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A case of Dravet syndrome with a novel SCN1A gross deletion involving the promoter region

Eri Nakahara Sakamoto¹, Shino Shimada^{1,2,3}✉, Tokito Yamaguchi², Tomoya Ishida^{2,4}, Katsumi Imai², Hidetaka Eguchi⁵, Yasushi Okazaki⁵ and Masami Arai³

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Here we present a case of Dravet syndrome in which a novel heterozygous deletion involving the promoter region of the *SCN1A* gene was identified using next-generation sequencing and multiple ligation-dependent probe amplification. This microdeletion is believed to reduce *SCN1A* transcription, leading to haploinsufficiency. This case highlights the importance of early genetic analysis, including that of promoter regions, before the diagnostic criteria are met for the induction of specific treatments.

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The *SCN1A* gene, located on 2q24.3, encodes the voltage-gated sodium channel α -subunit Nav1.1 (*SCN1A*) essential for generating and propagating action potential in nerve cells. This transmembrane protein forms functional channels through assembly with regulatory $\beta 1/\beta 2$ subunits, playing critical roles in channel function in inhibitory interneuron, particularly parvalbumin-positive (PV) GABAergic neuron. This cell-specific dysfunction disrupts the excitation–inhibition balance in neural circuits and induces network-level hyperexcitability. Approximately 70–80% of Dravet syndrome cases are associated with variants in the *SCN1A* gene, with more than 90% being de novo and not inherited from parents. These *SCN1A* mutations are considered loss-of-function variants associated with haploinsufficiency¹. Loss-of-function variants in *SCN1A* cause severe epilepsy, most notably Dravet syndrome, as well as milder phenotypes such as genetic epilepsy with febrile seizures plus². Recently, the gain of function of *SCN1A* has been linked to early infantile developmental and epileptic encephalopathy (for example, Epilepsy of infancy with migrating focal seizures (EIMFS)) with distinct features, including movement disorders. *SCN1A* variants are associated with Autism Spectrum Disorder (ASD), Sudden Unexpected Death in Epilepsy (SUDEP) and other neurological manifestations.

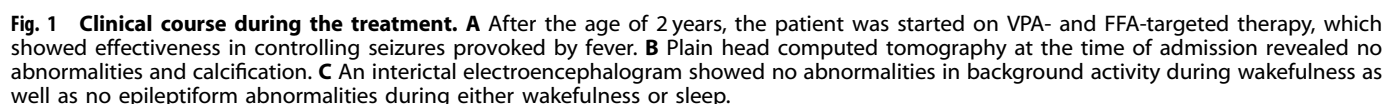
Dravet syndrome (OMIM: 607208) typically begins with a unilateral or generalized clonic or tonic–clonic seizure, either with or without fever, before the age of 1 year. Cognitive and behavioral impairments are often observed at the age of 2 years, and gait abnormalities such as crouch gait are usually present in the late toddler years³, with an overall prevalence of 6.5 per 100,000 live births⁴. Many *SCN1A* gene variants have been identified in Dravet syndrome, with over 2000 pathogenic variants of the *SCN1A* gene reported so far⁵, last evaluated on 26 May 2024⁶. The pathogenic variants primarily include single-nucleotide and multi-nucleotide variants, insertions and deletions, with a

small percentage involving microdeletions. More than 50% of these mutations result in truncations, and approximately 40% are missense mutations^{2,7–10}. The Human Gene Mutation Database (<http://www.hgmd.cf.ac.uk/ac/index.php>) includes 151 gross deletions in *SCN1A* that are relatively rare, although detailed clinical information is rarely reported. Here, we describe a novel intragenic large deletion, including the promoter region, in a patient diagnosed with Dravet syndrome at the age of 2 years and 3 months.

A 2-year-old boy was referred to the NHO Shizuoka Institute of Epilepsy and Neurological Disorders. He was the first child of a nonconsanguineous healthy Japanese parent, born at 40 weeks of gestation after a normal delivery, with a birth weight of 2740 g. The neonatal period was unremarkable. At the ages of 8 and 10 months, he experienced his first episodes of febrile focal clonic (hemiclonic) seizures, each lasting several minutes and with lateral asymmetry. First, self-limiting febrile seizures, which are common among Japanese children, were suspected, and prophylactic administration of diazepam suppositories was initiated at the age of 10 months. However, at 15 months, he experienced febrile seizures, generalized tonic–clonic seizures and prolonged seizures, which sometimes evolved into status epilepticus following fever due to infection or immunization (Fig. 1A). Mild developmental delays in language and motor skills were noted during the 18-month health checkup. He achieved independent walking ability at 18 months of age and began to speak meaningful single words at 24 months. At the age of 18 months, generalized seizures were triggered by strong light during play. After 23 months of age, he experienced recurrent afebrile focal seizures, including focal atonic and tonic seizures, with upward rolling of the eyeballs and cyanosis. Brain imaging revealed no abnormalities (Fig. 1B). An interictal electroencephalogram performed at 2 years and 2 months of age showed no abnormalities in background activity

