Burgess Rosemary (Orcid ID: 0000-0002-2664-4395)
Scheffer Ingrid (Orcid ID: 0000-0002-2311-2174)
Berkovic Samuel (Orcid ID: 0000-0003-4580-841X)

SCN1A variants in vaccine-related febrile seizures: a prospective study

Damiano JA [1*]; Deng L [2,3*]; Li WH [1, 4]; Burgess R [1]; Schneider AL [1], Crawford NW [5, 6]; Buttery J [6, 7];

Gold M [8,]; Richmond P [9, 10]; Macartney KK [2, 3]; Hildebrand MS [1,6]; Scheffer IE [1, 5, 6, 11], Wood N [2, 3];

Berkovic SF [1].

1. Department of Medicine, University of Melbourne, Austin Hospital, Heidelberg, Australia
2. National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, Sydney, Australia
3. Children's Hospital Westmead Clinical School, The University of Sydney, Sydney, Australia;
4. Department of Neurology, Children`s Hospital of Fudan University, Shanghai, China
5. Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Parkville, Australia
6. Murdoch Children's Research Institute, Parkville, Australia
7. Infection and Immunity, Monash Children's Hospital, Department of Paediatrics Monash Centre for Health Care Research and Implementation , Monash University, Clayton, Australia
8. Discipline of Paediatrics, School of Medicine, Women's and Children's Hospital, University of Adelaide, Adelaide, Australia
9. Vaccine Trials Group, Wesfarmer's Centre of Vaccines and Infectious Disease, Telethon Kids Institute, and Dept of General Paediatrics, Perth Children's Hospital, Nedlands, Australia
10. Division of Paediatrics, School of Medicine, University of Western Australia, Perth, Australia
11. The Florey Institute of Neurosciences and Mental Health, Melbourne, Victoria, Australia

*These authors contributed equally to this study

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Corresponding author:
Prof. Samuel F. Berkovic
Epilepsy Research Centre, L2 Melbourne Brain Centre
245 Burgundy Street
Heidelberg, VIC 3084, Australia.
Tel: +61 9035 7093
Fax: +61 9496 2291

Email: s.berkovic@unimelb.edu.au

Abstract

Objective: Febrile seizures may follow vaccination. Common variants in the sodium channel gene, *SCN1A*, are associated with febrile seizures and rare pathogenic variants in *SCN1A* cause the severe developmental and epileptic encephalopathy Dravet Syndrome. Following vaccination, febrile seizures may raise the spectre of poor outcome and inappropriately implicate vaccination as the cause. We aimed to determine the prevalence of *SCN1A* variants in children having their first febrile seizure either proximal to vaccination, or unrelated to vaccination compared to controls.

Methods: We performed *SCN1A* sequencing, blind to clinical category, in a prospective cohort of children presenting with their first febrile seizure as vaccine proximate (n=69), or as non-vaccine proximate (n=75), and children with no history of seizures (n=90) recruited in Australian paediatric hospitals.

Results: We detected two pathogenic variants in vaccine proximate cases (p.R568X and p.W932R), both of whom developed Dravet syndrome, and one in a non-vaccine proximate case (p.V947L) who had Febrile seizures plus from 9 months. All had generalised tonic-clonic seizures lasting longer than 15 minutes. We also found enrichment of a reported risk allele, rs6432860-T, in children with febrile seizures compared to controls (Odds Ratio 1.91 [95% CI 1.31- 2.81]).

Interpretation: Pathogenic *SCN1A* variants may be identified in infants with vaccine proximate febrile seizures. As early diagnosis of Dravet syndrome is essential for optimal management and outcome. *SCN1A* sequencing in infants with prolonged febrile seizures, proximate to vaccination, should become routine.

Vaccination is a highly effective public health intervention that has led to a dramatic reduction in childhood morbidity and mortality from many infectious diseases. While vaccines have an excellent safety profile and usually only cause mild adverse reactions such as a fever, some individuals experience more serious adverse events, such as febrile seizures (FS).

FS following pertussis and measles-mumps-rubella (MMR) containing vaccines, as well as influenza vaccines in combination with pneumococcal vaccines, are well recognised, albeit uncommon (1-4). While epidemiological studies show that the vast majority of children with a history of FS develop normally (5, 6), a small proportion develop epilepsies (7), including the severe developmental and epileptic encephalopathy (DEE), Dravet syndrome (8, 9).

