

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 04-1041V

Filed: April 15, 2010

To Be Published

JENNIFER STONE and GARY STONE,
Parents and Next Friends of AMELIA STONE,
a minor,

Petitioners,

v.

SECRETARY OF HEALTH AND HUMAN
SERVICES

Respondent.

Severe Myoclonic Epilepsy of Infancy
(SMEI); Dravet Syndrome; Complex
Febrile Seizure; SCN1A Gene Mutation;
DTaP Vaccine

Richard Gage, Richard Gage, PC, Cheyenne, WY for petitioners.

Alexis Babcock, United States Department of Justice, Washington, DC, for respondent.

DECISION¹

GOLKIEWICZ, Special Master.

Jennifer and Gary Stone seek compensation on behalf for their daughter, Amelia Stone, who suffers from Severe Myoclonic Epilepsy of Infancy (“SMEI”), which is also known as Dravet

¹ Because this Decision contains a reasoned explanation for the undersigned’s action in this case, the undersigned intends to post this Decision on the United States Court of Federal Claims’ website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002). As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction “of any information furnished by that party (1) that is trade secret or commercial or financial information and is privileged or confidential, or (2) that are medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of privacy.” Vaccine Rule 18(b). Otherwise, the entire Decision will be available to the public. Id.

Syndrome.² Petitioners allege a DTaP vaccination Amelia received was a substantial cause of her SMEI. Respondent denies the DTaP vaccination caused Amelia's injury. Respondent alleges that Amelia's SMEI is caused by a mutation in her SCN1A gene. The undersigned finds respondent has demonstrated by a preponderance of the evidence that Amelia's SCN1A gene mutation more likely than not caused her SMEI.

I. Procedural History

On June 21, 2004, petitioners, Jennifer and Gary Stone, filed a Petition on behalf of their daughter, Amelia Stone, pursuant to the National Vaccine Injury Compensation Program ("the Act" or "the Program").³ The Petition alleged that Amelia suffered a "Table" encephalopathy as a result of the Diphtheria-Tetanus-acellular-Pertussis ("DTaP") vaccine she received on August 27, 2001. Petition ("Pet.") at 3. In the alternative, petitioners "allege that the illness, disability, and condition which afflicted Amelia in the immediate wake of her . . . Comvax, DTaP, IPV, and Prevnar vaccinations on August 27, 2001, and Hepatitis B vaccine on April 19, 2002, were caused in fact by the vaccines and the reaction which Amelia suffered."⁴ *Id.* at 4. On March 11, 2005, respondent filed a Report pursuant to Vaccine Rule 4(c) contending that compensation was inappropriate and the Petition should be dismissed. R Report at 20, filed March 11, 2005.

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A particular epilepsy syndrome, severe myoclonic epilepsy of infancy (SMEI), has become increasingly recognised. SMEI begins in the first year of life in previously healthy children. Hemiclonic seizures, which may be long lasting, are characteristic and can be associated with fever. Myoclonic, absence, tonic-clonic, and partial seizures also occur. The epilepsy is refractory and developmental regression ensues.

Respondent's Exhibit ("R Ex") F3, Samuel F. Berkovic *et al.*, De-novo Mutations of the Sodium Channel Gene SCN1A in Alleged Vaccine Encephalopathy: A Retrospective Study, 5 LANCET NEUROL. 488 (2006)("Berkovic *et al.*"). The terms Dravet, Dravet Syndrome and SMEI are used synonymously throughout this Decision.

³ The National Vaccine Injury Compensation Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 *et seq.* (2006). Hereinafter, individual section references will be to 42 U.S.C.A. § 300aa of the Vaccine Act.

⁴ Petitioners ultimately pursued compensation on the theory that the DTaP vaccination "was a substantial cause" in-fact of her Severe Myoclonic Epilepsy of Infancy (SMEI). Petitioner's Post Hearing Memorandum ("P Memo") at 27; *see also* P Ex 48 (Dr. Kinsbourne states the "DTaP vaccination was the proximate cause or trigger of Amelia Stone's Dravet Syndrome (SMEI)"). Petitioners did not pursue a Table claim, or a cause in-fact claim relating to any of the other vaccinations Amelia received. In addition, petitioners chose not to prosecute this matter as a significant aggravation case. However, the undersigned would have reached the same conclusion in this matter had petitioners pursued a significant aggravation theory in this matter.

Thereafter, multiple expert reports were filed by the parties' respective experts. To elicit expert testimony, a Hearing was held on August 2, 2006. Petitioners presented Marcel Kinsbourne, M.D., as an expert witness. Respondent presented Michael Kohrman, M.D., as an expert witness. See Transcript, filed August 25, 2006 ("Tr 1"). The parties filed additional literature and reports from their respective experts subsequent to the Hearing, held August 2, 2006, and on October 19, 2006, filed a joint status report indicating that the record was complete. However, the undersigned required additional information from the parties' respective experts regarding the nature of Amelia's post-vaccination seizures before making a finding. See Order, filed March 14, 2007. In responding to the undersigned's inquiry, Dr. Kohrman indicated that "[n]ew and important data about genetics of vaccine associated encephalopathy and Dravet Syndrome ha[d] been published since [his] initial opinion and testimony in this case." That literature reported that Dravet Syndrome is caused "by mutations of the Sodium Channel 1a subunit gene [SCN1A]." R Ex F at 1-2.

Ultimately, petitioners filed a laboratory report of an SCN1A DNA Sequencing Test performed on Amelia that confirmed Amelia possesses a de novo variant, a mutation, in the SCN1A gene. Petitioners' Exhibit ("P Ex") 40 at 6.⁵ Respondent filed an expert report on March 5, 2008, by Gerald Raymond, M.D. Dr. Raymond is a board certified geneticist and neurologist, with a speciality in child neurology. R Ex K at 10. Dr. Raymond opined Amelia's SMEI is caused solely by her SCN1A gene mutation, a factor unrelated to her vaccinations. R Ex J at 5. Thereafter, the undersigned granted petitioners nearly an additional year in which to file an expert response to Dr. Raymond's opinion.⁶ Despite the undersigned's strong encouragement that petitioners retain an expert in genetics to respond to Dr. Raymond's report in addition to any response from Dr. Kinsbourne, petitioners ultimately decided to offer only the opinion of Dr. Kinsbourne and not that

⁵ The undersigned notes the parties made multiple filings arguing the effect of the gene mutation if Amelia was found positive for it and whether or not the undersigned could compel that Amelia be tested for the mutation. Initially, a Hearing was scheduled to address these issues. Thereafter, the parties agreed during a telephonic status conference on December 22, 2007, to cancel the Hearing as petitioners' counsel agreed Amelia would undergo genetic testing to determine if she had the SCN1A gene mutation. Subsequent to the status conference on December 22, 2007, and many months after this issue was first brought to light by Dr. Kohrman, petitioners' counsel discovered the genetic test had been administered to Amelia on January 25, 2005. Thus, petitioners should have been aware Amelia possessed this mutation associated with SMEI prior to the first Hearing conducted in this matter on August 2, 2006. Had this information been timely filed with the court, the procedural history of this case would have assuredly been far less drawn out.

⁶ Numerous status conferences were held to discuss the filing of petitioners' response to Dr. Raymond's report. See Stone v. Sec'y of Dept. of Health & Human Servs., No. 04-1041V, Minute Entries filed March 27, 2008, July 11, 2008, November 5, 2008, December 22, 2008. Petitioners initially indicated to the court they intended to retain a geneticist and file a report from both a geneticist and Dr. Kinsbourne. See Petitioners' Status Report filed April 11, 2008. Petitioners received numerous extensions of time to file both reports. See Orders filed March 28, 2008, May 15, 2008, July 11, 2008, September 11, 2008 (Non-PDF Order).

of a geneticist.⁷

On May 15, 2009, an expert Hearing was convened to take the testimony of Drs. Raymond and Kinsbourne regarding SCN1A gene mutations in general and the medical significance of the mutations in the case of Amelia Stone. For expediency, testimony was taken at the same time in a separate case pending before the undersigned, Hammitt v. Sec'y of Dept. of Health & Human Servs., No. 07-170V.⁸ Subsequently, the parties filed simultaneous Post-Hearing Briefs. This matter is now ripe for resolution.

II. Factual History

Amelia Stone was born on April 17, 2001. Pet at 1. On August 27, 2001, Amelia received a DTaP vaccination, as well as other childhood vaccinations. Id.; P Ex 1 at 1. At 5:00 a.m., on August 28, 2001, Amelia was given Tylenol due to “feeling sweaty” and to possibly treat a low-grade fever and any post-vaccination aches and pains. P Ex 7(a) at 3, 100, 105-06. Her mother reported Amelia was alert and feeding when she experienced her first seizure. Amelia “developed tonic-clonic activity of the upper left extremity with a very tightly clenched fist. . . . This shaking lasted about one-half hour.” P Ex 2 at 7. Amelia was taken to the emergency room at Mercy Medical Center in Oshkosh where Dr. Devermann recorded that Amelia had a “flaccid L[eft] U[pper] E[xtremity] and questionable weakness of the L[eft] L[ower] E[xtremity].” Id. at 9. Amelia’s temperature was noted to be 100.6 degrees, and she was described as “irritable but alert” and “want[ing] to feed.” Id. While being evaluated, Amelia had another severe seizure. It took “45 minutes to achieve [IV access] . . . IM Lorazepam . . . and rectal valium given, [and the] seizure stopped after about 30 minutes.” Id. Her temperature was taken during this seizure and was recorded at 101.2 degrees. Id. Dr. Devermann noted his impression to be “[s]eizure disorder, uncertain etiology. Infection/reaction to immunization/underlying metabolic disorder to be

⁷ The court’s notes indicate that at the December 15, 2008 status conference to discuss further proceedings in this matter, Minute Entry filed December 22, 2008, petitioners’ counsel indicated he did not intend to present the opinion of an expert geneticist in response to Dr. Raymond’s opinion. Thereafter, the court granted petitioners an additional two extensions of time to file Dr. Kinsbourne’s response. See Order, filed December 22, 2008; Order, filed February 24, 2009.

⁸ The undersigned notes the instant case and the Hammitt case present the same issue regarding the relationship of the SCN1A gene mutation to SMEI. Thus, the parties agreed for the convenience of the parties, the experts, and the court that testimony would be taken at a joint Hearing. The parties involved waived all applicable privacy provisions to allow for the joint Hearing and agreed the resultant transcript would be filed into the record of each case. On the day prior to the joint expert Hearing, a Hearing was conducted to elicit testimony solely regarding petitioners’ case-in-chief in Hammitt. The undersigned notes the Transcript for the May 15, 2009 (combined Stone and Hammitt) Hearing (“Tr 2”) begins on page 266. The parties agreed the voir dire of Dr. Kinsbourne conducted during May 14, 2009 Hearing in the Hammitt case would be filed into the record in the instant case. Order filed December 4, 2009 (“Tr 3”). The undersigned shall use the page numbers provided within each transcript, as opposed to those designated by the court’s electronic filing system, for citation purposes.

considered.” P Ex 2 at 10.

Dr. Devermann arranged to have Amelia flown to the Pediatric Intensive Care Unit (PICU) at University of Wisconsin Hospital in Madison (“UW Madison”). Id. Upon arrival at UW Madison, Amelia was described as “status epilepticus⁹,” P Ex 7(a) at 3; however, after extubation that same night “she quickly returned to her usual state of health and was feeding well.” Id. at 107. Among other tests, Amelia received an MRI while at UW Madison on August 29, 2001. Id. at 94. The MRI report was electronically signed by Victor M. Haughton, M.D., on August 31, 2001, and noted the following impression: “Normal head MRI for age with no findings to explain the patient’s symptoms.” Id. Amelia was discharged on August 31, 2001, and it was noted she “continued to feed well and showed no seizure activity or neurologic deficit.” Id. at 107. It was also noted that she should not receive further pertussis vaccinations “due to the possible relation of her four month immunizations” and subsequent seizure activity. Id.

Dr. Devermann saw Amelia for a follow-up examination on September 7, 2001. At this time Dr. Devermann noted she was “alert [and] smiling,” had “[g]ood head control” and that her “[e]ye movement [was] normal.” P Ex 1 at 17. Dr. Devermann’s assessment at that time was that Amelia had a “seizure disorder” of “uncertain etiology.” Id. He stated that it was “not clear [to him] if this [her seizure disorder] is primary or related to Pertussis,” but advised against further pertussis or Pevnar vaccinations. Id.

Amelia was found seizing again by her mother on September 26, 2001, at approximately 4:00 a.m. P Ex 2 at 22. Amelia was suffering from a runny nose and her temperature was measured at 102.9 degrees when she was brought into the emergency room. Id. She was also suffering from a “potential urinary tract infection” (UTI). Id. at 24. Her seizure continued until 5:30 a.m. when it was controlled by “two doses of Ativan.” Id. at 22. Amelia was stabilized and once again transferred to UW Madison by helicopter. Id. at 24. An MRI was again performed at UW Madison and the results were “normal.” P Ex 7(b) at 176.

Dr. Devermann saw Amelia for a follow-up on October 5, 2001, and noted the “working diagnosis” was a “generalized seizure disorder.” P Ex 1 at 21. Dr. Devermann noted at Amelia’s six-month check-up on December 19, 2001, that “[i]t appears now that she has a primary seizure disorder,” but that her “neurologic development has been appropriate.” Id. at 26. Amelia continued to experience seizures, both febrile and afebrile. See, e.g., Id. at 29, 39, 41, 44, 45, 48, 55-57, 61. Amelia was evaluated by Kenneth Mack, M.D., at the Mayo Clinic on May 30, 2002. He noted Amelia suffers from a “very aggressive seizure disorder.” P Ex 6 at 3. Dr. Mack also noted Amelia and her father both possess a chromosome 20 duplication. Id. at 2. Although Dr. Mack did not appear to believe the chromosome 20 duplication was related to Amelia’s condition, he did suggest the family meet with someone in genetics due to their anxiety about the duplication. Id. at 3. He

⁹ Status Epilepticus: “1. A continuous series of generalized tonic-clonic seizures without return to consciousness, a life-threatening emergency. . . .2. any prolonged series of seizures without return to full consciousness between them. . . .” STEDMAN’S MEDICAL DICTIONARY 1756 (27th ed. 2000).

also noted “[d]evelopmental regression is a concern.” *Id.* at 2.¹⁰ A September 14, 2003, hospital admission for continued seizures noted Amelia’s “[i]mmunizations are not up-to-date due to parental beliefs, and they do not intend to immunize her with pertussis or Prevnar.” P Ex 42, Part 2 at 39.

Amelia continues to suffer from this aggressive seizure disorder, which was ultimately diagnosed as Severe Myoclonic Epilepsy of Infancy, SMEI, or Dravet Syndrome,¹¹ on October 6, 2003, by Mary Zupanc, M.D., the Chief of Pediatric Neurology at the Children’s Hospital of Wisconsin. P Ex 10(o) at 104 (notes Amelia suffers “generalized epilepsy - probable severe myoclonic epilepsy”); P Ex 10 (b) at 24 (provides Dr. Zupanc’s credentials). Dr. Zupanc’s assessment on October 27, 2004 noted “SMEI is genetically determined, a sodium channelopathy, and very difficult to treat.” P Ex 42, Part 1, at 22. Genetic testing performed on January 25, 2005, revealed Amelia possesses a de novo mutation to her SCN1A gene. P Ex 40 at 6. These results were interpreted by the laboratory as follows: “[t]his finding is most consistent with this DNA variant being associated with a severe phenotype¹² (SMEI or SMEB) rather than a mild or normal phenotype.” P Ex 40 at 6.

III. Legal Standard

Causation in Vaccine Act cases can be established in one of two ways: either through the statutorily prescribed presumption of causation or by proving causation-in-fact. Petitioners must prove one or the other in order to recover under the Act. According to §13(a)(1)(A), claimants must prove their case by a preponderance of the evidence.¹³

¹⁰ Dr. Linda Lax at Children’s Memorial Hospital also noted the chromosome 20 duplication and noted that it “is felt to be clinically inconsequential.” P Ex 41 at 2.

¹¹ It was noted Amelia “probably” had SMEI on her June 10, 2003 hospital discharge. P Ex 42, Part 3 at 39.

¹² Two words used throughout this Decision and the record are genotype and phenotype. Genotype is defined as: “1. The genetic constitution of an individual. 2. Gene combination at one specific locus or any specified combination of loci.” STEDMAN’S MEDICAL DICTIONARY, 800 (28th ed. 2006). Phenotype is defined as: “The observable characteristics, at the physical, morphologic, or biochemical level, of an individual, as determined by genotype and environment.” STEDMAN’S MEDICAL DICTIONARY, 1478 (28th ed. 2006); see Tr 2 at 322 (In this case, Dr. Raymond explained “genotype is the alteration in DNA; phenotype is the clinical finding.”).

¹³ A preponderance of the evidence standard requires a trier of fact to “believe that the existence of a fact is more probable than its nonexistence before the [special master] may find in favor of the party who has the burden to persuade the [special master] of the fact’s existence.” In re Winship, 397 U.S. 358, 371-72 (1970)(Harlan, J. concurring)(quoting F. James, CIVIL PROCEDURE, 250-51 (1965)). Mere conjecture or speculation will not establish a probability. Snowbank Enter. v. United States, 6 Cl. Ct. 476, 486 (1984).

For presumptive causation claims, the Vaccine Injury Table lists certain injuries and conditions, which if found to occur within a prescribed time period, create a rebuttable presumption that the vaccine caused the injury or condition. §14(a). Petitioners have chosen to pursue this case as an off-Table injury for the DTaP vaccination, therefore petitioners must prove that the vaccinations in-fact caused Amelia's injuries.

