GENETIC VARIABILITY AND INTERETHNIC DIFFERENCES OF SELECTED PHARMACOGENETICALLY RELEVANT GENES IN AVERAGE HUNGARIAN AND ROMA POPULATION SAMPLES

Doctoral (Ph.D.) thesis

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„If it were not for the great variability among individuals
medicine might as well be a science and not an art.“
Sir William Osler, 1892

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ABBREVIATIONS

ADR	adverse drug reaction
DME	drug metabolizing enzyme
dNTP	deoxyribonucleotide triphosphate
SNP	single nucleotide polymorphism
PCR	polymerase chain reaction
RFLP	restriction fragment lenght polymorphism
CYP	cytochrome P450
CYP2C9	cytochrome P450 family 2 subfamily C polypeptide 9
VKORC1	vitamin K epoxide reductase complex subunit 1
MDR1	human multidrug resistance 1
P-gp	P-glycoprotein
EDTA	ethylenediaminetetraacetic acid
wt/wt	homozygous wild type
wt/mut	heterozygous mutant
mut/mut	homozygous mutant
EM	extensive metabolizer
IM	intermedier metabolizer
PM	poor metabolizer
UTR	untranslated region
MIM	Mendelian inheritance in man
WR	warfarin resistance
VKCFD2	multiple coagulation factor deficiency type 2

1. **INTRODUCTION**

One of the many reasons that pharmacology remains as much art as science is the extraordinary variation in patient response to medications (Lanfear 2007). Variation of genetic variability at the pharmacogenetically relevant genes is the most important cause of variable drug response.

Ethnic differences in drug response are well known, thus the optimal drug dose vary between populations of different origin. The population of Hungary is comprised largely of Hungarians, however, many ethnic minorities also reside here, with the Roma forming the largest group. It is well known, Roma minorities live all around the world, but the genetic profile of this minority is less studied. The Roma differ from all the populations of countries they live because of their origin. Evidences have been presented that Roma people are of Indian origin (Morar 2004b, Gresham 2001b, McKee 1997, Hajioff 2000, Kalaydjieva 2001b, Kalaydjieva 2001a, Mastana 1992), and thus have different genetic structure than people of Caucasian origin. On the historical basis Hungarians are from the eastern side of the Ural Mountains (Nadasi 2007, Semino 2000b), thus the ancestry of the ancient Magyars is also differs from the Europeans. Thus the different origin of Roma and Hungarians from neighbouring populations in Europe is important in the clinical therapy they receive.

In conclusion, understanding of human genomic variation and its application in pharmacogenetics might shift our focus away from interindividual differences towards interpopulation differences (Daar 2005).

1.1. Individual variation of drug response and adverse drug reactions

Individual variation in drug response and adverse effects is a substantial problem. Many factors can affect patient's response to the drug. Optimal drugs and drug doses depend on age, gender, body weight, co-morbidity, organ functions, disease states, drug-drug interactions, lifestyle, culture, race/ethnicity, genetics, smoking, diet (Brockmoller 2008). However, genetic variation can account for as much as 95% of variability in drug disposition and effect (Kalow 1998). As the main cause of the variation in drug response, attention has focused on the genetic polymorphisms. Single nucleotide polymorphism (SNP) of DNA produces a variation in drug responses and has become a representative research target in pharmacogenetics. Polymorphisms

of genes encoding drug metabolism enzymes, drug transporters, and drug receptors have been reported and association with drugeffect has been clarified.

More than 50% of ADRs are dose-related (Brockmoller 2008). Of the evaluable drug products 21% had dose changes (Cross 2002). ADR's were experienced by 10% of hospitalized patients and were estimated to be the 4th or the 6th leading cause of death in the USA (Lazarou 1998). Fifty nine percent of drugs causing ADRs are metabolized by polymorphic enzymes while only 7-22% of other randomly selected drugs are substrates for polymorphic enzymes (Phillips 2001). One priority area of pharmacogenetic research is to predict serious ADRs (Need 2005).

The clinical consequences of ADRs were observed all around the world. In the UK ~7 % of patients are affected by adverse drug reactions. These ADRs cost about £380 million a year (Wiffen 2002). In the US an estimated 2.216.000 patients suffered from serious ADRs, leading to approximately 106.000 patient death, and making ADR the fourth to sixth leading cause of death in 1994 (Lazarou 1998).

1.2. Genetic variation of the human population, interethnic differences in drug response

Genetic differences between people contribute to interindividual differences in the response to many drugs. Findings of the Human Genome Project cleared that 99.9 % of the information in the estimated 20.000 human genes is identical from one person to the next. The small differences in the remaining 0.1 % of genes are the key to each individual (www.genetics.edu.au). Very often the variability in DNA consists of only one nucleotide base change, and if this occurs in more than 100 subjects at a given position in the DNA, it is referred to as a single nucleotide polymorphism. SNPs make up about 90% of all human genetic variation. In 2008, about 12 million SNPs and a large amount of other types of genetic variation were known in the human genome (Brockmoller 2008). The remainder of the variation is caused by insertions, deletions, tandem repeats and microsatellites (Marsh 2006).

It is known, that many polymorphisms that influence drug response and which probably contribute significantly to phenotypic variation in drug response have significant allele frequency differences among racial or ethnic groups (Tate 2004, Engen 2006, Evans 1999a). In 1920s inter-ethnic variations in response to medication were observed. Paskind investigated the different effect of atropine sulphate on Caucasian and African-American people in USA as first

(Paskind 1921). Recent studies report differences between African and non-African population groups in the structure of sequence variation in the human genome (Tishkoff 2003). Known interethnic difference exist in warfarin dosing, with the lowest among Asian-Americans (24 mg), followed by Hispanics (31 mg), Caucasians (36 mg) and highest among African-Americans (43 mg) (Dang 2005). This fits with recent data showing that VKORC1 haplotypes predicting low dose are more common in Asian-American populations (89%) and less common in African-Americans (14%) than in European Americans (37%) (Rieder 2005).

Geographic patterns of genetic variation, including variation at drug metabolizing enzyme loci and drug targets, indicate that geographic structuring of inter-individual variation in drug response may occur frequently. This geographic distribution of certain variants has highlighted the possible importance of average differences in drug response across populations (Wilson 2001). For this reason we need to take into account not just differences between the genotypes of individuals, but the differences in genotypes between population groups of different origin and the substantial variation between the five main racial groups, which are based on continental ancestry (Daar 2005).

In conclusion, understanding of human genomic variation and its application in pharmacogenetics might shift our focus away from interindividual differences towards interpopulation differences (Daar 2005). Thus race or ethnicity will usually be a far inferior guide to response than direct determination of the underlying genetic variant (Need 2005).

1.3. Pharmacogenetics, pharmacogenomics

Individual variation in response to drugs is a substantial clinical problem. Individuality in drug response can be inherited. The genetically determined variability in drug response defines the research area known as pharmacogenetics. Pharmacogenetics has evolved in the past 50 years to a major driving force of clinical pharmacology. The first concept of pharmacogenetics was originated from Motulsky in 1957 (Motulsky 1957). The term pharmacogenetics was suggested by Vogel in 1959 (Vogel 1959), and the first book on the subject was written by Kalow (Kalow 1998). Evidence for an inherited basis for drug response phenotypes dates to the 1950s, when Alving et al. observed that hemolysis during anti-malarial drugs treatment was due to an enzymatic defect for the glucose-6-phosphate dehydrogenase

(ALVING 1956). The first molecular defect was identified by Frank Gonzalez in the late 1980s (Gonzalez 1988). The term pharmacogenetics is used to cover both germline and somatic predictors of drug response (Goldstein 2003). One of main directions in development of pharmacogenetics is identifying genes and allelic variants of genes that affect our response to drugs (Wolf 1999, Wolf 2000). To date, polymorphisms of genes encoding drug metabolism enzymes, drug transporters, and drug receptors, which are involved in drug responses, have been reported and in some of them the association between pharmacodynamics and drug efficacy has been clarified (Evans 1999a, Goldstein 2003).

Pharmacogenomics is an apparently new science about how the systematic identification of all the human genes, their products, interindividual variation, intraindividual variation in expression and function can be used both to predict the right treatment in individual patients and to design new drugs.

There are differences between pharmacogenetics and pharmacogenomics. Accordingly, most of scientists use pharmacogenetics to depict the study of single genes and their effects on interindividual differences in drug metabolizing enzymes, and pharmacogenomics usually used in broader context, to depict the study of not just single genes, but the functions and interactions of all genes in the genome in the overall variability of drug response, whether this is caused by pharmacokinetics, pharmacodynamics or both. Some have distinguished between pharmacogenetics and pharmacogenomics on the basis of either the type of genomic information or the quantity (Goldstein 2003). The differences between the pharmacogenetics and pharmacogenomics are the initial approach of the science. Pharmacogenetics is based on an unexpected drug response result and looks for a genetic cause, while pharmacogenomics looks for genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health problem (www.genetics.edu.au).

To summarize, classical pharmacogenetics has searched the genes for an abnormal drug response of proven clinical value, whereas pharmacogenomics presently and in the future will search the bearing if any of known genes, SNPs or haplotypes.

1.4. Individualized drug therapy

Clinical significance of personalized medicine and understanding of genetic role of variable drug response is an important goal of biomedical research (Wilson 2001). Patients with the same diagnosis may respond in different ways to the same drug. In the best case the prescribed drug is not toxic and beneficial, but in some cases it can be also not beneficial. In other cases the treatment can be toxic, but beneficial. The worse occurrence is when the drug is toxic and also not beneficial (Figure 1.).

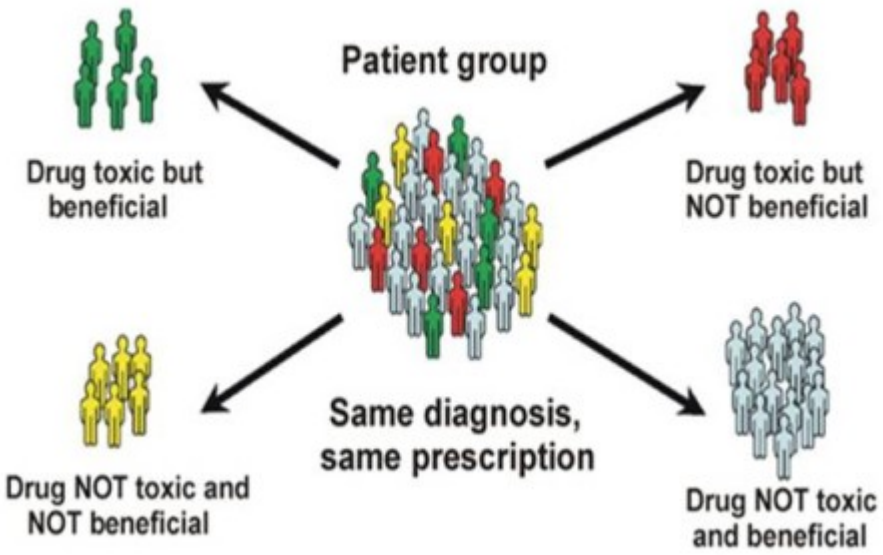

Figure 1. Individulized therapy means the use of pharmacogenomics to select the right drug for the right person prior to medication prescription (Marsh 2006)

Through the use of pharmacogenetics, physicians will be able to profile variations between indiviadual's DNA to predict responses to a particular medicine. Pharmacogenetics will have impact on medical care and medical aid at multiple levels (Roses 2000). Moreover, pharmacogenetic testing may provide the first example of a mechanism whereby DNA based testing can be applied to populations (Wolf 1999). The intersection of pharmacogenomics and medicine has the potential to yield a new set of molecular diagnostic tools that can be used to individualize and optimize drug therapy (Evans 2004).

1.5. Cytochrome P450s and cytochrome P450 2C9 (CYP2C9) genetics

Cytochrome P450 system plays a key role in the drug metabolism. The cytochrome P450s are a multigene family of enzymes found predominantly in the liver that are responsible for the metabolic elimination of most of the drugs currently used in medicine (Wolf 1999). Most drugs are lipophilic compounds that are mainly eliminated by oxidation catalyzed by the cytochrome P450 (CYP) enzyme system in the liver. The total number of *CYP* genes in all species is 270, but the human CYP superfamily consists of 57 CYP genes and 33 pseudogenes organized in 18 families and 42 subfamilies. The endogenous substrates for CYP include fatty acids, eicosanoids, sterols and steroids, bile acids, vitamin D, retinoids and uroporphyrogens. The CYP also represent the most important way for detoxification of many foreign chemical including drugs. The drug metabolizing CYP belong to families 1, 2 and 3. Phenotypes of P450 are divided into different groups. Extensive metabolizer (EM) that shows regular metabolic capacity, poor metabolizer (PM) that shows low metabolic capacity, and intermediate metabolizer (IM) that shows the metabolic capacity between the PM and the EM. In addition, the categorization includes the ultra-rapid metabolizer (UM) that shows higher metabolic capacity than the EM (Hiratsuka 2006).

Cytochrome P450 (CYP) 2C9 [MIM 601130] is one of the most important enzymes in human drug metabolism and its genetic polymorphisms are known to contribute to interindividual and interethnic variations in the metabolism of several drugs in humans (Daly 1993, Bertilsson 1995, Rogers 2002). CYP2C9 is involved in the metabolism of 10-20% of all drugs, including many clinically important pharmaceuticals such as coumarin anticoagulants, losartan, tolbutamide, sulfonylurea drugs, angiotensin II blockers, nonsteroidal anti-inflammatory drugs (NSAIDS) and phenytoin, some with narrow therapeutic index (Rogers 2002, Daly 2003, Takahashi 2006, Goldstein 1994, Xie 2001, Kirchheiner 2005, Garcia-Martin 2006, Miners 1998). A total number of drugs metabolized by CYP2C9 enzyme are more than 60.

