# In the United States Court of Federal Claims

**OFFICE OF SPECIAL MASTERS**

No. 05-306V
Filed: December 9, 2011

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| MADISON DERIBEAUX, a minor, by her parents and natural guardians, GUS DERIBEAUX and KIMBERLY BURSHIEM, | ) | TO BE PUBLISHED |
| Petitioners, | ) | Entitlement; Dravet syndrome; SMEI; Kawasaki syndrome; SCN1A; genetic mutation; GEFS+; seizure disorder; febrile; afebrile; epilepsy; DTaP vaccine |
| v. | ) | |
| SECRETARY OF HEALTH AND HUMAN SERVICES, | ) | |
| Respondent. | ) | |

Clifford J. Shoemaker, Shoemaker and Associates, Vienna, VA, for Petitioners;
Glenn A. MacLeod, United States Dep't of Justice, Washington, D.C., for Respondent.

## DECISION DISMISSING THE CASE[1]

**LORD,** Special Master.

### I. Introduction

On March 11, 2005, Petitioners Gus Deribeaux and Kimberly Burshiem filed a Petition on behalf of their daughter, Madison, under the National Vaccine Injury Compensation Program (the "Program"), see 42 U.S.C. § 300aa-1-34, alleging that Madison suffered a seizure disorder as a result of the acellular DPT (DTaP) vaccine she received on March 28, 2002. Pet. at 2, ¶8. On March 21, 2006, Respondent (the "Secretary") filed a report pursuant to Vaccine Rule 4(c) maintaining that compensation was inappropriate and that the Petition should be dismissed. Resp't 4(c) Rep. at 2.

A hearing was held on September 20, 2007, after which Special Master Millman granted entitlement to compensation. Deribeaux v. Sec'y of Dep't of Health & Human Servs., No. 05-306V, 2007 WL 4623461 (Fed. Cl. Spec. Mstr. Dec. 17, 2007). During the ensuing damages phase of the case, Petitioners for the first time produced medical

[1] In accordance with Vaccine Rule 18(b), a petitioner has 14 days to file a proper motion seeking redaction of medical or other information that satisfies the criteria in 42 U.S.C. § 300aa-12(d)(4)(B). Redactions ordered by the special master, if any, appear in the document as posted on the United States Court of Federal Claims' website.

records showing that Madison suffered from a genetic mutation known to cause a severe seizure and developmental disorder called Dravet's syndrome (DS). [2] The additional medical records showed that, once they learned of the mutation, Madison's treating physicians attributed her neurological symptoms, which are classic for DS, to that syndrome. Tr. II at 61-62; Pet'r Ex. 14 at 5 (consultation stating "finally she does have a diagnosis to her neurological problems. . . . Dravex [sic] syndrome, characterized by seizure disorder, mental retardation, ataxia and behavioral changes").[3]

The Secretary moved to re-open the issue of entitlement. After the case was transferred to me, I granted the Secretary's motion and conducted a second hearing to consider the impact of the new evidence.

At the second hearing, the Secretary conceded that vaccination likely triggered Madison's first, prolonged seizure. According to the Secretary, individuals with DS are prone to suffer seizures in the context of any temperature elevation. Resp't Ex. RR. at 5, ¶6. The Secretary's theory was that Madison experienced a fever following vaccination and that the fever caused her initial, prolonged seizure. The Secretary maintained that the course of Madison's disorder was not altered or aggravated by her initial seizure, however, and that the disabilities caused by her genetic mutation would have been the same with or without the vaccine-induced seizure.

Petitioners contended that, notwithstanding Madison's genetic mutation and diagnosis of Dravet's syndrome, it was vaccination that caused Madison's condition. According to Petitioners, vaccination not only caused Madison's initial seizure but also triggered an immune deficiency that led to additional disorders, including atypical Kawasaki disease, and further neurological damage.[4] Petitioners propounded several related theories of vaccine causation and/or aggravation, including that vaccination could precipitate a first seizure at a time when the victim was particularly vulnerable to neurological injury.

As explained in detail below, preponderant evidence demonstrated that Madison's genetic abnormality caused both her susceptibility to a post-vaccine seizure and, more importantly, her numerous subsequent seizures and other neurological

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[2] A "syndrome" is "a set of symptoms that occur together; the sum of signs of any morbid state; a symptom complex. In genetics, a pattern of multiple malformations thought to be pathogenetically related." Dorland's Illustrated Medical Dictionary 1819 (32nd ed. 2012). Among the symptoms of Dravet's Syndrome are uncontrollable seizures of varying types, developmental delay, and ataxia. See infra. A genetic "mutation" is defined as "A change of the DNA sequence within a gene or chromosome of an organism resulting in the creation of a new character or trait not found in the parental type." American Heritage Dictionary 1160 (4th ed. 2006).

[3] The transcript of the hearing held before Special Master Millman is designated as "Tr. I." The transcript of the supplemental hearing is designated as "Tr. II."

[4] Kawasaki disease is a rare, immune-mediated vasculitis that can affect the skin, heart, mucus membranes, eyes, mouth and central nervous system. Tr. I at 140. The experts described Madison's disease as "atypical" because she did not exhibit many of the typical features of the disorder. See Tr. I at 153, 156, 216.

problems. There is an association between Madison's initial febrile seizure and her vaccination, to be sure – the Secretary did not deny it – but no causative relationship was established between vaccination and the neurological problems that are known to occur in individuals with DS. As the authors of one study advised, "we found no evidence that vaccinations before or after disease onset affect outcome." Resp't Ex. VV-17, Anne McIntosh et al., Effects of Vaccination On Onset and Outcome of Dravet Syndrome: A Retrospective Study, 9 Lancet Neurol. 592, 592 (2010). The initial seizure triggered by Madison's vaccination was a symptom, not a cause, of her neurological condition, which would have been the same regardless of vaccination. Accordingly, I vacate the earlier entitlement ruling and hold that Petitioners are not entitled to compensation.

In the decision below, I describe the pertinent background, including the procedural developments that resulted in two hearings on entitlement. I describe Madison's medical condition, including the information concerning her testing for and diagnosis of DS. I also review the original evidence on entitlement and the previous special master's decision. I then describe the second entitlement proceeding, which focused on the Secretary's allegation of alternative causation by a factor unrelated to vaccination. In the Discussion section, I review the applicable standards of proof and analyze the arguments and evidence for and against DS as the sole substantial cause of Madison's neurological disorder.

## II. BACKGROUND

### A. Procedural Background

This case followed a peculiar course. It was filed in March 2005. Nine months later, in late December 2005, genetic testing showed that Madison had a de novo missense mutation in her SCN1A gene, resulting in a diagnosis of DS. See Pet'r Ex. 15 at 8-13, discussion infra. The vaccine injury case proceeded, however, without any evidence of the genetic testing or the diagnosis of DS being submitted. Indeed, none of the extensive records of treating physicians who diagnosed Madison with DS was filed into the record in advance of the hearing before Special Master Millman. See Pet'r Ex. 10 at 14, 17, 28; Pet'r Ex. 11 at 8, 22, 26; Pet'r Ex. 12 at 4, 15; Pet'r Ex. 13 at 26; Pet'r Ex. 14 at 5; Pet'r Ex. 15 at 5-6, 15-17. Apparently, Petitioners did not believe that they had any obligation to update the record with medical evidence after filing the initial claim for compensation.[5]

No evidence concerning Madison's genetic mutation or her diagnosis of DS was presented during the hearing on September 20, 2007. After Special Master Millman's

[5] In response to an order to explain why the records of Madison's genetic testing and diagnoses were not submitted in a timely fashion, Petitioners and counsel provided affidavits. See Status Report with Attendant Affidavits, May 5, 2011, ECF No. 88. As recounted in her affidavit, Madison's mother testified at the hearing before Special Master Millman but was not asked about Madison's diagnoses and did not reveal that Madison had been diagnosed with DS almost two years earlier. Affidavit of Kimberly Burshiem and Gus Deribeaux 2, May 5, 2011, ECF No. 88-3.

decision finding entitlement to compensation, the parties commenced the effort to quantify damages. Shoemaker Aff. 1, May 5, 2011, ECF No. 88-1. In the course of preparing for the award of damages, Petitioners for the first time filed the records evidencing Madison's diagnosis of DS. Id. at 2. The Secretary then moved to re-open the question of entitlement. Resp't Mot. to Reopen Case, Jan. 16, 2009, ECF No. 70.

Shortly after these developments, the case was transferred to me. Order Reassigning Case, June 22, 2009, ECF No. 76.[6] I have ruled in another context that, in fairness, the random event of transfer from one special master to another should not change the substantive outcome. See Sharkey v. Sec'y of Dep't of Health & Human Servs., No. 99-669V, 2010 WL 5507915, at *2 (Fed. Cl. Spec. Mstr. Dec. 10, 2010). Consistent with that view, and mindful of the resources of the parties and the Court, I deemed the evidence presented at the hearing conducted by Special Master Millman sufficient to set forth Petitioners' prima facie case, and to shift the burden of proof to the Secretary to establish alternative causation.[7] I directed that a supplemental hearing be held to focus on the question of whether the Secretary had rebutted Petitioners' prima facie case by showing that Madison's disorder was caused by an unrelated factor. See § 300aa-13(a)(1)(A)-(B). I heard expert testimony from both sides on June 28, 2011.[8]

The new evidence established that an unrelated factor, namely, genetic mutation, caused Madison's seizures and other neurological disorders. Accordingly, I set aside Special Master Millman's previous decision on entitlement and dismiss Petitioners' claim.

### B. Madison's Medical Condition

#### 1. Medical History Before Genetic Testing

This summation of the medical records is based primarily on the careful history in the initial report of Petitioners' expert, Dr. Carlo Tornatore, as well as on the reports of

[6] This re-assignment was included with a number of other cases that were transferred to me at the time my service as a special master commenced, on June 22, 2009. Because they came from other special masters' dockets, those cases were in various stages of development at the time of transfer.

[7] Special Master Millman's decision might have been different if she had had all of the evidence before her. In this regard, it is advantageous to Petitioners not to re-examine the sufficiency of their prima facie case in light of the new evidence of alternative causation. Evidence of Madison's SCN1A mutation might have persuaded the special master that Petitioners had not satisfied their burden to establish a prima facie case of entitlement. See Doe 11 v. Sec'y of Dep't of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010), cert denied, 131 S.Ct. 573 (2010) (special masters may evaluate evidence of alternative causation in determining whether petitioners have met their burden).

[8] The special master "may conduct such hearings as may be reasonable and necessary." 42 U.S.C. §300aa-12(d)(3)(B)(v). See also Hanlon v. Sec'y of Dep't of Health & Human Servs., 191 F.3d 1344, 1350 (Fed. Cir. 1999) (under the Act "it is not an abuse of discretion to consider new pertinent medical evidence that was not available at the time of the original petition"), citing McAllister v. Sec'y of Dep't of Health & Human Servs., 70 F.3d 1240, 1244 (Fed. Cir. 1995).

the other experts who appeared in this case, the transcript of the first entitlement hearing, and the medical records on file. See Pet'r Ex. 6 at 2-10.

Madison was born on August 19, 2001. Pet'r Ex. 1 at 1. She received the DTaP and other routine childhood vaccines on March 28, 2002, at seven months of age. Resp't Ex. RR at 1. The next day, she was taken to the emergency room at Baptist Hospital of Miami, having suffered a prolonged seizure around 7 p.m. Pet'r Ex. 6 at 2; Pet'r Ex. 5 at 1-2. When she arrived at the ER around 7:20 p.m., no fever was noted. Pet'r Ex. 2 at 88-89.[9] She continued to seize, despite medication, and was admitted to the Pediatric Intensive Care Unit. Pet'r Ex. 6 at 3. Later that night, her temperature was recorded as 103.6. Id.; Pet'r Ex. 2 at 158.

A doctor consulted on March 30, 2002, assessed Madison with "seizure of unclear etiology-suspect viral syndrome." Pet'r Ex. 6 at 3; Pet'r Ex. 2 at 45. A neurology consult that same day concluded that Madison had "prolonged seizure (?febrile seizure)." Pet'r. Ex. 6 at 3; Pet'r Ex. 2 at 46.

Madison remained at Baptist Hospital for several days. A note dated April 1, 2002, from a pediatric neurologist indicated that Madison had suffered no further seizures since admission and that her EEG and CT tests were normal. Pet'r Ex. 6 at 4; Pet'r Ex. 2 at 58. He felt Madison had had a febrile seizure. Pet'r Ex. 6 at 4; Pet'r Ex. 2 at 58. Madison continued to do well in the hospital on April 2-4, and an MRI of her brain on April 4, 2002, was reported as within normal limits. Pet'r Ex. 6 at 4; Pet'r Ex. 2 at 108.

On April 7, 2002, Madison had a generalized tonic-clonic seizure lasting 15 to 30 seconds. Pet'r Ex. 6 at 5; Pet'r Ex. 2 at 64. The seizure was accompanied by fever. Id. A pediatrician assessed Madison as having a viral syndrome with febrile seizures. Id. Another note documenting this event included the information, "Mom does have an upper respiratory infection." Pet'r Ex. 6 at 5; Pet'r Ex. 2 at 65. Madison was discharged on April 8, 2002. Pet'r Ex. 6 at 5.

The next day, April 9, 2002, Madison was re-admitted to Baptist Hospital after suffering a generalized seizure lasting approximately 10 minutes. Pet'r Ex. 6 at 5; Pet'r. Ex. 2 at 235, 243. She had a low-grade fever at the time of the seizure. Pet'r Ex. 6 at 5; Pet'r. Ex. 2 at 250. A consult on this date noted that Madison, during her previous admission, had had seizures even while on Phenobarbital, and the doctor recommended starting a metabolic workup to rule out other possible etiologies for her seizures. Pet'r Ex. 6 at 5-6; Pet'r Ex. 2 at 249. Madison had another generalized seizure at 4:00 a.m. on April 10, 2002, and was transferred at the request of her family to Miami Children's Hospital. Pet'r Ex. 6 at 6; Pet'r Ex. 2 at 258.

[9] This notation notwithstanding, experts for the Petitioners and Secretary characterized Madison's initial seizure as febrile. See, e.g., Tr. II at 52, 133.

An admission note recounting the history of Madison's seizures and fever recorded "complex febrile seizures x4 following DTaP, IPV immunization." Pet'r Ex. 6 at 6; Pet'r Ex. 4 at 1150. At 6:00 p.m. on April 10, Madison suffered a seizure lasting 15 minutes, despite anti-seizure treatment, and she was observed to have a macropapular rash over her entire body. Pet'r Ex. 6 at 6; Pet'r Ex. 4 at 1152, 53. She was transferred to the pediatric intensive care unit and thought to be in septic shock. Pet'r Ex. 6 at 6; Pet'r Ex. 4 at 1155.

An immunologist on April 16, 2002, reviewed Madison's case and noted the temporal association between her seizures and vaccinations. Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 1040-41. He discussed Madison's low levels of immunoglobulin but said they were "only mildly concerning," and might not even be "abnormal." Pet'r Ex. 4 at 1041.[10] "Overall this is more likely to be a transient hypogammaglobulinemia due to slow maturation of her immune system," the immunologist stated. Id. He recommended that she receive immune therapy "if her condition deteriorates," that she have a three-month follow up to evaluate her immune system, and that the pediatrician submit a report "for possible adverse vaccine reaction." Id.

Madison was seizure-free through April 18, 2002. Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 1189. Repeat MRI and EEG were reported as normal. Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 1190. All her cultures were negative. Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 1190. It was thought she might have had atypical Kawasaki's disease and she was treated with five days of intravenous immunoglobulin ("IVIG"). Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 1190. On April 20, she was discharged home. Pet'r Ex. 6 at 7.

On September 16 and 17, 2002, Madison was taken to the ER with febrile seizures. Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 623-67. Again, on January 29, 2003, Madison was seen in the ER with active, febrile seizures. Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 582. The admitting note in January 2003 states under Past Medical History: "Suspected super antigen vs. Kawasaki syndrome . . . ." Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 611. Following various blood tests and a normal EEG on January 30, 2003, an immunology consult concluded that Madison had "resolving hypogammaglobulinemia." Pet'r Ex. 6 at 8; Pet'r Ex. 4 at 593.

Madison was admitted to Miami Children's Hospital on April 28, 2003, with recurrent convulsive episodes. The discharge summary for May 2, 2003, stated that Madison was a 20-month-old with a seizure disorder starting at age six months, two days after DTaP vaccination, with subsequent admission and treatment for atypical Kawasaki disease. Pet'r Ex. 6 at 8; Pet'r Ex. 4 at 384. "The patient has been having febrile seizures and general tonic-clonic seizures. Most recently, the patient was having seizures without fever." Pet'r Ex. 6 at 8; Pet'r Ex. 4 at 384. An MRI on April 30, 2003 reported white matter abnormalities possibly related to hypomyelinization, or "a metabolic disease such as lysosomol or mitochondrial disease as well [as]

[10] Immunoglobulin is any of the structurally related glycoproteins that function as antibodies, divided into five classes (IgM, IgG, IgA, IgD, and IgE) on the basis of structure and biologic activity. Dorland's at 919.

metachromatic leukodystrophy." Pet'r Ex. 6 at 8; Pet'r Ex. 4 at 397.[11] Madison was subjected to extensive additional testing. Pet'r Ex. 6 at 8.

On July 23, 2003, Madison again was admitted to Miami Children's, with fever of unknown origin and daily seizures. Pet'r Ex. 6 at 8; Pet'r Ex. 4 at 358. An infectious disease consult noted "seizure disorder with hypomyelination process with persistent fevers. Also with serum enterovirus x 2 in the recent past." Pet'r Ex. 6 at 8; Pet'r Ex. 4 at 358.[12] The consult noted that Madison "possibly developed problems after 3rd dose of DTaP." Pet'r Ex. 6 at 8; Pet'r Ex. 4 at 358. Madison was noted to have had fevers daily starting in March 2003. Pet'r Ex. 6 at 8; Pet'r Ex. 4 at 358.

Testing for enterovirus on August 28, 2003, again was positive. Pet'r Ex. 6 at 9; Pet'r Ex 4 at 350.

Madison received semi-monthly doses of IVIG starting October 24, 2003. Pet'r Ex. 6 at 9; Pet'r Ex. 4 at 315.

An MRI of the brain on November 7, 2003 found "increased T2-weighted signal in the periventricular white matter . . . . Differential diagnosis includes gliosis versus hypomyelination." Pet'r Ex. 6 at 9; Pet'r Ex. 4 at 304.[13] Madison received additional doses of IVIG in November and December 2003. Pet'r Ex. 6 at 9; Pet'r Ex 4 at 298, 293, 283.

