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Genetic Effects on Exposure to Polycyclic Aromatic Hydrocarbons in a Korean Population

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A number of polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene, are carcinogenic and thought to contribute to the overall burden of human cancer (1). PAHs are ubiquitous in the environment and humans are exposed to them via multi-pathways, e.g. air or soil of urban areas, exposure to direct or indirect tobacco smoke, and ingestion of food or water polluted by combustion effluents (2-3). Because 1-hydroxypyrene (1-OHP) is a major metabolite of pyrene, one of the PAHs, urinary 1-OHP has been used as a PAH-exposure biomarker. To do proper biological monitoring of exposure to PAHs, individual differences in biotransformation of pyrene to 1-OHP should be considered. For example, if metabolic enzymes that are involved in bioproduction of 1-OHP are genetically polymorphic, their activities would be expected to vary between individuals: there are many reports that have examined the association between urinary 1-OHP and genetic polymorphisms in cytochrome P-450 (CYP) 1A1 and glutathione S-transferase (GST) M1 in small populations (4-11).

However, there are inconsistencies between the reports and it is not clear whether *CYP1A1* and *GSTM1* genetic polymorphisms affect biotransformation of urinary 1-OHP. On the other hand, CYP1B1 is an important contributor to activation of PAHs (12) and relationship between cancer and *CYP1B1* genetic polymorphism has been reported (13). In addition, *GSTM1* deficient people may have alternative metabolic pathways using GSTT1 (14). Thus, we investigated whether genetic polymorphisms of metabolic enzymes, which might be involved in metabolism of pyrene, affected urinary 1-OHP levels in 661 Koreans (male, 63 %; female, 37 % ; mean-age, 36 yrs ± 10.79 yrs) who were not occupationally exposed to PAHs. We obtained blood and urine species and information of multi-pathway-exposure to PAHs in the subjects using questionnaires. We analyzed urinary 1-OHP using a reverse phase HPLC method (15), and urinary creatinine using an ion pair reversed HPLC method (16). Genomic DNA was isolated from the buffy coat fraction of each blood sample by DNA isolation kit provided by Promega (Madison, Wisconsin). Genetic polymorphisms of *CYP1A1* are based on

substitutions of codon 461 in exon 7 (*Thr*461*Asn*: ACC (Thr) → AAC (Asn)) and 462 (*Ile*462*Val* : ATT (Ile) → GTT (Val)) (4). The CYP1B1 genotype was determined according to 7 SNPs, i.e. CYP1B1-*Arg48Gly, -Ala119Ser, -Asp374Asn, -Glu387Lys, -Leu432Val, -Asn453Ser, and - Arg469T* (17). *GSTM1* or *GST1*genotypee were determined by gene presence (14). Genotyping of the CYP1A1 and the 1B1 was achieved using single base extension method.

As results, urinary 1-OHP was detected in 76 % of the subjects (range, 0.001-3.8 μg/L; geometric mean, 0.0724 μg/L; geometric standard deviation, 0.0003). Urinary 1-OHP was associated with "sampling area (city)", " number of cigarette smoked", "time spent outdoor", and "consumption of fried food" ($p < 0.05$). After adjustment for age, sex, and body mass index, and the above environmental factors, *GSTT1* genotype affected urinary 1-OHP: i.e. the *GSTT1* present subjects showed approx. 1.5 fold higher urinary 1-OHP level than the *GSTT1* null subjects ($p < 0.05$). In a case of subjects who were also *GSTM1* null, this trend became stronger, i.e. the *GSTT1* present subjects showed approx. 2 fold higher urinary 1-OHP levels than the *GSTT1* null subjects ($p < 0.01$). However, genetic polymorphism of CYP1A1, CYP1B1, and GSTM1 alone did not affect urinary 1-OHP levels. This study suggests the *GSTT1* genotype should be considered for proper biological monitoring of exposure to PAHs with urinary 1-OHP levels and may be considered to be a genetic risk factor for PAH-related toxicity or cancer.

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