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Dominantly transmitted focal dystonia in families of patients with musician’s cramp

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No genetic cause of musician's dystonia, a type of focal task-specific dystonia (FTSD), has been mapped or identified, and little is known about the genetics of other forms of focal dystonia that represent the most common form of dystonia. Clinical examination of relatives of patients with focal dystonia revealed affected family members in approximately 25%.

The epidemiology of musician's dystonia suggests a possible genetic component also in this type of dystonia: 10% of musicians with dystonia report a positive family history of dystonia. In rare cases, a hereditary component has been demonstrated in patients with focal dystonia, such as the GAG deletion in the DYT1 gene. However, this mutation was excluded in a small group of musicians with dystonia.

In one family, focal dystonia has been linked to a specific gene locus (DYT7). We describe three multiplex families with musician’s dystonia and other forms of FTSD.

Methods. We conducted a pilot study on three families identified through three index patients with musician’s dystonia followed at the outpatient clinic of the Institute of Music Physiology and Musicians’ Medicine with a reported (Families A and B) or suspected (Family C) family history of FTSD. The families originated from different geographic regions in Germany (Families A and B) and the Ukraine/Russia (Family C). After approval of the study by the local ethics committee, the index patients were initially contacted by letter, followed by a telephone call. After obtaining written informed consent, pedigrees of the families were constructed. All family members with known or reported dystonia willing and able to participate underwent videotaped neurologic examinations. Questionnaires covering demographic information, handedness, and medical and occupational history were administered, and a blood sample was collected. The severity of the dystonia was rated with the Abnormal Involuntary Movement Scale in the most severely affected limb and the Global Disability Score (table). All other available and consenting family members underwent a telephone interview including the Beth Israel Dystonia Screen (BIDS) (adapted from Saunders-Pullman et al.).

Results. All three index patients with musician’s dystonia, a pianist and two guitarists, had two (n = 2) or three (n = 1) first-degree relatives identified with other forms of FTSD affecting the arms. The diagnosis of dystonia was definite in six and probable in one of the relatives. All affected family members had writer’s cramp, except one with “handicraft dystonia,” which occurred when threading a needle. A potential trigger of the dystonia (mostly increased practice) was reported by half of the dystonia patients.

Mode of transmission was compatible with autosomal dominant inheritance. In Families B and C, none of the affected individuals had related their dystonia to the musician’s dystonia in their family. Patient A.II.4, the mother of the pianist A.III.1, and Patient C.III.4, the sister of the guitarist C.III.1, were also professional pianists. They had writer’s cramp but did not show any dystonic signs when playing the piano. Patient B.III.1 with guitarist’s cramp reported additional discom-
fort when writing with his right hand and displayed slight writer's cramp.

The clinical examination and the video review confirmed the diagnosis in all cases identified with the BIDS. All four video examiners agreed with the diagnosis made by the in-person examiner (A.S.).

The known DYT1 mutations were excluded in all 10 patients.

Discussion. FTSD and, more specifically, musician's dystonia are currently considered mostly sporadic conditions. The findings in our three multiplex families have several interesting implications.

First, at least some cases of musician's dystonia and other forms of FTSD may have a shared underlying genetic cause. It is of note that all subjects, except C.II.1, had similar age at onset, brachial site of onset, and similar final distribution. As such, C.II.1 with later onset dystonia may either be an example of variable expressivity or represent a phenocopy. Interestingly, the pianist's mother and the sister of one of the guitarists were both professional pianists but showed exclusively writer's cramp and no musician's dystonia. Conversely, one musician's dystonia patient had additional slight writer's cramp. A recent study comparing seven patients with musician's dystonia with six patients with writer's cramp using transcranial magnetic stimulation suggested pathophysiologic differences between the

