Variant: NM_006767.4(LZTR1):c.742G>A (p.Gly248Arg)

Version: 1.2

CA358852

209088 (ClinVar)

Gene: LZTR1 (HGNC:8216)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8343c604-e796-4093-aa1e-f3c39aa13256
Approved on: 2024-09-17
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HGVS expressions

NM_006767.4:c.742G>A
NM_006767.4(LZTR1):c.742G>A (p.Gly248Arg)
NC_000022.11:g.20990476G>A
CM000684.2:g.20990476G>A
NC_000022.10:g.21344765G>A
CM000684.1:g.21344765G>A
NC_000022.9:g.19674765G>A
NG_034193.1:g.13208G>A
ENST00000700578.1:c.742G>A
ENST00000642151.1:c.573G>A
ENST00000646124.2:c.742G>A
ENST00000646506.1:n.321G>A
ENST00000215739.12:c.742G>A
ENST00000414985.5:c.*308G>A
ENST00000479606.5:n.888G>A
ENST00000480895.1:n.438G>A
ENST00000497716.5:n.125G>A
NM_006767.3:c.742G>A

Likely Pathogenic

Met criteria codes 5

PS2 | PS4_Moderate | PP3 | PS3_Supporting | PM2_Supporting

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.742G>A (p.Gly248Arg) variant in LZTR1 is a missense variant predicted to cause substitution of glycine by arginine at amino acid 248. Evidence supports that this variant is associated with AD NS and is not associated with AR NS. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.839, which is above the threshold of 0.7, evidence that correlates with impact to LZTR1 function (PP3). ERK1/2 phosphorylation assays in HEK293 cells showed enhanced EGF-dependent ERK1/2 phosphorylation indicating that this variant impacts protein function (PMID: 30481304)(PS3_Supporting). This variant has been reported in 3 probands with features of RASopathy (PS4_Moderate; PMID:25795793, 30859559, 31533111). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with features of RASopathy (PS2; PMID:30859559). Schwannomatosis has not been observed in individuals harboring this variant. In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant RASopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy VCEP: PS2, PS4_Moderate, PS3_Supporting, PM2_Supporting, PP3. (RASopathy VCEP specifications version 1.1; 9/17/2024)

Met criteria codes

PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with features of RASopathy (PS2; PMID:30859559).
PS4_Moderate	✔	This variant has been reported in 3 probands with features of RASopathy (PS4_Moderate; PMID:25795793, 30859559, 31533111).
PP3	✔	The computational predictor REVEL gives a score of 0.839, which is above the threshold of 0.7, evidence that correlates with impact to LZTR1 function (PP3).
PS3_Supporting	✔	ERK1/2 phosphorylation assays in HEK293 cells showed enhanced EGF-dependent ERK1/2 phosphorylation indicating that this variant impacts protein function (PMID: 30481304)(PS3_Supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Curation History

Showing 1 to 3 of 3 rows