A Genome-Wide Association Study of Myasthenia Gravis

Alan E. Renton, PhD; Hannah A. Pliner, BS; Carlo Provenzano, MD, PhD; Amelia Evoli, MD; Roberta Ricciardi, MD; Michael A. Nalls, PhD; Giuseppe Marangi, MD; Yevgeniya Abramzon; Sampath Arepalli, MS; Sean Chong, BS; Dena G. Hernandez, MS; Janel O. Johnson, PhD; Emanuela Bartoccioni, PhD; Flavia Scuderi; Michelangelo Maestri, MD; J. Raphael Gibbs, MS; Edoardo Errichiello; Adriano Chiò, MD; Gabriella Restagno, MD; Mario Sabatelli, MD; Mark Macek, MS; Sonja W. Scholz, MD, PhD; Andrea Corse, MD; Vinay Chaudhry, MD; Michael Benatar, MD, PhD; Richard J. Barohn, MD; April McBryde, PhD; Mamatha Pasnoor, MD; Zaeem Siddiqi, MD; Srikanth Muppidi, MD; Gil Wolfe, MD; David Richman, MD; Michelle M. Mezei, MD; James F. Howard Jr, MD; Wilma J. Koopman, RN; Michael W. Nicolle, MD; Robert M. Pascuzzi, MD; Alan Pestrkon, MD; Charlie Wulf; Julaine Florence, PhD; Derrick Blackmore, BSc; Aimee Soloway, RN; Zaeem Siddiqi, MD; Srikanth Muppidi, MD; Gil Wolfe, MD; David Richman, MD; Michelle M. Mezei, MD; Theresa Jiwa; Joel Oger, MD; Daniel B. Drachman, MD; Bryan J. Traynor, MD, PhD

**IMPORTANCE** Myasthenia gravis is a chronic, autoimmune, neuromuscular disease characterized by fluctuating weakness of voluntary muscle groups. Although genetic factors are known to play a role in this neuroimmunological condition, the genetic etiology underlying myasthenia gravis is not well understood.

**OBJECTIVE** To identify genetic variants that alter susceptibility to myasthenia gravis, we performed a genome-wide association study.

**DESIGN, SETTING, AND PARTICIPANTS** DNA was obtained from 1032 white individuals from North America diagnosed as having acetylcholine receptor antibody–positive myasthenia gravis and 1998 race/ethnicity-matched control individuals from January 2010 to January 2011. These samples were genotyped on Illumina OmniExpress single-nucleotide polymorphism arrays. An independent cohort of 423 Italian cases and 467 Italian control individuals were used for replication.

**MAIN OUTCOMES AND MEASURES** We calculated $P$ values for association between 8,114,394 genotyped and imputed variants across the genome and risk for developing myasthenia gravis using logistic regression modeling. A threshold $P$ value of $5.0 \times 10^{-8}$ was set for genome-wide significance after Bonferroni correction for multiple testing.

**RESULTS** In the overall case-control cohort, we identified association signals at $\text{CTLA4}$ (rs231770; $P = 3.98 \times 10^{-8}$; odds ratio, 1.37; 95% CI, 1.25-1.49), $\text{HLA-DQA1}$ (rs9271871; $P = 1.08 \times 10^{-8}$; odds ratio, 2.31; 95% CI, 2.02-2.60), and $\text{TNFRSF11A}$ (rs4263037; $P = 1.60 \times 10^{-9}$; odds ratio, 1.41; 95% CI, 1.29-1.53). These findings replicated for $\text{CTLA4}$ and $\text{HLA-DQA1}$ in an independent cohort of Italian cases and control individuals. Further analysis revealed distinct, but overlapping, disease-associated loci for early- and late-onset forms of myasthenia gravis. In the late-onset cases, we identified 2 association peaks: one was located in $\text{TNFRSF11A}$ (rs4263037; $P = 1.32 \times 10^{-12}$; odds ratio, 1.56; 95% CI, 1.44-1.68) and the other was detected in the major histocompatibility complex on chromosome 6p21 ($\text{HLA-DQA1}$; rs9271871; $P = 7.02 \times 10^{-18}$; odds ratio, 4.27; 95% CI, 3.92-4.62). Association within the major histocompatibility complex region was also observed in early-onset cases ($\text{HLA-DQA1}$; rs601006; $P = 2.52 \times 10^{-11}$; odds ratio, 4.0; 95% CI, 3.57-4.43), although the set of single-nucleotide polymorphisms was different from that implicated among late-onset cases.

