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Variant: NM_000527.5(LDLR):c.296C>G (p.Ser99Ter)

Version: 1.0

CA023685

161269 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: e668fde2-5aaa-456f-b07d-e4a3b84620f5
Approved on: 2021/6/7
Published on: 2021/6/24

HGVS expressions

NM_000527.5:c.296C>G
NM_000527.5(LDLR):c.296C>G (p.Ser99Ter)
NC_000019.10:g.11102769C>G
CM000681.2:g.11102769C>G
NC_000019.9:g.11213445C>G
CM000681.1:g.11213445C>G
NC_000019.8:g.11074445C>G
NG_009060.1:g.18389C>G
ENST00000252444.10:c.554C>G
ENST00000559340.2:c.296C>G
ENST00000560467.2:c.296C>G
ENST00000558518.6:c.296C>G
ENST00000252444.9:c.550C>G
ENST00000455727.6:c.296C>G
ENST00000535915.5:c.190+2424C>G
ENST00000545707.5:c.296C>G
ENST00000557933.5:c.296C>G
ENST00000557958.1:n.382C>G
ENST00000558013.5:c.296C>G
ENST00000558518.5:c.296C>G
NM_000527.4:c.296C>G
NM_001195798.1:c.296C>G
NM_001195799.1:c.190+2424C>G
NM_001195800.1:c.296C>G
NM_001195803.1:c.296C>G
NM_001195798.2:c.296C>G
NM_001195799.2:c.190+2424C>G
NM_001195800.2:c.296C>G
NM_001195803.2:c.296C>G

Pathogenic

Met criteria codes 5

PVS1 PM2 PS4 PP4 PS3_Supporting

Not Met criteria codes 21

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PM1 PM3 PM5 PM4 PM6
BA1 BS1 BS4 BS3 BS2 BP5
BP7 BP4 BP3 BP1 BP2 PS1
PS2 PP1 PP2 PP3

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.296C>G (p.Ser99Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PVS1, PS4, PM2, PP4 and PS3_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: PVS1 - Variant is nonsense, causing a stop at codon 99. It is upstream of amino acid 830, so PVS1 is Met. PS4 - Variant meets PM2. Identified in over 20 unrelated clinical FH cases (PMID: 7718019). PM2 - PopMax MAF = 0.000008791 (0.0009%) in european non-finnish exomes (gnomAD v2.1.1). PP4 - Variant meets PM2. Identified in over 20 unrelated clinical FH cases (PMID: 7718019). PS3_supporting - Level 3 assays: PMID 19148831: Epstein-Barr virus transformed lymphocytes from htz patients, FACS and RNA assays - results - ~60% gene expression, LDL-LDLR uptake and protein at cell surface ---- results are below 85% of wild-type, so PS3_supporting is Met

Met criteria codes

PVS1	✔	Variant is nonsense, causing a stop at codon 99. It is upstream of amino acid 830, so PVS1 is Met
PM2	✔	PopMax MAF = 0.000008791 (0.0009%) in european non-finnish exomes (gnomAD v2.1.1). MAF is under 0.02%, so PM2 is Met.
PS4	✔	Variant meets PM2. Identified in over 20 unrelated clinical FH cases (Clinical diagnosis according to Goldstein and Brown) from Norway (PMID: 7718019).
PP4	✔	Variant meets PM2. Identified in over 20 unrelated clinical FH cases (Clinical diagnosis according to Goldstein and Brown) from Norway (PMID: 7718019). --- PP4 is Met
PS3_Supporting	✔	Level 3 assays: PMID 19148831: Epstein-Barr virus transformed lymphocytes from htz patients, FACS and RNA assays - results - ~60% gene expression, LDL-LDLR uptake and protein at cell surface ---- results are below 85% of wild-type, so PS3_supporting is Met

Not Met criteria codes

PM1	✖	Nonsense variant, so PM1 is Not applicable
PM3	✖	not identified in individuals with other variants, so PM3 is Not Met
PM5	✖	Nonsense variant, PM5 not applicable

PM4	ℹ	✖	Nonsense variant (PVS1 is Met), PM4 is Not Met
PM6	ℹ	✖	no de novo cases were identified, so PM6 is Not Met
BA1	ℹ	✖	No FAF, just total MAF = 0.000003976 (0.0004%) in european non-finnish exomes (gnomAD v2.1.1). MAF is not above 0.5%, so BA1 is Not Met.
BS1	ℹ	✖	No FAF, just total MAF = 0.000003976 (0.0004%) in european non-finnish exomes (gnomAD v2.1.1). MAF is not above 0.2%, so BS1 is Not Met.
BS4	ℹ	✖	no family members were tested, so BS4 is Not Met
BS3	ℹ	✖	Level 3 assays: PMID 19148831: Epstein-Barr virus transformed lymphocytes from htz patients, FACS and RNA assays - results - ~60% gene expression, LDL-LDLR uptake and protein at cell surface ---- whole cycle is not above 95%, so BS3_supporting is Not Met
BS2	ℹ	✖	no unaffected individuals identified with the variant, so BS2 is Not Met
BP5	ℹ	✖	Not applicable
BP7	ℹ	✖	Nonsense variant, so BP7 is not applicable
BP4	ℹ	✖	PVS1 is Met, so BP4 is not applicable
BP3	ℹ	✖	Not applicable
BP1	ℹ	✖	Not applicable
BP2	ℹ	✖	not identified in individuals with other variants, so BP2 is Not Met
PS1	ℹ	✖	Nonsense variant, PS1 not applicable
PS2	ℹ	✖	no de novo cases were identified, so PS2 is Not Met
PP1	ℹ	✖	no family members were tested, so PP1 is Not Met
PP2	ℹ	✖	Not applicable
PP3	ℹ	✖	PVS1 is Met, so PP3 is not applicable

Curation History

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