

Research

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Glutathione S-Transferase, N-Acetyltransferase, Cytochrome P450 Polymorphisms in Patients with Basal Cell Carcinoma

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Abstract

Background: GST, NAT and CYP polymorphisms have been shown to influence the level of oxidative DNA damage. Also, there is a consensus that ROS play part in the epidermal carcinogenesis.

Aim: Our purpose was to investigate the GST, NAT and CYP polymorphism in patients with skin cancer.

Material and Methods: Ninety seven subjects, 34 women and 63 men, with basal cell carcinoma, and 117 healthy control subjects, 52 women and 65 men, were enrolled in the study. The polymorphisms of GSTT1, GSTM1, GSTP, NAT2*5A, NAT2*6A, NAT2*7A/B, NAT2*14A, CYP2C9*2, CYP2C9*3, CYP2C19*2, CYP2C19*3 were performed by real time PCR.

Results: Patients (51.5%) had a higher prevalence of the GSTM1 null genotype than the control group (33.3%) and we found a 2.12 fold increased risk of skin cancer in individuals with the GSTM1 null genotype when compared to the control group. In the patient group, the frequency of the NAT2*6A heterozygous genotype was higher in comparison with that of the control group and this increase was statistically significant ($p=0,004$ OR=3,70; 95% CI: 1,53-8,95). Patients with the NAT2*7A/B heterozygous genotype had a higher risk of skin cancer compared with individuals with the NAT2*7A/B wild genotype ($p=0,001$ OR = 0,17; 95% CI = 0,06-0,048). CYP2C9*3 heterozygous genotype was higher in patient group ($p=0.015$ OR=2.02; 95% CI: 1.14-3.57). Compared with the CYP2C19*2 wild genotype, CYP2C19*2 heterozygous genotype was associated with more than 2.8 fold increased risk of skin cancer ($p= 0.001$, 95% CI: 1.50-5.26). These varying enzyme activities are supposed to influence the individual metabolism of carcinogenic aromatic amines, thereby modifying the susceptibility to certain cancers.

Conclusion: In our study, the results from the patient group suggest that there may be a relation between GST, NAT and CYP gene polymorphisms and basal cell carcinoma.

Introduction

A large supergene family located at least on seven chromosomes encode the Glutathione S-transferase (GST) enzymes. Approxima-

tely 16 genes encode the enzymes in the tissue cytosoles and products of the six genes of this supergene family are expressed in membranes [1]. GST enzymes catalyse the conju-

gation of glutathione (GSH) to a variety of endogenous and exogenous electrophilic substrates including reactive oxygen species (ROS) and polycyclic aromatic hydrocarbons and play an important part in their detoxification process [2]. Many GST genes show well-defined polymorphisms and GST mu (GSTM), theta (GSTT) and pi (GSTP) class genes have been on the focus for a while [3]. Human arylamine N- acetyltransferases (NAT) are known to exist as two isoenzymes, NAT1 and NAT2, with different though overlapping substrate specificity. NAT are the enzymes present in the cells of most mammalian species. Two different genes code these enzymes: NAT1 and NAT2. Gene NAT1 is expressed in the cells of the majority of tissues and organs, whereas gene NAT2 only in the liver and intestine. Acetylation polymorphism is an important step in the biotransformation of many drugs and other arylamine xenobiotics. One of the well-described and genetically determined polymorphic drug metabolism is the NAT2 acetylation polymorphism [4]. Acetylation polymorphism and resultant division into the fast and free acetylator is caused by the occurrence of wild allele NAT2 and its mutant forms. A given person shows the fast acetylation phenotype if at least one allele NAT2 is wild. The presence of mutation in both alleles NAT2 is manifested by the free acetylation phenotype (slow acetylator) [5]. Many members of the cytochrome P450 (CYP) family are responsible for the metabolism of endogenous substrates, dietary compounds and environmental toxins. Additionally, CYP are known to be involved in the metabolism of commonly used medication. Two known allelic variants CYP2C9*2 (C430T) and CYP2C9*3 (A1075C) differ from the wild type CYP2C9*1 by a single nucleotide substitution. Literature indicates that both allelic variants are associated with an impaired enzyme activity towards the respective substrate [6, 7].

