INTERETHNIC DIFFERENCES OF GENES INFLUENCING TAMOXIFEN THERAPY IN HUNGARIAN AND ROMA POPULATION SAMPLES

PhD Thesis

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Pecs, 2020

1. Introduction

Just like nutrients which enter our body, medications and xenobiotics are eliminated through biotransformation, which show varying degrees of effectiveness and speed. This variability is a common and complex problem in clinical practice, which can be explained in 20-95% with the individual genetic profile. The subject of pharmacogenetics examines genetic variants behind different ways individuals react to medications, therapeutic effects and side effects. Pharmacogenomics examines the combined effects of genes involved in drug metabolism. In personalized medicine, our goal is to reveal the individual DNA profile by pharmacogenetic methods and to predict the individual response expected when using different drugs. Pharmacogenetic testing is now available in routine clinical practice for a number of variants which could be expected to produce serious side effects in the presence of genetic variants. The effect of these variants remains undetected until the individual has encountered the active substance in question during a treatment. These genetic polymorphisms are also found in genes of enzymes, transport proteins, or receptors which are involved in the metabolism of several medications. Pharmacogenetically speaking the most important hepatic microsomal monooxygenase enzyme is cytochrome P450 (CYP) enzyme which catalyzes phase I reactions. Single nucleotide polymorphisms (SNPs) in the genes of the cytochrome P450 family of utmost importance because they play a crucial role in the metabolic conversion of a significant proportion of medications used. It is a well-known fact that the incidence of certain diseases varies significantly between different racial and ethnic groups. Numerous previous studies report that the role of genetic variants in determining disease susceptibility and response to drugs also implies the need to determine the frequency of each variant in different populations. Breast cancer is the most common cancer in women worldwide. About 1.4 million cases occur every year. Tamoxifen in an oncological treatment, acts as a selective estrogen receptor modulator, represented the first targeted therapy as a forerunner of personalized medicine. Among the members of the cytochrome P450 enzyme system, tamoxifen is an important substrate for CYP2D6, CYP2B6 and CYP2C19.

2. Aims of the study

The main objective of my work was to study five pharmacogenetically important polymorphisms of three cytochrome P450 genes influencing tamoxifen therapy in Roma and Hungarian populations. The purposes of the work are the following:

- To determine the allele frequencies of functionally significant rs1065852 and rs3892097 polymorphisms of *CYP2D6* gene in healthy Hungarian and Roma population samples.

- To study the metabolizing phenotype distribution of *CYP2D6* in Hungarian and Roma populations.

- To determine the allele frequency of *CYP2B6* rs3745274 variant, which is responsible for decreased *CYP2B6* expression in both examined populations.

- To characterize the allele frequencies of *CYP2C19* rs4244285 and rs4986893 SNPs (determining *CYP2C19*2* and *CYP2C19*3* alleles, respectively*)* in Hungarian and Roma populations.

- To describe the distribution of predicted phenotypes based on *CYP2C19* genotypes in Hungarian and Roma subjects in point of tamoxifen therapy.

- To compare the allele frequencies of *CYP2D6, CYP2B6* and *CYP2C19* polymorphisms of Hungarian and Roma populations with results available for other ethnic populations in the literature, mainly with Caucasian and Indian populations.

3. Material and methods

Studied populations

The DNA samples of the Roma and the Hungarian population originated from the central Biobank governed by the University of Pecs, as part of the National Biobank Network of Hungary, which belongs also to the pan-European Biobanking and Biomolecular Resources Research Infrastructure project. The maintenance and governance principles of the Biobank have been approved by the National Scientific Research Ethics Committee (ETT TUKEB, Budapest, Hungary). The collection and usage of DNA samples and management of data followed the Helsinki Declaration of 1975.

We examined five pharmacogenetically relevant polymorphisms of three cytochrome P450 genes (*CYP2C19, CYP2B6, CYP2D6*).

