PhD Thesis

PHARMACOGENETICALLY RELEVANT POLYMORPHISMS OF CYTOCHROME P450 GENES IN HUNGARIAN AND ROMA POPULATIONS

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1. Introduction

Cytochrome P450 enzyme system

Cytochrome P450 (CYP) system is a universal enzyme superfamily. CYP enzymes have a key role in the biotransformation of endogen and exogen substrates. Physiological substrates of these enzymes include steroids, fatty acides, prostaglandins, leukotrienes and biogene amines, while xenobiotic substrates include drugs, herbal toxins and toxic chemicals from the environment. Cytochrome P450 enzymes predominantly catalyse oxidative reactions, serving as monooxigenases, oxidases and peroxidases. Further role of *CYP* enzymes is to participate in metabolic transformation of prodrugs, which require biotransformation to an active metabolite to elicit a therapeutic effect (e.g. codeine into morphine by *CYP2D6)*. Family CYP1, CYP2 and CYP3 are responsible for the phase I metabolism of 70-80% of clinically used drugs. The members of the CYP superfamily are highly variable and show appreciable inter-individual and inter-ethnic variability in catalytic activity. This is either due to genetic polymorphisms or to variability in expression levels. The major sources of inter-individual and intra-individual variability in CYP activity are environmental influences, including inhibition and induction by concomitant medications (drug-drug interactions), biological factors including sex and physiological determinants, such as hormonal status, disease, circadian rhythms and genetic polymorphisms in cytochrome P450 genes and their regulators. The Human Genome Project identified 57 functionally active CYP genes and 58 pseudogenes, which were classified into 18 families and 44 subfamilies based on sequence similarity.

Cytochrome P450 1A2 (CYP1A2) belongs to the phase I microsomal enzymes and participates in the metabolism of clinically important drugs (clozapine, paracetamol, verapamil, theophylline, caffeine) and several endogenous substrates (melatonin, bilirubin and estradiol). *CYP1A2* gene is responsible for the metabolic activation of procarcinogens (aromatic and heterocyclic amines, polycyclic aromatic hydrocarbons). Its activity is modifiable due to chemicals, dietary factors, smoking, proton pump inhibitor and oral contraceptive medications. Alterations in CYP1A2 expression modulate the risk to develop cancers, myocardial infarction, chronic obstructive pulmonary disease and several other medical conditions. CYP1A2 gene is highly variable; the described functional polymorphisms of *CYP1A2* are relevant in drug effect and show remarkable inter-individual

and racial variability. The most extensively studied single nucleotide polymorphisms (SNPs) in the non-coding region are -3860G>A, -2467delT, -729C>T and -163C>A.

Taxanes - paclitaxel (Taxol®) and the semi-synthetic analogue docetaxel (Taxotere®) - are primarily metabolized in the liver by the cytochrome P450 enzyme system. Previous studies tried to find relationship between polymorphisms in biologically relevant candidate CYP genes in the taxane pathway, which can modulate the effect or the metabolism of taxanes. CYP2C8 accounts for 7% of CYP content in the liver, and is expressed to a lesser extent in the kidney, adrenal gland, mammary gland, brain, ovary, uterus, and duodenum. While CYP2C8 is the principle enzyme in paclitaxel metabolism, docetaxel is eliminated predominantly by CYP3A5 mediated metabolism. CYP1B1 participates in the metabolic activation of several pre-carcinogenes and has a role in taxane, estrogen and amodiaquine pathway. A previous study has found association between variant of *CYP1B1* and patient survival, independent of paclitaxel clearance.

Cytochrome P450 4F2 catalyzes the NADPH-dependent oxidation of the terminal carbon of long and very long-chain fatty acids, the side chains of vitamin K_1 and K_2 and vitamin E, arachidonic acid and leukotriene B_4. Although CYP4F2 is predominantly expressed in the liver and kidneys, there is some evidence that it is expressed in human enteric microsomes. The major genetic determinants of drug response variability in anticoagulant treatment are *CYP2C9* and *VKORC1* pharmacogenes. *CYP4F2*, as additional candidate gene, supposed to have influence on anticoagulant therapy predominantly in minor ethnic populations. Studies confirmed, that *CYP4F2* V433M variant explains significant amount of inter-individual warfarin dose variance depending on the ethnic background.

