

Variant: *NM_000527.5(LDLR):c.1840T>A (p.Phe614Ile)*

Version: 1.0

CA10585641 [↗](#)

252061 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))

Condition: hypercholesterolemia, familial ([MONDO:0007750](#))

Inheritance Mode: Semidominant inheritance

UUID: c4198a80-aa3c-47c4-8d4a-cf47af9816b9

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HGVS expressions

NM_000527.5:c.1840T>A

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NC_000019.10:g.11116993T>A

CM000681.2:g.11116993T>A

NC_000019.9:g.11227669T>A

CM000681.1:g.11227669T>A

NC_000019.8:g.11088669T>A

NG_009060.1:g.32613T>A

ENST00000252444.10:c.2098T>A

ENST00000559340.2:c.1705+781T>A

ENST00000560467.2:c.1720T>A

ENST00000558518.6:c.1840T>A

ENST00000252444.9:c.2094T>A

ENST00000455727.6:c.1336T>A

ENST00000535915.5:c.1717T>A

ENST00000545707.5:c.1459T>A

ENST00000557933.5:c.1840T>A

ENST00000558013.5:c.1840T>A

ENST00000558518.5:c.1840T>A

ENST00000559340.1:c.426+781T>A

NM_000527.4:c.1840T>A

NM_001195798.1:c.1840T>A

NM_001195799.1:c.1717T>A

NM_001195800.1:c.1336T>A

NM_001195803.1:c.1459T>A

NM_001195798.2:c.1840T>A

NM_001195799.2:c.1717T>A

NM_001195800.2:c.1336T>A

NM_001195803.2:c.1459T>A

Likely Pathogenic

Met criteria codes **5**

PS3 PP1 PP3 PP4 PM2

Not Met criteria codes **16**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS4

BA1

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS2

BP7

BP4

BP3

BP2

Evidence Links 0

- [Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2](#)
- [PDF](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1840T>A (p.Phe614Ile) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS3, PM2, PP1, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 28 March 2025.. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v4.1.0). PP3: REVEL=0.912. PS3: Level 1 assays: PMID 35568682 (Graça et al., 2022): Heterologous cells (CHO-IdIA7 cells), cytometry assays - results - <60% surface LDLR, <60% LDL-LDLR binding, <60% uptake. ---- results are below 70% of wild-type, so functional study is consistent with damaging effect. PP4: Variant meets PM2 and is identified in 1 case with Possible FH by Simon Broome criteria from Cardiovascular Research group, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal, after alternative causes of high cholesterol were excluded. PP1: Variant segregates with FH phenotype in 2 informative meioses identified by Cardiovascular Research group, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal.

Met criteria codes

PS3			Level 1 assays: PMID 35568682: Heterologous cells (CHO-IdIA7 cells), cytometry assays - results - <60% surface LDLR, <60% LDL-LDLR binding, <60% uptake. ---- results are below 70% of wild-type, so functional study is consistent with damaging effect. PS3 is met.
PP1			Variant segregates with FH phenotype in 2 informative meioses identified by Cardiovascular Research Group, Instituto Nacional de Saúde Doutor Ricardo Jorge. So, PP1 is met.
PP3			REVEL=0.912. It is above 0.75, so PP3 is met.
PP4			Variant meets PM2. Identified in 1 FH case from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge with Simon Broome criteria of possible FH, after alternative causes of high cholesterol were excluded. So, PP4 is met.
PM2			This variant is absent from gnomAD (gnomAD v4.1.0). So, PM2 is met.

Not Met criteria codes

PS1			No other missense variant in the same codon.
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS4			Variant meets PM2. Identified in 1 FH case from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge with Simon Broome criteria of possible FH, after alternative causes of high cholesterol were excluded.
BA1			This variant is absent from gnomAD (gnomAD v4.1.0).
PM1			Not on exon 4. Not a cysteine residue.
PM3			No data available.
PM5			No other missense variant in the same codon.
PM4			No in-frame deletions/insertions.
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			This variant is absent from gnomAD (gnomAD v4.1.0).
BS4			No data available.
BS2			No data available.
BP7			Not a synonymous variant.
BP4			REVEL=0.912. It is above 0.5.
BP3			No in-frame deletions/insertions.
BP2			No data available.

Curation History 		
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