GENOME-WIDE ANALYSIS OF POPULATION STRUCTURE IN A MULTI-NATIONAL ARAB RHEUMATOID ARTHRITIS CASE-CONTROL STUDY

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Background: Genetic and ancestral risk factors underlying Rheumatoid Arthritis (RA) susceptibility in Arab populations are largely unknown. Elucidating these factors provide insights for the practice of precision medicine in Arab populations.

Objectives: 1) Examine population structure in Arab RA cases/controls, 2) test for association of ancestral principal components with RA risk, and 3) test if inbreeding, relatedness and markers of RA severity differ between individuals from the Gulf (G) vs. the Levant (L).

Methods: The study Genetics of Rheumatoid Arthritis in some Arab States examines the genetics & clinical features of Arab RA patients from Jordan, KSA, Lebanon, Qatar, and the UAE. To date, 604 cases & 444 controls enrolled. In a pilot of a GWAS targeted for 500 cases/controls, DNA from 163 subjects from Jordan, Qatar & the UAE was genotyped using the Illumina Human Core Exome Array. PC analysis was performed in Eigenstrat. Identity-by-state clustering, pair-wise identity-by-descent and the inbreeding coefficient based on observed vs. expected homozygous genotypes were calculated using Plink. T-tests were done to assess difference in inbreeding & relatedness between cases of G and L ancestry. Association between 10 PC of ancestry & RA status & between self-reported ancestry & seropositivity were assessed using logistic regression adjusting for age and gender.

Results: After quality control, genotype data were available for 93 cases and 59 controls for 539,346 SNPs. PC analysis including reference panels from the HapMap2 populations revealed proximity to the CEU European population, with most G and L subjects in a line from the European to the Yoruban African population & greater heterogeneity observed in G samples. Pair-wise identity by state distance-based clustering identified one primary Arab population group comprising all individuals. PC3, the principal component that clearly separated subjects from the Levant from those from the Gulf, was associated with RA ($p=0.038$), suggesting that subjects with G ancestry captured by this PC might be at greater RA risk. The Arab population showed more inbreeding than outbred populations, but no significant difference in the inbreeding coefficient was found between L and G populations. While overall, the study population was not highly related, cases from the Levant showed greater inter-relatedness than cases from the Gulf ($p=0.011$). After adjusting for age and gender, more patients with G ancestry compared to L ancestry reported either ACPA or RF positivity ($p=0.021$).

Conclusions: An Arab RA case-control sample with Gulf and Levant sub-components clusters as one population proximal to European populations and exhibits subtle population structure. The sub-population of G ancestry is more genetically diverse than the L sub-population, and may contain genetic variation that contributes to increased risk of RA, and seropositivity. Imminent GWAS should clarify if risk alleles for RA in European populations contribute to disease risk and/or severity in some Arab groups.

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