

The 49a,f Haplotype 11 is a New Marker of the EU19 Lineage that Traces Migrations from Northern Regions of the Black Sea

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ABSTRACT: Previous studies on human Y-chromosome polymorphisms in the European populations highlighted the high frequency of the 49a,f/TaqI haplotype 11 and of the Eu19 (M17) lineage in Eastern Europe. To better understand the origin and the evolution of the Eu19, and its relationship with 49a,f Ht11, this study surveyed 2,235 individuals (mainly from Europe and the Middle East) for the 49a,f Ht11 and for many biallelic markers defining the Eu19 lineage. As previously described, the highest frequency of Eu19 was found in Eastern Europe. All the Eu19 Y-chromosomes turned out to be 49a,f Ht11 or its derivatives, the distribution of which suggests that the Eu19/49a,f Ht11 emerged in Ukraine, probably in a Palaeolithic population. Thereafter, the spread of this

lineage toward Europe, Asia, and India occurred at different waves over a few thousands years. At present this seems to indicate the influence of the Ukraine Palaeolithic groups in the gene pool of modern populations. For the first time it is possible to make inferences about the evolution of some haplotypes of the 49a,f system. In spite of its unknown molecular base, this is one of the first most informative polymorphisms of the Y chromosome. *Human Immunology* 62, 922–932 (2001). © American Society for Histocompatibility and Immunogenetics, 2001. Published by Elsevier Science Inc.

KEYWORDS: Y-chromosome polymorphisms; East Europe; Ukraine; migrations

ABBREVIATIONS

MJ median joining network
RM reduced median
Ht haplotype

c-Ht compound haplotype
LGM Last Glacial Maximum

INTRODUCTION

The analysis of the Y-chromosome specific polymorphisms, which are not reshuffled by recombination, has proved to be powerful in identifying different male lineages in the genetic structure of human populations and in revealing traces of past human dispersals. Moreover,

for the reduced effective population size of the Y chromosome (1/4 with respect to autosomes), its variation is particularly sensitive to genetic drift and very suitable for detecting demographic expansions of small differentiated populations following climate improvement and/or in-

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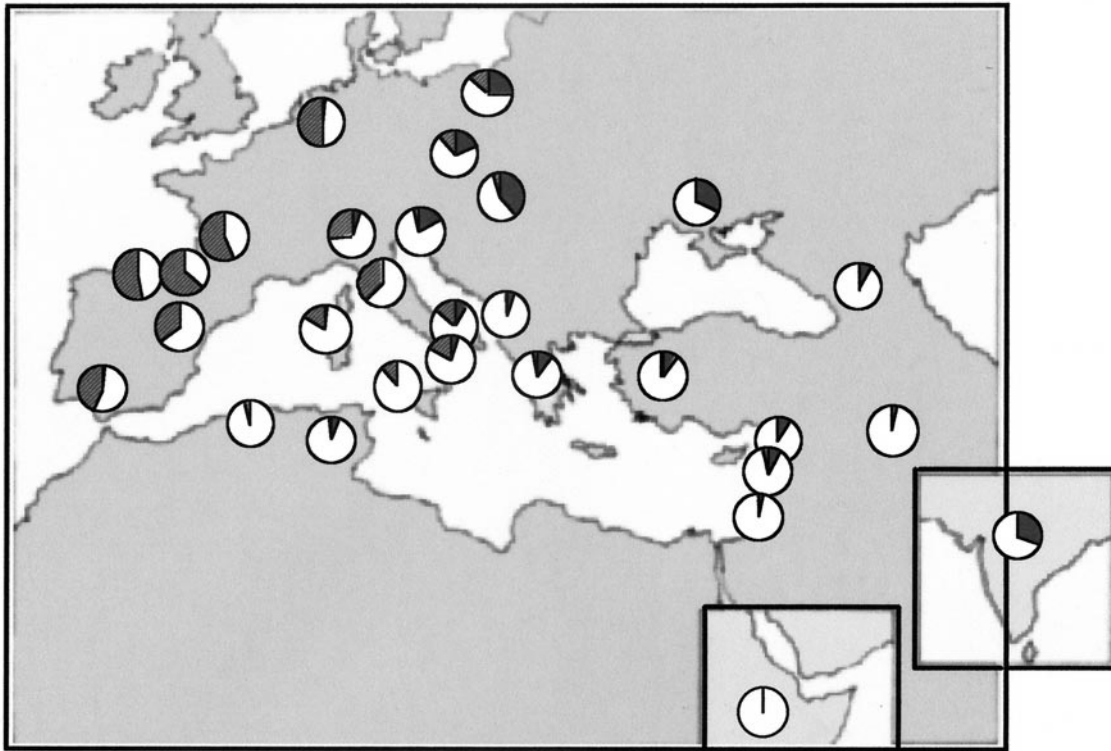