2. AIMS OF THE STUDY

The objective of our work was to study pharmacogenetically relevant polymorphisms of cytochrome P450 genes in Roma and Hungarian populations.

The main purposes of the work are:

- To determine the allele frequencies of functionally significant rs2069514, rs35694136, rs762551 and rs12720461polymorphisms in non-coding regions of *CYP1A2* gene in healthy Hungarian and Roma populations.

- To establish the haplotype profiles of *CYP1A2* gene in both examined populations.

- To characterize the allele frequencies of *CYP4F2* rs2108622 SNP, may influence the outcome of anticoagulant therapy in healthy Hungarian and Roma populations.

- To describe the allele frequencies of rs1056836, rs1058930 and rs776746 SNP-s of *CYP1B1, CYP2C8* and *CYP3A5* genes, respectively in Hungarian and Roma population subjects in point of taxane therapy.

- To compare the allele frequencies of *CYP1A2*, *CYP1B1*, *CYP2C8*, *CYP3A5* and *CYP4F2* gene polymorphisms of Hungarian and Roma populations with results available for other ethnic populations in literature, mainly with Caucasian and Indian populations.

3. MATERIALS AND METHODS

Studied populations

DNA samples and personal data of healthy Hungarian and healthy Roma subjects were derived from Hungary. Informed consent was obtained from all subjects. Roma people declared their Roma origin and Hungarian subjects made a statement to be not a member of any minor ethnic group. The DNA samples were collected from the central Biobank of the University of Pecs, which is part of the pan-European Biobanking and Biomolecular Resources Research Infrastructure. The maintenance and governance principles of the Biobank are approved by the National Scientific Research Ethics Committee (ETT TUKEB, Budapest, Hungary). During sample collection and management of data the 1975 Helsinki Declaration was followed. According to *CYP1A2* SNP-s (-163C>A, -729C>T, -2467T>delT, -3860G>A) 404 Roma (148 males, 256 females; mean age 35±11 years) and 396 Hungarian (236 males, 163 females; mean age 42±14 years) samples were analyzed. A total of 397 Roma (172 males, 225 females; mean age 36±14 years) and 412 Hungarian subjects (204 males, 208 females; mean age 41±22 years) were recruited to the examination of *CYP1B1*, *CYP2C8* and *CYP3A5* rs1056836, rs1058930 and rs776746 polymorphisms, respectively. DNA of total of 484 randomly selected Roma samples (230 males, 254 females, mean age 41 ± 20 years) and 493 randomly selected Hungarian samples (278 males, 215 females, mean age 37 ± 13 years) were used to determine the allele frequency of *CYP4F2*3* allele.

Molecular biology methods

Genomic DNA was isolated from peripheral leukocytes using routine salting out method.

PCR-RFLP and Real time PCR methods were applied to examine the cytochrome SNP-s and direct sequencing was performed by ABI PRISM 3100 AVANT Genetic Analyser on random samples to confirm our results. Regarding *CYP1A2*,we applied predesigned TaqMan Drug Metabolism Genotyping Real time PCR assay to identify the -2467delT polymorphism. PCR amplification was carried out using Chromo4 Real-Time PCR Detector with the following conditions: incubation for 2 min at 95℃, 40 cycles of denaturation for 20 s 95℃, annealing and primer extension for 40 s at 60℃. Genotypes were analyzed using MJ Opticon Monitor Analysis Software Version 3.1.