To date 34 CYP2C9 variant alleles have been reported (http://www.cypalleles.ki.se/). CYP2C9*1 is the wild-type allele, and besides there are two important single nucleotide polymorphisms the CYP2C9*2 (C430T, exon 3) associated with a functionally important Arg144Cys substitution and the CYP2C9*3 (A1075C, exon 7) associated with another

important Ile359Leu substitution. Both variants are encoding enzymes with reduced enzymatic activity (Xie 2001, Ingelman-Sundberg 2005, Aithal 1999). Several studies show that *3 is associated with a lower intrinsic clearance of substrate drugs than *2; and CYP2C9*3 has less than 5% of the activity of the wild-type enzyme, whereas CYP2C9*2 has about 12% of that activity (Aithal 1999, Sullivan-Klose 1996, Rettie 1999). However, the extent of reduction in catalytic activity caused by each variant is substrate specific (Takanashi 2000). In Caucasians the frequencies of the 6 different genotypes are 65-70 %, 15-20 % and 8-10 % for CYP2C9*1/*1, CYP2C9*1/*2 and CYP2C9*1/*3, respectively. The poor metabolizer genotypes CYP2C9*2/*2, CYP2C9*3/*3 and CYP2C9*2/*3 each occur in about 1-2%. Tolbutamide has been proposed to be a candidate for a model drug to probe for CYP2C9. The CYP2C9 polymorphisms are important determinants of the warfarin dose. The presence of CYP2C9 polymorphisms is associated with a reduction in the metabolism of S-warfarin (Higashi 2002, Takahashi 1998).

The allelic variants of human cytochrome P450 CYP2C9 gene vary in frequency among different ethnic groups (Xie 2001, Scordo 2004, Sipeky 2009b).

1.6. Vitamin K epoxide reductase complex subunit 1 (VKORC1) genetics

VKORC1 [MIM 608547] is the key enzyme of the vitamin K cycle and the molecular target of coumarins. Coumarins, including warfarin, acenocoumarol and phenprocoumon, are the fundamental drugs used for long-term treatment of thromboembolic diseases (Oldenburg 2007a, D'Andrea 2008). They exhibit large interindividual and interethnic variability in the dose requirement (El Rouby 2004, Kamali 2006, Sconce 2006). The vitamin K epoxide reductase complex subunit 1 (VKORC1) is the warfarin-sensitive enzyme in vitamin K metabolism and biosynthesis of vitamin K-dependent blood coagulation factors. Warfarin influences blood coagulation by inhibiting the VKORC1, thereby preventing the vitamin K regeneration, which leads to a reduced amount of vitamin K available to serve as a cofactor for gamma carboxylation of clotting factrors (II, VII, IX and X) and the anticoagulant protein C and S (Li 2004, Rost 2004, Stafford 2005). Genetic variations of VKORC1 gene can greatly affect the individual response to coumarins (Schalekamp 2007, Oldenburg 2007b, Gage 2008, Rieder 2005, Geisen 2005). Mutations in VKORC1 result in different phenotypes: resistance to coumarin derivates (warfarin resistance, WR) or warfarin sensitivity, or in a rare bleeding disorder known as

multiple coagulation factor deficiency type 2 (VKCFD2) (Rost 2004, Oldenburg 2000). VKORC1 has greatly improved our understanding of the vitamin K cycle and has led to the translation of basic research into clinical practice (Oldenburg 2007b).

The relatively recent discovery of the haplotype structure of the human genome, and the effect that this has on SNP inheritance, could help to simplify and reduce the costs of genotyping (Daar 2005).

Besides some common missens mutations in VKORC1 gene, the haplotypes already have been identified, which are known to affect the warfarin response (Carlquist 2006, Aquilante 2006, D'Andrea 2005, Wadelius 2005, Yuan 2005, Sconce 2005). Most of the VKORC1 haplotype literature uses either the terminology of Reider et al (Rieder 2005) or Geisen et al (Geisen 2005) when describing VKORC1 haplotypes. We decided to use the haplotype nomenclature of Geisen et al. The major natural VKORC1 haplotypes are determined by the combinations of the G-1639A, G9041A, C6009T haplotype tagging SNP-s of VKORC1 gene; with this approach the ancestral VKORC1*1, and three further major haplotypes, the VKORC1*2, *3, and *4 can be differentiated. The VKORC1*1 the putative ancestral haplotype, is characterized by the presence of ancestral allele of G1639A, G9041A, and C6009T polymorphisms. The VKORC1*2 haplotype is characterized by the presence of 1639A, G9041, and C6009 SNP combination. The VKORC1*3 haplotype is characterized by the 9041A, G1639, and C6009 SNPs. The VKORC1*4 haplotype is characterized by the presence of 6009T, G1639, and G9041 combination (Sipeky 2009a). Specific haplotype determining polymorphisms of the VKORC1 gene are summarized in Table 1. and the identification of haplotypes in Table 2.

Table 1. Studied polymorphisms of the VKORC1 gene

Marker	**Nucleotide position**		**Nucleotide change**	**Gene region**	**rs**
	DNA	**cDNA**			
M2	3673	c. -1639	G>A	Promoter	9923231
M23	9041	492+134	G>A	3'-region	7294
M16	6009	173+525	C>T	Intron1	17708472

Table 2. Haplotype determining polymorphisms of the VKORC1 gene

Haplotype	G-1639A	G9041A	C6009T
VKORC1*1	G	G	C
VKORC1*2	A	G	C
VKORC1*3	G	A	C
VKORC1*4	G	G	T

Interestingly, the VKORC1*1, the ancestral haplotype seems to only occur at high frequencies in populations of African origin, but VKORC1*1 is not the most common haplotype in the African population (Geisen 2005).

Haplotype *2 (H1 and H2, haplotype group A (defined by Rieder et al.)) includes a SNP in the promoter region (c. -1639 G>A, rs9923231) and is associated with response to a lower dose of warfarin. This polymorphism was shown to disrupt an E-box transcription factor binding-site, resulting in a significantly reduced promoter activity. VKORC*2 haplotype has pronounced differences in its frequency by different ethnic groups. VKORC1*2 is the predominant haplotype in the Asian population (around 90%), and it is also quite common among Caucasians, with an allele frequency typically around 40% in predominantly Caucasian populations. Haplotype frequency revealed an incidence of 95% for VKORC1*2 in Chinese subjects. This frequency corresponds well with the reported low warfarin dose requirement in Chinese and Malay subjects and in Europeans homozygous for VKORC1*2 (Geisen 2005, Rieder 2005). This haplotype also exists in African populations, but it is less frequent (Geisen 2005).

VKORC1*3 (H7 and H8, haplotype group B (Rieder et al)) is defined by the G9041A (3730 G>A, rs7294). G9041 is a SNP in the 3'UTR of VKORC1, and it is associated with a higher warfarin dose (D'Andrea 2005, Herman 2006). VKORC1*3 is the most common haplotype in the African population, and is also very common among Caucasians (38%) (Geisen 2005).

VKORC1*4 (H9, haplotype group B) is defined by the 6009 C>T variant. In the analysis of Rieder et al. and Herman et al. VKORC1*4 was associated with a higher dose of warfarin

(Rieder 2005, Herman 2006). The occurrence of VKORC1*4 haplotype in Caucasians is about 20% (Geisen 2005).

Rieder et al. (2005) identified a low-dose haplotype group (A) and a high-dose haplotype group (B). The analogy of haplotypes of VKORC1 gene defined by Rieder and Geisen and the classification of haplotypes into haplotype groups are shown in Table 3.

Table 3. Haplotype groups and analogy of haplotypes of VKORC1 gene according to the literature

Haplotype		**Haplotype group**
Geisen et al.	**Rieder et al.**	
VKORC1*2	H1 and H2	A (low dose)
VKORC1*3	H7 and H8	B (high dose)
VKORC1*4	H9	

The mean maintenance dose of warfarin differed significantly among the haplotype group combinations, at approximately 2.7 mg per day for A/A, 4.9 mg per day for A/B, and 6.2 mg per day for B/B (p less than 0.001). VKORC1 haplotype groups A and B explained approximately 25% of the variance in dose. Asian Americans had a higher proportion of group A haplotypes and African Americans a higher proportion of group B haplotypes. In conclusion, VKORC1 genotype was found to determine 25-40% of individual coumarin dose requirement (Bodin 2005, Schwarz 2006, Cooper 2008). The characterization of both the low-dose and high-dose defining haplotypes of the VKORC1 gene is clinically helpful, because we can identify with a simple test the two critical states of anticoagulated patients: the under- and overanticoagulation.

1.7. Human multidrug resistance 1 (MDR1) genetics

P-glycoprotein (P-gp), a large (170 kDa) transmembrane protein, functions as an energy-dependent drug-transport pump and it is responsible for the multidrug resistance in cancer cells (Kimchi-Sarfaty 2007b). P-glycoprotein is essential in building the blood-brain barrier (Schinkel 1996) and as transporter among other tissues (Fromm 2000), and it is an important prognostic factor in several tumor diseases. P-gp plays an important role in the bioavailability of a wide variety of drugs, including chemotherapeutic agents, cardiac drugs, antibiotics, steroids, immunosuppressants, HIV protease inhibitors and warfarin (Sparreboom 2003, Sakaeda 2002, Sakaeda 2005, Cascorbi 2001). Although the phisiological role of P-gp is not fully understood, it is conceivable that P-gp may prevent intracellular accumulation of potentially toxic substances and metabolites (Schinkel 1996).

P-gp is the product of the human multidrug resistance 1 (MDR1/ABCB1) gene. MDR1 is a typical stress-response gene, and a variety of different drugs potentially interact with MDR1 transcription, which results in an induction of P-glycoprotein expression (Schinkel 1996). MDR1 [MIM 171050] is located on chromosome 7q21.1 and consists of 28 exons (Chen 1990). The P-gp has 1280 amino acids, 12 transmembrane domains and two ATP-binding sites (Tang 2002). MDR1 is constituvely expressed in excretory and barrier tissues, such as the intestines, liver, kidney, pancreas, brain, testis, placenta, and so most likely have protective and elimination roles (Sakaeda 2005). Whereas MDR1 is highly expressed in cancer cells and plays a key role in anticancer and antiviral therapy (Dong 2008).

Another aspect is important from the viewpoint of human evulutionary genetics. MDR1 is involved in human resistance to various infections, conferring resistance to bacterial toxins and viruses (Schaeffeler 2001). Infections have been the most potent factors of natural selection in Homo sapiens populations throughout their history. Hence the genetic variation of MDR1 in modern populations is, to a great extent, a product of natural selection (Pel's IaR 2007).

MDR1 was among the first transporters extensively screened for genetic polymorphisms. Mutational analyses revealed that the MDR1 gene is highly polymorphic, with more than 100 polymorphic sites with a minor allele frequency greater than 5% (Fromm 2002). Studied polymorphisms of the MDR1 gene are summarized in Table 4.

Table 4. Studied polymorphisms of the MDR1 gene

MDR1 polymorphism	rs	Protein variant	Mutation	Location
C1236T	1128503	-	synonymous	exon 12
G2677T/A	2032582	Ala893Thr/Ser	non-synonymous	exon 21
C3435T	1045642	-	synonymous	exon 26

Among the MDR1 SNPs many researchers focused on C3435T (rs1045642, Ile1145Ile, exon 26) synonymous variant. The C3435T SNP is located in noncoding nonpromoter position in the MDR1 gene and hence is unlikely to regulate the expression of MDR1. It is possible that this SNP may function in concert with as yet unidentified regions of the MDR1 gene that regulate expression. In recent years the relationship between the MDR1 C3435T variant and susceptibility to some diseases, such as gastrointestinal tract infections (Schaeffeler 2001), Parkinson's disease (Lee 2004, Drozdzik 2003), nortryptilyne-indused postural hypotension (Roberts 2002), renal epithelial tumours (Siegsmund 2002) and childhood acute lymphoblastic leukaemia (ALL) (Jamroziak 2004) has been identified. These reports suggested that an assessment of C3435T variant could be useful for predicting some P-gp-dependent diseases.

Individuals, who are homozygous for the 3435T variant, have a significant decrease in intestinal P-gp expression, and increased plasma digoxin levels (Hoffmeyer 2000). Further studies also shown that 3435C allele is associated with increased and 3435T allele with decreased P-gp expression (Siddiqui 2003). Clinical studies have been shown that 3435CC genotype is associated with higher probability of complete remission in AML patients (Kim 2006), with drug-resistant epilepsy (Siddiqui 2003), and predicts longer steroid treatment in pediatric heart transplant patients (Zheng 2002). The 3435TT genotype predicted response to preoperative chemotherapy for breast cancer (Kafka 2003), and significantly associated with no or low level of MDR1 expression in carcinoma cell lines (Sauer 2002). It has been reported, that

the distribution of the C3435T polymorphism is significantly influenced by ethnicity (Cascorbi 2001, Ameyaw 2001, Balram 2003). The frequency of the homozygous CC genotype was highest among the African population and lowest in the south-west Asian groups (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1128503) (Kim 2001, Ameyaw 2001, Schaeffeler 2001). The frequency of 3435C allele is significantly higher in African than other ethnic populations. This is consistent with the high incidence of anticancer drug resistance and more aggressive tumors in individuals of African origin (Dong 2008).

Futher studies revealed that C3435T SNP was closely linked to other common polymorphisms, such as C1236T and G2677A/T. The body of work studying the effect of the 1236 C>T (rs1128503, Gly412Gly, exon 12) synonymous SNP is fairly small, with no conclusive findings to date. The 2677G>A/T (rs2032582, Ala893Thr/Ser, exon 21) nonsynonymous variant has been well studied. Associations between this SNP and P-gp function or expression have not been conclusively determined. Several studies revealed that 2677A-bearing subjects exhibit higher P-gp activity (Yi 2004). Some positive findings are that 2677GG is associated with higher probability of complete remission in AML patients (Kim 2006). The 2677A/T alleles are positive predictors of tacrolimus neurotoxicity in liver transplant patients (Yamauchi 2002). The 2677A/T variant also showed variability among different ethnic groups. The 2677A allele appeared more common in Japanese and Korean populations (Kim 2001).