FIGURE 1 Map of the frequency distribution of the 49a,f Ht 15 (dashed) and Ht 11 (grey) in the analysed populations.

roduction of new technologies. Illustrative examples of this are the distributions of some Y-chromosome markers that illustrate the expansion and dispersal of European Palaeolithic groups and of Neolithic farmers [1–5]. In a previous study on the European Y chromosomes in Europe, two major lineages, Eu18 and Eu19, with opposite frequency gradients in West/East direction were identified [4]. Similar gradients were also evidenced by different Y-chromosome markers [3, 5]. Because the Eu18 and Eu19 lineages share the Euroasiatic marker M173, their distribution was interpreted as due to the expansion of variants originating or “selected by drift” in the different refuges (Eu18 in Western and Eu19 in Eastern Europe) during the Last Glacial Maximum (LGM). An attempt to estimate the age of mutations M173 and M17, which characterize Eu19, was made [4] and the values obtained were compatible with a Palaeolithic origin. In reference to Eu19, a further diffusion of this haplogroup could have occurred in association with the spread of the Yamnaia culture [6].

In previous studies on European populations, by using the 49a,f/TaqI Y specific system [7], a very high frequency of the 49a,f15 haplotype (Ht) was observed in Western Europe [1, 8–12], and a high incidence of 49a,f Ht11 seemed to be typical of the East European popu-

lations [13, 14]. Moreover, the geographic distributions of these two haplotypes paralleled the same West/East opposite gradient of frequencies (Figure 1) observed for Eu18 and Eu19. This observation suggested that the 49a,f/TaqI system could be used to further characterize the two European haplotypes Eu18 and Eu19. In this study, attention was focused on Eu19 by searching for additional Y chromosomes that belonged to this lineage. These chromosomes were identified by screening the population samples of our collection with the biallelic polymorphisms 12f2 [15], YAP [16], DYS257 [17], and the Eu19 biallelic markers M9, M173, and M17 [18, 19]. Then, their variation was dissected and further investigated by the use of the 49a,f/TaqI system [7] and seven microsatellites.

MATERIALS AND METHODS

The sample consisted of 2,235 DNAs from unrelated males belonging to 29 populations, mainly from Europe and the Middle East listed in Table 1. Most populations were included in previous studies [1, 13, 14, 20].

The European and Middle Eastern populations were pooled into the following four major geographic groups:

1. The West European group is from regions west of the 15° meridian and includes Basque (Spanish and French), Bearnais, Catalan, Andalusian, Dutch, North and Central Italian, Sardinian, and Sicilian samples;

TABLE 1 Percent frequencies of Eu19 49a.f Ht 11 haplotypes and derivatives observed in a sample of 2,235 Y-chromosomes from 29 populations

Population	Number	Ht 11 $A_3C_0D_0F_1I_1$	Ht 64 $A_{3/5}C_0D_0F_1I_1$	Ht 84 $A_5C_0D_0F_1I_1$	Ht 39 $A_3C_0D_0F_1I_0$ -BHPR	Ht 51 $A_{2/5}C_0D_0F_1I_1$	Ht 59 $A_{4/5}C_0D_0F_1I_1$	HT5 $A_2C_0D_0F_1I_1$	Ht10 $A_3C_0D_0F_1I_0$	HT 55 $A_4C_0D_0F_1I_0$	Ht 150 $A_{5/5}C_0D_0F_1I_1$ -BHPR	Total Abs. (%)
West Europe	663											
Andalusian	93	2.2	1.1									3 (3.3)
Spanish Basque	52											
French Basque	44											
Béarnais	26		3.8									1 (3.8)
Catalan	28											
Dutch	34	2.9										1 (2.9)
North Italian ^a	44	4.5					0.9					2 (4.5)
Central Italian	113											1 (0.9)
Sicilian	85											
Sardinian	144	1.4										2 (1.4)
"Balkan"	423											
Croatian	48	18.8	2.1	2.1								11 (23.0)
Albanian	56	5.4	1.8	1.8					3.6			7 (12.6)
Greek	92	9.8	5.4	1.1	1.1							16 (17.4)
Apulian	86	9.3	2.3				1.2		1.2			12 (14.0)
Calabrian	141	5.7						0.7				10 (7.1)
East Europe	316											
Czechoslovak ^b	88	19.3	6.8	2.3		4.5						29 (32.9)
Hungarian ^c	49	42.8	2.0	6.1	4.1			4.1				29 (59.1)
Polish	97	24.7	11.3	17.5		1.0			5.2			58 (59.7)
Ukrainian	82	31.7	7.3	1.2	1.2	1.2			3.7	1.2		41 (50.0)
"Middle East"	397											
Turkish	129	9.3	0.8				0.8			0.8		15 (11.7)
Georgian	61	8.2	1.6									7 (11.4)
Sephardim ^b	85	3.5										3 (3.5)
Ashkenazim ^b	82	8.5										8 (9.7)
Lebanese ^b	40	7.5										3 (7.5)
Indian	76	28.9				1.3						23 (30.3)
Ethiopian ^d	69											
Tunisian	73	5.5										4 (5.5)
Algerian	58											
Chinese	193	1.6										3 (1.6)

