These observations have important implications for the mtDNA screening procedures currently used in molecular anthropology. The classification of ancient and modern mtDNAs as members of the Asian-specific haplogroup B should not be based solely on screening for the presence of the 9-bp deletion. Such an approach might lead to misclassification, particularly among Europeans and Africans, and it would have a certain level of error even among populations of Asian ancestry. Misclassification can be avoided, and a correct assignment to specific haplogroups of the mtDNAs characterized by the 9-bp deletion can be achieved, only if the molecular screening is accompanied by haplotype analysis.

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Normal CAG Repeat Variation at the DRPLA Locus in World Populations

To the Editor:

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder char-

acterized by a varying degree of myoclonus epilepsy, ataxia, dementia, and choreoathetosis (Naito and Oyanagi 1982). This is a progressive disease with a variable age at onset, between the 1st and 7th decade of life (Naito 1990). It became the seventh human genetic disorder shown to be caused by an expansion of a trinucleotide repeat, when two groups of investigators found that an array of CAG repeats is expanded in DRPLA patients in a gene located on chromosome 12p (Koide et al. 1994; Nagafuchi et al. 1994). This finding was based on using a clone CTG-B37, containing CAG trinucleotide repeats, isolated from a human brain cDNA library (Li et al. 1993). Anticipation and parental sex bias in transmission have been reported to be associated with DRPLA (Aoki et al. 1994; Koide et al. 1994; Nagafuchi et al. 1994), features also observed in other trinucleotide repeat–expansion diseases, such as fragile X, myotonic dystrophy, and Huntington disease. More common in Japan (Iizuka et al. 1984; Hirayama et al. 1994), DRPLA is rare in other parts of the world, with some familial cases being described in Europe and the United Sates (Smith et al. 1958; Burke et al. 1994*b*; Warner et al. 1994).

CAG repeat number at the DRPLA locus in normal individuals varies between 7 and 25 repeats, with a heterozygosity >80%, while affected individuals have a range between 49 and 75 repeats, with no intermediate-sized allele yet observed (Li et al. 1993; Koide et al. 1994; Nagafuchi et al. 1994; Warner et al. 1994). Although Burke et al. (1994*a*) have recently reported distribution of CAG repeats at the DRPLA locus in normal individuals of African-American, White, and Japanese ancestry, populations of defined origin on a broader scale have not yet been surveyed. Thus, the question remains whether there are allele frequency–distribution differences at this locus in normal individuals of defined ethnic and geographic origin; and, if so, is there a correlation between ethnic prevalence of the disease and presence of alleles of specific sizes?

To address these issues, we have analyzed the distribution of CAG repeats at the DRPLA locus in 10 geographically and ethnically diverse populations; 3 of these populations are of African origin—2 of which are from West Africa, namely, the Sokoto and the Benin from Nigeria—and the third is a Brazilian Black population; 4 populations are Caucasians, represented by a German sample from northern Germany, unrelated parents from the CEPH cohort, a Brahmin sample from northern India, and a White sample from Brazil; 2 Asian Mongoloid populations included in this study are a Chinese sample of Han origin and a Japanese sample from the Osaka area of Japan. In addition, we have studied a Pacific Polynesian population from the Samoan islands. PCR conditions and primer sequences used for amplification of the CAG repeat have been described elsewhere (Li et al. 1993).

