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SCA8 Repeat Expansion Coexists with SCA1—Not Only with SCA6

To the Editor:

Izumi et al. (2003) observed coexistence of the expanded spinocerebellar ataxia (SCA) type 8 (SCA8 [MIM 603680]) CTA/CTG repeat alleles and large SCA6 (MIM 183068) CAG repeat alleles. They speculated that the presence of the expanded SCA8 alleles could influence the function of the α_{1A}-voltage-dependent calcium channel gene (*CACNA1A* [MIM 601011]), the expanded CAG repeat of which is responsible for SCA6.

In 2 of 127 (1.6%) families with SCA6, Izumi et al. (2003) observed large expanded SCA8 alleles (≥85 CTA/CTG repeats), and, in 3 families, they observed intermediate-sized alleles (50–84 CTA/CTG repeats). Altogether, expanded SCA8 alleles were present in 5 of 127 (3.9%) families with SCA6. The authors wrote that coexistence with SCA8 expanded alleles may be "specific to SCA6 and is not seen in other…ataxias with CAG repeat expansions" (p. 707) (they have not found expanded SCA8 alleles in 118 families with SCA3/Machado-Joseph disease [MIM 607047] or in 45 families with SCA1 [MIM 164400], SCA2 [MIM 183090], SCA7 [MIM 164500], SCA17 [MIM 607136], or dentatorubral-pallidoluysian atrophy [MIM 125370]). Therefore, they suggested that there could be an interaction of the SCA6 and SCA8 genes and that the *SCA6* locus/product "should be included in a pathway of appearance of SCA8 phenotype" (p. 708). Here, we want to show that expanded SCA8 alleles may be present in SCA1, as well.

Table 1

Pedigrees with SCA1 in Whom Expanded CTA/CTG SCA8 Alleles Were Observed in Affected and Unaffected Subjects

Pedigree	Status	SCA1: CAG Repeat Length[a]	SCA8: CTA/CTG Repeat Length[b]	Ages at Examination/ Onset (years)
I-1	Affected	57/32	77/18	50/30
I-2	Unaffected	30/30	18/18	18/…
I-3	Unaffected	32/30	80/18	47/…
II-1	Affected	51/33	29/18	44/40
II-2	Unaffected	33/30	87/18	22/…
II-3	Affected	64/33	29/18	26/19
II-4	Affected	53/30	23/23	39/37
III-1	Unaffected	31/30	69/24	33/…
III-2	Unaffected	31/29	27/18	19/…
III-3	Affected	50/39/31[c]	27/24	57/35
IV-1	Affected	65/30	113/24	23/20
IV-2	Unaffected	32/30	116/24	20/…
IV-3	Unaffected	32/30	28/24	45/…
V-1	Affected	54/32	53/18	35/30

NOTE.—Intermediate-sized SCA8 CTA/CTG repeats were observed in four subjects (two affected with SCA1 and two unaffected); large SCA8 CTA/CTG repeats were observed in three subjects (one affected with SCA1 and two unaffected).

[a] The pathogenic SCA1 alleles range from 40 to 80 repeats and contain only uninterrupted CAG stretches; the nonpathogenic SCA1 CAG repeat alleles range from 6 to 39 repeats and contain a midstream CAT interruption (Orr et al. 1993; Chung et al. 1993).

[b] Izumi et al. (2003) tentatively classified the expanded CAT/CTG SCA8 alleles into intermediate-sized (50–84 repeats), large (85–399 repeats), and very large (≥400 repeats).

[c] A case of mosaicism (three SCA1 alleles) in DNA extracted from blood of the affected individual (III-3).

In a group of 58 Polish families with 101 molecularly confirmed cases of SCA1, we observed 5 (8.6%) families with expanded SCA8 CTA/CTG alleles, with repeat numbers ranging from 53 to 116 (table 1). The data presented in table 1 show that:

1. each subject with the expanded SCA1 CAG repeat was affected with SCA1;
2. in four patients (II-1, II-3, II-4, and III-3), only expanded SCA1 alleles were present;
3. in four unaffected subjects (I-3, II-2, III-1, and IV-2) with normal ranges of SCA1 CAG repeats, only expanded SCA8 alleles were present;
4. in two of the families with SCA1, the expanded SCA8 CTA/CTG repeat alleles were present only in unaffected subjects with normal number, of SCA1 CAG repeats (families II and III); and
5. in three patients (I-1, IV-1, and V-1), coexistence of expanded SCA1 and SCA8 alleles was observed, but their relatively early ages at onset of the disease appeared to depend on the number of SCA1 CAG repeats rather than on the presence of SCA8 CTA/CTG expanded alleles (compare, for instance, subjects II-3 and IV-1).

The rate of coexistence of the expanded SCA1 and SCA8 alleles in the entire group of patients with SCA1 was 3%.

The above data show that, although the expanded alleles of SCA8 may be present in families with SCA1, the role of the alleles as a modifying factor in SCA1 is uncertain or doubtful and, judging from the data of Izumi et al. (2003), less important than in SCA6.

Among 650 patients referred to us with the diagnosis of SCA, we also came across seven families with 18 (9 affected and 9 unaffected) subjects with expanded SCA8 alleles in the range of 79–150 CTA/CTG repeats; other types of SCAs with CAG expansions (SCA1, SCA2, SCA3, SCA6, SCA7, SCA12 [MIM 604326], SCA-17, and DRPLA) were excluded in these families.

We did not find SCA8 expanded alleles in any of the 26 cases of SCA2 or in 2 cases from one family with SCA17. Other types of SCA have not been detected in Poland; the absence of SCA3 is particularly striking, since it is relatively common in western Europe. Until now, we did not find homozygotes for expanded SCA8 alleles among Polish patients with SCA.

