A candidate gene for autoimmune myasthenia gravis

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ABSTRACT

Objective: We sought to identify a causative mutation in a previously reported kindred with parental consanguinity and 5 of 10 siblings with adult-onset autoimmune myasthenia gravis.

Methods: We performed genome-wide homozygosity mapping, and sequenced all known genes in the one region of extended homozygosity. Quantitative and allele-specific reverse transcriptase PCR (RT-PCR) were performed on a candidate gene to determine the RNA expression level in affected siblings and controls and the relative abundance of the wild-type and mutant alleles in a heterozygote.

Results: A region of shared homozygosity at chromosome 13q13.3–13q14.11 was found in 4 affected siblings and 1 unaffected sibling. A homozygous single nucleotide variant was found in the 3′-untranslated region of the ecto-NADH oxidase 1 gene (*ENOX1*). No other variants likely to be pathogenic were found in genes in this region or elsewhere. The *ENOX1* sequence variant was not found in 764 controls. Quantitative RT-PCR showed that expression of *ENOX1* decreased to about 20% of normal levels in lymphoblastoid cells from individuals homozygous for the variant and to about 50% in 2 unaffected heterozygotes. Allele-specific RT-PCR showed a 55%–60% reduction in the level of the variant transcript in heterozygous cells due to reduced mRNA stability.

Conclusion: These results indicate that this sequence variant in *ENOX1* may contribute to the familial autoimmune myasthenia in these patients. ***Neurology*® 2012;79:342–347**

GLOSSARY

AChR = acetylcholine receptor; **MG** = myasthenia gravis; **NAD** = nicotinamide adenine dinucleotide; **qRT-PCR** = quantitative reverse transcriptase PCR; **RT-PCR** = reverse transcriptase PCR.

Myasthenia gravis (MG) is usually sporadic, but about 4% of patients have a positive family history.[1] In addition to the congenital myasthenic syndromes caused by inherited defects in the acetylcholine receptor (AChR) and other constituents of the neuromuscular junction,[2–4] familial clustering has been reported with autoimmune MG.[1,5–7] A role for genetic factors in autoimmune MG has been suggested[6,8–10] including polymorphisms that may influence the production of anti-AChR antibodies.[11–13] However, no single gene defect has yet been implicated in familial autoimmune MG.

We previously reported an Italian American family with parental consanguinity where 5 out of 10 siblings had late-onset autoimmune MG.[10] No HLA haplotype was shared by all the affected family members, nor did polymorphisms in the AChR β subunit or the α and β subunits of the T-cell receptor cosegregate with the myasthenia.[10] We sought to identify and

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Editorial, page 304

Supplemental data at www.neurology.org

Supplemental Data

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characterize other candidate genes in this family and found a sequence variant in one gene, *ENOX1*, strongly linked to the disease in this family.

METHODS Standard protocol approvals, registrations, and patient consents. The collection of control samples was approved by the ethics committees of the contributing centers. Informed and written consent was obtained from all study participants.

Patients. Seven family members (4 affected, 2 unaffected, and 1 with uncertain diagnosis) were previously interviewed and examined by neurologists.[10] For the current study, B lymphoblastoid cell lines (unaffected siblings GM12023, GM12027; affected siblings GM11858, GM11947, GM12129, GM12355; unknown disease status GM12492; and unrelated controls GM12679, GM12560, GM12664, GM12671, GM12691) were obtained from the Coriell Institute (Coriell Institute for Medical Research, Camden, NJ).

Genetic analysis. Genomic DNA from the 7 siblings (4 affected, 2 unaffected, and 1 with unknown status) was used for a genome-wide scan with 2,000 microsatellite markers (DeCODE) and in SNP array analysis (Illumina Infinium II HumanHap550 SNP chips, Illumina, San Diego, CA).

Homozygosity mapping and multipoint analysis were performed, and a lod score was determined.[14,15] Haplotype reconstruction was done with the Genehunter software 2.0.[16] Coding regions and splice sites of all genes in the linked region were sequenced.

