THE IMPACT OF GENETIC POLYMORPHISMS IN CANDIDATE GENES ON SUSCEPTIBILITY TO EPILEPSY AND RESPONSIVENESS TO ANTIEPILEPTICS IN PATIENTS WITH EPILEPSY

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DISSERTATION SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICAL SCIENCE

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1. Sha'ari, H.M., Haerian, B.S., Baum, L., Saruwatari, J., Tan, H.J., Rafia, M.H., Raymond A.A., Kwan, P., Ishitsu, T., Nakagawa, K., Lim, K.S. & Mohamed, Z. (2014). *ABCC2* rs2273697 and rs3740066 polymorphisms and resistance to antiepileptic drugs in Asia Pacific epilepsy cohorts. *Pharmacogenomics*, *15*(4), 459-466. [Tier 1; Impact factor = 3.97] (ISI-cited publication)
2. Haerian, B.S., Sha'ari, H.M., Fong, C.Y., Tan, H.J., Wong, S.W., Ong, L.C., Raymond A.A., Tan, C.T. & Mohamed, Z. (2015). Contribution of *TIMP4* rs3755724 polymorphism to susceptibility to focal epilepsy in Malaysian Chinese. *Journal of Neuroimmunology*, *278*, 137-143. [Tier 2; Impact factor = 2.786] (ISI-cited publication)
3. Haerian, B.S., Sha'ari, H.M., Tan, H.J., Fong, C.Y., Wong, S.W., Ong, L.C., Raymond A.A., Tan, C.T. & Mohamed, Z. (2015). *RORA* gene rs12912233 and rs880626 polymorphisms and their interaction with SCN1A rs3812718 in the risk of epilepsy: A case-control study in Malaysia. *Genomics*, *105*(4), 229-236. [Tier 2; Impact factor = 2.79] (ISI-cited publication)
4. Sha'ari, H.M., Haerian, B.S., Baum, L., Tan, H.J., Rafia, M.H., Kwan, P., Cherny, S.S., Sham, P.C., Gui, H., Raymond A.A., Lim, K.S. & Mohamed, Z. (2016). Association of *BDNF* polymorphisms with the risk of epilepsy: A multicenter study. *Molecular Neurobiology*, *53*(5), 2869-2877. [Tier 1; Impact factor = 5.29] (ISI-cited publication)

Abstract

Epilepsy is a common neurological disorder with a prevalence of 1%, characterized by more than two seizures (de Boer et al., 2013). Medically intractable to antiepileptic drug (AED) treatment for epilepsy has led to the needs of pharmacogenomics study of AED-resistant in epilepsy patients. The aim of this study was to investigate the association of 17 candidate single nucleotide polymorphisms (SNPs) with susceptibility to epilepsy or drug responsiveness in 1152 epilepsy patients and 1532 healthy controls. Out of 1152 patients, 579 were drug responders while the remaining were drug non-responders, receiving AED for at least one year. Adjusted results by covariates showed significant associations between *BDNF* rs6265, rs7103411 and rs7127507 (OR 2.1, 95% CI 1.5-3.0, p = 0.0001; OR 0.5, 95% CI 0.4-0.7, p = 0.0003; and OR 0.6, 95% CI 0.4-0.8, p = 0.002, respectively), *CALHM1* rs11191692 (OR 0.6, 95% CI 0.4-0.8, p = 0.002), *ASIC1* rs844347 (OR 1.7, 95% CI 1.2-2.4, p = 0.002), and *GRIK2* rs4840200 (OR 1.6, 95% CI 1.2-2.2, p = 0.001) with susceptibility to epilepsy. The *ABCC2* rs2273697 and the *KCNAB1* rs2280032 showed significant association with AED responsiveness (OR 6.0, 95% CI 2.1-17.2, p = 0.001 and OR 0.4, 95% CI 0.3-0.7, p = 0.001, respectively). In conclusion, this study suggests that the *BDNF* rs6265, rs7103411 and rs7127507, *CALHM1* rs11191692, *ASIC1* rs844347 and *GRIK2* rs4840200 might be risk variants for susceptibility to epilepsy as well as the *ABCC2* rs2273697 and *KCNAB1* rs2280032 for drug responsiveness. Further studies with larger sample size are needed to prove these findings.

Abstrak

Epilepsi adalah gangguan neurologi biasa dengan kelaziman 1%, dicirikan oleh lebih daripada dua sawan (de Boer et al., 2013). Perubatan sukar dikawal dengan ubat anti-epileptik (AED) rawatan bagi epilepsi telah membawa kepada keperluan kajian farmakogenomik AED tahan pada pesakit epilepsi. Tujuan kajian ini adalah untuk menyiasat perkaitan antara 17 calon polimorfisme-polimorfisme nukleotid tunggal (SNPs) dengan kecenderungan terhadap epilepsy atau responsif terhadap ubat bagi 1152 pesakit epilepsi dan 1532 subjek kawalan sihat. Daripada 1152 pesakit, 579 adalah yang responsif terhadap ubat manakala yang selebihnya merupakan tidak responsif terhadap ubat, menerima AED bagi sekurang-kurangnya satu tahun. Keputusan diselaraskan dengan kovariat menunjukkan perkaitan yang signifikan antara *BDNF* rs*6265*, rs7103411 dan rs7127507 (OR 2.1, 95% CI 1.5-3.0, p = $0.00_0$1; OR 0.5, 95% CI 0.4-0.7, p = 0.0003; dan OR 0.6, 95% CI 0.4-0.8, p = 0.002, masing-masing), *CALHM1 rs111*91692 (OR 0.6, 95% CI 0.4-0.8, p = 0.00_2), *ASIC1* rs*844*347 (OR 1.7, 95% CI 1.2-2.4, p = 0.00_2), dan *GRIK2* rs*4840*200 (OR 1.6, 95% CI 1.2-2.2, p = 0.00_1) dengan kecenderungan terhadap epilepsi. *ABCC2* rs*2273*697 dan *KCNAB1 rs2280*032 menunjukkan perkaitan yang signifikan dengan responsif terhadap AED (OR 6.0, 95% CI 2.1-17.2, p = 0.001 dan OR 0.4, 95% CI 0.3-0.7, p = 0.001, masing-masing). Kesimpulannya, kajian ini menunjukkan bahawa *BDNF* rs*6265*, rs7103411 dan rs7127507, *CALHM1 rs111*91692, *ASIC1* rs*844*347 dan *GRIK2* rs*4840*200 mungkin varian risiko bagi kecenderungan terhadap epilepsi dan juga *ABCC2* rs*2273*697 dan *KCNAB1 rs2280*032 bagi responsif terhadap ubat. Kajian seterusnya dengan saiz sampel yang lebih besar diperlukan untuk membuktikan penemuan ini.

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-	minus
%	percent
.dup	duplicate sample
~	Tilde (equivalence)
°C	degree Celcius
µL	microliter
w/v	weight/volume
α	alpha
β	beta
χ^2	chi-square
ABC	ATP-binding cassette
ABCB	ATP-binding cassette (ABC) subfamily B
ABCB1	ATP-binding cassette (ABC) subfamily B, member 1
ABCC	ATP-binding cassette (ABC) subfamily C
ABCC2	ATP-binding cassette (ABC) subfamily C, member 2
ABCG2	ATP-binding cassette (ABC) subfamily G, member 2
Ach	acetylcholine
AED	antiepileptic drug
AEDs	antiepileptic drugs
Ala381Ala	Alanine381Alanine
ALDH5A1	aldehyde dehydrogenase 5 family, member A1
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
anti-GluR3	anti-glutamate receptor
ASIC1	acid-sensing ion channel 1
Asn40Asp	Asparagine40Aspartic acid
Aβ	amyloid
BBB	blood-brain barrier
BCRP	breast cancer resistant protein
BDNF	brain-derived neurotrophic factor
bp	base pair
C	healthy control

C.elegans	*Caenorhabditis elegans*
Ca	calcium
CA^{2+}	calcium ion
CAE	childhood absence epilepsy
CALHM1	calcium homeostasis modulator 1
CAMSAP2	calmodulin regulated spectrin-associated protein family, member 2
CBZ	carbamazepine
CE	cryptogenic epilepsy
CE_1	childhood epilepsy
CI	95% confidence interval
CNVs	copy number variations
CPS	complex partial seizures
CYP1A2	Cytochrome P450 1A2
CYP2A6	Cytochrome P450 2A6
CYP2C19	Cytochrome P450 2C19
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP3A4	Cytochrome P450 3A4
CYP450	Cytochrome P450
D’	value of linkage disequilibrium
dH_2O	distilled water
DMEs	drug metabolizing enzymes
DNA sequence A	DNA sequence adenine
DNA sequence C	DNA sequence cytosine
DNA sequence G	DNA sequence guanine
DNA sequence T	DNA sequence thymine
DNA	deoxyribonucleic acid
E	epilepsy case
E	east
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram

EGTCS	epilepsy with generalized tonic-clonic seizures
et al.	et alia (Latin), and others
FS	focal (partial) seizures
FS_1	febrile seizures
g	gage or thickness (needles)
g	gram
GABA	gamma-aminobutyric acid
$GABA_A$	ligand-gated ion channel (ionotropic receptor)
$GABA_B$	G protein-coupled receptor (metabotropic receptor)
GABRR2	gamma-aminobutyric acid (GABA) A receptor, rho 2
GJD2	gap junction protein, delta 2
GluR6	glutamate receptor 6
GRIK2	glutamate receptor, ionotropic, kainate 2
GS	generalised seizures
GST	glutathione S-transferases
GWAS	genome-wide association study
H_2O	water (dihydrogen monoxide)
HKL	Hospital Kuala Lumpur
HKU	the University of Hong Kong
HWE	Hardy-Weinberg equilibrium
i.e,	id est (Latin), that is
ID	identification
IE	idiopathic epilepsy
IGE	idiopathic generalized epilepsy
IGEs	idiopathic generalized epilepsies
ILAE	International League Against Epilepsy
JAE	juvenile absence epilepsy
JME	juvenile myoclonic epilepsy
K.L.	Kuala Lumpur
K^+	potassium ion
KA	kainate
kb	kilobase

KCNAB1	potassium voltage-gated channel, shaker-related subfamily, beta member 1
KCNMB4	potassium large conductance calcium-activated channel, subfamily M, beta member 4
Kv	voltage-gated
L	liter
LD	linkage disequilibrium
LFT	lowest frequency threshold
LGI1	leucine-rich, glioma inactivated 1
M	molar
MAF	minor allele frequency
MALDI-TOF	matrix-assisted laser desorption/ionization time of flight
mBDNF	mature BDNF
MDR1	multidrug-resistance protein 1
MDRs	multidrug-resistance proteins
MEC	Medical Ethics Committee
mEH	microsomal epoxide hydrolase
mg/mL	milligram/milliliter
min	minute
mL	milliliter
MOH	Ministry of Health Malaysia
MRP2	multidrug-resistance associated protein 2
MRPs	multidrug-resistance associated proteins
MTLE	mesial temporal lobe epilepsy
N	north
N	number
NA	not available
NA^+	sodium ion
NaOH	sodium hydroxide
NAT1	N-acetyltransferase 1
NAT2	N-acetyltransferase 2
ng/µL	nanogram/microliter

NMDA	n-methyl-D-aspartate
NMRR	National Medical Research Register
No.	number
NR	drug nonresponder
NR1I2	nuclear receptor subfamily 1, group I, member 2
OCD	obsessive-compulsive disorder
OD	optical density
OPRM1	opioid receptor, mu 1
OR	odds ratio
p	p-value
p^1	p-value (NR vs. R)
p^2	p-value (E vs. C)
PCR	Polymerase Chain Reaction
PE	partial epilepsy
PHT	phenytoin
Pro-BDNF	prodomain form of BDNF
PWE	people with epilepsy
PXR	pregnane X receptor
R	drug responder
Ref	referent
rpm	revolutions per minute
s	second
SCN1A	sodium channel voltage-gated type I alpha subunit
SCN8A	sodium channel voltage-gated type VIII alpha subunit
SD	standard deviation
SE	symptomatic epilepsy
Ser196Ser	Serine196Serine
Ser215Ser	Serine215Serine
SLC	solute carrier
SLC6A11	solute carrier family 6, member 11
SNP	single nucleotide polymorphism
SNPs	single nucleotide polymorphisms

SPS	simple partial seizures
SPSS	Statistical Package for the Social Sciences
SYN2	synapsin II
TBE	Tris-Base EDTA
TLE	temporal lobe epilepsy
UGT2B7	UDP-glucuronosyltransferase-2B7
UGTs	UDP-glucuronosyltransferases
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
UMMC	University of Malaya Medical Centre
US	unclassified seizures or multiple seizure types
UTR	untranslated region
UV	ultraviolet
V	voltage
Val417Ile	Valine417Isoleucine
Val66Met	Valine66Methionine
VPA	valproate
vs.	versus

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CHAPTER 1

INTRODUCTION

1.0 INTRODUCTION

1.1 Background of epilepsy

Epilepsy is a neurological disorder caused by sudden bursts of electrical activity in the brain and often with recurrent seizures, the seizure types of which include partial (focal) seizures and generalized seizures (Commission of ILAE, 1981). A diagnosis of epilepsy is made according to the International League Against Epilepsy (ILAE), which is a guideline used currently by all clinicians in the diagnoses of epilepsy disorders. The prevalence of epilepsy varies from 0.5% to 1.5% and the chances of occurrence of epilepsy are equal in men and in women. Epilepsy ranges in severity from those that are usually relatively mild, such as a blank stare, sudden and brief involuntary jerks and feeling of déjà vu, to those that can be badly affect social life, education, and career of the patient, like rigid violent muscular spasm, a drop head with loosening of the jaw and falling to the ground (Commision of ILAE, 1981).

The etiology of epilepsy is not clearly understood. Genetic factors however, may play an important role in its pathophysiology based on strong evidence found in familial aggregation and twin studies with an estimated case-wise concordance of idiopathic generalized epilepsies in monozygotic twins of 0.81 (Berkovic et al., 1998). This is also based on results from association studies that have found many susceptibility genes to be involved. On one hand, a patient may have epilepsy entirely due to genetic factors, while on the other, environmentally acquired factors are responsible, with many individuals falling along the spectrum with the etiology of their epilepsy including both genetic and acquired factors. The interaction between genetic and environmental factors is complex because it may occur at various levels and in various ways (Berkovic et al., 1998; Mulley et al., 2005).

In Malaysia, valproate is the most recommended first line antiepileptic drug (AED) used followed by carbamazepine and lamotrigine (Hasan et al., 2010). Newer drugs are less

commonly used which includes lamotrigine, phenytoin, gabapentin, levetiracetam, and topiramate. AEDs help to gradually decrease the frequency and severity of epileptic seizures and have been proven to have an efficiency rate of 60-70% in all treated epilepsy cases (WHO, 2012). However, about 30% of epilepsy patients do not respond adequately to AEDs.

The interindividual variability in efficacy of AEDs has been attributed to allelic variation in the genes (Wilson et al., 2001; Jimenez-Sanchez, 2003; Iafrate et al., 2004) and gives challenges in newly emerging area of pharmacogenomics. The genetic variations can potentially affect the individual responsiveness to AEDs at several steps, which include drug absorption, drug distribution, drug metabolism, drug elimination, and drug concentration at target sites (McCorry et al., 2004). The genetic variants with very high enzymatic activity may be associated with a need for higher drug dosages than usually prescribed, but low or absence of biotransformation capacity may result in treatment failure due to inadequate drug levels. Hence, a variety of potential mechanisms by which polymorphic drug metabolism can affect drug responsiveness to AED (Ferraro and Buono, 2005).

With regard to susceptibility to epilepsy or antiepileptic drugs (AEDs) response, synapsin II (*SYN2*), sodium channel voltage-gated type I alpha subunit (*SCN1A*) and pregnane X receptor (*PXR*) are gene polymorphisms which have been reported to play a role in the Malaysian population. Haerian et al. (2011a) reported that 30% of newly diagnosed epilepsy patients in the Klang Valley, Malaysia, were resistant to either carbamazepine (CBZ) or valproate (VPA) monotherapy. However, the *ABCB1* rs3789243 C>T, C1236T, G2677T/A, rs6949448 C>T and C3435T haplotypes did not play any significant roles in response to AED treatment in the Malaysian epilepsy patients.

Apart from *ABCB1*, *PXR* (G7635A) polymorphism was also investigated in 685 epilepsy patients and it was found to have no association with response to AED treatment (Haerian et al., 2011b). There are also systematic reviews and meta-analysis evidence suggesting that *ABCB1* gene polymorphisms might not be a risk for resistance to AEDs in epilepsy patients (Haerian et al., 2010; Haerian et al., 2011c). The findings from *SYN2* polymorphism with susceptibility to epilepsy (Haerian et al., 2011d) and *SCN1A* (IVS5N+5) polymorphism with response to VPA (Haerian et al., 2012) reflect the exposure of Malaysian population to other possible genetic variation in certain other candidate genes.

The main aims of the study were to investigate, in the same set of Malaysian population, whether the genetic polymorphisms are associated with susceptibility to epilepsy and drug responsiveness to carbamazepine or valproate monotherapy treatment. The selected candidate are the opioid receptor, mu 1 (*OPRM1*) gene, which play an important role in the pathogenesis of absence seizures (Przewlocka et al., 1998), genes that encode the ion channels (*KCNAB1* and *SCN8A* genes), genes that encode drug transporter and regulator (*ABCC2* and *NR1I2* genes) and other genes are *GJD2*, *SLC6A11*, *CAMSAP2*, *LGI1*, *ASIC1*, *GRIK2*, *CALHM1*, and *BDNF* genes.

The Malaysian population consists of three major ethnic subgroups, namely the Chinese, Indians, and Malays, each of which are presumably of different genetic pool, hence presenting a good opportunity to study the ethnic difference of susceptibility to epilepsy and drug responsiveness to carbamazepine or valproate monotherapy treatment with regard to genetic polymorphisms. Based on their interesting molecular functions, the genes were selected in order to investigate their association with either susceptibility to epilepsy or AEDs response in this study.

1.2 Objectives

The aims of this study are:

1. To investigate the association between single nucleotide polymorphisms (SNPs) of *GJD2*, *OPRM1*, *SLC6A11*, *CAMSAP2*, *LGI1*, *KCNAB1*, *ASIC1*, *NR1I2*, *GRIK2*, *CALHM1*, *SCN8A* and *BDNF* genes and their haplotypes with susceptibility to epilepsy in the three major ethnic groups of Malaysian patients.
2. To investigate the association between SNPs of *ABCC2*, *GJD2*, *OPRM1*, *SLC6A11*, *CAMSAP2*, *LGI1*, *KCNAB1*, *ASIC1*, *NR1I2*, *GRIK2*, *CALHM1*, and *SCN8A* genes and their haplotypes with drug responsiveness to carbamazepine or valproate monotherapy treatment in the three major ethnic groups of Malaysian epilepsy patients.

1.3 Justification of the study

Epilepsy is a most common neurological disorder that affects at least 60 million people worldwide (Szoeke et al., 2006). Lack of responsiveness to antiepileptic drugs (AEDs) is an important clinical problem in the treatment of epilepsy (Kwan et al., 2011). The study of pharmacogenomics in epilepsy is relatively new. Eventhough the association study of epilepsy in Malaysia was first started by Haerian and colleagues in the 2010 (Haerian et al., 2010), the more comprehensive study on the genetic association studies of epilepsy and drug responsiveness continued in 2012. This study investigated a growing list of functional polymorphisms found in different classes of genes encoding drug-metabolizing enzymes (DMEs), drug transporters, receptors and drug targets, which have been linked to carbamazepine or valproate monotherapy in epilepsy patients. The study was focused on the association of SNPs that were previously reported in epilepsy and drug responsiveness. This study reports the finding in a Malaysian population which consists of

three major ethnic groups, namely, the Chinese, Indians, and Malays. Each of the ethnic subgroups are presumably of different genetic pool, thus providing a good setting to study ethnic differences in their susceptibility to epilepsy and drug responsiveness to carbamazepine or valproate monotherapy. This study is an attempt to develop effective, safe medications and doses that will be a better understanding for the epilepsy treatment.

CHAPTER 2

LITERATURE REVIEW

2.0 LITERATURE REVIEW

2.1 Epilepsy overview

Epilepsy is one of the most common neurological conditions and is generally characterized by recurrent and unprovoked epileptic seizures (ILAE (International League Against Epilepsy) commission report, 1997; Fisher et al., 2005). Epileptic seizures are defined by the ILAE as transient occurrence of signs and/or symptoms due to abnormal excessive synchronous neuronal activity in the brain (Fisher et al., 2005). The epilepsy is diagnosed by two elements including a history of at least one seizure and evidence of an enduring alteration in the brain activity. The epilepsy is also reported to be associated with neurobiological, cognitive, psychological and social consequences (Fisher et al., 2005).

To date, due to significant evolution in the epilepsy study, particularly due to advances in molecular genetics and technologies, more number of people with epilepsy has been identified around the world (Figure 2.1). In developed countries, the incidence of epilepsy is 24-53 per 100,000 populations (Hauser and Hesdorffer, 1990), while the incidence of epilepsy in the delevoping countries is about 49 to 190 per 100,000 population (Jallon, 2002). According to ILAE (1997), the prevalence of active epilepsy is reported to be between 4-10/1,000 people in the general population. Extrapolated to Malaysian condition, this is approximately 11,856 patients receiving an initial diagnosis of epilepsy in Malaysia annually and more than 200,000 of the Malaysian population suffering from epilepsy (Zakaria, 1998). This condition probably has an approximately equal distribution amongst men and women in Malaysia, as found in Iceland (Olafsson et al., 2005), however, in the Sweden population, there is a slight predominance of males (Forsgren, 1992; Keränen and Riekkinen, 1988). Table 2.1 is a summarized clinical classification of patients in studies on epilepsy in the Asian countries (Mac et al., 2007).

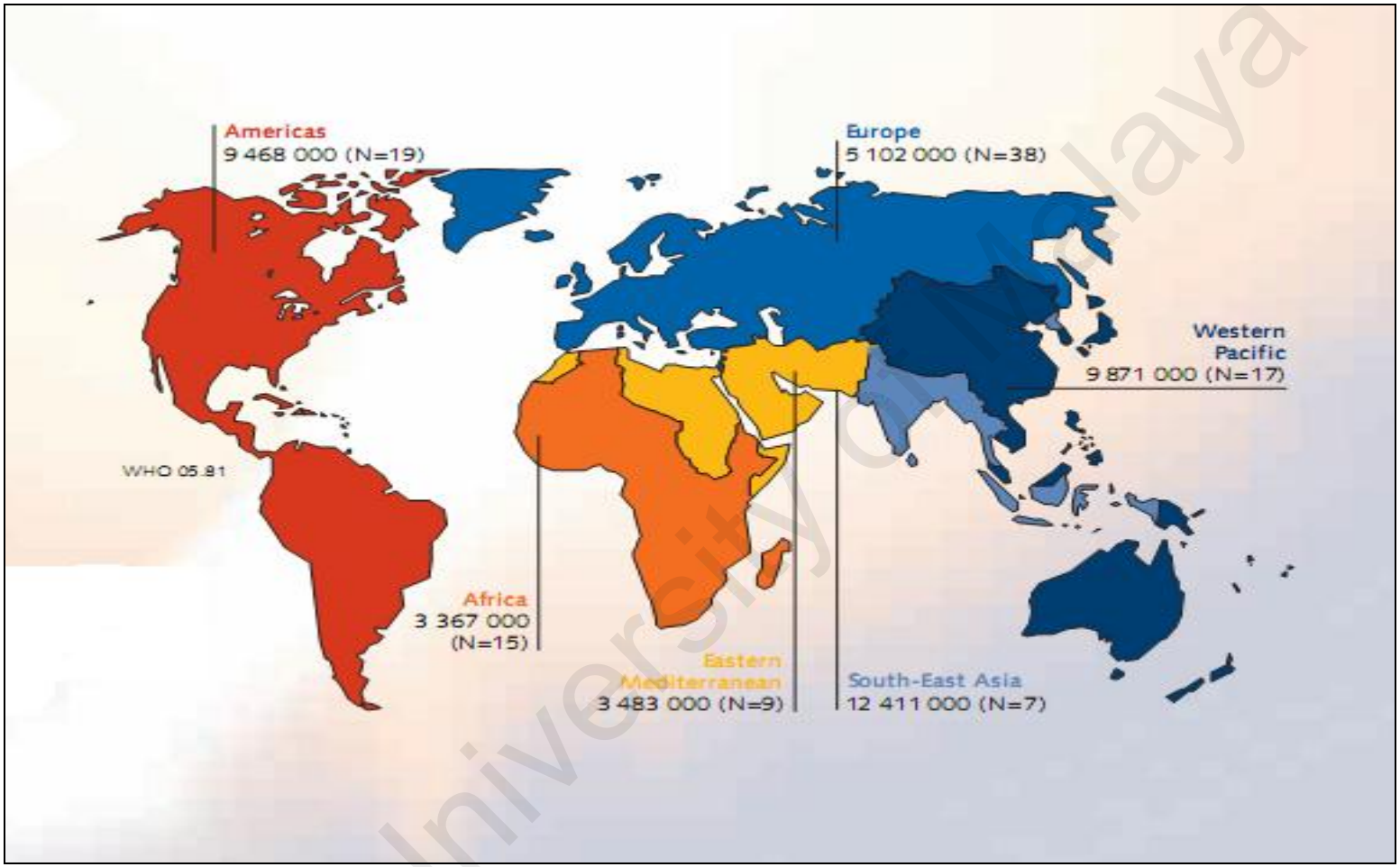

Figure 2.1: Worldwide distribution of epilepsy. Source: Atlas: Epilepsy Care in the World, 2005.

\

Table 2.1: Clinical classification of patients in studies on epilepsy in Asia. Source: Mac et al., 2007.

Country	Reference	Year	Seizure type classification			Aetiology classification			*N*	Method
			GS (%)	FS (%)	US (%)	IE (%)	CE (%)	SE (%)		
India	Radhakrishnan et al., 2000	2000	58.8	30.6	NA	NA	NA	NA	1175	Door-to-door survey
Laos	Tran et al., 2006	2006	63.6	27.3	9.1	27.3	48.5	24.2	33	Door-to-door survey
Hong Kong	Fong et al., 2003	2003	NA	NA	NA	38.7	13.6	38.7	736	Adult patient in hospital
Hong Kong	Wong, 2001	2001	NA	NA	NA	18.0	22.0	53.3	105	Children with West syndrome
Hong Kong	Ng et al., 2001	2001	NA	NA	NA	3.9	59.9	35.1	2952	Review of outpatient records
Hong Kong	Kwong et al., 2001	2001	49.5	48.2	2.3	42.4	16.8	40.8	309	Child patients
Indian	Thomas et al., 2005	2005	42.0	58.0	NA	NA	NA	NA	112	PWE with follow-up >12months at tertiary care epilepsy centre and aged >16 years
Malaysia	Win, 1993	1993	86.0	14.0	NA	NA	NA	NA	593	Adult patients with EEG
Malaysia	Win, 1993	1993	92.0	8.0	NA	NA	NA	NA	593	Child patients with EEG
Malaysia	Manonmani and Tan, 1999	1999	NA	NA	NA	78.0*		22.0	165	Newly diagnosed epilepsy
Singapore	Loh et al., 1997	1997	69.0	31.0	NA	NA	NA	NA	106	All epilepsy
Singapore	Loh et al., 1997	1997	29.0	64.0	7.0	NA	NA	NA	14	Refractory seizures

Abbreviations: GS, generalised seizures; FS, focal (partial) seizures; US, unclassified seizures or multiple seizure types; IE, idiopathic epilepsy; CE, cryptogenic epilepsy; SE, symptomatic epilepsy; *N*, number; NA, not available; PWE, people with epilepsy; EEG, electroencephalogram.

*This figure applies to IE and CE combined.

2.2 Types of epileptic seizures

According to Commision of ILAE (1981), only two major types of epileptic seizures are recognized in 1981 that is partial (focal) seizures and generalized seizures. The features that distinguish between these types are based on the site of the abnormal neuronal activity or seizure initiation, type of clinical presentation and brain activity by an electroencephalography manifestation (Shneker and Fountain, 2003; Browne and Holmes, 2001). However, a seizure is labeled as an unclassified seizure when it cannot be classified due to some reasons such as inadequate or incomplete medical data.

2.2.1 Partial seizures

A partial seizure usually begin with an electrical discharge in one limited area of the brain either only on one whole hemisphere of the brain or part of a lobe (Bradley, 2012). The symptoms are varied according to where the seizure occurs. The example of symptoms in partial seizures is simplified in Table 2.2. Partial seizures could be divided into three basic types which are: 1) Simple partial seizures, 2) Complex partial seizures, and 3) Secondarily generalized partial seizures. Table 2.3 summarizes the example of clinical features in partial seizures.

Table 2.2: The example of symptoms in partial seizures.

Affected area of the lobes in the brain	Symptoms
● In the frontal lobe	- A wave-like sensation in the head
● In the temporal lobe	- A feeling of déjà vu
● In the parietal lobe	- A numbness or tingling
● In the occipital lobe	- Visual disturbance or hallucination

Table 2.3: The example of clinical features in partial seizures.

Type of partial seizures	Clinical feature
1) Simple partial seizures (SPS)	- Patients retain consciousness and are able to remember what happens during the seizure. - it lasts for less than 2 minutes at a time ● **Four categories of SPS:** - motor signs (finger jerking or stiffening of part of the body) - sensory symptoms (simple hallucination) - autonomic symptoms or signs (flushing or sweating) - psychic symptoms (garbled speech or feeling of fear)
2) Complex partial seizures (CPS)	- impairment of consciousness during the seizures - some patients may experience an aura (or warning) ● **Additional features of CPS:** - occurrence of automatism symptoms (lip smacking or fumbling) - doing dangerous or embarrassing things during the seizures (walking into traffic or taking their clothes off)
3) Secondarily generalized partial seizures	- some partial seizures may evolve to generalized seizures - some patients may feel changes from consciousness to unconsciousness (followed by tonic-clonic phase), and then slowly back again to consciousness, with usually drowsy, confused, agitated, or depressed after the episode. - it lasts from 1 to 3 minutes ● **Symptoms during tonic-clonic phase:** - tongue or cheek biting - the face may turn a bit blue - urinary incontinence

Adapted and modified from Commision of ILAE (1981).

2.2.2 Generalized seizures

A generalized seizure is usually produced by electrical activity from throughout the entire brain (Commission of ILAE, 1981). The involvement of both sides of the brain at once may explain the occurrence of seizures on both sides of the body at the same time. The generalized seizures could be divided into six basic types based on the type of clinical feature. The six basic types of generalized seizures are: 1) Absence seizures, 2) Myoclonic seizures, 3) Clonic seizures, 4) Tonic seizures, 5) Tonic-clonic seizures, and 6) Atonic seizures. The example of clinical features in generalized seizures is simplified in Table 2.4.

Table 2.4: The example of clinical features in generalized seizures.

Type of generalized seizures	Clinical feature
1) Absence seizures	● **Typical absence seizures:** - an abrupt onset and a blank stare - interruption of the patient's current activity - consciousness is impaired during the seizure but regained quickly after the seizure - it lasts from a few seconds to half a minute and terminated as rapidly as it started ● **Atypical absence seizures:** - the onset and/or termination is not abrupt - changes in tone that are more pronounced
2) Myoclonic seizures	- a sudden and brief involuntary jerks (simple or multiple) - generalized or confined to a part of the body (face and trunk)
3) Clonic seizures	- repetitive rhythmic jerks in absence of tonic components
4)Tonic seizures	- rigid violent muscular spasms such as: - the limbs bind in some tense position - the eye/head deviation toward one side - a rotation of the whole body
5) Tonic-clonic seizures	- the most frequent type of generalized seizures ●**During the tonic phase:** - a sharp sudden muscle spasm - may experience respiratory problems, tongue biting or urinate involuntarily ● **During the clonic phase:** - tonic phase is then followed by the clonic convulsive movements - it lasts for a variable time period
6) Atonic seizures	- a sudden loss/reduction of postural tone which may lead to: - a drop head with loosening of the jaw - dropping of the limbs - falling to the ground

Adapted and modified from Commision of ILAE (1981).

2.3 Drug treatment for epilepsy

There are two types of treatments for epilepsy that can be used in clinical practice: antiepileptic drugs (AEDs) administration and surgery (Shorvon, 2005). The commonly used AEDs of epilepsy for partial and generalized seizures are summarized in Figure 2.2 (Hasan et al., 2010). Phenobarbital, phenytoin, valproate and carbamazepine are examples of the first line drugs and levetiracetam, topiramate, tiagabine, lamotrigine and pregabalin are from the second line drugs that have been used for treatment of epilepsy (Hasan et al., 2010). However, the type of medication prescribed is based on the type of epilepsy that the patients are undergoing such as partial or generalized seizures (Hasan et al., 2010). The surgery is usually an option for patients who are resistant to drug treatment.

Partial seizures (with or without secondary generalization)

- Carbamazepine*
- Phenytoin*
- Valproate*
- Phenobarbital
- Primidone
- Felbamate**
- Lamotrigine*
- Gabapentin
- Levetiracetam
- Oxcarbazepine
- Topiramate*
- Tiagabine
- Zonisamide

Generalized seizures

Absence

- Ethosuximide
- Valproate*
- Lamotrigine*
- Topiramate*
- Levetiracetam

Myoclonic

- Valproate*
- Clonazepam
- Lamotrigine*
- Topiramate*
- Levetiracetam
- Zonisamide

Tonic-clonic

- Valproate*
- Phenytoin*
- Carbamazepine*
- Felbamate**
- Lamotrigine*
- Topiramate*
- Levetiracetam
- Zonisamide

* commonly used AEDs in Malaysian hospitals (Hasan et al., 2010)
** for tonic-clonic seizures associated with Lennox-Gastaut syndrome

Figure 2.2: Commonly used antiepileptic drugs (AEDs).

2.4 Etiology of epilepsy

Rapid developments in research into molecular mechanisms of epilepsy have now resulted in better understanding of the pathophysiology of epilepsy. However, the specific causal genes and the exact mechanism underlying epilepsy remain largely unclear. A basic mechanism of the pathophysiology of epilepsy could be divided into two different physiological levels which are ictogenesis and epileptogenesis (Fisher et al., 2005). For the ictogenesis mechanism, it is said that the characterized prolonged hyperexcitation in the brain may originate from three factors: postsynaptic neuronal membrane, neuronal environment or neuronal networks (Engelborghs et al., 2000). The changes in neuronal depolarization can be caused by alteration in ion channels, ions concentration, metabolic, and neurotransmitter levels, biochemical modification of involved receptors and disrupted of glial cells functions. Those factors can thus facilitate excessive excitability in the brain and consequently lead to epileptic seizures (Engelborghs et al., 2000; Bordey and Sontheimer, 1998).

