

# B-cell lymphoblastic leukemia in an adolescent with Dravet syndrome

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## Abstract

A 19 year-old adolescent girl with Dravet syndrome, characterized by complex seizure disorder and global developmental delay, presented with B-cell acute lymphoblastic leukemia. The genetic basis for her Dravet syndrome was a pathogenic variant in SCN1A, a sodium channel subunit. SCN1A is chiefly expressed in neuronal tissue, but bioinformatic analysis demonstrated its presence in B cell lineage. One estimate suggested that 10% of children with pediatric cancer have a germline predisposition involving proto-oncogenes or tumor suppressors. This number might be even higher should non-classical genetic variants, such as that encoding a sodium channel subunit, be considered.

## Introduction

Dravet syndrome, also called severe myoclonic epilepsy in infancy. This disorder usually manifests in the first year as febrile or afebrile clonic and tonic-clonic, generalized, and unilateral seizures, often prolonged, in an apparently normal infant. Later, multiple seizure types, mainly myoclonic, atypical absences, and focal seizures appear, as well as a slowing of developmental and cognitive skills, and the appearance of behavioral disorders. Up to 80% of patients are tested positive for *SCN1A* mutation.<sup>1</sup> Dravet syndrome is usually accompanied by many comorbidities including psychiatric issues, urinary tract and bowel issues, sleep disorders and others.<sup>2</sup> Here, we describe an adolescent with Dravet syndrome who was diagnosed with B-cell type acute lymphoblastic leukemia (ALL) and suggest a possible correlation between these two disorders.

## Case presentation

A 19 year-old adolescent woman with Dravet syndrome, characterized by epilepsy, global developmental delay, microcephaly, broad-based ataxic gait and hypothyroidism, presented with pallor and bruising. Her complete blood counts progressively decreased over a month (**Table 1**). Her hemoglobin was 5.9 g/dl, white blood cells 4,300/uL, and platelets 117,000/ul. Bone marrow biopsy showed 98% lymphoblasts. There was no central nervous system involvement. Immunophenotype analysis cytometry demonstrated B cell lineage with expression of CD10, CD19, CD22, CD34, CD38, CD45 (very dim) and HLA-DR. Cytogenetics revealed hyperdiploidy: 58, XX, +X, +4,+4, +5, I(7)(q10), +8, inv(9)(p12q13)c, +10,+13, +19, +20, +21, +21, +mar1[cp0]/59, idem, +mar2[2]/46, XX, inv(9)(p12q13)c[12]. *FLT3* mutation not detected. Following her diagnosis of B-cell ALL, she received anti-leukemic therapy per Children's Oncology Group AALL1732 and is currently in complete remission.

She had first demonstrated seizures at age of 4 months 2-3 days after her immunizations, which consisted of staring and lasted for as long as 1 minute. Phenobarbital was administered, but seizures continued. At

age of 6 months, she started having left arm and leg jerking which worsened during fever or infection, then at age of 11 months, she developed grand mal seizures. At that time, general physical examination and neurological examination were unremarkable. Several blood tests, urine tests, brain computerized tomography scan, spinal fluid examination, and electroencephalogram showed normal results. She showed mild motor developmental and global delay involving speech delay. Magnetic resonance imaging confirmed right fronto-parietal malformation of cortical development. She tested negative for DNA methylation for Angelman syndrome/Prader-Willi syndrome. Her seizures were not significantly controlled despite the use of multiple anti-epileptic medications including phenobarbital, valproate, and lamotrigine. At age of 11 years, a pathogenic variant was identified *SCN1A* p. Ile227Ser. After then her treatment regimens were modified, and locasme was replaced by clobazam which showed good response. During 2020, she was admitted because of decreased oral intake, emesis, and an inability to take medications for 4 weeks prior to admission accompanied by altered mental status and hallucinations a week prior to admission. She became dependent on G-tube feeding. After discharge, she was re-admitted shortly with weakness and instability. Since then, she has been receiving her anti-epilepsy drug cocktail. Her leukemia remains in continuous complete remission.

To determine the expression of *SCN1A* in human hematopoietic cell lines, we used Bloodspot to generate a hierarchical differentiation tree based on *SCN1A* expression. Bloodspot analyzed publicly available microarray data (GSE24759).<sup>3</sup> The analysis revealed that B-cells progenitors have maximum expression of *SCN1A* among different hematopoietic cells (**Figure 1A**). Expression of *SCN1A* in non-neural, lymphoid tissue was confirmed by analysis of datasets from Children's Oncology Group P9906 (**Figure 1B**), and normal and corresponding leukemia samples (**Figure 1C**).<sup>4,5</sup> *SCN1A* expression was markedly elevated in the REH cell line, which was derived from an adolescent girl with B cell ALL that harbors the *ETV6::RUNX1* oncogene. Our patient had complex cytogenetics without that t(12;21) translocation.

