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Population study of 3 STR loci in the Basque Country (northern Spain)

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Abstract The tetrameric STRs, HUMTH01, HUMVWA31A and HUMFES/FPS, were studied in a population from the Basque Country (northern Spain) for their frequency distribution and applicability to identity and paternity testing. All systems conformed to Hardy-Weinberg equilibrium; pairwise comparisons demonstrated the allelic independence between loci, and furthermore, all systems seemed to be in agreement with expectations from the Stepwise Mutation Model (SMM) of the mutation-drift theory, which indicates the homogeneity of the population and suggests a replication slippage mechanism as a possible model for generating alleles. A comparison with other population groups appeared to indicate that frequencies are well conserved in Caucasians, but differ from other racial groups. The calculated parameters "a priori probability of exclusion" (PEX) and "index of discrimination" (ID), show the informativeness of these loci for the determination of identity and relatedness of individuals.

Key words STR · HUMTHO1 · HUMVWA31/A · HUMFES/FPS · Population genetics

Introduction

Microsatellite DNA consists of tandemly repeated units ranging in size from 1 to 7 bp, called STR loci (Short Tandem Repeats). STRs are highly represented in the human genome, and trimeric and tetrameric loci are estimated to be found every 15 Kb, i.e. approximately 200,000 of these loci are present across the human genome (Puers et al. 1993). These are located in genic and extragenic regions, and those in the genic regions are present not only in introns and flanking sequences, but also in coding regions.

These loci are frequently characterized by a polymorphism based on differences in the number of the repeat units that constitute the different alleles of each locus. The high variability of the tetrameric STRs and their simplicity when used as polymorphic markers, make them useful tools for population genetics and genetic identification purposes. While the applicability of these systems to paternity and identity testing is clear, relatively little is known about the processes that generate variability in these loci. As with some VNTR loci (Deka et al. 1991), STR loci could be expected to fit a neutral model. In this sense, the analysis of the dinucleotide STRs (Litt and Luty 1989) revealed Taq slippage during amplification, which resulted in secondary bands as artifacts. A process similar to this could be acting in the replication step, producing new alleles by slippage which could be mathematically explained by a stepwise mutation model.

Therefore, in this study 3 of the more useful STR loci, HUMTH01 (Polymeropoulos et al. 1991 b), HUMVWA31A (Kimpton et al. 1992) and HUMFES/FPS (Polymeropoulos et al. 1991 a), were selected to characterize the polymorphism and estimate their informativeness when applied to paternity and identity testing in a population from the Basque Country.

Materials and methods

Blood samples were obtained by venipuncture of peripheral blood from 100 unrelated individuals residing in the Basque Country. The current Basque population is composed of a mixture of people from different areas of Spain with the native Basque population. DNA was extracted from 700 µl of blood by the phenol-chloroform method (Smith et al. 1990). Samples were amplified in a Biometra Trio-Thermoblock, using 10 ng of template DNA, 1.5 mM $MgCl_2$, 50 mM KCl, 10 mM Tris-HCl at pH 9, 0.1% Triton X-100, 1 U Taq polymerase (Promega), 200 µM of each nu-

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cleotide and 1 μM of each primer in a final volume of 25 μl. The reaction mixture was overlaid with 25 μl of mineral oil. Primer sequences were as described by Edwards et al. (1992) for HUMTHO1 and by Kimpton et al. (1992) for HUMVWA31A and HUMFES/FPS.

Amplification parameters

HUMTH01	94° C 1 min, 64° C 1 min, 70° C 2 min	10 cycles
	90° C 1 min, 64° C 1 min, 70° C 2 min	17 cycles
HUMVWA31A	94° C 1 min, 50° C 1 min, 72° C 1 min 30 s	30 cycles
HUMFES/FPS	95° C 1 min, 54° C 1 min, 70° C 1 min 30 s	30 cycles
	72° C 10 min	1 cycle

Amplification products were separated as described by Wiegand et al. (1993) for TC11. Samples and allelic markers, composed of amplified DNA from individuals with known alleles, were applied every 2 lanes. Bands were visualized by silver staining as described by Budowle et al. (1991), with the modification that the ethanol step was omitted.

