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Case report

A novel mutation of KCNQ2 gene in a patient with self-limited non-familial neonatal epilepsy: a case report

Nguyen Le Trung Hieu[1], Nguyen Thi Quynh Mai[2,3,4], Le Thi Khanh Van[1], Nguyen Thuy Minh Thu[1], Le Tran Anh Ngan[1], Do Phuoc Huy[5], Huynh Thi Dieu Hien[2,3,4], Do Thi Thu Hang[2,3,4,*]

ABSTRACT

Background: In several genetic epilepsies, the genotype-phenotype relationship is complex in which pathogenic variants in the same gene may causes different epilepsy phenotypes. As a typical example, pathogenic variants of *KCNQ2* have been known to cause either self-limited familial (and non-familial) neonatal epilepsy or early-onset epileptic encephalopathies. In spite of very different prognosis in terms of both epilepsy and development, both usually present as neonatal seizures within the first week of life. **Case presentation:** The patient, who was born at term after an uneventful pregnancy, had onset of tonic seizures at 2 days of age. Family history was negative for seizures or epilepsies. During the early stage (from onset to 6 months of age), he exhibited some electroclinical features resembling epileptic encephalopathy, including marked abnormalities on electroencephalogram, poor response to epileptic medications, hypotonia, and mild motor developmental delay. However, his seizures remitted from 4 months of age. And at his last evaluation at 20 months old, he presented cognitive and motor development within the normal range. His outcome, therefore, is more consistent with self-limited neonatal epilepsy. Whole exome sequencing followed by Sanger sequencing confirmation revealed that the patient had a heterozygous mutation c.1030T>G (p.Trp344Gly) in *KCNQ2* gene which has not been previously reported. Examination of this mutation in the parents implied that this mutation occurred de novo. This mutation was classified as ``likely pathogenic'' according to standards of The American College of Medical Genetics and Genomics. **Conclusions:** This study reported a rare case of self-limited non-familial neonatal epilepsy with a novel *KCNQ2* gene mutation. It should be cautious that some patients with *KCNQ2*-self-limited non-familial neonatal epilepsy may present some features resembling epileptic encephalopathy at onset/early stage. The complex genotype–phenotype correlation of *KCNQ2*-related epilepsies and the genetic counselling involved with the case are also discussed in this case report.

Key words: KCNQ2, self-limited neonatal seizures, epileptic encephalopathy

[1]*Neurology Department, Children Hospital 2, Ho Chi Minh City, Vietnam*

[2]*Research Center for Genetics and Reproductive Health*

[3]*School of Medicine*

[4]*Vietnam National University HCMC, Ho Chi Minh City, Vietnam*

[5]*Vinmec Research Institute of Stem cell and Gene technology, Ha Noi, Vietnam*

Correspondence

Do Thi Thu Hang, Research Center for Genetics and Reproductive Health

School of Medicine

Vietnam National University HCMC, Ho Chi Minh City, Vietnam

Email: hangdo009@gmail.com

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BACKGROUND

Neonatal seizure is a group of heterogeneous disorders; its common aetiologies include hypoxic-ischemic encephalopathy, intracranial haemorrhage, hypoglycaemia, hypocalcaemia, electrolyte imbalance, infections, and metabolic disorders. Autosomal dominant, neonatal epilepsies are rare but also related. In several genetic epilepsies, the genotype-phenotype relationship is complicated in which pathogenic variants in the same gene may causes different epilepsy phenotypes. One such example is seen in different phenotypes resulted from variants of the *KCNQ2* gene [1,2].

KCNQ2 encodes for the KV7.2 subunit, which associates with the KV7.3 subunit (encoded by *KCNQ3)* to form the hetero-tetrameric voltage-gated potassium channels (KV7.2/KV7.3) [3]. These channels are widely expressed in the brain, where they mediate the M-current, a particular type of electrical signal. M current functions to ensure that the neurons are not constantly active or excitable [4].

