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GENETIC RELATIONSHIP OF HUMAN POPULATIONS AND ETHNIC
DIFFERENCES IN REACTION TO DRUGS AND FOOD

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For the past fifteen years, Nei and his colleagues have been studying the extent of genetic polymorphism and the evolutionary relationship of human populations by using gene frequency data (Nei and Roychoudhury 1972, 1974, 1982; Nei 1982, 1985). They have found that human populations contain a large amount of polymorphism both at the protein and DNA levels and that polymorphism data are very useful for elucidating the evolutionary relationship of human populations. In this paper, we present a review of these studies and discuss their implications for ethnic differences in reaction to drugs and food.

GENETIC VARIATION WITHIN THE THREE MAJOR RACES OF MAN

In the process of racial evolution of man, gene migration seems to have occurred almost always among neighboring populations. However, the three major races of man, Caucoid, Negroid, and Mongoloid, had apparently been isolated for a long time until worldwide navigation started around 1450. Coon (1965) argued that this isolation was caused mainly by two barriers, i.e., the Sahara Desert in Africa and the Movius line (high mountains in the west and south of Tibet). It is, therefore, interesting to know the extent of genetic variation within and between these three major races.

Protein and blood group loci

A simple way to study the extent of genetic variation

is to examine the proportion of polymorphic loci (P) and average heterozygosity (H) at structural loci. Nei and Roychoudhury (1982) studied these quantities by using gene frequency data for 62 protein loci and 23 blood group loci. Table 1 shows that about 47 to 61 percent of protein loci are polymorphic in all three major races. If we note that the human genome has about 50,000 structural genes, this indicates that human populations are polymorphic for about 25,000 loci at the electrophoretic level. Estimates of average heterozygosity show that an average individual is heterozygous at about 14 percent of structural loci.

The P and H values for blood group loci are considerably higher than those for protein loci (Table 1). However, this seems to be due to the fact that blood group loci are discovered only when there are some variant alleles (Lewontin 1967; Nei and Roychoudhury 1974). Therefore, these are probably overestimates of the P and H values for the entire genome.

DNA polymorphism

One of the most useful measures of DNA polymorphism is "nucleotide diversity" or the average number of nucleotide differences per nucleotide site between two randomly chosen DNA sequences (Nei and Li 1979). This quantity has recently been estimated for mitochondrial DNA, β -globin genes, and insulin genes in Caucasoids (Nei 1983). The estimates (π) are all about 0.003. A similar result was also obtained for the growth hormone genes (Chakravarti et al. 1984). The coding region of a structural gene usually consists of about 1000 nucleotide pairs. Therefore, two randomly chosen

Table 1. Proportions of polymorphic loci (P) and average heterozygosities (H) for protein and blood group loci in the three major races of man. (r = number of loci used)

	Protein loci		Blood group loci	
	r	H	r	H
Caucasoid	62	0.58	23	0.74
Negroid	62	0.61	23	0.65
Mongoloid	62	0.47	23	0.65

alleles seem to have on the average three nucleotide differences. Interestingly, many of these differences are observed at the third nucleotide position of codon and do not result in amino acid replacement. The human genome is known to consist of about 3×10^9 pairs of nucleotides. Therefore, if $\pi = 0.003$, an average person is heterozygous at about nine million nucleotide sites.

GENETIC VARIATION BETWEEN THE THREE MAJOR RACES

Nei (1973) devised a method for decomposing the total genetic variability (H_T) in a subdivided population into the intrapopulational (H_S) and interpopulational (D_{ST}) components. Nei and Roychoudhury (1972, 1982) and Nei (1982) have applied this method to protein, blood group, and mitochondrial DNA data for the three major races. Their results indicate that the interpopulational variation is only about 6 to 11 percent of the total variation. Thus, a large proportion of genetic variation in human populations exists within populations rather than between populations. This is true despite the fact that there are conspicuous morphological differences among the three major races.

