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PHARMACOGENETICS

Induction of CYP1A2 by heavy coffee consumption is associated with the *CYP1A2* −163C>A polymorphism

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Abstract
Objectives To investigate the association of *CYP1A2* genetic polymorphisms with the inducing effect of heavy coffee consumption on CYP1A2 activity in Serbian and Swedish populations, and to determine the frequency of the *CYP1A2* genetic polymorphisms in Serbs.
Methods Using PCR-RFLP and the tag-array minisequencing method, 126 Serbian healthy volunteers were genotyped for −3860G>A, −2467delT, −739T>G, −729C>T, −163C>A, 2159G>A, and 4795G>A. For 64 nonsmoking participants, the data on CYP1A2 activity (plasma paraxanthine/caffeine ratio) and coffee consumption habit were available from our previous study. The data on *CYP1A2* genotype, enzyme activity, and coffee consumption from 114 Swedish healthy nonsmoking subjects were included in the analyses.
Results In Serbs, *CYP1A2* polymorphisms −3860G>A, −2467delT, −739T>G, −729C>T, −163C>A, and 2159G>A were found at the frequencies of 0.4, 5.0, 3.4, 0.7, 61.1, and 56.0%, respectively, while 4795G>A was not detected. Significant association of heavy coffee consumption with high CYP1A2 enzyme activity was observed only in carriers of −163 A/A. Increasing effect of −163C>A on CYP1A2 inducibility was found in both Serbian (P=0.022) and Swedish (P=0.016) nonsmoking heavy coffee consumers. There was no significant difference in CYP1A2 enzyme activity among genotypes in non–heavy coffee consumers. The results indicate that 22 and 14% of the phenotypic variability among Serbian and Swedish heavy coffee consumers, respectively, might be explained by −163C>A polymorphism.
Conclusions *CYP1A2* polymorphism −163C>A has an important increasing effect on CYP1A2 inducibility by heavy coffee consumption and may possibly be a contributing factor for interindividual variations in CYP1A2 enzyme activity.

Keywords CYP1A2 · Polymorphisms · Induction · Coffee

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Introduction

Cytochrome P450 1A2 (CYP1A2) enzyme participates in the metabolism of numerous endogenous and foreign compounds and activates many procarcinogens [1, 2]. Therefore, any alteration in CYP1A2 activity affects drug metabolism and modifies the risk of developing cancers and other diseases [1–4]. CYP1A2 activity displays extensive inter- and intraindividual variability, and a number of environmental and genetic factors have been reported to contribute to these variations [5–10].

Polymorphism of the *CYP1A2* gene has been well described in many different populations, but only a few SNPs were associated with altered CYP1A2 activity [5, 10, 11]. On the other hand, numerous drugs, including oral contraceptives, have been reported to induce or inhibit CYP1A2 [2, 10, 12–14]. In addition, certain habits such as cigarette smoking also affect enzyme activity [9, 10], and this effect is observed to be associated with *CYP1A2*

polymorphism. Namely, substitution C>A at position −163 (rs762551) leads to increased enzyme inducibility in smokers [7, 10, 15], while carriers of −3860G>A (rs2069514) who smoke cigarettes display decreased CYP1A2 activity [8].

Recently, we reported that heavy coffee consumption (daily consumption of at least three cups of coffee) significantly increases CYP1A2 activity [9]. This inducing effect has been observed in two separate populations, Serbs and Swedes, while controlling for the effect of drug intake and cigarette smoking. Yet, the association of the described effect with *CYP1A2* polymorphism has not been explored at this time.

CYP1A2 genetic polymorphisms in the Swedish population have been previously reported [10]. However, to the best of our knowledge, *CYP1A2* genotype in the Serbian population has not been investigated so far. The aim of the present study was to investigate the association of *CYP1A2* genetic polymorphisms with the inducing effect of heavy coffee consumption on CYP1A2 activity in Serbian and Swedish populations, and to determine the frequency of the *CYP1A2* genetic polymorphisms in Serbs.

