
Abstract
Cytotoxic T-lymphocyte associated protein 4 (CTLA4) is a negative regulator of T-cell proliferation. Polymorphisms in CTLA4 have been inconsistently associated with susceptibility to rheumatoid arthritis (RA) in populations of European ancestry but have not been examined in African Americans. The prevalence of RA in most populations of European and Asian ancestry is approximately 1.0%; RA is purportedly less common in black Africans, with little known about its prevalence in African Americans. We sought to determine if CTLA4 polymorphisms are associated with RA in African Americans. We performed a 2-stage analysis of 12 haplotype tagging single nucleotide polymorphisms (SNPs) across CTLA4 in a total of 505 African American RA patients and 712 African American controls using Illumina and TaqMan platforms. The minor allele (G) of the rs231778 SNP was 0.054 in RA patients, compared to 0.209 in controls (4.462 x 10^-26, Fisher's exact). The presence of the G allele was associated with a substantially reduced odds ratio (OR) of having RA (AG+GG genotypes vs. AA genotype, OR 0.19, 95% CI: 0.13-0.26, p = 2.4 x 10^-28, Fisher's exact), suggesting a protective effect. This SNP is polymorphic in the African population (minor allele frequency [MAF] 0.09 in the Yoruba population), but is very rare in other groups (MAF = 0.002 in 530 Caucasians).

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Markers associated with RA in populations of European ancestry (rs3087243 [+60C/T] and rs231775 [+49A/G]) were not replicated in African Americans. We found no confounding of association for rs231778 after stratifying for the HLA-DRB1 shared epitope, presence of anti-cyclic citrullinated peptide antibody, or degree of admixture from the European population. An African ancestry-specific genetic variant of CTLA4 appears to be associated with protection from RA in African Americans. This finding may explain, in part, the relatively low prevalence of RA in black African populations.

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