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RESEARCH ARTICLE

Reconstruction of Patrilineages and Matrilineages of Samaritans and Other Israeli Populations From Y-Chromosome and Mitochondrial DNA Sequence Variation

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The Samaritan community, which numbered more than a million in late Roman times and only 146 in 1917, numbers today about 640 people representing four large families. They are culturally different from both Jewish and non-Jewish populations in the Middle East and their origin remains a question of great interest. Genetic differences between the Samaritans and neighboring Jewish and non-Jewish populations are corroborated in the present study of 7,280 bp of nonrecombining Y-chromosome and 5,622 bp of coding and hypervariable segment I (HVS-I) mitochondrial DNA (mtDNA) sequences. Comparative sequence analysis was carried out on 12 Samaritan Y-chromosome, and mtDNA samples from nine male and seven female Samaritans separated by at least two generations. In addition, 18–20 male individuals were analyzed, each representing Ethiopian, Ashkenazi, Iraqi, Libyan, Moroccan, and Yemenite Jews, as well as Druze and Palestinians, all currently living in Israel. The four Samaritan families clustered to four distinct Y-chromosome haplogroups according to their patrilineal identity. Of the 16 Samaritan mtDNA samples, 14 carry either of two mitochondrial haplotypes that are rare or absent among other worldwide ethnic groups. Principal component analysis suggests a common ancestry of Samaritan and Jewish patrilineages. Most of the former may be traced back to a common ancestor in the paternally-inherited Jewish high priesthood (Cohanim) at the time of the Assyrian conquest of the kingdom of Israel. Hum Mutat 24:248–260, 2004. © **2004 Wiley-Liss, Inc.**

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INTRODUCTION

The Samaritans constitute a distinct religious and cultural minority in the Middle East. The population of about 640 individuals is divided into two groups of about equal sizes, one residing in Holon, a suburb of Tel Aviv, and the other in Shechem (Nablus), near their holy site of Mount Gerizim. According to their tradition, they are the descendants of the ancient tribes of Menasseh and Ephraim (sons of Joseph) and Levitical priests from Shechem. They claim to be the remnants of the 10 lost tribes of Israel that remained in the kingdom of Israel after the Assyrian conquest of 722–721 BCE. The historian Talmon claims that the biblical description of them as foreigners resettled by the Assyrian king Sargon (Kings 2, 17:24) may have been intended to justify their ostracism by those Israelites who returned from the Babylonian exile in 520 BCE [Talmon, 2002]. In the fourth and fifth centuries CE, the Samaritans numbered 1.2 million, but centuries of persecutions reduced their numbers to 146 by the year 1917 [Ben Zvi, 1957].

Detailed pedigrees of the last 13 generations show that the Samaritans comprise four lineages [Cazes and Bonné-Tamir, 1984]: the Tsdaka lineage, which is claimed to have descended from the tribe of Menasseh; the Joshua-Marhiv and Danfi lineages, claiming descent from the tribe of Ephraim; and the priestly Cohen lineage from the tribe of Levi [Ben Zvi, 1957].

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Genetic and demographic investigations of the Samaritan community were carried out in the 1960s [Bonné, 1963, 1966]. The Samaritans exhibit differences in many genetic traits from those found in other populations in the region. For example, blood group O and color blindness are much higher and G6PD deficiency much lower in Samaritans than in neighboring Middle Eastern populations [Bonné et al., 1965; Bonné, 1966]. The majority of marriages, about 84%, occur between cousins, producing the highest inbreeding coefficient recorded for any population [Bonné-Tamir et al., 1997]. Female Samaritans who marry non-Samaritans are expelled from the sect, while the children of male Samaritans who marry outsiders are regarded as Samaritan.

To learn more about the origin of Samaritans and their genetic relation to other populations in the Middle East, in this study we resequenced 7,280 bp of nonrecombining Y-chromosome and 5,622 bp of coding and hypervariable segment I (HVS-I) mitochondrial DNA (mtDNA) sequences in four Samaritan families, as well as in six Jewish and two non-Jewish Israeli populations whose genetic relationship had been studied earlier by Rosenberg et al. [2001] using unlinked autosomal microsatellite data.

MATERIALS AND METHODS

DNA Samples

Samples were collected according to approved human subject protocols from 27 male and 20 female Samaritan individuals from Israel. A total of 12 of the males that were separated by two paternal generations or more were used for Y-chromosome analysis. Concordantly, nine males and seven females separated by two maternal generations or more were analyzed for mtDNA variation. Samples from 158 male individuals belonging to eight other Israeli populations were analyzed both for Y-chromosome and mtDNA sequence variation. These samples included 18 Ethiopian Jews (one of these failed to amplify in the Y-chromosome analysis due to low copy number) and 20 each from the following populations: Ashkenazi Jews of Polish origin, Iraqi Jews, Libyan Jews, Moroccan Jews, Yemeni Jews, Druze, and Palestinians. Included in the statistical analysis were sequence data generated previously from 23 Africans (five San, four Biaka Pygmy, four Mbuti Pygmy, five Sudanese, two Herero, one Tswana, one Ghanaian, and one Mandenka) and 21 Europeans (five Britons, two Czechs, two Finns, one Georgian, one Greek, three Icelanders, and seven Italians).

Genotyping and Resequencing

The Y-chromosome SNP markers genotyped (Table 1) included: M305 (haplogroup A3b2 in Y consortium nomenclature, phylogenetically equivalent to M13); M299 (A, M42); M294 (A/B, M168); M203 (D/E, YAP); PN2 (E3); M215 (E3b, M35); M78 (E3b1); M123 (E3b3); M34 (E3b3a); M213 (F, M89); M201 (G); P15 (G2); M304 (J, p12f2); M172 (J2); M67 (J2f); M314 (J2e, M12); M241 (J2e); M267 (J1); M170 (I); M307 (I1a); M9 (K); M175 (O); M231 (N, ancestral to TAT); M295 (L, M11); M272 (K2, M70); M45 (P); M207 (R); M198 (R1a1, M17); M269 (R1b10); and M242 (Q). All but three of the markers (M294, M299, and M305) had been published previously [Underhill et al., 2001; Seielstad et al., 2003; Cinnioglu et al., 2004]. We used denaturing high performance liquid chromatography (DHPLC) and dye-terminator sequencing to genotype each of the aforementioned markers and to characterize novel binary polymorphisms detected for the first time in this study by DHPLC. A total of 7,280 bp of nonrecombining Y-chromosome DNA, which included 21 of the 30 simple sequence polymorphisms mentioned above, was resequenced. Nine of the 30 markers were genotyped only in individuals carrying the following proximal markers: PN2 in individuals with M203, but not M215; M34 and M123 in individuals with M215, but not M78; P15 in individuals with M201; M304 in individuals with M213, but ancestral to M172 and M267; M241 and M314 in individuals with M172; M242 in individuals with M45; and M272 in individuals with M9, but not M45.

A total of 5,218 bp of coding plus 404 bp of HVS-I mtDNA sequence (NC_001807.4) was analyzed. The primer pairs used for sequencing of non-D loop mtDNA were STS02, 15, 17, 21, 24, 26, 28, 29, 30, 31, 39, and 40, available publicly at http://insertion.stanford.edu/primers_mitogenome.html. The primers used for amplification of the HVS-I region were 5′ACACCAGTCTT GTAAACCGG and 5′CCTGAAGTAGGAACCAGATG, respectively. For sequencing of the HVS-I region, the following two nested primers were employed: 5′CTCCACCATTAGCACC CAAAG, and 5′TGATTTCACGGAGGATGGTGG.