Epileptogenesis is a mechanism involved in transforming the normal brain into a brain that is prone to seizures. The hypersynchronicity in the brain may be derived from four factors: nonsynaptic mechanism, synaptic mechanism, thalamocortical networks or astrocytes (Blumenfeld, 2003; Acharya, 2002; Rogawski, 2005). Both nonsynaptic and synaptic mechanisms play an important role in synchronicity, signal amplification and spread of seizures which then promote epileptogenesis (Figure 2.4). There are some changes or abnormalities that could be observed during the hypersynchronicity which include failure in ion channels, changes in ionic concentration, reduced GABAergic inhibition and enhanced glutamatergic (Engelborghs et al., 2000; Löscher and Siemes,

1985). Figure 2.3 summarizes the mechanisms that are involved in epilepsy and the key molecular players.

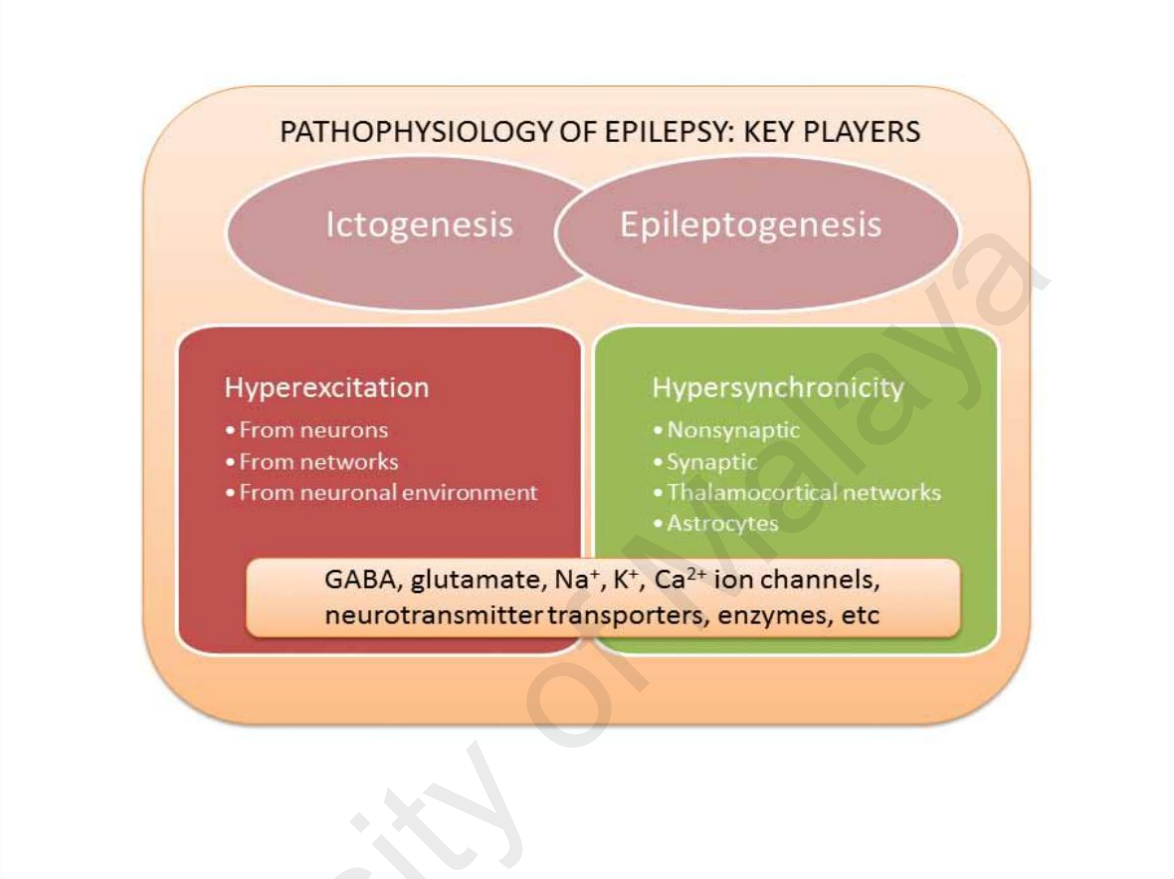

Figure 2.3: Summary of mechanisms involved in epilepsy and the key molecular players.

2.4.1 Pathophysiology underlying susceptibility to epilepsy

There are various brain conditions found to be associated with epilepsy-like status epilepticus, traumatic brain injury, neonatal and adult hypoxia-ischemia, and encephalitis, as well as certain degenerative disorder. The specific mechanisms underlying each of these conditions are still unclear, however, this may be explained by trigger events that lead to structural and functional changes in the brain that consequently initiate ictogenesis and epileptogenesis (Bialer and White, 2010). There are two pathophysiological causes of epilepsies: genetic and acquired factors. Genetic conditions include monogenic mutations

and genetic variation such as CNVs and SNPs, meanwhile the acquired factors may include neuronal migration and autoimmune pathogenesis.

2.4.1.1 Genetic factors

Monogenic mutations are complex modes of inheritance in most familial epilepsies that resulted from interaction of several genetic loci with environmental factors. In about 1% of patients with epileptic disorders the epilepsy appears to be associated with single-gene mutation, and mainly involving ion-channel proteins (Engelborghs et al., 2000). The epileptic syndromes that are associated with single-gene mutation are summarized in Table 2.5 (Chang and Lowenstein, 2003).

2.4.1.2 Acquired factors

Disruption in development of neurons in epilepsy can be caused by alteration and abnormal neuronal migration during early brain development. Other common examples of neurodevelopment disorder that are associated with epilepsy are tuberous sclerosis, x-linked lissencephaly and double cortex syndrome (Engelborghs et al., 2000). Seizures that arise from the autoimmune pathogenesis which is the term that describe the recent discovery of anti-GluR3 antibodies in patients with Rasmussen's encephalitis, particularly in children, are characterized by progressive hemiparesis with dementia and are typically resistant to AEDs (Engelborghs et al., 2000; Rogawski. 2011).

Table 2.5: Epilepsy syndromes associated with single-gene mutations. Source: Chang and Lowenstein, 2003.

Epilepsy syndrome	Mutated gene	Gene product
●Generalized epilepsy with febrile seizures plus	*SCN1B*	Sodium-channel subunit
	SCN1A	Sodium-channel subunit
	SCN2A	Sodium-channel subunit
	GABRG2	$GABA_A$ receptor subunit
●Benign familial neonatal epilepsy	*KCNQ2*	Potassium channel
	KCNQ3	Potassium channel
●Autosomal dominant nocturnal frontal-lobe epilepsy	*CHRNA4*	Neuronal nicotinic acetylcholine-receptor subunit
	CHRNB2	Neuronal nicotinic acetylcholine-receptor subunit
●Childhood absence epilepsy and febrile seizures	*GABRG2*	$GABA_A$ receptor subunit
●Autosomal dominant partial epilepsy with auditory features	*LG1*	Leucine-rich transmembrane protein

2.4.2 Pathophysiology underlying resistance to antiepileptic drugs

Antiepileptic drugs (AEDs) function through three ways including modulation of voltage- and/or ligand-gated ion channels, enhancement of synaptic inhibition and inhibition of synaptic excitation for treatment of epilepsy (Rogawski and Löscher, 2004).

2.4.2.1 Modulation of voltage- and/or ligand-gated ion channels

AEDs modulate the conductance of ligand-gated ion channels by binding to neurotransmitters that regulate inhibition and excitation. In order to suppress epileptic seizures, these systems are reported to cause enhancement in GABA-mediated inhibition and suppression in glutamatergic excitation (Meldrum and Rogawski, 2007; Rogawski, 2011). The AEDs that block voltage-gated calcium (CA^{2+}) channels are also important target for AEDs. It is particularly due to burst firing associated with synchronicity in the thalamus in absence seizure (Meldrum and Rogawski, 2007; Perez-Reyes, 2003).The Ca^{2+} entry into the cells via the neuronal T-type CA^{2+} channels can cause depolarization and also

activate other ion channels which then lead to burst firing and oscillatory activity as in both sleep and wake cycle (Rogawski and Löscher, 2004). Other examples of the voltage-gated ion channels that contribute to burst discharges by enhancing after-depolarization potential are NA^+ and K^+ channels (Meldrum and Rogawski, 2007). To date, there are some AEDs that inhibit NA^+ channel that would also be found to block T-type CA^{2+} channels (Rogawski and Löscher, 2004).

2.4.2.2 Enhancement of synaptic inhibition

The enhancement of synaptic inhibition will be achieved through interaction of AEDs with fast ionotropic GABA receptors or modification of enzyme activity and transporters that are involved in GABA synthesis and reuptake. GABA is the principal inhibitory neurotransmitter in the brain that binds postsynaptically to the ionotropic $GABA_A$ receptor and presynaptically to the metabotropic $GABA_B$ receptor (Meldrum and Rogawski, 2007).

2.4.2.3 Inhibition of synaptic excitation

The action of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on glutamatergic excitation will result in the suppression of synaptic excitation by mediating synaptic signaling (Rogawski, 2011). The AMPA receptors are the most abundant ionotropic glutamate receptors rather than n-methyl-D-aspartate (NMDA) and kainate (KA) receptors, and have lower glutamate affinity than NMDA receptors (Rogawski, 2011; Meldrum, 2000). Glutamate is the principal excitatory neurotransmitter that binds to both ionotropic and metabotropic types of receptors (Rogawski, 2011).

2.4.3 Mechanisms involved in drug resistance

According to Kwan and Brodie (2006), there are two hypotheses that have been proposed in relation to drug resistance in epilepsy such as target hypothesis and transporter hypothesis. Firstly, the target hypothesis proposed that alteration in cellular or molecular target of an antiepileptic drug (AED) can cause reduced sensitivity to the drug and consequently leads to drug resistance. For instance, the subtype of GABA receptor is shown to be altered in patients with uncontrolled temporal lobe epilepsy but it is still unclear whether it would itself affect the action of the AED sufficiently to cause drug resistance (Kwan and Brodie, 2006). Secondly, the multidrug transporter hypothesis proposed that overexpression of drug transporters belong to the ATP-binding cassette (ABC) transporter superfamily is also found to be implicated in drug resistance. As the ABC transporters like multidrug-resistance proteins (MDRs) which are encoded by the *ABCB* genes, multidrug-resistance associated proteins (MRPs) which encoded by the *ABCC* genes and breast cancer resistant protein (BCRP) which is encoded by the *ABCG2* gene (Robey et al., 2009) are extensively distributed in the blood-brain barrier and cerebrospinal fluid-brain barrier, these transporters are believed to cause lowered drug levels in the plasma by driving the flow of their substrates against their concentration. However, it is still unclear whether it occurs before the onset of epilepsy or if is a consequence of the seizures or the treatment (Lazarowski et al., 2007). Thus, the increasing interest of this field still remains and more researches are needed in future despite the existence of some supporting evidence on the transporter hypothesis.

2.5 Candidate genes for epilepsy susceptibility studies

In 400 BC, Hippocrates recognized that epilepsy had a hereditary component. This highlighted the key role of genetics in idiopathic generalized epilepsy (IGE). The term "idiopathic" is usually used synonymously with "genetic" at the beginning of the 21st century. This earlier claim is supported through familial aggregation studies comparing the prevalence of epilepsy in a group of relatives (cases) and in the general population (controls) and twin studies investigating concordance in monozygotic (identical) and dizygotic (non-identical) twin pairs in which both studies aimed at determining the genetic impact of the epilepsies (Helbig et al., 2008). The first-degree relatives of patients with IGE have an increased risk to develop IGE higher than observed in other epilepsies, and hence a strong genetic impact in IGE is implicated, even though most patients with IGE do not have a direct family history (Bianchi et al., 2003; Hemminki et al., 2006; Winawer and Shinnar, 2005). To date, there is some evidence to show that specific IGE sub-syndromes which include childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic-clonic seizures (EGTCS) have distinct genetic factors (Wallace et al., 2001; Cavalleri et al., 2007a; Stogmann et al., 2006). Meanwhile, the concordance in twin studies refers to the fact that both twins within a twin pairs are affected and approximately 70% concordance in monozygotic twins suggests a strong genetic contribution to IGE, while much lower concordance rates are observed in dizygotic twins (Lennox, 1951; Berkovic et al., 1998; Kjeldsen et al., 2003; Vadlamudi et al., 2004).

The common forms of IGE are complex genetic disorders, in which genetic and environmental factors are thought to interact. A febrile seizure is an example of a gene-environment interaction whereby a fever is an essential trigger for a seizure to occur.

Within this framework, genetic factors may represent risk factors with different degrees of pathogenicity, ranging from monogenic disorders, in which mutations are considered causal, to complex genetic disorders, in which individual genetic alterations may confer a relatively small risk (Mullen et al., 2009). The frequency of genetic variation within the population may range from rare (1%), like the epilepsies, to common (up to 50%) variations. Most febrile and afebrile seizures seen in the clinics are multifactorial with the underlying genetic basis being polygenic (Berkovic et al., 1998; Mulley et al., 2005). It will then result in a cumulative effect of a number of susceptibility alleles to produce a specific sub-syndrome or phenotype (Mulley et al., 2005; Dibbens et al., 2007; Mulley et al., 2008). Functional effects consistent with predisposition to epilepsy have been found experimentally for naturally occurring genetic variation found in a calcium ion channel gene and a GABA receptor subunit gene. There is increasing evidence for acquired channelopathies where environmentally acquired insults such as trauma, hypoxia or vascular lesions result in changes in transcription, assembly or function of ion channels. This thus suggests ion channel defects as a common pathogenic pathway in a multitude of epilepsies (Berkovic et al., 2006).

Association studies are one type of methods used in molecular genetic approach and are characterized to investigate the statistical association of the candidate single nucleotide polymorphisms (SNPs) in cases and controls (Page et al., 2003; Todd, 2006). According to Cavalleri et al. (2007b), a study of 279 candidate genes coding for ion channels, neurotransmitter receptors, metabolizers and transporters in a large cohort of 2717 cases with various epilepsy syndromes had failed to identify clear risk factors for different epilepsy phenotypes. But, significant associations of variation in five genes (*KCNAB1*, *GABRR2*, *KCNMB4*, *SYN2*, *ALDH5A1*) are found only in subpopulations and warrant

replication. Thus, it is hypothesized that the discrepancies in results reported among populations in genetic association study of certain candidate genes are possibly caused by genetic heterogeneity. Therefore, it would be of interest to perform analysis study of certain candidate gene polymorphisms in Malaysia, in which the population is made up of three major ethnicities namely Malay, Chinese and Indian, which have different genetic background but sharing similar geographical factor. The main aim in this study therefore, is to find if any variants of the selected candidate genes are significantly associated with risk of epilepsy and to response to antiepileptic drugs in the three major ethnic groups in single SNPs analysis and/or haplotype-based analysis.

2.6 Role of candidate genes in response to antiepileptic drugs

Based on the potential influence on AEDs response, pharmacogenetics of epilepsy could be divided into three major classes of genes: 1) drug transporters, 2) drug metabolizing enzymes (DMEs), and 3) AED targets (Shorvon, 2004; Mulley et al., 2005; Dibbens et al., 2007; Mulley, 2008). Figure 2.4 summarizes the genetic variability that affects interindividual variability in response to AEDs.

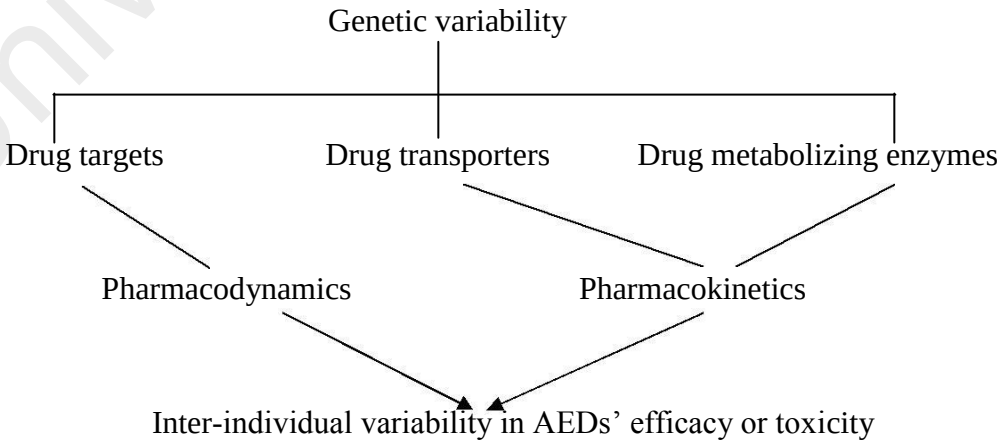

Figure 2.4: Genetic variability that affects interindividual variability in response to AEDs.

2.6.1 Genes encoding AED transporters

The increased activity of drug transporter proteins will cause insufficient amount of drug molecules in the epilepsy brain by decreasing uptake of AEDs into the brain and decreased absorption or increased excretion of the drug (Schmidt and Löscher, 2005; Tishler et al., 1995; Kwan and Brodie, 2005). The drug transporter proteins are membrane-bound efflux transporters that belong to the adenosine triphosphate (ATP)-binding cassette (ABC) proteins and the solute carrier (SLC) proteins. As the ABC transporter proteins like multidrug-resistance proteins (MDRs or *ABCB*) and multidrug-resistance associated proteins (MRPs or *ABCC*) are the most extensively studied transporters involved in drug disposition and effects (Borst et al., 2000; Evans and McLeod, 2003), genetic variation of the genes that encode these proteins are expected to cause alteration in the rate of drug uptake, distribution or efflux and thus resulting in variable drug concentrations, effectiveness and/or occurrence of side effects (Goldstein et al., 2003).

The MDRs are localized in many normal organs such as bile canaliculi in the liver, brush-border membrane of intestine, kidney, adrenal gland, uterus, testis, in endothelial cells of the blood-brain barrier (BBB) and in choroid plexus epithelial cells of the blood-cerebrospinal fluid barrier (Fojo et al., 1987; Arceci et al., 1988; Bradley et al., 1990; Fromm, 2000; Jetté et al., 1993) as well as in tumors (Fojo et al., 1987). Overexpression of MDRs is found to be associated with multidrug-resistant phenotypes (Kartner et al., 1983; Ling et al., 1984; Kartner et al., 1985) resulting in reduction of brain accumulation of many AEDs. The MDRs function as efflux transporters which are present to act as active defense mechanism in the brain. Their effects on drug disposition is further explained by decreased drug absorption from the gut lumen and increased drug excretion into the bile and urine, as co-expression of MDRs and *CYP3A4* are extensively discovered in the same cells and they

share a large number of substrates and modulators that are affected by both transporters and metabolism (Xie et al., 2001). According to Sisodiya and Mefford (2011), MDR1 and MRP2 are the presumed transporters for carbamazepine (CBZ) and MRPs as transporter for valproate (VPA). Therefore, it would be of a great interest to explore the genetic variation of drug transporters as a possible genetic factor responsible for drug resistant epilepsy and possibly contributing to variability in drug response to AEDs.

2.6.2 Genes encoding AED metabolizing enzymes

Generally, about 30 families of drug metabolizing enzymes (DMEs) are found in human (Evans and Relling, 1999; Ingelman-Sundberg et al., 1999) and many genetic variations of DMEs are reported to be translated into functional changes in the protein that they encode (Weinshilboum, 2003). The hepatic metabolism of drugs consist of two established phases that include phase I reaction (oxidation, reduction and hydrolysis) and phase II reaction (conjugation reactions between endogenous molecule such as glucuronic acid and a drug metabolite) that are mediated by several different DMEs which have important roles in enhancing their excretion from the body by producing metabolites which are more water soluble than the parent compounds (Nagasawa and Nakahara, 1992). According to previous studies, only *CYP2C9, CYP2C19* and *CYP3A4* variants are known to be most relevant to AED metabolism (Kirchheiner and Seeringer, 2007; Klotz, 2007). The gene encoding microsomal epoxide hydrolase (mEH) responsible for detoxification of epoxide intermediates is a candidate for variation in response to CBZ, phenobarbital and phenytoin (PHT).

In addition, the involvement of metabolic pathways in the elimination of most AEDs has been recently well defined (Ramachandran and Shorvon, 2003; Saruwatari et al.,

2010). As for the genes of AED metabolizing enzymes, functional polymorphisms will be expected to cause interindividual differences in metabolic profile and drug levels in the plasma that lead to differences in AED efficacy and/or toxicity (Ramachandran and Shorvon, 2003). The elimination of most AEDs (PHT, CBZ and VPA) is initially metabolized through biotransformation in the liver before the excretion in the kidneys (Klotz, 2007; Anderson, 2008). However, many of the newer AEDs are discovered to be directly eliminated through the kidneys without liver biotransformation. To be more specific, the CBZ is metabolized by epoxidation (*CYP3A4*, *CYP1A2* and *CYP2C8*), hydrolysis (mEH) and glucuronidation (*UGT2B7*), while VPA metabolism involves both -β-oxidation and glucuronidation (*CYP2A6*, *CYP2C9* and *CYP2C19*).

To date, more studies on many candidate genes of CYP450 that have influence on interindividual variability in the pharmacokinetic of AEDs has increasingly become the focus in AED pharmacogenetics as it may play an important role in encoding phase I metabolizing enzymes for many AEDs (Löscher et al., 2009; Saruwatari et al., 2010). According to Ferraro and Buono (2005), the genetic variants are also known to exist in all the major phase II enzyme systems including UDP-glucuronosyltransferases (UGTs), N-acetyltransferases (NAT1 and NAT2) and glutathione S-transferases (GST). Currently, the role of phase II enzymes to AED metabolism is not well characterized than that of phase I (Ferraro and Buono, 2005: Depondt, 2006). The altered function of DMEs in regulating AEDs blood levels and potentially affecting their availability to the target tissues is further supported by the variability in expression of DMEs among different ethnic or age groups, which makes them to be important candidates to explain interindividual variability in AED responsiveness (Ramachandran and Shorvon, 2003).

2.6.3 Genes encoding AED targets

Several first-line AEDs act by different mechanisms to modulate the excitability of drug responsive epilepsy and yet, the mechanism of action of some AEDs is not entirely understood. For CBZ, the main proposed targets are voltage-gated sodium channels and other targets are NMDA, adenosine, monoamine, serotonine and Ach receptors, while the plausible VPA targets are GABA synthesis and metabolism, aspartate and glutamate inhibition, Ca^{2+}, Na^{+} and K^{+} channels (Kwan et al., 2001; Shorvon, 2004).

PHT and CBZ are examples of AEDs that act through binding to and modulation of voltage-gated Na^{+} channel α-subunits. These AEDs modulate the Na^{+} channel in a use-dependent manner which then results in normalization of the hyperexcitable neurons (Macdonald and Kelly, 1993). Therefore, genetic variation of the genes that encode ion channel subunits may explain resistance to AEDs. Other candidates in this category include genes coding for effect or components downstream in the pathway of AED action and target. Mutations in the AEDs targets through a direct change (a structural change of the target affecting AED binding) or indirectly (through altered gating resulting in differential AED action) can be observed in other ion channel subunits and element of neurotransmitter pathways like K^{+} and Ca^{2+} channels, GABA and glutamate receptors, GABA transporters and GABA transaminase (Pitkänen and Lukasiuk, 2011).

According to Remy et al. (2003), the mechanism of action of CBZ which is a use-dependent blockade of voltage-dependent sodium channels is completely lost in patients with resistance to carbamazepine. This is further supported by a study by Tate et al. (2005) which suggests a polymorphism in *SCN1A* to be associated with drug responsiveness to PHT and CBZ. Thus, genetic variation of the genes that encode AED targets is expected to alter AED pharmacodynamics and then lead to interindividual variation in AED response

(Lucas et al., 2005; Goldstein et al., 2007; Rees, 2010). Recent studies showed that genetic variations of any gene with a role in the molecular pathology of epilepsy or mutation in different genes in syndromic epilepsies are also potential candidates for variation in AED response (Suzuki et al., 2004; Sisodiya and Mefford, 2011). The study carried out in this dissertation, was aimed at investigating the contribution of genetic variation of several candidate genes with susceptibility to epilepsy through comparison of genotypes and allele frequencies between epilepsy patients and control subjects. The study also aimed to examine the possible effects of the common SNPs in selected genes with AED response.

2.7 Candidate genes polymorphisms

2.7.1 Ion channels and regulators

- The voltage-gated potassium channel subunit beta-1 (*KCNAB1*) gene, located at 3q26.1, encodes potassium channels which are involved in various functions in the body, including regulation of neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction, and cell volume. This gene is highly expressed in brain and heart and plays an important role in shaping the action potential, and in neuronal excitability and plasticity (Tempel et al., 1988; Attali et al., 1992). The synonymous *KCNAB*1 rs2280032 polymorphism has previously been reported to be associated with risk of lateral temporal epilepsy in the subjects from Italy (Busolin et al., 2011).

- The sodium channel, voltage-gated, type VIII, alpha subunit (*SCN8A*) gene, located at 12q13.13, encodes a sodium channel which plays a critical role for the rapid membrane depolarization that occurs during the formation of the action potential in excitable neurons (Estacion et al., 2014). This gene is primarily expressed in the central nervous system (Tzoumaka et al., 2000). Some studies examined the association of the *SCN8A* in epilepsy in different populations, but results were inconsistent (Veeramah et al., 2012; Makoff et al., 2010).

2.7.2 Receptors

- The opioid receptor, mu 1 (*OPRM1*) gene, located at 6q25.2, encodes an opioid receptor which is involved in the generation of generalized spike-wave-activity and the pathogenesis of absence seizures (Przewlocka et al., 1998). Amongst the *OPRM1* gene variants, which have been tested for their association in various other disorders (Hishimoto et al., 2008; Gallagher et al., 2006; Barratt et al., 2006),

A118G (rs1799971) locus is the only variation that has been associated with susceptibility to epilepsy (Wilkie et al., 2002; Sander et al., 2000). Patients with idiopathic absence epilepsy showed high G-allele frequencies of the A118G compared to control subjects (Wilkie et al., 2002; Sander et al., 2000). These results indicate that the G-allele of the A118G SNP is a risk allele for epilepsy.

2.7.3 Drug transporters and regulators

- The ATP-binding cassette, sub-family C, member 2 (*ABCC2*) gene, located at 10q24.2, encodes a ABC transporter which is involved in multidrug resistance. The overexpression of this gene on BBB cells may contribute to drug resistance by increasing efflux AEDs to the capillary lumen to a level which may be inadequate to control seizures (Löscher and Potschka, 2005; Schmidt and Löscher, 2009). The mutated allele of the exonic rs2273697 (V417I) variant is reported to be associated with neurological adverse drug reactions as a result of taking CBZ or oxcarbazepine in patients from Germany (Ufer et al., 2011) with partial epilepsy, and in Koreans with epilepsy (Kim et al., 2010), but no association was reported from Austrian epilepsy patients (Leschziner et al., 2006).

- The nuclear receptor subfamily 1, group I, member 2 (*NR1I2*) gene, located at 3q13.33, encodes a phosphoglycoprotein which is involved in regulating the expression of *ABCB1* gene. Previous studies investigating the association between *ABCB1* and *NR1I2* polymorphisms and drug response in epilepsy have been carried out in different ethnic backgrounds with similar results that reported no association of *NR1I2* SNP with treatment response in epilepsy (Haerian et al., 2011; Hung et al., 2007). However, a recent study has explored the association of *NR1I2* gene

polymorphisms in relation to carbamazepine in epilepsy population (Puranik et al., 2013).

2.7.4 Others

- The brain-derived neurotrophic factor (*BDNF*) gene, located at 11p14.1, encodes BDNF proteins which are involved in the growth and differentiation of the neurons and synapses of the central nervous system (Fargali et al., 2012; Ichim et al., 2012). The rs6265 has been extensively studied among epilepsy and some other neurological and mental disorders, including suicidal behavior (Kim et al., 2008), obsessive-compulsive disorder (OCD) (Hall et al., 2003), bipolar disorder (Chang et al., 2013; Wang et al., 2012), and schizophrenia (Cheah et al., 2014; Li et al., 2013) given its function, with few epilepsy studies failed to find any associations (Tondo et al., 2011; Bragatti et al., 2010; Lohoff et al., 2005; Chou et al., 2004). However, evidence for an association with epilepsy is conflicting.

- The calcium homeostasis modulator 1 **(***CALHM1*) gene, located at 10q24.33, encodes a transmembrane glycoprotein which is involved in regulating the calcium homeostasis and amyloid β (Aβ) function. This glycoprotein plays an important role in development and maintenance of epilepsy excitability (Ma et al., 2012; Delorenzo et al., 2005). Apart from the other known variants of this gene, the rs11191692 was chosen in this study as it was the most replicated polymorphism in epilepsy (Lv et al., 2011a). Lv et al. (2011a) found the association between the rs11191692 and susceptibility to temporal lobe epilepsy patients (Lv et al., 2011a). However, there is no report from India for association of rs11191692 with susceptibility to epilepsy.

- The acid-sensing ion channel 1 (*ASIC1*) gene, located at 12q13.12, encodes an acid-sensing ion channel which is involved in the generation and maintenance of epileptic seizures through regulating the brain pH (Chen et al., 2005b). This gene has been previously associated with insulin resistance or with blood pressure levels (Lv et al., 2011b; Wu et al., 2010; Ko et al., 2008). However, it was only recently that rs844347 has been investigated in a study of susceptibility to temporal lobe epilepsy in the Han Chinese population (Lv et al., 2011b).

- The glutamate receptor, ionotropic, kainate 2 (*GRIK2*) gene, located at 6q16.3, encodes a glutamate receptor which is involved in reducing the synaptic concentration of glutamate that produces excessive excitability during development of the brain (Sanchez and Jensen, 2001; Shigeri et al., 2004; Maragakis and Rothstein, 2001). The *GRIK2* polymorphisms has previously been associated with epilepsy (Guo et al., 2012), obsessive-compulsive disorder (OCD) (Mattheisen et al., 2014; Cai et al., 2013; Sampaio et al., 2011), and autism disorders (Shuang et al., 2004; Jamain et al., 2002). Amongst these studies, a GWAS report from China found an association between the rs9390754, rs4840200 and rs9390790 and susceptibility to epilepsy in Han Chinese, but, these SNPs showed no association in the replication cohort (Guo et al., 2012).

2.8 Study objectives

The primary objective of this study is to determine the association of candidate gene polymorphisms and their haplotypes with susceptibility to epilepsy, and thereby determine the genetic risk factors that could be used in a more comprehensive epidemiological approach. The unique multi-ethnic population in Malaysia provides the opportunity to simultaneously study this in the three main ethnic groups of Malaysia.

The secondary objective in this study is to determine the association of candidate gene polymorphisms and their haplotypes with drug responsiveness to AEDs and to compare this association between Malaysian Chinese, Indian and Malay with epilepsy. This is important in order to add more information to explain and estimate the genetic differences in patient's responses to medication. The result from this study that covers genetic information could contribute towards the management of epilepsy in future. Besides, result from this study may also improve the understanding of the etiology of the epilepsy that will help in the development of more effective diagnosis tools and improving treatment medication of epilepsy.

CHAPTER 3

MATERIALS AND METHODS

3.0 MATERIALS AND METHODS

3.1 Materials

3.1.1 Blood collection

5 mL EDTA blood collection tubes (BD vacutainer tubes) (BD Franklin Lakes NJ, USA); blood collection needles, safety needles (22g or less), butterfly needles (21g or less) (TERUMO®, Philippines); syringes (TERUMO®, Philippines); tourniquet, alcohol swab, cotton wool, sterile plaster (Hansaplast); disposable latex examination gloves (Cross Protection®, Malaysia).

3.1.2 DNA extraction

GeneAll® Exgene™ Blood SV Mini (GeneAll Biotechnology, Seoul, South Korea); Absolute Ethanol (Merck, Germany) ; 1.5 mL microcentrifuge tube (Axygen, Poland).

3.1.3 Determination of DNA concentration

Nanodrop™ 2000c Spectrophotometer (Thermo Scientific, Waltham, MA); 1.5 mL microcentrifuge tube (Axygen, Poland).

3.1.4 SEQUENOM genotyping

96-well plate and plate sealing film; various primers (Integrated DNA Technologies, USA); SpectroClean Resin (Sequenom, San Diego, CA); SEQUENOM MassARRAY Technology Platform (Sequenom, San Diego, CA); MassARRAY Assay Design software package (version 4.0) (Sequenom, San Diego, CA); MassARRAY Nanodispenser (Sequenom, San Diego, CA); MassARRAY Analyzer Compact MALDI-TOF Mass Spectrometer (Sequenom, San Diego, CA).

3.1.5 Instrumentation

Freezer (Fisher & Paykel, Auckland); Refrigerator (TOSHIBA HYBRID PLASMA); Refrigerated Centrifuge SIGMA 2-16 PK (Sartorius); Micropipettes (2 µL, 10 µL, 20 µL, 200 µL and 1000 µL) (Eppendorf, Germany); Multichannel Pipette (HTL Lab Solutions , Poland); Gel Electrophoresis System with Power Pack (TRANSLAB, Malaysia & WEALTEC ELITE 300); UV Transilluminator System (G-Box, Syngene, UK); Ice-maker Machine (Scotsman AF 80); Maxi Mix II Vortex Machine (Thermolyne, USA); Thermo Block TDB-120 (BIOSAN); Nanodrop™ 2000c Spectrophotometer (Thermo Scientific, Waltham, MA); Sequenom MassARRAY (Sequenom, San Diego, CA).

3.2 Methods

3.2.1 Background of study methodology

This research project is an association study using the approach of genetic association between candidate genes and an outcome. Both prospective and retrospective data were used in this study. To achieve the objectives of this project, the study looked at two outcomes, and hence the study was divided into 2 parts. For part I, we explored whether the variation in genetic polymorphism contributes to the susceptibility to epilepsy among patients in the Malaysian population. For part II, we also identified the relationship between genetic variation and drug responsiveness of antiepileptic drugs (AEDs) in epilepsy patients who were receiving long term carbamazepine or valproate as monotherapy drug for a period of at least a year (Figure 3.1).

