Research Article

High interpopulation homogeneity in Central Argentina as assessed by Ancestry Informative Markers (AIMs)

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Abstract

The population of Argentina has already been studied with regard to several genetic markers, but much more data are needed for the appropriate definition of its genetic profile. This study aimed at investigating the admixture patterns and genetic structure in Central Argentina, using biparental markers and comparing the results with those previously obtained by us with mitochondrial DNA (mtDNA) in the same samples. A total of 521 healthy unrelated individuals living in 13 villages of the Córdoba and San Luis provinces were tested. The individuals were genotyped for ten autosomal ancestry informative markers (AIMs). Allele frequencies were compared with those of African, European and Native American populations, chosen to represent parental contributions. The AIM estimates indicated a greater influence of the Native American ancestry as compared to previous studies in the same or other Argentinean regions, but smaller than that observed with the mtDNA tests. These differences can be explained, respectively, by different genetic contributions between rural and urban areas, and asymmetric gene flow occurred in the past. But a most unexpected finding was the marked interpopulation genetic homogeneity found in villages located in diverse geographic environments across a wide territory, suggesting considerable gene flow.

Keywords: AIMs, Córdoba, San Luis, migration, population structure.

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Introduction

The population of Argentina, like those of other Latin American countries, has diverse ethnic origins, determined by immigration from Europe (mainly Spain and Italy) and Africa (people brought by force as slaves), and the subsequent cultural and genetic exchanges which took place between these populations and Native Americans (Sans, 2000). The arrival of the first Spaniards, five centuries ago, initiated the first of the two main periods in the immigration process: (a) the first half of the 16th century, characterized by the arrival of Europeans to colonize the territory, and the traffic of African slaves, to guarantee the exploitation of resources; and (b) the second half of the 19th and early 20th century, marked by a population expansion resulting from massive European immigration, favored by a process of economic internationalization (Pellegrino, 2002). More recently, immigration originates mainly from other countries of the American Southern Cone (Albarracín, 2005). All these people merged in a complex process, evidenced by the heterogeneous degrees of admixture observed in different regions of the country. Two aspects can be considered here: the relative contribution of the different parental groups and the migration from the rural areas of northern Argentina to the industrialized cities of the fertile Pampean region (Elizalde and Macció, 1990).

The degree of genetic admixture in Argentinean urban populations has been estimated by several studies, using blood groups (Avena *et al.*, 1999, 2001), GM/KM allotypes and mitochondrial DNA (Avena *et al.*, 2006, 2009), uniparental molecular markers (mtDNA and Y-chromosome) (Corach *et al.*, 2001; Salas *et al.*, 2008; Bobillo *et al.*, 2010), autosomal polymorphisms (Sala *et al.*, 1998; Demarchi *et al.*, 2005; Seldin *et al.*, 2007), and studies combining uniparental and biparental markers in the same individuals (Martínez-Marignac *et al.*, 2004; Corach *et al.*, 2010). As observed by Salzano (2002), although much information is already available, it is highly heteroge-

neous regarding both populations and types of genetic systems investigated.

An increasing number of publications have assessed the composition of human populations using ancestry-informative markers (AIMs) to estimate admixture and to identify population substructure (Mao *et al.*, 2007; Price *et al.*, 2007; Seldin *et al.*, 2007; Kosoy *et al.*, 2009; Santos *et al.*, 2010; Amorim *et al.*, 2011; Avena *et al.*, 2012). AIMs consist of single nucleotide polymorphisms (SNPs) distributed throughout the genome which show large differences in allele frequencies between populations of distinct geographic origins, thus distinguishing particular ancestral groups that correspond to continental populations. AIMs have been used previously for estimating admixture in a few Argentinean populations (Martínez-Marignac *et al.*, 2004; Seldin *et al.*, 2007; Corach *et al.*, 2010; Avena *et al.*, 2012).

The center of Argentina, particularly the provinces of Córdoba and San Luis, is a particularly interesting region because its crossroads geographic location can help to understand population forming processes in the southernmost region of South America. Besides, this region is crossed in the south/north direction by the old "Camino Real", one of the main roads used by Spaniards, African slaves and Native Americans in colonial times, a place of cultural and demographic exchanes. During the colonial period (from the 16th to the early 19th century), the province of Córdoba played a major role in the distribution of slaves and merchandise to other geographic regions of the Southern Cone (Rufer, 2004; UNESCO, 2005; Grosso, 2008).

