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.1028G>A (p.Gly343Asp)

Version: 1.0

CA10585258

251606 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 296222b4-2b23-4455-8916-41dc7d49aa17
Approved on: 2023/1/27
Published on: 2023/4/1

HGVS expressions

NM_000527.5:c.1028G>A
NM_000527.5(LDLR):c.1028G>A (p.Gly343Asp)
NC_000019.10:g.11110739G>A
CM000681.2:g.11110739G>A
NC_000019.9:g.11221415G>A
CM000681.1:g.11221415G>A
NC_000019.8:g.11082415G>A
NG_009060.1:g.26359G>A
ENST00000252444.10:c.1286G>A
ENST00000559340.2:c.1028G>A
ENST00000560467.2:c.941-775G>A
ENST00000558518.6:c.1028G>A
ENST00000252444.9:c.1282G>A
ENST00000455727.6:c.524G>A
ENST00000535915.5:c.905G>A
ENST00000545707.5:c.647G>A
ENST00000557933.5:c.1028G>A
ENST00000558013.5:c.1028G>A
ENST00000558518.5:c.1028G>A
ENST00000560173.1:n.27G>A
ENST00000560467.1:c.541-775G>A
NM_000527.4:c.1028G>A
NM_001195798.1:c.1028G>A
NM_001195799.1:c.905G>A
NM_001195800.1:c.524G>A
NM_001195803.1:c.647G>A
NM_001195798.2:c.1028G>A
NM_001195799.2:c.905G>A
NM_001195800.2:c.524G>A
NM_001195803.2:c.647G>A

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM2 PM5_Strong

Not Met criteria codes 2

PS3 PS4

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.1028G>A (p.Gly343Asp) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PM5_Strong) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1016/j.gim.2021.09.012). The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL=0.959, it is above 0.75. PP4: Variant meets PM2 and is identified in 1 index case who fulfil DLCN criteria for definite FH after alternative causes of high cholesterol were excluded, reported in ClinVar (SCV000583778.1) from U4M - Lille University & CHRU Lille, Universite de Lille - CHRU de Lille, France. PM5_Strong: Three other variants at the same codon: NM_000527.5(LDLR):c.1028G>T (p.Gly343Val)(ClinVarID 440618) classified as Likely Pathogenic, NM_000527.5(LDLR):c.1027G>A (p.Gly343Ser)(ClinVarID 183106) is classified as Pathogenic, NM_000527.5(LDLR):c.1027G>T (p.Gly343Cys)(ClinVarID 251605) is classified as Pathogenic by these guidelines, therefore PM5_Strong is met. PS4 not met: Variant meets PM2 and is reported in 1 index case and family fulfil FH criteria, reported from U4M - Lille University & CHRU Lille, Universite de Lille - CHRU de Lille, France. PS3 not met: Functional data is not available.

Met criteria codes

PP3	✔	REVEL=0.959, it is above 0.75.
PP4	✔	Variant meets PM2 and is identified in 1 index case who fulfil DLCN criteria for definite FH after alternative causes of high cholesterol were excluded, reported in ClinVar (SCV000583778.1) from U4M - Lille University & CHRU Lille, Universite de Lille - CHRU de Lille, France.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1).
PM5_Strong	✔	Three other variants at the same codon: NM_000527.5(LDLR):c.1028G>T (p.Gly343Val)(ClinVarID 440618) classified as Likely Pathogenic, NM_000527.5(LDLR):c.1027G>A (p.Gly343Ser)(ClinVarID 183106) is classified as Pathogenic, NM_000527.5(LDLR):c.1027G>T (p.Gly343Cys)(ClinVarID 251605) is classified as Pathogenic by these guidelines, therefore PM5_Strong is met.

Not Met criteria codes

PS3	✖	Functional data is not available.

PS4		✖	Variant meets PM2 and is reported in 1 index case and family fulfil FH criteria, reported from U4M - Lille University & CHRU Lille, Universite de Lille - CHRU de Lille, France.

Curation History

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