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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 haploinsuffiency (MONDO:0014493)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2f2bab08-120b-49e8-8a2e-881ea23294d0
Approved on: 2025/11/24
Published on: 2025/12/2

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

PVS1 PM2_Supporting PS4

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

Evidence submitted by expert panel

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

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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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).

Not Met criteria codes

PS3	✖	Flow cytometery 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).

Curation History

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