ผลการตรวจ Next-generation Sequencing และความสัมพันธ์ทางคลินิกในเด็กที่ไม่ทราบสาเหตุของโรคลมชัก ณ โรงพยาบาลเด็กระดับตติยภูมิในประเทศไทย

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Next-generation Sequencing Findings and Clinical Correlations in Children with Unknown Causes of Epilepsy at a Tertiary Care Pediatric Hospital in Thailand

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Abstract

Background: Next-generation sequencing (NGS) has become an increasingly important technique for identifying the unknown causes of pediatric epilepsy. NGS increased the diagnostic yield by at least 30-40% in children with epilepsy, but these data in Thai children is still limited. This study aimed to determine the diagnostic yield and factors associated with the detection of disease-causing genes by NGS in children with unknown causes of epilepsy in Thailand. **Methods:** A single-center retrospective study of 42 children with unknown causes of epilepsy who had available NGS results for the diagnosis of genetic epilepsy from Jan 1st, 2015 to June 30th, 2021, was conducted at Queen Sirikit National Institute of Child Health, Thailand. Patients with identified causes of epilepsy were excluded. Gene variants were classified based on their pathogenicity, and related clinical factors were determined. **Results:** Of the 42 unexplained causes of epilepsy with available results from their NGS tests, 50% had a disease-causing gene detected and were identified as genetically causing epilepsy. Among these 21 patients with NGS-identified genetic epilepsy, 57.1% were female, 33.3% had a family history of epilepsy, 4.8% had a history of consanguinity, and all of them were developmentally delayed. The most common identified disease-causing gene was SCN1A (38.1%). The factor significantly associated with the detection of disease-causing genes was Dravet phenotype (p-value = .004), and other clinical parameters were not significant factors. Furthermore,

the change in patient management after available NGS results was significantly greater in patients with NGS-identified genetic epilepsy than in those without NGS-identified genetic epilepsy (61.9% vs. 4.8%, p < .001). **Conclusions:** Genetic testing should be advised for finding disease-causing genes in children with undiscovered causes of epilepsy since genetic abnormalities were discovered by NGS in 50% of children with unknown causes of epilepsy, and the clinical care for these patients may change.

Keywords: Genetic, Epilepsy, Children, Next-generation sequencing (NGS)

บทคัดย่อ

ภูมิหลัง: Next - generation sequencing (NGS) เป็นวิธีการตรวจที่มีบทบาทสำคัญมากขึ้นในการระบุสาเหตุที่ไม่ทราบของโรคลมชักในเด็ก ช่วยเพิ่มผลการวินิจฉัยสาเหตุของโรคลมชักที่เกิดในเด็กได้อย่างน้อยร้อยละ 30 - 40 แต่ประเทศไทยยังมีข้อมูลเหล่านี้อย่างจำกัด **วัตถุประสงค์:** เพื่อหาผลการวินิจฉัยและปัจจัยที่เกี่ยวข้องกับการตรวจหายีนที่ก่อให้เกิดโรคด้วย NGS ในเด็กที่เป็นโรคลมชักที่ไม่ทราบสาเหตุในประเทศไทย **วิธีการ:** การศึกษาย้อนหลังแบบสถาบันเดียวของเด็กที่เป็นโรคลมชักไม่ทราบสาเหตุจำนวน 42 ราย ซึ่งมีผลการตรวจ NGS สำหรับการวินิจฉัยโรคลมชักจากพันธุกรรมตั้งแต่วันที่ 1 มกราคม พ.ศ. 2558 ถึง 30 มิถุนายน พ.ศ. 2564 ดำเนินการที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ประเทศไทยโดยไม่รวมผู้ป่วยที่ทราบสาเหตุของโรคลมชัก ความแตกต่างทางพันธุกรรมถูกจำแนกตามความสามารถในการก่อโรคและพิจารณาปัจจัยทางคลินิกที่เกี่ยวข้อง **ผล:** ผู้ป่วย 42 รายที่ไม่ทราบสาเหตุของโรคลมชัก ได้รับการตรวจทางพันธุกรรมและมีผลการตรวจ พบว่าร้อยละ 50 ตรวจพบยีนที่ก่อให้เกิดโรคและเป็นสาเหตุทางพันธุกรรมของโรคลมชัก ในผู้ป่วย 21 รายที่มีโรคลมชักทางพันธุกรรมที่ได้รับการวินิจฉัยโดย NGS พบว่าร้อยละ 57.1 เป็นเพศหญิง ร้อยละ 33.3 มีประวัติครอบครัวเป็นโรคลมชัก ร้อยละ 4.8 มีประวัติแต่งานในเครือญาติ และทั้งหมดมีพัฒนาการล่าช้า พบว่ายีนที่ก่อให้เกิดโรคที่พบมากที่สุดคือ SCN1A (ร้อยละ 38.1) โดยปัจจัยที่เกี่ยวข้องอย่างมีนัยสำคัญกับการตรวจพบยีนที่ก่อให้เกิดโรคคือ Dravet phenotype (p - value = .004) และพารามิเตอร์ทางคลินิกอื่น ๆ ไม่ใช่ปัจจัยที่มีนัยสำคัญ นอกจากนี้มีการเปลี่ยนแปลงการรักษาของผู้ป่วยที่ได้รับการวินิจฉัยหลังจากทราบผล NGS อย่างมีนัยสำคัญในผู้ป่วยโรคลมชักทางพันธุกรรมที่ได้รับการวินิจฉัยโดย NGS มากกว่าผู้ป่วยที่ไม่มีได้รับการวินิจฉัยโดย NGS (61.9% เทียบกับ 4.8%, p < .001) **สรุป**: แนะนำให้ทำการตรวจวินิจฉัยทางพันธุกรรมเพื่อค้นหายีนที่ก่อให้เกิดโรคในเด็กที่ไม่ทราบสาเหตุของโรคลมชัก เนื่องจากการตรวจ NGS พบความผิดปกติทางพันธุกรรมในเด็กร้อยละ 50 ในกลุ่มที่ไม่ทราบสาเหตุของโรคลมชัก และอาจเกิดการเปลี่ยนแปลงการดูแลรักษาทางคลินิกสำหรับผู้ป่วยที่ได้รับการวินิจฉัย