In this study, we investigated the genetic variability and relative parental contributions in 13 villages across the provinces of Córdoba and San Luis (Argentina), using biparental markers, represented by a set of 10 AIMs. The main objective was to examine admixture patterns and genetic structure in different population of central Argentina, in an attempt to understand the population history of this region, and to compare the results with those observed in other regions of the country and elsewhere. We also compared the results obtained in this study with previous results obtained by our group using mtDNA markers in the same samples.

Materials and Methods

Population samples

A total of 521 samples from healthy, unrelated individuals were collected in nine villages of the Córdoba province (N = 381) and four of the San Luis province (N = 140). The sample sizes for each locality are presented in Table 3.

Figure 1 shows the map of the area with the sampling places. The study area is located in the southern part of the Argentinean Sierras Pampeanas, at latitudes 30° S to 33° S and longitudes 62° W to 65° W, covering the mountain

ranges of the provinces of Córdoba and San Luis, as well as their eastern neighboring plains.

All the participants were informed of the objectives of this nonprofit scientific investigation and signed a written informed consent. The information obtained in the field regarding the birthplaces of the participants, their parents and grandparents indicated low to moderate mobility of the inhabitants of these villages, limited to their region of origin. Thus, we assume that the sample represents fairly well the actual population structure of the area.

Genotyping

Genomic DNA was extracted from cheek swabs, using the IsoQuick Kit (Orca Research, Bothell, Washington). Genotyping for ACKR1, WI14319, CKM, OCA2, TYR, WI11909, CYP3A4, TNFRSF1A and IL2 SNPs was performed with validated TaqMan genotyping assays (Real Time PCR, Applied Biosystems, California, USA) according to the manufacturer's protocol. PV92 was tested by standard PCR, according to Batzer *et al.* (1994). PV92 Alu insertion genotypes were directly determined in 2% agarose gel with ethidium bromide staining. Information from the National Center for Biotechnology Information (NCBI), reference number and chromosome location of the 10 markers are presented in Table 1. One measure of the informativeness of such markers is the allele frequency differential (δ), which is the absolute value of the difference of a particular allele between parental populations (Chakraborty and Weiss, 1988; Dean *et al.*, 1994). We selected
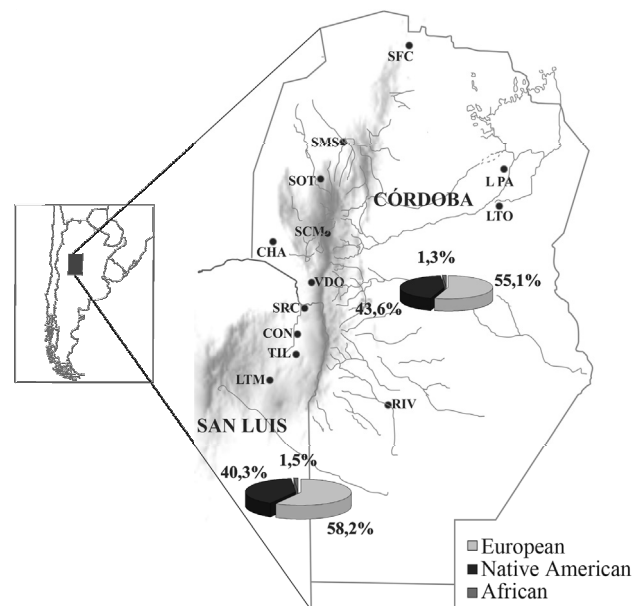

Figure 1 - Approximate area of the Sierras Centrales region of Argentina and sampling locations, with ancestry contributions estimated based on the populations of Córdoba and San Luis. SMS, San Marcos Sierras; LTO, La Tordilla; SFC, San Francisco del Chañar; SCM, San Carlos Minas; LPA, La Para; VDO, Villa Dolores; SOT, Villa de Soto; CHA, Chancaní; RIV, Río Cuarto; TIL, Tilisarao; SRC, Santa Rosa de Conlara; CON, Concarán; LTM, La Toma.

Table 1 - Ancestry Informative Markers used in this study.

Marker	Molecular technique[a]	Reference number (rs)[b]	Chromosome location
ACKR1	RT	2814778	1q23.2
WI14319	RT	2862	15q14
CKM	RT	4884	19q13.32
OCA2	RT	1800404	15q13.1
TYR	RT	1042602	11q14.3
WI11909	RT	2695	9q21.31
CYP3A4	RT	2740574	7q22.1
TNFRSF1A	RT	4149622	12p13.31
IL2	RT	2069762	4q27
PV92	PCR	3138523	16q23.3

[a]RT: Real Time; PCR: standard PCR.
[b]rs: Reference Number retrieved from dbSNP build 138, available on the human genome assembly (GRCh37/hg19).

