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Genetic Variability of CYP2C8, CYP2C9, and CYP3A4 Across European Populations: Implications for Pharmacogenetics

Karolina Borówka[1], Paulina Tymińska[1], Julia Frączek[1], Natalia Kawka[1], Grzegorz Machnik[2]

[1] Student at the Department of Molecular Biology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland.

[2] Department of Molecular Biology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland.

Karolina Borówka, s85616@365.sum.edu.pl, ORCID ID 0009-0001-5669-1491

Paulina Tymińska, s86287@365.sum.edu.pl, ORCID ID 0009-0004-5624-1599

Julia Frączek , s82577@365.sum.edu.pl, ORCID ID 0009-0005-0239-6824

Natalia Kawka, s85829@365.sum.edu.pl, ORCID ID 0009-0008-8441-7052

Grzegorz Machnik, gmachnik@sum.edu.pl, ORCID ID 0000-0002-9081-0984

Corresponding author: Karolina Borówka, Medical University of Silesia, ul. Medyków 18, 40-752 Katowice, Poland, Tel: +48 604 902 473, e-mail: s85616@365.sum.edu.pl

Abstract

Cytochrome P450 (CYP) enzymes are membrane-bound hemoproteins responsible for the metabolism of numerous important compounds. In humans, they are responsible for nearly 80% of oxidative reactions and approximately 50% of total drug elimination, mainly within the CYP1–CYP3 families. The CYP3A4 isoenzyme, involved in the metabolism of around 50% of drugs used in clinical practice, along with the highly polymorphic CYP2C9 and CYP2C8 genes, are key members of the cytochrome P450 subfamily. Their genetic variability, which may result in abolished, quantitatively or qualitatively altered or enhanced metabolism, varies among populations and geographical regions. This review presents the frequency and diversity of CYP2C8, CYP2C9 and CYP3A4 alleles across European countries.

Key words: cytochrome P450, CYP2C8, CYP2C9, CYP3A4, allele frequency, genetic polymorphism

1.Introduction

Pharmacogenetics is a field of genetics and pharmacology that investigates the influence of individual genes or their variants on the body's response to the administration of specific drugs [1]. This sphere of knowledge is mainly associated with cytochrome P450 enzymes, which are involved in the metabolism of many endogenous compounds and clinically important xenobiotics, including statins, sulphonamides, glinides and glitazones [2, 3].

The evolution of functionally significant polymorphisms in CYP genes has been strongly shaped by environmental factors and dietary habits. These genetic variations include copy number variations (CNVs), alterations to amino acid composition, premature stop codons, mutations that result in alternative splicing, and mutations that lead to either enhanced or reduced gene expression level [4]. Genetic variation in cytochrome P450 is an important predictor of the effectiveness and safety of various commonly prescribed drugs [3].

In particular, the isoenzyme CYP3A4 most often participates in drug metabolism and plays an important role in the metabolism of approximately 50% of the drugs used in clinical practice [6].

The CYP2C subfamily of cytochrome P450 consists of four isoenzymes: CYP2C8, CYP2C9, CYP2C18, and CYP2C19. Among these, CYP2C9 is the most prevalent in the liver, metabolizing about 20% of commonly used drugs, while CYP2C8 metabolizes approximately 5% of prescribed medications [7, 8]. The most frequently and extensively studied variants of these genes include CYP2C8*2, CYP2C8*3, CYP2C9*2, and CYP2C9*3. Notably, the CYP2C8 gene exhibits significant polymorphism, with over 700 variants identified. Genetic variability in these cytochromes may be an important source of interindividual differences in drug response and toxicity [7, 9].

Cytochrome polymorphism varies in different countries. Expanding knowledge in this area can provide valuable insights that will allow for therapy to be better tailored to the individual patient's needs, as well as the development of more personalized therapeutic strategies [10].

The aim of this review is to present the diversity of CYP2C8, CYP2C9 and CYP3A4 alleles in various European countries.

2. Materials and methods

Search strategy and data sources

This review focuses on the genetic variability of three important cytochrome P450 enzymes: CYP2C8, CYP2C9, and CYP3A across different European populations. These enzymes are important for drug metabolism, and their variations can influence individual responses to medications.