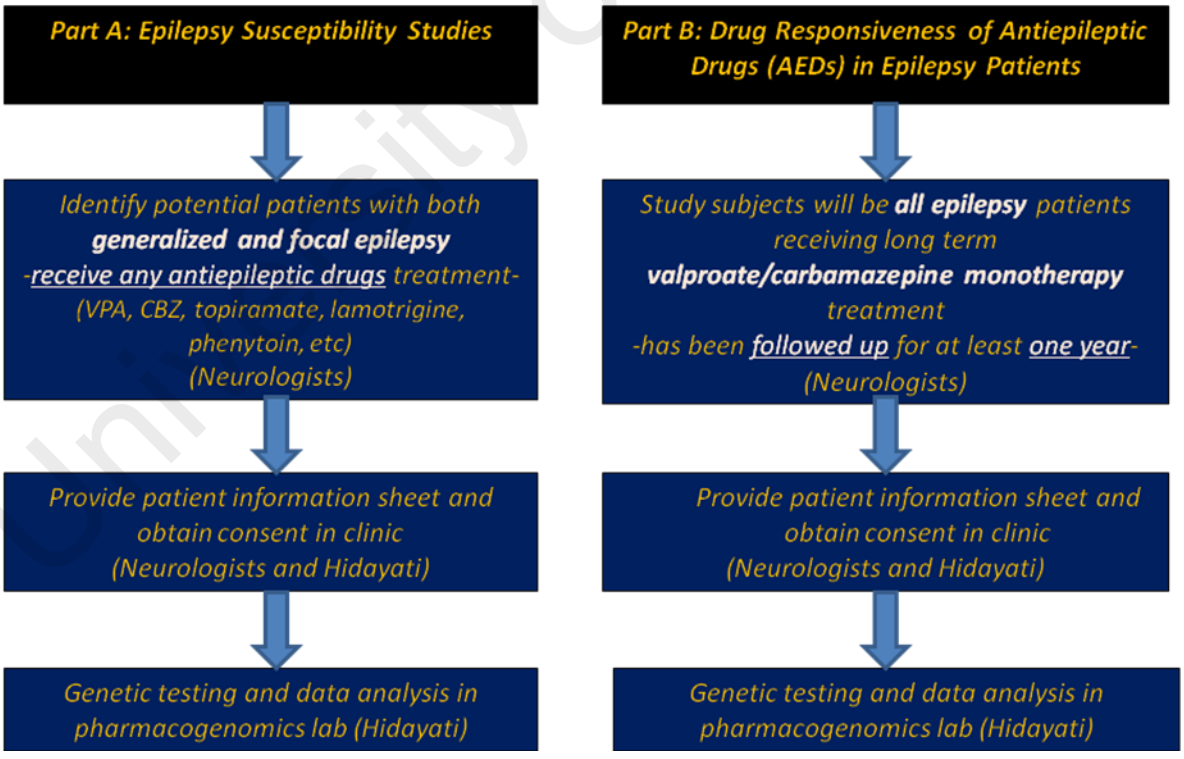

Figure 3.1: Description of each study.

3.2.2 Study population

All patients who participated in this study were recruited through three epilepsy clinics including 1) University of Malaya Medical Centre (UMMC, Lembah Pantai, Kuala Lumpur, Malaysia) 2) Universiti Kebangsaan Malaysia Medical Centre (UKMMC, Cheras, Kuala Lumpur, Malaysia) and 3) Hospital Kuala Lumpur (HKL, Jalan Pahang, Kuala Lumpur, Malaysia). Prior to sample collection, the study protocol was reviewed and approved by the ethics committee of UMMC (MEC Reference Number: 889.5) and UKMMC (Reference number: UKM 1.5.3.5/244/SPP2) and permission for conducting medical research in HKL was obtained from National Medical Research Register (NMRR) of the Ministry of Health Malaysia (MOH) (Unique NMRR Registration ID: NMRR-11-950-10301) (see Appendix A).

The clinic meetings were held and clinical neurologists and nurses were given detailed explanation of the aims, procedures, potential drawbacks and benefits of the study. On the day of blood sampling, all patients were informed that the participation in this study was entirely voluntary and they could withdraw from the study at any point of time without giving reasons for doing so. If they agreed to participate, their consent was obtained in the form of their dated signatures, and in the case of children, parents were approached for their consent on behalf of their children.

The study population was drawn from the epilepsy patients of the Malaysian population, especially who reside around Kuala Lumpur and Selangor areas (Figure 3.2). In the present study, the study population was recruited from unrelated epilepsy patients. Epilepsy was classified according to seizure type and epilepsy syndrome using the International League Against Epilepsy (ILAE).

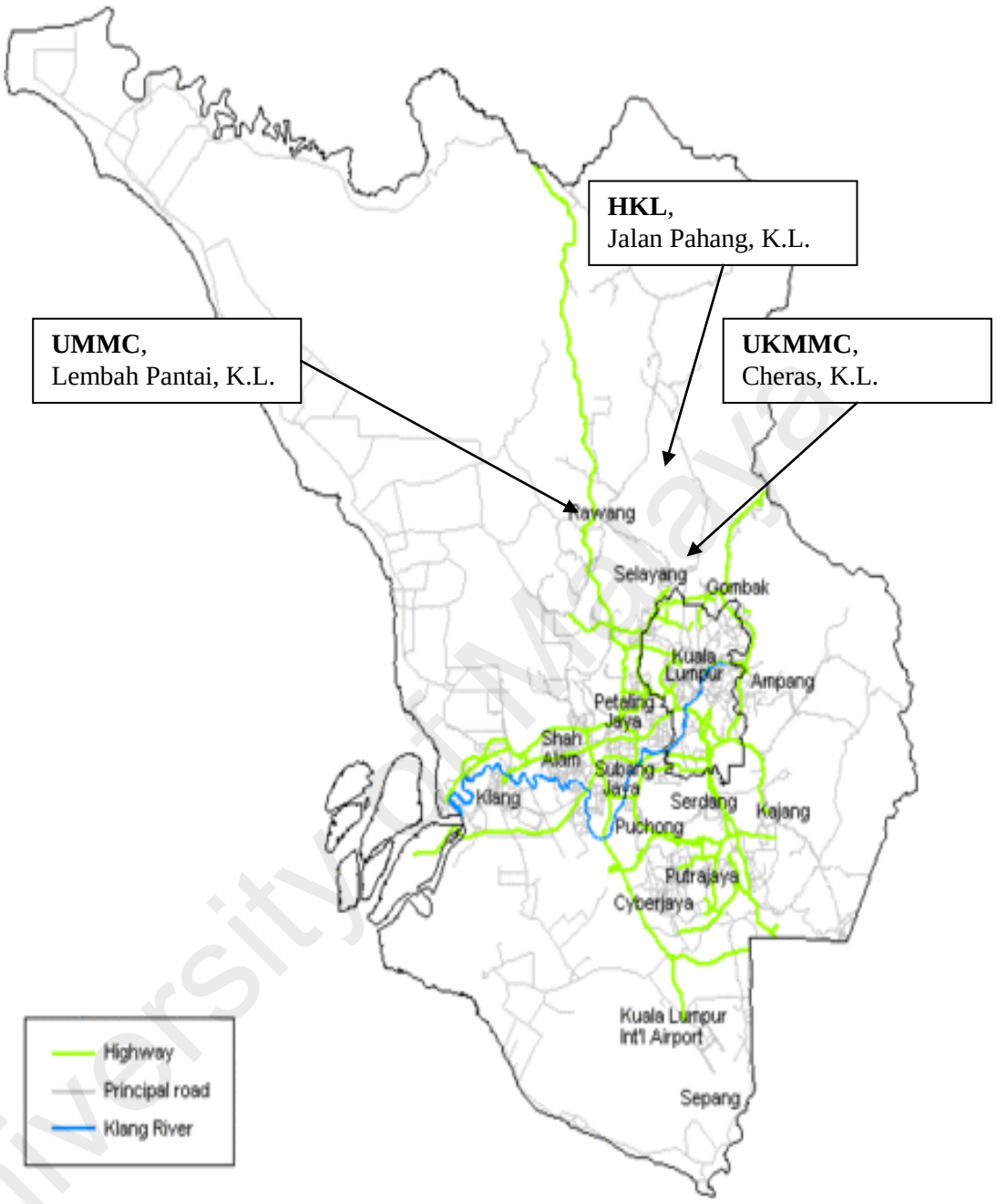

Figure 3.2: Principal cities within Klang Valley within the borders of state of Selangor and Federal Territory of Kuala Lumpur. Location of medical centres and hospitals were involved in this study. Source: http://en.wikipedia.org

3.2.3 Susceptibility to epilepsy study

3.2.3.1 Subject recruitment

A total of 699 epilepsy patients and 1532 healthy controls in UMMC were used in this study. Patients recruited from the collaborating epilepsy clinics were eligible for inclusion if they were diagnosed with generalized or focal epilepsy and taking any AED as monotherapy or polytherapy treatment at the time of the study. Patients with any of the following conditions were excluded from this study; presence of severe concomitant illness, history of pseudoseizures, unreliable medical record of seizure frequency, or positive hepatitis B and C results at the time of the study (Table 3.1).

Table 3.1: Inclusion and exclusion criteria of the susceptibility to epilepsy study.

Inclusion criteria	1) Generalized or focal epilepsy* **Subjects will be enrolled based on confirmed epilepsy diagnosis according to ILAE guidelines (Commision of ILAE, 1989)* 2) Human Immunodeficiency Virus (HIV) negative* **status of HIV must be confirmed via a HIV antibody test or other confirmatory tests available within 12 months before screening or at screening* 3) Receiving any antiepileptic drug 4) Male or female 5) Age ≥ 18 years 6) Written informed consent 7) Life expectancy > 3months
Exclusion criteria	1) Severe concomitant illness i.e. chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), active congestive cardiac failure (CCF), active angina pectoris, uncontrolled arrhythmia, uncontrolled hypertension 2) HIV positive* **status of HIV must be confirmed via a HIV antibody test or other confirmatory tests available within 12 months before screening or at screening* 3) History of pseudoseizures 4) Unreliable medical record of seizure frequency 5) Positive hepatitis B surface antigen (HBsAg) results 6) Known history of hepatitis C and recovery status has not been determined at time of screening 7) Severe intercurrent infections

3.2.3.2 Selection of healthy controls

The main criteria for selection of healthy controls were identified and were as follows: (a) they were not taking any medical drugs including antiepileptic drugs, (b) did not have any history of addictive drugs or alcohol abuses over the past 3 months. Prior to blood sampling, the healthy controls were questioned about their age, gender and ethnicity. The healthy controls that were mixed-race descendants for at least 3 generations were excluded from participating in this study. The number of participants and the mean ages of the three ethnic groups of epilepsy patients and healthy controls recruited throughout this study.

3.2.4 Drug responsiveness of antiepileptic drugs study

3.2.4.1 Subject recruitment

The study involved a total of 579 drug responders and 573 drug nonresponders. Subject were recruited from the collaborating epilepsy clinics were eligible for inclusion if they had been prescribed with AEDs for at least a year at the time of the study (Table 3.2). Drug responder was defined as being completely free of seizures for at least one year during treatment with AED. Drug nonresponder group was defined as the occurrence of seizures during a period of one year during treatment with AED monotherapy at maximally tolerated therapeutic dosages (Kwan et al., 2010). However, some of these drug nonresponder patients might be responsive to the second or third AEDs treatment. Subjects with any of the following conditions were excluded from this study; presence of severe concomitant illness, not compliance with AED, history of pseudoseizures, unreliable medical record of seizure frequency, or positive hepatitis B and C results at the time of the study (Table 3.2).

Table 3.2: Inclusion and exclusion criteria of the drug responsiveness of antiepileptic drugs study.

Inclusion criteria	1) Generalized and focal epilepsy* **Subjects will be enrolled based on confirmed epilepsy diagnosis according to ILAE guidelines* 2) Human Immunodeficiency Virus (HIV) negative* **Status of HIV must be confirmed via a HIV antibody test or other confirmatory tests available within 12 months before screening or at screening* 3) Receiving carbamazepine or valproate monotherapy and has been followed up for at least one year 4) Compliance with AED 5) No alcohol or illicit drug abuse 6) Male or female 7) Age ≥ 18 years 8) Written informed consent 9) Life expectancy > 3months
Exclusion criteria	1) Severe concomitant illness i.e. chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), active congestive cardiac failure (CCF), active angina pectoris, uncontrolled arrhythmia, uncontrolled hypertension 2) HIV positive* **status of HIV must be confirmed via a HIV antibody test or other confirmatory tests available within 12 months before screening or at screening* 3) Receiving carbamazepine or valproate monotherapy after less than one year 4) Not compliance with AED 5) History of pseudoseizures 6) Unreliable medical record of seizure frequency 7) Positive hepatitis B surface antigen (HBsAg) results 8) Known history of hepatitis C and recovery status has not been determined at time of screening 9) Severe intercurrent infections

3.2.5 DNA extraction

Five mL of blood were drawn from each subject and collected into EDTA tubes. These EDTA tubes were spun using centrifuge at 3000 x g for a minimum of 10 min. After centrifugation, three layers were formed; the plasma at the upper layer, the concentrated leukocytes (buffy coat) at the second layer and the concentrated erythrocytes at the bottom layer (Figure 3.3) (Imagen, 2008). A volume of 200µL of buffy coat that covered the top of the packed red blood cells was removed using a disposable sterile blue pipette tips prior to DNA extraction. GeneAll® Exgene™ Blood SV Mini (GeneAll Biotechnology, Seoul, Korea) was used to extract DNA from the concentrated buffy coat. For all of the collected buffy coats, the DNA extraction protocol was performed according to the manufacturer's instructions (GeneAll, 2012). All buffy coats were processed individually.

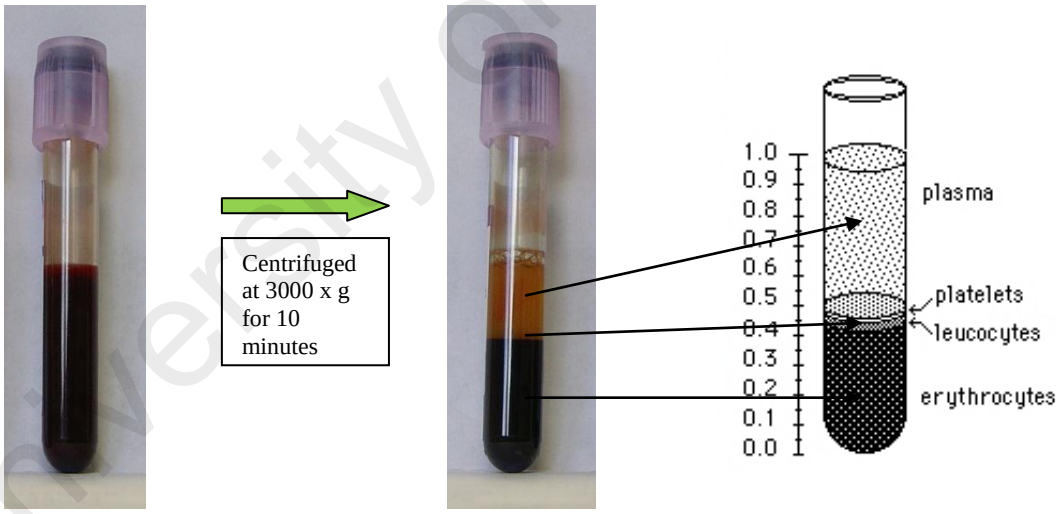

Figure 3.3: Picture of a whole blood EDTA tube (left) and a centrifuged EDTA tube (middle). Illustration of the layer formed after centrifugation at 3000 x g for 10 minutes (right). Source: Tecan Group Ltd., 2014.

Firstly, 20 µL of GeneAll® proteinase K solution (20 mg/mL) was pipetted into the bottom of a new and clean 1.5 mL microcentrifuge tube, following which approximately

200 µL of buffy coat was added to the same tube. A 200 µL volume of Buffer BL (lysis buffer) was added to the sample and mixed thoroughly by pulse-vortexing for 15 s to ensure efficient lysis. The mixture was incubated in a heating block at temperature of 56°C for 10 min. After the incubation period, the 1.5 mL microcentrifuge tube was centrifuged briefly to remove any drops from the inside of the lid. Next, 200 µL of absolute ethanol (99.9%) was added to the sample and mixed again by pulse-vortexing for 15 s, followed by a brief period of centrifuging.

Next, the mixture was transferred to the GeneAll® SV Mini spin column without wetting the rim which was placed in a 2 mL collection tube and centrifuged at 6000 x g (8000 rpm) for 1 min. The 2 mL collection tube that contained the pass-through was discarded and replaced with another new and clean 2 mL collection tube. A 600 µL of Buffer BW (wash buffer) was then added to the SV spin column for the first wash and centrifuged at 6000 x g (8000 rpm) for 1 min. Again, the 2 mL collection tube that contained the pass-through was discarded and replaced with another new and clean 2 mL collection tube. A 700 µL of Buffer TW (wash buffer) was added to the SV spin column for the second wash and centrifuged at 6000 x g (8000 rpm) for 1 min. The pass-through collected into the collection tube was discarded and the SV spin column was reinserted back into the same collection tube. The SV spin column was then centrifuged at full speed (14000 x g; 20000 rpm) for 1 min to remove residual wash buffer. Next, the SV spin column was placed in a new and sterile1.5 mL microcentrifuge tube. A 200 µL of Buffer AE (elution buffer) was added to the SV spin column and incubated at room temperature (15 – 25°C) for 1 min. Lastly, the mixture was centrifuged at 6000 x g (8000 rpm) for 1 min. The extracted DNA sample was stored in – 20°C prior to genotyping analysis (Figure 3.4).

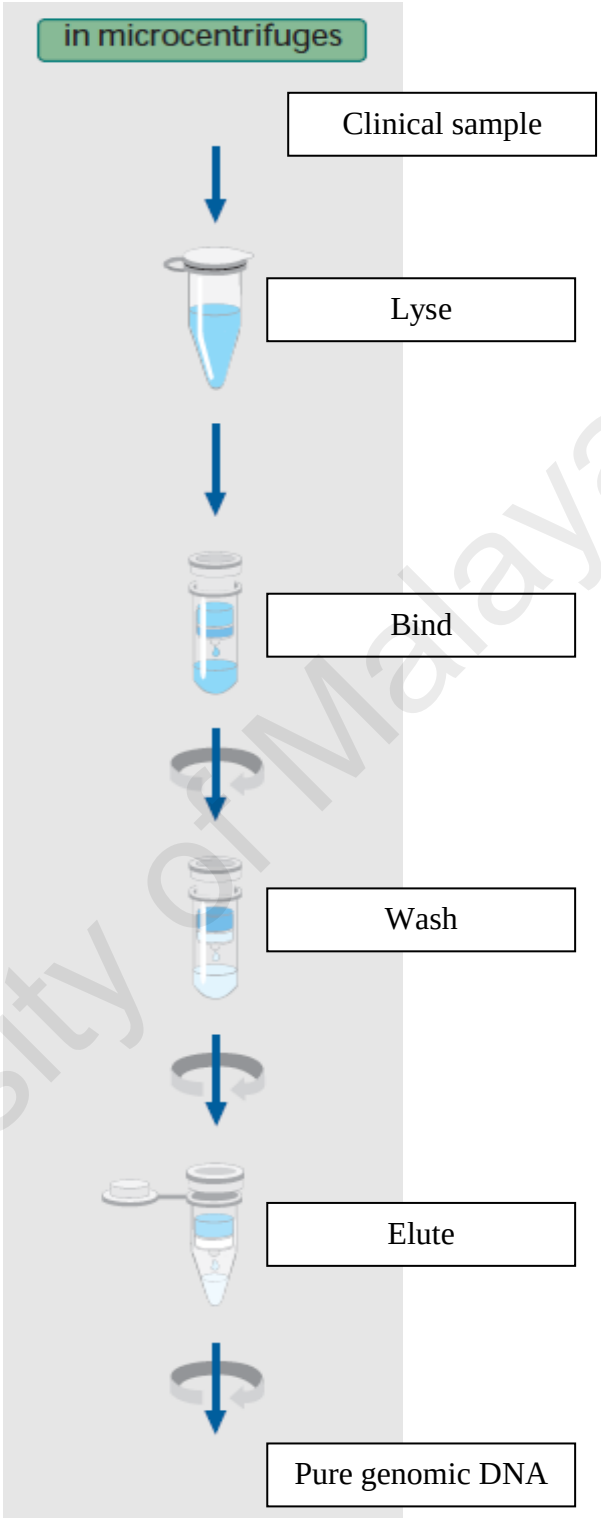

Figure 3.4: Schematic view of the DNA extraction protocol from buffy coat. Source: GeneAll® Exgene™ Blood SV Mini (GeneAll Biotechnology, Seoul, Korea) (GeneAll, 2012).

3.2.6 Selection of candidate genes and variants

The selection of candidate genes from previous studies were used based on the common single nucleotide polymorphisms (SNPs) that were associated with altered functions of the interested proteins (functional variants) or those with prior evidence of association with antiepileptic drug response (www.ncbi.nlm.nih.gov/snp). Table 3.3 summarized the candidate genes and SNPs that were selected for this study.

Table 3.3: Candidate genes and SNPs and their effect on protein products that were selected in this study.

Gene name	Chromosome location	Reference SNP ID (variant allele)	Physical location (bp)	Amino acid translation	Ancestral allele	Mutant allele
ABCC2	10q24.2	rs2273697	c.1249G>A	Val417Ile	G	A
GJD2	15q14	rs3743123	c.588C>T	Ser196Ser	C	T
OPRM1	6q25.2	rs1799971	c.118A>G	Asn40Asp	A	G
SLC6A11	3p25.3	rs2304725	c.645T>C	Ser215Ser	T	C
	3p25.3	rs2272394	c.1143G>A	Ala381Ala	G	A
CAMSAP2	1q32.1	rs2292096	c.4132-113A>G	-	A	G
LGI1	10q23.3	rs3758532	c.-731G>A	-	C	T
KCNAB1	3q25.3	rs2280032	c.1082-407A>C	-	T	G
	3q25.3	rs992353	c.*1925C>T	-	G	A
ASIC1	12q13.1	rs844347	c.558+7939A>C	-	A	C
NR1I2	3q13.3	rs6785049	c.912-93G>A	-	G	A
GRIK2	6q16.3	rs4840200	c.1525-10212T>C	-	T	C
CALHM1	10q24.3	rs11191692	c.-2214C>T	-	G	A
SCN8A	12q13.1	rs11169883	c.-55+6189C>T	-	C	T
BDNF	11p14.1	rs6265	c.196G>A	Val66Met	C	T
	11p14.1	rs7103411	c.-21-9993G>A	-	C	T
	11p14.1	rs7127507	c.-22+6827A>G	-	T	C

3.2.7 Genotyping methods

3.2.7.1 Background of genotyping assay

All candidate genetic polymorphisms (17 SNPs) were genotyped using matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry (MassARRAY®, Sequenom, San Diego, CA, USA) at the University of Hong Kong University Centre for Genomic Sciences (Pokfulam, Hong Kong). The genotyping assay were performed in a range of high technology machinery including a Sequenom Compact mass spectrometer, Samsung Nanodispenser and a series of Applied Biosystems 384-well PCR (polymerase chain reaction) machines by adding 5 µL of DNA samples for every assay group (double volume for duplicate samples) into the sterile 96-well skirted plate according to pattern given. The sample quality requirements are shown in Table 3.4.

Table 3.4: Sample quality requirements for genotyping in this study.

Characteristic	Requirement
DNA sample condition	• Double-stranded • Free of PCR inhibitor for example hemoglobin (from blood) and salts • Pure without contamination of any other genomic DNA • Intact (~10 – 20 kb) as shown on 1% agarose gel with proper size marker
Sample concentration	• 10 – 20 ng/µL
A260/280 ratios (UV absorbance)	• 1.7 – 2.0
Volume (µL per assay group)	• 5 uL (double volume for duplicate samples)

3.2.7.2 Sample preparation

All DNA samples were subjected to DNA quantification using Thermo Scientific Nanodrop™ 2000c spectrophotometer (Thermo Scientific, Waltham, MA) for measurement of DNA purity and concentration (Nanodrop Technologies, 2012). The ratio of A260/A280 of ~1.8 and above indicates DNA of high purity (Desjardins and Conklin, 2010). The DNA samples were thawed before being pipetted onto a measurement pedestral, approximately 1 µL DNA using 0 – 2 µL pipettor. Next, the OD measurement and DNA concentration data were recorded into a standardized template using Microsoft Office Excel® 2007 for Windows software.

The concentrated DNA samples were then diluted to its final concentration 10 ng/µL to the total volume of 5 µL using sterile distilled water for every assay group (double volume for duplicate samples). To ensure that quality of DNA samples were high and remained intact (~10 – 20 kb), six randomly selected samples and 2 duplicate check controls were analyzed by agarose gel electrophoresis. A volume of 1 µL of 100 bp DNA ladder (Fermentas, Lithuana) was run in parallel with 5 µL of DNA samples. The DNA samples were electrophoresed in 1% agarose gel with Tris-Borate-EDTA buffer and stained with ethidium bromide (see Appendix B) at a constant voltage of 90V for 60 min. After completion of electrophoresis, gels were visualized and documented using a UV transilluminator system (G-Box, Syngene, UK). Good quality of DNA results were indicated by the presence of DNA with expected sizes.

A total of 32 96-well plates were prepared gently for genotyping 2684 case and control samples according to the plate format given. The new and sterile 96-well plates were labeled with name, date and plate ID prior to loading 5 µL of DNA into the bottom of sample well. To run the duplicate samples, the final volume of DNA were then doubled up and pipetted into the respective sample wells. Out of 96-well plate, only 89 wells were

utilized for samples and the remaining 7 wells were left empty for five duplicate samples (.dup), one GRC control and one blank well (Figure 3.5). All 32 of the 96-well plates that contained DNA samples were sealed tightly with good adhesive film to prevent DNA from leaking out during the sample delivery to HKU (the University of Hong Kong) Centre for Genomic Sciences.

	1	2	3	4	5	6	7	8	9	10	11	12
A	S-01	S-08	S-16	S-23	S-30	S-38	S-45	S-53	S-60	S-68	S-76	S-83
B	S-02	**S-09**	**S-09.dup**	S-24	S-31	S-39	S-46	S-54	S-61	S-69	S-77	S-84
C	S-03	S-10	S-17	S-25	S-32	S-40	S-47	S-55	S-62	S-70	**S-78**	S-85
D	**GRC control**	S-11	S-18	S-26	S-33	S-41	S-48	S-56	S-63	S-71	S-79	**GRC control.dup**
E	S-04	S-12	S-19	S-27	S-34	S-42	S-49	S-57	S-64	S-72	S-80	S-86
F	S-05	**S-13**	S-20	**S-22.dup**	S-35	S-43	S-50	**Blank**	S-65	S-73	S-81	S-87
G	S-06	S-14	S-21	S-28	S-36	**S-13.dup**	S-51	S-58	S-66	S-74	**S-78.dup**	S-88
H	S-07	S-15	**S-22**	S-29	S-37	S-44	S-52	S-59	S-67	S-75	S-82	S-89

Figure 3.5: Arrangement of the samples, blank and control in the 96-well plate.

3.2.7.3 Basic principle of genotyping method

In the present study, genotyping of 17 SNPs were analyzed simultaneously by Sequenom MassARRAY system for 2684 case and control DNA samples. Recently, the high technology of MALDI-TOF (matrix-assisted laser desorption/ionization time of flight) mass spectrometry has helped to allow high-throughput SNP analysis using rapid real-time system on a Sequenom MassARRAY SNP genotyping platform where the reliability, accuracy and analytical process are enough to be used for genotyping applications on a large scale. The basic principle of MALDI-TOF mass spectrometry helped to produce different size products for each allele of a SNP through the extension of an oligonucleotide probe at a SNP site in a polymerase chain reaction (PCR) product. These extended products masses were then analysed using the Sequenom MALDI-TOF mass spectrometer, after the exact size of generated products have been determined through identification of the time-of-flight proportional to mass, and was converted into genotype information by the MassARRAY® Typer 4.0 software (Figure 3.6) (Gabriel et al., 2009).

The MALDI-TOF mass spectrometry was very useful for SNP genotyping in clinical samples particularly when the DNA concentrations were too low due to less amount of blood drawn off from patients or by stringent environments during transport of samples back to the laboratory. The molecular advance of MALDI-TOF mass spectrometry with a high mass resolution made the SNP genotyping a quicker and simpler one. The MALDI-TOF mass spectrometry was offered to perform multiplexed assays maximally up to 40 SNPs in a single well of a 384 well plate. To date, more than 10000 genotypes can be done in a day.

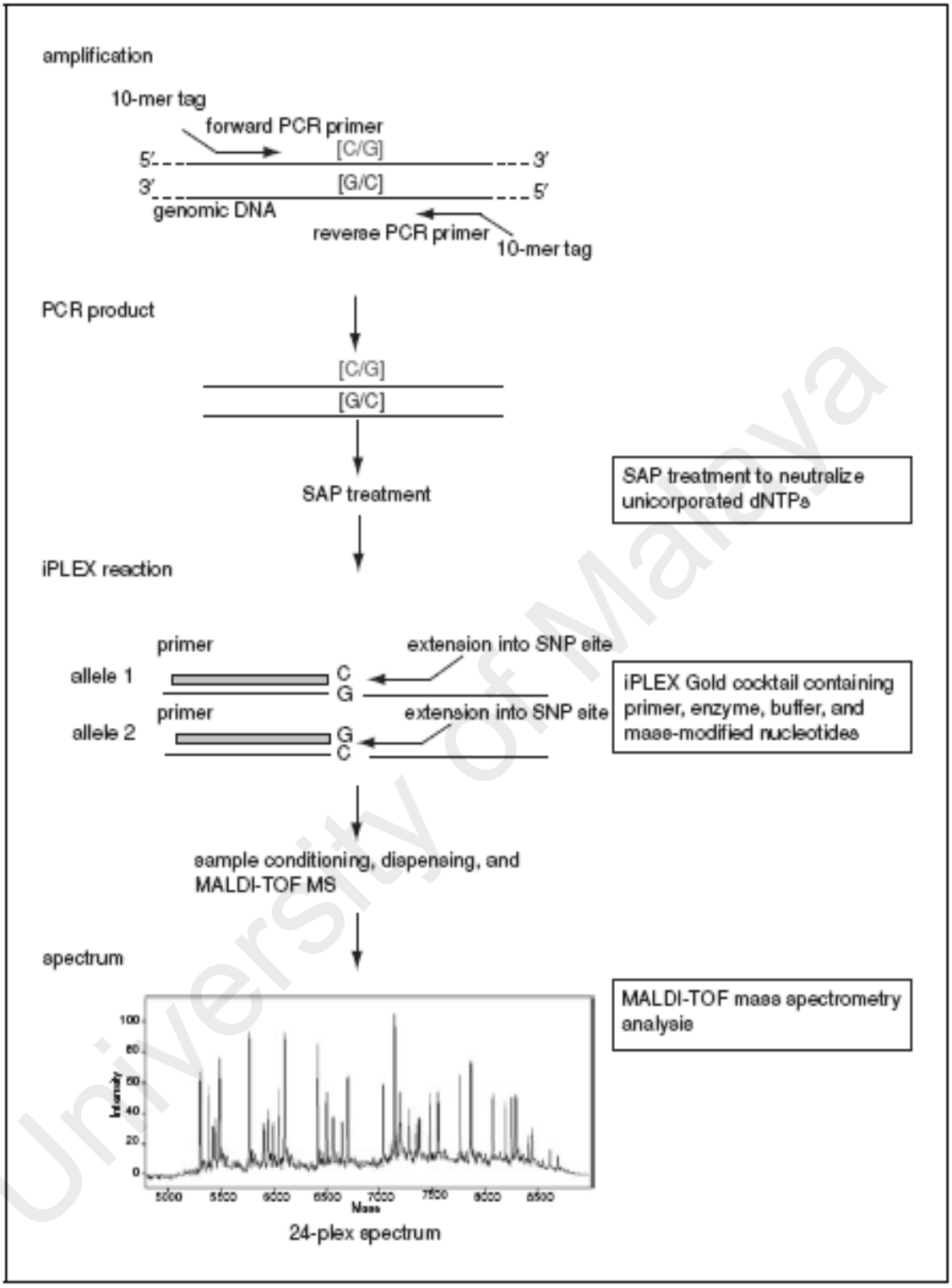

Figure 3.6: The basic principle behind SEQUENOM genotyping. Source: Gabriel et al., 2009.

3.3 Statistical analysis

Statistical analyses in this study were performed using Statistical Package for the Social Sciences (SPSS) statistical software version 16.0 (Chicago, IL, USA). All values were expressed as mean ± standard deviation and frequency for continuous and categorical data, respectively. Prior to statistical calculation, the distributions of continuous variables were checked for normality using the Kolmogorov-Smirnov test. The nonparametric Mann-Whitney *U* test or the Kruskal-Wallis rank sum test was used to compare the ages of participants at study entry and onset of seizure (not normally distributed variables) between drug responder and nonresponder groups. χ^2 test was used to calculate the difference of categorical data, including gender, seizure type and epilepsy syndrome between races. A goodness-of-fit χ^2 test with one degree of freedom was applied to test the Hardy-Weinberg equilibrium (HWE); $p < 0.05$ indicated a lack of agreement with HWE. Adjusted binomial logistic regression analysis for covariates, including ethnicity, gender, age at recruitment, age at onset of epilepsy, seizure type and epilepsy syndrome was used to obtain odds ratios with 95% confidence interval. Haplotype and linkage disequilibrium (LD) analysis for the SNPs was performed using SHEsis online tools (Shi and He, 2005) and corrected for multiple testing by using 100,000 permutations for each SNPs and haplotypes. The lowest frequency threshold (LFT) for haplotype analysis is 0.03 and any haplotype frequency less than 0.03 will not be considered in the analysis. The Bonferroni procedure was used for correction of multiple comparisons. *P*-value of less than 0.05 of two-sided tests of statistical significance was considered as the statistically significant *p*-value. An estimated sample size of 1059 cases and controls would provide 80% power at an α of 0.05 was performed by using Quanto 1.2.4 (Gauderman and Morrison, 2006).

