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Review article

Modern human origins and prehistoric demography of Europe in light of the present-day genetic diversity

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Abstract. Dynamic advance in DNA sequencing methods and progress in formal population genetics analyses made it possible to infer aspects of human evolution from the DNA diversity distribution and frequency in contemporary populations. While providing some general background concerning the origins of modern human, this paper focuses on the dynamics of prehistoric population in Europe. The relevance of the present-day genetic diversity studies in elucidating prehistoric events is presented in the context of archeological and paleoanthropological evidence. The questions of the Neanderthal admixture as well as of the relative contribution of different waves of prehistoric migrations to the gene pool of modern Europeans are discussed.

Key words: demographic expansion, European migrations, frequency distribution, human evolution, Neanderthal, phylogeography, population diversity.

Introduction

Population genetic in deciphering prehistoric demography

Until little more than a decade ago, the study of human evolution relied on the analysis of fossils and archeological artifact assemblages. Paleontologists, confronted with problems such as uncertainty about the validity of taxonomic units, disagreements about appropriate diagnostic criteria in the interpretation of sites or specimens with mixed diagnostic features, and – perhaps most importantly – with small, fragmentary, and generally inadequate samples for analysis, had no biological reference to cross-examine their theories. Added to these difficulties

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were ambiguities in dating, particularly with older excavations characterized by the great stratigraphic complexity.

Developments in molecular genetics revolutionized the field of human evolution studies, undermining the importance of fossils as the primary source of information about our past. To some extent, a fusion of paleontological and genetic approaches came with the extraction and sequencing of ancient DNA from Neanderthal specimens (KRINGS et al. 1997, 1999, 2000, OVCHINNIKOV et al. 2000), but understandably, this approach is likely to remain uncommon. More importantly, dynamic advance in DNA sequencing methods and progress in formal population genetics analyses made it possible to infer aspects of recent human history from the DNA diversity distribution and frequency in contemporary populations.

According to the neutral theory of evolution (KIMURA 1983), most of the intra-specific variability at the molecular level is selectively neutral and is maintained within the species by the balance between the mutational input and random extinction, such that polymorphisms at the DNA level represent a transient situation where one allele chosen at random is on its way to fixation. In the absence of selection, the amount of genetic variation in a population is shaped by the mutation rate (characteristic of a genomic segment) and random genetic drift (whose effect depends on the effective size of a population). Drift-driven differences between populations arise in the absence of gene flow (i.e. when populations are separated either by distance, or by geographical or cultural barriers) and may or may not be maintained when populations come into contact. In summary, when the mutation dynamics in the DNA segment under study is known, comparing genetic diversity observed in the present-day individuals with the theoretical predictions may provide insight into the prehistoric population structure and dynamics. Importantly, these inferences cannot be made without considering the non-genetic context. In many cases, a number of evolutionary interpretations can be provided to explain a given pattern of genetic variation and the choice of the most realistic scenario has to be backed up by some external knowledge. Archeological and paleontological evidence – as uncertain and/or fragmentary as it might be – provides such framework and makes it possible to infer plausible models, according to which predictions concerning levels and patterns of genetic diversity can be made.

This paper will focus on the application of genetic diversity studies in elucidating the demographic prehistory of populations in Europe – the continent for which the richest archeological and paleontological records existed and which, nevertheless, still harbors many unanswered questions. To place the European prehistory in a general context of human evolution, a short background concerning the global question of the modern human origins will be given as well.

Modern human origins

Competing models

The history of modern humans – when considered at the evolutionary time scale – is not very long. Archaic subpopulations of *Homo erectus* colonized Eurasia from Africa almost 2 million years ago (SWISHER et al.1994, GABUNIA, VEKUA 1995), but *H. sapiens sapiens* did not appear until ~100 thousand years ago (Kya). The sites in Omo Kibbish (Ethiopia), the Klasies River Mouth (South Africa), Qafzeh and Skhul (Israel), where the earliest fossils of anatomically modern human were found, are dated at ~120-100 Kya; similar findings outside Africa and Levant are much younger, ranging from ~60-50 Kya in South-East Asia and Australia and ~40-30 Kya in Europe (see e.g. BRAUER 1989, CHURCHILL, SMITH 2000).

The leading model of modern human origins based on these paleontological findings posits that a relatively small ancestral population of *H. s. sapiens* (10-20,000 of breeding individuals) appeared in Africa 150-100 thousand years ago (Kya) and expanded worldwide, replacing preexisting hominids, such as *H. erectus* in Asia or *H. Neanderthalensis* in Europe, with little or no interbreeding (STRINGER, ANDREWS 1988, LEAKEY 1994, LAHR, FOLEY 1994, MOUNTAIN, CAVALLI-SFORZA 1994, TATTERSALL 1997, KLEIN 1999). This "recent-out-of-Africa" model is consistent with the majority of genetic data, which reveal generally low genetic diversity of human species (LI, SADLER 1991) and its relative excess in African populations (e.g. CANN et al.1987, BOWCOCK et al. 1991, 1994, CAVALLI-SFORZA et al. 1994, BATZER et al. 1994, TISHKOFF et al. 1996, JORDE et al. 1997, HAMMER et al. 1998, CLARK et al. 1998, ZIĘTKIEWICZ et al. 1998). Increasing evidence indicates that the emergence of modern humans in Africa was temporally separated from their demographic growth and range expansion, and that colonization of the world occurred in multiple waves of migrations along different geographical routes (CAVALLI-SFORZA et al. 1988, 1994, LAHR, FOLEY 1994, 1999, ROGERS, JORDE 1995, QUINTANA-MURCI et al. 1999, KIVISILD et al. 1999, LABUDA et al. 2000).

Prevailing as it is, the "recent-out-of-Africa" model has its opponents, who propagate the model of "multiregional evolution", according to which modern humans evolved locally from preexisting hominids (WEIDENREICH 1943, WOLPOFF, CASPARI 1997, TEMPLETON 1997, WOLPOFF et al. 2001). The "multiregional" model, assuming that the most recent common ancestor dates back to over one million years ago, requires long-term gene flow to be strong enough to maintain species unity. This implies that human population be in order of 100,000 to 1 million, much larger than the present-day diversity data suggest (HARPENDING et al. 1993). In summary, most geneticists and a large part of the paleoanthropological community support the "recent-out-of-Africa" model. On the other hand, the possibility of a limited admixture from pre-modern hominids to the genetic pools of expanding *H. s. sapiens* remains an open question, well

exemplified by the debate on the place of Neanderthals in the evolution of modern Europeans (see below).

The environmental context of the *H. s. sapiens* evolution in Europe

The time span relevant for the evolution of modern humans in Europe encompasses the Upper Paleolithic (UP) through Neolithic, i.e. the period between ~50-5 Kya, during which the geo-climatic conditions in Europe oscillated between favourable and extremely harsh. In response to these changing conditions, the size and distribution of human populations as well as the technologies these early people were using were constantly undergoing recurrent transformations. In addition, all these processes were highly variable among different regions of Europe. A detailed review is far beyond the scope of this paper (more information can be found e.g. in CAVALLI-SFORZA et al. 1994, STRAUSS 1995, KLEIN 1999), the information given is intended to provide a general framework for the latter discussions concerning the population genetics data.