The analysis was based on data from the PubMed and Scopus databases. Additionally, publishing platforms like Springer, Frontiers, Elsevier, and the Multidisciplinary Digital Publishing Institute were explored to enhance the comprehensiveness of this review.

The following MeSH terms and keywords were used in the search: “Cytochrome P450”, “genetic polymorphism”, “allele frequency”, “pharmacogenetics”, “CYP2C8”, “CYP2C9”, “CYP3A4”, “gene variants”, “personalised medicine”.

Inclusion and exclusion criteria

A total of 38 articles published between 2004 and 2024 were included. No strict time limit was set, but the selected range includes both older and newer studies. The aim was to give a full and clear picture of the available research by including important studies in Europe from the past as well as recent findings.

Only studies conducted on humans were considered. Studies and reviews published in English were included. Research focusing on cytochrome distribution outside of Europe was excluded.

Study selection and screening

At first, 55 publications were found, but after some were excluded due to irrelevant focus or animal models, 38 studies were used in the review.

Identification

Records identified via PubMed, Scopus and publishing platforms (Springer, Frontiers, Elsevier, MDPI)

(n = 55)

Screening

Records after title/abstract screening and applying exclusion criteria

(n = 38)

Excluded

1 article (language barrier - Italian only)

16 articles (animal models or unrelated cytochromes)

(n = 17)

Eligibility

Full-text articles assessed for eligibility

(n = 38)

Included

Final studies analyzed

(n = 38)

The studies were selected through a systematic, multi-step procedure in accordance with a structured framework based on PRISMA methodology.

3.The landscape of CYP2C8, CYP2C9 and CYP3A4 variability in individual European countries

3.1 Alleles of cytochrome CYP2C8, CYP2C9, CYP3A4 and their functional consequences.

Response to medications can vary significantly between patients; studies show that up to 50% of people undergoing pharmacotherapy experience low treatment effectiveness or side effects [11, 12]. Cytochromes possess different gene variants (alleles) with distinct nucleotide sequences in their DNA, which can influence the enzyme's activity and drug metabolism capacity. Depending on the specific allele, a cytochrome may exhibit varying levels of functionality ranging from enhanced activity to reduced efficiency or complete inactivity [5].

In line with the subject of this review, three cytochromes were included in the study - CYP2C9, CYP2C8 and CYP3A4 - due to their role in the metabolism of drugs used to treat metabolic diseases such as diabetes, hypercholesterolemia and hypertriglyceridemia. The subject of the analysis is the distribution of functionally important alleles of these cytochromes in Europe.

Table 1. Alleles of cytochrome CYP2C8, CYP2C9, CYP3A4 and their functional consequences [11].

Enzyme	Function	Variants
CYP2C8	Normal	CYP2C8*1
	Decreased	CYP2C8*2, CYP2C8*4
	Controversial	CYP2C8*3
	Inactive	CYP2C8*5, CYP2C8*7, CYP2C8*11
CYP2C9	Normal	CYP2C9*1, CYP2C9*9
	Decreased	CYP2C9*2, CYP2C9*5, CYP2C9*8, CYP2C9*11, CYP2C9*12, CYP2C9*14, CYP2C9*16, CYP2C9*29, CYP2C9*31
	Inactive	CYP2C9*3, CYP2C9*6, CYP2C9*13
CYP3A4	Normal	CYP3A4*1
	Decreased	CYP3A4*8, CYP3A4*16, CYP3A4*18, CYP3A4*22

In some previously published articles, research results indicate slight differences in the functional consequences of alleles. In their paper [13], [14] as well as in CYP's Allele Nomenclature Database the enzyme activity of the CYP2C8*3, CYP2C9*3, CYP2C9*13 coding genes were described as decreased. Additionally, it should be noted that the functional consequences of the presence of the CYP3A4*11 and CYP3A4*13 genes are manifested as reduced activity, while CYP3A4*6 [15], CYP3A4*20 and CYP3A4*26 even demonstrate enzymatic inactivity. The characteristics of cytochromes continue to be the subject of verification in various studies – some confirm them, while others reveal distinct activities. For many alleles, the function still remains unknown, as is observed in the case of *CYP3A4* *2*, *CYP3A4* *3*, *CYP3A4* *4*, and *CYP3A4* *15*, where the function is undetermined [11].

