Variant: NM_006767.4(LZTR1):c.2178C>A (p.Tyr726Ter)

Version: 1.1

CA410779953

522799 (ClinVar)

Gene: LZTR1 (HGNC:8216)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7e7f14c1-b9c6-47df-be45-efa1dd51f7af
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HGVS expressions

NM_006767.4:c.2178C>A
NM_006767.4(LZTR1):c.2178C>A (p.Tyr726Ter)
NC_000022.11:g.20996071C>A
CM000684.2:g.20996071C>A
NC_000022.10:g.21350360C>A
CM000684.1:g.21350360C>A
NC_000022.9:g.19680360C>A
NG_034193.1:g.18803C>A
ENST00000700578.1:c.2178C>A
ENST00000415817.2:c.607C>A
ENST00000495142.6:n.2530C>A
ENST00000642151.1:c.2009C>A
ENST00000643578.1:n.2200C>A
ENST00000643710.1:n.1039C>A
ENST00000646124.2:c.2178C>A
ENST00000646506.1:n.2045C>A
ENST00000215739.12:c.2178C>A
ENST00000415354.6:c.607C>A
ENST00000415817.1:c.76C>A
ENST00000439171.5:c.577C>A
ENST00000452988.5:c.340C>A
ENST00000463909.1:n.893C>A
ENST00000479606.5:n.2324C>A
ENST00000498649.1:n.194C>A
NM_006767.3:c.2178C>A

Pathogenic

Met criteria codes 3
PM2_Supporting PM3 PVS1

Not Met criteria codes 3
BS1 PS3 BA1

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 c.2178C>A (p.Tyr726Ter) variant in LZTR1 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 18/21 is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The filtering allele frequency (the upper threshold of the 95% CI of 1/34568) of the c.2178C>A variant in LZTR1 is 0 for Admixed American chromosomes by gnomAD v2.1.1, which is lower than the ClinGen RASopathy VCEP threshold (≤0.000025) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). This variant has been detected in 1 individual with autosomal recessive RASopathy. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and was confirmed in trans by family testing (c.1943-256C>T, 1 PM3 point, PMID:29469822) (PM3). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive RASopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy VCEP: PVS1, PM3, PM2_Supporting. (ClinGen RASopathy VCEP specifications version 1.3; 12/3/2024)

Met criteria codes

PM2_Supporting	✔	The filtering allele frequency (the upper threshold of the 95% CI of 1/34568) of the c.2178C>A variant in LZTR1 is 0 for Admixed American chromosomes by gnomAD v2.1.1, which is lower than the ClinGen RASopathy VCEP threshold (≤0.000025) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PM3	✔	This variant has been detected in 1 individual with autosomal recessive RASopathy. They were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and was confirmed in trans by family testing (c.1943-256C>T, 1 PM3 point, PMID:29469822) (PM3).
PVS1	✔	The c.2178C>A (p.Tyr726Ter) variant in LZTR1 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 18/21 is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).

Not Met criteria codes

BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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