According to the fossil record, the first modern humans lived in the Levant (Near East) 120-100 Kya (the Middle Paleolithic/Middle Stone Age), but it was not until ~40-30 Kya, during the early-UP, that they appeared in Europe, inhabited at that time by the Neanderthals (BRAUER 1989, CHURCHILL, SMITH 2000). The dating of ~40-30 Kya coincides with the Würm Interpleniglacial, a period of moderate temperatures when some of glacial barriers associated with the preceding glacial maximum temporary melted. This might have promoted the first dispersals of the modern humans from the Near Eastern source. It is generally believed that modern (Cro-Magnon) humans in the early-UP Europe were associated with the Aurignacian technology, while the Neanderthals – with the more primitive Mousterian (and later, Chatelperronian) industries. The earliest Aurignacian artifacts, found together with the fossils characterized as modern, are dated at ~32 Kya, perhaps even 36 Kya (STRAUSS 1995), the most recent fossils with the Neanderthal anatomy are dated at 28-29 Kya (SMITH et al. 1999). The middle-UP technology, Gravettian, dated at 26-22 Kya, long postdates the last Neanderthal sites. The middle-UP (~30-18 Kya) was characterized by the gradual cooling of the climate, which reached its bottom stage approximately ~21-18 Kya during the so-called Last Glacial Maximum, LGM. Glaciers extended down to the latitude of 50 (most of the British Isles the Scandinavian peninsula, the north coast of the Baltic sea, and the present-day Baltic republics, Belarus and the NW part of Russia, as well as the Alps, were covered with ice-sheets). Because of the cold and aridity, and the resulting deforestation, the central Europe turned into polar deserts. As a result, the overwhelming part of the previously inhabited continent became abandoned. The human populations were confined to the glacial refuge areas in the South (the Iberian, Italian and Balkan peninsulas) as well as on the Ukraine/Central Russian Plain. The development of new technologies, such as the early Epigravettian or Solutrean, as well as of cave art, was presumably a re-

sponse to the increased competition due to the population density in the glacial refugia (STRAUSS 1995). The harsh LGM conditions lasted until ~16 Kya, when a slow process of global warming began. Starting at ~13 Kya, temperatures rose rapidly (although with a sharp reversal for a short period of time): the glaciers retreated, the sea level rose increased humidity promoted forestation of the continent. The post-glacial period, often referred to as the Mesolithic, was conducive to the population growth – within few millennia northward dispersals from the glacial refugia led to the recolonization of the whole sub-Scandinavian Europe. Approximately 10 Kya, the invention of farming in the Middle East changed the way of food production. This initiated the Neolithic revolution, i.e. the rapid spread of the new technologies (as reflected by the rich archeological records) and presumably of the Indo-European family of languages. As many believe, the Neolithic revolution was associated with the demographic expansion (demic diffusion) radiating from the Levant towards the West and the North (AMMERMAN, CAVALLI-SFORZA 1984).

Modern Europeans and Neanderthals

The dates associated with the modern human fossils in Qafzeh (~100 Kya) and the Neanderthal fossils from the nearby Kebara (~60 Kya) demonstrated a substantial temporal overlap of these two human forms in the Levant (BRAUER 1989). In Europe, the period of their coexistence estimated from the age of the earliest modern human and the most recent Neanderthal fossils was much shorter, lasting from ~36-32 Kya to ~28-29 Kya (STRAUSS 1995, SMITH et al. 1999). While there is little doubt that the arrival of Cro-Magnons in the early-UP Europe contributed to the extinction of the Neanderthals, the mechanism of the replacement remains a matter of the debate. The most relevant question is to what extent the contemporaneity of these two human forms in Europe led to a gene flow between them; in other words, did Neanderthals hybridize (and if so, to what extent) with the incoming modern humans?

Morphological and morphometrical analyses of the Neanderthals yielded competing views in this respect. Some researches regarded the Neanderthals as a distinct species with, at best, only marginal biological input into the early modern human populations in Eurasia (TATTERSALL, SCHWARTZ 1999). Others linked the Neanderthals in western Eurasia to early modern humans and advocated either some degree of ancestral status for the Neanderthals (WOLPOFF 1999) or a long-lasting period of genetic hybridization (DUARTE et al. 1999, CHURCHILL, SMITH 2000).

In face of the differing interpretations of the antropomorphological patterns, the genetic analyses received a lot of much-deserved attention. Two sequences of the control region fragments in the mitochondrial DNA (mtDNA) extracted from a single Neanderthal-type specimen from western Germany (KRINGS et al. 1997, 1999), compared with the patterns of mtDNA variation in the contemporary hu-

man samples, provided evidence that contradicted a Neanderthal contribution to the early modern human gene pool. Phylogenetic analyses based on these comparisons demonstrated that the Neanderthal sequences fall outside the variation of modern humans (even if in pairwise comparisons several of the human sequences were found to differ more than the Neanderthal differed from some humans). Furthermore, the time of divergence between the Neanderthal and modern human mtDNAs, estimated to have occurred between 317 and 741 Kya, was four times greater than the age of the common ancestor of all human mtDNAs, suggesting that the Neanderthals became extinct without contributing mtDNA to modern humans (KRINGS et al. 1999). Some researchers have questioned these conclusions, arguing that the genetic data were also compatible with models involving varying degrees of regional continuity (e.g. NORDBORG 1998). However, the most obvious weakness of the Neanderthal mtDNA analysis was that the sequence was from a single individual.

The recent sequencing of two other Neanderthal specimens, from the Caucasus (OVCHINNIKOV et al. 2000) and Croatia (KRINGS et al. 2000), not only confirmed distinct clustering of the Neanderthal and human mtDNA sequences, but made it possible to gain an admittedly shallow, but important insight into the Neanderthal genetic diversity. The estimated diversity of the Neanderthals was found to be restricted, resembling in this respect the diversity in modern humans rather than in the non-human primates (KRINGS et al. 2000). The age estimate of the most recent common ancestor of the mtDNA of the Neanderthals from Germany and the Caucasus (OVCHINNIKOV et al. 2000) pointed to 151-352 Kya, coinciding with the time of the Neanderthal lineage emergence in the palaeontological records. Together with the time of the most recent common ancestor of the contemporary human mtDNAs estimated at 106-246 Kya, and that of modern human and Neanderthal mtDNA at 365-853 Kya, these datings suggested that the Neanderthals did not contribute to the human mtDNA diversity. This still does not exclude the possibility that some Neanderthal genes entered the modern human gene pool through some extent of interbreeding. It seems, however, that such a contribution would not be strong enough to seriously alter the variation observed today, and in any case it could not have happened after the Neanderthals disappeared by ~28 Kya.

Prehistoric migrations in Europe

The fossil and archeological records, backed up by the paleoclimatic data, clearly indicate that prehistoric populations in Europe experienced recurrent demographic changes and movements. The three potentially most important large-scale phenomena are: the colonization of Europe by the first modern humans in the early Upper Paleolithic ~40-30 Kya, the Mesolithic dispersal from the glacial refugia ~16-10 Kya and the Neolithic expansion of farmers starting ~10 Kya.

To what extent the genetic diversity in the present-day Europe reflects these processes remains unclear. In particular, there is an ongoing discussion what proportion of the contemporary European gene pool is derived from the pre-agricultural, Paleolithic and Mesolithic people, as opposed to the Neolithic farmers migrating from the Middle East towards the West. It is not earlier than in the last two years that investigations of the mostly mitochondrial and Y-chromosome DNA variability started to distinguish genetic contributions of these prehistoric population movements.

Methodological considerations

To gain insight into past population processes from the present-day patterns of genetic diversity, two different approaches can be adopted (CAVALLI-SFORZA 1998). The remarks presented below are not intended to review the methodologies, but rather to illustrate a few important points relevant for the analysis of population histories.

(a) The first type of analyses is based on analysing the genetic diversity differences between populations. The diversity is expressed directly in the form of marker frequencies or as the derived genetic distances between pairs of populations in the bifurcating tree of populations. The time since the divergence event separating two populations can be estimated using the knowledge of how the genetic distance depends on the mutation rate (CAVALLI-SFORZA 1998). If the populations are in equilibrium, this method facilitates more direct inferences about population history than those based on the measure of genetic diversity between sequences (see below). However, the genetic distances and time estimations may be distorted in the presence of gene flow (HEY 1998) and population size fluctuations (REICH et al. 1999).

