Myotonia Congenita, A Case Series of a Possible Founder Mutation

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INTRODUCTION:

Myotonia congenita (MC) is one of the most common forms of non-dystrophic skeletal muscle channelopathies. MC is caused mainly by mutations in the Chloride channel 1 (*CLCN1*) located on chromosome 7q35 which encodes the skeletal muscle voltage gated chloride channel (ClC-1). *CLCN1* related MC can be inherited in dominant (Thomsen disease, OMIM#160800) or recessive (Becker disease, OMIM#255700). CLCN1 related MC was originally estimated to occur with frequency 1:23,000 for autosomal dominant form and 1:50,000 for autosomal recessive form.

MC is characterized by episodic muscle stiffness that improve with brief exercise (warm up phenomena), and muscle hypertrophy due to delayed relaxation after voluntary or evoked muscle contraction.

Molecular sequencing has identified over 200 pathogenic mutations in the *CLCN1* gene making the phenotype and classification more diverse. Most disease causing *CLCN1* mutations lead to loss-of-function phenotypes in the ClC-1 channel and thus increase membrane excitability in the muscles.

OBJECTIVES

We are describing a family with two affected siblings with childhood onset myotonia (clinical and electrodiagnostic) and novel *CLCN1* variant.

CASES (siblings)

Age of onset	4 years	4 years
Sex	Male	Male
Limb myotonia	++	++
Facial myotonia	–	–
Muscle hypertrophy	+	+
Periodic weakness	–	–
Provocative factors	Rest	Rest
Alleviating factors	Mild exercise (warm up phenomena)	Mild exercise (warm up phenomena)
Extra muscular involvement	–	–
Consanguinity	+	+
Family history	–	–
Grip myotonia	+	+
Percussion myotonia	–	–
Tounge myotonia	–	–

INVESTIGATIONS

Both cases shared very similar phenotype and results. The electrodiagnostic studies showed normal sensory and motor nerve conduction studies while the electromyography (EMG) showed classical neurophysiological evidence of waxing and waning myotonia. Whole exome sequencing showed homozygous likely pathogenic variant at *CLCN1:I VS19 (c.2365-1G>T*). This variant was not previously reported in clinical database (ClinVar).

DISCUSSION

Literature review demonstrated that Monies et al. has previously reported the *CLCN1:I VS19 (c.2365-1G>T*) variant in a Saudi adult male with MC phenotype, the previously reported case is not related to our cases and not from the same family or tribe.

Saudi Arabia, has a high consanguinity rate that can reach up to 50% which represents a unique resource to accelerate the discovery of unmask Mendeliane recessive trait. Monies et al, described the founder variants as variants that are observed with a minor allele frequency (MAF) > 0 in apopulation or that are present in two affected individuals who are not directly related but share the same haplotype and phenotype.

CONCLUSION

According to Monies et al. definition, the listed variant (c.2365-1G>T) is a founder mutation originating in Saudi Arabia. Our team are planning to explore the purposed hypothesis further through national collaboration.

REFERENCES

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