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Neonatal Non-Epileptic Myoclonus is a Prominent Clinical Feature of KCNQ2 Gain-of-Function Variants R201C and R201H

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Summary and Key Words:

Objective: To analyze whether *KCNQ2* R201C and R201H variants, which show atypical gain-of-function electrophysiological properties *in vitro*, have a distinct clinical presentation and outcome.

Methods: Ten children with heterozygous, *de novo KCNQ2* R201C or R201H variants were identified worldwide, using an IRB-approved *KCNQ2* patient registry and database. We reviewed medical records, and where possible, interviewed parents and treating physicians using a structured, detailed phenotype inventory focusing on the neonatal presentation and subsequent course.

Results: Nine patients had encephalopathy from birth and presented with prominent startle-like myoclonus, which could be triggered by sound or touch. In seven patients EEG was performed in the neonatal period and showed a burst-suppression pattern. However, myoclonus did not have an EEG correlate. In many patients the paroxysmal movements were misdiagnosed as seizures. Seven patients developed epileptic spasms in infancy. In all patients, EEG showed a slow background and multi-focal epileptiform discharges later in life. Other prominent features included respiratory dysfunction (perinatal respiratory failure and/or chronic hypoventilation), hypomyelination, reduced brain volume, and profound developmental delay. One patient had a later onset, and sequencing indicated that a low abundance (~15%) R201C variant had arisen by post-zygotic mosaicism.

Significance: Heterozygous *KCNQ2* R201C and R201H gain-of-function variants present with profound neonatal encephalopathy in the absence of neonatal seizures. Neonates present with non-epileptic myoclonus that is often misdiagnosed and treated as seizures. Prognosis is poor. This clinical presentation is distinct from the phenotype associated with loss-of-function variants, supporting the value of *in vitro* functional screening. These findings suggest that gain-of-function and loss-of-function variants need different targeted therapeutic approaches.

Key words: KCNQ2, neonatal seizures, myoclonus, epileptic encephalopathy, infantile spasms

Introduction:

Pathogenic variants in *KCNQ2*, a gene well-known to be involved in benign familial neonatal epilepsy (BFNE), have emerged as an important cause of neonatal onset epileptic encephalopathy (*KCNQ2* encephalopathy).[1-5] BFNE is characterized by seizure onset within the first days of life, seizure remission within months, a normal interictal EEG, normal development, but increased post-neonatal seizure risk.[2, 6] Patients with *KCNQ2* encephalopathy also present with frequent neonatal seizures, but their interictal EEG is severely abnormal and characterized by multifocal epileptiform abnormalities with random attenuations or a burst-suppression pattern, and they have moderate to profound developmental delay.[5, 7]

BFNE arises from *KCNQ2* alleles causing haploinsufficiency (including deletion of the entire gene) and from missense variants that exhibit partial loss-of-function *in vitro.*[8-10] Studies of several *KCNQ2* variants that cause *KCNQ2* encephalopathy reveal more extensive loss-of-function or a dominant negative effect.[11, 12] These studies suggest a potential direct relationship between the degree of loss-of-function and clinical severity.[11, 12] Recently, the

KCNQ2 missense variants R201C and R201H[5, 13] were shown to increase channel opening *in vitro*, a gain-of-function effect opposite to the loss-of-function produced by previous BFNE and *KCNQ2* encephalopathy variants.[14]

Given the distinctive molecular physiology of *KCNQ2* R201C and R201H *in vitro*, we investigated whether these variants result in a distinct phenotype. We report detailed clinical data on the neonatal presentation of 10 children heterozygous for *KCNQ2* R201C/H and describe a unique electro-clinical phenotype that includes neonatal encephalopathy *without* seizures, exaggerated startle response that is often misdiagnosed as seizures, burst-suppression EEG pattern at birth with evolution into multifocal epileptiform discharges, early hypoventilation and supplemental oxygen requirement, hypomyelination, and profound developmental delay with early mortality.

