Distribution of the 3′ VNTR Polymorphism in the Human Dopamine Transporter Gene in World Populations

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Abstract A polymorphism with a variable number of tandem repeats (VNTR) found in the 3′ untranslated region of the human dopamine transporter gene (*DAT1*) was scored in unrelated individuals drawn from 10 geographically widely dispersed populations in order to assess this marker's usefulness in human population genetics. The populations that were analyzed in this study included 4 indigenous groups of Siberia, natives of North and South America, as well as Caucasian and Oceanic groups, most of which represented small-scale societies. A total of 5 *DAT1* alleles were seen overall, but only in one Siberian population, the Altai-Kizhi, were all 5 present, and in the Native Americans of Colombia the locus was monomorphic. The most common allele, *DAT1*10*, ranged in frequency from 52% in Greeks to 100% in South Americans. The high frequency of the *DAT1*10* allele (~90%) among Mongoloid groups of north and east Asia distinguishes them from most Caucasian groups. The presence of the rare *DAT1*7* allele in relatively high frequency (~5%) among all Siberian groups suggests a close affinity with north Asian groups, especially Mongolians. The presence of the even rarer *DAT1*13* allele in one Siberian population, the Altai-Kizhi, reflects this group's long historical contact with Mongolians. The results demonstrated that the *DAT1* VNTR polymorphism is useful in investigating population relationships, and that rare alleles at this locus may be particularly valuable in understanding the extent of genetic affinity between neighboring groups and in situations where admixture is suspected. However, because of both the association and linkage of this VNTR locus with attention-

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deficit hyperactivity disorder (ADHD) in children, and its highly restricted polymorphism (usually 3 alleles) in most human groups, the possibility of selection constraints on the *DAT1* gene cannot be ignored.

The human dopamine transporter (*DAT1*) gene, located on chromosome 5p15.3 (Vandenbergh et al. 1992a; Giros et al. 1992) regulates the re-uptake of released dopamine back into presynaptic terminals after its synaptic release. Because of this function the *DAT1* gene has been suggested to play a role in a number of neurological and psychiatric disorders, as well as substance abuse (Ritz et al. 1987; Uhl 1990; Singer et al. 1991). To date, the *DAT1* locus has been employed chiefly in either association or linkage studies of particular behavioral disorders. Cook et al. (1995) reported an association between *DAT1* and attention-deficit hyperactivity disorder (ADHD)/undifferentiated attention-deficit disorder, and this finding was confirmed by Gill et al. (1997). More recently, Waldman et al. (1998), in a large study comprising 122 US schoolchildren and their families, further demonstrated clear association and linkage between the *DAT1* gene and ADHD. These studies represent one of the first replications of an association between a gene and a psychiatric illness in children. Other researchers have found no association between this locus and schizophrenia (Byerley et al. 1993; Li et al. 1994; Persico et al. 1995).

Analysis of the *DAT1* gene revealed a variable number of tandem repeats (VNTR) in the 3′ untranslated region, with the core sequence being ~40 bp in size (Vandenbergh et al. 1992a; Giros et al. 1992). Of those observed to date, the number of repeats (equivalent to alleles) ranged from 3 (~200 bp) to 13 (~600 bp) copies, but most of the alleles, especially those with low repeat units, were very rare (Vandenbergh et al. 1992b). Very few studies have examined the distribution of this polymorphism to determine its usefulness in human population genetics (Nakatome et al. 1995, 1996). The association and/or linkage studies that have been conducted concentrated on either major population groups, such as US Caucasians (Byerley et al. 1993) and Chinese (Li et al. 1994), or, even more confusingly, on 'mixed samples' of ethnically distinct groups, such as African Americans and US whites (Vandenbergh et al. 1992b) or African Americans, US whites, and US Hispanics (Cook et al. 1995). Accordingly, no clear inferences can be made on the pattern of *DAT1* allele distributions in human populations, though data suggest lower heterozygosity levels in Asian groups than in a 'mixed' population of the US (Nakatome et al. 1996). Also, alleles not found in Asian groups (*DAT1*3* and *DAT1*5*) were present in the US 'mixed' sample. Nakatome et al. (1996) found a significant difference between a US mixed population (Vandenbergh et al. 1992b) and their Mongolian sample. In an earlier study of Japanese, Nakatome et al. (1995) reported a significant excess of homozygous genotypes, especially for the *DAT1*7* allele.

