Int J Legal Med (2006) 120: 271–281
DOI 10.1007/s00414-006-0083-0

ORIGINAL ARTICLE

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Mitochondrial DNA sequence variation in Jewish populations

Received: 11 March 2003 / Accepted: 13 February 2006 / Published online: 18 May 2006

Abstract Sequence analysis of HVRI and HVRII mitochondrial DNA was carried out on 107 Jewish samples from Ashkenazi, Oriental, North African, and Sephardic origins. Control region sequences were assigned to a haplogroup by means of the analysis of the RFLP motif -7025 *AluI* or by using sequence motifs. A total of 88 different haplotypes were observed with a lower incidence of unique haplotypes (68.2%) than in other populations. Four individuals with one position of sequence heteroplasmy at nucleotides 16093, 16134, 16169, and 235, respectively, were detected. The mean pairwise difference in the Jewish population was 9.7 nucleotides. The gene diversity was 0.996, and the random match probability was 1.3%. When the data were compared with the autosomal and Y-chromosome markers previously studied in these populations, sex-specific differences could be observed in the Jewish populations. This fact must be taken into account for choosing suitable databases to correctly weigh the value of the evidence of a mtDNA and/or Y profile match.

Keywords mtDNA · HVRI · HVRII · Haplogroups · Jewish populations

Introduction

Sequence analysis of mitochondrial DNA proved to be of great interest in evolutionary studies and for forensic purposes. The reasons are that the mtDNA is highly polymorphic due to a rapid rate of evolution [17] and shows maternal inheritance [23]. The noncoding region of mtDNA, known as the control region, accumulates many more mutations than the rest of the molecule, making it a useful tool for studying short-term evolutionary phenomena [67] and the tool of choice for human forensic identification studies in cases where DNA is only present in reduced amounts or where it is degraded [24, 25, 36, 44]. The statistical interpretation of the results depends on the population frequency of a particular sequence or haplotype. Moreover, the occurrence of population-specific lineage groups [65] and an increase in the number of haplotypes with sample size [14] were described. Different studies have also shown the importance of taking into account the ethnical and/or geographical differences of the populations for forensic purposes [11, 21, 30, 43]. For these reasons, it is essential to determine the haplotype frequency distribution of HVRI and HVRII in the mtDNA in any population of interest so that databases can be expanded as much as possible.

Jews can be traced back to populations occupying a small geographic area in Israel several thousand years ago [12]. Modern Jews constitute one ethnic group split into several groups, the most numerous of which are the Ashkenazim who have resided in north-eastern Europe for centuries; the Sephardim ("Spanish" in Hebrew) who, after their expulsion from Spain in 1492, lived in other Mediterranean countries, especially Turkey; the North African where evidence exists of Jewish communities as early as the first centuries AD that were augmented as a consequence of the Spanish expulsion; and the Oriental Jews who have lived in Middle East countries throughout their history [5, 27]. Geneticists have studied Jewish populations since the turn of the 20th century in an attempt to unravel what must be a complex system of interrelationships among Jewish communities and their non-Jewish neighbors. Several studies of "classical" and DNA markers have attempted to describe these genetic relationships and to study the evolutionary factors that have occurred during the diaspora. These studies have provided evidence both

Electronic Supplementary Material Supplementary material, including all sequencing electropherograms, is available for this article at http://dx.doi.org/10.1007/s00414-006-0083-0

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Table 1 Variable positions in the mtDNA HVRI for 107 Jewish individuals

