

Variant: *NM_000527.5(LDLR):c.682G>A (p.Glu228Lys)*

Version: 2.0

CA023749 [↗](#)

3691 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: e72e629f-1640-40bb-97c4-aed2ca36bbe3

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HGVS expressions

NM_000527.5(LDLR):c.682G>A (p.Glu228Lys)

NM_000527.5:c.682G>A

NC_000019.10:g.11105588G>A

CM000681.2:g.11105588G>A

NC_000019.9:g.11216264G>A

CM000681.1:g.11216264G>A

NC_000019.8:g.11077264G>A

NG_009060.1:g.21208G>A

ENST00000252444.10:c.940G>A

ENST00000559340.2:c.682G>A

ENST00000560467.2:c.682G>A

ENST00000558518.6:c.682G>A

ENST00000252444.9:c.936G>A

ENST00000455727.6:c.314-1804G>A

ENST00000535915.5:c.559G>A

ENST00000545707.5:c.314-977G>A

ENST00000557933.5:c.682G>A

ENST00000558013.5:c.682G>A

ENST00000558518.5:c.682G>A

ENST00000560467.1:c.282G>A

NM_000527.4:c.682G>A

NM_001195798.1:c.682G>A

NM_001195799.1:c.559G>A

NM_001195800.1:c.314-1804G>A

NM_001195803.1:c.314-977G>A

NM_001195798.2:c.682G>A

NM_001195799.2:c.559G>A

NM_001195800.2:c.314-1804G>A

NM_001195803.2:c.314-977G>A

Pathogenic

Met criteria codes **7**

PP1_Strong

PS3

PS4

PP3

PP4

PM2

PM1

Evidence Links **0**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.682G>A (p.Glu228Lys) variant is classified as pathogenic for Familial Hypercholesterolemia by applying evidence code PS3, PS4, PM1, PM2, PP1_Strong, PP3 and 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: PM2 - PopMax MAF = 0.0001105 (0.01%) in East Asian exomes (gnomAD v2.1.1). PP3 - REVEL = 0.972. It is above 0.75. PM1 - Variant meets PM2 and is missense located in exon 4 . PS3 - Three studies contribute to PS3 attribution. One (PMID: 10978268) report a level 3 assay performed on heterozygous patient's fibroblasts with radiolabeled LDL consistent with damaging effect of the variant (50% LDLR activity). The second reports a level 2 assay performed on homozygous patient's fibroblasts with radiolabeled LDL consistent with damaging effect of the variant (< 2% LDLR activity).The third is performed on Heterologous cells (COS-7). FACS, CLSM and WB results in 24% LDLR expression and 21% LDL clearance. LDLR is retained in the ER. PS4 - Variant meets PM2 and is identified in 13 index cases who fulfil SB criteria for FH (n=1 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=1 Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; n=1 Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)) or DLCN criteria for FH (n=1 Roberts Research Institute; n=9 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière). PP1_Strong - Variant segregate with FH in 10 informatives meioses (6 relatives positive LDL-C > 75th percentile and 4 relatives negative LDLC < 50th percentile) from 2 families from Laboratory of Genetics and Molecular Cardiology, University of São Paulo and in 1 relative positive for variant (LDL-C > 75th percentile) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. PP4 - Variant meets PM2 and is identified in 13 index cases who fulfil SB criteria for FH (n=1 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=1 Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; n=1 Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)) or DLCN criteria for FH (n=1 Roberts Research Institute; n=9 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière).

Met criteria codes

PP1_Strong			Variant segregate with FH in 10 informatives meioses (6 relatives positive LDL-C > 75th percentile and 4 relatives negative LDLC < 50th percentile) from 2 families from Laboratory of Genetics and Molecular Cardiology, University of São Paulo and in 1 relative positive for variant (LDL-C > 75th percentile) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge.
PS3			Three studies contribute to PS3 attribution. One (PMID: 10978268) report a level 3 assay performed on heterozygous patient's fibroblasts with radiolabeled LDL consistent with damaging effect of the variant (50% LDLR activity). The second reports a level 2 assay performed on homozygous patient's fibroblasts with radiolabeled LDL consistent with damaging effect of the variant (< 2% LDLR activity).The third is performed on Heterologous cells (COS-7). FACS, CLSM and WB results in 24% LDLR expression and 21% LDL clearance. LDLR is retained in the ER.
PS4			Variant meets PM2 and is identified in 13 index cases who fulfil SB criteria for FH (n=1 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=1 Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; n=1 Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)) or DLCN criteria for FH (n=1 Roberts Research Institute; n=9 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)
PP3			REVEL = 0.972. It is above 0.75.
PP4			

Variant meets PM2 and is identified in 13 index cases who fulfil SB criteria for FH (n=1 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=1 Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; n=1 Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)) or DLCN criteria for FH (n=1 Robarts Research Institute; n=9 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)

PM2			PopMax MAF = 0.0001105 (0,01%) in East Asian exomes (gnomAD v2.1.1).
PM1			PM1 - Variant meets PM2 and is missense located in exon 4 .

Curation History

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