Pathogenic variants in the sodium channel alpha-1 subunit gene, *SCN1A,* cause Dravet syndrome in at least 80% of cases (8) and in 20% of cases of the milder syndrome of Genetic Epilepsy with Febrile Seizures plus (GEFS+) (10, 11). Vaccinations have been implicated in triggering earlier seizure onset in children with epilepsy with Dravet syndrome (12-15). We found that 30% (12/40) of a cohort of children with Dravet syndrome and *SCN1A* mutations had their first seizure within 2 days after vaccination (13). In terms of the frequency of *SCN1A*-associated Dravet syndrome amongst children with vaccination-related seizures, Verbeek *et al.* retrospectively identified 15/1269 (1.2%) children with Dravet syndrome presenting with seizures following vaccination in the first 2 years of life (16). Thus, rare variants in *SCN1A* are associated with genetic epilepsies and DEEs that present with FS. Conversely, common variants have been implicated in the pathogenesis of FS alone, with a common *SCN1A* exonic variant (rs6432860) associated with increased risk of FS in general, but not with MMR-related FS (17).

Aside from these retrospective studies, little is known about genetic variants in children with Vaccine-proximate Febrile Seizures (VP-FS) and if FS differ from those triggered by another cause. It is also

unknown whether the common rs6432860 variant, only identified in one population to date, is also a risk factor in non-Danish subjects with FS.

This study is the first to prospectively identify the presence and proportion of sodium channel variants among infants with VP-FS or Non-vaccine proximate Febrile Seizures (NVP-FS, compared with controls who have no history of seizures.

Methods

Study design and participants

This prospective study was conducted across four Australian tertiary paediatric hospitals that participate in the Paediatric Active Enhanced Disease Surveillance (PAEDS) network (18): The Children's Hospital at Westmead Sydney, Royal Children's Hospital Melbourne, Princess Margaret Hospital for Children Perth and Women's and Children's Hospital Adelaide. Participant recruitment occurred between 1 May 2013 and 20 April 2016.

From May 2013 to June 2014, children presenting with FS at these sites were identified through daily surveillance nurse screening of emergency presentations or hospital admissions coded with the ICD, Tenth Revision, Australian Modification (ICD-10-AM) diagnosis code for FS (code R56.0) as part of a larger cohort study (19). All VP-FS cases aged < 30 months from this larger cohort study were invited to participate in this prospective study and equivalent numbers of NVP-FS cases of similar age was invited. Due to low numbers of VP-FS presentations during the initial recruitment period, additional VP-FS cases were recruited from July 2014 to April 2016 through outpatient attendance to Specialist Immunisation Clinics at any of the participating hospitals for review of a FS following vaccination or through VP-FS reports to the Serious Adverse Events following Vaccination in the Community service responsible for the recording and follow-up of all adverse events following immunisation in Victoria.

Vaccine exposure was confirmed using immunisation records obtained from the Australian Immunisation Register, a national population-level register (20)

We defined a first FS case in this study as a child aged 30 months or less at the time of their first FS, the seizure fulfilled the Brighton Collaboration case definition as verified by clinician review of hospital records (21) and was associated with a temperature of ≥38◦C measured by the parents or documented in the medical records in a child with no previous history of seizures. To capture all seizures associated with a fever following vaccination, including those following the 6-week and 4-month vaccination time points, a lower age limit restriction was not used in this study. FS were categorised as VP-FS, defined as within 48 hours of an inactivated vaccine, or between 5-14 days of a live vaccine or within 14 days of a combination of inactivated and live vaccine. NVP-FS were defined as a FS outside of this period. Immunisation records obtained from the Australian Immunisation Register were used to confirm all vaccine exposures. (20)

Control participants were defined as children aged 12 to 42 months with no personal or family history of febrile or afebrile seizures. They were recruited through friends of children with FS already recruited into the study, children participating in other clinical trials at each recruitment site, and advertisements placed in local community newspapers, childcare centres and hospital notices. Children were excluded from the study if they had a pre-existing diagnosis of developmental delay, intellectual disability, medical or genetic condition that may affect cognition.

Thus, the phenotypic data allowed classification of participants into three groups: VP-FS, NVP-FS and aged matched controls without febrile seizures. This study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (HREC/14/SCHN/135).

