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Haplotype and Allele Frequencies for Three Genes of the Dopaminergic System in South American Indians

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ABSTRACT Haplotype and allele frequencies for the dopamine D2 receptor gene (DRD2), dopamine D4 receptor gene (DRD4), and dopamine transporter protein gene (SLC6A3) were determined in 135 individuals from five Brazilian Indian tribes, and the results integrated with those previously presented for this ethnic group. DRD2 and DRD4 were highly polymorphic. Haplotypes including TaqI A1 at DRD2, and the seven repeat allele at DRD4 were the most frequent variants, while the SLC6A3 locus was monomorphic for the 10 repeat allele in South American Indians. Genetic distances and the corresponding neighbor-joining tree indicated a geographic dichotomy between North + Central American and South American natives, with the exception of the Wai Wai, who live north of the Amazon river and are grouped in the northern cluster. G_{ST} estimates from these genes vary between 0.05 and 0.11 for North and South America, respectively, indicating a higher degree of differentiation of the latter groups. These results are in accordance with previous genetic data on other systems, as well as with the history and biodemographical data of South American Indians. Am. J. Hum. Biol. 12:638–645, 2000. © 2000 Wiley-Liss, Inc.

The human dopaminergic system is a very important focus of study in the fields of neuropsychiatry and pharmacology. Therefore, genes involved in dopaminergic transmission and metabolism have often been employed as candidate genes in association studies in an effort to identify genotype–phenotype relationships in neuropsychiatric disorders (Comings et al., 1991; Seeman, 1995; Inada et al., 1996).

The five known human dopamine receptors can be divided into two major subgroups (DRD1 and DRD5 vs. DRD2, DRD3, and DRD4) based on nucleotide sequence homology, genome organization, signal transduction, and tissue distribution (Seeman and Van Tol, 1994). The DRD2 receptor gene has been studied most extensively because it is a site of action of neuroleptic drugs and it is believed to be involved in the pathophysiology of various neuropsychiatric diseases, mainly alcoholism and addictive behaviors. Indeed, positive associations have been reported between the presence of several DRD2 alleles and diseases (Comings et al., 1991; Seeman and Van Tol, 1994; Seeman, 1995; Inada et al., 1996; Noble, 1998).

The dopamine D4 receptor is in the same class as the D2 receptor, but presents different pharmacological properties. The DRD4 receptor gene has an expressed 48 bp variable number of tandem repeats (VNTR) in the putative third cytoplasmic loop (Van Tol

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et al., 1992). The seven repeat allele has been associated with a variety of conditions characterized by impulsivity and/or hyperactivity tendencies (Rowe et al., 1998; Swanson et al., 1998), as well as with the personality trait of novelty-seeking (Benjamin et al., 1996; Ebstein et al., 1996) and harm-avoidance (Bau et al., 1999).

The dopamine transporter protein (DAT1) is responsible for taking released dopamine back up into presynaptic terminals and extinguishing dopaminergic activity (Parsian and Zhang, 1997). The dopamine transporter protein is encoded by the SLC6A3 locus which contains a VNTR in its 3′ untranslated region (Vandenbergh et al., 1992). Alleles of this VNTR are associated with cocaine-induced paranoia (Gelernter et al., 1994), attention-deficit hyperactivity disorder (Cook et al., 1995; Waldman et al., 1998), and the presence of alcohol withdrawal seizures or delirium (Sander et al., 1997).

The diversity of these three systems has recently been investigated on a global sample of 28, 36, and 8 populations, respectively, for DRD2, DRD4, and SLC6A3 (Chang et al., 1996; Gelernter et al., 1998; Kidd et al., 1998), including three Brazilian Indian groups for the first two markers and one for SLC6A3. Considering that surviving Native Americans exhibit remarkable cultural, linguistic, and biological diversity, the aims of this article are to extend this information to five more Brazilian Indian tribes, to disclose the full diversity of these markers in South American natives, and to integrate the results with those already available to verify the relationships among North, Central, and South American Indians.

SUBJECTS AND METHODS

The Brazilian Indian samples were collected in the period 1988–1990, and consisted of 135 individuals from the Suruí (22), Gavião (29), and Zoró (28), Tupi language speakers, Wai Wai (28, Carib), and Xavante (25, Ge) tribes. Additional linguistic, historical, demographic, and genetic information about these populations has been reported previously (Rodrigues, 1986; Greenberg, 1987; Coimbra, 1989; Santos, 1991; Santos and Coimbra, 1996; Callegari-Jacques et al., 1996; Salzano et al., 1997, 1998).

