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Variant: NM_005214.5:c.406C>G

Version: 1.0

CA350138731

Gene: CTLA4 (HGNC:1493)
Condition: autoimmune lymphoproliferative syndrome due to CTLA4 haploinsuffiency (MONDO:0014493)
Inheritance Mode: Autosomal dominant inheritance
UUID: 70f2a6da-9051-4244-8b25-8962179aec7a
Approved on: 2025/11/24
Published on: 2025/12/2

HGVS expressions

NM_005214.5:c.406C>G
NC_000002.12:g.203870882C>G
CM000664.2:g.203870882C>G
NC_000002.11:g.204735605C>G
CM000664.1:g.204735605C>G
NC_000002.10:g.204443850C>G
NG_011502.1:g.8097C>G
ENST00000696049.1:c.406C>G
ENST00000696479.1:c.478C>G
ENST00000427473.3:n.440C>G
ENST00000648405.2:c.406C>G
ENST00000650075.1:n.430C>G
ENST00000295854.10:c.406C>G
ENST00000302823.7:c.406C>G
ENST00000427473.2:c.295C>G
ENST00000472206.1:c.172+234C>G
ENST00000487393.1:n.110-1826C>G
NM_001037631.2:c.406C>G
NM_005214.4:c.406C>G
NM_001037631.3:c.406C>G

Likely Pathogenic

Met criteria codes 5

PS3_Supporting PP4 PM1 PM6 PM2_Supporting

Not Met criteria codes 4

PS4 PP3 PM5 BP4

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.406C>G (p.Pro136Ala) is a missense variant encoding the replacement of proline with alanine at amino acid 136. This variant is located within the MYPPPY functional domain (residues 134-139), which is required for interaction with CD80 and CD86 (PM1, PMID: 31396201). Two other missense variants at the same amino acid residue (p.Pro136Ser, p.Pro136Leu) have been observed in similarly affected patients, however, the PM5 code has not been counted in this direction in order to avoid circularity. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). At least one patient harboring this variant had a phenotype that included autoimmune cytopenias (2 pts), low circulating IgG and IgA (2 pts), lymphocytic or granulomatous organ infiltration of lung, kidney, and lymph nodes (1 pt), skin infection with Molluscum contagiosum (1 pt), and respiratory involvement including bronchiectasis, follicular bronchiolitis, otitis media, and sinusitis (4 pts), as well as genotyping to rule out an alternative basis for disease in LRBA and other loci, which is highly specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (10 total points, PMID: 27379089, PP4). The patient harbored the variant de novo, with confirmation of parental relationships not described in detail (PMID: 27379089, PM6). The computational predictors REVEL (0.405) and CADD (22.9) give scores below and above their respective ClinGen Antibody Deficiencies VCEP thresholds (>0.75 and >20 respectively), with no consistent predicted effect on CTLA4 function. Purified recombinant CTLA4 harboring this variant binds CD80 but not CD86, indicating that the variant disrupts CTLA4 interaction with one of its two ligands (PMID: 8557978, PS3_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Antibody Deficiencies VCEP: PM1, PM6, PM2_Supporting, PS3_Supporting, and PP4. (VCEP specifications version 1.0.0; date of approval 09/18/2025).

Met criteria codes

PS3_Supporting	✔	Purified recombinant CTLA4 harboring this variant appears to bind CD80 but not CD86, indicating that the variant disrupts CTLA4 interaction with one of its two ligands (PMID: 8557978, PS3_Supporting). Wild-type or variant CTLA4 were expressed as radioactive I125-labeled soluble Ig fusion proteins, purified, and then given the opportunity to bind to cells exogenously expressing CD80 or CD86 ligands. Wild-type CTLA4 bound to both CD80- and CD86-expressing cells. CTLA4 harboring the p.Pro136Ala mutation (referred to in the paper as "P101" or just "101") bound only to CD80-expressing but not CD86-expressing cells. This indicates that the variant disrupts CTLA4 interaction with one of its two ligands (Figure 5). PubMed:8557978
PP4	✔	At least one patient harboring this variant had a phenotype that included autoimmune cytopenias (2 pts), low circulating IgG and IgA (2 pts), lymphocytic or granulomatous organ infiltration of lung, kidney, and lymph nodes (1 pt), skin infection with Molluscum contagiosum (1 pt), and respiratory involvement including bronchiectasis, follicular bronchiolitis, otitis media, and sinusitis (4 pts), as well as genotyping to rule out an alternative basis for disease in LRBA and other loci, which is highly specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (10 total points, PMID: 27379089, PP4).
PM1	✔	This variant is located within the MYPPPY functional domain (residues 134-139), which is required for interaction with CD80 and CD86 (PM1, PMID: 31396201).
PM6	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual diagnosed with combined variable immune deficiency meeting the phenotypic criteria defined by the ClinGen Antibody Deficiencies VCEP (PM6, PMID: 27379089).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant has been reported twice in 1 proband meeting the VCEP standard for phenotypic criteria (PMID: 27379089, PMID: 29729943). However, PS4_Supporting cannot be applied because a minimum of 2 unrelated probands is required.
PP3	✖	The computational predictor REVEL gives a score of 0.405, which is below the ClinGen Antibody Deficiencies VCEP threshold of >0.75 and does not predict a damaging effect. The computational predictor CADD gives a PHRED score of 22.9, which is above the ClinGen Antibody Deficiencies VCEP threshold of >20 and predicts a damaging effect on CTLA4 function. Because the two predictors do not agree, this criterion is not met. Additionally, the splicing impact predictor SpliceAI gives a score of 0.08 for donor gain, which is below the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM5	✖	Two other missense variants at the same amino acid residue (p.Pro136Ser, p.Pro136Leu) have been observed in similarly affected patients, however, PM5 has not been applied in this variant curation in order to avoid circularity.
BP4	✖	The computational predictor REVEL gives a score of 0.405, which is above the ClinGen Antibody Deficiencies VCEP threshold of <0.25 and does not predict a non-damaging effect. The computational predictor CADD gives a PHRED score of 22.9, which is above the ClinGen Antibody Deficiencies VCEP threshold of >20 and predicts a damaging effect on CTLA4 function. Because neither predictor suggests no effect on CTLA4 function, this criterion is not met.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_005214.5:c.406C>G	Likely Pathogenic	Autoimmune Lymphoproliferative Syndrome Due To CTLA4 Haploinsuffiency	2025-12-02	1.0	ClinGen Antibody Deficiencies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CTLA4 Version 1.0.0	CTLA4

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