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Brief Communication

Alu insertion polymorphisms in four ethnic groups from northern Ivory Coast

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Abstract Patterns of genetic variation among geographically and ethnically diverse African populations have been under-represented in human genetics studies despite their importance for describing the evolutionary history of modern human populations. We conducted a study on 133 individuals, belonging to four northern Ivorian ethnic groups, based on the allele distribution of 11 *Alu* insertion loci, and compared the results with other African populations. All loci proved to be polymorphic in all ethnic groups, with the exception of HS2.43 and HS3.23, which were fixed for the absence and for the presence, respectively, of the *Alu* element. No significant departure from Hardy–Weinberg equilibrium was found among polymorphic loci, except for TPA25 loci in the Baoulé and Bété groups. Average heterozygosity (0.193 ± 0.042) was lower than that observed for the same loci in other African populations and the F_{ST} value among ethnic groups for all loci was also notably low (0.0456). Multidimensional scaling analysis clearly separated Ivorians from other African samples, while in the neighbor-joining tree this population represented a basal branch of the tree, close to the hypothetical ancestral lineage. The picture emerging from our analyses reveals a conspicuous genetic homogeneity among Dioulà, Sénoufos, Boulè, and Bètè despite their sociocultural subdivision. Moreover, this northern Ivory Coast population, as a whole, turns out to be relatively isolated from the other African populations, possibly as a consequence of local patterns of population history, limited migration rates, and random genetic drift.

Key words: genetic polymorphisms, SINE, Africa, population genetics

Introduction

The genetic structure of human populations is the result of historic, geographic, adaptive, and cultural factors. According to the 'out of Africa' model, modern humans first appeared in Africa about 200000 years ago and later migrated to other parts of the world (Tishkoff et al., 2009). Consequently, African populations are characterized by high levels of within-population genetic diversity and low levels of linkage disequilibrium among loci as compared to non-African populations (Lambert and Tishkoff, 2009; Pasino et al., 2011). Migration of modern humans out of Africa resulted in a series of population bottlenecks and a consequent loss of genetic diversity in the derived populations (Ramachandran et al., 2005; Liu et al., 2006).

North-west (NW) Africa presents a number of populations with different languages and ethnic identities. Nevertheless, despite the subdivision into several cultural and/or ethnical groups, some genetic evidence shows substantial similarities among NW African populations (Bosch et al., 2000).

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Several polymorphic genetic systems, notably mitochondrial DNA and Y-chromosome markers, have been used to study the genetic variation and evolutionary history of modern humans. On the whole, such studies reveal an overall pattern of higher levels of genetic diversity within African populations compared to the rest of the world (Tishkoff et al., 2009). Nevertheless, these genetic systems are characterized by high mutation rates, and hence their variation patterns probably reflect relatively recent divergence. Long-term subdivision among populations is more likely to be found in slow-mutating DNA sites which evolved only once in human history (Markovtsova et al., 2000; Romualdi et al., 2002). Biallelic polymorphisms, such as *Alu* insertions, are useful markers for studying the genetic structure and relationships among human populations (Batzer et al., 1994; Stoneking et al., 1997; Comas et al., 2000; Batzer and Deininger, 2002; Terreros et al., 2005; Ennafaa et al., 2006; Frigi et al., 2011). *Alu* sequences represent about 10% of the human genome and are the largest family of short interspersed repetitive elements (SINEs) typical of primate genomes (Roy-Engel et al., 2001). They are retrotransposons, about 300 bp in length, that are mobilized by a reverse transcription of the RNA polymerase III primary transcript to cDNA and subsequent integration into the genome (Dewannieux et al., 2003). The absence of the *Alu* element is the ancestral state of *Alu* polymorphic loci and the direction of mutational change is the acquisition of this element.

