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.190+4A>T

Version: 1.1

CA042227

225097 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: c7021a50-713d-4798-bd35-cce7eb2c158d
Approved on: 2022/2/9
Published on: 2022/7/12

HGVS expressions

NM_000527.5:c.190+4A>T
NM_000527.5(LDLR):c.190+4A>T
NC_000019.10:g.11100349A>T
CM000681.2:g.11100349A>T
NC_000019.9:g.11211025A>T
CM000681.1:g.11211025A>T
NC_000019.8:g.11072025A>T
NG_009060.1:g.15969A>T
ENST00000252444.10:c.448+4A>T
ENST00000559340.2:c.190+4A>T
ENST00000560467.2:c.190+4A>T
ENST00000558518.6:c.190+4A>T
ENST00000252444.9:c.444+4A>T
ENST00000455727.6:c.190+4A>T
ENST00000535915.5:c.190+4A>T
ENST00000545707.5:c.190+4A>T
ENST00000557933.5:c.190+4A>T
ENST00000557958.1:n.276+4A>T
ENST00000558013.5:c.190+4A>T
ENST00000558518.5:c.190+4A>T
ENST00000560502.5:n.280A>T
NM_000527.4:c.190+4A>T
NM_001195798.1:c.190+4A>T
NM_001195799.1:c.190+4A>T
NM_001195800.1:c.190+4A>T
NM_001195803.1:c.190+4A>T
NM_001195798.2:c.190+4A>T
NM_001195799.2:c.190+4A>T
NM_001195800.2:c.190+4A>T
NM_001195803.2:c.190+4A>T

Likely Pathogenic

Met criteria codes 4

PP4 PM2 PS3_Moderate PS4

Not Met criteria codes 21

PP1 PP2 PP3 BA1 PM1 PM3 PM5 PM4 PM6 PVS1 BS1 BS4 BS3 PS1 PS2 BP5 BP7 BP4 BP3 BP1 BP2

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 1.1*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.190+4A>T variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP4, PS4 and PS3_Moderate) 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 - PopMax MAF = 0.00020 (0.02%) in East Asian exomes+genomes (gnomAD v2.1.1). PP4 - Variant meets PM2. Variant identified in 11 unrelated index cases (1 case fulfilling Simon-Broome criteria published in PMID: 21418584; 3 cases fulfilling Simon-Broome criteria published in PMID: 20236128; 5 cases with Dutch lipid clinic network >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 1 case with Dutch lipid clinic network >=6 from Robarts Research Institute; 1 case with MedPed definite from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory. PS3_Moderate - Level 2 assays: PMID 19208450: Heterozygous patient cells, FACS/RT-PCR/Nothern blotting assays - result - 47% low-density lipoprotein particle receptor activity (LDLR activity reported as a mean value of cell-surface LDLR and LDL internalization measurements); aberrant transcript is not confirmed by sequencing (NMD expected) and is 40% of total transcripts. PS4 - Variant meets PM2. Variant identified in 11 unrelated index cases (1 case fulfilling Simon-Broome criteria published in PMID: 21418584; 3 cases fulfilling Simon-Broome criteria published in PMID: 20236128; 5 cases with Dutch lipid clinic network >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 1 case with Dutch lipid clinic network >=6 from Robarts Research Institute; 1 case with MedPed definite from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory.

Met criteria codes

PP4	✔	Variant meets PM2. Variant identified in 11 unrelated index cases (1 case fulfilling Simon-Broome criteria published in PMID: 21418584; 3 cases fulfilling Simon-Broome criteria published in PMID: 20236128; 5 cases with Dutch lipid clinic network >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 1 case with Dutch lipid clinic network >=6 from Robarts Research Institute; 1 case with MedPed definite from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory.
PM2	✔	PopMax MAF = 0.00020 (0.02%) in East Asian exomes+genomes (gnomAD v2.1.1).
PS3_Moderate	✔	Level 2 assays: PMID 19208450: Heterozygous patient cells, FACS/RT-PCR/Nothern blotting assays - result - 47% low-density lipoprotein particle receptor activity (LDLR activity reported as a mean value of cell-surface LDLR and LDL internalization measurements); aberrant transcript is not confirmed by sequencing (NMD expected) and is 40% of total transcripts.
PS4	✔	Variant meets PM2. Variant identified in 11 unrelated index cases (1 case fulfilling Simon-Broome criteria published in PMID: 21418584; 3 cases fulfilling Simon-Broome criteria published in PMID: 20236128; 5 cases with Dutch lipid

clinic network >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 1 case with Dutch lipid clinic network >=6 from Robarts Research Institute; 1 case with MedPed definite from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory.

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	Functional data available.
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

nowing 1 to 2 of 2 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.