

# Genome-Wide Association Study in Musician's Dystonia: A Risk Variant at the Arylsulfatase G Locus?

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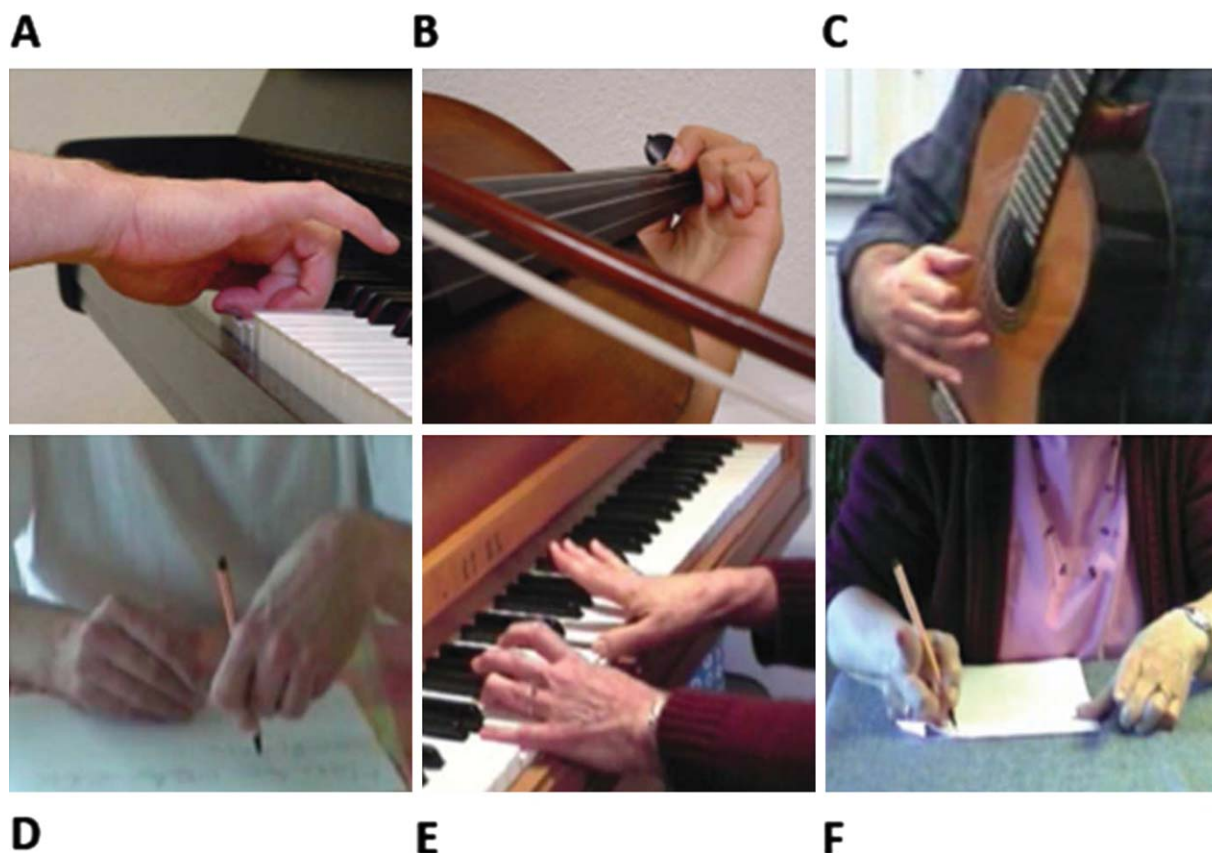
**ABSTRACT:** Musician's dystonia (MD) affects 1% to 2% of professional musicians and frequently terminates performance careers. It is characterized by loss of voluntary motor control when playing the instrument. Little is known about genetic risk factors, although MD or writer's dystonia (WD) occurs in relatives of 20% of MD patients. We conducted a 2-stage genome-wide association study in whites. Genotypes at 557,620 single-nucleotide polymorphisms (SNPs) passed stringent quality control for 127 patients and 984 controls. Ten SNPs revealed  $P < 10^{-5}$  and entered the replication phase including 116 MD patients and 125 healthy musicians. A genome-wide significant SNP ( $P < 5 \times 10^{-8}$ ) was also genotyped in 208 German or Dutch WD patients, 1,969 Caucasian, Spanish, and Japanese patients with other forms of focal or segmental dystonia as well as in 2,233 ethnically matched controls. Genome-wide significance with MD was observed for

