

Variant: *NM_005214.5(CTLA4):c.151C>T (p.Arg51Ter)*

Version: 1.0

CA173992 [↗](#)

161109 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 2f2bab08-120b-49e8-8a2e-881ea23294d0

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HGVS expressions

NM_005214.5(CTLA4):c.151C>T (p.Arg51Ter)

NM_005214.5:c.151C>T

NC_000002.12:g.203870627C>T

CM000664.2:g.203870627C>T

NC_000002.11:g.204735350C>T

CM000664.1:g.204735350C>T

NC_000002.10:g.204443595C>T

NG_011502.1:g.7842C>T

ENST00000696049.1:c.151C>T

ENST00000696479.1:c.223C>T

ENST00000427473.3:n.185C>T

ENST00000648405.2:c.151C>T

ENST00000650075.1:n.175C>T

ENST00000295854.10:c.151C>T

ENST00000302823.7:c.151C>T

ENST00000427473.2:c.40C>T

ENST00000472206.1:c.151C>T

ENST00000487393.1:n.110-2081C>T

NM_001037631.2:c.151C>T

NM_005214.4:c.151C>T

NM_001037631.3:c.151C>T

Pathogenic

Met criteria codes **3**

PS4

PM2_Supporting

PVS1

Not Met criteria codes **2**

PS3

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**

Antibody Deficiencies VCEP

NM_005214.5(CTLA4):c.151C>T (p.Arg51Ter) is a nonsense variant that introduces a premature stop codon into exon 2 of 4 and is predicted to lead to nonsense-mediated decay in CTLA4, in which loss-of-function is an established mechanism of disease (PVS1). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 3 apparently unrelated probands meeting the VCEP standard for phenotypic criteria. In 1 case, the proband exceeded 6 phenotypic points with genotyping that excluded causes in other loci (PMID: 25213377, PMID: 29200144). In 2 cases, the proband exceeded 10 phenotype points without genotyping that excluded causes in other loci (PS4_Moderate; PMID: 29729943, PMID:29330115, PMID: 32499327). At least one patient harboring this variant had a phenotype that included hypogammaglobulinemia (2 pts), thrombocytopenia (1 pt), respiratory involvement with pulmonary infiltrates (4 pts), brain infiltrates (1 pts), splenomegaly (2 pts), and eczema (1 pt), but lacked sufficient genotyping to rule out an alternative basis for disease in LRBA, which together were not sufficiently specific to meet PP4 for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (11 total points, PMID: 29729943). 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, PM2_Supporting, and PS4_Moderate. (VCEP specifications version 1.0.0; date of approval 09/18/2025).

Met criteria codes

PS4			This variant has been reported in at least 3 apparently unrelated probands meeting the VCEP standard for phenotypic criteria. In 1 case, the proband exceeded 6 phenotypic points with genotyping that excluded causes in other loci (PMID: 25213377, PMID: 29200144). In 2 cases, the proband exceeded 10 phenotype points without genotyping that excluded causes in other loci (PS4_Moderate; PMID: 29729943, PMID:29330115, PMID: 32499327).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PVS1			NM_005214.5(CTLA4):c.151C>T (p.Arg51Ter) is a nonsense variant that introduces a premature stop codon into exon 2 of 4 and is predicted to lead to nonsense-mediated decay in CTLA4, in which loss-of-function is an established mechanism of disease (PVS1).

Not Met criteria codes

PS3			Flow cytometry in patient regulatory T cells showed aberrations in expression indicating that this variant impacts protein function (PMID: 29200144). Since this experiment was performed in proband cells, the evidence was considered for PP4 rather than for PS3_Supporting.
PP4			At least one patient harboring this variant had a phenotype that included hypogammaglobulinemia (2 pts), thrombocytopenia (1 pt), respiratory involvement with pulmonary infiltrates (4 pts), brain infiltrates (1 pts), splenomegaly (2 pts), and eczema (1 pt), but lacked sufficient genotyping to rule out an alternative basis for disease in LRBA, which together were not sufficiently specific to meet PP4 for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (11 total points, PMID: 29729943).

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