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.1624G>A (p.Glu542Lys)

CA333572

31944 (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: 7ffcf400-d46a-4637-be35-8721447aa249
Approved on: 2022-02-12
Published on: 2022-02-12

HGVS expressions

NM_006218.4(PIK3CA):c.1624G>A (p.Glu542Lys)
NM_006218.4:c.1624G>A
NC_000003.12:g.179218294G>A
CM000665.2:g.179218294G>A
NC_000003.11:g.178936082G>A
CM000665.1:g.178936082G>A
NC_000003.10:g.180418776G>A
NG_012113.2:g.74772G>A
ENST00000263967.4:c.1624G>A
ENST00000462255.2:n.86G>A
ENST00000643187.1:c.1624G>A
ENST00000674534.1:n.1378G>A
ENST00000674622.1:n.127G>A
ENST00000675467.1:n.4431G>A
ENST00000675786.1:c.*191G>A
ENST00000263967.3:c.1624G>A
NM_006218.2:c.1624G>A
NM_006218.3:c.1624G>A

Pathogenic

The Expert Panel has overridden the computationally generated classification - "*Likely Pathogenic*"

Met criteria codes 4

PM2_Supporting PS2_Moderate PS4 PP2

Not Met criteria codes 22

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

Evidence Links 0

Expert Panel

Brain Malformations VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Brain Malformations VCEP

The c.1624G>A (NM_006218.4) variant in PIK3CA is a missense variant predicted to cause substitution of (p.Glu542Lys). Testing of unaffected and affected tissue show variable allelic fractions consistent with a post-zygotic event (PS2_Moderate; PMID: 22658544). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PS4_VS; PMIDs: 25722288, 25681199, 22658544, 29446767, 26851524, 25292196, 23100325; identified in 1 individual with neuroimaging demonstrating at least one large cerebral hemisphere with cortical malformation, at least 6 individuals with a clinical diagnosis of megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome; (MPPH) or megalencephaly-capillary malformation-polymicrogyria syndrome; (MCAP), at least 9 individuals with segmental overgrowth or vascular malformation of a limb or region of the body, and at least 9 tumor samples in the literature and COSMIC). 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). 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: PS2_M, PS4_VS, PM2_P, PP2; 12 points (VCEP specifications version 1; Approved: 1/31/2021)

Met criteria codes

PM2_Supporting	✔	The variant is absent from gnomAD with adequate coverage.
PS2_Moderate	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✔	PS4_VS This variant is present in over 1000 entries in COSMIC. Tumor types include Large intestine (427), Breast (402), Urinary tract (102), Endometrium (71), and Lung (54)
PP2	✔	PIK3CA ExAC constraint z-score is 5.77

Not Met criteria codes

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
BS1	✖	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
BP7	✖	

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

BP5	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
BP1		✖	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	ℹ	✖	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	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
PP4		✖	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
PP1		✖	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
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	Variant does not fall in any of the designated functional domains.
PM5	ℹ	✖	

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

PM6	✖	addressed in PS2

Curation History

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

No matching records found