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.979C>T (p.His327Tyr)

Version: 1.3

CA030996

251583 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 1f1cd05c-e5a0-47d6-875e-1f9b4bd69505
Approved on: 2022/7/22
Published on: 2025/3/7

HGVS expressions

NM_000527.5(LDLR):c.979C>T (p.His327Tyr)
NM_000527.5:c.979C>T
NC_000019.10:g.11110690C>T
CM000681.2:g.11110690C>T
NC_000019.9:g.11221366C>T
CM000681.1:g.11221366C>T
NC_000019.8:g.11082366C>T
NG_009060.1:g.26310C>T
ENST00000252444.10:c.1237C>T
ENST00000559340.2:c.979C>T
ENST00000560467.2:c.941-824C>T
ENST00000558518.6:c.979C>T
ENST00000252444.9:c.1233C>T
ENST00000455727.6:c.475C>T
ENST00000535915.5:c.856C>T
ENST00000545707.5:c.598C>T
ENST00000557933.5:c.979C>T
ENST00000558013.5:c.979C>T
ENST00000558518.5:c.979C>T
ENST00000560467.1:c.541-824C>T
NM_000527.4:c.979C>T
NM_001195798.1:c.979C>T
NM_001195799.1:c.856C>T
NM_001195800.1:c.475C>T
NM_001195803.1:c.598C>T
NM_001195798.2:c.979C>T
NM_001195799.2:c.856C>T
NM_001195800.2:c.475C>T
NM_001195803.2:c.598C>T

Uncertain Significance

Met criteria codes 4

PP3 PP4 PM2 PS4_Supporting

Not Met criteria codes 22

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

BP4 BP3 BP1 BP2 BP5 BP7
PS1 PS2 PS3 PP1 PP2 PM6
PM1 PM3 PM5 PM4 PVS1
BA1 BS2 BS1 BS4 BS3

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

NM_000527.5(LDLR):c.979C>T (p.His327Tyr) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 22 July 2022. The supporting evidence is as follows: PM2 - Variant is found in South Asian (gnomAD v2.1.1 (Popmax MAF = 0.0004900 (0.049%), total alleles number = 15), gnomAD v4.0.0 (Popmax MAF = 0.0006492 (0.06492%), total alleles number = 56)). Variant is absent from other populations in gnomAD v2.1.1 and is found in only 1 case from Remaining population in gnomAD v4.0.0 (Popmax MAF = 0.00001656 (0.001656%)). We assume founder effect due to isolated occurrence in the South Asian population. For this reason, we excluded the SA population from PM2 assessment. PP3 - REVEL = 0.958. PP4 - Variant meets PM2 and is identified in at least one case who fufills clinical criteria for FH (see PS4 for details), after alternative causes of high cholesterol were excluded. PS4_Supporting - Variant meets PM2 and is identified in 3 index cases (1 case with DLCN criteria>=6 from Robarts Research Institute, Canada; 1 case with Simon-Broome criteria in PMID: 9259195 (Day et al., 1997), UK; 1 case with DLCN criteria>=6 in PMID: 11810272 (Fouchier et al., 2001), The Netherlands).

Met criteria codes

PP3	✔	REVEL = 0.958
PP4	✔	Variant meets PM2 and is identified in at least one case who fufills clinical criteria for FH (see PS4 for details), after alternative causes of high cholesterol were excluded.
PM2	✔	Variant is found in South Asian (gnomAD v2.1.1 (Popmax MAF = 0.0004900 (0.049%), total alleles number = 15), gnomAD v4.0.0 (Popmax MAF = 0.0006492 (0.06492%), total alleles number = 56)). Variant is absent from other populations in gnomAD v2.1.1 and is found in only 1 case from Remaining population in gnomAD v4.0.0 (Popmax MAF = 0.00001656 (0.001656%)). We assume founder effect due to isolated occurrence in the South Asian population. For this reason, we excluded the SA population from PM2 assessment.
PS4_Supporting	✔	Variant meets PM2 and is identified in 3 index cases (1 case with DLCN criteria>=6 from Robarts Research Institute, Canada; 1 case with Simon-Broome criteria in PMID: 9259195 (Day et al., 1997), UK; 1 case with DLCN criteria>=6 in PMID: 11810272 (Fouchier et al., 2001), The Netherlands).

Not Met criteria codes

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	2 other missense variants in the same codon: - NM_000527.5(LDLR):c.980A>C (p.His327Pro) (ClinVar ID 918325) - Uncertain significance - insufficient evidence by these guidelines - NM_000527.5(LDLR):c.981C>A (p.His327Gln) (ClinVar ID 403665) - Uncertain significance - insufficient evidence by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.979C>T (p.His3…	Uncertain Significance	Hypercholesterolemia, Familial	2025-03-07	1.3	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR
View	NM_000527.5(LDLR):c.979C>T (p.His3…	Uncertain Significance	Hypercholesterolemia, Familial	2025-03-07	1.2	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR
View	NM_000527.5(LDLR):c.979C>T (p.His3…	Uncertain Significance	Hypercholesterolemia, Familial	2025-03-07	1.1	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR
View	NM_000527.5(LDLR):c.979C>T (p.His3…	Uncertain Significance	Hypercholesterolemia, Familial	2023-05-01	1.0	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR

owing 1 to 4 of 4 rows

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