In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 07-170V
Filed: August 31, 2010
To Be Published

SCOTT R. HAMMITT, as the Legal Representative of his Minor Daughter, RACHEL HAMMITT, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Severe Myoclonic Epilepsy of Infancy (SMEI); Dravet Syndrome; Complex Febrile Seizure; SCN1A Gene Mutation; DTaP Vaccine; Factor unrelated

Curtis Webb, Webb, Webb & Guerry, for petitioner.
Althea Davis, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

GOLKIEWICZ, Special Master.

Scott Hammitt seeks compensation on behalf his daughter, Rachel Hammitt, who suffers from Severe Myoclonic Epilepsy of Infancy ("SMEI"), which is also known as Dravet Syndrome.[2]

[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.

[2] 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.

Petitioner alleges a DTaP vaccination Rachel received was a substantial cause of her SMEI. Respondent denies the DTaP vaccination caused Rachel's injury. Respondent alleges that Rachel's SMEI is caused by a genetic mutation, one in her SCN1A gene. The undersigned finds respondent has demonstrated by a preponderance of the evidence that Rachel's SCN1A gene mutation more likely than not caused her SMEI.

I. Procedural History

On March 13, 2007, petitioner, Scott Hammitt filed a Petition on behalf of his daughter, Rachel, pursuant to the National Vaccine Injury Compensation Program ("the Act" or "the Program").[3] The Petition alleged that the Diphtheria-Tetanus-acellular-Pertussis ("DTaP") vaccine Rachel received on March 15, 2004, "caused her to develop a severe seizure disorder and to suffer profound developmental delays." Petition ("Pet.") at 1-2. On January 17, 2008, petitioner filed an expert report from Marcel Kinsbourne, M.D., in support of his petition. P Ex 9. On April 14, 2008, respondent filed a Report pursuant to Vaccine Rule 4(c) contending that compensation was inappropriate and the Petition should be dismissed. Respondent's Report at 11, filed April 14, 2008. Respondent's Report was supported by expert opinions from Max Wiznitzer, M.D., and Gerald Raymond, M.D. R Exs A, C. Drs. Wiznitzer and Raymond opined Rachel's injury, SMEI, is caused solely by her SCN1A gene mutation, a factor unrelated to her vaccinations. R Exs A, C. Particularly relevant to this decision is the fact that Dr. Raymond is a board certified geneticist and neurologist, with a speciality in child neurology. R Ex B.

Thereafter, petitioner was given additional time in which to file an expert response to respondent's expert opinions. Petitioner initially indicated in a Status Report filed September 22, 2008, that a geneticist was asked to review the case and provide an expert opinion. Despite the undersigned's repeated encouragement to present a geneticist's opinion, in a status report filed December 17, 2008, petitioner indicated he decided not to retain an additional expert witness. A response was filed by only Dr. Kinsbourne, a neurologist, on April 3, 2009, to respondent's experts' reports.

To elicit expert testimony, a two-part Hearing was held on May 14 and 15, 2009. On May 14, 2009, petitioner presented his case-in-chief through the testimony of petitioner's expert witness, Dr. Kinsbourne. Respondent presented Dr. Wiznitzer as an expert witness to rebut petitioner's case-

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Respondent's Exhibit ("R Ex") C1, 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.

in-chief. See Transcript, May 14, 2009, filed June 16, 2009, pages 1-172 (hereinafter "Tr. at").[4] On May 15, 2009, the testimony of Drs. Raymond and Kinsbourne was heard regarding SCN1A gene mutations in general and the medical significance of the mutations in the case of Rachel Hammitt. See Transcript, May 15, 2009, filed June 16, 2009, pages 266-488. For expediency, testimony was taken at the same time in a separate case pending before the undersigned, Stone v. Sec'y of Dept. of Health & Human Servs., 2010 WL 1848220, appeal docketed. No. 04-1041V (Fed. Cl. Spec. Mstr. April 15, 2010).[5] Subsequently, the parties filed simultaneous Post-Hearing Briefs, followed by replies. This matter is now ripe for resolution.

II. Factual History

Rachel Hammitt was born on November 9, 2003. P Ex 2(a) at 2. On March 15, 2004, Rachel received her second DTaP vaccination, as well as other childhood vaccinations. P Ex 3(a) at 8. Between 7:30 and 8:30 that evening, Rachel's mother observed her eye twitching, right arm twitching and Rachel was foaming at the mouth. Mrs. Hammitt gave Rachel ibuprofen and took her to the emergency room. P Ex 4(a) at 1. At 8:30, Rachel was admitted to the Pediatric Emergency Department of Hillcrest Hospital. P Ex 2(b) at 18. Rachel's mother reported Rachel experienced a forty-five minute long seizure. Id. Rachel's temperature upon admission was recorded at 38 degrees Celsius. Id. Rachel was given valium and stopped seizing within two minutes, however she remained stiff for an additional twenty to twenty-five minutes. Id. at 17. At 8:45, Rachel was given a CT scan, which was found to be normal. Id. at 19, 23. At 9:00 p.m. Rachel returned from her CT scan was crying and "moving her four extremities." Id. at 19. By 9:10 p.m. Rachel was breast feeding and by 9:30 she was asleep in her mother's arms. P Ex 2 at 19. Rachel was transferred to the Cleveland Clinic Foundation Children's Hospital ("CCF") at 9:45 p.m. Id. at 24. At CCF it was noted that Rachel had a "possible adverse event post vaccination" and an "atypical complex febrile seizure." P Ex 4(a) at 6. A neurology consult was preformed on March 16, 2004, by a pediatric neurology student. Id. at 7-10. It was noted that Rachel was playful and cheerful. Id. at 8. CCF records also indicate Rachel's assessment as a prolonged seizure following vaccination. Id. at 10. It was also noted a "DtaP reaction →seems most likely." Id. An EEG was performed and found to be within normal limits. Id. at 14. Rachel's discharge order from CCF on March 16, 2004, states her "principal diagnosis (reason after study for causing admission)" was "? (Febrile) Seizure - complex." Id. at 12.

On the morning of April 22, 2004, CCF Pediatric Intensive Care Unit ("PICU") notes indicate Rachel was found by her mother to be "grunting and limp with altered mental status." P Ex

[4] The Hearing took place on consecutive days. Although there is a gap in the page numbering, the Hearing Transcripts are cited herein as one transcript, with the page number after "Tr. at."

[5] The undersigned notes the instant case and the Stone case presented the same issue regarding the relationship of the SCN1A gene mutation to SMEI. Thus, the parties agreed, fully and without reservation, 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. 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.

4(b) at 20. Her parents called 911 and she was seen at an outside hospital where laboratory work and a CT scan were found to be within normal limits. Id. at 17. An EEG was performed at CCF PICU on April 23, 2004, "which showed focal epilepsy from the right posterior quandrant, but improved from the previous 24-hours." Id. at 18. The EEG also showed evidence of a "severe diffuse encephalopathy." Id. at 48. However, Rachel was noted to be alert, awake and playful. Id. at 29. Rachel was discharged from CCF to go home on April 26, 2004, with instructions to medicate with Dilantin and for a follow-up visit at CCF in eight weeks. Id. at 18.

Rachel thereafter continued to experience seizures, both febrile and afebrile. See, e.g., P Ex 2(c) at 28; P Ex 2(d) at 38, 41; P Ex 2(e) at 45-46; P Ex 2(f) at 53-54; P Ex 2(g) at 60-63; P Ex 2(h) at 72-76. Rachel's twelfth month examination record notes a diagnosis of epilepsy, but also records normal growth and development. P Ex 3(a) at 25-26. However, it was noted during a routine check-up at fourteen months that Rachel's verbal development was delayed, and that she was not walking and was unsteady. Id. at 29. While Rachel's growth and development was assessed as normal she was at this time referred for an assessment for global developmental delays. Id.

A video EEG was preformed on March 4-5, 2005 by the Department of Neurology at CCF. P Ex 5 at 32-36. Rachel was assessed as suffering generalized and multiregional epilepsy. Id. It was also noted Rachel suffered mild developmental delay in language. Id.

A report to Dr. Ajay Gupta following genetic testing ordered on May 3, 2005, revealed Rachel possesses a de novo mutation to her SCN1A gene. P Ex 12 at 2. These results were interpreted by the laboratory as follows: "[t]his finding . . . is far more consistent with [this DNA variant] being associated with a severe phenotype[6] (SMEI or SMEB) rather than a mild or normal phenotype." Id. Rachel saw Dr. Gupta for a follow-up visit on September 7, 2005 at which time Dr. Gupta indicated he believed Rachel's "clinical course, EEG, and SCN1A test . . . are suggestive of severe myoclonic epilepsy of infancy." P Ex 5 at 48-49.

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.[7]

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[6] 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. at 322 (In this case, Dr. Raymond explained "genotype is the alteration in DNA; phenotype is the clinical finding.").

[7] 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.

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). Petitioner chose to pursue this case as an off-Table injury for the DTaP vaccination, therefore petitioner must prove that the vaccinations in-fact caused Rachel's injuries.

