

Variant: *NM_000527.5(LDLR):c.1920C>T (p.Asn640=)*

Version: 1.0

CA037448 [↗](#)

237869 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 02241ae1-0fc0-41f4-ba1c-60a421eac6b6

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HGVS expressions

NM_000527.5(LDLR):c.1920C>T (p.Asn640=)

NM_000527.5:c.1920C>T

NC_000019.10:g.11120166C>T

CM000681.2:g.11120166C>T

NC_000019.9:g.11230842C>T

CM000681.1:g.11230842C>T

NC_000019.8:g.11091842C>T

NG_009060.1:g.35786C>T

ENST00000252444.10:c.2178C>T

ENST00000559340.2:c.1780C>T

ENST00000560467.2:c.1800C>T

ENST00000558518.6:c.1920C>T

ENST00000252444.9:c.2174C>T

ENST00000455727.6:c.1416C>T

ENST00000535915.5:c.1797C>T

ENST00000545707.5:c.1539C>T

ENST00000557933.5:c.1920C>T

ENST00000558013.5:c.1920C>T

ENST00000558518.5:c.1920C>T

ENST00000559340.1:c.501C>T

NM_000527.4:c.1920C>T

NM_001195798.1:c.1920C>T

NM_001195799.1:c.1797C>T

NM_001195800.1:c.1416C>T

NM_001195803.1:c.1539C>T

NM_001195798.2:c.1920C>T

NM_001195799.2:c.1797C>T

NM_001195800.2:c.1416C>T

NM_001195803.2:c.1539C>T

Benign

Met criteria codes 4

BA1 BS3_Supporting BP7 BP4

Not Met criteria codes 5

BP2 BS4 PP1 PP4 PS4

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

The NM_000527.5 (LDLR):c.1920C>T (p.Asn640=) variant is classified as Benign for Familial Hypercholesterolemia by applying evidence codes (BA1, BP4, BP7, BS3_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: BA1: FAF=0.03838 in Ashkenazi Jewish population in gnomAD (gnomAD 2.1.1). BP4: No REVEL, splicing evaluation required. A) not in limit. B) does not create AG or GT. C) there is a GT nearby. Var cryptic score/Wt cryptic score=0.69, it is not above 1.1, and Var cryptic score/Wt score= -0.80, it is not above 0.9. Variant is not predicted to alter splicing. BP7: Variant is synonymous and meets BP4. BS3_Supporting: Level 3 assay with heterozygous patients’ lymphocytes, RNA assays shown normal LDLR transcripts, reported by Medeiros et al, 2016, from Instituto Nacional de Saude Doutor Ricardo Jorge, Lisbon, Portugal, PMID 26020417. Functional data is consistent with no damaging effect. PP4, PS4 not met: Variant did not meet PM2. PP1 not met: There are 2 relatives without the variant had LDL-C <50th percentile in 1 family, however the index case did not meet Simon Broome criteria for FH diagnosis, reported in VCI from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. BS4 not met: There are 2 relatives without the variant had LDL-C >75th percentile in 1 family, however the index case did not meet Simon Broome criteria for FH diagnosis, and there is no instance where an unaffected family member carries the variant, reported in VCI from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. BP2 not met: Variant identified in an index case with heterozygous FH phenotype and an unspecified LDLR variant with unknown pathogenicity and phase, reported in VCI from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France.

Met criteria codes

BA1			FAF=0.03838 in Ashkenazi Jewish population in gnomAD (gnomAD 2.1.1).
BS3_Supporting			Level 3 assay with heterozygous patients’ lymphocytes, RNA assays shown normal LDLR transcripts, reported by Medeiros et al, 2016, from Instituto Nacional de Saude Doutor Ricardo Jorge, Lisbon, Portugal, PMID 26020417. Functional data is consistent with no damaging effect.
BP7			Variant is synonymous and meets BP4.
BP4			No REVEL, splicing evaluation required. A) not in limit. B) does not create AG or GT. C) there is a GT nearby. Var cryptic score/Wt cryptic score=0.69, it is not above 1.1, and Var cryptic score/Wt score= -0.80, it is not above 0.9. Variant is not predicted to alter splicing.

Not Met criteria codes

BP2			Variant identified in an index case with heterozygous FH phenotype and an unspecified LDLR variant with unknown pathogenicity and phase, reported in VCI from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France.
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BS4			There are 2 relatives without the variant had LDL-C >75th percentile in 1 family, however the index case did not meet Simon Broome criteria for FH diagnosis, and there is no instance where an unaffected family member carries the variant, reported in VCI from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge.
PP1			There are 2 relatives without the variant had LDL-C <50th percentile in 1 family, however the index case did not meet Simon Broome criteria for FH diagnosis, reported in VCI from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge.
PP4			Variant did not meet PM2.
PS4			Variant did not meet PM2.

Curation History 		
Showing 1 to 1 of 1 rows		

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