Genotyping of *CYP1A2* -163C>A, -3860G>A, -729C>T, *CYP1B1* rs1056836, *CYP2C8* rs1058930, *CYP3A5* rs776746 and *CYP4F2* rs2108622 polymorphisms were performed using PCR and a restriction endonuclease digestion (PCR-RFLP). Utilized primers, the PCR-RFLP conditions, the allele-specific restriction endonuclease enzymes and observed fragments for CYP variant genotyping are shown in Table 1. PCR amplification was carried out in a final volume of 50 μl containing each dNTP, Taq polymerase, reaction buffer, forward and reverse primers and extracted genomic DNA. PCR amplifications were performed on MJ Research PTC 200 thermal cyclers. Digested PCR products were separated by electrophoresis using a 3% agarose gel stained with ethidium-bromide and visualized by UV illumination.

Statistical evaluation

Statistical analyses were performed using SPSS Statistics 20.0 package for Windows. We applied Chi-square test to compare the differences between studied groups, $p \leq 0.05$ value was considered as statistically significant. For haplotype analyses we used Phase 2.1. software.

4. RESULTS

CYP1A2 gene

The prevalence rates of the examined four non-coding *CYP1A2* gene variants and genotypes are presented in Table 2. Concerning the *CYP1A2*1C* allele (-3860G>A) we found differences in the presence of -3860A allele in Hungarian population compared to the Roma samples (2.02% vs. 0%). The AA homozygous genotype was observed neither in Hungarians nor in Roma subjects. In regard of *CYP1A2*1F* allele (-163C>A), the AA homozygous genotype was the most common genotype identified in Hungarians (49.5%), while in Roma population the CA heterozygous genotype was the most frequent (50.0%). A remarkable differences were observed in the presence of AA genotypes in Roma population compared to Hungarians (31.9% vs. 49.5%, $p<0.001$) and in minor allele frequency (56.9% vs. 68.6%, $p=0.025$). For *CYP1A2*1D* (-2467delT), the -2467delT allele frequency was 6.81% in Roma and 5.81% in Hungarian samples. We found increased homozygous delT/delT genotype for *CYP1A2*1D* at position -2467 in Roma population samples compared with Hungarians, where this genotype was not detectable. The observed frequency of *CYP1A2* -729T allele was 0.25% in Hungarian samples, but this variant was not present in Roma population samples. The most frequent polymorphism in Romas and in Hungarians was the -163A; 56.9% vs. 6.81%, followed by -2467delT with frequency at 6.81% and 5.81%, respectively. The -3860A and -729T variants were considerably rare or absent.

Haplotype analysis was performed using the detected SNPs. Table 3 summarizes the determined five haplotypes (ht) and their frequencies in Roma and Hungarian samples. The prevalence of ht1, ht2, ht3, ht4, ht5 were 31.4%, 2.02%, 62.8%, 0.25% and 3.54% in Hungarians, respectively. The ht2 and ht3 were not present in Romas. The ht1, ht3 and ht5 haplotypes were detectable in Roma samples with the following frequencies: 43.1%, 50.1% and 6.81%, respectively.

CYP1B1, CYP2C8 and CYP3A5 genes

The frequency rates of *CYP1B1, CYP2C8* and *CYP3A5* gene variants and genotypes are presented in Table 4. For *CYP1B1*3* (c.4326C>G), significantly increased frequency was found in **3/*3* homozygous genotype in the Roma population compared to Hungarians (50.1% vs. 39.3%, p=0.002). The difference between the Roma and Hungarian samples for 4326G allele frequency was not statistically significant (69.4% vs. 64.2%, p=0.852). Concerning the *CYP2C8*4* allele (c.792C>G), we found significant differences in 792G allele frequency in Hungarian population compared to Romas (5.83% vs. 2.14%, p=0.001). The *4/*4 homozygous genotype was not found in Roma subjects, while in Hungarians this genotype was present with 1.46%. For *CYP3A5*3* (c.6986A>G), the 6986G variant was present in Roma and Hungarian samples with 0.757 and 0.920 prevalence, respectively (p=0.091). The frequency of homozygous *3/*3 genotype for this SNP was significantly increased in Hungarian samples compared to Roma samples (85.0% vs. 53.9%, p<0.001).