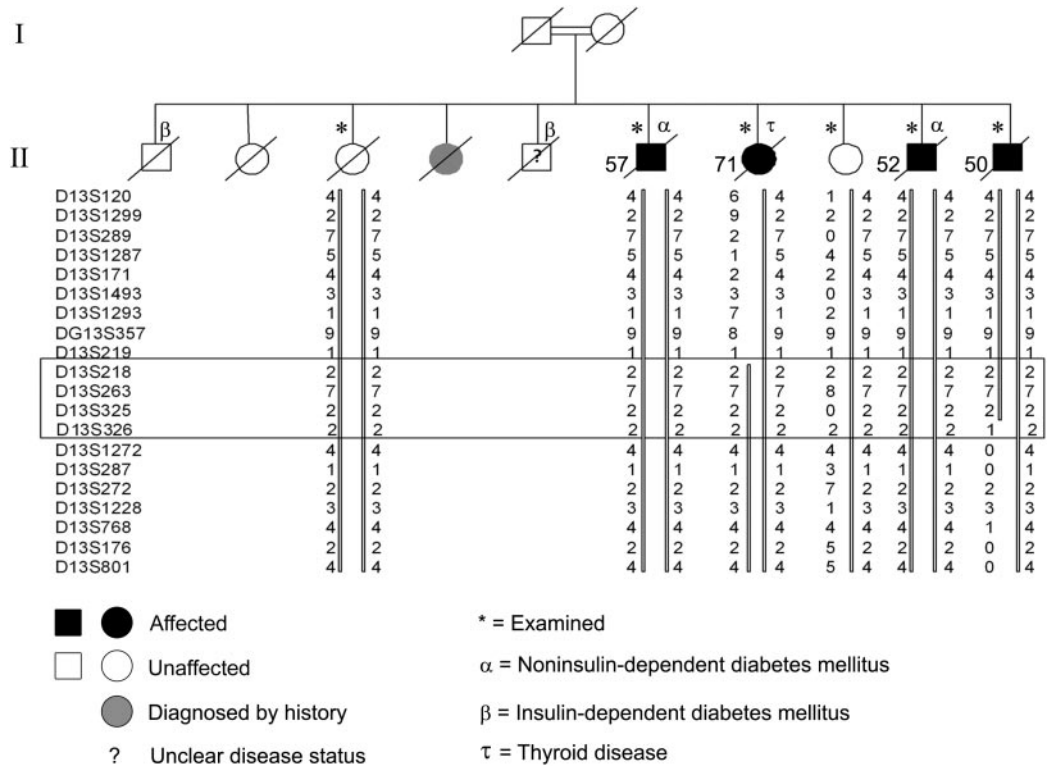
For exome sequencing, DNA from 4 affected individuals was enriched using SureSelect Exome target enrichment technology (version 1.0, Agilent, Santa Clara, CA) and sequenced on a Genome Analyzer IIx (Illumina). Sequence alignment and variant calling were performed against the reference human genome (UCSC hg 18) using the Genome Analysis Toolkit (Broad Institute, Cambridge, MA). The ClinSeq™ exomes were analyzed as previously described.[17,18]

Sequence variants were filtered against the dbSNP database (build 135), confirmed by Sanger sequencing, and tested in at least 200 ethnically matched controls, and in the ClinSeq™ cohort.[19]

RNA analysis. Specific primers and probes to amplify the internal control (human β-glucuronidase or 18S) and the *ENOX1* gene were purchased from Applied Biosystems (Foster City, CA). Quantitative reverse transcriptase PCR (qRT-PCR) reactions were performed for gene expression analysis using an ABI protocol (Applied Biosystems). We compared samples from all 7 available family members and 5 unrelated controls.

We performed allele-specific RT-PCR using RNA extracted from lymphoblastoid cells of the 2 heterozygotes (ABI TaqMan Allelic Discrimination genotyping platform, Applied Biosys-

Figure 1 Region of shared homozygosity on chromosome 13 found by linkage analysis using microsatellite markers and single nucleotide polymorphism arrays



A partial pedigree of the kindred shows the haplotype results with microsatellite markers. Haplotypes were reconstructed manually according to the most parsimonious requirement for recombination; the markers are ordered, from top to bottom, from p terminal to q terminal. The box indicates the shared homozygous region on chromosome 13. The homozygous region is between markers D13S219 and D13S326. Note that the parents' haplotype information has been inferred. Age at disease onset is indicated to the left of symbols.

