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Effect of genotype on steady-state *CYP1A1* gene expression in human peripheral lymphocytes

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Abstract

We have analyzed the steady-state levels of cytochrome P-450 1A1 (CYP1A1) mRNA in peripheral blood lymphocytes of 177 individuals with various *CYP1A1* genotypes using a quantitative reverse transcriptase–polymerase chain reaction technique that makes use of a homologous internal standard for accurate quantitation. We found no effects of ethnicity, age, or smoking status on *CYP1A1* gene expression in this population. We did see a significant 2-fold increase in the mean level of CYP1A1 mRNA in women compared with men for both Caucasians and African Americans. We observed no effect of the African American-specific polymorphism (*CYP1A1*3*) on expression of the gene. However, we found a significant 3-fold decrease in expression associated with the homozygous *Msp*I restriction fragment length polymorphism (*CYP1A1*2A/*2A*).

Keywords: Polymorphisms; Cytochrome P-450; Gene induction; mRNA; African American; RT–PCR

1. Introduction

The *CYP1A1* gene is inducible by exposure to agents such as dioxin or aromatic hydrocarbons, and a very wide range of inducibility in human peripheral blood lymphocytes has always been seen [1]. The molecular basis for these differences in *CYP1A1* inducibility has been investigated, and it does not appear to be related to genotype at the *CYP1A1* locus. A recent report showed an effect of an *Ahr* gene polymorphism on *CYP1A1* inducibility [2], but this might not explain the total variation commonly observed. In contrast to inducibility, steady-state levels of *CYP1A1* gene expression are difficult to determine in PBL, because in the absence of mitogen stimulation and gene induction such expression is very low.

The phenotypic consequences of genetic polymorphisms in *CYP1A1* have been studied with diverse results. *In vitro* experiments detected no effects on AHH enzymatic activity or gene expression for any of the three variant *CYP1A1* alleles (**2A*, *2B*, or *3*) [3]. We previously evaluated the effects of the *Msp*I and exon 7 polymorphisms in human lymphocytes on AHH activity, and found an increased level of 7-ethoxyresorufin *O*-deethylation (EROD) activity associated with the exon 7 mutation (which substitutes valine for isoleucine in the active site) [4]. We found no effects associated with the *Msp*I RFLP, which is located upstream of the regulatory domain. To date, no studies have been published on the functional consequences of the **3* African American-specific RFLP.

In previous work, we found that the African-specific RFLP in intron 7, upstream of the poly(A) site, was associated with a small but significant elevation of risk for lung adenocarcinoma, but not for lung cancer overall [5,6]. This association between adenocarcinoma of the lung in African Americans and heterozygosity for the *CYP1A1*3* allele was not confirmed by another study [7]. We also found a surprising association of the genotype *CYP1A1*2A/*2A*—the homozygous *Msp*I RFLP—with breast cancer in African American but not in Caucasian women [8].

In an investigation into the possible functional role of the *CYP1A1*3* allele, we hypothesized that this polymorphism, found just upstream of the poly(A) site, outside of the coding region, might have an effect on message stability,

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Abbreviations: AHH, aromatic hydrocarbon hydroxylase; CYP1A1, cytochrome P-450 1A1; HIS, homologous internal standard; PBL, peripheral blood lymphocytes; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT–PCR, reverse transcriptase–polymerase chain reaction; SNP, single nucleotide polymorphism.

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rather than on gene induction. Therefore, we decided to investigate the basal, steady-state levels of mRNA in people of African descent (as well as Caucasians) as a function of the *CYP1A1* genotype. To be able to detect the low level of steady-state CYP1A1 transcripts in non-stimulated PBL in a quantitative manner, we used the HIS method of RT–PCR [9], which uses a homologous gene from another species as an internal standard.

2. Materials and methods

We enrolled 254 healthy subject volunteers from the New York metropolitan area, as part of a community outreach program aimed at enrolling healthy volunteers for a survey of genotype frequency among Caucasians and African Americans. From Mali, subjects were recruited from among employees of the University of Bamako. Women taking oral contraceptives at the time of the interview were excluded from the study. All subjects signed a written informed consent form before enrollment, completed a self-administered brief standardized questionnaire on demographic and anthropometric data, smoking and drinking habits, and current medication, and donated 10 cc of peripheral blood. Peripheral blood lymphocytes were prepared by standard methods [4] and stored frozen until used.

