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MITOCHONDRIAL DNA AND HUMAN EVOLUTION

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■ **Abstract** Several unique properties of human mitochondrial DNA (mtDNA), including its high copy number, maternal inheritance, lack of recombination, and high mutation rate, have made it the molecule of choice for studies of human population history and evolution. Here we review the current state of knowledge concerning these properties, how mtDNA variation is studied, what we have learned, and what the future likely holds. We conclude that increasingly, mtDNA studies are (and should be) supplemented with analyses of the Y-chromosome and other nuclear DNA variation. Some serious issues need to be addressed concerning nuclear inserts, database quality, and the possible influence of selection on mtDNA variation. Nonetheless, mtDNA studies will continue to play an important role in such areas as examining socio-cultural influences on human genetic variation, ancient DNA, certain forensic DNA applications, and in tracing personal genetic history.

INTRODUCTION

Human mitochondrial DNA (mtDNA) is a circular double-stranded molecule, 16,569 base pairs (bp) in length that codes for 13 subunits of the oxidative phosphorylation system, 2 ribosomal RNAs (rRNAs), and 22 transfer RNAs (tRNAs) (2) (Figure 1). It is present in hundreds to thousands of copies in each cell, not within the nucleus, but within the cell's energy-generating organelles, the mitochondria. MtDNA consists predominantly of coding DNA, with the exception of a ∼1100-bp long fragment that has mainly regulatory functions and is therefore termed the control region. Since the first in-depth study of human mtDNA variation 25 years ago (22), it has become widely used for studies of human evolution, migration, and population histories (e.g., 24, 66, 68, 81, 93, 117, 157, 165, 170). This widespread use is due to unique features of mtDNA that make it particularly amenable to evolutionary studies. These features include a high copy number, maternal inheritance, lack of recombination, and a generally higher mutation rate than found in nuclear DNA.

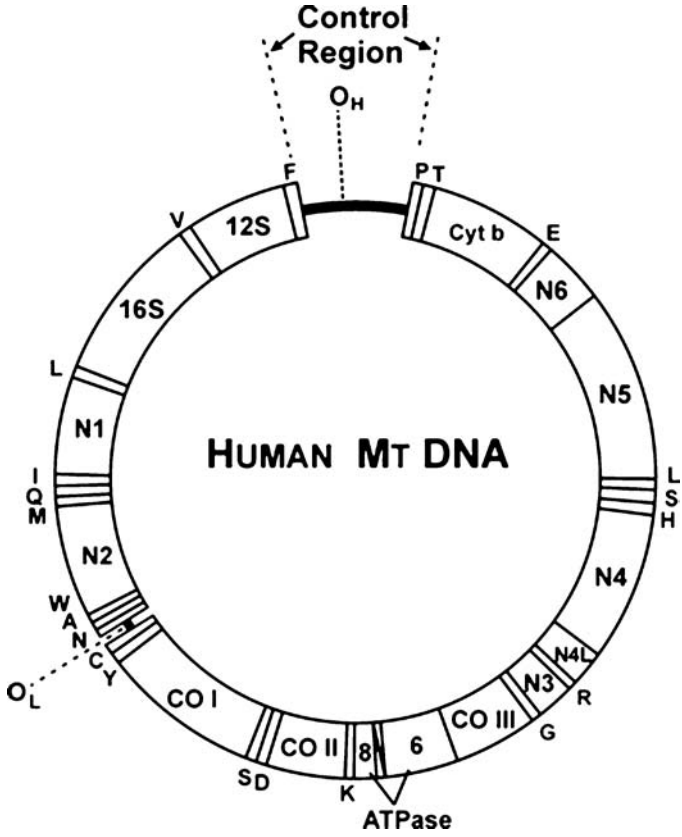

Figure 1 Schematic representation of the human mitochondrial DNA genome, with functional regions indicated as follows: two ribosomal RNA genes (12S and 16S), three genes for subunits of cytochrome oxidase (COI–COIII), seven genes for subunits of NADH dehydrogenase (N1-N6, N4L), two genes for subunits of F1ATPase (6 and 8), the cytochrome b gene, 22 transfer RNA genes (designated by the standard single letter code), two origins of replication (O_H and O_L), and the control region (the major noncoding region).

