

Variant: *NM_000527.5(LDLR):c.1951G>T (p.Asp651Tyr)*

Version: 1.0

CA10585693 [↗](#)

252127 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: f9cc13a9-0509-451a-a856-60c50af7c90d

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HGVS expressions

NM_000527.5:c.1951G>T

NM_000527.5(LDLR):c.1951G>T (p.Asp651Tyr)

NC_000019.10:g.11120197G>T

CM000681.2:g.11120197G>T

NC_000019.9:g.11230873G>T

CM000681.1:g.11230873G>T

NC_000019.8:g.11091873G>T

NG_009060.1:g.35817G>T

ENST00000252444.10:c.2209G>T

ENST00000559340.2:c.*20G>T

ENST00000560467.2:c.1831G>T

ENST00000558518.6:c.1951G>T

ENST00000252444.9:c.2205G>T

ENST00000455727.6:c.1447G>T

ENST00000535915.5:c.1828G>T

ENST00000545707.5:c.1570G>T

ENST00000557933.5:c.1951G>T

ENST00000558013.5:c.1951G>T

ENST00000558518.5:c.1951G>T

ENST00000559340.1:c.532G>T

NM_000527.4:c.1951G>T

NM_001195798.1:c.1951G>T

NM_001195799.1:c.1828G>T

NM_001195800.1:c.1447G>T

NM_001195803.1:c.1570G>T

NM_001195798.2:c.1951G>T

NM_001195799.2:c.1828G>T

NM_001195800.2:c.1447G>T

NM_001195803.2:c.1570G>T

Likely Pathogenic

Met criteria codes **4**

PP3 PP4 PS3 PM2

Not Met criteria codes **18**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PVS1

BA1

BP4

BP3

BP2

BS2

BS1

BS4

BS3

PP1

PS1

PS2

PS4

PM6

PM1

PM3

PM5

PM4

Evidence Links

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- 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>T (p.Asp651Tyr) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PS3, PM2, PP3, 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: PS3: Level 1 assays: PMID 32937241: Heterologous cells (CHO) - results - 53% LDLR expression, 50% binding, and 80% uptake. Expression and binding are below 70% of wild-type, so functional study is consistent with damaging effect. PS3 is met. PM2: This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PP3: REVEL = 0.933. It is above 0.75, so PP3 is met. PP4: Variant meet PM2. PMID: 16389549 (Humphries et al., 2005) - 1 case who fulfills Simon-Broome criteria for FH. So PP4 is met.

Met criteria codes

PP3			REVEL = 0.933. It is above 0.75, so PP3 is met.
PP4			Variant meet PM2. PMID: 16389549 (Humphries et al., 2005) - 1 case who fulfills Simon-Broome criteria for FH. So PP4 is met.
PS3			Level 1 assays: PMID 32937241: Heterologous cells (CHO) - results - 53% LDLR expression, 50% binding, and 80% uptake. Expression and binding are below 70% of wild-type, so functional study is consistent with damaging effect. PS3 is met.
PM2			This variant is absent from gnomAD (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			This variant is absent from gnomAD (gnomAD v2.1.1)
BP4			REVEL = 0.933 (>0.5)
BP3			Not a in-frame deletions/insertions variant
BP2			No data available.

BS2			No data available.
BS1			This variant is absent from gnomAD (gnomAD v2.1.1)
BS4			No data available.
BS3			No experimental study available
PP1			No data available.
PS1			No other missense variant in the same codon resulting in the same amino acid change.
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			Variant meet PM2. PMID: 16389549 (Humphries et al., 2005) - 1 case who fulfills Simon-Broome criteria for FH.
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			Not in exon 4 and not a cysteine residue.
PM3			No data available.
PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1951G>A (p.Asp651Asn) (ClinVar ID 183128) - Uncertain significance 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/insertions variant

Curation History 

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