GST, NAT and CYP polymorphisms have been shown to influence the level of oxidative DNA damage [2, 8, 9, 10]. Also, there is a consensus that ROS play part in the epidermal carcinogenesis [2]. These varying enzyme activities are supposed to influence the individual metabolism of carcinogenic aromatic amines, thereby modifying the susceptibility to certain cancers. Therefore GST, NAT and CYP enzymes take part in the defence mecha-

nisms against skin cancers and polymorphism of these genes may influence the susceptibility of skin carcinogenesis in humans [11]. Human GST, CYP and NAT, which are encoded by the polymorphic GST, CYP and NAT genes respectively, have been shown to have wide interindividual variations in metabolic capacity and may be the potential modifiers of an individual's susceptibility to certain types of cancers [12,13,14]. Our purpose was to investigate the GST, NAT and CYP polymorphism in patients with basal cell carcinoma.

Materials and Methods

Subjects: Ninety seven subjects, 34 women and 63 men, with skin cancer, and 117 healthy control subjects (52 women and 65 men) were enrolled in the study. The mean (\pm SD) age was 60.00 \pm 13.64 in patients, and 49.35 \pm 13.14 in control subjects (Table 1).

The skin cancer group consisted of 97 patients who were diagnosed as basal cell carcinoma (BCC). All the diagnoses of BCC were confirmed by biopsies. This was a hospital-based case-control study conducted at the University of Mersin Hospital. The patients and controls were from the same geographic region and of the same ethnic origin. Also, cases and controls were unrelated. Control subjects were selected among people who had no history of cardiovascular disease, cancer, chronic degenerative neurological disease, chronic obstructive pulmonary disease, autoimmune diseases and hepatitis. This study was approved by the Ethics Committee of Mersin University, School of Medicine.

DNA extraction and genotyping of GST, NAT2, CYP2C9 and CYP2C19: Blood was collected in EDTA-containing tubes and DNA was extracted from the leucocytes by high pure template preparation kit (Roche Diagnostics, GmbH, Mannheim, Germany). The polymorphisms of GSTT1, GSTM1 and GSTP1 were performed by real time PCR with LightCycler instrument using hybridization probes in combination with the LightCycler DNA Master Hybridization Probes Kit

Table 1. Characteristics of the Study Population

	Patients (n: 97)	Controls (n: 117)
Age (years)	60.00 \pm 13.64	49.35 \pm 13.14
Sex		
Male	63 (64.95)	65 (55.6)
Female	34 (35.05)	52 (44.4)

(Roche Diagnostics). Both the PCR primers and hybridization probes were synthesized by TIB MOLBIOL (Berlin, Germany). NAT2*5A, NAT2*6A, NAT2*7A/B, NAT2*14A, CYP2C9*2, CYP2C9*3, CYP2C19*2, CYP2C19*3 alleles were detected by using Light Cycler- NAT2, CYP2C9 and CYP2C19 mutation detection kits by real time PCR with Light Cycler instrument (Roche diagnostics, GmbH, Mannheim, Germany; catalog no: 3113914).

Statistical analysis: Patient ages were compared with Student's t test. All values are represented as mean and standard deviation (SD). Chi-square or (Fisher's F) exact tests were used to evaluate the distribution of the GST, NAT2, CYP2C9 and CYP2C19 genotypes among patients and control subjects. The association between GST, NAT2, CYP2C9 and CYP2C19 genotypes and patients was estimated by computing odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression analyses. All statistical calculations were performed using the SPSS software package version (11.0 for Windows SPSS Inc., Chicago, IL). All tests were conducted at the $p < 0.05$ level of significance.