Despite some limitations (e.g. low level of polymorphism

and lack of phylogenetic resolution) *Alu* markers are widely used to determine the degree of genetic relationship between populations. Indeed, they have some important characteristics: (i) they are autosomal markers and thus reflect both the maternal and paternal history of a population; (ii) they arose as unique events in human evolutionary history and thus these elements are identical by descent from a common ancestor (Batzer and Deininger, 1991; Batzer et al., 1994); (iii) they are subject to very limited amounts of gene conversion (Batzer et al., 1996).

Reconstruction of evolutionary history among ethnically diverse human populations is essential for understanding the genetic basis of phenotypic adaptation (Campbell and Tishkoff, 2008). Despite the importance of African populations to the evolutionary history of modern humans, patterns of genetic diversity across geographically and ethnically diverse groups are largely uncharacterized (Tishkoff et al., 2009). In this paper, we investigated the genetic diversity among four ethnic groups from Ouangolodougou, northern Ivory Coast, using 11 *Alu* insertion polymorphisms. Ouangolodougou is a village characterized by strong social fragmentation, due to distinct languages, cultures and ethnic identities. Previous studies conducted on this population showed remarkably high heterozygosity for a number of gene polymorphisms, as well as frequent deviation from Hardy–Weinberg equilibrium, suggesting that natural selection played a role in shaping the observed genetic background (Santovito et al., 2008, 2010, 2012a, b). On the other hand, no significant differences in the genetic variability of X-short tandem repeat markers were observed between Ivorians and other sub-Saharan African populations belonging to the Niger–Kordofanian linguistic group (Pasino et al., 2011).

The aim of the present study was to further investigate the genetic structure of this Ivorian population, analysing the allelic distribution of 11 polymorphic *Alu* loci in order to compare the pattern of genetic variation with other North African and sub-Saharan populations.

Materials and Methods

Population and study area

The sampling was performed in 2010 at Ouangolodougou (9°58' N 5°09' W), a small town with about 20000 inhabitants located in a rural savannah region of northern Ivory Coast. One hundred and thirty-three unrelated individuals (62 males and 71 females, mean age 31.9 ± 14.5 years, range 3–67 years) were analysed. The sampling was conducted to include members from four ethic groups: Dioulà (n = 69), which represent about 90% of the inhabitants of Ouangolodougou, Sénoufos (n = 16), Boulè (n = 23) and Bètè (n = 25). The participants in the study were extensively interviewed following a detailed questionnaire and each was anonymously identified by a numerical code. All the subjects were randomly chosen healthy volunteers, received detailed information about the study, and gave their informed consent prior the analyses. The study was approved by the University of Turin ethics committee in 2010 and was performed in agreement with the ethical standards laid down in the 1964 Declaration of Helsinki.

Laboratory analyses

We analysed 11 human-specific *Alu* insertion polymorphisms, A25, ACE, APO, B65, D1, F13B, H2.36, H2.43, H3.23, PV92, and TPA25, representing the most analysed *Alu* insertion polymorphisms in the population genetics literature (Table 1) (Stoneking et al., 1997; Comas et al., 2000; Cherni et al., 2011). This characteristic offered us an opportunity to compare the genetic structure of our studied population with those reported for other African ethnic groups (Table 2). Peripheral blood samples (5–10 ml venipuncture) were collected in heparinized vacutainers and stored at –20°C. To extract DNA we used the Chelex® solution protocol as described by Walsh et al. (1991). Each DNA sample was amplified by polymerase chain reaction (PCR) using locus-specific primers as described in Arcot et al. (1995). PCR reactions were carried out in a total volume of 25 µl, with a final concentration of 1× Reaction Buffer, 2.5 mM $MgCl_2$, 5% DMSO, 0.25 mM dNTPs and 50 pmol of each primer, according to the conditions reported in literature (Arcot et al., 1995). Amplified PCR products were run on 2.5% agarose gel, stained with ethidium bromide, and visualized under UV light. The allele assignment was performed by two researchers independently and some random samples (n = 30) were repeated.