To demonstrate entitlement to compensation in an off-Table case, petitioner 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, "[petitioner must] show a medical theory causally connecting the vaccination and the injury." Grant, 956 F.2d at 1148 (citations omitted);see also 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; see also 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; see also Jay, 998 F.2d at 984; Hodges 9 F.3d at 961;[8] see also H.R. Rep.

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).

[8] 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). See also Cedillo v. Sec'y of Dept. of Health & Human Servs., __ F.3d __, No. 2010-5004, slip op. at 12-14, 2010 WL 3377325 (Fed. Cir. Aug. 27, 2010)(approving the use of the Daubert factors in examining the reliability of expert testimony); Moberly v. Sec'y of Dept. of Health & Human Servs., 592 F.3d 1315, 1324 (Fed. Cir. 2010)(citing Daubert; approving of the use of the Daubert factors in determining expert reliability). 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

No. 99-908, Pt. 1, at 15 (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 petitioner's 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

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> 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.

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).

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 petitioner's 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 . . .

Andreu, 569 F.3d at 1380 (citing Bunting, 931 F.2d 867, 873 (Fed. Cir. 1991)).

Furthermore, "[a]lthough a Vaccine Act claimant is not required to present proof of causation to the level of scientific certainty, the special master is entitled to require some indicia of reliability to support the assertion of the expert witness." Moberly v. Sec'y of Dept. of Health & Human Servs., 592 F.3d 1315, 1324 (Fed. Cir. 2010)(citing Terran v. Sec'y of Dept. of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999)(holding that the factors set forth in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993), may be applied in assessing the reliability of an

expert witness's testimony.)) Special masters, as "finders of fact[,] are entitled - indeed, expected - to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence." Moberly, 592 F.3d at 1326.

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 Cedillo v. Sec'y of Dept. of Health & Human Servs., __ F.3d __, No. 2010-5004, slip op. at 12-13, 2010 WL 3377325 (Fed. Cir. Aug. 27, 2010); 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); but cf. Doe 11 v. Sec'y of Dept. of Health & Human Servs., 601 F.3d 1349 (Fed. Cir. 2010)(approving the use of evidence of alternative causation as rebuttal evidence, not evidence of a factor unrelated). 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 v. Sec'y of Dept. of Health & Human Servs., 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"). Petitioner's case is measured against the above standards.

IV. Discussion

After reviewing the entire record, considering the testimony of the experts and the relevant binding case law discussed above, the undersigned finds respondent has demonstrated that Rachel's SMEI was caused by the genetic mutation located in her SCN1A gene. See §13(a)(1). A full discussion follows. The undersigned notes that the following is very similar to the Decision filed in the case heard alongside Rachel's, Stone v. Sec'y of Dept. of Health & Human Servs., 2010 WL 1848220, appeal docketed. No. 04-1041V (Fed. Cl. Spec. Mstr. April 15, 2010). In fact, the discussion is identical in several parts and utilizes the same reasoning. Although the result is the same, the cases differed in their factual underpinnings. Specifically, the genetic mutations of the children in each case share similarities; however, the specific location and amino acid change is different. Where applicable, the two Decisions share analysis because they rely upon the same medical theories, but care was taken to ensure each child's case was viewed independently considering the different facts. See Cedillo v. Sec'y of Dept. of Health & Human Servs., __ F.3d __, No. 2010-5004, slip op. at 12-14, 2010 WL 3377325 (Fed. Cir. Aug. 27, 2010)(discussing the taking and using of common expert evidence in multiple cases presenting similar medical issues, while ensuring the appropriate consideration of the individual claim).

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 petitioner's case-in-chief presented by Dr. Kinsbourne and rebutted by Dr. Wiznitzer. Third, the undersigned discusses respondent's presentation of evidence, specifically the testimony and opinion of Dr. Raymond. Finally, the undersigned discusses petitioner's 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 10; see generally Tr. 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 10. 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 authored or co-authored a large number of articles in medical journals and texts. Id. at 5-31. 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, at *7 (Fed. Cl. Spec. Mstr. Feb. 21, 2008), more recently the undersigned criticized Dr. Kinsbourne's testimony at length and 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, at *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, at *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 previous cases were unfortunately apparent with respect to Dr. Kinsbourne's testimony in the instant case. See discussion infra pp. 51-53.

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. 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 reflected his lack of recent clinical practice. His testimony was highly generalized and lacked any grounding in practice. While Dr. Kinsbourne may keep current with medical literature, Tr. 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. Dr. Kinsbourne does not publish, research, teach, counsel, attend meetings or conferences, or have any special training in the field of genetics. Tr. 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. 51-53.

2. Max Wiznitzer, M.D.

Dr. Max Wiznitzer is a pediatric neurologist at Rainbow Babies and Children's Hospital and an associate professor of medicine at Case Western Reserve University in Ohio. Tr. at 78, 81; R Ex D at 1-2. He is board certified in pediatrics and neurology, "with special competence in child neurology" and neurodevelopmental disabilities. Tr. at 79; R Ex D at 5. Dr. Wiznitzer attended medical school at Northwestern University and completed his residency at Children's Hospital Medical Center. R Ex D at 1. Dr. Wiznitzer also completed a fellowship in Developmental Disorders at Cincinnati Center for Developmental Disorders, as well as a fellowship in Pediatric Neurology at Children's Hospital of Philadelphia. Id. Subsequently, Dr. Wiznitzer completed a National Institutes of Health fellowship in higher cortical function disorders and electrophysiology training at Albert Einstein College of Medicine in New York. Id. Dr. Wiznitzer teaches medical students and residents in pediatrics, family medicine, child psychiatry, and adult neurology. Id. Further, Dr. Wiznitzer is involved in several research studies, and has published extensively. Id. at 83; R Ex D at 12-22. He also serves as a journal reviewer for multiple medical journals, and sits on the editorial board of the Journal of Child Neurology and Lancet Neurology. R Ex D at 6.

Dr. Wiznitzer currently serves in many capacities at Rainbow Babies and Children's Hospital. He has an active clinical practice seeing patients five days a week and reading EEGs one day a week. Tr. at 81. Dr. Wiznitzer also serves as the Director of the hospital's autism program, Rainbow Autism Center. Id. at 81-82; R Ex D at 3. Further, Dr. Wiznitzer is part of the hospital's epilepsy team where he is "responsible for admissions to the epilepsy monitoring unit for children" during his rotation once every six weeks. Id. at 82. Dr. Wiznitzer testified that approximately eighty-five percent of his practice was clinical, five percent administrative, and ten percent research oriented. Id. at 83-84. Dr. Wiznitzer sees hundreds of patients a year in his practice, which includes a number of children with seizure disorders. Id. at 85-86. He currently treats children with genetic bases for their seizure disorders, including eight children with Dravet syndrome. Id. at 87. Dr. Wiznitzer testifies from a position of knowledge and current experience and his testimony was highly persuasive.

3. Gerald Raymond, M.D.

Dr. Raymond's CV reflects current and impressive credentials in both pediatric neurology and genetics. R Ex B. He is an associate professor in neurology at Johns Hopkins University and

the director of neurogenetics at the Kennedy Kreiger Institute, an affiliate of Johns Hopkins Medical School. Id. at 1; Tr. 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. 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 B at 9-10.

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

B. Petitioner's Case-In-Chief

Given the ultimate conclusion in this case, it is unnecessary to delve deeply into petitioner's case-in-chief. As discussed previously, after being vaccinated on March 15, 2004, Rachel Hammitt appears to have experienced a fever and, at between 7:30 and 8:30 p.m. that same day, Rachel suffered a seizure lasting approximately forty-five minutes. Rachel's March 15, 2004, seizure met the definition of status epilepticus and complex febrile seizure. Rachel was subsequently diagnosed with a severe seizure disorder, described as severe myoclonic eplilepsy of infancy, or SMEI.[9]

Dr. Kinsbourne agrees with Rachel's diagnosis of SMEI. P Ex 9, 2. He opined and testified that Rachel was predisposed to suffer seizures due to her SCN1A genetic mutation. P Ex 9, 3-4; Tr. at 18. However, Dr. Kinsbourne further opined that Rachel's DTaP vaccination was a substantial contributing cause of her seizure disorder in addition to her genetic predisposition. P Ex 9, 4. Dr. Kinsbourne opined that Rachel's March 15, 2004, DTaP vaccination caused her to experience a fever and that fever caused her to experience a seizure that evening, which classified as a complex febrile seizure. Dr. Kinsbourne stated his theory of vaccine causation as follows:

> Well, she developed the fever and developed the seizure, which is a sequence of events which quite familiar in infants. Infants more than any other stage of life, if they have a propensity to [have] seizures of any kind, are apt to express that propensity at the time when the temperature is rising or has risen. . . . . It seems

[9] See supra p. 1-2, fn. 2; Tr. at 15 ("[A] severe seizure disorder starting in infancy usually between six and nine months of age[,] characterized by seizures, often prolonged, both generalized and lateralized, and subsequently other seizure forms as well, and over time a diminution of mental function.").

> likely that her brain was affected so as to predispose her to further seizures, that the severe prolonged seizure that she experienced [on March 15, 2004,] had a detrimental effect on key areas of the brain such that she became epileptic, meaning that she then subsequently had seizures both with and without fever.

