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ORIGINAL ARTICLE

KCNQ2 neonatal epilepsy: Impact of prompt diagnosis and treatment, and early predictors of outcome severity

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Abstract

Objective: To determine whether prompt genetic diagnosis in children with KCNQ2 neonatal epilepsy enabling targeted therapy is associated with improved outcomes, and identify early predictors of developmental outcomes.

Methods: Thirty-seven children with KCNQ2 neonatal epilepsy were recruited from five pediatric centers. We reviewed demographic, clinical, EEG, and genetic data. We determined differences in outcomes between individuals with prompt (greater than 30 days from seizure onset) and later genetic diagnosis, and we identified neonatal factors associated with developmental outcome.

Results: Baseline characteristics were similar between children with prompt ($n = 6$, median age at genetic diagnosis 15 days) and later ($n = 31$, median age 309 days, $p < .05$) diagnosis. All with prompt diagnosis received sodium channel blocking (SCB) anti-seizure medication (ASM) in the neonatal period compared with 15/31 (48%) in the later diagnosis group. Children with prompt diagnosis had higher rates of seizure freedom at age 12 months than those with later diagnosis (6/6 [100%] vs. 17/31 [54%]; p .049], and lower number of emergency department representations (median 0 vs. 2), and hospital readmissions (median 0 vs. 1). Factors in the neonatal period associated with abnormal developmental outcome included neurological abnormalities (e.g., abnormal tone) and markedly abnormal neonatal EEG background (11/11 [100%] with markedly abnormal EEG vs. 11/24 [46%] with normal to moderately abnormal EEG).

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For affiliations refer to page 959.

Significance: Prompt genetic diagnosis was associated with targeted therapy, resulting in improved seizure control and reduced hospital representation. Clinical features present in the neonate assist in predicting outcome severity, which is critically important in counselling families receiving a KCNQ2 diagnosis soon after seizure onset.

Plain Language Summary: In *KCNQ2* neonatal epilepsy, sodium channel blocking antiseizure medicines are recommended, but the benefits of starting treatment early have been uncertain. Our findings show that prompt genetic diagnosis enabled early targeted treatment, with potential to improve outcomes. Specifically, prompt genetic diagnosis was associated with improved seizure control and reduced hospital visits compared with delayed diagnosis. However, a prospective, long-term study is needed to determine whether early treatment also improves developmental outcomes. Predicting outcome severity in newborns remains challenging, although abnormal neurological examination and markedly abnormal EEG in the newborn period were linked to abnormal developmental outcomes.

KEYWORDS

KCNQ2, neonatal epilepsy, outcome, prompt genetic diagnosis, sodium channel blocking antiseizure medication

1 | INTRODUCTION

KCNQ2, encoding the voltage-gated potassium channel $K_v7.2$, is one of the most common genetic causes of neonatal epilepsy.[1] *KCNQ2* neonatal epilepsies range in severity from self-limited (familial) neonatal epilepsy (SeLNE) to developmental and epileptic encephalopathy (DEE), with developmental outcomes ranging from normal to profound impairment.[2–5] At present, outcome severity can be challenging to predict in the neonatal period. We therefore need a deeper understanding of factors that determine outcome severity to critically inform prognostic and genetic counseling.

Rapid (weeks, typically 2–3) and ultrarapid (days, typically 3–5) genomic testing is increasingly used in the neonatal intensive care unit.[6–9] Genomic testing has a high yield in neonates with epilepsy, and diagnosis frequently impacts management.[10,11] Diagnosis of *KCNQ2* neonatal epilepsy enables implementation of targeted treatments with sodium channel blocking (SCB) antiseizure medication (ASM), which can improve seizure control.[12] While there are case reports of favorable outcomes with prompt genetic diagnosis and implementation of SCB ASM, it is not clear whether this improves the ongoing risk of seizures, developmental, and other health-related outcomes.[4,12–14]

In this study, we aimed to determine whether prompt genetic diagnosis in infants with *KCNQ2* neonatal epilepsy, enabling early administration of targeted therapy, is associated with improved outcomes, and to identify early predictors of developmental outcomes.

Key points

- Sodium channel blocking antiseizure medication (SCB ASM) is indicated in *KCNQ2* neonatal epilepsy, but the benefit of prompt commencement is not clear.
- Prompt *KCNQ2* diagnosis and SCB ASM treatment improved seizure control and reduced hospital representation compared with delayed diagnosis.
- A prospective, longitudinal study will be required to determine if prompt diagnosis and treatment with SCB ASM improve development.
- Predicting outcome severity in the neonatal period can be difficult in *KCNQ2* neonatal epilepsy.
- Abnormal neurologic examination and markedly abnormal EEG in the neonatal period were associated with abnormal developmental outcome.

