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Population Migration and the Variation of Dopamine D4 Receptor (DRD4) Allele Frequencies Around the Globe

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This article reports an association between the variation of dopamine D4 receptor (DRD4) allele frequencies around the globe and population migration patterns in prehistoric times. After compiling existing data on DRD4 allele frequencies of 2,320 individuals from 39 populations and on the migration pattern of these groups, we found that, compared to sedentary populations, migratory populations showed a higher proportion of long alleles for DRD4. The correlation between macro-migration (long-distance group migration) and the proportion of long alleles of DRD4 was .85 ($p < .001$), and that between micro-migration (sedentary vs. nomadic settlement) and the proportion of long alleles was .52 ($p = .001$). We discussed the adaptive value of long alleles of DRD4—a genetic trait that has been linked in some studies to the personality trait of novelty-seeking and to hyperactivity— in migratory societies and the possibility of natural selection for a migration gene.   © 1999 Elsevier Science Inc.

KEY WORDS: Dopamine D4 receptor (DRD4); Migration; Natural selection.

A s one of the most important neurotransmitters in the brain, dopamine has received extensive attention from researchers. The most significant developments in this area during the past several years include the isolation of the dopamine receptor genes and the identification of their expressed polymorphism in coding sequences. Compared to other dopamine receptors, D4 exhibits the largest number of polymorphisms. It is one of the most polymorphic of all genes studied so far. Its polymorphism is revealed in the variable number of imperfect 48-bp tandem repeats on exon III, ranging from 2 to 11 repeat units, with 4- and 7-repeats being the most common.

The implications of DRD4 polymorphism are still not well understood, but recent research has uncovered several possibilities. For example, several recent studies have demonstrated an association between DRD4 polymorphism and variation in personality traits such as novelty-seeking (Benjamin et al. 1996; Ebstein et al. 1996, 1997; Hamer 1997; Ono et al. 1997), although some studies failed to replicate such findings (Malhotra et al. 1996; Sullivan et al. 1998; Vandenbergh et al. 1997). Other studies have shown that long alleles of DRD4 are associated with attention deficit/hyperactivity disorder (ADHD) (LaHoste et al. 1996; Smalley et al. 1998; Swanson et al. 1998) and risk-taking behaviors such as gambling (Castro et al. 1997).

These findings are consistent with experimental research on animals that has shown the role of dopamine receptors in exploratory behavior. For example, research on mice has shown that the injection of dopamine agonists markedly increases the frequency and duration of spontaneous exploratory activity and also facilitates the initiation, speed, and vigor of locomotion (Fink and Smith 1980; Le Moal and Simon 1991).

Although the biochemical mechanisms involved in the link between DRD4 polymorphism and human exploratory behavior are not entirely clear, there was good evidence that the variations in the variable number of tandem repeats of DRD4 cause people to produce dopamine receptors of different sizes, a feature that is linked to the ability of the receptor to bind to dopamine-like molecules (Hamer 1997). Researchers also believe that DRD4 polymorphism can affect signal transduction through interactions with intracellular proteins because the DRD4 repeats encode a proline-rich protein domain that is in a cytoplasmic loop of the DRD4 (Asghari et al. 1995; Lichter et al. 1993).

Another interesting feature of DRD4 polymorphism is its great variation among populations. East Asians have a low proportion of long alleles (e.g., 1% or fewer alleles with 7-repeats), whereas South American Indians have a high proportion of them (up to 78% alleles with 7-repeats) (Chang et al. 1996). As is the case with other polymorphic genes (e.g., those for sickle cell and blood group O), natural selection also may play a significant role in the global variation of the DRD4 gene. Thus far, however, researchers have paid little attention to the possible factors involved in the natural selection of the DRD4 gene. In this article, we propose that migration may be a key natural selection factor that accounts for the global variation of DRD4 gene. In the following sections, we (a) present the data on the DRD4 gene in various populations and their migration history, (b) discuss a clear association between the two, (c) test and rule out alternatives to the migration hypothesis, and fi-

nally (d) discuss the mechanisms that might be involved in the natural selection of the DRD4 gene.

