

Variant: *NM_000527.5(LDLR):c.313+2T>C*

Version: 1.1

CA023690 [↗](#)

189296 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: be57d00e-452f-4bdc-b48a-3ee5b727c648

Approved on: 2022/2/14

Published on: 2022/7/12

HGVS expressions

NM_000527.5:c.313+2T>C

NM_000527.5(LDLR):c.313+2T>C

NC_000019.10:g.11102788T>C

CM000681.2:g.11102788T>C

NC_000019.9:g.11213464T>C

CM000681.1:g.11213464T>C

NC_000019.8:g.11074464T>C

NG_009060.1:g.18408T>C

ENST00000252444.10:c.571+2T>C

ENST00000559340.2:c.313+2T>C

ENST00000560467.2:c.313+2T>C

ENST00000558518.6:c.313+2T>C

ENST00000252444.9:c.567+2T>C

ENST00000455727.6:c.313+2T>C

ENST00000535915.5:c.191-2432T>C

ENST00000545707.5:c.313+2T>C

ENST00000557933.5:c.313+2T>C

ENST00000557958.1:n.401T>C

ENST00000558013.5:c.313+2T>C

ENST00000558518.5:c.313+2T>C

NM_000527.4:c.313+2T>C

NM_001195798.1:c.313+2T>C

NM_001195799.1:c.191-2432T>C

NM_001195800.1:c.313+2T>C

NM_001195803.1:c.313+2T>C

NM_001195798.2:c.313+2T>C

NM_001195799.2:c.191-2432T>C

NM_001195800.2:c.313+2T>C

NM_001195803.2:c.313+2T>C

Pathogenic

Met criteria codes **7**

PP1_Moderate

PS3_Moderate

PS4

PP4

PM2

PM3

PVS1_Strong

Not Met criteria codes **15**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

BS1

BS4

BS3

BP7

BP4

BP2

PS1

PS2

PP3

BA1

PM6

PM1

PM5

PM4

Evidence Links

0

- 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.313+2T>C variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PS3_moderate, PVS1_strong, PP1_moderate, 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: PM2 - PopMax MAF = 0.00002941 (0.002941%) in European (non-Finnish) exomes (gnomAD v3.1.2), so PM2 is Met. PS3_moderate - Level 2 assays: PMID 19026292: Homozygous patient cells, 125I-LDL assays - result - 10% LDLR activity. ---- functional study is consistent with damaging effect, so PS3_Moderate is Met. PVS1_strong - Variant is in +2 intronic position, but there are no studies on effect predicted, so give PVS1_Strong to be conservative. PP1_moderate - Variant segregates with FH phenotype in 4 informative meioses from 2 families: 2 relatives with the phenotype and the variant from Robarts Research Institute, and 2 affected family members with the variant from Germany (PMID: 26036859), so PP1_Moderate is Met. PS4 - Variant meets PM2 and is identified in 19 unrelated index cases from different labs (4 index cases with DLCN>6 from Robarts Research Institute; 4 index cases with DLCN>6 from Color Health, Inc; 1 index case who fulfills the following criteria for FH: i) total cholesterol >= 9.5 mmol/l, ii) triglycerides < 2 mmol/l, iii) presence of tendon xanthomas; or iv) occurrence of hypercholesterolemia or early onset of coronary artery disease in first degree relatives, from The Netherlands (PMID: 7616128); 3 index cases with DLCN>6 (LDL between 7,98 - 9,50 mmol/l and hypercholesterolemia in 1st degree relative) from Germany (PMID: 11462246); 1 index case who fulfills the following criteria for FH: (1) LDL > 95th percentile and triglycerides below 2 mmol/l, and (2) the presence of xanthoma or CHD in the proband or 1st degree relative with type IIa hypercholesterolemia, xanthoma, or CVD, from France (PMID: 12436241); 1 index case with SB criteria for FH (Total cholesterol >290 mg/dL and LDL >200 mg/dL and severe hypercholesterolemia in 1st degree relatives), from Germany (PMID: 14974088); 1 index case with definite FH according to SB criteria from Northern Ireland (PMID: 16159606); 3 index cases fulfilling the following criteria for FH: i) total cholesterol > 8.0 mmol/l and LDL > 6 mmol/l; (ii) premature coronary or vascular disease, or a family history of cardiovascular disorder; and (iii) the presence of tendon xanthoma, from Denmark (PMID: 16542394); 1 index case with definite FH according to SB criteria (total cholesterol = 658 mg/dl and presence of xanthomas, and primary hypercholesterolemia in the probands’ parents or 1st degree relatives), from USA (PMID: 19026292)), so PS4 is Met. PM3 - Variant meets PM2 and is identified in a true homozygous with total cholesterol = 658 mg/dl (PMID: 19026292), so PM3 is Met. PP4 - Variant meets PM2 and is identified in 19 unrelated index cases from different labs as described, so PP4 is Met.