Following another admission to Miami Children's with fevers and increased seizures, Pet'r Ex. 6 at 9; Pet'r Ex. 4 at 258, Madison was discharged on December 28, 2003, with what was believed to be a viral syndrome. Pet'r Ex. 6 at 9; Pet'r Ex. 4 at 275. She received additional IVIG infusions throughout 2004. Pet'r Ex. 6 at 9-10; Pet'r Ex. 4 at 207, 197, 195, 173, 170, 130, 126, 121, 108, 102, 73, 94, 85.

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[11] Hypomyelinization is the disappearance or inadequate formation of myelin sheaths on nerves. Dorland's at 903. (Note "myelinization" and "myelination" are used interchangeably, see id. at 1218). Metabolic disease is a general term for diseases caused by disruption of a normal metabolic pathway because of a genetically determined enzyme defect. Id. at 538. Mitochondrial diseases are a diverse group of mainly multisystemic and maternally inherited disorders caused by mutations of mitochondrial DNA. Manifestations include encephalopathy. Id. at 539. Metachromatic leukodystrophy is an autosomal recessive genetic disorder. The infantile form usually begins in the second year of life and is additionally characterized by developmental delay, seizures, optic atrophy, ataxia, weakness, loss of speech, and progressive spastic quadriparesis. Id. at 1029.

[12] Enterovirus is a genus of viruses that preferentially inhabit the intestinal tract. Infection is usually asymptomatic or mild but may result in a variety of disease syndromes. Most strains of human enterovirus cause only mild symptoms such as fever. Dorland's at 626-27.

[13] Gliosis is an excess of astroglia in damaged areas of the central nervous system. Dorland's at 784. A related term is "astrocytosis," which is the proliferation of astrocytes (a type of neuroglial cell, see id. at 169), owing to the destruction of nearby neurons during a hypoxic or hypoglycemic episode. Id. at 170.

A physical therapy consult dated April 13, 2004, noted that Madison had delayed fine motor skills, poor attention, and hyperactive behavior. Pet'r Ex. 6 at 10; Pet'r Ex. 4 at 163.

An MRI on November 15, 2004, found further myelinization of the brain but myelinization was still "incomplete." Pet'r Ex. 6 at 10; Pet'r Ex. 4 at 113.

Madison was admitted to Miami Children's on February 8, 2005 to initiate a ketogenic diet in an effort to control her seizures. Pet'r Ex. 6 at 10; Pet'r Ex. 4 at 21-67.[14] It was noted that her development had stopped after one year of age. Pet'r Ex. 6 at 10; Pet'r Ex. 4 at 64.

Madison continued to have intractable seizures. See, e.g., Pet'r Ex. 13 at 228 (Pediatric history dated February 8, 2005, noting intractable seizures. Have "been trying several different meds [but she continues] having recurrent episodes more and more frequently. Currently since the past 2 months she has been having 3-4 seizure episodes per week, despite current medications."); Pet'r Ex. 13 at 149 (Discharge summary dated August 17, 2005, noting that "[t]he patient presents for 7 seizures on day of admission."). Over time, the types of seizures changed and became more frequent. See, e.g., Pet'r Ex. 13 at 280. Some appeared to be febrile, but others were not. See, e.g., Pet'r Ex. 13 at 35, 43, 68 (Emergency physician records where epileptic, not febrile, is circled); Id. at 334 ("Seizures mainly fever-related. Delayed immunization [secondary] to seizures with vaccines-induced fevers. This episode of persistent-recurrent fevers started after last IVIG infussion [sic] . . . ."); Id. at 411 ("The patient had been having febrile seizures and general tonic-clonic seizures. Most recently, the patient was having seizures without fever.").

Dr. Tornatore's report of Madison's medical history did not cover Madison's subsequent genetic testing or diagnosis of DS. By the time he submitted his report, however, which was transmitted by facsimile to counsel for Petitioners on January 31, 2006, see Pet'r Ex. 6 at 1, Madison had been diagnosed with DS. Dr. Tornatore apparently was not informed of Madison's genetic testing in November 2005 and her diagnosis in December 2005. After the information was revealed in this proceeding, Special Master Millman asked Dr. Tornatore whether his opinion changed in light of the new evidence. Dr. Tornatore responded with a letter in which he stated simply, "It does not." Pet'r Ex. 19 at 3. Accordingly, I rely for the history of Madison's genetic disorder and diagnosis of DS on the Secretary's expert, Dr. Gerald Raymond, and on the medical records.

### 2. Medical History After Genetic Testing

Madison was treated in Miami Children's Hospital November 2-4, 2005, for "status epilepticus with multiple generalized tonoclonic [sic] seizures during the night

[14] Ketogenic refers to the formation of ketone bodies. Dorland's at 983. Ketone bodies are produced by fatty acid and carbohydrate metabolism in the liver and can be used as fuels by muscle and brain tissue. Id. at 233.

prior to admission." Pet'r Ex. 13 at 106. The medical records stated that Madison was "admitted yesterday with persistent seizures and 'low grade' fevers[,]" and that Madison had a history of "recurrent fevers." Id. at 117; see also id. at 130 ("inc[reased] seizure activity over past 3 mos"). On November 3, 2005, the physician's impression was "Intractable Epilepsy, r/o Dravet." Id. at 115. The same note stated, "DNA Dravet's Mom aware she is due to pay $299 for [illegible] ct test & wishes to have it done." Id. On November 4, 2004, a neurology note stated that the plan was "For blood enterovirus PCR & DNA SCN1A sequencing to Athena this AM." Id. at 123.

At the end of December 2005, the results of Madison's genetic testing were reported. The report noted a DNA sequence variation in Madison's SCN1A gene. "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. Pet'r. Ex. 15 at 8 (Athena Diagnostics report).[15] The laboratory analysis indicated that the genetic mutation resulted in a different amino acid being expressed by Madison than is normal, and that the variant "is not present in either parent and therefore arose de novo ([i.e.,] was not inherited)." Id. While not excluding the possibility that Madison's mutation, which did not correlate with the specific mutations that had previously been studied, might be benign, the report noted that approximately 90% of amino acid variants associated with the more severe phenotypes of SMEI or SMEB arise de novo, while the inherited variations are associated with milder disorders. Id. "[B]ased on this single analysis," the report cautioned, "it is not possible to conclude with any reasonable degree of clinical certainty at this time whether or not this variant is associated with the phenotype in question." Id. at 9.

As the report explained, SCN1A encodes for the neuronal voltage-gated sodium channel alpha 1 subunit protein. Pet'r Ex. 15 at 9.

> Mutations in the SCN1A gene have been associated with several overlapping epilepsy syndromes ranging from severe to mild phenotypes . . . . The severe phenotypes include SMEI, Severe Myoclonic Epilepsy of Infancy or Dravet syndrome, and SMEB (SMEI borderline) with some, but not all, of the classical features of SMEI. . . . SMEI has a poor prognosis, including developmental delay and refractory seizures.

Pet'r Ex. 15 at 9-10. As noted in the laboratory report, a variety of factors may influence the expression of SMEI; therefore, "molecular analysis must be carefully reconciled with the clinical presentation and family history." Id. at 10.

Following the report of Madison's genetic mutation, her treating physicians consistently noted the diagnosis of DS and/or SCN1A mutation in association with her chronic seizures and developmental delays. For example, Dr. Pablo Laufer, an infectious disease specialist, had treated Madison's chronic enteroviral infection with

[15] SMEI stands for Severe Myoclonic Epilepsy of Infancy. It is another name for DS. See Pet'r Ex. 60 at 1, Renzo Guerrini et al., Neuroimaging and Neuropathology of Dravet Syndrome, 52 (Suppl. 2) Epilepsia 30, 30 (2011).

monthly doses of IVIG. Pet'r Ex. 14 at 5. On September 19, 2006, Dr. Laufer noted, "[I]t is important to say that finally she does have a diagnosis to her neurological problems. She had Dravex [sic] syndrome, characterized by seizure disorder, mental retardation, ataxia and behavioral changes." Id. This treating specialist in infectious diseases looked no farther than her diagnosis of DS for the cause of Madison's chronic neurological problems. "She suffers from chronic seizure disorder secondary to a genetic condition[,]" he stated in notes dated October 2, 2007. Pet'r Ex. 14 at 3.

Within 10 days of the report of Madison's genetic testing, Dr. Trevor Resnick, her treating neurologist, also noted Madison's variant of SCN1A in association with her seizures, developmental delay and ataxia. Pet'r Ex. 15 at 4. Dr. Resnick's reports thereafter noted uniformly the assessment of Dravet's syndrome in connection with Madison's intractable epilepsy and other neurological symptoms. See Pet'r Ex. 15 at 5, 7; see also Pet'r Ex 12 at 84 (physician's statement by Trevor Resnick, "Intractable epilepsy, Dravet's syndrome," noting "[s]eizures will persist [throughout] lifetime").

The records of Madison's visit to the ER on March 27, 2007, noted "Dravets [sic] syndrome" as the "Assessment" and classified the seizures as "symptomatic." Pet'r Ex. 13 at 27. Dr. Adriana Castrol, Madison's pediatrician, noted the diagnosis and assessed Madison with Dravet's on August 24, 2007, Pet'r Ex. 10 at 7, March 14, 2007, id. at 10, November 6, 2006, id. at 14, and August 4, 2006, id. at 17.[16]

Madison's 2006 school records also noted the diagnosis of DS and the consequences for Madison's cognition, development and behavior. Pet'r Ex. 12 at 14-17, 84, 89-93, 95; Pet'r Ex. 16 at 29.

### 3. Dravet's Syndrome

Dr. Gerald Raymond, the Secretary's expert, is a board certified specialist in pediatric neurology and genetics. Tr. II at 9. He is a professor of neurology at Johns Hopkins University School of Medicine and the chief of neurogenetics at the Kennedy-Krieger Institute. Tr. II at 6-7. His expert report explained the nature of Madison's genetic mutation and its effects. See Resp't Ex. RR.

[16] Madison's parents apparently avoided vaccinating her after her first seizure, and her medical records contain frequent references to possible DTaP reaction as the cause of her seizures. In most instances, it appears that the association between vaccination and Madison's neurological disorders was made by Petitioners, not by Madison's treating physicians. See, e.g., Petr Ex. 10 at 47 (Memo from pediatrician Adriana M. Castro: "Mrs. De Ribeaux, . . . We can give her a DT which has no pertussis (same for Gus) & is licensed under 7 yrs of age. After 7 they have an adult version of DT also without pertussis. . . . Let me know if you want to give it to them); Pet'r Ex. 11 at 9 (Family Wellness Center records indicating "Immunizations are not up to date due [to] being allergic to vaccination."). See Cedillo v. Sec'y of Dept of Health & Human Servs., 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), at *128, aff'd 89 Fed. Cl. 158 (2009), aff'd 617 F.3d 1328 (Fed. Cir. 2010) (finding letter to physician from parent seeking vaccination exemption not indicative of physician's belief in vaccine causation).

DS or Severe Myoclonic Epilepsy of Infancy (SMEI) was first identified in 1978 and is recognized as a distinct epilepsy syndrome. Resp't Ex. RR at 2. It usually presents in the first year of life. Id.

> Infants have normal development for the first months of life, but then develop seizures in a characteristic fashion. The first seizure is usually a generalized or unilateral tonic-clonic or clonic seizure which may be preceded by a fever. However, unlike simple febrile seizures, these first episodes are often prolonged and advance to status epilepticus.

Id. Affected individuals may thereafter manifest a variety of types of seizures, not associated with fever, which are refractory to therapy. Id.

After the first year of life, developmental delays appear in DS patients. "[M]ost children will have mental retardation and significant speech and language delays." Resp't Ex. RR at 2. In addition, the children commonly exhibit a specific pattern abnormal movement, termed ataxia. Id.

> After early prolonged febrile seizures, most patients experience multiple, intractable seizure types, especially clonic or hemiclonic convulsive seizures, but also myoclonic, absences, and focal seizures, often triggered by fever. Developmental skills are initially normal, cognitive stagnation or deterioration and behavioral problems become apparent from the second year of life. Ataxic gait, or motor awkwardness and hyperactivity, and a jerky movement pattern are also reported in many children.

Pet'r Ex. 60 at 1, Renzo Guerrini et al., Neuroimaging and Neuropathology of Dravet Syndrome, 52 (Suppl. 2) Epilepsia 30, 30 (2011) (citations omitted). About 30 years after the first clinical description of DS, scientists discovered a link between DS and mutations of the gene encoding the neuronal voltage-gated sodium channel alpha 1 subunit, called SCN1A. Resp't Ex. VV-16 - 4. According to Dr. Raymond, "a relatively high" percentage of mutations in SCN1A have been found in patients with DS. Resp't Ex. RR at 3.

Alterations in SCN1A affect the functioning of neurons in the central nervous system. Resp't Ex. RR at 3. The SCN1A gene encodes a portion of a membrane channel in neurons that control the transport of sodium molecules across cell membranes. Id. The flow of sodium molecules permits appropriate transmission of information from one cell to another. Id. Mutations in SCN1A affect cell function in various ways, depending on the particular mutation. Some mutations result in more severe disease than others. Resp't Ex. RR at 3-4.

The significance of the SCN1A gene has been demonstrated in laboratory experiments using mice that are missing the gene. The result is an animal that has spontaneous seizures (febrile and afebrile), ataxia, and premature death. Resp't Ex.

RR at 4. Seizures in these mice occur without "any bacterial, viral, or immune altering agent or precipitant, including immunizations." Id.

Mutations arising spontaneously in the SCN1A gene cause most cases of SMEI. Resp't Ex. RR at 5. Madison's alteration, characterized as a "missense" point mutation, substituted a single base pair of nucleotides in the gene, which resulted in the coding of a different amino acid from the normal one, leading to sodium channel dysfunction. Id. The precise location of Madison's point mutation is reported in the results of her genetic testing. Pet'r Ex. 15 at 8. "Other individuals with mutations in this region have SMEI." Resp't Ex. RR at 5.[17]

### C. Entitlement – Part I (Prima Facie Causation)

This section summarizes the proceedings leading up to Special Master Millman's entitlement decision. I review these proceedings to demonstrate that I considered all the evidence of record, at every stage of the litigation, before reaching my decision on causation by an unrelated factor.

#### 1. Petitioners' Experts' Testimony

Two medical experts testified for Petitioners. Dr. Tornatore is an associate professor of neurology at Georgetown University School of Medicine and serves as director of its neurology residency program. Tr. I at 12-13. He worked for six years at the National Institutes of Health (NIH), beginning in 1994, as a postdoctoral fellow studying viral pathogenesis in the pediatric brain. Id. at 12. "I spent quite a bit of time doing pediatric infectious disease type of research as well as pediatric, the overlay with pediatric immunology." Id. at 12-13. He also is director of the multiple sclerosis and autoimmune disorders clinic at Georgetown. Id. at 13. "[M]y predominant interest is in those patients who have autoimmune disorders, the majority of whom have MS, but we have a group of patients with vasculitis, who have myasthenia gravis, who have Guillain-Barré, who had CIDP, and I have a group of patients that we follow who were also [HIV] positive since that's our area of interest also." Id. at 13.

Dr. Tornatore is board certified in neurology. He is not board certified in genetics or pediatrics. Tr. II at 160-61; Pet'r Ex. 6 (Curriculum Vitae).

Dr. Tornatore testified that Madison had a poorly-functioning immune system and therefore an acute reaction to her vaccination, resulting in the initial seizure episode and all the neurological sequelae. Tr. I at 18, 26. He attributed the reaction to endotoxin in the DTaP vaccine. Id. at 26. This would be his conclusion, Dr. Tornatore stated, whether or not Madison also had Kawasaki disease, a rare syndrome of unknown

[17] At hearing, Dr. Raymond testified that he was unaware of another case in which the individual has exactly the same mutation found in Madison. This was not unusual, he testified. See Tr. II at 218-19 (some mutations are "private"). The location of Madison's mutation, however, was consistent with other cases of DS. Tr. II at 220.

etiology usually associated with vasculitis of the large coronary vessels and numerous other systemic signs, including fever. Id. at 34-35.

According to Dr. Tornatore, Madison's initial seizure resulted in "an area of the brain which is now a seizure focus, the nerves have been injured, it's like an electrical wire that is now short circuiting." Tr. I at 35. Madison's Kawasaki disease also was caused by the DTaP vaccine, Dr. Tornatore testified. Id. at 36-42. Dr. Tornatore recognized, however, that status epilepticus "would be atypical for Kawasaki." Id. at 57.

Dr. Joseph Bellanti is a professor of pediatrics in microbiology and immunology at Georgetown University School of Medicine. Tr. I at 136. He also directs the International Center for Interdisciplinary Studies of Immunology. Id. He testified that the vaccinations Madison received triggered an inflammatory response that cascaded into all the conditions from which she suffered. Tr. I at 145 ("[S]he had the convulsion due to the endotoxin, [which] could have sensitized her [to the Kawasaki disease] . . . ."); id. at 148 ("pro-inflammatory cytokines");[18] id. at 149 ("[W]e're dealing with a set of cascading events – hypogammaglobulinemia, subsequent infection, the viruses – but the main trigger that tipped the balance here by history, by the temporal relationship, based upon knowledge from both basic and clinical observations, was the DPT [sic] vaccine . . . ."); id. at 165 ("We don't really know what causes Kawasaki, but we know it is a vasculitis and we know that DPT can cause a vasculitis, and we know that vasculitis is more common in children with hypogammaglobulinemia . . . ."). Dr. Bellanti testified that Madison's initial fever on March 28, 2002, was due to her vaccinations. Tr. I at 170-71. Her subsequent fevers may have been due to vasculitis. Tr. I at 177.

### 2. The Secretary's Experts' Testimony

Dr. Russell Snyder is a neurologist in the Department of Neurology at the University of New Mexico School of Medicine, and is board certified in neurology, pediatrics, and pediatric neurology. Tr. I at 182-83. In addition to his background in the education of medical students, Dr. Snyder has an active practice in the field of child neurology and sees pediatric patients twice weekly. Tr. I at 183. Dr. Snyder testified that Madison's disorder could be explained completely by Kawasaki disease, which has been associated with enterovirus, an infectious disorder that Madison also had around the time of her vaccination. Tr. I at 184, 190-94. In opposition to Dr. Tornatore's testimony, Dr. Snyder testified that there was no evidence that Madison's initial seizure following vaccination resulted in brain injury. Tr. I at 186-87, 227. All her neurological tests following the first seizure were normal. Tr. I at 187. Dr. Snyder discounted the theory that Madison's hypogammaglobulinemia caused an unusual vaccine response; he stated that Madison's compromised immune status would have resulted in a diminished rather than exaggerated response to vaccination. Tr. I at 188. He opined that there was no known association between DTaP and Kawasaki disease. Tr. I at

[18] Cytokine is a generic term for non-antibody proteins released by one cell population on contact with specific antigen. Cytokines act as intercellular mediators, as in the generation of an immune response. Dorland's at 466.

196. Dr. Snyder testified that DTaP vaccination can cause febrile seizures but not chronic seizure disorders in children. Tr. I at 203-04.

