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Novel *COLQ* mutation 950delC in synaptic congenital myasthenic syndrome and symptomatic heterozygous relatives

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Abstract

The synaptic form of congenital myasthenic syndrome (CMS) is a rare autosomal recessive disease affecting neuromuscular transmission. Mutations in the *COLQ* gene that encodes the collagenic tail subunit (*ColQ*) of asymmetric acetylcholinesterase lead to endplate acetylcholinesterase deficiency. We report two children suffering from synaptic CMS due to two compound heterozygous *COLQ* mutations, IVS1-1G > A and a novel mutation, 950delC. Furthermore, we found familial occurrence of congenital ptosis in heterozygous carriers of 950delC, mimicking a dominant negative effect. Considering the lack of a clear genotype–phenotype-relation in synaptic CMS, several authors speculated on the influence of additional modifying factors. Consequently, involvement of such factors in this report of familial congenital ptosis cannot be excluded.

Keywords: Congenital myasthenic syndrome; *COLQ*; Heterozygosity

1. Introduction

The diagnosis of synaptic congenital myasthenic syndrome (CMS) is based on myasthenic symptoms but absence of acetylcholine receptor (AchR)-antibodies, a negative Edrophonium test as well as a lack of response to long-acting cholinesterase inhibitors, and mutation analysis of the *COLQ* gene [1,2]. Biochemical analysis of the neuromuscular endplate shows absence of asymmetric acetylcholinesterase [3]. Specific neuromuscular findings such as repetitive compound muscle action potential (CMAP) and slow pupil reaction are helpful but inconstant diagnostic clues [4,5]. The family history of affected patients is usually unremarkable regarding neuromuscular disorders. Until now, 25 different *COLQ* mutations have been reported to cause endplate acetylcholinesterase deficiency, with an assumed autosomal recessive mode of inheritance [6,7]. Here, we report a novel *COLQ* mutation found in two siblings with synaptic CMS and symptomatic heterozygous relatives.

2. Case report

2.1. Patient 1

The second of three children of non-consanguineous German parents was born at term with congenital ptosis, muscular weakness, and difficulties in pulmonary adaption. At the age of 2 weeks, the boy opened his eyes for the first time. Within early infancy, delayed gross motor development, muscular weakness, a myopathic facies, and external ophthalmoplegia became apparent, and the boy was suspected of having myopathy or infantile myasthenic disease. In this context, his parents reported several episodes of deteriorating muscular

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strength during febrile infections. At the age of 3 years, the boy died after developing fulminant sepsis and acute respiratory insufficiency without a diagnosis of the underlying disorder.

2.2. Patient 2

The younger sister of patient 1 presented similar clinical features. As her brother, she was born with congenital ptosis and muscular weakness. Her gross motor development was delayed, her facial mimics were poor, and she presented repeated episodes of acute respiratory distress so that parents and clinicans assumed the same disorder in both children. Edrophonium test was negative. Standard histological examination of a muscle biopsy from the vastus lateralis muscle taken at the age of 4 years revealed only unspecific findings such as a predominance of type I fibres. At present, the 5-year-old girl is able to climb stairs hand in hand with her mother.

2.3. Family of patients

The oldest of the three siblings, an 11-year-old boy, their mother, and their maternal grandparents never demonstrated any neuromuscular impairment. However, their father and their paternal grandmother both suffered from congenital ptosis. In both of them, ptosis improved during childhood, but was still detectable in adulthood. The grandmother's ptosis worsened again around the 60th year of life.

2.4. Mutation analysis

DNA was isolated from blood or fixed tissue (liver) and was screened for mutations in the *COLQ* gene by PCR and DNA-sequencing. The analysis of patients 1 and 2 revealed two compound heterozygous mutations. IVS1-1G > A, which is also found in their older brother and their mother, is an exon 2 splicing mutation. It affects the proline-rich attachment domain (PRAD) of the *ColQ* protein and was first reported by Ishigaki et al. [8]. A novel mutation 950delC, also carried by their father and their paternal grandmother, leads to a frame-shift in exon 13 and truncates the collagen-encoding region. The asymptomatic paternal grandfather is heterozygous for an amino acid exchange (312Ser/Gly) in exon 13, which was previously reported as benign polymorphism (www.ncbi.nlm.nih.gov/SNP/). In patient 2, all 17 exons including adjoining intronic regions were analyzed. Subsequently, exons 2 and 13 were screened for the above-mentioned mutations in siblings, parents, and paternal grandparents. Involvement of a third *COLQ* mutation in congenital ptosis of generations F1 and F2 can be excluded by Mendelian rules (Fig. 1).

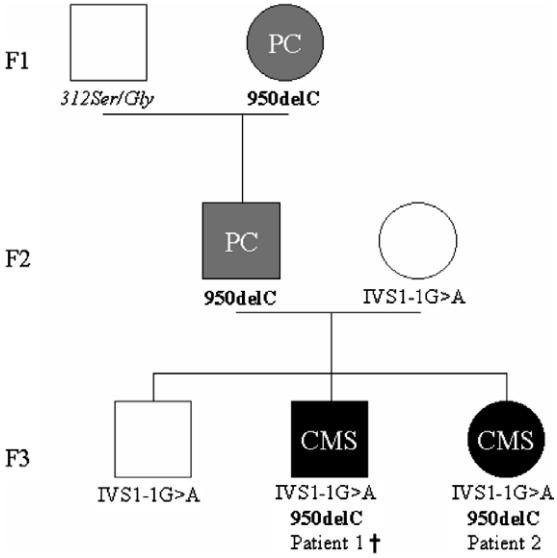

Fig. 1. Both CMS patients are compound heterozygous for IVS1-1G > A and 950delC. Heterozygosity of 950delC is found in relatives suffering from congenital ptosis (PC) whereas heterozygous carriers of IVS1-1G > A are asymptomatic. 312Ser/Gly, carried by the asymptomatic paternal grandfather, is a benign polymorphism.

2.5. Histology

Archived muscle tissue from patient 2 was re-examined to confirm the diagnosis of endplate acetylcholinesterase deficiency. Unfixed cryosections were serially stained with first rhodamine-conjugated alpha-bungarotoxin to localize motor endplates and second cholinesterase staining with a modified bromoindoxyl-acetate technique [9]. As the second procedure abolishes the rhodamine fluorescence, the locations of the endplates were re-identified by diffraction morphology using digital overlaying. In contrast to a perfect match of both reactions in normal control sections, we found the histochemical absence of cholinesterase reactivity at the sites of motor endplates of patient 2 (Fig. 2).

2.6. Electrophysiology

Compound muscle action potential (CMAP) was recorded from the abductor pollicis brevis muscle using a train of 10 supramaximal stimulations of the median nerve at 2 Hz as previously described [4]. Repetitive CMAP and myasthenic decrement were detected in patient 2 whereas neither of them could be detected in generation F2 and F3 heterozygous carriers.

3. Discussion

Here we report a novel mutation in the *COLQ* gene (950delC), which in combination with a previously