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LETTER TO THE EDITOR

A novel sporadic sodium channel mutation in a young adult patient with paramyotonia congenita

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Myotonia is a clinical finding characterized by delayed muscle relaxation following voluntary contraction, typically resulting from ion channel abnormalities at the muscle membrane level. Diseases in which myotonia is observed are generally classified into two main groups: dystrophic and nondystrophic myotonias. Myotonic dystrophies are more common and represent the most frequent form of muscular dystrophy in adulthood.[1] Nondystrophic myotonias are a rarer group of monogenetic muscle disorders caused by mutations in the voltage-gated skeletal muscle sodium or chloride ion channel genes, leading to muscle membrane hyperexcitability.

Paramyotonia congenita (PC), a type of nondystrophic myotonia first described by Eulenberg in 1886, is a rare hereditary skeletal muscle channelopathy characterized by cold and exercise induced myotonia, with paradoxical worsening of stiffness upon repeated activity.[2] It is typically inherited in an autosomal dominant (AD) manner, with most cases associated with mutations in the SCN4A gene encoding the voltage-gated sodium channel $Na_v1.4$.[3] To the best of our knowledge, there is no established prevalence rate for PC in Türkiye. However, some studies that included all nondystrophic congenital myotonias have reported prevalence rates of 0.75 per 100,000 in the UK and 1.70 per 100,000 in the Netherlands.[3] Clinical hallmarks include paradoxical myotonia that worsens with activity and cold exposure, sometimes accompanied by transient weakness.[2,3] Episodic weakness may also be observed in patients with PC; however, this symptom is generally less prominent.[4] Although familial cases are more common, sporadic or de novo mutations have been documented.[5] Identifying these cases is essential to avoid misdiagnosis and to implement appropriate therapy. Herein, we reported a young adult patient with a presumed sporadic SCN4A mutation leading to PC, with no family history and characteristic clinical features.

A 22-year-old male patient was admitted to the neuromuscular clinic with complaints of muscle stiffness and weakness that had been present since early childhood (approximately 3-4 years of age). The symptoms included difficulty climbing stairs, easy fatigability, and worsening stiffness in cold environments. The patient reported a notable improvement in symptoms during the summer. Repetitive physical activity exacerbated the condition. There was no history of myoglobinuria, cardiac complaints, or respiratory issues. The patient stated that he had previously fasted during Ramadan but had since stopped due to increased symptom burden. He described a few episodes of generalized fatigue affecting the entire body, which resolved spontaneously with rest and did not lead to any formal diagnosis or treatment. There was no family history of neuromuscular disorders and no known parental consanguinity. The patient had two siblings, both of whom were healthy. Written informed consent was obtained from the patient.

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The patient, a university student, exhibited preserved cognitive function. The neurological examination revealed mild muscle weakness, more pronounced in the lower extremities and proximal muscles, along with a positive Gowers' sign. Prominent action myotonia was observed in both hands (Figure 1), with only very mild involvement in the ocular muscles. The patient did not exhibit a markedly hypertrophic appearance (Figures 2). There was no significant percussion myotonia. The patient reported increased difficulty in climbing stairs, easy fatigability, and stiffness in the hands with delayed muscle relaxation, particularly exacerbated in cold environments. Gait was independent, although a mild pelvic sway was noted. The reflexes and the sensory exam were normal. The patient had no history of significant episodic weakness. The patient's body mass index was 32.1 kg/m^2 (height: 180 cm; weight: 104 kg). The patient covered 350 m in the 6-min walk test, with notable worsening of symptoms during and after the test.

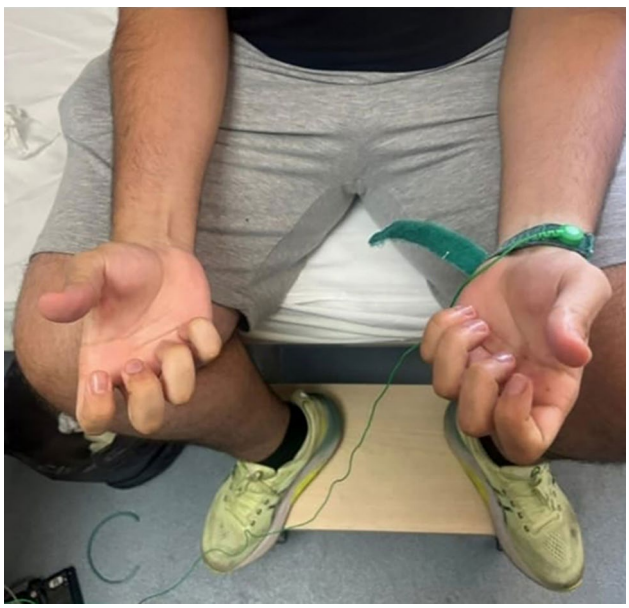

Figure 1. The patient's myotonia state.

