

Variant: *NM_000527.5(LDLR):c.1176C>A (p.Cys392Ter)*

Version: 1.0

CA032391 [↗](#)

251699 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

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HGVS expressions

NM_000527.5(LDLR):c.1176C>A (p.Cys392Ter)

NM_000527.5:c.1176C>A

NC_000019.10:g.11111629C>A

CM000681.2:g.11111629C>A

NC_000019.9:g.11222305C>A

CM000681.1:g.11222305C>A

NC_000019.8:g.11083305C>A

NG_009060.1:g.27249C>A

ENST00000252444.10:c.1434C>A

ENST00000559340.2:c.1176C>A

ENST00000560467.2:c.1056C>A

ENST00000558518.6:c.1176C>A

ENST00000252444.9:c.1430C>A

ENST00000455727.6:c.672C>A

ENST00000535915.5:c.1053C>A

ENST00000545707.5:c.795C>A

ENST00000557933.5:c.1176C>A

ENST00000558013.5:c.1176C>A

ENST00000558518.5:c.1176C>A

ENST00000560173.1:n.175C>A

ENST00000560467.1:c.656C>A

NM_000527.4:c.1176C>A

NM_001195798.1:c.1176C>A

NM_001195799.1:c.1053C>A

NM_001195800.1:c.672C>A

NM_001195803.1:c.795C>A

NM_001195798.2:c.1176C>A

NM_001195799.2:c.1053C>A

NM_001195800.2:c.672C>A

NM_001195803.2:c.795C>A

Pathogenic

Met criteria codes **6**

PVS1

PS4_Moderate

PP1_Strong

PP4

PM2

PM3

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 20

BS2

BS1

BS4

BS3

BP4

BP3

BP1

BP2

BP5

BP7

BA1

PS1

PS2

PS3

PP2

PP3

PM6

PM1

PM5

PM4

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1176C>A (p.Cys392Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PVS1, PP1_Strong, PM2, PM3, PS4_Moderate 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: PVS1 - variant is nonsense, causing a premature stop codon amino-terminal of amino acid 830 (NM_000527.5:p.Lys830), so PVS1 is met. PP1_strong - variant segregates with FH phenotype in: - 7 informative meioses from 1 family from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 4 relatives positive for variant with LDL-C >75th percentile, and 3 relatives negative for variant with LDL-C <50th percentile. - 1 informative meiosis from 1 family from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): 1 relative positive for variant with LDL-C >75th percentile. - 11 informative meioses from 1 family from PMID: 8831933 (Langenhoven et al. 1996): 11 relatives are positive for the variant and have LDL-C >75th percentile (9 have >5.0mmol, 2 have 4.6 and 4.3mmol) Segregation was observed in 19 informative meioses from 3 families, so PP1_Strong is met. PM2 - PopMax MAF = 0.00003267 (0.003%) in South asian exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met. PM3 - variant meets PM2 and was identified in 1 index case who also carries NM_000527.5(LDLR):c.1A>T (p.Met1Leu), confirmed in trans, who has LDL 17.3mmol/L from PMID: 8831933 (Langenhoven et al. 1996 Aug 23;125(1):111-9. --- 2nd variant is classified as Pathogenic with these guidelines, so PM3 is met. PS4_moderate - variant meets PM2 and was identified in: - 1 index case who fulfills Simon-Broome criteria of possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Portugal; - 1 index case with DLCN>=6 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 unrelated index cases, all with Dutch lipid clinic network >=6, from Robarts Research Institute, Canada; - 1 Index case (iii-4) with DLCN at least 8 (LDL-C 17.3mmol at 4yo with tendon xanthoma) from PMID: 8831933 (Langenhoven et al. 1996), South Africa; - 1 index case with heterozygous FH per MEDPED criteria from PMID: 11933210 (Salazar et al. 2002), Brazil; - at least 1 index case with definite FH ("definite heterozygous FH by cardiologists and internists using a uniform protocol and internationally accepted criteria [Defesche, 2000].") from PMID 11810272 (Fouchier et al. 2001), The Netherlands. 9 unrelated cases, so PS4_Moderate is met. PP4 - variant meets PM2 and was identified in 9 unrelated index cases who fulfill clinical FH criteria from different labs (see PS4 for details), so PP4 is met.

