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Variant: NM_005214.5(CTLA4):c.416A>G (p.Tyr139Cys)

Version: 2.0

CA350138752

623475 (ClinVar)

Gene: CTLA4 (HGNC:1493)
Condition: autoimmune lymphoproliferative syndrome due to CTLA4 haploinsufficiency (MONDO:0014493)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4319133b-bebd-402a-899d-fd471b1ab6bc
Approved on: Mon, 14 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_005214.5:c.416A>G
NM_005214.5(CTLA4):c.416A>G (p.Tyr139Cys)
NC_000002.12:g.203870892A>G
CM000664.2:g.203870892A>G
NC_000002.11:g.204735615A>G
CM000664.1:g.204735615A>G
NC_000002.10:g.204443860A>G
NG_011502.1:g.8107A>G
ENST00000696049.1:c.416A>G
ENST00000696479.1:c.488A>G
ENST00000427473.3:n.450A>G
ENST00000648405.2:c.416A>G
ENST00000650075.1:n.440A>G
ENST00000295854.10:c.416A>G
ENST00000302823.7:c.416A>G
ENST00000427473.2:c.305A>G
ENST00000472206.1:c.172+244A>G
ENST00000487393.1:n.110-1816A>G
NM_001037631.2:c.416A>G
NM_005214.4:c.416A>G
NM_001037631.3:c.416A>G

Pathogenic

Met criteria codes 6

PS2_Supporting PP3 PM1 PS4 PM2_Supporting PS3_Supporting

Not Met criteria codes 2

PP4 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.416A>G (p.Tyr139Cys) is a missense variant encoding replacement of tyrosine with cysteine at amino acid 139. This variant is located within the MYPPPY functional domain (residues 134-139), which is required for interaction with CD80 and CD86 (PM1, PMID: 31396201). This variant is absent from gnomAD v4.1.1 (PM2_Supporting). This variant has been reported in 4 apparently unrelated probands meeting the VCEP standard for phenotypic criteria. Two published cases exceeded 6 phenotypic points each with genotyping that excluded causes in other loci (PMID: 31396201, PMID: 29375547). Two unpublished cases exceeded 10 phenotype points each with genotyping that excluded causes in other loci (SCV002073326.1, SCV005627751.2, PS4). This variant has been reported in at least 2 other published cases (PMID: 37740092, PMID: 39218359), but it is not clear whether these are related or unrelated to those already scored. One proband harboring this variant had phenotypes including pancytopenia (1 pt), recurrent upper respiratory tract infections (4 pts), lymphadenopathy and splenomegaly (2 pts), gastroenteritis (4 pts) with lymphocytic infiltrates (1 pt), and hypogammaglobulinemia (2 pt), with genotyping that excludes alternative genetic causes in LRBA and other loci, however, PP4 was not applied as the proband was included in PS4 instead (PMID: 29375547). This variant has been identified as a de novo occurrence in 1 individual with CTLA4 insufficiency, with parental relationships confirmed through the use of trio whole genome sequencing. The individual showed IgM deficiency (2 pts) polyarthritis (1 pt) with autoantibodies (1 pt), and autoimmune hepatitis (4 pts), which together are consistent with CTLA4 insufficiency, but genotyping did not exclude alternative causes in other loci (PS2_Supporting, PMID: 31396201). The computational predictor REVEL gives a score of 0.717, which is above the ClinGen Antibody Deficiencies VCEP threshold of >0.644, while the computational predictor CADD gives a PHRED score of 26.0, which is above the ClinGen Antibody Deficiencies VCEP threshold of >25.3, both of which predict a deleterious effect on CTLA4 function (PP3). Additionally, the splicing impact predictor SpliceAI gives a score of 0.00, which is below the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. Jurkat T cells expressing the variant showed a partial defect in expression, a complete defect in CD80 and CD86 uptake, and complete loss of the ability to block T cell proliferation in co-culture. CTLA4-Ig harboring the variant also showed complete loss of the ability to bind to cells expressing the CD80 and CD86 ligands (PS3_Supporting, PMID: 29375547). 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: PM1, PM2_Supporting, PS4, PS2_Supporting, PP3, and PS3_Supporting. (VCEP specifications version 2.0.0).

Met criteria codes

PS2_Supporting	✔	At least one affected patient with unaffected parents genotyped by trio whole genome sequencing was found to harbor the variant in the de novo state, and exhibited phenotypes of IgM deficiency (2 pts) polyarthritis (1 pt) with autoantibodies (1 pt), and autoimmune hepatitis (4 pts), (0.5 de novo pts, PMID: 31396201).
PP3	✔	The computational predictor REVEL gives a score of 0.717, which is above the ClinGen Antibody Deficiencies VCEP threshold of >0.644, while the computational predictor CADD gives a PHRED score of 26.0, which is above the ClinGen Antibody Deficiencies VCEP threshold of >25.3, both of which predict a deleterious effect on CTLA4 function (PP3). Additionally, the splicing impact predictor SpliceAI gives a score of 0.00, which is below the ClinGen Antibody Deficiencies VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
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).
PS4	✔	This variant has been reported in 4 apparently unrelated probands meeting the VCEP standard for phenotypic criteria. Two published cases exceeded 6 phenotypic points each with genotyping that excluded causes in other loci (PMID: 31396201, PMID: 29375547). Two unpublished cases exceeded 10 phenotype points each with genotyping that excluded causes in other loci (SCV002073326.1, SCV005627751.2, PS4). This variant has been reported in at

least 2 other published cases (PMID: 37740092, PMID: 39218359), but it is not clear whether these are related or unrelated to those already scored.

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

PS3_Supporting ✔ Flow cytometry of CTLA4 antibody-stained Jurkat (T) cells expressing wild-type CTLA4 or the p.Tyr139Cys variant showed a partial defect in expression for the variant, a complete defect in CD80 and CD86 uptake, and complete loss of the ability to block healthy patient T cell proliferation when co-cultured in vitro. CTLA4-Ig harboring the variant also showed complete loss of the ability to bind to EBV cells expressing CD80 and CD86 (PS3_Supporting, PMID: 29375547).

Not Met criteria codes

PP4 ✖ At least one patient harboring this variant had phenotypes including pancytopenia (1 pt), recurrent upper respiratory tract infections (4 pts), lymphadenopathy and splenomegaly (2 pts), gastroenteritis (4 pts) with lymphocytic infiltrates (1 pt), and hypogammaglobulinemia (2 pt), with genotyping that excludes alternative genetic causes in LRBA and other loci. Together these details are specific for autoimmune lymphoproliferative syndrome due to CTLA4 haploinsuffiency (14 pts, PMID: 29375547.). The proband was not counted for PP4 due to inclusion in PS4 instead. Please note that the proband also harbored the p.Arg840Cys variant in JAK3 in the heterozygous state.

BP4 ✖ The computational predictor REVEL gives a score of 0.717, which is above the ClinGen Antibody Deficiencies VCEP threshold of <0.25 and does not predict a non-damaging effect on CTLA4 function. The computational predictor CADD gives a PHRED score of 26.0, which is above the ClinGen Antibody Deficiencies VCEP threshold of <20 and does not predict a non-deleterious effect on CTLA4 function. Because the two predictors do not agree on a non-damaging effect, this criterion is not met.

Curation History

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