Genomic Analysis on Subjects Exposed to Arsenic Identifies Genetic Risk Variants Associated with Bladder Cancer and Variants Under Recent Adaptive Selection

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INTRODUCTION AND OBJECTIVES: Only a small fraction of arsenic-exposed subjects is affected by malignant diseases. This suggests the existence of genetic risk factors influencing susceptibility to arseniasis and its consequences, such as bladder cancer (BC). Here, we evaluate this hypothesis by performing a case-control genome-wide association study (GWAS) for BC in subjects exposed to significantly elevated drinking-water arsenic levels in Northern Chile. Furthermore, since native people of this region have been exposed for thousands of years to arsenic present in underground water due to volcanic activity, they and their descendants might have adapted to this selective pressure. Therefore, we tested for adaptive selection since we also hypothesized that control subjects from this cohort might have inherited protective genetic variants.

METHODS: Demographic and clinical data were collected using a structured questionnaire and a blood sample was obtained. DNA samples were analyzed using Affymetrix Genome-Wide SNP Array 6.0. After filtering by missingness per individual and per marker allele frequency and Hardy Weinberg Equilibrium we obtained 788,705 SNPs to be analyzed. Estimates of adaptive (Darwinian) selection by comparing allele frequencies that are unusually high in one vs. two related populations were performed using the Population Branch Statistics (PBS) test.
RESULTS: Several associations reaching genome-wide significance were identified after adjusting for global ancestry, age, sex, smoking habit and occupational risk factors. Whereas some of these variants mapped in genes without a previous relation to BC and thus constitute novel candidates for BC carcinogenesis, others were located in genes related to BC. For instance, an intron variant associated with CTNNA2, a gene linked to BC after undergoing epigenetic modifications in response to arsenic exposure. We further found a variant close to CHL1, which has been associated with arsenic toxicity in cell lines and also to occurrence of BC by acting as a tumor suppressor. PBS test found several candidate variants for adaptive selection in the control group when compared to populations from Asia (CHB/JPT) and Central/ North America (Maya/Nahua). Several of these variants have also been associated with BC and arsenic-related processes, including two intron variants in CTNNA2.

CONCLUSIONS: The results of this study contribute to a better understanding of the genetic factors affecting BC in subjects exposed to arsenic and shed light into the recent evolutionary history of Native Americans. Candidate risk SNPs identified need to be further validated in independent analyses.

Source of Funding: Fondecyt Regular 1120987, Conicyt, Chile