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Hereditary myoclonus–dystonia associated with epilepsy

E.M.J. Foncke, C. Klein, J.H.T.M. Koelman,
P.L. Kramer, K. Schilling, B. Müller,
J. Garrels, P. de Carvalho Aguiar, L. Liu,
A. de Froe, J.D. Speelman, L.J. Ozelius,
M.A.J. Tijssen

Abstract

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A five-generation Dutch family with inherited myoclonus–dystonia (M-D) is described. Genetic analysis revealed a novel truncating mutation within the ϵ -sarcoglycan gene (SGCE). In three of five gene carriers, epilepsy and/or EEG abnormalities were associated with the symptoms of myoclonus and dystonia. The genetic and clinical heterogeneity of M-D is extended. EEG changes and epilepsy should not be considered exclusion criteria for the clinical diagnosis of M-D.

Introduction

Myoclonus–dystonia (M-D) is a rare movement disorder with myoclonus and mild dystonia. Alcohol often dramatically alleviates the symptoms. Other neurologic deficits are absent, and the EEG is normal. The clinical criteria for M-D have recently been revised.^{1,2} The mode of inheritance is autosomal dominant with variable severity and incomplete penetrance. A major locus for M-D on chromosome 7q21–q31 has been reported in several families. Until now, sequence analysis of genes at this locus identified eight loss-of-function mutations in the ϵ -sarcoglycan gene (SCGE).^{3,4} In two families, the dopamine D2-receptor gene (DRD2) on chromosome 11q has been implicated,^{3,5} and in another family, a novel mutation in the DYT1 gene has been described.⁶ In two of these three families, an additional mutation of the SCGE gene has been isolated.^{3,7} Recently, a new locus was mapped on chromosome 18p11.⁸ These findings suggest genetic heterogeneity in M-D. Here we present a Dutch family with M-D with a novel mutation in the SCGE gene and previously undescribed associated epilepsy.

Patients and methods

Patients

A detailed clinical description of this Dutch pedigree has been reported by Doheny et al. as Family 3.³ All participating family members gave informed consent. History was taken, and neurologic examination, brain MRI scan, and EEG were performed.

Marker analysis

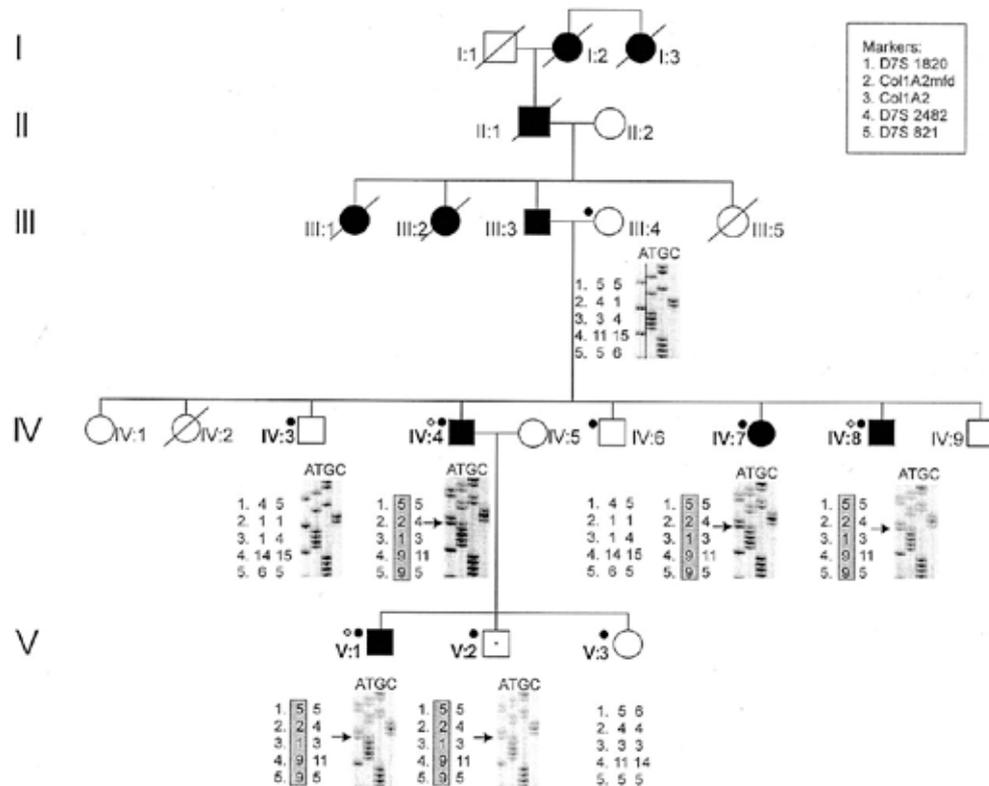
A venous blood sample was drawn and DNA extracted following standard methods. Genotyping of the SCGE and DRD2 regions was performed according to published PCR protocols (Research Genetics, Huntsville, AL; www.resgen.com) using an automated sequencing machine (LI-COR, Lincoln, NE). The following markers were used for haplotype analysis: D7S2204–4.48 - D7S2212–5.38 - D7S2410–4.05 - D7S646 - 0.0 - D7S657–1.06 - D7S1820–2.67 - D7S2482 - 0.53 - D7S821–4.80 - D7S1799 (chromosome 7) and D11S (chromosome 11) (map order according to the Genetic Location Database [http://cedar.genetics.soton.ac.uk/public_html/ldb.html] and distances taken from the Marshfield Clinics Database [<http://research.marshfieldclinic.org/genetics/>]).

