A novel mutation in the sodium channel α1 subunit gene in a child with Dravet syndrome in Turkey

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Abstract

Dravet syndrome is a rare epileptic encephalopathy characterized by frequent seizures beginning in the first year of life and behavioral disorders. Mutations in the sodium channel α1 subunit gene are the main cause of this disease. We report two patients with refractory seizures and psychomotor retardation in whom the final diagnosis was Dravet syndrome with confirmed mutations in the sodium channel α1 subunit gene. The mutation identified in the second patient was a novel frame shift mutation, which resulted from the deletion of five nucleotides in exon 24.

Key Words

neural regeneration; clinical practice; Dravet syndrome; sodium channel α1 subunit gene; mutation; child; Turkish; epilepsy; refractory seizures; neuroregeneration

Research Highlights

(1) In this study, we report two patients with Dravet syndrome with confirmed mutations in the sodium channel α1 subunit gene.
(2) The mutation identified in the second patient was a novel frame shift mutation, which resulted from the deletion of five nucleotides in exon 24.
(3) We also review the identified mutations in the Turkish population.
(4) Defining the clinical and genetic features of more cases with Dravet syndrome will provide new insights for the disease.

INTRODUCTION

Dravet syndrome, or severe myoclonic epilepsy in infancy, is a rare form of epilepsy which is characterized by impaired psychomotor and neurologic development, occurring in the first year of life in an apparently normal infant[1]. The actual frequency is not known, but an incidence of < 1 per 40 000 live births and 1/20 000 or 30 000 was reported from the United States and France, respectively[2-3]. The disease starts with generalized, unilateral, or alternating unilateral febrile and afebrile clonic seizures in the first year of life. Later on, multiple seizure types, mainly myoclonic, atypical absences and focal seizures appear. As the disease progresses, developmental and cognitive skills slow and behavioral disorders occur. Electroencephalography is normal at onset, but generalized spikes, spike and waves, polyspikes and focal abnormalities appear on follow up. Photosensitivity is an important trigger of epileptic discharges on electroencephalography. A family history of febrile seizure and epilepsy is present in
20–54% of patients with Dravet syndrome\(^{[4]}\). Dravet syndrome has a genetic etiology and 70–80% of patients carry sodium channel α1 subunit gene abnormalities. Most of the mutations are de novo and they are randomly distributed across the sodium channel α1 subunit protein\(^{[5]}\). Truncating mutations account for about 40% and are associated with an earlier age of seizure onset. Missense mutations also account for about 40%, and the remaining are the splice-site mutations. The clinical and electroencephalography criteria for diagnosing Dravet syndrome include (1) high frequency of familial seizures; (2) normal developmental skills before onset; (3) generalized, unilateral, or alternating unilateral febrile and afebrile clonic seizures beginning in the first year of life, with subsequent myoclonic and partial seizures; (4) normal electroencephalography at onset, with later generalized spike-wave and polyspike wave discharges, focal abnormalities and photosensitivity; (5) delayed developmental skills from the second year of life onward; (6) refractoriness of seizures to antiepileptic drugs\(^{[4]}\).

Some patients do not have myoclonic and atypical absences and they are accepted as borderline Dravet patients\(^{[6]}\).

Here, we report two patients with Dravet syndrome in whom different mutations were identified in the sodium channel α1 subunit gene. We also review the mutations of the sodium channel α1 subunit gene that were identified in the Turkish population.

**CASE REPORT**

**Case 1**
The first patient was a 7-year-old boy whose parents were healthy and non-consanguineous. The prenatal and birth history were uneventful. The convulsions started at 6 months of age with prolonged unilateral febrile seizures. He was initially given phenobarbital at 6 months of age, but valproate was added at 12 months due to recurrent febrile seizures. After 2 years of age, generalized clonic, tonic and myoclonic seizures started. The seizures were refractory to anticonvulsive drugs at 7 years old. His psychomotor development was delayed and he sometimes had stereotypic movements. Brain MRI was normal, but electroencephalography revealed generalized spikes and polyspikes (Figure 1). The electroencephalographic and clinical findings suggested Dravet syndrome and mutation analyses of the sodium channel α1 subunit gene revealed a heterozygous nucleotid substitution in exon 4 (c.602+1G>A; n.19003).

