MOLECULAR ATLAS · VARIANT CARD

WFS1 H323R — Wolframin

Histidine → Arginine at position 323 inside wolframin's first transmembrane helix (TM1). ClinVar Pathogenic/Likely pathogenic, associated with optic atrophy. AlphaMissense 0.687 (moderately pathogenic), DynaMut2 ΔΔG -0.02 kcal/mol — essentially neutral. A bilayer-embedded substitution where charge state amplifies but doesn't reverse.

IDENTITY

Variant	H323R (p.Histidine323Arginine)
DNA change	c.968A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000872210
Amino acid change	Histidine (H) → Arginine (R) — titratable basic residue replaced by permanently positively-charged guanidinium-bearing residue. The variant moves from pH-dependent charge to constant positive charge.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 323	**76.94** HIGH CONFIDENCE
Domain	TM1 (314-334), helical transmembrane
Position context	TM1 (residues 314–334) · position 323 is mid-helix, bilayer-embedded (pLDDT 77).
IDR flag	No — pLDDT well above 50 threshold

Position 323 sits in the middle of TM1. The AlphaFold model places H323 within 5 Å of HIS322 (2.5 Å — TWO histidines adjacent), ILE324 (2.5 Å), PRO320 (3.5 Å), ALA326 (4.3 Å — partner of A326E Atlas card), and THR321 (4.5 Å — partner of T321R/T321P Atlas cards). The local environment is unusually dense with charged/titratable residues for a TM helix: two adjacent histidines (H322, H323) plus the nearby A326 and T321 positions. The wild-type histidine at 323 has pH-dependent charge — neutral in the typical bilayer interior, possibly protonated near the membrane interface. Replacing it with arginine fixes the position to permanently positive charge. In the bilayer hydrophobic core this is energetically unfavorable; the arginine side chain likely extends toward the membrane-water interface. The |ΔΔG| of

essentially zero (-0.02) indicates fold accommodates the substitution easily. The mechanism is functional: loss of pH-regulated charge state where the wild-type histidine could titrate, plus permanent positive charge in a TM context. AlphaMissense's 0.687 + optic atrophy clinical evidence confirm pathogenic mechanism.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.687	**-0.02** kcal/mol	**76.94**
am_class: **LPath** — threshold > 0.564	Destabilising · Job 177991408145	high confidence

CLINICAL EVIDENCE

ClinVar classification	**PATHOGENIC/LIKELY PATHOGENIC**
Review status	criteria provided, multiple submitters, no conflicts
Last evaluated	2020/01/01 00:00
Inheritance	Optic atrophy documented.
WFS1 variant landscape	H323R 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. |ΔΔG| = 0.02 kcal/mol — fold essentially unchanged. AlphaMissense 0.687 + optic atrophy confirm pathogenic functional consequence.

The mechanism is loss of pH-regulated histidine character — the wild-type

residue's ability to titrate between neutral and protonated states is replaced by permanent positive charge. Therapeutic strategy: site-directed at the H322-H323-A326-T321 TM1 microregion.

H323R is part of a dense Atlas variant cluster at TM1 (with W314R, A326E, T321R, T321P, H313Y) — six variants in or near TM1 in the broader Atlas. The region is a recurring drug-discovery target.
