

Variant: *NM_005214.5(CTLA4):c.105C>A (p.Cys35Ter)*

Version: 1.0

CA173996 [↗](#)

161112 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 8e9de9f6-62fc-4c73-b8f4-064921299471

Approved on: 2025/11/24

Published on: 2025/12/2

HGVS expressions

NM_005214.5(CTLA4):c.105C>A (p.Cys35Ter)

NM_005214.5:c.105C>A

NC_000002.12:g.203868047C>A

CM000664.2:g.203868047C>A

NC_000002.11:g.204732770C>A

CM000664.1:g.204732770C>A

NC_000002.10:g.204441015C>A

NG_011502.1:g.5262C>A

ENST00000696049.1:c.105C>A

ENST00000696479.1:c.177C>A

ENST00000648405.2:c.105C>A

ENST00000295854.10:c.105C>A

ENST00000302823.7:c.105C>A

ENST00000472206.1:c.105C>A

ENST00000487393.1:n.105C>A

NM_001037631.2:c.105C>A

NM_005214.4:c.105C>A

NM_001037631.3:c.105C>A

Pathogenic

Met criteria codes **3**

PVS1

PP1_Strong

PP4

Not Met criteria codes **6**

PM2

BA1

BS1

BS4

PS3

PS4

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.105C>A (p.Cys35Ter) is a nonsense variant that introduces a premature stop codon into exon 1 of 4 and is predicted to trigger nonsense-mediated decay in CTLA4, in which loss-of-function is an established mechanism of disease (PVS1). Chinese hamster ovary cells overexpressing the variant showed abolished uptake of labeled CD80-Ig ligand relative to the wild-type CTLA4 control, indicating that this variant disrupts protein function (PMID: 25329329). However, PVS1 has already been met, so the PS3_Supporting code is not counted. This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.000001242, with 2 alleles / 1,609,900 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.000000143. This variant has a GrpMax allele frequency of 0.00000028, with 2 alleles / 1,176,158 total alleles in the European (non-Finnish) population, which is lower than the BS1 threshold of >0.00000111, so no population code is met. At least one patient harboring this variant has a phenotype that includes diarrhea / enteropathy (4 pts), hypogammaglobulinemia (2 pts), respiratory tract infections (4 pts), splenomegaly (2 pts), autoimmune thyroiditis (1 pt), and autoimmune arthritis (1 pt), with genotyping by exome sequencing identifying no alternative basis for disease in other loci, which together are specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (14 total points, PMID: 25329329, PP4). The variant has been reported to segregate with autoimmune and lymphoproliferative syndrome due to CTLA4 haploinsufficiency through 5 affected meioses from 1 family (PMID: 25329329, PP1_Strong). Affected status has been confirmed for all 4 family members (at least 6 phenotype points). In summary, this variant meets the criteria to be classified as pathogenic 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: PVS1, PP4, and PP1_Strong. (VCEP specifications version 1.0.0; date of approval 09/18/2025).

Met criteria codes

PVS1			NM_005214.5(CTLA4):c.105C>A (p.Cys35Ter) is a nonsense variant that introduces a premature stop codon into exon 1 of 4 and is predicted to trigger nonsense-mediated decay in CTLA4, in which loss-of-function is an established mechanism of disease (PVS1). Chinese hamster ovary cells expressing the p.Cys35Ter variant showed abolished uptake of labeled CD80 ligand (PMID: 25329329).
PP1_Strong			The variant has been reported to segregate with autoimmune and lymphoproliferative syndrome due to CTLA4 haploinsufficiency through 5 affected meioses from 1 family (PMID: 25329329, PP1_Strong). All 4 affected family members are confirmed to be severely affected (at least 6 phenotype points).
PP4			At least one patient harboring this variant has a phenotype that includes diarrhea / enteropathy (4 pts), hypogammaglobulinemia (2 pts), respiratory tract infections (4 pts), splenomegaly (2 pts), autoimmune thyroiditis (1 pt), and autoimmune arthritis (1 pt), with genotyping by exome sequencing identifying no alternative basis for disease in other loci, which together are specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (14 total points, PMID: 25329329, PP4).

Not Met criteria codes

PM2			This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.000001242, with 2 alleles / 1,609,900 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.000000143.
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			This variant is present in gnomAD v4.1.0 at a GrpMax allele frequency of 0.00000028, with 2 alleles / 1,176,158 total alleles in the European (non-Finnish) population, which is lower than the BS1 threshold of >0.00000111.

BS4			All family members affected carry the variant p.Cys50Ter. By contrast, some family members considered healthy were found to be carriers of the variants. Subsequent clinical follow-up indicated that some carriers showed mild or incomplete phenotypes compare to affected individuals.
PS3			Transendocytosis assay in Chinese hamster ovary cells overexpressing the variant showed completely abolished CD80-Ig ligand transendocytosis relative to the wild-type control, indicating that this variant disrupts protein function (PMID: 25329329). PVS1 has already been met, so the PS3_Supporting code was not counted.
PS4			This variant has been reported in 1 proband meeting the ClinGen Antibody Deficiencies VCEP standard for phenotypic criteria. The proband exceeded 10 phenotypic points without genotyping that excluded causes in other loci, which together are highly consistent with CTLA4 insufficiency (PMID: 25329329). The proband was already counted for PP4, so PS4_Supporting was not met.

Curation History 		
<div><div></div><div>▼</div><div>▼</div></div>		
Showing 1 to 1 of 1 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.