

Variant: NM_000527.5(LDLR):c.1567G>A (p.Val523Met)

Version: 1.0

CA023525 [↗](#)

3696 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 807ceefc-47d3-4100-bd75-2ef587f3e26b

Approved on: 2023/1/27

Published on: 2024/10/7

HGVS expressions

NM_000527.5:c.1567G>A

NM_000527.5(LDLR):c.1567G>A (p.Val523Met)

NC_000019.10:g.11113743G>A

CM000681.2:g.11113743G>A

NC_000019.9:g.11224419G>A

CM000681.1:g.11224419G>A

NC_000019.8:g.11085419G>A

NG_009060.1:g.29363G>A

ENST00000252444.10:c.1825G>A

ENST00000559340.2:c.1567G>A

ENST00000560467.2:c.1447G>A

ENST00000558518.6:c.1567G>A

ENST00000252444.9:c.1821G>A

ENST00000455727.6:c.1063G>A

ENST00000535915.5:c.1444G>A

ENST00000545707.5:c.1186G>A

ENST00000557933.5:c.1567G>A

ENST00000558013.5:c.1567G>A

ENST00000558518.5:c.1567G>A

ENST00000559340.1:c.288G>A

NM_000527.4:c.1567G>A

NM_001195798.1:c.1567G>A

NM_001195799.1:c.1444G>A

NM_001195800.1:c.1063G>A

NM_001195803.1:c.1186G>A

NM_001195798.2:c.1567G>A

NM_001195799.2:c.1444G>A

NM_001195800.2:c.1063G>A

NM_001195803.2:c.1186G>A

Pathogenic

Met criteria codes **7**

PP1_Strong

PS4

PP3

PP4

PS3_Moderate

PM2

PM3

Not Met criteria codes **10**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR): c.1567G>A (p.Val523Met) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PP1_Strong, PM2, PM3, PS3_Moderate, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 27 January 2023. The supporting evidence is as follows: PM2: PopMax MAF = 0.00003266 (0.003%) in East Asian (gnomAD v2.1.1). PP3: REVEL = 0.917. PS3_Moderate: Functional studies: PMID 1301956 (Hobbs et al., 1992), Level 2 assay using homozygous patients' fibroblasts, 125I-LDL assays - 15-30% LDLR activity (but all cycle was tested) // PMID 9974426 (Bertolini et al., 1999), Level 2 assay using homozygous patient fibroblast, 125I-LDL assays - 25% LDLR activity, (mention of testing LDL binding, internalization, and degradation) // PMID 21865347 (Romano et al., 2011), Level 3 assays using heterozygous patients' Epstein-Barr virus transformed lymphocytes and FACS assays - 30-40% LDLR activity. // PMID 25647241 (Thormaehlen et al., 2015), functional studies using HeLa cells and alternative microscopy assay showed that the LDLR activity is decreased compared to WT and was considered as "disruptive" ----- Overall, functional studies (PMID 1301956, 9974426, 21865347) show an activity below 70% of wild-type, consistent with damaging effect and PS3 is met. PS4, PP4: Variant meets PM2 and is identified in at least 22 unrelated cases, 2 fulfilling Simon-Broome criteria (GeneDx) and 20 with DLCN score >=6 (Service de Biochimie et de Biologie Moléculaire, France; Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine, Italy; Robarts Research Institute, Canada). PP1_Strong: variant segregates with FH phenotype in 14 informative meioses in 8 families from different labs (Service de Biochimie et de Biologie Moléculaire, France; Laboratory of Genetics and Molecular Cardiology, Brazil; Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine, Italy): 11 affected family members have the variant and 3 non-affected family members do not have the variant. PM3: 1 case reported from Service de Biochimie et de Biologie Moléculaire, France (homozygous and LDL-cholesterol 12 mmol/L at 4 years old).

Met criteria codes

PP1_Strong			PP1_Strong: variant segregates with FH phenotype in 14 informative meioses in 8 families from different labs (Service de Biochimie et de Biologie Moléculaire, France; Laboratory of Genetics and Molecular Cardiology; and, Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine): 11 affected family members have the variant and 3 non-affected family members do not have the variant. So, PP1_Strong is met.
PS4			PS4: Variant meets PM2 and is identified in at least 22 unrelated cases, 2 fulfilling Simon-Broome criteria (GeneDx) and 20 presenting Dutch lipid clinic network >=6 criteria (Service de Biochimie et de Biologie Moléculaire, France; Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine; and, Robarts Research Institute). In the relevant evidence column are mentioned several PMIDs reporting more individuals).
PP3			PP3: REVEL = 0.917. It is above 0.75.
PP4			PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills possible/definite FH criteria (DLCN>=6/SB) after alternative causes of high cholesterol were excluded from the Service de Biochimie et de

Biologie Moléculaire, France; Laboratory of Genetics and Molecular Cardiology; and, Research Lab of Molecular Genetics of Lipid Metabolism).

PS3_Moderate			PS3_Moderate: Functional studies: (PMID: 1301956) Level 2 assay using Homozygous patients' fibroblasts, 125I-LDL assays - results - 15-30% LDLR activity (but all cycle was tested) // (PMID: 9974426) Level 2 assay using Homozygous patient fibroblast, 125I-LDL assays - results - 25% LDLR activity, (mention of testing LDL binding, internalization, and degradation) // (PMID: 21865347) Level 3 assays using Heterozygous patients' Epstein-Barr virus transformed lymphocytes and FACS assays - results - 30-40% LDLR activity. // (PMID:25647241) functional studies using HeLa cells and alternative microscopy assay showed that the LDLR activity is decreased compared to WT and was considered as "disruptive" ----- Overall, functional studies (PMID:1301956, 9974426, 21865347) show an activity below 70% of wild-type, so functional study is consistent with damaging effect and PS3 is met.
PM2			PM2: PopMax MAF = 0.00003266 (0.003%) in East Asian (gnomAD v2.1.1). PM2 is met since PopMax MAF < 0.02%.
PM3			PM3: 1 case reported in the VCI (from Service de Biochimie et de Biologie Moléculaire, France) is homozygous and presents LDLc 12 mmol/L at 4 years old.

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			Not applicable
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No instance of variant non-segregation with FH phenotype in at least 2 informative meiosis from at least 2 families with at least one unaffected relative (LDL-C <50th centile) who is positive for the variant.
PM1			PM1_Not Met : Variant meets PM2 but it is in exon 10.
PM5			PM5_Not Met : There are 2 missense variants that lead to a different amino acid change (c.1567G>C and c.1567G>T (p.Val523Leu)) but they are not classified as pathogenic by these guidelines.
BP5			Not applicable
BP4			REVEL = 0.917. It is not below 0.50.
BP1			Not applicable

Curation History 

Showing 1 to 1 of 1 rows

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