

Variant: *NM_000527.5(LDLR):c.1750T>C (p.Ser584Pro)*

Version: 1.0

CA10585598 [↗](#)

252015 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: e5017f83-49fb-4db7-9727-4adac110d7d2

Approved on: 2025/3/28

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HGVS expressions

NM_000527.5(LDLR):c.1750T>C (p.Ser584Pro)

NM_000527.5:c.1750T>C

NC_000019.10:g.11116903T>C

CM000681.2:g.11116903T>C

NC_000019.9:g.11227579T>C

CM000681.1:g.11227579T>C

NC_000019.8:g.11088579T>C

NG_009060.1:g.32523T>C

ENST00000252444.10:c.2008T>C

ENST00000559340.2:c.1705+691T>C

ENST00000560467.2:c.1630T>C

ENST00000558518.6:c.1750T>C

ENST00000252444.9:c.2004T>C

ENST00000455727.6:c.1246T>C

ENST00000535915.5:c.1627T>C

ENST00000545707.5:c.1369T>C

ENST00000557933.5:c.1750T>C

ENST00000558013.5:c.1750T>C

ENST00000558518.5:c.1750T>C

ENST00000559340.1:c.426+691T>C

NM_000527.4:c.1750T>C

NM_001195798.1:c.1750T>C

NM_001195799.1:c.1627T>C

NM_001195800.1:c.1246T>C

NM_001195803.1:c.1369T>C

NM_001195798.2:c.1750T>C

NM_001195799.2:c.1627T>C

NM_001195800.2:c.1246T>C

NM_001195803.2:c.1369T>C

Likely Pathogenic

Met criteria codes 4

PS3 PP3 PP4 PM2

Not Met criteria codes 3

PS4 PM1 BP4

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.1750T>C (p.Ser584Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS3, PM2, 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 = 0.86. PS3: Level 1 assays: PMID: 32015373 (Galicia-Garcia et al., 2020): heterologous CHO-IIdIA7 cells, cytometry assay, <20% surface LDLR, <10% LDL-LDLR binding, <10% uptake. ---- results are below 70% of wild-type, so functional study is consistent with damaging effect. PP4: Variant meets PM2 and is identified in at least 1 index case fulfilling FH criteria (1 case with Dutch Lipid Clinic Network Criteria score ≥ 6 from PMID 19318025 (Alonso et al., 2009), Spain), after alternative causes of high cholesterol were excluded.

Met criteria codes

PS3			Level 1 assays: PMID: 32015373: heterologous CHO-IIdIA7 cells, cytometry assay, <20% surface LDLR, <10% LDL-LDLR binding, <10% uptake. ---- results are below 70% of wild-type, so functional study is consistent with damaging effect.
PP3			REVEL = 0.86.
PP4			Variant meets PM2. PMID: 19318025 (Alonso et al., 2009), Spain - 1 case with clinical Dutch Lipid Clinic Network Criteria score ≥ 6.
PM2			This variant is absent from gnomAD (gnomAD v4.1.0).

Not Met criteria codes

PS4			Only 1 FH patient with DLCN>=6 from PMID: 19318025.
PM1			Variant meets PM2 but it is not in exon 4 (located in exon 12) and does not alter a critical Cys residue.
BP4			REVEL = 0.86.

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