HIGH LIGHT

Myoclonus-dystonia, obsessive-compulsive disorder, and alcohol dependence in *SGCE* mutation carriers

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Abstract—Although myoclonus and dystonia are the hallmarks of myoclonus-dystonia (M-D), psychiatric features, particularly obsessive-compulsive disorder and alcohol dependence, have been reported in three families linked to chromosome 7q21. As the epsilon sarcoglycan (*SGCE*) gene for M-D was subsequently identified, we evaluated the relationship between psychiatric features and *SGCE* mutations in these original and two additional families and confirm that OCD and alcohol dependence are associated with manifesting mutated *SGCE*.

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Inherited myoclonus-dystonia (M-D) is caused by mutations in the epsilon sarcoglycan gene (*SGCE*) and is characterized by myoclonic jerks that are often accompanied by dystonia (*DYT11*).[1] Symptoms of the disease may be suppressed with alcohol ingestion.[2] In addition to the motor features of M-D, psychiatric features, including obsessive-compulsive disorder (OCD), alcohol misuse, depression, and anxiety, have been reported.[1-5] The largest systematically studied group of individuals with M-D was described in 7q21 linked families[6] and showed an increased rate of OCD in manifesting haplotype carriers (MCs) vs nonmanifesting haplotype carriers (NMCs) plus noncarriers (NCs), as well as in all haplotype carriers (MCs + NMCs) vs NCs. An increased rate of alcohol dependence was also shown among MCs vs asymptomatic individuals (NMCs + NCs). It was postulated that OCD is a manifestation of the gene, whereas alcohol dependence is secondary to self-treatment of M-D by alcohol and not a gene effect.[6] To further investigate possible psychiatric manifestations of *SGCE* mutations, we report psychiatric assessment of the initial 7q21-linked cohort described in 2002 for whom mutation status is now available, as well as for two additional families with *SGCE* mutations.

Methods. Subjects were ascertained from three families with M-D who were previously reported as demonstrating linkage to chromosome 7q21[6] as well as two new families harboring *SGCE* mutations. Determination of clinical status using review of standardized videotape examination is as previously described.[6] Evaluation of psychiatric features was determined using a telephone-administered computerized version of the Composite International Diagnostic Interview (CIDI) (http://www3.who.int/cidi/), and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnoses of OCD, generalized anxiety disorder (GAD), major affective disorder ([MAD] consisting of recurrent depression or bipolar mania), alcohol abuse or dependence, and drug abuse or dependence were as previously reported.[6] Individuals were considered to have GAD even if CIDI exclusion criteria for comorbid diagnoses were met. We compared rates of disorders between the MCs, NMCs, and NCs using χ^2 analyses and the Fisher exact test for small cell sizes. For each diagnosis, rates in all carriers (MCs + NMCs) were compared with those in NCs to determine whether psychiatric features are a manifestation of the *SGCE* gene. Rates in MCs were also compared with asymptomatic individuals (NMCs + NCs) to determine whether psychiatric symptoms are reactive to the clinical manifestation of M-D. All 12 exons and flanking intron regions of the *SGCE* gene were tested using either denaturing high-performance liquid chromatography or single-strand conformation polymorphism analysis followed by cycle sequencing of observed band shifts on an automated sequencing machine.[7,8]

Results. Genotype data were available for 95 individuals from five M-D families. Sixty-four individuals from five families participated in the psychiatric evaluation: 20 MCs, 10 NMCs, and 34 NCs. Demographics are shown in table 1, *SGCE* mutations are shown in table 2, and results from the CIDI are shown in table 3. We found an excess of alcohol dependence in the MCs compared with the asymptomatic group (NMCs + NCs) (35% vs 11.4%, $p = 0.032$), but this was not significant for the carrier group overall [(MCs + NMCs) vs NCs, 23% vs 14%]. Alcohol abuse was not increased in either the symptomatic carriers or the carriers overall. OCD was associated with manifesting the mutated M-D gene (MCs) vs the asymptomatic (NMCs +

