

Variant: *NM_000527.5(LDLR):c.662A>G (p.Asp221Gly)*

Version: 1.0

CA023739 [↗](#)

183092 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: f2f41bd9-ad4d-4237-b618-832f5cbc6885

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HGVS expressions

NM_000527.5(LDLR):c.662A>G (p.Asp221Gly)

NM_000527.5:c.662A>G

NC_000019.10:g.11105568A>G

CM000681.2:g.11105568A>G

NC_000019.9:g.11216244A>G

CM000681.1:g.11216244A>G

NC_000019.8:g.11077244A>G

NG_009060.1:g.21188A>G

ENST00000252444.10:c.920A>G

ENST00000559340.2:c.662A>G

ENST00000560467.2:c.662A>G

ENST00000558518.6:c.662A>G

ENST00000252444.9:c.916A>G

ENST00000455727.6:c.314-1824A>G

ENST00000535915.5:c.539A>G

ENST00000545707.5:c.314-997A>G

ENST00000557933.5:c.662A>G

ENST00000558013.5:c.662A>G

ENST00000558518.5:c.662A>G

ENST00000560467.1:c.262A>G

NM_000527.4:c.662A>G

NM_001195798.1:c.662A>G

NM_001195799.1:c.539A>G

NM_001195800.1:c.314-1824A>G

NM_001195803.1:c.314-997A>G

NM_001195798.2:c.662A>G

NM_001195799.2:c.539A>G

NM_001195800.2:c.314-1824A>G

NM_001195803.2:c.314-997A>G

Pathogenic

Met criteria codes **9**

PS3_Moderate BS4 PP1_Strong

PS4 PP3 PP4 PM2 PM1

PM3

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 17 [Criteria Specifications for this VCEP](#)

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

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR): c.662A>G (p.Asp221Gly) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PP1_strong, PS3_moderate, PS4, PM1, PM2, PM3, PP3, PP4 and 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:

PP1_strong - Variant segregates with FH phenotype in 92 informative meioses in at least 37 families from different labs (Robarts Research Institute; Laboratory of Genetics and Molecular Cardiology, University of São Paulo; Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)): 55 affected family members have the variant, 37 unaffected family members don't have the variant. **PS3_moderate** - PMID: 9974426 - Level 2 assay - Homozygous patients' fibroblasts, 125I-LDL assays: 8% LDLR activity; PMID: 25647241 - Level 3 assay - Heterologous cells (HeLa), CLSM assay: most of mutant LDLR is in ER, LDLR activity decreased compared to WT - considered as disruptive. **PS4** - Variant meets PM2. Variant identified in 48 unrelated index cases (2 cases with DLCN≥6 from Robarts Research Institute; 21 cases (13 patients with DLCN≥6, and 8 patients with possible FH (Simon Broome)) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 17 cases with possible/definite FH (Simon-Broome) from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 1 case with Possible FH (Simon-Broome) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 5 cases with DLCN≥6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 2 cases with DLCN≥6 from Color Health, Inc. **PM1** - Variant meets PM2 and is missense in exon 4. **PM2** - PopMax MAF = 0.0001152 (0.01152%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1). **PM3** - Index case from Ambry Genetics has LDL = 750 mg/dl and also LDLR c.2140+1G>T (pathogenic by these guidelines, confirmed to be in trans). **PP3** - REVEL = 0.986. **PP4** - Variant meets PM2. Identified in 48 FH cases from different labs (for list see PS4) with clinical Dutch Lipid Clinic Network Criteria score ≥ 6 or Simon-Broome possible/definite FH, after alternative causes of high cholesterol were excluded. **BS4** - 30 nonsegregations in 12 families (Laboratory of Genetics and Molecular Cardiology, University of São Paulo). Variant has 2 Strong plus 4 Moderate plus 2 Supporting evidence codes towards Pathogenic, enough to classify as Pathogenic, and only 1 Strong evidence codes towards Benign. The Pathogenic criteria overwhelms the Benign criteria, so we are confident in classifying this variant as Pathogenic.

Met criteria codes

PS3_Moderate			PMID: 9974426 - Level 2 assay - Homozygous patients' fibroblasts, 125I-LDL assays: 8% LDLR activity; PMID: 25647241 - Level 3 assay - Heterologous cells (HeLa), CLSM assay: most of mutant LDLR is in ER, LDLR activity decreased compared to WT - considered as disruptive.
BS4			30 nonsegregations in 12 families (Laboratory of Genetics and Molecular Cardiology, University of São Paulo).
PP1_Strong			Variant segregates with FH phenotype in 92 informative meioses in at least 37 families from different labs (Robarts Research Institute; Laboratory of Genetics and Molecular Cardiology, University of São Paulo; Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and

Transplantation); Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)): 55 affected family members have the variant, 37 unaffected family members don't have the variant.			
PS4			Variant meets PM2. Variant identified in 48 unrelated index cases (2 cases with DLCN≥6 from Robarts Research Institute; 21 cases (13 patients with DLCN≥6, and 8 patients with possible FH (Simon Broome)) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 17 cases with possible/definite FH (Simon-Broome) from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 1 case with Possible FH (Simon-Broome) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 5 cases with DLCN≥6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 2 cases with DLCN≥6 from Color Health, Inc.
PP3			REVEL = 0.986
PP4			Variant meets PM2. Identified in 48 FH cases from different labs (for list see PS4) with clinical Dutch Lipid Clinic Network Criteria score ≥ 6 or Simon-Broome possible/definite FH, after alternative causes of high cholesterol were excluded.
PM2			PopMax MAF = 0.0001152 (0.01152%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1).
PM1			Variant meets PM2 and is missense in exon 4.
PM3			Index case from Ambry Genetics has LDL = 750 mg/dl and also LDLR c.2140+1G>T (pathogenic by these guidelines, confirmed to be in trans).

Not Met criteria codes

BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			If PM1 is met, PM5 is not applicable.
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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