

Variant: NM_000527.5(LDLR):c.1463T>A (p.Ile488Asn)

Version: 1.0

CA10585466 [↗](#)

251856 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 5e75692c-3c39-4f57-a4d7-31e4981e73d2

Approved on: 2023/6/23

Published on: 2025/6/30

HGVS expressions

NM_000527.5(LDLR):c.1463T>A (p.Ile488Asn)

NM_000527.5:c.1463T>A

NC_000019.10:g.11113639T>A

CM000681.2:g.11113639T>A

NC_000019.9:g.11224315T>A

CM000681.1:g.11224315T>A

NC_000019.8:g.11085315T>A

NG_009060.1:g.29259T>A

ENST00000252444.10:c.1721T>A

ENST00000559340.2:c.1463T>A

ENST00000560467.2:c.1343T>A

ENST00000558518.6:c.1463T>A

ENST00000252444.9:c.1717T>A

ENST00000455727.6:c.959T>A

ENST00000535915.5:c.1340T>A

ENST00000545707.5:c.1082T>A

ENST00000557933.5:c.1463T>A

ENST00000558013.5:c.1463T>A

ENST00000558518.5:c.1463T>A

ENST00000559340.1:c.184T>A

NM_000527.4:c.1463T>A

NM_001195798.1:c.1463T>A

NM_001195799.1:c.1340T>A

NM_001195800.1:c.959T>A

NM_001195803.1:c.1082T>A

NM_001195798.2:c.1463T>A

NM_001195799.2:c.1340T>A

NM_001195800.2:c.959T>A

NM_001195803.2:c.1082T>A

Likely Pathogenic

Met criteria codes **5**

PP1 PP3 PP4 PM2

PS4_Supporting

Not Met criteria codes **17**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

BS1

PM5

BP2

PS2

BS4

PM4

PVS1

PS3

BS3

BS2

BA1

PM1

BP7

PM6

PM3

BP4

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>A (p.Ile488Asn) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PS4_Supporting, PP1, 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 = 0.84. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 4 unrelated FH index cases (2 cases meeting Simon-Broome criteria from PMID 11668640 (García-García et al., 2001), Spain; 1 case meeting Simon-Broome criteria from PMID 10978268 (Bertolini et al., 2000), Italy; at least 1 case with definite FH by DLCN criteria from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583834.1)). PP1: Variant segregates with FH phenotype in at least 2 informative meiosis from 1 family from PMID 10978268 (Bertolini et al., 2000), Italy: 2 affected family members have the variant.

Met criteria codes

PP1			Variant segregates with FH phenotype in at least 2 informative meiosis from 1 family from Italy (PMID: 10978268): 2 affected family members have the variant, so PP1 is Met.
PP3			REVEL = 0.84. It is above 0.75, so PP3 is Met.
PP4			Variant meets PM2 and is identified in at least 4 unrelated index cases: 2 cases with Simon-Broome criteria from Spain (PMID: 11668640), 1 index case with Simon-Broome of possible/definite FH from Italy (PMID: 11668640) and at last 1 case with DLCN criteria of definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583834.1), after alternative causes of high cholesterol were excluded, so PS4_Supporting is Met.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met.
PS4_Supporting			Variant meets PM2 and is identified in at least 4 unrelated index cases: 2 cases with Simon-Broome criteria from Spain (PMID: 11668640), 1 index case with Simon-Broome of possible/definite FH from Italy (PMID: 11668640) and at last 1 case with DLCN criteria of definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583834.1), after alternative causes of high cholesterol were excluded, so PS4_Supporting 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.
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), so BA1 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.
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>G (p.Ile488Ser) (ClinVar ID 251858) - VUS 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.
BS2			Case-control data not reported, so BS2 is Not Met.
BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.84. 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 [↗](#)

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.