To demonstrate entitlement to compensation in an off-Table case, petitioners must affirmatively demonstrate by a preponderance of the evidence that the vaccination in question more likely than not caused or significantly aggravated the injury alleged. See, e.g., Bunting v. Sec'y of Dept. of Health & Human Servs., 931 F.2d 867, 872 (Fed. Cir. 1991); Hines v. Sec'y of Dept. of Health & Human Servs., 940 F.2d 1518, 1525 (Fed. Cir. 1991); Grant v. Sec'y of Dept. of Health & Human Servs., 956 F.2d 1144, 1146, 1148 (Fed. Cir. 1992); see also §§11(c)(1)(C)(ii)(I) and (II). To meet this preponderance of the evidence standard, “[petitioners must] show a medical theory causally connecting the vaccination and the injury.” Grant, 956 F.2d at 1148 (citations omitted); Shyface v. Sec'y of Dept. of Health & Human Servs., 165 F.3d 1344, 1353 (Fed. Cir. 1999). A persuasive medical theory is shown by “proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury.” Hines, 940 F.2d at 1525; Grant, 956 F.2d at 1148; Jay v. Sec'y of Dept. of Health & Human Servs., 998 F.2d 979, 984 (Fed. Cir. 1993); Hodges v. Sec'y of Dept. of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993); Knudsen v. Sec'y of Dept. of Health & Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994). Furthermore, the logical sequence of cause and effect must be supported by “[a] reputable medical or scientific explanation,” which is “evidence in the form of scientific studies or expert medical testimony.” Grant, 956 F.2d at 1148; Jay, 998 F.2d at 984; Hodges 9 F.3d at 961;¹⁴ see also H.R. Rep. No. 99-908, Pt. 1, at 15

¹⁴ The general acceptance of a theory within the scientific community can have a bearing on the question of assessing reliability while a theory that has attracted only minimal support may be viewed with skepticism. Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 594 (1993). Although the Federal Rules of Evidence do not apply in Program proceedings, the United States Court of Federal Claims has held that “Daubert is useful in providing a framework for evaluating the reliability of scientific evidence.” Terran v. Sec'y of Dept. of Health & Human Servs., 41 Fed. Cl. 330, 336 (1998), aff'd, 195 F.3d 1302, 1316 (Fed. Cir. 1999), cert. denied, Terran v. Shalala, 531 U.S. 812 (2000). In Daubert, the Supreme Court noted that scientific knowledge “connotes more than subjective belief or unsupported speculation.” Daubert, 509 U.S. at 590. Rather, some application of the scientific method must have been employed to validate the expert's opinion. Id. In other words, the “testimony must be supported by appropriate validation – i.e., ‘good grounds,’ based on what is known.” Id. Factors relevant to that determination may include, but are not limited to:

Whether the theory or technique employed by the expert is generally accepted in the scientific community; whether it's been subjected to peer review and publication; whether it can be and has been tested; and whether the known potential rate of error is acceptable.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1316 (9th Cir. 1995) (Kozinski, J.), on remand from, 509 U.S. 579 (1993); see also Daubert, 509 U.S. at 592-94.

(1986), reprinted in 1986 U.S.C.C.A.N. 6344.

While petitioners need not show that the vaccine was the sole or even predominant cause of the injury, petitioners bear the burden of establishing “that the vaccine was not only a but-for cause of the injury but also a substantial factor in bringing about the injury.” Shyface, 165 F.3d at 1352. Petitioners do not meet their affirmative obligation to show actual causation by simply demonstrating an injury bearing similarity to a Table injury or to the Table time periods. Grant, 956 F.2d at 1148; see also H.R. Rep. No. 99-908, Pt. 1, at 15 (1986), reprinted in 1986 U.S.C.C.A.N. 6344. Nor do petitioners satisfy this burden by merely showing a proximate temporal association between the vaccination and the injury. Grant, 956 F.2d at 1148 (quoting Hasler v. United States, 718 F.2d 202, 205 (6th Cir. 1983), cert. denied, 469 U.S. 817 (1984) (stating “inoculation is not the cause of every event that occurs within the ten day period [following it]. . . . Without more, this proximate temporal relationship will not support a finding of causation”)); Hodges, 9 F.3d at 960. Finally, petitioners do not demonstrate actual causation by solely eliminating other potential causes of the injury. Grant, 956 F.2d at 1149-50; Hodges, 9 F.3d at 960.

In Althen v. Sec’y of Dept. of Health & Human Servs., 418 F.3d 1274,1278 (Fed. Cir. 2005), the Court of Appeals for the Federal Circuit reiterated that petitioners’ burden is to produce “preponderant evidence” demonstrating: “(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between the vaccination and injury.” The Federal Circuit stated further that “requiring that the claimant provide proof of medical plausibility, a medically-acceptable temporal relationship between the vaccination and the onset of the alleged injury, and the elimination of other causes – is merely a recitation of this court’s well-established precedent.” Id. at 1281. The Federal Circuit concluded that to support petitioners’

However, the court also cautioned about rejecting novel scientific theories that have not yet been subjected to peer review and/or publication. The court pointed out that the publication “does *not* necessarily correlate with reliability,” because “in some instances well-grounded but innovative theories will not have been published.” Daubert, 509 U.S. at 593. However, the Supreme Court has provided guidance to the lower courts in determining the reliability of a novel proposition:

submission to the scrutiny of the scientific community is a component of “good science,” in part because it increases the likelihood that substantive flaws in methodology will be detected. (citation omitted). The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised.

Id. at 593-94; see Althen v. Sec’y of Dept. of Health & Human Servs., 418 F.3d 1274,1280 (Fed. Cir. 2005) (“the purpose of the Vaccine Act’s preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body.”); see also, Gall v. Sec’y of Dept. of Health & Human Servs., No. 91-1642V, 1999 WL 1179611, at *8 (Fed. Cl. Spec. Mstr. Oct. 31, 1999).

theory of causation, there is no requirement in the Vaccine Act's preponderant evidence standard that petitioners submit "objective confirmation," such as medical literature. Id. at 1279. The Federal Circuit explained that requiring medical literature "prevents the use of circumstantial evidence envisioned by the preponderance standard and negates the system created by Congress, in which close calls regarding causation are resolved in favor of the injured claimants." Id. at 1280 (citing Knudsen, 35 F.3d 543, 549 (Fed. Cir. 1994)); see also Capizzano v. Sec'y of Dept. of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006) ("Capizzano III"). Moreover, the Federal Circuit stated, [t]he purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." Id.

However, the legal requirement that petitioners support their proposed causation theory with a "sound and reliable medical or scientific explanation" is undisturbed. Knudsen, 35 F. 3d 543, 548 (Fed. Cir. 1994). As the Federal Circuit recently reiterated:

Although Althen and Capizzano make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury. See Daubert, 509 U.S. at 593-97, 113 S.Ct. 2786 (noting that one factor in assessing the reliability of expert testimony is whether the theory espoused enjoys general acceptance within a relevant scientific community). . . . Althen makes clear that a claimant's theory of causation must be supported by a "reputable medical or scientific explanation." 418 F.3d at 1278.

Andreu v. Sec'y of Dept. of Health & Human Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); see also Grant, 956 F.2d at 1148 ("A reputable or scientific explanation must support this logical sequence of cause and effect."). The Federal Circuit further explained in Andreu:

The assessment of whether a proffered theory of causation is "reputable" can involve assessment of the relevant scientific data. Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard

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Andreu, 569 F.3d at 1380 (citing Bunting v. Sec'y of Dept. of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991)). Thus, when considering the evidence in a case, the special master is to "consider all relevant and reliable evidence, governed by the principles of fundamental fairness to both parties." Vaccine Rule 8(c); see also Campbell v. Sec'y of Dept. of Health & Human Servs., 69 Fed. Cl. 775, 781 (2006) (Althen's requirement of a "reputable medical or scientific explanation" "[l]ogically . . . requires a special master to rely on reliable medical or scientific evidence . . ."); Manville v. Sec'y of Dept. of Health & Human Servs., 63 Fed. Cl. 482, 491 (2004); de Bazan v. Sec'y of Dept. of Health & Human Servs., 70 Fed. Cl. 687, 699 n.12 (2006) rev'd 539 F.3d 1347 (2008) (reversed on other grounds).

A finding that petitioners established their *prima facie* burden does not end the inquiry. The Act provides that a petitioner may not receive compensation “if the court finds by a preponderance of the evidence on the record as a whole ‘that the illness, disability, injury, condition, or death described in the petition is due to factors unrelated to the administration of the vaccine described in the petition.’” Knudsen, 35 F.3d at 547 (citing §13(a)(1)(B)) (emphasis in original). In Knudsen, the Federal Circuit explained that because the special master “found causation between the vaccine and the injury, he is required under the Vaccine Act to make further finding on the question of alternative causation or etiologies.” Knudsen, 35 F.3d at 551 (citing Grant, 956 F.2d at 1149-50); see also Hanlon v. Sec’y of Dept. of Health & Human Servs., 191 F.3d 1344, 1348 (Fed. Cir. 1999). The Federal Circuit summarized the burden placed on each party in de Bazan v. Sec’y of Dept. of Health & Human Servs., 539 F.3d 1347, 1353-54 (Fed. Cir. 2008) by explaining

The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of petitioner’s evidence on a requisite element of the petitioner’s case-in-chief. . . . [T]he petitioner’s case-in-chief concerns the medical evidence relating to the possible role the *vaccine* had in causing her injury. The government’s burden, in contrast, concerns “factors unrelated to the administration of the vaccine described in the petition.” While a failure of proof that the vaccine was the cause of the petitioner’s injury suggests that some other cause was responsible, that is not equivalent to having proven by preponderant evidence that a *particular* agent or condition (or multiple agents/conditions) unrelated to the vaccine was in fact the sole cause (thus excluding the vaccine as a substantial factor). This latter showing is the government’s burden once the petitioner has met her burden. In other words, successfully proving the elements of the Althen test establishes that the medical evidence indicating that the vaccine may have caused the petitioner’s injury is strong enough to infer causation-in-fact *absent proof that some other factor was the actual cause*. The government then must provide that proof by identifying a particular such factor (or factors) and presenting sufficient evidence to establish that it was the sole substantial factor in bringing about the injury.

Id. (internal citations omitted); see also Walther, 485 F.3d at 1150. “A plain reading of the statutory text more naturally places the burden on the government [respondent] to establish that there is an alternative cause by a preponderance of the evidence.” Walther, 485 F.3d at 1150. Notably the “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. It is axiomatic that the government’s burden to prove causation, like petitioner’s burden, involves the special master “ascertaining whether a sequence of cause and effect is ‘logical’ and legally probable, not medically or scientifically certain.” Id. at 548-49; see also Hanlon, 191 F.3d 1344 at 1349 (citing Knudsen) (“[b]ased on a ‘logical and legally probable’ sequence of cause and effect, she [the special master] determined that TS was the actual alternative cause of Michael’s seizures. A reversal of this finding would improperly require proof of causation that is ‘medically or scientifically certain’”). Petitioners’ case is measured against the above standards.

IV. Discussion

After reviewing the entire record, considering the testimony of both experts, the relevant binding case law discussed above, as well as the undersigned's decisions in Simon Sec'y of Dept. of Health & Human Servs., No. 05-941V, 2007 WL 1772062 (Fed. Cl. Spec. Mstr. June 1, 2007) and Mersburgh Sec'y of Dept. of Health & Human Servs., No. 04-997V, 2007 WL 5160384 (Fed. Cl. Spec. Mstr July 9, 2007), and also former Special Master Edwards' decision in Cusati v. Sec'y of Dept. of Health & Human Servs., No. 05-5049V, 2005 WL 4983872 (Fed. Cl. Spec. Mstr. Mar. 9, 2006), and for the reasons set forth below, the undersigned finds that petitioners would have likely demonstrated entitlement to compensation if respondent had not demonstrated that Amelia's SMEI was caused by the genetic mutation located in her SCN1A gene. See §13(a)(1). A full discussion follows.

The discussion is broken into four parts. First, the undersigned provides a brief overview of the experts presented by each party in this matter. Second, the undersigned discusses petitioners' case-in-chief presented by Dr. Kinsbourne and rebutted by Dr. Kohrman. Third, the undersigned discusses respondent's presentation of evidence, specifically the testimony and opinion of Dr. Raymond. Finally, the undersigned discusses petitioners' rebuttal to respondent's evidence.

A. The Parties' Experts

1. Marcel Kinsbourne, M.D.

Dr. Kinsbourne's curriculum vitae ("CV") reflects a long history of experience in neurology, having begun practice as a physician in England in 1955, following medical education at Oxford University, England. P Ex 12 at 1; see generally Tr 3 at 5-11. Soon thereafter, his CV reflects work in the field of neurology, namely as Senior House Officer, Neurosurgery, in London between 1956 and 1957. P Ex 12 at 1. Dr. Kinsbourne is certified by the American Board of Pediatrics. Id. Among many distinguished professional appointments, Dr. Kinsbourne served as an associate professor in pediatrics and in neurology from 1967 until 1974 at Duke University Medical Center; director of the Behavioral Neurology Department, Eunice Kennedy Shriver Center, from 1981 until 1991; lecturer in neurology at Harvard Medical School from 1981 until 1991; and has held numerous professorships over the years. Id. at 1-2. Dr. Kinsbourne has authored or co-authored a large number of articles in medical journals and texts. Id. at 5-37. He has earned numerous awards and honors and has both previously and currently served on many neurology-related editorial boards. Id. at 2-4. Dr. Kinsbourne currently, *inter alia*, teaches courses in the field of psychology at the New School University. Id. at 2.

Dr. Kinsbourne has testified in the National Vaccine Injury Compensation Program from its inception. Over the years, Dr. Kinsbourne has been found to be persuasive, but also has been criticized. While the undersigned recognized Dr. Kinsbourne's good efforts in Simon v. Sec'y of Dept. of Health & Human Servs., No. 05-941, 2009 WL 623833, *7 (Fed. Cl. Spec. Mstr. Feb. 21,

2008), more recently the undersigned criticized Dr. Kinsbourne's testimony at length with regard to that case but notably discussed the decline in the quality of Dr. Kinsbourne's testimony in recent years. Egan v. Sec'y of Dept. of Health & Human Servs., No. 05-1032, 2009 WL 1440240 at *17-19 (Fed. Cl. Spec. Mstr. May 1, 2009)(unpublished). My colleague expressed similar concerns about Dr. Kinsbourne in Snyder v. Sec'y of Dept. of Health & Human Servs., No. 01-162, 2009 WL 332044, *11-12 (Fed. Cl. Spec. Mstr. February 12, 2009), aff'd, 88 Fed. Cl. 706 (2009). He was also harshly criticized by my former colleague in Moberly ex rel. Moberly v. Sec'y of Dept. of Health & Human Servs., No. 98-910V, 2006 WL 659522, *5-6 (Fed. Cl. Spec. Mstr. Feb. 28, 2006), aff'd, 85 Fed. Cl. 571 (2009), aff'd, 592 F.3d 1315 (Fed. Cir. 2010). The concerns and criticisms raised in these cases were unfortunately apparent with respect to Dr. Kinsbourne's testimony in the instant case. See discussion infra pp. 49-51.

A significant concern regarding Dr. Kinsbourne's reliability as an expert witness is that he has not maintained a "hospital based clinical pediatric neurology practice" since 1981. Tr 3 at 33. Thus, despite his familiarity with cases involving seizure-related disorders alleging vaccine causation and his many past distinguished professional appointments in neurology, Dr. Kinsbourne no longer maintains a clinical practice treating patients with seizure disorders in an acute setting, and has not done so in almost thirty years. Dr. Kinsbourne has continued to see only patients related to the "behavioral aspects" of pediatric neurology after 1981. Id. Dr. Kinsbourne's testimony at the Hearing on May 15, 2009, reflected his lack of recent clinical practice. His testimony is highly generalized and lacks any grounding in practice. While Dr. Kinsbourne may keep current with medical literature, Tr 2 at 437, his testimony amounts to little more than repeating snippets from that literature. He has no current experience or context outside of "behavioral aspects" of pediatric neurology with which to apply, question, or discuss an article's teachings. Dr. Kinsbourne testified he has not focused his practice, research or teaching for the past twenty-five years in the area of seizure disorders. Id. In fact, Dr. Kinsbourne testified he has not "managed seizure disorders since 1980." Tr 1 at 24. Dr. Kinsbourne does not publish, research, teach, counsel, attend meetings or conferences, or have any special training in relation to the field of genetics. Tr 2 at 437-39. Nor does Dr. Kinsbourne have any "experience or training or knowledge in clinical genetics, molecular genetics, and neurogenetics." Id. at 439. The fact that for the past twenty-five years Dr. Kinsbourne has not focused his practice, research or teachings in the field of seizure disorders, and that Dr. Kinsbourne has no expertise in the field of genetics significantly limited his ability to offer reliable, persuasive, and cogent testimony in this case. See discussion infra pp. 49-51.

2. Michael Kohrman, M.D.

Dr. Michael Kohrman is an associate Professor of Pediatrics and Neurology at the University of Chicago. Tr 1 at 28. He is board certified in both pediatrics and neurology with an "added qualification in clinical neurophysiology." Id. He is board certified by the American Board of Clinical Neurophysiology and by the American Board of Sleep Medicine. Id. at 28-29. Dr. Kohrman testified at the Hearing on August 2, 2006, in this matter that approximately 80 percent of his practice was clinical, "split about 90 percent doing epilepsy and ten percent doing sleep medicine." Id. at 29. Dr. Kohrman's patients range in age from premature infants to young adults.

Id. Dr. Kohrman teaches residents, fellows, and medical students at the University of Chicago. Id. Dr. Kohrman testifies from a position of knowledge and current experience and his testimony is highly persuasive. However, his testimony did not figure prominently in the ultimate outcome of this case.

3. Gerald Raymond, M.D.

Dr. Raymond's CV reflects current and impressive credentials in both pediatric neurology and genetics. R Ex K. He is an associate professor in neurology at Johns Hopkins University and the director of neurogenetics at the Kennedy Krieger Institute, an affiliate of Johns Hopkins Medical School. Id. at 1; Tr 2 at 273. Dr. Raymond's specialty is in neurogenetics and he is board certified in neurology with a special competence in both pediatric neurology and clinical genetics. Tr 2 at 276. As a professor at Johns Hopkins Medical School, he teaches neurology to medical students, residents, and fellows. Id. at 275. Dr. Raymond divides his time between clinical research, in which he spends the vast majority of his time, and clinical practice. Id. at 274. Dr. Raymond spends one month as an attending physician each year in the pediatric neurology service, as well as one month each year in the genetics service at Johns Hopkins Hospital. Id. Dr. Raymond performs consulting services in genetics at various other clinics and services with Johns Hopkins. Id. Dr. Raymond provides genetics counseling and consultation to families in relation to the results of genetics tests. Id. at 279. Dr. Raymond acts as a reviewer for a number of medical journals, including the American Journal of Medical Genetics and Neurology. R Ex K at 9-10.

Dr. Raymond's knowledge and experience with neurology and clinical genetics is extensive. His essentially un rebutted testimony was very persuasive and was relied upon heavily in deciding this case.

B. Petitioners' Case-In-Chief

Given the ultimate conclusion in this case, it is unnecessary to delve deeply into petitioners' case-in-chief. As discussed previously, supra p. 4, after being vaccinated on August 27, 2001, Amelia Stone appears to have experienced a fever, and at approximately 5:00 a.m. on August 28, 2001, fourteen hours after being vaccinated, Amelia suffered a seizure lasting approximately thirty minutes. Amelia was taken to the emergency room where she suffered a second seizure that met the definition of status epilepticus. Amelia went on to ultimately develop a severe seizure disorder described as SMEI. SMEI, Dr. Kinsbourne testified,

refers to severe epileptic syndromes starting basically in the first year of life. Being severe they start with prolonged seizures, often status epilepticus, maybe repeated status epilepticus. And as is typical in any infant seizure almost they are often, though not always, triggered by a fever.