Results

In the patient group, the frequency of the NAT2*6A heterozygous genotype was higher in comparison with that of the control group and this increase was significant ($p = 0.004$, OR = 3.70; 95% CI: 1.53-8.95). Patients with the NAT2*7A/B heterozygous genotype had a lower risk of skin cancer compared with individuals with the NAT2*7A/B wild genotype ($p = 0.001$, OR = 0.17; 95% CI: 0.06-0.48). NAT2*5A, NAT2*14A polymorphisms were not significant risk factors for skin cancer. NAT2*5A, NAT2*6A and NAT2*14A mutant genotypes were related with 2.97, 4.15 and 1.5 fold increased risk but this was not statistically significant ($p > 0.05$) (Table 2).

Patients (51.5%) had a higher prevalence of the GSTM1 null genotype than the control group (33.3%) and we found a 2.12 fold increased risk of skin cancer in individuals with the GSTM1 null genotype ($p = 0.008$, 95% CI: 1.22-3.70) when compared to control group but this increase was not significant. Distributions of GST T1 present and null genotypes in patient and control group are 66%, 34%; 71.8%, 28.2% respectively. GST T1 null ge-

notype were not significant risk factors for skin cancer ($p = 0.376$). GSTP1 homozygous Val/Val genotype had a 0.40 fold increased risk of skin cancer when compared to control group ($p = 0.03$, 95% CI: 0.17-0.92), but this increase was not important (Table 2).

CYP2C9*2 was not significant ($p = 0.376$), but CYP2C9*3 heterozygous genotype higher in comparison with that of the control group and this increase was significant ($p = 0.015$, OR = 2.02; 95% CI: 1.14-3.57). Compared with the CYP2C19*2 wild genotype, CYP2C19*2 heterozygous genotype was associated with more than 2.8 fold increased risk of skin cancer ($p = 0.001$, 95% CI: 1.50-5.26). All of patient and control group have CYP2C19*3 wild genotype (Table 2).

Discussion

It is an established fact that ultraviolet (UV) light plays a major role in the development of cutaneous malignancies [15]. UV radiation can damage cell DNA directly or indirectly [16]. Energy carried by the photons of ultraviolet radiation can be absorbed by other chromophores than DNA. These chromophores then transfer the absorbed energy to DNA or molecular oxygen. The latter way leads to reactive oxygen species (ROS) which are also capable of damaging cellular DNA. This indirect way is thought to play an important role in UVA carcinogenesis [17]. UVA is dependent on molecular oxygen for its biological activities [16]. An induction of anti-oxygen free radical mechanisms in skin cancer tissues has also been shown [18]. So, a variation, especially a homozygote deletion of the GST gene, and also NAT and CYP polymorphisms can lead to an increased risk of skin carcinogenesis [8, 9, 10, 19].

GSTM1 null genotype and GSTP1 homozygous 105 Ile/Ile and Val/Val genotype prevalences were higher in our patients. Kanetsky et al observed that absence of both GSTM1 and GSTT1 were associated with increased risk for melanoma [20]. The relevance of GSTP1 to skin cancer risk is also shown in studies on mice lacking pi class GST genes [18]. Ramsay et al have previously shown that the frequency of GSTM1 null genotype is increased in a cohort of nontransplant patients with BCC and SCC in accordance with

Table 2. GST, NAT2, CYP2C9 and CYP2C19 Genotypes and the Risk of Developing Skin Cancer
 (*From conditional logistic regression. OR, Odds ratio; CI, confidence interval.
 n, number of sample. **Odds ratio can not be calculated)

