

Variant: *NM_000527.5(LDLR):c.3G>T (p.Met1Ile)*

Version: 1.0

CA10584721 [↗](#)

250969 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: d6e0032f-77ff-4e94-ad24-e9f089ef4990

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HGVS expressions

NM_000527.5:c.3G>T

NM_000527.5(LDLR):c.3G>T (p.Met1Ile)

NC_000019.10:g.11089551G>T

CM000681.2:g.11089551G>T

NC_000019.9:g.11200227G>T

CM000681.1:g.11200227G>T

NC_000019.8:g.11061227G>T

NG_009060.1:g.5171G>T

ENST00000559340.2:c.3G>T

ENST00000560467.2:c.3G>T

ENST00000558518.6:c.3G>T

ENST00000455727.6:c.3G>T

ENST00000535915.5:c.3G>T

ENST00000545707.5:c.3G>T

ENST00000557933.5:c.3G>T

ENST00000557958.1:n.89G>T

ENST00000558013.5:c.3G>T

ENST00000558518.5:c.3G>T

ENST00000560502.5:n.89G>T

NM_000527.4:c.3G>T

NM_001195798.1:c.3G>T

NM_001195799.1:c.3G>T

NM_001195800.1:c.3G>T

NM_001195803.1:c.3G>T

NM_001195798.2:c.3G>T

NM_001195799.2:c.3G>T

NM_001195800.2:c.3G>T

NM_001195803.2:c.3G>T

NR_163945.1:n.109C>A

Likely Pathogenic

Met criteria codes **5**

PVS1_Moderate

PP1

PP4

PM5

PM2

Not Met criteria codes **8**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.3G>T (p.Met1Ile) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PVS1_Moderate, PM5, PP1, 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 - variant is absent from gnomAD (v2.1.1). PVS1_Moderate - variant is predicted to affect the initiation codon. PP1- variant segregates with phenotype in 2 informative meioses in 1 family (Centre for Cardiovascular Surgery and Transplantation - 1 family: 2 affected relatives with the variant). PP4 - variant meets PM2 and is identified in 1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded. PM5 - Three other missense variants at this same codon have been reported, and one is Pathogenic: 1) NM_000527.5(LDLR):c.1A>C (p.Met1Leu) - Pathogenic by these guidelines. 2) NM_000527.5(LDLR):c.1A>G (p.Met1Val) - Likely pathogenic by these guidelines. 3) NM_000527.4(LDLR):c.2T>C (p.Met1Thr) - Likely pathogenic by these guidelines. Note: One other variant resulting in the same amino acid change at this codon has been reported: 1) NM_000527.4(LDLR):c.3G>A (p.Met1Ile) - Likely pathogenic by these guidelines. -PS1 is not applicable as such variants must be Pathogenic.

Met criteria codes

PVS1_Moderate			Variant is predicted to affect the initiation codon.
PP1			Variant segregates with phenotype in 2 informative meioses in 1 family (Centre for Cardiovascular Surgery and Transplantation - 1 family: 2 affected relatives with the variant)
PP4			Variant meets PM2 and is identified in 1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
PM5			Three other missense variants at this same codon have been reported, and one is Pathogenic: 1) NM_000527.5(LDLR):c.1A>C (p.Met1Leu) – Pathogenic by these guidelines. 2) NM_000527.5(LDLR):c.1A>G (p.Met1Val) - Likely pathogenic by these guidelines. 3) NM_000527.4(LDLR):c.2T>C (p.Met1Thr) - Likely pathogenic by these guidelines.
PM2			Variant is absent from gnomAD (v2.1.1).

Not Met criteria codes

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			Note: One other variant resulting in the same amino acid change at this codon has been reported: 1) NM_000527.4(LDLR):c.3G>A (p.Met1Ile) - Likely pathogenic by these guidelines. -PS1 not applicable as such variants must be Pathogenic.
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
   owing 1 to 1 of 1 rows		

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