DNA from the blood samples was extracted by the salting out procedure described by Miller et al. (1988). Four DRD2 markers were typed by PCR-based methods, three TaqI RFLPs and a CA dinucleotide short tandem repeat polymorphism (STRP) in intron 2. The TaqI A RFLP was typed using primers and amplification protocols as described by Grandy et al. (1993); the TaqI B site and STRP with the methods described by Castiglione et al. (1995); and the TaqI D RFLP according to Kidd et al. (1996).

After amplification, the three TaqI RFLPs were digested with TaqI restriction enzyme at the manufacturer's recommended conditions. Subsequently the digestion fragments were electrophoresed in 2% agarose gels containing ethidium bromide. The STRP alleles were identified after electrophoresis as described previously (Lu et al., 1996).

The DRD4 region containing the exon 3 VNTR was amplified by PCR and the genotypes identified as previously described (Roman et al., 1999), while the 3′ untranslated region VNTR of the SLC6A3 locus was amplified with primers and protocols reported in Sano et al. (1993). Genotypes were obtained by size resolution of the alleles in 5% polyacrylamide gels.

Allele frequencies at the individual loci were estimated by counting. Hardy-Wein berg equilibrium (HWE) was tested using a χ^2 goodness-of-fit test when the observed and expected numbers in all cells were large enough to meet validity requirements, and otherwise an exact test was employed (Gou and Thompson, 1992) using the GENEPOP program (Raymond and Rousset, 1995). For DRD2, maximum likelihood estimates of haplotype frequencies were calculated from the multisite marker data using the Arlequin ver. 1.1 program (Schneider et al., 1997). Heterozygosities were obtained according to Nei (1987), the genetic distance matrix was calculated using the D_A distance (Nei et al., 1983; Nei and Roychoudhury, 1993) and the phylogenetic tree was constructed by the neighbor-joining method (Saitou and Nei, 1987). All these estimations were performed using the NJBAFD program (Takezaki, 1999).

RESULTS AND DISCUSSION

Haplotypes at the DRD2 locus identified in Brazilian Indians are listed in Table 1, together with those observed in other Native Americans (Kidd et al., 1998). Two samples of Suruí have been investigated,

TABLE 1. DRD2 haplotype frequencies in Native American populations

	Haplotypes																			
Population	B1 D2 17 A1	B1 D2 16 A1	B1 D2 15 A1	B1 D2 14 A1	B1 D2 12 A1	B1 D2 16 A2	B1 D2 14 A2	B2 D1 15 A1	B2 D1 16 A2	B2 D1 15 A2	B2 D1 14 A2	B2 D1 13 A2	B2 D2 14 A1	B2 D2 13 A1	B2 D2 16 A2	B2 D2 15 A2	B2 D2 14 A2	B2 D2 13 A2[a]	Others	2n[a]
North America																				
Cheyenne[b]	0.098	0.607	0.020	0.011	0	0	0	0	0	0.041	0	0	0	0	0	0	0.156	0.010	0.057	114
J. Pueblo[b]	0	0.670	0	0	0	0.023	0	0	0	0	0	0	0	0	0	0	0.205	0.102	0	88
Pima (AZ)[b]	0	0.605	0	0	0	0	0	0	0	0	0	0	0	0	0	0.016	0.262	0.082	0.035	86
Maya[b]	0.047	0.504	0.010	0.087	0.021	0.013	0.012	0	0.018	0	0	0	0.011	0	0.069	0	0.142	0.040	0.026	100
South America																				
Ticuna[b]	0	0.416	0	0	0	0.016	0	0.070	0	0.018	0.042	0.022	0.010	0.010	0.006	0	0.309	0.018	0.063	134
Karitiana[b]	0	0.595	0	0	0	0	0.028	0	0	0	0	0	0	0	0	0	0.377	0	0	106
Suruí I[b]	0	0.531	0.011	0.011	0	0	0.066	0	0.022	0	0	0	0	0	0.012	0	0.268	0.035	0.044	92
Suruí II[c]	0	0.820	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.140	0.040	0	44
Zoró[c]	0	0.200	0	0	0	0	0	0	0	0	0	0	0	0	0.280	0.040	0.360	0.120	0	56
Xavante[c]	0	0.840	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.160	0	0	56
Gavião[c]	0	0.470	0	0	0	0	0	0	0	0	0.020	0	0	0	0.160	0	0.210	0.090	0.050	58
Wai Wai[c]	0	0.610	0	0	0	0	0	0	0	0.040	0	0	0	0	0.070	0	0.150	0.110	0.020	54

[a]Number of chromosomes studied.
[b]Kidd et al., 1998.
[c]Present investigation.

