

Variant: NM_000527.5(LDLR):c.551G>A (p.Cys184Tyr)

Version: 1.4

CA023721 [↗](#)

3739 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 2f05ce00-876a-478f-b36c-26dfc18742c8

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HGVS expressions

NM_000527.5:c.551G>A

NM_000527.5(LDLR):c.551G>A (p.Cys184Tyr)

NC_000019.10:g.11105457G>A

CM000681.2:g.11105457G>A

NC_000019.9:g.11216133G>A

CM000681.1:g.11216133G>A

NC_000019.8:g.11077133G>A

NG_009060.1:g.21077G>A

ENST00000252444.10:c.809G>A

ENST00000559340.2:c.551G>A

ENST00000560467.2:c.551G>A

ENST00000558518.6:c.551G>A

ENST00000252444.9:c.805G>A

ENST00000455727.6:c.314-1935G>A

ENST00000535915.5:c.428G>A

ENST00000545707.5:c.314-1108G>A

ENST00000557933.5:c.551G>A

ENST00000558013.5:c.551G>A

ENST00000558518.5:c.551G>A

ENST00000560467.1:c.151G>A

NM_000527.4:c.551G>A

NM_001195798.1:c.551G>A

NM_001195799.1:c.428G>A

NM_001195800.1:c.314-1935G>A

NM_001195803.1:c.314-1108G>A

NM_001195798.2:c.551G>A

NM_001195799.2:c.428G>A

NM_001195800.2:c.314-1935G>A

NM_001195803.2:c.314-1108G>A

Pathogenic

Met criteria codes **7**

PP1_Strong

PS3

PS4

PP3

PP4

PM2

PM1

Not Met criteria codes **6**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BS1

BS4

BS3

BA1

PS2

PM6

 Criteria Specifications for this VCEP

Evidence Links

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Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.551G>A (p.Cys184Tyr) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS3, PS4, PP1_Strong, PM1, PM2, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 28 January 2022. The supporting evidence is as follows: PM2 - PopMax MAF = 0.00019 (0.019%) in European Non-Finnish genomes (gnomAD v2.1.1). PP3 - REVEL = 0.85, which is above the threshold of 0.75. PM1 - variant meets PM2 and is located in exon 4. PS3 - Level 1 functional studies performed - Heterologous cells (CHO), FACS: Result of normal cell surface LDLR (100%), 4% LDL binding and 18% LDL uptake, compared to wild-type (PMID: 34167030). PS4 - Variant meets PM2 and is identified in at least 22 unrelated index cases who fulfill clinical criteria for FH (8 cases with SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 6 cases with DLCN criteria from Robarts Research Institute; 5 cases with DLCN criteria from PathWest Laboratory Medicine WA; 2 cases with DLCN criteria from Color; 1 case with MEDPED criteria from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory). PP1_Strong - Variant segregates with phenotype in 14 informative meioses from 8 families (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge - 4 families: 8 relatives affected with the variant and 1 relative unaffected without the variant; Robarts Research Institute - 2 families: 2 relatives affected with the variant; PathWest Laboratory Medicine WA - 2 families: 2 affected relative with the variant and 1 unaffected relative without the variant) PP4 - variant meets PM2 and is identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.

Met criteria codes

PP1_Strong			Variant segregates with phenotype in 14 informative meioses from 8 families (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – 4 families: 8 relatives affected with the variant and 1 relative unaffected without the variant; Robarts Research Institute – 2 families: 2 relatives affected with the variant; PathWest Laboratory Medicine WA – 2 families: 2 affected relative with the variant and 1 unaffected relative without the variant)
PS3			Level 1 functional studies performed - Heterologous cells (CHO), FACS: Result of normal cell surface LDLR (100%), 4% LDL binding and 18% LDL uptake, compared to wild-type (PMID: 34167030).
PS4			Variant meets PM2 and is identified in at least 22 unrelated index cases who fulfill clinical criteria for FH (8 cases with SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 6 cases with DLCN criteria from Robarts Research Institute; 5 cases with DLCN criteria from PathWest Laboratory Medicine WA; 2 cases with DLCN criteria from Color; 1 case with MEDPED criteria from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory).
PP3			REVEL=0.854
PP4			Variant meets PM2 and is identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
PM2			PopMax MAF = 0.00019 (0.019%) in European Non-Finnish genomes (gnomAD v2.1.1).
PM1			Variant meets PM2 and is located in exon 4.

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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