

Variant: *NM_000527.5(LDLR):c.2099A>G (p.Asp700Gly)*

Version: 1.0

CA10585773 [↗](#)

252220 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 2a2037a5-71ae-40c0-bd4e-5330cb1f1f50

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HGVS expressions

NM_000527.5:c.2099A>G

NM_000527.5(LDLR):c.2099A>G (p.Asp700Gly)

NC_000019.10:g.11120481A>G

CM000681.2:g.11120481A>G

NC_000019.9:g.11231157A>G

CM000681.1:g.11231157A>G

NC_000019.8:g.11092157A>G

NG_009060.1:g.36101A>G

ENST00000252444.10:c.2357A>G

ENST00000559340.2:c.*168A>G

ENST00000560467.2:c.1979A>G

ENST00000558518.6:c.2099A>G

ENST00000252444.9:c.2353A>G

ENST00000455727.6:c.1595A>G

ENST00000535915.5:c.1976A>G

ENST00000545707.5:c.1606+248A>G

ENST00000557933.5:c.2099A>G

ENST00000558013.5:c.2099A>G

ENST00000558518.5:c.2099A>G

NM_000527.4:c.2099A>G

NM_001195798.1:c.2099A>G

NM_001195799.1:c.1976A>G

NM_001195800.1:c.1595A>G

NM_001195803.1:c.1606+248A>G

NM_001195798.2:c.2099A>G

NM_001195799.2:c.1976A>G

NM_001195800.2:c.1595A>G

NM_001195803.2:c.1606+248A>G

Likely Pathogenic

Met criteria codes **5**

PS3

PP3

PP4

PM2

PS4_Supporting

Not Met criteria codes **17**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

BS2BS1BS4BS3BP4BP2

PVS1BP7BA1PS1PS2

PP1PM6PM1PM3PM5

PM4

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.2099A>G (p.Asp700Gly) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PS3, PS4_Supporting, PM2, PP3 and 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: PS3 - Level 1 assays: PMID 32015373: Heterologous cells (CHO), FACS assays - result - 35% cell surface LDLR, 60% binding and 52% uptake. ---- activity is below 70% of wild-type, so PS3 is Met. PS4_Supporting - Variant meets PM2 and is identified in 2 unrelated index cases: 1 index case with FH criteria (CT>95th percentile, plus tendon xanthomata or pCHD in proband or 1st degree and hypercholesterolemia in family) from Spain (PMID: 11668640) and at least 1 index case with SB criteria for FH from China (PMID: 22353362), so PS4_Supporting is Met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met. PP3 - REVEL = 0.875. It is above 0.75, so PP3 is Met. PP4 - Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH from several labs (see PS4 for details), so PP4 is Met.

Met criteria codes

PS3			Level 1 assays: PMID 32015373: Heterologous cells (CHO), FACS assays - result - 35% cell surface LDLR, 60% binding and 52% uptake. ---- activity is below 70% of wild-type, so PS3 is Met.
PP3			REVEL = 0.875. It is above 0.75, so PP3 is Met.
PP4			Variant meets PM2 and is identified in 2 unrelated index cases: 1 index case with FH criteria (CT>95th percentile, plus tendon xanthomata or pCHD in proband or 1st degree and hypercholesterolemia in family) from Spain (PMID: 11668640) and at least 1 index case with SB criteria for FH from China (PMID: 22353362), so PP4 is Met.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met.
PS4_Supporting			Variant meets PM2 and is identified in 2 unrelated index cases: 1 index case with FH criteria (CT>95th percentile, plus tendon xanthomata or pCHD in proband or 1st degree and hypercholesterolemia in family) from Spain (PMID: 11668640) and at least 1 index case with SB criteria for FH from China (PMID: 22353362), so PS4_Supporting is Met.

Not Met criteria codes

BS2			No control individuals tested, so BS2 is Not Met.
BS1			No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BS1 is Not Met.

BS4			Lack of segregation data not reported, so BS4 is Not Met.
BS3			Level 1 assays: PMID 32015373: Heterologous cells (CHO), FACS assays - result - 35% cell surface LDLR, 60% binding and 52% uptake. ---- activity is below 70% of wild-type, so BS3 is not met.
BP4			REVEL = 0.875. It is not below 0.50, so BP4 is Not Met.
BP2			Not observed in trans with other LP/P variants, so BP2 is Not Met.
PVS1			Variant is missense, so PVS1 is Not Met.
BP7			Variant is not synonymous, so BP7 is Not Met.
BA1			No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BA1 is Not Met.
PS1			No more missense variants at the same codon, so PS1 is Not Met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.
PP1			Segregation data not reported, so PP1 is Not Met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.
PM1			Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM3			Not observed in trans with other LP/P variants, so PM3 is Not Met.
PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.2098G>A (p.Asp700Asn) (ClinVar ID 200923) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.2100C>G (p.Asp700Glu) (ClinVar ID 252221) - VUS by these guidelines No more missense variants at the same codon, classified as Pathogenic, so PM5 is Not Met.
PM4			Variant meets PM2 and is missense, so PM4 is Not Met.

Curation History 

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