2 | METHODS

We undertook a retrospective study of children with *KCNQ2* neonatal epilepsy at five Australian tertiary pediatric centers involved in the Australian Genomics Acute Care study of ultrarapid trio genomic sequencing (tGS).[6,8] Patients with prompt diagnosis after seizure onset at the participating centers were identified from the Acute Care Genomics study database, while those diagnosed at any time via alternative testing pathways were identified through research and clinical databases at each center. Patients with later diagnosis were an older cohort, some being born prior to genetic testing being routine in clinical practice and others at a time where genetic testing was available but often took many months; these patients had a range of genomic technologies performed (e.g., gene panel, exome sequencing) as singleton or trio.

We included patients with a pathogenic/likely pathogenic *KCNQ2* variant, onset of seizures in the neonatal period, and available seizure and developmental data to at least age one year.[15] We excluded children with dual diagnoses or *KCNQ2*-containing chromosome 20q deletions (due to possible influence of other genes on phenotypes and/or outcomes), and those with *KCNQ2* variants known to result in gain-of-function (as gain-of-function variants have a different presentation and treatment implications to variants that cause KCNQ2 neonatal epilepsy).

Medical records were reviewed for demographic, genetic findings (variant, age at molecular diagnosis), clinical features (including seizure onset age and semiology, ASM use, neurological findings, and developmental progress), and details of hospital use (emergency department presentations, hospital admissions). Neonatal EEGs were reviewed for background abnormalities and interictal epileptiform discharges (IEDs). EEG background was classified according to the neonatal EEG background classification described by Shellhaas et al.[16] (normal vs. mildly, moderately, or markedly abnormal). With this classification, markedly abnormal EEG backgrounds include burst-suppression patterns, moderately abnormal backgrounds were discontinuous (but not burst suppression) and had a paucity of background features and reduced state differentiation, and mildly abnormal backgrounds were those with excessive discontinuity or asynchrony in quiet sleep but not other states. Frequency of IEDs was categorized as nil compared with 0%–25%, 25%–50%, or >50% of the whole EEG recording (typically approximately one-hour recording).

Epilepsy syndromes were determined based on the ILAE classification, with individuals assigned to SeLNE or *KCNQ2*-DEE syndromes.[4] Individuals who fit criteria for SeLNE other than having a more abnormal EEG background than is characteristic for this syndrome (i.e., at least moderately abnormal EEG background) were assigned to an 'intermediate' epilepsy syndrome category.

Developmental outcomes were categorized as normal, mild-moderately abnormal, or severe-profoundly abnormal, at age 12 months, and at the most recent review, based on a developmental quotient inferred from motor and language developmental milestones attained. We considered DQ >70 to be normal, DQ 35–69 to be mild-moderately abnormal, and DQ <35 severe-profoundly abnormal.

Medical literature and the ClinVar database were searched to identify whether each individual's variant had been previously reported, and the associated phenotype in previously reported individuals.[17]

We determined differences in health resource use in the first year of life and developmental and epilepsy outcomes at age 12 months between children with prompt (defined as <30 days from seizure onset) and later (>30 days from seizure onset) genetic diagnosis. We identified clinical, EEG, and genetic factors in the neonatal period associated with developmental outcome (normal vs. abnormal) at the last review.

Chi-square test and Fisher's exact test were used to determine differences between groups for categorical variables, and the Mann–Whitney *U* test was used to compare median values. We corrected for multiple comparisons by using the Benjamini–Hochberg procedure, controlling the false discovery rate at 5%. We then used a heat map to represent neonatal factors associated with developmental outcomes (categorical variables) as participant numbers were too small to conduct a multivariate analysis.

3 | RESULTS

3.1 | Cohort

We identified 49 children with *KCNQ2* epilepsy. Of these, 12 were excluded for the following reasons: presumed *KCNQ2* epilepsy based on being affected relatives of other individuals with confirmed pathogenic *KCNQ2* variants, but not tested themselves (4), postneonatal seizure onset and/or known gain-of-function mutation (5), 20q deletion (1), dual genetic diagnosis (1), and inadequate data (1).

Thirty-seven children (17 [45%] male) were included in this study (Table 1). Children were a median of 3 days (interquartile range [IQR] 1–4 days) at seizure onset and were followed for a median of 3.8 years (IQR 1.3–7 years). *KCNQ2* variants were missense in 29 (78%) and protein truncating in 8 (21%). Eleven (27%) had a family history of neonatal or infantile epilepsy (3 probands had confirmed *KCNQ2* variants in affected family members and family members were not tested for 8 probands).

TABLE 1 Phenotypic and genetic data of 37 children with *KCNQ2* neonatal epilepsy.