mtDNA HVRI		1111111111	1111111111	1111111111	1111111111	1111111111	1111111111	1111111111	1111111111	1111111111	
		6666666666	6666666666	6666666666	6666666666	6666666666	6666666666	6666666666	6666666666	6666666666	
		0000000011	1111111111	1111111111	1112222222	2222222222	2222222222	3333333333	3333333333	3333333333	
		5668889912	2234456666	7777888888	8990122333	4445666677	8889999999	0001112222	4455555666		**Length**
		1790262344	6945873789	1239023488	9239834149	3896014508	4780124689	1491890458	3424567026		**Heteroplasmy**
				.1							
Anderson	Hg	ACCACTTTCT	TGCGCTACCC	ATCCAAACC-	TCCTCCTTCC	TCTCCCCACC	ACTCCCCCTA	CTATAGCTTC	ACTCCTTCTC		
Ashkenazi											
Ash2	**U7**	....	....	.........-	....	....	....T.....	.C..T.....	....		
Ash1	**-**	....	....	.........-	....	....	....	....	....		
Ash7	**H**	....	....	.........-	....	....	....	....	....		
Ash12	**H**	...G......	....	......C..-	C.........	....	....	....	.....C.T..	16183-16193	
Ash5	**HV1**	.T........	....	......C..-	C.........	....	....	....	....	16183-16193	
Ash19	**(PreHV)**	1..........	C.........	.........-	....	....	..C.......	....	........C.		
Ash8	**I**	....	.A........	.........-	.....T....	......T.T.	....	...C.A....	........C.		
Ash10	**I**	....	.A........	.........-	.....T....	......T.T.	....	...C.A....	........C.		
Ash20	**J1**	..T...C...	C.........	.........-	....	.....T....	....	....	....		
Ash17	**K**	....	....	.........-	......C...	....	....	...C......	....		
Ash4	**K**	....	....	.........-	......C...	....	....	...C......	....		
Ash13	**K**	....	....	.........-	......C...	....	....	...C......	....		
Ash3	**K**	....	....	.........-	......C.T.	....	....	...C......	....		
Ash15	**K**	....	....	.........-	......C.T.	....	....	...C......	....		
Ash9	**K**	....	....	.........-	......C.T.	....	....	...C......	....		
Ash6	**K**	....	....	.........-	.....TC.T.	....	....	...C......	....		
Ash11	**K**	....	....	.........-	.....TC.T.	....	....	...C......	....		
Ash14	**T4**	.......C..	C.........	.........-	....	....	......TT..	.......C..	....		
Ash16	**W**	....	....	.........-	.....T....	....	.....T....	....	....		
Ash18	**X**	....	....	......C..-	C....T....	.........T	....	....	......C...	16183-16193	
Oriental											
Irq4	**B**	....	.A........	.....CC..-	C.......T.	....	....	....	....	16182-16193	
Irq8	**H**	....	....	.........-	....	....	....	...C......	....		
Irn16	**H**	....	....	.........-	....	....	G.........	....	........C.		
Irn17	**H**	....	....	.........-	....	....	G.........	....	........C.		
Irn22	**H**	....	....	.........-	....	....	G.........	....	........C.		
Irn21	**H**	....	....	.........-	....	....	G.........	....	........C.		
Irn23	**H**	....	....	.........-	....	...T......	....	....	..C.......		
Irq3	**J**	..T.......	C.........	.........-	....	....	.T........	...C.A....	....		
Irn20	**J2**	..T.......	C.........	........T-	..T.......	....	....	....	....		
Irn18	**JT**	....	C...T.....	.........-	...C......	....T.....	....	..G.T.....	....		
Irn19	**JT**	....	C...T.....	.........-	...C......	....	....	..G.T.....	....		
Irq7	**T**	....	C.........	.........-	....	....	......TT..	....	....		
Irn13	**T2**	....	C..A......	.........-	....	....	......T...	.C........	....		
Irq1	**T3**	....	C.........	.........-	....	....	.....TTT..	....	....		
Irq11	**T3**	....	C.........	.........-	....	....	.....TTT..	....	....		
Irn12	**T3**	....	C.........	.........-	....	....	.....TTT..	....	....		
Irq9	**T3**	....	C.........	.........-	....	....	.....TTT..	....	....		
Irq6	**U1**	....	....	.........-	....	..C.......	.....TTT..	....	....		
Irq10	**U3**	.....C....	....	.........-	....	....	....	....	G.........		
Irq2	**-**	....	....	.........-	.....T....	....	.........G	...C......	....		
Irq5	**-**	....	....	.........-	.....T....	....T.....	........C.	....	....		
Irn14	**-**	..T.......	...A......	.........-	....	.....T....	...T......	....	....		
Irn15	**-**	..T.......	...A......	.........-	....	.....T....	...T......	....	....		
North African											
Mor11	**H**	....	....	.........-	....	....	....	....	....		
Mor12	**H**	....	....	.........-	....	....	....	....	....		
Tun31	**H**	....	....	.........-	....	....	....	....	....		
Mor16	**H**	....	....	.........-	....	....	....	....	...T......		
Lib4	**H**	....	....	.........-	.T........	....	....	....	....		
Lib8	**H**	....	....	.........-	....	.....G....	.........G	....	....		
Mor17	**H**	....	.....C....	.........-	C.........	....	....	....	....	16184-16193	
Tun26	**H**	.......C..	....	.........-	.T........	....	....	....	....		
Mor19	**HV1**	.T........	....	.C.......-	....	....	....	....	....		
Lib3	**(PreHV)**	1..........	C........Y	.........-	....	....	....	....	........C.		
Tun25	**(PreHV)**	1..........	C.........	.........-	....	....	....	....	........C.		
Lib5	**(PreHV)**	1..........	C.........	.........-	....	....	....	....	........C.		
Tun29	**I**	....	.A........	.........-	.....T....	....	....	...C......	....		
Tun30	**I**	....	.A........	.........-	.....T....	....	....	...C......	....		
Lib7	**J1**	..T.......	C..A......	.........-	....	.....T....	....	....	....		
Mor13	**J1**	..T.......	C..A......	.C.......-	.T........	.....T....	....	....	.T........		
Mor18	**J2**	..T.......	C.........	.........-	..T.......	..C....T..	....	....	....		
Mor10	**K**	....	....	G........-	......C...	....	....	...C......	....		
Mor20	**K**	....	....	.........-	......C...	....	....	...C..T...	....		
Tun32	**L3b**	C	....	.........-	.....T....	.........T	....	....	........C.		
Lib1	**R1**	....	..T.......	...T.....-	A....T....	.........T	....	...C......	....		
Lib2	**R1**	....	..T.......	.........-	A....T....	.........T	....	...C......	....		
Lib6	**R1**	....	..T.......	.........-	A....T....	.........T	....	...C......	....		
Tun24	**R1**	....	..Y.......	.........-	A....T....	.........T	....	...C......	....		
Tun27	**R1**	....	..T.......	.........-	A....T....	.........T	....	...C......	....		
Tun33	**R1**	....	..T.......	.........-	A....T....	.........T	....	...C......	....		
Mor14	**T2**	....	C......T..	.........-	....	.....T....	......TT..	.C........	....		
Tun23	**T2**	....	C.........	.........-	....	....	......TT..	.C........	.T........		

