

Variant: *NM_000527.5(LDLR):c.1381G>T (p.Gly461Cys)*

Version: 1.0

CA023475 [↗](#)

183113 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 06d695fb-5e52-4733-8541-911f729d96cf

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HGVS expressions

NM_000527.5(LDLR):c.1381G>T (p.Gly461Cys)

NM_000527.5:c.1381G>T

NC_000019.10:g.11113557G>T

CM000681.2:g.11113557G>T

NC_000019.9:g.11224233G>T

CM000681.1:g.11224233G>T

NC_000019.8:g.11085233G>T

NG_009060.1:g.29177G>T

ENST00000252444.10:c.1639G>T

ENST00000559340.2:c.1381G>T

ENST00000560467.2:c.1261G>T

ENST00000558518.6:c.1381G>T

ENST00000252444.9:c.1635G>T

ENST00000455727.6:c.877G>T

ENST00000535915.5:c.1258G>T

ENST00000545707.5:c.1000G>T

ENST00000557933.5:c.1381G>T

ENST00000558013.5:c.1381G>T

ENST00000558518.5:c.1381G>T

ENST00000559340.1:c.102G>T

ENST00000560467.1:c.861G>T

NM_000527.4:c.1381G>T

NM_001195798.1:c.1381G>T

NM_001195799.1:c.1258G>T

NM_001195800.1:c.877G>T

NM_001195803.1:c.1000G>T

NM_001195798.2:c.1381G>T

NM_001195799.2:c.1258G>T

NM_001195800.2:c.877G>T

NM_001195803.2:c.1000G>T

Likely Pathogenic

Met criteria codes 4

PP1_Strong

PS4_Supporting

PP4

PM2

Not Met criteria codes 17

PVS1

BA1

BP4

BP2

BP7

BS2

BS1

BS4

BS3

PP3

PS1

PS2

PS3

PM6

PM3

PM5

PM4

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 1.2*

[PDF](#)

[Criteria Specification Approval History](#)

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1381G>T (p.Gly461Cys) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PP1_Strong, PM2, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: MAF= 0.00002331 (0.002331%) in European (Non-Finnish) exomes (gnomAD v4.0.0). PS4_Supporting, PP4: Three unrelated index cases fulfill FH criteria, reported in PMID 23815734 (Mollaki et al., 2013 - Greece) and 16465405 (Cefalù et al., 2006 - Italy). PP1_Strong: Variant segregates with phenotype in 8 informative meioses from 3 families, affected relatives tested positive for the variant, reported in PMID 23815734 and 16465405.

Met criteria codes

PP1_Strong		✓	Variant segregates with phenotype in eight informative meioses from three families, affected relatives tested positive for the variant, reported in PMID 23815734 and 16465405.
PS4_Supporting		✓	Three unrelated index cases fulfill FH criteria, reported in PMID 23815734 and 16465405.
PP4		✓	Three unrelated index cases fulfill FH criteria, reported in PMID 23815734 and 16465405.
PM2		✓	MAF= 0.00002331 (.002331 %) in European (Non-Finnish) exomes gnomAD version 4.0.0

Not Met criteria codes

PVS1		✗	Not a null variant.
BA1		✗	Not met.
BP4		✗	REVEL= 0.574, it is not below 0.50.
BP2		✗	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP7			Not a synonymous variant.
BS2			Not met.
BS1			Not met.
BS4			Not met.
BS3			PMID 25647241 did not study whole LDLR cycle.
PP3			REVEL= 0.574, it is not above 0.75, splicing evaluation required. Scenario A) Not in limits Scenario B) Does not create AG Scenario C) Not in limits. Variant is not predicted to alter splicing.
PS1			Not met.
PS2			Not met.
PS3			Not met.
PM6			Not met.
PM3			Not met.
PM5			Not met.
PM4			Not an in-frame deletion/insertion.

Curation History [↗](#)

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