Tr. at 17-19. Petitioner also reiterated his theory of the case in his Post-Hearing Brief and in his reply to respondent's Post-Hearing Memorandum: "[T]he DTaP vaccine Rachel received on March 15, 2004 caused her to have a fever; that fever caused a prolonged seizure classified as a complex febrile seizure; and that seizure damaged Rachel's brain, lowering Rachel's "level of seizure propensity, thus facilitating further seizures." P Reply Brief, p. 7, filed September 25, 2009; see also P Post-Hearing Brief, p. 7-8, filed August 19, 2009 ("P Brief").

In reaching his conclusion, Dr. Kinsbourne relies upon two articles, Holmes and Aicardi. See P Ex 9; Tr. at 19-20. This reliance 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 v. Sec'y of Dept. of Health & Human Servs., 2007 WL 1772062, at *3. And as the undersigned explained further in Mersburgh v. Sec'y of Dept. of Health & Human Servs.:

> 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, supra, at 231.[10]

Mersburgh v. Sec'y of Dept. of Health & Human Servs., 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

[10] The Holmes and Aicardi literature was filed into the record of this case as petitioner's Exhibits 21 and 22.

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 [child], and that harm was reflected in a lowering of level of seizure propensity, thus facilitating further seizures.

Tr. at 443.

Dr. Kinsbourne also appears to rely at least partially on the National Childhood Encephalopathy Study of 1981 (NCES). P Ex 9 at 3-4, 7-8; Tr. at 11, 19-21. As was discussed in Simon, 2007 WL 1772062, 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. 44-46; but see Johnson v. Sec'y of the Dept. of Health & Human Servs., No. 07-138, slip op. (Fed. Cl. Spec. Mstr. July 30, 2010)(relying upon the NCES study in deciding a Petition involving the DTaP vaccination).

Dr. Kinsbourne's *prima facie* theory of causation also relies upon an article by Nieto-Barrera et. al, which is discussed later at length, infra pp. 44-46.

Further, Dr. Kinsbourne relies upon a review of information from the article, Epileptogenesis in the Developing Brain: What Can We Learn from Animal Models. P Ex 19, Roland A. Bender & Tallie Z. Baram, Epileptogenesis in the Developing Brain: What Can We Learn from Animal Models, 48 (supp. 5) EPILEPSIA 2, (2007)[hereinafter "Baram & Bender"]. This study investigates the development of temporal lobe epilepsy in rats and from it, petitioner argued that Rachel's prolonged febrile seizures could cause a reorganization of the brain, leading to her epilepsy. P Post-Hearing Brief at 10-12 ("P Brief"). The authors discuss a model wherein an inciting event promotes a change in the brain, without cell death or damage, "of the previously normal circuit, changing it into an 'epileptic' one." Baram & Bender, 1. Respondent criticizes the use of this article because it is inapplicable to the disorder at hand, SMEI. See Tr. At 118-28; R Post-Hearing Memorandum ("R Brief"). In fact, at the Hearing, respondent's expert efficiently disposed of this article's use in Rachel's case. When asked "whether this article represent[ed] a model that applies to [SMEI]," Dr. Wiznitzer responded:

> No. . . . This article basically talks about the development of temporal lobe epilepsy. . . . And it's an animal model of the development of temporal lobe epilepsy. . . . The seizures did not actually start until [the rodents] were older, and they were temporal lobe seizures. They were not multiregional, they were not generalized, they were temporal lobe seizures. That clearly is not what we're talking about when we're talking about [SMEI]. . . . Temporal lobe epilepsy is basically a seizure disorder . . . where seizures arise from a specific area of the brain, the temporal lobe, and the kind that this model talks about involves the limbic regions, which is the hippocampus and the amygdala. . . . And in Dravet[, SMEI], the seizures that occur basically are a multitude of seizures, where you have generalized convulsions . . . a generalized epileptiform discharge. Which means there's seizure discharges coming out from both sides of the brain simultaneously. . . . So while clinically they may look a little bit the same, the origins are different. So you're talking about two totally different epilepsies that are present here. And the animal model that's proffered here and they're using as their basis for alleged injury that occurs to the brain is not applicable in [SMEI].

Tr. at 119-128.[11] Although the use of animal studies has been approved, see Andreu, 569 F.3d 1367, fn. 9, the model in Bender & Baram does not appear applicable to Rachel's condition, SMEI. Considering the disparity between these forms of epilepsy as discussed by Dr. Wiznitzer, and without more, including some explanation or support from Dr. Kinsbourne, the undersigned cannot find this article reliable as it pertains to petitioner's case.

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., Tr. 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 Rachel's first severe seizure. Tr. at 133 (Dr. Wiznitzer agreed "yes" in response to whether Rachel's vaccination on March 15, 2004, caused her to develop a fever that evening and whether "the fever that Rachel Hammitt have on March 15, 2004, cause[d] her the seizure she experienced that evening."). However, the parties disagree on both the impact of that first seizure and whether the vaccination played any causative role in Rachel's SMEI.

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[11] The undersigned notes that petitioner's counsel objected to Dr. Wiznitzer's references to articles cited to within the Bender & Baram article as they had not been previously introduced in this case. Tr. at 122. While acknowledging the validity of petitioner's objection, testimony continued. Id. at 122-26. The undersigned also notes that Dr. Wiznitzer's criticism of the use of this article retreated from the use of the substance of these articles and was ultimately based on the difference between SMEI and temporal lobe epilepsy. In that respect, his criticisms and explanation are valid and were based upon the information contained within Baram & Bender, the fact that they were utilizing a model of temporal lobe epilepsy.

Respondent's expert, Dr. Wiznitzer, testified that while Rachel's vaccinations are associated with her first seizure on March 15, 2004, the vaccinations did not contribute to **causing** her SMEI. Dr. Wiznitzer testified:

> You have someone who is destined to develop SMEI, there's no doubt about that. The genetic mutation tells us, this is going to happen. This is going to happen whether it's going to happen on March 15th or March 18th or in April or on June 2nd, or whatever day, you are destined to have a seizure due to SMEI. You get exposed to a fever, irrespective of the source of the fever. . . because you have this tendency towards fever-provoking seizures in SMEI, because we know that happens in these individuals, irrespective of the source of the fever, you will probably have a seizure associated with it. . . . . and she had the genetic mutation[,] that more likely than not she was going to have a seizure. It did not alter her clinical history. Her clinical history would evolve the same whether she's had a fever that day or some other time.

Tr. at 134-35. Thus while Dr. Wiznitzer agreed "that seizures which last about an hour" can cause brain injury, he testified "it doesn't cause Dravet Syndrome. It does not cause SMEI." Id. at 136-37. Dr. Wiznitzer testified SMEI follows a certain clinical course and the clinical course of Rachel's SMEI was not impacted by her March 15, 2004, vaccination or post-vaccination seizure. Tr. at 91. Dr. Wiznitzer explained SMEI is a clinical diagnosis. Id. at 97. Elaborating, he stated:

> there is a characteristic pattern here. And the characteristic pattern is the timing of onset of seizures, the evolution of the seizures, the appearance of different types of seizures. And by the way just for the court's information, while seizures may be provoked by fever in the first year of life, we find that there's other provocations as they get older.

Id. Dr. Wiznitzer testified that, in addition to looking at an individual's medical history and clinical picture in order to make a clinical diagnosis for a child suspected of having SMEI, you can conduct genetic testing. He explained "[y]ou can basically look for genetic underpinnings, and you'll do lab testing to look for genetic underpinnings of the condition, specifically for a child you suspect having SMEI, you do a test for changes in the SCN-1A gene." Id. at 98. Dr. Wiznitzer elaborated "it [genetic testing] basically gives parents an explanation for the epilepsy. Again, SMEI is a clinical diagnosis, people still want to know why, and parents will frequently ask that. So point number one would be to identify and show the parents the genetic reason." Id. at 99.

Thus, Dr. Wiznitzer testified consistently with the written opinion that "there is no evidence that the immunizations administered on 3/15/2004 either caused or aggravated Rachel Hammitt's epilepsy. . . . Rachel's Hammitt's epilepsy is due to a mutation of the SCN1A gene with a clinical manifestation of severe myoclonic epilepsy of infancy." R Ex C at 2-3. Additionally, Dr. Wiznitzer provided extensive rebuttal to the literature presented by Dr. Kinsbourne in petitioner's *prima facie* case. Tr. at 103-31. Since this literature was also discussed at length in petitioner's rebuttal to respondent's SCN1A gene mutation evidence, the undersigned will address it in that portion of this

decision. See infra pp. 29-48.

Based upon the above-cited literature from Holmes and Aicardi, the facts presented and petitioner's expert testimony, the possibility exists that petitioner has demonstrated a showing of entitlement to compensation under the Act consistent with the decisions in Simon and Mersburgh. See discussion infra fn.12. As the undersigned discussed in Simon and Mersburgh:

> [w]hat we face in this case is an unprovable event, unprovable utilizing the higher 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 Rachel's SCN1A gene mutation**, the undersigned likely would have found for petitioner based upon the foregoing discussion. However, as discussed at length in the following sections, respondent has demonstrated by a preponderance of the evidence that Rachel's SCN1A gene mutation was both the "but for" cause and the "substantial factor" that caused her SMEI. See Shyface, 165 F.3d at 1352. Accordingly, the undersigned concludes that petitioner's claim fails.

