Variant: NM_006767.4(LZTR1):c.1943-256C>T

Version: 1.1

CA10119150

522800 (ClinVar)

Gene: LZTR1
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal recessive inheritance
UUID: 18f4ca55-c967-4dd9-970b-992922e00cc0
Approved on: 2024-12-03
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HGVS expressions

NM_006767.4(LZTR1):c.1943-256C>T
NM_006767.4:c.1943-256C>T
NC_000022.11:g.20995490C>T
CM000684.2:g.20995490C>T
NC_000022.10:g.21349779C>T
CM000684.1:g.21349779C>T
NC_000022.9:g.19679779C>T
NG_034193.1:g.18222C>T
ENST00000700578.1:c.1943-256C>T
ENST00000415817.2:c.371+6C>T
ENST00000495142.6:n.2039C>T
ENST00000642151.1:c.1774-256C>T
ENST00000643578.1:n.1965-256C>T
ENST00000643710.1:n.804-256C>T
ENST00000646124.2:c.1943-256C>T
ENST00000646506.1:n.1810-256C>T
ENST00000215739.12:c.1943-256C>T
ENST00000415354.6:c.371+6C>T
ENST00000439171.5:c.341+6C>T
ENST00000452988.5:c.122-273C>T
ENST00000463909.1:n.402C>T
ENST00000479606.5:n.2089-256C>T
ENST00000491432.5:n.364-256C>T
ENST00000495142.5:n.559-256C>T
NM_006767.3:c.1943-256C>T

Pathogenic

Met criteria codes 5

PM2_Supporting PM3_Strong PS3_Supporting PP1_Strong PVS1

Not Met criteria codes 2

BA1 BS1

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.1943-256C>T (p.T648fs*36) variant in LZTR1 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 17/21 is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001557 (2/22704 alleles) in the South Asian population, which is lower than the ClinGen RASopathy VCEP threshold (≤0.000025) for PM2_Supporting, meeting this criterion (PM2_Supporting). This variant has been detected in 4 individuals with RASopathy. All were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and 3 of those were confirmed in trans by parental testing (c.27dup (p.Gln10Alafs*24), c.1030del (p.Ser344fs), c.2178C>A (p.Tyr726Ter), c.27dupG (p.Gln10Alafs*24), 3.5 PM3 points, PMIDs: 29469822 and 32623905, SCV000748478.4, SCV001445973.1, GeneDx, Broad Center for Mendelian Genomics) (PM3_Strong). The variant has been reported to segregate with RASopathy in ≥7 affected meioses from 4 families (PP1_Strong; PMIDs: 29469822 and 32623905, SCV000748478.4, SCV001445973.1, GeneDx, Broad Center for Mendelian Genomics). ERK activation assay in patient-specific cardiomyocytes showed significantly increased levels of phosphorylated ERK indicating that this variant impacts protein function (PMID:32623905)(PS3_Supporting). 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_Strong, PP1_Strong, PS3_Supporting, PM2_Supporting. (ClinGen RASopathy VCEP specifications version 1.3; 12/3/2024)

Met criteria codes

PM2_Supporting ✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001557 (2/22704 alleles) in the South Asian population, which is lower than the ClinGen RASopathy VCEP threshold (≤0.000025) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PM3_Strong ✔	This variant has been detected in 4 individuals with RASopathy. All were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and 3 of those were confirmed in trans by parental testing (c.27dup (p.Gln10Alafs*24), c.1030del (p.Ser344fs), c.2178C>A (p.Tyr726Ter), c.27dupG (p.Gln10Alafs*24), 3.5 PM3 points, PMIDs: 29469822 and 32623905, SCV000748478.4, SCV001445973.1, GeneDx, Broad Center for Mendelian Genomics) (PM3_Strong).
PS3_Supporting ✔	ERK activation assay in patient-specific cardiomyocytes showed significantly increased levels of phosphorylated ERK indicating that this variant impacts protein function (PMID:32623905)(PS3_Supporting).
PP1_Strong ✔	The variant has been reported to segregate with RASopathy in ≥7 affected meioses from 4 families (PP1_Strong; PMIDs: 29469822 and 32623905, SCV000748478.4, SCV001445973.1, GeneDx, Broad Center for Mendelian Genomics).
PVS1 ✔	The c.1943-256C>T (p.T648fs*36) variant in LZTR1 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 17/21 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

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

Curation History

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