^aTorroni *et al.*, 1990 [8]; ^bSantachiara-Benerecetti *et al.*, 1993 [13]; ^cSemino *et al.*, 2000 [14]; ^dPassarino *et al.*, 1998 [20].

TABLE 2 Eu19 compound haplotypes and their distributions in 261 samples of the present study

Compound haplotypes	49a,f haplotypes	Microsatellites			Geographic areas						Total
		YCAIIa	YCAIIb	DYS19	West Europe	East Europe	"Balkans"	"Middle East"	India	China	
1	5	23	19	14		1	1	1			3
2	5	23	19	16				1			1
3	5	23	19	17		1					1
4	10	23	19	15		1	1				2
5	10	23	19	16		2					2
6	11	19	19	16					2		2
7	11	21	19	16				2			2
8	11	21	19	15					1		1
9	11	21	19	14		1					1
10	11	21	20	15	1						1
11	11	22	19	17		1					1
12	11	22	19	15				1		2	3
13	11	22	19	16		1		1			2
14	11	23	17	15			1				1
15	11	23	18	16		1					1
16	11	23	19	15	3	20	9	12	5		49
17	11	23	19	16	2	30	12	10	8		62
18	11	23	19	17		9	3				12
19	11	23	19	14	1	13	2		6		22
20	11	23	20	15			2				2
21	11	23	20	14			1				1
22	11	23	21	15	3		1	1			5
23	11	23	22	15	1						1
24	11	23	23	15			1	2			3
25	11	23	23	16		1					1
26	11	24	20	15			1				1
27	11	24	23	16						1	1
28	39	23	19	16			1				1
29	39	23	19	15		2					2
30	39	23	19	14		1					1
31	55	24	19	16				1			1
32	55	24	19	17		1					1
33	84	19	19	15		1					1
34	84	23	19	16		3	1				4
35	84	23	19	17		16	2				18
36	84	24	19	16		1					1
37	51	21	19	14					1		1
38	51	23	19	17		2					2
39	51	23	19	15		1					1
40	51	25	23	15		1					1
41	59	22	19	15		1					1
42	59	23	19	14			1				1
43	59	23	23	15				1			1
44	59	25	19	16	1						1
45	64	19	19	16		1					1
46	64	19	19	15		2					2
47	64	22	19	15		1					1
48	64	23	19	15		1	4				5
49	64	23	19	16	1	10	6	1			18
50	64	23	19	14	1	1					2
51	64	23	19	17		5	1	1			7
52	64	24	19	16			1				1
53	150	23	19	15		1					1
TOTAL					14	134	52	35	23	3	261

