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Maternal and paternal lineages in Albania and the genetic structure of Indo-European populations

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Mitochondrial DNA HV1 sequences and Y chromosome haplotypes (DYS19 STR and YAP) were characterised in an Albanian sample and compared with those of several other Indo-European populations from the European continent. No significant difference was observed between Albanians and most other Europeans, despite the fact that Albanians are clearly different from all other Indo-Europeans linguistically. We observe a general lack of genetic structure among Indo-European populations for both maternal and paternal polymorphisms, as well as low levels of correlation between linguistics and genetics, even though slightly more significant for the Y chromosome than for mtDNA. Altogether, our results show that the linguistic structure of continental Indo-European populations is not reflected in the variability of the mitochondrial and Y chromosome markers. This discrepancy could be due to very recent differentiation of Indo-European populations in Europe and/or substantial amounts of gene flow among these populations. *European Journal of Human Genetics* (2000) **8**, 480–486.

Keywords: human genetic diversity; mitochondrial DNA; Y-chromosome; linguistics; AMOVA; Albania

Introduction

Mitochondrial DNA (mtDNA) and Y chromosome polymorphisms have been studied extensively in the context of human population genetics. They are very convenient because of the lack of recombination and their haploid mode of transmission.¹ Their simultaneous analysis in a set of populations also raises the interesting possibility of contrasting evolutionary processes experienced by males and females.^{2,3}

As a contribution to the evaluation of the biological history of the Albanian population, we have studied the sequence variability of the first hypervariable segment of mtDNA control region (HV1) in 42 individuals and that of Y-specific haplotypes based on microsatellite DYS19 and the Alu insertion (YAP) in 56 individuals. The Albanian population had never been examined for these polymorphisms. Its study is of particular interest in the context of the settlement of the

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European continent, due to the fact that the Albanian language is a separate lineage of the Indo-European linguistic family. It is indeed very distinct from the Italic, Greek, Celtic, Germanic and Balto-Slavic sub-families that represent the vast majority of the languages spoken in Europe. A recent study on blood groups distributions (AB0, MN and Rh) suggested that Albanians may be indeed quite different from other Balkan populations.⁴

Albanian diversity for these haploid molecular markers was compared with that of other published samples from continental Europe, in order to evaluate the level of differentiation among Indo-Europeans and to check the correlation between genetic and linguistic affinities for these populations.

Materials and methods Samples

Specimens of hairs were taken, and preserved in alcohol, from Albanian individuals, born and residing in 24 Albanian districts and in the adjacent regions of Macedonia, Kosovo and Montenegro. Individual DNA was extracted from 2-3 dried hair roots using standard protocols.⁵

mtDNA amplification and sequencing

HV1 sequences were PCR amplified according to published forward⁶ and reverse⁷ primers in a standard PCR reaction mix. Direct sequencing was performed with L15996 and H16401 primers.⁸

Microsatellite (STR) and YAP analyses

DYS19 STR and YAP insertions were amplified according to published protocols.^{9,10} DNA samples typed by sequencing were used as ladders to assign allele sizes.¹¹

Data analysis

Statistical analyses of the samples were carried out using the Arlequin software package.¹² Gene diversity indexes were computed for both mtDNA sequences and Y specific haplotypes (on the basis of the number of repeats at locus DYS19 and the presence/absence of the Alu insertion). The level of genetic structure within the European populations was assessed with an AMOVA analysis¹³ by comparing haplotype frequencies (F_{ST} statistics) or by taking molecular differences into account (Φ_{ST} statistics). For Y haplotypes, we used the information on allelic similarity or dissimilarity, instead of the number of repeat differences between DYS19 alleles, because the variance of the resulting statistics is large when only a few loci are examined.¹⁴ A hierarchical structure of populations was tested by AMOVA, in which populations were grouped into the major sub-families of the Indo-European linguistic family (see Tables 2 and 3). F and Φ statistic significance were assessed by a permutation procedure (100000 permutations).¹³ The mismatch distribution of HV1 sequences was computed to check for the sign of a potential population demographic expansion.¹⁵ The parameters of a stepwise demographic expansion

