



Rapid Communication

The frequency of HLA-B*57:01 and the risk of abacavir hypersensitivity reactions in the majority population of Costa Rica



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ABSTRACT

HLA-B*57:01 is a well-known and cost-effective pharmacogenetic marker for abacavir hypersensitivity. As with other HLA alleles, there is widespread variation in its frequency across populations. The Costa Rica Central Valley Population (CCVP) is the major population in this country. The frequency of HLA-B*57:01 in this population has not been described yet. Thus, our aim was to determine the frequency of this allele in the CCVP. 200 unrelated healthy volunteer donors born in the CCVP were typed. HLA-B*57-positive samples identified by HLA intermediate resolution typing methods were further typed by SBT to high resolution. An HLA-B*57:01 carrier frequency of 5.00% was determined 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 should be considered in this country.

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1. Introduction

Abacavir, a guanosine nucleoside inhibitor of the reverse transcriptase of the human immunodeficiency virus (HIV)-1, has been associated with hypersensitivity reactions in 5–8% of Caucasian patients [1,2]. Primary hypersensitivity reactions to this drug are multi-organ idiosyncratic syndromes occurring within the first 6 weeks of treatment. Rechallenge with the drug can result in severe and potentially fatal reactions. This property, and the fact that the first reports noted that reactions were much more frequent in Caucasians than in African American patients [3], prompted the hypothesis of an immune mechanism underlying these events.

Human leukocyte antigen (HLA)-B*57:01, and not its closely related alleles HLA-B*57:02 or HLA-B*57:03, was noted to be highly frequent in patients that developed hypersensitivity to

abacavir [4] demonstrating Odds Ratios of over 100 [5]. Larger clinical studies [6] have confirmed the strength of this association, and the usefulness of prospective genotyping for HLA-B*57:01 in reducing or abolishing the prevalence of adverse events caused by abacavir treatment [7], both in Caucasian and African American populations [8]. Moreover, a direct involvement of the HLA-B*57:01 molecule in the triggering of an altered self-peptide presentation by the binding of abacavir to one of its peptide-binding pockets has been recently described by molecular mechanisms [9–11], and, as of 2008, the Food and Drug Administration in the United States have recommended screening for HLA-B*57:01 before initiating abacavir therapy [12].

As for most HLA alleles, there is widespread variation in the frequency of these alleles among human populations [13–15]. Consequently, the risk of abacavir hypersensitivity reactions is a function of the prevalence of HLA-B*57:01 in a given population. Thus, the description of the prevalence of drug hypersensitivity markers in a population is the first step towards evaluating the feasibility and usefulness of pharmacogenetic testing for this drug. The Costa Rican Central Valley population is the major population in this country, accounting for over 60% of the Costa Rican inhabitants

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concentrated in a 2500 km² intermontane region [16]. This mainly urban population can trace its origin to a trihybrid admixture of Iberian Europeans, Amerindians and sub-Saharan Africans, albeit with a predominant Caucasian component [17]. Interesting historic, demographic and genetic characteristics of this hybrid population have attracted researchers interested in testing genetic associations for various diseases [18–26]. However, as for most Latin American countries, pharmacogenetic studies are still lacking. In this study, we set out to determine the prevalence of HLA-B*57:01 in a sample of unrelated individuals from Costa Rica's main population.

2. Materials and methods

2.1. Samples

A sample of 200 unrelated healthy volunteer donors was randomly selected for the study. All participants were born in the CCVP and were recruited as part of the University of Costa Rica's Centre for Research in Hematology and Related Disorders (CIHATA) DNA bank. Subjects gave written informed consent and the study was approved by the University of Costa Rica's Institutional Bioethics Review Board. Peripheral blood or saliva samples from unrelated healthy 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 [27]. For the saliva samples, the manufacturer's extraction method was followed. DNA concentration was measured by spectrophotometry and adjusted as required by the typing methods. Samples were stored at –20 °C until used.

