Efficacy of oral Manganese and D-Galactose therapy for a novel TMEM165-CDG patient

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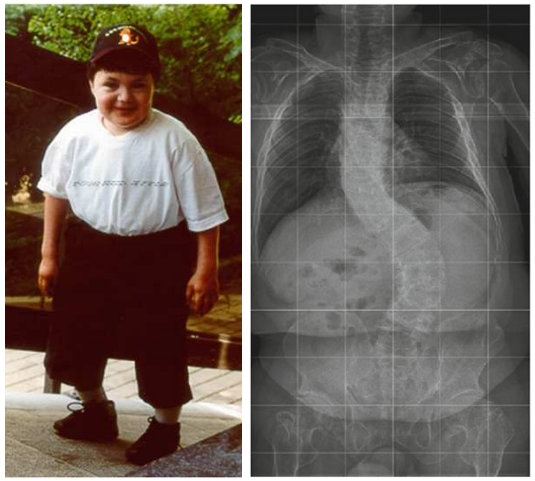
E-Rare

TMEM165-CDG



Zeevaert, 2013

Few described patients

(<10 cases)

Typical phenotype

- Growth retardation
- Major bone impairment
- Intellectual defect

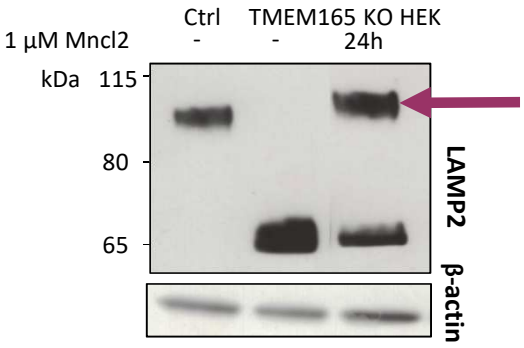
Golgi homeostasis defect (notably hypogalactosylation)

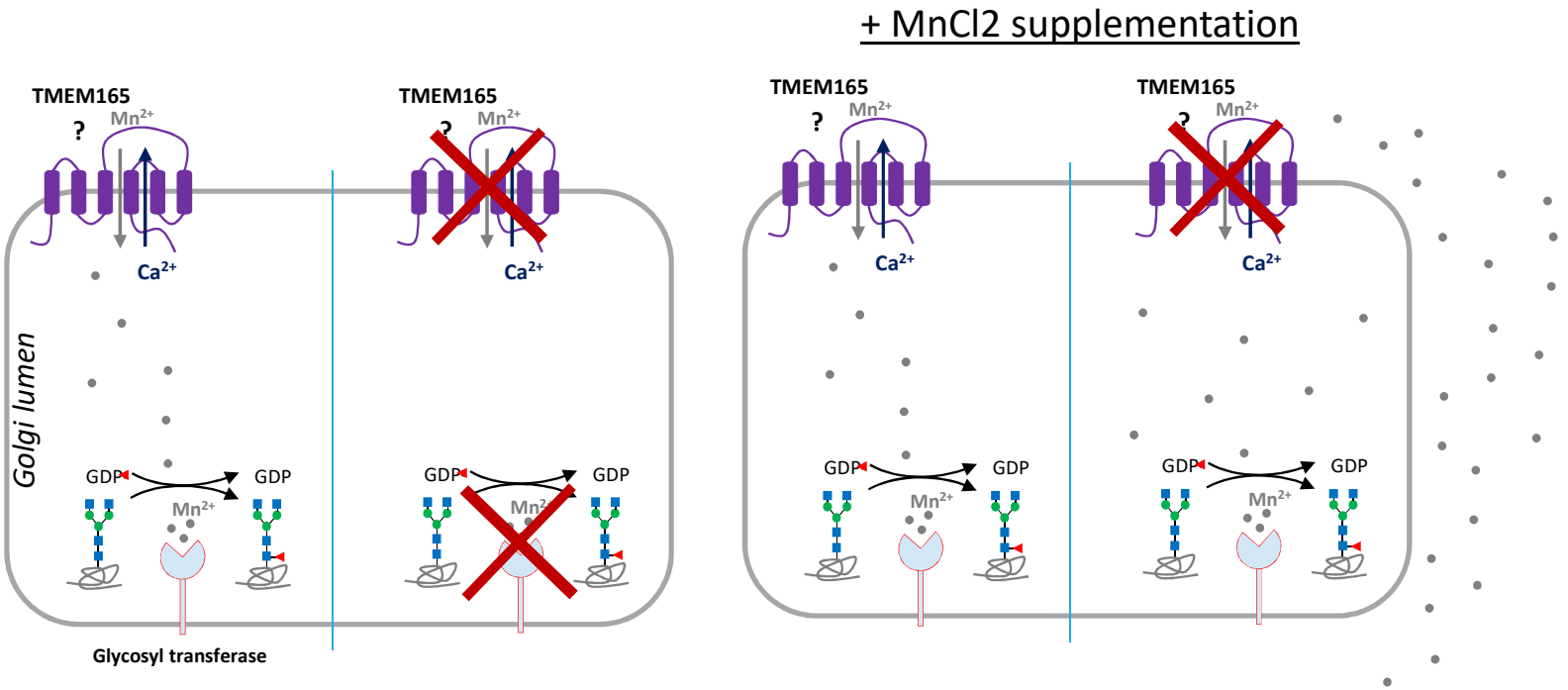
- *N*-Glycosylation
- *O*-glycosylation
- Glycolipids
- GAG synthesis,

Current treatment

D-galactose supplementation (1 g/kg rescued *N*-glycosylation, endocrine and coagulation defects in two patients)

TMEM165 function





- Mn supplementation → Rescue of the observed glycosylation defect
  - TMEM165 → Major Mn importer in the Golgi apparatus

A novel patient?