Clinical details and follow up

For FS cases, initial seizure details were collected from medical records and parent/carer interviews. Cases were contacted 12 to 24 months following the initial FS. Data on the occurrence, type (febrile or afebrile) and frequency of subsequent seizures following the initial FS and developmental progression were obtained from parent/carer interview and review of medical records, where available. Participants' development, executive function and behaviour were formally assessed using standardised assessment tools 12 to 24 months following their initial FS. Participants were assessed using Bayley Scales for Infant and Toddler Development, Third Edition, Woodcock-Johnson Tests of Achievement, Third Edition, Behavior Rating Inventory of Executive Function and Preschool Version and Child Behaviour Checklist – Preschool. Outcomes of these assessments will be reported separately. Additional history regarding subsequent developmental progression was obtained via medical records for cases with SCN1A variants.

DNA extraction

For gene variant screening, whole blood was obtained and genomic DNA extracted using QIAamp DNA Maxi Kits (Qiagen, Valencia, CA, USA). In some cases, saliva samples was obtained using Oragene kits and genomic DNA extracted using prepIT▪L2P kits (DNA Genotek Inc., Ottawa, ON, Canada).

PCR and Sanger Sequencing

Coding regions of *SCN1A* (Chromosome 2: 165,984,641-166,149,214; NM_001165963; ENST00000303395.8) including splice sites and up to 200 base pairs of intronic sequence were sequenced. Amplicons were PCR amplified using gene-specific primers designed to the reference human gene transcript (22). Primer sequences are available upon request. Amplification reactions were cycled using a standard protocol on a Veriti Thermal Cycler (Applied Biosystems, Carlsbad, CA). Bidirectional sequencing of all exons and flanking regions including splice sites was completed with a BigDye TM v3.1 Terminator Cycle Sequencing Kit (Applied Biosystems) according to the

manufacturer's instructions. Sequencing products were resolved using a 3730xl DNA Analyzer (Applied Biosystems). All sequencing chromatograms were compared to published cDNA sequence and flanking intronic sequences. Nucleotide changes were detected using Codon Code Aligner (CodonCode Corporation, Dedham, MA). Molecular analysis was performed blind to the patients' clinical status.

Variant Classification

Each variant detected in *SCN1A* was classified into pathogenic, likely pathogenic, uncertain significance, likely benign and benign, according to according to American College of Medical Genetics (ACMG) consensus guidelines (23).

The following online genetic databases were used to help determine classification of variants: Database of Single Nucleotide Polymorphisms (dbSNP)(24), ClinVar(25), Genome Aggregation Database (gnomAD)(26), and Guangzhou Medical University Institute of Neuroscience *SCN1A* Mutation Database(27).

Statistical analysis

The three groups were compared using Pearson's chi-square or Fisher's exact test for categorical values and independent t-test for parametric continuous values. The primary outcome measure was the proportion of pathogenic and likely pathogenic *SCN1A* variants between groups compared using Fisher's Exact test. Pearson's chi-square or Fisher's Exact tests were also used to compare allele frequencies and genotype differences for synonymous and intronic variants between all three groups and between all FS and controls. The Bonferroni-Holm method was applied to control the error rate for multiple comparisons.

Results

Study cohort

Of the 269 participants initially recruited, 35 were excluded: 26 for history of previous FS; 6 for no DNA sample collected or no consent given for genetic testing; 1 for lack of documented fever on case review; and 2 for withdrawal from the study. Of the remaining 234 subjects, 69 had VP-FS, 75 had NVP-FS, and 90 were controls. (Figure 1)

There were no differences in proportion of FS cases with a family history of FS or epilepsy between VP-FS and NVP-FS groups. Participants with VP-FS were younger at time of first FS than those with NVP-FS (12.8 months vs 14.3 months, p=0.05) and more frequently had complex FS, defined by one of three criteria: lasting more than 15 minutes, focal features or more than one FS in 24 hours (39.1% vs. 22.7%, p=0.03) (Table 1). There was no difference in the proportion of patients' with recurrent FS or afebrile seizures over a similar follow-up period (VP-FS vs NVP-FS: 37.7% vs 34.7%, p=0.66 for FS; 11.6% vs. 5.3%, p=0.17 for afebrile seizures; follow-up 16.1 (SD 4.8) vs 17.2 (SD 3.2) months, p=0.09)

Variant Detection

We detected 90 variants in *SCN1A* in the 234 subjects. The variants comprised of 1 nonsense (stop gain), 8 missense, 9 synonymous and 28 intronic variants; 44 variants were observed more than once. Table 2 shows the distribution of variants according to clinical group and ACMG guidelines (23).

