

Variant: *NM_000527.5(LDLR):c.1747C>G (p.His583Asp)*

Version: 1.0

CA023564 [↗](#)

183124 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 8e9e2ceb-e493-4190-93bf-def265f1ee65

Approved on: 2023/11/7

Published on: 2024/12/24

HGVS expressions

NM_000527.5(LDLR):c.1747C>G (p.His583Asp)

NM_000527.5:c.1747C>G

NC_000019.10:g.11116900C>G

CM000681.2:g.11116900C>G

NC_000019.9:g.11227576C>G

CM000681.1:g.11227576C>G

NC_000019.8:g.11088576C>G

NG_009060.1:g.32520C>G

ENST00000252444.10:c.2005C>G

ENST00000559340.2:c.1705+688C>G

ENST00000560467.2:c.1627C>G

ENST00000558518.6:c.1747C>G

ENST00000252444.9:c.2001C>G

ENST00000455727.6:c.1243C>G

ENST00000535915.5:c.1624C>G

ENST00000545707.5:c.1366C>G

ENST00000557933.5:c.1747C>G

ENST00000558013.5:c.1747C>G

ENST00000558518.5:c.1747C>G

ENST00000559340.1:c.426+688C>G

NM_000527.4:c.1747C>G

NM_001195798.1:c.1747C>G

NM_001195799.1:c.1624C>G

NM_001195800.1:c.1243C>G

NM_001195803.1:c.1366C>G

NM_001195798.2:c.1747C>G

NM_001195799.2:c.1624C>G

NM_001195800.2:c.1243C>G

NM_001195803.2:c.1366C>G

Likely Pathogenic

Met criteria codes **4**

PS3_Supporting

PP3

PM2

PM5

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

BS1

BS4

BS3

BP4

BP3

BP1

BP2

PVS1

BP5

BP7

BA1

PS1

PS2

PS4

PP1

PP2

PP4

PM6

PM1

PM3

PM4

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.1747C>G (p.His583Asp) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM5, PP3 and PS3_Supporting 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: PopMax MAF = 0.000008790 (0.0008790%) in European (non-Finnish) (gnomAD v2.1.1). PP3: REVEL = 0.798. 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). PS3_Supporting: Functional studies (PMID 25647241, Thormaehlen et al., 2015) using HeLa-Kyoto cells, LDLR-GFP construct, WB and CLSM assays - results - most of mutant LDLR is in ER, LDLR activity decreased compared to WT - considered as disruptive. Therefore, PS3_Supporting is met.

Met criteria codes

PS3_Supporting			Functional studies (PMID: 25647241, Thormaehlen et al) using HeLa-Kyoto cells, LDLR-GFP construct, WB and CLSM assays - results - most of mutant LDLR is in ER, LDLR activity decreased compared to WT - considered as disruptive. Therefore, PS3_Supporting is met (according to FHVCEP considerations).
PP3			REVEL = 0.798. It is above 0.75, so PP3 is met.
PM2			PopMax MAF = 0.000008790 (0.0008790%) in European (non-Finnish) (gnomAD v2.1.1). PopMax MAF < 0.02%, therefore PM2 is met.
PM5			NM_000527.5(LDLR):c.1747C>T (p.His583Tyr) (ClinVar ID: 200921) considered as pathogenic by these guidelines.

Not Met criteria codes

BS2			Not identified in normolipidemic individuals
BS1			Since PM2 is met (PopMax MAF < 0.02%), BS1 is not met.
BS4			No family members identified.
BS3			Not met, no reports
BP4			REVEL not bellow 0.5. Therefore, BP4 is not met

BP3			Missense variant in LDLR exon 12.
BP1			N/A according to FHVCEP guidelines
BP2			Not identified for index cases with more than 1 variant
PVS1			Missense variant in LDLR exon 12.
BP5			N/A according to FHVCEP guidelines
BP7			Missense variant in LDLR exon 12.
BA1			Since PM2 is met (PopMax MAF < 0.02%), BA1 is not met.
PS1			No other variant with same amino acid change identified
PS2			No de novo cases identified
PS4			No index cases identified.
PP1			No family members identified.
PP2			N/A according to FHVCEP guidelines
PP4			No index cases identified.
PM6			No de novo cases identified
PM1			Variant in exon 12 of the LDLR gene (not located at exon 4)
PM3			Not identified for index cases with more than 1 variant
PM4			Missense variant in LDLR exon 12.

Showing 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.