For the purposes of the discussion that follows, the undersigned will analyze respondent's evidence concerning Rachel's SNC1A gene mutation as a factor unrelated to her vaccination pursuant to §13(a)(1)(B).[12] See Nordwall v. Sec'y of the Dept. of Health & Human Servs., No. 05-

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[12] The undersigned notes that the government has contested, both prior to and subsequent to the Hearing, whether the burden has in fact shifted to the government to demonstrate a factor unrelated. Respondent argued that petitioner failed to prove a *prima facie* case under the Vaccine Act; and as such Dr. Raymond's testimony as to Rachel's genetic mutation is evidence offered to rebut petitioner's *prima facie* case. See generally R Reply to Petitioner's Post-Hearing Brief at 1-3 ("R Reply Brief"); see e.g., Doe 11 v. Sec'y of Dept. of Health & Human Servs., 601 F.3d 1349 (Fed. Cir. 2010)(approving the use of evidence of alternative causation as rebuttal evidence, not as evidence of a factor unrelated). In Doe 11 v. Sec'y of Dept. of Health & Human Servs., the Federal Circuit found that the special master did not err in considering evidence of an alternative cause as rebuttal evidence to petitioner's *prima facie* case.

In the alternative, respondent argued "the evidence of an alternative cause . . . also establishes a factor unrelated defense" should the undersigned find petitioner proved a *prima facie* case. Id. at 3-4. As the undersigned has informally addressed with the parties at various status conferences leading up to the Hearing on May 14 and 15, 2009, **the undersigned's ultimate finding would not be impacted if the undersigned analyzed respondent's evidence concerning Rachel's SCN1A as evidence submitted in rebuttal to petitioner's *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 Rachel's SCN1A gene mutation was both the "but for" cause and a "substantial factor" that caused her SMEI. Accordingly, the undersigned finds that Rachel's DTaP vaccination was neither a

123, 2008 WL 857661, at *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 cases. Two notable exceptions are the Knudsen and Hanlon cases, cited supra pp. 8-9. 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, also, 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, 2008 WL 857661, at *12 (finding a factor unrelated to the vaccine caused the infant's death); Stone v. Sec'y of Dept. of Health & Human Servs., 2010 WL 1848220, appeal docketed. No. 04-1041V (Fed. Cl. Spec. Mstr. April 15, 2010). Thus, the undersigned turns to whether the respondent proved by preponderant evidence that Rachel's SCN1A gene mutation was the "but for" cause and the "substantial factor" that caused her SMEI. Shyface,

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"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, 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 at 1353-54("[t]his latter showing is the government's burden once the petitioner has met her burden."); but see Pafford v. Sec'y of the Dept. of Health & Human Servs., 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. Mstr. 2008)

The decision in Doe 11 was issued after briefing concluded in the case *sub judice* and therefore the parties did not have the opportunity to discuss its application. Given that the burden for respondent's factor unrelated evidence is a higher burden than merely providing rebuttal evidence, and that burden was met in this case, the undersigned finds it unnecessary to address this issue.

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 at 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-two year experience, seizures may constitute the most commonly alleged injury following immunization throughout the history of the Program.

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 as 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 v. Sec'y of the Dept. of Health & Human Servs., No.95-266V, 2002 WL 31965744 (Fed. Cl. Spec. Mstr. 2002)(finding 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.);[13] Jenkins v. Sec'y of the Dept. of Health & Human Servs., No. 90-3717V, 1999 WL 476255 (Fed. Cl. Spec. Mstr. 1999)(concluding, as a general matter, that the DTP vaccine can cause seizures within seven days of vaccination; however, 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.

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[13] The Supreme Court has granted certiorari to the petitioners in this case on a claim filed outside the Vaccine Act, but unrelated to their Petition under the Act. See Bruesewitz v. Wyeth, Inc., 130 S. Ct. 1734, 2010 WL 757696 (2010).

1. Rachel'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 Rachel's vaccinations neither caused nor exacerbated her SMEI, but rather a mutation in her SCN1A gene is solely responsible for her SMEI. R Ex A at 5, Tr. 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. 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 "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 Rachel's SMEI is solely the result of the mutation to her SCN1A gene.[14] In the final analysis, Dr. Raymond's testimony proved highly persuasive and reliable. Petitioner failed to mount any serious rebuttal to Dr. Raymond.

2. Genetics Background

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. at 285. DNA provides the blueprint for cellular structure and function. See, e.g., R Ex A at 3. 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 mutation[15] in the DNA can affect the functionality of that protein, consequently causing disease. Id. Dr. Raymond described this process in great detail at the Hearing on May 15, 2009. Tr. at 285-302.

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[14] Although Dr. Raymond opines that Rachel's mutation is the "sole cause" of her condition, see, e.g., Tr. at 336, and the undersigned uses "sole cause" when discussing Dr. Raymond's opinion, the undersigned is cognizant that preponderant evidence is respondent's burden in proving a factor unrelated caused the alleged injury.

[15] 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).

See also Respondent's Trial Exhibit A ("R T Ex A").[16]

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. at 289; R T Ex A at 7-8.[17] 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. at 286-87. Dr. Raymond explains:

> there are exons[18] and introns[19] 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 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. 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.[20] At this step, Dr. Raymond explains, "the mRNA passes out of the nucleus and joins up with the ribosomal RNA," Tr. at 292; R T Ex A at 11, "and using a very complicated machinery it's now read codon by codon." Tr. 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).[21] For example, U plus U plus U codes for the amino acid Phenylalanine. See R T Ex A at

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[16] 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.

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

[18] 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).

[19] 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.

[20] 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. at 287.

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

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." Id. at 14. Inevitably, you get a rather complex structure, see Id. at 15, which Dr. Raymond testified appears deceptively simple on paper. Tr. 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. 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. A mutation alters normal function.

b. Mutations - Generally

Dr. Raymond testified that mutations occur during DNA synthesis or replication, which occurs during the cell division processes of mitosis or meiosis.[22] Tr. 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.[23] 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. at 300-01; R T

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[22] 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).

[23] 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. However, he clarified that Rachel's case involves a mutation in the exon. Id. at 300.

Ex A at 18. A point mutation, which is at issue in Rachel's case, involves a single base pair of the DNA being replaced by another base pair. Tr. at 300.[24] 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. Dr. Raymond testified Rachel Hammitt 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." Id. at 301; R T Ex A at 19. A mutation may result in the coding for 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 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 Rachel's mutation is a missense, non-conservative mutation in her SCN1A gene.** Tr. at 337. Therefore, hers is a mutation where a base pair in her DNA has been replaced by a different base pair, and this results in an amino acid with very different characteristics than the amino acid that is normally produced. Dr. Raymond explained that the functional effects from such mutations can range from loss of function to abnormal function, even 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.[25]

c. The SCN1A Gene

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

[25] 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. 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).

The SCN1A gene encodes a particular structure of a neuron.[26] "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 A at 3. 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 Rachel'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.

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 A 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:

> 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 ("GEFS+"), and Rachel'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."[27] 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. Rachel's Mutation and Dr. Raymond's Theory of Causation

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[26] 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).

[27] 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. 38-41.

a. Rachel's Mutation

Utilizing the above background information, we come to Rachel's specific mutation, which Dr. Raymond opines is the sole cause of her condition. The laboratory testing conducted and interpreted by Athena Diagnostics revealed that she possesses a "DNA sequence variant [mutation] . . . in the SCN1A gene." P Ex 12 at 1.[28] Specifically, Rachel has "a transition for A to G at nucleotide position 352 at codon 118 resulting in the amino acid change of arginine to glycine." R Ex A at 2; see also P Ex 12 at 1. As one can see from the discussion above and as affirmed by Dr. Raymond in his report, this change alters an important region of the channel. R Ex A at 3. Further testing and analysis revealed Rachel's SCN1A gene mutation "arose de novo (was not inherited)" from her parents. P Ex 12 at 1. 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 Rachel Hammitt's SCN1A gene mutation is the sole cause 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. at 310-11. "[T]here are things that we as geneticists do to judge whether [the mutation is] having an impact or not." Tr. 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, Rachel's mutation arose de novo, as both of her parents tested negative for the SCN1A gene mutation. Id. at 336; P Ex 12 at 1; R Ex A at 2. Dr. Raymond testified the fact that a mutation arose de novo is significant. Id. at 330; see also P Ex 12 at 1-2. "If this is de novo or spontaneous, this is a powerful indicator that it is disease causing." R Ex A at 4.

Next, Dr. Raymond testified that a geneticist examines the type of mutation presented. This concerns the characteristics of Rachel's mutation, 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 19-21. 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,

[28] Pin cites to this exhibit refer to the internal pagination of the report itself.

> 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. at 303.

