THE FREQUENCY OF HLA-B*57:01 AND THE RISK OF ABACAVIR HYPERSENSITIVITY REACTIONS IN THE COSTA RICA CENTRAL VALLEY POPULATION

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Introduction

HLA-B*57:01 is a now a well-known pharmacogenetic marker for Abacavir hypersensitivity among HIV+ individuals, which can be fatal and leads to treatment failure and important economic costs for health systems. The utility and cost-effectiveness of the typing of this allele as a prospective marker has been confirmed to decrease or abolish Abacavir hypersensitivity reactions in these patients. However, as for other HLA alleles, there is widespread variation in its frequency across populations. Thus, characterization of the frequency of this marker in a given population is the first step towards the evaluation of the feasibility and need of pharmacogenetic screening for this drug.

The Costa Rica Central Valley Population (CCVP) is the major population in this country. Approximately 60% of this country's population lives within this region, which represents less than 5% of its territory. **Figure 1** shows its location and a detail of its major urban centers. The CCVP has been used as a hub for genetic studies due to its interesting demographic and ethnographic characteristics. We have recently described the frequency of HLA allele groups in a sample of healthy volunteer donors from the CCVP. However, the high-resolution frequency of HLA-B*57:01 in this population has not been described yet. An important Caucasian component in this admixed population (**Figure 2**) may favor the presence of this allele. Consequently, in an exploratory study, we set out to determine the frequency of this allele in a sample of unrelated healthy donors.

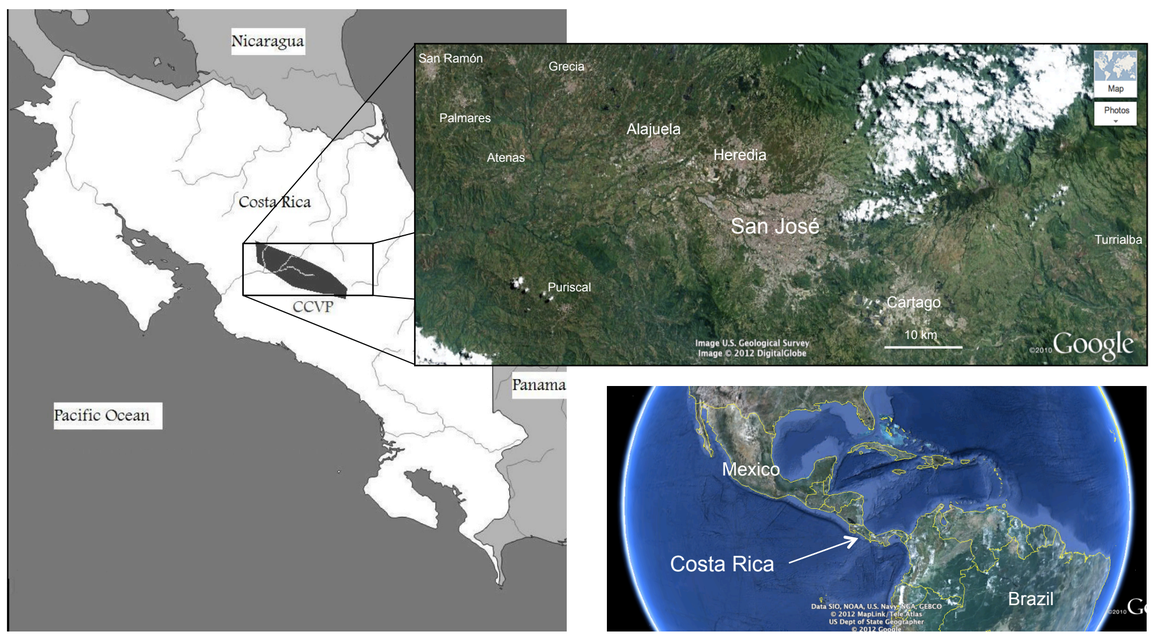

Figure 1 Diagram showing the location and detail of the CCVP within Costa Rica. The CCVP is the major population of this country and it concentrates most of the major Costa Rican cities in an intermontane region of approximately 90x25 km.

