Am. J. Hum. Genet. 58:1309–1322, 1996

The Genetic Relationship between the Finns and the Finnish Saami (Lapps): Analysis of Nuclear DNA and mtDNA

Päivi Lahermo,[1] Antti Sajantila,[3,4,*] Pertti Sistonen,[6] Matti Lukka,[5] Pertti Aula,[1] Leena Peltonen,[4] and Marja-Liisa Savontaus[1,2]

Departments of [1]Medical Genetics and [2]Genetics, University of Turku, Turku, Finland; [3]Institute of Zoology, Ludwig Maximilians University, Munich; Departments of [4]Human Molecular Genetics and [5]Immunobiology, National Public Health Institute, and [6]Finnish Red Cross Blood Transfusion Service, Helsinki

Summary

The genetic relationships between two Finno-Ugric–speaking populations, the Finns and the Finnish Saami (Lapps), were studied by using PCR for six nuclear-DNA marker loci, mitochondrial restriction-site polymorphism, and sequence variation of a 360-bp segment of the mitochondrial control region. The allele frequencies of each of the nuclear-DNA marker loci and the frequencies of mtDNA restriction haplotypes were significantly different between the populations. The Saami showed exceptionally low variation in their mtDNA restriction sites. The 9-bp deletion common in East Asian populations was not observed, nor did the haplotype data fit into the haplogroup categorization of Torroni et al. The average number of nucleotide substitutions from the mtDNA haplotype data indicated that the Finnish Saami may be closer to the Finns than to the other reference populations, whereas nuclear DNA suggested that the Finns are more closely related to the European reference populations than to the Finnish Saami. The similarity of the Finns to the other Europeans was even more pronounced according to the sequence data. We were unable to distinguish between the Finns and either the Swiss or Sardinian reference populations, whereas the Finnish Saami clearly stood apart. The Finnish Saami are distinct from other Circumarctic populations, although two of the lineages found among the Saami showed closer relationship to the Circumarctic than to the European lineages. The sequence data indicated an exceptionally high divergence for the Saami mtDNA control lineages. The distribution of the pairwise nucleotide differences in the Saami suggested that this population has not experienced an expansion similar to what was indicated for the Finns and the reference populations.

Received December 21, 1994; accepted for publication March 11, 1996.

Address for correspondence and reprints: Dr. Päivi Lahermo, Department of Medical Genetics, University of Turku, Kiinamyllynkatu 10, FIN-20520 Turku, Finland. E-mail: pailah@utu.fi

*Present address: Department of Forensic Medicine, University of Helsinki, Helsinki.

© 1996 by The American Society of Human Genetics. All rights reserved.

0002-9297/96/5806-0025$02.00

Introduction

The present Saami population inhabits the circumpolar regions of Finland, Sweden, Norway, and Russia (fig. 1), totaling 50,000–80,000 individuals, ~6,000 of whom live in Finland (Lehtivirta and Seurujärvi-Kari 1991). There are ~5 million Finns living in today's Finland.

The oldest archaeological evidence of settlement in Finland dates back to ~9,000 years ago. The origin of these people is not known. The displacement of the Saami to the north, under pressure by agricultural Finns, appears to have been slow and to have extended over the past 3,000–4,000 years (Eriksson 1988).

The Finnish and Saami (Lappish) languages, together with, for example, Hungarian and Estonian, belong to the Uralic language group, more specifically to the Finno-Ugric languages (Ruhlen 1987). The Uralic languages constitute a major non–Indo-European language group inside Europe. However, the genetic relationships of the speakers of the Uralic languages to the surrounding populations, as well as the mutual genetic relationships of the Uralic speakers, are not well understood. The present work is a detailed analysis of the genetic relationship between two Finno-Ugric speaker populations living in Finland: the Finns and the Finnish Saami.

The Finns and the Saami speak related languages, occupy partly overlapping areas of habitation, and may share a partially common history. On the other hand, fundamental differences in culture and livelihood have separated them over the past millennia. The origin of the Saami people is not known. It has been suggested that they may be an old European population, whose ancestors survived the last glacial period on the coasts of Scandinavia (Eriksson 1988; Sajantila et al. 1995). Alternatively, they might be descended from different small populations that migrated up to the north, at least some of whom had unique gene frequencies (Eriksson 1988). Thus their relationships not only to their linguistic cousins the Finns but also to the present-day Circumarctic populations are of particular interest.

Knowledge of the origins of the Finnish and Saami gene pool is based mainly on several studies of polymor-

Figure 1 Map of approximate principal area inhabited by the Saami (*shaded*).

phic protein and blood-group markers (Nevanlinna 1972; Eriksson 1973, 1988; Sistonen 1984). The Finnish population structure is characterized by homogeneity, a limited number of "founders," slow settlement and population growth, and isolation even during historical times (Nevanlinna 1972). However, strong evidence exists that there is in the Finns a gene admixture from Baltic peoples (Estonians, Lithuanians, and Latvians) (Sistonen 1984). The Saami seem to deviate markedly from their surrounding populations, including the Finns, in many genetic characteristics (Eriksson 1973). According to Eriksson, however, there is considerable Saami admixture in the Finns, as well as Finnish admixture in the Saami. Furthermore, on the basis of calculations made with polymorphic blood-group and protein marker frequencies, the genetic distance between the Saami and the Finns is shorter than the distances between the Saami and any of 26 other European populations. On the other hand, the Finns seem to be more closely related to some other European populations than to the Saami. Nevertheless, both of these populations have been termed as "outlying" in the picture of genetic relationships in Europe (Cavalli-Sforza and Piazza 1993). Classical polymorphisms suggest that the Saami represent a genetic admixture in which European genes predominate, whereas genes shared with peoples from the Uralic region may constitute 20%–50% (Guglielmino et al. 1990).

In recent years both nuclear-DNA and mtDNA analyses have been used increasingly in population genetic studies. It is known that the human genome is enriched with highly variable minisatellite loci (Jeffreys et al. 1985) and microsatellite loci (Litt and Luty 1989; Weber and May 1989). The high degree of polymorphism and the high heterozygosity rate that result in enhanced informativity make these loci suitable for population genetics (Edwards et al. 1992). On the other hand, the rapid accumulation of mutations (Brown et al. 1979), as well as maternal inheritance (Giles et al. 1980; Hauswirth and Laipis 1986), make mtDNA an excellent tool for the reconstruction of population history by use of maternal lineages (e.g., see Johnson et al. 1983; Cann et al. 1984; Torroni et al. 1993*a*, 1993*b*) and for estimating the degree of mtDNA diversity within populations (Horai and Matsunaga 1986).

The lack of recombination in mtDNA makes it possible to follow maternal lineages without the ambiguity caused by recombination, mutation being the only source of variation, whereas in nuclear genes the maternal and paternal genetic material is mixed in every generation. Thus mtDNA variation may be capable of demonstrating older population history than can nuclear variation. Since microsatellite loci and mtDNA polymorphism may give different perspectives on the evolution of present-day populations, we have used both these methods here to explore the genetic relationship between the Finns and the Finnish Saami, as well as their relationship to other populations.

Material and Methods

DNA Samples

DNA samples of 125 Finns were obtained for the mini- and microsatellite study, through routine paternity cases analyzed at the National Public Health Institute, Helsinki. mtDNA samples of 32 maternally unrelated individuals from different parts of Finland, representing the general Finnish population, were used in the sequencing of the control region. These individuals constituted part of the population sample ($n = 112$) in a study by Vilkki et al. (1988). The population sample of 129 unrelated Saami from eastern parts of Finnish Lapland were obtained from the local public health–care center. DNA either was extracted from the blood samples by using the Chelex-resin method (Walsh et al. 1991), as described by Sajantila et al. (1992*a*), or was purified by using the organic extraction method, as described by Vilkki et al. (1988).

Analysis of the Mini- and Microsatellite Loci

Four minisatellite loci and two microsatellite loci were analyzed. The minisatellite loci were D1S80 (MCT118) (Kasai et al. 1990), D17S30 (YNZ22) (Horn et al. 1989), hypervariable regions close to the 3′ end of the apolipoprotein B gene (APOB) (Boerwinkle et al. 1989), and the collagen 2A1 gene (COL2AI) (Wu et al. 1990). The microsatellite loci were tetranucleotide repeats located in intron 40 of the human von Willebrandt factor gene (VWA; F8VWF) (Kimpton et al. 1992) and in in-

tron 1 of the human tyroxine hydroxylase gene (TH) (Edwards et al. 1991).

