Is musician’s dystonia an inherited condition?

Alexander Schmidt¹, Hans-Christian Jabusch², Eckart Altenmüller³, Johann Hagenah¹, Rachel Saunders-Pullman⁴⁵, Susan B. Bressman⁴⁵, Alexander Münchau⁶, and Christine Klein¹

¹ Department of Neurology, University of Lübeck, Germany
² Institute of Musicians’ Medicine, Dresden University of Music
Carl Maria von Weber, Germany
³ Institute of Music Physiology and Musicians’ Medicine, Hanover University
of Music and Drama, Germany
⁴ Department of Neurology, Albert Einstein College of Medicine, USA
⁵ Department of Neurology, Beth Israel Medical Center, USA
⁶ Department of Neurology, University Medical Center, Hamburg-Eppendorf, Germany

Musician’s dystonia (MD) is generally considered a sporadic disorder that presents with loss of voluntary motor control of extensively trained movements. To test the hypothesis of a genetic etiology in at least a subset of MD, we initiated a large clinical genetic study. The families of 28 index patients with MD, 14 with a reported positive family history of focal task-specific dystonia (FTSD) and 14 with no known family history (FH-), underwent a standardized telephone screening interview using the Beth Israel Dystonia Screen. Videotaped neurological examinations were performed on all participants who screened positive, and consensus diagnoses were established. All patients were investigated for the GAG deletion in DYT1; suitable families were tested for linkage to DYT7. A diagnosis of dystonia was established in all 28 index patients and in 19 of 97 examined relatives (MD: n=8, other FTSD: n=9, other dystonias: n=2), 5 of whom were members of FH- families. In total, 18 families were multiplex with 2-4 affected members. The GAG deletion was not present in any of the tested patients. Linkage to DYT7 could be excluded in one of the 11 informative families. Our results suggest a genetic contribution to MD with phenotypic variability including FTSD.

Keywords: musician's dystonia; focal task-specific dystonia; genetics; movement disorders; DYT1 gene
Musician’s dystonia (MD), a type of focal task-specific dystonia (FTSD), presents with painless muscular incoordination or loss of voluntary motor control of extensively trained movements when a musician is playing the instrument (Altenmüller 2003). While the pathophysiology remains largely elusive, MD has been associated with intensive training regimes and thus been considered a form of occupational cramp. However, the epidemiology also suggests a possible hereditary component: 10% of MD patients report a positive family history of dystonia (Altenmüller 2003). In rare cases of focal dystonia, a hereditary component has been demonstrated, such as the GAG deletion in the DYT1 gene (Defazio et al. 2007). However, this mutation was excluded in a small group of MD patients (Friedman et al. 2000). In two families, focal dystonia has been linked to a specific gene locus on chromosome 18 (DYT7) (Defazio et al. 2007). More recently, the report of three families with putative autosomal dominant inheritance of FTSD in relatives of patients with MD has lent support to the concept of a genetic contribution to MD (Schmidt et al. 2006). To test the hypothesis of a genetic etiology in at least a subset of MD and to explore a possible relationship between MD and other forms of FTSD, we initiated a large clinical genetic study of MD based on systematic examination of 28 families (Schmidt et al. 2009).

METHOD

Recruitment of study sample and onsite examination

After approval of the study by the local ethics committee and obtaining informed consent, we included 28 professional musicians diagnosed with focal dystonia at the outpatient clinic of the Hanover Institute of Music Physiology and Musicians’ Medicine (index patients). Based on history and clinical features, all were classified as having likely primary dystonia. Fourteen of these index patients had a reported positive family history (FH+) of FTSD and were matched to 14 patients with no known family history (FH-) for age, sex, instrument group, and type of dystonia (limb versus embouchure). In a first telephone contact, all index patients were asked to report known cases of dystonia in their families (family history interview). All available first- and second-degree relatives with no known dystonia underwent a standardized telephone screening interview using a modified version of the Beth Israel Dystonia Screen containing additional questions screening for MD (BIDS, adapted from Saunders-Pullman et al. 2005). Videotaped neurological examinations were performed at a home visit by the same examiner (AS) in all 28 index patients, in all 15 relatives with a known or reported form of FTSD, and in all 11 relatives who screened positive for dystonia in the BIDS.
Diagnostic criteria, video rating, and consensus diagnosis

A diagnosis of dystonia was made following previously published criteria (Altenmüller 2003, Bressman et al. 2002):

• Definite: muscle contractions producing characteristic twisting, flexion, or extension movements and postures consistently present
• Probable: movements and postures of insufficient intensity or consistency to merit classification as definite
• Possible: muscle contractions not considered abnormal but remotely suggestive of dystonia
• No dystonia

All examined family members were diagnosed in a three-step process: first, by onsite examination including information about pedigree structure and medical history (AS); second, by blinded independent video review by four movement disorders specialists (EA, JH, CK, and AM), one of whom is an expert in MD (EA); third, by evaluation of questionable cases by two blinded external collaborators (SB and RSP). Finally, a consensus diagnosis was established.

