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Variant: NM_000527.5(LDLR):c.542C>G (p.Pro181Arg)

Version: 1.0

CA023717

183089 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: c2e8a4a2-bae2-4d81-aa9a-f795650a42fa
Approved on: 2024/2/23
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HGVS expressions

NM_000527.5(LDLR):c.542C>G (p.Pro181Arg)
NM_000527.5:c.542C>G
NC_000019.10:g.11105448C>G
CM000681.2:g.11105448C>G
NC_000019.9:g.11216124C>G
CM000681.1:g.11216124C>G
NC_000019.8:g.11077124C>G
NG_009060.1:g.21068C>G
ENST00000252444.10:c.800C>G
ENST00000559340.2:c.542C>G
ENST00000560467.2:c.542C>G
ENST00000558518.6:c.542C>G
ENST00000252444.9:c.796C>G
ENST00000455727.6:c.314-1944C>G
ENST00000535915.5:c.419C>G
ENST00000545707.5:c.314-1117C>G
ENST00000557933.5:c.542C>G
ENST00000558013.5:c.542C>G
ENST00000558518.5:c.542C>G
ENST00000560467.1:c.142C>G
NM_000527.4:c.542C>G
NM_001195798.1:c.542C>G
NM_001195799.1:c.419C>G
NM_001195800.1:c.314-1944C>G
NM_001195803.1:c.314-1117C>G
NM_001195798.2:c.542C>G
NM_001195799.2:c.419C>G
NM_001195800.2:c.314-1944C>G
NM_001195803.2:c.314-1117C>G

Likely Pathogenic

Met criteria codes 5

PP4 PM2 PM1 PS3_Moderate PS4_Moderate

Not Met criteria codes 17

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP1 PP3 BA1 PM6 PM3 PM5 PM4 BS2 BS1 BS4 BS3 PS1 PS2 BP4 BP3 BP2 PVS1

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.542C>G (p.Pro181Arg) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM1, PM2, PS3_Moderate, PS4_Moderate and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: PopMax MAF = 0.00005 (0.005%) in European (Non-Finnish) exomes+genomes (gnomAD v4.0.0). PM1: Variant meets PM2 and is a missense in exon 4. PS3_Moderate: Level 2 assay: PMID 21868016 (Garcia-Garcia A et al., 2011): COS-7 cells. Mature/precursor LDLR forms ratio ~60% ---- Overall LDLR biosynthesis is below 70% of wild-type activity. PS4_Moderate, PP4: Variant meets PM2 and is identified in at least 6 unrelated index cases who fulfill criteria for FH (1 case from PMID 16250003 (Fouchier SW et al., 2005); 2 cases with MedPed and Simon Broome criteria from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic, and PMID 22698793 (Tichý L et al., 2012); 2 cases meeting Simon Broome and DLCN criteria from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; 1 case with DLCN score>=6 from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia).

Met criteria codes

PP4	✔	Variant meets PM2 and is identified at least 6 unrelated index cases who fulfill clinical criteria for FH from several labs and articles (see PS4 for details), after alternative causes of high cholesterol were excluded.
PM2	✔	PopMax MAF = 0.00005 (0.005%) in European (Non-Finnish) exomes+genomes (gnomAD v4.0.0). So, PM2 is met.
PM1	✔	Variant meets PM2 and it is exon 4 (codon 542). So, PM1 is met.
PS3_Moderate	✔	Level 2 assay: PMID 21868016: COS-7 cells - results - Mature/precursor LDLR forms ratio ~60% ---- Overall LDLR biosynthesis is below 70% of wild-type activity. So, PS3_Moderate is met.
PS4_Moderate	✔	Variant meets PM2 and is identified in at least 6 unrelated individuals, as follows: 1 case with FH based on Defesche 2000 from PMID 16250003, 2 cases with MedPed and Simon Broome criteria from Molecular Genetics Laboratory, 2 cases with Simon Broome and DLCN criteria from Centre de Génétique Moléculaire et Chromosomique, and 1 case with DLCN criteria from Cardiovascular Genetics Laboratory. So, PS4_Moderate is met.

Not Met criteria codes

PP1	✖	Variant segregates with FH phenotype in 3 informative meioses in 1 family from PMID 21868016. Only one of them is carrier of the variant with a documented FH.

PP3		✖	REVEL=0.713, it is not above 0.75, splicing evaluation required. A) not on limits B) does not create AG or GT C) There is AG and GT nearby For GT: Wt score: 7.67, Wt cryptic: -14.77, var cryptic: -17.23 var cryptic/wt cryptic: 1.16, var cryptic/wt score: -2.24 For AG: wt score: 8.16, wt cryptic: -4.13, var cryptic: -7.29 var cryptic/wt cryptic: 1.76, var cryptic/wt score: -0.89 Variant is not predicted to alter splicing.
BA1		✖	PopMax MAF = 0.00005 (0.005%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1).
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3		✖	No data available
PM5		✖	1 other missense variants in the same codon: - NM_000527.5(LDLR):c.542C>T (p.Pro181Leu) (ClinVar ID 431512) - Likely pathogenic by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4		✖	No in-frame deletions/insertions
BS2		✖	2 individuals with the variant and normal lipid levels.
BS1		✖	PopMax MAF = 0.00005 (0.005%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1).
BS4		✖	1 family member with FH and without the variant.
BS3		✖	Level 3 assays - PMID 25647241: HeLa cells, in vitro microscopy assays - results - LDLR activity similar to WT.
PS1		✖	No other missense variant with the same amino acid change
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	REVEL=0.713. It is >0.5.
BP3		✖	No in-frame deletions/insertions
BP2		✖	One proband with LDLR variant D471N (suspected to be in trans) and LDLc=310 mg/dl from Centre de Génétique Moléculaire et Chromosomique. 1) The trans alignment is not definite. 2) classification of the other variant (NM_000527.5(LDLR):c.1474G>A (p.Asp492Asn)) is conflicting and some centers considered it likely pathogenic and even VUS.
PVS1		✖	Not a null variant (nonsense, frameshift, canonical +/- 1 or 2 splice sites, initiation codon, single or multiexon deletion)

Curation History

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