Materials and Methods

Peripheral blood or saliva samples from healthy unrelated volunteer donors were obtained by venipuncture or by collection of saliva using the ORAGENE-ONE collection kits (DNA Genotek Inc., Ottawa). In the case of blood samples, DNA was extracted by an in-house salting-out method. For the saliva samples, the manufacturer's extraction method was followed. All participants were born in the Costa Rican Central Valley and signed an informed consent. A total of 153 samples from CCVP inhabitants were genotyped. The samples were typed to intermediate resolution by SSO or SSP methods, and samples that were HLA-B*57-positve were further typed by SBT in order to define the alleles to four-digit resolution.

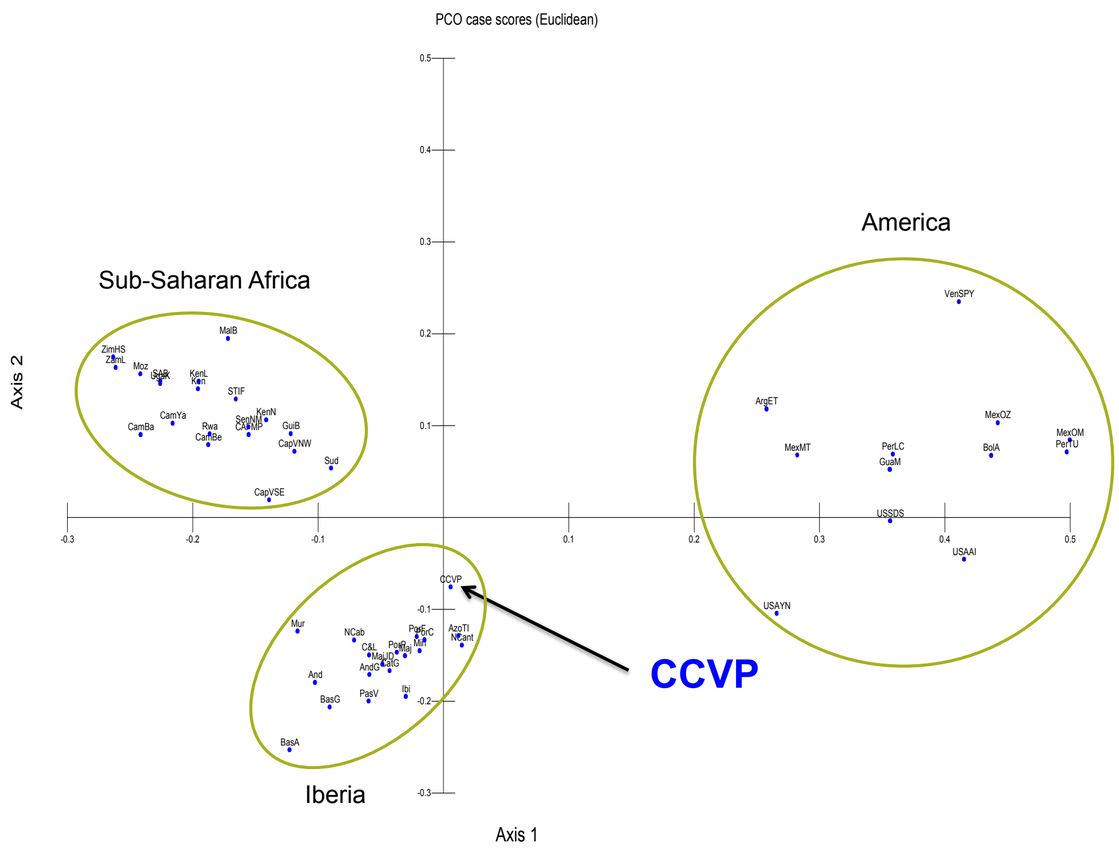

Figure 2 The CCVP has an important Caucasian component. Principal Coordinates Analysis (PCO, 59.1% cumulative variance) of the CCVP and 50 ancestral populations from Sub-Saharan Africa (upper left quadrant), Iberia (lower left quadrant) and America (right quadrants) based on 47 HLA-A and HLA-B allele group frequencies.