**Case 2**
The second patient was a 6-year-old boy who was the first child of healthy and non-consanguineous parents. The prenatal and birth history were unremarkable. The convulsions started at 4 months of age after pertussis vaccine administration. Generalized and focal febrile convulsions that were refractory to phenobarbital and valproate treatments continued until 2 years of age. After this age, generalized tonic, clonic, myoclonic and atypical absence seizures started. The myoclonic seizures were photosensitive. His psychomotor development was delayed and he had hyperactive behaviors. Brain MRI was normal. Electroencephalography of the patient revealed generalized spikes and polyspikes and waves with photosensitivity. Despite appropriate combinations of antiepileptic drugs, atypical absences and myoclonic seizures continued with a frequency of 10–15 times per day.

![Figure 1](Interictal sleep electroencephalography of a 7-year-old boy with Dravet syndrome (case 1) showing frequent generalized spikes.)
Mutation analysis of the sodium channel α1 subunit gene revealed heterozygous deletion of five nucleotides in exon 24 (E24 n.77532-535, c.4486-4490delCAAGA, p.Gln1496ArgfsX14).

**DISCUSSION**

Dravet syndrome is a distinct epileptic syndrome characterized by frequent seizures and impaired neurologic and psychomotor development beginning in the first year of life. Our cases had all the diagnostic criteria of the disease except history of familial seizures. To the best of our knowledge, 14 cases with Dravet syndrome were reported from Turkey[7-8]. All of these patients had classical findings of the disease and none of them was reported as borderline Dravet syndrome.

Mutations of the sodium channel α1 subunit gene are responsible for 70–80% cases of Dravet syndrome[9]. In children with suspected Dravet syndrome, the three criteria that best predicted a mutation in sodium channel α1 subunit were reported as seizure exacerbation with hyperthermia, normal development before seizure onset, and the appearance of ataxia, pyramidal signs or interictal myoclonus[9].

Mutations in the sodium channel α1 subunit gene result in either the reduction or complete loss of sodium current or in noninactivating sodium channels with abnormal kinetics. Sodium channel α1 subunit mutations have also been found in generalized epilepsy with febrile seizures plus, infantile spasms and severe epilepsy of infancy[9]. More than 500 mutations have been reported in Dravet syndrome and most of them are de novo. 5–10% of cases have familial mutations most of which are missense in nature. Mutations are randomly distributed along the gene. Sequencing mutations are found in about 70% of cases and comprise truncating (40%) and missense mutations (40%) with the remaining being splice-site changes. Phenotype-genotype correlation studies have failed to show a clear relationship between the type of mutation and phenotypic expression[9]. In the study of Arlier et al[7], a total of 13 patients from Istanbul University Cerrahpaşa School of Medicine with the diagnosis of Dravet syndrome were studied and authors reported heterogeneous point mutations in six patients (46%). Two missense mutations (G2585A, G2860A); one frameshift mutation (T1033del); two nonsense mutations (C1738T, C3733T); and one splice site mutation (Int14 [+]) G1A) were identified. Of the six patients, four of the mutations were novel (66%), while the other two (C1738T, C3733T) had been previously reported. Five of the six identified mutations corresponded to coding segments of the sodium channel α1 subunit gene, while one was at a splice site. The two previously reported mutations resulted in theoretical premature stop codons. Two novel missense mutations resulted in theoretical intolerable amino acid changes. A novel deletion in exon 8, T1033, is also expected to cause a premature stop codon secondary to frameshift. A splice site mutation is thought to theoretically compromise the mRNA sequence and result in an aberrant protein product. In the case of Gökbcn et al[9], mutation analysis in the proband revealed a heterozygous silent nucleotide substitution in exon 9 (c.1245A > G; p.V415V; rs7580482) and a nonsense amino acid mutation in exon 26 (c.4933 C > T; p.R1645X). The R1645X mutation is located in the D4 / S4 domain that is implicated in voltage sensing of fast inactivation. The same nucleotide substitutions in exon 9 and exon 26 were also found in the father. The mother had silent nucleotide substitutions in exon 9 and exon 13. Inherited truncating mutations in sodium channel α1 subunit gene in Dravet syndrome are rare. Although the patient and father shared the same nonsense mutation, their clinical phenotypes were completely different. The father had only a few febrile seizures during childhood, but his daughter had Dravet syndrome. The mutation in our first patient was a splice donor mutation which impaired the splicing of mRNA. This mutation was previously reported in eleven patients with Dravet syndrome. The mutation identified in the second patient was a novel frame shift mutation that resulted from the deletion of five nucleotides in exon 24.

Taken together, the diagnosis of Dravet syndrome is easier in patients presenting with typical clinical findings, but the diagnosis is difficult in patients whose seizures are atypical and/or the psychomotor development is normal. Sodium channel α1 subunit gene mutations are not found in all patients and genotype-phenotype correlations are not elucidated. Defining the clinical and genetic features of more cases with Dravet syndrome should provide new insights for the disease.

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