Tr 1 at 12. Dr. Kinsbourne opined at the first Hearing in this matter, prior to any evidence being submitted regarding Amelia's SCN1A gene mutation, that Amelia's seizure disorder was caused in

fact by her DTaP vaccination.¹⁵ Dr. Kinsbourne further opined in a report dated April 6, 2007, subsequent to the first Hearing in this matter, that Amelia's initial seizures experienced after her vaccinations were complex febrile seizures. Expert Report filed April 7, 2007. Dr. Kinsbourne opined the characterization of Amelia's seizures as status epilepticus, "a potentially life-threatening emergency," "does not contradict, but subsumes, the diagnosis of febrile complex partial seizure." Id.

This is significant because in the Simon decision, 2007 WL 1772062, the undersigned noted that the following fact pattern is seen frequently in vaccine cases: "An otherwise healthy petitioner receives a vaccination, the vaccine causes a fever, which in turn causes or triggers a complex febrile seizure." Simon, 2007 WL 1772062, at *3. And as the undersigned explained further in Mersburgh:

If a case fits this described pattern, as the case at hand does, the undersigned is strongly inclined to find in favor of the petitioner. As the literature explains,

[c]omplex febrile seizures are "seizures lasting longer than 15 minutes, occurring more than once in a 24 hours, or having focal features." Gregory L. Holmes, M.D., Diagnosis and Management of Seizures in Children, 228 (W.B. Saunders Staff eds., 1987). As discussed by Dr. Holmes, if the first febrile seizure is complex, the risk for developing epilepsy increases significantly. Id. at 228-229; See also Jean Aicardi, M.D., Epilepsy in Children, 231 (Joseph French et al. eds. 1986). In addition, while recognizing that the impact of febrile seizures on intellectual and motor development "has been an area of controversy," citing numerous studies Holmes reported that prolonged or complex seizures are recognized as the antecedent of sequelae. Holmes, supra, at 227-228; see also Aicardi,

¹⁵ In reaching this finding Dr. Kinsbourne appears to rely at least partially on the National Childhood Encephalopathy Study of 1981 (NCES). P Ex 11 at 2-3; Tr 1 at 11, 19-21. The undersigned notes, as in Simon, 2007 WL 1772062, that the undersigned does not find the NCES, its ten year follow up study, or the 1994 report issued by the Institute of Medicine persuasive evidence regarding cases involving the DTaP vaccine. Simon, 2007 WL 1772062, at *7. The aforementioned studies and report concerned the DPT vaccine not the DTaP vaccine. "Thus, it appears to the undersigned the NCES and the ten year follow-up study cannot be utilized to support DTaP causation." Id. The undersigned does not dispute that both DTP and DTaP vaccines may result in the same neurological reactions, however, these events do not occur with the same frequency, nor are the same relative risks present. Id. Thus, the use of these studies to support DTaP causation is highly questionable. Id.; see also Grace v. Sec'y of the Dept. of Health & Human Servs., 2006 WL 3499511 (Fed. Cl. Spec. Mstr. Nov. 30, 2006); see also infra pp. 43-44.

supra, at 231.¹⁶

Mersburgh, 2007 WL 5160384, at * 3 (quoting Simon, 2007 WL 1772062, at *3); see also Cusati v. Secretary of HHS, No. 05-5049V, 2005 WL 4983872 (Fed. Cl. Spec. Mstr. Mar. 9, 2006). Dr. Kinsbourne, consistent with the above-cited literature and cases, summarized his causation theory in the instant matter as follows:

My theory as to the effect of the vaccine is that vaccinations were given at age about four-month in birth children [sic]; that the vaccinations, probably the pertussis vaccination caused the fever; that the fever caused a prolonged seizure classifiable as complex febrile, and indeed status epilepticus. That seizure caused harm to the children, and that harm was reflected in a lowering of level of seizure propensity, thus facilitating further seizures.

Tr 2 at 443. It is important to recognize that the parties in this case agree that a vaccination can cause a fever; a fever can trigger a seizure, including a complex febrile seizure; and a complex febrile seizure can cause brain damage. See, e.g., id. at 342 (Dr. Raymond stated, “DTAP can cause fever, and in some children that can result in febrile seizures.” Dr. Raymond further agreed that “yes” these seizures can be complex febrile seizures.). Further the parties agree the vaccination in this case probably did trigger a fever, and that fever probably did trigger Amelia’s first severe seizure. Id. at 334. However, the parties disagree on both the impact of that first seizure and whether the vaccination played any causative role in Amelia’s SMEI. See Respondent’s Post-Hearing Memorandum filed August 19, 2009 (“R Memo”) at 16-17.

Respondent’s expert, Dr. Kohrman, initially opined that the cause of Amelia’s seizure disorder was unknown or explained by her diagnosis of SMEI, which has an “idiopathic label or an unknown label.” Tr 1 at 33. But in his opinion, Amelia’s SMEI was not caused in-fact by her DTaP immunization. Id. at 34. Rather, Dr. Kohrman, in his initial reports and at the August 2, 2006, Hearing, opined that Amelia possessed a genetic predisposition, most likely her Chromosome 20 duplication, which caused her to suffer SMEI. The undersigned notes Dr. Kohrman hypothesized that Amelia’s Chromosome 20 duplication or another genetic predisposition caused her to suffer SMEI. Nothing in the record at the time of the first Hearing in this matter provided reliable evidence that Amelia’s seizure disorder was caused by factors unrelated to her vaccination.

Based upon the above cited literature from Holmes and Aicardi, the facts presented and the expert testimony offered in the first Hearing in this case, and consistent with the decisions in Simon and Mersburgh, it initially appeared that petitioners had demonstrated a showing of entitlement to compensation under the Act. As the undersigned discussed in Simon and Mersburgh:

[w]hat we face in this case is an unprovable event, unprovable utilizing the higher

¹⁶ The Holmes and Aicardi literature was filed into the record of this case as Court’s Exhibits 1 and 2 on March 14, 2007.

standard of medical certainty. However, on a probability scale, it is exceedingly reasonable to conclude that where the vaccine is associated with fever and seizure and the seizure is of a complex nature, **in the absence of proof of an alternative cause**, it is the vaccine that is responsible for a subsequent epilepsy and residual sequelae.

Mersburgh, 2007 WL 5160384, at *5 (citing Simon, 2007 WL 1772062, at *6 (emphasis added)). Accordingly, in the absence of the evidence presented regarding Amelia's SCN1A gene mutation the undersigned most likely would have found for petitioners based upon the above discussion. However, as discussed at length in the following sections, respondent has demonstrated by a preponderance of the evidence that Amelia's SCN1A gene mutation was both the "but for" cause and the "substantial factor" that caused her SMEI. Shyface, 165 F.3d at 1352. Accordingly, petitioners' claim fails. For the purposes of the discussion that follows and utilizing the highest standard under the Act, the undersigned will analyze respondent's evidence concerning Amelia's SNC1A gene mutation as a factor unrelated to her vaccination pursuant to §13(a)(1)(B).¹⁷ See

¹⁷ The undersigned notes that the government has contested, both prior to and subsequent to the Hearing on May 15, 2009, whether the burden has in fact shifted to the government to demonstrate a factor unrelated. Respondent argued petitioners have failed to prove a *prima facie* case under the Vaccine Act; and as such Dr. Raymond's testimony as to Amelia's genetic mutation is evidence offered to rebut petitioners' *prima facie* case. See generally R Memo at 5-11. In the alternative, Respondent argued "the evidence of an alternative cause . . . also establishes a factor unrelated defense" should the undersigned find petitioners have proven a *prima facie* case. Id. at 9, fn 14. As the undersigned has informally addressed with the parties at various status conferences leading up to the Hearing on May 15, 2009, **the undersigned's ultimate finding would not be impacted if the undersigned analyzed respondent's evidence concerning Amelia's SCN1A as evidence submitted in rebuttal to petitioners' *prima facie* case as opposed to evidence regarding a factor unrelated.** This is because upon review of all of the evidence in the record, the undersigned was convinced by a preponderance of the evidence that Amelia's SCN1A gene mutation was both the "but for" cause and a "substantial factor" that caused her SMEI. Accordingly, the undersigned finds that Amelia's DTaP vaccination was neither a "substantial factor" nor a "but for" cause of her injury. See Shyface, 165 F.3d at 1352. While the undersigned interprets the Federal Circuit's decisions in Walther and de Bazan to require respondent to bear the burden of demonstrating the SCN1A mutation is a factor unrelated to the vaccination in an inquiry separate from weighing petitioner's burden in demonstrating a *prima facie* case, the answer to this legal question does not impact the result in this case. See Walther, 485 F. 3d at 1151 (citing Grant v. Sec'y of Dept. of Health & Human Servs., 956 F.2d at 1149("As we have previously noted, the text and structure of '[t]he Vaccine Act separates the inquiry for alternative etiologies from the inquiry for causation. These are two separate inquiries under the statute.'")); de Bazan, 539 F.3d 1347, 1353-54("'[t]his latter showing is the government's burden once the petitioner has met her burden.'"). But see Pafford, 451 F.3d at 1355 (explaining the three prongs in Althen "must cumulatively show that the vaccination was a 'but-for' cause of the harm, rather than just an insubstantial contributor in, or one among several possible causes of, the harm."); Althen, 418 F.3d at 1281 ("[T]he elimination of other causes . . . is merely a recitation of this court's well-established precedent."). The undersigned notes the guidance from the Federal Circuit on this point appears somewhat confusing and possible contradictory. See Heinzelman v. Sec'y of the Dept. of Health & Human Servs., 2008 WL 5479123 (Fed. Cl. Spec.

Nordwall v. Sec’y of the Dept. of Health & Human Servs., 2008 WL 857661, *12 (Fed. Cl. Spec. Mstr. 2008) (discussing how it is necessary to determine who bears the burden of proof on the “factor unrelated” issue only if the evidence concerning the issue is in equipoise).

C. Respondent’s Case

The undersigned notes that a factor unrelated is rarely demonstrated or presented by respondent in vaccine causes. Two notable exceptions are the Knudsen and Hanlon cases, cited supra p. 10. In Vaccine Act cases, the Federal Circuit has instructed:

[t]he sole issues for the special masters are, based on the record as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the child’s injury or that the child’s injury is a table injury, and whether it has been shown by a preponderance of the evidence that a factor unrelated to the vaccine caused the child’s injury.

Knudsen, 35 F.3d at 549 (citing §§ 13(a)(1), (b)(1)); see, e.g., Hanlon, 191 F.3d at 1349 (citing Knudsen) (the special master “determined that TS was the actual alternative cause of Michael’s seizures. A reversal of this finding would improperly require proof of causation that is “medically or scientifically certain”); Nordwall v. Sec’y of the Dept. of Health & Human Servs., 2008 WL 857661, *12 (finding a factor unrelated to the vaccine caused the infant’s death). Thus, the undersigned turns to whether the respondent proved by preponderant evidence that Amelia’s SCN1A gene mutation was the “but for” cause and the “substantial factor” that caused her SMEI. Shyface, 165 F.3d at 1352; see also de Bazan, 539 F.3d at 1354. The Federal Circuit instructs that “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.

The undersigned approaches this case cognizant of its significance within the Vaccine Program. Seizures following vaccination have a long history in the Program, having been compensated from the beginning of the Program, initially as a Table Injury, see § 14, and later as part of off-Table causation in fact claims. See, e.g., Andreu, 569 F.3d 1382 (“[T]he totality of the evidence - including the striking temporal connection between the vaccine and Enrique’s initial seizure, the testimony of treating physicians, and the biologic and scientific plausibility of Tornatore’s theory of causation - are sufficient to meet the Vaccine Act’s preponderant evidence standard.”). In fact, based upon the undersigned’s twenty-one year experience, throughout the history of the Program seizures may constitute the most commonly alleged injury following immunization.

However, while often compensated, the claim that vaccines cause seizure disorders is **not** universally accepted. With changes in 1995, seizure disorders were removed from the Table list of

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presumptive injuries for pertussis vaccines. See 60 FR 7694 (Feb. 8, 1995). Also, special masters have found that certain types of seizures were not caused by vaccines. See, e.g., Bruesewitz, No.95-266V, 2002 WL 31965744 (Fed. Cl. Spec. Mstr. 2002)(The special master found that the infant vaccinee’s neurologic disorder was not shown to be caused by a DTP vaccination, even though the vaccinee suffered an afebrile seizure lasting more than thirty minutes, within two days of her DTP vaccination.);¹⁸ Jenkins, No. 90-3717V, 1999 WL 476255 (Fed. Cl. Spec. Mstr. 1999)(the special master concluded, as a general matter, that the DTP vaccine can cause seizures within seven days of vaccination; however, the master concluded that in this case the petitioners failed to show that their son’s neurological disorder was vaccine-caused, because that disorder fell within the category of “infantile spasms,” a specific disorder that was found by the 1991 IOM Report not to be causally related to the DPT vaccine). Furthermore, the causal link between vaccinations and seizures has not been universally accepted by the medical community. See, e.g., Kathleen R. Stratton et al., Institute of Medicine, Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality, 78-82 (1994).

The emergence of research involving the SCN1A gene mutation is a new issue to be carefully examined when determining a vaccine’s role in causing certain seizure disorders. With this newly developed evidence and its use in the case *sub judice*, the undersigned is careful to stress the causative role of the mutation must be determined on a case by case basis and weighed carefully against any evidence of damage caused by a vaccine-induced seizure. The meaning of this cautionary statement will be evident from the discussion below.

1. Amelia’s Factor Unrelated

In this case, respondent presented an expert report and testimony at the May 15, 2009, Hearing from Dr. Raymond. Dr. Raymond opined that Amelia’s vaccinations neither caused nor exacerbated her SMEI, but rather a mutation in her SCN1A gene is solely responsible for her SMEI. R Ex J at 5, Tr 2 at 335. Dr. Raymond noted that while there are a variety of seizure disorders that have been associated with SCN1A mutation, the most common is SMEI. Tr 2 at 316. “[I]f we lump [SMEI] together with the borderline severe [myoclonic] epilepsy of infancy,” labeling them Dravet Syndrome, “that makes up the majority of mutations that have been associated with the SCN1A source.” Id. On direct examination and based upon the work he reviewed, Dr. Raymond stated that the “around 80 to 90 percent” of children who suffer from SMEI also possess a SCN1A mutation. Id. at 316-17. Dr. Raymond opined in his written report and consistently testified that Amelia’s SMEI is solely the result of the mutation to her SCN1A gene. In the final analysis, Dr. Raymond’s testimony proved highly persuasive and reliable. Petitioners failed to mount any serious rebuttal to Dr. Raymond.

2. Genetics Background

¹⁸ The Supreme Court has granted certiorari to the petitioners in this case, on an issue unrelated to their petition under the Act, on a claim filed outside the Vaccine Act. See Bruesewitz v. Wyeth, Inc., - - S. Ct. - - -, 2010 WL 757696 (2010).

Prior to analyzing Dr. Raymond's theory of causation in this matter, the undersigned will discuss necessary contextual information presented by respondent through Dr. Raymond concerning genetic mutations and the SCN1A gene.

a. DNA and Protein Synthesis

As an initial matter, Dr. Raymond explained "the human genom[e] is a term we use for all of our genetic information" and the "human genom[e] is comprised in these structures which are called chromosomes, which are made up of DNA and proteins." Tr 2 at 285. DNA provides the blueprint for cellular structure and function. See, e.g., R Ex J at 2. From those blueprints, "[t]he DNA sequence is translated into a specific string of amino acids which produces a protein. A disease-causing mutation in the DNA results in a dysfunction of the protein." Id. The process by which proteins are created from the DNA blueprint is called protein synthesis; thus, a change or mutation¹⁹ in the DNA can affect the functionality of that protein, therefore causing disease. Id. Dr. Raymond described this process in great detail at the Hearing on May 15, 2009. Tr 2 at 285-302. See also Respondent's Trial Exhibit A ("R T Ex A").²⁰

Protein synthesis begins with transcription, wherein the double helix of DNA opens and then cellular processes "make . . . a copy of the DNA into RNA, or messenger RNA." Tr 2 at 289; R T Ex A at 7-8.²¹ Dr. Raymond explained, "in the gene there [are] both exons and introns; exons being the portion of the gene that[are] going to be transcribed out" of the cell, and introns "are separating material . . . between these exons." Tr 2 at 286-87. Dr. Raymond explains:

there are exons²² and introns²³ and so the messenger RNA actually forms - - [it] reads all the way through this, reads through the pieces that are coding the exons, but also

¹⁹ Mutation is defined as: "1. A change in the chemistry of a gene that is perpetuated in subsequent divisions of the cell in which it occurs; a change in the sequence of base pairs in the chromosomal molecule." STEDMAN'S MEDICAL DICTIONARY, 1264 (28th ed. 2006).

²⁰ When citing to a particular page of this exhibit the undersigned will cite to the page number at the top of the page generated by the court's electronic filing system.

²¹ Messenger RNA is abbreviated as mRNA. STEDMAN'S MEDICAL DICTIONARY, 1232 (28th ed. 2006).

²² Exon is defined as: "A portion of DNA that codes for a section of the mature messenger RNA obtained from that DNA, and is therefore expressed ('translated' into protein) at the ribosome." STEDMAN'S MEDICAL DICTIONARY, 683 (28th ed. 2006).

²³ Intron is defined as: "A portion of DNA that lies between two exons, is transcribed into RNA, but does not appear in that [messenger] RNA after maturation because the [intron] is removed and the exons spliced together, and so is not expressed (as protein) in protein synthesis." STEDMAN'S MEDICAL DICTIONARY, 995 (28th ed. 2006). "By customary usage, the term is extended to the corresponding regions in the primary transcript of [messenger] RNA before maturation." Id.

those intervening sequence[s] of introns, and you get this long messenger RNA, and now the cell needs to cut out those intervening sequences, and so there is splicing that occurs[.]

Tr 2 at 290-91. Eventually during the protein synthesis process, the introns are cut out and not expressed. Id. at 291; see also R T Ex A at 9-10.