There were three pathogenic or likely pathogenic variants found. Two were in the VP-FS group (2.9%) and one in the NVP-FS group (1.3%), with no difference between the three groups. Case 1 with VP-FS had a recurrent nonsense mutation, p.R568X,,that was pathogenic in a patient with Dravet syndrome (28). Case 2 with VP-FS and 3 with NVP-FS had novel missense variants, p.W932R and p.V947L, respectively, both classified as "likely pathogenic" (variant details according to ACMG guidelines in footnotes to Table 3)

Three missense changes were classified as 'unknown significance' p.A1161T (rs201079458); p.E1957G (rs121918802); p.T1250M (rs140731963)], which all were previously reported with a minor allele frequency (MAF) <0.01 in gnomAD, each had low predictions of functional effect from *in silico* tools or are reported as inherited (29); (30); (31). In our study, all three were found in the NVP-FS group and none of the cases had a family history of FS; segregation data was not available. A further three missense variants (p. R542Q (rs121918817), p. A1067T (rs2298771), p. T1174S (rs121918799), were classified as 'likely benign' or 'benign'.

The remaining variants of unknown significance comprised; three previously unreported intronic variants (c.4339-96delC; c.1-182delT; c.4339-110 delT) and a further nine rare intronic changes (rs571600918, rs749370340, rs73969742, rs549232924, rs75022359, rs76220226, rs8191989, rs773635222, rs148640356). We also identified six synonymous variants (rs140237315, rs141051370, rs374087499, rs144679294, rs569598595, rs145101180) with a minor allele frequency (MAF) <0.01 according to the Exome Aggregation Consortium (ExAC) database (26). The significance of these rare variants to FS is unknown.

Common Variant Burden

Three common coding variants c.3199G>A; p. A1067T (rs2298771), c.1212 A>G; p. V404V (rs7580482), c.2292; T>C;p. V764V (rs6432860) and two intronic variants, one c.603-91G>A (rs3812718) previously implicated as a risk allele for FS in a genome-wide study (17), and one in close proximity c.603-106 T>G (rs3812719), were investigated for differences in allele frequencies and genotype frequency between the groups (Table 4).The synonymous change, c.2292; C>T; p.V764V, rs6432860, was more frequently found in FS cases compared to controls (OR 1.91 [95% CI 1.31- 2.81]; p=0.004). There was, however, no difference in frequency between the VP-FS and NVP-FS groups (Table 5).

***SCN1A* pathogenic variant cases: phenotype and outcome**

The phenotypes of the three children with pathogenic or likely pathogenic *SCN1A* variants are described in Table 3. The two VP-FS cases had seizure onset within 24 hours of receiving their 4-month vaccinations with Infanrix Hexa® (hexavalent vaccine with diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and haemophilus influenza type B), Prevenar13® (13-valent pneumococcal conjugate vaccine) and Rotarix® (oral live-attenuated rotavirus vaccine). Both had prolonged generalised tonic-clonic seizures (GTCS), lasting 30 and 15 minutes respectively, and developed later seizure types that were not vaccine-proximate, including myoclonic, absence, hemiclonic, generalised clonic seizures and status epilepticus in the first two years of life. Case 1 with nonsense mutation, p.R568X, had developmental stagnation from 12 to 18 months with subsequent regression and developmental delay. Case 2 with the novel p.W932R mutation, had significant speech delay with no language or social-emotional developmental progression from age 18 months. The classical electro-clinical history led to a diagnosis of Dravet syndrome in both children. Both cases have subsequently received further vaccinations under close medical supervision, with regular anti-pyretic and benzodiazepine administration following vaccination in addition to their regular anti-epileptic medication, without experiencing a seizure.

The NVP-FS case with a “likely pathogenic”, novel variant, p.V947L, was a dizygous twin who had his first FS at 9 months; a 57 minute episode of tonic-clonic status epilepticus in the context of an upper respiratory tract infection. He proceeded to have frequent (up to 10 per year) tonic-clonic seizures, many but not all associated with fever. His co-twin did not have seizures, but their father had a history of frequent FS. His last known seizure was at age 5 years. Bayleys-III assessment at 18 months revealed mild fine motor delay and language delay. The diagnosis was febrile seizures plus (FS+), in the setting of a family with GEFS+ (10, 11).

