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Variant: NM_004958.3(MTOR):c.5930C>A (p.Thr1977Lys)

Version: 2.0

CA248390

156702 (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: 9187950f-2c32-459c-b678-3bd146dec7ec
Approved on: 2022/2/12
Published on: 2022/2/12

HGVS expressions

NM_004958.3(MTOR):c.5930C>A (p.Thr1977Lys)
NM_004958.3:c.5930C>A
NC_000001.11:g.11128107G>T
CM000663.2:g.11128107G>T
NC_000001.10:g.11188164G>T
CM000663.1:g.11188164G>T
NC_000001.9:g.11110751G>T
NG_033239.1:g.139445C>A
ENST00000703118.1:c.*1305C>A
ENST00000703131.1:n.1734C>A
ENST00000703139.1:c.567C>A
ENST00000703140.1:c.5717C>A
ENST00000703141.1:c.*1250C>A
ENST00000703142.1:c.*2760C>A
ENST00000361445.9:c.5930C>A
ENST00000361445.8:c.5930C>A
ENST00000376838.5:c.545C>A
NM_004958.4:c.5930C>A
NM_001386500.1:c.5930C>A
NM_001386501.1:c.4682C>A

Pathogenic

Met criteria codes 6

PM2_Supporting PP2 PS3_Supporting PM1_Supporting PS4 PS2_Moderate

Not Met criteria codes 20

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

Evidence Links 3

Expert Panel

Brain Malformations VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Brain Malformations VCEP

The c.5930C>A (NM_004958.4) variant in MTOR is a missense variant predicted to cause substitution of (p.Thr1977Lys). 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 (PMID: 24631838) (PS3_Supporting). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4; PMIDs w/ phenotypes). 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

PM2_Supporting	✔	absent from gnomAD
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3_Supporting	✔	AKT phosphrylation PubMed:24631838
PM1_Supporting	✔	kinase domain
PS4	✔	5 tumor samples in COSMIC FCD-14 PubMed:29281825 FCD116 & FCD145 PubMed:25799227
PS2_Moderate	✔	FCD145 1.5% in brain, absent from saliva PubMed:25799227

Not Met criteria codes

BA1	✖	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
PM6		✖	FCD145 1.5% in brain, absent from saliva PubMed:25799227
PVS1		✖	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	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	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	ℹ	✖	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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