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SHORT RESEARCH ARTICLE

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Epidemiology and etiology of infantile developmental and epileptic encephalopathies in Tasmania

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Abstract

We sought to determine incidence, etiologies, and yield of genetic testing in infantile onset developmental and epileptic encephalopathies (DEEs) in a population isolate, with an intensive multistage approach. Infants born in Tasmania between 2011 and 2016, with seizure onset <2 years of age, epileptiform EEG, frequent seizures, and developmental impairment, were included. Following review of EEG databases, medical records, brain MRIs, and other investigations, clinical genetic testing was undertaken with subsequent research interrogation of whole exome sequencing (WES) in unsolved cases. The incidence of infantile DEEs was 0.44/1000 per year (95% confidence interval 0.25 to 0.71), with 16 cases ascertained. The etiology was structural in 5/16 cases. A genetic basis was identified in 6 of the remaining 11 cases (3 gene panel, 3 WES). In two further cases, WES identified novel variants with strong in silico data; however, paternal DNA was not available to support pathogenicity. The etiology was not determined in 3/16 (19%) cases, with a candidate gene

identified in one of these. Pursuing clinical imaging and genetic testing followed by WES at an intensive research level can give a high diagnostic yield in the infantile DEEs, providing a solid base for prognostic and genetic counseling.

KEYWORDS
developmental and epileptic encephalopathy, incidence, whole exome sequencing

1 | INTRODUCTION

Infantile developmental and epileptic encephalopathies (DEEs) have a range of etiologies including >60 genetic causes, and in many patients, the cause remains unknown. The infantile DEEs comprise a group of epilepsy syndromes with infantile spasms (West syndrome) typically accounting for over half the cases.[1,2] The incidence of DEEs overall was estimated as 0.27/1000 births in the North London study[1] and as 0.54/1000 per year in our recent Victorian study;[2] the difference was probably related to methodology as each had different inclusion criteria and only those with a specific syndrome were counted in the North London estimate. Reliable epidemiological data for the infantile DEEs is required for health services planning and will inform the need for genetic testing in the diagnosis and management in these severe epilepsies.

Genetic investigations have revolutionized understanding of the causes of DEEs. This knowledge has begun to be implemented in the clinic, predominantly using gene panel testing, and diagnostic yields are growing as new discoveries are made.[3] Incorporating whole exome sequencing (WES) into the diagnostic protocol of DEEs increases the yield and reduces overall costs associated with reaching a diagnosis.[2]

The Australian island state of Tasmania is a population isolate of ~515 000 residents served by only two EEG laboratories in its major cities, making it an ideal population for epidemiological studies. More than 94% of Tasmanians have a Caucasian ancestry. In this paper, we characterize the phenotypic, genetic, and epidemiologic features of infantile DEEs in a captured population over a six-year period, utilizing next-generation molecular investigations in a multistage approach from clinical gene panels to whole exome sequencing.

2 | METHODS

Inclusion criteria were infants born in Tasmania between 2011 and 2016, with onset of seizures <2 years of age, epileptiform features on EEG, frequent seizures defined as >daily for a week or >weekly for a month, and evidence of developmental delay, plateauing, or regression. Infants with infantile spasms were included irrespective of seizure frequency. Patients with acute symptomatic seizures such as those associated with hypoxic-ischemic encephalopathy were excluded. Patients were identified through contact with all Tasmanian pediatricians and pediatric neurologists and comprehensive review of EEG reports. EEG reports were reviewed from 2009 to 2016 to ensure full inclusion. All EEGs reported abnormal were reviewed by two neurologists (TLW and DLJ) to confirm the presence of definitive epileptiform discharges.

The ascertainment process is shown in Figure S1. We screened >1200 EEG records and identified 89 patients with epileptiform features. Seventy-three cases were excluded; 40 due to age or date of onset; 24 had a mild or self-limited epilepsy syndrome; 4 had normal developmental outcome; and 5 had acute symptomatic seizures (four with neonatal hypoxic-ischemic encephalopathy and one with traumatic brain injury).