Many VNTRs have a large number of alleles (hence their attraction to forensic science and paternity testing centers), but it has been increasingly

recognized that tandem repeat loci with high variances are proving somewhat equivocal in human evolutionary studies (Jorde et al. 1997). The *DAT1* VNTR locus differs from many VNTR loci in that it has a small number of common alleles (two or three) detected by a standard polymerase chain reaction (PCR) protocol. This study presents data on the distribution of the *DAT1* VNTR polymorphism in 10 populations drawn from Europe, Africa, Asia, the Americas, and Australia, in order to measure its usefulness in human population genetics.

Materials and Methods

Subjects. The populations sampled ranged from small hunter-foraging groups to peasant and urban societies, and comprised representatives from all the inhabited continents. Four ethnic Central Siberian populations were sampled for this study: the Altai-Kizhi, Evenki, Ket, and Sel'kups. The Altai-Kizhi ($n = 49$), who are pastoralists, were all from the village of Mendor-Sokkon, near the Katun River, in the Altai mountains. The Evenki ($n = 61$), who hunt and herd reindeer, were from the villages of Poligus and Surinda on the Stony Tunguska river, a tributary of the Yenisey River. The Ket ($n = 16$), who speak a unique language with no known phylum affiliation, were all from the village of Sulamai, which lies at the juncture of the Yenisey and Stony Tunguska rivers. The Sel'kup ($n = 29$) were from 5 different villages: Farkovo, Rechka, Krasnoselkup, Ratta, and Tolka Pur. The Greeks ($n = 21$) lived in Melbourne, Australia, but were born in Greece, Cyprus, Crete, or Egypt. The Chuvash ($n = 33$) were from villages located near the towns of Ceboksary and Zel'onodol'sk, approximately 600 km east of Moscow. Two Native American populations were also included in this study. Those ($n = 19$) from the United States were mainly from Colorado and Arizona and included Na-Dene and Amerind speakers. Those ($n = 27$) from Colombia were from 3 tribal groups; the Coreguaje, who inhabit the Amazon region and belong to the Macro-Tukano linguistic group, and the Arsario and Kogui, who inhabit the region of Sierra Nevada de Santa Marta in the northeast, and belong to Macro-Chibcha linguistic stock. One Oceanic population was also included: the Yolngu ($n = 18$) are Australian Aborigines from northeast Arnhem Land in the Northern Territory. A small ($n = 10$) sample from North Africa was also included, comprising individuals from Mauritania, Algeria, Tunisia, and Morocco.

Methods. Amplification was carried out in a Perkin Elmer Gene-Amp PCR System 2400 Thermocycler. Each 50 μl reaction contained; 1 μl DNA, 1 U Taq polymerase (Perkin Elmer), 1 μl each primer (0.01 μg/μl), 1 μl each dNTP (10 mM), 5 μl 10 $\times$ PCR Reaction Buffer I, 1 μl BSA (1/10 dilution) and 35.5 μl H_2O. T4 (Boehringer Mannheim) was used instead of BSA on