3.2 The distribution of CYP2C8, CYP2C9 and CYP3A4 in Europe in comparison to other continents according to published data [11, 13, 14, 16, 17, 18, 19, 20].

Table 2. The distribution of CYP2C8 in Europe in comparison to other continents.

Allele	**Variant number acc. to dbSNP database (lit.)**	**Europe (%)**	**Africa (%)**	**East Asia (%)**	**South Asia(%)**	**America(%)**
CYP2C8						
***1**	None	82.8	80.8	98.7	92.6	90.1
***2**	rs11572103	0	15.9	0	1.9	0.9
***3**	rs10509681, rs11572080	11.2	2.1	<0.1	4	6.7
***4**	rs1058930	6.0	1.1	0	1.5	2.3
***5**	rs72558196	0	0	0.2	0	0
***6**	rs142886225	0	0	0.5	0	0
***7**	rs72558195	0	<0.1	<0.1	<0.1	0
***11**	rs78637571	0	0	0.4	0	<0.1
***12**	rs3832694	0	0	<0.1	0	0
***14**	rs188934928	0	0	0.1	<0.1	0

As shown in Table 2, the most common allele - CYP2C8*1 - is outstandingly frequent in Asian populations, where it reaches almost 100% frequency. A high level of the CYP2C8 *2 allele has been found within African population, unlike other continents, especially Europe and East Asia, where this allele is virtually absent. In the case of CYP2C8 *3 and CYP2C8 *4, alleles that are less common, their frequency varies by region, being most common in Europe. The remaining alleles appear with far lower frequency or are even absent in particular populations.

Table 3. The distribution of CYP2C9 in Europe in comparison to other continents.

Allele	**Variant number acc. to dbSNP database (lit.)**	**Europe (%)**	**Africa (%)**	**East Asia (%)**	**South Asia (%)**	**America (%)**
CYP2C9						
***1**	None	81.8	78.4	95.7	81.3	88.9
***2**	rs1799853	11.7	2.4	<0.1	4.6	6.6
***3**	rs1057910	5.6	1.3	3.4	11.3	3.6
***4**	rs56165452	0	<0.1	0	0	0
***5**	rs28371686	0	1.3	0	0	<0.1
***6**	rs9332131	0	1	0	0	<0.1
***7**	rs67807361	0	0	0	0.3	0
***8**	rs7900194	0	5.6	<0.1	<0.1	0.2
***9**	rs2256871	0	7.5	<0.1	<0.1	0.2
***11**	rs28371685	0.5	2.1	<0.1	0.2	0.2
***12**	rs9332239	0.2	<0.1	0	<0.1	0.1
***13**	rs72558187	0	0	0.2	0	0

***14**	rs72558189	0	<0.1	<0.1	2.0	<0.1
***15**	rs72558190	0	0	<0.1	0	0
***16**	rs72558192	0	0	0.3	0	0
***29**	rs182132442	0.1	0	0.2	<0.1	<0.1
***30**	rs781583846	<0.1	<0.1	<0.1	<0.1	<0.1
***31**	rs57505750	0	0.2	0	0	0
***33**	rs200183364	0	<0.1	0	<0.1	0
***36**	rs114071557	0	0.2	<0.1	<0.1	<0.1
***42**	rs12414460	<0.1	<0.1	<0.1	0	<0.1
***44**	rs200965026	0	0	<0.1	0	<0.1
***45**	rs199523631	<0.1	<0.1	0	< 0.1	<0.1

Meanwhile, CYP2C9 has the largest number of alleles identified so far. The most common allele in each of the populations is the ancestral CYP2C9*1, with its highest frequency in East Asia (95.7%) and a relatively low frequency within African the population (78.4%). A CYP2C9*2 variant with reduced enzymatic activity and an inactive CYP2C9*3 variant are common in Europe, where the CYP2C9*2 allele constitutes 11.7% and CYP2C9*3 5.6% of the populational frequency. Both of these alleles are also present in American populations, although they are observed with lower frequencies, at 6.6% for CYP2C9*2 and 3.6% for CYP2C9*3 respectively. Interestingly, in southern Asia, the presence of the CYP2C9*3 allele is particularly pronounced, appearing there with a frequency of 11.3%.

