MOLECULAR ATLAS · VARIANT CARD

WFS1 S308C — Wolframin

Serine → Cysteine at position 308 in N-terminal cytoplasmic domain. ClinVar Conflicting including congenital bilateral perisylvian syndrome. AlphaMissense 0.642, ΔΔG -0.01 (neutral). pLDDT 61 borderline.

IDENTITY

Variant	S308C (p.Serine308Cysteine)
DNA change	c.923C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001496445
Amino acid change	Serine (S) → Cysteine (C) — small polar hydroxyl replaced by small thiol. Both small; chemistry shifts from OH to SH.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 308	**61.47** CONFIDENT
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 308 (pLDDT 61 borderline). Near the TM1 boundary.
IDR flag	No — pLDDT well above 50 threshold

Position 308 near TM1 boundary. Neighbors: ARG309 (2.5 Å — same R309 as H313Y region), ALA307 (2.5 Å), ILE304 (3.8 Å), ASP305 (4.1 Å). Replacing S308 with cysteine swaps hydroxyl for thiol. In the cytosol, the new C308 thiol is less reactive than in the ER lumen, but free cysteines in cytosol can still participate in glutathionylation or other regulatory thiol chemistry. ΔΔG essentially neutral; AM 0.642 + congenital syndrome confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.642		**61.47**

am_class: **LPath** — threshold > 0.564

-0.01 kcal/mol

Destabilising · Job 177992466332

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/07/27 00:00
Inheritance	Congenital bilateral perisylvian syndrome documented.
WFS1 variant landscape	S308C is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Congenital bilateral perisylvian syndrome

RESEARCH PATH DECISION TREE

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ΔΔG < 2 + binding site affected → CATEGORY 3 — docking experiments ΔΔG 2–4 → CATEGORY 2 — pharmacological chaperones ΔΔG > 4 → CATEGORY 1 — gene therapy pLDDT < 50 → CATEGORY 5 — IDR, experimental only Stable fold + functional site hit → CATEGORY 4 — site-specific docking
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Category 4 — Stable Fold, Function Disrupted. ΔΔG ≈ 0. AlphaMissense 0.642 + congenital syndrome confirm severe consequence.

Mechanism: hydroxyl-to-thiol substitution near R309. Therapeutic: site-directed at the cytoplasmic-TM1 boundary region.

S308C joins the TM1-boundary cluster (with W314R, H313Y) and introduces a novel thiol regulatory chemistry consideration.