Materials and methods

Study subjects One hundred twenty-six unrelated healthy Serbian volunteers, 60 men and 66 women, were enrolled in the genotype analyses. As a part of the previous study [16], a 20-ml venous blood sample was collected into EDTA-containing Vacutainer tubes (Sarstedt, Nümbrecht, Germany) and frozen at −80°C. All samples were packed on dry ice and sent to Karolinska Institutet, Stockholm, Sweden, for genotyping analyses. For 64 nonsmoking participants, the data on CYP1A2 activity [plasma paraxanthine (17X)/caffeine (137X) ratio] and coffee consumption were available from our previous study [9]. Additionally, data on *CYP1A2* genotype and activity of 114 Swedish nonsmoking subjects [10] were included in the analyses. There were no oral contraceptive users among the study subjects. All subjects participated voluntarily after written informed consent had been obtained. The study was approved by the ethics committees at the Medical Faculty, University of Kragujevac, Serbia, and at Karolinska Institutet, Sweden. The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions.

CYP1A2 genotyping DNA was extracted from the whole blood samples using QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany). Genotyping for six *CYP1A2* polymorphisms (−3860G>A, −163C>A, −739T>G, −729C>T, 2159G>A, and 4795G>A) was carried out using the tag-array minisequencing method, described by Lindroos et al. [17] with some modifications. The multiplex PCR and minisequencing primers (Table 1) were designed using OligoPerfect Designer (www.invitrogen.com) and AutoPrimer software (http://www.autoprimer.com/) (Beckman Coulter, Fullerton, CA, USA), and purchased from Integrated DNA Technologies (IDT, Coralville, IA, USA). Genotyping for −2467delT was carried out using the PCR-RFLP method described by Chida et al. [11].

Statistical analysis Haplotype analysis and haplotype frequency calculations were carried out using the population genetic software program Arlequin, version 3.11 (http://cmpg.unibe.ch/software/arlequin3). Chi-squared test was used to compare observed with expected allele frequencies (Hardy-Weinberg equilibrium). The 17X/137X ratio was log-transformed before statistical analyses. One-way ANOVA followed by the post-hoc analyses (Fisher test) was used to assess the effect of genotype and coffee consumption on CYP1A2 enzyme activity. Statistical analyses were performed with Statistica, version 7.1 (StatSoft, Tulsa, OK, USA), and $P<0.05$ was considered as significant.

Results

The frequencies of the *CYP1A2* SNPs, haplotypes, and genotypes in the Serbian population are summarized in Table 2. The most frequent SNPs in Serbs were −163C>A and 2159G>A. Seven different haplotypes were found, including two novel ones that were assigned as *CYP1A2*1X* (−739T>G, −163C>A, 2159G>A) and *CYP1A2*1Y* (−2467delT, −739T>G, −729G>A, −163C>A). All haplotypes were in Hardy-Weinberg equilibrium ($\chi^2<0.10$, $P=0.05$).

To investigate the influence of genotype on CYP1A2 inducibility by coffee consumption, we analyzed both Serbian and Swedish heavy and non–heavy coffee consumers. Cigarette smokers and oral contraceptive users were not included in the comparison. In heavy coffee consumers, the only genotype-phenotype association revealed by comparison of log-transformed 17X/137X ratios included −163C>A polymorphism. The observed difference in CYP1A2 activity was significant in both Serbian (Fig. 1, $P=0.022$) and Swedish (Fig. 2, $P=0.016$) heavy coffee consumers, with the highest mean 17X/137X ratio in the −163 A/A genotype group (Table 3). The coefficients of determination indicate that 22% ($r^2=0.22$) and 14% ($r^2=0.14$) of the phenotypic variability among Serbian and Swedish heavy coffee consumers, respectively, might be explained by the −163C>A polymorphism. On the other

Table 1 SNPs and primers used in genotyping of CYP1A2 gene by the tag-array minisequencing method