In the African population, several rare alleles can be seen that are virtually absent in other regions. For example, CYP2C9*8 and CYP2C9*9 alleles occur at relatively high frequencies of 5.6% and 7.5% respectively, while in other populations their presence is marginal.

Other CYP2C9 alleles, such as CYP2C9*4, CYP2C9*5 and CYP2C9*6, are extremely rare, occurring mainly at or below the level of 0.1% or even being completely absent.

Table 4. The distribution of CYP3A4 in Europe in comparison to other continents.

Allele	Variant number acc. to dbSNP database (lit.)	Europe (%)	Africa (%)	East Asia (%)	South Asia (%)	America (%)
CYP3A4						
***1**	None	91.5	96.6	97	99.1	96.9
***2**	rs55785340	1.1	0	0	0	0
***3**	rs4986910	2.1	0.1	0	0	0.2
***4**	rs55951658	0	0	0.6	<0.1	<0.1
***5**	rs55901263	0	0	<0.1	0	0
***6**	rs4646438	0	0	0.2	<0.1	<0.1
***7**	rs56324128	0.1	0	0	0	0
***8**	rs72552799	0.1	0	0	<0.1	<0.1
***9**	rs72552798	0	0	0	0	<0.1
***10**	rs4986908	<0.1	0.2	<0.1	0.1	<0.1
***11**	rs67784355	0	<0.1	<0.1	<0.1	0
***12**	rs12721629	0	0.3	0	<0.1	<0.1

***13**	rs4986909	0	0	0	0	<0.1
***15**	rs4986907	0	2.5	0	<0.1	0.2
***16**	rs12721627	0	0	0.1	0	0
***18**	rs28371759	0	0.2	1.9	0	<0.1
***19**	rs4986913	0	0	0	<0.1	0
***20**	rs67666821	0	<0.1	0	0	<0.1
***22**	rs35599367	5.0	<0.1	0	0.6	2.6
***26**	rs138105638	0	<0.1	0	<0.1	<0.1

Within CYP3A4, the most common allele in all the investigated populations is CYP3A4*1, which reaches very high values, from 91.5% in Europe to as much as 99.1% in southern Asia.

According to published data, the distinctive CYP3A4*22 variant is relatively common in Europe (5.0%) and in America (2.6%), while it appears only very rarely or not at all in other regions. By contrast, the CYP3A4*15 variant is relatively common in the African population (2.5%), and is also present in the American population (0.2%), but is virtually absent in other regions.

Other rare CYP3A4 variants, such as CYP3A4*3 and CYP3A4*4, occur only sporadically, mainly in Europe, Africa and East Asia, but their overall frequency is low (approximately of 0.1-2.1%). The remaining alleles, i.e. CYP3A4*7, CYP3A4*9, CYP3A4*13 and CYP3A4*16, occur very rarely in populations, usually with a frequency below 0.1% or are not detectable at the populational level.

3.3 Numerous papers have focused on European populations in the context of CYP allele frequencies. These encompass, for example, the distribution of CYP2C8, CYP2C9 and CYP3A4 in individual regions of Europe: [11, 13, 21, 22]

Table 5. The distribution of CYP2C8 in individual regions of Europe.

Allele	Variant number acc. to dbSNP database (lit.)	Overall	Southern Europe (%)	Northwestern Europe (%)	Finland (%)
CYP2C8					
***1**	None	82.9	81	82.6	83.1
***2**	rs11572103	0.3	0.6	0.2	<0.1
***3**	rs10509681, rs11572080	11.3	13.2	11.8	11.1
***4**	rs1058930	5.4	5.2	5.3	5.8
***5**	rs72558196	0	0	0	0
***7**	rs72558195	<0.1	<0.1	<0.1	<0.1
***11**	rs78637571	0	0	0	0

Based on the available data, distinct cohorts have been observed within European societies according to the frequencies of particular CYP polymorphisms. This shows that the most common allele is CYP2C8*1, which dominates in all the groups analysed, reaching the highest frequency in Finland (83.1%). The CYP2C8*3 and CYP2C8*4 variants are also noticeably present in European populations. In the case of CYP2C8*3, the highest frequency is reached in southern Europe (13.2%), which is of special importance due to the controversial activity observed for the enzyme coded by this allele. In turn, the CYP2C8*4 allele, associated with reduced enzymatic activity, is most common in Finland, where its frequency is 5.8%. In contrast to the alleles mentioned above, the CYP2C8*2 allele occurs relatively rarely within Europeans, with the highest frequency of 0.6% in southern Europe, while in Finland it is practically absent (<0.1%). The remaining analysed variants are rare or practically absent in the analysed regions.

