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The Geographic Distribution of Monoamine Oxidase Haplotypes Supports a Bottleneck During the Dispersion of Modern Humans from Africa

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Abstract. Every genetic locus mingles the information about the evolutionary history of the human species with the history of its own evolution. Therefore, to address the question of the origin of humans from a genetic point of view, evolutionary histories from many genetic loci have to be gathered and compared. We have studied two genes residing on the X chromosome encoding monoamine oxidases A and B (*MAOA* and *MAOB*). Both genes have been suggested to play a role in psychiatric and/or behavioral traits. To search for DNA variants of the *MAO* genes, the sequences of exonic and flanking intronic regions of these two genes were determined in a group of Swedish males. The sequence analysis revealed several novel polymorphisms in the *MAO* genes. Haplotypes containing high-frequency *MAOA* polymorphisms were constructed, and their frequencies were determined in additional samples from Caucasian, Asian, and African populations. We found two common haplotypes with similar frequencies in Caucasian and Asian populations. However, only one of them was also the most frequent haplotype in Africans, while the other haplotype was present in only one Kenyan male. This profound change in haplotype frequencies from Africans to non-Africans supports a possible bottleneck during the dispersion of modern humans from Africa.

Key words: Monoamine oxidase — DNA polymorphisms — Human evolution — Demographic bottleneck — Genetic variation — Haplotype distribution

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Introduction

Studies of human DNA variation provide a remarkable resource of data for dissecting the history of human evolution. They also open up new possibilities to identify genetic variants associated to complex human traits. Each genetic locus contains partial information about the evolutionary history of the human species combined with information about the evolution of the particular locus, which is affected by numerous recombination and segregation events. Therefore, different genetic loci might result in different genealogies, making the inference about the origin of the human species complicated. Only if the information from many genetic loci is combined can the genuine scenario of the evolution of modern humans be unraveled (Paabo 1999).

Genetic loci on the X chromosome of males have the advantage over autosomal loci in that the construction of haplotypes is straightforward because males have only one allele at each X-chromosomal locus.

We have studied the genes encoding the MAOA and MAOB enzymes, which are associated with certain psychiatric and behavioral traits (Shih and Thompson 1999). MAOA and MAOB are nuclear-encoded mitochondrial isoenzymes responsible for the oxidative deamination of biogenic and xenobiotic amines. They differ in their substrate specificity and sensitivity to inhibitors (Shih et al. 1999). The genes encoding MAOA and MAOB are adjacent on the X-chromosome (Xp11.23–11.4) in a tail-to-tail orientation, and they are separated by 50 kb of noncoding DNA.

The human *MAO* genes are 70% homologous at the amino acid level, and they are postulated to have origi-

nated from a duplication of an ancestral *MAO* gene more than 500 million years ago. Both *MAO* genes exhibit identical structures of exon–intron organization (Chen et al. 1995). Multiple single-nucleotide or length polymorphisms have been described in the *MAOA* gene (Black et al. 1991; Hinds et al. 1992; Hotamisligil and Breakefield 1991; Ozelius et al. 1988, 1989; Sabol et al. 1998; Tivol et al. 1996) and in the *MAOB* gene (Ho et al. 1995; Konradi et al. 1992; Sobell et al. 1997). Most of them are located in the noncoding regions of the gene or are silent nucleotide substitutions.

Information on the frequency distribution of the *MAOA* and *MAOB* allelic variants in different human populations is sparse. Some of the variants are present only in one specific human population. For example, seven of the eight known single-nucleotide polymorphisms (SNPs) in the *MAOB* gene are restricted to African-American and/or Native-American populations and are nonpolymorphic in Caucasians and Asians (Sobell et al. 1997). Three of the polymorphisms in the *MAOA* exons described (Tivol et al. 1996) have a frequency of only 3 to 4% in the studied sample (Tivol et al. 1996). Therefore, the DNA variants of the *MAO* genes identified so far are not sufficient for allelic association studies trying to investigate the role of the *MAO* genes in psychiatric and behavioral traits.

In this study, we describe previously unidentified frequent polymorphisms in the *MAOA* gene and low-frequency polymorphisms in the *MAOB* genes present in a set of Swedish individuals. We also construct haplotypes containing the novel high-frequency *MAOA* polymorphisms in Caucasians, Africans, and Asians. Our results support a demographic bottleneck during the dispersion of modern humans from Africa.