Linkage analysis

We conducted two-point and multipoint linkage analyses using the VITESSE program, assuming autosomal dominant inheritance of a rare allele (frequency=0.0001) with reduced penetrance. We used an ‘affected-only’ model, in which only those with features of definite myoclonus, definite dystonia, or both were considered affected.

Mutation screening

Denaturing high-performance liquid chromatography (DHPLC) analysis was performed for all 12 exons of the *SGCE* gene. DHPLC analysis was performed using the Transgenomic WAVE DNA fragment analysis system. Elution gradients and analysis temperatures for each exon were predicted based on the target sequence using the Transgenomic WAVEMaker software. PCR products were eluted from a DNASep analytical column (Transgenomic) with a binary gradient of 0.1 M triethylammonium acetate (TEAA) and 0.1 M TEAA/25% acetonitrile at a flow rate of 0.9 mL/min. Direct cycle sequencing of exon 7 of the *SGCE* gene was performed with the primers 5'-aagaatgcttagtgc-3' (exon 7 forward) and 5'-tggtatcttagcaggatctc-3' (exon 7 reverse) on an automated sequencing machine (LI-COR) in all available family members.



Results

The pedigree consists of 22 family members (4 married in spouses) spanning five generations (**figure 1**).

Neurologic examination was performed on individuals IV:3, IV:4, IV:7, IV:8, V:1, V2, and V3. Individual III:3 was interviewed by telephone. Individuals IV:3, IV:4, IV:8, V:1 (**figure 2**), and V3 underwent a MRI and EEG. Five living individuals and three deceased individuals with clinical M-D were identified. Blood samples were obtained for DNA analysis from nine family members: four clinically affected and five clinically unaffected individuals (one

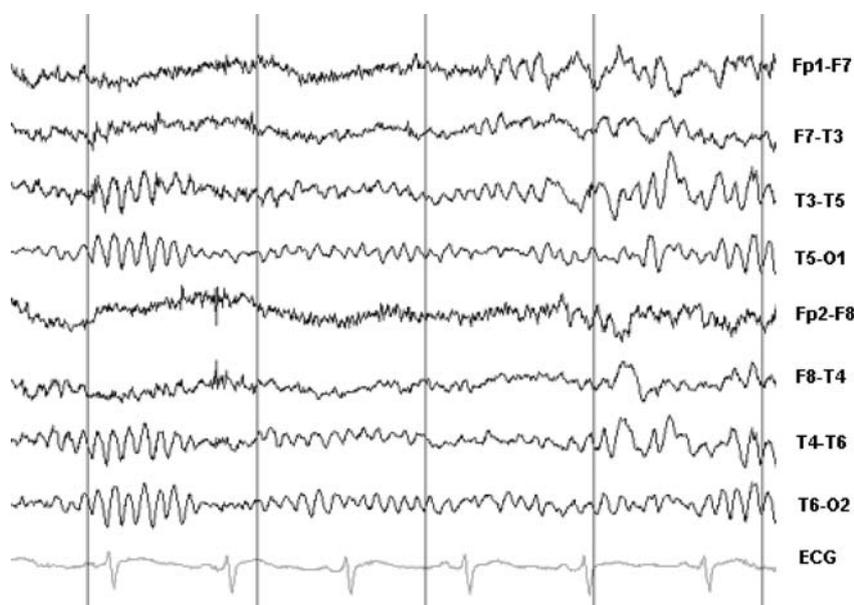


Figure 2. EEG findings of the index patient (V:1): a short run of sharp-wave slow-wave complexes starting at the left frontotemporal region (Fp1-F7/T3-T5) but also clearly visible on the right side (T4-T6). The first 3 seconds of the depicted recording show a normal background pattern.

