Variant: NM_005026.5(PIK3CD):c.3061G>A (p.Glu1021Lys)

Version: 1.0

CA145460

88675 (ClinVar)

Gene: PIK3CD (HGNC:5293)
Condition: immunodeficiency 14 (MONDO:0014222)
Inheritance Mode: Autosomal dominant inheritance
UUID: a8a25652-37fa-4433-ac24-ae3bd5ba8e93
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HGVS expressions

NM_005026.5:c.3061G>A
NM_005026.5(PIK3CD):c.3061G>A (p.Glu1021Lys)
NC_000001.11:g.9726972G>A
CM000663.2:g.9726972G>A
NC_000001.10:g.9787030G>A
CM000663.1:g.9787030G>A
NC_000001.9:g.9709617G>A
NG_023434.1:g.80241G>A
ENST00000481137.2:c.*2315G>A
ENST00000698709.1:c.2965G>A
ENST00000698710.1:c.3058G>A
ENST00000698712.1:c.3061G>A
ENST00000698713.1:c.3061G>A
ENST00000698714.1:c.2917G>A
ENST00000698715.1:c.3058G>A
ENST00000698716.1:c.3049G>A
ENST00000698719.1:n.2222G>A
ENST00000377346.9:c.3061G>A
ENST00000361110.6:c.3133G>A
ENST00000377346.8:c.3061G>A
ENST00000536656.5:c.3133G>A
ENST00000543390.2:c.3133G>A
ENST00000628140.2:c.3133G>A
NM_005026.3:c.3061G>A
NM_001350234.1:c.3058G>A
NM_001350235.1:c.2974G>A
NM_005026.4:c.3061G>A
NM_001350234.2:c.3058G>A

Pathogenic

Met criteria codes 6

PS2 PS3 PS4 PP4 PM2_Supporting PP1_Strong

Not Met criteria codes 1

PP3

Expert Panel

Antibody Deficiencies VCEP

Criteria Specification Information

Evidence Links 4

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.3061G>A (p.Glu1021Lys) is a missense variant causing substitution of glutamic acid with lysine at amino acid 1021. This variant is present in gnomAD v4.1.0 at a total combined allele frequency of 0.0000006196, with 1 allele / 1,613,974 total alleles across all populations of gnomAD, which is lower than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.00000132 (PM2_Supporting). This variant has been reported in at least 7 apparently unrelated probands from a single study (PMID: 24136356) who have met the VCEP standard for phenotypic criteria (PS4; PMID: 24136356). Additional probands have been reported in other papers as well (PMID: 24165795). The variant co-segregated with the immunodeficiency 14 phenotype through at least 4 affected segregations total from 2 apparently unrelated families (PP1_Strong; 24136356). This variant has been identified an affected individual with a phenotype that includes increased circulating IgM level (1 pt), recurrent respiratory infections (4 pts), recurrent herpes (2 pts), reduced antibodies to Haemophilus Influenzae type B (1 pt), and lymphocytopenia (4 pts), high circulating transitional B cells (2 pts), and low circulating class switched memory B cells (1 pt), with genotyping by whole exome sequencing that excludes alternative causes in other loci (15 pts; PMID: 24136356). These features are highly specific for immunodeficiency 14. Additionally, patient lymphocytes showed over-activation of the PI3K pathway through increased levels of pAKT (PMID:24136356, PP4). This variant has already met PP1_Strong, so PP4_Moderate was downgraded to PP4. This variant has been identified as a de novo occurrence in 1 individual with immunodeficiency 14, with parental relationships confirmed through the use of genome-wide identity-by-descent analysis and a phenotype that was highly specific for immunodeficiency 14 (PS2; PMID: 24136356). Knock-in mice harboring this variant generated by either CRISPR/Cas9 (PMID: 32099075, PMID: 30018075, PMID: 30738173) or Lox-CRE recombination (PMID: 30194267) exhibited 1.25X to 2.5X-fold increases in phosphorylation of AKT (Ser473) and S6 (PMID: 32099075), increased serum IgM (PMID: 30194267), reduced B cells (PMID: 30194267), and increased T cells (PMID: 30738173), as well as defects in IgG secretion and isotype switching that are correctable with leniolisib (PMID: 30018075). Additional functional evidence linked the variant to enhanced association with the membrane and higher kinase activity (PMID: 24136356). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant immunodeficiency 14 based on the ACMG/AMP criteria applied, as specified by the ClinGen Antibody Deficiencies VCEP: PM2_Supporting, PS4, PP1_Strong, PP4, PS2, and PS3. (VCEP specifications version 1.0.0).