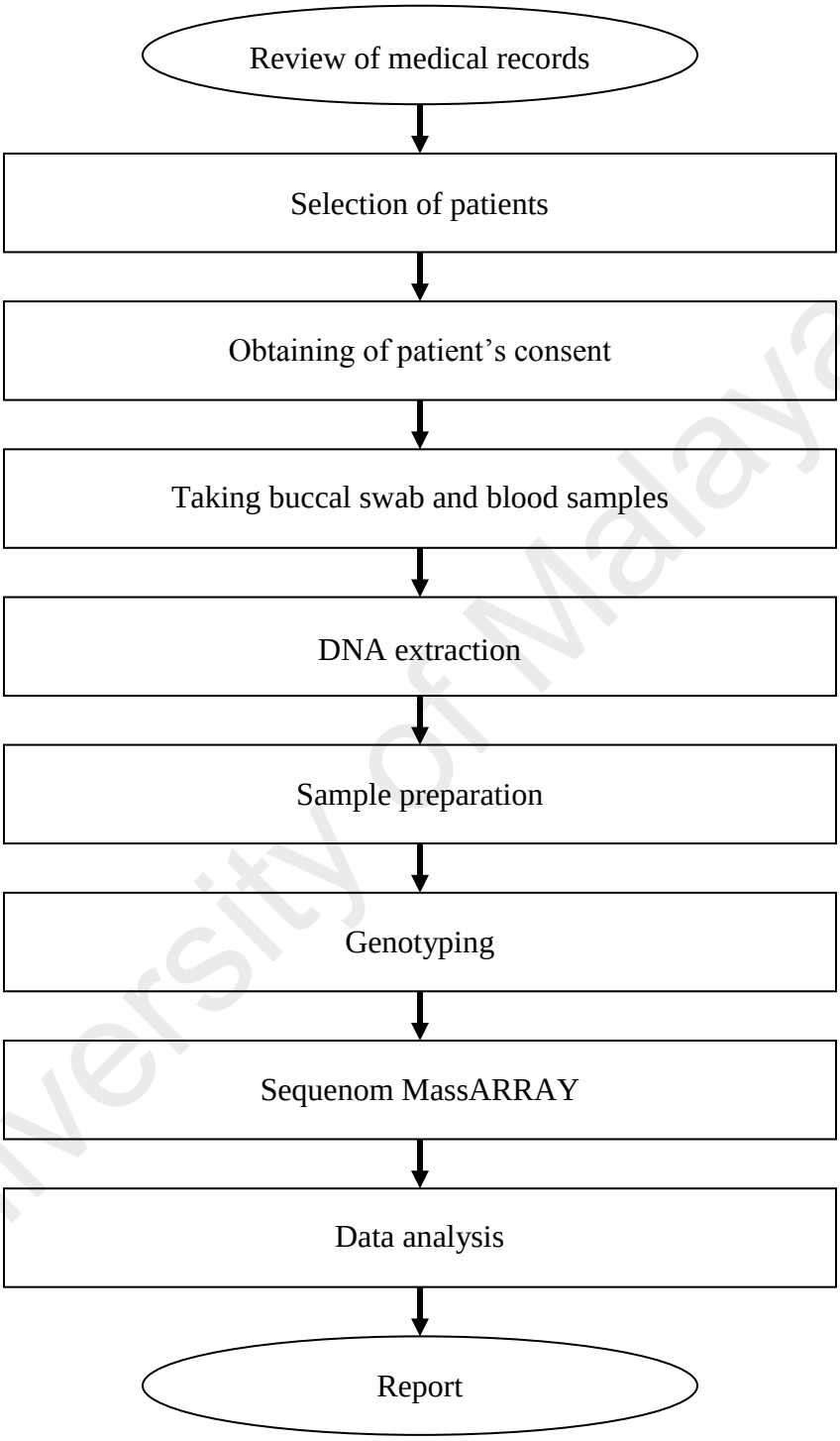

Figure 3.7: Summary of the methods.

CHAPTER 4

RESULTS

4.0 RESULTS

4.1 Demographics and clinical data

Table 4.1 shows demographic and clinical data of 2684 subjects (1152 epilepsy patients and 1532 healthy participants). Out of these patients, 423 (37%), 298 (26%) and 431 (37%) were Chinese, Indians and Malays, respectively. Of the 1152 epilepsy patients, 579 (50%) were drug responders and the remaining were drug nonresponders. Out of the 1532 controls, 638 (42%), 324 (21%) and 570 (37%) were Chinese, Indians and Malays, respectively. There was significant difference of mean age at study between epilepsy patients and healthy controls in the pooled subjects influenced by Malays group ($p < 0.01$). Epilepsy was started earlier in the drug nonresponder than drug responders ($p = 0.01$). The difference of male ratio in patients and controls was not significant in all subgroups. In the pooled subjects, partial seizure was significantly higher in drug nonresponders as compared with drug responders ($p < 0.01$). Idiopathic epilepsy was significantly different of drug nonresponders than drug responders in the Indians ($p < 0.01$).

Table 4.1: Demographics and clinical data of the subjects.

Features	Chinese (1061)					Indians (622)					Malays (1001)					Total subjects (2684)				
	Epilepsy, E (423)		C (638)	p^1	p^2	Epilepsy, E (298)		C (324)	p^1	p^2	Epilepsy, E (431)		C (570)	p^1	p^2	Epilepsy, E (1152)		C (1532)	p^1	p^2
	NR (211)	R (212)				NR (146)	R (152)				NR (216)	R (215)				NR (573)	R (579)			
Age , year, Mean (SD)	36 (16)	37 (18)	35 (13)	0.7	0.1	36 (15)	34 (16)	33 (13)	0.4	0.1	33 (14)	33 (15)	30 (12)	1.0	<0.01	35 (15)	35 (17)	33 (13)	0.9	<0.01
Onset age of seizure , year, Mean (SD)	16 (17)	19 (17)	-	0.1	-	16 (13)	15 (13)	-	0.6	-	13 (12)	17 (15)	-	0.01	-	15 (14)	17 (15)	-	0.01	-
Gender, *N*																				
Female	92 (44)	91 (43)	258 (40)	Ref	Ref	65 (45)	71 (47)	132 (41)	-	-	102 (47)	107 (50)	241 (42)	Ref	Ref	259 (45)	269 (47)	631 (41)	Ref	Ref
Male	119 (56)	121 (57)	380 (60)	0.9	0.4	81 (55)	81 (53)	192 (59)	0.7	0.2	114 (53)	108 (50)	329 (58)	0.6	0.1	314 (55)	310 (53)	901 (59)	0.7	0.12
Seizure type, *N*																				
Generalized	81 (40)	104 (54)	-	Ref	-	65 (46)	85 (59)	-	Ref	-	87 (44)	107 (55)	-	Ref	-	233 (43)	296 (56)	-	Ref	-
Partial	120 (60)	90 (46)	-	0.01	-	75 (54)	59 (41)	-	0.03	-	111 (56)	88 (45)	-	0.03	-	306 (57)	237 (44)	-	<0.01	-
Unspecified*	10	18	-	-	-	6	8	-	-	-	18	20	-	-	-	34	46	-	-	-
Epilepsy syndrome, *N*																				
Cryptogenic	71 (34)	80 (38)	-	Ref	-	58 (40)	33 (22)	-	Ref	-	75 (35)	85 (40)	-	Ref	-	204 (36)	198 (35)	-	Ref	-
Idiopathic	55 (27)	65 (31)	-	0.8	-	48 (33)	77 (51)	-	<0.01	-	65 (30)	77 (36)	-	0.8	-	168 (30)	219 (38)	-	0.04	-
Symptomatic	82 (39)	67 (31)	-	0.2	-	39 (27)	40 (27)	-	0.1	-	74 (35)	50 (24)	-	0.03	-	195 (34)	157 (27)	-	0.2	-
Unspecified*	3	-	-	-	-	1	2	-	-	-	2	3	-	-	-	6	5	-	-	-

Data are expressed as a percentage for categorical data.
Binary logistic regression and *Mann-Whitney U Test. **Excluded from analysis.
Abbreviations: *N*: number; SD: standard deviation; NR: drug nonresponder; R: drug responder; E: epilepsy patient; C: healthy control; p^1: p-value (NR vs. R); p^2: p-value (E vs. C); Ref: referent

4.2 Genetic association data

Genetic association study was performed for susceptibility to epilepsy or to drug responsiveness in epilepsy. In each association study, polymorphisms and haplotypes were performed for the 17 candidate SNPs from 12 genes. Of these SNPs, 16 and 14 SNPs were analyzed for susceptibility to epilepsy and drug responsiveness, respectively (Table 4.2). The observed genotype frequencies for all the polymorphisms were in Hardy-Weinberg equilibrium (HWE) ($p > 0.05$).

Table 4.2: Selected gene polymorphisms involved in this study.

No.	Gene	Polymorphism	Location		MAF	Allele	Amino acid	Association	
			Chromosome	Gene				Susceptibility	Responsiveness
1	*ABCC2*	rs2273697	10:99804058	Exon	0.17	G > A	Val417Ile	-	Yes[7]
2	*GJD2*	rs3743123	15:34752856	Exon	0.29	C > T	Ser196Ser	No	No
3	*OPRM1*	rs1799971	6:154039662	Exon	0.19	A > G	Asn40Asp	No	No
4	*NR1I2*	rs6785049	3:119814886	Intron	0.44	G > A	-	No	No
5	*SLC6A11*	rs2304725	3:10844235	Exon	0.34	T > C	Ser215Ser	No	No
		rs2272394	3:10926026	Exon	0.04	G > A	Ala381Ala	No	No
6	*CAMSAP2*	rs2292096	1:200857641	Intron	0.15	A > G	-	No	No
7	*GRIK2*	rs4840200	6:101879428	Intron	0.20	T > C	-	Yes[1]	No
8	*LGI1*	rs3758532	10:93757414	3'-UTR	0.09	C > T	-	No	No
9	*CALHM1*	rs11191692	10:103454008	3'-UTR	0.28	G > A	-	Yes[2]	No
10	*KCNAB1*	rs2280032	3:156531002	Intron	0.45	T > G	-	No	Yes[8]
		rs992353	3:156538672	3'-UTR	0.44	G > A	-	No	No
11	*ASIC1*	rs844347	12:50067893	Intron	0.28	A > C	-	Yes[3]	No
12	*SCN8A*	rs11169883	12:51597548	Intron	0.21	C > T	-	No	No
13	*BDNF*	rs6265	11:27658369	Exon	0.23	C > T	Val66Met	Yes[4]	-
		rs7103411	11:27678578	Intron	0.26	C > T	-	Yes[5]	-
		rs7127507	11:27693337	Intron	0.29	T > C	-	Yes[6]	-

Abbreviation: No.: number; MAF: minor allele frequency
[1]Significant in Malays symptomatic epilepsy; [2]Significant in Indians cryptogenic epilepsy; [3]Significant in Malays idiopathic epilepsy; [4]Significant in both Indians overall epilepsy and Indians cryptogenic epilepsy; [5]Significant in Indians overall epilepsy, Indians cryptogenic epilepsy, Indians symptomatic epilepsy, pooled samples of overall epilepsy and pooled samples of cryptogenic epilepsy; [6]Significant in Indians cryptogenic epilepsy; [7]Significant in Chinese idiopathic epilepsy; [8]Significant in Malays cryptogenic epilepsy.

According to Table 4.2, 6 SNPs of 4 genes (*GRIK2* rs4840200, *ASIC1* rs844347, *CALHM1* rs11191692 and *BDNF* rs6265, rs7103411 and rs7127507) and 2 SNPs of 2 genes (*ABCC2* rs2273697 and *KCNAB1* rs2280032) were associated with susceptibility to epilepsy and drug responsiveness in epilepsy patients, respectively.

4.3 Susceptibility to epilepsy study

4.3.1 Polymorphisms

Results of susceptibility to epilepsy are reviewed in Table 4.3-4.6. Out of the total genes polymorphisms, 6 SNPs (*BDNF* rs6265, rs7103411 and rs7127507, *CALHM1* rs11191692, *ASIC1* rs844347 and *GRIK2* rs4840200) showed significant associations with susceptibility to epilepsy ($p < 0.005$). The *BDNF* rs6265 T, rs7103411 C and rs7127507 T alone or their haplotypes were risk factors for susceptibility to epilepsy in the Indians. However, *KCNAB1* rs2280032 G and rs992353 A and *SLC6A11* rs2304725 C and rs2272394 A alone or in combination was not associated with risk of epilepsy in Malaysian patients.

4.3.1.1 *BDNF* gene

The *BDNF* rs6265, rs7103411 and rs7127507 were associated with cryptogenic and symptomatic epilepsy in Indians (Table 4.4 and 4.6). The alleles and genotypes of *BDNF* rs6265 were associated with cryptogenic epilepsy in Indians (Table 4.4, OR 2.1, 95% CI 1.5-3.0, p 0.00004 and OR 4.6, 95% CI 1.9-11.1, p 0.001, respectively). The alleles and genotypes of *BDNF* rs7103411 were associated with cryptogenic and symptomatic epilepsy in Indians (Table 4.4 and 4.6, OR 1.9, 95% CI 1.3-2.7, p 0.0003 and OR 3.5, 95% CI 1.6-7.5, p 0.001, and OR 1.9, 95% CI 1.3-2.8, p 0.0004 and OR 3.7, 95% CI 1.8-7.9, p 0.001, respectively). The alleles of *BDNF* rs7127507 were associated with cryptogenic epilepsy in Indians (Table 4.4, OR 0.6, 95% CI 0.4-0.8, p 0.003). The rs6265 T allele and TT genotype in the Indian patients with cryptogenic epilepsy was significantly higher than in controls (38% vs. 23% and 12% vs. 4%, respectively). In this ethnicity, the rs7103411 C allele and CC genotype in the patients with cryptogenic or symptomatic epilepsy were significantly higher than in controls (44% vs. 29% and 18% vs. 9% or 44% vs. 29% and 21% vs. 9%,

respectively). Additionally, the rs7127507 T allele in the patients with cryptogenic epilepsy was significantly higher than in controls (75% vs. 63%). After Bonferroni correction, results remained significant. Therefore, in Indians, *BDNF* rs6265 T and rs7103411 C for cryptogenic and symptomatic epilepsy and rs7127507 T for cryptogenic epilepsy confer risk variants.

4.3.1.2 *CALHM1* gene

The alleles and genotypes of *CALHM1* rs11191692 were associated with cryptogenic epilepsy in Indian ethnic group (Table 4.4, OR 0.6, 95% CI 0.4-0.8, p 0.001 and OR 0.3, 95% CI 0.1-0.6, p 0.002, respectively). In this ethnicity, G allele and GG genotype in the patients with cryptogenic epilepsy were significantly higher than in controls (66% vs. 52% and 42% vs. 28%, respectively). After Bonferroni correction, results remained significant. Therefore, *CALHM1* rs11191692 G confers a risk variant against cryptogenic epilepsy in Indians.

4.3.1.3 *ASIC1* gene

The alleles of *ASIC1* rs844347 were associated with idiopathic epilepsy in Malay ethnic group (Table 4.5, OR 1.7, 95% CI 1.2-2.3, p 0.002). In this ethnicity, C allele in the patients with idiopathic epilepsy was significantly higher than in controls (23% vs. 15%). After Bonferroni correction, results remained significant. Therefore, *ASIC1* rs844347 C confers a risk variant for idiopathic epilepsy in Malays.

4.3.1.4 *GRIK2* gene

The alleles and genotypes of *GRIK2* rs4840200 were associated with symptomatic epilepsy in Malay ethnic group (Table 4.6, OR 1.6, 95% CI 1.2-2.1, p 0.001 and OR 2.5,

95% CI 1.3-4.5, p 0.003, respectively). In this ethnicity, C allele and CC genotype in the patients with symptomatic epilepsy were significantly higher than in controls (45% vs. 34% and 18% vs. 12%, respectively). After Bonferroni correction, results remained significant. Therefore, *GRIK2* rs4840200 C confers a risk variant for symptomatic epilepsy in Malays.

Table 4.3: Association tests of selected gene polymorphisms between epilepsy patients and healthy controls with susceptibility to overall epilepsy in Malaysian population.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
1	*GJD2*	rs3743123																
		CC	358 (56)	217 (52)	-	-	99 (31)	106 (36)	-	-	312 (55)	225 (53)	-	-	769 (50)	548 (48)	-	-
		CT	240 (38)	178 (42)	1.2 (0.9-1.6)	0.1	156 (48)	138 (47)	0.8 (0.6-1.2)	0.3	220 (38)	171 (40)	1.1 (0.8-1.4)	0.6	616 (40)	487 (43)	1.1 (0.8-1.3)	0.2
		TT	36 (6)	27 (6)	1.2 (0.7-2.1)	0.4	69 (21)	52 (17)	0.7 (0.4-1.1)	0.1	38 (7)	30 (7)	1.1 (0.7-1.8)	0.7	143 (10)	109 (9)	1.1 (0.8-1.4)	0.6
		C	956 (75)	612 (73)	-	-	354 (55)	350 (59)	-	-	844 (74)	621 (73)	-	-	2154 (70)	1583 (69)	-	-
		T	312 (25)	232 (27)	1.2 (1.0-1.4)	0.1	294 (45)	242 (41)	0.8 (0.7-1.0)	0.1	296 (26)	231 (27)	1.1 (0.9-1.3)	0.6	902 (30)	705 (31)	1.1 (0.9-1.2)	0.3
2	*OPRM1*	rs1799971																
		AA	241 (38)	154 (37)	-	-	100 (31)	88 (30)	-	-	156 (27)	138 (32)	-	-	497 (33)	380 (33)	-	-
		AG	305 (48)	199 (47)	1.0 (0.8-1.3)	0.9	167 (52)	147 (49)	1.0 (0.7-1.4)	1.0	288 (51)	196 (46)	0.8 (0.6-1.0)	0.1	760 (50)	542 (47)	0.9 (0.8-1.1)	0.4
		GG	85 (14)	68 (16)	1.3 (0.9-1.8)	0.2	56 (17)	62 (21)	1.3 (0.8-2.0)	0.3	126 (22)	95 (22)	0.9 (0.6-1.2)	0.4	267 (17)	225 (20)	1.1 (0.9-1.4)	0.4
		A	787 (62)	507 (60)	-	-	367 (57)	323 (54)	-	-	600 (53)	472 (55)	-	-	1754 (58)	1302 (57)	-	-
		G	475 (38)	335 (40)	1.1 (0.9-1.3)	0.3	279 (43)	271 (46)	1.1 (0.9-1.4)	0.4	540 (47)	386 (45)	0.9 (0.8-1.1)	0.3	1294 (42)	992 (43)	1.0 (0.9-1.2)	0.6
3	*NR1I2*	rs6785049																
		GG	225 (36)	141 (34)	-	-	84 (26)	81 (28)	-	-	265 (46)	177 (41)	-	-	574 (38)	399 (35)	-	-
		GA	311 (49)	202 (48)	1.0 (0.8-1.4)	0.8	153 (47)	144 (49)	1.0 (0.7-1.4)	0.9	238 (42)	196 (46)	1.2 (0.9-1.6)	0.1	702 (46)	542 (47)	1.1 (0.9-1.3)	0.2
		AA	97 (15)	78 (18)	1.3 (0.9-1.8)	0.2	86 (27)	69 (23)	0.8 (0.5-1.3)	0.4	67 (12)	56 (13)	1.3 (0.8-1.9)	0.3	250 (16)	203 (18)	1.2 (0.9-1.5)	0.2
		G	761 (60)	484 (58)	-	-	321 (50)	306 (52)	-	-	768 (67)	550 (64)	-	-	1850 (61)	1340 (59)	-	-
		A	505 (40)	358 (42)	1.1 (0.9-1.3)	0.2	325 (50)	282 (48)	0.9 (0.7-1.1)	0.4	372 (33)	308 (36)	1.2 (1.0-1.4)	0.1	1202 (39)	948 (41)	1.1 (1.0-1.2)	0.1
4	*SLC6A11*	rs2304725																
		TT	192 (30)	122 (29)	-	-	58 (18)	57 (19)	-	-	160 (28)	127 (30)	-	-	410 (27)	306 (27)	-	-
		TC	302 (47)	194 (46)	1.0 (0.8-1.4)	0.9	167 (51)	150 (51)	0.9 (0.6-1.4)	0.7	279 (49)	207 (48)	0.9 (0.7-1.3)	0.7	748 (49)	551 (48)	1.0 (0.8-1.2)	0.9
		CC	144 (23)	106 (25)	1.2 (0.8-1.6)	0.4	99 (31)	89 (30)	0.9 (0.6-1.5)	0.7	130 (23)	93 (22)	0.9 (0.6-1.3)	0.6	373 (24)	288 (25)	1.0 (0.8-1.3)	0.8
		T	686 (54)	438 (52)	-	-	283 (44)	264 (45)	-	-	599 (53)	461 (54)	-	-	1568 (51)	1163 (51)	-	-
		C	590 (46)	406 (48)	1.1 (0.9-1.3)	0.4	365 (56)	328 (55)	1.0 (0.8-1.2)	0.7	539 (47)	393 (46)	0.9 (0.8-1.1)	0.6	1494 (49)	1127 (49)	1.0 (0.9-1.1)	0.8
		rs2272394																
		GG	439 (70)	291 (69)	-	-	274 (85)	232 (79)	-	-	394 (69)	322 (75)	-	-	1107 (72)	845 (74)	-	-
		GA	173 (27)	118 (28)	1.0 (0.8-1.4)	0.8	45 (14)	60 (20)	1.6 (1.0-2.4)	0.04	160 (28)	101 (24)	0.8 (0.6-1.0)	0.1	378 (25)	279 (24)	1.0 (0.8-1.2)	0.7
		AA	21 (3)	12 (3)	0.9 (0.4-1.8)	0.7	4 (1)	3 (1)	0.9 (0.2-4.0)	0.9	16 (3)	6 (1)	0.5 (0.2-1.2)	0.1	41 (3)	21 (2)	0.7 (0.4-1.1)	0.1
		G	1051 (83)	700 (83)	-	-	593 (92)	524 (89)	-	-	948 (83)	745 (87)	-	-	2592 (85)	1969 (86)	-	-
		A	215 (17)	142 (17)	1.0 (0.8-1.3)	0.9	53 (8)	66 (11)	1.4 (1.0-2.1)	0.1	192 (17)	113 (13)	0.7 (0.6-1.0)	0.02	460 (15)	321 (14)	0.9 (0.8-1.1)	0.3
5	*CAMSAP2*	rs2292096																
		AA	413 (65)	293 (70)	-	-	263 (82)	237 (80)	-	-	446 (78)	331 (77)	-	-	1122 (74)	861 (75)	-	-
		AG	201 (32)	114 (27)	0.8 (0.6-1.1)	0.1	59 (18)	57 (19)	1.1 (0.7-1.6)	0.7	120 (21)	98 (23)	1.1 (0.8-1.5)	0.5	380 (25)	269 (23)	0.9 (0.8-1.1)	0.4
		GG	18 (3)	14 (3)	1.1 (0.5-2.2)	0.8	1 (0)	3 (1)	3.3 (0.3-32.2)	0.3	4 (1)	2 (0)	0.7 (0.1-3.7)	0.7	23 (1)	19 (2)	1.1 (0.6-2.0)	0.8
		A	1027 (81)	700 (83)	-	-	585 (91)	531 (89)	-	-	1012 (89)	760 (88)	-	-	2624 (86)	1991 (87)	-	-
		G	237 (19)	142 (17)	0.9 (0.7-1.1)	0.3	61 (9)	63 (11)	1.1 (0.8-1.6)	0.5	128 (11)	102 (12)	1.1 (0.8-1.4)	0.7	426 (14)	307 (13)	1.0 (0.8-1.1)	0.5
6	*GRIK2*	rs4840200																
		TT	149 (24)	127 (30)	-	-	177 (55)	165 (56)	-	-	251 (44)	165 (39)	-	-	577 (38)	457 (40)	-	-
		TC	336 (53)	216 (51)	0.8 (0.6-1.0)	0.1	128 (40)	108 (36)	0.9 (0.6-1.3)	0.6	253 (44)	200 (47)	1.2 (0.9-1.6)	0.2	717 (47)	524 (46)	0.9 (0.8-1.1)	0.3
		CC	148 (23)	78 (19)	0.6 (0.4-0.9)	0.01	18 (5)	24 (8)	1.4 (0.7-2.7)	0.3	66 (12)	60 (14)	1.4 (0.9-2.1)	0.1	232 (15)	162 (14)	0.9 (0.7-1.1)	0.3
		T	634 (50)	470 (56)	-	-	482 (75)	438 (74)	-	-	755 (66)	530 (62)	-	-	1871 (61)	1438 (63)	-	-
		C	632 (50)	372 (44)	0.8 (.07-0.9)	0.01	164 (25)	156 (26)	1.0 (0.8-1.4)	0.7	385 (34)	320 (38)	1.2 (1.0-1.4)	0.1	1181 (39)	848 (37)	0.9 (0.8-1.0)	0.2

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.3: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
7	*LGI1*	rs3758532																
		CC	331 (53)	236 (56)	-	-	208 (65)	177 (60)	-	-	306 (54)	212 (50)	-	-	845 (56)	625 (55)	-	-
		CT	254 (40)	157 (37)	0.9 (0.7-1.1)	0.3	99 (31)	107 (36)	1.3 (0.9-1.8)	0.2	214 (38)	181 (42)	1.2 (0.9-1.6)	0.1	567 (37)	445 (39)	1.1 (0.9-1.2)	0.5
		TT	47 (7)	26 (6)	0.8 (0.5-1.3)	0.3	13 (4)	12 (4)	1.1 (0.5-2.4)	0.8	48 (8)	33 (8)	1.0 (0.6-1.6)	1.0	108 (7)	71 (6)	0.9 (0.6-1.2)	0.5
		C	916 (72)	629 (75)	-	-	515 (80)	461 (78)	-	-	826 (73)	605 (71)	-	-	2257 (74)	1695 (74)	-	-
		T	348 (28)	209 (25)	0.9 (0.7-1.1)	0.2	125 (20)	131 (22)	1.2 (0.9-1.5)	0.3	310 (27)	247 (29)	1.1 (0.9-1.3)	0.4	783 (26)	587 (26)	1.0 (0.9-1.1)	1.0
8	*CALHM1*	rs11191692																
		GG	285 (45)	196 (47)	-	-	90 (28)	102 (35)	-	-	266 (47)	178 (42)	-	-	641 (42)	476 (42)	-	-
		GA	273 (43)	179 (42)	1.0 (0.7-1.2)	0.7	160 (49)	140 (47)	0.8 (0.5-1.0)	0.2	252 (44)	194 (45)	1.2 (0.9-1.5)	0.3	685 (45)	513 (45)	1.0 (0.9-1.2)	0.9
		AA	77 (12)	45 (11)	0.9 (0.6-1.3)	0.4	74 (23)	53 (18)	0.6 (0.4-1.0)	0.05	52 (9)	54 (13)	1.6 (1.0-2.4)	0.04	203 (13)	152 (13)	1.0 (0.8-1.3)	0.9
		G	843 (66)	571 (68)	-	-	340 (52)	344 (58)	-	-	784 (69)	550 (65)	-	-	1967 (64)	1465 (64)	-	-
		A	427 (34)	269 (32)	0.9 (0.8-1.1)	0.4	308 (48)	246 (42)	0.8 (0.6-1.0)	0.04	356 (31)	302 (35)	1.2 (1.0-1.5)	0.05	1091 (36)	817 (36)	1.0 (0.9-1.1)	0.9
9	*KCNAB1*	rs2280032																
		TT	125 (20)	88 (21)	-	-	88 (27)	73 (25)	-	-	159 (28)	118 (28)	-	-	372 (24)	279 (24)	-	-
		TG	306 (48)	202 (48)	0.9 (0.7-1.3)	0.7	160 (49)	149 (51)	1.1 (0.8-1.6)	0.6	281 (49)	207 (48)	1.0 (0.7-1.3)	1.0	747 (49)	558 (49)	1.0 (0.8-1.2)	1.0
		GG	205 (32)	132 (31)	0.9 (0.6-1.3)	0.6	76 (24)	70 (24)	1.1 (0.7-1.7)	0.6	130 (23)	102 (24)	1.1 (0.7-1.5)	0.8	411 (27)	304 (27)	1.0 (0.8-1.2)	0.9
		T	556 (44)	378 (45)	-	-	336 (52)	295 (51)	-	-	599 (53)	443 (52)	-	-	1491 (49)	1116 (49)	-	-
		G	716 (56)	466 (55)	1.0 (0.8-1.1)	0.6	312 (48)	289 (49)	1.1 (0.8-1.3)	0.6	541 (47)	411 (48)	1.0 (0.9-1.2)	0.8	1569 (51)	1166 (51)	1.0 (0.9-1.1)	0.9
		rs992353																
		GG	122 (19)	92 (22)	-	-	90 (28)	74 (25)	-	-	157 (28)	125 (29)	-	-	369 (24)	291 (26)	-	-
		GA	305 (49)	196 (47)	0.9 (0.6-1.2)	0.3	160 (49)	148 (51)	1.1 (0.8-1.6)	0.5	285 (50)	205 (48)	0.9 (0.7-1.2)	0.5	750 (49)	549 (48)	0.9 (0.8-1.1)	0.4
		AA	201 (32)	133 (31)	0.9 (0.6-1.2)	0.5	73 (23)	69 (24)	1.2 (0.7-1.8)	0.5	128 (22)	98 (23)	1.0 (0.7-1.4)	0.8	402 (27)	300 (26)	0.9 (0.8-1.2)	0.6
		G	549 (44)	380 (45)	-	-	340 (53)	296 (51)	-	-	599 (53)	455 (53)	-	-	1488 (49)	1131 (50)	-	-
		A	707 (56)	462 (55)	0.9 (0.8-1.1)	0.5	306 (47)	286 (49)	1.1 (0.9-1.3)	0.5	541 (47)	401 (47)	1.0 (0.8-1.2)	0.8	1554 (51)	1149 (50)	1.0 (0.9-1.1)	0.6
10	*BDNF*	rs6265																
		CC	181 (29)	111 (26)	-	-	188 (58)	136 (46)	-	-	180 (32)	147 (34)	-	-	549 (36)	394 (34)	-	-
		CT	319 (50)	200 (48)	1.0 (0.8-1.4)	0.9	121 (38)	127 (43)	1.5 (1.0-2.0)	0.03	288 (50)	207 (49)	0.9 (0.7-1.2)	0.4	728 (48)	534 (47)	1.0 (0.9-1.2)	0.8
		TT	133 (21)	111 (26)	1.4 (1.0-1.9)	0.1	14 (4)	31 (11)	3.1 (1.6-6.0)	0.001*	102 (18)	73 (17)	0.9 (0.6-1.3)	0.5	249 (16)	215 (19)	1.2 (1.0-1.5)	0.1
		C	681 (54)	422 (50)	-	-	497 (77)	399 (68)	-	-	648 (57)	501 (59)	-	-	1826 (60)	1322 (58)	-	-
		T	585 (46)	422 (50)	1.2 (1.0-1.4)	0.1	149 (23)	189 (32)	1.6 (1.2-2.0)	0.0004*	492 (43)	353 (41)	0.9 (0.8-1.1)	0.4	1226 (40)	964 (42)	1.1 (1.0-1.2)	0.1
		rs7103411																
		TT	187 (31)	108 (26)	-	-	157 (50)	101 (36)	-	-	167 (31)	133 (32)	-	-	511 (35)	342 (31)	-	-
		TC	292 (49)	199 (47)	1.2 (0.9-1.6)	0.3	126 (41)	136 (48)	1.7 (1.2-2.4)	0.004*	273 (51)	205 (49)	0.9 (0.7-1.3)	0.7	691 (48)	540 (48)	1.2 (1.0-1.4)	0.1
		CC	122 (20)	112 (27)	1.6 (1.1-2.3)	0.01	27 (9)	46 (16)	2.6 (1.5-4.5)	0.0004*	100 (18)	80 (19)	1.0 (0.7-1.5)	1.0	249 (17)	238 (21)	1.4 (1.1-1.8)	0.002*
		T	666 (55)	415 (49)	-	-	440 (71)	338 (60)	-	-	607 (56)	471 (56)	-	-	1713 (59)	1224 (55)	-	-
		C	536 (45)	423 (51)	1.3 (1.1-1.5)	0.01	180 (29)	228 (40)	1.6 (1.3-2.1)	0.0001*	473 (44)	365 (44)	1.0 (0.8-1.2)	1.0	1189 (41)	1016 (45)	1.2 (1.1-1.3)	0.002*
		rs7127507																
		TT	496 (79)	336 (80)	-	-	119 (38)	137 (46)	-	-	365 (65)	269 (64)	-	-	980 (65)	742 (65)	-	-
		TC	124 (20)	76 (18)	0.9 (0.7-1.2)	0.5	160 (50)	132 (45)	0.7 (0.5-1.0)	0.1	181 (32)	135 (32)	1.0 (0.8-1.3)	0.9	465 (31)	343 (30)	1.0 (0.8-1.2)	0.8
		CC	7 (1)	7 (2)	1.5 (0.5-4.2)	0.5	38 (12)	26 (9)	0.6 (0.3-1.0)	0.1	14 (3)	18 (4)	1.7 (0.9-3.6)	0.1	59 (4)	51 (5)	1.1 (0.8-1.7)	0.5
		T	1116 (89)	748 (89)	-	-	398 (63)	406 (69)	-	-	911 (81)	673 (80)	-	-	2425 (81)	1827 (80)	-	-
		C	138 (11)	90 (11)	1.0 (0.7-1.3)	0.8	236 (37)	184 (31)	0.8 (0.6-1.0)	0.03	209 (19)	171 (20)	1.1 (0.9-1.4)	0.4	583 (19)	445 (20)	1.0 (0.9-1.2)	0.9

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value. *After Bonferroni correction, results remained significant.

