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RESEARCH ARTICLE

# A Brief Introduction to Microhaplotypes and their Uses

**Kenneth K. Kidd, Professor Emeritus**
Department of Genetics
Yale University School of Medicine.
New Haven, CT 06520

**Daniele Podini, Assoc. Professor and Chair**
Department of Forensic Sciences
The George Washington University
Washington, DC 20007

***Corresponding author:** kenneth.kidd@yale.edu

ABSTRACT

Microhaplotypes are genetic markers that are short DNA sequences, typically consisting of two or more single nucleotide polymorphisms (SNPs) sufficiently close molecularly (<300 basepairs) that their alleles are inherited together from parent to child. Microhaplotypes can be considered a special class of haplotypes, "micro" because they extend for only a few dozens of basepairs, not thousands of basepairs. The advantage of microhaplotypes is that, with massively parallel sequencing of a small segment, the phase is known. Microhaps have been shown to be highly informative in demonstrating uniqueness of DNA profiles and in determining the biogeographic ancestry of an individual. Tests of biologic relationships, such as paternity tests, can be done with microhaplotypes. Deconvolution of DNA mixtures is an area in which microhaplotypes appear to be especially promising. This brief introductory review presents the scientific background for the development of microhaplotypes as a new type of genetic marker and examples of some of the recent applications.

## Introduction

Microhaplotypes (microhaps, MHs) are only a decade old [1-3] while human haplotypes have been studied for over six decades. The term 'haplotype' was first introduced by Ruggero Ceppellini in the late 1960's to describe alleles (originally antigens) at loci within the human leucocyte antigen (HLA) region that are inherited together as a block [4]. Haplotypes can be multiallelic because the comprising single nucleotide polymorphisms (SNPs) can present different combinations of alleles at the sites on the chromosomes (DNA molecules) in the population, as illustrated in Figure 1. The specific combination is known as the phase of the alleles at the individual sites. The two combinations on the two chromosomes of an individual are the alleles that constitute the genotype for the haplotyped segment of DNA.

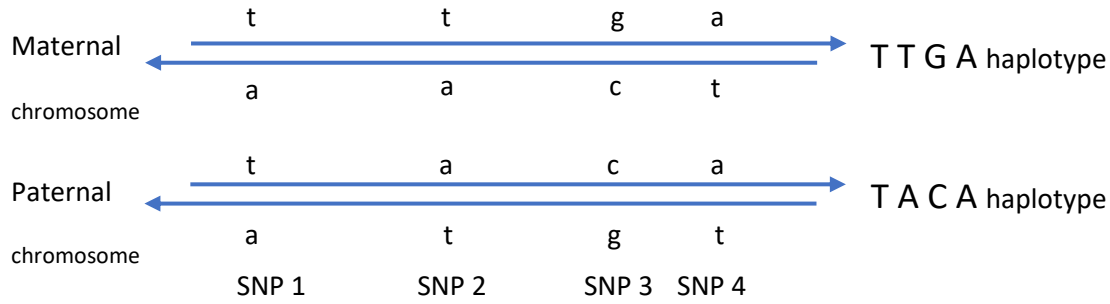


**Figure 1.** Schematic of the genotype of an individual for a 4-SNP microhaplotype. The two chromosomes, one from each parent, contain different sets of SNP alleles. In this case SNP 2 and SNP 3 differ between the maternal and paternal haplotype. In considering the genotype one generally uses the nucleotide on the forward strand of the DNA double helix, depicted here as the upper strand of the two. The other strand, on the bottom, is the reverse strand and is complementary.at every nucleotide.

DNA-based haplotypes have been studied since SNPs became common in the early 1980's; the individual SNPs have been typed by various methods. These haplotypes usually extend across kilobases (kbp) of DNA and the phase can be determined by computer analyses using the EM algorithm (e.g.[5]) or using a Markov-Chain algorithm [6].

Such haplotypes are useful for ancestry studies and have provided evidence of selection having operated at specific genes in some human populations. One example is the cluster of alcohol metabolizing (ADH) genes on Chromosome 4. Haplotypes in this region have been associated with alcoholism and esophageal cancer [7] and have provided evidence that natural selection increased the frequencies of specific haplotypes in certain populations .[8] One ADH study involved a total of 118 SNPs that extend across ~453 kb of the ADH gene cluster with a density of ~1 SNP per 3.8 kb [9]; haplotypes in this study provided new evidence that selection had increased the frequency of a rapid metabolizing form of the liver ADH enzyme in Middle East populations, including Ashkenazi Jews.