PCR

The PCR protocol comprised an initial denaturation at 95°C for 10 min; 14 cycles of denaturation at 94°C for 20 sec, primer annealing at 63–56°C with 0.5°C decrements, and extension at 72°C for 1 min; followed by 20 cycles at 94°C for 20 sec, 56°C for 1 min, and 72°C for 1 min, and a final 5-min extension at 72°C. Each 50-μl PCR contained 1 U of AmpliTaq Gold polymerase, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 2.5 mM MgCl2, 0.1 mM each of the four deoxyribonucleotide triphosphates, 0.2 μM each of forward and reverse primers, and 50 ng of genomic DNA. PCR yields were determined on ethidium bromide-stained agarose gels.

DHPLC Analysis

Unpurified PCR products were mixed at an equimolar ratio with a reference Y-chromosome and subjected to a 3-min 95°C denaturing step followed by gradual renaturing from 95°C to 65°C over 30 min. Each mixture (10 μl) was loaded onto a DNASep™ column (Transgenomic, Omaha, NE), and the amplicons were eluted in 0.1 M triethylammonium acetate (pH 7) with a linear acetonitrile gradient, at a flow rate of 0.9 ml/min. Under appropriate temperature conditions, optimized by computer simulation [Jones et al., 1999], simple sequence polymorphisms showed two or more peaks/shoulders in the elution profiles.

DNA Sequencing

Amplicons were purified with Qiagen (Valencia, CA) QIAquick® spin columns and sequenced with the Applied Biosystems (Foster City, CA) Dye Terminator Cycle Sequencing Kit on an ABI PRISM® 3700 DNA Analyzer.

Statistical Analysis

Insertions and deletions were treated as single-nucleotide substitutions. The nucleotide diversity, π, in a sample of n chromosomes was estimated from the equation

$$\pi = \sum_{i<j} \pi_{ij}/n_c, \qquad [1]$$

where π_{ij} is the number of nucleotide differences between the ith and jth DNA sequences and n_c is the total number of sequence comparisons. The latter is derived from $n(n-1)/2$ [Nei, 1987], where n is the number of sequences examined.

TABLE 1. Description of Y-Chromosome Markers

Marker no.	Primers (5′–3′)		DHPLC temp (°C)	SNP in GenBank ref or dbSNP(ss)[a]
	Forward	Reverse		
P15[h]	agagagttttctaacagggcg	tgggaatcacttttgcaact	57	AC007876.2: g.95842C>T
PN2[g]	ggtaacacccataaaggttg	ttcactaccagcctaagtac	58	AC010137.3: g.4152G>A
M9[e]	gcagcatataaaactttcagga	actgaatctttttttcctcatttt	54	ss3937: g.68C>G
M34[e]	cacttcacatttgtttttagg	agtcattatttagtcattccag	59	AC003032.1: g.4961C>A
M45[e]	gctggcaagacacttctgag	aatatgttcctgacaccttcc	58	ss2941595: g.109G>A
M67[e]	ccagtcagcagtacaaaagttg	gcatttctttgattatagaagcaa	54	ss2941592: g.327A>T
M78[e]	cttcaggcattatttttttttggt	atagtgttccttcacctttcctt	55	AF273841.1: g.46295G>A
M123[e]	tggtaaactctacttagttgccttt	cagcgaattagattttcttgc	56	AC010889.3: g.2935C>T
M170[d,e]	tgcttcacacaaatgcgttt	ccaattactttcaacatttaagacc	53	ss2941560: g.327A>C
M172[e]	ttgaagttacttttataatctaatgctt	ataatttattactttacagtcacagtgg	55	ss2941568: g.197T>G
M175[d,e]	ttgagcaagaaaaatagtaccca	ctccattcttaactatctcaggga	54	ss2941642: g.79_83delTTCTC
M198[e]	tgaggtggaatgtatcagtatacc	tgatttcaaggatttgttagtctt	53	ss2941550: g.45C>T
M201[e]	tatgcatttgttgagtatatgtc	gttctgaatgaaagttcaaacg	56	ss2941600:g.136G>T
M203[e]	gagtgccaagctgaggatga	aaattctgctgtgctctcca	62	ss2941617: g.248G>C
M207[e]	aggaaaaatcagaagtatccctg	caaaattcaccaagaatccttg	55	ss2941622: g.79A>G
M213[e]	tataatcaagttaccaattactggc	ttttgtaacattgaatggcaaa	53	ss2941629: g.290T>C
M215[e]	gtaaaactcagatatatacatcccatg	aaaaaaaaagaatcactatcttaacg	54	ss2941618: g.163A>G
M224[e]	cttcaggcattatttttttttggt	atagtgttccttcacctttcctt	55	AF273841.1: g.46299A>G
M231[c,d]	cctattatcctggaaaatgtgg	attccgattcctagtcacttgg	55	ss12724427: g.110G>A
M241[f]	aactcttgataaaccgtgctg	tccaatctcaattcatgcctc	53	ss9807255: g.57G>A
M242[i]	aactcttgataaaccgtgctg	tccaatctcaattcatgcctc	57	ss9807254: g.180C>T
M267[f]	caaaaacacacttcaaaagcct	tgtagagacacggttgtaccct	57	ss12724467: g.427T>G
M269[j]	ctaaagatcagagtatctccctttg	actatacttcttttgtgtgccttc	54	ss13606447: g.201T>C
M272[c]	caggaggggaccatgtttt	cagcaaagatttaatggacattt	58	ss12724462: g.212A>G
M285[b,f]	caaaaacacacttcaaaagcct	tgtagagacacggttgtaccct	57	ss23129251: g.349G>C
M289[b,c]	ccagtcagcagtacaaaagttg	gcatttctttgattatagaagcaa	59	ss23129241: g.227G>A
M290[b,c]	ccagtcagcagtacaaaagttg	gcatttctttgattatagaagcaa	55	ss23129242: g.343C>T
M294[c]	catggtccaagcaatttatttt	gctggctaatacttccacagag	53	ss12724472: g.305C>T
M295[c]	catggtccaagcaatttatttt	gctggctaatacttccacagag	53	ss12724473: g.411T>C
M299[c]	cggacttggtctgtgcttt	tgatctgtcacaatggcagt	55	ss23129218: g.127T>G
M304[f]	caaagtgctgggattacagg	cttctagcttcatctgcattgt	55	ss23129223: g.421A>C
M305[c]	aacttgtgaaacaactggtgat	attacatttgttgcctctgctt	53	ss23129224: g.331C>T
M307[c,d]	ttattggcatttcaggaag	agagggtgaggcaggaaa	56	ss23129226: g.282G>A
M314[c]	tggaattgtttctgagtagtac	aaggctaacaagatgccctc	57	ss23133240: g.128A>C
M318[b,c]	catggtccaagcaatttatttt	gctggctaatacttccacagag	53	ss23129245: g.353T>C
M319[b,c]	gtaaaactcagatatatacatcccatg	aaaaaaaaagaatcactatcttaacg	52	ss23129246: g.124T>A
M320[b,c]	tgaggtggaatgtatcagtatacc	tgatttcaaggatttgttagtctt	54	ss23129247: g.60T>G
M321[b,c]	tgaggtggaatgtatcagtatacc	tgatttcaaggatttgttagtctt	54	ss23129248: g.171C>T
M322[b,c]	cctattatcctggaaaatgtgg	attccgattcctagtcacttgg	55	ss23129249: g.126C>A
M323[b,c]	gctggcaagacacttctgag	aatatgttcctgacaccttcc	58	ss23129250: g.40C>T
M342[f]	agagagttttctaacagggcg	tgggaatcacttttgcaact	57	AC007876.2: g.95758C>T

[a]Nucleotide position from 5′ end of GenBank/dbSNP reference sequence.
[b]Sites found first in this study.
[c]Markers reported here for the first time.
[d]Markers that were monomorphic in this study.
[e]Underhill et al. [2001]; [f]Cinnioglu et al. [2004]; [g]Hammer et al. [1997]; [h]Hammer et al. [2000]; [i]Seielstad et al. [2003]; [j]Cruciani et al. [2002].