SNPs with large frequency differences between continental populations (African, European, and Native American) (Shriver *et al.*, 2003; Yang *et al.*, 2005; Zembrzuski *et al.*, 2010). Genetic markers with the largest genetic distances between parental populations are the best candidates for population differentiation (Shriver *et al.*, 2004). The putative parental population frequencies were estimated using previously reported genotypes, recently updated, retrieved from different databases (Table 2).

Statistical analysis

Allele frequency estimates were obtained by direct gene count. Tests of observed and expected heterozygosity, Hardy-Weinberg equilibrium (HWE), and Analysis of Molecular Variance (AMOVA) at two hierarchical levels were

carried out using the Arlequin v. 3.1 software package (Excoffier *et al.*, 2005). The HWE tests were performed using 100,000 steps in the Markov chain, setting the significance level at $p < 0.05$. The P-values for F_{ST} and AMOVA estimates were obtained after 10,100 permutations, employing the same significance level. Chakrabortys method for the estimation of admixture proportions by means of gene identity (Chakraborty, 1985) was performed using the ADMIX95 program. The fit of this model can be evaluated in terms of R-square, which is an expected multiple correlation coefficient of the allele frequencies in a hybrid population and those of the parental populations, under the assumption of a true admixture model (Chakraborty, 1986). To evaluate the statistical significance of genetic affinities among populations based on AIMs frequencies, principal components analysis was used.

Results

Allele frequencies and HWE

The allele frequencies of the 10 biallelic AIMs observed in the pooled samples of Córdoba and San Luis and in the parental stocks (Europeans, Native Americans, and Africans) are presented in Table 2. Most of the studied markers were in Hardy-Weinberg equilibrium, with the exception of CKM ($p = 0.027$), and WI-11909 ($p = 0.011$) in Córdoba, and ACKR1 ($p = 0.031$) in San Luis. These marginal deviations are most likely due to sampling errors.

Population structure

Heterozygosity was similar in the 13 subpopulations, ranging from 0.322 in San Carlos Mina to 0.405 in La Tordilla (Table 3). The intergroup genetic differences were not significant ($F_{ST} = 0.004$, $p = 0.054$). The AMOVA re-

Table 2 - Summary of 10 AIM allele frequencies in the provinces of Córdoba and San Luis, and in the European, Native American and African parental stocks.

Marker	Córdoba	San Luis	N	Parental populations[a]		
				European	Native American	African
ACKR1*T	0.962	0.950	487	0.995	0.994	0.021
WI14319*C	0.389	0.350	500	0.231	0.716	0.352
CKM*T	0.495	0.439	509	0.289	0.860	0.167
OCA2*A	0.580	0.611	514	0.753	0.434	0.127
TYR*A	0.311	0.277	512	0.465	0.059	0.002
WI11909*G	0.475	0.507	518	0.774	0.186	0.815
CYP3A4*A	0.898	0.918	519	0.967	0.959	0.211
TNFRSF1A *G[b]	0.105	0.093	506	0.000	0.050	0.650
IL2*G[b]	0.656	0.668	508	0.232	0.170	0.000
PV92*1	0.445	0.496	427	0.161	0.781	0.210

[a]The frequencies were retrieved from the dbSNP NCBI. (http://www.ncbi.nlm.nih.gov/SNP/), under the submitter handle PSU-ANTH, HapMap, and ALFRED database.
[b]Data from Zembrzuski *et al.* (2010).

Table 3 - Percentage of continental parental contribution for autosomal AIMs (SD, Standard Deviation) and mitochondrial haplogroups, and heterozygosity values for 13 villages of central Argentina.