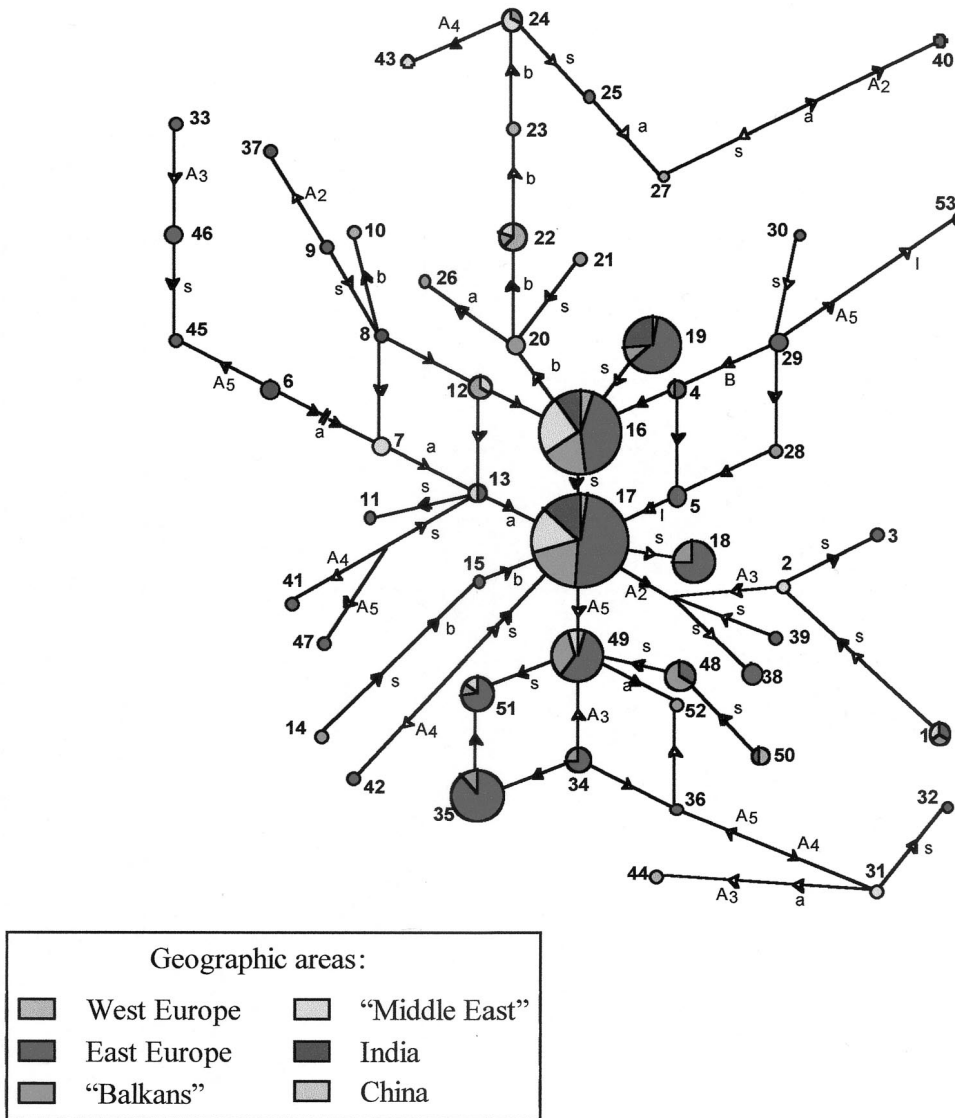


FIGURE 2 Median joining network (MJ) of the Eu19 Y-chromosomes compound haplotypes (c-Hts). These c-Hts are defined by the 49a,f Ht 11, the microsatellites YCAIIa, YCAIIb, and DYS19 variations. The MJ was calculated on the data pre-processed by reduced median (RM) algorithm. European and Middle Eastern populations have been pooled in four major geographic regions (see materials and methods section). This network includes the 53 c-Hts observed in 261 Y-chromosomes. The c-Hts are represented as circles, with areas proportional to frequencies, whereas the area of the sectors

within circles is proportional to the frequency in each geographic region. Arrows on the link point to a repeat gain, and parallel links in a reticulation indicate the same mutation. Capital letters represent fragment changes at 49a,f loci (the capital letter B indicates the BHPR deletion), and the small letters a, b, and s represent changes at YCAIIa, YCAIIb, and DYS19 loci, respectively. The allelic state of c-Ht 17 is the following: 49a,f Ht 11, a = 23, b = 19, s = 16 (repeats). The four Tunisian samples were included in the West European group.

2. The "Balkan" group is from regions east of the 15° meridian and facing the Adriatic and the Ionic seas and includes Croatian, Albanian, Greek, Apulian, and Calabrian samples;
3. The East European group includes Czechoslovak, Polish, Hungarian, and Ukrainian samples;
4. The "Middle Eastern" group includes Ashkenazim

and Sephardim Jewish, Lebanese, Turkish, and Georgian samples.

The 12f2 and 49a,f/TaqI RFLPs were analyzed by Southern blotting as previously described [20]. All the other markers (YAP [21]; DYS257 [17]; M9, M17, and M173 [18, 19]; microsatellites DYS19 [22], YCAIIa,