METHODS

Data on the Gene

Data on the global distribution of DRD4 allele frequencies were compiled from 12 studies (Castro et al. 1997; Chang et al. 1996; Ebstein et al. 1996; Gelernter et al. 1997; Geijer et al. 1997; Hong et al. 1997; Inoue et al. 1993; Li et al. 1997; Nanko et al. 1993; Ono et al. 1997; Petronis et al. 1992; Tanaka et al. 1995). [It should be noted that most studies included both samples with psychiatric disorders and controls. Only data from controls (i.e., normal samples) were included in this present study. There were other studies on DRD4, especially in the United States. However, due to a lack of detailed distribution of DRD4 alleles, they could not be included in this study.] The 12 studies examined a total of 4,640 alleles of 2,320 individuals from 39 different populations. Details about the procedures used in each study were described in the original studies. Although methods used in extracting DNA and polymerase chain reaction (PCR) amplification of DRD4 were not exactly the same across all studies, all methods meet rigorous standards for yielding reliable data. In general and for most of the cases, a hot-start procedure including dimethyl sulfoxide was used for PCR (Chester and Marshak 1993), and the Southern blot and hybridization procedures were used to confirm the DRD4 origin of PCR products (Kidd et al. 1991). Because the distribution of allele frequencies for DRD4 in the human population is bimodal (4- and 7-repeats), the number of 7-repeats has been used commonly as an index of genotype in the molecular biology literature. In the present study, we used two indices of allele frequencies: the proportion of DRD4 7-repeats and the proportion of long alleles (5- to 11-repeats).

Data on Migration

Information about migration patterns came from different sources for different populations (Cavalli-Sforza 1986; Cavalli-Sforza and Cavalli-Sforza 1995; Cavalli-Sforza et al. 1994; Levinson 1991–1996; Murdock 1967; Nimuendaju 1952; Steward 1946–1950; von Furer-Haimendorf 1985). Two variables were created to characterize the migration patterns of these populations: macro-migration and micro-migration. Macro-migration was measured in thousands of miles, based on evidence from archaeology and historical linguistics. In this study, we focused on the effects of migration that took place over a long period of time, rather than with the contemporary migrations of the past few decades. The time frame for the latter migrations is too short for the kind of processes that we are studying. (Contemporary migration/immigration will be discussed in a separate section because it provides information relevant to the testing of alternative hypotheses.) The time frame for the migrations that we coded was between 1,000 and 30,000 years in the past. In some cases, migration distance was estimated as the distance of the population from the probable

homeland of its language family. Groups with no known evidence of large-scale migration were coded as having migrated 0 miles. These include groups that are currently located near the probable homeland of their language family.

Most of the societies in our sample fall within six well-known migration routes: (a) the migrations of American Indians from Northeast Asia to North America and onward to Central and South America (10 societies); (b) migrations from China to Japan, Taiwan, Southeast Asia, and the Pacific (7 societies); (c) Melanesian migrations from Southeast Asia (2 societies); (d) Jewish migrations to Ethiopia, Yemen, and Europe (4 societies); (e) migrations from West Africa to Central, Eastern, and Southern Africa (4 societies); and (f) Indo-European migrations from the Black Sea region to Europe (5 cases). The clustering of most societies within a few historical groups raises the statistical problem of autocorrelation, which we discuss in a subsequent section.

Micro-migration was coded from published sources on the 39 societies. In many cases we were able to use published codes (Murdock 1967) and in several other cases we used descriptions in the *Encyclopedia of World Cultures* (Levinson 1991–1996). For a few cases we consulted original ethnographies published in the past 40 years. In most cases, the dates of ethnographic observations were early to mid-20th century. Micro-migration codes are intended to measure survival strategies that required exploration of new environments. They represent lifestyles that have a long time depth, often several thousand years. Initially, all societies were coded for subsistence pattern (nine categories) and settlement pattern (six categories). The two variables were highly correlated ($r = .81$) and thus were combined to create a simple dichotomized variable: sedentary versus nomadic settlements. There were 28 societies with sedentary settlement and 11 with nomadism (Table 1). The correlation between macro-migration and micro-migration was .39 ($p < .05$).

RESULTS

Association between Migration and DRD4 Allele Frequencies

Table 2 shows societies' names, geographical locations, macro-migration, the two indices of DRD4 allele frequency distribution, and allele sample size. Results are shown separately by migration routes. Overall, a clear and common pattern emerged from these data. The populations that remained near their origins showed a lower proportion of long alleles of DRD4 than those that migrated farther away. This finding was consistent across all six migration routes.