an intronic variant in the arylsulfatase G (*ARSG*) gene (rs11655081;  $P = 3.95 \times 10^{-9}$ ; odds ratio [OR], 4.33; 95% confidence interval [CI], 2.66-7.05). rs11655081 was also associated with WD ( $P = 2.78 \times 10^{-2}$ ) but not with any other focal or segmental dystonia. The allele frequency of rs11655081 varies substantially between different populations. The population stratification in our sample was modest ( $\lambda = 1.07$ ), but the effect size may be overestimated. Using a small but homogenous patient sample, we provide data for a possible association of *ARSG* with MD. The variant may also contribute to the risk of WD, a form of dystonia that is often found in relatives of MD patients. © 2013 International Parkinson and Movement Disorder Society

**Key Words:** dystonia; association study; risk factor; sulfatase

Musician's dystonia (MD) is an important medical problem in musicians<sup>1</sup> that is known to affect 1% to 2% of professional instrumentalists.<sup>2</sup> As a type of focal task-specific dystonia (FTSD), it presents with

painless muscular incoordination or loss of voluntary motor control when a musician is playing his or her instrument (Fig. 1A-C).<sup>3,4</sup> Typical symptoms include involuntary flexion or extension of individual fingers.



**FIG. 1.** Musician's dystonia. Musician's dystonia (MD) presents with involuntary muscle contractions and abnormal posturing when playing the instrument. **A-C:** Flexion dystonia of individual fingers in a pianist (**A**), a violinist (**B**), and a guitarist (**C**). **D:** MD may be complicated by additional writer's dystonia (WD). MD may have a positive family history: relative with MD (**E**); relative with WD (**F**).

Although available therapies including botulinum toxin injections may improve symptoms in selected patients, MD has to be regarded as incurable and, in many cases, terminates musical performance careers.<sup>4,5</sup> Thus, MD is not only of great medical but also of sociocultural interest, given a registered 176,200 professional musicians in the United States alone,<sup>6</sup> with prominent musicians affected, including both contemporary (eg, Leon Fleisher) and historical (eg, Robert Schumann) artists.

Notably, 44% of MD patients develop more complex types of dystonia, mostly combined with writer's dystonia (WD; Fig. 1D).<sup>7</sup> Both tasks, playing an instrument and writing, are accomplished through highly trained fine finger and hand movements and have been associated with intensive training and repetitive movements, that is, overlearned behavior.<sup>1,8</sup> Accordingly, their pathophysiology has been related to aberrant brain plasticity and to loss of inhibition on cortical, spinal, and brainstem levels.<sup>9</sup> Recent findings in MD and other forms of focal dystonia indicate, however, that the condition has a high heritability and is thus at least partly genetic in origin.<sup>7,10-13</sup> About 20% of MD patients report a positive family history, often including WD or even MD (Fig. 1E,F), but only rarely other (non-task-specific) forms of dystonia, such as cervical dystonia or blepharospasm.<sup>10,11</sup> Nevertheless, extended multiplex families are rare,<sup>14</sup> suggesting that genetic susceptibility factors may play a larger role than pure monogenic causes. However, genetic variants conferring risk of dystonia are currently unknown.

Genome-wide association studies (GWASs) have proven a valuable approach to identifying genetic risk factors for many traits,<sup>15</sup> but no GWAS has been published to date for any form of dystonia. One explanation for this might be the marked phenotypic and genotypic heterogeneity,<sup>16</sup> which decreases the power to find novel loci. Here, we report the first GWAS in dystonia and focus on a homogeneous subtype, that is, MD. We identified 1 locus with genome-wide significance. This single-nucleotide polymorphism (SNP) also showed an association with WD but not with other forms of focal or segmental dystonia.

## Patients and Methods

### Study Participants

The study was approved by the local ethics committee at the University of Lübeck, Lübeck, Germany (reference number 04-180), and all subjects gave written informed consent. We collected 257 unrelated white professional musicians diagnosed with focal dystonia at the Hanover Institute of Music Physiology and Musicians' Medicine who were included in the GWAS stage or the replication. The diagnostic workup was conducted by a senior neurologist and a

physician, both with special expertise in musicians' medicine and movement disorders and a university degree in music (E.A. and H.-C.J.) and included a complete neurological examination and visual inspection while patients were playing their instruments. Further, 208 patients with WD were recruited at 4 movement disorder centers—Lübeck, Kiel, and Tübingen (Germany) and Amsterdam (The Netherlands)—by experienced movement disorders specialists. Finally, 1,969 patients with other forms of focal or segmental dystonia were recruited at movement disorder clinics in Rome, Milan, and Bari (Italy), Sevilla (Spain), Hamburg, Lübeck, and Tübingen (Germany), Amsterdam (The Netherlands), Belgrade (Serbia), and Tokushima and Kyoto (Japan). Based on history, clinical features, and absence of atypical signs, all patients were classified as having primary dystonia.