## Discussion

We identified an adolescent with Dravet syndrome who developed B-cell lineage ALL. In addition, there are at least two other cases of ALL in children with Dravet syndrome (personal communication, Veronica Hood, PhD). One with Dravet syndrome due to *SCN1A* variant was diagnosed with B cell ALL at age 7 years, having been on multiple anti-epileptics including valproate. The incidence of Dravet syndrome among live births is estimated at 1/15,000. According to the National Cancer institute, the incidence rate of ALL in those below the age 19 in US is 1 per 1,000.

Dravet syndrome commonly appears during the first year of life usually related to fever or vaccination. The first seizure typically is generalized clonic then the child develops multiple seizure types (convulsive seizures, myoclonic seizures, atypical absence seizures, focal seizures, or rarely, tonic seizures).<sup>1</sup> Patients often develop psychomotor delay, behavioral disturbances, and cognitive impairment. Autistic features usually persist into adulthood.<sup>6</sup>

Eighty percent of patients with Dravet syndrome harbor a heterozygous *SCN1A* gene mutation,<sup>1</sup> resulting in its loss-of-function. *SCN1A* encodes the alpha subunit of a sodium channel Nav1.1. In disease-associated *SCN1A* variants, interneurons can no longer inhibit the electrical activity.<sup>7</sup> Loss-of-function mutations of *SCN1A* cause functional impairments in the GABAergic neurons and lead to a loss of appropriate inhibition in neuronal networks and a predisposition to seizures. Over 650 missense and nonsense *SCN1A* mutations have been described in these patients; some are *de novo*.<sup>8</sup>

Although rarely reported, non-central nervous system cancers could present in the context of seizure and/or autism disorders (AD). One case reported ALL in a nine-year-old girl with isodicentric chromosome 15 syndrome, which is associated with early central hypotonia, developmental delay, cognitive dysfunction, autism spectrum disorders, and seizures.<sup>9</sup> A retrospective cohort study of 8000 Taiwanese children and adolescents showed that cancer occurred more frequently in pediatric patients with AD. The standardized incidence ratio's estimate is 1.94 (95% CI 1.18-2.99). During the observation period, 20 patients with AD developed cancers. Five patients had leukemia, two of them (one with intellectual disability, the second one

seizures) had ALL.<sup>10</sup> Multiple copy number variants identified in autism patients are found with individuals with cancer, suggesting a link with chromosomal abnormalities and carcinogenesis.<sup>11</sup> According to a cohort study done on patients with AD, there was an increased risk of developing cancer by midlife.<sup>12</sup> Other studies have not suggested an increased association.<sup>13,14</sup> The prevalence of autism in a North Carolina population found that out of 702 cancer patients, seven (1%, 95% CI of 0.4% - 2.04%) were labeled as AD in their medical records. The diagnosis of AD was made prior to cancer presentation in five of the seven of the patients; in the other two, obvious behavioral issues at cancer presentation led to an evaluation which suggested AD.<sup>13</sup>

While we cannot at this time conclude that patients with Dravet syndrome are at increased risk for developing acute leukemia, it is tempting to speculate that associated metabolic disturbances could produce intracellular stress.<sup>15</sup> Seizures can induce endoplasmic reticulum stress, and mouse models suggest that this results in the expression and distribution of Mdm2 and down-regulation of Tp53.<sup>16</sup> A complex host-environment interaction would include long-term use of anti-seizure drugs. For instance, hematologic side effects of valproate are well known<sup>17</sup> and can be associated with transient neoplasia.<sup>18</sup> Occurrence of cancer in children, a rare event, with non-hematologic monogenic disorders, a rare event, should be considered as a candidate predisposition syndrome. Hence, the number of pediatric and adult patients with cancer predisposition syndromes may be even greater by expanding the list of candidate genes not classically associated with hematologic malignancies.

**Conflict of Interests :** The authors declare no conflict of interests.

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**Table 1. Complete Blood Counts Preceding Diagnosis of ALL**

CBC/ date	4/30/2022 ALL diagnosis	3/16/2022	7/1/2021	5/28/2021	9/24/2019
WBC	4.21	4.3	6.7	9.6	7.9
RBC	2.09	2.71	4.13	4.36	4.00
Hb	7.1	9.1	13.9	14.6	13.6
MCV	106.2	99.6	97.6	97.5	103.0
Plt	94	124	298	289	246

## Figure Legend

**Figure 1 .** A) Bioinformatic analysis and confirmation of SCN1A expression in human B cell progenitors. B) Shown is the gene expression of SCN1A (two probe sets) among different ALL patient samples (pediatric ALL trial COG P9906). C) Normal and corresponding leukemia samples, which showed no difference in expression levels with the exception of REH cells. One-way ANOVA analysis was performed.

