

Variant: *NM\_000527.5(LDLR):c.1965C>G (p.Phe655Leu)*

Version: 1.0

CA10585700 [↗](#)

252135 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Semidominant inheritance

**UUID:** f4f2a927-e1d2-47a5-a59b-828b25fd786a

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### *HGVS expressions*

**NM\_000527.5:c.1965C>G**

**NM\_000527.5(LDLR):c.1965C>G (p.Phe655Leu)**

NC\_000019.10:g.11120211C>G

CM000681.2:g.11120211C>G

NC\_000019.9:g.11230887C>G

CM000681.1:g.11230887C>G

NC\_000019.8:g.11091887C>G

NG\_009060.1:g.35831C>G

ENST00000252444.10:c.2223C>G

ENST00000559340.2:c.\*34C>G

ENST00000560467.2:c.1845C>G

ENST00000558518.6:c.1965C>G

ENST00000252444.9:c.2219C>G

ENST00000455727.6:c.1461C>G

ENST00000535915.5:c.1842C>G

ENST00000545707.5:c.1584C>G

ENST00000557933.5:c.1965C>G

ENST00000558013.5:c.1965C>G

ENST00000558518.5:c.1965C>G

ENST00000559340.1:c.546C>G

NM\_000527.4:c.1965C>G

NM\_001195798.1:c.1965C>G

NM\_001195799.1:c.1842C>G

NM\_001195800.1:c.1461C>G

NM\_001195803.1:c.1584C>G

NM\_001195798.2:c.1965C>G

NM\_001195799.2:c.1842C>G

NM\_001195800.2:c.1461C>G

NM\_001195803.2:c.1584C>G

**Likely Pathogenic**

Met criteria codes **4**

PP1\_Strong

PP4

PM2

PS4\_Supporting

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**



[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

***Familial Hypercholesterolemia VCEP***

**NM\_000527.5(LDLR):c.1965C>G (p.Phe655Leu) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PP1\_Strong, PM2, 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: PP1\_strong - Segregation data are published in PMID: 8634338 = 6 informative meiosis. PM2 - No population data was found for this variant in gnomAD (gnomAD v2.1.1). PP4 - Variant meets PM2. 2 cases fulfilling Simon-Broome criteria published in PMID: 8634338. PS4\_supporting - Variant meets PM2. Variant identified in 2 unrelated index cases (2 cases fulfilling Simon-Broome criteria published in PMID: 8634338).**

**Met criteria codes**

|                       |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PP1_Strong</b>     |  |  | Segregation data are published in PMID: 8634338 (family of index case #1: 2 affected 1st degree family members (LDL-C 7.1mmol/L, 5.3mmol/L) have the variant and 2 unaffected 1st degree family members (LDL-C 2.8mmol/L, 2.9mmol/L) do not have the variant. family of case index #2: 1 affected 1st degree family member (LDL-C 6.5mmol/L) has the variant and 1 unaffected 1st degree family member (LDL-C 3.4mmol/L) does not have the variant) = 6 informative meiosis. |
| <b>PP4</b>            |  |  | Variant meets PM2. 2 cases fulfilling Simon-Broome criteria published in PMID: 8634338                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>PM2</b>            |  |  | No population data was found for this variant in gnomAD (gnomAD v2.1.1)                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>PS4_Supporting</b> |  |  | Variant meets PM2. Variant identified in 2 unrelated index cases (2 cases fulfilling Simon-Broome criteria published in PMID: 8634338).                                                                                                                                                                                                                                                                                                                                      |

**Not Met criteria codes**

|            |  |  |                                                                |
|------------|--|--|----------------------------------------------------------------|
| <b>PS1</b> |  |  | No variant described that leads to the same amino acid change. |
| <b>PS2</b> |  |  | No de novo cases were identified.                              |
| <b>PS3</b> |  |  | No functional assays performed/found - not applicable.         |
| <b>PP2</b> |  |  | Not applicable.                                                |

|             |                                                                                     |                                                                                     |                                                                                                               |
|-------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| <b>PP3</b>  |       |       | REVEL: 0,661. Score is not above 0,75. Splicing predictors - negative.                                        |
| <b>BA1</b>  |    |    | No population data was found for this variant in gnomAD (gnomAD v2.1.1)                                       |
| <b>PM6</b>  |    |    | No de novo cases were identified.                                                                             |
| <b>BS1</b>  |    |    | No population data was found for this variant in gnomAD (gnomAD v2.1.1)                                       |
| <b>BS4</b>  |    |    | No non-segregations were identified/found.                                                                    |
| <b>BS3</b>  |    |    | No functional assays performed/found - not applicable.                                                        |
| <b>PM1</b>  |    |    | Missense at codon 655. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable. |
| <b>PM3</b>  |    |    | Not identified in individuals with other variants.                                                            |
| <b>PM5</b>  |    |    | This variant is the only variant found in this codon in ClinVar (assessed 4 June 2020).                       |
| <b>PM4</b>  |    |    | Missense variant. Not applicable.                                                                             |
| <b>BS2</b>  |  |  | No unaffected individuals identified with the variant.                                                        |
| <b>BP5</b>  |  |  | Not applicable.                                                                                               |
| <b>BP7</b>  |  |  | Missense variant. Not applicable.                                                                             |
| <b>BP4</b>  |  |  | REVEL: 0,661. Score is not below 0,50.                                                                        |
| <b>BP3</b>  |  |  | Not applicable.                                                                                               |
| <b>BP1</b>  |  |  | Not applicable.                                                                                               |
| <b>BP2</b>  |  |  | Not identified in individuals with other variants.                                                            |
| <b>PVS1</b> |  |  | Missense variant. Not applicable.                                                                             |

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