TABLE 2. DRD4 allele frequencies in Native Americans

Populations	Alleles							2n[a]
	DRD4.2	DRD4.3	DRD4.4	DRD4.5	DRD4.6	DRD4.7	DRD4.8	
North America								
Muskoke[b]	0.04	0.09	0.54	0.04	0	0.29	0	24
Jemez Pueblo[b]	0.04	0.01	0.70	0.02	0.03	0.19	0.01	86
Cheyenne[b]	0.01	0	0.52	0.02	0.11	0.34	0	96
Pima[b]	0.01	0	0.74	0.03	0	0.22	0	70
Maya[b]	0.01	0	0.57	0	0.03	0.39	0	100
South America								
Quechua[b]	0	0	0.41	0	0.14	0.45	0	44
Colombians[b]	0	0	0.23	0	0.15	0.62	0	26
Karitiana[b]	0	0	0.39	0	0	0.60	0.01	108
Ticuna[b]	0.02	0	0.20	0	0	0.78	0	128
Surui I[b]	0.14	0	0.16	0.01	0	0.69	0	90
Suruí II[c]	0.11	0	0.14	0.02	0	0.73	0	44
Wai Wai[c]	0.02	0	0.52	0.05	0.18	0.23	0	56
Xavante[c]	0	0	0.32	0.04	0.04	0.43	0.18	56
Gavião[c]	0.03	0	0.28	0	0	0.69	0	58
Zoró[c]	0	0	0.36	0	0	0.64	0	56

[a]Number of chromosomes studied.
[b]Chang et al., 1996.
[c]Present investigation.

TABLE 3. Variability observed in the DRD2 and DRD4 genes of Native Americans

Populations	Heterozygosity			Number of haplotypes or alleles observed		Number of haplotypes or alleles with frequency >5%	
	DRD2	DRD4	Both loci	DRD2	DRD4	DRD2	DRD4
Cheyenne	0.60	0.61	0.60	10	5	3	3
Jemez Pueblo	0.50	0.47	0.49	4	7	3	2
Pima	0.56	0.41	0.49	5	4	3	2
Maya	0.71	0.53	0.62	14	4	4	2
Ticuna	0.72	0.35	0.54	15	3	3	2
Karitiana	0.50	0.49	0.50	3	3	2	2
Suruí I	0.64	0.48	0.56	11	4	3	3
Suruí II	0.31	0.44	0.38	3	4	2	3
Zoró	0.75	0.47	0.61	5	2	4	2
Xavante	0.27	0.70	0.48	2	5	2	3
Gavião	0.71	0.45	0.58	6	3	5	2
Wai Wai	0.60	0.65	0.62	6	5	4	3

*TABLE 4. Genetic distances (×1,000) based on the DRD2 and DRD4 loci in Native Americans**

	1	2	3	4	5	6	7	8	9	10	11
2	98										
3	95	36									
4	75	107	108								
5	163	186	158	158							
6	127	110	93	124	99						
7	154	162	144	120	95	92					
8	153	127	133	164	106	88	56				
9	240	201	165	148	158	146	168	197			
10	124	104	129	166	181	75	170	113	246		
11	170	148	142	109	104	108	87	91	60	175	
12	89	67	101	107	212	169	178	162	174	141	139

*Populations: 1. Cheyenne; 2. Jemez Pueblo; 3. Pima; 4. Maya; 5. Ticuna; 6. Karitiana; 7. Suruí I; 8. Suruí II; 9. Zoró; 10. Xavante; 11. Gavião; 12. Wai Wai.

one derived from a lymphoblastoid cell line (Suruí I) (Kidd et al., 1998), while Suruí II (present study) was collected independently; some individuals, however, could have been represented in both samples.

Only two haplotypes (B1D216A1 and B2D214A2) where shared by all Native Americans. The third most common haplotype (B2D213A2) was absent in the Karitiana and Xavante tribes only. These haplo-

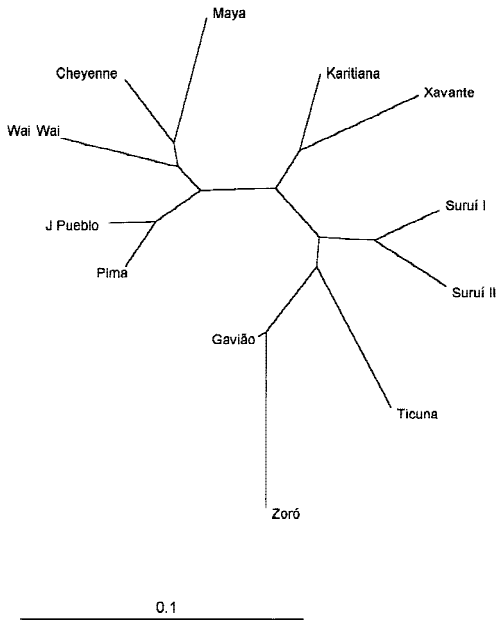

Fig. 1. Unrooted tree obtained for 11 Native American tribes, considering the DRD2 and DRD4 loci.

types account for 100% (Xavante) to 68% (Zoró and Maya) of all chromosomes in Native Americans. They are also the most frequent in Asians, with whom they probably share more recent common ancestors. In Asian populations these three haplotypes account for 92% to 66% of the chromosomes investigated (Kidd et al., 1998).

