The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2025/3/28
Published on: 2025/6/30

HGVS expressions

NM_000527.5(LDLR):c.1840T>A (p.Phe614Ile)
NM_000527.5:c.1840T>A
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 PM6 PM1
PM3 PM5 PM4 BA1 BS2
BS1 BS4 BP4 BP3 BP2 BP7

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-ldlA7 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-ldlA7 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.
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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.
BA1		✖	This variant is absent from gnomAD (gnomAD v4.1.0).
BS2		✖	No data available.
BS1		✖	This variant is absent from gnomAD (gnomAD v4.1.0).
BS4		✖	No data available.
BP4		✖	REVEL=0.912. It is above 0.5.
BP3		✖	No in-frame deletions/insertions.
BP2		✖	No data available.
BP7		✖	Not a synonymous variant.

Curation History

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