

Variant: *NM_005214.5:c.370A>C*

Version: 1.0

CA350138646 [↗](#)

2203245 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: c50ebd08-d4de-4d57-a511-d156aa6c6f67

Approved on: 2025/11/24

Published on: 2025/12/2

HGVS expressions

NM_005214.5:c.370A>C

NC_000002.12:g.203870846A>C

CM000664.2:g.203870846A>C

NC_000002.11:g.204735569A>C

CM000664.1:g.204735569A>C

NC_000002.10:g.204443814A>C

NG_011502.1:g.8061A>C

ENST00000696049.1:c.370A>C

ENST00000696479.1:c.442A>C

ENST00000427473.3:n.404A>C

ENST00000648405.2:c.370A>C

ENST00000650075.1:n.394A>C

ENST00000295854.10:c.370A>C

ENST00000302823.7:c.370A>C

ENST00000427473.2:c.259A>C

ENST00000472206.1:c.172+198A>C

ENST00000487393.1:n.110-1862A>C

NM_001037631.2:c.370A>C

NM_005214.4:c.370A>C

NM_001037631.3:c.370A>C

Uncertain Significance

Met criteria codes **4**

PS3_Supporting

PP3

PM2_Supporting

PS4_Supporting

Not Met criteria codes **4**

BP4

PP1

PP4

PM5

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.370A>C (p.Thr124Pro) is a missense variant replacing threonine with proline at amino acid 124. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in 1 proband meeting the VCEP standard for phenotypic criteria, with a phenotype that includes splenomegaly and lymphadenopathy (2 pts), autoimmune hemolytic anemia (2 pts), autoimmune thyroiditis (1 pt), hypogammaglobulinemia (2 pts), granulomatous lymphocytic interstitial lung disease (4 pts), and organ infiltration of the bone marrow, kidney, brain, and liver (1 pt), without genotyping that excluded causes in other loci (12 total points, PMID: 25329329, PMID: 34111452, PMID: 27418640, PS4_Supporting). The computational predictor REVEL gives a score of 0.812 (which is above the threshold of 0.75) and the computational predictor CADD gives a score of 24.7 (which is above the threshold of 20) (PP3). The splicing impact predictor SpliceAI gives a score of 0.00, which is below the ClinGen Antibody Deficiencies VCEP recommended threshold of >0.2 and does not predict an impact on CTLA4 splicing. A soluble CD80 ligand uptake assay performed in CHO cells expressing either wild-type or mutant CTLA4 showed that the percentage of CD80-Ig-posititve cells was 5.99% in mutated cells (PMID: 25329329).The percentage of CD80-Ig-posititve cells in wild type cells was 55.4%. These results indicate that this variant impacts protein function by impairing the cells' ability to take up soluble CD80-immunoglobulin fusion protein (PMID: 25329329, PS3_Supporting). In summary, this variant meets the criteria to be classified as a variant of uncertain significance 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: PS3_Supporting, PS4_Supporting, PM2_Supporting, and PP3. (VCEP specifications version 1.0.0; date of approval 09/18/2025).

Met criteria codes

PS3_Supporting			Transendocytosis and CD80 ligand uptake assays indicate that this variant impacts CD80 ligand capture in the cell. A transendocytosis assay in CD4+FOXP3+ Treg cells showed that Treg cells from healthy CTLA4+/+ individuals transendocytosed efficiently with 10–25% becoming positive for CD80-GFP; this percentage was reduced to only 2–3% in individuals bearing CTLA4 mutations, indicating a deficit in ligand capture (PMID: 25329329)(PS3_Supporting). Additionally, soluble CD80 ligand uptake assays from the same group performed in CHO cells expressing either wild-type or mutant CTLA4 showed that the percentage of CD80-Ig-posititve cells was 5.99% in mutated cells. The percentage of CD80-Ig-posititve cells in wild type cells was 55.4%. These results indicate that this variant impacts protein function by impairing the cells' ability to take up soluble CD80-immunoglobulin fusion protein (PMID: 25329329)(PS3_Supporting).
PP3			The computational predictor REVEL gives a score of 0.812 (which is above the threshold of 0.75) and the computational predictor CADD gives a score of 24.7 (which is above the threshold of 20) (PP3). Additionally, the splicing impact predictor SpliceAI gives a score of 0.00, which is below the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting			This variant has been reported in 1 proband meeting the VCEP standard for phenotypic criteria, with a phenotype that includes splenomegaly and lymphadenopathy (2 pts), autoimmune hemolytic anemia (2 pts), autoimmune thyroiditis (1 pt), hypogammaglobulinemia (2 pts), granulomatous lymphocytic interstitial lung disease (4 pts), and organ infiltration of the bone marrow, kidney, brain, and liver (1 pt), without genotyping that excluded causes in other loci (12 total points, PMID: 25329329, PMID: 34111452, PMID: 27418640, PS4_Supporting).

Not Met criteria codes

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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PP1			Family D from PMID: 25329329 has one genotype+/phenotype+ patient. This patient's mother is an unaffected carrier of the mutation. Not applied because the variant needs to be present in the proband + at least 2 more family members.
PP4			At least one patient harboring this variant had a phenotype that included hypogammaglobulinemia (2 pts), autoimmune hemolytic anemia (2 pts), interstitial lung disease (4 pts) with granulomatous lymphocytic infiltration (1 pt), lymphadenopathy (2 pts), autoimmune thyroiditis (1 pt), and splenomegaly. However, it is not clear whether genotyping to rule out an alternative basis for disease in LRBA had been performed, so the phenotype was not sufficiently specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency to meet PP4 (PMID: 25329329, PMID: 34111452, PMID: 27418640).
PM5			Thr124Met variant also in this codon. However, this variant is classified as benign by Antibody Deficiencies VCEP.

Curation History 	
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