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## Figure 1

A.

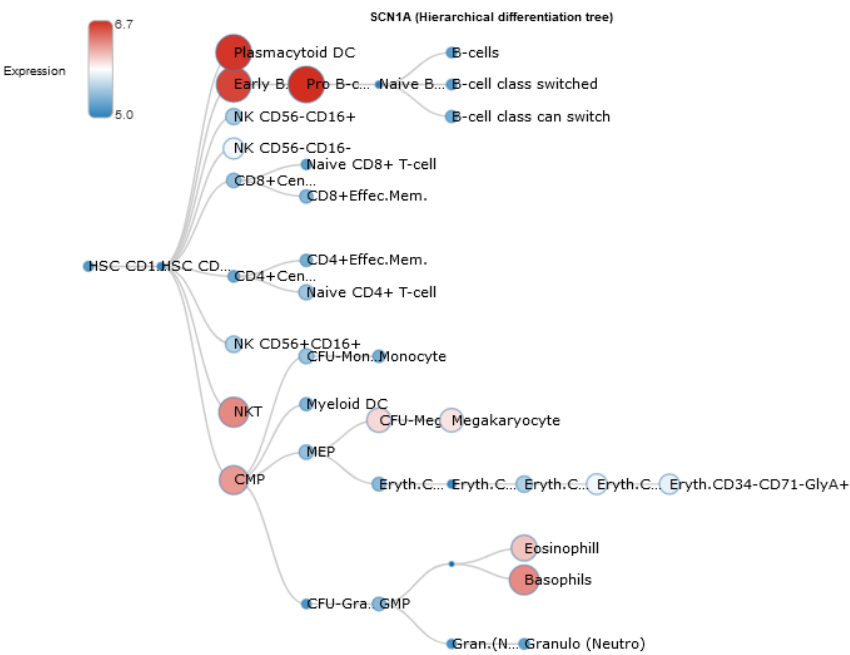


Figure 1B.

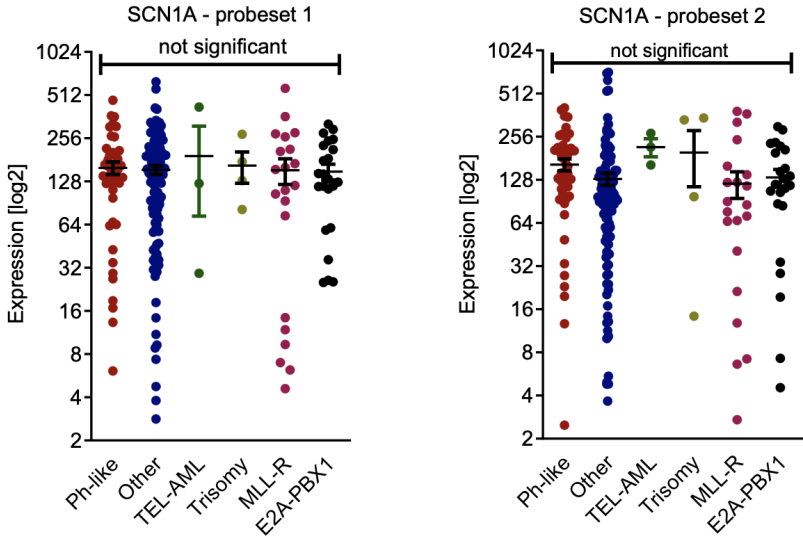
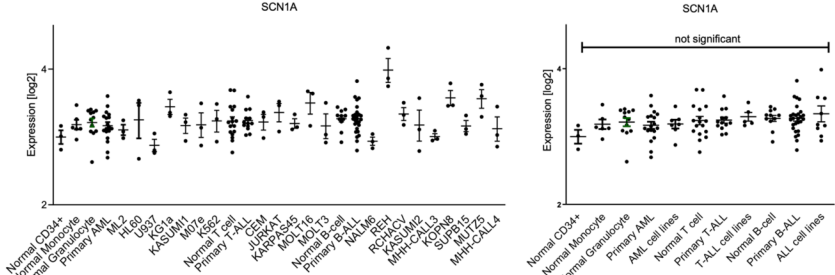


Figure 1C



## Hosted file

SCN1A analysis.pptx available at <https://authorea.com/users/592587/articles/628019-b-cell-lymphoblastic-leukemia-in-an-adolescent-with-dravet-syndrome>