		Skin cancer (n=97) N (%)	Control (n=97) N (%)	P	OR (%95 CI)*	Lower	Upper
GST M1				0.008			
	Present	47 (48.5)	78 (66.7)		1 (reference)		
	Null	50 (51.5)	39 (33.3)		2.12	1.223	3.701
GST T1				0.376			
	Present	64 (66)	84 (71.8)		1 (reference)		
	Null	33 (34)	33 (28.2)		1.31	0.733	2.349
GST P1							
	Ile/Ile	41 (42.3)	46 (39.3)	0.034	1 (reference)		
	Ile/Val	46 (47.4)	43 (36.8)	0.545	1.20	0.664	2.169
	Val/Val	10 (10.3)	28 (23.9)	0.032	0.40	0.174	0.924
NAT2*5A	Wild	37 (38.1)	51 (43.6)	0.091	1 (reference)		
	Heterozygous	45 (46.4)	58 (49.6)	0.998	0.99	0.432	2.310
	Mutant	15 (15.5)	8 (6.80)	0.081	2.97	0.875	10.08
NAT2*6A	Wild	52 (53.6)	66 (56.4)	0.013	1 (reference)		
	Heterozygous	39 (40.2)	44 (37.6)	0.004	3.70	1.537	8.950
	Mutant	6 (6.20)	7 (6.0)	0.068	4.15	0.924	18.71
NAT2*14A	Wild	66 (68.0)	66 (56.4)	0.874	1 (reference)		
	Heterozygous	30 (30.9)	50 (42.7)	0.644	123	0.507	2.995
	Mutant	1 (1.0)	1 (0.90)	0.776	1.50	0.089	25.53
NAT2*7A/B	Wild	75 (77.3)	70 (59,8)	0.003	1 (reference)		
	Heterozygous	21 (21.6)	44 (37,6)	0.001	0.17	0.060	0.483
	Mutant	1 (1.0)	3 (2.60)	0.081	0.10	0.009	1.316
CYP2C9*2				0.092			
	Wild	72 (80,3)	98 (78.8)		1 (reference)		
	Heterozygous	25 (19.7)	19 (21.2)		1.79	0.917	3.499
CYP2C9*3				0.015			
	Wild	54 (74.2)	84 (83.8)		1 (reference)		
	Heterozygous	43 (25.8)	33 (16.2)		2.02	1.149	3.577
CYP2C19*2				0.001			
	Wild	60 (61.9)	96 (82.1)		1 (reference)		
	Heterozygous	37 (38.1)	21 (17.9)		2.81	1.509	5.267
CYP2C19*3	Wild **	97 (100)	117 (100)	-	-	-	-

our study [21]. Ramachandran et al found that GST-M1 AB, and GSTT1 null genotypes were significantly associated with BCC [14]. Shimizu et al indicated the expression of placental-type glutathione S-transferase (GST-

pi) in actinic keratosis and Bowen's disease [22].

The relationship between NAT and CYP polymorphisms and incidence, clinicopathologic parameters and prognosis had been studied

in many cancers such as cholangiosarcoma, hepatic, gastric, lung, urinary, breast, prostate, and testicular tumors [12, 23, 24, 25, 26, 27, 28, 29]. *Katoh* et al suggested that the NAT1*10 allele could be a genetic determinant of oral SCC among Japanese people [30]. However, *Fronhoffs* et al found no significant association between the risk of SCC of head and neck and any of the NAT1 alleles in a caucasian population [31]. We observed that the presence of the NAT2*6A and 7A/B heterozygous alleles significantly increased the risk of skin cancer. There are numerous occupational and environmental carcinogens, such as arsenic and aromatic hydrocarbons, that predispose to SCC and BCC [32,33]. Exposure to insecticides and herbicides have also been associated with SCC [34]. Human metabolism of these carcinogenic compounds is complex and involves acetylation as an important pathway in order to mutate DNA and initiate carcinogenesis (5). In humans, two N-acetyltransferases (NAT1 and NAT2) have been identified, which catalyze detoxification and activation of various amines by N-acetylation and O-acetylation, respectively. Both NAT1 and NAT2 genes are known to be polymorphic in humans, corresponding to slow and rapid acetylator phenotypes. These varying enzyme activities are supposed to influence the individual metabolism of carcinogenic aromatic amines, thereby modifying the susceptibility to certain cancers [31]. CYP2C9*3 and CYP2C19*2 heterozygous genotypes were higher in our patients. This polymorphisms may lead to BCC because of imbalance of metabolism of endogenous substrates, dietary compounds, drugs and environmental toxins.

In our study, the results from the patient group suggest that there may be a relation between GST, NAT and CYP gene polymorphisms and skin cancer. But further studies on larger groups are needed to determine the prevalence of GST NAT and CYP polymorphisms in patients with BCC and to determine whether they constitute a major risk factor in the development of skin cancers.

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