Data analysis

Allele frequencies, heterozygosity, and F_{ST} values among these Ivorian ethnic groups were calculated by Genepop software, v. 3.1. F_{ST}-related genetic distances were computed between pairs of populations (Reynolds et al., 1983) and were used to reconstruct a neighbor-joining (NJ) tree (Saitou and Nei, 1987) by means of the PHYLIP 3.5c package (Felsenstein, 1989). Statistical support for internal branches was calculated by performing bootstrap analyses of 1000 replications. Genetic relationships among populations were also analysed via non-metric multidimensional scaling (MDS) analysis of allele frequencies, as implemented in SYSTAT 10.0 (Systat Software, Inc., Chicago, IL, USA), and by plotting the positions of the populations using the two principal dimensions. We computed the Euclidean distance for each pair of populations using *Alu* insertion frequencies. This dissimilarity matrix was used to generate a MDS plot of population variation in two dimensions. For MDS analysis seven *Alu* insertion loci (ACE, APO, B65, D1, FXIIIB, PV92, and TPA25) were selected in order to provide the best comparison with data available in the literature (Stoneking et al., 1997; Comas et al., 2000; Bahari et al., 2008; Cherni et al., 2011).

Results and Discussion

The genotypic and allele frequencies of the ethnic groups sampled in Ouangolodougou are reported in Table 1. All loci were polymorphic in all groups, with the exception of HS2.43, which was fixed for the absence of the *Alu* element, and HS3.23, which was fixed for the presence of the *Alu* element. No significant departure from Hardy–Weinberg equilibrium was found among polymorphic loci, except for TPA25 in Baoulé and Bété.

The average heterozygosity value for all loci was 0.208

Table 1. Population statistics for 11 *Alu* insertion polymorphisms in four ethnic groups of northern Ivory Coast

Ethnic group	A25	ACE	APO	B65	D1	FXIIIB	HS2.36	HS2.43	HS3.23	PV92	TPA25	All loci
Dioulà (*n* = 69)												
Ins. Freq.	0.203	0.217	0.297	0.036	0.138	0.239	0.725	0.000	1.000	0.087	0.058	
Genotypes												
–/–	46	43	33	64	53	40	6	69	0	57	62	
–/+	18	22	31	5	13	25	26	0	0	12	6	
+/+	5	4	5	0	3	4	37	0	69	0	1	
P-value	0.275	0.8720	0.821	0.952	0.230	0.999	0.898	—	—	0.731	0.238	
Het	0.261	0.319	0.449	0.072	0.188	0.362	0.377	0.000	0.000	0.174	0.087	
Het/locus ± SE												**0.208 ± 0.047**
Sénoufo (*n* = 16)												
Ins. Freq.	0.188	0.188	0.219	0.031	0.156	0.250	0.750	0.000	1.000	0.094	0.063	
Genotypes												
–/–	11	11	10	15	12	11	1	16	0	13	14	
–/+	4	4	5	1	3	4	6	0	0	3	2	
+/+	1	1	1	0	1	1	9	0	16	0	0	
P-value	0.773	0.7730	0.943	0.992	0.513	0.773	1.000	—	—	0.918	0.965	
Het	0.250	0.217	0.313	0.063	0.188	0.250	0.375	0.000	0.000	0.188	0.063	
Het/locus ± SE												**0.173 ± 0.038**
Baoulé (*n* = 23)												
Ins. Freq.	0.217	0.152	0.239	0.043	0.174	0.261	0.717	0.000	1.000	0.087	0.065	
Genotypes												
–/–	15	17	14	21	17	15	2	23	0	19	21	
–/+	6	5	7	2	4	6	9	0	0	4	1	
+/+	2	1	2	0	2	2	12	0	23	0	1	
P-value	0.5350	0.752	0.7350	0.977	0.167	0.535	0.986	—	—	0.901	0.009	
Het	0.261	0.248	0.304	0.087	0.174	0.261	0.391	0.000	0.000	0.174	0.043	
Het/locus ± SE												**0.177 ± 0.039**
Bété (*n* = 25)												
Ins. Freq.	0.200	0.160	0.240	0.040	0.140	0.200	0.740	0.000	1.000	0.080	0.060	
Genotypes												
–/–	17	18	15	23	19	17	2	25	0	21	23	
–/+	6	6	8	2	5	6	9	0	0	4	1	
+/+	2	1	2	0	1	2	14	0	25	0	1	
P-value	0.458	0.8660	0.828	0.979	0.200	0.458	0.949	—	—	0.910	0.005	
Het	0.240	0.240	0.320	0.080	0.698	0.240	0.360	0.000	0.000	0.160	0.040	
Het/locus ± SE												**0.225 ± 0.061**
Totals (*n* = 133)												
Ins. Freq.	0.203	0.192	0.267	0.038	0.143	0.222	0.729	0.000	1.000	0.086	0.060	
Genotypes												
–/–	89	89	72	123	101	83	11	133	0	110	120	
–/+	34	37	51	10	26	42	50	0	0	23	10	
+/+	10	7	10	0	6	9	72	0	133	0	3	
P-value	0.053	0.4980	0.9730.	0.904	0.067	0.467	0.859	—	—	0.551	0.001	
Het	0.256	0.278	0.383	0.075	0.195	0.308	0.376	0.000	0.000	0.173	0.075	
Het/locus ± SE												**0.193 ± 0.042**
F_{ST}/locus	0.0232	0.0079	0.0024	–0.0062	0.0014	—	0.2356	—	—	0.0463	—	**0.0456**
						0.0078					0.0054	