SNP	rs#	Primer name	Sequence 5′ to 3′	PCR product (bp)
−3860G>A	rs2069514	CYP1A2*1C-F	TGGAGTGCAGTGGTGCGA	90
		CYP1A2*1C-R	TTCCAGCTACTCGGGAAG	
		CYP1A2*1C-MS-fo	GAGTAGCCTTCCCGAGCATTTGGCTCACCGCAACCTCCGCCTCTC	
−739T>G	rs2069526	CYP1A2*1J*1K-F	AAGCTAGTGGGGACAGAAAGA	130
		CYP1A2*1J*1K-R	TTAAAAATGGCTTAGTCCAAACTG	
		CYP1A2*1J-MS-fo	AAACCATCGACTCACGGGATGGGGAGCCTGGGCTAGGTGTAGGGG	
−729C>T	rs12720461	CYP1A2*1J*1K-F	AAGCTAGTGGGGACAGAAAGA	130
		CYP1A2*1J*1K-R	TTAAAAATGGCTTAGTCCAAACTG	
		CYP1A2*1K-MS-re	ATTGACCAAACTGCGGTGCGAGTCAAGAGCTGGGTAGCAAAGCCC	
−163C>A	rs762551	CYP1A2*1F-F	AATCTTGAGGCTCCTTTCCA	107
		CYP1A2*1F-R	AGCTGGATACCAGAAAGACTAAGC	
		CYP1A2*1F-MS-fo	ATTAACTCGACTGCCGCGTGTGCTCAAAGGGTGAGCTCTGTGGGC	
2159G>A	rs2472304	CYP1A2rs2472304-F	AGAAGGAGCTGGGTACATGG	101
		CYP1A2rs2472304-R	AGCAGGCACATAACAGGTGT	
		CYP1A2rs2472304-MS-fo	AACAACGATGAGACCGGGCTACCCTATAGCCAGGAGAAGCCTTGA	
4795G>A	rs12904742	CYP1A2rs12904742-F	TACACGGGAGGCTCAGGT	97
		CYP1A2rs12904742-R	TATCACCCAGGCTGGAGTAC	
		CYP1A2rs12904742-MS-fo	AAGGCACGTATCATATCCCTGGTTGGCTTGAGCTGGGGAGGCAGA	

hand, in non–heavy coffee consumers there was no significant difference in CYP1A2 enzyme activity among the different genotype groups, in Serbs ($P \geq 0.15$) or in Swedes ($P \geq 0.31$).

To further evaluate the effect of heavy coffee consumption on CYP1A2 activity, we compared log-transformed 17X/137X ratios between heavy and non–heavy coffee consumers within each *CYP1A2* −163 genotype group. As expected, in both Serbs and Swedes the inducing effect of heavy coffee consumption on CYP1A2 was observed only in carriers of −163 A/A (Table 3).

Discussion

In the present study, we investigated the association of *CYP1A2* genetic polymorphisms and the induction of CYP1A2 by heavy coffee consumption in Serbs and Swedes, using caffeine as a probe drug and plasma 17X/137X ratio as an index of CYP1A2 enzyme activity. To the best of our knowledge, this is the first study to report increased CYP1A2 inducibility by heavy coffee consumption in carriers of −163 A/A genotype. In addition, we described the frequencies of the seven most important SNPs of *CYP1A2* gene, as well as haplotypes and genotypes, in the Serbian population.

The frequencies of investigated *CYP1A2* genetic variations, as well as of corresponding alleles and genotypes in Serbs, were comparable with the results previously published for other Caucasians [5, 10, 18–20]. So far, only a few variations of the *CYP1A2* gene were associated with altered enzyme inducibility [2]. Nakajima et al. [8] described −3860G>A as a causal factor of decreased CYP1A2 induction in Japanese smokers. On the contrary, in Korean smokers CYP1A2 activity was not found to be affected by this polymorphism [10]. Substitution of G>A at the position −3860 of the *CYP1A2* gene is known as a feature of Asian populations [10, 12], and it is very rare in Caucasians [19]. As expected, in both Serbs and Swedes −3860G>A occurred at a very low frequency (less than 1%) [10]. Therefore, in the present study the proposed decreasing effect of this polymorphism on CYP1A2 induction could not be tested. Association of *CYP1A2*1K* (−739T>G, −729C>T, −163C>A) with low enzyme activity in Ethiopians [5] was reported previously, but this allele is also rare in both Asians and Caucasians.

