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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
UUID: 5c5a4e2a-f56f-44ac-a851-2c0f201354f2
Approved on: Mon, 14 Sep 2026 00:00:00 +0000
Published on: Mon, 14 Sep 2026 00:00:00 +0000

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

PS4_Moderate PM1 PM5 PM2_Supporting PP1_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

Evidence submitted by expert panel

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

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).
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.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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.

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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