Methods:

We studied a cohort of patients with *de novo KCNQ2* R201C or R201H variants that were included in the Rational Intervention of KCNQ2 Epileptic Encephalopathy (RIKEE) database (http://www.RIKEE.org), a curated database aggregating published information and unpublished patient data since 2011 provided by physicians or families after parental informed consent. Based on the electroclinical features of a newly diagnosed newborn with a *de novo* R201C variant (patient A, Table 1), a detailed clinical questionnaire was sent to the referring physician of all identified patients, including the one previously published patient with a R201C variant (patient D in current study and patient B in Weckhuysen et al[5]). Data requested included information on neonatal neurologic exam, presence of paroxysmal events/seizures or abnormal movements in the neonatal period and later in life, whether seizures were EEG-confirmed, EEG findings in the neonatal period and during follow-up, anti-seizure drugs used, neuroimaging findings, other body systems' involvement, neurodevelopment, and mortality. The actual video-EEG recordings, when available, were reviewed by a neonatal neurophysiologist (MRC). For some patients, members of the investigative team spoke directly with the parent via conference call to better understand the early presentation and course. The respective *KCNQ2* variants were identified in different diagnostic or research laboratories, using targeted gene panels that included *KCNQ2* or single gene Sanger sequencing. All variants were proven to occur *de novo*. Parental consent was obtained to include patient videos.

Results:

Neurologic Presentation

Eight patients with heterozygous *de novo* R201C variants and two patients with heterozygous *de novo* R201H variants were identified (Table 1). The majority of infants were born at term after uncomplicated gestations and deliveries. Patient C had bradycardia prior to delivery via caesarian section. One child (patient H) was found to carry a post-zygotic mosaic variant; this patient had later symptom onset and is discussed below.

The remaining nine patients presented with encephalopathy at birth (milder in the R201H cases) and developed prominent, abnormal body movements within the first 2 days of age. The movements were characterized by high amplitude spontaneous myoclonic jerks that were triggered by touch and sound, suggesting an exaggerated startle response (video 1). These paroxysmal movements were clinically considered as epileptic seizures in eight patients and treated with anti-seizure medications without success. However, where available for review (patients A, D, G), neonatal video-EEGs demonstrated that the abnormal paroxysmal movements lacked EEG correlate and were consistent non-epileptic myoclonus.

EEG was performed in the neonatal period in seven infants, and in all of them it demonstrated an invariant burst-suppression pattern (Figure 1A). Neurologic exam was notable for diffuse hypotonia and marked hyperreflexia in eight patients. Brain MRI in five patients was obtained at ≤ 10 days of age and either was reported as normal (n = two) or showed mild reduced brain volume (n = three).

After one month of age, the EEG showed a pattern of multi-focal epileptiform discharges in all 10 infants (Figure 1B). Seven infants developed epileptic spasms at a median age of five months (range three to 24 months). All four infants who had neonatal EEG and developed epileptic spasms showed a burst-suppression pattern in the neonatal period. Brain MRI was obtained in eight infants between one and 24 months of age and revealed hypomyelination and reduced brain volume in six patients (Figure 2) and abnormal signal in the basal ganglia in one patient (F). Reduced brain volume became more evident on follow-up brain MRI. Patient A also had subependymal heterotopias (Figure 2). The patients had profound developmental delay without the achievement of discernable developmental motor milestones and were non-verbal. One patient (patient I) later in life (video 2)

developed severe choreoathetosis; however it is possible that similar movement disorders, including choreoathetosis and myoclonus-dystonia, occurred in some of the other patients. Four patients had early mortality ranging from 4.5 months to 6.3 years. The other six children are alive and currently between 19 months and five years of age.

One patient (patient H) did not have encephalopathy nor paroxysmal events as a newborn. She was noted to have only mild axial hypotonia, and by age one year could sit, crawl in a supine position and roll over independently, and, although showing some developmental delay, she could reach milestones not attained by the other nine patients. However, in the second year of life, developmental regression occurred coinciding with the onset of epileptic spasms despite aggressive physical therapy efforts. At age five years, she was non-verbal, non-ambulatory, but could smile and communicate pleasure to her family. Whole exome sequencing revealed a low abundance KCNQ2 c.601C>T variant in 16 of 81 reads, or 19.8% (95% confidence interval, 11.7% - 30.1%). The difference between the observed frequency and 50% (expected for heterozygosity) was highly significant ($P = 3.6 \times 10^{-8}$, Binomial exact test). [15] Consistent with whole exome sequencing results, when bidirectional Sanger seqeuncing was performed in parallel on the trio, the variant peak was estimated as 15-25% of the total at base 601.

Treatment

All patients were trialed on multiple medications (Table 1). Given the genetic mutation in *KCNQ2*, five patients were trialed on retigabine/ezogabine (European name/United States name) between 17 days and four years of age with little or no response. Patient A was slowly escalated to a dose of 7mg/kg every eight hours over a period of three weeks to a level of 1,600ng/mL. While on ezogabine, the EEG continued to have a pattern of severe encephalopathy and there was no clinical improvement in respiratory or neurological status. GGT became elevated to 404 U/L, although AST and ALT remained normal. Given the lack of response, ezogabine was discontinued. Patient G had clinical worsening on retigabine at six months of age with increased paroxysmal events, prolonged apneas, and severe sedation. Patient E had subjective improvement with increased wakefulness when on retigabine at four years of age. Three patients with epileptic spasms were treated with hormonal therapy (adrenocorticotropic hormone) with poor response (patients F, H, and J). In two of these patients, spasms reduced, although did not resolve, after starting vigabatrin.