CYP4F2 gene

Allele and genotype frequencies of the *CYP4F2*3* (c.1297G>A) polymorphism were in Hardy–Weinberg equilibrium both in Roma and Hungarian subjects (Table 5). The frequencies of the *CYP4F2* 1297G>A SNP the GG, GA, AA genotypes and A variant allele in the Roma population were 46.5%, 42.6%, 10.9% and 32.2%, and in Hungarians 50.1%, 42.2%, 7.7% and 22.8%, respectively. Interestingly, more than half of the Roma population has a variant A allele (GA + AA, 53.5%), and the Hungarians have also high carrier allele frequency (GA + AA, 49.9%),

5. DISCUSSION

Our results show remarkable interethnic differences between the two studied populations. The frequency of *CYP1A2* -3860G>A polymorphism, which causes decreased enzyme activity, in Hungarians is similar to previously reported allele frequency rates from Europe. Based on our results, the slow metabolizer genotype is rare or missing in the two studied population. The observed -2467delT allele frequency in Hungarians is approximately equal to data were formerly found in Caucasian samples. The -2467delT variant in the promoter region is involved in the induction of CYP1A2, mostly in smokers. It is suggested that this polymorphism alters the binding region of the xenobiotic responsive element, thereby elevates CYP1A2 induction by components of smoke. These results suggest that tobacco user Roma people may have elevated cancer risk due to increased CYP1A2 induction, activity and intensified polycyclic aromatic hydrocarbons activation. Regarding to the *CYP1A2*1F* allele, the frequency rate in Hungarians is in accordance with the measured rate in Caucasians and other European population. The **1F* allele frequency measured in Roma samples is nearly similar to data was found in Indians by other researchers. The prevalence of variant *CYP1A2* -729T allele in Hungarian population was higher than in average European populations. This SNP is absent in Roma, Nigerian and Japanese populations.

After the haplotype analysis, the most frequent allelic constellation was -3860G/-2467T/-729C/-163A (**1F*), followed by -3860G/-2467T/-729C/-163C (**1A*) in Roma and Hungarian population. For -3860G/-2467delT/-729C/-163A constellation a remarkable increased frequency was observed in Roma population compared to Hungarians.

Apart from genetic background, many other factors affect the induction and inhibition of CYP1A2 enzyme activity, including dietary compounds, environmental and occupational exposure, concomitant medications, biological factors and smoking.

Concerning genetic polymorphisms of the examined *CYP1B1*, *CYP2C8* and *CYP3A5* genes involved in taxane drug metabolism and effect, we also found appreciable differences between the two populations.

In point of *CYP1B1*3*, the 4326G allele frequency was slightly elevated, and the homozygous **3/*3* genotype was significantly increased in Roma samples compared to Hungarians. The observed *CYP1B1*3* frequency in Hungarian population is 1.5-fold increased compared to previously reported Caucasian data. The obtained *CYP1B1* 4326G allele frequency in Roma population was also increased compared to results from other population with north Indian ancestry.

Regarding the examined *CYP2C8*4* variant, we assume, that Hungarians show decreased metabolism of CYP2C8 substrate drugs due to the more than two-fold elevated frequency of *CYP2C8*4* allele and the significantly increased presence of **4/*4* homozygous genotype compared to Romas. The prevalence of **4* allele in Hungarian population was found to roughly correspond with other Caucasian population data, while **4* allele frequency in Roma samples is only half of the previously reported north Indian rates.

For *CYP3A5*3*, the allele frequency in Hungarian samples was almost equal than in other European populations. In our Roma group the frequency of this variant was found to be increased compared to north Indian population. The increased prevalence rates of **3/*3* homozygous non-expressor genotype may frequently contribute to the slower metabolism of docetaxel in Hungarians compared to Roma population.