Table 6. The distribution of CYP2C9 in individual regions of Europe.

Allele	Variant number acc. to dbSNP database (lit.)	Overall	Southern Europe (%)	Northwestern Europe (%)	Finland (%)
CYP2C9					
***1**	None	79.9	76.7	79.7	81.5
***2**	rs1799853	12.6	14.2	13.1	11.4
***3**	rs1057910	6.8	8.5	6.5	6.3
***5**	rs28371686	<0.1	<0.1	<0.1	0
***6**	rs9332131	<0.1	<0.1	<0.1	0
***8**	rs7900194	<0.1	<0.1	<0.1	0
***9**	rs2256871	<0.1	<0.1	<0.1	0
***11**	rs28371685	0.3	0.2	0.3	0.6
***12**	rs9332239	0.3	0.3	0.2	0.2
***13**	rs72558187	0	0	0	0
***14**	rs72558189	<0.1	<0.1	<0.1	0
***16**	rs72558192	<0.1	0	0	0

29	rs182132442	<0.1	<0.1	<0.1	<0.1
31	rs57505750	0	0	0	0

For CYP2C9, the most common alleles in the European population are CYP2C9*1 and CYP2C9*2, with the highest frequencies noted in Finland (81.5%) and in southern Europe (14.2%) respectively. A clinically important, inactive variant, albeit with a noticeable frequency, is CYP2C9*3 characterised by the highest presence in southern Europe (8.5%), and the lowest among Finns (6.3%). The remaining alleles, that is CYP2C9*5, CYP2C9*6, CYP2C9*8 and CYP2C9*9, are extremely rare or completely absent in some regions. In most cases, their incidence does not exceed 0.1%.

Table 7. The distribution of CYP3A4 in individual regions of Europe.

Allele	**Variant number acc. to dbSNP database (lit.)**	**Overall**	**Southern Europe (%)**	**Northwestern Europe (%)**	**Finland (%)**
CYP3A4					
1	None	94.7	98.4	93.9	93.4
2	rs55785340	<0.1	0	<0.1	1
3	rs4986910	0.7	0.6	0.7	1.8
4	rs55951658	0	0	0	0
8	rs72552799	0.1	<0.1	<0.1	0.2
15	rs4986907	<0.1	<0.1	<0.1	0
16	rs12721627	0	0	0	0
18	rs28371759	0	0	0	0
22	rs35599367	4.4	0.9	5.4	3.6

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As shown in Table 7, the most common allele in the European population is CYP3A4*1, which is unambiguously dominant in all the studied regions, reaching its highest frequency in southern Europe (98.4%). Another variant characterized by reduced enzymatic activity, namely CYP3A4*22, occurs with moderate frequency - its overall frequency is 4.4%. The highest rate has been reported in northwestern Europe (5.4%) and in Finland (3.6%), while in southern Europe it has been reported to be as rare as 0.9%. The *CYP3A4* *2*, CYP3A4*3 and CYP3A4*8 alleles are very infrequent, while the remaining variants are practically absent in the analysed regions.

3.4 There are also selective studies for individual countries.

Table 8. The frequencies of CYP2C8 alleles in various European countries [9, 21,23].

Country	CYP2C8 *2 Frequency (%)	CYP2C8 *3 Frequency (%)
Portugal	~1	~19
Spain	~2	~15.5
Finland	0.1	~12
Czech Republic	0.2	~11
United Kingdom	0	~11
Sweden	~0.5	~10
Russia	0	~9
Scotland	N/A	15.1
Hungary	N/A	8.8

CYP2C8*4 allele is common in many European countries, with the highest frequency in the United Kingdom (up to 7.5%).

As shown in Table 8 the CYP2C8*3 allele is much more common in European countries than the CYP2C8*2 allele. The highest frequency of CYP2C8*3 is reported in Portugal (~19%), while it is rarest in Hungary, where its frequency reaches 8.8%. This allele also occurs with high frequency in Spain (~15.5%) and in Scotland (15.1%) indicating its relatively high occurrence in Western European countries.

