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Case Report / Olgu Sunumu

Susceptibility to Juvenile Myoclonic Epilepsy Associated with the *EFHC1* Gene: First Case Report in Turkey

Jüvenil Miyoklonik Epilepside EFHC1 Geni ile İlişkili Yatkınlık: Türkiye'den İlk Olgu Sunumu

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Abstract

Juvenile myoclonic epilepsy (JME), characterized by predominating myoclonic seizures, is one of the most common forms of genetic generalized epilepsy. Genetic studies in JME reported susceptibility associated with *EFHC1* gene. A 26-year-old male patient was admitted to our epilepsy outpatient clinic unit with one generalized tonic-clonic seizure and with previous myoclonic seizures started at the age of 17 years described as jerky movements. His neurologic examination and neuroimaging studies were normal. The family history was unremarkable. His electroencephalography was recorded under treatment and showed short-lasting paroxysms consisting of 6-7 Hz generalized slow waves and superimposed sharp contoured waves, slightly prominent over the posterior halves of the hemispheres, interpreted as generalized paroxysmal abnormality. After performing whole exom sequencing and investigating epilepsy-related genes, a heterozygous missense variant was found in *EFHC1* gene causing amino acid change [rs137852776: NM_018100.4: c.685T>C;p 15 (Phe229Leu)]. His seizures are still under control with valproate 1000 mg/d. Variants in *EFHC1* gene are the most commonly observed genetic abnormalities in patients with familial JME in different countries. Our study reported a *EFHC1* gene variation in a patient typical JME for the first time in our country. Our finding is important for future clinical studies and genetic counseling in JME.

Keywords: Juvenile myoclonic epilepsy, *EFHC1* gene, exom sequencing, risk factor, genetic susceptibility

Öz

Jüvenil miyoklonik epilepsi (JME), miyoklonik nöbetlerin ön planda olduğu, genetik jeneralize epilepsilerin en sık görülen formlarından biridir. JME'de yapılan genetik çalışmalarda *EFHC1* geni ile ilişkili yatkınlık saptanmıştır. Yirmi altı yaşında erkek hasta, 17 yaşında başlamış olan sıçrayıcı karakterde atmalar şeklinde miyoklonik nöbetler ve bir kez tüm vücutta olan tonik-klonik nöbet nedeniyle epilepsi polikliniğimize başvurdu. Nörolojik muayenesi normaldi ve kraniyal görüntülemede bir özellik saptanmadı. Aile öyküsünde bir özellik belirtilmedi. Hastanın tedavi altındaki elektroensefalografisi; hemisferlerin arka yarılarında hafifçe belirgin, kısa süreli, jeneralize, 6-7 Hz frekansında, bazen keskin kontürlü olabilen yavaş dalgaların gözlendiği jeneralize tipte paroksismal bir anormallikle uyumlu olarak yorumlandı. Tüm ekzom dizilemesi yapılarak epilepsi ile ilişkisi bilinen genler incelendiğinde *EFHC1* geninde amino asit değişikliğine yol açan heterozigot formda missens bir varyant tespit edildi [rs137852776 NM_018100.4: c.685T>C;p. 15 (Phe229Leu)]. Olgumuzun halen nöbetleri 1000 mg/gün valproat ile kontrol altında seyretmektedir. Farklı ülkelerde yapılan çalışmalarda *EFHC1* gen varyasyonları ailesel geçişli JME'nin saptanabilen en yaygın genetik sebebidir. Biz de kendi çalışmamız kapsamında ilk defa Türkiye'den tipik bir JME olgusunda bir *EFHC1* gen varyasyonunu tespit ettik. Bulgularımız gelecekteki klinik çalışmalar ve JME'de genetik danışmanlık açısından önemlidir.

Anahtar Kelimeler: Jüvenil miyoklonik epilepsi, *EFHC1* geni, ekzom dizileme, risk faktörü, genetik yatkınlık

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Introduction

Juvenile myoclonic epilepsy (JME) is the most common form of genetically generalized epilepsy, accounting for about 5-10% of all epilepsies (1). Seizures typically start in adolescence in JME and JME-related seizures include myoclonic seizures triggered by sleep deprivation in mornings, generalized tonic-clonic seizures, which are the most common cause of admission to clinics, and absence seizures, which occur in one-third of cases (2). In electroencephalography (EEG), generalized epileptiform findings and typically multiple spikes, sharp and slow waves are observed, which may also be accompanied by focal paroxysmal findings. Patients with JME often respond well to appropriately chosen treatment. EEG may be normal or nonspecific in individuals receiving treatment.