KCNQ2 variants were first identified in self-limited familial neonatal epilepsy (SFNE), formerly known as benign familial neonatal epilepsy in 1998 [5,6]. SFNE has autosomal dominant inheritance pattern and self-limiting nature. Although seizures in SFNE often start between 3 and 7 days after birth and become increasingly frequent, they subsequently remit by around 4–6 months of age spontaneously. The patients with SFNE often have an excellent neurodevelopment prognosis [7]. Besides SFNE, *de novo* mutations in *KCNQ2* have been reported in some sporadic cases of self-limited non-familial neonatal seizures. Self-limited familial neonatal epilepsy and self-limited non-familial neonatal seizures, abbreviated as S(F)NE when mentioned together, have very

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similar electroclinical features and are mainly distinguished on the basis of family history. In addition, variants in *KCNQ2* have been rarely identified in cases with self-limited familial (and non-familial) infantile (and neonatal-infantile) epilepsy[8]. This syndrome is similar to S(F)NE in terms of benign prognosis but it has a later onset[9].

More recently, *de novo* KCNQ2 missense variants were found to be also associated with neonatal *KCNQ2* – related epileptic encephalopathy (*KCNQ2*-EE), a much more severe phenotype[10,11]. As in S(F)NE, neonates with *KCNQ2*-EE often present with early onset, often tonic, seizures. However, these seizures are much more difficult to control and the patients soon exhibit developmental delay. In addition, unlike B(F)NE, the interictal EEG always showed marked abnormalities such as a burst-suppression pattern or multifocal epileptic activities[11].

In this study, we report a 20-month-old male with a novel *KCNQ2* gene mutation. During the patient's early postnatal life, he exhibited some electroclinical features indicative of epileptic encephalopathy. However, his later progression is more consistent with diagnosis of self-limited neonatal epilepsy. The genotype-phenotype correlation of *KCNQ2*-related epilepsies and the related genetic counselling are also discussed.

CASE PRESENTATION

Clinical presentation

The patient was referred to our clinic, the Research Center for Genetics and Reproductive Health, School of Medicine, Vietnam National University, Ho Chi Minh City, Vietnam, at the age of 20 months for genetic testing and counselling. He is the first child of nonconsanguineous parents. The pregnancy was uneventful and he was born at term by vaginal delivery. At birth, he weighed 2900 g and had no malformations. The family history was negative for seizures or epilepsies.

Right after birth, his condition was good, and he started breastfeeding regularly. On the second day after birth, he was noted to have generalized tonic seizures associated with cyanosis. His seizures repeated about 8–10 times a day with each seizure lasted about 30–40 s. One week after birth, he was diagnosed with epileptic encephalopathy by a City Children's Hospital (Ho Chi Minh City, Vietnam). However, the investigation results were not available for our evaluation. Treatment with phenobarbital (PHB, 5 mg/kg/day) was started at 26 days of age. The patient responded only partially to this therapy: the seizure frequency decreased from 8–10 times per day to for 5–6 times per day. At 1 month and 27 days of age, the patient was subsequently admitted to the Neurology Department of Children's Hospital 2 (Ho Chi Minh City, Vietnam). Interictal neurological examination revealed his muscle tone was weaker than normal. Video electroencephalography (EEG) recorded a 40-s generalized tonic seizure coupled with slow waves, slow spike-and-wave discharges, and polyspikes. Interictal EEG showed an atypical burst-suppression pattern (burst at 100 - 150 μV for 3-4s and suppression for 7–10 s) and multi-focal epileptiform discharges (Figure 1). Brain magnetic resonance imaging (MRI) was normal and metabolic investigations were unremarkable. Based on these electroclinical features, the patient was suspected to suffer epileptic encephalopathy. PHB was stopped and replaced with levetiracetam – with a gradual increase in the dose. Topiramate and pyridoxine were then added because there was no improvement with levetiracetam monotherapy. However, the child still had 3–4 seizures/day while taking polytherapy of levetiracetam (35 mg/kg/day), topiramate (2.5 mg/kg/day), and pyridoxine (30 mg/kg/day). From 2–3 months of age, the patient was followed up at a local hospital. PHB was reintroduced and both levetiracetam and topiramate and pyridoxine were stopped. At 3–4 months of age, he exhibited clusters of short generalized tonic seizures, 1 s/seizure $\times$ 5–6 seizures/cluster $\times$ 4–5 clusters/day. These seizures, however, remitted at 4 months of age (with PHB 7 mg/kg/day). Thereafter, the PHB dose was gradually reduced and the patient has been seizure-free up to now with a maintenance dosage of PHB (2.5 mg/kg/day). A developmental assessment at 6 months of age showed that the patient had mild motor developmental delay (delayed rolling over and poor head control). At 20 months old, however, his psychomotor development was within normal limits according to the Denver Developmental Screening Test II.