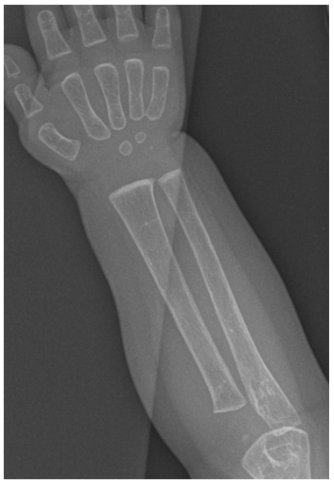
Two year-old girl, child of first-cousins (Kabyle origin)

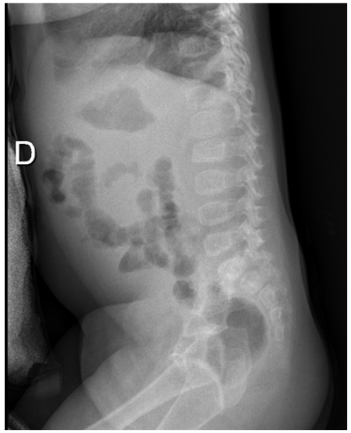
Growth retardation, enteropathy with hypovolemic shock, hepatosplenomegaly

Abnormal liver and coagulation tests

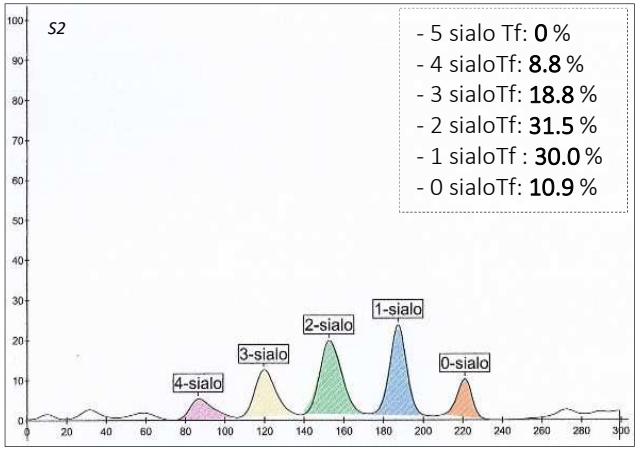
Bone hypomineralisation (???)

→ Evocative of CDG - TMEM165?

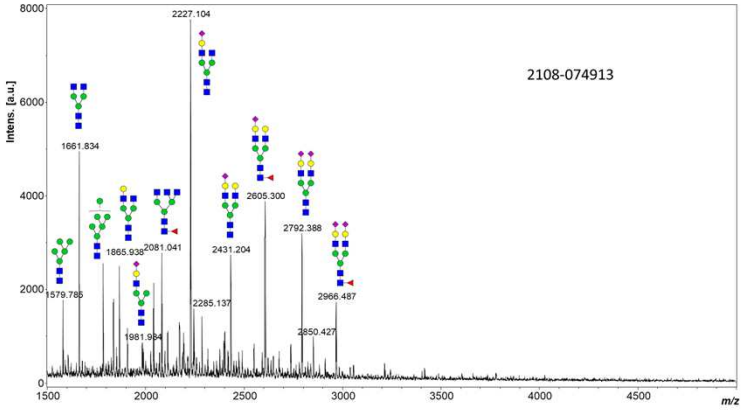




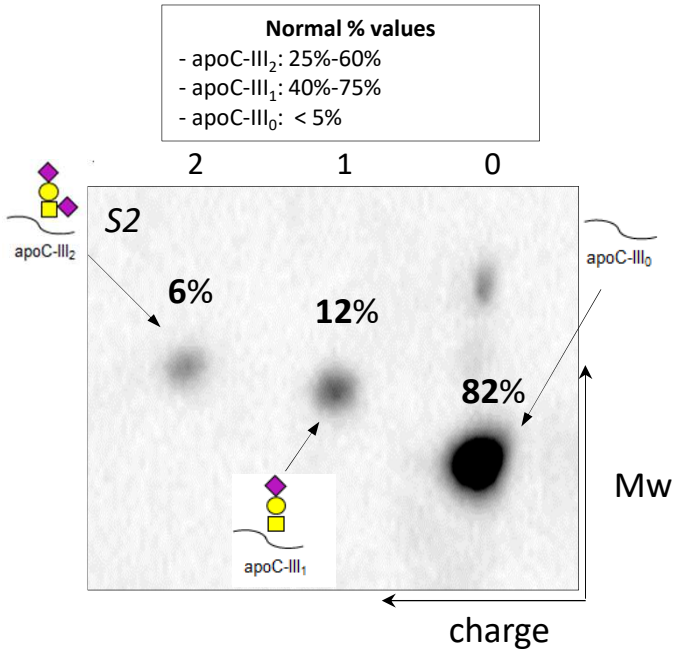
Biochemical CDG screening



Type II transferrin profile



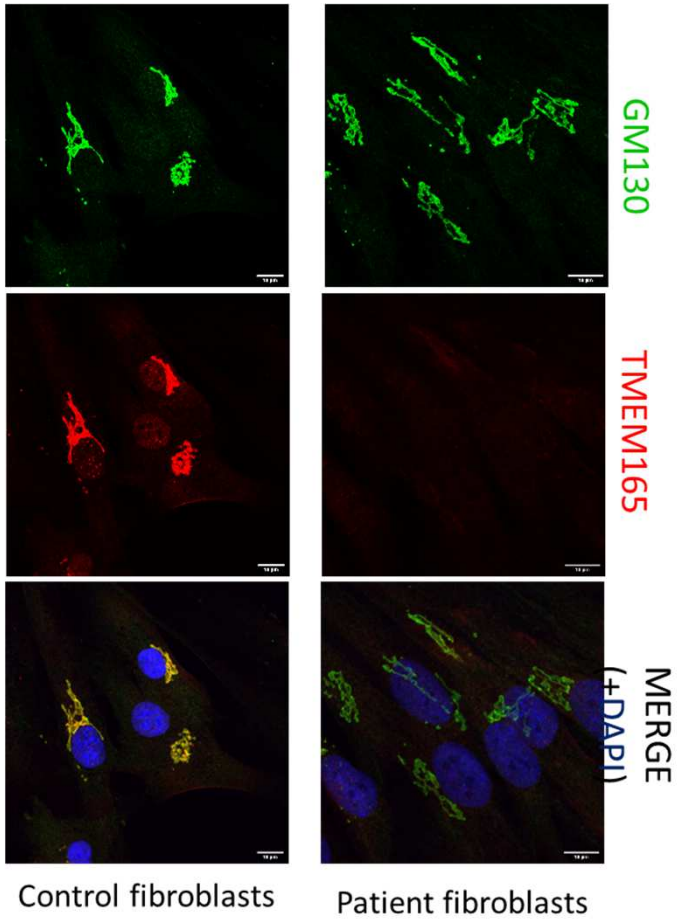
N-glycome type II CDG - hypogalactosylation



