**Original Article**

**De novo SCN2A mutation in a Chinese infant with severe early-onset epileptic encephalopathy, bronchopulmonary dysplasia, and adrenal hypofunction**

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Received July 11, 2017; Accepted August 27, 2017; Epub October 1, 2017; Published October 15, 2017

**Abstract:** Early-onset epileptic encephalopathies (EOEEs) are a group of phenotypically and genetically heterogeneous neurodevelopmental disorders. Mutations of SCN2A, the gene encoding the αII subunit of the voltage-gated sodium channel (Nav1.2), have been detected in some EOEE patients. This report describes a 4-month-old female who presented with severe EOEE as well as bronchopulmonary dysplasia and adrenal hypofunction. Whole-exome sequencing revealed a novel missense mutation in SCN2A (c.1261T > G; p.L421V) that was not detected in either her parents or her brother. The mutation was confirmed by Sanger sequencing and characterized as pathogenic by several prediction programs. This finding of a de novo SCN2A mutation in an ethnic Chinese infant with EOEE as well as multi-organ dysfunction expands the phenotypic spectrum of SCN2A mutations.

**Keywords:** SCN2A, epileptic encephalopathy, bronchopulmonary dysplasia, adrenal hypofunction

**Introduction**

Early-onset epileptic encephalopathy (EOEE) is a highly heterogeneous constellation of disorders characterized by infantile-onset intractable epilepsy, prominent interictal epileptiform discharges on the electroencephalogram (EEG), and unfavorable developmental outcomes in childhood [1, 2]. Gene mutations, metabolic disorders, neurostructural defects, and acquired damage (e.g., from hypoxia-ischemia) can lead to various forms of EOEE [3, 4]. In most cases, however, the precise etiology is not determined.

Over the last decade, next-generation sequencing modalities, especially whole-exome sequencing, have revealed a variety of novel genetic causes of EOEE. Recently, mutations in the voltage-gated sodium channel αII subunit gene (SCN2A, 2q24) were identified in several EOEE patients [5-7].

In this report, we describe an ethnic Chinese case of SCN2A-associated EOEE also presenting with bronchopulmonary dysplasia and adrenal hypofunction. Such de novo missense mutations in SCN2A may lead to more severe phenotypes, including EOEE with multiple congenital deficits.

**Case presentation**

A 4-month-old female infant was born at 37+5 weeks’ gestation after a normal pregnancy. She was delivered by cesarean section due to fetal distress as evidenced by deceleration on cardiotocography. Birth weight was 2240 g, head circumference at birth was normal, and Apgar score was 9 at 1 minute and 5 minutes. She was the second child of healthy non-consanguineous parents. Her brother and father’s brother had developed seizures during a febrile illness in childhood. The infant exhibited difficulty breathing 10 minutes after birth and received a few days of invasive synchronized intermittent-mandatory ventilation due to neonatal respiratory distress syndrome. Difficult weaning from mechanical ventilation required re-initiation of synchronized intermittent-man-
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She developed seizures on the tenth day of life, manifested as eye blinking, clonic jerking, eye deviation to the left, and bicycling of the legs, followed by increased heart rate and oxygen desaturation. The seizures lasted from a few seconds to 1-2 minutes and occurred more than 50-60 times per day. Seizure episodes occurred both while awake and asleep. At the neonatal care unit of a local hospital, initial electroencephalogram showed a suppression-burst pattern and numerous multifocal seizures, while brain MRI (Magnetic Resonance Imaging) was unremarkable. The patient was diagnosed with infantile epilepsy and initially treated with phenobarbital, levetiracetam, and valproate. The patient continued to have seizures, however, and was referred to our department at 48 days of age. On presentation, body weight was 2.24 kg, body height 53 cm, and head circumference 37 cm. Continuous positive airway pressure ventilation was administered at admission. The infant exhibited weak crying and contacting convulsions but there was no eye contact or interactions. Auscultation revealed dry rale, no moist rale, and three depressions sign (+). Neurological examination revealed a weak sucking reflex, weak corneal reflex, mild hypotonia, and ankle clonus (+). The rest of the examination was unremarkable.

Results of urine, blood, and cerebrospinal fluid analyses were all normal. A second brain MRI was also normal. An EEG at 3 months of age showed a suppression-burst pattern with alternating high-amplitude EEG activity and low-amplitude EEG activity (Figure 2). Whole-exome sequencing revealed a novel mutation, c.1261T > G (p.L421V), in the SCN2A gene. This mutation has not been reported previously, and was not found in controls. The leucine at position 421 is conserved among mammals and assigned to the intracellular linker between domains I and II (Figure 3). This mutation is characterized as pathogenic by several prediction programs (http://www.mutationtaster.org; http://genetics.bwh.harvard.edu/pph2/index.shtml). Sanger sequencing confirmed mutation in the patient but not in her parents or brother, characterizing it as de novo (Figure 4).