Discussion

This is the first prospective study examining the frequency of *SCN1A* variants in children with FS triggered by vaccination compared those with FS unrelated to vaccination, and controls with no history of seizures. Of 144 patients with FS, only three (2%) had pathogenic variants in *SCN1A*. There was no statistical difference in the frequency of pathogenic *SCN1A* variants between the groups from our cohort. It is of clinical relevance, however, that all three infants with pathogenic variants had prolonged FS and the two infants with vaccine-proximate FS both developed the features of Dravet syndrome. The third child with FS *unrelated* to vaccination had complex FS and afebrile seizures with a diagnosis of FS+. Our data suggest that a prolonged VP-FS in the first 6 months of life, lasting 15 minutes or more, in the presence of a pathogenic *SCN1A* variant, is suggestive of Dravet syndrome.

These findings are congruent with the retrospective analysis of a Dutch passive reporting database (16) which found that 1.2% (15/1269) of children with seizures, including febrile, afebrile and unclassified seizures, after vaccination in the first 2 years of life had *SCN1A*-related Dravet syndrome. Our two Dravet syndrome patients presented with prolonged seizures at 4 months occurring within 24 hours of vaccination, similar to the Dutch cases. The younger age at presentation of these children, compared to the median onset of FS at age 18 months, mirrors our finding of vaccine-proximate onset in Dravet syndrome being associated with seizure onset at 4 months rather than the mean onset of Dravet syndrome of 6 months (8, 13). The reported vaccine-related first seizures in Verbeek's study involved whole-cell pertussis vaccines, whereas the *SCN1A*-related Dravet cases in our cohort had their first FS following acellular vaccines, suggesting that the genetic immunological interaction may be independent of the type of pertussis vaccine involved. While a follow up study by Verbeek *et al*.(32) showed a reduction in risk of subsequent vaccine related seizures with acellular pertussis vaccines, as with the general paediatric population (33) , the type of vaccine does not appear to affect the initial vaccine related seizure presentation in children with Dravet syndrome.

In addition to the pathogenic and likely pathogenic variants identified, we confirmed a higher frequency of the common *SCN1A* variant allele, c.2292; C>T; p.V764V in FS cases compared to controls. This FS risk allele was first identified in a Danish genome-wide association study (17) and we are the first to confirm the association of this allele to FS outside of a Danish population. As our study only examined *SCN1A* variants, we could not verify the other loci reported to be associated with MMR-related FS and FS.

This study has some limitations. With the yield of pathogenic variants that we found, our sample size was not powered to detect a significant difference between the groups using Fisher's Exact test in the frequency of *SCN1A* variants. The *SCN1A* mutation rate may also be underestimated as Sanger sequencing cannot reliably detect intragenic deletions (34) and mosaicism rates below 20% that have been previously found in *SCN1A*-associated FS(35). Other genes associated with FS including other sodium channel genes (*SCN1B*, *SCN8A*, and *SCN2A*), the γ2-subunit of gamma-aminobutyric acid (GABA) receptor subunit (*GABRG2*) (36), and Protocadherin 19 (*PCDH19*) were not examined.

Our prospective study suggests that in an infant with vaccine proximate, prolonged FS, the detection of a pathogenic *SCN1A* variant should raise the suspicion of Dravet syndrome. Given that a higher rate of seizures with subsequent vaccinations occurs in Dravet syndrome (32), screening for SCN1A variants in children 12 months and under with prolonged VP-FS, should be considered for early diagnosis and optimal management. Early initiation and appropriate choice of anti-epileptic medication for children with Dravet syndrome can lead to better long-term outcomes (37, 38). As children receive multiple vaccines in the first 18 months of life, early identification of this at-risk group can also assist in the planning of safe administration of subsequent vaccinations in these children to reduce the risk of vaccine-preventable diseases and associated complications.

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Author contribution

NW, SFB and IES contributed to the conception and design of the study. JAD, LD, LWH, RB, ALS, NWC, JB, MG, PR, KKM and MSH contributed to the acquisition and analysis of data. J.A.D. and L.D. drafted the text, figure and tables with support from SFB, NW and IES.

Potential conflict of interest

S.F.B and I.E.S's institution (University of Melbourne) receives payments for a patent for *SCN1A* testing held by Bionomics Inc and licensed to various diagnostic companies. The remaining authors have no conflicts of interest.