Met criteria codes

PP1_Moderate			Variant segregates with FH phenotype in 4 informative meioses from 2 families: 2 relatives with the phenotype and the variant from Robarts Research Institute, and 2 affected family members with the variant from Germany (PMID: 26036859), so PP1_Moderate is Met.
PS3_Moderate			Level 2 assays: PMID 19026292: Homozygous patient cells, 125I-LDL assays - result - 10% LDLR activity. ---- functional study is consistent with damaging effect, so PS3_Moderate is Met.
PS4			Variant meets PM2 and is identified in 19 unrelated index cases from different labs (4 index cases with DLCN>6 from Robarts Research Institute; 4 index cases with DLCN>6 from Color Health, Inc; 1 index case who fulfills the following criteria for FH: i) total cholesterol >= 9.5 mmol/l, ii) triglycerides < 2 mmol/l, iii) presence of tendon xanthomas; or iv) occurrence of hypercholesterolemia or early onset of coronary artery disease in first degree relatives, from The Netherlands (PMID: 7616128); 3 index cases with DLCN>6 (LDL between 7,98 - 9,50 mmol/l and

hypercholesterolemia in 1st degree relative) from Germany (PMID: 11462246); 1 index case who fulfills the following criteria for FH: (1) LDL > 95th percentile and triglycerides below 2 mmol/l, and (2) the presence of xanthoma or CHD in the proband or 1st degree relative with type IIa hypercholesterolemia, xanthoma, or CVD, from France (PMID: 12436241); 1 index case with SB criteria for FH (Total cholesterol >290 mg/dL and LDL >200 mg/dL and severe hypercholesterolemia in 1st degree relatives), from Germany (PMID: 14974088); 1 index case with definite FH according to SB criteria from Northern Ireland (PMID: 16159606); 3 index cases fulfilling the following criteria for FH: i) total cholesterol > 8.0 mmol/l and LDL > 6 mmol/l; (ii) premature coronary or vascular disease, or a family history of cardiovascular disorder; and (iii) the presence of tendon xanthoma, from Denmark (PMID: 16542394); 1 index case with definite FH according to SB criteria (total cholesterol = 658 mg/dl and presence of xanthomas, and primary hypercholesterolemia in the probands’ parents or 1st degree relatives), from USA (PMID: 19026292)), so PS4 is Met.

PP4			Variant meets PM2 and is identified in 19 unrelated index cases from different labs (4 index cases with DLCN>6 from Roberts Research Institute; 4 index cases with DLCN>6 from Color Health, Inc; 1 index case who fulfills the following criteria for FH: i) total cholesterol >= 9.5 mmol/l, ii) triglycerides < 2 mmol/l, iii) presence of tendon xanthomas; or iv) occurrence of hypercholesterolemia or early onset of coronary artery disease in first degree relatives, from The Netherlands (PMID: 7616128); 3 index cases with DLCN>6 (LDL between 7,98 - 9,50 mmol/l and hypercholesterolemia in 1st degree relative) from Germany (PMID: 11462246); 1 index case who fulfills the following criteria for FH: (1) LDL > 95th percentile and triglycerides below 2 mmol/l, and (2) the presence of xanthoma or CHD in the proband or 1st degree relative with type IIa hypercholesterolemia, xanthoma, or CVD, from France (PMID: 12436241); 1 index case with SB criteria for FH (Total cholesterol >290 mg/dL and LDL >200 mg/dL and severe hypercholesterolemia in 1st degree relatives), from Germany (PMID: 14974088); 1 index case with definite FH according to SB criteria from Northern Ireland (PMID: 16159606); 3 index cases fulfilling the following criteria for FH: i) total cholesterol > 8.0 mmol/l and LDL > 6 mmol/l; (ii) premature coronary or vascular disease, or a family history of cardiovascular disorder; and (iii) the presence of tendon xanthoma, from Denmark (PMID: 16542394); 1 index case with definite FH according to SB criteria (total cholesterol = 658 mg/dl and presence of xanthomas, and primary hypercholesterolemia in the probands’ parents or 1st degree relatives), from USA (PMID: 19026292)), so PP4 is Met.
PM2			PopMax MAF = 0.00002941 (0.002941%) in European (non-Finnish) exomes (gnomAD v3.1.2), so PM2 is Met.
PM3			Variant meets PM2 and is identified in a true homozygous with total cholesterol = 658 mg/dl (PMID: 19026292), so PM3 is Met.
PVS1_Strong			Variant is in +2 intronic position, but there are no studies on effect predicted, so give PVS1_Strong to be conservative.

Not Met criteria codes

BS2			Not observed in 1000 normolipidemic individuals from Roberts Research Institute, so BS2 is Not Met.
BS1			FAF = 0.000004880 (0.0004880%) in European (non-Finnish) exomes (gnomAD v3.1.2), so BS1 is not met.
BS4			Variant does not segregate with FH phenotype in 2 informative meioses from 1 family from Germany (PMID: 26036859), so BS4 is Not Met.
BS3			

Level 2 assays: PMID 19026292: Homozygous patient cells, 125I-LDL assays - result - 10% LDLR activity. ----
functional study is consistent with damaging effect, so BS3 is not met.

BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			Functional data available and PVS1 is given, so BP4 is not applicable.
BP2			Variant identified in 8 cases with heterozygous FH phenotype (LDL means of 6.19 mmol/l and 6.11 mmol/l) and LDLR variant c.313+1G>C, but is not in trans (PMID: 22095935), so BP2 is not met.
PS1			Variant is in a non-coding region, so PS1 is Not Met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.
PP3			Functional data available and PVS1 is given, so PP3 is not applicable.
BA1			FAF = 0.000004880 (0.0004880%) in European (non-Finnish) exomes (gnomAD v3.1.1), so BA1 is not met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.
PM1			Variant meets PM2 but is not missense, so PM1 is Not Met.
PM5			Variant is in a non-coding region, so PM5 is Not Met.
PM4			Variant meets PM2 and is not in frame, so PM4 is Not Met.

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.

[ClinGen Terms of Use.](#)

[⌕ Powered by BCM's Genboree.](#)