

Variant: *NM_000527.5(LDLR):c.967G>T (p.Gly323Cys)*

Version: 1.0

CA16602321 [↗](#)

375806 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: dbcd27a3-5bf2-491c-b76f-fc194354d4f8

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HGVS expressions

NM_000527.5(LDLR):c.967G>T (p.Gly323Cys)

NM_000527.5:c.967G>T

NC_000019.10:g.11110678G>T

CM000681.2:g.11110678G>T

NC_000019.9:g.11221354G>T

CM000681.1:g.11221354G>T

NC_000019.8:g.11082354G>T

NG_009060.1:g.26298G>T

ENST00000252444.10:c.1225G>T

ENST00000559340.2:c.967G>T

ENST00000560467.2:c.941-836G>T

ENST00000558518.6:c.967G>T

ENST00000252444.9:c.1221G>T

ENST00000455727.6:c.463G>T

ENST00000535915.5:c.844G>T

ENST00000545707.5:c.586G>T

ENST00000557933.5:c.967G>T

ENST00000558013.5:c.967G>T

ENST00000558518.5:c.967G>T

ENST00000560467.1:c.541-836G>T

NM_000527.4:c.967G>T

NM_001195798.1:c.967G>T

NM_001195799.1:c.844G>T

NM_001195800.1:c.463G>T

NM_001195803.1:c.586G>T

NM_001195798.2:c.967G>T

NM_001195799.2:c.844G>T

NM_001195800.2:c.463G>T

NM_001195803.2:c.586G>T

Likely Pathogenic

Met criteria codes **5**

PP1

PP3

PP4

PM2

PS4_Supporting

Not Met criteria codes **21**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

PS1

PS2

PS3

PP2

BA1

PM6

BS1

BS4

BS3

PM1

PM3

PM5

PM4

BS2

BP5

BP7

BP4

BP3

BP1

BP2

PVS1

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.967G>T (p.Gly323Cys) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP1, PP3, PS4_Supporting 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. PP1 - variant segregates with the FH phenotype in 2 informative meioses (1 from each family) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): 2 relatives with LDL>75th percentile have the variant, so PP1 is met. PP3 - REVEL = 0.903. It is above 0.75, so PP3 is met. PS4_supporting - variant meets PM2 and was identified in 4 unrelated index cases who fulfill at least SB Possible criteria for FH from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), so PS4_Supporting is met PP4 - variant meets PM2 and was identified in 4 unrelated index cases who fulfill clinical criteria for FH after alternative causes for high cholesterol were excluded (please see PS4 for details), so PP4 is met.

Met criteria codes

PP1			variant segregates with the FH phenotype in 2 informative meioses (1 from each family) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): 2 relatives with LDL>75th percentile have the variant. so PP1 is met
PP3			REVEL = 0.903. It is above 0.75, so PP3 is met
PP4			variant meets PM2 and was identified in 4 unrelated index cases who fulfill at least SB Possible criteria for FH from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière). so PP4 is met
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met
PS4_Supporting			variant meets PM2 and was identified in 4 unrelated index cases who fulfill at least SB Possible criteria for FH from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière). so PS4_Supporting is met

Not Met criteria codes

PS1			no other missense variant leads to the same amino acid change, so not met
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PS2			no de novo occurrence
PS3			There are no functional studies performed for this variant
PP2			not applicable
BA1			This variant is absent from gnomAD (gnomAD v2.1.1).
PM6			no de novo occurrence
BS1			This variant is absent from gnomAD (gnomAD v2.1.1).
BS4			there is no evidence of lack of segregation
BS3			There are no functional studies performed for this variant
PM1			variant is missense and meets PM2, but it is not in exon 4 and does not alter Cys, so not met
PM3			variant was not identified in cases with more than 1 variant
PM5			1 other missense variant in the same codon: - NM_000527.5(LDLR):c.967G>A (p.Gly323Ser) - classified as Uncertain significance by the FH VCEP so PM5 is not met
PM4			variant is missense, so not applicable
BS2			not identified in normolipidemic individuals, so not met
BP5			not applicable
BP7			variant is missense, so not applicable
BP4			REVEL = 0.903. It is not below 0.50, so BP4 is not met
BP3			not applicable
BP1			not applicable
BP2			variant was not identified in cases with more than 1 variant
PVS1			variant is missense and not in initiation codon, so not applicable

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Curation History 		
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