 $\theta_0 = 2N_0\mu$, $\theta_1 = 2N_1\mu$, and $\tau = 2t\mu$,

(where N_0 and N_1 are the population sizes before and after the instantaneous expansion, respectively, t is the number of generations since that expansion occurred, and μ is the mutation rate per generation for the whole sequence) were estimated by the method of least-squares,¹⁵ as implemented in the Arlequin software.¹² The inferred expansion model was tested by a parametric bootstrap method, based on the sum of squared differences (SSD) between the observed and expected mismatch distributions, as described by Schneider and Excoffier.¹⁶ The selective neutrality of HV1 sequences and the demographic equilibrium of the Albanian sample were examined using Tajima's D^{17} and Fu's Fs^{18} statistics, the significance of which were assessed by simulations based on the coalescent algorithm described in Hudson.¹⁹ Pairwise genetic distances between populations were computed as described in Slatkin.¹⁴ The Indo-European linguistic classification by Ruhlen²⁰ was used to compute linguistic distances between populations, as described in Poloni et al.² The significance of the correlation between genetic and linguistic distances was evaluated by a Mantel test.²¹

Results

MtDNA

Thirty-one different HV1 sequences are found among 42 individuals (Table 1). As in the rest of Europe, the Cambridge sequence²² is quite frequent in Albania (16.7%). Of the 31 Albanian sequences, 21 are similar to those previously described in other populations for overlapping nucleotides.²³ The other 10 HV1 sequences are unique to Albanians. With the only exception of sequence 22, which matches the L1a African haplogroup HVI motifs, the other Albanian sequences clearly display the nucleotide substitution pattern described in Europe.²⁴ According to the classification outlined by Macaulay et al^{24} for HVI, three sequences belong to haplogroup J, three to haplogroup T, six to haplogroup U5, one to haplogroup K and one to haplogroup V. The nucleotide diversity of Albanians (h = 0.0147) falls within the range of variation of other Indo-Europeans from continental Europe (Table 2). Albanian mtDNA sequences show a clear unimodal mismatch distribution, typical of populations having gone through a recent expansion.^{25,15} A similar pattern is observed in all other European populations with the exception of the Saami.²⁶ The least-squares estimates of the parameters of a stepwise expansion are as follows: $\theta_0 = 0.60 \text{ CI}_{95\%}(0-2.00), \quad \theta_1 = 43.48 \text{ CI}_{95\%}(13.99-7202.23),$ and $\tau = 3.64 \text{ CI}_{95\%}(1.95-6.02)$. The *P*-value of the SSD statistic is 0.693, validating the hypothesis of a recent expansion corresponding to the above estimated demographic parameters. Assuming a divergence rate of 33% per million years,²⁷ a τ value of 3.64 corresponds to about 36788 years (CI_{95%}[19647-60808]). Assuming the mutation rate is correct, the molecular diversity of Albanians is in agreement with a late Pleistocene expansion as is the majority of European populations.²⁶ These results are strengthened by significant negative values of Tajima's D (-2.0308, P = 0.0004) and Fu's F_s (-25.54; P = 0 with 10000 simulations), all indicative of a recent demographic expansion.^{17,18,28} The hypotheses of selective neutrality and population equilibrium are also rejected for most tested samples using Tajima's D, and for all samples using Fu's F_s (Table 2).

Y chromosome

In the Albanian sample, 14.3% of Y chromosomes bear the Alu insertion (YAP⁺ chromosomes). At the DYS19 locus, the alleles observed are: A (186 bp), B (190 bp), C (194 bp), D (198 bp) and E (202 bp), with frequencies of 19,6%, 37,5%, 33,9%, 7,1% and 1,8%, respectively. We analysed Y chromosome variability by combining the information relative to both DYS19 and YAP polymorphisms. A total of 7 DYS19/YAP haplotypes were observed, the more frequent being B/YAP⁻ (35.7%) and C/YAP⁻ (33.9%). The other observed haplotypes are: A/YAP⁺ (12.5%), A/YAP⁻ (7.1%), D/YAP⁻ (7.1%), E/YAP⁻ (1.8%), and B/YAP⁺ (1.8%). In Albania, as in the rest of Europe,²⁹ the DYS19 allele most frequently associated with the Alu insertion is allele A. This tight association was tested by an exact test of linkage disequilibrium,³⁰ and found to be

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Table 2 Continental Indo-European sample genetic properties for mtDNA HV1. Sequences of other populations' samples are included in the data set by Handt $et al^{23}$