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Table 1 *Demographics*

	MCs (n = 20)	NMCs (n = 10)	NCs (n = 34)
Males, no. (%)	13 (65.0)	6 (60.0)	13 (38.2)*
Females, no. (%)	7 (35.0)	4 (40.0)	21 (61.8)
Mean age, y (± SD, range)	41.2 (14.88, 16–70)	59.3 (15.92, 35–86)	40.9 (15.55, 16–79)†
Mean years education (± SD, range)	12.6 (1.9, 8–17)	12.2 (2.3, 8–16)	13.0 (2.4, 9–21)‡

* Chi-square test, $p = 0.169$.
† Analysis of variance, $p = 0.004$; the age of nonmanifesting haplotype carriers was older than the ages of the manifesting haplotype carriers and noncarriers.
‡ Analysis of variance, $p = 0.601$.

MCs = manifesting haplotype carriers; NMCs = nonmanifesting haplotype carriers; NCs = noncarriers.

NCs) group (25% vs 2.3%, $p = 0.01$). There was an increase in the rate of OCD in carriers overall (MCs and NMCs vs NCs); however, this was not significant (16.67% vs 2.94%). The rates of GAD, MAD, drug dependence, and drug abuse without dependence were not different between manifesting and asymptomatic individuals or between carriers and noncarriers of the *SGCE* gene. No case of OCD was identified among nonmanifesting *SGCE* mutation carriers (one individual previously reported[6] as carrying the haplotype did not have the family mutation). In all four cases of OCD with known age at onset of M-D, the reported age at M-D onset preceded the age at onset of OCD, with mean age at onset of M-D of 8.3 years (range 4 to 13) and a mean age at onset of OCD of 19.8 years (range 6 to 40).

Discussion. Our finding of an increased rate of OCD among MCs is consistent with a previous haplotype-based analysis in a subset of these families.[6] It appears that the *SGCE* gene is pleiotropic with OCD as a manifestation, although it is not clear whether this can occur in the setting of isolated OCD or only when coexpressed with motor features because no NMCs with OCD were found. Increased rates of OCD have also been reported in other movement disorders such as Tourette syndrome, cervical dystonia, and blepharospasm, which may share a similar pathologic mechanism as M-D.[6,8] The *SGCE* gene does not, however, appear to be associated with typical sporadic childhood-onset Tourette syndrome[9] or with comorbid Tourette syndrome and OCD.[8] Because of the very early age at onset of M-D and the expected later onset of OCD, the temporal relationship between the two disorders is not helpful in determining whether OCD is an effect of the gene or of manifesting the symptoms of M-D. However, unlike depression, OCD is usually not considered to be reactive to medical disease, and thus it is likely a gene expression triggered after manifestation of movement symptoms. It has been suggested that OCD may be a mutation-specific manifestation,[3] but we found OCD in MCs with a variety of mutations, including nonsense, frameshift, and splice mutations on exons 3, 6, and 7 and intron 1.

M-D is known to have reduced penetrance among individuals maternally inheriting the gene as a result of maternal imprinting.[1] One MC studied who inherited the mutation maternally had GAD and alcohol abuse. Another who inherited the gene paternally but did not manifest motor symptoms had MAD and, despite report of possible OCD by family members, did not meet criteria for OCD. Further evaluation of nonpenetrant, paternally inherited *SGCE* mutation carriers might lend more insight into the effect of the gene on OCD.