Localities[a]	N	% parental contribution						Heterozygosity
		European		Native American		African		
		AIMs	mtDNA[b]	AIMs	mtDNA[b]	AIMs	mtDNA[b]	
Villa de Soto[1]	58	66.7 (3.6)	13	32.6 (2.9)	77	0.7 (3.5)	10	0.385 ± 0.257
San Carlos Mina[1]	17	67.8 (6.1)	16	38.2 (5.1)	79	- 6.0 (4.6)	5	0.322 ± 0.230
Villa Dolores[1]	23	49.9 (5.0)	12	49.9 (3.2)	82	0.2 (4.1)	6	0.370 ± 0.215
Chancaní[1]	24	55.0 (5.7)	13	49.0 (3.9)	73	- 4.0 (4.4)	14	0.348 ± 0.203
San Marcos Sierras[1]	33	49.1 (3.8)	11	48.4 (2.6)	75	2.5 (3.4)	14	0.375 ± 0.239
San Fco. del Chañar[1]	52	48.7. (4.4)	4	46.4 (2.7)	84	4.9 (4.1)	12	0.365 ± 0.205
Río Cuarto[2]	85	56.7 (4.6)	26	43.9 (2.6)	74	- 0.6 (3.8)	0	0.403 ± 0.266
La Tordilla[2]	24	56.6 (2.2)	27	39.8 (1.7)	62	3.6 (2.2)	11	0.405 ± 0.234
La Para[2]	65	49.5 (4.9)	18	47.5 (3.3)	76	3.0 (3.9)	6	0.340 ± 0.209
Córdoba Total	**381**	**55.1 (4.2)**	**16**	**43.6 (2.5)**	**76**	**1.3 (3.7)**	**8**	
Santa Rosa de Conlara[1]	33	52.1 (4.9)	6	44.8 (3.6)	94	3.1 (2.9)	0	0.378 ± 0.213
Concarán[1]	29	61.9 (3.7)	14	37.2 (2.4)	81	0.9 (2.4)	5	0.374 ± 0.212
Tilisarao[1]	30	56.8 (2.8)	4	39.7 (2.0)	92	3.5 (2.6)	4	0.335 ± 0.196
La Toma[1]	48	50.8 (6.5)	13	54.0 (4.7)	84	- 4.8 (4.4)	3	0.350 ± 0.202
San Luis Total	**140**	**58.2 (3.8)**	**11**	**40.3 (2.5)**	**88**	**1.5 (3.4)**	**3**	

[a]Geographic regions: [1]Sierras; [2]Plains.
[b]Pauro *et al.* (2001).

sults are presented in Table 4. No statistically significant genetic differences were found between provinces (Córdoba *vs.* San Luis) or geographic regions (Plains *vs.* Mountains); the interpopulation variation between subpopulations within each of these units was only marginally significant.

Admixture estimates

Admixture analysis using the 10 AIMs was performed to estimate the mean contributions of European, African, and Native American parental populations to the contemporary population. The tri-hybrid admixture model showed to be adequate for estimating parental contributions in all populations (R-square = 0.991). The results are shown in Table 3. The European component was the most frequently represented in all subpopulations, except in Villa Dolores (Córdoba) and La Toma (San Luis), where the Native American component was of the same or greater magnitude. Admixture estimation by province showed a slightly higher proportion of European ancestry in San Luis than in Córdoba (0.582 ± 0.038 *vs.* 0.551 ± 0.042), whereas in Córdoba there was a relatively higher proportion of Native American ancestry than in San Luis (0.435 ± 0.025 *vs.* 0.403 ± 0.025). The African component was negligible in all the subpopulations investigated. There were differences when AIMs and mtDNA were considered, with the latter consistently showing higher Native American and African ancestries.

Table 4 - Analysis of the molecular variance between provinces (Córdoba *vs.* San Luis) and between geographic regions (Sierras *vs.* Plains) in central Argentina based on the frequencies of 10 AIMs. La Tordilla, Río Cuarto, and La Para are plain populations, while the other sampling sites are located in the sierras region.

Source of variation	Degrees of freedom	Variance component	Percentage of variation
Between provinces	1	-0.002	-0.11 (p = 0.786)
Among populations within provinces	11	0.006	0.42 (p = 0.043)
Within populations	1029	1.558	99.69 (p = 0.049)
Between geographic regions	1	-0.001	-0.06 (p = 0.658)
Among populations within geographic regions	11	0.006	0.40 (p = 0.051)
Within populations	1029	1.558	99.66 (p = 0.064)

In the principal component analysis (Figure 2), the subpopulations of Córdoba and San Luis appeared close to each other, with the villages showing no clear distribution pattern. This compact cluster falls halfway between Native Americans and Europeans, but is closer to the latter and very distant from Africans.

