The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000527.5(LDLR):c.760C>T (p.Gln254Ter)

Version: 1.0

CA10585116

251436 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: c8ddc916-8f19-4334-ad28-b49e531f6f19
Approved on: 2022/8/28
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HGVS expressions

NM_000527.5(LDLR):c.760C>T (p.Gln254Ter)
NM_000527.5:c.760C>T
NC_000019.10:g.11106630C>T
CM000681.2:g.11106630C>T
NC_000019.9:g.11217306C>T
CM000681.1:g.11217306C>T
NC_000019.8:g.11078306C>T
NG_009060.1:g.22250C>T
ENST00000252444.10:c.1018C>T
ENST00000559340.2:c.760C>T
ENST00000560467.2:c.760C>T
ENST00000558518.6:c.760C>T
ENST00000252444.9:c.1014C>T
ENST00000455727.6:c.314-762C>T
ENST00000535915.5:c.637C>T
ENST00000545707.5:c.379C>T
ENST00000557933.5:c.760C>T
ENST00000558013.5:c.760C>T
ENST00000558518.5:c.760C>T
ENST00000558528.1:n.275C>T
ENST00000560467.1:c.360C>T
NM_000527.4:c.760C>T
NM_001195798.1:c.760C>T
NM_001195799.1:c.637C>T
NM_001195800.1:c.314-762C>T
NM_001195803.1:c.379C>T
NM_001195798.2:c.760C>T
NM_001195799.2:c.637C>T
NM_001195800.2:c.314-762C>T
NM_001195803.2:c.379C>T

Pathogenic

Met criteria codes 4
PM3 PM2 PVS1 PP4

Not Met criteria codes 22

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PM1 PM5 PM4 PM6 BA1
BS2 BS1 BS4 BS3 BP5 BP7
BP4 BP3 BP1 BP2 PS1 PS2
PS3 PS4 PP1 PP2 PP3

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.760C>T (p.Gln254Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PVS1, PM2, PM3 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: PVS1 - Variant leads to stop at codon 254. It is amino-terminal of amino acid 830, so PVS1 is met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PM3 - variant meets PM2 and was identified in 1 index case (Patient F3) with LDLc 18.21 mmol/l and compound heterozygote with NM_000527.5(LDLR):c.1216C>A (p.Arg406=) from Du et al. 2016 (PMID: 28028493). -- 2nd variant is classified as Likely Pathogenic by these guidelines and patient has phenotype of homozygous FH, so PM3 is met. PP4 - variant meets PM2 and was identified in 1 index case with DLCN at least 14 (LDL of 18.21mmol/L and xanthomas), from Du et al. 2016 (PMID: 28028493), China, so PP4 is met.

Met criteria codes

PM3	✔	variant meets PM2 and was identified in 1 index case (Patient F3) with LDLc 18.21 mmol/l and compound heterozygote with NM_000527.5(LDLR):c.1216C>A (p.Arg406=) from Du et al. 2016 (PMID: 28028493). -- 2nd variant is classified as Likely Pathogenic by these guidelines and patient has phenotype of homozygous FH, so PM3 is met
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met
PVS1	✔	Variant leads to stop at codon 254. It is amino-terminal of amino acid 830, so PVS1 is met
PP4	✔	variant meets PM2 and was identified in - 1 index case with DLCN at least 14 (LDL of 18.21mmol/L and xanthomas), from Du et al. 2016 (PMID: 28028493), China. so PP4 is met

Not Met criteria codes

PM1	✖	variant is nonsense, so not applicable
PM5	✖	variant is nonsense, so not applicable
PM4	✖	variant is nonsense, so not applicable
PM6	✖	no de novo occurrence

BA1		✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS2		✖	variant was not identified in normolipidemic individuals, so not met
BS1		✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS4		✖	no segregation data
BS3		✖	this variant was not studied in functional studies
BP5		✖	not applicable
BP7		✖	variant is nonsense, so not applicable
BP4		✖	variant meets PVS1, so not applicable
BP3		✖	not applicable
BP1		✖	not applicable
BP2		✖	not identified in index cases with other variants and phenotype of heterozygous FH, so not met
PS1		✖	variant is nonsense, so not applicable
PS2		✖	no de novo occurrence
PS3		✖	this variant was not studied in functional studies
PS4		✖	variant meets PM2 and was identified in - 1 index case with DLCN at least 14 (LDL of 18.21mmol/L and xanthomas), from Du et al. 2016 (PMID: 28028493), China. not enough, so not met
PP1		✖	no segregation data
PP2		✖	not applicable
PP3		✖	variant meets PVS1, so not applicable

Curation History

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