**CONCLUSIONS AND RELEVANCE** Our genetic data provide insights into aberrant cellular mechanisms responsible for this prototypical autoimmune disorder. They also suggest that clinical trials of immunomodulatory drugs related to $\text{CTLA4}$ and that are already Food and Drug Administration approved as therapies for other autoimmune diseases could be considered for patients with refractory disease.

Published online February 2, 2015.
A genome-wide association study of myasthenia gravis

Methods

Samples

From January 2010 to January 2011, DNA was collected from patients attending myasthenia gravis clinics at 14 centers throughout North America using Oragene DNA Saliva Collection kits (DNA Genotek Inc). All patients included in the case cohort had been diagnosed by a neurologist specializing in myasthenia gravis, had onset of symptoms after age 18 years, and were of non-Hispanic white race/ethnicity (eTable 1 in the Supplement). The diagnosis of myasthenia gravis was based on standard clinical criteria of characteristic weakness, fatigue, and electrophysiological and/or pharmacological abnormalities, and it was confirmed by the presence of anti-AChR antibodies.* Patients with positive test results for antibodies to muscle-specific kinase (anti-MuSK) were excluded from enrollment. For the control cohort, we downloaded genotype data from dbGAP (http://www.ncbi.nlm.nih.gov/gap; phs000196.v2.p1) for 1998 US neurologically normal individuals. The control cohort was matched to the case cohort for race/ethnic group but not for age or sex.

Written consent was obtained from all patients enrolled in this study. Institutional review board approval was obtained at all participating institutions including Johns Hopkins University and the National Institute on Aging.

Genome-Wide Genotyping

The case cohort was genotyped in the Laboratory ofNeurogenetics, National Institute on Aging, using HumanOmniExpress BeadChips (Illumina), which assay 730,525 single-nucleotide polymorphisms (SNPs) across the genome. Individual-level genotypes for the myasthenia gravis case cohort are available on the dbGAP web portal (phs000726.v1.p1). The control cohort had been previously genotyped at the Center for Inherited Disease Research at Johns Hopkins University on HumanOmni-Quad BeadChips (Illumina) as part of a GWAS of Parkinson disease. Analyses were confined to the 677,673 autosomal SNPs that were common to both chips.

Genotyping Assays in the Replication Cohort

Rs231770, rs4263037, and rs9270986 were analyzed using Taqman genotyping assays and scanned on an ABI 7900HT Real-Time polymerase chain reaction system (Applied Biosystems) according to the manufacturer’s protocol. Rs601006 and rs9271850 in the MHC region were analyzed by sequencing using the Big-Dye Terminator version 3.1 sequencing kit (Applied Biosystems), run on an ABI 3730xl DNA analyzer, and analyzed with Sequencher software (version 4.2; Gene Codes) and Mutation Surveyor (version 4.0.9; Softgenetics). Primers and polymerase chain reaction conditions are listed in eTable 2 in the Supplement.