	Cohort, $N=37$	Prompt diagnosis, $N=6$	Later diagnosis, $N=31$	p Value
Demographics				
Family history neonatal/infantile epilepsy	11 (27%)	0	11 (35%)	0.08
SeLFNE phenotype (family history and normal EEG)	4 (10%)	0	4 (13%)	
Genetic data				
Variant type				
Missense	29 (78%)	5 (83%)	24 (64%)	0.74
Nonsense/frameshift/splice site	8 (21%)	1 (16%)	7 (22%)	
Variant inheritance				
De novo	22 (59%)	6 (100%)	16 (51%)	
Inherited	3 (8%)	0	3 (9%)	
Unknown (but +ve FHx)	8 (21%)	0	8 (25%)	
Unknown (no FHx)	4 (10%)	0	4 (12%)	
Baseline neonatal data				
Age seizure onset (days), Median (IQR)	3 (1–4)	1 (1–2)	3 (1–4.5)	0.87
No. of seizure days in first month ($n=35$)				
<7	17 (45%)	1 (16%)	16 (51%)	0.17
>7	18 (48%)	5 (83%)	13 (41%)	
No. of >hourly seizure days in first month ($n=23$)				
<7	19 (51%)	5 (83%)	14 (45%)	1.0
>7	4 (10%)	0	4 (12%)	
EEG background ($n=35$)				
Normal	7 (18%)	0	7 (22%)	0.08
Mildly abnormal	9 (24%)	2 (33%)	7 (22%)	
Moderately abnormal	8 (21%)	3 (50%)	5 (16%)	
Markedly abnormal	11 (29%)	0	11 (35%)	
EEG IEDS ($n=29$)				
Nil	6 (16%)	0	6 (19%)	0.67
<50%	10 (27%)	2 (33%)	8 (25%)	
>50%	13 (35%)	3 (50%)	10 (32%)	
Neurologic state				
Any abnormality	21 (56%)	5 (83%)	16 (51%)	0.15
Visual attention not appropriate	7 (18%)	1 (16%)	6 (19%)	0.87
Neurologic examination abnormal	14 (37%)	2 (33%)	12 (38%)	0.80
Supplemental feeding required	18 (48%)	5 (83%)	13 (41%)	0.06
Intubation required	6 (16%)	2 (33%)	4 (12%)	0.21

Abbreviations: FHx, family history; IEDs, interictal epileptiform discharges; IQR, interquartile range; No., number; SeLFNE, self-limited familial neonatal epilepsy.

3.2 | Prompt vs. later genetic diagnosis

Genetic diagnosis was prompt in six children (16%) (median 15 days, IQR 13.5–15 days) and later in 31 (84%) (median 10 months, IQR 4–55 months) (Table 2). Baseline characteristics (Table 1) were similar between children with prompt and later diagnosis, but last review was more recent in the prompt (median 16 months) compared with the later group (median 50 months). At presentation, the EEG background in the later diagnosis group ranged from normal to markedly abnormal, whereas those in the prompt diagnosis group had a mildly or moderately

TABLE 2 Intervention and outcome data of 37 children with *KCNQ2* neonatal epilepsy.

	Cohort, $N=37$	Prompt diagnosis, $N=6$	Nonprompt diagnosis, $N=31$	p Value (unadjusted)	p Value (adjusted for multiple comparisons)
Intervention data					
Age at genetic diagnosis (days), median (IQR)	233 (54–1133)	15 (13.5–15)	309 (131–1674)	**<0.001**	**0.007**
SCB use ($n=30$)					
Given SCB in neonatal period	21 (56%)	6 (100%)	15 (48%)	**0.004**	**0.017**
Given SCB b/w age 1–12 months	6 (16%)	0	6 (19%)		
No SCB in first year	10 (27%)	0	10[a] (32%)		
No SCB used ever	7 (18%)	0	7 (22%)		
Age at first SCB use (days), median (IQR)	14 (9–78)	11 (7–15)	16 (10–122)	0.23	0.25
PB used in neonatal period	29 (78%)	6 (100%)	23 (74%)		
Outcome data at age 12 months					
Seizures					
Became seizure-free without SCB	7 (18%)	0	7 (22%)		
Age first seizure-free (days), median (IQR)	42 (13–180)	26 (22–28)	60 (12.5–255)	0.207	0.245
Seizure recurrence (after initial 3 m seizure-free)	9 (24%)	2 (33%)	9 (29%)		
Seizure-free at age 12 m	23 (62%)	6 (100%)	17 (54%)	**0.03**	**0.049**
No. of seizures in first year					
<50	19 (51%)	3 (50%)	16 (51%)		
50–200	4 (10%)	3 (50%)	1 (3%)		
>200	11 (29%)	0	11 (35%)	**0.006**	**0.018**
ASM					
Total number ASM, median (range)	4 (1–8)	5.5 (3 to 7)	4 (1–8)	0.20	0.245
Hospital resource use					
Duration of neonatal admission (days), median (IQR)	21 (10–32)	25 (21.5–34)	19.5 (9–32)	0.26	0.26
No. of re-presentations to ED	2 (0–5)	0 (0–2)[b]	2 (0–5)	**0.007**	**0.018**
No. of readmissions ($n=21$)	1 (0–2)	0 (0–1)[b]	1 (0–4)	**0.022**	**0.048**
Duration of readmissions (days), median (IQR)	7 (2–31)	0 (0–2)	7 (2–31)	**<0.001**	**0.007**
Outcomes at most recent review					
Development					
Normal	15 (40%)	2 (33%)	13 (45%)	**0.03**	**0.049**
Mild-mod DD	8 (21%)	4 (66%)	4 (12%)		
Sev-prof DD	14 (37%)	0	14 (45%)		
Seizures ($n=34$)					
Ongoing seizures	14 (37%)	0	14 (45%)	0.12	0.173
Seizure-free	20 (54%)	6 (100%)	14 (45%)		