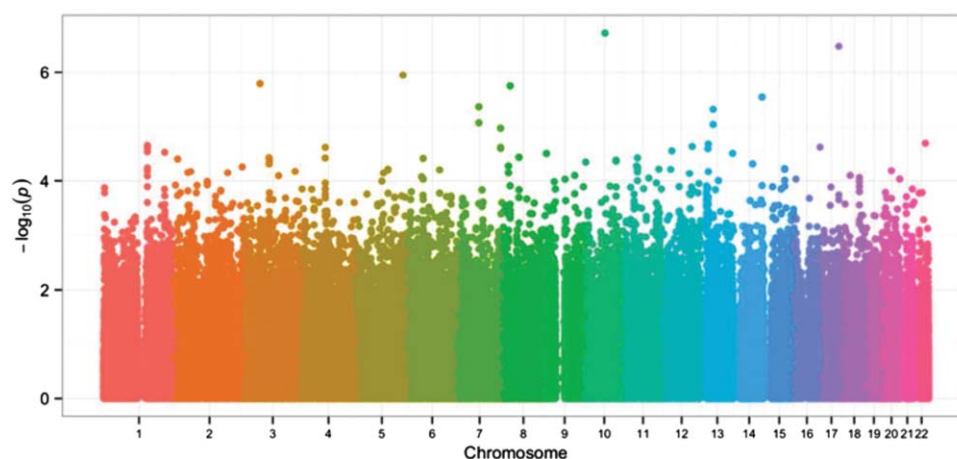
Samples from the PopGen cohort<sup>17</sup> served as controls for the initial genotyping step (GWAS stage). As controls for the replication step, we collected DNA samples from 125 healthy professional musicians from Germany who underwent a personal interview that included structured questionnaires covering general medical conditions and dystonia as well as a brief examination. Another control group consisted of 278 newly collected healthy subjects from the population-based control cohort EPIPARK from Lübeck, Germany.<sup>18</sup> In addition, ethnically matched controls were provided by the participating movement disorder centers (Supporting Table 1).

### Genotyping

Genomic DNA was isolated from peripheral blood lymphocytes. Genotype analysis at the GWAS stage was carried out for patients and controls separately using the Affymetrix Genome-Wide Human SNP Array 6.0. For replication and validation, genotyping was performed by Sanger sequencing in a single laboratory using the same machine, thus excluding differences in genotyping platforms.

### Quality Control of GWAS Samples

Quality control was performed as described in detail elsewhere.<sup>19</sup> In brief, 32 samples failed to yield genotyping signals and were excluded from genotype calling. Another 208 samples were excluded because of autosomal heterozygosity > 3 standard deviations from the mean or genotyping call fractions < 97%. An additional 4 individuals (all cases) were excluded because of the biological relationship indicated by a proportion of identity by descent  $\geq 0.125$  to other members of the GWAS group. From each group of putatively related individuals, those with the highest SNP call rates were kept in the study sample. SNPs with minor allele frequencies < 1%, genotyping fractions < 98% per study group, and  $P < 10^{-4}$  from the Hardy-Weinberg lack-of-fit test were excluded. Remaining SNPs yielding



**FIG. 2.** Manhattan plot of the genome-wide association. The results of the first stage of the association study are shown for all subjects. Manhattan plot for genome-wide association with dystonia using 557,620 genotyped SNPs.  $-\log_{10} P$  values are plotted against chromosomal positions.

association signals of  $P < 10^{-5}$  underwent an additional quality control step by visual inspection of signal intensity plots (Fig. S1). A total of 557,620 SNPs were used for the GWAS after extensive quality control.

