Myotonia congenita associated to multiple sclerosis in a Tunisian family

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INTRODUCTION

Myotonic syndromes are hereditary conditions related to genetic abnormalities that cause a disorder of skeletal muscle excitability. Myotonic syndromes are separated into two groups: dystrophic myotonic syndromes comprising dystrophic myotonia type I and type II and non-dystrophic myotonia (the rarest type which do not affect the heart muscle).

Non-dystrophic forms can be separated into chloride and sodium channelopathies, with gene-defects in genes coding for muscle chloride (CLCN1) and sodium (SCN4A) ion channels. They can be separated, according to clinical, electrophysiological and molecular criteria, into three categories: congenital myotonia, congenital paramyotonia and sodium channel myotonia.

Multiple sclerosis is a disease that impacts the brain, spinal cord and optic nerves causing a wide range of symptoms, including arm or leg movement, sensation or balance. Symptoms, such as myokymia, myotonia, spasms, and stiffness, have been demonstrated to be due to a concurrent non-dystrophic myotonia.

Confirming the presence of a channelopathy in Multiple sclerosis patients may be important, since dysfunction of ion channels may need proper therapeutic management.

OBJECTIVES

The CLCN family of voltage-dependent chloride channel genes comprises nine members (CLCN1-7, Ka and Kb) which demonstrate quite diverse functional characteristics while sharing significant sequence homology. Here, we report a CLCN1 gene mutation associated to myotonia congenita and multiple sclerosis.

MATERIALS AND METHODS

Neurological examinations, biological and electrophysiological investigations were offered to a Tunisian female child suffering from learning difficulties and muscle weakness/hypertrophy as well as her parents who were candidate for an artificial reproduction technique (ART) attempt.

They attended our genetic counselling at the medical university of Sfax and requested genetic counselling and molecular explorations to assess the risk of recurrence of their first child condition (to be able to carry on a subsequent prenatal diagnosis).

In addition, the father suffered from multiple sclerosis associated to stigmatas of non-dystrophic myotonias and he complained for a secondary male infertility.

Besides, karyotyping and molecular screening of Y chromosome microdeletion and CFTR mutations, molecular investigation of CLCN1 gene was conducted for the couple and their girl.

RESULTS

A CLCN1 mutation of the codon 1592 (amino acid 531) was detected in the child diagnosed with myotonia congenita and her non-consanguineous Tunisian parents. Family history was apparently negative for neuromuscular diseases. Ectrophysiological investigation in the parents did not show any muscle abnormality.

Molecular results were concordant with the recessive inheritance mode of the detected CLCN1 mutation in our Tunisian family.

Genetic counseling provided to the non-consanguineous couple before ART was offered with multiple reservations. In fact, the non-consanguinity and the description of the same mutation in literature in association with the two forms of myotonia congenital: recessive and dominant forms were confusing (Figure 1). The association in the father of multiple sclerosis with the patient-reported clinical myotonia was also intriguing.

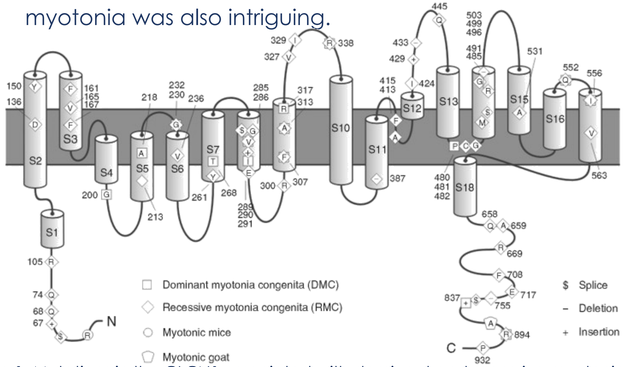

Figure 1: Mutations in the CLCN1 associated with dominant and recessive myotonia (1)

CONCLUSION

Here, a Tunisian heterouzygous CLCN1 mutation may be responsible of the clinical association underlying a unique channelopathy simultaneously involving the peripheral and the central nervous system.

Other studies in the Tunisian population are needed to confirm our hypothesis.

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