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.681C>G (p.Asp227Glu)

Version: 1.0

CA023747

3690 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 6b534fab-a9cf-4d1a-bd7c-7d69822bbe48
Approved on: 2022-04-29
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HGVS expressions

NM_000527.5:c.681C>G
NM_000527.5(LDLR):c.681C>G (p.Asp227Glu)
NC_000019.10:g.11105587C>G
CM000681.2:g.11105587C>G
NC_000019.9:g.11216263C>G
CM000681.1:g.11216263C>G
NC_000019.8:g.11077263C>G
NG_009060.1:g.21207C>G
ENST00000252444.10:c.939C>G
ENST00000559340.2:c.681C>G
ENST00000560467.2:c.681C>G
ENST00000558518.6:c.681C>G
ENST00000252444.9:c.935C>G
ENST00000455727.6:c.314-1805C>G
ENST00000535915.5:c.558C>G
ENST00000545707.5:c.314-978C>G
ENST00000557933.5:c.681C>G
ENST00000558013.5:c.681C>G
ENST00000558518.5:c.681C>G
ENST00000560467.1:c.281C>G
NM_000527.4:c.681C>G
NM_001195798.1:c.681C>G
NM_001195799.1:c.558C>G
NM_001195800.1:c.314-1805C>G
NM_001195803.1:c.314-978C>G
NM_001195798.2:c.681C>G
NM_001195799.2:c.558C>G
NM_001195800.2:c.314-1805C>G
NM_001195803.2:c.314-978C>G

Pathogenic

Met criteria codes 7

PP1_Strong PS4 PP3 PP4 PM2 PM1 PS3_Moderate

Evidence Links 1

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.681C>G (p.Asp227Glu) variant, also known as ‘FH Afrikaner-1’ or ‘FH Maine’, is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PP1_Strong, PS3_Moderate, PM1, PM2, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 29 April 2022. The supporting evidence is as follows: PM2: PopMax MAF = 0.00002899 (0.003%) in Latino/Admixed American exomes (gnomAD v2.1.1). PP3: REVEL = 0.864. PM1: Variant meets PM2 and is missense located in exon 4. PS3_Moderate: Level 2 assay PMID 1301956 (Hobbs et al., 1992): Homozygous patient's fibroblasts studied with radiolabeled LDL results in 5-15% LDLR activity. Functional study is consistent with damaging effect. Level 2 assay PMID 2569482 (Leitersdorf et al., 1989): Partial cycle of LDLR studied in CHO Cells. WB after immunoprecipitation of radiolabelled LDLR variant show <50% of WT LDLR expression. PS4, PP4: Variant meets PM2 and is identified in 33 index cases who fulfil SB criteria for FH (n=1 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) or DLCN criteria for FH (n=2 Robarts Research Institute; n=2 Color Health, Inc.; n=3 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=25 Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA). PP1_Strong: Variant segregates with FH in at least 22 informatives meioses from at least 2 families from different labs (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia): 20 affected family members have the variant and 2 unaffected family members do not have the variant.

Met criteria codes

PP1_Strong	✔	Variant segregate with FH in 2 informatives meiosis (LDL-C > 75th percentile) from 1 family from CGMC, UFGOD (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) and in 18 relatives positive for variant (LDL-C > 75th percentile) and 2 relatives negative for variant (LDL-C < 50th percentile) from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA).
PS4	✔	Variant meets PM2 and is identified in 33 index cases who fulfil SB criteria for FH (n=1 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) or DLCN criteria for FH (n= 2 Robarts Research Institute; n=2 Color Health, Inc.; n=3 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=25 Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA))
PP3	✔	REVEL = 0.754. It is above 0.75
PP4	✔	Variant meets PM2 and is identified in 29 index cases who fulfil SB criteria for FH (n=1 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) or DLCN criteria for FH (n= 2 Robarts Research Institute; n=2 Color Health, Inc.; n=4 CGMC, UFGOD, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière; n=25 Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA))
PM2	✔	PopMax MAF = 0.00002899 (0,003%) in Latino/Admixed American exomes (gnomAD v2.1.1).
PM1	✔	Variant meets PM2 and is missense located in exon 4 .
PS3_Moderate	✔	Level 2 assay PMID: 1301956: Homozygous patient's fibroblasts studied with radiolabeled LDL results in 5-15% LDLR activity. Functionnal study is consistent with damaging effect." Level 2 assay PMID: 2569482 Partial cycle of LDLR

studied in CHO Cells. WB after immunoprecipitation of radiolabelled LDLR variant show <50% of WT LDLR expression.

Level 2 assay CHO Cells, 125I-LDL assays <50% LDLR expression PubMed:2569482

Curation History

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