The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000527.5(LDLR):c.1003G>T (p.Gly335Cys)

Version: 1.0

CA404082719

1395739 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: f40ccd74-b0bc-4f96-bbe1-ad5342f0c802
Approved on: 2023/4/28
Published on: 2023/5/1

HGVS expressions

NM_000527.5:c.1003G>T
NM_000527.5(LDLR):c.1003G>T (p.Gly335Cys)
NC_000019.10:g.11110714G>T
CM000681.2:g.11110714G>T
NC_000019.9:g.11221390G>T
CM000681.1:g.11221390G>T
NC_000019.8:g.11082390G>T
NG_009060.1:g.26334G>T
ENST00000252444.10:c.1261G>T
ENST00000559340.2:c.1003G>T
ENST00000560467.2:c.941-800G>T
ENST00000558518.6:c.1003G>T
ENST00000252444.9:c.1257G>T
ENST00000455727.6:c.499G>T
ENST00000535915.5:c.880G>T
ENST00000545707.5:c.622G>T
ENST00000557933.5:c.1003G>T
ENST00000558013.5:c.1003G>T
ENST00000558518.5:c.1003G>T
ENST00000560173.1:n.2G>T
ENST00000560467.1:c.541-800G>T
NM_000527.4:c.1003G>T
NM_001195798.1:c.1003G>T
NM_001195799.1:c.880G>T
NM_001195800.1:c.499G>T
NM_001195803.1:c.622G>T
NM_001195798.2:c.1003G>T
NM_001195799.2:c.880G>T
NM_001195800.2:c.499G>T
NM_001195803.2:c.622G>T

Likely Pathogenic

Met criteria codes 4

PS3_Moderate | PP3 | PP4 | PM2

Not Met criteria codes 22

BP5 | BP7 | BP4 | BP3 | BP1 | BP2
PS1 | PS2 | PS4 | PP1 | PP2 | PM6
PM1 | PM3 | PM5 | PM4 | PVS1
BA1 | BS2 | BS1 | BS4 | BS3

Evidence Links 1

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1003G>T (p.Gly335Cys) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PS3_Moderate, 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: PM2 - This variant is absent from gnomAD (gnomAD v2.1.1). PS3_moderate - Level 2 FS: Hu et al. 2021 (PMID: 34970301): Heterologous cells (HEK293), Western blot and Dil-LDL (just uptake) assays - results: less mature LDLR detected, 43% uptake. ---- part of the LDLR cycle (uptake) is less than 70% activity of wild-type, so PS3_Moderate is met. PP3 - REVEL = 0.889. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in 1 index case from Hu et al. 2021 (PMID: 34970301) with 5.5mmol/L LDL under no medication, and family history of hypercholesterolemia, so Simon-Broome possible is met; so PP4 is met.

Met criteria codes

PS3_Moderate	✔	Level 2 FS: Hu et al. 2021 (PMID: 34970301): Heterologous cells (HEK293), Western blot and Dil-LDL (just uptake) assays - results: less mature LDLR detected, 43% uptake. ---- part of the LDLR cycle (uptake) is less than 70% activity of wild-type, so PS3_Moderate is met Heterologous cells (HEK293), Western blot and Dil-LDL (just uptake) assays - results: less mature LDLR detected, 43% uptake. PubMed:34970301
PP3	✔	REVEL = 0.889. It is above 0.75, so PP3 is met
PP4	✔	variant meets PM2 and was identified in - 2 unrelated index cases from Leren et al. 2021 (PMID: 33740630), but inclusion criteria was "No stringent criteria have been used to select hypercholesterolemic subjects for genetic testing, except that a value for total serum cholesterol of at least 6 mmol/l has been required for molecular genetic testing in adults.", which is not enough to insure clinical FH criteria, so not considered; - 1 index case from Hu et al. 2021 (PMID: 34970301) with 5.5mmol/L LDL under no medication, and family history of hypercholesterolemia, so Simon-Broome possible is met; so PP4 is met
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

