**Summary**

A GAG deletion at position 946 in DYT1, one of the genes responsible for autosomal dominant idiopathic torsion dystonia (ITD), has recently been identified. We tested 24 families and six isolated cases with ITD and found 14 individuals from six French families who carried this mutation, indicating that 20% of the affected families carried the DYT1 mutation. Age at onset was always before 20 years (mean, 9 ± 4 years). Interestingly, the site of onset was the upper limb in all but one patient. Dystonia was generalized in seven patients and remained focal or segmental in three patients. The absence of common haplotypes among DYT1 families suggests that at least six independent founder mutations have occurred. In addition, one Ashkenazi Jewish family carried the common haplotype described previously in Ashkenazi Jewish patients, but it was absent in the other family. Moreover, the dystonia remained focal in the latter family when compared with the usual generalized phenotype in patients with the common Ashkenazi Jewish haplotype. This indicates that there are at least two founder mutations in this population.

**Keywords:** idiopathic torsion dystonia; Ashkenazi Jews; linkage disequilibrium; DYT1; torsin A

**Abbreviation:** ITD = idiopathic torsion dystonia

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**Introduction**

Idiopathic torsion dystonia (ITD) is characterized by involuntary sustained muscle contractions, causing twisting and repetitive movements or abnormal postures. ITD is transmitted as an autosomal dominant disorder with low penetrance (30–40%) (Bressman et al., 1989; Kramer et al., 1994). Clinical expression is highly variable but is partly determined by the age at onset. When onset occurs before the age of 20 the disease is usually severe and generalized, often affecting a leg before progressing to other limbs and the trunk. Late-onset forms are milder and often remain segmental or focal. The first locus (DYT1) of this genetically heterogeneous disease was mapped to chromosome 9q34 (Ozelius et al., 1989), and the corresponding gene, encoding a small polypeptide, torsin A, has recently been identified (Ozelius et al., 1997a). The mutation is a deletion of a GAG codon at position 946. ITD linked to chromosome 9 is particularly prevalent in Ashkenazi Jews due to a founder effect (Ozelius et al., 1997b). The DYT1 phenotype, defined by clinical characterization of carriers of the ancestral haplotype in this population, is early limb-onset generalized dystonia (Bressman et al., 1994). The 946delGAG mutation, linked to chromosome 9, was found in all patients and obligate carriers of 68 ITD families, 64 of whom were of Ashkenazi Jewish origin (Ozelius et al., 1997a). In the present study, we determined the frequency of the DYT1 mutation in 30 French families with ITD and analysed the corresponding phenotype.

**Method**

**Patients**

We tested 51 individuals (24 women and 27 men) from 30 families with ITD for the presence of the DYT1 mutation. The families were ascertained at the Hôpital de la Salpêtrière according to the following criteria: (i) clinical evidence of dystonic movements or postures, without pyramidal, cerebellar, sensory or intellectual deficits; (ii) no history of kernicterus, perinatal asphyxia or other predisposing causes of dystonia; (iii) at least two first-degree relatives with ITD cases for the familial cases. There were 14 families with affected individuals in two generations, eight families with at least two patients in one generation and eight isolated cases. In nine families, all patients suffered from focal dystonia, in four from generalized dystonia, and in one
dystonia was segmental in all patients (Fahn, 1988). In the other families \((n = 8)\), patients were affected with different types of dystonia. In addition, eight members of two families with autosomal dominant non-alcohol-responsive myoclonic dystonia were tested. We excluded families with dopamine-responsive dystonias and paroxysmal kinesigenic choreoathetosis. The families were classified into three categories according to Özelius et al. (1997a), where the
Table 1  Clinical characteristics of 10 DYT1 patients

<table>
<thead>
<tr>
<th>Positive family history</th>
<th>Sex</th>
<th>Age at onset (years)</th>
<th>Disease duration (years)</th>
<th>Site of onset</th>
<th>Distribution</th>
<th>Tremor</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAL-405-003 Siblings</td>
<td>F</td>
<td>10</td>
<td>40</td>
<td>Hand</td>
<td>Arm, both legs</td>
<td>Writing</td>
<td></td>
</tr>
<tr>
<td>SAL-405-004 Siblings</td>
<td>M</td>
<td>11</td>
<td>37</td>
<td>Unknown</td>
<td>Neck, arms, legs, trunk</td>
<td>Writing</td>
<td></td>
</tr>
<tr>
<td>SAL-405-005 Siblings</td>
<td>M</td>
<td>Childhood</td>
<td>38</td>
<td>Arm</td>
<td>Generalized</td>
<td>No</td>
<td>Bilateral thalamotomy</td>
</tr>
<tr>
<td>SAL-416-009 Daughter</td>
<td>F</td>
<td>20</td>
<td>22</td>
<td>Hand</td>
<td>Foot, arm</td>
<td>Writing, head</td>
<td></td>
</tr>
<tr>
<td>SAL-416-014 Mother</td>
<td>F</td>
<td>9</td>
<td>3</td>
<td>Hand</td>
<td>Both arms</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SAL-417-009 Son</td>
<td>M</td>
<td>7</td>
<td>30</td>
<td>Hand</td>
<td>Writer’s cramp</td>
<td>No</td>
<td>Postural</td>
</tr>
<tr>
<td>SAL-417-014 Father</td>
<td>M</td>
<td>7</td>
<td>3</td>
<td>Hand</td>
<td>Larynx, both arms, trunk</td>
<td>No</td>
<td>Postural</td>
</tr>
<tr>
<td>SAL-420-011 Grandfather</td>
<td>F</td>
<td>6</td>
<td>3</td>
<td>Hand</td>
<td>Both arms, leg</td>
<td>No</td>
<td>Postural</td>
</tr>
<tr>
<td>SAL-449-016 No</td>
<td>M</td>
<td>9</td>
<td>45</td>
<td>Foot</td>
<td>Cranial, neck, arms, legs, trunk</td>
<td>No</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>SAL-451-011 No</td>
<td>M</td>
<td>5</td>
<td>13</td>
<td>Hand</td>
<td>Cranial, neck, legs, arms, trunk</td>
<td>Postural, writing</td>
<td>Nystagmus, decreased reflexes</td>
</tr>
</tbody>
</table>