	N	k	т	S	h	D	Fs	Indo-European sub-family
Albania	42	31	300	45	0.015 (0.008)	-2.031ª	-25.54 ^a	Albanian
Bulgaria	30	22	360	37	0.013 (0.007)	–1.878 ^c	-14.39 ^a	Balto-Slavic
Catalonia	15	10	255	13	0.012 (0.008)	–0.878 ns	-3.99 ^c	Italic
Spain	41	21	302	38	0.019 (0.010)	–1.283 ns	-6.51 ^c	Italic
Portugal	54	37	302	39	0.012 (0.007)	–1.978 ^b	-26.11 ^a	Italic
Trento	20	20	360	39	0.017 (0.009)	–1.771°	-17.20 ^a	Italic
Tuscany	52	40	360	55	0.014 (0.008)	-2.025 ^a	-25.53 ^a	Italic
Sardinia	69	46	385	53	0.011 (0.006)	-2.035 ^a	-25.80 ^a	Italic
Denmark	33	26	287	29	0.019 (0.010)	–0.897 ns	-18.79 ^a	Germanic
Iceland	39	29	360	32	0.014 (0.008)	–1.167 ns	-22.19 ^a	Germanic
England	100	71	360	67	0.012 (0.007)	-2.141 ^a	-25.71 ^a	Germanic
Cornish	69	43	276	50	0.013 (0.007)	-2.170 ^a	-26.11 ^a	Celtic
Welsh	92	45	277	47	0.012 (0.007)	-2.105 ^a	-26.40 ^a	Celtic
Bavaria	49	34	276	36	0.014 (0.008)	–1.783 ^c	-25.96 ^a	Germanic
North Germany	100	73	282	60	0.017 (0.009)	–1.863 ^b	-25.54 ^a	Germanic
German-Switzerland	44	14	225	14	0.009 (0.006)	–1.492 ^c	-7.83 ^a	Germanic
Latin-Switzerland	16	10	225	10	0.010 (0.006)	-1.646 ^c	-6.69 ^a	Italic
Romansh-Switzerland	16	10	224	13	0.011 (0.007)	–1.453 ns	-4.72 ^a	Italic

^a*P*<0.005; ^b*P*<0.01; ^c*P*<0.05. *N*: sample size; *k*: number of different sequences; *m*: sequence length; *S*: number of polymorphic sites, *h*: gene diversity, *D*: Tajima's D; *F*_S: Fu's F_S.

very significant (P = 0; 1000000 steps in the Markov Chain). In particular, we found a very strong association between allele A and YAP⁺ (P = 0), and between allele C and YAP⁻ (P = 0.02). The observed gene diversity for Albanians (h = 0.744, Table 3) is similar to that of other European populations, although slightly lower values are observed for some Northern European samples.

As reported in Table 4, a low but significant level of genetic differentiation among populations is observed for mtDNA HV1 sequences, both when molecular information is used ($\Phi_{ST} = 0.011$, P < 0.00001) and when it is not ($F_{ST} = 0.021$, P < 0.00001). Populations grouped within the Indo-European linguistic sub-families are also significantly differentiated (F_{SC} and Φ_{SC} indexes in Table 4). However, our results fail to reveal any significant level of genetic differentiation between the linguistic sub-families (F_{CT} and Φ_{CT} indexes in Table 4). Note that the AMOVA analyses for mtDNA HV1

sequences lead to significant *F* statistics that are higher than the Φ statistics. This suggests that a substantial amount of evolutionary 'noise' is introduced in the analysis of genetic structure when molecular information is used, possibly because of frequent homoplasic events occurring in the D-loop. We also performed an AMOVA using only the frequencies of some nucleotide positions (16069, 16129, 16224, 16270, 16278, 16292, 16294 and 16298), which define mtDNA haplogroups previously described,²⁴ and found a similarly low and significant level of genetic structure for Indo-Europeans of Europe ($F_{ST} = 0.015$, P < 0.00001; $F_{CT} = 0.004$, NS).