¹Department of Pediatrics and Adolescent Medicine, Juntendo University Graduate School of Medicine, Bunkyo, Japan. ²Department of Pediatrics, NHO, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan. ³Department of Clinical Genetics, Juntendo University Graduate School of Medicine, Bunkyo, Japan. ⁴Department of Pediatrics, Sagamidai Hospital, Shizuoka, Japan. ⁵Diagnostics and Therapeutics of Intractable Diseases, Intractable Disease Research Center, Juntendo University Graduate School of Medicine, Bunkyo, Japan. ✉email: s-shimada@juntendo.ac.jp

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We provided genetic counseling to his parents and obtained written informed consent for genetic testing. Targeted panel sequencing of *SCN1A*, *SCN1B*, *SCN2A* and *GABRG2* genetic DNA extracted from the patient's peripheral blood lymphocytes using the hybrid capture method was performed at the Kazusa DNA Research Institute, Chiba, Japan. No pathogenic single-nucleotide variants or small indels were detected. Quantitative analysis of the captured sequence reads suggested a possible large deletion encompassing exons 4–19 of *SCN1A* (NM001165963.4, MANE-select), although further analysis is required to confirm this finding. This study was approved by the Institutional Ethical Review Board at Juntendo University School of Medicine (E21-0153). Upon obtaining informed consent from the patient's parent, a peripheral blood sample of the patient was provided. We then conducted multiplex ligation-dependent probe amplification (MLPA) analysis using SALSA MLPA Kit P137 Probes (version C1) (MRC-Holland). A large deletion was identified extending from the 5' untranslated region (2 probes, 15943–118069 and 15942–118068 on non-coding exon 1) to exon 19 (probe 04537L03926) in *SCN1A* (Fig. 2A, B). The *SCN1A* (NM001165963.4) consists of 28 exons, with a coding sequence initiated in exon 4. Heterozygous large deletions include the upstream enhancer/promoter regions that impact *SCN1A* protein expression and regulation, leading to reduced transcription and causing haploinsufficiency². This variant in *SCN1A* was absent from controls in public databases, such as dbSNP (<http://www.ncbi.nlm.nih.gov/snp/>) and gnomAD (<https://gnomad.broadinstitute.org/>), and is not listed in ClinVar (<https://www.ncbi.nlmf13.nih.gov/clinvar/>) or the Human Gene Mutation Database (<https://www.hgmd.cf.ac.uk/ac/index.php>). Following the guidelines of the American College of Medical Genetics and Genomics¹¹, the variants were classified as pathogenic (PVS1, PM2,

Importantly, Dravet syndrome has specific therapeutic approaches. SCN1A-related epilepsies, particularly Dravet syndrome, have well-established therapeutic guidelines. Evidence supports the use of combination therapy with FFA, stiripentol, clobazam and VPA. Conversely, sodium channel blockers such as carbamazepine, lamotrigine and phenytoin are known to exacerbate seizure activity in these patients and should therefore be avoided. In the case of Dravet syndrome we reported, the

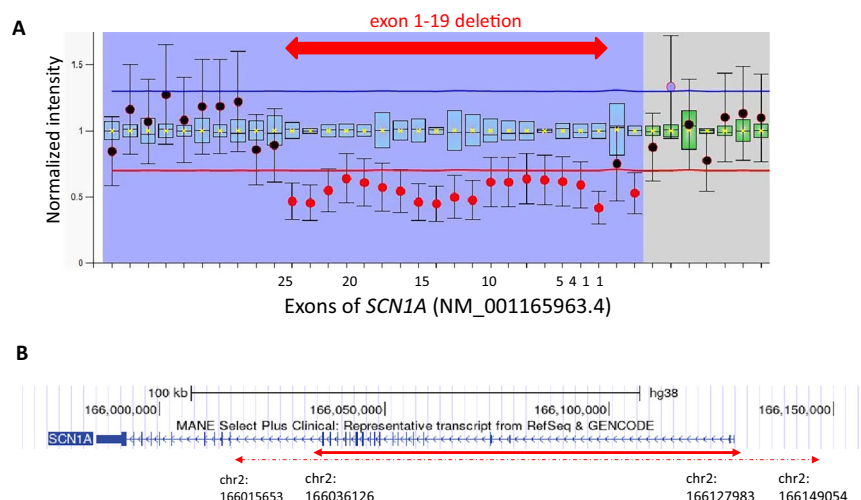


Fig. 2 Schematic Representation of the Deleted Region in SCN1A. **A** Deletion in SCN1A 5' untranslated region and exons 1–19 was detected by MLPA. **B** A schematic representation of the deleted region in SCN1A detected by MLPA. The maximum predicted deletion region is indicated by the dashed lines, and the minimum predicted deletion region is indicated by the solid bar. Coordinates are given according to the GRCh38 reference genome assembly.

