

Variant: *NM_000527.5(LDLR):c.259T>G (p.Trp87Gly)*

Version: 1.0

CA023683 [↗](#)

3685 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: fe3c7d4d-c876-42cf-b2ec-d228ee2c5d24

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HGVS expressions

NM_000527.5(LDLR):c.259T>G (p.Trp87Gly)

NM_000527.5:c.259T>G

NC_000019.10:g.11102732T>G

CM000681.2:g.11102732T>G

NC_000019.9:g.11213408T>G

CM000681.1:g.11213408T>G

NC_000019.8:g.11074408T>G

NG_009060.1:g.18352T>G

ENST00000252444.10:c.517T>G

ENST00000559340.2:c.259T>G

ENST00000560467.2:c.259T>G

ENST00000558518.6:c.259T>G

ENST00000252444.9:c.513T>G

ENST00000455727.6:c.259T>G

ENST00000535915.5:c.190+2387T>G

ENST00000545707.5:c.259T>G

ENST00000557933.5:c.259T>G

ENST00000557958.1:n.345T>G

ENST00000558013.5:c.259T>G

ENST00000558518.5:c.259T>G

NM_000527.4:c.259T>G

NM_001195798.1:c.259T>G

NM_001195799.1:c.190+2387T>G

NM_001195800.1:c.259T>G

NM_001195803.1:c.259T>G

NM_001195798.2:c.259T>G

NM_001195799.2:c.190+2387T>G

NM_001195800.2:c.259T>G

NM_001195803.2:c.259T>G

Pathogenic

Met criteria codes **6**

PP3

PP4

PS3

PS4

PM2

PP1_Moderate

Not Met criteria codes **20**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BP5

BP7

BP4

BP3

BP1

BP2

BS1

BS4

BS3

BS2

PP2

PS1

PS2

BA1

PM1

PM3

PM5

PM4

PM6

PVS1

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.259T>G (p.Trp87Gly) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PS3, PS4, PP1_Moderate, PM2, PP3 and PP4) 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: PS3 - Level 1/2 assays: PMID 31578082: Hmz patients' lymphocytes, FACS assays and Heterologous cells (CHO), WB, FACS and CLSM assays - results - lymphocytes: normal cell surface LDLR, 40% LDL-LDLR binding, 35% uptake; CHO: normal (100%) LDLR expression, 20% LDL-LDLR binding, 35% uptake ---- binding and uptake are below 70% of wild-type, so PS3 is Met. PS4 - Variant meets PM2. Variant identified in at least 13 unrelated index cases with Dutch Lipid Clinic score equal or above 6 from different labs. PP1_moderate - variant segregates with FH phenotype in 5 informative meiosis in 2 families from different labs. PM2 - PopMax MAF = 0.00005418 (0.0054%) in european non-finnish exomes (gnomAD v2.1.1). PP3 - REVEL = 0.892. PP4 - Variant meets PM2. Identified in 13 unrelated index cases with Dutch Lipid Clinic score equal or above 6 from different labs.

Met criteria codes

PP3			REVEL = 0.892. It is above 0.75, so PP3 is Met
PP4			Variant meets PM2. Identified in 13 unrelated index cases with Dutch Lipid Clinic score equal or above 6 from different labs (University of British Columbia (UBC, Canada) and Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)). ---- PP4 is Met
PS3			Level 1/2 assays: PMID 31578082: Hmz patients' lymphocytes, FACS assays and Heterologous cells (CHO), WB, FACS and CLSM assays - results - lymphocytes: normal cell surface LDLR, 40% LDL-LDLR binding, 35% uptake; CHO: normal (100%) LDLR expression, 20% LDL-LDLR binding, 35% uptake ---- binding and uptake are below 70% of wild-type, so PS3 is Met (PS3_moderate would also be Met, but PS3 is already Met) / Level 3 assays: PMID 10735631: Htz patients' stimulated T-lymphocytes, FACS - results - 79% LDLR cell surface, 68% LDL-LDLR binding and 88% uptake, they suggests that the W66G mutation disrupts the recycling of LDL receptors (class V) ---- cell surface and binding are below 85% of wild-type, so PS3_supporting would be Met, but PS3 is already Met / Level 2 assays: PMID 1301956: Hmz patients' fibroblasts, 125I-LDL assays - results - 25-100% LDLR activity (25 to 55% of normal in subject 1, 30 to 50% in subject 2, and 65 to 100% in subject 3) ---- too much variability, do not use in either BS3 or PS3 / Level 2 assays: PMID 7584986: Hmz patients' fibroblasts, 125I-LDL assays - results - 20-90% LDLR activity ---- too much variability, do not use in either BS3 or PS3
PS4			Variant meets PM2. Variant identified in at least 13 unrelated index cases with Dutch Lipid Clinic score equal or above 6 from different labs (Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) and University of British Columbia --- PS4 is Met
PM2			PopMax MAF = 0.00005418 (0.0054%) in european non-finnish exomes (gnomAD v2.1.1).

