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Variant: NM_005026.5:c.241G>A

Version: 1.0

CA338300169

Gene: PIK3CD (HGNC:5293)
Condition: immunodeficiency 14 (MONDO:0014222)
Inheritance Mode: Autosomal dominant inheritance
UUID: b0b1fd47-57a4-4bc9-be3c-ffee5a993886
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HGVS expressions

NM_005026.5:c.241G>A
NC_000001.11:g.9715640G>A
CM000663.2:g.9715640G>A
NC_000001.10:g.9775698G>A
CM000663.1:g.9775698G>A
NC_000001.9:g.9698285G>A
NG_023434.1:g.68909G>A
ENST00000481137.2:c.241G>A
ENST00000698706.1:n.492G>A
ENST00000698708.1:n.449G>A
ENST00000698709.1:c.241G>A
ENST00000698710.1:c.241G>A
ENST00000698711.1:n.594G>A
ENST00000698712.1:c.241G>A
ENST00000698713.1:c.241G>A
ENST00000698714.1:c.241G>A
ENST00000698715.1:c.241G>A
ENST00000698716.1:c.241G>A
ENST00000377346.9:c.241G>A
ENST00000361110.6:c.241G>A
ENST00000377346.8:c.241G>A
ENST00000536656.5:c.241G>A
ENST00000543390.2:c.241G>A
ENST00000628140.2:c.241G>A
NM_005026.3:c.241G>A
NM_001350234.1:c.241G>A
NM_001350235.1:c.241G>A
NM_005026.4:c.241G>A
NM_001350234.2:c.241G>A

Likely Pathogenic

Met criteria codes 6

PS2_Moderate PS4_Supporting PS3_Supporting PP4_Moderate PP3 PM2_Supporting

Expert Panel

Antibody Deficiencies VCEP

Criteria Specification Information

Not Met criteria codes 1

PM6

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Criteria Specification: *ClinGen Antibody Deficiencies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PIK3CD Version 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Antibody Deficiencies VCEP

NM_005026.5(PIK3CD):c.241G>A (p.Glu81Lys) is a missense variant causing substitution of glutamic acid by lysine at amino acid 81. This variant is present in gnomAD v4.1.0 at a total combined allele frequency of 0.0000006197, with 1 allele / 1,613,806 total alleles across all populations of gnomAD, which is lower than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.00000132 (PM2_Supporting). At least one patient with this variant had a phenotype that included recurrent sinopulmonary infections and otitis media (4 pts), lymphoma (1 pt), lymphadenopathy (4 pts), eczema (1 pt), increased circulating antibody levels (0.5 pts), increased proportion of transitional B cells (2 pts), and lymphopenia (1 pt), with genotyping to rule out an alternative basis for disease in the PIK3R1 gene (13.5 total points, PMID: 28414062). Additionally, a phospho-AKT assay in patient T cells revealed over-activation of the PI3K pathway, which was rescued by inhibition using idelalisib (PMID: 28414062, PP4_Moderate). A second proband has a phenotype including lymphoproliferation with splenomegaly (4 pts), hepatic fibrosis and portal hypertension with gastrointestinal bleeding (1 pt), bronchiectasis (4 pts), lymphopenia (1 pt), and decreased IgG (0.5 pts), with genotyping that excluded an alternative basis for disease in PIK3R1 (10.5 pts, PMID:28428270). The variant was identified as a de novo occurrence with unconfirmed parental relationships in the proband (PS2_Moderate; PMID: 28428270). A kinase activity assay using this PIK3CD variant in healthy (non-patient) T cells showed increased phospho-AKT, indicating that the variant disrupts protein function (PS3_Supporting; PMID: 28414062). The computational predictor REVEL gives a score of 0.661, which is above the ClinGen Antibody Deficiencies VCEP threshold of >0.644 and predicts a damaging effect on PIK3CD function. The computational predictor CADD gives a PHRED score of 31.0, which is above the ClinGen Antibody Deficiencies VCEP threshold of >25.3 and predicts a deleterious effect on PIK3CD function. The two predictors agree on a damaging effect (PP3). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant immunodeficiency 14 based on the ACMG/AMP criteria applied, as specified by the ClinGen Antibody Deficiencies VCEP: PS2_Moderate, PS4_Supporting, PP4_Moderate, PM2_Supporting, PS3_Supporting, and PP3. (VCEP specifications version 1.0.0).

Met criteria codes

PS2_Moderate ✔

This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with immunodeficiency 14. The individual met phenotypic criteria (>10 phenotypic points) and had alternative causes in other loci excluded by genotyping, which together are highly consistent with APDS (PS2_Moderate; PMID: 28428270).

PS4_Supporting ✔

This variant has been reported in at least 2 unrelated probands meeting the VCEP standard for phenotypic criteria, one of whom has a phenotype including lymphoproliferation with splenomegaly (4 pts), hepatic fibrosis and portal hypertension with gastrointestinal bleeding (1 pt), bronchiectasis (4 pts), lymphopenia (1 pt), and decreased IgG (0.5 pts), with genotyping that excluded an alternative basis for disease in PIK3R1 (10.5 pts, PMID:28428270). The other proband has already been counted for PP4_Moderate (PS4_Supporting).

PS3_Supporting ✔

A kinase activity assay using this PIK3CD variant in healthy (non-patient) T cells showed increased phospho-AKT, indicating that the variant disrupts protein function (PS3_Supporting; PMID:28414062).

When overexpressed in healthy T cells, this variant resulted in increased phosphorus-AKT. PubMed:28414062

PP4_Moderate		✔	At least one patient (Patient B.1 in PMID:28414062) with this variant had a phenotype that included recurrent sinopulmonary infections and otitis media (4 pts), lymphoma (1 pt), lymphadenopathy (4 pts), eczema (1 pt), increased circulating antibody levels (0.5 pts), increased proportion of transitional B cells (2 pts), and lymphopenia (1 pt), with genotyping to rule out a variant in PIK3R1, PIK3CG, and PTEN which is highly specific for immunodeficiency 14. Additionally, a phospho-AKT assay in patient T cells revealed over-activation of the PI3K pathway, which was rescued by inhibition using idelalisib (13.5 total points, PMID: 28414062, PP4_Moderate).
PP3		✔	The computational predictor REVEL gives a score of 0.661, which is above the ClinGen Antibody Deficiencies VCEP threshold of >0.644 and predicts a damaging effect on PIK3CD function. The computational predictor CADD gives a PHRED score of 31.0, which is above the ClinGen Antibody Deficiencies VCEP threshold of >25.3 and predicts a deleterious effect on PIK3CD function. The two predictors agree on a damaging effect (PP3).
PM2_Supporting		✔	This variant is present in gnomAD v4.1.0 at a total combined allele frequency of 0.0000006197, with 1 allele / 1,613,806 total alleles across all populations of gnomAD, which is lower than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.00000132 (PM2_Supporting).

Not Met criteria codes

PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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