Clinical details obtained included developmental history, seizure semiology, and comorbidities from interview, review of medical records, and a validated seizure questionnaire.[4] EEG findings, neuroimaging, and metabolic investigations were reviewed. Specific epilepsy syndromes were diagnosed where possible.

Research WES was conducted using Agilent SureSelect XT Human All Exon + UTR v5 (75 Mb) kit and 100 bp paired-end sequencing on the HiSeq 2500 System. Trio WES analysis including both parents was performed to allow segregation of variants, where possible. WES read mapping, alignment processing, and variant calling were performed using GATK best practices.[5] Initially, a panel of 423 candidate genes was interrogated from the WES for single nucleotide variants and, if this was negative, exome-wide analysis was performed. Ultrarare variants predicted to result in functional changes and segregating with affected status were validated by Sanger sequencing. Plausible connections to epilepsy or neurodevelopmental conditions were investigated by review of the literature and performing functional studies (reported separately;[6] Berecki et al, in submission). Pathogenicity of variants was assessed according to ACMG criteria.[7] Data from unsolved cases were regularly re-reviewed at 6- to 12-month intervals. Ethical approval was obtained from the Human Research and Ethics Committee (Tasmania) Network (Reference H0013627).

3 | RESULTS

Sixteen patients met the criteria for incident infantile DEEs in the six-year period. All were of Anglo-Australian

background. All patients were identified from review of EEG records or by pediatric neurologists servicing Tasmania. Correspondence with pediatricians around the state did not identify any additional patients.

Of the 16 patients, 5 were male. Clinical and molecular findings are summarized in Table 1. Twelve had abnormal development prior to seizure onset or as newborn infants. Median seizure onset was 6 months (range 3 days to 20 months). Six patients had West syndrome with infantile spasms.

There were 36 408 births in Tasmania in 2011-2016 with net migration in this period being negligible.[8] The incidence of infantile DEEs and infantile spasms in Tasmania was 0.44/1000 (95% confidence interval 0.25 to 0.71) per year and 0.17/1000 (95% confidence interval 0.06 to 0.36) per year, respectively.

At ascertainment, five infants had an established etiology based on history and neuroimaging (Table 1). Cases 1 and 2 had lissencephaly including one with a causative copy number variant (17p13.3 Miller-Dieker microdeletion) and the second with a mosaic microduplication at 17p regarded as likely pathogenic. One patient had focal cortical dysplasia, and one had clinically confirmed tuberous sclerosis (genetic testing not performed). Case 5 had extensive unilateral cystic encephalomalacia, consistent with a large perinatal anterior circulation infarct. As this patient presented with infantile spasms, she met our inclusion criteria despite the acquired cause. There were no metabolic etiologies identified in our cohort.

The etiology was unknown at ascertainment in the remaining 11 patients (cases 6-16); however, three subsequently had positive clinical genetic testing. Two had de novo *KCNQ2* variants, and one had an intronic change in *ARX* resulting in retention of intron 4 and predicted early termination of the ARX protein;[6] the variant segregated with autism spectrum disorder in his mildly affected mother and brother.

Three patients had pathogenic or likely pathogenic variants identified on research genetic testing in *DHDDS, GABRB2* (reported in[9]), and *CACNA1G*. For case 12 with a variant in *CACNA1G,* in vitro electrophysiological evaluation showed a pathogenic gain of function (Berecki et al, in submission). Cases 9 and 13, with heterozygous variants in *SCN8A* and *SNAP25,* respectively, were regarded as likely solved, as their clinical patterns were consistent with the literature, and there was strong in silico data. However, as both were novel variants and paternal DNA was unavailable for segregation, the ACMG classification for these two cases remained "uncertain significance."

Three cases were regarded as currently unsolved. Case 14 had compound heterozygous variants in *FAT1*; segregation analysis confirmed one variant was inherited from each parent. Both variants were regarded as damaging on in silico analysis, but the gene is not established as a DEE gene, so the variants were regarded as of uncertain significance.