All 10 infants were treated with vigabatrin early in life. In five patients, a noticeable reduction in either the exaggerated startle/myoclonic jerks (patients A and C) or a reduction in spasms (patients F, G, and H) was noted. Interestingly, patient A was treated with vigabatrin for control of exaggerated startle and jerking at four months of age and did not develop epileptic spasms.

Other System Involvement

Respiratory problems, including respiratory failure and recurrent aspiration pneumonia, were common among these patients (Table 1). In six patients (A-D, F, and G) there was respiratory failure and hypoventilation at birth and mechanical ventilation or oxygen supplementation was required. Patient A required invasive mechanical ventilation until two weeks of age and then required non-invasive positive pressure ventilation until two months of age due to hypoventilation and chronically elevated pCO_2, unresponsive to caffeine, theophylline, and aminophylline treatments. After discontinuation of mechanical ventilation, patient A exhibited excessive sighing and atypical periodic breathing associated with intermittent hypoxia (Figure 3). Congenital central hypoventilation syndrome (CCHS) was considered, although patients with CCHS usually have a normal EEG. However, Sanger sequencing revealed no variants in *PHOX2b* nor did whole exome sequencing reveal a mutation in other genes linked to CCHS.[16] Chronic compensated respiratory acidosis with an irregular breathing pattern was seen in patient G who received supplemental oxygen until six months of age. Patient D also had chronically elevated pCO_2, received supplemental oxygen, and died suddenly, overnight, without preceding infection. Patients E, I, and J had recurrent aspiration pneumonias and often required admission to the intensive care unit for respiratory insufficiency. Patient J had clubbing of the finger nails at five years of age.

Three patients developed diabetes insipidus (A, C, and F) between one to two months of age that in patient A required prolonged DDAVP and did not self-resolve. The only dysmorphic feature documented in the infants was an abnormal palate; patient D had a cleft soft palate, patient G had a cleft palate, and patient C had a high-arched palate. All patients were fed by gastrostomy tube.

Discussion:

Patients with the gain-of-function *KCNQ2* R201C and R201H variants have a severe form of *KCNQ2* encephalopathy with a phenotype that is novel and distinct from what has been reported for other *KCNQ2* encephalopathy variants. Previously undescribed features include neonatal encephalopathy *without* seizures, exaggerated and prolonged startle response with bilateral high amplitude myoclonic jerks *without* EEG correlate, hypoventilation with periodic breathing, and profound developmental impairment with early mortality. Our electro-clinical data support the hypothesis that *in vitro* gain-of function correlate *in vivo* with clinical features that are different from the ones observed in neonates with variants causing loss-of-function.

The position of the variant likely has an impact on the clinical expression. While BFNE-associated variants are randomly distributed throughout the channel protein and include missense, splice, stop, and frameshift variants as well as exon and whole-gene deletions, currently known *KCNQ2* encephalopathy variants are missense or single codon deletions, clustering in four functionally important protein domains: the voltage sensor domain, the pore, the C-terminus proximal region, and the calmodulin-binding B helix region.[17] Within the voltage sensor domain, most *KCNQ2* variants causing encephalopathy reduce channel function (often with dominant-negative effects).[11, 12] However, a few affecting residues involved in voltage sensor domain resting state stabilization (i.e. R201C, R201H, and R198Q) produce gain-of-function effects by shifting activation to more hyperpolarized potentials and/or increasing maximal current density.[14, 18, 19]

Both *de novo* loss-of-function and the R201C/H gain-of-function variants lead to a neonatal encephalopathy characterized by a burst-suppression EEG pattern. However, even though 70% of the patients in our series developed epileptic spasms in infancy, the absence of seizures in the neonatal period seems to be a peculiarity of the gain-of-function variants. In fact, no neonatal seizures or encephalopathy were reported in four patients carrying a milder KCNQ2 R198Q gain-of-function variant who later developed epileptic spasms at 4-6 months of age.[19]

