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Variant: NM_000527.5(LDLR):c.1027G>A (p.Gly343Ser)

Version: 1.0

CA023406

183106 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 2fc03ee7-785f-44c9-bac0-10c93ad52227
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HGVS expressions

NM_000527.5:c.1027G>A
NM_000527.5(LDLR):c.1027G>A (p.Gly343Ser)
NC_000019.10:g.11110738G>A
CM000681.2:g.11110738G>A
NC_000019.9:g.11221414G>A
CM000681.1:g.11221414G>A
NC_000019.8:g.11082414G>A
NG_009060.1:g.26358G>A
ENST00000252444.10:c.1285G>A
ENST00000559340.2:c.1027G>A
ENST00000560467.2:c.941-776G>A
ENST00000558518.6:c.1027G>A
ENST00000252444.9:c.1281G>A
ENST00000455727.6:c.523G>A
ENST00000535915.5:c.904G>A
ENST00000545707.5:c.646G>A
ENST00000557933.5:c.1027G>A
ENST00000558013.5:c.1027G>A
ENST00000558518.5:c.1027G>A
ENST00000560173.1:n.26G>A
ENST00000560467.1:c.541-776G>A
NM_000527.4:c.1027G>A
NM_001195798.1:c.1027G>A
NM_001195799.1:c.904G>A
NM_001195800.1:c.523G>A
NM_001195803.1:c.646G>A
NM_001195798.2:c.1027G>A
NM_001195799.2:c.904G>A
NM_001195800.2:c.523G>A
NM_001195803.2:c.646G>A

Pathogenic

Met criteria codes 9

PP1_Strong | BS4 | PS3 | PS4 | PP3 | PP4 | PM2 | PM3 | PM5

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.1027G>A (p.Gly343Ser) variant is classified as Pathogenic (modified) for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PS3, PP4, PS4, PP1_Strong, PM5, PM3, BS4) 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: PopMaxMAF=0.00005 in East Asian population from gnomAD (gnomAD v2.1.1). PP3: REVEL=0.929, it is above 0.75. PS3: Level 1 assays: PMID 15100232. Heterologous cells (CHO) were used in WB, FACS and NMR Spectroscopy. The experiments shown <60% cell surface LDLR expression (Fig 5C), and >80% expressed receptor bind and release LDL upon low pH condition (Fig 6B), the amount of LDL bound to the mutant receptor correlates tightly with cell-surface LDLR expression, NMR indicates misfolding defects of the receptor. Functional data is consistent with damaging effect. This study is reported by Boswell et al, 2004, from Department of Biochemistry, Division of Structural Biology, University of Oxford, UK. PP4: Variant meets PM2 and is identified in at least ˃1 index cases who fulfil criteria for FH after alternative causes of high cholesterol were excluded. PS4: Variant meets PM2 and is identified in at least 26 index cases reported in VCI and PubMed. There are 14 unrelated index case reported in VCI who fulfil criteria for FH diagnosis: Twelve cases fulfil DLCN criteria, 7 reported from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France, 1 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), 2 from Research Lab of Molecular Genetics of Lipid Metabolism; and 2 from Robarts Research Institute, Canada; two cases fulfil Simon Broome possible criteria, reported from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. Variant is reported in PubMed in at least 12 index cases fulfil criteria for FH diagnosis: 8 cases fulfil DLCN probable/definite FH criteria in PMID 11040093, 11810272, 32977124, 30270055, 27784735; 1 case fulfil Simon Broome possible FH criteria in PMID 26748104; 3 cases fulfil MedPed criteria in PMID 8882879, 27824480. PP1_Strong: Variant segregates with FH phenotype in 18 informative meiosis from 6 families reported from 4 different labs in VCI: 11 affected carries and 7 unaffected non-carriers reported from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Laboratory of Genetics and Molecular Cardiology, and Research Lab of Molecular Genetics of Lipid Metabolism. PM5: Three other variants at the same codon: NM_000527.5(LDLR):c.1028G>T (p.Gly343Val)(ClinVarID 440618) classified as Likely Pathogenic, NM_000527.5(LDLR):c.1028G>A (p.Gly343Asp)(ClinVarID 251606) is classified as Likely Pathogenic, NM_000527.5(LDLR):c.1027G>T (p.Gly343Cys)(ClinVarID 251605) is classified as Pathogenic, by these guidelines, therefore PM5 is met. PM3: Variant meets PM2 and is identified in an index case with homozygous FH phenotype (untreated LDL-C > 500mg/dL, or LDL-C > 300 mmol/dL on high-intensive lipid-lowering therapy and the presence of tendon xanthomas before 10 year of age), reported by Sanchez-Hernandez et al, 2016, Universitario Insular Materno Infantil de Gran Canaria, Spain, PMID 27784735. This variant met enough pathogenic criteria toward Pathogenic classification by these guidelines before PM3 code applied. BS4: Variant does not segregate with FH phenotype in total of 6 informative meiosis reported in VCI. Five affected relatives without the variant and had LDL-C>75th percentile, 2 cases from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), 1 case each from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Laboratory of Genetics and Molecular Cardiology, and Research Lab of Molecular Genetics of Lipid Metabolism. There is 1 instance reported from 1 laboratory, where an unaffected family member had LDL-C<50th percentile and carries the variant, reported in VCI from Laboratory of Genetics and Molecular Cardiology, GTR LabID 505581. Variant has 3 Strong, 3 Moderate and 2 Supporting evidence codes toward Pathogenic, enough to classify as Pathogenic, and only 1 Strong evidence code towards Benign. The Pathogenic criteria overwhelms the Benign criteria, so we are confident in classifying this variant as Pathogenic.