2.2. Genotyping

Initial HLA class I genotyping at intermediate resolution was performed by sequence-specific primer (Micro SSP™ HLA DNA Typing Trays, One Lambda, Inc., Canoga Park, California) or sequence-specific oligonucleotide-based (Luminex xMAP®, Austin, Texas) methods. Samples that were positive for HLA-B*57 were selected for further typing at high resolution. High resolution typing was done by an in-house sequence-based typing (SBT) method amplifying exons 2, 3 and 4 of the HLA-B gene. The ~1.8 kilobases (kb) amplicon was purified and each exon was sequenced with specific forward and reverse primers using the Big Dye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). Sequencing products were purified by ethanol precipitation and run on an ABI 3730xL DNA Analyzer. Sequence analysis was done with Assign-SBT software (Conexio Genomics, Freemantle, Australia) using IMGT/HLA database release 3.9.0 [28]. Hardy–Weinberg equilibrium was tested with a Markov Chain Monte Carlo analysis. All homozygous samples were confirmed by at least two techniques.

2.3. Extended haplotype analysis

Samples that were confirmed to bear HLA-B*57:01 were further typed by in-house SBT at HLA-A (exons 2, 3 and 4) and HLA-DRB1 (exon 2) as described above. Based on previously reported maximum likelihood HLA allele group haplotype frequencies for the CCVP [29] and previous knowledge on the frequencies of HLA alleles in the parental populations of this admixed population, we reconstructed the most likely high resolution extended haplotypes that include HLA-B*57:01 in this population.

2.4. Population comparison

For comparison with the CCVP, a selection of 60 populations from Iberia, America and Sub-Saharan Africa with available DNA-based typing data for HLA-A and HLA-B allele groups was made and their details are shown in [Supplementary Table 1](#). These 60 populations are native population samples from the three ancestral regions that have contributed majorly to the CCVP gene pool: Iberian Caucasians (18 populations), Amerindians (22 populations), and Sub-Saharan Africans (SSA, 20 populations). In total, the population array included 38,694 chromosomes. HLA frequency data was extracted from journal articles and/or the allele frequencies database [30].

Principal Coordinates Analysis (PCO) based on Euclidean distances calculated from 47 HLA-A and HLA-B allele group frequencies from the 60 ancestral populations and the CCVP was carried out with the Multi-Variate Statistical Package (MVSP, Kovach Computing Services, Anglesey, Wales). The Eigenanalysis for the PCO was performed at an accuracy of 1E-7 and axes were extracted according to Kaiser's rule [31].

In addition, we selected previous studies in order to compare the specific frequencies of HLA-B*57 alleles in the CCVP with other populations of Latin American origin. Selected publications include studies in Chileans [32], Mexicans [33], Cubans [15], Brazilians [34] and US Hispanics [35].

3. Results

HLA typing was successful in all of the samples. Among the 200 subjects, a total of 27 HLA-B allele groups were seen. The sample was found to be in Hardy–Weinberg equilibrium ($p > 0.05$). The results for the allele groups are shown in [Table 1](#). Of these, 13 (6.5%) were HLA-B*57-positive and were further typed.

When these samples were typed at high resolution, three different HLA-B*57 alleles were identified ([Table 2](#)). HLA-B*57:01 was present in 5.0% of the subjects, corresponding to a 2.5% allele

Table 1
HLA-B allele group typing among the CCVP subjects.

Allele group	No. observed	Allele frequency	Homozygotes	Carrier frequency
B*35	66	0.1650	5	30.5
B*07	49	0.1225	1	24.0
B*40	45	0.1125	4	20.5
B*44	38	0.0950	3	17.5
B*15	29	0.0725	1	14.0
B*14	20	0.0500	0	10.0
B*18	19	0.0475	0	9.5
B*39	17	0.0425	0	8.5
B*08	15	0.0375	0	7.5
B*53	15	0.0375	1	7.0
B*57	13	0.0325	0	6.5
B*37	12	0.0300	0	6.0
B*51	11	0.0275	0	5.5
B*38	8	0.0200	0	4.0
B*45	8	0.0200	0	4.0
B*41	8	0.0200	0	4.0
B*58	5	0.0125	0	2.5
B*49	4	0.0100	0	2.0
B*52	3	0.0075	0	1.5
B*55	3	0.0075	0	1.5
B*56	2	0.0050	0	1.0
B*48	2	0.0050	0	1.0
B*13	2	0.0050	0	1.0
B*27	2	0.0050	0	1.0
B*50	2	0.0050	0	1.0
B*42	1	0.0025	0	0.5
B*73	1	0.0025	0	0.5
Total	400	1.0000	15	

Table 2
Frequency of the HLA-B*57 alleles in a sample of the CCVP (2n = 400) and in other Latin American populations.