condition was initially considered relatively mild during early childhood; however, febrile seizures recurred as the patient aged. Despite multiple adjustments in antiepileptic drug therapy, seizure control remained inadequate, highlighting the urgent need for the development of more fundamental therapeutic strategies, such as gene therapy. Early initiation of treatment, particularly aimed at preventing status epilepticus, may improve the neurological prognosis. In clinical practice, analysis methods that focus solely on exon regions may miss deletions involving promoter and intronic regions. Therefore, genetic analysis methods that include enhancer/promoter and intron regions should be generalized to clinical settings to enhance diagnostic accuracy.

HGV DATABASE

The relevant data from this Data Report are hosted at the Human Genome Variation Database at <https://doi.org/10.6084/m9.figshare.hgv.3527>.

REFERENCES

- Meng, H. et al. The SCN1A mutation database: updating information and analysis of the relationships among genotype, functional alteration, and phenotype. *Hum. Mutat.* **36**, 573–580 (2015).
- Depienne, C. et al. Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. *J. Med. Genet.* **46**, 183–191 (2009).
- Dravet, C. Severe myoclonic epilepsy in infants and its related syndromes. *Epilepsia* **41**, 7 (2000).
- Symonds, J. D. et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. *Brain* **142**, 2303–2318 (2019).
- Veltra, D. et al. SCN1A Channels a wide range of epileptic phenotypes: report of Novel and known variants with variable presentations. *Int. J. Mol. Sci.* **25**, 5644 (2024). <https://www.hgmd.cf.ac.uk/index.php> (2025).
- Ishii, A., Watkins, J. C., Chen, D., Hirose, S. & Hammer, M. F. Clinical implications of SCN1A missense and truncation variants in a large Japanese cohort with Dravet syndrome. *Epilepsia* **58**, 282–290 (2017).
- Lim, B. C. et al. Epilepsy phenotype associated with a chromosome 2q24.3 deletion involving SCN1A: migrating partial seizures of infancy or atypical Dravet syndrome? *Epilepsy Res.* **109**, 34–39 (2015).
- Zuberi, S. M. et al. Genotype–phenotype associations in SCN1A-related epilepsies. *Neurology* **76**, 594–600 (2011).
- Cetica, V. et al. Clinical and genetic factors predicting Dravet syndrome in infants with SCN1A mutations. *Neurology* **88**, 1037–1044 (2017).
- Richards, S. et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* **17**, 405–424 (2015).
- Hattori, J. et al. A screening test for the prediction of Dravet syndrome before one year of age. *Epilepsia* **49**, 626–633 (2008).
- Epilepsy Phenome/Genome Project Epi4K Consortium. Copy number variant analysis from exome data in 349 patients with epileptic encephalopathy. *Ann. Neurol.* **78**, 323–328 (2015a).
- Catarino, C. B. et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. *Brain* **134**, 2982–3010 (2011).
- de Lange, I. M. et al. Mosaicism of de novo pathogenic SCN1A variants in epilepsy is a frequent phenomenon that correlates with variable phenotypes. *Epilepsia* **59**, 690–703 (2018).
- Guerrini, R. et al. Variable epilepsy phenotypes associated with a familial intra-genic deletion of the SCN1A gene. *Epilepsia* **51**, 2474–2477 (2010).
- Hanafusa, H. et al. Dravet syndrome and hemorrhagic shock and encephalopathy syndrome associated with an intronic deletion of SCN1A. *Brain Dev.* **45**, 317–323 (2023).
- Lim, B. C. et al. SCN1A mutational analysis in Korean patients with Dravet syndrome. *Seizure* **20**, 789–794 (2011).
- Marini, C. et al. SCN1A duplications and deletions detected in Dravet syndrome: implications for molecular diagnosis. *Epilepsia* **50**, 1670–1678 (2009).
- Nakayama, T. et al. Deletions of SCN1A 5' genomic region with promoter activity in Dravet syndrome. *Hum. Mutat.* **31**, 820–829 (2010).

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Shino Shimada.

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