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Genetic polymorphisms of *CYP2C9*, *CYP2C19*, and *CYP3A5* in Kosovar population

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Cytochrome P450 genetic polymorphisms are responsible for individual variations in drug metabolism and drug-drug interactions. They are very important for pharmacogenetics, and their frequency varies across different populations. There is a big gap in the knowledge about the CYP gene family polymorphisms in the population of Kosovo, and the aim of our study was to fill that gap by determining the frequency of the most important variant alleles of *CYP2C9*, *CYP2C19*, and *CYP3A5* in 234 nonrelated Kosovars. The allele frequencies of *CYP2C9*2* and *2C9*3* were 17.52 %, and 10.89 %, respectively. Sixteen participants (6.81 %) were *CYP2C9* poor metabolisers. The *CYP2C19*2* and *17* variant frequencies were 13.03 % and 19.01 %, respectively. There were 2.13 % CYP2C19 poor and 4.27 % ultra-rapid metabolisers (homozygous carriers of the *17* allele). With regard to *CYP3A5*, the frequency of the *3* variant allele was 98.29 % (non-expressors), while the remaining participants (1.70 %) were expressors of CYP3A5. These findings are comparable with other European ethnicities, specifically those of Southeast Europe.

KEY WORDS: *cytochrome P450 enzyme system; drug metabolism; pharmacogenetics*

Individual variability in response to the most common drugs presents one of the major challenges to pharmacotherapy today. This variability depends on a variety of factors (drug interactions, hepatorenal disorders, sex, age, and lifestyle), but the most challenging are the genetic polymorphisms that have a direct and important impact on drug-detoxifying enzymes, drug targets, and drug transporters (1-3). Phase I enzymes metabolise nearly 59 % of the drugs reported for adverse drug reactions (ADR), and cytochromes P450 (CYP450 or CYP) make 75–86 % of these phase I enzymes (2, 4). Their genetic variants are responsible for unintended drug metabolism and interactions (5) that can lead to toxicity or failed pharmacotherapy (6). This has been recognised by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), as both push policies requiring that pharmacogenetic information is provided for drug development and postmarketing surveillance (7, 8).

The most important genetic variants of CYP in clinical practice include those of *CYP2C9, CYP2C19*, and *CYP3A5*. Their frequencies vary across populations, and mapping them, so to speak, can be very useful in designing specific pharmacotherapy. To the best of our knowledge no such mapping has been done for the population of Kosovo, a southeast European country of over 1.7 million people, 93 % of whom are ethnic Albanians. The aim of our study was to address this gap and determine the frequency of the pharmacologically most important variant alleles of *CYP2C9*, *CYP2C19*, and *CYP3A5* in Kosovo population, hoping that our findings could help to optimise pharmacotherapy in the country.

PARTICIPANTS AND METHODS

This study included a mixed population of 234 randomly selected Caucasians (116 women and 118 men) with no blood relation from all parts of Kosovo. Their age ranged between 18 and 65 years (median: 36 years). The main exclusion criteria were mental illnesses or a history of serious physical illness.

The study was approved by the Ethics Committee of the University Clinical Centre of Kosovo in Prishtina (Kosovo) and by the Faculty of Pharmacy in Skopje (Macedonia), where genotyping was performed. Prior to enrolment, all participants gave their written consent for

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participation. The study was performed according to the principles expressed in the Declaration of Helsinki.

We determined the frequencies of the most common variant alleles of polymorphic CYP enzymes: *CYP2C9*2* (c.430C>T, rs1799853), *CYP2C9*3* (c.1075A>C, rs1057910), *CYP2C19*2* (c.681G>A, rs4244285), *CYP2C19*17* (c. 806C>T, rs12248560), and *CYP3A5*3* (g.6986A>G, rs776746). The *CYP2C19*3* (c.636G>A, rs57081121) allele was excluded as very rare in the European population (9, 10).

