

Variant: *NM_000527.5(LDLR):c.1961T>C (p.Leu654Pro)*

Version: 1.0

CA404093213 [↗](#)

979168 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 0de395d2-5f72-42ba-b390-c1c0b221781c

Approved on: 2024/10/28

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HGVS expressions

NM_000527.5(LDLR):c.1961T>C (p.Leu654Pro)

NM_000527.5:c.1961T>C

NC_000019.10:g.11120207T>C

CM000681.2:g.11120207T>C

NC_000019.9:g.11230883T>C

CM000681.1:g.11230883T>C

NC_000019.8:g.11091883T>C

NG_009060.1:g.35827T>C

ENST00000252444.10:c.2219T>C

ENST00000559340.2:c.*30T>C

ENST00000560467.2:c.1841T>C

ENST00000558518.6:c.1961T>C

ENST00000252444.9:c.2215T>C

ENST00000455727.6:c.1457T>C

ENST00000535915.5:c.1838T>C

ENST00000545707.5:c.1580T>C

ENST00000557933.5:c.1961T>C

ENST00000558013.5:c.1961T>C

ENST00000558518.5:c.1961T>C

ENST00000559340.1:c.542T>C

NM_000527.4:c.1961T>C

NM_001195798.1:c.1961T>C

NM_001195799.1:c.1838T>C

NM_001195800.1:c.1457T>C

NM_001195803.1:c.1580T>C

NM_001195798.2:c.1961T>C

NM_001195799.2:c.1838T>C

NM_001195800.2:c.1457T>C

NM_001195803.2:c.1580T>C

Uncertain Significance

Met criteria codes **4**

PS4_Supporting

PP3

PP4

PM2

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

PVS1

BS1

BS4

BS3

BP4

BP3

BP1

BP2

BP5

BP7

PS1

PS2

PS3

BA1

PP1

PP2

PM1

PM3

PM5

PM4

PM6

Evidence Links

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- 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.1961T>C (p.Leu654Pro) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 28 October 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v4.1.0). PP3: REVEL = 0.911. PS4_Supporting, PP4: Variant meets PM2 and is identified in 2 unrelated index cases who fulfill modified DLCN criteria >=6 from Setia et al., 2020 (PMID 32044282).

Met criteria codes

PS4_Supporting		✓	Variant meets PM2 and is identified in 2 unrelated index cases who fulfill modified DLCN criteria>=6 from PMID: 32044282
PP3		✓	REVEL = 0.911. It is above 0.75, so PP3 is met.
PP4		✓	Variant meets PM2 and is identified in at least 1 index case fulfilling Simon Broome criteria for possible FH criteria, after alternative causes of high cholesterol were excluded, from PMID: 32044282
PM2		✓	This variant is absent from gnomAD (gnomAD v4.1).

Not Met criteria codes

BS2		✗	Not identified in normolipidemic controls
PVS1		✗	Missense variant
BS1		✗	This variant is absent from gnomAD (gnomAD v4.1).
BS4		✗	No non-segregation reported
BS3		✗	not met (no information or reports of functional data).
BP4		✗	REVEL not below 0.5, therefore BP4 is not met

BP3			Missense variant
BP1			Not applicable
BP2			Not identified in index cases with more than one variant
BP5			Not applicable
BP7			Missense variant
PS1			No variant with same amino acid change identified as pathogenic
PS2			No de novo occurrence
PS3			not met (no information or reports of functional data).
BA1			This variant is absent from gnomAD (gnomAD v4.1).
PP1			PP1: from PMID:32044282 (Table 2), segregation in 1/2 family members is indicated, and it is stated that "positive segregation was indicated in family members with premature CAD or historical LDL-C elevations". However phenotype of relatives are unclear, and therefore this data was not considered.
PP2			Not applicable
PM1			Variant meets PM2 but is not located in exon 4, and is not one of 60 highly conserved cysteine residues
PM3			Not identified in index cases with more than one variant
PM5			NM_000527.5(LDLR):c.1960C>T (p.Leu654Phe) (ClinVar ID: 252132) considered as VUS by these guidelines.
PM4			Missense variant
PM6			No de novo occurrence

Showing 1 to 1 of 1 rows

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