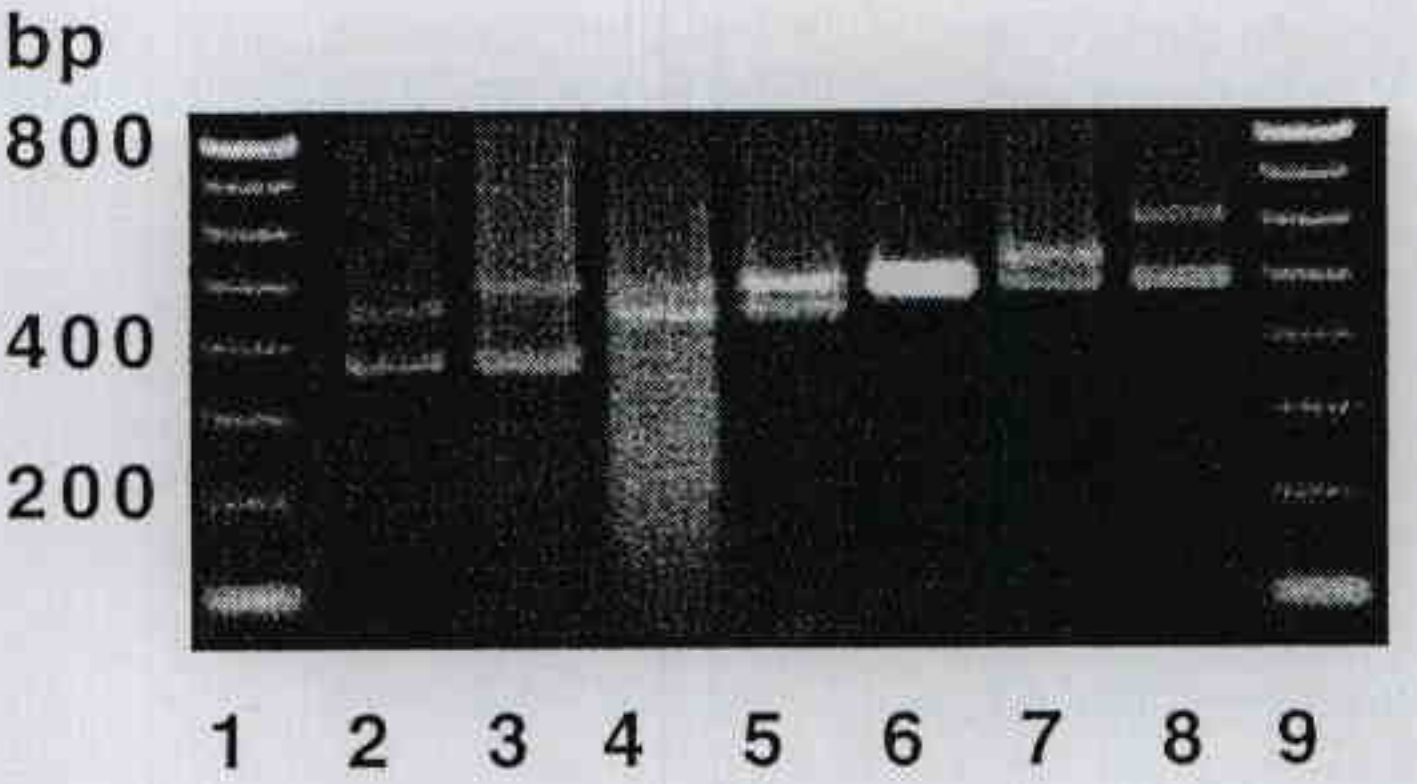

Figure 1. Agarose gel electrophoresis of DAT1 phenotypes. Lanes 1 and 9 = 100 bp marker; lane 2 = phenotype 7/9; lane 3 = 7/10; lane 4 = 9/9; lane 5 = 9/10; lane 6 = 10/10; lane 7 = 10/11; lane 8 = 10/13.

some occasions. The primers were those of Vandenbergh et al. (1992b): 5′-TGTGGTGTAGGGAACGGCCTGAG-3′ and 5′-CTTCCTGGAGGT-CACGGCTCAAGG-3′.

The program consisted of an initial denaturation of 3 min at 93°C, followed by 30 cycles of: 93°C for 1 min, 65°C for 1 min, and 72°C for 1 min, then 72°C for 5 min in a final extension. Then, 15 μl aliquots of the PCR product plus 2 μl of stop buffer were electrophoresed in a 2% agarose gel at 70 V, 70 mA for 3 hours, followed by staining with ethidium bromide and visualization under ultraviolet light. The size marker used was a 100-bp ladder (Pharmacia Biotech).