It should be noted, however, that although the interpopulational genetic variation in protein or blood group loci is very small, it is significantly different from 0. Therefore, we can estimate the genetic distances (Nei 1972) between the three major races. The estimates obtained are presented in Table 2. Protein data indicate that Caucasoid and Mongoloid are more closely related to each other than to Negroid, whereas blood group data indicates a close relationship between Caucasoid and Negroid. If the latter relationship is correct, it suggests that there was a considerable amount of gene migration between Caucasoid and Negroid in the past. However, the relationship between blood group phenotype and nucleotide sequence in the gene is not clear, so that protein data seem to be more reliable. If we accept the genetic relationship from protein data, it is possible to estimate the times since divergence of these races (see Nei and Roychoudhury 1982). The results obtained suggest that Negroid and the Caucasoid and Mongoloid group diverged about 110,000 years ago, whereas Caucasoid and Mongoloid diverged about 40,000 years ago. These estimates of divergence times are compatible with the fossil records, since a number of authors have reported fossils of modern men which

are as old as 120,000 years (Day et al. 1980; Kennedy 1980).

In recent years, a number of authors (e.g. Brown 1980; Cann 1982; Johnson et al. 1983; Wallace et al. 1985) have studied restriction-site polymorphisms of mitochondrial DNA (mtDNA) in various human populations. Nei (1985) used Cann's data to study the genetic variation between the three major races. The human mtDNA consists of about 16,500 nucleotide pairs, and a large number of polymorphic sequences exist. In population genetic studies, the nucleotide differences between a pair of mtDNAs are usually estimated from the differences in restriction enzyme cleavage sites. Using Cann's (1982) data, Nei estimated the numbers of nucleotide differences per site for all pairs of 10 mtDNAs sampled from each of Caucasian, Negroid, and Mongoloid. He then constructed a phylogenetic tree for the 30 mtDNAs examined (Figure 1). It is clear that although there is some tendency for the mtDNAs sampled from the same race to cluster, most of them are genealogically mixed with those from other races. However, this is what is theoretically expected when closely related populations are studied (Takahata and Nei 1985).

Theoretically, it is still possible to compute the inter-racial genetic distances from this set of data. In the present case, however, the standard errors of the distances are very large so that no meaningful conclusion can be obtained concerning the racial divergences (Nei 1985).

Figure 1 shows that there is one Negroid mtDNA which is quite different from other mtDNAs. Cann (1982) and Johnson et al. (1983) have also found several Negroid mtDNAs which are considerably different from the mtDNAs from Caucasian and Mongoloid. By contrast, Caucasian and Mongoloid share many

Table 2. Genetic distances and effective divergence times between the three major races of man

Comparison	Blood			Effective divergence time(years)
	Proteins (62 loci)	groups (23 loci)	Total (85 loci)	
Caucasoid/Negroid	0.030	0.038	0.032	113,000
Caucasoid/Mongoloid	0.011	0.043	0.019	41,000
Negroid/Mongoloid	0.031	0.096	0.047	116,000

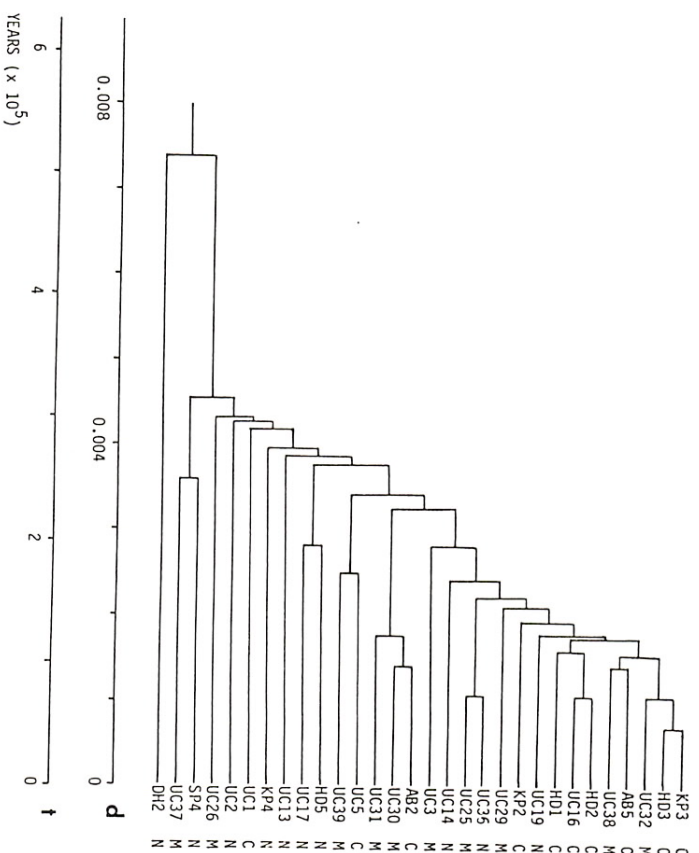


Figure 1. Phylogenetic tree of mitochondrial DNAs for 30 individuals sampled from the Caucasian (C), Negroid (N), and Mongoloid (M) populations.