Table 1 (continued)

Mor15	**U3**	....	....	.........-	....	....	....	...C......	G.........	
Tun22	**U4**	....	....	.........-	....	....	....	....	.....C....	
Tun28	**V**	....	....	.........-	....	....	........C.	....	....	
Lib9	**X**	....	..T.T.....	.........-	C....T....	.........T	....	...C......	....	
Mor21	**X**	....	....	......C..-	C....T....	.T.......T	....	....	....	16184-16193
Sephardic										
Tuk5	**H**	....	....	.........-	....	....	....	....	....	16183-16193
Tuk15	**H**	....	....	.........-	....	....	....	....	....	
Tuk11	**H**	....	....	.........-	....	....	....	....	....	
Tuk2	**H**	....	....	.........-	.........T	....	....	....	........C.	
Tuk3	**H**	.....C....	....	.........-	....	....	....	....	....	
Tuk21	**H**	.....C....	....	.........-	....	....	....	....	....	
Tuk4	**H**	........T.	....	.........-	....	....	....	....	....	
Tuk7	**H**	....	...A......	.........-	....	....	....	....	....	
Tuk13	**H**	....	....	.........-	....	....	....	...C......	........C.	
Tuk22	**H**	....	....	.........-	....	....	....	...C......	........C.	
Tuk18	**H**	....	....T.....	.........-	....	...T......	....	.....A....	....	
Tuk19	**H**	....	....	.........-	....	....	....	........C.	....	
Tuk8	**H**	....	....	.........-	....T.....	....	....	.........A	........C.	
Tuk25	**H**	....	....	.........-	....T.....	....	....	.........A	........C.	
Tuk26	**H**	....	....	.........-	....T.....	....	....	.........A	........C.	
Tuk27	**H**	G.........	....	.........-	....	....	....	....	....	
Tuk28	**H**	....	....	...T.....-	....	....	....	....	....	
Tuk30	**H**	....	....	.........A	.T........	....	....	....	........C.	
Tuk1	**J**	..T.......	C.........	.........-	....	....	....	...C......	....	
Tuk24	**J**	..T.......	C.........	.........-	....	.........T	....	....	.........T	
Tuk14	**J1a**	..T.......	C..A......	.........-	.......C..	.....T....	....	....	....	
Tuk17	**J2**	..T.......	C.........	G...G....-	..T.......	.........T	....	....	....	
Tuk29	**J2**	..T.......	C.........	.........-	..T.......	....	......T...	....	....	
Tuk20	**K**	....	.A......T.	.........-	C.....C...	....	....	...C......	....	16184-16193
Tuk23	**T**	....T.....	C.....G...	.C.......-	C.........	C.........	......T...	....	....	16184-16193
Tuk12	**T2**	....	C.........	.........-	....	....	......TT..	.C........	....	
Tuk31	**U4**	....	....	.........-	....	....	....	....	.....C....	
Tuk9	**V**	....	....	.........-	....	....	........C.	....	....	
Tuk10	**X**	....	....	......C..-	C.........	.........T	....	....	....	16183-16193
Tuk16	-	.T........	....	..T...C..-	C.........	....	....	T.........	....	16183-16193
Tuk6	-	.......**Y**..	....	.......T.-	....	....	....	....	....T.C...	

Point mutation heteroplasmy was designated according to recommendations of International Union of Pure and Applied Chemistry

Heteroplasmic positions were indicated in bold

The position of the insertions found was been indicated with a number followed by a dot and a number *Ash* Ashkenazi, *Irq* Iraqui, *Irn* Iranian, *Lib* Libyan, *Mor* Moroccan, *Tun* Tunisian and *Tuk* Turkey and *Hg*=haplogroup

for the common genetic origin of Jewish communities and for admixture between Jewish communities and their host peoples ([8, 41, 42, 56] among others), although the extent of this admixture is controversial [1, 7, 28, 34, 35, 37, 40, 46]. Studies based on low-resolution mtDNA RFLP [57, 63] or HVRI sequences [2, 62] were published, but these studies lack HVRII sequences and are therefore forensically useless, especially because many mtDNA types are very similar to each other in HVRI. Therefore, no mtDNA HVRI and II databases were reported to date for Jewish populations, which are essential to estimate random match probabilities in forensic casework.

The purposes of the present study were: (1) to develop a HVRI and HVRII sequence mtDNA database from Jewish individuals, (2) to compare the results with other non-Jewish circum-Mediterranean populations, and (3) to compare the differences in mtDNA found in Jews and non-Jews with those found using Y-chromosome and autosomal microsatellite data obtained from the same population samples.

Materials and methods

Population

DNA samples of 107 Jewish individuals were obtained from the collection of The National Laboratory for the Genetics of Israeli Populations at Tel-Aviv University. Following classical criteria, they were categorized into four groups: Ashkenazi (20 individuals), Oriental (12 Iranian and 11 Iraqi individuals), North African (12 Moroccan, 12 Tunisian, and nine Libyan individuals), and Sephardic (31 individuals from Turkey).

mtDNA amplification and sequencing

The mtDNA regions subjected to analysis were 16045–16366 (HVRI region) and 69–374 (HVRII). Amplifications were performed using 2.5 µl of the sample in a 25-µl reaction volume on a 2400 GeneAmp Thermal Cycler (Perkin-Elmer). The temperature profile for 30 amplification cycles was 94°C for 1 min, 50°C for 1 min, and 72°C for 1 min. The primers used in these reactions were L15996 (5′-CTC CAC CAT TAG CAC CCA AAG C-3′) and H16401 (5′-TGA TTT CAC GGA GGA TGG TG-3′) for HVRI and L048 (5′-CTC ACG GGA GCT CTC CAT GC-3′) and H408 (5′-CTG TTA AAA GTG CAT ACC GCC A-3′)

for HVRII. For those sequences containing a homopolymeric cytosine stretch from positions 16184 to 16193 (usually associated with length heteroplasmy), additional amplification and sequencing were performed using primers L16209 (5′-CCC CAT GCT TAC AAG CAA GT-3′) and H16164 (5′-TTT GAT GTG GAT TGG GTT-3′). In HVRII, when necessary, additional sequencing was carried out with primer H285 (GGG GTT TGG TGG AAA TTT TTT G). Amplicons were purified with a QIAquick PCR purification kit (Qiagen, Germany) and the sequence

