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.2475C>G (p.Asn825Lys)

Version: 1.0

CA023675

161265 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: a366bd5f-25ad-4977-b948-cb45aa320c0c
Approved on: 2023/3/20
Published on: 2023/3/31

HGVS expressions

NM_000527.5(LDLR):c.2475C>G (p.Asn825Lys)
NM_000527.5:c.2475C>G
NC_000019.10:g.11129598C>G
CM000681.2:g.11129598C>G
NC_000019.9:g.11240274C>G
CM000681.1:g.11240274C>G
NC_000019.8:g.11101274C>G
NG_009060.1:g.45218C>G
ENST00000252444.10:c.2733C>G
ENST00000559340.2:c.*544C>G
ENST00000560467.2:c.2355C>G
ENST00000558518.6:c.2475C>G
ENST00000252444.9:c.2729C>G
ENST00000455727.6:c.1971C>G
ENST00000535915.5:c.2352C>G
ENST00000545707.5:c.1941C>G
ENST00000557933.5:c.2537C>G
ENST00000558013.5:c.2475C>G
ENST00000558518.5:c.2475C>G
ENST00000560628.1:n.108+1944C>G
NM_000527.4:c.2475C>G
NM_001195798.1:c.2475C>G
NM_001195799.1:c.2352C>G
NM_001195800.1:c.1971C>G
NM_001195803.1:c.1941C>G
NM_001195798.2:c.2475C>G
NM_001195799.2:c.2352C>G
NM_001195800.2:c.1971C>G
NM_001195803.2:c.1941C>G

Likely Pathogenic

Met criteria codes 5

PM2 PS4_Supporting PS1 PP3 PP4

Not Met criteria codes 1

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PS3

Evidence Links 0

Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2*

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.2475C>G (p.Asn825Lys) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PS1, PP4, PS4_Supporting) 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: PopMax MAF = 0.00002 in European (Non-Finnish) in gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.803. PS1: One other missense variant that leads to the same amino acid change at same codon, NM_000527.5 (LDLR):c.2475C>A (p.Asn825Lys), (ClinVarID 252341), is classified as Pathogenic by these guidelines. 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 5 index cases who fulfil FH diagnostic criteria. Four index cases met DLCN criteria for definite or probable FH: 1 case from Department of Medicine and Cardiology, Aarhus Amtssygehus University Hospital, Denmark, PMID 10532689; 1 case from Department of Vascular Medicine, Academic Medical Center at the University of Amsterdam, The Netherlands, PMID 11810272; 1 case from Robarts Research Institute, Canada, PMID 11668627; 1 case submitted to ClinVar from U4M - Lille University & CHRU Lille, France. One proband with LDLC >10mmol/l and xanthoma, reported by Jiang et al, 2016, Department of atherosclerosis, Capital Medical University, China, PMID 27830735.

Met criteria codes

PM2	✔	PopMax MAF = 0.00002 in European (Non-Finnish) in gnomAD (gnomAD v2.1.1).
PS4_Supporting	✔	Variant meets PM2 and is identified in 5 index cases who fulfil FH diagnostic criteria. Four index cases met DLCN criteria for definite or probable FH: 1 case from Department of Medicine and Cardiology, Aarhus Amtssygehus University Hospital, Denmark, PMID 10532689; 1 case from Department of Vascular Medicine, Academic Medical Center at the University of Amsterdam, The Netherlands, PMID 11810272; 1 case from Robarts Research Institute, Canada, PMID 11668627; 1 case submitted to ClinVar from U4M - Lille University & CHRU Lille, France. One proband with LDLC >10mmol/l and xanthoma, reported by Jiang et al, 2016, Department of atherosclerosis, Capital Medical University, China, PMID 27830735.
PS1	✔	One other missense variant that leads to the same amino acid change at same codon, NM_000527.5 (LDLR):c.2475C>A (p.Asn825Lys), (ClinVarID 252341), is classified as Pathogenic by these guidelines.
PP3	✔	REVEL = 0.803
PP4	✔	Variant meets PM2 and is identified in >1 index cases who fulfil FH diagnostic criteria after alternative causes of high cholesterol were excluded.

Not Met criteria codes

PS3		✖	Functional data is not available.

Curation History

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