

# WFS1 F810L — Wolframin

Phenylalanine → Leucine at position 810 in wolframin's C-terminal luminal domain. ClinVar Conflicting classifications including Wolfram syndrome 1. AlphaMissense 0.994 (near-maximum), DynaMut2  $\Delta\Delta G$  +0.08 kcal/mol — essentially neutral. Conservative-looking aromatic-to-aliphatic swap with strong pathogenic signal.

## IDENTITY

Variant	F810L (p.Phenylalanine810Leucine)
DNA change	c.2430C>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV000517479
Amino acid change	Phenylalanine (F) → Leucine (L) — aromatic hydrophobic replaced by branched aliphatic hydrophobic. Aromatic character lost; volume modestly reduced.

## STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 810	<b>86.50</b> <span style="background-color: #e0ffe0;">HIGH CONFIDENCE</span>
Domain	C-terminal luminal domain (653-869)
Position context	C-terminal luminal domain · position 810 in the ER lumen (pLDDT 86).
I DR flag	No — pLDDT well above 50 threshold

Position 810 sits in wolframin's C-terminal luminal domain near the E809K region (Atlas card adjacent). The AlphaFold model places F810 within 5 Å of GLU809 (2.5 Å — partner of E809K), LYS811 (2.5 Å), SER807 (3.9 Å), SER808 (4.3 Å), and LEU814 (4.5 Å). Replacing F810 with leucine eliminates the aromatic ring and replaces it with branched aliphatic. The local environment — with E809 and K811 as charged neighbors and multiple serines — was sized around the wild-type aromatic ring. The variant fold accommodates the substitution easily (essentially neutral  $\Delta\Delta G$ ). AlphaMissense's 0.994 (near-maximum) confirms severe functional consequence despite the conservative chemistry. The mechanism is loss of the F810 aromatic packing that the wild-type fold depended on for the E809-K811 salt bridge geometry — F810's

aromatic ring likely positions E809 and K811 in the productive salt-bridge orientation.

## COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

**0.994**

am\_class: **LPath** —  
threshold > 0.564

DYNAMUT2  $\Delta\Delta G$

**0.08** kcal/mol

Stabilising · Job  
177992013681

PLDDT (ALPHAFOLD)

**86.50**

high confidence

## CLINICAL EVIDENCE

ClinVar classification

### CONFLICTING CLASSIFICATIONS OF PATHOGENICITY

Review status

criteria provided, conflicting classifications

Last evaluated

2017/07/13 00:00

Inheritance

Conflicting classifications including Wolfram syndrome 1.

WFS1 variant landscape

F810L is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- Wolfram syndrome 1

## RESEARCH PATH DECISION TREE

$\Delta\Delta G < 2$  + binding site affected → CATEGORY 3 – docking experiments  $\Delta\Delta G$  2–4 → CATEGORY 2 – pharmacological chaperones  $\Delta\Delta G > 4$  → CATEGORY 1 – gene therapy pLDDT < 50 → CATEGORY 5 – IDR, experimental only Stable fold + functional site hit → CATEGORY 4 – site-specific docking

**Category 4 — Stable Fold, Function Disrupted.**  $\Delta\Delta G = +0.08$  — fold essentially unchanged. AlphaMissense 0.994 (near-maximum) confirms severe functional consequence.

Mechanism is loss of F810 aromatic packing that supported E809-K811 salt-bridge geometry. Therapeutic strategy: same microregion as E809K.

F810L + E809K are sister variants at adjacent positions, both pathogenic, both perturbing the local salt-bridge geometry from different angles.