Ins. Freq., insertion frequency of the *Alu* element; Het, observed heterozygosity; Het/locus, average heterozygosity per locus; SE, standard error.
–/–, homozygote genotype for the absence of the insertion; +/–, heterozygote genotype; +/+, homozygote genotype for the presence of the insertion.
The *P*-value is referred to the chi-squared test for Hardy–Weinberg equilibrium between the expected and observed genotype counts.

Table 2. *Alu* insertion frequencies in various African populations

Populations	*n*	A25	ACE	APO	B65	D1	FXIIIB	H2.36	H2.43	H3.23	PV92	TPA25	Het/locus ± SE	References
Ivory Coast	133	0.203	0.192	0.267	0.038	0.143	0.222	0.729	0.000	1.000	0.086	0.060	0.193 ± 0.042	Present study
North Africa														
Algeria	47	0.106	0.266	0.915	0.734	0.149	0.315		0.085	0.840	0.287	0.532	0.337 ± 0.042	Comas et al. (2000)
Libya	52		0.240	0.615	0.432	0.317	0.355				0.296	0.451	0.443 ± 0.019	Cherni et al. (2011)
Morocco	350	0.164	0.300	0.874	0.577	0.289	0.312				0.336	0.523		
North Morocco	111	0.113	0.333	0.910	0.608	0.288	0.338		0.045	0.833	0.333	0.617	0.330 ± 0.046	Comas et al. (2000)
West Morocco	140	0.143	0.314	0.929	0.614	0.304	0.294		0.071	0.821	0.343	0.575	0.338 ± 0.042	Comas et al. (2000)
South Morocco	49	0.235	0.265	0.847	0.510	0.194	0.306		0.020	0.878	0.398	0.510	0.344 ± 0.045	Comas et al. (2000)
Arabs	50	0.163	0.290	0.810	0.577	0.370	0.310		0.055	0.824	0.270	0.390	0.418 ± 0.025	Chbel et al. (2000)
Tunisia	293		0.366	0.731	0.411	0.305	0.328				0.271	0.515		
Autochthonous	48	0.167	0.240	0.875	0.594	0.245	0.344		0.052	0.750	0.313	0.604	0.301 ± 0.045	Comas et al. (2000)
Bousalem	47		0.276	0.638	0.276	0.276	0.340				0.255	0.531	0.436 ± 0.014	Cherni et al. (2011)
Thala	48		0.604	0.833	0.718	0.645	0.500				0.468	0.538	0.444 ± 0.030	Cherni et al. (2011)
Smar	64		0.343	0.656	0.355	0.156	0.289				0.062	0.601	0.373 ± 0.051	Cherni et al. (2011)
Zarzis	86		0.116	0.651	0.110	0.203	0.168				0.255	0.302	0.322 ± 0.038	Cherni et al. (2011)
West Africa														
Nigeria	11	0.220	0.270	0.500	0.830	0.000	0.080				0.090	0.410	*	Stoneking et al. (1997)
Saharawi	58	0.138	0.284	0.836	0.534	0.259	0.371		0.009	0.862	0.310	0.397	0.341 ± 0.045	Comas et al. (2000)
Central Africa														
Pigmy	34	0.530	0.322	0.852	0.820	0.590	0.030				0.352	0.238		
Central African Republic	17	0.530	0.324	0.853	0.820	0.590	0.030				0.353	0.235	*	Stoneking et al. (1997)
Zaire	17	0.530	0.320	0.850	0.820	0.590	0.030				0.350	0.240	*	Stoneking et al. (1997)
South Africa														
!Kung	40	0.610	0.290	0.880	0.500	0.160	0.170				0.200	0.170	*	Stoneking et al. (1997)
Nguni	43	0.410	0.400	0.600	0.600	0.270	0.120				0.240	0.210	*	Stoneking et al. (1997)
Sotho	48	0.390	0.380	0.680	0.480	0.310	0.180				0.290	0.330	*	Stoneking et al. (1997)

