MOLECULAR ATLAS · VARIANT CARD

WFS1 E680Q — Wolframin

Glutamate → Glutamine at position 680 in wolframin's C-terminal lumenal domain. ClinVar Likely pathogenic, optic atrophy. AlphaMissense 0.321 (below threshold) — AM under-call. DynaMut2 ΔΔG +0.12 kcal/mol — essentially neutral. Conservative charge-to-amide swap.

IDENTITY

Variant	E680Q (p.Glutamate680Glutamine)
DNA change	c.2038G>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV003250050
Amino acid change	Glutamate (E) → Glutamine (Q) — negatively-charged carboxylate replaced by neutral polar amide. Same side-chain length; charge lost.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 680	**84.12** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 680 in the ER lumen (pLDDT 84).
IDR flag	No — pLDDT well above 50 threshold

Position 680 sits in wolframin's C-terminal lumenal domain. The AlphaFold model places E680 within 5 Å of THR681 (2.5 Å), LYS679 (2.5 Å — likely salt-bridge partner), ALA677 (4.0 Å), ARG676 (4.1 Å — second nearby basic), and TRP678 (4.7 Å). The wild-type glutamate likely forms a salt bridge with K679 and contributes to the local electrostatic surface that includes R676 nearby. Replacing E680 with glutamine eliminates the negative charge while preserving similar volume and H-bonding capacity. The |ΔΔG| of essentially zero (+0.12) indicates fold accommodates the conservative swap. AlphaMissense's 0.321 is below threshold — AM under-call. ClinVar Pathogenic + optic atrophy confirm clinical relevance.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.321	**0.12** kcal/mol	**84.12**
am_class: **LBen** — threshold > 0.564	Stabilising · Job 177992010269	high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	no assertion criteria provided
Last evaluated	2018/01/01 00:00
Inheritance	Optic atrophy documented.
WFS1 variant landscape	E680Q is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Optic atrophy

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 (AM under-call). ΔΔG = +0.12 — fold unchanged. AlphaMissense 0.321 below threshold.

Mechanism is loss of E680-K679 salt bridge. Therapeutic strategy: site-directed at the K679 microregion.

E680Q joins the AM-under-call class. Drug discovery for this class requires multi-metric evaluation rather than AM-alone.