

Variant: *NM_000527.5(LDLR):c.1955T>C (p.Met652Thr)*

Version: 1.1

CA10576326 [↗](#)

226382 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 7dfb2299-5dd6-4bd2-800b-7353722033a5

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HGVS expressions

NM_000527.5(LDLR):c.1955T>C (p.Met652Thr)

NM_000527.5:c.1955T>C

NC_000019.10:g.11120201T>C

CM000681.2:g.11120201T>C

NC_000019.9:g.11230877T>C

CM000681.1:g.11230877T>C

NC_000019.8:g.11091877T>C

NG_009060.1:g.35821T>C

ENST00000252444.10:c.2213T>C

ENST00000559340.2:c.*24T>C

ENST00000560467.2:c.1835T>C

ENST00000558518.6:c.1955T>C

ENST00000252444.9:c.2209T>C

ENST00000455727.6:c.1451T>C

ENST00000535915.5:c.1832T>C

ENST00000545707.5:c.1574T>C

ENST00000557933.5:c.1955T>C

ENST00000558013.5:c.1955T>C

ENST00000558518.5:c.1955T>C

ENST00000559340.1:c.536T>C

NM_000527.4:c.1955T>C

NM_001195798.1:c.1955T>C

NM_001195799.1:c.1832T>C

NM_001195800.1:c.1451T>C

NM_001195803.1:c.1574T>C

NM_001195798.2:c.1955T>C

NM_001195799.2:c.1832T>C

NM_001195800.2:c.1451T>C

NM_001195803.2:c.1574T>C

Likely Pathogenic

Met criteria codes 4

PP1_Strong

PP4

PM2

PS4_Supporting

Not Met criteria codes 5

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1955T>C (p.Met652Thr) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP4, PP1_Moderate and PS4_Supporting 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 = 0.00005 in East Asians (gnomAD v2.1.1). PS4_Supporting: Variant meets PM2 and is identified in at least 2 unrelated index cases who fulfil clinical criteria for FH: 1 patient with DLCN >6 from the Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA, Australia; VCI); 1 patient with Simon Broome = Definite FH (PMID: 20236128). PP1_Strong: Variant segregates with the FH phenotype in 8 informative meioses from 1 family from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA, Australia; VCI): 5 affected family members have the variant and 3 non-affected family members do not have the variant. PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills clinical criteria for FH (Cardiovascular Genetics Laboratory - PathWest Laboratory Medicine WA, Australia; VCI), after alternative causes of high cholesterol were excluded.

Met criteria codes

PP1_Strong			PP1_Strong : Variant segregates with FH phenotype in 8 informative meiosis from 1 family (5 relatives with the phenotype and the variant and 3 relatives without the phenotype and without the variant) from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), so PP1_strong is met
PP4			2 patients with definite FH (1 from the Cardiovascular Genetics Laboratory - PathWest Laboratory Medicine WA - as defined by DLCN>6 and 1 from PMID: 20236128 as defined by Simon Broome score = definite).
PM2			Allele frequency is 0.00005 (18394 alleles) in the East Asian subpopulation in GnomAD (gnomAD v2.1.1).
PS4_Supporting			4 index cases with clinical criteria of FH: 1 from the Cardiovascular Genetics Laboratory - PathWest Laboratory Medicine WA - with DLCN>6, 1 from PMID: 20236128 with Simon-Broome criteria of definite FH, 1 from Ambry Genetics with DLCN = 8, and 1 from PMID:31993549 with Simon-Broome criteria of possible FH. PMID:20829525, PMID:22883975 and PMID: 28964736 were not considered because of 3 carriers with FH did not fulfil FH clinical criteria

Not Met criteria codes

BP4			REVEL score is 0.588
PS1			2 variants were found in the same codon but led to different aa change
PS3			no functional data available
PP3			REVEL score is 0.588

PM5



2 variants were found in the same codon leading to a different aa change. However, all these variants were classified as VUS by these guidelines

Curation History [↗](#)

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Showing 1 to 2 of 2 rows

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