The CYP2C8*2 allele seems to be relatively rare in all the countries studied. Nevertheless its highest frequency was observed in Spain (~2%) and in Sweden (~0.5%) while in Finnish population CYP2C8*2 occurs only at the level of 0.1%. In the Czech Republic, this allele occurs with a frequency of 0.2%, while in Portugal it attains

approximately 1%. This variant is virtually not present in the UK or within the Russian population, while no data is available for Scotland and Hungary (N/A).

Table 9. The frequencies of CYP2C9 alleles in various European countries [21, 24, 25, 26, 27, 28].

Region/country	**CYP2C9 *2 Frequency (%)**	**CYP2C9 *3 Frequency (%)**
Southern Europe		
Bosnia and Herzegovina	9.0	-
Croatia	16.5	9.5
Greece	12.9	8.1
Italy	12.4	9.4
Portugal	13.2	8.0
Serbia	12.3	7.9
Spain	13.8	10.1
Turkey	10.5	9.8
Northern Europe		
Denmark	12.1	5.3
Estonia	8.4	7.2
Finland	11.4	6.3
Norway	9.9	6.5
Sweden	11.7	6.5

Central and Eastern Europe		
Bulgaria	12.5	7.5
Czech Republic	11.6	5.9
Germany	14.0	5.0
Hungary	12.5	8.8
North Macedonia	12.4	7.1
Poland	-	4.7
Romania	11.3	9.3
Russia	10.5	6.7
Slovakia	10.0	8.0
Slovenia	12.2	6.3
Western Europe		
Belgium	10.0	7.4
France	15.0	8.0
Netherlands	13.0	6.0
UK	10.2	5.7

Figure 1. The frequencies of CYP2C9*2 alleles in various European countries.