apoC-III_0 2-DE profile
Golgi homeostasis defect?

TMEM165-CDG?

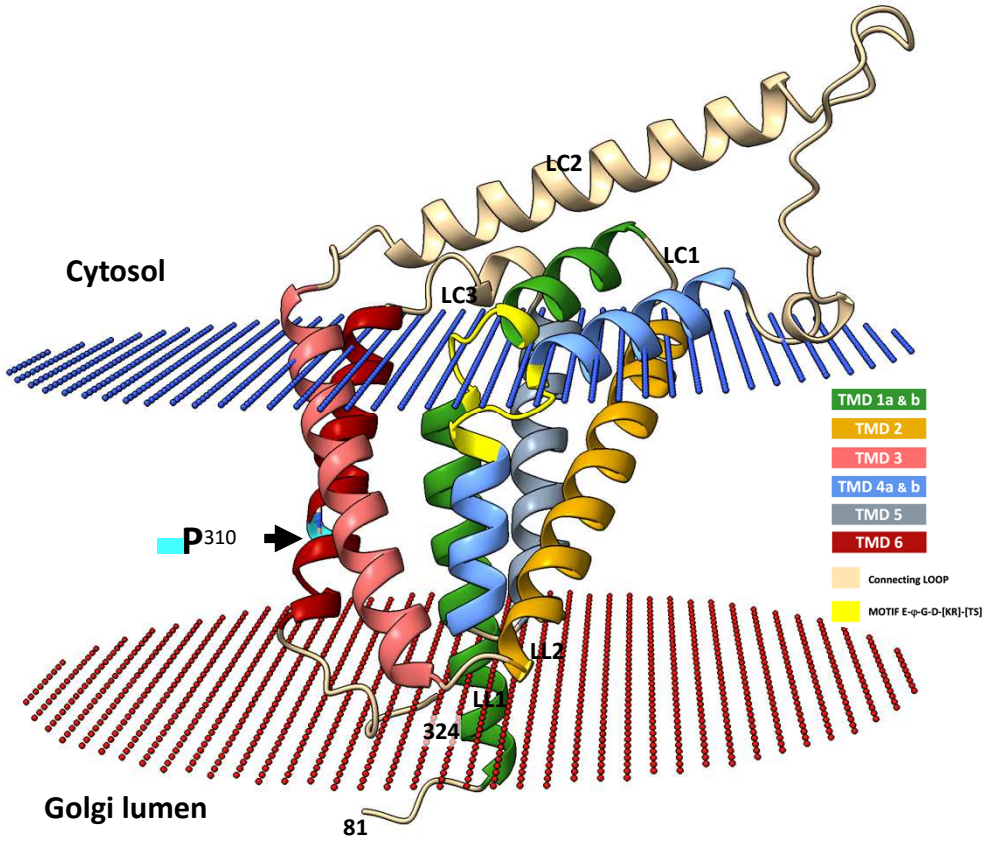
TMEM165 expression in patient cells



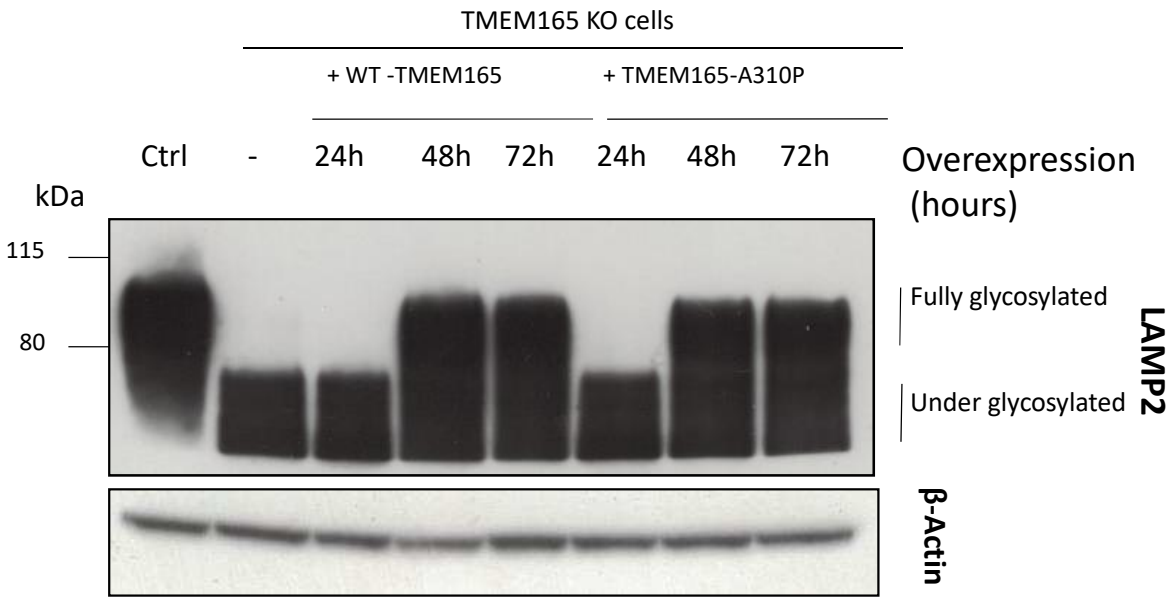
- No expression of TMEM165 in patient cells
- → Sequencing of *TMEM165?*

A novel mutation

- A mutation in TMEM165 was found
  - A310P
  - Never described before
- Is this mutation pathogenic?

