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# *Variant: NM_000527.5(LDLR):c.912C>G (p.Asp304Glu)*

Version: 1.0

*CA10576290*

*226336 (ClinVar)*

**Gene**: LDLR (HGNC:3949)
**Condition**: hypercholesterolemia, familial (MONDO:0007750)
**Inheritance Mode**: Semidominant inheritance
**UUID:** f3d3ae92-0a85-414d-b0ba-b872f7a9c1b3
**Approved on**: 2022/4/5
**Published on**: 2022/4/5

## *HGVS expressions*

**NM_000527.5:c.912C>G**
**NM_000527.5(LDLR):c.912C>G (p.Asp304Glu)**
NC_000019.10:g.11107486C>G
CM000681.2:g.11107486C>G
NC_000019.9:g.11218162C>G
CM000681.1:g.11218162C>G
NC_000019.8:g.11079162C>G
NG_009060.1:g.23106C>G
ENST00000252444.10:c.1170C>G
ENST00000559340.2:c.912C>G
ENST00000560467.2:c.912C>G
ENST00000558518.6:c.912C>G
ENST00000252444.9:c.1166C>G
ENST00000455727.6:c.408C>G
ENST00000535915.5:c.789C>G
ENST00000545707.5:c.531C>G
ENST00000557933.5:c.912C>G
ENST00000558013.5:c.912C>G
ENST00000558518.5:c.912C>G
ENST00000558528.1:n.427C>G
ENST00000560467.1:c.512C>G
NM_000527.4:c.912C>G
NM_001195798.1:c.912C>G
NM_001195799.1:c.789C>G
NM_001195800.1:c.408C>G
NM_001195803.1:c.531C>G
NM_001195798.2:c.912C>G
NM_001195799.2:c.789C>G
NM_001195800.2:c.408C>G
NM_001195803.2:c.531C>G

**Likely Pathogenic**

**Met criteria codes** 5

PP3 PP4 PM2 PM5 PS4_Supporting

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

**Not Met criteria codes** 17

PS1 PS2 PS3 PP1 PM6 PVS1 PM1 PM3 PM4 BA1 BS1 BS4 BS3 BS2 BP7 BP4 BP2

Evidence Links 0

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Familial Hypercholesterolemia VCEP***

**The NM_000527.5(LDLR):c.912C>G (p.Asp304Glu) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PM5, PS4_supporting, PP4 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: PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met. PP3 - REVEL = 0.871. It is above 0.75, so PP3 is Met. PM5 - 4 other missense variants in the same codon: - NNM_000527.5(LDLR):c.910G>A (p.Asp304Asn) (ClinVar ID 3692) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.910G>C (p.Asp304His) (ClinVar ID 440612) - VUS by these guidelines - NM_000527.5(LDLR):c.911A>T (p.Asp304Val) (ClinVar ID 440613) - VUS by these guidelines - NM_000527.5(LDLR):c.910G>T (p.Asp304Tyr) (ClinVar ID 251517) - Likely pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines, so PM5 is Met. PS4_supporting - Variant meets PM2 and is identified in at least 2 unrelated index cases: 1 index case who fulfils DLCN>6 criteria for FH from Robarts Research Institute and 1 index case who fulfils Simon Broome criteria for FH from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996), so PS4_Supporting is Met. PP4 - Variant meets PM2 and is identified in at least 2 unrelated index cases as described in PS4, PP4 is Met.**

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**Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✔ | REVEL = 0.871. It is above 0.75, so PP3 is Met. |
| **PP4** | ✔ | Variant meets PM2 and is identified in at least 2 unrelated index cases: 1 index case who fulfils DLCN>6 criteria for FH from Robarts Research Institute and 1 index case who fulfils Simon Broome criteria for FH from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996), so PP4 is Met. |
| **PM2** | ✔ | This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met. |
| **PM5** | ✔ | 4 other missense variants in the same codon: - NNM_000527.5(LDLR):c.910G>A (p.Asp304Asn) (ClinVar ID 3692) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.910G>C (p.Asp304His) (ClinVar ID 440612) - VUS by these guidelines - NM_000527.5(LDLR):c.911A>T (p.Asp304Val) (ClinVar ID 440613) - VUS by these guidelines - NM_000527.5(LDLR):c.910G>T (p.Asp304Tyr) (ClinVar ID 251517) - Likely pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines, so PM5 is Met. |
| **PS4_Supporting** | ✔ | Variant meets PM2 and is identified in at least 2 unrelated index cases: 1 index case who fulfils DLCN>6 criteria for FH from Robarts Research Institute and 1 index case who fulfils Simon Broome criteria for FH from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996), so PS4_Supporting is Met. |

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**Not Met criteria codes**

| | | |
|---|---|---|
| **PS1** | ✖ | There is no other missense variants in the same codon, so PS1 is Not Met. |
| **PS2** | ✖ | No evidence added, so PS2 is Not Met. |
| **PS3** | ✖ | There is no functional studies reported for this variant, so PS3 is Not Met. |
| **PP1** | ✖ | No family members were identified, so PP1 is Not Met. |

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|---|---|---|---|
| **PM6** | | ✖ | No evidence added, so PM6 is Not Met. |
| **PVS1** | | ✖ | Variant is missense, so PVS1 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 identified in index case with more than 1 variant, so PM3 is Not Met. |
| **PM4** | | ✖ | Variant meets PM2 but is missense, so PM4 is Not Met. |
| **BA1** | | ✖ | No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BA1 is Not Met. |
| **BS1** | | ✖ | No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BS1 is Not Met. |
| **BS4** | | ✖ | No family members were identified, so BS4 is Not Met. |
| **BS3** | | ✖ | There is no functional studies reported for this variant, so BS3 is Not Met. |
| **BS2** | | ✖ | Not observed in controls (although the number of controls tested is not specified), so BS2 is Not Met. |
| **BP7** | | ✖ | Variant is not synonymous, so BP7 is Not Met. |
| **BP4** | | ✖ | REVEL = 0.871. It is not below 0.50, so BP4 is Not Met. |
| **BP2** | | ✖ | not identified in index case with more than 1 variant, so BP2 is Not Met. |

Curation History

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| ee Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
|---|---|---|---|---|---|---|---|
| View | NM_000527.5(LDLR):c.912C>G (p.Asp3... | Likely Pathogenic | Hypercholesterolemia, Familial | 2022-04-05 | 1.0 | - | LDLR |

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