

Variant: *NM_000527.5(LDLR):c.232C>T (p.Arg78Cys)*

Version: 1.0

CA023658 [↗](#)

161289 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c0820c58-696d-4193-ae01-ff55edbec638

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HGVS expressions

NM_000527.5:c.232C>T

NM_000527.5(LDLR):c.232C>T (p.Arg78Cys)

NC_000019.10:g.11102705C>T

CM000681.2:g.11102705C>T

NC_000019.9:g.11213381C>T

CM000681.1:g.11213381C>T

NC_000019.8:g.11074381C>T

NG_009060.1:g.18325C>T

ENST00000252444.10:c.490C>T

ENST00000559340.2:c.232C>T

ENST00000560467.2:c.232C>T

ENST00000558518.6:c.232C>T

ENST00000252444.9:c.486C>T

ENST00000455727.6:c.232C>T

ENST00000535915.5:c.190+2360C>T

ENST00000545707.5:c.232C>T

ENST00000557933.5:c.232C>T

ENST00000557958.1:n.318C>T

ENST00000558013.5:c.232C>T

ENST00000558518.5:c.232C>T

NM_000527.4:c.232C>T

NM_001195798.1:c.232C>T

NM_001195799.1:c.190+2360C>T

NM_001195800.1:c.232C>T

NM_001195803.1:c.232C>T

NM_001195798.2:c.232C>T

NM_001195799.2:c.190+2360C>T

NM_001195800.2:c.232C>T

NM_001195803.2:c.232C>T

Uncertain Significance

Met criteria codes **3**

PS4_Supporting

PP4

PM2

Not Met criteria codes **23**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BA1BS2BS1BS4BS3BP4BP3BP1BP2PVS1BP5BP7PS1PS2PS3PP1PP2PP3PM1PM3PM5PM4PM6

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.232C>T (p.Arg78Cys) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, PS4_Supporting and PP4) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PM2 - PopMax MAF = 0.0001002 (0.010%) in South Asian exomes (gnomAD v2.1.1). PP4 - Variant meets PM2. Identified in 2 FH cases from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with Dutch Lipid Clinic score ≥ 6. PS4_supporting - Variant meets PM2. Variant identified in at least 4 unrelated index cases with Simon-Broome criteria for FH or Dutch Lipid Clinic score equal or above 6 from different labs.

Met criteria codes

PS4_Supporting			Variant meets PM2. Variant identified in at least 4 unrelated index cases with Simon-Broome criteria for FH or Dutch Lipid Clinic score equal or above 6 from different labs (at least 1 from Color, 1 from GeneDx Inc. and 2 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)) --- PS4_Supporting is Met
PP4			Variant meets PM2. Identified in 2 FH cases from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with Dutch Lipid Clinic score ≥ 6. ---- PP4 is Met
PM2			PopMax MAF = 0.0001002 (0.010%) in South Asian exomes (gnomAD v2.1.1).

Not Met criteria codes

BA1			FAF = 0.00001897 (0.002%) in east asian exomes (gnomAD v2.1.1). FAF is not above 0.5%, so BA1 is Not Met.
BS2			no unaffected individuals identified with the variant, so BS2 is Not Met
BS1			FAF = 0.00001897 (0.002%) in east asian exomes (gnomAD v2.1.1). FAF is not above 0.2%, so BS1 is Not Met
BS4			no family members were tested, so BS4 is Not Met
BS3			no functional assays performed, not applicable
BP4			REVEL = 0.707. It is not below 0.15, so BP4 is Not Met

BP3			Not applicable
BP1			Not applicable
BP2			not identified in individuals with other variants, so BP2 is Not Met
PVS1			Missense variant, PVS1 Not Met
BP5			Not applicable
BP7			Missense variant, so BP7 is not applicable
PS1			No variant described that leads to the same amino acid change, so PS1 is Not Met
PS2			no de novo cases were identified, so PS2 is Not Met
PS3			no functional assays performed, not applicable
PP1			no family members were tested, so PP1 is Not Met
PP2			Not applicable
PP3			REVEL = 0.707. It is not above 0.75, splicing evaluation required. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50 bp upstream of canonical donor, but it does not create AG. C) there is no AG nearby. No splicing prediction is applicable, so PP3 is Not Met
PM1			Missense at codon 78. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed, so PM1 is Not Met
PM3			not identified in individuals with other variants, so PM3 is Not Met
PM5			One more missense variant described in same codon: (1)NM_000527.5(LDLR):c.233G>A (p.Arg78His) (ClinVar ID 251085) - VUS by these guidelines --- variant is classified as VUS, so PM5 is Not Met.
PM4			Missense variant, not applicable
PM6			no de novo cases were identified, so PM6 is Not Met

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