Furthermore, haplotype analyses may play an important role in the identification of genetic differences between ethnic groups. Using the three common exonic polymorphisms enabled us to establish the haplotype profile of the Roma and Hungarian populations by allele counting. Haplotype determination of the MDR1 gene is summarized in Table 5.

Table 5. Haplotype determination of MDR1 gene

MDR1 haplotype	**MDR1 haplotype symbol**	**MDR1 polymorphisms**						
		C1236T		**G2677A/T**			**C3435T**	
		Alleles						
		C	**T**	**G**	**A**	**T**	**C**	**T**
		1	2	1	2	3	1	2
CGC	111	1		1			1	
CGT	112	1		1				1
CAC	121	1			1		1	
CAT	122	1			1			1
CTC	131	1				1	1	
CTT	132	1				1		1
TGC	211		1	1			1	
TGT	212		1	1				1
TAC	221		1		1		1	
TAT	222		1		1			1
TTC	231		1			1	1	
TTT	232		1			1		1

The functional effects of P-gp activity may also be related to haplotypes in the MDR1 gene (Kimchi-Sarfaty 2007a). Several clinical studies have shown that the haplotype 1236T-2677T-3435T is associated with reduced P-gp activity (Wong 2005).

Some studies revealed that MDR1 haplotypes differed greatly between ethnic groups (Kim 2001, Kroetz 2003, Tang 2002, Tang 2004). With respect to global drug development and treatment, the distribution of functionally important MDR1 mutations in populations of different ethnic origins should be evaluated (Cascorbi 2001). In summary, knowledge of genetic variability of ABC transporters between different ethnic groups is relevant pharmacological factor that can be used to understand variability in drug response (Balram 2003).

1.8. Origin of the Hungarian population: historical perspective

The Hungarians are unique among the other surrounding European populations because of the ancestry of the Magyars, the founders of the Hungarian state 1100 years ago (Nadasi 2007, Semino 2000b). The Hungarian nation traces its history to the early Magyars, who settled in the Carpathian Basin at the end of the 9th century after two millennia of migration from behind the Urals, via the steppe zone (Serre 2004)(Bálint 1996). This region had been settled for thousands of years before the Magyar's arrival, by Dacians, Romans, Sarmatians, Goths, Huns, Avars, Slavs. It is known that at the time of the Hungarian Conquest the majority of the indigenous population was Slavic. Estimates of the fraction of the total population of the Carpathian-Basin consisting of newly arrived Hungarians ranged from 10 to 50% (Cavalli-Sforza 1994).

In order to study the genetic structure in populations living in the Carpatian Basin from the time of the Hungarian Conquest, polymorphisms of mitochondrial DNA, Y chromosomal binary marker investigations, and also array based SNP studies had been performed.

The analysis of the maternal lineage shows that the linguistic isolation of Hungarian-speaking populations in the Carpathian Basin did not lead to significant genetic isolation. Mitochondrial DNA sequences of 27 ancient samples (10-11th centuries), 101 contemporary Hungarian, and 76 Hungarian-speaking Szekler (isolated minority in Transylvania) samples from Transylvania were analyzed (Tomory 2007). The data were compared with sequences of 7752 individuals representing 57 European and Asian populations, including Finno-Ugric populations, and statistical analyses were performed to study their genetic relationships. Only 2 of 27 ancient Hungarian samples are unambiguously Asian, the rest belong to one of the Eurasian haplogroups, but some Asian affinities, and the genetic effect of populations who likely mingled with ancient Hungarians during their migrations are seen. Recent Hungarian-speaking populations possess specifically European mitochondrial haplogroups. The results suggest that the ancient population from the 10th-11th centuries was genetically heterogeneous, and some Asian genetic influence is seen in the Hungarian conqueror population. In the contemporary Hungary, likely there is a dominating effect of populations already living in the Carpatian Basin, with influence from the Balkans and West Eurasia, while in the Szeklers the genetic effect of Eastern and Southern Europeans is more visible.

Paternal lineages, which usually give a higher geographical resolution than maternal, have also been studied. Total of 22 biallelic polymorphisms were typed from the non-recombining region of the human Y chromosome in 100 men from modern Hungary and 97 Szeklers. The results were compared with data from other European populations studied by Semino et al. (Semino 2000a), and the phylogeographic context of the Y chromosome pool of the populations has been analysed (Csanyi 2008). One specific Y-chromosomal base substitution (Tat, T→C) a relatively recent event (95% confidence interval 3140-6200 years) is a valuable marker in Finno-Ugric population studies (Zerjal 1997a). The C allele of the Tat polymorphism is widespread in all Uralic-speaking populations, except that it is absent or extremely rare among modern Hungarian-speaking populations (Semino 2000a, Zerjal 1997b, Lahermo 1999, Semino 2000c, Tambets 2004) (Rootsi 2000, Tambets 2001). Among the modern individuals, only one Szekler carries the Tat C allele, whereas out of four skeletal remains, from the time of the Hungarian conquest, two possess the allele. The latter finding appears to indicate a Siberian lineage of the invading Hungarians, which later has largely disappeared.

In the two recent Hungarian-speaking populations the Y-chromosomal binary markers share similar components described for other European populations, except for the presence of the haplogroup P*(xM173) in Szekler samples, which may reflect a Central Asian connection, and high frequency of haplogroup J in both Szeklers and Hungarians. MDS analysis based on haplogroup frequency values, confirms that modern Hungarian and Szekler populations are genetically closely related, and similar to populations from Central Europe and the Balkans.

Another study analysing a total of 6,501 Y chromosomes of 81 populations, including samples collected from 106 random avarage Hungarian males, there was no statistical difference in the prevalence of the E-M78 and E-V13 haplogropus between Hungarians and the surrounding nations (Cruciani 2007).

The lactase non-persistence (hypolactasia) is inherited as an autosomal recessive trait (Sahi 1973). The prevalence of adult type lactase non-persistence is 3-70% among Caucasian populations in Europe, rare in Northern Europe, but it increases in the south and west. It reaches approximately 100% in Asians (Suarez 1997, Gudmand-Hoyer 1996). Recently a T/C SNP variant upstream of the LCT gene was proved to be associated with lactase non-persistence, and the functional role of C/T_{-13910} polymorphism in regulation of lactase gene expression was characterized (Olds 2003, Troelsen 2003). The prevalence of different C/T_{-13910} lactase

genotypes in recent population of Hungary with random sampling was evaluated. (Nagy 2009) Allele frequencies associated with lactase persistence (T_{-13910}) and non-persistence (C_{-13910}) were 37.8% and 62.2%, respectively. The 62.2% frequency of the lactase persistence in the Hungarian population is lower than that in Sweden and Finland (81.5%), higher than in France (43.1%) and Northern Italy (35.7%) and similar to Portugal (62%) (Ingram 2009). On the other hand the frequency of lactase non-persistence among those recent populations, which lived in close vicinity with the Magyars in the Siberian homeland, contrary to the recent Hungarian population is similarly high; 71% in Northern Mansi, 78% in Nenets, 50% in Komi-Permiak and 59% in Udmurtian (Kozlov 1998).

More recently, in a study with analysis of more than 270,000 SNPs, genotyped with Illumina 318K/370CNV chips, studying 3,112 individuals across 16 European countries, including 50 Hungarians, no unique genotype could be revealed in the Hungarian samples, they exhibited a high degree of similartity compared with the neighbouring nations (Nelis 2009).

1.9. Roma (Gypsy/Romani) population: origin, Roma in the world and in Hungary

Roma believed to have originated in the northern part of Indian subcontinent. They began their migration about 1000 years ago. The reason for their diaspora remains an enigma. However, the most probable conclusion is that the Roma were part of the military in Northern India. The absence of a written history has meant that the origin and early history of the Romani people was long not clear. Roma emigrated from India towards the northwest no earlier than the 11th century. Contemporary populations sometimes suggested as sharing a close relationship with the Roma are the Dom people of Central Asia and the Banjara of India.

Social sciences, comparative linguistic studies hinted their Asian origin. Genetic evidences also suggested the Indian origin of Roma. 47.3% of Romani man carry the Y chromosome haplogroup of H-M82 which is rare outside of the Indian subcontinent. Mitochondrial haplogroup M most common in Indian subjects and rare outside Southern Asia, accounts for nearly 30% of Romani people (Kalaydjieva 2005). A more detailed study of Polish Roma shows this to be of the M5 lineage, which is specific to India (Malyarchuk 2006). Moreover, a form of the inherited disorder congenital myasthenia is found in Romani subjects. This form of the disorder, caused by the 1267delG mutation, is otherwise only known in

subjects of Indian ancestry. This is considered to be the best evidence of the Indian ancestry of the Romanies (Morar 2004a).

In conclusion, Gypsies are a conglomerate founder population with Asian roots, imbedded into a Caucasian, genetically different population (Kalaydjieva 2005). According to the genealogy data Roma could be best described as a mosaic of founder populations, which were shaped by their migrations in Europe (Morar 2004b).

Roma populations live in many countries throughout the world and are well known for their preserved traditions. Currently, the total Roma population size is estimated to be about 12 million in the world, and 8-10 million Gypsies live in Europe today (Morar 2004b, Gresham 2001a). Hungary is the fourth in Europe considering the estimated size of the Roma population, which is about 700.000 people (Gresham 2001a). The Figure 2. shows the distribution of the Romani people in Europe.

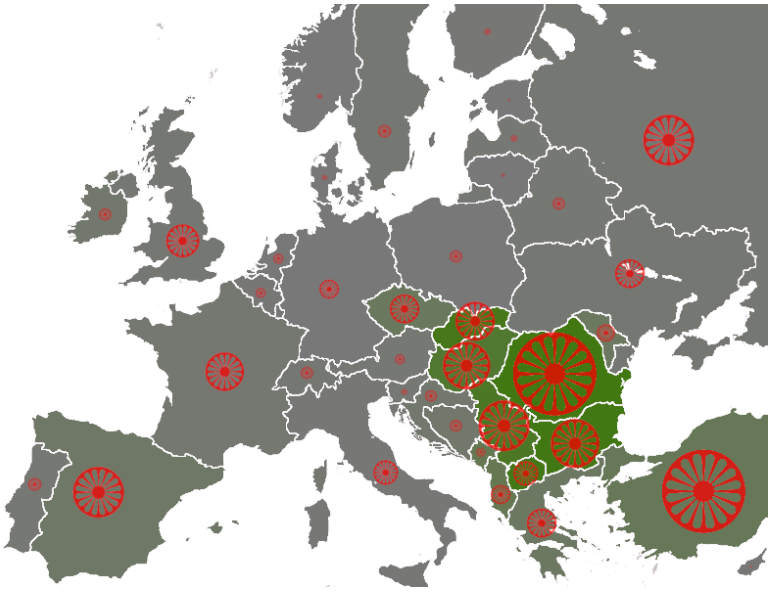

Figure 2. Distribution of the Romani people in Europe (2007 Council of Europe "average estimates": 9.8 million)

* The size of the wheel symbols reflects absolute population size

* The gradient reflects the percent in the country's population: 0% 10%.

(Reference:http://www.coe.int/t/dg3/romatravellers/Documentation/strategies/statistiques_en.asp#P11_143)

The population of Hungary is comprised largely of Hungarians, however, several ethnic minorities also reside there, with the Roma forming the largest group (Irwin 2007). The number of Roma in Hungary is hard to estimate. According to the census of 2001 the Roma minority has about 200.000 members, self identified as Roma. According to the 2008 survey the number of Roma is between 600.000 and 800.000 in Hungary (www.ksh.hu). Moreover, the statistical survey of sociologists estimates the number of Roma between 600.000 and 1 million in Hungary. Figure 3. shows the distribution of Roma in Hungary according to the census in 2001.