n, number of subjects sampled.
* Stoneking et al. (1997) reported a single heterozygosity value of 0.402 ± 0.030 calculated as the mean value for the populations indicated.

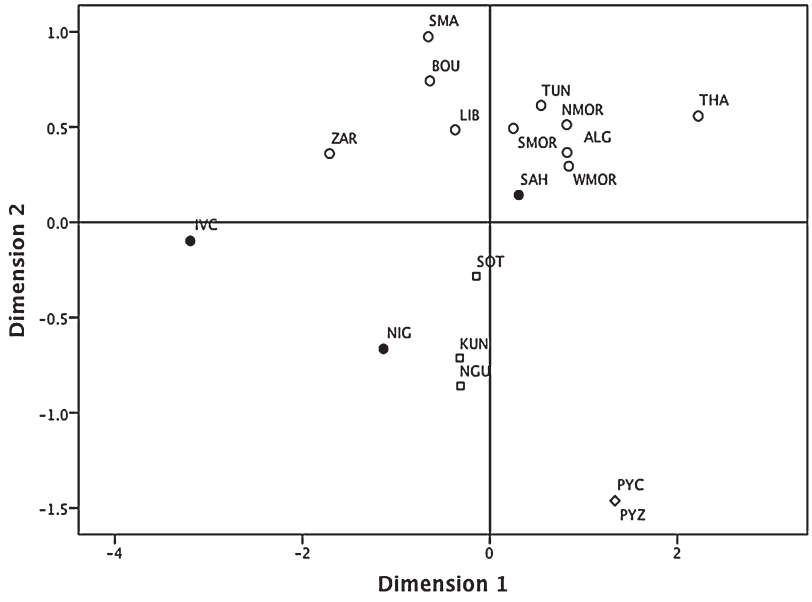

Figure 1. Plot of the MDS analysis of the allele frequencies at seven *Alu* insertion polymorphic loci (ACE, APO, B65, D1, FXIIIB, PV92, and TPA25) from the African populations listed in Table 2. A25, H2.36, H2.43, and H3.23 frequency values were not used because these were missing for some populations. The two dimensions account for 96% of the variation in allele frequencies (dimension 1 accounts for 71% of the total variance, while dimension 2 accounts for 25% of the total variance). North Africa (empty circles): Algeria (ALG), Libya (LIB), Morocco (NMOR, SMOR, and WMOR), Tunisia (SMA, THA, TUN, and ZAR); Central Africa (empty diamond): Pygmy (PYC and PYZ); West Africa (black circle): Ivory Coast (IVC, present study), Nigeria (NIG) and Saharawis (SAH); South Africa (empty square): !Kung (KUN), Nguni (NGU), and Sotho (SOT).

