CYP1A1 genetic polymorphisms in Ecuador, South America

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Abstract. A total of 108 individuals from the Ecuadorian population from rural and urban places were analyzed for two *CYP1A1* gene polymorphisms. The frequency of the val allele at codon 462 was 0.50, while the frequency of the Msp I restriction site, m2 allele at the T6235C position was 0.70. These polymorphisms in Ecuador have higher frequencies if we compare with others around the world, with the exception of some South American population in Brazil and Chile.

Keywords: Phase I enzymes, *CYP 1A1*, PCR-RFLP

1. Introduction

Phase I activation enzymes belonging to the cytochrome P450 family are encoded by a number of polymorphic *CYP* genes. The *CYP1A1* gene encodes biotransforming enzymes that participate in the activation and detoxification of xenobiotics and various carcinogens. Metabolically activated chemical compounds may interact with DNA and cause damage [1]. The *CYP1A1* gene encodes the inducible extrahepatic enzyme aryl hydrocarbon hydroxylase which initiates a multienzyme pathway that activates polycyclic aromatic hydrocarbons [2]. Two known polymorphisms that are associated with inducibility phenotypes have been described for the *CYP1A1* gene.

One of the polymorphisms we study is in the 3'-flanking region where a Restriction Fragment Length Analysis revealed an MspI restriction site. The variant polymorphism is derived from a base substitution (T6235C) that creates this Msp I recognition site [3]. The other polymorphism named m2 or val is the result of an A → G substitution in exon 7, causing the

aminoacid exchange (462 Ile → Val) in the heme binding region of the protein. This is called val allele and shows an almost two fold increase in catalytic enzyme activity relative to the ile form. The genotypes val and m2 occur frequently in oriental populations and are strongly correlated with lung cancer incidence among Japanese people [1–4]. Studies on Caucasians show rather controversial results mainly due to low incidences of both polymorphisms (val or m2) (10%) [5]. The polymorphisms of the *CYP* genes have been studied in two South American populations: the Mapuche Indians in Chile [6] and in the Brazilian Native Population [2]. The aim of the presvestigation was to identify the frequency of these markers in Ecuadorian Mestizo population.

2. Methods

2.1. Subjects

Blood samples were obtained from 174 unrelated individuals of both sexes (71 males, 103 females), with ages ranging from 19–60 years and living in various places of Ecuador. Ecuador is a multiethnic country with a mixture of Native Amerindians, Spanish and Mestizo population. All samples were obtained after written consent from participants. Genomic DNA was

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isolated from blood samples using a salting out procedure [7] and both *CYP1A1* polymorphisms (Msp I and exon7) were studied.

PCR based restriction fragment length polymorphism (RFLP) and allele specific PCR were used to examine the polymorphism of interest.

For the Msp I site, PCR amplification was carried out using primers and procedures previously described in the literature by Kawajiri et al. [3]. This technique yielded a 340 bp fragment which was digested with the MspI enzyme. The digestion generates fragments of 340 bp, 270 bp and 133 bp that were separated in a 2.5% agarose gel.

For the exon 7 polymorphism we used primers for allele specific PCR in separate amplifications as described by Chan et al. [8] and obtained 204 bp fragments.

3. Results and discussion

There is little information about the *CYP1A1* gene polymorphisms in South American population; this study contributes to establish the frequency of the polymorphisms in the Latin American population which is a little bit complex because of the high degree of interracial mixture. Ecuador has 500 years of history of admixture between the Native Amerindians and Spanish population mainly. Genotype frequencies for *CYP1A1* polymorphisms are reported in Table 1, the allele frequencies for the Ecuadorian population were 0.70 for m2 and 0.50 for val. These are very similar to Amerindians from Brazil whose average frequencies are 0.87 for m2 and 0.76 for val [2] and the Mapuche population (Chile) with 0.83 for m2 and 0.77 for val [6,10]. The next frequency is this scale that of the Japanese population with 0.33 m2 and 0.22val [3,5]. In addition 90% of the population was heterozygote for Ile462Val. Table 2 shows a summary of the literature on the two polymorphisms in different populations. As we mentioned previously this table shows that the highest frequencies have been reported in South American populations [2,6,9] following by Asian populations [9–11], Hawaii [5,12], Taiwan [13], Iberic (Spain) [14] and finally Caucasians with the lowest frequencies [5, 15–17].

It has been previously shown that the rare *CYP* alleles have higher frequencies in South America. Our results show that Ecuador has one of the highest frequencies after Brazilian and Native Chilean populations [6]. There is a hypothesis that explains that the

South American population originated from Asiatic individuals that crossed through Beringia [9], however, it is hard to establish if a founder effect has caused such differences. These may reflect diet differences which ones may have evolved due to ecological advantage to the specie. Nowadays *CYP1A1* variants are related to environmental exposure cancer and in some populations is considered as a potential predictor of genetic susceptibility to lung cancer [3] and *CYP1A1* gene studies as well as other metabolic genes may help to evaluate high risk populations to genotoxic exposure.

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