

Variant: *NM_005214.5(CTLA4):c.223C>T (p.Arg75Trp)*

Version: 1.1

CA350138320 [↗](#)

945024 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: f221734e-c21b-4a55-adf2-8607eb04563f

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HGVS expressions

NM_005214.5:c.223C>T

NM_005214.5(CTLA4):c.223C>T (p.Arg75Trp)

NC_000002.12:g.203870699C>T

CM000664.2:g.203870699C>T

NC_000002.11:g.204735422C>T

CM000664.1:g.204735422C>T

NC_000002.10:g.204443667C>T

NG_011502.1:g.7914C>T

ENST00000696049.1:c.223C>T

ENST00000696479.1:c.295C>T

ENST00000427473.3:n.257C>T

ENST00000648405.2:c.223C>T

ENST00000650075.1:n.247C>T

ENST00000295854.10:c.223C>T

ENST00000302823.7:c.223C>T

ENST00000427473.2:c.112C>T

ENST00000472206.1:c.172+51C>T

ENST00000487393.1:n.110-2009C>T

NM_001037631.2:c.223C>T

NM_005214.4:c.223C>T

NM_001037631.3:c.223C>T

Pathogenic

Met criteria codes 4

PP4_Moderate

PS4_Moderate

PP1_Strong

PS2

Not Met criteria codes 7

BA1

BS1

BP4

PS3

PP3

PM5

PM2

Evidence Links 1

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**

Antibody Deficiencies VCEP

NM_005214.5(CTLA4):c.223C>T (p.Arg75Trp) is a missense variant encoding the substitution of arginine with tryptophan at amino acid 75. Another missense variant in the same codon, NM_005214.5(CTLA4):c.224G>A (p.Arg75Gln), has been reported in a patient with autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (PMID: 25329329), however, PM5 has not been considered in order to avoid circularity. This variant is present in gnomAD v4.1.1 at a total allele frequency of 0.000001239, with 2 alleles / 1,614,188 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.000000143. The variant is present in gnomAD v4.1.0 at an allele frequency of 0.00001666, with 1 allele / 60,028 total alleles in the Admixed American population, which is higher than the ClinGen Antibody Deficiencies VCEP BS1 threshold of >0.00000111. However, 1 allele is lower than the BS1 requirement for at least 3 alleles total across all populations in gnomAD, so no population code is met. At least 1 patient with this variant has a phenotype that includes diarrhea/enteropathy (4 pts), decreased circulating antibody level (2 pts), upper and lower respiratory tract infections (4 pts), granulomatous lymphocytic interstitial lung disease (1 pt), splenomegaly and and lymphadenopathy (2 pts), autoimmune thrombocytopenia and hemolytic anemia (2 pts), and CD4+ T cells showing reduced CD80-GFP transendocytosis from co-cultured CHO cells relative to the healthy control patient cells, with genotyping by exome sequencing identifying no alternative basis for disease in other loci, which together are highly specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (15 total pts, PMID: 25329329, PMID: 29729943, PP4_Moderate). This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency, with 15 phenotype points and genotyping by whole exome sequencing indicating a phenotype highly specific for the gene (2 de novo points, PMID: 25329329, PS2). This variant has been reported in at least 2 additional apparently unrelated probands meeting the VCEP standard for phenotypic criteria, with at least 10 phenotype points but without genotyping to exclude causes in other loci such as LRBA (PMID: 29729943, PS4_Moderate). The variant has been reported to segregate with CTLA4 insufficiency through at least 5 affected meioses from 1 family, with affected status counted only for family members with at least 6 phenotype points (PP1_Strong; PMID: 29729943). The computational predictor REVEL gives a score of 0.864, which is above the ClinGen Antibody Deficiencies VCEP threshold of >0.644. The computational predictor CADD gives a PHRED score of 24.7, which is below the ClinGen Antibody Deficiencies VCEP threshold of >25.3. The two predictors do not agree on a damaging effect on CTLA4 function, so PP3 is not met. The splicing impact predictor SpliceAI gives a score of 0.07 for donor gain, which is below the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. In summary, this variant meets the criteria to be classified as Pathogenic for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Antibody Deficiencies VCEP: PS4_Moderate, PP4_Moderate, PS2, and PP1_Strong. (VCEP specifications version 2.0.0).

