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_006767.4(LZTR1):c.1234C>T (p.Arg412Cys)

Version: 1.0

CA501019

373089 (ClinVar)

Gene: LZTR1 (HGNC:8216)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: c382a894-de4a-4be7-85f1-8003be6e6f47
Approved on: 2022-05-09
Published on: 2024-09-25

HGVS expressions

NM_006767.4:c.1234C>T
NM_006767.4(LZTR1):c.1234C>T (p.Arg412Cys)
NC_000022.11:g.20992878C>T
CM000684.2:g.20992878C>T
NC_000022.10:g.21347167C>T
CM000684.1:g.21347167C>T
NC_000022.9:g.19677167C>T
NG_034193.1:g.15610C>T
ENST00000700578.1:c.1234C>T
ENST00000495142.6:n.579C>T
ENST00000642151.1:c.1065C>T
ENST00000643578.1:n.1256C>T
ENST00000646124.2:c.1234C>T
ENST00000646506.1:n.813C>T
ENST00000215739.12:c.1234C>T
ENST00000479606.5:n.1380C>T
ENST00000492480.1:n.290C>T
NM_006767.3:c.1234C>T

Uncertain Significance

Met criteria codes 1

PS4_Supporting

Not Met criteria codes 5

PP3 PM2 BA1 BS1 BP4

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for LZTR1 Version 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

RASopathy VCEP

The NM_006767.4:c.1234C>T (p.Arg412Cys) variant in LZTR1 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 412. Evidence supports that this variant is associated with AD NS and is not associated with AR NS. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003850 (1/25972 alleles) in the Ashkenazi Jewish population (PM2_Supporting, BS1, and BA1 are not met). The computational predictor REVEL gives a score of 0.351, which is neither above nor below the thresholds predicting a damaging or benign impact on LZTR1 function. This variant has been reported in 1 proband with features of RASopathy (PS4_Supporting; PMID:32981126). Schwannomatosis has not been observed in individuals harboring this variant. In summary, this variant meets the criteria to be classified as uncertain significance for autosomal dominant RASopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy VCEP: PS4_Supporting. (RASopathy VCEP specifications version 2; 5/9/2022)

Met criteria codes

PS4_Supporting	✔	This variant has been reported in 1 proband with features of RASopathy (PS4_Supporting; PMID:32981126).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.351, which is neither above nor below the thresholds predicting a damaging or benign impact on LZTR1 function.
PM2	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003850 (1/25972 alleles) in the Ashkenazi Jewish population (PM2_Supporting, BS1, and BA1 are not met).
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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