Table 2 Variable positions in the mtDNA HVRII for 107 Jewish individuals

mtDNA HVRII											
	11111111	1111111222	22222**2**2222	222223	3	3	33	3
	7714555588	8889999000	0112**2**3445	667990	0	0	11	7
	2346012323	5893459034	7575**5**9290	371259	9	9	59	4
				.1.2.3.1				
Anderson	TACTCCTACA	GAAACTTAGT	GATGGATCAT	ATCTC-	-	-	-T	A
Ashkenazi								
Ash2	.G...TC...	....	....	G....C	-	-	C.	.
Ash1	....	....	....	G....-	-	-	C.	.
Ash7	....	....	....	G....C	-	-	C.	.
Ash12	.........G	....	....	G....C	C	C	C.	.
Ash5	......C...	....	....	G....C	-	-	C.	.
Ash19	....	....	....	G....C	-	-	C.	.
Ash8	.G........	......C..C	C	G....-	-	-	C.	.
Ash10	.G........	......C..C	C	G....C	-	-	C.	.
Ash20	.G........	A.........	....A.....	G...T-	-	-	C.	.
Ash17	.G.C..C...	....	....	G....-	-	-	C.	.
Ash4	.G.C..C...	....	....	G....-	-	-	C.	.
Ash13	.G.C..C...	....	....	G....C	-	-	C.	.
Ash3	.GT.......	....	....	G....-	-	-	C.	.
Ash15	.GT.......	....	....	G....-	-	-	C.	.
Ash9	.G........	....	....	G....-	-	-	C.	.
Ash6	.GT.......	....	....	G....-	-	-	C.	.
Ash11	.GT.......	....	....	G....-	-	-	C.	.
Ash14	.G........	....	.....**R**....	G....-	-	-	C.	.
Ash16	.G........	....TCC..C	A.........	G....-	-	-	C.	.
Ash18	.G.....G..	.....C..A.	...A......	G....-	-	-	C.	.
Oriental								
Irq4	.G....C...	.....C....	....	G....C	C	-	C.	.
Irq8	....	....	....	G....-	-	-	C.	.
Irn16	....	....	......C...	G....C	-	-	C.	.
Irn17	....	....	......C...	G....C	-	-	C.	.
Irn22	....	....	......C...	G....C	-	-	C.	.
Irn21	....	.....C....	......C...	G....C	-	-	C.	N
Irn23	...C......	....	....	G....C	-	-	C.	.
Irq3	.G........	....	....A.....	G...T-	-	-	C.	.
Irn20	.G....C...	....	....A.....	G...T-	-	-	C.	.
Irn18	.G.C.TC...	....	....	G....C	-	-	C.	.
Irn19	.G.C.TC...	....	....	G....C	-	-	C.	.
Irq7	.G........	....	.G........	G....C	-	-	C.	.
Irn13	.G....C...	....	....	G....-	-	-	C.	.
Irq1	.G....C...	....	....	G....C	-	-	C.	.
Irq11	.G....C...	....	....	G....C	-	-	C.	.
Irn12	.G....C...	....	....	G....C	C	-	C.	.
Irq9	.G....C...	....	....	G....C	C	-	C.	.
Irq6	.G....C...	....	....	G....C	-	-	C.	.
Irq10	.G..T.....	....	....	G....C	-	-	C.	.
Irq2	.G........	......C..C	C	G....-	-	-	C.	.
Irq5	.G........	....TC.G.C	A.........	G....C	-	-	C.	.
Irn14	.G..T.....	....	....	G.T.TC	C	-	C.	.
Irn15	.G..T.....	....	....	G.T.TC	-	-	C.	.
North African								
Mor11	....	.....C....	....	G....-	-	-	C.	N
Mor12	....	.....C....	....	G....-	-	-	C.	.
Tun31	....	....	....	G....C	C	-	C.	.
Mor16	....	....	....	G....C	-	-	C.	.
Lib4	....	.....C....	....	G....C	-	-	C.	.
Lib8	....T.C...	....	....	G....-	-	-	C.	.
Mor17	....	....	....	G....C	C	-	C.	.
Tun26	....	.....C....	....	G....-	-	-	C.	.
Mor19	........T.	....	....	G....C	-	-	C.	.
Lib3	....	....	....	G....-	-	-	C.	.
Tun25	....	....	....	G....-	-	-	C.	.
Lib5	....	....	....	G....-	-	-	C.	.
Tun29	.G..T.....	......C..C	C	G....-	-	-	C.	.
Tun30	.G..T.....	......C..C	C	G....-	-	-	C.	.
Lib7	.G........	....	....	G...T-	-	-	C.	.
Mor13	.G.C......	....	.......T..	G...T-	-	-	C.	.
Mor18	.G..T.C...	....	....	G...TC	-	-	C.	.
Mor10	.G........	....	....	G....-	-	-	C.	.
Mor20	.G.C..C..G	....	....	G....-	-	-	C.	.
Tun32	.G........	....	..C.......	G....C	-	-	C.	.

Table 2 (continued)