Statistical approaches

As some genotypes showed expected frequencies lower than 5, HWE conditions were tested with the exact test of homogeneity of Odelberg et al. (1989), which combines the frequencies of all heterozygotes and homozygotes. The levels of significance were estimated from the binomial distribution. An unbiased estimate of heterozygosity was calculated as proposed by Nei (1978). To test for linkage disequilibrium (i.e. allelic independence across loci), the procedure described by Risch and Devlin (1992) was used. Pairwise comparisons between the loci were made with the individuals typed for the 3 systems. Table 2×2 were constructed with the 2 rows being match/no match at the first locus and the 2 columns being match/no match at the second locus. The expected values were the product of dividing the marginals by the total number of comparisons. As this statistic does not have a chi-squared distribution, the statistical significance of the obtained χ^2 value was than evaluated by forming 2-loci genotypes by randomly and independently choosing one-locus genotypes from the database. This procedure was repeated 1000 times and each time a 2×2 table was formed as described above. The proportion of thus obtained χ^2 values greater than that obtained with the original data was the P value. Systems were further analysed by comparing the observed and expected number of alleles under the premises of the infinite allele model as proposed by Chakraborty and Daiger (1991) and the stepwise-mutation model (Chakraborty 1977) of the mutation-drift theory.

Populations were pairwise compared by testing the homogeneity of their allele frequencies by the χ^2 test, eliminating those alleles with observed frequencies equal to 0 in any of the 2 populations to be tested, and the statistical significance was obtained from a chi-squared distribution (degrees of freedom = number of alleles – 1). Comparisons of HUMFES/FPS with the referenced populations required alleles 10.1 and 10.3 in the Basque Country frequency distribution to be grouped with alleles 10 and 11 respectively.

The parameters "a priori probability of exclusion" (PEX) and "index of discrimination" (ID), of interest in legal medicine, were calculated as proposed by Smouse and Chakraborty (1986) and Wong et al. (1987), respectively.

Fig. 1 Allele frequency distributions of HUMTH01 different populations ▶

Fig. 2 Allele frequency distributions of HUMVWA31A in different populations

Fig. 3 Allele frequency distributions of HUMFES/FPS in different populations

Results

The allele frequencies in the Basque Country population for every system analysed, are presented in Table 1. The frequency distributions show differences among loci. Locus HUMVWA31A is unimodal, while the distributions for HUMTH01 and HUMFES/FPS are bimodal, that of HUMFES/FPS symmetric, and HUMTH01 asymmetric. However, when alleles 10.1 and 10.3 were grouped with alleles 10 and 11 respectively which is necessary to compare data with those in the literature the distribution of HUMFES/FPS appears unimodal (Figs. 1, 2 and 3). The highest observed heterozygosity was found to locus HUMVWA31A (0.87), those of loci HUMTH01 and HUMFES/FPS being 0.83 and 0.73 respectively (Table 1). Expected heterozygosities, calculated as proposed by Nei (1978), are shown in Table 4.

