Novel Lys215Asn mutation in an Italian family with Thomsen myotonia

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Dear Sir,

Myotonia congenita is a non-dystrophic muscular disease characterized by impaired muscle relaxation after voluntary or evoked contraction and muscle stiffness. Myotonia typically occurs after a period of rest and decreases after repetitive movement, the so-called warm-up phenomenon [1]. Muscular hypertrophy is an- other important clinical sign.

Myotonia congenita, both in dominant (Thomsen disease) and in recessive form (Becker disease), is caused by mutations in the *CLCN1* gene that encodes the major skeletal muscle chloride channel [2]. Dysfunction of this channel causes hyperexcitability of the skeletal muscle membrane and repetitive firing of muscle action potentials [3]. More than 150 *CLCN1* pathogenic variants have been identified.

We present an Italian family with Thomsen myotonia (Fig. 1) in which a novel mutation in the *CLCN1* gene was detected.

A 60-year-old man (patient II:1) complained from childhood of transient stiffness and weakness that improved with activity and got worse with cold temperatures. Neurological examination revealed generalized muscle hypertrophy, most prominent in quadriceps and gastrocnemius muscles, with normal strength. Grip and lip myotonia were evident. Percussion of the thenar eminence elicited brief opposition. CPK were 360 U/L (nv 60-190). EMG revealed profuse myotonic discharges in all examined muscles with normal motor unit potentials.

The 32-year-old firstborn son (patient III:1) presented the same symptoms of the father from infancy. Neurological examination showed Hercules-like appearance. Myotonia was present in all four limbs and in facial muscles including lids. Percussion of the thenar eminence elicited brief opposition. CPK were 420 U/L. EMG showed abundant myotonic discharges in all tested muscles and mild myopathic changes in iliopsoas and deltoids muscles.

In both patients Mexiletine 200 mg bid was started with improvement.

After genetic counseling, probands and their familiars underwent to the screening for *CLCN1* gene. Sequence analysis evidenced the previously reported p.Phe167Leu on exon 4, and the nucleotide change c.645G>T on exon 5 leading to the missense p.Lys215Asn (Fig. 2). This variant was unreported; therefore, 160 control alleles were checked for this novel variant, and none resulted positive. The possible pathological meaning of the variant was evaluated by in silico tools (PROVEAN provean.jcvi.org; MutationTaster www.mutationtaster.org; MutPred mutpred.mutdb.org) and was unanimously predicted as pathogenic. Subjects II:1 and III:2 were heterozygous for p.Lys215Asn; II:2 carried p.Phe167Leu, III:1 was a compound heterozygote of both mutations.

Thereupon, we clinically evaluated subject III:2, who did not complain any symptoms. Neurological examination revealed only generalized muscle hypertrophy. CPK were normal. EMG showed myotonic discharges of proximal and distal muscles but not at masseter.

Mutations in *CLCN1* gene are causative of congenital myotonia. We report a novel mutation in a family with two males suffering from myotonia congenita and one

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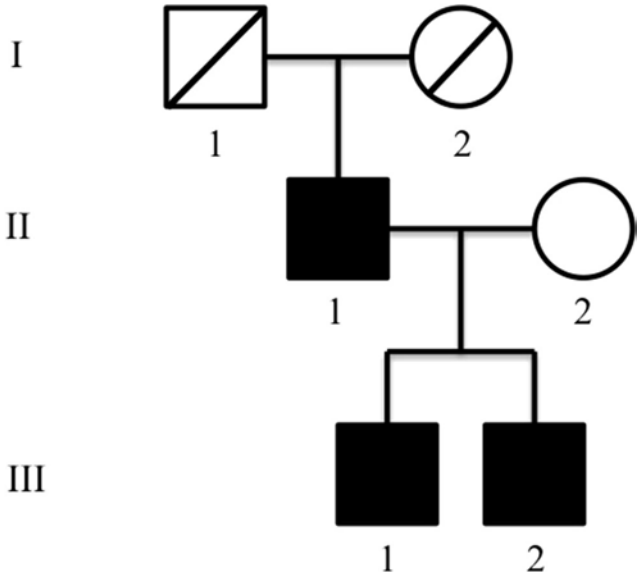

Fig. 1 Family pedigree

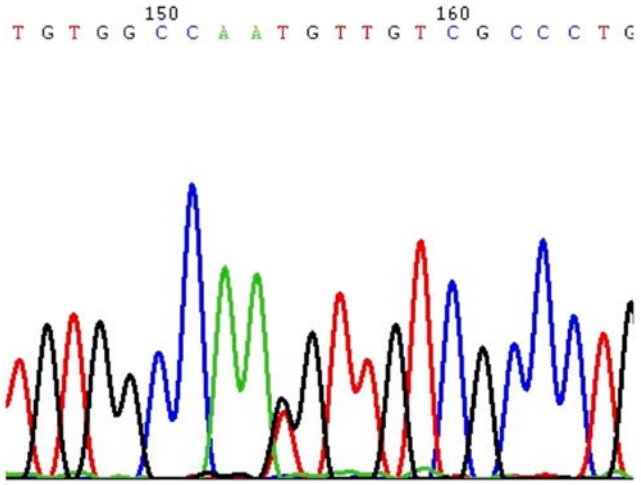

Fig. 2 Electropherogram showing the heterozygous nucleotide change c.645G>T on exon 5 in CLCN1 gene, leading to the missense p.Lys215Asn

asymptomatic carrier. Serendipitously, the wife presented a known mutation, transmitted to the symptomatic son. Subject III:2 probably represents a subclinical variant of Thomsen disease. In fact, heterozygotes for *CLCN1* mutation are often asymptomatic, and mild myotonia is revealed only by physical examination, but some subjects presented pronounced myotonia [4]. Several mutations behave as partially dominant with a reduced penetrance, and mutations in *CLCNl* gene do not necessarily have a classic Mendelian pattern [5].

Lysin 215 lies in the E domain of the channel, embedded in the membrane, though this residue seems to be far from the one (Glu 232) catching chloride ions in the protopore. p.Lys215Asn is likely a dominant mutation without complete penetrance. Other dominant mutations with reduced penetrance are described before, suggesting a strong influence of other unclear genetic factors [4–6].

Several studies reported that Phe167Leu mutation has very mild effects, and the clinical signs of the pathology have mostly been attributed to compound heterozygosis with other mutations [7]. It is likely that in our patient with double mutation, the Phe167Leu mutation strengthens the symptomatology through a gene dosage effect due to the presence of a second mutation with more severe phenotype.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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