Met criteria codes

PP1_Strong	✔	Variant segregates with FH phenotype in 18 informative meiosis from 6 families reported from 4 different labs in VCI: 11 affected carries and 7 unaffected non-carriers reported from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Laboratory of Genetics and Molecular Cardiology, and Research Lab of Molecular Genetics of Lipid Metabolism.
BS4	✔	Variant does not segregate with FH phenotype in total of 6 informative meiosis reported in VCI. Five affected relatives without the variant and had LDL-C>75th percentile, 2 cases from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), 1 case each from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Laboratory of Genetics and Molecular Cardiology, and Research Lab of Molecular Genetics of Lipid Metabolism. There is 1 instance reported from 1 laboratory, where an unaffected family member had LDL-C<50th percentile and carries the variant, reported in VCI from Laboratory of Genetics and Molecular Cardiology, GTR LabID 505581.
PS3	✔	Level 1 assays: PMID 15100232. Heterologous cells (CHO) were used in WB, FACS and NMR Spectroscopy. The experiments shown <60% cell surface LDLR expression (Fig 5C), and >80% expressed receptor bind and release LDL upon low pH condition (Fig 6B), the amount of LDL bound to the mutant receptor correlates tightly with cell-surface LDLR expression, NMR indicates misfolding defects of the receptor. Functional data is consistent with damaging effect. This study is reported by Boswell et al, 2004, from Department of Biochemistry, Division of Structural Biology, University of Oxford, UK.
PS4	✔	Variant meets PM2 and is identified in at least 26 index cases reported in VCI and PubMed. There are 14 unrelated index case reported in VCI who fulfil criteria for FH diagnosis: Twelve cases fulfil DLCN criteria, 7 reported from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France, 1 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), 2 from Research Lab of Molecular Genetics of Lipid Metabolism; and 2 from Robarts Research Institute, Canada; two cases fulfil Simon Broome possible criteria, reported from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. Variant is reported in PubMed in at least 12 index cases fulfil criteria for FH diagnosis: 8 cases fulfil DLCN probable/definite FH criteria in PMID 11040093, 11810272, 32977124, 30270055, 27784735; 1 case fulfil Simon Broome possible FH criteria in PMID 26748104; 3 cases fulfil MedPed criteria in PMID 8882879, 27824480.
PP3	✔	REVEL=0.929, it is above 0.75.
PP4	✔	Variant meets PM2 and is identified in ˃1 index cases who fulfil criteria for FH after alternative causes of high cholesterol were excluded.
PM2	✔	PopMaxMAF=0.00005 in East Asian population from gnomAD (gnomAD v2.1.1).
PM3	✔	Variant meets PM2 and is identified in an index case with homozygous FH phenotype (untreated LDL-C > 500mg/dL, or LDL-C > 300 mmol/dL on high-intensive lipid-lowering therapy and the presence of tendon xanthomas before 10 year of age), reported by Sanchez-Hernandez et al, 2016, Universitario Insular Materno Infantil de Gran Canaria, Spain, PMID 27784735. This variant met enough pathogenic criteria toward Pathogenic classification by these guidelines before PM3 code applied.
PM5	✔	Three other variants at the same codon: NM_000527.5(LDLR):c.1028G>T (p.Gly343Val)(ClinVarID 440618) classified as Likely Pathogenic, NM_000527.5(LDLR):c.1028G>A (p.Gly343Asp)(ClinVarID 251606) is classified as Likely

Pathogenic, NM_000527.5(LDLR):c.1027G>T (p.Gly343Cys)(ClinVarID 251605) is classified as Pathogenic, by these guidelines, therefore PM5 is met.

Curation History

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