Despite the broad interest in and value of such haplotypes in general they were not appropriate markers for forensics for many reasons. The markers in a haplotype were sufficiently separated that they needed to be typed individually. Population databases that were needed for the statistical interpretation of the data were generally lacking. The early 2010's saw two developments that led to conceptualizing microhaplotypes for forensic applications. First, a new sequencing method—massively parallel sequencing (MPS)—was developing and could provide phase-known sequence of small segments of up to about 250 base pairs. MPS of microhaplotypes enables the determination of the parental SNP haplotypes by clonal sequencing of the alleles separately on the paternal and maternal chromosomes .[10] These single base pair sequence variations comprising a microhaplotype are present in single-copy and in non-repetitive regions of DNA. This promised to eliminate the problems of statistical phasing of molecularly close SNPs and multiple loci could be sequenced at the same time with MPS technology. Second, the 1000 Genomes project [11] was presenting whole genome sequencing (WGS) data on a broad selection of 26 populations. These WGS data could be used to estimate the allele frequencies of microhaplotypes in these populations. It is out of this field of population genetics and the study of DNA polymorphisms forming haplotypes that the concept of microhaplotypes arose .[1,12]

Microhaplotypes are a promising tool in forensic genetics (e.g., .[3,13-15]), especially for interpreting DNA samples that are mixtures from two or more

individuals. Unlike traditional DNA markers, such as single nucleotide polymorphisms (SNPs) and short tandem repeats (STRs), microhaplotypes are short DNA sequences of <250 basepairs (bp) that encompass two or more SNPs. The resulting single-strand haplotypes are multi-allelic with lower mutation rates than the STRs and no stutter. Stutter is an artifact caused by DNA-polymerase slippage during PCR of short tandem repeat regions yielding sequences of different length. Microhaps are selected to avoid repeat sequences thereby eliminating the possibility of stutter.

Over the past decade the literature on microhaplotypes has grown; in January 2024, the keyword "microhaplotype" in PubMed retrieved 38 papers on microhaplotypes published in 2023 and a total of 138 in the past decade. Most of those publications have dealt with applications in humans but some have involved applications in the conservation of various species (e.g., fish .[16], turtles [17]). Microhaplotypes of *P. falciparum* are even used to study the ecology of the parasite .[18]

When one compares microhaplotypes typed using MPS with the current STR loci typed using capillary electrophoresis (CE), the microhaplotypes have several advantages. As noted above, microhaps have lower mutation rates and do not generate stutter artifacts. Microhaplotypes can have greater power of discrimination than STRs even when using similar numbers of markers in an assay.[19] Moreover, the alleles within a microhaplotype locus have the same size, contrasting to the potential dropout of longer STR alleles. These features are particularly important for mixture deconvolution. Both types of loci require databases for analyses, and they differ in that the STR loci have been standardized for many years so that allele frequencies for many populations exist. Also, large comparison databases now exist of profiles for convicted individuals, unsolved crime scene samples, and missing persons. Microhaps have only the 26 populations of the 1000 Genomes project for calculating individual random match probabilities (RMP) and biogeographic ancestry likelihoods. Because no database of convicted offenders yet exists for microhaplotypes, it is unlikely that they will replace STR loci for routine casework anytime soon. However, microhaplotypes have already been shown to have great potential to complement STR loci in four different areas of forensics: individualization, ancestry inference, kinship analysis, and mixture deconvolution.

One statistic that is used to compare the information content of microhap loci is the effective number of alleles ($A_e$) [20] calculated as the inverse of the homozygosity of a locus in a particular population. It is statistically the number of equally frequent alleles that would yield the same heterozygosity. $A_e$ is especially relevant for multiallelic loci such as microhaps. The locus-population $A_e$ value is the minimum number of alleles at that locus in that population. Of course, microhaplotypes usually have more actual alleles in the population,

## Microhaplotypes: Applications and ongoing research

As yet no commercial kits of microhaplotypes for forensic casework have been marketed but soon that may change because microhaplotypes are gaining ground within the forensic DNA community because of their ability to improve capabilities for human identification, ancestry prediction, kinship, and mixture deconvolution .[12] The following sections briefly describe some of the research in each of those areas.

INDIVIDUALIZATION.

The standard statistic for the rarity of a person's genotype is the random match probability (RMP). It is used in forensics to evaluate the chance that the profile of a sample from the crime scene would also match that of someone other than the defendant. Given that the defendant already matches the crime scene profile, a low RMP argues that no one else has the same profile. The RMP can be compared to the total population of the world ($< 10^{10}$). The standard STR markers in US forensics are the CODIS panel of 20 highly informative STR loci.[21] Some applications use 4 additional markers to augment the basic 20 loci. One set of 24 augmented CODIS loci yielded a RMP of about $10^{-28}$ depending on population; one set of 24 microhaplotypes yields a RMP of about $10^{-30}$ depending on the same geographic distribution of populations (Table 1).[19] A global average $A_e>5$ was used to select the 24 microhaplotype loci. A set of nearly 100 diverse microhaplotypes [22,23] can easily yield a RMP of $<10^{-100}$. These infinitesimally small probabilities make it clear that every individual (independently conceived) is expected to be genetically unique; one needs only to study enough markers to demonstrate that within a set of individuals.

