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.642G>A (p.Trp214Ter)

Version: 1.1

CA10585029

251340 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: ecdf9c5f-f262-4f76-aee8-d7a7e435de78
Approved on: 2021/12/13
Published on: 2022/7/11

HGVS expressions

NM_000527.5:c.642G>A
NM_000527.5(LDLR):c.642G>A (p.Trp214Ter)
NC_000019.10:g.11105548G>A
CM000681.2:g.11105548G>A
NC_000019.9:g.11216224G>A
CM000681.1:g.11216224G>A
NC_000019.8:g.11077224G>A
NG_009060.1:g.21168G>A
ENST00000252444.10:c.900G>A
ENST00000559340.2:c.642G>A
ENST00000560467.2:c.642G>A
ENST00000558518.6:c.642G>A
ENST00000252444.9:c.896G>A
ENST00000455727.6:c.314-1844G>A
ENST00000535915.5:c.519G>A
ENST00000545707.5:c.314-1017G>A
ENST00000557933.5:c.642G>A
ENST00000558013.5:c.642G>A
ENST00000558518.5:c.642G>A
ENST00000560467.1:c.242G>A
NM_000527.4:c.642G>A
NM_001195798.1:c.642G>A
NM_001195799.1:c.519G>A
NM_001195800.1:c.314-1844G>A
NM_001195803.1:c.314-1017G>A
NM_001195798.2:c.642G>A
NM_001195799.2:c.519G>A
NM_001195800.2:c.314-1844G>A
NM_001195803.2:c.314-1017G>A

Pathogenic

Met criteria codes 3

PVS1 PM2 PP4

Not Met criteria codes 23

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PM1 PM3 PM5 PM4 PM6
BA1 BS1 BS4 BS3 BS2 BP5
BP7 BP4 BP3 BP1 BP2 PS1
PS2 PS3 PS4 PP1 PP2 PP3

Evidence Links 0

Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.642G>A (p.Trp214Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PVS1, PM2 and 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: PVS1 - variant is nonsense in exon 4 (amino terminal of amino acid 830), so PVS1 is met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PP4 - variant meets PM2 and was identified in at least 1 index case with SB criteria of definite FH (A+B) (Diagnostic criteria for heterozygous FH used in the paper were a TC>8.0 mmol/l and LDL- C>6.0 mmol/l if available, tendon xanthomata in the patient or in a first-degree relative, and a family history of hypercholesterolemia) from PMID 10532689 (Jensen et al., 1999), Denmark. so PP4 is met.

Met criteria codes

PVS1	✔	variant is nonsense in exon 4 (amino terminal of amino acid 830), so PVS1 is met
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met
PP4	✔	variant meets PM2 and was identified in: - at least 1 index case with SB criteria of definite FH (A+B) (Diagnostic criteria for heterozygous FH used in the paper were a TC>8.0 mmol/l and LDL- C>6.0 mmol/l if available, tendon xanthomata in the patient or in a first-degree relative, and a family history of hypercholesterolemia) from PMID 10532689 (Jensen et al., 1999), Denmark. so PP4 is met

Not Met criteria codes

PM1	✖	variant is nonsense, so not applicable
PM3	✖	no other variants identified in index cases
PM5	✖	variant is nonsense, so not applicable
PM4	✖	variant is nonsense, so not applicable
PM6	✖	no de novo occurrence identified
BA1	✖	This variant is absent from gnomAD (gnomAD v2.1.1).

BS1		✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS4		✖	no segregation data
BS3		✖	variant was not studied in functional study
BS2		✖	variant was not searched in normolipidemic individuals
BP5		✖	not applicable
BP7		✖	variant is nonsense, so not applicable
BP4		✖	variant meets PVS1, so not met
BP3		✖	not applicable
BP1		✖	not applicable
BP2		✖	no other variants identified in index cases
PS1		✖	variant is nonsense, so not applicable
PS2		✖	no de novo occurrence identified
PS3		✖	variant was not studied in functional study
PS4		✖	variant meets PM2 and was identified in: - at least 1 index case with SB criteria of definite FH (A+B) (Diagnostic criteria for heterozygous FH used in the paper were a TC>8.0 mmol/l and LDL- C>6.0 mmol/l if available, tendon xanthomata in the patient or in a first-degree relative, and a family history of hypercholesterolemia) from PMID 10532689 (Jensen et al., 1999), Denmark. not enough for PS4, so not met
PP1		✖	no segregation data
PP2		✖	not applicable
PP3		✖	variant meets PVS1, so not met

Curation History

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