The last step in the protein synthesis process then occurs, which is called translation.²⁴ At this step, Dr. Raymond explains, “the mRNA passes out of the nucleus and joins up with the ribosomal RNA,” Tr 2 at 292; R T Ex A at 11, “and using a very complicated machinery it’s now read codon by codon.” Tr 2 at 292; R T Ex A at 12. A codon is a “set of three consecutive nucleotides in a strand of DNA or RNA that provides the genetic information to code for a specific amino acid that will be incorporated into a protein chain” STEDMAN’S MEDICAL DICTIONARY, 404 (28th ed. 2006).²⁵ For example, U plus U plus U codes for the amino acid Phenylalanine. See R T Ex A at 12.

The string of amino acids produced from each codon in turn comprises the protein. Essentially, “[s]ingle amino acids with different side chains...can bond to form...a strand of amino acids, part of a protein.” R T Ex A at 14. Inevitably, you get a rather complex structure, see R T Ex A at 15, which Dr. Raymond testified appears deceptively simple on paper. Tr 2 at 297; see also, R T Ex A at 13-15. Dr. Raymond explained the primary protein structure is:

going to have a secondary structure right off the bat just based upon you - - - you can’t put more than a few amino acids together and not start to get a secondary structure here. . . . When you start to really stretch it out, it[‘s] going to fold and you’re going to get a tertiary structure . . . if you start to put peptides together. So strings of amino acids may - - you may have created a peptide of several hundred amino acids long, and they’re going to come now together to make even a bigger structure, an assembled unit, and that has a quaternary structure.

Tr 2 at 298; R T Ex A at 15. As discussed earlier, the proteins formed by this process determine how cells are formed and how they function. Mutation alters normal function.

b. Mutations - Generally

Dr. Raymond testified that mutations occur during DNA synthesis or replication, which

²⁴ Dr. Raymond simplifies translation as “the information has to be translated from this DNA which is basically a recipe or set of instructions out into making proteins” Tr 2 at 287.

²⁵ Three bases, nucleotides, are required to code for one amino acid. Tr 2 at 293; R T Ex A at 12.

occurs during the cell division processes of mitosis or meiosis.²⁶ Tr 2 at 299. Dr. Raymond explained “[m]utations can occur at a number of points,” but “[t]he ones that we tend to focus on are those that occur in the exon which is again the coding region, . . . where we think most of the pertinent information is going to be transcribed . . . into a protein.” Id.²⁷ Dr. Raymond explained that when discussing mutations, we are discussing “changing the base pairs” on the strand of DNA and this can produce different types of results. Id. at 300.

Dr. Raymond discussed three different types of mutations: 1) point mutations, which consist of missense mutations and nonsense mutations; 2) deletions; and 3) insertions. Tr 2 at 300-01; R T Ex A at 18. A point mutation, which is at issue in Amelia’s case, involves a single base pair of the DNA being replaced by another base pair. Tr 2 at 300. The result of this replacement may be a nonsense mutation, which codes for no amino acid during the protein synthesis process and thus the change “just doesn’t mean anything.” Id. Alternatively, the substituted base pair may code for a different amino acid, which is referred to as a missense mutation. Id.²⁸ Dr. Raymond testified Amelia Stone has “a point mutation resulting in a missense.” Id. at 301.

Dr. Raymond explained the type of mutation that is present, whether it is an insertion, a deletion, a point missense or a point nonsense mutation, “play[s] into the ultimate effect on the organism,” due to the impact on translation. Id. at 301; R T Ex A at 19. For example, a missense mutation replaces one base pair with another, however this could cause only a small change. Tr 2 at 301-02. A mutation may result in the coding of the same amino acid, which is “referred to as . . . silent, because you have the same amino acid.” Id. Thus, the change in the base pair codes for the same amino acid that was originally intended and does not affect the person’s clinical presentation. Id. at 302. Alternatively, “if you change [a base pair] to something . . . where it gets translated as, or transcribed as an amino acid that’s very, very similar it’s referred to as conservative . . .” Id. The description of a mutation as conservative is relative, based upon “how close it is chemically to [to the original amino acid] and also what is the function in the ultimate protein.” Id. Changes that result in an amino acid with very different physical properties, such as “large to small, water loving to water hating,” are referred to as non-conservative mutations. Id. One may also see

²⁶ Mitosis is defined as “[t]he usual process of somatic reproduction of cells consisting of a sequence of modifications of the nucleus . . . that result in the formation of two daughter cells with exactly the same chromosome and nuclear DNA content as that of the original cell.” STEDMAN’S MEDICAL DICTIONARY, 1216 (28th ed. 2006). Meiosis is defined as: “A special process of cell division comprising two nuclear divisions in rapid succession that result in four gametocytes [sex cells], each containing half the number of chromosomes found in somatic cells.” STEDMAN’S MEDICAL DICTIONARY, 1174 (28th ed. 2006).

²⁷ Dr. Raymond also noted that he had testified earlier “introns need to be spliced out [during protein synthesis], and so there can also be mutations that affect that mechanism, so they are what are referred to as splicing mutations.” Id. Although, he clarified that Amelia’s case involves a mutation in the exon. Id. at 300.

²⁸ Finally, a deletion will result from removal of a base pair, and an insertion will result from addition of a base pair. Tr 2 at 301; R T Ex A at 18.

changes that result in “a stop codon, and so protein synthesis will just stop right there.” Id. To provide some context here and as it will be discussed below, **Dr. Raymond testified that Amelia’s mutation is a missense non-conservative mutation in her SCN1A gene.** Tr 2 at 302. Therefore, hers is a mutation where a base pair in her DNA has been replaced by a different base pair, which has very different characteristics than the typical base pair found at that gene location. Dr. Raymond explained that the functional effects from such mutations can range from loss of function to abnormal function to death of the organism. Id. at 303.

Dr. Raymond also explained that if you have a change but “no alteration in function, you have what is referred to as a polymorphism.” Id. at 304. A polymorphism is “seen in unaffected members of the population” where the change has a neutral effect. Id. at 304-05.²⁹

c. The SCN1A Gene

The SCN1A gene encodes a particular structure of a neuron.³⁰ “Neurons, the principal cells of the nervous system, maintain an electrical potential . . . across the cell membrane at rest and use changes in [this] potential to carry information.” R Ex J at 2. A “key element of this gradient is the ability to control the flow of charged molecules . . . This role is carried out by membrane channels.” Id. “Membrane channels are proteins that serve as passageways for specific molecules” and may be comprised of one or several proteins. Id.

The gene at issue in Amelia’s case, the SCN1A gene, encodes for a sodium channel, which is “a portion of a channel that allows the transport of sodium molecules across cell membranes in the neurons.” Id. Sodium is a charged molecule and “needs to be tightly regulated in the flow across the cell membrane to maintain the gradient so that the neuron may send information in an appropriate way.” Id. at 2-3.

Three units comprise this sodium channel, an α subunit and two β subunits. Id. at 3. It is the α subunit that is encoded by the SCN1A gene and “is a large molecule that forms a[n] . . . opening across the membrane.” R Ex J at 3. Dr. Raymond stated, “[i]t is important to recognize that this is not simply a hole in the fabric of the cell, but a highly complex chemical environment that allows the net passage of sodium from one side to another.” Id. Dr. Raymond continued discussing the structure of the α subunit:

²⁹ An example of a polymorphism that is seen in the general population is the blood type “O,” Dr. Raymond explained an “individual may have an A side chain, some individuals may have a B side chain, but some individuals have an altered side chain or . . . they don’t have a side chain at all, so they have the O blood group, and that’s a variation, and to some extent the polymorphism in the population.” Tr 2 at 305-06. Polymorphism is defined as: “Occurrence in more than one form; existence in the same species or other natural group of more than one morphologic type.” STEDMAN’S MEDICAL DICTIONARY, 1536 (28th ed. 2006).

³⁰ A neuron is “[t]he morphologic and functional unit of the nervous system, consisting of the nerve cell body, the dendrites, and the axon.” STEDMAN’S MEDICAL DICTIONARY, 1311 (28th ed. 2006).

it is not just a single pore, but is rather four . . . domains which are numbered by the Roman numerals - I through IV. Each of these domains is made . . . up of six segments that span the entire width of the membrane. The region between segments five and six serve as the sodium pore for each of the domains while the preceding fourth segment serves as the voltage responsive switch. When the voltage is at a certain level, the pores [or]space between segments five and six, ‘opens’ and sodium ions are allowed through.

Id.

Several neurologic conditions are associated with mutations of the SCN1A gene: familial hemiplegic migraines, several epilepsy syndromes, including Generalized Epilepsy with Febrile Seizures plus or GEFS+, and Amelia’s condition, SMEI. Id. This range of diseases “resulting from alterations in SCN1A rests on the structure of the channel and how the genetic mutation affects the function.”³¹ Id. Mutations in DNA “that affect the primary function of the channel such as the pore region have been demonstrated to have a more severe disease or phenotype associated with them.” Id.

3. Amelia’s Mutation and Dr. Raymond’s Theory of Causation

a. Amelia’s Mutation

Putting all of the above background information together, we come to Amelia’s specific mutation, which Dr. Raymond opines is the sole cause of her condition. The initial laboratory testing³² conducted and interpreted by Athena Diagnostics revealed that she possesses a “DNA sequence variant [mutation] . . . in the SCN1A gene.” P Ex 40 at 6. Specifically, “[t]he alteration seen in Amelia (T>C at nucleotide position 4387)[, at codon location 1463,] results in the substitution of the amino acid leucine for the amino acid phenylalanine in segment 6 of the [third] transmembrane domain of the SCN1A molecule.” R Ex J at 3; see also P Ex 40 at 6. As one can see from the discussion above and as affirmed by Dr. Raymond in his report, this change alters the pore region of the channel. R Ex J at 3. Further testing and analysis revealed Amelia’s SCN1A gene mutation “arose de novo (was not inherited [from her parents]).” P Ex 40 at 6. The “Revised Interpretation Based on Parental Testing” notes “[t]his finding is most consistent with this DNA variant being associated with a severe phenotype (SMEI or SMEB) rather than a mild or normal phenotype.” Id.

b. Dr. Raymond’s Causation Theory

Dr. Raymond based his opinion that Amelia Stone’s SCN1A gene mutation is the sole cause

³¹ As will be discussed below, part of petitioner’s attack on Dr. Raymond’s theory focuses on the variations of disease found in patients with the SCN1A mutation. See, e.g., *infra* pp. 37-39.

³² Athena Diagnostics provided both an “original interpretation” and a “revised interpretation” of Amelia’s SCN1A test results after her parents were also tested for the mutation. P Ex 40 at 6.

of her SMEI on several factors. These factors *cumulatively* demonstrate to him that the mutation is the cause of her disorder. Dr. Raymond explained that a geneticist usually begins to work with a patient who is experiencing a clinical manifestation of a disease or illness. A geneticist generally works backwards, starting with a change in function and “looking for evidence of causality.” Tr 2 at 310-11. “[T]here are things that we as geneticists do to judge whether [the mutation is] having an impact or not.” *Id.* at 311. Dr. Raymond testified that there are certain factors that he or any geneticist examines to determine if the mutation found in a patient is the cause of the patient’s disease.

As an initial matter, a geneticist examines the patient’s family to determine whether the mutation is inherited or arose de novo in that individual. *Id.* at 304. As noted above, Amelia’s mutation arose de novo, as both of her parents tested negative for the SCN1A gene mutation. *Id.* at 330; P Ex 40 at 6. Dr. Raymond testified the fact that a mutation arose de novo is significant. *Id.* at 330; see also P Ex 40 at 6. “Amelia has Dravet, and has this alteration which neither of her parents have, and again it’s added evidence that this is a functionally significant alteration in the amino acid.” Tr 2 at 330.

Next, Dr. Raymond testified that a geneticist examines the type of mutation presented. This concerns the type of mutation Amelia has, which is a missense non-conservative mutation in her SCN1A gene. As discussed earlier, the type of mutation affects the clinical presentation or phenotype of the organism. *Id.* at 301; R T Ex A at 19. Dr. Raymond analogized the functional effects of these types of mutations to the proteins as:

proteins are building blocks . . . so you’ve got nice bricks over here and you’re making it, but now you’ve got the other side, the other protein is now making circles, you’re putting circular bricks in with the rectangular bricks, your wall is not going to be as strong, and so now you have this protein being formed which is having a very negative effect on the rest - - the ultimate structure.

Tr 2 at 303.

In the case of Amalia’s mutation, Dr. Raymond explained the change of these building blocks is a change from phenylalanine, which is “an amino acid with a large aeromedical [sic] group and that little hexagonal figure, [referring to R T Ex A at 27] is actually made up of over six carbons at each of the corners, and now it’s been replaced by a much smaller amino acid, here leucine, which has - - the difference is clearly in size, as well as [in] its basic chemical properties.” Tr 2 at 330; R T Ex A at 27. The switch in amino acids with “different physiochemical properties alters the shape and function of the pore,” through which the sodium ions pass. R Ex J; R T Ex A at 27 (graphic contrasting phenylalanine to leucine). In Amelia’s case, the change from phenylalanine to leucine “is a non-conservative mutation so it’s changing the nature of the amino acid” significantly. Tr 2 at 332.

Dr. Raymond testified that a geneticist also examines the location of the mutation. Specifically, one examines whether the change in the protein created from the DNA is located in an

area that is a functionally important part of the protein. Id. at 311-12. Amelia's mutation affects "segment 6 of the [third] transmembrane domain of the SCN1A molecule. . . . this is one of the pore regions of the channel." R Ex J at 3. Dr. Raymond elaborated, "there are regions of proteins that you may get by with a little twist, but there are also regions that are the key function of the protein. So in a [sodium] channel, it's the pore . . . because every time we go and tweak it we get into trouble." Tr 2 at 312-13.

Another factor to consider regarding the mutation's location, Dr. Raymond testified, is whether the mutation occurs in a region that "normally doesn't change across species, what we refer to as well conserved regions." Id. at 311. Dr. Raymond explained that where the mutation occurs is significant because:

there are regions that have identical sequences of DNA across multiple species, and so human, cows, dogs, whatever, and it's generally accepted that cross species conservation that's been maintained [a]cross a variety of species indicated that it's [an] important [area]. If it wasn't important, it would - - there is an evolutionary decay or changes that occur at any moment, and if it wasn't important, you know you would just start to accumulate errors or changes. So when it's maintained, you go, okay, it's here, it's in humans, it's in chimpanzees, okay, they are pretty close to us. Well, it's [also] in the mouse or rat. Well, that's suggesting that the only way that protein can function is to have that DNA in that particular location and coding that particular thing [amino acid]. . . . [N]ature doesn't like to reinvent the wheel, and so if it's worked . . . and you go and change it . . . [the change] had better work out for you or you won't be around in the next generation.

Id. at 311-12. Amelia's mutation occurs in such a conserved region, as demonstrated by the sequences charted in Respondent's Trial Exhibit. R T Ex A at 28. The chart illustrates that Amelia's mutation occurs in an area that is well conserved, meaning it "normally does not change across species," and thus a change is likely to have a significant, adverse outcome. R T Ex A at 22, 28; Tr 2 at 311-12.

Dr. Raymond testified that the next point of inquiry for a geneticist in determining whether the mutation plays a causative role in the condition is comparing the patient's mutation to other non-related patients to learn if the mutation has been previously reported and studied. Tr 2 at 313. He would also confirm that it is not a polymorphism, a change with a neutral effect, found in the normal population. Id. Dr. Raymond noted that Amelia's exact amino acid change at its precise location has *not* been previously reported. However, he testified that a SCN1A gene mutation from phenylalanine to serine, another small amino acid, has been reported. Dr. Raymond stated "this alteration is very similar, and this individual also had Dravet syndrome." Id. at 333. Further, due to the characteristics between serine and leucine, that mutation is "functionally the same as the one reported in Amelia Stone." Id. In addition, Dr. Raymond discussed other mutations that are reported to occur in the same region as Amelia's mutation. "If you look at what's occurring in that transmembrane region [the region affected by Amelia's mutation], all that you're seeing are other cases of Dravet, or severe [myoclonic] epilepsy of infancy. So that the flanking regions, again, are

well conserved. If you alter them, you are going to get Dravet syndrome.” Id. at 334; R T Ex A at 31(illustration of Amelia’s mutation and surrounding mutations).

For clarity, the undersigned lists the factors emphasized by Dr. Raymond as significant to his opinion that the SCN1A mutation is responsible for Amelia’s condition:

- Amelia’s mutation arose de novo;
- the mutation at issue results in a non-conservative amino acid change with the new amino acid having very different physical properties from what is found at that location in non-affected individuals;
- the mutation affects the pore of a sodium channel, a functionally important region;
- the mutation occurs in an area that is well conserved across species, signaling significant ramifications when altered;
- there are reports evidencing similar or comparable mutations resulting in SMEI; and
- there is an absence of the mutation in the normal population.

Dr. Raymond testified that these points, when examined by a geneticist, *cumulatively* demonstrate that Amelia’s SMEI is caused by her SCN1A mutation. See generally Tr 2 at 301-13; 332, 361,400-01; R Ex T A at 22. Ultimately, Dr. Raymond testified that if he was providing counseling to this family as a geneticist in his clinical practice, “I would say to them that this[, Amelia’s SCN1A mutation,] is the sole cause of her Dravet syndrome” Tr 2 at 331. The undersigned finds Dr. Raymond’s testimony described above reliable, as well as highly persuasive. See, e.g., infra pp. 49-51.

D. Petitioners’ Rebuttal to Respondent’s Evidence

As previously stated, the Federal Circuit has found the “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. The Federal Circuit has made clear that a non moving party, in the case of a factor unrelated that is petitioner, may provide rebuttal evidence. de Bazan, 359 F.3d at 1353. Accordingly, petitioners presented rebuttal evidence to respondent’s factor unrelated defense. Petitioners posited that the SCN1A gene plays “a role in the cause of SMEI but it is not the sole or overwhelming cause of SMEI in children with SCN1A variants,” and allege that “fever caused by pertussis vaccinations modifies the course of SMEI.” P Memo at 26 (citations omitted)(emphasis omitted).

Dr. Kinsbourne agreed at the May 15, 2009 Hearing “that SMEI has a genetic bas[is] . . . there is a genetic component.” Tr 2 at 485. Dr. Kinsbourne described the genetic component as “a very powerful one.” Id. However, Dr. Kinsbourne maintained that “the pertussis vaccination caused fever, the fever triggered the seizure, the seizure lasted a long time” and caused damage by lowering Amelia’s seizure “threshold.” Id. at 475. Dr. Kinsbourne agreed with the undersigned that the issue presented in this case “is the role of [Amelia’s] initial seizure, this complex seizure in altering whatever mutation we have.” Id. at 486.

