CLINICAL STUDY AND MOLECULAR GENETIC ANALYSES OF MALAYSIAN GEFS+ PATIENTS

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1 INTRODUCTION

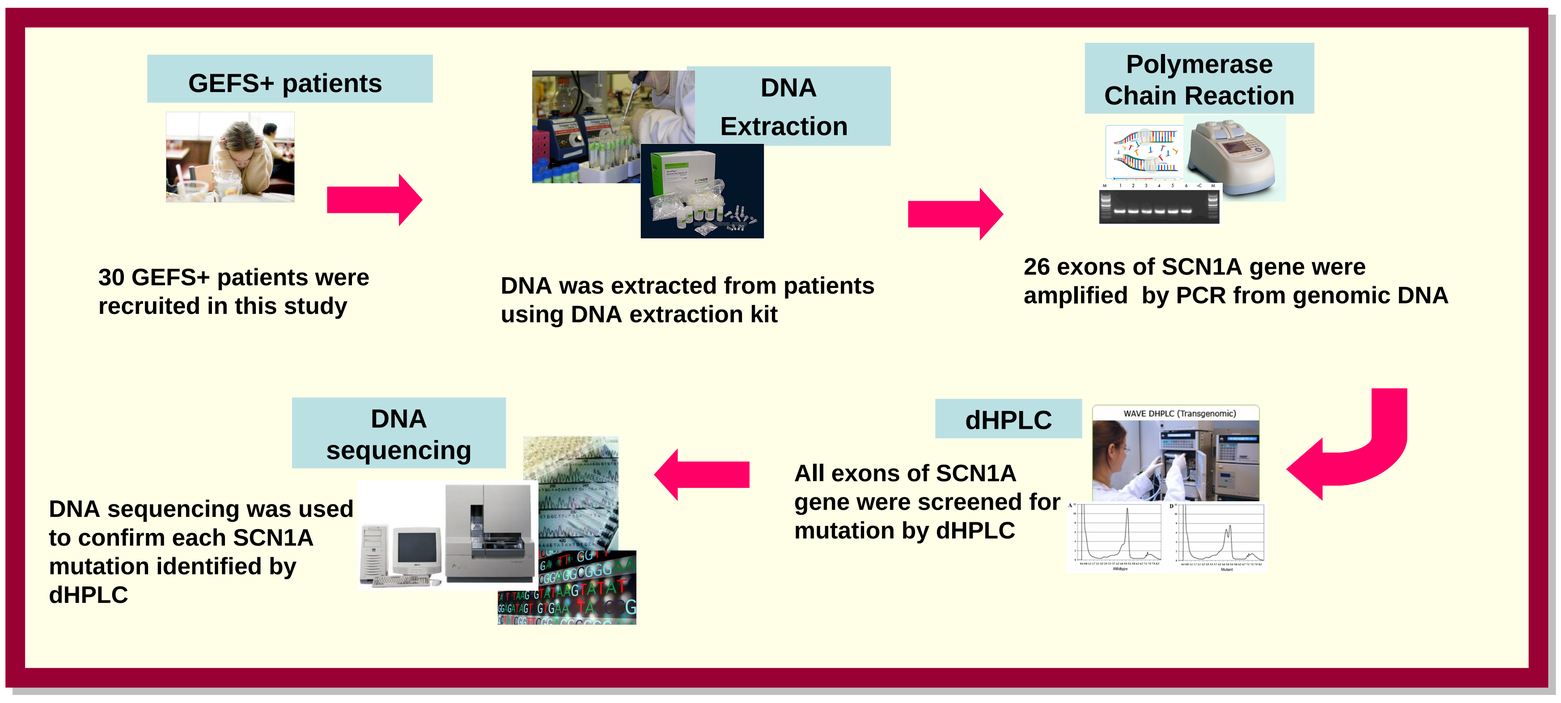
Generalized epilepsy with febrile seizure plus (GEFS+) has been described as an autosomal dominant inherited epilepsy disorder associated with febrile and afebrile seizures (Scheffer and Berkovic., 1997). Individuals with GEFS+ are characterized by febrile seizures in children and continue beyond 6 years of age (Escayg et al., 2000).

The common phenotypes of GEFS+ are heterogenous afebrile seizures that may include tonic-clonic, myoclonic, atonic and absence seizures (Wallace et all., 2001). GEFS+ was associated with mutations in the neuronal voltage-gated sodium channel subunit gene (*SCN1A, SCN2A, SCN1B*) and ligand-gated gamma aminobutyric acid receptor gene (*GABRG2, GABRD*).

