

Variant: *NM_000527.5(LDLR):c.2126G>A (p.Arg709Lys)*

Version: 1.0

CA023641 [↗](#)

183132 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 881f0b90-6bad-48a9-8769-6b78bdc81962

Approved on: 2024/10/28

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HGVS expressions

NM_000527.5(LDLR):c.2126G>A (p.Arg709Lys)

NM_000527.5:c.2126G>A

NC_000019.10:g.11120508G>A

CM000681.2:g.11120508G>A

NC_000019.9:g.11231184G>A

CM000681.1:g.11231184G>A

NC_000019.8:g.11092184G>A

NG_009060.1:g.36128G>A

ENST00000252444.10:c.2384G>A

ENST00000559340.2:c.*195G>A

ENST00000560467.2:c.2006G>A

ENST00000558518.6:c.2126G>A

ENST00000252444.9:c.2380G>A

ENST00000455727.6:c.1622G>A

ENST00000535915.5:c.2003G>A

ENST00000545707.5:c.1606+275G>A

ENST00000557933.5:c.2126G>A

ENST00000558013.5:c.2126G>A

ENST00000558518.5:c.2126G>A

NM_000527.4:c.2126G>A

NM_001195798.1:c.2126G>A

NM_001195799.1:c.2003G>A

NM_001195800.1:c.1622G>A

NM_001195803.1:c.1606+275G>A

NM_001195798.2:c.2126G>A

NM_001195799.2:c.2003G>A

NM_001195800.2:c.1622G>A

NM_001195803.2:c.1606+275G>A

Uncertain Significance

Met criteria codes **2**

PP3

PM2

Not Met criteria codes **5**

PS3

PS4

PP4

PM5

BS3

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

- [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.2126G>A (p.Arg709Lys) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2 and PP3 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 28 October 2024. The supporting evidence is as follows: PM2: PopMax MAF=0.000003390 in non-Finnish European exomes+genomes (gnomAD v4.1.0). PP3: REVEL=0.842.

Met criteria codes

PP3			REVEL=0.842, which is above impact threshold.
PM2			PopMaxMAF=0.000003390 in non-Finnish European exomes+genomes (gnomAD v4.1.0).

Not Met criteria codes

PS3			Functional data is not available.
PS4			Clinical data is not available.
PP4			Clinical data is not available.
PM5			One other variant in the same codon: NM_000527.5 (LDLR):c. 2125A>G (p.Arg709Gly)(ClinVarID 375833) is classified as VUS by these guidelines. Therefore, PM5 is not met.
BS3			BS3_Supporting not met – In vitro microscopy assays in HeLa cells shown LDLR activity similar to WT - considered as non-disruptive, reported by Thormaehlen et al, 2015 in PMID2564724, from University of Heidelberg, Germany. However, it has been decided by FH VCEP that the results from PMID2564724 are ok to be used towards PS3_Supporting, but not towards BS3_Supporting, because the functional study from this report did not look at the whole LDLR cycle.

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