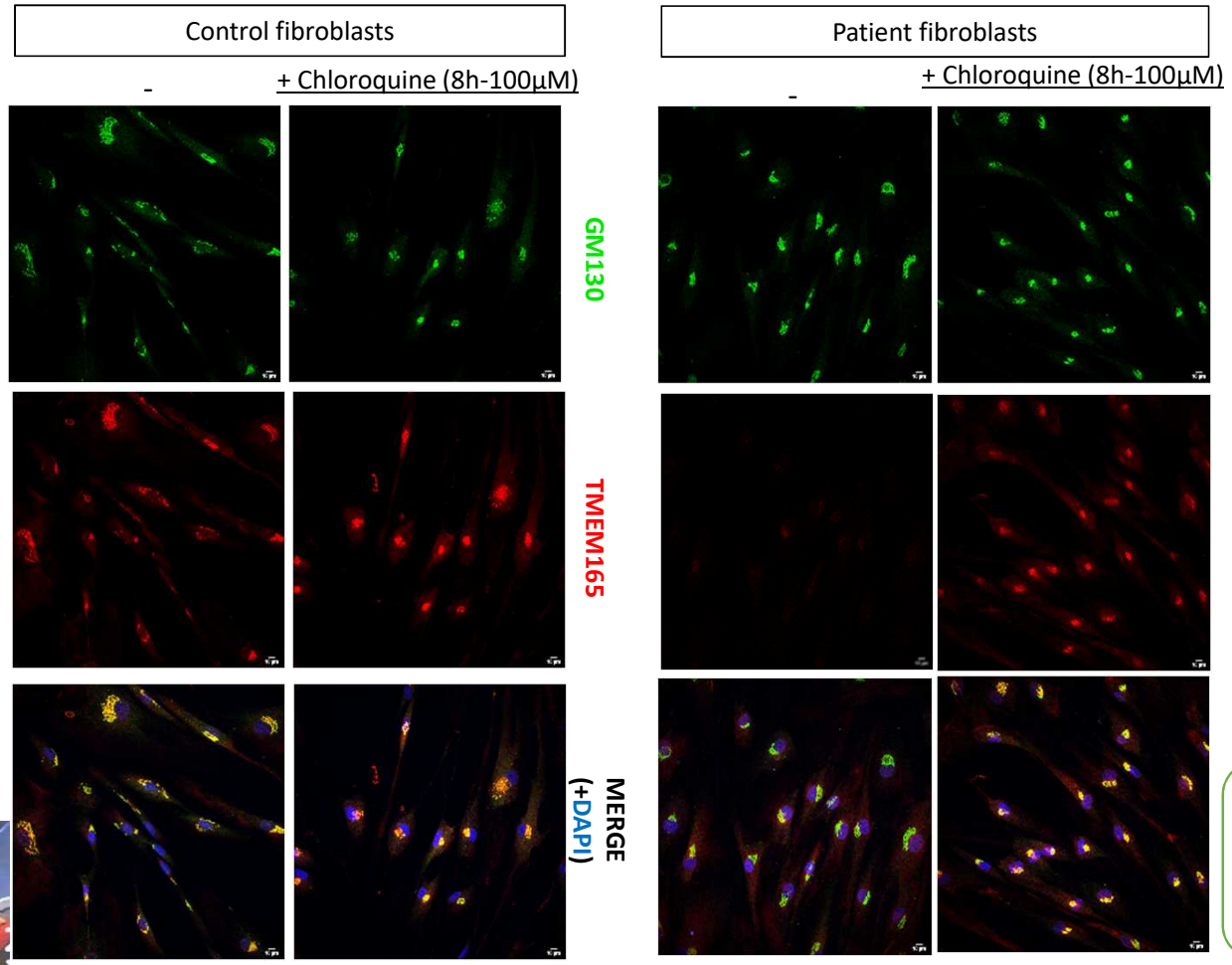


A310P TMEM165 is functional



- Rescue of LAMP2 migration profile with WT-TMEM165
- Rescue of LAMP2 migration profile with A310P-TMEM165
- → The **mutant is functional !**
- Where does the patient phenotype comes from?

A310P TMEM165 stability is affected



- TMEM165 normal turn-over is *via* lysosomes
- Chloroquine inhibits lysosomes acidification

→TMEM165 is back in patient's cells

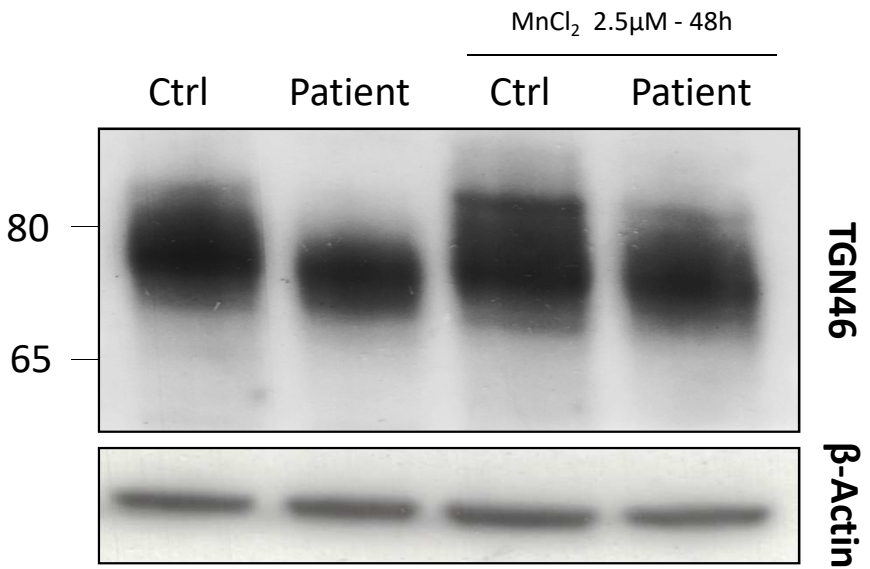
The pathogenicity would come from a increased degradation, not a loss of function

Patient treatment?