For the first route of migration (from northeastern Asia to Americas), South Americans have the largest proportion of long alleles (69%), followed by the one Central American group (42%), whereas North Americans have the lowest proportion of long alleles (32%). Moreover, all American groups have more long alleles than northern and eastern Asians (i.e, Yakut, Japanese, Chinese, and Taiwanese averaged 5% long alleles). The latter societies are presumed to share common ancestors with American Indians (Chu et al. 1998). These variations across the four regions were highly significant [$\chi^2 (3, N = 2,372) = 842.90, p < .001$].

Table 1. Categories of Micro-Migration (Settlement Types)

Codes of micro-migration	Settlement types	Populations
0	Sedentary (mostly agrarian societies, some with limited pastoralism)	Yemen Jews, Falasha, Roman Jews, Ashkenazi Jews, Druze, Danes, Adygei, Sardinians, Finns, Swedes, Spanish, Mixed Europeans, South African Bantu, Han Chinese, Ami, Atayal, Japanese, Malay, Cambodians, Thoti, Kachari, Papua New Guineans, Melanesians, Samoans, Micronesians, Jemez Pueblos, Mayans, Quechuans (28 societies)
1	Nomadic (foraging, pastoralism, or slash and burn agriculture)	Biaka, Mbuti, San, Cheyenne, Muskoke, Pima, Guahibo, Karitiana, R. Surui, Ticuna, Yakut (11 societies)

Results for the other routes of migration were similar to those for the first route. Malay, Samoans, and Micronesians who migrated from Taiwan several thousand years ago showed more long alleles (especially 7-repeats) than Taiwanese aboriginal people. Nasioi Melanesians, who covered a longer distance than New Guineans, showed a higher proportion of long alleles of DRD4 than the latter, and both groups showed higher proportions of long alleles than any other groups in Asia. Taken together, East Asians had 5% long alleles, whereas Pacific Islanders had 21% [$\chi^2 (1, N = 1,706) = 65.52, p < .001$].

Similarly, Jews who had migrated a longer distance eastward to Rome and Germany also showed a higher proportion of long alleles than those who migrated a shorter distance southward to Ethiopia and Yemen [$\chi^2 (3, N = 490) = 17.85, p < .001$]. Among the four groups of Africans, Bantu who lived in South Africa was the group that had migrated a long distance from Cameroon. Bantu showed a higher proportion of long alleles [$\chi^2 (3, N = 194) = 11.40, p < .01$]. Finally, among Indo-Europeans, the Sardinians, who live geographically closest to the origin of their language family, had 0% long alleles (with a very small sample, $2n = 26$), whereas the average for other European groups was 20% [$\chi^2 (1, N = 898) = 6.37, p < .05$].

If we consider the different routes of migration (and their associated separate legs of migration, e.g., from North Asia to North America, from North America to Central America, and from Central America to South America) as independent "natural" experiments, the hypothesized relation between long alleles of DRD4 and migration has received support from all tests conducted. Moreover, when analyzed across all 39 samples to show the significance of the overall pattern, the correlations between macro-migration and DRD4 allele frequency distributions were .85 (proportion of 7-repeats) and .85 (proportion of long alleles) ($p < .001$). Figure 1 shows the association between macro-migration and proportion of long alleles across all 39 populations.

Like macro-migration, micro-migration also was associated with the long alleles of the DRD4 gene. Within each region, the societies with the lowest percentage of long alleles (e.g., Pueblos in North America and Quechuans in South America)

Table 2.   Population Macro-Migration and DRD4 Variable Number Tandem Repeat Allele Frequencies

