

INVITED EDITORIAL

The Peopling of Europe from the Maternal and Paternal Perspectives

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Europe and the Expansion of Neolithic Farmers

It is generally accepted that the earliest human occupants of Europe arrived during the Paleolithic, on the order of 40,000–50,000 years before the present (YBP), and that agriculture arose in the Near East during the Neolithic, ~10,000 YBP. However, debate has arisen over the mechanism of dispersal of farming within Europe. The demic-diffusion model proposed by Ammerman and Cavalli-Sforza (1984) postulates that extensive migrations of Near Eastern farmers during the Neolithic brought agricultural techniques to the European continent. Under this model, the migrant farming populations expanded with little admixture with the Mesolithic European inhabitants, so that a large proportion of the present-day European gene pool should be derived from the Neolithic migrants. In contrast, others have proposed a cultural-diffusion model (Dennell 1983) in which the transfer of agricultural technology occurred without significant population movement. Under this model, the majority of the genetic diversity within Europe would have its roots in the Paleolithic.

Genetic evidence in support of the demic-diffusion model initially came from analyses of classic gene-frequency data (Menozzi et al. 1978; Cavalli-Sforza et al. 1994; Piazza et al. 1995). In these studies, synthetic genetic maps of Europe and the Near East were constructed with the use of principal-components analysis to condense the information from numerous loci. In general, it was observed that the first principal component summarized one-quarter to one-third of the total variation and that it appeared to support a clinal pattern of geographic distribution resembling the archaeological map of the spread of early farming. A later study of seven hypervariable nuclear DNA markers offered similar interpretations of a northward and westward

Neolithic expansion from the Near East (Chikhi et al. 1998).

Variation of the paternally inherited Y chromosome has also been interpreted as supporting the demic diffusion model. Clinal variation of the p12f2 (DYS11) 8-kb allele and the 49a,f (DYS1) haplotype 15 seemed to suggest a large-scale expansion from the Near East. The p12f2 8-kb allele appeared to be an indicator of the Neolithic demic expansion, and the 49a,f haplotype 15 seemed to represent a proto-European lineage diluted by mixing with the Neolithic migrants (Semino et al. 1996). Further analyses using Y chromosome microsatellites again showed general east-west gradients within Europe (Malaspina et al. 1998; Quintana-Murci et al. 1999b).

In contrast to the gradients observed for classic gene frequencies and other nuclear DNA markers, including the Y chromosome, initial studies of European variation in the maternally inherited mtDNA did not seem to support the demic diffusion of Neolithic farmers. The mtDNA landscape of Europe appeared very homogeneous, with little geographic clustering of types (Richards et al. 1996; Comas et al. 1997). In particular, Richards et al. (1996) argued that the genetic contributions of Neolithic migrants had been greatly exaggerated and that the major extant lineages of Europe could be traced back to the Upper Paleolithic. This questioning of the demic-diffusion model for the peopling of Europe engendered a lively debate over the interpretations of the genetic studies supporting the competing models (Cavalli-Sforza and Minch 1997; Richards et al. 1997, 1998; Barbujani et al. 1998; Richards and Sykes 1998).

In addition to the early Paleolithic and Neolithic expansions into Europe, recent mtDNA studies in Europe have suggested a Late Upper Paleolithic population expansion from southeastern Europe, as evidenced by clines radiating from Iberia (Torroni et al. 1998). However, a more recent study has questioned this conclusion (Simoni et al. 2000).

Two articles in the *Journal* now extend the genetic analysis of the colonization of Europe. The first, by Richards et al. (2000 [in the November issue]), studied the distribution of mtDNA lineages throughout Europe and the Near East, identified by sequence variation in the non-coding control region, augmented with the

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analysis of informative restriction endonuclease site variants (designated “RFLPs” in that article). The second article, by Rosser et al. (in this issue), examined the European distribution of Y-chromosome variation using selected biallelic markers.

The Use of mtDNA and Y-Chromosome Variation to Study Human Origins

The mtDNA and Y chromosome have the potential to be particularly informative for studies of recent migrations, such as those that populated Europe. Both components of the human genome are inherited from only one parent. Therefore, neither can recombine, and, thus, both change by the accumulation of sequential mutations along radiating lineages. Since all of the sequence variants of a mtDNA or Y chromosome remain associated with each other in total linkage disequilibrium, the sum of the sequence variant sites of a mtDNA or Y chromosome are designated its “haplotype.” Groups of haplotypes sharing distinctive sequence variants inherited from a common ancestor are known as “haplogroups.”