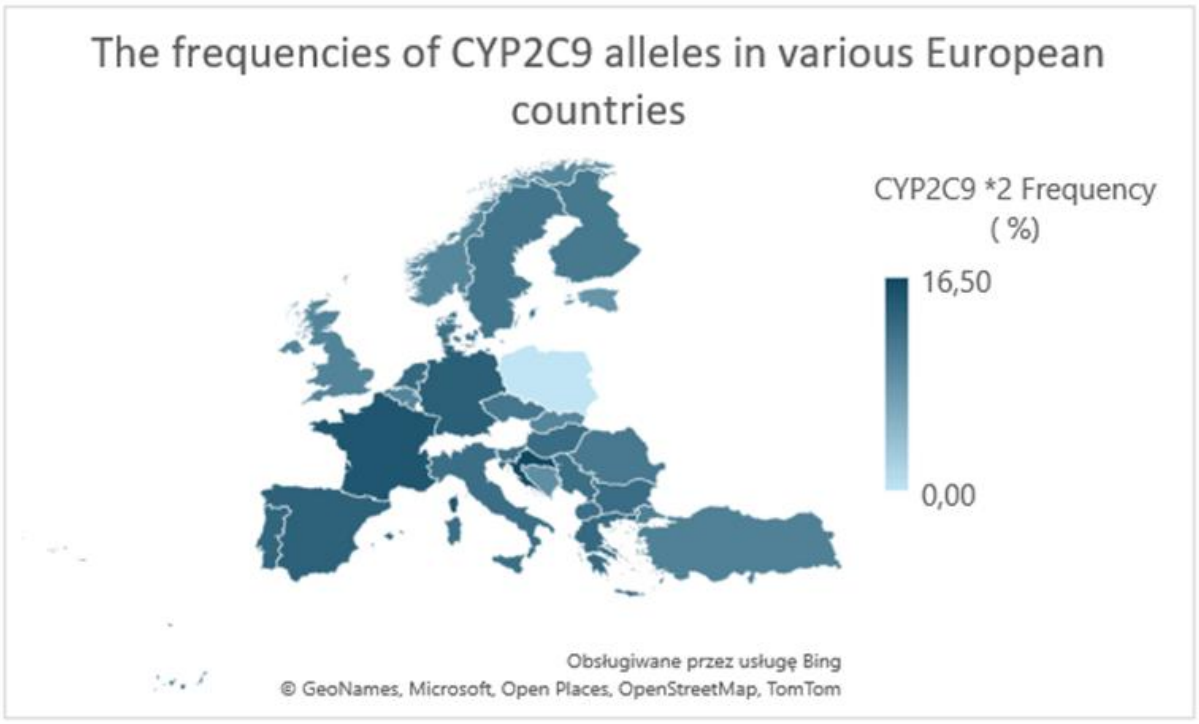
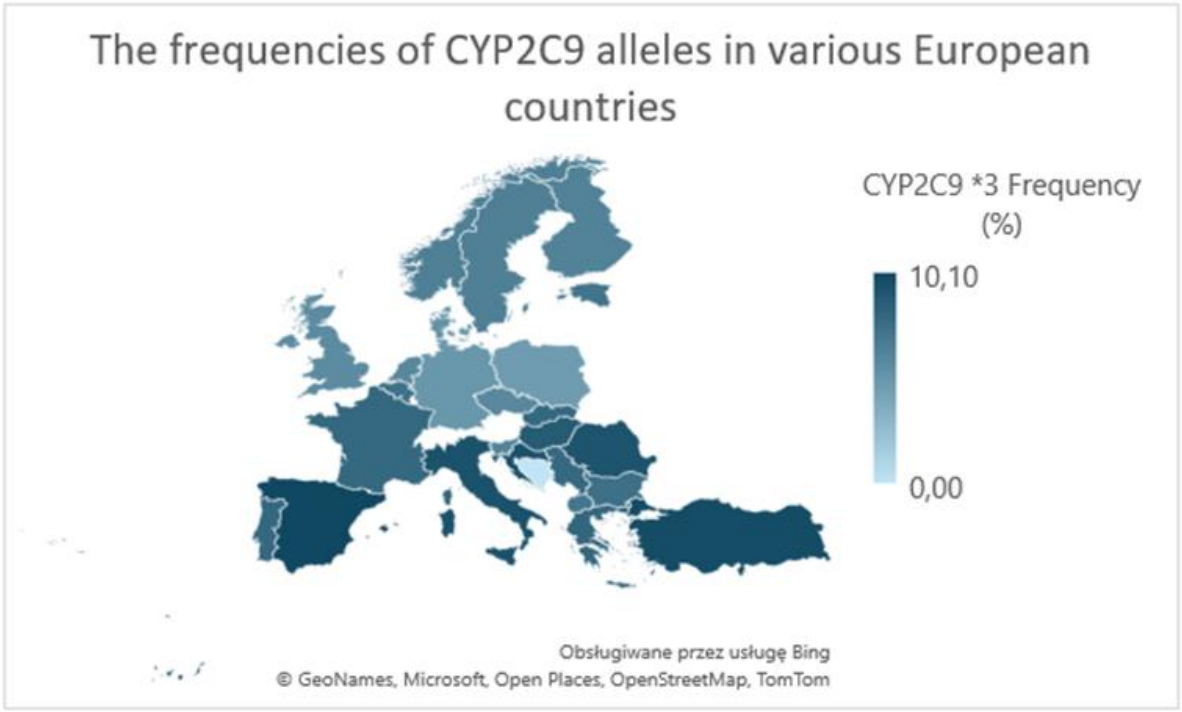


Figure 2. The frequencies of CYP2C9*3 alleles in various European countries.



Overall, in the case of CYP2C9 polymorphism, the CYP2C9*2 allele is more common than the CYP2C9*3 allele in all European countries analyzed. In southern Europe, CYP2C9*2 reaches relatively high frequencies, especially

in Croatia (16.5%) and in Portugal (13.2%). In other countries of this region its prevalence ranges from 9.0% in Bosnia and Herzegovina to 13.8% in Spain. The CYP2C9*3 allele is also evident in this part of Europe, reaching the highest values in Spain (10.1%) and in Italy (9.4%).

In northern Europe the CYP2C9*2 variant occurs to a lesser extent compared to the souther region ranging from 8.4% in Estonia to 12.1% in Denmark. The frequency of CYP2C9*3 allele in this group of countries ranges from 5.3% in Denmark to 7.2% in Estonia.

