

Variant: *NM_004958.4(MTOR):c.5005G>T (p.Ala1669Ser)*

Version: 2.1

CA338402061 [↗](#)

1296997 (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: 9899ece2-f041-4754-ae5d-c5d883442448

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HGVS expressions

NM_004958.4:c.5005G>T

NM_004958.4(MTOR):c.5005G>T (p.Ala1669Ser)

NC_000001.11:g.11139429C>A

CM000663.2:g.11139429C>A

NC_000001.10:g.11199486C>A

CM000663.1:g.11199486C>A

NC_000001.9:g.11122073C>A

NG_033239.1:g.128123G>T

ENST00000703118.1:c.*380G>T

ENST00000703131.1:n.925G>T

ENST00000703140.1:c.4792G>T

ENST00000703141.1:c.*325G>T

ENST00000703142.1:c.*1835G>T

ENST00000361445.9:c.5005G>T

ENST00000361445.8:c.5005G>T

ENST00000476768.1:n.135G>T

ENST00000495435.1:n.511G>T

NM_004958.3:c.5005G>T

NM_001386500.1:c.5005G>T

NM_001386501.1:c.3757G>T

Likely Pathogenic

Met criteria codes **5**

PM2_Supporting

PM1_Supporting

PS2_Moderate

PP2

PS4_Supporting

Evidence Links **0**

Expert Panel

Brain Malformations VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Brain Malformations Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1.1.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Brain Malformations VCEP

The NM_004958.4:c.5005G>T variant in MTOR is a missense variant predicted to cause substitution of alanine by serine at amino acid 1669. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). MTOR, in which the variant was identified, is defined by the ClinGen Brain Malformations Variant Curation Expert Panel (BM VCEP) 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 focal adhesion kinase targeting domain of MTOR that is defined as a critical functional domain by the ClinGen BM VCEP (PM1_Supporting; PMIDs: 23322780, 27482884, 21210909). This variant has been identified in one patient with diffuse cortical dysplasia (PS4_Supporting, PMID: 25599672). In this patient, the variant was present at an alternate allele frequency of 44% in the brain but was not detectable in blood (PS2_Moderate). In summary, this variant meets the criteria to be classified as likely pathogenic for overgrowth syndrome and/or cerebral malformations due to abnormalities in MTOR pathway genes based on the ACMG/AMP criteria applied, as specified by the ClinGen BM VCEP Panel: PM2_Supporting, PP2, PM1_Supporting, PS4_Supporting, PS2_Moderate (ClinGen Brain Malformations VCEP Specifications Version 1.1).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0
PM1_Supporting			This variant resides within the focal adhesion kinase targeting domain of MTOR that is defined as a critical functional domain by the ClinGen BM VCEP
PS2_Moderate			In one patient, the variant was present at an alternate allele frequency of 44% in the brain but was not detectable in blood
PP2			MTOR is defined by the BM VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease.
PS4_Supporting			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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Showing 1 to 3 of 3 rows

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