In the case of Rachel's mutation, Dr. Raymond explained the change of these building blocks is a change from arginine, which "is a large, charged – has a large charged side chain, and she has now gone from arginine to the smallest amino acid, glycine . . ." Tr. at 336; R T Ex A at 31. "Arginine is an amino acid with a side chain that contains a carboxyl and nitrogen group. The chemical properties of this side chain result in it being referred to as a basic (versus acidic), polar amino acid since it will interact readily with water molecules." R Ex A at 4-5. "Glycine is a very different type of amino acid. It is the simplest of amino acids and the side chain is a single hydrogen molecule. This results in an amino acid of very small size and nonpolar in its interactions." Id. at 5; see also R T Ex A at 31 (graphic contrasting arginine to glycine). In Rachel's case, the change from arginine to glycine "is a non-conservative mutation . . . ." Tr. at 337.

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. In Rachel's case, the mutation occurs in the beginning of the resultant protein, the N-terminus, an area where only SMEI has been reported as the manifestation of the mutations in this area. R Ex A at 5; R T Ex A at 33-35. In comparison, Dr. Raymond discussed a reported mutation that, by his estimation, exhibits a "comparable functionally significant change[]." Tr. at 375 (discussing **a reported mutation at the same location as Rachel's**, wherein the patient also exhibited SMEI, see P Ex 17, Zucca, et al., Cryptogenic epileptic syndromes related to SCN1a: Twelve novel mutations identified, 65 Arch. Neurol. 4, 489-94 (2008)(hereinafter "Zucca et al.")).

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." Tr. at 311. Dr. Raymond explained that the location 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. Rachel's mutation occurs in such a conserved region, as demonstrated by the sequences charted in Respondent's Trial Exhibit. R T Ex A at 32. The chart illustrates that Rachel'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 32; Tr. 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. at 313. He would also confirm that it is not a polymorphism, a change with a neutral effect, found in the normal population. Id. As previously discussed, there exists a previously reported mutation at the same location as Rachel's. See supra p. 26; Tr. at 337-38; R T Ex A at 33. In the reported case, the amino acid arginine is changed to serine, whereas Rachel's is changed from arginine to glycine. R T Ex A at 33; Tr. at 337-38. Although the amino acid change is not identical to Rachel's, the change is similar and results in a "functionally equivalent way," also resulting in SMEI. Tr. at 338. Further, due to the characteristics between glycine and serine, that mutation is "functionally the same" as the one reported in Rachel Hammitt. Id. In addition, Dr. Raymond discussed other mutations that are reported to occur in the same region as Rachel's mutation. "[A]ll of the mutations in this region, including the one that was previously reported . . . what one sees here is all of the individuals in the neighborhood have Dravet syndrome, indicating that alterations in this region are resulting in a very severe phenotype." Tr. at 338-39; R T Ex A at 34-35(illustration of Rachel'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 Rachel's condition:

- Rachel'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 causes change to the beginning of the resultant protein, at the N-terminus, affecting a location where only SMEI has been reported with mutations;
- 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 Rachel's SMEI is caused by her SCN1A mutation. See generally Tr. at 301-13, 335-40, 400-01; R Ex T A at 20-21. Ultimately, Dr. Raymond testified that if he was providing counseling to this family as a geneticist in his clinical practice, "I would say that this[, the mutation,] is the sole cause of their child's illness." Tr. at 336. The undersigned finds Dr. Raymond's testimony described above reliable, as well as highly persuasive. See, e.g., infra pp. 51-53.

D. Petitioner's 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; Doe 11 v. Sec'y of Dept. of Health & Human Servs., 601 F.3d 1349 (Fed. Cir. 2010). Accordingly, petitioner presented rebuttal arguments to respondent's factor unrelated defense. Petitioner posited that the SCN1A gene "plays a role in the cause of SMEI but it is not the sole cause or overwhelming cause of SMEI in children with SCN1A variants," and allege that "fever caused by pertussis vaccinations modifies the course of SMEI." P Brief at 35-36 (emphasis omitted). Ultimately, petitioner asserted that "no objective evidence supports the proposition that Rachel Hammitt's SCN1A variant is the overwhelming cause of her SMEI." Id.

Dr. Kinsbourne agreed at the May 15, 2009 Hearing "that SMEI has a genetic bas[is] . . . there is a genetic component." Tr. 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 Rachel's seizure threshold. Id. at 475. Dr. Kinsbourne agreed with the undersigned that the issue presented in this case "is the role of [Rachel's] initial seizure, this complex seizure in altering whatever mutation we have." Id. at 486.

It is important to note that petitioner did not contest Dr. Raymond's tutorial on the foundation of genetics. Nor did petitioner offer the testimony of a geneticist to rebut the testimony of Dr. Raymond. Rather, petitioner presented a series of arguments intended to undermine Dr. Raymond's conclusion. These arguments essentially consisted of petitioner: 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 role, specifically a vaccine's 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 petitioner; 6) and criticizing the qualifications of Dr. Raymond in petitioner's Reply to respondent's Post-Hearing Memorandum. These arguments are examined below.

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

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

As discussed previously, Dr. Raymond utilized a synthesis of multiple factors in reaching his conclusion that Rachel's SCN1A gene mutation is the sole cause of her SMEI. These factors were: the fact that Rachel's mutation arose de novo; that it is a missense non-conservative mutation, that it occurs in the beginning of the resultant protein, the N-terminus, which codes for a functionally

important region of the sodium channel where only SMEI is seen with mutations; 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; 31-35, Tr. 304-35, 361-62. It is critical to keep in mind that these factors were utilized **cumulatively**. Petitioner disassembled and attacked the factors individually in an effort to undermine Dr. Raymond's testimony. Petitioner, in one breath, recognizes that "Dr. Raymond acknowledges that the presence of any of these characteristics alone would not have been sufficient evidence that Rachel's variant would cause her to suffer SMEI," then, in his next breath, proceeds to criticize these characteristics as if they were presented individually. P Brief at 28.

Petitioner argued Dr. Raymond's following factors "are not objective or reliable criteria for predicting the clinical effect of a SCN1A variant." P Brief at 27. Petitioner questions: 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 Rachel's SCN1A variant arose de novo; and, d) whether the mutation occurred in a functionally important region, a region well conserved through evolution. P Brief at 27-35.

Petitioner's attacks are unpersuasive for several overriding reasons. Petitioner misconstrued the analysis performed by Dr. Raymond, as a clinical geneticist, and fails to consider the factors cumulatively. Petitioner also placed an improper burden of scientific certainty upon Dr. Raymond's analysis. Finally, petitioner failed to consider the evidence from the literature that supports Dr. Raymond's analysis. 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, petitioner failed to present persuasive evidence or argument to the contrary. While these overarching deficiencies in petitioner's rebuttal are sufficient to reject petitioner's argument, the undersigned will address the individual components of petitioner's argument. Petitioner's 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 subsequent section, 1(b).

i. Petitioner argues an amino acid change from simple to complex, a non-conservative mutation, is not predictive of the clinical outcome.

First, petitioner argued 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 Brief at 28. Petitioner first contends that Dr. Raymond's opinion regarding the functional effect of Rachel's mutation is an assumption because it has not been studied. Id. Petitioner further argues the functional effect of an amino acid change does not predict an individual's clinical outcome. To support the instant argument, petitioner cited 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 Brief 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.")).[29] For further support, petitioner discussed a variant found in the literature that involved the same amino acid change as that found in Rachel, Arginine to Glycine, in a **different location** of the gene, where the mutation is a benign polymorphism. P Brief at 29 (citing P Ex 18, R.H. Wallace et al., Neurona Sodium-Channel α1-Subunit Mutations in Generalized Epilepsy with Febrile Seizures Plus, 68 AM. J. HUM. GENET. 859, 863 (2001) ("Wallace"); P Ex 16, Alfons Macaya, Significance of the SCN1A p.R1928G Change in Severe Myoclonic Epilepsy of Infancy, 65 (4) ARCH. NEUROL. 489 (2008)("Macaya"); Tr. 362-372). The undersigned notes that during the Hearing, when Dr. Raymond was questioned regarding this mutation found in the literature, R1928G, both the expert and petitioner's counsel admitted this mutation might actually be "associated with seizure." Tr. 370-373 (referencing Wallace at 863; Macaya at 1-2; Zucca et al. at 492).

Petitioner also argues this point utilizing an amino acid change synonymous to that in the Stone case. Petitioner points to the same amino acid change again at a **different location**, that resulted in the child with Autism. P Brief at 29-30 (citing P Ex 14, Christoph Lossin, Lossin, A Catalog of SCN1a Variants, BRAIN & DEV. (2008) (Epub. ahead of print) [hereinafter Lossin]).

Petitioner's expert, Dr. Kinsbourne, was not helpful in discussing this point of petitioner's criticism.[30] Dr. Kinsbourne evaded respondent's question regarding the functional impact of an amino acid change that is the same as Rachel's. Dr. Kinsbourne stated, "it depends on what you mean by functional impact. It is not clear what either of these two changes[, amino acid and location,] in fact do to the sodium channels. I mean, they could impair them severely, but I don't know." Tr. 450.

ii. Petitioner argues the location of an SCN1A variant is not predictive of clinical outcome

Next petitioner alleged the "evidence does not support the proposition that a SCN1A variant on the N-terminus of the gene (generally) or at the amino acid position 118 (specifically) will cause SMEI." P Brief at 30. Petitioner argues that the functional effect of the location of a mutation has not been studied for mutations at the N-terminus and a vast majority of SCN1A variants. P Brief at 30. Petitioner cites Rhodes et al., which states, "different amino acid substitutions of the same

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[29] 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.