Of some significance to the controversy now before me, Dr. Snyder, in the course of cross-examination, happened to discuss the known relationship between SCN1A gene mutations and DS. Tr. I at 204-206. Dr. Snyder described the symptoms of the genetic disorder resulting from the SCN1A mutation, noting that, "it usually begins with a febrile seizure," and then "they go on to have other febrile seizures and other forms of seizures that aren't febrile, and ultimately have developmental delay." Id. at 235-36.

Dr. Snyder noted that the SCN1A mutation does not require a triggering event to manifest its effects, and that children do not sometimes "grow out of it" in the absence of a triggering event, as suggested by Petitioners' counsel. Tr. I at 205-06. In fact, "There has been a lot of genetic testing for this abnormality, and it seems that practically [it] always manifest[s]. In other words, there aren't non-manifesting carriers of this genetic abnormality." Id. at 206. As a result, "I can't say every child, but almost every child with this gene develops the condition." Id. It has a trigger only in the sense that "something has to trigger everything[.]" Id. at 207. Thus, vaccination might lead to a fever that could cause an initial seizure in such a case. Id. at 210. The fever would be a trigger, but it would not be a "cause" of the child's neurological problems. Id. at 228. The "cause" would be "underlying genetic problems." Id. at 228-29, 231.[19] If Madison had a genetic disorder, Dr. Snyder's opinion would be the same: vaccination was not a causative factor in her condition. Id. at 235.

Rounding out the field of experts at the first entitlement hearing was Dr. Brian Ward, an infectious disease specialist from McGill University. Tr. I at 239-40. He testified that Madison's condition was caused by enterovirus. Id. at 241-43. In Dr. Ward's view, Madison's initial seizure was unrelated to her vaccination. "[A]ll infectious diseases have to start sometime. They usually manifest at some point, and my best guess is that her enterovirus manifested right around the time that she got the DTaP/Hib immunizations and that what we have here is a very unfortunate coincidence of timing." Id. at 245. Dr. Ward agreed that the vaccinations could have contributed to the fever, Id. at 246, but said they did not result in brain damage. Id. at 252. He expressed skepticism of the claim that DTaP could cause Kawasaki disease. Id. at 253. He also testified that Madison's persistent fevers in the months after her immunizations were not related to her vaccinations. Id. at 269. He stated that the enterovirus itself could explain Madison's fevers in 2002, as well as her "abnormal MRI" on April 30, 2003. Id. at 241-43, 270.

[19] Despite the apparent pertinence of these matters, see Tr. I at 235 ("The Court: Are you saying that Madison has a genetic defect but we don't know what it is?"), neither Petitioners (one of whom, Ms. Bursheim, participated in the hearing by telephone), nor their counsel (if he knew), informed the Court of Madison's genetic mutation or her December 2005 diagnosis of DS.

### 3. Special Master Millman's Decision

The special master concluded that "but for the acellular DPT and HiB vaccinations, Madison would not have had seizures and a seizure disorder." Deribeaux v. Sec'y of Dep't of Health & Human Servs., No. 05-306V, 2007 WL 4623461, at *36 (Fed. Cl. Spec. Mstr. Dec. 17, 2007). She cited 1997 decisions in which the special master held that "acellular DPT may cause a fever prompting a seizure followed by a seizure disorder." Id. at *28 (citing Noel v. Sec'y of Dep't of Health & Human Servs., No. 99-538V, 2004 WL 3049764, at *17 (Fed. Cl. Spec. Mstr. Dec. 14, 2004); McMurry v. Sec'y of Dep't of Health & Human Servs., No. 95–682V, 1997 WL 402407 (Fed. Cl. Spec. Mstr. June 27, 1997)). She also cited Shyface v. Sec'y of Dep't of Health & Human Servs., 165 F.3d 1344 (Fed. Cir. 1999), in which the Federal Circuit held that each of two factors (vaccine and infection) was substantial in causing a high fever and death; accordingly, petitioners were entitled to compensation. Deribeaux, 2007 WL 4623461, at *31.

> That [Madison] subsequently had Kawasaki disease (which the vaccines may have been substantial factors in causing together with her enterovirus infection) and a subclinical enterovirus infection does not remove Respondent's liability for compensating petitioners for all the damage to Madison which, from her subsequent MRIs, appear to come from gliosis or neuron death. Her Kawasaki disease gave her repetitive fevers, which prompted more (but not all) of Madison's seizures after her initial seizures. Secretary takes his victim as he finds her.

Id. at *36. The special master's conclusion rested on the impossibility of separating out "the effect of the enterovirus from the effects of the vaccines or the effect of the Kawasaki disease from the effects of the vaccines." Id. Special Master Millman's decision directed the parties to proceed to determine damages. Id.

### 4. Motion to Re-Open Based on Newly-Acquired Evidence

On March 6, 2008, three months after Special Master Millman's decision on entitlement, Petitioners filed Exhibits 10-16 in response to the Secretary's request for medical records for the purpose of determining an appropriate award of damages. See Resp't's Post-Hr'g Br. Issue of Entitlement 2-3, June 14, 2010, ECF No. 81. These documents revealed for the first time in this proceeding that Madison had been diagnosed early in 2006 with DS, and that her treating physicians recognized that DS was the cause of her neurological disorders. In response to this new evidence, the Secretary moved to set aside Special Master Millman's decision on entitlement and re-open the entitlement phase of the case. Id. at 3. See Mot. to Reopen, Jan. 16, 2009, ECF No. 70. Petitioners did not formally oppose the motion. See Pet'r's Resp. to Mot. to Reopen, Jan. 30, 2009, ECF No. 71.

On January 9, 2009, Special Master Millman ordered the parties to file supplemental reports on the issue of DS and its impact. Scheduling Order, Jan. 9,

2009, ECF No. 72. Dr. Tornatore filed his supplemental report on June 11, 2009, which consisted of one paragraph, in which he stated, "My opinion as outlined in my reports and at the hearing remain unchanged." Pet'r Ex. 19 at 1. The Secretary filed the report of Dr. Raymond, which has been described above. Dr. Raymond opined that the sole cause of Madison's neurological disorders was her genetic mutation, and that vaccination neither caused nor aggravated her condition. Resp't Ex. RR at 6.

A supplemental hearing was required to afford the parties a full and fair opportunity to present evidence and arguments concerning Madison's DS and SCN1A mutation.[20]

## D. Entitlement – Part II (Alternative Factor)

### 1. Medical Literature

#### a. The Secretary's Medical Literature [21]

The Secretary submitted several articles from peer-reviewed journals establishing the link between SCN1A mutations and DS. These articles also pertain to many of the points raised by Petitioners against the proposition that genetic mutation, rather than vaccination, caused Madison's condition. A sampling of the most pertinent articles appears below.

-- Lieve Claes et al., De Novo Mutations in the Sodium-Channel Gene SCN1A Cause Severe Myoclonic Epilepsy of Infancy, 68 Am. J. Hum. Genet. 1327 (2001). The authors described DS as it was first identified in 1978. "Early manifestations of the disease are tonic, clonic, and tonic-clonic seizures that occur within the first year of life. These seizures are often prolonged, generalized, and associated with fever." Resp't Ex. VV-1 - 1. The authors continued, "Later in life, patients with SMEI have afebrile seizures, including myoclonic, tonic-clonic, absence, and simple and complex partial seizures." Id. The authors noted that "Early psychomotor and speech development is normal, but developmental stagnation occurs during the second year of life." Id. In addition, "Patients often become ataxic, and speech development is delayed. In general, SMEI is very resistant to all forms of pharmacotherapy." Id.

The authors of the Claes article studied seven patients, their unaffected parents, and 92 healthy control subjects selected at random. Resp't Ex. VV-1 at 1. They described in detail the organization of the SCN1A gene and the methodology for identifying mutations. Id. at 1-3. In each patient with DS, they observed a single aberrant SCN1A fragment. Id. at 3. Each mutation was different. Id. Among the seven

[20] A hearing was twice scheduled and then canceled at Petitioners' request. When Petitioners requested a third continuance, to "sometime" in the fall of 2011, I ordered the parties to find a convenient date by the first week of July 2011 on which the hearing could take place. See Scheduling Order, May 16, 2011, ECF No. 89.

[21] Because it was Secretary's burden to demonstrate alternative factor causation, her evidence on this issue is considered first.

patients, the age at onset was two to six months. Id. at 4. The earliest seizures were generalized and in four of the seven cases they were associated with fever. Id. Subsequently, the individuals suffered a variety of seizures, which were resistant to therapy in all cases. Id. "All patients became mentally retarded, and five patients have ataxia." Id.

The authors concluded that the presence of a heterozygous mutation in the SCN1A gene, absent in the parents, provided "substantial evidence that (1) SMEI has a genetic etiology and (2) de novo mutations in the SCN1A are probably a major cause of SMEI." Resp't Ex. VV-1 at 4.[22] The authors attributed the difference in the nature and severity of the disorder to variations in SCN1A mutations. Id. In a later study, they noted that "most mutations are missense mutations," demonstrating that "de novo mutations in SCN1A are a major cause of isolated SMEI." Resp't Ex. VV-7 - 1, Lieve Claes et al., De Novo SCN1A Mutations Are a Major Cause of Severe Myoclonic Epilepsy of Infancy, 21 Hum. Mutat. 615 (2003).

-- Carla Marini et al., SCN1A Duplication and Deletions Detected in Dravet Syndrome: Implications for Molecular Diagnosis, 50 Epilepsia 1670 (2009). The authors discussed their study of the SCN1A mutation, which was described as "currently the most clinically relevant epilepsy gene[,]" predominantly associated with DS. Resp't Ex. VV-2 - 2.

-- Another study noted that "Heterozygous mutations in SCN1A, the gene encoding the voltage-gated neuronal sodium channel alpha 1 subunit . . . , are a major cause of Dravet syndrome." Resp't Ex. VV-3 - 2, Christel Depienne et al., Spectrum of SCN1A Gene Mutations Associated With Dravet Syndrome: Analysis of 333 Patients, 46 J. Med. Genet. 183, 183 (2009). The authors noted that "All types of mutations in SCN1A are observed in patients with SMEI, including missense mutations and all types of truncating mutations." Id. at 2-3, 6-7. The study blamed loss of function of the mutated gene for SMEI, "as confirmed by the recent development of knock-out and knock-in mouse models. . . ." Id. at 2.

-- Christoph Lossin, A Catalog of SCN1A Variants, 31 Brain & Develop.114, 114 (2009). Lossin explained that SMEI is caused by a "channelopathy" that creates "excitatory havoc" in brain cells. Resp't Ex. VV-4 - 1. "One isoform in particular, [the gene SCN1A], appears to be an epilepsy *superculprit*," resulting in a variety of phenotypes "ranging from benign to extremely severe." Id. (emphasis in original). The article explained that voltage-gated sodium channels are responsible for action-potential initiation in neuronal cells. "Any alteration of the finely tuned kinetics that determine the gating of these channels can have decisive impact on cellular excitability," and hence on cell function. Id. at 2-3. The review cited Claes and noted the wide array of epilepsies and other abnormalities that have been associated with mutations in SCN1A. Id. at 3.

[22] Heterozygous means having different alleles at one or more corresponding chromosomal loci. American Heritage Dictionary at 824. An allele is one member of a pair or series of genes that occupy a specific position on a specific chromosome. Id. at 46.

-- John Gargus & Anne Tournay, Novel Mutation Confirms Seizure Locus SCN1A is Also Familial Hemiplegic Migraine Locus FHM3, 37 Pediatr. Neurol. 407, 407-08 (2007). The authors noted that SCN1A "is a well-recognized target of mutations underlying a spectrum of epilepsy syndromes," and such mutations "have been unambiguously shown to be pathogenic." Resp't Ex. VV-5 - 1-2.[23]

-- John Mulley et al., SCN1A Mutations and Epilepsy, 25 Hum. Mutat. 535 (2005). This article discussed variations in the type and severity of disorders caused by various SCN1A mutations. Among the criteria for determining pathogenicity of a mutation is whether the mutation "changes an amino acid at a position in the protein conserved through evolution (in the same sodium channel across species) . . . ." Resp't Ex. VV-8 - 5. Such a mutation is considered strong proof of causation. Id. De novo mutation "is even stronger proof." Id.

-- John Oakley et al., Temperature- and Age-Dependent Seizures in a Mouse Model of Severe Myoclonic Epilepsy in Infancy, 106 Proc. Nat'l. Acad. Sci. 3994 (2009). This study reported that mice with DS caused by deletion of the SCN1A gene revealed "a close correspondence between human and mouse SMEI" with regard to temperature sensitivity and age dependence. Resp't Ex. VV-9 - 1. The research "demonstrate[s] that temperature elevation alone is sufficient to reliably induce seizures" in mice with SMEI, and "therefore implicates a temperature-dependent mechanism, rather than an inflammatory mechanism, in the genesis of febrile seizures . . . ." Id. at 2.

This article noted that infants with DS "frequently have febrile seizures before developing spontaneous seizures." Id. at 3. According to the authors, "This suggests a developmentally regulated seizure susceptibility in which initial seizures are usually realized only with an additional provoking factor such as elevated temperature." Id. There is "evidence that hot baths alone are sufficient to provoke febrile seizures" in children with DS. Id. at 4. "[T]hermal sensitivity," the authors conclude, "is a fundamental feature of hyperexcitability caused by loss of [voltage-gated sodium] channels in the early phase of SMEI." Id. The study noted the "surprising fidelity" of the disease pattern in humans and the studied mice. Id. at 5.

-- Kazue Kimura et al., A Missense Mutation in SCN1A in Brothers With Severe Myoclonic Epilepsy in Infancy (SMEI) Inherited From a Father With Febrile Seizures, 27 Brain & Develop. 424 (2005). The researchers studied two brothers with DS who demonstrated somewhat different clinical features of the disorder. Resp't Ex. VV-10 - 5-6. The authors stated, "Our results correspond with previous reports suggesting that genetic factors other than SCN1A mutations and/or some environmental factors may be important in modifying SMEI phenotypes." Id. at 6.

-- Several studies suggested that "somatic mosaicism may account for variable expressivity of SCN1A mutations in SMEI families . . . ." Resp't Ex. VV-11 - 7, Maria Mancardi et al., Familial Occurrence of Febrile Seizures and Epilepsy in Severe Myoclonic Epilepsy of Infancy (SMEI) Patients With SCN1A Mutations, 47 Epilepsia

[23] This article also was submitted by Petitioners. See Pet'r Ex. 50.

1629, 1635 (2006). This "would suggest that SMEI is a monogenic rather than a multifactorial condition." Id.[24] To the same effect, see Resp't Ex. VV-13 - 1, Masafumi Morimoto et al., SCN1A Mutation Mosaicism in a Family with Severe Myoclonic Epilepsy in Infancy, 47 Epilepsia 1732 (2006).

-- Samuel Berkovic et al., De-novo Mutations of the Sodium Channel Gene SCN1A in Alleged Vaccine Encephalopathy: A Retrospective Study, 5 Lancet Neurol. 488 (2006), addressed directly whether the sudden occurrence of seizures and developmental regression after vaccination in previously healthy infants indicated a causal link. Resp't Ex. VV-14 - 1. Noting the similarity between some reports of vaccine encephalopathy and DS, the authors studied 14 cases of epileptic encephalopathy adjudged to have been caused by vaccines. "Molecular genetic analysis showed heterozygous mutations of SCN1A in 11 of 14 cases." Id. at 2. In nine of the 11 cases, the mutations arose de novo. Id. at 3. The same study noted the argument that vaccination might be a "trigger" for the encephalopathy, "perhaps via fever or an immune mechanism." Id. at 4. But the authors concluded that "vaccination as a significant trigger for the encephalopathy is unlikely" because (1) although vaccines might trigger seizures, "there is no evidence of long-term adverse outcomes[;]" (2) a minority of patients had documented fever with their first seizures, "which indicates that fever is not essential[;]" and (3) "neuroimaging data showed no evidence of an inflammatory or destructive process." Id. The authors also noted that testing of hundreds of healthy individuals did not reveal the genetic mutations found in individuals with DS; moreover, individuals with SCN1A mutations seemed to develop DS whether or not they were immunized in the first year of life. Id. "The identification of a genetic cause of encephalopathy in a particular child should finally put to rest the case for vaccination being the primary cause." Id.

-- Andrew Excayg & Alan Goldin, Sodium Channel SCN1A and Epilepsy: Mutations and Mechanisms, 51 Epilepsia 1650 (2010). This article described the primary effect of mutations in the SCN1A gene as decreasing the activity of GABAergic inhibitory neurons. Resp't Ex. VV-15 - 1.[25] The article noted that a "large number" of SCN1A missense mutations have been identified in DS patients, and that most arise de novo in the affected child. Id. at 3. The result of the mutation likely is to abolish sodium channel function. Id. Additionally, this article discussed two experiments that reproduced the human disorder in mice with altered SCN1A genes. Id. at 5-7. The results suggested a mechanism by which the mutation actually produces seizures. Id. at 7.

-- Carla Marini et al., The Genetics of Dravet Syndrome, 52 Epilepsia 24 (2011), noted that, at present, more than 500 mutations of the SCN1A gene have been

[24] Monogenic is defined as pertaining to or influenced by a single gene. Dorland's at 1177. "Multifactorial" in genetics means arising as the result of the interaction of several genes and usually, to some extent, of non-genetic factors. Id. at 1187.

[25] Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the brain. Dorland's at 62. GABAergic means transmitting or secreting gamma-aminobutyric acid; said of nerve fibers, synapses, and other neural structures. Id. at 753.

associated with DS. Resp't Ex. VV-16 - 1. This article also explained that some patients with a clinical diagnosis of DS may test negative for SCN1A sequence-based mutations but may nevertheless have abnormalities in that gene. Id. at 2. The article noted that some individuals suffer more severe disability from similar mutations, "suggesting that modifier genes, the genetic background, and/or environmental factors may also play a role in some patients, and thus DS may sometimes follow a complex model of inheritance." Id. at 3. Marini stated that "reduced firing of inhibitory neurons and compromised network inhibition could be the major pathophysiologic mechanism causing SCN1A-related genetic epilepsies." Id. at 4. The article concluded, "About 30 years after the first clinical description of the distinctive epilepsy syndrome of DS, the genetic etiology of 70-80% of patients has been solved." Id.

-- Anne McIntosh et al., Effects of Vaccination on Onset and Outcome of Dravet Syndrome: A Retrospective Study, 9 Lancet Neurol. 592 (2010).[26] This article examined the effects of vaccination on onset and outcome of DS. Resp't Ex. VV-17. The study, which was not controlled, 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. at 1. The authors advised, however, that "vaccination should not be withheld from children with SCN1A mutations because we found no evidence that vaccinations before or after disease onset affect outcome." Id.