Results

HLA-B*57 alleles were present in a 6.5% of the subjects (**Table 1**). Moreover, an HLA-B*57:01 carrier frequency of 5.23% (allele frequency of 2.61%) was determined in this sample. **Table 2** shows the frequencies of HLA-B*57 alleles in this sample. This frequency is relatively high in comparison to reports from other populations in Latin America. These results suggest that there is a considerable frequency of HLA-B*57:01 in the CCVP and that pharmacogenetic testing for HIV+ patients who are going to receive Abacavir-based treatment schemes is likely to benefit the security of this therapy. According to WHO data, we hypothesize that some 200,000 persons in this country would be susceptible to Abacavir-induced hypersensitivity, and that some 15,000 HIV+ people living in Costa Rica could benefit from prospective HLA-B*57:01 genotyping.

Table 1 HLA-B allele groups identified in a sample of the CCVP (2N=306).

Allele group	No. Observed	Frequency	Homozygotes	Phenotype frequency
B*35	50	0.1634	3	30.7
B*07	37	0.1209	1	23.5
B*44	31	0.1013	3	18.3
B*40	29	0.0948	2	17.6
B*15	25	0.0817	1	15.7
B*14	20	0.0654	0	13.1
B*08	13	0.0425	0	8.5
B*39	13	0.0425	0	8.5
B*18	11	0.0359	0	7.2
B*57	10	0.0327	0	6.5
B*38	8	0.0261	0	5.2
B*53	8	0.0261	1	4.6
B*37	8	0.0261	0	5.2
B*58	7	0.0229	0	4.6
B*41	7	0.0229	0	4.6
B*51	6	0.0196	0	3.9
B*45	6	0.0196	0	3.9
B*52	4	0.0131	0	2.6
B*56	2	0.0065	0	1.3
B*48	2	0.0065	0	1.3
B*49	2	0.0065	0	1.3
B*55	2	0.0065	0	1.3
B*13	1	0.0033	0	0.7
B*42	1	0.0033	0	0.7
B*27	1	0.0033	0	0.7
B*50	1	0.0033	0	0.7
B*73	1	0.0033	0	0.7
Total :	306	1.0000	11	

Table 2 Frequency of the HLA-B*57 alleles in a sample of the CCVP (2N=306) and in other Latin American populations.

HLA-B*57 allele	Frequency in the CCVP	Carriers in the CCVP (%)	Carriers among Chileans (Poggi H *et al.* 2010)	Carriers among Mexicans (Sánchez-Girón F *et al.* 2011)	Carriers among Cubans[1] (Middleton D *et al.* 2000)	Carriers among US Hispanics (Maiers M *et al.* 2007)
HLA-B*57:01	0.0261	5.23	3.70	2.00	7.10	2.53
HLA-B*57:02	0.0033	0.65	ND	ND	0.00	0.07
HLA-B*57:03	0.0033	0.65	ND	ND	0.00	1.23

[1] Cuban Caucasians. ND, non determined.

Conclusions

HLA-B*57:01 is present in the CCVP at a relevant frequency and thus, it is likely that people that carry this allele in this population are at risk of suffering Abacavir-mediated hypersensitivity reactions. This is evidence towards the need for the development of pharmacogenetic testing among HIV-positive patients who will be receiving Abacavir as part of their treatment. However, clinical studies that show the relation between these reactions and this allele in the CCVP must be carried out.

Costa Rica is the only country in the Central American subregion with universal access to antiretroviral therapy for people living with HIV/AIDS. In 2010, there were 165 new cases of AIDS and 442 cases of HIV-positivity nationwide. Every year, Costa Rica spends over $11 million on HIV care, and more than 50% of this expenditure is due to first and second line antiretroviral drugs. Consequently, the Costa Rican Social Security System could benefit from prospective typing for this allele in view of the potential prevention of hypersensitivity reactions and treatment failures as well as the costs associated with them, considering the relatively great amount of financial resources that are invested in the treatment of these patients.

We are currently continuing the definition of high-resolution HLA allele and haplotype frequencies for this and other Costa Rican populations in order to assess the frequency of other potentially clinically relevant HLA alleles among its inhabitants.

Acknowledgements

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