

Variant: *NM_000527.5(LDLR):c.798T>A (p.Asp266Glu)*

Version: 1.0

CA023765 [↗](#)

161287 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: da36a90c-1718-424e-83fa-5e42e5af70fa

Approved on: 2021/6/7

Published on: 2021/6/24

HGVS expressions

NM_000527.5:c.798T>A

NM_000527.5(LDLR):c.798T>A (p.Asp266Glu)

NC_000019.10:g.11106668T>A

CM000681.2:g.11106668T>A

NC_000019.9:g.11217344T>A

CM000681.1:g.11217344T>A

NC_000019.8:g.11078344T>A

NG_009060.1:g.22288T>A

ENST00000252444.10:c.1056T>A

ENST00000559340.2:c.798T>A

ENST00000560467.2:c.798T>A

ENST00000558518.6:c.798T>A

ENST00000252444.9:c.1052T>A

ENST00000455727.6:c.314-724T>A

ENST00000535915.5:c.675T>A

ENST00000545707.5:c.417T>A

ENST00000557933.5:c.798T>A

ENST00000558013.5:c.798T>A

ENST00000558518.5:c.798T>A

ENST00000558528.1:n.313T>A

ENST00000560467.1:c.398T>A

NM_000527.4:c.798T>A

NM_001195798.1:c.798T>A

NM_001195799.1:c.675T>A

NM_001195800.1:c.314-724T>A

NM_001195803.1:c.417T>A

NM_001195798.2:c.798T>A

NM_001195799.2:c.675T>A

NM_001195800.2:c.314-724T>A

NM_001195803.2:c.417T>A

Pathogenic

Met criteria codes **6**

PS3_Moderate

PP1_Strong

PM5_Strong

PP4

PM2

PS4

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes **20**

BA1 BP5 BP7 BP4 BP3 BP1
BP2 BS2 BS1 BS4 BS3 PP2
PP3 PM1 PM3 PM4 PM6
PVS1 PS1 PS2

[Criteria Specifications for this VCEP](#)

Evidence Links **0**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.798T>A (p.Asp266Glu) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PS4, PP1_Strong, PM5_Strong, PM2, PS3_Moderate and PP4) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PS4 - Variant meets PM2. Identified in over 10 unrelated index cases from Center of molecular biology and gene therapy with FH diagnosis. PP1_strong - variant segregates with phenotype in over 30 informative meioses in several families from different laboratories. PM5_strong - Four more missense variants described in same codon: --- 3 variants classified as Pathogenic, so PM5_Strong is met. PM2 - PopMax MAF = 0.00007740 (0.008%) in european non-finnish exomes (gnomAD v2.1.1). PS3_moderate - Level 2 assay: PMID 1301956: Hmz patients' fibroblasts, 125I-LDL assays - results - 15-30% LDLR activity (but all cycle was tested) ---- Overall LDLR activity is below 70% of wild-type activity, so PS3_moderate is Met. PP4 - Variant meets PM2. Identified in over 10 unrelated index cases from Center of molecular biology and gene therapy with FH diagnosis.

Met criteria codes

PS3_Moderate			Level 2 assay: PMID 1301956: Hmz patients' fibroblasts, 125I-LDL assays - results - 15-30% LDLR activity (but all cycle was tested) ---- Overall LDLR activity is below 70% of wild-type activity, so PS3_moderate is Met
PP1_Strong			variant segregates with phenotype in over 30 informative meioses in several families from different laboratories (Center of molecular biology and gene therapy, GeneDx Inc. and GeneDx Inc.): 39 affected family members have the variant. --- PP1_Strong is Met
PM5_Strong			Four more missense variants described in same codon: (1)NM_000527.5(LDLR):c.796G>T (p.Asp266Tyr) (ClinVar ID 251456) - classified as Pathogenic by these guidelines. (2)NM_000527.5(LDLR):c.796G>A (p.Asp266Asn) (ClinVar ID 226334) - classified as Pathogenic by these guidelines. (3)NM_000527.5(LDLR):c.797A>T (p.Asp266Val) (ClinVar ID 251458) - classified as Likely pathogenic by these guidelines. (4)NM_000527.5(LDLR):c.797A>G (p.Asp266Gly) (ClinVar ID 251457) - classified as Pathogenic by these guidelines --- 3 variants classified as Pathogenic, so PM5_Strong is met
PP4			Variant meets PM2. Identified in over 10 unrelated index cases from Center of molecular biology and gene therapy with FH diagnosis. ---- PP4 is Met
PM2			PopMax MAF = 0.00007740 (0.008%) in european non-finnish exomes (gnomAD v2.1.1). FAF is under 0.02%, so PM2 is Met.
PS4			Variant meets PM2. Identified in over 10 unrelated index cases from Center of molecular biology and gene therapy with FH diagnosis. --- PS4 is Met

Not Met criteria codes

BA1			FAF = 0.00003418 (0.0034%) in european non-finnish exomes (gnomAD v2.1.1). FAF is not above 0.5%, so BA1 is Not Met.
BP5			Not applicable
BP7			Missense variant, so BP7 is not applicable

BP4			REVEL = 0.739. It is not below 0.15, BP4 is Not Met
BP3			Not applicable
BP1			Not applicable
BP2			Variant identified in 4 index cases from Center of molecular biology and gene therapy with other LDLR variants - in 1 phenotype is of Homozygous FH - in 3 phenotype does not confirm or exclude homozygous FH. in all the 2nd variant is not specified, so BP2 is Not Met
BS2			no unaffected individuals identified with the variant, so BS2 is Not Met
BS1			FAF = 0.00003418 (0.0034%) in european non-finnish exomes (gnomAD v2.1.1). FAF is not above 0.2%, so BS1 is Not Met.
BS4			Variant does not segregate with phenotype in 1 informative meiosis from 1 family from Center of molecular biology and gene therapy: 1 affected family member does not have the variant. there is not enough evidence to meet BS4 -- - BS4 is Not Met
BS3			Level 3(benign) assays: PMID 1301956: Hmz patients' fibroblasts, 125I-LDL assays - results - 15-30% LDLR activity (but all cycle was tested) ---- Results are not above 95% of activity, so BS3_supporting Not Met
PP2			Not applicable
PP3			REVEL = 0.739. It is not above 0.75, splicing evaluation is required. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp downstream from canonical acceptor site, but it does not create GT. C) there is no GT nearby. No splicing prediction is applicable, so PP3 is Not Met
PM1			Missense at codon 266. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed, so PM1 is Not Met
PM3			Identified in 4 index cases from Center of molecular biology and gene therapy with other LDLR variants - in 1 phenotype is of Homozygous FH - in 3 phenotype does not confirm or exclude homozygous FH. in all the 2nd variant is not specified, so PM3 is Not Met
PM4			Missense variant, not applicable
PM6			no de novo cases were identified, so PM6 is Not Met
PVS1			Missense variant, PVS1 Not Met
PS1			No variant described that leads to the same amino acid change, so PS1 is Not Met
PS2			no de novo cases were identified, so PS2 is Not Met



Curation History [↗](#)

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