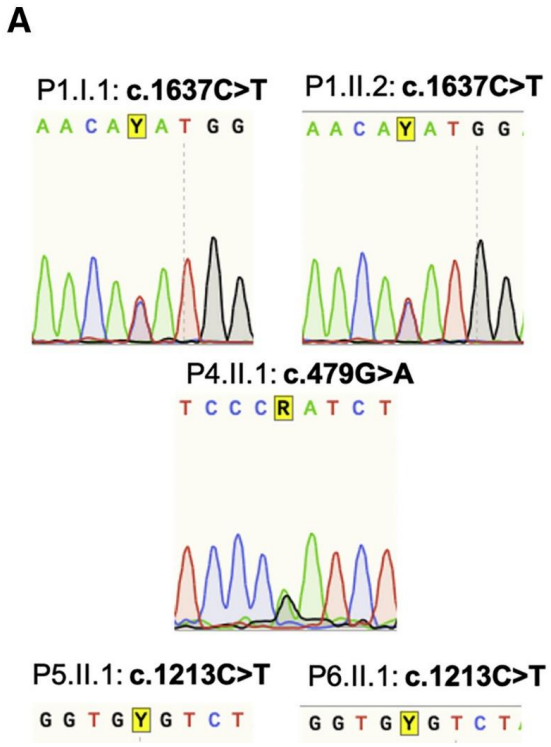
Is it possible that STT3A could cause an AD disease?

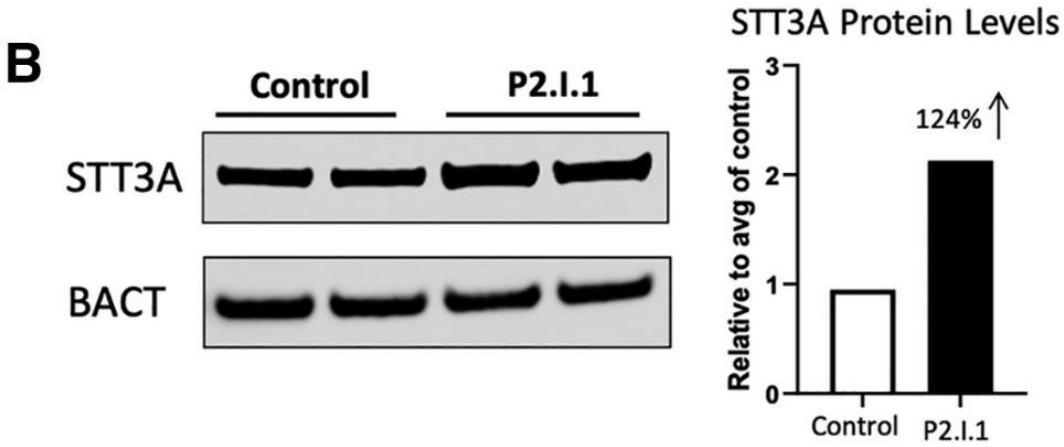


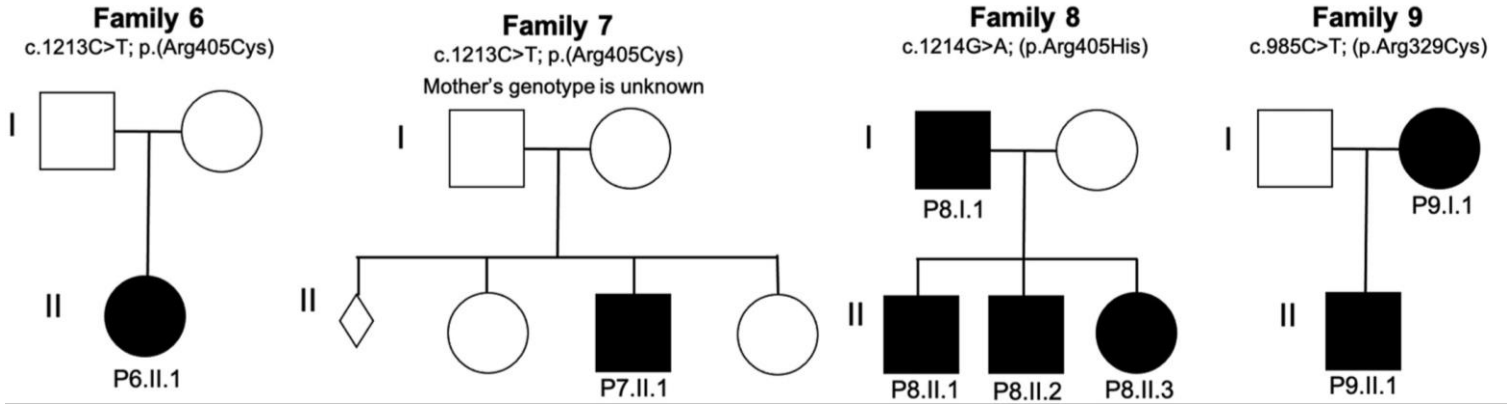
Search for other families (AD unsolved CDG or STT3A carriers)