Note: Bolded values indicate statistically significant difference between normal and abnormal development groups.

Abbreviations: ASM, antiseizure medication; DD, developmental delay; ED, emergency department; IQR, interquartile range; No., number; PB, phenobarbitone; SCB, sodium channel blocking ASM.

[a]7/10 were seizure-free at 12 months without using SCB.

[b]One participant had two ED presentations and one admission, which were unrelated to seizures (due to COVID-19 infection and another viral illness).

abnormal EEG background. Notably 3/6 (50%) neonates in the prompt group had IEDs occupying >50% of the EEG at presentation, compared with 10/31 (32%) in the later group.

SCB ASMs (carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenytoin) were used as a regular medication in the first year of life in 27 infants, with 21 receiving them during the neonatal period. The proportion of infants administered regular SCB ASM in the neonatal period was higher in infants with prompt diagnosis [6/6 (100%) vs. 15/31 (48%)]. The number of other ASMs (e.g., phenobarbitone, levetiracetam, but also including vitamins such as pyridoxine) used before receiving a regular SCB ASM was similar between the two groups, with a median of 4 (range 2–7) in the prompt diagnosis group and a median of 3 (range 1–6) in the later diagnosis group.

All children had focal seizures at presentation. Those with prompt diagnosis had lower seizure burden in the first year of life compared with those with later diagnosis [0/6 (0%) vs. 11/31 (35%), $p = 0.018$]. There were also higher rates of seizure freedom at age 12 months in the prompt diagnosis group [6/6 (100%) vs. 17/31 (54%), $p = 0.049$]. Of the 31 children with a later diagnosis, three developed epileptic spasms in infancy; two of whom had not received SCB ASM prior to spasm onset. None in the prompt diagnosis group developed epileptic spasms.

At age 12 months, the number of ASMs being taken was no different between the promptly diagnosed infants (median 1, range 0–2) and those diagnosed later (median 1, range 0–6) ($p = .245$). Three of the six promptly diagnosed children weaned SCB ASM after age 12 months; seizures recurred in two at ages 12 and 13 months and were controlled with SCB recommencement.

The duration of the initial hospital admission was comparable between the two groups (later diagnosis median 19.5 days vs. prompt median 25 days). In contrast, patients with later diagnosis had more emergency department representations (median 2 vs. 0, $p = .018$), hospital readmissions (median 1 vs. 0, $p = .022$), and longer duration of hospital readmissions (median 7 vs. 0 days, $p = .007$) than those with prompt diagnosis.

No patient with a prompt diagnosis had severe-profound developmental delay at last review, compared with 13/31 (42%) individuals with later diagnosis ($p = .049$).

Four patients had SeLNE phenotypes at presentation (i.e., positive family history, normal neonatal EEG, normal neurologic examination), all in the later diagnosis group. We repeated analyses with these four patients excluded (later diagnosis group $n = 27$) and saw no difference in all the results.

We also undertook a subanalysis of the 15 infants in the later diagnosis group who had early use of SCB ASM. At age 12 months, 10/15 (67%) were seizure-free. Following the initial admission, these infants had 0–1 days of hospital readmission in the first year of life.

3.3 | Epilepsy syndrome and molecular-syndrome classification

Epilepsy syndromes were not always able to be definitively diagnosed in the neonatal period. On review of all available data, 14 children had SeLNE (1 prompt, 13 later), 20 had DEE (3 prompt, 17 later), and 3 had an intermediate phenotype (2 prompt, 1 later). There was no difference in epilepsy syndromes between those with prompt or later diagnosis ($p = .39$).

DEE or intermediate phenotypes were seen in 21/29 (72%) of individuals with missense variants, and 2/8 (25%) with protein-truncating variants. Missense variant location was intracellular (IC) in 7/29 individuals, extracellular (EC) in 2/29, and transmembrane (TM) in 20/29 (S3 in 1, S4 in 4, S5 in 4, pore-forming loop in 6, and S6 in 5). We did not see a difference between missense variant location and epilepsy syndrome (DEE = 3 IC, 1 EC, 11 TM [including S3 in 1], intermediate = 1 IC, 2 TM, and SeLNE = 3 IC, 1 EC, 7 TM [including pore-forming loop in 3, and S6 in 2]). Similarly, for the 8 individuals with protein-truncating variants, we did not see a difference in epilepsy syndrome for truncations in the C-terminal segments compared with those occurring more proximally (i.e., N-terminal and S1-S6 regions) (DEE = 2 C-terminal, 2 proximal, intermediate = 1 C-terminal, SeLNE = 2 C-terminal, 1 proximal).

