

Variant: NM_000527.5(LDLR):c.1958_1959delinsCC
(p.Val653Ala)

Version: 1.0

CA2322775423 [↗](#)

1008168 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))
Condition: hypercholesterolemia, familial ([MONDO:0007750](#))
Inheritance Mode: Semidominant inheritance
UUID: 1cf991f6-8acb-487b-be82-4115fea5b23a
Approved on: 2024/2/23
Published on: 2025/9/15

HGVS expressions

NM_000527.5:c.1958_1959delinsCC
NM_000527.5(LDLR):c.1958_1959delinsCC (p.Val653Ala)
NC_000019.10:g.11120204_11120205delinsCC
CM000681.2:g.11120204_11120205delinsCC
NC_000019.9:g.11230880_11230881delinsCC
CM000681.1:g.11230880_11230881delinsCC
NC_000019.8:g.11091880_11091881delinsCC
NG_009060.1:g.35824_35825delinsCC
ENST00000252444.10:c.2216_2217delinsCC
ENST00000559340.2:c.*27_*28delinsCC
ENST00000560467.2:c.1838_1839delinsCC
ENST00000558518.6:c.1958_1959delinsCC
ENST00000252444.9:c.2212_2213delinsCC
ENST00000455727.6:c.1454_1455delinsCC
ENST00000535915.5:c.1835_1836delinsCC
ENST00000545707.5:c.1577_1578delinsCC
ENST00000557933.5:c.1958_1959delinsCC
ENST00000558013.5:c.1958_1959delinsCC
ENST00000558518.5:c.1958_1959delinsCC
ENST00000559340.1:c.539_540delinsCC
NM_000527.4:c.1958_1959delinsCC
NM_001195798.1:c.1958_1959delinsCC
NM_001195799.1:c.1835_1836delinsCC
NM_001195800.1:c.1454_1455delinsCC
NM_001195803.1:c.1577_1578delinsCC
NM_001195798.2:c.1958_1959delinsCC
NM_001195799.2:c.1835_1836delinsCC
NM_001195800.2:c.1454_1455delinsCC
NM_001195803.2:c.1577_1578delinsCC

Uncertain Significance

Met criteria codes 1

PM2

Not Met criteria codes 6

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

PM5

PS3

PS4

BP4

PP3

PP4

Evidence Links

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- Criteria Specification Information
- 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.1958_1959delinsCC (p.Val653Ala) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence code PM2 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: The multi-nucleotide variant 19-1230880-TT-CC is observed once in at least 251454 total alleles from gnomAD (gnomAD v2.1.1). PopMax MAF for 19-11230880-T-C (NM_000527.5 (LDLR):c.1958T>C (p.Val653Ala) (CA305302665) is 0.00009921 (1/10080 alleles) in Ashkenazi Jewish population (gnomAD v2.1.1), whereas 19-11230881-T-C (NM_000527.5 (LDLR):c.1959T>C (p.Val653=) (ClinVar ID 252131) is a common variant with Grpmax FAF of 0.5225 (gnomAD v2.1.1).

Met criteria codes

PM2	i	✓	The multi-nucleotide variant 19-1230880-TT-CC is observed once in at least 251454 total alleles from gnomAD (gnomAD v2.1.1). PopMax MAF for 19-11230880-T-C (NM_000527.5 (LDLR):c.1958T>C (p.Val653Ala) (CA305302665) is 0.00009921 (1/10080 alleles) in Ashkenazi Jewish population (gnomAD v2.1.1), whereas 19-11230881-T-C (NM_000527.5 (LDLR):c.1959T>C (p.Val653=) (ClinVar ID 252131) is a common variant with Grpmax FAF of 0.5225 (gnomAD v2.1.1).
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Not Met criteria codes

PM5	i	✗	Three other missense variants in the same codon: NM_000527.5 (LDLR):c.1958T>G (p.Val653Gly) (ClinVar ID 252130), classified as VUS by these guidelines; NM_000527.5 (LDLR):c.1957G>T (p.Val653Phe) (ClinVar ID 252129), classified as VUS by these guidelines; NM_000527.5 (LDLR):c.1957G>A (p.Val653Ile) (ClinVar ID 628891), classified as VUS by these guidelines, therefore PM5 is not met.
PS3	i	✗	Functional data not available.
PS4	i	✗	Clinical data not available.
BP4	i	✗	REVEL score for NM_000527.5 (LDLR):c.1958_1959delinsCC (p.Val653Ala) is not available; REVEL score for NM_000527.5 (LDLR):c.1958T>C (p.Val653Ala) is 0.546. Splicing evaluation for c.1958_1959delinsCC performed. MES: A) variant not on limits. B) Variant not on limit creating de novo acceptor; variant is on limit however does not create GT. C) there is not a GT nearby. Variant is not predicted to alter splicing, and this result is confirmed by SpliceAI.
PP3	i	✗	

REVEL score for NM_000527.5 (LDLR):c.1958_1959delinsCC (p.Val653Ala) is not available; REVEL score for NM_000527.5 (LDLR):c.1958T>C (p.Val653Ala) is 0.546. Splicing evaluation for c.1958_1959delinsCC performed. MES: A) variant not on limits. B) Variant not on limit creating de novo acceptor; variant is on limit however does not create GT. C) there is not a GT nearby. Variant is not predicted to alter splicing, and this result is confirmed by SpliceAI.

PP4



Clinical data not available.

Curation History [↗](#)

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