closely related mtDNAs. Interestingly, a similar pattern of restriction-site polymorphism has also been observed in the γ -globin region of human nuclear DNA (Weatherall 1985). These results are consistent with those obtained from protein polymorphism data. Figure 1 gives estimates of the times of divergence for the mtDNAs studied. These estimates were obtained from the rate of nucleotide substitution for mtDNA (Nei 1985). It is clear that the majority of currently polymorphic mtDNAs diverged much earlier than the time of racial divergence. This indicates that polymorphic alleles in a population persist for a very long time as theoretically predicted (Kimura and Ohta 1973; Maruyama 1974; Tajima 1983).

GENETIC RELATIONSHIPS OF VARIOUS HUMAN POPULATIONS

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There seems to be no agreement among anthropologists concerning the classification of human populations. Some anthropologists (e.g. Boyd 1963) prefer to classify human populations into five major groups, adding Amerindian and Australoid (or Oceanian) to the three major races we have considered. We have, therefore, studied the genetic relationships of various human populations within each of these five groups by using Nei's genetic distance (Nei and Roychoudhury 1982). In this study, we have used gene frequency data for protein and blood group loci jointly because the data for protein loci were limited in some populations. In this paper, we shall not present all the results because of space limitation. Rather, we present the genetic relationship of 18 representative populations of the world and then discuss the factors that caused genetic differentiation of populations.

Eighteen representative populations

The 18 populations given in Figure 2 have been chosen mainly because they are of anthropological interest and the gene frequency data for them were available. All five racial groups are represented by them. The genetic distances were obtained by using 14 protein loci and nine blood group loci (Nei and Roychoudhury 1982). It is clear from the dendrogram in Figure 2 that Caucasoid and Mongoloid populations are again more closely related to each other than to Negroid populations. However, Amerindians and Australoids, who are supposed to be closely related to Asian Mongoloids, make separate clusters. This is apparently due to the effect of inbreeding that has occurred in these small tribal populations. The relatively large distance between Australian Aborigines and Papuans is also apparently caused by inbreeding. It is known that when population size is drastically reduced, genetic distance rapidly increases (Chakraborty and Nei 1977) and that the clustering method used here (UPGMA) distorts the actual genetic relationship of populations for this type of data.

It is noted that the genetic distance between English and Italian is very small compared with the distances between other populations. It is less than 1/10 of the distance between Chinese and Japanese, and 1/200 of that between Australian Aborigines and Papuans. Actually, all western European populations are genetically closely related

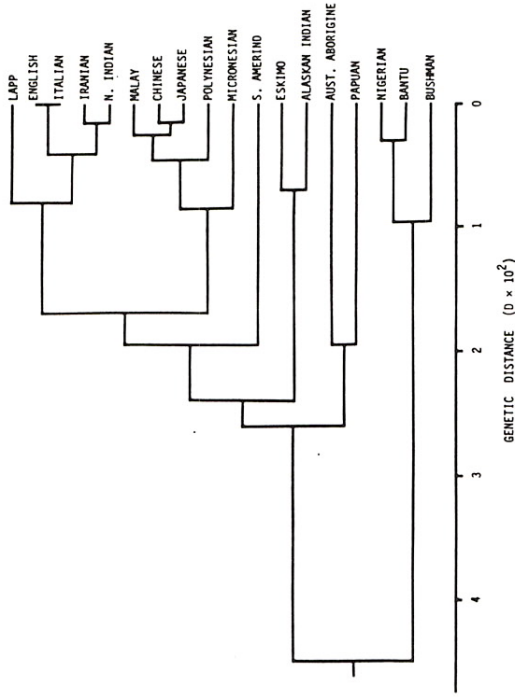


Figure 2. Dendrogram for 18 representative populations of man.