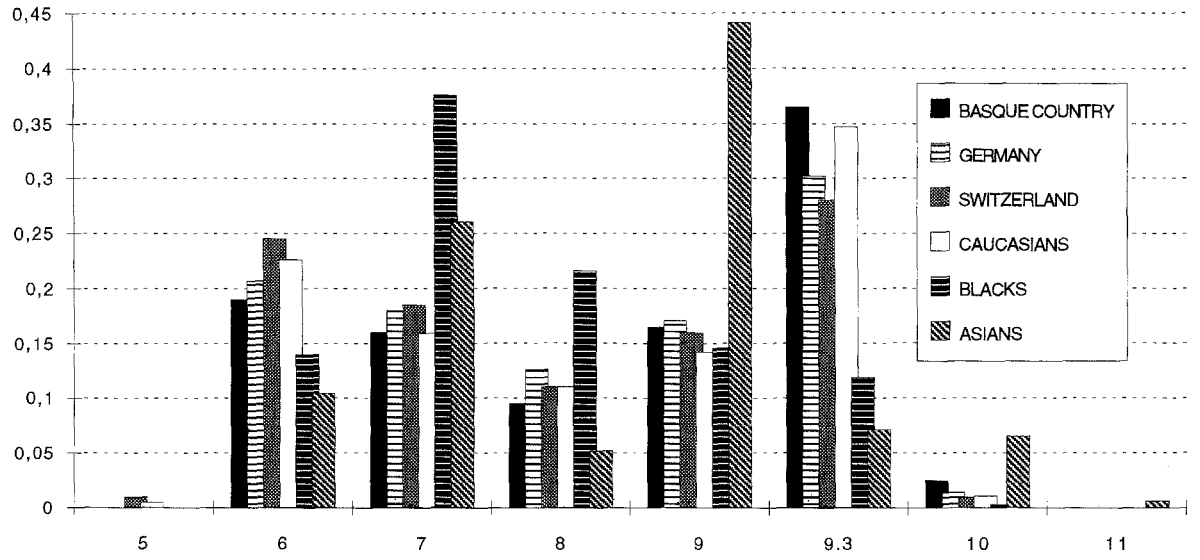
In order to check the Hardy-Weinberg equilibrium, we carried out the exact test of homogeneity (Odelberg et al. 1989). In all cases, there is good agreement between the observed values and those expected under Hardy-Weinberg equilibrium (Table 1). Moreover, pairwise comparisons between loci (Risch and Devlin 1992) showed allelic independence for all the 2-loci comparisons (Table 2).

As all these loci show a high heterozygosity and conform to Hardy-Weinberg expectations, it is also of interest to assess their utility in the establishment of identity and relatedness. For this the following probabilities were cal-

Table 1 Allele frequencies for the 3 STR systems in the Basque resident population and test[a] for Hardy-Weinberg equilibrium

HUMTH01		HUMVWA31A		HUMFES/FPS	
Allele	Frequency ± SD	Allele	Frequency ± SD	Allele	Frequency ± SD
6	0.190 ± 0.028	14	0.100 ± 0.021	8	0.015 ± 0.009
7	0.160 ± 0.026	15	0.135 ± 0.024	10	0.295 ± 0.032
8	0.095 ± 0.021	16	0.225 ± 0.029	10.1	0.060 ± 0.017
9	0.165 ± 0.026	17	0.275 ± 0.032	10.3	0.005 ± 0.005
9.3	0.365 ± 0.034	18	0.200 ± 0.028	11	0.360 ± 0.034
10	0.025 ± 0.011	19	0.065 ± 0.017	12	0.220 ± 0.029
				13	0.045 ± 0.015
Obs H[b]	0.83	Obs H[b]	0.87	Obs H[b]	0.73
χ^2	1.919	χ^2	2.668	χ^2	0.004
P	0.152	P	0.101	P	0.911