HLA-B*57 allele	Frequency in the CCVP	Carriers in the CCVP (%) N = 200	Carriers among Chileans [32] N = 300	Carriers among Mexicans [33] N = 300	Carriers among Cubans ¹ [15] N = 70	Carriers among NE Brazilians [34] N = 243	Carriers among US Hispanics [35] N = 1195
HLA-B*57:01	<u>0.0250</u>	<u>5.00</u>	<u>3.70</u>	<u>2.00</u>	<u>7.10</u>	<u>3.40</u>	<u>2.53</u>
HLA-B*57:02	0.0050	1.00	ND	ND	0.00	ND	0.07
HLA-B*57:03	0.0025	0.50	ND	ND	0.00	ND	1.23

Underlined corresponds to B*57:01 frequencies.
¹ Cuban Caucasians. CCVP, Costa Rica Central Valley population; HLA, human leukocyte antigen; ND, non determined; NE, north-eastern; US, United States.

Table 3
Extended HLA genotypes for the HLA-B*57:01-positive samples in the CCVP.

HLA-A	HLA-B	HLA-C	HLA-DRB1
<u>01:01</u>	02:01	<u>57:01</u>	<u>06:02</u>
<u>01:01</u>	02:05	<u>57:01</u>	<u>06:02</u>
<u>01:01</u>	24:02	<u>57:01</u>	<u>03:05</u>
<u>02:01</u>	02:01	<u>57:01</u>	<u>06:02</u>
01:01	<u>24:02</u>	<u>57:01</u>	<u>06:02</u>
<u>01:01</u>	31:01	<u>57:01</u>	<u>04:01</u>
02:01	<u>29:02</u>	<u>57:01</u>	<u>06:02</u>
<u>01:01</u>	02:06	<u>57:01</u>	<u>06:02</u>
<u>01:01</u>	24:02	<u>57:01</u>	<u>03:04</u>
<u>02:01</u>	66:02	<u>57:01</u>	<u>06:02</u>

HLA, human leukocyte antigen.
Bold and italic correspond to alleles most likely to be found in the B*57:01-bearing haplotype.

frequency. As shown in Table 2, the frequency of HLA-B*57:01 in the CCVP is relatively high when compared to other reports from Latin American populations for which similar studies have been carried out, being higher than in other admixed populations and only second to that found among Cubans of Caucasian descent.
HLA-B*57:01 samples were typed at high resolution for HLA-A, HLA-C and HLA-DRB1 in order to characterize the extended haplotypes that contain HLA-B*57:01 in this population. Results from this analysis are shown in Table 3. Based on previous knowledge on the maximum-likelihood HLA haplotype frequencies and linkage disequilibrium (LD) in this population [29], and the known distributions of HLA alleles and haplotypes in its ancestral populations, a total of 5 HLA-B*57:01-bearing extended haplotypes were found (shown in bold). The most common HLA-B*57:01-bearing extended haplotype is HLA-A*01:01~C-06:02~B*57:01~DRB1*04:04,