± 0.047 for Dioulà, 0.173 ± 0.038 for Sénoufo, 0.177 ± 0.039 for Baoulé and 0.225 ± 0.061 for Bété. In the total Ivorian sample, the heterozygosity values were high variables, ranging from 0.000 for HS2.43 and HS3.23 to 0.383 for APO, with an average heterozygosity/locus value of 0.193 ± 0.042. The F_{ST} value calculated for all loci was very low (0.0456), suggesting high levels of gene flow among the four Ivorian ethnic groups considered here.

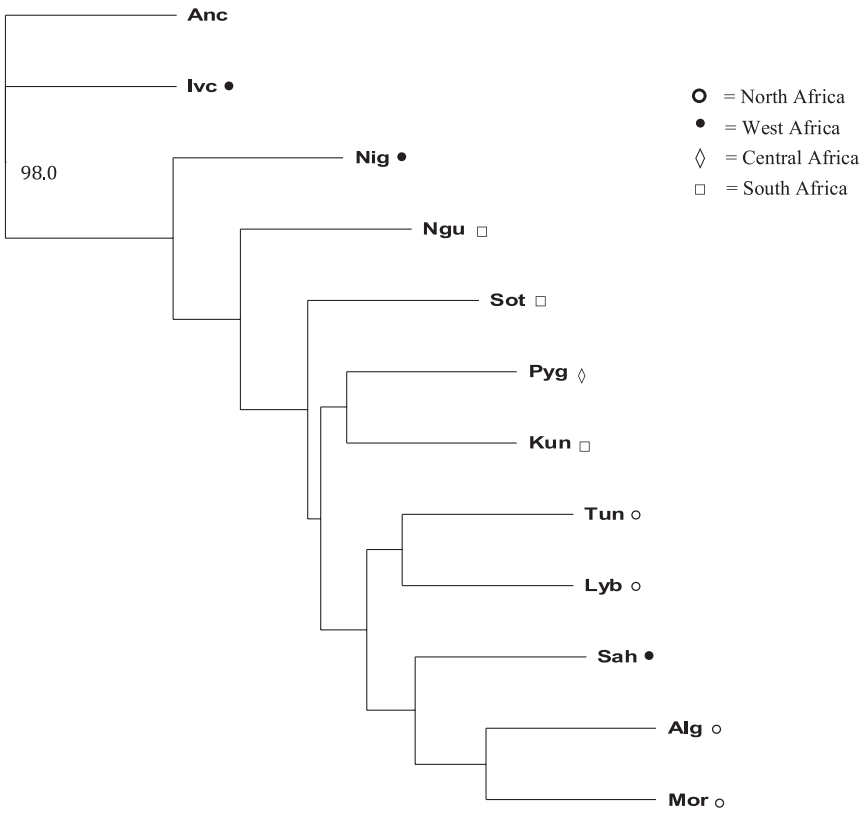

Figure 2. Neighbor-joining phylogenetic analysis of Ivory Coast population and other African populations. Bootstrap values (percentages) based on 1000 replications are shown when greater than 50%. Anc = Ancestor, hypothetical ancestral population with *Alu* insertion frequencies set at 0% for each locus; Alg = Algeria; Kun = !Kung (Botswana, Angola, and Namibia); Bao = Baoulé (Ivory Coast, present study); Bet = Bété (Ivory Coast, present study); Dio = Dioulà (Ivory Coast, present study); Ivc = total sample of Ivory Coast (present study); Kun = !Kung (South Africa); Lib = Libya; Ngu = Nguni (South Africa); Nig = Nigeria; Mor = Morocco; Pyg = Pygmy (Central Africa Republic and Zaire); Sah = Saharawis (North-Western Africa); Sen = Sénoufo (Ivory Coast, present study); Sot = Sotho (South Africa); Tun = Tunisia.