Lib1	.G....G..	.....C....	...A......	G....C - - C. .
Lib2	.G....G..	.....C....	...A......	G....- - - C. .
Lib6	.G....G..	.....C....	...A......	G....C - - C. .
Tun24	.G....G..	.....C....	...A......	G....C - - C. .
Tun27	.G....G..	.....C....	...A......	G....C - - C. .
Tun33	.G....G..	.....C....	....	G....C - - C. .
Mor14	.G.......	....	A.........	G....C - - C. .
Tun23	.G...TC...	....	....	G....C - - C. .
Mor15	.G..T.....	....	....	G....- - - C. .
Tun22	.G.......	.....C....	....	G....- - - C. .
Tun28	C........	....	....	G....- - - C. .
Lib9	.G....G..	.....C....	...A......	G....C - - C. .
Mor21	.G.......	.....C....	....	G....C C - C. .
Sephardic				
Tuk5	....	....	....	GC...- - - C. .
Tuk15	....	....	....	GC...C - - C. .
Tuk11	....	....	....	G....- - - C. .
Tuk2	....	....	....	G....C C - C. .
Tuk3	....	....	....	G....- - - C. .
Tuk21	....	....	....	G....- - - C. .
Tuk4	....	....	....	G....- - - C. .
Tuk7	....	....	....	G....- - - C. .
Tuk13	....	....	......C...	G....C - - C. .
Tuk22	....	....	......C...	G....C - - C. .
Tuk18	....	..GG......	........G.	G....C C - C. .
Tuk19	.....TC...	....	....	G....- - - C. .
Tuk8	....	....	........-.	G..C.- - - C. .
Tuk25	....	....	........-.	G..C.- - - C. .
Tuk26	....	....	........-.	G..C.- - - C. .
Tuk27	......C...	....	....	G....C C - C. .
Tuk28	....	....	....	G....C - - C. .
Tuk30	....	....	......C...	G....C - - C. .
Tuk1	.G.......	A.........	....A.....	G...T- - - C. G
Tuk24	.G.......	AG........	....A.....	G...T- - - C. .
Tuk14	.G..T.C...	.....C....	.G........	G...TC - - CC .
Tuk17	.G..T.C...	....	....	G...T- - - C. .
Tuk29	.G.C..C...	....	....	G...TC C - C. .
Tuk20	.G.......	....	....	G....- - - C. .
Tuk23	.G.......	....	....	G....C - - C. .
Tuk12	.G.......	....	....	G....C C - C. .
Tuk31	.G.......	.....C....	....	G....- - - C. .
Tuk9	C........	....	....	G....C - - C. .
Tuk10	.G.......	.....C....	...A......	G....- - - C. .
Tuk16	......C...	....	....	G....C C C C. .
Tuk6	....	.......G..	....	G....- - - C. .

Point mutation heteroplasmy was designated according to recommendations of International Union of Pure and Applied Chemistry
Heteroplasmic positions were indicated in bold
The position of the insertions found has been indicated with a number followed by a dot and a number
Ash Ashkenazi, *Irq* Iraqui, *Irn* Iranian, *Lib* Libyan, *Mor* Moroccan, *Tun* Tunisian and *Tuk* Turkey and *Hg*=haplogroup

analysis was performed directly on the purified products, using the same primers and the Big Dye Terminator Ready Reaction kit (Perkin-Elmer) following the manufacturer's instructions. Sequencing reaction products were purified by ethanol precipitation and were analyzed using an ABI PRISM 310 (PE/ABD) automated DNA sequencer. Each template was sequenced in both directions and the consensus sequence was aligned and compared with the Cambridge reference sequence (CRS) using the software SeqEd ver. 1.0.3 (PE/ABD). Proficiency testing of the GEP-ISFH WG (http://www.gep-isfg.org) was carried out as a quality control.

The RFLP motif-7025 *AluI* was also analyzed in the samples to determine those that showed haplogroup H. In non-H samples, every control region sequence was assigned to a haplogroup by using the sequence motifs indicated by Richards et al. [54] in supplementary data. Each haplogroup was associated with a specific set of substitutions involving some of the 117 nucleotide sites considered polymorphic in our analysis. In the cases in which a sequence contained mutations characteristic of two different haplogroups, a parsimony criterion to assign each case to the most probable haplogroup was followed. With both methodological approaches, a total of 93.5% of the sequences could be unambiguously assigned to one haplogroup.

Statistical analysis

The genetic diversity of each population was estimated in two different ways: (1) the mean pairwise differences performed by the ARLEQUIN package [59] and (2) employing the algorithm $h=n(1-\sum\chi^2)/(n-1)$ [61] where n is the sample size and χ is the frequency of each mtDNA haplotype. The probability of genetic identity was calculated using the formula $p=\sum\chi^2$. Pairwise genetic distance matrices between populations and neighbor-joining trees were obtained by using the phylogeny inference package (PHYLIP) [20].

Y-chromosome STRs data from the literature were used to build a neighbor-joining tree based on Reynolds's distance [51] by applying the PHYLIP package.

Table 3 The number of different haplotypes, variable sites, number of unique haplotypes, mean pairwise differences, gene diversity, and probability of identity that were found for HVRI, HVRII, and both regions taken together in 107 Jewish individuals

	HVRI	HVRII	HVRI + HVRII
Number of different haplotypes	74	65	88
Number of variable sites	79	38	117
Number of indels	1	4	5
Number of unique haplotypes	58	48	73
Mean pair wise differences	5.55	4.13	9.67
Gene diversity	0.988±0.004	0.981±0.005	0.996±0.002
Probability of genetic identity	0.021	0.028	0.013

Results and discussion

The region between positions 16045 and 16366 in HVRI and the region between positions 69 and 374 in HVRII were sequenced in 107 Jewish individuals from four different origins (Ashkenazi, Oriental, North African, and Sephardic) (Tables 1 and 2). Table 3 shows that for the HVRI region, 79 variable sites were detected and 74 different sequences (or haplotypes) were observed. For the HVRII region, 38 variable sites and 65 different haplotypes were observed in the 107 individuals studied. A total of 88 different sequences (or haplotypes) were identified from both regions I and II, defined by 117 variable positions. In total, 73 (68.2%) unique haplotypes were observed; 13 of which were detected in Ashkenazi, 16 in Oriental, 22 in North African, and 22 in Sephardic. In the literature, the majority of the mtDNA sequences are reported to be present only once within each population group, although this can change depending on the sequence and the population studied, ranging from a low frequency of unique haplotypes (60%) in the Asian American sequences to a high frequency (85%) in the French sequences [14]. In European populations, the frequency of unique haplotypes is usually about 80% [14, 18, 38, 50, 66, 68]. Thus, in the Jewish population studied, there was a low incidence of unique haplotypes. In relation to shared haplotypes, 15 haplotypes were shared by two or more individuals, 13 within the same population, and 2 from two populations (Table 4). The most frequent haplotype in Caucasian populations is the sequence defined by the transition of an adenine at position 263 to guanine and the insertion of a cytosine between positions 311 and 315 (with frequencies ranging between 3 and 5%) [14, 18, 66, 68]. In our study, this sequence was found in only two individuals (1.9%). Moreover, the haplotype 263G-309.1C-315.1C, which is among the most frequent sequences in Caucasoids, was only found in one Ashkenazi Jew. Also, it could be seen that each of the different Jewish groups had different modal haplotypes, which are not common in non-Jewish populations. Thomas et al. [62], studying HVRI, found a wide range of different modal haplotypes in different Jewish communities and pointed out that the non-CRS modal

