De Novo SCN8A Pathogenic Variant (c.5630A>G; p. Asn1877Ser) Presenting with a Relatively Mild Phenotype

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Voltage-gated sodium channels are composed of one pore-forming α subunit and one or two auxiliary β subunits. So far, nine voltage-gated sodium channel α -subunits ($\text{Na}_v1.1$ – $\text{Na}_v1.9$) have been identified [1]. Among them, $\text{Na}_v1.6$ is encoded by the *SCN8A* gene, and widely expressed in the projection neurons of the cerebral cortex, hippocampus, and cerebellum [2]. In general, pathogenic variants (PVs) in *SCN8A* associated with early onset epileptic encephalopathy are *de novo* missense variants, and electrophysiological studies of such PVs typically reveal ‘gain of function’ leading to enhanced sodium current [3]. Since the first report of *SCN8A*-related epilepsy in 2012, more than 100 cases have been reported. *SCN8A* PVs mostly causes early onset epileptic encephalopathy type 13, which presents with infantile onset epilepsy accompanied with developmental delay and cognitive impairment [1]. However, recent reports have demonstrated that missense PVs in *SCN8A* present with mild phenotypes [1,2,4].

A 6-month-old male infant was admitted to the emergency department at Ulsan University Hospital due to seizure. Until the day before admission, the infant was healthy with no history of medication, head trauma, or recent immunization. Upon arrival at the emergency department, the patient’s seizure had already ceased. His body

temperature was 37.1°C; heart rate was 158 beats/min; and respiratory rate was 26 breaths/min. His pupils were isocoric, and the light reflex of both eyes was prompt. One hour after arrival at the emergency department, another generalized tonic-clonic seizure developed, and it subsided soon after intramuscular administration of lorazepam. The patient was born at 40 weeks’ gestation via a cesarean section without complications. His growth and development was age appropriate. The patient’s parents had no history of neurological diseases, including epilepsy. He had no siblings. Laboratory results revealed that sodium was 136 mmol/L, total calcium 11.1 mg/dL, and glucose 99 mg/dL. Electroencephalography revealed normal finding. Magnetic resonance imaging of the brain showed no abnormalities except a small developmental venous anomaly in right frontal lobe. On day 1, the patient showed a third generalized tonic-clinic seizure in the pediatric ward, and it was managed with intravenous phenobarbital. He had no additional seizure afterward, and was discharged on day 4. After discharge, the patient maintained oral phenobarbital administration (5 mg/kg/day) without further seizure for 2 months. However, at the time of a phenobarbital taper, the patient developed two additional generalized seizures lasting about 1 minute within 3 hours, and

was readmitted to the emergency department. During the second hospitalization, he had 10 additional seizures, all of which were generalized tonic-clonic seizures lasting between 15 seconds and 15 minutes. Intravenous valproate and levetiracetam, and oral clobazam failed to control the seizures. The patient's seizures were eventually controlled with commencement of oxcarbazepine administration on day 15. He was discharged on day 21 with discharge medications of oxcarbazepine, valproate, and clobazam. For molecular diagnosis, we performed targeted gene sequencing of 118 epilepsy-related gene panel at GC genome (Yongin, Korea), which revealed two missense variants in *SCN8A* (NM_014191.3:c.5630A>G;p.Asn1877Ser) and *CHRNA2* (NM_000748.2:c.691C>T;p.Arg231Cys). The *SCN8A* variant has not been observed in the pop-

ulation databases, but has previously been reported in patients with epilepsy (PMID: 27210545, 27875746, 29100083, 27864847, 28923014, 31487502, 31164858, 30851583, 30776697). On the other hand, the population frequency of the *CHRNA2* variant was estimated to be 0.0028% in the population database (gnomAD; <https://gnomad.broadinstitute.org/>), but has not been reported in patients with epilepsy. By Sanger sequencing of the *SCN8A* and *CHRNA2* variants in the patient and his parents, the *SCN8A* variant was not observed in both parents while the *CHRNA2* variant was observed in his father confirming *de novo* occurrence of the *SCN8A* variant (Fig. 1). Although the *CHRNA2* gene is known to be associated with autosomal dominant nocturnal frontal lobe epilepsy, the patient's father never had a seizure in his life and had no neuro-

A Next-generation sequencing (NGS)

B Sanger sequencing

Fig. 1. Identification of *de novo* *SCN8A* variant. (A) Next-generation sequencing of the patient revealed a heterozygous variant in the *SCN8A* gene (NM_014191.3:c.5630A>G;p.Asn1877Ser). (B) Sanger sequencing of the patient and both parents confirmed the *de novo* occurrence of the *SCN8A* variant.