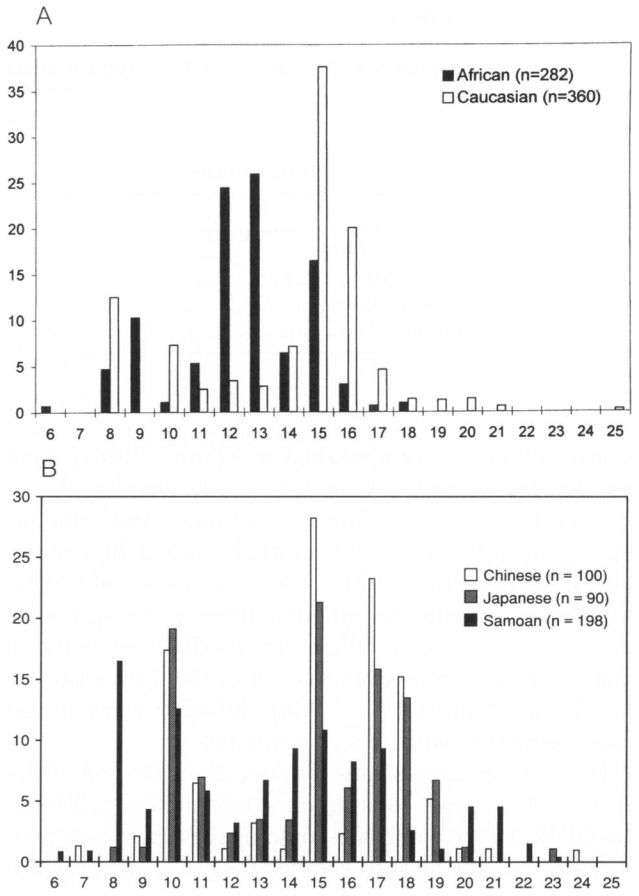

Figure 1 Frequency distribution of CAG repeats at the DRPLA locus in Africans and Caucasians (*A*) and in Japanese, Chinese, and Samoans (*B*). Repeat numbers are shown on the *x*-axis, and allele frequencies (in %) are shown on the *y*-axis.

The results are summarized graphically in figure 1. A total of 20 alleles in the range of 6 to 25 CAG repeats were detected. Since we did not observe any significant difference in the distribution of alleles among the African populations or among the Caucasian populations, these populations were pooled as African and Caucasian, respectively (fig. 1*A*). The allele frequency distributions in Japanese, Chinese, and Samoans have been plotted separately (fig. 1*B*). These along with the data shown in table 1 clearly demonstrate that alleles of ≥18 repeats are more frequent in populations of Asian and Pacific origin. Frequencies of these alleles in Japanese, Chinese, and Samoan samples are significantly ($P < .01$) elevated in comparison with those in Africans and Caucasians. This is parallel to the pattern of decreasing incidence of DRPLA from Japanese to Caucasian to African populations. Although the cutoff at allele of ≥18 repeats is somewhat arbitrary, qualitatively the same conclusion holds when other cutoff alleles are chosen beyond the modal allele 15. While the average allele sizes in the examined populations appear close to each other (table

Table 1

Frequency of Alleles of ≥18 CAG Repeat Units at the DRPLA Locus in Global Populations

Population (No. of Individuals)	Frequency ± Standard Error of Alleles ≥18 Repeats (%)	Average Allele Size ± Standard Error (repeat units)
African (141)	1.1 ± .6	12.5 ± .1
Caucasian (180)	4.7 ± 1.1	14.0 ± .2
Chinese (50)	23.0 ± 4.2	15.2 ± .3
Japanese (45)	22.2 ± 4.4	14.6 ± .4
Samoan (99)	14.6 ± 2.5	13.4 ± .3

1, last column), a nonparametric Mann-Whitney rank test (Snedecor and Cochran 1967) indicates that the allele size distributions in Japanese, Chinese, and Samoans are significantly ($P < .03$) shifted toward higher-size alleles, in comparison with those in Africans and Caucasians. This test also reveals that there is no significant ($P > .33$) difference in allele size distributions between Chinese and Japanese, but in each of them the distribution is significantly ($P < .004$) shifted toward higher sizes, compared with that in Samoans.

These observations raise the question, Do the alleles of size ≥18 repeats constitute the intermediate alleles at the DRPLA locus, and are some of these alleles predisposed to expansion into the disease range. Although it is not yet known if DRPLA is present in Chinese, Samoan, and other Asian or Pacific populations, the parallel observation of relatively higher prevalence of these alleles in Japanese and known higher incidence of DRPLA in this population leads to a speculation in favor of this argument. Our results are in complete agreement with the proposition of Burke et al. (1994*a*)—that larger alleles in the Japanese population constitute a source for expansion to the disease-causing range. They had similarly observed a significantly greater proportion of alleles of ≥19 repeats in Japanese individuals compared with the African-Americans and Whites. These findings at the DRPLA locus are analogous to the ones at the DM locus. Myotonic dystrophy is more common in Europeans, who have a significant proportion of large normal CTG-repeats compared with the Africans, among whom DM is very rare or absent (Imbert et al. 1993; Goldman et al. 1994). On the basis of this distribution pattern and linkage disequilibrium data, a model has been proposed in which the large normal DM alleles in Europeans form the reservoir for recurrent DM mutations (Imbert et al. 1993; Neville et al. 1994). De novo expansion of large normal alleles has also been implicated in new mutations at the HD locus (Goldberg et al. 1993; Myers et al. 1993). These findings suggest that large normal alleles in triplet-repeat diseases form an important source for disease predisposition, and they illustrate the potential of the field of molecular epidemiology.

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