Table 4 Haplotypes observed (%) in the Jewish populations that were found in at least two individuals

Haplotypes	Ashkenazi (20)	Oriental (23)	North African (33)	Sephardic (31)
16224 (C), 16234 (T), 16311 (C), 73 (G), 114 (T), 263 (G), 315.1 (C)	10.0	0	0	0
16224 (C), 16311 (C), 73 (G), 146 (C), 152 (C), 263 (G), 315.1 (C)	10.0	0	0	0
16223 (T), 16224 (C), 16234 (T), 16311 (C), 73 (G), 114 (T), 263 (G), 315.1 (C)	10.0	0	0	0
263 (G), 315.1 (C)	5.0	0	0	3.2
16284 (G), 16362 (C), 239 (C), 263 (G), 309.1 (C), 315.1 (C)	0	13.0	0	0
16126 (C), 16292 (T), 16294 (T), 16 296 (T), 73 (G), 152 (C), 263 (G), 309.1 (C), 315.1 (C)	0	8.7	0	0
16126 (C), 16292 (T), 16294 (T), 16 296 (T), 73 (G), 152 (C), 263 (G), 309.1 (C), 309.2 (C), 315.1 (C)	0	8.7	0	0
195 (C), 263 (G), 315.1 (C)	0		6.1	
16126 (C), 16362 (C), 263 (G), 315.1 (C)	0	0	9.1	0
16129 (A), 16223 (T), 16311 (C), 73 (G), 150 (T), 199 (C), 204 (C), 250 (C), 263 (G), 315.1 (C)	0	0	6.1	0
16134 (T), 16189 (A), 16223 (T), 16278 (T), 16311 (C), 73 (G), 153 (G), 195 (C), 225 (A), 263 (G), 309.1 (C), 315.1 (C)	0	0	9.1	0
16356 (C), 73 (G), 195 (C), 263 (G), 315.1 (C)	0	0	3.0	3.2
16218 (T), 16328 (A), 16362 (C), 249d, 263 (G), 292C, 315.1 (C)	0	0	0	9.7
16086 (C), 263 (G), 315.1 (C)	0	0	0	6.5
16311 (C), 16362 (C), 239 (C), 263 (G), 309.1 (C), 315.1 (C)	0	0	0	6.5

Modal haplotypes in each group are underlined

Table 5 mtDNA haplogroup distribution and diversity in Jewish populations

Haplogroups	Ashkenazi	Oriental	North African	Sephardic
B	–	1 (4.3)	–	–
U7	1 (5.0)	–	–	–
H	2 (10.0)	6 (26.1)	8 (24.2)	18 (58.1)
HV1	1 (5.0)	–	1 (3.0)	–
(PreHV)1	1 (5.0)	–	3 (9.1)	–
I	2 (10.0)	–	2 (6.1)	–
JT	–	2 (8.7)	–	–
J	–	1 (4.3)	–	2 (6.5)
J1	1 (5.0)	–	2 (6.1)	–
J1a	–	–	–	1 (3.2)
J2	–	1 (4.3)	1 (3.0)	2 (6.5)
L3b	–	–	1 (3.0)	–
R1	–	–	6 (18.2)	–
T	–	1 (4.3)	–	1 (3.2)
T2	–	1 (4.3)	2 (6.1)	1 (3.2)
T3	–	4 (17.4)	–	–
T4	1 (5.0)	–	–	–
U				
U1	–	1 (4.3)	–	–
U3	–	1 (4.3)	1 (3.0)	–
U4	–	–	1 (3.0)	1 (3.2)
K	8 (40.0)	–	2 (6.1)	1 (3.2)
V	–	–	1 (3.0)	1 (3.2)
W	1 (5.0)	–	–	–
X	1 (5.0)	–	2 (6.1)	1 (3.2)
Others	1 (5.0)	4 (17.4)	–	2 (6.5)
Total	20 (100)	23 (100)	33 (100)	31 (100)
Haplogroup diversity	0.842	0.890	0.903	0.665

Number of individuals with the percentage in parentheses

haplotypes in these populations are generally rare in the non-Jewish populations.

Insertions and deletions relative to the CRS are usually rather rare, except at sites nt 303-nt 309 and nt 311-nt 315 within a stretch of C's. We detected insertions in three positions: in position 16188 (+A) one sequence; at position 303–309 we identified 41 sequences with an insertion of a single C residue, 12 sequences with an insertion of two C residues, and two sequences with an insertion of three residues; and finally, at position 311–315, six cytidine residues, instead of the five in the Anderson reference sequence, were observed in all the 107 individuals analyzed. Moreover, we found three Sephardic individuals with a deletion in position 249.

