

Variant: *NM_000527.5(LDLR):c.2120A>T (p.Asp707Val)*

Version: 1.0

CA10585780 [↗](#)

252227 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c0d3fbae-235c-4b00-b3f7-a931f508370b

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HGVS expressions

NM_000527.5(LDLR):c.2120A>T (p.Asp707Val)

NM_000527.5:c.2120A>T

NC_000019.10:g.11120502A>T

CM000681.2:g.11120502A>T

NC_000019.9:g.11231178A>T

CM000681.1:g.11231178A>T

NC_000019.8:g.11092178A>T

NG_009060.1:g.36122A>T

ENST00000252444.10:c.2378A>T

ENST00000559340.2:c.*189A>T

ENST00000560467.2:c.2000A>T

ENST00000558518.6:c.2120A>T

ENST00000252444.9:c.2374A>T

ENST00000455727.6:c.1616A>T

ENST00000535915.5:c.1997A>T

ENST00000545707.5:c.1606+269A>T

ENST00000557933.5:c.2120A>T

ENST00000558013.5:c.2120A>T

ENST00000558518.5:c.2120A>T

NM_000527.4:c.2120A>T

NM_001195798.1:c.2120A>T

NM_001195799.1:c.1997A>T

NM_001195800.1:c.1616A>T

NM_001195803.1:c.1606+269A>T

NM_001195798.2:c.2120A>T

NM_001195799.2:c.1997A>T

NM_001195800.2:c.1616A>T

NM_001195803.2:c.1606+269A>T

Uncertain Significance

Met criteria codes **4**

PS4_Supporting PP3 PP4 PM2

Not Met criteria codes **16**

PVS1 BS1 BS4 BS3 BP4
BP3 BP1 BP5 BP7 PS3 BA1

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.2120A>T (p.Asp707Val) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.964. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 3 unrelated index cases who fulfill criteria for FH, after alternative causes of high cholesterol were excluded (2 cases with DLCN score ≥ 6 from the Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; 1 case with DLCN score ≥ 6 from Robarts Research Institute, Canada).

Met criteria codes

PS4_Supporting			PS4_Supporting: Variant meets PM2 and is identified in at least 3 index cases who fulfill criteria for FH, after alternative causes of high cholesterol were excluded: 2 unrelated index cases with DLCN criteria ≥ 6 from the Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (Hôpital de la Pitié-Salpêtrière); plus, 1 index case who fulfills clinical DLCN criteria for FH (DLCN ≥ 6) from Robarts Research Institute.
PP3			PP3: REVEL = 0.964. It is above 0.75, so PP3 is met.
PP4			PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills clinical DLCN criteria for FH (DLCN ≥ 6) from Robarts Research Institute, after alternative causes of high cholesterol were excluded.
PM2			- PM2: This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

PVS1			This variant is misense, therefore PVS1 is not met.
BS1			This variant is absent from gnomAD (gnomAD v2.1.1), therefore BS1 is not met.
BS4			not met, (no information of several index cases or segregation data/cases in different families) only, data from one family from the Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (Hôpital de la Pitié-Salpêtrière)

BS3			not met (no information or reports of functional data).
BP4			BP4: REVEL = 0.964, not bellow 0.50. Therefore, BP4 is not met.
BP3			N/A according to FH VCEP Guidelines
BP1			N/A according to FH VCEP Guidelines
BP5			N/A according to FH VCEP Guidelines
BP7			This variant is misense, therefore BP7 is not met.
PS3			not met (no information or reports of functional data).
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), therefore BA1 is not met.
PP1			not met, (no information of several index cases or segregation data/cases in different families) only, data from one family from the Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (Hôpital de la Pitié-Salpêtrière)
PP2			N/A according to FH VCEP Guidelines
PM1			Variant is not located in exon 4. and does not affect an higly conserved Cys residue.
PM5			NM_000527.5(LDLR):c.2119G>T (p.Asp707Tyr) (ClinVar ID: 252226) considered as Likely Pathogenic by these guidelines NM_000527.5(LDLR):c.2119G>A (p.Asp707Asn) (ClinVar ID: 252225) considered as VUS by these guidelines.
PM4			This variant is misense, therefore PM4 is not met.

Curation History 



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