

**In the United States Court of Federal Claims**  
**OFFICE OF SPECIAL MASTERS**

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ESFANDIAR SANTINI and LAURIE	*	
OMIDVAR, legal representatives of a	*	No. 06-725V
minor child, AYDIEN CLIFF OMIDVAR,	*	Special Master Christian J. Moran
	*	
Petitioners,	*	
	*	
v.	*	Filed: December 15, 2014
	*	
SECRETARY OF THE DEPARTMENT	*	Entitlement; significant
OF HEALTH AND HUMAN SERVICES,	*	aggravation; SCN1A mutation;
	*	severity (six-month) requirement;
Respondent.	*	DTaP vaccine.

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Curtis R. Webb, Twin Falls, ID, for petitioners;  
Voris E. Johnson, Jr., United States Dep't of Justice, Washington, DC, for  
respondent.

**PUBLISHED DECISION DENYING COMPENSATION<sup>1</sup>**

Esfandiar Santini and Laurie Omidvar are the parents of Aydien Omidvar, a developmentally delayed child, who is 11 years old. When he was born, Aydien had a mutation in a gene, known as the SCN1A gene, that creates a particular type of sodium channel. This sodium channel, which is known as Na<sub>v</sub>1.1, contributes to preventing seizures. When Aydien was approximately four months old, he received a set of vaccines, including a diphtheria-tetanus-acellular pertussis (“DTaP”) vaccine. Later that day, Aydien suffered his first seizure.

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<sup>1</sup> The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), requires that the Court post this decision on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

This first seizure is now recognized as the first manifestation of Dravet syndrome. People suffering from Dravet syndrome typically experience various types of seizures and developmental delay. The developmental delay can vary in severity from mild to severe.

Here, Mr. Santini and Ms. Omidvar allege that the DTaP vaccine significantly aggravated Aydien's Dravet syndrome. In other words, Mr. Santini and Ms. Omidvar maintain that "but for" the DTaP vaccine, Aydien would have been less delayed. They seek compensation through the National Childhood Vaccine Injury Compensation Program, 42 U.S.C. § 300aa—10 through 34 (2006). Their primary source of evidence is the opinion of Jean-Ronel Corbier, a pediatric neurologist.

The Secretary disagrees with Mr. Santini's and Ms. Omidvar's allegation. The Secretary has presented opinions from Max Wiznitzer, a pediatric neurologist, and Gerald Raymond, a neurologist and geneticist. Both Dr. Wiznitzer and Dr. Raymond maintain that the DTaP vaccination did not affect the degree to which Aydien is delayed. In their view, the SCN1A mutation was sufficient, by itself, to cause Aydien's outcome.

For the reasons discussed in more detail below in sections VI and VII, the Secretary's position is persuasive. Section VI discusses Mr. Santini's and Ms. Omidvar's claim that the DTaP vaccine significantly aggravated Aydien's Dravet syndrome. Mr. Santini's and Ms. Omidvar have failed to demonstrate that the DTaP vaccination affected Aydien in any meaningful way. Conversely, the Secretary has established that the SCN1A mutation most likely determined Aydien's outcome. Section VII reviews a separate deficit in Mr. Santini and Ms. Omidvar's case: they failed to present preponderant evidence that any harm caused by the DTaP vaccine lasted more than six months as the Vaccine Act requires.

The simplest reason for this case's outcome is that Dr. Wiznitzer's and Dr. Raymond's opinions were more persuasive than the opinion from Dr. Corbier. Dr. Wiznitzer and Dr. Raymond explained the relevant medical concepts and showed how those principles were the foundations for their opinions. Dr. Corbier did not. Dr. Wiznitzer and Dr. Raymond supported their opinions with articles from peer-reviewed medical journals. Dr. Corbier often misinterpreted or misconstrued the most important articles. Finally, the academic and professional backgrounds of the Secretary's experts made them better qualified than Dr. Corbier to discuss the issues in the case.

## **I. Biographies of Witnesses**

The parties rely upon the doctors whom they retained to explain the significance of events in Aydien's life. Thus, the following sections provide some context for the opinions discussed throughout this decision.

### **A. Dr. Corbier**

Dr. Corbier graduated from medical school at Michigan State University. Exhibit 51 at 1. He completed his residency training also through Michigan State University and then went to Cincinnati Children's Hospital, and the University of Cincinnati, to do his neurology fellowship training. Tr. 12. In 2002, Dr. Corbier became board-certified in neurology with a special qualification in child neurology. Exhibit 51 at 2.

Dr. Corbier has been in clinical practice, as a full-time general pediatric neurologist, since 2000. For six years, he practiced in Montgomery, Alabama, before moving to Concord, North Carolina, where he has practiced since 2007. Tr. 12; exhibit 51 at 2-3. Through his practice, Dr. Corbier has "been able to see a lot of kids with a variety of neurological problems including epilepsy, and in severe cases, like Dravet and other conditions." Tr. 13. Dr. Corbier has treated "a handful" of patients with Dravet syndrome, some of whom he diagnosed himself. Tr. 92.

Dr. Corbier has written two self-published books about autism, but has not written any articles published in peer-reviewed journals. Further, because Dr. Corbier's professional work occurs in a clinical practice, his teaching responsibilities are limited to a small number of residents that circulate through a clinic. Tr. 91-92.

### **B. Dr. Raymond**

Dr. Raymond graduated from medical school at the University of Connecticut. Tr. 221. Subsequently, he completed a residency in pediatrics at Johns Hopkins, and then went to Massachusetts General Hospital to study neurology with an emphasis on child neurology. Id. Dr. Raymond spent a year

abroad at the Université catholique de Louvain in Brussels, and then returned to Massachusetts General to complete a fellowship in genetics and teratology.<sup>2</sup> Id.

Dr. Raymond is board-certified in clinical genetics, as well as neurology with a special qualification in child neurology. Tr. 223. According to Dr. Raymond, fewer than ten other individuals hold dual certifications in these areas. Tr. 223. Dr. Raymond has been invited to give lectures in the field of neurogenetics, and has reviewed publications for several medical journals. Tr. 226. Further, Dr. Raymond has several of his own publications in the field of neurogenetics. Id.

Dr. Raymond is currently employed as a Professor of Neurology, and as Director of Pediatric Neurology, at the University of Minnesota. Tr. 220-21. In his position, Dr. Raymond conducts clinical research, focusing predominantly on the interaction between neurology and genetics. Tr. 222. In the clinical side of his practice, Dr. Raymond's patient population is drawn from individuals who have neurogenetic issues, including Dravet syndrome. Tr. 222-24.

### **C. Dr. Wiznitzer**

Dr. Wiznitzer graduated from medical school at Northwestern University. Tr. 335. He completed a pediatrics residency at Cincinnati Children's Hospital, a developmental pediatrics fellowship at the Cincinnati Center for Developmental Disorders, and a child neurology fellowship at the University of Pennsylvania Children's Hospital of Philadelphia. Tr. 336. He then finished his education with a National Institutes of Health-funded fellowship in higher cortical functions in children at the Albert Einstein College of Medicine in New York. Id.

Dr. Wiznitzer is board-certified in pediatrics and neurology with special qualification in child neurology and in neurodevelopmental disabilities. Tr. 339. He has written approximately 60 articles published in peer-reviewed journals, and serves on the editorial boards of the Journal of Child Neurology and Lancet Neurology.

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<sup>2</sup> Teratology is "the branch of embryology and pathology which deals with abnormal development and the production of congenital anomalies." Dorland's Illustrated Medical Dictionary 1883 (32d ed. 2012).

Since 1986, Dr. Wiznitzer has worked in Cleveland, Ohio, at Rainbow Babies & Children's Hospital as a child neurologist. Id. He currently is responsible for the outpatient practice, and also serves on the hospital's inpatient service. In his clinical practice, Dr. Wiznitzer commonly treats patients with epilepsy, and has treated 6-10 children with Dravet syndrome. Tr. 342-43. Dr. Wiznitzer is also an Associate Professor of Pediatric Neurology and International Health at Case Western Reserve University. Tr. 338.

Collectively, these doctors described the relevant concepts and principles underlying Dravet syndrome.

## **II. SCN1A Genes and Dravet Syndrome**

At conception, the embryo receives a set of genes from its mother and father. Tr. 229. The set of genes may contain spontaneous mutations, meaning that neither the mother nor father carried the particular gene. These spontaneous mutations are said to arise *de novo*. See Dorland's at 1214; Tr. 169, 240.

Genes contain DNA. DNA is composed of sequences of four nucleotides: adenine, thymine, guanine, and cytosine. Billups-Rothenberg, Inc. v. Assoc. Reg'l and Univ. Pathologists, Inc., 642 F.3d 1031, 1032 (Fed. Cir. 2011). A sequence of nucleotides in a gene is transcribed and translated by a cell to produce a chain of amino acids. Tr. 231-33. In translation, the mRNA translates the amino acid sequence into a protein. Tr. 234. A set of three amino acids determines the type of protein being created. Tr. 233; see also Billups-Rothenberg, at 1032 (discussing genes, amino acids, and proteins).

Genes affect traits of individuals. Tr. 295. For example, eye color is determined by genes. Tr. 154, 296. Genes are expressed at certain times in a person's development. The medical term for how genes are turned on/off is methylation. Tr. 160, 294. For example, Huntington's disease is a genetically caused disease that appears later in life, usually during the fourth decade. Tr. 155, 158-59, 419-20, Dorland's at 536.