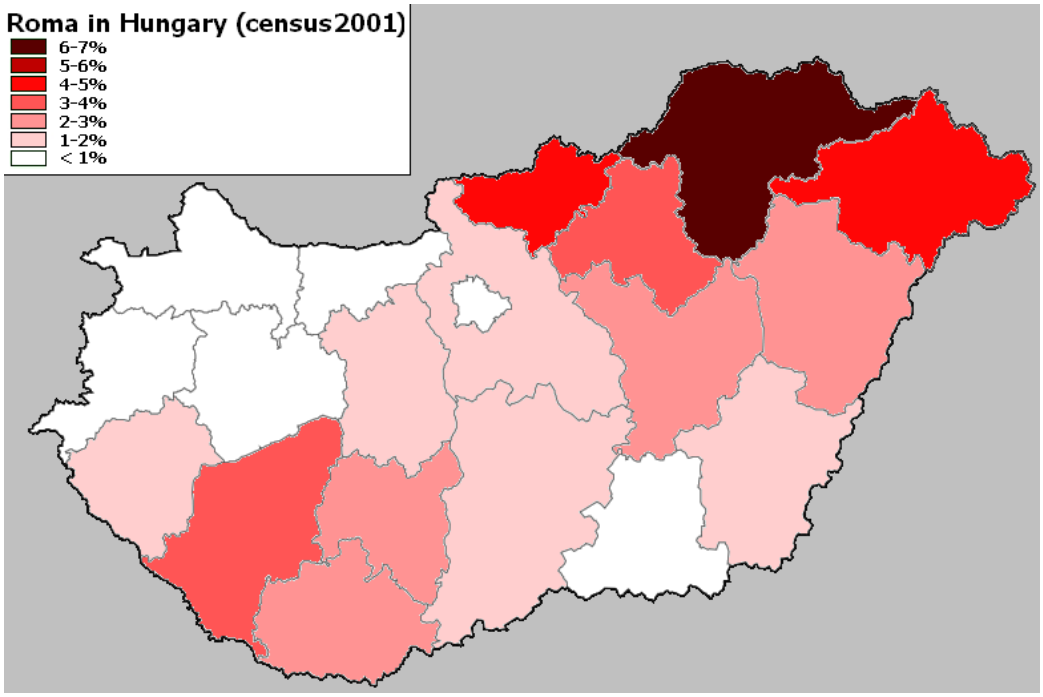

Figure 3. The distribution of Roma in Hungary (%) according to the census in 2001. (Reference: http://en.wikipedia.org/wiki/File:Hungary_roma_2001.PNG)

The Roma in Hungary are composed of three main subpopulations according to their history and language: the Romungro, the Olah and the Beas (Crowe 1991). The Romungro (Hungarian Roma) is the oldest Roma subpopulation in the Carpathian-Basin. They settled around 16th, 17th centuries. They named themselves Hungarian Roma, and they speak Hungarian in general. In the past most of them lived in separate, isolated settlements ("colonies") near the villages. The profession of these people is mostly musician, some earned their living with hired labour in the agriculture. The most of Roma, about 71%, belong to this group in Hungary. The Olah (the Hungarian name of Romanian people) subpopulation got this name because the

members of this group came from Romania at the 19th century. The other name of them is Wallachian Roma. In the past they were nomads with traditional occupations, connected with offering of different kinds of commodities and services. Now Olah Romani people live in all regions of Hungary, but mostly in cities. They use the Lovari language and speak Hungarian also. Olah people form about 21% of the Romani. The most of Beas (Boyash) Romani people live in villages in South-Transdanubian region of Hungary. In this region they form about 30% of the whole Romani population. In Baranya and Somogy county the majority of Roma belong to the Beas subgroup. Beas speak Hungarian and archaic Roman language, and form only 8% of the Romani population (Crowe 1991).

The greatest number of the Roma was integrated into the Hungarian population, and they live together in many settlements of Hungary. The members of the Roma population marry traditionally only within their own community. Therefore they preserve a closed genetic system. As the Roma and Hungarian have completely other origin, the Roma came from Indian subcontinent and Hungarians moved from Asia, they have entirely different genetic structure.

Due to the previous international studies, some special hereditary disorders in the rare disease categories of the Roma population are already known. Thus, hereditary motor and sensory neuropathy, congenital cataracts facial dysmorphysm neuropathy, congenital myasthenia syndrome, limb-girdle muscular dystrophy, galactokinase deficiency and polycystic kidney disease are known to accumulate in different European Romani populations. The accumulation of recessively inherited autosomal multiplex malformation syndromes was observed in some Hungarian gypsy colonies. A special form is accepted now as orofaciodigital type VI, and as Váradi-Papp syndrome in the McKusick catalogue (OMIM %277170) (Varadi 1980). High incidence of short rib-polydactyly syndrome type VI was recognized in a Hungarian Roma sub-population (Kovacs 2006). A Roma patient with bigenic connexin mutations associated with hydrotic ectodermal dysplasia was also observed. The patient harbored a novel sporadic mutation (V41L) in GJA1 (Cx43) as well as a heterozygous coding variant (R127H) of GJB2 (Cx26) (Kellermayer 2005). Molecular genetic analysis of the SLC22A5 gene in two non-consanguineous Hungarian Roma children with carnitine responsive cardiomyopathy and in postmortem tissue specimens from sudden infant death cases revealed a homozygous deletion of 17081C of the SLC22A5 gene (Melegh 2004). Genomic DNA sequencing revealed novel mutation in the signal transducer and activator of transcription 3 gene

(STAT3; H332Y) in a Gipsy family (Jiao 2008). Finally, a homozygous K76N mutation was also detected in two sisters from a consanguineous Gipsy family (Miltenberger-Miltenyi 2005).

2. OBJECTIVES OF THE WORK

Although the polymorphisms of CYP2C9, VKORC1 and MDR1 genes are well documented in several populations, there is no report considering the Roma and Hungarian populations. In this way the main purposes of the work are:

- To determine the allele frequencies of functionally significant polymorphisms of clinically important DME, the CYP2C9, in healthy Hungarian and Roma populations.

- To characterize the allele frequencies of the drug target, VKORC1, in healthy Hungarian and Roma population subjects.

- To describe the allele frequencies of most relevant SNP-s of the MDR1 drug transporter in healthy Hungarian and Roma population subjects.

- To establish the haplotype profiles of both the VKORC1 and MDR1 genes in healthy Hungarian and Roma population samples.

- To compare the allele and haplotype frequencies of CYP2C9, VKORC1 and MDR1 genes of the Hungarian and Roma populations with results available for other ethnic populations in literature, mainly with Caucasian and Indian populations.

- To give useful informations in connection with the origin of the Hungarian and Roma populations.

The results would be very useful as serves basis for future drug and disease related studies, and could provide information for therapy of many diseases in Hungarian and Roma populations.

3. MATERIALS AND METHODS

3.1. Study populations

The study was done using DNA from healthy Roma and healthy Hungarian subjects. The Roma and Hungarian Caucasian samples are originated from different regions of Hungary. During personal interviews, the Hungarians did not enroll themselves to any minor ethnic groups living in Hungary.

The DNA samples were from the central Biobank of the University of Pecs that is part of the National Biobank Network of Hungary (www.biobank.hu). The governance principles and maintenance management of the Biobank had been approved by the Hungarian National Research Ethics Committee. During the collection and analysis of DNA samples and processing of the accompanying clinical and personal data the guidelines and regulations of the Helsinki Declaration in 1975 and the currently operative National regulations were followed.

In CYP2C9 study DNA of total of 535 healthy Hungarian (251 males and 284 females, mean age 49±16 years, range: 20-92 years) and 465 healthy Roma samples (300 males and 165 females, mean age 40±16 years, range: 18-90 years) were used.

A total of 510 healthy Hungarian DNA samples (179 males and 331 females, mean age 41±13 years, range 20-78 years) and 451 samples collected from Roma people (157 males and 294 females, mean age 42±16 years, range 18-88 years) were used for the VKORC1 study.

In MDR1 study DNA of total of 503 healthy Hungarian (269 males and 234 females, mean age 49±16 years, range: 20-97 years) and 465 healthy Roma samples (167 males and 298 females, mean age 40±16 years, range: 18-90 years) were used.

3.2. Molecular methods

Genomic DNA was isolated from peripherial leukocytes using routine salting out method. In order to genotype the samples we applied PCR/RFLP assays to characterize the polymorphisms of studied genes. For primer design the sequences deposited into the GenBank were used. PCR amplification was carried out in a final volume of 50 µl containing 200 µM of each dNTP, 1 U of Taq polymerase, 5 µl of reaction buffer (10 mM Tris-HCl, pH 9.0, containing 500 mM KCl, 14 mM $MgCl_2$), 0.2 mM of each primers and 1 µg DNA extracted on

an MJ Research PTC 200 thermal cycler. The amplicons were digested by allele-specific restriction endonucleases. In the amplicons there was an obligatory cleavage site to enable us to monitor the efficacy of the digestion. The digested PCR products were separated by electrophoresis using a 3% agarose gel stained with etidium bromide and were visualized by UV illumination.

The CYP2C9*2 (Arg144Cys) mutation was detected using the following forward and reverse primers 5'-GGGAGGATGGAAAACAGAGACTT-3' and 5'-GGTCAGTGATATGGAGTAG GGTCA-3', respectively. PCR conditions were as follows: predenaturation for 2 min at 95ºC, followed by 40 cycles of denaturation for 30 sec at 95ºC, annealing for 30 sec at 55ºC, primer extension for 30 sec at 72ºC, the final extension at 72ºC for 5 min. 10 µl PCR product was digested by 1U Cfr13I (AsuI) restriction enzyme. In samples with CYP2C9*2 CC genotype the Cfr13I cleaves the 309 bp long PCR product into 48 bp, 84 bp and 177 bp fragments. If the CYP2C9*2 430T allele was present in homozygouse form 48 bp and 261 bp fragments could be detected (Sipeky 2009b). Genotyping of CYP2C9*3 (Ile359Leu) polymorphism was performed as previously described by Sullivan-Klose et al., as this method gave highly specific amplification of the CYP2C9 gene confirmed by DNA sequencing (Sullivan-Klose 1996, Xie 2002, Yasar 1999). For random control of both the assays we used direct sequencing with the same primers utilizing an ABI PRISM 3100 AVANT genetic analyser.

Three polymorphisms of the VKORC1 (MIM *608547) gene including c.-1639 G/A (3673G/A, M2) in the promoter region, c.492+134 G/A (9041 G/A, M23) in the 3'-UTR region, and c.173+525 C/T (6009 C/T, M16) in intron1 were analyzed.

For determination of the 3673 G/A polymorphism (rs9923231) the following primers were used: 5'-ATCCCTCTGGGAAGTCAAGC-3', and 5'-CACCTTCAACCTCTCCATCC-3'; to test the 9041G/A (rs7294) SNP the 5'-TTTAGAGACCCTTCCCAGCA-3' and 5'-AGCTCCAGAGAAGGCAACAC -3' oligonucleotides were used. For the amplification of the target sequence of C6009T (rs17708472) the 5'-AGGCGTTAGCATAATGACGG -3' and 5'-GGGTGGAACCAGGTTAGGAC-3' primers were utilized. Annealing temperature for the 3673 G/A, 9041 G/A and 6009 C/T primers were 60°C, 59°C and 65°C, respectively. The 636 bp amplicon of VKORC1 3673 G/A SNP was digested with BcnI endonuclease. In the samples

with GG genotype the digestion resulted in 50, 114 and 472 bp fragments; in AA homozygotes 114 and 522 bp fragments were produced. The SsiI was used to cleave the 674 bp PCR product of VKORC1 G9041A variant. For GG homozygotes 117, 216 and 341 bp products, while in AA homozygotes 117 and 557 bp restriction fragments could be detected. For the C6009T polymorphism the FspBI enzyme was used and the following fragments of the 725 bp amplicon could be detected: 109 and 616 bp sequences for the major allele (C), 109, 133 and 483 bp for the minor allele (T) (Sipeky 2009a). Approximately 10% of the total PCR products were selected randomly for direct sequencing to confirm the results obtained by PCR-PFLP procedure by an ABI PRISM 3100 AVANT Genetic Analyser.

Three polymorphisms of the MDR1 (MIM*171050) gene including C1236T (exon 12), G2677T/A (exon 21), and C3435T (exon 26) were analyzed.

For detection of the C1236T (rs1128503) polymorphism the following primers were used: 5'-AGCTATTCGAAGAGTGGGCA-3', and 5'-GTCTAGCTCGCATGGGTCAT-3'. The G2677T/A (Ala893Thr/Ser) (rs2032582) SNP was detected using two set of primers: 5'-GGTTCCAGGCTTGCTGT AAT-3' (1) forward, 5'- TTTAGTTTGACTCACCTTCCCTG-3' (1) reverse, and 5'-CAGCATTCTGAAGTCATGGAA-3' (2) forward, 5'-GTCCAAGAACTGGCTTT GCT-3' (2) reverse. For the amplification of the target sequence of C3435T (rs1045642) the 5'-GATGTCTTGTGGGAGAGGGA-3' and 5'-GCATGTATGTTGGCCTCCTT-3' primers were utilized. PCR conditions were as follows: predenaturation for 2 min at 96ºC, followed by 35 cycles of denaturation for 30 sec at 95ºC, annealing for 30 sec by primer specific temperature, primer extension for 30 sec at 72ºC, the final extension at 72ºC for 5 min. Annealing temperature for the C1236T, G2677T/A (1), G2677T/A (2) and C3435T primers were 57°C, 57°C, 55°C and 56°C, respectively. 10 µl PCR product of the C1236T, G2677T/A (1), G2677T/A (2) and C3435T primers was digested by BsuRI, HpyCH4V, RsaI and MboI restriction enzymes, respectively. In the samples with 1236 CC genotype the BsuRI cleaves the 418 bp long PCR product in 35 bp, 105 bp and 278 bp fragments. If the 1236 T allele was present in homozygouse form the 105 bp and 313 bp fragments could be detected. For GG homozygotes the 213 bp PCR product (first set of primers) of G2677T/A variant was digested into 23, 72, and 118 bp fragments. By the presence of G and A/T basis (A group) the digestion resulted in 23, 72, 95, 118 bp fragments; and if the A/T basis (B group) were presented 95 and 118 bp amplicons could be detected. All the samples analysed

with the first set of primers were amplified by the help of second set of primers except the samples with GG genotype. If the digestion of the 577 bp PCR amplicon of the second set of G2677T/A primers resulted in 277 and 300 bp fragments: GT (A group) and TT (B group) genotypes could be detected; by the presence of 82, 195, 277 and 300 bp fragments the GA (A group) and TA (B group) genotypes could be detected. In the samples with AA homozygous genotype the digestion resulted in 82, 195 and 300 bp fragments. The 451 bp amplicon of the C3435T SNP in the samples with CC genotype was digested into 34, 172 and 245 bp long fragments; in TT homozygotes the digestion resulted in 206 and 245 bp fragments (Sipeky 2010). For random control of the assays we used direct sequencing with the same primers utilizing an ABI PRISM 3100 AVANT genetic analyser.

3.3. Statistical analyses of data

We used the Chi-square test (nonparametric test for discrete variables) to compare the differences between the two groups studied. The value of $p<0.05$ was considered as statistically significant. Statistical analyses were performed applying Excel for Windows and SPSS 11.5 package for Windows (SPSS Inc., Chicago, IL).

4. RESULTS

4.1. CYP2C9 gene

The distribution of CYP2C9*1, *2, *3 alleles as well the *1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3 genotypes in Hungarian and Roma populations are presented in Table 6.