For Y chromosome haplotypes, a low but significant level of differentiation is observed among populations when the analysis is based only on haplotype frequencies ($F_{ST} = 0.021$, P = 0.043), but it becomes not significant when the number of mutations between haplotypes is used ($\Phi_{ST} = 0.017$,

Table 3	Continental Indo-European	samples genetic	properties for Y	chromosome	YAP/DYS19 haplotypes
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	Ν	k	h	Indo-European sub-family	Reference
Albania	56	7	0.744 (0.03)	Albanian	Present study
Apulia	20	4	0.739 (0.055)	Italic	Ciminelli et al ²⁹
Calabria	26	6	0.702 (0.064)	Italic	Ciminelli et al29
Crete (Greeks)	24	5	0.743 (0.052)	Greek	Ciminelli et al29
Sweden	40	4	0.541 (0.067)	Germanic	Saiantila <i>et al</i> 42
Switzerland	51	5	0.657 (0.054)	Germanic	Saiantila <i>et al</i> ⁴²
England	19	4	0.708 (0.074)	Germanic	Hammer et al ³⁵
Venetia	21	4	0.729 (0.058)	Italic	Hammer <i>et al</i> ³⁵
North Sardinia	28	5	0.794 (0.041)	Italic	Hammer <i>et al</i> ³⁵
South Sardinia	27	5	0.766 (0.039)	Italic	Hammer <i>et al</i> ³⁵
Germany	30	5	0.667 (0.063)	Germanic	Hammer et al ³⁵

N: sample size; k: number of haplotypes; h: gene diversity

	Table	4	AMOVA	analy	/ses
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	mtDNA	Y chromosome
Number of populations ^a	18	11
Number of groups ^b	5	4
F_{ST} (among populations)	0.021 ^c	0.021 ^d
<i>F_{sc}</i> (among populations within groups)	0.024 ^c	0.002 ns
F _{CT} (among groups)	–0.004 ns	0.019 ns
\prod_{sT} (among populations)	0.011 ^c	0.017 ns
\square sc (among populations within groups)	0.013 ^c	0.003 ns
□ cT (among groups)	-0.002 ns	0.014 ns

^aIndo-European populations compared with Albanians for mtDNA HV1 sequences are listed in Table 2; Indo-European populations compared with Albanians for Y chromosomes are listed in Table 3; ^bPopulations are grouped according to their linguistic classification into Indo-European sub-families; ^cP<0.0001; ^dP<0.05; ns: not significant.

P = 0.061). No significant level of genetic structure is detected either among populations within sub-families nor among sub-families (Table 4).

Population comparisons using both pairwise F_{ST} and Φ_{ST} measures on Y chromosome diversity reveal that the Albanian sample is not significantly different from the other tested populations, with the exception of the Swedish sample. The same analyses performed on mtDNA haplotype frequencies shows that the Albanian sample is significantly different from the samples from Spain, Germany, Iceland, and German Switzerland. When molecular information is considered, Albania is only found significantly different from Denmark.

Comparisons of genetic, linguistic and geographic distance matrices are reported in Table 5. Values from 0 to 3 were assigned to the linguistic distances among pairs of languages within Indo-European sub-families, depending on their mutual relatedness. Linguistic distances among sub-families were varied from 4 (close relationship) to 16 (very distant relationship) to study the effect of different time depth of language evolution on the corresponding correlation coefficients. Our results show that the variability of mtDNA sequences among populations is not significantly correlated to the linguistic and geographic diversity. In contrast, linguistic information accounts for about 5% (r = 0.22) of the genetic variability between populations for the Y chromosome.

However, this contribution becomes not significant when the weight given to linguistic distances between Indo-European sub-families is increased (Table 5). Y chromosome diversity is also significantly correlated with geography. However, partial correlations of genetics with geography and linguistics are not significant, suggesting the impossibility of distinguishing independent geographic and linguistic factors which have contributed to the genetic differentiation of the populations (Table 5).

Discussion

Despite belonging to a separate branch of the Indo-European language family, the Albanian population is found to be very similar to most other European populations for mtDNA HV1, as attested by the low genetic distances observed between populations and the 36 HV1 Albanian sequences out of 42 shared with other populations. This result is in keeping with the observation of generally low but significant levels of variability in Europe,^{31,32} with the exception of Ladins³³ and the Saami.34 A similar pattern is observed for the two Y chromosome polymorphisms. As already pointed out, ³⁵ YAP⁺ chromosomes are less frequent in Northern (0-7%) than Southern Europe (8-20%), and the Albanians, with 14.3% of YAP⁺ chromosomes, are quite typical of Southern European populations. Also as among Europeans in general, the DYS19 alleles B and C are the most frequent among Albanians.²⁹ In fact, most of the genetic distances between Albanians and the other European samples, inferred from DYS19/YAP haplotypes, are not significant.