On the other hand, Sachse et al. [7] observed higher enzyme inducibility in the presence of −163 A/A genotype, and the effect was also restricted to smokers. The importance of −163C>A polymorphism for CYP1A2 enzyme induction was confirmed by a number of studies, reporting higher CYP1A2 enzyme activity in the presence of the *CYP1A2* inducers, such as cigarette smoking or omeprazol [10, 12, 15, 21]. Substitution C>A at position −163 is one of the most common *CYP1A2* polymorphisms in Caucasians, with frequencies that range from 33.8% in British [20] to 71.4% in Swedish population [10]. In Serbs, −163C>A was the most frequently observed SNP,

Table 2 SNP and haplotype frequencies of *CYP1A2* gene in Serbs

		Observed frequency	95% CI
SNP	−3860G>A	0.004 (1/274)	0.000, 0.023
	−2467delT	0.050 (14/280)	0.030, 0.083
	−739T>G	0.034 (9/264)	0.017, 0.065
	−729G>A	0.007 (2/274)	0.000, 0.028
	−163C>A	0.611 (160/262)	0.550, 0.668
	2159G>A	0.560 (149/266)	0.500, 0.618
	4795G>A	0.000 (0/274)	0.000, 0.017
Haplotype[a]	*CYP1A2*1A*	0.385 (97/252)	0.327, 0.446
	*CYP1A2*1C*	0.004 (1/252)	0.000, 0.025
	*CYP1A2*1M*	0.548 (138/252)	0.486, 0.608
	*CYP1A2*1V*	0.028 (7/252)	0.013,0.058
	*CYP1A2*1W*	0.012 (3/252)	0.003, 0.036
	*CYP1A2*1X*	0.016 (4/252)	0.005, 0.042
	*CYP1A2*1Y*	0.008 (2/252)	0.000, 0.031
Genotype	*CYP1A2*1A/*1A*	0.143 (18/126)	0.092, 0.216
	*CYP1A2*1A/*1M*	0.429 (54/126)	0.346, 0.516
	*CYP1A2*1A/*1V*	0.024 (3/126)	0.005, 0.072
	*CYP1A2*1A/*1W*	0.016 (2/126)	0.001, 0.060
	*CYP1A2*1A/*1X*	0.008 (1/126)	0.000, 0.049
	*CYP1A2*1A/*1Y*	0.008 (1/126)	0.000, 0.049
	*CYP1A2*1C/*1M*	0.008 (1/126)	0.000, 0.049
	*CYP1A2*1M/*1M*	0.294 (37/126)	0.221, 0.379
	*CYP1A2*1M/*1V*	0.032 (4/126)	0.010, 0.082
	*CYP1A2*1M/*1W*	0.008 (1/126)	0.000, 0.049
	*CYP1A2*1M/*1X*	0.024 (3/126)	0.005, 0.072
	*CYP1A2*1M/*1Y*	0.008 (1/126)	0.000, 0.049

[a] *CYP1A2*1A* (wild type), *CYP1A2*1C* (−3860G>A), *CYP1A2*1M* (−163C>A, 2159G>A), *CYP1A2*1V* (−2467delT, −163C>A), *CYP1A2*1W* (−2467delT, −163C>A, −739T>G), *CYP1A2*1X* (−739T>G, −163C>A, 2159G>A), *CYP1A2*1Y* (−2467delT, −739T>G, −729G>A, −163C>A)

with a frequency that fitted well with the expected range. To investigate the effect of −163C>A on induction of CYP1A2 by heavy coffee consumption, we compared enzyme activity among Serbian and Swedish heavy coffee consumers, controlling for the effect of cigarette smoking and oral contraceptive use. Our results demonstrate significant differences in 17X/137X ratios among −163C>A genotypes in heavy coffee consumers, with the highest CYP1A2 enzyme activity detected in carriers of −163 A/A genotype. The inducing effect of heavy coffee consumption was observed only in subjects homozygous for the variant type allele, which designates the −163A allele as a recessive factor necessary for the CYP1A2 induction. As expected, the influence of −163C>A was not observed either in Serbian or in Swedish non–heavy coffee consumers.