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tems; primers and probes outlined in table e-1 on the *Neurology*® Web site at www.neurology.org) cultured in the presence or absence of 5 μg/mL actinomycin D for up to 8 hours to inhibit transcription. The ratio of mutant to wild-type transcripts was determined by allele-specific RT-PCR.

RESULTS **Clinical findings.** As reported previously,[10] ages at MG onset ranged from 50 to 71 years (figure 1). Symptoms included ptosis, diplopia, and weakness in the neck and extremities, and neurologic examination showed fatigability of upward and lateral gaze. Three patients had elevated anti-AChR antibody titers. A fourth patient had normal anti-AChR antibody titer, but complained of drooping eyelids and double vision with diurnal variation. His neurologic examination showed marked fatigability and horizontal diplopia on lateral gaze. Other autoimmune diseases including insulin-dependent diabetes mellitus and thyroid disease were present in family members with and without MG.

Genetic analysis. We found evidence for linkage in a region of shared homozygosity on chromosome 13q13.3–13q14.11 with a lod score of 3.18 in the affected individuals; it was confirmed by haplotype reconstruction showing homozygosity in all affected siblings and 1 unaffected sibling (figure 1); genotyping failed for 1 unaffected sibling. The region of homozygosity included 7.4 Mb of genomic DNA, and contained 37 known protein-encoding genes. Another locus of shared compound heterozygous haplotypes in the affected siblings was found using multipoint analysis at chromosome 2q36.3–2q37.1 with a lod score of 2.18 (figure e-1A).

High-resolution SNP genotyping of samples from the 4 available affected individuals confirmed the region of homozygosity on chromosome 13 (figure e-1B). Sequencing of the coding region of all 37 genes in the homozygous region on chromosome 13 identified 2 homozygous single nucleotide variants. One is located in the 3′ UTR of *ENOX1* (c.*35A>G). This change was present in all 4 available affected siblings and in the unaffected homozygous sister (II-1, figure 1). This variant was not found in 215 ethnically matched controls and in 559 exomes sequenced in the ClinSeq™ cohort.[19]

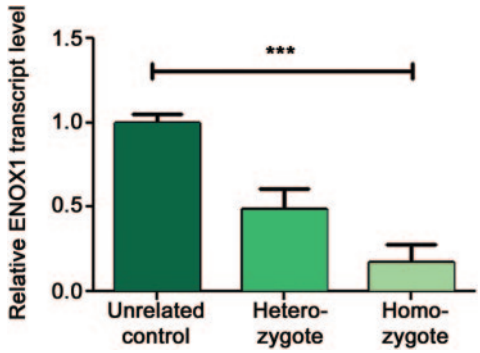
We subsequently sequenced *ENOX1* in 83 UK patients with sporadic autoimmune MG, but none had the c.*35A>G sequence variant. We thus do not have evidence to implicate mutations in *ENOX1* in sporadic myasthenia. This variant was also not found in 6 Italian patients with familial autoimmune MG. In addition to this change in *ENOX1*, a homozygous variant was identified in the coding region of the periostin gene (*POSTN*) (c.1944C>A). This variant was not seen in 196 European and American controls, but is predicted to be synonymous (I648I).

We did not find sequence variants in the coding regions of any other gene in the region of homozygosity on chromosome 13, or in the genes for AChR subunits δ and γ, located on chromosome 2.

Whole exome sequencing identified a heterozygous sequence variant (c.649G>T, p.Ala217Ser) in all 4 affected individuals in the SPHK1-interactor, AKAP domain-containing gene (*SPHKAP*) located in the chromosome 2q36.3 region. Sequencing of its coding region in all available siblings identified another heterozygous sequence variant (c.4771G>A, p.Glu1591Lys), which cosegregated with the phenotype. However, these variants were either seen in controls and ClinSeq™ subjects or listed in dbSNP database. Screening of 38 patients with late-onset autoimmune MG showed 2 heterozygous sequence variants in *SPHKAP* (p.Val90Met and p.Glu1329Lys) that were also seen in ClinSeq™ samples.

