

Variant: *NM_005214.5(CTLA4):c.410C>G (p.Pro137Arg)*

Version: 1.0

CA350138740 [↗](#)

827701 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 0cb7f92f-e6de-4b26-9a0b-4236cdc7072e

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HGVS expressions

NM_005214.5(CTLA4):c.410C>G (p.Pro137Arg)

NM_005214.5:c.410C>G

NC_000002.12:g.203870886C>G

CM000664.2:g.203870886C>G

NC_000002.11:g.204735609C>G

CM000664.1:g.204735609C>G

NC_000002.10:g.204443854C>G

NG_011502.1:g.8101C>G

ENST00000696049.1:c.410C>G

ENST00000696479.1:c.482C>G

ENST00000427473.3:n.444C>G

ENST00000648405.2:c.410C>G

ENST00000650075.1:n.434C>G

ENST00000295854.10:c.410C>G

ENST00000302823.7:c.410C>G

ENST00000427473.2:c.299C>G

ENST00000472206.1:c.172+238C>G

ENST00000487393.1:n.110-1822C>G

NM_001037631.2:c.410C>G

NM_005214.4:c.410C>G

NM_001037631.3:c.410C>G

Likely Pathogenic

Met criteria codes 4

PS4_Moderate

PS3_Supporting

PM2_Supporting

PM1

Not Met criteria codes 5

BP4

PP3

PP4

PM5

PM6

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.410C>G (p.Pro137Arg) is a missense variant encoding the substitution of proline with arginine at amino acid 137. 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 variant in the same codon, NM_005214.5(CTLA4):c.410C>T (p.Pro137Leu), has been reported in a patient with CTLA4 insufficiency (PMID: 27102614), but has not been counted for PM5 in order to avoid circularity. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in 2 apparently unrelated probands meeting the VCEP standard for phenotypic criteria, both exceeding 10 phenotype points without genotyping that excluded causes in other loci (PMID: 27102614, PMID: 29729943, PS4_Moderate). A third proband harboring the p.Pro137Arg variant with apparently de novo origins (parental genotyping methods not described) has been diagnosed with inherited immunodeficiency and has a phenotype that includes recurrent bacterial infections (1 pt) and severe viral infections (2 pts), but lacks the additional phenotype points required for inclusion in PM6_Supporting (SCV001190136.1). At least one patient harboring this variant had a phenotype that included bronchiectasis (4 pts), type I diabetes mellitus (1 pt), autoimmune cytopenia (2 pts), and enteropathy (4 pts), but was genotyped by methods that were not sufficient to rule out an alternative basis for disease in LRBA, which together were not sufficiently specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency to meet PP4 (11 total points, PMID: 27102614). The computational predictor REVEL gives a score of 0.364, 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 24.0, 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. The splicing impact predictor SpliceAI gives a score of 0.02 for donor loss, which is below the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. Chinese hamster ovary cells expressing the variant showed defective uptake of CD80-Ig or CD86-Ig ligands relative to the wild-type control in a soluble ligand endocytosis assay (PMID: 27102614) and ablation of binding to both soluble ligands in a flow cytometry assay (PMID: 35999394), indicating a damaging effect on protein function (PS3_Supporting). 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: PM1, PM2_Supporting, PS4_Moderate, and PS3_Supporting. (VCEP specifications version 1.0.0; date of approval 09/18/2025).

Met criteria codes

PS4_Moderate			This variant has been reported in 2 apparently unrelated probands meeting the VCEP standard for phenotypic criteria, both exceeding 10 phenotype points without genotyping that excluded causes in other loci (PMID: 27102614, PMID: 29729943, PS4_Moderate).
PS3_Supporting			Chinese hamster ovary cells expressing the variant showed defective uptake of CD80-Ig or CD86-Ig ligands relative to the wild-type control in a soluble ligand endocytosis assay (PMID: 27102614) and ablation of binding to both soluble ligands in a flow cytometry assay (PMID: 35999394), indicating a damaging effect on protein function (PS3_Supporting).
			The variant was expressed in CHO cells and tested by flow cytometry for the ability to bind to soluble CD80-Ig or CD86-Ig ligand, showing ablation of binding to both ligands, consistent with the location of the variant within the known ligand-binding site of CTLA4 (Figure 5b). PubMed:35999394 
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).

Not Met criteria codes

BP4			The computational predictors REVEL gives a score of 0.364, which is above the ClinGen Antibody Deficiencies VCEP threshold of <0.25 and does not predict a benign effect. The computational predictor CADD gives a PHRED score of 24.0, which is above the ClinGen VWD VCEP threshold of <20 and does not predict a benign effect on CTLA4 function. This criterion is not met.
PP3			The computational predictor REVEL gives a score of 0.364, 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 24.0, 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 loss, 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 bronchiectasis (4 pts), type I diabetes mellitus (1 pt), autoimmune cytopenia (2 pts), and enteropathy (4 pts), but was genotyped by methods that were not sufficient to rule out an alternative basis for disease in LRBA, which together were not sufficiently specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency to meet PP4 (11 total points, PMID: 27102614).
PM5			Another missense variant in the same codon has been reported in a patient with CTLA4 insufficiency, (NM_005214.5(CTLA4):c.410C>T (p.Pro137Leu), PMID: 27102614, ClinVar Variation ID: 432079). However, this criterion has not been scored in order to avoid circularity (PM5 not met).
PM6			A third proband harboring the p.Pro137Arg variant with apparently de novo origins (parental genotyping methods not described) has been diagnosed with inherited immunodeficiency and has a phenotype that includes recurrent bacterial infections (1 pt) and severe viral infections (2 pts), but lacks the additional phenotype points required for inclusion in PM6_Supporting (SCV001190136.1).

Curation History



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