Although in principle this approach may be based on the allele frequencies from a single locus, it is always better to analyse data from different loci, as this not only makes it possible to overcome the possible impact of the selection, but also decreases the high variance intrinsic to the analysis of a single gene. To jointly analyse population data from many different loci, the so-called principal component (PC) analysis is usually employed (CAVALLI-SFORZA et al. 1994, PIAZZA et al. 1995). PCs combine the diversity data from many genes, presenting them as distances between populations. Each PC (1st, 2nd etc.) depicts a fraction of the diversity grouped not by genes, but by scenarios; each next PC summarizes another part of the diversity that may reflect a different phenomenon. Similarly to allele frequencies, PC values can be plotted against the geographic distance or presented as synthetic maps. If relations among populations predicted by an external scenario are consistent with the map of a given PC, then the fraction of the total diversity summarized by this PC can be considered to reflect that scenario.

The significance of a correlation between genetic distances among populations and geographic distances between localities where the samples were collected can

be estimated using the autocorrelation analysis. A spatially random distribution of the genetic distances results in a series of insignificant correlation values; a gradual change in the correlation values from significant to insignificant with the increasing geographic distance is expected under isolation by distance (i.e. when genetic diversity reflects only genetic drift and short-range gene flow); a set of correlation coefficients which are significant all along the analysed geographic distance may indicate a cline due to a migration event (BERTORELLE, BARBUJANI 1995).

A cline (frequency gradient or a gradient of genetic distances) may reflect a past population expansion (if the expanding population differed genetically from those already present in the newly occupied area) or a continuous gene flow between stationary groups that initially differed in allele frequencies. Clines may also reflect adaptation to variable environments (selection), but when observed for many loci, which are not likely to be affected in the same way, they usually reflect demographic changes.

(b) The other group of methods summarizes the DNA variation in the form of gene genealogies (trees or networks of sequences, not populations). This approach assumes a lack of recombination in the analysed segment. Sequential accumulation of mutations can be retraced along the lineages, making reconstruction of the resulting haplotypes' genealogy relatively straightforward; groups of haplotypes sharing sequence variants inherited from a common ancestor are known as "haplogroups." The uniparentally inherited (and therefore not recombining) mtDNA and Y-chromosome have the potential of being particularly informative for studies based on gene genealogies. Moreover, mtDNA and Y-chromosome have a 4 times smaller effective population size than autosomes, which makes them much more prone to the random drift and founder effects during population constrictions.

Under reasonable assumptions about mutation rates, the lineages (or, more precisely, the underlying mutations) can be dated using the coalescent approach which estimates the time to the most recent common ancestor of the haplotype sequences in the genealogy (see e.g. HARDING 1996). Geographical patterns in the distribution of ages of clusters or clades can be detected by superimposing the population apportionment of the lineages on the sequence genealogy (phylogeography). Importantly, unless populations descend from genetically monomorphic set of founders (which rarely happens), gene trees are usually much older than population trees (TAJIMA 1983).

European diversity – classical genetic markers and autosomal DNA sequences

Synthetic PC maps based on a number of protein markers (MENOZZI et al. 1978, CAVALLI-SFORZA et al.1994, PIAZZA et al. 1995) demonstrated that the first PC, accounting for 26% of the overall European genetic diversity, displayed a gradient

extending from the Levant into the northern and western Europe. Spatial autocorrelation confirmed that one-third of the European diversity was clinally distributed over the entire continent (SOKAL et al. 1989, 1991). Allele frequencies summarized by the first PC correlated with the archeological dates that indicated a westward cline in the spread of the Neolithic technology (CAVALLI-SFORZA et al. 1994). This frequency cline was also found to correlate with the distribution of the Indo-European family of languages (RENFREW 1987, BARBUJANI, SOKAL 1990, PIAZZA et al. 1995). These highly correlated gradients were taken as an indication that farming spread through the process of demic (as opposed to cultural) diffusion and suggested that the present-day genetic structure of Europeans had been determined mainly by the Neolithic dispersal of farming population from the middle East (AMMERMAN, CAVALLI-SFORZA 1984). The second PC (~21% of the diversity) was suggested to be associated with the spread of Uralic languages and the third one (8.8%) was found to correlate with the spread of the nomad Kurgan people who, alternatively to Neolithic farmers, could be responsible for the spread of the Indo-European language (PIAZZA et al. 1995).

Clinal patterns detected in the classical genetic markers were traditionally associated, because of their consistency with the archeological and linguistic data, with the relatively recent population movements. However, theoretical analyses indicated that they could also reflect the earlier demographic events (BARBUJANI et al. 1995). For example, if the Upper Paleolithic population dispersal had been accompanied by the founder effects, then under the successive short-distance gene flow this would also have resulted in continent-wide clines of allele frequencies resembling the first PC. Discerning these possibilities obviously required incorporating time estimates into the analysis of the genetic diversity distribution in European populations.

The analysis of the autosomal DNA variants provided support for the major impact of the Neolithic expansion from the Middle East. In a spatial autocorrelation analysis of seven hypervariable loci, broad clinal patterns of DNA variation were recognized (CHIKHI et al. 1998). The observed clines closely matched those described at the protein level, with the Northern and Western populations showing the highest divergence from the Middle Eastern ones, and the intermediate situations in between. Importantly, estimates of the time since these populations diverged , based on the microsatellite diversity in the analysed segment, provided no evidence for population splits older than 10 Ky. The only predictable exception were the Saami (Lapps), well-recognized outliers, whose divergence from other populations was estimated at 20-25 Ky.

European migrations from the Y-chromosome perspective

Patterns revealed by the analyses of polymorphisms in the non-recombining portion of the Y-chromosome (NRY) demonstrated the presence of continent-wide clines in European populations, broadly resembling the distribution of the protein markers.

An extensive analysis of biallelic polymorphisms and the derived NRY haplogroups in over 3,600 Y-chromosomes demonstrated highly nonrandom patterns of geographic differentiation among European populations (ROSSER et al. 2000). Spatial autocorrelation analysis demonstrated significant clines in the haplogroups distribution. Two haplogroups, HG1 and HG9 (representing together 45% of the chromosomes), displayed continent-wide, southeast-to-northwest clines, resembling the first PC of the genetic variation in protein loci. Clines for three other haplogroups were regionally restricted and most likely reflected distinct population movements. One of these, HG3 gradient from the north of the Black Sea, resembled the third PC in protein analysis (PIAZZA et al. 1995, see also Eu19 below). PC analysis of the Y-chromosome haplotypes and genetic-barrier analysis suggested that the populations were related on the basis of geography rather than linguistic affinity (see also ZERJAL et al. 2001). The limitation of this study was that no dates for the dispersal of the haplogroups were available.

Another study of NRY haplotypes in 1007 chromosomes from European populations (SEMINO et al. 2000) also demonstrated that the geographic distribution of the NRY haplotypes was correlated with the patterns displayed by the protein markers (PIAZZA et al. 1995). The coalescent age of the NRY haplotypes, estimated from the genealogical analysis of the haplotypes, was compatible with multiple migratory episodes that have contributed to the modern European gene pool. Two clusters (including, respectively, haplotypes Eu18, Eu19 and Eu7, Eu8) appeared to have been present in Europe since the Paleolithic times (based on the age of the mutation defining these clusters, estimated at 30 Kya and 22 Kya, respectively). The remaining lineages (Eu4, Eu9, Eu10 and Eu11, estimated origin at 15 to 20 Kya) entered Europe later, most likely during independent Neolithic migrations from the Middle East and the Urals; their spread correlated with the first PC based on autosomal protein markers, reflecting the diffusion of Neolithic markers (PIAZZA et al. 1995). The contribution of the Neolithic farmers to the European gene pool seemed to be more pronounced along the Mediterranean coast than in Central Europe. The differentiation and the distribution of Eu18 and Eu19 (50% chromosomes) were interpreted as signatures of the post-glacial expansions of these Paleolithic lineages radiating from isolated population foci in the Iberian peninsula (reflected by the second PC in protein data) and the present-day Ukraine (associated with the spread of the Kurgan people revealed by the third PC in protein data); Eu7 and Eu8 presumably underwent a secondary dispersal after LGM. The recent extension of this study to 2,235 chromosomes (PASSARINO et al. 2001), including the Middle East populations, confirmed that Eu19 originated in the Ukraine, probably in a Paleolithic population; the spread of this lineage apparently occurred at different waves over a few thousand years.