Materials and Methods

DNA Samples

The *MAOA* and *MAOB* genes were initially sequenced from DNA samples taken from 10 Swedish male blood donors. The identified polymorphisms were further investigated in an additional set of 16 Swedish, 37 British, 10 Mexican, 20 Ghanaian, 20 Kenyan, 13 Chinese, and 20 Indian/Pakistani males. Informed consent was obtained from the volunteers providing blood samples and all the samples were analyzed anonymously to ensure confidentiality. To obtain the orthologous sequences in closely related primate species, DNA samples from one gorilla and one chimpanzee (both females) were sequenced.

Searches for DNA Polymorphisms In Silico

To search for polymorphisms in the *MAOA* and *MAOB* genes *in silico*, BLAST searches were performed for each exon in the NCBI databases (http://www.ncbi.nlm.nih.gov/). The resulting multiple sequences were aligned and viewed by the BLIXEM software, which creates a graphical representation of a BLAST output (Sonnhammer and Durbin 1994). The criterion for considering a DNA variant as a candidate polymorphism was that it was different from the reference sequence and that it was present in more than one clone or, if present in a single clone, that it was in a region of high-quality sequence. The polymorphism searches *in silico* exposed 28 candidate SNPs for the *MAOA* gene and 30 SNPs for the *MAOB* gene. As most of the clones were from EST databases, the majority of the candidate DNA variations were localized in exons or in exon–intron boundaries.

Sequencing

The genomic sequence information for the *MAOA* and *MAOB* genes, available in the GenBank database (http://www.ncbi.nlm.nih.gov/Genbank), was used to design PCR primers flanking the exons. For the *MAOB* gene, the complete genomic sequence was represented in locus *HS27K14* (accession number Z95125), while locus *HS201D17* (accession number AL020990), containing the *MAOA* gene, lacked sequences for exons 1, 2, 4, and 5. Therefore, primers for exons 1 to 15 of the *MAOB* gene, and exons 3 and 6 to 15 for the *MAOA* gene, were used. PCR products varied in length from 290 to 670 bp. Information about primer sequences and PCR conditions are available upon request. The PCR products were sequenced on an ABI 377 automated sequencer (PE Biosystems, Foster City, CA, USA) using the BigDye terminator cycle sequencing kit (PE Biosystems). The PCR primers were also used as sequencing primers. DNA samples from gorilla and chimpanzee were amplified and sequenced with the primers for the human sequences. The obtained sequences were analyzed and aligned using the Sequence Navigator software (PE Biosystems). The length of the sequenced *MAOA* gene was 4260 and 5860 bp for the *MAOB* gene. The sequenced fragments were distributed over 50 and 77 kb of the genomic sequence of the *MAOA* and *MAOB* genes, respectively. The total length of the coding region sequenced was 1220 bp for the *MAOA* gene and 1510 bp for the *MAOB* gene, constituting 29 and 26% of the total genomic sequence analyzed for the *MAOA* and *MAOB* genes, respectively.

Genotyping

Five polymorphic loci found in the *MAOA* gene and one polymorphic position in the *MAOB* gene were selected for genotype determinations in larger sample sets. Their positions are indicated under Results and in Fig. 1. These polymorphisms were genotyped using the solid-phase minisequencing primer extension method (Syvanen et al. 1993).

PCR primers for amplifying DNA regions spanning the six selected polymorphic positions were designed (sequences available upon request). One primer of each pair was biotinylated at its 5′ end. The minisequencing detection primers were located immediately adjacent to the polymorphic sites on the DNA strand of opposite polarity to the biotinylated PCR primer. After PCR, with 0.2 μmol of the biotinylated primer and 1 μmol of the unbiotinylated primer, 10-μl aliquots of the biotinylated PCR products were captured on streptavidin-coated microtiter plate wells (Combiplate 8; Labsystems, Helsinki, Finland). The wells were washed, the captured PCR products were denatured, and the minisequencing reactions were performed with 0.2 μmol of the detection primer, 0.1 μCi of one ^{3}H-dNTP, and 0.05 U of AmpliTaq at 50°C for 10 min as described previously (Syvanen et al. 1993). The incorporated ^{3}H-dNTP was measured in a liquid scintillation counter (1450 MicroBeta; Wallac, Finland).

