

Variant: NM_000527.5(LDLR):c.846C>A (p.Phe282Leu)

Version: 1.0

CA023778 [↗](#)

183098 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 793a906e-889c-4bc4-8d0b-c59588d0f381

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HGVS expressions

NM_000527.5(LDLR):c.846C>A (p.Phe282Leu)

NM_000527.5:c.846C>A

NC_000019.10:g.11107420C>A

CM000681.2:g.11107420C>A

NC_000019.9:g.11218096C>A

CM000681.1:g.11218096C>A

NC_000019.8:g.11079096C>A

NG_009060.1:g.23040C>A

ENST00000252444.10:c.1104C>A

ENST00000559340.2:c.846C>A

ENST00000560467.2:c.846C>A

ENST00000558518.6:c.846C>A

ENST00000252444.9:c.1100C>A

ENST00000455727.6:c.342C>A

ENST00000535915.5:c.723C>A

ENST00000545707.5:c.465C>A

ENST00000557933.5:c.846C>A

ENST00000558013.5:c.846C>A

ENST00000558518.5:c.846C>A

ENST00000558528.1:n.361C>A

ENST00000560467.1:c.446C>A

NM_000527.4:c.846C>A

NM_001195798.1:c.846C>A

NM_001195799.1:c.723C>A

NM_001195800.1:c.342C>A

NM_001195803.1:c.465C>A

NM_001195798.2:c.846C>A

NM_001195799.2:c.723C>A

NM_001195800.2:c.342C>A

NM_001195803.2:c.465C>A

Likely Pathogenic

Met criteria codes 5

PS3_SupportingPP3PP4PM2PS4_Supporting

Not Met criteria codes 16

BA1BP4BP3BP2BS1BS4BS2PP1PM6PM1PM3PM5PM4PS1PS2PVS1

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

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.846C>A (p.Phe282Leu) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PS3_Supporting, PS4_Supporting, PM2, PP3, and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1016/j.gim.2021.09.012>). The supporting evidence is as follows:

PS3_Supporting: Level 3 assays: PMID 25647241: HeLa cells, In vitro microscopy assays - result - 66% wild type LDLR expression (below 70%, Figure 3). ---- functional study is consistent with damaging effect. So, PS3_Supporting is met.

PS4_Supporting: Variants meets PM2 and is identified in 2 cases from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille with diagnosis of probable FH based on DLCN criteria. So, PS4_Supporting is met.

PM2: PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes (gnomAD v2.1.1). So, PM2 is met.

PP3: REVEL=0.877. It is above 0.75, so PP3 is met.

PP4: Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH (see PS4 for details), after alternative causes for high cholesterol were excluded.

Met criteria codes

PS3_Supporting			Level 3 assays: PMID 25647241: HeLa cells, In vitro microscopy assays - result - 66% wild type LDLR expression (below 70%, Figure 3). ---- functional study is consistent with damaging effect. So, PS3_Supporting is met.
PP3			REVEL=0.877. It is above 0.75, so PP3 is met
PP4			Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH (see PS4 for details), after alternative causes for high cholesterol were excluded.
PM2			PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes (gnomAD v2.1.1). So, PM2 is met.
PS4_Supporting			Variants meets PM2 and is identified in 2 cases from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille with diagnosis of probable FH based on DLCN criteria. So, PS4_Supporting is met.

Not Met criteria codes

BA1			PopMax FAF= 0.000003977
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BP4			REVEL=0.877 (>0.5).
BP3			No in-frame deletions/insertions
BP2			No data available
BS1			PopMax FAF= 0.000003977
BS4			No data available.
BS2			No data available.
PP1			No data available.
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			Not in exon 4. Not a cysteine residue.
PM3			No data available
PM5			3 other missense variants in the same codon: - NM_000527.5(LDLR):c.845T>A (p.Phe282Tyr) (ClinVar ID 1763461) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.845T>C (p.Phe282Ser) (ClinVar ID 1466547) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.845T>G (p.Phe282Cys) (ClinVar ID 977997) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4			No in-frame deletions/insertions
PS1			One more missense variant that leads to the same amino acid change: - NM_000527.5(LDLR):c.844T>C (p.Phe282Leu) (ClinVar ID 977996) - classified as uncertain significance by these guidelines
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			Not a null variant

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