PCR amplification.—PCR (Saiki et al. 1985) was carried out in a programmable heat block (MJ Research) by using 20 nmol of each dNTP, 100 pmol of each primer, 2.5 units of *Taq* DNA polymerase (Promega Biotech) in 100 μl of 50 mM Tris-HCl, pH 8.8, 15 mM $(NH_4)_2SO_4$, 1.5 mM $MgCl_2$, 0.1% Triton X-100, 0.01% gelatin. Aliquots of either 1–5 μl of Chelex resin-extracted DNA or 1–20 ng of DNA from organic extracts were used for PCR. Prior to the first cycle, a "hot start" (Chou et al. 1992) was performed by initially heating the samples to 95°C for 5 min and then adding the *Taq* DNA polymerase when the components of the PCR were at ~80°C. The PCR temperature-time profiles for mini-/microsatellite loci were as described in the literature. An additional 10-min incubation was performed at 72°C after the last cycle.

Analysis of the amplified microsatellite alleles.—The amplified microsatellite alleles were resolved by discontinuous PAGE, by using a LKB 2001 vertical electrophoresis unit as described by Sajantila and Lukka (1993). In brief, the composition of the 12 × 14 × 0.075-cm separation gels varied from 6% T to 10% T and from 1.6% C to 4.8% C, depending on the locus. The composition of the 4-cm-long stacking gel was 3% T, and the cross-linker concentration was the same as that in the separation gel. The gel buffer contained 7% glycerol and 33 mM Trizma-sulfate, pH 4.5, and the electrophoresis buffer was 90 mM Tris, 90 mM boric acid, 2 mM EDTA, pH 9.0. Aliquots of 10–15 μl of the PCR product with 1 μl of the loading buffer (20% sucrose, 12.5% Ficoll, 0.2% bromophenol blue) were applied to the gel. Electrophoresis was performed for 3–5 h at 200 V. In each gel, several locus-specific allele ladders, constructed by amplifying a mixture of DNA from individuals with known alleles in the Finnish population (Sajantila et al. 1992*b*), was run adjacent to the samples. The silver-staining procedure was modified from that of Allen et al. (1989) and is described in detail elsewhere (Sajantila et al. 1992*a*).

Restriction-Site Analysis of mtDNA

PCR amplification and restriction-site analysis.— The mtDNA of each sample was amplified in nine partially overlapping segments by using the primers published by Torroni et al. (1992). PCR was performed in a programmable heat block (MJ Research) in a total volume of 100 μl by using 20 nmol of each dNTP, 50 pmol of each primer, 1.5 units of DynaZyme DNA polymerase (Finnzymes) in 1 × DynaZyme buffer containing 10 mM Tris-HCl pH 8.8, 1.5 mM $MgCl_2$, 50 mM KCl, 0.1% Triton X-100. Approximately 100 ng of total DNA was used for the PCR. Each reaction consisted of 30 cycles, unless otherwise indicated. An additional incubation, of 4 min at 94°C at the beginning of each reaction and of 5 min at 72°C at the end of each reaction, was performed.

Each of the amplified mtDNA regions was analyzed by using the restriction enzymes *Ava*II, *Bam*HI, *Hae*II, *Hinc*II/*Hind*II, *Hpa*I, and *Msp*I, one at a time, to reveal restriction-site polymorphism in the amplified product. The samples were further analyzed to determine the haplogroups A–D, described by Torroni et al. (1992), by using the enzymes *Alu*I, *Dde*I, and *Hae*III. Fragments 2, 6, and 7 were digested with enzyme *Alu*I to detect the site loss at nt 5176 (Anderson et al. 1981) and the site gains at nt 10397 and nt 13262. Also, fragment 6 was digested with *Dde*I to detect the site gain at nt 10394, and fragment 9 was digested with *Hae*III to detect the site gains at nt 663 and nt 16517. Restriction-enzyme digestions were performed in accordance with the manufacturer's recommendations, with use of reagents supplied by New England Biolabs. After digestion, the products were run on agarose gel electrophoresis using 0.8% or 1.5% Sea Kem LE-agarose or 1% Sea Kem LE + 1% NuSieve agarose, 0.5 mg ethidium bromide/ml, 1 × Tris-borate EDTA buffer, according to the expected fragment size. Boehringer Mannheim DNA molecular-weight marker VI was used as the fragment-size standard. The DNA fragments were visualized under UV light. The results were recorded on Polaroid 667 ISO 3000/36° film. In ambiguous cases a further sequencing was performed, to determine the exact nature of the polymorphism.

Haplotype determination.—The mtDNA haplotypes and morphs were named according to the protocol of Vilkki et al. (1988), by using the data obtained with restriction enzymes *Ava*II, *Bam*HI, *Hae*II, *Hinc*II/*Hin*dII, *Hpa*I, and *Msp*I. The data obtained by using *Alu*I, *Dde*I, and *Hae*III were not included in this haplotype analysis.

Sequence Analysis of mtDNA

A 404-bp segment of the hypervariable region I (HV-I) (Vigilant et al. 1989) of mitochondrial control region was amplified for 35 cycles by using the primers L15997 and H16401 (Ward et al. 1991). After purification with Qiaquick PCR spin columns, the first 360 nt (nt 16024–16383) of the hypervariable region were directly sequenced by using the Sanger dideoxy chain–termination method (Sanger et al. 1977). The use of all reagents was as recommended by the manufacturer (United States Biochemicals). The primers for sequencing were the same as those used for the PCR. The DNA was labeled with α-35^S-dATP (Amersham). Electrophoresis was performed by using IBI Base Runner for 2–5 h at 45°C (60 W), with use of a 6% polyacrylamide gel with 7 M urea in 90 mM Tris, 90 mM boric acid, 2 mM EDTA, pH 9.0. The results were visualized after 16–72 h autoradiography on X-ray film (Fuji Medical X-ray film).

Detection of the 9-bp Deletion

To determine the presence or absence of the 9-bp deletion of a tandem repeat at nt 8272–8289 in the intergenic region between the genes for COII and $tRNA^{Lys}$ (Cann and Wilson 1983; Wrischnik et al. 1987), a 121-bp segment between nt 8196 and nt 8316 was amplified for 35 cycles under the conditions described by Wrischnik et al. (1987). The PCR product was then run on Mini Protean 7 × 10 cm 6% polyacrylamide gel in 90 mM Tris, 90 mM boric acid, 2 mM EDTA, pH 9.0, at 200 V for ~30 min and was visualized by silver staining as recommended by the reagent supplier (Bio-Rad). Four microliters of DNA and 1 μl of loading buffer (25% Ficoll, 0.25% bromophenol blue) were applied to the gel. The size of the PCR product was compared with a fragment-size standard (Stratagene φX174/*Hin*fI DNA marker), and, if the product was of a length other than the predicted 121 bp, the fragment was sequenced as described above, to specify the nature of the difference in length.

Statistical Evaluation

Evaluation of the Hardy-Weinberg equilibrium for nuclear-DNA markers was based on comparisons of observed and expected heterozygotes and homozygotes by using the χ^2 test and G-test (Bishop et al. 1989) and the likelihood-ratio test ($-2\ln L_0/L_1$ statistic) based on genotype permutation (Deka et al. 1991). However, since all these tests gave essentially identical results, the G-test was selected for presentation. Comparison of the allele frequencies between the populations was performed by using χ^2 tests of R×C contingency tables with a correction for multiple testing. Genetic distances for marker-frequency data were computed by using Nei's standard distances with a correction for the sampling size (Nei 1978). Unbiased heterozygosity (H) was calculated as described by Edwards et al. (1992). Polymorphism and variance of between- and within-population mtDNA sequences consisting of restriction-site data were estimated according to the method of Nei and Miller (1990).

mtDNA data was used to calculate intra- and interpopulation mean pairwise sequence differences and genetic distances and to create phylogenetic trees of mitochondrial lineages, on the basis of the neighbor-joining algorithm implemented in the NEIGHBOR program of the PHYLIP 3.5 program package (Felsenstein 1993). The genetic distances for the tree programs were computed by using program DNADIST with a correction for the transition:transversion ratio bias of 20:1. The original sequence data were bootstrapped, and either the genetic distances were used directly in the tree building or the between population means were estimated by using the program NEIREP (courtesy of Dr. Lynn B. Jorde) before the tree construction. The divergence-time estimates from the mean pairwise sequence differences were based on the time scale given by Shields et al. (1993), 1% sequence divergence corresponding to 8,950 years. In the estimation of the compound parameter θ ($2\mu N_e$, twice the mutation rates in the effective population size of breeding females), the formula given by Ward et al. (1991) was used.

