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# *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
**Approved on**: 2023/4/28
**Published on**: 2023/4/30

## *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 PS3_Moderate PS4_Supporting PP3 PP4

**Not Met criteria codes** 16

## Expert Panel

Familial Hypercholesterolemia VCEP

## Criteria Specification Information

PM3 PM5 PM4 PM6 BA1
BS2 BS1 BS4 BS3 BP7 BP4
BP2 PVS1 PS1 PS2 PP1

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***

**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.**

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**Met criteria codes**

| | | |
|---|---|---|
| **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 |
| **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. |
| **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. |

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**Not Met criteria codes**

| | | |
|---|---|---|
| **PM3** | ✖ | Not met. |
| **PM5** | ✖ | Not met. |
| **PM4** | ✖ | Not met. |
| **PM6** | ✖ | Not met. |
| **BA1** | ✖ | Not met. |
| **BS2** | ✖ | Not met. |
| **BS1** | ✖ | Not met. |

| | | | |
|---|---|---|---|
| **BS4** | | ✖ | Not met. |
| **BS3** | | ✖ | Not met. |
| **BP7** | | ✖ | Not met. |
| **BP4** | | ✖ | Not met. |
| **BP2** | | ✖ | Not met. |
| **PVS1** | | ✖ | Not met. |
| **PS1** | | ✖ | Not met. |
| **PS2** | | ✖ | Not met. |
| **PP1** | | ✖ | Not met. |

## Curation History

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