Family and twin studies show that genetic factors play an important role in JME. In order to explain the genetic basis of JME, both the Mendelian-type inheritance model, in which a single or several major genes are effective, and complex genetic models, in which weak but a large number of genetic and environmental factors contribute to the pathology, have been proposed. In this context, the genetic basis of JME was studied on a broad scale of methods, including linkage analysis, sequencing of candidate genes, association analyses, and in recent years, with next-generation sequencing methods in which the entire exome and genome are sequenced (3). Genes that may be associated with JME were identified as a result of these studies including (calcium voltage-gated channel auxiliary subunit beta 4, MIM:601949), calcium-sensing receptor, (MIM:601199), (gamma-amino butyric acid type A receptor alpha1 subunit, MIM:137160), (gamma-amino butyric acid type A receptor delta subunit, MIM:137163) and [EF-hand domain containing 1 (*EFHC1*), MIM:608815].

The *EFHC1* gene was the first gene demonstrated using linkage analysis and is located on chromosome 6p12.2. The major transcript (ENST00000371068/NM_018100.4) of the *EFHC1* gene encodes a protein called myoclonin 1, which consists of 640 amino acids and binds to calcium (ENSEMBL database: https://www.ensembl.org/). Myoclonin 1 is synthesized in the cortex, hippocampus, and cerebellum of the adolescent and adult mouse brain (4). Myoclonin 1 was shown to be a protein associated with microtubule proteins, which have a structural role in cell division, and to cause microtubule-related anomalies in cell division in the presence of pathogenic variations (5). It is also known to play a role in cell division and neuronal migration during cortical development (6).

It is extremely important to study the genetic variants associated with different societies and to make phenotype correlations because JME syndrome is a common type of epilepsy and also an important component of genetic epilepsy studies. In this study, we would like to present our patient in whom we found a genetic risk factor in the *EFHC1* gene that might be associated with JME using whole-exome sequencing. This type of study is also important to revive the genetic counseling and protective approach in epilepsy.

Case Report

Our case was a male patient who was aged 26 years at the time of our last examination. Myoclonic seizures were present and relatively prominent in the right arm in the form of jerks. He was once previously admitted to our epilepsy outpatient clinic because of having a generalized tonic-clonic seizure.

The patient had a history of normal birth in the hospital in a timely, trouble-free manner. His motor and mental development steps were normal. He had no other history of illness and no drug use. He had no history of smoking and drank alcohol at the social-drinker level. There was no kinship between their parents and there was no history of epilepsy in his family. He was first admitted in 2010, aged 18 years, for further examinations and treatment. Starting at the age of 17 years, he had seizures every two to three months, relatively prominent in the right arm in the form of jerks, which were more frequent in the mornings after sleep deprivation. He had a bilateral tonic-clonic seizure, in which he developed a loss of consciousness, spreading throughout the body, which lasted for 1-3 minutes following myoclonic jerks in his right arm when he was hungry and sleepless in the morning. There was a feeling of fatigue after the seizure. Sodium valproate 1000 mg/day was started by a neurologist in a center to where he was taken as an emergency and there was no repeat of seizures. The neurologic examination performed when he was admitted was normal. No abnormalities were detected in cranial imaging. The patient's EEG under treatment revealed a generalized type of paroxysmal abnormality, prominent in the posterior halves of the hemispheres, which were consisted of short-term slow waves, sometimes with sharp contours, at a frequency of 6-7 Hz.

The patient is currently being followed up by us in the epilepsy outpatient clinic of İstanbul Medical Faculty Neurology Clinic and the seizures are currently under control.

Genetic Research and Findings

In line with the informed consent of our patient, peripheral blood samples were taken and DNA was isolated from this sample and banked in the Istanbul University, Aziz Sancar Institute of Experimental Medicine. Exome sequencing of this DNA sample was conducted by the Epi25 consortium under an international project approved by the Ethics Committee of the Istanbul University Faculty of Medicine. Analysis of exome sequencing raw data was conducted by the Epi25 team. The interpretation of variant invocation files sent to us for further genetic analysis under the protocol at gene, protein, frequency, and phenotype levels was made using the Ensembl-Variant Effect Provider (7). A missense variant was identified in heterozygous form leading to amino acid change in the *EFHC1* gene in this patient when examining genes known to have an association with epilepsy [rs137852776: NM_018100.4:c.685T>C; p.(Phe229Leu)]. Our patient was appropriately informed of this genetic trait.