[a] As proposed by Odelbert et al. (1989)
[b] Observed heterozygosity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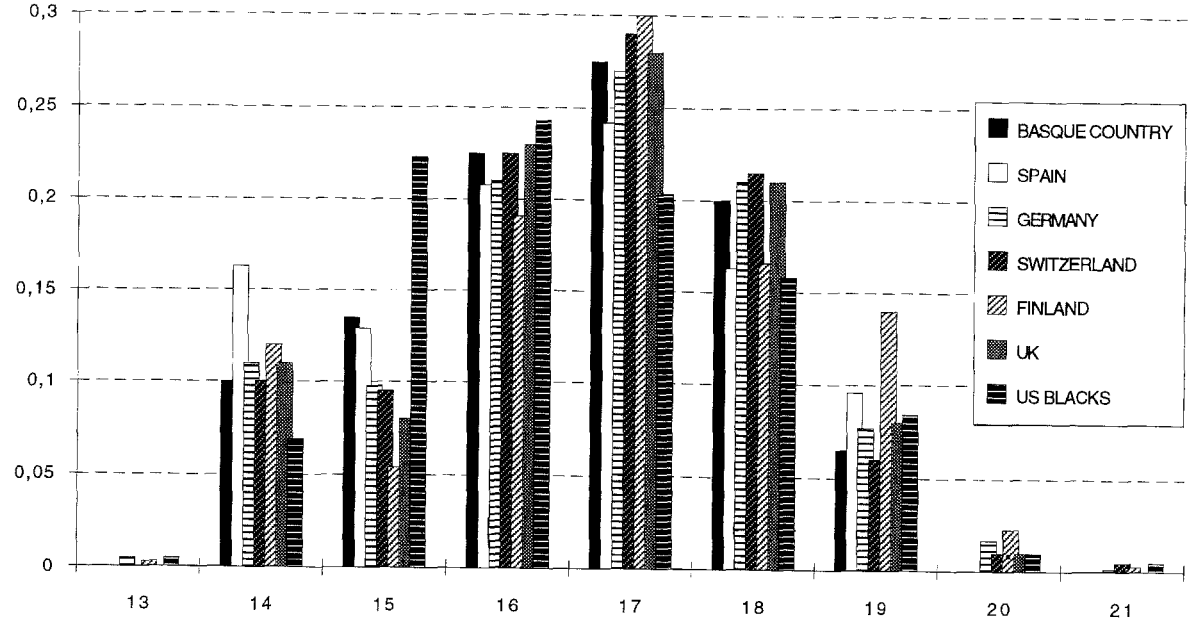
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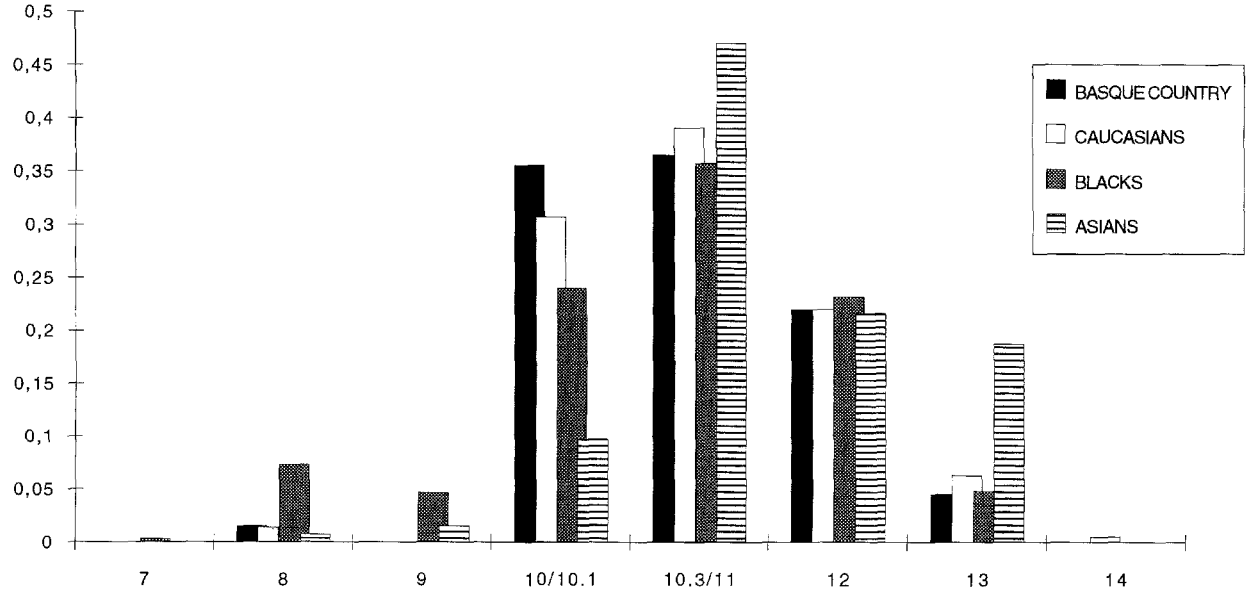
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BASQUE COUNTRY
CAUCASIANS
BLACKS
ASIANS

culated: (i) the probability that 2 non-related random individuals share the same genotype (ID) and (ii) the "a priori" probability that a falsely accused father will be excluded (PEX). The values ID and PEX for every system are shown in Table 3 and are similar to those found in other Caucasian population. (Wiegand et al. 1993; Puers et al. 1993; Möller et al. 1993; Kimpton et al. 1993; Hammond et al. 1994; Sajantila et al. 1994). The allelic independence enables the combined ID and PEX values, which are 0.00078 and 0.9114 respectively, to be estimated. This shows the advantages that these markers offer for medico-legal investigations.