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Figure legend

Figure 1: *Study cohort*

Table Legends

Table 1: *Clinical details for Vaccine Proximate-FS (VP-FS), Non-Vaccine Proximate-FS (NVP-FS) and control groups*

FS=febrile seizure, AFS=afebrile seizure, SD=standard deviation, NA=not applicable
Complex FS = febrile seizure > 15 minutes, focal seizure or repeat seizure within 24h of initial
*Where there is no value for control group, p value compares VP-FS and NVP-FS groups only

Table 2: *SCN1A variants by group allocation and variant class*

VP-FS=vaccine proximate febrile seizure, NVP-FS=non-vaccine proximate febrile seizure
ACMG= American College of Medical Genetics
* Variants of unknown significance were all intronic in VP-FS and control groups; NVP-FS group had three missense, 1 synonymous and four intronic variants

Table 3: *Clinical characteristics of participants with pathogenic/likely pathogenic variants*

FS=febrile seizure, VP-FS=vaccine proximate FS, NVP-FS=non-vaccine proximate FS, FS+ = febrile seizures plus, DTPa-IPV-HepB-HiB=hexavalent diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, haemophilus influenza B vaccine, PCV13=13 valent pneumococcal conjugate vaccine, GTCS=generalised tonic-clonic seizures; GCS=generalised clonic seizures; M=myoclonic seizures; Ab=absences; SE=status epilepticus; H=hemiclonic; NA=not applicable.
† Classification according to ACMG guidelines (23) is listed and qualifying criteria specified
# Null variant, previously reported (8, 29)
* Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before (39); located in a mutational hot spot; absent from controls
^Located in a mutational hot spot; absent from controls; Multiple lines of computational evidence support a deleterious effect on the gene, Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease

Table 4: *Allele frequency differences for the 5 common single nucleotide polymorphisms (SNPs) detected within SCN1A*

[a] Includes both VP-FS and NVP-FS cases
*p value corrected for multiple comparisons using Bonferroni method using 5 tests

Table 5: *Allele frequency comparisons for single nucleotide polymorphism (SNP) c.2292; C>T; p.V764V; rs6432860 according to clinical groups assignment*

FS=febrile seizure, VP-FS=vaccine proximate FS, NVP-FS=non-vaccine proximate FS
*p value corrected for multiple comparisons using Bonferroni method using 4 tests

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Corresponding Author's Name: Samuel F Berkovic

5. Manuscript Title: SCN1A variants in vaccine-related febrile seizures: a prospective study

6. Manuscript Identifying Number (if you know it): ANA-19-1109

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Corresponding Author's Name: Samuel F Berkovic

5. Manuscript Title: SCN1A variants in vaccine-related febrile seizures: a prospective study

6. Manuscript Identifying Number (if you know it): ANA-19-1109

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Dr. Deng reports grants from University of Sydney, during the conduct of the study.

