Association of genetic variation in cystathionine-B-synthase and arsenic metabolism

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Resumen

Variation in individual susceptibility to arsenic-induced disease may be partially explained by genetic differences in arsenic metabolism. Mounting epidemiological evidence and in vitro studies suggest that methylated arsenic metabolites, particularly monomethylarsonic (MMA3), are more acutely toxic than inorganic arsenic; thus, MMA3 may be the primary toxic arsenic species. To test the role of genetic variation in arsenic metabolism, polymorphisms in genes involved in one-carbon metabolism [methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), cystathionine-B-synthase (CBS), thymidylate synthase (TYMS), dihydrofolate reductase (DHFR), serine hydroxymethyltransferase 1 (SHMT1)] and glutathione biosynthesis [glutathione-S-transferase omega 1 (GSTO1)] were examined in an arsenic-exposed population to determine their influence in urinary arsenic metabolite patterns. In 142 subjects in Cordoba Province, Argentina, variant genotypes for CBS rs234709 and rs4920037 SNPs compared with wild-type homozygotes were associated with 24% and 26% increases, respectively, in the mean proportion of arsenic excreted as monomethylarsonic acid (%MMA). This difference is within the range of differences in %MMA seen between people with arsenic-related disease and those without such disease in other studies. Small inverse associations with CBS rs234709 and rs4920037 variants were also found for the mean levels of the proportion of arsenic excreted as dimethylarsinous acid (%DMA). No other genetic associations were found. These findings are the first to suggest that CBS polymorphisms may influence arsenic metabolism in humans and susceptibility to arsenic-related disease.

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