Mutations in genes can produce a variety of outcomes. Some mutations are benign, such as when one amino acid is substituted for a similar amino acid. At the other extreme, some genetic combinations may not be consistent with life. Tr. 284. Factors contributing to the extent to which a genetic mutation affects a person's health, if at all, include the type of mutation, the location of the mutation,

whether the mutation arose in a conserved region,<sup>3</sup> and whether the mutation was inherited or arose de novo. Tr. 236-40 (Dr. Raymond); see also Tr. 166-69 (Dr. Corbier).

The brain's development is largely determined by genes. In a child's first six months, neurons are growing rapidly. Tr. 157-58. Within the infant's brain, sodium channels evolve in the first six months of life. Humans contain a variety of sodium channels, which are part of cells that are incorporated into different organs. Tr. 241; Escayg at 1650; Lossin at 114.<sup>4</sup> Sodium channels regulate electrical excitability. Escayg at 1650. The channel is activated by membrane depolarization resulting in increased permeability to sodium ions. Id. Later, the sodium channel closes, decreasing the permeability of sodium ions and the membrane returns to resting level. Id.

As a fetus and shortly after birth, humans and other mammals rely on a sodium channel known as Na<sub>v</sub>1.3. Tr. 362.<sup>5</sup> At around two-to-three months of age, a different sodium channel, Na<sub>v</sub>1.1, becomes predominant. Tr. 300; see also Tr. 247-48. The Na<sub>v</sub>1.1 form is primarily expressed in GABAergic interneurons. Tr. 242, 359. These neurons help maintain balance in the brain and an imbalance can lead to seizures. Tr. 243, 247.

A gene primarily responsible for the body's creation of the Na<sub>v</sub>1.1 sodium channel is known as the SCN1A gene. Tr. 51, 259. The ensuing protein has more than 2000 amino acids. Lossin at 115. A mutation in an SCN1A gene can have a deleterious effect on a person. Dr. Raymond and Dr. Wiznitzer, as discussed below, opined that the SCN1A mutation in Aydien was the sole cause of his developmental delay because the mutation prevented the creation of a properly functioning sodium channel. Without a properly functioning sodium channel, it was inevitable that Aydien would have seizures. While Dr. Corbier did not agree,

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<sup>3</sup> A conserved region is an aspect that is preserved through evolution in many species. The repetition of genes suggests that changes are not easily tolerated. Tr. 265, 269.

<sup>4</sup> This decision cites to medical articles by the last name of the first author. A full citation is provided at the end of the decision.

<sup>5</sup> The discussion about sodium channels largely relies upon Dr. Raymond because Dr. Corbier did not know much about sodium channels. Tr. 160.

he still acknowledged that “SCN1A mutation is not good.” Tr. 165. Some people with an SCN1A mutation develop Dravet syndrome.<sup>6</sup>

Dravet syndrome is a clinical diagnosis, meaning doctors identify the illness by how the child presents. Tr. 255, 355-57. Typical presentation includes an onset, between four and eight months, of clonic or hemi-clonic seizures. The initial seizure is sometimes an episode of status epilepticus. In the second or third year of life, the seizures evolve into different types of seizures including myoclonic seizures, absence seizures, and complex partial seizures. Although the initial development is normal, by the time the child becomes a toddler, his or her development stagnates. Tr. 350-51, 358. After a doctor suspects a child suffers from Dravet syndrome, the doctor will order genetic testing to confirm. Tr. 255-56 (Dr. Raymond), 357 (Dr. Wiznitzer).

Dravet syndrome encompasses a range of severity. Tr. 357. Particular subtypes have been known as generalized epilepsy with febrile seizures (GEFS), severe myoclonic epilepsy – borderline (SMEB), and severe myoclonic epilepsy in infancy (SMEI) and these have been considered to be conditions occurring on a spectrum. Tr. 278-79.

To understand more about the consequence of an SCN1A mutation, researchers have studied animals with mutations in their SCN1A gene. While animal studies do not always inform a situation involving people, Isaac v. Sec'y of Health & Human Servs., 108 Fed. Cl. 743, 752-53 (2013) (quoting 2011 report from the Institute of Medicine), aff'd, 540 Fed. Appx. 999 (Fed. Cir. 2013), the experts agreed that rodents can model the human condition with regard to an SCN1A mutation. Tr. 110-11 (Dr. Corbier), 184 (discussion of Dr. Corbier's report), 208-09 (Dr. Corbier), 281-87 (Dr. Raymond). One advantage of animal models is that they reduce the influence of any environmental factors. Tr. 318-19 (Dr. Raymond). A group of researchers led by Dr. William Catteral have used rodents with SCN1A mutations in a series of experiments.

The mice in these experiments are known as “knock out mice.” A portion of the mouse's SCN1A gene has been deleted (or knocked out). This produces a

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<sup>6</sup> Some SCN1A mutations are also associated with other conditions such as migraines. Tr. 191. The difference in outcome, as discussed in the text below, depends upon factors such as the location of the mutation and the nature of the mutation.

truncated mutation. Tr. 245-46, 282. The mice with this mutation display symptoms analogous to the symptoms of some humans with Dravet syndrome.

According to Dr. Raymond, the development of these mice is consistent with SMEI. In one study, researchers demonstrated that heating mice to replicate a fever provoked a seizure in genetically mutated mice only when the mice were a certain age. Tr. 245-46; Oakley at 4. Dr. Raymond explained that the delay in onset corresponds to the switch from  $\text{Na}_v1.3$  to  $\text{Na}_v1.1$ . Tr. 247-48. Dr. Corbier agreed. Tr. 182, 532-36.

Another experiment discovered a different consequence of an SCN1A mutation. Unlike the Oakley experiment in which the mice were heated to provoke a seizure, the mice in the second experiment were not heated. They were left alone. Without the introduction of any outside (environmental) factor, the mice with a defective SCN1A gene had seizures spontaneously.<sup>7</sup> Yu at 1144; Tr. 248; see also Tr. 284-88. For the proposition that these knock out mice suffer seizures spontaneously, other researchers have cited the Yu article. See Catarino; Escayg (also citing Oakley), and Martin.

Another group of researchers, who are from Japan, explored the long-term consequence of the genetic mutation in the knock out mice. The researchers found that the defect in the  $\text{Na}_v1.1$  “causes autistic behaviors and cognitive decline in addition to epileptic seizures” in the knock out mice “as well as in patients with Dravet syndrome.” Ito at 29. As discussed by Dr. Raymond, Tr. 318-19, the researchers’ conclusion was even stronger in dismissing environmental factors. They stated:

Although it has been proposed that polytherapy and long-term use of anticonvulsants have potentials to affect the cognitive function and behaviors of Dravet syndrome patients, . . . our present results on mouse models suggest that the  $\text{Na}_v1.1$  haploinsufficiency is fundamentally responsible for the behavioral and cognitive impairments in Dravet syndrome patients and those impairments should occur in patients even without medications.

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<sup>7</sup> Mice that had no SCN1A gene (“null mice”) died within 15 days of birth. Yu at 1143.



Ito at 39. Dr. Wiznitzer interpreted this article as well as an article by Ceulemans as showing the cause of the developmental problems is “not just the seizures themselves. The excitation / inhibition abnormality associated with the sodium channelopathy also impacts cognitive development in an independent manner from the epilepsy.” Tr. 411-12.

### **III. Facts<sup>8</sup>**

Aydien was born on July 6, 2003. Exhibit 1 at 1. When he was born, he already possessed the genetic mutation that is at the center of this case. Tr. 73, 95. Aydien’s SCN1A gene was not normal. Specifically, at codon 1756, there is supposed to be an amino acid known as cysteine. Instead, Aydien’s gene creates a different amino acid, known as tyrosine. Exhibit 29 at 1. At the hearing, Dr. Raymond presented a two-dimensional image of this change. The creation of cysteine at codon 1756 is a conserved feature. Tr. 267, 316, 391.

When he was born, no one suspected that anything was wrong with Aydien. His birth was not complicated. Exhibit 3. At his first visit with his pediatrician, the pediatrician did not note any concerns. Exhibit 4 at 4 (visit on July 10, 2003). When he was approximately seven weeks, he was described as developing well. Exhibit 4 at 2. At his well-baby visit for two months, Aydien received a set of vaccines without complications. Exhibit 6. During this period, Aydien’s brain was using a fetal sodium channel, Na<sub>v</sub>1.3. Tr. 509.

The appointment for Aydien’s four month well-baby checkup was on November 7, 2003. The pediatrician again did not note any concerns. Aydien received another set of vaccines, including a dose of the DTaP vaccine. Exhibit 6 at 1; see also Tr. 83 (Dr. Corbier’s description of Aydien before vaccination).

Approximately ten hours after vaccination, Aydien had two seizures, lasting about two minutes each. In these seizures, Aydien’s left arm jerked and then his entire body jerked. Exhibit 8 at 1; exhibit 80A at 1, 9; exhibit 84A at 4, 8.