(Nei and Roychoudhury 1982). Even the Basques, who speak a non-Indo-European language, are known to be closely related to the other European populations. In Europe, the only distantly related population is the Lapps, who are considered to have been isolated from other populations for a long time.

As mentioned above, Amerindian and Australoid populations have apparently been subjected to inbreeding due to small population size. We have, therefore, reexamined the genetic relationship of the 18 populations by using Farris' (1972) clustering method, which is relatively insensitive to inbreeding effects. This method does not produce a rooted tree, but an unrooted tree as shown in Figure 3 can be obtained. According to this tree, Caucasoid, Negroid, and Mongoloid populations again make separate groups. Furthermore, as is generally believed, Australoid, Polynesian, and Amerindian populations are now more closely related to Mongoloid populations than to Caucasoid or Negroid populations.

Factors affecting gene differentiation

Our study of the genetic relationships of various human

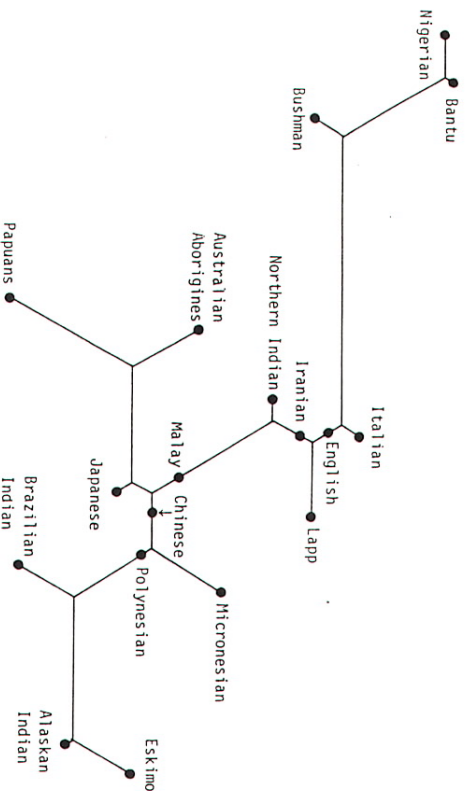


Figure 3. Distance-Wagner unrooted tree showing the genetic relationship of 18 representative populations of man.

populations suggests that the most important factors affecting gene differentiation among populations are isolation and genetic drift. Figure 2 clearly shows that a pair of populations that have been isolated for a long time (e.g. Bushmen and Japanese) generally show a large genetic distance. Thus, isolation is obviously the most important factor. The importance of genetic drift is indicated by the fact that a pair of tribal populations such as Australian Aborigines and Papuans generally have a large distance. This tendency was observed in many tribal populations in America, Africa, and Southeast Asia (Nei and Roychoudhury 1982). Gene migration has an effect opposite to isolation. In the process of human evolution, migration apparently occurred quite often among neighboring populations.

In human populations, language can be a barrier to inter-racial hybridization. In practice, however, genetic distance is not clearly related to linguistic difference, except among very closely related populations. This is understandable because the language of a human population can change rapidly under certain circumstances. The relationship between genetic distance and morphological difference is also generally weak. For example, the Negritos and Aboriginal Malays in Southwest

Asia, Papuans in New Guinea, and Pygmies and Bushmen in Africa have a number of common morphological features such as short stature, dark skin, and frizzy hairs. Because of these similarities, some anthropologists believe that they have originated from the same common stock. Nei and Roychoudhury's (1982) genetic distance study, however, indicates that the African and Southeast Asian populations are genetically quite different and that they are generally more closely related to their neighboring populations. This suggests that the evolutionary change of morphological characters are quite different from those of average genes. Apparently morphological characters are subject to stronger natural selection than average genes (Nei and Roychoudhury 1972).

IMPLICATIONS FOR ETHNIC DIFFERENCES IN REACTION TO DRUGS OR FOOD

In recent years, many polymorphisms with respect to drug resistance or tolerance to certain food have been discovered. The genetic basis of these polymorphisms is not always simple, but there are a substantial number of cases where the polymorphism is controlled by simple Mendelian genes (Vogel and Motulsky 1979).

When there is a polymorphism with respect to drug resistance or food intolerance, it is tempting to explain the polymorphism in terms of some kind of natural selection. Indeed, there are cases in which selection is clearly involved. One example is the polymorphism of G6PD deficiency, which is due to an X-linked recessive gene. An individual with this deficiency shows anemia when primaquine, an antimalarial drug, is administered. In the Mediterranean area, however, the frequency of this deficiency allele is very high because the individuals with this deficiency allele are resistant to malaria.