Met criteria codes

PP4_Moderate			At least 1 patient with this variant has a phenotype that includes diarrhea/enteropathy (4 pts), decreased circulating antibody level (2 pts), upper and lower respiratory tract infections (4 pts), granulomatous lymphocytic interstitial lung disease (1 pt), splenomegaly and and lymphadenopathy (2 pts), autoimmune thrombocytopenia and hemolytic anemia (2 pts), and CD4+ T cells showing reduced CD80-GFP transendocytosis from co-cultured CHO cells relative to the healthy control patient cells, with genotyping by exome sequencing identifying no alternative basis for disease in other loci, which together are highly specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (15 total pts, PMID: 25329329, PMID: 29729943, PP4_Moderate).
PS4_Moderate			This variant has been reported in at least 2 unrelated probands meeting the VCEP standard for phenotypic criteria, with at least 10 phenotype points but without genotyping to exclude causes in other loci such as LRBA (PMID: 29729943, PS4_Moderate). Please note that a third proband from the same publication has been documented in other publications and has already been used for the PP4 code (PMID: 25329329, PMID: 28366794, PMID: 29305966).
PP1_Strong			The variant has been reported to segregate with CTLA4 insufficiency through at least 5 affected meioses from 1 family (PP1_Strong; PMID: 29729943). Affected status was counted only for family members with at least 6

phenotype points.

PS2





This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with CTLA4 insufficiency (PMID: 25329329). The 15 phenotype points for this case and genotyping by whole exome sequencing (facilitating exclusion of LRBA variants as an alternative basis for disease) indicate a phenotype highly specific for the gene (2 de novo points, PS2).

Not Met criteria codes

BA1





This variant is present in gnomAD v4.1.0 at an allele frequency of 0.00001666, with 1 allele / 60,028 total alleles in the Admixed American population, which is higher than the ClinGen Antibody Deficiencies VCEP BA1 threshold of >0.0000111, however, the BA1 requirement is not met for at least 5 alleles total across all populations in gnomAD.

BS1





This variant is present in gnomAD v4.1.0 at an allele frequency of 0.00001666, with 1 allele / 60,028 total alleles in the Admixed American population, which is higher than the ClinGen Antibody Deficiencies VCEP BS1 threshold of >0.00000111. However, 1 allele is lower than the BS1 requirement for at least 3 alleles total across all populations in gnomAD, so no population code is met.

BP4





The computational predictor REVEL gives a score of 0.864, which is above the ClinGen Antibody Deficiencies VCEP threshold of <0.25 and does not predict a benign effect on CTLA4 function. The computational predictor CADD gives a PHRED score of 24.7, which is above the ClinGen Antibody Deficiencies VCEP threshold of <20 and does not predict a benign effect on CTLA4 function. This criterion is not met.

PS3





Transendocytosis assay performed with patient CD4+ T cells expressing the p.Arg75Trp variant or non-variant CTLA4 showed reduced CD80-GFP uptake from co-cultured CHO cells, indicating that this variant has a damaging effect on protein function (PMID: 29729943). This evidence has been considered for PP4 rather than for PS3_Supporting.

Transendocytosis assay performed with patient CD4+ T cells expressing the p.Arg75Trp variant or wild-type CTLA4 showed reduced CD80-GFP uptake from co-cultured CHO cells, indicating that this variant has a damaging effect on protein function. This evidence has been considered for PP4 rather than for PS3_Supporting. [PubMed:29729943](#) 

PP3





The computational predictor REVEL gives a score of 0.864, which is above the ClinGen Antibody Deficiencies VCEP threshold of >0.644. The computational predictor CADD gives a PHRED score of 24.7, which is below the ClinGen Antibody Deficiencies VCEP threshold of >25.3. The two predictors do not agree on a damaging effect on CTLA4 function, so PP3 is not met. The splicing impact predictor SpliceAI gives a score of 0.07 for donor gain, which is below the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.

PM5





Another missense variant in the same codon, NM_005214.5(CTLA4):c.224G>A (p.Arg75Gln), has been reported in a patient with autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (PMID: 25329329), however, PM5 has not been considered in order to avoid circularity.

PM2



This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.000001239, with 2 alleles / 1,614,188 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.000000143.

Curation History	
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