Table 6. Allele and genotype frequencies and the predicted phenotype of CYP2C9 in the healthy Hungarian and Roma population samples; data are compared with those reported for Indian and Caucasian populations.

CYP2C9	Current study		Reported data	
	Hungarian n=535	Roma n=465	Indian (Adithan 2003) n=135	Italian Caucasian (Scordo 2004) n=360
Allele frequency				
*1	0.787	0.727[a,b]	0.907	0.778
*2	0.125	0.118[b]	0.026	0.125
*3	0.088	0.155[a,b,c]	0.067	0.097
Genotype frequency				
*1/*1	0.620	0.533[a,b,c]	0.823	0.619
*1/*2	0.195	0.168[b]	0.044	0.172
*1/*3	0.139	0.219[a,b,c]	0.127	0.145
*2/*2	0.021	0.011	ND	0.028
*2/*3	0.015	0.047[a,b]	0.007	0.022
*3/*3	0.011	0.022	ND	0.014
Phenotype frequency				
wt/wt (EM)	0.620	0.533[a,b,c]	0.823	0.619
wt/mut (IM)	0.334	0.387[b,c]	0.171	0.317
mut/mut (PM)	0.047	0.080[a,b]	0.007	0.064

[a]$p<0.03$, when Roma are compared with Hungarian population
[b]$p<0.04$, when Roma are compared with Indian population
[c]$p<0.04$, when Roma are compared with Caucasian population
No significant difference was observed between Hungarian and Caucasian population considering the CYP2C9 gene.
n, number of subjects

All CYP2C9 allele and genotype frequencies were in Hardy-Weinberg equilibrium both in Roma and in Hungarian subjects. Beside the wild-type allele, the CYP2C9*2 was the most common allele identified in Hungarians, while in the Roma population the CYP2C9*3 was the most frequent. In addition, we found a significant (1.8-fold) increase in CYP2C9*3 prevalence in Roma population compared to Hungarian samples, which has therapeutic consequences ($p<0.001$). Furthermore, the frequency of *1/*3 genotype observed here was considerably higher in the Roma group than in Hungarians (0.219 vs. 0.139, $p<0.001$). Interestingly, the *1/*1 genotype in the Hungarian population was more common than in Roma subjects ($p<0.005$). Based on the distribution of CYP2C9 gene variants, the proportion of subjects homozygous for the wild-type allele (genotypically identified as extensive metabolizer, EM) was higher in Hungarians ($p<0.005$), while subjects carrying two detrimental alleles (with impaired enzyme activity, poor metabolizer, PM) are more frequent in Roma population ($p<0.03$).

Many studies have shown interethnic differences in the frequencies of CYP2C9 alleles. The results of this study were also compared with compiled data reported for other populations, with special regard to the Caucasian population and the Indians (Table 6. and Table 7.) (Adithan 2003, Scordo 2004).

Table 7. Comparison of allele and genotype frequencies of CYP2C9 reported from different ethnic populations

Populations	n	CYP2C9 alleles			CYP2C9 genotypes						Ref.
		*1	*2	*3	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	
Hungarian (patient)	421	0.814	0.110	0.076	0.656	0.185	0.131	0.007	0.021	ND	(Mark 2006)
Croatian	200	0.740	0.165	0.095	0.740	0.225		0.035			(Bozina 2003)
Italian (healthy)	360	0.778	0.125	0.097	0.619	0.172	0.145	0.028	0.022	0.014	(Scordo 2004)
Italian (healthy)	157	0.796	0.112	0.092	0.650	0.153	0.140	0.025	0.019	0.013	(Scordo 2001)
Caucasian	325	0.784	0.124	0.092	0.606	0.203	0.157	0.012	0.016	ND	(Gaedigk 2001)
Swedish (healthy)	430	0.819	0.107	0.074	0.667	0.186	0.116	0.005	0.019	0.007	(Yasar 1999)
Spanish (healthy)	102	0.745	0.156	0.098	0.578	0.196	0.137	0.039	0.039	0.01	(Dorado 2003)
Spanish (healthy)	157	0.694	0.143	0.162	0.497	0.159	0.235	0.019	0.089	ND	(Garcia-Martin 2001)
*Belgian	121	0.822	0.100	0.074	0.670	0.182	0.116	ND	0.016	0.008	(Allabi 2003)
British	561	0.841	0.110	0.053	0.699	0.191	0.095	0.005	0.011	ND	(Taube 2000)
British	100	0.790	0.125	0.085	0.620	0.190	0.150	0.030	ND	0.010	(Stubbins 1996)
White-American	140	0.825	0.132	0.043	0.671	0.221	0.086	0.021	ND	ND	(Dickmann 2001)
White-American	100	0.860	0.080	0.060	0.720	0.160	0.120	ND	ND	ND	(Sullivan-Klose 1996)
Afro-American	100	0.985	0.010	0.005	0.970	0.020	0.010	ND	ND	ND	(Sullivan-Klose 1996)
Afro-American	120	0.946	0.025	0.013	0.892	0.050	0.025	ND	ND	ND	(Dickmann 2001)
Mexican-American	98	0.86	0.08	0.06	0.74	0.15	0.1	ND	0.01	ND	(LLerena 2004)
Canadian Indian	114	0.910	0.030	0.060	0.825	0.061	0.114	ND	ND	ND	(Gaedigk 2001)
Inuit	151	0.100	ND	ND	0.100	ND	ND	ND	ND	ND	(Gaedigk 2001)
Ethiopian	150	0.933	0.043	0.023	0.867	0.087	0.046	ND	ND	ND	(Scordo 2001)
*Beninese	111	0.955	ND	ND	0.910	ND	ND	ND	ND	ND	(Allabi 2003)
Egyptians	247	0.820	0.120	0.060	0.664	0.190	0.117	0.024	ND	0.004	(Hamdy 2002)
Chinese	115	0.983	ND	0.017	0.965	ND	0.035	ND	ND	ND	(Wang 1995)
Chinese	102	0.951	ND	0.049	0.892	ND	0.108	ND	ND	ND	(Gaedigk 2001)
Japanese	140	0.982	ND	0.018	0.964	ND	0.036	ND	ND	ND	(Kimura 1998)
Japanese	218	0.979	ND	0.021	0.959	ND	0.041	ND	ND	ND	(Nasu 1997)
Korean	574	0.989	ND	0.011	0.977	ND	0.023	ND	ND	ND	(Yoon 2001)
Taiwanese	98	0.974	ND	0.026	0.918	ND	0.082	ND	ND	ND	(Sullivan-Klose 1996)
Turkish	499	0.794	0.106	0.100	0.617	0.180	0.172	0.010	0.011	0.008	(Aynacioglu 1999)
Iranian	160	0.793	0.110	0.097	0.644	0.175	0.137	0.025	ND	0.019	(Peyvandi 2002)
Indian (healthy)	135	0.907	0.026	0.067	0.823	0.044	0.127	ND	0.007	ND	(Adithan 2003)
Faroese (Denmark)	311	0.867	0.088	0.053	0.733	0.177	0.106	ND	0.016	ND	(Halling 2005)
Bolivian	778	0.992	0.048	0.03	0.847	0.093	0.057	ND	0.004	ND	(Bravo-Villalta 2005)

n, number of subjects; ND, not detectable; *There were other alleles and genotypes also detected

4.2. VKORC1 gene

All VKORC1 allele frequencies were in Hardy-Weinberg equilibrium both in Hungarian, and in Roma subjects. The frequency of allelic variants and genotypes of VKORC1 tagging polymorphisms in the Roma group and Hungarians are summarized in Table 8.

Table 8. VKORC1 haplotype tagging SNPs in Roma and Hungarian populations; data are also compared with data reported from India, or deposited into database for Caucasians.

VKORC1 polymorphism	Genotype	Current study		Data from other studies	
		Roma n=451 (%)	Hungarian n=510 (%)	Indian (Lee 2006) n=43 (%)	Caucasian (NCBI) n=22/n=23/ n=21 (%)
G-1639A	GG	214 (47.5)	180 (35.3)[a]	36 (83.8)[b]	7 (31.8)
	GA	206 (45.7)	262 (51.4)	4 (9.50)[b]	11 (50.0)
	AA	31 (6.87)	68 (13.3)[a]	3 (6.80)	4 (18.2)[c]
	GA+AA	237 (52.6)	330 (64.7)[a]	7 (16.3)[b]	15 (68.2)
	A allele frequency	0.297 (29.7)	0.390 (39.0)[a]	0.116 (11.6)[b]	0.432 (43.2)
G9041A	GG	132 (29.3)	206 (40.4)[a]	4 (8.10)[b]	10 (43.5)
	GA	220 (48.8)	233 (45.7)	8 (18.9)[b]	11 (47.8)
	AA	99 (22.0)	71 (13.9)[a]	31 (73.0)[b]	2 (8.7)
	GA+AA	319 (70.8)	304 (59.6)[a]	39 (91.9)[b]	13 (56.5)
	A allele frequency	0.463 (46.3)	0.368 (36.8)[a]	0.814 (81.4)[b]	0.326 (32.6)
C6009T	CC	293 (65.0)	319 (62.5)	38 (87.8)[b]	13 (61.9)
	CT	144 (31.9)	170 (33.3)	5 (12.2)[b]	7 (33.3)
	TT	14 (3.10)	21 (4.12)	0 (0.00)	1 (4.80)
	CT+TT	158 (35.0)	191 (37.4)	5 (12.2)[b]	8 (38.1)
	T allele frequency	0.191 (19.1)	0.208 (20.8)	0.058 (5.8)[b]	0.214 (21.4)

www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=9923231;www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=7294;www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=17708472

[a]Hungarian population is compared with Roma; $p<0.001$

[b]Indian population is compared with Roma; $p<0.01$

[c]Caucasian population is comapred with Roma; $p<0.05$

For the G-1639A polymorphism significant differences were observed in the prevalence of homozygous GG and AA genotypes, GA+AA carriers, and in minor allele frequency between the Roma and Hungarian samples ($p<0.001$); for the G9041A SNP exactly the same distribution patterns could be detected. By contrast, the genotype and allele distributions for the C6009T SNP did not differ between Roma and Hungarians (Table 8.).

In the Hungarian population sample (Table 9.) the haplotypes in decreasing order of their frequencies were the *2 (39%), *3 (37%), *4 (21%) and *1 (3%), while in the Roma population samples *3 (46%), *2 (30%), *4 (19%), and *1 (5%). The statistical analysis revealed significant difference in the prevalence rate of VKORC1*2 and VKORC1*3 haplotypes between the Roma and average Hungarian population ($p<0.005$).

Table 9. Ethnic distribution of VKORC1 haplotype frequencies.

Haplotype identification code	Hungarian (n=510)	Roma (n=451)	European (Geisen 2005) GER (n=200)	Italian (Spreafico 2008) (n=220)	Israeli (Loebstein 2007) (n=99)†	Chinese (Perlegen) CHN (n=24)	African (Perlegen) AFR (n=23)	Americans with origin of (Rieder 2005)			
								European (n=186)†	European (n=119)†	Asian (n=120)†	African (n=96)†
VKORC1*1	0.03 (35)	0.05 (44)	<0.001	0.03 (15)	0.01	<0.001	0.31 (14)	<0.001	<0.001	<0.001	<0.001
VKORC1*2	0.39 (400)[a]	0.30 (269)	0.42 (168)	0.43 (189)	0.41	0.95 (46)	0.14 (6)	0.36 (131)	0.38 (89)	0.89 (213)	0.13 (26)
VKORC1*3	0.37 (373)[a]	0.46 (417)	0.38 (152)	0.36 (158)	0.37	0.04 (2)	0.43 (20)	0.43 (160)	0.35 (83)	0.10 (25)	0.43 (82)
VKORC1*4	0.21 (212)	0.19 (172)	0.20 (80)	0.18 (78)	0.18	<0.01	0.12 (6)	0.21 (77)	0.24 (56)	<0.01 (2)	0.06 (11)

Chinese (www.perlegen.com)

African (www.perlegen.com)

[a]Hungarian population is compared with Roma; $p<0.005$

†Other haplotypes were also identified in low percentile rates.

Haplotype <0.001 means that this haplotype was not found, but its existence cannot be excluded (definition is from Geisen 2005)

By using the above VKORC1 haplotypes we could determine the VKORC1 genotypes of each subject in the studied populations (Table 10.).

Table 10. VKORC1 genotype distribution in Roma, Hungarian and Italian Caucasian population, and the predicted warfarin dose.

VKORC1 genotypes	**Predicted dose**	**Genotype frequency (%)**		
		Roma n=451 (%) (healthy)	**Hungarian n=510 (%) (healthy)**	**Italian (Spreafico 2008) n=220 (%) (anticoagulated)**
***1/*1**	Ancestral†	1 (0.22)	1 (0.20)	0 (0.00)
***1/*2**	Ancestral/Low†	14 (3.10)	18 (3.53)	3 (1.4)
***1/*3**	Ancestral/High†	18 (3.99)	15 (2.94)	8 (3.6)
***1/*4**	Ancestral/High†	10 (2.22)	0 (0.00)[a]	4 (1.8)[c]
***2/*2**	Low	31 (6.87)	69 (13.6)[a]	48 (21.8)[b,c]
***2/*3**	Intermediate	130 (28.8)	146 (28.6)	60 (27.3)
***2/*4**	Intermediate	63 (14.0)	98 (19.2)[a]	30 (13.6)
***3/*3**	High	99 (22.0)	70 (13.8)[a]	29 (13.2)[b]
***3/*4**	High	71 (15.7)	72 (14.1)	32 (14.5)
***4/*4**	High	14 (3.10)	21 (4.12)	6 (2.7)

†Functional significance of these genotypes is still not clear.
[a]Hungarian population is compared with Roma; $p<0.04$
[b]Italian population is compared with Roma; $p<0.01$
[c]Italian population is compared with Hungarian; $p<0.01$

The ancestral VKORC1 *1/*1 genotype could be found both in Roma and in Hungarians. This ancestral genotype was also detected in combination with other genotypes (*1/*2, *1/*3, *1/*4), but the *1/*4 was not detectable in Hungarian population. Comparing the Roma with the Hungarians significant difference was observed in prevalence of *1/*4, *2/*2,*2/*4 and *3/*3 genotypes ($p<0.04$).

