EMMA - RESEARCH BRIEF - AUGUST 2026

Can restoring normal ALG1 correct Emma's fibroblast glycosylation defect?

Emma has a severe congenital neurodevelopmental disorder. Her patient-derived fibroblasts show abnormal glycosylation, while standard blood-based testing has been largely non-diagnostic. One pathogenic ALG1 allele is known; the causal story is still incomplete.

CURRENT EVIDENCE

Four facts define the case

ESTABLISHED

One pathogenic ALG1 variant

ALG1 c.773C>T, p.Ser258Leu (transcript-dependent numbering). A second pathogenic ALG1 event has not been identified.

ESTABLISHED

Fibroblasts show a glycosylation phenotype

LAMP2 hypoglycosylation has been demonstrated. ADAMTS13-related abnormalities were repeatedly reported. Total ALG1 quantity appeared preserved on the current Western blot.

ESTABLISHED

Serum is not classical for ALG1-CDG

Transferrin was repeatedly normal / once borderline. Serum MALDI-TOF was not typical of published ALG1-CDG, although one of four potential biomarkers was detected at low level.

UNRESOLVED

The diagnosis remains open

Fibroblast RNA-seq did not show abnormal ALG1 mRNA splicing. A de novo mosaic CHAMP1 p.Arg548Cys variant remains a VUS and should not be treated as the diagnosis.

WHY ALG1 REMAINS COMPELLING

p.Ser258Leu has direct published functional precedent.

Published patient-cell studies involving p.Ser258Leu found impaired early ALG1-dependent mannosylation, and reference ALG1 complementation corrected the cellular glycosylation defect in a foundational study. This makes wild-type ALG1 rescue the most discriminating causal experiment for Emma's fibroblast phenotype.

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STATUS AND PROPOSED WORK

What has happened, what is pending, and what should come next.

2020-2024	**Genetic testing did not give a complete diagnosis.** Exome-based testing identified a mosaic CHAMP1 VUS and one pathogenic ALG1 allele, but no second pathogenic ALG1 event.
2025	**Fibroblasts produced the clearest glycosylation signal.** LAMP2 hypoglycosylation was demonstrated; ALG1 protein quantity appeared preserved; ADAMTS13-related abnormalities had also been repeatedly observed.
Nov 2025	**Bratislava glycomics was arranged.** The metabolic team arranged research glycomic work and considered a 4-PBA fibroblast experiment feasible, but preferred to obtain RNA results and a better biomarker first.
Dec 2025	**RNA-seq did not reveal an ALG1 splice defect.** The known pathogenic p.Ser258Leu allele was detected in fibroblast RNA, but no abnormal canonical ALG1 splicing was found.
Mar 2026	**Serum glycomics remained atypical.** MALDI-TOF did not show a classical ALG1-CDG N-glycan profile. One of four potential biomarkers was present at low level.
Now - pending	**PENDING: Bratislava fibroblast glycomics / ALG1 biomarker analysis is still outstanding.** The fibroblast culture is available and reported to be in good condition. The pending work includes interest in the ALG1-associated N-tetrasaccharide. Published ALG1 cases show that fibroblast abnormalities may be detectable despite normal blood-based testing.

PROPOSED NEXT STEPS

Three useful research directions

PRIORITY 1

Wild-type ALG1 complementation

Add reference ALG1 to Emma's fibroblasts and ask whether pathway-specific glycosylation and an independent glycoprotein endpoint improve toward controls.

IN PARALLEL

Search for the hidden second ALG1 event

Deep genomic review of the ALG1 locus, including structural, noncoding and allele-specific mechanisms.

PROPOSED CELL EXPERIMENT

4-PBA rescue test

Test 4-PBA in vitro and ask whether it corrects the glycosylation phenotype. A positive cell result would be a mechanistic signal, not a treatment claim.

Patient-derived fibroblasts already exist.

Clinical, genetic and biochemical documentation can be shared with serious research collaborators subject to the appropriate clinical and research arrangements. Contact: jan.vlcek@gmail.com

SELECTED REFERENCES

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