To further assess population relationships, an MDS analysis based on *Alu* frequencies was carried out comparing the Ivorian sample with other African populations (Stoneking et al., 1997; Comas et al., 2000; Watkins et al., 2001; Terreros et al., 2005; Ennafaa et al., 2006) (Figure 1). MDS analysis was used to represent the data generated by the R matrix on a two-dimensional genetic map that accounted for 96% of the total variance (71% and 25% for DM1 and DM2, respectively). Ivorians were segregated to the left of the plot, whereas the North African populations were clustered together in the upper section in relatively close proximity with Saharawi (NW African population).

In addition to the MDS plots, phylogenetic relationships among African populations were reconstructed by NJ analysis (Figure 2). A hypothetical population with *Alu* insertion frequencies set at 0% for each locus was included to represent the ancestral group (Batzer et al., 1994). The Ivorian populations are represented as a basal branch of the tree, close to the hypothetical ancestral population in both NJ trees, with high bootstrap values.

Our analyses produced some insights about the genetic structure of the Ivorian population from Ouangolodougou. Despite their clear individual cultural and linguistic identities, the four ethnic groups sampled in the area exhibit a remarkable degree of genetic homogeneity, as indicated by the low F_{ST} values. Moreover, as a whole the Ivorian sample showed the lowest heterozygosity values among the African populations and were well separated from the other Africans in the MDS analysis. The low frequency of *Alu* insertions in our data also contributed to situating the Ivorians near the root of the NJ reconstruction, further suggesting a peculiar genetic makeup for this population. These results indicate a very limited role of sociocultural structure in shaping the genetic dynamics of people from Ouangolodougou, which appears to have been influenced by a more local pattern of population history and possibly random genetic drift. Low levels of heterozygosity and the relative isolation of our population in the MDS are suggested to be the consequence of a limited migration rate and gene flow possibly associated with random genetic drift acting on a relatively small population (3 out of 11 loci were not in Hardy–Weinberg equilibrium). NW Africa is populated by several populations with different languages, cultures and ethnic identities. Nevertheless, previous analyses showed substantial genetic similarities among most of the populations of this region, without evident patterns of genetic discrimination between sociocultural or ethnic groups (Bosch et al., 2000).

The basal branching of Ivorians in the NJ tree, associated with the low frequency of the observed *Alu* insertions, seem to suggest genotypic similarities with ancestral lineages.

These results (especially the NJ reconstruction, flawed by the absence of significant bootstrap support at most nodes) do not necessarily imply that Ivorians maintain primitive genetic features from a common ancestor. More realistically, these polymorphisms have undergone several historical microevolutionary processes (genetic drift and limited migration rate), leading to an apparent retention of primitive genotypic features.

Finally, NW Africa populations (Nigerians and Saharawi) and Ivorians do not appear to form a genetically homogeneous group, in contrast with the North African samples included in the analyses. Consistent with previous studies (Comas et al., 2000), in the MDS plot the North African populations clustered together, confirming the hypothesis of separate historical and genetic dynamics of Northern Africans compared to sub-Saharan populations (Cherni et al., 2011; Terreros et al., 2005). The Sahara Desert played a major role as geographical barrier and constrained human movements through North Africa principally to an east–west axis.

In conclusion, the picture emerging from our analyses indicates remarkable genetic homogeneity among Ivorian ethnic groups and a relative differentiation of this population from both North African and other sub-Saharan populations. However, because of the peculiarity of Ouangolodougou, it would be advisable to increase the sampling of Ivorian and other neighbouring populations in order to further clarify the genetic structure and the evolutionary processes involved in shaping the genetic landscape of modern NW African populations.

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