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LETTER TO THE EDITOR

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Multiple founder effects in Japanese families with primary torsion dystonia harboring the GAG deletion in the *TOR1A* (*DYT1*) gene

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Sirs,

Primary torsion dystonia (PTD) is a movement disorder, which is clinically characterized by involuntary sustained muscle contractions. The 3-bp (GAG) deletion in the *TOR1A* (*DYT1*) gene was found in patients with PTD linked to 9q34 [1]. PTD linked to 9q34 is highly prevalent among Ashkenazi Jews (AJ), which is thought to result from a single founder chromosome [2]. Although PTD linked to 9q34 is predominant among AJ, the GAG deletion in the *TOR1A* (*DYT1*) gene has been reported in non-Jewish populations [3, 4, 5]. Haplotype analyses of the *TOR1A* (*DYT1*) region revealed that non-Jewish patients do not share the same haplotype as that found among AJ [3]. These findings suggest that the GAG deletion occurred independently among different populations.

In the present study, we compared the haplotypes tightly linked to the *TOR1A* (*DYT1*) gene in Japanese DYT1 families carrying the GAG deletion. We examined 21 individuals, including 11 affected individuals, 2 asymptomatic carriers, and 8 unaffected individuals, from six unrelated pedigrees (pedigrees 13, 468, 1,286, 1,305, 1,375, and 1,997) carrying the GAG deletion in the *TOR1A* (*DYT1*) gene. The clinical features of these pedigrees have been described elsewhere [4, 5]. Haplotypes were determined for locus, D9S62b-D9S2158-D9S2160-D9S2161-D9SS63-D9S2162-ASS (Fig. 1A), which spans a genetic distance of ~1.8 cM including the *TOR1A* (*DYT1*) gene [6]. Comparison of the haplotype of AJ with those of Japanese families was carried out by simultaneously analyzing an AJ sample kindly provided by Dr. Breakefield and those of Japanese families.

Haplotypes of the six Japanese families are summarized in Fig. 1B. None of the haplotypes in Japanese families shares strong similarity to the AJ haplotype, 8-4-4-5-16-4-12 (Fig. 1B), suggesting that the GAG deletion occurred independently in the Japanese population. However, we can not completely exclude the possibility that PEDS 13, 1,305, and 1,997 might share a common founder chromosome with AJ patients based on the similarity of the haplotypes, 16–4, at D9S63-D9S2162. Among haplotypes of Japanese families, we found that the haplotype of 2–2-6–9-1 at S9S2160-D9S2161-D9SS63-D9S2162-ASS was shared among PEDS 468 and 1,375, and that the haplotype of 2–16–4-1 at D9S2161-D9S63-D9S2162-ASS was shared among PEDS 13, 1,305, and 1,997 (Fig. 1B and C). The haplotype in PED 1,286 did not exhibit similarities to the haplotypes found in other Japanese pedigrees. Although the results indicate that multiple independent events resulted in this deletion, we found two common haplotypes between D9S2161 and ASS loci shared by unrelated Japanese pedigrees. Thus, the deletion in the *TOR1A* (*DYT1*) gene appears to occur a limited number of times.

We previously described two clinical phenotypes associated with the Japanese DYT1 families: postural dystonia phenotype observed in PED 468 and action dystonia phenotype found in PEDS 13, 1,286, 1,305, 1,375, and 1997 [5]. We could not detect any correlation between these clinical phenotypes and the haplotypes in our present study. Since there are broad clinical features as well as a wide range of age at onset, factors other than the *TOR1A* (*DYT1*) gene are likely to modulate the phenotypic expression of the disease.

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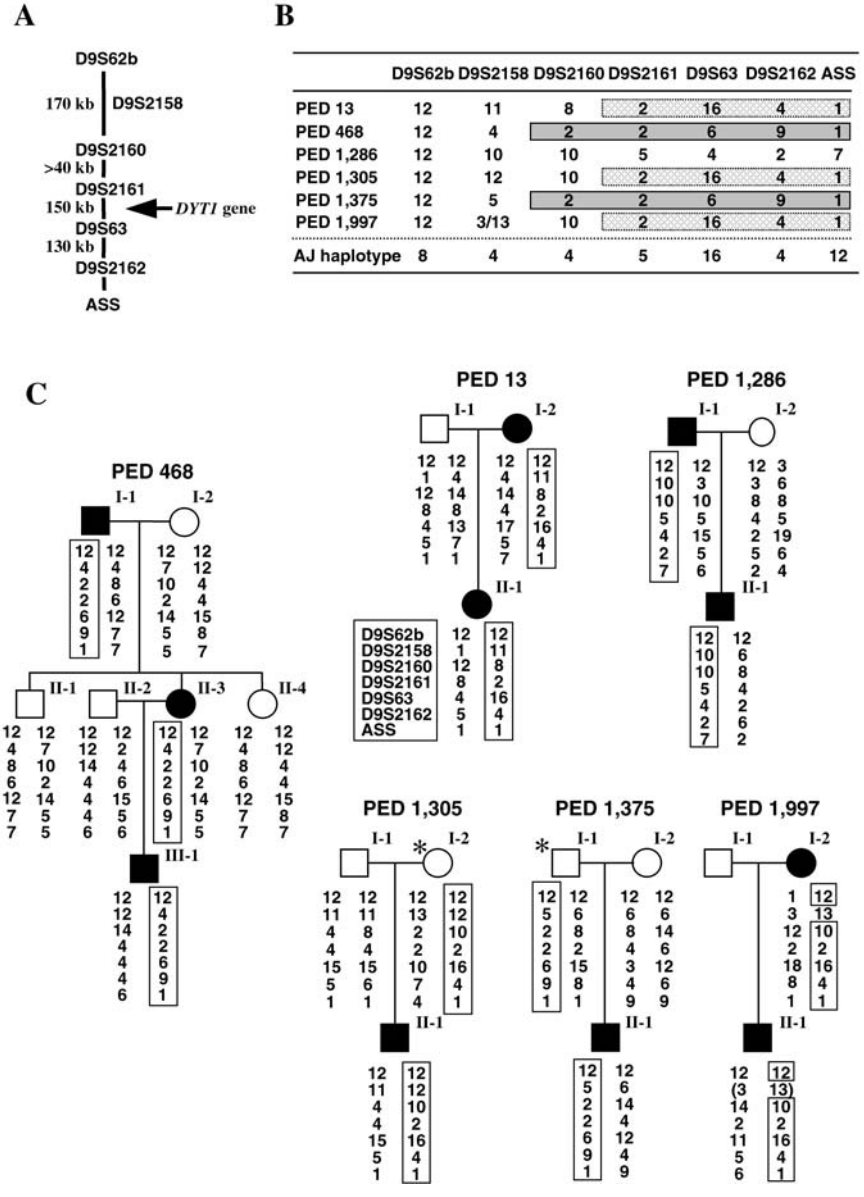

Fig. 1A–C Haplotype analysis of the *TOR1* (*DYT1*) gene region in six unrelated Japanese *DYT1* pedigrees. **A** Estimated physical distance between markers based on YAC and cosmid contig [1, 6]. The *TOR1A* (*DYT1*) gene is located between D9S2161 and D9S63 loci. **B** Comparison of haplotypes in six Japanese pedigrees with that of Ashkenazi Jews. Common haplotypes are boxed and shaded. **C** Haplotype analysis of the six unrelated pedigrees with Japanese *DYT1* pedigrees. Haplotypes segregating with the GAG deletion are enclosed by *boxes*. *Black symbols* denote affected individuals; *unfilled symbols* represent healthy members; *asterisks* indicate asymptomatic carriers

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