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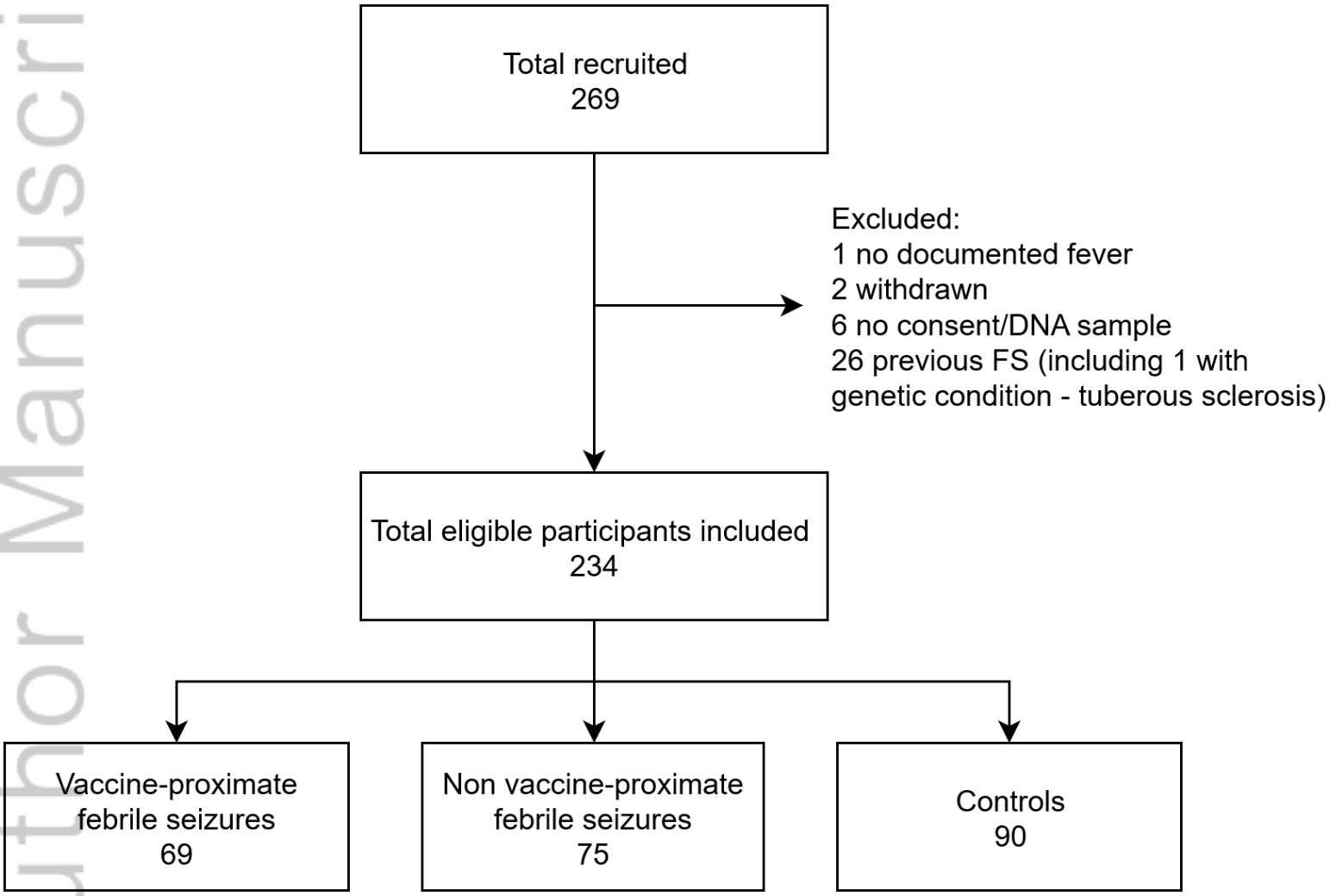

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1. Given Name (First Name): Peter
2. Surname (Last Name): Richmond
3. Date: 15-October-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Samuel F Berkovic

5. Manuscript Title: SCN1A variants in vaccine-related febrile seizures: a prospective study

6. Manuscript Identifying Number (if you know it): ANA-19-1109

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Table 1: Clinical details for Vaccine Proximate-FS (VP-FS), Non-Vaccine Proximate-FS (NVP-FS) and control groups

	VP-FS n (%)	NVP-FS n (%)	Control n (%)	p*
n	69	75	90	
Sex (male)	37 (53.6%)	32 (42.7%)	55 (61.1%)	0.06
Family history FS				
FS	25 (36.2%)	25 (33.3%)	NA	0.72
Epilepsy	9 (13.0%)	13 (17.3%)	NA	0.47
First FS				
Age (months)	12.8 (SD 3.8)	14.3 (SD 5.2)	NA	0.05
Complex FS	27 (39.1%)	17 (22.7%)	NA	0.03
FS recurrence				
Follow up duration (months)	16.1 (SD 4.8)	17.2 (SD 3.2)	NA	0.09
FS recurrence	26 (37.7%)	26 (34.7%)	NA	0.71
AFS following initial FS	8 (11.6%)	4 (5.3%)	NA	0.23

FS=febrile seizure, AFS=afebrile seizure, SD=standard deviation, NA=not applicable
Complex FS = febrile seizure > 15 minutes, focal seizure or repeat seizure within 24h of initial
*Where there is no value for control group, p value compares VP-FS and NVP-FS groups only

Table 2: *SCN1A* variants by group allocation and variant class

ACMG Variant Class(23)	VP-FS (n=69)	NVP-FS (n=75)	Control (n=90)
Pathogenic	1	0	0
Likely pathogenic	1	1	0
Unknown significance*	4	8	4
Likely benign	2	2	4
Benign	20	22	21

VP-FS=vaccine proximate febrile seizure, NVP-FS=non-vaccine proximate febrile seizure
ACMG= American College of Medical Genetics
* Variants of unknown significance were all intronic in VP-FS and control groups; NVP-FS group had three missense, 1 synonymous and four intronic variants