Population	Locations[a] (long.; lat.)	Macro-migration (in k miles)	7-repeat (%)	long alleles (%)	Sample size $(2n)$[b]
(a) Migration from Northern Asia to Americas					
Jemez Pueblo (U.S.)	36N; 107W	6.5	19	25	86
Cheyenne (U.S)	35N; 99W	6.6	34	47	96
Pima (U.S.)	33N; 112W	6.7	22	25	70
Muskoke (U.S.)	33N; 84W	7.1	29	33	24
(North Americans averaged)		(6.7)	(26)	(32)	
Mayan (Yucatan)	19N; 91W	8.6	39	42	100
Guahibo (Colombia)	8N; 73W	9.9	62	77	26
R. Surui (Brazil)	11S; 62W	10.6	69	70	90
Quechuan (Peru)	12S; 77W	11.1	45	59	44
Karitiana (Brazil)	10S; 63W	11.2	60	61	108
Ticuna (Colombia)	3S; 70W	11.3	78	78	128
(South Americans averaged)		(10.8)	(63)	(69)	
(b) Migration from China					
Han (China)	—[c]	0.0	0	5	576
Atayal (Taiwan)	23N; 122E	0.8	0	4	56
Ami (Taiwan)	23N; 122E	0.8	0	6	76
Japanese	30–40N; 103–145E[d]	1.4	1	6	814
Malay	3N; 100E	4.3	17	25	24
Samoans	14S; 172W	6.6	5	5	22
Micronesians	8N; 150E	6.7[e]	3	11	52
(c) Migration from Southeast Asia					
Papua New Guineans	5S; 145E	3.0	25	25	40
Nasioi Melanesians	4S; 154E	3.6	30	34	46
(e) Migration of Jews from Israel					
Yemen Jews	16N; 44E	1.2	0	0	74
Falasha (Ethiopia)	10N; 40E	1.8	11	14	124
Roman Jews	42N; 13E	2.3	19	23	44
Ashkenazi Jews (Israel)[f]	—	2.4	17	19	248
(f) Migration of African groups					
Biaka (CAR[g])	3N; 18E	0	14	24	50
Mbuti (Zaire)	1N; 29E	0	16	17	36
San (South Africa)	30S; 20E	0.5	0	9	80
Bantu (South Africa)	30S; 20E	4.2	19	34	28
(g) Indo-European groups with migration distance estimated from probable origin of language family					
Sardinians	40N; 9E	0.5	0	0	26
Danes	55N; 9E	1.0	14	16	64
Swedes	58N; 18E	1.0	16	19	130
Spanish	40N; 3W	1.0	18	18	136
Mixed Europeans (U.S.)	—[h]	1.0	16	22	542

(*Continued*)

were traditionally sedentary, whereas the other societies in the region were nomadic. The correlations between micro-migration and DRD4 allele frequencies were .52 (proportion of 7-repeats) and .52 (proportion of long alleles) ($p < .001$).

Regression analyses further showed that both macro-migration and micro-migration were significantly related to the allele frequencies of the DRD4 gene, with macro-migration being the better predictor. It was estimated that the proportion of long alleles increased by 4.3 percentage points for each 1,000 miles of macro-migration ($\beta = .76$, $t = 8.79$, $p < .001$). In terms of micro-migration, nomadic societies

Table 2. Continued

Population	Locations[a] (long.; lat.)	Macro-migration (in k miles)	7-repeat (%)	long alleles (%)	Sample size (2n)[b]
(h) Other groups with migration distance estimated from probable origin of language family					
Kachari (Assam, India)	24–27N; 90–95E	0.6	11	11	54
Adygei	45N; 36E	0.5	12	15	104
Finns	62N; 25E	1.1	6	10	66
(i) Other groups with no known migration					
Yakut (Mongolia)	52N; 105E	0	4	8	78
Cambodians	10–15N; 102–108E	0	0	10	100
Thoti (India)	19N; 78E	0	0	0	128
Druze	32N: 35E	0	6	6	50

Notes.

[a]Most of the information on the geographical location of the groups was provided by the original studies. For the following seven groups, no geographical information was available from the original studies; thus their locations were estimated by taking the central point of their settlements: Danes, Finns, Malay, Nasioi Melanesians, Micronesians, Muskoke, and Ticuna.

[b]The sample size of alleles, i.e., 2× no. of individuals.

[c]The data for Chinese (Han) were averaged from three studies (see Table 3 for details) that collected data from Han Chinese in Mainland China, Taiwan, and the San Francisco Bay Area (Chinese immigrants). These groups came from all over China; thus, information on longitude and latitude was omitted.

[d]The data for Japanese were averaged from five studies (see Table 3 for details).

[e]This number represents the average distance of two routes of migration, one through Samoa and the other through the Caroline Islands.

[f]Data were estimated from Figure 1 of Ebstein et al. (1996). Data collected from samples in Israel that included 73% Ashkenazi Jews, 20% Sephardic Jews, and 7% others. No ethnic breakdown of the data was provided, but the authors did not find significant ethnic differences in DRD4 allele frequency.

[g]CAR = Central African Republic.

