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.664T>C (p.Cys222Arg)

Version: 1.0

CA044260

226332 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 89bd8cb7-28fa-4f78-9174-47bf4d529f71
Approved on: 2023/4/28
Published on: 2023/5/1

HGVS expressions

NM_000527.5(LDLR):c.664T>C (p.Cys222Arg)
NM_000527.5:c.664T>C
NC_000019.10:g.11105570T>C
CM000681.2:g.11105570T>C
NC_000019.9:g.11216246T>C
CM000681.1:g.11216246T>C
NC_000019.8:g.11077246T>C
NG_009060.1:g.21190T>C
ENST00000252444.10:c.922T>C
ENST00000559340.2:c.664T>C
ENST00000560467.2:c.664T>C
ENST00000558518.6:c.664T>C
ENST00000252444.9:c.918T>C
ENST00000455727.6:c.314-1822T>C
ENST00000535915.5:c.541T>C
ENST00000545707.5:c.314-995T>C
ENST00000557933.5:c.664T>C
ENST00000558013.5:c.664T>C
ENST00000558518.5:c.664T>C
ENST00000560467.1:c.264T>C
NM_000527.4:c.664T>C
NM_001195798.1:c.664T>C
NM_001195799.1:c.541T>C
NM_001195800.1:c.314-1822T>C
NM_001195803.1:c.314-995T>C
NM_001195798.2:c.664T>C
NM_001195799.2:c.541T>C
NM_001195800.2:c.314-1822T>C
NM_001195803.2:c.314-995T>C

Likely Pathogenic

Met criteria codes 6

PM1 PM3 PS4_Supporting PM2 PP3 PP4

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

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.664T>C (p.Cys222Arg) variant is classified as a Likely pathogenic variant for Familial Hypercholesterolemia by applying evidence codes PM2, PM1, PM3, PS4_supporting, PP3, and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1101/2021.03.17.21252755). The supporting evidence is as follows: PM2: PopMax MAF = 0.0001098 (0.01%) in East Asian exomes (gnomAD v2.1.1) PM1: Variant meets PM2 and alters Cys222, one of the cysteine residues listed. PM3: Variant meets PM2 and is identified in two index cases with homozygous FH phenotype (LDL mmol/L = 17.9 and 14.09 respectively), PMID: 15823276 PS4_supporting: Variant meets PM2 and is identified in at least 5 index cases who fulfill SB possible/definite FH or DLCN>=6 criteria for FH from GeneDx Inc., Ambry Genetics, and the Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) PP3 : REVEL = 0.966. PP4: Variant meets PM2 and identified in at least 2 FH case from GeneDx Inc, 1 FH case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), and 1 FH case from Ambry Genetics, all of them fulfilling SB criteria for possible/definite FH or DLCN > 6.

Met criteria codes

PM1	✔	Variant meets PM2 and alters Cys222, one of the cysteine residues listed.
PM3	✔	Variant meets PM2 and is identified in two index cases with homozygous FH phenotype (LDL mmol/L = 17.9 and 14.09 respectively), PMID: 15823276
PS4_Supporting	✔	Variant meets PM2 and is identified in at least 5 index cases who fulfill SB possible/definite FH or DLCN>=6 criteria for FH from GeneDx Inc., Ambry Genetics, and the Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)
PM2	✔	PopMax MAF = 0.0001098 (0.01%) in East Asian exomes (gnomAD v2.1.1)
PP3	✔	REVEL = 0.966
PP4	✔	Variant meets PM2 and identified in at least 2 FH case from GeneDx Inc, 1 FH case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), and 1 FH case from Ambry Genetics, all of them fulfilling SB criteria for possible/definite FH or DLCN > 6.

Curation History

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