Molecular analysis

Peripheral blood samples were collected from all probands, and DNA was extracted and screened for the known three-nucleotide (GAG) deletion in the DYT1 gene. To test for a possible involvement of the DYT7 locus, suitable families were investigated for linkage using the following six DNA microsatellite markers: D18S481, D18S54, D18S976, D18S452, D18S843, and D18S1153.

RESULTS

Consensus diagnoses

The study procedure and main results are illustrated in Figure 1. MD was established by onsite examination and videotape review in all 14 FH+ (definite: n=13, probable: n=1) and in all 14 FH- (definite: n=14) index patients. In total, 97 (56 FH+, 41 FH-) first- and second-degree relatives of these index patients were examined. Seventeen of the 56 FH+ relatives had a previously known FTSD (MD: n=7, writer’s cramp (WC): n=10), two of these relatives were deceased. Family history interview revealed another two deceased relatives with MD, one FH+ and one FH-. Using the BIDS in 78 putatively unaf-
Figure 1. Flow chart of the study displaying study procedure and results. FH+ = reported positive family history of FTSD, FH- = no known family history, pts. = patients, MD = musician’s dystonia, FTSD = focal task-specific dystonia, BIDS = Beth Israel Dystonia Screen, def = definite, prob = probable, poss = possible, (+) = additional dystonias or additional other movement disorders in some individuals definitely, probably, or possibly present. (See full color version at www.performancescience.org.)

A type of dystonia was confirmed as definite or probable in 19 of the 26 relatives who had a previously known form of FTSD or screened positive with the BIDS. Fourteen of these 19 probands were members of FH+ (MD: n=7, other FTSD: n=6, other dystonias: n=1) and five of FH- (MD: n=1, other FTSD: n=3, other dystonias: n=1) families. In 27 of the 47, FH+ and FH- family members with definite or probable dystonia one (n=18), two (n=8), or three (n=3) additional forms of dystonia were present at least possibly—i.e. these patients were not only affected with one dystonia type (e.g. MD) but also with another FTSD (e.g. WC) or additional other dystonias (e.g. cervical dystonia). In 23 of the aforementioned 47 family members, one (n=20), two (n=2), or three (n=1) additional other movement disorders or movement abnormalities were diagnosed as definitely or probably present, including tremor (n=6), tics (n=4), chorea (n=2), involuntary perioral movements (n=2), athetosis (n=1), mirror movements (n=8), and parkinsonian features (n=4). In total, 18 (13 FH+, 5 FH-) of the entire set of 28 families were multiplex families (based on definite, probable, and possible diagnoses of dystonia) with two to four affected family members in one (n=6), two (n=10), or three
(n=2) generations, compatible with autosomal dominant inheritance in at least 12 families.

**Molecular findings**

The DYT1 GAG deletion was not present in any of the tested patients. Due to the small number of affected family members, linkage to the DYT7 locus could not be excluded in 10 of the 11 informative families. In one family, affected offspring did not share a common DYT7 haplotype with their affected father. Therefore, linkage to the DYT7 locus could be excluded in this family.

**DISCUSSION**

The present study expands previous findings of the presence of dystonia in a considerable number of relatives of index patients with MD with an autosomal dominant pattern of transmission (Schmidt et al. 2006). Affected relatives were identified both of index FH+ and FH- patients. Although none of the 14 FH- index patients reported any cases of dystonia in their families, five of them (36%) had affected relatives with dystonia on clinical examination. MD, however, has long served as a textbook example of a purely occupational dystonia, even more so than other forms of FTSD such as writer’s cramp (WC). Due to the large number of familial cases observed also in MD, the concept of MD as a sporadic and solely “environmentally” acquired type of dystonia needs to be reconsidered. Surprisingly, a considerable number of identified patients with MD or WC displayed additional types of dystonia. In addition, an unexpected number of other hypo- and hyperkinetic movement disorders, some of them unusual, were present in a considerable number of participants. As a broad intra- and interfamilial phenotypic spectrum is known for many genetic movement disorders, it is tempting to speculate that at least part of the observed additional movement disorders in our patients are due to a shared underlying genetic cause. Not surprisingly, none of our patients carried the GAG deletion in the DYT1 gene that has only rarely been linked to focal dystonia (Defazio et al. 2007). Due to relatively small number of affected family members, linkage to the DYT7 gene locus that has been described in two families with focal dystonia (Defazio et al. 2007) could not be definitively excluded in all but one family. Based on the results of the present study, our main hypothesis is that at least some cases of MD, other forms of FTSD, and possibly even other types of movement disorders may have a shared underlying genetic cause. The genetic factors that cause or contribute to focal dystonia still have to be identified.
Acknowledgments

The authors thank the patients and family members for their participation in the study. This work was supported by a grant from the Dystonia Medical Research Foundation, the Bachmann Strauss Foundation, and the Volkswagen Foundation. CK is a recipient of a Schilling Award from the Hermann and Lilly Schilling Foundation.

Address for correspondence

Alexander Schmidt, Department of Neurology, University of Lübeck, Ratzeburger Allee 160, Lübeck 23538, Germany; Email: alexander.schmidt@neuro.uni-luebeck.de

References


