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_000527.4(LDLR):c.313+1G>A

Version: 1.0

CA023688

3736 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 1f8ff66d-e0d4-47ed-af0f-b63b943b5e33
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HGVS expressions

NM_000527.4:c.313+1G>A
NM_000527.4(LDLR):c.313+1G>A
NC_000019.10:g.11102787G>A
CM000681.2:g.11102787G>A
NC_000019.9:g.11213463G>A
CM000681.1:g.11213463G>A
NC_000019.8:g.11074463G>A
NG_009060.1:g.18407G>A
ENST00000252444.10:c.571+1G>A
ENST00000559340.2:c.313+1G>A
ENST00000560467.2:c.313+1G>A
ENST00000558518.6:c.313+1G>A
ENST00000252444.9:c.567+1G>A
ENST00000455727.6:c.313+1G>A
ENST00000535915.5:c.191-2433G>A
ENST00000545707.5:c.313+1G>A
ENST00000557933.5:c.313+1G>A
ENST00000557958.1:n.400G>A
ENST00000558013.5:c.313+1G>A
ENST00000558518.5:c.313+1G>A
NM_001195798.1:c.313+1G>A
NM_001195799.1:c.191-2433G>A
NM_001195800.1:c.313+1G>A
NM_001195803.1:c.313+1G>A
NM_000527.5:c.313+1G>A
NM_001195798.2:c.313+1G>A
NM_001195799.2:c.191-2433G>A
NM_001195800.2:c.313+1G>A
NM_001195803.2:c.313+1G>A

Pathogenic

Met criteria codes 6

PM2 PS4 PP4 PS3_Moderate PP1_Strong PVS1_Strong

Not Met criteria codes 20

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

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

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.4(LDLR):c.313+1G>A variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PVS1_Strong, PS4, PP1_Strong, PM2, PS3_Moderate and PP4) 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_strong - Variant is in canonical GT +1 splice site, predicted to lead to exon 3 skipping (in frame). PS4 - Variant meets PM2. Identified in at least 14 unrelated index cases from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with DLCS equal or above 6. PP1_strong - variant segregates with FH phenotype in 6 informative meiosis in 5 families from different laboratories. PM2 - PopMax MAF = 0.00006156 (0.006%) in European non-Finnish exomes (gnomAD v2.1.1). PS3_moderate Level 2 assays: PMID 19361455: Hmz patients' Epstein-Barr tranformed lymphocytes, RNA and FACS assays - results - Alternative splicing: skipping of exon 3 or inclusion of intron 3; amount of cell-surface LDLR 33% of normal (Hmz); 12% LDL-LDLR uptake in Hmz ---- Aberrant transcripts confirmed by sequencing and above 25% of total transcript, and uptake is below 70% of wild-type, so PS3_moderate is Met. PP4 - Variant meets PM2. Identified in 3 FH cases from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge who fulfill Simon-Broome criteria and in 13 FH cases from University of British Columbia (UBC, Canada) and 14 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with clinical Dutch Lipid Clinic Network Criteria score ≥ 6.