4.3. MDR1 gene

The allele and genotype frequencies of studied MDR1 polymorphisms in the Hungarian group and Roma are shown in Table 11.

Table 11. Allele and genotype frequencies of MDR1 in the healthy Hungarian and Roma population samples; data are compared with those reported for Indian and Caucasian populations.

MDR1 SNP	Genotype and allele	Current study		Reported data	
		Roma n=465 (%)	Hungarian n=503 (%)	Indian (Lakhan 2009) n=96, n=101, n=97 (%)	German Caucasian (Cascorbi 2001) n=461 (%)
C1236T	CC	96 (20.7)[a,c]	167 (33.2)	15 (15.6)	158 (34.4)
	CT	226 (48.6)	226 (44.9)	45 (46.9)	227 (49.2)
	TT	143 (30.8)[a,c]	110 (21.9)[d]	36 (37.5)	76 (16.4)
	Carrier	369 (79.4)[a,c]	336 (66.8)	81 (84.4)	303 (65.6)
	T allele frequency	0.551[a,c]	0.443	0.609	0.410
G2677T/A	GG	125 (26.9)[b]	154 (30.6)	14 (13.9)	143 (30.9)
	GT	228 (49.0)	235 (46.7)	48 (47.5)	227 (49.2)
	TT	94 (20.2)	103 (20.5)	26 (25.7)	74 (16.1)
	GA	11 (2.37)	8 (1.59)	4 (4.00)	9 (2.00)
	TA	6 (1.30)[b]	3 (0.60)	9 (8.90)	8 (1.80)
	AA	1 (0.22)	0 (0.00)	0 (0.00)	0 (0.00)
	Carrier	340 (73.1)[b]	349 (69.4)	87 (86.1)	318 (69.1)
	T allele frequency	0.454[b]	0.441	0.540	0.416
	A allele frequency	0.020[b]	0.011	0.064	0.019
C3435T	CC	124 (26.7)[c]	112 (22.3)	24 (24.7)	96 (20.8)
	CT	234 (50.3)	252 (50.1)	40 (41.2)	233 (50.5)
	TT	107 (23.0)[b]	139 (27.6)	33 (34.0)	132 (28.6)
	Carrier	341 (73.3)[c]	391 (77.7)	73 (75.2)	365 (79.1)
	T allele frequency	0.482[a,c]	0.527	0.546	0.539

[a]$p<0.04$, when Roma are compared with Hungarian population
[b]$p<0.02$, when Roma are compared with Indian population
[c]$p<0.03$, when Roma are compared with Caucasian population
[d]$p<0.03$, when Hungarians are compared with Caucasian population

The allele and genotype frequencies of studied MDR1 SNPs did not show a significant deviation from Hardy-Weinberg equilibrium neither in Roma nor in Hungarian subjects.

Considering the MDR1 C1236T polymorphism, a significant difference was observed in the presence of CC (20.7 vs. 33.2%) and TT (30.8 vs. 21.9%) genotypes, the CT+TT (79.4 vs. 66.8%) carriers and the T allele frequency in Roma compared to Hungarians ($p<0.002$), respectively. The 1236C (0.557) was the most common allele identified in Hungarians, while in Roma population the 1236T (0.551) allele was most frequent. By contrast, no significant difference was observed between Roma and Hungarian populations considering the G2677T/A polymorphism. However, subjects carrying two of mutated alleles (TA) are two-times more common in Roma population than in Hungarians (1.3 vs. 0.6%). The frequency of the 2677A allele was almost two-fold higher in Roma than in Hungarian group, however the difference did not reach the statistical significance level (0.020 vs. 0.011, $p=0.078$). In MDR1 exon 26 (C3435T), higher frequency of the T allele was observed in Hungarians compared with Roma (0.527 vs. 0.482, $p<0.05$).

The genetic variability of the major MDR1 polymorphisms vary among several ethnic groups and are summarized in Table 12.

Table 12. (A) Comparison of allele and genotype frequencies of MDR1 C1236T (exon 12) polymorphism reported from different ethnic populations (ND, not detected NA, not analized)

Population	n	Genotype frequency			Allele frequency	References
		CC	CT	TT	T	
Caucasians						
Czech	189	0.317	0.471	0.212	0.447	(Pechandova 2006)
Polish	96	0.291	0.563	0.146	0.427	(Jamroziak 2009)
Polish	139	0.353	0.468	0.180	0.414	(Tan 2004)
Polish	135	0.304	0.496	0.200	0.448	(Wasilewska 2007)
German	188	0.380	0.490	0.130	0.380	(Hoffmeyer 2000)
Russian	59	0.240	0.560	0.200	0.483	(Goreva 2004)
French	223	0.330	0.490	0.180	0.424	(Jeannesson 2007)
Portuguese	100	0.270	0.550	0.180	0.455	(Jeannesson 2007)
Slovenian	355	0.164	0.447	0.389	0.390	(Potocnik 2008)
Caucasian	97	0.299	0.485	0.216	0.459	(Komoto 2006)
European Caucasian	60	0.350	0.517	0.133	0.392	[100]
Asians						
Japanese	154	0.110	0.468	0.422	0.656	(Komoto 2006)
Japanese	45	0.178	0.489	0.333	0.578	[100]
Chinese Han	165	0.115	0.497	0.388	0.636	(Li 2007)
Chinese Uygur	161	0.161	0.491	0.348	0.407	(Li 2007)
Chinese Kazakh	108	0.139	0.380	0.481	0.329	(Li 2007)
Chinese Han	200	0.105	0.475	0.420	0.657	(Zhang 2008)
Chinese	206	0.155	0.413	0.432	0.638	(Tan 2005)
Chinese	96	0.083	0.396	0.521	0.718	(Chowbay 2003)
Malay	92	0.120	0.446	0.435	0.658	(Chowbay 2003)
Indian	87	0.138	0.379	0.483	0.672	(Chowbay 2003)
Chinese	45	0.111	0.400	0.489	0.689	[100]
Others						
Brazilians (White)	106	0.400	0.390	0.210	0.410	(Estrela 2008)
Brazilians (Intermediate)	114	0.470	0.380	0.160	0.340	(Estrela 2008)
Brazilians (Black)	100	0.460	0.410	0.130	0.330	(Estrela 2008)
Ashkenazi Jewish	101	0.400	0.370	0.240	0.420	(Kimchi-Sarfaty 2007a)
Turkish	100	0.200	0.510	0.290	0.545	(Gumus-Akay 2008)
Sub-Saharan African	57	0.772	0.211	0.018	0.123	[100]

(B) Comparison of allele and genotype frequencies of MDR1 G2677T/A (exon 21) polymorphism reported from different ethnic populations

Population	n	Genotype frequency						Allele frequency		References
		GG	GT	TT	TA	GA	AA	T	A	
Caucasians										
Czech	189	0.296	0.471	0.222	ND	0.050	ND	0.458	0.003	(Pechandova 2006)
Polish	96	0.333	0.532	0.135	ND	ND	ND	0.401	ND	(Jamroziak 2009)
Polish	139	0.339	0.468	0.173	0.014	0.007	ND	0.414	0.576	(Tan 2004)
Polish	204	0.387	0.397	0.176	0.020	0.020	ND	0.385	0.020	(Kurzawski 2006)
British	285	0.329	0.474	0.147	0.025	0.025	ND	0.396	0.025	(Onnie 2006)
Scottish	370	0.276	0.470	0.254	NA	NA	NA	0.498	NA	(Ho 2005)
Italian	450	0.280	0.524	0.153	0.016	0.027	ND	0.423	0.021	(Palmieri 2005)
Russian	290	0.303	0.449	0.183	0.024	0.041	0.000	0.419	0.033	(Gaikovitch 2003)
Slovenian	355	0.375	0.445	0.180	NA	NA	NA	0.400	NA	(Potocnik 2008)
Caucasian	98	0.276	0.418	0.245	0.020	0.031	0.010	0.464	0.036	(Komoto 2006)
European Caucasian	59	0.322	0.559	0.119	ND	ND	ND	0.398	ND	[101]
Asians										
Japanese	154	0.195	0.318	0.182	0.130	0.149	0.026	0.406	0.166	(Komoto 2006)
Japanese	117	0.128	0.385	0.094	0.137	0.239	0.017	0.355	0.205	(Horinouchi 2002)
Chinese	206	0.277	0.388	0.131	0.078	0.102	0.024	0.364	0.114	(Tan 2005)
Chinese Han	200	0.175	0.375	0.210	0.105	0.110	0.025	0.450	0.133	(Zhang 2008)
Chinese Han	165	0.200	0.382	0.164	0.133	0.109	0.012	0.421	0.133	(Li 2007)
Chinese Uygur	161	0.217	0.429	0.267	0.050	0.037	0.000	0.506	0.043	(Li 2007)
Chinese Kazakh	108	0.269	0.343	0.185	0.065	0.139	0.000	0.389	0.102	(Li 2007)
Indian	87	0.138	0.310	0.414	0.058	0.081	ND	0.598	0.069	(Chowbay 2003)
Korean	632	0.191	0.339	0.163	0.117	0.155	0.035	0.391	0.171	(Lee 2005)
Vietnamese	142	0.393	0.303	0.176	0.030	0.098	ND	0.356	0.063	(Lee 2005)
Asian	23	0.130	0.261	0.304	0.174	0.130	ND	0.522	0.152	[101]
Others										
Bulgarian	160	0.344	0.431	0.225	NA	NA	NA	0.441	NA	(Petrova 2008)
Brazilians (White)	106	0.400	0.400	0.180	ND	0.020	ND	0.380	0.010	(Estrela 2008)
Brazilians (Intermediate)	114	0.500	0.380	0.080	0.020	0.020	ND	0.280	0.020	(Estrela 2008)
Brazilians (Black)	100	0.650	0.330	0.010	0.010	ND	ND	0.180	0.010	(Estrela 2008)
Ashkenazi Jewish	101	0.360	0.480	0.170	NA	NA	NA	0.410	NA	(Kimchi-Sarfaty 2007a)
Turkish	70	0.300	0.443	0.257	ND	ND	ND	0.470	ND	(Sapmaz 2008)
Sub-Saharan African	60	1.000	ND	ND	ND	ND	ND	ND	ND	[101]

(C) Comparison of allele and genotype frequencies of MDR1 C3435T (exon 26) polymorphism reported from different ethnic populations

Population	n	Genotype frequency			Allele frequency	References
		CC	CT	TT	T	
Caucasians						
Czech	189	0.212	0.449	0.339	0.564	(Pechandova 2006)
Polish	96	0.281	0.500	0.219	0.469	(Jamroziak 2009)
Polish	139	0.216	0.525	0.259	0.522	(Tan 2004)
Polish	122	0.420	0.410	0.170	0.380	(Jamroziak 2002)
Polish (West)	204	0.220	0.510	0.270	0.520	(Kurzawski 2006)
German	188	0.278	0.483	0.239	0.481	(Hoffmeyer 2000)
British	190	0.240	0.480	0.280	0.420	(Ameyaw 2001)
British	280	0.218	0.486	0.296	0.539	(Onnie 2006)
Russian	290	0.214	0.486	0.300	0.543	(Gaikovitch 2003)
Italian	450	0.256	0.533	0.211	0.478	(Palmieri 2005)
Spanish	408	0.260	0.520	0.220	0.480	(Bernal 2003)
Spanish (North)	204	0.270	0.510	0.220	0.480	(Vicente 2008)
French	81	0.360	0.420	0.220	0.430	(Anglicheau 2003)
Portuguese	100	0.220	0.420	0.360	0.570	(Ameyaw 2001)
Slovenian	355	0.227	0.487	0.286	0.530	(Potocnik 2008)
Caucasian	99	0.212	0.444	0.343	0.566	(Komoto 2006)
European Caucasian	58	0.155	0.603	0.241	0.543	[102]
Asians						
Japanese	154	0.357	0.474	0.169	0.406	(Komoto 2006)
Japanese	114	0.351	0.526	0.123	0.386	(Sakaeda 2001)
Japanese	168	0.292	0.571	0.137	0.423	(Sugimoto 2008)
Japanese	48	0.290	0.440	0.270	0.490	(Tanabe 2001)
Japanese	50	0.340	0.460	0.200	0.430	(Schaeffeler 2001)
Japanese	117	0.350	0.530	0.120	0.385	(Horinouchi 2002)
Japanese	44	0.250	0.545	0.205	0.477	[102]
Chinese	206	0.422	0.461	0.117	0.347	(Tan 2005)
Chinese	45	0.400	0.400	0.200	0.400	[102]
Chinese Han	200	0.300	0.535	0.165	0.433	(Zhang 2008)
Chinese Han	179	0.380	0.514	0.106	0.363	(Kwan 2007)
Chinese Han	265	0.320	0.480	0.200	0.440	(Li 2006)
Chinese Han	165	0.382	0.479	0.139	0.379	(Li 2007)
Chinese Uygur	161	0.248	0.447	0.304	0.528	(Li 2007)
Chinese Kazakh	108	0.380	0.444	0.176	0.398	(Li 2007)
Lahu (Southern China)	104	0.163	0.587	0.250	0.543	(Dong 2008)
Wa (Southern China)	101	0.297	0.495	0.208	0.455	(Dong 2008)
Bulang (Southern China)	100	0.360	0.500	0.140	0.390	(Dong 2008)
Han Chinese (Hong Kong)	199	0.447	0.442	0.111	0.332	(Dong 2008)
Chinese (Malaysia)	288	0.372	0.489	0.139	0.384	(Teh 2007)
Chinese (Singapore)	98	0.245	0.439	0.316	0.541	(Balram 2003)
Chinese (Southwest)	132	0.318	0.424	0.258	0.470	(Ameyaw 2001)

