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.1432G>A (p.Gly478Arg)

Version: 1.1

CA023495

161277 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: d3424058-b37e-4bce-b932-0695abc3af1d
Approved on: 2021/12/14
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HGVS expressions

NM_000527.5:c.1432G>A
NM_000527.5(LDLR):c.1432G>A (p.Gly478Arg)
NC_000019.10:g.11113608G>A
CM000681.2:g.11113608G>A
NC_000019.9:g.11224284G>A
CM000681.1:g.11224284G>A
NC_000019.8:g.11085284G>A
NG_009060.1:g.29228G>A
ENST00000252444.10:c.1690G>A
ENST00000559340.2:c.1432G>A
ENST00000560467.2:c.1312G>A
ENST00000558518.6:c.1432G>A
ENST00000252444.9:c.1686G>A
ENST00000455727.6:c.928G>A
ENST00000535915.5:c.1309G>A
ENST00000545707.5:c.1051G>A
ENST00000557933.5:c.1432G>A
ENST00000558013.5:c.1432G>A
ENST00000558518.5:c.1432G>A
ENST00000559340.1:c.153G>A
ENST00000560467.1:c.912G>A
NM_000527.4:c.1432G>A
NM_001195798.1:c.1432G>A
NM_001195799.1:c.1309G>A
NM_001195800.1:c.928G>A
NM_001195803.1:c.1051G>A
NM_001195798.2:c.1432G>A
NM_001195799.2:c.1309G>A
NM_001195800.2:c.928G>A
NM_001195803.2:c.1051G>A

Pathogenic

Met criteria codes 5

PP3 PP4 PM2 PP1_Strong PS4

Not Met criteria codes 21

PP2 BA1 PM6 PM1 PM3
PM5 PM4 BS2 BS1 BS4
BS3 PS1 PS2 PS3 BP4 BP3
BP1 BP2 PVS1 BP5 BP7

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 1.1*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1432G>A (p.Gly478Arg) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PP1_strong, PS4, 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: PP1_strong - variant segregates with FH phenotype in 10 informative meiosis from 4 families from 2 labs: - Laboratory of Genetics and Molecular Cardiology - Data from 1 family: 2 relatives positive for variant with LDL-C >75th percentile, 1 relative negative for variant with LDL-C <50th percentile; - Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge - Data from 3 families. F1: 3 relatives with the phenotype are positive for the variant plus 1 relative without the phenotype is negative for the variant. F2: 1 relative with the phenotype and positive for the variant plus 1 relative without the phenotype is negative for the variant. F3: 1 relative with the phenotype is positive for the variant. so PP1_Strong is met PS4 - variant meets PM2 and was identified in at least 11 unrelated index cases who fulfill clinical FH criteria from different labs: - 1 case with Simon-Broome criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); - 1 case with DLCN score >= 6 from Color Health, Inc; - 4 unrelated cases with DLCN score >= 6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); - 4 unrelated cases with Simon-Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; - 1 case with DLCN score >= 6 from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory), so PS4 is met PM2 - PopMax MAF = 0.0001234 (0.01234%) in African/African-American exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met. PP3 - REVEL = 0.985. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in at least 11 unrelated index cases who fulfill clinical FH criteria from different labs (see details in PS4), so PP4 is met.

Met criteria codes

PP3	✔	REVEL = 0.985. It is above 0.75, so PP3 is met
PP4	✔	variant meets PM2 and was identified in at least 11 unrelated index cases who fulfill clinical FH criteria from different labs (see details in PS4) so PP4 is met
PM2	✔	PopMax MAF = 0.0001234 (0.01234%) in African/African-American exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met
PP1_Strong	✔	variant segregates with FH phenotype in 10 informative meiosis from 4 families from 2 labs: - Laboratory of Genetics and Molecular Cardiology - Data from 1 family: 2 relatives positive for variant with LDL-C >75th percentile, 1 relative negative for variant with LDL-C <50th percentile; - Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge - Data from 3 families. F1: 3 relatives with the phenotype are positive for the variant plus 1 relative without the phenotype is negative for the variant. F2: 1 relative with the phenotype and positive for the

variant plus 1 relative without the phenotype is negative for the variant. F3: 1 relative with the phenotype is positive for the variant. so PP1_Strong is met