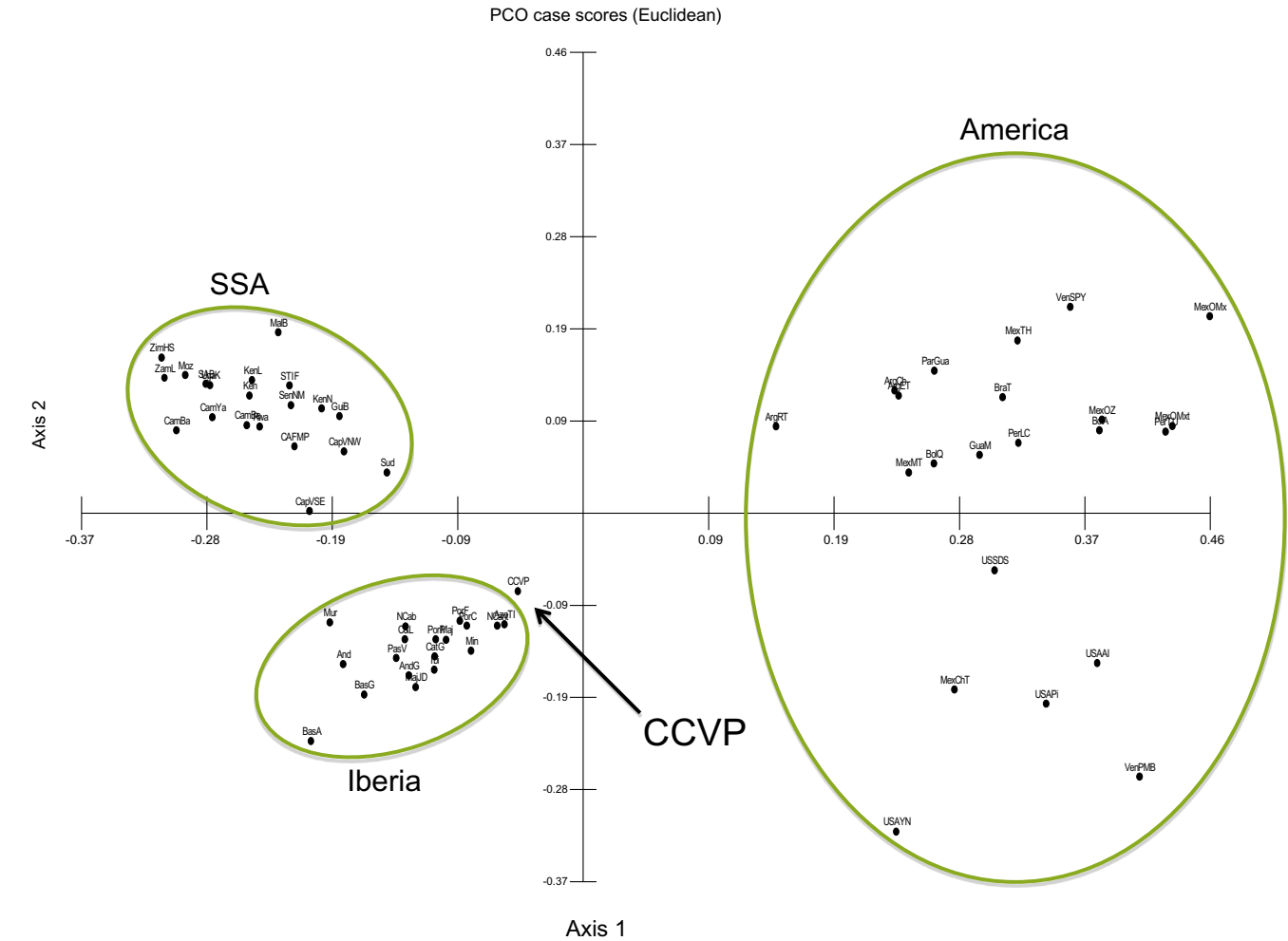


Fig. 1. The CCVP has an important Caucasian component. Principal Coordinates Analysis (PCO, 57.4% cumulative variance) of the CCVP and 60 ancestral populations from Sub-Saharan Africa (upper left quadrant), Iberia (lower left quadrant) and America (right quadrants) based on 47 HLA-A and HLA-B allele group frequencies.

which has a carrier frequency of 2.5% (1.25% haplotype frequency) in this population.

In order to explain the high relatively high frequency of HLA-B*57:01 carriers in this population, a PCO analysis comparing 47 HLA-A (data not shown) and HLA-B allele group frequencies between the CCVP and 60 ancestral populations was performed. Fig. 1 shows a map of the first two PCs of this analysis. As it is clearly seen, the CCVP clusters more closely to the Iberian populations and, thus, the high frequency of HLA-B*57:01 in the CCVP could be explained by the strong Caucasian component present in this admixed population.

4. Discussion

The results from this study suggest that HLA-B*57:01 is a very common allele in the CCVP. When compared with populations that share common origins with this population, the CCVP shows a frequency only surpassed by the Cuban Caucasians, while doubling that among Mexican mestizos and US Hispanics. This finding underscores the importance of not extending previous genetic findings in related but not necessarily similar populations, especially in such a genetically diverse region as Latin America [36].

Among not recently admixed populations, this allele is only common in those of Caucasian origin, especially those native to Western Europe [30]. This, together with the complete absence and very low frequency of this allele among Amerindians and SSA [14], respectively, suggests that a Caucasian input is responsible for the presence of HLA-B*57:01 in tri-hybrid Latin American populations such as the CCVP. This population has been recognized as having an important Caucasian component [17,37], which would be a likely explanation for the results presented in this study. This is also supported by the LD and extended HLA haplotypes that have been estimated for this population [29], as well as by our PCO analysis, which showed the CCVP mapping closely to the Iberian cluster.

