The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_006218.4(PIK3CA):c.2176G>A (p.Glu726Lys)

Version: 2.0

CA16602910

376476 (ClinVar)

Gene: PIK3CA (HGNC:5290)
Condition: overgrowth syndrome and/or cerebral malformations due to abnormalities in MTOR pathway genes (MONDO:0016054)
Inheritance Mode: Autosomal dominant inheritance (mosaic)
UUID: 8d9a648c-9ee0-4820-8635-a9b83415906d
Approved on: 2022-02-12
Published on: 2022-02-12

HGVS expressions

NM_006218.4:c.2176G>A
NM_006218.4(PIK3CA):c.2176G>A (p.Glu726Lys)
NC_000003.12:g.179221146G>A
CM000665.2:g.179221146G>A
NC_000003.11:g.178938934G>A
CM000665.1:g.178938934G>A
NC_000003.10:g.180421628G>A
NG_012113.2:g.77624G>A
ENST00000263967.4:c.2176G>A
ENST00000462255.2:n.638G>A
ENST00000643187.1:c.2176G>A
ENST00000674534.1:n.3084G>A
ENST00000674622.1:n.597G>A
ENST00000675467.1:n.4983G>A
ENST00000675786.1:c.*743G>A
ENST00000263967.3:c.2176G>A
ENST00000462255.1:n.450G>A
NM_006218.2:c.2176G>A
NM_006218.3:c.2176G>A

Pathogenic

Met criteria codes 4

PM2_Supporting PS2 PS4 PP2

Not Met criteria codes 22

PM6 PM4 PM3 PM1 PM5 BA1 BS2 BS4 BS3 BS1 BP3 BP2 BP4 BP1 BP7 BP5 PVS1 PS3 PS1 PP4 PP1 PP3

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.2176G>A (NM_006218.4) variant in PIK3CA is a missense variant predicted to cause substitution of (p.Glu726Lys). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). PIK3CA, 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). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4_VS; identified in at least 15 individuals with a clinical diagnosis of megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome; (MPPH) or megalencephaly-capillary malformation-polymicrogyria syndrome; (MCAP), it has been shown to significantly increase phosphorylation levels in patient cell lines (PMID: 28566443), and is in at least 15 tumor samples in the literature and COSMIC (PMID: 22729224, PMID: 28941273, PMID: 24497998)). This variant has been confirmed de novo and has been identified with variable allelic fractions consistent with a post-zygotic event (PS2_Strong; PMIDs: 22729224, 22729224). 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, PS4_VS, PS2; 14 points (VCEP specifications version 1; Approved: 1/31/2021)

Met criteria codes

PM2_Supporting	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✔	LR08-261 (12% blood 41% buccal), LR06-333 (14% LCL and 15% saliva) PubMed:22729224
PS4	✔	15MCAP, 104 tumors in cosmic 001P, 333, 261 all have MCAP PubMed:22729224 10 individuals with MCAP PubMed:27631024 P2 and P3 have MCAP 8% and 18% in lymph tissue PubMed:28941273
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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Not Met criteria codes

PM6	✖	LR08-261 (12% blood 41% buccal), LR06-333 (14% LCL and 15% saliva) PubMed:22729224
PM4	✖	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
PM1	✖	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

BA1	✖	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
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	Patient cell lines show increased phos PubMed:28566443
BS1	✖	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
BP2	✖	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
BP1	✖	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
BP5	✖	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
PS3	✖	Patient cell lines show increased phos PubMed:28566443
PS1	✖	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

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

Curation History

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene

No matching records found