It is important to note that petitioners did not contest Dr. Raymond's tutorial on the foundation of genetics. Nor did petitioners offer the testimony of a geneticist to rebut the testimony of Dr. Raymond. Rather petitioners presented a series of arguments in an effort to undermine Dr. Raymond's conclusion. These arguments essentially consisted of petitioners: 1) criticizing the testimony presented by Dr. Raymond regarding the factors a geneticist analyzes in determining a genotype-phenotype relationship; 2) arguing that the SCN1A gene mutation is not a reliable indicator of clinical outcome; 3) arguing that the scientific literature supports an environmental (vaccine role) in causation; 4) arguing that the vaccine was responsible for the first seizure which was a complex febrile seizure and complex febrile seizures damage the brain; 5) arguing that the undersigned's prior rulings in Simon and Mersburgh require a finding on behalf of petitioners; and 6) criticizing Dr. Raymond's qualifications. These arguments are examined below.

1. The Factors Utilized by Dr. Raymond in his Analysis of Amelia's Case

a. Petitioners' Criticism of Dr. Raymond's "Rules"

As discussed previously, Dr. Raymond utilized a synthesis of multiple factors in reaching his conclusion that Amelia's SCN1A gene mutation is the sole cause of her SMEI. These factors were: the fact that Amelia's mutation arose de novo; that it is a missense non-conservative mutation, that it occurs in the pore - a functionally important region- of the sodium channel; that it occurs in an area that is "conserved" across species; that the mutation's "functional" effect is greatly altered (*i.e.*, complex amino acid changed to a simple one); that the reported comparable mutations result in SMEI; and finally that there is an absence of the mutation in normal population. See R T Ex A at 18-22; 26-29, Tr 2 304-35. It is critical to keep in mind that these factors were utilized *cumulatively*.

Petitioners attacked several of the factors individually in an effort to undermine Dr. Raymond's testimony. Petitioners characterized pejoratively Dr. Raymond's analysis as his own personal "rules" for predicting phenotype: that "if variable A is present then B will be the outcome." P Memo at 7. Petitioners argued Dr. Raymond's following factors "are not objective or reliable criteria for predicting the clinical effect of an SCN1A variant:" a) whether an amino acid changed from simple to complex is predictive of the clinical outcome; b) whether the location of an SCN1A variant is predictive; c) whether there is significance that Amelia's SCN1A variant arose de novo; and, d) whether the mutation occurred in a functionally important region, a region well conserved through evolution. P Memo at 19-26.

Petitioners' attacks are unpersuasive for several overriding reasons. Petitioners misconstrued the analysis performed by Dr. Raymond, as a clinical geneticist, and fail to consider the factors in tandem. Petitioners also placed an improper burden of scientific certainty upon Dr. Raymond's analysis. Finally, petitioner's failed to consider the evidence from the literature that supports Dr. Raymond's analysis. Petitioners consistently miscast Dr. Raymond's testimony. Dr. Raymond repeatedly and unequivocally stated that it is the collective clinical evidence, not the individual pieces, that convinced him that the SCN1A gene mutation is the causative agent in this case. Ultimately, petitioners failed to present persuasive evidence to the contrary. While these deficiencies

in petitioners' rebuttal alone are sufficient reason to reject petitioners' argument, the undersigned will address the individual components of petitioners' argument, which also proved to be unpersuasive. Petitioners' individual attacks on Dr. Raymond's theory are presented and addressed as follows in the instant section, 1(a), followed by respondent's response and the undersigned's analysis in the following section, 1(b).

I. Petitioners argue an amino acid change from simple to complex, a non-conservative mutation, is not predictive of the clinical outcome.

First, petitioners argue that "the evidence does not support the proposition that an SCN1A variant which changes a complex amino acid to a simple one will cause SMEI." P Memo at 19. Petitioners first contend that Dr. Raymond does not know what the functional effect of Amelia's mutation is because it has not been studied. *Id.* at 20. Petitioners further argue the functional effect of an amino acid change does not predict an individual's clinical outcome. To support the instant argument, petitioners cite to the Rhodes *et al.*, finding "that different amino acid substitutions of the same residue may give rise to similar biophysical defects yet be associated with clinical phenotypes of widely divergent severity. Mutation R1648G causes GEFS+, whereas R1648C is associated with SMEI." P Memo at 20-21 (citing P Ex 49, Thomas H. Rhodes *et al.*, Noninactivating Voltage-gated Sodium Channels in Severe Myoclonic Epilepsy of Infancy, 101 PROC. OF THE NAT'L ACAD. OF SCI. 11147, 11151 (2004)("Rhodes *et al.*")).³³ For further support, petitioners discuss a variant found in the literature that involved the same amino acid change as that found in Amelia, Phenylalanine to Leucine in a different location of the gene, wherein a child suffered from autism. P Memo at 20 (citing P Ex 44, Christoph Lossin, A Catalog of SCN1a Variants, BRAIN & DEV. (2008) (Epub. ahead of print)("Lossin")). Petitioners compare the amino acid change seen in the Hammitt case,³⁴ Arginine to Glycine, which resulted in SMEI, to a case in the literature where this same amino acid change in a different gene location resulted in a benign polymorphism. P Memo at 20 (citing R.H. Wallace *et al.*, Neuronal Sodium Channels α 1-Subunit Mutation in Generalized Epilepsy with Febrile Seizures Plus, 68 AM. J. HUM. GENET. 859, 863 (2001)("Wallace *et al.*")) and Electronic Letter from Alfons Macaya, Significance of the SCN1A p.R1928G Change in Severe Myoclonic Epilepsy of Infancy (Jun. 2008) (discussing Claudio Zucca *et al.*, Cryptogenic Epileptic Syndromes Related to SCN1A: Twelve Novel Mutations Identified, 65 ARCHNEUROL 489 (Apr. 2008)("Macaya")).³⁵

Petitioners' expert, Dr. Kinsbourne, was not helpful in discussing this point of petitioners' criticism. When asked if he "would agree that the amino acid change in Amelia Stone has the same

³³ When citing to medical articles the undersigned will utilize the page number within the articles, as opposed to the page numbers provided by the court's electronic filing system.

³⁴ See supra fn 8.

³⁵ The undersigned notes Wallace *et al.* and Macaya are cited in Petitioners Memo, but do not appear to be filed into the record in the instant case. These articles were filed into the record of the Hammitt case.

functional impact as a case reported in the literature that has a mutation at the same site.” Tr 2 at 448-49. Dr. Kinsbourne responded, “I understand those facts. I don’t know what to conclude from them.” Id. at 449. When asked “does the change have the same functional impact on the protein?” Id. at 450. Dr. Kinsbourne responded, “I don’t know the functional impact of the protein.” Id.

ii. Petitioners argue the location of an SCN1A variant is not predictive of clinical outcome

Next petitioners alleged the “evidence does not support the proposition that the location of an SCN1A variant is predictive of outcome.” P Memo at 21. Petitioners noted that “Familial Hemiplegic Migraine (FHA) and Myoclonic Atastic Epilepsy (MAE) have been observed in persons with SCN1A gene variants in the same location of which Amelia’s Stone’s SCN1A variant occurs.” Id. at 22 (citing Lossin, at 4, 8, 13). Petitioners offered the Rhodes et al. statement that “different amino acid substitutions of the same residue may give rise to similar biophysical defects yet be associated with widely different severity” as evidence that the location of an SCN1A mutation is not a reliable indicator of clinical outcome. Rhodes et al. at 11151; P Memo at 20.

Petitioners’ counsel additionally argued the population of SCN1A genetic mutations is biased in favor of mutations resulting in SMEI and thus it is unknown how many normal individuals may possess SCN1A variants in the same location as Amelia. P Memo at 22. Petitioners argued this is supported by the following observation from Lossin regarding data representation:

It is uncertain whether the numbers and specification of the published SCN1A variants are a good representation of naturally occurring genetic changes. Many of the mutations were identified after it had been discovered that SCN1A abnormality can lead to SMEI. This of course creates bias and one cannot say whether the mutation and phenotype percentages calculated in this review approach reality.

P Memo at 23 (quoting Lossin at 13). This concern was also addressed by Dr. Kinsbourne at the Hearing on May 15, 2009. Tr 2 at 427-28. Thus, petitioners posited that the population of variants is biased in favor of variants associated with SMEI as a result of treating neurologists being more likely to order expensive DNA testing on a patient who is experiencing more severe clinical symptoms than a patient who is not experiencing a severe clinical presentation. Tr 2 at 427.

iii. Petitioners argue the fact that the SCN1A variant arose de novo does not support that it is the sole cause of Amelia’s SMEI

Third, petitioners’ counsel argues the fact that a mutation arose de novo is not indicative that Amelia’s SCN1A variation is the cause of her SMEI. In making this argument petitioners rely upon the Amelia’s genetic testing results from Athena Labs Report, which found that Amelia’s mutation arose de novo and states:

[a]pproximately 90% of amino acid variants associated with the more severe phenotypes of SMEI or SMEB arose de novo in the affected individual and are not present in either parent. Conversely the vast majority of amino acid variants associated with the milder phenotype of GEFS+ are inherited from one of the parents. For these reasons, the finding that the amino acid variant arose de novo is far more consistent with it being associated with a severe phenotype (SMEI or SMEB) than with a mild or normal phenotype. However, genotype-phenotype correlations do not exist in the current literature of this specific variant and the possibility that it is a rare sporadic benign polymorphism cannot be excluded.

P Memo at 23-24 (quoting P Ex 40 at 6). Petitioners argue that the “associated with” language used in the Athena Labs Report does not mean the mutation was the sole cause of Amelia’s SMEI. Petitioners’ counsel also states the de novo mutation does not rule out the possibility that the variant could result in a polymorphism as opposed to making the child vulnerable to SMEI. *Id.* at 24. Petitioners cite to examples in the literature where de novo variants have been associated with milder seizure disorders. *Id.* (citing P Ex 43, Dennis J. Dlugos *et al.*, Novel de Novo Mutation of a Conserved SCN1A Amino-Acid Residue (R1596), 37 PEDIATRIC NEUROL. 303, (2007)(“Dlugos *et al.*”); Wallace, R., A Plethora of SCN1A mutations: What Can They Tell Us, *Epilepsy Currents*, Jan.-Feb. 2005, at 17 (“Wallace”)).³⁶ Petitioners also cite to studies that find “about 10% of SCN1A variants in children with SMEI are inherited from mostly normal parents.” P Memo at 24 (citing P Ex 29, R. Nabbout *et al.*, Spectrum of SCN1A Mutations in Severe Myoclonic Epilepsy of Infancy, 60 NEUROL. 1961,1962 (2003) (“Nabbout *et al.*”); P Ex 45, Christel Depienne *et al.*, Spectrum of SCN1A Gene Mutations Associated With Dravet Syndrom: Analysis of 333 Patients, J. MED. GENET. 1, (E-table B) (2008) (Epub. ahead of print)(“Depienne *et al.*”).

On this point, Dr. Kinsbourne testified to his general agreement with Dr. Raymond that “[t]here’s a general feeling that de novo mutations tend to be as a group more likely to be severe than ones that are familial, but that doesn’t tell me anything about this particular case.” Tr 2 at 451. He elaborated by stating, de novo mutations “have some significance” but there was “[j]ust not enough to identify what this genotype is really doing.” Tr 2 at 451-52.

iv. Petitioners argue a mutation occurring in a functionally important region, a region well conserved through evolution, is not predictive of outcome

Finally, petitioners contended that Depienne *et al.* found SCN1A variants resulting in a polymorphisms in “highly conserved amino acids of the protein.” P Memo at 25 (citing Depienne *et al.*, at 6). They quote this study, stating:

Forty polymorphisms, 24 of which are novel, were identified in SCN1A and are

³⁶ The undersigned notes Wallace appears to have never been filed by either party as an exhibit in the instant case although it was filed in the Hammitt case.

listed in E-Table D. This table includes the polymorphisms detected in asymptomatic patients' relatives and controls. The eight non-synonymous variants . . . were present in an asymptomatic parent, suggesting that they are benign variants. They were not found, however, in 100 Caucasian controls individuals, indicating that they are either rare or possibly specific to populations from different geographic origin. Surprisingly, all these variants also affect highly conserved amino-acids of the proteins with the exception of [one].

Id. at 25 (citing Depienne et al. at 6). Petitioners argue that the findings from Depienne et al. mitigate against the "assumed significance" in the medical literature of the impact of an amino acid change in a well-conserved region. Id.

b. Respondent's counter argument and undersigned's analysis

Based on the above, petitioners argue Dr. Raymond's analysis is not reliable, is not based on objective evidence, it is not supported by the medical literature, and it therefore fails. P Memo at 19-24. However, the undersigned reviewed all of the cited literature, considered petitioners' arguments and concludes that it is petitioners' arguments that fail. In short petitioners' arguments: I) misconstrue the analysis performed by Dr. Raymond, a clinical geneticist, and fail to consider Dr. Raymond's factors in tandem; ii) fail to develop the argument regarding SCN1A gene database population bias; iii) fail to consider the objective evidence from the literature which supports Dr. Raymond's analysis; and iv) place a burden of scientific certainty upon Dr. Raymond's analysis.

I. Factors considered in tandem and the expertise of a clinical geneticist

Dr. Raymond explained **multiple factors considered together**³⁷ contributed to his conclusion that Amelia's SCN1A gene mutation is the sole cause of her SMEI. Dr. Raymond made this point on numerous occasions during his testimony. See Tr 2 at 357, 361-62. These factors considered together along with Amelia's clinical history allowed him as a clinical geneticist to make the finding that Amelia's disease was caused solely by her gene variant. As respondent notes, "these 'rules' are standard scientific principles routinely employed by clinical geneticists to study the impact of various genetic mutations." Respondent's Post-Hearing Reply Memorandum ("R Reply") at 4 (citing Tr 2 at 311). "Although an individual factor or criterion, taken in isolation, may not itself be sufficient to 'predict the outcome,' when examined in combination these factors are highly instructive." Id. at 5. Dr. Raymond openly cautioned at the Hearing on May 15, 2009, that it would be a mistake to examine any of these factors standing alone, explaining "I think you would certainly be . . . a fool to use one [factor] independently of all the other available information that you have."

³⁷ As discussed previously, these factors include: the fact that Amelia's mutation arose de novo, is a missense non-conservative mutation, occurs in the pore - a functionally important region, occurs in an area that is "conserved" across species, the "functional" effect (e.g., complex amino acid changed to a simple one) and the reported comparable mutations resulting in SMEI. See, e.g., supra pp. 23-26.

Tr 2 at 373; see also R Reply at 4-6.

As Dr. Raymond explained, when petitioners' counsel inquired if the amino acid change of arginine to glycine³⁸ would always result in SMEI, you cannot assess the factors independently and expect the same outcome. That in addition to the amino acid change:

[l]ocation, biophysical properties are important. . . . [Y]ou can't just separate it out, and say, well arginine to glycine at some other location would result in Dravet. That gets to the whole argument we were having before about genom [sic] type correlation. You're taking it in a vacuum, and you don't have – you have to take it in the context of what we know, where it is located, what's changing, and what material do we have that goes before this and that helps me understand this.

Tr 2 at 361-62. Thus, all factors regarding a particular variant must be analyzed together, including the clinical picture, which in the case of Amelia Stone, was known to be SMEI. Dr. Raymond readily acknowledged SCN1A gene mutations are associated with a wide range of phenotypes, including polymorphisms. R Ex J at 3; R Ex T A at 24; Tr 2 at 387. Thus, Dr. Raymond explained he examines more than just the existence of a mutation or the individual characteristics of the mutation. Dr. Raymond discussed that he analyzes this case as a clinical geneticist who treats and advises patients on genetic disorders.

I mean that is the perspective I'm coming from is that as a clinical geneticist I'm putting the entire picture in rather than worrying about - - rather than just taking a mutation in isolation, and that's in fact some of the difficulties molecular DNA labs also have is that all they've got is a blood sample, as so they've got to be broad enough when they do a report whereas, you know, when I have a patient in front of me in a clinical situation with other clinical information.

Tr at 382. Dr. Raymond specifically addressed the fact one cannot examine one factor, the amino acid change for example, and not also consider the location where the amino acid change occurred. Thus, contrary to petitioners' assertion, the finding that one factor resulted in a different phenotype does not mean that factor is not a relevant factor for a clinical geneticist to consider when attributing genotype-phenotype causation. For example, a de novo mutation in one case, resulting in a polymorphism or GEFS+³⁹, does not independently make irrelevant the fact that Amelia's mutation arose de novo.

Specifically regarding the relevance of whether a mutation arose de novo, petitioners argue

³⁸ The mutation found in the Hammitt case.

³⁹ GEFS+ is at the lower end of the clinical spectrum of seizure disorders associated with the SCN1A gene mutation as compared to SMEI. See Dlugos et al. at (303) (“Severe myoclonic epilepsy of infancy can be considered an extreme end of the large SCN1A spectrum.”).

a de novo mutation is not evidence that Amelia's SCN1A variant is the sole cause of her SMEI. Again, the undersigned notes, as discussed by Dr. Raymond, the fact the mutation arose de novo is one factor analyzed as evidence that Amelia's SMEI was caused by her mutation; however, again, it is not the only factor considered by Dr. Raymond. Further, it is axiomatic that if approximately 90% of the variants associated severe phenotypes arise de novo, then 10% are inherited. Dr. Raymond never testified a patient will **always** have SMEI if the mutation arose de novo. Nor did he testify that a mild phenotype could not result from a de novo variant. Rather, regarding this factor, he noted the fact that Amelia's mutation arose de novo "was added evidence that this is a functionally significant alteration in the amino acid." Tr 2 at 330. Amelia's genetic testing report even stated, "the finding that the amino acid variant arose de novo is far more consistent with it being associated with a severe phenotype (SMEI or SMEB) than with a mild or normal phenotype." P Ex 40 at 6.

Furthermore, Dr. Raymond addressed the limiting language in the report that petitioners point to stating, "genotype-phenotype correlations do not exist in the current literature of this specific variant and the possibility that it is a rare sporadic benign polymorphism cannot be excluded." P Ex 40 at 6. Dr. Raymond explained "they [Athena Labs] are using language that will cover them in all circumstances, and they do not have a child in front of them So if in a specific circumstance . . . it did turn out to be a benign polymorphism . . . they put something in for the lawyers." Tr 2 at 395-97. Thus, as Dr. Raymond explained, this limiting language from Athena Labs is boilerplate language put in "every single one of their DNA reports" so that the Lab is not held to be legally liable in the event that a more rare possibility occurs. Id. at 397. In addition, Dr. Raymond agreed in his testimony that evidence of Amelia's specific genotype-phenotype does not currently exist. Id. at 332-33. However, this absence of literature on the exact genotype-phenotype correlation did not overly concern Dr. Raymond since similar mutations in nearby areas are documented. Id. at 333-34; see supra p. 25. The phenotype for these reported mutations is predominantly SMEI. Id. at 334; R T Ex at 31. The undersigned finds Dr. Raymond's explanation highly persuasive.

