

Variant: *NM_005214.5:c.563A>G*

Version: 1.3

CA2067131 [↗](#)

4683122 (ClinVar) [↗](#)

Gene: CTLA4 ([HGNC:1493](#))

Condition: autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency ([MONDO:0014493](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: a0b3a8d5-92e4-4678-a5f0-1e6bc6e1162f

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HGVS expressions

NM_005214.5:c.563A>G

NC_000002.12:g.203871483A>G

CM000664.2:g.203871483A>G

NC_000002.11:g.204736206A>G

CM000664.1:g.204736206A>G

NC_000002.10:g.204444451A>G

NG_011502.1:g.8698A>G

ENST00000696049.1:c.507+56A>G

ENST00000696479.1:c.635A>G

ENST00000427473.3:n.491+550A>G

ENST00000648405.2:c.563A>G

ENST00000650075.1:n.587A>G

ENST00000295854.10:c.457+550A>G

ENST00000302823.7:c.563A>G

ENST00000427473.2:c.346+550A>G

ENST00000472206.1:c.172+835A>G

ENST00000487393.1:n.110-1225A>G

NM_001037631.2:c.457+550A>G

NM_005214.4:c.563A>G

NM_001037631.3:c.457+550A>G

Benign

Met criteria codes **1**

BA1

Not Met criteria codes **2**

BP4

PP3

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 CTLA4 Version 1.0.0*

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Antibody Deficiencies VCEP

NM_005214.5(CTLA4):c.563A>G (p.Lys188Arg) is a missense variant encoding substitution of lysine by arginine at residue 188. This variant is present in gnomAD v4.1.1 at a GrpMax allele frequency of 0.0001370, with 11 alleles / 44,874 total alleles in the East Asian population, which is higher than the ClinGen Antibody Deficiencies VCEP BA1 threshold of >0.0000111 (BA1). The computational predictor REVEL gives a score of 0.035, which is below the ClinGen Antibody Deficiencies VCEP threshold of <0.290, while the computational predictor CADD gives a PHRED score of 20.3, which is below the ClinGen Antibody Deficiencies VCEP threshold of <22.7, with both predictors agreeing on a non-deleterious effect on CTLA4 function. The splicing impact predictor SpliceAI gives a delta score of 0.10 for donor loss and donor gain, which is above the ClinGen Antibody Deficiencies VCEP recommended BP4 threshold of <0.1 yet does not strongly predict an impact on CTLA4 splicing. In summary, this variant meets the criteria to be classified as Benign for autosomal dominant autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Antibody Deficiencies VCEP: BA1. (VCEP specifications version 2.0.0).

Met criteria codes

BA1



This variant is present in gnomAD v4.1.0 at a GrpMax allele frequency of 0.0001370, with 11 alleles / 44,874 total alleles] in the East Asian population, which is higher than the ClinGen Antibody Deficiencies VCEP BA1 threshold of >0.0000111 (BA1).

Not Met criteria codes

BP4



The computational predictor REVEL gives a score of 0.035, which is below the ClinGen Antibody Deficiencies VCEP threshold of <0.290, while the computational predictor CADD gives a PHRED score of 20.3, which is below the ClinGen Antibody Deficiencies VCEP threshold of <22.7, with both predictors agreeing on a non-deleterious effect on CTLA4 function. The splicing impact predictor SpliceAI gives a delta score of 0.10 for donor loss and donor gain, which is above the ClinGen Antibody Deficiencies VCEP recommended threshold of <0.1 and does not strongly predict an impact on CTLA4 splicing.

PP3



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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