Since only one mtDNA or Y-chromosome type can be transmitted by a couple to each of their offspring, compared with four autosomal alleles, the mtDNA and Y chromosome have a much smaller effective population size—one-quarter that of the autosomes. This makes them much more prone to founder effects during population constrictions. As a result, the mtDNA and Y chromosome exhibit striking population-specific diversity, which greatly facilitates the identification of founders, aiding in the reconstruction of ancient migrations.

The mtDNA and Y chromosome differ, however, in the sex of the transmitting parent and in the size and mutation rate of the two DNA molecules. The mtDNA is small (16,569 bp) but has a very high sequence-mutation rate, particularly in the non-coding control region. As a result, the mtDNA mutation rate has been determined, and relatively fine distinctions in lineages and their resident populations can now be made. By contrast, the Y chromosome is ~60 Mb, with a low average mutation rate. Since there are at present relatively few informative Y-chromosome markers and the mutation rate remains undetermined, only broad migration patterns can be deduced from Y-chromosome variation, and accurate determination of the timing of mutations is still uncertain. Consequently, mtDNA still provides the most detailed insight into the dispersal of modern humans.

mtDNA Analysis of European Radiation

To analyze the origins and dispersal of modern Europeans, using mtDNA, it is first necessary to outline the origins and global dispersion of mtDNAs, a topic that has been elucidated during the past 20 years. It is now generally accepted that the progenitors of all modern mtDNAs arose in Africa ~150,000–200,000 YBP (Johnson et al. 1983; Cann et al. 1987; Vigilant et al. 1989, 1991; Wallace et al. 1999). The most ancient two-thirds of the African mtDNA lineages harbor a distinctive RFLP, defined by a C→T transition at np 3594, which creates an *HpaI* site at np 3592 (+3592 *HpaI*) (Denaro et al. 1981). This +3592 *HpaI* polymorphism occurs together with an A→G transition at np 10394, which creates a *DdeI* site at np 10394 (+10394 *DdeI*). All mtDNA haplotypes with these two sites are lumped into the African-specific macrohaplogroup L*, which is subdivided into the African haplogroups L1 and L2. The loss of the +3592 *HpaI* in African mtDNAs results in haplogroup L3 (Chen et al. 1995, 2000).

All European and Asian mtDNAs radiate from L3. In Asia, half of the mtDNAs fall into macrohaplogroup M, defined by the presence of the np 10394 *DdeI* site plus an adjacent C→T transition at np 10400, creating an *AluI* site at np 10397 (designated as [+/+]). The remaining Asian and European mtDNAs have been assigned to macrohaplogroup N, which lacks the np 10397 *AluI* site (+/-) and can also lack the np 10394 *DdeI* site (-/-) (Ballinger et al. 1992; Quintana-Murci et al. 1999a). Macrohaplogroup M encompasses a number of Asian-specific haplogroups, including C, D, G, E, Y, and Z (Ballinger et al. 1992; Starikovskaya et al. 1998; Schurr et al. 1999; Wallace et al. 1999). Macrohaplogroup N encompasses multiple Asian-specific (-/-) lineages, including A, B, and F, as well as the western-Eurasian lineages H, I, J, K, R, T, U, V, W, and X. Haplogroups I, J, and K are (+/-), whereas the others are (-/-).

The origins of the M and N lineages are still being investigated. However, one possibility is that they arose in northeastern Africa (Quintana-Murci et al. 1999a; Wallace et al. 2000). The western-Eurasian haplogroup U has been found at low frequencies in western as well as eastern Africa, raising the possibility of a relatively ancient African origin for this haplogroup (Torroni et al. 1996; Chen et al. 2000). If so, then haplogroup U might have participated in one of the earliest migrations from Africa to the Near East and Europe. This deduction is supported by the work of Richards et al. (2000).

To determine the number, nature, and timing of the various migrations that peopled Europe, Richards et al. (2000) have endeavored to identify the founders of the various European haplogroups and subhaplogroups (e.g., U1, U2, U3,...) by sequence analysis of a portion

of the mtDNA control region in >4,000 individuals from Europe and the Near East. Founder candidates (f_0) were identified as sequence types shared between Europe and the Near East, as well as unsampled but inferred matches based on the European and Near Eastern phylogeny. Three additional stringency levels were used to identify the most likely founders of Near Eastern origin. Levels f_1 and f_2 required, respectively, one or two additional sequences to be derived from a founder type in the Near East, allowing for the detection of sequence matches due to recurrent mutation or back-migration. Furthermore, to allow for the relative probabilities or detecting rare or common founder types, the f_s criteria allowed for scaling of the number of derivative sequences required for founder status on the basis of frequency. By this analysis, two lineages (U5 and V) were identified as being European in origin. By calculation of their frequency in the Near East, it was estimated that 10%–20% of the modern Near Eastern variation was due to recent back-migration from Europe.

