The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000527.5(LDLR):c.1749C>A (p.His583Gln)

Version: 1.0

CA10585596

252014 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 295fc36b-5d7c-4f30-bf9c-8e36ef2a340b
Approved on: 2023/11/7
Published on: 2024/12/24

HGVS expressions

NM_000527.5:c.1749C>A
NM_000527.5(LDLR):c.1749C>A (p.His583Gln)
NC_000019.10:g.11116902C>A
CM000681.2:g.11116902C>A
NC_000019.9:g.11227578C>A
CM000681.1:g.11227578C>A
NC_000019.8:g.11088578C>A
NG_009060.1:g.32522C>A
ENST00000252444.10:c.2007C>A
ENST00000559340.2:c.1705+690C>A
ENST00000560467.2:c.1629C>A
ENST00000558518.6:c.1749C>A
ENST00000252444.9:c.2003C>A
ENST00000455727.6:c.1245C>A
ENST00000535915.5:c.1626C>A
ENST00000545707.5:c.1368C>A
ENST00000557933.5:c.1749C>A
ENST00000558013.5:c.1749C>A
ENST00000558518.5:c.1749C>A
ENST00000559340.1:c.426+690C>A
NM_000527.4:c.1749C>A
NM_001195798.1:c.1749C>A
NM_001195799.1:c.1626C>A
NM_001195800.1:c.1245C>A
NM_001195803.1:c.1368C>A
NM_001195798.2:c.1749C>A
NM_001195799.2:c.1626C>A
NM_001195800.2:c.1245C>A
NM_001195803.2:c.1368C>A

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM2 PM5

Not Met criteria codes 20

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PS1 PS3 PS4 PP1 PP2 PM1 PM3 PM4 BA1 BS2 PVS1 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7

Evidence Links 0

Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2*

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.1749C>A (p.His583Gln) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM5, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 7 November 2023. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.805. PM5: There is 1 variant in the same codon classified as Pathogenic by these guidelines, NM_000527.5(LDLR):c.1747C>T (p.His583Tyr) (ClinVar ID: 200921). PP4: Variant meets PM2 and is identified in at least 1 index case with DLCN score >=6, after alternative causes of high cholesterol were excluded, from PMID 19318025 (Alonso et al., 2009).

Met criteria codes

PP3	✔	REVEL = 0.805. It is above 0.75, so PP3 is met.
PP4	✔	Variant meets PM2 and is identified in at least 1 index case fulfilling DLCN criteria ≥ 6 for FH, after alternative causes of high cholesterol are excluded, from PMID: 19318025.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1).
PM5	✔	NM_000527.5(LDLR):c.1747C>T (p.His583Tyr) (ClinVar ID: 200921) considered as pathogenic by these guidelines.

Not Met criteria codes

PS1	✖	Another variant gives the same amino acid change, NM_000527.5(LDLR):c.1749C>G (p.His583Gln) (ClinVar ID: 441220), but is classified as uncertain significance by these guidelines.
PS3	✖	not met (no information or reports of functional data).
PS4	✖	not met, (no information of index cases or report of segregation data/cases).
PP1	✖	not met, (no information of index cases or report of segregation data/cases).
PP2	✖	N/A according to FHVCEP guidelines
PM1	✖	Variant in exon 12 of the LDLR gene (not located at exon 4)

PM3		✖	Not identified in index cases with more than one variant
PM4		✖	Missense variant, exon 12 - LDLR gene
BA1		✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS2		✖	not met, (no information of index cases or report of segregation data/cases).
PVS1		✖	Missense variant, exon 12 - LDLR gene
BS1		✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS4		✖	not met, (no information of index cases or report of segregation data/cases).
BS3		✖	not met (no information or reports of functional data).
BP4		✖	REVEL = 0.805. It is not bellow 0.5, so BP4 is not met.
BP3		✖	Missense variant, exon 12 - LDLR gene
BP1		✖	N/A according to FHVCEP guidelines
BP2		✖	Not identified in index cases with more than one variant
BP5		✖	N/A according to FHVCEP guidelines
BP7		✖	Missense variant, exon 12 - LDLR gene

Curation History

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