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.1739C>T (p.Ser580Phe)

Version: 1.0

CA305301758

438325 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: a48735f3-cd3e-4da7-96bf-e0823e89c216
Approved on: 2023/11/7
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HGVS expressions

NM_000527.5:c.1739C>T
NM_000527.5(LDLR):c.1739C>T (p.Ser580Phe)
NC_000019.10:g.11116892C>T
CM000681.2:g.11116892C>T
NC_000019.9:g.11227568C>T
CM000681.1:g.11227568C>T
NC_000019.8:g.11088568C>T
NG_009060.1:g.32512C>T
ENST00000252444.10:c.1997C>T
ENST00000559340.2:c.1705+680C>T
ENST00000560467.2:c.1619C>T
ENST00000558518.6:c.1739C>T
ENST00000252444.9:c.1993C>T
ENST00000455727.6:c.1235C>T
ENST00000535915.5:c.1616C>T
ENST00000545707.5:c.1358C>T
ENST00000557933.5:c.1739C>T
ENST00000558013.5:c.1739C>T
ENST00000558518.5:c.1739C>T
ENST00000559340.1:c.426+680C>T
NM_000527.4:c.1739C>T
NM_001195798.1:c.1739C>T
NM_001195799.1:c.1616C>T
NM_001195800.1:c.1235C>T
NM_001195803.1:c.1358C>T
NM_001195798.2:c.1739C>T
NM_001195799.2:c.1616C>T
NM_001195800.2:c.1235C>T
NM_001195803.2:c.1358C>T

Likely Pathogenic

Met criteria codes 6

PP1 PP3 PP4 PM2 PS4_Supporting PS3_Supporting

Not Met criteria codes 16

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PS1 PS2 PM6 PM1 PM3
PM5 PM4 BA1 BS2 PVS1
BS1 BS4 BS3 BP4 BP3 BP2

Criteria Specifications for this VCEP

Evidence Links 1

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1739C>T (p.Ser580Phe) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP1, PP3, PP4, PS3_Supporting and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 7 November 2023. The supporting evidence is as follows: PM2: PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1). PP3: REVEL=0.907. PS3_Supporting: Level 3 assay: PMID 35474963 (Pfisterer SG et al., 2022): Heterozygous patient monocytes and lymphocytes. 25-50% of control low-density lipoprotein particle uptake and LDLR surface expression. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 3 unrelated index cases who fulfill DLCN score >=6 (1 case from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 2 cases from Research Lab of Molecular Genetics of Lipid Metabolism, Italy - Prof. M. Arca). PP1: Variant segregates with FH phenotype in 2 informative meioses identified by Research Lab of Molecular Genetics of Lipid Metabolism, Italy - Prof. M. Arca. 1 affected family member has the variant and 1 unaffected family member does not have the variant.

Met criteria codes

PP1	✓	variant segregates with FH phenotype in 2 informative meioses identified by Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca (1 family member positive for variant with LDL-C >75th percentile and 1 family member negative for the variant with LDL-C <50th percentile). So, PP1 is met.
PP3	✓	REVEL=0.907. It is above 0.75, so PP3 is met.
PP4	✓	Variant meets PM2 and is identified in 3 unrelated index cases who fulfill clinical criteria for FH from several labs (see PS4 for details), after alternative causes of high cholesterol were excluded.
PM2	✓	PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1). So, PM2 is met.
PS4_Supporting	✓	Variant meets PM2 and is identified in 3 unrelated index cases (1 case with DLCN criteria>=6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 2 cases with DLCN criteria>=6 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca). So, PS4_Supporting is met.
PS3_Supporting	✓	Level 3 assay: PMID 35474963: Heterozygous patients monocytes and lymphocytes - results - 25-50% low-density lipoprotein particle uptake and LDLR surface expression. ---- Overall LDLR expression and activity is below 85% of wild-type activity. So, PS3_Supporting is met. het monocytes and lymphocytes used; 25-50% LDL uptake and LDLR surface expression (Fig 1G, 2A, 2B, SF1J) PubMed:35474963

Not Met criteria codes

PS1	✖	No other missense variant in the same codon resulting in a similar amino acid change
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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	✖	2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1738T>C (p.Ser580Pro) (ClinVar ID 375822) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.1739C>G (p.Ser580Cys) (ClinVar ID 921461) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4	✖	No in-frame deletion/insertion
BA1	✖	PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1).
BS2	✖	No data available
PVS1	✖	Not a null variant
BS1	✖	PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1).
BS4	✖	variant segregates with FH phenotype in 2 informative meioses identified by Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca (1 family member positive for variant with LDL-C >75th percentile and 1 family member negative for the variant with LDL-C <50th percentile).
BS3	✖	Level 2 assay: PMID 21865347: Heterozygous patients' Epstein-Barr virus transformed lymphocytes, FACS assays - results - 64% low-density lipoprotein particle receptor activity ---- Overall LDLR activity is below 85% of wild-type activity.
BP4	✖	REVEL=0.907. It is above 0.5
BP3	✖	No in-frame deletion/insertion
BP2	✖	No data available

Curation History

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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.