Variants in 30 patients were previously reported in the medical literature or ClinVar database; 4 variants have been previously associated with both SeLNE and DEE phenotypes, and the remainder with only one of SeLNE or DEE. Eleven individuals with SeLNE in our cohort had previously reported variants; seven patients had a variant previously associated with DEE (and two had variants associated with both DEE and SeLNE). One individual with DEE had a variant previously associated with SeLNE (and two had variants associated with both SeLNE and DEE).

The discrepancy between the previously reported epilepsy syndrome for a particular variant and that reported in patients in our cohort with the same variant did not vary by prompt or later diagnosis ($p = .50$). Of 5 patients in our cohort with prompt diagnosis and variants that had previously been associated with DEE, 3 had DEE, 1 had an intermediate phenotype, and 1 had SeLNE. Of 19 patients with later diagnosis and variants previously reported in people with DEE, 11 had DEE, 1 had an intermediate phenotype, and 7 had SeLNE.

3.4 | Early predictors of developmental outcome

At the most recent review, 15 (41%) patients had normal development, and 22 (59%) had abnormal development (8 mild-moderate, 14 severe-profound).

Only children with abnormal developmental outcomes had a markedly abnormal neonatal EEG background (11/22 (50%) vs. 0/15 (0%), p 0.027) (Figure 1, Table 3). However, the neonatal EEG background was moderately abnormal in 2/15 (13%) with normal developmental outcomes. Eleven of the 13 (85%) patients with IEDs occupying >50% of their neonatal EEG had abnormal developmental outcomes. No patient with severe-profound developmental impairment had a normal neonatal EEG, although one child with a normal EEG had mild–moderate developmental impairment at last review.

A heat map displaying the factors associated with developmental outcomes in each child (Figure 1) highlights that some aspects of the neurologic status in the neonatal period were also associated with normal versus abnormal developmental outcomes. All individuals with normal developmental outcome, including the two with moderately abnormal neonatal EEG background, had normal visual attention and neurologic examination in the neonatal period, whereas 14/22 (64%) with abnormal developmental outcomes had either or both abnormal visual attention or neurologic examination. In contrast, the need for endotracheal intubation or supplemental feeding (i.e., nasogastric tube) were not associated with developmental outcome.

We saw no association between developmental outcome and age at genetic diagnosis, variant type (missense vs. truncation), number of days with seizures in the neonatal period (categorized as < or >7 days), or age at first

Development at most recent assessment		Patient ID	EEG features in the neonatal period		Clinical features in the neonatal period			
			Neonatal EEG	EEG IEDS	Intubation/ ventilation	Supplemental feeding	Visual attention	Neuro exam
Normal		1	Mod abnormal	>50%	Yes	Yes	Normal	Normal
		8	Mild abnormal	<50%	No	Yes	Normal	Normal
		15	Mild abnormal	<50%	No	No	Normal	Normal
		20	Mild abnormal	<50%	No	No		
		25	Normal	0	No		Normal	Normal
		26	Normal	0	No	No	Normal	Normal
		27	Mod abnormal	>50%	No	Yes	Normal	Normal
		32	Normal	0	No	No	Normal	Normal
		33			No	No	Normal	Normal
		35	Normal	0	No	No	Normal	Normal
		37			Yes	Yes	Normal	Normal
		39	Normal		No	Yes	Normal	Normal
		42	Mild abnormal	<50%	No	No	Normal	Normal
		52	Normal	0	No	No		Normal
		53	Mild abnormal	<50%	No	No	Normal	Normal
Abnormal	Mild-moderate	2	Mild abnormal	>50%	No	Yes	Abnormal	Abnormal
		3	Mild abnormal	<50%	No	Yes	Normal	Abnormal
		4	Mod abnormal	<50%	No	Yes		Normal
		17	Normal	0	No	No	Normal	
		38	Mod abnormal	>50%	No	No	Normal	Normal
		46	Markedly abnormal		No	No		Normal
		10	Mild abnormal	<50%	No	Yes	Normal	Abnormal
		12	Mod abnormal	>50%	No	Yes	Normal	Abnormal
	Severe-profound	9	Markedly abnormal	>50%		Yes	Abnormal	Abnormal
		11	Mild abnormal	<50%				
		21	Markedly abnormal	>50%	No	No		
		23	Mod abnormal			Yes		
		28	Markedly abnormal	>50%	No	No	Abnormal	Abnormal
		30	Mod abnormal	>50%	No	No	Normal	Normal
		47	Markedly abnormal	>50%	Yes	Yes		Abnormal
		48	Markedly abnormal		No	Yes		Abnormal
		50	Markedly abnormal	>50%	No	Yes	Normal	Abnormal
		51	Mod abnormal		No	No		Abnormal
		16	Markedly abnormal	>50%	Yes	Yes	Abnormal	Abnormal
		18	Markedly abnormal	<50%	No	Yes	Abnormal	Abnormal
		36	Markedly abnormal	>50%	Yes	Yes	Abnormal	Abnormal
		49	Markedly abnormal		Yes	No	Abnormal	Abnormal