A third seizure began and Aydien’s parents called 911 at 8:21 P.M. Exhibit 21 at 12. Emergency Medical Services (“EMS”) arrived, recorded that his

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<sup>8</sup> The parties generally accept the accuracy of medical records created close in time to the events being memorialized. Resp’t’s Postthr’g Br., filed Nov. 22, 2013, at 1.

temperature was 100.8 degrees, and transported Aydien to a local hospital. Exhibit 8 at 1. While going there, EMS personnel observed continuous seizure activity for 30 minutes. Id. at 2. Two doses of Valium were needed to stop the seizure. Exhibit 80A at 1, 9; exhibit 84A at 4, 8.

When Aydien was in the local hospital, his temperature was 100.8 degrees. Exhibit 80A at 9; see also Tr. 79 (Dr. Corbier's discussion of Aydien's temperature). He remained in the local hospital for only two hours. During this time, his rating on the Glasgow Coma Scale was 14-15 (maximum score is 15). Exhibit 8 at 7. He was taken, via air ambulance, to San Diego Children's Hospital. Exhibit 84A at 4-10.

On November 7, 2003, when he arrived at Children's Hospital, his temperature was 100.2 degrees. Exhibit 84A at 5; exhibit 9 at 2. The admitting doctor, Natasha Fein, stated that "[t]he etiology of seizures is suspicious for adverse side effect of immunization, despite receiving 2-month immunizations without complications. Other possibilities include infection." Exhibit 9 at 3.

Aydien remained in Children's Hospital for two days. Tests on his blood, urine and cultures were normal. Exhibit 9 at 5-9. Tr. 102. When he was discharged, his diagnosis was seizures due to DTaP immunization. Exhibit 10 at 1; see also Tr. 101-02 (Dr. Corbier stating Aydien returned to baseline before he was discharged).

Aydien's seizures continued. On December 3, 2003, he had a short seizure. Exhibit 79 at 11. On December 13, 2003, and December 19, 2003, Aydien had longer seizures lasting approximately 20 minutes and 30-60 minutes, respectively. For the latter two seizures, Aydien was treated at Children's Hospital. Exhibit 79 at 10-11; exhibit 48F at 150-53; exhibit 80B at 25-26; exhibit 84A at 90-96; see also Tr. 75. A doctor at Children's Hospital ordered an MRI. The results were essentially normal. Exhibit 84A at 20; CH&N at 224 (testing on December 15, 2003).<sup>9</sup>

On May 10, 2004, a neurologist saw Aydien. The doctor recorded that Aydien was laughing, playing, and eating appropriately, despite having seizures.

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<sup>9</sup> "CH&N" refers to an unnumbered exhibit that Mr. Santini and Ms. Omidvar filed, on a pro se basis, on October 20, 2006.

Aydien was diagnosed as having epilepsy but was otherwise “developmentally appropriate.” Exhibit 84B at 244; see also Tr. 432 (Dr. Wiznitzer’s discussion about Aydien’s history in the first year of life).

After another ten months of seizures during which Aydien continued to make developmental progress, see exhibit 23 at 33, on March 14, 2005, Aydien had an EEG. The EEG was abnormal, showing “abundant interictal epileptiform discharges.” Exhibit 81D at 233. He was diagnosed as suffering “gross developmental delay.” Exhibit 81A at 3; see also Tr. 76 (Dr. Corbier’s testimony that Aydien deteriorated at about one year).

As discussed in the procedural history, Mr. Santini and Ms. Omidvar filed this claim in 2006. This submission led to Dr. Wiznitzer’s review of Aydien’s medical record and his recommendation that Aydien be tested for an SCN1A mutation. Exhibit A at 2; see also Tr. 432-35 (Dr. Wiznitzer).

Athena Diagnostic’s testing of Aydien took place in October 2007. Exhibit D-E. Athena Diagnostic later tested Aydien’s parents to see whether the mutation that it had identified in Aydien was present in his parents. It was not. The final report from Athena Diagnostic explained the significance of this information: “[p]arental testing indicates that the amino acid variant identified in this individual arose de novo (was not inherited). This finding is most consistent with this DNA variant being associated with a severe phenotype (SMEI or SMEB) rather than a mild or normal phenotype.” Exhibit 29 at 1; accord Tr. 267.

Various pharmaceutical interventions and the placement of a vagus nerve stimulator have failed to control these seizures. The petitioners have reported that Aydien has approximately four seizures per week during which he loses consciousness. He walks unsteadily and can speak approximately 50 single words. Pet’rs’ Prehr’g Br. at 4; see also Tr. 77 (Dr. Corbier’s testimony about current condition).

#### **IV. Procedural History**

Mr. Santini and Ms. Omidvar began this action when they, appearing pro se, filed a petition on October 20, 2006. They submitted a set of medical records. Less than one month later, Andrew W. Dodd became counsel of record for the

petitioners and Mr. Dodd filed an amended petition on November 2, 2006.<sup>10</sup> The amended petition alleged that a diphtheria pertussis and tetanus vaccination, given to Aydien, caused him to suffer an encephalopathy as defined in the Vaccine Injury Table. Am. Pet. ¶¶ 2.h, 6.

The Secretary reviewed the medical records about Aydien in her report submitted pursuant to Vaccine Rule 4. The Secretary noted that the records show that Aydien received a dose of the acellular formulation of the pertussis vaccine, not the whole cell version. Resp't's Rep't at 1 n.1; see also exhibit 5. The Secretary argued that Aydien did not qualify as an on-Table encephalopathy because he did not suffer a decreased level of consciousness for 24 hours. Resp't's Rep't at 11, citing exhibit 8 at 7. Thus, the petitioners would be entitled to compensation only if they established that the DTaP vaccine was the cause in fact of Aydien's injury. On this point, the Secretary argued that Mr. Santini and Ms. Omidvar had not met their burden of proof. The Secretary also proposed that a forthcoming report would provide additional information. Id. at 15.

On February 26, 2007, the Secretary submitted an expert report and curriculum vitae for Max Wiznitzer, a pediatric neurologist. Dr. Wiznitzer stated "Aydien Omidvar's history is consistent with the diagnosis of severe myoclonic encephalopathy of infancy (SMEI or Dravet's syndrome)." Exhibit A at 2. He continued, "[t]his disorder is usually caused by a mutation of the SCN1A gene . . . and, therefore, is genetic in origin. There is no evidence that immunizations (such as DTaP) either cause or aggravate this order." Id. Dr. Wiznitzer recommended genetic testing.

After status conferences with the special master, the parties started pursuing genetic testing. The Secretary filed the results as exhibit D on February 6, 2008. At the ensuing status conference, the special master ordered that the Secretary file a letter from Dr. Wiznitzer explaining the significance of those results and to state whether she intended to obtain a report from a geneticist. Order, filed Feb. 15, 2008.

Dr. Wiznitzer's short letter stated that Aydien's mutation "is consistent with a symptomatic mutation causally related to his clinical diagnosis of [SMEI]." Dr.

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<sup>10</sup> Mr. Dodd represented the petitioners until he died. The petitioners' current counsel of record, Curtis R. Webb, became counsel of record on March 25, 2009.

Wiznitzer recommended testing Aydien's parents to determine whether the mutation rose de novo. Exhibit E at 2. In addition, the Secretary represented that she would file a report from Dr. Raymond, a geneticist in approximately two months.

Dr. Raymond's April 7, 2008 report began with a summary of Aydien's medical history, including the genetic mutation. Dr. Raymond provided a brief overview of Dravet syndrome. He explained how the SCN1A gene encodes a sodium channel. Exhibit I at 1-4.

Dr. Raymond also discussed Aydien's specific mutation. Dr. Raymond expected that his mutation would cause a disease because of details about the structure of the resulting sodium channel in Aydien. Dr. Raymond noted that although Aydien's parents had not been tested, he expected that Aydien's mutation "will be a spontaneous event without familial antecedent." Exhibit I at 5. Dr. Raymond concluded "Aydien Omidvar is a child who has Severe Myoclonic Epilepsy of Infancy or Dravet syndrome secondary to a mutation in his SCN1A gene. This is the sole cause of his epilepsy syndrome including his subsequent developmental delay. It was not caused [ ]or exacerbated by any of the immunizations that he received." Id. at 6.

The parties discussed Dr. Raymond's report, including his recommendation for parental testing at the next status conference. The special master requested more information from Dr. Raymond. In addition, the special master noted that the issue of the SCN1A mutation was involved in other cases and proposed that the petitioners' attorneys work together. The special master noted a concern about going to a hearing in which the Secretary offered the opinion of a neurogeneticist (Dr. Raymond) and the petitioners did not. See order, filed June 12, 2008.

Dr. Raymond's letter addressed the need for parental testing. In his view, even if one of Aydien's parents had a genetic mutation, his opinion would remain that "SMEI is a genetic disorder secondary to a defect in SCN1A and is not altered by immunizations." Exhibit K. Dr. Raymond also stated that "the finding of no alteration in either of the parents would reinforce the evidence that this gene alteration is the sole cause of SMEI." Id.

During a September 23, 2008 status conference, Mr. Santini and Ms. Omidvar reported that they planned to have genetic testing done on themselves. They filed these results on December 11, 2008. Exhibit 29.

As mentioned in footnote 10 above, Mr. Webb became counsel of record. During the first status conference in which he participated, the parties discussed whether this case should be stayed in light of the pending adjudications in Stone v. Sec’y of Health & Human Servs., No. 04-1041V, 2010 WL 1848220 (Fed Cl. Spec. Mstr. Apr. 15, 2010) and Hammitt v. Sec’y of Health & Human Servs., No. 07-170V, 2010 WL 3735705 (Fed. Cl. Spec. Mstr. Aug. 31, 2010).<sup>11</sup> On September 21, 2009, Mr. Santini and Ms. Omidvar requested a stay pending those cases.