Etiology for two patients remains unknown despite detailed review of exome-wide variants. For one, trio data are available, but for the other parental DNA was not available. Further clinical descriptions and variant details are given in the supporting information.

4 | DISCUSSION

The incidence of the infantile DEEs in Tasmania (0.44/1000 per year) is consistent with estimates from North London, UK, and Victoria, Australia.[1,2] Our incidence of infantile spasms (0.17/1000 per year) was at the lower end of previous estimates, which ranged from 0.2-0.45/1000 per year).[1,2,10,11] The Victorian study also included patients with acquired brain injuries (12% of the cohort), whereas these patients were excluded from our study with the exception of one who had infantile spasms (an automatic inclusion).

The etiology of the epilepsy was definitively identified in 11 of our 16 patients (69%). Five had a major structural abnormality. Genetics was important in this group with a defined genetic etiology in the two lissencephaly cases and a presumed but unstudied genetic abnormality in the tuberous sclerosis case.

Of the nonstructural cases, 6/11 had a definite genetic etiology. If we include cases 9 and 13, where the identified genes were highly plausible in terms of pathogenicity (*SCN8A*, *SNAP25*), but the absence of proof of a de novo etiology precluded strict ACMG classification as pathogenic, then the diagnostic success rate for the whole cohort climbs to 81% (Figure 1). Although our sample size was small, this high success rate in identifying the etiology can be attributed in part to the intensive scrutiny of WES data. This included trio testing where possible, consideration of various modes of inheritance including mosaicism and repeated interrogation incorporating newly published data into our analysis after standard clinical testing. Our rigorous testing identified genetic etiologies in two cases that were negative on initial exome-wide analysis, as has also been shown to be valuable in other studies of unsolved DEE cases.[12,13]

The reported diagnostic yield of genetic testing in infantile DEEs depends on the methods used, the inclusion criteria of the sample population, and whether "solved" patients with prior testing have been excluded. Recent studies generally find that 25%-50% of cases are solved,[2,14–17] although one study of a selected group of 14 cases studied by trio whole genome sequencing claimed diagnostic findings in all.[18] Our findings provide a "real-world" estimate reflecting that parental samples are not always obtainable from an epidemiologically ascertained cohort.

Strengths of our study are that the cohort was ascertained by comprehensive review of all EEG recordings performed in Tasmania from 2009 to 2016 and contact with all pediatricians and neurologists caring for children. The data are thus likely to be complete, which is supported by our incidence estimates being in broad agreement with others. It is possible, but unlikely,

TABLE 1 Clinical and etiology findings in epidemiological cohort of infantile DEEs