		D-Galactose	Manganese
Glycosylation defects in TMEM165-CDG:	**N-glycosylation**	✓	✓
	O-Glycosylation	✗	✓
	Glycosaminoglycanes	✗	✓
	Glycolipids	✗	✓

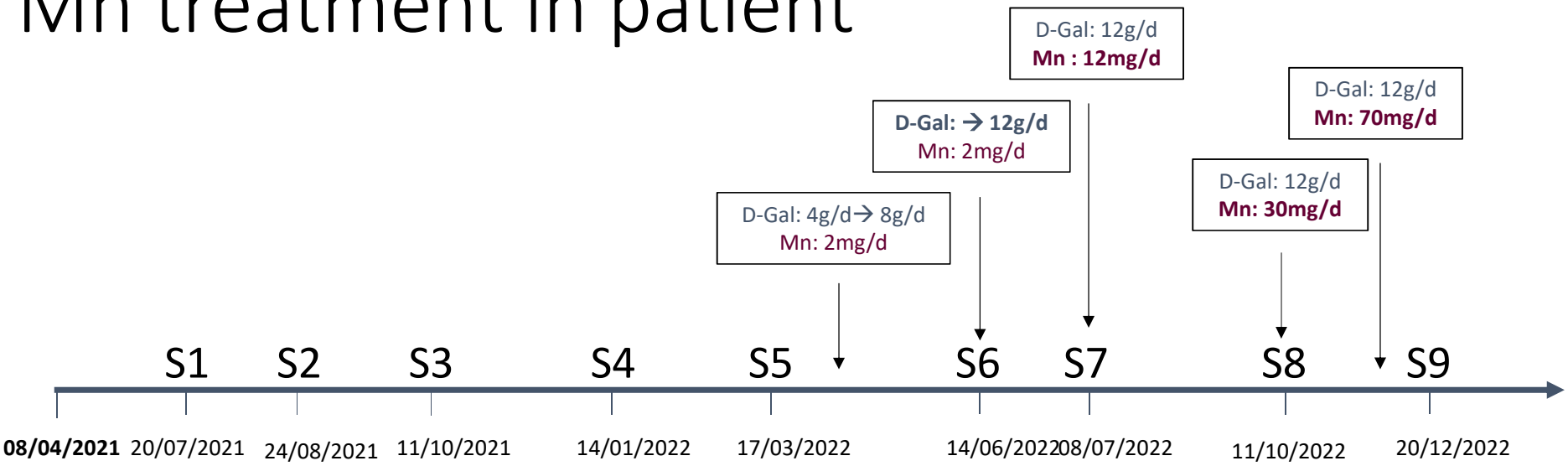
BEST TREATMENT OPTION

Mn treatment



- Rescue of LAMP2 migration profile with MnCl2
- Rescue of LAMP2 with chloroquine
- BUT : cell mortality higher with chloroquine