PROPERTIES OF HUMAN MITOCHONDRIAL DNA

High Copy Number

MtDNA is present in high copy number in human cells. The average somatic cell has just two copies of any given nuclear gene or DNA segment, but hundreds to thousands of copies of mtDNA (123). This property, along with the extranuclear, cytoplasmic location of mtDNA, makes it easier to obtain mtDNA for analysis, and also makes mtDNA the molecule of choice for analyzing ancient DNA and for certain forensic DNA applications.

However, this property also complicates the population genetics of mtDNA because there are several levels at which populations of mtDNA molecules can be defined—within a single mitochondrion, within a single cell, within a particular tissue, within an individual, and within a group of individuals (the traditional definition of a population). The multiple copies of the mtDNA genome within an individual need not all be identical; the existence of different mtDNA types within an individual is known as heteroplasmy. The observed frequency of heteroplasmy among humans depends on how it is measured. Initial estimates of little or no heteroplasmy relied on relatively insensitive methods; the current best estimate is that about 14% of the population has a second mtDNA type present at a frequency of at least 1% (167), and indeed it is quite likely that all of us harbor more than one mtDNA type among the trillions and trillions of mtDNA genomes in our bodies. Nevertheless, the overall homogeneity of mtDNA within individuals indicates that a substantial bottleneck in the number of mitochondria occurs early in oogenesis; studies of the segregation of mtDNA heteroplasmy across generations indicate that there are on the order of only 10 segregating units per individual (15, 21, 114).

Maternal Inheritance

Although paternal inheritance of mtDNA occurs in mussels (184), and has been shown for inter- and intraspecific *Drosophila*, mouse, and bird hybrids (47, 70, 76, 83), for years the strictly maternal inheritance of human mtDNA was regarded as an unshakable dogma of the field (150, 153, 172). This uniparental mode of inheritance is one of the great advantages of mtDNA, as it enables researchers to trace related lineages back through time, highlighting the maternal ancestry of a population, without the confounding effects of biparental inheritance and recombination inherent in nuclear DNA. Recently, however, a report of a man with severe exercise intolerance whose muscular mtDNA was of predominantly paternal origin cast doubt on the validity of the assumption of strict maternal inheritance of mtDNA (134), and voices were raised calling for caution in making inferences about human populations and history based on the now-questionable assumption of strict maternal inheritance (20). Subsequent investigations of more patients with mitochondrial myopathies have yielded no further cases of paternal inheritance (39, 136, 160). It has been known for some years that sperm mitochondria are selectively destroyed in the oocyte (92, 139), and it has been shown that paternal mtDNA is marked for destruction in the oocyte by ubiquitination (155, 156). Therefore, it seems highly probable that the one case of paternal inheritance of mtDNA recorded in humans so far represents a breakdown in the normal recognition and elimination of the paternal mtDNA molecules, and that this remains an exceedingly rare phenomenon. Moreover, thousands of maternal-offspring comparisons have failed to yield any indication of paternal inheritance (45, 63, 67, and references therein). Therefore, at present maternal inheritance of mtDNA in humans can still be regarded as the rule (135).

Lack of Recombination

Another tenet of molecular anthropology that was shaken a few years ago is that mtDNA does not undergo recombination. This was regarded as an established fact (150, 153, 172) until 1999–2000, when four papers claimed evidence for recombination in human mtDNA (5, 6, 38, 49). Three of these studies were based on phylogenetic and statistical analyses of mtDNA sequences, with the authors arguing that the excess of homoplasmic sites observed in phylogenetic trees of mtDNA sequences (38), and the correlation of linkage disequilibrium with distance across the mtDNA genome (5, 6), provided evidence for recombination. The fourth study claimed to have direct evidence for recombination in Melanesia (49). However, it was subsequently shown that the phylogenetic/statistical studies used faulty data and/or questionable statistical methods, with reanalyses giving no significant results (3, 69, 82, 89, 95, 110), and the claim for direct observation of recombination in Melanesian mtDNAs was based on an alignment error and had to be retracted (50). Three subsequent studies of the correlation of linkage disequilibrium and distance in large data sets of complete mtDNA sequences (33, 66, 113) found no evidence for recombination, although again an excess of homoplasmic sites was detected (113)—this, however, is generally attributed to heterogeneous mutation rates in human mtDNA (37, 62, 151). Recently, however, a case of observed recombination in human mtDNA was reported in the only known human with both maternal and paternal mtDNA (78, 134). Here, recombination between the maternal and the paternal mtDNA occurred in approximately 0.7% of the total mtDNA in the patient's muscle tissue. This finding underlines that recombination is possible because mitochondria possess a functional recombinase (161), although it is still unclear to what extent mitochondria within a cell are able to fuse and exchange contents (35, 86, 104). However, because leakage of paternal mtDNA is a very rare phenomenon, recombination is not the major issue that it is sometimes made out to be (48, 146)—in the absence of heteroplasmic DNA molecules, any recombination events would result in mtDNAs that do not differ from the original.

