Frequency and Phenotypic Variability of the GAG Deletion of the DYT1 Gene in an Unselected Group of Patients With Dystonia

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Background: Dystonia is a clinically and genetically heterogeneous movement disorder characterized by sustained muscle contractions affecting one or more sites of the body, frequently causing twisting and repetitive movements or abnormal postures. A 3-base pair (GAG) deletion in the DYT1 gene is held responsible for most cases of early-onset primary generalized dystonia in the Ashkenazi Jewish population as well as in non-Jewish patients.

Objectives: To investigate the prevalence of the GAG deletion in the DYT1 gene and the phenotypic variability in the general population by testing patients with different subtypes of dystonia from 4 different movement disorder outpatient clinics in Germany.

Methods: Two hundred fifty-six patients were tested for the GAG deletion mutation in the DYT1 gene by means of published primers and polymerase chain reaction amplification to determine GAG deletion status.

Results: Six of the 256 patients did carry the GAG-deletion in the DYT1 gene. However, only 2 of the 6 mutation carriers presented with what is thought to represent classic features of early-onset primary generalized dystonia. The DYT1 mutation was also detected in 2 patients with multifocal dystonia, 1 of them presenting with involvement of cranial and cervical muscles, and in 2 patients with writer’s cramp of both hands with only slight progression. Our findings demonstrate that the mutation may be associated with not only generalized but also segmental and multifocal forms of dystonia.

Conclusions: Our data underline the wide range of phenotypic variability of the DYT1 mutation. A priori prediction of the mutation carrier status in dystonic patients and genetic counseling of affected families with respect to the clinical manifestation may prove difficult.

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Dystonia is a clinically and genetically heterogeneous movement disorder characterized by sustained muscle contractions affecting one or more sites of the body, frequently causing twisting and repetitive movements or abnormal postures. Dystonia can be classified as primary or secondary. In primary forms, dystonia is the only symptom; it occurs spontaneously or familial and is often termed primary torsion dystonia (PTD). In secondary forms, dystonia develops because of a known environmental or metabolic cause or is associated with other hereditary neurodegenerative disorders. Primary torsion dystonia is the most prevalent form of dystonia and has a wide clinical spectrum including generalized, multifocal, segmental, and focal dystonia.

The syndrome is generally classified by clinical criteria, such as age at onset, distribution of symptoms and body parts involved, drug responsiveness, and family history. While most adult-onset dystonias are focal or segmental, involving mainly the neck and face with little or no progression, the typical early-onset variant is characterized by childhood onset (age <26 years), first manifestation in a limb, and generalization to other body parts during the course of disease. This categorization is more and more replaced by a genetic classification. At least 12 different gene loci have been implicated in the primary dystonias, mostly with autosomal dominant inheritance and reduced penetrance, but the underlying genes are known for only 2 subtypes: autosomal dominant or recessive dopa-responsive dystonia and DYT1 dystonia.

The PTD caused by mutations in the DYT1 gene (torsin A) is transmitted as an autosomal dominant trait with reduced penetrance of 30% to 40%. The disease is particularly prevalent in people of Ashkenazi Jewish descent because of a founder effect. A single mutation accounts for most cases of PTD in this population but has also
been identified in non-Jewish families. Haplotype data are compatible with the assumption that the same mutation has arisen independently more than once in different populations. The underlying 3-base pair (bp) (GAG) deletion in the coding region of the DYT1 gene results in the loss of one of a pair of glutamic acid residues near the carboxy terminus of torsin A.

Recently, another 18-bp deletion (Phe323-Tyr328) in the DYT1 gene was identified that causes the loss of 6 amino acids at the carboxy terminus, including the putative phosphorylation site of torsin A. This mutation has been described in a patient with early-onset dystonia and myoclonus; however, most cases of early-onset generalized dystonia (about 70%) are thought to be caused by the GAG deletion.

The phenotypic spectrum of this mutation characterized by a wide variability has been delineated in North American, British, French, German, and Russian patients. Frequently, the mutation is associated with a very distinct phenotype with early onset in a limb and generalization to other body parts within the next few years. Phenotypic variability less commonly includes focal dystonias such as writer’s cramp, torticollis, and spasmodic dysphonia.

