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>A (p.Gly335Ser)

Version: 1.0

CA023402

183105 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 50e4f7aa-2e0a-433c-88ba-08d28e21d8e2
Approved on: 2023/4/28
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HGVS expressions

NM_000527.5(LDLR):c.1003G>A (p.Gly335Ser)
NM_000527.5:c.1003G>A
NC_000019.10:g.11110714G>A
CM000681.2:g.11110714G>A
NC_000019.9:g.11221390G>A
CM000681.1:g.11221390G>A
NC_000019.8:g.11082390G>A
NG_009060.1:g.26334G>A
ENST00000252444.10:c.1261G>A
ENST00000559340.2:c.1003G>A
ENST00000560467.2:c.941-800G>A
ENST00000558518.6:c.1003G>A
ENST00000252444.9:c.1257G>A
ENST00000455727.6:c.499G>A
ENST00000535915.5:c.880G>A
ENST00000545707.5:c.622G>A
ENST00000557933.5:c.1003G>A
ENST00000558013.5:c.1003G>A
ENST00000558518.5:c.1003G>A
ENST00000560173.1:n.2G>A
ENST00000560467.1:c.541-800G>A
NM_000527.4:c.1003G>A
NM_001195798.1:c.1003G>A
NM_001195799.1:c.880G>A
NM_001195800.1:c.499G>A
NM_001195803.1:c.622G>A
NM_001195798.2:c.1003G>A
NM_001195799.2:c.880G>A
NM_001195800.2:c.499G>A
NM_001195803.2:c.622G>A

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM2 PS4_Supporting PS3_Supporting

Not Met criteria codes 21

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

Evidence Links 0

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>A (p.Gly335Ser) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PP4, PS3_Supporting and 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 - PopMax MAF = 0.00005431 (0.005431%) in European non-Finnish exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met. PP3 - REVEL = 0.843. It is above 0.75, so PP3 is met. PS4_supporting - variant meets PM2 and was identified in: - 3 unrelated index cases who fulfill Dutch lipid clinic network >=6 from Robarts Research Institute, Canada; - at least 1 index case with Dutch Lipid Clinic Scoring : Definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583773.1), France; - 1 index case with DLNC > or = 6 from Bañares et al. 2017 (PMID: 28502510), Argentina; at least 5 unrelated index cases with clinical FH criteria, so PP4 is met. PP4 - variant meets PM2 and was identified in at least 5 unrelated index cases with clinical FH criteria (see PS4_Supporting for details), so PP4 is met.
PS3_supporting - Level 3 FS: Hobbs et al. 1992 (PMID: 1301956): Heterozygous patients' fibroblasts, 125I-LDL assays - results: 30-40% LDLR activity. --- activity is below 85% of wild-type, so PS3_Supporting is met.

Met criteria codes

PP3	✔	REVEL = 0.843. It is above 0.75, so PP3 is met
PP4	✔	variant meets PM2 and was identified in: - 3 unrelated index cases who fulfill Dutch lipid clinic network >=6 from Robarts Research Institute, Canada; - at least 1 index case with Dutch Lipid Clinic Scoring : Definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583773.1), France; - 1 index case with DLNC > or = 6 from Bañares et al. 2017 (PMID: 28502510), Argentina at least 5 unrelated index cases, so PP4 is met
PM2	✔	PopMax MAF = 0.00005431 (0.005431%) in European non-Finnish exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met
PS4_Supporting	✔	variant meets PM2 and was identified in: - 3 unrelated index cases who fulfill Dutch lipid clinic network >=6 from Robarts Research Institute, Canada; - at least 1 index case with Dutch Lipid Clinic Scoring : Definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583773.1), France; - 1 index case with DLNC > or = 6 from Bañares et al. 2017 (PMID: 28502510), Argentina at least 5 unrelated index cases, so PS4_Supporting is met
PS3_Supporting	✔	Level 3 FS: Thormaehlen et al. 2015 (PMID: 25647241): In vitro studies where the variant is introduced into LDLR'-GFP and transiently expressed in He-La cells- results: variant slightly decreases LDL expression, but it is not

significantly altered compared to WT. --- Hobbs et al., 1992 study represents more accurately biological function, so this study is disregarded. Level 3 FS: Hobbs et al. 1992 (PMID: 1301956): Heterozygous patients' fibroblasts, 125I-LDL assays - results: 30-40% LDLR activity. --- activity is below 85% of wild-type, so PS3_Supporting is met

Not Met criteria codes

PS1	✖	There is no other variant that leads to the same amino acid change, so not met
PS2	✖	no de novo occurrence
PP1	✖	no segregation data
PP2	✖	not applicable
PM6	✖	no 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 with LDL = 243mg/dl under medication (40mg rosuvastatin and 10mg ezetimibe) (calculated untreated LDL = 243/0.7 = 347mg/dl) who is a compound heterozygote in trans with LDLR: c.1731G>C, p.Trp577Cys, from Laboratory of Genetics and Molecular Cardiology, Brasil. --- index case does not have a clearly homozygous phenotype (untreated LDL>500mg/dl), so PM3 is not met
PM5	✖	There are 4 other missense variants in the same codon: NM_000527.4(LDLR):c.1003G>C, p.(Gly335Arg) (ClinVar ID 926520) - classified as VUS by these guidelines NM_000527.4(LDLR):c.1004G>A, p.(Gly335Asp) (ClinVar ID 225181) - classified as VUS by these guidelines NM_000527.4(LDLR):c.1004G>T, p.(Gly335Val) (ClinVar ID 251587) - classified as VUS by these guidelines NM_000527.5(LDLR):c.1003G>T (p.Gly335Cys) (ClinVar ID 1395739) - classified as Likely pathogenic by these guidelines. There is no Pathogenic variant in the same codon, so not met
PM4	✖	variant is missense, so not met
BA1	✖	FAF = 0.00002298 (0.002298%) in European non-Finnish exomes (gnomAD v2.1.1). It is not above 0.5%, so not met
BS2	✖	variant was not identified in normolipidemic individuals: 0/1000 controls from Robarts Research Institute, so not met
PVS1	✖	variant is missense and not in initiation codon, so not met
BS1	✖	FAF = 0.00002298 (0.002298%) in European non-Finnish exomes (gnomAD v2.1.1). It is not above 0.2%, so not met
BS4	✖	no segregation data
BS3	✖	

Level 3 FS: Thormaehlen et al. 2015 (PMID: 25647241): In vitro studies where the variant is introduced into LDLR'-GFP and transiently expressed in He-La cells- results: variant slightly decreases LDL expression, but it is not significantly altered compared to WT. --- this study does not test the whole LDLR cycle, so not met Level 3 FS: Hobbs et al. 1992 (PMID: 1301956): Heterozygous patients' fibroblasts, 125I-LDL assays - results: 30-40% LDLR activity. --- activity is not above 95% of wild-type, so BS3_Supporting is not met

BP4		✖	REVEL = 0.843. It is not below 0.50, so BP4 is not met
BP3		✖	not applicable
BP1		✖	not applicable
BP2		✖	variant identified in 1 index case with LDL = 243mg/dl under medication (40mg rosuvastatin and 10mg ezetimibe) (calculated untreated LDL = 243/0.7 = 347mg/dl) who is a compound heterozygote in trans with LDLR: c.1731G>C, p.Trp577Cys, from Laboratory of Genetics and Molecular Cardiology, Brasil. --- index case does not have a clearly heterozygous phenotype (untreated LDL>310mg/dl), so BP2 is not met
BP5		✖	not applicable
BP7		✖	variant is missense, so not met

Curation History

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