

Variant: *NM_000527.5(LDLR):c.1576C>T (p.Pro526Ser)*

Version: 1.0

CA023533 [↗](#)

183120 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: fd1d2de9-2acd-4e4a-820d-02e74d6b59b6

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HGVS expressions

NM_000527.5(LDLR):c.1576C>T (p.Pro526Ser)

NM_000527.5:c.1576C>T

NC_000019.10:g.11113752C>T

CM000681.2:g.11113752C>T

NC_000019.9:g.11224428C>T

CM000681.1:g.11224428C>T

NC_000019.8:g.11085428C>T

NG_009060.1:g.29372C>T

ENST00000252444.10:c.1834C>T

ENST00000559340.2:c.1576C>T

ENST00000560467.2:c.1456C>T

ENST00000558518.6:c.1576C>T

ENST00000252444.9:c.1830C>T

ENST00000455727.6:c.1072C>T

ENST00000535915.5:c.1453C>T

ENST00000545707.5:c.1195C>T

ENST00000557933.5:c.1576C>T

ENST00000558013.5:c.1576C>T

ENST00000558518.5:c.1576C>T

ENST00000559340.1:c.297C>T

NM_000527.4:c.1576C>T

NM_001195798.1:c.1576C>T

NM_001195799.1:c.1453C>T

NM_001195800.1:c.1072C>T

NM_001195803.1:c.1195C>T

NM_001195798.2:c.1576C>T

NM_001195799.2:c.1453C>T

NM_001195800.2:c.1072C>T

NM_001195803.2:c.1195C>T

Uncertain Significance

Met criteria codes **4**

PS4_Supporting

PP3

PP4

PM2

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

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

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.1576C>T (p.Pro526Ser) variant is classified as variant of Uncertain significance for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4 and PS4_Supportive) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PM2 - PopMax MAF = 0.00002326 (0.002%) in European-non Finnish exomes (gnomAD v2.1.1). PP3 - REVEL: 0,952. PP4 - Variant meets PM2. Variant identified in 5 index cases (1 case from Color laboratory with Simon-Broome criteria; 1 case from GeneDx laboratory with Simon Broome criteria; 1 cases from University of British Columbia with DLCN criteria; 2 cases fulfilling Simeon-Broome criteria published in PMID: 9259195). PS4_supporting - Variant meets PM2. Variant identified in 5 index cases.

Met criteria codes

PS4_Supporting			Variant meets PM2. Variant identified in 5 index cases (1 case from Color laboratory with Simon-Broome criteria; 1 case from GeneDx laboratory with Simon Broome criteria; 1 cases from University of British Columbia with DLCN criteria; 2 cases fulfilling Simeon-Broome criteria published in PMID: 9259195).
PP3			REVEL: 0,952. Score is above 0,75.
PP4			Variant meets PM2. Variant identified in 5 index cases (1 case from Color laboratory with Simon-Broome criteria; 1 case from GeneDx laboratory with Simon Broome criteria; 1 cases from University of British Columbia with DLCN criteria; 2 cases fulfilling Simeon-Broome criteria published in PMID: 9259195).
PM2			PopMax MAF = 0.00002326 (0.002%) in European-non Finnish exomes (gnomAD v2.1.1). MAF is below 0.02%.

Not Met criteria codes

BA1			FAF = 0.000002920 (0.0002920%) in European-non Finnish exomes (gnomAD v2.1.1). FAF is not above 0.5%
BS2			No unaffected individuals identified with the variant.
BS1			FAF = 0.000002920 (0.0002920%) in European-non Finnish exomes (gnomAD v2.1.1). FAF is not above 0.2%
BS4			No family members tested. Not applicable.
BS3			PMID: 1301956 - Htz with unknown. Not applicable.

BP4			REVEL: 0.952. Score is not below 0,15.
BP3			Not applicable.
BP1			Not applicable.
BP2			Not identified in individuals with other variants.
PVS1			Missense variant. Not applicable.
BP5			Not applicable.
BP7			Missense variant. Not applicable.
PS1			No variant described that leads to the same amino acid change.
PS2			No de novo cases were identified.
PS3			PMID: 1301956 - Htz with unknown. Not applicable.
PP1			No family members tested. Not applicable.
PP2			Not applicable.
PM1			Missense at codon 526. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable.
PM3			Not identified in individuals with other variants.
PM5			No other missense variants classified as Pathogenic in the same codon. Four missense variants described in the same codon (accessed 19 August 2020): (1)NM_000527.5(LDLR):c.1576C>A (p.Pro526Thr) (ClinVar ID 251903) - classified as VUS by these guidelines; (2)NM_000527.4(LDLR):c.1577C>A (p.Pro526His) (ClinVar ID 496019) - classified as VUS by these guidelines; (3)NM_000527.4(LDLR):c.1577C>T (p.Pro526Leu) (ClinVar ID 431531) - classified as VUS by these guidelines; (4)NM_000527.5(LDLR):c.1577C>G (p.Pro526Arg) (ClinVar ID 251904) - classified as VUS by these guidelines.
PM4			Missense variant. Not applicable.
PM6			No de novo cases were identified.

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