There have been few genetic studies in unselected patients presenting with different subtypes of dystonias. In particular, the genetic contribution to adult-onset focal dystonia such as blepharospasm, torticollis, or writer’s cramp has not been investigated thoroughly, to our knowledge. Although these disorders are likely to be heterogeneous with respect to their etiologies, DYT1 mutation carriers may display only focal dystonia, and patients with focal dystonias have been described in families with other members who have generalized PTD.

In this study, the GAG deletion of the DYT1 gene was analyzed in 256 patients with different subtypes of dystonias to investigate the prevalence of this mutation in the general German population and to determine its phenotypic variability. Our data may be used to decide on the appropriate application of DNA diagnostic testing and may support genetic counseling.

## METHODS

### PATIENTS

Two hundred fifty-six patients were tested for the GAG deletion mutation in the DYT1 gene. Patients were recruited from movement disorder outpatient clinics of 4 participating centers: Departments of Neurology of the University Hospitals of Tübingen, Bochum, Rostock, and Münster, Germany. Inclusion criteria were as follows: (1) focal, segmental, multifocal, or generalized dystonia as defined by published clinical criteria and (2) a clinical course compatible with PTD without features indicating secondary dystonia.

All patients underwent complete neurologic examination, and the diagnosis of primary dystonia was established clinically. Age at onset and site of onset were determined by patients’ self-report and review of medical records if available. Patients were classified by age at onset, presence or absence of family history, and site of manifestation with dystonia at the last examination (focal, segmental, multifocal, and generalized).

### RESULTS

Among the 256 index patients tested for the GAG deletion mutation in the DYT1 gene, 12 (4 men and 8 women) had generalized dystonia, 11 (9 men and 2 women) presented with multifocal dystonia, 46 (16 men and 30 women) had segmental dystonia, and 187 (59 men and 128 women) presented with late-onset focal dystonia (Table 1). Among those with focal dystonia were 127 patients with torticollis, 44 with blepharospasm, 10 with writer’s cramp, 1 with pharyngolaryngeal dystonia, 3 with oromandibular dystonia, and 2 with trunk dystonia. Mean ± SE age at onset was 18 ± 6 years in patients presenting with generalized dystonia, which was significantly earlier than in patients with focal dystonia (46 ± 1 years) and in patients with segmental dystonia (41 ± 3 years) \(P < .001\), unpaired \(t\) test), but only slightly earlier than in patients with multifocal dystonia (32 ± 5 years; \(P < .07\), unpaired \(t\) test) (Table 1). Only 9 of the 12 patients presenting with generalized dystonia had clinical features typical of early-onset PTD with onset of symptoms before the age of 26 years according to the classification of Fahn et al. Three patients presented with generalized dystonia but age at onset was older than 40 years.

Most of the patients were white and none of them had Jewish ancestors. Six (2%) of the 256 index patients have been found to be carriers of the GAG deletion mutation in the DYT1 gene. Patients were classified by age at onset, presence or absence of family history, and site of manifestation with dystonia at the last examination (focal, segmental, multifocal, and generalized).
carried the GAG deletion. Mean age at onset of these patients was 15 ± 5 years. One patient developed symptoms only at age 41 years. If this patient were excluded from the calculation of the age at onset, mean age at onset would drop to 9 ± 0.1 years, which is significantly earlier than in DYT1-negative patients (mean age at onset, 44 ± 1 years; P < .001; unpaired t test). Two patients with features of typical, early-onset PTD were shown to be positive for the GAG deletion in the DYT1 gene. Patient 1 developed focal dystonia in her foot at age 7 years with subsequent generalization. Patient 2 developed gait difficulties at age 7 years and within years, developed dystonia of the arms with spread to the neck and the face (blepharospasm, oromandibular dystonia, cervical dystonia) (Table 2). Neither of these 2 patients had a family history of movement disorders. On the other hand, 10 patients presenting with generalized dystonia did not carry the GAG deletion of the DYT1 gene.

The DYT1 mutation was also detected in 2 patients with multifocal dystonia and in 2 patients with segmental dystonia. One patient presenting with multifocal dystonia (patient 3; Table 2) originated from Egypt. At age 10 years, the patient developed dystonic symptoms in the left lower leg (inversion of the foot). Within the next 3 years, dystonic symptoms involved the other leg and the right arm (writer’s cramp). His father was also shown to be GAG positive but did not show any dystonic symptoms only at age 41 years, with involvement of cranial muscles, which is uncommon for the dystonia subtype caused by the GAG deletion in DYT1. Furthermore, his brother, who had bilateral writer’s cramp, had a much longer course of disease (8 years) without any progression of the disease thus far.