According to *CYP2B6* c.516G>T (rs3745274), *CYP2D6* c.100C>T (rs1065852) and *CYP2D6* c.1846G>A (rs3892097) SNP-s 426 Roma (151 males, 275 females; mean age 43.3±10 years) and 431 Hungarian (248 males, 138 females; mean age 37.6±13 years) DNA samples were analyzed.

Furthermore, a total of 500 Roma (178 males, 322 females; mean age 39±16 years) and 370 Hungarian subjects (176 males, 194 females; mean age 50±19 years) were recruited to the examination of *CYP2C19*2* (rs4244285) and *CYP2C19*3* (rs4986893) polymorphisms.

Molecular biology methods

Genomic DNA was isolated from peripheral EDTA-anticoagulated blood samples using a standard desalting method.

Regarding *CYP2B6* and *CYP2D6* variants, we applied predesigned TaqMan Drug Metabolism Genotyping Real time PCR assay to identify the *CYP2B6* c.516G>T, *CYP2D6* c.100C>T and c.1846G>A polymorphism. PCR amplification was carried out using Chromo4 Real-Time PCR Detector with the following conditions: incubation for 2 min at 95°C, 40 cycles of denaturation for 20 s 95°C, annealing and primer extension for 40 s at 60°C. Genotypes were analyzed using MJ Opticon Monitor Analysis Software Version 3.1.

Genotyping of *CYP2C19* rs4244285 (*CYP2C19*2*) és rs4986893 (*CYP2C19*3*) polymorphisms were performed using PCR and a restriction endonuclease digestion (PCR-

RFLP). 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.

Direct sequencing was performed by ABI 3500 Genetic Analyzer (Applied Biosystems [CA, USA]) on random samples to confirm our results using BigDye Terminator v.1.1 cycle sequencing kit.

Statistical evaluations

Statistical analyses were performed using SPSS Statistics 20.0 package for Windows. We applied Chi-square (χ^2) test to compare the differences between studied groups, $p \leq 0.05$ value was considered as statistically significant.

4. Results

CYP2D6, CYP2B6

CYP2D6 and *CYP2B6* allele frequencies and genotype rates were in Hardy-Weinberg equilibrium in both of Hungarian and Roma groups. The prevalence rates of the examined *CYP2D6* and *CYP2B6* gene variants are presented in Table 1, Table 2 and Table 4.

For *CYP2B6* c.516G>T the T allele frequency was significantly higher in the Roma group than in Hungarian population (33.6% vs. 21.4%, respectively, $p < 0.001$). A significant increase was found in genotype frequencies for homozygous minor allele carrier in Roma participants (9.9%) compared to Hungarians (5.6%) ($p = 0.018$).

Furthermore, a significant increase was found in minor allele frequencies for both *CYP2D6* variants when comparing Roma subjects to Hungarians. The minor *CYP2D6* 100T allele frequency was 26.6% in Roma and 20.5% in Hungarian samples ($p = 0.003$). The same result was observed when we compared the two groups for *CYP2D6* c.1864G>A polymorphism. We found higher frequency of the detrimental 1864A allele in Roma population compared to Hungarians (22.5% vs. 18.1%, $p = 0.022$). Regarding the *CYP2D6* polymorphisms we found significantly ($p = 0.017$) increased prevalence for TT homozygous genotype for c.100C>T in Roma population compared with Hungarians (10.8% vs. 6.3%), for c.1846G>A polymorphism the homozygous AA genotype rate was lower in Roma samples compared with Hungarians (4.2% vs. 5.3%, $p = 0.446$). The *CYP2D6* genotypes and the related predicted phenotypes are presented in Table 3. In Roma subjects the following *CYP2D6* genotypes were identified with the following occurrence: *1/*1 (55.4%), *1/*4 (2.1%), *1/*10 (3.1%), *4/*10 (38.7%), *10/*10 (0.7%) and *4/*4 was not detectable. In Hungarian samples the genotypes were: *1/*1 (62.6%), *1/*4 (1.6%), *1/*10 (5.1%), *4/*10 (28.3%), *10/*10 (1.4%) and *4/*4 (0.9%).

