Variant: NM_006767.4(LZTR1):c.1234C>T (p.Arg412Cys)

Version: 2.0

CA501019

373089 (ClinVar)

Gene: LZTR1 (HGNC:8216)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: c382a894-de4a-4be7-85f1-8003be6e6f47
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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

Pathogenic

Met criteria codes 2

PS2_Very Strong | PS4

Not Met criteria codes 5

PM2 | BA1 | BS1 | BP4 | PP3

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 1.3.0*
- **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 autosomal dominant Noonan Syndrome and is not associated with autosomal recessive Noonan Syndrome. 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 (no codes met). This variant has been reported in 7 with features of RASopathy that are included in this curation (PS4; > 5.0 pts.; PMID: 32981126; GeneDx (SCV000491652), Prevention Genetics (SCV004118816), and Genome Diagnostics Laboratory (Hospital for Sick Children; SCV002060883) internal data). This variant has been identified as de novo with confirmed parental relationships in 2 probands included in this curation (PS2_VeryStrong, > 4.0 pts.; Genome Diagnostics Laboratory (Hospital for Sick Children; SCV002060883) and GeneDx (SCV000491652) internal data). More cases are available, but the thresholds to apply PS4 and PS2 at the strongest levels have already been met. A heterozygous knock-in mouse model of this mutation showed, in addition to death of 75 % of mice by 2 years of age, that the mutants had reduced body lengths and weights compared to the wild-type before 10 weeks old. The mutant mice also had facial and skeletal anomalies, including smaller and more round skulls, abnormal snouts, and hypertelorism, as well as splenomegaly and renal hypertrophy, features consistent with other mouse models of RASopathies (PMID: 39352760). However, PS3 was not applied as it is not currently in the guidelines for LZTR1 variants. In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant RASopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy VCEP: PS4, PS2_VeryStrong (RASopathy VCEP specifications version 1.3.0; 7/8/2025).

Met criteria codes

PS2_Very Strong	✔	This variant has been identified as de novo with confirmed parental relationships in 2 probands included in this curation (PS2_VeryStrong, 4.0 pts.; Genome Diagnostics Laboratory (Hospital for Sick Children; SCV002060883) and GeneDx (SCV000491652) internal data).
PS4	✔	his variant has been reported in 7 with features of RASopathy that are included in this curation (PS4; > 5.0 pts.; PMID: 32981126; GeneDx (SCV000491652), Prevention Genetics (SCV004118816), and Genome Diagnostics Laboratory (Hospital for Sick Children; SCV002060883) internal data).

Not Met criteria codes

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
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.

Curation History

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