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Variant: NM_005214.5(CTLA4):c.410C>T (p.Pro137Leu)

Version: 1.1

CA350138741

432079 (ClinVar)

Gene: CTLA4 (HGNC:1493)
Condition: autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (MONDO:0014493)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2ed11642-b976-47ec-90e0-8b696daf12c1
Approved on: Mon, 14 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_005214.5(CTLA4):c.410C>T (p.Pro137Leu)
NM_005214.5:c.410C>T
NC_000002.12:g.203870886C>T
CM000664.2:g.203870886C>T
NC_000002.11:g.204735609C>T
CM000664.1:g.204735609C>T
NC_000002.10:g.204443854C>T
NG_011502.1:g.8101C>T
ENST00000696049.1:c.410C>T
ENST00000696479.1:c.482C>T
ENST00000427473.3:n.444C>T
ENST00000648405.2:c.410C>T
ENST00000650075.1:n.434C>T
ENST00000295854.10:c.410C>T
ENST00000302823.7:c.410C>T
ENST00000427473.2:c.299C>T
ENST00000472206.1:c.172+238C>T
ENST00000487393.1:n.110-1822C>T
NM_001037631.2:c.410C>T
NM_005214.4:c.410C>T
NM_001037631.3:c.410C>T

Likely Pathogenic

Met criteria codes 2

PS4 PM1

Not Met criteria codes 6

PP3 PP4 PM5 PM2 BS1 BP4

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.410C>T (p.Pro137Leu) is a missense variant encoding substitution of proline with leucine at amino acid 137. 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.410C>G (p.Pro137Arg), has been classified as likely pathogenic for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency by the ClinGen Antibody Deficiencies VCEP (PMID: 27102614). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants, however, the comparison variant has a higher Grantham score (103) than the variant under investigation (98), so PM5 is not met. This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.0000006195, with 1 allele / 1,614,162 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.000000143. This variant has an allele frequency of 0.0000008474, with 1 allele / 1,180,014 total alleles in the European (non-Finnish) population, which is lower than the BS1 threshold of >0.00000111, so no population code is met. This variant has been reported in at least 4 apparently unrelated probands meeting the VCEP standard for phenotypic criteria, with 3 exceeding 10 phenotype points without genotyping that excluded causes in other loci (PMID: 29729943, PMID: 27102614), and 1 reaching 8 phenotype points with exome sequencing-based genotyping that did not identify an alternative basis for disease in the LRBA gene (PMID: 33275711, PS4). Additional reports of this variant in affected patients are available, but some patient phenotypes are not described in detail (PMID: 34111452), and author lists are overlapping so that the cases are not likely to represent distinct individuals (PMID: 30250467, PMID: 27577878, PMID: 39218359, PMID: 34111452). At least 1 proband had a phenotype that included episodes of headache, hearing impairment, and diplopia with enhancing anomaly in the brain parenchyma and progressive brain lesions (1 pt), hemolytic anemia and thrombocytopenia (2 pts), lymphoid hyperplasia and splenomegaly (2 pts), shingles (2 pts), modest hypogammaglobulinemia (2 pt), decreased specific antibody response to vaccination (1), and defective B-cell differentiation (decreased memory B cells), however, PP4 was not applied since the patient was counted under the PS4 code instead (PMID: 33275711). In summary, this variant meets the criteria to be classified as Likely 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: PM1 and PS4. (VCEP specifications version 2.0.0).

Met criteria codes

PS4	✔	This variant has been reported in at least 4 apparently unrelated probands meeting the VCEP standard for phenotypic criteria, with 3 exceeding 10 phenotype points without genotyping that excluded causes in other loci (PMID: 29729943, PMID: 27102614), and 1 reaching 8 phenotype points with exome sequencing-based genotyping that did not identify an alternative basis for disease in the LRBA gene (PMID: 33275711, PS4). Additional reports of this variant in affected patients are available, but some patient phenotypes are not described in detail (PMID: 34111452), and author lists are overlapping so that the cases are not likely to represent distinct individuals (PMID: 30250467, PMID: 27577878, PMID: 39218359, PMID: 34111452).
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).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.355, 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 24.5, 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 0.04 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.

PP4	✖	The variant has been observed in at least 1 patient with genotyping by exome sequencing excluding the possibility of an alternative basis for disease in other loci, exhibiting episodes of headache, hearing impairment, and diplopia with enhancing anomaly in the brain parenchyma and progressive brain lesions (1 pt), hemolytic anemia and thrombocytopenia (2 pts), lymphoid hyperplasia and splenomegaly (2 pts), shingles (2 pts), modest hypogammaglobulinemia (2 pt), decreased specific antibody response to vaccination (1), and defective B-cell differentiation (decreased memory B cells), which together are specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (10 total pts, PMID: 33275711). However, PP4 was not applied since the patient was counted under the PS4 code instead.
PM5	✖	Another missense variant in the same codon, NM_005214.5(CTLA4):c.410C>G (p.Pro137Arg), has been classified as likely pathogenic for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency by the ClinGen Antibody Deficiencies VCEP (PMID: 27102614). Splicing prediction using SpliceAI did not strongly predict an effect on splicing due to either of these variants, however, the comparison variant has a higher Grantham score (103) than the variant under investigation (98), so PM5 is not met.
PM2	✖	This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.0000006195, with 1 allele / 1,614,162 total alleles across all populations of gnomAD, which is higher than the ClinGen Antibody Deficiencies VCEP PM2_Supporting threshold of <0.000000143, so PM2_Supporting is not met.
BS1	✖	This variant is present in gnomAD v4.1.0 at an allele frequency of 0.0000008474, with 1 allele / 1,180,014 total alleles in the European (non-Finnish) population, which is lower than the BS1 threshold of >0.00000111, so no population code is met.
BP4	✖	The computational predictor REVEL gives a score of 0.355, which is below the ClinGen Antibody Deficiencies VCEP threshold of <0.25 and does not predict a benign effect. The computational predictor CADD gives a PHRED score of 24.5, which is above the ClinGen Antibody Deficiencies VCEP threshold of <20 and fails to predict a benign effect on CTLA4 function. This criterion is not met.

Curation History

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