Molecular studies

The protocol for this research approved by the Institutional Review Board of Children's Hospital 2 (Ref. No. CS/ND2/18/04HT). Written consent was obtained from the parents for molecular analysis and publication. DNA from the patient was extracted from peripheral blood lymphocytes. Libraries were generated from the genomic DNA using the Human Core Exome Kit (Twist Bioscience) and then sequenced on an HiSeq 4000 (Illumina). The sequencing reads were mapped to the human reference

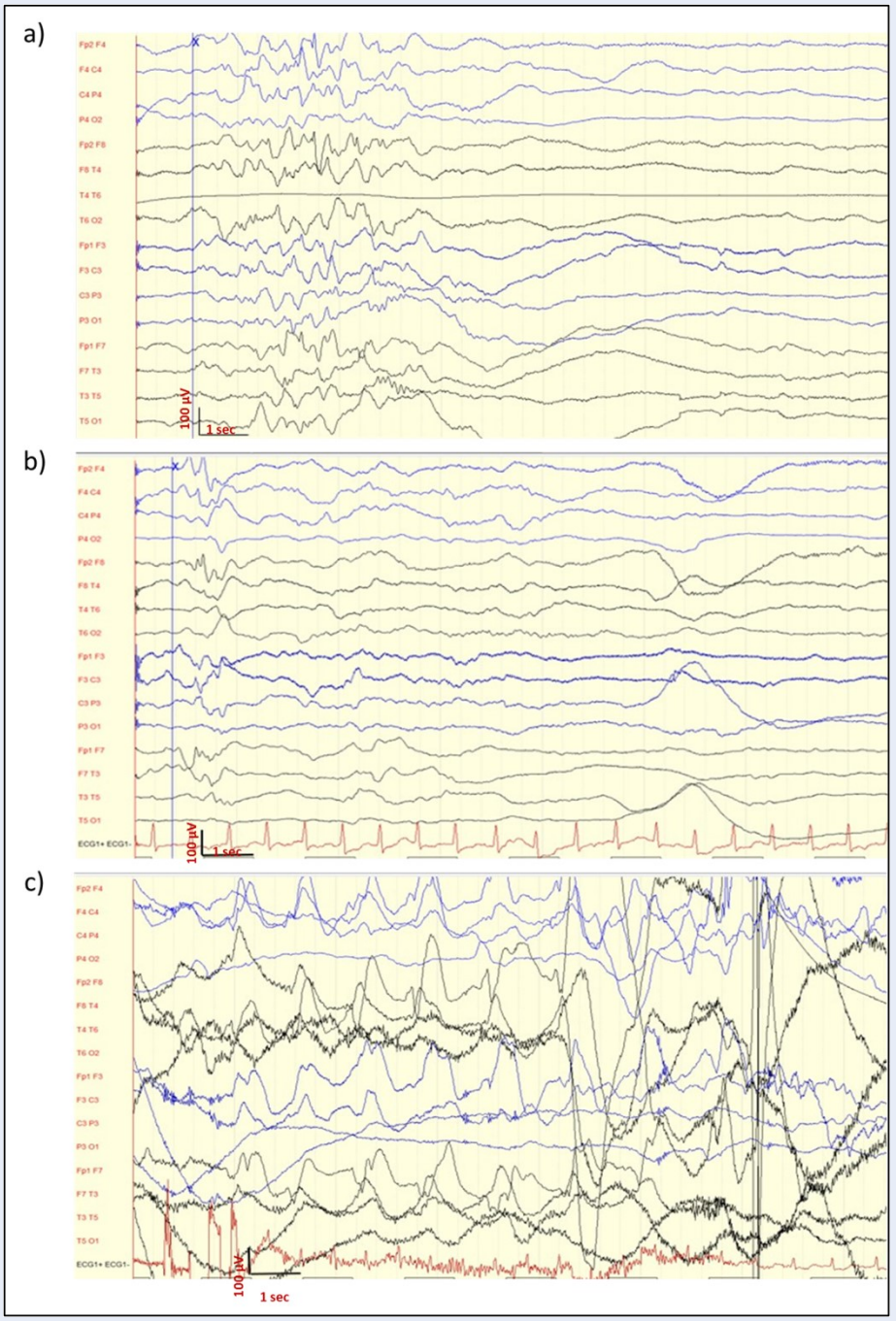

Figure 1: EEG investigation of the patient at 1 month and 27 days. (a) Interictal EEG in natural sleep is not normal; theta and delta waves are absent and there is atypical burst-suppression pattern (average amplitude 100–150 μV, burst duration 3–4 s, and suppression duration 10 s). (b) Interictal EEG in natural sleep in which background is symmetrical and synchronous with some paroxysmal activities in the frontal lobe (average amplitude 70–100 μV). (c) Ictal EEG showed generalized sharp spikes and slow waves (average amplitude 200–400 μV).

