


Variant: *NM_000527.5(LDLR):c.1775G>A (p.Gly592Glu)*

Version: 1.0

[CA023577](#) 

[161271 \(ClinVar\)](#) 

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

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

Inheritance Mode: Semidominant inheritance

UUID: cd0c4aea-7158-4181-83f0-1c4cce449e45

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HGVS expressions

NM_000527.5:c.1775G>A

NM_000527.5(LDLR):c.1775G>A (p.Gly592Glu)

NC_000019.10:g.11116928G>A

CM000681.2:g.11116928G>A

NC_000019.9:g.11227604G>A

CM000681.1:g.11227604G>A

NC_000019.8:g.11088604G>A

NG_009060.1:g.32548G>A

ENST00000252444.10:c.2033G>A

ENST00000559340.2:c.1705+716G>A

ENST00000560467.2:c.1655G>A

ENST00000558518.6:c.1775G>A

ENST00000252444.9:c.2029G>A

ENST00000455727.6:c.1271G>A

ENST00000535915.5:c.1652G>A

ENST00000545707.5:c.1394G>A

ENST00000557933.5:c.1775G>A

ENST00000558013.5:c.1775G>A

ENST00000558518.5:c.1775G>A

ENST00000559340.1:c.426+716G>A

NM_000527.4:c.1775G>A

NM_001195798.1:c.1775G>A

NM_001195799.1:c.1652G>A

NM_001195800.1:c.1271G>A

NM_001195803.1:c.1394G>A

NM_001195798.2:c.1775G>A

NM_001195799.2:c.1652G>A

NM_001195800.2:c.1271G>A

NM_001195803.2:c.1394G>A

Pathogenic

Met criteria codes **6**

PS3_Moderate PP1_Strong PM2

PS4 PP3 PP4

Not Met criteria codes **20**

Expert Panel

Familial Hypercholesterolemia VCEP 

Criteria Specification Information 



Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.1775G>A (p.Gly592Glu) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PS4, PP1_Strong, PM2, PS3_Moderate, 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: PS4 - Variant meets PM2. Variant identified in 239 index cases. PP1_strong - 130 informative meioses (1 from Robarts Research Institute; 83 from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 19 from Laboratory of Genetics and Molecular Cardiology; 2 from University of British Columbia; 25 from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge). PM2 - PopMax MAF = 0.0001161 (0.012%) in European non-Finnish exomes (gnomAD v2.1.1). PS3_moderate - Level 2 assay - PMID:21865347 - study on hmz patient's lymphocytes, FACS, LDLR activity value range: 39-53%. PP3 - REVEL: 0,938. PP4 - Variant meets PM2. Variant identified in 239 index cases fulfill specific clinical criteria for FH (3 cases with Simon-Broome from Color laboratory; 189 cases with MedPed criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 5 cases with Simon-Broome criteria from GeneDx; 15 cases with Siom-Broome criteria from Laboratory of Genetics and Molecular Cardiology; 2 cases with DLCN criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 6 cases with DLCN criteria from University of British Columbia; 19 cases with Simon-Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge).

Met criteria codes

PS3_Moderate	✓	Level 2 assay - PMID:21865347 - study on hmz patient's lymphocytes, FACS, LDLR activity value range: 39-53%.
PP1_Strong	✓	130 informative meioses (1 from Robarts Research Institute; 83 from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 19 from Laboratory of Genetics and Molecular Cardiology; 2 from University of British Columbia; 25 from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge).
PM2	✓	PopMax MAF = 0.0001161 (0.012%) in European non-Finnish exomes (gnomAD v2.1.1). MAF is below 0.02%.
PS4	✓	Variant meets PM2. Variant identified in 239 index cases (3 cases with Simon-Broome from Color laboratory; 189 cases with MedPed criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 5 cases with Simon-Broome criteria from GeneDx; 15 cases with Siom-Broome criteria from Laboratory of Genetics and Molecular Cardiology; 2 cases with DLCN criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 6 cases with DLCN criteria from University of British Columbia; 19 cases with Simon-Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge).
PP3	✓	REVEL: 0,938. Score is above 0,75.

PP4	✓	Variant meets PM2. Variant identified in 239 index cases fulfill specific clinical criteria for FH (see PS4).
Not Met criteria codes		
PVS1	✗	Missense variant. Not applicable.
BS2	✗	2 cases of nonsegregation - due to incomplete penetrance of 0,95. 2 nonsegregation from 49 informative meioses = 4% = OK.
BS1	✗	FAF = 0.00004735 (0.004735%) in European non-Finnish exomes (gnomAD v2.1.1). FAF is not above 0.2%
BS4	✗	Total 7 nonsegregations - VCEP LDLR guidelines needs at least 2 cases in at least 2 families. All reported non-segregation arised from isolated cases in separated families.
BS3	✗	No functional study showing non-damaging effect on protein function or splicing.
BP5	✗	Not applicable.
BP7	✗	Missense variant. Not applicable.
BP4	✗	REVEL: 0,938. Score is not below 0,15.
BP3	✗	Not applicable.
BP1	✗	Not applicable.
BP2	✗	Not identified in individuals with other variants.
PM6	✗	No de novo cases were identified.
PM1	✗	Missense at codon 592. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable.
PM3	✗	2 cases of homozygosity (LDLc: 9.95 mmol/l and 9.99 mmol/l respectively - not fulfill the levels for HoFH defined as LDL above 500mg/dl. untreated values of index case 19 are TC of 600mg/dl); 5 cases of compound heterozygosity (no proven pathogenic variants in double).
PM5	✗	No other missense variants classified as Pathogenic in the same codon. One other missense variant described in the same codon (accessed 19 August 2020): (1)NM_000527.4(LDLR):c.1774G>A (p.Gly592Arg) (ClinVar ID 373769) - classified as VUS by these guidelines.
PM4	✗	Missense variant. Not applicable.
PS1	✗	No variant described that leads to the same amino acid change.

PS2	✘	No de novo cases were identified.
BA1	✘	FAF = 0.00004735 (0.004735%) in European non-Finnish exomes (gnomAD v2.1.1). FAF is not above 0.5%
PP2	✘	Not applicable.

Curation History [↗](#)

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