The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
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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

PP1 PP2 BA1 PM1 PM3
PM4 PM6 PVS1 BS2 BS1
BS4 BS3 PS1 PS2 PS3 PS4
BP5 BP7 BP4 BP3 BP1 BP2

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

PP1	✖	no segregation data
PP2	✖	not applicable

BA1	✖	This variant is absent from gnomAD (gnomAD v2.1.1), so BA1 is not met
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
PM4	✖	variant is missense, so PM4 is not applicable
PM6	✖	no de novo occurrence
PVS1	✖	variant is missense and not in initiation codon, so PVS1 is not applicable
BS2	✖	variant not identified in normolipidemic individuals: not identified in 60 healthy controls from PMID 11668640, so not met
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
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
BP5	✖	not applicable
BP7	✖	variant is missense, so BP7 is not applicable
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

Curation History

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