[h]Data for mixed Europeans in the U.S. were averaged from three studies (see Table 3 for details).

had on average a 10.4 percentage points higher rate of long alleles than the sedentary societies after controlling for macro-migration ($\beta = .23$, $t = 2.59$, $p < .05$). The adjusted R^2 for the regression equation was .76 [$F(2, 36) = 60.15$, $p < .001$]. The regression equation for 7-repeats was almost the same as that for long alleles.

Issue of Autocorrelation

Autocorrelation occurs when sampling units are not independent. This is a common problem with cross-cultural comparisons, because most human societies are historically linked with one another, and many groups of societies are known to have common ancestors. Cross-cultural researchers have attempted to minimize autocorrelation by stratifying samples by cultural groupings or by regions (Murdock and White 1969), but it is difficult to develop a sample of societies with no known historical linkages, and such samples will be small. Rather than drawing our sample by stratified sampling methods, we included in our sample all the available data collected by different researchers. This sample over-represents American Indian societies that are known to share a common ancestry so we must take into account the possibility of autocorrelation.

The statistical problems caused by autocorrelation have been widely misunderstood. A common misunderstanding is to think that autocorrelation causes inflation
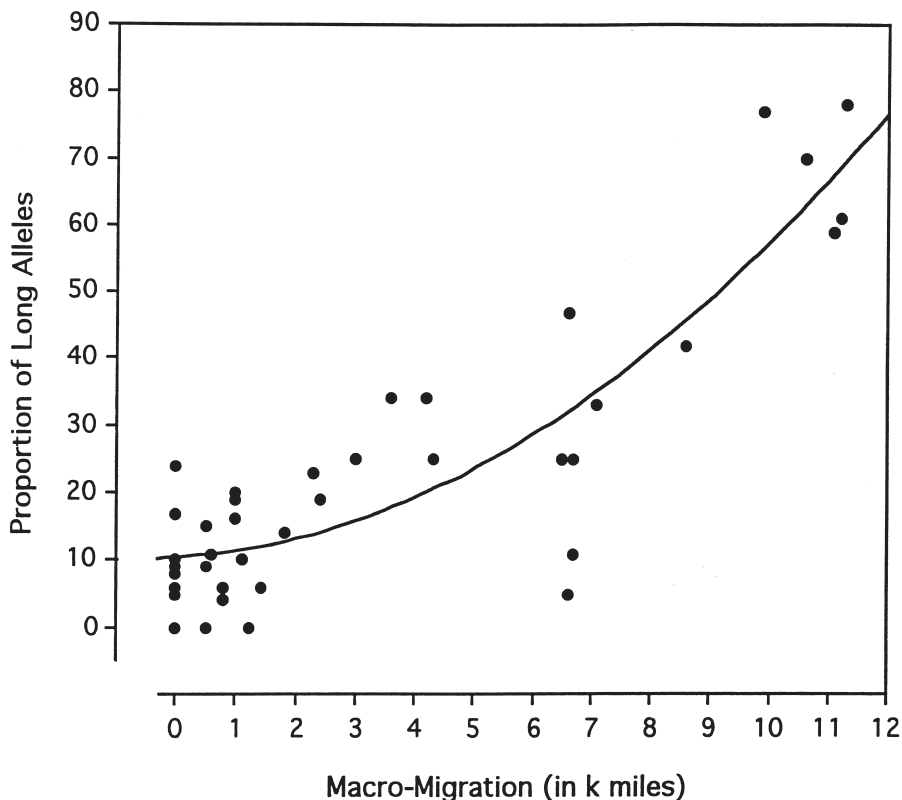
FIGURE 1.   Scatter plot of proportion of long alleles for the 39 populations by the distance of their macro-migration. A linear regression line would be: $Y = 6.54 + 4.80 * X$ ($R^2 = .73$). A quadratic function would be (shown in the figure): $Y = 10.42 + .59 * X + .41 * X^2$ ($R^2 = .78$).

of correlations. A more accurate view is that autocorrelation increases the variance in correlations and in regression beta weights in ordinary least squares (OLS) models (Dow et al. 1981). The net effect will be an excess of type I errors (i.e., faulty rejection of the null hypothesis).