Mutation Rate

The mutation rate of mtDNA is several orders of magnitude higher than that of nuclear genes, with an estimated rate of 0.017×10^{-6} substitutions per site per year for the whole genome excluding the control region (66). However, in the two hypervariable regions (HVR I and HVR II) of the noncoding control region, the rate is even higher—although exactly how high is a matter of controversy. Phylogenetic comparisons, based on either interspecific or intraspecific comparisons, yielded estimates of $0.075–0.165 \times 10^{-6}$ substitutions/site/year (52, 152, 158, 174). However, direct observations of mtDNA mutations in families or deep-rooting pedigrees led to estimates ranging from $0.0–1.46 \times 10^{-6}$ substitutions/site/year, with an overall average (based on more than 2600 transmissions) of 0.47×10^{-6} substitutions/site/year, which is significantly higher than phylogenetic

estimates (63 and references therein). There is now a debate as to which rate reflects the "true" state of affairs, and which to use for studies of population history (56, 61, 63, 67, 90, 107, 111, 141).

A clue to understanding the discrepancy between phylogenetic- and pedigree-based estimates of the mtDNA mutation rate comes from the observation that within the control region the mutation rate is very heterogeneous, with some "mutational hot spots" mutating four to five times as fast as the average site (37, 52, 56, 96, 171). Although some claim that recombination would be a better explanation for the observed recurrent mutations (38, 48), analyses of mutations in tumors, in pedigree studies, and at heteroplasmic sites have shown that such newly arising mutations occur preferentially at phylogenetically defined mutational hot spots (56, 151). Furthermore, DNA damage in ancient DNA occurs preferentially at phylogenetically defined mutational hot spots in the control region (44), suggesting that these mutational hot spots may be hypermutable because they are more prone to damage.

The most likely explanation for the discrepancy between phylogenetically based and pedigree-based estimates of the mutation rate in human mtDNA is that fast-evolving sites are preferentially detected in pedigree studies, whereas phylogenetic studies (which encompass a larger number of transmissions) pick up mutations at the slowly evolving sites as well (56, 67, 90, 107). However, Howell et al. (63) argue that the difference in mutation rates estimated from pedigree and phylogenetic studies does not have one causal factor, but instead is due to mutational hot spots, genetic drift, selection, and lack of detection of recurrent mutations in phylogenetic studies. In any event, because a significant number of the mutations observed in pedigree data have arisen recently and will probably not become fixed, the phylogenetic rate (which represents mutations that have reached an appreciable frequency in the population) may be preferable for studies of deep history, whereas it may be advisable to use the pedigree rate for studies of recent history (90, 107). Alternatively, studies of population history could incorporate models that allow for different classes of sites with different evolutionary rates (52, 56, 158). For example, Hasegawa et al. (52) showed that a model that includes rate variation in the mtDNA control region gave an estimate for the age of the human mtDNA ancestor that was half that obtained when a single mutational rate was assumed. Therefore, average estimates of the mutation rate for human mtDNA do not reflect the true state of affairs, and should be viewed as simplistic tools for phylogenetic studies.

HUMAN MITOCHONDRIAL DNA VARIATION

What is Studied?

