

Variant: NM_005214.5:c.407C>T

Version: 1.1

CA350138735 [↗](#)

1711524 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

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HGVS expressions

NM_005214.5:c.407C>T

NC_000002.12:g.203870883C>T

CM000664.2:g.203870883C>T

NC_000002.11:g.204735606C>T

CM000664.1:g.204735606C>T

NC_000002.10:g.204443851C>T

NG_011502.1:g.8098C>T

ENST00000696049.1:c.407C>T

ENST00000696479.1:c.479C>T

ENST00000427473.3:n.441C>T

ENST00000648405.2:c.407C>T

ENST00000650075.1:n.431C>T

ENST00000295854.10:c.407C>T

ENST00000302823.7:c.407C>T

ENST00000427473.2:c.296C>T

ENST00000472206.1:c.172+235C>T

ENST00000487393.1:n.110-1825C>T

NM_001037631.2:c.407C>T

NM_005214.4:c.407C>T

NM_001037631.3:c.407C>T

Likely Pathogenic

Met criteria codes 5

PM2_Supporting

PM1

PM5

PP1_Moderate

PS4_Moderate

Not Met criteria codes 3

PS3

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 CTLA4 Version 1.0.0

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

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

Antibody Deficiencies VCEP

NM_005214.5(CTLA4):c.407C>T is a missense variant encoding a substitution of proline with leucine at amino acid 136. This variant is located within the MYPPPY functional domain (residues 134-139), which is required for interaction with CD80 and CD86 (PM1, PMID: 31396201). Another missense variants in the same codon, NM_005214.5(CTLA4):c.406C>G (p.Pro136Ala), has a lower Grantham score (27) than the variant under investigation (98) and has been classified as likely pathogenic for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency by the ClinGen Antibody Deficiencies VCEP (PM5, PMID: 27379089, PMID: 29729943). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The computational predictors REVEL (0.453) and CADD (25.4) give scores below and above their respective ClinGen Antibody Deficiencies VCEP thresholds (>0.75 and >20 respectively), with no consistent predicted effect on CTLA4 function. This variant has been reported in 3 apparently unrelated probands meeting the VCEP standard for phenotypic criteria, exceeding 10 phenotype points without genotyping that excluded causes in other loci (PS4_Moderate, PMID: 29729943). At least one patient harboring this variant had a phenotype that included decreased circulating antibody level (2 pts), non-malignant lymphoproliferation (1 pt), viral infections with herpes and EBV (1 pt), EBV-associated lymphoma (1 pt), mycoplasma or tuberculosis infection (1 pt), diarrhea and enteropathy (4 pts), autoimmune thrombocytopenia and hemolytic anemia, neutropenia in presence of anti-neutrophil antibodies (1 pt), neurological involvement (1 pt), and eczema and alopecia (1pt), (PMID: 29729943). Additionally, patient Treg cells endogenously expressing the p.Pro136Leu variant showed reduced CTLA-4 expression at the cell surface and reduced transendocytosis-mediated uptake of exogenously expressed CD80-GFP from co-cultured Chinese hamster ovary cells, relative to Treg cells from unaffected patients (PMID: 34111452). However, genotyping to rule out an alternative basis for disease in LRBA had not been performed, so the phenotype was not sufficiently specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency to meet PP4 (PMID: 29729943). The variant has been reported to segregate with CTLA4 insufficiency through at least 2 affected meioses from 1 family (PP1; PMID: 29729943, PMID: 30250467). The second affected family member had phenotypes that included gastrointestinal involvement / enteropathy (4 pts,) dermatological involvement (1 pt), and neurological involvement (1 pt), while the third affected family member had a phenotype that included diarrhea and enteropathy (4 pts), neurological involvement (1 pt), vitiligo (1 pt), and autoimmune thyroiditis and type 1 diabetes (1 pt). Together, these features were sufficient to confirm affected status. In summary, this variant meets the criteria to be classified as Likely 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, PM2_Supporting, PP1_Moderate, PM1, and PM5. (VCEP specifications version 2.0.0).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PM1			This variant is located within the MYPPPY functional domain (residues 134-139), which is required for interaction with CD80 and CD86 (PM1, PMID: 31396201).
PM5			Another missense variants in the same codon, NM_005214.5(CTLA4):c.406C>G (p.Pro136Ala), has a lower Grantham score (27) than the variant under investigation (98) and has been classified as likely pathogenic for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency by the ClinGen Antibody Deficiencies VCEP (PM5, PMID: 27379089, PMID: 29729943). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants.
PP1_Moderate			The variant has been reported to segregate with CTLA4 insufficiency through at least 2 affected meioses from 1 family (PP1; PMID: 29729943, PMID: 30250467). The second affected family member had phenotypes that included gastrointestinal involvement / enteropathy (4 pts,) dermatological involvement (1 pt), and neurological involvement (1 pt), while the third affected family member had a phenotype that included low IgM and IgA (2 pts), lower respiratory infections including pneumonia and granulomatous lymphocytic interstitial lung disease (4 pts), type 1 diabetes (1 pt), herpes and clinical EBV infections (1 pt), diarrhea and enteropathy (4 pts), and alopecia (1 pt). Together, these features were sufficient to confirm affected status.

PS4_Moderate			This variant has been reported in 3 probands meeting between 11 and 16 phenotype points (PMID: 29729943). The three eligible cases meet the number of unrelated probands required (PS4_Moderate).
Not Met criteria codes			
PS3			Patient Treg cells endogenously expressing the p.Pro136Leu variant show reduced CTLA-4 expression at the cell surface and reduced transendocytosis-mediated uptake of exogenously expressed CD80-GFP from co-cultured Chinese hamster ovary cells, relative to Treg cells from unaffected patients (PMID: 34111452). However, this result is eligible to be incorporated into the PP4 code rather than PS3_Supporting.
PP3			The computational predictor REVEL gives a score of 0.453, which is below the ClinGen Antibody Deficiencies VCEP threshold of >0.75 and does not predict a damaging effect. The computational predictor CADD gives a PHRED score of 25.4, which is above the ClinGen Antibody Deficiencies VCEP threshold of >20 and predicts a damaging effect on CTLA4 function. Because the two predictors do not agree, this criterion is not met. Additionally, the splicing impact predictor SpliceAI gives a score of 0.02 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.
PP4			At least one patient harboring this variant had a phenotype that included decreased circulating antibody level (2 pts), non-malignant lymphoproliferation (1 pt), viral infections with herpes and EBV (1 pt), EBV-associated lymphoma (1 pt), mycoplasma or tuberculosis infection (1 pt), diarrhea and enteropathy (4 pts), autoimmune thrombocytopenia and hemolytic anemia, neutropenia in presence of anti-neutrophil antibodies (1 pt), neurological involvement (1 pt), and eczema and alopecia (1pt), (PMID: 29729943). Additionally, patient Treg cells endogenously expressing the p.Pro136Leu variant showed reduced CTLA-4 expression at the cell surface and reduced transendocytosis-mediated uptake of exogenously expressed CD80-GFP from co-cultured Chinese hamster ovary cells, relative to Treg cells from unaffected patients (PMID: 34111452). However, genotyping to rule out an alternative basis for disease in LRBA had not been performed, so the phenotype was not sufficiently specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency to meet PP4 (PMID: 29729943).

Curation History 			
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