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.530C>T (p.Ser177Leu)

Version: 1.0

CA023715

3686 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 50f0c43e-cc4f-40fa-b9f2-0e1dbe5c246a
Approved on: 2022/6/3
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HGVS expressions

NM_000527.5(LDLR):c.530C>T (p.Ser177Leu)
NM_000527.5:c.530C>T
NC_000019.10:g.11105436C>T
CM000681.2:g.11105436C>T
NC_000019.9:g.11216112C>T
CM000681.1:g.11216112C>T
NC_000019.8:g.11077112C>T
NG_009060.1:g.21056C>T
ENST00000252444.10:c.788C>T
ENST00000559340.2:c.530C>T
ENST00000560467.2:c.530C>T
ENST00000558518.6:c.530C>T
ENST00000252444.9:c.784C>T
ENST00000455727.6:c.314-1956C>T
ENST00000535915.5:c.407C>T
ENST00000545707.5:c.314-1129C>T
ENST00000557933.5:c.530C>T
ENST00000558013.5:c.530C>T
ENST00000558518.5:c.530C>T
ENST00000560467.1:c.130C>T
NM_000527.4:c.530C>T
NM_001195798.1:c.530C>T
NM_001195799.1:c.407C>T
NM_001195800.1:c.314-1956C>T
NM_001195803.1:c.314-1129C>T
NM_001195798.2:c.530C>T
NM_001195799.2:c.407C>T
NM_001195800.2:c.314-1956C>T
NM_001195803.2:c.314-1129C>T

Pathogenic

Met criteria codes 9

BS4 PP1_Strong PS3 PS4 PM1 PM3 PM2 PP3 PP4

Not Met criteria codes 17

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PVS1 BS2 BS1 BS3 BP4
BP3 BP1 BP2 BP5 BP7 PS1
PS2 BA1 PM5 PM4 PM6
PP2

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR): c.530C>T (p.Ser177Leu) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PS3, PS4, PM1, PM2, PM3, PP1_Strong, PP3, PP4 and BS4) 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 - PMID: 31578082 - Level 1 assay - Heterologous cells (CHO), FACS assays and CLSM: 65% cell surface LDLR, 10% binding and <2% uptake. PMID: 2760205 - Level 2 assay - Homozygous patient fibroblast, 125I-LDL assays: <2% LDLR activity. PMID: 25647241 - Level 3 assay - Heterologous cells (HeLa), CLSM assays: LDLR activity decreased compared to WT - considered as disruptive. PS4 - Variant meets PM2. Variant identified in 30 unrelated index cases (5 cases (2 with DLCN≥6; 3 with Simon-Broome possible) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 1 case with Simon-Broome possible from GeneDx Inc.; 11 cases with Simon-Broome possible from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge; 13 cases with Simon-Broome possible/definite from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation). PM1 - Variant meets PM2 and is missense in exon 4. PM2 - PopMax MAF = 0.00006533 (0.006533%) in South Asian exomes+genomes (gnomAD v2.1.1). PM3 - Patient 3 from PMID: 18263977 has LDL = 19.7 mmol/l and also LDLR p.Arg350* in trans - Pathogenic by these guidelines. Two true homozygotes (FHF23 and FHF57) published in PMID: 27816806 had LDL = 16.2 mmol/l and 22.6 mmol/l, respectively. PP1_Strong - Variant segregates with FH phenotype in 52 informative meiosis in 26 families from different labs (Laboratory of Genetics and Molecular Cardiology, University of São Paulo; Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge): 43 relatives tested positive had LDL-C >75th percentile + 9 relatives tested negative had LDL-C <50th percentile. PP3 - REVEL = 0.886. PP4 - Variant meets PM2. Variant identified in 30 unrelated index cases who fulfill clinical criteria for FH from several labs (see PS4 for details). BS4 - Variant does not segregate with phenotype in 14 informative meiosis from at least 6 families from different labs (Laboratory of Genetics and Molecular Cardiology, University of São Paulo; Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge): 13 relatives tested negative but had LDL-C >75th percentile + 1 relative tested positive but LDL-C <50th percentile. Variant has 3 Strong, 3 Moderate and 2 Supporting evidence codes towards Pathogenic, enough to classify as Pathogenic, and only 1 Strong evidence codes towards Benign. The Pathogenic criteria overwhelms the Benign criteria, so we are confident in classifying this variant as Pathogenic.

Met criteria codes

BS4	✔	Variant does not segregate with phenotype in 14 informative meiosis from at least 6 families from different labs (Laboratory of Genetics and Molecular Cardiology, University of São Paulo; Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge): 13 relatives tested negative but had LDL-C >75th percentile + 1 relative tested positive but LDL-C <50th percentile.
PP1_Strong	✔	Variant segregates with FH phenotype in 52 informative meiosis in 26 families from different labs (Laboratory of Genetics and Molecular Cardiology, University of São Paulo; Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); Cardiovascular Research

Group,Instituto Nacional de Saude Doutor Ricardo Jorge): 43 relatives tested positive had LDL-C >75th percentile + 9 relatives tested negative had LDL-C <50th percentile.

PS3	✔	PMID: 31578082 - Level 1 assay - Heterologous cells (CHO), FACS assays and CLSM: 65% cell surface LDLR, 10% binding and <2% uptake. PMID: 2760205 - Level 2 assay - Homozygous patient fibroblast, 125I-LDL assays: <2% LDLR activity. PMID: 25647241 - Level 3 assay - Heterologous cells (HeLa), CLSM assays: LDLR activity decreased compared to WT - considered as disruptive.
PS4	✔	Variant meets PM2. Variant identified in 30 unrelated index cases (5 cases (2 with DLCN≥6; 3 with Simon-Broome possible) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 1 case with Simon-Broome possible from GeneDx Inc.; 11 cases with Simon-Broome possible from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge; 13 cases with Simon-Broome possible/definite from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation).
PM1	✔	Variant meets PM2 and is missense in exon 4.
PM3	✔	Patient 3 from PMID: 18263977 has LDL = 19.7 mmol/l and also LDLR p.Arg350* in trans - Pathogenic by these guidelines. Two true homozygotes (FHF23 and FHF57) published in PMID: 27816806 had LDL = 16.2 mmol/l and 22.6 mmol/l, respectively.
PM2	✔	PopMax MAF = 0.00006533 (0.006533%) in South Asian exomes+genomes (gnomAD v2.1.1).
PP3	✔	REVEL = 0.886
PP4	✔	Variant meets PM2. Variant identified in 30 unrelated index cases (5 cases (2 with DLCN≥6; 3 with Simon-Broome possible) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 1 case with Simon-Broome possible from GeneDx Inc.; 11 cases with Simon-Broome possible from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge; 13 cases with Simon-Broome possible/definite from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation).

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	1 other missense variant in the same codon: - NM_000527.5(LDLR):c.529T>C (p.Ser177Pro) (ClinVar ID 403631) - Likely pathogenic by these guidelines (classification was made without case level data from other labs) There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4	✖	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
PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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