The Turkish Journal of Occupational / Environmental Medicine and Safety

Vol:1, Issue Supplement 1 Web: http://www.turjoem.com ISSN : 2149-4711 Oral Presentation

S1. TOXICOGENOMICS OF HEALTH EFFECTS OF ARSENIC EXPOSURE

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Arsenic exposure to human is a major public health issue in many countries, increasing risk for a wide array of diseases, including cancer, cardiovascular and respiratory diseases. However, the molecular and genomic basis of arsenic toxicity in human is not well understood. Through a genome-wide association study of nearly 3,000 Bangladesh individuals we identified the *AS3MT* gene (arsenite methyltransferase; 10q24.32) variants to be associated with arsenic-related metabolism and toxicity phenotypes, confirming the basis for genetically-determined susceptible subgroups for arsenic toxicity in humans. Among a sample of 1,800 participants with genome-wide SNP and gene expression data, we evaluated differential gene expressions in relation to arsenic exposure. These analyses identified a large number of arsenic-associated genes from various biological pathways, revealing a number of molecular targets of arsenic exposure in humans. Finally, we evaluated the association between blood and urinary total arsenic concentrations, and epigenome-wide white blood cell DNA methylation in a subset of 400 individuals.We identified fourgenome-wide significant differentially methylated CpG sites (*PLA2G2C, SQSTM1*,*SLC4A4* and *IGH* genes) to be associated with urinary and blood total arsenic concentration, suggesting that epigenetic modifications may be an important pathway underlying arsenic toxicity. In conclusion, our integrated toxicogenomic analyses of arsenic exposure identified specific genetic susceptibility variants as well as arsenic-associated differentially methylated and expressed loci which may inform mechanisms underlying arsenic toxicity as well as potential pathways for future interventions. Details of these genomic determinants and molecular alterations related to arsenic toxicity will be presented at the conference.