Variant: NM_004958.4(MTOR):c.4448G>A (p.Cys1483Tyr)

Version: 2.1

CA16602888

376453 (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: 5cb91dd4-9595-443c-bc27-cd95f8241c6a
Approved on: 2022-02-17
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HGVS expressions

NM_004958.4:c.4448G>A
NM_004958.4(MTOR):c.4448G>A (p.Cys1483Tyr)
NC_000001.11:g.11157173C>T
CM000663.2:g.11157173C>T
NC_000001.10:g.11217230C>T
CM000663.1:g.11217230C>T
NC_000001.9:g.11139817C>T
NG_033239.1:g.110379G>A
ENST00000703118.1:c.4448G>A
ENST00000703131.1:n.368G>A
ENST00000703140.1:c.4235G>A
ENST00000703141.1:c.4448G>A
ENST00000703142.1:c.*1278G>A
ENST00000361445.9:c.4448G>A
ENST00000361445.8:c.4448G>A
NM_004958.3:c.4448G>A
NM_001386500.1:c.4448G>A
NM_001386501.1:c.3200G>A

Pathogenic

Met criteria codes 6

PM2_Supporting PS2_Moderate PM1_Supporting PP2 PM5 PS4

Not Met criteria codes 20

BS2 BS1 BS4 BS3 PP1 PP3 PP4 PM3 PM4 PM6 PS1 PS3 BA1 PVS1 BP4 BP3 BP1 BP2 BP5 BP7

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.4448G>A (NM_004958.4) variant in MTOR is a missense variant predicted to cause substitution of (p.Cys1483Tyr). 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). A different amino acid change (p.Cys1483Arg), at this locus is classified as pathogenic for Overgrowth with or without cerebral malformations due to abnormalities in MTOR-pathway genes by the ClinGen BMEP (PM5). 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). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4; PMIDs: 22729223; 28892148; 25599672; 26619011; identified in 2 individuals with neuroimaging demonstrating at least one large cerebral hemisphere with cortical malformation(s), 1 individual with macrocephaly (>=2 SD) and Developmental Delay or Intellectual disability without cortical malformations, it has been shown to demonstrate an increase cell growth phenotype in patient cell lines and at least 3 tumor samples in the literature and COSMIC). This variant has been confirmed de novo and has been identified with variable allelic fractions consistent with a post-zygotic event (PS2_Strong; PMID: 28892148). 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, PM5, PM1_P, PS4, PS2; 13 points(VCEP specifications version 1; Approved: 1/31/2021)

Met criteria codes

PM2_Supporting	✔	absent from gnomAD
PS2_Moderate	✔	Patient P2 showed by NGS the mutant allele in 2% of blood sample, 11% in saliva 18% in hyperpigmented skin, and 28% in hypopigmented skin - confirmed by pyrosequencing PubMed:28892148 Variant not found in blood sample but found in 8-36% of central operculum regions in indivdual with cortical dyslamination, cytomegalic neuron, ectopic neurons, and hypomelanosis of Iso PubMed:22729223
PM1_Supporting	✔	kinase domain
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✔	p.Cys1483Arg at the same amino acid position is Path., but not the same amino acid change
PS4	✔	2 COSMIC tumor samples Patient P2, Spanish, 8 years old, male. Diagnosed with Smith-Kingsmore syndrome: Has megalencephaly/macrocephaly, ID, seizures, hypertelorism, open mouth appearance, smooth philtrum, hyperpigmented skin, strabismus, hypotonia. CNS image shows ventriculomegaly, gliosis, cavum vergae, periventricular venous malformation. "Mosaic in all studied tissues(blood, saliva, skin)" PubMed:28892148 1 tumor sample PubMed:26619011 Individual HME-1 with mosaic mutation. alternate allele frequency 14%; HME confirmed by MRI and neuropathology PubMed:25599672 Individual HME-1563: 5 y/o female with cortical dyslamination, cytomegalic neuron, ectopic neurons, hypomelanosis of Iso. Variant is somatic. Performed pathology PubMed:22729223

Not Met criteria codes

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	✖	immunostained brain sections of patient with antibodies specific to the phosphorylated epitopse of S6 protein in a standard assay for activation of mTOR signaling. Cells with cytomegalic neurons were strongly labeled for phosphorylated S6 in DAB staining of HME brians. Concluded that the p.C1483Y variant increases mTOR signaling in affected brain regions PubMed:22729223
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
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	Patient P2 showed by NGS the mutant allele in 2% of blood sample, 11% in saliva 18% in hyperpigmented skin, and 28% in hypopigmented skin - confirmed by pyrosequencing PubMed:28892148 Variant not found in blood sample but found in 8-36% of central operculum regions in indivdual with cortical dyslamination, cytomegalic neuron, ectopic neurons, and hypomelanosis of Iso PubMed:22729223
PS1	✖	variant at the same amino acid position is Path., but not the same amino acid change
PS3	✖	patient derived tissue immunostained brain sections of patient with antibodies specific to the phosphorylated epitopse of S6 protein in a standard assay for activation of mTOR signaling. Cells with cytomegalic neurons were strongly labeled for phosphorylated S6 in DAB staining of HME brians. Concluded that the p.C1483Y variant increases mTOR signaling in affected brain regions PubMed:22729223
BA1	✖	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
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
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

Curation History

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