

Variant: NM_000527.5(LDLR):c.1433G>A (p.Gly478Glu)

Version: 1.1

CA404085998 [↗](#)

440642 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 8b8852d5-2828-4890-8e43-8b948918b0e7

Approved on: 2022/1/31

Published on: 2022/7/11

HGVS expressions

NM_000527.5:c.1433G>A

NM_000527.5(LDLR):c.1433G>A (p.Gly478Glu)

NC_000019.10:g.11113609G>A

CM000681.2:g.11113609G>A

NC_000019.9:g.11224285G>A

CM000681.1:g.11224285G>A

NC_000019.8:g.11085285G>A

NG_009060.1:g.29229G>A

ENST00000252444.10:c.1691G>A

ENST00000559340.2:c.1433G>A

ENST00000560467.2:c.1313G>A

ENST00000558518.6:c.1433G>A

ENST00000252444.9:c.1687G>A

ENST00000455727.6:c.929G>A

ENST00000535915.5:c.1310G>A

ENST00000545707.5:c.1052G>A

ENST00000557933.5:c.1433G>A

ENST00000558013.5:c.1433G>A

ENST00000558518.5:c.1433G>A

ENST00000559340.1:c.154G>A

ENST00000560467.1:c.913G>A

NM_000527.4:c.1433G>A

NM_001195798.1:c.1433G>A

NM_001195799.1:c.1310G>A

NM_001195800.1:c.929G>A

NM_001195803.1:c.1052G>A

NM_001195798.2:c.1433G>A

NM_001195799.2:c.1310G>A

NM_001195800.2:c.929G>A

NM_001195803.2:c.1052G>A

Likely Pathogenic

Met criteria codes 4

PP3PP4PM5PM2

Not Met criteria codes 22

BP5BP7BP4BP3BP1BP2BS1BS4BS3BS2PP1PP2PS1PS2PS3PS4BA1PM1PM3PM4PM6PVS1

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

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_000527.4(LDLR):c.1433G>A (p.Gly478Glu) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PM5, 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 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PM5 - 2 other missense variants in the same codon: (1) NM_000527.5(LDLR):c.1432G>A (p.Gly478Arg) - 1 star, Conflicting interpretations of pathogenicity: Likely pathogenic(8);Pathogenic(1);Uncertain significance(4) - Pathogenic by these guidelines (FH VCEP training Aug 2021) (2) NM_000527.5(LDLR):c.1432G>T (p.Gly478Trp) - 1 star, VUS in ClinVar - VUS by these guidelines --- there is 1 Pathogenic variant in the same codon, so PM5 is met. PP3 - REVEL = 0.984. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in 1 index case who fulfills Simon-Broome criteria from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge, so PP4 is met

Met criteria codes

PP3		✓	REVEL = 0.984. It is above 0.75, so PP3 is met
PP4		✓	variant meets PM2 and was identified in 1 index case who fulfills Simon-Broome criteria from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge. -- so PP4 is met
PM5		✓	2 other missense variants in the same codon: (1) NM_000527.5(LDLR):c.1432G>A (p.Gly478Arg) - 1 star, Conflicting interpretations of pathogenicity: Likely pathogenic(8);Pathogenic(1);Uncertain significance(4) in ClinVar - Pathogenic by these guidelines (FH VCEP training Aug 2021) (2) NM_000527.5(LDLR):c.1432G>T (p.Gly478Trp) - 1 star, VUS in ClinVar - VUS by these guidelines 1 Pathogenic variant in the same codon, so PM5 is met
PM2		✓	This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met

Not Met criteria codes

BP5		✗	not applicable
BP7		✗	variant is missense, so BP7 is not met

BP4			REVEL = 0.984. It is not below 0.5, so BP4 is not met
BP3			not applicable
BP1			not applicable
BP2			not identified in index cases with other variants
BS1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met
BS4			no segregation data
BS3			there are no published functional studies for this variant
BS2			not identified in normolipidemic individuals, 0/92 non-FH individuals from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so BS2 is not met
PP1			no segregation data
PP2			not applicable
PS1			no other missense variant leads to the same amino acid change, so PS1 is not met
PS2			no de novo occurrence
PS3			there are no published functional studies for this variant
PS4			variant meets PM2 and was identified in 1 index case who fulfills Simon-Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. -- not enough, so not met
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met
PM1			variant is missense and meets PM2, but it is not in exon 4 and does not alter Cys, so PM1 is not met.
PM3			not identified in index cases with other variants
PM4			variant is missense, so PM4 is not met
PM6			no de novo occurrence
PVS1			variant is missense and not in initiation codon, so PVS1 is not met

Curation History ↗		
Showing 1 to 2 of 2 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.