Table 1. *Genotypes and minor allele frequencies of CYP2D6 c.100C>T polymorphism*

***CYP2D6* c.100C>T**	**Roma n=426 (%)**	**Hungarian n=431 (%)**
CC	245 (57.5)	281 (65.2)
CT	135 (31.7)	123 (28.5)
TT	46 (10.8)*	27 (6.3)
T allele frequency	26.6 %*	20.5%

*p<0.05 vs Hungarian population

Table 2. *Genotypes and minor allele frequencies of CYP2D6 c.1846G>A polymorphism*

***CYP2D6* c.1846G>A**	**Roma n=426 (%)**	**Hungarian n=431 (%)**
GG	252 (59.2)	298 (69.1)
GA	156 (36.6)	110 (25.5)
AA	18 (4.2)	23 (5.3)
A allele frequency	22.5%*	18.1%

*p<0.05 vs Hungarian population

Table 3. *Genotype frequencies and the predicted phenotypes of CYP2D6*

Phenotypes	**Genotypes**	**Genotype frequencies**	
		Roma n=426 (%)	**Hungarian n=431 (%)**
EM	*1/*1	236 (55.4)	270 (62.6)
	*1/*10	13 (3.1)	22 (5.1)
IM	*10/*10	3 (0.7)	6 (1.4)
	*1/*4	9 (2.1)	7 (1.6)
	*4/*10	165 (38.7)	122 (28.3)
PM	*4/*4	-	4 (0.9)

EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer

Table 4. *Genotypes and minor allele frequencies of CYP2B6 c.516G>T polymorphism*

CYP2B6 **c.516G>T**	**Roma** **n=426 (%)**	**Hungarian** **n=431 (%)**
GG	182 (42.7)	271 (62.9)
GT	202 (47.4)	136 (31.6)
TT	42 (9.9)*	24 (5.6)
T allele frequency	33.6 %*	21.4 %

*p<0.05 vs Hungarian population

CYP2C19

The allele and genotype frequencies of the *CYP2C19* c.681G>A polymorphism in Roma and Hungarian populations are shown in Table 5. The allele and genotype frequencies were in Hardy–Weinberg equilibrium both in Roma and Hungarian subjects. None of the subjects in our study populations of Roma and Hungarian samples was found to carry the *CYP2C19* c.636G>A SNP (*CYP2C19*3* allele). Significant differences were found when we compared the genotype frequencies of the *CYP2C19* 681 variant in the Roma and Hungarian populations: GG 63.6 versus 75.9%, GA 31.8 versus 23.0 %, AA 4.6 versus 1.1 %, GA+AA 36.4 versus 24.1%. Furthermore, the A allele frequency also displayed a difference (0.205 vs. 0.125, respectively).

CYP2C19 allele, genotype and predicted phenotype frequencies were compared between the two studied groups, and with data reported from different ethnic populations (**Table 8**). Striking differences were found between the Roma and Hungarian samples studied in the distribution of the *CYP2C19*1* (79.5 vs. 87.4%) and *CYP2C19*2* (20.5 vs. 12.6%) alleles, respectively. The most common *CYP2C19* genotype was the EM phenotype predicting *1/*1 wild type both in Roma (0.636) and in Hungarian (0.759) samples. The frequency of the *1/*2 genotype, which predicts the IM phenotype, was significantly higher in Roma than in Hungarians (0.318 vs. 0.230). Furthermore, the prevalence of the *2/*2 genotype, defining PM status, was 0.046 in Roma and 0.011 in the samples from the Hungarian population. The *1/*3, *2/*3 and *3/*3 genotypes were found neither in Roma nor in Hungarian samples studied. An important finding of our study is, that according to the genotype data the proportion of predicted PM phenotype was more than fourfold higher in Roma population than in Hungarians. Moreover, the predicted IMs were found also significantly more frequent in Roma than in Hungarians.