The haplotype diversity, h, in a population of n chromosomes was estimated using

$$h = n\left(1 - \sum_{i=1}^{m} x_i^2\right)/(n-1), \quad [2]$$

where x_i is the population frequency of the ith haplotype and m is the number of haplotypes [Tajima, 1989a].

Tajima's D statistic [Tajima, 1989b] is defined by the equation

$$D = d/\sqrt{\hat{V}(d)},\ d = \pi - S/\sum_{i=1}^{n-1} 1/i, \quad [3]$$

where S is the number of segregating nucleotides, and $\hat{V}(d)$ estimates the variance of d. D is expected to be 0 for selectively neutral mutations in a constant population, infinitely many sites model.

ARLEQUIN2000 [Schneider et al., 2000] was used to test the hypothesis of a random distribution of haplotypes among population groups and to perform analyses of molecular variance (AMOVA) [Excoffier et al., 1992]. F_{st} values were calculated from individual haplotypes.

RESULTS AND DISCUSSION

Y-chromosome

We resequenced 7,280 bp of nonrecombining Y-chromosome sequence flanking 21 major haplogroup-defining markers for the 169 males of Samaritan, Jewish, Druze, and Palestinian origin. Eight new single nucleotide polymorphisms (SNPs) were discovered. Five fall in the M172 (J2) clade (M289, M318, M319, M321, and M322; see Fig. 1). The other three are M272, M290, and M320 in clades Q, E3b3a, and

K2, respectively. Markers M170 (I), M175 (O), and M231 (N, ancestral to TAT) were ancestral in all samples.

Figure 1 shows a parsimonious Y phylogeny of the 30 haplogroups observed in the nine Israeli populations and provides increased resolution over previously published phylogenies from the Levant [Hammer et al., 2000; Thomas et al., 2000; Nebel et al., 2001]. The majority of individuals from each population (30–83%), excluding Ethiopian Jews and Palestinians, belong to Haplogroup J, defined by M304 [Cinnioglu et al., 2004], an SNP marker phylogenetically equivalent to the 8-kb deletion p12f2 [Casanova et al., 1985]. M304 is located in intron 4 (*c.271-57A>C*) of the *EIF1AY* gene (GenBank: AF000987.1, OMIM: 400014). Except for a single Ashkenazi, all haplogroup J lineages could be subclassified into subhaplogroups J1 and J2 using markers M267 and M172, respectively. The former is located in intron 2 (*c.115+241T>G*) of the *EIF1AY* gene and expands the original definition of subhaplogroup J1 by M62. In this study, M267 occurred at frequencies ranging from 5% (Druze) to 30% (Yemeni Jews), while its frequency in 523 Turkish Y-chromosomes was 9% [Cinnioglu et al., 2004]. A total of 22 (13.0%) of the 169 individuals studied partitioned into haplogroup J1, and 32 (18.9%) partitioned into J2. Of the 32 individuals carrying the derived allele of M172, 22 could be further subclassified into eight haplogroups. Noteworthy is haplogroup J2e1, defined by M241. This polymorphism was discovered originally in two Italian Y-chromosomes and subsequently in five Turkish Y-chromosomes [Cinnioglu et al., 2004]. Here, we observed it in six out of 20 Libyan Jewish Y-chromosomes. It is likely to be found throughout the Mediterranean area and in Central and South Asia, where carriers of haplogroup J2e have been observed at frequencies of 1 to 10% [Underhill et al., 2000; Scozzari et al., 2001; Kivisild et al., 2003].

Of the 12 Samaritan males, 10 (83%) belong to haplogroup J, which captures three of the four Samaritan families. The family Joshua-Marhiv belongs to subhaplogroup J1, while families Danfi and Tsdaka belong to subhaplogroup J2, and can be further distinguished by M67, the derived allele of which has been found in the Danfi family.

The paternal ancestry of Ethiopian Jews resembles that of Africans, with seven out of 17 (41.2%) belonging to haplogroup A3b2, and three (17.6%) belonging to E*. Haplogroup E3b1, defined by M78, was found in all nine populations at frequencies of 10–16.7%. The Samaritan family Cohen carries this haplotype. Haplogroup E3b3, defined by M123, was present at 5 to 20% in Ethiopian, Ashkenazi, Libyan, and Yemenite Jews, and in Palestinians. Only two individuals, one Ethiopian and one Moroccan, belong to E3b* and carry neither M78 nor M123.

Haplogroup R appears at 10 to 30% in all Israeli populations but the Ethiopian Jews and Palestinians. Its frequency is highest (30%) in our Ashkenazim of Polish ancestry, two-thirds of whom belong to R1a, most