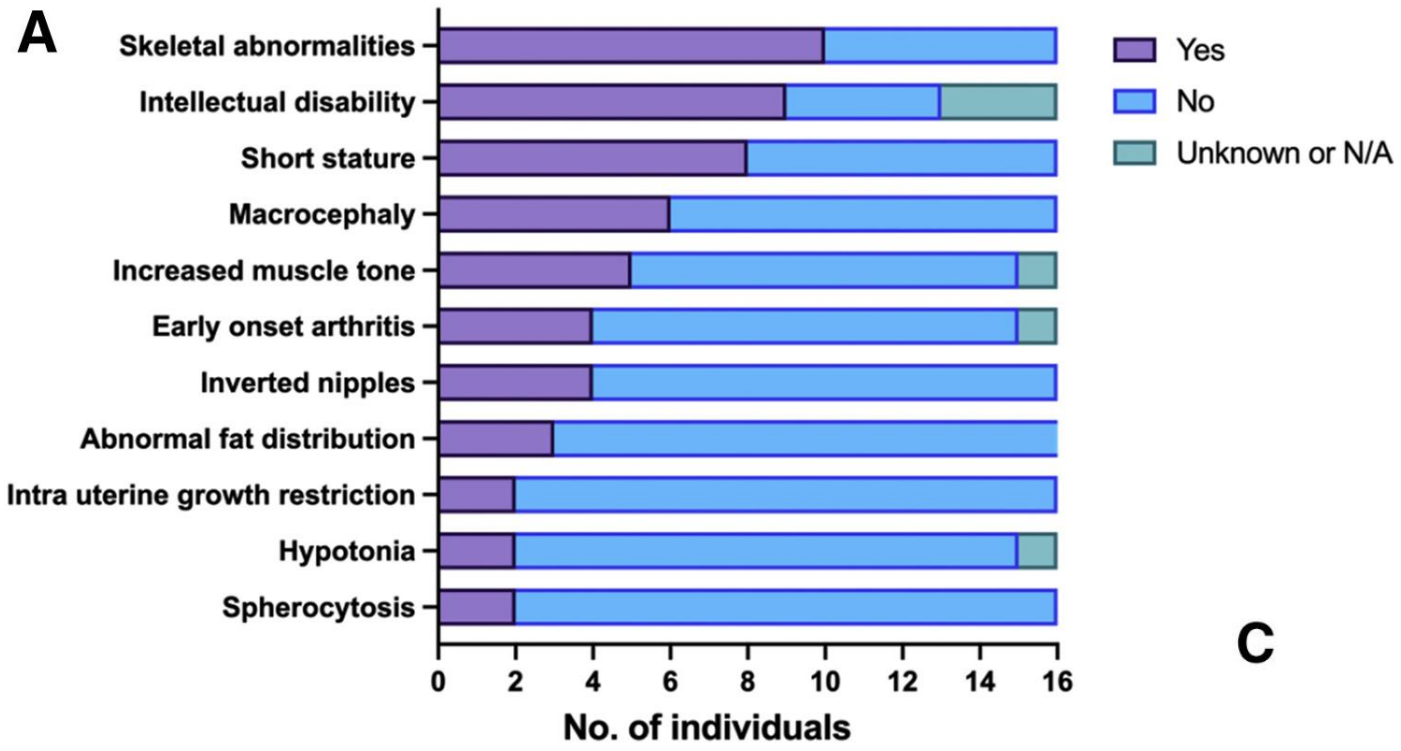
Several other families show AD or de novo STT3A single variant