Results

The sequence analysis of the *MAOA* gene in 10 Swedish individuals disclosed five polymorphisms: a T-to-G transition at position 96 of exon 8, a 5-bp (AACAT) deletion/insertion at the 3′ end of intron 8 (139 bp upstream of exon 9), a G-to-A transition at the 3′ end of intron 9 (46 bp upstream of exon 10), an A-to-G transition at the 5′ end of intron 12 to (69 bp downstream of exon 12), and

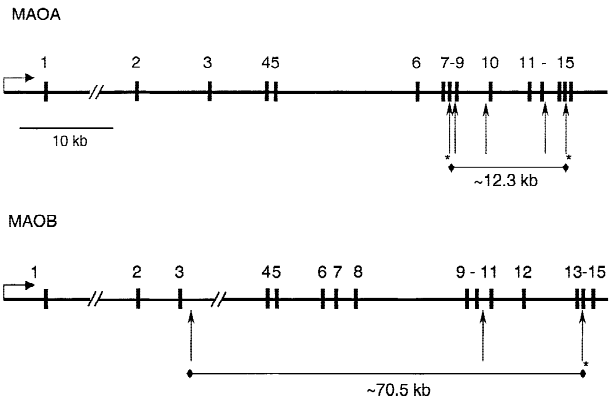

Fig. 1. Schematic representation of the *MAOA* and *MAOB* genes indicating the positions of the identified polymorphisms. *Vertical black bars* with numbers above them symbolize exons. *Horizontal arrows* denote the promoters. *Vertical arrows* indicate the positions of the polymorphic sites identified in this study. The exact positions are indicated in the text. *Asterisks* below the arrows denote previously known polymorphisms. Distances in kilobases between the most distant polymorphic positions found in each gene are indicated below the horizontal arrows. The *MAOA* and *MAOB* genes lie adjacent to each other in a tail-to-tail orientation and the distance between them is approximately 80 kb. For simplicity, both genes are shown in the same orientation. The lengths of the introns are taken from the sequences of published clones.

a C-to-T transition at position 36 of exon 14 (Fig. 1). All five polymorphisms had a frequency of 50% among the 10 Swedish individuals sequenced. The polymorphisms in exons 8 and 14 were also identified through our searches *in silico* and have been described previously (Cargill et al. 1999; Hotamisligil and Breakefield 1991), while the other three polymorphisms are not present in sequence databases or described in the literature. We did not find any of the other known SNPs or the SNP candidates we found by *in silico* analysis in the 10 Swedish individuals studied.

Sequencing of the *MAOB* gene revealed three polymorphic positions: a T-to-G transition at the 5′ end of intron 3 (253 bp downstream of the exon 3), an A-to-G transition at the 5′ end of intron 10 (140 bp downstream of exon 10), and an A-to-G transition at the 3′ end of intron 13 (36 bp upstream of exon 14) (Fig. 1). The substitutions in introns 3 and 10 were identified in a single person each (10% frequency), while the change in intron 13, which has been described previously (Ho et al. 1995), was found in 4 of the 10 individuals (40% frequency).

Nucleotide diversity, compared to the deduced ancestral sequence common for the three species sequenced (human, gorilla, and chimpanzee), was greater for the *MAOB* than for the *MAOA* gene (not shown). The average nucleotide diversity of the *MAOA* gene for all three species was 0.004 substitution per base pair, while it was 0.006 substitution per base pair for the *MAOB* gene. The greater average nucleotide diversity for the *MAOB* gene was due to a higher number of nucleotide substitutions in intronic sequences: 0.005 substitution per intronic base pair for the *MAOA* gene and 0.007 substitution per intronic base pair for the *MAOB* gene. The diversity in exonic sequences was similar for the two genes with 0.003 substitution per exonic base pair and 0.004 substitution per exonic base pair for the *MAOA* and *MAOB* genes, respectively.