Gene expression was measured in lymphocytes of 177 subjects; the remaining subjects were excluded either because the samples did not contain enough material for genotyping or because a complete genotype was not available.

For analysis of the *CYP1A1* genotypes, DNA was extracted from PBL and amplified by PCR before digestion with *Msp*I, as previously described [6], to allow for simultaneous detection of both the *Msp*I and **3* RFLPs. The ILE/VAL exon 7 polymorphism was determined by allele-specific PCR as previously described [6,10]. This method does not distinguish between the **2B* and **4* alleles, which result from SNPs only 2 bp apart [11]. The presence of the exon 7 SNP in the absence of *Msp*I RFLP was, therefore, scored as the **4* allele.

Total cellular RNA was isolated directly from PBL using a rapid guanidinium–phenol extraction method as previously described [4]. For analysis of steady-state CYP1A1 mRNA in non-cultured, non-stimulated PBL, we used the HIS technique described previously [9,12]. Briefly, the method uses a homologous gene from a non-human species as a quantitative standard that is added to all tubes in a known quantity. In this case, we used 1 ng of cloned mouse CYP1A1 plasmid (ATCC No. 63006) as the standard. cDNA synthesis was initiated by the addition of 1 μg of the antisense primer 5′-CCGGATGTGGCCCTTCTCA-3′ to a reaction mixture containing dNTPs, 10 units AMV reverse transcriptase (US Biochemicals), and the mixture was incubated for 2 hr at 42°. The sense primer 5′-CCAATGTCATCTGTGCCAT-3′ was end-labeled by reaction with T4 polynucleotide kinase and [^{32}P]ATP. The PCR reaction was initiated by adding 500 ng of the above end-labeled sense primer, 400 μg of dNTPs, and 2 units of Ampli*taq* (Perkin Elmer Cetus) to the cDNA product. The PCR conditions were: denaturation at 94° for 1 min, annealing at 62° for 1 min, and extension at 72° for 1 min for 30 cycles. These conditions and primers result in amplification of both the human and mouse *CYP1A1* gene with equal efficiency. PCR products were digested with *Bst*NI (which cuts only the mouse product) before electrophoresis. The undigested human band at 255 bp and the digested mouse band at 164 bp were cut from the gel and counted by liquid scintillation. All experiments were run in triplicate with coefficients of variation between replicates less than 10%. Most replicates were run together; however, several samples were specifically (and blindly) retested to determine reproducibility of the assay, which proved to be within 12%. The ratios of counts from human to mouse bands for each sample were normalized with respect to the ratio for a standard control (MCF-7 mRNA) run on each gel, to give the relative quantitation of CYP1A1 mRNA in each sample [11,12]. Values presented are percents of this standard ratio times 100. Representative raw data and calculations are shown in Table 1.

Table 1
Data analysis for CYPlAl mRNA in a frozen human blood sample by HIS RT–PCR

Sample	Human band (cpm)	Mouse band (cpm)	Ratio (H/M)	Normalized ratio × 100
MCF-7	10,300	18,199	0.54	100
3032	992	14,080	0.066	12
3032	1,514	25,194	0.060	12
3032	2,119	26,039	0.081	15
Mean ± SEM				13 ± 1

MCF-7 was the positive control run with each gel. The three data points are for sample 3032 run on the same gel. The normalized ratio was obtained by dividing each sample ratio (human/mouse cpm) by that of the positive control × 100.

Data were log transformed when necessary to obtain normal distribution. We applied the unpaired *t*-test for comparison of the mean values of gene expression between two groups. Multivariate analysis using the general linear model (GLM) procedure, which is an extension of the ANOVA analysis, was performed for analysis of the simultaneous effects of several factors (age, gender, race, smoking, gene polymorphisms) on gene expression, setting CYP1A1 mRNA values as the dependent variable, and sex, age, and genotype as independent variables.

