

Variant: NM_000527.5(LDLR):c.1027G>T (p.Gly343Cys)

Version: 1.0

CA10585257 [↗](#)

251605 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: e65fb077-97df-4afc-b5c3-c4ffbb0958de

Approved on: 2023/4/28

Published on: 2023/5/1

HGVS expressions

NM_000527.5:c.1027G>T

NM_000527.5(LDLR):c.1027G>T (p.Gly343Cys)

NC_000019.10:g.11110738G>T

CM000681.2:g.11110738G>T

NC_000019.9:g.11221414G>T

CM000681.1:g.11221414G>T

NC_000019.8:g.11082414G>T

NG_009060.1:g.26358G>T

ENST00000252444.10:c.1285G>T

ENST00000559340.2:c.1027G>T

ENST00000560467.2:c.941-776G>T

ENST00000558518.6:c.1027G>T

ENST00000252444.9:c.1281G>T

ENST00000455727.6:c.523G>T

ENST00000535915.5:c.904G>T

ENST00000545707.5:c.646G>T

ENST00000557933.5:c.1027G>T

ENST00000558013.5:c.1027G>T

ENST00000558518.5:c.1027G>T

ENST00000560173.1:n.26G>T

ENST00000560467.1:c.541-776G>T

NM_000527.4:c.1027G>T

NM_001195798.1:c.1027G>T

NM_001195799.1:c.904G>T

NM_001195800.1:c.523G>T

NM_001195803.1:c.646G>T

NM_001195798.2:c.1027G>T

NM_001195799.2:c.904G>T

NM_001195800.2:c.523G>T

NM_001195803.2:c.646G>T

Pathogenic

Met criteria codes 6

PP1_StrongPP3PP4PM2PM3PM5

Not Met criteria codes 1

PS3

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.1027G>T (p.Gly343Cys) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PP1_Strong, PM5, PM3) 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 in gnomAD (gnomAD v2.1.1). PP3: REVEL=0.92, it is above 0.75. PP4: Variant meets PM2 and is identified in 1 index case who fulfil criteria for FH after alternative causes of high cholesterol were excluded. The patient had LDL-C level of 16.62 mmol/L with xanthomas and CHD, reported by Jelassi et al, 2009 and 2010, from Research Unit of Genetic and Biologic Factors of Atherosclerosis, Faculty of Medicine, Monastir, Tunisia, PMID 18757057 and 20144596. PP1_Strong: Variant segregates with FH phenotype in 6 informative meioses from 1 family: 5 affected relatives were positive, 1 unaffected relative was negative for the variant, reported by Jelassi et al, PMID 18757057 and 20144596. PM5: Three other variants at the same codon: NM_000527.5(LDLR):c.1028G>T (p.Gly343Val)(ClinVarID 440618) classified as Likely Pathogenic, NM_000527.5(LDLR):c.1028G>A (p.Gly343Asp)(ClinVarID 251606) is classified as Likely Pathogenic, NM_000527.5(LDLR):c.1027G>A (p.Gly343Ser)(ClinVarID 183106) is classified as Pathogenic by these guidelines, therefore PM5 is met. PM3: Variant meets PM2 and is identified in an index case with homozygous FH phenotype with plasma LDL-C 16.62 mmol/L, reported by Jelassi et al, PMID 18757057. This variant met enough pathogenic criteria toward Pathogenic classification by these guidelines before PM3 code applied. PS4 not met: Variant meets PM2 and is reported in 1 index case fulfil FH criteria and with homozygous FH phenotype, by Jelassi et al, PMID 18757057 and 20144596. PS3 not met: Functional data is not available.

Met criteria codes

PP1_Strong			Variant segregates with FH phenotype in 6 informative meioses from 1 family: 5 affected relatives were positive, 1 unaffected relative was negative for the variant, reported by Jelassi et al, PMID 18757057 and 20144596.
PP3			REVEL=0.92, it is above 0.75.
PP4			Variant meets PM2 and is identified in 1 index case who fulfil criteria for FH after alternative causes of high cholesterol were excluded. The patient had LDL-C level of 16.62 mmol/L with xanthomas and CHD, reported by Jelassi et al, 2009 and 2010, from Research Unit of Genetic and Biologic Factors of Atherosclerosis, Faculty of Medicine, Monastir, Tunisia, PMID 18757057 and 20144596.
PM2			This variant is absent in gnomAD (gnomAD v2.1.1).
PM3			Variant meets PM2 and is identified in an index case with homozygous FH phenotype with plasma LDL-C 16.62 mmol/L, reported by Jelassi et al, PMID 18757057. This variant met enough pathogenic criteria toward Pathogenic

classification by these guidelines before PM3 code applied.

PM5



Three other variants at the same codon: NM_000527.5(LDLR):c.1028G>T (p.Gly343Val)(ClinVarID 440618) classified as Likely Pathogenic, NM_000527.5(LDLR):c.1028G>A (p.Gly343Asp)(ClinVarID 251606) is classified as Likely Pathogenic, NM_000527.5(LDLR):c.1027G>A (p.Gly343Ser)(ClinVarID 183106) is classified as Pathogenic by these guidelines, therefore PM5 is met.

Not Met criteria codes

PS3



Functional data is not available.

Curation History [↗](#)

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