Excessive startle response as a prominent neonatal feature was observed for the R201C/H gain-of-function variants. The paroxysmal movements were described as myoclonic in many of the cases. Myoclonic jerks associated with encephalopathy and a burst-suppression EEG pattern are seen in neonates with Early Myoclonic Encephalopathy (EME). However, in EME, myoclonus is typically fragmentary, erratic, of low amplitude, tends to

shift from one body part to another in a random asynchronous fashion, and is not induced by a stimulus.[20] In our patients, the myoclonic movements were massive, elicited by tactile or acoustic stimuli, tended to persist after the end of the stimulus, and were difficult to distinguish from epileptic movements without simultaneous video-EEG recording. They were indeed clinically diagnosed as seizures and treated as such in most cases of our series. Such a misdiagnosis is not surprising, since it is often impossible to accurately differentiate between seizures and non-epileptic paroxysmal movements in neonates using clinical evaluation alone.[21]

Semiologically, the exaggerated startle response is reminiscent of hyperekplexia, a genetic condition due to mutations affecting spinal glycine neurotransmission that is characterized by an exaggerated startle response to stimuli, with a brief period of stiffness following the startle reflex.[22] However, EEG in hyperekplexia is normal and there is no encephalopathy.[22, 23] The movements of R201C/H neonates are different from the myokymia that affects older patients with some specific loss-of-function *KCNQ2* variants.[24, 25] Such myokymia is rhythmic, and is a sign of lower motor neuron hyperexcitability.

One patient harboring the R201C variant had a less severe phenotype and lacked the early neonatal features that were consistently seen among the other nine patients. Her genetic testing indicated post-zygotic mosaicism, which was previously shown to underlie milder presentation of *KCNQ2* encephalopathy loss-of-function variants.[4, 26]

Synchronized activity during prenatal and postnatal periods is essential for the development of cortical neuronal circuits.[27] Our findings suggest that the R201C gain-of-function may disrupts network activity in the neonatal period, but (unlike loss-of-function variants) somehow prevents some aspects of synchronization and/or excitability required for expression of seizures. *KCNQ2* channels are also found in neurons of the dorsal root ganglia and nociceptive afferent terminals, where they play a role in pain sensation.[28-30] Since the paroxysmal movements in our patients were triggered by tactile stimulation, it could be hypothesized that the exaggerated startle response may be secondary to an abnormal sensation to touch.

Early central hypoventilation and abnormal breathing patterns are additional prominent clinical features observed in patients with *KCNQ2* R201C/H variants. Apneic episodes and respiratory failure along with neonatal encephalopathy and severe hypotonia have been described in males with methyl-CpG-binding protein 2 (*MECP2*) mutations,[31] but

these infants lack both the distinct paroxysmal movements and severe EEG findings observed in infants with *KCNQ2* gain-of-function variants. Apneas are described in loss-of-function variants of *KCNQ2* encephalopathy and typically occur as part of a tonic seizure.[5, 32] In our R201C variant patients however, hypoventilation and apnea observed in the neonatal period were demonstrated to be associated with central hypoventilation rather than seizure activity. Interestingly, the KCNQ2 channel has key functions in respiratory drive.[33] Chemosensitive neurons in the retrotrapezoid nucleus of the brainstem are regulated through a pathway which involves serotonergic inhibition of KCNQ2 channels to increase respiratory drive in response to a change in CO_2/H^+.[34] A gain-of-function channel variant by causing excessive channel opening may result in a reduction of respiratory drive due to a decreased sensitivity to inhibition by serotonin despite chronic elevated CO_2 levels in infants with a gain-of-function variant. Sulthiame, a carbonic anhydrase inhibitor, given to patient G had a beneficial effect on breathing. KCNQ2 potassium channel subunits have also been detected in branches of the carotid sinus nerve, which provides sensory innervation to the carotid body chemoreceptors, as well as in carotid body glomus cells, which are the main O_2-sensing cell in the carotid bodies.[35] Little is known about the role of *KCNQ2* in the carotid body glomus cells or carotid sinus nerve fibers. Of note, mice homozygous for a *KCNQ2* mutation die of respiratory failure after birth.[36] Respiratory problems may contribute to early mortality in *KCNQ2* encephalopathy due to R201C/H variants. Animal model and human studies are needed to understand the effect of gain-of-function variants on central and peripheral chemoreflex respiratory control.

In the majority of our patients, MRI showed progressive diffuse brain volume reduction, thin corpus callosum and hypomyelination. The thinning of the corpus callosum could reflect the bilateral volume loss in the cortex as seen in many other encephalopathies. Brain MRI at three months of age in one infant (patient A) showed an additional finding of altered neuronal migration with gray matter heterotopias. Interestingly, a neuropathological report of a neonate with *KCNQ2* encephalopathy found mild malformation of cortical development and heterotopic gray matter,[37] and heterotopias were also found in a KCNQ2 transgenic mouse model.[38] The cellular and circuit mechanisms through which altered KCNQ2 channel activity results in such neurodevelopmental structural abnormalities are currently unknown.