คำสำคัญ: โรคลมชักสาเหตุจากพันธุกรรม, เด็ก, เทคโนโลยีการถอดรหัสทางพันธุกรรม

Introduction

Epilepsy is a most common chronic neurological disease that affects individuals of all ages and has a worldwide distribution[1] The incidence of epilepsy in children ranges from 41 - 187/100,000.[2] According to the 2017 International League Against Epilepsy (ILAE) Classification of the Epilepsies, there are six subgroups of epilepsy etiologies: structural, genetic, infectious, metabolic, immune, and unknown. These subgroups were chosen due to their potential therapeutic implications.[3] Although many underlying disease mechanisms can lead to epilepsy, the cause of the disease is still unknown in about 50% of cases globally.[1]

Genetics has had a long - recognized role in epilepsy, particularly familial epilepsy and epilepsy of unknown cause, which was formerly called “idiopathic epilepsy”[4]. The American College of Medical Genetics has recommended the term “variant” as the preferred term, with various levels of evidence for pathogenicity that can be attributed to each variant. These are based on the strengths of association between a gene and a given phenotype (gene - level evidence), as well as on amino acid conservation across species and gene paralogs, family segregation data, and presence or absence in clinical and research databases or population databases[4]. The main types of gene variants associated with epilepsy, as well as other diseases, are 1) single nucleotide variants (1 base pair), 2) small insertions

and deletions that may or may not result in a shift in the reading frame of the gene, and 3) structural variation in the form of microdeletions/microduplications or chromosomal monosomy/trisomy or chromosomal rearrangements.[4]

However, prior to the development of next-generation sequencing (NGS), low-throughput technologies for genetic testing (primarily Sanger sequencing), and phenotypic and genotypic heterogeneity prevented the majority of patients from receiving a molecular diagnosis, even if they had disorders with a clear genetic etiology. Since the beginning of the 21st century, NGS, notably in monogenic epilepsy syndromes, has gained importance as a method for identifying the enigmatic causes of pediatric epilepsy.[5] In recent studies, NGS boosted the diagnostic yield of unknown causes of epilepsy by at least 30-40%.[5] These findings have considerably benefited in understanding the etiologies of epilepsy in the clinical practice, and set the stage for developing molecularly focused treatments.[6]

Despite these notable advancements, the molecular causes of the majority of pediatric patients with epilepsy remain elusive. Furthermore, most of these studies have been conducted among children from developed countries[6], particularly the Caucasian population, and fewer among Asian and Thai children. This study aimed to determine the diagnostic yield and factors associated with the detection of disease-causing genes by NGS in children with unknown causes of epilepsy.