PS4	ℹ	✔	variant meets PM2 and was identified in at least 11 unrelated index cases who fulfill clinical FH criteria from different labs: - 1 case with Simon-Broome criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); - 1 case with DLCN score >= 6 from Color Health, Inc; - 4 unrelated cases with DLCN score >= 6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); - 4 unrelated cases with Simon-Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; - 1 case with DLCN score >= 6 from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory). so PS4 is met

Not Met criteria codes

PP2	ℹ	✖	not applicable
BA1	ℹ	✖	FAF = 0.00002138 (0.002%) in African/African-American exomes (gnomAD v2.1.1). It is not above 0.5%, so BA1 is not met
PM6	ℹ	✖	no de novo occurrence identified
PM1	ℹ	✖	variant is missense and meets PM2, but it is not in exon 4 and does not alter Cys, so PM1 is not met
PM3	ℹ	✖	1 index case from Ambry with LDL pretreatment >400 is also het for LDLR p.V429M variant (phase unknown) - phenotype is not above 500mg/dl, so not applicable so not met
PM5	ℹ	✖	2 other missense variants in the same codon: - NM_000527.4(LDLR):c.1432G>T (p.Gly478Trp) - 1 star, Uncertain significance - VUS by these guidelines - NM_000527.4(LDLR):c.1433G>A (p.Gly478Glu) - 0 stars, Pathogenic - VUS by these guidelines no Pathogenic with these guidelines, so PM5 is not met
PM4	ℹ	✖	variant is missense, so not applicable
BS2	ℹ	✖	not identified in normolipidemic individuals: 0/104 non-FH individuals from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge and 0/100 normolipidemic individuals from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), so BS2 is not met
BS1	ℹ	✖	FAF = 0.00002138 (0.002%) in African/African-American exomes (gnomAD v2.1.1). It is not above 0.2%, so BS1 is not met
BS4	ℹ	✖	only 1 non-segregation was identified: 1 relative negative for variant with LDL-C >75th percentile from Laboratory of Genetics and Molecular Cardiology , not enough, so BS4 is not met
BS3	ℹ	✖	this variant was not studied in published functional studies yet
PS1	ℹ	✖	no other variant leads to the same amino acid change, so PS1 is not met

PS2		✖	no de novo occurrence identified
PS3		✖	this variant was not studied in published functional studies yet
BP4		✖	REVEL = 0.985. It is not below 0.50, so BP4 is not met
BP3		✖	not applicable
BP1		✖	not applicable
BP2		✖	1 index case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) (with DLCS >=6) is also heterozygous for NM_000527.5(LDLR):c.1816G>T (p.Ala606Ser) and has a phenotype of HeFH. - 2 stars, Uncertain significance- VUS by these guidelines 1 index case from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies also have LDLR, c.-168-100G>T, p.?, - but no phenotype, so not applicable; 1 index case from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies also have LDLR, c.1135T>C, p.Cys379Arg, - but no phenotype, so not applicable; 1 index case from Ambry with LDL pretreatment >400 is also het for LDLR p.V429M variant (phase unknown) - phenotype is not below 350mg/dl, so not applicable 1 index case from Ambry with LDL 268mg/dl is also het for APOB p.Y1247C - VUS, which is leaning VLB per lab no index case with heterozygous phenotype was identified with another pathogenic variant, so not met
PVS1		✖	variant is missense and not in initiation codon, so PVS1 is not met
BP5		✖	not applicable
BP7		✖	variant is missense, so not applicable

Curation History

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