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Variant: NM_000527.5(LDLR):c.58G>A (p.Gly20Arg)

Version: 1.0

CA023728

161272 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: be4b2a4c-4d4f-4372-99c1-a538940653d5
Approved on: 2021-06-07
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HGVS expressions

NM_000527.5:c.58G>A
NM_000527.5(LDLR):c.58G>A (p.Gly20Arg)
NC_000019.10:g.11089606G>A
CM000681.2:g.11089606G>A
NC_000019.9:g.11200282G>A
CM000681.1:g.11200282G>A
NC_000019.8:g.11061282G>A
NG_009060.1:g.5226G>A
ENST00000559340.2:c.58G>A
ENST00000560467.2:c.58G>A
ENST00000558518.6:c.58G>A
ENST00000455727.6:c.58G>A
ENST00000535915.5:c.58G>A
ENST00000545707.5:c.58G>A
ENST00000557933.5:c.58G>A
ENST00000557958.1:n.144G>A
ENST00000558013.5:c.58G>A
ENST00000558518.5:c.58G>A
ENST00000560502.5:n.144G>A
NM_000527.4:c.58G>A
NM_001195798.1:c.58G>A
NM_001195799.1:c.58G>A
NM_001195800.1:c.58G>A
NM_001195803.1:c.58G>A
NM_001195798.2:c.58G>A
NM_001195799.2:c.58G>A
NM_001195800.2:c.58G>A
NM_001195803.2:c.58G>A
NR_163945.1:n.54C>T

Benign

Met criteria codes 4

BS2 BS4 BS3 PP1_Moderate

Not Met criteria codes 22

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

BA1 BS1 BP5 BP7 BP4 BP3
BP1 BP2 PS1 PS2 PS3 PS4
PP2 PP3 PP4 PVS1 PM1
PM3 PM5 PM4 PM6 PM2

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.58G>A (p.Gly20Arg) variant is classified as Benign for Familial Hypercholesterolemia by applying evidence codes (BS2, BS3, BS4 and PP1_Moderate) 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: BS2 - Variant identified in 5 unaffected relatives from Centre of molecular biology and gene therapy and 1 elderly heterozygous from the ABraOM database. BS3 - Level 1 assays: PMID 27175606: Heterologous cells (CHO), CLSM assays - result - normal cell surface LDLR, normal LDL-LDLR binding. ---- although not quantified, assume whole cycle is above 90% of wild-type, so BS3 is Met. BS4 - Variant does not segregate with FH phenotype in 8 informative meiosis from at least 3 families from different labs (Centre of molecular biology and gene therapy, University of British Columbia and Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge). PP1_moderate - variant segregates with FH phenotype in 5 informative meiosis from Centre of molecular biology and gene therapy. Variant has 3 strong evidence codes towards Benign, enough to classify as Benign, and only 1 moderate evidence code towards Pathogenic. The Benign criteria overwhelms the Pathogenic criteria, so we are confident in classifying this variant as Benign.

Met criteria codes

BS2	✔	Variant identified in 5 unaffected relatives from Centre of molecular biology and gene therapy and 1 elderly heterozygous from the ABraOM database. --- BS2 is Met
BS4	✔	Variant does not segregate with FH phenotype in 8 informative meiosis from at least 3 families from different labs (Centre of molecular biology and gene therapy, University of British Columbia and Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge): 8 affected family members do not have the variant. ---- BS4 is Met
BS3	✔	Level 1 assays: PMID 27175606: Heterologous cells (CHO), CLSM assays - result - normal cell surface LDLR, normal LDL-LDLR binding. ---- although not quantified, assume whole cycle is above 90% of wild-type, so BS3 is Met
PP1_Moderate	✔	variant segregates with FH phenotype in 5 informative meiosis from Centre of molecular biology and gene therapy. ---- PP1_Moderate is Met

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Not Met criteria codes

BA1	✖	FAF = 0.0009803 (0.098%) in exomes of european non-finnish (gnomAD v2.1.1). FAF is not above 0.5%, so BA1 is Not Met.
BS1	✖	FAF = 0.0009803 (0.098%) in exomes of european non-finnish (gnomAD v2.1.1). FAF is not above 0.2%, so BS1 is Not Met.
BP5	✖	Not applicable
BP7	✖	Missense variant, so BP7 is not applicable
BP4	✖	REVEL = 0.558. It is not below 0.15, so BS4 is Not Met
BP3	✖	Not applicable

BP1	✖	Not applicable
BP2	✖	variant identified in (1) 1 index case with heterozygous FH phenotype and another LDLR variant 'LDLR PATH HET (phase unknown)', from GeneDx Inc. (#4). --- 2nd variant is not specified, so BP2 is Not Met. (2) 1 index case with heterozygous FH phenotype with also NM_000527.5(LDLR):c.974G>A p.Cys325Tyr (ClinVar ID 251580), classified as Likely pathogenic by these guidelines, from University of British Columbia. --- 2nd variant is not classified as Pathogenic, so BS2 is not met --- BP2 is Not Met
PS1	✖	No variant described that leads to the same amino acid change, so PS1 is Not Met
PS2	✖	no de novo cases were identified, so PS2 is Not Met
PS3	✖	Level 1 assays: PMID 27175606: Heterologous cells (CHO), CLSM assays - result - normal cell surface LDLR, normal LDL-LDLR binding. ---- results are not below 70% of wild-type, so PS3 is Not Met
PS4	✖	variant does not meet PM2, so PS4 is Not Met
PP2	✖	Not applicable
PP3	✖	REVEL = 0.558. It is not above 0.75, splicing evaluation required. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp downstream from canonical acceptor site, but it does not create GT. C) there is no GT nearby. No splicing prediction is applicable, so PP3 is Not Met
PP4	✖	Variant does not meet PM2, so PP4 is Not Met
PVS1	✖	Missense variant, PVS1 Not Met
PM1	✖	Missense at codon 20. PM2 is Not Met, it is not exon 4 or any of the 60 Cys residues listed, so PM1 is Not Met
PM3	✖	Variant meets PM2 and is identified in compound heterozygocity with other variants in 3 index cases from Centre of molecular biology and gene therapy. --- 2nd variant and phenotypes are not specified, so PM3 is Not Met
PM5	✖	One more missense variant described in same codon: (1)NM_000527.4(LDLR):c.59G>A (p.Gly20Glu) (ClinVar ID 631358) - VUS by these guidelines --- variant is classified as VUS, 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 = 0.002460 (0.246%) in Ashkenazi Jewish exomes (gnomAD v2.1.1).

Curation History

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