### Statistical Analysis

Analysis for association of single SNPs with MD susceptibility was performed with additive SNP coding using linear logistic regression with PLINK.<sup>20</sup> In previous studies, we and others extensively investigated population stratification in the German population<sup>21,22</sup> as well as in the Dutch and German populations<sup>23</sup> and showed that genetic differentiation is low within Germany (northern vs. southern Germany,  $F_{st} = 1.7 \times 10^{-4}$ ; eastern vs. southern Germany,  $F_{st} = 5.4 \times 10^{-4}$ ) and between Germany and The Netherlands. Such minor degrees of population substructure cannot be detected without using prior information of subpopulation membership. Even when including the extreme  $P$  values, this finding is supported by both a genomic-control  $\lambda$  of 1.07 in our study and the Q-Q plot (Fig. S2). Twenty-seven SNPs with  $P < 10^{-5}$  were identified, of which 10 SNPs were selected for wet-lab replication after visual inspection of signal intensity plots. For the first stage,  $P$  values are given as 2-tailed values, whereas in the following stages only 1-tailed  $P$  values were calculated.

For combined analysis of the initial GWAS and the replication stage, a fixed-effects approach was used with inverse-variance weighting. Effect estimates and 95% confidence intervals were estimated from logistic regression with additive SNP coding. Attributable risks among the exposed were estimated using odds ratios. SNP associations were considered to be genome-wide significant if the pooled  $P < 5 \times 10^{-8}$ .

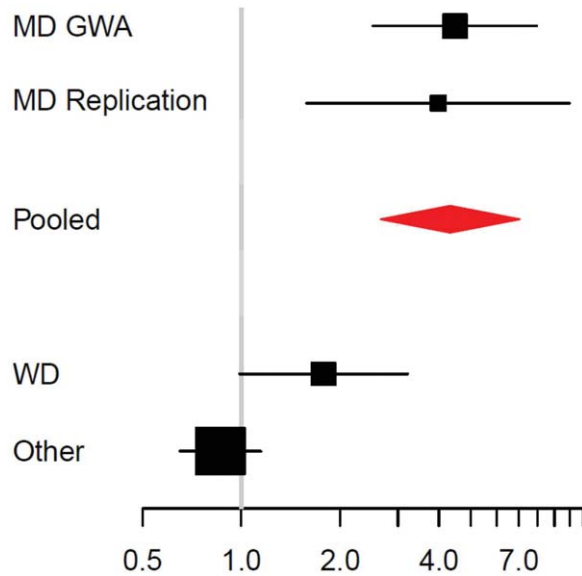
## Results

In the initial MD case-control GWAS stage, we included 141 mostly German MD patients (Table S1) and 1,214 population-based controls from northern Germany (PopGen)<sup>17</sup> to identify genetic risk factors with large effects contributing to MD. Genotypes at 557,620 SNPs in 127 patients and 984 controls passed stringent GWA-stage quality control. Genotype frequencies of these SNPs in the patients and controls can be found online in the Supporting Material. Individual genotypes are available on request. Population stratification in the German population was modest,<sup>21</sup> as confirmed by an estimated  $\lambda$  of 1.07 (Fig. S2). A total of 10 SNPs from 8 genetic regions revealed  $P < 10^{-5}$  after extensive quality control (Fig. 2; Table S2).

For independent replication, these 10 SNPs were put forward to a new sample of 116 German MD patients