The linguistic peculiarity of the Albanian population is thus not reflected in our genetic data. Actually, the AMOVA analyses reveal a general absence of genetic structure for both maternal and paternal markers associated with the differentiation of Indo-European linguistic sub-families in Europe (Table 4). This general lack of structure suggests either a very recent radiation of the major Indo-European language subfamilies from Europe, or the occurrence of large amounts of

	linguistic distance			linguistic distance		
	between sub-families	mtDNA		between sub-families	Y chromosome	
Number of samples		18			11	
Correlation geography-linguistics	4	0.360	<i>P</i> <0.01	4	0.560	<i>P</i> <0.001
Correlation genetics-geography		-0.001	ns		0.335	<i>P</i> <0.05
Correlation genetics-linguistics	4	0.047	ns	4	0.224	<i>P</i> <0.05
Correlation genetics-linguistics	6	0.041	ns	6	0.224	ns
Correlation genetics-linguistics	8	0.038	ns	8	0.220	ns
Correlation genetics-linguistics	16	0.032	ns	16	0.213	ns
Partial correlation genetics-geography	(controlled for linguistics)			4	0.259	ns
Partial correlation genetics-linguistics (4	0.050	ns	

Table 5Correlations between matrices of genetic, geographic and linguistic distances for mtDNA and Y chromosome. Partialcorrelations are computed only for Y chromosome variation

ns: not significant

gene flow among European populations. Note that for mtDNA, the inclusion in the analysis of an Indo-European sample from the Indian sub-continent (Havik, Indic sub-family of languages)³⁶ raises the levels of genetic structure observed, but these values are still not significant ($F_{CT} = 0.024$, P = 0.305; $\Phi_{CT} = 0.018$, P = 0.126).

Even though the AMOVA analyses on mtDNA HV1 and Y chromosome polymorphisms are not strictly comparable, since the data sets available for the two molecular markers are somewhat different, a slightly lower level of genetic structure is observed for Y chromosome DYS19/YAP polymorphisms than for mtDNA HV1 sequences. An ascertainment bias cannot be totally excluded for one or both markers, but unfortunately another overlapping data set for the Y chromosome does not yet exist for a sufficient size of population to control for that problem. Nevertheless, for mtDNA we observe a low but significant level of differentiation between populations within the Indo-European linguistic sub-families $(F_{SC} = 0.024, P < 0.00001; F_{ST} = 0.021, P < 0.00001).$ This raises the possibility that a female-specific genetic structure of Indo-European populations actually exists, but that the pattern associated with this structure is defined by a factor other than the history of language differentiation. In contrast, no alternative genetic structure among Indo-Europeans is apparent from the study of male-specific markers $(F_{SC} = 0.002, P = 0.496; F_{ST} = 0.021, P = 0.043).$

The correlation study confirms the general lack of structure observed in the AMOVA analyses (Table 5). The linguistic fission history of Indo-European populations is not associated with mtDNA variation. When the Indian Havik sample is included in the analysis, the contribution of linguistics on mtDNA diversity increases by about 3%, but is still not significant. The very weak association observed between the Indo-European linguistic structure and the genetic distances among populations based on Y chromosome markers (r = 0.22, Table 5) suggests a possible correlation of the malespecific genetic radiation process with the differentiation of Indo-European language families. However, this correlation becomes non-significant when the weight attributed to linguistic differences between major Indo-European subfamilies is increased. This could suggest that the differentiation of the Indo-European sub-families was indeed very recent, implying that the differentiation of genes proceeds at a slower pace than that of language. However, it is very likely that substantial amounts of gene flow have occurred among linguistic sub-families on the continent, which would have erased any former association between the linguistic and genetic radiation processes.

The low correlation between linguistic and genetic distances observed in this study for both maternal and paternal markers falls within the range of values observed for a large set of classical polymorphisms (correlation coefficients from -0.042, ns to 0.455, P = 0.004).³⁷ This range of variation underlines the fact that, because of their particular history, different genes or regions of the genome will present distinct patterns of variability among populations. Indeed, several studies have pointed to a correlation between linguistics and genetics among Indo-Europeans, but have also demonstrated the substantial effect of gene flow between populations in Europe in reducing the extent of their differentiation.^{38–41}

In conclusion, on the basis of the polymorphisms here analysed, the Albanian population does not reveal any specific pattern that distinguishes it from the Indo-European gene pool of Europe. As for classic polymorphisms, the study of additional autosomal molecular markers could give us better clues to the genetic and linguistic history of Indo-European populations.

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