Whole exome sequencing revealed a heterozygous missense variant in the SCN4A gene (ENST00000435607.3) c.2065C>G, resulting in a p.Leu689Val amino acid substitution (ENSP00000396320.1). The variant was located at chromosome 17 (Chr17:63957473, G→C) and lacked a ClinVar record. According to the American College of Medical Genetics and Genomics criteria, it was evaluated as "likely pathogenic" since it had extremely low frequency in population databases (PM2), it was located in a mutational hot spot (PM1), the in-silico computational prediction tools support a deleterious effect (PP3), and a different amino acid change represented a known pathogenic variant (PM5). These data suggested that the variant was a novel mutation. This variant had not been previously reported in association with PC, and its pathogenicity is under evaluation.

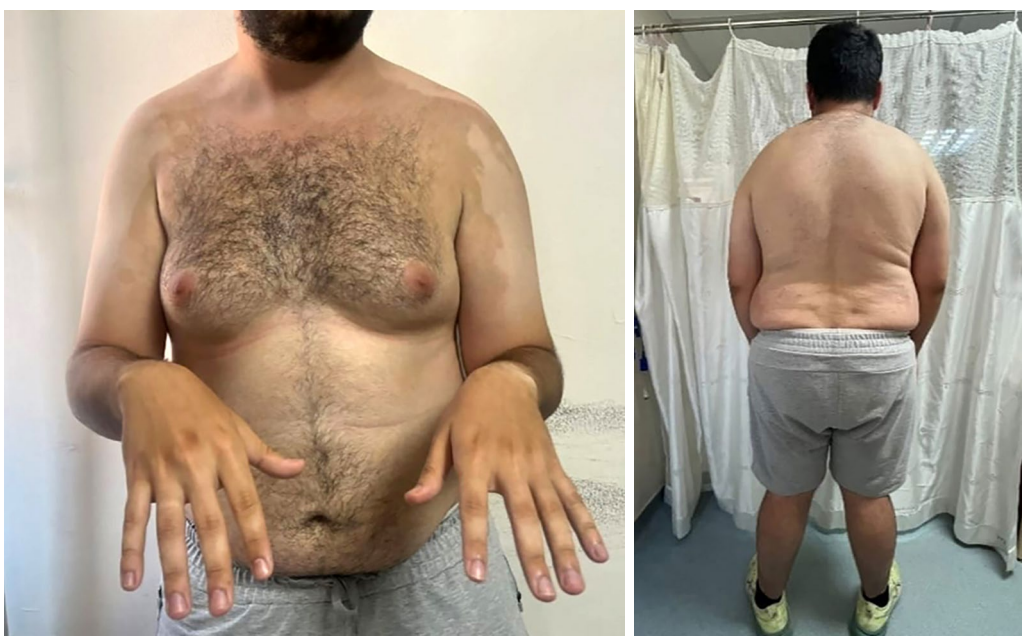

Figure 2. No significant trophic changes.

