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Genetic variants of STAT4 associated with rheumatoid arthritis in persons of Asian and European ancestry do not replicate in African-Americans

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Rheumatoid arthritis (RA) was recently genetically associated with signal transducer and activator of transcription 4 (*STAT4*) in Caucasians [1]. This study included over 6,000 participants to produce an odds ratio of 1.32 at rs7574865 ($p = 2.8 \times 10^{-7}$). Three other single nucleotide polymorphisms (SNPs) located in intron 3 of *STAT4* (rs8179673, rs10181656, rs6752770), 3 SNPs in strong linkage disequilibrium with rs7574865 ($r^2 = 1.0$; rs7582694, rs7568275, rs11889341), and a haplotype driven by the T allele of rs7574865 also associated with RA susceptibility [1]. Association with rs7574865 replicated in several Asian and European-based populations. See Table 1. Since racial/ethnic differences have been observed at RA susceptibility loci, including *CTLA4*, *PADI4*, *PTPN22*, *RUNX1*, and *SLC22A4*, we aimed to determine if an association with these *STAT4* markers and RA susceptibility is consistent in African-Americans.

We used ABI TaqMan allelic discrimination assays to genotype rs8179673, rs10931481, rs11889341, rs7574865, rs10181656, and rs10207044 in 723 African-American RA patients and 690 African-American controls from the Consortium for the Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis (CLEAR) Registry as described previously [9]. All participants were recruited with informed consent under approval of an Institutional Review Board. Chi square tests were performed on GraphPad Prism v4.03 (San Diego, CA).

We did not observe a genetic association with rs7574865 (χ^2 $p = 0.23$) or with the other previously associated SNPs. See Table 2. No association was found regardless of stratification by *HLA-DRB1* allele or anti-CCP antibody status – factors known to influence genetic association with RA susceptibility.

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Since our study population is African-American, our findings may be complicated by possible confounding due to population admixture. We cannot assess local admixture among this group of STAT4 SNPs given the absence of ancestry informative markers in this localized region; however, the lack of large differences in minor allele frequencies between HapMap populations reduces the likelihood of admixture confounding. See Table 2. This study is also smaller than some collections [1] and is subsequently less powered to detect a genetic association. Yet, our study is comparable (or even larger) in size than several studies that previously detected an association with these *STAT4* markers [2, 3, 5, 7]. Furthermore, when performing a power calculation using a similar odds ratio to the previous association [1], there is only a 10% chance of a false negative result (α=0.05).

To date, the association of rs7574865 with susceptibility to RA has been replicated in all populations studied, including those of Asian and European descent[1]. See Table 1. We are the first to explore this susceptibility marker in African-Americans and do not reproduce the finding. Given the limited region of the the gene that we examined, it is possible that another region of *STAT4* associates with RA susceptibility in populations of African ancestry. Regardless, the ethnic-based differential association of specific STAT4 markers with RA susceptibility suggests a need for additional study into the genetics of this entire gene in multiple populations.

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Table 1

Previously Published Genetic Associations with the T allele of rs7574865 and Susceptibility to Rheumatoid Arthritis

Studies report that they did not overlap patient enrollment with previous studies if examining the same population [5]. Both populations from North American were of European ancestry.

Population	Number of Patients	Number of Controls	P Value	Odds Ratio (95% Confidence Interval)	Study
African-American	723	660	0.23	1.22 (0.91–1.63)	Current
Columbia	274	421	0.01	1.36 (1.08–1.71)	[2]
Greece	311	344	2.0×10^{-4}	1.90 (1.46–2.50)	[3]
Japan	3567	2199	8.4×10^{-9}	1.27 (1.17–1.37)	[4]
Netherlands	920	924	0.03	1.45 (1.21–1.73)	[5]
North America	1013	1326	6.3×10^{-4}	1.28 (1.11–1.47)	[1]
North America	607	1309	8.3×10^{-5}	1.37 (1.17–1.60)	[1]
South Korea	1123	1008	6.5×10^{-3}	1.27 (1.11–1.45)	[6]
Spain	971	1370	1.0×10^{-3}	1.26 (1.09–1.45)	[5]
Spain	575	723	1.2×10^{-6}	1.59 (1.07–1.55)	[7]
Sweden	1529	881	0.02	1.18 (1.02–1.36)	[1]
Sweden	288	288	0.03	1.35 (1.03–1.77)	[5]
United Kingdom	3399	3024	1.4×10^{-4}	1.17 (1.08–1.28)	[8]

Table 2

Lack of Association of STAT4 SNPs with Susceptibility to Rheumatoid Arthritis

MAF – minor allele frequency. YRI – HapMap Yoruban Population. CEPH – HapMap Caucasian Population. Position reflects the genomic location in NCBI contig NT_005403.16. P values are for the comparison of MAF in African-American (Af-Am) RA patients compared to MAF Af-Am controls.

SNP	Minor Allele	Position	MAF Af-Am RA Patients	MAF Af-Am Controls	MAF - YRI	MAF - CEPH	χ^2 p value
rs11889341	T	42153159	0.141	0.133	0.161	0.208	0.70
rs10931481	G	42164269	0.364	0.352	0.383	0.325	0.24
rs7574865	T	42174050	0.149	0.133	0.158	0.208	0.23
rs8179673	C	42178758	0.157	0.142	0.143	0.213	0.29
rs10181656	G	42179296	0.158	0.142	0.158	0.217	0.25