The undersigned does not find petitioners' argument persuasive. Evidence shows 90-95% of SMEI cases involving an SCN1A mutation arise de novo. R Ex G1, Harkin et al., The Spectrum of SCN1A-Related Infantile Epileptic Encephalopathies, 130 *Brian* 843, 844 (2007)(Harkin et al.). See infra p. 35. Simply because the other 5-10% of mutations are inherited, this does not make the fact that a mutation arose de novo irrelevant. As discussed by Dr. Raymond and discussed in the Athena Labs report and literature, it remains a relevant factor to consider in evaluating genotype-phenotype causation.

It cannot be over-emphasized that the examples cited above by petitioners isolate each factor individually and independently, rather than addressing Dr. Raymond's factors cumulatively. As explained by Dr. Raymond, "I think in the circumstances in front of me that I have presented evidence. . . . as a clinical geneticist using all the tools that I have available, that I am making a perfectly reasonable assumption. . . . If I was struck with a de novo mutation in a different region, I think the situation would have to be evaluated." Tr 2 at 356-57.

ii. Response to petitioners' concern regarding population

bias of SCN1A mutation statistics

Dr. Kinsbourne contended that the SCN1A gene variant pool is biased in favor of mutations that result in SMEI due to more DNA testing ordered by doctors for patients with severe phenotypes. Tr 2 at 427 (referencing Lossin at 13 (“It is uncertain whether the numbers and specifications of the published SCN1A variants are a good representation of naturally occurring genetic changes. Many of the mutations were identified after it had been discovered that SCN1A abnormality can lead to SMEI.”)). Dr. Raymond addressed this argument by stating “these centers that are doing testing for Dravet are also collecting samples from normal individuals and running them against [samples from individuals with severe phenotypes].” Tr 2 at 393; see also id. at 404 (Dr. Raymond explained “[T]here is always this bias when you start to do this sort of thing, but you have a large normal population what [sic] compared it to.”); id. at 406 (“That is standard molecular genetics practice.”). Petitioners simply failed to develop fully this argument. Other than the general contention and several general observations made by Dr. Kinsbourne, no convincing evidence was presented which would color Dr. Raymond’s testimony. Again, however, it is important not to lose sight of Dr. Raymond’s reliance on a confluence of factors for his opinion. Tr 2 at 355. As he notes, Lossin is a Ph.D., not a clinical geneticist. Id. at 355-56. As a clinical geneticist, Dr. Raymond testified, “I think if Lossin was presented with these mutations, I think a reasonable clinical geneticist if presented with this information that we have in front of us today would come to the same conclusions that I have.” Id. at 357.

iii. Objective evidence from medical literature supporting Dr. Raymond’s analysis

Petitioners also attacked Dr. Raymond’s testimony contending that there is no objective support for the factors Dr. Raymond analyzed as being indicative of SMEI. However, as addressed above, Dr. Raymond, a highly qualified geneticist and neurologist, explained this is what he does as a clinical geneticist, examining each factor cumulatively alongside the patient’s clinical picture. See Tr 2 at 357, 382. Further, the undersigned, while certainly not a geneticist, notes comments in the literature that appear to support Dr. Raymond’s analysis. Notably, these comments were not addressed by or distinguished by petitioners.

The following passage from the medical literature underscores the significance of considering whether an amino acid change in a well-conserved region is one predicative factor, as Dr. Raymond explained, that the variant is disease-causing:

If the variant postulated to have a pathogenic effect changes an amino acid at a position in the protein conserved through evolution (in the same sodium channel across species), or a position conserved within proteins encoded by the same gene family (subtypes of the human sodium channel), this is strong circumstantial evidence that the variant is pathogenic.

R Ex F8, John C. Mulley et al., SCN1A Mutations and Epilepsy, 25 HUMAN MUTATION 535, 539 (2005)(“Mulley et al.”). Nabbout et al., while emphasizing the difficulty of making a genotype-

phenotype prediction based on the mutation alone, underscored the importance of analyzing the clinical picture along with the genetic picture, as Dr. Raymond explained a geneticist would. “Nevertheless, a clinical picture of SMEI can be suggested even in the first year of life. The finding of a SCN1A mutation would encourage more aggressive treatment after a first FS [febrile seizure] with early onset.” Nabbout *et al.* at 7. Dlugos *et al.* discuss a case study of a 6 year old boy with an SCN1A gene mutation and generalized epilepsy with febrile seizures plus (GEFS+) and in analyzing whether the “mutation is the cause of the patients’ epilepsy” note that

[t]here are no absolute criteria yet established for distinguishing disease-associated mutations from susceptibility alleles from benign polymorphisms. **Published criteria for considering a missense mutation [Amelia’s mutation is missense] as pathogenic included the following: the mutation is not reported among common variants; it results in a nonconservative amino-acid change; it arises de novo.**⁴⁰

Dlugos *et al.* at 304-05 (emphasis added). The authors note this case study involves a “de novo, nonconservative mutation in a region of the protein with a high degree of conservation across evolution. Taken together, the evidence forms a compelling argument for considering R1596C a disease-associated mutation.” *Id.* at 305. Multiple articles note the high rate of SCN1A de novo mutations in persons with SMEI. *See* Mulley at 538 (95% of cases where parents have been tested report de novo mutations); Harkin at 844 (“Approximately 95% of SCN1A mutations in SMEI patients arise de novo.”). Mulley, in discussing “proof of a causal relationship,” states “[d]e novo mutation associated with sporadic occurrence of disease is even stronger proof” of causation. Mulley at 539. Thus, with this brief review, it appears to the undersigned that petitioners’ allegation that Dr. Raymond’s analysis is not supported by the literature or by objective evidence is simply not accurate. In addition, it cannot be overstated that petitioners’ rebuttal suffered from the lack of credible expert testimony. Dr. Kinsbourne simply was not qualified or able to counter the testimony of Dr. Raymond. Petitioners thus had to rely upon cherry-picked snippets from the medical literature, presented in their Post Hearing Briefs, in an effort to undermine Dr. Raymond. That effort failed.

iv. Scientific certainty is not the standard of proof for either party in a Vaccine Act case

Dr. Kinsbourne repeatedly questioned Dr. Raymond’s testimony as not scientifically certain. Tr 2 at 446, 448, 460. Dr. Kinsbourne testified that he did not believe the SCN1A gene mutation was the cause of SMEI in this case as “the medical literature indicates that location and the nature and whether it’s de novo do not in fact give one a 100 percent genotype/phenotype correlation.” Tr 2 at 460. Thus, Dr. Kinsbourne is looking for scientific certainty to establish the SCN1A gene mutation in this case is the sole cause of Amelia’s condition.

⁴⁰ The authors do question why the patient displayed GEFS+ and not SMEI in light of the fact that they boy’s mutation arose de novo. However, again the undersigned notes the analysis of Dr. Raymond centers on whether a gene variant is disease causing and GEFS+ is a disease on the same spectrum as SMEI.

The undersigned notes, each party is held to the same standard in regard to their respective burdens; the standard is preponderant evidence or “more likely than not,” neither party is held to a standard of scientific certainty. As my colleague Special Master Abell explains, the preponderant standard is proof akin to 50% and a feather. Whitener v. Sec’y of Dept. of Health & Human Servs., No. 06-0477V, 2009 WL 3007380 *1 (Fed. Cl. Spec. Mstr. Sep. 2, 2009). The Federal Circuit has made it abundantly clear that the burden is probability; not scientific certainty. Knudsen, 35 F.3d at 548-549. Again, the government’s burden to prove alternate causation, like petitioners’ burden, involves the special master “ascertaining whether a sequence of cause and effect is ‘logical’ and legally probable, not medically or scientifically certain.” Id.; see also Hanlon, 191 F.3d 1344 at 1349 (citing Knudsen) (“[b]ased on a ‘logical and legally probable’ sequence of cause and effect, she [the special master] determined that TS [tubular sclerosis] was the actual alternative cause of Michael’s seizures. A reversal of this finding would improperly require proof of causation that is ‘medically or scientifically certain.’”). While one cannot predict with absolute certainty the outcome of SCN1A mutations, utilizing the factors presented by Dr. Raymond along with Amelia’s clinical presentation, the undersigned finds based upon Dr. Raymond’s cogent testimony it is more likely than not that the SCN1A mutation is the cause of Amelia’s SMEI. Tr 2 at 335. (In answer to the question “so what was the role of her SCN1A mutation?” Dr. Raymond replied: “Her SCN1A is the sole cause of her having Dravet syndrome.”).

2. The SCN1A Gene Mutation as an Indicator of Clinical Outcome

a. Petitioners’ support for the assertion that presence of the SCN1A mutation is not predictive

In addition to criticizing the specific analysis performed by Dr. Raymond in drawing his conclusion that Amelia’s SMEI is caused by her mutation, petitioners argue more broadly that the case examples and medical literature indicate you cannot predict an individual’s outcome based solely on the presence of the SCN1A gene mutation. See Tr 2 at 417-26, 430-33; P Memo at 13-14. With this somewhat overlapping but more global argument, petitioners’ counsel cites further examples found in the SCN1A literature of divergent outcomes found in individuals with the same mutation. P Memo at 10-13. Petitioners’ counsel references this as evidence that you cannot reliably predict outcome based upon the SCN1A gene variant alone. Id.

First, petitioners’ counsel noted that “[a]bout ten (10%) of the SCN1A gene variants found in children with SMEI are inherited from normal parents” and go on to list examples of this fact found in the literature. Id. at 10 (citing Depienne et al.; Nabbout et al.). Their argument is as follows: ten percent of children with an SCN1A mutation did not have that mutation arise de novo, and their parents did not have any adverse outcome despite having an SCN1A gene mutation. Second, petitioners provided two examples of children with SMEI who inherited their SCN1A mutations from a parent who suffered other, milder seizure disorders and not SMEI. Id. at 11 (citing Nabbout et al. at 1963; Kimkura at 429). Third, petitioners also discuss cases found in the literature where the same SCN1A variant resulted in different types of seizure disorders within in the same family. Id. at 11-12. One such study discussed by Dr. Kinsbourne at the May 15, 2009 Hearing found “[o]ne person in the program had SMEI, his sister with the same mutation had a milder type

of GEFS plus, and the father had FS plus.” Tr at 432 (citing P Ex 23, Grazia Annesi et al., Two Novel SCN1A Missense Mutations in Generalized Epilepsy with Febrile Seizures Plus, 44 EPILEPSIA 1257, (2003)(“Annesi et al.”). Fourth, petitioners cited reports of two SCN1A variants that resulted in different clinical outcomes in individuals from different families. P Memo at 12. Petitioners argue this is evidence that a SCN1A gene mutation is not a reliable indicator of clinical outcome.

Aside from these examples, petitioners further support this proposition by citing to authors’ conclusions in the medical literature, stating the SCN1A mutation is not predictive of clinical outcome. Specifically, petitioners cited to passages in the following articles:

Throughout the writing of this article, I made several attempts to identify patterns in the pool of SNC1A mutations. There is no scarcity of data with a total of some 330+ genetic alterations, but a truthful correlation between the reported phenotypes and genotypes is exceedingly difficult to establish.

Tr at 418 (quoting Lossin at 13); see also P Memo at 13;

Questions regarding epilepsy prognosis and the fate of an AED withdrawal cannot be answered without improved genotype-phenotype correlation, because the SCN1A mutation spectrum is so broad. The risk of epilepsy in the patient’s siblings is low, because neither parent harbors the mutation. The risk of epilepsy in the patient’s future children may be as high as 50%, but the phenotype is impossible to predict.

P Memo at 13-14 (quoting Dlugos et al., at 305); see also Nabbout et al. at 1965(“[C]urrent data show that an SCN1A mutation does not necessarily lead to SMEI. . . . these findings emphasize the difficulty of predicting SMEI phenotype based on the finding of SCN1A gene mutation.”).

Petitioners argued that based upon the differing outcomes found in the medical literature and the specific statements quoted above, the SCN1A gene mutation is not indicative of a clinical outcome. P Memo at 13-14.

b. Response to and analysis of petitioners’ support for the assertion that presence of the SCN1A mutation is not predictive

Petitioners’ above argument fails as it does not offer persuasive rebuttal to Dr. Raymond’s reasoned conclusion that Amelia’s SMEI is caused by her SCN1A gene mutation; nor does petitioners’ argument offer any evidence that the vaccine was a substantial cause of her SMEI in addition to the mutation for the following reasons. First, in making this argument, petitioners fail to address that the majority of the examples petitioners cite to involve divergent conditions displayed within family members with the same mutation (e.g., inherited mutations). Respondent, Dr. Raymond and the Athena Lab Report note that Amelia’s mutation arose *de novo* and was not inherited. See, e.g., R Reply at 9; Tr 2 at 330; P Ex 40 at 6. Second, none of these reports described above discuss mutations that involve the same amino acid change as Amelia’s mutation, or discuss

a mutation at codon 1463, which Amelia possesses. Petitioners' cited examples are not comparable and thus are not persuasive rebuttal of Dr. Raymond's analysis.

As respondent notes, the cited literature seems to take a neutral position as to other influencing factors. R Reply at 7-8. Specifically, it is unknown whether there may be additional genetic components or unknown environmental factors influencing the diverse clinical outcome when one examines variants, which largely involve inherited mutations. See Nabbout et al. at 1961 (The article abstract notes that ten percent of SCN1A mutations involving SMEI involve asymptomatic parents and concludes "[t] increased frequency of familial epilepsy indicates that other genetic factors may contribute to this disorder."). Nabbout et al. further note that, even excluding inherited mutations, a high percentage of seizure disorders were found in the family members of individuals with an SCN1A mutation and a clinical outcome of SMEI "emphasizing that an additional genetic predisposition is likely to act with SCN1A mutations to determine the disease. This suggests complex inheritance of the SMEI phenotype" Nabbout et al. at 8. However, the undersigned, petitioners' counsel and Dr. Kinsbourne are not clinical geneticists. It is critical to note that the examples cited by petitioners are argued by petitioners' counsel, or at best Dr. Kinsbourne, to be indicative of an inability to predict clinical outcome based upon a SCN1A gene mutation. However again, neither petitioners' counsel nor Dr. Kinsbourne is qualified to analyze this literature and discuss its significance in relation to the facts of this case. This is why the undersigned urged petitioners to offer the testimony of a geneticist in this matter and gave petitioners numerous extensions of time in order to retain a geneticist. However, petitioners chose not to offer the testimony of a geneticist and Dr. Kinsbourne's efforts were simply insufficient to rebut the qualified testimony of Dr. Raymond.

Dr. Raymond, a qualified clinical geneticist, addressed the above cited paragraph, see supra pp. 37, from Lossin, who is not a clinical geneticist or an M.D., but rather a Ph.D. research associate, by agreeing with the statement, but explaining

he [Lossin] says that there is no scarcity of data but a truthful correlation between reported phenotypes and genotypes is exceedingly difficult to establish, but there is data out there. So when you use all of your data available, you can make a reasonable genotype, phenotype correlation. As a clinical geneticist, which Lossin isn't, I would have to say that we take what's available to us, this is how I would use it in the clinic.

Tr 2 at 355. Dr. Raymond also noted that while researchers and laboratories typically have a blood sample to examine, they may or may not have any clinical information. Tr 2 at 396. In making his conclusion, Dr. Raymond is acting as a clinical geneticist correlating all available data and applying that data in a specific, individual case, while Lossin is acting as a researcher analyzing data from numerous cases. The efforts are separate and distinct and utilize different evaluating standards: Dr. Raymond's in this court is preponderance of the evidence; Lossin's standard, as a researcher, is

scientific certainty.⁴¹

Finally, as previously discussed, Dr. Raymond stated on re-direct examination at the Hearing on May 15, 2009, that he did not purport a 100% genotype-phenotype relationship between SCN1A mutations and SMEI. Tr 2 at 322-23. He is not stating that every SCN1A mutation results in SMEI. Rather, he or any clinical geneticist makes a reasoned causal conclusion based upon multiple factors regarding the genetic mutation presented with the patient's clinical picture to determine whether the genetic variant caused the disease. Tr 2 at 355. And in this case, Dr. Raymond reached his conclusion looking retrospectively at Amelia's clinical picture, as well as at specific factors of her mutation (e.g., its location, the amino acid change involved, that it occurred in a well conserved region, that it arose de novo, see, e.g., supra pp. 23-26) to draw the conclusion that Amelia's SMEI is genetically caused solely by her SCN1A gene mutation. Thus, Dr. Raymond is not arguing in favor of a perfect genotype-phenotype correlation. In the final analysis, petitioners' argument misses the mark and is unpersuasive.

3. Environmental (Vaccine) Factors Change the Outcome of Persons with SCN1A Mutations

⁴¹ Dr. Raymond also testified that mosaicism may explain why you sometimes see different clinical outcomes in family members with the same genetic mutations. See Tr 2 at 325-26, 354, 400, 474. As discussed in respondent's Memo:

[m]osaicism allows for the presence and growth of two different "populations" or sets of cells in one person's body. One group of cells might have completely normal DNA, while the other group might contain DNA with a particular mutation. Once a cell develops a mutation within its genetic material, it passes that mutation on as it continues to divide and create new cells. As explained in one of the filed articles, "[t]he rate of mosaicism in a given individual is determined by the timing of the occurrence of the mutation during the postfertilization development." Resp. Ex. L at 3. Thus, if the mutation developed immediately after fertilization, the percentage of mutated cells present in the body would be far greater than if the mutation occurred much later in development. Furthermore, as the mutation is only present in some cells, it might not be found throughout the entire body. If it is not present in brain cells, the parent might be completely normal, and if it is only present in some (but not all) brain cells, the parent might be mildly affected. Finally, if the mutation is present in germline cells (i.e., egg and sperm cells), it can be passed on to offspring, who will then harbor the mutation in all of their cells and be more likely to suffer from the most severe clinical outcome: Dravet syndrome.

R Reply at 8-9. None of petitioners' articles about mutations inherited from normal or mildly affected parents discuss whether tests were performed to determine whether the parent was mosaic for the SCN1A mutation. R Reply at 8-9. The undersigned notes this explanation was mentioned, but not fully developed by respondent, however it was also not challenged by petitioner. Nonetheless, the undersigned again notes, Amelia's gene mutation was not inherited, it arose de novo. P Ex 40 at 6. As respondent states, petitioners' reliance on literature discussing inherited genetic mutations is "misplaced." R Reply at 9.

