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Variant: NM_005214.5(CTLA4):c.457G>A (p.Asp153Asn)

Version: 1.0

CA350138843

636389 (ClinVar)

Gene: CTLA4 (HGNC:1493)
Condition: autoimmune lymphoproliferative syndrome due to CTLA4 haploinsuffiency (MONDO:0014493)
Inheritance Mode: Autosomal dominant inheritance
UUID: d8e5dbe0-16a7-4c78-9e02-3bdc8c821832
Approved on: 2025/11/24
Published on: 2025/12/2

HGVS expressions

NM_005214.5:c.457G>A
NM_005214.5(CTLA4):c.457G>A (p.Asp153Asn)
NC_000002.12:g.203870933G>A
CM000664.2:g.203870933G>A
NC_000002.11:g.204735656G>A
CM000664.1:g.204735656G>A
NC_000002.10:g.204443901G>A
NG_011502.1:g.8148G>A
ENST00000696049.1:c.457G>A
ENST00000696479.1:c.529G>A
ENST00000427473.3:n.491G>A
ENST00000648405.2:c.457G>A
ENST00000650075.1:n.481G>A
ENST00000295854.10:c.457G>A
ENST00000302823.7:c.457G>A
ENST00000427473.2:c.346G>A
ENST00000472206.1:c.172+285G>A
ENST00000487393.1:n.110-1775G>A
NM_001037631.2:c.457G>A
NM_005214.4:c.457G>A
NM_001037631.3:c.457G>A

Pathogenic

Met criteria codes 3

PVS1 PP4 PM2_Supporting

Not Met criteria codes 3

PS3 PS4 PP3

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.457G>A (p.Asp153Asn) is a variant in the final nucleotide of exon 2. The splicing impact predictor SpliceAI gives scores of 0.77 for donor loss and 0.58 for donor gain, which are above the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and predict a damaging impact on splicing. RNA sequencing from patient peripheral blood mononuclear cells showed approximately 50% loss of CTLA4 sequencing reads starting 67 base pairs upstream of the 3' end of exon 2, indicating that this variant triggers cryptic splice site usage and a truncated transcript (PMID: 32562209). PP3 and PS3_Supporting were not met as this predictive and experimental evidence of a splicing defect were considered indications of a null impact instead (PVS1). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). At least one patient harboring this variant had a phenotype that included chronic diarrhea (4 pts) with lymphocytic infiltration (1 pt), Kaposi's sarcoma secondary to HHV8 infection (2 pts), neurodevelopmental delay (1 pt), lymphopenia (1 pt), skin findings (1 pt), and arthritis (1 pt), as well as genotyping by whole genome sequencing to rule out an alternative basis for disease in LRBA and DEF6, which together are highly specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (11 total points, PMID: 32562209, PP4). 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 PP4. (VCEP specifications version 1.0.0; date of approval 09/18/2025).

Met criteria codes

PVS1	✔	NM_005214.5(CTLA4):c.457G>A (p.Asp153Asn) is a variant in the final nucleotide of exon 2. The splicing impact predictor SpliceAI gives scores of 0.77 for donor loss and 0.58 for donor gain, which are above the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and predict a damaging impact on splicing. RNA sequencing from patient peripheral blood mononuclear cells showed approximately 50% loss of CTLA4 sequencing reads starting 67 base pairs upstream of the 3' end of exon 2, indicating that this variant triggers cryptic splice site usage and a truncated transcript (PMID: 32562209). PP3 and PS3_Supporting were not met as this predictive and experimental evidence of a splicing defect was incorporated into the PVS1 code instead.
PP4	✔	At least one patient harboring this variant had a phenotype that included chronic diarrhea (4 pts) with lymphocytic infiltration (1 pt), Kaposi's sarcoma secondary to HHV8 infection (2 pts), neurodevelopmental delay (1 pt), lymphopenia (1 pt), skin findings (1 pt), and arthritis (1 pt), as well as genotyping by whole genome sequencing to rule out an alternative basis for disease in LRBA and DEF6, which together are highly specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (11 total points, PMID: 32562209, PP4).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS3	✖	RNA sequencing from patient peripheral blood mononuclear cells showed approximately 50% loss of CTLA4 sequencing reads starting 67 base pairs upstream of the 3' end of exon 2, indicating that this variant triggers cryptic splice site usage and a truncated transcript (PMID: 32562209). PS3_Supporting was not met as this evidence was incorporated into the PVS1 code instead.
PS4	✖	This variant has been reported in 2 probands, neither of which meets the Antibody Deficiencies VCEP phenotype criteria (PMIDs: 31156616, 29682684).
PP3	✖	

The splicing impact predictor SpliceAI gives scores of 0.77 for donor loss and 0.58 for donor gain, which are above the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and predict a damaging impact on splicing. PP3 was not met as this evidence was incorporated into the PVS1 code instead.

Curation History

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