Functional conclusions from the study of *CYP4F2* rs2108622 variant are that the risk allele frequency of Roma was in higher range, and of Hungarians in lower range, as compared with other world populations. The carrier allele frequencies of Roma suggest the need for higher daily mean warfarin dose requirement compared to ancestral G allele carriers.

6. SUMMARY

1. In the studied Hungarian population compared to Roma population, we found significantly increased variant allele frequencies for *CYP1A2*1F* and *CYP2C8*4* alleles.

2. Significantly increased homozygous variant genotype frequency was observed for *CYP3A5*3* and *CYP1A2*1F* SNP-s in Hungarian samples and for *CYP1B1*3* allele in Roma samples.

3. Due to the low incidence of -3860A variant allele in *CYP1A2* gene (*CYP1A2*1C)*, the slow metabolizer genotype is rare, thus the risk for toxicity of CYP1A2 substrate drugs is low in Roma and Hungarian populations.

4. Based on our results regarding the increased frequency of *CYP1A2*1D* allele in Romas, it is suggested that Roma people may have elevated risk of developing malignant tumors.

5. The significantly high prevalence of functional *CYP1A2*1F* allele in Hungarian people may lead to increased chance for breast-, lung- and ovarian cancer, mostly in case of susceptible exposure.

6. We could detect 5 different haplotypes from the allelic constellations of -3860G>A, -2467T>delT, -729C>T and -163C>A non-coding variants of *CYP1A2* gene in Hunagarian samples, while in Roma samples the ht2 and ht4 haplotype were not detectable.

7. For *CYP1B1*3* polymorphism, we found an increased *3/*3 homozygous genotype frequency rate in Romas, which could explain the insufficient response to taxane treatment and decreased survival rate among cancer patients.

8. Hungarian people compared to Romas have higher plausibility for impaired metabolism of taxane drugs, therethrough for docetaxel and paclitaxel induced toxicity due to the more frequent presence of slow metabolizer *CYP2C8*4* and *CYP3A5*3* variants.

9. The higher prevalence of *CYP4F2*3* carrier genotypes in Roma samples suggest the need for higher daily warfarin dose requirement to achieve a therapeutic anticoagulant response compared to Hungarians.

7. PUBLICATIONS

PUBLICATIONS SUPPORTING THE DISSERTATION:

1. **Szalai R**, Magyari L, Matyas P, Duga B, Banfai Z, Szabo A, Kovesdi E, Melegh B.
Genetic polymorphisms in promoter and intronic regions of CYP1A2 gene in Roma and Hungarian population samples. Environ Toxicol Pharmacol. 2014;38(3):814-20.
IF: 2,084

2. **Szalai R**, Ganczer A, Magyari L, Matyas P, Bene J, Melegh B.
Interethnic differences of cytochrome P450 gene polymorphisms may influence outcome of taxane therapy in Roma and Hungarian populations. Drug Metab Pharmacokinet. 2015.
***IF: 2,568** (2014)*

3. Sipeky C, Weber A, Melegh BI, Matyas P, Janicsek I, **Szalai R**, Szabo I, Varnai R, Tarlos G, Ganczer A, Melegh B.
Interethnic variability of CYP4F2 (V433M) in admixed population of Roma and Hungarians. Environ Toxicol Pharmacol. 2015;40(1):280-3.
***IF: 2,084** (2014)*

OTHER PUBLICATIONS:

1. Szalai R, Matyas P, Varszegi D, Melegh M, Magyari L, Jaromi L, Sumegi K, Duga B, Kovesdi E, Hadzsiev K, Melegh B.
Admixture of beneficial and unfavourable variants of GLCCI1 and FCER2 in Roma samples can implicate different clinical response to corticosteroids. Mol Biol Rep. 2014 Nov;41(11):7665-9.
IF: 2,024

2. Weber A, **Szalai R**, Sipeky C, Magyari L, Melegh M, Jaromi L, Matyas P, Duga B, Kovesdi E, Hadzsiev K, Melegh B.
Increased prevalence of functional minor allele variants of drug metabolizing CYP2B6 and CYP2D6 genes in Roma population samples. Pharmacol Rep. 2015 Jun;67(3):460-4.
IF: 1,928

3. Sipeky C, Matyas P, Melegh M, Janicsek I, **Szalai R**, Szabo I, Varnai R, Tarlos G, Ganczer A, Melegh B.

Lower carrier rate of GJB2 W24X ancestral Indian mutation in Roma samples from Hungary: implication for public health intervention. Mol Biol Rep. 2014 Sep;41(9):6105-10.

