MOLECULAR ATLAS · VARIANT CARD

# WFS1 E680A — Wolframin

Glutamate → Alanine at position 680 in lumenal domain. ClinVar Conflicting including monogenic diabetes + Wolfram. AlphaMissense 0.34 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.23 kcal/mol. Same position as E680Q — second substitution at 680.

## IDENTITY

| | |
|---|---|
| Variant | E680A (p.Glutamate680Alanine) |
| DNA change | c.2039A>C |
| Gene · Protein | WFS1 · Wolframin (890 aa) |
| UniProt | O76024 · WFS1_HUMAN |
| ClinVar accession | VCV000286507 |
| Amino acid change | Glutamate (E) → Alanine (A) — small negatively-charged carboxylate replaced by small methyl-bearing hydrophobic. Charge lost + side chain reduced. |

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## STRUCTURAL CONTEXT

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|---|---|
| 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 (pLDDT 84). |
| IDR flag | No — pLDDT well above 50 threshold |

> Position 680 same neighbors as E680Q: THR681 (2.5 Å), LYS679 (2.5 Å — wild-type salt-bridge partner), ALA677 (4.0 Å), ARG676 (4.1 Å — second nearby basic). E680A is more drastic than E680Q — eliminates the charge AND removes the side chain (compared to E680Q which kept H-bonding capacity through the amide). The E680-K679 salt bridge is lost entirely. The R676 nearby basic loses its electrostatic counterpart through this position. AlphaMissense's 0.34 is below threshold (AM under-call); monogenic diabetes + Wolfram confirm pathogenicity.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.342**

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

**-0.23** kcal/mol

Destabilising · Job 177992493528

PLDDT (ALPHAFOLD)

**84.12**

high confidence

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## CLINICAL EVIDENCE

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|---|---|
| ClinVar classification | **CONFLICTING CLASSIFICATIONS OF PATHOGENICITY** |
| Review status | criteria provided, conflicting classifications |
| Last evaluated | 2026/01/30 00:00 |
| Inheritance | Multi-phenotype. |
| WFS1 variant landscape | E680A is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar) |

- Monogenic diabetes
- Wolfram syndrome 1

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## 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 3/4 — Most Druggable (AM under-call).** |ΔΔG| = 0.23. AlphaMissense 0.34 below threshold but monogenic diabetes + Wolfram confirm pathogenicity.

Mechanism: complete loss of E680-K679 salt bridge plus side-chain volume reduction. Therapeutic strategy: same K679 microregion as E680Q.

E680A + E680Q at same position — both pathogenic at the K679 salt-bridge partner site.