FIGURE 1 Heat map showing electroclinical factors in the neonatal period which were associated with developmental outcome. Shading of cells: Light gray = normal (or not more than mildly abnormal for electrical features), orange = abnormal, dark gray = missing data.

TABLE 3 Factors at initial presentation associated with developmental outcomes in 37 children with *KCNQ2* neonatal epilepsy.

	Normal development, $N=15$	Abnormal development, $N=22$	p Value, normal vs. impaired (unadjusted)	p Value, normal vs. impaired (adjusted)
Genetic data				
Variant type				
Missense	11 (73%)	18 (81%)	0.66	0.85
Nonsense/frameshift/splice site	4 (26%)	4 (18%)		
Variant inheritance				
De novo	8 (53%)	14 (63%)	0.77	0.85
Inherited	2 (13%)	1 (4%)		
Unknown (but positive FHx)	4 (26%)	4 (18%)		
Unknown (no FHx)	1 (6%)	3 (13%)		
Neonatal data				
Age seizure onset (days), median (IQR)	3 (2–4)	2.5 (1–4)	0.56	0.85
No of seizure days in first month ($n=35$)				
<7	11 (73%)	6 (27%)	**0.01**	**0.027**
>7	4 (26%)	14 (63%)		
No of >hourly seizure days in first month ($n=23$)				
<13	9 (60%)	12 (54%)	0.23	0.41
>13	0	2 (9%)		
EEG background ($n=35$)				
Normal	6 (40%)	1 (4%)	**0.005**	**0.027**
Mild abnormal	5 (33%)	4 (18%)		
Mod abnormal	2 (13%)	6 (27%)		
Marked abnormal	0	11 (50%)		
EEG IEDS ($n=29$)				
Nil	5 (33%)	1 (4%)	**0.01**	**0.027**
<50%	5 (33%)	5 (22%)		
>50%	2 (13%)	11 (50%)		
Neurologic state				
Any abnormality	5 (33%)	16 (72%)	**0.01**	**0.027**
Visual attention not appropriate	0	7 (31%)	**0.006**	**0.027**
Neurologic examination abnormal	0	14 (63%)	**<0.001**	**0.016**
Supplemental feeding required	5 (33%)	13 (59%)	0.18	0.40
Intubation required	2 (13%)	4 (18%)	0.67	0.85
Intervention data				
Age at genetic diagnosis (days), med (IQR)	110 (50–309)	425 (131–1179)	0.20	0.40
SCB use ($n=30$)				
Given SCB in neonatal period	8 (53%)	12 (54%)	0.80	0.85
Age at first SCB use (days), median (IQR)	14 (8.5–77)	18 (9.5–61)	0.90	0.90
Phenobarbitone used in neonatal period ($n=29$)	12 (80%)	17 (77%)	0.80	0.85

Note: Bolded values indicate statistically significant difference between normal and abnormal development groups.

Abbreviations: FHx, family history; IEDs, interictal epileptiform discharges; IQR, interquartile range; SCB, sodium channel blocking antiseizure medication.

SCB use. Family history of neonatal seizures was associated with a range of developmental outcomes (normal 6, mild–moderately abnormal 2, severe-profoundly abnormal 3). Genetic testing of parents and/or other affected family members was only performed in 3/11 individuals with a positive family history. This means we are not able to determine whether *KCNQ2* was the cause of the neonatal seizures in relatives of the probands in all these families, nor whether any affected parents were mosaic for the variant seen in germline form in the proband.

We did not observe differences in neonatal neurologic examination parameters between patients with mild-moderate and severe-profound developmental impairment.

4 | DISCUSSION

Our study demonstrates that prompt genetic diagnosis in children with *KCNQ2* neonatal epilepsy enables early use of SCB ASM, which may improve outcomes. Infants with prompt diagnosis had lower hospital resource use in the first year of life and higher rates of seizure freedom at age 12 months, compared with infants who received a later genetic diagnosis. These findings highlight the benefits of rapid genetic diagnosis, which allows management to be targeted with the potential to improve outcomes. We also identify electroclinical features in the newborn period that assist in predicting normal versus abnormal developmental outcome, which is critical in counseling families receiving a *KCNQ2* epilepsy diagnosis early in life.