3. Results

The characteristics of the population included in this study are shown in Table 2. The population consisted of 57 African Americans, 58 Africans, and 62 Caucasians. There

Table 2
Study population characteristics

Total number of subjects	177
European Americans	62
African Americans	57
Africans	58
Women	96
Men	80
Mean age (±SD)	39.1 ± 13
Median age	39
Smokers	80
Non-smokers	96

were 96 women and 80 men in the study. Gender was not available for one subject. Data on smoking (ever/never) were available for all subjects. We also obtained information on cigarettes smoked/day and lifetime smoking (pack-years) for most of the subjects.

As illustrated in Table 3, there was no difference in the mean steady-state level of lymphocyte CYP1A1 mRNA between Whites and Blacks. African Americans and Africans also showed no differences between them as groups or between subgroups stratified by sex, age, or smoking status. No effect of age was seen for the whole population ($R^2 = 0.014$) or for any ethnic group. Neither smoking status (ever/never) nor cigarettes/day, nor packyears smoked, had any effect on the CYP1A1 mRNA level in unstimulated noncultured lymphocytes. The lack of effect of smoking was seen in the whole population and in all subgroups. A significant difference with sex was observed, with women showing an approximately 2-fold higher average level of expression than men.

There were no significant differences in steady-state levels of CYP1A1 mRNA in PBL between individuals of any heterozygous genotype compared with the wild-type *CYP1A1*1/*1*. The results for people of African descent who were heterozygous for the African-specific **3* allele suggest that this polymorphism has no effect on steady-state CYP1A1 mRNA levels, at least in the heterozygous

Table 3
Influence of demographic factors and smoking on *CYP1A1* gene expression

Black[a]	62.2 ± 6.1 (115)
White	57.3 ± 8.2 (62)
African American	58.5 ± 10.9 (57)
African	65.9 ± 5.7 (58)
Men	44.6 ± 4.5 (79)
Women	73.5 ± 7.9 (97)[b]
Smokers	57.3 ± 8.2 (80)
Non-smokers	63.2 ± 5.8 (96)

Values are means ± SEM. Number of subjects is given in parentheses.
[a] Black refers to African American and Africans combined.
[b] $P < 0.002$ by *t*-test. $P < 0.02$ by multivariate analysis, adjusting for age, race, genotype, and smoking.

Table 4
CYP1A1 gene expression as a function of genotype

Genotype[a]	mRNA relative level	(Men, Women, Total)	*P*[b]
*CYP1A1*1/*1*	56.1 ± 6.6	(36, 51, 87)	NS
*CYP1A1*1/*3*	81.3 ± 21	(5, 11, 16)	NS
*CYP1A1*1/*2*	68.2 ± 9.8	(26, 26, 52)	NS
*CYP1A1*2A/*3*	66.3 ± 20	(3, 3, 6)	NS
*CYP1A1*1/*4*	45.4 ± 4	(1, 4, 5)	NS
*CYP1A1*2A/*2A*	20.2 ± 6.8	(6, 2, 8)	<0.001[c]

Values are means ± SEM. Number of subjects is given in parentheses.
[a] **2* refers to both **2A* and **2B* alleles.
[b] By Student *t*-test.
[c] $P < 0.005$ by multivariate analysis, adjusting for age, sex, race, and smoking.

form. No homozygous **3/*3* individuals were found in this study.

A significant suppression of *CYP1A1* gene expression to about 30% of the normal population values was seen for subjects who were homozygous for the *Msp*I (*CYP*2A/*2A*) allele (Table 4). Although there were more men with this genotype than women, the result was not an artifact due to differences in expression caused by the effect of gender, since in this group the average value of gene expression was actually higher in the men (22.3) than in the women (14.0). Furthermore, multivariate analysis, adjusting for race, sex, age, and smoking, confirmed that the decreased expression was significantly associated with this genotype.

