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.2098G>A (p.Asp700Asn)

Version: 1.1

CA023633

200923 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 619b90b1-2290-483a-be56-533034937ce0
Approved on: 2022/3/25
Published on: 2022/7/12

HGVS expressions

NM_000527.5(LDLR):c.2098G>A (p.Asp700Asn)
NM_000527.5:c.2098G>A
NC_000019.10:g.11120480G>A
CM000681.2:g.11120480G>A
NC_000019.9:g.11231156G>A
CM000681.1:g.11231156G>A
NC_000019.8:g.11092156G>A
NG_009060.1:g.36100G>A
ENST00000252444.10:c.2356G>A
ENST00000559340.2:c.*167G>A
ENST00000560467.2:c.1978G>A
ENST00000558518.6:c.2098G>A
ENST00000252444.9:c.2352G>A
ENST00000455727.6:c.1594G>A
ENST00000535915.5:c.1975G>A
ENST00000545707.5:c.1606+247G>A
ENST00000557933.5:c.2098G>A
ENST00000558013.5:c.2098G>A
ENST00000558518.5:c.2098G>A
NM_000527.4:c.2098G>A
NM_001195798.1:c.2098G>A
NM_001195799.1:c.1975G>A
NM_001195800.1:c.1594G>A
NM_001195803.1:c.1606+247G>A
NM_001195798.2:c.2098G>A
NM_001195799.2:c.1975G>A
NM_001195800.2:c.1594G>A
NM_001195803.2:c.1606+247G>A

Likely Pathogenic

Met criteria codes 4

PM2 PS3_Moderate PS4_Supporting PP4

Not Met criteria codes 18

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PM6 PM1 PM3 PM5 PM4
BA1 BS1 BS4 BS3 BS2 BP7
BP4 BP2 PVS1 PS1 PS2
PP1 PP3

Evidence Links 0

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

The NM_000527.5(LDLR):c.2098G>A (p.Asp700Asn) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PS3_Moderate, PS4_supporting and PP4 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 = 0.00006199 (0.006199%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so PM2 is Met. PS3_Moderate - Level 2 assays: PMID 34869944: Heterologous cells (CHO), FACS assays - result - 20% uptake. ---- functional study is consistent with damaging effect, so PS3_Moderate is Met. PS4_supporting - Variant meets PM2 and is identified in 2 unrelated index cases: 1 index case with DLCN>=6 from Color Health, Inc, and 1 index case with Simon Broome criteria (TC of 9.8 mmol/L and personal or family history of CHD) from UK (PMID: 23669246), so PS4_Supporting is Met. PP4 - Variant meets PM2 and is identified in 2 unrelated index cases (see PS4 for details), so PP4 is Met.

Met criteria codes

PM2	✔	PopMax MAF = 0.00006199 (0.006199%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so PM2 is Met.
PS3_Moderate	✔	Level 2 assays: PMID 34869944: Heterologous cells (CHO), FACS assays - result - 20% uptake. ---- functional study is consistent with damaging effect, so PS3_Moderate is Met.
PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated index cases: 1 index case with DLCN>=6 from Color Health, Inc, and 1 index case with Simon Broome criteria (TC of 9.8 mmol/L and personal or family history of CHD) from UK (PMID: 23669246), so PS4_Supporting is Met.
PP4	✔	Variant meets PM2 and is identified in 2 unrelated index cases: 1 index case with DLCN>=6 from Color Health, Inc, and 1 index case with Simon Broome criteria (TC of 9.8 mmol/L and personal or family history of CHD) from UK (PMID: 23669246), so PP4 is Met.

Not Met criteria codes

PM6	✖	de novo occurrence data not reported, so PM6 is Not Met.
PM1	✖	Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM3	✖	Observed in 1 index case (phenotype not reported) with APOB c.10580G>A/p.(Arg3527Gln) classified as Pathogenic, from Ambry Genetics, so PM3 is not met.

PM5		✖	2 other missense variants in the same codon: - NM_000527.5(LDLR):c.2099A>G (p.Asp700Gly) (ClinVar ID 252220) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.2100C>G (p.Asp700Glu) (ClinVar ID 252221) - VUS by these guidelines No more missense variants at the same codon, classified as Pathogenic, so PM5 is Not Met.
PM4		✖	Variant meets PM2 and is missense, so PM4 is Not Met.
BA1		✖	FAF = 0.00001686 (0.001686%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BA1 is not met.
BS1		✖	FAF = 0.00001686 (0.001686%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BS1 is not met.
BS4		✖	Lack of segregation data not reported, so BS4 is Not Met.
BS3		✖	Level 2 assays: PMID 34869944: Heterologous cells (CHO), FACS assays - result - 20% uptake. ---- functional study is consistent with damaging effect, so BS3 is not met.
BS2		✖	Not observed in 140 000 individuals from the the UKBB, so BS2 is Not Met.
BP7		✖	Variant is not synonymous, so BP7 is Not Met.
BP4		✖	REVEL = 0.683. It is not below 0.50, so BP4 is not met.
BP2		✖	Variant identified in an index case with heterozygous FH phenotype (LDL<400) and LDLR c.1358+2T>A, but cannot determine if the variants are in trans, from GeneDx Inc., so BP2 is not met.
PVS1		✖	Variant is missense, so PVS1 is Not Met.
PS1		✖	No more missense variants at the same codon, so PS1 is Not Met.
PS2		✖	de novo occurrence data not reported, so PS2 is Not Met.
PP1		✖	Segregation data not reported, so PP1 is Not Met.
PP3		✖	REVEL = 0.683, it is not above 0.75, so splicing evaluation is required. Functional data on splicing not available. A) variant not on limits B) does not create GT C) no GT nearby --- PP3 is not met.

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.2098G>A (p.Asp...	Likely Pathogenic	Hypercholesterolemia, Familial	2022-07-12	1.1	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1	LDLR
View	NM_000527.5(LDLR):c.2098G>A (p.Asp...	Likely Pathogenic	Hypercholesterolemia, Familial	2022-04-05	1.0	-	LDLR

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