Table 2 Pairwise test of allelic independence between loci[a]

Combination	Pairs of individuals				χ^2 value	P
	++	+−	−+	−−		
HUMTH01-HUMVWA31A	0	4	2	42	0.18972	0.899
HUMTH01-HUMFES/FPS	0	3	7	36	0.57602	0.284
HUMVWA31A-HUMFES/FPS	1	3	6	36	0.32496	0.324

[a] As proposed by Risch and Devlin (1992)

The pairs of individuals with identical 2 loci genotypes were designated ++, those showing a match in the first locus only +−, those with a match only in the second, −+. Those showing a no-match/no-match were designated −−

Table 3 ID and PEX values for the 3 STR systems analysed in the Basque resident population

HUMTH01	HUMVWA31A	HUMFES/FPS	Combined
ID 0.092	ID 0.068	ID 0.124	0.00078
PEX 0.559	PEX 0.607	PEX 0.489	0.9114

Table 4 Fit to the infinits allele and stepwise mutation models

Locus	Exp H[a] ± SD	Observed number of alleles	Expected number of alleles	
			IAM	SMM
HUMTH01	0.772 ± 0.01	6	12	5.8
HUMVWA31A	0.805 ± 0.01	6	14	6.5
HUMFES/FPS	0.733 ± 0.01	7	10	5.1

[a] Expected heterozygosity as proposed by Nei (1978)

The comparison of the gene freuqencies for the 3 systems in the population under study and other previous studies, are shown in Figs. 1 to 3 and Table 5. For HUMTH01, there were no significant differences to the American Caucasian population (Puers et al. 1993) (χ^2_{5df} = 3.243, P = 0.6625), the German population (Wiegand et al. 1993) (χ^2_{5df} = 4.422, P = 0.4904) nor to the Swiss population (Hochmeister et al. 1994) (χ^2_{5df} = 5.504, P = 0.3575). However, there were statistically significant differences to Blacks and Asians (Puers et al. 1993) (χ^2_{5df} = 77.623, $P < 0.0001$ and χ^2_{5df} = 69.041, $P < 0.0001$ respectively). The comparison of gene frequencies for HUMVWA31A between the Basque population and the German population (Möller et al. 1993) (χ^2_{5df} = 2.563, P = 0.767), the Swiss population (Hochmeister et al. 1994) (χ^2_{5df} = 1.597, P = 0.902), the English population (Kimpton et al. 1992) (χ^2_{5df} = 4.689, P = 0.455), the US Black (Sajantila et al. 1994) (χ^2_{5df} = 9.244, P = 0.0997) and the Spanish population (Lorente et al. 1994) (χ^2_{5df} = 5.971, P = 0.309), showed no significant differences. Nevertheless, there were statistically significant differences to the Finnish population (Sajantila et al. 1994) (χ^2_{5df} = 18.379, P = 0.0025). For HUMFES/FPS there were no significant differences between the Basque population and the Caucasian population (Hammond et al. 1994) (χ^2_{4df} = 1.869, P = 0.7597) but these were statistically significant differences to the Black and Asian populations (Hammond et al. 1994) (χ^2_{4df} = 13.631, P = 0.0086 and χ^2_{4df} = 39.859, $P < 0.0001$ respectively).

