Variant: NM_004958.3(MTOR):c.4447T>C (p.Cys1483Arg)

Version: 2.0

CA16602264

374796 (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: 6ed31c33-11e4-468c-82e0-419ec860d576
Approved on: 2022-02-11
Published on: 2022-02-11

HGVS expressions

NM_004958.3:c.4447T>C
NM_004958.3(MTOR):c.4447T>C (p.Cys1483Arg)
NC_000001.11:g.11157174A>G
CM000663.2:g.11157174A>G
NC_000001.10:g.11217231A>G
CM000663.1:g.11217231A>G
NC_000001.9:g.11139818A>G
NG_033239.1:g.110378T>C
ENST00000703118.1:c.4447T>C
ENST00000703131.1:n.367T>C
ENST00000703140.1:c.4234T>C
ENST00000703141.1:c.4447T>C
ENST00000703142.1:c.*1277T>C
ENST00000361445.9:c.4447T>C
ENST00000361445.8:c.4447T>C
NM_004958.4:c.4447T>C
NM_001386500.1:c.4447T>C
NM_001386501.1:c.3199T>C

Pathogenic

Met criteria codes 6

PS4 PP2 PS2_Moderate PM2_Supporting PM1_Supporting PS3_Supporting

Not Met criteria codes 20

PS1 PP1 PP3 PP4 PM3 PM5 PM4 PM6 PVS1 BA1 BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2

Evidence Links 4

Expert Panel

Brain Malformations VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Brain Malformations VCEP

The c.4447T>C (NM_004958.4) variant in MTOR is a missense variant predicted to cause substitution of (p.Cys1483Arg). 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). This variant resides within the kinase domain of MTOR that is defined as a critical functional domain by the ClinGen BMEP (PMIDs: 23322780, 27482884, 21210909) (PM1_Supporting). This variant has been shown to significantly increase phosphorylation levels in experiments with case and control cells of similar isogenic backgrounds indicating that this variant impacts protein function (PMIDs: 25799227, 24631838) (PS3_Supporting). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4; PMIDs: 28864461, 25799227; identified in 2 individuals with neuropathology confirmatory of a malformation of cortical development, 1 individual with neuroimaging demonstrating at least one large cerebral hemisphere with cortical malformation(s), 3 tumor samples in the literature and COSMIC). Testing of unaffected and affected tissue show variable allelic fractions consistent with a post-zygotic event (PS2_Moderate; PMID: 25799227). 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: PM2_P, PP2, PM1_P, PS3_P, PS4, PS2_M; 10 points (VCEP specifications version 1; Approved: 1/31/2021)

Met criteria codes

PS4	✔	3 tumor samples in COSMIC FCD Iib w/ neuopath PubMed:28864461 MRI HMEG PubMed:25799227 says based on MRI and neuropathology, patient FCD-8 had FCD Iib PubMed:29281825
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2_Moderate	✔	brain - 6.4% hyb capture, 9.8% / 6.6% amplicon; saliva - 0% PubMed:25799227 brain 10.0-10.6% but no note of testing in nonaffected tissue PubMed:29281825
PM2_Supporting	✔	absent from gnomAD
PM1_Supporting	✔	located in the kinase domain
PS3_Supporting	✔	increased S6K1 phosphorylation in transfected HEK293T cells and not in wt transfected cells PubMed:24631838 increased S6 phosphorylation in transfected HEK293T cells and not in wt transfected cells PubMed:25799227

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
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	✖	brain - 6.4% hyb capture, 9.8% / 6.6% amplicon; saliva - 0% PubMed:25799227 brain 10.0-10.6% but no note of testing in nonaffected tissue PubMed:29281825
PVS1	✖	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
BS2	✖	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
BS4	✖	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
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	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

BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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