Discussion

The aim of this study was to investigate the genetic structure and admixture patterns in populations living across central Argentina, using biparentally inherited ancestry informative markers (AIMs). The low intergroup differentiation (F_{ST} = 0.004, p = 0.054) suggests sustained gene flow among populations and absence of geographic or ethnic barriers. In previous studies, we investigated the distribution of mtDNA markers in the same villages. Despite having different histories and being located in diverse geographic environments across a wide territory, a surprisingly low genetic variation among villages was observed (García and Demarchi, 2009; Pauro *et al.*, 2010, and García A, 2011, Doctoral Thesis, Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba), as confirmed by our results in the present study. Previous studies of human groups from central Argentina have proposed the existence of regionalism, in an attempt to demarcate differential geographic areas whose boundaries were dependent on the particularities or traits that circumscribed each of these studies. For example, the existence of different evolutionary histories between the mountains and plains populations was proposed by Serrano (1945). However, in this study we did not find statistically significant differences when geographic regions (plains *vs.* sierras) or provinces (Córdoba *vs.* San Luis) were compared, despite
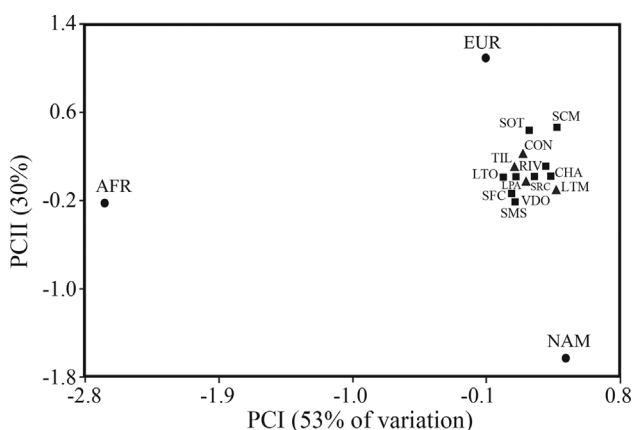

Figure 2 - Principal Component Analysis based on the frequencies of 10 AIMs in 13 populations of central Argentina and 3 parental stocks. NAM (Native American); AFR (African), EUR (European). SMS, San Marcos Sierras; LTO, La Tordilla; SFC, San Francisco del Chañar; SCM, San Carlos Minas; LPA, La Para; VDO, Villa Dolores; SOT, Villa de Soto; CHA, Chancaní; RIV, Río Cuarto; TIL, Tilisarao; SRC, Santa Rosa de Conlara; CON, Concarán; LTM, La Toma. Squares and triangles represent sites of Córdoba and San Luis, respectively.

the innumerable succession of historical demographic events that occurred in ancient times and, above all, after the Conquest (aggregations, dismemberments, and transfers). These results suggest a geographic and temporal continuity of the gene pool of the population that inhabited the central region of Argentina.

The two parental populations that contributed most to the gene pool of the populations of Córdoba and San Luis are the European (55% and 58%) and the Native American (44% and 40%) sets. These values are different from those obtained by Seldin *et al.* (2007) in the province of Córdoba using 78 AIMs (respectively 77.2% and 22.8%), while the African component is virtually absent in both samples.

In previous studies that focused on genetic admixture using AIM markers, differential ancestral contributions were observed in different regions of Argentina. In general, much lower Native American and much higher European ancestry proportions were detected in most of these studies, as compared to what we observed here. For instance, Corach *et al.* (2010) and Avena *et al.* (2012) found that, in the Buenos Aires population, the average European and Native American ancestry components were, respectively, 78.6% and 17.3%, and 65% and 31%. A similar picture was found by Martínez-Marignac *et al.* (2004) for the relative European and Native American contributions to the gene pool of La Plata, namely 67.6%, and 25.9%, respectively. Based on the ABO system phenotypes of population samples from the six provinces of northwest Argentina (NWA) (Jujuy, Salta, Tucuman, Catamarca, La Rioja, and Santiago del Estero), Morales *et al.* (2000) found a Native American component of over 60% in the provinces of Jujuy and Salta, while the Spanish (European) contribution predominated in Catamarca, La Rioja and Tucumán. An African component of over 20% was found in Santiago del Estero, Tucumán, and Catamarca. On the other hand, Alfaro *et al.* (2005), based on HLA-A and HLA-B allele frequencies of the same NWA population samples, observed, for the whole region, 50% of Spanish, 40% of Native American and 10% of African contributions. In contrast with our findings, they found a marked inter-population heterogeneity in the genetic admixture.