PP1_Moderate			variant segregates with FH phenotype in 5 informative meioses in 2 families from different labs (Center of molecular biology and gene therapy and University of British Columbia): 5 affected family members have the variant. --- PP1_Moderate is Met
Not Met criteria codes			
BP5			Not applicable
BP7			Missense variant, so BP7 is not applicable
BP4			REVEL = 0.892. It is not below 0.15 and PP3 is Met, so BP4 is Not Met
BP3			Not applicable
BP1			Not applicable
BP2			1 index case from University of British Columbia (#5) also has NM_000527.5(LDLR):c.718G>A (p.Glu240Lys) (ClinVar ID 200920) variant but phenotype does not rule out or confirm Homozygous FH. --- BP2 is not met
BS1			FAF = 0.00002853 (0.003%) in european non-finnish exomes (gnomAD v2.1.1). FAF is not above 0.2%, so BS1 is Not Met.
BS4			no non-segregations were identified, so BS4 is Not Met
BS3			Level 1/3(benign) assays: PMID 31578082: Hmz patients' lymphocytes, FACS assays and Heterologous cells (CHO), WB, FACS and CLSM assays - results - lymphocytes: normal cell surface LDLR, 40% LDL-LDLR binding, 35% uptake; CHO: normal (100%) LDLR expression, 20% LDL-LDLR binding, 35% uptake ---- whole cycle is not above 90% of wild-type, so BS3/BS3_supporting are Not Met / Level 3 assays: PMID 10735631: Htz patients' stimulated T-lymphocytes, FACS - results - 79% LDLR cell surface, 68% LDL-LDLR binding and 88% uptake, they suggests that the W66G mutation disrupts the recycling of LDL receptors (class V) ---- whole cycle is not above 95% of wild-type, so BS3_supporting is Not Met / Level 3(benign) assays: PMID 1301956: Hmz patients' fibroblasts, 125I-LDL assays - results - 25-100% LDLR activity (25 to 55% of normal in subject 1, 30 to 50% in subject 2, and 65 to 100% in subject 3) ---- too much variability, do not use in either BS3 or PS3 / Level 3(benign) assays: PMID 7584986: Hmz patients' fibroblasts, 125I-LDL assays - results - 20-90% LDLR activity ---- too much variability, do not use in either BS3 or PS3
BS2			no unaffected individuals identified with the variant, so BS2 is Not Met
PP2			Not applicable
PS1			No other reported missense variant that leads to the same amino acid change, PS1 is Not Met
PS2			no de novo cases were identified, so PS2 is Not Met

BA1			FAF = 0.00002853 (0.003%) in european non-finnish exomes (gnomAD v2.1.1). FAF is not above 0.5%, so BA1 is Not Met
PM1			Missense at codon 87. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed, so PM1 is Not Met
PM3			1 index case from University of British Columbia (#5) also has NM_000527.5(LDLR):c.718G>A (p.Glu240Lys) (ClinVar ID 200920) variant but phenotype does not rule out or confirm Homozygous FH. --- PM3 is not met
PM5			One more missense variant in the same codon: (1)NM_000527.4(LDLR):c.259T>C (p.Trp87Arg) (ClinVar ID 440552) - VUS by these guidelines. so PM5 is Not Met
PM4			Missense variant, not applicable
PM6			no de novo cases were identified, so PM6 is Not Met
PVS1			Missense variant not in initiation codon, PVS1 Not Met

Curation History 		
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