

Variant: NM_000527.5(LDLR):c.718G>A (p.Glu240Lys)

Version: 1.1

CA023755 [↗](#)

200920 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 54c170e0-5a9b-4b98-b1d4-806c3082ce85

Approved on: 2022/2/14

Published on: 2022/7/12

HGVS expressions

NM_000527.5(LDLR):c.718G>A (p.Glu240Lys)

NM_000527.5:c.718G>A

NC_000019.10:g.11106588G>A

CM000681.2:g.11106588G>A

NC_000019.9:g.11217264G>A

CM000681.1:g.11217264G>A

NC_000019.8:g.11078264G>A

NG_009060.1:g.22208G>A

ENST00000252444.10:c.976G>A

ENST00000559340.2:c.718G>A

ENST00000560467.2:c.718G>A

ENST00000558518.6:c.718G>A

ENST00000252444.9:c.972G>A

ENST00000455727.6:c.314-804G>A

ENST00000535915.5:c.595G>A

ENST00000545707.5:c.337G>A

ENST00000557933.5:c.718G>A

ENST00000558013.5:c.718G>A

ENST00000558518.5:c.718G>A

ENST00000558528.1:n.233G>A

ENST00000560467.1:c.318G>A

NM_000527.4:c.718G>A

NM_001195798.1:c.718G>A

NM_001195799.1:c.595G>A

NM_001195800.1:c.314-804G>A

NM_001195803.1:c.337G>A

NM_001195798.2:c.718G>A

NM_001195799.2:c.595G>A

NM_001195800.2:c.314-804G>A

NM_001195803.2:c.337G>A

Pathogenic

Met criteria codes 5

PP3PP4PM3PM2PS4

Not Met criteria codes 17

BA1BP7BP4BP2BS2BS1BS4BS3PP1PM1PM5PM4PM6PVS1PS1PS2PS3

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.718G>A (p.Glu240Lys) variant is classified as U Pathogenic for Familial Hypercholesterolemia by applying evidence codes PP3, PM2, PS4, PM3, PP4 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: PP3 - REVEL = 0.865. It is above 0.75, so PP3 is Met. PM2 - PopMax MAF = 0.00005418 (0.005418%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so PM2 is Met. PS4 - Variant meets PM2 and is identified in at least 11 unrelated index cases: 2 index cases with Simon Broome possible from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 1 index case with DLCN>6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 2 index cases with DLCN>6 from Robarts Research Institute; 2 index cases with DLCN>6 from Color Health, Inc; 2 index cases fulfilling the following criteria: children with a) TC >200 mg/dl or LDL >120 mg/dl and b) presence of primary hypercholesterolemia in 1st degree relatives with autosomal dominant mode of inheritance or c) family history of pCHD or d) presence of xanthomas in proband or in parents, from Greece (PMID: 25463123); at least 1 index case with Simon Broome criteria from China (PMID: 28235710); 1 index case with Definite FH (LDL >13 mmol/l and presence of xanthomas and hypercholesterolemia in both parents) from Italy (PMID: 32977124), so PS4 is Met. PM3 - Variant meets PM2 and is identified in an italian index case with homozygous FH phenotype (LDL>13 mmol/l) with another LDLR variant, in trans (PMID: 32977124). In PMID: 28965616 is identified an italian index case (phenotype not reported) with LDLR variant c.304C>T (p.Gln102*), classified as Pathogenic by these guidelines, but cannot determine if the variants are in trans (PMID: 28965616). Assuming that is the same homozygous index case (same lab), PM3 is Met. PP4 - Variant meets PM2 and is identified in at least 11 unrelated index cases as reported above, so PP4 is Met.

Met criteria codes		
PP3		REVEL = 0.865. It is above 0.75, so PP3 is Met.
PP4		Variant meets PM2 and is identified in at least 11 unrelated index cases: 2 index cases with Simon Broome possible from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 1 index case with DLCN>6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 2 index cases with DLCN>6 from Robarts Research Institute; 2 index cases with DLCN>6 from Color Health, Inc; 2 index cases fulfilling the following criteria: children with a) TC >200 mg/dl or LDL >120 mg/dl and b) presence of primary hypercholesterolemia in 1st degree relatives with autosomal dominant mode of inheritance or c) family history of pCHD or d) presence of xanthomas in proband or in parents, from Greece (PMID: 25463123); at least 1 index case with Simon Broome criteria from China (PMID: 28235710); 1 index case with Definite FH (LDL >13 mmol/l and presence of xanthomas and hypercholesterolemia in both parents) from Italy (PMID: 32977124), so PP4 is Met.

PM3			Variant meets PM2 and is identified in an italian index case with homozygous FH phenotype (LDL>13 mmol/l) with another LDLR variant, in trans (PMID: 32977124). In PMID: 28965616 is identified an italian index case (phenotype not reported) with LDLR variant c.304C>T (p.Gln102*), classified as Pathogenic by these guidelines, but cannot determine if the variants are in trans (PMID: 28965616). Assuming that is the same homozygous index case (same lab), PM3 is Met.
PM2			PopMax MAF = 0.00005418 (0.005418%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so PM2 is Met.
PS4			Variant meets PM2 and is identified in at least 11 unrelated index cases: 2 index cases with Simon Broome possible from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 1 index case with DLCN>6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 2 index cases with DLCN>6 from Robarts Research Institute; 2 index cases with DLCN>6 from Color Health, Inc; 2 index cases fulfilling the following criteria: children with a) TC >200 mg/dl or LDL >120 mg/dl and b) presence of primary hypercholesterolemia in 1st degree relatives with autosomal dominant mode of inheritance or c) family history of pCHD or d) presence of xanthomas in proband or in parents, from Greece (PMID: 25463123); at least 1 index case with Simon Broome criteria from China (PMID: 28235710); 1 index case with Definite FH (LDL >13 mmol/l and presence of xanthomas and hypercholesterolemia in both parents) from Italy (PMID: 32977124), so PS4 is Met.

Not Met criteria codes

BA1			FAF = 0.00002293 (0.002293%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so BA1 is not met.
BP7			Variant is not synonymous, so BP7 is Not Met
BP4			REVEL = 0.865. It is not below 0.50, so BP4 is Not Met.
BP2			Observed in an index case (phenotype not reported) with another LDLR variant c.304C>T (p.Gln102*), classified as Pathogenic by these guidelines, but cannot determine if the variants are in trans (PMID: 28965616), so BP2 is Not Met.
BS2			Not observed in 10000 normolipidemic individuals from Robarts Research Institute, so BS2 is note met.
BS1			FAF = 0.00002293 (0.002293%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so BA1 is not met.
BS4			Lack of segregation data not reported, so BS4 is Not Met.
BS3			Functional studies are performed in compound heterozygous patients cells or the type of assays are not validated, so BS3 is not applicable.
PP1			Segregation data not reported, so PP1 is Not Met.
PM1			Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.

PM5			No more missense variants at the same codon, so PM5 is Not Met.
PM4			Variant meets PM2 and is missense, so PM4 is Not Met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.
PVS1			Variant is missense, so PVS1 is Not Met.
PS1			No more missense variants that lead to the same amino acid change, so PS1 is Not Met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.
PS3			Functional studies are performed in compound heterozygous patients cells or the type of assays are not validated, so PS3 is not applicable.

Curation History 		
Showing 1 to 2 of 2 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.