

Variant: *NM_000527.5(LDLR):c.265T>C (p.Cys89Arg)*

Version: 1.1

CA10584817 [↗](#)

251102 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 7f250f74-e4cd-4624-ad04-72229035c1dc

Approved on: 2022/3/25

Published on: 2022/7/12

HGVS expressions

NM_000527.5(LDLR):c.265T>C (p.Cys89Arg)

NM_000527.5:c.265T>C

NC_000019.10:g.11102738T>C

CM000681.2:g.11102738T>C

NC_000019.9:g.11213414T>C

CM000681.1:g.11213414T>C

NC_000019.8:g.11074414T>C

NG_009060.1:g.18358T>C

ENST00000252444.10:c.523T>C

ENST00000559340.2:c.265T>C

ENST00000560467.2:c.265T>C

ENST00000558518.6:c.265T>C

ENST00000252444.9:c.519T>C

ENST00000455727.6:c.265T>C

ENST00000535915.5:c.190+2393T>C

ENST00000545707.5:c.265T>C

ENST00000557933.5:c.265T>C

ENST00000557958.1:n.351T>C

ENST00000558013.5:c.265T>C

ENST00000558518.5:c.265T>C

NM_000527.4:c.265T>C

NM_001195798.1:c.265T>C

NM_001195799.1:c.190+2393T>C

NM_001195800.1:c.265T>C

NM_001195803.1:c.265T>C

NM_001195798.2:c.265T>C

NM_001195799.2:c.190+2393T>C

NM_001195800.2:c.265T>C

NM_001195803.2:c.265T>C

Likely Pathogenic

Met criteria codes **7**

PM1 PM3 PM2 PS4_Supporting

PP1 PP3 PP4

Not Met criteria codes **15**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PM5

PM4

PM6

BS1

BS4

BS3

BS2

PVS1

PS1

PS2

PS3

BP7

BP4

BP2

BA1

Evidence Links

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- Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1*
- PDF
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.265T>C (p.Cys89Arg) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM1, PM2, PM3, PS4_Supporting, PP1, PP3 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: PM1 - Variant meets PM2 and alters Cys89, one of the cysteine residues listed, so PM1 is Met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met. PM3 - Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL = 18.05 mmol/L) and LDLR variant c.1775G>A/p.(Gly592Glu), classified as Pathogenic by these guidelines, in trans, from Italy (PMID: 9974426), so PM3 is Met. PS4_Supporting - Variant meets PM2 and is identified in 5 unrelated index cases: 1 index case with possible FH (Simon-Broome criteria) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, at least 1 index case with definite heterozygous FH from The Netherlands (PMID: 16250003), 1 index case fulfilling MedPed criteria for FH from Spain (PMID: 16627557), 2 index cases fulfilling WHO criteria for FH from Poland (PMID: 20145306), so PS4_Supporting is Met. PP1 - Variant segregates with FH phenotype in 3 informative meioses from 1 family from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 2 affected family members have the variant and 1 non-affected family member does not have the variant, so PP1 is Met. PP3 - REVEL = 0.973. It is above 0.75, so PP3 is Met. PP4 - Variant meets PM2 and is identified in 5 unrelated index cases fulfilling clinical criteria for FH from several labs (see PS4 for details), so PP4 is Met.

Met criteria codes

PM1			Variant meets PM2 and alters Cys89, one of the cysteine residues listed, so PM1 is Met.
PM3			Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL = 18.05 mmol/L) and LDLR variant c.1775G>A/p.(Gly592Glu), classified as Pathogenic by these guidelines, in trans, from Italy (PMID: 9974426), so PM3 is Met.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met.
PS4_Supporting			Variant meets PM2 and is identified in 5 unrelated index cases: 1 index case with possible FH (Simon-Broome criteria) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, at least 1 index case with definite heterozygous FH from The Netherlands (PMID: 16250003), 1 index case fulfilling MedPed criteria for FH from Spain (PMID: 16627557), 2 index cases fulfilling WHO criteria for FH from Poland (PMID: 20145306), so PS4_Supporting is Met.
PP1			Variant segregates with FH phenotype in 3 informative meioses from 1 family from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 2 affected family members have the variant and 1 non-affected family member does not have the variant, so PP1 is Met.
PP3			REVEL = 0.973. It is above 0.75, so PP3 is Met.

PP4			Variant meets PM2 and is identified in 5 unrelated index cases: 1 index case with possible FH (Simon-Broome criteria) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, at least 1 index case with definite heterozygous FH from The Netherlands (PMID: 16250003), 1 index case fulfilling MedPed criteria for FH from Spain (PMID: 16627557), 2 index cases fulfilling WHO criteria for FH from Poland (PMID: 20145306), so PP4 is Met.
Not Met criteria codes			
PM5			Variant meets PM1 (alters Cys89, one of the cysteine residues listed), so PM5 is not met.
PM4			Variant meets PM2 and is missense, so PM4 is Not Met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.
BS1			No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BS1 is Not Met.
BS4			Lack of segregation data not reported, so BS4 is not met.
BS3			Functional studies are performed in compound heterozygous patients cells, so BS3 is not applicable.
BS2			Not observed in 208 non-FH alleles tested from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so BS2 is not met.
PVS1			Variant is missense, so PVS1 is Not Met.
PS1			Variant meets PM1 (alters Cys89, one of the cysteine residues listed), so PS1 is not met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.
PS3			Functional studies are performed in compound heterozygous patients cells, so PS3 is not applicable.
BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.973. It is not below 0.50, so BP4 is Not Met.
BP2			Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL = 18.05 mmol/L) and LDLR variant c.1775G>A/p.(Gly592Glu), classified as Pathogenic by these guidelines, in trans, from Italy (PMID: 9974426), so BP2 is not met.
BA1			No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BA1 is Not Met.

Curation History 



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