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Variant: NM_000527.5(LDLR):c.1045C>T (p.Gln349Ter)

Version: 1.0

CA031354

251611 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 5243c8a2-1b30-4b61-9b6b-262a4531302a
Approved on: 2022/4/25
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HGVS expressions

NM_000527.5(LDLR):c.1045C>T (p.Gln349Ter)
NM_000527.5:c.1045C>T
NC_000019.10:g.11110756C>T
CM000681.2:g.11110756C>T
NC_000019.9:g.11221432C>T
CM000681.1:g.11221432C>T
NC_000019.8:g.11082432C>T
NG_009060.1:g.26376C>T
ENST00000252444.10:c.1303C>T
ENST00000559340.2:c.1045C>T
ENST00000560467.2:c.941-758C>T
ENST00000558518.6:c.1045C>T
ENST00000252444.9:c.1299C>T
ENST00000455727.6:c.541C>T
ENST00000535915.5:c.922C>T
ENST00000545707.5:c.664C>T
ENST00000557933.5:c.1045C>T
ENST00000558013.5:c.1045C>T
ENST00000558518.5:c.1045C>T
ENST00000560173.1:n.44C>T
ENST00000560467.1:c.541-758C>T
NM_000527.4:c.1045C>T
NM_001195798.1:c.1045C>T
NM_001195799.1:c.922C>T
NM_001195800.1:c.541C>T
NM_001195803.1:c.664C>T
NM_001195798.2:c.1045C>T
NM_001195799.2:c.922C>T
NM_001195800.2:c.541C>T
NM_001195803.2:c.664C>T

Pathogenic

Met criteria codes 6

PP4 PM2 PM3 PVS1 PS4_Supporting PP1_Moderate

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Not Met criteria codes 1

PS3

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1045C>T (p.Gln349Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PVS1, PP4, PS4_Supporting, PM3, PP1_Moderate) 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 = 0.00006 in South Asian population in gnomAD (gnomAD v2.1.1). PVS1: The variant causing a premature stop codon amino-terminal of amino acid 830 (NM_000527.5:p.Lys830). PP4: This variant meets PM2 and is identified in >1 index case who met clinical criteria for FH after alternative causes for high cholesterol were excluded. PS4_Supporting: Variant meets PM2, and is identified in 3 unrelated index cases: 1 case fulfil Simon Broome possible FH criteria (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 1 case fulfil DLCN criteria (Robarts Research Institute, Canada); 1 case met criteria of total and LDL-C levels over the 95th percentile corrected for age and sex, plus two of: tendon xanthomata, premature coronary heart disease in the proband or in a first-degree relative and hypercholesterolemic children in the family (Instituto de Investigaciones Citológicas, Fundación Valenciana de Investigaciones Biomédicas, Valencia, Spain, PMID 11668640). PM3: Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL-C: 11.1mmol/l at age of 5 yr.) and is homozygous for the variant (Robarts Research Institute, Canada). PP1_Moderate: Variant segregates with FH phenotype in 4 informative meiosis from 2 families from 2 research labs. One affected relative tested positive for the variant from one family (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière). Three affected relative tested positive for the variant from another family (Robarts Research Institute, Canada).

Met criteria codes

PP4	✔	This variant meets PM2 and is identified in >1 index case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
PM2	✔	PopMax MAF = 0.00006 in South Asian population in gnomAD (gnomAD v2.1.1).
PM3	✔	Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL-C: 11.1mmol/l at age of 5 yr.) and is homozygous for the variant (Robarts Research Institute, Canada).
PVS1	✔	The variant causing a premature stop codon amino-terminal of amino acid 830 (NM_000527.5:p.Lys830).
PS4_Supporting	✔	Variant meets PM2, and is identified in 3 unrelated index cases: 1 case fulfil Simon Broome possible FH criteria (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière); 1 case fulfil DLCN criteria (Robarts Research Institute, Canada); 1 case met criteria of total and LDL-C levels over the 95th percentile corrected for age and sex, plus two of: tendon xanthomata, premature coronary heart disease in the proband or in a first-degree relative and hypercholesterolemic children in the family (Instituto de Investigaciones Citológicas, Fundación Valenciana de Investigaciones Biomédicas, Valencia, Spain, PMID 11668640).
PP1_Moderate	✔	

Variant segregates with FH phenotype in 4 informative meiosis from 2 families from 2 research labs. One affected relative tested positive for the variant from one family (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière). Three affected relative tested positive for the variant from another family (Robarts Research Institute, Canada).

Not Met criteria codes

PS3		✖	Functional data is not available.

Curation History

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