Table 5. *Genotype and allele frequencies of CYP2C19*2 polymorphism in healthy Roma and Hungarian population samples*

CYP2C19 polymorphism	**Genotypes**	**Roma n (%)**	**Hungarian n (%)**	**p**
*CYP2C19*2*	GG	318 (63.6)	281 (75.9)	<0.001
(c.681G>A)	GA	159 (31.8)	85 (23.0)	0.004
(Pro227Pro)	AA	23 (4.6)	4 (1.1)	0.003
	GA+AA	182 (36.4)	89 (24.1)	<0.001
	A allele frequency	20.5	12.6	<0.001

5. Discussion

CYP2B6 and CYP2D6

Several drugs are metabolized through cytochrome P450 enzymes. Two members of this enzyme system including CYP2B6 and CYP2D6 show marked interethnic differences in allele distribution. Genotype profile defines distinct dose requirements in different populations. The presence of polymorphisms in *CYP2B6* and *CYP2D6* has clinical relevance in patients treated with medications with narrow therapeutic window such as cyclophosphamide and tamoxifen. The c.516G>T polymorphism in *CYP2B6* gene is responsible for a splicing defect resulting in low CYP2B6 expression, higher clearance and shorter half-life of cyclophosphamide.

We found significant differences between Roma and Hungarian samples in 516T allele frequencies and TT homozygous genotype. The occurrence of *CYP2B6* c.516G>T polymorphism is more common in Roma people than in Hungarians, thus they have a greater likelihood for aberrant splicing, reduced protein activity and side effects through impaired CYP2B6-mediated drug metabolism. Homozygous *CYP2B6* 516TT genotype was found with a frequency of 9.9% in Roma population. This rate is the closest to data from Kenya (10.1%), lower than in African and American people, but almost threefold higher than in East Asian populations (3.5%). The obtained Hungarian *CYP2B6* 516T allele frequency (21.4%) is less than in other European populations (German, Spanish, Swiss and British). In Romas this prevalence is lower than the reported data from India.

Genotyping of *CYP2D6* and prediction of a metabolizer phenotype have clinical relevance in tamoxifen treated patients. In *CYP2D6* the examined two SNPs have altered prevalence in dissimilar populations because of various descents. Asian populations are less likely to possess *CYP2D6*4* allele, but have a higher likelihood for *CYP2D6*10*. In contrast, **4* is one of the most common variant alleles in Caucasian people. The observed *CYP2D6 *4* and **10* allele frequencies in Roma and Hungarian populations compared to other nations are shown in **Table 6**. Our Roma results for **4* and **10* allele are markedly higher than South and Malay Indian population rates. For **4* we obtained a slightly elevated allele frequency in Roma samples compared to Sinhalese and American Indian populations. In contrast, our Hungarian results reflect other European and Caucasian population data in particular for **4*. The **10* allele was not determined in several studies.

We also investigated the genotypical alterations and the predicted phenotype distribution in point of *CYP2D6* polymorphisms between Roma and Hungarian samples. The

obtained *CYP2D6* genotypes and predicted phenotypes are presented in **Table 3**. As reported, in Caucasians the occurrence of phenotype groups is 70% are EMs, 20% are IMs and 8% are PMs. In our investigation of Hungarian Caucasian samples the following frequencies were obtained: 67.7% were EMs, 31.3% were IMs, 0.9% were PMs. In contrast, in Roma samples the rates were 58.5%, 41.5% for EMs and IMs, respectively. The PM phenotype (*4/*4 genotype) was not present. In conclusion, the examined genetic polymorphisms in Roma samples differ from Hungarian, Caucasian and Indian populations. We determined the distribution of allele, genotype and phenotype frequencies of major variants of *CYP2B6* and *CYP2D6* in Roma and Hungarian population samples. Summarizing our findings, Roma people have greater risk for lower hepatic CYP2B6 and CYP2D6 protein expression and activity due to the more frequent presence of reduced and non-functional variants when compared to Hungarians.