Chinese (Singapore)	224	0.280	0.500	0.220	0.410	(Lee 2004)
Indian	87	0.184	0.368	0.448	0.632	(Chowbay 2003)
Tamilians (South India)	185	0.180	0.560	0.260	0.540	(Ramasamy 2006)
Indian (Malaysia)	171	0.170	0.438	0.392	0.611	(Teh 2007)
Indian (Singapore)	93	0.180	0.390	0.430	0.620	(Balram 2003)
Malay (Malaysia)	304	0.362	0.487	0.151	0.395	(Teh 2007)
Malay (Singapore)	99	0.253	0.465	0.283	0.520	(Balram 2003)
Vietnamese	142	0.451	0.366	0.183	0.366	(Lee 2005)
Vietnamese (Kinh)	72	0.319	0.556	0.125	0.403	(Veiga 2009)
Korean	632	0.384	0.445	0.171	0.393	(Lee 2005)
Iranian	300	0.440	0.450	0.110	0.201	(Farnood 2007)
Filipino	60	0.380	0.420	0.200	0.410	(Ameyaw 2001)
Saudi	96	0.370	0.380	0.260	0.450	(Ameyaw 2001)
Southwest Asians	89	0.150	0.380	0.47	0.663	(Ameyaw 2001)
Africans						
Egyptian	50	0.240	0.480	0.280	0.520	(Ebid 2007)
Egyptian	200	0.340	0.515	0.145	0.403	(Hamdy 2003)
Ghanaian	206	0.670	0.340	0.000	0.170	(Ameyaw 2001)
Kenyan	80	0.700	0.260	0.040	0.170	(Ameyaw 2001)
Sudanese	51	0.520	0.430	0.060	0.270	(Ameyaw 2001)
African-American	88	0.680	0.310	0.010	0.165	(Ameyaw 2001)
Sub-Saharan African	59	0.797	0.186	0.017	0.110	[102]
South-Americans						
Brazilians (White)	106	0.320	0.450	0.230	0.450	(Estrela 2008)
Brazilians (Intermediate)	114	0.400	0.520	0.080	0.340	(Estrela 2008)
Brazilians (Black)	100	0.500	0.410	0.090	0.310	(Estrela 2008)
Chilean (Pascuense)	52	0.560	0.380	0.060	0.250	(Wielandt 2004)
Chilean (Mestizo)	104	0.460	0.430	0.120	0.330	(Wielandt 2004)
Chilean (Mapuche)	96	0.490	0.310	0.200	0.350	(Wielandt 2004)
Others						
Central American	229	0.290	0.470	0.240	0.470	(Vicente 2008)
Bulgarian	160	0.269	0.444	0.287	0.509	(Petrova 2008)
Ashkenazi Jewish	101	0.310	0.390	0.310	0.500	(Kimchi-Sarfaty 2007a)
Turkish (Aegean-Denizli Province)	150	0.200	0.530	0.270	0.530	(Turgut 2006)
Turkish (Southeast)	96	0.290	0.470	0.240	0.474	(Kerb 2001)
Ashkenazi Jewish	100	0.420	0.460	0.120	0.350	(Ostrovsky 2004)
New Zealander	160	0.210	0.520	0.270	0.530	(Roberts 2002)

Reference internet sites:

[100] http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1128503

[101] http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=2032582

[102] http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1045642

Subsequent analyses of the MDR1 haplotype frequencies, estimated from the genotype data, were compared between the two studied groups (Table 13.).

Table 13. Haplotype frequencies derived from C1236T, G2677T/A and C3435T polymorphisms of MDR1 gene in healthy Roma and Hungarian populations

Number of haplotypes	Haplotype	Haplotype frequency n (%)				
		Roma n=465	Hungarian n=503	Czech (Bandur 2008) n=533	Caucasian (Kroetz 2003) n=247	Indian (South) (epilepsy) (Vahab 2009) n=129
1	**TTT**	335 (36.0)[b,c,d]	377 (37.5)[f]	419 (39.3)	101 (41.0)	33 (25.2)
2	**CGC**	328 (35.3)[a,c,d]	416 (41.4)[e,f]	398 (37.3)	91 (37.0)	18 (13.6)
3	**TGC**	68 (7.31)[a,b,c]	17 (1.68)	30 (2.80)	3 (1.00)	14 (11.0)
4	**TTC**	62 (6.67)[a,b,c,d]	21 (2.08)	13 (1.20)	6 (2.50)	8 (6.20)
5	**CGT**	56 (6.02)[a,b]	91 (9.04)[f]	103 (9.70)	29 (12.0)	13 (9.90)
6	**TGT**	37 (3.98)[b,c]	27 (2.68)[f]	22 (2.10)	1 (0.50)	9 (7.10)
7	**CTC**	15 (1.61)	17 (1.68)	27 (2.50)	4 (1.50)	5 (4.20)
8	**CTT**	10 (1.08)[a,b,d]	29 (2.88)[f]	32 (3.00)	3 (1.00)	29 (22.8)
9	**TAT**	7 (0.75)[b,c]	4 (0.39)[e]	ND	ND	ND
10	**CAC**	6 (0.65)[b]	4 (0.39)[e]	17 (1.60)	6 (2.50)	ND
11	**CAT**	3 (0.32)	3 (0.29)	5 (0.50)	3 (1.00)	ND
12	**TAC**	3 (0.32)	ND	ND	ND	ND

ND, not detected
[a]$p<0.009$, when Roma are compared with Hungarian population
[b]$p<0.04$, when Roma are compared with Czech population
[c]$p<0.05$, when Roma are compared with Caucasian population
[d]$p<0.02$, when Roma are compared with Indian population
[e]$p<0.03$, when Hungarians are compared with Czech population
[f]$p<0.02$, when Hungarians are compared with Caucasian population

There were 12 possible MDR1 haplotypes and the frequencies of these were statistically different between the Roma and Hungarian populations. All 12 possible haplotypes were observed in Roma, compared with 11 haplotypes in Hungarians. The 1236T/2677A/3435C haplotype was not detectable in Hungarian population. The two most frequent MDR1 haplotypes both in Roma and Hungarian populations were TTT (36.0 vs.

37.5%) and CGC (35.3 vs. 41.4%). The haplotypes TTT, CGC, TGC, TTC, CGT occured at high frequencies in Roma population (6.02-36.0%), whereas in Hungarians TTT, CGC and CGT were the most common identified haplotypes. The statistical analysis revealed significant difference in the prevalence rate of CGC, TGC, TTC, CGT and CTT haplotypes between the healthy Roma and Hungarian populations ($p<0.009$). The occurrence of 1236T/2677G/3435C haplotype was four-fold higher in Roma than in Hungarians. In addition, the presence of 1236T/2677T/3435C haplotype was three-fold higher in Roma than in Hungarians. Whereas the frequency of 1236C/2677T/3435T haplotype was two-fold higher in Hungarian than in Roma group.

Comparison of haplotype profile of both studied groups and other populations is also provided in Table 13. and Table 14. For the Caucasians two sets of data are listed, as there were considerable differences between the two groups found in the literature. The Roma population showed significant differences in TTT, CGC, TGC, TTC, CGT, TGT, CTT, TAT, CAC haplotypes when compared to Caucasians and to the Czech population ($p<0.05$) (Table 13.) (Kroetz 2003, Bandur 2008). However, Roma were more similar to the Indian population and difference could be observed only in TTT, CGC, TTC and CTT haplotypes ($p<0.02$) (Vahab 2009). The haplotype structure of Hungarian population differed also from the Caucasian and Czech populations. Significant difference was found in TTT, CGC, CGT, TGT, CTT, TAT and CAC haplotypes ($p<0.03$) (Kroetz 2003, Bandur 2008). In a previous study of Hungarian acute lymphoblastic leukaemia patients the dominating haplotypes were TTT and CGC, in accordance with our results (Erdelyi 2006).

Table 14. Comparison of haplotype frequencies of MDR1 gene reported from different ethnic populations

Number of haplotypes	Haplotype	Haplotype frequency (%)								
		Chinese Han (Li 2007) n=165	Chinese Uygur (Li 2007) n=161	Chinese Kazakh (Li 2007) n=108	Korean (epilepsy) (Kim 2006) n=99	Ashkenazi Jewish (Kimchi-Sarfaty 2007a) n=101	Tuvinians (Pel's IaR 2007) n=142	Kyrgyz (South) (Pel's IaR 2007) n=44	Kyrgyz (North) (Pel's IaR 2007) n=41	Japanese (Komoto 2006) n=154
1	**TTT**	33.3	45.3	34.5	15.7	23.6	31.67	25.25	33.1	36.4
2	**CGC**	20.1	30.1	21.9	17.2	31.7	23.48	24.76	18.7	16.2
3	**TGC**	22.2	8.60	24.8	19.4	6.90	5.43	14.4	6.07	22.7
4	**TTC**	5.60	2.20	4.40	9.13	5.20	7.66	5.40	2.72	3.90
5	**CGT**	1.20	3.10	1.50	ND	14.4	12.46	8.94	10.86	1.30
6	**TGT**	1.00	3.30	2.70	4.68	6.40	7.58	11.08	16.86	2.60
7	**CTC**	1.70	2.00	ND	16.1	6.20	0.42	4.05	ND	ND
8	**CTT**	1.60	1.10	ND	1.44	5.60	2.14	ND	2.93	0.30
9	**TAT**	0.40	ND	ND	8.95	NA	0.89	ND	ND	ND
10	**CAC**	11.3	4.30	8.40	6.62	NA	6.39	3.43	8.75	16.6
11	**CAT**	0.40	ND	1.10	ND	NA	1.24	2.69	ND	ND
12	**TAC**	1.20	ND	0.70	0.59	NA	0.64	ND	ND	ND

5. DISCUSSION

5.1. CYP2C9 gene

Much of the interindividual and interethnic differences in effects of drugs are attributed nowadays in part to genetic differences in their metabolism and utilization (Sadee 2005). A number of drugs are metabolized by the human cytochrome P450 system (Xie 2001). The CYP2C9 is the most abundant of the CYP2C enzymes (Lapple 2003). It is involved in the metabolism of more than 100 drugs (Kirchheiner 2005, Miners 1998). It is well known that the metabolism of S-enantiomers of coumarins, warfarin, acenocoumarol and phenprocoumon, was significantly decreased by the presence of both the CYP2C9*2 and CYP2C9*3 alleles (Scordo 2002, Kirchheiner 2005, Kamali 2004, Lindh 2008, Becquemont 2008). Administration of genotype-adjusted dosage of drugs having narrow therapeutic range may result in faster anticoagulation and reduced toxicity (Takahashi 2003, Higashi 2002).

The prevalence of CYP2C9*2 and *3 alleles observed in our study of healthy Hungarian subjects were very close to that found in Hungarian patients (Mark 2006) and other Caucasian populations (Scordo 2004, Xie 2002, Yasar 1999, Bozina 2003, Scordo 2001, Gaedigk 2001, Dorado 2003, Allabi 2003, Taube 2000, Stubbins 1996), but proved to be higher than in Orientals (Sullivan-Klose 1996, Gaedigk 2001, Wang 1995, Kimura 1998, Nasu 1997, Yoon 2001) (Table 7.). Interestingly, CYP2C9*2 and *3 variants appear to be more prevalent in Europeans and white Americans (8-16% and 4-9%, respectively) (Sullivan-Klose 1996, Scordo 2004, Yasar 1999, Mark 2006, Bozina 2003, Scordo 2001, Gaedigk 2001, Dorado 2003, Allabi 2003, Taube 2000, Dickmann 2001) than in Asians (0% and 1-5%, respectively) or African-Americans (1-2% and 0.5-1%, respectively) (Sullivan-Klose 1996, Gaedigk 2001, Dickmann 2001, Wang 1995, Kimura 1998, Yoon 2001). Moreover, the allele frequencies of CYP2C9*2 and CYP2C9*3 tend to decrease from West to East (Table 7.).

Although the *3/*3 genotype frequency in numerous studies was very low or not detectable, in Hungarians it seems to be in a higher range among Caucasians (Garcia-Martin 2006, Scordo 2004, Yasar 1999, Mark 2006, Bozina 2003, Scordo 2001, Gaedigk 2001, Dorado 2003, Allabi 2003, Taube 2000, Stubbins 1996). Similarly, we found the homozygous mutants for the *3 polymorphism in Roma population samples at the highest frequency level (0.022) considering the published literature (Table 7.). It has been shown that *3/*3 genotype is associated with clinically significant alterations in the pharmacokinetics of CYP2C9 substrates, therefore our finding in healthy Hungarian and especially in Roma population is of

special clinical importance (Scordo 2002, Kirchheiner 2007, Lee 2002). We found significant differences in the genotype and allele frequencies of CYP2C9*2 and *3 variants in Roma group versus the Indian population ($p<0.04$) published in the literature, except the *2/*2 and *3/*3 genotypes, which were not detected in Indians (Adithan 2003). In addition, significant differences were found in *3 allele frequency and the *1/*1, *1/*3 genotype prevalence between the Roma group and other Caucasian population ($p<0.04$) (Scordo 2004). It has been suggested that the CYP2C9*3 allele is responsible for the largest reduction in metabolic activity *in vitro*, as compared to *1 (Lee 2002), thus the higher proportion of *3 allele (0.155) in Roma population compared to other ethnic groups is of special importance (Sullivan-Klose 1996, Scordo 2004, Yasar 1999, Mark 2006, Bozina 2003, Scordo 2001, Gaedigk 2001, Dorado 2003, Allabi 2003, Taube 2000, Dickmann 2001, Wang 1995, Kimura 1998, Nasu 1997, Yoon 2001, Adithan 2003, Stubbins 1996, Lee 2002, Hamdy 2002, LLerena 2004, Aynacioglu 1999, Peyvandi 2002, Halling 2005, Bravo-Villalta 2005).