Because haplogroup H encompasses ~40% of the European mtDNA variation, it was necessary to identify subhaplogroups of H and to analyze their independent migrations. For example, one subhaplogroup had the same control-region sequence as the Cambridge Reference Sequence and thus was designated “H-CRS.” Using the various haplogroups and subhaplogroups, it was deduced that the Neolithic agricultural expansion from the Near East to Europe, occurring ~9,000 YBP, brought haplogroups J (root type and sublineage J1a), T1, T3, and others to Europe. These haplotypes account for ~23% of mtDNAs in modern Europe. Prior to this, during the Late Upper Paleolithic, at ~14,500 YBP, haplogroups H-CRS, H-16304, H-16362-16482, K, T*, T2, W, and X migrated from the Near East into Europe and now account for ~36% of the European mtDNAs. Migrations during the Middle Upper Paleolithic, ~26,000 YBP, brought haplogroups HV*, U1, and possibly U2 and U4 into Europe, and they now represent ~25% of European mtDNAs. Finally, the earliest migration in the Early Upper Paleolithic, at ~45,000 YBP, brought haplogroup U5 from the Near East into Europe and now accounts for ~7% of European mtDNAs. Thus, the original Early Upper Paleolithic immigrants to Europe contributed about one-tenth of the mtDNAs to the modern European gene pool, whereas the Neolithic farmers contributed one-fifth to one-quarter of the genes.

Under the assumption that Europe was populated by successive waves of migration out of the Near East, one might expect that the earliest European mtDNA haplogroups, when close to their Near Eastern origin, would have been diluted out by the mtDNAs of subsequent migrations. However, this influence would diminish as one moved farther away from the Near East.

This deduction was borne out. The Early Upper Paleolithic haplogroups were found in their highest frequencies (14%–15%) in the Basques, Scandinavians, and northeastern Europeans but were at their lowest frequencies (5%–9%) in the western Mediterranean, the Alps, and north-central and northwest Europe. They were at intermediate levels (11%–13%) in the eastern, southeastern, and central Mediterranean. By contrast, the Neolithic haplogroups were most strongly represented in the southeastern, north-central, Alpine, northeastern, and northwestern European populations (15%–22%) but were found at lower frequencies in the Basques (7%) and Scandinavians (12%). Throughout the various regions of Europe, the mtDNA haplogroups that arrived during the Late Upper Paleolithic predominate (43%–58%). These mtDNAs were the most prevalent in the western Mediterranean and the Basques (56%–59%), which could support a southwest to northern migration. However, the relatively shallow distribution of Late Upper Paleolithic mtDNA variation suggests that additional population movements, such as secondary migrations from the Near East, may have contributed to Paleolithic populations.

Y Chromosome Analysis of European Radiation

Studies of Y-chromosome variation in Europe have generally lagged behind mtDNA investigations because of a paucity of informative, easy-to-type markers. Rosser et al. (2000) have provided the most detailed survey of European Y-chromosome variation to date, with their analysis of 11 biallelic markers in 3,677 males from 48 European and circum-European populations. The geographic distribution of Y-chromosome diversity, as well as the relative influences of language and geography on this diversity, was examined.

The most striking finding of Rosser and colleagues was the clinal distribution of five of the six major European Y-chromosome lineages identified. Y-chromosome haplogroups 1 and 9, which together encompassed almost half of the chromosomes in this study, were distributed at virtually complementary frequencies along a southeast-northwest cline. Haplogroup 9 reached its highest frequency in the Caucasus and in Anatolia, with a distribution similar to that of the p12f2 8-kb allele (Semino et al. 1996). Conversely, haplogroup 1 was found at its highest frequency in western Ireland, with decreasing frequencies to the east, as with haplotype 15 of the 49a,f system (Semino et al. 1996). In addition to concordance with previous Y-chromosome studies, these clinal distributions also resemble the first principal component of classic gene frequencies, which have been interpreted as supporting the demic-diffusion model. The authors note that previous age estimates for haplogroup 1 (23,000 YBP; Karafet et al. 1999) and hap-

logroup 9 ($14,800 \pm 9,700$ YBP; Hammer et al. 2000) would make them old enough to have spread through a Neolithic expansion. However, uncertainties surrounding Y-chromosome mutation-rate estimates make it difficult to rule out an earlier origin and dispersal of these lineages.

