

Variant: *NM_005214.5(CTLA4):c.75del (p.Leu28fs)*

Version: 1.0

CA173994 [↗](#)

161110 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 12aeb683-a044-492f-bbce-7f80ca5be1e9

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HGVS expressions

NM_005214.5:c.75del

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NC_000002.12:g.203868017del

CM000664.2:g.203868017del

NC_000002.11:g.204732740del

CM000664.1:g.204732740del

NC_000002.10:g.204440985del

NG_011502.1:g.5232del

ENST00000696049.1:c.75del

ENST00000696479.1:c.147del

ENST00000648405.2:c.75del

ENST00000295854.10:c.75del

ENST00000302823.7:c.75del

ENST00000472206.1:c.75del

ENST00000487393.1:n.75del

NM_001037631.2:c.75del

NM_005214.4:c.75del

NM_001037631.3:c.75del

Pathogenic

Met criteria codes **2**

PP4_Moderate

PVS1

Not Met criteria codes **4**

PS3

PS4

PM2

BS1

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**

Evidence submitted by expert panel

Antibody Deficiencies VCEP

NM_005214.5(CTLA4):c.75del (p.Leu28PhefsTer?) is a frameshift 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). This variant is present in gnomAD v4.1.0 at an allele frequency of 0.0000006195, with 1 allele / 1,614,092 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.000000143, so PM2_Supporting is not met. This variant is present in gnomAD v4.1.0 at a GrpMax allele frequency of 0.000000847, with 1 allele / 1,179,912 total alleles in the European (non-Finnish) population, which is lower than the BS1 threshold of >0.00000111, so BS1 is not met. The variant has been observed in at least 1 patient with a phenotype that includes hepatosplenomegaly (2 pts), autoimmune hemolytic anemia and thrombocytopenia (2 pts), pulmonary nodules (4 pts), infiltrative lesions (2 pts) in the cerebrum (1 pt), and activated T cells showing a partial decrease in expression of CTLA-4 by flow cytometry, with genotyping by exome sequencing identifying no alternative basis for disease in other loci, which together are highly specific for CTLA4 insufficiency (11 total pts, PMID: 25213377, PP4_Moderate). 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 and PP4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/18/2025).

Met criteria codes

PP4_Moderate			The variant has been observed in at least 1 patient with a phenotype that includes hepatosplenomegaly (2 pts), autoimmune hemolytic anemia and thrombocytopenia (2 pts), pulmonary nodules (4 pts), infiltrative lesions (2 pts) in the cerebrum (1 pt), and activated T cells showing a partial decrease in expression of CTLA-4 by flow cytometry, with genotyping by exome sequencing identifying no alternative basis for disease in other loci, which together are highly specific for CTLA4 insufficiency (11 total pts, PMID: 25213377, PP4_Moderate).
PVS1			This is a frameshift 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).

Not Met criteria codes

PS3			Activated T cells from a patient harboring the variant exhibit a partial decrease in expression of CTLA-4, demonstrated by flow cytometry (PMID: 25213377). Since this experiment was performed in proband cells, the evidence was considered for PP4 rather than for PS3_Supporting.
			Activated T cells from the patient harboring the variant exhibit a partial decrease in expression of CTLA-4, demonstrated by flow cytometry (Figure S2). PubMed:25213377 
PS4			This variant has been reported in 1 proband meeting the VCEP standard for phenotypic criteria (PMID: 25213377), however, PS4_Supporting cannot be applied because the proband has already been counted under the PP4 code.
PM2			This variant is present in gnomAD v4.1.0 at an allele frequency of 0.0000006195, with 1 allele / 1,614,092 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.000000143, so PM2_Supporting is not met.
BS1			This variant is present in gnomAD v4.1.0 at a GrpMax allele frequency of 0.000000847, with 1 allele / 1,179,912 total alleles in the European (non-Finnish) population, which is lower than the BS1 threshold of >0.00000111, so BS1 is not met.

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