Taken these findings together, this is the first study to document the allele and genotype frequencies of two major variants of CYP2C9 gene in healthy Roma and Hungarian population samples. The distribution of CYP2C9 alleles in Roma population showed variation when compared with Hungarians, Indians and Caucasians. The analyses of allele and genotype frequencies both in Hungarian and Roma populations and their comparison with data obtained in other ethnic groups provide genetic evidence of the origin of different populations.

5.2. VKORC1 gene

Oral anticoagulant dose requirements vary across ethnic groups, by and large the Chinese and Japanese people require lower, while African-Americans need higher doses than the Caucasians (Dang 2005, Gan 2003). Polymorphisms in CYP2C9 and VKORC1 account for 5–22% and 6–37% of the inter-individual variability of warfarin response, respectively; thus, VKORC1 has high impact on the ethnic differences of warfarin sensitivity (El Rouby 2004, Rieder 2005, Geisen 2005, Yuan 2005, Scott 2008, Osman 2006, Oner 2008, Lee 2006). The current knowledge about the genetic background determining the anticoagulant therapy derives from studies carried out mainly in populations of American, Western European or Asian origin; this is the first study about the allele, haplotype, and genotype frequencies of VKORC1 gene in Hungarian and Roma population samples.

The clinical significance of the VKORC1 comes from the genetic variations in the warfarin-treated individuals. In the literature the most extensively studied level is the haplotype-tagging SNP and the haplotype analysis. Besides to comparing them to each other, we compared our results of VKORC1 tagging SNP-s with data reported for people from India (Lee 2006) because of the postulated origin of the Roma tribes, and also with European Caucasian(www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=9923231,www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=7294,www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=17708472) populations (Table 8.). While difference was seen for G-1639A and G9041A variants between the Hungarians and Roma, no considerable difference was observed between Hungarian and Caucasian population for these and also for C6009T haplotype-tagging SNPs (www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=9923231,www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=7294, www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=17708472). The latter observation is consistent with the growing body of observations suggesting, that despite of the origin of the ancient tribes, the majority of the modern Hungarians do not differ from the European Caucasian lineages (Nadasi 2007). The Roma population was compared to data from India (Lee 2006), and with the exception of the -1639AA variant, significant differences were observed for all SNPs. The difference in VKORC1 haplotype tagging SNPs between the Roma studied by us and the Indian population reported can be attributable to the fact that in the subcontinent of India ethnogeographycally distinct subpopulations can be found. Thus, available data we cited could cover only a part of heterogeneity of such populations. However, in the literature no other data are available for VKORC1 tagging SNPs for people of India so far.

Special interest is devoted to the -1639G/A polymorphism, which occures at the second nucleotide of an E-box (CANNTG) in the 5'-untranslated region of the gene (Yuan 2005). This polymorphism has an important role on VKORC1 gene promoter activity, being associated with variable mRNA levels. Actually the G allele shows a 44% increase of the gene transcription activity when compared with the A allele, since the A allele disrupts the binding of a transcription factor in VKORC1 promoter region, therefore fewer functional copies of the mature VKORC1 protein are synthesized, associating thereby ultimately with low-warfarin-dose phenotype (Yuan 2005). In Japanese (Obayashi 2006, Kimura 2007) and Chinese (Yuan 2005, Wang 2008) subjects the frequency of the VKORC1 -1639AA genotype is significantly higher than in Caucasians (Bodin 2005). Homozygous carriers of -1639A allele, which occurres in humans only in the *2/*2 genotype (see below), require the lowest dose of coumarin and require therefore special care to prevent the serious bleeding

complications. In Hungarians we found this genotype essentially in the same range as in Caucasians reported by others (Geisen 2005, Sconce 2005), while the Roma findings of ours more resembled to that reported previously by others for population samples from India (Table 8). This can fit to the data about origin of the Gypsies, however, differences in other SNPs do not support this assumption.

In the VKORC1 population genetic studies the haplotype profile is the second most frequently studied in the literature. Besides our findings, in Table 9. we also summarized some relevant population-specific data reported by others. While significant difference was found in VKORC1*1 and VKORC1*2 haplotype frequencies between Roma and European population reported (Geisen 2005), however, comparing the Hungarian and European population difference could be observed only in the frequency of VKORC1*1 haplotype, while the distribution of VKORC1*2, *3, *4 haplotypes in average Hungarian samples were consistent with the profiles characteristic for European Caucasians (Geisen 2005), and the Hungarian profile was similar also to the European American sample representatives (Rieder 2005).

For the daily clinical patient care the whole VKORC1 genetic status characterizing the patient's warfarin need is required; this is possible with simultaneous characterization of both alleles (i.e. both haplotypes) of the patients. The patients can be conventionally stratified into low-, intermediate- and the high-warfarin-dose requiring genotypes (www.warfarindosing.org/Source/Home.aspx). Despite of this clinical significance, the research papers reporting the genotypes in different population studies are rarer. Moreover, another type of clinical classification is also available (Rieder 2005). Comparing the genotypes of Roma and Hungarian populations using a widespread and simple method, difference was found in the *2/*2, *2/*4, and 3*3 natural VKORC1 genomic haplotype combinations, individually each representing the low-, intermediate- and the high-warfarin-dose requiring genotypes, respectively. The *2/*2 genotype frequency was approximately half in Roma population compared with the Hungarian samples, but in Italian Caucasians (Spreafico 2008) it was almost twice as common as in Hungarians (Table 10.). The *3/*3 genotype, requiring the highest dose, was more frequent in Roma than in Italian Caucasians (Spreafico 2008).

The results of our study show, that albeit the VKORC1 genetic profile of a mixed average Hungarian population exhibited some differences when compared with surrounding European Caucasians or Americans of European origin, the data suggest relatively high degree of similarity. By contrast, the VKORC1 profiles of Roma people show an isolated

genetic structure from the surrounding populations, the data available from India are also not consistent with our results found in the Roma population samples.

5.3. MDR1 gene

Interethnic differences in response to drugs have been related to genotypic variants of key enzymes and proteins that affect the safety and efficacy of a drug in the individual patient (Evans 1999b). MDR1 polymorphisms alter P-gp conformation and inhibit its function by changing the substrate specificity, which results in decreased activity of P-gp (Hoffmeyer 2000, Kimchi-Sarfaty 2007a).

The results of this study were compared with compiled data of MDR1 gene polymorphisms reported for other populations (Table 11.). The frequency of 1236T allele vary between 0.123 in Sub-Saharan African population (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1128503) and 0.718 in Chinese (Chowbay 2003); with Asians in higher range (0.656-0.718) (Komoto 2006, Li 2007, Zhang 2008, Tan 2005, Chowbay 2003) and Caucasians in lower range (0.380-0.483) (Pechandova 2006, Jamroziak 2009, Tan 2004, Wasilewska 2007, Hoffmeyer 2000, Goreva 2004, Jeannesson 2007, Potocnik 2008, Komoto 2006). The 1236T allele frequency in Hungarians (0.443) was similar to most other Caucasians. Interestingly, the 1236T allele frequency in the Roma population differs significantly from the Caucasians (0.551 vs. 0.410, $p<0.001$) (Cascorbi 2001) and was very similar to that found in Indian populations (0.609, 0.672) (Lakhan 2009, Chowbay 2003).

The frequency of the T allele in exon 21 (G2677A/T) shows also variations when compared between ethnic groups. The lowest frequency was observed in Brazilians (0.180) (Estrela 2008) and the highest in Indians (0.598) (Chowbay 2003) . The frequency of 2677A allele vary between 0.003 in Checz population (Pechandova 2006) and 0.576 in Polish (Tan 2004), and could not be detected in a number of populations. Interestingly, we did not find any difference in G2677A/T genotype and allele distribution between both of our studied groups and the Caucasian population (Cascorbi 2001). However, the Roma population differs from the Indians in 2677T and 2677A allele frequencies both ($p<0.004$) (Lakhan 2009).

However, the 3435T allele ranged from 0.110 in Sub-Saharan African (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1045642) to 0.663 in Southwest Asian population (Ameyaw 2001). Studies in African populations reported far less frequent presence of the 3435T allele: Ghanaian and Kenyan 0.170 both, Sudanese 0.270, African-American 0.165 (Ameyaw 2001), except the Egyiptians (0.403, 0.520) (Ebid 2007, Hamdy

2003). The dominance of the C allele may be a consequence of natural selection representing an advantage against gastrointestinal tract infections (Schaeffeler 2001). The Hungarians were very similar to the Caucasians in 3435T allele frequency. Considering the 3435T allele frequency in the Roma population we can conclude that the Roma population differs significantly from the Caucasians ($p<0.01$) (Cascorbi 2001), but the frequency found in Roma was also much lower than in Indians (Lakhan 2009, Chowbay 2003, Ramasamy 2006, Teh 2007, Balram 2003).

The majority of studies have focused on C3435T SNP alone, instead of accounting for all the polymorphisms potentially linked in each subject (Woodahl 2004). To explain the association between the MDR1 genotype and clinical outcome in different ethnic groups haplotype considerations are needed. From the findings in the literature it is clear that the establishment of detailed ABCB1 gene haplotype profiles specific for each ethnic group is important (Sai 2006). Few of the MDR1 haplotypes have shown association to phenotypes with over-expression of the protein (Hoffmeyer 2000). Bandur et al. reported that the CGT haplotype increased the risk of acute rejection 1.4 times in renal transplant patients (Bandur 2008). The CGC, TGC and TTT haplotypes were previously associated with drug resistant epilepsy (Vahab 2009). Futhermore, in the study of Panczyk et al. the TTT haplotype was associated with colorectal cancer (Panczyk 2009). A detailed description of haplotype profile of other populations is also provided in Table 14. Interestingly, in Chinese and Japanese populations dominates three haplotypes, the TTT, CGC and the TGC too (Table 14.) (Li 2007, Komoto 2006). In the Korean people the MDR1 haplotypes split more evenly, with TGC, CGC, CTC and TTT the largest proportion (Kim 2006). In Asian groups there are also some haplotypes that could not be detected (Kim 2006, Li 2007, Pel's IaR 2007, Komoto 2006). The distribution of MDR1 haplotypes in Hungarian population is very similar to the Ashkenazi Jewish group (Kimchi-Sarfaty 2007a).

In conclusion, this is the first major study reporting the MDR1 polymorphisms and haplotypes in Hungarian and Roma populations too. The Roma population differed significantly from the Hungarians and Caucasians in most of MDR1 variants studied, and also from the Indians. Our findings revealed that Roma people are at increased risk of drug-induced side effects and resistance development to a number of drugs due to diminished drug elimination, compared to the Hungarian population. In addition, we can conclude that Hungarians did not differ significantly from the Caucasians in major MDR1 variants, but some difference was observed in MDR1 haplotype structure of the individual persons. Results considering the distribution of MDR1 polymorphisms and haplotypes in populations of

different origin may contribute to explaining interindividual and interethnic differences in drug response and side-effects.

6. SUMMARY OF NEW OBSERVATIONS

1. According to our results there is a significant increase in CYP2C9*3 prevalence in Roma population compared to Hungarian samples. We found homozygous mutants for the *3 polymorphism in Hungarians and in Roma in a higher range considering the published literature. The proportion of extensive metabolizers is higher in Hungarians, while poor metabolizers are more frequent in Roma.
2. We showed significant difference of VKORC1 G-1639A polymorphism and VKORC1*2 and VKORC1*3 haplotypes between the Roma and Hungarian samples. No considerable difference was observed between Hungarian and Caucasian population for the VKORC1 SNPs and distribution of VKORC1*2, *3, *4 haplotypes. Except of the -1639AA variant significant difference was observed for all VKORC1 SNPs between the Roma and Indian populations, and for VKORC1*1 and VKORC1*2 haplotype frequencies between Roma and European population.
3. We presented a significant difference in the MDR1 C1236T polymorphism, while no difference was observed in the G2677T/A SNP between the Roma and Hungarians, and higher frequency of the 3435T allele was observed in Hungarians. We found difference in the prevalence rate of CGC, TGC, TTC, CGT and CTT haplotypes between the healthy Roma and Hungarian populations, and of CGC, TGC, TTC, CGT, TGT, CTT, TAT, CAC haplotypes between the Roma and Caucasians. Difference could be observed only in TTT, CGC, TTC and CTT haplotypes when comparing Roma to Indians. The haplotype structure of Hungarian population differed in TTT, CGC, CGT, TGT, CTT, TAT and CAC haplotypes from Caucasians.
4. We demonstrated that the CYP2C9, VKORC1 and MDR1 genetic profile of average Hungarian population is relatively similar to that observed in Caucasian populations. Contrarily, the Roma population differs from Hungarians, from most of other Caucasians and from Indians in the incidence of selected pharmacogenetically relevant genes.
5. Evaluation of genetic profile of CYP2C9, VKORC1 and MDR1 genes in two biggest populations in Hungary help to characterize their pharmacogenetic profile, to reach the goal of personalized medicine and to estimate the global genetic diversity.
6. Through this study several new pharmacogenetic diagnostic methods are available in routine for Hungarian patients, and serve as basis for genotype-assessed dosing regimen and lowering the risk of therapeutic failure.

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8. PUBLICATIONS

Publications supporting the dissertation

Papers

Sipeky C, Csongei V, Jaromi L, Safrany E, Maasz A, Szabo M, Takacs I, Beres J, Melegh B: *Genetic variability of MDR1 (ABCB1) C1236T, G2677T/A and C3435T polymorphisms and natural haplotype profile in Roma and Hungarian populations with a review of the literature.* Pharmacogenomics. (Under consideration)

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