The 2 carriers of the DYT1 mutation presenting with segmental dystonia also developed writer’s cramp at the ages of 10 and 12 years, with slight progression in subsequent years involving the shoulder and the other arm. One of these patients had a positive family history of severe early-onset generalized dystonia affecting his mother and 1 of 6 brothers. At age 9 years, the younger brother developed spasmodic torticollis. Subsequently, symptoms spread to the trunk and the legs and, to a lesser extent, to the upper extremities. At age 15 years he was wheelchair bound. His mother developed writer’s cramp at age 10 years with further generalization to the legs and the trunk. She was also wheelchair bound at the time of the study.

None of the patients with focal dystonia carried the mutation.

Of the 256 patients tested, the family history was positive in 52 (20%) and negative in 200 patients (78%). In 4 patients data on family history were not available. Among the 6 carriers of the GAG mutation, family history was positive in 3 cases (50%). Concerning the topography of dystonia, family history was positive in 2 (17%) of 12 patients with generalized dystonia, in 2 (18%) of 11 patients with multifocal dystonia, and in 10 (22%) of 46 patients with segmental dystonia. Thirty-eight (20%) of 187 patients with focal dystonia reported a positive family history.

To investigate prevalence and phenotypic variability of the GAG deletion in the DYT1 gene, we tested patients with different subtypes of dystonia from 4 different movement disorder outpatient clinics in Germany. While our cohort mainly consisted of German patients, frequency and phenotypic spectrum of the DYT1 mutation in our series seems to be similar to that observed previously in white populations.1-7 Our findings, therefore, seem to reflect well the clinical heterogeneity of the European population8 and thereby also partly that of the North American population.

Most of our patients were regularly seen for botulinum toxin treatment. Six of 256 patients were heterogeneous for a 3-bp (GAG) deletion of the DYT1 gene. However, only 2 of the 6 mutation carriers presented with typical PTD (ie, manifestation in a limb and onset of the disease in childhood). Both patients had no family history of movement disorders. Taking the incomplete penetrance, the occurrence of de novo mutations, and a selection bias in earlier studies into account, the lack of a positive family history is not surprising. Two patients with the GAG deletion had multifocal dystonia (patients 3 and 4; Table 2). Considering the short course of disease (3 and 5 years) thus far, they carry a significant risk of developing generalized dystonia within years. Patient 4 presented with atypical features of generalized dystonia, developing dystonic symptoms only at age 41 years, with involvement of cranial muscles, which is uncommon for the dystonia subtype caused by the GAG deletion in DYT1. Furthermore, his brother, who had bilateral writer’s cramp, had a much longer course of disease (8 years) without any progression of the disease thus far.

Two patients with segmental dystonia and with a longer course of disease (11 years each) also tested positive for the DYT1 mutation. Both developed dystonia at age 10 years with onset in one limb but with only slight progression in the following years. However, 1 patient (patient 5; Table 2) had a positive family history for PTD with a very severe course of disease, so the milder expression of symptoms might be due to lower penetrance. Patient 6 (Table 2), in contrast, presented with bilateral writer’s cramp and involvement of the upper arm and shoulder, without apparent family history of dystonia or other movement disorders.

### Table 2. Characteristics of DYT1-Positive Patients

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>Type of Dystonia</th>
<th>Age at Onset, y</th>
<th>Onset Localization</th>
<th>Course of Disease</th>
<th>Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>Generalized</td>
<td>7</td>
<td>Foot</td>
<td>28</td>
<td>Negative</td>
</tr>
<tr>
<td>2/M</td>
<td>Generalized</td>
<td>7</td>
<td>Foot</td>
<td>25</td>
<td>Negative</td>
</tr>
<tr>
<td>3/M</td>
<td>Multifocal</td>
<td>10</td>
<td>Foot</td>
<td>5</td>
<td>Positive</td>
</tr>
<tr>
<td>4/M</td>
<td>Multifocal</td>
<td>41</td>
<td>Writer’s cramp</td>
<td>3</td>
<td>Positive</td>
</tr>
<tr>
<td>5/M</td>
<td>Segmental</td>
<td>10</td>
<td>Writer’s cramp</td>
<td>11</td>
<td>Positive</td>
</tr>
<tr>
<td>6/F</td>
<td>Segmental</td>
<td>12</td>
<td>Writer’s cramp</td>
<td>11</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Patients positive for a GAG deletion in one allele of the DYT1 gene usually have a very distinct phenotype, developing dystonia in childhood with onset in one limb and generalization to other body parts during the course of disease. Involvement of the muscles of the neck and face is uncommon for the dystonia caused by the DYT1 GAG deletion.22