Initial studies of human mtDNA variation were based on restriction fragment length polymorphisms (RFLPs) of either purified genomic DNA or purified mtDNA (e.g., 22, 24, 68). With the advent of the polymerase chain reaction (PCR) and methods

of rapid sequencing of PCR products, RFLP analysis of mtDNA PCR products as well as sequence analysis of the first hypervariable segment (HVR I) of the control region took over, with a huge amount of data generated in the 1990s [a recent paper addressing the origins of the Saami analyzed 17,541 sequences from Eurasia alone (157)]. In recent years, with the development of high-throughput sequencing technology, it has become more and more common to sequence the whole mitochondrial genome, even for population studies (27, 40, 55, 65, 66, 77, 88, 159). Phylogenetic trees based on whole genome sequences do provide better resolution than trees based only on HVR1 sequences (64). However, it is not clear whether the additional effort involved in whole genome sequencing is truly worthwhile, as informative point mutations can be individually assayed by RFLP assays or, as recently shown, by multiplex SNaPshot assays (18). Furthermore, a potential future development is using sequencing microarrays for mtDNA; this was successfully tested for clinical purposes (91). Whole mtDNA genome sequence studies have yet to reveal any insights into human population history that were not already provided by RFLP and/or HVR1 sequence studies, although there are recent claims that HVR1 sequences alone do provide significantly lower estimates of the genetic distance between populations than do mtDNA coding sequences (176). It remains to be seen if the insights gained are worth the additional cost and effort of obtaining whole genome sequences versus RFLP and/or HVR1 sequences; a reasonable alternative might be to combine control region sequences with partial coding region sequences (77, 142).

How are the Data Analyzed?

There are two basic approaches to using mtDNA in studies of human evolution: the lineage-based approach and the population-based approach. The lineage-based approach attempts to unravel the history of mtDNA lineages, called haplogroups, while the population-based approach attempts to study the prehistory of individual populations, of geographical regions, or of population migrations by using human population groups as the unit of study and applying population genetic methods to the data (42). The haplogroups studied in the lineage-based approach were initially defined by RFLP data (7, 131). Unfortunately, the detection, and therefore the naming, of new haplogroups and subhaplogroups has progressed in a rather haphazard manner, resulting in nonmonophyletic groupings receiving the same designation [e.g., macrohaplogroup L, cf. (88)], and branches of monophyletic groupings receiving different designations [e.g., the clade comprising branches N9, Y1b, and Y2 in figure 2 of Reference 159]. An organized attempt at a consistent nomenclature, as was accomplished for the Y-chromosome haplogroups (180), would be highly appreciated. Haplogroups represent related groups of sequences that are defined by shared mutations and which tend to show regional specificity. Thus, macrohaplogroup L with subgroups L1, L2, and L3 (all of which contain further subhaplogroups) is restricted to Africa (127, 175), whereas macrohaplogroups M and N originated in eastern Africa on a L3 background and dispersed into Eurasia and the New World (98, 115). Haplogroups H, I, J, N1b, T, U, V, and W

are characteristic of people of European descent, and haplogroups A, B, C, and D are found in Asia and the New World, with haplogroups G, Y, and Z predominantly in Siberia (98, 133). Haplogroup X is found at low frequencies in North Africa and West Asia, in Europe and Central Asia, and in the New World; however, it is generally not found in Siberia or East Asia (119). Because haplogroups reflect shared ancestry of mtDNAs, they can be helpful for estimating admixture proportions in populations inhabiting known routes of migration (28, 162) or originating from diverse geographical regions (1, 112, 128). Furthermore, they were useful in establishing the bottleneck that occurred during the colonization of the New World (131, 148, 149, 165).

A problem with the lineage-based approach of studying haplogroups is that it only elucidates the history of the haplogroups themselves, and does not provide direct insights into the history of the individual populations in which they are present. There has been an unfortunate tendency to equate the age of a haplogroup with the age of a population, and to assume that the spread of each individual haplogroup reflects a separate migration. The reality, of course, is that when a population migrates, it carries all of its haplogroups with it, not just one of them, and the ages of the haplogroups in the migrating population indicate when the point mutations defining the haplogroup occurred, not when the migration occurred (145). To study the prehistory of human populations, it is crucial to use statistical methods that examine population relationships, e.g., calculating genetic distance values and displaying population relationships in trees or multidimensional scaling (MDS) plots (Figure 2). Fortunately, more and more studies recognize the value of analyzing both haplogroup affiliations and population affinities using a population genetics approach (73, 122, 125, 157). Although HVR I sequence data alone do not have the resolving power to reveal all haplogroups, the high mutation rate of this segment ensures a sufficient number of polymorphic sites for population genetic analyses.