This study is of particular interest because the authors set out to determine precisely the question that occupies the parties in this case, whether there is reliable evidence that vaccination causes neurological damage in children with DS. The authors examined (1) whether there "was a genuine temporal association of seizure onset with vaccination," and (2) "whether patients who had onset of Dravet syndrome shortly after vaccination had any specific clinical, molecular, or outcome differences" to differentiate their cases from those of other patients with DS. Resp't Ex. VV-17 at 2.

The authors divided the studied group into those whose DS was noted within two days following vaccination (the vaccination-proximate group), and those whose DS was noted two days or more after vaccination or before vaccination (vaccination-distant group). Resp't Ex. VV-17 at 1. The study showed that about one-third of patients with DS had disease onset less than 2 days after vaccination, "and the mean age at onset in these patients was significantly lower than that of patients whose disease onset was vaccination-distant." Id. at 5. "The mean age at disease onset was 7.8 weeks earlier in the vaccination-proximate group than in the vaccination-distant group . . . [.]" Id.

"[A]ll other clinical and outcome measures did not differ between groups." Resp't Ex. VV-17 at 5. Accordingly, the authors concluded that, "although vaccination might sometimes seem to trigger the onset of Dravet syndrome, there is no evidence that patients in the vaccination-proximate group had a different disorder from those in the vaccination-distant group." Id. Of particular relevance here, the authors stated that "the similarity in clinical and outcome measures between patients in the vaccination-

[26] Petitioners submitted the same article. See Pet'r Ex. 48.

proximate group and those in the vaccination-distant group is not consistent with vaccination itself affecting the severity" of DS. Id. at 5-6. The authors noted the "environmental effect" of vaccination temporally shifting the age at onset of DS, and suggested that further research might be useful "to formally assess and examine the basis of such an interaction." Id. at 6. They concluded, however, that there is "no rational basis" for withholding DTP immunization "for fear of causing Dravet syndrome or injuring the brain by a direct or presumed immune-mediated mechanism." Id.

There was a subsidiary point of interest in the McIntosh article. In determining which individuals with missense mutations in the SCN1A gene to include in their study, the authors identified as "causative" of DS only those mutations that had previously been reported in DS cases, or that "predict a non-conservative [missense] amino acid change in an evolutionarily conserved residue and are absent from single nucleotide polymorphism databases of healthy individuals." Resp't Ex. VV-17 at 2.[27] The authors noted that other missense mutations, not meeting these criteria, caused milder epilepsy syndromes and, rarely, some missense variants occurred in healthy individuals. Id. at 2.

### b. Petitioners' Medical Literature

I reviewed all of Petitioners' medical literature in the entire record. I summarize below the items most pertinent to the question of causation by an alternative factor, DS.

-- Gazia Annesi et al., Two Novel SCN1A Missense Mutations in Generalized Epilepsy with Febrile Seizures Plus, 44 Epilepisa 1257 (2003), reported on nine Italian families with generalized epilepsy with febrile seizures plus (GEFS+), in which two had mutations of the SCN1A gene.[28] Pet'r Ex. 26. The results of the study "confirm that missense mutations in the SCN1A gene are the major causes of GEFS+." Id. at 1. One of the individuals in the study had DS. Id. The authors concluded, "these findings greatly strengthen the view that SMEI represents the very severe end of the spectrum within the GEFS+ phenotype, rather than being considered a distinct entity, outside the GEFS+ spectrum, that is related to de novo frameshift and nonsense mutations." Id. at 2.

-- Berten Ceulemans et al., Clinical Correlations of Mutations in the SCN1A Gene: From Febrile Seizures to Severe Myoclonic Epilepsy in Infancy, 30 Pediatr. Neurol. 236, 236 (2004), described the history of DS and its classic characteristics. Pet'r Ex. 27 at 2. The authors reviewed the published cases of mutations in SCN1A at that time as well as four additional cases. They correlated the severity of the disorders with the type of mutations and found a range, from "febrile seizures, febrile seizures

[27] These criteria fit Madison's case, according to Dr. Raymond. See Tr. II at 34 ("But if it has been shown to be a non-conservative mutation, it's going to have a loss of function."); Resp't Ex. UU at 17-18.

[28] GEFS+ "is a form of an SCN1A alteration that actually does run in families from generation to generation, where they have febrile seizures, may have some other seizure types, but is not as severe as Dravet's syndrome." Tr. II at 46.

plus, over a milder type to the classical form of severe myoclonic epilepsy in infancy, and confirmed the clinical experience that severe myoclonic epilepsy in infancy is the most severe form on this spectrum." Id. The authors concluded that "The first clinical expression of a mutation in SCN1A is recurrent, often prolonged, seizures provoked by fever in infancy." According to the authors, "[a]n even more specific symptom, when present, is a fever-associated status epilepticus before 1 year of age." Id. at 6. Further, the authors noted "a high correlation between classical SMEI [DS] and mutations in SCN1A." Id. They stated that the effect of different "missense" mutations in SCN1A was difficult to predict. Id. at 8. The authors noted that they could not fully explain the difference in phenotype between members of GEFS+ families. Id. In those cases, "Influence of other genes, environmental factors, or evolution of the epilepsy itself . . . may in part explain the phenotype." Id. The authors advised, "In clinical practice, mutations in SCN1A should be suspected in every child with a long-lasting, fever-provoked seizure." Id.

-- Tateki Fujiwara, Clinical Spectrum of Mutations in SCN1A Gene: Severe Myoclonic Epilepsy in Infancy and Related Epilepsies, 70 Epilepsy Res. 223, 224 (2006), stated that "the concept that SCN1A is the major gene responsible for SMEI [is] established." Pet'r Ex. 28 at 3. The article suggested that in approximately 20% of the patients who fulfilled the diagnostic criteria for SMEI but did not have abnormalities in the SCN1A gene, their condition might be explained by other genetic mutations. Id. at 4. Based on the study of monozygotic twins with DS, the authors opined "that gene mutation is associated not only with the onset of SMEI but also with the long-term clinical course." Id. The article explored the difficulty of making an exact correlation between genotype and phenotype in these cases, but noted that earlier "while missense mutations were observed exclusively in GEFS+ cases that tend to be milder," such mutations "were subsequently detected even in severe epilepsies such as SMEI . . . ." Id. at 5. The article also noted that "SMEI and GEFS+ may represent a continuum." Id. at 6.

-- Rima Nabbout et al., Spectrum of SCN1A Mutations in Severe Myoclonic Epilepsy of Infancy, 60 Neurology 1961 (2003). The researchers studied the spectrum of SCN1A mutations in DS, concluding that the pathogenic role of single amino acid substitutions was difficult to establish, but that nevertheless, "most evolutionarily conserved amino acids . . . are probably fundamental to protein function." Pet'r Ex. 29 at 6. Despite "the difficulty of predicting the SMEI phenotype based on the finding of SCN1A mutation . . . [,] a clinical picture of SMEI can be suggested even in the first year of life." Id. at 7. The study suggested that "an additional genetic predisposition is likely to act with SCN1A mutations to determine the disease." Id. at 8.

-- Manuel Nieto-Barrera, Severe Myoclonic Epilepsy in Infancy. An Analytical Epidemiological Study, 30 Rev. Neurol. 620 (2000). This article, published in 2000, apparently without knowledge of the link between SCN1A mutations and DS, repeatedly characterized SMEI as a rare disorder of "unknown" etiology. See, e.g., Pet'r Ex. 31 at 1, 5. Nieto-Barrera analyzed the records of 28 children with DS, taking into consideration the following data in trying to determine a cause for DS:

> sex; age of parents; order of birth; prenatal records; infections; exposure to toxins (tobacco, alcohol, drugs etc.); perinatal backgrounds; gestational age, childbirth, weight at birth; newborn period and psychomotor development until the first convulsion; rural habitat or urban and social class; family records of epilepsy with or without febrile seizures; causes or circumstances of first convulsion.

Id. at 2. The author found "no prenatal cause of interest" and no association with class status or rural/urban environment. Id. at 3-4. Although not listed as one of his analytical criteria, Nieto-Barrera nevertheless reported that in 16 patients, the first seizure was related to a DTP vaccination. Id. at 5. "Our study highlights," he stated, "the high frequency with which there is a relationship to the first convulsion with the DTP vaccination . . . a fact that we consider, with discreet reservations, something more than a coincidence." Id. at 6. He noted that, "The relationship among the DTP vaccine and convulsions have [sic] been widely discussed." Id.[29] He described a case of DS following DTP and oral polio vaccinations, leading to sudden death at 19 months of age. Id. "In the absence of autoimmune or inflammatory findings [discovered during autopsy] it was suggested that the vaccine could have acted as the leading factor." Id. He posited that the greatest incidence of post-DTP seizures occurs after the second dose "as a result of prior sensitization produced by the first dose," id. at 6, and concluded that:

> a constitutional factor, or a conditional genetic predisposition to seizures or with relation to immune disfunction [sic], or multifocal cortical microdisgenesis or other minimal structural alterations probably exists in the pathogenesis of SMEI, and that clinical manifestation[s] are triggered by factors that are probably toxic-allergic, therefore, the high incidence of post-vaccine seizures as the first clinical manifestation.

Id. at 7.

-- Moncef Yakoub et al., Early Diagnosis of Severe Myoclonic Epilepsy in Infancy, 14 Brain & Develop. 299 (1992), noted the diagnostic criteria that permitted a reliable diagnosis of DS within the first year of life. Pet'r Ex. 32. The study discussed various aspects of the disorder, observing that fever "was an evident triggering factor in all cases" for seizures in patients with DS, "often [with] only a moderate increase in temperature." Id. at 3. Additionally, photic stimulation, cold water, and emotional situations, were also "provocative conditions." Id.

-- An "Opinion" letter from two psychologists promoted "opportunities for collaboration between experimental neuroscience and research on gene-environment interactions" in order to "solve the biggest mystery of human psychopathology: how does an environmental factor, external to the person, get inside the nervous system and alter its elements to generate the symptoms of a disordered mind?" Petr's Ex. 35 at 1,

[29] This article was imperfectly translated from the original Spanish.

Avshalom Caspi & Terrie Moffitt, Gene-Environment Interactions in Psychiatry: Joining Forces With Neuroscience, 7 Neuroscience 583 (2006). This article did not focus on DS. The letter speculated on environmental factors affecting a multitude of human ailments, but not epilepsy. See id. at 2 (mentioning substance-use disorders, antisocial disorders, depression, schizophrenia-spectrum disorders, Alzheimer's-type dementia, ADHD, cancer, diabetes, cardiovascular disease, immune/infectious and respiratory diseases). The opinion letter represented a frank effort to rehabilitate the "ignoble reputation" of "psychiatric genetics," see id. at 4, and did not purport to be an objective, scientific study.

-- Elena Gennaro et al., Familial Severe Myoclonic Epilepsy of Infancy: Truncation of Nav1.1 and Genetic Heterogeneity, 5 Epileptic Disorders 21 (2003), discussed DS as a severe disorder on a "wide spectrum of clinical phenotypes." Pet'r. Ex. 38 at 1. The thrust of the article was that "making genotype-phenotype correlations" based on SCN1A polymorphisms is "difficult." Id. at 3. "SCN1A mutations probably confer a predisposition to seizures, frequently manifesting with febrile episodes, and other alleles could be necessary to develop more complex epileptic phenotypes." Id.

-- Dennis Dlugos et al., Novel De Novo Mutation of a Conserved SCN1A Amino-Acid Residue (R1596), 37 Pediatr. Neurol. 303 (2007), reported on a patient with a de novo missense SCN1A mutation. Pet'r. Ex. 39. The individual was diagnosed within the spectrum of generalized epilepsy with febrile seizure plus (GEFS+). The article noted, "There are no absolute criteria yet established for distinguishing disease-associated mutations from susceptibility alleles from benign polymorphisms." Id. at 2. The article noted the published criteria for making such distinctions.

-- Christel Depienne et al., Spectrum of SCN1A Gene Mutations Associated With Dravet Syndrome: Analysis of 333 Patients, 46 J. Med. Genet. 183 (2009) (citations are to an advance version of the article originally published online Nov. 13, 2008, J. Med. Genet. doi:10.1136/jmg.2008.062323, available at http://www.jmg.bmj.com).[30] The authors reported on the "mutation spectrum" of 333 patients with DS. Pet'r Ex. 40 at 3. SCN1A point mutations were identified in 228 patients. Id. The study reported that, "Loss of function of the mutated allele is likely responsible for SMEI, as confirmed by the recent development of knock-out and knock-in mouse models, whereas another mechanism could lead to GEFS+." Id. at 4.[31] In the individuals studied, "Point mutations leading theoretically to missense amino-acids substitutions were the most frequent mutation type, encountered in 42% of the patients (96/228)." Id. at 6. The mutation occurred de novo in 133 cases out of 149 patients (89%) where both parents were available for genetic analysis. Id. at 7.

[30] The Secretary submitted the same study. See Resp't Ex. VV-3.

[31] The study noted that, "Core features required for classification as classical Dravet syndrome were defined as following: normal cognitive and motor development previous to seizures onset, onset of the seizures before one year, seizures mainly triggered by fever, long-lasting seizures (>15 min, that might evolve to *status epilepticus*), later occurrence of various seizures types (febrile and afebrile) and later cognitive regression." Pet'r Ex. 40 at 5.

-- Thomas Rhodes et al., Noninactivating Voltage-Gated Sodium Channels in Severe Myoclonic Epilepsy of Infancy, 101 Proc. Nat'l. Acad. Sci. 11147 (2004). This article described different outcomes in patients with SCN1A mutations, concluding that "a complex relationship exists between phenotype and aberrant sodium channel function in these inherited epilepsies." Pet'r Ex. 41 at 1. The data from the study suggested "that other genetic, developmental or environmental factors may interact with the biophysical defect to dictate the final clinical expression of neuronal sodium channelopathies." Id. The authors recognized as speculative the possibility that "certain individuals in the population [could] be especially vulnerable to seizure-induced neuronal injury" and stated that further analysis was warranted. Id. at 5. The article did not identify vaccines as possible factors influencing the severity of epileptic disorders resulting from SCN1A mutations.

-- Erick Sell & Berge Minassian, Demystifying Vaccination-Associated Encephalopathy, 5 Lancet Neurol. 465 (2006), which appeared to be another opinion letter, noted the "wonderful recent interplay between advances in the genetics and the phenomenology of disease: crystallisation of the SMEI phenotype and advances in genetic methods allowed identification of the SMEI gene, SCN1A." Pet'r Ex. 42 at 1. The authors asked whether "the SCN1A mutation [is] a predisposing factor waiting to be triggered by fever or other stress" and guessed "probably so" based on the article by Neito-Barrera cited above. Id. at 2. No science, only opinion, is presented in this publication.

-- An announcement from a drug company concerned its licensing of genetic tests for DS. Pet'r Ex. 44, Press Release, Bionomics Limited, Bionomics Licensee Labcorp Launches Genetic Test For Epilepsy (June 8, 2006).

-- Juan Caraballo et al., Dravet Syndrome: A Study of 53 Patients, 70S Epilepsy Res. S231 (2006), reported on a study of 53 patients with DS. Pet'r Ex. 45. The article noted, "The onset of febrile seizures or seizures related to infectious disease or vaccination that are focal or generalized, prolonged in time, occurring in the first year of life, is especially suggestive of DS." Pet'r Ex. 45 at 5. The article concluded by noting that "An ion-channel disorder could explain the association between DS and paroxysmal diskynesias [sic]." Id. at 6.

-- A chapter from a 2005 textbook on epileptic disorders focused on febrile seizures. Pet'r Ex. 46, Epileptic Syndromes in Infancy, Childhood and Adolescence 159 (Joseph Rogers et al. eds., 4th ed. 2005). At the outset, the authors noted that "two epileptic syndromes may be confused with febrile seizures," Dravet's syndrome (to which the textbook devotes a separate chapter), and GEFS+. Id. at 4. "In Dravet's Syndrome prolonged partial febrile seizures in the first year of life are followed by devastating intractable epilepsy and mental handicap. This disorder is fortunately quite rare and will not be considered further[,]" the authors stated. Id. The chapter then sets forth extensive information on various aspects of childhood febrile seizures, noting that the "vast majority" of children who have a complex febrile seizure do not develop epilepsy. Id. at 6. The authors pointed out that, "[t]wo massive febrile seizure cohorts

have proven that febrile seizures are benign." Id. at 10. In addition, the authors noted that the "etiology of febrile seizures is unknown but there is evidence for an important genetic influence." Id. The authors also stated,

> Seizures occurring soon after immunization with whole cell [DPT] and measles vaccines should not be regarded as a direct adverse effect of the vaccine. Such seizures are believed to be 'ordinary febrile seizures' triggered by fever induced by the vaccine. Their subsequent clinical course is identical to other febrile seizures, with no increased risk for subsequent afebrile seizures or abnormal neurologic development.

Id. at 5 (citations omitted).

-- A marketing pamphlet produced by a manufacturer concerned an SCN1A diagnostic test. Pet'r Ex. 52, Genetic Technologies Corp., SCN1A Epilepsy Gene Test, (2005).

-- A letter commented on the McIntosh article discussed above. Pet'r Ex. 54, Yuval Shafrir, Vaccination and Dravet Syndrome, 9 Lancet Neurol. 1147 (2010). The letter branded as "premature and maybe even dangerous" the conclusion in the McIntosh article that there is no data to justify withholding vaccination from children with "severe" SCN1A mutations. Id. at 2. Dr. Shafrir asserted that McIntosh "ignores the tendency towards severe intellectual disability in the vaccination-proximate group[.]" Id. Dr. Shafrir also asserted that, "Other channelopathies have also shown age-dependent vulnerability." Id. He posited that "seizure in the neonatal and infant brain might be more harmful developmentally than are seizures at an older age." Id. He suggested screening all newborns for SCN1A mutations in advance of vaccination, postponing vaccination or using prophylactic antiepileptic treatments. Id.

The authors of the McIntosh article replied to Dr. Shafrir. Pet'r Ex. 54 at 2. Among other points, the authors stated that "post-hoc analysis for severe disability versus all other cases did not reveal an effect" on severity of intellectual outcome as between vaccine-proximate and vaccine-distant patients. Id. at 2. "[P]erhaps our best evidence against his assertion is our data for children vaccinated after disorder onset, in whom no effect or negative trends regarding regression or intellectual outcome were seen." Id. They noted as "very unlikely," the suggestion that some asymptomatic individuals "escape" developing DS, despite having a deleterious mutation, because, "The missense mutations and mutations resulting in protein truncation that are seen in children with Dravet syndrome have not been found in healthy controls." Id. at 3.

-- Lata Vadlamudi et al., Timing of De Novo Mutagenesis – A Twin Study of Sodium-Channel Mutations, 363 N. Engl. J. Med. 1335 (2010), presented a study to determine the point during embryonic development when mutations of the SCN1A gene occur. Pet'r Ex. 55. The study noted that patients with DS who have heterozygous mutations in the SCN1A gene usually do not have siblings or parents who are affected by the disorder. This is because the mutations in 95% of these cases arose de novo.

