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.1243G>C (p.Asp415His)

Version: 1.0

CA10585371

251748 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 2031df77-308b-4d89-9625-dff44bf8c877
Approved on: 2023/6/23
Published on: 2025/6/30

HGVS expressions

NM_000527.5:c.1243G>C
NM_000527.5(LDLR):c.1243G>C (p.Asp415His)
NC_000019.10:g.11113334G>C
CM000681.2:g.11113334G>C
NC_000019.9:g.11224010G>C
CM000681.1:g.11224010G>C
NC_000019.8:g.11085010G>C
NG_009060.1:g.28954G>C
ENST00000252444.10:c.1501G>C
ENST00000559340.2:c.1243G>C
ENST00000560467.2:c.1123G>C
ENST00000558518.6:c.1243G>C
ENST00000252444.9:c.1497G>C
ENST00000455727.6:c.739G>C
ENST00000535915.5:c.1120G>C
ENST00000545707.5:c.862G>C
ENST00000557933.5:c.1243G>C
ENST00000558013.5:c.1243G>C
ENST00000558518.5:c.1243G>C
ENST00000560173.1:n.242G>C
ENST00000560467.1:c.723G>C
NM_000527.4:c.1243G>C
NM_001195798.1:c.1243G>C
NM_001195799.1:c.1120G>C
NM_001195800.1:c.739G>C
NM_001195803.1:c.862G>C
NM_001195798.2:c.1243G>C
NM_001195799.2:c.1120G>C
NM_001195800.2:c.739G>C
NM_001195803.2:c.862G>C

Likely Pathogenic

Met criteria codes 4

PM3 PM2 PP3 PP4

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

- **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.1243G>C (p.Asp415His) variant is classified as Likely Pathogenic, for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM3, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 June 2023. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.805. PP4: Variant meets PM2 and is identified in at least 1 index case fulfilling criteria for FH from PMID 11810272 (Fouchier et al., 2001), The Netherlands. PM3: Variant meets PM2 and was identified in an index case with homozygous FH phenotype (LDL-c 893 mg/dL) and LDLR variant (Cys143*) in trans, classified as Pathogenic by these guidelines, from PMID 26894473 (Sanna et al., 2016), Belgium.

Met criteria codes

PM3	✔	- PM3: Variant meets PM2 and was identified in an index case with homozygous FH phenotype (LDL-c 893 mg/dL) and LDLR variant (Cys143*) in trans, classified as Pathogenic by these guidelines, from lab PMID: 26894473.
PM2	✔	- PM2: This variant is absent from gnomAD (gnomAD v2.1.1).
PP3	✔	- PP3: REVEL = 0.805. It is above 0.75, so PP3 is met.
PP4	✔	- PP4: Variant meets PM2 and is identified in at least 1 index case fulfilling Simon Broome criteria for definite or possible FH phenotype from PMID:11810272.

Not Met criteria codes

PM5	✖	NM_000527.5(LDLR):c.1244A>G (p.Asp415Gly) (ClinVar ID: 251749) considered as Likely Pathogenic by these guidelines. NM_000527.5(LDLR):c.1244A>T (p.Asp415Val) (ClinVar ID: 251750) considered as VUS by these guidelines.

Curation History

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