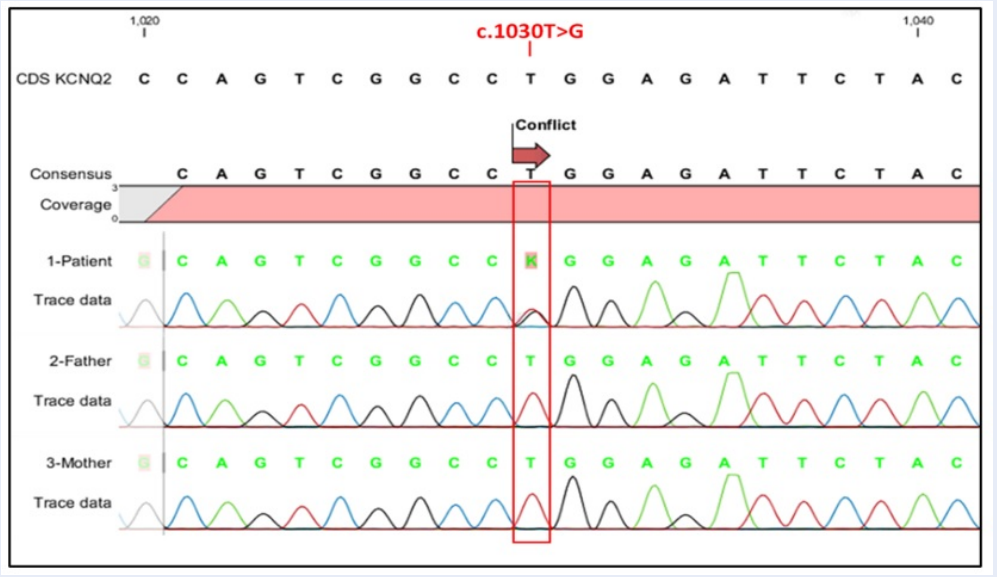

Figure 2: Electropherograms of Sanger sequencing of peripheral blood lymphocyte DNA showed that the patient has a heterozygous mutation – c.1030T>G (p.Trp344Gly) – in the *KCNQ2* gene. Both of his parents are wild type, implying that the mutation from the patient occurred *de novo*.

genome (version hg19) using the Burrows–Wheeler Alignment tool. Both Platypus and Genome Analysis Toolkit were used to call variants (i.e. single nuclear polymorphisms (SNPs) and short indels). Variants were searched in 248 epilepsy-associated genes including X-linked genes (Table S1). A heterozygous mutation – c.1030T>G (p.Trp344Gly) (W344G) – in *KCNQ2* (transcript: NM-172107.4) was identified as the strongest candidate variant. This mutation was then confirmed by Sanger sequencing with the primer pairs: F 5′-GGCTTGCCTGTCTGTCCTAC-3′ and R 5′-AGAAGCAACGCCTCGAAATA-3′. Further Sanger sequencing analysis showed that neither parent carried the mutation (Figure 2). Hence, the mutation in the patient was *de novo*. *In silico* analysis using annotation tools including Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (https ://sift.bii.a-star.edu.sg/), and PROVEAN (http://pro vean.jcvi.org/) predicted the mutation to be probably damaging (score = 1), damaging (score = 0.001), and deleterious (score = -11.89), respectively. Further analysis showed that this mutation was absent from the 1000 Genomes Project database, the Exome Variant Server database, and the Genome Aggregation Database. This mutation had not been reported in Human Gene Mutation Database or Clinvar. Using the ACMG InterVar classification tool (http://w intervar.wglab.org/), this mutation was classified as 'likely pathogenic' (PS2, PM1, PM2, and PP3 criteria applied).