Id. at 2. The absence of mutations in parental DNA "led to the inference that the usual mechanism" by which the mutation occurred "involves a spontaneous mutation in SCN1A in parental gonadal tissue (i.e., testicular or ovarian cells)." Id. at 1-2.

The authors examined embryologic tissue lineages in a monozygous pair of twins who were discordant for DS, that is, one twin had a mutation that the other twin did not have. Pet'r Ex. 55 at 2. They concluded that, since the mutation was found in all cell lines from different tissues in the affected individual but not in her twin, "the de novo mutation probably occurred in the premorula embryo, most likely at the two-cell stage." Id. at 5-6 and Figure 2. Such findings, the authors noted, are useful for purposes of genetic counseling. Id. at 6. The Vadlamudi article illuminated a concept that is pertinent to understanding the typical lack of an "inheritance pattern" in DS. That is the concept of "mosaicism," which is "the presence of two genetically different cell lines arising after fertilization, and it informs the timing of postzygotic mutagenesis." Id. at 5. According to this article, there are two types, somatic and germ-line mosaicism. Id. This concept explains cases in which mildly or unaffected parents engender offspring with DS. Id.

-- Louise Harkin et al., The Spectrum of SCN1A-Related Infantile Epileptic Encephalopathies, 130 Brain 843 (2007). This article explored the phenotypic variability associated with SCN1A mutations. Pet'r Ex. 56. The article reviewed individuals identified as suffering from epileptic encephalopathies and noted a high correlation with SCN1A mutations. Id. at 4. The article described different types of mutations that give rise to the variety of conditions discussed. Id. at 4-6. The article asserted, "Recently we showed that so-called 'vaccine encephalopathy' should be regarded as SMEI/SMEB on clinical and molecular grounds." Id. at 6. It also noted that while "SCN1A was originally associated with a small proportion of patients with the mild phenotypes characteristically seen in the GEFS+ syndrome, mutations within this gene have been identified far more often in patients with more severe forms of epilepsy." Id. (citations omitted). The authors' most recent study of the role of SCN1A mutations in epileptic encephalopathies beginning in the first year of life had expanded the phenotypic spectrum further. Id. at 9. The article noted that "SCN1A is the first gene shown to have a role in epilepsies previously regarded as cryptogenic," i.e., of unknown etiology. Id.

### 2. Hearing on June 28, 2011

As noted above, consistent with the statutory allocation of the burden of proof to the Secretary to demonstrate an alternative causative factor, the usual order of presentation of testimony was reversed at the second hearing on entitlement.

#### a. The Secretary's Expert

#### Dr. Raymond's Report

According to Dr. Raymond, Madison's medical condition met the clinical criteria for DS. Resp't Ex. RR at 2. Because Madison's condition was consistent with DS, Dr.

Raymond opined that it was unnecessary to look further for explanations of her seizures. Resp't Ex. RR at 5-6. "[I]ndividuals with this condition are exquisitely sensitive to elevated temperatures from whatever the cause and many individuals with this condition have been misdiagnosed as having encephalopathy secondary to immunization[,]" he reported. Resp't Ex. RR at 5; see Resp't Ex. VV-14 at 1 (Berkovic). Whether or not Madison may have had concurrent conditions, such as immune deficiency, or a "cryptic vasculitis of the nervous system from an 'atypical' presentation of Kawasaki disease[,]" is not significant from the standpoint of determining the cause of her fevers, refractory epilepsy, cognitive and motor delays. Resp't Ex. RR at 6. "These features are all . . . consistent with Dravet syndrome." Id.

**Dr. Raymond's Testimony**

Dr. Raymond is one of a limited number of physicians in the United States who holds board certifications in neurology and genetics, as well as special competence in child neurology and clinical genetics. Tr. II at 8-10; Resp't Ex. TT at 10. He was accepted at hearing as an expert in the fields of neurogenetics and pediatric neurology. Tr. II at 15. He works as a neurologist and geneticist at the Kennedy-Krieger Institute and is a professor of neurology at Johns Hopkins School of Medicine. Tr. II at 6-7. He has published about 75 articles and dozens of book chapters dealing mainly with neurologic and genetic issues. Id. at 14. He has treated four to six patients with DS over the years. Id. at 12.

Dr. Raymond testified that DS was the "sole cause" of Madison's condition. "Her initial course in terms of febrile seizure, as well as her subsequent course, characterized by difficult-to-control seizure disorder, intellectual disability, and ataxia, are all consistent with a Dravet's Syndrome secondary to an SCN1A mutation." Tr. II at 16.

Dr. Raymond explained in detail the process of genetic transcription, protein formation, and the effect of genetic point mutations such as the SCN1A mutation detected in Madison. Tr. II at 17-31; see Resp't Ex. UU. He distinguished between "silent" mutations that do not result in disease, compared to mutations that cause loss of function. Id. at 32-34. Mutations that affect functionality commonly are missense mutations, i.e., mutations serious enough to result in failure to code for the proper protein. Such mutations are known to affect function, especially if they arise de novo (without a similar mutation in the parents' genome), in an evolutionarily conserved region. Id. at 32-43. Regions of the brain that are conserved by evolution across organisms indicate that the particular region is significant for brain function. Id. at 43-44.

Madison's mutation was significant for all of the factors described by Dr. Raymond as affecting brain function. Tr. II at 47-51. Further, she had a "classical clinical presentation" for DS. Id. at 52.

> It's exactly – she has Dravet's syndrome, so she presented at six, seven months of life, with a febrile convulsion. Many of the individuals with

> Dravet's syndrome will have a long febrile convulsion, which she did. She seized, I believe, for an hour. And then . . . seems to be perfectly fine following that.
>
> They often go on to have several more febrile seizures. But after a few months, they then begin having afebrile seizures. Usually development is still looking very normal at that point, so that at 12 months of age, people are saying, okay, she has had febrile seizures, some of them might have been prolonged. But then they begin having afebrile seizures, some with myoclonus, just limb shaking, some partial seizures.

Id. In the second year of life, Dr. Raymond testified, children with DS begin "to manifest language and motor delay, and ataxia becomes evident." Id. at 53. He noted that "this is actually recapitulated exactly almost epoch to epoch in the mouse model." Id.; see Resp't Ex. VV-9 (Oakley).

The SCN1A mutation, he explained, "has more and more of a role to play as our brains develop and as the circuits need to be laid down. So that's when it becomes evident." Tr. II at 53. After the first year of life, "just about all of the individuals with the severe end of the spectrum have mental retardation and developmental disabilities, ataxia, with language and motor delays." Id. at 54. This "exactly mirrors" the progression of Madison's neurological disorder. Id.

Dr. Raymond opined that Madison's initial seizure likely was caused by fever resulting from her vaccinations on March 28, 2002. Tr. II at 54-55, 116-17. He explained,

> [W]e know that the vaccines can result in a slight elevation in temperature when administered, and these children are prone to any elevation in temperature, whether it be from vaccine or whether it be from illness or whether it be from environmental temperature, such as a hot bath . . . . So it doesn't matter what the elevation in temperature is due to. They will seize when their temperature gets hot enough.

Id. at 55.

Dr. Raymond conceded that the precise functional effects of SCN1A mutations on a molecular level are not known. Tr. II at 88. He explained, however, the mechanism by which it is believed that SCN1A mutations produce seizures. Based on experiments using mice, the gene is expressed in the course of development in cells called inhibitory interneurons. Id. at 121-22. "[W]hen these inhibitory interneurons are not forming – not acting correctly, they're not having that inhibitory effect on excitatory actions." Id. at 122. Therefore, the mutation results in a propensity for seizures. The same cells are critical in many regions of the brain and therefore affect a variety of functions. Thus, "the ataxia or the unsteadiness, the uncoordination of movements that

is so commonly reported in these children . . . you would not presume is a[n] outcome of a prolonged seizure [but is] explained by the genetic manifestations of this disorder." Id.

Dr. Raymond noted several factors that distinguish DS from other seizure disorders. These distinctions weighed strongly against the possibility that Madison's initial seizure, rather than her underlying genetic disorder, actually caused the neurological damage she suffered. He pointed to the fact that DS is refractory to anti-epileptic drug treatment. This, he stated, is evidence that the underlying cause of brain dysfunction is more than just the tissue scarring due to seizures. "[T]hese channelopathies actually make [the seizures] extraordinarily resistant to most of the medications that we have available." Tr. II at 123.

He also testified that a prolonged initial seizure resulting in status epilepticus is characteristic of children with DS, but uncharacteristic of children suffering a simple febrile seizure. Tr. II at 118-19. In addition, children with DS typically recover significantly after the initial episode. "They're usually normal EEGs, normal MRIs and other neural imaging, no changes in their cerebrospinal fluid. Their development seems to go on, and it's only later that another seizure, a couple weeks later another seizure, a couple of weeks later, until – so that's the classic course of Dravet's." Id. at 119. Ataxia and intellectual disability are not known to result from a prolonged febrile seizure in the absence of DS. Id. at 120-21.

Dr. Raymond stated that there was "no evidence" that Madison's initial, prolonged seizure following her immunizations damaged her brain. Tr. II at 55-56, 198-205. He relied on neuroimaging results in the year or two following her first seizures that "showed no evidence of injury." Id. at 56. The initial evaluation showed "no evidence" of "any infection or inflammation in her brain." Id. He contrasted Madison's MRIs with the typical pattern that one sees in an individual who has been injured by prolonged seizure. "[C]lassically, you see hippocampal sclerosis, which is scarring," but in Madison's case there was no "evidence that she had any scarring of the cortex or injury to the cerebrum, or what I would think of as injury to the cerebellum." Id. at 57; see also Tr. II at 68-69 ("I have a child [Madison] who again while having a rash and a fever has no subsequent evidence of brain injury consistent with a vaccine injury, has no evidence of an inflammatory response in her cerebral spinal fluid, and has a course that is completely consistent with Dravet's syndrome.").

Dr. Raymond testified that vaccination did not cause Madison's DS or in any way change her clinical course. Tr. II at 58-59, 75-76. He disputed the assertion that the onset of Madison's DS was "triggered" by vaccination. Id. at 96. "[T]he disease . . . is part and parcel of the individual . . . . [W]hat we are seeing is it's [sic] unmasking . . . . But there is nothing in the literature or subsequently that the course of the disease varies between" individuals with DS who have initial seizures post-vaccination and those who do not. Id. at 96-97. He stated that children with DS do not outgrow the propensity to seize at elevated temperatures; accordingly DS would not be avoided or ameliorated by delaying vaccination. Tr. II at 100-01.

Dr. Raymond acknowledged that not all SCN1A mutations result in DS. For example, some individuals with an SCN1A mutation develop a condition called familial hemiplegic migraine. Tr. II at 64. The mutations leading to that condition are known to pass from generation to generation; they do not arise de novo. Id. at 64-65. In addition, the physiochemical changes caused by those mutations are "less dramatic, and they're not generally in the regions that have been shown to be important" in DS. Id. at 65. The mutations in such cases are different from Madison's SCN1A mutation. "Madison . . . has . . . a missense alteration . . . a de novo alteration. It results in a significant alteration in the subsequent amino acid. And it is in a highly conserved region, in a region that we know from previous reports has resulted in Dravet's syndrome." Id. at 66. Dr. Raymond noted it is not uncommon in genetic disorders to find "either a spectrum or sometimes even a slightly different disorder . . . . But the mutations, when you have those different disorders, are different mutations." Id.[32]

Dr. Raymond pointed to a study in mice whose SCN1A genes were altered. See Resp't Ex. VV-9 (Oakley). He testified that the altered mice experienced seizures in response to temperature elevation, and that the subsequent development of the mice "mimics the Dravet's syndrome." Tr. II at 70-72. The mouse model proved, Dr. Raymond asserted, that it does not require an infectious agent, vaccination, or inflammation to produce the neurological symptoms occurring in individuals with DS. Id. at 72. He reasoned, consistent with this observation concerning the mouse model, that Madison's neurological condition would be the same without vaccination. Id. "The vaccine if anything caused a slight elevation in temperature, which resulted in a prolonged seizure on that day, but did not subsequently set in motion any of her other events." Id. at 78.

**b. Petitioners' Expert**

**Dr. Tornatore's Report**

On May 31, 2009, Petitioners filed a letter from Dr. Tornatore in response to Special Master Millman's request. The letter stated that Madison's "recent diagnosis" of Dravet's disease did not change Dr. Tornatore's opinion, as outlined in the report filed in the first entitlement hearing. Pet'r. Ex. 19.[33]

In his original report, Dr. Tornatore presented several theories of possible vaccine causation: vaccine-induced fever with subsequent seizure; direct toxicity to the nervous system from components of the vaccine; immune dysactivation with resulting

[32] He explained further that children with DS can be born to parents with the same mutations but less severe disorders. This phenomenon has been explained by the occurrence of "mosaicism," a process in which individuals develop two lines of cells. Their offspring therefore may inherit a mutated or non-mutated SCN1A gene. "So the offspring, if they inherit the mutated [gene] is going to have Dravet's syndrome." Tr. II at 74. See Resp't Ex. VV-12, Carla Marini et al., Mosaic SCN1A Mutation in Familial Severe Myoclonic Epilepsy of Infancy, 47 Epilepsia 1737 (2006); Resp't Ex. VV-13 (Morimoto).

[33] Madison was diagnosed with DS more than four years before the date of Dr. Tornatore's letter. See Pet'r Ex. 15 at 8-14.

fevers; and Kawasaki's disease. Pet'r Ex. 6 at 10-11. He noted that 33% of children with Kawasaki's disease had one or more infections at the time of diagnosis, consistent with an immunodeficient state. Id. at 11. "This would explain the presence of enterovirus nucleic acids in Madison's blood." Id.

Dr. Tornatore opined "that the DTaP vaccine triggered fever, seizures and the subsequent diagnosis of atypical Kawasaki's disease." Id. He stated that the 12 days from vaccination to Madison's development of a rash would be "in the appropriate time frame for an aberrant response to a foreign antigen." Id. at 11. He added that development of Kawasaki's "strengthens the argument that the DTaP vaccine was the inciting event in Madison's chronic illness." Id. A key element in Dr. Tornatore's complex analysis was that "Madison was fine up until the time of the vaccination, immediately following which he [sic] had the onset of the persistent fevers and seizures." Id.

**Dr. Tornatore's Testimony**

Dr. Tornatore's credentials are discussed above in connection with the first hearing in this case. In contrast to Dr. Raymond, who had special qualifications in pediatrics, neurology and genetics, Dr. Tornatore was not formally trained as a specialist in pediatrics and had no official certification as a specialist in genetics. Tr. II at 150-51. It was unclear whether he holds himself out as an expert in "neurogenetics." "Again, it's how you're going to parse the term neurogenetics. I think it's a big umbrella group. If you're saying clinical neurogenetics, then I would say no." Id. at 151.

Dr. Tornatore offered additional information concerning his qualifications to opine in this case. At the NIH, he stated, "we did basic science work that was predominantly in the realm of pediatric disorders, and . . . most of our work was molecular genetics and molecular virology, so we did a lot of gene cloning, gene mutation." Tr. II at 132.

> We worked with pediatric tissue, both in vitro, including human astrocytes, human neurons, as well as looking at pediatric tissue that was injured. Specifically we were looking at HIV in children. So we have a lot of overlap with a lot of the basic science material that was presented here today [referring to Dr. Raymond's testimony].

Id. He currently treats one patient with DS "that we see roughly every three to four months for management of their spasticity." Id.

> I think the more cogent point, though, is the – a lot of the discussion about the genetics of this particular disorder, as well as the molecular genetics and the sodium channels are areas that we did work in, not specifically, but the techniques were very cogent to this case.

Tr. II at 132.

He reiterated his previous opinion, which was unchanged by the revelation of Madison's genetic disorder. "[T]he DTaP and HIBB [sic] vaccine led to the appearance of Kawasaki's syndrome, atypical . . . Kawasaki's . . . with subsequent fevers that persisted over time and . . . led to significant convulsive episodes and . . . changes on the MRI probably from the Kawasaki's." Tr. II at 133.[34] "The sodium channel mutation made her more susceptible to have febrile seizures . . . . However, the fevers were spiked because of the Kawasaki's." Id. He explained that Madison's Kawasaki's was "precipitated or triggered" by vaccination because "Madison had very low immunoglobulin levels[.]" Id. at 134. According to Dr. Tornatore "pertussis endotoxin is a lipopolysaccharide, which can lead to an augmentation of the immune response, particularly in somebody who has a disregulated immune systems [sic], could then cause the fevers, the subsequent vasculitic process, and then the seizures." Id. Dr. Tornatore also noted evidence from the first hearing that Madison:

> interestingly, had enterovirus in her bloodstream on two separate occasions over the course of the year. And so she had kind of a perfect storm going on that seemed to precede the time of the vaccination, but then the vaccination kind of triggered the ultimate presentation of the Kawasaki's.

Tr. II at 135-36.

Dr. Tornatore indicated three possible mechanisms explaining adverse reactions to DTP vaccine: (1) the endotoxin itself, directly causing a toxic event; (2) fever leading to convulsive events; and (3) inflammatory response independent of the pertussis toxin. Tr. II at 137-38. Any of these mechanisms could have caused Madison's initial seizure. "[T]he inhibitory neurons[] are not working adequately. And so there is a lowering of the seizure threshold. And so anything that irritates the brain could potentially lead to a convulsive event." Id. at 138-39.[35]

Dr. Tornatore noted that one-third of the children who were reported in the McIntosh article, see Pet'r Ex. 48; Resp't Ex. VV-17, to have suffered seizures following vaccination did not have fever, "suggesting that vaccination might work with an alternative mechanism to trigger seizure onset earlier than might otherwise have occurred." Tr. II at 139-40. He also commented that the mouse study, see Resp't Ex. VV-9 (Oakley), showed that there must be "different mechanisms besides fever" to explain the seizures suffered by the genetically altered mice. Tr. II at 141. This was based on his observation that, if the pattern proposed in the McIntosh study held true, older mice would have suffered seizures more than the younger ones, but the opposite was the case. Id. at 141-42. "The animal model would have predicted that those that

[34] It was unclear at times from Dr. Tornatore's testimony whether he blamed both the "DTaP and HiB" vaccines for Madison's condition, or only the pertussis vaccine (lipopolysaccharide). Tr. II at 133, 134.

[35] Although counsel asked Dr. Tornatore about the DTP vaccine, I assume that his testimony also pertained to the DTaP vaccination Madison received. I note, however, that the acellular form of the pertussis vaccine is less reactogenic than its predecessors. See, e.g., Grace v. Sec'y of Dep't of Health & Human Servs., No. 04-[redacted]V, 2006 WL 3499511, at *9 (Fed. Cl. Spec. Mstr. Nov. 30, 2006).

had the vaccination proximate events, because that's when you would have fever, would be older because as the animal progresses, you would presumably have more sodium channel mutation leading to more cellular problems." Id. at 142.

