Occupational exposures to LMW agents and irritants, and asthma: effect modification by glutathione S-transferase Z1 and ATP-binding cassette transporters polymorphisms.

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Occupational asthma (OA) is a good model to study the pathophysiology of asthma. Around 15% of adult asthma would be caused by occupational exposures, and more than 400 distinct agents have been identified as causing OA. The mechanisms of asthma induced by potential irritants, such as cleaning and chemical products, are unclear but could be related to oxidative/nitrosative stress. Our goal was to identify polymorphisms (SNPs) in genes involved in the response to oxidative/nitrosative stress interacting with occupational exposures known to have an effect on asthma, in the familial case-control French Epidemiological study of the Genetic and Environmental factors of Asthma (EGEA, https://egeanet.vjf.inserm.fr/).

A large set of genes (162 genes, 4979 SNPs) was selected according to a pathway-based strategy, that integrates biological knowledge related to occupational exposures. Occupational exposure to potential irritants was evaluated using the asthma job exposure matrix (Asthma JEM, http://cesp.vjf.inserm.fr/asthmajem/) and job-specific questionnaires for cleaners and healthcare workers. First, the marginal association between each SNP and current asthma, and the SNP by occupational exposures interactions were estimated separately using GEE logistic regression models, adjusted for age, sex and principal components for population ancestry in 1254 adults (45 years old, 38% with current asthma, 32% exposed). Then, the marginal genetic associations and the gene by environment interactions were simultaneously tested as proposed by Dai (Dai, AJE, 2012). 17 SNPs had Dai P values lower than 1x10^-3. Among these SNPs, one in ABCC1 (ATP-binding cassette, sub-family C (CFTR/MRP), member 1) and one in GSTZ1 (glutathione S-transferase Z1) showed suggestive evidence for interaction with occupational exposures (p=2x10^-4 and 7x10^-4 respectively). In addition, SNPs in PARK2 and NDUFS4 showed association signals with current asthma (p<1x10^-3). Although replication of our results is needed, it is interesting to note that GSTZ1 is a member of the GSTs super-family which encodes multifunctional enzymes important in the detoxification of electrophilic molecules by conjugation with glutathione, and that ABCC1 mediates ATP-dependent transport of glutathione and glutathione conjugates, and other xenobiotics.