The stay extended while Stone and Hammitt proceeded through appellate review. The ultimate result was the petitioners were not entitled to compensation. The identical outcomes are not surprising because the evidence about the effects of an SCN1A mutation largely overlapped.<sup>12</sup> The special master found that “respondent has demonstrated by a preponderance of the evidence that Amelia’s SCN1A gene mutation was more likely than not the ‘but for’ and ‘substantial factor’ that caused her Severe Myoclonic Epilepsy of Infancy or Dravet Syndrome.” Stone, 2010 WL 1848220, at \*42 (Fed. Cl. Spec. Mstr. Apr. 15, 2010). The same language concludes the special master’s decision in Hammitt, 2010 WL 3735705, at \*47 (Fed. Cl. Spec. Mstr. Aug. 31, 2010).

After an intervening remand in each case, which did not change the result, the cases were consolidated at the Federal Circuit. The Federal Circuit upheld the special master’s findings of fact. “In sum, because of Dr. Raymond's expert testimony and the considerable evidentiary support for his views in the record, we cannot conclude that the special master's conclusion that the SCN1A gene mutation was solely responsible for Amelia [Stone’s] SMEI was arbitrary or capricious.” Stone v. Sec’y of Health & Human Servs., 676 F.3d 1373, 1384 (Fed. Cir. 2012), cert. denied, 133 S. Ct. 2022 (2013).

On May 9, 2012, the case was reassigned to the undersigned special master and a status conference was held on May 31, 2012. The status of the case as of that date was that the most recent medical records about Aydien had been filed in

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<sup>11</sup> Mr. Webb represented the petitioner in Hammitt.

<sup>12</sup> In Stone, the petitioners relied upon Dr. Marcel Kinsbourne, a pediatric neurologist, and the Secretary relied upon Dr. Michael Kohrman, a pediatric neurologist, and Dr. Raymond. 2010 WL 1848220, at \*2. In Hammitt, the petitioner relied upon Dr. Kinsbourne and the Secretary relied upon Dr. Wiznitzer and Dr. Raymond. 2010 WL 3735705, at \*2.

2006, the Secretary had filed reports from Dr. Wiznitzer and Dr. Raymond, and the petitioners had not filed any expert reports. As an immediate step, Mr. Santini and Ms. Omidvar planned to obtain updated medical records. They also planned to seek a report from Jean-Ronel Corbier.

In this status conference, Mr. Webb also proposed consolidating this case with Barclay, No. 06-705V, another case involving a child (Matthews Ramirez) with an SCN1A mutation. The Secretary concurred that having one hearing would conserve resources. Following this discussion, the two cases moved in sequence together and portions of the expert's reports are the same in the two cases. The petitioners in Barclay filed a report from Dr. Corbier on May 16, 2012; a similar report from Dr. Corbier was filed in this case on January 4, 2013. Exhibit 50.

For Aydien Omidvar, Dr. Corbier stated that the "first question is whether that initial seizure [the seizure Aydien experienced ten hours after vaccination] had any bearing on the subsequent severe seizure disorder that developed?" Exhibit 50 at 5. Dr. Corbier answered his question by relying upon "epidemiological and prospective studies linking prolonged febrile seizures to subsequent temporal lobe epilepsy." Among the studies that Dr. Corbier cited were articles by McClelland, Dube, and Bender.

Dr. Corbier maintained that an SCN1A genetic mutation does not determine the outcome. He stated that some children with an SCN1A genetic mutation do not have Dravet syndrome. Other children with Dravet syndrome have genetic mutations that are not from the SCN1A gene. In Dr. Corbier's view, "the range of mutations throughout the entire gene is so broad that the phenotype so variable that other factors including additional genetic factors and non-genetic, environmental factors are likely very important." Exhibit 50 at 9, citing Gambardella.

Dr. Corbier implicitly treated the DTaP vaccine as one environmental factor that affected Aydien's outcome. He concluded that "DTaP was 'point A' in a complex cascade of events that led to Dravet syndrome. Due to the underlying SCN1A mutation, DTaP caused new onset of [ ]prolonged seizures that made a significant contribution and was a catalyst for the development of Aydien's epilepsy and Dravet syndrome." Exhibit 50 at 9.

In conjunction with petitioners' submission of Dr. Corbier's report, the case was set for a hearing in June 2013. To complete the record, the Secretary filed

reports from Dr. Raymond (exhibit S) and Dr. Wiznitzer (exhibit U), who responded to Dr. Corbier's December 28, 2012 report.

Dr. Raymond's February 11, 2013 report provided basic information about genetics and Dravet syndrome. Dr. Raymond identified characteristics about genetic mutations that are relevant to determining whether the mutation will cause a disease, including whether the mutation arose de novo, what part of the sodium channel is affected, and the type of amino acid change. Exhibit S at 7.

Dr. Raymond discussed Dr. Corbier's report and the articles on which Dr. Corbier relied. Dr. Raymond extensively reviewed the McIntosh article. In Dr. Raymond's opinion, McIntosh and colleagues believed that "vaccination was not playing a role in the etiology of Dravet syndrome." Exhibit S at 10.

Dr. Wiznitzer, too, relied upon the McIntosh article. Dr. Wiznitzer quoted the McIntosh article as stating "outcome was not influenced by vaccination." Exhibit U at 3, quoting McIntosh at 592-98. The finding in McIntosh was repeated in a study by Brunklaus. Thus, in Dr. Wiznitzer's opinion, "[t]here is no evidence that his immunizations caused or aggravated" Aydien's Dravet syndrome. Exhibit U at 4.

In the two months immediately preceding the hearing, the parties filed additional materials that were primarily useful for making the record in Aydien's case complete. For example, on April 17, 2013, Mr. Santini and Ms. Omidvar filed a copy of a report that Dr. Corbier had originally written for the Barclay case. Exhibit 85. In addition, they refiled certain medical records in electronic form, replacing records that were filed in paper form originally. The parties also filed briefs.

The parties' briefs accurately predicted the experts' testimony at the hearing, which was held on June 5-6, 2013, in Charlotte, North Carolina. Drs. Corbier, Wiznitzer, and Raymond testified in accord with their expert reports. In the course of the hearing, the parties stipulated that all materials should be considered part of the record regardless of whether the particular article or report was in only either Matthew Ramirez's case or Aydien Omidvar's case. Tr. 27.



At the end of the hearing, the parties requested an opportunity to submit briefs.<sup>13</sup> Mr. Santini and Ms. Omidvar filed an initial brief, the Secretary filed one brief, and then Mr. Santini and Ms. Omidvar filed a reply. With the submission of the reply brief, the matter is ready for adjudication.

## **V. Elements Required to Establish Entitlement to Compensation and Standards for Adjudication**

For petitioners to be awarded compensation, the special master must find that they established the “matters” listed in section 11(c)(1) and “there is not a preponderance of the evidence that the illness . . . is due to factors unrelated to the administration of the vaccine.” 42 U.S.C. § 300aa—13(a)(1). Section 11(c)(1), in turn, lists five items in paragraphs (A) through (E). Here, the elements in controversy correspond to paragraphs C (causation / significant aggravation) and D (severity).

Paragraph C requires some showing that the vaccine harmed the person. For certain vaccines and injuries, the Vaccine Act and its associated regulations establish a presumptive causal connection for injuries within a defined time. The injury may be either an initial injury or the significant aggravation of a preexisting injury. 42 U.S.C. § 300aa—11(c)(1)(C); 42 C.F.R. § 100.3. These claims are known as “Table claims.” For cases not based upon the Vaccine Injury Table, the petitioners are not entitled to a presumption that a vaccine caused an injury.

Here, Mr. Santini and Ms. Omidvar are pursuing an off-Table claim that the DTaP vaccine significantly aggravated their son’s Dravet syndrome. As confirmed in W.C. v. Sec’y of Health & Human Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013), the elements of an off-Table significant aggravation case were stated in Loving. There, the Court blended the test from Althen v. Sec’y of Health & Human Servs., 418 F.3d 1274, 1279 (Fed. Cir. 2005), which defines off-Table causation cases, with a test from Whitecotton v. Sec’y of Health & Human Servs., 81 F.3d 1099, 1107 (Fed. Cir. 1996), which concerns on-Table significant aggravation cases. The resultant test has six components. These are:

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<sup>13</sup> Mr. Santini and Ms. Omidvar also filed a motion requesting an interim award of attorneys’ fees and costs. They were awarded, on May 24, 2013, a total of \$75,097.32. 2013 WL 3117024.

(1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a “significant aggravation” of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144.

After Loving, the Federal Circuit has explained that possible alternative causes may be considered in determining whether petitioner has presented a persuasive claim. See Stone v. Secretary of Health & Human Servs., 676 F.3d 1373, 1380 (Fed. Cir. 2012). In context of an SCN1A case, the Federal Circuit held that the special master did not err in finding, after considering the entire record, that the “Secretary proved by preponderant evidence its ‘factors unrelated’ defense by showing that the gene mutations were the sole cause of the seizure disorders.” Snyder v. Sec’y of Health & Human Servs., 553 F. App’x 994, 999 (Fed. Cir. 2014).