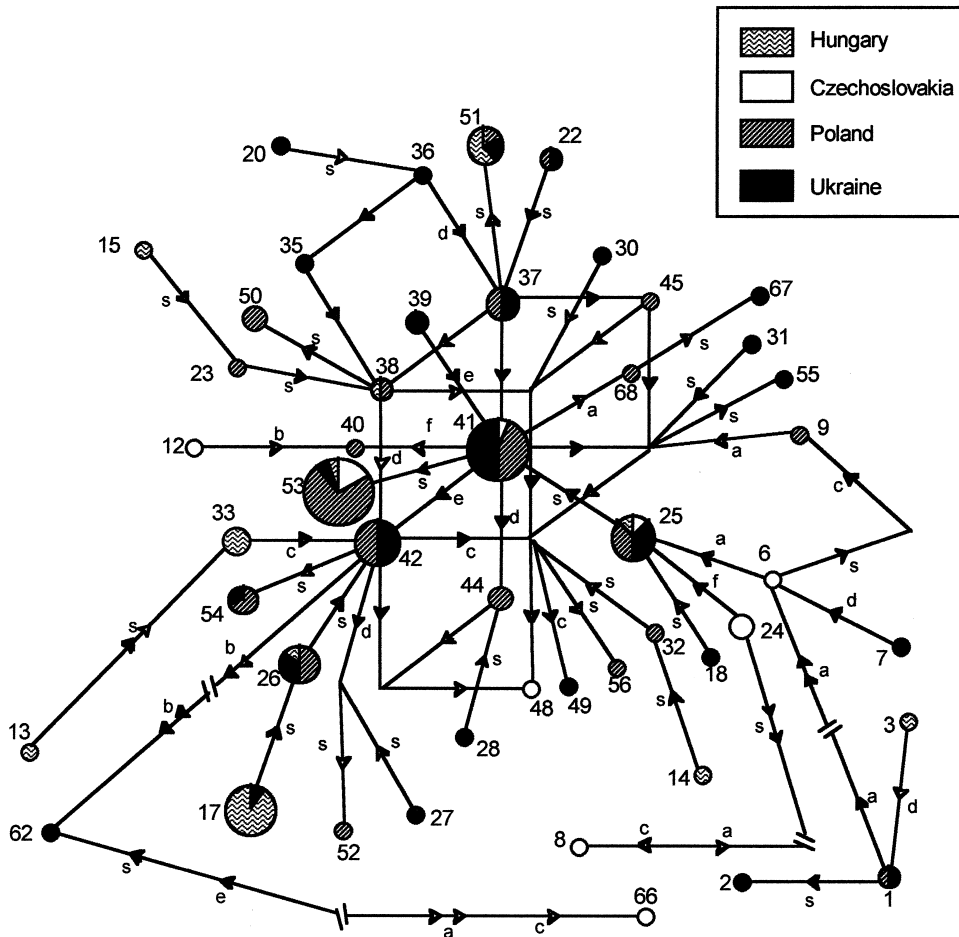


FIGURE 3 Median joining network (MJ) of the 48 Eu19 Y-chromosome compound haplotypes (c-Hts) observed in East Europe. The MJ was calculated on the data pre-processed by reduced median (RM) algorithm. The c-Hts are defined by the seven microsatellites: YCAIIa, YCAIIB, DYS19, DYS389b, DYS390, DYS391, and DYS392. The c-Hts are represented as circles, with areas proportional to frequencies, whereas the area of the sectors within circles is proportional to the frequency in

the corresponding population. Haplotypes shared by networks have the same number. Arrows on the link point to a repeat gain, and parallel links in a reticulation indicate the same mutation. The small letters a, b, c, d, e, f, and s (associated with arrows) represent changes at YCAIIa, YCAIIB, DYS389b, DYS390, DYS391, DYS392, and DYS19, respectively. The c-Ht 41 allelic state is the following: a = 23; b = 19; c = 10; d = 25; e = 10; f = 11; s = 16 (repeats).

YCAIIB [23], DYS389b, DYS390, DYS391, and DYS392 [24]) were examined according to the authors who first described the polymorphism.

Phylogenetic relationships between the different compound haplotypes of the lineage were obtained by using the program NETWORK 2.0 (University of Hamburg, Hamburg, Germany [25]). The median joining method ($\epsilon = 0$) [26] was performed on raw data or on data preprocessed by reduced median (RM) algorithm ($r = 2$) [27]. The different loci were weighted according to their relative variability in the lineage as follows: 49a,f A band = 3; 49a,f BHPR, band = 56; 49a,f I band = 22; YCAIIa and YCAIIB = 4; DYS389b = 3; DYS390 and DYS391 = 2; DYS392 = 6; and DYS19 = 1.

The coalescence time was calculated by using the variation at the seven microsatellite loci studied. The

variances obtained from the data were computed by using equation 2 from Goldstein *et al.* [28]. We assumed mutation rates of 5.6×10^{-4} for YCAIIa and b [29], 2.1×10^{-3} for the other microsatellites [30], a population size of 4,500, and a generation time of 27 years [28]. For dating we used two approaches: the first used the weighted average of the two mutation rates and the average of the microsatellite variances; the second used the average of the times calculated for each microsatellite.