However, if we compare the present results with those obtained with lineage-specific genetic markers, the patterns are different. After five centuries of colonization and cultural exchanges, these populations continue to maintain most of their maternal Native American gene pool (~80%, García and Demarchi, 2009). In contrast, the survival of indigenous paternal lineages is extremely low (6% and 10% in Córdoba and San Luis, respectively), due to asymmetric gene flow (García and Demarchi, 2006 and García A, 2011, Doctoral Thesis, Facultad de Ciencias Exactas, Físicas y Naturales, Universidad Nacional de Córdoba), similarly to what is practically the rule in Latin American populations (Wang *et al.*, 2008 and literature therein). In another study, Salas *et al.* (2008) analyzed a

hospital sample from the province of Córdoba using mtDNA sequences and Y-chromosome microsatellites (STRs). As expected, most of the Y-STR haplotypes observed (97%) could be assigned to typically European lineages, whereas only a small fraction corresponded to haplotypes of likely Native American origin (2%). But, in contrast with our results, these authors found a maternal Native American component of only 41%.

These differences could be due to the source of the samples, although the different markers used also have distinct degrees of efficiency for the estimation of admixture. In this study, we worked with samples collected from relatively small rural towns (with the exception of Río Cuarto and Villa Dolores, cities with more than 10,000 inhabitants). While there is no detailed information about the origin of the samples analyzed by Salas *et al.* (2008), we can infer that they came from urbanized geographic areas, most likely from Córdoba city, a large, cosmopolitan capital with around 1.5 million inhabitants. Overall, the American continent is characterized by historical differences in patterns of colonization and migration, resulting in a range of different genetic contributions between rural and urban areas (Sans, 2000) and, as a rule, urbanization resulted in a greater prevalence of the European component (Avena *et al.*, 2012).

On the other hand, similar values of African ancestry have been found in the previously mentioned studies (Martínez-Marignac *et al.*, 2004; Seldin *et al.*, 2007; Corach *et al.*, 2010; Avena *et al.*, 2012). In general, the African contribution to the gene pool of the Argentinean population is relatively low when compared to other South American countries (Brazil, Colombia, and Uruguay, for example). Our results are consistent with those of a previous study (Fejerman *et al.*, 2005) based on autosomal markers that showed limited African admixture (2.2%) in Buenos Aires.

A great genetic heterogeneity in the ancestral origins at the individual level was observed in Argentina by Martínez-Marignac *et al.* (2004), Seldin *et al.* (2007), Corach *et al.* (2010), and Avena *et al.* (2012). As for the differences between Córdoba and San Luis, it has to be kept in mind that the European settlement started much earlier in the province of Córdoba, the center of socio-cultural and demographic exchanges at the time of the Conquest and during the Colonial period in Argentina (Rufer, 2004). Therefore, the slightly higher percentage of European ancestry in San Luis reported by Corach *et al.* (2010) could be due to a larger proportion of individuals of European ancestry from the most recent migratory waves.

There is, however, another aspect to be considered: during the construction of the Argentinean Nation, governments privileged an ideological process that denied the existence of a non-European background in the country's population (Chamosa, 2008). The objective was to build "a future without memory". The mechanism employed was to replace the native population with European immigrants,

but this process did not occur with the same intensity throughout Argentina. The immigration waves had less impact in the north-central and northwestern regions, which were in turn, historically, the most populated areas of the country. Although Córdoba has traditionally been regarded as one of the large "white" cities, along with Rosario and Buenos Aires (Grosso, 2008), its migration process was different from those experienced across rural areas of its province. Our results indicated the need to rethink common-sense assumptions, which generally refer to the absence or complete extinction of the Argentinean Native Americans, with a detachment of the official history from itspre-Hispanic past. And yet this past is still present in the people`s genomes.

In conclusion, the European component was the most highly represented in all 13 villages, with the Native American contribution being almost as frequent, and the African contribution reaching only about one percent. There is, however, a much higher Native American representation in the mitochondrial DNA results, reflecting the asymmetrical nature of interethnic unions occurred in the past. Yet, the most striking finding of our study was the genetic homogeneity observed among populations with different histories living across a wide territory. Some of the differences found between our results and previous reports may be due to the different types of markers used, as well as to the fact that we investigated mainly rural communities, while most of the other investigations examined urban groups, where the European genetic influence is more marked. Finally, the most general lesson learned from all this is that the complexity of the human evolutionary process defies simple explanations or easy generalizations.

Acknowledgments

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