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.941-12G>A

Version: 1.0

CA10585217

251552 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 803c0db9-0b64-448c-bd5c-162426ea0ce2
Approved on: 2022-03-30
Published on: 2022-03-30

HGVS expressions

NM_000527.5:c.941-12G>A
NM_000527.5(LDLR):c.941-12G>A
NC_000019.10:g.11110640G>A
CM000681.2:g.11110640G>A
NC_000019.9:g.11221316G>A
CM000681.1:g.11221316G>A
NC_000019.8:g.11082316G>A
NG_009060.1:g.26260G>A
ENST00000252444.10:c.1199-12G>A
ENST00000559340.2:c.941-12G>A
ENST00000560467.2:c.941-874G>A
ENST00000558518.6:c.941-12G>A
ENST00000252444.9:c.1195-12G>A
ENST00000455727.6:c.437-12G>A
ENST00000535915.5:c.818-12G>A
ENST00000545707.5:c.560-12G>A
ENST00000557933.5:c.941-12G>A
ENST00000558013.5:c.941-12G>A
ENST00000558518.5:c.941-12G>A
ENST00000560467.1:c.541-874G>A
NM_000527.4:c.941-12G>A
NM_001195798.1:c.941-12G>A
NM_001195799.1:c.818-12G>A
NM_001195800.1:c.437-12G>A
NM_001195803.1:c.560-12G>A
NM_001195798.2:c.941-12G>A
NM_001195799.2:c.818-12G>A
NM_001195800.2:c.437-12G>A
NM_001195803.2:c.560-12G>A

Likely Pathogenic

Met criteria codes 5

PP1 PP4 PM2 PS3_Supporting PS4_Supporting

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR): c.941-12G>A variant is classified as Likely Pathogenic evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, PP4, PS4_Supporting, PP1) 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 Met: This variant is absent in gnomAD (gnomAD v2.1.1). PP4 Met: This variant meets PM2 and is identified in >1 index cases who met clinical criteria for FH after alternative causes for high cholesterol were excluded. PS4_Supporting Met: Variant meets PM2, and is identified in 4 unrelated index cases who fulfil DLCN criteria for FH diagnosis from 2 different labs: Three cases from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); one case from Robarts Research Institute, Canada. PP1 Met: Variant segregates with FH phenotype in 3 informative meiosis in one family (Institut National de la Santé et de la Recherche Médicale,and Université Paris Descartes, Paris, France, PMID: 20809525). PS3_Supporting: RNA assay using patient monocytes (level 3 functional assay) was reported from one research lab. Abnormal splicing of intron 6 was observed by gel electrophoresis only in patient cDNA but not in controls, using forward primer with 5' end located at c.864 (exon 6) and the reverse primer with 3' end at c.941-11. Sequencing confirmation on abnormal RT-PCR product was not performed and aberrant transcript was not quantified (Institut National de la Santé et de la Recherche Médicale,and Université Paris Descartes, Paris, France, PMID: 20809525).

Met criteria codes

PP1	✔	Variant segregates with FH phenotype in 3 informative meiosis in one family (Institut National de la Santé et de la Recherche Médicale,and Université Paris Descartes, Paris, France, PMID: 20809525).
PP4	✔	This variant meets PM2 and is identified in >1 index cases who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
PM2	✔	This variant is absent in gnomAD (gnomAD v2.1.1).
PS3_Supporting	✔	RNA assay using patient monocytes (level 3 functional assay) was reported from one research lab. Abnormal splicing of intron 6 was observed by gel electrophoresis only in patient cDNA but not in controls, using forward primer with 5' end located at c.864 (exon 6) and the reverse primer with 3' end at c.941-11. Sequencing confirmation on abnormal RT-PCR product was not performed and aberrant transcript was not quantified (Institut National de la Santé et de la Recherche Médicale,and Université Paris Descartes, Paris, France, PMID: 20809525).
PS4_Supporting	✔	Variant meets PM2, and is identified in 4 unrelated index cases who fulfil DLCN criteria for FH diagnosis from 2 different labs: Three cases from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); one case from Robarts Research Institute, Canada.

Curation History

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