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# *Variant: NM_000527.5(LDLR):c.828C>A (p.Cys276Ter)*

Version: 1.0

*CA023773*

*189298 (ClinVar)*

**Gene**: LDLR (HGNC:3949)
**Condition**: hypercholesterolemia, familial (MONDO:0007750)
**Inheritance Mode**: Semidominant inheritance
**UUID:** d2cd233c-9b00-4d8a-98ff-e565329f22ff
**Approved on**: 2023/3/20
**Published on**: 2023/3/31

## *HGVS expressions*

**NM_000527.5:c.828C>A**
**NM_000527.5(LDLR):c.828C>A (p.Cys276Ter)**
NC_000019.10:g.11107402C>A
CM000681.2:g.11107402C>A
NC_000019.9:g.11218078C>A
CM000681.1:g.11218078C>A
NC_000019.8:g.11079078C>A
NG_009060.1:g.23022C>A
ENST00000252444.10:c.1086C>A
ENST00000559340.2:c.828C>A
ENST00000560467.2:c.828C>A
ENST00000558518.6:c.828C>A
ENST00000252444.9:c.1082C>A
ENST00000455727.6:c.324C>A
ENST00000535915.5:c.705C>A
ENST00000545707.5:c.447C>A
ENST00000557933.5:c.828C>A
ENST00000558013.5:c.828C>A
ENST00000558518.5:c.828C>A
ENST00000558528.1:n.343C>A
ENST00000560467.1:c.428C>A
NM_000527.4:c.828C>A
NM_001195798.1:c.828C>A
NM_001195799.1:c.705C>A
NM_001195800.1:c.324C>A
NM_001195803.1:c.447C>A
NM_001195798.2:c.828C>A
NM_001195799.2:c.705C>A
NM_001195800.2:c.324C>A
NM_001195803.2:c.447C>A

**Pathogenic**

**Met criteria codes** 6

PVS1 PS4 PP1 PP4 PM2 PM3

**Not Met criteria codes** 3

BS4 PS3 PM1

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***

**The NM_000527.5(LDLR):c.828C>A (p.Cys276Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PVS1, PS4, PM2, PM3, PP1, 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 is predicted to result in a stop codon at amino acid 276, which is amino-terminal of amino acid 830. -PS4: Variant meets PM2 and is identified in 12 unrelated index cases (3 cases with Simon-Broome criteria of possible FH and 6 cases with Simon-Broome criteria of definite FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 1 case with DLCN>=6 from PMID: 32977124, homozygous FH; 1 cases with SB possible FH from PMID: 26036859, and 1 case with FH by MedPed criteria from PMID 21310417). -PM2: This variant is absent from gnomAD (gnomAD v2.1.1). -PM3: Variant identified as homozygous state in an index case with homozygous FH phenotype from PMID: 32977124. -PP1: Variant segregates with FH phenotype in at least 2 informative meiosis from 2 families from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation). -PP4: Variant meets PM2 and is identified in 12 unrelated index cases (3 cases with Simon-Broome criteria of possible FH and 6 cases with Simon-Broome criteria of definite FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 1 case with DLCN>=6 from PMID: 32977124, homozygous FH; 1 cases with SB possible FH from PMID: 26036859, and 1 case with FH by MedPed criteria from PMID 21310417), after alternative causes of high cholesterol were excluded.**

**Met criteria codes**

| | | |
|---|---|---|
| **PVS1** | ✔ | Variant is predicted to result in a stop codon at amino acid 276, which is amino-terminal of amino acid 830. |
| **PS4** | ✔ | Variant meets PM2 and is identified in 12 unrelated index cases (3 cases with Simon-Broome criteria of possible FH and 6 cases with Simon-Broome criteria of definite FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 1 case with DLCN>=6 from PMID: 32977124, homozygous FH; 1 cases with SB possible FH from PMID: 26036859, and 1 case with FH by MedPed criteria from PMID 21310417). |
| **PP1** | ✔ | Variant segregates with FH phenotype in at least 2 informative meiosis from 2 families from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation). |
| **PP4** | ✔ | Variant meets PM2 and is identified in 12 unrelated index cases (3 cases with Simon-Broome criteria of possible FH and 6 cases with Simon-Broome criteria of definite FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 1 case with DLCN>=6 from PMID: 32977124, homozygous FH; 1 cases with SB possible FH from PMID: 26036859, and 1 case with FH by MedPed criteria from PMID 21310417), after alternative causes of high cholesterol were excluded. |

| | | | |
|---|---|---|---|
| **PM2** | | ✔ | This variant is absent from gnomAD (gnomAD v2.1.1). |
| **PM3** | | ✔ | Variant identified as homozygous state in an index case with homozygous FH phenotype from PMID: 32977124. |

**Not Met criteria codes**

| | | | |
|---|---|---|---|
| **BS4** | | ✖ | there is 1 non-segregation in 1 family from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) and another one non-segregation from PMID: 26036859 in one family. However, for BS4, data must be available on >=2 informative meiosis in each family, so BS4 not met. |
| **PS3** | | ✖ | PMID: 32977124 mentioned result of <5% residual activity, however, assay was not clearly stated in the manuscript itself nor in the mentioned reference, did not count this one. In PMID 22698793, it was mentioned that functional characterization through the use of transfection of HepG2 cells and the luciferase reporter assay was performed for c.-153C > T and c.- 120C > T, not this specific variant, did not count either. |
| **PM1** | | ✖ | missense variant at the one of the 60 cysteine residues involved in disulfide bond formation, cys276, but this is missense, so PM1 not met. |

Curation History

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