Genomic DNA from the Italian replication cohort was used for the Taqman assays. Owing to low quantities, the remaining genomic DNA was amplified using the REPLI-g kit according to the manufacturer’s protocol (Qiagen), and the amplified DNA was used in the Sanger sequencing experiments.
Table 1. Loci Showing Genome-Wide Association With Myasthenia Gravis

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Nearest Genes</th>
<th>EAF Stage 1</th>
<th>Stage 2</th>
<th>Stages 1 + 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>No.</td>
</tr>
<tr>
<td>1</td>
<td>rs231770</td>
<td>CTLA4</td>
<td>0.45</td>
<td>0.38</td>
<td>2949</td>
</tr>
<tr>
<td>2</td>
<td>rs927181</td>
<td>HLA-DRB1, HLA-DQA1</td>
<td>0.87</td>
<td>0.85</td>
<td>2949</td>
</tr>
<tr>
<td>3</td>
<td>rs4263037</td>
<td>TNFRSF11A</td>
<td>0.46</td>
<td>0.38</td>
<td>2949</td>
</tr>
</tbody>
</table>

Abbreviations: EAF, effect allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.

Statistical Analysis

Genome-Wide Association

Statistical analyses were performed using R statistical software (version 2.15.2). We applied standard quality-control procedures to the data: exclusion of samples with SNP call rates of less than 95%, non-European ancestry, or cryptic relatedness defined as identity-by-descent proportion of inheritance (πh from the PLINK software toolset version 1.06) greater than 0.1, as well as exclusion of SNPs with call rates of less than 95%, minor allele frequency less than 0.01 in the control cohort, and Hardy-Weinberg equilibrium (P < .001) in the control cohort. The cryptic-relatedness threshold led to the exclusion of individuals who shared more than 10% of their genome, which meant that related individuals down to third- or fourth-degree relatives were not included in the final analysis. The index individual whose sample had the better call rate from each related pair was excluded from the analysis (17 related pairs).

After quality control, we used a Markov chain–based HaploTyper (version 1.0.16) to impute genotypes for all participants.25 A total of 8,114,394 SNPs (consisting of 513,081 genotyped SNPs and 7,601,313 imputed SNPs) were available for analysis.

We calculated P values using logistic regression modeling incorporating the first 2 principal components as covariates to compensate for any residual population stratification. Principal components were generated using Genome-wide Complex Trait Analysis software package implementation of eigenstrat.26 A threshold of 5.0 × 10^-8 was set for genome-wide significance after Bonferroni correction for multiple testing.

Probability Analysis and Heritability Estimates

We used density estimation to generate posterior probabilities of developing myasthenia gravis based on age and sex.

The Genome-wide Complex Trait Analysis package uses covariance matrices and mixed modeling to estimate the heritability of a trait in an ostensibly outbred population.26,28,29 We applied this method to compare each case series (all cases, early-onset cases, and late-onset cases) to all control individuals. For each model, we compared 2 separate subsets of SNPs, one inclusive of all genotyped SNPs and another including only SNPs within ±1 MB from the loci identified as genome-wide significant in the discovery phase of analyses (Table 1). Only SNPs and samples passing quality control were used to evaluate the heritability and all analyses were adjusted for population substructure by using C1 and C2 from principal component analysis as covariates. Further details are provided in the eAppendix in the Supplement.

Results

GWAS Identifies Loci Influencing Risk for Myasthenia Gravis

After imputation and quality-control measures, 8,114,394 genotyped and imputed SNPs from 972 North American patients diagnosed as having AChR antibody–positive myasthenia gravis and 1977 North American control individuals were available for analysis. Quartile–quartile plots did not show evidence of significant population stratification (Figure 1A; genomic inflation factor λ = 1.036).

In addition to the previously reported MHC class II region signal near the MHC class II DQ α1 (HLA-DQA1) gene,30 we observed a strong association signal on chromosome 2q33 in the CTLA4 locus with a P value that reached genome-wide significance (rs231770; P = 3.98 × 10^-8; odds ratio [OR], 1.37; 95% CI, 1.25-1.49; Figure 1B). We also identified a strong association peak on chromosome 18q21.33 within the tumor necrosis factor receptor 4 superfamily, member 11a, NFκB activator (TNFRSF11A) gene (rs4263037; P = 1.60 × 10^-9; OR, 1.41; 95% CI, 1.29-1.53).