Reporter assays of ENOX1 3′ UTR activity. Use of miRBase microRNA prediction software (http://www.mirbase.org/search.shtml) indicated that the 3′ UTR variant we identified in *ENOX1* might destroy 2 existing microRNA-binding sites, hsa-miR-432 and hsa-miR-324-3p, and create a new one, hsa-miR-518c*. However, we did not detect changes in the activity of a wild-type *ENOX1* 3′ UTR luciferase reporter in the presence of exogenous hsa-miR-324-3p or hsa-mir-432. Nor did exogenous hsa-mir-518c* affect the activity of the patient-derived mutant 3′ UTR *ENOX1* luciferase reporter (figure e-2).

Figure 2 **Quantitative reverse transcriptase PCR assays of the *ENOX1* transcript levels (y-axis) in the family members and unrelated controls**



The results are the mean of 3 replicates done in triplicate experiments relative to HGUSB, and are normalized to the mean of the 2 unrelated controls using the 2-ΔΔCt method. Note that the homozygous affected siblings have about 20% of the normal *ENOX1* transcript levels and the heterozygous unaffected individuals have about 50% of the normal levels. Values represent mean ± SEM; ***$p < 0.001$.

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Table 1 Relative transcript levels of *ENOX1* transcripts

Sample	ΔΔCt[a]	Wild type	Mutant
Carrier 1	−1.18	0.69	0.31
Carrier 2	−1.38	0.72	0.28

[a] $\Delta\Delta Ct = (Ct \text{ of allele}_1\text{-specific PCR} - Ct \text{ of allele}_2\text{-specific PCR}) - (\Delta Ct \text{ 1:1 ratio})$. Frequency of $\text{allele}_1 = 1/(2^{\Delta\Delta Ct} + 1)$.

RNA analysis. Quantitative RT-PCR showed that the expression of *ENOX1* was lower in the homozygous siblings than in either the heterozygous sister or unrelated controls in a gene dose-dependent manner. The homozygotes had approximately 20% and the unaffected heterozygotes 50% of the control level (figure 2). Allele-specific RT-PCR showed a 55%–60% lower level of the mutant transcript than the wild-type in heterozygous cells (table 1). Moreover, mRNA stability assays showed faster degradation of the mutant transcripts, as reflected by decreasing mutant/wild-type ratios with time after addition of actinomycin D to inhibit transcription (table 2).

By contrast, we found no patient/control difference in *POSTN* transcript levels by RT-PCR, and no evidence of a splicing defect by cDNA sequencing (data not shown). In addition, Western blot analysis with an anti-periostin antibody showed no difference between affected and unaffected siblings (figure e-3).

DISCUSSION Familial clustering of autoimmune MG has been reported previously. Although no causative mutation has yet been identified, this seems likely in the present family because of the parental consanguinity and the late onset of MG in 5 siblings who had lived apart for up to 50 years. Sequencing of all known genes across the linked region of chromosome 13 showed homozygous single nucleotide variants in 2 genes (*ENOX1* and *POSTN*). Based on RNA and protein analysis, the variation in the *POSTN* gene is unlikely to be causative in this family. One asymptomatic sibling (II-1; figure 1) was also homozygous for the haplotype shared by the affected individuals at the chromosome 13 locus, possibly because of incomplete penetrance.

Ecto-NADH oxidase (ENOX) proteins are growth-related cell surface enzymes that catalyze hydroquinone oxidation and protein disulfide-thiol interchange. The 2 enzymatic activities oscillate with a periodicity of 24 minutes for constitutively expressed *ENOX1*, unlike any other oxidases or protein disulfide isomerases.[20] In principle, the *ENOX1* mutation might predispose to MG by affecting the autoimmune response or the motor endplate (or both). *ENOX1* is highly expressed in fetal brain and at lower levels in skeletal muscle, thymus, and lymph nodes. It plays a role in plasma membrane transport pathways reducing nicotinamide adenine dinucleotide (NAD+) to NADH. NAD and its metabolites are involved in energy metabolism, signal transduction, aging, and cellular injury. They also are involved in immune regulation by inhibiting T-lymphocyte proliferation[24] and control of signaling via CD38.[21–23] Studies have implicated NAD+ and NADH in the induction of cell death in CD4+ and CD25+ cells,[24] which, in cooperation with natural killer T cells, may play a role in the prevention of autoimmune MG.[25] Other studies have shown that NAD+ and NADH are involved in the regulation of gene expression.[26]