Materials and Methods

We conducted a retrospective study at Queen Sirikit National Institute of Child Health (QSNICH), a 435-bed national tertiary care children's hospital located in Bangkok, Thailand. This study was approved by the Ethics Committee of QSNICH, Department of Medical Services, Ministry of Public Health, Thailand (REC 052/2564).

Patients aged 18 years or younger (from birth to 18 years old) with a diagnosis of epilepsy with unknown cause who had available NGS results at QSNICH between January 1st, 2015, and June 30th, 2021, were included. Exclusion criteria included epilepsy were caused by structural abnormality, metabolic, central nervous system (CNS) infection and immune caused, Known caused of genetic epilepsy such as chromosomal anomaly, tuberous sclerosis or syndromic caused, and lacking information. NGS test included epilepsy gene panel, whole exome sequencing (WES), and whole genome sequencing (WGS) were performed in individual patient depending upon availability of the test at the time. The NGS tests of study patients was sent to Department of Medical Science, Ministry of Public Health (Thailand), Excellent Center for Medical Genetics, King Chulalongkorn Memorial Hospital (Thailand), or the laboratory of INVITAE company (Thailand). Patients with known causes of epilepsy (structural, infectious, metabolic, and immune causes) and certain genetic epilepsy with known syndromic or chromosomal etiologies were excluded. All patients were examined and diagnosed by a pediatric neurologist.

Data collected from patient medical records included demographic information, history of epilepsy, underlying co-morbidities, results of specific investigations (i.e., electroencephalography (EEG), brain imaging, and metabolic screening), clinical management, and patient outcomes.

Gene variants were classified into the following categories according to Standards and Guidelines for the Interpretation of Sequence Variants: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign based on their pathogenicity, and related clinical factors for the detected gene variants[7]. NGS-identified genetic epilepsy was defined as epilepsy in which disease-causing genes (pathogenic variants or likely pathogenic variants) were discovered by NGS tests

Statistical analysis

Data were presented as numbers and percentages for categorical data and as mean and standard deviation for normally distributed data

or median and range for non-normally distributed data. Quantitative variables were compared using the t-test or Mann-Whitney U test, while qualitative variables were compared using Fisher's exact test or chi-square test. All statistical analyses were performed using IBM SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA). A p-value of 0.05 or lower was considered statistically significant.

Results

Forty-two pediatric patients with unknown causes of epilepsy were included in this study; 47.6% of them were female, the median age was 59.5 months (range 6.0 to 218.0 months). Developmental delay was observed in nearly all patients (n = 41, 97.6%), and perinatal complications were found in 33.3% of them (Table 1).

Twenty-one patients (50%) were classified as having NGS-identified genetic epilepsy. The most common identified disease-causing gene was SCN1A (38.1%). Other disease-causing gene were also observed, such as KCNT1, KCNQ2, SCN8A, STXBP1, GABRB3, and CKNSR2 (Table 2). Among these patients, 57.1% were female, 33.3% had a family history of epilepsy, 4.8% had a history of consanguinity, and all of them were developmentally delayed. Generalized tonic seizures were the most common seizure type (61.9%).

In comparisons between patients with or without NGS-identified genetic epilepsy, proportion of co-morbidities including intellectual disability, mental retardation was higher in patients without NGS-identified genetic epilepsy compared to those with NGS-identified genetic epilepsy (28.6% vs 4.8%, p = < .05) (Table 1). Ten patients who were suspicious of the Dravet phenotype were included in our study had a history of severe myoclonic epilepsy in infancy and pertussis vaccine encephalopathy, starting in the first year of life, triggered by febrile or afebrile conditions with recurrent status epilepticus (SE), as well as a slowing of developmental and cognitive skills. In our study showed patients with Dravet phenotype were more likely to have NGS-identified genetic epilepsy than those without NGS-identified genetic epilepsy (42.9% vs. 4.8%, p = .004) (Table 1). Changing management after being genetically identified occurred in 13 patients with NGS-identified genetic epilepsy compared to those without NGS-identified genetic epilepsy (61.9% vs. 4.8%, p < .001) (Table 1). For example, in patients with the SCN1A gene variant, the avoidance of sodium channel anti-seizure medicine was recommended by responsible physicians. While rates of seizure-free status at 6 months following the availability of NGS results did not differ between the two groups (Table 1).