Subject number/Gender age at last review	Onset age of seizures Syndrome	Clinical details	Etiology
1/ F 2 y4 mo	8 mo West syndrome	Epileptic spasms Profound GDD EEG: Hypsarrhythmia MRI: Moderate lissencephaly, gradient: posterior more severe than anterior	Lissencephaly Miller-Dieker 17p13.3 microdeletion
2/ M 6 y1 mo	7 mo West syndrome	Spasms, focal motor seizures Profound GDD EEG: Hypsarrhythmia MRI: Moderate lissencephaly, gradient: posterior more severe than anterior, pontine hypoplasia	Lissencephaly 17p mosaic microduplication
3/ M 2 y6 mo	20 mo DEE	Unifocal seizures Regression with seizures. Surgery curative. Mild language delay EEG: Left frontotemporal IEDs MRI: Segmental focal cortical dysplasia, subependymal nodules	Focal cortical dysplasia Genetic testing not done
4/ F 4 y4 mo	2 wk DEE	Focal tonic, FIAS Plateau with seizures. Mild language delay. EEG: Multifocal IEDs. MRI: Multifocal tubers.	Tuberous sclerosis complex Genetic testing not done
5/ F 4 y1 mo	5 mo West syndrome	Spasms, Focal motor seizures Hemiplegia, regression with spasms EEG: Hypsarrhythmia; unifocal centro-temporal spike IEDs MRI: Antenatal venous infarction with multicystic encephalomalacia	Antenatal clastic vascular Genetic testing not done
6/ F 2 y3 mo	3 d EIMFS	Focal seizures, migrating focal seizures Mild GDD EEG: Ictal rhythms migrating between hemispheres; 6 mo & 13 mo normal MRI: Normal	***KCNQ2*** c.637C>T p.Arg213Trp[a] de novo Pathogenic[b]
7/ F 2 y1 mo	2 mo West syndrome	Focal tonic seizures, spasms, multifocal myoclonia Acquired microcephaly, dyskinesia, profound GDD EEG: Hypsarrhythmia; multifocal discharges MRI: Acquired moderate cerebral atrophy	***KCNQ2*** c.593G>A p.Arg198Gln[a] de novo Pathogenic[b]
8/ M 19 mo	4 wk DEE	Tonic-clonic seizures, focal tonic seizures Severe GDD EEG: Bilateral occipital IEDs MRI: Hypoplastic corpus callosum	***ARX*** c.1449-1 G>C p.Leu484*[c] Pathogenic[b]
9/ F 5 y4 mo	6 mo DEE	Tonic-clonic seizures, FBTC Language delay EEG: 11 mo-Ictal rhythm midline to frontocentral regions; 2 y1 mo-GSW, PSW MRI: Normal	***SCN8A*** c. 5009T>G p.Met1670Arg[c] Uncertain significance[b] (de novo status unproven)

(Continues)

TABLE 1 (Continued)

Subject number/Gender age at last review	Onset age of seizures Syndrome	Clinical details	Etiology
10/ F 5 y10 mo	6 mo DEE	Absence with eyelid myoclonia, absence, eyelid myoclonia, myoclonic jerks, tonic-clonic seizures, NCSE Profound GDD, visual impairment EEG: Marked photosensitivity, 3-4Hz GSW, PSW, myoclonic-atonic seizure MRI: Normal	***DHDDS*** c.632G>A p.Arg211Gln[a] de novo Pathogenic[b]
11/ M deceased 17 d	5 d EME	Myoclonic jerks Decreased activity, poor feeding, jitteriness EEG: Burst suppression MRI: Normal	***GABRB2*** c.851C>A p.Thr284Lys[c] *de novo* Likely pathogenic[b]
12/ F 8 y3 mo	7 mo DEE	Febrile seizures, vibratory tonic seizures, tonic-clonic seizures, absence Profound GDD, hypotonia, truncal ataxia, ambulating with walker at 4 y EEG: GSW, multifocal discharges, PSW MRI: Normal, no cerebellar atrophy	***CACNA1G*** c.2727G>C p.Leu909Phe[c] Likely pathogenic (gain of function in vitro [unpublished]; de novo status unproven)[b]
13/ F 4 y7 mo	5 mo West syndrome	Spasms Remission at 8 mo, severe ID and GDD, seizure free without medication EEG: Hypsarrhythmia MRI: Normal	***SNAP25*** c. 526C>T p.Arg176Cys[c] Uncertain significance[b] (de novo status unproven)
14/ F 4 y10 mo	13 mo DEE	Myoclonic jerks; Focal motor seizures at 2 y Hypotonia, delayed visual maturation, severe ID and GDD EEG: Multifocal discharges, normal at 23 mo MRI: Normal	Unknown **Candidate gene: *FAT1*** c.8626G>C p.Asp2876His[c] c.7655A>G p.Glu2552Gly[c] Uncertain significance[b]
15/ M 4 y6 mo	9 mo West syndrome	Spasms Developmental plateau with spasms EEG: Hypsarrhythmia MRI: Normal	Unknown
16/ F 6 y9 mo	10 mo DEE	Focal tonic seizures, tonic-clonic seizures, FIAS Specific learning difficulties EEG: 15 mo-normal; 21 mo-occipital ictal rhythm; 22 mo-occipital IEDs; 4 y-normal MRI: Normal	Unknown

Abbreviations: BS, burst suppression; DEE, developmental and epileptic encephalopathy; EIMFS, epilepsy of infancy with migrating focal seizures; EME, early myoclonic encephalopathy; FBTC, focal to bilateral tonic-clonic seizure; FIAS, focal impaired awareness seizure; GDD, global developmental delay; GSW, generalized spike-wave; ID, intellectual disability; IEDs, interictal epileptiform discharges; MFDs, multifocal discharges; NCSE, nonconvulsive status epilepticus; PSW, polyspike-wave.