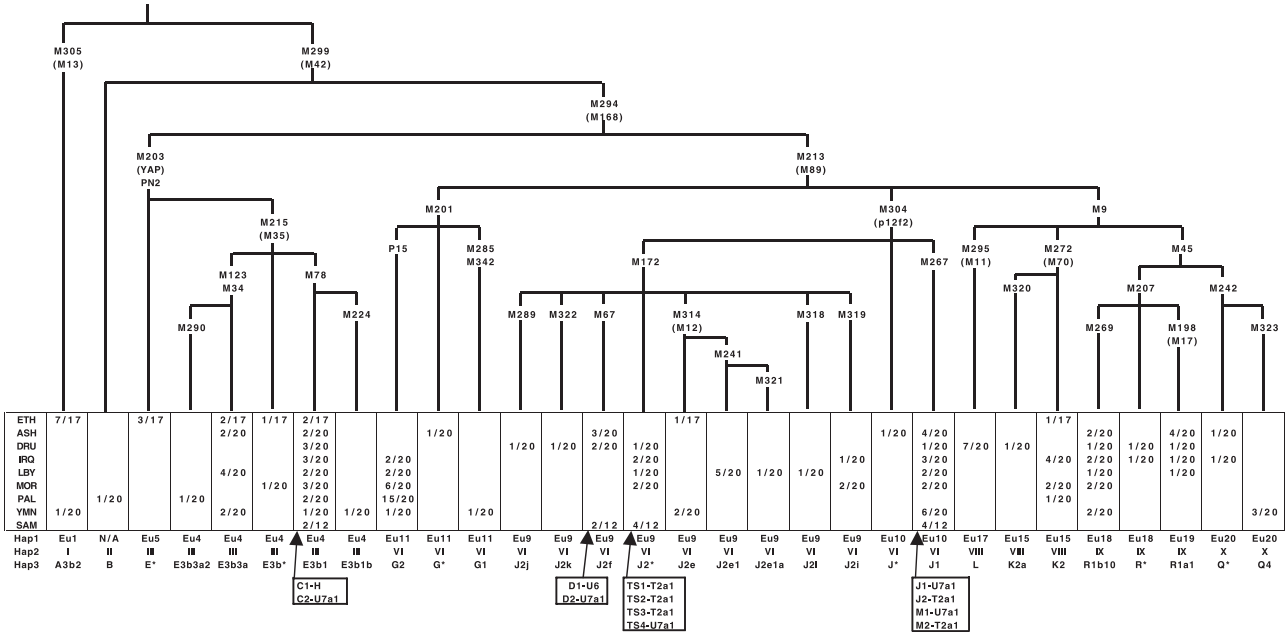

FIGURE 1. **Parsimonious Y-chromosome phylogeny and haplotype frequencies of the Samaritan and eight other populations sampled in Israel. The nine populations were: ETH, Ethiopian; ASH, Ashkenazi; DRU, Druze; IRQ, Iraqi; LBY, Libyan; MOR, Moroccan; PAL, Palestinian; YMN, Yemeni; and SAM, Samaritan. Hap1, Hap2, and Hap3 define haplogroups according to the nomenclatures proposed by Semino et al. [2000], Underhill et al. [2001], and the Y Chromosome Consortium [2002], respectively, all three of which are given here to facilitate comparison with literature on Y-chromosomal phylogeography. An asterisk indicates that a haplogroup is potentially paraphyletic. The 12 Samaritan males have letters indicating the family affiliation: C, Cohen; D, Danfi; TS, Tsadaka; J, Joshua; and M, Marhiv. The mtDNA haplogroup of each Samaritan male is given below the Y-chromosome haplogroups.**

commonly found in Eastern Europe [Semino et al., 2000]. In the other Israeli populations, concordant with their Sephardic ancestry, 77% belong to R1b and R*, which are most frequent on the Iberian Peninsula [Semino et al., 2000; Bosch et al., 2001].

The frequency of haplogroup G is highest in Georgia (30%) and decreases to 10% in Southern Europe and Turkey [Semino et al., 2000; Cinnioglu et al., 2004]. Among Israeli populations, haplogroup G appears typically in 5 to 10% of the males and is most frequent (30%) in Moroccan Jews. Contrary to previous reports showing only a minor (3–6%) frequency of haplogroup G among Palestinians as compared to over 50% of haplogroup J [Hammer et al., 2000; Nebel et al., 2001], 15 of the 20 Palestinian samples (75%) studied here belonged to haplogroup G, and none to haplogroup J. This suggests high heterogeneity among Palestinians Y-chromosomes.

Haplogroup L defined by M295 was found only in Druze, at a frequency of 35%. This haplogroup appears to be most frequent (12%) in South Asia, dropping to $\leq 6\%$ in Central Asian, Siberian, Kurdish, Turkish, and European populations [Underhill et al., 2000; Kivisild et al., 2003; Cinnioglu et al., 2004]. To date, it has not been observed in Jews, Palestinians, or Bedouins [Semino et al., 2000; Underhill et al., 2000; Nebel et al., 2001].

The Y-chromosome nucleotide diversities (π) for the Middle Eastern populations studied are quite uniform, ranging from 4.38×10^{-4} to 5.63×10^{-4}. Exceptions are the Palestinians ($\pi = 2.41 \times 10^{-4}$) and Samaritans ($\pi = 3.50 \times 10^{-4}$). The slightly positive or negative Tajima's D values estimated for the nine populations do not depart from standard neutral expectations (Table 2).

Table 3 presents the pair-wise genetic distances (F_{st}) between 11 populations from AMOVA applied to the Y-chromosomal and mitochondrial data. For the Y-chromosome, all Jewish groups, except for the Ethiopians, are closely related to each other. They do not differ significantly from Samaritans (0.041) and Druze (0.033), but are different from Palestinians (0.163), Africans (0.219), and Europeans (0.111) (Table 4).

Figure 2A shows a principal component analysis using population frequencies of the Y-chromosome haplotypes displayed in Figure 1. Samaritans and Jewish populations, except Ethiopian Jews, form a cluster separated from Palestinians and Druze. Ethiopian Jews are related more closely to Africans.

Mitochondrial DNA

Sequencing of 5,218 bp of non-D loop and 404 bp of HVS-I mtDNA (GenBank: NC_001807.4) in 174 individuals of the nine populations yielded 348 polymorphic sites (99 in HVS-I). Polymorphisms included one deletion in the 12S rRNA region, one triallelic site (silent Gly in both cases) in the MTCYB gene (MIM 516020), and two heteroplasmic sites (*m.1219T>Y* in one Moroccan Jew, and *m.9732C>Y* in one Ethiopian Jew). A parsimony tree (Figure 3) based on all 346 nonheteroplasmic sites was constructed. In addition,

TABLE 2. Nucleotide Diversities (π), Haplotype Diversities (h), and Tajima's D

	Ychromosome (7280 bp)				mtDNA (5218 bp)			
	n	π ($\times 10^{-4}$)	h	D	n	π ($\times 10^{-4}$)	h	D
Ashkenazi	20	5.63 ±2.97	0.905	0.43	20	21.0 ±14.9	0.916	−1.07
Iraqi	20	4.73 ±2.97	0.921	−0.22	20	23.2 ±18.7	0.979	−1.46
Libyan	20	4.63 ±3.16	0.900	−0.54	20	12.9 ±10.1	0.800	−1.25
Moroccan	20	4.59 ±2.77	0.879	−0.04	20	13.9 ±12.0	0.979	−1.55
Yemenite	20	5.52 ±3.75	0.889	−0.61	20	18.4 ±14.7	0.979	−1.39
Ethiopian	17	4.38 ±2.29	0.809	0.72	18	28.0 ±20.5	0.967	−1.22
Druze	20	5.21 ±3.55	0.868	−0.59	20	17.2 ±12.8	0.968	−1.18
Palestinian	20	2.41 ±1.99	0.442	0.74	20	21.5 ±18.2	0.995	−1.58
Samaritan	12	3.50 ±2.11	0.788	0.38	16	16.0 ±7.7	0.733	0.62

TABLE 3. Pairwise Fst Between Populations for Y-Chromosome (Bottom) and mtDNA (Top)

Y\mtDNA	European	Ashkenazi	Iraqi	Libyan	Moroccan	Yemenite	Samaritan	Druze	Palestinian	Ethiopian	African
European		0.065*	0.042*	0.159	0.056*	0.027*	0.153	0.040*	0.023*	0.271	0.396
Ashkenazi	0.075*		0.113	0.242	0.182	0.081	0.242	0.135	0.112	0.287	0.398
Iraqi	0.082*	0.000*		0.114	0.077*	0.035*	0.105*	0.118	0.037*	0.209	0.347
Libyan	0.182	0.051*	0.072*		0.093	0.130	0.325	0.134	0.087	0.245	0.376
Moroccan	0.155	0.035*	0.000*	0.042*		0.046*	0.238	0.011*	0.026*	0.257	0.392
Yemenite	0.120	0.000*	0.000*	0.026*	0.007*		0.203	0.061*	0.006*	0.219	0.360
Samaritan	0.267	0.079*	0.092*	0.073*	0.071*	0.037*		0.261	0.173	0.337	0.432
Druze	0.123	0.023*	0.005*	0.095*	0.060*	0.042*	0.122*		0.050*	0.275	0.400
Palestinian	0.369	0.257	0.229	0.217	0.094*	0.204	0.344	0.300		0.145	0.302
Ethiopian	0.373	0.218	0.247	0.163	0.216	0.165	0.297	0.265	0.378		0.128
African	0.417	0.265	0.293	0.220	0.257	0.219	0.336	0.313	0.414	0.087*	

*Nonsignificant values ($p > 0.01$).

markers *m.270G>A*, *m.3010G>A*, *m.3847T>C*, *m.8014A>T*, and *m.15904C>T* were sequenced to allow assignment to haplogroups H, H1 or J1, (pre-HV)1, HV1, and V, respectively.