If there is preponderant evidence that the vaccine caused some harm as set forth in paragraph C of section 11(c)(1), the petitioner must also establish that the harm was severe pursuant to paragraph D. The Vaccine Act lists three potential avenues, and the one requirement that Mr. Santini and Ms. Omidvar could arguably fulfill is the vaccinee “suffered the residual effects or complications of such illness, disability, injury or condition for more than 6 months after the administration of the vaccine.” 42 U.S.C. § 300aa—11(c)(1)(D)(i). Additional guidance about this element is set forth in section VII below.

The burden of proof is preponderance of the evidence. The party bearing the burden of proof need not establish a proposition to the level of scientific certainty. Althen, 418 F.3d at 1278; Knudsen v. Sec’y of Health & Human Servs., 35 F.3d 543, 549 (Fed. Cir. 1994).

## **VI. Significant Aggravation**

### **A. Parties' Positions**

To explain how a vaccine could change the effect of an SCN1A mutation, Dr. Corbier presented three overlapping theories in his testimony. A first idea is that people with an SCN1A mutation are vulnerable or susceptible to developing an adverse reaction to the DTaP vaccine. Tr. 20, 78, 103. A second theory is that vaccines cause Dravet syndrome to manifest earlier by bringing about seizures before they would have occurred otherwise. Tr. 30, 104, 140. For these two theories, Dr. Corbier relied primarily upon material relating to SCN1A mutations. A third concept from Dr. Corbier is that the vaccines cause a more prolonged seizure and the prolonged seizure inflicts additional damage. Tr. 32, 144. For this theory, Dr. Corbier based much of his opinion upon HCN channels.<sup>14</sup>

Dr. Raymond and Dr. Wiznitzer agreed only with the portion of Dr. Corbier's presentation concerning the onset of the first seizure. Dr. Raymond and Dr. Wiznitzer acknowledged that the vaccination preceded the first seizure and the vaccination, most likely, provoked a fever that triggered the first seizure. Tr. 256 (Dr. Raymond), 353 (Dr. Wiznitzer). Dr. Raymond and Dr. Wiznitzer disagreed with the remaining portions of Dr. Corbier's testimony. In their view, the SCN1A mutation is the sole cause of the developmental delay. Tr. 227, 254 (Dr. Raymond), 359, 416, 446 (Dr. Wiznitzer).

Dr. Raymond and Dr. Wiznitzer stated vaccines did not alter the ultimate outcome for Aydien. Tr. 254 (Dr. Raymond), 302 (Dr. Raymond discussing Aydien Omidvar), 359 (Dr. Wiznitzer), 454 (Dr. Wiznitzer discussing Aydien Omidvar). They provided several reasons for their opinions, including details about genetic mutation, rodent studies, and studies on people.

### **B. Evidence regarding SCN1A Mutations**

#### **1. Genetic Mutation**

Dr. Raymond, the board-certified geneticist, stated practitioners look for details about the mutation, including the nature of the mutation, whether the

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<sup>14</sup> In the context of evaluating Dr. Corbier's opinion, Section IV.C. provides more information about HCN channels.

mutation arose de novo, and whether the mutation is in a conserved region. Tr. 317.

Here, Dr. Raymond discussed the details of Aydien's mutation. Aydien has a base pair switch. Tr. 267. Additionally, it is a missense mutation where there is a change which alters the chemical properties. Id. Aydien's mutation is de novo since neither of his parents carries the gene. Id.

Dr. Raymond's opinion is supported by Athena. When Athena detected the genetic mutation, the laboratory correlated the mutation with a disease, not a normal development. Exhibit 49H. Aydien's gene was defective, creating incorrect wiring in his brain. Tr. 417 (Dr. Wiznitzer).

## **2. Rodent Studies**

As explained above, the rodent studies showed that mammals with a severe SCN1A mutation will have problems. Yu, in particular, showed that even without a fever, the mice will develop seizures. The seizures in the Yu experiment happened spontaneously and not in response to the introduction of an outside force. Yu at 1144.

When Dr. Corbier was asked questions about this study, his answers were vague and confusing. See Tr. 536-41. Dr. Corbier seemingly did not appreciate that the Yu study contradicted his theory that an environmental factor (like a vaccine) affects the consequence of an SCN1A mutation.

These two points provide a strong and reliable foundation for the opinions that genes are the sole cause of the Dravet syndrome and vaccinations do not contribute to developmental delay. But, more evidence buttresses these conclusions. Dr. Raymond and Dr. Wiznitzer also cited various studies on people.

## **3. People Studies**

As more has become known about SCN1A mutations and seizures in mammals, scientists have investigated the connection between the mutation and epilepsy. In that research, the scientists have re-opened the question of whether vaccinations are causing epilepsy. The four important articles are by Berkovic, McIntosh, Tro-Baumann, and Brunklaus.

**a) Berkovic**

In 2006, Berkovic and colleagues were interested in explaining why pertussis vaccination has been alleged to cause an encephalopathy that involves seizures and intellectual impairment. The researchers postulated that in the cases of so-called vaccine encephalopathy, the individuals could have mutations in the SCN1A gene because of a clinical resemblance to SMEI for which such mutations have been identified. Berkovic et al. retrospectively studied 14 patients with an alleged encephalopathy in whom the first seizure occurred within 72 hours of vaccination. SCN1A mutations were identified in 11 of the 14 patients. Clinical-molecular correlation showed mutations in eight of eight cases with phenotypes of SMEI, in three of four cases with borderline SMEI, but not in two cases with Lennox-Gastaut syndrome.

The researchers concluded that cases of alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose de novo. Specifically, the researchers found,

In the presence of *SCN1A* mutations, vaccination can still be argued to be a trigger for the encephalopathy, perhaps via fever or an immune mechanism. [B]ut the role of vaccination as a significant trigger for encephalopathy is unlikely for several reasons. First, although vaccination might trigger seizures as shown by the increased risk of febrile seizures on the day of triple antigen or MMR vaccination, there is no evidence of long-term adverse outcomes. Second, less than half of our patients had documented fever with their first seizure, which indicates that fever is not essential. Third, our neuroimaging data showed no evidence of an inflammatory or destructive process. Finally, truncation and missense mutations reported in conserved parts of *SCN1A* have not been found in many hundreds of healthy patients. Thus, individuals with such mutations seem to develop SMEI or SMEB whether or not they are immunized in the first year of life. We do not think that avoiding vaccination, as a potential trigger, would prevent onset of this devastating disorder in patients who already harbour the *SCN1A* mutation.

Berkovic at 491.

The Berkovic article has been influential. For example, the undersigned special master has previously found Dr. Raymond's opinion that vaccinations do not cause Dravet syndrome persuasive because, in part, it was consistent with the scientific literature, specifically the Berkovic article. Snyder, 2011 WL 3022544, at \*5. When the case reached the Federal Circuit, the Federal Circuit ruled that accepting Dr. Raymond's opinion was not arbitrary because "the researchers of the Berkovic article did not believe that 'avoiding vaccination, as a potential trigger, would prevent onset of this devastating disorder in patients who already harbor the SCN1A mutation.'" Snyder, 553 Fed. Appx. at 1002. Other special masters have also found Berkovic to be a persuasive basis for finding that the child's SCN1A gene mutation was the sole cause of the Dravet Syndrome. Barnette v. Sec'y of Health & Human Servs., No. 06-868V, 2012 WL 5285414, at \*11 (Fed. Cl. Spec. Mstr. Sept. 26, 2012), mot. for rev. denied, 110 Fed. Cl. 34 (Fed. Cl. 2013); Deribeaux v. Sec'y of Health & Human Servs., No. 05-306V, 2011 WL 6935504, at \*34 (Fed. Cl. Spec. Mstr. Dec. 9, 2011), mot. for rev. denied, 105 Fed. Cl. 583 (2012), aff'd, 717 F.3d 1363 (Fed. Cir. 2013); Stone v. Sec'y of Health & Human Servs., No. 04-1041V, 2010 WL 1848220, at \*34 (Fed. Cl. Spec. Mstr. Apr. 15, 2010), mot. for rev. denied, 99 Fed. Cl. 187, 191 (Fed. Cl. 2011), aff'd, 676 F.3d 1373 (Fed. Cir. 2012). In addition to these legal determinations, the Berkovic article has inspired at least three other investigations about the potential link between vaccination and Dravet syndrome.

#### **b) McIntosh**

McIntosh and colleagues were interested in explaining why pertussis vaccination has been alleged to cause an encephalopathy that involves seizures and intellectual disability. In 2010, McIntosh and colleagues conducted a study in which they aimed to establish whether the apparent association of Dravet syndrome with vaccination was a result of recall bias and, if not, whether vaccination affected the onset or outcome of the disorder.<sup>15</sup>

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<sup>15</sup> Recall bias is a phenomenon in which people remember events incorrectly. The McIntosh researchers minimized recall bias by relying upon documents. McIntosh at 593. Dorland's at 212.

The authors retrospectively studied 40 patients with Dravet syndrome, who had mutations in the SCN1A gene, and whose first seizure was a convulsion. McIntosh at 593-94. The authors examined medical and vaccination records to determine whether there was an association between vaccination and onset of seizures in these patients. Patients were separated into a vaccination-proximate group (seizure 0-1 day from vaccination) and vaccination-distant group (seizure 2+ days after vaccination), and the authors compared clinical features, intellectual outcome, and type of SCNIA mutation between the groups. Id. at 594. Twelve patients were in the vaccination-proximate group and 28 patients were in the vaccination-distant group. Id.