Table 3: Clinical characteristics of participants with pathogenic/likely pathogenic variants

Case (sex)	Group	First FS			Vaccine (seizure onset time post-vaccination)	Later seizures	Epilepsy syndrome	*SCN1A* variant[†]
		Age (months)	Duration (minutes)	Description				
1 M	VP-FS	4.0	30	GTCS	DTPa-IPV-HepB-HiB, PCV13, rotavirus (10 hours)	M, Ab, GTCS	Dravet	c.1702C>T; p.R568X Pathogenic#
2 M	VP-FS	4.4	15	GTCS	DTPa-IPV-HepB-HiB, PCV13, rotavirus (18 hours)	M, GCS, GTCS, H, SE	Dravet	c.2794 T>A; p.W932R Likely Pathogenic*****
3 M	NVP-FS	9.7	57	GTCS	NA	GTCS	FS+	c.2839 G>T; p.V947L Likely Pathogenic**^**

FS=febrile seizure, VP-FS=vaccine proximate FS, NVP-FS=non-vaccine proximate FS, FS+ = febrile seizures plus
DTPa-IPV-HepB-HiB=hexavalent diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, haemophilus influenza B vaccine
PCV13=13 valent pneumococcal conjugate vaccine
GTCS=generalised tonic-clonic seizures; GCS=generalised clonic seizures; M=myoclonic seizures; Ab=absences; SE=status epilepticus; H=hemiclonic; NA=not applicable.

[†] Classification according to ACMG guidelines (23) is listed and qualifying criteria specified
Null variant, previously reported (8, 29)
***** Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before (39); located in a mutational hot spot; absent from controls
^Located in a mutational hot spot; absent from controls; Multiple lines of computational evidence support a deleterious effect on the gene, Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease

Table 4: Allele frequency differences for the 5 common single nucleotide polymorphisms (SNPs) detected within *SCN1A*

			Minor Allele Frequency (MAF)		
Variant	**Location**	**Rs number**	**Febrile Seizures[a]**	**Controls**	**p***
c.2292; C>T; p.V764V	Exon 13	rs6432860	148/288 (0.51)	64/180 (0.36)	0.004
c.1212 A>G; p.V404V	Exon 9	rs7580482	137/288 (0.48)	67/180 (0.37)	0.14
c.3199 G>A; p. A1067T	Exon 16	rs2298771	75/288 (0.26)	54/180 (0.30)	1.00
c.603-91 G>A	Intron 4	rs3812718	117/288 (0.41)	81/180 (0.45)	1.00
c.603-106 T>G	Intron 4	rs3812719	55/288 (0.19)	53/180 (0.29)	0.50

[a] Includes both VP-FS and NVP-FS cases
*p value corrected for multiple comparisons using Bonferroni method using 5 tests

Table 5: Allele frequency comparisons for single nucleotide polymorphism (SNP) c.2292; C>T; p.V764V; rs6432860 according to clinical groups assignment

	Minor Allele Frequency (MAF)			
Analyses	**Cases (%)**	**Controls**	**OR (95% CI)**	**p***
VP-FS vs. controls	74/138 (53.6%)	64/180 (35.5%)	2.10 (1.33 - 3.30)	0.17
NVP-FS vs. controls	74/150 (49.3%)	64/180 (35.5%)	1.77 (1.13-2.75)	0.40
VP-FS vs. NVP-FS	74/138 (53.6%)	74/150 (49.3%)	1.19 (0.75-1.89)	1.00
All FS vs. controls	148/288 (51.4%)	64/180 (35.6%)	1.91 (1.31- 2.81)	0.003

FS=febrile seizure, VP-FS=vaccine proximate FS, NVP-FS=non-vaccine proximate FS
*p value corrected for multiple comparisons using Bonferroni method using 4 tests

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Corresponding Author's Name: Samuel F Berkovic

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Dr. Wood reports grants from National Health and Medical Research Council Australia, during the conduct of the study; .

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Author/s:
Damiano, JA; Deng, L; Li, W; Burgess, R; Schneider, AL; Crawford, NW; Buttery, J; Gold, M; Richmond, P; Macartney, KK; Hildebrand, MS; Scheffer, IE; Wood, N; Berkovic, SF

Title:
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Date:
2019-12-12

Citation:
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