Met criteria codes

PM2	✔	PopMax MAF = 0.00006156 (0.006%) in European non-Finnish exomes (gnomAD v2.1.1).
PS4	✔	Variant meets PM2. Identified in at least 14 unrelated index cases from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with DLCS equal or above 6. ---- PS4 is Met
PP4	✔	Variant meets PM2. Identified in 3 FH cases from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge who fulfill Simon-Broome criteria and in 13 FH cases from University of British Columbia (UBC, Canada) and 14 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with clinical Dutch Lipid Clinic Network Criteria score ≥ 6. ---- PP4 is Met
PS3_Moderate	✔	Level 2 assays: PMID 19361455: Hmz patients' Epstein-Barr tranformed lymphocytes, RNA and FACS assays - results - Alternative splicing: skipping of exon 3 or inclusion of intron 3 (p.Pro105_Ala860delinsArgLysCysGlyProAlaPheAlaIleGluProIle); amount of cell-surface LDLR 33% of normal (Hmz); 12% LDL-LDLR uptake in Hmz ---- Aberrant transcripts confirmed by sequencing and above 25% of total transcript, and uptake is below 70% of wild-type, so PS3_moderate is Met / Level 2 assays: PMID 19148831: Epstein-Barr virus (EBV) transformed lymphocytes from Hmz patients, FACS, WB and RNA assays - results - amount of protein 10% of wild-type, 10% uptake, amount of transcripts 60-70% of wild-type ---- Uptake and amount of protein are below 70% of wild-type, so PS3_moderate is Met / Level 3 assays: PMID 8829662: Hmz patients' lymphocytes, RNA assays - results - skipping of exon 3 (p.Leu64_Pro105delinsSer) ---- Aberrant transcripts confirmed by sequencing, so PS3_supporting would be Met, but PS3_moderate is already Met

PP1_Strong	✔	variant segregates with FH phenotype in 6 informative meiosis in 5 families from different laboratories (University of British Columbia and Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge): 5 affected family members have the variant and 1 non-affected family member does not have the variant. --- PP1_Strong is Met
PVS1_Strong	✔	Variant is in canonical GT +1 splice site, predicted to lead to exon 3 skipping (in frame), so PVS1_Strong is Met

Not Met criteria codes

PM6	✖	no de novo cases were identified, so PM6 is Not Met
PM1	✖	Intronic variant, so PM1 is Not applicable
PM3	✖	not identified in individuals with other variants, so PM3 is Not Met
PM5	✖	Intronic variant, PM5 not applicable
PM4	✖	Intronic variant (predicted to cause in frame skipping of 1 whole exon - in PM4 is only considered indels smaller than whole exon to avoid double counting with PVS1), so PM4 is Not Met
PS1	✖	Intronic variant, PS1 not applicable
PS2	✖	no de novo cases were identified, so PS2 is Not Met
BA1	✖	FAF = 0.00002854 (0.003%) in european non-finnish exomes (gnomAD v2.1.1). FAF is not above 0.5%, so BA1 is Not Met.
PP2	✖	Not applicable
PP3	✖	PVS1_Strong is Met, so PP3 is not applicable
BS2	✖	no unaffected individuals identified with the variant, so BS2 is Not Met
BS1	✖	FAF = 0.00002854 (0.003%) in european non-finnish exomes (gnomAD v2.1.1). FAF is not above 0.2%, so BS1 is Not Met.
BS4	✖	no non-segregations were identified, so BS4 is Not Met
BS3	✖	Level 3(benign) assays: PMID 19361455: Hmz patients' Epstein-Barr tranformed lymphocytes, RNA and FACS assays - results - Alternative splicing: skipping of exon 3 or inclusion of intron 3 (p.Pro105_Ala860delinsArgLysCysGlyProAlaPheAlaIleGluProIle); amount of cell-surface LDLR 33% of normal (Hmz); 12% LDL-LDLR uptake in Hmz ---- Aberrant transcripts confirmed by sequencing and whole cycle not above 90% of wild-type, BS3_supportig is Not Met / Level 3(benign) assays: PMID 19148831: Epstein-Barr virus (EBV) transformed lymphocytes from Hmz patients, FACS, WB and RNA assays - results - amount of protein 10% of wild-type, 10% uptake, amount of transcripts 60-70% of wild-type ---- Whole cycle not above 90% of wild-type, BS3_supporting is

Not Met / Level 3(benign) assays: PMID 8829662: Hmz patients' lymphocytes, RNA assays - results - skipping of exon 3 (p.Leu64_Pro105delinsSer) ---- Aberrant transcripts confirmed by sequencing, so BS3_supporting is Not Met

BP4	✖	PVS1_Strong 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
BP5	✖	Not applicable
BP7	✖	Intronic variant, so BP7 is not applicable

Curation History

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