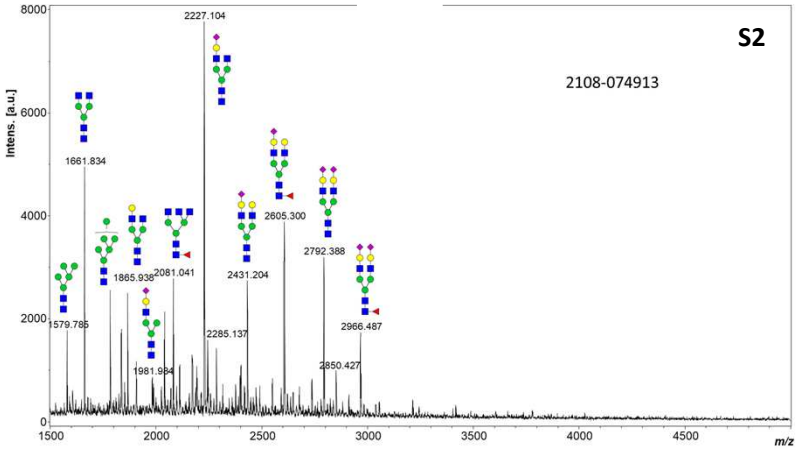
Mn treatment in patient

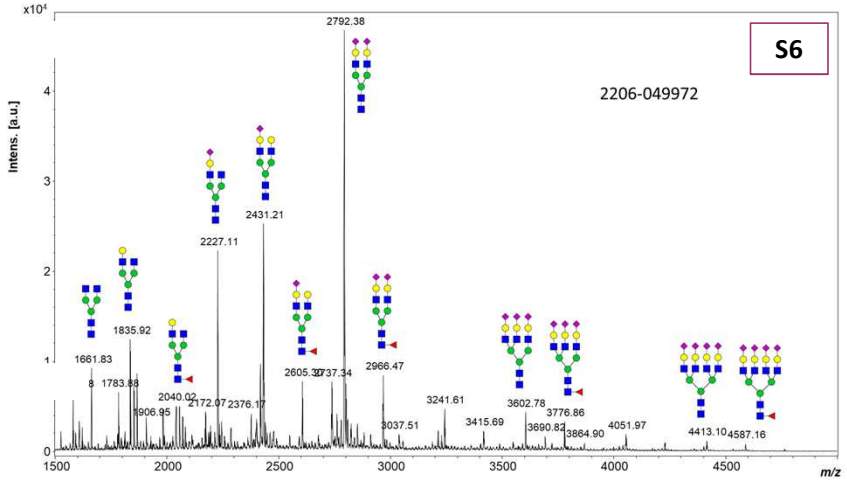


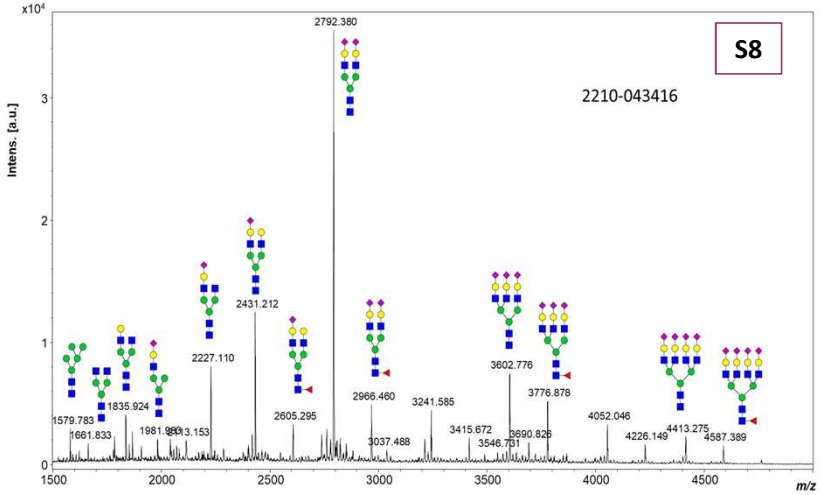
- What is the right dosage for Mn?
- In SLC39A8-CDG between 65 and 195mg/day