For genotyping we collected 5 mL of peripheral blood from each subject into test tubes with the anticoagulant ethylene diamine tetra-acetic acid (EDTA). Genomic DNA was extracted from whole blood using a QIAGEN DNA extraction kit (QIAGEN AS, Oslo, Norway). The extracted DNA concentrations were determined with a NanoDrop 2000™ spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA).

*CYP2C9*2* (C_25625805_10), *CYP2C9*3* (C_27104892_10), *CYP2C19*2* (C_25986767_70), *CYP2C19*17* (C_469857_10), and *CYP3A5*3* (C_26201809_30) were genotyped using a TaqMan® drug metabolism genotyping assay or a TaqMan® single nucleotide polymorphism (SNP) genotyping assay (Applied Biosystems, Foster City, CA, USA) on an Mx3005P real-time quantitative polymerase chain reaction (QPCR) system with pertaining MxPro software) (Agilent Technologies, Santa Clara, CA, USA) following the manufacturer's instructions.

In order to multiply a DNA segment, we mixed 2 µL of DNA with 10.5 µL of PCR and incubated the mixture under the following conditions: uracil-N-glycosylase incubation (2 min at 50 °C), AmpliTaq Gold® activation (10 min at 95 °C), PCR [50 cycles: denaturation (15 sec at 92 °C); annealing/extension (60 sec at 60 °C)].

Statistical analysis

The variables were analysed with an SPSS statistical program (SPSS Inc., Chicago, IL, USA, 20.0 version) and online calculator (available at https://www.allto.co.uk/tools/statistic-calculators/confidence-interval-for-proportions-calculator). Allele and genotype frequencies were estimated using the gene counting method, and their distribution was tested with the chi-squared test for the Hardy-Weinberg equilibrium.

Using the chi-squared test with Yate's correction we compared our allele frequency distribution with other studies to establish differences or similarities with other populations, Caucasian in particular. The threshold of significance was set at a 5 %, where all differences above p=0.05 were considered non-significant between our results and the reported frequencies in other populations.

RESULTS AND DISCUSSION

Our findings of the *CYP* gene polymorphisms in the Kosovar sample are similar to other European populations reported in several publications (11–13). Tables 1–3 show genotype distribution and the predicted phenotypes of *CYP2C9*, *CYP2C19*, and *CYP3A5*. All genotype frequencies were in line with the Hardy-Weinberg principle.

CYP2C9

The *CYP2C9* allele frequencies compare to other European Caucasians, such as Croats (Southeast Europe) and the French (West Europe) (14, 15). The *CYP *2* and *3* allele frequencies in our sample were 17.52 % and 10.89 %, respectively. The frequency of CYP2C9 poor metabolisers was 6.8 %, which is similar to the Spanish (5.0 %) (16) and Macedonian (5.1 %) population, but differs from England's population (3.2 %) (17, 18). The following frequencies of *CYP2C9*2* have been reported for the European Mediterranean and other European countries: Spain (16.0 %), Greece (12.9 %), Croatia (14.0 %), Romania (11.3 %), Germany (14.0 %), France (15.0 %), and Sweden (10.7 %) (19–25). *CYP2C9*3* has the highest prevalence in Southern Asian populations (10.1 %) (25), while in the Western, Central, and Southeastern Europe it is present in

Table 1 CYP2C9 *genotype frequencies and predicted phenotypes in the Kosovar population sample (N=234)*

Genotype	No. of participants (N)	Frequency (%)	95 % confidence interval	Predicted phenotype	Investigated allele	No. of alleles (2n) / (%)
*CYP2C9*1/*1*	117	50.00	43.59 - 56.41	EM	*CYP2C9*1*	335 (71.58)
*CYP2C9*1/*2*	62	26.49	20.84 - 32.14	IM	*CYP2C9*2*	82 (17.52)
*CYP2C9*1/*3*	39	16.66	11.89 - 21.43	IM	*CYP2C9*3*	51 (10.89)
*CYP2C9*2/*2*	8	3.41	1.08 - 5.74	PM		
*CYP2C9*2/*3*	4	1.70	0.04 - 3.36	PM		
*CYP2C9*3/*3*	4	1.70	0.04 - 3.36	PM		