To assess the population distribution of the five polymorphisms in the *MAOA* gene, we genotyped these positions in an additional set of DNA samples from 63 Caucasian, 33 Asian, and 40 African males. The eight haplotypes observed in this analysis and their frequencies in the tested populations are summarized in Fig. 2. The five polymorphic positions segregated as two haplotypes, denoted B and E, with distributions of 62 and 38%, respectively, in 26 Swedish males. Further screening of the polymorphisms in 37 British and 10 Mexican males revealed two additional haplotypes (F and H in Fig. 2), which were seen in a single person each, but in general, only the two main haplotypes B and E were observed in Caucasians. The set of 33 Asian samples contained the same B and E haplotypes, while 40 African males displayed seven haplotypes (A–E, G, and H in Fig. 2). Haplotype B, which was the most frequent in Caucasians and Asians, was also the most frequent in Africans (Fig. 3A). On the other hand, haplotype E, which was the second most frequent haplotype in Caucasians and Asians, was found in only a single Kenyan male, indicating a profound change in haplotype frequencies from Africans to non-Africans (Fig. 3A).

Figure 3B shows the proposed evolutionary relationship among the current African haplotypes. The haplotypes of the monkeys are identical to the African haplotype A, indicating that A is the ancestral haplotype.

Discussion

We have constructed haplotypes with novel polymorphisms found in the *MAOA* gene. As expected, there were low recombination rates for the haplotypes since the *MAO* genes are located in a region close to the centromere. Surprisingly, one of the *MAOA* haplotypes had a much higher frequency in non-Africans compared to Africans. In addition, Caucasians and Asians displayed only two main haplotypes with similar frequencies. The simplest explanation for this phenomenon is that a demographic bottleneck (Slatkin and Muirhead 1999) occurred during the migration of modern humans from Africa and before their expansion to the rest of the world. An alternative explanation is that one of the haplotypes or some other locus linked to the haplotype has conferred a selective advantage to the individuals that migrated from Africa. We regard this as less likely and it would require additional investigations.

The MAO polymorphisms were originally identified in a sample of Swedes, therefore introducing an ascer-

		All Africans N=40			All Asians N=33			All Caucasians N=73			
		Kenyans N=20	Ghanaians N=20	**Overall frequency**	Chinese N=13	Indian/Pakistani N=20	**Overall frequency**	Swedish N=26	English N=37	Mexican* N=10	**Overall frequency**
A	T ins G A C		0.05	**0.025**							
B	T ins G G C	0.60	0.70	**0.650**	0.69	0.45	**0.545**	0.62	0.70	0.50	**0.644**
C	T ins G A T	0.20	0.25	**0.225**							
D	T ins A A T	0.05		**0.025**							
E	G del A A T	0.05		**0.025**	0.31	0.55	**0.455**	0.38	0.27	0.40	**0.329**
F	G del A A C								0.03		**0.014**
G	T ins A G C	0.05		**0.025**							
H	T ins G G T	0.05		**0.025**						0.10	**0.014**

Fig. 2. Population frequencies of the identified haplotypes. The haplotypes are shown in the *horizontal bars* on the left. Haplotype A, *shaded with a gray background*, is identical to the haplotype found in gorilla and chimpanzee and most likely represents the ancestral haplotype. The nucleotides that are different from the ancestral ones are shown with a *white background.* N, number of individuals tested. *Mexican genes are mainly of Caucasian and Native American origin (Lisker et al. 1986).

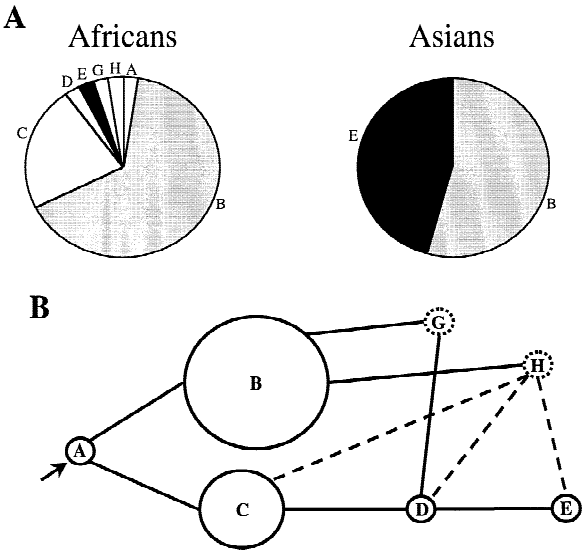

Fig. 3. **A** Pie charts of the frequency distributions of the *MAOA* gene haplotypes found in Africans, Asians, and Caucasians. The *letters* refer to the same haplotypes shown in Fig. 2. **B** Proposed evolutionary relationship among the current African haplotypes. The *arrow* indicates the probable ancestral haplotype. The area of the circles is proportional to the haplotype frequencies in Africans. *Dashed circles* enclose most likely recombinant haplotypes: haplotype G is a recombinant between the B and the D haplotypes, while haplotype H is a recombinant between the B and either the C, the D, or the E haplotype. The length of the lines connecting the haplotypes is not proportional to the time of divergence between them.

tainment bias toward the polymorphisms present in Europe. In spite of this bias, subsequent genotyping of the polymorphisms revealed that Africans display greater haplotypic variation. Therefore, our conclusions are unlikely to be affected by the bias that reduces African diversity.