In addition to the major cline consistent with a demic-diffusion model, three of the other Y-chromosome haplogroups defined in this study showed distinct, regional clinal variation. Haplogroup 21 decreased in frequency on a gradient extending north from northern Africa and was noted to resemble the second principal component of Cavalli-Sforza et al. (1994), previously proposed to reflect climatic changes. Haplogroup 3 reached its highest frequency in central Europe, consistent with a recent major Eurasian expansion. Haplogroup 16 was concentrated in the north, at high frequencies in all Uralic-speaking populations as well as in geographically proximal non-Uralic speakers.

The regional distributions within Europe of Y-chromosome haplogroups 3 and 16 point to the need for further analysis of Asian populations. As was noted by Rosser et al. (2000), Europe is a political construct rather than a geographic entity. Physical continuity with Asia may well be reflected in genetic continuity, as evidenced by previous studies, which revealed a wide distribution of the SRY-1532 marker (haplogroup 3) in Europe and Asia (Zerjal et al. 1999) and a connection between central Asia and northern Europe based on the Tat polymorphism (haplogroup 16) (Zerjal et al. 1997). The historical human migrations carrying the haplotype 3 and 16 Y chromosomes to Europe would seem to be clearly distinct from those that resulted in the haplogroup 1 and 9 Y chromosomes becoming established along a southeast-northwest gradient. A broader survey of populations along the European/Asian corridor for these and other Y chromosome markers will greatly assist in defining all of the events leading to the modern-day patterns of European Y-chromosome variation.

The geographic differentiation of these Y chromosomes is all the more striking in light of the lack of correlation, based on principal-components analysis, between European Y-chromosome genetic variation and language. This was dramatically shown for the Uralic speakers, who shared similar Y-chromosome distributions with adjacent non-Uralic speakers. For example, the Indo-European-speaking Lithuanians and Latvians had Y chromosomes similar to the proximal Uralic speakers, despite speaking very different languages. In addition, analyses of genetic barriers showed that most zones of abrupt genetic change did not correlate well with comparable changes in linguistic association. Thus, the Y-chromosome variation observed in extant European populations appeared to reflect ancient population histories, and this system should therefore continue to

provide a useful counterpart to mtDNA studies for deducing human population histories.

Beginnings of a Consensus on the Role of Neolithic Farmers in European Origins

Although Rosser et al. (2000) have provided the most comprehensive survey to date of European Y-chromosome variation, their studies were limited by their ability to estimate dates for the dispersal of the observed haplogroups. Hence, a direct comparison of Y-chromosome and mtDNA results in Europeans remains tenuous. This limitation may be eased in the near future, as additional single-nucleotide polymorphisms are identified and used in population surveys (e.g., Underhill et al. 1997) and as more accurate locus-specific microsatellite mutation rates are determined (Heyer et al. 1997; Bianchi et al. 1998; Kayser et al. 2000).

Even given the current limitations of the Y-chromosome analysis, the emerging similarities in the geographic patterns of autosomal, mtDNA, and Y-chromosome variation are striking. With the current articles, we are beginning to see congruence in the results of all three systems in relation to the demic expansion of the Neolithic Near Eastern farmers into Europe. Richards et al. (2000) now propose that approximately one-fifth (23% using their most stringent founder-identification criteria) of the extant European mtDNA lineages arrived during the Neolithic. This value is very near the proportion of variance described by the first principal component of classic genetic-marker studies (26%–28%) (Menozzi et al. 1978; Cavalli-Sforza et al. 1994, 1997; Piazza et al. 1995). Similarly, Rosser et al. (2000) have proposed that almost half of the European Y chromosomes exhibit a major southeast-northwest cline, consistent with a major Neolithic expansion. Since haplogroups 1 and 9, respectively, are only three and two mutational steps removed from the ancestral Y-chromosome haplotype, there is a good possibility that additional biallelic markers will reveal greater structure in the European Y-chromosome haplogroups, allowing for more accurate descriptions of Y-chromosome expansions. Perhaps as more refined estimates of Y-chromosome locus-specific microsatellite mutation rates are obtained (e.g., Kayser et al. 2000) and applied to the dating of lineages, the ages of the European Y-chromosome expansions will be found to coincide with those of the mtDNA and the classic markers. Thus, even allowing for real differences in the evolutionary history of mtDNA and Y-chromosome molecules, it is not unreasonable to hope that in the not-too-distant future they will be found to provide complementary information on the peopling of Europe.

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