A fourth haplotype (B2D216A2), which was absent or has low frequencies in most Native American populations (Table 1), was detected in 28% of the Zoró chromosomes, being the second most common haplotype, while in the Gavião, another Tupi-Mondé tribe, it is the third most frequent (16%). The genetic similarity of these two populations had been observed at several other nuclear DNA markers (Hutz et al., 1999), and they also share a large number of mtDNA lineages (Ward et al., 1996). This is not unexpected, since they speak similar languages, have many cultural traits in common, live in relatively close geographical proximity, and intertribal marriages have been observed among them (Salzano et al., 1998).

Table 2 shows the allele frequencies of the DRD4 48 bp repeat VNTR in Native Americans. The four and seven repeat alleles are the most prevalent and are shared by all Native Americans, but their relative frequencies vary when they are separated according to geographical distribution. In North and Central America, the four repeat allele is more frequent, while in South America the seven repeat allele is the most common, the exception being the Wai Wai, who have an allele distribution closer to that observed in northern populations.

In contrast to New World populations, the seven repeat allele is quite rare in Asia (Chang et al., 1996). This finding is similar to that observed with mtDNA. The scarcity of New World founding mtDNA haplogroups in Asian populations has been used as evidence against multiple colonizing migrations from different source populations (Merriwether et al., 1995). Although the number of Asian and Amerindian populations investigated for DRD4 is much less than those studied for mtDNA, the results reviewed here could be considered as another evidence to support the hypothesis of a single founding migration to the New World (Bonatto and Salzano, 1997).

No variation was observed for the 3′ untranslated VNTR at the SLC6A3 locus. The 10 repeat allele was detected in all individuals from the five populations investigated. In another study the Suruí were also found to be monomorphic for this allele. In the Maya, however, the 9 and 11 repeat alleles were observed in 6% and 1% of the chromosomes, respectively (Gelernter et al., 1998). Their presence there could be due to admixture with non-Indians, or could also reflect differences in North and Central Native Americans in relation to southern populations.

Heterozygosity for DRD2 and DRD4 separately, and for both loci, is shown in Table 3. This table also presents the total number of DRD2 haplotypes and DRD4 alleles identified in each population. The differences among tribes are not large and did not show marked tendencies.

To further evaluate the differences observed in gene frequencies, genetic distances were estimated (Table 4) and a dendrogram constructed based on them (Fig. 1). Brazilian Indians, except the Wai Wai, formed one cluster, while the Central and Northern Native Americans with the Wai Wai formed another group. This tribe is the only one among the South American Indians studied here that live north of the Ama-

TABLE 5. Gene diversity estimates among sets of populations

Clustering level	Number of populations	Total heterozygosity	Interpopulation diversity	G_{ST}	G_{ST}'
I. North + Central Americans	4	0.56	0.02	0.03	0.05
II. South Americans	8	0.58	0.05	0.10	0.11
III. All populations	12	0.60	0.07	0.11	0.12

zon river. The average genetic distances between these northern populations is 0.088, while the estimate for the tribes living south of the Amazon region is 0.132. The average genetic distance of the Wai Wai in relation to the other Brazilian groups is 0.168. This geographic dichotomy was also observed in a larger number of tribes considering protein polymorphisms by Salzano et al. (1991) and Callegari-Jacques et al. (1994). The present results, therefore, corroborate the hypothesis that the Amazon river would constitute a barrier to north–south gene flow or that the differences may reflect past migrations into the continent.

Table 5 shows several estimates of gene diversity. The G_{ST}', which considers the number of populations examined (Livishits and Nei, 1990) is relatively high in South American Indians, indicating substantial genetic isolation among them. The population structure of these groups and the fission–fusion processes which occurs within a tribe (Salzano and Callegari-Jacques, 1988) suggest that the variability observed in South America is probably related to "in situ" differentiation.

Since the three genes investigated in the present study are expressed in the brain and have been associated with the risk for psychiatric illness, the variability observed may be related to selective pressures. Jensen et al. (1997) proposed a hypothesis in which impulsivity and hyperactivity, depending on the nature of the environment, could be potentially adaptive in hunter–gatherer societies. Although still controversial, alleles DRD2 TaqI A1, DRD4.7, and SLC6A3 10, the most frequent in Amerindians, are those most commonly associated with these characteristics (Comings et al., 1991; Cook et al., 1995; Noble, 1998; Rowe et al., 1998; Swanson et al., 1998; Waldman et al., 1998). Our findings, therefore, may also provide some insight into complex issues of behavioral adaptation.

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