

Variant: *NM_000527.5(LDLR):c.693C>G (p.Cys231Trp)*

Version: 1.0

CA10585085 [↗](#)

251400 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 85e34844-d082-4855-ae9a-838120d2675c

Approved on: 2021/6/7

Published on: 2021/6/24

HGVS expressions

NM_000527.5:c.693C>G

NM_000527.5(LDLR):c.693C>G (p.Cys231Trp)

NC_000019.10:g.11105599C>G

CM000681.2:g.11105599C>G

NC_000019.9:g.11216275C>G

CM000681.1:g.11216275C>G

NC_000019.8:g.11077275C>G

NG_009060.1:g.21219C>G

ENST00000252444.10:c.951C>G

ENST00000559340.2:c.693C>G

ENST00000560467.2:c.693C>G

ENST00000558518.6:c.693C>G

ENST00000252444.9:c.947C>G

ENST00000455727.6:c.314-1793C>G

ENST00000535915.5:c.570C>G

ENST00000545707.5:c.314-966C>G

ENST00000557933.5:c.693C>G

ENST00000558013.5:c.693C>G

ENST00000558518.5:c.693C>G

ENST00000560467.1:c.293C>G

NM_000527.4:c.693C>G

NM_001195798.1:c.693C>G

NM_001195799.1:c.570C>G

NM_001195800.1:c.314-1793C>G

NM_001195803.1:c.314-966C>G

NM_001195798.2:c.693C>G

NM_001195799.2:c.570C>G

NM_001195800.2:c.314-1793C>G

NM_001195803.2:c.314-966C>G

Likely Pathogenic

Met criteria codes **5**

PP3 PP4 PM1 PM2

PS4_Supporting

Not Met criteria codes **21**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BP5	BP7	BP4	BP3	BP1	BP2
BS1	BS4	BS3	BS2	PP1	PP2
PS1	PS2	PS3	BA1	PM3	
PM5	PM4	PM6	PVS1		

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.693C>G (p.Cys231Trp) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM1, PM2, PP3, PP4 and PS4_Supporting) 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: PM1 - Missense at codon 231. PM2 is Met and Cys231 is one of the 60 Cys residues listed, so PM1 is Met. PM2 - No population data was found for this variant in gnomAD (gnomAD v2.1.1). PP3 - REVEL = 0.708. It is not above 0.75, splicing evaluation is required. Functional data on splicing not available. A) variant located -3 to +6 from canonical donor site MES scores: canonical site variant = 5.84; canonical site wt = 7.67. Ratio variant/wt canonical: 5.84/7.67 = 0.761. --- ratio is below 0.8, so PP3 is Met. PP4 - Variant meets PM2. Variant identified in at least 3 unrelated index cases with Simon-Broome criteria for FH from different labs. PS4_supporting - Variant meets PM2. Variant identified in at least 3 unrelated index cases with Simon-Broome criteria for FH from different labs.

Met criteria codes

PP3			REVEL = 0.708. It is not above 0.75, splicing evaluation is required. Functional data on splicing not available. A) variant located -3 to +6 from canonical donor site MES scores: canonical site variant = 5.84; canonical site wt = 7.67. Ratio variant/wt canonical: 5.84/7.67 = 0.761. --- ratio is below 0.8, so PP3 is Met
PP4			Variant meets PM2. Variant identified in at least 3 unrelated index cases with Simon-Broome criteria for FH (1 from Ambry Genetics and 2 from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge) ---- PP4 is Met
PM1			Missense at codon 231. PM2 is Met and Cys231 is one of the 60 Cys residues listed, so PM1 is Met
PM2			No population data was found for this variant in gnomAD (gnomAD v2.1.1).
PS4_Supporting			Variant meets PM2. Variant identified in at least 3 unrelated index cases with Simon-Broome criteria for FH (1 from Ambry Genetics and 2 from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge) --- PS4_Supporting is Met

Not Met criteria codes

BP5			Not applicable
BP7			Missense variant, so BP7 is not applicable

BP4			REVEL = 0.708. 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
BS1			No population data was found for this variant in gnomAD (gnomAD v2.1.1).
BS4			no non-segregations were identified, so BS4 is Not Met
BS3			no functional assays performed, not applicable
BS2			no unaffected individuals identified with the variant, so BS2 is Not Met
PP1			variant segregates with phenotype in 1 informative meiosis in 1 family from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 1 affected family member has the variant. not enough evidence to meet PP1 --- PP1 is Not Met
PP2			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
BA1			No population data was found for this variant in gnomAD (gnomAD v2.1.1).
PM3			not identified in individuals with other variants, so PM3 is Not Met
PM5			Variant meets PM1, so PM5 is not applicable.
PM4			Missense variant, not applicable
PM6			no de novo cases were identified, so PM6 is Not Met
PVS1			Missense variant, PVS1 Not Met

Curation History [↗](#)

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