

Variant: *NM_000527.5(LDLR):c.796G>A (p.Asp266Asn)*

Version: 1.0

CA10576288 [↗](#)

226334 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: febc36e7-3293-4e52-8666-7a907e25a4a9

Approved on: 2022/5/4

Published on: 2022/6/30

HGVS expressions

NM_000527.5(LDLR):c.796G>A (p.Asp266Asn)

NM_000527.5:c.796G>A

NC_000019.10:g.11106666G>A

CM000681.2:g.11106666G>A

NC_000019.9:g.11217342G>A

CM000681.1:g.11217342G>A

NC_000019.8:g.11078342G>A

NG_009060.1:g.22286G>A

ENST00000252444.10:c.1054G>A

ENST00000559340.2:c.796G>A

ENST00000560467.2:c.796G>A

ENST00000558518.6:c.796G>A

ENST00000252444.9:c.1050G>A

ENST00000455727.6:c.314-726G>A

ENST00000535915.5:c.673G>A

ENST00000545707.5:c.415G>A

ENST00000557933.5:c.796G>A

ENST00000558013.5:c.796G>A

ENST00000558518.5:c.796G>A

ENST00000558528.1:n.311G>A

ENST00000560467.1:c.396G>A

NM_000527.4:c.796G>A

NM_001195798.1:c.796G>A

NM_001195799.1:c.673G>A

NM_001195800.1:c.314-726G>A

NM_001195803.1:c.415G>A

NM_001195798.2:c.796G>A

NM_001195799.2:c.673G>A

NM_001195800.2:c.314-726G>A

NM_001195803.2:c.415G>A

Pathogenic

Met criteria codes **7**

PS4 PS3_Moderate PP1 PP3
PP4 PM5_Strong PM2

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 19

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

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c. c.796G>A (p.Asp266Asn) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS4, PM2, PM5_Strong, PS3_Moderate, PP1, PP3 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. Variant identified in 10 unrelated index cases (1 case fulfilling Simon-Broome criteria published in PMID: 12414836; 1 case probably fulfilling Simon-Broome criteria published in PMID: 12417285; 1 case with DLCN criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 4 cases with Simon-Broome criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 3 cases with DLCN criteria from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory); PM2 - PopMax MAF = 0.00006533 (0.006533%) in South Asian exomes (gnomAD v2.1.1); PM5_Strong - 4 other missense variants in the same codon: - NM_000527.5(LDLR): c.796G>T (p.Asp266Tyr) (ClinVar ID 251456) - Pathogenic by these guidelines. - NM_000527.5(LDLR): c.797A>T (p.Asp266Val) (ClinVar ID 251458) - Likely Pathogenic by these guidelines. - NM_001195803.2(LDLR):c.797A>G (p.Asp266Gly) (ClinVar ID 251457) - Likely pathogenic by these guidelines. - NM_001195803.2(LDLR): c.798T>A (p.Asp266Glu) - (ClinVar ID 161287) - Pathogenic by these guidelines. There are 2 variants in the same codon classified as Pathogenic by these guidelines. PS3_Moderate - Level 2 assay: PMID 12414836: Homozygous patient cells, 125I assays - result - <2% LDL-LDLR binding and internalisation. Functional study is consistent with damaging effect; PP1 - 3 informative meioses identified by Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); PP3 - REVEL = 0,83; PP4 - Variant meets PM2. Identified in at least 1 FH case fulfilling Simon-Broome criteria published in PMID 12414836.

Met criteria codes

PS4			Variant meets PM2. Variant identified in 10 unrelated index cases (1 case fulfilling Simon-Broome criteria published in PMID: 12414836; 1 case probably fulfilling Simon-Broome criteria published in PMID: 12417285; 1 case with DLCN criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 4 cases with Simon-Broome criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 3 cases with DLCN criteria from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory).
PS3_Moderate			Level 2 assays: PMID 12414836: Homozygous patient cells, 125I assays - result - <2% LDL-LDLR binding and internalisation (only results of binding and internalisation at 37°C are shown). ---- functional study is consistent with damaging effect
PP1			3 informative meioses identified by Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)
PP3			REVEL = 0,83
PP4			Variant meets PM2. Variant identified in 10 unrelated index cases (1 case fulfilling Simon-Broome criteria published in PMID: 12414836; 1 case probably fulfilling Simon-Broome criteria published in PMID: 12417285; 1 case with DLCN

criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 4 cases with Simon-Broome criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 3 cases with DLCN criteria from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory).

PM5_Strong			4 other missense variants in the same codon: - NM_000527.5(LDLR):c.796G>T (p.Asp266Tyr) (ClinVar ID 251456) - Pathogenic by these guidelines. - NM_000527.5(LDLR):c.797A>T (p.Asp266Val) (ClinVar ID 251458) - Likely Pathogenic by these guidelines. - NM_001195803.2(LDLR):c.797A>G (p.Asp266Gly) (ClinVar ID 251457) - Likely pathogenic by these guidelines. - NM_001195803.2(LDLR):c.798T>A (p.Asp266Glu) - (ClinVar ID 161287) - Pathogenic by these guidelines. There are 2 variants in the same codon classified as Pathogenic by these guidelines.
PM2			PopMax MAF = 0.00006533 (0.006533%) in South Asian exomes (gnomAD v2.1.1).

Not Met criteria codes

BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
▼ ▼		
Showing 1 to 1 of 1 rows		