As exemplified by the studies presented above, the Y-chromosome proved to be a sensitive system for detecting population movements that have shaped European genetic diversity. Generally, while retaining a strong (but not necessarily

prevailing, see SEMINO et al. 2000) signal of the Neolithic expansion from the Near East, Y-chromosome diversity data suggested that the demographic history of Europe had been complex and influenced by other major population movements, as well as language, geography and the effects of the drift (SEMINO et al. 1996, MALASPINA et al. 1998, QUINTANA-MURCI et al. 1999, ROSSER et al. 2000, SEMINO et al. 2000, ZERJAL et al. 2001, PASSARINO et al. 2001).

European migrations from the mtDNA perspective

Studies based on RFLP haplotype data from the mtDNA coding sequence combined with sequence data in its control region led to the complete characterization of the European mtDNA diversity (TORRONI et al. 1996, 2000, MACAULAY et al. 1999). Seven haplogroups, H, V, I, J, K, T, and W, are Caucasoid-specific, whereas U and X are shared with the Africans and northern Amerindians, respectively. The presence of the Asian superhaplogroup M and the African haplogroups L1 and L2 most probably represents recent admixture events. Analyses of both the frequency, variation, and distribution of the haplogroups within populations and of genealogical relations and sequence diversity among the haplogroups have been used to evaluate current models concerning the process of colonization of the European continent.

In contrast to the autosomal and Y-chromosome studies, where strong continentally-wide clinal patterns of the genetic diversity in Europe had been found and interpreted as consistent with the important impact of the Neolithic demic diffusion, mtDNA analyses suggested that such clines – if identified at all – often indicated earlier population movements.

The population tree analysis based on the comparison of the mtDNA control region sequences in European and West Asian populations (COMAS et al. 1997) revealed a gradient in spite of a generally low genetic heterogeneity: the within-population diversity ascertained through various parameters declined from the east to the west, in a pattern compatible with the ancient population migration and expansion from the Middle East. The expansion time estimates, based on the distribution of pairwise sequence differences within populations (from 135-50 Kya in the Middle East to 42-15 Kya in the Basques), indicated that the east-west gradient was compatible with the Upper Paleolithic rather than the Neolithic event.

Phylogeographic analysis using median networks of the mtDNA haplotypes (RICHARDS et al. 1996, 1997) demonstrated a very low heterogeneity among European populations and a sharp difference between the European and the Middle East diversities (the only clear within-continental difference being that between Basques and the other populations). The network-based coalescent time estimates indicated that most European mtDNA haplotype clusters coalesced much earlier than 10 Kya. The possible Upper Palaeolithic contribution to the present day diversity was estimated at 85%, while the Neolithic contribution at 15% only (see

also discussion in CAVALLI-SFORZA, MINCH 1998 and RICHARDS et al. 1998a). Further cladistic analysis of the phylogenetic networks performed separately for each major European lineage cluster, combined with the coalescent analysis of the time depth of each cluster (RICHARDS et al. 1998b), confirmed that only <20% of the contemporary European mtDNA lineages date back to the fresh immigrations during the Neolithic ~10 Kya. Interestingly, only ~10% (represented by haplogroup U5) was considered likely to have been introduced with the first modern human migrants during the earliest Upper Palaeolithic settlement of the continent ~50 Kya. The majority of the European lineages appeared to have been introduced during the early UP, ~20-50 Kya, and expanded during the post-glacial Mesolithic period ~15 Kya. Expansion time estimates in these analyses were derived from the coalescent analysis of the sequences assuming that the depth of the cluster genealogy (time to the founder) is supposed to well approximate the age of the population's migration into the new territory. The cladistic character of the analyses (i.e. considering the depth of the genealogy only within clusters of lineages descending from a well-defined founder) seemingly validated this approach (RICHARDS, SYKES 1998), although some criticism was raised concerning the application of the sequence genealogy results to date demographic events (BARBUJANI et al. 1998). This discussion aside, the extended phylogeographic analysis of the haplotype clusters derived from the well-defined founders analysis, performed using large samples from the Near Eastern, European, and northern-Caucasus populations (RICHARDS et al. 2000), indicated that (i) the immigrant Neolithic component is likely to comprise less than one-quarter of the mtDNA pool of the modern Europeans, (ii) the majority of extant mtDNA lineages entered Europe in several waves during the Upper Palaeolithic, (iii) there was a founder effect or bottleneck associated with the Last Glacial Maximum (LGM), ~20 Kya, from which the largest fraction of surviving lineages derives.

Extensive phylogeographic analyses of the European haplogroups H and V (TORRONI et al. 1998, 2001) provided support for a major Mesolithic population expansion from glacial refugia in southwestern Europe. The European-specific haplogroup V has been identified as a mtDNA marker for this expansion. Haplogroup V has a limited geographical distribution. Except for the Berbers of North Africa (~10%) it is observed only in Europe, where it reaches high frequencies in some Iberian populations (~20-30%) and Scandinavian Saami (~40%), being absent among the populations of southeastern Europe (and the Near East). Its progenitor sequence, the rather uncommon haplogroup pre*V, is found scattered throughout Europe (and northwestern Africa; this distribution together with the age estimate support the scenario that pre*V originated in Europe before the LGM (TORRONI et al. 2001). The sequence divergence estimates suggest that haplogroup V originated ~13 Kya in the Iberian Peninsula, i.e. during the post-glacial period after the LGM. The haplogroup V gradient centered in the Iberian Peninsula, consistent with the second PC of Europe based on the distribution of classical markers (MENOZZI et al. 1978, CAVALLI-SFORZA et al.1994)

and with the Y-chromosome data (SEMINO et al. 2000), suggests that haplogroup V was dispersed throughout the continent during the Mesolithic population expansion from southwestern to central Europe (but see IZAGIRRE, de la RUA 1999). Its sister haplogroup H is distributed throughout the entire range of Caucasoid populations, with the highest frequencies (40%–60%) in western and northern Europe. The age estimates based on its diversity suggest that haplogroup H originated in the Near East ~30-25 Kya. It probably expanded in Europe ~25-20 Kya, before the LGM, becoming the most common haplogroup in the populations living in southwestern Europe during the LGM. Subsequent Mesolithic expansions from glacial refugia dispersed haplogroup H, along with haplogroup V, into central and northern Europe. In summary, phylogeographic analyses of haplotypes H and V/pre*V demonstrated that a substantial contribution of a Paleolithic population to the gene pool of all modern populations of central-northern Europe was achieved through a post-glacial expansion from the southwestern Ice Age refugia.

In contrast, the possibility of a significant Mesolithic reexpansion from glacial refugia was not an option according to another work based on the spacial correlation analysis of the west Eurasian mtDNA control region sequences (SIMONI et al. 2000). No global clines in the European variation distribution were detected in this study and limited geographic patterning observed in the global analysis was largely due to a marked difference between the Saami isolate and all the other populations. At the regional scale, an area of significant clinal variation was identified only around the Mediterranean Sea. No such cline was observed in the northern part of the continent, even though the allele frequencies in the two regions did not significantly differ. While the Paleolithic expansion rendering the observed pattern of mtDNA diversity remained an option, the authors considered the Neolithic demic diffusion of farmers as the most plausible cause for longitudinal clines of mtDNA. No south-north clines or genetic boundaries (zones of sharp genetic differences) expected to have occurred along the routes of a Mesolithic reexpansion from glacial refugia were found.

In summary, while the analyses of nuclear loci underscore a crucial role of the Neolithic demographic transition, the interpretation of mtDNA evidence is controversial. Some of the studies support the major impact of the Neolithic (SIMONI et al. 2000), while some underscore the Paleolithic (COMAS et al. 1997) or Mesolithic (TORRONI et al. 1998, 2001) components, or both (RICHARDS et al.1996, 1998b, 2000). The discrepancies between nuclear genes and mtDNA may stem from the properties of the genetic systems analysed, but the incongruity among the mtDNA studies most probably reflects different approaches used in the analysis of the observed diversity.

