DAMAGING FUNCTIONAL IMPACT OF SINGLE NUCLEOTIDE POLYMORPHISMS IN ARSENIC RESPONSIVE GENES ASSOCIATED WITH SKIN NEOPLASMS

Raphael D. Isokpehi, Barbara G. Graham, Udensi K. Udensi and Hari H.P. Cohly

RCMI Center for Environmental Health & Department of Biology, Jackson State University, Jackson Mississippi 39217, USA

Abstract: The Inorganic arsenic is classified by the United States Environmental Protection Agency (U.S. EPA) as a Group A carcinogen based on sufficient evidence of carcinogenicity in humans. It is the only known substance to cause cancer by inhalation and ingestion. Chronic oral exposure to inorganic arsenic can have adverse affects on tissues in the human body systems. In particular, arsenic-induced skin lesions are early warning markers for development of cancers in internal organs. The avalanche of genome sequences combined with genome-enabled datasets from high-throughput gene expression, genotyping, haplotyping and protein assays is making it possible to gain biological insights into previously unknown gene-toxicant interactions. Specifically, the functional effects of single nucleotide polymorphisms (SNPs) associated with arsenic responsive genes in different populations could provide biomarkers for an individual’s susceptibility to arsenic-induced diseases. Well-developed and sophisticated technologies exist to measure and analyze the presence of SNPs in populations. Furthermore, the dense distribution of SNPs across the genome makes them ideal markers for large-scale genome-wide association studies to discover genes in common complex diseases, such as cancer. There are at least 1,400 human genes curated in the Comparative Toxicogenomics Database with evidence for interaction with arsenicals. However, there has been no report of large-scale analysis of the SNPs associated with arsenic-interacting genes. An integrative computational analysis pipeline was developed to identify SNPs in arsenic-responsive genes with potential pathological effects to human health. The functional impact of 9,903 SNPs linked to 1,294 arsenic responsive genes was extracted from dbSNP. The functional impacts extracted from dbSNP were 174 frame shift, 5,281 missense, 133 nonsense and 4,315 synonymous SNPs. Furthermore, the assessment of potential damaging impact was performed using the Functional SNP (F-SNP) database which provides integrated information about the functional effects predicted and indicated at the splicing, transcriptional, translational, and post-translational level obtained from 16 bioinformatics tools and databases. A total of 473 SNPs (347 genes) with F-SNP score of 1 indicating damaging functional impact were identified. Further filtering of the gene list for curated interaction with arsenic trioxide, a dermatotoxic arsenical resulted in 138 genes including matrix metalloproteinase-9 (MMP9) secretion, an enzyme often secreted by cancer cells to help invade through the local extra-cellular matrix. The predicted functional impact in the Ensembl database for SNPs rs25650 and rs1805088 associated with MMP9 were stop gained and non-synonymous coding. In conclusion, the SNP modified genes may be used as models for studying gene variant-arsenic interactions and response to intervention.

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