

Variant: *NM_000527.5:c.651TGG[1]*

Version: 1.0

CA023734 [↗](#)

226329 (ClinVar) [↗](#)

Gene: [LDLR](#)

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

Inheritance Mode: Semidominant inheritance

UUID: f93a6a4d-f43a-4d61-ab69-e4a067024147

Approved on: 2022/6/2

Published on: 2022/6/30

HGVS expressions

NM_000527.5:c.651TGG[1]

NC_000019.10:g.11105560_11105562del
CM000681.2:g.11105560_11105562del
NC_000019.9:g.11216236_11216238del
CM000681.1:g.11216236_11216238del
NC_000019.8:g.11077236_11077238del
NG_009060.1:g.21180_21182del
ENST00000252444.10:c.912_914del
ENST00000559340.2:c.654_656del
ENST00000560467.2:c.654_656del
ENST00000558518.6:c.654_656del
ENST00000252444.9:c.908_910del
ENST00000455727.6:c.314-1832_314-1830del
ENST00000535915.5:c.531_533del
ENST00000545707.5:c.314-1005_314-1003del
ENST00000557933.5:c.654_656del
ENST00000558013.5:c.654_656del
ENST00000558518.5:c.654_656del
ENST00000560467.1:c.254_256del
NM_000527.4:c.654_656del
NM_001195798.1:c.654_656del
NM_001195799.1:c.531_533del
NM_001195800.1:c.314-1832_314-1830del
NM_001195803.1:c.314-1005_314-1003del
NM_000527.5:c.654_656del
NM_001195798.2:c.654_656del
NM_001195799.2:c.531_533del
NM_001195800.2:c.314-1832_314-1830del
NM_001195803.2:c.314-1005_314-1003del

Pathogenic

Met criteria codes **6**

PP1_Strong PS4 PS3_Moderate
PP4 PM2 PM4

Not Met criteria codes **20**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BP5BP7BP4BP3BP1BP2

PS1PS2PP2PP3PM6

PM1PM3PM5PVS1BA1

BS2BS1BS4BS3

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.651TGG[1] (p.Gly219del) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PP1_strong, PS3_moderate, PS4, PM2, PM4 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 phenotype in 9 informative meioses in 5 families from different labs (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 Genetics Laboratory (PathWest Laboratory Medicine WA)); 9 affected family members have the variant. PS3_moderate - PMID: 2088165 - Level 2 assay - Homozygous patients' fibroblasts, 125I-LDL assays: <2% LDLR activity. PS4 - Variant meets PM2. Variant identified in 10 unrelated index cases (1 case with DLCN ≥ 6 from Robarts Research Institute; 2 cases 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); 4 cases with Simon Broome possible/definite FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 1 case with DLCN ≥ 6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 2 cases with Simon Broome possible/definite FH from GeneDx Inc. PM2 - PopMax MAF = 0.000008826 (0.0008826%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1). PM4 - Variant meets PM2 and is in frame deletion. PP4 - Variant meets PM2. Identified in 4 FH case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with clinical Simon Broome possible/definite FH, after alternative causes of high cholesterol were excluded.

Met criteria codes

PP1_Strong			Variant segregates with phenotype in 9 informative meioses in 5 families from different labs (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 Genetics Laboratory (PathWest Laboratory Medicine WA)); 9 affected family members have the variant.
PS4			Variant meets PM2. Variant identified in 10 unrelated index cases (1 case with DLCN ≥ 6 from Robarts Research Institute; 2 cases 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); 4 cases with Simon Broome possible/definite FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 1 case with DLCN ≥ 6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 2 cases with Simon Broome possible/definite FH from GeneDx Inc.
PS3_Moderate			PMID: 2088165 - Level 2 assay - Homozygous patients' fibroblasts, 125I-LDL assays: <2% LDLR activity.
PP4			Variant meets PM2. Identified in 4 FH case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with clinical Simon Broome possible/definite FH, after alternative causes of high cholesterol were excluded.

PM2			PopMax MAF = 0.000008826 (0.0008826%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1).
PM4			Variant meets PM2 and is in frame deletion.
Not Met criteria codes			
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
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
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
PP3			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
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM5			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
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BS4			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

Curation History 		
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