Table 1. Patient characteristics between patients with Next Generation Sequencing (NGS) identified genetic epilepsy and those with negative NGS

	Total patients (n = 42) n (%)	NGS-identified genetic epilepsy (n = 21) n (%)	NGS-negative (n = 21) n (%)	p-value
Female gender	20 (47.6)	12 (57.1)	8 (38.1)	.216
Age (months) (min-max)	59.5 (6.0-218.0)	62.0 (24.0-190.0)	57.0 (6.0-218.0)	.725
Birth weight (grams) (min-max)	2,890 (2,100-3,890)	2,850 (2,200-3,890)	2,940 (2,100-3,890)	.237
Co-morbidities	7 (16.7)	1 (4.8)	6 (28.6)	.038
Developmental delay	41 (97.6)	21 (100)	20 (95.2)	.311

	Total patients (n = 42) n (%)	NGS-identified genetic epilepsy (n = 21) n (%)	NGS-negative (n = 21) n (%)	p-value
Family history of epilepsy	20 (47.6)	7 (33.3)	13 (61.9)	.064
Consanguinity	1 (2.4)	1 (4.8)	0 (0)	.311
History of perinatal complications	14 (33.3)	7 (33.3)	7 (33.3)	1.000
Types of seizures*				
1. Focal seizure	20 (47.6)	8 (38.1)	12 (57.1)	.217
2. Generalized seizure				
2.1 Generalized tonic-clonic	17 (40.5)	11 (52.4)	6 (28.6)	.116
2.2 Generalized tonic	20 (47.6)	13 (61.9)	7 (33.3)	.064
2.3 Generalized clonic	7 (16.7)	3 (14.3)	4 (19.0)	.679
2.4 Myoclonic	15 (35.7)	10 (47.6)	5 (23.8)	.107
3. Multiple types of seizures	24 (57.1)	14 (66.7)	10 (47.6)	.212
Status epilepticus	15 (35.7)	8 (38.1)	7 (33.3)	.747
Neonatal seizure	7 (16.7)	4 (19.0)	3 (14.3)	.679
Age of seizure onset (months) (min-max)	5.0 (0.07-172.0)	4.0 (0.1-144.0)	5.0 (0.07-172.0)	.743
Seizure onset before 1 year of age	31 (73.8)	16 (76.2)	15 (71.4)	.726
Age of epilepsy onset (months) (min-max)	6.0 (0.1-176.0)	6.0 (0.1-145.0)	7.0 (0.1-176.0)	.753
Numbers of current ASMs	2 (1-4)	2 (1-4)	3 (1-4)	.425
Numbers of ASMs failure (min-max)	2 (0-8)	2 (0-8)	3 (0-8)	.207
Characteristics of epilepsy				
- Epileptic encephalopathy	19/41 (46.3)	7/21 (33.3)	12/20 (60.0)	.087
- Any epilepsy syndromes	16 (38.1)	11 (52.4)	5 (23.8)	.057
- Dravet phenotype	10 (23.8)	9 (42.9)	1 (4.8)	.004
- Drug-resistant epilepsy	26 (61.9)	10 (47.6)	16 (76.2)	.057
- Abnormal EEG	33/39 (84.6)	15/20 (75.0)	18/19 (94.7)	.088
Management and outcomes of epilepsy				
Change in management after knowing NGS results[a]	14 (33.3)	13 (61.9)	1 (4.8)	< .001
Seizure-free status at 6 months after knowing NGS results	14/38 (36.8)	6/20 (30.0)	8/18 (44.4)	.357

*ASM = Antiseizure medication, *Some patients had > 1 seizure types.*

[a] i.e., avoid sodium channels in SCN1A, quinidine-sulfate in KCNT1, high-dose phenytoin in SCN8A, and carbamazepine in KCNQ2.

Table 2. Disease-causing genes discovered by NGS in this study

Disease-causing genes	Numbers of patients n (%)
ATP1A2	1 (4.8)
CDKL5	1 (4.8)
CLCN5	1 (4.8)
CLCN8	1 (4.8)
CNKSR2	1 (4.8)
GABRA3	1 (4.8)
GABRA5	1 (4.8)
KCNB1	1 (4.8)
KCNQ2	1 (4.8)
KCNT1	1 (4.8)
SCN1A	8 (38.1)
SCN8A	1 (4.8)
STXBP1	1 (4.8)
UNC80	1 (4.8)

Discussion

This study showed a number of significant findings: First, 50% of Thai children with unidentified causes of epilepsy had disease - causing genes discovered by NGS tests. Second, SCN1A was shown to be the most common disease - causing gene, accounting for 40% of the patients. Third, the change in clinical care was demonstrated in approximately 70% of patients with known disease - causing genes.