Met criteria codes

PVS1			variant is nonsense, causing a premature stop codon amino-terminal of amino acid 830 (NM_000527.5:p.Lys830), so PVS1 is met
PS4_Moderate			variant meets PM2 and was identified in - 1 index case who fulfills Simon-Broome criteria of possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Portugal; - 1 index case with DLCN>=6 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 unrelated index cases, all with Dutch lipid clinic network >=6, from Robarts Research Institute, Canada; - 1 Index case (iii-4) with DLCN at least 8 (LDL-C 17.3mmol at 4yo with tendon xanthoma) from PMID: 8831933 (Langenhoven et al. 1996), South Africa; - 1 index case with heterozygous FH per MEDPED criteria from PMID: 11933210 (Salazar et al. 2002), Brazil; - at least 1 index case with definite FH ("definite heterozygous FH by cardiologists and internists using a uniform protocol and

internationally accepted criteria [Defesche, 2000].") from PMID 11810272 (Fouchier et al. 2001), The Netherlands. 9 unrelated cases, so PS4_Moderate is met

PP1_Strong			variant segregates with FH phenotype in: - 7 informative meiosis from 1 family from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge: 4 relatives positive for variant with LDL-C >75th percentile, and 3 relatives negative for variant with LDL-C <50th percentile. - 1 informative meiosis from 1 family from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): 1 relative positive for variant with LDL-C >75th percentile. - 11 informative meiosis from 1 family from PMID: 8831933 (Langenhoven et al. 1996): 11 relatives are positive for the variant and have LDL-C >75th percentile (9 have >5.0mmol, 2 have 4.6 and 4.3mmol) Segregation was observed in 19 informative meiosis from 3 families, so PP1_Strong is met
PP4			variant meets PM2 and was identified in - 1 index case who fulfills Simon-Broome criteria of possible FH from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge, Portugal; - 1 index case with DLCN>=6 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 unrelated index cases, all with Dutch lipid clinic network >=6, from Robarts Research Institute, Canada; - 1 Index case (iii-4) with DLCN at least 8 (LDL-C 17.3mmol at 4yo with tendon xanthoma) from PMID: 8831933 (Langenhoven et al. 1996), South Africa; - 1 index case with heterozygous FH per MEDPED criteria from PMID: 11933210 (Salazar et al. 2002), Brazil; - at least 1 index case with definite FH ("definite heterozygous FH by cardiologists and internists using a uniform protocol and internationally accepted criteria [Defesche, 2000].") from PMID 11810272 (Fouchier et al. 2001), The Netherlands. so PP4 is met
PM2			PopMax MAF = 0.00003267 (0.003%) in South asian exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met
PM3			variant meets PM2 and was identified in 1 index case who also carries NM_000527.5(LDLR):c.1A>T (p.Met1Leu), confirmed in trans, who has LDL 17.3mmol/L from PMID: 8831933 (Langenhoven et al. 1996 Aug 23;125(1):111-9. --- 2nd variant is classified as Pathogenic with these guidelines, so PM3 is met

Not Met criteria codes

BS2			variant not identified in normolipidemic individuals: 0/200 non-FH alleles from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge and 0/1000 normolipidemic individuals from Robarts Research Institute, so BS2 is not met
BS1			no FAF, just total MAF = 0.000003990 (0.0004%) in South asian exomes (gnomAD v2.1.1). It is not above 0.2%, so BS1 is not met
BS4			There was lack of segregation observed in: - 1 informative meiosis from 1 family from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge: 1 relative negative for variant with LDL-C >75th percentile. it is not enough, so BS4 is not met
BS3			there is no published functional study on this variant
BP4			PVS1 is met, so BP4 is not applicable

BP3			not applicable
BP1			not applicable
BP2			no other variants identified in index cases
BP5			not applicable
BP7			variant is nonsense, so not applicable
BA1			no FAF, just total MAF = 0.000003990 (0.0004%) in South asian exomes (gnomAD v2.1.1). It is not above 0.5%, so BA1 is not met
PS1			variant is nonsense, so not applicable
PS2			no de novo occurence
PS3			there is no published functional study on this variant
PP2			not applicable
PP3			PVS1 is met, so PP3 is not applicable
PM6			no de novo occurence
PM1			variant is nonsense, so not applicable
PM5			variant is nonsense, so not applicable
PM4			variant is nonsense, so not applicable

Curation History [↗](#)

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