Because autocorrelation manifests itself as interdependencies among error terms, one can often perceive it by looking for clusterings of residuals by region or language family. Our OLS regression residuals varied significantly by continent ($p = .025$), suggesting the presence of autocorrelation. Among the American groups, the mean of South American residuals was positive (8.8), whereas the mean of North American residuals was negative (-7.8) indicating that the autocorrelation process is not uniform across the American Indian groups, as one might have thought in view of their historical linkages. Given this pattern of residuals, we must be concerned about making type I errors.

Many analytical methods have been developed to deal with autocorrelated data of this nature. Here we use a method of network regression proposed by Krackhardt (1988). This method was designed and shown, through Monte Carlo simulations, to

overcome the problem of type I errors while at the same time not requiring trouble-some assumptions as would other analytical methods.[1]

Network regression requires us to convert the three variables to a network format. We did this by computing differences among all pairs of cases. For example, the network value for macro-migration for row 1 and column 2 in the matrix of macro-migration data would be the difference between the macro-migration value for society 1 and the macro-migration value for society 2. Readers familiar with time-series autocorrelation analysis will perceive the analogy between this approach and the method of taking first-differences between adjacent time-points.

Application of the network regression model to our data produced the *same* unstandardized coefficients as the OLS models for 7-repeats and long alleles (4.3 for macro-migration and 10.4 for micro-migration). Macro-migration remained significant at $p < .001$. However, the significance level for micro-migration dropped to .11, suggesting that the OLS model made a type I error with respect to micro-migration (which was probably a result of the small number of sedentary societies in the Americas). Hence, our main hypothesis about macro-migration remained supported, but support for the secondary hypothesis about micro-migration was weakened somewhat by the correction for autocorrelation.

Further Analysis I: Any Other Known Genes with the Same Pattern of Association with Migration?

The findings revealed a very strong association between the proportion of long alleles of the DRD4 gene in a population and its prehistorical macro-migration histories. One wonders whether a wide variety of other genes might show similarly high levels of association with migration. If so, bottleneck effects (e.g., limited gene pool for the American Indians due to the small size of the original population) could easily account for such findings. In that case, migration becomes a less plausible explanation for the association between geographical regions and allele frequencies of the DRD4 gene. Up to now only a small fraction of the 50,000 to 100,000 genes in the human genome have been studied extensively across a large number of populations. *The History and Geography of Human Genes* by Cavalli-Sforza et al. (1994) presents the best summary of such research on 128 alleles. We examined the variations of those alleles according to the different migration routes we examined in our study and found that *none* of the 128 alleles showed a consistent pattern of relation with migration. At most, two of the alleles (blood group O and haptoglobin 1) showed similar variation to that of the DRD4 gene for one or two migration routes or one leg within the first route of migration (e.g., Asians vs. North Americans).

Of course, we do not suggest that this evidence demonstrates that the long alleles of the DRD4 gene are the only genotypes associated with migration. This analysis is only meant to show that the association of the DRD4 gene and migration is not a chance finding either statistically, as shown in the previous section, or as a result of simple factors such as bottleneck effects on genes. We venture a hypothesis that at

least several other genes, most likely genes for other neurotransmitters, would be selected in the migratory societies along with long alleles of the DRD4 gene.

Further Analyses II: Determining Causal Direction

Although the analyses revealed a close association between the DRD4 gene and population migration, the causal relationship between the two is unclear. On the one hand, a higher proportion of long alleles might contribute to the exploratory behaviors of the group, and thus group migration. In other words, the ancestors of the migratory groups might have been people who migrated because of the personality and behavioral consequences of having long alleles of the DRD4 gene. If this were the case, current variations in DRD4 allele frequencies among groups might well be a result of such "founders' effects" and might have stayed the same according to the Hardy-Weinberg law. On the other hand, an equally plausible scenario is that groups migrated not because of the founding fathers' genetic makeup, but due to other causes such as war and the depletion of natural resources. The eventual differences in the allele frequencies of DRD4 between those who migrated and those who did not were a result of natural selection (or deselection) of the gene over the millennia.

An ideal way to resolve the two different perspectives would be to examine genetic data from the ancestors of current populations. For example, if we found that Asians who lived 15,000 years ago had a similarly low proportion of long alleles of DRD4 as today's Asians, whereas the first American Indians had a similarly high proportion of long alleles as today's American Indians, the founders' effect hypothesis would appear to be supported. On the other hand, if the early American Indians had a similar proportion of long alleles as Asians 15,000 years ago, then the natural selection hypothesis would be supported.

