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Variant: NM_004958.4(MTOR):c.7280T>C (p.Leu2427Pro)

Version: 2.0

CA338380762

417723 (ClinVar)

Gene: MTOR (HGNC:2475)
Condition: overgrowth syndrome and/or cerebral malformations due to abnormalities in MTOR pathway genes (MONDO:0100283)
Inheritance Mode: Autosomal dominant inheritance (mosaic)
UUID: d9f52cde-a2d2-4580-9f3d-af90946ce1f9
Approved on: 2022/2/12
Published on: 2022/2/12

HGVS expressions

NM_004958.4(MTOR):c.7280T>C (p.Leu2427Pro)
NM_004958.4:c.7280T>C
NC_000001.11:g.11114338A>G
CM000663.2:g.11114338A>G
NC_000001.10:g.11174395A>G
CM000663.1:g.11174395A>G
NC_000001.9:g.11096982A>G
NG_033239.1:g.153214T>C
ENST00000703118.1:c.*2655T>C
ENST00000703131.1:n.3198T>C
ENST00000703139.1:c.2068T>C
ENST00000703140.1:c.7067T>C
ENST00000703141.1:c.*2797T>C
ENST00000703142.1:c.*4110T>C
ENST00000361445.9:c.7280T>C
ENST00000361445.8:c.7280T>C
ENST00000376838.5:c.1895T>C
ENST00000455339.1:c.248T>C
ENST00000473471.5:n.292T>C
ENST00000490931.1:n.323T>C
NM_004958.3:c.7280T>C
NM_001386500.1:c.7280T>C
NM_001386501.1:c.6032T>C

Pathogenic

Met criteria codes 5

PS3 PP2 PS4_Moderate PS2_Moderate PM2_Supporting

Not Met criteria codes 11

PS1 PP1 PP3 PP4 PM1 PM3 PM5 PM4 PM6 PVS1 BS3

Evidence Links 0

Expert Panel

Brain Malformations VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Brain Malformations VCEP

The c.7280T>C (NM_004958.4) variant in MTOR is a missense variant predicted to cause substitution of (p.Leu2427Pro). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4_M; PMIDs: 25799227, 25159823; identified in 2 individuals with neuropathology confirmatory of a malformation of cortical development, 1 tumor sample in the literature and COSMIC). An animal model generated with this variant shows a seizure phenotype which responded to treatment with rapamycin indicating that this variant impacts protein function (PMID: 29937275) (PS3_Strong). Testing of unaffected and affected tissue show variable allelic fractions consistent with a post-zygotic event (PS2_Moderate; PMID: 25799227). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). MTOR, in which the variant was identified, is defined by the ClinGen Brain Malformations Expert Panel as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). In summary, this variant meets the criteria to be classified as Pathogenic for mosaic autosomal dominant overgrowth with or without cerebral malformations due to abnormalities in MTOR-pathway genes based on the ACMG/AMP criteria applied, as specified by the ClinGen Brain Malformations Expert Panel: PS4_M, PS3, PS2_M, PM2_P, PP2; 10 points (VCEP specifications version 1; Approved: 1/31/2021)

Met criteria codes

PS3	✔	Mouse model electroporated with this variant developed seizures, which stopped upon treatment with rapamycin
PP2	✔	The Z score for MTOR is 7.02
PS4_Moderate	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2_Moderate	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2_Supporting	✔	The variant is absent from gnomAD with adequate coverage.

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	

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

PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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