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Human Cytochrome P450IIE1 Gene: *Dra*I Polymorphism and Susceptibility to Cancer

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**Department of Cancer Chemotherapy and Prevention, †Department of Internal Medicine and ‡Department of Clinical Cancer Chemotherapy, The Research Institute for Tuberculosis and Cancer, Tohoku University, Sendai 980*

UEMATSU, F., KIKUCHI, H., MOTOMIYA, M., ABE, T., ISHIOKA, C., KANAMARU, R., SAGAMI, I. and WATANABE, M. *Human Cytochrome P450IIE1 Gene: DraI Polymorphism and Susceptibility to Cancer.* Tohoku J. Exp. Med., 1992, **168** (2), 113-117 —— Human cytochrome P450IIE1 (CYP2E) is involved in the metabolic activation of procarcinogens such as N-nitrosodimethylamine, benzene and ethyl carbamate. We screened DNA from 28 individuals for restriction fragment length polymorphisms (RFLPs) is the human P450IIE1 gene and detected an RFLP for the restriction endonuclease *Dra*I. The distribution of the genotypes of this polymorphism among lung cancer patients ($n=74$) differed from that among controls ($n=73$) with statistical significance of $p<0.05$. In addition, the distribution among patients with cancers of the digestive system ($n=38$) was also different from that among controls. Our findings indicate an association between the *Dra*I polymorphism of the IIE1 gene and susceptibility to cancers of the lung and the digestive system. ———— human cytochrome P450IIE1 gene; *Dra*I polymorphism; susceptibility to cancer; lung cancer; cancers of the digestive system

Cytochrome P450 (P450) enzymes are components of the microsomal multisubstrate monooxygenase system responsible for the oxidative metabolism of numerous endogenous and exogenous compounds (Gonzalez 1989). P450-mediated reactions often result in the production of substances active in tumor initiation and/or promotion stages. Human cytochrome P450IIE1 (CYP2E) is involved in the oxidation of carcinogens such as N-nitrosodimethylamine, benzene, styrene, carbon tetrachloride, trichloroethane, ethylene dichloride, ethyl carbamate, vinyl carbamate and trichloroethylene (Guengerich et al. 1991). Differences in the genotypes or phenotypes of P450IIE1 may therefore be responsible for interindividual variations in susceptibility to cancers caused by these chemicals. Protein levels and catalytic activities of P450IIE1 can vary widely among individuals (Wrighton et al. 1986; Yoo et al. 1988), although the genetic

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basis of such differences is unknown.

We screened DNA from 28 individuals for restriction fragment length polymorphisms (RFLPs) of the P450IIE1 gene and detected an RFLP for the restriction endonuclease *Dra*I (Uematsu et al. 1991a). To investigate the association between the genotypes of P450IIE1 and susceptibility to cancer, we have examined the distribution of the genotypes of the *Dra*I RFLP in cancer patients and controls. We report here an association between *Dra*I polymorphism of the P450IIE1 gene and susceptibility to cancers of the digestive system as well as lung cancer.

Subjects and Methods

The study population consisted of 73 controls and 112 cancer patients, as indicated in Table 1. Controls were chosen from the population without known history of cancer. Cancer patients were divided into two groups: Group A consisted of 74 patients with lung cancer; Group B consisted of 38 patients with cancers of the digestive system, as shown in

Table 1. *Distribution of the genotypes of the DraI polymorphism at P450IIE1 gene among various populations*

Populations	Genotypes			Total
	CC	CD	DD	
	(%)	(%)	(%)	(%)
Control	10 (13.7)	21 (28.8)	42 (57.5)	73 (100)
Lung cancer	2 (2.7)	34 (45.9)	38 (51.4)	74 (100)
Squamous cell carcinoma	0	10	13	23
Small cell carcinoma	0	9	7	10
Large cell carcinoma	0	5	5	10
Adenocarcinoma	2	10	13	25
Cancers of the digestive system	3 (7.9)	21 (55.3)	14 (36.8)	38 (100)
Total cancers	5 (4.5)	55 (49.1)	52 (46.4)	112 (100)

Table 2. *Site of cancers of the digestive system*

	Number of patients
Stomach	11
Colon and rectum	9
Esophagus	9
Liver (HCC)	3
Pancreas	2
Gallbladder	2
Bile duct	1
Parotid gland	1

Table 2. All the patients had definite diagnosis proven by histology or cytology from samples obtained at biopsy. Southern blot analysis was done as previously described (Uematsu et al. 1991b) using the cDNA probe λhPD4 (Komori et al. 1989).

