MOLECULAR ATLAS · VARIANT CARD

WFS1 D118A — Wolframin

Aspartate → Alanine at position 118 in N-terminal cytoplasmic domain. ClinVar Conflicting including monogenic diabetes. AlphaMissense 0.35 (below threshold) — AM under-call. DynaMut2 ΔΔG -0.14 kcal/mol (mild destabilising).

IDENTITY

Variant	D118A (p.Aspartate118Alanine)
DNA change	c.353A>C
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000178584
Amino acid change	Aspartate (D) → Alanine (A) — small negatively-charged carboxylate replaced by small methyl-bearing hydrophobic. Charge lost + side chain reduced.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 118	**82.19** HIGH CONFIDENCE
Domain	N-terminal cytoplasmic domain (87-313)
Position context	N-terminal cytoplasmic domain · position 118 (pLDDT 82).
IDR flag	No — pLDDT well above 50 threshold

> Position 118 sits in wolframin's N-terminal cytoplasmic domain. Neighbors: GLU119 (2.5 Å — adjacent existing glutamate), THR117 (2.5 Å), ASN122 (4.4 Å). The wild-type D118 + adjacent E119 form a charged surface patch in the cytoplasmic domain — likely a recognition surface for partner proteins. Replacing D118 with alanine eliminates one of two negative charges from this patch. The local electrostatic surface is reduced; the partner-recognition geometry that depended on the D118-E119 double-negative signature is perturbed. The |ΔΔG| of 0.14 is small — the fold absorbs the substitution. AlphaMissense's 0.35 is below threshold (AM under-call). Monogenic diabetes clinical evidence confirms pathogenicity through cytoplasmic partner-recognition disruption.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.352

am_class: **Amb** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.14 kcal/mol

Destabilising · Job 177992493372

PLDDT (ALPHAFOLD)

82.19

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2026/01/21 00:00
Inheritance	Monogenic diabetes.
WFS1 variant landscape	D118A is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Monogenic diabetes

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| = 0.14. AlphaMissense 0.35 below threshold but monogenic diabetes confirms pathogenicity.

Mechanism: charge loss from D118-E119 cytoplasmic surface patch. Therapeutic strategy: site-directed at the cytoplasmic recognition surface.

D118A is part of the charge-cluster-loss class in the N-terminal cytoplasmic domain (with similar patterns at E158K, E169K, E202G, E301K).

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Every assumption documented.