**Table 1.** Comparison of an enhanced CODIS panel of STRs with a panel of microhaplotypes [19].

| Geographic Region | RMP for 24 STRs by CE | RMP for 24 Microhaps by MPS |
|---|---|---|
| Sub-Saharan Africa | $1.5 \times 10^{-27}$ | $4.5 \times 10^{-35}$ |
| Europe | $2.8 \times 10^{-28}$ | $3.0 \times 10^{-32}$ |
| South Asia | $3.0 \times 10^{-28}$ | $3.6 \times 10^{-29}$ |
| East Asia | $2.9 \times 10^{-27}$ | $2.1 \times 10^{-28}$ |
| Admixed Native American | $1.1 \times 10^{-21}$ | $2.3 \times 10^{-24}$ |

BIOGEOGRAPHIC ANCESTRY

SNPs have been used to study human DNA polymorphisms since the 1978 discovery of variation measured directly in the DNA.[24] SNPs quickly became one of the tools to study biogeographic ancestry, a field of population genetics and anthropology research that has existed since the turn of the 20th century. SNPs were being used to estimate biogeographic ancestry of individual samples but the low information from a marker with only two alleles made them difficult to study in large enough numbers. Modern ancestry studies use STRUCTURE [25] and Principal Component Analysis (PCA) to cluster individuals into populations and estimate the relative relationships of populations. Many different panels of SNPs have been proposed for ancestry e.g.,.[26]

Microhaplotypes are much more informative per locus than a single SNP and are being used to give more refined analyses of population relationships. Most groups have used the 1000 Genomes dataset to show that a set of microhaps provides good ancestry resolution.[11] When tested on the 1000 Genomes populations, most MH panels of at least a few dozen loci tend to identify four or five "continental" groups of populations: sub-Saharan Africa, Europe, South Asia, East Asia, and admixed American.[27] A problem is that the populations included in the 1000 Genomes dataset are geographically clustered into those groups and much of the globe is poorly represented. For example, no populations from SW Asia are included. In studies that included populations from SW Asia and/or North Asia in addition to the 1000 Genomes populations, those two groups were distinct clusters.[28,29] When minimally admixed Native American populations were included, they formed a distinct cluster that was related to the North Asian cluster.

KINSHIP

Kinship analysis attempts to reconstruct and evaluate relationships within families as opposed to population ancestry and genetic similarity of randomly chosen individuals.[30] Paternity testing is the most commonly used form of kinship analysis and the average paternity index (PI) is closely related to the average $A_e$ value. The high level of allelic variation makes microhaplotypes excellent for determining the alleles contributed by the biological father to a child. A pregnant woman carries small cell free fragments of her fetus's DNA in her circulation; these fragments can encompass the variation and small size of microhaplotypes makes it possible to do prenatal paternity testing using a sample of the mother's blood .[31,32] Additionally, the mutation rate of microhaps is several orders of magnitude lower than that of STRs; a mutation can lower confidence of paternity when it occurs in an STR. Other relationship questions are being addressed with microhaps.[30,33-34] Missing persons studies are another use.[35] For example, evaluation of human remains to compare the profile with the estimate of the genotype of the missing person based on the missing person's family can involve incorporating the DNA marker profiles of all available relatives.

MIXTURE DECONVOLUTION

DNA methodology has become very sensitive in recent years and it is increasingly the case that crime scene DNA samples show traces of more than one individual. The forensic issue becomes determining whether the comparison sample of the suspect is compatible with the mixture from the crime scene.[36] It is in mixture analysis that the advantages of microhaplotypes are most evident. Stutter, a clear problem with polymerase slippage of STR sequences, does not exist for the single copy sequences in microhaplotypes. Also, there are fewer stochastic effects such as preferential sequencing of short alleles since both alleles of a microhaplotype locus are the same length. As with other uses of microhaplotypes noted above, the high levels of variation are a strength in mixture analyses. The same high throughput sequencing methods used for individualization, ancestry and kinship analyses are used and the data will support mixture analyses when a "single source sample" turns out to be a mixture .[37-38] Some of the early research on mixtures is very promising, showing great sensitivity for the detection of a minor component in a mixture of DNA from several different individuals.[39]

## Conclusion

The research objective today is not just to find more microhaplotypes, but to find more independent and

highly informative microhaplotypes usable globally. More panels of loci with a globally high average $A_e$ are needed before microhaplotypes are likely to become commonly used in forensic practice. Using a global average $A_e>5$ is a good criterion for selecting microhaplotypes from which a standard forensic panel will eventually be selected. Commercial panels of microhaplotypes should soon be available and that will foster the transition from the research laboratories now studying microhaplotypes to crime labs for use in cases. The transition will be facilitated by the use of MPS to type STR loci so that a single method can simultaneously generate results for both types of genetic markers.

**Conflict of interest:** The authors declare no conflict of interest.

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