Results

Nuclear-DNA Markers

The allele distribution for the six mini-/microsatellite loci in the general Finnish and the Finnish Saami population samples are given in table 1. There were no statistically significant differences between the observed and expected heterozygosities for any of the six nuclear-DNA loci (P values varied between .12 and .88). The tests for Hardy-Weinberg equilibrium indicated that both the Finnish and the Finnish Saami populations are in equilibrium (panmictic) for the markers tested. However, for each of the six nuclear-DNA marker loci a statistically significant difference between the Finns and the Finnish Saami was observed. The differences were highly significant for five of the marker loci (D1S80, D17S30, APOB, F8VWF, and COL2A1) and were significant for TH. The mean H values were .78, and .75 for the Finns and the Finnish Saami, respectively, and were not significantly different.

mtDNA Restriction-Site Analysis

The frequencies of Saami mtDNA haplotypes are given in table 2, together with those of the Finnish haplotypes according to Vilkki et al. (1988). For comparison, the frequencies of selected haplotypes (of 76 haplotypes presented in the papers referred to in table 2) in several other populations are given. The "heterozygosity" value was extremely low among the Saami (H = .12). Only four haplotypes were found among them, one of these being haplotype 1, which is predominant in most of the human populations studied so far (e.g., see Vilkki et al. 1988). This haplotype was more common in the Saami than in the majority of populations studied. Besides haplotype 1, only haplotype 38S was shared between the Finns and the Finnish Saami. This haplotype is defined by a T→C transition at nt 4336, creating a new *Ava*II restriction site and the morph *Ava*II-15S. We sequenced the samples carrying haplotype 38 in the population reported by Vilkki et al. (1988) and found them to be 38S. Haplotype 38, published earlier, has a morph, *Ava*II-15, resulting from a new restriction site at approximately nt 4280 (Bonné-Tamir et al. 1986) or at either nt 4311 or nt 4336 (Sartoris et al. 1988). Two other new haplotypes, numbered here as "158" and "159," were also found. The morphs *Hpa*I-4 and *Hinc*II-3 of haplotype 158 have previously been found in Orientals

Table 1

Frequencies of Six Nuclear-DNA Marker Loci in Finns and Finnish Saami Each Consisting of 125 Samples

Haplotype	Finns	Saami
D1S80:		
18	.27	.20
19	.02	.01
20	.03	.04
21	.02	.06
22	.00	.00
23	.01	.00
24	.36	.24
25	.09	.11
26	.01	.00
27	.00	.00
28	.08	.08
29	.02	.00
30	.00	.00
31	.05	.24
32	.02	.02
>32	.01	.00
Statistical Data		
HWE G^{2} [a]	2.31	2.42
P	.13	.12
H [b]	.78	.82
Finns vs. Saami:		
χ^2	42.85	
df	7	
P	<.001	

Haplotype	Finns	Saami
D17S30:		
1	.03	.05
2	.19	.16
3	.19	.13
4	.28	.12
5	.02	.00
6	.04	.22
7	.00	.01
8	.02	.04
9	.06	.03
10	.08	.22
11	.00	.00
12	.03	.00
13	.00	.00
>13	.04	.02
Statistical Data		
HWE G^{2} [a]	1.89	1.07
P	.17	.30
H [b]	.83	.85
Finns vs. Saami:		
χ^2	82.09	
df	8	
P	<.001	

Haplotype	Finns	Saami
APOB:		
28	.00	.00
30	.06	.03
31	.02	.02
32	.06	.01
34	.29	.48
35	.01	.00
36	.30	.33
37	.01	.00
38	.01	.00
40	.00	.00
42	.06	.02
44	.02	.00
46	.04	.05
47	.01	.00
48	.09	.06
50	.00	.00
>50	.01	.00
Statistical Data		
HWE G^{2} [a]	.02	.38
P	.88	.54
H [b]	.81	.66
Finns vs. Saami:		
χ^2	28.7	
df	6	
P	<.001	

Haplotype	Finns	Saami
F8VWF:		
14	.11	.06
15	.08	.08
16	.18	.04
17	.28	.42
18	.20	.16
19	.11	.21
20	.03	.02
21	.00	.00
>21	.00	.00
Statistical Data		
HWE G^{2} [a]	2.12	.25
P	.15	.62
H [b]	.82	.74
Finns vs. Saami:		
χ^2	43.32	
df	6	
P	<.001	

Haplotype	Finns	Saami
TH:		
6	.20	.19
7	.25	.14
8	.15	.14
9	.13	.11
10	.26	.42
Statistical Data		
HWE G^{2} [a]	1.69	1.00
P	.19	.32
H [b]	.79	.74
Finns vs. Saami:		
χ^2	17.5	
df	4	
P	.02	

Haplotype	Finns	Saami
COL2A1:		
10	.00	.00
11	.10	.20
14	.00	.00
15	.00	.00
19	.50	.52
20	.06	.14
23	.29	.12
26	.03	.02
32	.00	.00
Statistical Data		
HWE G^{2} [a]	.62	.14
P	.43	.71
H [b]	.65	.66
Finns vs. Saami:		
χ^2	34.51	
df	3	
P	<.001	

[a] Hardy-Weinberg equilibrium tested by G^2 statistics given by Bishop et al. (1989).
[b] Evaluated as by Edwards et al. (1992).

Table 2

mtDNA Haplotypes in Finns and Finnish Saami, with Published Data on Major Population Groups Shown for Comparison

	Frequency[b] (%)				
Haplotype[a]	Finns (n = 112)[c]	Saami (n = 129)	European (n = 537)[d]	Oriental (n = 334)[e]	African (n = 260)[f]
1 (2-1-1-1-1-2)	77.7	93.8	63.3	73.4	20.0
6 (2-1-2-1-1-2)	1.8	...	7.4	.6	...
11 (2-2-3-1-5-2)	3.6	...	1.7	.3	...
18 (2-3-1-4-9-2)	2.7	...	9.1	.6	...
21 (2-1-1-1-2-2)	7.1	...	2.4	...	...
38S (2-1-1-1-15^{Fin}-2)	1.8	.8	...	...	...
47/55 (2-1-1-1-3-2)	1.8	...	2.0	.6	...
63 (2-2-12-1-5-2)	.9	...	...	...	.4
64 (2-1-1-4-13-2)	.9	...	...	...	.8
65 (2-1-1-1-1-15)	1.8	...	...	...	...
158 (4-1-1-1-1-3)	...	4.7	...	...	...
159 (2-1-1-1-12^{Jap}-2)	...	.8	...	...	...
Other	...	...	14.1	24.5	78.8
H^g	.39	.12	.58	.46	.81

[a] *Hpa*I-*Bam*HI-*Hae*II-*Msp*I-*Ava*II-*Hinc*II; only haplotypes found in Finns and Finnish Saami are shown.
[b] Computation includes 73 five-enzyme haplotypes at least one of which is observed in one of the populations.
[c] Source: Vilkki et al. (1988).
[d] Sources: Johnson et al. (1983), Bonné-Tamir et al. (1986), Santachiara-Benerecetti et al. (1988), De Benedictis et al. (1989), and Semino et al. (1989). Data are for two to four haplotypes, without *Hinc*II.
[e] Sources: Johnson et al. (1983), Brega et al. (1986), and Harihara et al. (1986, 1988). Data are for two to four haplotypes, without *Hinc*II.
[f] Sources: Johnson et al. (1983) and Scozzari et al. (1988). Data are for two to four haplotypes, without *Hinc*II.
[g] H here equals the adjusted probability of finding two different mtDNA haplotypes.

(Denaro et al. 1981; Blanc et al. 1983), but not in the same combination of six enzymes. Similarly, the morph *Ava*II-12Jap of haplotype 159 has been previously reported in the Japanese, by Horai and Matsunaga (1986). An overall comparison of nucleotide diversity (see table 3) vis-à-vis European, African, and Oriental population samples indicated that the least variation of restriction sites exists among the Finnish Saami and the Finns.

The haplogroups A–D, characterized by specific mutations common to each haplotype in the haplogroup, have been used previously in reconstructing the peopling of the Americas (Torroni et al. 1992, 1993*b*). The polymorphisms defining the haplogroups A–C were not detected in the present study. The six Saami samples (4.7%) (table 4) belonging to haplotype 158 also harbored the *Alu*I site loss at nt 5176 defining the haplogroup D. Other "haplogroups" that lack the markers characterizing the haplogroups A–D are presented in table 4.