Markers that achieved genome-wide significance in the analysis of the whole cohort are shown in Table 1, and SNPs associated at P < 1.0 × 10^-6 are listed in eTable 3 in the Supplement.
Early- and Late-Onset Myasthenia Gravis Possess Distinct Genetic Architecture

Density estimate plots confirmed a bimodal sex distribution within our case cohort, with myasthenia gravis being more common in younger women and older men (Figure 1C). To elucidate the genetic architecture underlying this age difference, we performed GWAS of early-onset cases (235 cases with onset at age <40 years and 1977 control individuals) and late-onset cases (737 cases with onset at age >40 years and 1977 control individuals). The TNFRSF11A and HLA-DQA1 association signals were significantly enhanced among late-onset cases (rs4263037, $P = 1.32 \times 10^{-12}$; OR, 1.56; 95% CI, 1.44-1.68 and rs9271871, $P = 7.02 \times 10^{-18}$; OR, 4.27; 95% CI, 3.92-4.62, respectively; Figure 1D; Table 1). In contrast, there was no evidence of association within TNFRSF11A in the young-onset cases (rs4263037; $P = .83$; Figure 1E). Furthermore, although an association signal was present near HLA-DQA1 in the younger patients, the most significantly associated SNPs were different compared with those observed in the late-onset cohort (rs601006; $P = 2.52 \times 10^{-11}$; OR, 4.0; 95% CI, 3.57-4.43; eTables 4 and 5 in the Supplement).

Myasthenia Gravis Risk Loci Replicated in an Independent Cohort

We selected 3 SNPs from the risk loci identified on chromosomes 2, 6, and 18 in the overall cohort for genotyping in an independent replication collection consisting of 423 Italian AChR antibody–positive myasthenia gravis cases and 467 Italian AChR antibody–positive myasthenia gravis cases and 467 Italian...
We also attempted to replicate the most highly associated SNPs observed in the early- and late-onset cases using the same Italian replication collection. Rs601006 near HLA-DQA1 was significantly associated among early-onset cases (169 Italian myasthenia gravis cases and 467 control individuals; \( P = 5.53 \times 10^{-5} \); Table 1; Figure 2C). This SNP was not associated among late-onset cases (250 cases and 467 control individuals; \( P = .22 \)), recapitulating the pattern observed in the discovery cohort.

Regional association plots of the signals at the major histocompatibility complex (MHC) region (A) and CTLA4 (B) in all myasthenia gravis cases (972 cases and 1977 control individuals), as well as the MHC region in early-onset myasthenia gravis cases (C, 235 cases and 1977 control individuals), the MHC region in late-onset cases (D), and TNFRSF11A in late-onset myasthenia gravis cases (E, 737 cases and 1977 control individuals). Single-nucleotide polymorphisms are colored on the basis of their linkage disequilibrium with the labeled hit single-nucleotide polymorphism. Recombination rates estimated from the CEU HapMap population are represented by the blue line and genes are marked as arrows. Red diamonds represent the most associated single-nucleotide polymorphism in the discovery cohort and blue diamonds, \( P \) values for the combined discovery and replication cohorts. F. CTLA4 regulates T-cell activation by antigen-presenting cells (APCs). TCR indicates T-cell receptor.
Similarly, we replicated the SNPs observed near HLA-DQA1 and within TNFRSF11A in the late-onset cases. Rs59271850 near HLA-DQA1 was significantly associated in the late-onset Italian cohort (P = 8.15 × 10^-4; Table 1; Figure 2D) but was not associated among the early-onset cases (P = .53). Rs426307 located on chromosome 18 showed a trend toward significance (P for patients aged ≥40 years at symptom onset = .09; Figure 2E). This SNP became progressively more associated with increasing age of the replication cohort (P for patients aged ≥50 years at symptom onset = .04; P for patients aged ≥70 years = 8.75 × 10^-3).