In many other polymorphisms, however, it is not easy to prove involvement of selection. It is now well known that most Oriental adults are intolerant to lactose because of the low level of lactase in the small intestine, whereas most northern Europeans are capable of absorbing lactose without any trouble. Lactose tolerance in northern Europeans is due to a high frequency of a dominant gene that keeps the level of lactase high even after weaning. For convenience, we denote this allele by PLA^+ . Here, PLA stands for the persistence of lactase acti-

vity (Flatz and Rotthauwe 1977.) Many authors have argued that PLA^+ has increased in northern Europe because of the selective advantage in milk-drinking societies (e.g. Simoons 1970; Johnson et al. 1974). However, the selective advantage of PLA^+ over its allelic gene PLA^- occurs only when fresh milk is consumed in large quantity, and this situation probably did not happen until systematic animal breeding was introduced a few centuries ago (Flatz and Rotthauwe 1977). Simoons (1978) has argued that natural selection for the PLA^+ allele started about 7000 to 8000 years ago in Africa and Southwest Asia, where sheep and goats were domesticated. At this time, however, the amount of milk consumed per person must have been so small that the problem of lactose malabsorption probably did not occur even for PLA^- homozygotes. Furthermore, if the problem occurred, the homozygotes could easily eat non-milk food or fermented milk which contains little lactose. These arguments make it very difficult to accept the hypothesis of selective advantage of PLA^+ .

Because of this difficulty, Flatz and Rotthauwe (1977) suggested that the increase in frequency of PLA^+ in northern Europe was caused by the enhancement of calcium absorption in the presence of lactose. In northern Europe, calcium absorption is important to prevent rickets or osteomalacia. Simoons (1978), however, indicates that a high frequency of PLA^+ occurs not only in northern Europe but also in some parts of Africa and Pakistan where vitamin D is abundant and the problem of rickets does not occur.

When there is no definite conclusion available about the maintenance of polymorphism, it is helpful to examine the geographical distribution of gene frequencies. Comparing this distribution with that of a polymorphic locus which is subject to no apparent selection, one may obtain some insight into the selective pattern. In the following, we shall consider three examples.

Lactose tolerance

Figure 4 shows the geographical distribution of the frequency of PLA^+ . Note that most investigators use the frequency of lactose absorbers (y) instead of the frequency (x) of PLA^+ . The former can be obtained from x by $y = x^2 + 2x(1 - x)$. It is seen from Figure 4 that northern European countries have a frequency of 0.6 to 0.8, but southern Europe

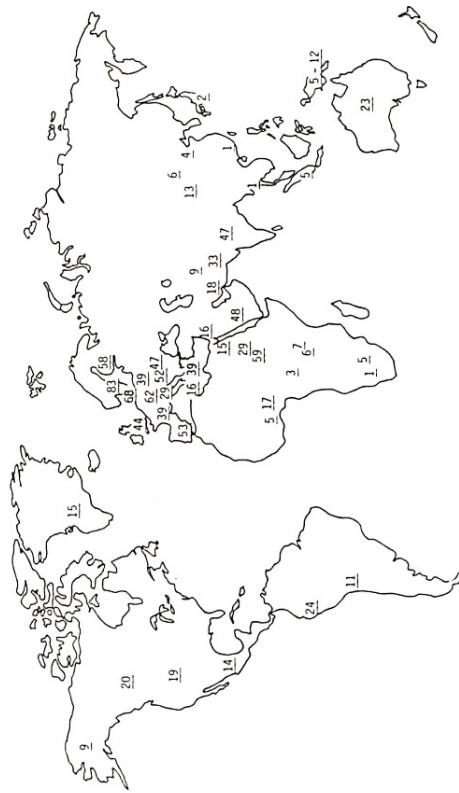


Figure 4. Geographical distribution of the frequency (%) of the lactose absorption gene (PLA^+).

