

Variant: *NM_000527.5(LDLR):c.1463T>G (p.Ile488Ser)*

Version: 1.0

CA10585468 [↗](#)

251858 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 1149b986-2c29-48b7-89e4-5188e29d9620

Approved on: 2023/6/23

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HGVS expressions

NM_000527.5(LDLR):c.1463T>G (p.Ile488Ser)

NM_000527.5:c.1463T>G

NC_000019.10:g.11113639T>G

CM000681.2:g.11113639T>G

NC_000019.9:g.11224315T>G

CM000681.1:g.11224315T>G

NC_000019.8:g.11085315T>G

NG_009060.1:g.29259T>G

ENST00000252444.10:c.1721T>G

ENST00000559340.2:c.1463T>G

ENST00000560467.2:c.1343T>G

ENST00000558518.6:c.1463T>G

ENST00000252444.9:c.1717T>G

ENST00000455727.6:c.959T>G

ENST00000535915.5:c.1340T>G

ENST00000545707.5:c.1082T>G

ENST00000557933.5:c.1463T>G

ENST00000558013.5:c.1463T>G

ENST00000558518.5:c.1463T>G

ENST00000559340.1:c.184T>G

NM_000527.4:c.1463T>G

NM_001195798.1:c.1463T>G

NM_001195799.1:c.1340T>G

NM_001195800.1:c.959T>G

NM_001195803.1:c.1082T>G

NM_001195798.2:c.1463T>G

NM_001195799.2:c.1340T>G

NM_001195800.2:c.959T>G

NM_001195803.2:c.1082T>G

Uncertain Significance

Met criteria codes **3**

PP3

PP4

PM2

Not Met criteria codes **19**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS3

PS4

BA1

PP1

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS3

BS2

BP7

BP4

BP2

PVS1

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.1463T>G (p.Ile488Ser) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes PM2, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 June 2023. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.905. PP4: Variant meets PM2 and is identified in at least 1 FH index case with definite FH by Simon Broome criteria from PMID 20236128 (Taylor et al., 2010), UK, after alternative causes of high cholesterol were excluded.

Met criteria codes

PP3			REVEL = 0.905. It is above 0.75, so PP3 is Met.
PP4			Variant meets PM2 and is identified in at least 1 FH index case with SB criteria of definite FH from UK (PMID: 20236128), after alternative causes of high cholesterol were excluded, so PP4 is Met.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met.

Not Met criteria codes

PS1			No more missense variants that lead to the same amino acid change, so PS1 is Not Met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.
PS3			There are no functional studies reported for this variant, so PS3 is not met.
PS4			Variant meets PM2 and is identified in only index case with SB criteria of definite FH from UK (PMID: 20236128), after alternative causes of high cholesterol were excluded, so PS4 is not met.
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), so BA1 is not met.
PP1			Segregation data not reported, so PP1 is Not Met.
PM1			Variant meets PM2 but is not located in exon 4 or alters a cysteine residue, so PM1 is Not Met.

PM3		✖	Not observed in trans with other LP/P variants, so PM3 is Not Met.
PM5		✖	2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1463T>C (p.Ile488Thr) (ClinVar ID 251857) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.1463T>A (p.Ile488Asn) (ClinVar ID 251856) - Likely pathogenic by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4		✖	Variant meets PM2 and is missense, so PM4 is Not Met.
PM6		✖	de novo occurrence data not reported, so PM6 is Not Met.
BS1		✖	This variant is absent from gnomAD (gnomAD v2.1.1), so BS1 is not met.
BS4		✖	Lack of segregation data not reported, so BS4 is Not Met.
BS3		✖	There are no functional studies reported for this variant, so BS3 is not met.
BS2		✖	Case-control data not reported, so BS2 is Not Met.
BP7		✖	Variant is not synonymous, so BP7 is Not Met.
BP4		✖	REVEL = 0.905. It is not below 0.50, so BP4 is Not Met.
BP2		✖	Not observed in trans with other LP/P variants, so BP2 is Not Met.
PVS1		✖	Variant is missense, so PVS1 is Not Met.

Curation History 		
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