Data on genetic variation give information about the history of human evolution. However, since the genealogy of sequences at different locations in the genome differs (Paabo 1999), it is important to study whether the same or similar patterns can be inferred from many different genes or segments of the genome.

Some previous studies have argued for population bottlenecks during the history of human evolution (Ambrose 1998; Kimmel et al. 1998; Reich and Goldstein 1998), although the time points at which the bottleneck might have occurred vary, ranging from the time when hominoids split from chimpanzees to relatively recent times when subpopulations of modern humans left Africa and occupied the rest of the world. In general, modern humans exhibit considerably lower genetic variation compared to other primate species (Crouau-Roy et al. 1996). This would be anticipated if the modern human population had experienced a recent major bottleneck in population size or the human species persisted as a small population for a long time (Jorde et al. 1998). Several studies exploring the variability of mitochondrial (Gagneux et al. 1999) and nuclear genomes (Harpending et al. 1998; Kimmel et al. 1998; Reich and Goldstein 1998; Zietkiewicz et al. 1998) indicate that a bottleneck followed by a later expansion might have occurred in the ancestral population for modern humans. However, studies examining genetic variation in other nuclear genes, such as the pyruvate dehydrogenase E1 α subunit (Hey

1997), the apoliprotein C-II gene (Xiong et al. 1991), and MHC loci (Ayala 1995) as well as the β-globin locus (Harding et al. 1997) have argued against an ancestral bottleneck. Still, a moderate reduction in population size (up to 10,000 breeding individuals) for a long period would be consistent with their data (Rogers and Jorde 1995).

Studies of genome variation have also been helpful in attempts to decipher the dispersion of modern humans. Though it is clear that the genus *Homo* originated in Africa, the disagreement concerns the subsequent evolution of modern humans (Templeton 1997). The fact that we have found similar haplotype frequencies of the *MAOA* gene in modern Asians and Caucasians would favor the out-of-Africa replacement hypothesis, as it is unlikely that independently evolving modern humans in different parts of the world would result in similar frequencies of the same haplotypes.

Data on microsatellite variation in autosomes (Bowcock et al. 1994; Shriver et al. 1997) and the Y chromosome (Seielstad et al. 1999), Alu insertion polymorphisms (Stoneking et al. 1997), and mitochondrial DNA variation (Watson et al. 1997) showed a higher nucleotide diversity in Africans compared to non-Africans, and the root of an evolutionary tree for all the variants was placed in Africa. This indicates that non-African populations might have an African origin and have gone through a bottleneck after the dispersion from Africa. On the contrary, other studies investigating population diversity of restriction fragment length polymorphisms in nuclear genomes found greater nucleotide variation in non-Africans than in Africans (Bowcock et al. 1991). However, the data could be misleading because they analyzed polymorphisms ascertained in European populations, and such polymorphisms might not be present in Africans (Jorde et al. 1998).

A more informative picture of the history of human evolution can be obtained from studies comparing the distributions of haplotypes instead of single polymorphisms. Although these studies are yet scarce, some common patterns of haplotype distributions are emerging for different loci. In accordance with our results as well as with the nucleotide diversity data mentioned above, several studies have shown that African populations displayed a higher haplotype diversity compared to other populations. Moreover, Eurasian haplotypes constituted a subset of African haplotypes (Hammer 1995; Kaessmann et al. 1999; Tishkoff et al. 1996; Watson et al. 1997). These findings strengthen the evidence for an African origin as well as for a bottleneck in the ancestral Eurasian population. On the contrary, haplotype diversity studies of the β-globin locus (Harding et al. 1997) and the dystrophin gene (Zietkiewicz et al. 1998) have found similar frequencies of the old polymorphisms between Africans and non-Africans. However, these observations do not necessarily contradict the occurrence of a bottleneck during modern human migration. In fact, it is possible that the migrating groups had frequencies similar to those of the rest of the population at these particular loci. Moreover, it has been shown that the dystrophin gene has a very high mutation rate, and any deleterious mutation together with linked neutral variants is strongly subjected to natural selection (Prior et al. 1995). Therefore, it is likely that the diversity pattern of the dystrophin locus is very different from those of other neutrally evolving loci. In general, it is possible that different studies have looked at different windows of human evolution, depending on the age of the polymorphisms present in each locus.