Consistent with previous reports [Ritte et al., 1993; Torroni et al., 1996; Behar et al., 2003], almost half of the Ashkenazi Jews (9/20) belong to haplogroup K (Table 5). The only known exception to this pattern is the British Ashkenazi sample of Thomas et al. [2002]. Six of the nine K lineages share transitions at nucleotide positions (nps) 11470 and 11914, which are specific to clade K1a [Herrnstadt et al., 2002]. Other than in Ashkenazi Jews, the K1a HVS-I motif 16224-16234-16311 has been detected in one Palestinian, one Romanian, one Czech, and one Basque [Richards et al., 2000]. The J1 and T2b haplotypes observed in Ashkenazim have exact HVS-I matches in Europe [Richards et al., 2000], suggesting historic admixture. In contrast, it is difficult to assess whether haplogroups U7 and HV, as well as the HVS-I haplotypes of the Ashkenazi K2, I, W, and U2 lineages represent the original gene pool of the Jewish founders or are due to admixture with European populations, because they exist both in the Middle East and Europe [Richards et al., 2000].

TABLE 4. **Fst Values for Y-Chromosome and mtDNA for Pooled Jewish Sub-populations**

	Y	mtDNA
J-Sam	0.041*	0.159
J-P	0.163	0.009*
J-D	0.033*	0.045*
J-Afr	0.219	0.4
J-Eur	0.111	0.016*
J-Eth	0.187	0.239
J-J	0.022*	0.116
Sam-P	0.344	0.173
Sam-Eth	0.297	0.337
Sam-Afr	0.336	0.432
Sam-Eur	0.267	0.153
Sam-D	0.122	0.261
Eth-Afr	0.087*	0.128

*Nonsignificant values ($p > 0.01$).
J, Jewish populations of Ashkenazi, Iraqi, Libyan, Moroccan and Yemenite; Sam, Samaritan; P, Palestinian; D, Druze; Eur, European; Afr, African; Eth, Ethiopian Jews.

Haplogroup U3 is the most common haplogroup among Iraqi Jews, while it is absent in Jews from Iran [Thomas et al. 2002]. In the general Iraqi population, the frequency of U3 is only about 5% [Richards et al., 2000]. The six (30%) U3 lineages detected here among the Iraqi Jews fall into four haplotypes distinguished by eight coding region markers (Fig. 3), pointing to multiple founding lineages. Four of the Iraqi Jewish sequences (20%), including one haplotype shared with a Moroccan Jew, belong to a rare T2c subclade (Fig. 3). One Iraqi Jewish sequence, with its characteristic transition at np 16104 in haplogroup X1a, and one sequence in haplogroup M1, show affinity to Northeast-African populations [Quintana-Murci et al., 1999; Reidla et al., 2003]. Haplogroup HV3, defined here by four substitutions in the coding region (Fig. 3) and a transition at np 16217 in HVS-I, was found in one Iraqi and two Yemeni Jews. Its HVS-I motif occurs frequently in South and West Asia [Kivisild et al., 2003].

Eight of the 21 Ethiopian Jewish mtDNA sequences investigated belong to the African haplogroups L0–L3 [Mishmar et al. 2003; Salas et al. 2004]. The L0a1a and L0a2 sequences are common in East and Southeast African populations [Salas et al., 2002]. The new haplogroup L5a (L1e2 in Salas et al. [2002]), present in two Ethiopian Jews, and haplogroup L0f are typical for East Africa, but rare elsewhere in Africa [Salas et al., 2002]. Haplogroup L2a1 is the most ubiquitous haplogroup in Africa. Its derived HVS-I haplotypes in

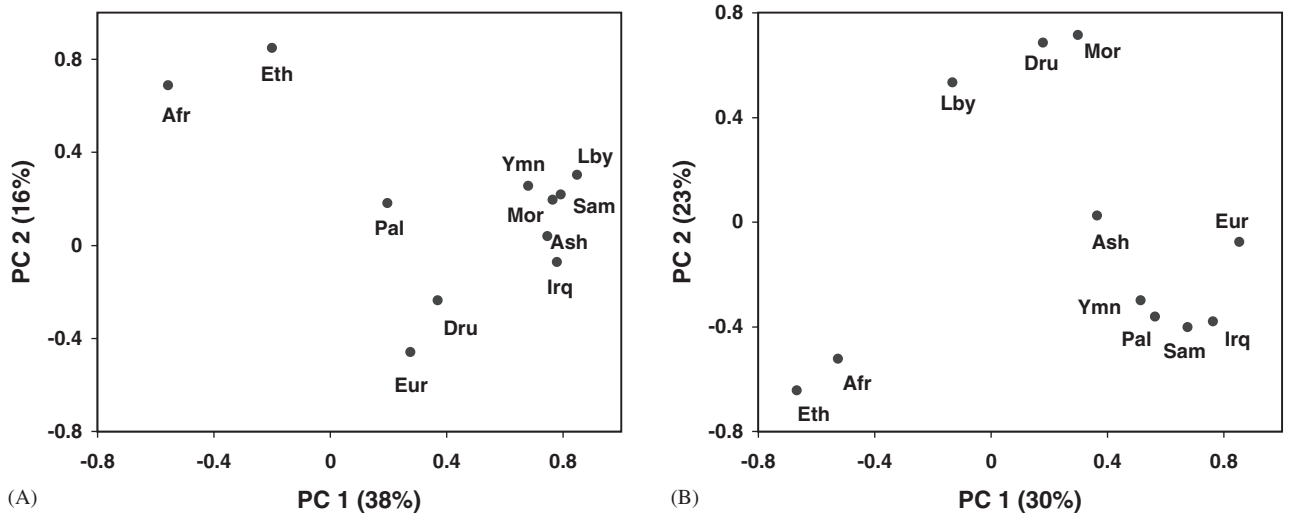

FIGURE 2. **Principal component analysis for Y-chromosome haplogroups (A) and mtDNA haplotypes (B) in 11 populations. In addition to nine populations sampled in Israel, two reference populations of 23 Africans (five San, four Biaka Pygmy, four Mbuti Pygmy, five Sudanese, two Herero, one Tswana, one Ghanaian, and one Mandenka) and 21 Europeans (five Britons, two Czechs, two Finns, one Georgian, one Greek, three Icelanders, and seven Italians) were added. In the Y chromosome (A), factor 1 accounts for 38% and factor 2 accounts for 16% of the variance. In mtDNA (B), factor 1 accounts for 30% and factor 2 accounts for 23% of the variance.**