The positive impact of SCB ASM in improving seizure control in *KCNQ2* neonatal epilepsy is well-established, and their preferential use over other ASM is recommended.[3,4,12] However, while SCB use has been reported to shorten the duration of NICU admission, the magnitude of benefit on seizures, need for other ASM, developmental outcomes and hospital resource use beyond the initial neonatal hospitalization are incompletely understood.[18] Further, while rapid genetic diagnosis is increasingly possible, the longer-term impacts of implementing prompt, optimal therapy were not clear.

Overall, prompt diagnosis (and implementation of SCB therapy) was associated with earlier seizure control and higher rates of seizure freedom compared with later diagnosis. Seizures were controlled in all six patients at age 12 months compared with approximately half of individuals with later diagnosis. Our study also demonstrated that seizure freedom was possible with SCB monotherapy in all the promptly diagnosed patients, meaning that prompt diagnosis may enable early cessation of (or lack of need for) other ASM.

Further, we demonstrated reduced health system resource use, with no seizure-related re-presentations to hospital in the prompt diagnosis group in the first year of life. Emergency department presentations and hospital readmissions are not only extremely stressful for families, but they also carry important economic costs to the health system. The average cost of hospital admission in Australia is AU$2884/day, and the cost of tGS, whether ultrarapid (turn-around-time [TAT] 3–5 days) or rapid (TAT 3 weeks), is AU$15 000 and AU$8900 respectively.[19–21] A reduction in days of readmission by approximately 5 and 3 days per patient respectively would therefore recoup the costs of genomic testing. This was achieved in the first year of life, with a median of zero readmission days in those with prompt diagnosis compared with seven days in the later diagnosis group. We did not quantify additional direct costs, such as diagnostic investigations avoided or the cost of ASM prescriptions. Further cost-savings relating to prompt diagnosis have not been analyzed, but are also important to consider, including indirect costs to families, such as lost work productivity.

We could not determine the impact of prompt genetic diagnosis on development, as the high phenotypic variability and our relatively crude measures of developmental outcome meant that it was not possible to determine whether the outcome deviated from that expected for any individual child. Nevertheless, we saw no severe-profoundly impaired children in the prompt diagnosis group, despite their clinical features at onset and duration of initial hospitalization being similar to the later diagnosis group. This absence of severe-profoundly impaired children cannot be attributed to the assumption that the prompt diagnosis group had SeLNE; ultimately, only one met criteria for this syndrome. Of the remaining five, none had inherited variants or a family history of epilepsy, none had a normal interictal EEG at baseline, 3/6 had IEDs occupying >50% of neonatal EEG, 2/6 had an abnormal neonatal neurologic examination, and 2/6 had seizure recurrence after SCB were weaned after infancy (indicating their epilepsy had not resolved as would be expected in SeLNE). The prompt and later diagnosis groups were also similar in the duration of initial admission, suggesting the groups were not dissimilar in terms of severity in the neonatal period. However, none with a prompt diagnosis had a markedly abnormal neonatal interictal EEG, so our prompt group is likely to have been missing infants at the most severe end of the *KCNQ2* DEE spectrum.

When considering early predictors of outcome, we did not see a higher rate of early use of SCB ASM in those with normal compared with abnormal developmental outcomes. This does not imply lack of benefit with prompt treatment, however. The categorization of normal versus

abnormal development is likely too crude, and looking at this variable in isolation from related factors like total number of ASM and baseline severity may mask benefit. Further study, with quantitative and serial measurement of development in babies with *KCNQ2* epilepsies, is needed to understand the impact of prompt diagnosis and early use of SCB ASM monotherapy on developmental outcomes. Our observation of abnormal developmental outcomes in some promptly diagnosed and treated individuals is consistent with the knowledge that *KCNQ2* neonatal epilepsies have a developmental encephalopathy component that is independent of the epileptic encephalopathy. These observations reinforce the need for better treatments, ideally targeted at the underlying cause.[13]

Availability of ultrarapid and rapid genomic sequencing remains limited around the world, which is a limitation to the generalizability of our findings. However, given recent updates to the ILAE neonatal seizure consensus guidelines,[22] which now state that SCB ASM may be preferred for neonates with presumed channelopathy (presumption based on one or more of a number of clinical features, including no other identified etiology for seizures), SCB ASM will likely be utilized earlier in infants with *KCNQ2*-epilepsy, prior to genetic confirmation. Early use of SCB ASM, rather than the genetic diagnosis itself, is likely the main driver of favorable seizure outcome (although other contributory factors guided by the genetic diagnosis are possible, given that in our cohort, all 6 promptly diagnosed infants were seizure-free at age 12 months compared with only 10/15 infants with later diagnosis but early SCB ASM use). However, we believe it likely that the genetic diagnosis will yield additional benefit, such as providing confidence in early cessation of other ASM and therefore minimizing overall ASM burden.