To further characterize the systems, it is of interest to analyse the processes that generate variability in these loci. For this, we studied the fit of the observed number of alleles to the infinite allele model (IAM), and to the 'stepwise' mutation model (SMM). The number of observed alleles in all these loci is lower than the value expected

Table 5 χ^2 comparisons with the Basque Country resident population

HUMTH01					HUMVWA31					HUMFES/FPS				
Population	N	χ^2	P	Ref.	Population	N	χ^2	P	Ref.	Population	N	χ^2	P	Ref.
Germany	110	4.42	0.490	[1]	Spain	120	5.97	0.309	[7]	Caucasians	182	1.87	0.760	[8]
Switzerland	100	5.50	0.358	[5]	Germany	321	2.56	0.767	[3]	Blacks	164	13.63	0.009	[8]
Caucasians	185	3.24	0.663	[2]	Switzerland	100	1.60	0.902	[5]	Asians	67	39.86	<0.0001	[8]
Blacks	285	77.62	<0.0001	[2]	Finland	175	18.38	0.003	[6]					
Asians	77	69.04	<0.0001	[2]	UK	200	4.69	0.455	[4]					
					US Blacks	101	9.24	0.100	[6]					

N = number of individuals analysed in the referenced work

[1] Wiegand et al. (1993)
[2] Puers et al. (1993)
[3] Möller et al. (1993)
[4] Kimpton et al. (1992)
[5] Hochmeister et al. (1994)
[6] Sajantila et al. (1994)
[7] Lorente et al. (1994)
[8] Hammond et al. (1994)

from the IAM (Table 4) however, the values observed show a better fit to the SMM.

Discussion

The resident population of the Basque Country is the result of an admixture of several populations. The Basque native population, characterized by having been genetically isolated and considered to be among the oldest European populations with its own language, probably from pre-indoeuropean roots, received during its recent history (mainly in the second half of the nineteenth century, and again in 1950–70) a migratory flow coming from geographically close populations, basically from northern Spain and to a lesser extent from Extremadura (mid-western Spain) and Andalucia (southern Spain), whereas the contributions from the Spanish mediterranean area are very low. In general terms, it may be considered that the current resident Basque population is mainly composed of a mixture from the western and northern areas of Spain with the native Basque population.

The analysis of the STR loci in this population sample from northern Spain, revealed that their allele frequencies are distributed in a similar fashion to those observed in other previously studied Caucasian populations and the observed heterozygosity is also similar.

Due to the low frequencies of some alleles, (alleles 8, 10.1, 10.3 and 11 in HUMFES/FPS, alleles 8 and 10 in HUMTH01, alleles 14 and 19 in HUMVWA31A) it has been necessary to carry out the equilibrium test proposed by Odelberg et al. (1989). The results obtained reveal that there is no significant excess of heterozygotes, which along with the allelic independence of the systems (demonstrated by the test of Risch and Devlin 1992), seem to indicate that this population can be considered homogeneous, with random mating between individuals. This therefore, allows the product rule of the genotype frequencies to be applied in paternity and identification casework.

The comparison of the allele frequency distributions of the 3 loci for the Basque population studied and those observed in other Caucasian populations (Germany, UK, Switzerland, Spain, US Caucasians) revealed that they are very similar, despite their diverse geographical distribution. These data, seem to indicate that the allele distributions in these systems are well conserved, at least in the Caucasian group. Interestingly enough, with the locus showing the highest heterozygosity, HUMVWA31A, the US Black population (Sajantila et al. 1994) did not show significant differences in the allele frequency distribution when compared with the Basque population. However, the Finnish population does show a singificantly different allele frequency distribution, which agrees with its genetic isolation demonstrated by polymorphic protein markers; this however, disagrees with other findings at the DNA level which failed to show significant differences with other more heterogeneous Caucasian populations (Sajantila et al. 1991).

The appearance of shared modal alleles among different racial groups, as occurs in some VNTR systems (Deka et al. 1991, 1992a), could indicate that these alleles are the most ancient ones. When the modal alleles in one system differ by a considerable number of repeats, this bimodality could be explained through an infrequent unequal crossing-over mechanism, which could have taken place before the geographical dispersal of human races, whereas the less frequent alleles are the result of processes such as insertion-deletion of bases and/or replication slippage (Deka et al. 1992a). However, this model can not be extended to all VNTR systems, as modal alleles are not conserved as for instance in locus D17S5 (Deka et al. 1992b).

