

Variant: *NM_000527.5(LDLR):c.2000G>A (p.Cys667Tyr)*

Version: 1.0

CA023621 [↗](#)

3689 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 218276d3-2d8e-4ff6-8f45-a17666d02565

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HGVS expressions

NM_000527.5(LDLR):c.2000G>A (p.Cys667Tyr)

NM_000527.5:c.2000G>A

NC_000019.10:g.11120382G>A

CM000681.2:g.11120382G>A

NC_000019.9:g.11231058G>A

CM000681.1:g.11231058G>A

NC_000019.8:g.11092058G>A

NG_009060.1:g.36002G>A

ENST00000252444.10:c.2258G>A

ENST00000559340.2:c.*69G>A

ENST00000560467.2:c.1880G>A

ENST00000558518.6:c.2000G>A

ENST00000252444.9:c.2254G>A

ENST00000455727.6:c.1496G>A

ENST00000535915.5:c.1877G>A

ENST00000545707.5:c.1606+149G>A

ENST00000557933.5:c.2000G>A

ENST00000558013.5:c.2000G>A

ENST00000558518.5:c.2000G>A

ENST00000559340.1:c.581G>A

NM_000527.4:c.2000G>A

NM_001195798.1:c.2000G>A

NM_001195799.1:c.1877G>A

NM_001195800.1:c.1496G>A

NM_001195803.1:c.1606+149G>A

NM_001195798.2:c.2000G>A

NM_001195799.2:c.1877G>A

NM_001195800.2:c.1496G>A

NM_001195803.2:c.1606+149G>A

Likely Pathogenic

Met criteria codes **6**

PP3

PP4

PS3_Moderate

PM2

PM1

PS4_Supporting

Not Met criteria codes **20**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

PS1	PS2	PP1	PP2	BA1
PM6	BS1	BS4	BS3	PM3
PM5	PM4	BS2	BP5	BP7
BP4	BP3	BP1	BP2	PVS1

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.2000G>A (p.Cys667Tyr) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM1, PM2, PS3_Moderate, PP3, PP4 and PS4_Supporting) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PM1 - Variant meets PM2 and is one of listed Cysteine. PM2 - PopMax MAF = 0.000008794 (0.0009%) in European non-Finnish exomes (gnomAD v2.1.1). PS3_moderate - PMID:2318961 - Level 2 assay - study on hmz patient's fibroblasts, after 2 hours pulse-chase, only 20% of receptors were processed to the mature form. Also here PMID: 14993243 and here PMID: 10906332 is shown that this mutant is retained on ER. In last two papers not whole LDLR cycle was studied. PP3 - REVEL: 0,986. PP4 - Variant meets PM2. Variant found in 5 unrelated index cases fulfilling validated clinical criteria for FH. PS4_supporting - Variant meets PM2. Variant identified in 5 unrelated index cases (1 case from Color laboratory with Simon-Broome criteria; 1 case from Ambry Genetics with Simon-Broome criteria; 1 case from GeneDx Inc. with Simon-Broome criteria; 2 cases from University of British Columbia with DLCN score 16 and 10, respectively).

Met criteria codes

PP3			REVEL: 0,986. Score is above 0,75.
PP4			Variant meets PM2. Variant found in 5 unrelated index cases fulfilling validated clinical criteria for FH.
PS3_Moderate			PMID:2318961 - Level 2 assay - study on hmz patient's fibroblasts, after 2 hours pulse-chase, only 20% of receptors were processed to the mature form. Also here PMID: 14993243 and here PMID: 10906332 is shown (CHO cells, Chang cells respectively) that this mutant is retained on ER. In last two papers not whole LDLR cycle was studied.
PM2			PopMax MAF = 0.000008794 (0.0008794%) in European non-Finnish exomes (gnomAD v2.1.1). MAF is below 0.02%.
PM1			Variant meets PM2 and is one of listed Cysteine. S-S bond with Cys681.
PS4_Supporting			Variant meets PM2. Variant identified in 5 unrelated index cases (1 case from Color laboratory with Simon-Broome criteria; 1 case from Ambry Genetics with Simon-Broome criteria; 1 case from GeneDx Inc. with Simon-Broome criteria; 2 cases from University of British Columbia with DLCN score 16 and 10, respectively).

Not Met criteria codes

PS1			Variant meets PM1, so not applicable
PS2			No de novo cases were identified.

			
PP1		✗	No family members tested.
PP2		✗	Not applicable.
BA1		✗	no FAF, just total MAF = 0.000003978 (0.0004%) in European non-Finnish exomes (gnomAD v2.1.1). MAF is not above 0.5%
PM6		✗	No de novo cases were identified.
BS1		✗	no FAF, just total MAF = 0.000003978 (0.0004%) in European non-Finnish exomes (gnomAD v2.1.1). MAF is not above 0.2%
BS4		✗	No family members tested.
BS3		✗	PMID:2318961 - Level 2 assay - only 20% of receptors were processed to the mature form. Also here PMID: 14993243 and here PMID: 10906332 is shown that this mutant is retained on ER. BS3 is not met.
PM3		✗	Not identified in individuals with other variants.
PM5		✗	Variant meets PM1, so not applicable
PM4		✗	Missense variant. Not applicable.
BS2		✗	No unaffected individuals identified with the variant.
BP5		✗	Not applicable.
BP7		✗	Missense variant. Not applicable.
BP4		✗	REVEL: 0,986. Score is not below 0,50.
BP3		✗	Not applicable.
BP1		✗	Not applicable.
BP2		✗	Not identified in individuals with other variants.
PVS1		✗	Missense variant. Not applicable.

Curation History 

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