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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
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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

PP1_Strong PM5_Strong PM2 PS4 PS3_Moderate PP4

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Not Met criteria codes 20

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

Evidence Links 0

Criteria Specifications for this VCEP

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 meiosis 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

PP1_Strong	✔	variant segregates with phenotype in over 30 informative meiosis 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
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
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. ---- PP4 is Met

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Not Met criteria codes

PM6	✖	no de novo cases were identified, so PM6 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
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.
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
BS2	✖	no unaffected individuals identified with the variant, so BS2 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
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
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

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.798T>A (p.Asp2...	Pathogenic	Hypercholesterolemia, Familial	2021-06-24	1.0	-	LDLR

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