

Variant: *NM\_000527.5(LDLR):c.1720C>T (p.Arg574Cys)*

Version: 1.1

CA023561 [↗](#)

183123 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Semidominant inheritance

**UUID:** e9709543-f8c5-4cee-8658-2fcd762aa55a

**Approved on:** 2022/3/7

**Published on:** 2022/7/12

### *HGVS expressions*

**NM\_000527.5:c.1720C>T**

**NM\_000527.5(LDLR):c.1720C>T (p.Arg574Cys)**

NC\_000019.10:g.11116873C>T

CM000681.2:g.11116873C>T

NC\_000019.9:g.11227549C>T

CM000681.1:g.11227549C>T

NC\_000019.8:g.11088549C>T

NG\_009060.1:g.32493C>T

ENST00000252444.10:c.1978C>T

ENST00000559340.2:c.1705+661C>T

ENST00000560467.2:c.1600C>T

ENST00000558518.6:c.1720C>T

ENST00000252444.9:c.1974C>T

ENST00000455727.6:c.1216C>T

ENST00000535915.5:c.1597C>T

ENST00000545707.5:c.1339C>T

ENST00000557933.5:c.1720C>T

ENST00000558013.5:c.1720C>T

ENST00000558518.5:c.1720C>T

ENST00000559340.1:c.426+661C>T

NM\_000527.4:c.1720C>T

NM\_001195798.1:c.1720C>T

NM\_001195799.1:c.1597C>T

NM\_001195800.1:c.1216C>T

NM\_001195803.1:c.1339C>T

NM\_001195798.2:c.1720C>T

NM\_001195799.2:c.1597C>T

NM\_001195800.2:c.1216C>T

NM\_001195803.2:c.1339C>T

Uncertain Significance

Met criteria codes **5**

PP3

PP4

PM2

BS3\_Supporting

PS4\_Supporting

Not Met criteria codes **21**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS3

BA1

PP1

PP2

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS2

BP5

BP7

BP4

BP3

BP1

BP2

PVS1

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

NM\_000527.5(LDLR):c.1720C>T (p.Arg574Cys) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PS4\_supporting and BS3\_supporting) 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 = 0.0001384 (0.01384%) in Other populations exomes+genomes (gnomAD v2.1.1). PP3 - REVEL = 0.967. PP4 - Variant meets PM2. Variant identified in 5 FH cases (1 case 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 case with Dutch Lipid Clinic Network score ≥ 6 published in PMID: 11462246; 1 case with Dutch Lipid Clinic Network score ≥ 6 published in PMID: 29290422; 1 case with Dutch Lipid Clinic Network score ≥ 6 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca; 1 case with Simon-Broome register possible/definite published in PMID: 26892515. PS4\_supporting - Variant meets PM2. Variant identified in 5 unrelated index cases (1 case with Simon-Broome 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 case with Dutch Lipid Clinic Network score ≥ 6 published in PMID: 11462246; 1 case with Dutch Lipid Clinic Network score ≥ 6 published in PMID: 29290422; 1 case with Dutch Lipid Clinic Network score ≥ 6 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca; 1 case with Simon-Broome register criteria published in PMID: 26892515. BS3\_supporting - PMID: 25647241: Level 3 assay - study on HeLa-Kyoto cells, LDLR-GFP construct, WB + CLSM assays, whole cycle is above 100% of wild-type activity. - functional study is consistent with no damaging effect.

Met criteria codes

|                |  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------|--|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3            |  |  | REVEL = 0.967                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| PP4            |  |  | Variant meets PM2. Variant identified in 5 FH cases (1 case 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 case with Dutch Lipid Clinic Network score ≥ 6 published in PMID: 11462246; 1 case with Dutch Lipid Clinic Network score ≥ 6 published in PMID: 29290422; 1 case with Dutch Lipid Clinic Network score ≥ 6 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca; 1 case with Simon-Broome register possible/definite published in PMID: 26892515. |
| PM2            |  |  | PopMax MAF = 0.0001384 (0.01384%) in Other populations exomes+genomes (gnomAD v2.1.1).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| BS3_Supporting |  |  | PMID: 25647241 - Level 3 assay - study on HeLa-Kyoto cells, LDLR-GFP construct, WB + CLSM assays, whole cycle is above 100% of wild-type activity. - functional study is consistent with no damaging effect                                                                                                                                                                                                                                                                                                                                                                                                                               |
| PS4_Supporting |  |  | Variant meets PM2. Variant identified in 5 unrelated index cases (1 case with Simon-Broome 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 case with Dutch Lipid Clinic Network score ≥ 6 published in PMID: 11462246; 1 case with Dutch Lipid Clinic Network score ≥ 6 published in PMID: 29290422; 1 case with Dutch Lipid                                                                                                                                                                                   |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                       |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PS1 |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| PS2 |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| PS3 |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| BA1 |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| PP1 |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| PP2 |   |   | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| PM1 |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| PM3 |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| PM5 |  |  | 2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1721G>A (p.Arg574His) (ClinVar ID 251996) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.1721G>T (p.Arg574Leu) (ClinVar ID 237867) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines. |
| PM4 |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |
| PM6 |  |  | 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 code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                            |

|      |                                                                                     |                                                                                     |                                                                                                                            |
|------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| BS2  |     |      | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| BP5  |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| BP7  |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| BP4  |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| BP3  |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| BP1  |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| BP2  |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| PVS1 |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

| Curation History  |  |  |
|------------------------------------------------------------------------------------------------------|--|--|
| Showing 1 to 2 of 2 rows                                                                             |  |  |
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