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Variant: NM_000527.5(LDLR):c.270T>A (p.Asp90Glu)

Version: 1.1

CA10584821

251107 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: c59d43d0-b343-44d0-b9cb-f1b7f782876f
Approved on: 2021/12/30
Published on: 2022/7/11

HGVS expressions

NM_000527.5(LDLR):c.270T>A (p.Asp90Glu)
NM_000527.5:c.270T>A
NC_000019.10:g.11102743T>A
CM000681.2:g.11102743T>A
NC_000019.9:g.11213419T>A
CM000681.1:g.11213419T>A
NC_000019.8:g.11074419T>A
NG_009060.1:g.18363T>A
ENST00000252444.10:c.528T>A
ENST00000559340.2:c.270T>A
ENST00000560467.2:c.270T>A
ENST00000558518.6:c.270T>A
ENST00000252444.9:c.524T>A
ENST00000455727.6:c.270T>A
ENST00000535915.5:c.190+2398T>A
ENST00000545707.5:c.270T>A
ENST00000557933.5:c.270T>A
ENST00000557958.1:n.356T>A
ENST00000558013.5:c.270T>A
ENST00000558518.5:c.270T>A
NM_000527.4:c.270T>A
NM_001195798.1:c.270T>A
NM_001195799.1:c.190+2398T>A
NM_001195800.1:c.270T>A
NM_001195803.1:c.270T>A
NM_001195798.2:c.270T>A
NM_001195799.2:c.190+2398T>A
NM_001195800.2:c.270T>A
NM_001195803.2:c.270T>A

Pathogenic

Met criteria codes 6

PP3 PP4 PM2 PM5 PP1_Strong PS4_Supporting

Not Met criteria codes 20

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP2 PM6 PM1 PM3 PM4
BA1 BS2 PVS1 BS1 BS4
BS3 BP5 BP7 BP4 BP3 BP1
BP2 PS1 PS2 PS3

Evidence Links 0

Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.270T>A (p.Asp90Glu) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence PP1_Strong, PM2, PM5, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1101/2021.03.17.21252755). The supporting evidence is as follows: PP1_strong - variant segregates with FH phenotype in 11 informative meiosis from 2 families from PMID 20809525 (Marduel et al., 2010): F1: 4 affected relatives have the variant and 3 unaffected relatives do not have the variant; F2: 3 affected relatives have the variant and 1 unaffected relative does not have the variant, so PP1_Strong is met. PM2 - This variant was not identified in gnomAD (gnomAD v2.1.1), so PM2 is met. PM5 - 4 other missense variants is the same codon: - NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.268G>T (p.Asp90Tyr) - classified as Likely pathogenic by the FH VCEP, with these guidelines - NM_000527.5(LDLR):c.269A>C (p.Asp90Ala) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.269A>G (p.Asp90Gly) - Pathogenic by these guidelines There is 1 variant classified as Pathogenic by these guidelines, so PM5 is met. PP3 - REVEL = 0.833. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in 4 index cases with SB criteria of FH (total and LDL-cholesterol levels above the 95th percentile of a sex and age-matched French population and autosomal dominant transmission of hypercholesterolemia in the family) from PMID 20809525 (Marduel et al., 2010), so PP4 is met. PS4_supporting - variant meets PM2 and was identified in 4 index cases with SB criteria of FH from PMID 20809525 (Marduel et al., 2010), (see PP4 for details), so PS4_Supporting is met.

Met criteria codes

PP3	✔	REVEL = 0.833. It is above 0.75, so PP3 is met
PP4	✔	variant meets PM2 and was identified in 4 index cases with SB criteria of FH (total and LDL-cholesterol levels above the 95th percentile of a sex and age-matched French population and autosomal dominant transmission of hypercholesterolemia in the family) from PMID 20809525 (Marduel et al., 2010), so PP4 is met
PM2	✔	This variant was not identified in gnomAD (gnomAD v2.1.1), so PM2 is met
PM5	✔	4 other missense variants is the same codon: - NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.268G>T (p.Asp90Tyr) - classified as Likely pathogenic by the FH VCEP, with these guidelines - NM_000527.5(LDLR):c.269A>C (p.Asp90Ala) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.269A>G (p.Asp90Gly) - Pathogenic by these guidelines There is 1 variant classified as Pathogenic by these guidelines, so PM5 is met.
PP1_Strong	✔	variant segregates with FH phenotype in 11 informative meiosis from 2 families from PMID 20809525 (Marduel et al., 2010): F1: 4 affected relatives have the variant and 3 unaffected relatives do not have the variant; F2: 3 affected relatives have the variant and 1 unaffected relative does not have the variant (4-3, 3-1 in paper), so PP1_Strong is met

PS4_Supporting	ℹ	✔	variant meets PM2 and was identified in: - at least 1 index case with DLCN score of definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583647.1), France - 4 index cases with SB criteria of FH (total and LDL-cholesterol levels above the 95th percentile of a sex and age-matched French population and autosomal dominant transmission of hypercholesterolemia in the family) from PMID 20809525 (Marduel et al., 2010), France only count 4 cases to avoid double counting, so PS4_Supporting is met

Not Met criteria codes

PP2	ℹ	✖	not applicable
PM6	ℹ	✖	no de novo occurrence
PM1	ℹ	✖	variant is not in exon 4 and does not alter Cys, so not met
PM3	ℹ	✖	no index cases with more than 1 variant were identified
PM4	ℹ	✖	variant is missense, so not met
BA1	ℹ	✖	This variant was not identified in gnomAD (gnomAD v2.1.1), so not met
BS2	ℹ	✖	not identified in normolipidemic individuals, so not met
PVS1	ℹ	✖	variant is missense and not in initiation codon, so not met
BS1	ℹ	✖	This variant was not identified in gnomAD (gnomAD v2.1.1), so not met
BS4	ℹ	✖	no lack of segregation was identified, so not met
BS3	ℹ	✖	no functional studies performed, so not met
BP5	ℹ	✖	not applicable
BP7	ℹ	✖	variant is missense, so not met
BP4	ℹ	✖	REVEL = 0.833. It is not below 0.50, so BP4 is not met
BP3	ℹ	✖	not applicable
BP1	ℹ	✖	not applicable

BP2	✖	no index cases with more than 1 variant were identified
PS1	✖	no other missense variant leads to the same amino acid change, so not met
PS2	✖	no de novo occurrence
PS3	✖	no functional studies performed, so not met

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.270T>A (p.Asp9...	Pathogenic	Hypercholesterolemia, Familial	2022-07-11	1.1	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1	LDLR
View	NM_000527.5(LDLR):c.270T>A (p.Asp9...	Pathogenic	Hypercholesterolemia, Familial	2022-01-01	1.0	-	LDLR

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