Results

Amplified products representing several of the *DAT1* alleles and genotypes scored in the present study are shown in Figure 1. Among all 10 population samples scored, a total of 5 *DAT1* alleles were identified; *DAT1*7* (360 bp), **9* (440 bp), **10* (480 bp), **11* (520 bp), and **13* (600 bp). Allele *DAT1*10* was predominant, ranging from a low of 52% in Greeks to fixation in native Colombians (Table 1). Only one population, the Altai-Kizhi, exhibited all 5 alleles; the Evenki had 4; most samples had 3; Australian aboriginals had 2; and native Americans had either 2 (USA) or 1 (Colombians). All populations shown in Table 1 had *DAT1* genotypes in Hardy-Weinberg proportions, except for the Evenki ($p < 0.001$), in which there was a marked excess of homozygotes, in particular genotype *11/11*. Heterozygosity values for the 10 populations investigated in the present study, together with those scored previously for the *DAT1* polymorphism, are shown in Table 2. All the

Table 1. Distribution of Alleles at the *DAT1* VNTR Locus in 10 Populations

Population	*Number Tested*	*DAT1 Allele Frequency*						
		*7	*8	*9	*10	*11	*12	*13
Greeks	21	—	—	0.381	0.524	0.095	—	—
Chuvash, Russia	33	—	—	0.106	0.879	0.015	—	—
Evenki	61	0.057	—	0.033	0.787	0.123	—	—
Ket	16	0.031	—	0.031	0.938	—	—	—
Sel'kup	29	0.086	—	0.207	0.707	—	—	—
Altai-Kizhi	48	0.031	—	0.052	0.865	0.031	—	0.021
US Native Americans	19	—	—	0.240	0.760	—	—	—
Amerindians, Colombia	27	—	—	—	1.000	—	—	—
Australian Aboriginal	18	0.028	—	—	0.972	—	—	—
North Africa	10	—	—	0.200	0.750	0.050	—	—

values are low for a VNTR locus; they ranged from 0 in the Native Americans of Colombia to a maximum of 52% in Greeks. Overall, Europeans have higher levels than East Asian groups.

The rare allele *DAT1*13* was observed only in the Altai-Kizhi, and the similarly rare allele *DAT1*7* was restricted to aboriginal groups of both Siberia and Australia. The frequency of allele *DAT1*7* in Siberian groups is quite high (~5%), even allowing for the effects of small sample size in some cases, and it is present in all four groups though some of them (Altai-Kizhi and Sel'kup) are separated by hundreds of miles.

Statistical analysis was conducted by comparing the number of *DAT1*10* alleles versus all other *DAT1* alleles across samples using contingency chi-square tables. The Greeks were significantly different from the Chuvash, $\chi^2 = 16.4$, 1 d.f., $p < 0.001$. Among Siberian groups the only significant differences were those between the Sel'kup and Altai-Kizhi, $\chi^2 = 5.74$, 1 d.f., $p < 0.025$, and the Sel'kup and Ket, $\chi^2 = 6.68$, 1 d.f., $p < 0.01$. When correction is made for the number of simultaneous tests, the differences between the Sel'kup and Altai-Kizhi are insignificant. Small numbers prohibited any sensible statistical analysis of the remaining samples in Table 1.

Discussion

Investigation of 10 geographically widespread populations failed to find any new alleles at the *DAT1* VNTR locus. Thus it can be assumed that this VNTR locus has relatively few alleles and that only two of them (*DAT1*9* and *DAT1*10*) are commonly present in most human populations. When the present data are added to the limited reports in the literature, the essential features of the *DAT1* distribution can be discerned (Table 3). Firstly, the

