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.261G>A (p.Trp87Ter)

Version: 1.0

CA10584814

251100 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: e7e3458e-bc95-482d-b7a2-3b7ab1a7d3e5
Approved on: 2021/6/7
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HGVS expressions

NM_000527.5:c.261G>A
NM_000527.5(LDLR):c.261G>A (p.Trp87Ter)
NC_000019.10:g.11102734G>A
CM000681.2:g.11102734G>A
NC_000019.9:g.11213410G>A
CM000681.1:g.11213410G>A
NC_000019.8:g.11074410G>A
NG_009060.1:g.18354G>A
ENST00000252444.10:c.519G>A
ENST00000559340.2:c.261G>A
ENST00000560467.2:c.261G>A
ENST00000558518.6:c.261G>A
ENST00000252444.9:c.515G>A
ENST00000455727.6:c.261G>A
ENST00000535915.5:c.190+2389G>A
ENST00000545707.5:c.261G>A
ENST00000557933.5:c.261G>A
ENST00000557958.1:n.347G>A
ENST00000558013.5:c.261G>A
ENST00000558518.5:c.261G>A
NM_000527.4:c.261G>A
NM_001195798.1:c.261G>A
NM_001195799.1:c.190+2389G>A
NM_001195800.1:c.261G>A
NM_001195803.1:c.261G>A
NM_001195798.2:c.261G>A
NM_001195799.2:c.190+2389G>A
NM_001195800.2:c.261G>A
NM_001195803.2:c.261G>A

Pathogenic

Met criteria codes 5

PP4 PM2 PVS1 PS3_Supporting PS4

Not Met criteria codes 21

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP1 PP2 PP3 BA1 PM1
PM3 PM5 PM4 PM6 BS2
BS1 BS4 BS3 PS1 PS2 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.261G>A (p.Trp87Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PVS1, PS4, PM2, PP4 and PS3_Supporting) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1101/2021.03.17.21252755). The supporting evidence is as follows: PVS1 - Variant is nonsense, causing a premature stop at codon 87. It is upstream of amino acid 830, so PVS1 is Met. PS4 - Variant meets PM2. Identified in 10 FH index cases with Dutch Lipid Clinical Network score 10.3 ± 4.1 (Mean ± standard deviation of DLCN score) from PMID: 21990180. PM2 - No population data was found for this variant in gnomAD (gnomAD v2.1.1). PP4 - Variant meets PM2. Identified in 10 FH index cases with Dutch Lipid Clinical Network score 10.3 ± 4.1 (Mean ± standard deviation of DLCN score) from PMID: 21990180. PS3_supporting - Level 3 assays: PMID 21990180: Htz patient lymphocytes, FACS and CLSM assays - results - FACS: 40% cell surface LDLR; 60% LDL-LDLR binding; 75% uptake, CLSM: 50-60% cell surface LDLR and LDL-LDLR binding ---- Results are below 85% of wild-type, so PS3_supporting is Met

Met criteria codes

PP4	✔	Variant meets PM2. Identified in 10 FH index cases with Dutch Lipid Clinical Network score 10.3 ± 4.1 (Mean ± standard deviation of DLCN score) from PMID: 21990180. --- PP4 is Met
PM2	✔	No population data was found for this variant in gnomAD (gnomAD v2.1.1).
PVS1	✔	Variant is nonsense, causing a premature stop at codon 87. It is upstream of amino acid 830, so PVS1 is Met
PS3_Supporting	✔	Level 3 assays: PMID 21990180: Htz patient lymphocytes, FACS and CLSM assays - results - FACS: 40% cell surface LDLR; 60% LDL-LDLR binding; 75% uptake, CLSM: 50-60% cell surface LDLR and LDL-LDLR binding ---- Results are below 85% of wild-type, so PS3_supporting is Met
PS4	✔	Variant meets PM2. Identified in 10 FH index cases with Dutch Lipid Clinical Network score 10.3 ± 4.1 (Mean ± standard deviation of DLCN score) from PMID: 21990180. --- PS4 is Met

Not Met criteria codes

PP1	✖	no family members were tested, so PP1 is Not Met
PP2	✖	Not applicable
PP3	✖	PVS1 is Met, so PP3 is not applicable

BA1	✖	No population data was found for this variant in gnomAD (gnomAD v2.1.1).
PM1	✖	Nonsense variant, so PM1 is Not applicable
PM3	✖	not identified in individuals with other variants, so PM3 is Not Met
PM5	✖	Nonsense variant, PM5 not applicable
PM4	✖	Nonsense variant (PVS1 is Met), so PM4 is Not Met
PM6	✖	no de novo cases were identified, so PM6 is Not Met
BS2	✖	no unaffected individuals identified with the variant, so BS2 is Not Met
BS1	✖	No population data was found for this variant in gnomAD (gnomAD v2.1.1).
BS4	✖	no family members were tested, so BS4 is Not Met
BS3	✖	Level 3 assays: PMID 21990180: Htz patient lymphocytes, FACS and CLSM assays - results - FACS: 40% cell surface LDLR; 60% LDL-LDLR binding; 75% uptake, CLSM: 50-60% cell surface LDLR and LDL-LDLR binding ---- Whole cycle is not above 95% of wild-type, so BS3_supporting is Not Met
PS1	✖	Nonsense variant, PS1 not applicable
PS2	✖	no de novo cases were identified, so PS2 is Not Met
BP5	✖	Not applicable
BP7	✖	Nonsense variant, so BP7 is not applicable
BP4	✖	PVS1 is Met, so BP4 is not applicable
BP3	✖	Not applicable
BP1	✖	Not applicable
BP2	✖	not identified in individuals with other variants, so BP2 is Not Met

Curation History

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