

Variant: *NM_000527.5(LDLR):c.1048C>T (p.Arg350Ter)*

Version: 1.0

CA031387 [↗](#)

226342 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: bf884b04-1e33-40c4-997c-e13fd8755871

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HGVS expressions

NM_000527.5(LDLR):c.1048C>T (p.Arg350Ter)

NM_000527.5:c.1048C>T

NC_000019.10:g.11110759C>T

CM000681.2:g.11110759C>T

NC_000019.9:g.11221435C>T

CM000681.1:g.11221435C>T

NC_000019.8:g.11082435C>T

NG_009060.1:g.26379C>T

ENST00000252444.10:c.1306C>T

ENST00000559340.2:c.1048C>T

ENST00000560467.2:c.941-755C>T

ENST00000558518.6:c.1048C>T

ENST00000252444.9:c.1302C>T

ENST00000455727.6:c.544C>T

ENST00000535915.5:c.925C>T

ENST00000545707.5:c.667C>T

ENST00000557933.5:c.1048C>T

ENST00000558013.5:c.1048C>T

ENST00000558518.5:c.1048C>T

ENST00000560173.1:n.47C>T

ENST00000560467.1:c.541-755C>T

NM_000527.4:c.1048C>T

NM_001195798.1:c.1048C>T

NM_001195799.1:c.925C>T

NM_001195800.1:c.544C>T

NM_001195803.1:c.667C>T

NM_001195798.2:c.1048C>T

NM_001195799.2:c.925C>T

NM_001195800.2:c.544C>T

NM_001195803.2:c.667C>T

Pathogenic

Met criteria codes **5**

PP1_Strong

PS4

PP4

PM2

PVS1

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 2

[Criteria Specifications for this VCEP](#)

PS3

BS4

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1048C>T(p.Arg350Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PVS1, PP4, PS4, PP1_Strong) 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: PopMax MAF = 0.00005 in East Asian population in gnomAD (gnomAD v2.1.1). PVS1: The variant causing a premature stop codon amino-terminal of amino acid 830 (NM_000527.5:p.Lys830). PP4: This variant meets PM2 and is identified in >1 index case who met clinical criteria for FH after alternative causes for high cholesterol were excluded. PS4: Variant meets PM2 and is identified in 23 unrelated index cases fulfil clinical criteria for FH. Ten cases fulfil Simon Broome FH criteria (5 cases from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies , APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; 3 cases from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, PMID 22698793; 1 case from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 1 case from Division of Cardiology, Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan (PMID 20538126)). Thirteen cases fulfil DLCN criteria (10 cases from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA; 1 case each from Lipid Clinic, Fundación Jiménez Díaz, Madrid, Spain (PMID 19318025); Department of Genetics and Pathology, Pomeranian Medical Academy, Szczecin, Poland (PMID 9654205); GeneDx). PP1_Strong: Variant segregates with FH phenotype in 20 informative meioses from at least 11 families. Fifteen affected relatives tested positive for the variant from at least 6 families from 4 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; GeneDx; Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA). Five unaffected relatives tested negative for the variant from 5 families (Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA).

Met criteria codes

PP1_Strong



Variant segregates with FH phenotype in 20 informative meioses from at least 11 families. Fifteen affected relatives tested positive for the variant from at least 6 families from 4 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; GeneDx; Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA). Five unaffected relatives tested negative for the variant from 5 families (Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA).

PS4



Variant meets PM2 and is identified in 23 unrelated index cases fulfil clinical criteria for FH. Ten cases fulfil Simon Broome FH criteria (5 cases from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies , APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; 3 cases from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, PMID 22698793; 1 case from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 1 case from Division of Cardiology, Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan (PMID 20538126)). Thirteen cases fulfil DLCN criteria (10 cases from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA; 1 case each from Lipid Clinic, Fundación Jiménez Díaz, Madrid, Spain (PMID 19318025); Department of Genetics and Pathology, Pomeranian Medical Academy, Szczecin, Poland (PMID 9654205); GeneDx).

PP4



This variant meets PM2 and is identified in >1 index case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.

PM2			PopMax MAF = 0.00005 in East Asian population in gnomAD (gnomAD v2.1.1).
PVS1			The variant causing a premature stop codon amino-terminal of amino acid 830 (NM_000527.5:p.Lys830).
Not Met criteria codes			
PS3			Functional data is not available.
BS4			Variant does not segregate with FH phenotype in 3 relatives in 3 families from 3 different labs. Three affected relatives tested negative for the variant, 1 case each from: Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation; Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA; Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. However, there is no instance where unaffected family member carry the variant. Therefore BS4 is not met.

Curation History 			
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