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Article *in* Hereditary Genetics · January 2012

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Apaydin et al., Hereditary Genet 2012, 1:3
http://dx.doi.org/10.4172/2161-1041.1000110

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A Novel Mutation in Exon 6 of the Epsilon-Sarcoglycan Gene in Myoclonus Dystonia Syndrome

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Abstract

Myoclonus-dystonia syndrome (MDS) is a rare hereditary movement disorder characterized by the early onset of myoclonus in the first or second decade of life. The first locus for MDS was mapped to chromosome 7q21 and identified as the epsilon-sarcoglycan (SGCE) gene, and numerous mutations were subsequently identified. We here present the first reported Turkish MDS patient identified with a novel mutation in exon 6 of the SGCE gene, which resulted in truncation of the protein before the transmembrane domain, presumably causing the loss of function either by mislocalization of the protein away from the plasma membrane or through nonsense-mediated decay.

Keywords: Myoclonus-dystonia syndrome; Epsilon-sarcoglycan gene; Exon 6; Novel mutation

Introduction

Myoclonus-dystonia syndrome (MDS) is a rare hereditary movement disorder. The first definition of this syndrome was made in a large German family as "myoclonic dystonia with lightning jerks responsive to alcohol" [1]. It is characterized by the early onset of myoclonus in the first or second decade of life, frequently accompanied by dystonia involving the neck, arms, and face. The severity of MDS varies ranging from mild subtle features, to marked impairment due to severe myoclonus and/or dystonia [2]. On the other hand, patients generally have a normal life-span. Alleviation of symptoms in response to alcohol but not to L-dopa is well established even though the response to treatment varies.

Segregation analysis in MDS families showed autosomal dominant inheritance with reduced penetrance, but the syndrome also occurs sporadically. Mutations in the epsilon-sarcoglycan (SGCE) gene were identified as a cause for MDS [3]. Here we present the first reported Turkish MDS patient with a novel nonsense mutation in exon 6 of the SGCE gene.

Case Report

A 22-year-old, right-handed man was admitted with involuntary twisting movements of the hands and head causing adduction of the arms, and deviation of the neck to the right-side and backwards; which started at the age of 4 years, showed some progression, but then remained stationary for years. The patient stated that these movements caused dropping objects, interfered with writing and walking, and worsened with stress or attempts to write. He refused to take alcoholic beverages to test the response.

His past medical history was unremarkable. He was born after a normal pregnancy and delivery; his psychomotor development was normal. His family history was negative for any movement disorders; there was no consanguinity. His neurological examination revealed retrocollis, dystonic hyperextension posture and myoclonic jerks involving his trunk and both arms being more prominent on the left side with hypertrophia of the affected muscles (Figure 1) which worsened with action (Video segment). The patient was given a variety of drugs including: haloperidol, biperiden, clonazepam, piracetam, levetiracetam, olanzapine, venlafaxine, sodium valproate and diazepam, with either no or limited effect. He was then treated with botulinum toxin-A for selected dystonic muscle groups, which resulted in significant relief. On his last examination, retrocollis was obviously decreased; some difficulties with the hand movements and writing were still present.

Biochemical tests and cranial magnetic resonance imaging were normal. We obtained informed consent from the patient for DNA analysis. The DNA sample was screened for mutations in the SGCE gene by direct sequencing using previously published primers and conditions [4], and a novel nonsense mutation, c.727 C>T; p.Q243X, was identified in exon 6.

Discussion

Our patient presented with clinically typical MDS characterized by dystonia and myoclonus of the upper body. The full phenotypic spectrum of this syndrome, however, is quite diverse and still being defined [2,5]. Although early disease onset, onset with both myoclonus and dystonia, and axial dystonia were detected significantly more often in the mutation carriers [6], there has been no clear phenotype-genotype associations identified to date suggesting other genetic or environmental factors as modifiers.

The first locus for MDS was mapped to chromosome 7q21 and identified as the epsilon-sarcoglycan gene [1,3]. Subsequently, numerous mutations in this gene have been described [5]. A second MDS locus was mapped to chromosome 18p11 [7]. Mutations in SGCE are usually associated with familial MDS cases [8]. Recently, MDS in a patient with 18p deletion syndrome was also described [9]. A few sporadic cases with *de novo* SGCE mutation have also been reported [5]. Different genetic mutations in exon 3, exon 4, and also in exon 6 were previously reported underlying the importance to register novel mutations and to add them to the preexisting list of known mutations in order to ensure an as fast and cost-effective diagnostic procedure as possible [4,8,10,11]. The authors suggested that exon rearrangement results in the generation of premature stop codons downstream of the deleted exon. We identified a novel mutation in exon 6 of the SGCE

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Received January 10, 2012; **Accepted** June 06, 2012; **Published** June 10, 2012

Citation: Apaydin H, Benbir G, Ozelius L, Ozekmekci S (2012) A Novel Mutation in Exon 6 of the Epsilon-Sarcoglycan Gene in Myoclonus Dystonia Syndrome. Hereditary Genet 1:110. doi:10.4172/2161-1041.1000110

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Figure 1. Retrocollis, dystonia on his trunk and both arms being more prominent on left side, worsening with purposeful movements, and hypertrophia of the affected muscles were observed.

gene in the first Turkish patient described with MDS. The mutation, Q243X, results in a truncation of the protein before the transmembrane domain presumably causing loss of function either by mislocalization of the protein away from the plasma membrane or through nonsense-mediated decay. The location (extracellular domain) and mutational mechanism (loss of function) described in this patient, are typical of different mutations previously found in this gene [5]. SGCE exon dosage assays may identify other SGCE mutations, and may help better definition of phenotype-genotype correlation.

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