Dr. Tornatore placed particular significance on the MRI taken on November 7, 2003. See Tr. II at 147 ("kind of to me the smoking gun"). He stated that, in general, "the MRI of somebody with Dravet's is normal." Tr. II at 143. On the November 7th MRI, however, "'there is increased T2-weighted signal in the periventricular white matter that is more marked posteriorly.'" Id. at 144; see Pet'r Ex. 4 at 304. He quoted the spectroscopy report of that date, which examined the chemistry of the brain and concluded that "'This is most likely related to underlying gliosis . . . .' So the radiologist is saying this is scarred . . . . Madison had evidence of scar tissue in the brain." Tr. II at 144-45; see Pet'r Ex. 4 at 303. Dr. Tornatore contrasted this report with earlier MRI assessments stating that Madison's brain showed delayed myelination. He concluded that "this type of gliosis is not seen with Dravet's, and that's extremely important. Something else had to have caused this." Tr. II at 145; see also Tr. II at 156. He stated that Kawasaki's, "which was induced by the vaccine," was the cause of the gliosis. Id. at 146.[36]

Dr. Tornatore offered yet another theory to explain Madison's condition, as he described it, "the old dogma is seizure begets seizures, that as you have an area of the brain which is firing erratically, you're going to have rewiring of that area, and it makes it more difficult to control the convulsive events in that area." Id. at 147. He noted several additional possible adverse effects of seizures, including hypoxia and "just from electrical activity that's going on." Id.[37]

> [S]o the idea that once you have that initial insult – so the theory we put forth and that Special Master Millman agreed with was that the Kawasaki's caused an injury. The vaccine triggered the Kawasaki's. The Kawasaki's is an inflammation of the blood vessels, and so that caused an inflammation that subsequently became evident by scarring in the brain.

Id. at 148. He concluded, "That, in conjunction with the Dravet's, makes her brain much, much more likely to then have convulsive episodes." Id.

On cross-examination, Dr. Tornatore appeared unwilling to agree that Madison even had DS. Tr. II at 152-53. He referred to the report accompanying Madison's genetic testing, which noted that, although "the finding that the amino acid variant was

[36] In the course of his testimony, Dr. Tornatore repeatedly emphasized that Dr. Snyder, an expert for Secretary, had testified at the first hearing that Madison's disorder was due to Kasawaki's, not vaccination. See, e.g., Tr. II at 146, 675. As noted above, Dr. Snyder also testified at the first hearing that mutation in the SCN1A gene could lead to the symptoms Madison exhibited. Tr. I at 204-07. Dr. Snyder did not know at the time he testified that Madison actually did have an SCN1A mutation and had been diagnosed with DS. Tr. II at 213. Medical opinions may change based on new data.

[37] Hypoxia is a reduction in oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. Dorland's at 908.

de novo is far more consistent with the theme associated with severe phenotype than normal or mild phenotype . . . the possibility that this is a rare, sporadic, benign polymorphism cannot be excluded." Id. at 154-55. He also noted disclaimers in the printed material accompanying the report, which stated that a clinical diagnosis could not be made solely on the basis of the testing results. Id. at 154-56. He did concede, however, that Madison's "treating physicians have called her Dravet's." Id. at 152.

Although he had testified that Madison's genetic mutation made her vulnerable to seizures, he disputed that the mutation resulted in a neurological abnormality, stating that it is not known "definitively" when "the sodium channel expression shows." Tr. II at 188. "Just because you have a gene doesn't mean it gets turned on, and it also doesn't mean there couldn't be some other gene that is protective." Id. at 189. Nevertheless, he testified that "clearly vaccination in somebody with the mutation has a differential effect." Id. at 190.

Dr. Tornatore testified that it would be difficult to ascertain brain damage in a child Madison's age at the time of vaccination. Tr. II at 191. He declined repeatedly to identify Madison's first seizure as a manifestation of her DS. Id. at 192. "I would say no because it was clearly triggered by the vaccination febrile event. So the fever, which was a manifestation of her Kawasaki's, was what led to the convulsive episode. If the Dravet's made her more susceptible to that, as we've just discussed, that's possible." Id. He repeated that the first seizure could have been caused by any of a number of factors, not necessarily DS. "You can't be so dogmatic" concerning the genetic mutation, he asserted. Id.

Although he had indicated that the differential diagnosis in November 2003 of "gliosis" was "a smoking gun," Dr. Tornatore declined to state that gliosis accounted for Madison's developmental delay. Tr. II at 193-94. The indications of gliosis on the November 30, 2003, MRI, he stated were "non-specific." Tr. II at 194-95. Dr. Tornatore indicated that Madison's gliosis was caused by her atypical Kawasaki's. See, e.g., Tr. II at 196 ("diffuse injury throughout the subcortical white matter . . . speaks to a more diffuse toxic event . . . that is again triggered by something like a Kawasaki's, where you have a vasculitic process"); Tr. II at 146 ("we agreed Kawasaki's, which was induced by the vaccine, was indeed the cause of the gliosis").

### c. Dr. Raymond – Re-Direct

Dr. Raymond disputed Dr. Tornatore's interpretation of Madison's MRIs. He stated that in the course of his practice in neurology and genetics he had used MR spectroscopy in over 100 individuals clinically and experimentally and published four articles on that subject. Tr. II at 198. He testified that Dr. Tornatore overstated the significance of the MRI spectroscopy report dated November 7, 2003. See Pet'r Ex. 4 at 303. According to Dr. Raymond, Madison's MRI "is actually a normal variation of the typical progression of myelination that occurs in children." Tr. II at 200. The interpretation of the physician who read the study was "very broad," constituting a "differential diagnosis." Id. "It includes gliosis versus hypomyelination." Id.

Dr. Raymond argued against the interpretation of the study as showing "true gliosis" because of the absence of "any [systemic] changes on the T1-weighted images" which, he stated, would typically be seen in such a case. Tr. II at 200. He added that the gliosis was "not in an area that is typically seen in repetitive seizures or status epilepticus." Id.; see also Tr. II at 201-02.

He also testified that, contrary to Dr. Tornatore's view, in a child Madison's age at the time of her first seizure, we would "expect to see . . . immediate evidence of encephalopathy" if an initial, prolonged seizure had damaged the brain. Tr. II at 203. "[Y]ou're going to have alterations in consciousness, alterations in motor abilities, alterations in language, alterations in eye contact . . . ." Id. Madison's pediatric neurologist, who saw her the day following her initial seizure, "[did] not identify any manifestations of an encephalopathy." Id. at 204. If Madison had suffered immediate brain injury from her initial injury, Dr. Raymond also would have expected to see some evidence of that on her first MRI. Tr. II at 204-05.[38]

As discussed below, Dr. Raymond also disputed Dr. Tornatore's interpretation of the Oakley mouse study. Tr. II at 206; see Resp't Ex. VV-9. In addition, he maintained that the disclaimers in the material accompanying the results of Madison's genetic testing were not medically significant. Tr. II at 207-08. He noted that Madison's treating physicians viewed the genetics report as evidence of a disease-causing mutation that explained Madison's condition. Id. at 208-09. He agreed that the McIntosh study reported seizures with or without fever following vaccination in DS patients, but he disagreed with Dr. Tornatore's interpretation of the study. Tr. II at 221-22.

### E. Post-hearing – Court Exhibit 1

Following the hearing, I entered into evidence Court Exhibit 1, Sarah von Spiczak et al., A Retrospective Population-Based Study on Seizures Related to Childhood Vaccination, 52 Epilepsia 1506 (2011) (the "Spiczak article").[39] The study focused on reports from 2006-2008 in the national German database of seizures and epilepsies in children aged 0-6 years following immunization. Ct. Ex. 1 at 1. The authors found that of 247 cases of confirmed seizures, 55.1% suffered febrile seizures and 17.8% had afebrile seizures. Id. at 3. Of those individuals with confirmed seizures, 11.7% were identified with severe childhood epilepsy syndromes, including DS. Id. at 4. The first

[38] Dr. Raymond testified that the MRI of April 30, 2003, which showed a delay in myelination, did not indicate a specific injury. Tr. II at 56-57 ("[I]t's not the typical pattern that one sees in an individual who has been injured by either prolonged seizure or hypotension or some other metabolic formation."); Tr. II at 69 ("Hypomyelination again doesn't point to a specific . . . prolonged seizure injury. It really points to some delays in average development. And these kinds of things have been reported in Dravet's syndrome."); Tr. II at 115 ("All we see is hypomyelination on the MRI").

[39] Special masters traditionally have supplemented the record where necessary and appropriate. In accordance with due process, the parties were afforded an opportunity to review and respond to the Court's exhibit. See generally Snyder ex rel. Snyder v. Sec'y of Dep't of Health & Human Servs., 88 Fed Cl. 706, 713-14 (2009) (noting the legislative history establishing the special masters' "inquisitorial" role under the Vaccine Act).

documented seizure in 51.7% of those cases followed vaccination, including four out of four cases of "confirmed" DS. Id.

I required the parties to file responses to the exhibit, if any, on or before October 31, 2011. Order, Oct. 21, 2011, ECF No. 107. The purpose was to offer the parties' experts an opportunity to expound their views on the relationship between vaccination and initial seizures in individuals with DS, a point of contention at the hearing and a significant issue for consideration in the Vaccine Program.

In a report filed October 31, 2011, Dr. Raymond described the study, noting that the authors "state that children with SCN1A mutations specifically are destined to develop the epilepsy syndrome irrespective of immunization." Resp't Ex. WW at 3. He highlighted the authors' conclusion that children who have vaccine-related seizures "should be assessed for Dravet and other causes of severe childhood epilepsy." Id. He reiterated that genetic epilepsies may or may not present with their first seizure at the time of vaccination, but that "the uncovering of genetic epilepsy is not a rare event in this circumstance." Id. Dr. Raymond stated that the Spiczak article reinforced his argument that SCN1A mutation is the sole cause of Madison's epilepsy "and that immunization has not altered her diagnosis or course." Id.

On November 7, 2011, Dr. Tornatore submitted a report in which he described the Spiczak article and appended a supplemental table from the article, which he obtained on the Epilepsia website. Pet'r Ex. 67 at 2. Dr. Tornatore stated that the article "presents further evidence that in patients with rare genetic mutations, within 24 hours of administration, vaccination may precipitate the first convulsive episode, as was the case in all 4 of the children with genetically confirmed Dravet syndrome in this study." Id. Dr. Tornatore reiterated his opinion "that not only did the vaccination precipitate her convulsive episodes, but also resulted in Kawasaki's syndrome, as was extensively discussed at the first hearing in Madison's case." Id. at 3.

On November 22, 2011, the Secretary filed Dr. Raymond's reply to Dr. Tornatore's comments on Court Exhibit 1. In particular, he commented on the supplementary information in the tables accompanying the Spiczak article. He disagreed with the suggestion that only one out of the four children identified with DS suffered a febrile seizure. Resp't Ex. XX at 1. He interpreted the data as showing that one out of four had a febrile seizure "and 1 out of 4 had what was described as an afebrile seizure, but no temperature is recorded for that child. The other two do not have recorded information." Id. He emphasized that children with DS are "more sensitive to slight elevations in temperature below what is commonly ascribed as a fever and therefore listed as afebrile at the time of their event." Id.

Dr. Raymond also commented on the clustering of seizure "events" between the ages of four to six months. "This is the typical age of onset of Dravet syndrome whether it is associated with vaccination or not[,]" he stated. Resp't Ex. XX at 1-2. He explained that, "Children have to be at the neurodevelopmental stage where temperature sensitive seizures may occur, but then transition to more varied seizure types which are

unassociated with fever." Id. at 2. He stated that this pattern has been recapitulated in the animal studies, demonstrating the importance of the sodium channels affected by SCN1A mutation. Id. Dr. Raymond conceded that "vaccines may skew to an earlier first seizure," but there is no evidence they cause or alter the genetic mutation Madison has. Id.

## III. DISCUSSION

### A. Overview of the Discussion

The discovery by medical science in recent years of a genetic cause for some severe epilepsy disorders has permitted the Secretary to establish alternative causation in cases where a child suffers a prolonged seizure following vaccination.[40] Based on Madison's test results, the Secretary's expert's testimony, and the medical literature supporting the expert's testimony, Madison's neurological problems were caused by the missense mutation, arising de novo, in a biologically conserved region of her SCN1A gene. Such mutations have been shown reliably to produce the collection of symptoms from which Madison suffered, a condition known as Dravet's Syndrome (DS) or Severe Myoclonic Epilepsy of Infancy (SMEI).

It is undisputed that vaccination triggered Madison's initial seizure. The Secretary maintained that Madison's vaccination likely caused a slight increase in her temperature, and that the seizure occurred because children with DS are exquisitely sensitive to temperature changes. The Secretary argued that the initial seizure did not cause any permanent brain damage.

Petitioners' expert testified that vaccination triggered an array of adverse events, including atypical Kawasaki disease. According to Petitioners, Madison's genetic disorder confirmed entitlement to vaccine injury compensation. They reasoned that she was a susceptible individual who only needed the impetus of vaccination, or some other environmental factor, to succumb. Petitioners argued that, had Madison not been vaccinated, or been vaccinated later in life, she would not have suffered the neurological problems that led to her current condition, or those problems would not have been as severe.

Preponderant evidence favored the Secretary's argument that, notwithstanding the association between vaccination and the initial seizure, it was DS that caused Madison's neurological problems. Petitioners' expert's speculative opinion concerning

[40] Stone v. Sec'y of Dep't of Health & Human Servs., 95 Fed. Cl. 233 (2010), aff'd, 99 Fed. Cl. 187 (2011); Hammitt ex rel. Hammitt v. Sec'y of Dept of Health & Human Servs., 98 Fed. Cl. 719 (2011). In two more recent decisions, the Court of Federal Claims reversed a special master's ruling denying compensation for vaccinees with known SCN1A mutations. See Snyder v. Sec'y of Dept of Health & Human Servs., No. 07-59V, slip op. (Fed. Cl. Nov. 28, 2011); Harris v. Sec'y of Dept of Health & Human Servs., No. 07-60V, slip op. (Fed. Cl. Nov. 28, 2011). All the decisions involve different facts and expert testimony. See Hanlon v. Sec'y of Dep't of Health & Human Servs., 40 Fed. Cl. 625, 630 (1998), aff'd, 191 F.3d 1344 (Fed. Cir. 1999) (special masters are not bound by their own or other special masters' decisions, or those of the Court of Federal Claims, except in the same case).

vaccine causation lacked power to persuade in light of the Secretary's clear explanation and abundant scientific corroboration.

On this record, it was established that the type of mutation Madison had would have resulted in the clinical symptoms she developed, with or without vaccination. Vaccination did indeed appear to have played a role in triggering Madison's first seizure, most likely by elevating her temperature. But vaccination did not cause or contribute to the condition that led to the seizure. That condition was present long before vaccination and would, inevitably, have resulted in Madison's symptoms as her brain developed. "[G]iven that truncation or missense mutations in conserved regions of the SCN1A gene have not been found in healthy control subjects, children carrying the mutation would seem destined to develop the epilepsy syndrome irrespective of immunization." Ct. Ex. 1 at 5.

This is not to say that medical science has all the answers to questions about DS, vaccinations, and/or genetics. Genetic causation does not necessarily exclude the possibility that environmental factors may play a role in the way genes are expressed, even changing the outcome for an individual. Much more research will be needed to explore these possible interactions. See, e.g., Pet'r Ex. 60 at 1 (Guerrini) ("It has become obvious that the underlying genetic defect confers a peculiar profile of seizure susceptibility but is not the sole determinant of severity."). The possibilities for variation in individuals with DS, and their cause, are complex and have yet to be explored. See id. But "definitive" proof, to borrow Dr. Tornatore's term, is not required to prove that genetic causation is more likely than not. Proof of an unrelated factor does not, under the Vaccine Act, require absolute certainty. Here, there is more than preponderant evidence that a genetic abnormality was the sole substantial cause of Madison's neurological condition. Further, no reliable evidence implicated vaccines as causative or exacerbating agents in cases of DS.

### B. Factor Unrelated – Burden and Standard of Proof

The Vaccine Act authorizes compensation when a petitioner has demonstrated by a preponderance of the evidence the matters that are required to be proven, and "there is not a preponderance of evidence that the . . . condition . . . described in the petition is due to other factors unrelated to the administration of the vaccine described in the petition." § 300aa-13(a)(1)(A)-(B). The Secretary must demonstrate "by a preponderance of the evidence[] that a factor unrelated to the vaccine caused the injury." Hanlon v. Sec'y of Dep't of Health & Human Servs., 191 F.3d 1344, 1348 (Fed. Cir. 1999), citing Knudsen v. Sec'y of Dep't of Health & Human Servs., 35 F.3d 543, 547 (Fed. Cir. 1994). The Secretary's burden is to identify a particular alternative factor or factors and present "sufficient evidence to establish that it was the sole substantial factor in bringing about the injury." de Bazan v. Sec'y of Dep't of Health & Human Servs., 539 F.3d 1347, 1354 (Fed. Cir. 2008) (citing Knudsen, 35 F.3d at 548). The Secretary must show a sequence of cause and effect that is logical and legally probable but is not required to establish an unrelated factor to a medical or scientific certainty. Knudsen, 35 F.3d at 548-49; see Hanlon, 191 F.3d at 1349 (medical or scientific

certainty not required to prove actual alternative cause). "[T]he standards that apply to a petitioner's proof of actual causation in fact in off-table cases should be the same as those that apply to the government's proof of alternative actual causation in fact." Knudsen, 35 F.3d at 549. Thus, to establish alternative causation, the government must satisfy the three prongs of Althen, by a preponderance of the evidence. See Althen v. Sec'y of Dep't of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005); see also Knudsen, 35 F.3d at 550 ("Having concluded that a 'viral infection' *can* be an alternative causation . . . we come to the Knudsens' challenge . . . in this case that the unspecified viral infection *was* in fact an alternative causation.") (emphasis in original).

### C. Althen Prong 1

Under Althen prong 1, a petitioner must set forth a biologically plausible theory explaining how the vaccine could cause the injury complained of. This requirement has been interpreted as "can [the] vaccine(s) at issue cause the type of injury alleged?" Pafford v. Sec'y of Dep't of Health & Human Servs., 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). The Secretary under Althen prong 1 must make a commensurate showing: that mutation of the SCN1A gene could cause the epilepsy syndrome from which Madison suffered. As is the case with Petitioners, the Secretary's theory of causation need not be corroborated by medical literature or epidemiological evidence, but must be sound, reliable, and reputable – in other words, the theory need not be scientifically certain, but it must have a sound scientific basis. See Knudsen, 35 F.3d at 548 (actual causation "must be supported by a sound and reliable medical or scientific explanation"). In this case, the Secretary presented convincing evidence that the type of mutation Madison had in the SCN1A gene could cause Dravet's syndrome.

