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_005026.5(PIK3CD):c.1573G>A (p.Glu525Lys)

Version: 1.0

CA156207

132807 (ClinVar)

Gene: PIK3CD (HGNC:5293)
Condition: immunodeficiency 14 (MONDO:0014222)
Inheritance Mode: Autosomal dominant inheritance
UUID: a4139850-e671-403b-b169-b8312b110191
Approved on: 2025/12/19
Published on: 2025/12/23

HGVS expressions

NM_005026.5(PIK3CD):c.1573G>A (p.Glu525Lys)
NM_005026.5:c.1573G>A
NC_000001.11:g.9720793G>A
CM000663.2:g.9720793G>A
NC_000001.10:g.9780851G>A
CM000663.1:g.9780851G>A
NC_000001.9:g.9703438G>A
NG_023434.1:g.74062G>A
ENST00000481137.2:c.*827G>A
ENST00000698709.1:c.1573G>A
ENST00000698710.1:c.1570G>A
ENST00000698712.1:c.1573G>A
ENST00000698713.1:c.1573G>A
ENST00000698714.1:c.1573G>A
ENST00000698715.1:c.1570G>A
ENST00000698716.1:c.1561G>A
ENST00000698718.1:n.643G>A
ENST00000698788.1:n.402G>A
ENST00000698789.1:c.249G>A
ENST00000377346.9:c.1573G>A
ENST00000361110.6:c.1645G>A
ENST00000377346.8:c.1573G>A
ENST00000536656.5:c.1645G>A
ENST00000543390.2:c.1645G>A
ENST00000628140.2:c.1645G>A
NM_005026.3:c.1573G>A
NM_001350234.1:c.1570G>A
NM_001350235.1:c.1486G>A
NM_005026.4:c.1573G>A
NM_001350234.2:c.1570G>A

Pathogenic

Met criteria codes 4

PP1_Strong | PS4 | PM2_Supporting | PS3_Supporting

Not Met criteria codes 5

PM1 | PM5 | PS2 | PP3 | PP4

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.1573G>A (p.Glu525Lys) is a missense variant causing substitution of glutamate with lysine at amino acid 525. At least two other missense variants affecting the same amino acid residue, NM_005026.5(PIK3CD):c.1574A>G (p.Glu525Gly) and NM_005026.5(PIK3CD):c.1574A>G (p.Glu525Ala), are described in the PIK3CD literature (PMID: 34692603). However, PM5 has not been evaluated in order to avoid circularity. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 5 unrelated probands meeting the VCEP standard for phenotypic criteria. In 3 cases, the proband reached 6 phenotypic points with genotyping that excluded causes in other loci (PMID: 24165795). In 2 other cases, the proband exceeded 10 phenotype points but lacked genotyping that excluded causes in other loci (PMID: 28190860, PMID: 28104464; PS4). A 6th family was reported in multiple publications but did not reach sufficient phenotype points for inclusion (PMID: 27577878, PMID: 28327206, PMID: 29330011). At least one patient harboring this variant had a phenotype including recurrent sinopulmonary infections (4 pts), chronic active Epstein-Barr virus infection (3 pts), lymphocytic infiltration of various mucosa, and high B memory cells, as well as use of whole exome sequencing-based genotyping to rule out alternative genetic causes in other loci, which together was not sufficient to establish specificity for immunodeficiency 14, so PP4 was not met. Additionally, AKT phosphorylation at Thr308 in patient CD4+ or CD8+ T cell blasts was increased relative to control cells from healthy control patients (PMID: 24165795). This variant has been identified as a potential de novo occurrence with untested parental relationships in 1 individual, which was insufficient to apply the PS2_Moderate code (PMID: 27577878). The most recent genotyping analysis of this individual yielded a result more consistent with full heterozygosity (PMID: 29330011). The variant has been reported to segregate with the immunodeficiency phenotype within the proband and 2 additional affected family members in at least two apparently unrelated families (PMID: 24165795, PMID: 29330011, PP1_Strong). AKT kinase activity assays (both in vitro), lipid kinase activity assay, PIK3R1 protein binding assay, and hydrogen-deuterium exchange mass spectrometry-based conformational dynamics assays collectively support a damaging effect of the variant on the gene product (PS3_Supporting, PMID: 24165795, PMID: 28167755). The computational predictor REVEL gives a score of 0.400, 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 29.6, 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 pathogenic for immunodeficiency 14 based on the ACMG/AMP criteria applied, as specified by the ClinGen Antibody Deficiencies VCEP: PS4, PS3_Supporting, PM2_Supporting, and PP1_Strong. (VCEP specifications version 1.0.0).

Met criteria codes

PP1_Strong	✔	The variant has been reported to segregate with the immunodeficiency phenotype within the proband and 2 additional affected family members in at least two apparently unrelated families (PMID: 24165795, PMID: 29330011, PP1_Strong). 3 related individuals have been reported in another publication (PMID: 27555459), and may or may not represent a third independent family.
PS4	✔	This variant has been reported in at least 5 unrelated probands meeting the VCEP standard for phenotypic criteria. In 3 cases, the proband reached 6 phenotypic points with genotyping that excluded causes in other loci (PMID:

24165795). In 2 other cases, the proband exceeded 10 phenotype points but lacked genotyping that excluded causes in other loci (PMID: 28190860, PMID: 28104464; PS4). A 6th family was reported in multiple publications but did not reach sufficient phenotype points for inclusion (PMID: 27577878, PMID: 28327206, PMID: 29330011).

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS3_Supporting	✔	AKT kinase activity assays (in vitro), lipid kinase activity assay, and hydrogen-deuterium exchange mass spectrometry-based conformational dynamics assays collectively support a gain of function effect caused by the variant (PS3_Supporting, PMID: 24165795, PMID: 28167755).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	At least two other missense variants affecting the same amino acid residue, NM_005026.5(PIK3CD):c.1574A>C (p.Glu525Ala) and NM_005026.5(PIK3CD):c.1574A>G (p.Glu525Ala) are described in the PIK3CD literature (PMID34692603). However, PM5 has not been evaluated in order to avoid circularity.
PS2	✖	This variant has been identified as a potential de novo occurrence with untested parental relationships in 1 individual, which was insufficient to apply the PS2_Moderate code (PMID: 27577878). The most recent genotyping analysis of this individual yielded a result more consistent with full heterozygosity (PMID: 29330011).
PP3	✖	The computational predictor REVEL gives a score of 0.400, 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 29.6, 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	✖	At least one patient harboring this variant had a phenotype including recurrent sinopulmonary infections (4 pts), chronic active Epstein-Barr virus infection (2 pts), lymphocytic infiltration of various mucosa, and high B memory cells, as well as use of whole exome sequencing-based genotyping to rule out alternative genetic causes in other loci, which together was not sufficient to establish specificity for immunodeficiency 14, so PP4 was not met. Additionally, AKT phosphorylation at Thr308 in patient CD4+ or CD8+ T cell blasts was increased relative to control cells from healthy control patients (PMID: 24165795).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.