The "genetic system" problem might be that mtDNA and Y-chromosome reflect separate histories of, respectively, maternal and paternal lineages (with autosomal data falling in between). The recent data indicate that some aspects of these histories may differ, reflecting for example different migration patterns in men and women (e.g. SCOZZARI et al. 1997, SEIELSTADT et al. 2000, HAMMER

et al. 2001). Moreover, because of a strict linkage among all the loci in the non-recombining portion of the mitochondrial genome, and similarly in the Y-chromosome, these genetic systems effectively behave as single loci; as a result, their evolution may be skewed by selection. Therefore, to infer conclusions about the history of modern humans from the patterns of genetic diversity, one has to consider a number of independent genomic segments, including autosomal and X-chromosome DNA.

The second problem may be exemplified by the discussion surrounding the analysis of mtDNA using the "population trees" versus "gene trees" approach. Generally, the analyses based on the comparison of populations tend to return shorter times for the population splits than the analyses based on gene genealogies. It is possible to reconcile both approaches, but attention must be taken to realize the possible pitfalls of each methodology.

The debate on just what proportion of the contemporary European gene pool is derived from the Paleolithic and Mesolithic people, as opposed to the Neolithic farmers migrating from the Middle East towards West, still continues. However, even if the discrepancies concerning the dating of European prehistoric migrations persist, the general picture is that, while the present day structure of both nuclear and mitochondrial genetic diversity undoubtedly reflects the important contribution of the Neolithic farmers, the impact of pre-agricultural paleodemographic events becomes increasingly evident as well.

Conclusions

Investigating the problems of modern human origins, the Neanderthal admixture or prehistoric migrations in Europe are just few – though by no means minor – examples of the applications of the population genetic diversity studies in elucidating evolutionary and demographical processes of the past. There is a wide range of interesting questions that can be – and in many cases have actually been – addressed. With the Middle East being the main source of the European gene pool, be it directly during the Paleolithic or Neolithic dispersals or indirectly during the Mesolithic reexpansions from glacial refugia, an input of genes from other locations has to be considered too, although these effects are largely regional. For example, there is some discernible gene flow between Northwestern Africa and the Iberian Peninsula (RANDO et al. 1998, COMAS et al. 2000, FLORES et al. 2000, BOSCH et al. 2001), while an Asian influence can be distinguished in the Scandinavian populations of Saami (SAJANTILA et al. 1995, MEINILA et al. 2001, LARSEN et al. 2001). The population of Basques – the isolate with the most evident signal of the pre-Neolithic genetic component – deserves the question in itself (BERTRANPETIT et al. 1995, COMAS et al. 1998, ALONSO, ARMOUR 1998). Then, one has to consider the recent local European effects: bottlenecks and founder effects e.g. in Finns and the Saami (SAJANTILA et al. 1995, LAHERMO

et al. 1999) or in the Romani (KALAYDJIEVA et al. 2001), the influence of geographic and linguistic barriers on the local gene flow (HURLES et al. 1999, COMAS et al. 2000, BOSCH et al. 2001, STEFAN et al. 2001), recent local histories of particular populations (SISTONEN et al. 1999, HELGASON et al. 2000, MALYARCHUK, DERENKO 2001, SCOZZARI et al. 2001, TOMAS et al. 2001), etc. The practical impact of these investigations goes well beyond the academic exercise – investigating population fissions and hybridizations as well as founder effects is necessary to understand how the diversity – both neutral and that involved in the disease – arises and is maintained in populations, and it constitutes a necessary step for the studies in genetic epidemiology and medical population genetics.

REFERENCES

ALONSO S., ARMOUR A.L. (1998). MS205 Minisatellite diversity in Basques: evidence for a pre-Neolithic component. Genome Res. 8: 1289-1298.

AMMERMAN A.J., CAVALLI-SFORZA L.L. (1984). The Neolithic Transition and the Genetics of Populations Europe. Princeton University Press, Princeton, NJ.

BARBUJANI G., SOKAL R.R. (1990). Zones of sharp genetic change in Europe are also linguistic boundaries. Proc. Natl. Acad. Sci. USA 87: 1816-1819.

BARBUJANI G., SOKAL R.R. ODEN N.L. (1995). Indo-European origins: a computer simulation test of five hypotheses. Am. J. Phys. Anthropol. 96: 109-132.

BARBUJANI G., BERTORELLE G., CHIKHI L. (1998). Evidence for Paleolithic and Neolithic gene flow in Europe. Am. J. Hum. Genet. 62: 488-492.

BATZER M.A., STONEKING M., ALEGRIA-HARTMAN M., BAZAN H., KASS D.H., SHAIKH T.H., NOVICK G.E., IOANNOU P.A., SCHEER W.D., HERRERA R.J., DEININGER P.L. (1994). African origin of human-specific polymorphic Alu insertions. Proc. Natl. Acad. Sci. USA 91: 12288-12292.

BERTORELLE G., BARBUJANI G. (1995). Analysis of DNA diversity by spatial autocorrelation. Genetics 140: 811-819.

BERTRANPETIT J., SALA J., CALAFELL F., UNDERHILL P.A., MORAL P., COMAS D. (1995). Human mitochondrial DNA variation and the origin of Basques. Ann. Hum. Genet. 59: 63-81.

BOSCH E., CALAFELL F., COMAS D., OEFNER P.J., UNDERHILL P.A., BERTRANPETIT J. (2001). High-resolution analysis of human Y-chromosome variation shows a sharp discontinuity and limited gene flow between Northwestern Africa and the Iberian Peninsula. Am. J. Hum. Genet. 68: 1019-1029.

BOWCOCK A.M., KIDD J., MOUNTAIN J.L., HEBERT J.M., CAROTENUTO L., KIDD K.K., CAVALLI-SFORZA L.L. (1991). Drift, admixture, and selection in human evolution: A study with DNA polymorphisms. Proc. Natl. Acad. Sci. USA 88: 839-843.

BOWCOCK A.M., RUIZ-LINARES A., TOMFOHRDE J., MINCH E., KIDD J.R., CAVALLI-SFORZA L.L. (1994). High resolution of human evolutionary trees with polymorphic microsatellites. Nature 368: 455-457.

BRÄUER G. (1989). The evolution of modern humans: a comparison of the African and non-African evidence. In: The Origins and Dispersal of Modern Humans: Behav-

ioural and Biological Perspectives (P. Mellars, C.B. Stringer, eds.). Edinburgh University Press, Edinburgh: 124-154.

CANN R.L., STONEKING M., WILSON A.C. (1987). Mitochondrial DNA and human evolution. Nature 325: 31-36.

CAVALLI-SFORZA L.L., PIAZZA A., MENOZZI P., MOUNTAIN J. (1988). Reconstruction of human evolution: bringing together genetic, archaeological, and linguistic data. Proc. Natl. Acad. Sci. USA 85: 6002-6006.

CAVALLI-SFORZA L.L., MENOZZI P., PIAZZA A. (1994). The History and Geography of Human Genes. Princeton University Press, Princeton, New Jersey.

CAVALLI-SFORZA L.L., MINCH E. (1998). Paleolithic and Neolithic lineages in the European mitochondrial gene pool. Am. J. Hum. Genet. 61: 247–251.

CAVALLI-SFORZA L.L. (1998). The DNA revolution in population genetics. Trends Genet. 14/2: 2-7.

CHIKHI L., BESTRO-BISOL G., BERTORELLE G., PASCALI V., BARBUJANI G. (1998). Clines of nuclear DNA markers suggest a largely Neolithic ancestry of the European gene pool. Proc. Natl. Acad. Sci. USA 95: 9053-9058.

CHURCHILL S.E., SMITH F.H. (2000). Makers of the early Aurignacian of Europe. Am. J. Phys. Anthropol. 113: 61-115.

CLARK A., WEISS K.M., NICKERSON D.A., TAYLOR S.L., BUCHANAN A., STENGARD J., SALOMAA V., VARTIAINEN E., PEROLA M., BOERWINKLE E., SING C.F. (1998). Haplotype structure and population genetic inferences from nucleotide-sequence variation in human lipoprotein lipase. Am. J. Hum. Genet. 63: 595-612.