We would also like to mention that, in a group consisting of 250 subjects (mean age ± SD: 58.8 ± 20.7) with different forms of hyperlipidemia but with no history of neurological disorders, we found three subjects carrying large SCA8 alleles of 91, 95, and 100 CTA/CTG repeats. We did not find any case of the expanded SCA8 alleles in a group of 100 patients affected with Huntington disease (MIM 143100).

Our data, like those of the Japanese study, show that expanded SCA8 CTA/CTG alleles tend to be more frequent in the group of patients with SCA and in members of their families. The difference between the Polish and Japanese data is in our observation of SCA8 allele expansions in some families with SCA1 (table 1).

The two data sets, the Japanese and the Polish, seem to be complementary to each other and suggestive of a possible transacting factor role for the SCA8 locus in the expansion mechanism in SCA repeat disorders; Izumi et al. (2003) proposed a possible pathomechanism with SCA8 locus involvement in SCA6—the disease caused by the mutation of the gene, the product of which has a known function—but their hypothesis needs to be confirmed.

The role of the expanded SCA8 locus in other types of SCA, including SCA1 and SCA8—which is not yet a very distinctly defined genetic entity—remains to be established.

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Electronic-Database Information

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SCA1, SCA2, SCA3/Machado-Joseph disease, CACNA1A/SCA6, SCA7, SCA17, SCA8, SCA12, dentatorubral-pallidoluysian atrophy, and Huntington disease)

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Table 1

Rank of Icelanders, Danes, and Germans for HVS1 Summary Statistics among 26 European Populations

	Results of											
	Helgason et al. (2000)						Arnason (2003)					
			Rank						Rank			
Population	*N*	*k*	Gene Diversity	Pairwise Difference	θ_k	θ_S	*N*	*k*	Gene Diversity	Pairwise Difference	θ_k	θ_S
Icelanders	447	125	9	8	14	13	520	128	7–9	9	13	11
Danes	31	25	5	2	13	24	33	19	23	24	25	25
Germans	418	219	6	14	2	1	423	217	10–15	21	2	1

Note.—The population with the highest value has a rank of 1, and the population with the lowest value has a rank of 26. *N* is sample size, and *k* is the number of distinct haplotypes. θ_k and θ_S are population-mutation rate parameters that are based on the number of haplotypes and the number of variable sizes, respectively.

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Erroneous Claims about the Impact of Mitochondrial DNA Sequence Database Errors

To the Editor:

In a recent letter to the *Journal*, Herrnstadt et al. (2003, p. 1,585) assert that sequence errors in an mtDNA study of Icelanders contributed to an "erroneous conclusion about the genetic diversity of these people." Herrnstadt et al. (2003) do not explicitly refer to the study in question, nor do they provide any evidence to support their allegation. Rather, they cite a recent article by Arnason (2003) that states that errors in sequences obtained from a database had a material effect on the results and, hence, on conclusions of an article published in the *Journal* by Helgason et al. (2000). We demonstrate here, contrary to this claim and its reiteration by Forster (2003) and Herrnstadt et al. (2003), that sequence errors have no impact on the conclusions of Helgason et al. (2000) about the genetic diversity of Icelanders.

Helgason et al. (2000) analyzed a total of 4,064 mtDNA control-region sequences: 2,969 from hypervariable segment 1 (HVS1) in 26 populations and 1,095 from hypervariable segment 2 (HVS2) in 10 populations. A subset of these sequences was obtained from HVRBASE (Handt et al. 1998), among which were 140 HVS1 sequences from Denmark and Germany (Richards et al. 1996). Arnason (2003) points out that some of these latter sequences were incorrectly recorded in HVRBASE. After correcting the erroneous sequences, Arnason recalculates genetic diversity statistics presented in table 1 of Helgason et al. (2000) and concludes that "[t]he estimation of statistics and relative rank of countries with respect to diversity and effective population size is materially affected by the errors" (Arnason 2003, p. 9). He moreover concludes that "[c]laims about a special genetic homogeneity of Icelanders relative to European populations would be suspect to the extent that they depended on anomalous data instead of the primary data" (Arnason 2003, p. 14). In an accompanying editorial comment, Forster (2003, p. 2) elaborates: "Arnason demonstrates [that HVRBASE] is riddled with copying errors in the case of the Danes and Germans, resulting in a *qualitatively different* ranking of Icelandic genetic diversity" (emphasis added).

Our comparison of the German and Danish sequences, stored in HVRBASE, with the original sequences submitted to GenBank has revealed that 14 of 33 Danish and 29 of 107 German HVS1 sequences contained database transcription errors. The impact of these errors on the summary statistics (gene diversity and mean pairwise differences, θ_k and θ_S, respectively) calculated by Helgason et al. (2000) for Icelanders, Danes, and Germans can be evaluated through a comparison with Arnason's (2003) recalculations (see table 1).

Table 1 shows that the rank of the Danish sample changes for all summary statistics, a finding that is not surprising, given that almost half of the Danish sequences contained errors. In the case of the Germans, we observe noticeable changes with respect to gene diversity and mean pairwise differences but no changes in rank for θ_k and θ_S. What is most important in the present context is that table 1 shows that the erroneous Danish and German sequences have almost no effect on the relative position of Icelanders among the 26 European populations for all four summary statistics. This clearly contradicts the aforementioned claims, made by Arnason (2003) and repeated by Forster (2003) and Herrnstadt et al. (2003), that sequence errors in the study by Helgason et al. (2000) have an impact on conclusions about the relative genetic diversity of the Icelanders.