A Genome-wide Admixture Scan for Ancestry-linked Genes Predisposing to Sarcoidosis in African Americans

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RATIONALE: A genetic predisposition to sarcoidosis, a multi-organ granulomatous inflammatory disease, has long been posited with genome-wide linkage and association studies having uncovered disease-associated variants. African Americans are more commonly affected by sarcoidosis, implying that African ancestry may influence disease pathogenesis.

METHODS: We conducted the first sarcoidosis genome-wide ancestry scan using a map of 1,384 highly ancestry informative single nucleotide polymorphisms genotyped on 2,060 self-identified African American subjects, consisting of 1,357 sarcoidosis cases and 703 unaffected controls drawn from two family studies and a case-control study. Using the admixture mapping program ADMIXMAP, we analyzed a subset of unrelated 1,026 cases and 316 controls.

RESULTS: We estimated African ancestry proportions to be 82.9% in the cases and 81.5% in the controls (p=0.03). The most significant ancestry association was at marker rs11966463 on chromosome 6p22.3 (ancestry association odds ratio (aOR)= 1.90; p=0.0002). Eight other chromosomal regions met our statistical criterion for suggestive ancestry association, including marker rs1462906 on chromosome 8p12 which was the most significant signal associated with European ancestry (aOR=0.65; p=0.002), and chromosomes 5p13 (aOR=1.46; p=0.005) and 5q31 (aOR=0.67; p=0.005), which correspond to two chromosome 5 regions we previously identified through sib pair linkage analyses. Sex-stratified analyses showed that sarcoidosis ancestry associations were often sex-specific. Analyses of chest radiographic phenotypes yielded the most significant ancestry association for Scadding stage IV cases to marker rs7919137 on chromosome 10p11.22 (aOR=0.27; p=2x10⁻⁵), a region not associated with disease susceptibility.

CONCLUSION: Using admixture mapping, we have identified several putative candidate loci for sarcoidosis that could lead to identification of novel risk variants for this disease.