Variant: NM_005026.5(PIK3CD):c.1642C>T (p.Arg548Trp)

Version: 1.0

CA577276

806050 (ClinVar)

Gene: PIK3CD (HGNC:5293)
Condition: immunodeficiency 14 (MONDO:0014222)
Inheritance Mode: Autosomal dominant inheritance
UUID: c6dcc9ff-882d-4aaa-972c-0d114fdabf56
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HGVS expressions

NM_005026.5:c.1642C>T
NM_005026.5(PIK3CD):c.1642C>T (p.Arg548Trp)
NC_000001.11:g.9720862C>T
CM000663.2:g.9720862C>T
NC_000001.10:g.9780920C>T
CM000663.1:g.9780920C>T
NC_000001.9:g.9703507C>T
NG_023434.1:g.74131C>T
ENST00000481137.2:c.*896C>T
ENST00000698709.1:c.1642C>T
ENST00000698710.1:c.1639C>T
ENST00000698712.1:c.1642C>T
ENST00000698713.1:c.1642C>T
ENST00000698714.1:c.1642C>T
ENST00000698715.1:c.1639C>T
ENST00000698716.1:c.1630C>T
ENST00000698718.1:n.712C>T
ENST00000698788.1:n.471C>T
ENST00000698789.1:c.318C>T
ENST00000377346.9:c.1642C>T
ENST00000361110.6:c.1714C>T
ENST00000377346.8:c.1642C>T
ENST00000536656.5:c.1714C>T
ENST00000543390.2:c.1714C>T
ENST00000628140.2:c.1714C>T
NM_005026.3:c.1642C>T
NM_001350234.1:c.1639C>T
NM_001350235.1:c.1555C>T
NM_005026.4:c.1642C>T
NM_001350234.2:c.1639C>T

Uncertain Significance

Not Met criteria codes 7

BP4 PS4 PP3 PP4 PM5 PM2 BS1

Evidence Links 0

Expert Panel

Antibody Deficiencies VCEP

Criteria Specification Information

- **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.1642C>T (p.Arg548Trp) is a missense variant causing substitution of arginine by tryptophan at amino acid 548. Another missense variant in the same codon, NM_005026.5(PIK3CD):c.1643G>A (p.Arg548Gln), has been reported in association with immunodeficiency 14 (SCV002301644.3) but has been classified as a VUS by the ClinGen Antibody Deficiencies VCEP, so PM5 is not met. This variant is present in gnomAD v4.1.0 at a total combined allele frequency of 0.00003730, with 60 alleles / 1,608,744 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.00000132. The variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.0001338, with 3 alleles / 6,074 total alleles in the Middle Eastern population, which is lower than the BS1 threshold of >0.000316, so no population code can be applied. This variant has been reported in 1 affected proband with a phenotype including recurrent fever, neurodevelopmental abnormalities (0.5 pts), and diarrhea (1 pt), which are not sufficient to meet the phenotype requirements for inclusion of the proband in PS4_Supporting (1.5 total points, ClinVar Accession #: SCV002524004.1). The computational predictor REVEL gives a score of 0.349, 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 29.0, 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 a variant of uncertain significance for autosomal dominant immunodeficiency 14 based on the ACMG/AMP criteria applied, as specified by the ClinGen Antibody Deficiencies VCEP: None. (VCEP specifications version 1.0.0).

Not Met criteria codes

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant has been reported in 1 affected proband with a phenotype including recurrent fever, neurodevelopmental abnormalities (0.5 pts), and diarrhea (1 pt), which are not sufficient to meet the phenotype requirements for inclusion of the proband in PS4_Supporting (1.5 total points, ClinVar Accession #: SCV002524004.1).
PP3	✖	The computational predictor REVEL gives a score of 0.349, 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 29.0, 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.
PP4	✖	Clinical Features: Recurrent fever (present) = 2 points (recurrent infection?) Neurodevelopmental abnormality (present) = 2 points (developmental delay?) Diarrhea (present) = 1 point (failure to thrive?) 5 PS4 points?

PM5		✖	The NM_005026.5(PIK3CD):c.1643G>A (p.Arg548Gln) is classified as VUS by the Antibody VCEP rules.
PM2		✖	This variant is present in gnomAD v4.1.0 at a total combined allele frequency of 0.00003730, with 60 alleles / 1,608,744 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.00000132.
BS1		✖	This variant is present in gnomAD v.4.1.0 at a GrpMax allele frequency of 0.0001338, with 3 alleles / 6,074 total alleles in the Middle Eastern population, which is lower than the BS1 threshold of >0.000316, so no population code can be applied.

Curation History

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