Dr. Kinsbourne opined the DTaP vaccination caused Amelia to experience a fever, which in turn caused her to suffer a complex febrile seizure, which “triggered the onset of her Dravet Syndrome,” P Ex 48 at 1, by “lower[ing] her seizure threshold.” Tr 2 at 443; see supra p. 15. However, Dr. Kinsbourne conceded that the SCN1A gene mutation plays a role in Amelia’s SMEI. He described this role as “the propensity or susceptibility that rare children have to pertussis vaccination as well as, of course, to other provocations too.” Tr 2 at 444. Thus, Dr. Kinsbourne maintained that the “mutation alone does not predict the form the seizure disorder would take Modifying factors resulting in causation or significant aggravation must exist.” P Ex 48 at 4. Petitioners argued the medical literature supports the role of environmental modifying factors to SCN1A gene mutations, including DTP and DTaP vaccination. P Memo at 14. Petitioners’ arguments to support this allegation include citations to the medical literature that petitioners allege demonstrate the following: a) that environmental factors change the clinical outcome in persons with SCN1A gene variants; b) that seizures change the outcome in persons with SCN1A gene variants; and c) that fever caused by pertussis is a recognized trigger of SMEI. Id. at 14-19. The discussion of these contentions follows.

a. Environmental factors change the clinical outcome in persons with SCN1A gene variants

To support their argument that an environmental factor modifies the clinical course of SMEI, petitioners’ counsel again pointed to comments in the medical literature that consider whether other genetic or environmental factors may modify the clinical outcome in persons with SCN1A gene mutations. P Memo at 14-15. These assertions are based upon the divergent outcomes resulting from the same SCN1A mutations. Id.

Therefore SCN1A could be considered a susceptibility factor for both disorders [GEFS+ and SMEI] in which the severity is modified by other environmental and genetic factors. Thorough investigation of genetic and environmental modifying factors is important to determine their influence on disease manifestation and progression.

Wallace at 19.

Interestingly, we report two mutations, . . . previously reported in patients with cryptogenic focal epilepsy in patients with typical SMEI. This suggests that the variation in clinical presentation is not intrinsic to the mutations themselves but rather to the interaction with other yet unidentified genetic or environmental factors.

Depienne et al. at 10.

Dr. Kinsbourne also read the above passage from Depienne et al. into the record during the Hearing on May 15, 2009 at the request of counsel. Tr 2 at 418-19.

Respondent pointed out that the above citations from Wallace and Depienne et al. are actually

neutral as to whether a genetic component or an environmental component may modify the outcome in persons with SCN1A gene mutations. R Reply at 7-8. Thus, respondent argued it is “untenable for petitioners to claim that the articles bolster their assertion that Amelia’s DTaP vaccine changed her clinical course.” *Id.* at 8.⁴² The undersigned agrees with respondent’s point. The authors of the above studies merely **hypothesize** regarding an unknown genetic or environmental modifiers’ effect on the outcome of persons with SCN1A mutations. Critically, these articles do not support the proposition that a vaccine, specifically the DTaP vaccine, modifies the clinical outcome in individuals with an SCN1A variant.

b. Seizures change the outcome in persons with SCN1A gene variants

Petitioners argue that two medical articles demonstrate that seizures change the outcome in persons with SCN1A variants. P Memo at 15-16. Petitioners’ counsel alleges the following statement from Rhodes *et al.* “provide[s] an hypothosis [sic] for how underlying predisposition to have seizures created by the SCN1A gene and subsequent damage due to each seizure each contribute to SMEI.” P Memo at 16.

The disparity in clinical severity between GEFS+ and SMEI probably requires explanation other than just difference in channel behavior. We would like to speculate that the severe neurologic consequences of SMEI are caused by a combination of sodium channel dysfunction (either gain or loss of function) with predisposing genetic or developmental factors that lead to a great chance of neuronal injury. In this model, the sodium channel defect creates the initial seizure predisposition, but concaminant [sic] excitotoxicity [that is brain injury due to seizures] is the direct cause for other neurological feature of the disorder.

Id. (quoting Rhodes at 11151)(emphasis in P Memo). Petitioners also cite, and Dr. Kinsbourne’s May 15, 2009 testimony relies upon, the following passage from the literature to support an environmental cause of Amelia’s SMEI.

But even [analyses of the functional effect of variants] cannot fully explain the difference between members of GEFS+ families. Influence of other genes, environmental factors, or evolution of epilepsy itself (kindling phenomena?) may in part explain the phenotype.

P Memo at 16 (quoting P Ex 25, Ceulemans *et. al.*, Clinical Correlations of Mutations in the SCN1A Gene: From Febrile Seizures to Severe Myoclonic Epilepsy in Infancy, 30 PEDIATRIC NEUROL. 236, 242 (2004) (“Ceulemans *et. al.*”))(emphasis in P Memo). However, although not addressed by

⁴² Respondent also argues the divergent outcomes can also be explained by mosaicism. This point is discussed *supra* fn 41. Since this point was not developed, the undersigned did not rely upon this argument.

respondent or Dr. Raymond, the undersigned notes Dr. Kinsbourne is not accurately characterizing this article and is “cherry picking” passages. What Dr. Kinsbourne and petitioners fail to acknowledge is that Ceulemans et. al., also state in another section, titled “Phenotype/Genotype Correlation” that “detailed analyses of all published patients for whom sufficient clinical and genetic information is available **clearly demonstrate phenotype/genotype correlation.**” Ceulemans et. al. at 241 (emphasis added). Further, the authors of this study conclude “[t]here is sufficient evidence that a severe disturbance of the function of SCN1A is a major cause of the epileptic syndrome known as Dravet syndrome or SMEI,” and go on to advise “[i]n clinical practice, mutations in SCN1A should be suspected in every child with a long lasting, fever-provoked seizure.” Id. at 242 (emphasis added). The undersigned is not persuaded by petitioners’ arguments above that Amelia’s vaccination or her initial post-vaccination seizure was either the “but for” or “substantial factor” that caused her SMEI. See Shyface, 165 F.3d 1353.

Additionally, as respondent notes and petitioners concede, the authors of these studies are again speculating, speculation is not evidence either of any concrete environmental factor that modifies the clinical course of persons SCN1A mutations, and certainly is not evidence of a vaccine modifier. R Reply at 9; P Memo at 16 (discussing the hypothesis by Rhodes et al.). The undersigned finds that Ceulemans et al. supports Dr. Raymond’s testimony that the SCN1A mutation is the cause of Amelia’s SMEI, that fever is often associated with SMEI, and that this disease and the inquiry of its genetic causality must be clinically examined.

c. Fever caused by pertussis is a recognized trigger of SMEI

Petitioners argue a 2000 study by Nieto-Barrerra et al.,⁴³ a commentary by Erick Sell and Berge A. Minassian,⁴⁴ and a 2006 study by Berkovic et al. support their theory that the vaccine is an environmental factor that changes the clinical outcome in persons with the SCN1A gene mutation.

I. Nieto-Barrerra et al.

Dr. Kinsbourne’s testimony,⁴⁵ and Petitioner’s Memo, relied extensively on the Nieto-Barrerra et al. study, which found twelve of twenty-eight children with SMEI received a DTP vaccination within seventy-two hours of seizure onset and concluded that “there is likely a

⁴³ P Ex 31, M. Nieto-Barrerra et al., Severe Myoclonic Epilepsy in Infancy. Analytic Epidemic Study, 30 REV. NEUROL. 620, (2000)(“Nieto-Barrerra et al.”).

⁴⁴ P Ex 50, Erick Sell & Berge A. Minassian, Demystifying Vaccination-Associated Encephalopathy, 5 LANCET NEUROL. 465 (2006)(“Sell & Minassian”).

⁴⁵ The undersigned will not discuss the testimony of Dr. Kinsbourne discussing this article at the May 14, 2009 Hammitt Hearing, although petitioners cite to this testimony in Petitioners Memo, as this testimony is not part of the instant record. See P Memo at 19-21 (this refers to the transcript that is part of the record in Hammitt only). Nonetheless, the undersigned notes that testimony does not alter the undersigned’s opinion.

constitutional factor or convulsive predisposition that is genetically conditioned . . . which [is] probably triggered by toxic-allergic factors; which explains the high incident of post-vaccine seizures as the initial clinical manifestation.” P Memo at 17-18 (citing M. Nieto-Barrerra et al., Severe Myoclonic Epilepsy in Infancy. Analytic Epidemic Study, 30 REV. NEUROL. 620, (2000)(“Nieto-Barrerra et al.”))⁴⁶; Tr 2 at 420-25, 461-66; P Ex 22 at 5; see also R Ex J9 at 5. Dr. Kinsbourne asserted that this article suggests “that vaccinations **might** be one of those environmental factors that contribute to SMEI.” Tr 2 at 421 (emphasis added).

Dr. Raymond opined at the May 15, 2009 Hearing that Nieto-Barrerra et al. has significant limitations. Dr. Raymond explained the study was conducted in 2000, which was “before the SCN1A gene mutation was understood.” Tr 2 at 320. Additionally and significantly, Dr. Raymond explained the study **involved a different vaccine**, the DTP vaccine, and was a retrospective study that examined factors associated with onset of SMEI in a small sample of subjects. Tr 2 at 321. Dr. Raymond explained that while approximately half of the children had a DTP vaccine prior to experiencing their first seizure and “about 50 percent have a viral illness by report, gastroenteritis, colds, URIs, things like that, all things that you would potentially associate with a fever.” Id. at 321. The undersigned agrees with Dr. Raymond’s analysis of this article.

Furthermore, Dr. Kinsbourne’s reliance on a study discussing the DTP vaccine is misplaced. Dr. Kinsbourne has previously acknowledged there are substantial differences between the DTP vaccine and the DTaP vaccine. The undersigned addressed this issue in that case as follows:

[T]he undersigned finds unpersuasive Dr. Kinsbourne’s theory based upon the National Childhood Encephalopathy Study of 1981, the ten year follow up to that study, and the 1994 report issued by the Institute of Medicine, that the pertussis toxin in the DTaP vaccine was the cause of the initial seizure activity that was experienced by Devin. Tr. at 27. Dr. Kinsbourne testified the NCES study demonstrated a strong correlation between a child receiving DTP vaccine and a child suffering an encephalopathy or seizure lasting greater than thirty minutes within three days, as the relative risk of these events was found to be five to seven times more likely than in the control group. Tr. at 28. Dr. Kinsbourne further testified that the follow-up study ten years later found that the children who had experienced severe seizures at the time of the NCES study were likely to have developed epilepsy in the intervening time period. Tr. at 29. However, the aforementioned studies and report concerned the DPT vaccine not the DTaP vaccine. Dr. Kinsbourne acknowledged that the DTaP vaccine was developed in response to [the findings in the NCES study]. Dr. Kinsbourne testified that studies involving the DTaP demonstrate the same types of reactions documented following the DTP vaccine are occurring following the DTaP vaccine. Tr. at 35. However, the neurological events following the DTaP vaccination are greatly reduced to only around 30-40 percent of the reaction rate seen

⁴⁶ The undersigned notes petitioners cited to a translated version of Nieto-Barrerra et al. that was filed into the Hammitt case and differs slightly from the version filed into the instant case record.

following the DTP vaccination. Tr. at 30-31. Thus, it appears to the undersigned that the NCES and the ten year follow-up study cannot be utilized to support DTaP causation. The undersigned does not dispute that both vaccines may result in the same neurological reactions, however as Dr. Kinsbourne noted these events do not occur with the same frequency. Accordingly the relative risks of an adverse event from the DTP vaccine found in those DTP related epidemiological studies do not attach to a DTaP vaccine. Dr. Kinsbourne gave no convincing explanation to the contrary. Thus, it appears that the DTP studies cannot be used to support DTaP causation. See also Grace v. Department of HHS, 2006 WL 3499511 (Fed. Cl. Spec. Mstr. Nov. 30, 2006).

Simon, 2007 WL 1772062, at *7. The undersigned has the same concerns as expressed above in regard to the fact that the Nieto-Barrerra et al. study, like the NCES, involves DTP not DTaP. Again, the undersigned does not find DTP studies reliable evidence to support DTaP causation. This fact taken in conjunction with the additional limiting factors at issue in this study, discussed above, evidences to the undersigned that Nieto-Barrerra et al. is not persuasive evidence regarding the issues presented in Amelia's case.

ii. **Berkovic et al.**

Dr. Kinsbourne's May 15, 2009, testimony also discusses an article by Berkovic et al. to support the theory that vaccines play a significant causal role in persons with SCN1A mutations and the resulting SMEI. See P Ex 24, S.F. Berkovic et al., De novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: A retrospective study, 5 LANCET NEUROL. 488-92 (2006) ("Berkovic et al."). During his testimony, Dr. Kinsbourne stated he referenced this article because "the authors say that they could neither rule in or rule out the role of vaccination in the experimental design, whatever their opinions were." Tr 2 at 470. Dr. Kinsbourne's opinion quotes Berkovic, et al., stating, "Berkovic and colleagues acknowledge that 'in the presence of SCN1A mutations, vaccinations can still be argued to be a trigger for the encephalopathy.'" P Ex 22 at 5.

Respondent, however, notes that Dr. Kinsbourne "clearly mischaracterizes" Berkovic et al. R Memo at 14-15. In fact, "Dr. Kinsbourne conceded on cross examination, the authors of the study made no findings on whether vaccines are a trigger for encephalopathy via fever or another immune mechanism." Id. (citing Tr 2 at 469, in response to the statement: "[T]hey didn't make a finding whether vaccines could be argued to be a trigger." Dr. Kinsbourne replied: No they didn't."). Further respondent correctly notes that in quoting Berkovic et al., Dr. Kinsbourne failed to acknowledge the language following his remark that "in the presence of SCN1A mutations, vaccinations can still be argued to be a trigger for the encephalopathy." The article goes on to state that this "trigger" is unlikely and explains precisely why vaccinations do not play a significant role in SMEI in persons with SCN1A mutations:

[B]ut the role of vaccination as a significant trigger for encephalopathy is unlikely for several reasons. First, although vaccination might trigger seizures as shown by the increased risk of febrile seizures on the day of triple antigen or MMR

vaccination, there is no evidence of long-term adverse outcomes. Second, less than half of our patients had documented fever with their first seizure, **which indicates that fever is not essential**. Third, our neuroimaging data showed no evidence of an inflammatory or destructive process. Finally, truncation and missense mutations reported in conserved parts of SCN1A have not been found in many hundreds of healthy patients. **Thus, individuals with such mutations seem to develop SMEI or SMEB whether or not they are immunized in the first year of life. We do not think that avoiding vaccination, as a potential trigger, would prevent onset of this devastating disorder in patients who already harbour the SCN1A mutation.**

Berkovic et al. at 5 (emphasis added). It is evident that Berkovic et al. does not support petitioners' case. In fact, the undersigned finds the above-cited language to be supportive of Dr. Raymond's testimony that the SCN1A gene mutation is the sole cause of SMEI. See also Harkin et al. at 848 (discussing Berkovic et al., "Recently we showed that the so-called 'vaccine encephalopathy' should be regarded as SMEI/SMEB on clinical and molecular grounds.").

iii. Sell & Minassian

To bolster the conclusions by Nieto-Barrerra et al., petitioners and Dr. Kinsbourne rely upon a quote from a commentary by Sell & Minassian. P Memo at 18. Petitioners and Dr. Kinsbourne quote the following passage from Sell & Minassian, "[is] the SCN1A gene mutation a predisposing factor waiting to be triggered by fever or by other stress? Probably so. In fact as early as 2000, Nieto-Barrerra and colleagues noted that more than 50 percent of patients SMEI had their first seizure after the DPT vaccination." Sell & Minassian at 466; see also Tr 2 at 422-23 (citing Sell & Minassian). Respondent argues this article is not persuasive evidence as it is a commentary. The undersigned agrees this article presents no new findings or evidence and, as Dr. Kinsbourne acknowledges, commentaries are simply "peer reactions to the research." Tr 2 at 421. Additionally, given the problems discussed above regarding Nieto-Barrerra et al., the undersigned approaches with caution literature relying upon Nieto-Barrerra et al. However, upon review of Sell & Minassian the undersigned once again believes petitioners mischaracterized the literature. The focus of the short commentary is largely upon Berkovic et al. Sell & Minassian state:

In their article in this issue of The Lancet Neurology, Berkovic and colleagues ask a brilliant question: could some cases of encephalopathy attributed to vaccination have an alternative cause? . . . The question seems to have arisen as a result of the wonderful recent interplay between advances in the genetics and the phenomenology of the disease, crystallization of the SMEI phenotype and advances in genetic methods allowed identification of the SMEI gene, SCN1A, making it a testable entity, which raised awareness among neurologists and insightful questions such as that posed by Berkovic's team. The question was answered in the positive with the identification of mutations in SCN1A in 11 of 14 patients with purported vaccine encephalopathy.

Sell & Minassian at 465-66. And while in their commentary Sell & Minassian do rely upon Nieto-

Barrerra *et al.* to argue that in their opinion the SCN1A gene is “probably . . . a predisposing factor waiting to be triggered by fever or other stress,” they go on to note “[c]omplications of naturally contracted infections are much higher than those associated with vaccination.” Sell & Minassian at 466.

Thus, these articles do not provide reliable or persuasive evidence that DTaP is an environmental factor that is a substantial cause, in addition to the SCN1A gene, of Amelia’s SMEI. Berkovic *et. al.* in fact informs why the vaccine does not play a significant role in SMEI and Sell & Minassian offer support for the role of the gene mutation. Unfortunately, the literature Dr. Kinsbourne relied heavily upon in this case is not persuasive because the articles often either do not ultimately stand for the proposition he stated, are dated, involve studies of limited application, or the articles discuss the DTP vaccination as opposed to the DTaP vaccination. Contrary to petitioners arguments, the evidence does not support the vaccine as an environmental component that is a substantial cause of SMEI in persons with Amelia’s SCN1A variants.

