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Variant: NM_000527.5(LDLR):c.970G>A (p.Gly324Ser)

Version: 1.0

CA023801

161263 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: ffcac230-1fce-4800-8865-926e499ad6fc
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HGVS expressions

NM_000527.5:c.970G>A
NM_000527.5(LDLR):c.970G>A (p.Gly324Ser)
NC_000019.10:g.11110681G>A
CM000681.2:g.11110681G>A
NC_000019.9:g.11221357G>A
CM000681.1:g.11221357G>A
NC_000019.8:g.11082357G>A
NG_009060.1:g.26301G>A
ENST00000252444.10:c.1228G>A
ENST00000559340.2:c.970G>A
ENST00000560467.2:c.941-833G>A
ENST00000558518.6:c.970G>A
ENST00000252444.9:c.1224G>A
ENST00000455727.6:c.466G>A
ENST00000535915.5:c.847G>A
ENST00000545707.5:c.589G>A
ENST00000557933.5:c.970G>A
ENST00000558013.5:c.970G>A
ENST00000558518.5:c.970G>A
ENST00000560467.1:c.541-833G>A
NM_000527.4:c.970G>A
NM_001195798.1:c.970G>A
NM_001195799.1:c.847G>A
NM_001195800.1:c.466G>A
NM_001195803.1:c.589G>A
NM_001195798.2:c.970G>A
NM_001195799.2:c.847G>A
NM_001195800.2:c.466G>A
NM_001195803.2:c.589G>A

Benign

Met criteria codes 5

PP1 PP3 BA1 BS2 BP2

Not Met criteria codes 21

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP2 PP4 PM1 PM3 PM5
PM4 PM6 PM2 PVS1 BS1
BS4 BS3 PS1 PS2 PS3 PS4
BP4 BP3 BP1 BP5 BP7

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.970G>A (p.Gly324Ser) variant is classified as Benign for Familial Hypercholesterolemia by applying evidence codes (BA1, BS2, BP2, PP1 and PP3) 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: BA1 - FAF = 0.01153 (1.153%) in African/African American exomes (gnomAD v2.1.1). BS2 - Identified in 4 heterozygous non-affected family members from different labs. BP2 - variant identified 1 index case with heterozygous FH phenotype who is double heterozygous with NM_000384.3(APOB):c.10580G>A p.Arg3527Gln (ClinVar ID 17890) - classified as Pathogenic by the general ACMG guidelines (Chora et al., 2018). PP1 - variant segregates with phenotype in 2 informative meiosis in 1 family from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge. PP3 - REVEL = 0.815. Variant has 1 stand alone, 1 Strong and 1 Supporting evidence codes towards Benign, enough to classify as Benign, and only 2 Supporting codes towards Pathogenic. The Benign criteria overwhelms the Pathogenic criteria, so we are confident in classifying this variant as Benign.

Met criteria codes

PP1	✔	variant segregates with phenotype in 2 informative meiosis in 1 family from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge: 2 affected family members have the variant. --- PP1 is Met
PP3	✔	REVEL = 0.815. It is above 0.75, so PP3 is Met
BA1	✔	FAF = 0.01153 (1.153%) in African/African American exomes (gnomAD v2.1.1). FAF is above 0.5%, so BA1 is Met.
BS2	✔	identified in 4 heterozygous non-affected family members from different labs (Robarts Research Institute and Laboratory of Genetics and Molecular Cardiology). --- BS2 is Met
BP2	✔	variant identified in - 1 index case with heterozygous FH phenotype from GeneDx Inc. (#)2 with another LDLR variant 'LDLR PATH HET (phase unknown)'. --- 2nd variant is not specified, so BP2 is Not Met - 2 index cases from Laboratory of Genetics and Molecular Cardiology with other variants, but in cis, so BP2 is Not Met - 1 index case with phenotype of Heterozygous FH from University of British Columbia with also the NM_000527.5(LDLR):c.301G>A p.Glu101Lys variant (ClinVar ID 161266) -- classified as Likely pathogenic by these guidelines, so BP2 is not met - 1 index case with heterozygous FH phenotype from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge is double heterozygous with NM_000384.3(APOB):c.10580G>A p.Arg3527Gln (ClinVar ID 17890) - classified as Pathogenic by the general ACMG guidelines (Chora et al., 2018) --- BP2 is Met

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Not Met criteria codes

PP2	✖	Not applicable
PP4	✖	Variant does not meet PM2, so PP4 is Not Met
PM1	✖	Missense at codon 324. PM2 is Not Met, it is not exon 4 or any of the 60 Cys residues listed, so PM1 is Not Met
PM3	✖	not identified in individuals with other variants and phenotype of Homozygous FH ---- PM3 is Not Met
PM5	✖	One more missense variant in the same codon: (1)NM_000527.5(LDLR):c.970G>T (p.Gly324Cys) (ClinVar ID 920048) - classified as VUS by these guidelines so PM5 is not met

PM4	✖	Missense variant, not applicable
PM6	✖	no de novo cases were identified, so PM6 is Not Met
PM2	✖	PopMax MAF = 0.01357 (1.36%) in African/African American exomes (gnomAD v2.1.1). MAF is not under 0.02%, so PM2 is Not Met
PVS1	✖	Missense variant, PVS1 Not Met
BS1	✖	FAF = 0.01153 (1.153%) in African/African American exomes (gnomAD v2.1.1). FAF is above 0.2%, but BA1 is Met, so BS1 is Not Met
BS4	✖	no non-segregations were identified, so BS4 is Not Met
BS3	✖	no functional assays performed, not applicable
PS1	✖	No more reported missense variants in same codon, PS1 is Not Met
PS2	✖	no de novo cases were identified, so PS2 is Not Met
PS3	✖	no functional assays performed, not applicable
PS4	✖	variant does not meet PM2, so PS4 is Not Met
BP4	✖	REVEL = 0.815. It is not below 0.15 and PP3 is Met, so BP4 is Not Met
BP3	✖	Not applicable
BP1	✖	Not applicable
BP5	✖	Not applicable
BP7	✖	Missense variant, so BP7 is not applicable

Curation History

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