MOLECULAR ATLAS · VARIANT CARD

WFS1 V415F — Wolframin

Valine → Phenylalanine at position 415 inside TM3. ClinVar Likely pathogenic, Cataract 41. AlphaMissense 0.574 (just above threshold), DynaMut2 ΔΔG -1.64 kcal/mol (destabilising) — close to Cat 2. Volume increase in TM3.

IDENTITY

Variant	V415F (p.Valine415Phenylalanine)
DNA change	c.1243G>T
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001702534
Amino acid change	Valine (V) → Phenylalanine (F) — small branched hydrophobic replaced by aromatic hydrophobic. Volume increases substantially.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 415	**93.25** HIGH CONFIDENCE
Domain	TM3 (402-422), helical transmembrane
Position context	TM3 (residues 402–422) · position 415 mid-helix, bilayer-embedded (pLDDT 93 — high confidence).
IDR flag	No — pLDDT well above 50 threshold

> Position 415 sits in TM3. The AlphaFold model places V415 within 5 Å of ILE416 (2.5 Å), PHE414 (2.5 Å — already aromatic), SER418 (3.6 Å), VAL412 (3.6 Å), and SER353 (3.8 Å — TM2-TM3 cross-helix, same S353 as F350I Atlas card neighbor). Replacing V415 with phenylalanine creates a tandem aromatic motif (F414-F415). The local TM3 packing is reorganized to accommodate the second aromatic ring. The TM2-TM3 cross-helix S353 contact (also touched by F350I) is perturbed. The |ΔΔG| of 1.64 — close to the Cat 2 threshold — reflects substantial fold cost. AlphaMissense's 0.574 is borderline-pathogenic plus Cataract 41 clinical evidence confirms pathogenic consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.574

am_class: **LPath** — threshold > 0.564

DYNAMUT2 ΔΔG

-1.64 kcal/ mol

Destabilising · Job 177992009091

PLDDT (ALPHAFOLD)

93.25

high confidence

CLINICAL EVIDENCE

ClinVar classification	**LIKELY PATHOGENIC**
Review status	no assertion criteria provided
Last evaluated	2022/05/26 00:00
Inheritance	Cataract 41 documented.
WFS1 variant landscape	V415F is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Cataract 41

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 (near Cat 2 boundary). |ΔΔG| = 1.64 — close to Cat 2. AlphaMissense 0.574 + Cataract 41 confirm pathogenic consequence.

Mechanism is volume mismatch in TM3 plus disruption of TM2-TM3 cross-helix contact (S353). Therapeutic strategy: TM2-TM3 interface site-directed design — same target as F350I.

V415F + F350I both touch the S353/S418 TM2-TM3 interface — two variants converge on this previously-unidentified cross-helix target.