PM - poor metabolisers; IM - intermediate metabolisers; EM - extensive metabolisers

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Table 2 CYP2C19 *genotype frequencies and predicted phenotype in the Kosovar population sample (N=234)*

Genotype	No. of participants (N)	Frequency (%)	95 % confidence interval	Predicted phenotype	Investigated allele	No. of alleles (2n) / (%)
CYP2C19*1/*1	107	45.72	39.34 - 52.1	EM	CYP2C19*1	318 (67.94)
CYP2C19*1/*2	43	18.37	13.41 - 23.33	IM	CYP2C19*2	61 (13.03)
CYP2C19*2/*2	5	2.13	0.28 - 3.98	PM	CYP2C19*17	89 (19.01)
CYP2C19*2/*17	8	3.41	1.08 - 5.74	IM		
CYP2C19*1/*17	61	26.06	20.44 - 31.68	UM		
CYP2C19*17/*17	10	4.27	1.68 - 6.86	UM		

PM - poor metabolisers; IM - intermediate metabolisers; EM - extensive metabolisers; UM - ultra-rapid metabolisers

the following frequencies: France 8.0 %, Belgium 7.4 %, Hungary 8.8 %, Croatia 9.5 %, Greece 8.1 %, and Macedonia 7.3 % (14, 15, 23, 26–28)..

CYP2C19

Genotyping the *CYP2C19* alleles in Kosovars revealed the *2 and *17 allele frequencies of 13.03 % and 19.01 %, respectively, which are comparable to other Caucasians. *CYP2C19*2* is the most common variant allele in Caucasians, and its frequency varies from 13.1 % to 18.7 % (23, 29). We found high similarity of our distribution with both Macedonia (14.9 %; p=0.55) and Greece (13.1 %; p=1.00) (23, 28).

As the *CYP2C19*2* is an inactivating allele, knowing its distribution in a population is important when prescribing medicines such as clopidogrel, which is a pro-drug that must be activated by CYP2C19 (30). In this study, five participants (2.13 %) were discovered to be homozygous carriers of the *2 allele (*CYP2C19*2/*2* genotype.

Our findings of the *CYP2C19*17* frequency in Kosovars are very similar to reports from the neighbouring countries, Greece (19.61 %, p=0.69) and Macedonia (20.2 %; p=0.84) in particular (23, 24, 31). In Caucasians its frequency varies from 15.4 % to 20.2 % (17). The *CYP2C19*17* allele was documented to be more frequent in the Mediterranean and Middle East than in Eastern Asia (32). Even though carriers of the *CYP2C19*1/*17* and *CYP2C19*17/*17* genotype were predicted to be ultra-rapid metabolisers, only homozygous carriers of the *17/*17 genotype have shown a higher rate of metabolism of the CYP2C19 substrates, such as tricyclic antidepressants and esomeprazole when compared to extensive metabolisers (33-35). Clopidogrel

receiving carriers of the *CYP2C19*17* allele were reported for increased risk of bleeding, the highest risk being for those who carried the *CYP2C19*17/*17* genotype. Eight participants (3.41 %) in our sample were the carriers of the *CYP2C19*2/*17* combined genotype. Their metabolic phenotype is difficult to predict and remains a matter of debate. Some data suggest that the presence of the *CYP2C19*17* allele may not compensate for the inactivating effect of *CYP2C19*2* (36).

Finally, our results indicate a significant difference from other Caucasians, such as Russian (*CYP2C19*1/*1*; p<0.001) (37).