Table 4.3: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
11	*ASIC1*	rs844347																
		AA	469 (74)	310 (75)	-	-	209 (65)	220 (75)	-	-	406 (72)	272 (64)	-	-	1084 (71)	802 (71)	-	-
		AC	151 (24)	93 (23)	0.9 (0.7-1.3)	0.6	104 (32)	69 (23)	0.6 (0.4-0.9)	0.01	149 (26)	132 (31)	1.3 (1.0-1.8)	0.1	404 (27)	294 (26)	1.0 (0.8-1.2)	0.9
		CC	10 (2)	8 (2)	1.2 (0.5-3.1)	0.7	9 (3)	6 (2)	0.6 (0.2-1.8)	0.4	13 (2)	19 (5)	2.2 (1.1-4.5)	0.03	32 (2)	33 (3)	1.4 (0.9-2.3)	0.2
		A	1089 (86)	713 (87)	-	-	522 (81)	509 (86)	-	-	961 (85)	676 (80)	-	-	2572 (85)	1898 (84)	-	-
		C	171 (14)	109 (13)	1.0 (0.8-1.3)	0.8	122 (19)	81 (14)	0.7 (0.5-0.9)	0.01	175 (15)	170 (20)	1.4 (1.1-1.7)	0.01	468 (15)	360 (16)	1.0 (0.9-1.2)	0.6
12	*SCN8A*	rs11169883																
		CC	565 (89)	366 (87)	-	-	212 (66)	220 (75)	-	-	503 (88)	367 (85)	-	-	1280 (84)	953 (83)	-	-
		CT	69 (11)	54 (13)	1.2 (0.8-1.8)	0.3	102 (31)	68 (23)	0.6 (0.4-0.9)	0.02	66 (12)	59 (14)	1.2 (0.8-1.8)	0.3	237 (15)	181 (16)	1.0 (0.8-1.3)	0.8
		TT	1 (0)	2 (0)	3.1 (0.3-34)	0.4	9 (3)	7 (2)	0.7 (0.3-2.0)	0.6	1 (0)	4 (1)	5.5 (0.6-49.3)	0.1	11 (1)	13 (1)	1.6 (0.7-3.6)	0.3
		C	1199 (94)	786 (93)	-	-	526 (81)	508 (86)	-	-	1072 (94)	793 (92)	-	-	2797 (92)	2087 (91)	-	-
		T	71 (6)	58 (7)	1.2 (0.9-1.8)	0.2	120 (19)	82 (14)	0.7 (0.5-1.0)	0.03	68 (6)	67 (8)	1.3 (0.9-1.9)	0.1	259 (8)	207 (9)	1.1 (0.9-1.3)	0.5

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.4: Association tests of selected gene polymorphisms between epilepsy patients and healthy controls with susceptibility to cryptogenic epilepsy in Malaysian population.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
1	*GJD2*	rs3743123																
		CC	358 (56)	74 (49)	-	-	99 (31)	33 (36)	-	-	312 (55)	84 (54)	-	-	769 (50)	191 (48)	-	-
		CT	240 (38)	64 (42)	1.3 (0.9-1.9)	0.2	156 (48)	42 (46)	0.8 (0.5-1.4)	0.4	220 (38)	60 (38)	1.0 (0.7-1.5)	0.9	616 (40)	166 (42)	1.1 (0.9-1.4)	0.5
		TT	36 (6)	13 (9)	1.7 (0.9-3.5)	0.1	69 (21)	16 (18)	0.7 (0.4-1.4)	0.3	38 (7)	13 (8)	1.3 (0.6-2.5)	0.5	143 (10)	42 (10)	1.2 (0.8-1.7)	0.4
		C	956 (75)	212 (70)	-	-	354 (55)	108 (59)	-	-	844 (74)	228 (73)	-	-	2154 (70)	548 (69)	-	-
		T	312 (25)	90 (30)	1.3 (1.0-1.7)	0.1	294 (45)	74 (41)	0.8 (0.6-1.2)	0.3	296 (26)	86 (27)	1.1 (0.8-1.4)	0.6	902 (30)	250 (31)	1.1 (0.9-1.3)	0.3
2	*OPRM1*	rs1799971																
		AA	241 (38)	56 (37)	-	-	100 (31)	26 (29)	-	-	156 (27)	43 (27)	-	-	497 (33)	125 (31)	-	-
		AG	305 (48)	72 (48)	1.0 (0.7-1.5)	0.9	167 (52)	45 (50)	1.0 (0.6-1.8)	0.9	288 (51)	77 (48)	1.0 (0.6-1.5)	0.9	760 (50)	194 (49)	1.0 (0.8-1.3)	0.9
		GG	85 (14)	23 (15)	1.2 (0.7-2.0)	0.6	56 (17)	19 (21)	1.3 (0.7-2.6)	0.4	126 (22)	39 (25)	1.1 (0.7-1.8)	0.6	267 (17)	81 (20)	1.2 (0.9-1.7)	0.2
		A	787 (62)	184 (61)	-	-	367 (57)	97 (54)	-	-	600 (53)	163 (51)	-	-	1754 (58)	444 (56)	-	-
		G	475 (38)	118 (39)	1.1 (0.8-1.4)	0.6	279 (43)	83 (46)	1.1 (0.8-1.6)	0.5	540 (47)	155 (49)	1.1 (0.8-1.4)	0.7	1294 (42)	356 (44)	1.1 (0.9-1.3)	0.3
3	*NR1I2*	rs6785049																
		GG	225 (36)	52 (34)	-	-	84 (26)	30 (34)	-	-	265 (46)	71 (44)	-	-	574 (38)	153 (38)	-	-
		GA	311 (49)	69 (46)	1.0 (0.6-1.4)	0.8	153 (47)	45 (50)	0.8 (0.5-1.4)	0.5	238 (42)	69 (43)	1.1 (0.7-1.6)	0.7	702 (46)	183 (46)	1.0 (0.8-1.2)	0.9
		AA	97 (15)	30 (20)	1.3 (0.8-2.2)	0.3	86 (27)	14 (16)	0.5 (0.2-0.9)	0.03	67 (12)	20 (13)	1.1 (0.6-2.0)	0.7	250 (16)	64 (16)	1.0 (0.7-1.3)	0.8
		G	761 (60)	173 (57)	-	-	321 (50)	105 (59)	-	-	768 (67)	211 (66)	-	-	1850 (61)	489 (61)	-	-
		A	505 (40)	129 (43)	1.1 (0.9-1.4)	0.4	325 (50)	73 (41)	0.7 (0.5-1.0)	0.03	372 (33)	109 (34)	1.1 (0.8-1.4)	0.6	1202 (39)	311 (39)	1.0 (0.8-1.1)	0.8
4	*SLC6A11*	rs2304725																
		TT	192 (30)	48 (32)	-	-	58 (18)	12 (13)	-	-	160 (28)	47 (30)	-	-	410 (27)	107 (27)	-	-
		TC	302 (47)	66 (44)	0.9 (0.6-1.3)	0.5	167 (51)	50 (55)	1.4 (0.7-2.9)	0.3	279 (49)	71 (45)	0.9 (0.6-1.3)	0.5	748 (49)	187 (47)	1.0 (0.7-1.3)	0.8
		CC	144 (23)	37 (24)	1.0 (0.6-1.7)	0.9	99 (31)	29 (32)	1.4 (0.7-3.0)	0.4	130 (23)	39 (25)	1.0 (0.6-1.7)	0.9	373 (24)	105 (26)	1.1 (0.8-1.5)	0.6
		T	686 (54)	162 (54)	-	-	283 (44)	74 (41)	-	-	599 (53)	165 (53)	-	-	1568 (51)	401 (50)	-	-
		C	590 (46)	140 (46)	1.0 (0.8-1.3)	1.0	365 (56)	108 (59)	1.1 (0.8-1.6)	0.5	539 (47)	149 (47)	1.0 (0.8-1.3)	1.0	1494 (49)	397 (50)	1.0 (0.889-1.2)	0.6
		rs2272394																
		GG	439 (70)	101 (67)	-	-	274 (85)	68 (75)	-	-	394 (69)	118 (74)	-	-	1107 (72)	287 (72)	-	-
		GA	173 (27)	43 (28)	1.1 (0.7-1.6)	0.7	45 (14)	22 (24)	2.0 (1.1-3.5)	0.02	160 (28)	39 (25)	0.8 (0.5-1.2)	0.3	378 (25)	104 (26)	1.1 (0.8-1.4)	0.6
		AA	21 (3)	7 (5)	1.4 (0.6-3.5)	0.4	4 (1)	1 (1)	1.0 (0.1-9.2)	1.0	16 (3)	2 (1)	0.4 (0.1-1.8)	0.2	41 (3)	10 (2)	0.9 (0.5-1.9)	0.9
		G	1051 (83)	245 (81)	-	-	593 (92)	158 (87)	-	-	948 (83)	275 (87)	-	-	2592 (85)	678 (85)	-	-
		A	215 (17)	57 (19)	1.1 (0.8-1.6)	0.4	53 (8)	24 (13)	1.7 (1.0-2.8)	0.04	192 (17)	43 (13)	0.8 (0.5-1.1)	0.2	460 (15)	124 (15)	1.0 (0.8-1.3)	0.8
5	*CAMSAP2*	rs2292096																
		AA	413 (65)	112 (74)	-	-	263 (82)	74 (81)	-	-	446 (78)	118 (74)	-	-	1122 (74)	304 (76)	-	-
		AG	201 (32)	33 (22)	0.6 (0.4-0.9)	0.02	59 (18)	16 (18)	1.0 (0.5-1.8)	0.9	120 (21)	41 (25)	1.3 (0.9-1.9)	0.2	380 (25)	90 (22)	0.9 (0.7-1.1)	0.3
		GG	18 (3)	6 (4)	1.2 (0.5-3.2)	0.7	1 (0)	1 (1)	3.64 (0.2-57.5)	0.4	4 (1)	1 (1)	0.9 (0.1-8.5)	1.0	23 (1)	8 (2)	1.3 (0.6-2.9)	0.5
		A	1027 (81)	257 (85)	-	-	585 (91)	164 (90)	-	-	1012 (89)	277 (87)	-	-	2624 (86)	698 (87)	-	-
		G	237 (19)	45 (15)	0.8 (0.5-1.1)	0.1	61 (9)	18 (10)	1.1 (0.6-1.8)	0.9	128 (11)	43 (13)	1.2 (0.8-1.8)	0.3	426 (14)	106 (13)	0.9 (0.7-1.2)	0.6
6	*GRIK2*	rs4840200																
		TT	149 (24)	47 (31)	-	-	177 (55)	42 (46)	-	-	251 (44)	68 (43)	-	-	577 (38)	157 (39)	-	-
		TC	336 (53)	71 (47)	0.7 (0.4-1.0)	0.1	128 (40)	40 (44)	1.3 (0.8-2.1)	0.3	253 (44)	73 (46)	1.1 (0.7-1.5)	0.7	717 (47)	184 (46)	0.9 (0.7-1.2)	0.6
		CC	148 (23)	33 (22)	0.7 (0.4-1.2)	0.2	18 (5)	9 (10)	2.1 (0.9-5.0)	0.1	66 (12)	17 (11)	1.0 (0.5-1.7)	0.9	232 (15)	59 (15)	0.9 (0.7-1.3)	0.7
		T	634 (50)	165 (55)	-	-	482 (75)	124 (68)	-	-	755 (66)	209 (66)	-	-	1871 (61)	498 (62)	-	-
		C	632 (50)	137 (45)	0.8 (0.6-1.1)	0.2	164 (25)	58 (32)	1.4 (1.0-2.0)	0.1	385 (34)	107 (34)	1.0 (0.8-1.3)	1.0	1181 (39)	302 (38)	1.0 (0.8-1.1)	0.6

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.4: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
7	*LGI1*	rs3758532																
		CC	331 (53)	84 (56)	-	-	208 (65)	51 (57)	-	-	306 (54)	80 (51)	-	-	845 (56)	215 (54)	-	-
		CT	254 (40)	57 (38)	0.9 (0.6-1.3)	0.5	99 (31)	34 (38)	1.4 (0.9-2.3)	0.2	214 (38)	66 (42)	1.2 (0.8-1.7)	0.4	567 (37)	157 (40)	1.1 (0.9-1.4)	0.5
		TT	47 (7)	9 (6)	0.8 (0.4-1.6)	0.5	13 (4)	4 (5)	1.3 (0.4-4.0)	0.7	48 (8)	12 (7)	1.0 (0.5-1.9)	0.9	108 (7)	25 (6)	0.9 (0.6-1.4)	0.7
		C	916 (72)	225 (75)	-	-	515 (80)	136 (76)	-	-	826 (73)	226 (72)	-	-	2257 (74)	587 (74)	-	-
		T	348 (28)	75 (25)	0.9 (0.7-1.2)	0.4	125 (20)	42 (24)	1.3 (0.9-1.9)	0.2	310 (27)	90 (28)	1.1 (0.8-1.4)	0.7	783 (26)	207 (26)	1.0 (0.9-1.2)	0.9
8	*CALHM1*	rs11191692																
		GG	285 (45)	77 (51)	-	-	90 (28)	38 (42)	-	-	266 (47)	58 (37)	-	-	641 (42)	173 (43)	-	-
		GA	273 (43)	59 (39)	0.8 (0.5-1.2)	0.2	160 (49)	44 (48)	0.7 (0.4-1.1)	0.1	252 (44)	80 (50)	1.5 (1.0-2.1)	0.1	685 (45)	183 (46)	1.0 (0.8-1.3)	0.9
		AA	77 (12)	15 (10)	0.7 (0.4-1.3)	0.3	74 (23)	9 (10)	0.3 (0.1-0.6)	0.002*	52 (9)	20 (13)	1.8 (1.0-3.2)	0.1	203 (13)	44 (11)	0.8 (0.6-1.2)	0.2
		G	843 (66)	213 (71)	-	-	340 (52)	120 (66)	-	-	784 (69)	196 (62)	-	-	1967 (64)	529 (66)	-	-
		A	427 (34)	89 (29)	0.8 (0.6-1.1)	0.2	308 (48)	62 (34)	0.6 (0.4-0.8)	0.001*	356 (31)	120 (38)	1.3 (1.0-1.7)	0.02	1091 (36)	271 (34)	0.9 (0.8-1.1)	0.3
9	*KCNAB1*	rs2280032																
		TT	125 (20)	35 (23)	-	-	88 (27)	22 (25)	-	-	159 (28)	43 (27)	-	-	372 (24)	100 (25)	-	-
		TG	306 (48)	68 (45)	0.8 (0.5-1.3)	0.3	160 (49)	45 (50)	1.1 (0.6-2.0)	0.7	281 (49)	74 (47)	1.0 (0.6-1.5)	0.9	747 (49)	187 (47)	0.9 (0.7-1.2)	0.6
		GG	205 (32)	48 (32)	0.8 (0.5-1.4)	0.5	76 (24)	22 (25)	1.2 (0.6-2.3)	0.7	130 (23)	40 (26)	1.1 (0.7-1.9)	0.6	411 (27)	110 (28)	1.0 (0.7-1.4)	1.0
		T	556 (44)	138 (46)	-	-	336 (52)	89 (50)	-	-	599 (53)	160 (51)	-	-	1491 (49)	387 (49)	-	-
		G	716 (56)	164 (54)	0.9 (0.7-1.2)	0.5	312 (48)	89 (50)	1.1 (0.8-1.5)	0.7	541 (47)	154 (49)	1.1 (0.8-1.48)	0.6	1569 (51)	407 (51)	1.0 (0.9-1.2)	1.0
		rs992353																
		GG	122 (19)	37 (25)	-	-	90 (28)	22 (25)	-	-	157 (28)	43 (27)	-	-	369 (24)	102 (26)	-	-
		GA	305 (49)	66 (44)	0.7 (0.5-1.1)	0.1	160 (49)	45 (50)	1.2 (0.7-2.0)	0.6	285 (50)	74 (47)	0.9 (0.6-1.4)	0.8	750 (49)	185 (46)	0.9 (0.7-1.2)	0.4
		AA	201 (32)	47 (31)	0.8 (0.5-1.3)	0.3	73 (23)	22 (25)	1.2 (0.6-2.4)	0.5	128 (22)	41 (26)	1.2 (0.7-1.9)	0.5	402 (27)	110 (28)	1.0 (0.7-1.3)	0.9
		G	549 (44)	140 (47)	-	-	340 (53)	89 (50)	-	-	599 (53)	160 (51)	-	-	1488 (49)	389 (49)	-	-
		A	707 (56)	160 (53)	0.9 (0.7-1.1)	0.4	306 (47)	89 (50)	1.1 (0.8-1.5)	0.5	541 (47)	156 (49)	1.1 (0.8-1.4)	0.5	1554 (51)	405 (51)	1.0 (0.9-1.2)	1.0
10	*BDNF*	rs6265																
		CC	181 (29)	33 (22)	-	-	188 (58)	32 (35)	-	-	180 (32)	54 (34)	-	-	549 (36)	119 (30)	-	-
		CT	319 (50)	69 (46)	1.2 (0.8-1.9)	0.5	121 (38)	48 (53)	2.3 (1.4-3.9)	0.001*	288 (50)	79 (50)	0.9 (0.6-1.4)	0.7	728 (48)	196 (49)	1.2 (1.0-1.6)	0.1
		TT	133 (21)	49 (32)	2.0 (1.2-3.3)	0.01	14 (4)	11 (12)	4.6 (1.9-11.1)	0.001*	102 (18)	26 (16)	0.9 (0.5-1.4)	0.5	249 (16)	86 (21)	1.6 (1.2-2.2)	0.004*
		C	681 (54)	135 (45)	-	-	497 (77)	112 (62)	-	-	648 (57)	187 (59)	-	-	1826 (60)	434 (54)	-	-
		T	585 (46)	167 (55)	1.4 (1.1-1.9)	0.01	149 (23)	70 (38)	2.1 (1.5-3.0)	0.00004*	492 (43)	131 (41)	0.9 (0.7-1.2)	0.5	1226 (40)	368 (46)	1.3 (1.1-1.5)	0.003*
		rs7103411																
		TT	187 (31)	38 (25)	-	-	157 (50)	25 (30)	-	-	167 (31)	49 (32)	-	-	511 (35)	112 (29)	-	-
		TC	292 (49)	67 (45)	1.1 (0.7-1.8)	0.6	126 (41)	43 (52)	2.1 (1.2-3.7)	0.01	273 (51)	74 (48)	0.9 (0.6-1.4)	0.7	691 (48)	184 (48)	1.2 (0.9-1.6)	0.1
		CC	122 (20)	44 (30)	1.8 (1.1-2.9)	0.02	27 (9)	15 (18)	3.5 (1.6-7.5)	0.001*	100 (18)	31 (20)	1.1 (0.6-1.8)	0.8	249 (17)	90 (23)	1.6 (1.2-2.3)	0.002*
		T	666 (55)	143 (48)	-	-	440 (71)	93 (56)	-	-	607 (56)	172 (56)	-	-	1713 (59)	408 (53)	-	-
		C	536 (45)	155 (52)	1.3 (1.0-1.7)	0.02	180 (29)	73 (44)	1.9 (1.3-2.7)	0.0003*	473 (44)	136 (44)	1.0 (0.8-1.3)	0.9	1189 (41)	364 (47)	1.3 (1.1-1.5)	0.002*
		rs7127507																
		TT	496 (79)	125 (83)	-	-	119 (38)	48 (53)	-	-	365 (65)	96 (62)	-	-	980 (65)	269 (68)	-	-
		TC	124 (20)	24 (16)	0.8 (0.5-1.2)	0.3	160 (50)	40 (44)	0.6 (0.4-1.0)	0.1	181 (32)	52 (34)	1.1 (0.7-1.6)	0.7	465 (31)	116 (29)	0.9 (0.7-1.2)	0.4
		CC	7 (1)	1 (1)	0.6 (0.1-4.7)	0.6	38 (12)	3 (3)	0.2 (0.1-0.7)	0.01	14 (3)	6 (4)	1.6 (0.6-4.4)	0.3	59 (4)	10 (3)	0.6 (0.3-1.2)	0.2
		T	1116 (89)	274 (91)	-	-	398 (63)	136 (75)	-	-	911 (81)	244 (79)	-	-	2425 (81)	654 (83)	-	-
		C	138 (11)	26 (9)	0.8 (0.5-1.2)	0.2	236 (37)	46 (25)	0.6 (0.4-0.8)	0.003*	209 (19)	64 (21)	1.1 (0.8-1.6)	0.4	583 (19)	136 (17)	0.9 (0.7-1.1)	0.2

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value. *After Bonferroni correction, results remained significant.

Table 4.4: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
11	*ASIC1*	rs844347																
		AA	469 (74)	108 (74)	-	-	209 (65)	70 (77)	-	-	406 (72)	107 (67)	-	-	1084 (71)	285 (72)	-	-
		AC	151 (24)	35 (24)	1.0 (0.7-1.5)	1.0	104 (32)	19 (21)	0.5 (0.3-1.0)	0.03	149 (26)	46 (29)	1.2 (0.8-1.7)	0.4	404 (27)	100 (25)	0.9 (0.7-1.2)	0.6
		CC	10 (2)	3 (2)	1.3 (0.4-4.8)	0.7	9 (3)	2 (2)	0.7 (0.1-3.1)	0.6	13 (2)	6 (4)	1.8 (0.7-4.7)	0.3	32 (2)	11 (3)	1.3 (0.7-2.6)	0.5
		A	1089 (86)	251 (86)	-	-	522 (81)	159 (87)	-	-	961 (85)	260 (82)	-	-	2572 (85)	670 (85)	-	-
		C	171 (14)	41 (14)	1.0 (0.7-1.5)	0.8	122 (19)	23 (13)	0.6 (0.4-1.0)	0.1	175 (15)	58 (18)	1.2 (0.9-1.7)	0.2	468 (15)	122 (15)	1.0 (0.8-1.2)	1.0
12	*SCN8A*	rs11169883																
		CC	565 (89)	135 (89)	-	-	212 (66)	67 (74)	-	-	503 (88)	141 (88)	-	-	1280 (84)	343 (85)	-	-
		CT	69 (11)	15 (10)	0.9 (0.5-1.6)	0.8	102 (31)	21 (23)	0.7 (0.4-1.1)	0.1	66 (12)	18 (11)	1.0 (0.6-1.7)	0.9	237 (15)	54 (14)	0.9 (0.6-1.2)	0.3
		TT	1 (0)	1 (1)	4.2 (0.3-67.3)	0.3	9 (3)	3 (3)	1.1 (0.3-4.0)	0.9	1 (0)	1 (1)	3.6 (0.2-57.4)	0.4	11 (1)	5 (1)	1.7 (0.6-4.9)	0.3
		C	1199 (94)	285 (94)	-	-	526 (81)	155 (85)	-	-	1072 (94)	300 (94)	-	-	2797 (92)	740 (92)	-	-
		T	71 (6)	17 (6)	1.0 (0.6-1.7)	1.0	120 (19)	27 (15)	0.8 (0.5-1.2)	0.2	68 (6)	20 (6)	1.1 (0.6-1.8)	0.9	259 (8)	64 (8)	0.9 (0.7-1.2)	0.6

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.5: Association tests of selected gene polymorphisms between epilepsy patients and healthy controls with susceptibility to idiopathic epilepsy in Malaysian population.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
1	*GJD2*	rs3743123																
		CC	358 (56)	63 (53)	-	-	99 (31)	40 (32)	-	-	312 (55)	72 (51)	-	-	769 (50)	175 (46)	-	-
		CT	240 (38)	51 (42)	1.2 (0.8-1.8)	0.4	156 (48)	62 (50)	1.0 (0.6-1.6)	0.9	220 (38)	57 (40)	1.1 (0.8-1.7)	0.6	616 (40)	170 (44)	1.2 (1.0-1.5)	0.1
		TT	36 (6)	6 (5)	0.9 (0.4-2.3)	0.9	69 (21)	22 (18)	0.8 (0.4-1.4)	0.4	38 (7)	12 (9)	1.4 (0.7-2.8)	0.4	143 (10)	40 (10)	1.2 (0.8-1.8)	0.3
		C	956 (75)	177 (74)	-	-	354 (55)	142 (57)	-	-	844 (74)	201 (71)	-	-	2154 (70)	520 (68)	-	-
		T	312 (25)	63 (26)	1.1 (0.8-1.5)	0.6	294 (45)	106 (43)	0.9 (0.7-1.2)	0.5	296 (26)	81 (29)	1.1 (0.9-1.5)	0.3	902 (30)	250 (32)	1.1 (1.0-1.4)	0.1
2	*OPRM1*	rs1799971																
		AA	241 (38)	42 (35)	-	-	100 (31)	41 (33)	-	-	156 (27)	56 (40)	-	-	497 (33)	139 (36)	-	-
		AG	305 (48)	58 (49)	1.1 (0.7-1.7)	0.7	167 (52)	56 (45)	0.8 (0.5-1.3)	0.4	288 (51)	60 (42)	0.6 (0.4-0.9)	0.01	760 (50)	174 (45)	0.8 (0.6-1.1)	0.1
		GG	85 (14)	19 (16)	1.3 (0.7-2.3)	0.4	56 (17)	28 (22)	1.2 (0.7-2.2)	0.5	126 (22)	26 (18)	0.6 (0.3-1.0)	0.04	267 (17)	73 (19)	1.0 (0.7-1.3)	0.9
		A	787 (62)	142 (60)	-	-	367 (57)	138 (55)	-	-	600 (53)	172 (61)	-	-	1754 (58)	452 (59)	-	-
		G	475 (38)	96 (40)	1.1 (0.8-1.5)	0.4	279 (43)	112 (45)	1.1 (0.8-1.4)	0.7	540 (47)	112 (39)	0.7 (0.6-0.9)	0.02	1294 (42)	320 (41)	1.0 (0.8-1.1)	0.6
3	*NR1I2*	rs6785049																
		GG	225 (36)	39 (33)	-	-	84 (26)	29 (23)	-	-	265 (46)	56 (39)	-	-	574 (38)	124 (32)	-	-
		GA	311 (49)	59 (50)	1.1 (0.7-1.7)	0.7	153 (47)	63 (51)	1.2 (0.7-2.0)	0.5	238 (42)	69 (49)	1.4 (0.9-2.0)	0.1	702 (46)	191 (50)	1.3 (1.0-1.6)	0.1
		AA	97 (15)	21 (17)	1.2 (0.7-2.2)	0.5	86 (27)	32 (26)	1.1 (0.6-1.9)	0.8	67 (12)	17 (12)	1.2 (0.7-2.2)	0.6	250 (16)	70 (18)	1.3 (0.9-1.8)	0.1
		G	761 (60)	137 (58)	-	-	321 (50)	121 (49)	-	-	768 (67)	181 (64)	-	-	1850 (61)	439 (57)	-	-
		A	505 (40)	101 (42)	1.1 (0.8-1.471)	0.5	325 (50)	127 (51)	1.0 (0.8-1.4)	0.8	372 (33)	103 (36)	1.2 (0.9-1.5)	0.2	1202 (39)	331 (43)	1.2 (1.0-1.4)	0.1
4	*SLC6A11*	rs2304725																
		TT	192 (30)	34 (28)	-	-	58 (18)	24 (20)	-	-	160 (28)	39 (28)	-	-	410 (27)	97 (25)	-	-
		TC	302 (47)	53 (44)	1.0 (0.6-1.6)	1.0	167 (51)	60 (48)	0.9 (0.5-1.5)	0.6	279 (49)	67 (47)	1.0 (0.6-1.5)	0.9	748 (49)	180 (47)	1.0 (0.8-1.3)	0.9
		CC	144 (23)	33 (28)	1.3 (0.8-2.2)	0.3	99 (31)	40 (32)	1.0 (0.5-1.8)	0.9	130 (23)	35 (25)	1.1 (0.7-1.8)	0.7	373 (24)	108 (28)	1.2 (0.9-1.7)	0.2
		T	686 (54)	121 (50)	-	-	283 (44)	108 (44)	-	-	599 (53)	145 (51)	-	-	1568 (51)	374 (49)	-	-
		C	590 (46)	119 (50)	1.1 (0.9-1.5)	0.3	365 (56)	140 (56)	1.0 (0.7-1.4)	1.0	539 (47)	137 (49)	1.1 (0.8-1.4)	0.7	1494 (49)	396 (51)	1.1 (0.9-1.3)	0.2
		rs2272394																
		GG	439 (70)	86 (72)	-	-	274 (85)	101 (82)	-	-	394 (69)	107 (76)	-	-	1107 (72)	294 (77)	-	-
		GA	173 (27)	31 (26)	0.9 (0.6-1.4)	0.7	45 (14)	22 (18)	1.3 (0.8-2.3)	0.3	160 (28)	31 (22)	0.7 (0.5-1.1)	0.1	378 (25)	84 (22)	0.8 (0.6-1.1)	0.2
		AA	21 (3)	3 (2)	0.7 (0.2-2.5)	0.6	4 (1)	0 (0)	-	-	16 (3)	3 (2)	0.7 (0.2-2.4)	0.6	41 (3)	6 (1)	0.6 (0.2-1.3)	0.2
		G	1051 (83)	203 (85)	-	-	593 (92)	224 (91)	-	-	948 (83)	245 (87)	-	-	2592 (85)	672 (88)	-	-
		A	215 (17)	37 (15)	0.9 (0.6-1.3)	0.6	53 (8)	22 (9)	1.1 (0.7-1.8)	0.7	192 (17)	37 (13)	0.7 (0.5-1.1)	0.1	460 (15)	96 (12)	0.8 (0.6-1.0)	0.1
5	*CAMSAP2*	rs2292096																
		AA	413 (65)	72 (60)	-	-	263 (82)	97 (78)	-	-	446 (78)	114 (80)	-	-	1122 (74)	283 (73)	-	-
		AG	201 (32)	42 (35)	1.2 (0.8-1.8)	0.4	59 (18)	25 (20)	1.1 (0.7-1.9)	0.6	120 (21)	28 (20)	0.9 (0.6-1.4)	0.7	380 (25)	95 (25)	1.0 (0.8-1.3)	0.9
		GG	18 (3)	6 (5)	1.9 (0.7-5.0)	0.2	1 (0)	2 (2)	5.4 (0.5-60.5)	0.2	4 (1)	0 (0)	-	-	23 (1)	8 (2)	1.4 (0.6-3.1)	0.4
		A	1027 (81)	186 (78)	-	-	585 (91)	219 (88)	-	-	1012 (89)	256 (90)	-	-	2624 (86)	661 (86)	-	-
		G	237 (19)	54 (22)	1.3 (0.9-1.8)	0.2	61 (9)	29 (12)	1.3 (0.8-2.0)	0.3	128 (11)	28 (10)	0.9 (0.6-1.3)	0.5	426 (14)	111 (14)	1.0 (0.8-1.3)	0.8
6	*GRIK2*	rs4840200																
		TT	149 (24)	40 (34)	-	-	177 (55)	76 (61)	-	-	251 (44)	61 (44)	-	-	577 (38)	177 (46)	-	-
		TC	336 (53)	62 (52)	0.7 (0.4-1.1)	0.1	128 (40)	39 (32)	0.7 (0.5-1.1)	0.1	253 (44)	60 (43)	1.0 (0.7-1.5)	0.9	717 (47)	161 (42)	0.7 (0.6-0.9)	0.01
		CC	148 (23)	17 (14)	0.4 (0.2-0.8)	0.01	18 (5)	9 (7)	1.2 (0.5-2.7)	0.7	66 (12)	19 (13)	1.2 (0.7-2.1)	0.6	232 (15)	45 (12)	0.6 (0.4-0.9)	0.01
		T	634 (50)	142 (60)	-	-	482 (75)	191 (77)	-	-	755 (66)	182 (65)	-	-	1871 (61)	515 (67)	-	-
		C	632 (50)	96 (40)	0.7 (0.5-0.9)	0.01	164 (25)	57 (23)	0.9 (0.6-1.2)	0.5	385 (34)	98 (35)	1.1 (0.8-1.4)	0.7	1181 (39)	251 (33)	0.8 (0.7-0.9)	0.002