[30] Regarding the same issue in Stone case, heard alongside Rachel's, supra fn. 5, when Dr. Kinsbourne was asked if he "would agree that the amino acid change in Amelia Stone has the same functional impact as a case reported in the literature that has a mutation at the same site." Tr. 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. This colloquy highlighted Dr. Kinsbourne's lack of knowledge and effectiveness in this case.

[location] may give rise to similar biophysical defects yet be associated with widely divergent severity." Id. Citing Lossin, petitioner lists phenotypes found in locations on the N-terminus near the location where Rachel's mutation exists. These mutations resulted in individuals diagnosed with other seizure disorders, Febrile Seizures ("FS") and GEFS+. Id. at 30-31. Again, petitioner 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 Brief at 30. Petitioner also 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[31] occurs." Id. at 31 (citing Lossin, at 4, 8, 13).

Petitioner's 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 Rachel. P Brief at 31-32. Petitioner 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 Brief at 32 (quoting Lossin at 13). This concern was also addressed by Dr. Kinsbourne at the Hearing on May 15, 2009. Tr. at 427-28. Thus, petitioner 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. at 427.

iii. Petitioner argues the fact that the SCN1A variant arose de novo does not support that it is the sole cause of Rachel's SMEI

Third, petitioner's counsel argued the fact that a mutation arose de novo is not indicative of Rachel's SCN1A variation causing her SMEI. P Brief at 32. Petitioner acknowledges that de novo variants are more likely than inherited variants to be associated with SMEI, id., but states this characteristic of the mutation does not mean the mutation is the sole cause of her condition. Id. at 33. In making this argument petitioner relied upon the Rachel's genetic testing results from Athena Labs Report, which found that Rachel's mutation arose de novo and states:

> [a]pproximately 90% of amino acid variants associated with the more severe

[31] Amelia Stone is the injured child in the case heard alongside Rachel's case. See supra fn. 5.

> 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.

Id. at 33 (quoting P Ex 12 at 1). Petitioner argued that the "associated with" language used in the Athena Labs Report does not mean the mutation was the sole cause of Rachel's SMEI. Petitioner's counsel also stated 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. Petitioner's counsel cited to examples in the literature where de novo variants have been associated with milder seizure disorders. Id. at 33-34 (citing P Ex 13, 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."); Harkin et al., The Spectrum of SCN1A-Related Infantile Epileptic Encephalopathies, 130 Brian 843, 844 (2007)("Harkin et al."); Wallace, R., A Plethora of SCN1A mutations: What Can They Tell Us, Epilepsy Currents, Jan.-Feb. 2005, at 17 ("Wallace")). Petitioner also cited to studies that find "about 10% of SCN1A variants in children with SMEI are inherited from mostly normal parents." P Brief at 33 (citing P Ex 11Q, R. Nabbout et al., Spectrum of SCN1A Mutations in Severe Myoclonic Epilepsy of Infancy, 60 NEUROL. 1961,1962 (2003) ("Nabbout et al."); P Ex 15, 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. 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. at 451-52.

iv. Petitioner argues a mutation occurring in a functionally well conserved amino acid location is not predictive of outcome

In this last criticism of Dr. Raymonds factors, petitioner contended that Depienne et al. found SCN1A variants resulting in a polymorphisms in "highly conserved amino acids of the protein." P Brief at 35-35. Petitioner quoted this study, stating:

> Forty polymorphisms, 24 of which are novel, were identified in SCN1A and are 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. (citing Depienne et al., at 6, E-Table D). Petitioner argued 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, petitioner argued that 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 Brief at 15-36. However, the undersigned reviewed all of the cited literature, considered petitioner's arguments and concludes that it is petitioner's arguments that fail. In short petitioner's 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**[32] contributed to his conclusion that Rachel's SCN1A gene mutation is the sole cause of her SMEI. Dr. Raymond made this point on numerous occasions during his testimony. See Tr. at 357, 361-62. These factors considered together along with Rachel's clinical history allowed him as a clinical geneticist to make the finding that Rachel's disease was caused solely by her genetic variant. As respondent notes,

> Dr. Raymond adequately explained the methodology used by clinical geneticists in evaluating pa patient who presents with evidence of a genetic defect. . . . he looked at the report from the diagnostic lab that performed the genetic testing; he considered the fact that Rachel's mutation arose de novo. . .; that it was a missense mutation . . .; that it was a non-conservative mutation. . .; and that the mutation occurred in a conserved region . . . Finally, Dr. Raymond located in the literature a report of an individual with SMEI [who] had a SCN1A mutation in the exact same location, involving a similar alteration. All of the mutations reported by Dr. Lossin in that

[32] As discussed previously, these factors include: the fact that Rachel's mutation arose de novo, is a missense non-conservative mutation, occurs in the N-terminus - a functionally important region where mutations have only resulted in SMEI, 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. 25-28.

region involved individuals with SMEI.

Respondent's Reply to Petitioner's Post-Hearing Brief ("R Reply") at 5. Indeed, 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." Tr. at 373; see also R Reply at 7.

As Dr. Raymond explained, when petitioner's counsel inquired if the amino acid change of arginine to glycine would always result in SMEI, one 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. at 361-62. Thus, all factors regarding a particular variant must be analyzed together, including the clinical picture, which in the case of Rachel Hammitt, 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. 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 analyzed 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 that one cannot examine a single factor, the amino acid change for example, and not also consider the location where the amino acid change occurred. Thus, contrary to petitioner's assertion, the finding that a similar change in one factor resulted in a different phenotype in another individual does not mean that factor is not relevant to a clinical geneticist when analyzing genotype-phenotype correlation. For example, a de novo mutation in one case, resulting in a polymorphism or GEFS+[33], does not independently make

[33] 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

irrelevant the fact that Rachel's mutation also arose de novo.

Specifically regarding the relevance of whether a mutation arose de novo, petitioner argued a de novo mutation is not evidence that Rachel'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 aspect of the mutation analyzed as evidence that Rachel's SMEI was caused by her mutation; however, again, it is not the only factor considered. 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 that the de novo aspect of Rachel's mutation "was added evidence that this is a functionally significant alteration in the amino acid." Tr. at 330. Rachel'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 12 at 1.

Furthermore, Dr. Raymond addressed the limiting language in the report that petitioner points 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 Brief at 33; see P Ex 12. 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. 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 Rachel's specific genotype-phenotype does not currently exist. Id. at 337-38. However, this absence of literature on the exact genotype-phenotype correlation did not overly concern Dr. Raymond since a similar mutation in the same location is reported and the child also has SMEI. Id. at 338; see supra p. 26-27. Further, the phenotype for mutations near the same location also report as predominantly SMEI or SMEB. Tr. at 338-39; R T Ex at 34-35. The undersigned finds Dr. Raymond's explanation highly persuasive.

The undersigned does not find petitioner's 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.). Simply because the other 5-10% of mutations are inherited 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 petitioner isolate each factor individually and independently, rather than addressing Dr. Raymond's factors cumulatively. As

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infancy can be considered an extreme end of the large SCN1A spectrum.").

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. at 356-57.

ii. Response to petitioner's 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. 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.")); see also P Brief at 31-32. 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. at 393; see also id. at 404 (Dr. Raymond explained "there 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."). Petitioner 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, including the SCN1A genetic tests that have been reported or examined. Tr. 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

Petitioner also attacked Dr. Raymond's testimony contending that there is no objective support for the factors Dr. Raymond analyzed as being indicative of SMEI. See e.g., P Brief at 35. However, Dr. Raymond, a highly qualified geneticist and neurologist, explained this is what a clinical geneticist does – examining each factor cumulatively alongside the patient's clinical picture. See Tr. 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 petitioner.

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 A5, 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 SNC1A 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 six year old boy with a SCN1A gene mutation and generalized epilepsy with febrile seizures plus ("GEFS+") and in analyze whether the "mutation is the cause of the patients' epilepsy," noting 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 [Rachel's mutation is a 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.**[34]

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 de novo SCN1A 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 petitioner's allegation that Dr. Raymond's analysis is not supported by the literature or by objective evidence is simply inaccurate. In addition, it cannot be overstated that petitioner's rebuttal suffered from the lack of credible expert testimony. Dr. Kinsbourne simply was not qualified or able to counter the testimony of Dr. Raymond. Petitioner thus had to rely upon cherry-picked snippets from the medical literature, presented in his 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

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

Dr. Kinsbourne repeatedly questioned Dr. Raymond's testimony as not scientifically certain. Tr. at 446, 448, 460. Dr. Kinsbourne testified that he did not believe the SCN1A gene mutation was the cause of SMEI in this case because "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. at 460 (emphasis added). Thus, Dr. Kinsbourne is looking for scientific certainty to establish the SCN1A gene mutation in this case is the sole cause of Rachel's condition.

