1. Introduction

Focal dystonia is the most common form of primary dystonia characterized by involuntary twisting, abnormal postures and repetitive movements in a specific body part. Musician’s dystonia (MD) is a type of focal task-specific dystonia that presents with loss of voluntary motor control of extensively trained movements when a musician is playing his instrument. The pathophysiology of focal dystonia remains largely unknown, however, we have recently reported an aggregation of different types of movement disorders in the families of MD patients suggesting a genetic contribution to the disease [1].

To date, seven genes have been mapped for hereditary primary dystonia, however only two of these genes have been identified [2]: The three-base pair GAG deletion in the Tor1A gene (DYT1) typically causes early, limb-onset, generalized dystonia. While this mutation has also been identified in rare focal dystonia cases [2], it was previously excluded in a small group of MD patients [3]. Likewise, mutations in the recently identified THAP1 gene (DYT6) cause early-onset generalized or segmental dystonia but have also been found in rare focal dystonia patients [2]. We have recently screened a large series of MD patients for THAP1 mutations and identified one variant of unknown pathogenicity in the 5’ untranslated region [4]. To further elucidate the role of Tor1A in MD, we here screened a large number of patients for mutations.

2. Methods

All experiments of the study were conducted in accordance with the Declaration of Helsinki and were approved by the local ethics committee. After obtaining written informed consent of participating subjects, 184 unrelated primary MD patients (136 men, 48 women, age: 43.4 ± 12.1 [18–75] years, age at onset (AAO): 33.2 ± 10.7 [13–72] years, disease duration: 10.2 ± 8.7 [0–38] years), followed at the Hanover Institute of Music Physiology and Musicians’ Medicine, were neurologically examined by a movement disorder specialist (AS, EA). Peripheral blood samples were collected of patients for mutations. We have recently reported cramping when writing but were not available for further investigations. The remainder of her neurological examination and a brain MRI scan were normal. Any medical treatment was refused. Except for known polymorphisms (Exon 2: p.A82A, Intron 3: c.445–22G > A, Exon 4: p.D216H), no other Tor1A variant was detected in the subgroup of the 34 patients, who underwent complete sequencing of the gene. Details of methods and results of the study are illustrated in the Table 1.

3. Results

The majority of the 184 MD patients originated from Germany, three were Ashkenazi Jews. A positive family history of movement disorders was reported by 39 patients (21.2%). Isolated task-specific MD, i.e. MD with one or more additional features of primary dystonia (other types of dystonia or tremor in the same or other body parts), was present in 72 patients (39.1%).

Among the 184 patients, one was identified with the GAG deletion in the Tor1A gene (c.904_906delGAG) (0.5%). This 26 year-old woman developed a complex MD at the age of 13 years with involuntary cramping of her dominant right hand while playing the guitar and writing, terminating her instrumental education. She adjusted to writing with her left hand, but at age 22 years also developed left-sided writer’s cramp. Both of her parents also reported cramping when writing but were not available for further investigations. The remainder of her neurological examination and a brain MRI scan were normal. Any medical treatment was refused. Except for known polymorphisms (Exon 2: p.A82A, Intron 3: c.445–22G > A, Exon 4: p.D216H), no other Tor1A variant was detected in the subgroup of the 34 patients, who underwent complete sequencing of the gene. Details of methods and results of the study are illustrated in the Table 1.

4. Discussion

Our genetic screening study of one of the largest series of MD patients identified the GAG deletion in the Tor1A gene as an infrequent cause of MD with a mutation frequency of 0.5%. The GAG deletion-positive patient presented with early-onset complex MD and a probably positive family history. In a previous screening study of 18 MD patients this mutation was absent [3], however, rare GAG deletion-positive cases with other types of focal dystonia have been reported [2]. One of the detected Tor1A polymorphisms (D216H) has recently been suggested as a susceptibility factor for focal dystonia in familial cases, however not for MD [2]. Likewise, THAP1 mutations do not play a major role in MD since we found only one variant of unknown pathogenicity in the 5’ untranslated region (c.<32C>T) in 168 recently screened patients [4].

Therefore, it is conceivable that mutations at other known primary dystonia loci or as yet unknown other genetic factors may cause or contribute to the development of MD. Recently, an increased risk to develop complex MD has been demonstrated for patients with a positive family history of movement disorders, suggesting a genetic contribution particularly to these cases [5]. In keeping with this notion, our GAG deletion-positive patient also suffered from probably familial, complex MD. In addition, an early AAO, as seen in our patient, generally suggests a genetic cause of dystonia [2]. Therefore, based on the current knowledge, genetic testing for mutations in the Tor1A and THAP1
genes may be considered in patients with familial, early-onset, complex MD.

Acknowledgments

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References


Table 1

Clinical and genetic characteristics of the study population.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Type of MD (hand/embouchure)</th>
<th>Gender (women/men)</th>
<th>Age (years)</th>
<th>Age at onset (years)</th>
<th>Disease duration (years)</th>
<th>Positive family history</th>
<th>Tor1A GAG deletion frequency</th>
<th>Tor1A sequenced rs2296793 (Exon 2; p.A82A)</th>
<th>Tor1A sequenced rs10988526 (Intron 3; c.445-22G &gt; A)</th>
<th>Tor1A sequenced rs17849354 (Exon 4; p.D216H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated</td>
<td>112</td>
<td>82/30</td>
<td>34/78</td>
<td>42 ± 12</td>
<td>34 ± 11</td>
<td>9 ± 8[0–38]</td>
<td>14</td>
<td>0/112</td>
<td>20</td>
<td>6/20 het; 2/20 hom</td>
<td>1/20 het; 1/20 hom</td>
</tr>
<tr>
<td>MD</td>
<td>Complex</td>
<td>72</td>
<td>65/7</td>
<td>45 ± 13</td>
<td>32 ± 10</td>
<td>12 ± 9[0–37]</td>
<td>25</td>
<td>1/72</td>
<td>14</td>
<td>3/14 het; 0/14 hom</td>
<td>3/14 het</td>
</tr>
<tr>
<td>Complex</td>
<td>MD</td>
<td>72</td>
<td>14/58</td>
<td>45 ± 13</td>
<td>32 ± 10</td>
<td>12 ± 9[0–37]</td>
<td>25</td>
<td>0/112</td>
<td>14</td>
<td>0/14 hom</td>
<td>3/14 het</td>
</tr>
</tbody>
</table>

* Clinical characteristics of 73 patients have already been described elsewhere[5].