

Variant: *NM_000527.5(LDLR):c.666C>T (p.Cys222=)*

Version: 1.0

CA505743509 [↗](#)

440592 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 98e5ae0b-297c-4df3-9153-87e79f07cc45

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HGVS expressions

NM_000527.5(LDLR):c.666C>T (p.Cys222=)

NM_000527.5:c.666C>T

NC_000019.10:g.11105572C>T

CM000681.2:g.11105572C>T

NC_000019.9:g.11216248C>T

CM000681.1:g.11216248C>T

NC_000019.8:g.11077248C>T

NG_009060.1:g.21192C>T

ENST00000252444.10:c.924C>T

ENST00000559340.2:c.666C>T

ENST00000560467.2:c.666C>T

ENST00000558518.6:c.666C>T

ENST00000252444.9:c.920C>T

ENST00000455727.6:c.314-1820C>T

ENST00000535915.5:c.543C>T

ENST00000545707.5:c.314-993C>T

ENST00000557933.5:c.666C>T

ENST00000558013.5:c.666C>T

ENST00000558518.5:c.666C>T

ENST00000560467.1:c.266C>T

NM_000527.4:c.666C>T

NM_001195798.1:c.666C>T

NM_001195799.1:c.543C>T

NM_001195800.1:c.314-1820C>T

NM_001195803.1:c.314-993C>T

NM_001195798.2:c.666C>T

NM_001195799.2:c.543C>T

NM_001195800.2:c.314-1820C>T

NM_001195803.2:c.314-993C>T

Uncertain Significance

Met criteria codes **3**

BP7

BP4

PM2

Not Met criteria codes **2**

PM1

PM5

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

- [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.666C>T (p.Cys222=) variant is classified as Uncertain significance - conflicting evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, BP4, BP7) 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: PopMax MAF = 0.000008864 (0.0008864%) in European (non-Finnish) exomes (gnomAD v2.1.1). - BP4: No REVEL, splicing evaluation required. Functional data on splicing not available. B) variant is exonic and at least 50bp downstream from canonical acceptor site and creates GT MES scores: de novo variant = 5.19; canonical donor = 7.67. Ratio de novo variant/canonical donor = 5.19/7.67 = 0.67 --- it is below 0.8 Variant is not predicted to alter splicing. - BP7: Variant is synonymous and meets BP4.

Met criteria codes

BP7			Variant is synonymous and meets BP4.
BP4			No REVEL, splicing evaluation required. Functional data on splicing not available. B) variant is exonic and at least 50bp downstream from canonical acceptor site and creates GT MES scores: de novo variant = 5.19; canonical donor = 7.67. Ratio de novo variant/canonical donor = 5.19/7.67 = 0.67 --- it is below 0.8 Variant is not predicted to alter splicing.
PM2			PopMax MAF = 0.000008864 (0.0008864%) in European (non-Finnish) exomes (gnomAD v2.1.1).

Not Met criteria codes

PM1			Even though Cys222 is one of the 60 cysteine residues involved in disulfide bond formation, however, this is synonymous, so PM1 not MET.
PM5			Other pathogenic variants in the same codon, but this is synonymous, so PM5 does not apply.

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