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.1618G>T (p.Ala540Ser)

Version: 1.0

CA10585529

251938 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 6f238252-988b-448e-966f-3865fda9608c
Approved on: 2022/8/28
Published on: 2022/8/28

HGVS expressions

NM_000527.5(LDLR):c.1618G>T (p.Ala540Ser)
NM_000527.5:c.1618G>T
NC_000019.10:g.11116125G>T
CM000681.2:g.11116125G>T
NC_000019.9:g.11226801G>T
CM000681.1:g.11226801G>T
NC_000019.8:g.11087801G>T
NG_009060.1:g.31745G>T
ENST00000252444.10:c.1876G>T
ENST00000559340.2:c.1618G>T
ENST00000560467.2:c.1498G>T
ENST00000558518.6:c.1618G>T
ENST00000252444.9:c.1872G>T
ENST00000455727.6:c.1114G>T
ENST00000535915.5:c.1495G>T
ENST00000545707.5:c.1237G>T
ENST00000557933.5:c.1618G>T
ENST00000558013.5:c.1618G>T
ENST00000558518.5:c.1618G>T
ENST00000559340.1:c.339G>T
NM_000527.4:c.1618G>T
NM_001195798.1:c.1618G>T
NM_001195799.1:c.1495G>T
NM_001195800.1:c.1114G>T
NM_001195803.1:c.1237G>T
NM_001195798.2:c.1618G>T
NM_001195799.2:c.1495G>T
NM_001195800.2:c.1114G>T
NM_001195803.2:c.1237G>T

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM5 PM2

Not Met criteria codes 22

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP1 PP2 BA1 PM1 PM3
PM4 PM6 PVS1 BS2 BS1
BS4 BS3 PS1 PS2 PS3 PS4
BP5 BP7 BP4 BP3 BP1 BP2

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1618G>T (p.Ala540Ser) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PM5, PP3, PP4 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 - variant was not identified in gnomAD (gnomAD v2.1.1), so met. PM5 - 1 other missense variant in the same codon: - NM_000527.5(LDLR):c.1618G>A (p.Ala540Thr) - 2 stars, Pathogenic/Likely pathogenic - Pathogenic by these guidelines so PM5 is met. PP3 - REVEL = 0.821. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in: - at least 1 index case with definite FH ((in the paper: "All patients were clinically diagnosed with definite heterozygous hypercholesterolemia by cardiologists and internists using a uniform protocol and internationally accepted criteria [Defesche, 2000].") from PMID 16250003 (Fouchier et al., 2005), The Netherlands. so PP4 is met.

Met criteria codes

PP3	✔	REVEL = 0.821. It is above 0.75, so PP3 is met
PP4	✔	variant meets PM2 and was identified in: - at least 1 index case with definite FH ((in the paper: "All patients were clinically diagnosed with definite heterozygous hypercholesterolemia by cardiologists and internists using a uniform protocol and internationally accepted criteria [Defesche, 2000].") from PMID 16250003 (Fouchier et al., 2005), The Netherlands. so PP4 is met
PM5	✔	1 other missense variant in the same codon: - NM_000527.5(LDLR):c.1618G>A (p.Ala540Thr) - 2 stars, Pathogenic/Likely pathogenic - Pathogenic by these guidelines so PM5 is met
PM2	✔	This variant was not identified in gnomAD (gnomAD v2.1.1), so met

Not Met criteria codes

PP1	✖	no segregation data
PP2	✖	not applicable
BA1	✖	This variant was not identified in gnomAD (gnomAD v2.1.1), so not met
PM1	✖	variant is missense and meets PM2, but it is not in exon 4 and does not alter Cys, so not met

PM3		✖	not identified in index cases with other variants
PM4		✖	variant is missense, so not applicable
PM6		✖	no de novo occurrence
PVS1		✖	variant is missense and not in initiation codon, not applicable
BS2		✖	there is no data on normolipidemic individuals
BS1		✖	This variant was not identified in gnomAD (gnomAD v2.1.1), so not met
BS4		✖	no segregation data
BS3		✖	there is no functional study on this variant
PS1		✖	no other variant leads to the same amino acid change, so not met
PS2		✖	no de novo occurrence
PS3		✖	there is no functional study on this variant
PS4		✖	variant meets PM2 and was identified in: - at least 1 index case with definite FH ((in the paper: "All patients were clinically diagnosed with definite heterozygous hypercholesterolemia by cardiologists and internists using a uniform protocol and internationally accepted criteria [Defesche, 2000].") from PMID 16250003 (Fouchier et al., 2005), The Netherlands. not enough, so PS4 is not met
BP5		✖	not applicable
BP7		✖	variant is missense, so not applicable
BP4		✖	REVEL = 0.821. It is not below 0.50, so BP4 is not met
BP3		✖	not applicable
BP1		✖	not applicable
BP2		✖	not identified in index cases with other variants

Curation History

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