Recognition of genotype-phenotype correlations in patients with *KCNQ2* variants can have important treatment implications. Retigabine/ezogabine, a KCNQ-channel opener

and therefore a presumed targeted therapy for epilepsy involving *KCNQ2* loss-of-function,[5, 39] did not impact the myoclonic jerks and/or the encephalopathy in patients with R201C/H variants and even seemed to lead to a worsening of the symptoms in at least one patient (patient G). Given this observation, it is possible that treatment with retigabine/ezogabine in patients with a gain-of-function variant may result in a detrimental clinical effect. *KCNQ2*-related epilepsies are therefore a prime example of the need for functional classification of allele subgroups, as gain-of-function and loss-of function require different targeted therapeutic approaches.

The patients with *KCNQ2* R201C and R201H variants described in this report define a distinct and very severe form of neonatal encephalopathy and provide a clinical translation of *in vitro* functional studies. We believe that gain-of-function variants of *KCNQ2* should be considered in newborns with unexplained severe encephalopathy, burst-suppression EEG pattern, and stimulus sensitive myoclonic jerks, in the *absence of epileptic seizures*, as well as in newborns with central hypoventilation. In our series, prognosis was poor. Future investigations should aim at identifying drugs that counteract excessive channel opening as an early targeted therapy that may improve outcome.

Key Point Box

- The *KCNQ2* gain-of-function variants R201C and R201H lead to a phenotype clearly distinct from the one associated with *KCNQ2* loss-of-function variants
- Children have a neonatal encephalopathy with non-epileptic myoclonic jerks, central hypoventilation, and profound developmental delay with early mortality
- *In vitro* functional studies in KCNQ2 translate to *in vivo* clinical entities, supporting the use of distinct targeted treatments for specific patient subgroups

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Ethical Publication Statement

The authors confirm that they 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

Supplementary material legend

Videos Legends

Video 1

Paroxysmal myoclonic movements, without EEG correlate, that are stimulus sensitive in an infant with the R201C variant at 2 months of age.

Video 2

Chorea is shown in a 4 year old girl with the R201H variant. The movements wax and wane with episodes that last for a few days.

Figure Legends

Figure 1: Evolution of EEG during Early Infancy (Patient A)

A. EEG (7μV/mm) at two days of age showing a burst-suppression pattern. B. EEG (7μV/mm) at 47 days of age showing a pattern of multi-focal epileptiform discharges with random areas of attenuation while on ezogabine (level 1600ng/mL). C. EEG (7μV/mm), just prior to discharge from the neonatal intensive care unit at 106 days of age showing a pattern of multifocal epileptiform discharges on vigabatrin 50mg/kg/day.

Figure 2. Brain MRI at Three months of age in Infant with *KCNQ2* R201C Variant

A. Axial T2 weighted image shows diffuse reduced brain volume with ex vacuo enlargement of the lateral ventricles, also notice subependymal heterotopias in the right ventricular atrium (white arrow). B. Sagittal T1 weighted image shows diffuse thinning of the corpus callosum (white arrow) that reflects bilateral volume loss in the cortex. C. Axial T1 weighted inversion recovery image shows no myelination in the anterior limb of internal capsule (should be present at three months of age), suggesting hypomyelination (patient A).

Figure 3. Respiratory and SpO_2 Recording in Infant with *KCNQ2* R201C Variant

Respiratory and pulse oximetry recording at three months of age showing excessive sighing and unusual periodic breathing associated with intermittent hypoxia (patient A).

Table 1A. Clinical features of R201C/H associated KCNQ2 encephalopathy.

