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Variant: NM_000527.5(LDLR):c.2050G>A (p.Ala684Thr)

Version: 1.0

CA038311

252192 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: c82cc57e-8c67-461c-aa6b-22e0178cec0a
Approved on: 2025/2/20
Published on: 2025/6/17

HGVS expressions

NM_000527.5(LDLR):c.2050G>A (p.Ala684Thr)
NM_000527.5:c.2050G>A
NC_000019.10:g.11120432G>A
CM000681.2:g.11120432G>A
NC_000019.9:g.11231108G>A
CM000681.1:g.11231108G>A
NC_000019.8:g.11092108G>A
NG_009060.1:g.36052G>A
ENST00000252444.10:c.2308G>A
ENST00000559340.2:c.*119G>A
ENST00000560467.2:c.1930G>A
ENST00000558518.6:c.2050G>A
ENST00000252444.9:c.2304G>A
ENST00000455727.6:c.1546G>A
ENST00000535915.5:c.1927G>A
ENST00000545707.5:c.1606+199G>A
ENST00000557933.5:c.2050G>A
ENST00000558013.5:c.2050G>A
ENST00000558518.5:c.2050G>A
NM_000527.4:c.2050G>A
NM_001195798.1:c.2050G>A
NM_001195799.1:c.1927G>A
NM_001195800.1:c.1546G>A
NM_001195803.1:c.1606+199G>A
NM_001195798.2:c.2050G>A
NM_001195799.2:c.1927G>A
NM_001195800.2:c.1546G>A
NM_001195803.2:c.1606+199G>A

Uncertain Significance

Met criteria codes 4

PP1 PP3 PP4 PM2

Not Met criteria codes 2

PS4 PM5

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2*

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.2050G>A (p.Ala684Thr) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP1, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 20 February 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.01337% in East Asian exomes/genomes (gnomAD v4.1.0). PP3: REVEL score = 0.807. PP4: 1 case with DLCN>=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, France. PP1: Variant segregates with FH phenotype in 2 informative meioses from 1 family (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, France): 1 affected family member has the variant and 1 non-affected family member does not have the variant.

Met criteria codes

PP1	✔	This variant has been reported to segregate with FH phenotype in 2 informative meioses from 1 family (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)). Proband Dutch lipid clinic network >=6; 1 family member positive for variant with LDL-C >75th percentile and 1 family member negative for variant with LDL-C <50th percentile.
PP3	✔	REVEL score = 0.807.
PP4	✔	One patient 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) fulfils DLCN >=6
PM2	✔	PopMax MAF = 0.0001337 (0.01337%) in East Asian exomes/genomes (gnomAD v4.1.0).

Not Met criteria codes

PS4	✖	Besides the variant was identified in 1 FH case Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), the same variant was also identified in a patient reported PMID 11005141, however, the patient did not fulfill the criteria for a definite FH diagnosis.
PM5	✖	No missense variants at the same codon predict a different amino acid change classified as pathogenic.

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.2050G>A (p.Ala...	Uncertain Significance	Hypercholesterolemia, Familial	2025-06-17	1.0	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR

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