Myasthenia Gravis Is Highly Heritable
The relative importance of genetic factors in a complex disease like myasthenia gravis can be estimated by quantifying heritability. We generated heritability estimates for AChR antibody-positive myasthenia gravis using a sophisticated algorithm (Genome-wide Complex Trait Analysis) that analyzes all of the genome-wide SNPs simultaneously (Table 2). Our genotype data accounted for 25.6% (95% CI, 18.6-32.6) of the phenotype variance observed in all myasthenia gravis cases. Analysis of more precise phenotypes (early- and late-onset cases) generated even higher estimates of heritability (37.9%; 95% CI, 16.8-59.0 and 35.3%; 95% CI, 27.1-43.5, respectively). These estimates are substantially higher than heritability identified using genome-wide-associated SNPs alone (1%-3%), indicating that additional risk loci remain to be identified.

Discussion
Our GWAS of AChR antibody-positive myasthenia gravis identified several new loci that drive susceptibility to develop disease. We also provide strong evidence that early- and late-onset myasthenia gravis have distinct, but overlapping, genetic architecture, thereby confirming previous epidemiological and clinical data suggesting a division between these 2 forms of disease. Genetic variation within the TNFRSF11A locus drives susceptibility to disease only among older cases, whereas different haplotypes across the same HLA region on chromosome 6 were identified in early- and late-onset cases. CTLA4 exerts a significant effect regardless of age at symptom onset, suggesting that it plays a central role in generating the aberrant autoimmune response that leads to neuromuscular junction dysfunction.

CTLA4 is a 45-kD immunoglobulin protein expressed by activated T cells and sharing significant sequence identity with CD28 (Figure 2F). CTLA4 increases T-cell motility and reduces contact periods between T cells and antigen-presenting cells leading to decreased cytokine production and proliferation. In this way, CTLA4 is thought to down-regulate T-cell activation, terminate T-cell responses, and protect against autoimmunity.32 CTLA4-deficient mice have high serum immunoglobulin concentrations and develop massive lymphocyte infiltration of lymph nodes and spleen, suggesting that CTLA4 plays an inhibitory role in regulating lymphocyte expansion.32 The mechanism of CTLA4’s regulatory action is controversial; however, evidence suggests that cells expressing CTLA4 avidly endocytose the costimulatory factors CD80 and CD86 on antigen-presenting cells and degrade them.33 Genetic variant in the CTLA4 locus has been implicated in other autoimmune disorders including celiac disease,34 type 1 diabetes mellitus,35 thyroiditis,36 and rheumatoid arthritis.37 Indeed, abatacept and belatacept are commercially available proteins consisting of CTLA4 rendered soluble by fusion to antibodies (CTLA4-IgG) approved for use in the treatment of refractory rheumatoid arthritis38 and as first-line immunosuppressants for renal transplant patients immune to Epstein-Barr virus.39 Clinical trials of these agents are also under way in inflammatory bowel disease, systemic lupus erythematosus, and other autoimmune diseases. They have not previously been used therapeutically in myasthenia gravis, although our experimental studies demonstrated the effectiveness of CTLA4-Ig in the treatment of rats with experimental autoimmune myasthenia gravis.40,41

Genetic analysis of additional case-control cohorts will be required to confirm the association observed for the TNFRSF11A locus. Nevertheless, the pattern of association uncovered for this locus, with a large effect in late-onset disease that is absent in younger patients, led us to speculate that age-related changes in local gene expression predispose toward an aberrant immune response to autoantigens. TNFRSF11A encodes the 4.5-kDa receptor activator of nuclear factor-κ B expressed on the surface of antigen-presenting dendritic cells.42 This receptor is an important regulator of the interaction between T cells and dendritic cells that is essential for immune surveillance and the regulation of specific immunity.42 Furthermore, TNFRSF11A is critical for lymph node organogenesis and osteoclast differentiation.43 Mutations in this gene are responsible for a form of familial Paget disease of the bone44 and for autosomal recessive osteopetrosis associated with defective immunoglobulin production.45 Receptor activator of nuclear factor-κ B knockout mice also have profound osteopetrosis resulting from a complete lack of osteoclasts, as well as near total absence of peripheral lymph nodes.43,45

