

Variant: *NM_000527.5(LDLR):c.661G>T (p.Asp221Tyr)*

Version: 1.0

CA10585046 [↗](#)

251356 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 0c078f82-bf62-4550-a36c-aa3db8e89b02

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HGVS expressions

NM_000527.5(LDLR):c.661G>T (p.Asp221Tyr)

NM_000527.5:c.661G>T

NC_000019.10:g.11105567G>T

CM000681.2:g.11105567G>T

NC_000019.9:g.11216243G>T

CM000681.1:g.11216243G>T

NC_000019.8:g.11077243G>T

NG_009060.1:g.21187G>T

ENST00000252444.10:c.919G>T

ENST00000559340.2:c.661G>T

ENST00000560467.2:c.661G>T

ENST00000558518.6:c.661G>T

ENST00000252444.9:c.915G>T

ENST00000455727.6:c.314-1825G>T

ENST00000535915.5:c.538G>T

ENST00000545707.5:c.314-998G>T

ENST00000557933.5:c.661G>T

ENST00000558013.5:c.661G>T

ENST00000558518.5:c.661G>T

ENST00000560467.1:c.261G>T

NM_000527.4:c.661G>T

NM_001195798.1:c.661G>T

NM_001195799.1:c.538G>T

NM_001195800.1:c.314-1825G>T

NM_001195803.1:c.314-998G>T

NM_001195798.2:c.661G>T

NM_001195799.2:c.538G>T

NM_001195800.2:c.314-1825G>T

NM_001195803.2:c.314-998G>T

Pathogenic

Met criteria codes **7**

PP1_Strong

PS3

PS4_Moderate

PP3

PP4

PM2

PM1

Not Met criteria codes **19**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

PS1PS2PP2BA1PM6BS1BS4BS3PM3PM5PM4BS2BP5BP7BP4BP3BP1BP2PVS1

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.661G>T (p.Asp221Tyr) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PP1_Strong, PS3, PM1, PM2, PS4_Moderate, PP3 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 7 informative meioses in at least 4 families from different labs (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)): 6 affected family members have the variant and 1 non-affected family members do not have the variant. PS3 - PMID: 34167030 - Level 1 assay - Heterologous cells (CHO), FACS: Normal cell surface LDLR, 5% LDL-LDLR binding and 8% uptake. PM1 - Missense at codon 221. PM2 is Met and it is exon 4. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1). PS4_moderate - Variant meets PM2. Variant identified in 9 unrelated index cases (1 case with Simon-Broome published in PMID 32331935; 2 cases with Simon Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 6 cases with DLCN/Simon Broome criteria from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)). PP3 - REVEL = 0.978. PP4 - Variant meets PM2. Variant identified in 9 unrelated index cases (1 case with Simon-Broome published in PMID 32331935; 2 cases with Simon Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 6 cases with DLCN/Simon Broome criteria from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)).

Met criteria codes

PP1_Strong			Variant segregates with phenotype in 7 informative meioses in at least 4 families from different labs (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)): 6 affected family members have the variant and 1 non-affected family members do not have the variant.
PS3			PMID: 34167030 - Level 1 assay - Heterologous cells (CHO), FACS: Normal cell surface LDLR, 5% LDL-LDLR binding and 8% uptake.
PS4_Moderate			Variant meets PM2. Variant identified in 9 unrelated index cases (1 case with Simon-Broome published in PMID 32331935; 2 cases with Simon Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 6 cases with DLCN/Simon Broome criteria from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)).
PP3			REVEL = 0.978
PP4			

Variant meets PM2. Variant identified in 9 unrelated index cases (1 case with Simon-Broome published in PMID 32331935; 2 cases with Simon Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 6 cases with DLCN/Simon Broome criteria from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière).			
PM2			This variant is absent from gnomAD (gnomAD v2.1.1)
PM1			Missense at codon 221. PM2 is Met and it is exon 4
Not Met criteria codes			
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
BA1			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
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
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			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

BS2			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
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

Curation History 		
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