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.352G>T (p.Asp118Tyr)

Version: 1.0

CA023697

183085 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: e8a7cc28-f4d2-40e2-808b-9f8b9c94219c
Approved on: 2024/2/23
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HGVS expressions

NM_000527.5(LDLR):c.352G>T (p.Asp118Tyr)
NM_000527.5:c.352G>T
NC_000019.10:g.11105258G>T
CM000681.2:g.11105258G>T
NC_000019.9:g.11215934G>T
CM000681.1:g.11215934G>T
NC_000019.8:g.11076934G>T
NG_009060.1:g.20878G>T
ENST00000252444.10:c.610G>T
ENST00000559340.2:c.352G>T
ENST00000560467.2:c.352G>T
ENST00000558518.6:c.352G>T
ENST00000252444.9:c.606G>T
ENST00000455727.6:c.314-2134G>T
ENST00000535915.5:c.229G>T
ENST00000545707.5:c.314-1307G>T
ENST00000557933.5:c.352G>T
ENST00000558013.5:c.352G>T
ENST00000558518.5:c.352G>T
NM_000527.4:c.352G>T
NM_001195798.1:c.352G>T
NM_001195799.1:c.229G>T
NM_001195800.1:c.314-2134G>T
NM_001195803.1:c.314-1307G>T
NM_001195798.2:c.352G>T
NM_001195799.2:c.229G>T
NM_001195800.2:c.314-2134G>T
NM_001195803.2:c.314-1307G>T

Likely Pathogenic

Met criteria codes 5

PP1 PP4 PM2 PM1 PS4_Moderate

Not Met criteria codes 8

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP3 PM3 PM5 BS4 BS3 PS3 BP4 BP2

Evidence Links 0

Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2*

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.352G>T (p.Asp118Tyr) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS4_Moderate, PM1, PM2, PP1 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: PopMax MAF = 0.000004496 (0.0004%) in European (non-Finnish) exomes (gnomAD v4.0.0). PM1: Variant meets PM2 and is missense in exon 4. PS4_Moderate, PP4: Variant meets PM2 and is identified in at least 6 unrelated index cases who fulfill criteria for FH (1 case with possible FH by Simon Broome criteria from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), France; 4 cases with DLCN score >=6 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine, Italy; 1 case with DLCN score >=6 from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia). PP1: Variant segregates with phenotype in 2 informative meiosis in 2 families from different labs (1 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), France, and 1 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine, Italy): 2 affected family members have the variant.

Met criteria codes

PP1	✔	PP1 - Variant segregates with phenotype in 2 informative meiosis in 2 families from different labs: 1 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) and 1 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine)
PP4	✔	PP4 - Variant meets PM2 and is identified in at least 1 index case who fulfills clinical criteria for FH, after alternative causes of high cholesterol were excluded (see PS4 for details).
PM2	✔	PM2 - PopMax MAF = 0.000004496 (0.0004%) in European (non-Finnish) exomes (gnomAD v4.0.0)
PM1	✔	PM1 - Variant meets PM2 and is missense (exon 4).
PS4_Moderate	✔	PS4_Moderate: Variant meets PM2 and was found in 6 unrelated index cases: 1 with Simone-Broome from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), 4 with DLCN score >6 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine and 1 with DLCN criteria >6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA).

Not Met criteria codes

PP3	✖	PP3_Not Met: REVEL=0.66, splicing evaluation needed. A) Variant not on limits B) does not create AG C) there is an AG nearby MES score: variant cryptic site=-8.43, wt cryptic site=-8.56, canonical donor site=8.16 Ratio variant cryptic site/wt cryptic site= -8.43/-8.56-=0.98 --- not > 1.1 Ratio variant cryptic site/canonical donor site= -8.43/8.16= -1.03 --- not > 0.9 PP3 is not met.
PM3	✖	PM3 - Variant meets PM2 and is identified in an index case with homozygous FH phenotype in Bertolini et al., 1999 (PMID 9974426) with LDL = 12.58mmol/L and compound heterozygous for c.1567G>T, p.Val523Met, classified by the FH VCEP as Likely pathogenic. However, LDL is not >13 mmol/L and the variants have not been confirmed to be in trans.
PM5	✖	PM5 - Missense variants at the same codon predicting a different amino acid change (Asp118Asn, Asp118Ala), but variants are only classified as of uncertain significance by these guidelines.
BS4	✖	BS4 - Variant does not segregate with FH phenotype in 2 informative meiosis in 2 families from 2 different labs: Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies - APHP Sorbonne Université, Hôpital de la Pitié-Salpêtrière and Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine). However, no unaffected relatives were positive for the variant, so BS4 cannot be applied.
BS3	✖	BS3_Not Met: in PMID: 9974426 and PMID: 25647241 there aren't functional evidence for this variant.
PS3	✖	PS3_Not Met: in PMID: 9974426 and PMID: 25647241 there aren't functional evidence for this variant.
BP4	✖	BP4_Not Met: REVEL is not <0.50.
BP2	✖	BP2_Not Met: 4 individuals with HeFH phenotype from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine with c.1187-7C>A (in cis).

Curation History

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