

Variant: *NM\_000527.5(LDLR):c.682G>T (p.Glu228Ter)*

Version: 1.0

CA044327 [↗](#)

226333 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Semidominant inheritance

**UUID:** 4ba182f6-7685-483b-b36f-bde68e89e7af

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### *HGVS expressions*

**NM\_000527.5(LDLR):c.682G>T (p.Glu228Ter)**

**NM\_000527.5:c.682G>T**

NC\_000019.10:g.11105588G>T

CM000681.2:g.11105588G>T

NC\_000019.9:g.11216264G>T

CM000681.1:g.11216264G>T

NC\_000019.8:g.11077264G>T

NG\_009060.1:g.21208G>T

ENST00000252444.10:c.940G>T

ENST00000559340.2:c.682G>T

ENST00000560467.2:c.682G>T

ENST00000558518.6:c.682G>T

ENST00000252444.9:c.936G>T

ENST00000455727.6:c.314-1804G>T

ENST00000535915.5:c.559G>T

ENST00000545707.5:c.314-977G>T

ENST00000557933.5:c.682G>T

ENST00000558013.5:c.682G>T

ENST00000558518.5:c.682G>T

ENST00000560467.1:c.282G>T

NM\_000527.4:c.682G>T

NM\_001195798.1:c.682G>T

NM\_001195799.1:c.559G>T

NM\_001195800.1:c.314-1804G>T

NM\_001195803.1:c.314-977G>T

NM\_001195798.2:c.682G>T

NM\_001195799.2:c.559G>T

NM\_001195800.2:c.314-1804G>T

NM\_001195803.2:c.314-977G>T

**Pathogenic**

Met criteria codes **6**

PP1\_Moderate

PS3

PS4

PP4

PM2

PVS1

Evidence Links **0**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

*Familial Hypercholesterolemia VCEP*

NM\_000527.5(LDLR):c.682G>T (p.Glu228Ter) variant is classified as pathogenic for Familial Hypercholesterolemia by applying evidence code PVS1, PS3, PS4, PM2, PP1\_Moderate and PP4 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 = 0.00006530 (0.006%) in African/African American exomes (gnomAD v2.1.1). PVS1 - Variant leads to stop at codon 228, amino-terminal of amino acid 830. PS3 - Two studies contribute to PS3 attribution. One (PMID: 1301956) report a level 2 assay performed on homozygous patient's fibroblasts with radiolabeled LDL consistent with damaging effect of the variant (< 2% LDLR activity). The second reports a level 1 assay (PMID: 17087781) performed on Heterologous cells (COS7). FACS, CLSM and WB results in <5% LDLR activity. LDLR precursor protein does not mature. PS4 - Variant meets PM2 and is identified in 22 index cases who fulfil SB criteria for FH (n=2 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) or DLCN criteria for FH (n=4 Color Health, Inc.; n=14 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=2 Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)) PP1\_Moderate - Variant segregate with FH in 3 informatives meiosis (LDL-C > 75th percentile) and not segregate with variant in 1 relative with LDL-C <25th percentile from at least 1 family from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA). PP4 - Variant meets PM2 and is identified in 22 index cases who fulfil SB criteria for FH (n=2 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) or DLCN criteria for FH (n=4 Color Health, Inc.; n=14 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=2 Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA))

Met criteria codes

|              |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP1_Moderate |    |    | Variant segregate with FH in 3 informatives meiosis (LDL-C > 75th percentile) and not segregate with variant in 1 relative with LDL-C <25th percentile from at least 1 family from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA).                                                                                                                                                          |
| PS3          |   |   | Two studies contribute to PS3 attribution. One (PMID: 1301956) report a level 2 assay performed on homozygous patient's fibroblasts with radiolabeled LDL consistent with damaging effect of the variant (< 2% LDLR activity). The second reports a level 1 assay (PMID: 17087781) perfomed on Heterologous cells (COS7). FACS, CLSM and WB results in <5% LDLR activity. LDLR precursor protein does not mature. |
| PS4          |  |  | Variant meets PM2 and is identified in 22 index cases who fulfil SB criteria for FH (n=2 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) or DLCN criteria for FH (n=4 Color Health, Inc.; n=14 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=2 Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA))                                          |
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| PM2          |  |  | PopMax MAF = 0.00006530 (0,006%) in African/African American exomes (gnomAD v2.1.1).                                                                                                                                                                                                                                                                                                                              |
| PVS1         |  |  | Variant leads to stop at codon 228, amino-terminal of amino acid 830.                                                                                                                                                                                                                                                                                                                                             |

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