

Variant: NM_000527.5(LDLR):c.97C>T (p.Gln33Ter)

Version: 1.2

CA023802 [↗](#)

3683 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: b06630f4-ec3c-49d3-9864-25957fc07c36

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Published on: 2024/12/2

HGVS expressions

NM_000527.5(LDLR):c.97C>T (p.Gln33Ter)

NM_000527.5:c.97C>T

NC_000019.10:g.11100252C>T

CM000681.2:g.11100252C>T

NC_000019.9:g.11210928C>T

CM000681.1:g.11210928C>T

NC_000019.8:g.11071928C>T

NG_009060.1:g.15872C>T

ENST00000252444.10:c.355C>T

ENST00000559340.2:c.97C>T

ENST00000560467.2:c.97C>T

ENST00000558518.6:c.97C>T

ENST00000252444.9:c.351C>T

ENST00000455727.6:c.97C>T

ENST00000535915.5:c.97C>T

ENST00000545707.5:c.97C>T

ENST00000557933.5:c.97C>T

ENST00000557958.1:n.183C>T

ENST00000558013.5:c.97C>T

ENST00000558518.5:c.97C>T

ENST00000560502.5:n.183C>T

NM_000527.4:c.97C>T

NM_001195798.1:c.97C>T

NM_001195799.1:c.97C>T

NM_001195800.1:c.97C>T

NM_001195803.1:c.97C>T

NM_001195798.2:c.97C>T

NM_001195799.2:c.97C>T

NM_001195800.2:c.97C>T

NM_001195803.2:c.97C>T

Pathogenic

Met criteria codes 6

PP1_StrongPS3PS4PP4PM2PVS1

Evidence Links 0

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

NM_000527.5(LDLR):c.97C>T (p.Gln33Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence code PVS1, PS3, PS4, PP1_Strong, PM2 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 25 March 2022. The supporting evidence is as follows: PM2 - PopMax MAF = 0.00001759 (0.002%) in European non-Finnish exomes (gnomAD v2.1.1). PVS1 - Variant leads to stop at codon 33, amino-terminal of amino acid 830. PS3 - Two studies contribute to PS3 attribution. One (PMID:2088165) 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 performed on Heterologous cells (CHO-IdIA7). FACS, CLSM and WB results in 10% expression, binding and uptake of LDLR which is retained in the ER. PS4 - Variant meets PM2 and is identified in at least 10 unrelated index cases from CGMC UFGOD (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière). 8 cases fulfil SB possible criteria and 14 fulfil DLCN >= 6 criteria. PP1_Strong- Variant segregates with phenotype in >6 informative meioses in >1 family [data from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) and Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)]: 14 affected family members have the variant. PP4 - Variant meets PM2 and is identified in 22 unrelated index cases from CGMC UFGOD (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière).

Met criteria codes

PP1_Strong			Variant segregates with phenotype in >6 informative meioses in >1 family [data from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) and Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)]: 14 affected family members have the variant.
PS3			Two studies contribute to PS3 attribution. One (PMID:2088165) 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 performed on Heterologous cells (CHO-IdIA7). FACS, CLSM and WB results in 10% expression, binding and uptake of LDLR which is retained in the ER.
PS4			Variant meets PM2 and is identified in at least 10 unrelated index cases from CGMC UFGOD (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière). 8 cases fulfil SB possible criteria and 14 fulfil DLCN >= 6 criteria.
PP4			Variant meets PM2 and is identified in 22 unrelated index cases from CGMC UFGOD (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière).

PM2			PopMax MAF = 0.00001759 (0,002%) in European non-Finnish exomes (gnomAD v2.1.1).
PVS1			Variant leads to stop at codon 33 amino-terminal of amino acid 830.

Curation History 			
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