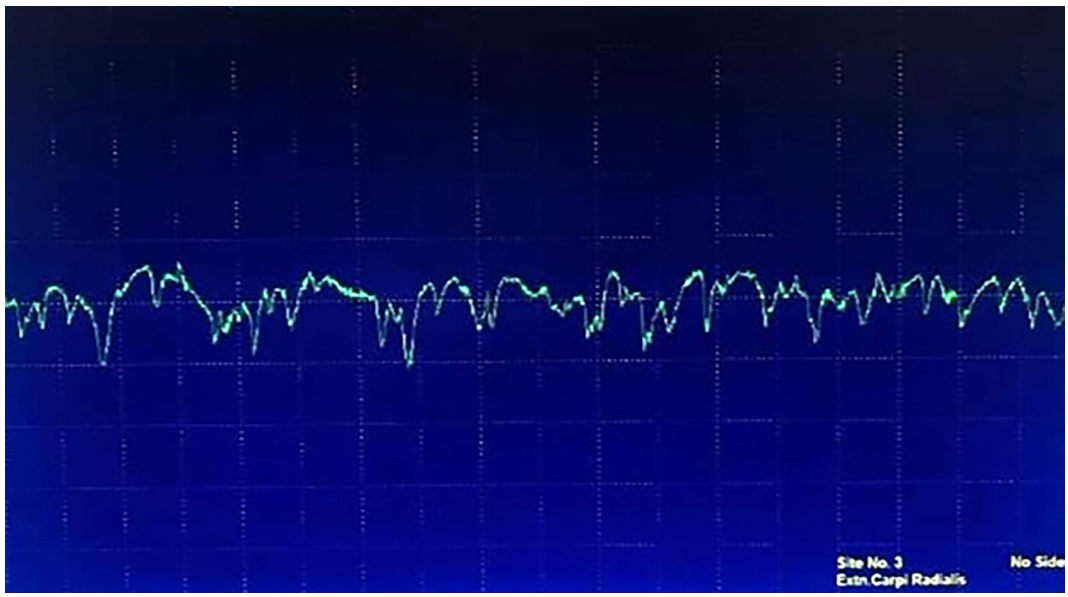

Figure 3. Electrophysiological findings of myotonia.

The serum creatine kinase level was 2525 U/L. Other routine biochemical parameters were within normal limits. Electrocardiography and echocardiography revealed no abnormalities. The nerve conduction study was normal. Electromyography revealed significant myotonic activities in all evaluated muscles (Figure 3).

Paramyotonia congenita is a well-characterized channelopathy resulting from dysfunctional sodium channels in skeletal muscle fibers. Mutations in the SCN4A cause persistent sodium influx and prolonged depolarization, manifesting clinically as cold-sensitive myotonia and weakness. Our patient demonstrated the classic features of PC: early-onset stiffness, paradoxical worsening with exercise, cold sensitivity, and elevated creatine kinase levels.

Among sodium channel-related myotonic syndromes with AD inheritance, PC and sodium channel myotonia are defined as distinct subtypes. Due to the presence of paradoxical myotonia (worsening with exercise) and marked cold sensitivity, our patient was clinically classified as having PC.

Genetic testing identified a previously unreported heterozygous missense variant in SCN4A (c.2065C>G; p.Leu689Val) located at Chr17:63957473 (G→C). This variant is not listed in ClinVar, the Human Gene Mutation Database, or population databases such as gnomAD and is therefore considered likely novel. Given the patient's classical clinical phenotype and the established role of SCN4A in skeletal muscle excitability, this variant is highly suspected to be pathogenic. Functional studies are needed to confirm its role in channel dysfunction. The sporadic nature of the mutation further supports the hypothesis of a de novo pathogenic variant. The lack of family history strongly suggests a de novo mutation, a possibility supported by other similar cases in the literature. The patient's phenotype is consistent with previously reported SCN4A variants.

Some myotonic patients can manage their myotonia by adapting lifestyle and exercise, while others require pharmacologic therapy to improve quality of life.[6] Due to their sodium channel blocking effects, antiepileptic and cardiac antiarrhythmic drugs and some other drugs have long been used empirically for the symptomatic treatment of myotonia.[3,6] Mexiletine, a class IB antiarrhythmic drug that acts by increasing the rapid inactivation of sodium channels, is currently known as the most effective drug in nondystrophic myotonias.[3,7] Other drugs that have demonstrated efficacy include carbamazepine, phenytoin,[2,5] lamotrigine,[3,8] and ranolazine.[3,9] In addition to sodium channel blockers, the carbonic anhydrase inhibitor acetazolamide has also been used for symptomatic treatment. Although its efficacy remains unclear, it is thought to reduce muscle fiber excitability through its effect on intracellular pH. However, its effectiveness has not been

conclusively demonstrated in randomized clinical trials.[6,10]

In conclusion, this case illustrated the clinical features of PC due to a presumed sporadic sodium channel mutation. We underscore the importance of recognizing PC, even in the absence of family history, and support early therapeutic intervention to improve patient outcomes. Genetic analysis remains a cornerstone for confirmation and classification of such channelopathies.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: M.Y.K, G.K.: Designed and directed the project; B.O.: Performed the genetic analyses; M.Y.K., Y.S., A.S.C.: Wrote the article.

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