Met criteria codes

PS2	✔	This variant has been identified as a de novo occurrence in 1 individual with immunodeficiency 14, with parental relationships confirmed through the use of genome-wide identity-by-descent analysis, and with the phenotype considered highly specific for immunodeficiency 14 (2 pts, PMID: 24136356, PS2).
PS3	✔	Knock-in mice harboring this variant generated by either CRISPR/Cas9 (PMID: 32099075, PMID: 30018075, PMID: 30738173) or Lox-CRE recombination (PMID: 30194267) exhibit 1.25X to 2.5X-fold increases in phosphorylation of AKT (Ser473) and S6 (PMID: 32099075), increased serum IgM (PMID: 30194267), reduced B cells (PMID: 30194267), and increased T cells (PMID: 30738173), as well as defects in IgG secretion and isotype switching that are correctable with leniolisib (PMID: 30018075). Additional functional evidence linked the variant to enhanced association with the membrane and higher kinase activity (PMID: 24136356). Knock-in mice harboring this variant generated by CRISPR/Cas9 editing exhibit 1.25X to 2.5X-fold increases in phosphorylation of AKT (Ser473) and S6 (PMID: 32099075). PubMed:32099075

Knock-in mice harboring this variant generated by CRISPR/Cas9 exhibit increased T cells (PMID: 30738173). PubMed:30738173

Knock-in mice harboring this variant generated by CRISPR/Cas9 exhibit defects in IgG secretion and isotype switching that are correctable with leniolisib (PMID: 30018075). PubMed:30018075

Knock-in mice harboring this variant generated by Lox-CRE recombination exhibit increased serum IgM and reduced B cells (PMID: 30194267). PubMed:30194267

PS4	✔	This variant has been reported in at least 7 apparently unrelated probands from a single study (PMID: 24136356) who have met the VCEP standard for phenotypic criteria. In all 7 cases, the proband exceeded 6 phenotypic points with genotyping that excluded causes in other loci (PS4; PMID: 24136356). Additional probands have been reported in other papers as well (PMID: 24165795).
PP4	✔	This variant has been identified an affected individual with a phenotype that includes increased circulating IgM level (0.5 pts), recurrent respiratory infections (4 pts), recurrent herpes (3 pts), reduced antibodies to Haemophilus Influenzae type B, lymphocytopenia (1 pt), high circulating transitional B cells (2 pts), and low circulating class switched memory B cells (1 pt), with genotyping by whole exome sequencing that excludes alternative causes in other loci, which together are highly specific for immunodeficiency 14 (11.5 pts; PMID: 24136356). Additionally, patient lymphocytes showed over-activation of the PI3K pathway through increased levels of pAKT (PMID:24136356, PP4). This variant has already met PP1_Strong, so PP4_Moderate was downgraded to PP4.
PM2_Supporting	✔	This variant is present in gnomAD v4.1.0 at a total combined allele frequency of 0.0000006196, with 1 allele / 1,613,974 total alleles across all populations of gnomAD, which is lower than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.00000132 (PM2_Supporting).
PP1_Strong	✔	The variant has been reported to segregate with immunodeficiency 14 through at least 4 affected segregations total from 2 apparently unrelated families (PMID: 24136356, PP1_Strong).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.627, 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 31, 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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