We also found an increased rate of alcohol dependence among MCs but not among carriers overall. However, unlike the relationship between M-D and OCD, we believe the increased rate of alcohol dependence in MCs may be due to the palliative effect of alcohol on the motor symptoms rather than a direct effect of the gene. Because alcohol often provides temporary relief from the symptoms of M-D[2] and given that a significant difference was found only in MCs and only in the most severe form of alcohol use, we think that it is likely that the pattern of alcohol dependence may begin when alcohol is used to self-treat motor symptoms.[6]

A number of small studies[3-5] examined psychiatric features in families with reported *SGCE* mutations: alcohol dependence was noted in MCs,[5] and, as men-

Table 2 *Mutations in SGCE families*

Family	No.	MCs	NMCs	Mutation type	Exon/intron	Sequence change
1	41	8	9	Nonsense	Ex 3	289C>T
2	12	5	0	Frameshift	Ex 6	795delA
3	4	3	1	Splicing	In 1	109+1G>A
4	3	3	0	Frameshift	Ex 6	771-772delAT
5*	4	1	0	Frameshift	Ex 7	835-839delACAAA

* The mutation in Family 5 was identical to a family previously reported.[3]

MCs = manifesting haplotype carriers; NMCs = nonmanifesting haplotype carriers.

Table 3 *Composite International Diagnostic Interview results in SGCE family member*

DSM-IV diagnosis	MCs (n = 20)	NMCs (n = 10)	NCs (n = 34)	Population estimate*
OCD	5 (25.0)	0	1 (3.0)	1.6%
Male	4 (30.8)	0	1 (7.7)	
Female	1 (14.3)	0	0	
Generalized anxiety disorder†	4 (20.0)	0	4 (11.8)	5.7%
Male	2 (15.4)	0	2 (15.4)	
Female	2 (28.6)	0	2 (9.5)	
Major affective disorder (depression-recurrent and bipolar disorder)	5 (25.0)	2 (20.0)	6 (17.6)	‡
Male	3 (23.1)	1 (16.7)	1 (7.7)	
Female	2 (28.6)	1 (25.0)	5 (23.8)	
Alcohol abuse without dependence	4/13 (30.1)	4/10 (40.0)	6/29 (20.7)	13.2%
Male	3 (23.1)	3 (50.0)	5 (38.5)	
Female	1 (14.3)	1 (25.0)	1 (4.8)	
Alcohol dependence	7 (35.0)	0	5 (14.7)	5.4%
Male	4 (30.1)	0	2 (15.4)	
Female	3 (42.9)	0	3 (14.3)	
Drug abuse without dependence	3/18 (16.7)	1/10 (10.0)	1/30 (3.3)	7.9%
Male	2 (15.4)	1 (16.7)	1 (7.7)	
Female	1 (14.3)	0	0	
Drug dependence	2 (10.0)	0	4 (11.8)	3.0%
Male	2 (15.4)	0	3 (23.1)	
Female	0	0	1 (4.8)	

Of the nine subjects from two new families not previously reported,[6] one MC had OCD and none were diagnosed with Alzheimer disease.

* Prevalence estimates from National Comorbidity Survey Replication.[10]
† Limited to individuals without comorbid diagnoses; including those with comorbid diagnoses, there were six MC, one NMC, and four NC with generalized anxiety disorder.
‡ Population estimate for major affective disorder is not available using this instrument; the estimate for major depressive disorder is 16.6%.

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; MCs = manifesting haplotype carriers; NMCs = nonmanifesting haplotype carriers; NCs = noncarriers; OCD = obsessive-compulsive disorder.

tioned, most[3,4] but not all[5] who evaluated subjects systematically for OCD demonstrated an association with manifesting the gene.

Although the increased rate of GAD among MCs in the present study was not significant, other studies have also suggested that anxiety disorders[4] or other psychiatric disorders[3] may be associated with M-D. However, unlike OCD, GAD in MCs is more likely to be reactive to living with the disease.

Further studies with larger sample sizes are needed to determine whether mutations in the *SGCE* gene predispose to OCD in those who do not manifest motor symptoms. As associations between psychiatric features (particularly OCD[3,4,6] and alcohol misuse[5,6]) and M-D have now been well reported, it is important that future studies include systematic psychiatric evaluations using reproducible tools to further our understanding of the relationship between these two disease entities.

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