Results

There were eight index cases with typical, 13 with atypical and nine with uncertain phenotype. The phenotype was concordant among patients in 14 of the 22 families. The 946delGAG mutation in the DYT1 gene was found in four of the typical families (SAL-405, SAL-416, SAL-417 and SAL-420), two of the uncertain families (SAL-449 and SAL-451) and none of the atypical families. The mutation occurred in 10 patients, three unaffected parents aged 71 (SAL-405–2), 42 (SAL-451–7) and 39 (SAL-420–8) years, and one unaffected sibling (SAL-417–15) (Fig. 1). In family SAL-420, the grandfather was reported by the family to have suffered from writer’s cramp. Only two families (SAL-416 and SAL-449) were Ashkenazi Jews. The mutation was not detected in families with non-alcohol-responsive myoclonic dystonia.

The clinical characteristics of the 10 patients from the six DYT1 families are described in Table 1. All patients had their first dystonic posture at or before the age of 20. The mean age at onset was 9 ± 4 years (range 5–20 years) and patients were examined after a mean disease duration of 22 ± 17 years (range 3–45 years). The site of onset was an upper limb in all but one patient, who had onset in the foot. This is an unusual finding and is perhaps due to the small number of patients. At the time of examination, dystonia was generalized in seven patients. In three patients with disease durations ranging from 3 to 30 years, dystonia remained focal or segmental. Six patients had tremor, which was evident in four of them when writing. The two apparently sporadic cases (in families SAL-449 and SAL-451) were classified as uncertain because of the cranial involvement with facial and oromandibular dystonia in one and blepharospasm in the other.

The mean age of onset of dystonia in patients without the DYT1 mutation was significantly later (31 ± 23 years; range 3–74 years, n = 34) than in those with the deletion (P < 0.01). In families with generalized or mixed phenotypes, however, the mean age at onset was similar in DYT1 carriers.
which shared alleles of the common Ashkenazi Jew haplotype. haplotype but generalized in the patient from family SAL-449, of family SAL-416 without the common Ashkenazi Jew distribution of dystonia was different between the two patients with the dystonia could have been missed. In addition, our sample of were not systematically examined and mild arm onset observed for the onset of dystonia in the arm may be due to factors modulating the penetrance and phenotypic expression of the disease in addition to the DYT1 gene mutation. For clinical practice, it is important to consider the possibility that the DYT1 mutation is present in patients with focal dystonia.

A common founder effect is excluded in the French DYT1 families, which probably all derive from independent founder mutations. Furthermore, one Ashkenazi Jew patient carried the common Ashkenazi Jew haplotype, but it was absent in the other Ashkenazi Jew family, indicating at least another ancestral mutation among the Ashkenazi Jew population. At least six independent ancestral mutations can therefore be suspected in the French population.

Genetic counselling for ITD is difficult because of the low penetrance and variable clinical expression in DYT1 gene carriers, as well as the existence of further genetic heterogeneity demonstrated by linkage analysis in large pedigrees. Most of our families with early-onset generalized ITD did not have the 946delGAG mutation, and two new loci have recently been identified on chromosomes 8 (Almasy et al., 1997) and 18p (Leube et al., 1997), which are associated with different dystonic phenotypes.

Discussion

We report the screening of 30 families or isolated cases with idiopathic torsion dystonia for the DYT1 mutation, a GAG deletion at position 946. Six out of our 30 families carried the mutation. This indicates that the mutation frequency varies according to the population studied, since the majority of cases with typical early-onset dystonia in both Ashkenazi Jewish and non-Jewish patients carried the mutation studied previously (Ozelius et al., 1994; L. Ozelius, personal communication).

As predicted from previous reports, the DYT1 mutation was associated with early onset. The symptoms at onset differed, however, in patients who were reported in the literature before the DYT1 gene had been identified, but who were identified as haplotype carriers in family studies using linkage analysis with respect to the DYT1 locus on chromosome 9 (Bressman et al., 1994). In that study, 42 out of 90 (47%) patients had onset in the leg and 43 out of 90 (48%) in the arm compared with one out of nine and eight out of nine, respectively, in the present study. The difference observed for the onset of dystonia in the arm may be due to the fact that in the study of Bressman et al., the relatives were not systematically examined and mild arm onset dystonia could have been missed. In addition, our sample of patients with the DYT1 mutation is relatively small. The distribution of dystonia was different between the two Ashkenazi Jewish families, remaining focal in one patient of family SAL-416 without the common Ashkenazi Jew haplotype but generalized in the patient from family SAL-449, which shared alleles of the common Ashkenazi Jew haplotype.

Incomplete penetrance of ITD, estimated at 30–40% (Bressman et al., 1989), was confirmed by this study, since four individuals who carried the mutation were still unaffected at ages ranging from 7 to 71, later than the latest onset in three other carriers. However, onset up to 44 years of age was reported in the haplotype carrier study of Bressman et al. (1994). Expression of the disease was also incomplete in several other cases, since the disease did not become generalized in all patients, even after disease durations ranging up to 30 years. This suggests that there are other factors modulating the penetrance and phenotypic expression of the disease in addition to the DYT1 gene mutation. For clinical practice, it is important to consider the possibility that the DYT1 mutation is present in patients with focal dystonia.

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References