Different frequencies of CYP2C9*2 and CYP2C9*3 alleles are observed in the populations of Central and Eastern Europe. The CYP2C9*2 allele reaches the highest frequency in Germany (14.0%), and slightly lower, but still significant values in Bulgaria and in Hungary (12 (?), 12.0% each). 5%). At the opposite extreme is Slovakia, where this allele occurs at a level of 10.0% illustrating the range of variability in the region. In turn, the CYP2C9*3 allele is most common in Romania (9.3%) and in Hungary (8.8%) while its frequency is much lower in Germany (5.0%) and in the Czech Republic (5.9%).

In Western European countries such as Belgium, France, the Netherlands and the United Kingdom, the CYP2C9 variant 2 is present at levels ranging from 10.0% in Belgium to 15.0% in France. CYP2C9 allele 3 is less common here, ranging from 5.7% in the UK to 8.0% in France.

Research on the distribution of CYP3A4 is still ongoing, and detailed country-specific data is currently lacking. Developing knowledge in this area is crucial for further progress in sciences such as pharmacogenetics and pharmacology, enabling a better understanding of differences in drug metabolism between populations.

4. Discussion

Previous literature reviews have presented detailed maps of interethnic differences in CYP variability, focusing on single genes or alleles [7-11,13-14,16-28]. However, it is worth noting that differences in the genotyping strategies used between studies may influence allele frequency estimates [11]. The assessment of genetic polymorphisms of the discussed CYP genes in European populations illustrates regional differences that may affect drug metabolism and personalization of pharmacological therapy. The occurrence of individual alleles is not uniform across Europe and their frequency varies both between regions and among individual countries.

CYP2C8 plays a key role in the metabolism of many clinical drugs, including chemotherapeutic agents, thiazolidinediones, glinides and non-steroidal anti-inflammatory drugs [9, 29, 30, 31]. Moreover, CYP2C8 variants with reduced enzymatic activity are associated with slower paclitaxel clearance and increased drug exposure, which is associated with a higher risk of drug-induced neuropathy [9,32]. The most common CYP2C8 allele in Europe is CYP2C81; however, there are noticeable differences in the frequency of CYP2C83 and CYP2C84, which are more prevalent in Southern Europe and Finland, respectively. The high occurrence of CYP2C83 in Portugal (~19%) and Spain (~15.5%) may have significant clinical implications. In contrast, the CYP2C8*2 allele, which is common in African populations, is very rare in Europe, with its highest frequency observed in Spain (~2%) while being virtually absent in Finland (<0.1%). Due to the high frequency and significant geographical diversity of CYP2C8 alleles with controversial or reduced activity, it is important to take into account the specific genetic characteristics of a given population to optimize regional therapeutic protocols [9].

The functionality of CYP2C9 is highly significant in pharmacotherapy used for the treatment of diabetes, anticoagulant therapy with coumarin derivatives, as well as in the metabolism of phenytoin and many nonsteroidal anti-inflammatory drugs (NSAIDs) [24, 33, 34, 35]. The above review noted significant differences in the genetic variability of this cytochrome between northern, southern and central-eastern Europe. The CYP2C9*2 allele, associated with reduced enzymatic activity, is most common in Southern Europe, especially in Croatia (16.5%) and Portugal (13.2%). A similar variation concerns CYP2C9*3, the highest frequency of which is observed in Spain (10.1%) and Italy (9.4%), while in Northern Europe its frequency is noticeably lower, e.g. in Denmark it is only 5.3%. These data suggest that there may be a greater risk of altered response to drugs metabolized by CYP2C9 in southern Europe, which should be considered in clinical practice.

Analyzing the CYP3A4 gene, the CYP3A4*1 allele is the dominant variant across Europe. However, it is worth noting that the CYP3A4*22 variant, characterized by reduced enzymatic activity, shows geographical variations—it is most common in Northwestern Europe (5.4%) and Finland (3.6%), while in Southern Europe its frequency is very low (0.9%). As a consequence, this may lead to altered pharmacokinetics of certain anticancer drugs, statins, and immunosuppressive medications that are metabolized by this cytochrome. [36, 37, 38].

Observing the genetic variability of the discussed cytochromes across different European countries, the presence of subpopulations with distinct pharmacogenetic profiles can be noticed even within the same continent. This highlights the need for further research in this area to tailor treatments to individual patient characteristics and to implement personalized medicine.

Authors' Contributions

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