RESULTS

All 294 Y chromosomes belonging to the Eu19 lineage (M17-deleted allele/M173-C/M9-G/12f2-10kb/YAP⁻/DYS257-A) turned out to be 49a,f Ht 11 or its derivatives. As illustrated in Table 1, where their distribution

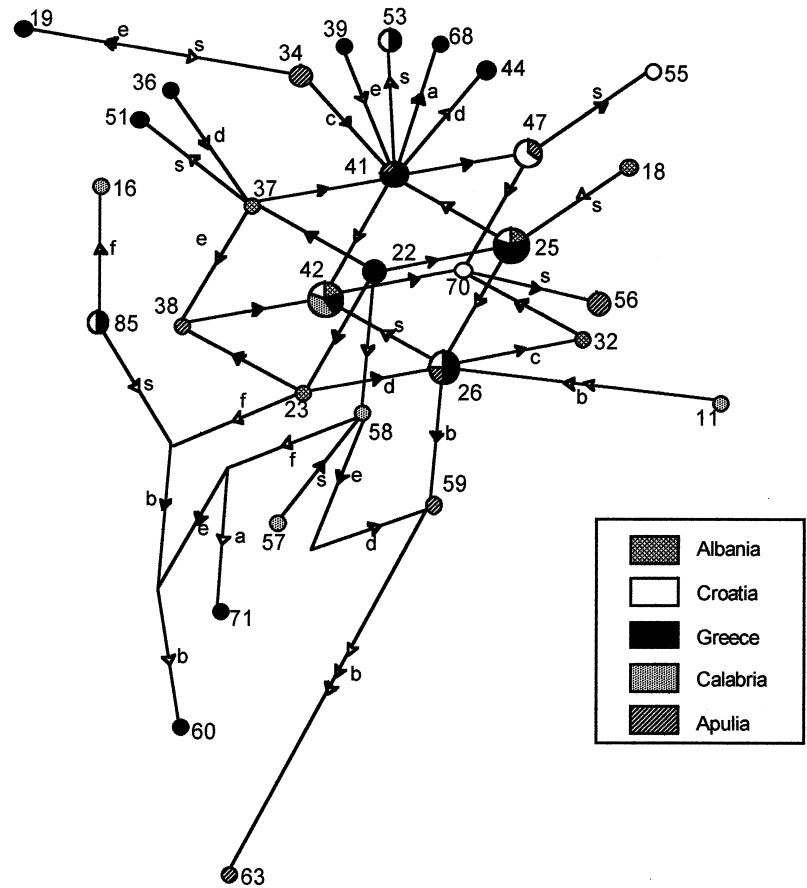


FIGURE 4 Median joining network (MJ) of the 31 Eu19 Y-chromosome compound haplotypes (c-Hts) observed in the "Balkan" area. The MJ was calculated on the data pre-processed by reduced median (RM) algorithm. For additional information, see the legend of Figure 3.

is reported, in addition to Ht 11 ($A_3C_0D_0F_1I_1$), nine of its derivatives were observed among the Eu19 Y chromosomes. They differ from Ht 11 for one band change, with the exception of Ht 55 ($A_4C_0D_0F_1I_0$), Ht 150 ($A_{5/3}C_0D_0F_1I_1$ -BHPR), and Ht 39 ($A_3C_0D_0F_1I_0$ -BHPR) that differ for two changes. In Ht 39 and Ht 150 the simultaneous absence of the BHPR bands, which has rarely been observed in other haplotypes [8, 13], is considered as a unique mutational event probably due to a deletion involving adjacent fragments. With the exception of Ht 64 ($A_{5/3}C_0D_0F_1I_1$) and Ht 84 ($A_5C_0D_0F_1I_1$), which are mainly found in Eastern Europe and reach the highest incidence in Poland (11.3% and 17.5%, respectively), most of the other derivative haplotypes are represented by single individuals.

As to the geographic distribution of these 294 Y chromosomes out of Europe, they were found in the Middle East and, at a high frequency, in India. Four were present in the Tunisian sample and only three were seen in about 200 Chinese, giving a frequency of the same order as that observed by Su *et al.* [31] for H16 (M17) in some populations of Northeastern Asia and Cambodia.