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. Based on our findings and according to World Health Organization data [38], we hypothesize that some 200,000 persons in this country would be susceptible to abacavir-induced hypersensitivity, and that up to 15,000 HIV+ people living in Costa Rica [39] could benefit from prospective HLA-B*57:01 genotyping. 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.

The rs2395029 polymorphism in the HLA complex protein 5 gene, located 100 kb centromeric to HLA-B, has been proposed as a screening marker for HLA-B*57:01 carriage [33,40–42]. However, this has been a subject of recent debate [43–45]. The confirmation of the direct relationship between the HLA-B*57:01 molecule and the alteration of the HLA-presented self-peptide repertoire by the non-covalent binding of abacavir to one of the pockets of the class I protein [9–11] favors the use of direct HLA-B*57:01 typing techniques. Low cost sequence-specific primer-based [46] and practical real-time polymerase chain reaction-based [47] methods could be an alternative to other techniques.

Costa Rica is the only country in the Central American region with universal access to antiretroviral therapy for people living with HIV/AIDS [39]. In 2011, there were 157 new cases of AIDS and 488 cases of HIV-positivity nationwide, corresponding to incidences of 3.4 and 10.6 per 100,000, respectively [48]. Every year, Costa Rica spends over \$11 million on HIV diagnosis and care, and more than 50% of this expenditure is due to first and second line antiretroviral drugs, which represents 2.25% of the Costa Rican

Social Security System's drug expenses. This effort has caused AIDS mortality to drop to 2.88 per 100,000 in 2011 and an absence of perinatal transmission [48]. 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.

This study is the first to characterize the frequency of an HLA genetic risk marker in this country and, to our knowledge, in Central America. It is also one of the few pharmacogenetic studies in this population and one of few studies on the frequency of HLA-B*57:01 in Latin America. Thus, it is likely that this study contributes to providing a stimulus to this discipline in the clinical practice in the whole region. Further studies in other Central American countries must be pursued in order to ameliorate the quality of the response to HIV/AIDS in these populations.

In view of the results presented in this study, controlled clinical studies should be carried out in order to assess the clinical relevance of HLA-B*57:01 typing in this population. Moreover, because of differential admixture proportions among the CCVP and other Costa Rican populations [37], regional studies looking at the frequency of this allele must be carried out.

The recently published *Guidelines for antiretroviral treatment of HIV infection in Costa Rica* [49] include abacavir as a therapeutic option for patients in this country. Unfortunately, no reference to markers for genetic risk for hypersensitivity reactions to this drug has been made in these guidelines. The information presented in this study is likely to modify the way that anti-retroviral therapy is handled in the clinical practice in Costa Rica.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.humimm.2014.09.011>.

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Table 1. Summary and details of the ancestral populations included in the comparison with the CCVP.