Table 6. *Comparison of CYP2D6*4 and *10 allele frequencies of Romas and Hungarians in relation to previously published data.*

Population	n	CYP2D6	
		*4 (%)	*10 (%)
Roma	426	22.5	26.6
Hungarian	431	18.1	20.5
Tamil	106	6.6	20.3
Tamil	30	6.7	35.0
Malay Indian	86	8.0	15.0
Malay	107	2.8	49.5
Sinhalese	30	21.7	40.0
South Indian	447	7.3	10.2
American Indian	187	20.8	1.34
Indian	125	10.0	26.8
North Indian	300	15.8	ND
Danish	228	21.9	ND
Norwegian	151	20.5	ND
Swedish	254	18.5	ND
German	323	18.6	ND
Netherlands	765	18.4	ND
Russian	290	18.2	4.2
Caucasian	454	18.8	2.8
Caucasian	142	18.2	19.6

ND, not determined

Table 7. *CYP2B6 516T allele frequencies in Roma and Hungarian samples compared other population data*

Population	**n**	**c.516G>T (%)**
Roma	426	33.6
Hungarian	431	21.4
Turkish	172	28.0
German	215	28.0
Spaniard	180	23.0
Swiss	141	24.8
British	135	28.1
South Indian	72	44.0
Central American	181	25.0

CYP2C19

The drug metabolizing enzyme CYP2C19 is responsible for activation and detoxification of several clinically important drugs. Inter-ethnic variation in the frequency of *CYP2C19* variant alleles, that define clinical phenotypes with normal, medium and low rates of drug metabolism (EM, IM, PM) are important from clinical perspective, as patients in these groups require different drug dosage to achieve the best therapeutic response and lowest rate of adverse events.

The prevalence of the *CYP2C19* allele, genotype and predicted phenotype frequencies reported from different ethnic populations residing in different geographic areas are summarized in **Table 8**. The highest frequency of *CYP2C9*2* allele was found in East Asian (23.0–45.5%) and Indian (29.7-41.7%) populations, however, the lowest frequency can be found in European (9.1–18.8%) and West Asian (12.0–15.0%) populations. It should be noted that the *CYP2C19*2* variant being represented in different ethnic groups at a similar and relatively high frequency implies that this determining mutation is quite old, occurred before the Black, Oriental and Caucasian racial group split. The *CYP2C9*3* variant was found in increasing order in different populations as follows: Europeans (0.0–0.9%), North Americans (0.0–0.2%), West Asians (0.0–1.0%), Indians (0.0–2.2%), Africans (0.0–3.0%) and East Asians (1.0–14.0%). In contrast, very low frequency or total absence of the *CYP2C19*3* variant in different Caucasian populations and its relatively high prevalence (25%) in Oriental racial group indicate that this mutation occurred quite recently, after the differentiation of the Caucasian and Oriental racial groups. Various studies reported a prevalence of 0–25.6% *CYP2C19* PM phenotype among different populations. The highest incidence of PMs has been reported among East Asians (5.60–24.0%) and populations from India (9.8–20.2%). In contrast, North Americans (1.3–9.0 %), Africans (0.0–5.3 %), Europeans (0.7–4.3%) and West Asians (0.7–3.1%) have much lower PM frequencies in average. Comparing the Roma and Hungarian populations, Roma have significanly higher frequency of the *CYP2C19*2* variant and a higher prevalence of IMs, and a remarkable fourfold increase of the PM phenotype. Therefore, this indicates, that Roma are at increased risk for developing adverse effects treated by CYP2C19 subtrates. The prevalence of the common observed *CYP2C19* allelic variants, genotypes and predicted EM, IM and PM phenotypes in Roma population is in accordance with dose observed in the North Indian population, except the clinically relevant *CYP2C19*2* allele; Roma have a significantly lower *CYP2C19*2* frequency. The genotype and the corresponding phenotype distribution of the *CYP2C19* gene in the Roma population appear to represent a transition