By combining the 49a,f with the DYS19, YCAIIa, and YCAIIb variations in 261 Y-chromosomes Eu19,

which for Europe and the Middle East were grouped in four major geographic areas, a total of 53 compound haplotypes (c-Hts) were obtained (Table 2). The phylogenetic relationships between them are illustrated in the median joining network (Figure 2), where for each c-Ht it is possible to identify, as different sectors, the geographic origin of Y chromosomes. It can be seen that the majority of c-haplotypes are found in the East European populations, and the East European component predominates in all the most frequent c-haplotypes. In this network the two most frequent c-haplotypes are c-Ht 17 (62 subjects) and c-Ht 16 (49 subjects). They were found in all the examined areas, and differ from each other because of the DYS19 allelic state (16 and 15 repeats). In addition, c-Ht 17 reveals the highest number of links and it could be the most ancient c-haplotype of this lineage. Other frequent c-haplotypes are c-Ht 19, c-Ht 35, and c-Ht 49 (22, 18, and 18 subjects, respectively) but they have a more limited geographic distribution. The 19 c-Ht is interesting because it has been found almost exclusively in the Eastern European and Indian populations. Unfortunately, poor knowledge of the molecular basis of the complex 49a,f system and the complete ignorance of its mutational rate do not allow any attempt

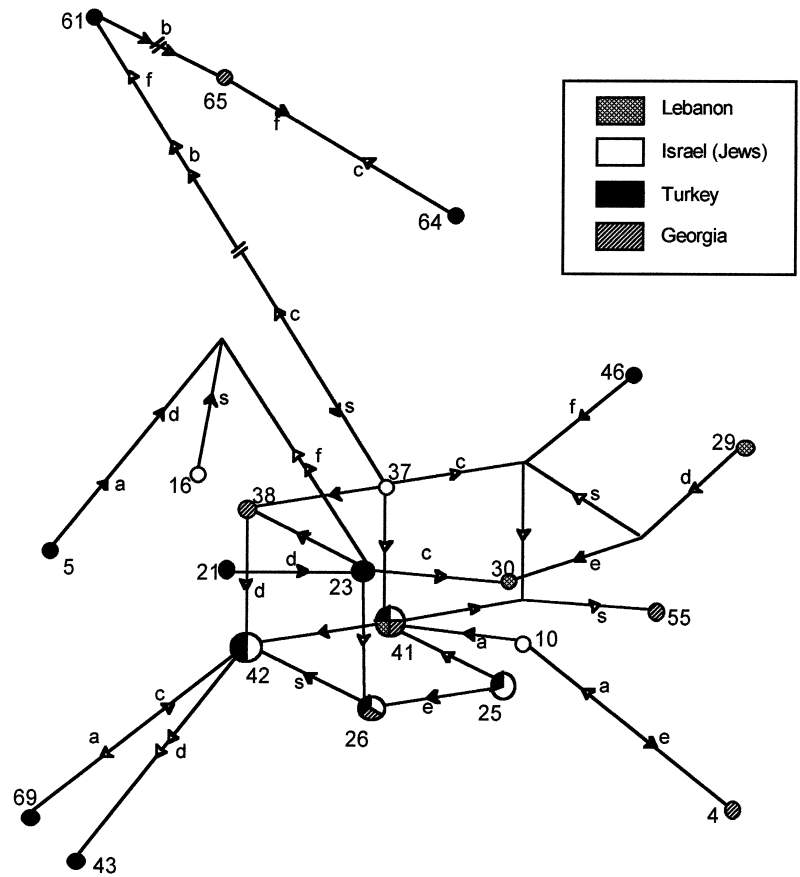


FIGURE 5 Median joining network (MJ) of the 21 Eu19 Y-chromosome compound haplotypes (c-Hts) observed in the “Middle East”. The MJ was calculated on the data pre-processed by reduced median (RM) algorithm. The Ashkenazim and Sephardim Jews were pooled. For additional information, see the legend of Figure 3.

to date this phylogeny. However, an attempt to date the Eu19 lineage was made by combining the microsatellite variations (YCAIIa, YCAIIb, DYS19, DYS389b, DYS390, DYS391, and DYS392) resulting from the analysis of 243 Y chromosomes. By the two approaches used (see methods), ages of 7,654 and 13,031 years were obtained. A total of 85 c-Hts were identified, and their phylogenetic relationships in East Europe, the “Balkans,” the “Middle East,” and India are illustrated in Figures 3–6. Considering the East European network (Figure 3), the most represented c-haplotypes are the c-Hts 53, 41, 42, 25, 26, and 17; four of these c-haplotypes (41, 42, 25, and 26) are common in all networks. In India, however, the most frequent c-haplotype appears to be c-Ht 17 that is present, with high incidence, only in the East European regions (ten subjects). On the other hand, this has just been illustrated by c-Ht 19 (Figure 2), which includes c-Ht 17. The East European network, however, also provides additional information. All subjects, except one from Ukraine, with c-Ht 17 belong to the Hungarian population. Moreover, the most frequent c-Ht 53 in East Europe (18 subjects) is mainly accounted for by Polish samples (13 subjects).