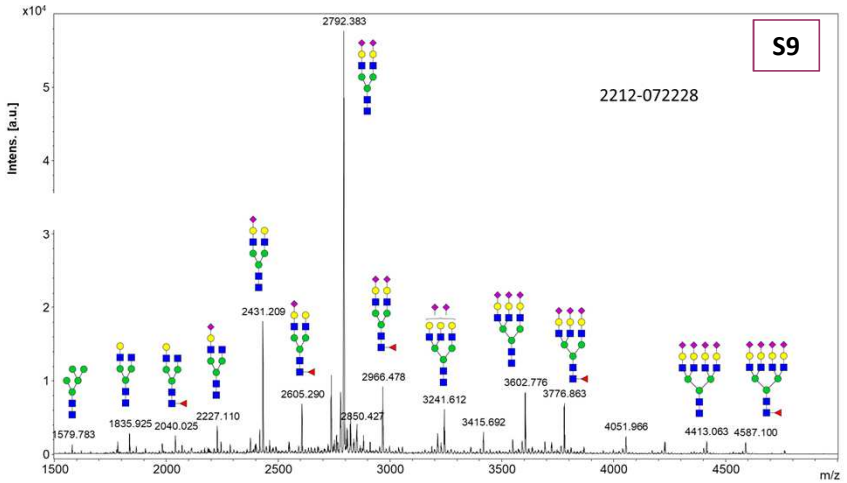
→ Slow increase of the dose

N-glycome profile normalization

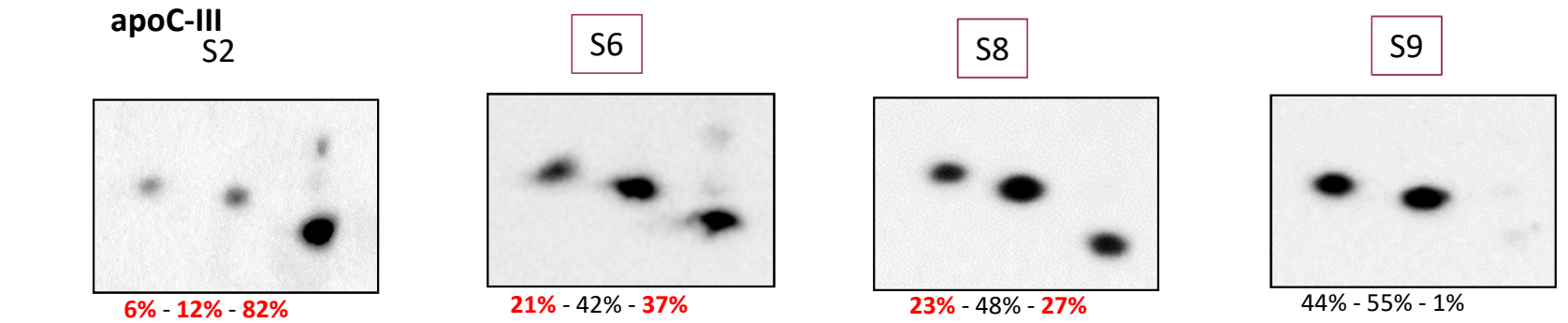


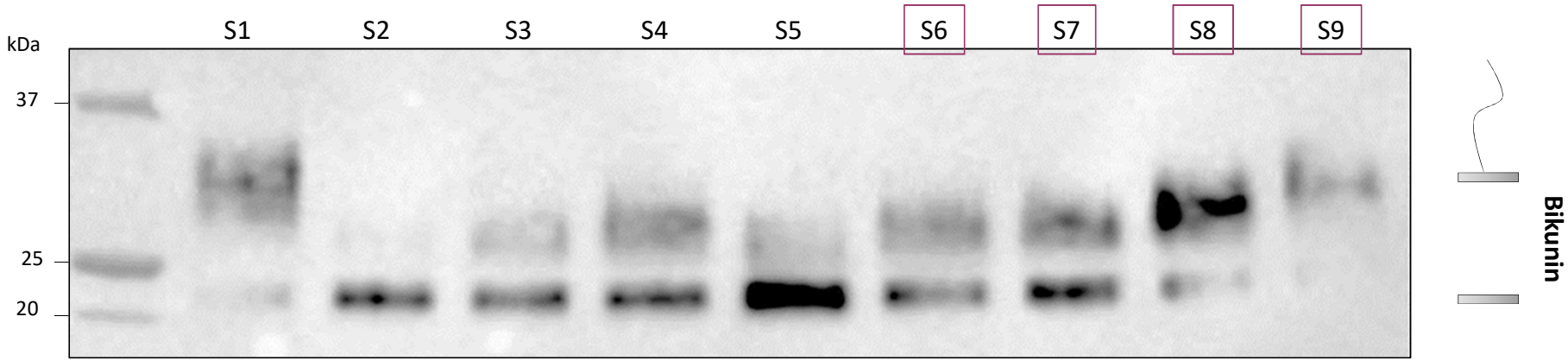




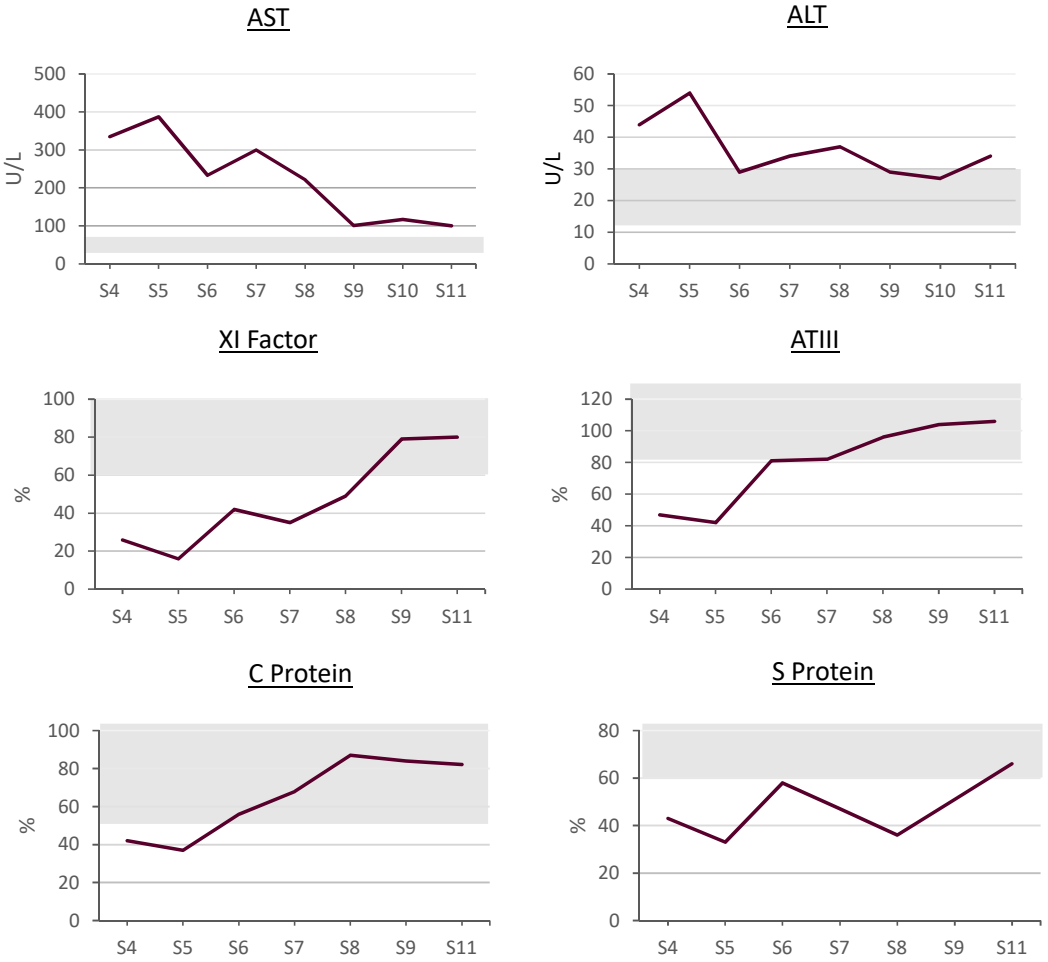


apoC-III and bikunin profiles normalization



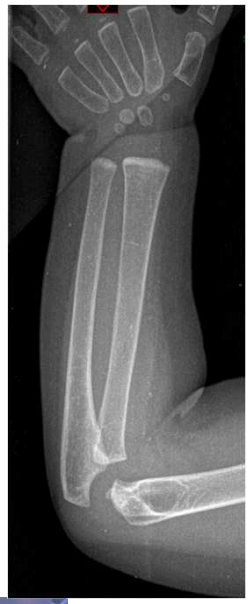


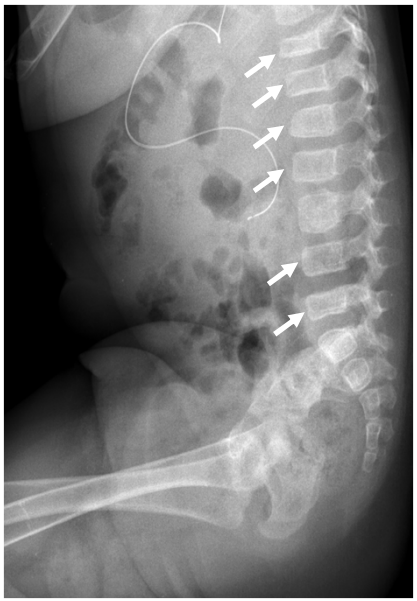
Biochemical markers



- Clear improvements in liver and coagulation labs

Clinical phenotype after 1 year of treatment



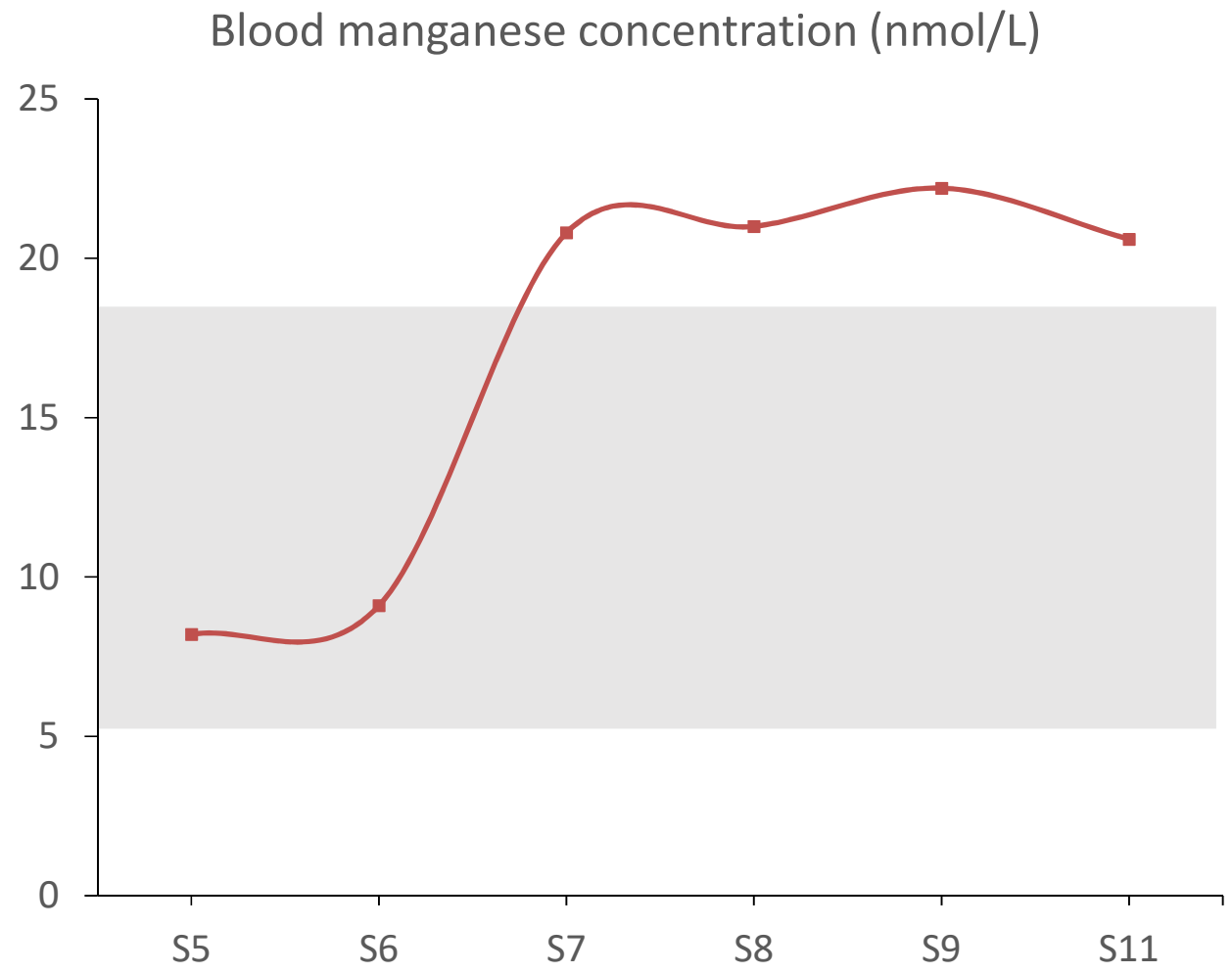


- Still present a developmental delay
- Bone hypomineralisation