The authors found “no differences in intellectual outcome, subsequent seizure type, or mutation type between the two groups.” Id. at 592. The authors concluded that vaccination might trigger earlier onset of Dravet syndrome in children who, because of an SCN1A mutation, are destined to develop the disease. Id. However, the authors found “no evidence that vaccinations before or after disease onset affect[ed] outcome.” Id.

Dr. Corbier interpreted McIntosh as establishing a definitive association between Dravet syndrome and vaccination. He also emphasized that seizures immediately after a vaccine were likely to occur at a younger age than seizures occurring more than two days after the vaccination. Tr. 23. Dr. Corbier explained that McIntosh did not find a recall bias. Further, Dr. Corbier disagreed with the McIntosh conclusion that the vaccinations did not affect outcome. Dr. Corbier contended that because the study was not designed to address outcomes, but rather to determine if there is a relationship at all, several variables were not included, and a proper conclusion cannot be drawn. Tr. 114.

Dr. Raymond maintained that there was no statistically significant effect on outcome between the vaccination-proximate and vaccination-distant groups. Tr. 322.

Dr. Wiznitzer opined that McIntosh suggests that children with Dravet syndrome who have an initial seizure in temporal proximity to a vaccination still have similar clinical outcomes to children whose initial seizures are not temporally related to vaccination. Tr. 404. Further, Dr. Wiznitzer explained that the only significant factor was that the age of onset was earlier for individuals who received vaccinations — but age of onset did not change the outcome. Tr. 407.

**c) Tro-Baumann**

In 2011, to gain a further understanding of the relationship between Dravet syndrome and vaccination, Blanca Tro-Baumann and colleagues conducted another retrospective analysis of 70 patients with Dravet syndrome and SCN1A mutations. Through examining medical records and conducting parental interviews, Tro-Baumann et al. found that seizures following vaccinations were reported in 27 percent of these patients. Tro-Baumann at 176. In 16 percent of the 70 patients (that is, 58 percent of all patients with seizures following vaccination) the vaccination-related seizures represented the first clinical manifestation of the Dravet syndrome. Id. Two-thirds of the seizures following vaccination occurred in the context of fever. Id.

The authors suggested that vaccination-related seizures represent a possible presenting feature of Dravet syndrome. Tro-Baumann at 177. Furthermore, the authors characterized an assumed causal connection between vaccine-related seizures and Dravet syndrome as a “misinterpretation.” Id.

Dr. Corbier interpreted Tro-Baumann as establishing a “clear connection between Dravet and vaccination with DTP.” Tr. 22. When Dr. Corbier was questioned about what whether “connection” meant “causation,” his answer revealed the challenges in trying to say whether the vaccine affected the outcome. He stated:

Well, it depends what we mean by causation. If causation means an inciting factor that in the right condition with the right associated factors can then lead to a disease, then causation fits. If we mean causation whereby the vaccine by itself would have caused the Dravet, then no. So when I use the term causation, what I mean is that the vaccine in a patient who's very vulnerable because of an underlying genetic mutation, there's a whole series of reactions that occur due to that initial vaccine, or it can be a fever or a virus that then changes brain function and circuitry that will result in long-term epilepsy.

Tr. 196.



Moreover, Dr. Corbier contended that the article suggests that vaccines can cause Dravet Syndrome to “occur earlier.” Tr. 30. On cross-examination, Dr. Corbier repeated that “vaccine-related seizures . . . represent a possible presenting feature” of Dravet syndrome. Tr. 121. When pressed to explain whether the vaccine-related seizures were the cause of the Dravet syndrome, Dr. Corbier stated the Tro-Baumann article showed “that we cannot ignore the role of vaccine in being a presenting feature in many patients with Dravet syndrome, so vaccination, with or without fever, plays an important role as a presenting feature in many patients with Dravet.” Tr. 122.

When Dr. Wiznitzer was questioned about Tro-Baumann, he opined that vaccination is associated with the onset of Dravet syndrome only so far as the vaccination causes temperature elevation, and temperature elevation, regardless of source, can cause seizures. Tr. 398. Dr. Wiznitzer maintained that the relationship is not a significant aggravation or a causal connection. Tr. 401.

Dr. Raymond did not comment on Tro-Baumann beyond noting that it did not study differences in outcomes. Tr. 333.

#### **d) Brunklaus**

In 2012, Brunklaus and colleagues examined a large cohort of patients with SCN1A mutation-positive Dravet syndrome. They intended to identify predictors of developmental outcome and to determine specific clinical and demographic features. During a 5-year study of 355 patients, Brunklaus et al. collected information about several aspects of Dravet syndrome, including epilepsy phenotype, electroencephalography data, imaging studies, and mutation class. Id. at 2329. They also rated each child’s developmental status. The developmental status was classified by the referring clinician using a five-point scale. The raters had expertise in the assessment of developmental status including rating of gross and fine motor skills, communication and cognitive abilities, and age appropriate adaptive behavior. Id. at 2330.

The authors found that clinical features predicting a worse developmental outcome included status epilepticus, interictal electroencephalography abnormalities in the first year of life, and motor disorder. Id. at 2329. No significant effect was seen for seizure precipitants, magnetic resonance imaging abnormalities, or mutation class. Id.

Brunklaus also investigated the precipitants of seizures. The authors found that fever or illness had precipitated the majority of seizures, one-third had no precipitant, and vaccination triggered 7 percent of the seizures. Brunklaus at 2333. Moreover, the authors found that vaccination-triggered seizures presented significantly earlier than those without precipitant or with fever/illness. Id. at 2333-34. However, citing McIntosh, the authors concluded that the vaccination itself had no effect on the developmental outcome. Id. at 2334.

Further, the authors contend that “children carrying a SCN1A mutation are destined to develop the disease, which in turn can be precipitated by a series of factors such as fever/illness, vaccination or a bath.” Id. However, the nature of the trigger has no effect on overall developmental outcome. Id. The authors acknowledged that their understanding of the functional effect of mutations is still unrefined, and classification models lack accuracy to reflect the true mutation impact. Id. at 2335.

Dr. Corbier interpreted the study as establishing a definitive link between vaccination and the onset of Dravet syndrome and seizures. Tr. 25. Specifically, Dr. Corbier emphasized that the study indicated that children who suffered the onset of seizures associated with a vaccination suffered the onset of seizures at a significantly earlier time. Tr. 26. Moreover, Dr. Corbier explained that the Brunklaus article found that children who had status epilepticus have a worse developmental outcome. Tr. 54.

Dr. Raymond interpreted the Brunklaus study as finding that vaccination itself does not affect developmental outcome. Tr. 331. However, Dr. Raymond acknowledges that the Brunklaus study did not present their data in the published article. Tr. 332.

Dr. Wiznitzer explained that the Brunklaus study clearly states that the authors looked at their data and found that vaccination does not alter developmental outcome, a finding that confirmed the conclusion reached in McIntosh. Tr. 406. Dr. Wiznitzer asserted that this was an independent finding by the Brunklaus authors and was not simply a reiteration of the McIntosh finding. Tr. 405. Furthermore, on cross-examination, Dr. Wiznitzer acknowledged that the Brunklaus study found that the mutation class did not predict a worse outcome, and one of the mutation classes listed was a frame shift mutation. Tr. 450.

#### 4. Assessment

When Dr. Corbier testified in rebuttal, he recognized that this type of mutation is severe and “explains a lot of things.” Tr. 501. But, Dr. Corbier maintained that the genetic mutation does not explain everything. The SCN1A mutation, in Dr. Corbier’s view, made individuals “more susceptible for environment insults.” Id.

An opinion that a SCN1A mutation explains almost everything, leaving room for an environmental factor is not persuasive. As Dr. Raymond and Dr. Wiznitzer thoroughly discussed, the nature of the genetic mutation in these children makes the creation of a normally functioning sodium channel in the brain impossible. Without an effective  $\text{Na}_v1.1$ , controlling the flow of sodium ions in the brain is impaired. The occurrence of seizures is inevitable. Dr. Corbier did not rebut Dr. Raymond’s assessment that the genetic mutation was severe. Similarly, Dr. Corbier did not answer Dr. Wiznitzer’s assertion that the problem was defective wiring.

Thus, there is no reliable basis for crediting Dr. Corbier’s first theory that people with an SCN1A mutation are vulnerable to developing an adverse reaction to the DTaP vaccine. Similarly, there is no reliable basis for crediting Dr. Corbier’s second theory that vaccines worsen Dravet syndrome by bringing about seizures before they would have occurred otherwise. Tr. 30, 104, 140. Although there may be an earlier manifestation, Dr. Corbier has not demonstrated how it affects the child’s outcome. Dr. Raymond and Dr. Wiznitzer rested their opinion on Berkovic, McIntosh, and Brunklaus. Dr. Corbier, on the other hand, had no support for his opinions that the vaccines change the outcome. These studies showed that children with SCN1A mutations have consistent symptoms, regardless of whether the initial seizure followed a seizure.