	Patient A	Patient B	Patient C	Patient D*	Patient E
Mutation	c.601C>T; p.R201C	c.601C>T; p.R201C	c.601C>T; p.R201C	c.601C>T; p.R201C	c.601C>T; p.R201C
Age at inclusion	13m (deceased-cardiopulmonary arrest)	2 yr	4 mo (deceased)	2 yr 5 mo (deceased-SUDEP)	6 yr 4 mo (deceased)
Encephalopathy at birth	Yes	Yes	Yes	Yes	Yes (day 5)
Presenting paroxysmal events and EEG correlate	1st day of life-exaggerated and sustained startle reaction to touch (no EEG correlate)	1st day of life-exaggerated and sustained startle reaction to noise/touch, apnea	1st day of life-exaggerated startle response, apnea	2nd day of life - myoclonic movements intermixed with tonic component and apnea. (no EEG correlate)	2nd day of life-myoclonic jerky spontaneous movements, pronounced startle responses
Early neurologic exam	Axial hypotonia, increased peripheral tone, hyperreflexia	Severe diffuse hypotonia, hyperreflexiatremor	Mixed tone, hyperreflexia	Axial hypotonia	Unknown
Neonatal EEG	BS (Figure 1A)	BS	BS	BS	BS
Follow-up EEG	Multi-focal epileptiform discharges with random attenuation (Figure 1B)	Multi-focal epileptiform discharges	Multi-focal epileptiform discharges	Multi-focal epileptiform discharges	Multi-focal epileptiform discharges (2 yrs)
Infantile spasms	None at 13 mo of age	Early tonic seizures, IS at 4 mo		IS after few months	
Retigabine/ezo-gabine (Yes/No), effect	Yes (17 days), no clinical response on startle/body movements	Yes (7 wks), decrease in apneas, no clinical response on startle/body movements	Yes (3 mo), no clinical response	No	Yes, (4 yrs) more wakefulness
Vigabatrin	Yes, reduced	Yes, increased	Yes, reduced	Yes, no effect	Yes, no effect

(Yes/No), effect	startle movements	hypotonia	startle movements		
Anti-epileptic medications	CLZ, P5P, B6, FA	PB, VPA, PHT, B6, P5P, FA, TPM, LEV, ZNS, LOC, CBZ, STM, KD, CBD enriched cannabis	CBZ, CLZ, PB, P5P, FA, PHT	PB, LEV, TPM, VPA, CLZ, KD	PB, LEV, VPA, LTG, TPM, RUF, CLB
Brain MRI	Mild cerebral atrophy (1 wk), hypomyelination, diffuse brain volume loss, subependymal heterotopias (3 mo) (Figure 2)	Mild brain volume loss (1 wk)	Severe hypomyelination (2 and 4 mo)	Mild frontal lobe volume loss, hypomyelination of the posterior limb of internal capsule, prominent ventricles (1 wk)	Hypomyelination, reduced brain volume (8 mo)
Development	Profound delay	Profound delay	Profound delay	Profound delay	Profound delay
Respiratory involvement	Chronic hypoventilation, ventilator first 2 wks, non-invasive PPV until 2 mo, caffeine, theophylline, Aminophylline with limited effect, irregular breathing pattern (Figure 3), remains on supplemental O_2	Ventilator required at birth, apneas stopped at 3 mo, recurrent aspiration pneumonias	Respiratory failure, rare short periods off the ventilator, caffeine tried with mild effect	Respiratory impairment with need for supplemental O_2, recurrent respiratory infections	History of frequent aspiration pneumonias, O_2-dependent at 23 mo, parents decided not to ventilate mechanically

Abbreviations: PB-phenobarbital; CLZ-clonazepam; PHT-phenytoin; VPA-valproic acid; LEV-levetiracetam; TPM-topiramate; ZNS-zonisamide; LOC-lacosamide; CBZ-carbamazepine; OXC-oxcarbazepine; STM-sulthiame; LTG-lamotrigine; CLB-clobazam; RUF-rufinamide; CBD-cannabidiol; FA-folinic acid; B6-pyridoxine; P5P-pyridoxal-5-phosphate; KD-ketogenic diet; PPV- positive pressure ventilation; IS-infantile spasms