The association signal that we identified in the MHC region was distinct from that reported by Gregersen et al35 to increase susceptibility for myasthenia gravis. Furthermore, our study did not show any evidence of association in the PTPN22 or TNIP1 loci found by the same study (eTable 6 in the Supplement).15 These disparities likely arise from differences in the populations studied. In their study, patients and control individuals from 7 countries were included.35 Such population stratification impedes the identification of true association and increases the rate of false-positive associations particularly in the HLA region that is known to be highly divergent across races/ethnicities.47 In contrast, we attempted to reduce clinical heterogeneity by selecting only cases from North America for the discovery cohort and from Italy for the replication cohort.

We considered the possibility that our study may have had population stratification, especially because we used an outbred American population as our original discovery cohort. The lack of age and sex matching of control samples to cases also may have introduced artifacts into our analysis.
To avoid this, we applied strict filters to exclude outlying samples and incorporated principal components generated from the genome-wide data into the analysis model to compensate for residual population stratification between case and control samples. Furthermore, we replicated our results in a case-control cohort drawn from a distinct single population and found identical patterns of association among early- and late-onset cases.

Heritability can be considered the proportion of a disease that arises from genetics. Prior studies have estimated that only between 3.8% and 7.1% of individuals who receive a diagnosis of myasthenia gravis have a family history of disease.\textsuperscript{14,48} The genome-wide nature of our data set yielded a higher estimate of the heritability associated with myasthenia gravis risk by capturing more of the polygenic variance. This pattern is consistent with other neurological diseases, such as amyotrophic lateral sclerosis and Parkinson disease, where heritability estimates are significantly higher than the rate of familial disease.\textsuperscript{49,50} Furthermore, our heritability estimates suggest that there are genetic factors contributing to the disease that have yet to be identified and that GWASs involving larger cohorts will yield additional loci. To that end, we have made our raw genotype data publicly available on dbGaP to facilitate meta-analysis with existing and future studies.

A strength of our study was that genetic analysis was confined to patients diagnosed as having AChR antibody-positive myasthenia gravis. This approach decreased disease heterogeneity and improved the power of the study to identify association signals. Approximately 85% of patients with myasthenia gravis have detectable AChR antibodies and approximately 40% of the remainder are MuSK antibody positive.\textsuperscript{2,51,52} Furthermore, AChR antibody-negative myasthenia gravis is less common among elderly individuals,\textsuperscript{52} and MuSK-positive patients are more likely to be women.\textsuperscript{53} In light of this, care should be taken in generalizing our results to the AChR antibody-negative myasthenia gravis population. Nevertheless, we do support the existence of distinct, but overlapping, genetic profiles for patients with early- and late-onset myasthenia gravis with detectable AChR antibodies.

### Conclusions

Our GWAS identified susceptibility loci for AChR antibody-positive myasthenia gravis at CTLA4, HLA-DRB1/HLA-DQA1, and TNFRSF11A, and it showed distinct, but overlapping, genetic risk factors underlying early- and late-onset disease. Although future studies involving deep resequencing of these loci will be required to identify the functional variants underlying these association signals, our data also suggest that clinical trials of CTLA4 immunomodulatory therapies could be considered in patients with myasthenia gravis with refractory disease failing to respond to standard therapies.

