

Variant: *NM_000527.5(LDLR):c.233G>A (p.Arg78His)*

Version: 1.0

CA042534 [↗](#)

251085 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 8be0642c-9230-4c24-9637-a26525d228e6

Approved on: 2022/8/28

Published on: 2022/8/28

HGVS expressions

NM_000527.5:c.233G>A

NM_000527.5(LDLR):c.233G>A (p.Arg78His)

NC_000019.10:g.11102706G>A

CM000681.2:g.11102706G>A

NC_000019.9:g.11213382G>A

CM000681.1:g.11213382G>A

NC_000019.8:g.11074382G>A

NG_009060.1:g.18326G>A

ENST00000252444.10:c.491G>A

ENST00000559340.2:c.233G>A

ENST00000560467.2:c.233G>A

ENST00000558518.6:c.233G>A

ENST00000252444.9:c.487G>A

ENST00000455727.6:c.233G>A

ENST00000535915.5:c.190+2361G>A

ENST00000545707.5:c.233G>A

ENST00000557933.5:c.233G>A

ENST00000557958.1:n.319G>A

ENST00000558013.5:c.233G>A

ENST00000558518.5:c.233G>A

NM_000527.4:c.233G>A

NM_001195798.1:c.233G>A

NM_001195799.1:c.190+2361G>A

NM_001195800.1:c.233G>A

NM_001195803.1:c.233G>A

NM_001195798.2:c.233G>A

NM_001195799.2:c.190+2361G>A

NM_001195800.2:c.233G>A

NM_001195803.2:c.233G>A

Uncertain Significance

Met criteria codes **4**

PP3

PP4

PM2

PS4_Supporting

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

PS1

PS2

PS3

BA1

PP1

PP2

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS3

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.233G>A (p.Arg78His) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes PM2, 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 - PopMax MAF = 0.0001202 (0.012%) in African/African American exomes+genomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met. PP3 - REVEL = 0.806. It is above 0.75, so PP3 is met. PS4_supporting - variant meets PM2 and was identified in: - 1 index case with SB criteria of FH from PMID 31993549 (Garg et al., 2019), North America; - 1 index case with DLCN at least 8 (TC>10mmol/L and xanthomas) from PMID 27830735 (Jiang et al. 2016), China; - 1 index case with MEDPED criteria of FH from Benyahya et al. (2010) (paper cited in HGMD), Morocco; 3 unrelated index cases, so PS4_Supporting is met. PP4 - variant meets PM2 and was identified in 3 unrelated index cases who fulfill clinical criteria for FH after alternative causes of high cholesterol were excluded (please see PS4 for details), so PP4 is met.

Met criteria codes

PP3			REVEL = 0.806. It is above 0.75, so PP3 is met
PP4			variant meets PM2 and was identified in: - 1 index case with SB criteria of FH from PMID 31993549 (Garg et al., 2019), North America - 1 index case with DLCN at least 8 (TC>10mmol/L and xanthomas) from PMID 27830735 (Jiang et al. 2016), China - 1 index case with MEDPED criteria of FH from Benyahya et al. (2010) (paper cited in HGMD), Morocco so PP4 is met
PM2			PopMax MAF = 0.0001202 (0.012%) in African/African American exomes+genomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met
PS4_Supporting			variant meets PM2 and was identified in: - 1 index case with SB criteria of FH from PMID 31993549 (Garg et al., 2019), North America - 1 index case with DLCN at least 8 (TC>10mmol/L and xanthomas) from PMID 27830735 (Jiang et al. 2016), China - 1 index case with MEDPED criteria of FH from Benyahya et al. (2010) (paper cited in HGMD), Morocco so PS4_Supporting is met

Not Met criteria codes

PS1			there is no other missense variant that leads to the same amino acid change, so not met
PS2			no de novo occurrence

PS3			there are no functional studies performed in this variant
BA1			FAF = 0.00006011 (0.006%) in European non-Finnish exomes (gnomAD v2.1.1). It is not above 0.5%, so not met
PP1			no segregation data
PP2			not applicable
PM1			variant is missense and meets PM2, but it is not on exon 4 and does not alter Cys, so not met
PM3			variant identified in 1 index case with also NM_000527.5(LDLR):c.1474G>A (p.Asp492Asn) and a LDL-C max of 400mg/dl from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) --- not clearly a heterozygous phenotype, so not met
PM5			1 other missense variant in the same codon: NM_000527.5(LDLR):c.232C>T (p.Arg78Cys) - classified as VUS by the FH VCEP so PM5 is not met
PM4			variant is missense, so not applicable
PM6			no de novo occurrence
BS1			FAF = 0.00006011 (0.006%) in European non-Finnish exomes (gnomAD v2.1.1). It is not above 0.2%, so not met
BS4			no segregation data
BS3			there are no functional studies performed in this variant
BS2			variant was not searched in normolipidemic individuals, so not met
BP5			not applicable
BP7			variant is missense, so not applicable
BP4			REVEL = 0.806. It is not below 0.50, so BP4 is not met
BP3			not applicable
BP1			not applicable
BP2			variant identified in 1 index case with also NM_000527.5(LDLR):c.1474G>A (p.Asp492Asn) and a LDL-C max of 400mg/dl from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des

Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) --- not clearly a heterozygous phenotype, so not met

PVS1 ⓘ ✖ variant is missense and not in initiation codon, so not applicable

Curation History ↗

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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.