between the values for populations from different areas of India and the European Caucasian populations. Interestingly, in European Caucasian populations a slight decrease in *CYP2C19*2* allele frequency can be observed from North to South. In this perspective, the Hungarian population can be placed in the middle of this gradient. Despite its unique ethnic origin, the studied Hungarian population exhibited frequencies of the *CYP2C19*2* and *CYP2C19*3* variant alleles similar to those in other Caucasian populations. We found that the Roma population differed significantly from the Hungarians and from Caucasians, however comparing to population samples reported from India no difference could be observed, except for the *CYP2C19*2* variant allele. In contrast, contemporary Hungarian people do not differ significantly from other European Caucasian populations in relation to the prevalence of common *CYP2C19* variants. Our findings suggest that Roma people are at increased risk of variation in CYP2C19 substrate metabolic and drug response compared to the Hungarian population.

Table 8. *Comparison of allele, genotype and predicted phenotype frequencies of CYP2C19 gene reported from different ethnic populations*

Population	n	CYP2C19 Alleles			CYP2C19 Genotypes						Predicted phenotypes		
		*1	*2	*3	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	EM	IM	PM
Hungarian	500	79.5*	20.5*	0.0	63.6*	31.8*	0.0	4.6*	0.0	0.0	63.6	31.8*	4.6*
Roma													
Hungarian	370	87.4	12.6	0.0	75.9	23.0	0.0	1.1	0.0	0.0	75.9	23.0	1.1
Hungarian	112	82.6	16.5	0.9	-	-	-	-	-	-	67.0	31.2	1.8
Europe													
Dutch	765	86.5	13.3	0.2	-	-	-	-	-	-	74.8	22.4	2.8
Swedish	83	85.0	14.0	0.1	71.0	27.0	1.0	1.0	0.0	0.0	71.0	28.0	1.0
Danish	239	84.0	16.0	0.0	71.5	24.7	0.0	3.8	0.0	0.0	71.5	24.7	3.8
Faroese	310	81.8	18.8	0	66.2	31.2	0	3.2	0.0	0.0	66.2	31.2	3.2
Belgian	121	90.9	9.1	0.0	83.5	14.9	0.0	1.6	0.0	0.0	83.5	14.9	1.6
German	140	85.0	15.0	0.0	-	-	-	-	-	-	-	-	-
Russian	290	88.3	11.4	0.3	78.7	19.0	0.3	1.7	0.3	0.0	78.7	19.3	2.0
Croatian	200	85.0	15.0	0.0	73.0	24.0	0.0	3.0	0.0	0.0	73.0	24.0	3.0
Italian	360	88.9	11.1	0.0	79.4	18.9	0.0	1.7	0.0	0.0	79.4	18.9	1.7
Greek	283	86.9	13.1	0.0	75.9	21.9	0.0	2.2	0.0	0.0	75.9	21.9	2.2
Portuguese	153	87.0	13.0	0.0	-	-	-	-	-	-	-	-	1.0
India													
Aryan (North)	121	70.3	29.7	0.0	47.9	44.6	0.0	7.4	0.0	0.0	47.9	44.6	7.4
Tamilian	112	59.8	37.9	2.2	29.5	58.0	2.7	8.0	1.8	0.0	29.5	60.7	9.8
(South)													
Tamilian	292	-	-	-	34.9	44.2	0.7	19.5	0.7	0.0	34.9	44.9	20.2
(South)													
Andhra Pradesh	115	67.0	33.0	0.0	46.0	42.0	0.0	12.0	0.0	0.0	46.0	42.0	12.0
Dravidian	220	-	-	-	-	-	-	-	-	-	32.2	52.8	15.0
(South)													
Kerala (South)	118	68.0	31.0	1.0	47.0	42.0	1.0	9.0	1.0	0.0	47.0	43.0	10.0
Karnataka	108	60.0	39.0	1.0	39.0	43.0	0.0	17.0	1.0	0.0	39.0	43.0	18.0
Maharashtrian	139	57.1	41.7	1.2	33.8	45.3	1.4	18.7	0.7	0.0	33.8	46.7	19.4
(West)													
Gujrati and	164	-	-	-	-	-	-	-	-	-	89.6	0.0	10.4
Marwadi													
Africa													
Tanzanians	251	81.0	18.0	1.0	66.0	30.0	1.0	3.0	0.0	0.0	66.0	31.0	3.0
Egyptian	247	88.8	11.0	0.2	78.6	20.2	0.4	0.8	0.0	0.0	78.6	20.6	0.8
Ethiopians	114	85.0	14.0	3.0	75.0	19.0	1.0	3.0	3.0	0.0	75.0	20.0	5.2