#### C. Analogy to HCN channels

To support the theory that “seizures beget seizures,” Dr. Corbier relies upon articles by McClelland, Dube, Bender, Brewster, Chen, and Jung, and also testified about them individually. Tr. 32-48.<sup>16</sup> Some of these articles present results of

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<sup>16</sup> Dr. Corbier appeared to know relatively less about HCN channels than the Secretary’s experts. For example, Dr. Corbier did not know whether a test could detect defects in HCN

experiments and some of these articles are review articles that summarize experiments conducted elsewhere. In the articles that reported the results of an experiment, the researchers were generally exploring a hypothesis that febrile seizures lead to long-term epilepsy because the febrile seizures damage an HCN channel. See Tr. 552.

The HCN channels are located in the hippocampal region. Tr. 132, 382 (Dr. Wiznitzer's discussion of 2001 Chen). HCN channels are ion channels, which allow substances such as sodium and potassium to enter and to exit the cell membrane. Tr. 363. The purpose of HCN channels is to balance and polarize the cell to limit the cell's excitability. Tr. 364.

After a summary about each article, Dr. Corbier was asked about their combined teaching. He stated:

I think taken collectively, these articles show that we have an explanation for prolonged febrile seizures causing permanent changes, permanent epileptic changes in a brain that may start out normal, for example, Dravet patients. We know that before six months, before they start having seizures, they appear normal. They don't have seizures. They have a prolonged febrile event or a prolonged febrile seizure. Something changes. They develop epilepsy, so this can explain why and how a prolonged febrile seizure vis-a-vis these HCN channels can result in these long-term changes.

Tr. 50. Dr. Corbier also opined about these studies' relevance:

They're relevant because we have to have a mechanism, we have to have an explanation to show why. Even if you have an important mutation such as SCN1A mutation, the changes from a SCN1A mutation that lead to refractory epilepsy do not occur in a vacuum. There

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channels and he did not know how a defect in an HCN channel would be observable in a clinical setting. Tr. 138.

needs to be an explanation from going from no seizures to very refractory seizures unresponsive to medication.

Tr. 51.

Dr. Corbier's logic is flawed in many respects. First, he states that something alters "a brain that may start out normal, for example, Dravet patients." Tr. 50. It is not correct to say that these children's brains "start[ed] out normal." Dr. Corbier recognized that "these kids probably come into the world with that SCN1A mutation." Tr. 41. Although Dr. Corbier qualified his answer by using the term "probably," he later agreed that Aydien was born with the SCN1A mutation. Tr. 94-95.

The second error in Dr. Corbier's assessment relates to the first. Dr. Corbier asserted that "the changes from a SCN1A mutation that lead to refractory epilepsy do not occur in a vacuum." Tr. 51. There is not a vacuum. The seizures and attendant developmental delays begin after the switch from Na<sub>v</sub>1.3 to Na<sub>v</sub>1.1. See Brewster at 4597; Tr. 137.

Third, HCN channels are not sodium channels. Tr. 363 (Dr. Wiznitzer). HCN channels regulate the excitability and inhabitability in the cell. Tr. 364. HCN channels involve not only sodium ions, which cause the cell to be hyperpolarized, but also involve potassium ions. Id. "The HCN channel is not the same thing as an SCN1A channel. It's built differently. It has different components. It has different genes. It probably has different transcriptional regulation." Tr. 470. When Dr. Corbier was asked to comment upon the similarities and differences as part of his rebuttal testimony, he did not address the question very well, beginning his answer "I don't claim to be an expert in channelopathies." Tr. 524. Dr. Corbier's non-answer left unrebutted Dr. Wiznitzer's assertion that "You're dealing with two different creatures here. So I think you can't take the leap from one to the other." Tr. 471.

Fourth, the consequence of a problem in an HCN channel may be temporal lobe epilepsy.<sup>17</sup> But temporal lobe epilepsy is not the same as Dravet syndrome.

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<sup>17</sup> The text uses the conditional terminology "may be" because the connection between HCN channels and temporal lobe epilepsy is not established. Tr. 516-19 (Dr. Corbier's discussion of Bender), 526-27 (Dr. Corbier).

Tr. 367-68, 372, 385; see also Tr. 498-99 (movement disorders seen in Dravet syndrome do not originate in the hippocampal region).

#### **D. Synopsis**

All these reasons contribute to a finding that Dr. Corbier was not persuasive in his opinion that vaccinations affected Aydien's outcome. The flip side of this coin is that Dr. Raymond and Dr. Wiznitzer were persuasive in opining that the SCN1A mutation was the sole cause. Consequently, Mr. Santini and Ms. Omidvar have failed to establish the first prong of Althen and the Secretary has established an alternative factor.

Although this resolution means that Mr. Santini and Ms. Omidvar cannot be awarded compensation, there is a second aspect to their case. Whether Aydien suffered a severe injury due to the vaccine is discussed below.

### **VII. Severity of Injury**

#### **A. Legal Principles**

Another way of evaluating an alleged effect of vaccination on Aydien is to consider how he would be if he had not received a vaccination. In a variety of contexts, the Federal Circuit has held that the person claiming compensation for another's injury must establish a "but for" model. E.g. Nycal Offshore Dev. Corp. v. United States, 743 F.3d 837, 844 (Fed. Cir. 2014) (oil and gas leases); Kellogg Brown & Root Servs., Inc. v. United States, 728 F.3d 1348, 1371 (Fed. Cir. 2013) (government counterclaim pursuant to anti-kick back act), reh'g denied, 2014 WL 1284763 (Fed. Cir. March 28, 2014). Consistent with common law principles, the Federal Circuit has also held that petitioners in the Vaccine Program have the burden to show "but for" the vaccine, they would not have suffered an injury. Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Pursuant to the Vaccine Act, the injury suffered must be severe, such as lasting more than six months. 42 U.S.C. § 300aa—11(c)(1)(D).

In the context of a cause of action alleging a vaccine caused a discrete injury, the "but for" world is readily identified. Petitioners maintain that but for a vaccine, they would not have suffered any injury. However, Mr. Santini and Ms. Omidvar in the case at hand are not proceeding on an initial-onset claim. They are

instead pursuing a cause of action that the vaccines significantly aggravated Aydien's underlying disorder.

In significant aggravation cases, constructing a hypothetical scenario without the vaccination is more challenging. Because the physiologic basis for the disease existed before vaccination, petitioners must present some persuasive evidence about the natural or expected course of the disease. From this benchmark, petitioners should show their outcome is worse than what would normally occur. Locane v. Sec'y of Health & Human Servs., 99 Fed. Cl. 715, 731-32 (2011), aff'd, 685 F.3d 1375 (Fed. Cir. 2012); Loving v. Sec'y of Health & Human Servs., No. 02-469V, 2009 WL 3094883, at \*11-12 (Fed. Cl. Spec. Mstr. July 30, 2009), clarified on denial of reconsideration, 2010 WL 1076124 (Fed. Cl. Spec. Mstr. March 2, 2010).

In the cases involving an SCN1A mutation, the petitioners' inability to explain how the children would have fared without the vaccination was one reason the petitioners were not compensated. Harris, 2011 WL 2446321 at \*33; Snyder, 2011 WL 3022544, at \*34. The Federal Circuit specifically ruled that these findings were not arbitrary and capricious. Snyder, 553 Fed. Appx. at 999, 1003; cf. Deribeaux, 717 F.3d at 1369 (ruling the special master was not arbitrary in finding the SCN1A mutation to be the sole cause of the child's injuries).

## **B. Assessment of Evidence**

For the case at hand, Mr. Santini and Ms. Omidvar's proof again falters. They failed to establish Aydien would be different today if he had not received the DTaP vaccination. They have not demonstrated any sequela to his initial seizure after which he returned to his baseline. Mr. Santini and Ms. Omidvar also have not established any change in outcome.

All experts agree that there is a causal relationship between the vaccinations and the initial seizure. More specifically, the DTaP vaccine prompted a fever and fever, in children with an SCN1A mutation, can prompt a seizure. The Secretary's experts conceded this point without dispute. Tr. 320 (Dr. Raymond), 448 (Dr. Wiznitzer).

A fever and an associated seizure, however, do not meet the Vaccine Act's severity requirement. Following the seizures, Aydien remained in the hospital for less than four days. Exhibit 84A at 4-9. He underwent various tests including an

EEG and an MRI. The results of these tests were normal. Exhibit 84A at 8, CH&N Recs. at 224. Upon discharge, Aydien was said to be in good condition. Exhibit 84A at 9; see also Tr. 144, 423, 427, 437. Consequently, Mr. Santini and Ms. Omidvar cannot receive compensation for just the initial fever and initial seizure. Therefore, Mr. Santini and Ms. Omidvar must look to Aydien's outcome after the initial presentation.

Mr. Santini and Ms. Omidvar have not demonstrated Aydien would have been worse. Dr. Corbier, on cross-examination, was asked if Aydien did not have his initial seizure, how would he be today? Dr. Corbier responded: "the simple answer is I don't know." He elaborated: "I can take an educated guess that if he did have seizures, it would have occurred later on." Tr. 104. In the subsequent discussion, Dr. Corbier suggested that Aydien may not have had any seizures. When questioned about the basis for this possibility, Dr. Corbier answered:

Is it possible that he could go without seizure despite the fact that he has an SCN1A mutation disease producing type of mutation? The answer is maybe.

I can't say for sure. I don't have any evidence to back me up, but I don't see why not. . . .

[B]ut if we're able to control all of the potential triggers, could we be left without a seizure disorder? Perhaps.

