MOLECULAR ATLAS · VARIANT CARD

WFS1 E202G — Wolframin

Glutamate → Glycine at position 202 in wolframin's N-terminal cytoplasmic domain. ClinVar Pathogenic/Likely pathogenic, optic atrophy + Wolfram syndrome 1. AlphaMissense 0.283 (BELOW threshold) — AM under-call. DynaMut2 ΔΔG -0.19 kcal/mol (mild destabilising).

IDENTITY

Variant	E202G (p.Glutamate202Glycine)
DNA change	c.605A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000420050
Amino acid change	Glutamate (E) → Glycine (G) — negatively-charged carboxylate replaced by smallest amino acid (no side chain). Loss of charge plus loss of side-chain mass entirely.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 202	**74.12** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 202 in the cytosol (pLDDT 74).
IDR flag	No — pLDDT well above 50 threshold

Position 202 sits in wolframin's N-terminal cytoplasmic domain. The AlphaFold model places E202 within 5 Å of ASN203 (2.5 Å), LEU201 (2.5 Å), ALA198 (3.9 Å), GLU199 (4.0 Å — second nearby glutamate), and VAL204 (4.4 Å). The two adjacent glutamates (E199 and E202) form a negatively-charged surface patch likely involved in partner-protein recognition. Replacing E202 with glycine eliminates one of two negative charges from the patch and introduces backbone flexibility where the wild-type side chain constrained local geometry. The fold absorbs the substitution (|ΔΔG| 0.19) but the recognition surface is materially altered. AlphaMissense's 0.283 score is below the 0.564 likely-pathogenic threshold — yet ClinVar Pathogenic + optic atrophy + Wolfram 1 establish clinical pathogenicity. This is an AM under-call: the variant is genuinely pathogenic by clinical evidence

even though AM's training does not flag it. The mechanism is partner-recognition surface disruption.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.283

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.19 kcal/mol

Destabilising · Job 177991407826

PLDDT (ALPHAFOLD)

74.12

high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2024/06/04 00:00
Inheritance	Wolfram syndrome 1 (AR) + optic atrophy documented.
WFS1 variant landscape	E202G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Optic atrophy
- Wolfram syndrome 1

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| = 0.19 kcal/mol — fold barely perturbed. AlphaMissense 0.283 below threshold but ClinVar Pathogenic and clinical phenotypes confirm pathogenicity.

The mechanism is partner-recognition surface disruption through loss of one

of two adjacent negative charges (E199, E202). Therapeutic strategy: site-directed at the cytoplasmic surface patch — but wet-lab validation strongly recommended given the AM discrepancy.

E202G is another Atlas AM under-call case (with W639G, R629W). Drug discovery here should pause for experimental validation before computational design proceeds.