[a]previously published variant.

[b]ACMG classification.

[c]Novel variant.

that patients with infantile DEEs may have been missed if they had not come to the attention of the mainstream medical profession or are cared for solely by a general practitioner, especially in the remote areas of Tasmania. Also, our combined clinical and research genetic approach resulted in a very high yield.

A weakness of our study is the small sample size; thus, while our global estimates are robust, we cannot provide estimates of the frequency of individual syndromes or genes. Indeed, based on established estimates of the incidence of Dravet syndrome, one to two cases of Dravet syndrome might have been expected in our cohort.[19] The lack of Dravet cases in our cohort is most likely because they will not have satisfied inclusion criteria. It is likely that their EEG is normal in the first 2 years of life, seizures

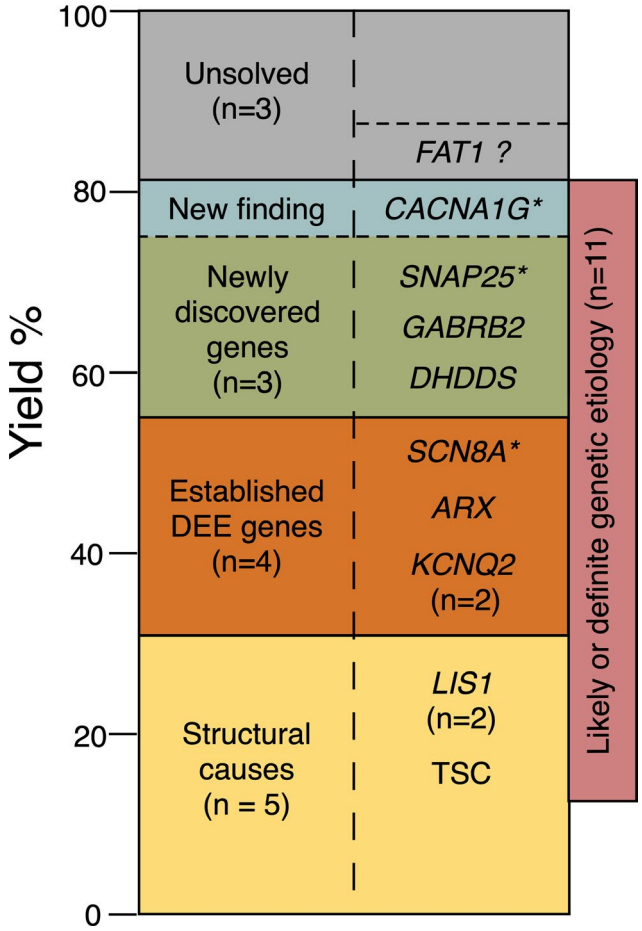

FIGURE 1 Yield of etiological diagnosis in 16 epidemiologically ascertained cases of Developmental and Epileptic Encephalopathy. Three of the "structural" cases had a definite or likely genetic etiology. *De novo status not confirmed

may be infrequent in infancy and always associated with fever (therefore diagnosed as febrile seizures), and developmental decline may not yet be apparent.[20] Whole genome sequencing studies may reveal pathogenic variants not identified by WES.

Our hypothesis-free, intensive, multistage approach to genetic testing identified pathogenic or likely pathogenic variants in a number of DEE genes. Our findings directly informed diagnosis, treatment, and prognostic planning for these infants and enabled accurate reproductive counseling for their parents.

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CONFLICTS OF INTEREST

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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