

Variant: *NM_000527.5(LDLR):c.977C>T (p.Ser326Phe)*

Version: 1.1

CA10585236 [↗](#)

251582 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 8b8d2602-1d5a-4183-a896-7fa1f17b6d6e

Approved on: 2022/1/28

Published on: 2022/7/11

HGVS expressions

NM_000527.5:c.977C>T

NM_000527.5(LDLR):c.977C>T (p.Ser326Phe)

NC_000019.10:g.11110688C>T

CM000681.2:g.11110688C>T

NC_000019.9:g.11221364C>T

CM000681.1:g.11221364C>T

NC_000019.8:g.11082364C>T

NG_009060.1:g.26308C>T

ENST00000252444.10:c.1235C>T

ENST00000559340.2:c.977C>T

ENST00000560467.2:c.941-826C>T

ENST00000558518.6:c.977C>T

ENST00000252444.9:c.1231C>T

ENST00000455727.6:c.473C>T

ENST00000535915.5:c.854C>T

ENST00000545707.5:c.596C>T

ENST00000557933.5:c.977C>T

ENST00000558013.5:c.977C>T

ENST00000558518.5:c.977C>T

ENST00000560467.1:c.541-826C>T

NM_000527.4:c.977C>T

NM_001195798.1:c.977C>T

NM_001195799.1:c.854C>T

NM_001195800.1:c.473C>T

NM_001195803.1:c.596C>T

NM_001195798.2:c.977C>T

NM_001195799.2:c.854C>T

NM_001195800.2:c.473C>T

NM_001195803.2:c.596C>T

Likely Pathogenic

Met criteria codes **4**

PP3 PP4 PM5 PM2

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

PVS1

BS1

BS4

BS3

BP4

BP3

BP1

BP2

BP5

BP7

PS1

PS2

PS3

PS4

BA1

PP1

PP2

PM1

PM3

PM4

PM6

Evidence Links 0

- [Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1](#)
- [PDF](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.977C>T (p.Ser326Phe) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PM5, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1016/j.gim.2021.09.012>). The supporting evidence is as follows: PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PM5 - There are 2 other missense variants in the same codon: (1) NM_000527.5(LDLR):c.977C>G (p.Ser326Cys) - 2 stars, Likely pathogenic in ClinVar; Pathogenic by these guidelines (FH VCEP training August 2020). (2) NM_000527.5(LDLR):c.976T>C (p.Ser326Pro) - 1 star, VUS in ClinVar; VUS by these guidelines (PM2, PM5, PP3) with no case data. There is 1 variant in the same codon classified as Pathogenic by these guidelines, so PM5 is met PP3 - REVEL = 0.937. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in 1 index case who fulfills SB criteria (clinical criteria according to PMID 8891383 (Chaves et al., 1996): TC and LDL-C over the 95th percentile corrected for age and sex, with TG not exceeding 200 mg/dl; plus two of the following: tendon xanthomata, premature coronary heart disease in the proband or in a first-degree relative, and hypercholesterolemic children in the family) from PMID 11668640 (García-García et al. 2001), Spain; so PP4 is met

Met criteria codes

PP3			REVEL = 0.937. It is above 0.75, so PP3 is met
PP4			variant meets PM2 and was identified in: - 1 index case who fulfills SB criteria (clinical criteria according to PMID 8891383 (Chaves et al., 1996): TC and LDL-C over the 95th percentile corrected for age and sex, with TG not exceeding 200 mg/dl; plus two of the following: tendon xanthomata, premature coronary heart disease in the proband or in a first-degree relative, and hypercholesterolemic children in the family) from PMID 11668640 (García-García et al. 2001); Spain -- so PP4 is met
PM5			There are 2 other missense variants in the same codon: (1) NM_000527.5(LDLR):c.977C>G (p.Ser326Cys) - 2 stars, Likely pathogenic in ClinVar - Pathogenic by these guidelines (FH VCEP training August 2020) (2) NM_000527.5(LDLR):c.976T>C (p.Ser326Pro) - 1 star, VUS in ClinVar - VUS by these guidelines (PM2, PM5, PP3) with no case data so PM5 is met
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met

Not Met criteria codes

BS2			variant not identified in normolipidemic individuals: not identified in 60 healthy controls from PMID 11668640, so not met
PVS1			variant is missense and not in initiation codon, so PVS1 is not applicable

BS1			This variant is absent from gnomAD (gnomAD v2.1.1), so BS1 is not met
BS4			no segregation data
BS3			There are no functional studies published for this variant
BP4			REVEL = 0.937. It is not below 0.50, so BP4 is not met
BP3			not applicable
BP1			not applicable
BP2			variant not identified in index cases with more than 1 variant
BP5			not applicable
BP7			variant is missense, so BP7 is not applicable
PS1			no other variant leads to the same amino acid change, so PS1 is not met
PS2			no de novo occurrence
PS3			There are no functional studies published for this variant
PS4			variant meets PM2 and was identified in: - 1 index case who fulfills SB criteria (clinical criteria according to PMID 8891383 (Chaves et al., 1996): TC and LDL-C over the 95th percentile corrected for age and sex, with TG not exceeding 200 mg/dl; plus two of the following: tendon xanthomata, premature coronary heart disease in the proband or in a first-degree relative, and hypercholesterolemic children in the family) from PMID 11668640 (García-García et al. 2001); Spain -- not enough, so PS4 is not met
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), so BA1 is not met
PP1			no segregation data
PP2			not applicable
PM1			variant meets PM2 and is missense, but it is not in exon 4 and does not alter Cys, so not met
PM3			variant not identified in index cases with more than 1 variant