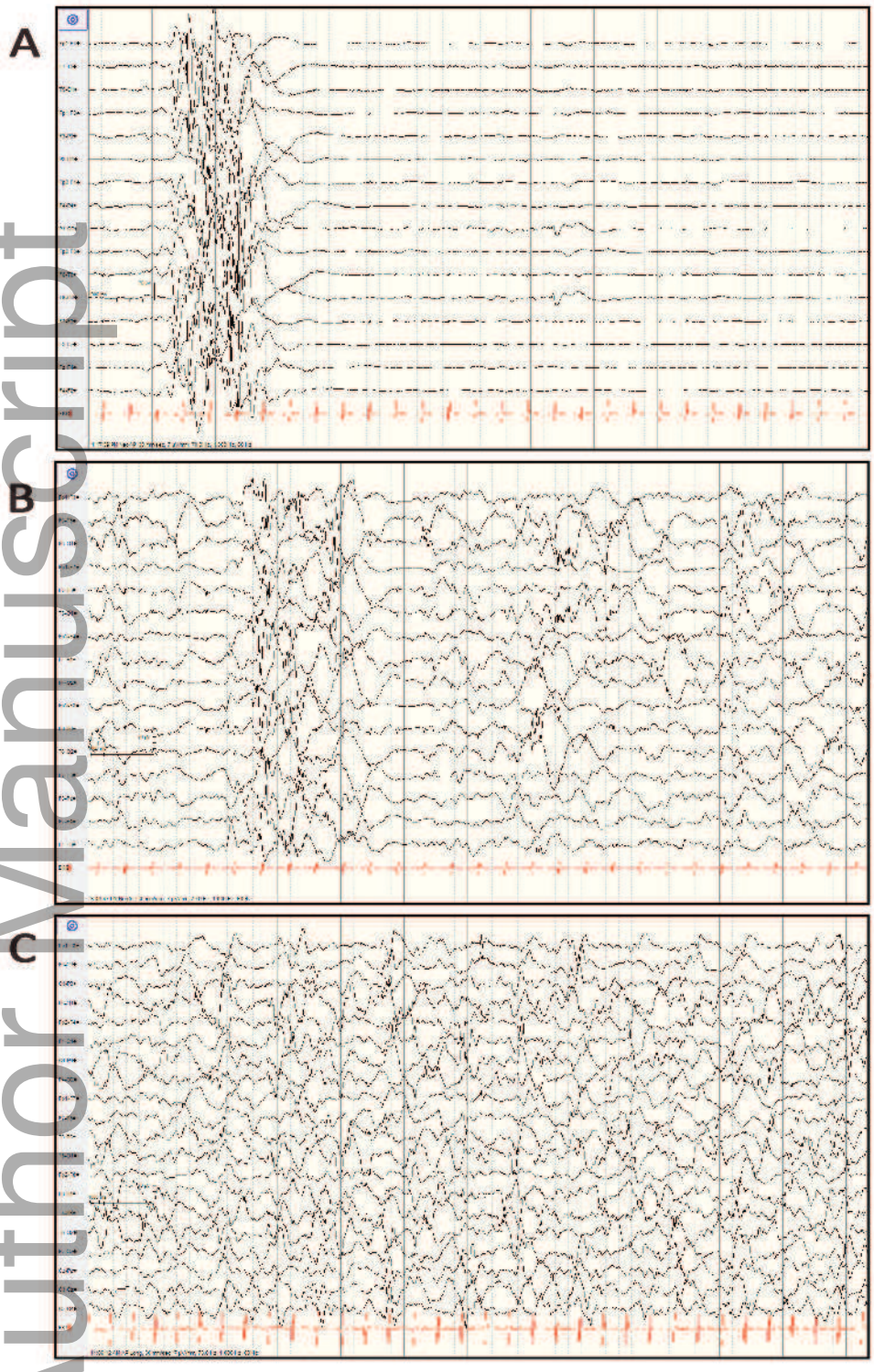
Table 1B. Clinical features of R201C/H associated KCNQ2 encephalopathy.

	Patient F	Patient G	Patient H	Patient I	Patient J
Mutation	c.601C>T; p.R201C	c.601C>T; p.R201C	c.601C>T; p.R201C (mosaic)	c.602G>A; p.R201Hs	c.602G>A; p.R201H
Age at inclusion	3 yr	19 mo	5 yr	4 yr 6 mo	4 yr 10 mo
Encephalopathy at birth	Yes	Yes	No	Yes (mild)	Yes (mild)
Presenting paroxysmal	2nd day of life-stiffening	1st day of life-multi-focal erratic	None reported during infancy	1st day of life-myoclonic	1st day of life-early neonatal