The genetic distances of the nuclear-DNA markers and the average numbers of net nucleotide substitutions between the mtDNA haplotypes are presented in table

Table 3

Average Number of Net Nucleotide Substitutions (Nei and Miller 1990) for mtDNA Restriction-Site Data; $d_A \times 100$ Estimated as $d_A = d_{xy} - (d_x + d_y)/2$ (above the Diagonal) and Genetic Distances for Six Nuclear-DNA Marker Loci (below the Diagonal) between Finns, Saami, and Three General Reference Populations, Where Available

	Saami	Finns	Caucasians[a]	Orientals	Africans
Saami	.09	6.03	10.03	7.32	32.54
Finns	10.41	.53	13.18	10.71	35.93
Caucasians[a]	4.96	11.34	1.08	14.63	39.20
Orientals	NA	NA	NA	.75	35.60
Africans	NA	NA	NA	NA	2.21

Note.—Entries on the diagonal are π values for mtDNA restriction-site data. NA = not available. For references on mtDNA haplotype data, see table 2.
[a] Sources: Edwards et al. (1992) (TH); Pena et al. (1994) (F8VWF); and Kádasi et al. (1994) (D1S80, D17S30, COL2A1, and APOB).

Table 4

Haplogroups Found in Finns and Finnish Saami

Haplogroup[a] and Mutation	Frequency (%)	
	Finns (n = 32)	Saami (n = 129)
D:		
−5176 *Alu*I	...	4.7
Others:		
+16517 *Hae*III	46.9	1.6
+10394 *Dde*I	3.1	5.4
+16517 *Hae*III/+10394 *Dde*I	25.0	.8
+16517*Hae*III/+10394 *Dde*I/ +10397 *Alu*I	...	1.6
None of the above mutations	25.0	86.0

[a] As designated by Torroni et al. (1992).

3. The restriction-site frequencies include data with five enzymes from the three larger population groups shown in table 2. The mtDNA haplotype data suggested that the Finnish Saami are closer to the Finns than to the other populations used for comparison. Both the Finnish Saami and the Finns show a closer relationship to the Oriental populations than to the Caucasians.

mtDNA Sequence Analysis

The sequence of the first 360 bp of the HV-I region of the mitochondrial control region was determined for 32 Finnish and 22 Saami individuals (table 5), revealing 22 and 12 lineages, respectively. These lineages were defined by 38 polymorphic nucleotide positions. Only 2 of these 34 lineages were shared between the Finns and the Saami (table 5), and only one was haploidentical. One of the shared lineages (S34/F34) is also found among other Europeans (Di Rienzo and Wilson 1991; Pult et al. 1994), whereas the other (S59/F127) has been reported both among Europeans (Di Rienzo and Wilson 1991; Pult et al. 1994) and among Circumarctic peoples (Shields et al. 1993). Eight other sequences (F1, F2, F11, F23, F25, F36, F98, and F135) found among the Finns have been found previously in other Europeans and in two in Asian populations (Di Rienzo and Wilson 1991; Stoneking et al. 1991; Pult et al. 1994). Two of the sequences also have been found in Circumarctic peoples (Shields et al. 1993). The remaining 21 sequences, as far as we know, have not been reported elswhere.

None of the Saami sequences but four (12.5%) of the Finnish samples were identical to the published human reference "Cambridge" sequence (Anderson et al. 1981). The number of transversions among the Saami was high, 3 transversions among a total of 25 different substitutions. In the Finns, 26 substitutions were observed; all were transitions.

The mean pairwise sequence differences and genetic distances of the Finns and Finnish Saami are presented in table 6. The corresponding values for five reference populations are given for comparison. Although fewer lineages were found in the Saami, the sequence differences were approximately two times as high as those in the Finns. The genetic distances between the Saami and the Finns were equal to the distances between the Saami and the two European reference populations. Furthermore, the genetic distances between the Finns and the European populations were insignificant.

The frequency distribution of within-population pairwise sequence differences in the Saami, the Finns, and the reference populations is presented in figure 2. The frequencies of pairwise sequence differences in the Saami deviate strikingly from the unimodal distribution shown both by the Finns and by the reference populations. According to Harpending et al. (1993), the type of within-population sequence-difference distribution observed in the Saami could be a result of an extended period during which the population size remained constant. On the other hand, the distributions in the other populations could indicate a population expansion during the past. The distribution of the within-population differences in the Saami has a major peak at the leading edge of the distribution, representing the most ancient population history. In each comparison the between-population distribution peak for the Saami tends to be shifted right with regard to the corresponding within-population peak of the other population. This could signify isolation of the Saami from the other populations compared. The distributions of within-population pairwise differences in the Finns and the Europeans coincide with each other and with between-population distribution, indicating that the expansion wave has probably occurred at the same time in these populations. In contrast, the between-population sequence-difference distribution in the Finns and the Circumarctic populations as compared with the within-population distributions leads the within-population distributions by several steps. This could be interpreted as indicating a time difference in the expansion waves for the two populations (Harpending et al. 1993), the expansion for the Circumarctic being more ancient than that for the Finns (or other Europeans).

A tree constructed from individual lineages (fig. 3) revealed two major Saami lineages that had very long branch lengths and that appeared to have the closest relationship to lineages representing the Circumarctic and Altai populations. These included the lineages S12 and S94, constituting 27% of the sequenced Saami samples. Although the statistical support for this relationship remained insufficient, it was further strengthened by the fact that the same samples belonged to haplotype 158 harboring the *Alu*I site loss that defines haplogroup

Table 5

Control-Region Sequence of 360 nt in 32 Finns and 22 Saami Representing All Haplotypes Observed

	Polymorphic Nucleotide Positions in Sequence (16024–16383)[a]				No. of Identical Sequences within Haplotype
	0111111111	1111122222	2222222222	23333333	
	6122344567	8888911223	5667799999	90135666	
	9469648362	2359267344	6010112456	84154026	
Cambridge	CCTGTTCGAT	AACTCATCTC	CCCCTCCCCC	TTTACCTC	
Finns (haplotype):					
F25 (1)	----------	----------	----------	--------	3
F1 (1)	----------	----------	----------	C-------	1
F127 (1) (boxed)	----------	----------	----------	-C------	1
F34 (1) (boxed)	----------	----------	----------	--C-----	1
F23 (1)	----------	----------	----------	----T---	1
F2 (1)	----------	----------	T--T------	--------	1
F24 (1)	T---------	----------	--T-------	--------	1
F35 (1)	-----C----	---C------	---T------	--------	1
F135 (6)	----------	--------C-	----------	--C-----	1
F93 (6)	----------	----T---C-	----------	--C-----	1
F126 (11)	---A------	-------T--	----------	--------	4
F90 (18)	--C-------	----------	----------	--------	1
F98 (18)	--C-------	----------	-------T-T	-C------	2
F51 (21)	----------	----------	----------	--------	1
F36 (21)	----------	-------T--	------T---	--------	2
F39 (21)	----------	-------T-T	------T---	--------	1
F11 (21)	----------	-------T--	------T-T-	--------	2
F74 (38S)	--------G-	----------	----------	-C------	1
F112 (38S)	----------	------C---	----------	-C------	1
F4 (47/55)	----------	----------	-----T----	--------	1
F72 (47/55)	T-C-------	----------	----------	-------T	1
F149 (63)	---A-----C	-------T--	----------	--C-----	1
F14 (65)	----------	-----G----	--T-------	C-------	2
Saami (haplotype):					
S34 (1) (boxed)	----------	----------	----------	--C-----	1
S5 (1)	-------A--	----------	----------	C-------	2
S11 (1)	----------	---C------	---T------	--------	1
S20 (1)	----------	-$\underline{C}$-C------	---T------	--------	1
S18 (1)	-----CT---	---C------	----------	--------	1
S3 (1)	-----CT---	---C------	---T------	--------	2
S1 (1)	-----CT---	---C------	---T------	---G----	5
S14 (1)	---A------	--T----TC-	-T--------	--------	1
S59 (38S) (boxed)	----------	----------	----------	-C------	1
S94 (158)	--C-------	$\underline{C}\underline{C}$-C---T--	----------	-----TC-	1
S12 (158)	--C-C-----	$\underline{C}\underline{C}$-C---T--	----------	-----TC-	5
S19 (159)	-$\underline{A}$--------	----T-----	T--TC--T--	--------	1

[a] Transversions are underlined; and sequences common to both populations are boxed.