**TABLE 1.** Association signals of rs11655081 for dystonia with genome-wide significance

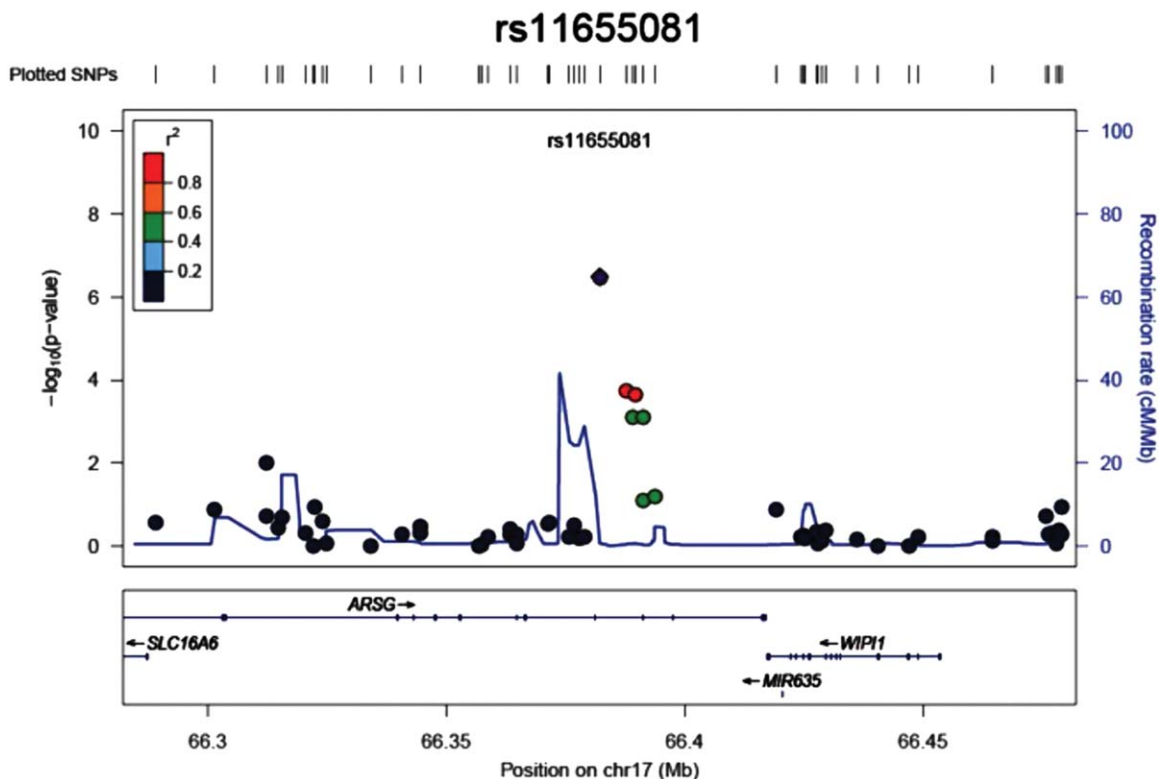
| SNP        | Chr | Physical position | Gene | Stage     | Risk allele frequency cases/controls | n cases/controls | OR   | 95% CI     | $P$                   |
|------------|-----|-------------------|------|-----------|--------------------------------------|------------------|------|------------|-----------------------|
| rs11655081 | 17  | 63893804          | ARSG | GWAS      | 0.08/0.02                            | 127/972          | 4.47 | 2.52-7.95  | $3.30 \times 10^{-7}$ |
|            |     |                   |      | MD        | 0.09/0.02                            | 116/125          | 3.98 | 1.58-10.01 | $1.66 \times 10^{-3}$ |
|            |     |                   |      | Pooled MD | 0.08/0.02                            | 243/1097         | 4.33 | 2.66-7.05  | $3.95 \times 10^{-9}$ |
|            |     |                   |      | WD        | 0.06/0.04                            | 208/278          | 1.78 | 0.99-3.21  | $2.78 \times 10^{-2}$ |



**FIG. 3.** Forest plot of odds ratios for rs11655081. Initial genome-wide association study (GWAS) replication stage with patients with musician's dystonia (MD) and healthy musicians and further validations in patients with writer's dystonia (WD) versus healthy population-based controls as well as German and Dutch patients with other forms of focal or segmental dystonia versus ethnically matched controls. Signals in MD and WD indicate an increased risk. Notably, the effect is more pronounced for MD than for WD. There is no effect for other forms of dystonia.

and 125 healthy musicians. This approach also aimed to exclude an association with musicality per se. Assuming a risk allele frequency in the controls of 4% and a genome-wide significance level of  $P = 5 \times 10^{-8}$ , we had a power of 69% to reach genome-wide significance. Only one of the tested SNPs showed an association with MD in the replication phase (rs11655081) and reached genome-wide significance ( $P < 5 \times 10^{-8}$ ) in the combined analysis of both stages (Table 1). Based on these data, the attributable risk among the exposed is 76.19% (95% CI, 60.73%-85.57%) for this variant. There was no correlation between age at onset in MD patients and their carrier status for rs11655081 (mean,  $34.0 \pm 10.7$  years; range, 15–70 years in noncarriers vs. mean,  $35.1 \pm 11.7$  years; range, 18–64 years in heterozygous carriers). Further, we computed the false-positive report probability (FPRP) for rs11655081.<sup>24</sup> Assuming that 1 in 5000 SNPs is a true-positive finding, the lower boundary of the 95% confidence interval of the odds ratio (2.66), the FPRP, is 0.001.

Genotyping this SNP in 208 patients with WD and 278 population-based controls (Table S1) also revealed an association with WD (Table 1). The minor allele was again more frequent among patients compared with controls, but the effect size was lower (Fig. 3).