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," and 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 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.; 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, his cogent testimony and Rachel's clinical presentation, the undersigned finds it is more likely than not that the SCN1A mutation caused Rachel's SMEI. Tr. at 335-340 (In answer to the question "so what was the role of the SCN1A genetic mutation?" Dr. Raymond replied: It is the sole cause. The dysfunction in the channel secondary to the SCN1A is the sole cause of her sever[e] myoclonic epilepsy of infancy." Tr. at 340).

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

a. Petitioner's support for the assertion that the presence of the SCN1A mutation is not predictive

In addition to criticizing the specific analysis performed by Dr. Raymond in drawing his conclusion that Rachel's SMEI is caused by her mutation, petitioner argued 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. at 417-26, 430-33; P Brief at 17-22. With this somewhat overlapping but more global argument, petitioner's counsel cited further examples found in the SCN1A literature of divergent outcomes found in individuals with the same mutation. Petitioner's counsel references this as evidence that you cannot reliably predict outcome based upon the SCN1A gene variant alone. P Brief at 17-22.

First, petitioner's 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 17-18 (citing Depienne et al.; Nabbout et al.). The 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, petitioner provided two examples of children with SMEI who inherited their SCN1A mutations from a parent who suffered another, milder seizure disorder and not SMEI. Id. at 18-19 (citing Nabbout et al. at 1963; P Ex 11M, Kimkura et al., A missense mutation in SCN1A in brothers with severe myoclonic epilepsy of infancy (SMEI) inherited from a father with febrile seizures, 27(6) Brain Dev 424, 429 (2005)("Kimura et al.")). Third, petitioner also discussed cases found in the literature where the same SCN1A variant resulted in different types of seizure disorders within the same family. Id. at 19. 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 11B, Grazia Annesi et al., Two Novel SCN1A Missense Mutations in Generalized Epilepsy with Febrile Seizures Plus, 44 EPILEPSIA 1257 (2003)("Annesi et al.")). Fourth, petitioner cited reports of two SCN1A variants that resulted in different clinical outcomes in individuals from different families. P Brief at 19-20. Petitioner argued this is evidence that a SCN1A gene mutation is not a reliable indicator of clinical outcome.

Aside from these examples, petitioner further support this proposition by citing to authors' conclusions in the medical literature, stating the SCN1A mutation is not predictive of clinical outcome. Specifically, petitioner 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 Brief at 21;

> 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 Brief at 21 (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.").

Petitioner 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 Brief at 17-22.

b. Response to and analysis of petitioner's support for the assertion that presence of the SCN1A mutation is not predictive

Petitioner's above argument fails as it does not offer persuasive rebuttal to Dr. Raymond's reasoned conclusion that Rachel's SMEI is caused by her SCN1A gene mutation; nor does petitioner's 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, petitioner fails to address that the majority of the examples petitioner cited to involve divergent conditions displayed within family members with the same mutation; therefore, they were inherited mutations. Respondent, Dr. Raymond and the Athena Lab Report note that Rachel's mutation arose de novo and was not inherited. See, e.g., R Reply at 9; Tr. at 330; P Ex 40 at 6. Second, none of these reports described above discuss mutations that involve the same amino acid change as Rachel's mutation, or discuss a mutation at nucleotide position 352 at codon 118, which Rachel possesses. Petitioner's cited examples are not comparable and thus are not persuasive rebuttal of Dr. Raymond's analysis.

As respondent notes, the cited literature appears 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, petitioner's counsel and Dr. Kinsbourne are not clinical geneticists. It is critical to note that the examples cited by petitioner are argued by petitioner's counsel, or at best Dr. Kinsbourne, to be indicative of an inability to predict clinical outcome based upon a SCN1A gene mutation. Neither petitioner's counsel nor Dr. Kinsbourne is qualified to analyze this literature and discuss its significance in relation to the facts of this case. However, petitioner 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. 39, from Lossin, who is not a clinical geneticist or a medical doctor, 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. 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. 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.[35]

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. 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. at 355. And in this case, Dr. Raymond reached his conclusion looking retrospectively at Rachel'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. 25-28) to draw the conclusion that Rachel'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, petitioner's argument misses the mark and is unpersuasive.

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

Dr. Kinsbourne opined the DTaP vaccination caused Rachel 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 9 at 2-3, by "lower[ing] her seizure threshold." Tr. at 443; see supra p. 12-18. However, Dr. Kinsbourne conceded that the SCN1A gene mutation plays a role in Rachel's SMEI. See P Ex 9 at 10; Tr. at 443-44. 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. at 444. Thus, Dr. Kinsbourne maintained that the "mutation alone appears not to be sufficient to account for SMEI. This supports the alternative view that there is a gene-environment interaction, with an environmental trigger." P Ex 9 at 6. Petitioner argued that the medical literature supports the role of environmental modifying factors to SCN1A gene mutations, including DTP and DTaP vaccination. P Brief 22-27; P Ex 9; P Ex 20. Petitioner's arguments to support this allegation

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[35] 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. at 325-26, 354, 400, 474. Mosaicism, or being mosaic, is "the juxtaposition in an organism of genetically different tissues." STEDMAN'S MEDICAL DICTIONARY, 1228 (28th ed. 2006). As discussed in respondent's Post-Hearing Reply Brief, "Petitioner's arguments also ignore the fact that many of the various outcomes they rely on may be explained by mosaicism. Respondent submitted literature that explained mosaicism, but, because Rachel's mutation was de novo, mosaicism is not an issue in this case." R Reply Brief at 6, n. 6 (citing R Ex A8). However, the undersigned does note that this argument regarding mosaicism was never fully developed. Regardless, even ignoring whether mosaicism exists in the case reports relied upon by petitioner, the undersigned finds petitioner's reliance on examples of inherited mutations misplaced when no effort was made to explain how inherited mutations are relevant to de novo mutations.

include citations to the medical literature that petitioner alleges 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. P Brief at 9-12, 22-27; P Reply Brief 7-19, 22-25. The discussion of these contentions follows.

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

To support the argument that an environmental factor modifies the clinical course of SMEI, petitioner's counsel again pointed to comments in the medical literature that consider whether other genetic or environmental factors modify the clinical outcome in persons with SCN1A gene mutations. P Brief at 22-23. 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. At the request of counsel, Dr. Kinsbourne also read the above passage from Depienne et al. into the record during the Hearing on May 15, 2009. Tr. 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 8-9. Thus, respondent argued it is "untenable for petitioner to claim that the articles bolster [the] assertion that Rachel's DTaP vaccine changed her clinical course." Id. at 8. 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, modified Rachel's clinical outcome.

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

Petitioner argued that two medical articles demonstrate that seizures change the outcome in persons with SCN1A variants. P Brief at 23-24. Petitioner's counsel alleges the following statement

from Rhodes et al. provides a hypothesis "for how underlying predisposition to have seizures created by the SCN1A gene and subsequent damage due to each seizure each contribute to SMEI." P Brief at 24.

> 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 et al. at 11151)(emphasis in P Brief). The passage utilized by petitioner specifically states the authors "would like to speculate" regarding the disparity between the two seizure disorders.

Petitioner also cited, and Dr. Kinsbourne's testimony relied upon, the following passage from the literature to support an environmental cause of Rachel'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 Brief at 23-24 (quoting P Ex 11F, 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 Brief). Although not addressed by respondent or Dr. Raymond, the undersigned notes Dr. Kinsbourne does not accurately characterize this article and is "cherry picking" passages. What Dr. Kinsbourne and petitioner 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 petitioner's arguments above that Rachel'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.

As respondent notes, 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 Brief 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 Rachel'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

Petitioner argued a 2000 study by Nieto-Barrerra et al.,a commentary by Erick Sell and Berge A. Minassian,[36] and a 2006 study by Berkovic et al. support his theory that the vaccine is an environmental factor that changes the clinical outcome in persons with the SCN1A gene mutation. P Ex 11R, M. Nieto-Barrerra et al., Severe Myoclonic Epilepsy in Infancy. Analytic Epidemic Study, 30 REV. NEUROL. 620 (2000)("Nieto-Barrerra et al."); P Ex 11C, 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 (2006)("Berkovic et al."); P Ex 11U, Erick Sell & Berge A. Minassian, Demystifying Vaccination-Associated Encephalopathy, 5 LANCET NEUROL. 465 (2006)("Sell & Minassian").

i. Nieto-Barrerra et al.

Dr. Kinsbourne's testimony at the May 14, 2009, Hearing and Petitioner's Brief, at 24-27, 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 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 Brief at 26-27 (citing M. Nieto-Barrerra et al., Severe Myoclonic Epilepsy in Infancy. Analytic Epidemic Study, 30 REV. NEUROL. 620, (2000)("Nieto-Barrerra et al.")]); Tr. at 420-25, 461-66; P Ex 11R(2); see also R Ex A13. Dr. Kinsbourne asserted that this article suggests "that vaccinations **might** be one of those environmental factors that contribute to SMEI." Tr. 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. 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. 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 previously acknowledged there are substantial differences between the DTP vaccine

[36] P Ex 50, Erick Sell & Berge A. Minassian, Demystifying Vaccination-Associated Encephalopathy, 5 LANCET NEUROL. 465 (2006)("Sell & Minassian").