What Have We Learned?

One important finding of mtDNA analyses is the corroboration of the "Recent African Origin" hypothesis of modern human origins, initially put forward on the basis of fossil evidence (19, 154). Studies of mtDNA variation in worldwide populations have repeatedly found further evidence for this hypothesis, with the most recent common ancestor of human mtDNA located in Africa about 100,000–200,000 years ago (24, 66, 88, 170). Moreover, direct analyses of mtDNA from fossils of Neandertals and their contemporaries, early modern humans from Europe, indicate no contribution of Neandertal mtDNA to modern humans (25, 79–81, 106, 130, 137).

Another insight gained from studies of mtDNA is a better understanding of the migrations that shaped human populations, such as the peopling of the New World (75, 131, 142, 148, 149, 165), the colonization of the Pacific (87, 94, 100, 118), the initial migration to New Guinea and Australia (65, 116, 117, 168), and the settlement of Europe (120, 121, 144, 163). However, mtDNA is only one locus, and

only reflects the maternal history of a population; the history of a single locus may not accurately reflect the history of a population because of chance (drift) effects or because of selection acting on that locus. It has therefore become abundantly clear that studies of mtDNA variation need to be complemented with data on the male-specific Y-chromosome, and ideally with autosomal data as well (9, 14, 29, 102, 138, 157, 179). The use of mtDNA alone in studies of human evolution will probably decrease in the future, which indicates that studies of human variation are maturing beyond the single locus approach.

However, the field has recently been confronted with several serious issues that need careful consideration. First, there is the increasing realization that nuclear inserts of mtDNA (numts) are more common than formerly thought (16, 53, 97, 103, 166). Analyses of the human genome sequence have revealed between 250 and more than 600 such inserts of differing length, with the largest fragment encompassing nearly the whole mitochondrial genome (16, 97, 166). Because mitochondrial inserts in the nuclear genome evolve at the nuclear rate, which is lower than that of mtDNA, known numts may have their uses as "molecular fossils" (97, 183). However, a problem with numts is that they may not be detectable with standard methods (17, 103), and there are examples of numts that were mistakenly thought to represent authentic mtDNA sequences, leading to erroneous phylogenetic or medical conclusions precisely because of their slower rate of evolution (30, 31, 57, 103, 173).

A second problem is the lack of quality control in published data. Reports of incorrect mtDNA sequences being published and submitted to databases are increasing in number (4, 11, 41, 124, 182), and even forensic databases have been accused of containing erroneous data (12, 181). However, not all purported errors are truly errors (10, 13, 23a), and the phylogenetic and forensic conclusions are rarely severely affected (e.g., 23a, 54, 143). Nevertheless, it is highly desirable that the data used in population genetic and evolutionary studies are of the highest quality, and statistical methods that aid in the detection of sequencing artefacts (e.g., 11) can be useful and should be used routinely. However, statistical analyses alone cannot uncover all errors, and are by no means a substitute for good laboratory practice. Unfortunately, we notice to our dismay a trend for more and more laboratories to sequence only one strand of the PCR product (e.g., 164), which in our experience does not ensure adequate detection of sequencing artefacts.

A third serious issue is the increasing evidence that mtDNA may not be selectively neutral, as previously assumed (34, 51, 98, 99, 101, 126, 178). The rate of nonsynonymous mutations at several mitochondrial genes is higher than that of synonymous mutations within humans, but not between humans and chimps (51, 101, 178). This could be due to most mutations being slightly deleterious, so that they would contribute to polymorphism within populations, but would not become fixed and so would not contribute to differences between species (51, 101). However, the apparent excess of polymorphism within species could actually reflect an underestimate of the true divergence between species, due to the inability to detect recurrent mutations (43), which have occurred since the divergence of chimpanzees and humans (74).

