The Pharmacogenomics Journal (2009) 9, 306–310

www.nature.com/tpj

ORIGINAL ARTICLE

Prevalence of *CYP2C9* polymorphisms in the south of Europe

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Received 9 March 2009; accepted 16 March 2009; published online 21 April 2009

CYP2C9 is a major liver enzyme responsible of the metabolism of many clinically important drugs. The presence of *CYP2C9* genetic polymorphisms has been associated with marked interindividual variability in its catalytic activity that could result in drug toxicity. Here we present frequencies of the most common *CYP2C9* coding variants *CYP2C9*2* (C430T) and *CYP2C9*3* (A1075C) in representative samples of four regions from Spain (Basque Country, $n=358$; Catalonia, $n=240$; Central Spain, $n=190$ and Galicia, $n=288$) and one northern Italian region, (Verona, $n=164$), which range between 0.125 and 0.165 in the case of *CYP2C9*2* and between 0.071 and 0.085 for *CYP2C9*3*. No significant differences between *CYP2C9* allele frequencies were found comparing all the sampled populations. A more extensive comparative analysis using allele frequency data of populations widely spread over Europe was performed, showing significant differences in the *CYP2C9*2* allele frequencies distribution between some of the regions, being quite homogeneous in the case of *CYP2C9*3* variant. The results obtained show that above 40% of our samples carry a mutate allele, which can result in a poor metabolization of low therapeutic index drugs as oral anticoagulants (warfarin, acenocoumarol), oral antidiabetic drugs and some non-steroidal anti-inflammatory drugs. Our study constitutes both a large ($n=1240$) and robust allele frequency database on *CYP2C9* polymorphisms, which represents one of the most numerous *CYP2C9*2* and **3* database existing to date.
The Pharmacogenomics Journal (2009) **9,** 306–310; doi:10.1038/tpj.2009.16; published online 21 April 2009

Keywords: CYP2C9 polymorphism; CYP2C9 5′-flanking region; allele frequency; Spain; Italy

Introduction

Families 1–3 of the Cytochrome P450 enzymes play a critical role in the oxidative metabolism of the majority of clinically used drugs. These enzymes display polymorphism and their prevalence varies among different populations.[1–3]

In particular, the polymorphic enzyme CYP2C9 is the most abundant of the CYP2C enzymes,[4] and it influences the metabolism of about 10–20% of therapeutically important drugs,[5] some with a narrow therapeutic index. A high number of genetic polymorphisms associated with wide interindividual variability in the hepatic metabolism of target drugs have been described in the regulatory and coding regions of *CYP2C9* gene;[6] however, only two coding variants, *CYP2C9*2* (C430T) and *CYP2C9*3* (A1075C), with functional consequences are common. *CYP2C9*2* codes for a R144C substitution and *CYP2C9*3* reflects an I359L change in the amino-acid sequence.[7] It is thought that these variants are both associated with significant reductions in intrinsic clearance of a