The presence of two or more mtDNA populations in a single individual has shown a significant incidence in several studies [4, 18, 31, 60]. Following the criteria suggested to differentiate artifacts from true heteroplasmy, i.e., replication of sequences, sequence analysis of the opposite strand [45] and the proportions of the two peaks (secondary peak of more than 40% peak height below the primary peak) [31], we found four individuals with one position of heteroplasmy at nucleotides 16093, 16134, 16169 (mixture of cytosine and thymine), and 235 (mixture of adenine and guanine). Length heteroplasmy due to the presence of several populations of mtDNA molecules differing in the number of cytosines was described in HVRI and HVRII, especially in the homopolymeric tracts of cytosines between nt 16184–16193 and between nt 303–315 where a T to C transition at nt 16189 and nt 310, respectively, determines a polycytosine stretch [3, 39]. In this study, the T to C transition at position 16189 was observed in 11 subjects (10.3%) out of the 107 samples. Of these, the transition in nt 16189 was coupled with an A to C transversion at position 16183 in six sequences and with a double A to C transversion at nt 16182 and 16183 in one sequence, generating 11 and 12 cytosine stretches, respectively. In the remaining four samples, the stretch was ten cytosines long. Direct sequencing beyond these tracts showed the characteristic unclear sequence by overlap of different sequences derived from length heteroplasmy [3].

From among the parameters important for statistical evaluation of mtDNA typing in forensic casework, we calculated the random match probability (0.013) and the genetic diversity (0.996) (Table 3). These values were similar to those found in other Caucasian populations (i.e., [18, 60, 66, 68]).

In Tables 1 and 2 the corresponding haplogroup for every sample was also indicated. The frequencies of the haplogroups observed in all samples are summarized in Table 5. The more predominant haplogroup in Sephardic, Oriental, and North African samples was H with a frequency that except for the Sephardic (58.1%), was in the range reported for Near Eastern populations (~25–30%), which have lower H frequencies than European populations (~50%) [55]. In Ashkenazi, the most predominant was K with a high frequency (40%), which is similar to the results found by Behar et al. [2]. This high frequency of K among Ashkenazi Jews contrasts with its much lower frequency (<6%) found in the other Jewish groups studied and by other authors in both Near Eastern and European non-Jews [54]. Behar et al. [2] pointed out that within haplogroup K, based on HVRI sequences, there are two subtypes that are almost entirely restricted to Ashkenazi communities [16224–16234–16311 (7.6%) and 16223–16224–16234–16311 (10.6%)] whereas other K-subtypes are geographically widespread. In our Jewish samples, 11 individuals with haplotype K were found. They belonged to the K-common subtype in six individuals (three Ashkenazi, two North African, and one Sephardic) and to the Ashkenazi-K subtypes in five Ashkenazi Jews [16224–16234–16311 (15%) and 16223–16224–16234–16311 (10%)]. The European contribution [64] encompassed most of the examined Ashkenazi and Sephardic mtDNAs whereas the frequency of these haplogroups was lower in North African and Oriental Jews. Oriental Jews showed a high frequency (26%) of T and its subhaplogroups, which have a known origin in the Near East [53]. Other haplogroups also with known Near East origin, like

Table 6 Parameters of sequence divergence in HVRI in different populations

Population	N	K	A	K/N (%)	Gene diversity	π	Pi	I
Ashkenazi Jews	20	13	30	65.00	0.953±0.028	0.017±0.009	5.500±2.761	0.095
Oriental Jews	23	16	34	69.57	0.949±0.031	0.018±0.010	5.897±2.922	0.092
North African Jews	33	24	37	72.73	0.968±0.019	0.017±0.009	5.388±2.665	0.061
Sephardic Jews	31	25	45	80.65	0.983±0.014	0.015±0.008	4.753±2.388	0.049
Galicia	92	53	56	57.61	0.929±0.023	0.009±0.005	3.110±1.629	0.081
Basques	45	27	32	60.00	0.948±0.021	0.009±0.005	3.236±1.700	0.073
Morocco	50	34	38	68.00	0.960±0.018	0.014±0.008	4.604±2.298	0.059
NE Spain	118	83	59	70.34	0.969±0.011	0.013±0.007	4.348±2.165	0.039
Valencia	42	39	50	92.86	0.995±0.006	0.011±0.006	4.555±2.284	0.029
Majorca	45	31	40	68.89	0.957±0.022	0.011±0.006	4.765±2.373	0.064
Minorca	46	35	40	76.09	0.987±0.007	0.011±0.006	4.802±2.388	0.034
Germany	199	132	89	66.33	0.974±0.007	0.012±0.007	4.067±2.037	0.031
Italy	83	62	62	74.69	0.971±0.013	0.012±0.006	4.786±2.362	0.041
Sicily	106	61	62	57.58	0.928±0.022	0.011±0.006	4.259±2.128	0.081
Turkey	45	40	55	88.89	0.994±0.007	0.016±0.008	5.333±2.622	0.028
M East	41	38	63	92.68	0.996±0.006	0.019±0.010	7.018±3.365	0.028

N Number of individuals, *K* number of different sequences found, *A* number of variable nucleotide positions, π nucleotide diversity, *Pi* mean nucleotide pairwise differences, and *I* probability of genetic identity
Galicia [58], Basques [6], Morocco [10], Northeastern Spain [18], Valencia, Majorca and Minorca [48], Germany [38], Italy [60], Sicily [16], Turkey [15], and Middle East [19]

Pre-HV and U1 were found in five out of 107 individuals: three North African and one Ashkenazi belong to Pre-HV and one Oriental Jew was U1. The African contribution represented by haplogroups U6 and L only found sporadically in European populations was detected in one North African individual that exhibited L3b. In the sample from North African Jews, it is remarkable that the second most common haplogroup (18.2%) was R1 because this is an uncommon haplogroup in other populations.