It has also been suggested that the geographical variation seen in mtDNA haplogroups may reflect selection acting on specific lineages as humans spread from Africa to different climatic conditions (98, 126). In particular, it has been claimed that haplogroups A, C, and D, which are characteristic of Siberians and Native Americans, have been strongly influenced by selection to uncouple the heat production and ATP production aspects of mitochondrial oxidative phosphorylation in order to produce more heat in colder climates (126). However, these provocative claims rest largely on statistical analyses of the distribution of nonsynonymous versus synonymous mutations in a phylogenetic tree of complete mtDNA sequences from the various haplogroups; detailed biochemical analyses are required to determine if there indeed has been a functional change in oxidative phosphorylation in individuals with these haplogroups. Because the A, C, and D haplogroups also occur in tropical environments in the Americas, where they have presumably been for at least 10,000 years (132), a further test of this hypothesis would be to see if these haplogroups have undergone further mutations in the Americas to more tightly couple heat and ATP generation.

Moreover, Elson et al. (34) see no such evidence for climate-induced geographically varied selection in a data set of 560 coding region sequences. They do see evidence for mainly negative selection acting on the 13 protein-coding genes of mtDNA, with the exception of ATP6, which shows signs of balancing or positive selection in Europeans and Asians [in agreement with the findings of Mishmar et al. (98)]. There also is evidence of regional violations of clock-like evolution of mtDNA in Africa (60, 164). The overall consensus is that mainly purifying selection has been acting on human mtDNA; because the unit of inheritance is the whole genome, which does not undergo recombination, the noncoding control region is subject to the same selective forces as the coding DNA. This means that care must be taken when using mtDNA data to date phylogenetic events, as the underlying assumption of neutral clock-like evolution may not hold. However, the basic results of mtDNA studies, such as a recent initial migration out of Africa and subsequent world-wide dispersal of modern humans, are not affected by non-neutral evolution, and, furthermore, are supported by a wide array of other loci (26, 36).

What is mtDNA Still Good For?

Even though mtDNA will probably be used less and less as the sole marker for elucidating human evolution and population history, it is still important for a wide range of questions. First of all, it is useful for unraveling socio-cultural effects that might have influenced human evolution, such as polygyny (32, 71, 129, 177), the effects of matrilocality versus patrilocality (105, 176), or the social stratification induced by the caste system (8, 179).

Furthermore, because of the high copy number of mtDNA versus the diploid autosomes and haploid Y-chromosome, mtDNA is crucial in studies of ancient DNA and in some applications of forensics. Depending on the age of the fossil sample, often only mtDNA will still be present, and therefore this is the only insight one can get into the genetic affinities of ancient populations (72, 148,

149, 169). However, a major problem with ancient DNA studies is contamination with modern DNA, an issue that is unfortunately not yet widely recognized (58, 108). This is particularly a problem when ancient samples of modern humans are analyzed, because the contaminating mtDNA will not differ greatly from the authentic mtDNA. Therefore, caution should be exercised when evaluating studies of ancient DNA in modern humans. This holds especially true for very old fossils, such as Neandertals or ancient modern humans. Nevertheless, it was possible to amplify and sequence mtDNA in a number of these (25, 79–81, 106, 130, 137).

And in forensic applications, using mtDNA enables identification of otherwise unidentifiable victims, if maternal relatives are alive for comparison (46, 147). This is becoming increasingly relevant for victims of war or terror (59, 84, 85). Problems and issues in the use of mtDNA in forensic analyses were recently reviewed in this journal (23).

Finally, mtDNA is increasingly used in so-called personalized genetic histories (140). This is the use of genetic testing to investigate individual genealogies, including tracing the origins of immigrant/slave ancestors. Currently, of 11 companies offering such testing, 7 use mtDNA in addition to Y-chromosomal markers, and 2 companies offer only mtDNA analyses (140). Unfortunately, this use of mtDNA is fraught with difficulties that the average customer may not be aware of. For example, many people request such testing with the expectation that they will learn a very specific place of origin, such as which village they come from. The reality is that current mtDNA databases are not sufficiently detailed to allow such a high degree of geographic resolution, and even if they were, mtDNA types in general do not show sufficient geographic specificity to allow one to pinpoint such a specific origin. Furthermore, many customers inevitably confuse the place of origin of their maternal lineage with the place of origin of all of their biological ancestry, with potentially profound effects on how they view themselves and their identity. It must be kept in mind that mtDNA comprises only 0.0006% of the total human genome; as informative as mtDNA analyses have been and will continue to be for understanding human population history and evolution, when it comes to questions about personal genetic ancestry (as well as questions about human population history and evolution), it would be desirable to have some information on the remaining 99.9994% of the genome.