COMAS D., CALAFELL F., MATEU E., PEREZ-LEZAUN A., BOSCH E., BERTRANPETIT J. (1997). Mitochondrial DNA variation and the origin of the Europeans. Hum. Genet. 99: 443-449.

COMAS D., MATEU E., CALAFELL F., PEREZ-LEZAUN A., BOSCH E., MARTINEZ-ARIAS R., BERTRANPETIT J. (1998). HLA class I and class II DNA typing and the origin of Basques. Tissue Antigens 51: 30-40.

COMAS D., CALFELL F., BENCHEMSI N., HELAL A., LEFRANC A., STONEKING M., BATZER M.A., BERTRANPETIT J., SAJANTILA A. (2000). Alu insertion polymorphisms in NW Africa and the Iberian Peninsula: evidence for a strong genetic boundary through the Gibraltar Straits. Hum. Genet. 107: 312-319.

DUARTE C., MAURÝCIO J., PETTITT P.B., SOUTO P., TRINKAUS E., VAN DER PLICHT H., ZILHAO J. (1999). The early Upper Paleolithic human skeleton from the Abrigo do Lagar Velho (Portugal) and modern human emergence in Iberia. Proc. Natl. Acad. Sci. USA 96: 7604-7609.

FLORES C., MACA-MEYER N., GONZALES A.M., CABRERA V.M. (2000). Northwest African distribution of the CD4/Alu microsatellite haplotypes. Ann. Hum. Genet. 64: 321-327.

GABUNIA L., VEKUA A. (1995). A Plio-Pleistocene hominid from Dmanisi, East Georgia, Caucasus. Nature 373: 509-512.

HAMMER M.F., KARAFET T., RASANAYAGAM A., WOOD E.T., ALTHEIDE T.K., JENKINS T., GRIFFITHS R.C., TEMPLETON A.R., ZEGURA S.L. (1998). Out of Africa and back again: nested cladistic analysis of human Y chromosome variation. Mol. Biol. Evol. 15: 427-441.

HAMMER M.F., KARAFET T.M., REDD A.J., JARJANAZI H., SANTACHIARA-BENERECETTI S., SOODYAL H., ZEGURA S.L. (2001). Hierarchical patterns of global human Y-chromosome diversity. Mol. Biol. Evol. 18: 1189-1203.

HARDING R.M. (1996). Using the coalescent to interpret gene trees. In: Molecular Biology and Human Diversity (A.J. Boyce, C.G.N. Mascie-Taylor, eds.). Cambridge University Press.

HARPENDING H.C., SHERRY S.T., ROGERS A.R., STONEKING M. (1993). The genetic structure of ancient human populations. Curr. Anthropol. 34: 483-496.

HELGASON A., SIGURETHARDOTTIR S., GULCHER J.R., WARD R., STEFANSSON K. (2000). mtDNA and the origin of the Icelanders: deciphering signals of recent population history. Am. J. Hum. Genet. 66: 999-1016.

HEY J. (1998). Population genetics and human origins – haplotypes are key! Trends Genet. 14: 303-304.

HURLES M.E., VEITIA R., ARROYO E., ARMENTEROS M., BERTRANPETIT J., PEREZ-LEZAUN A., BOSCH E., SHLUMUKOVA M., CAMBON-THOMSEN A., MCELREAVEY K., LOPEZ DE MUNAIN A., ROHL A., WILSON I.J., SINGH L., PANDYA A., SANTOS F.R., TYLER-SMITH C., JOBLING M.A. (1999). Recent male-mediated gene flow over a linguistic barrier in Iberia, suggested by analysis of a Y-chromosomal DNA polymorphism. Am. J. Hum. Genet . 65: 1437-1448.

IZAGIRRE N., DE LA RUA C. (1999). A mtDNA analysis in ancient Basque population: implications for haplogroup V as a marker for a major Paleolithic expansion from southwestern Europe. Am. J. Hum. Genet. 65: 199-207.

JORDE L.B., ROGERS A.R., BAMSHAD M., WATKINS W.S., KRAKOWIAK P., SUNG S., KERE J., HARPENDING H. (1997). Microsatellite diversity and the demographic history of modern humans. Proc. Natl. Acad. Sci. USA 94: 3100-3103.

KALAYDJIEVA L., CALAFELL F., JOBLING M.A., ANGELICHEVA D., DE KNIJF P., ROSSER Z.H., HURLES M., UNDERHILL P., TOURNEV I., MARUSHIAKOVA E., POPOV V. (2001). Patterns of inter– and intra-group genetic diversity in the Vlax Roma as revealed by Y – chromosome and mitochondrial lineages. Eur. J. Hum. Genet. 9: 97-104.

KIMURA M. (1983). The Neutral Theory of Molecular Evolution. Cambridge University Press, Cambridge.

KIVISILD T., BAMSHAD M.J., KALDMA K., METSPALU M., METSPALU E. REIDLA M., LAOS S., PARIK J., WATKINS W.S., DIXON M.E., PAPIHA S.S., MASTANA S.S., MIR M.R., FERAK V., VILLEMS R. (1999). Deep common ancestry of Indian and western-Eurasian mitochondrial DNA lineages. Current Biology 9: 1331-1334.

KLEIN R.G. (1999). The Human Career. Human Biological and Cultural Origins. The University of Chicago Press. Chicago, London.

KRINGS M., STONE A., SCHMITZ R.W., KRAINITZKI H., STONEKING M., PAABO S. (1997). Neanderthal DNA sequences and the origin of modern humans. Cell 90: 19-30.

KRINGS M., GEISERT H., SCHMITZ R.W., KRAINITZKI H., PAABO S. (1999). DNA sequence of the mitochondrial hypervariable region II from the Neanderthal type specimen. Proc. Natl. Acad. Sci. USA 96: 5581-5585.

KRINGS M., CAPELLI C., TSCHENTSCHER F., GEISERT H., MEYER S., VON HAESELER A., GROSSSCHMIDT K., POSSNERT G., PAUNOVIC M., PAABO S. (2000). A view of Neanderthal genetic diversity. Nat. Genet. 26: 144-146.

LABUDA D., ZIETKIEWICZ E., YOTOVA V. (2000). Archaic lineages in the history of modern humans. Genetics 156: 799-808.

LAHERMO P., SAVONTAUS M.L., SISTONEN P., BERES J., DE KNIJFF P., AULA P., SAJANTILA A. (1999). Y chromosomal polymorphisms reveal founding lineages in the Finns and the Saami. Eur. J. Hum. Genet. 7: 447-458.

LAHR M.M., FOLEY R. (1994). Multiple dispersals and modern human origins. Evol. Anthropol. 3: 48-60.

LAHR M.M., FOLEY R.A. (1999). Towards a theory of modern human origins: geography, demography, and diversity in recent human evolution. Am. J. Phys. Anthropol. 27: 137-176.

LARSEN L.A., VUUST J., NYSTAD M., EVSEEVA I., VAN GHELUE M., TRANABJAERG L. (20001). Analysis of FMR1 (CGG)(n) alleles and DXS548-FRAXAC1 haplotypes in the European circumpolar populations: traces of genetic relationship with Asia. Eur. J. Hum. Genet. 9: 724-727.

LEAKEY R. (1994). The Origin of Humankind. BasicBooks, A Division of Harper Collins Publishers.

LI W.H., SADLER L.A. (1991). Low nucleotide diversity in man. Genetics 129: 513-523.

MACAULAY V., RICHARDS M., HICKEY E., VEGA E., CRUCIANI F., GUIDA V., SCOZZARI R., BONNÉ-TAMIR B., SYKES B., TORRONI A. (1999). The emerging tree of west Eurasian mtDNAs: a synthesis of control-region sequences and RFLPs. Am. J. Hum. Genet. 64: 232-249.