Code	Population	Size (2n)	Reference
<i>Amerindians</i>			
ArgCh	Argentinian Chiriguano	108	(Gonzalez-Galarza <i>et al.</i> , 2011)
ArgET	Argentinian Eastern Toba	270	(Cerna <i>et al.</i> , 1993; Fernandez-Vina <i>et al.</i> , 1997)
ArgRT	Argentinian Toba from Rosario	172	(Gonzalez-Galarza <i>et al.</i> , 2011)
BolA	Bolivian Aymara	204	(Arnaiz-Villena <i>et al.</i> , 2005)
BolQ	Bolivian Quechua	160	(Martinez-Laso <i>et al.</i> , 2006)
BraT	Brazilian Terena	120	(Lazaro <i>et al.</i> , 1999)
GuaM	Guatemalan Maya	264	(Gomez-Casado <i>et al.</i> , 2003)
MexChT	Mexican Tarahumara from Chihuahua	88	(Garcia-Ortiz <i>et al.</i> , 2006)
MexMT	Mexican Tarasco from Michoacán	260	(Loeza <i>et al.</i> , 2002)
MexOMx	Mexican Mixe from Oaxaca	110	(Hollenbach <i>et al.</i> , 2001)
MexOMxt	Mexican Mixtec from Oaxaca	206	(Hollenbach <i>et al.</i> , 2001)
MexOZ	Mexican Zapotec from Oaxaca	180	(Hollenbach <i>et al.</i> , 2001)
MexTH	Mexican Teenek from Huasteca region	110	(Vargas-Alarcon <i>et al.</i> , 2003)
ParGua	Paraguayan Guaraní	80	(Benitez <i>et al.</i> , 2011)
PerLC	Peruvian Lama	166	(Gonzalez-Galarza <i>et al.</i> , 2011)
PerTU	Peruvian Uro	210	(Arnaiz-Villena <i>et al.</i> , 2009)
VenPMB	Venezuelan Bari	110	(Mack, 2007)
VenSPY	Venezuelan Yucpa	146	(Layrisse <i>et al.</i> , 2001)
USAYN	Alaska Yupik Natives	504	(Leffell <i>et al.</i> , 2002)
USAAI	Arizona Gila River Indian	984	(Williams <i>et al.</i> , 2009)
USAPi	Arizona Pima	200	(Mack, 2007)
USSDS	South Dakota Lakota Sioux	604	(Leffell <i>et al.</i> , 2004)
<i>Iberians</i>			
BasA	Basques from Arratia Valley	166	(Sanchez-Velasco <i>et al.</i> , 2003)
BasG	Basques from Guipuskoa	200	(Comas <i>et al.</i> , 1998)
C&L	Castilians	3,880	(Alcoceba <i>et al.</i> , 2011)
CatG	Catalonians from Girona	176	(Comas <i>et al.</i> , 1998)
And	Spanish from Andalucía	198	(Gonzalez-Galarza <i>et al.</i> , 2011)
AndG	Spanish Gypsy from Andalucía	198	(Gonzalez-Galarza <i>et al.</i> , 2011)
Ibi	Spanish from Ibiza	176	(Crespi <i>et al.</i> , 2002)
Maj	Majorcans	814	(Crespi <i>et al.</i> , 2002)
MajJD	Majorcans of Jewish Descent	206	(Crespi <i>et al.</i> , 2002)
Min	Minorcans	188	(Crespi <i>et al.</i> , 2002)
Mur	Murcians	346	(Muro <i>et al.</i> , 2001)
NCab	North Cantabrians	190	(Sanchez-Velasco <i>et al.</i> , 2003)
NCant	North Cantabrians	166	(Sanchez-Velasco <i>et al.</i> , 2003)
PasV	Spanish from Pas Valley	176	(Sanchez-Velasco <i>et al.</i> , 2003)
AzoTI	Azoreans from Terceira Island	260	(Gonzalez-Galarza <i>et al.</i> , 2011)
PorC	Portuguese from Central Portugal	1,124	(Gonzalez-Galarza <i>et al.</i> , 2011)
PorP	Portuguese from Porto	15,874	(Gonzalez-Galarza <i>et al.</i> , 2011)
PorF	Portuguese from Faro	2,484	(Gonzalez-Galarza <i>et al.</i> , 2011)
<i>Sub-Saharan Africans</i>			
CamBa	Cameroon Bamileke	154	(Torimiro <i>et al.</i> , 2006)
CamBe	Cameroon Beti	348	(Torimiro <i>et al.</i> , 2006)
CamYa	Cameroon Yaounde	184	(Ellis <i>et al.</i> , 2000)
CapVNW	Cape Verdeans from NW island	124	(Spinola <i>et al.</i> , 2005)
CapVSE	Cape Verdeans from SE island	124	(Spinola <i>et al.</i> , 2005)
CAFMP	Pygmy from the Central African Republic	72	(Bruges Armas <i>et al.</i> , 2003)
GuiB	Guineans	130	(Spinola <i>et al.</i> , 2005)
Ken	Kenyans	288	(Mack, 2007)
KenL	Kenyans-Luo	530	(Cao <i>et al.</i> , 2004)
KenN	Kenyans-Nandi	480	(Cao <i>et al.</i> , 2004)
MalB	Mali Bandiagara	276	(Cao <i>et al.</i> , 2004)
Moz	Mozambicans	500	(Assane <i>et al.</i> , 2010)
Rwa	Rwandans	560	(Tang <i>et al.</i> , 2000)
STIF	Sao Tome Islanders (Forro)	132	(Saldanha, 2009)
SenNM	Senegalese (Madenka)	330	(Sanchez-Mazas <i>et al.</i> , 2000)
SAB	Black South Africans	400	(Paximadis <i>et al.</i> , 2012)
Sud	Sudanese	400	(Gonzalez-Galarza <i>et al.</i> , 2011)
UgaK	Ugandan from Kampala	350	(Kijak <i>et al.</i> , 2009)
ZamL	Zambians from Lusaka	88	(Cao <i>et al.</i> , 2004)
ZimHS	Zimbabwe Harare Shona	460	(Mack, 2007)
Total	60	38,694	

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