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CME

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

Abstract—Musician's dystonia is generally considered a sporadic disorder. The authors present three families with the index patient affected by musician's dystonia, but other forms of upper limb focal task–specific dystonia (FTSD), mainly writer's cramp, in seven relatives. Our results suggest a genetic contribution to FTSD with phenotypic variability, including musician's dystonia.

NEUROLOGY 2006;67:1–1

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fn1 No genetic cause of musician's dystonia, a type of focal task–specific dystonia (FTSD),[1,2] 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%.[3] The epidemiology of musician's dystonia suggests a possible hereditary component also in this type of dystonia: 10% of musicians with dystonia report a positive family history of dystonia.[1] In rare cases, a hereditary component has been demonstrated in patients with focal dystonia, such as the GAG deletion in the *DYT1* gene.[4] However, this mutation was excluded in a small group of musicians with dystonia.[5] In one family, focal dystonia has been linked to a specific gene locus (DYT7).[6] 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.[7]). If screened positive, the same examinations as described for family members with known dystonia were performed. If negative, only questionnaires and blood samples were collected by mail. The videotapes were independently reviewed by four members of the team (E.A., H.-.C.J., J.H., and C.K.), and a consensus diagnosis was established. A diagnosis of dystonia was made following previously published criteria[1,8]: 1) definite: muscle contractions producing characteristic twisting or flexion or extension movements and postures consistently present; 2) probable: movements and postures of insufficient intensity or consistency to merit classification as definite; 3) possible: muscle contractions not considered abnormal but remotely suggestive of dystonia; 4) no dystonia. All patients were tested for the known mutations in the *DYT1* gene. T1

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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, including two of the three musicians. Detailed demographic, clinical, and pedigree information on all 10 patients and all examined relatives is summarized in the table and the figure. No patient reported neuroleptic exposure or significant peripheral trauma of the affected arm. F1

Mode of transmission was compatible with autosomal dominant inheritance. Although all affected individuals reported symptoms, none had sought medical treatment. 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

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This work was supported by the Volkswagen Foundation, the Dystonia Medical Research Foundation, and the Bachmann-Strauss Dystonia & Parkinson's Foundation, Inc.

Disclosure: The authors report no conflicts of interest.

Received January 10, 2006. Accepted in final form April 20, 2006.

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<article article-type="brief-report"> •
<article-id pub-id-type="doi">10.1212/01.wnl.0000230148.00035.f9</article-id>

Table *Demographic data and clinical findings in 15 family members from three patients with musician's dystonia*

Subject	Sex/age, y/ age at onset, y	Profession	Handedness	Type of dystonia	Site of dystonia	Possible trigger (last 6 mo before onset)	Disease course	Benefit from sensory trick	BIDS	AIMS P-S	Disability Score	Therapy (past 6 mo)
A.II.3	M/77/—	Medical doctor	R	None	NA	NA	NA	NA	Neg.	NA	NA	None
A.II.4	F/74/28	Musician, Medical doctor	R	Writer's cramp	Arm (R)	Increased practice	Progressive	None	Not done	3-3	2+	None
A.II.5	M/81/—	Librarian	R	None	NA	NA	NA	NA	Neg.	NA	NA	None
A.III.1	M/40/27	Musician, Medical doctor	R	Pianist's cramp	Hand (R)	Pain syndrome	Progressive	Use of glove	Not done	1-4	1+	None
A.III.2	F/42/30	Teacher	R	Writer's cramp	Arm (R)	Increased practice	Progressive	None	Not done	1-3	1+	None
B.II.6	F/66/—	Salesperson	R	None	NA	NA	NA	NA	Neg.	NA	NA	None
B.II.7	M/71/20	Commercial clerk	R	Writer's cramp	Hand (R)	None	Stable	None	Pos.	1-2	1+	None
B.II.8	M/68/—	Chemical worker	R	None	NA	NA	NA	NA	Neg.	NA	NA	None
B.II.9	M/69/—	Lift engineer	L	None	NA	NA	NA	NA	Neg.	NA	NA	None
B.III.1	M/45/23	Musician, Medical doctor	R	Guitarist's cramp, writer's cramp	Hands	None	Stable	None	Not done	L 2-3, R 1-1	1+	None
B.III.2	F/46/33	Art historian	Ambidextrous	Writer's cramp	Arm (R)	Increased practice	Progressive	None	Not done	2-4	2+	None
C.II.1	F/79/75	Housewife	R	"Handicraft" dystonia	Hands	None	Stable	None	Pos.	L 1-2, R 1-3	1+	None
C.III.1	M/46/30	Musician	R	Guitarist's cramp	Hand (R)	Increased practice	Stable before BT	None	Not done	2-3	1+	BT: improvement
C.III.3	M/54/20	Businessman, watchmaker	R	Writer's cramp	Hand (R)	None	Stable	None	Pos.	1-1	1+	None
C.III.4	F/45/35	Musician	R	Writer's cramp	Hand (R)	None	Stable	None	Pos.	1-2	1+	None

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.

AQ: 1 R = right; L = left; NA = not applicable; BIDS = Beth Israel Dystonia Screen.

show any dystonic signs when playing the piano. Patient B.III.1 with guitarist's cramp reported additional discomfort 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.

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 writ-

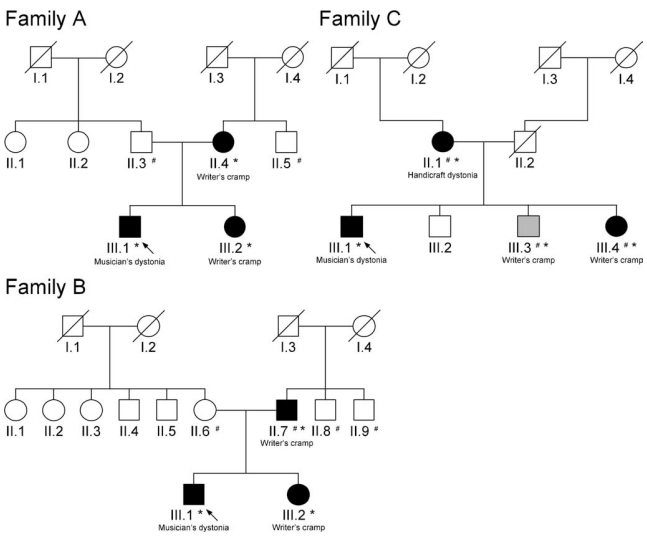

Figure. Pedigrees of Families A, B, and C. Asterisks (*) indicate personally examined patients that are shown on the videotape (on the Neurology Web site at www.neurology.org). Family members interviewed with the Beth Israel Medical Center Dystonia Screen are marked with a pound sign (#). Symbols of definitely affected family members are shaded in black; symbols of probably affected family members are shaded in gray; index patients (with musician's dystonia) are marked with an arrow.

er's cramp using transcranial magnetic stimulation suggested pathophysiologic differences between the two conditions.[9] 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.[3] 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.[4] 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.

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