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

Version: 1.1

CA350138732

4683129 (ClinVar)

Gene: CTLA4 (HGNC:1493)
Condition: autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (MONDO:0014493)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7031aeab-5c4c-497a-a1bd-d026b0aa03fa
Approved on: Mon, 14 Sep 2026 00:00:00 +0000
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HGVS expressions

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

Likely Pathogenic

Met criteria codes 6

PM1 PM5 PP1 PP4 PM2_Supporting PS4_Supporting

Not Met criteria codes 1

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.406C>T (p.Pro136Ser)is a missense variant encoding the replacement of proline with serine 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). Another missense variant in the same codon, NM_005214.5(CTLA4):c.406C>G (p.Pro136Ala), has a lower Grantham score (27) than the variant under investigation (74) and has been classified as likely pathogenic for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency by the ClinGen Antibody Deficiencies VCEP (PM5, PMID: 27379089, PMID: 29729943). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). This variant has been reported in at least 1 proband with a phenotype that includes autoimmune cytopenias (2 pts), recurrent parotitis (4 pts), autoimmune gastrointestinal findings (4 pts), hepatosplenomegaly (2 pts), and recurrent viral infections (2 pts), with genotyping based on exome sequencing to exclude an alternative basis of disease in other loci such as LRBA, which together is highly specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (14 pts, PMID: 32009323, PP4). This variant has been reported in at least one other apparently unrelated patient reaching at least 10 phenotypic points, with a phenotype that includes recurrent upper and lower respiratory tract infections (4 pts), enteropathy and diarrhea (4 pts), T cell infiltration of the lung and gut (1 pt), autoimmune thrombocytopenia and autoimmune hemolytic anemia (2 pts), severe viral infection including skin findings (2 pts), recurrent fungal infections (1 pt), splenomegaly and lymphoproliferative disorder (2 pts), decreased circulating IgG level (2 pts), and post-vaccination measles (1 pt), without genotyping to exclude an alternative basis for disease in other loci (19 pts, PMID: 29729943, PS4_Supporting). The variant has been reported to segregate with autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency through at least 1 affected meiosis from 1 family, with the affected status of the second family member confirmed to include hypogammaglobulinemia (2 pts), markedly decreased B-cells (1 pt), multiple episodes of illness including anemia and/or thrombocytopenia, abnormal lymphocyte subsets (1 pt), viral infection (2 pts), and malignancies (PMID: 32009323, PP1). The computational predictor REVEL gives a score of 0.490, 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 24.9, 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, PP3 is not met. Additionally, the splicing impact predictor SpliceAI gives a score of 0.02 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. 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, PM5, PM2_Supporting, PS4_Supporting, PP1, and PP4. (VCEP specifications version 2.0.0).

Met criteria codes

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).
PM5	✔	Another missense variants in the same codon, NM_005214.5(CTLA4):c.406C>G (p.Pro136Ala), has a lower Grantham score (27) than the variant under investigation (74) and has been classified as likely pathogenic for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency by the ClinGen Antibody Deficiencies VCEP (PM5, PMID: 27379089, PMID: 29729943). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants.
PP1	✔	At least 1 family is available with 1 segregation between the two affected siblings, with the affected status of the second family member confirmed to include hypogammaglobulinemia (2 pts), markedly decreased B-cells (1 pt), multiple episodes of illness including anemia and/or thrombocytopenia, abnormal lymphocyte subsets (1 pt), viral infection (2 pts), and malignancies such as gastric cancer or myelodysplastic syndrome (PMID: 32009323, PP1).
PP4	✔	This variant has been reported in at least 1 proband with a phenotype that includes autoimmune cytopenias (2 pts), recurrent parotitis (4 pts), autoimmune gastrointestinal findings (4 pts), hepatosplenomegaly (2 pts), and recurrent viral infections (2 pts), with genotyping based on exome sequencing to exclude an alternative basis of disease in

other loci such as LRBA, which together is highly specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (14 pts, PMID: 32009323, PP4).

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting	✔	At least one patient harboring this variant had at least 10 phenotypic points, with a phenotype that includes recurrent upper and lower respiratory tract infections (4 pts), enteropathy and diarrhea (4 pts), T cell infiltration of the lung and gut (1 pt), autoimmune thrombocytopenia and autoimmune hemolytic anemia (2 pts), severe viral infection including skin findings (2 pts), recurrent fungal infections (1 pt), splenomegaly and lymphoproliferative disorder (2 pts), decreased circulating IgG level (2 pts), and post-vaccination measles (1 pt), without genotyping to exclude an alternative basis for disease in other loci (PMID: 29729943, PS4_Supporting).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.490, 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 24.9, 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 0.02 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.

Curation History

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