The 3′ UTRs of mRNAs play important roles in post-transcriptional regulation of gene expression, by modulating mRNA localization, stability, and translation, in part through association with microRNAs.[27] The sequence variant identified here in *ENOX1* was predicted to destroy 2 existing microRNA-binding sites and to create a new one. However, we did not detect changes in reporter activity of the wild-type or mutant *ENOX1* 3′ UTR luciferase reporter in the presence of these specific microRNAs. Nevertheless, it remains possible that this variant affects the binding of other microRNAs that are not predicted by current algorithms. Alternatively, the variant may affect the secondary structure of the transcript, altering its stability.

Based on the homozygosity mapping and sequence data, and also on its reduced expression and what is known of its function, *ENOX1* is a candidate gene for the autoimmune MG in the family described here. Although other factors cannot be fully

Table 2 Relative allele ratios of *ENOX1* transcripts after incubation with actinomycin D[a]

Normalized ratios: carrier 1				
Incubation time, h	0	2	4	8
Mutant/wild type allele ratio, mean ± SD	0.43 ± 0.32	0.25 ± 0.25	0.18 ± 0.36	0.12 ± 0.42
Normalized ratios: carrier 2				
Incubation time, h	0	2	4	8
Mutant/wild type allele ratio, mean ± SD	0.38 ± 0.39	0.24 ± 0.35	0.15 ± 0.46	0.11 ± 0.57

[a] Data represent 3 independent experiments.

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excluded, this finding may provide novel insights into the etiology of MG and other autoimmune diseases.

AUTHOR CONTRIBUTIONS

Guida Landouré, MD, PhD: contributed to linkage analysis, completed sequencing, mutagenesis RNA and miRNA analysis, and drafted the manuscript. Melanie A. Knight, PhD: designed experiments and performed sequencing and RNA analysis. Horia Stanescu, MD, PhD: performed the linkage analysis. Addis A. Taye, BS: performed sequencing and Western blotting. Yijun Shi, BS: performed sequencing and cloning. Oumarou Diallo, MD: sequenced controls and sporadic autoimmune myasthenia patients. Janel O. Johnson, PhD: performed exome sequencing. Dena Hernandez, MSc: performed homozygosity SNP analysis. Bryan J. Traynor, MD: performed exome sequencing. Leslie G. Biesecker, MD: performed ClinSeq exome analysis. Abdel Elkahloun, PhD: performed expression analysis. Carlo Rinaldi, MD: performed sequencing of Italian familial autoimmune myasthenia patients. Angela Vincent, MD, MSc, FRCPath: provided autoimmune myasthenia gravis patient samples. Nick Willcox, MD, PhD: provided autoimmune myasthenia gravis patient samples. Robert Kleta, MD, PhD: performed the linkage analysis. Kenneth H. Fischbeck, MD: co-directed the study and co-wrote manuscript. Barrington G. Burnett, PhD: co-directed the study, designed experiments, performed gene expression analysis, RNA and miRNA analysis, and completed the manuscript. Statistical analysis performed by Barrington G. Burnett.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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AAN Publishes Guideline Update on Infantile Spasms

The AAN has published evidence-based recommendations for the treatment of infantile spasms that update a 2004 guideline. "Evidence-based Guideline Update: Medical Treatment of Infantile Spasms," published in the June 12, 2012, issue of *Neurology*®, suggests that the therapy adrenocorticotropic hormone, also known as ACTH, and the antiepileptic drug vigabatrin (VGB) may be effective in the treatment of infantile spasms in children.

To read the guideline and access PDF summaries for clinicians and patients, a slide presentation, and a clinical example, visit *www.aan.com/go/practice/guidelines*. For more information, contact Julie Cox at *jcox@aan.com* or (612) 928-6069.

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