

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**

PS4

PS3_Supporting

PP4

PM2

PVS1

Not Met criteria codes **21**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

PS1PS2BP5BP7BP4BP3

BP1BP2PP1PP2PP3

PM1PM3PM5PM4BA1

PM6BS1BS4BS3BS2

[Criteria Specifications for this VCEP](#)

Evidence Links 0

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

PS4			Variant meets PM2. Identified in over 20 unrelated clinical FH cases (Clinical diagnosis according to Goldstein and Brown) from Norway (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
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
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.
PVS1			Variant is nonsense, causing a stop at codon 99. It is upstream of amino acid 830, so PVS1 is Met

Not Met criteria codes

PS1			Nonsense variant, PS1 not applicable
PS2			no de novo cases were identified, so PS2 is Not Met
BP5			Not applicable

BP7			Nonsense variant, so BP7 is not applicable
BP4			PVS1 is Met, so BP4 is not applicable
BP3			Not applicable
BP1			Not applicable
BP2			not identified in individuals with other variants, so BP2 is Not Met
PP1			no family members were tested, so PP1 is Not Met
PP2			Not applicable
PP3			PVS1 is Met, so PP3 is not applicable
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			Nonsense variant (PVS1 is Met), PM4 is Not Met
BA1			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.
PM6			no de novo cases were identified, so PM6 is Not Met
BS1			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			no family members were tested, so BS4 is Not Met
BS3			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			no unaffected individuals identified with the variant, so BS2 is Not Met

⛶

☰

▼

⬇

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.