Our data on the haplotype distribution of MAOA outside of Africa revealed the prevalence of two haplotypes. In fact, the presence of two main clades of haplotypes has been reported previously for other loci: lipoprotein lipase and angiotensin-1 converting enzyme (Clark et al. 1998; Keavney et al. 1998). However, the time for the origin of the two clades is different for the lipoprotein lipase and monoamine oxidase data. We found only two main haplotypes present in Eurasians and several haplotypes present in Africans. However, the two main clades observed for the lipoprotein lipase locus were also present in populations with African genetic components (i.e., in African-Americans). It was then suggested that these two clades are very old and originated just after the human–chimpanzee split. Thereafter, the two lineages could have been sustained after a moderate bottleneck following the human/chimpanzee split (Harpending et al. 1998) or by natural selection (Clark et al. 1998; Rieder et al. 1999).

Although large efforts are being carried out to create a collection of human variable sites in coding regions (Halushka et al. 1999), our study shows that it is also important to obtain information from intronic segments, to allow the construction of informative human haplotypes. The novel haplotypes described here could be used for association studies of the different genetic subtypes with extreme values of monoamine oxidase activity levels in humans. It has been observed that there are up to 30-fold differences in the stable activity levels of platelet MAOB among healthy individuals (Murphy et al. 1976) and up to 100-fold interindividual differences in MAOA activity measured in skin fibroblasts (Castro Costa et al. 1980). The variation in the activity of the enzymes is determined substantially by genetic components (Hotamisligil and Breakefield 1991; Pedersen et al. 1993), and the absence of MAOA has been clearly associated with abnormal human behavior (Brunner et al. 1993). Therefore, several studies attempting to find an association between DNA polymorphisms in the *MAO* genes and human traits have been performed but have obtained inconclusive or controversial results. For example, association of susceptibility to Parkinson disease with the A allele at the polymorphic site in intron 13 of the *MAOB*

gene was suggested in a study on Caucasians (Kurth et al. 1993) but was not replicated in a Japanese population (Morimoto et al. 1995) or in an Australian cohort (Mellick et al. 1999), and more surprisingly, the other allele at the polymorphic site in intron 13 was related to Parkinson's disease in another sample of Caucasians (Costa et al. 1997). Confusing results were also obtained in allelic association studies analyzing the involvement of MAO in bipolar disorders (Furlong et al. 1999; Kunugi et al. 1999) as well as in alcoholism (Parsian 1999; Samochowiec et al. 1999). A more extensive panel of DNA variants and haplotypes could help to find segments of the gene that are in linkage disequilibrium with the functional polymorphisms responsible for the different levels of monoamine oxidase activity in human populations.

Single nucleotide polymorphisms are a good choice for association studies because they have a low mutation rate and are amenable to automation (Halushka et al. 1999). On the other hand, the power of linkage disequilibrium mapping using SNPs as markers for unknown causative polymorphisms depends on several parameters including the density and number of tested SNPs at a given locus, the frequencies of the SNPs in the population, the age of the mutations, the proportion of the variance of a given phenotype attributable to a causative polymorphism within the tested locus, and the evolutionary history of a studied population (Kruglyak 1999). The use of haplotypes instead of single polymorphisms for association studies can increase the information obtained by an association analysis and will require the development of special statistical analysis (Terwilliger and Weiss 1998).

In conclusion, haplotype variation reflects demographic events and diverse action of evolutionary forces that have been taking place during the history of modern humans (Przeworski et al. 2000). Consequently, the pattern and degree of linkage disequilibrium differ among different populations and different genetic loci. Therefore, a detailed picture of haplotype variation at different loci of the human genome is essential not only to reveal the history of modern humans, but also for the successful design of genetic association studies to identify genes involved in the etiology of complex human traits.

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