DISCUSSION

The frequency distribution of the 49a,f Ht 11 and the observation that all of the few tested Eu19 chromosomes carried this haplotype [32], suggested that the 49a,f Ht 11 characterized the Eu19 lineage. The extension of the analyses for both the 49a,f system and the Eu19 markers to the 2,235 Y chromosomes of our collection has revealed that all those (294) belonging to the Eu19 lineage were 49a,f Ht 11 or its derivative haplotypes. Their frequencies in the different geographic areas, in which our samples were pooled, clearly reveal the high prevalence of Ht 11 and derivatives in East Europe (49.7% vs 1.5% in West Europe, 13.2% in the “Balkan” group, and 9.1% in the “Middle East”), in spite of the minor size of the Eastern European group with respect to the others (Table 1). Although this study could not include the variation of the 49a,f Ht11 in order to date the Eu19 lineage, estimates of 7,654 and 13,031 YBP were obtained by the seven microsatellite variations. These values are compatible with the dates referring to the 1D [33] and Hg3 [5] haplogroups to which the Eu19 lineage appears to be phylogenetically equivalent. With respect to Hg3, however, our dates lie towards the upper limit of

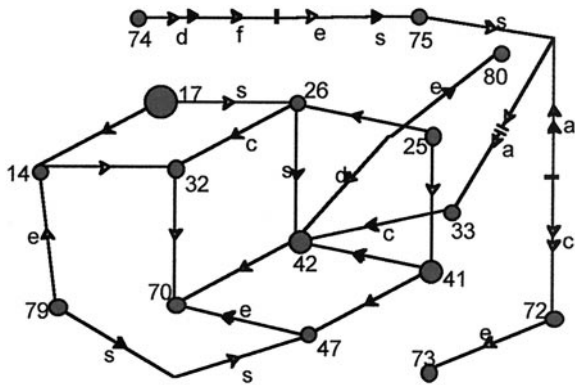


FIGURE 6 Median joining network (MJ) of the 16 Eu19 Y-chromosome compound haplotypes (c-Hts) observed in India. The MJ was calculated on the raw data. For additional information, see the legend of Figure 3.

the Hg3 range of values. Apart from these age estimates, which can be biased by many factors and then have to be interpreted with great caution, present data allow some inferences to be drawn, such as the existence of an additional marker, the 49a,f Ht 11 that displays a major diversification in East Europe with respect to the other areas. Actually, in East Europe, all the derivatives of the 49a,f Ht 11 were observed (9 vs 6 in the “Balkans,” 4 in the “Middle East,” 1 in India, and 2 in West Europe). Moreover, Ukraine presents at least twice as many derivatives as the other East European populations (Table 1). These findings suggest that East Europe is the place where this lineage originated or started to expand, particularly in Ukraine, which also includes a refuge area during the LGM [4]. If the Eu19 were present in that area during the LGM, it could have expanded and diffused after that period, when important population growth and repopulating of the previously glaciated regions occurred. However, other expansions/migrations from the same or other areas, at different times, could also have spread this lineage [3–5]. Some of them might be the migrations associated with the diffusion of the Yamnaia culture, which are thought to have brought the Indo-European languages to Europe and, through Central Asia, to India [34, 35].

The presence of Hg3 in some groups of Central Asia has been reported [33, 36], but its frequency is rather low with the exception of a peak in the Altai region where it reaches about 50%. High frequencies of Hg3 in the Eastern Caspian area, Eastern Iran and Pakistan (about 30%) have suggested that this was the route of the migration/s to India [37]. Although we do not have the 49a,f classification of the Hg3 Y chromosomes and that of the Eu19 Y chromosomes in the Mari and Udmurt populations [4], it is likely that these Y chromosomes carry the 49a,f Ht 11 similarly to the Eu19/49a₂,f Ht 11 found in India and China.

The comparison between the four networks suggests that either c-Ht 41 or c-Ht 42 (both included into c-Ht17 of Figure 2) is the ancestral c-haplotype of Eu19, but that all the shared 25, 26, 41, and 42 c-Hts were involved in the geographic diffusion of the lineage. In addition, the features of the East European network suggest that some local late expansions occurred, as revealed by the c-Hts 53 and 17 (Figure 3), which are mainly accounted for by Polish and Hungarian Y chromosomes, respectively.

In conclusion, the combined analysis of the Eu19 biallelic markers with the 49a,f system has provided interesting information concerning past human migrations in Eurasia. The 49a,f system has allowed a further characterization of the Eu19 lineage by a new marker, the 49a,f Ht11. On the other hand, the Eu19 lineage has provided stable markers to identify all those haplotype variants deriving from the 49a,f Ht 11. These variants, in turn, by subclassifying the Eu19 lineage, have given insights on its geographic subdivision and a new hint that Ukraine may be the area where the Eu19/Ht 11 spread from.

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