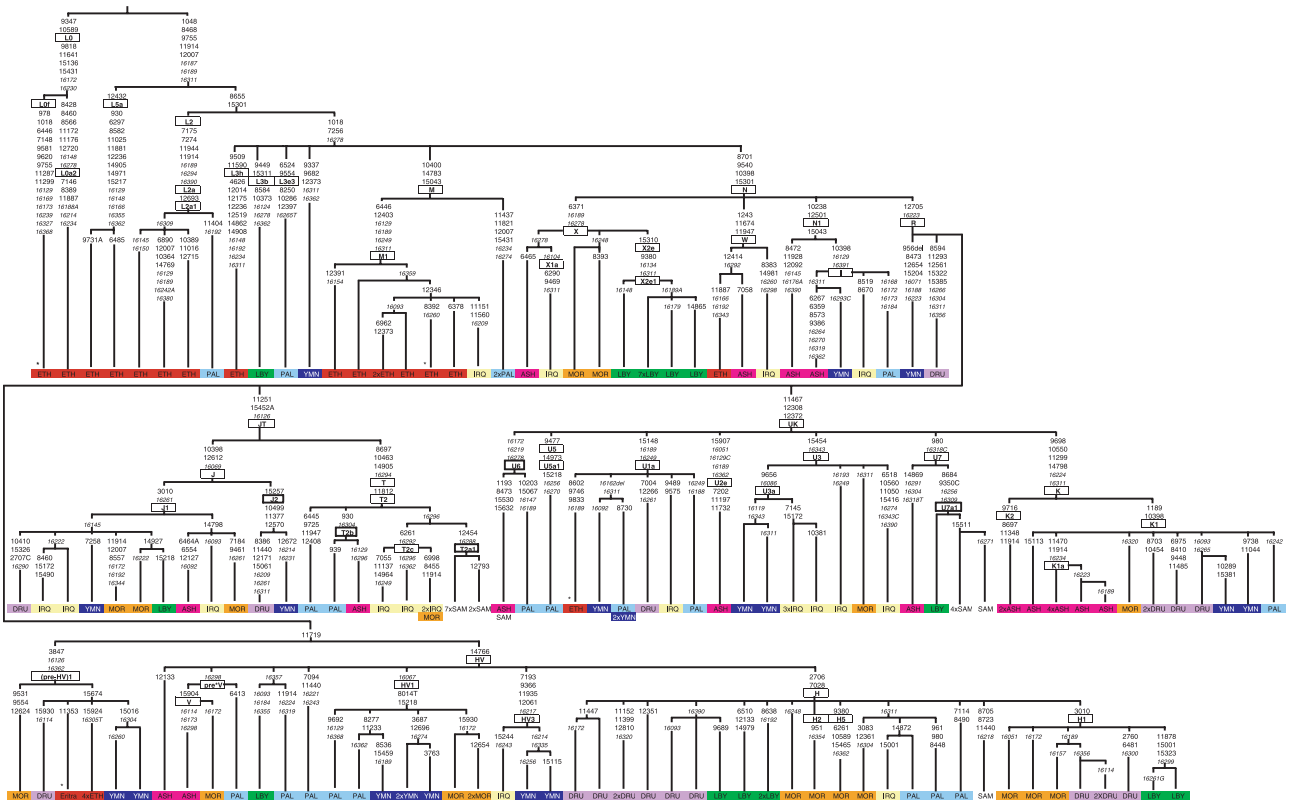

FIGURE 3. **Parsimony phylogeny of 178 human mtDNA samples from nine populations sampled in Israel based on 5,218 bp of coding and 404 bp of HSV-I sequences. The symbols for populations are as in Figure 1. Three additional female Ethiopian Jews and one Eritrean (labeled with asterisks) were added to the tree. Locations of branch-defining mutations are listed relative to the revised reference sequence [Andrews et al., 1999]. Italics refer to the HSV-I region.**

TABLE 5. **Distribution of mtDNA Haplogroups in 9 Israeli Populations**

			Number of individuals in each mtDAN haplogroups																				
Populations	**No. Ind.**	**No. Hap.**	**L0-L3**	**M**	**X**	**W**	**N1/I**	**R***	**J**	**T2**	**U1a**	**U3**	**U6**	**U7**	**U5/U2**	**K**	**(preHV)1**	**pre*V**	**HV***	**HV1**	**HV3**	**H***	**H1**
Ethiopian	21	17	8	7		1					1						4						
Ashkenazi	20	16			1	1	2		1	1			1	1	1	9		1	1				
Iraqi	20	17		1	1	1	1		3	4	1	6									1	1	
Libyan	20	13	1		10				1					1					1			4	2
Moroccan	20	19			2				3	1		1				1	1	1		3		4	3
Yemenite	20	18	1				1	1	2		3	2				2	2			4	2		
Samaritan	16	6								9			1	5								1	
Druze	20	17						1	2		1					4	1					7	4
Palestinian	20	19	2	2			1			2	2		1		1	1		1	2	2		3	

Ethiopian Jews (samples 2234 and 2238), however, have not been detected so far [Salas et al., 2002]. The rare motif of transitions at nps 16229 and 16291 in L2a2 has been observed to date only in Mbuti Pygmies [Watson et al., 1997]. Of the remaining 13 Ethiopian Jewish mtDNA sequences, 11 belong to clades M1 and (pre-HV1), and showed exact HVS-I haplotype matches with East African [Krings et al., 1999] and Arab sequences [Quintana-Murci et al., 1999; Richards et al., 2003].

One-half of the Libyan Jews belong to a rare subclade of haplogroup X2e, defined by a transition at np 15310, that is widespread in the Caucasus and Central Asia [Reidla et al., 2003]. The X2e sequences of Libyan Jews are characterized by additional mutations at nps 9380, 16134, and 16311, showing no match in a survey covering 13,589 Eurasian and African mtDNAs [Reidla et al. 2003]. Previously, 27% of Druze were reported to carry haplogroup X sequences [Brown et al., 1998]. None were observed in our Druze sample, but a diverse set of haplogroup H sequences (11/20) was detected. The Libyan and Palestinian L3b and L3e types have exact matches only in Northwest African populations [Salas et al., 2002].

Palestinian maternal lineages were widely distributed across different mtDNA haplogroups with no evidence of particular founder effects. The observed HVS-I haplotypes included exact matches within one or two mutational steps from West Asian, Middle Eastern, and European sequences. Curiously, the unusual M haplotype of an unknown subclade, which is represented by two

Palestinians, is not present in the 4,100 West Eurasians studied by Richards et al. [2000].

Moroccan Jews show a relatively high level of haplotype diversity (Table 2) and haplotype sharing (six shared haplotypes) with the other Israeli populations. However, the presence of haplogroup V sequences, which are rare or absent in populations from the Middle East, suggests that Moroccan Jews are related more closely to their Northwest African host population [Rando et al., 1998]. The most frequent haplogroup among Moroccan Jews, represented by five different lineages, is H (35%). Three Moroccan Jews clustered together in a subclade of haplogroup HV1, defined by transitions at nps 15930 and 16172. HV1 was also found in Palestinians and Yemeni Jews. It is infrequent in the Middle East and Caucasus, and virtually absent elsewhere. Similarly, haplogroup (pre-HV)1 has been observed predominantly in East Africa and the Middle East, but not in 268 Northwest Africans [Rando et al., 1998], suggesting a Middle Eastern origin for some of the Moroccan Jewish population. This view is supported by haplotype sharing in haplogroup T2c between a Moroccan and two Iraqi Jews. Neither a Northwest African nor a Middle Eastern origin could be inferred for Moroccan Jewish K1, U3, J1, and X sequences, because matching HVS-I motifs are spread widely [Rando et al., 1998; Krings et al., 1999; Richards et al., 2000].

In Yemeni Jews, no haplotype occurred more than twice. The R* individual likely belongs to a novel clade characterized by a rare HVS-I transition at np 16071. But in contrast to other haplogroup R sequences found at low frequencies in West Asian populations [Richards et al., 2000], it carries the T rather than the consensus C allele at np 16223. Four Yemeni, three Moroccan Jews, and two Palestinians shared common HVS-I haplotypes in haplogroup HV1 with populations of the Middle East, Caucasus, and West Asia [Richards et al., 2000]. The Yemeni Jews share a rare U3a subclade with Iraqi Jews, defined by transitions at nps 9656 and 16086, suggesting a shared ancestry.