### Table 2. Heritability Estimates Based on the Discovery Cohort of Myasthenia Gravis

<table>
<thead>
<tr>
<th>Group</th>
<th>All SNPs Significant Loci Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heritability Estimate, % (95% CI)</td>
</tr>
<tr>
<td>All cases</td>
<td>25.6 (18.6–32.6)</td>
</tr>
<tr>
<td>Early-onset cases</td>
<td>37.9 (16.6–59.0)</td>
</tr>
<tr>
<td>Late-onset cases</td>
<td>35.3 (27.1–43.5)</td>
</tr>
</tbody>
</table>

Abbreviation: SNPs, single-nucleotide polymorphisms.

**ARTICLE INFORMATION**

**Accepted for Publication:** November 6, 2014.

**Published Online:** February 2, 2015.


**Author Affiliations:** Neuromuscular Diseases Research Unit, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland (Renton, Pliner, Marangi, Abramzon, Johnson, Errichello, Traynor); Institute of General Pathology, Catholic University, Rome, Italy (Provenzano, Bartocci, Scuderi); Institute of Neurology, Catholic University, Rome, Italy (Evoli, Sabatelli); Department of Neuroscience, Cisanello Hospital, University of Pisa, Pisa, Italy (Ricciardi, Maestri); Molecular Genetics Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland (Nalls); Institute of Medical Genetics, Catholic University, Rome, Italy (Marangi); Genomics Technology Group, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland (Arepalli, Chong, Hernandez); Computational Biology Core, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Porter Neuroscience Research Center, Bethesda, Maryland (Gibbs); Rita Levi Montalcini Department of Neuroscience, University of Turin, Turin, Italy (Errichello, Chiol); Molecular Genetics Unit, Department of Clinical Pathology, ASO OIRM-S Anna, Turin, Italy (Restagno); Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland (Macek, Scholz, Corse, Chaudhry, Drachman, Traynor); Department of Neurology, University of Miami, Miami, Florida (Benatar); Department of Neurology, University of Kansas Medical Center, Kansas City (Barohn, McVey, Pasnoor, Dimachkie); Department of Neurology, University of Illinois College of Medicine, Chicago (Rowin); Department of Neurology, Ohio State University Medical Center, Columbus (Kissel, Freimer); Department of Neurology, George Washington University, Washington, DC (Kaminski); Department of Neurology, Duke University Medical Center, Durham, North Carolina (Sanders, Lipscomb, Massey); Department of Neurology, University of North Carolina, Chapel Hill (Chopra, Howard); Department of Clinical Neurosciences, London Health Sciences Centre, London, Ontario, Canada (Koopman, Nicolle); Department of Neurology, Indiana University–Purdue University, Indianapolis (Pascuzzi); Department of Neurology, Washington University School of Medicine, St Louis, Missouri (Pestronk, Wulf, Florence); Department of Medicine, University at Buffalo Hospital, Buffalo, New York (Muppidi, Wolfe); Department of Neurology, University of California, Davis Medical Center (Richman); Division of Neurology, University of British Columbia, Vancouver, British Columbia, Canada (Mezei, Jiwa, Oger).

**Author Contributions:** Drs Drachman and Traynor had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Renton, Provenzano, Evoli, Ricciardi, Drachman, and Traynor, and Ms Pliner contributed equally to this work.

**Study concept and design:** Drachman, Traynor.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Drachman, Traynor.
**REFERENCES**

Call for Papers

We are asking for papers to be submitted on the subject of Neuromodulation to appear in a theme issue on Neuromodulation to be published at the time of the American Neurological Association Satellite Symposium on “Circuits and Circuit Disorders: Approaches to Neuromodulation” on September 26, 2015, cosponsored by the Annals of Neurology and JAMA Neurology, at the 140th Annual Meeting of the American Neurological Association in Chicago, Illinois, at the Marriott Downtown Hotel. Articles on deep brain stimulation related to movement disorders, Tourette syndrome, obsessive-compulsive disease, depression, chemogenetics, and related disorders will be considered.

Articles must be received by May 1, 2015, to allow time for peer review and necessary revisions, so that they may appear online in JAMA Neurology in September.