DS is "a catastrophic early life epilepsy disorder in which the seizures are usually refractory to treatment and are associated with intellectual disability." Resp't Ex. VV-15 at 3 (Excayg). The disorder "is characterized by febrile hemiclonic seizures or generalized status epilepticus starting at approximately 6 months of age, with other seizure types including partial, absence, atonic, and myoclonic seizures occurring after 1 year. In classical DS, development is delayed and patients often experience motor impairment, including spasticity and ataxia." Id. "The usual long-term outcome includes intellectual disability and intractable epilepsy." Pet'r Ex. 55 at 1 (Vadlamudi).

An abundance of peer-reviewed medical literature established beyond dispute the association between mutation of the SCN1A gene, especially a missense mutation arising de novo in a biologically conserved region, as in Madison's case, and Dravet's syndrome. See, e.g., Pet'r Ex. 56 at 2 (Harkin). "SCN1A, the gene encoding the sodium channel alpha 1 subunit, has emerged as the most important of the epilepsy genes currently known. SCN1A mutations underlie more than 70% of patients with the epileptic encephalopathy severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome)." Id. (citations omitted). The Harkin article (submitted by Petitioners) also

noted that "Approximately 95% of SCN1A mutations in SMEI patients arise *de novo*." Id.; see generally Resp't Ex. VV-5 at 1, 2 (Gargus) (noting that SCN1A "is a well-recognized target of mutations underlying a spectrum of epilepsy syndromes," and such mutations "have been unambiguously shown to be pathogenic").

Over the past decade, medical research has revealed that errors in the amino acid sequences necessary for the proper functioning of voltage-gated sodium channels in brain cells result in various neurological disorders, including DS. See Resp't Ex. VV-4 at 1 (Lossin). "Any alteration of the finely tuned kinetics that determine the gating of these channels can have decisive impact of cellular excitability." Id. at 3. DS is caused by a channelopathy that creates "excitatory havoc" in brain cells. Id. at 1. The gene SCN1A "appears to be an epilepsy *superculprit*," resulting in a spectrum of epilepsy syndromes. Id. (emphasis in original); see Resp't Ex. VV-5 (Gargus); Resp't. Ex. VV-4 (Lossin); Resp't. Ex. VV-14 (Berkovic). As evidenced by the extensive literature summarized above, both the fact of the causal association between de novo SCN1A mutation and DS, as well as the underlying biological basis for this association, have been studied extensively. The medical research is well documented in the record and establishes that mutation of the SCN1A gene, without any other factor, genetic or environmental, can cause the symptoms characterized as DS. See, e.g., Resp't Ex. VV-14 (Berkovic) (reporting that individuals with SCN1A mutations like Madison's seemed to develop DS whether or not they were immunized in the first year of life).

In so concluding, I do not rule out the possibility that further research may disclose additional factors that combine to produce the symptoms of DS in a particular individual. No such factor appeared in this record, however. Instead, all of Madison's neurological symptoms were demonstrated by a preponderance of evidence to have resulted solely from her known genetic disorder.

### D. Althen Prong 2

The second prong of Althen requires a petitioner (and, with regard to alternative causation, the Secretary) to prove "'a logical sequence of cause and effect showing that the vaccination was the reason for the injury[.]'" Andreu v. Sec'y of Dep't of Health & Human Servs., 569 F.3d 1367, 1374 (Fed. Cir. 2009) (quoting Althen, 418 F.3d at 1278). The sequence of cause and effect must be "'logical' and legally probable, not medically or scientifically certain." Knudsen, 35 F.3d at 548-49. Under prong 2 of Althen, parties are not required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect . . . ." Capizzano v. Sec'y of Dep't of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, circumstantial evidence and reliable medical opinions may be sufficient to satisfy the second Althen factor. See Capizzano, 440 F.3d at 1325-26; Andreu, 569 F.3d at 1375-77 (treating physician testimony).

In this case, the Secretary was able to demonstrate a compelling cause and effect relationship between mutation of the SCN1A gene and Madison's epilepsy

syndrome. Madison's clinical course was consistent with DS. She appeared to be normal until about age six months. She suffered an initial, prolonged and probably febrile seizure, but exhibited no immediate neurological damage. After a few weeks, however, she suffered additional seizures of varying types, which proved to be intractable. Over the next year, Madison experienced developmental disorders consistent with neurological abnormalities known to result from DS. These ultimately included ataxia and other conditions associated with the syndrome. See Tr. II at 16, 54. As Dr. Raymond testified, the development of Madison's disorder is typical for children afflicted with DS.

Dr. Raymond testified cogently that the particular type of mutation Madison had affects neuronal function severely. See Tr. II at 47-51. The laboratory that tested Madison for the SCN1A mutation corroborated Dr. Raymond's assessment. Specifically, Madison's genetic profile included a DNA sequence variation in the SCN1A gene "most consistent with . . . a severe phenotype . . . rather than a mild or normal phenotype." Pet'r Ex. 15 at 8. The laboratory report stated further that Madison's mutation was "not present in either parent and therefore arose de novo," adding that "[a]pproximately 90% of amino acid variants associated with the more severe phenotypes . . . ar[i]se de novo[.]" Id.

The laboratory cautioned that a variety of factors may influence the expression of the mutated gene; therefore, "molecular analysis must be carefully reconciled with the clinical presentation and family history." Pet'r Ex. 15 at 10. As described herein, Madison's clinical profile was consistent with the severe phenotype resulting from SCN1A mutation. Importantly, as noted above, Madison's treating physicians recognized that her neurological symptoms were attributable to the genetic mutation resulting in DS. See Tr. II at 60-62; Pet'r Ex. 14 at 5 (treating immunologist noting Madison's neurological problems caused by DS); Pet'r Ex. 15 at 5-6, 15-17 (neurologist noting DS in follow-up consultations).

I address below Petitioners' specific challenges to the Secretary's presentation establishing a logical sequence of cause and effect between Madison's SCN1A mutation and her severe epilepsy syndrome.

### 1. Evidence of brain damage due to initial seizure

Both experts agreed that if Madison had suffered brain damage as the result of her initial, prolonged seizure, that damage would be vaccine-induced and not attributable to her underlying genetic disorder. Petitioners maintained that later MRI reports showed damage to Madison's brain due to scarring (gliosis), and their expert attempted to link the results of the later MRI to Madison's initial seizure. Tr. II at 144-46. As Dr. Tornatore stated, "the old dogma is seizure begets seizures, that as you have an area of the brain which is firing erratically, you're going to have rewiring of that area, and it makes it more difficult to control the convulsive events in that area." Id. at 147. He noted several additional possible adverse effects of seizures, including hypoxia and "just from the electrical activity that's going on." Id.

To substantiate his theory that Madison actually suffered brain injury due to her initial seizure, Dr. Tornatore relied on evidence of Madison's MRIs. Madison's first MRI was taken on April 4, 2002, and was reported within normal limits. Pet'r Ex. 6 at 4; Pet'r Ex. 2 at 108. A second MRI was performed on April 12, 2002. Pet'r Ex. 6 at 7; Pet'r Ex. 4 at 687. Dr. Tornatore testified that this MRI also was normal. Tr. II at 157. Dr. Tornatore maintained that it would have been too soon after the first seizure episode to detect brain injury on the MRI, in any event. Id. at 163-64.

A third MRI was taken approximately one year later, on April 30, 2003. Tr. II at 157; Pet'r Ex. 4 at 397. The physician who interpreted the April 30, 2003, MRI, Dr. Santiago Medina, found:

> [T]he myelination has progressed. However, the myelination is still delayed for the patient's age. There is increased T2 signal intensity involving the periventricular white matter adjacent to the atrium of the lateral ventricles. The white matter of the centrum semiovale also shows increased T2 signal intensity.
> . . . .

Pet'r Ex. 4 at 397. Dr. Medina concluded:

> Abnormal signal intensity of the periventricular white matter and white matter of the centrum semiovale. These findings may be related to a hypomyelinization. Other possibility is a metabolic disease such as lysosomol or mitochondrial disease as well [as] metachromatic leukodystrophy. Delayed myelination.

Id.

A fourth MRI, as well as a Magnetic Resonance Spectroscopy (MRS) was taken on November 7, 2003. Tr. II at 143; Pet'r Ex. 4 at 304, 303. The spectroscopy results, on which Dr. Tornatore placed great emphasis ("smoking gun"), were reported approximately 18 months after Madison's initial seizure. Tr. II at 143; Pet'r Ex. 4 at 303. In that study, Dr. Medina found, "Mild elevation of the myoinositol peak in the left posterior periventricular white matter." Pet'r Ex. 4 at 303. He concluded, "This is most likely related to underlying gliosis and less likely hypomyelination. See differential diagnosis in the brain MR report from the same date." Id.

Dr. Tornatore stated that the first three MRIs were not specifically diagnostic but that the fourth MRI, taken on November 7, 2003, was significant because it included spectroscopy, "a chemical analysis that allows you to get that specificity." Tr. II at 167 ("The MRI is a picture. It shows us different ability to magnetize tissue. But it doesn't always give us the specificity."). Based on the "differential diagnosis" of gliosis in the periventricular white matter in the fourth MRI, Dr. Tornatore concluded that DS did not cause Madison's neurological problems. See Tr. II at 168 (the scarring "makes it separate from the Dravet, that there was something other than that sodium channel. . . . The MRI changes, the gliosis, is due to – is not due to the Dravet, but rather is due to

either the Kawasaki's or the frequent convulsive episodes."). See also Tr. II at 196 (the "diffuse injury throughout the subcortical white matter . . . speaks to a more diffuse toxic event or event that is again triggered by something like a Kawasaki's, where you have a vasculitic process.") [41]

Dr. Tornatore emphasized that "the MRI of somebody with Dravet's is normal." Tr. II at 143. "[T]his type of gliosis is not seen with Dravet's, and that's extremely important. Something else had to have caused this." Id. at 145; see also Tr. II at 156. Kawasaki's, "which was induced by the vaccine," was the cause of the gliosis. Id. at 146.

I asked Dr. Tornatore to clarify his testimony concerning the impact of DS on Madison's condition:

> THE COURT: Your opinion is that Dravet's did not cause Madison Deribeaux's condition.
>
> THE WITNESS: It is.
>
> THE COURT: What caused her condition was scarring due to seizures, correct?
>
> THE WITNESS: No. The MRI changes, the gliosis, is due to – is not due to the Dravet, but rather is due to either the Kawasaki's or the frequent convulsive episodes. Subsequent to that, her decline is probably a combination of the two. I think it would be wrong to just completely dismiss and say that sodium channel mutations have no impact on her.
>
> THE COURT: Okay. When did the Dravet's start to have an impact on her?
>
> THE WITNESS: I can't say that. I don't know if I would be able to state that.
>
> THE COURT: Why do you say it then?
>
> THE WITNESS: That it was –
>
> THE COURT: That at some point in time it began to have an impact on her condition?
>
> THE WITNESS: Your point is well taken. It could be perhaps this particular mutation would not lead to this manifestation, but rather all of her subsequent cognitive decline and seizures could be due to something

[41] Differential diagnosis is the determination of which one of two or more diseases or conditions a patient is suffering from, by systematically comparing and contrasting their clinical findings. Dorland's at 507.

other than that mutation. You know, I have no way of discerning which is which downstream.

Tr. II at 168-69. This testimony did not clarify his opinion. Dr. Tornatore conceded that he could not determine whether the changes reported on the fourth MRI resulted from Madison's initial seizure or her numerous, subsequent convulsions. Tr. II at 193.

Dr. Raymond refuted Dr. Tornatore's opinion regarding alleged evidence of scarring on Madison's MRI. Dr. Raymond testified that, if Madison had suffered a brain injury following her initial seizure, there would have been clinical symptoms. See Tr. II at 56-57. No such symptoms were noted by treating medical personnel, and the record indicated that Madison appeared to be behaving normally in the post-seizure period. Tr. II at 56; see Tr. II at 56-57 ("she made a good recovery and actually went home from the hospital").

Dr. Raymond also rebutted Dr. Tornatore's testimony that Madison's fourth MRI and spectroscopy demonstrated gliosis. See Tr. II at 198-205. Dr. Raymond testified that Madison's fourth MRI "is actually a normal variation of the typical progression of myelination that occurs in children." Tr. II at 200. Dr. Raymond is a child neurologist, while Dr. Tornatore is an adult neurologist. Tr. II at 203. As a pediatric neurologist, Dr. Raymond routinely examines MRIs and spectroscopy reports for children with brain disorders. His opinion is afforded great weight, as it is within Dr. Raymond's area of expertise.[42]

Dr. Raymond disagreed with Dr. Tornatore's interpretation of the report of the physician who read the MRI. That opinion was "very broad," constituting a "differential diagnosis. It includes gliosis versus hypomyelination." Tr. II at 200. Dr. Raymond argued against the interpretation of "true gliosis" because of the absence of any [systemic] changes on the T1-weighted images which, he stated, would typically be seen with gliosis. He added that the gliosis was "not in an area that is typically seen in repetitive seizures or status epilepticus." Id.; see also Tr. II at 201-02.

Dr. Raymond's testimony was persuasive. No reliable medical evidence supported the allegation that Madison's initial seizure caused brain damage that led to further seizures. The great preponderance of the medical and scientific evidence in this case, as explained by Dr. Raymond, weighed against such a sequence of events. Madison showed no signs or symptoms of brain damage in the aftermath of her initial seizure, notwithstanding that it was prolonged and resulted in status epilepticus. See

[42] I also weighed Dr. Tornatore's opinion, notwithstanding that he is not an expert in pediatric neurology. I considered his practical experience conducting pertinent research at the NIH at an earlier stage in his career. In so doing, I looked for an analogy to the federal courts applying Federal Rule of Evidence 702. Under that rule, "Differences in expertise bear chiefly on the weight to be assigned to the testimony by the trier of fact, not its admissibility." Huss v. Gayden, 571 F.3d 442, 452 (5th Cir. 2009) (citing Daubert v. Merrell Dow Pharm. Inc., 509 U.S. 579, 596 (1993). A special master may use Daubert "as a tool or framework for conducting the inquiry into the reliability of the evidence." Terran ex rel. Terran v. Sec'y of Dept' of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999).

Tr. II at 55-56; see also Pet'r Ex. 6 at 2 (describing the events surrounding the initial seizure episode).

On the basis of preponderant evidence, I conclude that Madison's MRI results did not indicate brain damage from her initial seizure. The MRI and spectroscopy report on which Dr. Tornatore relied dated from a year and a half after Madison's vaccination. By then, she had had numerous additional, uncontrolled seizures of various types. Dr. Tornatore was unable to establish a persuasive link between possible gliosis on Madison's fourth MRI and her initial post-vaccination seizure, as opposed to Madison's many intervening convulsions. See Pet'r Ex. 60 at 1 (Guerrini ) ("The temporal distribution of cognitive decay makes it likely that the intractable seizures and epileptiform abnormalities contribute to the progressive disturbance in cerebral function, epitomizing the concept of epileptic encephalopathy."). In addition, despite the differential diagnosis in the test report, Dr. Tornatore did not establish that the MRI actually revealed "true gliosis," for the reasons provided by Dr. Raymond.

Moreover, the pattern of an initial, prolonged seizure without evidence of brain damage is characteristic of DS. Thus, the medical record concerning Madison's initial seizure comports with all the other indications that her neurological symptoms were caused by DS. Consequently, I cannot conclude, as I might in the absence of any other explanation, that the initial seizure caused further seizures, ultimately resulting in severe brain damage.

### 2. Madison's Lower Seizure Threshold

At times, Petitioners claimed that Madison's DS caused her to have a "lower seizure threshold" than normal, arguing that her vaccination therefore triggered a seizure that would not otherwise have occurred. Tr. II at 169-70.[43] On the other hand, Dr. Tornatore testified, "I don't think that was the initial event, though." Id. at 170. I sought clarification:

> THE COURT: "[W]e all agree that the vaccine caused Madison to have the febrile seizure. . . . And Dr. Raymond says, that's just what I would expect with Dravet's because Dravet's patients are sensitive to heightened temperature, and that's just when they're going to seize, is when their temperature goes up.
>
> But what I hear you saying is, I'm discounting that. I don't think that played any role in that. I think what happened here is this child was predisposed by her immune system to suffer a vaccine injury, and the Dravet's didn't play any part in that. . . .
>
> THE WITNESS: No. And I will – and so I take that line of reasoning is not my line of reasoning. . . . If we start with she has a genetic predisposition

[43] This would appear to be undisputed. Dr. Raymond testified at length that children with Dravet's are prone to seize for a variety of reasons. Temperature elevation is a common factor precipitating an initial seizure in children with DS. See Tr. II at 55.

> to having seizures, if we accept that that sodium channel mutation does make you more likely to have a convulsive episode, then you put that in the context, but she had not seized yet. She had really normal development to that point.
>
> And it is important that not all genes get expressed all the time. Certain genes will get expressed at different times during development. Other genes may compensate for problematic genes. It's a little bit more complicated than if you have one bad gene, you're going to have the disease.
>
> Be that as it may, if we accept that there was probably a genetic propensity to having seizures, she then had the vaccination which led to a febrile seizure. However, it's more complicated than just a febrile seizure. She then developed Kawasaki's, and that febrile seizure, the fever is actually due to the immune deficiency that she had. And that immune deficiency was triggered by the vaccination, by the lipopolysaccharides in that. So you have somebody who is more prone to have a seizure, and then a vaccine that triggers febrile events that allow those seizures to come out. And those episodes lead to gliosis in the [b]rain. Why is that? Because that gliosis is not what you subsequently [see] with Dravet's.

Tr. II at 171-72. This testimony did not clarify Dr. Tornatore's opinion. He seemed to be saying, "it might be heads, but it could be tails." See also Tr. II at 167 ("So to be conclusive, the Kawasaki's could have caused the scarring. The seizures could have caused the scarring."). He appeared to be unable to provide a clear statement of his opinion concerning causation. As the trier of fact, I cannot rely on such ambiguous and contradictory testimony.

According to Dr. Tornatore, the outcome in Madison's case cannot be explained simply by her known genetic disorder. Dr. Tornatore repeatedly indicated that the mutation in Madison's genome might not have been "expressed" or that another gene might have "protected" her from the defect in SCN1A. See, e.g., Tr. II at 188-89 ("you don't know definitively – and this is a very important part. . . . Just because you have a gene doesn't mean it gets turned on . . . ."). This line of reasoning appeared to be highly speculative and lacked support in the evidentiary record or the medical literature. Dr. Raymond's testimony on this point, in contrast, was precise and cogent: when the SCN1A gene is "turned on," as it must be for normal cell activity to occur, it will fail to function properly if it is mutated in the way Madison's gene was. That failure will result in severe loss of function, as described by Dr. Raymond and in the medical literature. I respect Dr. Tornatore's expertise, but his opinion did not reflect the great weight of medical evidence as represented in the scientific literature of record. The record was replete with reliable statements that the existence of a de novo missense mutation in this region of the SCN1A gene results, without more, in a severely adverse outcome.