(Italy, Greece, etc.) has a somewhat lower frequency (0.16 ~ 0.39). In Africa, geographic variation in gene frequency is high, the frequency ranging from 0.01 to 0.59. Variation is also quite high in Near East to Southwest Asia. As is well known, Southeast Asia and Far East Asia tend to show a low frequency (0.01 to 0.05), but northern China has a relatively high frequency (0.13). It is interesting to note that Australian Aborigines and Amerindians, who are remotely related to Europeans and were previously hunter-gatherers, have a fairly high frequency of PLA^+ (0.11 to 0.24).

It is obvious from Figure 4 that the PLA^+ allele exists worldwide and that the geographical variation of gene frequency is only quantitative. Furthermore, some non-milking populations (e.g. Australian Aborigines) have nearly the same gene frequency as that of some milking populations (e.g. Italians). The difference between the highest frequency (Scandinavia) and the lowest frequency (Thailand) is about 0.7. This difference is certainly large, but if we examine many polymorphic (protein) loci in man, there are several that show this magnitude of difference (Roychoudhury and Nei, unpublished). Examples are the loci for β -lipoprotein: Ag

system, haptoglobin, acetylator system, acid phosphatase (p^b allele), glutamic pyruvic transaminase, and group specific component. While it is not known whether or not these loci are maintained by selection, this observation indicates that the extent of geographic variation in the frequency of the PLA^+ allele is not exceptional.

Another important point revealed from Figure 4 is that the age of the PLA^+ allele is very old. Previously, we presented evidence that the three major races of man diverged probably 40,000 to 100,000 years ago. Since all the three major races have the PLA^+ allele in appreciable frequency, this allele must have existed at least from the time of racial divergence, i.e., for more than 100,000 years. This time period is much longer than that considered by previous authors for the evolution of the PLA^+ allele. At this point, it is worth noting that most mammalian species do not maintain the activity of intestinal lactase after weaning. Therefore, they seem to have allele PLA^- , as do most Oriental people. Thus, it is likely that allele PLA^+ occurred as a mutation from PLA^- more than 100,000 years ago in the human lineage and had reached at least some appreciable frequency before the divergence of the three major races. It is not clear whether the increase in the frequency of PLA^+ was due to some type of selection or genetic drift, but the increase during this period was almost certainly unrelated to milk consumption. In this connection, it is instructive to note that one species of monkey (*Macaca fascicularis*) is tolerant to lactose and apparently has a high frequency of PLA^+ (Wen et al. 1973).

If the above argument is correct, it seems likely that the present geographic distribution of the gene frequency of PLA^+ was established largely independently of lactose tolerance before milking culture was introduced. As Bayless (1971) indicated, it is possible that northern Europeans had a rather high frequency of PLA^+ before they started to drink milk. Of course, once they started drinking milk, natural selection might have operated to increase the gene frequency. However, the amount of increase that occurred during the last few centuries must have been rather small.

It should be noted that the above argument is dependent on the assumption that the mutation from PLA^- to PLA^+ does not occur recurrently. If the mutation from PLA^- to PLA^+ occurs recurrently with an appreciable frequency, the PLA^+

allele may not be as old as is assumed here. It is known that PLA^- is a regulatory gene that turns off the production of lactase at the time of weaning and that the enzyme lactase produced by genotype PLA^+/PLA^+ is identical with that produced by PLA^-/PLA^- (Potter et al. 1985). Since most mammals have allele PLA^- , it seems that the mutation rate from PLA^- to PLA^+ is very low even if the mutation recurs.

Aldehyde dehydrogenase-I isozyme deficiency

Another interesting example is the polymorphism of the aldehyde dehydrogenase-I (ALDH-I) isozyme deficiency studied by Goedde et al. (1979, 1985). About 50 percent of Oriental people are deficient in this isozyme, and this deficiency has been implicated to be responsible for "alcohol sensitivity" manifested by many Orientals. Figure 5 shows the distribution of the proportion of individuals deficient in this isozyme. Although the distribution has not been extensively studied, it seems obvious that this deficiency is confined to Mongoloids and their derivative populations. It is interesting that both Orientals and Amerindians have nearly the same frequency, though there is considerable variation within each group, probably because of genetic drift. Amerindians are