Such a direct test of the two competing hypotheses is, however, obviously not possible until we can extract population genetic information for a large enough sample of ancestors from several populations and from different time periods. An indirect test is to examine the relation between the DRD4 gene and modern-day migration, with the caution that the environments associated with modern-day migration are different from those that existed during prehistoric migration. If the long alleles of the DRD4 gene had been responsible for initiating migration (rather than a result of adapting to migratory lifestyles), we should be able to detect a difference in the allele frequencies of that gene between modern-day immigrants and their counterparts in their home country.

Among the data compiled for this study, we have genetic data on several groups of Chinese, Japanese, and Europeans who resided in the U.S. (Chinese and Japanese immigrants and offspring of European immigrants) and comparable groups who remained in their home countries. As shown in Table 3, there is little evidence for the "founders' effects" hypothesis. The rate of long alleles of DRD4 is about the same for immigrants as for their respective comparison groups in the home country. These results suggest that the increased rate of long alleles among migratory groups may have been a result of adaptation to the particular demands of migration.

Table 3.   Comparisons of Immigrant Groups with Groups in their Home Countries

	Percentage of 7-repeat	Percentage of long alleles	Sample size (2n)
Japanese			
Japanese in Japan (summary)	1	6	712
Study 1 (Nanko et al. 1993)	1	7	162
Study 2 (Inoue et al. 1993)	0	6	104
Study 3 (Ono et al. 1997)	0	6	306
Study 4 (Tanaka et al. 1995)	1	5	140
Japanese in the U.S.			
(Chang et al. 1996)	0	4	102
Han Chinese			
Han Chinese in China			
(Li et al. 1997)	0	4	308
Han Chinese in Taiwan (summary)	0	8	170
Study 1 (Hong et al. 1997)	0	7	86
Study 2 (Chang et al. 1996)	0	9	84
Han Chinese in the U.S.			
(Chang et al. 1996)	0	2	98
Europeans			
Europeans in Europe (from Table 1)			
Danes	14	16	64
Swedes	16	19	130
Finns	6	10	66
Spanish	18	18	136
Europeans in the U.S. (summary)	16	22	542
Study 1 (Chang et al. 1996)	21	25	176
Study 2 (Gelernter et al. 1997)	18	26	66
Study 3 (Petronis et al. 1992)	12	19	300

This conclusion is, of course, extremely tentative given the vast amounts of differences between modern-day and prehistorical migration. This piece of evidence aside, however, the natural selection/deselection hypothesis appears to better account for several phenomena found in the data. First, as evidenced by the excellent fit between the data and the multiple regression model, the almost linear increase of long alleles of DRD4 with distance of migration across several different migration routes certainly points to the possibility of natural selection. Founders' effects should have resulted in more abrupt changes in allele frequencies. There is no inherent reason to expect that the "founders" were chosen to have a systematic change of only 4% to 5% long alleles for every 1,000 miles of macro-migration.

Second, compared to the founders' effect hypothesis, the natural selection/deselection hypothesis provides a more coherent explanation for the low proportion of long alleles of DRD4 among the sedentary groups. There were no apparent historical connections among various populations around the world that had low proportions of long alleles, e.g., East Asians, Yemenite Jews, Druze, Finns, and Sardinians. The only common mechanism appears to be the fact that all of these groups have remained in their current location for thousands of years, although all of them must have been migratory at some point. For instance, modern human beings arrived in Asia about 60,000 years ago. We speculate that having been foragers for a

very long time, they had a relatively high proportion of long alleles of DRD4. However, beginning from 10,000 to 15,000 years ago, these groups had more stable settlements and began rudimentary agriculture. Since then, the long alleles of the gene may have experienced the process of deselection.

Deselection also would explain the effects of micro-migration (sedentary vs. migratory settlements) on DRD4. Jemez Pueblos and Quechuans had covered a similar distance of macro-migration as their neighboring groups, but showed a lower proportion of long alleles of DRD4. We speculate that Jemez Pueblos and Quechuans may have had similar levels of long alleles as their neighboring groups at the time of their settlement. Their sedentary lifestyles, however, might have contributed to the deselection of the long alleles of the DRD4 gene over the millennia.