Petitioners in vaccine cases often advance the theory that individuals with unspecified genetic characteristics have a lower seizure threshold and that vaccination pushes them over the edge, resulting in a first seizure followed by further, ultimately

devastating convulsions. Such an allegation might constitute a viable theory of causation if all one knew about such cases was that a child had a seizure following vaccination. But much more has been revealed by medical science in cases like Madison's. Individuals with DS have serious channelopathies that interfere with normal neuronal activity. Susceptibility to febrile seizures is only one aspect of their disorder. An initial febrile seizure is followed by more seizures of all types, with and without fever. Ataxia and developmental delay occur because of pervasive brain dysfunction. This is a known syndrome, not an isolated case of a vaccination followed by seizures. In light of what is known, one cannot say that Madison's neurological condition was caused by vaccination, even if her initial seizure was triggered by the vaccination. It is not Madison's seizure that caused her condition, but her condition that caused the seizure. DS would have taken its tragic toll on Madison's health whether or not she was vaccinated on March 28, 2002. See Resp't Ex. WW at 3 (Dr. Raymond stating that the Spiczak article reinforced his argument that SCN1A mutation is the sole cause of Madison's epilepsy "and that immunization has not altered her diagnosis or course.").

The overwhelming evidence established that the genetic mutation Madison possessed resulted in cellular abnormalities severely and specifically impairing brain function. As Dr. Raymond explained, vital structures in Madison's brain cells were not "built" properly because one of the building blocks (an amino acid) was effectively missing, due to the missense mutation. Tr. II at 48-51 (noting substitution of an amino acid with different chemical properties). Unfortunately, science has not discovered how to correct genetic abnormalities. As a result, the structure of Madison's brain cells was permanently flawed.

Petitioners also maintained that Madison had at most a latent genetic problem that became active only when she was vaccinated. Pet'r Post-Hr'g. Br. at 11-12. Parts of Dr. Tornatore's testimony echoed this argument. But his testimony that Madison had "really normal development" up to the time of her first seizure conflicted with the science: a child with a mutation like Madison's does not have "normal" development. She may have seemed normal to parents and even treating physicians. But she was not in fact developing normally because she had, from conception, a serious medical condition that interfered with normal development.[44] The disabilities caused by the mutation were bound to become manifest, in the manner they did, as Madison's brain developed. Dr. Tornatore's testimony concerning SCN1A mutations and DS clashed with a well-developed body of scientific knowledge, undermining the persuasiveness of his opinions.

The record does not support Dr.Tornatore's insistence that, because the vaccine triggered Madison's first seizure, the initial seizure must have played some role in causing her neurological condition. I credit instead Dr. Raymond's testimony that, if Madison had not suffered an initial seizure following her vaccination, she would have suffered a similar seizure soon thereafter, because that is the known pattern in cases of

[44] The Secretary's expert, Dr. Raymond, testified that vaccination "unmask[ed]" Madison's DS. Tr. II at 96-97. In other words, the initial seizure was the first symptom of Madison's underlying neurological disorder. Until she suffered that first convulsion, she appeared normal, but she was not.

DS. Madison's vaccine reaction was just one manifestation of many she suffered from her severe, underlying genetic disorder.

In short, the injury in Madison's case occurred following vaccination but not because of vaccination. Any febrile event might have produced the same injury in someone with DS, particularly at Madison's stage of development. Madison was destined from infancy to suffer a variety of febrile and afebrile seizures, because of the underlying neurological dysfunction produced by the mutation in her SCN1A gene. The same dysfunction would inevitably have resulted in additional developmental and other disabilities, as the effects of her underlying genetic disorder continued to manifest. The first seizure, triggered by vaccination, was merely a symptom, not a cause, of Madison's disorder. There was no reliable evidence in this record to the contrary.

### 3. Other challenges to logical cause and effect

**(a)** In opposition to the Secretary's assertion of causation due to genetic mutation, Dr. Tornatore also criticized some of the literature relied upon by Dr. Raymond. In particular, he testified that the mouse experiments reported in the Oakley article, Resp't Ex. VV-9, did not produce the expected outcomes. Tr. II at 139-43. Dr. Tornatore took issue with the assertion in the Oakley mouse study that there was a "close correspondence" between human and mouse subjects with regard to temperature and age dependence and the incidence of seizures. In particular, he challenged the close correspondence between age and seizures. Tr. II at 139-43; see Resp't Ex. VV-9 at 1.

Assuming without deciding that the Oakley study is vulnerable to criticism on this point, it would not diminish the impact of the study's finding that alteration of the SCN1A gene produced the symptoms of DS in mice. Even if the authors of the Oakley article were wrong about the fidelity of the disease pattern in humans and mice, it would not significantly change the balance of the other evidence in the record overwhelmingly favoring the conclusion that the sole cause of Madison's initial seizure was genetic mutation.

**(b)** Dr. Tornatore noted that a substantial number of children with DS who suffered post-vaccination seizures were not reported to have had fever at the time of seizure. Tr. II at 183. This was an attempt to challenge Dr. Raymond's assertion that Madison's initial seizure resulted from the sensitivity of DS sufferers to even slight elevation in temperature, by suggesting that something else about vaccination, not solely fever, was the precipitating factor. Dr. Tornatore appeared to be correct, but his observation did not vitiate the impact of Madison's diagnosis of DS. Regardless of what triggered her initial seizure (and it does appear from the literature that fever is the triggering event in many cases), the evidence was overwhelming that Madison had the genetic mutation known to cause DS, she had DS, and DS causes the symptoms from which she suffered. Another way of addressing Dr. Tornatore's criticism is to note again that the Secretary is not required to present an air-tight case of alternative factor causation, any more than petitioners are required to establish causation-in-fact with

anything approaching certainty. See de Bazan, 539 F.3d at 1354; Knudsen, 35 F.3d at 548-49; Hanlon, 191 F.3d at 1349.[45]

**(c)** In cross-examination of Dr. Raymond, counsel for Petitioners attempted to undercut his testimony that DS, not vaccination, explained Madison's disabilities. Dr. Raymond agreed that Madison's SCN1A mutation was not identical to those of other subjects with DS. Tr. II at 87, 218-19. It was clear, however, that the de novo missense mutation Madison possessed occurred in a region of the SCN1A gene that is known to produce severe epilepsy syndromes, including DS. Although Madison's SCN1A mutation was not identical to those of other subjects with DS, it was the type of mutation that is well known in the medical community to result in the disorder. See Resp't Ex. VV-8 at 5 (Mulley). Dr. Raymond's testimony and the literature the Secretary submitted more than preponderantly supported the conclusion that the type of mutation in Madison's case would likely have caused her DS. There was no medical evidence that would support the contention that the mutation must be identical to one previously identified in order to produce the characteristics known to result from the type of mutation in question. Nor is it logical to require proof of an identical mutation in order to establish a chain of cause and effect between the mutation and the disorder.

**(d)** Similarly, counsel elicited Dr. Raymond's agreement that it is not known how many people in the general population have "Madison's mutation." See Tr. II at 210-11. Petitioners sought to establish that Madison's mutation might be harmless, suggesting that people in the general population may have similar mutations. Petitioners presented no evidence in support of this speculative proposition. The literature submitted by the Secretary tended strongly to refute that notion. See, e.g., Resp't Ex. VV-17 at 2 (McIntosh) (indicating an absence of this type of single nucleotide polymorphism in the databases of healthy individuals).

**(e)** As discussed above, Dr. Tornatore continued to propose an immunological component to explain Madison's initial seizure and subsequent disorder. The evidence of an immunological reaction was greatly outweighed by the evidence of a genetic cause, however. Even assuming that an immunological deficiency coupled with vaccination accounted for Madison's first seizure, the long course of her subsequent seizures and, in particular, her other developmental problems, can best be explained by DS, which is notable for exactly such a clinical course. Dr. Tornatore's theory of spiking fevers due to atypical Kawasaki's disease, caused by an immunological deficit coupled with vaccination, did not explain Madison's ataxia, for example. Nor, as Dr. Raymond pointed out, did it explain why Madison's seizures were refractory to conventional anti-convulsant drug therapy. Tr. II at 123.

Madison's immunological deficiency was treated for years with IVIG infusions. The treatments did not relieve her neurological symptoms. She may have had an immunological disorder as well as DS but, considering the great weight of the evidence,

[45] I also find persuasive Dr. Raymond's explanation that children with DS are so sensitive to even slight elevation in temperature that their first seizures may be febrile but are not recorded as such. See Resp't Ex. XX at 1.

an immunological deficiency did not cause her neurological injuries. It is most notable that Madison's treating physicians, once they learned the results of her genetic tests, agreed that her neurological problems were caused by DS. Tr. II at 61-62; Pet'r Ex.14 at 5 ("finally she does have a diagnosis to her neurological problems").

### E. Althen Prong 3

To show causation, a petitioner must establish that the injury occurred within a time frame that is consistent with the theory of causation set forth. See Pafford, 451 F.3d at 1358. The Secretary must establish that the harm alleged by Petitioner occurred within an appropriate time frame, given the nature of the alleged alternative causation factor. A proximate temporal relationship must be within a "medically acceptable" timeframe. de Bazan, 539 F.3d at 1352. What constitutes an appropriate temporal association is a question of fact and will vary with the particular theory of causation advanced. See Pafford, 451 F.3d at 1358; de Bazan, 539 F.3d at 1352.

The Secretary proved with expert testimony and medical literature that Madison's initial seizure occurred at the time of life when such an event typically would occur in a child with DS. The initial, prolonged seizure happens in children with DS around the age of six months (when Madison's seizure in fact occurred). The onset of the first seizure within 24 hours of vaccination is reported commonly in children with severe epilepsy syndromes. See Ct. Ex. 1 at 1 (Spiczak).

Madison's subsequent medical history, including the development of additional seizures of various types and associated neurological disorders as she aged, also occurred during an appropriate time frame for DS to be the cause. See Tr. II at 16, 52-55.

There was persuasive evidence that the time frame in which Madison's symptoms developed was consistent with the diagnosis of DS. The fact that her treating physicians found the diagnosis DS appropriate in Madison's case added further support to this fact finding. Petitioner offered no evidence that the timing of Madison's symptoms was inconsistent with DS.

In sum, Respondent submitted more than preponderant evidence that an alternative factor, Madison's genetic mutation, was the sole substantial cause of her neurological condition. [46]

### F. Significant Aggravation

Special Master Millman's decision did not address the question of significant aggravation, which apparently was not alleged originally as an alternative theory of

[46] Having found that Madison's SCN1A mutation was the sole substantial cause of her neurological condition, there is no occasion here to apply the holding in Shyface v. Sec'y of Dep't of Health & Human Servs., 165 F.3d 1344 (Fed. Cir. 1999), which permits an award of compensation where both vaccination-related and non-vaccination-related factors caused injury.

entitlement. While I have again taken into account all the proceedings and evidence from the beginning of this case, I render this part of my decision on a clean slate. I conclude that Petitioners failed to carry their burden to establish a prima facie case of significant aggravation and that Respondent, in any event, carried her burden to prove alternative causation.

### 1. Burden and standard of proof

Significant aggravation is defined as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." 42 U.S.C. § 300aa-33(4). The burden of showing a prima facie case of significant aggravation is on the petitioner, and the Secretary "'is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief.'" Doe 11 v. Sec'y of Dep't of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010) (quoting de Bazan, 539 F.3d at 1353), cert. denied, 131 S.Ct. 573 (2010). Only if the petitioner satisfies the prima facie burden is the Secretary required to prove "'that the pre-existing condition was, in fact, the cause of the individual's post-vaccination significant aggravation.'" Loving ex rel. Loving v. Sec'y of Dep't of Health & Human Servs., 86 Fed. Cl. 135, 144 (quoting Whitecotton v. Sec'y of Dep't of Health & Human Servs., 81 F.3d 1099, 1107 (Fed. Cir. 1996)).

The Secretary may rebut a prima facie showing of significant aggravation with preponderant evidence that the significant aggravation was "due to factors unrelated to the administration of the vaccine[.]" 42 U.S.C. § 300aa-13(a)(1)(B); see Knudsen, 35 F.3d at 548-49.

### 2. Analysis of Significant Aggravation

Petitioners did not carry their prima facie burden to establish significant aggravation of a pre-existing condition. Madison's condition, Dravet's syndrome, progressed in the manner to be expected and was not aggravated by vaccination. Doe 11, 601 F.3d at 1358 (Fed. Cir. 2010). Even assuming Petitioners were deemed to have established their prima facie case, the Secretary submitted more than preponderant evidence that an unrelated factor, DS, was the sole substantial cause of Madison's condition, as discussed above.

Petitioners claimed that simply because Madison suffered a seizure for the first time after her vaccination, the requirement for proving "significant aggravation" of a pre-existing condition had been met. See Pet'r Post-Hr'g Br. at 14-15. Petitioners' argument overlooked a key element of the claim for significant aggravation. The Vaccine Act requires proof of "the action of the vaccine on a pre-existing condition, i.e., a condition not precipitated by the vaccination in question." Childs v. Sec'y of Dep't of Health & Human Servs., 33 Fed. Cl. 556, 559 (1995). Petitioners must prove that Madison had a condition before the vaccination that was significantly aggravated.

Petitioners did not undertake to provide such proof; on the contrary, they maintained that Madison was "really normal" before vaccination. Tr. II at 171.

As noted in Childs, application of the "pre-existing condition" language in the statute as written is compelled by the legislative history. See Childs, 33 Fed. Cl. at 559 (quoting legislative history noting that significant aggravation "is meant to encompass serious deterioration (*e.g.*, a child with monthly seizures who, after vaccination has seizures on a daily basis)."). Thus, vaccination "could not both be [a] cause [of] the injury and simultaneously aggravate it." Id. at 559.

Applying that principle to this case, I conclude that no viable claim for significant aggravation was presented. Madison had had no seizures before her vaccination on March 28, 2002. The occurrence of a first seizure after that date did not constitute significant aggravation of a seizure disorder. If, on the other hand, the pre-existing condition alleged were Madison's genetic disorder, that condition was not aggravated at all. It manifested itself at the time and in the manner to be expected based on the characteristics of Madison's SCN1A mutation. As stated in the McIntosh article:

> Our findings show that although vaccination might sometimes seem to trigger the onset of Dravet syndrome, there is no evidence that patients in the vaccination-proximate group had a different disorder from those in the vaccination/distant group. In particular, the similarity in clinical and outcome measures between patients in the vaccination/proximate group and those in the vaccination/distant group is not consistent with vaccination itself affecting the severity of the disorder.

Resp't Ex. VV-17 at 5-6 (McIntosh).

If the pre-existing condition were immune dysfunction, enterovirus infection or atypical Kawasaki syndrome, or any other condition proposed before it was known that Madison had DS, the requirement set forth in Childs theoretically could be met. The Secretary, however, rebutted the allegation that Madison's immune dysfunction or other alleged illnesses were significantly aggravated by vaccination. The Secretary proved that her condition could be entirely explained by, and was directly and solely attributable to, a different cause: SCN1A mutation. Establishment of the reason Madison was prone to seizures and other developmental disorders overwhelmed the vague and speculative claims that vaccination exacerbated pre-existing immune dysfunction or some other latent defect. See Resp't Ex. RR at 6 (Dr. Raymond: "Whether Madison had Kawasaki disease or not is immaterial to her initial presentation in March and her subsequent course which are completely consistent with Dravet syndrome. The same applies to the concerns that she may have immune deficiency."); see also Resp't Ex. XX at 2 ("With the benefit of all of the information that we now have, this tentative considering of 'atypical Kawasaki syndrome' should be dismissed."). The Secretary more than carried the burden of proving that any aggravation of Madison's pre-existing condition was due to a cause unrelated to the administration of a vaccine. See 42 U.S.C. § 300aa-13(a)(1)(B); Knudsen, 35 F.3d at 547.

### 3. Petitioners' Other Arguments Regarding Significant Aggravation Are Not Supported By Preponderant Evidence.

#### a. Milder disorders resulting from SCN1A mutation

Petitioners argued that not all individuals with SCN1A mutations get DS, and this is true. But those who have de novo missense mutations in a conserved region of the genome are highly likely to have DS. See Tr. II at 48-51; Pet'r Ex. 15 at 8-9. This cannot reasonably be disputed on the record in the case, including the abundant medical literature linking these mutations with severe phenotypes. Madison's mutation was completely consistent with the severity of her disorder.

#### b. Initial Seizure Would Not Have Occurred When It Did Absent Vaccination.

The medical literature established an association between vaccination and initial seizures in children with DS. See Resp't Ex. VV-17 (McIntosh); Ct. Ex. 1. No reliable evidence was adduced, however, to show that seizure after vaccination affects the outcome in children who have DS. In Madison's case, her first seizure occurred at age seven months, around the time when it would be expected to occur in a child with DS without vaccination. As noted above, there was no reliable evidence that the first seizure caused damage to Madison's brain, whether or not it was caused by vaccination.[47] No reliable scientific data supported the suggestion that delaying vaccination would have ameliorated her condition: children do not "grow out of" Dravet's syndrome. Tr. II at 100-01. In sum, the great weight of the evidence refutes the allegation that vaccination, because it induced a seizure, worsened Madison's condition.

## IV. CONCLUSION

The Secretary proved that Madison's DS made her likely to experience an initial, prolonged seizure at around six months of age. In patients with DS, it is known that elevated temperature can trigger seizures. That was the Secretary's theory to explain Madison's initial seizure following vaccination. Other seizures in DS victims may occur following vaccination, without fever. This did not diminish the power of the scientific evidence concerning the devastating effect of Madison's type of mutation. Nor did it change the fact that the outcome is the same in DS cases, with or without vaccination. Some event will trigger an initial seizure followed by numerous, intractable seizures of various kinds, and serious developmental problems. There was no reliable evidence that an initial seizure, even if induced by vaccination, causes or exacerbates DS.

Unlike cases in which the cause of an initial first seizure is unknown and, in a field bereft of knowledge, see Althen, 418 F.3d at 1280, may therefore be presumed to

[47] Petitioners relied on one study, by Nieto-Barrera, that plainly was conducted and published without the author's having knowledge of the effect of SCN1A mutations. Pet'r Ex. 31. The author's speculation that vaccination might cause encephalopathy lacked any persuasive value, because he evidently did not know or study the genetic basis for DS.

result in sequelae, in this case DS provided a complete, alternative explanation for Madison's condition. Her initial seizure was the first symptom of a genetic syndrome that produced all the neurological effects documented in her medical record.

For the foregoing reasons, Petitioners have not established entitlement to compensation under the Vaccine Act, and their Petition must be **DISMISSED**. In the absence of a timely motion for review filed pursuant to Vaccine Rule 23, the Clerk is directed to enter judgment according to this decision.

**IT IS SO ORDERED.**

s/ Dee Lord
Dee Lord
Special Master