D (Torroni et al. 1992). For the rest of the Saami lineages a more close relationship to the European lineages was likely.

Figure 4 represents a summary tree of the genetic distances of 320 DNA lineages in the seven populations analyzed. The tree indicates close relationship between the Finns and the two European reference populations; in contrast, the Finnish Saami represent outliers in this phylogenetic tree, whereas the Altai and Circumarctic populations consistently group together.

Analysis of the 9-bp Deletion

The COII/tRNA^{Lys} intergenic 9-bp deletion at nt 8272–8289 (Cann and Wilson 1983; Wrischnik et al. 1987), originally detected in East Asian populations and, later, also in Africa (Chen et al. 1994), was not

Table 6

Mean Pairwise Sequence Differences (above the Diagonal) and Corresponding Genetic Distances (100 × *D*; below the Diagonal) Within and Between Finnish Saami, Finns, and Five Reference Populations

	Saami	Finns	Swiss	Sardinian	Altai	Circumarctic	!Kung
	6.56	6.40	6.17	6.46	7.45	9.09	11.83
		3.80	3.77	4.08	5.04	7.05	10.44
Saami	1.87		3.63	3.96	5.10	7.22	10.28
Finns	.35	1.07		4.21	5.43	7.53	10.24
Swiss	.30	.02	1.02		5.51	6.61	11.62
Sardinian	.30	.02	.01	1.19		2.69	13.08
Altai	.41	.11	.15	.16	1.56		4.13
Circumarctic	1.28	1.08	1.16	1.16	.72	.76	
!Kung	1.88	1.86	1.84	1.74	1.97	2.80	1.17

NOTE.—The corresponding within-population figures are separated by a diagonal space. The between-population genetic distances were estimated as $D = D_{xy} - (D_x + D_y)/2$, where D_{xy}, D_x, and D_y are the average genetic distances between lineages and within populations x and y, respectively. For the reference populations, see references cited in figure 2. The total number of the lineages was 320.

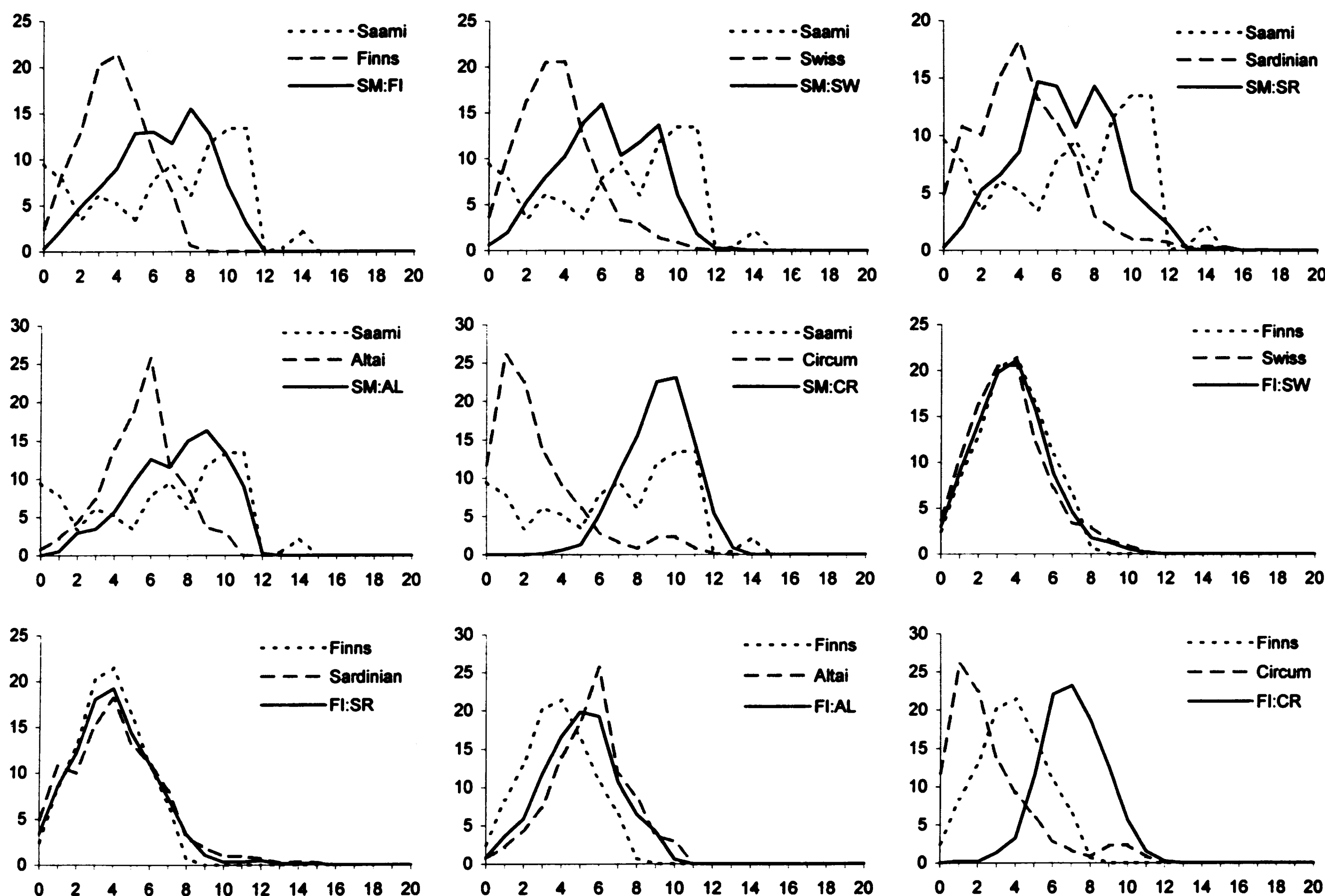

Figure 2 Frequency distribution of within-population (*broken lines*) and between-population (*unbroken line*) pairwise sequence differences in the Saami, Finns, and four reference populations: Swiss (Pult et al. 1994), Sardinian (Di Rienzo and Wilson 1991), Circumarctic (Shields et al. 1993), and Altai (Shields et al. 1993). The number of pairwise base differences is shown on the ordinate, and their relative occurrence (in %) is shown on the abscissa.