Family history is usually positive for dystonia. A typical clinical phenotype is both a sensitive and a specific indicator of the GAG status. However, expression can greatly vary, and penetrance is reduced to 30% to 40%. Whereas clinical expression of the GAG deletion is limited in the Ashkenazi Jewish population, clinical homogeneity is not found to the same extent in non-Jewish patients. In these patients, the course of disease is often milder, and a larger proportion had late onset. In support of this view, the findings in our patient group clearly demonstrate that carriers of the GAG deletion do not inevitably present with the typical features of early-onset generalized dystonia. The GAG deletion may also be present in patients with isolated writer’s cramp (brother of patient 4), and symptoms may remain segmental or multifocal with slight or no progression as shown in patients 4, 5, and 6. Furthermore, we found cervical and cranial dystonia in 2 of 6 mutation carriers. In one family member (patient 5; Table 2) dystonia started in the neck (torticollis), whereas patient 4 (Table 2) developed orofacial dystonia.

Writer’s cramp is apparently not an uncommon manifestation of the DYT1 mutation and seems to be more likely associated with GAG deletion than other focal subtypes. A total of 9 DYT1 carriers with predominant writer’s cramp, including 5 patients with bilateral segmental dystonia, have been described thus far in 7 families. The relatively high proportion of patients with cranial or cervical involvement might be due to the fact that patients were recruited from botulinum toxin clinics, possibly inducing a selection bias. In botulinum toxin clinics, patients with generalized dystonia usually are underrepresented, as they do not benefit from toxin treatment to the same extent as patients with focal or segmental dystonia.

These findings suggest that the phenotype associated with the DYT1 mutation might be milder and more focal than previously assumed. Mutations in the DYT1 gene have to be considered in clinical practice, particularly in writer’s cramp but also in patients presenting with cervical and cranial dystonia, in case of juvenile onset or if a family history of dystonia is present. In these cases, genetic testing is usually recommended. Family history was positive in only 3 (50%) of the 6 patients positive for the GAG deletion. This is much lower than reported earlier and might be due to the small number of patients in our cohort who tested positive for the deletion.

With one exception, we did not perform presymptomatic genetic analysis in unaffected family members. Therefore, we could not trace the parental origin of the mutation in all cases. However, in patient 3, the father who was asymptomatic proved to have the GAG deletion. On the other hand, a negative family history does not exclude the presence of GAG deletion because de novo mutations occur. Of the 12 patients with early-onset generalized dystonia in our series, only 2 carried the GAG deletion, which is significantly lower than findings in other studies, which report the mutation in up to 70% of patients with the typical DYT1 phenotype. Most likely, these differences reflect differences in the patient recruitment pattern. In our series, there were cases presenting with the characteristic DYT1 phenotype; however, we also included patients with generalized forms of dystonia but with a phenotype distinct from DYT1 dystonia. In particular, these patients showed prominent cranial involvement, which is thought to be more frequent in DYT1-negative patients. With most of our cases recruited through an epidemiologic study, the selection bias is likely to be less relevant. Taking differences in study design and patient recruitment into account, it is conceivable that our data represent a more accurate estimate of the true proportion of DYT1-positive cases in an unselected population of patients with dystonia in Europe.

None of the 187 patients with focal dystonia carried the DYT1 mutation. This confirms previous findings that most cases of focal dystonia seem to be sporadic by history and do not carry the GAG deletion. Positive family history was reported in 20% of our patients with focal dystonia, which is somewhat lower than rates in previous studies, which report affected relatives in 25% of patients. We did not investigate other genes known to cause dystonia, such as the DRD2 gene or genes underlying autosomal-dominant or recessive dopa-responsive dystonia, as they are associated with a very distinct phenotype. However, the high frequency of a positive family history in patients who do not carry the GAG deletion, particularly among patients with focal dystonia, suggests that other genes apart from DYT1 exist. In fact, there is increasing evidence of the genetic heterogeneity of dystonia, especially within the subtype of focal dystonia. Therefore, other genes remain to be characterized in dystonia.

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