Muscle cramps may be a clue for GFPT1 gene related congenital myasthenic syndrome

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INTRODUCTION

Congenital Myasthenic Syndrome (CMS) is a genetically and clinically heterozygous group of disorders with compromised neuromuscular transmission. To date, up to 30 genes have been identified to cause CMS and The *GFPT1* gene is one of these genes. *GFPT1* encodes an isoform of glutamine:fructose-6-phosphate amidotransferase (GFAT), which catalyzes the transfer of an amino group from glutamine onto fructose-6- phosphate, yielding glucosamine 6-phosphate and glutamate. It is the first and rate-limiting enzyme of the hexosamine biosynthetic pathway. Hexosamine is the obligatory source of essential amino sugars for the synthesis of glycoproteins, glycolipids, and proteoglycans. Congenital myasthenic syndrome-12 is an autosomal recessive neuromuscular disorder characterized by onset of proximal muscle weakness in the first decade by the homozygous mutations in *GFPT1* gene.

OBJECTIVES

We present three pediatric-onset cases from 2 unrelated families, with homozygous *GFPT1* gene mutations, who were diagnosed as congenital myasthenic syndrome type 12 with tubular aggregates (CMS12) following molecular genetic studies.

METHODS

A WES analysis was performed by using xGen Exome Research Panel v2. VCF files were annotated using Qiagen Ingenuity Variant Analysis and Clinical Insight Interpret (QIAGEN GmbH).

RESULTS

Patients were referred to our clinic for their progressive proximal weakness, easy fatigability, muscle cramps starting around 9-10 years of age. Currently, they are 22 (Case-1, male), 17 (Case-2, female), and 11 years (Case-3, male), of age, respectively. All patients could walk independently, however gait unsteadiness, and waddling gait were observed. The progressive limb-girdle weakness with positive Gower's sign was observed in all. Case-1 and 2, who are siblings, also had muscle atrophy and intermittent mild ptosis. None of them had an involvement of bulbar, neck and respiratory muscles. Deep tendon reflexes were absent. Decremental compound motor action potential response to repetitive nerve stimulation and myopathic findings seen on electroneuromyography in Case-1. Case-3 is a Syrian immigrant, has a definitive limb muscle hypertrophy, predominantly observed in lower limbs and can not be reached after the molecular diagnosis for the treatment. Patients were referred to the Medical Genetics Department of Ankara City Hospital with a pre-diagnosis of congenital myasthenia and muscular dystrophy. The same *GFPT1* gene homozygous mutations were determined at c.331C>T in siblings (figure-1 for sister) and c.738_739delAG in Case-3 (figure-2). No communication was established with case-3 after molecular genetic diagnosis. Pridostigmine treatment was started for siblings, awaiting evaluation for response.

CONCLUSION

This condition is related to an abnormality of the carbohydrate-deficient glycoprotein in general terms. These 3 patients, from 2 unrelated families, with similar clinical phenotypes further expand the clinical spectrum of CMS12. Muscle cramps along with fatigue and proximal weakness in a progressive manner can be considered as clinical clues. On the other hand, no manifestation with respiratory insufficieny and no manifestation within the first decade of life are not the commonly observed in CMS12.

REFERENCES

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Figure 1 shows the mutation of Case-1 and Case-2

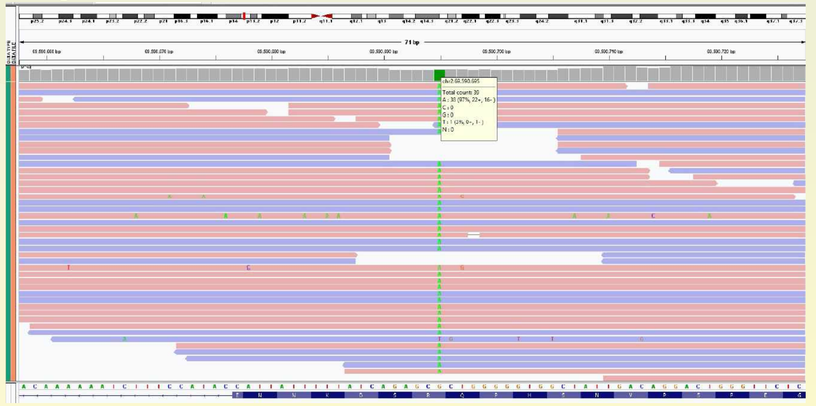
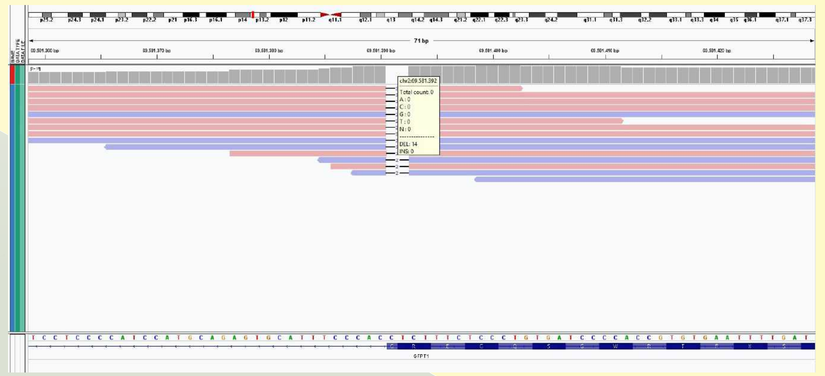


Figure 2 shows the mutation of Case-3



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