

Variant: *NM_000527.5(LDLR):c.2113G>T (p.Ala705Ser)*

Version: 1.0

CA10585777 [↗](#)

252224 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 94ff5c68-d4d0-4282-8457-c124233dec6d

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HGVS expressions

NM_000527.5:c.2113G>T

NM_000527.5(LDLR):c.2113G>T (p.Ala705Ser)

NC_000019.10:g.11120495G>T

CM000681.2:g.11120495G>T

NC_000019.9:g.11231171G>T

CM000681.1:g.11231171G>T

NC_000019.8:g.11092171G>T

NG_009060.1:g.36115G>T

ENST00000252444.10:c.2371G>T

ENST00000559340.2:c.*182G>T

ENST00000560467.2:c.1993G>T

ENST00000558518.6:c.2113G>T

ENST00000252444.9:c.2367G>T

ENST00000455727.6:c.1609G>T

ENST00000535915.5:c.1990G>T

ENST00000545707.5:c.1606+262G>T

ENST00000557933.5:c.2113G>T

ENST00000558013.5:c.2113G>T

ENST00000558518.5:c.2113G>T

NM_000527.4:c.2113G>T

NM_001195798.1:c.2113G>T

NM_001195799.1:c.1990G>T

NM_001195800.1:c.1609G>T

NM_001195803.1:c.1606+262G>T

NM_001195798.2:c.2113G>T

NM_001195799.2:c.1990G>T

NM_001195800.2:c.1609G>T

NM_001195803.2:c.1606+262G>T

Uncertain Significance

Met criteria codes **3**

PP4

PM2

PS4_Supporting

Not Met criteria codes **3**

PS3

PP3

PM5

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR): c.2113G>T (p.Ala705Ser) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, PP4, PS4_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 Met: PopMAX MAF = 0.00004 in European (Non-Finnish) population in gnomAD (gnomAD v2.1.1). PP4 Met: This variant meets PM2 and is identified in >1 index cases who met clinical criteria for FH after alternative causes for high cholesterol were excluded. PS4_Supporting Met: Variant meets PM2 and is identified in 2 unrelated index cases who fulfil DLCN criteria or Simon Broome criteria for FH from 2 different labs: 1 case met DLCN criteria from Robarts Research Institute, Canada; 1 case met Simon Broome criteria from Centre for Cardiovascular Genetics, British Heart Foundation Laboratories, Royal Free and University College London Medical School, London, UK, PMID 17142622. PP3 not met: REVEL score = 0.673, which is below the threshold of 0.75. Functional data on splicing is not available, in silico splicing prediction is required. Variant is exonic and at least 50bp downstream from acceptor site and creates GT. MES scores: de novo donor = -6.49, authentic donor = 7.81. De novo score is negative and not used, therefore the variant is not predicted to alter splicing. BP4 not applicable: REVEL score is > 0.5, therefore BP4 is not applicable. PS3 not met: There is no functional experiment reported for this variant. PM5 not met: There is one other variant in the same codon: LDLR: NM_000527:c.2113G>C (p.Ala705Pro) is classified as Uncertain significance - insufficient evidence by these guidelines. Therefore PM5 is not met.

Met criteria codes

PP4			This variant meets PM2 and is identified in >1 index cases who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
PM2			PopMAX MAF = 0.00004 in European (Non-Finnish) population in gnomAD (gnomAD v2.1.1).
PS4_Supporting			Variant meets PM2 and is identified in 2 unrelated index cases from 2 different labs: 1 case met DLCN criteria from Robarts Research Institute, Canada; 1 case met Simon Broome criteria from Centre for Cardiovascular Genetics, British Heart Foundation Laboratories, Royal Free and University College London Medical School, London, UK, PMID 17142622.

Not Met criteria codes

PS3			There is no functional experiment reported for this variant.
PP3			REVEL score = 0.673, which is below the threshold of 0.75. Functional data on splicing is not available, in silico splicing prediction is required. Variant is exonic and at least 50bp downstream from acceptor site and creates GT. MES scores: de novo donor = -6.49, authentic donor = 7.81. De novo score is negative and not used, therefore the variant is not predicted to alter splicing.
PM5			There is one other variant in the same codon: LDLR: NM_000527:c.2113G>C (p.Ala705Pro) is classified as Uncertain significance - insufficient evidence by these guidelines. Therefore PM5 is not met.

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