

Variant: *NM_000527.5(LDLR):c.1598G>A (p.Trp533Ter)*

Version: 1.0

CA035378 [↗](#)

251926 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))

Condition: hypercholesterolemia, familial ([MONDO:0007750](#))

Inheritance Mode: Semidominant inheritance

UUID: bf9aaff6-ebfa-43dd-8599-f96ac01722f1

Approved on: 2022/8/28

Published on: 2022/8/28

HGVS expressions

NM_000527.5:c.1598G>A

NM_000527.5(LDLR):c.1598G>A (p.Trp533Ter)

NC_000019.10:g.11116105G>A

CM000681.2:g.11116105G>A

NC_000019.9:g.11226781G>A

CM000681.1:g.11226781G>A

NC_000019.8:g.11087781G>A

NG_009060.1:g.31725G>A

ENST00000252444.10:c.1856G>A

ENST00000559340.2:c.1598G>A

ENST00000560467.2:c.1478G>A

ENST00000558518.6:c.1598G>A

ENST00000252444.9:c.1852G>A

ENST00000455727.6:c.1094G>A

ENST00000535915.5:c.1475G>A

ENST00000545707.5:c.1217G>A

ENST00000557933.5:c.1598G>A

ENST00000558013.5:c.1598G>A

ENST00000558518.5:c.1598G>A

ENST00000559340.1:c.319G>A

NM_000527.4:c.1598G>A

NM_001195798.1:c.1598G>A

NM_001195799.1:c.1475G>A

NM_001195800.1:c.1094G>A

NM_001195803.1:c.1217G>A

NM_001195798.2:c.1598G>A

NM_001195799.2:c.1475G>A

NM_001195800.2:c.1094G>A

NM_001195803.2:c.1217G>A

Pathogenic

Met criteria codes **4**

PVS1

PS4_Supporting

PP4

PM2

Not Met criteria codes **18**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BA1BP3BP2BP5BP7BS2BS1BS4BS3PP1PS1PS2PS3PM6PM1PM3PM5PM4

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.1598G>A (p.Trp533Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PVS1, PM2, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1016/j.gim.2021.09.012>). The supporting evidence is as follows: PVS1 - variant is nonsense upstream of amino acid 830, so PVS1 is met. PM2 - PopMax MAF = 0.000008792 (0.0009%) in European Non-Finnish exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met. PP4 - variant meets PM2. identified in: - 1 index case who fulfills SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. - 1 index case who fulfills SB criteria from Marduel et al. 2010 (PMID: 20809525). so PP4 is met. PS4_supporting - variant meets PM2 and was identified in 2 unrelated index cases from different labs (please see PP4 for details), so PS4_Supportitng is met.

Met criteria codes

PVS1			variant is nonsense upstream of amino acid 830, so PVS1 is met
PS4_Supporting			variant meets PM2. identified in: - 1 index case who fulfills SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. - 1 index case who fulfills SB criteria from Marduel et al. 2010 (PMID: 20809525). so PS4_Supporting is met
PP4			variant meets PM2. identified in: - 1 index case who fulfills SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. - 1 index case who fulfills SB criteria from Marduel et al. 2010 (PMID: 20809525). so PP4 is met
PM2			PopMax MAF = 0.000008792 (0.0009%) in European Non-Finnish exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met

Not Met criteria codes

BA1			no FAF, just total MAF = 0.000003977 (0.0004%) in European Non-Finnish exomes (gnomAD v2.1.1). so BA1 is not met
BP3			not applicable
BP2			index case from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge with LDL = 258mg/dl also has NM_000527.5(LDLR):c.1875C>T (p.Asn625=) - Likely benign by these guidelines. Also, there is no certainty if the 2 variants are in trans, so BP2 is not met

BP5			not applicable
BP7			variant is nonsense, so not applicable
BS2			not identified in normolipidemic individuals: 0/190 non-FH alleles from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so BS2 is not met
BS1			no FAF, just total MAF = 0.000003977 (0.0004%) in European Non-Finnish exomes (gnomAD v2.1.1). so BS1 is not met
BS4			no evidence of lack of segregation
BS3			there are no functional studies
PP1			Variant segregates with FH phenotype in 1 informative meiosis from 1 family from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 1 relative has the phenotype and the variant. not enough, so not met
PS1			variant is nonsense, so not applicable
PS2			no de novo occurrence
PS3			there are no functional studies
PM6			no de novo occurrence
PM1			variant is nonsense, so not applicable
PM3			no index case with homozygous phenotype
PM5			variant is nonsense, so not applicable
PM4			variant is nonsense, so not applicable

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