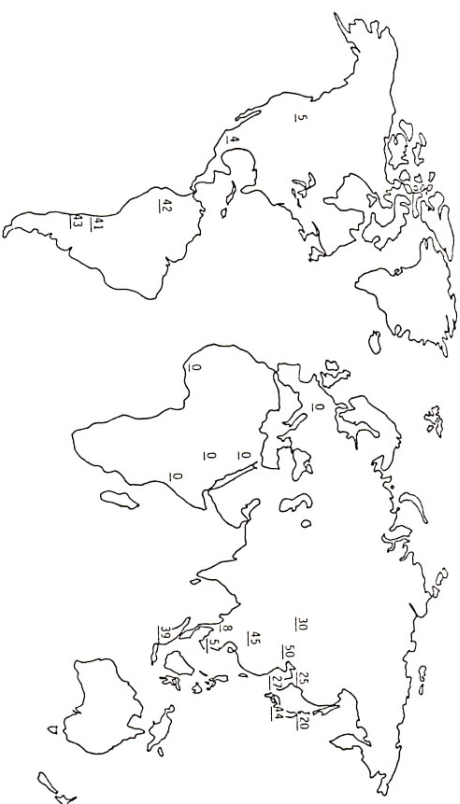


Figure 5. Geographical distribution of the frequency (%) of aldehyde dehydrogenase-I isozyme deficiency.

considered to have been derived from Mongoloids who crossed the Bering Strait about 30,000 years ago. Therefore, the ALDH-I deficiency allele must have existed for at least 30,000 years. The ALDH-I deficiency individuals are considered to include both the homozygotes and heterozygotes for the deficiency allele. Therefore, the allele frequency for Orientals seems to be about 0.3 or less.

Why did the ALDH-I deficiency allele increase in Orientals and Amerindians? The most likely explanation is again random genetic drift because the deficiency of the ALDH-I isozyme does not appear to give any selective advantage. In the present case, there are other ALDH isozymes encoded by separate loci, so that nonfunctionalization of the first locus (see Yoshida et al. 1985) does not seem to matter for the survival of an individual. When Mongoloid was separated from Caucasoid (or Negroid), the population size was probably quite small, and it was at this stage that the ALDH-I deficiency allele probably increased in frequency by genetic drift.

Pseudocholesterase variants

The pseudocholesterase E_1 locus is known to have several different mutant alleles that cause an extremely prolonged muscular paralysis and apnea when suxamethonium, a muscle relaxant drug, is administered. The most common variant is the "atypical" allele (E_1^a). The frequency of this allele is 0.01 to 0.02 in Caucasian populations. In other populations, the frequency is lower or virtually zero. However, other alleles such as E_1^b and E_1^c are often observed with a low frequency (Giblett 1969; Roychoudhury and Nei, unpublished). In general, this locus seems to have some variant alleles in all populations. This suggests that the variant alleles at this locus are maintained by the balance between mutation and weak selection.

Why then are the variant alleles selected against in natural conditions? The answer to this question seems to be that some food contains toxins which have an effect similar to that of suxamethonium. For example, potatoes contain a toxic substance called solanine, and this substance is known to cause disturbances in respiration and cardiac activity and significant hemolysis (Harris and Whittaker 1959; Chakraborty et al. 1978). Many known variant alleles at the pseudocholesterase E_1 locus apparently affect the active site of pseudocholesterase

esterase and block or reduce the ability of this enzyme to hydrolyze toxic substrates (Giblett 1969).

SUMMARY

Using gene frequency data for a large number of protein and blood group loci and restriction-site data for mitochondrial DNA, we studied the genetic variation within and between the three major races of man, Caucasoid, Negroid, and Mongoloid. In all the three major races, about 50 percent of structural loci seem to be polymorphic at the electrophoretic level, and the average heterozygosity is about 14 percent. The genetic variation between the three major races is small compared with that within the races. However, even this small interracial variation seems to be the result of geographic isolation for 40,000 to 110,000 years. Genetic distance analysis indicates that Amerindian and Australoid are genetically closer to Mongoloid than to Caucasoid and Negroid, as expected. It is indicated that the evolutionary mechanism of ethnic differences in reaction to drugs and food should be studied with the knowledge that different groups of human populations have been separated for a long time in the evolutionary process. The geographic distributions of the genes for lactose absorption and aldehyde dehydrogenase-I isozyme deficiency suggest that they have existed for a very long time in human populations and that genetic drift has been an important factor in the geographic differentiation of the frequencies of these genes. By contrast, the variant alleles at the pseudocholesterase locus seem to be maintained by the balance between mutation and weak selection.

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