4. Impact of Amelia’s Initial Complex Febrile Seizure

Dr. Kinsbourne testified that he “**inferred** . . . complex febrile seizures, and particularly prolonged ones like this one [Amelia’s seizure], were apt to cause **brain damage** which, of course, would be superimposed on the propensity to have the seizure disorder that might have been - - to have the seizure disorder in some form represented by the SCN1A variant.” Tr 2 at 476 (emphasis added). Thus, Dr. Kinsbourne posits that Amelia’s condition has two substantial causes: 1) the SCN1A mutation, which in Dr. Kinsbourne’s opinion increased Amelia’s susceptibility to suffer seizures; and 2) the vaccine, which resulted in Amelia experiencing a fever, which then caused her to suffer a complex febrile seizure, which in turned caused brain damage.⁴⁷

Dr. Kinsbourne stated the clinical evidence for his theory rests upon the fact “that the vaccine was given, that [her] temperature was elevated, and . . . the seizure occurred and how long it was . . .” and that further seizures followed. *Id.* at 475-76. However, Dr. Kinsbourne stated “no” in response to the undersigned’s inquiry of whether “there was any other clinical manifestation of the brain damage you maintain occurred.” *Id.* at 476. Further, Dr. Kinsbourne conceded Amelia experienced no developmental delay until after the first year of life. *Id.* at 476-77. Then in response to the undersigned question “[d]oes your theory of lower seizure threshold account for developmental delay after the first year?” Dr. Kinsbourne responded “[n]ot necessarily, no. And there are two ways of looking at it one or both may be correct . . .” *Id.* at 476-77. In response to the undersigned’s question regarding whether “the [first] seizures themselves contribute[d] to additional damage,” Dr. Kinsbourne replied: “I don’t remember it well enough.” *Id.* at 477. To which the undersigned noted “[s]o the impairment of the sodium channels is a possible explanation for this for [her] subsequent condition . . . ?” Dr. Kinsbourne replied: “That’s one way of looking at it.” Tr 2

⁴⁷ Dr. Kinsbourne’s theory that Amelia first complex febrile seizure experienced post vaccination caused her to suffer brain damage appears to be in addition to Dr. Kinsbourne’s theory that Amelia’s initial complex febrile seizure resulted in a weakening of her seizure threshold and led to further seizures resulting in her ultimate diagnosis of SMEI. *See infra* p. 15.

at 478.

Dr. Raymond, Tr 2 at 342, and Dr. Kohrman, Tr 1 at 40, conceded the vaccine may have caused Amelia's fever, which in turn may have triggered her initial complex febrile seizure in this case; however, there is nothing in the record demonstrating Amelia's vaccination on August 27, 2001, or her seizures suffered on August 28, 2001, caused any brain damage or injury that contributed to her SMEI. See Tr 2 at 346. Dr. Kinsbourne conceded, "a trigger doesn't necessarily have to have a further deeper impact." Id. at 482. And Dr. Raymond explained that while complex febrile seizures **can** injure the brain, "you have to put that in context of these cases **where we have no evidence that the complex febrile seizures actually injure the brain**; that their course was in any, shape or form different than any other individual who [has] Dravet syndrome." Tr 2 at 346 (emphasis added). Dr. Raymond explained approximately 80 to 90 percent of children with SMEI have the SCN1A gene mutation. Id. at 317. The typical age of onset of SMEI is two months to nine months and onset [of the first seizure] is associated with a temperature elevation. Id. In fact Ceulemans et al. state:

The first clinical expression of a mutation in the SCN1A gene is recurrent, often prolonged, seizures provoked by fever in infancy. An even more specific symptom, when present, is a fever-associated status epilepticus before 1 year of age.

Ceulemans et al. at 240. Thus, based upon Dr. Raymond's testimony, it is not surprising that Amelia, at just over four months old, suffered a rise in temperature after her vaccination and then experienced a severe seizure.

Dr. Raymond testified the temperature elevation does not "play any sort of causal role in the disease." Tr 2 at 317. To demonstrate this point Dr. Raymond discussed a critical study involving a mouse model published by the National Academy of Sciences. Id. at 318; R Ex M, John C. Oakley et al., Temperature and Age-Dependent Seizures in a Mouse Model of Severe Myoclonic Epilepsy of Infancy, 106 PROC. OF THE NAT'L ACAD. OF SCI 3994, (2009) ("Oakley et al."). Oakley et al. discusses "that the first seizure in infants with SMEI occurs during fever or less frequently during a hot bath." Oakley et al. at 3994. Interestingly, in addition to rises in temperature associated with underlying infection or inflammation, precipitating seizures in individuals with SMEI, Oakley et al. noted "**evidence that hot baths alone are sufficient to provoke febrile seizures in SMEI.**" Id. at 3997 (emphasis added). Therefore, Oakley et al. studied mice designed to have an SCN1A gene mutation and then elevated the core body temperature of mice to mimic a typical fever.⁴⁸ Oakley et al. at 3994. One question Oakley et al. addressed was whether seizures could be induced by "elevated body core temperature." Id. at 3997. Oakley et al. "demonstrated that elevated temperature alone, in the absence of infection, is sufficient to provoke seizures" in the mice, thus "suggesting that temperature elevation alone is responsible for seizure provocation." Id. at 3997.

⁴⁸ The undersigned notes that Oakley explains "that the mice model recapitulates the human disease with surprising fidelity" and thus makes this a useful model. Oakley et al. at 3998. See Andreu, 569 F.3d 1367, fn 9 (approving the appropriate use of animal studies).

In other words, it is the temperature change that occurs with a fever and not the underlying infection (or vaccination) which can induce seizures in mice with SMEI. This study was addressed by Dr. Raymond at the May 15, 2009 Hearing:

Okay, the Oakley model is a knock-out mouse, which is a mouse model that recapitulates the severe [myoclonic] epilepsy of infancy very well, and in this model there is a dysfunction in the SCN1A gene that results in a pattern as I said mimics the human situation so that the mice early on have normal development. They then develop temperature-sensitive seizures. These temperature sensitive seizures then progress to seizures without temperature elevation, and you can call it fever but they are actually raising the environmental - - they are actually raised the body core temperature of the mouse, so it doesn't have to be an infection or inflammation. In fact they found no evidence of infection or inflammation in the mouse model.

Tr. 2 at 318. As respondent notes in her post-hearing memorandum, this study is evidence that the SCN1A gene mutation is responsible for Amelia's seizure disorder, and not an environment-gene interaction, be it an infection or as petitioners argue a vaccination. R Memo at 16.

The Oakley et al. study results are also supported by the conclusion of Berkovic et al., see supra pp. 44-45, that the role of vaccination as a significant trigger for encephalopathy is unlikely. Berkovic et al. at 5; see also Harkin et al. at 848 (discussing Berkovic et al., "Recently we showed that the so-called 'vaccine encephalopathy' should be regarded as SMEI/SMEB on clinical and molecular grounds.")).

Again, it is critical to note, Dr. Kinsbourne conceded the mutation played a substantial causative role in Amelia's SMEI, the issue that ultimately must be resolved is whether respondent has demonstrated that the mutation is the substantial causal factor, or in other words that the vaccine did not also play a substantial causal role in Amelia's SMEI. See Shyface, 165 F.3d 1344; see also de Bazan, 539 F.3d at 1354. There is simply no evidence that Amelia's initial seizure caused any brain damage, or somehow affected the expression of her genetic mutation in such a way that caused her to develop SMEI or experience further seizures. As discussed supra p. 5, among other tests conducted during her hospitalization following her first seizure on August 27, 2001, Amelia received an MRI at UW Madison on August 29, 2001. P Ex 7(a) at 94, 106-107. The MRI finding was "[n]ormal head MRI for age with no findings to explain patients symptoms." Id. at 94. Amelia was discharged on August 31, 2001 and it was noted she "continued to feed well and showed no seizure activity or neurologic deficit." Id. at 107. r. Kinsbourne was unable to point to any evidence demonstrating that Amelia's vaccination acted as anything more than a trigger to her initial fever induced seizure. Dr. Raymond's testimony explained there is "no evidence that it [an SCN1A gene mutation] would not manifest itself." Tr. 2 at 325. Dr. Kinsbourne was unable to point to any evidence that Amelia's initial complex febrile seizure caused her injury, which when combined with her mutation was a substantial cause of her SMEI. Tr 2 at 482-86. Rather, as the evidence supports, Dr. Raymond opined that the initial fever-induced seizure was part of the normal progression of Amelia's SMEI. Dr. Raymond concisely explained, "she had a fever from [the DTaP] but her subsequent development of [SMEI] is completely unrelated to the fact she had an immunization that

day.” Tr 2 at 335.

5. The Simon and Mersburgh Decisions

Petitioners argue the undersigned’s findings in the Mersburgh and Simon cases compel a finding on behalf of petitioners in the instant matter. See P Memo at 6-7; Petitioner’s Post-Hearing Reply Memorandum (“P Reply”) at 6-7. The undersigned might agree with this argument, if no testimony or evidence had been presented regarding Amelia’s SCN1A gene mutation. Again the undersigned found in the Mersburgh and Simon cases “on a probability scale, it is exceedingly reasonable to conclude that where the vaccine is associated with fever and seizure and the seizure is of a complex nature, **in the absence of proof of an alternative cause**, it is the vaccine that is responsible for a subsequent epilepsy and residual sequelae.” Mersburgh, 2007 WL 5160384, at *5 (citing Simon, 2007 WL 1772062, at *6)(emphasis added). However, Mersburgh and Simon can be readily distinguished from the instant case as **those cases contained none of the SCN1A gene mutation evidence and testimony that was presented in this matter**. While respondent contested Simon and Mersburgh⁴⁹ and argued a possible genetic predisposition was responsible for the injuries in those cases, there was no evidence presented that the children in those cases possessed the SCN1A gene mutation or any other mutation which played a causative role in the seizure disorders. In the instant case respondent presented credible, persuasive evidence of an alternative cause to Amelia’s injury, her SCN1A gene mutation. As discussed, Dr. Kinsbourne and petitioners failed to demonstrate how Amelia’s vaccination or her fever resulting from her vaccination altered the course of her genetically based seizure disorder.

6. Weighing Expert Reliability

Petitioners attack the credentials of Dr. Raymond and the reliability of his testimony. Dr. Raymond’s testimony is discussed at length previously, see, e.g., supra pp. 18-26, and petitioners’ arguments regarding the reliability of his analysis are also discussed previously, see, e.g., supra pp. 27-38. Petitioners argue that Dr. Raymond is not qualified to testify as his area of expertise is not in SCN1A gene mutations. P Reply at 4. However, Dr. Raymond, as opposed to Dr. Kinsbourne is a clinical geneticist. The undersigned will note again, Dr. Raymond’s testimony was well explained, cogent, based upon the knowledge and practices of a clinical geneticist, and supported by the medical literature. The juxtaposition between the testimony of Dr. Raymond and Dr. Kinsbourne was striking. In contrast to Dr. Raymond’s cogent explanations, Dr. Kinsbourne was unable to adequately address the issues presented in this case. When the undersigned asked Dr. Kinsbourne the critical question upon which his theory hinged, “is there an article that talks about environmental effect that says the environmental effect [vaccination, etc] is something more than a trigger, that it actually has an impact on the genetic abnormality?” Dr. Kinsbourne responded “[t]hat’s a lovely

⁴⁹ In fact respondent raised the defense that the injury alleged in Mersburgh was indeed caused by a genetic mutation, however this allegation and subsequent request for genetic testing in that case was presented in an untimely fashion and the undersigned denied respondent’s motion to order genetic testing. Mersburgh, 2007 WL 5160384, at *3.

question which I wish you had asked me earlier meaning like a month ago so I could have researched it.” The undersigned then noted “it’s a jump to say that the trigger actually alters the path.” Tr 2 at 482. To which Dr. Kinsbourne responded:

It is. I understand that fully. My thought is that if a potentially damaging event acts as a trigger, it really acts both as a trigger and a damaging event, so that we have in fact, this particular trigger was a vaccine elicited status epilepticus, and right there we have a damaging event. . . . So the first assault on the brain, which was highly predisposed, not able to cope with the assault, was mediated by a vaccine launched effect.

Id. at 484-85 (emphasis added). The undersigned finds Dr. Kinsbourne’s testimony unpersuasive. Again there is no evidence of the initial vaccine triggered fever and seizure causing any **damage** to Amelia. Nor is there any cogent explanation for how an environmental trigger, specifically a vaccine, significantly contributed to Amelia’s SMEI. Dr. Kinsbourne’s testimony, discussed above, is extremely speculative; speculative testimony does not provide preponderant evidence. Hennessey v. Sec’y of Dept. of Health & Human Servs., 91 Fed. Cl. 126 (Fed. Cl. 2010) (“The special master may not demand scientific certainty, but neither may she accept mere speculation.”); Doyle v. Sec’y of Dept. of Health & Human Servs., ___ Fed. Cl. ___, 2010 WL 1135742 at * 8 (“[P]roof of causation entails more than having a well-qualified expert proclaim that the vaccination caused a disease. Mere conclusory opinions – or ones that are nearly so as unaccompanied by elaboration of critical premises – will not suffice as proof of causation, no matter how vaunted or sincere the offeror. See, e.g., Moberly, 592 F.3d at 1324 (“the special master is entitled to require some indicia of reliability to support the assertion of the expert witness”)).

As respondent notes, knowledge regarding SCN1A gene mutations has evolved enormously over the past several years. It is noteworthy that the literature petitioners rely upon is dated. Unfortunately for petitioners they made the decision not to present a geneticist, but rather relied upon Dr. Kinsbourne, who is a well credentialed neurologist, but one who has not practiced in a clinical setting involving seizure disorders in over twenty-five years and relies upon reading literature to maintain his knowledge. Further, Dr. Kinsbourne has no past or present experience or credentials in the field of genetics. Given his lack of a current clinical practice, he is at a distinct disadvantage when discussing current knowledge and practices regarding alleged vaccine-caused injuries; this fact becomes quite obvious when comparing the quality and depth of testimony at the Hearing held on May 15, 2009. Dr. Kinsbourne’s testimony does not measure up, particularly compared to the detailed testimony Dr. Raymond provided. Dr. Raymond provided a complete and thorough review of the underlying genetics in this matter and then applied the medical principles and his clinical experience as a geneticist and pediatric neurologist to the facts of this case. Further, Dr. Raymond was able to thoroughly and competently address questions raised by respondent’s counsel on direct, as well as queries by the undersigned and petitioners’ counsel on cross-examination.

Dr. Kinsbourne’s testimony in comparison was striking; several examples regarding critical medical components of this case are noted. Upon cross-examination Dr. Kinsbourne was asked “whether he would agree that the amino acid change in Amelia Stone has the same functional impact

as a case reported in the medical literature that has a mutation at the same site.” Tr 2 at 448-49. Dr. Kinsbourne replied, “ I understand those facts. I don’t know what to conclude from them.” *Id.* at 449. Dr. Kinsbourne repeated on further questioning “I don’t know the functional impact of the change.” *Id.* at 450. Elaborating, he stated, “I don’t know what happened to the sodium channels.” *Id.* Unfortunately for petitioners, Dr. Kinsbourne’s testimony did little to illuminate the causation issues presented in this case. Again, the undersigned contrasts this testimony with the testimony of Dr. Raymond and the disparity is overwhelming.

V. Conclusion

As discussed *supra* pp. 17-18, seizures are perhaps one of the most common vaccine-related allegation seen in Program cases, as discussed in *Simon* and *Mersburgh*, among other cases. Advances in genetics inevitably cause changes in our understanding of seizures. Dr. Raymond’s testimony regarding the meaning and implication of genetic mutations and application to the instant case cannot be gainsaid. He clearly, systematically, and persuasively explained how a qualified geneticist would interpret various genetic factors encountered in this case. Dr. Raymond powerfully concluded if a patient presented to him in his clinical practice with the same genetic test results as Amelia Stone, he would counsel the family and explain the SCN1A gene mutation “is the sole cause of her Dravet syndrome.” Tr 2 at 331.

However, the undersigned cautions that an SCN1A mutation or any other genetic mutation should not automatically be considered the cause of a vaccinee’s injury. Again, the undersigned finds the SCN1A mutation is responsible for **Amelia’s condition** for the following reasons:

- Amelia’s mutation arose de novo;
- the mutation at issue results in a non-conservative amino acid change with the new amino acid having very different physical properties from what is found at that location in non-affected individuals;
- the mutation affects the pore of a sodium channel, a functionally important region;
- the mutation occurs in an area that is well conserved across species, signaling significant ramifications when altered;
- there are reports evidencing similar or comparable mutations resulting in SMEI;
- and there is an absence of the mutation in the normal population.

Further, petitioners failed to present evidence that the vaccine-induced seizure caused injury to Amelia’s brain.

Based upon the cumulative reasons set forth above, the undersigned finds that respondent has met the burden of proving a factor unrelated to the vaccination caused Amelia’s SMEI. Respondent’s burden mirrors that of a petitioner.

Thus, respondent establishes a *prima facie* alternative actual causation case by adducing ‘preponderant evidence’ of: (1) a medical theory causally connecting the [factor unrelated to the administration of the vaccine] and the injury; (2) a logical sequence of cause and effect showing that the [factor unrelated to the administration

of the vaccine] was the reason for the injury; and (3) a showing of a proximate temporal relationship between [the factor unrelated to the administration of the vaccine] and injury.’

Walther v. Sec’y of the Dept. of Health & Human Servs., 2008 WL 243762 (Fed. Cl. Spec. Mstr. 2008)(citing Althen, 418 F.3d at 1278; see also Capizzano, 440 F.3d 1317; Knudsen, 35 F.3d 543; Grant, 956 F.2d at 1148)). The undersigned finds that respondent, through Dr. Raymond’s opinion and testimony, fulfills this burden.

The undersigned does find it significant that Dr. Raymond and Dr. Kohrman agree with Dr. Kinsbourne and petitioners that a DTaP vaccination can cause a fever and that in “some children that [fever] can result in febrile seizures” including complex febrile seizures. Tr 2 at 342 (quoting Dr. Raymond); see also Tr 1 at 40 (Dr. Kohrman likewise agrees the “DTAP vaccine, in this instance, was likely what caused the fever that triggered the initial seizure.”). Dr. Raymond agrees a complex febrile seizure can injure the brain; however, in the instant case Dr. Raymond notes there is no evidence the initial seizure injured the brain. Tr 2 at 346. Dr. Kinsbourne agreed. Based on the concessions made by Dr. Raymond, the undersigned notes that if a similar case presented, but was one that demonstrated **evidence of brain injury** subsequent to a complex seizure caused by a post-vaccination fever, the undersigned would be inclined to find the vaccine was a substantial factor contributing to the injury regardless of the nature of the gene mutation. See Shyface, 165 F.3d 1352-53. But, **that is not the case here**. There is no persuasive evidence that the vaccine was a “substantial factor” or the “but for” cause of Amelia’s SMEI. Id.

Based upon the totality of evidence and as discussed above, the undersigned finds that respondent has demonstrated by a preponderance of the evidence that Amelia’s SCN1A gene mutation was more likely than not the “but for” and “substantial factor” that caused her Severe Myoclonic Epilepsy of Infancy or Dravet Syndrome. Shyface, 165 F.3d 1353; see, e.g., de Bazan, 539 F.3d at 1354. Compensation is denied. The Clerk is directed to enter judgment accordingly.

IT IS SO ORDERED.

s/Gary J. Golkiewicz
Gary J. Golkiewicz
Special Master