Several previous studies using plasma levels of haloperidol [22]; caffeine as a probe; urinary (AFMU+1U+1X)/17U [23], (AAMU+AFMU+1U+1X)/17U [20], or (AFMU+1U+1X+17U+17X)/137X ratio [5] or theophilline as a probe; and plasma (1U+3X)/TP ratio [24] as index of CYP1A2 activity failed to find any correlation of −163C>A polymorphism with CYP1A2 induction. Nevertheless, some of the studies [20, 24] had too low sample power, which might be the reason for the lack of significance in genotype-phenotype association. In addition, incomplete determination of the different haplotypes existing in the populations was suggested as one of the possible explanations for the discrepant results [5, 10], suggesting that functional impact of −163C>A probably depends on whether this polymorphism occurs alone or in linkage disequilibrium with other SNPs. Furthermore, none of the previous studies took into account heavy

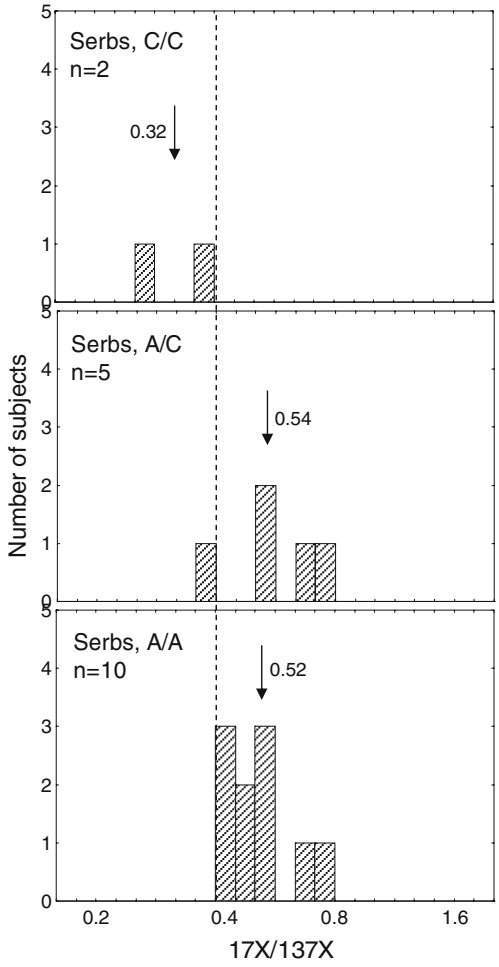

Fig. 1 The frequency distributions of the log-transformed 17X/137X ratios in Serbian heavy coffee consumers, with respect to −163C>A variation of *CYP1A2* gene. The arrows indicate the medians and the numbers along them are antilog values. The vertical line shows the reference antilog value of 0.4

