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Variant: NM_000527.5(LDLR):c.1987+10G>T

Version: 1.0

CA037694

252149 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: cf7b231e-0673-441b-a83b-170433c8ce09
Approved on: 2025/3/24
Published on: 2025/3/24

HGVS expressions

NM_000527.5:c.1987+10G>T
NM_000527.5(LDLR):c.1987+10G>T
NC_000019.10:g.11120243G>T
CM000681.2:g.11120243G>T
NC_000019.9:g.11230919G>T
CM000681.1:g.11230919G>T
NC_000019.8:g.11091919G>T
NG_009060.1:g.35863G>T
ENST00000252444.10:c.2245+10G>T
ENST00000559340.2:c.*56+10G>T
ENST00000560467.2:c.1867+10G>T
ENST00000558518.6:c.1987+10G>T
ENST00000252444.9:c.2241+10G>T
ENST00000455727.6:c.1483+10G>T
ENST00000535915.5:c.1864+10G>T
ENST00000545707.5:c.1606+10G>T
ENST00000557933.5:c.1987+10G>T
ENST00000558013.5:c.1987+10G>T
ENST00000558518.5:c.1987+10G>T
ENST00000559340.1:c.568+10G>T
NM_000527.4:c.1987+10G>T
NM_001195798.1:c.1987+10G>T
NM_001195799.1:c.1864+10G>T
NM_001195800.1:c.1483+10G>T
NM_001195803.1:c.1606+10G>T
NM_001195798.2:c.1987+10G>T
NM_001195799.2:c.1864+10G>T
NM_001195800.2:c.1483+10G>T
NM_001195803.2:c.1606+10G>T

Uncertain Significance

Met criteria codes 4

PS4_Supporting BP4 PP4 PM2

Not Met criteria codes 14

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

BA1 BS2 BS1 BS4 BS3 BP3 BP1 PVS1 BP7 PS3 PP1 PP2 PP3 PM4

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.1987+10G>T variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP4, PS4_Supporting and BP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 24 March 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.00008220 (0.00822%) in Non-Finnish European (gnomAD v4.1.0). PS4_Supporting, PP4: Variant meets PM2 and is identified in 2 unrelated cases who fulfill Simon Broome criteria for possible FH from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France. BP4: No REVEL, splicing evaluation required. SpliceAI: acceptor loss = 0.01, donor loss = 0.04. Variant is not predicted to alter splicing.

Met criteria codes

PS4_Supporting	✔	Variant meets PM2 and is identified in at least 2 index cases who fulfill criteria for FH (SB possible), after alternative causes of high cholesterol were excluded: 2 index cases Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)
BP4	✔	No REVEL, splicing evaluation required. Functional data on splicing not available, the variante not on limits. Variant outside the limits considered to alter splicing, and therefore BP4 is considered as met. (SlipeAI results - Acceptor Loss 0.01 and Donor Loss 0.04)
PP4	✔	Variant meets PM2 and is identified in at least 1 index case fulfilling FH criteria (SB possible), after alternative causes of high cholesterol were excluded, 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	✔	PopMax MAF = 0.0000822 (0.00822%) in European (non-Finnish) (gnomAD v4.0). PM2 is met since PopMax MAF<0.02%

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	not met, (no information of index cases or report of segregation data/cases).
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS4		✖	not met, (no information of index cases or report of segregation data/cases).
BS3		✖	not met (no information or reports of functional data).
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
PVS1		✖	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
PS3		✖	not met (no information or reports of functional data).
PP1		✖	not met, (no information of index cases or report of segregation data/cases).
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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