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.1748A>G (p.His583Arg)

Version: 1.0

CA10585595

252012 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: e544d995-1e9d-46dd-ab67-e144025f2189
Approved on: 2023/11/7
Published on: 2024/12/24

HGVS expressions

NM_000527.5(LDLR):c.1748A>G (p.His583Arg)
NM_000527.5:c.1748A>G
NC_000019.10:g.11116901A>G
CM000681.2:g.11116901A>G
NC_000019.9:g.11227577A>G
CM000681.1:g.11227577A>G
NC_000019.8:g.11088577A>G
NG_009060.1:g.32521A>G
ENST00000252444.10:c.2006A>G
ENST00000559340.2:c.1705+689A>G
ENST00000560467.2:c.1628A>G
ENST00000558518.6:c.1748A>G
ENST00000252444.9:c.2002A>G
ENST00000455727.6:c.1244A>G
ENST00000535915.5:c.1625A>G
ENST00000545707.5:c.1367A>G
ENST00000557933.5:c.1748A>G
ENST00000558013.5:c.1748A>G
ENST00000558518.5:c.1748A>G
ENST00000559340.1:c.426+689A>G
NM_000527.4:c.1748A>G
NM_001195798.1:c.1748A>G
NM_001195799.1:c.1625A>G
NM_001195800.1:c.1244A>G
NM_001195803.1:c.1367A>G
NM_001195798.2:c.1748A>G
NM_001195799.2:c.1625A>G
NM_001195800.2:c.1244A>G
NM_001195803.2:c.1367A>G

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM2 PM5

Not Met criteria codes 20

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PS1 PS2 PS3 PS4 PP1 PP2
PM6 PM1 PM3 PM4 BA1
PVS1 BS1 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.1748A>G (p.His583Arg) 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 = 0.819. 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 possible FH by Simon Broome criteria, after alternative causes of high cholesterol were excluded, from the Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic (PMID 22698793, Tichý et al., 2012).

Met criteria codes

PP3	✔	REVEL = 0.819. It is above 0.75, so PP3 is met.
PP4	✔	Variant meets PM2 and is identified in at least 1 index case fulfilling SB criteria for possible FH, after alternative causes of high cholesterol are excluded from the Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), This index case is published in PMID: 22698793
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	✖	No other variant with same amino acid change identified
PS2	✖	No de novo occurrence
PS3	✖	Functional studies (PMID: 32695144) performed using Heterologous cells (CHO), WB and FACS - results - 77% expression and 80% internalisation. ----- Overall, the results are not below 70%, so PS3 is not met.
PS4	✖	PS4_Supporting: 1 index case (PMID:2698793) fulfilling SB criteria or untreated total and/or LDL levels above P95th of age/sex/population not considered to avoid double-counting.
PP1	✖	

Variant segregates with FH phenotype in 1 informative meiose (only 1 family) from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) - 1 relative does not have the variant and has LDL<50th percentile.

PP2	✖	N/A according to FHVCEP guidelines
PM6	✖	No de novo occurrence
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 - LDLR exon 12
BA1	✖	This variant is absent from gnomAD (gnomAD v2.1.1).
PVS1	✖	Missense variant - LDLR exon 12
BS1	✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS3	✖	Functional studies (PMID: 32695144) performed using Heterologous cells (CHO), WB and FACS - results - 77% expression and 80% internalisation. ----- Overall, results are not above 90/95%, so BS3 is not met either.
BP4	✖	REVEL = 0.819. It is not bellow 0.5, so BP4 is not met.
BP3	✖	Missense variant - LDLR exon 12
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 - LDLR exon 12

Curation History

nowing 1 to 1 of 1 rows

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.