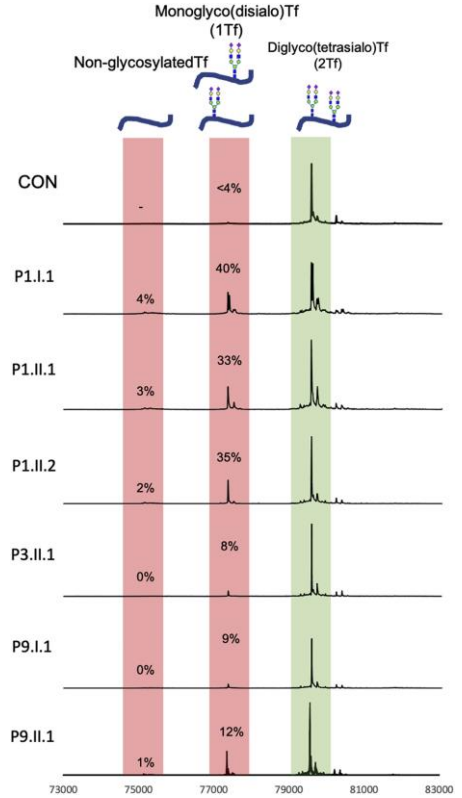


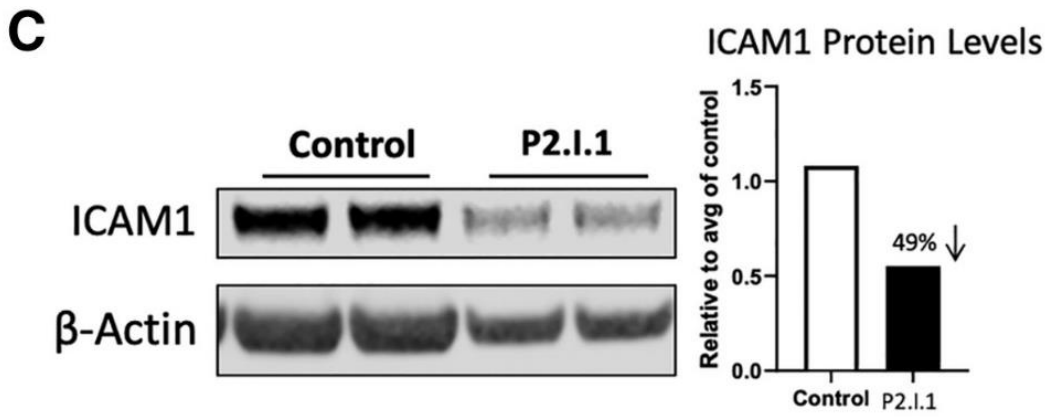




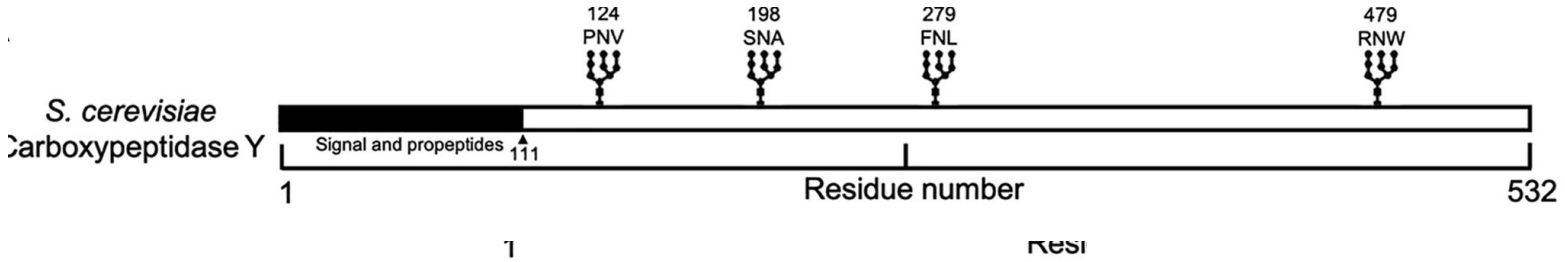
Biochemical and clinical phenotype

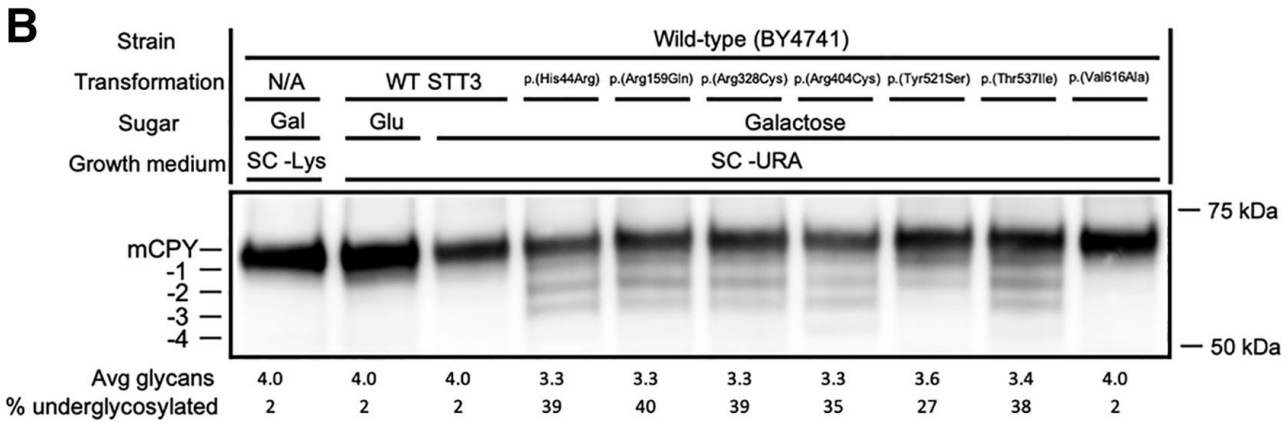


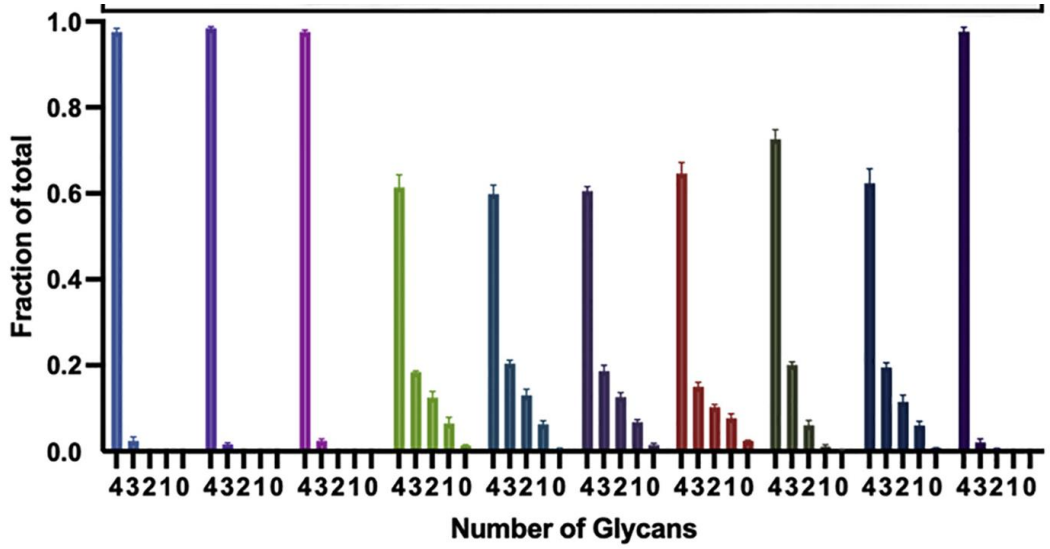




Yeast model of STT3A defect shows abnormal glycosylation







Autosomal dominant forms and their AR sister in CDG:

	AD	AR
ALG8 and ALG9:	Polycystic kidney disease	PCKD/PMR
COG4:	Saul Wilson syndrome	Hepatopathy/PMR
SLC37A4:	Coagulopathy and PMR	GSD type Ib

Thank you

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