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 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 as discussed above, evidences to the undersigned that Nieto-Barrerra et al. is not persuasive evidence regarding the issues presented in Rachel'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 11C, 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 (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. at 470. Dr. Kinsbourne's opinion criticizes the article but also 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 9 (citing P Ex 11C, Berkovic et al.).

Regarding the above statement from Berkovic, respondent argues that Dr. Kinsbourne "clearly mischaracterizes" the Berkovic article. R Brief at 16-17. The undersigned agrees. Dr. Kinsbourne conceded on cross examination that the authors of the study made no findings on whether vaccines are a trigger for encephalopathy via fever or another immune mechanism." R Brief at 16 (citing Tr. at 469, in response to the question: "[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 and petitioner failed to acknowledge the authors' language following the 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 petitioner's 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., petitioner and Dr. Kinsbourne rely upon a quote from a commentary by Sell & Minassian. P Brief at 26. Petitioner 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." P Brief at 26; Sell & Minassian at 466; see also Tr. at 422-23 (citing Sell &

Minassian). The undersigned finds this article presents no new findings or evidence and, as Dr. Kinsbourne acknowledges, commentaries are simply "peer reactions to the research." Tr. 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. Further, upon review of Sell & Minassian the undersigned once again believes petitioner 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 0f 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 that 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 Rachel'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 petitioner's arguments, the evidence does not support the vaccine as an environmental component that is a substantial cause of SMEI in persons with Rachel's SCN1A variants.

4. Impact of Rachel's Initial Complex Febrile Seizure

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

complex febrile seizure, which in turned caused brain damage.[37]

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 Rachel experienced no developmental delay until after the first year of life. Id. at 476-77. Then in response to the undersigned's question, "[d]oes your theory of lower seizure threshold account for developmental delay after the first year?" Dr. Kinsbourne responded, "Not 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. at 478.

Dr. Raymond, Tr. at 342, and Dr. Wiznitzer, Tr. at 133-34, conceded the vaccine may have caused Rachel's fever, which in turn may have triggered her initial complex febrile seizure in this case; however, there is nothing in the record demonstrating Rachel's vaccination on March 15, 2004, or her subsequent seizures shortly thereafter, caused any brain damage or injury that contributed to her SMEI. See Tr. at 346-47. 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. at 346 (emphasis added).[38] 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 Rachel, at just over four months old, suffered a rise in temperature after her vaccination and then experienced

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[37] Dr. Kinsbourne's theory that Rachel's first complex febrile seizure experienced post-vaccination caused her to suffer brain damage appears to be in addition to, or a variation of, Dr. Kinsbourne's theory that Rachel's initial complex febrile seizure resulted in a lowering of her seizure threshold and led to further seizures resulting in her ultimate diagnosis of SMEI. See infra p. 14-15.

[38] Dr. Raymond's reference to "these cases" refers either to the children in this case and the Stone case, see supra fn. 5, or generally to cases where seizures leave no evidence of brain damage.

a severe seizure.

Dr. Raymond testified the temperature elevation does not "play any sort of causal role in the disease." Tr. 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."). The Oakley et al. article 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). 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.[39] 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. The study "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. 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. at 318. As respondent notes in her Post-Hearing Memorandum, this study is evidence that the SCN1A gene mutation is responsible for Rachel's seizure disorder, and not an environment-gene interaction, be it an infection or, as petitioner argued, a vaccination. R Brief at 18, n. 15.

The Oakley et al. study results are also supported by the conclusion of Berkovic et al., see supra pp. 46-47, 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.")).

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[39] 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).

Again, it is critical to note, Dr. Kinsbourne conceded the mutation played a substantial causative role in Rachel's SMEI. See P Ex 9 at 10; Tr. at 443-44, 485. The issue that ultimately must be resolved is whether respondent 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 Rachel's SMEI. See Shyface, 165 F.3rd 1344; see also de Bazan, 539 F.3d at 1354. There is simply no evidence that Rachel'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 previously, tests following Rachel's first seizure were normal. At 8:45 p.m. on the day of her first seizure, Rachel was given a CT scan, which was found to be normal. P Ex 2(b) at 19, 23. On the next day at CCF, a neurology consult was preformed and it was noted that Rachel was playful and cheerful. P Ex 4(a) at 8. An EEG was performed at found to be within normal limits. Id. at 14.

Dr. Kinsbourne was unable to point to any evidence demonstrating that Rachel'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 [an SCN1A gene mutation] would not manifest itself." Tr. at 325. Dr. Kinsbourne was unable to point to any evidence that Rachel's initial complex febrile seizure caused her injury, which when combined with her mutation was a substantial cause of her SMEI. Tr. at 482-86. Rather, as the evidence supports, Dr. Raymond opined that the initial fever-induced seizure was part of the normal progression of Rachel's SMEI. When asked whether Rachel's temperature elevation and subsequent seizure played a role in her SMEI, Dr. Raymond explained, "in terms of her overall clinical course, no. She was going to have [SMEI]. . . . the substantial facter to her having [SMEI] is the mutation . . . [the seizure] occurred in the context of her having a mutation and [SMEI], and it is consistent with her [having SMEI]. . . . Except for her having a seizure with fever, [the DTaP vaccination] had no significant role in the development of her having [SMEI]." Tr. at 339-40. The undersigned finds Dr. Raymond's testimony compelling.

5. The Simon and Mersburgh Decisions

Petitioner argued that the undersigned's findings in the Mersburgh and Simon cases compel a finding on behalf of petitioner in the instant matter. See P Brief at 12-13. The undersigned might consider this argument, if no testimony or evidence had been presented regarding Rachel's SCN1A gene mutation. 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 Mersburgh[40] and argued a possible genetic predisposition was

[40] 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.

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 that played a causative role in the seizure disorders. In the case *sub judice*, respondent presented credible, persuasive evidence of an alternative cause to Rachel's injury – her SCN1A gene mutation. As discussed, Dr. Kinsbourne and petitioner failed to demonstrate how Rachel's vaccination or her fever resulting from her vaccination altered the course of her genetically based seizure disorder.

6. Weighing Expert Reliability

In his Reply to respondent's Post-Hearing Brief, petitioner criticized the credentials of Dr. Raymond, P Reply Brief at 6, and the overall reliability of his testimony. P Brief 17-36. Dr. Raymond's testimony is discussed at length previously, see, e.g., supra pp. 18-28, and petitioner's arguments regarding the reliability of his analysis are also discussed previously, see, e.g., supra pp. 28-41. Petitioner briefly discussed Dr. Raymond's qualifications and stated, "Petitioner does not argue that either Dr. Wiznitzer or Dr. Raymond lacks the medical credentials to provide a reliable opinion in this case, only that their experience with regard to the cause of Rachel Hammitt's SMEI is not very different than and no better than Dr. Kinsbourne's." P Reply Brief at 6.

The undersigned does not agree with petitioner's view of the experts. Notably, Dr. Raymond, as opposed to Dr. Kinsbourne, is a clinical neurogeneticist. He is also board certified in neurology, with a special emphasis on pediatric neurology. Dr. Raymond's specialties appear highly relevant to this case. Further, the undersigned found 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, specifically those relating to genetics. As an example, when asked the critical question upon which at least a portion of 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 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. 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 Rachel. Nor is there any cogent explanation for how an environmental trigger, specifically a vaccine, significantly contributed to Rachel'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., 92 Fed. Cl.1, 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 petitioner relied upon is dated. Unfortunately for petitioner, he 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 petitioner's 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. at 448-49 (referencing the case, Stone v. Sec'y of Dept. of Health & Human Servs., No. 04-1041V, which was heard alongside Rachel's case). 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 petitioner, 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 previously, seizures are perhaps one of the most common vaccine-related allegations 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 Rachel Hammitt, he would counsel the family and explain the SCN1A gene mutation "is the sole cause of [Rachel's] illness." Tr. at 336.

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 **Rachel's condition** for the following reasons:

- Rachel'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 beginning of the resultant protein, the N-terminus, a functionally important region, as evidenced by reports of only SMEI resulting from mutations in this 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 in or near the same location as Rachel's;
- and there is an absence of the mutation in the normal population.

Further, petitioner failed to present evidence that the vaccine-induced seizure caused injury to Rachel's brain.

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, 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)). Based upon the cumulative reasons set forth above, the undersigned finds that respondent, through Dr. Raymond's opinion and testimony, has met the burden of proving a factor unrelated to the vaccination caused Rachel's SMEI.

The undersigned does find it significant that Dr. Raymond and Dr. Wiznitzer agree with Dr. Kinsbourne and petitioner 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. at 342 (quoting Dr. Raymond); see also Tr. at 132-33 (Dr. Wiznitzer agrees the "Was [the vaccine-induced fever] the reason that [initial] seizure occurred? More likely than not, yes."). Dr. Raymond agrees a complex febrile seizure can injure the brain; however, in the instant case Dr. Raymond notes there in no

evidence the initial seizure injured the brain. Tr. 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 Rachel'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 Rachel'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.[41]

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

[41] This document constitutes a final "decision" in this case pursuant to 42 U.S.C. § 300aa-12(d)(3)(A). Unless a motion for review of this decision is filed within 30 days, the Clerk of the Court shall enter judgment in accord with this decision.