married in spouse). **The table** summarizes the clinical findings, epileptic features, EEG, and MRI findings of the individuals who underwent neurologic examination. Patients IV:4, IV:8, and V:1 had epileptic seizures. In all three, the epilepsy started prior to the use of medication. Patient IV:4 had his seizures during childhood and after the age of 15 for several years and was successfully treated with carbamazepine and clobazam. Patient IV:8 also noticed a positive effect of antiepileptic drugs on his attacks. The episodes of amnesia in Patient V:1 are suggestive of partial complex seizures. After taking a single dose of clonazepam 4 mg, he suddenly became uncontrollably aggressive and fell through a window. He had amnesia for this accident. The effect of other antiepileptic drugs remains unclear.

Table Characteristics of examined individuals of the Dutch M-D pedigree

N	GS	AgeE, y	Age O,y	MS	Clinical signs of epilepsy	EEG	MRI
IV:3	-	49	-	-	None	n	n
IV:4	+	47	17	M of A and N, D of N	Episodes of reduced consciousness consisting of staring and lack of communication, lasting few seconds to several minutes, preceded by strange feeling in stomach	Slowing of activity in centrotemporal regions	n
IV:7	+	43	15	M of H, D of N and T	None	ND	ND
IV:8	+	39	15	M of H, D of N and T	Epilepsy starting with strange odor and followed by panic attack lasting several minutes; incidentally, involvement to partial complex seizures with reduced consciousness; several times seizures showed secondary generalization	During antiepileptic treatment (carbamazepine and clobazam) revealed no epileptiform activity	n
V:1	+	23	17	M of F, N, S, and A, D of N, T	Episodes of amnesia several times a day lasting a few seconds	Short runs of sharp wave and slow wave complexes at both temporal sites, most pronounced on the left (figure 2)	n
V:2	+	21		No symptoms	None	ND	ND
V:3	-	19		No symptoms	None	n	n

N = pedigree number; GS = genetic status; AgeE = age at examination; AgeO = age at onset; MS = motor symptoms at examination; M = myoclonus; D = dystonia; A = arm; N = neck; H = head; F = face; S = shoulder; T = trunk; n = normal; ND = not done.

Linkage analysis

Haplotype analysis was compatible with linkage to the SGCE region (lod score 0.91 at $\theta=0.0$) and excluded the DRD2 region. This lod score value approaches the theoretical maximum score for a family of this size and structure. All affected individuals carry the complete D7S2212 to D7S821 haplotype. One individual, V:2, without clinical signs of M-D also carries the complete haplotype.

Mutation screening

DHPLC analysis of the SGCE gene showed an altered pattern in exon 7. Sequence analysis of this exon revealed a 1-bp insertion (885Tins), resulting in frameshift and subsequent protein truncation at amino acid 297. This mutation was found in all carriers of the linked haplotype. Individual V:2 appeared to be an asymptomatic gene carrier.

Discussion

In this M-D family, the typical motor symptoms are accompanied by epilepsy. Epilepsy has not been reported in other M-D families and is considered an exclusion criterion for the clinical diagnosis.^{1,2} The association appears valid, although the size of sampling is limited. The seizures were not drug induced as no temporal relationship to the epileptic features and the initiation of therapy for the motor symptoms was noted. The extreme response to 4 mg of clonazepam in Patient V:1 possibly reflects drug-induced worsening of epilepsy.

Review of the literature revealed two patients with sporadic M-D with epileptiform changes on EEG but no history of epileptic seizures.⁹ No genetic defect has been described in these patients. Alcohol withdrawal seizures have been reported in M-D pedigrees¹⁰ but were not the case in this family. The epilepsy in the Dutch family suggests temporal–limbic origin. Interestingly, the feelings of panic during the seizures of Patient IV:8 have a strong similarity to the panic disorders described in several M-D families.³ Genetic analysis revealed a 1-bp insertion (885Tins) in the SGCE gene that was not previously reported. The role of the SGCE gene is not clear, but broad expression of the message includes expression in the basal ganglia and cerebral cortex.⁴ Changes in the cerebral cortex are hypothesized to lead to cortical disturbances in the current M-D family.

The clinical features of this M-D pedigree with a novel SGCE mutation expand the clinical phenotype and suggest that epilepsy and EEG abnormalities should not be considered exclusion criteria for clinical diagnosis. As epilepsy has not been reported in other MD families and not all MD families have been genotyped for specific mutation, this may be an important issue in discussions of genotype–phenotype correlations as well as diagnostic–prognostic issues based on specific mutations.

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