The spectrum of severity of *KCNQ2* neonatal epilepsy is broad, and prediction of outcome severity soon after seizure onset can be difficult. Some factors have been reported to predict outcomes, such as a burst-suppression pattern on EEG which is associated with poor outcomes, and a family history of *KCNQ2*-SeLNE and variant location (S2-3 domain more likely SeLNE, S5-6 domain more likely DEE), which are associated with favorable outcomes.[4,23] De novo variants may be associated with both SeLNE and DEE.[3,24] However, these variant factors are incompletely predictive as, in our cohort, we saw children with de novo variants with normal outcomes and children with inherited variants whose outcomes were abnormal. Specific genetic variants may not be predictive, as variability in phenotypic severity has been reported for a number of recurrent variants, and discordance with the previously reported phenotype for a particular variant was observed in numerous individuals with recurrent variants in our cohort (e.g., SeLNE where variant previously associated with DEE).[25,26] Machine learning models trained on the genetic variant have to date had greater success with predicting benign versus pathogenic variants, than predicting normal versus abnormal outcome, with authors concluding that these tools are potentially useful in conjunction with phenotypic analysis, rather than in isolation.[27] With prompt diagnosis an increasing reality, more precise prognostication is critical for families, to guide appropriate medical management (e.g., around duration of ASM use, and likely need for therapies to maximize developmental outcomes), reproductive counseling, and to support parental wellbeing in the early months of life, as uncertainty is an important contributor to poor psychological health.[28]

The clinical features in the neonatal period that were most predictive of poor outcome were abnormalities of visual attention or neurologic examination. They were both highly specific, although not sensitive, as they occurred in only 31% and 63% of those with abnormal developmental outcomes, respectively. The need for intubation or supplemental feeding did not predict outcome. This may be because they were related to sedation from ASM or seizure characteristics (e.g., apnea with seizures), rather than solely the underlying severity of the disease.

Like others, we found that a markedly abnormal neonatal EEG was universally associated with abnormal developmental outcome.[29] However, we saw normal developmental outcomes in two infants with IEDs occupying >50% of the EEG and/or moderately abnormal EEG background, which, in the classification by Shellhaas et al. that we applied, encompassed features such as interburst intervals of up to 15 s, poor state differentiation and a paucity of background features.[16] We considered whether the EEG abnormalities in these infants could be explained by ASM use, as both received phenobarbitone and one a midazolam infusion in the neonatal period (although whether they were on these ASM at the time of their neonatal EEG was difficult to determine). However, while such ASM could explain background abnormalities, they do not explain the frequent IEDs. Both infants had normal visual attention and neurologic examination, which could potentially be reassuring factors in the context of prominent EEG abnormalities, although our numbers are too small to conclude this definitively. Overall, we found that normal, mildly and moderately abnormal EEG background did not consistently predict normal or abnormal outcome, nor did the proportion of EEG occupied by IEDs, although there was a higher likelihood of poor outcome with more severe EEG abnormalities.

Overall, our findings enable greater prediction of abnormal outcomes, rather than confidently identifying neonatal factors associated with normal outcomes. We did not identify any factors that clearly differentiated

mild-moderately abnormal developmental outcomes from severe-profoundly abnormal outcomes. Our study was limited in addressing this, by virtue of small cohort size, short follow-up duration, and lack of quantitative developmental data. Thus, there remains an urgent need for identification of more sensitive predictors of outcome, potentially through more detailed prospective study of a larger patient group with early molecular diagnosis.

We acknowledge that our study is limited by its small number of promptly diagnosed patients, retrospective nature, and the inability to control for variability in clinical practice. This may influence the available data (e.g., EEG acquisition methods varied, with variable duration of wake and sleep recordings, which could impact IED frequency), and impact clinical and health economic outcomes over and above the underlying severity of the disease. Notably, given the infants with a prompt diagnosis were born in more recent years (reflecting the availability of rapid and ultrarapid genomic testing), we did not see major differences in first- or second line ASM use (e.g., phenobarbitone use similar in the prompt and later diagnosis group) or supportive treatments used in the neonatal unit. This highlights that other major changes in neonatal practice over time are not likely to be determining the differences that we found between groups.

Our findings emphasize that prompt diagnosis of *KCNQ2* neonatal epilepsy and early implementation of SCB ASM can enable seizure freedom, typically with monotherapy, and reduce the need for hospital readmission in the first year of life. In addition to the health economic benefits, the clinical benefit to patients and families of prompt molecular diagnosis cannot be overestimated.

AUTHOR CONTRIBUTIONS

TJ, SEB, IES, ZS, KBH: study concept and design. All authors: acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content. TJ, SEB, IES, KBH, ZS: drafting of the manuscript. ZS, SL, KBH: obtained funding. ZS, KBH: study supervision.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Melbourne Health Human Research Ethics Committee as part of the Australian Genomics Health Alliance protocol: HREC/16/MH/251.

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