

Variant: *NM_000527.5(LDLR):c.1951G>A (p.Asp651Asn)*

Version: 1.0

CA354422 [↗](#)

183128 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))

Condition: hypercholesterolemia, familial ([MONDO:0007750](#))

Inheritance Mode: Semidominant inheritance

UUID: 553eb123-6677-44dd-acb4-b7cbdf6514e5

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HGVS expressions

NM_000527.5:c.1951G>A

NM_000527.5(LDLR):c.1951G>A (p.Asp651Asn)

NC_000019.10:g.11120197G>A

CM000681.2:g.11120197G>A

NC_000019.9:g.11230873G>A

CM000681.1:g.11230873G>A

NC_000019.8:g.11091873G>A

NG_009060.1:g.35817G>A

ENST00000252444.10:c.2209G>A

ENST00000559340.2:c.*20G>A

ENST00000560467.2:c.1831G>A

ENST00000558518.6:c.1951G>A

ENST00000252444.9:c.2205G>A

ENST00000455727.6:c.1447G>A

ENST00000535915.5:c.1828G>A

ENST00000545707.5:c.1570G>A

ENST00000557933.5:c.1951G>A

ENST00000558013.5:c.1951G>A

ENST00000558518.5:c.1951G>A

ENST00000559340.1:c.532G>A

NM_000527.4:c.1951G>A

NM_001195798.1:c.1951G>A

NM_001195799.1:c.1828G>A

NM_001195800.1:c.1447G>A

NM_001195803.1:c.1570G>A

NM_001195798.2:c.1951G>A

NM_001195799.2:c.1828G>A

NM_001195800.2:c.1447G>A

NM_001195803.2:c.1570G>A

Likely Pathogenic

Met criteria codes **4**

PS4_Moderate

PP1

PP4

PM2

Not Met criteria codes **18**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PVS1

BA1

BP4

BP3

BP2

BS2

BS1

BS4

BS3

PP3

PS1

PS2

PS3

PM6

PM1

PM3

PM5

PM4

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.1951G>A (p.Asp651Asn) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PS4_Moderate, PM2, PP1, 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: PS4_Moderate: Variant meets PM2 and is identified in 8 unrelated index cases (1 case with Simon-Broome criteria of possible FH and 1 case with Simon-Broome criteria of definite FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 2 cases with Simon-Broome criteria of possible FH and 1 case with DLCN>6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, and 3 cases in PMID 15241806 (Mozas P et al., 2004)). So PS4_Moderate is met. PM2: PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1). So PM2 is met. PP1: Variant segregates with FH phenotype in 3 informative meioses identified by Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies. So PP1 is met. PP4: Variant meets PM2 and is identified in2 unrelated index cases who fulfill clinical criteria for FH (see PS4 for details). So PP4 is met.

Met criteria codes

PS4_Moderate			Variant meets PM2 and is identified in 8 unrelated index cases (1 case with Simon-Broome criteria of possible FH and 1 case with Simon-Broome criteria of definite FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 2 cases with Simon-Broome criteria of possible FH and 1 case with DLCN>6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, and 3 cases in PMID 15241806 (Mozas P et al., 2004)). So PS4_Moderate is met.
PP1			Variant segregates with FH phenotype in 3 informative meioses identified by Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies. So PP1 is met.
PP4			Variant meets PM2 and is identified in2 unrelated index cases who fulfill clinical criteria for FH (see PS4 for details). So PP4 is met.
PM2			PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1). So PM2 is met.

Not Met criteria codes

PVS1			Not a null variant (nonsense, frameshift, canonical +/- 1 or 2 splice sites, initiation codon, single or multiexon deletion)
BA1			No PopMax FAF available. PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1).

BP4			REVEL = 0.697. It is above 0.5, so BP4 is not met.
BP3			Not a in-frame deletions/insertion variant
BP2			Variant identified in an index case with FH phenotype and c.662A>G (p.Asp221Gly) variant, classified as Pathogenic by the general ACMG guidelines from PMID 29396260. The LDL-C level is 232 mg/dl. However, this participant is taking rosuvastatin 40 mg and ezetimibe. Based on 2019 ESC guidelines for the management of dyslipidemias, a combination of high-intensity statin and ezetimibe results in 65% reduction in LDL-C. So, the untreated LDL-C value would be around 663 mg/dl (homozygous FH phenotype).
BS2			No data available
BS1			No PopMax FAF available. PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1).
BS4			No data available
BS3			In vitro microscopy assays in HeLa cells: LDLR activity is equal to WT - considered as non-disruptive. It is a part of the LDLR cycle, so BS3 is not met.
PP3			REVEL = 0.697. It is not above 0.75, so splicing evaluation is required. Functional data on splicing is not available. A) variant is not located at -20 to +3 bases from canonical acceptor splice site/-3 to +6 from canonical donor splice site B) Variant is not on limits of acceptor site. It is located within the range of the donor site but does not create denovo GT site. C) Variant is not on limits of acceptor site. It is located within the range of the donor site but there is no GT in downstream or upstream. The variant does not affect splicing process.
PS1			No other missense variant in the same codon with the same amino acid change
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No data available
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			Not located in exon 4. Not a cysteine residue.
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1951G>T (p.Asp651Tyr) (ClinVar ID 252127) - Likely Pathogenic by these guidelines - NM_000527.5(LDLR):c.1952A>T (p.Asp651Val) (ClinVar ID 252128) - Likely pathogenic by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.

PM4



Not a in-frame deletions/insertion variant

Curation History

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