Variant: NM_005026.5(PIK3CD):c.2002C>A (p.Leu668Met)

Version: 1.0

CA338304786

2534434 (ClinVar)

Gene: PIK3CD (HGNC:5293)
Condition: immunodeficiency 14 (MONDO:0014222)
Inheritance Mode: Autosomal dominant inheritance
UUID: 34e3113f-ad65-4155-abd8-4675d7d78cb0
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HGVS expressions

NM_005026.5:c.2002C>A
NM_005026.5(PIK3CD):c.2002C>A (p.Leu668Met)
NC_000001.11:g.9721807C>A
CM000663.2:g.9721807C>A
NC_000001.10:g.9781865C>A
CM000663.1:g.9781865C>A
NC_000001.9:g.9704452C>A
NG_023434.1:g.75076C>A
ENST00000481137.2:c.*1256C>A
ENST00000698709.1:c.1906C>A
ENST00000698710.1:c.1999C>A
ENST00000698712.1:c.2002C>A
ENST00000698713.1:c.2002C>A
ENST00000698714.1:c.1858C>A
ENST00000698715.1:c.1999C>A
ENST00000698716.1:c.1990C>A
ENST00000698718.1:n.1245C>A
ENST00000698719.1:n.304C>A
ENST00000377346.9:c.2002C>A
ENST00000361110.6:c.2074C>A
ENST00000377346.8:c.2002C>A
ENST00000536656.5:c.2074C>A
ENST00000543390.2:c.2074C>A
ENST00000628140.2:c.2074C>A
NM_005026.3:c.2002C>A
NM_001350234.1:c.1999C>A
NM_001350235.1:c.1915C>A
NM_005026.4:c.2002C>A
NM_001350234.2:c.1999C>A

Uncertain Significance

Met criteria codes 2

BP4 PM2_Supporting

Not Met criteria codes 2

BS3 PS4

Expert Panel

Antibody Deficiencies VCEP

Criteria Specification Information

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.2002C>A (p.Leu668Met) is a missense variant that causes substitution of leucine by methionine at amino acid 668. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The variant has been observed in at least one individual subjected to genetic testing, however it is not clear whether the individual was affected with a relevant clinical condition (ClinVar accession number SCV003968830.2). The computational predictor REVEL gives a score of 0.231, which is below the ClinGen Antibody Deficiencies VCEP threshold of <0.290 and predicts a non-damaging effect on PIK3CD function. The computational predictor CADD gives a PHRED score of 16.99, which is below the ClinGen Antibody Deficiencies VCEP threshold of <22.7 and predicts a non-deleterious effect on PIK3CD function. The two predictors agree on a non-damaging effect (BP4). 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: PM2_Supporting and BP4. (VCEP specifications version 1.0.0).

Met criteria codes

BP4	✔	The computational predictor REVEL gives a score of 0.231, which is below the ClinGen Antibody Deficiencies VCEP threshold of <0.290 and predicts a non-damaging effect on PIK3CD function. The computational predictor CADD gives a PHRED score of 16.99, which is below the ClinGen Antibody Deficiencies VCEP threshold of <22.7 and predicts a non-deleterious effect on PIK3CD function. The two predictors agree on a non-damaging effect (BP4).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

BS3	✖	A base editing screen in primary T cells introducing another variant at the same codon, p.Leu668Pro, showed a log2 enrichment score of 0.82059 in the high-phospho-AKT / high-phospho-S6 fraction of cells relative to the low-phospho-AKT / low-phospho-S6 fraction of cells, with a two-sided p-value of 0.12839, indicating no significant disruption of the PI3K pathway (PMID: 40543502). Because this is a different amino acid change, BS3_Supporting was not evaluated. A base editing screen in primary T cells introducing another variant at the same codon, p.Leu668Pro, showed a log2 enrichment score of 0.82059 in the high-phospho-AKT / high-phospho-S6 fraction of cells relative to the low-phospho-AKT / low-phospho-S6 fraction of cells, with a two-sided p-value of 0.12839, indicating no significant disruption of the PI3K pathway (PMID: 40543502). Because this is a different amino acid change, BS3_Supporting was not evaluated. PubMed:40543502
PS4	✖	The variant has been observed in at least one individual subjected to genetic testing, however it is not clear whether the individual was affected with a relevant clinical condition (SCV003968830.2).

Curation History

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