2 OBJECTIVE

To study the clinical presentations and to analyze the *SCN1A* gene associated with Malaysian GEFS+ patients.

3 MATERIALS & METHODS



4 RESULTS

Clinical features

6 clinically GEFS+ patients (Table 1) with variety of seizure types and neurological deficits including global developmental delay, ataxia and behavioural concerns.

Patient (sex; age)	Type of seizures	Psychiatric/ other neurological disorders	Intellectual disability	Clinical classification of epilepsy
G3 (F:7Y)	FS, Partial to GTCS	-	Learning difficulty, ADHD	GEFS+
G6 (M:15Y)	FS, GTCS	Ataxia, Social anxiety	DD, MR, Learning difficulty	GEFS+
G11 (F:16Y)	FS, GTCS	-	-	GEFS+
G12 (F:15Y)	FS, GTCS	Social anxiety	-	GEFS+
G21 (M:13Y)	FS, GTCS	Social anxiety	MR, Learning difficulty	GEFS+
G22 (M:6Y)	FS, GTCS	-	DD, Learning difficulty	GEFS+

Table 1. Clinical features of GEFS+ patients
Key: M, male; F, female; Y, year; FS, febrile sizures; GTCS, generalized tonic clonic seizures; MR, mental retardation; DD, developmental delay; ADHD, attention deficit disorder

Genetic study

Direct sequencing of *SCN1A* revealed seven sequence variants that associated with GEFS+ (Table 2). A base substitution c. 4765 A>G transition in exon 25 of SCN1A (Fig 1) was detected in the GEFS+ patient. The amino acid translation show the His1586Arg amino acid substitution.

Exon/Intron	Variant nomenclature	Classification	Amino acid change
Intron 7	IVS7-21	Noncoding	No
Exon 9	c. 1212 A>G	Silent	No (Val404Val)
Exon 13	c. 2167 T>C	Silent	No (Val723Val)
Exon 25	c. 4731 T>C	Silent	No (Thr1574Thr)
Exon 25	c. 4765 A>G	Missense	Yes (His1586Arg)
Exon 26	c. 5115 A>G	Silent	No (Leu1705Leu)
Exon 26	c. 5197 A>G	Missense	Yes (Asn1733Asp)

Table 2. Summary of SCN1A mutations found in the 30 GEFS+ patients

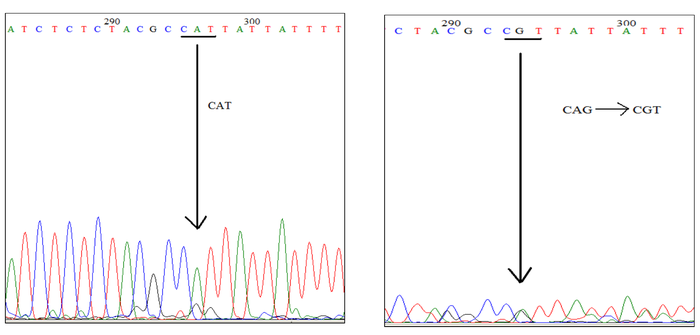


Figure 1. Sequencing traces (forward direction) showing heterozygous in c. 4765 A>G transition in exon 25 of *SCN1A* of the patient's genomic DNA. The amino acid translation show the H1586R amino acid substitution

5 DISCUSSION

We report a comprehensive clinical and genetic study of GEFS+ patients, the clinical presentation is variable as the case of GEFS+ (Scheffer and Berkovic., 1997) with the affected individuals had a variable of phenotype including anxiety disorders and neuropsychiatric disease.

The clinical characterization of GEFS+ as an autosomal dominant disease (Scheffer and Berkovic., 1997) also lead to identification of mutation in *SCN1A* gene (Escayg et al., 2000). We identified a novel missense mutation in the *SCN1A* gene in Malaysian GEFS+ patient, the mutation leads to an amino acid change in a conserved region and was not found in healthy controls. This suggests that mutations in *SCN1A* gene cause of GEFS+ in Malaysia.

ACKNOWLEDGEMENTS

We sincerely thank to Universiti Sains Malaysia for providing the Research University Grant (PSKBP/1001/8120195) as part of Brain Cluster Research and for awarding me the Postgraduate Scholarship Scheme (USM Fellowship).