MALASPINA P., CRUCIANI F., CIMINELLI B.M., TERRENATO L., SANTOLAMAZZA P., ALONSO A., BANYKO J., BRDICKA R., GARCIA O., GAUDIANO C., GUANTI G., KIDD K.K., LAVINHA J., AVILA M., MANDICH P., MORAL P., QAMAR R., MEHDI S.Q., RAGUSA A., STEFANESCU G., CARAGHIN M., TYLER-SMITH C., SCOZZARI R., NOVELLETTO A. (1998). Network analyses of Y-chromosomal types in Europe, northern Africa, and western Asia reveal specific patterns of geographic distribution. Am. J. Hum. Genet. 63: 847-860.

MALYARCHUK B.A., DERENKO M.V. (2001). Mitochondrial DNA variability in Russians and Ukrainians: implication for the origin of the Eastern Slavs. Ann. Hum. Genet. 65: 63-78.

MEINILA M., FINNILA S., MAJAMAA K. (2001). Evidence for mtDNA admixture between the Finns and the Saami. Hum. Hered. 52: 160-170.

MENOZZI P., PIAZZA A., CAVALLI-SFORZA L.L. (1978). Synthetic maps of human gene frequencies in Europeans. Science 201: 786-792.

MOUNTAIN J.L., CAVALLI-SFORZA L.L. (1994). Inference of human evolution through cladistic analysis of nuclear DNA restriction polymorphisms. Proc. Natl. Acad. Sci. USA 91: 6515-6519.

NORDBORG M. (1998). On the probability of Neanderthal ancestry. Am. J. Hum. Genet. 63: 1237-1240.

OVCHINNIKOV I.V., ANDERS GOTHERSTROM A., ROMANOVA G.P., KHARITONOV V.M., KERSTIN LIDEN K., GOODWIN W. (2000). Molecular analysis of Neanderthal DNA from the northern Caucasus. Nature 404: 490-493.

PASSARINO G., SEMINO O., MAGRI C., AL-ZAHERY N., BENUZZI G., QUINTANA-MURCI L., ANDELLNOVIC S., BULLC-JAKUS F., LIU A., ARSLAN A., SANTACHIARA- BENERECETTI A.S. (2001). The 49a,f haplotype 11 is a new marker of the Eu19 lineage that traces migrations from northern regions of the Black Sea. Hum. Immunol. 62: 922-932.

PIAZZA A., RENDINE S., MINCH E., MENOZZI P., MOUNTAIN J., CAVALLI-SFORZA L.L. (1995). Genetics and the origin of European languages. Proc. Natl. Acad. Sci. USA 92: 5836-5840.

QUINTANA-MURCI L., SEMINO O., MINCH E., PASSARINO G., BREGA A., NASIDZE I., SANTACHIARA-BENERECETTI A.S. (1999). Further characteristics of proto-European Y chromosomes. Eur. J. Hum. Genet. 7: 603-608.

RANDO J.C., PINTO F., GONZALEZ A.M., HERNANDEZ M., LARRUGA J.M., CABRERA V.M., BANDELT H.J. (1998). Mitochondrial DNA analysis of northwest African populations reveals genetic exchanges with European, near-eastern and sub-Saharan populations. Ann. Hum. Genet. 62: 531-550.

REICH D.E., FELDMAN M.W., GOLDSTEIN D.B. (1999). Statistical properties of two tests that use multilocus data sts to detect population expansions. Mol. Biol. Evol. 16: 453-466.

RELETHFORD J.H. (1995) Genetics and modern human origins. Evol. Anthropol. 4: 53-63.

RELETHFORD J.H., JORDE L.B. (1999). Genetic evidence for larger African population size during recent human evolution. Am. J. Phys. Anthropol. 108: 251-260.

RENFREW C. (1987). Archaeology and Language: the Puzzle of Indo-European Origins. Jonathan Cape, London.

RICHARDS M., CORTE-REAL H., FORSTER P., MACAULAY V., WILKINSON-HERBOTS H., DEMAINE A., PAPIHA S., HEDGES R., BANDELT H.J., SYKES B. (1996). Paleolithic and Neolithic lineages in the European mitochondrial gene pool. Am. J. Hum. Genet. 59: 185-203.

RICHARDS M.B., MACAULAY V.A., SYKES B.C., PETTITT P., HEDGES R., FORSTER P., BANDELT H.J. (1998a). Reply to Cavalli-Sforza and Minch. Am. J. Hum. Genet. 61: 251-254.

RICHARDS M.B., MACAULAY V.A., BANDELT H.J., SYKES B.C. (1998b). Phylogeography of mitochondrial DNA in western Europe. Ann. Hum. Genet. 62: 241-260.

RICHARDS M.B., SYKES B. (1998). Reply to Barbujani et al. Am. J. Hum. Genet. 62: 491-492.

RICHARDS M., MACAULAY V., HICKEY E., VEGA E., SYKES B., GUIDA V., RENGO C., SELLITTO D., CRUCIANI F., KIVISILD T., VILLEMS R., THOMAS M., RYCHKOV S., RYCHKOV O., RYCHKOV Y., GOLGE M., DIMITROV D., HILL E., BRADLEY D., ROMANO V., CALI F., VONA G., DEMAINE A., PAPIHA S., TRIANTAPHYLLIDIS C., STEFANESCU G., HATINA J., BELLEDI M., DI RIENZO A., OPPENHEIM A., NORBY S., AL-ZAHERI N., SANTACHIARA-BENERECETTI S., SCOZZARI R., TORRONI A., BANDELT H.J. (2000). Tracing European Founder Lineages in the Near Eastern mtDNA Pool. Am. J. Hum. Genet. 67: 1251-1276.

ROGERS A.R., JORDE L.B. (1995). Genetic evidence on modern human origins. Hum. Biol. 67: 1-36.

ROSSER Z.H., ZERJAL T., HURLES M.E., ADOJAAN M., ALAVANTIC D., AMORIM A., AMOS W., ARMENTEROS M., ARROYO E., BARBUJANI G., BECKMAN G., BECKMAN L., BERTRANPETIT J., BOSCH E., BRADLEY D.G., BREDE G., COOPER G., CORTE-REAL H.B., DE KNIJFF P., DECORTE R., DUBROVA Y.E., EVGRAFOV O., GILISSEN A., GLISIC S., GOLGE M., HILL E.W., JEZIOROWSKA A., KALAYDJIEVA L., KAYSER M., KIVISILD T., KRAVCHENKO S.A., KRUMINA A., KUCINSKAS V., LAVINHA J., LIVSHITS L.A., MALASPINA P., MARIA S., MCELREAVEY K., MEITINGER T.A., MIKELSAAR A.V., MITCHELL R.J., NAFA K., NICHOLSON J., NORBY S., PANDYA A., PARIK J., PATSALIS P.C., PEREIRA L., PETERLIN B., PIELBERG G., PRATA M.J., PREVIDERE C., ROEWER L., ROOTSI S., RUBINSZTEIN D.C., SAILLARD J., SANTOS F.R., STEFANESCU G., SYKES B.C., TOLUN A., VILLEMS R., TYLER-SMITH C., JOBLING M.A. (2000). Y-chromosomal diversity in Europe is clinal and influenced primarily by geography, rather than by language. Am. J. Hum. Genet. 67: 1526-1543.

SAJANTILA A., LAHERMO P., ANTTINEN T., LUKKA M., SISTONEN P., SAVONTAUS M.-L., AULA P., BECKMAN L., TRANEBJAERG L., GEDDE-DAHL T., ISSEL-TARVER L., DIRIENZO A., PAABO S. (1995). Genes and languages in Europe: an analysis of mitochondrial lineages. Genome Res. 5: 42-52.

SAJANTILA A., SALEM A.H., SAVOLAINEN P., BAUER K., GIERIG C., PAABO S. (1996). Paternal and maternal DNA lineages reveal a bottleneck in the founding of the Finnish population. Proc. Natl. Acad. Sci. USA 93: 12035-12039.