DISCUSSION

Given the common origin of human beings, genetic variations among groups mainly result from spontaneous mutation, founders' effects, and natural selection. The systematic and strong association between migration and the allele frequencies of the DRD4 gene has ruled out proposals about spontaneous mutation or genetic drift (Chang et al. 1996). We also provided indirect evidence that founders' effects cannot adequately account for the global variations in the DRD4 gene. Taken together with all evidence, this study tends to favor the natural selection/deselection hypothesis.

We speculate that the long alleles of the DRD4 gene were selected by migration because they had adaptive value in migratory societies. As previous research has shown, long alleles (e.g., 7-repeats) of the DRD4 gene have been linked to novelty-seeking personality, hyperactivity, and risk-taking behaviors (Benjamin et al. 1996; Castro et al. 1997; Ebstein et al. 1996, 1997; Hamer 1997; LaHoste et al. 1996; Ono et al. 1997; Smalley et al. 1998; Swanson et al. 1998). The commonality among these behaviors appears to be the exploratory aspect of human nature. It can be argued reasonably that exploratory behaviors are adaptive in migratory societies because they allowed for more successful exploitation of resources in the particular environment migration entails—usually harsh, frequently changing, and always providing a multitude of novel stimuli and ongoing challenges to survival.

Conversely, sedentary populations obtain resources not by exploring new environments but by developing intensive methods for using limited amounts of land (Netting 1993). Within these societies, novelty-seeking and exploratory behaviors would have serious social costs and would be selected against. Therefore, the fit between the behavioral consequences of long alleles of DRD4 in migratory societies ensures the selection of that gene and the lack of fit in sedentary societies ensures the deselection of that gene.

The findings of this study also raise the possibility that some contemporary disorders, such as ADHD, which has been linked to long alleles of the DRD4 gene, may have been a by-product of human adaptation to the migration process. The once-adaptive components of those disorders (e.g., high level of activity, attention diversion) become problematic in highly structured modern societies. This specula-

tion is consistent with recent arguments on the adaptability of ADHD in particular environments (Jensen et al. 1997).

The arguments and conclusions of the present study need to be further tested with additional empirical evidence. For example, if data from Madagascar populations, aboriginal Australians, and Polynesians (all of whom have experienced significant macro-migration) were to show a high rate of long alleles of DRD4, they would be consistent with our hypothesis that migration selects the long alleles. Further research on the link between migration and the DRD4 gene also could be conducted with nonhuman primates who have been found to show polymorphism of DRD4 (Livak et al. 1995).

ENDNOTE

1. Autocorrelated data are a common problem in many areas of research. In dealing with the data from interrelated human societies, evolutionary biologists and biological anthropologists have mostly used phylogenetic methods (Holden and Mace 1997; Huelsenbeck and Rannala 1997; Mace and Pagel 1994). Cultural anthropologists have adopted a more general approach that deals with not only phylogenetic relations, but also other kinds of cultural relations. For example, Dow et al. (1981) proposed a network model of the autocorrelation process based on regression models for spatial autocorrelation analysis (Doreian 1980; Ord 1975). Compared to the spatial autocorrelation model, the more general network autocorrelation model has the distinct advantage that it can index the nonphylogenetic historical linkages among societies that are not spatially proximal (e.g., England and the New Zealand Maori). Therefore, the network model is a general method that allows for a variety of kinds of relationships among sampling units, including spatial, cultural, and phylogenetic relationships. This model has been tested with cross-cultural data (Burton and White 1984; White et al. 1981).

Nevertheless, the network model of Dow et al. and all phylogenetic methods require that one specify, or assume, which process caused autocorrelation (e.g., phylogenetic relations or diffusion through political and economic contact). Given the multiple possibilities for gene exchanges among populations and the role of historical processes such as political and economic systems in the diffusion of human traits, it often is difficult to specify the process or processes that cause the autocorrelation. As suggested by this study, migration might be a causal agent in population variations of genes. Therefore, we need a newer method that does not require one to make specific assumptions about the particular causes of linkages or commonalities among societies.

Krackhardt (1988) recently proposed a newer network regression model based on a variant of the quadratic assignment procedure (Hubert and Schultz 1976; Mantel 1967), a standard approach in dealing with bivariate analysis in biological anthropology (Barbujani et al. 1996; Relethford and Crawford 1995). Krackhardt's network regression extends the bivariate approach to allow for a multivariate regression model. Like the quadratic assignment procedure, Krackhardt's network regression uses a permutation test that is more appropriate for our kind of sample than are most standard statistical models.

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