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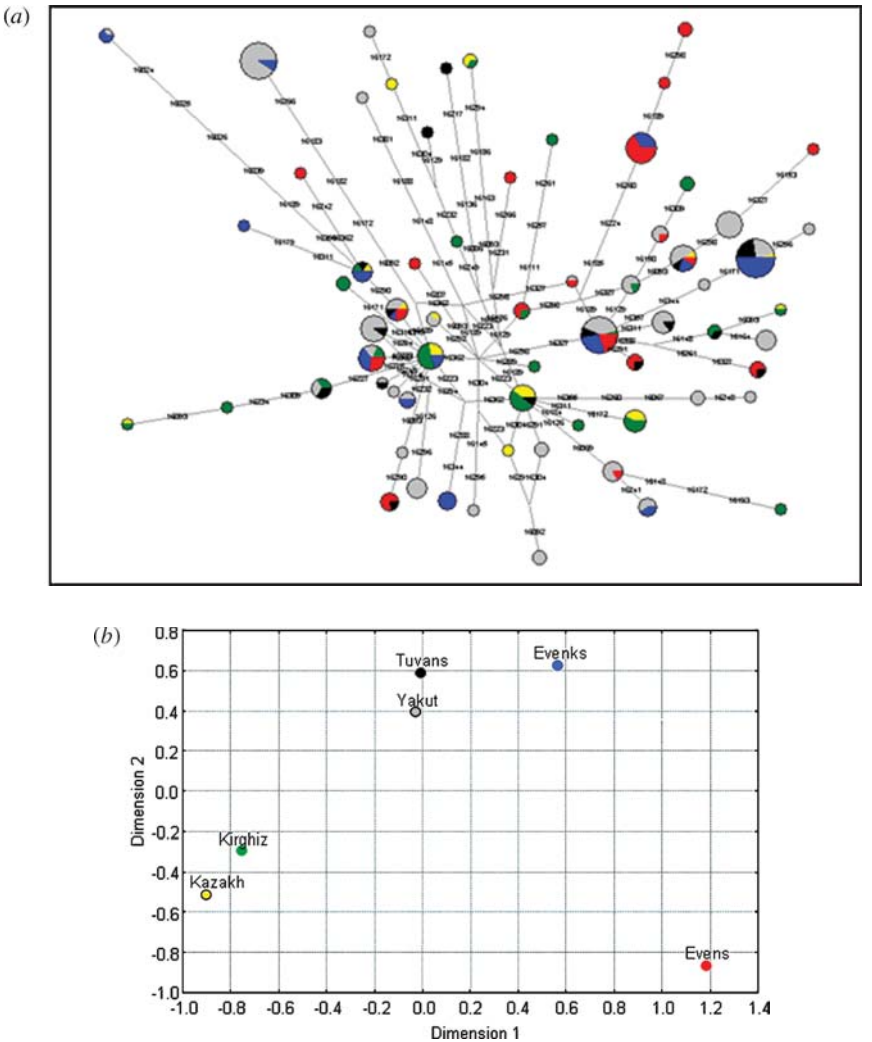

Figure 2 Comparison of the lineage-based and population-based approaches in studies of population history. (*a*) Median-joining (MJ) network of HVR1 sequences from six Eurasian populations, with fast-evolving sites downweighted and singletons excluded. Yellow, Kazakh; green, Kirghiz; gray, Yakut; black, Tuvans; red, Evens; blue, Evenks. Data from Reference 109 and references therein. The mutated nucleotide positions are indicated on the branches. The MJ network thus indicates how the mtDNA lineages have evolved, but it is difficult to visualize how the populations are related. (*b*) Multidimensional scaling (MDS) plot based on genetic (Fst) distances of the same data. The population relationships are clearly visualized in the MDS plot, but there is no indication as to how the mtDNA sequences are related.

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