events and EEG correlate	events (not captured on EEG)	myoclonic movements exaggerated with stimuli (No EEG correlate)		spontaneous movements, exaggerated startle to noise/touch	myoclonic events
Early neurologic exam	Severe hypotonia, hyperreflexia	Severe hypotonia	Mild axial hypotonia	Axial hypotonia, increased peripheral tone, hyperreflexia	Unknown
Neonatal EEG	BS	BS	N/A	Unknown	None
Follow-up EEG	Multi-focal epileptiform discharges, slow background	Multi-focal epileptiform discharges, slow background	Multifocal epileptiform abnormalities, slow background.	Multi-focal epileptiform discharges (3mo), hypsarrythmia (3mo)	Multi-focal epileptiform discharges (3mo), hypsarrythmia (5mo), multi-focal epileptiform discharges, slow background (4 yrs)
Infantile spasms	IS at 7mo	IS	IS (age 2yr)	IS at 2 mo	IS at 5 mo
Retigabine/ezo-gabine (Yes/No), effect	No	Yes (6 mo), worsening seizures, prolonged apneas, severe sedation	No	No	No
Vigabatrin (Yes/No), effect	Yes, reduced spasms	Yes, reduced spasms	Yes, controlled spasms, caused sedation	Yes, no effect	Yes, limited effect on spasms
Anti-epileptic medications	PB, TPM, ACTH, KD, LEV, CLZ, FA, B6, P5P	LEV, OXC, PB, STM, TPM, PHT VPA	ACTH, LEV	CBZ, ZNS, PB, P5P, FA	ACTH, PHT, VPA, TPM, LEV
Brain MRI	Normal (1 wk), Increased T2 signal in the basal ganglia (1 yr)	Normal (1.5 wks), hypo myelination (1 mo)	Hypomyelination (10 mo), marked hypomyelination and enlarged subarachnoid spaces (4 yr)	Hypo myelination, diffuse brain volume loss (3 mo)	Persistent cavum septum pellucidum (5 wks), abnormal (2 yr)
Development	Profound motor delay	Profound delay	Age 1 yr- mild developmental delay Age 5 yr- severe delay	Profound delay	Profound motor delay, rare words, responsive smile/laugh

Respiratory involvement	Ventilator required at birth for 4 days, discharged from NICU on supplemental O_2, has occasional apneas	Supplemental O_2 until age 6 mo due to chronic compensated respiratory acidosis (venous pCO_2 ≥75 mmHg), irregular breathing pattern, STM had a good effect on O_2 need	Frequent respiratory illnesses requiring home nebulizer	Recurrent aspiration pneumonias, many admissions to the pediatric intensive care unit for ventilation	Frequent respiratory illnesses, aspiration pneumonia, clubbing of finger nails

Abbreviations: PB-phenobarbital; CLZ-clonazepam; PHT-phenytoin; VPA-valproic acid; LEV-levetiracetam; TPM-topiramate; ZNS-zonisamide; LOC-lacosamide; CBZ-carbamazepine; OXC-oxcarbazepine; STM-sulthiame; LTG-lamotrigine; CLB-clobazam; RUF-rufinamide; CBD-cannabidiol; FA-folinic acid; B6-pyridoxine; P5P-pyridoxal-5-phosphate; KD-ketogenic diet; PPV- positive pressure ventilation; IS-infantile spasms



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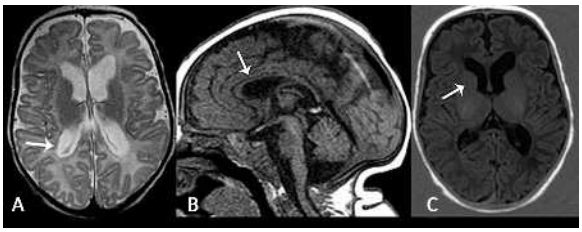

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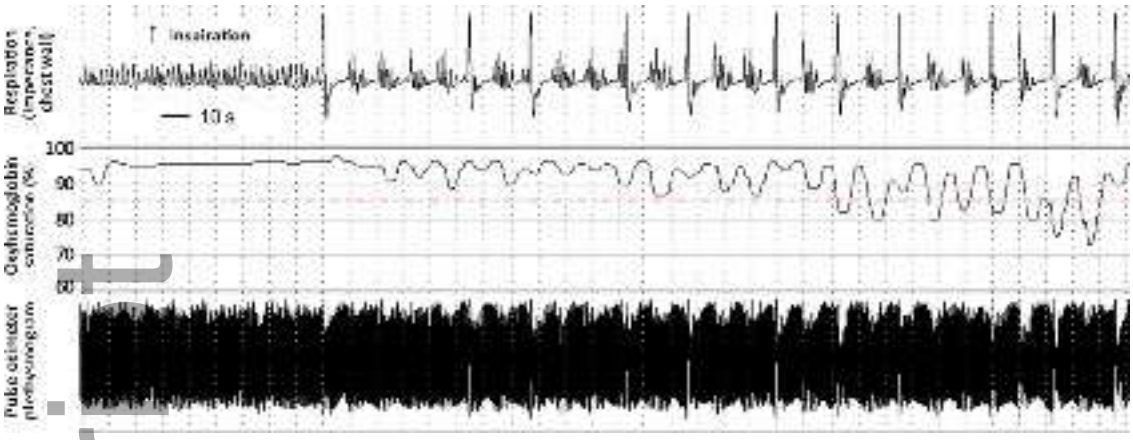

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