Five different mtDNA haplotypes belonging to clades T2a1, U7, U6, and H were observed in 16 Samaritans. Nine sequences belong to a rare subclade of haplogroup T2a, which is defined by transitions at nps 12454 (Val to Ile change in the ND5 gene) and 16288. Two Samaritans share an additional transition at np 12793. The *m.12454G>A* mutation has been observed only once to date in an individual of European ancestry (#252 in Herrnstadt et al. [2002]). The associated HVS-I motif is also rare and has been detected only in one Italian sequence [Richards et al., 2000]. Five Samaritans fall into haplogroup U7, which ranges from India to the Middle East [Richards et al., 2000; Kivisild et al., 2003], but is rare or absent elsewhere. These five Samaritan U7 mitochondria share a transition at np 15511, which is not found among other Middle Eastern sequences. The Samaritan U6 lineage is likely a descendant from a non-Samaritan female [Bonné-Tamir et al., 2003]. Thus, 14 out of 16 Samaritans carried two distinct haplotypes that are rare or absent in other West Eurasian populations.

Estimates of mtDNA nucleotide diversity vary greatly in the Israeli populations. The highest are found in Ethiopian, Iraqi and Ashkenazi Jews, as well as in Palestinians ($21–28 \times 10^{-4}$), while values in Libyan and Moroccan Jews ($13–14 \times 10^{-4}$) are low. In contrast to the Y-chromosome pattern, in which Palestinians showed the lowest nucleotide diversity, mtDNA diversity of the Palestinians is among the highest (Table 2). Haplotype diversity is the lowest in Samaritans. This and the positive Tajima's D value suggest a history of endogamy for the Samaritan maternal lineages. Otherwise, mitochondrial Tajima's D values are more negative than those estimated for the Y-chromosome, though they do not depart significantly from neutrality. There are several explanations for this, which are not necessarily mutually exclusive. First, the average ratio of the rates of nonsynonymous to synonymous substitutions estimated from 277 worldwide mitochondrial genomes (data not shown) was 0.40, which differed significantly from the expectation of 3.45 under neutrality. This suggests that directional selection is acting on the human mitochondrial genome (see also Elson et al. [2004] and Ruiz-Pesini et al. [2004]). Second, the more negative mtDNA Tajima's D values could reflect a faster expanding mitochondrial than Y-chromosomal gene pool. Third, the difference could be the result of the observed greater mitochondrial than Y-chromosomal population substructure, without changes in population size [Hammer et al., 2003].

As with the Y-chromosome data, principal component analysis of the mtDNA haplotypes places Africans and Ethiopian Jews in a distinct cluster (Fig. 2B). But unlike the Y-chromosome, non-Ethiopian Jewish populations do not form a close cluster that separates them from other Middle Eastern and European populations. Rather the mtDNA lineages of Iraqi and Yemeni Jews form a cluster with Samaritans and Palestinians that also includes Ashkenazi Jews and Europeans, while Libyan and Moroccan Jews cluster with Druze.

Combined Analysis of Y-chromosome and mtDNA Haplogroups

The matrix of pie charts in Figure 4 depicts the distribution of pairs of Y-chromosome and mtDNA haplogroups in 18 sub-Saharan Africans, five Sudanese, 17 Ethiopian Jews, 12 Samaritans, 21 Europeans, and 20 each of Ashkenazi Jews, Libyan Jews, Moroccan Jews, Yemeni Jews, Iraqi Jews, Druze, and Palestinians. Africans and non-Africans form two distinct clusters. This is consistent with a small number of Africans having founded the expansion into Eurasia. Sub-Saharan Africans belong generally to Y-haplogroups A, B, and E [Cruciani et al., 2002; Semino et al., 2002], and mtDNA haplogroups L0–L3 [Salas et al., 2002; Mishmar et al., 2003]. Ethiopian Jews and Sudanese are also represented in the Y-chromosome haplogroups J2 and K. In a larger study of 608 male subjects from 22 African populations

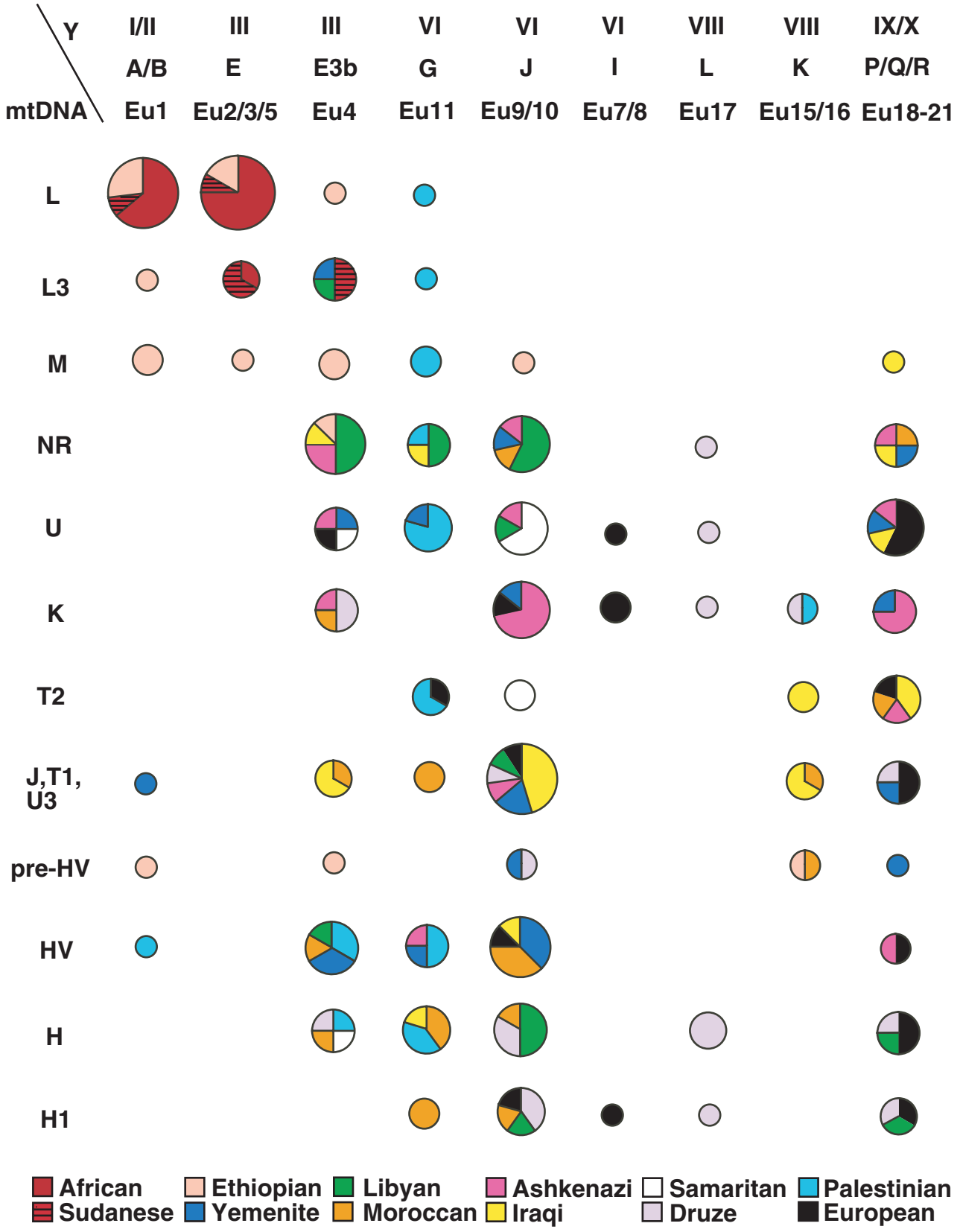

FIGURE 4. Distribution of Y-chromosome and mtDNA haplogroups of 208 male individuals in the 11 populations described in Figure 2. Three sets of Y haplotype nomenclatures are given, as in Figure 1. The populations are in different colors as indicated. The area of each pie chart represents on a linear scale the number of individuals carrying a particular combination of Y-chromosome and mtDNA haplotypes, with the smallest representing single individuals.

