

Variant: *NM_000527.5(LDLR):c.1729T>G (p.Trp577Gly)*

Version: 1.0

CA10585585 [↗](#)

252000 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: adb0184f-0bcb-4ed0-a59a-783932dac98b

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HGVS expressions

NM_000527.5(LDLR):c.1729T>G (p.Trp577Gly)

NM_000527.5:c.1729T>G

NC_000019.10:g.11116882T>G

CM000681.2:g.11116882T>G

NC_000019.9:g.11227558T>G

CM000681.1:g.11227558T>G

NC_000019.8:g.11088558T>G

NG_009060.1:g.32502T>G

ENST00000252444.10:c.1987T>G

ENST00000559340.2:c.1705+670T>G

ENST00000560467.2:c.1609T>G

ENST00000558518.6:c.1729T>G

ENST00000252444.9:c.1983T>G

ENST00000455727.6:c.1225T>G

ENST00000535915.5:c.1606T>G

ENST00000545707.5:c.1348T>G

ENST00000557933.5:c.1729T>G

ENST00000558013.5:c.1729T>G

ENST00000558518.5:c.1729T>G

ENST00000559340.1:c.426+670T>G

NM_000527.4:c.1729T>G

NM_001195798.1:c.1729T>G

NM_001195799.1:c.1606T>G

NM_001195800.1:c.1225T>G

NM_001195803.1:c.1348T>G

NM_001195798.2:c.1729T>G

NM_001195799.2:c.1606T>G

NM_001195800.2:c.1225T>G

NM_001195803.2:c.1348T>G

Pathogenic

Met criteria codes **6**

PP3

PP4

PS3

PM2

PS4_Supporting

PP1_Moderate

Evidence Links **0**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1729T>G (p.Trp577Gly) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS3, PP1_moderate, PM2, PP3, PS4_supporting, PP4, 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: PS3: Level 1 assays: PMID 25378237: Heterologous cells, FACS assays -10-15% LDL-LDLR binding; 5% LDL-LDLR uptake; 5% cell surface LDLR ---- activity is below 70% of wild-type, so functional study is consistent with damaging effect. PP1_moderate: Variant segregates with FH phenotype in at least 4 informative meioses from 1 family from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.937. PS4_supporting: Variant meets PM2 and is identified in 2 index cases (1 case with DLCN criteria ≥6 from Robarts Research Institute; 1 case with DLCN criteria ≥6 from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)) PP4: Variant meets PM2 and is identified in 2 index cases who fulfill clinical criteria for FH from several labs (see PS4 for details), after alternative causes of high cholesterol were excluded.

Met criteria codes

PP3			REVEL = 0.937.
PP4			Variant meets PM2 and is identified in 2 index cases (1 case with DLCN criteria ≥6 from Robarts Research Institute; 1 case with DLCN criteria ≥6 from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)), after alternative causes of high cholesterol were excluded.
PS3			Level 1 assays: PMID 25378237: Heterologous cells, FACS assays -10-15% LDL-LDLR binding; 5% LDL-LDLR uptake; 5% cell surface LDLR ---- activity is below 70% of wild-type, so functional study is consistent with damaging effect.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1).
PS4_Supporting			Variant meets PM2 and is identified in 2 index cases (1 case with DLCN criteria ≥6 from Robarts Research Institute; 1 case with DLCN criteria ≥6 from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation))
PP1_Moderate			Variant segregates with FH phenotype in at least 4 informative meioses from 1 family from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)

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