To compare the results with other non-Jewish circum-Mediterranean populations, only HVRI data were used due to the larger availability of data on HVRI sequences in the literature. Table 6 shows the parameters of sequence

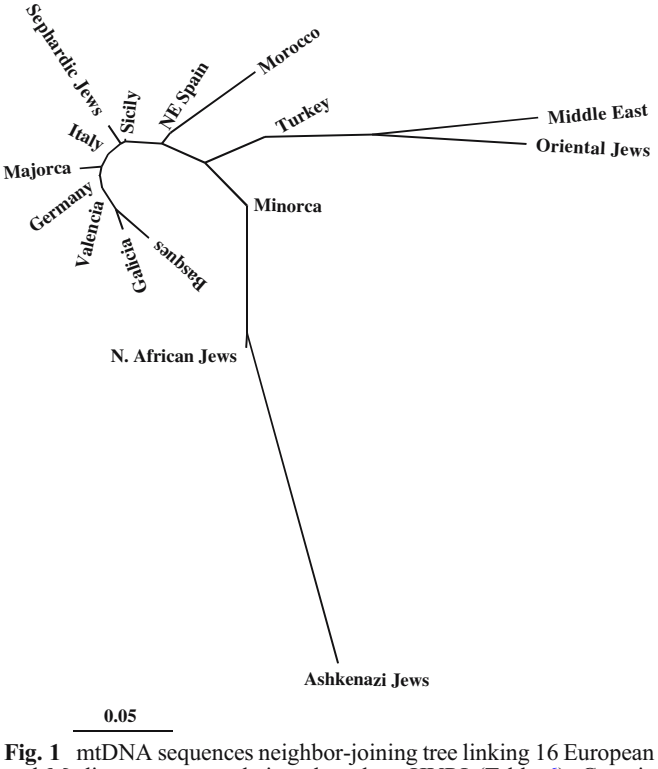

Fig. 1 mtDNA sequences neighbor-joining tree linking 16 European and Mediterranean populations based on HVRI (Table 6). Genetic distances are pairwise distances

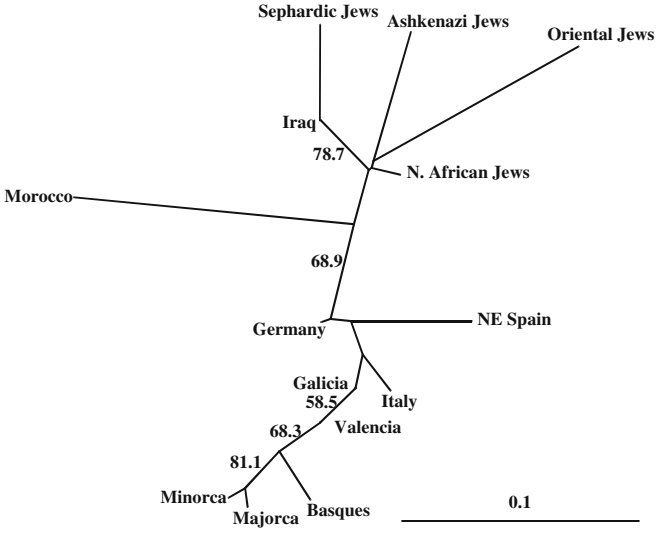

Fig. 2 Neighbor-joining tree based on Y-chromosome STRs (minimal haplotype) using Reynold's distance. The *numbers* indicate the bootstrap values (>50) in percentages. [Jewish populations (Picornell et al. 49); Galicia and Basques (González-Neira et al. 26); Morocco (Bosch et al. 9); Northeastern Spain (Gené et al. 22); Valencia, Majorca, and Minorca (Jiménez et al. 32, 33); Germany (Hidding and Schmitt 29); Italy (Ricci et al. 52); Iraq (Brinkmann et al. 13)]

divergence detected in each population in the present study and in seven populations taken from the literature. The mean pairwise differences in the Jewish populations were in the range of 5.4–5.9 with the exception of Sephardic Jews that had a lower value of 4.8. A clinal decrease of this value with longitude was detected by Salas et al. [58] from the Middle East (7.0) to the Basques and Galicians (3.1–3.2), which is compatible with the hypothesis of an ancient expansion from the Middle East to the Atlantic coast. The studied Jewish populations followed the trend of this cline, taking into account their Middle Eastern origin. The gene diversity showed values between 0.95 and 0.98 in the same range as the other circum-Mediterranean populations and the random match probability, based on HVRI, was between 4.9 and 9.5%.

Figure 1 shows a neighbor-joining tree linking European and Mediterranean populations based on HVRI sequences. It can be seen that most of the non-Jewish populations occur in a central cluster with no internal structure as reflected by the short interpopulation branches. Jewish populations show a considerable distance between them and, except for the Sephardim who are grouped with non-Jewish populations, they are linked to the tree through longer branches, reflecting their genetic differentiation. These results agree with Thomas et al. [62] who indicated that each of the different Jewish communities formed independently around distinct groups of maternal founders and that subsequent gene flow from the host populations was limited on the female side.

Autosomal microsatellite data obtained from the same population samples showed no significant differences between all four populations studied or between them and other circum-Mediterranean populations [47]. Y-chromosome data based on the so-called minimal haplotype [49] showed, as can be seen in Fig. 2, that all the Jewish populations were grouped in the same cluster together with the non-Jewish Near Eastern population and presented a clear differentiation with respect to the other non-Jewish populations. Therefore, sex-specific differences can be observed in Jewish populations and this fact must be taken into account for a suitable choice of databases to correctly weigh the value of the evidence of a mtDNA and/or Y profile match.

Acknowledgements This work was supported by grant PM97-0041 from the Dirección General de Enseñanza Superior (Spain) and by grants PRDIB-2002-GC3-15 and PRDT-2003-12099 from the Direcció General de Recerca, Desenvolupament Tecnològic i Innovació (Comunitat Autònoma de les Illes Balears). We thank Dr. Lourdes Prieto for her helpful technical assistance.

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