IF: 2,024

4. Magyari L, Varszegi D, Sarlos P, Jaromi L, Melegh BI, Duga B, Kisfali P, Kovesdi E, Matyas P, Szabo A, **Szalai R**, Melegh B.

Marked differences of haplotype tagging SNP distribution, linkage, and haplotype profile of IL23 receptor gene in Roma and Hungarian population samples. Cytokine. 2014 Feb;65(2):148-52.

IF: 2,664

5. Nagy A, **Szalai R**, Magyari L, Bene J, Toth K, Melegh B.

Extreme differences in SLCO1B3 functional polymorphisms in Roma and Hungarian populations. Environ Toxicol Pharmacol. 2015 May;39(3):1246-51.

IF: 2,084

6. Sumegi K, Jaromi L, Magyari L, Kovesdi E, Duga B, **Szalai R**, Maasz A, Matyas P, Janicsek I, Melegh B.

Functional Variants of Lipid Level Modifier MLXIPL, GCKR, GALNT2, CILP2, ANGPTL3 and TRIB1 Genes in Healthy Roma and Hungarian Populations. Pathol Oncol Res. 2015 Jan 9.

IF: 1,855

7. Nagy A, Sipeky C, **Szalai R**, Melegh B I, Matyas P, Ganczer A, Toth K, Melegh B

Marked differences in frequencies of statin therapy relevant SLCO1B1 variants and haplotypes between Roma and Hungarian populations. BMC Genetics.

IF: 2,40

Impact factor of publications which have served as a base for the thesis: **6,736**

Impact factor of other published articles: **14,979**

Cumulative impact factor: **21,715**

8. ACKNOWLEDGEMENTS

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Table 1. Primers and PCR-RFLP conditions used for genotyping of cytochrome P450 gene polymorphisms

Gene	Variant	Primers (5'-3')		PCR annealing temperature(℃)	PCR product (bp)	Endonuclease	Fragments (bp)	Genotype
CYP1A2	rs2069514	Forward	TCATCAAGCTACACATGATCGAG	59	611	BseLI (BslI)	123, 139, 349	GG
							123, 139, 349, 488	GA
		Reverse	TGCGTGTCAGGTCTCTTCAC				123, 488	AA
	rs762551	Forward	GGTATCAGCAGAAAGCCAGC	59	298	Bme1390I (ScrFI)	46, 66, 186	CC
							46, 66, 186, 232	CA
		Reverse	CCCAGCTGGATACCAGAAAG				66, 232	AA
	rs12720461	Forward	ACTCACCTAGAGCCAGAAGCTC	60	250	Bme1390I (ScrFI)	28, 33, 67, 122	CC
							28, 33, 67, 95 122	CT
		Reverse	AATGGCTTAGTCCAAACTGCC				33, 95, 122	TT
CYP1B1	rs1056836	Forward	TCATCACTCTGCTGGTCAGG	57	311	BseNI (BsrI)	22, 95, 194	CC
							22, 95, 117, 194	CG
		Reverse	AGAATTGGATCAGGTCGTGG				117, 194	GG
CYP2C8	rs1058930	Forward	GGTCTGCAATAATTTCCCTC	55	500	TaqI	83, 150, 267	CC
							83, 150, 233, 267	CG
		Reverse	TGATATTCATCTTCAGTTTGTGG				233, 267	GG
CYP3A5	rs776746	Forward	GTGGTCCAAACAGGGAAGAGGT	62	309	RsaI	96, 213	AA
							22, 74, 96, 213	AG
		Reverse	GCCCATACAGGCAACATGACTTAG				22, 74, 213	GG
CYP4F2	rs2108622	Forward	ATCAACCCGTTCCCACCT	60	492	PvuII	176, 316	GG
							176, 316, 492	GA
		Reverse	ACATTGTGCTCCCAGACG				492	AA