Population	n	CYP2C19											
		Alleles			Genotypes						Predicted phenotypes		
		*1	*2	*3	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	EM	IM	PM
Zimbabweans	168	87.0	13.0	0.0	77.0	19.0	0.0	4.0	0.0	0.0	77.0	19.0	4.0
Venda	152	78.3	21.7	0.0	61.8	32.9	0.0	5.3	0.0	0.0	61.8	32.9	5.3
Beninese	111	87.0	13.0	0.0	73.9	26.1	0.0	0.0	0.0	0.0	73.9	26.1	0.0
Japanese	53	67.0	23.0	10.4	-	-	-	-	-	-	-	-	-
Japanese	217	61.8	27.4	10.8	-	-	-	-	-	-	-	-	15.2
Japanese	186	59.0	29.0	12.0	-	-	-	-	-	-	-	-	18.8
Chinese Han	101	55.9	36.6	7.4	-	-	-	-	-	-	-	-	-
Chinese Bai	202	69.0	26.0	5.0	-	-	-	-	-	-	-	-	13.4
Chinese	121	50.0	45.5	4.5	-	-	-	-	-	-	-	-	24.0
Chinese Dai	193	66.3	30.3	3.4	-	-	-	-	-	-	-	-	9.3
Chinese Mongolian	280	72.0	24.0	4.0	51.0	35.0	6.0	6.0	1.0	1.0	51.0	41.0	8.0
Chinese Taiwanian	118	63.0	32.0	5.5	-	-	-	-	-	-	-	-	-
Chinese Malaysian	68	59.0	31.0	10.0	36.8	38.2	5.9	5.9	11.8	1.5	36.8	44.1	19.2
Malaysians	142	66.0	28.0	6.0	42.0	40.0	6.0	6.0	6.3	1.0	42.0	46.0	13.4
Malaysian Indian	20	63.0	38.0	0.0	35.0	55.0	0.0	10.0	0.0	0.0	35.0	55.0	10.0
Taiwanese	179	62.6	32.4	5.0	36.5	44.9	6.7	8.4	3.4	0.0	36.5	51.6	11.8
Filippino	52	54.0	39.0	8.0	-	-	-	-	-	-	-	-	23.0
Koreans	103	67.5	20.9	11.7	-	-	-	-	-	-	-	-	11.7
Burmese	127	66.0	30.0	4.0	44.1	39.4	5.5	9.4	1.6	0.0	44.1	44.9	11.0
Thai (Burma)	774	68.0	29.0	3.0	44.5	42.6	3.7	6.7	2.1	0.4	44.5	46.3	9.2
Karen (Burma)	131	71.0	28.0	1.0	51.1	39.7	0.8	7.6	0.8	0.0	51.1	40.5	8.4
Vietnamese	90	62.0	24.0	14.0	-	-	-	-	-	-	-	-	20.0
Turkish	404	87.0	12.0	0.4	76.0	22.3	0.74	0.9	0.0	0.0	76.0	23.0	1.0
Israeli Jewish	140	84.0	15.0	1.0	70.7	26.4	1.4	2.0	0.0	0.0	70.7	27.8	2.0
Saudi Arabian	97	85.0	15.0	0.0	-	-	-	-	-	-	-	-	2.0
Iranian	147	86.0	13.0	1.0	74.1	25.2	0.6	0.0	0.6	0.0	74.1	2.52	0.68
Iranian	200	86.0	14.0	0.0	75.0	22.0	0.0	3.0	0.0	0.0	75.0	22.0	3.0
North America													
Canadian Native Indian	115	80.9	19.1	0.0	-	-	-	-	-	-	-	-	7.0
Canadian Inuit	152	88.0	12.0	0.0	-	-	-	-	-	-	-	-	-
African Americans	517	81.0	19.0	0.0	66.0	30.0	0.0	3.0	0.1	0.0	66.0	30.0	3.1
African Americans	76	80.9	19.1	0.0	48.0	27.0	0.0	1.0	0.0	0.0	48.0		1.3
African Americans	100	84.0	16.0	0.0	70.0	28.0	0.0	2.0	0.0	0.0	70.0	28.0	2.0

