The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000527.5(LDLR):c.1186G>A (p.Gly396Ser)

Version: 1.0

CA10585341

251704 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 559f3e37-527d-46af-af4f-f0b16e81b6bc
Approved on: 2022/10/28
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HGVS expressions

NM_000527.5(LDLR):c.1186G>A (p.Gly396Ser)
NM_000527.5:c.1186G>A
NC_000019.10:g.11111639G>A
CM000681.2:g.11111639G>A
NC_000019.9:g.11222315G>A
CM000681.1:g.11222315G>A
NC_000019.8:g.11083315G>A
NG_009060.1:g.27259G>A
ENST00000252444.10:c.1444G>A
ENST00000559340.2:c.1186G>A
ENST00000560467.2:c.1066G>A
ENST00000558518.6:c.1186G>A
ENST00000252444.9:c.1440G>A
ENST00000455727.6:c.682G>A
ENST00000535915.5:c.1063G>A
ENST00000545707.5:c.805G>A
ENST00000557933.5:c.1186G>A
ENST00000558013.5:c.1186G>A
ENST00000558518.5:c.1186G>A
ENST00000560173.1:n.185G>A
ENST00000560467.1:c.666G>A
NM_000527.4:c.1186G>A
NM_001195798.1:c.1186G>A
NM_001195799.1:c.1063G>A
NM_001195800.1:c.682G>A
NM_001195803.1:c.805G>A
NM_001195798.2:c.1186G>A
NM_001195799.2:c.1063G>A
NM_001195800.2:c.682G>A
NM_001195803.2:c.805G>A

Likely Pathogenic

Met criteria codes 6

PS4_Supporting PP1_Moderate PP3 PP4 PM2 PM3

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Not Met criteria codes 2

BS3 PM5

Evidence Links 1

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1186G>A (p.Gly396Ser) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PS4_Supporting, PM3, PP1_Moderate) 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: PM2: This variant is absent from gnomAD (gnomAD version 2.1.1). PP3: REVEL=0.774, which is above threshold of 0.75, met PP3, splicing prediction is not required by these guidelines. However, this variant is located at the end of exon 8 within canonical donor motif, and is predicted to affect donor site splicing process in scenario A, donor site: The variant is located at -3 to +6 bases of canonical donor splicing site of exon 8. Wild type canonical donor motif: TGGGTGAGC, MES: 7.23; Variant canonical donor motif: TGAGTGAGC, MES: 3.38. Var/Wt ratio = 0.47 (<0.8), also met PP3. PP4: Variant meets PM2 and is identified in >1 index cases who fulfil FH diagnostic criteria after alternative causes of high cholesterol were excluded. PS4_Supporting: Variant meets PM2 and is identified in 2 unrelated index case who fulfil DLCN criteria for FH diagnosis, one case reported by Koivisto et al, 1995, University of Helsinki, Finland; PMID 7573037; one case reported from Robarts Research Institute, Canada. PM3: This variant meets PM2, and is identified in a HoFH index case (LDLC 14.9 mmol/l at age of 3yrs) and LDLR:c.16_17insTTCCT:p.W6fs (ClinVarID 369864), classified as Pathogenic by these guidelines. Two variants are confirmed in trans, reported from Robarts Research Institute, Canada. PP1_Moderate: Variant segregates with FH phenotype in at least 4 informative meiosis from two families. Three affected family members tested positive for the variant from one family, reported from Robarts Research Institute, Canada. At least 1 co-segregation with hypercholesterolemia was observed from one family, reported by Koivisto et al, 1995, University of Helsinki, Finland; PMID 7573037. BS3 not met: Level 1 assays of whole LDLR cycle performed in LDLR-/- fibroblasts (549T cells) infected with recombinant retroviruses expressing WT LDLR and the variant. Assay results shown cells expressing G396S had no effect on lipoprotein uptake and no defects in receptor distribution, lipoprotein binding, or acid-dependent release, reported by Zhao and Michaely, 2011, Department of Cell Biology at the University of Texas Southwestern Medical Center, US, PMID 21511053. The functional study is not consistent with damaging effect. The experiments did not include splicing mechanism, variant affecting splicing process would not be validated in this study. PM5 not met: Three other missense variants in the same codon: NM_000527.5 (LDLR):c.1186G>C (p.Gly396Arg), (ClinVarID 870321), NM_000527.5 (LDLR):c.1187G>T (p.Gly396Val), (ClinVarID 924165), NM_000527.5 (LDLR):c.1187G>A (p.Gly396Asp), (ClinVarID 440630). None is classified as Pathogenic by these guidelines, therefore PM5 is not met.

Met criteria codes

PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated index case who fulfil DLCN criteria for FH diagnosis, one case reported by Koivisto et al, 1995, University of Helsinki, Finland; PMID 7573037; one case reported from Robarts Research Institute, Canada.
PP1_Moderate	✔	Variant segregates with FH phenotype in at least 4 informative meiosis from two families. Three affected family members tested positive for the variant from one family, reported from Robarts Research Institute, Canada. At least 1 co-segregation with hypercholesterolemia was observed from one family, reported by Koivisto et al, 1995, University of Helsinki, Finland; PMID 7573037.
PP3	✔	REVEL=0.774, which is above threshold of 0.75, splicing prediction is not required by these guidelines. However, this variant is located at the end of exon 8 within canonical donor motif, and is predicted to affect donor site splicing process in scenario A, donor site: The variant is located at -3 to +6 bases of canonical donor splicing site of exon 8. Wild type canonical donor motif: TGGGTGAGC, MES: 7.23; Variant canonical donor motif: TGAGTGAGC, MES: 3.38. Var/Wt ratio = 0.47 (<0.8), also met PP3.

PP4	✔	Variant meets PM2 and is identified in >1 index cases who fulfil FH diagnostic criteria after alternative causes of high cholesterol were excluded.
PM2	✔	This variant is absent from gnomAD (gnomAD version 2.1.1).
PM3	✔	This variant meets PM2, and is identified in a HoFH index case (LDLC 14.9 mmol/l at age of 3yrs) and LDLR:c.16_17insTTCCT:p.W6fs (ClinVarID 369864), classified as Pathogenic by these guidelines. Two variants are confirmed in trans, reported from Robarts Research Institute, Canada.

Not Met criteria codes

BS3	✖	Level 1 assays of whole LDLR cycle performed in LDLR-/- fibroblasts (549T cells) infected with recombinant retroviruses expressing WT LDLR and the variant. Assay results shown cells expressing G396S had no effect on lipoprotein uptake and no defects in receptor distribution, lipoprotein binding, or acid-dependent release, reported by Zhao and Michaely, 2011, Department of Cell Biology at the University of Texas Southwestern Medical Center, US, PMID 21511053. The functional study is not consistent with damaging effect. The experiments did not include splicing mechanism, variant affecting splicing process would not be validated in this study. Level 1 assays of whole LDLR cycle performed in LDLR-/- fibroblasts (549T cells) infected with recombinant retroviruses expressing WT LDLR and variants. Cells expressing G396S had no effect on lipoprotein uptake and no defects in receptor distribution, lipoprotein binding, or acid-dependent release. PubMed:21511053
PM5	✖	Three other missense variants in the same codon: NM_000527.5 (LDLR):c.1186G>C (p.Gly396Arg), (ClinVarID 870321), NM_000527.5 (LDLR):c.1187G>T (p.Gly396Val), (ClinVarID 924165), NM_000527.5 (LDLR):c.1187G>A (p.Gly396Asp), (ClinVarID 440630). None is classified as Pathogenic by these guidelines, therefore PM5 is not met.

Curation History

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