Tr. 107-08. Because Dr. Corbier's answer suggested that triggers were not needed, he was asked more questions about this point. Dr. Corbier stated "this is a question, the answer of which I don't know based on not seeing any particular study designed to address that particular question. [B]ut at least hypothetically, you know, I don't see why not." Tr. 109.

Later, Dr. Corbier was again asked to differentiate Aydien from what happens in Dravet syndrome generally. But, Dr. Corbier did not provide any meaningful information. Tr. 142-43. Because Dr. Corbier did not explain his opinion regarding the difference between a hypothetical Aydien Omidvar (who did not receive the vaccination) and the real Aydien Omidvar (who did receive the vaccination), Dr. Corbier was asked about this topic again. But, once more, he



could say only that the seizures occurred earlier. He could not say that the earlier onset affected Aydien's longer term outcome. Tr. 185-91.

These vague responses largely undermined the value of Dr. Corbier's earlier testimony, on direct examination, that the children at issue in the consolidated cases were worse after the vaccination. Tr. 77 (Aydien). In the sense that the children had seizures, they were worse. But this conclusion is too facile. It ignores the role the mutation plays and the natural course of Dravet syndrome.

The opinions from Dr. Raymond and Dr. Wiznitzer that the mutation determined the children's outcome were much more persuasive. In their view, the vaccinations did not affect the Dravet syndrome. Tr. 263 (Dr. Raymond on Matthew Ramirez), 270 (Dr. Raymond on Aydien), 319 (Dr. Raymond on Aydien), 423 (Dr. Wiznitzer on Matthew), 454 (Dr. Wiznitzer on both). Dr. Raymond and Dr. Wiznitzer based their opinions that the gene caused the developmental delay on biology. As explained above, neither child can produce a normally functioning Na<sub>v</sub>1.1.

The medical literature also supports the opinion that vaccinations did not affect the outcome. Tr. 302-06 (Dr. Raymond citing McIntosh), 439 (Dr. Wiznitzer citing McIntosh, and Brunklaus). For example, Brunklaus and colleagues studied more than 300 cases with an SCN1A mutation. They attempted to determine whether different variables accounted for the range of developmental outcomes in patients with Dravet syndrome. The authors concluded that their finding "supports the argument that children carrying a SCN1A mutation are destined to develop the disease, which in turn can be precipitated by a series of factors such as fever/illness, vaccination or a bath. However, the nature of the trigger has no effect on overall developmental outcome and thus does not seem to be responsible for the subsequent encephalopathy." Brunklaus at 2334. In addition to their own data, Brunklaus and colleagues cited the articles by Tro-Baumann, Berkovic and McIntosh. When asked about this passage from the Brunklaus article, Dr. Corbier said "I don't see proof." Dr. Corbier's assessment of Brunklaus is not credible.

Overall, the evidence overwhelmingly demonstrated that Aydien would be the same even if he did not receive the vaccine. The vaccination did not affect or contribute to his developmental delay. Mr. Santini and Ms. Omidvar have failed to meet their burden of establishing, by preponderant evidence, that he suffered an injury for more than six months.

## VIII. Additional Comments

The results in the case at bar match the results in previous cases involving an SCN1A mutation. The identical outcome is not surprising because human biology has not changed. The SCN1A genes still largely control the creation of Na<sub>v</sub>1.1. Furthermore, the evidence is largely the same. Dr. Raymond and Dr. Wiznitzer testified in previous cases. They cited to the same articles, such as Oakley and Yu. The newer articles such as Brunklaus reinforce the opinions of Dr. Raymond and Dr. Wiznitzer.

Potential petitioners who intend to claim a vaccine injured a child with an SCN1A mutation should consider carefully whether there is a reasonable basis for their claims. Special masters have consistently credited evidence that the gene is the sole cause of developmental problems.<sup>18</sup> An expert's opinion that a vaccine can trigger an initial seizure in a child with an SCN1A mutation has been insufficient to demonstrate that the vaccine caused a subsequent seizure disorder in such a child, at least in the absence of evidence regarding a difference in the ultimate outcome. Against this backdrop, future claims involving an SCN1A mutation may lack a reasonable basis.

## IX. Conclusion

Dravet syndrome has interfered with Aydien's development since its manifestation following the November 7, 2003 DTaP vaccination. The timing of events (in that Aydien experienced his first seizure within one day of the vaccination) understandably led to a hypothesis that the vaccination contributed to the Dravet syndrome.

However, scientific research, as Dr. Raymond and Dr. Wiznitzer ably explained, has shown that a genetic mutation caused Aydien's Dravet syndrome. It is more likely than not that Aydien would be the same today whether he received the vaccination or not. Mr. Santini and Ms. Omidvar have failed to demonstrate that they are entitled to compensation from the Vaccine Program. Consequently, the Clerk's Office is instructed to enter judgment in accord with this decision.

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<sup>18</sup> The list of final opinions in other SCN1A cases includes: Snyder, 553 Fed. Appx. 994; Deribeaux, 717 F.3d 1363; Stone, 676 F.3d 1373; Barnette v. Sec'y of Health & Human Servs., 110 Fed. Cl. 34 (2013); and Waters v. Sec'y of Health & Human Servs., No. 08-76V, 2014 WL 300936 (Fed. Cl. Spec. Mstr. Jan. 7, 2014).

**IT IS SO ORDERED.**

s/ Christian J. Moran  
Christian J. Moran  
Special Master

Appendix: Full Citation for Journal Articles

Title	Exhibit in Barclay	Exhibit in Santini
Alex C. Bender et al., <u>SCN1A mutations in Dravet syndrome: impact of interneuron dysfunction on neural networks and cognitive outcome</u> , 23 <i>Epilepsy Behav.</i> 177 (2012).	K3	53; W.2; U.6
Samuel F. Berkovic et al., <u>De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study</u> , 5 <i>Lancet Neurology</i> 488 (2006).	20	54; C
Amy Brewster et al., <u>Developmental febrile seizures modulate hippocampal gene expression of hyperpolarization-activated-channels in an isoform-and cell-specific manner</u> , 22(11) <i>J. Neuroscience</i> 4591 (2002).	42	86a
A. Brunklaus et al., <u>Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome</u> , 135 <i>Brain</i> 2329 (2012).	I34; K6	S.1; U.4
Claudia B. Catarino et al., <u>Dravet syndrome as epileptic encephalopathy: evidence form long-term course and neuropathy</u> , 134 <i>Brain</i> 2982 (2011).	I28; K1	55; U.1
Kang Chen et al., <u>Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability</u> , 7(3) <i>Nat. Med.</i> 331(2001).	43	88
Berten Ceulemans, <u>Overall management of patients with Dravet syndrome</u> , 53(Supp. 2) <i>Devel. Med. Child Neurology</i> 19 (2011).	K4	U.7
Celine M. Dube et al., <u>Febrile seizures: Mechanism and relationship to epilepsy</u> , 31 <i>Brain &amp; Devel.</i> 366 (2009).	25	59
Andrew Escayg and Alan L. Godin, <u>Sodium channel SCN1A and epilepsy: Mutations and mechanism</u> , 51(9) <i>Epilepsia</i> 1650 (2010).	I10	S.8
Dale C. Hesdorffer et al., <u>Design and phenomenology of the FEBSTAT study</u> , 53(9) <i>Epilepsia</i> 1471 (2012).	I26	
Susumu Ito et al., <u>Mouse with Na<sub>v</sub>1.1 haploinsufficiency, a model for Dravet syndrome, exhibits lowered sociability and learning impairment</u> , 49 <i>Neurobiology of</i>	I15	S.13

Title	Exhibit in Barclay	Exhibit in Santini
<u>Disease 29 (2013).</u>		
Sangwook Jung et al., <u>Progressive dendritic HCN channelopathy during epileptogenesis in the rat pilocarpine model of epilepsy</u> , 27 (47) J. Neuroscience 13012 (2007).	45	89
Christoph Lossin, <u>A catalog of SCN1A variants</u> , 31(2) Brain Dev. 114 (2009).	I29	62
Melinda S. Martin et al., <u>The voltage-gated sodium channel Scn8a is a genetic modifier of severe myoclonic epilepsy of infancy</u> , 16(23) Hum. Mol. Genet. 2892 (2007).	I22	S.19
Shawn McClland et al., <u>Epileptogenesis after prolonged febrile seizures: Mechanism, biomarkers and therapeutic opportunities</u> , 497(3) Neuroscience Letters 155 (2011).	I25	U.2
Anne M. McIntosh et al., <u>Effects on vaccination on onset and outcome of Dravet syndrome: a retrospective study</u> , 9 Lancet Neurology 592 (2010).	I32; K5	66; S.24; U.3
John C. Oakley et al., <u>Temperature -and age-dependent seizures in a mouse model of severe myoclonic epilepsy in infancy</u> , 106 Proc. Nat'l Acad. Sci. USA 3994 (2009).	I9; K2	69; S.7; U.5
Francesca Ragona et al., <u>Cognitive development in Dravet syndrome: A retrospective, multicenter study of 26 patients</u> , 52(2) Epilepsia 386 (2011).	K8	
Blanca Tro-Baumann et al., <u>A retrospective study of the relation between vaccination and occurrence of seizures in Dravet syndrome</u> , 52(1) Epilepsia 175 (2011).	I33	73
Frank H. Yu et al., <u>Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy</u> , 9(9) Nat. Neuroscience 1142 (2006).	I11	S.9