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Variant: NM_005026.5:c.371G>A

Version: 1.0

CA338300460

2733822 (ClinVar)

Gene: PIK3CD (HGNC:5293)
Condition: immunodeficiency 14 (MONDO:0014222)
Inheritance Mode: Autosomal dominant inheritance
UUID: 42475cad-a762-4c93-ac2f-2f516266eb17
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HGVS expressions

NM_005026.5:c.371G>A
NC_000001.11:g.9715849G>A
CM000663.2:g.9715849G>A
NC_000001.10:g.9775907G>A
CM000663.1:g.9775907G>A
NC_000001.9:g.9698494G>A
NG_023434.1:g.69118G>A
ENST00000481137.2:c.371G>A
ENST00000698709.1:c.371G>A
ENST00000698710.1:c.371G>A
ENST00000698711.1:n.724G>A
ENST00000698712.1:c.371G>A
ENST00000698713.1:c.371G>A
ENST00000698714.1:c.371G>A
ENST00000698715.1:c.371G>A
ENST00000698716.1:c.371G>A
ENST00000698717.1:n.9G>A
ENST00000377346.9:c.371G>A
ENST00000361110.6:c.371G>A
ENST00000377346.8:c.371G>A
ENST00000481137.1:n.72G>A
ENST00000536656.5:c.371G>A
ENST00000543390.2:c.371G>A
ENST00000628140.2:c.371G>A
NM_005026.3:c.371G>A
NM_001350234.1:c.371G>A
NM_001350235.1:c.371G>A
NM_005026.4:c.371G>A
NM_001350234.2:c.371G>A

Likely Pathogenic

Met criteria codes 4

PS3_Supporting PP4_Moderate PM2_Supporting PS4_Moderate

Not Met criteria codes 2

Expert Panel

Antibody Deficiencies VCEP

Criteria Specification Information

BP4 PP3

Evidence Links 0

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.371G>A (p.Gly124Asp) is a missense variant encoding the replacement of glycine with aspartic acid at amino acid 124. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). At least one proband harboring this variant had a phenotype that included recurrent sinopulmonary infections including severe pneumonia and bronchiectasis (4 pts), lymphadenopathy and lymphadenitis (4 pts), Epstein-Barr virus infection, plantar warts (3 pts), decreased proportion of naive CD4 T cells, and reduced antibody responses to multiple vaccines, as well as markedly increased phospho-AKT levels in the patient's T cells, with genotyping by whole exome sequencing that did not identify an alternative basis for disease in the PIK3R1 gene, which together are highly specific for immunodeficiency 14 (11 total pts, PMID: 28414062, PP4_Moderate). This variant has been reported in at least 2 other apparently unrelated probands meeting the VCEP standard for phenotypic criteria, in addition to the proband already counted for PP4_Moderate. Both probands exceeded 6 phenotypic points with next-generation sequencing-based genotyping that did not identify an alternative basis for disease in the PIK3R1 gene (PS4_Moderate; PMID: 28428270). The computational predictor REVEL gives a score of 0.244, which is below the ClinGen Antibody Deficiencies VCEP threshold of >0.644 and does not predict a damaging effect on PIK3CD function. The computational predictor CADD gives a PHRED score of 32, which is above the ClinGen Antibody Deficiencies VCEP threshold of >25.3 and predicts a deleterious effect on PIK3CD function. Because the two predictors do not agree on a damaging effect, PP3 is not met. Cultured cells exogenously expressing the variant exhibit higher phospho-AKT (Ser473) signal relative to control cells (PMID: 28428270, PMID: 28414062). Lipid kinase phosphorylation signal associated with the variant was 10-fold to 15-fold higher than wild-type (PMID: 28414062). Hydrogen deuterium exchange mass spectrometry also showed increased exchange at the interfaces between the variant and PIK3R1 (PMID: 28414062, PS3_Supporting). 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: PM2_Supporting, PP4_Moderate, PS4_Moderate, and PS3_Supporting. (VCEP specifications version 1.0.0).

Met criteria codes

PS3_Supporting	✔	Cultured cells exogenously expressing the variant exhibit higher phospho-AKT (Ser473) signal relative to control cells (PMID: 28428270, PMID: 28414062). Lipid kinase phosphorylation signal associated with the variant was 10-fold to 15-fold higher than wild-type (PMID: 28414062). Hydrogen deuterium exchange mass spectrometry also showed increased exchange at the interfaces between the variant and PIK3R1 (PMID: 28414062, PS3_Supporting).
PP4_Moderate	✔	At least one proband harboring this variant had a phenotype that included recurrent sinopulmonary infections including severe pneumonia and bronchiectasis (4 pts), lymphadenopathy and lymphadenitis (4 pts), Epstein-Barr virus infection, plantar warts (3 pts), decreased proportion of naive CD4 T cells, and reduced antibody responses to multiple vaccines, as well as markedly increased phospho-AKT levels in the patient's T cells, with genotyping by whole exome sequencing that did not identify an alternative basis for disease in the PIK3R1 gene, which together are highly specific for immunodeficiency 14 (11 total pts, PMID: 28414062, PP4_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4_Moderate	✔	This variant has been reported in at least 3 apparently unrelated probands meeting the VCEP standard for phenotypic criteria. In all three cases, the probands exceeded 6 phenotypic points with genotyping that excluded causes in other loci. One proband had already been counted for the PP4_Moderate code (PS4_Moderate; PMID:

28414062, PMID: 28428270). The two other patients had CD4+ lymphopenia (1 pt), infantile onset, and adenoidectomy (1 pt) combined in one case with recurrent otitis media and sinusitis (4 pts), high IgM serum levels (0.5 pts, low serum IgG2 and IgG4 (0.5 pts), and decreased memory B cells (1 pt), and in the other case with splenomegaly and lymphadenopathy (4 pts), growth retardation (0.5 pts), elevated transitional B cells (2 pts), and reduced IgA. Both patients were genotyped by next-generation sequencing panel for primary immunodeficiencies (PMID: 28428270).

Not Met criteria codes

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	The computational predictor REVEL gives a score of 0.244, which is below the ClinGen Antibody Deficiencies VCEP threshold of >0.644 and does not predict a damaging effect on PIK3CD function. The computational predictor CADD gives a PHRED score of 32, which is above the ClinGen Antibody Deficiencies VCEP threshold of >25.3 and predicts a deleterious effect on PIK3CD function. Because the two predictors do not agree on a damaging effect, PP3 is not met.

Curation History

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