The etiology of epilepsy disorders includes genetic variables quite significantly. Numerous gene variants from individuals with epilepsy have been found in recent genomic research employing NGS techniques. These discoveries have greatly aided in determining the etiology of epilepsy, and laid the foundation for creating molecularly targeted therapies.[4-6] However, there are a limited number of studies focused on genetically causing epilepsy in Thai children[8, 9]. Most of these publications were case reports and case series with a small number of study participants[10-14].

Our findings were similar to those of other large studies from Asian countries. The recent study in Thailand demonstrated the diagnostic yield was 64% evaluating 103 unrelated children with infantile - onset drug - resistant epilepsy who had exome NGS as the first - tier genetic testing. The most frequent disease - causing genes were SCN1A (13%), followed by KCNQ2 (8%) and 43% of patients had their management changed as a result of a molecular diagnosis.[9] The study in China revealed pathogenic or likely pathogenic variants were observed in 37% of 320 children with epilepsy who had genetic sequencing with the most frequently observed disease - causing genes were SCN1A (11%), PRRT2 (8%), and TSC2 (7%); and 13% were found to be specifically treatable for the underlying genetic cause identified by genome sequencing.[15]

As previously described in the literature, the diagnostic yield of NGS tests for genetic epilepsy may vary from 3 - 50%;[16] the variations in the diagnostic yield of NGS for genetic epilepsy in several studies can be explained by differences in the profiles of study patients as well as differences in the numbers, selected genes, and techniques included in the genetic test panels.[9, 15, 16] Larger genetic panels and WES demonstrate significantly higher yields.[16]

SCN1A was the most often found disease - causing gene in other studies from Asian countries, which is similar to our study;[6, 9, 15, 17, 18] nevertheless, the reports of detected pathologic or likely pathologic variants in children with unexplained causes of epilepsy may differ among clinical settings, regions, and timeframes.[16]

Numerous studies have investigated how a particular genetic diagnosis affects management, similar to this study.[16, 19] In the large cohort of pediatric patients referred for epilepsy gene panel testing, 33% of the >1,500 patients with a positive molecular genetic diagnosis had an actionable variant. Over 50% of the actionable findings related to the avoidance of contraindicated antiseizure medications,

primarily sodium channel blockers in SCN1A - related epilepsies, and 40% of the actionable findings related to appropriate anti - epileptic drug selection.[19]

Contrary to earlier studies[16, 20], this study did not find that presentation in the first month of life, drug - resistant seizures, presence of developmental and epileptic encephalopathy, and the presence of neurodevelopmental comorbidities were significantly associated with an increased likelihood of a positive diagnostic result for genetic epilepsy.[16, 20] This is likely because there were very few patients (7 cases) in this study having neonatal seizures.

The strength of this study included the fact that it was the first study to focus on children with unknown causes of epilepsy in Thailand. We acknowledged the limitations: First, the retrospective nature of this study may impact the study findings due to missing data and selective bias. Second, the small number of study patients limited us to further subgroup analysis. Third, advancing genetic methods for the diagnosis of genetic epilepsy may influence the probability of the detection of patients' genetic abnormalities and result in a change in diagnostic yield and clinical management. Fourth, this is a single center study, that may prevent generalizability to other healthcare levels.

Identification of genetic etiologies of epilepsy can help with the choice of appropriate pharmacotherapeutic approaches, reduction in the number of unnecessary diagnostic procedures required, and timely administration of other non - antiepileptic drug therapies. In addition, further research is needed to recognize the clinical implications and possible utility of NGS in Thailand's standard clinical practice.

Conclusions

Genetic abnormalities were identified by NGS in 50% of pediatric patients with unknown causes of epilepsy in Thailand, and the management of the patient was modified in 70% after the availability of genetic test results. These findings highlight the importance of genetic testing should be performed in selected pediatric patients with unknown causes of epilepsy.

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Declarations

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Competing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval: This study was approved by the Institutional Review Board of QSNICH

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