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.5: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
7	*LGI1*	rs3758532																
		CC	331 (53)	67 (57)	-	-	208 (65)	72 (58)	-	-	306 (54)	65 (46)	-	-	845 (56)	204 (53)	-	-
		CT	254 (40)	42 (36)	0.8 (0.5-1.2)	0.3	99 (31)	49 (39)	1.4 (0.9-2.2)	0.1	214 (38)	63 (45)	1.4 (0.9-2.0)	0.1	567 (37)	154 (40)	1.1 (0.9-1.4)	0.3
		TT	47 (7)	9 (7)	0.9 (0.4-2.0)	0.9	13 (4)	4 (3)	0.9 (0.3-2.8)	0.8	48 (8)	12 (9)	1.2 (0.6-2.3)	0.6	108 (7)	25 (7)	1.0 (0.6-1.5)	0.9
		C	916 (72)	176 (75)	-	-	515 (80)	193 (77)	-	-	826 (73)	193 (69)	-	-	2257 (74)	562 (73)	-	-
		T	348 (28)	60 (25)	0.9 (0.7-1.2)	0.5	125 (20)	57 (23)	1.2 (0.9-1.7)	0.3	310 (27)	87 (31)	1.2 (0.9-1.6)	0.2	783 (26)	204 (27)	1.0 (0.9-1.3)	0.6
8	*CALHM1*	rs11191692																
		GG	285 (45)	53 (44)	-	-	90 (28)	35 (29)	-	-	266 (47)	62 (44)	-	-	641 (42)	150 (39)	-	-
		GA	273 (43)	57 (48)	1.1 (0.7-1.7)	0.6	160 (49)	64 (52)	1.0 (0.6-1.7)	0.9	252 (44)	60 (43)	1.0 (0.7-1.5)	0.9	685 (45)	181 (48)	1.1 (0.9-1.4)	0.3
		AA	77 (12)	9 (8)	0.6 (0.3-1.3)	0.2	74 (23)	24 (19)	0.8 (0.5-1.5)	0.6	52 (9)	18 (13)	1.5 (0.8-2.7)	0.2	203 (13)	51 (13)	1.1 (0.8-1.5)	0.7
		G	843 (66)	163 (69)	-	-	340 (52)	134 (55)	-	-	784 (69)	184 (66)	-	-	1967 (64)	481 (63)	-	-
		A	427 (34)	75 (31)	0.9 (0.7-1.2)	0.5	308 (48)	112 (45)	0.9 (0.7-1.2)	0.6	356 (31)	96 (34)	1.1 (0.9-1.5)	0.3	1091 (36)	283 (37)	1.1 (0.9-1.3)	0.5
9	*KCNAB1*	rs2280032																
		TT	125 (20)	21 (18)	-	-	88 (27)	26 (21)	-	-	159 (28)	42 (30)	-	-	372 (24)	89 (23)	-	-
		TG	306 (48)	64 (53)	1.2 (0.7-2.1)	0.4	160 (49)	67 (55)	1.4 (0.8-2.4)	0.2	281 (49)	62 (44)	0.8 (0.5-1.3)	0.4	747 (49)	193 (51)	1.1 (0.8-1.4)	0.6
		GG	205 (32)	35 (29)	1.0 (0.6-1.8)	1.0	76 (24)	29 (24)	1.3 (0.7-2.4)	0.4	130 (23)	37 (26)	1.1 (0.7-1.8)	0.8	411 (27)	101 (26)	1.0 (0.7-1.4)	0.9
		T	556 (44)	106 (44)	-	-	336 (52)	119 (49)	-	-	599 (53)	146 (52)	-	-	1491 (49)	371 (48)	-	-
		G	716 (56)	134 (56)	1.0 (0.7-1.3)	0.9	312 (48)	125 (51)	1.1 (0.8-1.5)	0.4	541 (47)	136 (48)	1.0 (0.8-1.3)	0.8	1569 (51)	395 (52)	1.0 (0.9-1.2)	0.9
		rs992353																
		GG	122 (19)	22 (18)	-	-	90 (28)	26 (22)	-	-	157 (28)	48 (34)	-	-	369 (24)	96 (25)	-	-
		GA	305 (49)	63 (53)	1.1 (0.7-1.9)	0.6	160 (49)	68 (56)	1.5 (0.9-2.5)	0.1	285 (50)	61 (43)	0.7 (0.5-1.1)	0.1	750 (49)	192 (50)	1.0 (0.7-1.3)	0.9
		AA	201 (32)	35 (29)	1.0 (0.5-1.7)	0.9	73 (23)	27 (22)	1.3 (0.7-2.4)	0.4	128 (22)	33 (23)	0.8 (0.5-1.4)	0.5	402 (27)	95 (25)	0.9 (0.7-1.2)	0.6
		G	549 (44)	107 (45)	-	-	340 (53)	120 (50)	-	-	599 (53)	157 (55)	-	-	1488 (49)	384 (50)	-	-
		A	707 (56)	133 (55)	1.0 (0.7-1.3)	0.8	306 (47)	122 (50)	1.1 (0.8-1.5)	0.4	541 (47)	127 (45)	0.9 (0.7-1.2)	0.4	1554 (51)	382 (50)	1.0 (0.8-1.1)	0.5
10	*BDNF*	rs6265																
		CC	181 (29)	30 (25)	-	-	188 (58)	64 (52)	-	-	180 (32)	45 (32)	-	-	549 (36)	139 (36)	-	-
		CT	319 (50)	62 (52)	1.2 (0.7-1.9)	0.5	121 (38)	50 (41)	1.2 (0.8-1.9)	0.4	288 (50)	68 (48)	0.9 (0.6-1.4)	0.8	728 (48)	180 (47)	1.0 (0.8-1.3)	0.9
		TT	133 (21)	28 (23)	1.3 (0.7-2.2)	0.4	14 (4)	9 (7)	1.9 (0.8-4.6)	0.2	102 (18)	28 (20)	1.1 (0.6-1.9)	0.7	249 (16)	65 (17)	1.0 (0.7-1.4)	0.9
		C	681 (54)	122 (51)	-	-	497 (77)	178 (72)	-	-	648 (57)	158 (56)	-	-	1826 (60)	458 (60)	-	-
		T	585 (46)	118 (49)	1.1 (0.9-1.5)	0.4	149 (23)	68 (28)	1.3 (0.9-1.8)	0.2	492 (43)	124 (44)	1.0 (0.8-1.3)	0.8	1226 (40)	310 (40)	1.0 (0.9-1.2)	0.9
		rs7103411																
		TT	187 (31)	33 (28)	-	-	157 (50)	50 (41)	-	-	167 (31)	43 (31)	-	-	511 (35)	126 (33)	-	-
		TC	292 (49)	54 (46)	1.0 (0.7-1.7)	0.8	126 (41)	57 (47)	1.4 (0.9-2.2)	0.1	273 (51)	68 (49)	1.0 (0.6-1.5)	0.9	691 (48)	179 (48)	1.0 (0.8-1.4)	0.7
		CC	122 (20)	31 (26)	1.4 (0.8-2.5)	0.2	27 (9)	14 912)	1.6 (0.8-3.3)	0.2	100 (18)	27 (20)	1.0 (0.6-1.8)	0.9	249 (17)	72 (19)	1.2 (0.8-1.6)	0.3
		T	666 (55)	120 (51)	-	-	440 (71)	157 (65)	-	-	607 (56)	154 (56)	-	-	1713 (59)	431 (57)	-	-
		C	536 (45)	116 (49)	1.2 (0.9-1.6)	0.2	180 (29)	85 (35)	1.3 (1.0-1.8)	0.1	473 (44)	122 (44)	1.0 (0.8-1.3)	0.9	1189 (41)	323 (43)	1.1 (0.9-1.3)	0.4
		rs7127507																
		TT	496 (79)	88 (75)	-	-	119 (38)	50 (40)	-	-	365 (65)	92 (66)	-	-	980 (65)	230 (61)	-	-
		TC	124 (20)	26 (22)	1.2 (0.7-1.9)	0.5	160 (50)	60 (49)	0.9 (0.6-1.4)	0.6	181 (32)	41 (30)	0.9 (0.6-1.4)	0.6	465 (31)	127 (33)	1.2 (0.9-1.5)	0.2
		CC	7 (1)	3 (3)	2.4 (0.6-9.5)	0.2	38 (12)	14 (11)	0.9 (0.4-1.8)	0.7	14 (3)	6 (4)	1.7 (0.6-4.5)	0.3	59 (4)	23 (6)	1.7 (1.0-2.7)	0.05
		T	1116 (89)	202 (86)	-	-	398 (63)	160 (65)	-	-	911 (81)	225 (81)	-	-	2425 (81)	587 (77)	-	-
		C	138 (11)	32 (14)	1.3 (0.8-1.9)	0.2	236 (37)	88 (35)	0.9 (0.7-1.3)	0.6	209 (19)	53 (19)	1.0 (0.7-1.4)	0.9	583 (19)	173 (23)	1.2 (1.0-1.5)	0.04

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.5: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
11	*ASIC1*	rs844347																
		AA	469 (74)	88 (76)	-	-	209 (65)	90 (73)	-	-	406 (72)	80 (59)	-	-	1084 (71)	258 (69)	-	-
		AC	151 (24)	26 (22)	0.9 (0.6-1.5)	0.7	104 (32)	31 (25)	0.7 (0.4-1.1)	0.1	149 (26)	49 (36)	1.7 (1.1-2.5)	0.01	404 (27)	106 (28)	1.1 (0.9-1.4)	0.5
		CC	10 (2)	2 (2)	1.1 (0.2-4.9)	0.9	9 (3)	3 (2)	0.8 (0.2-2.9)	0.7	13 (2)	7 (5)	2.7 (1.1-7.1)	0.04	32 (2)	12 (3)	1.6 (0.8-3.1)	0.2
		A	1089 (86)	202 (87)	-	-	522 (81)	211 (85)	-	-	961 (85)	209 (77)	-	-	2572 (85)	622 (83)	-	-
		C	171 (14)	30 (13)	0.9 (0.6-1.4)	0.8	122 (19)	37 (15)	0.8 (0.5-1.1)	0.2	175 (15)	63 (23)	1.7 (1.2-2.3)	0.002*	468 (15)	130 (17)	1.1 (0.9-1.4)	0.2
12	*SCN8A*	rs11169883																
		CC	565 (89)	106 (89)	-	-	212 (66)	95 (77)	-	-	503 (88)	116 (82)	-	-	1280 (84)	317 (82)	-	-
		CT	69 (11)	12 (10)	0.9 (0.5-1.8)	0.8	102 (31)	25 (20)	0.5 (0.3-0.9)	0.0	66 (12)	23 (16)	1.5 (0.9-2.5)	0.1	237 (15)	60 (16)	1.0 (0.8-1.4)	0.9
		TT	1 (0)	1 (1)	5.3 (0.3-85.9)	0.2	9 (3)	4 (3)	1.0 (0.3-3.3)	1.0	1 (0)	3 (2)	13.0 (1.3-126.2)	0.03	11 (1)	8 (2)	2.9 (1.2-7.4)	0.02
		C	1199 (94)	224 (94)	-	-	526 (81)	215 (87)	-	-	1072 (94)	255 (90)	-	-	2797 (92)	694 (90)	-	-
		T	71 (6)	14 (6)	1.1 (0.6-1.9)	0.9	120 (19)	33 (13)	0.7 (0.4-1.0)	0.1	68 (6)	29 (10)	1.8 (1.1-2.8)	0.01	259 (8)	76 (10)	1.2 (0.9-1.5)	0.2

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value. *After Bonferroni correction, results remained significant.

Table 4.6: Association tests of selected gene polymorphisms between epilepsy patients and healthy controls with susceptibility to symptomatic epilepsy in Malaysian population.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
1	*GJD2*	rs3743123																
		CC	358 (56)	78 (53)	-	-	99 (31)	33 (42)	-	-	312 (55)	67 (55)	-	-	769 (50)	178 (51)	-	-
		CT	240 (38)	62 (42)	1.2 (0.8-1.7)	0.4	156 (48)	32 (41)	0.6 (0.4-1.1)	0.1	220 (38)	52 (42)	1.1 (0.7-1.6)	0.6	616 (40)	146 (42)	1.0 (0.8-1.3)	0.8
		TT	36 (6)	8 (5)	1.0 (0.5-2.3)	1.0	69 (21)	13 (17)	0.6 (0.3-1.2)	0.1	38 (7)	4 (3)	0.5 (0.2-1.4)	0.2	143 (10)	25 (7)	0.8 (0.5-1.2)	0.2
		C	956 (75)	218 (74)	-	-	354 (55)	98 (63)	-	-	844 (74)	186 (76)	-	-	2154 (70)	502 (72)	-	-
		T	312 (25)	78 (26)	1.1 (0.8-1.5)	0.5	294 (45)	58 (37)	0.7 (0.5-1.0)	0.1	296 (26)	60 (24)	0.9 (0.7-1.3)	0.6	902 (30)	196 (28)	0.9 (0.8-1.1)	0.5
2	*OPRM1*	rs1799971																
		AA	241 (38)	55 (37)	-	-	100 (31)	20 (25)	-	-	156 (27)	38 (31)	-	-	497 (33)	113 (32)	-	-
		AG	305 (48)	67 (45)	1.0 (0.6-1.4)	0.9	167 (52)	44 (56)	1.3 (0.7-2.4)	0.4	288 (51)	55 (45)	0.8 (0.5-1.2)	0.3	760 (50)	166 (48)	1.0 (0.7-1.3)	0.8
		GG	85 (14)	26 (18)	1.3 (0.8-2.3)	0.3	56 (17)	15 (19)	1.3 (0.6-2.8)	0.4	126 (22)	30 (24)	1.0 (0.6-1.7)	0.9	267 (17)	71 (20)	1.2 (0.8-1.6)	0.4
		A	787 (62)	177 (60)	-	-	367 (57)	84 (53)	-	-	600 (53)	131 (53)	-	-	1754 (58)	392 (56)	-	-
		G	475 (38)	119 (40)	1.1 (0.9-1.4)	0.4	279 (43)	74 (47)	1.2 (0.8-1.6)	0.4	540 (47)	115 (47)	1.0 (0.7-1.3)	0.9	1294 (42)	308 (44)	1.1 (0.9-1.3)	0.5
3	*NR1I2*	rs6785049																
		GG	225 (36)	48 (33)	-	-	84 (26)	21 (27)	-	-	265 (46)	48 (39)	-	-	574 (38)	117 (34)	-	-
		GA	311 (49)	73 (49)	1.1 (0.7-1.6)	0.6	153 (47)	36 (45)	0.9 (0.5-1.7)	0.8	238 (42)	55 (45)	1.3 (0.8-2.0)	0.3	702 (46)	164 (47)	1.1 (0.9-1.5)	0.3
		AA	97 (15)	27 (18)	1.3 (0.8-2.2)	0.3	86 (27)	22 (28)	1.0 (0.5-2.0)	0.9	67 (12)	19 (16)	1.6 (0.9-2.8)	0.1	250 (16)	68 (19)	1.3 (1.0-1.9)	0.1
		G	761 (60)	169 (57)	-	-	321 (50)	78 (49)	-	-	768 (67)	151 (62)	-	-	1850 (61)	398 (57)	-	-
		A	505 (40)	127 (43)	1.1 (0.9-1.5)	0.3	325 (50)	80 (51)	1.0 (0.7-1.4)	0.9	372 (33)	93 (38)	1.3 (1.0-1.7)	0.1	1202 (39)	300 (43)	1.2 (1.0-1.4)	0.1
4	*SLC6A11*	rs2304725																
		TT	192 (30)	40 (27)	-	-	58 (18)	21 (27)	-	-	160 (28)	39 (31)	-	-	410 (27)	100 (29)	-	-
		TC	302 (47)	74 (50)	1.2 (0.8-1.8)	0.5	167 (51)	37 (47)	0.6 (0.3-1.1)	0.1	279 (49)	67 (54)	1.0 (0.6-1.5)	0.9	748 (49)	178 (51)	1.0 (0.7-1.3)	0.9
		CC	144 (23)	34 (23)	1.1 (0.7-1.9)	0.6	99 (31)	20 (26)	0.6 (0.3-1.1)	0.1	130 (23)	18 (15)	0.6 (0.3-1.0)	0.1	373 (24)	72 (20)	0.8 (0.6-1.1)	0.2
		T	686 (54)	154 (52)	-	-	283 (44)	79 (51)	-	-	599 (53)	145 (59)	-	-	1568 (51)	378 (54)	-	-
		C	590 (46)	142 (48)	1.1 (0.8-1.4)	0.6	365 (56)	77 (49)	0.8 (0.5-1.1)	0.1	539 (47)	103 (41)	0.8 (0.6-1.0)	0.1	1494 (49)	322 (46)	0.9 (0.8-1.1)	0.2
		rs2272394																
		GG	439 (70)	102 (70)	-	-	274 (85)	61 (78)	-	-	394 (69)	92 (74)	-	-	1107 (72)	255 (73)	-	-
		GA	173 (27)	43 (29)	1.1 (0.7-1.6)	0.7	45 (14)	15 (19)	1.5 (0.8-2.9)	0.2	160 (28)	31 (25)	0.8 (0.5-1.3)	0.4	378 (25)	89 (26)	1.0 (0.8-1.3)	0.9
		AA	21 (3)	2 (1)	0.4 (0.1-1.8)	0.2	4 (1)	2 (3)	2.2 (0.4-12.5)	0.4	16 (3)	1 (1)	0.3 (0.04-2.0)	0.2	41 (3)	5 (1)	0.5 (0.2-1.4)	0.2
		G	1051 (83)	247 (84)	-	-	593 (92)	137 (88)	-	-	948 (83)	215 (87)	-	-	2592 (85)	599 (86)	-	-
		A	215 (17)	47 (16)	0.9 (0.7-1.3)	0.7	53 (8)	19 (12)	1.6 (0.9-2.70	0.1	192 (17)	33 (13)	0.8 (0.5-1.1)	0.2	460 (15)	99 (14)	0.9 (0.7-1.2)	0.6
5	*CAMSAP2*	rs2292096																
		AA	413 (65)	107 (73)	-	-	263 (82)	63 (80)	-	-	446 (78)	95 (77)	-	-	1122 (74)	265 (76)	-	-
		AG	201 (32)	38 (26)	0.7 (0.5-1.1)	0.1	59 (18)	16 (20)	1.1 (0.6-2.1)	0.7	120 (21)	28 (22)	1.1 (0.7-1.7)	0.7	380 (25)	82 (23)	0.9 (0.7-1.2)	0.5
		GG	18 (3)	2 (1)	0.4 (0.1-1.9)	0.3	1 (0)	0 (0)	-	-	4 (1)	1 (1)	1.2 (0.1-10.6)	0.9	23 (1)	3 (1)	0.6 (0.2-1.9)	0.3
		A	1027 (81)	252 (86)	-	-	585 (91)	142 (90)	-	-	1012 (89)	218 (88)	-	-	2624 (86)	612 (87)	-	-
		G	237 (19)	42 (14)	0.7 (0.5-1.0)	0.1	61 (9)	16 (10)	1.1 (0.6-1.9)	0.8	128 (11)	30 (12)	1.1 (0.7-1.7)	0.7	426 (14)	88 (13)	0.9 (0.7-1.1)	0.3
6	*GRIK2*	rs4840200																
		TT	149 (24)	40 (27)	-	-	177 (55)	45 (57)	-	-	251 (44)	34 (28)	-	-	577 (38)	119 (34)	-	-
		TC	336 (53)	81 (55)	0.9 (0.6-1.4)	0.6	128 (40)	28 (35)	0.9 (0.5-1.5)	0.6	253 (44)	66 (54)	1.9 (1.2-3.0)	0.004	717 (47)	175 (50)	1.2 (0.9-1.5)	0.2
		CC	148 (23)	27 (18)	0.7 (0.4-1.2)	0.2	18 (5)	6 (8)	1.3 (0.5-3.5)	0.6	66 (12)	22 (18)	2.5 (1.3-4.5)	0.003*	232 (15)	55 (16)	1.1 (0.8-1.6)	0.4
		T	634 (50)	161 (54)	-	-	482 (75)	118 (75)	-	-	755 (66)	134 (55)	-	-	1871 (61)	413 (59)	-	-
		C	632 (50)	135 (46)	0.8 (0.7-1.1)	0.2	164 (25)	40 (25)	1.0 (0.7-1.5)	1.0	385 (34)	110 (45)	1.6 (1.2-2.1)	0.001*	1181 (39)	285 (41)	1.1 (0.9-1.3)	0.3

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value. *After Bonferroni correction, results remained significant.

Table 4.6: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
7	*LGI1*	rs3758532																
		CC	331 (53)	84 (57)	-	-	208 (65)	51 (65)	-	-	306 (54)	62 (51)	-	-	845 (56)	197 (56)	-	-
		CT	254 (40)	57 (38)	0.9 (0.6-1.3)	0.5	99 (31)	24 (30)	1.0 (0.6-1.7)	1.0	214 (38)	52 (42)	1.2 (0.8-1.8)	0.4	567 (37)	133 (38)	1.0 (0.8-1.3)	1.0
		TT	47 (7)	7 (5)	0.6 (0.3-1.3)	0.2	13 (4)	4 (5)	1.3 (0.4-4.0)	0.7	48 (8)	9 (7)	0.9 (0.4-2.0)	0.8	108 (7)	20 (6)	0.8 (0.5-1.3)	0.4
		C	916 (72)	225 (76)	-	-	515 (80)	126 (80)	-	-	826 (73)	176 (72)	-	-	2257 (74)	527 (75)	-	-
		T	348 (28)	71 (24)	0.8 (0.6-1.1)	0.2	125 (20)	32 (20)	1.0 (0.7-1.6)	0.8	310 (27)	70 (28)	1.1 (0.9-1.4)	0.7	783 (26)	173 (25)	0.9 (0.8-1.1)	0.6
8	*CALHM1*	rs11191692																
		GG	285 (45)	66 (45)	-	-	90 (28)	29 (37)	-	-	266 (47)	54 (44)	-	-	641 (42)	149 (43)	-	-
		GA	273 (43)	61 (41)	1.0 (0.7-1.4)	0.9	160 (49)	32 (41)	0.6 (0.4-1.1)	0.1	252 (44)	53 (43)	1.0 (0.7-1.6)	0.9	685 (45)	146 (42)	0.9 (0.7-1.2)	0.5
		AA	77 (12)	20 (14)	1.1 (0.6-2.0)	0.7	74 (23)	17 (22)	0.7 (0.4-1.4)	0.3	52 (9)	16 (13)	1.5 (0.8-2.9)	0.2	203 (13)	53 (15)	1.1 (0.8-1.6)	0.5
		G	843 (66)	193 (66)	-	-	340 (52)	90 (58)	-	-	784 (69)	161 (65)	-	-	1967 (64)	444 (64)	-	-
		A	427 (34)	101 (34)	1.0 (0.8-1.4)	0.8	308 (48)	66 (42)	0.8 (0.6-1.2)	0.2	356 (31)	85 (35)	1.2 (0.9-1.6)	0.3	1091 (36)	252 (36)	1.0 (0.9-1.2)	0.8
9	*KCNAB1*	rs2280032																
		TT	125 (20)	30 (20)	-	-	88 (27)	24 (31)	-	-	159 (28)	30 (24)	-	-	372 (24)	84 (24)	-	-
		TG	306 (48)	69 (47)	0.9 (0.6-1.5)	0.8	160 (49)	36 (46)	0.8 (0.5-1.5)	0.5	281 (49)	70 (57)	1.3 (0.8-2.1)	0.2	747 (49)	175 (50)	1.0 (0.8-1.4)	0.8
		GG	205 (32)	49 (33)	1.0 (0.6-1.7)	1.0	76 (24)	18 (23)	0.9 (0.4-1.7)	0.7	130 (23)	24 (19)	1.0 (0.5-1.8)	0.9	411 (27)	91 (26)	1.0 (0.7-1.4)	0.9
		T	556 (44)	129 (44)	-	-	336 (52)	84 (54)	-	-	599 (53)	130 (52)	-	-	1491 (49)	343 (49)	-	-
		G	716 (56)	167 (56)	1.0 (0.8-1.3)	1.0	312 (48)	72 (46)	0.9 (0.7-1.3)	0.7	541 (47)	118 (48)	1.0 (0.8-1.3)	1.0	1569 (51)	357 (51)	1.0 (0.8-1.2)	0.9
		rs992353																
		GG	122 (19)	31 (21)	-	-	90 (28)	25 (32)	-	-	157 (28)	31 (25)	-	-	369 (24)	87 (25)	-	-
		GA	305 (49)	66 (45)	0.9 (0.5-1.4)	0.5	160 (49)	34 (44)	0.8 (0.4-1.4)	0.4	285 (50)	69 (56)	1.2 (0.8-2.0)	0.4	750 (49)	169 (48)	1.0 (0.7-1.3)	0.8
		AA	201 (32)	51 (34)	1.0 (0.6-1.6)	1.0	73 (23)	19 (24)	0.9 (0.5-1.8)	0.8	128 (22)	23 (19)	0.9 (0.5-1.6)	0.8	402 (27)	93 (27)	1.0 (0.7-1.4)	0.9
		G	549 (44)	128 (43)	-	-	340 (53)	84 (54)	-	-	599 (53)	131 (53)	-	-	1488 (49)	343 (49)	-	-
		A	707 (56)	168 (57)	1.0 (0.8-1.3)	0.9	306 (47)	72 (46)	1.0 (0.7-1.4)	0.8	541 (47)	115 (47)	1.0 (0.7-1.3)	0.8	1554 (51)	355 (51)	1.0 (0.8-1.2)	0.9
10	*BDNF*	rs6265																
		CC	181 (29)	48 (32)	-	-	188 (58)	39 (51)	-	-	180 (32)	44 (36)	-	-	549 (36)	131 (38)	-	-
		CT	319 (50)	66 (45)	0.8 (0.5-1.2)	0.2	121 (38)	28 (36)	1.1 (0.7-1.9)	0.7	288 (50)	60 (49)	0.9 (0.6-1.3)	0.5	728 (48)	154 (44)	0.9 (0.7-1.1)	0.4
		TT	133 (21)	34 (23)	1.0 (0.6-1.6)	0.9	14 (4)	10 (13)	3.4 (1.4-8.3)	0.01	102 (18)	18 (15)	0.7 (0.4-1.3)	0.3	249 (16)	62 (18)	1.0 (0.7-1.5)	0.8
		C	681 (54)	162 (55)	-	-	497 (77)	106 (69)	-	-	648 (57)	148 (61)	-	-	1826 (60)	416 (60)	-	-
		T	585 (46)	134 (45)	1.0 (0.7-1.2)	0.8	149 (23)	48 (31)	1.5 (1.0-2.2)	0.04	492 (43)	96 (39)	0.9 (0.6-1.1)	0.3	1226 (40)	278 (40)	1.0 (0.8-1.2)	1.0
		rs7103411																
		TT	187 (31)	37 (25)	-	-	157 (50)	25 (33)	-	-	167 (31)	37 (31)	-	-	511 (35)	99 (29)	-	-
		TC	292 (49)	75 (50)	1.3 (0.8-2.4)	0.2	126 (41)	35 (46)	1.7 (1.0-3.1)	0.1	273 (51)	63 (52)	1.0 (0.7-1.6)	0.9	691 (48)	173 (50)	1.3 (1.0-1.7)	0.1
		CC	122 (20)	37 (25)	1.5 (0.9-2.6)	0.1	27 (9)	16 (21)	3.7 (1.8-7.9)	0.001*	100 (18)	21 (17)	0.9 (0.5-1.7)	0.9	249 (17)	74 (21)	1.5 (1.1-2.1)	0.01
		T	666 (55)	149 (50)	-	-	440 (71)	85 (56)	-	-	607 (56)	137 (57)	-	-	1713 (59)	371 (54)	-	-
		C	536 (45)	149 (50)	1.2 (1.0-1.6)	0.1	180 (29)	67 (44)	1.9 (1.3-2.8)	0.0004*	473 (44)	105 (43)	1.0 (0.7-1.3)	0.9	1189 (41)	321 (46)	1.2 (1.1-1.5)	0.01
		rs7127507																
		TT	496 (79)	120 (81)	-	-	119 (38)	37 (48)	-	-	365 (65)	77 (62)	-	-	980 (65)	234 (67)	-	-
		TC	124 (20)	26 (17)	0.9 (0.5-1.4)	0.5	160 (50)	31 (40)	0.6 (0.4-1.1)	0.1	181 (32)	41 (33)	1.1 (0.7-1.6)	0.7	465 (31)	98 (28)	0.9 (0.7-1.1)	0.3
		CC	7 (1)	3 (2)	1.8 (0.5-7.0)	0.4	38 (12)	9 (12)	0.8 (0.3-1.7)	0.5	14 (3)	6 (5)	2.0 (0.8-5.5)	0.2	59 (4)	18 (5)	1.3 (0.7-2.2)	0.4
		T	1116 (89)	266 (89)	-	-	398 (63)	105 (68)	-	-	911 (81)	195 (79)	-	-	2425 (81)	566 (81)	-	-
		C	138 (11)	32 (11)	1.0 (0.6-1.5)	0.9	236 (37)	49 (32)	0.8 (0.5-1.1)	0.2	209 (19)	53 (21)	1.2 (0.8-1.7)	0.3	583 (19)	134 (19)	1.0 (0.8-1.2)	0.9

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value. *After Bonferroni correction, results remained significant.

Table 4.6: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
11	*ASIC1*	rs844347																
		AA	469 (74)	112 (77)	-	-	209 (65)	58 (75)	-	-	406 (72)	83 (68)	-	-	1084 (71)	253 (73)	-	-
		AC	151 (24)	31 (21)	0.9 (0.6-1.3)	0.5	104 (32)	18 (24)	0.6 (0.4-1.1)	0.1	149 (26)	35 (28)	1.1 (0.7-1.8)	0.5	404 (27)	84 (24)	0.9 (0.7-1.2)	0.4
		CC	10 (2)	3 (2)	1.3 (0.3-4.6)	0.7	9 (3)	1 (1)	0.4 (0.1-3.2)	0.4	13 (2)	5 (4)	1.9 (0.7-5.4)	0.2	32 (2)	9 (3)	1.2 (0.6-2.6)	0.6
		A	1089 (86)	255 (87)	-	-	522 (81)	134 (87)	-	-	961 (85)	201 (82)	-	-	2572 (85)	590 (85)	-	-
		C	171 (14)	37 (13)	0.9 (0.6-1.4)	0.7	122 (19)	20 (13)	0.6 (0.4-1.1)	0.1	175 (15)	45 (18)	1.2 (0.9-1.8)	0.3	468 (15)	102 (15)	1.0 (0.8-1.2)	0.7
12	*SCN8A*	rs11169883																
		CC	565 (89)	122 (82)	-	-	212 (66)	55 (71)	-	-	503 (88)	106 (86)	-	-	1280 (84)	283 (81)	-	-
		CT	69 (11)	27 (18)	1.8 (1.1-2.9)	0.02	102 (31)	22 (29)	0.8 (0.5-1.4)	0.5	66 (12)	17 (14)	1.2 (0.7-2.2)	0.5	237 (15)	66 (19)	1.3 (0.9-1.7)	0.1
		TT	1 (0)	0 (0)	-	-	9 (3)	0 (0)	-	-	1 (0)	0 (0)	-	-	11 (1)	0 (0)	-	-
		C	1199 (94)	271 (91)	-	-	526 (81)	132 (86)	-	-	1072 (94)	229 (93)	-	-	2797 (92)	632 (91)	-	-
		T	71 (6)	27 (9)	1.7 (1.1-2.7)	0.03	120 (19)	22 (14)	0.7 (0.4-1.2)	0.2	68 (6)	17 (7)	1.2 (0.7-2.0)	0.6	259 (8)	66 (9)	1.1 (0.8-1.5)	0.4

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

4.3.2 Haplotypes

4.3.2.1 *BDNF* rs6265-rs7103411-rs7127507

Haplotype analyses were performed for *BDNF* rs6265, rs7103411 and rs7127507 polymorphisms (Table 4.7, Figure 4.1). Only haplotypes with frequencies above 3% were included in the analysis. Following 1000 permutation test was performed for correction of multiple comparisons, results were significant for some ethnic groups. The $rs6265_C$-$rs7103411_T$-$rs7127507_T$ in epilepsy patients was significantly higher than controls in the pooled subjects (OR 0.8, 95% CI 0.7-0.9, p 0.001). Subsidiary analysis by ethnicity and epilepsy syndrome demonstrated that the $rs6265_T$-$rs7103411_C$-$rs7127507_T$ haplotype was more frequent in the Indian patients with cryptogenic epilepsy than in controls (OR 2.1, 95% CI 1.5-3.1, p 0.00005, 37% vs. 21%, respectively), while the $rs6265_C$-$rs7103411_T$-$rs7127507_C$ in the patients was less frequent than in controls (OR 0.5, 95% CI 0.4-0.8, p 0.002, 24% vs. 36%, respectively). In the Chinese with symptomatic epilepsy, the $rs6265_C$-$rs7103411_C$-$rs7127507_T$ haplotype was more frequent in the patients than in controls (OR 4.0, 95% CI 2.2-7.2, p 0.000002, 7% vs. 2%, respectively). Therefore, Indians, the $rs6265_T$-$rs7103411_C$-$rs7127507_T$ and $rs6265_C$-$rs7103411_T$-$rs7127507_C$ haplotypes might be a risk for susceptibility and a protector against cryptogenic epilepsy, respectively. However, the $rs6265_C$-$rs7103411_C$-$rs7127507_T$ was risk factor for symptomatic epilepsy in the Chinese. Therefore, these variants of *BDNF* alone or in combination were associated with different types of epilepsy syndrome in the Chinese and Indians. There was a strong linkage disequilibrium (LD) between the *BDNF* rs6265-rs7103411-rs7127507 gene polymorphisms in overall or in each ethnic group with various type of epilepsy syndrome (D' > 80%) (Figure 4.1).

Table 4.7: Haplotype frequencies of *BDNF* polymorphisms between epilepsy patients and healthy controls with susceptibility to epilepsy in Malaysian population.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
1	*BDNF*	rs6265-rs7103411-rs7127507																
		Total epilepsy																
		CTC	117 (10)	87 (11)	1.1 (0.8-1.4)	0.7	221 (36)	164 (30)	0.7 (0.6-0.9)	0.01	181 (17)	163 (20)	1.2 (0.9-1.5)	0.1	521 (18)	414 (19)	1.0 (0.9-1.2)	0.7
		CTT	494 (41)	290 (35)	0.7 (0.6-0.9)	0.002*	198 (33)	164 (30)	0.9 (0.7-1.1)	0.3	384 (36)	285 (35)	0.9 (0.8-1.1)	0.4	1073 (38)	740 (34)	0.8 (0.7-0.9)	0.001*
		TCT	495 (42)	383 (46)	1.2 (1.0-1.4)	0.1	128 (21)	172 (31)	1.7 (1.3-2.2)	0.0001*	424 (40)	321 (39)	0.9 (0.8-1.1)	0.6	1047 (37)	875 (40)	1.1 (1.0-1.3)	0.05
		CCT	23 (2)	35 (4)	2.2 (1.3-3.8)	0.002*	47 (8)	43 (8)	1.0 (0.7-1.5)	1.0	37 (3)	32 (4)	1.1 (0.7-1.8)	0.7	108 (4)	110 (5)	1.3 (1.0-1.7)	0.04
		Other**	57 (5)	33 (4)	-	-	11 (2)	10 (1)	-	-	38 (4)	18 (2)	-	-	107 (3)	61 (2)	-	-
		Cryptogenic epilepsy																
		CTC	117 (10)	26 (9)	0.9 (0.6-1.4)	0.5	221 (36)	40 (24)	0.5 (0.4-0.8)	0.002*	181 (17)	62 (21)	1.3 (0.9-1.7)	0.2	521 (18)	128 (17)	0.9 (0.7-1.1)	0.4
		CTT	494 (41)	100 (34)	0.7 (0.5-0.9)	0.01	198 (33)	52 (31)	0.9 (0.6-1.3)	0.7	384 (36)	99 (34)	0.9 (0.7-1.1)	0.3	1073 (38)	249 (33)	0.8 (0.7-0.9)	0.01
		TCT	495 (42)	148 (50)	1.4 (1.1-1.8)	0.02	128 (21)	61 (37)	2.1 (1.5-3.1)	0.00005*	424 (40)	119 (40)	1.0 (0.7-1.3)	0.9	1047 (37)	327 (43)	1.3 (1.1-1.5)	0.002*
		CCT	23 (2)	6 (2)	-	-	47 (8)	12 (7)	0.9 (0.5-1.8)	0.8	37 (3)	12 (4)	1.2 (0.6-2.32)	0.6	108 (4)	31 (4)	1.1 (0.7-1.6)	0.8
		Other**	57 (5)	16 (5)	-	-	11 (2)	1 (1)	-	-	38 (4)	4 (1)	-	-	107 (3)	22 (3)	-	-
		Idiopathic epilepsy																
		CTC	117 (10)	30 (13)	1.3 (0.9-2.1)	0.2	221 (36)	80 (34)	0.9 (0.6-1.2)	0.5	181 (17)	51 (19)	1.1 (0.8-1.6)	0.6	521 (18)	160 (22)	1.2 (1.0-1.5)	0.05
		CTT	494 (41)	79 (34)	0.7 (0.5-1.0)	0.04	198 (33)	72 (31)	0.9 (0.7-1.2)	0.5	384 (36)	96 (35)	1.0 (0.7-1.3)	0.8	1073 (38)	248 (34)	0.8 (0.7-1.0)	0.02
		TCT	495 (42)	107 (46)	1.2 (0.9-1.6)	0.2	128 (21)	64 (27)	1.4 (1.0-1.9)	0.1	424 (40)	109 (40)	1.0 (0.8-1.3)	1.0	1047 (37)	280 (38)	1.0 (0.9-1.2)	0.7
		CCT	23 (2)	7 (3)	1.6 (0.7-3.8)	0.3	47 (8)	17 (7)	0.9 (0.5-1.6)	0.8	37 (3)	7 (3)	0.8 (0.3-1.7)	0.5	108 (4)	32 (4)	1.1 (0.8-1.7)	0.6
		Other**	57 (5)	7 (4)	-	-	11 (2)	2 (1)	-	-	38 (4)	8 (3)	-	-	107 (3)	19 (2)	-	-
		Symptomatic epilepsy																
		CTC	117 (10)	32 (11)	1.1 (0.7-1.7)	0.7	221 (36)	43 (29)	0.7 (0.5-1.1)	0.2	181 (17)	49 (20)	1.2 (0.9-1.7)	0.3	521 (18)	123 (18)	1.0 (0.8-1.2)	0.8
		CTT	494 (41)	108 (37)	0.8 (0.6-1.0)	0.1	198 (33)	38 (26)	0.7 (0.5-1.1)	0.2	384 (36)	84 (35)	0.9 (0.7-1.2)	0.6	1073 (38)	231 (34)	0.8 (0.7-1.0)	0.05
		TCT	495 (42)	125 (42)	1.0 (0.8-1.3)	1.0	128 (21)	45 (31)	1.7 (1.1-2.6)	0.01	424 (40)	90 (38)	0.9 (0.7-1.2)	0.4	1047 (37)	260 (38)	1.1 (0.9-1.3)	0.5
		CCT	23 (2)	22 (7)	4.0 (2.2-7.2)	0.000002*	47 (8)	14 (10)	1.3 (0.7-2.4)	0.4	37 (3)	12 (5)	1.5 (0.8-2.9)	0.3	108 (4)	47 (7)	1.9 (1.3-2.7)	0.0004*
		Other**	57 (5)	9 (3)	-	-	11 (2)	6 (4)	-	-	38 (4)	4 (2)	-	-	107 (3)	20 (3)	-	-

Abbreviation: C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

* After 1000 permutation, results remained significant.