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex/age, y/</th>
<th>Profession</th>
<th>Handedness</th>
<th>Type of dystonia</th>
<th>Site of dystonia</th>
<th>Possible trigger (last 6 mo before onset)</th>
<th>Disease course</th>
<th>Benefit from sensory trick</th>
<th>BIDS</th>
<th>AIMS F-S</th>
<th>Disability Score (past 6 mo)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.II.3</td>
<td>M/77—</td>
<td>Medical doctor</td>
<td>R</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Neg.</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>A.II.4</td>
<td>F/74/28</td>
<td>Musician, Medical doctor</td>
<td>R</td>
<td>Writer's cramp</td>
<td>Arm (R)</td>
<td>Increased practice</td>
<td>Progressive</td>
<td>None</td>
<td>Not done</td>
<td>3-3</td>
<td>2+</td>
<td>None</td>
</tr>
<tr>
<td>A.II.5</td>
<td>M/81—</td>
<td>Librarian</td>
<td>R</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Neg.</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>A.III.1</td>
<td>M/40/27</td>
<td>Musician, Medical doctor</td>
<td>R</td>
<td>Pianist's cramp</td>
<td>Hand (R)</td>
<td>Pain syndrome</td>
<td>Progressive</td>
<td>Use of glove</td>
<td>Not done</td>
<td>1-4</td>
<td>1+</td>
<td>None</td>
</tr>
<tr>
<td>A.III.2</td>
<td>F/42/20</td>
<td>Teacher</td>
<td>R</td>
<td>Writer's cramp</td>
<td>Arm (R)</td>
<td>Increased practice</td>
<td>Progressive</td>
<td>None</td>
<td>Not done</td>
<td>1-3</td>
<td>1+</td>
<td>None</td>
</tr>
<tr>
<td>B.II.6</td>
<td>F/66—</td>
<td>Salesperson</td>
<td>R</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Neg.</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>B.II.7</td>
<td>M/71/20</td>
<td>Commercial clerk</td>
<td>R</td>
<td>Writer's cramp</td>
<td>Hand (R)</td>
<td>Stable</td>
<td>None</td>
<td>Pos.</td>
<td>1-2</td>
<td>1+</td>
<td>1-1</td>
<td>None</td>
</tr>
<tr>
<td>B.II.8</td>
<td>M/68—</td>
<td>Chemical worker</td>
<td>R</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Neg.</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>B.II.9</td>
<td>M/89—</td>
<td>Lift engineer</td>
<td>L</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Neg.</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>B.III.1</td>
<td>M/45/23</td>
<td>Musician, Medical doctor</td>
<td>R</td>
<td>Guitarist's cramp, writer's cramp</td>
<td>Hands</td>
<td>None</td>
<td>Stable</td>
<td>None</td>
<td>Not done</td>
<td>L 2-3, R 1-1</td>
<td>1+</td>
<td>None</td>
</tr>
<tr>
<td>B.III.2</td>
<td>F/46/33</td>
<td>Art historian</td>
<td>Ambidextrous</td>
<td>Writer's cramp</td>
<td>Arm (R)</td>
<td>Increased practice</td>
<td>Progressive</td>
<td>None</td>
<td>Not done</td>
<td>2-4</td>
<td>2+</td>
<td>None</td>
</tr>
<tr>
<td>C.II.1</td>
<td>F/79/75</td>
<td>Housewife</td>
<td>R</td>
<td>&quot;Handicraft&quot; dystonia</td>
<td>Hands</td>
<td>None</td>
<td>Stable</td>
<td>None</td>
<td>Pos.</td>
<td>L 1-2, R 1-3</td>
<td>1+</td>
<td>None</td>
</tr>
<tr>
<td>C.II.2</td>
<td>M/46/30</td>
<td>Musician</td>
<td>R</td>
<td>Guitarist's cramp</td>
<td>Hand (R)</td>
<td>Increased practice</td>
<td>Stable before BT</td>
<td>None</td>
<td>Not done</td>
<td>2-3</td>
<td>1+</td>
<td>BT: improvement</td>
</tr>
<tr>
<td>C.III.3</td>
<td>M/54/20</td>
<td>Businessman, watchmaker</td>
<td>R</td>
<td>Writer's cramp</td>
<td>Hand (R)</td>
<td>None</td>
<td>Stable</td>
<td>None</td>
<td>Pos.</td>
<td>1-1</td>
<td>1+</td>
<td>None</td>
</tr>
<tr>
<td>C.III.4</td>
<td>F/45/05</td>
<td>Musician</td>
<td>R</td>
<td>Writer's cramp</td>
<td>Hand (R)</td>
<td>None</td>
<td>Stable</td>
<td>None</td>
<td>Pos.</td>
<td>1-2</td>
<td>1+</td>
<td>None</td>
</tr>
</tbody>
</table>

Abnormal Involuntary Movement Scale (AIMS): P = provoking factor: 0 = no dystonia at rest or on action; 1 = dystonia on particular action; 2 = dystonia on many actions; 3 = dystonia on action of distant part of body, or intermittently at rest; 4 = dystonia present commonly at rest; S = severity factor arm: 0 = no dystonia present; 1 = slight dystonia, clinically insignificant; 2 = mild, obvious dystonia, but not disabling; 3 = moderate, able to grasp or playing an instrument, with some manual function; 4 = severe, no useful grasp or playing an instrument.

Disability Score: Global Assessment: 0 = no dystonia present; 1+ = mild dystonia, little functional impairment; 2+ = moderate dystonia, functional impairment or pronounced dystonic movements or postures present; 3+ = severe dystonia, wheelchair required or forceful uncomfortable dystonic spasms present.

R = right; L = left; NA = not applicable; BIDS = Beth Israel Dystonia Screen; BT = botulinum toxin.
two conditions. Given the possible common genetic cause of musician’s dystonia and FTSD in a subset of patients, observed differences in the patterns of sensorimotor interaction could be interpreted as a secondary rather than a primary phenomenon in such patients.

Second, our pilot study confirms previous findings of the presence of dystonic signs in a considerable number of relatives of index patients with focal dystonia with an autosomal dominant transmission pattern. Currently, a total of 360 professional musicians with musician’s dystonia are followed in Hanover, at least 25 of whom have a reported or suspected family history of dystonia (unpublished data based on a review of the medical charts). It is expected that this number will increase upon systematic family history taking and neurologic examination of the families. Therefore, the notion of musician’s dystonia and FTSD as a sporadic and purely occupational type of dystonia should be reconsidered.

Third, it may be speculated that families collected through an index patient with musician’s dystonia would represent a more homogeneous patient group than, for example, a consecutively ascertained patient sample with mixed types of dystonia attending a botulinum toxin clinic. Further underlining the homogeneity of our families, all 10 affected members had a form of upper limb dystonia. Not surprisingly, none of our patients carried the DYT1 mutation that has only occasionally been linked to focal dystonia. Although our families are too small to perform meaningful linkage analyses and the identification of large pedigrees with musician’s dystonia/FTSD suitable for a classic genome scan with microsatellite markers is unlikely, modern methods of genome-wide linkage in a large number of multiplex families with musician’s dystonia/FTSD or of association in musician’s dystonia cases compared with controls may lead to the identification of the genetic factors that cause or contribute to focal dystonia, the most common form of dystonia.

Acknowledgment
The authors thank the patients and family members for their participation.

References
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