BP5		✖	not applicable
BP7		✖	variant is missense, so not met
BP4		✖	REVEL = 0.889. It is not below 0.50, so BP4 is not met
BP3		✖	not applicable
BP1		✖	not applicable
BP2		✖	variant identified in 1 index case from Hu et al. 2021 (PMID: 34970301) who is also heterozygous (confirmed in trans) for LDLR c.226G>C, p.Gly76Arg and has LDL of 5.62mmol/L under atorvastatin 20mg. Calculated untreated LDL: 5.62 / 0.57 (Ruel et al., 2018) = 9.86mmol/L, which is not clearly a homozygous phenotype (>13mmol/L) nor a clearly heterozygous phenotype (<8mmol/L), so not met.
PS1		✖	There are no other variants that lead to the same amino acid change, so not met
PS2		✖	there is no data on de novo occurrence
PS4		✖	variant meets PM2 and was identified in - 2 unrelated index cases from Leren et al. 2021 (PMID: 33740630), but inclusion criteria was "No stringent criteria have been used to select hypercholesterolemic subjects for genetic testing, except that a value for total serum cholesterol of at least 6 mmol/l has been required for molecular genetic testing in adults.", which is not enough to insure clinical FH criteria, so not considered; - 1 index case from Hu et al. 2021 (PMID: 34970301) with 5.5mmol/L LDL under no medication, and family history of hypercholesterolemia, so Simon-Broome possible is met; ---- 1 index case, not enough, so not met
PP1		✖	variant identified in - 2 relatives from Leren et al. 2021 (PMID: 33740630), but there is no data on phenotype, so not considered; - 1 family from Hu et al. 2021 (PMID: 34970301), but there are 2 variants in the family, so not considered.
PP2		✖	not applicable
PM6		✖	there is no data on de novo occurrence
PM1		✖	variant is missense and meets PM2, but it is not in exon 4 and does not alter Cys, so not met
PM3		✖	variant identified in 1 index case from Hu et al. 2021 (PMID: 34970301) who is also heterozygous (confirmed in trans) for LDLR c.226G>C, p.Gly76Arg and has LDL of 5.62mmol/L under atorvastatin 20mg. Calculated untreated LDL: 5.62 / 0.57 (Ruel et al., 2018) = 9.86mmol/L, which is not clearly a homozygous phenotype (>13mmol/L) nor a clearly heterozygous phenotype (<8mmol/L), so not met.
PM5		✖	There are 4 other missense variants in the same codon: - NM_000527.5(LDLR):c.1003G>A (p.Gly335Ser) ClinVar ID 183105 - classified as Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.1003G>C (p.Gly335Arg) ClinVar ID 926520 - classified as VUS by these guidelines - NM_000527.5(LDLR):c.1004G>A (p.Gly335Asp) ClinVar ID 225181

- classified as VUS by these guidelines - NM_000527.5(LDLR):c.1004G>T (p.Gly335Val) ClinVar ID 251587 - classified as VUS by these guidelines no variant classified as Pathogenic, so not met

PM4	✖	variant is missense, so not met
PVS1	✖	variant is missense and not in initiation codon, so not met
BA1	✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS2	✖	Variant has not been identified in normolipidemic individuals, so not met
BS1	✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS4	✖	variant identified in - 2 relatives from Leren et al. 2021 (PMID: 33740630), but there is no data on phenotype, so not considered; - 1 family from Hu et al. 2021 (PMID: 34970301), but there are 2 variants in the family, so not considered.
BS3	✖	Level 2 FS: Hu et al. 2021 (PMID: 34970301): Heterologous cells (HEK293), Western blot and Dil-LDL (just uptake) assays - results: less mature LDLR detected, 43% uptake. ---- part of the LDLR cicle (uptake) is less than 70% activity of wild-type, so BS3 is not met

Curation History

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