Table 1. Clinical features in four cases of the *SCN8A* c.5630A>G (p.Asn1877Ser) variant presenting with a mild phenotype

Study	Pt.	Age/sex	Seizure onset	Seizure type	Motor development	Cognitive outcome	EEG	MRI	Respond to AEDs (+) effective, (-) not effective
Anand et al. (2016, UK) [4]	1	16 mo/M	5 mo	Focal seizure followed by generalization	Normal (head control at 3 mo; sit independently at 6 mo; walk and climb stairs at 16 mo)	Normal (babble, say a few words at 16 mo)	Normal (5 mo); slow, disorganized background rhythm for age (8 mo)	Normal (5 mo)	(+) PHT, CBZ
	2 ^a	42 yr/M	4 mo	GTC	Normal	Normal	Unavailable	Normal	(+) PHT, VPA
Wang, et al. (2017, China) [1]	3	1 yr/F	5 mo	Focal seizure followed by generalization	Slightly delayed (head control at 2 mo; sit independently at 9 mo)	Normal	Spikes in right frontal; 3–4 Hz slow-waves in occipital region (8 mo)	Normal (7 mo)	(-) LEV, VPA
									(+) OXC
Present study	4	14 mo/M	6 mo	GTC	Normal (head control at 3 mo; sit independently at 8 mo; walk unaided at 14 mo)	Normal (say "Mama" and "Papa" at 13 mo)	Normal (6 mo, 8 mo)	Normal (6 mo)	(-) LEV, CLB
									(+) OXC, VPA, PB

Pt, patient; EEG, electroencephalography; MRI, magnetic resonance imaging; AED, anti-epileptic drug; PHT, phenytoin; CBZ, carbamazepine; GTC, generalized tonic-clonic seizure; VPA, valproate; LEV, levetiracetam; OXC, oxcarbazepine; CLB, clobazam; PB, phenobarbital.

^aPatient 2 is the father of Patient 1.

psychological problems. Hence the *CHRNA2* variant was regarded as likely benign. After the second discharge, clobazam was discontinued, and oxcarbazepine (25 mg/kg/day) and valproate (20 mg/kg/day) was maintained. So far, the patient has remained seizure free for more than 6 months. He has reached normal developmental milestones, with saying "Mama" and "Papa" at 13 months of age and walking unaided at 14 months of age.

In general, seizures caused by *SCN8A* PVs begin in infancy, particularly within 6 months of age. Although focal seizures are the most common, diverse seizure types, including epileptic spasms, atypical absence, myoclonic, and generalized tonic-clonic, can present. Seizures in patients with *SCN8A* PVs are often controlled effectively by sodium channel blockers, such as phenytoin, carbamazepine, and oxcarbazepine, although other anti-epileptic drugs fail to control seizures [3]. Although infants with *SCN8A* PVs show normal or mildly delayed development prior to seizure onset, the majority of patients have apparent developmental delay or regression after seizure onset. Motor manifestations, such as hypotonia, dystonia, hyperreflexia, and ataxia can also be presented [3]. Recently, however, Gardella et al. [2] reported that 16 individuals in 3 families with the same missense variant (c.4447G > A, p. Glu1483Lys) in *SCN8A* gene presented with benign infantile seizures and paroxysmal dyskinesia.

To the best of our knowledge, so far four cases with *SCN8A* c.5630A > G (p.Asn1877Ser) variant presenting with a mild phenotype, including the present case, were documented (Table 1) [1,4]. However, the same variant presenting with a more severe

phenotype of epilepsy and intellectual disability has been also reported [5]. The *SCN8A* c.5630A > G (p.Asn1877Ser) is located at the proximal 2/3 of the c-terminal domain of Nav1.6 [4]. This is a highly conserved part of the Nav1.6 protein which contains binding sites for interacting proteins. One report speculated that protective genetic variants, or modifier genes which diminish the severity of the *SCN8A*, could result in a milder phenotype [4].

This case demonstrated that *SCN8A* c.5630A > G (p.Asn1877Ser) variant can present with relatively mild neurological manifestations. Early genetic testing in patients with refractory seizures with unknown etiology is critical, since identification of epilepsy related to specific gene mutations may help determine the most effective medication, such as sodium channel blockers for *SCN8A*-related epilepsy, and predict the prognosis.

This study was approved by the Institutional Review Board of Ulsan University Hospital (IRB No. 2020-03-011). Informed consent was waived by the board.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization: KYL. Data curation: EK, CSK, SP, and KYL. Formal analysis: CSK and KYL. Methodology: CSK, SP, and KYL. Visualization: CSK. Writing-original draft: EK and KYL. Writing-review & editing: CSK and KYL.

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