Figure 1. Chest CT showed inhomogeneous density and small cysts in the right lung field.

Figure 2. An EEG at 3 months of age showed a suppression-burst pattern with high amplitude EEG activity and low amplitude EEG activity.
During hospitalization in our department, she also suffered from adrenal hypofunction and received hydrocortisone. She continued to have frequent seizures despite trials of multiple antiepileptic drugs (midazolam, phenobarbitone, valproate, oxcarbazepine clonazepam, and levetiracetam, topiramate, alone or in combination).

Currently, the patient receives care in the home and relies on an extra oxygen supply of 0.5 L/min (FiO₂ 23%) day and night. Although symptoms were ameliorated with three-combined antiepileptic drugs (phenobarbital, topiramate, clonazepam), the infant is still having approximately 3-5 seizures per day. Visual contact is still only occasional, and spontaneous movements are rare and undirected. She has profound hypotonia with head lag and brisk reflexes with an exhausting ankle clonus. In spite of hydrocortisone treatment, the infant still suffers from recurrent hyponatremia and hyperkalemia.

Discussion

Mutations of the neuronal voltage-gated sodium channel alpha II subunit gene (SCN2A) are associated with mild cases of epilepsy such as febrile seizures and benign familial neonatal-infantile seizures [8, 9]. Mutations in the gene product (NaV1.2) have been reported in a broad spectrum of EOEEs, including Dravet syndrome, infantile spasm, Ohtahara syndrome, and West syndrome [10-13]. However, there are few reports of SCN2A mutations in ethnic Chinese patients with an early-onset seizure disorder. Wong [14] reported a SCN2A mutation in a 6-year-old male with infantile spasm in Hong Kong. Here we report the first case of SCN2A-related EOEE in an ethnic Chinese patient accompanied by multi-organ dysfunction.

In addition to EOEE, the infant presented with bronchopulmonary dysplasia and adrenal hypofunction. The patient’s phenotype partially resembled early myoclonic encephalopathy or Ohtahara syndrome, but did not fit well with any known epilepsy syndrome. We performed an extensive metabolic work-up consisting of urine, blood, and cerebrospinal fluid analyses. Metabolic profiles, MRI, and EEG did not reveal the cause of her condition. Rather, whole-exome sequencing was required to identify the cause, a de novo SCN2A mutation in the proband but not in her unaffected parents and brother. This mutation in SCN2A has never been reported, expanding the phenotypic spectrum of SCN2A mutations to EOEE plus bron-
chopulmonary dysplasia and adrenal hypofunction. The presence of an SCN2A mutation in our patient suggests that genetic testing of SCN2A should be routine for EOEE.

Both de novo and inherited SCN2A mutations show genetic pleiotropy and cause variable neurodevelopmental phenotypes such as autism, psychomotor delay, movement disorders, neurobehavioral abnormalities, and intellectual disability [15, 16]. In addition to nervous system involvement, congenital malformations were also reported in a 3-year-old male with SCN2A-related encephalopathy and microcephaly [17]. The clinical phenotype of our patient is more severe than described previously in patients with SCN2A point mutations as she demonstrated bronchopulmonary dysplasia and adrenal hypofunction in addition to a 3-4-month history of seizure episodes. These additional features have not been reported in EOEE cases with SCN2A mutations. Only one previously reported case is similar to ours. Vaher et al. [18] presented a case with a de novo heterozygous missense mutation (c.3979A > G; p.Ile1327Val) in the voltage-gated sodium-channel αVIII subunit gene SCN8A presenting with neonatal epileptic encephalopathy and movement disorders as well as multiple congenital anomalies (dysmorphic facial appearance, hip dysplasia, congenital multiple arthrogryposis, inguinal hernia, and hydrocele). Our patient also suffered from congenital anomalies (bronchopulmonary dysplasia and adrenal hypofunction). Neither multiple-organ involvement nor neonatal onset has been described previously in SCN2A-related EOEE.

The question remains whether these additional features are also related to the SCN2A mutation. We propose that the phenotype of SCN2A mutations may be quite broad and that the novel SCN2A mutation in our EOEE patient could be responsible for the more severe phenotype (i.e., congenital anomalies as well as epilepsy). Additional mechanistic and clinical studies are clearly required to validate this speculation.

In conclusion, we have identified a novel de novo SCN2A mutation in an ethnic Chinese infant. The patient presented with EOEE plus bronchopulmonary dysplasia and adrenal hypofunction, suggesting that certain SCN2A gene mutations may cause both neurodevelopmental and somatic disorders.

**Acknowledgements**

This research was supported by National Key Clinical Specialty Construction Project (2011-872) and the Project of Science and Technology Plan of Guang Dong Province in Social Development (No. 2013B021800276, 2015-10010148).

**Disclosure of conflict of interest**

None.

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