SCOZZARI R., CRUCIANI F., MALASPINA P., SANTOLAMAZZA P., CIMINELLI B.M., TORRONI A., MODIANO D., WALLACE D.C., KIDD K.K., OLCKERS A., MORAL P., TERRENATO L., AKAR N., QAMAR R., MANSOOR A., MEHDI S.Q., MELONI G., VONA G., COLE D.E., CAI W., NOVELLETTO A. (1997). Differential structuring of human populations for homologous X and Y microsatellite loci. Am. J. Hum. Genet. 61: 719-733.

SCOZZARI R., CRUCIANI F., PANGRAZIO A., SANTOLAMAZZA P., VONA G., MORAL P., LATINI V., MEMMI M., ROMANO V., DE LEO G., GENARELLI M., JARUZELSKA J., VILLEMS R., PARIK J., MACAULAY V., TORRONI A. (2001). Human Y-chromosome variation in the western Mediterranean area: implications for the peopling of the region. Hum. Immunol. 62: 871-884.

SEIELSTADT M. (2000). Asymmetries in the maternal and paternal genetic histories of Colombian populations. Am. J. Hum. Genet. 67: 1062-1066.

SEMINO O., PASSARINO G., BREGA A., FELLOUS M., SANTACHIARA-BENERECETTI A.S. (1996). A view of the Neolithic demic-diffusion in Europe through two Y chromosome-specific markers. Am. J. Hum. Genet. 59: 964-968.

SEMINO O., PASSARINO G., OEFNER P.J., LIN A.A., ARBUZOVA S., BECKMAN L.E., DE BENEDICTIS G., FRANCALACCI P., KOUVATSI A., LIMBORSKA S., MARCIKIAE M., MIKA A., MIKA B., PRIMORAC D., SANTACHIARA-BENERECETTI A.S., CAVALLI-SFORZA L.L., UNDERHILL P.A. (2000). The genetic legacy of paleolithic homo sapiens sapiens in extant europeans: A Y chromosome perspective. Science 290: 1155-1159.

SIMONI L., CALAFELL F., PETTENER D., BERTRANPETIT J., BARBUJANI G. (2000). Geographic patterns of mtDNA diversity in Europe. Am. J. Hum. Genet. 66: 262-278.

SISTONEN P., VIRTARANTA-KNOWLES K., DENISOVA R., KUCINSKAS V., AMBRASIENE D., BECKMAN L. (1999). The LWb blood group as a marker of prehistoric Baltic migrations and admixture. Hum. Hered. 49: 154-158.

SMITH F.H., TRINKAUS E., PETTIT P.B., KARAVANIC I., PAUNOVIC M. (1999). Direct radiocarbon dates for Vindija G1 and Velika Pecina Late Pleistocene hominid remains. PNAS 96 : 12281-12286.

SOKAL R.R., HARDING R.M., ODEN N.L. (1989). Spatial patterns of human gene frequencies in Europe. Am. J. Phys. Anthropol. 80: 267-294.

SOKAL R.R., ODEN N.L., WILSON C. (1991). Genetic evidence for the spread of agriculture in Europe by demic diffusion. Nature 351: 143-145.

STEFAN M., STEFANESCU G., GAVRIL L., TERRENATO L., JOBLING M.A., MALASPINA P., NOVELLETTO A. (2001). Y-chromosome analysis reveals a sharp boundary in the Carpathian region. Eur. J. Hum. Genet. 9: 27-33.

STRAUSS L.G. (1995). The upper Paleolithic of Europe: An overview. Evol. Anthropol. 4: 4-16.

STRINGER C.B., ANDREWS P. (1988). Genetic and fossil evidence for the origin of modern humans. Science 239: 1263-1268.

SWISHER C.C. III., CURTIS G.H., JACOB T., GETTY A.G., SUPRIJO A., WIDIASMORO (1994). Age of the earliest known hominids in Java, Indonesia. Science 263: 1118-1121.

TAJIMA F. (1983). Evolutionary relationship of DNA sequences in finite populations. Genetics 105: 437-460.

TATTERSALL I. (1997). Out of Africa again... and again? Scientific American 276: 60-67.

TATTERSAL I., SCHWARTZ J.H. (1999). Hominids and hybrids: the place of Neanderthals in human evolution. Proc. Natl. Acad. Sci. USA 96: 7117-7119.

TEMPLETON A.R. (1997). Out of Africa? What do genes tell us? Curr. Opin. Genet. Dev. 7: 841-847.

TISHKOFF S.A., DIETZSCH E., SPEED W., PAKSTIS A.J., KIDD J.R., CHEUNG K., BONNÉ-TAMIR B., SANTACHIARA-BENERECETTI A.S., MORAL P., KRINGS M., PAABO S., WATSON E., RISCH N., JENKINS T., KIDD K.K. (1996). Global patterns of linkage disequilibrium at the CD4 locus and modern human origins. Science 271: 1380-1387.

TOMAS C., PICORNELL A., CASTRO J.A., RAMON M.M. (2001). Genetic analyses in five western Mediterranean populations: variation at five tetrameric short tandem repeat loci. Hum. Biol. 73: 349-363.

TORRONI A., HUOPONEN K., FRANCALACCI P., PETROZZI M., MORELLI L., SCOZZARI R., OBINU D., SAVONTAUS M.-L., WALLACE D.C. (1996). Classification of European mtDNAs from an analysis of three European populations. Genetics 144: 1835-1850.

TORRONI A., BANDELT H.J., D'URBANO L., LAHERMO P., MORAL P., SELLITTO D., RENGO C., FORSTER P., SAVONTAUS M.L., BONNE-TAMIR B., SCOZZARI R. (1998). mtDNA analysis reveals a major late Paleolithic population expansion from southwestern to northeastern Europe. Am. J. Hum. Genet. 62: 1137-1152.

TORRONI A., RICHARDS M., MACAULAY V., FORSTER P., VILLEMS R., NORBY S., SAVONTAUS M.L., HUOPONEN K., SCOZZARI R., BANDELT H.J. (2000). mtDNA haplogroups and frequency patterns in Europe. Am. J. Hum. Genet. 66: 1173-1177.

TORRONI A., BANDELT H.J., MACAULAY V., RICHARDS M., CRUCIANI F., RENGO Ch., MARTINEZ-CABRERA V., VILLEMS R., KIVISILD T., METSPALU E., PARIK J., TOLK H.V., TAMBETS K., FORSTER P., KARGER B., FRANCALACCI P., RUDAN P., JANICIJEVIC B., RICKARDS O., SAVONTAUS M.L., HUOPONEN K., LAITINEN V., KOIVUMAKI S., SYKES B., HICKEY E., NOVELLETTO A., MORAL P., SELLITTO D., COPPA A., AL-ZAHERI N., SANTACHIARA-BENERECETTI A.S., SEMINO O., SCOZZARI R. (2001). A signal, from human mtDNA, of postglacial recolonization in Europe. Am. J. Hum. Genet. 69: 844-852.

WEIDENREICH F. (1943). The skull of *Sinanthropus pekinensis*: a comparative study of a primitive hominid skull. Palarontol Sinica n.s. D, 10: (whole series) 127.

WOLPOFF M., CASPARI R. (1997). Race and Human Evolution. (Simon, Schuster eds.), New York, NY.

WOLPOFF M. (1998). Concocting a divisive theory. Evol. Anthropol. 7: 1-3.

WOLPOFF M.H., HAWKS J., FRAYER D.W., HUNLEY K. (2001). Modern human ancestry at the peripheries: a test of the replacement theory. Science 291: 293-297.

ZERJAL T., BECKMAN L., BECKMAN G., MIKELSAAR A.V., KRUMINA A., KUCINSKAS V., HURLES M.E., TYLER-SMITH C. (2001). Geographical, linguistic, and cultural influences on genetic diversity: Y-chromosomal distribution in Northern European populations. Mol. Biol. Evol. 18: 1077-1087.

ZIETKIEWICZ E., YOTOVA V., JARNIK M., KORAB-LASKOWSKA M., KIDD K.K., MODIANO D., SCOZZARI R., STONEKING M., TISHKOFF S., BATZER M., LABUDA D. (1998). Genetic structure of the ancestral population of modern humans. J. Mol. Evol. 47: 146-155.