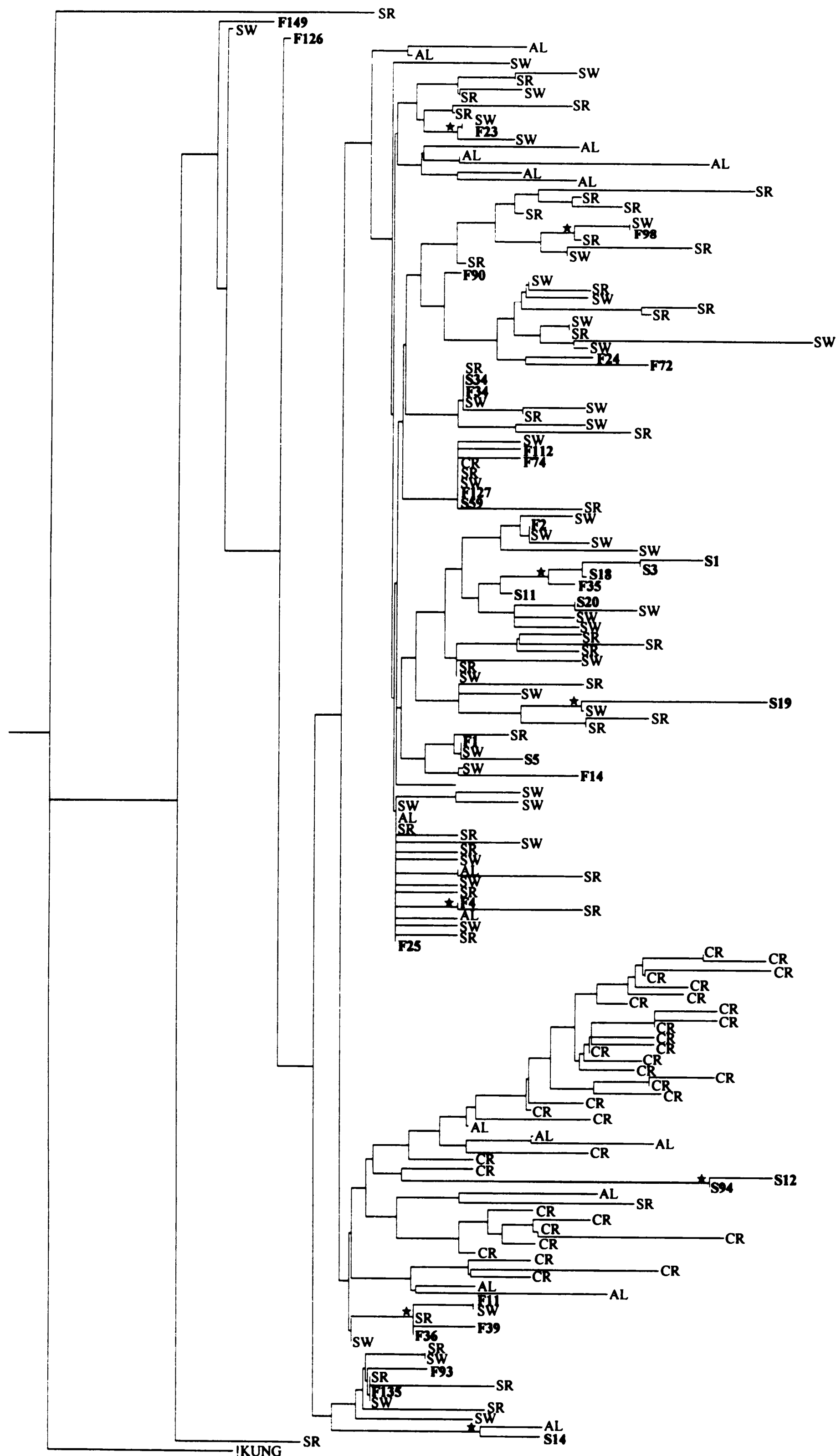

Figure 3 Phylogenetic neighbor-joining tree of 173 mtDNA lineages of six of the populations analyzed in this study. The tree was constructed by using the NEIGHBOR program (PHYLIP program package; Felsenstein 1993). A !Kung lineage (identified as lineage "1" in Vigilant et al. 1989) was used as an outgroup for the tree. The symbols at the tips of the tree denote populations as follows: SR = 46 Sardinian lineages (Di Rienzo and Wilson 1991); CR = Circumarctic populations (33 lineages; Shields et al. 1993); F = 22 Finnish lineages; SW = 44 Swiss lineages (Pult et al. 1994); AL = 16 Altai lineages (Shields et al. 1993); and S = 12 Finnish Saami lineages. The Finnish and Saami lineages, highlighted by boldface lettering, are identified. A star at the node indicates that the lineages including the Finns or the Saami to the right of the branching point were present (though not necessarily in the order given for the actual tree) in ⩾50% of trees constructed from 500 times bootstrapped data.

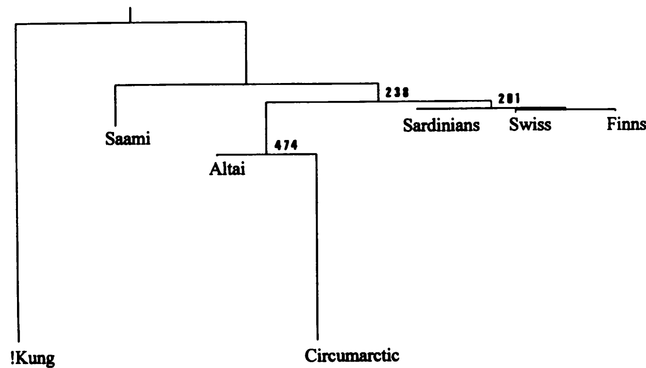

Figure 4 Phylogenetic neighbor-joining tree of mean genetic distances (table 6) between the Finns, the Finnish Saami, and the five reference populations. The figures at the branches of the tree indicate the times at which the structure below the point in the actual tree shown was obtained from 500 bootstrap replicates, by use of the majority-rule and strict-consensus-tree program. The tree was rooted to !Kung.

found in the present study. One Finnish individual had a 9-bp deletion at nt 8270–8278, partially overlapping the region in question. This deletion has not been reported elsewhere.

Discussion

PCR for nuclear mini-/microsatellites, mtDNA haplotyping, and mtDNA sequencing have not been previously used in the same study in human population genetics. Here these three different types of polymorphisms were employed to elucidate the genetic background and relationship of the Finns and the Finnish Saami, in the light of their known population history. From the sequence data, four main conclusions emerge. First, the results do not indicate a close genetic relationship between the Finnish Saami and the Finns. Second, the Saami are genetically distinct from all other populations tested so far, which is in line with the results of earlier studies of nuclear markers. Third, the Finns seem to be genetically indistinguishable from the European reference populations, contradicting previous data on blood groups and other classical markers. Fourth, our results suggest that the Finnish Saami and Finns have divergent population histories.

Genetic distances calculated from mtDNA sequence data indicate that the Saami are genetically approximately equally separated from the Finnish, the other two European, and the Altai populations. The distances between the Saami and the other Circumarctic populations are three times as high. The high divergence and ensuing long branch lengths of the Saami lineages suggest a very ancient coalescence (fig. 3). On the other hand, it also could be interpreted as a result of admixture (e.g., of the lineages S94 and S12) with the long branch lengths, indicating that the event must be far in the past. The lineages closer to the European ones may represent admixture between the Saami and surrounding (most likely Finnish) populations. Again, a rather long divergence time is indicated for some of those lineages (lineages S19 and S1 in the well-supported group including S3, S18, and the Finnish lineage F35). On the contrary, the Finns seem to be closely related to the two European populations, suggesting that these populations have a common primary gene pool. This is in disagreement with earlier results, based on classical marker data, according to which both the Finns and Finnish Saami (and also the Sardinians) are distinct outliers, the Finns being the closest relatives of the Saami (Cavalli-Sforza and Piazza 1993).

The disagreement between earlier, classical marker data and our mtDNA sequence data may be explained by several factors, including the different patterns of inheritance. mtDNA sequence variation may reflect more reliably a deep time perspective less confounded by the factors affecting the gene frequencies of classical markers. mtDNA lacks recombination, and, thus, old maternal lineages are preserved through generations, mutation and admixture being the only sources of new variation, whereas, in nuclear DNA, maternal and paternal DNA are mixed in every generation. Also, selection may affect these types of DNA polymorphisms differently, especially selection of polymorphic marker systems that apply to polymorphisms based on the classical marker frequencies. Furthermore, it is likely that the infinite-allele model most often assumed introduces some bias when marker frequencies are considered (i.e., the presumed allelic identity may not hold). The difference between the results of mtDNA haplotypes and sequence analyses may be due to the different resolution power of the methods. It is likely that more than five enzymes (available for comparison here) should be used in the haplotype analysis, to obtain reliable results.

Distributions of pairwise differences (fig. 3) suggest that the Finns and the Finnish Saami have different population histories. The pairwise differences in the Finns as well as in the two European populations could indicate a population expansion—for example, the spread of Neolithic farmers to Europe some 40,000 years ago (Harpending et al. 1993). On the other hand, the pairwise differences in the Saami deviate drastically. Since the Saami do not show a unimodal pattern, and since comparison shows a consistent tendency for the difference distribution between the Saami and the reference populations to be shifted to the right vis-à-vis the within-difference distributions, the Saami might have a long history of being independent from the other European populations. Furthermore, the distribution in the Saami does not indicate a bottleneck effect with a following period of exponential growth in the population's size.

The formula given by Ward et al. (1991) can be used for estimation of the compound parameter θ, the product of effective population size and mutation rate ($2\mu N_e$ for haploid inheritance). In fact, sequence data should be ideal for this kind of estimation, since each ancestor lineage can be considered to consist of a single independently evolving population. The sequence data from the Saami samples resulted in a θ value of 10.0, whereas that for the Finns gave an estimated θ value of 29.8. Given a generation length of 25 years and the mutation rate of 1% in 8,950 years ($\mu = 1.4 \times 10^{-5}$; Shields et al. 1993), this would result in an effective female population size of 1,000 for the Saami (12 lineages; total census size 50,000–80,000 and, for the Finnish Saami, ~6,000) and 3,000 for the Finns (22 lineages; census size ~5 million). The estimates are on the low side when compared with the total census sizes (the estimate should be approximately one-sixth of this). Such a deviation could be due either to several reasons violating the basic equilibrium assumptions used (constant population size, panmixia, no admixture, etc.), a sampling error (e.g., lineages are not presented in correct proportion to the sampling size), or both. The Finns, and particularly the Saami, have shown a strong tendency to much smaller geographical breeding isolates (see Nevanlinna 1972; Eriksson 1988) than the total extent of their inhabited area, which has led to discontinuities in their population structure and to microdifferentiation and, consequently, to violation of at least the panmixia rule.