**FIG. 4.** Detailed results from the genome-wide association for the significantly associated locus. Regional association plots are shown for the *ARSG* locus (17q24.2). Disease associations as indicated by  $-\log_{10} P$  values are plotted against chromosomal positions. Levels of linkage disequilibrium ( $r^2$ ) with the best-associated SNP (blue diamonds) are color-coded.<sup>31</sup> Blue lines indicate recombination fractions according to the HapMap CEU sample. Horizontal arrows mark structural human genes as annotated by Human Genome Build 37.3/hg19 of the UCSC (Genome Bioinformatics Group, University of California, Santa Cruz; <http://genome.ucsc.edu/cgi-bin/hgTracks>).

Investigation of rs11655081 in 1,969 patients with cervical dystonia, blepharospasm, other forms of focal dystonia, or segmental dystonia and 2,233 ethnically matched controls did not reveal any association in German, Dutch, Italian, Serbian, Spanish, and Japanese samples (Table S3). Notably, relative excess heterozygosity<sup>25</sup> analysis in the 6 control groups demonstrated that there was no deviation from Hardy-Weinberg equilibrium ( $P = 0.354$ ) over all 6 groups. However, results varied between studies ( $I^2 = 73.69\%$ ; 95% CI, 0.00%-94.97%). Specifically, there was a tendency for more heterozygous subjects than expected in the Japanese control group, whereas there was a trend toward a lack of heterozygous subjects in the Dutch and the German control groups. We have no explanation for this heterogeneity between studies, and it might represent a chance finding.

## Discussion

Using a genome-wide approach with an independent replication and validation in other forms of dystonia, we identified the intronic variant rs11655081 in the *ARSG* gene as the first possible genetic risk factor for MD with genome-wide significance. Notably, an association was also observed in patients with WD, another form of FTSD but not in other types of focal or segmental dystonia that may be in keeping with a distinct pathophysiological mechanism for MD and also WD.

*ARSG* is located on chromosome 17q24.2 and belongs to the family of sulfatase genes whose gene products hydrolyze sulfate esters. These proteins are involved in cell signaling, protein degradation, and hormone biosynthesis.<sup>26</sup> *ARSG* is ubiquitously expressed in adults<sup>27</sup> and is strongly expressed in the developing choroid plexus in mice.<sup>28</sup> In dogs, a homozygous mutation in the *arsg* gene causes neuronal ceroid lipofuscinosis,<sup>29</sup> whereas *arsg*-deficient mice accumulate heparan sulfate in visceral organs and the central nervous system and develop neuronal cell death and behavioral deficits.<sup>30</sup> Interestingly, dystonia has been described as a feature of ceroid lipofuscinosis. Thus, a pathophysiological role of *ARSG* in dystonia and especially in MD is conceivable based on its proposed function.

However, an important limitation of our study is the rather small patient group and therefore limited power to detect an association. The SNP in *ARSG* associated with MD has an estimated OR > 4. However, that allele frequencies of rs11655081 vary substantially across different populations (from 5% to 56% according to public databases [dbSNP] and only 2% and 4% in our northern German controls) indicates two important issues. First, this SNP is unlikely to be the causal variant that is most likely to be located in the *ARSG* gene (Fig. 4).

Second, although population stratification in our sample was modest ( $\lambda = 1.07$ ), different recruitment strategies for our German patients and northern German population-based controls may have led to an overestimation of the effect size. It is even conceivable that the association is a false-positive finding because of the small sample size of patients and slight differences in the ascertainment of patients and population-based controls in the first 2 stages of the analysis, as well as differences in the allele frequency of rs11655081 across populations. However, arguments in favor of a true association include (1) an FPRD of 0.001, which indicates that the probability of rs11655081 representing a false-positive finding is as low as 0.1%; and (2) an observed association in 3 different stages (GWAS, replication, and first validation). In the second validation stage, in which we included about 2,000 patients, no association was observed, possibly suggesting a false-positive finding, but this may also be related to the difference in phenotype (not task-specific dystonia). Therefore, further replication of our findings in independent groups of MD patients and other forms of task-specific dystonia is required.

Taken together, using a genome-wide approach in a homogenous patient sample, we identified an intronic variant in *ARSG* as a possible genetic risk factor for MD with genome-wide significance. The substantial differences in the allele frequencies of rs11655081 among diverse populations warrant further replication of our findings to reveal the causative variant and to estimate the true effect size. Given the overall rarity of MD, this will require a multicenter, international collaborative effort, ideally by a consortium dedicated to the genetic risk of MD and other focal task-specific dystonias. ■

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