Table 2. Genotypes and allele frequencies of *CYP1A2* polymorphisms in Roma and Hungarian population samples

Polymorphism	Genotype	Genotype frequency		Allele	Allele frequency	
		Roma n=404 (%)	Hungarian n=396 (%)		Roma (%)	Hungarian (%)
-163C>A	C/C	73 (18,1)	49 (12,4)	C	43,1	31,4
	C/A	202 (50,0)	151 (38,1)	**A**	56,9	68,6*
	A/A	129 (31,9)	196 (49,5)#			
-3860G>A	G/G	404 (100,0)	380 (95,9)	G	100,0	98,0
	G/A	0 (0,0)	16 (4,04)	**A**	0,0	2,0
	A/A	0 (0,0)	0 (0,0)			
-2467delT	T/T	352 (87,1)	350 (88,4)	T	93,2	94,2
	T/delT	49 (12,1)	46 (11,6)	**delT**	6,8	5,8
	delT/delT	3 (0,74)	0 (0,0)			
-729C>T	C/C	404 (100,0)	394 (99,5)	C	100,0	99,7
	C/T	0 (0,0)	2 (0,5)	**T**	0,0	0,3
	T/T	0 (0,0)	0 (0,0)			

*p=0,025
#p<0,001

Table 3. Observed frequencies of detected haplotypes (ht) created by the examined CYP1A2 variants in Roma and Hungarian samples

Haplotype	Allelic constellation				Frequency	
	-3860G>A	-2467T>delT	-729C>T	-163C>A	Roma n (%)	Hungarian n (%)
ht1	G	T	C	C	348 (43,1)	249 (31,4)
ht2	A	delT	C	A	-	16 (2,02)
ht3	G	T	C	A	405 (50,1)	497 (62,8)
ht4	G	delT	T	A	-	2 (0,25)
ht5	G	delT	C	A	55 (6,81)	28 (3,54)

Table 4. Distributin of genotype and allele frequencies of examined cytochrome P450 gene polymorphisms in Roma and Hungarian population samples

Gene	Polymorphism	Genotype	Hungarian n=412 (%)	Roma n=397 (%)
CYP1B1	c.4326C>G	CC	45 (10,92)	45 (11,34)
		CG	205 (49,76)	153 (38,54)
		GG	162 (39,32)	199 (50,12)*
		G allele frequency	0,642 (64,2)	0,694 (69,4)
CYP2C8	c.792C>G	CC	370 (89,80)	380 (95,72)
		CG	36 (8,74)	17 (4,28)
		GG	6 (1,46)	0 (0,00)
		G allele frequency	0,058 (5,83)	0,021 (2,14)[#]
CYP3A5	c.6986A>G	AA	4 (0,97)	10 (2,52)
		AG	58 (14,08)	173 (43,58)
		GG	350 (84,95)	214 (53,90)[¥]
		G allele frequency	0,920 (92,0)	0,757 (75,7)

*p=0,002 [#]p=0,001 [¥]p<0,001

Table 5. Genotype and allele frequencies of *CYP4F2* c.1297G>A polymorphism in Roma and Hungarian populations

Gene	Polymorphism	Genotype	Hungarian n=493 (%)	Roma n=484 (%)
CYP4F2	c.1297G>A	GG	247 (50,1)	225 (46,5)
		GA	208 (42,2)	206 (42,6)
		AA	38 (7,7)	53 (10,9)
		A allélfrekvencia	0,228 (22,8)	0,322 (32,2)