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.2473A>G (p.Asn825Asp)

Version: 1.0

CA10585869

252340 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 39d43aca-1749-4ce4-9fa8-d7ff03c0e481
Approved on: 2023/3/20
Published on: 2023/3/31

HGVS expressions

NM_000527.5:c.2473A>G
NM_000527.5(LDLR):c.2473A>G (p.Asn825Asp)
NC_000019.10:g.11129596A>G
CM000681.2:g.11129596A>G
NC_000019.9:g.11240272A>G
CM000681.1:g.11240272A>G
NC_000019.8:g.11101272A>G
NG_009060.1:g.45216A>G
ENST00000252444.10:c.2731A>G
ENST00000559340.2:c.*542A>G
ENST00000560467.2:c.2353A>G
ENST00000558518.6:c.2473A>G
ENST00000252444.9:c.2727A>G
ENST00000455727.6:c.1969A>G
ENST00000535915.5:c.2350A>G
ENST00000545707.5:c.1939A>G
ENST00000557933.5:c.2535A>G
ENST00000558013.5:c.2473A>G
ENST00000558518.5:c.2473A>G
ENST00000560628.1:n.108+1942A>G
NM_000527.4:c.2473A>G
NM_001195798.1:c.2473A>G
NM_001195799.1:c.2350A>G
NM_001195800.1:c.1969A>G
NM_001195803.1:c.1939A>G
NM_001195798.2:c.2473A>G
NM_001195799.2:c.2350A>G
NM_001195800.2:c.1969A>G
NM_001195803.2:c.1939A>G

Likely Pathogenic

Met criteria codes 5

PS4_Supporting PP3 PP4 PM2 PM5

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.2473A>G (p.Asn825Asp) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PS4_Supporting, PM5) 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 v2.1.1). PP3: REVEL = 0.93. 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 cases who fulfil FH diagnostic criteria. One index case fulfil criteria of TC > 8mmol/l and strong family history of CAD, Laurie et al, 2004, Canterbury Health Laboratories, New Zealand, PMID: 15556094. One index case with DLCN score ≥6, Meshkov et al, 2021, National Medical Research Center for Therapy and Preventive Medicine, Russia, PMID: 33418990. PM5: Two other missense variants in the same codon: NM_000527.5 (LDLR):c.2475C>G (p.Asn825Lys), (ClinVarID 161265), is classified as Likely Pathogenic; NM_000527.5 (LDLR):c.2475C>A (p.Asn825Lys), (ClinVarID 252341), is classified as Pathogenic by these guidelines, therefore PM5 is met.

Met criteria codes

PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated index cases who fulfil FH diagnostic criteria. One index case fulfil criteria of TC > 8mmol/l and strong family history of CAD, Laurie et al, 2004, Canterbury Health Laboratories, New Zealand, PMID: 15556094. One index case with DLCN score ≥6, Meshkov et al, 2021, National Medical Research Center for Therapy and Preventive Medicine, Russia, PMID: 33418990.
PP3	✔	REVEL = 0.93
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 v2.1.1).
PM5	✔	Two other missense variants in the same codon: NM_000527.5 (LDLR):c.2475C>G (p.Asn825Lys), (ClinVarID 161265), is classified as Likely Pathogenic; NM_000527.5 (LDLR):c.2475C>A (p.Asn825Lys), (ClinVarID 252341), is classified as Pathogenic by these guidelines, therefore PM5 is met.

Not Met criteria codes

PS3	✖	Functional data is not available.

Curation History

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