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.1204TTC[1] (p.Phe403del)

Version: 1.0

CA10585356

251731 (ClinVar)

Gene: LDLR
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 5f27e072-31eb-415e-a56b-be4715f15dab
Approved on: 2023/1/27
Published on: 2024/10/7

HGVS expressions

NM_000527.5:c.1204TTC[1]
NM_000527.5(LDLR):c.1204TTC[1] (p.Phe403del)
NC_000019.10:g.11113298_11113300del
CM000681.2:g.11113298_11113300del
NC_000019.9:g.11223974_11223976del
CM000681.1:g.11223974_11223976del
NC_000019.8:g.11084974_11084976del
NG_009060.1:g.28918_28920del
ENST00000252444.10:c.1465_1467del
ENST00000559340.2:c.1207_1209del
ENST00000560467.2:c.1087_1089del
ENST00000558518.6:c.1207_1209del
ENST00000252444.9:c.1461_1463del
ENST00000455727.6:c.703_705del
ENST00000535915.5:c.1084_1086del
ENST00000545707.5:c.826_828del
ENST00000557933.5:c.1207_1209del
ENST00000558013.5:c.1207_1209del
ENST00000558518.5:c.1207_1209del
ENST00000560173.1:n.206_208del
ENST00000560467.1:c.687_689del
NM_000527.4:c.1207_1209del
NM_001195798.1:c.1207_1209del
NM_001195799.1:c.1084_1086del
NM_001195800.1:c.703_705del
NM_001195803.1:c.826_828del
NM_000527.5:c.1207_1209del
NM_001195798.2:c.1207_1209del
NM_001195799.2:c.1084_1086del
NM_001195800.2:c.703_705del
NM_001195803.2:c.826_828del

Likely Pathogenic

Met criteria codes 4

PM4 PM2 PP4 PS4_Supporting

Expert Panel

Familial Hypercholesterolemia VCEP

Not Met criteria codes 16

PM1 PM3 PM5 PM6 BA1 BS1 BS4 BS3 BS2 BP5 BP2 PS1 PS2 PS3 PP1 PP3

Evidence Links 0

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.1207_1209del (p.Phe403del) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM4, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 27 January 2023. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (v2.1.1). PM4: Variant meets PM2 and is an in-frame deletion. PS4_Supporting, PP4: Variant meets PM2 and was identified in at least 5 unrelated index cases who fulfill criteria for FH (4 patients from PMID 22698793 (Tichý et al., 2012) and 1 patient from PMID 11462246 (Nauck et al., 2001), reported as 1205delTCT).

Met criteria codes

PM4	✔	PM4 - Variant meets PM2 and is an in frame deletion.
PM2	✔	PM2 - Variant is absent from gnomAD (v2.1.1).
PP4	✔	PP4 - Variant meets PM2 and was identified in at least 5 patients meeting clinical FH criteria (PMID: 22698793 and PMID 11462246), after alternative causes of high cholesterol were excluded.
PS4_Supporting	✔	PS4_Supporting - Variant meets PM2 and was identified in 4 patients (PMID: 22698793) with MEDPED score of FH and and in 1 patient (PMID 11462246) reported as 1205delTCT with TC 10.33 and LDL-C 8.03.

Not Met criteria codes

PM1	✖	PM2 is Met, but variant is not a missense in exon 4 or any of the 60 Cys residues listed. Not applicable.
PM3	✖	Variant meets PM2 but is not identified in an index case with heterozygous or homozygous FH phenotype as well as LDLR variant, in trans, or APOB/PCSK9 variant classified as Pathogenic by these or general ACMG guidelines.
PM5	✖	Not applicable
PM6	✖	No de novo cases were identified.
BA1	✖	Variant is absent from gnomAD (v2.1.1).

BS1		✖	Variant is absent from gnomAD (v2.1.1).
BS4		✖	No information or report of segregation data/cases
BS3		✖	There is no functional evidence in ClinVar for this variant
BS2		✖	Variant not identified in normolipidemic individuals
BP5		✖	not applicable
BP2		✖	Variant meets PM2 but is not identified in an index case with heterozygous or homozygous FH phenotype as well as LDLR variant, in trans, or APOB/PCSK9 variant classified as Pathogenic by these or general ACMG guidelines.
PS1		✖	Not applicable
PS2		✖	No de novo cases were identified.
PS3		✖	There is no functional evidence in ClinVar for this variant
PP1		✖	PP1 - no information or report of segregation data/cases
PP3		✖	PP3 - No REVEL (not a missense variant). In silico prediction/evaluation (MaxEnsScan) is not recommended for indels.

Curation History

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