Discussion and conclusions

B(F)NE and *KCNQ2*-EE are two main phenotypes associated with *KCNQ2* mutations. Both syndromes may start within the first days after birth. The clinical features indicative of B(F)NE include absence of abnormality on brain MRI, normal interictal neurologic exam, normal early development, and remission of seizures (often spontaneously) by 12 months of age (generally by 4 months of age). On the other hand, the suspicion of *KCNQ2* -EE is mainly based on absence of structural lesions in the brain, severe abnormality on EEG background activity, poor response to epileptic medications, and developmental delay at different levels. The patient in this study had seizure remission from 4 months of age and normal development at 20 months. Therefore, his present outcome is presumably associated with self-limited neonatal seizures. Nevertheless, it is notable that in the early stage he presented several electroclinical features resembling epileptic encephalopathy including hypotonia, poor response to medications, delayed motor development, and especially, marked abnormalities on EEG (atypical burst-suppression pattern and multifocal epileptiform discharges). In S(F)NE, although the interictal EEG may show a theta pointu alternant pattern (seen in half of cases) or there may be focal or multi-focal epileptiform abnormalities, the presence of a burst-suppression pattern including an atypical pattern as observed in our case, has not been re-

ported. Laccetta et al. (2019) described a case of de novo *KCNQ2*-related self-limited neonatal seizures with seizure semiology at the onset stage similar to that of infantile epilepsy, with migrating focal seizures evolving into epileptic spasms[12]. The treatment required multiple anticonvulsants for seizure control, and the patient exhibited mild motor delay at 12 months old. Similar to our case, this patient was also initially hypothesised to suffer from epileptic encephalopathy. Therefore, clinicians should remember that some patients with *KCNQ2*-related self-limited (familial) neonatal epilepsy may represent features resembling epileptic encephalopathy at the onset/early stage and this should be considered in the differential diagnosis of epileptic encephalopathy.

The Kv7.2 protein consists of six transmembrane domains (S1–S6) and the intracellular N- terminal and C-terminal regions. The S4 domain operates as the voltage sensor while S5, S6, and S5-S6 loop build the ion channel pore domain[5]. The C-terminal region is especially long and it consists of four α-helical domains (A–D). These domains contain several protein interaction regions[13]. The mutation in our patient is located on the helix A domain of the protein (Figure 3). Helix A, together with helix B, has been known to play important roles in Kv7.2 function. Both contain binding sequences for calmodulin (CaM), which accounts for the folding and trafficking of Kv7.2[14]. The mutations in the CaM domain have been reported to substantially impair Kv7 channel maturation and plasma membrane expression[15]. Helix A, via syntaxin-1A, also mediates a direct interaction between Kv7.2 and other plasma membrane proteins[16]. By analyzing a large number of *KCNQ2* variants, Goto et al. recently found that missense variants located in the intracellular domain between S2 and S3 are more likely to cause B(F)NE, while those located in S6 and adjacent regions tend to cause *KCNQ2*-DEE. Differently, variants in helix A seem to associate with both B(F)NE and *KCNQ2*-EE[2]. Therefore, the phenotypes of variants located in this region are especially unpredictable based on the genetic characteristics of variants. In addition, it has been suggested that besides variant characteristics, additional genetic/epigenetic, or environmental factors are also very important in determining different phenotypes. There have been reports of families in which family members with the same genotype (same *KCNQ2* variants) exhibited different phenotypes (RIKEE project database: http://www.rikee.org, accessed 22 August 2020). For the variant identified in our case, another amino acid substitution at the same position (p.Trp344Arg) was previously reported in a family with self-limited familial neonatal epilepsy[14]. In this family, five individuals in three generations were affected. Among the five individuals, two had persistent drug-resistant seizures and one had cognitive impairment. Therefore, the genotype–phenotype correlations of *KCNQ2*-related epilepsies are highly complex and additional investigations are needed.

In our case, based on the patient's benign progression and combined with the *KCNQ2* mutations identified via genetic testing, a diagnosis of self-limited non-familial neonatal epilepsy diagnosis is proper. Based on this diagnosis, a patient can be counseled that the risk of seizure recurrence is minimal, even without treatment. Therefore, it is reasonable for the patient to gradually taper and finally stop his phenobarbital oral therapy. However, a proportion of patients with self-limited familial (and non-familial) neonatal epilepsy may experience other forms of epilepsy later in childhood, and learning difficulties occur in rare cases. Hence, the patient should be strictly followed up[17,18]. Given that we did not find the mutation identified in the patient in his parents using Sanger sequencing, there is a low risk for recurrence of the mutation in (an) additional child(ren). However, low percentages of mosaicism and, especially, purely gonadal mosaicism cannot be detected by routine Sanger sequencing. Therefore, further investigations such as deep sequencing on gonadal tissues are needed to completely rule out the parental mosaicism in this presented case.