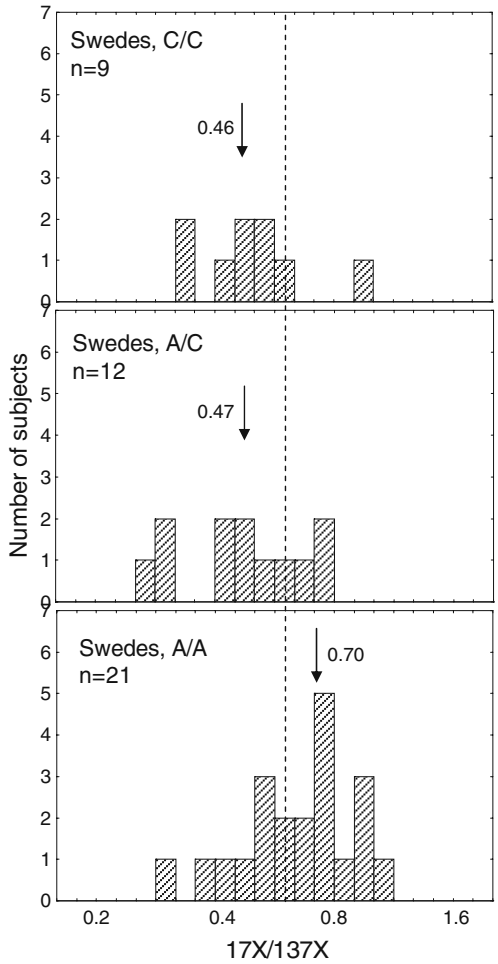

Fig. 2 The frequency distributions of the log-transformed 17X/137X ratios in Swedish heavy coffee consumers, with respect to −163C>A variation of *CYP1A2* gene. The arrows indicate the medians and the numbers along them are antilog values. The vertical line shows the reference antilog value of 0.6

coffee consumption as a possible confounding factor [9]. Our study demonstrates that heavy coffee consumption habit might be a possible confounding factor for the discrepant findings from studies that investigated the association of the −163C>A polymorphism with CYP1A2 enzyme induction.

Caffeine as a metabolic probe has several important advantages: rapid and complete absorption, wide distribution, low plasma protein binding, complete biotransformation, short half-life, and negligible renal excretion [25]. After ingestion, caffeine (137X) is predominantly metabolized by CYP1A2 to paraxanthine (17X), and the 17X/137X ratio in plasma has been suggested as the most robust and valid measurement of CYP1A2 activity [26, 27]. In the present study, CYP1A2 activity was estimated by plasma 17X/137X ratio, after administration of 100 mg oral dose of caffeine [9, 10]. Possible competitive inhibition with caffeine from other dietary sources was avoided by abstaining from intake of any caffeine-containing food, beverage, and medication for at least 24 h prior to and during the study [9, 10]. On the other hand, it is known that cigarette smoking induces and oral contraceptive use inhibits CYP1A2 [28, 29]. To avoid the effect of these confounders, in the present study smokers and oral contraceptive users were excluded from the comparison.

Recently, we reported significantly lower CYP1A2 activity in Serbs compared to Swedes [9]. In addition, while in Swedes −163C>A polymorphism most frequently occurred alone (*CYP1A2*F*) [10], in Serbs it was always in linkage disequilibrium with other SNPs, mostly with 2159G>A (*CYP1A2*M*). To avoid the described confounding effect of ethnicity, Serbian and Swedish heavy coffee consumers were analyzed separately. The influence of −163C>A on CYP1A2 activity was significant in both Serbian and Swedish heavy coffee consumers, while other *CYP1A2* polymorphisms, including 2159G>A, did not affect enzyme activity. Additionally, in both Serbs and Swedes, the inducing effect of heavy coffee consumption on CYP1A2 was observed only in carriers of −163A/A. The results strongly suggest that −163C>A polymorphism has an important increasing effect on CYP1A2 inducibility by heavy coffee consumption, regardless of possible linkage disequilibrium with other *CYP1A2* SNPs.

Table 3 Comparisons of mean 17X/137X ratios between non–heavy and heavy coffee consumers in Serbs and Swedes based on the *CYP1A2* −163C>A genotype

	Non–heavy coffee consumers		Heavy coffee consumers		*P* value
	n	Mean ± SD	*n*	Mean ± SD	
Serbs					
C/C	10	0.38±0.13	2	0.32±0.09	0.63
C/A	25	0.44±0.13	5	0.56±0.13	0.07
A/A	12	0.38±0.13	10	0.54±0.11	0.005
Swedes					
C/C	19	0.50±0.22	9	0.51±0.19	0.73
C/A	28	0.54±0.20	12	0.49±0.17	0.45
A/A	25	0.47±0.10	21	0.68±0.20	<0.0001

In conclusion, the results of the study indicate that the −163C>A *CYP1A2* polymorphism has an important increasing effect on CYP1A2 inducibility by heavy coffee consumption. In heavy coffee consumers, genotyping for −163C>A should be considered as a factor affecting interindividual variations in drug metabolism, as well as susceptibility to diseases associated with CYP1A2 activity.

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Conflict of interest statement The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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