** Haplotypes with frequency less than 3% were excluded from analysis.

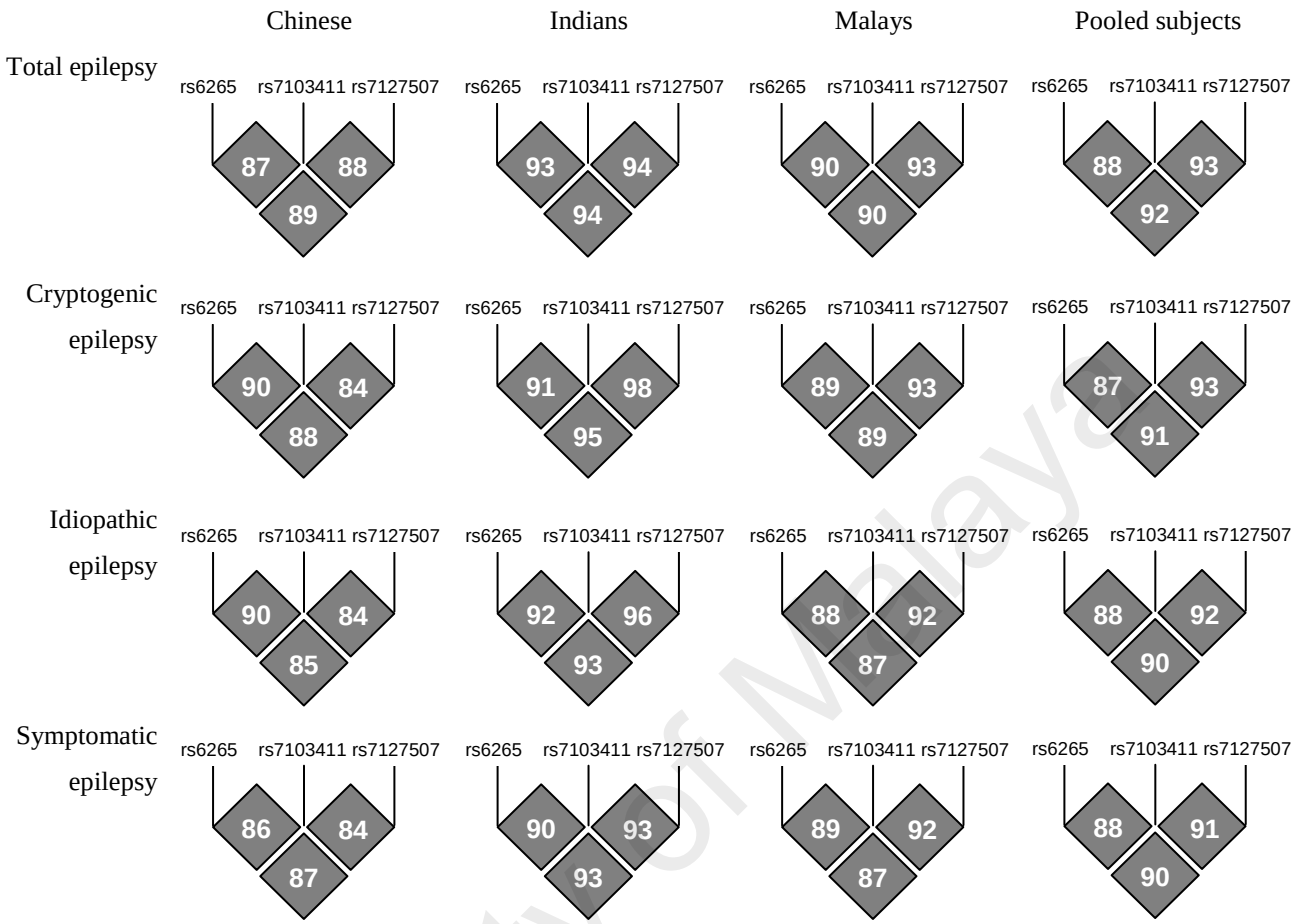

Figure 4.1: Pattern of linkage disequilibrium (D') between three SNPs of *BDNF* gene (rs6265-rs7103411-rs7127507) among the epilepsy patients and healthy controls with susceptibility to epilepsy from the Chinese, Indians and Malays in each epilepsy syndrome.

4.3.2.2 *KCNAB1* rs2280032-rs992353 and *SLC6A11* rs2304725-rs2272394

Haplotype analyses were performed for *KCNAB1* rs2280032 and rs992353 and *SLC6A11* rs2304725 and rs2272394 polymorphisms (Table 4.8, Figure 4.2 and 4.3). Only haplotypes with frequencies above 3% were included in the analysis. Following 1000 permutation test performed for correction of multiple comparisons, the significant results were lost. Therefore, haplotypes of these genes are not risk factors for epilepsy in Malaysia. There was a strong LD were observed between *KCNAB1* rs2280032 and rs992353 (D' > 80%, Figure 4.2), but it was very weak between the *SLC6A11* rs2304725 and rs2272394 (D' < 80%, Figure 4.3).

Table 4.8: Haplotype frequencies of *KCNAB1* and *SLC6A11* polymorphisms between epilepsy patients and healthy controls with susceptibility to epilepsy in Malaysian population.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p	C	E	OR (95% CI)	p
1	*KCNAB1*	rs2280032-rs992353																
		Total epilepsy																
		GA	701 (56)	456 (54)	0.9 (0.8-1.1)	0.6	305 (47)	281 (48)	1.1 (0.8-1.3)	0.6	535 (46)	392 (46)	1.0 (0.8-1.2)	1.0	1541 (51)	1129 (50)	1.0 (0.9-1.1)	0.7
		TG	542 (43)	372 (44)	1.1 (0.9-1.3)	0.6	334 (52)	290 (50)	0.9 (0.8-1.2)	0.6	593 (52)	437 (51)	1.0 (0.8-1.2)	1.0	1469 (48)	1099 (48)	1.0 (0.9-1.1)	0.7
		Other **	11 (1)	12 (2)	-	-	7 (1)	9 (2)	-	-	12 (2)	23 (3)	-	-	30 (1)	44 (2)	-	-
		Cryptogenic epilepsy																
		GA	701 (56)	157 (52)	0.9 (0.7-1.2)	0.5	305 (47)	85 (48)	1.1 (0.8-1.5)	0.6	535 (46)	153 (49)	1.1 (0.8-1.4)	0.6	1541 (51)	395 (50)	1.0 (0.8-1.2)	0.9
		TG	542 (43)	134 (45)	1.1 (0.9-1.4)	0.5	334 (52)	86 (49)	0.9 (0.7-1.3)	0.6	593 (52)	159 (51)	0.9 (0.7-1.2)	0.6	1469 (48)	379 (48)	1.0 (0.9-1.2)	0.9
		Other **	11 (1)	9 (3)	-	-	7 (1)	5 (3)	-	-	12 (2)	2 (0)	-	-	30 (1)	16 (2)	-	-
		Idiopathic epilepsy																
		GA	701 (56)	133 (55)	1.0 (0.7-1.3)	0.8	305 (47)	122 (50)	1.1 (0.8-1.5)	0.4	535 (46)	123 (44)	0.9 (0.7-1.1)	0.3	1541 (51)	378 (50)	1.0 (0.8-1.1)	0.8
		TG	542 (43)	106 (44)	1.0 (0.8-1.4)	0.8	334 (52)	118 (49)	0.9 (0.7-1.2)	0.4	593 (52)	144 (51)	1.0 (0.7-1.3)	0.8	1469 (48)	368 (48)	1.0 (0.9-1.2)	0.8
		Other **	11 (1)	1 (1)	-	-	7 (1)	2 (1)	-	-	12 (2)	15 (5)	-	-	30 (1)	18 (2)	-	-
		Symptomatic epilepsy																
		GA	701 (56)	165 (56)	1.0 (0.8-1.3)	1.0	305 (47)	71 (45)	0.9 (0.7-1.3)	0.7	535 (46)	113 (46)	1.0 (0.7-1.3)	0.9	1541 (51)	349 (50)	1.0 (0.8-1.2)	0.9
		TG	542 (43)	127 (43)	1.0 (0.8-1.3)	1.0	334 (52)	83 (53)	1.1 (0.8-1.5)	0.7	593 (52)	127 (52)	1.0 (0.8-1.3)	0.9	1469 (48)	337 (48)	1.0 (0.9-1.2)	0.9
		Other **	11 (1)	2 (1)	-	-	7 (1)	2 (2)	-	-	12 (2)	6 (2)	-	-	30 (1)	10 (2)	-	-
2	*SLC6A11*	rs2304725-rs2272394																
		Total epilepsy																
		CG	490 (39)	343 (41)	1.1 (0.9-1.3)	0.3	325 (50)	291 (50)	1.0 (0.8-1.2)	0.8	449 (39)	342 (40)	1.0 (0.9-1.2)	0.7	1270 (42)	977 (43)	1.1 (0.9-1.2)	0.4
		TG	561 (44)	357 (42)	0.9 (0.8-1.1)	0.4	268 (42)	232 (39)	0.9 (0.7-1.2)	0.5	498 (44)	396 (47)	1.1 (0.9-1.3)	0.2	1321 (43)	984 (43)	1.0 (0.9-1.1)	0.9
		CA	100 (8)	62 (7)	0.9 (0.7-1.3)	0.6	40 (6)	36 (6)	1.0 (0.6-1.6)	1.0	90 (8)	51 (6)	0.8 (0.5-1.1)	0.1	224 (7)	148 (7)	0.9 (0.7-1.1)	0.2
		TA	115 (9)	80 (10)	1.1 (0.8-1.4)	0.7	13 (2)	29 (5)	2.5 (1.3-4.8)	0.01	101 (9)	61 (7)	0.8 (0.6-1.1)	0.2	235 (8)	171 (7)	1.0 (0.8-1.2)	0.8
		Cryptogenic epilepsy																
		CG	490 (39)	120 (40)	1.0 (0.8-1.3)	0.8	325 (50)	90 (49)	1.0 (0.7-1.3)	0.8	449 (39)	133 (43)	1.1 (0.9-1.5)	0.3	1270 (42)	342 (43)	1.1 (0.9-1.2)	0.5
		TG	561 (44)	125 (41)	0.9 (0.7-1.1)	0.4	268 (42)	68 (38)	0.8 (0.6-1.2)	0.3	498 (44)	137 (44)	1.0 (0.8-1.3)	1.0	1321 (43)	331 (41)	0.9 (0.8-1.1)	0.4
		CA	100 (8)	20 (7)	0.8 (0.5-1.4)	0.5	40 (6)	18 (10)	1.7 (0.9-3.0)	0.1	90 (8)	16 (5)	0.6 (0.4-1.1)	0.1	224 (7)	55 (7)	0.9 (0.7-1.3)	0.6
		TA	115 (9)	37 (12)	1.4 (0.9-2.1)	0.1	13 (2)	6 (3)	1.6 (0.6-4.2)	0.4	101 (9)	26 (8)	0.9 (0.6-1.5)	0.8	235 (8)	68 (9)	1.1 (0.9-1.5)	0.4
		Idiopathic epilepsy																
		CG	490 (39)	102 (43)	1.2 (0.9-1.6)	0.3	325 (50)	128 (52)	1.1 (0.8-1.5)	0.6	449 (39)	111 (40)	1.0 (0.8-1.3)	0.9	1270 (42)	342 (45)	1.1 (1.0-1.3)	0.1
		TG	561 (44)	101 (42)	0.9 (0.7-1.2)	0.5	268 (42)	95 (39)	0.9 (0.7-1.2)	0.5	498 (44)	132 (47)	1.1 (0.9-1.5)	0.3	1321 (43)	327 (43)	1.0 (0.8-1.1)	0.8
		CA	100 (8)	17 (7)	0.9 (0.5-1.5)	0.7	40 (6)	11 (5)	0.7 (0.4-1.4)	0.4	90 (8)	26 (9)	1.2 (0.7-1.9)	0.5	224 (7)	53 (7)	0.9 (0.7-1.3)	0.7
		TA	115 (9)	20 (8)	0.9 (0.6-1.5)	0.7	13 (2)	10 (4)	2.0 (0.9-4.7)	0.1	101 (9)	11 (4)	0.4 (0.2-0.8)	0.1	235 (8)	42 (5)	0.7 (0.5-1.0)	0.04
		Symptomatic epilepsy																
		CG	490 (39)	117 (40)	1.0 (0.8-1.3)	0.8	325 (50)	73 (47)	0.9 (0.6-1.2)	0.4	449 (39)	94 (38)	0.9 (0.7-1.3)	0.7	1270 (42)	282 (40)	1.0 (0.8-1.1)	0.6
		TG	561 (44)	130 (44)	1.0 (0.8-1.3)	1.0	268 (42)	64 (41)	1.0 (0.7-1.4)	0.9	498 (44)	121 (49)	1.2 (0.9-1.6)	0.2	1321 (43)	317 (45)	1.1 (0.9-1.3)	0.3
		CA	100 (8)	24 (8)	1.1 (0.7-1.7)	0.8	40 (6)	4 (2)	0.4 (0.1-1.1)	0.1	90 (8)	9 (3)	0.4 (0.2-0.9)	0.01	224 (7)	39 (6)	0.7 (0.5-1.1)	0.1
		TA	115 (9)	23 (8)	0.8 (0.5-1.3)	0.4	13 (2)	15 (10)	5.2 (2.4-11.1)	0.000003*	101 (9)	24 (10)	1.1 (0.7-1.8)	0.6	235 (8)	60 (9)	1.1 (0.8-1.5)	0.4

Abbreviation: No.: number; C: healthy control; E: epilepsy patient; OR: odds ratio; CI: 95% confidence interval; p: p-value

* After 1000 permutation, results remained significant.

** Haplotypes with frequency less than 3% were excluded from analysis.

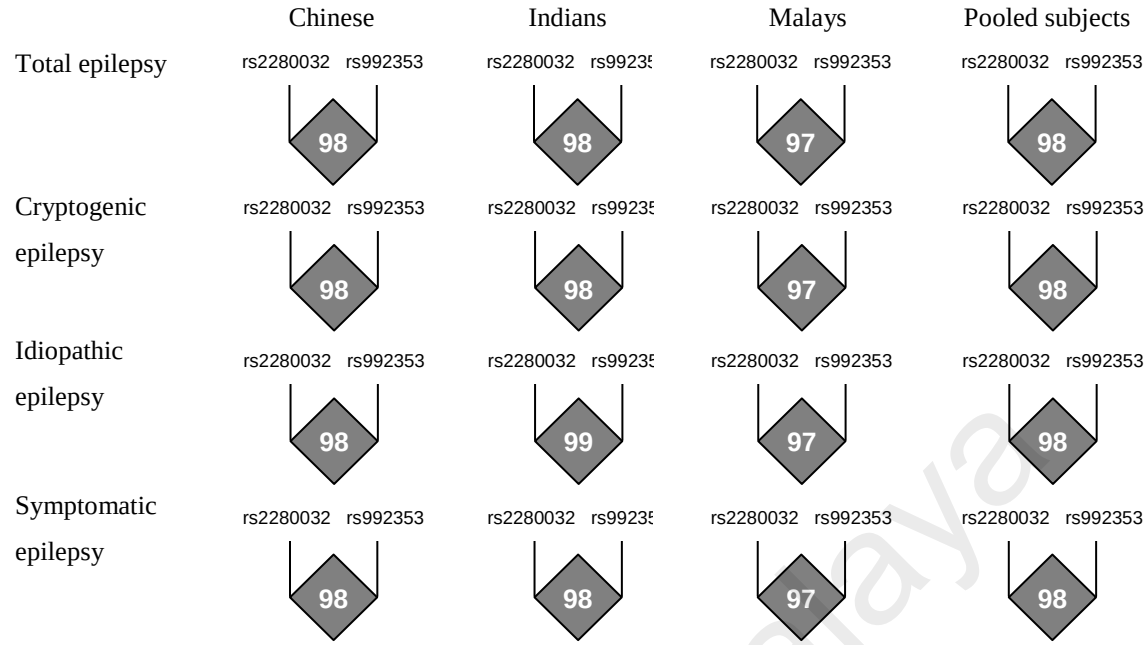

Figure 4.2: Pattern of linkage disequilibrium (D') between two SNPs of *KCNAB1* gene (rs2280032-rs992353) among the epilepsy patients and healthy controls with susceptibility to epilepsy from the Chinese, Indians and Malays in each epilepsy syndrome.

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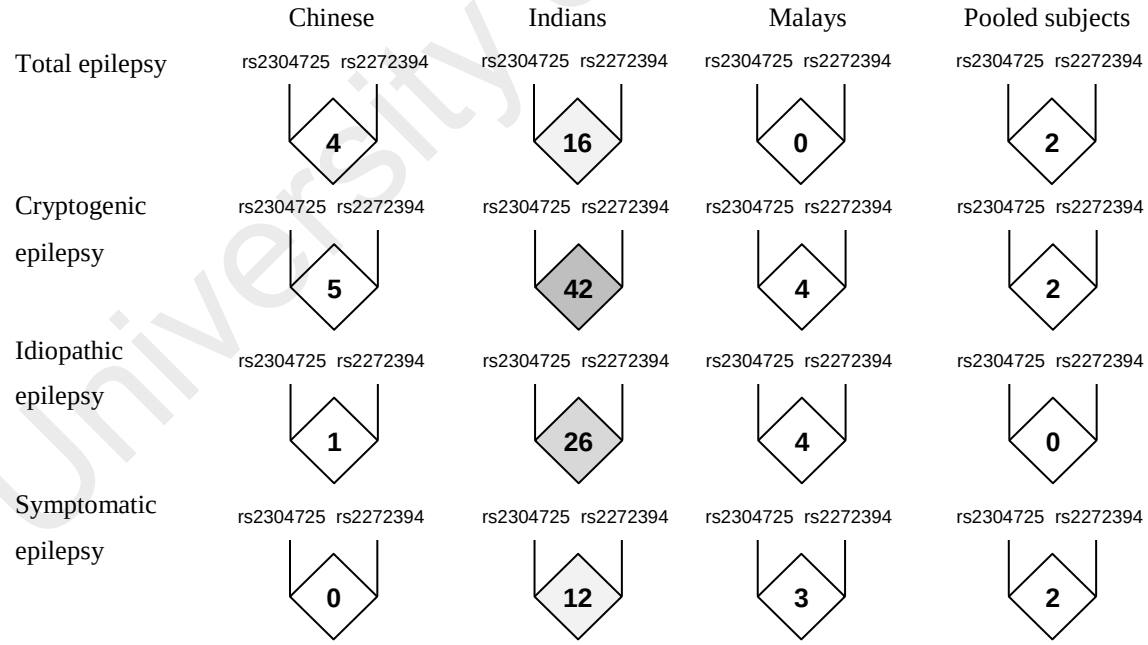

Figure 4.3: Pattern of linkage disequilibrium (D') between two SNPs of *SLC6A11* gene (rs2304725-rs2272394) among the epilepsy patients and healthy controls with susceptibility to epilepsy from the Chinese, Indians and Malays in each epilepsy syndrome.

4.4 Drug responsiveness of antiepileptic drugs study

4.4.1 Polymorphisms

Results of drug responsiveness have been reviewed in Table 4.9-4.12. Of 14 polymorphisms, 2 SNPs (*ABCC2* rs2273697 and *KCNAB1* rs2280032) showed significant associations with drug responsiveness ($p < 0.01$).

4.4.1.1 *KCNAB1* gene

The alleles and genotypes of *KCNAB1* rs2280032 were associated with drug responsiveness in Malay cryptogenic epilepsy (Table 4.10, OR 0.5, 95% CI 0.3-0.8, p 0.005 and OR 0.3, 95% CI 0.1-0.7, p 0.007, respectively). In this ethnicity, T allele and TT genotype in the patients with cryptogenic epilepsy were significantly higher than in controls (60% vs. 44% and 38% vs. 18%, respectively). After Bonferroni correction, results remained significant. Therefore, *KCNAB1* rs2280032 T confers a risk variant for drug responsiveness in the Malays with cryptogenic epilepsy.

4.4.1.2 *ABCC2* gene

The alleles and genotypes of *ABCC2* rs2273697 were associated with drug responsiveness in Chinese idiopathic epilepsy (Table 4.11, OR 3.1, 95% CI 1.4-7.1, p 0.007 and OR 4.9, 95% CI 1.9-12.8, p 0.001, respectively). In this ethnicity, T allele and CT genotype in the patients with idiopathic epilepsy were significantly higher than in control (19% vs. 7% and 38% vs. 11%, respectively). After Bonferroni correction, results remained significant. Therefore, *ABCC2* rs2273697 T confers a risk variant for drug responsiveness in the Chinese with idiopathic epilepsy.

Table 4.9: Association tests of selected gene polymorphisms between nonresponders and responders to CBZ or VPA monotherapy in Malaysian epilepsy patients.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
1	*ABCC2*	rs2273697																
		CC	179 (85)	167 (79)	-	-	91 (60)	85 (58)	-	-	172 (80)	170 (79)	-	-	442 (77)	422 (74)	-	-
		CT	30 (14)	41 (20)	1.5 (0.9-2.5)	0.1	55 (36)	54 (37)	1.1 (0.7-1.7)	0.8	38 (18)	44 (20)	1.2 (0.7-1.9)	0.5	123 (21)	139 (24)	1.2 (0.9-1.6)	0.2
		TT	1 (1)	3 (1)	3.2 (0.3-31.2)	0.3	6 (4)	7 (5)	1.2 (0.4-3.9)	0.7	4 (2)	2 (1)	0.5 (0.1-2.8)	0.4	11 (2)	12 (2)	1.1 (0.5-2.6)	0.8
		C	388 (92)	375 (89)	-	-	237 (78)	224 (77)	-	-	382 (89)	384 (89)	-	-	1007 (87)	983 (86)	-	-
		T	32 (8)	47 (11)	1.5 (0.9-2.4)	0.1	67 (22)	68 (23)	1.1 (0.7-1.6)	0.7	46 (11)	48 (11)	1.0 (0.7-1.6)	0.9	145 (13)	163 (14)	1.2 (0.9-1.5)	0.3
2	*GJD2*	rs3743123																
		CC	115 (55)	102 (48)	-	-	45 (30)	61 (42)	-	-	106 (50)	119 (56)	-	-	266 (46)	282 (50)	-	-
		CT	85 (40)	93 (44)	1.2 (0.8-1.8)	0.3	80 (53)	58 (40)	0.5 (0.3-0.9)	0.02	87 (41)	84 (39)	0.9 (0.6-1.3)	0.5	252 (44)	235 (41)	0.9 (0.7-1.1)	0.3
		TT	11 (5)	16 (8)	1.6 (0.7-3.7)	0.2	26 (17)	26 (18)	0.7 (0.4-1.4)	0.4	19 (9)	11 (5)	0.5 (0.2-1.1)	0.1	56 (10)	53 (9)	0.9 (0.6-1.3)	0.6
		C	315 (75)	297 (70)	-	-	170 (56)	180 (62)	-	-	299 (71)	322 (75)	-	-	784 (68)	799 (70)	-	-
		T	107 (25)	125 (30)	1.2 (0.9-1.7)	0.2	132 (44)	110 (38)	0.8 (0.6-1.1)	0.2	125 (29)	106 (25)	0.8 (0.6-1.1)	0.1	364 (32)	341 (30)	0.9 (0.8-1.1)	0.4
3	*OPRM1*	rs1799971																
		AA	79 (38)	75 (36)	-	-	48 (32)	40 (27)	-	-	67 (31)	71 (33)	-	-	194 (34)	186 (33)	-	-
		AG	100 (47)	99 (47)	1.0 (0.7-1.6)	0.8	71 (47)	76 (52)	1.3 (0.8-2.2)	0.4	95 (45)	101 (47)	1.0 (0.6-1.6)	1.0	266 (46)	276 (48)	1.1 (0.8-1.4)	0.6
		GG	32 (15)	36 (17)	1.2 (0.7-2.1)	0.6	32 (21)	30 (21)	1.1 (0.6-2.2)	0.7	52 (24)	43 (20)	0.8 (0.5-1.3)	0.4	116 (20)	109 (19)	1.0 (0.7-1.4)	0.9
		A	258 (61)	249 (59)	-	-	167 (55)	156 (53)	-	-	229 (54)	243 (57)	-	-	654 (57)	648 (57)	-	-
		G	164 (39)	171 (41)	1.1 (0.8-1.4)	0.6	135 (45)	136 (47)	1.1 (0.8-1.5)	0.6	199 (46)	187 (43)	0.9 (0.7-1.2)	0.4	498 (43)	494 (43)	1.0 (0.8-1.2)	1.0
4	*NR1I2*	rs6785049																
		GG	70 (33)	71 (34)	-	-	38 (25)	43 (30)	-	-	86 (40)	91 (42)	-	-	194 (34)	205 (36)	-	-
		GA	108 (52)	94 (44)	0.9 (0.6-1.3)	0.5	78 (52)	66 (46)	0.7 (0.4-1.3)	0.3	98 (46)	98 (46)	0.9 (0.6-1.4)	0.8	284 (49)	258 (45)	0.9 (0.7-1.1)	0.3
		AA	32 (15)	46 (22)	1.4 (0.8-2.5)	0.2	35 (23)	34 (24)	0.9 (0.5-1.6)	0.6	30 (14)	26 (12)	0.8 (0.4-1.5)	0.5	97 (17)	106 (19)	1.0 (0.7-1.5)	0.8
		G	248 (59)	236 (56)	-	-	154 (51)	152 (53)	-	-	270 (63)	280 (65)	-	-	672 (58)	668 (59)	-	-
		A	172 (41)	186 (44)	1.1 (0.9-1.5)	0.4	148 (49)	134 (47)	0.9 (0.7-1.3)	0.6	158 (37)	150 (35)	0.9 (0.7-1.2)	0.5	478 (42)	470 (41)	1.0 (0.8-1.2)	0.9
5	*SLC6A11*	rs2304725																
		TT	66 (31)	56 (27)	-	-	32 (21)	25 (17)	-	-	60 (28)	67 (31)	-	-	158 (27)	148 (26)	-	-
		TC	98 (47)	96 (45)	1.2 (0.7-1.8)	0.5	78 (52)	72 (50)	1.2 (0.6-2.2)	0.6	104 (49)	103 (48)	0.9 (0.6-1.4)	0.6	280 (49)	271 (47)	1.0 (0.8-1.4)	0.8
		CC	47 (22)	59 (28)	1.5 (0.9-2.5)	0.1	41 (27)	48 (33)	1.5 (0.8-2.9)	0.2	48 (23)	45 (21)	0.8 (0.5-1.4)	0.5	136 (24)	152 (27)	1.2 (0.9-1.6)	0.3
		T	230 (55)	208 (49)	-	-	142 (47)	122 (42)	-	-	224 (53)	237 (55)	-	-	596 (52)	567 (50)	-	-
		C	192 (45)	214 (51)	1.2 (0.9-1.6)	0.1	160 (53)	168 (58)	1.2 (0.9-1.7)	0.2	200 (47)	193 (45)	0.9 (0.7-1.2)	0.5	552 (48)	575 (50)	1.1 (0.9-1.3)	0.3
		rs2272394																
		GG	153 (73)	138 (66)	-	-	119 (79)	113 (78)	-	-	157 (73)	165 (77)	-	-	429 (75)	416 (73)	-	-
		GA	52 (25)	66 (31)	1.4 (0.9-2.2)	0.1	30 (20)	30 (21)	1.1 (0.6-1.9)	0.9	53 (25)	48 (22)	0.9 (0.6-1.3)	0.5	135 (23)	144 (25)	1.1 (0.8-1.4)	0.5
		AA	5 (2)	7 (3)	1.6 (0.5-5.0)	0.5	1 (1)	2 (1)	2.1 (0.2-23.5)	0.5	4 (2)	2 (1)	0.5 (0.1-2.6)	0.4	10 (2)	11 (2)	1.1 (0.5-2.7)	0.8
		G	358 (85)	342 (81)	-	-	268 (89)	256 (88)	-	-	367 (86)	378 (88)	-	-	993 (87)	976 (86)	-	-
		A	62 (15)	80 (19)	1.4 (0.9-1.9)	0.1	32 (11)	34 (12)	1.1 (0.7-1.9)	0.7	61 (14)	52 (12)	0.8 (0.6-1.2)	0.4	155 (13)	166 (14)	1.1 (0.9-1.4)	0.5
6	*CAMSAP2*	rs2292096																
		AA	146 (70)	147 (70)	-	-	118 (78)	119 (81)	-	-	164 (76)	167 (77)	-	-	428 (74)	433 (76)	-	-
		AG	59 (28)	55 (26)	0.9 (0.6-1.4)	0.7	31 (21)	26 (18)	0.8 (0.5-1.5)	0.5	50 (23)	48 (22)	0.9 (0.6-1.5)	0.8	140 (24)	129 (22)	0.9 (0.7-1.2)	0.5
		GG	5 (2)	9 (4)	1.8 (0.6-5.5)	0.3	2 (1)	1 (1)	0.5 (0.04-5.5)	0.6	1 (1)	1 (1)	1.0 (0.1-15.8)	1.0	8 (2)	11 (2)	1.4 (0.5-3.4)	0.5
		A	351 (84)	349 (83)	-	-	267 (88)	264 (90)	-	-	378 (88)	382 (88)	-	-	996 (87)	995 (87)	-	-
		G	69 (16)	73 (17)	1.1 (0.7-1.5)	0.7	35 (12)	28 (10)	0.8 (0.5-1.4)	0.4	52 (12)	50 (12)	1.0 (0.6-1.4)	0.8	156 (13)	151 (13)	1.0 (0.8-1.2)	0.8