6. Summary

- We found significantly increased variant allele frequency for the examined CYP2D6 c.100C>T polymorphism and homozygous variant CYP2D6 100TT genotype frequency in Roma samples compared to Hungarian samples.

- Based on the *CYP2D6* genotypes, the most frequent predicted phenotype is the extensive metabolizer phenotype in both groups. The poor metabolizer phenotype (*CYP2D6 *4/*4* genotype) was not detectable in Roma population. The most frequently found genotype was the *CYP2D6 *4/*10* (intermediate metabolizer phenotype) in both examined population.

- For *CYP2B6* c.516G>T polymorphism, we found significantly elevated frequency in TT homozygous genotype and 516T SNP in Roma population samples compared to Hungarians.

- The *CYP2C19*3* allele was not detectable either in Roma or in Hungarian samples. For the *CYP2C19*2* polymorphism the frequency of **2* variant allele and **2/*2* homozygous variant genotype was significantly increased in Romas.

- Regarding *CYP2C19*2*, the intermediate metabolizer phenotype (characterized by *1/*2 genotype) and poor metabolizer phenotype (characterized by *2/*2 genotype) was significantly increased in Roma samples.

- Our results for *CYP2B6* in Roma samples was in tune with Caucasian data, Hungarian samples showed decreased rate compared to Caucasians. For the examined *CYP2D6* variants, our Hungarian results reflect other European and Caucasian population data, our Roma results reflect Indian rate. The studied Hungarian population exhibited frequencies of the *CYP2C19*2* and *CYP2C19*3* variant alleles similar to those in other Caucasian populations. We found that the Roma population differed significantly from Caucasians and from Indians.

7. Acknowledgements

Fist of all, I would like to express my greatest thanks to my supervisor, Professor Béla Melegh, who supported me throughout my research. I also thank him for his useful advices during my work, for his leadership and help. I am very grateful to Dr. Renáta Szalai, Dr. Judit Bene and Dr. Márta Czakó for their scientific help. I am also thankful to all the collaborator of the Department of Medical Genetics, for their excellent technical help.

PUBLICATIONS SUPPORTING THE DISSERTATION

Weber A, Szalai R, Sipeky C, Magyari L, Melegh M, Jaromi L, Matyas P, Duga B, Kovesdi E, Hadzsiev K, Melegh B.

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IF: 1.958

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Environ Toxicol Pharmacol. 2015;40(1):280-3.

IF: 2.187

Impact factor of publication which have served as a base for the thesis: **4.209**

Impact factor of other published articles: **4.33**

Cumulative impact factor: **8.539**