Table 2. Heterozygosity Values for the *DAT1* VNTR Polymorphism

Population	*Number Tested*	*Heterozygosity*	*Reference*
Africa			
N. Africa	10	0.395	ps
Europe			
Greeks	21	0.522	ps
Chuvash	33	0.216	ps
Asia			
Sel'kup	29	0.45	ps
Evenki	61	0.361	ps
Ket	16	0.118	ps
Altai-Kizhi	48	0.247	ps
Mongolia	156	0.179	Nakatome et al. 1996
Chinese	203	0.177	Li et al. 1994
Japanese	107	0.133	Sano et al. 1993
Japanese	176	0.166	Nakatome et al. 1995
Americas			
US Native	19	0.365	ps
Colombia	27	0	ps
Oceania			
Australian	18	0.054	ps
Mixed			
USA	129	0.439	Vandenbergh et al. 1992b
USA	84	0.368	Cook et al. 1995

ps = present study

frequency of *DAT1*10* is significantly higher in the Mongoloid groups of north Asia, especially Japan and China, than in Europeans (except Chuvash), but it attains its maximum frequency in descendants of earlier Asians, the Native Americans, in some of whom it is at fixation. Secondly, the presence of allele *DAT1*9* in US Native Americans may be due to either admixture with Europeans, in whom it appears to have the greatest incidence (38% in Greeks), or because the sample comprises Na-Dene (Navajo) as well as Amerind-speakers, and the former group may possess this allele. Thirdly, the finding of the very rare allele *DAT1*13* in the Altai-Kizhi is not surprising, given its presence in their close neighbors, the Mongolians, a group known to have had contact, through means of both trade and war, with the Altai-Kizhi over many centuries (McComb et al. 1996). These are the only two populations with this largest of the *DAT1* alleles.

In addition, *DAT1*7* seems to be concentrated among Asian populations, among whom it can reach fairly high frequencies, particularly in Siberian aborigines. The frequency of allele *DAT1*7* among indigenous Siberians ($> 5\%$) is clearly not a result of admixture with Europeans, in whom

Table 3. *DAT1* VNTR Allele Frequency Distributions in Worldwide Populations

Populations	*Number Tested*	*DAT1 Allele Frequency*								*Reference*
		*3	*5	*7	*8	*9	*10	*11	*13	
Africa										
North Africa	10	—	—	—	—	0.200	0.750	0.050	—	Present study
Europe										
Greeks	21	—	—	—	—	0.381	0.524	0.095	—	Present study
Chuvash	33	—	—	—	—	0.106	0.879	0.015	—	Present study
Asia										
Sel'kup	29	—	—	0.086	—	0.207	0.707	—	—	Present study
Evenki	61	—	—	0.057	—	0.033	0.787	0.123	—	Present study
Ket	16	—	—	0.031	—	0.031	0.938	—	—	Present study
Altai-Kizhi	48	—	—	0.031	—	0.052	0.865	0.031	0.021	Present study
Mongolia	156	—	—	0.026	—	0.051	0.904	0.013	0.006	Nakatome et al. (1996)
Chinese Han	203	—	—	—	0.015	0.060	0.905	0.020	—	Li et al. (1994)
Japanese	107	—	—	0.009	—	0.042	0.930	0.019	—	Sano et al. (1993)
Japanese	176	—	—	0.017	—	0.063	0.912	0.009	—	Nakatome et al. (1995)
Americans										
US Natives	19	—	—	—	—	0.240	0.760	—	—	Present study
Amerindians, Colombia	27	—	—	—	—	—	1.000	—	—	Present study
Oceania										
Australian Aboriginal	18	—	—	0.028	—	—	0.972	—	—	Present study
Mixed										
US Mixed	129	0.008	—	0.012	0.019	0.240	0.700	0.016	—	Vandenbergh et al. (1992b)
US Mixed	84	0.012	—	—	—	0.226	0.762	—	—	Cook et al. (1995)

the allele appears to be absent. However, the present data cannot distinguish whether the indigenous Siberians possess this allele as a result of admixture with other Asian groups, such as Mongolians, as a result of past or present gene flow in the opposite direction, or as a result of the *DAT1*7* allele having been present in the common ancestor of these groups. It should be noted that allele *DAT1*7* is absent from the relatively large sample of Han Chinese (Li et al. 1994), but that the exceedingly rare allele *DAT1*8* is present. The latter *DAT1* allele has otherwise only been reported in a mixed sample of US blacks and whites (Vandenbergh et al. 1992b).