The Finnish Saami inhabit Arctic regions, and there is some evidence of remote genetic relationship with the other Circumarctic populations. This conclusion is to some extent supported by the restriction-site data (table 3), and the findings of haplotype and sequence analysis lend some evidence in favor of the interpretation. One of the Finnish Saami mtDNA haplotypes, excluding type 1, has been found in the other Circumarctic peoples. This is haplotype 158, which forms part of haplotype 28 which has been found in the Evenks (Torroni et al. 1993*b*). The same haplotype also has been found in Native Americans (Torroni et al. 1993*a*). The sequences associated with this haplotype also showed a relationship, although a remote one, to the Circumarctic lineages used in comparison.

The Finns and the Finnish Saami do not fit well into the A–D haplogroup categorization of Torroni et al. (1992), haplotypes that are predominant in Native Americans but also in Siberian populations (Torroni et al. 1993*b*). Neither did the Finnish Saami, Finns, Europeans, or the Circumarctic populations have the 9-bp deletion (Shields et al. 1993), common in East Asian populations and also among Native Americans.

According to Torroni et al. (1994), the majority of Caucasians can be classified into four (H–K) mtDNA haplogroups defined by mutations that are rarely seen in Africans and Orientals. The mutations characterizing these four groups were not screened in the present study. However, on the basis of our earlier study (Vilkki et al. 1988) 4.5% of the Finnish population sample belonged to one of the Caucasian haplogroups (haplogroup I) (Torroni et al. 1994).

Heterozygosity values obtained by using nuclear markers do not deviate much between the Finns and the Finnish Saami (table 1), even though the populations do have markedly different allele frequencies. Very likely the similar heterozygosities could be due to the high mutation rate for the repeat DNA marker loci, implying reduced resolving power in studies of population ancestry. On the other hand, the "heterozygosity" value for mtDNA haplotypes in the Saami ($H = .12$; degree of within-population mtDNA diversity (π) = .09 ± .08) indicates even less variation than in the Finns ($H = .39$; $\pi = .53 \pm .45$), a population also very homogeneous compared with other major population groups ($H = .46 - 0.81$; $\pi = [.75 \pm .32] - [2.21 \pm 1.27]$). Deviations between these values obtained by using the nuclear marker data versus mtDNA restriction-site polymorphisms may indicate selection or differences in the population history of males and females or merely may reflect the chance effects that are due to small population size and that are exacerbated by haploid inheritance restricted to one sex.

To conclude, our data show a considerable difference between the genetic background of the Finns and that of the Finnish Saami. On the basis of genetic distances for our marker data, the Saami are not closely related to their linguistic or geographical neighbors. Considering their common historical and linguistic background with the Finns, the degree of admixture is surprisingly low. The two populations seem to have a separate genetic background, the Finns being more closely related to the European populations. Thus far, no close genetic relations have been found for the Saami. In the light of the present data their population history and genetic background might be interpreted to conform to an early isolation from other populations in Europe, with an equally ancient admixture from the Circumarctic populations.

Acknowledgments

We wish to express our thanks to all our blood donors. We acknowledge the help of Lynn B. Jorde, who made his program NEIREP available to us. We are also indebted to Leena Semenoja of Inari, for her valuable help in obtaining the Saami samples. Ilona Carlsson and Pirkko Jalava gave us excellent technical help in preparing and analyzing the mtDNA samples. We also thank Kirsti Höök, Soili Johansson, Liisa Kosonen, Maikki Latto, Harry Lybeck, Lea Näsänen, and Anneli Suomela for their technical assistance in the microsatellite analysis.

Furthermore, we wish to thank an anonymous reviewer for many helpful suggestions. This work was supported by grant 29432 from the Academy of Finland.

References

Allen RC, Graves G, Budowie B (1989) Polymerase chain reaction amplification products separated on rehydratable polyacrylamide gels stained with silver. Biotechniques 7:736–744

Anderson S, Bankier AT, Barrel BG, De Bruijn MHL, Coulson AR, Drouin J, Eperon IC, et al (1981) Sequence and organization of the human mitochondrial genome. Nature 290: 457–465

Bishop YM, Fienberg SE, Holland PW (1989) Discrete multivariate analysis: theory and practice. MIT Press, Cambridge

Blanc H, Chen K-H, D'Amore MA, Wallace DC (1983) Amino acid change associated with the major polymorphic Hinc II site of Oriental and Caucasian mitochondrial DNAs. Am J Hum Genet 35:167–176

Boerwinkle W, Fourest E, Chan L (1989) Rapid typing of tandemly repeated hypervariable loci by the polymerase chain reaction: application to the apolipoprotein B 3′ hypervariable region. Proc Natl Acad Sci USA 86:212–216

Bonné-Tamir B, Johnson MJ, Natali A, Wallace DC, Cavalli-Sforza LL (1986) Human mitochondrial DNA types in two Israeli populations—a comparative study at the DNA level. Am J Hum Genet 38:341–351

Brega A, Gardella R, Semino O, Morburgo G, Astaldi Ricotti GB, Wallace DC, Santachiara-Benerecetti AS (1986) Genetic studies on the Tharu population of Nepal: restriction endonuclease polymorphisms of mitochondrial DNA. Am J Hum Genet 39:502–512

Brown WM, George M, Wilson AC (1979) Rapid evolution of animal mitochondrial DNA. Proc Natl Acad Sci USA 76: 1967–1971

Cann RL, Brown WM, Wilson AC (1984) Polymorphic sites and the mechanisms of evolution in human mitochondrial DNA. Genetics 106:479–499

Cann RL, Wilson AC (1983) Length mutations in human mitochondrial DNA. Genetics 104:699–711

Cavalli-Sforza LL, Piazza A (1993) Human genomic diversity in Europe: a summary of recent research and prospects for the future. Eur J Hum Genet 1:3–18

Chen YS, Torroni A, Wallace DC (1994) Mitochondrial DNA variation in African populations. Am J Hum Genet Suppl 55:A148

Chou Q, Russell M, Birch DE, Raymond J, Bloch W (1992) Prevention of pre-PCR mis-priming and primer dimerization improves low-copy-number amplifications. Nucleic Acids Res 20:1717–1723

De Benedictis G, Rose G, Passarino G, Quagliariello C (1989) Restriction fragment length polymorphism of human mitochondrial DNA in a sample population from Apulia (southern Italy). Ann Hum Genet 53:311–318

Deka R, Chakraborty R, Ferrel RE (1991) A population genetic study of six VNTR loci in three ethnically defined populations. Genomics 11:83–92

Denaro M, Blanc H, Johnson MJ, Chen KH, Wilmsen E, Cavalli-Sforza LL, Wallace DC (1981) Ethnic variation in *HpaI* endonuclease cleavage patterns of human mitochondrial DNA. Proc Natl Acad Sci USA 78:5768–5772

Di Rienzo A, Wilson AC (1991) Branching pattern in the evolutionary tree for human mitochondrial DNA. Proc Natl Acad Sci USA 88:1597–1601

Edwards A, Civitello A, Hammond HA, Caskey CT (1991) DNA typing and genetic mapping with trimeric and tetrameric tandem repeats. Am J Hum Genet 49:746–756

Edwards A, Hammond HA, Jin L, Caskey TC, Chakranorty R (1992) Genetic variation at five trimeric and tetrameric tandem repeat loci in four human population groups. Genomics 12:241–253

Eriksson AW (1973) Genetic polymorphism in Finno-Ugrian populations. Isr J Med Sci 9:1156–1170

——— (1988) Anthropology and health of Lapps. Coll Anthropol 2:197–235

Felsenstein J (1993) PHYLIP (phylogeny inference package), version 3.5c. University of Washington, Seattle

Giles RE, Blanc H, Cann HM, Wallace DC (1980) Maternal inheritance of human mitochondrial DNA. Proc Natl Acad Sci USA 77:6715–6719

Guglielmino CR, Piazza A, Menozzi P, Cavalli-Sforza LL (1990) Uralic genes in Europe. Am J Phys Anthropol 83:57–68

Harihara S, Hirai M, Omoto K (1986) Mitochondrial DNA polymorphism in Japanese living in Hokkaido. Jpn J Hum Genet 31:73–83

Harihara S, Saitou N, Hirai M, Gojobori T, Park KS, Misawa S, Ellepola SB, et al (1988) Mitochondrial DNA polymorphism among five Asian populations. Am J Hum Genet 43:134–143