→ She progresses, but at her own pace, without aggravation

Mn^{2+} accumulation?

- Mn^{2+} toxicity: risk of neurological disorder (Parkinson-like)
- However, no clear-cut biomarker of Mn^{2+} toxicity…
- Clinical and imaging follow-up required (Brain MRI)



Novel TMEM165-CDG patient

- Early diagnosis

Novel mutation A310P

- Functional but unstable

First Mn treatment to our knowledge

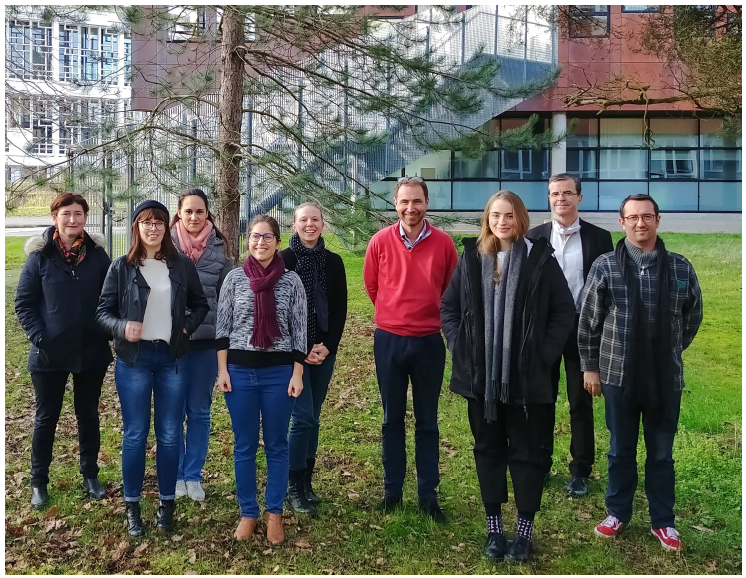
- Full rescue of initial glycosylation defect

Follow-up needed

- Mn Toxicity?
- Impact on the global phenotype?

Acknowledgments

Team « 020 » of Dr François Foulquier



Team CDG-Bichat-Necker