4. Discussion

We previously discovered a polymorphism (*CYP1A1*3*) in 14–25% of individuals of African descent, which has never been detected in Caucasians or Asians [13]. Because of the position of this mutation upstream of the poly adenylation site, we hypothesized that this polymorphism might have an adverse effect on mRNA stability, leading to a decreased steady-state level of CYP1A1 mRNA. Our present results argue against this, and provide no evidence for any functional role of the *CYP1A1*3* polymorphism in the expression of the *CYP1A1* gene.

The *CYP1A1* gene is induced through the Ah pathway, and the molecular mechanism of induction of CYP1A1 transcription involving the Ah receptor is well characterized. Among the potent inducers of CYP1A1 transcription are the polycyclic aromatic hydrocarbons (PAHs), major ingredients of cigarette smoke. We had found previously by northern blot analysis that mitogen-stimulated cultured lymphocytes from smokers showed no increased CYP1A1 mRNA compared with non-smokers. This contrasted with a 10-fold increased induction in the placenta from the same individuals [14]. Our current negative findings on the effects of smoking on *CYP1A1* gene expression suggest that these results are not due to artifacts resulting from culture and mitogen stimulation, but instead are related to

some property of PBL, which make them a poor marker tissue for the effects of smoking. Similar negative results for the effects of smoking were reported for *CYP1A1* gene expression [15], and for expression of other genes [16,17] in Caucasians. Other biomarker endpoints such as DNA adducts and chromosomal or cytogenetic markers are often associated with smoking to a lesser extent in PBL than in other tissues, and/or to an extent less than would be expected if PBL were a truly useful surrogate tissue for the effects of smoking [18–23].

We observed that the steady-state level of CYP1A1 mRNA in PBL of women was almost twice that of men, confirming an earlier report by Mollerup *et al*. [24] that used a different quantitative PCR methodology. Gender-specific differences in gene expression have been found for a variety of genes, often related to hormonal effects [25–28]. While the *CYP1A1* gene is known to participate in estrogen metabolism, hormonal influences on its induction are less well understood and remain controversial [29,30].

Finally, we had previously found a strong association between the homozygous *CYP1A1*2A/*2A* genotype and breast cancer in African American, but not in Caucasian women [8]. This result was surprising given the presumed lack of any functional activity of the **2A* allele, as has been demonstrated by us in Asians [4], and by others in *in vitro* assays [3]. However, in this present report, we found that precisely this genotype is the only one with a strong effect on the steady-state levels of CYP1A1 mRNA.

More recent findings from a large pooled analysis study [31] implicate the same **2A/*2A* genotype as a risk factor for lung cancer among Caucasians [32] and in young non-smokers [33].

No gene dosage effect was seen for the *CYP1A1*2A* allele. In fact, the level of expression of the heterozygotes was slightly higher (though far from significantly so) than for *CYP1A1*1/*1*. This further supports the idea that the observed effect of the homozygous *2A* genotype is not due directly to the *2A* allele, but to some other genetic variant (such as a homozygous deletion) that is in linkage disequilibrium with the homozygous **2A/*2A* genotype.

Some early reports from Japan had implicated the **2* alleles in both heterozygous and homozygous forms as risk factors for smoking-related lung cancer [10]. It had been hypothesized that the mechanism behind this observation was an increased metabolism of procarcinogens such as PAHs by the gene product of the variant allele. Further work has not supported this concept. The association of the heterozygous *Msp*I RFLP with cancer, even in Asians, was weak or negative when larger populations were examined [19]. Furthermore, no phenotypic consequence of the heterozygous *2A* genotype has been seen, and several laboratories have found no correlation between the *CYP1A1*1/*2A* polymorphism and either enzyme activity or gene expression [3,4].

No molecular mechanism for the effect of the homozygous *CYP1A1*2A/*2A* genotype on gene expression is apparent, since the mutation site lies outside the promoter or other regulatory regions of the gene. The rarity of this genotype makes it difficult to study in populations much smaller than 100 individuals. Even in this study, the small number of homozygous individuals increases the possibility that the results presented, although statistically significant, could be a chance observation. Further research on linkage between this genotype and polymorphisms in other genes related to CYP1A1 expression are warranted to resolve this issue.

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