Harpending HC, Sherry ST, Rogers AR, Stoneking M (1993) The genetic structure of ancient human populations. Curr Anthropol 34:483–496

Hauswirth WW, Laipis PJ (1986) Transmission genetics of mammalian mitochondria: a molecular model and experimental evidence. In: Quagliarello E, Slater EC, Palmieri F, Saccone C, Kroon AM (eds) Achievements and perspectives in mitochondrial research. Vol 2: Biogenesis. Elsevier, New York and Amsterdam, pp 49–60

Horai S, Matsunaga E (1986) Mitochondrial DNA polymorphism in Japanese. II. Analysis with restriction enzymes of four or five base pair recognition. Hum Genet 72:105–117

Horn GT, Richards B, Klinger KW (1989) Amplification of a highly polymorphic VNTR segment by polymerase chain reaction. Nucleic Acids Res 17:2140

Jeffreys AJ, Wilson V, Thein SL (1985) Hypervariable "minisatellite" regions in human DNA. Nature 314:67–73

Johnson MJ, Wallace DC, Ferris SD, Rattazzi MC, Cavalli-Sforza LL (1983) Radiation of human mitochondrial DNA types analyzed by restriction endonuclease cleavage patterns. J Mol Evol 19:255–271

Kádasi L, Gécz J, Ferákova I, Lubyyová B, Bohušová T, Feráková E, Poláková H (1994) Distribution of ApoBII, MCT118 (D1S80), YNZ22 (D17S30), and COL2A1 AmpFLPs (amplified fragment length polymorphisms) in caucasoid population of Slovakia. Gene Geogr 8:121–127

Kasai K, Nakamura Y, White R (1990) Amplification of a variable number of tandem repeats (VNTR) locus (pMCT118) by the polymerase chain reaction (PCR) and its application for forensic science. J Forensic Sci 35:1196–1200

Kimpton C, Walton A, Gill P (1992) A further tetranucleotide repeat polymorphism in the vWF gene. Hum Mol Genet 1:287

Lehtivirta J, Seurujärvi-Kari I (1991) Saamelaiset. In: Laakso J (ed) Uralilaiset kansat: tietoa suomen sukukielistä ja niiden puhujista (in Finnish). WSOY, Helsinki, pp 123–155

Litt M, Luty JA (1989) A hypervariable microsatellite revealed by in vitro amplification of a dinucleotide repeat within the cardiac muscle actin gene. Am J Hum Genet 44:397–401

Nei M (1978) The theory of genetic distance and evolution in human races. Jpn J Hum Genet 23:341–369

Nei M, Miller JC (1990) A simple method for estimating average number of nucleotide substitutions within and between populations from restriction data. Genetics 125:873–879

Nevanlinna HR (1972) The Finnish population structure: a genetic and genealogical study. Hereditas 71:195–236

Pena SDJ, de Souza KT, de Andrande M, Chakraborty R (1994) Allelic associations of two polymorphic microsatellites in intron 40 of the human von Willebrand factor gene Proc Natl Acad Sci USA 91:723–727

Pult I, Sajantila A, Simanainen J, Georgiev O, Schaffner W, Pääbo S (1994) Mitochondrial DNA sequences from Switzerland reveal striking homogeneity of European populations. Biol Chem Hoppe Seyler 375:837–840

Ruhlen M (1987) A guide to the world's languages. Vol 1: Classification. Edward Arnold, London

Saiki RK, Scharf S, Faloona F, Mullis KB, Horn GT, Erlich HA, Arnheim N (1985) Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. Science 230:1350–1354

Sajantila A, Budowie B, Ström M, Johnsson V, Lukka M, Peltonen L, Ehnholm C (1992*a*) PCR amplification of alleles at the D1S80 locus: comparison of a Finnish and a North American Caucasian population sample, and forensic casework evaluation. Am J Hum Genet 50:816–825

Sajantila A, Lahermo P, Anttinen T, Lukka M, Sistonen P, Savontaus M-L, Aula P, et al (1995) Genes and languages in Europe: an analysis of mitochondrial lineages. Genome Res 5:42–52

Sajantila A, Lukka M (1993) Improved separation of PCR amplified VNTR alleles by a vertical polyacrylamide gel electrophoresis. Int J Legal Med 105:355–359

Sajantila A, Puomilahti S, Johnsson V, Engholm C (1992*b*) Amplification of reproducible allele markers for amplified fragment length polymorphism (Amp-FLP) analysis. Biotechniques 12:16–22

Sanger F, Nicklen S, Coulson AR (1977) DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci USA 74:5463–5467

Santachiara-Benerecetti AS, Scozzari R, Semino O, Torroni A, Brega A, Wallace DC (1988) Mitochondrial DNA polymorphism in Italy. II. Molecular analysis of new and rare morphs from Sardinia and Rome. Ann Hum Genet 52:39–56

Sartoris S, Varetto O, Migone N, Cappello N, Piazza A, Ferrara GB, Cappellini R (1988) Mitochondrial DNA polymorphism in four Sardinian villages. Ann Hum Genet 52:327–340

Scozzari R, Torroni A, Semino O, Sirugo G, Brega A, Santachiara-Benerecetti AS (1988) Genetic studies on the Senegal population. I. Mitochondrial DNA polymorphisms. Am J Hum Genet 43:534–544

Semino O, Torroni A, Scozzari R, Brega A, De Benedictis G, Santachiara-Benerecetti AS (1989) Mitochondrial DNA polymorphism in Italy. III. Population data from Sicily: a possible quantitation of maternal African ancestry. Ann Hum Genet 53:193–202

Shields GF, Schmiechen AM, Frazier BL, Redd A, Voevoda MI, Reed JK, Ward RH (1993) mtDNA sequences suggest a recent evolutionary divergence for Beringian and northern North American populations. Am J Hum Genet 53:549–562

Sistonen P (1984) The LW (Landsteiner-Wiener) blood group system: elucidation of the genetics of the LW blood group based on the finding of a "new" blood group antigen. PhD diss, University of Helsinki, Finland

Stoneking M, Hedgecock D, Higuchi RG, Vigilant L, Erlich HA (1991) Population variation of human mtDNA control region sequences detected by enzymatic amplification and sequence-specific oligonucleotide probes. Am J Hum Genet 48:370–382

Torroni A, Schurr TG, Yang C-C, Szathmary EJE, Williams RC, Schanfield MS, Troup GA, et al (1992) Native American mitochondrial DNA analysis indicates that the Amerind and the Nadene populations were founded by two independent migrations. Genetics 130:153–162

Torroni A, Lott MT, Cabell MF, Chen Y-S, Lavergne L, Wallace DC (1994) mtDNA and the origin of Caucasians: identification of ancient Caucasian-specific haplogroups, one of which is prone to a recurrent somatic duplication in the D-loop region. Am J Hum Genet 55:760–776

Torroni A, Schurr TG, Cabell MF, Brown MD, Neel JV, Larsen M, Smith DG, et al (1993*a*) Asian affinities and continental radiation of the four founding Native American mtDNAs. Am J Hum Genet 53:563–590

Torroni A, Sukernik RI, Schurr TG, Starikovskaya YB, Cabell MF, Crawford MH, Comuzzie AG, et al (1993*b*) mtDNA variation of aboriginal Siberians reveals distinct genetic affinities with Native Americans. Am J Hum Genet 53:591–608

Vigilant L, Pennington R, Harpending H, Kocher TD, Wilson AC (1989) Mitochondrial DNA sequences in hairs from a southern African population. Proc Natl Acad Sci USA 86: 9350–9354

Vilkki J, Savontaus ML, Nikoskelainen EK (1988) Human mitochondrial DNA types in Finland. Hum Genet 80:317–321

Walsh PS, Metzger DA, Higuchi R (1991) Chelex-100 as a medium for simple extraction of DNA for PCR-based typing from forensic material. Biotechniques 10:506–513

Ward RH, Frazier BL, Dew-Jager K, Pääbo S (1991) Extensive mitochondrial diversity within a single Amerindian tribe. Proc Natl Acad Sci USA 88:8720–8724

Weber JL, May PE (1989) Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. Am J Hum Genet 44:388–396

Wrischnik LA, Higuchi RG, Stoneking M, Erlich HA, Arnheim N, Wilson AC (1987) Length mutations in human mitochondrial DNA: direct sequencing of enzymatically amplified DNA. Nucleic Acids Res 15:529–542

Wu S, Senio S, Bell GI (1990) Human collagen, type II, alpha I (Col2A1), gene: VNTR polymorphism detected by gene amplification. Nucleic Acids Res 18:3102