[Cruciani et al. 2002], haplogroup J2 occurred at low frequency in northern Africa and Ethiopia only, while haplogroup K was found both in Ethiopia (1/22) and the Fulbe from Cameroon (3/17), likely due to back migration of Asian Y-chromosomes to sub-Saharan Africa. The majority of mitochondrial lineages of Ethiopian Jews belong to haplogroups L0–L5 and M1. Previously, haplogroup M1 had been found in the Amara people, who are of both Cushitic and Abyssinian ancestry, and in the Cushitic speaking Oromo people [Passarino et al., 1998; Quintana-Murci et al., 1999].

Outside Africa, carriers of Y-chromosome haplogroups A and B are rare. In a study of 1,007 European and West Asian Y-chromosomes [Semino et al., 2000], a single haplogroup A individual was detected in Sardinia. In the present study, one Yemeni haplogroup A and one Palestinian haplogroup B individual were observed. The rarity of African haplogroups A and B in Israeli populations is surprising given the geographic vicinity of the Arabian Peninsula to Ethiopia and Sudan, where haplogroup A and B Y-chromosomes are common [Cruciani et al., 2002]. It is also astonishing that the mitochondrial lineages L and M, with the exception of four Palestinians and one Iraqi Jew, were not observed in any other Israeli populations, although haplogroup M has been found at high frequency in the South-Arabian Peninsula [Quintana-Murci et al., 1999] and India [Passarino et al., 1996]. The origin of the five pre-HV lineages observed in East Africa is unclear, but they may have originated during the colonization of Abyssinia by the Semitic Sabaeans, who ruled Southern Arabia for more than one millennium until the first century AD.

Figure 4 underscores the paucity of Y-chromosomal haplotype diversity in our Palestinian sample (Table 2). In contrast, Palestinians show the greatest diversity of mitochondrial haplotypes. This discrepancy in haplotype diversity between the uniparental systems is similar to that reported in the El-Bayadia and El-Sawarka tribes in northern Sinai, whose Y-chromosomal gene pool showed extremely low genetic diversity compared to 153 men from the Nile Delta and Valley [Salem et al., 1996]. By contrast, the same study found no reduction in diversity in the mitochondrial gene pool of Sinai. This was attributed to the longstanding social practices of male polygamy and patrilocal exogamy of Sinai tribal groups.

High diversity of mtDNA haplotypes over all Israelis suggests that the female founders of each Jewish group were few in number and of different ancestries, while there may have been migration of males among the Jewish populations. Subsequent transmission of Jewishness through the female line maintained this between-group mtDNA variation. Although matrilineal group structure has been reported previously [Oota et al., 2001], it is more usual that variation among populations for Y-chromosome genotypes exceeds that for mtDNA haplotypes [Seielstad et al., 1998; Wilson et al., 2001], and the latter is usually attributed to the patrilocal structure of the social system.

Origins and History of Samaritans

This study confirms the strong male-based endogamy of the Samaritan culture. First, the Y-chromosome nucleotide diversity (Table 2) is lower than any except our Palestinian sample. Haplotype diversity in Samaritans, on the other hand, is relatively high. This is due to the continuity of four distinct paternal lineages, which have persisted even though the population size of Samaritans fell drastically by the early 20th century. The low level of haplotype diversity in Samaritan maternal lineages was comparable to the pattern observed throughout different Jewish communities, each showing obvious founder effects, though not overlapping in ancestry. Nevertheless, the data in Tables 3 and 4 indicate that the Samaritan and Jewish Y-chromosomes have a much greater affinity than do those of the Samaritans and their longtime geographical neighbors, the Palestinians. However, this is not the case for the mtDNA haplotypes. In fact, Table 4 shows that distances of Samaritans to Jews and Palestinians for mtDNA are about the same. Further, the low mitochondrial haplotype diversity suggests that the rate of maternal gene flow into the Samaritan community has not been very high despite their tradition to regard children of male Samaritans born to females from outside as Samaritan.

The Cohen family represents an interesting subgroup of the Samaritans. It can be traced to a single individual some 250 years ago [Cazes and Bonné-Tamir, 1984]. Consistent with a previous report [Bonné-Tamir et al. 2003], the Samaritan Cohens did not carry the Cohen modal haplotype (data not shown), which is defined by the repeat numbers 14, 16, 23, 10, 11, and 12 at the Y-chromosome microsatellite loci DYS19, DYS388, DYS 390, DYS391, DYS392, and DYS393, respectively [Thomas et al., 1998]. This six-microsatellite haplotype, together with its one-mutation neighbors, form a cluster that is found at frequencies of 69.4 and 61.4% in Ashkenazi and Sephardic Cohanim, while its frequency in the general Jewish population is about 14% [Thomas et al., 1998; Nebel et al., 2001]. The Cohen modal cluster is invariably associated with haplogroup J, which probably originated some 15,000 years ago in the northern part of the Fertile Crescent [Hammer et al., 2000; Quintana-Murci et al., 2001], whence it began its expansion throughout the Middle East 7,500 years ago [Nebel et al., 2001; Quintana-Murci et al., 2001]. To our surprise, all non-Cohen Samaritan Y-chromosomes belonged to the Cohen modal cluster. The single exception was an M67 lineage from the Danfi family. It was two microsatellite mutation steps removed from the Cohen modal haplotype. Based on the classification by Nebel et al. [2001], the Samaritan M172 lineages carried the so-called Muslim Kurd modal haplotype (14-15-23-10-11-12). The Samaritan M267 lineages differed from the classical Cohen modal haplotype at DYS391, carrying 11 rather than 10 repeats. Based on the close relationship of the Samaritan haplogroup J six-microsatellite haplotypes with the Cohen modal haplotype, we speculate that the Samaritan M304 Y-chromosome

lineages present a subgroup of the original Jewish Cohanim priesthood that did not go into exile when the Assyrians conquered the northern kingdom of Israel in 721 BC, but married Assyrian and female exiles relocated from other conquered lands, which was a typical Assyrian policy to obliterate national identities. This is in line with biblical texts that emphasize a common heritage of Jews and Samaritans, but also record the negative attitude of Jews towards the Samaritans because of their association with people that were not Jewish. Such a scenario could explain why Samaritan Y-chromosome lineages cluster tightly with Jewish Y-lineages (Fig. 2A), while their mitochondrial lineages are closest to Iraqi Jewish and Palestinian mtDNA sequences (Fig. 2B). Finally, the high degree of homogeneity in each of the four male Samaritan lineages, which holds with two exceptions even over 13 microsatellite loci (data not shown), underscores the strong male-based endogamy of the Samaritan culture that has effectively limited any male-driven gene flow between the four families.

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