

Variant: *NM_000527.5(LDLR):c.284G>A (p.Cys95Tyr)*

Version: 1.0

CA10584826 [↗](#)

251113 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: de75f52a-4aaa-4b08-a993-f560e5b916a0

Approved on: 2024/2/23

Published on: 2025/8/29

HGVS expressions

NM_000527.5(LDLR):c.284G>A (p.Cys95Tyr)

NM_000527.5:c.284G>A

NC_000019.10:g.11102757G>A

CM000681.2:g.11102757G>A

NC_000019.9:g.11213433G>A

CM000681.1:g.11213433G>A

NC_000019.8:g.11074433G>A

NG_009060.1:g.18377G>A

ENST00000252444.10:c.542G>A

ENST00000559340.2:c.284G>A

ENST00000560467.2:c.284G>A

ENST00000558518.6:c.284G>A

ENST00000252444.9:c.538G>A

ENST00000455727.6:c.284G>A

ENST00000535915.5:c.190+2412G>A

ENST00000545707.5:c.284G>A

ENST00000557933.5:c.284G>A

ENST00000557958.1:n.370G>A

ENST00000558013.5:c.284G>A

ENST00000558518.5:c.284G>A

NM_000527.4:c.284G>A

NM_001195798.1:c.284G>A

NM_001195799.1:c.190+2412G>A

NM_001195800.1:c.284G>A

NM_001195803.1:c.284G>A

NM_001195798.2:c.284G>A

NM_001195799.2:c.190+2412G>A

NM_001195800.2:c.284G>A

NM_001195803.2:c.284G>A

Likely Pathogenic

Met criteria codes **4**

PP3 PP4 PM2 PM1

Not Met criteria codes **17**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

BS1

BS4

BS3

BP4

BP3

BP1

PVS1

BP5

BP7

BA1

PS3

PS4

PP1

PP2

PM5

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

The NM_000527.5(LDLR):c.284G>A (p.Cys95Tyr) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM1, PM2, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.918. PM1: Variant meets PM2 and alters one highly conserved Cys residue (Cys95). PP4: Variant meets PM2 and is identified in at least 1 index case fulfilling Simon Broome criteria or with DLCN score >=6, after alternative causes of high cholesterol were excluded, from PMID 28502510 (Bañares et al., 2017).

Met criteria codes

PP3			- PP3: REVEL = 0.918. It is above 0.75, so PP3 is met.
PP4			- PP4: Variant meets PM2 and is identified in at least 1 index case fulfilling DLCN>=6 criteria or SB criteria for FH, after alternative causes of high cholesterol are excluded from PMID:28502510. (in this PMID, children fulfilled SB criteria for FH and adults fulfilled DLCN>=6 criteria. It is not stated if the index case with the variant is an adult or a child, however, for both cohorts FH specific criteria is fulfilled).
PM2			- PM2: This variant is absent from gnomAD (gnomAD v2.1.1).
PM1			- PM1: Variant meets PM2 and alters one highly conserved Cys residue (Cys95).

Not Met criteria codes

BS2			* BS2 / BS4 / PP1: not met, (no information of several index cases or segregation data/cases in different families)
BS1			This variant is absent from gnomAD (gnomAD v2.1.1), therefore BS1 is not met.
BS4			* BS2 / BS4 / PP1: not met, (no information of several index cases or segregation data/cases in different families)
BS3			* BS3 / PS3: not met (no information or reports of functional data).
BP4			BP4: REVEL = 0.918, not below 0.50. Therefore, BP4 is not met.

BP3			N/A according to FH VCEP Guidelines
BP1			N/A according to FH VCEP Guidelines
PVS1			This variant is misense, therefore PVS1 is not met.
BP5			N/A according to FH VCEP Guidelines
BP7			This variant is misense, therefore BP7 is not met.
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), therefore BA1 is not met.
PS3			* BS3 / PS3: not met (no information or reports of functional data).
PS4			* PS4: (PMID:18096825) Variant meets PM2 and is identified in 3 index cases from the Spanish FH register. Specific clinical data is presented in Table 1, only with mean range values of age/CT/LDL. Since clinical and familial data of these 3 subjects is unclear, they were not counted towards PS4 "All patients had been referred to the Lipid Clinic of Hospital Clínic in Barcelona for diagnosis of severe hypercholesterolemia or alleged refractoriness to treatment (...) Subjects underwent sonographic assessment of femoral atherosclerosis (...) Subjects with clinical FH are recruited into the Spanish FH Register (...) All subjects were assessed for family history of early-onset CHD, clinical history, medication use, CV risk and presence of tendon xanthomas". // (PMID:19318025) at least 1 index case with the variant and DLCN criteria≥ 6, supp material was not possible to access to confirm the variant and number of cases // (PMID:23375686) Variant identified in at least one index case fulfilling DLCN criteria for "possible", "probable" or "definite FH", after alternative causes of high cholesterol are excluded. As it is not stated DLCN score of this index case, this case was not counted.
PP1			* BS2 / BS4 / PP1: not met, (no information of several index cases or segregation data/cases in different families)
PP2			N/A according to FH VCEP Guidelines
PM5			* PM5 / PS1 not met: NM_000527.5(LDLR):c.283T>G (p.Cys95Gly) (ClinVar ID: 251112) considered as VUS by these guidelines
PM4			This variant is misense, therefore PM4 is not met.

Curation History

--

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.