Discussion

The variations the *EFHC1* gene are the most common detectable genetic causes of hereditary JME with myoclonic and tonic-clonic seizures. Many familial or sporadic *EFHC1* variations have been identified in different societies since this gene was first associated with JME in 2004. In a retrospective study performed in 2017, all known *EFHC1* variations and the community and family structures in which they were identified were summarized (8). That study showed that *EFHC1* variations associated with JME could be seen in a wide geography extending from America to Europe and Japan.

We also identified an *EFHC1* variation in a patient with JME from Turkey for the first time within the scope of our study, and wanted to present it together with clinical analysis. The variation detected in our study was found in the gnomAD database in controls from different populations with frequencies ranging from 0.1% to 0.8% (http://gnomad.broadinstitute.org; rs137852776). However, the phenotype penetration of this variation was not fully demonstrated in previous family segregation studies and it was determined that healthy family members could carry this variation, as well as their sick relatives (9). In the retrospective study mentioned above, all *EFHC1* variations were re-analyzed and classified in terms of clinical pathogenicity (8). For this classification, EEG findings of people who appeared to be clinically 'normal' were also taken into account during the evaluation of the penetrance factor. It was seen that the penetration value of NM_018100.4:c.685T>C;p.(Phe229Leu) variant rose markedly, and even became full penetrant in a family. A total of 54 *EFHC1* variations were evaluated within the scope of this study. Nine of these variations, including NM_018100.4:c.685T>C; p.(Phe229Leu) were classified as pathogenic. It was also suggested that variations in the *EFHC1* gene associated with JME might be tolerated in some societies (10). Therefore, this variation is defined as a risk factor for JME with the current data (ClinVar database: https://www.ncbi.nlm.nih.gov/clinvar/; rs137852776). It was observed in *in vitro* studies that the protein produced with this variation disrupted *EFHC1* function (9). In light of this information, it can be thought that the rs137852776 variant, which is present in heterozygous form in an individual, will disrupt one of the two *EFHC1* gene alleles of an individual. JME will manifest itself depending on whether the level of the normal protein synthesized from the other allele is sufficient for that individual. In addition, predicting how a structural protein involved in cell division will affect the brain tissue of individuals with different genetic infrastructures can be very difficult by studying the presence of mere variation. Therefore, investigation of patients with JME who are well characterized clinically with long-term follow-up and treatment programs is extremely important in different societies in terms of *EFHC1* gene variations.

The biologic roles of *EFHC1* vary. *EFHC1* is associated with apoptosis through interaction with voltage-dependent Cav2.3 channel activities, and with microtubules through interaction with the redox-sensitive TRPM2 channel to mediate neuronal migration and apoptosis during cortical development (6,9,11). Changes in cortical morphology and increased cerebral cortex thickness were reported in patients with JME (12,13). It was suggested that the structural change in thalamocortical networks was associated with increased risk of JME (14). Therefore, the etiopathogenesis of JME focuses on genes that regulate microtubular dynamics that confirm neuronal migration and neuronal binding (5). *EFHC1* is a new microtubule-associated protein that is very important in regulating neuronal migration during cell division and development. Accordingly, it is thought that microdysgenesis in individuals with JME may be caused by radial neuronal migration defects. During cortical maturation, these disturbances lead to abnormal epileptogenic circuitry that will be responsible for JME at the onset of puberty (15).

EFHC1 is associated with JME in different societies and does not encode an ion channel protein, unlike most genes associated with epilepsy. *EFHC1* has brought a new perspective to the physiopathology of JME and to genetic epilepsies in general with this aspect, noting that epilepsies are not limited to ion channelopathies. This discovery supports the idea that JME is a neuro-developmental disease besides the classic theory of channelopathy, which causes genetic generalized epilepsy (2,15). Multifactorial etiologies of epileptic disorders require that the roles of potentially causal genes be carefully studied in geographically diverse populations.

As a result, this important heterozygous risk factor detected in patients with JME in different geographic regions is worth investigating in genetic analyses. The determination of its existence in our country is important in terms of preventive medicine and counseling.

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Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.B.Ş., N.B., B.B., Concept: N.B., B.B., S.A.U.İ., Design: P.B.Ş., B.S., F.Y.K., S.A.U.İ., N.B., B.B., Data Collection or Processing: P.B.Ş., B.S., F.Y.K., S.A.U.İ., B.B., Analysis or Interpretation: P.B.Ş., B.S., S.A.U.İ., B.B., Literature Search: P.B.Ş., S.A.U.İ., B.B., Writing: P.B.Ş., B.S., S.A.U.İ., B.B.

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