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Variant: NM_005026.5:c.1574A>C

Version: 1.0

CA338303812

Gene: PIK3CD (HGNC:5293)
Condition: immunodeficiency 14 (MONDO:0014222)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4edf9254-5447-4c2c-981a-dee08ebea662
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HGVS expressions

NM_005026.5:c.1574A>C
NC_000001.11:g.9720794A>C
CM000663.2:g.9720794A>C
NC_000001.10:g.9780852A>C
CM000663.1:g.9780852A>C
NC_000001.9:g.9703439A>C
NG_023434.1:g.74063A>C
ENST00000481137.2:c.*828A>C
ENST00000698709.1:c.1574A>C
ENST00000698710.1:c.1571A>C
ENST00000698712.1:c.1574A>C
ENST00000698713.1:c.1574A>C
ENST00000698714.1:c.1574A>C
ENST00000698715.1:c.1571A>C
ENST00000698716.1:c.1562A>C
ENST00000698718.1:n.644A>C
ENST00000698788.1:n.403A>C
ENST00000698789.1:c.250A>C
ENST00000377346.9:c.1574A>C
ENST00000361110.6:c.1646A>C
ENST00000377346.8:c.1574A>C
ENST00000536656.5:c.1646A>C
ENST00000543390.2:c.1646A>C
ENST00000628140.2:c.1646A>C
NM_005026.3:c.1574A>C
NM_001350234.1:c.1571A>C
NM_001350235.1:c.1487A>C
NM_005026.4:c.1574A>C
NM_001350234.2:c.1571A>C

Likely Pathogenic

Met criteria codes 4

PP1_Moderate PP4_Moderate PM2_Supporting PM5

Not Met criteria codes 3

Expert Panel

Antibody Deficiencies VCEP

Criteria Specification Information

PS3 PS4 PP3

Evidence Links 1

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.1574A>C (p.Glu525Ala) is a missense variant causing substitution of glutamate with alanine at amino acid 525. Another missense variant at the same position, NM_005026.5(PIK3CD):c.1573G>A (p.Glu525Lys), has a Grantham's Distance score (56) lower than the current variant of interest (107) and has been previously classified as pathogenic for immunodeficiency 14 by the ClinGen Antibody Deficiencies VCEP (PM5). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 1 proband diagnosed with primary immunodeficiency and genotyped by whole exome sequencing excluding causes in other loci, with phenotypes including recurrent lower respiratory tract infections (4 pts), hepatosplenomegaly (4 pts), recurrent herpes infection (3 pts), thrombocytopenia (1 pt), decreased proportion of class-switched memory B cells (1 pt), and increased circulating IgM (0.5 pts), which together are highly specific for APDS (13.5 pts, PMID: 27426521). Additionally, activated T cells from the patient harboring the variant exhibited a 1.4X to 7.9X increase in phosphorylation of AKT at serine 473 and a 1.5X to 4.9X increase in S6 phosphorylation, as demonstrated by western blotting (PMID: 27426521, PP4_Moderate). The variant has been reported to segregate with an APDS phenotype through at least 2 affected meioses from 1 family (PP1_Moderate; PMID: 27426521). The computational predictor REVEL gives a score of 0.393, 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 28.0, 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, the PP3 code is not met. In summary, this variant meets the criteria to be classified as likely pathogenic for immunodeficiency 14 based on the ACMG/AMP criteria applied, as specified by the ClinGen Antibody Deficiencies VCEP: PM2_Supporting, PM5, PP1_Moderate, and PP4_Moderate. (VCEP specifications version 1.0.0).

Met criteria codes

PP1_Moderate	✔	The variant has been reported to segregate with an APDS phenotype through at least 2 affected meioses from 1 family (PP1_Moderate; PMID: 27426521).
PP4_Moderate	✔	This variant has been reported in at least 1 proband diagnosed with primary immunodeficiency and genotyped by whole exome sequencing excluding causes in other loci, with phenotypes including recurrent lower respiratory tract infections (4 pts), hepatosplenomegaly (4 pts), recurrent herpes infection (3 pts), thrombocytopenia (1 pt), decreased proportion of class-switched memory B cells (1 pt), and increased circulating IgM (0.5 pts), which together are highly specific for APDS (13.5 pts, PMID: 27426521). Additionally, activated T cells from the patient harboring the variant exhibited a 1.4X to 7.9X increase in phosphorylation of AKT at serine 473 and a 1.5X to 4.9X increase in S6 phosphorylation, as demonstrated by western blotting (PMID: 27426521, PP4_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM5	✔	Another missense variant at the same position, NM_005026.5(PIK3CD):c.1573G>A (p.Glu525Lys), has a Grantham's Distance score (56) lower than the current variant of interest (107) and has been previously classified as pathogenic for immunodeficiency 14 by the ClinGen Antibody Deficiencies VCEP (PM5).

Not Met criteria codes

PS3	✖	Activated T cells from a patient harboring the variant exhibit a 1.4X to 7.9X increase in phosphorylation of AKT at serine 473 and a 1.5X to 4.9X increase in S6 phosphorylation, as demonstrated by western blotting (PMID: 27426521). This evidence was considered part of the patient phenotype and used in the PP4_Moderate code. Activated T cells from a patient harboring the variant exhibit a 1.4X to 7.9X increase in phosphorylation of AKT at serine 473 and a 1.5X to 4.9X increase in S6 phosphorylation, as demonstrated by western blotting and flow cytometry (PMID: 27426521, Figure 4). PubMed:27426521
PS4	✖	The proband has accumulated 11 total phenotype points, but has already been used for the PP4 code (PMID: 27426521)
PP3	✖	The computational predictor REVEL gives a score of 0.393, 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 28.0, 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, the PP3 code is not met.

Curation History

Showing 1 to 1 of 1 rows

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