In conclusion, we report a novel variant, 1030T>G (p.Trp344Gly), in the *KCNQ2* gene and suggest that some patients with *KCNQ2*-self-limited non-familial neonatal epilepsy may present some features resembling epileptic encephalopathy at onset/early stage. In addition, genotype-phenotype correlations of *KCNQ2*-related epilepsies are complex and additional investigations are warranted.

LIST OF ABBREVIATIONS

CaM: Calmodulin

DNA: Deoxyribonucleic acid

EE: Epieptic encephalopathy

EEG: Electroencephalogram

KCNQ2 -EE: *KCNQ2* – related epileptic encephalopathy

MRI: Magnetic resonance imaging

NGS: Next-generation sequencing

PCR: Polymerase chain reaction

SFNE: Self-limited familial neonatal epilepsy **S(F)NE**: Self-limited (familial) neonatal epilepsy : Single nuclear polymorphisms

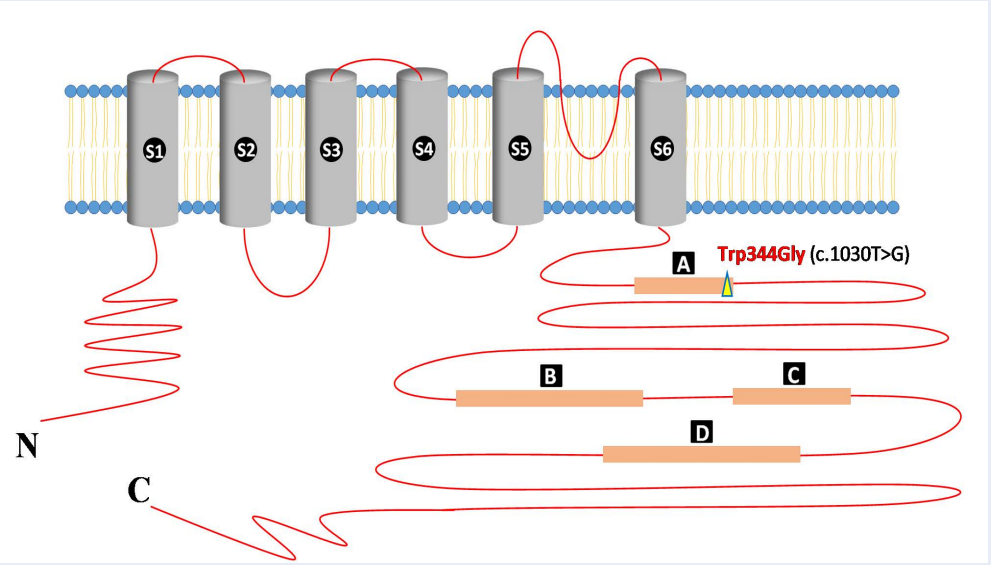

Figure 3: The structure of the Kv7.2 protein encoded by *KCNQ2* consists of six transmembrane domains (S1–S6) and intracellular N- and C-terminal regions. The novel *de novo* heterozygous variant identified in our patient, c.1030T>G (p.Trp344Gly), is located in the helix A domain of the C-terminal region.

CONSENT FOR PUBLICATION

Written informed consent of this case report was obtained from the patient's parents

ACKNOWLEDGEMENTS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol for this research study was approved by the Institutional Review Board of Children Hospital 2. Written consent was obtained from the patient's parents for participation in this study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

DTTH designed and wrote the manuscript. DTTH, NTQM, and HTDH were involved in the molecular studies and their interpretation. NLTH, LTKV, NTMT, DPH, and LTAN were involved in the medical care of the patient. NLTH reviewed the manuscript critically. All authors read and approved the final manuscript.