CYP3A5

Over 98.3 % of our participants had the *CYP3A5*3/*3* genotype and are classified as non-expressors. This finding corresponds to the other reports for Caucasians (18, 24, 28), as it varies from 85 to 96 % (38). The *CYP3A5*3* allele plays an important role in the pharmacokinetics of tacrolimus (basic therapy for immunosuppression in patients who undergo solid organ and haematopoietic stem cell transplantation) and imatinib (a tyrosine kinase inhibitor, which is the drug of choice in treating blood malignancies such as chronic myeloid leukaemia) (39). Statistical analysis showed a significant similarity with Croats (95.5 %; p=0.072), Basques (96.0 %; p=0.143), and Poles (96.3 %; p=0.180) (16, 24, 40).

CONCLUSION

Even though our study is limited to the most important *CYP* alleles (SNPs) and a relatively small sample, it clearly

Table 3 CYP3A5 *genotype frequencies and predicted phenotype in the Kosovar population sample (N=234)*

Genotype	No. of participants (N)	Frequency (%)	95 % confidence interval	Predicted phenotype
CYP3A5*1/*1	4	1.7	0.04 - 3.36	expressor
CYP3A5*1/*3	0	0	0	expressor
CYP3A5*3/*3	230	98.3	96.64 - 99.96	non-expressor

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shows a distribution that is consistent with the Caucasian ethnicity, especially with the Southeast and Mediterranean European populations.

Knowing the distribution of these gene variants in Kosovo may prove very useful for the future research of certain complex diseases and for determining the impact of geographical and climatic conditions in their pathogenesis. Our data will form the basis for detecting the genetic risk factors related to specific diseases, including the toxic potential of numerous environmental pollutants. In addition, they can prove relevant to clinical pharmacokinetic studies and dosage recommendations for the Kosovo population.

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Genski polimorfizam CYP2C9, CYP2C19 i CYP3A5 u populaciji Kosova

Vrlo visok stupanj polimorfnosti, zbog interindividualne genske varijabilnosti, enzima citokroma P450 (CYP) značajno pridonosi raznolikosti u odnosima između primijenjene doze lijeka, koncentracije lijeka u serumu, kao i terapijskoga odgovora, ali i interakcije lijekova. Podaci o poznatim polimorfizmima CYP vrlo su važni u kliničkoj primjeni saznanja farmakogenetike tj. u samoj farmakoterapiji. Učestalost pojedinih polimorfizama može značajno varirati između različitih populacija te je bitno provesti istraživanja učestalosti u pojedinim populacijama. Do sada nema objavljenih podataka o učestalosti polimorfizama gena CYP u populaciji Kosova te je cilj ovog istraživanje bio utvrditi učestalost najvažnijih varijanti alela CYP2C9, CYP2C19 i CYP3A5 u toj populaciji. Istraživanje je obuhvatilo 234 stanovnika Kosova koji nisu u rodbinskoj vezi. U ispitanika je otkrivena učestalost alela CYP2C9*2, 17,52 %, a alela CYP2C9*3 10,89 %, te je otkriveno šesnaest ispitanika (6,81 %) sporih metabolizatora CYP2C9. Što se tiče CYP2C19 enzima, učestalost alela CYP2C19*2 je 13,03 %, a za alel CYP2C19*17 učestalost je 19,01 %. Uz to, dokumentirano je 2,13 % sporih metabolizatora CYP2C19 te 4,27 % homozigotnih nositelja alela *17 (fenotip vrlo brzih metabolizatora). S obzirom na CYP3A5 enzim, zabilježena je učestalost alela *3 od 98,29 % (fenotip neekspresora), a 1,70 % ispitanika kategorizirano je kao ekspresori. Rezultati istraživanja pokazali su da je varijabilnost alela, genotipova i fenotipova u populaciji Kosova u velikoj mjeri u skladu s drugim europskim populacijama, konkretnije s populacijama jugoistočne Europe.

KLJUČNE RIJEČI: citokromi P450; metabolizam lijeka; farmakogenetika