

Variant: *NM_004958.4(MTOR):c.6644C>A (p.Ser2215Tyr)*

Version: 2.1

CA16602587 [↗](#)

376129 (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: 92c55e08-6866-4c47-ade5-8db428335094

Approved on: 2022/2/17

Published on: 2022/2/17

HGVS expressions

NM_004958.4(MTOR):c.6644C>A (p.Ser2215Tyr)

NM_004958.4:c.6644C>A

NC_000001.11:g.11124516G>T

CM000663.2:g.11124516G>T

NC_000001.10:g.11184573G>T

CM000663.1:g.11184573G>T

NC_000001.9:g.11107160G>T

NG_033239.1:g.143036C>A

ENST00000703118.1:c.*2019C>A

ENST00000703131.1:n.2645C>A

ENST00000703139.1:c.1281C>A

ENST00000703140.1:c.6431C>A

ENST00000703141.1:c.*2161C>A

ENST00000703142.1:c.*3474C>A

ENST00000361445.9:c.6644C>A

ENST00000361445.8:c.6644C>A

ENST00000376838.5:c.1259C>A

NM_004958.3:c.6644C>A

NM_001386500.1:c.6644C>A

NM_001386501.1:c.5396C>A

Pathogenic

Met criteria codes 6

PS4 PS2_Moderate PP2

PS3_Supporting PM5

PM2_Supporting

Not Met criteria codes 20

PS1 PP1 PP3 PP4 BA1

PM6 BS1 BS4 BS3 PM1

PM3 PM4 BS2 BP5 BP7

BP4 BP3 BP1 BP2 PVS1

Evidence Links 1

Expert Panel

Brain Malformations VCEP [↗](#)

Criteria Specification Information **!**

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

Brain Malformations VCEP

The c.6644C>A (NM_004958.4) variant in MTOR is a missense variant predicted to cause substitution of (p.Ser2215Tyr). 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.Ser2215Phe), 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 has been shown to significantly increase phosphorylation levels in experiments with case and controls cells of similar isogenic backgrounds indicating that this variant impacts protein function (PMIDs: 20190810, 24631838, 28963468) (PS3_Supporting). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4; PMID: 27830187, 29281825, 225401301, 26619011; identified in 5 individuals with neuropathology confirmatory of a malformation of cortical development, 1 individual with neuroimaging appearance consistent with a malformation of cortical development (without neuropathology), 1 individual with neuroimaging demonstrating at least one large cerebral hemisphere with cortical malformation(s), 15 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: 26018084). 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, PS3_P, PS4, PS2_M; 11 points (VCEP specifications version 1; Approved: 1/31/2021)

Met criteria codes

PS4			15 tumor samples in COSMIC https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=20417
PS2_Moderate			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3_Supporting			variant shown to be activating in vitro and sensitive to rapamycin exposure PubMed:20190810 
PM5			Ser2215Phe pathogenic
PM2_Supporting			absent from gnomAD

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
BA1		✖	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
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
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
PM4		✖	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
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
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
		<div></div> <div>▼</div> <div>▼</div>
Showing 1 to 3 of 3 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.