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Báo cáo lâm sàng

Báo cáo lâm sàng: Động kinh sơ sinh tự giới hạn không có tính chất gia đình với đột biến mới trên gen *KCNQ2*

Nguyễn Lê Trung Hiếu[1], Nguyễn Thị Quỳnh Mai[2,3,4], Lê Thị Khánh Vân[1], Nguyễn Thuỵ Minh Thư[4], Lê Trần Ánh Ngân[1], Đỗ Phước Huy[5], Huỳnh Thị Diệu Hiền[2,3,4], Đỗ Thị Thu Hằng[2,3,4,*]

TÓM TẮT

Tổng quan: Trong một số bệnh động kinh di truyền, mối liên hệ kiểu gen – kiểu hình có thể rất phức tạp trong đó các biến thể trên cùng 1 gen có thể gây ra các kiểu hình khác nhau. Một ví dụ điển hình là các biến thể gây bệnh trên gen *KCNQ2* đã được công bố trong cả bệnh động kinh sơ sinh tự giới hạn có tính chất gia đình (hoặc không gia đình) cũng như trong bệnh não động kinh khởi phát sớm. Cả hai nhóm động kinh trên tuy có tiên lượng rất khác nhau về cả động kinh và phát triển nhưng đều thường biểu hiện bởi co giật sơ sinh trong tuần đầu tiên.

Ca lâm sàng: Bệnh nhi được sinh sau quá trình mang thai và chuyển dạ bình thường, nhưng bắt đầu có các cơn co cứng vào ngày thứ 2 sau sinh. Gia đình không có tiền sử co giật hay động kinh. Trong giai đoạn đầu (từ lúc khởi phát co giật đến lúc 6 tháng tuổi), bệnh nhi biểu hiện các đặc điểm lâm sàng-điện não khá tương tự bệnh não động kinh bao gồm bất thường điện não rõ nét, đáp ứng điều trị kém, giảm trương lực, chậm phát triển vận động nhẹ. Tuy nhiên, từ 4 tháng tuổi, bệnh nhi hết dần co giật và thăm khám lúc 20 tháng tuổi cho thấy bệnh nhi đạt mức phát triển tâm thần vận động trong ngưỡng bình thường. Do đó, chẩn đoán về sau của bệnh nhi phù hợp hơn với động kinh sơ sinh tự giới hạn không có tính chất gia đình. Giải trình tự toàn bộ vùng mã hóa và kiểm tra lại bằng Sanger cho thấy bệnh nhi mắc một đột biến phát sinh mới dạng dị hợp c.1030T>G (p.Trp344Gly) trên gen *KCNQ2*. Đột biến này chưa từng được công bố trước đó. Kiểm tra trên bố mẹ cho thấy đây là đột biến phát sinh mới. Đột biến này được phân loại là ``có thể gây bệnh'' theo tiêu chuẩn phân loại của Hiệp hội Di truyền Y học Hoa kỳ.,

Kết luận: Bài báo cáo ca mô tả 1 ca động kinh sơ sinh tự giới hạn không có tính chất gia đình, một nhóm bệnh động kinh hiếm gặp trong đó bệnh nhi mắc một đột biến mới chưa được công bố trên gen *KCNQ2*. Ca báo cáo lưu ý rằng trong giai đoạn khởi phát, động kinh sơ sinh tự giới hạn có thể biểu hiện giống với bệnh não động kinh. Mối liên hệ kiểu gen-kiểu hình phức tạp của bệnh động kinh liên quan đến gen *KCNQ2* và tư vấn di truyền liên quan đến ca bệnh cũng được thảo luận.

Từ khoá: KCNQ2, co giật sơ sinh tự hết, bệnh não động kinh

[1]*Khoa Thần Kinh, Bệnh viện Nhi Đồng 2, TP HCM, Việt Nam*

[2]*Trung tâm nghiên cứu Di truyền và Sức khoẻ Sinh sản*

[3]*Khoa Y*

[4]*Đại học Quốc gia TP HCM, Linh Trung, Thủ Đức, TP HCM, Việt Nam*

[5]*Viện nghiên cứu Tế Bào Gốc và Công Nghệ Gen Vimec, Hà Nội, Việt Nam*

Liên hệ

Đỗ Thị Thu Hằng, Trung tâm nghiên cứu Di truyền và Sức khoẻ Sinh sản

Khoa Y

Đại học Quốc gia TP HCM, Linh Trung, Thủ Đức, TP HCM, Việt Nam

Email: hangdo009@gmail.com

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