In this sense, the HUMTH01 allele distribution, does not show shared modal alleles. The most frequent alleles in Caucasians are 6 and 9.3, while in Asians they are 7 and 9, and 7 in Blacks. Moreover, the allele distributions in the different racial groups, also show inversions of the frequencies, as is the case of the modal allele in Caucasians, which displays low frequencies in Asians and Blacks, while the model allele in Asians shows low frequencies in Caucasians and Blacks. In the case of HUMVWA31A, all Caucasian populations, Finnish included, have allele 17 as the most frequent one, while the in US Black population allele 16 is the modal one. However, in HUMFES/FPS, all 3 racial groups analysed (Caucasians, Blacks and Asians) possess the same modal allele (allele 11), although Asians characteristically have a higher frequency of allele 13 and a lower frequency of allele 10, and Blacks show a higher frequency of allele 8. Sequencing of alleles, the study of mutation rates and the analysis of microsatellite DNA in more human and primate populations would allow the ancestral state and the evolutionary dynamics of these loci to be explored. In this way, it could be possible to identify the mechanisms involved in the development of the polymorphism and in the generation of allele frequency distributions through the study of their evolutionary lineages (Gray and Jeffreys 1991).

With the aim to further analyse the mechanisms that generate variability in these systems, the observed data were compared to the expectations that follow from the neutral mutation theory (Chakraborty and Daiger 1991), (which assumes a single, homogeneous population), checking whether the observed number of alleles is greater than the expected values for the SMM and the IAM. The number of observed alleles in all 3 loci analysed was always inferior to that expected under the IAM, but showed a better fit to SMM. There may exist some additional allele differences not detectable electrophoretically, but as no sequencing of the samples has been performed in this study, we cannot assess the extent of this polymorphism. Despite this limitation, the current analysis is not inconsistent with the SMM, as this model includes the hidden variation (Deka et al. 1991).

This apparently indicates that the degree of divergence among the populations from the different regions constituting the current population of the Basque Country is at least very reduced with regard to these systems.

HUMFES/FPS shows the greatest departure from the expected value under SMM, but this can be decreased, considering that, of the 7 observed alleles, one is a singleton (allele 10.3) which could reduce the observed number of alleles to 6. This could indicate that the mechanism involved in the generation of variability, at least for these 3 STR loci, might be a replication, slippage rather than sister chromatid exchange. This could show a better fit for a VNTR system, where due to their longer alleles, greater variations are more probable, and a reversion to a pre-existing allele size seems to be improbable.

On the other hand, an excess of the expectations from the neutral theory in the number of alleles, could be due to a) a bottleneck effect during the recent evolution of the population, b) to selection or c) to a hidden substructuring (Chakroborty and Daiger 1991). As mentioned above, the biological history of the population studied here, seems to indicate that it has not passed through any recent bottleneck. Also, the loci studied do not seem to have any selective advantage or disadvantage, so any possible deviation from the proposed model could be a sign of population substructuring due to the recent gene flow coming from other populations in the Iberian Peninsula.

Therefore, the fit to the proposed model, along with the independence of alleles across loci, appear to indicate that there is no detectable population heterogeneity. In this sense, the lack of singificant differences in HUMVWA31A to a population composed of people living in Andalucia (southern Spain) (Lorente et al. 1994), is consistent with this point. The analysis of more population groups from areas such as Castilla, Leon and Galicia, would be of great help to check the validity of this hypothesis.

As is expected from the comparison of the allele frequency distributions of Caucasian populations, PEX and ID values obtained in the 3 loci analysed, are very similar. Therefore, the highly informative characteristics of these loci, apart from their concordance to Hardy-Weinberg equilibrium, as well as the conservation of the allele frequencies in diverse Caucasian populations, indicate the suitability of these loci as a powerful DNA typing technique and the interest of their generalized application to medico-legal casework.

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