

Variant: *NM_000527.5(LDLR):c.665G>T (p.Cys222Phe)*

Version: 1.0

CA10585053 [↗](#)

251362 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 9bd3b83b-b8ff-4ed8-84d5-c0735c0618bb

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HGVS expressions

NM_000527.5(LDLR):c.665G>T (p.Cys222Phe)

NM_000527.5:c.665G>T

NC_000019.10:g.11105571G>T

CM000681.2:g.11105571G>T

NC_000019.9:g.11216247G>T

CM000681.1:g.11216247G>T

NC_000019.8:g.11077247G>T

NG_009060.1:g.21191G>T

ENST00000252444.10:c.923G>T

ENST00000559340.2:c.665G>T

ENST00000560467.2:c.665G>T

ENST00000558518.6:c.665G>T

ENST00000252444.9:c.919G>T

ENST00000455727.6:c.314-1821G>T

ENST00000535915.5:c.542G>T

ENST00000545707.5:c.314-994G>T

ENST00000557933.5:c.665G>T

ENST00000558013.5:c.665G>T

ENST00000558518.5:c.665G>T

ENST00000560467.1:c.265G>T

NM_000527.4:c.665G>T

NM_001195798.1:c.665G>T

NM_001195799.1:c.542G>T

NM_001195800.1:c.314-1821G>T

NM_001195803.1:c.314-994G>T

NM_001195798.2:c.665G>T

NM_001195799.2:c.542G>T

NM_001195800.2:c.314-1821G>T

NM_001195803.2:c.314-994G>T

Likely Pathogenic

Met criteria codes **6**

PM1 PM2 PS4_Supporting

PS3_Moderate PP3 PP4

Not Met criteria codes **16**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PM3

PM5

PM4

PM6

BS1

BS4

BS3

BS2

PVS1

PS1

PS2

BP7

BP4

BP2

BA1

PP1

Evidence Links

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- 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.665G>T (p.Cys222Phe) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM1, PM2, PS3_Moderate, PP3, PP4, PS4_Supporting 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: PM1: Variant meets PM2 and is missense in exon 4 PM2: This variant is absent from gnomAD v 2.1.1. PS3_Moderate: PMID: 24671153 Heterologous cells, 30 % cell surface LDLR and internalization PP3: REVEL is 0.971, which is greater than 0.75. PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills DLCN>=6 criteria for FH from PMID 24671153, after alternative causes of high cholesterol were excluded.. PS4_Supporting: Variant meets PM2 and is identified in at least 2 unrelated index cases. 1 index case from PMID 11810272 who fulfilled unspecified clinical criteria for FH, and 1 index case from PMID 24671153 who fulfilled DLCN>6 criteria for FH.

Met criteria codes

PM1			Variant meets PM2 and is missense in exon 4
PM2			This variant is absent from gnomAD v 2.1.1.
PS4_Supporting			Variant meets PM2 and is identified in at least 2 unrelated index cases. 1 index case from PMID 11810272 who fulfilled unspecified clinical criteria for FH, and 1 index case from PMID 24671153 who fulfilled DLCN>6 criteria for FH.
PS3_Moderate			PMID: 24671153 Heterologous cells, 30 % cell surface LDLR and internalization
PP3			REVEL is 0.971, which is greater than 0.75.
PP4			Variant meets PM2 and is identified in at least 1 index case who fulfills DLCN>=6 criteria for FH from PMID 24671153, after alternative causes of high cholesterol were excluded.

Not Met criteria codes

PM3			Not met.
PM5			Not met.
PM4			Not met.
PM6			Not met.
BS1			Not met.
BS4			Not met.
BS3			Not met.

BS2			Not met.
PVS1			Not met.
PS1			Not met.
PS2			Not met.
BP7			Not met.
BP4			Not met.
BP2			Not met.
BA1			Not met.
PP1			Not met.

Curation History 		
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