Variant: NM_004958.3(MTOR):c.6644C>T (p.Ser2215Phe)

Version: 2.0

CA248393

156703 (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: d0c7e9a9-5d12-4d15-9442-bf75fb5f4d15
Approved on: 2022-02-12
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HGVS expressions

NM_004958.3:c.6644C>T
NM_004958.3(MTOR):c.6644C>T (p.Ser2215Phe)
NC_000001.11:g.11124516G>A
CM000663.2:g.11124516G>A
NC_000001.10:g.11184573G>A
CM000663.1:g.11184573G>A
NC_000001.9:g.11107160G>A
NG_033239.1:g.143036C>T
ENST00000703118.1:c.*2019C>T
ENST00000703131.1:n.2645C>T
ENST00000703139.1:c.1281C>T
ENST00000703140.1:c.6431C>T
ENST00000703141.1:c.*2161C>T
ENST00000703142.1:c.*3474C>T
ENST00000361445.9:c.6644C>T
ENST00000361445.8:c.6644C>T
ENST00000376838.5:c.1259C>T
NM_004958.4:c.6644C>T
NM_001386500.1:c.6644C>T
NM_001386501.1:c.5396C>T

Pathogenic

Met criteria codes 5

PS3_Supporting PP2 PS2 PS4 PM2_Supporting

Not Met criteria codes 21

PP1 PP3 PP4 PS1 PM6 PM1 PM3 PM5 PM4 PVS1 BA1 BP4 BP3 BP1 BP2 BP5 BP7 BS2 BS1 BS4 BS3

Evidence Links 2

Expert Panel

Brain Malformations VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Brain Malformations VCEP

The c.6644C>T (NM_004958.4) variant in MTOR is a missense variant predicted to cause substitution of (p.Ser2215Phe). 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 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 (PMID: 27159400) (PS3_Supporting). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4; PMIDs: 27159400, 27830187 ; identified in 8 individuals with neuropathology confirmatory of a malformation of cortical development and 19 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; PMIDs: 27159400, 27159400, 27830187). 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, PS3_P, PS4, PS2; 11 points (VCEP specifications version 1; Approved: 1/31/2021)

Met criteria codes

PS3_Supporting	✔	Mutant alleles tested in S6 phosphorylation and neuronal cell culture experiments, the latter with reversal of phenotype upon everolimus treatment PubMed:27159400
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✔	2 IIb, 1 IIa with somatic mutations (no functional assay) PubMed:27830187 Study designed using trios with filtration for absence in parents; subjects with FCD on neuroimaging, FCD2a on neuropathology, no mention of macroephaly. Mutant alleles tested in S6 phosphorylation and neuronal cell culture experiments, the latter with reversal of phenotype upon everolimus treatment. PubMed:27159400
PS4	✔	19 tumor samples in COSMIC 2 IIb, 1 IIa with somatic mutations (no functional assay) PubMed:27830187 subjects with FCD on neuroimaging, FCD2a on neuropathology, no mention of macroephaly. Mutant alleles tested in S6 phosphorylation and neuronal cell culture experiments, the latter with reversal of phenotype upon everolimus treatment PubMed:27159400
PM2_Supporting	✔	absent from gnomAD

Not Met criteria codes

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

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	2 IIb, 1 IIa with somatic mutations (no functional assay) PubMed:27830187 Study designed using trios with filtration for absence in parents; subjects with FCD on neuroimaging, FCD2a on neuropathology, no mention of macroephaly. Mutant alleles tested in S6 phosphorylation and neuronal cell culture experiments, the latter with reversal of phenotype upon everolimus treatment. PubMed:27159400
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
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
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

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

Curation History

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