Though the Mongolians, Japanese, and Han Chinese share most of their alleles with the four Siberian groups, both the Sel'kups and Evenki are significantly different in frequencies from all 3 of them ($p < 0.001$), chiefly because of the lower incidence of allele *DAT1*10* in the two Siberian groups. The differences in *DAT1* allele frequencies among the Chinese, Japanese, and Mongolians are statistically insignificant.

The presence of allele *DAT1*7* (represented by a single allele) in native Australians is interesting, since it is most unlikely to have been introduced by European admixture (the usual source of 'exotic' genes in this group). However, it could be a product of admixture with Indonesians, especially Makassans from Sulawesi (the former Celebes) who are known to have visited the shores of northern Australia for trepang (sea cucumber) from 1500 CE. Unfortunately, there are no data on the *DAT1* locus from any Indonesian island. Alternatively, it may have been introduced even more recently through contact with either Chinese traders or Japanese pearl fishers. There is also the possibility that allele *DAT1*7* represents a new (step-wise) mutation or the product of an unequal crossover.

Though the mutation rate at this VNTR locus is unknown, the frequency distribution of the alleles in all populations suggests it may be relatively low. Most of the alleles, other than *DAT1*9* and *DAT1*10*, are rare and also often geographically restricted; for example, allele DAT1*13 is limited to two neighboring groups. Therefore, unlike many VNTRs in which the mutation rate is suspected to be high, shared *DAT1* alleles, especially the rarer ones, among populations are more likely to reflect common ancestry rather than recurrent mutation.

Our data demonstrate that the *DAT1* VNTR polymorphism is useful in investigating population variability, and that rare alleles at this locus may be particularly valuable in understanding the extent of genetic affinity between groups or the extent of admixture. Because the *DAT1* VNTR polymorphism lies in a transcribed region of the gene and also shows a considerably reduced polymorphism compared to other VNTRs, there is the possibility that this locus may be under some selective constraint. This hypothesis gains support from the observation that in all types of populations scored for the polymorphism, whether major human groups (Africans and Europeans) or small-scale societies (Native American tribes and Australian aboriginals), the number of

alleles is around three. Also, heterozygosity levels are relatively in all populations scored so far (Table 2). The recent paper by Waldman et al. (1998) replicating, in a large family study, the earlier investigations of Cook et al. (1995) and Gill et al. (1997), confirmed the association and linkage between the *DAT1* gene and ADHD in children (the high-risk allele is 480 bp or *DAT*10*). These findings confirm the candidate gene status of *DAT1* with respect to other neurological and psychiatric disorders related to dopaminergic function because of the key role of dopamine in motor activity.

The marked excess of homozygotes at the *DAT1* VNTR locus, as seen in the Evenki, has been reported previously. Nakatome et al (1995) reported a highly significant homozygous excess, especially for allele *DAT1*7*, in their Japanese sample. In the Evenki, the excess is most marked for allele *DAT1*11*, (but also considerable for allele *DAT1*10*), but not for allele *DAT1*7*. Nakatome et al. (1996) suggested that the increase in homozygosity may indicate that the VNTR may actually lie in a coding region of the *DAT1* gene and not the 3′ untranslated region, as reported by Vandenbergh et al (1992a). However, in our study of 10 populations, significant excess homozygosity is limited to 1, the Evenki, semi-nomadic reindeer hunter/herders who live in relatively small, isolated communities in the taiga of Siberia. This life-style creates a demographic structure conducive to the microevolutionary forces of drift and inbreeding that would produce disequilibrium of allele frequencies.

It is possible that the method of DNA analysis used in this study is insufficient to detect all mutations that may be present at the VNTR locus. There may be hidden sequence heterogeneity in the *DAT1* alleles that cannot be detected by the relatively simple and robust separation technique employed here. Future study will focus on sequencing *DAT1* alleles to determine the extent of structural similarity among them. This would show, firstly, whether the polymorphism is truly restricted to a few alleles, or is considerably greater than described here, but requires improved techniques for detection. Secondly, such an analysis would reveal, for example, whether the *DAT1*7* allele found in Siberian and Australian aboriginals shares an identical molecular structure.

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