Results and Discussion

*Dra*I detected two constant bands at 2.3 kb and 1.3 kb and a two-allele polymorphism with bands at 4.7 kb (C) or 4.1 kb (D) (Fig. 1). We made a restriction map of the P450IIE1 gene for *Dra*I on the basis of the published genomic sequence data (Umeno et al. 1988) and located the RFLP site to intron 6 of the gene (Fig. 2). The population was divided into three genotypes, namely, CC, CD and DD. Table 1 shows the distribution of the three genotypes of the *Dra*I polymorphism of the P450IIE1 gene in each group. In the control group, the distribution was in Hardy-Weinberg equilibrium, gene frequencies being 0.28 for allele C and 0.72 for allele D. The distribution among lung cancer patients differed from that among controls with statistical significance of $p<0.05$ ($\chi^2=8.06$

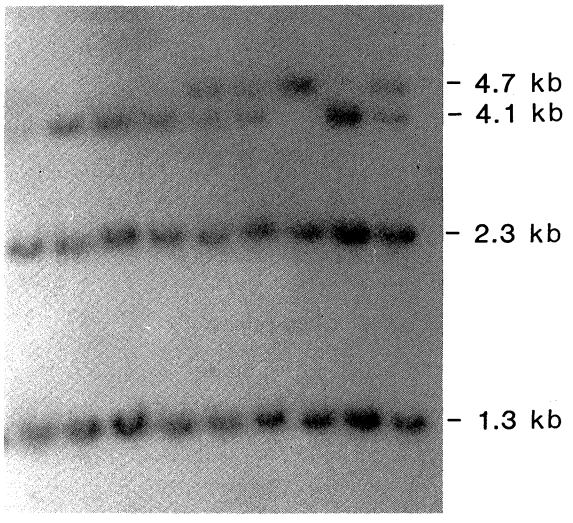

Fig. 1. *Dra*I polymorphism of the human P450IIE1 gene.

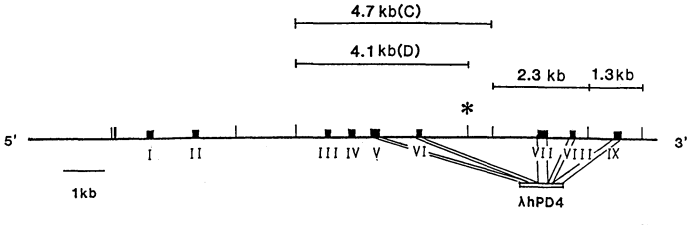

Fig. 2. Map of *Dra*I cleavage sites in the human P450IIE1 gene. Solid boxes indicate exons. The symbol * in intron 6 denotes the RFLP site. Fig. 1 in our previous report (Uematsu et al. 1991b) should be corrected.

with 2 degrees of freedom). In addition, the distribution among patients with cancers of the digestive system was also different from that among controls ($\chi^2 = 7.48$ with 2 degrees of freedom). These findings suggest that the *Dra*I polymorphism of the P450IIE1 gene is associated with susceptibility to cancers both of he lung and of the digestive system.

The frequency of the heterozygote (CD) in the two groups of cancer patients was higher than that in the control group, while the frequencies of the homozygotes (CC and DD) were lower. Therefore, it would be difficult to conclude at present that either of the two alleles is associated with high susceptibility. The polymorphism is caused by the presence or absence of a *Dra*I site in intron 6 of the gene (Fig. 2), and this mutation, as such, may not affect the gene expression. One possible explanation for the association indicated here would be linkage disequilibrium between the RFLP site and another mutation in the same gene involved in the structure or regulation of the gene products. Another possibility would be linkage disequilibrium with nearby tumor-related genes, such as an oncogene, tumor suppressor gene, or the structural or regulatory genes for other P450s. It would be important to investigate the relation between this polymorphism and the expression of the P450IIE1 gene. This might help to elucidate the role which P450IIE1 plays in human carcinogenesis.

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