Abbreviation: R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.9: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
7	*GRIK2*	rs4840200																
		TT	62 (30)	65 (31)	-	-	85 (56)	80 (55)	-	-	84 (40)	81 (38)	-	-	231 (40)	226 (40)	-	-
		TC	106 (50)	110 (52)	1.0 (0.6-1.5)	1.0	57 (38)	51 (35)	1.0 (0.6-1.5)	0.8	97 (46)	103 (48)	1.1 (0.7-1.7)	0.6	260 (46)	264 (46)	1.0 (0.8-1.3)	0.8
		CC	42 (20)	36 (17)	0.8 (0.5-1.4)	0.5	9 (6)	15 (10)	1.8 (0.7-4.3)	0.2	31 (14)	29 (14)	1.0 (0.5-1.8)	0.9	82 (14)	80 (14)	1.0 (0.7-1.4)	1.0
		T	230 (55)	240 (57)	-	-	227 (75)	211 (72)	-	-	265 (63)	265 (62)	-	-	722 (63)	716 (63)	-	-
		C	190 (45)	182 (43)	0.9 (0.7-1.2)	0.5	75 (25)	81 (28)	1.2 (0.8-1.7)	0.4	159 (37)	161 (38)	1.0 (0.8-1.3)	0.9	424 (37)	424 (37)	1.0 (0.9-1.2)	0.9
8	*LGI1*	rs3758532																
		CC	119 (57)	117 (56)	-	-	97 (65)	80 (55)	-	-	107 (50)	105 (49)	-	-	323 (56)	302 (53)	-	-
		CT	77 (37)	80 (38)	1.1 (0.7-1.6)	0.8	49 (33)	58 (40)	1.4 (0.9-2.3)	0.1	84 (40)	97 (45)	1.2 (0.8-1.8)	0.4	210 (37)	235 (41)	1.2 (0.9-1.5)	0.1
		TT	14 (6)	12 (6)	0.9 (0.4-2.0)	0.7	4 (2)	8 (5)	2.4 (0.7-8.3)	0.2	21 (10)	12 (6)	0.6 (0.3-1.2)	0.2	39 (7)	32 (6)	0.9 (0.5-1.4)	0.6
		C	315 (75)	314 (75)	-	-	243 (81)	218 (75)	-	-	298 (70)	307 (72)	-	-	856 (75)	839 (74)	-	-
		T	105 (25)	104 (25)	1.0 (0.7-1.4)	1.0	57 (19)	74 (25)	1.4 (1.0-2.1)	0.1	126 (30)	121 (28)	0.9 (0.7-1.3)	0.6	288 (25)	299 (26)	1.1 (0.9-1.3)	0.5
9	*CALHM1*	rs11191692																
		GG	97 (46)	99 (47)	-	-	50 (34)	52 (36)	-	-	83 (39)	95 (44)	-	-	230 (40)	246 (43)	-	-
		GA	91 (44)	88 (42)	0.9 (0.6-1.4)	0.8	74 (49)	66 (45)	0.9 (0.5-1.4)	0.6	98 (46)	96 (45)	0.9 (0.6-1.3)	0.5	263 (46)	250 (44)	0.9 (0.7-1.1)	0.4
		AA	21 (10)	24 911)	1.1 (0.6-2.1)	0.7	26 (17)	27 (19)	1.0 (0.5-1.9)	1.0	31 (15)	23 (11)	0.6 (0.4-1.2)	0.2	7788 (14)	74 (13)	0.9 (0.6-1.3)	0.5
		G	285 (68)	286 (68)	-	-	174 (58)	170 (59)	-	-	264 (62)	286 (67)	-	-	723 (63)	742 (65)	-	-
		A	133 (32)	136 (32)	1.0 (0.8-1.4)	0.9	126 (42)	120 (41)	1.0 (0.7-1.4)	0.9	160 (38)	142 (33)	0.8 (0.6-1.1)	0.2	419 (37)	398 (35)	0.9 (0.8-1.1)	0.4
10	*KCNAB1*	rs2280032																
		TT	38 (18)	50 (24)	-	-	46 (31)	27 (19)	-	-	55 (26)	63 (30)	-	-	139 (24)	140 (24)	-	-
		TG	104 (49)	98 (46)	0.7 (0.4-1.2)	0.2	71 (48)	78 (54)	1.9 (1.1-3.3)	0.03	106 (49)	101 (47)	0.8 (0.5-1.3)	0.4	281 (49)	277 (49)	1.0 (0.7-1.3)	0.9
		GG	69 (33)	63 (30)	0.7 (0.4-1.2)	0.2	30 (21)	40 (27)	2.3 (1.2-4.4)	0.02	53 (25)	49 (23)	0.8 (0.5-1.4)	0.4	152 (27)	152 (27)	1.0 (0.7-1.4)	1.0
		T	180 (43)	198 (47)	-	-	163 (55)	132 (46)	-	-	216 (51)	227 (53)	-	-	559 (49)	557 (49)	-	-
		G	242 (57)	224 (53)	0.8 (0.6-1.1)	0.2	131 (45)	158 (54)	1.5 (1.1-2.1)	0.02	212 (49)	199 (47)	0.9 (0.7-1.2)	0.4	585 (51)	581 (51)	1.0 (0.8-1.2)	1.0
		rs992353																
		GG	41 (20)	51 (24)	-	-	47 (32)	27 (19)	-	-	61 (29)	64 (30)	-	-	149 (26)	142 (25)	-	-
		GA	99 (47)	97 (46)	0.8 (0.5-1.3)	0.3	68 (46)	80 (55)	2.0 (1.2-3.6)	0.01	106 (49)	99 (46)	0.9 (0.6-1.4)	0.6	273 (48)	276 (49)	1.1 (0.8-1.4)	0.7
		AA	70 (33)	63 (30)	0.7 (0.4-1.2)	0.2	32 (22)	37 (26)	2.0 (1.0-3.9)	0.04	47 (22)	51 (24)	1.0 (0.6-1.8)	0.9	149 (26)	151 (26)	1.1 (0.8-1.5)	0.7
		G	181 (43)	199 (47)	-	-	162 (55)	134 (47)	-	-	228 (53)	227 (53)	-	-	571 (50)	560 (49)	-	-
		A	239 (57)	223 (53)	0.8 (0.6-1.1)	0.2	132 (45)	154 (53)	1.4 (1.0-2.0)	0.04	200 (47)	201 (47)	1.0 (0.8-1.3)	0.9	571 (50)	578 (51)	1.0 (0.9-1.2)	0.7
11	*ASIC1*	rs844347																
		AA	158 (77)	152 (74)	-	-	107 (71)	113 (78)	-	-	132 (63)	140 (65)	-	-	397 (71)	405 (72)	-	-
		AC	43 (21)	50 (24)	1.2 (0.8-1.9)	0.4	40 (27)	29 (20)	0.7 (0.4-1.2)	0.2	66 (32)	66 (31)	0.9 (0.6-1.4)	0.8	149 (26)	145 (26)	1.0 (0.7-1.2)	0.7
		CC	4 (2)	4 (2)	1.0 (0.3-4.2)	1.0	3 (2)	3 (2)	0.9 (0.2-4.8)	0.9	11 (5)	8 (4)	0.7 (0.3-1.8)	0.4	18 (3)	15 (2)	0.8 (0.4-1.6)	0.6
		A	359 (88)	354 (86)	-	-	254 (85)	255 (88)	-	-	330 (79)	346 (81)	-	-	943 (84)	955 (85)	-	-
		C	51 (12)	58 (14)	1.2 (0.8-1.7)	0.5	46 (15)	35 (12)	0.8 (0.5-1.2)	0.3	88 (21)	82 (19)	0.9 (0.6-1.2)	0.5	185 (16)	175 (15)	0.9 (0.7-1.2)	0.6
12	*SCN8A*	rs11169883																
		CC	188 (89)	178 (85)	-	-	112 (75)	108 (74)	-	-	184 (86)	183 (85)	-	-	484 (84)	469 (82)	-	-
		CT	24 (11)	30 (14)	1.3 (0.7-2.3)	0.3	35 (23)	33 (23)	1.0 (0.6-1.7)	0.9	29 (13)	30 (14)	1.0 (0.6-1.8)	0.9	88 (15)	93 (16)	1.1 (0.8-1.5)	0.6
		TT	0 (0)	2 (1)	-	-	3 (2)	4 (3)	1.4 (0.3-6.3)	0.7	2 (1)	2 (1)	1.0 (0.1-7.2)	1.0	5 (1)	8 (2)	1.7 (0.5-5.1)	0.4
		C	400 (94)	386 (92)	-	-	259 (86)	249 (86)	-	-	397 (92)	396 (92)	-	-	1056 (92)	1031 (90)	-	-
		T	24 (6)	34 (8)	1.5 (0.9-2.5)	0.2	41 (14)	41 (14)	1.0 (0.7-1.7)	0.9	33 (8)	34 (8)	1.0 (0.6-1.7)	0.9	98 (8)	109 (10)	1.1 (0.9-1.5)	0.4

Abbreviation: R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.10: Association tests of selected gene polymorphisms between nonresponders and responders to CBZ or VPA monotherapy in Malaysian cryptogenic epilepsy patients.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
1	*ABCC2*	rs2273697																
		CC	66 (83)	61 (86)	-	-	21 (64)	32 (55)	-	-	74 (87)	57 (76)	-	-	161 (81)	150 (74)	-	-
		CT	14 (17)	9 (13)	0.7 (0.3-1.7)	0.4	10 (30)	23 (40)	1.5 (0.6-3.8)	0.4	11 (13)	18 (24)	2.1 (0.9-4.9)	0.1	35 (18)	50 (24)	1.5 (0.9-2.5)	0.1
		TT	0 (0)	1 (1)	-	-	2 (6)	3 (5)	1.0 (0.2-6.4)	1.0	0 (0)	0 (0)	-	-	2 (1)	4 (2)	2.1 (0.4-11.9)	0.4
		C	146 (91)	131 (92)	-	-	52 (79)	87 (75)	-	-	159 (94)	132 (88)	-	-	357 (90)	350 (86)	-	-
		T	14 (9)	11 (8)	0.9 (0.4-2.0)	0.8	14 (21)	29 (25)	1.2 (0.6-2.6)	0.6	11 (6)	18 (12)	2.0 (0.9-4.3)	0.1	39 (10)	58 (14)	1.5 (1.0-2.3)	0.1
2	*GJD2*	rs3743123																
		CC	40 (50)	34 (48)	-	-	11 (33)	22 (38)	-	-	43 (52)	41 (55)	-	-	94 (48)	97 (48)	-	-
		CT	36 (45)	28 (39)	0.9 (0.5-1.8)	0.8	18 (55)	24 (41)	0.7 (0.3-1.7)	0.4	32 (39)	28 (38)	0.9 (0.5-1.8)	0.8	86 (44)	80 (39)	0.9 (0.6-1.4)	0.6
		TT	4 (5)	9 (13)	2.6 (0.7-9.4)	0.1	4 (12)	12 (21)	1.5 (0.4-5.7)	0.6	8 (9)	5 (7)	0.7 (0.2-2.2)	0.5	16 (8)	26 (13)	1.6 (0.8-3.1)	0.2
		C	116 (73)	96 (68)	-	-	40 (61)	68 (59)	-	-	118 (71)	110 (74)	-	-	274 (70)	274 (68)	-	-
		T	44 (27)	46 (32)	1.3 (0.8-2.1)	0.4	26 (39)	48 (41)	1.1 (0.6-2.0)	0.8	48 (29)	38 (26)	0.8 (0.5-1.4)	0.5	118 (30)	132 (32)	1.1 (0.8-1.5)	0.5
3	*OPRM1*	rs1799971																
		AA	31 (39)	25 (35)	-	-	12 (38)	14 (24)	-	-	23 (27)	20 (27)	-	-	66 (34)	59 (29)	-	-
		AG	40 (50)	32 (45)	1.0 (0.5-2.0)	1.0	12 (38)	33 (57)	2.4 (0.9-6.5)	0.1	41 (49)	36 (48)	1.0 (0.5-2.1)	1.0	93 (47)	101 (49)	1.2 (0.8-1.9)	0.4
		GG	9 (11)	14 (20)	1.9 (0.7-5.2)	0.2	8 (24)	11 (19)	1.2 (0.4-3.9)	0.8	20 (24)	19 (25)	1.1 (0.5-2.6)	0.8	37 (19)	44 (22)	1.3 (0.8-2.3)	0.3
		A	102 (64)	82 (58)	-	-	36 (56)	61 (53)	-	-	87 (52)	76 (51)	-	-	225 (57)	219 (54)	-	-
		G	58 (36)	60 (42)	1.3 (0.8-2.0)	0.3	28 (44)	55 (47)	1.2 (0.6-2.1)	0.6	81 (48)	74 (49)	1.0 (0.7-1.6)	0.8	167 (43)	189 (46)	1.2 (0.9-1.5)	0.3
4	*NR1I2*	rs6785049																
		GG	32 (40)	20 (28)	-	-	11 (33)	19 (34)	-	-	37 (44)	34 (45)	-	-	80 (40)	73 (36)	-	-
		GA	37 (46)	32 (45)	1.4 (0.7-2.9)	0.4	18 (55)	27 (48)	0.9 (0.3-2.3)	0.8	37 (44)	32 (43)	0.9 (0.5-1.8)	0.9	92 (47)	91 (45)	1.1 (0.7-1.7)	0.7
		AA	11 (14)	19 (27)	2.8 (1.1-7.0)	0.03	4 (12)	10 (18)	1.4 (0.4-5.7)	0.6	11 (12)	9 (12)	0.9 (0.3-2.4)	0.8	26 (13)	38 (19)	1.6 (0.9-2.9)	0.1
		G	101 (63)	72 (51)	-	-	40 (61)	65 (58)	-	-	111 (65)	100 (67)	-	-	252 (64)	237 (59)	-	-
		A	59 (37)	70 (49)	1.7 (1.1-2.6)	0.03	26 (39)	47 (42)	1.1 (0.6-2.1)	0.7	59 (35)	50 (33)	0.9 (0.6-1.5)	0.8	144 (36)	167 (41)	1.2 (0.9-1.6)	0.1
5	*SLC6A11*	rs2304725																
		TT	22 (28)	26 (37)	-	-	6 (18)	6 (10)	-	-	25 (30)	22 (30)	-	-	53 (27)	54 (27)	-	-
		TC	37 (46)	29 (41)	0.7 (0.3-1.4)	0.3	19 (58)	31 (54)	1.6 (0.5-5.8)	0.4	38 (46)	33 (44)	1.0 (0.5-2.1)	1.0	94 (48)	93 (46)	1.0 (0.6-1.6)	0.9
		CC	21 (26)	16 (22)	0.6 (0.3-1.5)	0.3	8 (24)	21 (36)	2.6 (0.7-10.6)	0.2	20 (24)	19 (26)	1.1 (0.5-2.5)	0.9	49 (25)	56 (27)	1.1 (0.7-1.9)	0.7
		T	81 (51)	81 (57)	-	-	31 (47)	43 (37)	-	-	88 (53)	77 (52)	-	-	200 (51)	201 (50)	-	-
		C	79 (49)	61 (43)	0.8 (0.5-1.2)	0.3	35 (53)	73 (63)	1.5 (0.8-2.8)	0.2	78 (47)	71 (48)	1.0 (0.7-1.6)	0.9	192 (49)	205 (50)	1.1 (0.8-1.4)	0.7
		rs2272394																
		GG	55 (69)	46 (65)	-	-	26 (79)	42 (72)	-	-	64 (75)	54 (73)	-	-	145 (73)	142 (70)	-	-
		GA	22 (27)	21 (30)	1.1 (0.6-2.3)	0.7	7 (21)	15 (26)	1.3 (0.5-3.7)	0.6	21 (25)	18 (24)	1.0 (0.5-2.1)	1.0	50 (25)	54 (27)	1.1 (0.7-1.7)	0.7
		AA	3 (4)	4 (5)	1.6 (0.3-7.5)	0.6	0 (0)	1 (2)	-	-	0 (0)	2 (3)	-	-	3 (2)	7 (3)	2.4 (0.6-9.4)	0.2
		G	132 (83)	113 (80)	-	-	59 (89)	99 (85)	-	-	149 (88)	126 (85)	-	-	340 (86)	338 (83)	-	-
		A	28 (17)	29 (20)	1.2 (0.7-2.2)	0.5	7 (11)	17 (15)	1.4 (0.6-3.7)	0.4	21 (12)	22 (15)	1.2 (0.7-2.4)	0.5	56 (14)	68 (17)	1.2 (0.8-1.8)	0.3
6	*CAMSAP2*	rs2292096																
		AA	61 (76)	51 (72)	-	-	27 (82)	47 (81)	-	-	66 (78)	52 (69)	-	-	154 (78)	150 (74)	-	-
		AG	16 (20)	17 (24)	1.3 (0.6-2.8)	0.5	5 (15)	11 (19)	1.3 (0.4-4.0)	0.7	18 (21)	23 (31)	1.6 (0.8-3.3)	0.2	39 (20)	51 (25)	1.3 (0.8-2.2)	0.2
		GG	3 (4)	3 (4)	1.2 (0.2-6.2)	0.8	1 (3)	0 (0)	-	-	1 (1)	0 (0)	-	-	5 (2)	3 (1)	0.6 (0.1-2.6)	0.5
		A	138 (86)	119 (84)	-	-	59 (89)	105 (91)	-	-	150 (88)	127 (85)	-	-	347 (88)	351 (86)	-	-
		G	22 (14)	23 (16)	1.2 (0.6-2.3)	0.6	7 (11)	11 (9)	0.9 (0.3-2.4)	0.8	20 (12)	23 (15)	1.4 (0.7-2.6)	0.4	49 (12)	57 (14)	1.2 (0.8-1.7)	0.5

Abbreviation: R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.10: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
7	*GRIK2*	rs4840200																
		TT	25 (31)	22 (31)	-	-	17 (52)	25 (43)	-	-	31 (37)	37 (50)	-	-	73 (37)	84 (42)	-	-
		TC	33 (41)	38 (54)	1.3 (0.6-2.7)	0.5	14 (42)	26 (45)	1.3 (0.5-3.1)	0.6	41 (49)	32 (43)	0.7 (0.3-1.3)	0.2	88 (45)	96 (47)	0.9 (0.6-1.5)	0.8
		CC	22 (28)	11 (15)	0.6 (0.2-1.4)	0.2	2 (6)	7 (12)	2.4 (0.4-12.9)	0.3	12 (14)	5 (7)	0.3 (0.1-1.1)	0.1	36 (18)	23 (11)	0.6 (0.3-1.0)	0.1
		T	83 (52)	82 (58)	-	-	48 (73)	76 (66)	-	-	103 (61)	106 (72)	-	-	234 (59)	264 (65)	-	-
		C	77 (48)	60 (42)	0.8 (0.5-1.2)	0.3	18 (27)	40 (34)	1.4 (0.7-2.7)	0.3	65 (39)	42 (28)	0.6 (0.4-1.0)	0.1	160 (41)	142 (35)	0.8 (0.6-1.0)	0.1
8	*LGI1*	rs3758532																
		CC	49 (61)	35 (50)	-	-	20 (65)	31 (53)	-	-	44 (52)	36 (49)	-	-	113 (58)	102 (51)	-	-
		CT	25 (31)	32 (46)	1.8 (0.9-3.5)	0.1	11 (35)	23 (40)	1.3 (0.5-3.4)	0.5	32 (38)	34 (46)	1.3 (0.7-2.5)	0.4	68 (35)	89 (44)	1.5 (1.0-2.2)	0.1
		TT	6 (8)	3 (4)	0.7 (0.2-3.0)	0.6	0 (0)	4 (7)	-	-	8 (10)	4 (5)	0.6 (0.2-2.2)	0.5	14 (7)	11 (5)	0.9 (0.4-2.0)	0.7
		C	123 (77)	102 (73)	-	-	51 (82)	85 (73)	-	-	120 (71)	106 (72)	-	-	294 (75)	293 (73)	-	-
		T	37 (23)	38 (27)	1.2 (0.7-2.1)	0.4	11 (18)	31 (27)	1.7 (0.8-3.7)	0.2	48 (29)	42 (28)	1.0 (0.6-1.6)	1.0	96 (25)	111 (27)	1.2 (0.8-1.6)	0.4
9	*CALHM1*	rs11191692																
		GG	43 (54)	34 (48)	-	-	16 (49)	22 (38)	-	-	31 (37)	27 (37)	-	-	90 (46)	83 (41)	-	-
		GA	30 (37)	29 (41)	1.2 (0.6-2.4)	0.6	15 (45)	29 (50)	1.4 (0.6-3.4)	0.5	42 (50)	38 (51)	1.0 (0.5-2.0)	0.9	87 (44)	96 (47)	1.2 (0.8-1.8)	0.4
		AA	7 (9)	8 (11)	1.4 (0.5-4.4)	0.5	2 (6)	7 (12)	2.5 (0.5-13.9)	0.3	11 (13)	9 (12)	0.9 (0.3-2.6)	0.9	20 (10)	24 (12)	1.3 (0.7-2.5)	0.4
		G	116 (73)	97 (68)	-	-	47 (71)	73 (63)	-	-	104 (62)	92 (62)	-	-	267 (68)	262 (65)	-	-
		A	44 (27)	45 (32)	1.2 (0.7-2.0)	0.4	19 (29)	43 (37)	1.5 (0.8-2.8)	0.3	64 (38)	56 (38)	1.0 (0.6-1.6)	1.0	127 (32)	144 (35)	1.2 (0.9-1.5)	0.3
10	*KCNAB1*	rs2280032																
		TT	17 (21)	18 (25)	-	-	12 (39)	10 (17)	-	-	15 (18)	28 (38)	-	-	44 (23)	56 (28)	-	-
		TG	37 (46)	31 (44)	0.8 (0.4-1.8)	0.6	12 (39)	33 (57)	3.3 (1.1-9.6)	0.03	43 (51)	31 (43)	0.4 (0.2-0.8)	0.02	92 (47)	95 (47)	0.8 (0.5-1.3)	0.4
		GG	26 (33)	22 (31)	0.8 (0.3-1.9)	0.6	7 (22)	15 (26)	2.6 (0.8-8.8)	0.1	26 (31)	14 (19)	0.3 (0.1-0.7)	0.007*	59 (30)	51 (25)	0.7 (0.4-1.2)	0.2
		T	71 (44)	67 (47)	-	-	36 (58)	53 (46)	-	-	73 (44)	87 (60)	-	-	180 (46)	207 (51)	-	-
		G	89 (56)	75 (53)	0.9 (0.6-1.4)	0.6	26 (42)	63 (54)	1.6 (0.9-3.1)	0.1	95 (56)	59 (40)	0.5 (0.3-0.8)	0.005*	210 (54)	197 (49)	0.8 (0.6-1.1)	0.2
		rs992353																
		GG	18 (23)	19 (27)	-	-	12 (38)	10 (17)	-	-	15 (18)	28 (38)	-	-	45 (23)	57 (28)	-	-
		GA	36 (46)	30 (42)	0.8 (0.4-1.8)	0.6	12 (38)	33 (58)	3.3 (1.1-9.6)	0.03	44 (52)	30 (40)	0.4 (0.2-0.8)	0.01	92 (47)	93 (46)	0.8 (0.5-1.3)	0.4
		AA	25 (31)	22 (31)	0.8 (0.4-2.0)	0.7	8 (24)	14 (25)	2.1 (0.6-7.0)	0.2	25 (30)	16 (22)	0.3 (0.1-0.8)	0.02	58 (30)	52 (26)	0.7 (0.4-1.2)	0.2
		G	72 (46)	68 (48)	-	-	36 (56)	53 (47)	-	-	74 (44)	86 (58)	-	-	182 (47)	207 (51)	-	-
		A	86 (54)	74 (52)	0.9 (0.6-1.4)	0.7	28 (44)	61 (53)	1.5 (0.8-2.7)	0.2	94 (56)	62 (42)	0.6 (0.4-0.9)	0.01	208 (53)	197 (49)	0.8 (0.6-1.1)	0.2
11	*ASIC1*	rs844347																
		AA	61 (79)	47 (68)	-	-	24 (73)	46 (79)	-	-	55 (65)	52 (69)	-	-	140 (72)	145 (72)	-	-
		AC	14 (18)	21 (31)	1.9 (0.9-4.2)	0.1	8 (24)	11 (19)	0.7 (0.3-2.0)	0.5	26 (31)	20 (27)	0.8 (0.4-1.6)	0.6	48 (25)	52 (26)	1.0 (0.7-1.7)	0.8
		CC	2 (3)	1 (1)	0.6 (0.1-7.4)	0.7	1 (3)	1 (2)	0.5 (0.03-8.7)	0.7	3 (4)	3 (4)	1.1 (0.2-5.5)	0.9	6 (3)	5 (2)	0.8 (0.2-2.7)	0.7
		A	136 (88)	115 (83)	-	-	56 (85)	103 (89)	-	-	136 (81)	124 (83)	-	-	328 (85)	342 (85)	-	-
		C	18 (12)	23 (17)	1.5 (0.8-3.0)	0.2	10 (15)	13 (11)	0.7 (0.3-1.7)	0.4	32 (19)	26 (17)	0.9 (0.5-1.6)	0.7	60 (15)	62 (15)	1.0 (0.7-1.5)	1.0
12	*SCN8A*	rs11169883																
		CC	72 (90)	63 (89)	-	-	25 (76)	42 (73)	-	-	74 (87)	67 (89)	-	-	171 (86)	172 (84)	-	-
		CT	8 (10)	7 (10)	1.0 (0.3-2.9)	1.0	7 (21)	14 (24)	1.2 (0.4-3.3)	0.7	10 (12)	8 (11)	0.9 (0.3-2.4)	0.8	25 (13)	29 (14)	1.2 (0.6-2.1)	0.6
		TT	0 (0)	1 (1)	-	-	1 (3)	2 (3)	1.2 (0.1-13.8)	0.9	1 (1)	0 (0)	-	-	2 (1)	3 (2)	1.5 (0.2-9.0)	0.7
		C	152 (95)	133 (94)	-	-	57 (86)	98 (85)	-	-	158 (93)	142 (95)	-	-	367 (93)	373 (91)	-	-
		T	8 (5)	9 (6)	1.3 (0.5-3.4)	0.6	9 (14)	18 (15)	1.2 (0.5-2.8)	0.7	12 (7)	8 (5)	0.7 (0.3-1.9)	0.5	29 (7)	35 (9)	1.2 (0.7-2.0)	0.5

Abbreviation: R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value. *After Bonferroni correction, results remained significant.

Table 4.11: Association tests of selected gene polymorphisms between nonresponders and responders to CBZ or VPA monotherapy in Malaysian idiopathic epilepsy patients.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
1	*ABCC2*	rs2273697																
		CC	56 (87)	34 (62)	-	-	51 (66)	26 (54)	-	-	53 (70)	52 (80)	-	-	160 (74)	112 (67)	-	-
		CT	7 (11)	21 (38)	4.9 (1.9-12.8)	0.001*	26 (34)	19 (40)	1.4 (0.7-3.1)	0.4	20 (26)	11 (17)	0.6 (0.2-1.3)	0.2	53 (24)	51 (30)	1.4 (0.9-2.2)	0.2
		TT	1 (2)	0 (0)	-	-	0 (0)	3 (6)	-	-	3 (4)	2 (3)	0.7 (0.1-4.2)	0.7	4 (2)	5 (3)	1.8 (0.5-6.8)	0.4
		C	119 (93)	89 (81)	-	-	128 (83)	71 (74)	-	-	126 (83)	115 (88)	-	-	373 (86)	275 (82)	-	-
		T	9 (7)	21 (19)	3.1 (1.4-7.1)	0.007*	26 (17)	25 (26)	1.7 (0.9-3.2)	0.1	26 (17)	15 (12)	0.6 (0.3-1.3)	0.2	61 (14)	61 (18)	1.4 (0.9-2.0)	0.1
2	*GJD2*	rs3743123																
		CC	39 (60)	24 (44)	-	-	22 (29)	18 (37)	-	-	40 (53)	32 (49)	-	-	101 (47)	74 (44)	-	-
		CT	24 (37)	27 (49)	1.8 (0.9-3.9)	0.1	42 (55)	20 (42)	0.6 (0.3-1.3)	0.2	28 (37)	29 (45)	1.3 (0.6-2.6)	0.5	94 (43)	76 (45)	1.1 (0.7-1.7)	0.7
		TT	2 (3)	4 (7)	3.3 (0.6-19.1)	0.2	12 (16)	10 (21)	1.0 (0.4-2.9)	1.0	8 (10)	4 (6)	0.6 (0.2-2.3)	0.5	22 (10)	18 (11)	1.1 (0.6-2.2)	0.8
		C	102 (79)	75 (68)	-	-	86 (57)	56 (58)	-	-	108 (71)	93 (72)	-	-	296 (68)	224 (67)	-	-
		T	28 (21)	35 (32)	1.7 (1.0-3.0)	0.1	66 (43)	40 (42)	0.9 (0.6-1.6)	0.8	44 (29)	37 (28)	1.0 (0.6-1.6)	0.9	138 (32)	112 (33)	1.1 (0.8-1.5)	0.7
3	*OPRM1*	rs1799971																
		AA	24 (37)	18 (33)	-	-	25 (33)	16 (33)	-	-	25 (32)	31 (48)	-	-	74 (34)	65 (39)	-	-
		AG	31 (48)	27 (50)	1.2 (0.5-2.6)	0.7	34 (44)	22 (46)	1.0 (0.4-2.3)	1.0	33 (43)	27 (41)	0.7 (0.3-1.4)	0.3	98 (45)	76 (45)	0.9 (0.6-1.4)	0.6
		GG	10 (15)	9 (17)	1.2 (0.4-3.6)	0.7	18 (23)	10 (21)	0.9 (0.3-2.3)	0.8	19 (25)	7 (11)	0.3 (0.1-0.8)	0.02	47 (21)	26 (16)	0.6 (0.4-1.1)	0.1
		A	79 (61)	63 (58)	-	-	84 (55)	54 (56)	-	-	83 (54)	89 (69)	-	-	246 (56)	206 (62)	-	-
		G	51 (39)	45 (42)	1.1 (0.7-1.9)	0.7	70 (45)	42 (44)	0.9 (0.6-1.6)	0.8	71 (46)	41 (31)	0.5 (0.3-0.9)	0.01	192 (44)	128 (38)	0.8 (0.6-1.1)	0.1
4	*NR1I2*	rs6785049																
		GG	17 (26)	22 (40)	-	-	16 (21)	13 (27)	-	-	32 (42)	24 (37)	-	-	65 (30)	59 (35)	-	-
		GA	35 (55)	24 (44)	0.5 (0.2-1.2)	0.1	40 (53)	23 (48)	0.7 (0.3-1.7)	0.4	34 (44)	35 (54)	1.4 (0.7-2.8)	0.4	109 (50)	82 (49)	0.8 (0.5-1.3)	0.4
		AA	12 (19)	9 (16)	0.6 (0.2-1.7)	0.3	20 (26)	12 (25)	0.7 (0.3-2.1)	0.6	11 (14)	6 (9)	0.7 (0.2-2.2)	0.6	43 (20)	27 (16)	0.7 (0.4-1.3)	0.2
		G	69 (54)	68 (62)	-	-	72 (47)	49 (51)	-	-	98 (64)	83 (64)	-	-	239 (55)	200 (60)	-	-
		A	59 (46)	42 (38)	0.7 (0.4-1.2)	0.2	80 (53)	47 (49)	0.9 (0.5-1.4)	0.6	56 (36)	47 (36)	1.0 (0.6-1.6)	1.0	195 (45)	136 (40)	0.8 (0.6-1.1)	0.2
5	*SLC6A11*	rs2304725																
		TT	22 (34)	12 (22)	-	-	17 (23)	7 (15)	-	-	17 (23)	22 (34)	-	-	56 (26)	41 (24)	-	-
		TC	30 (46)	23 (42)	1.4 (0.6-3.4)	0.5	36 (47)	24 (50)	1.6 (0.6-4.5)	0.4	39 (51)	28 (43)	0.6 (0.3-1.2)	0.1	105 (48)	75 (45)	1.0 (0.6-1.6)	0.9
		CC	13 (20)	20 (36)	2.8 (1.0-7.6)	0.04	23 (30)	17 (35)	1.8 (0.6-5.3)	0.3	20 (26)	15 (23)	0.6 (0.2-1.5)	0.2	56 (26)	52 (31)	1.3 (0.7-2.2)	0.4
		T	74 (57)	47 (43)	-	-	70 (46)	38 (40)	-	-	73 (48)	72 (55)	-	-	217 (50)	157 (47)	-	-
		C	56 (43)	63 (57)	1.8 (1.1-3.0)	0.03	82 (54)	58 (60)	1.3 (0.8-2.2)	0.3	79 (52)	58 (45)	0.7 (0.5-1.2)	0.2	217 (50)	179 (53)	1.1 (0.9-1.5)	0.4
		rs2272394																
		GG	47 (72)	39 (71)	-	-	61 (81)	40 (83)	-	-	51 (67)	56 (86)	-	-	159 (74)	135 (80)	-	-
		GA	16 (25)	15 (27)	2.30 (0.5-10.0)	0.3	14 (19)	8 (17)	0.9 (0.3-2.3)	0.8	22 (29)	9 (14)	0.3 (0.2-0.9)	0.04	52 (24)	32 (19)	0.7 (0.4-1.2)	0.2
		AA	2 (3)	1 (2)	2.2 (0.1-61.9)	0.6	0 (0)	0 (0)	-	-	3 (4)	0 (0)	-	-	5 (2)	1 (1)	0.2 (0.0-2.0)	0.2
		G	110 (85)	93 (85)	-	-	136 (91)	88 (92)	-	-	124 (82)	121 (93)	-	-	370 (86)	302 (90)	-	-
		A	20 (15)	17 (15)	1.0 (0.5-2.0)	1.0	14 (9)	8 (8)	0.9 (0.4-2.2)	0.8	28 (18)	9 (7)	0.3 (0.1-0.7)	0.01	62 (14)	34 (10)	0.7 (0.4-1.0)	0.1
6	*CAMSAP2*	rs2292096																
		AA	39 (60)	33 (60)	-	-	57 (75)	40 (83)	-	-	59 (77)	55 (85)	-	-	155 (71)	128 (76)	-	-
		AG	24 (37)	18 (33)	0.9 (0.4-1.9)	0.8	18 (24)	7 (15)	0.6 (0.2-1.5)	0.2	18 (23)	10 (15)	0.6 (0.3-1.4)	0.2	60 (28)	35 (21)	0.7 (0.4-1.1)	0.2
		GG	2 (3)	4 (7)	2.4 (0.4-13.7)	0.3	1 (1)	1 (2)	1.4 (0.1-23.5)	0.8	0 (0)	0 (0)	-	-	3 (1)	5 (3)	2.0 (0.5-8.6)	0.3
		A	102 (79)	84 (76)	-	-	132 (87)	87 (91)	-	-	136 (88)	120 (92)	-	-	370 (85)	291 (87)	-	-
		G	28 (21)	26 (24)	1.1 (0.6-2.1)	0.7	20 (13)	9 (9)	0.7 (0.3-1.6)	0.4	18 (12)	10 (8)	0.6 (0.3-1.4)	0.3	66 (15)	45 (13)	0.9 (0.6-1.3)	0.5

Abbreviation: R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value. *After Bonferroni correction, results remained significant.

Table 4.11: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
7	*GRIK2*	rs4840200																
		TT	18 (28)	22 (40)	-	-	46 (60)	30 (63)	-	-	36 (48)	25 (38)	-	-	100 (46)	77 (46)	-	-
		TC	38 (59)	24 (44)	0.5 (0.2-1.2)	0.1	25 (33)	14 (29)	0.9 (0.4-1.9)	0.7	27 (36)	33 (51)	1.8 (0.9-3.6)	0.1	90 (42)	71 (42)	1.0 (0.7-1.6)	0.9
		CC	8 (13)	9 (16)	0.9 (0.3-2.9)	0.9	5 (7)	4 (8)	1.2 (0.3-4.9)	0.8	12 (16)	7 (11)	0.8 (0.3-2.4)	0.7	25 (12)	20 (12)	1.0 (0.5-2.0)	0.9
		T	74 (58)	68 (62)	-	-	117 (77)	74 (77)	-	-	99 (66)	83 (64)	-	-	290 (67)	225 (67)	-	-
		C	54 (42)	42 (38)	0.8 (0.5-1.4)	0.5	35 (23)	22 (23)	1.0 (0.5-1.8)	1.0	51 (34)	47 (36)	1.1 (0.7-1.8)	0.7	140 (33)	111 (33)	1.0 (0.8-1.4)	0.9
8	*LGI1*	rs3758532																
		CC	35 (55)	32 (59)	-	-	50 (65)	22 (46)	-	-	35 (47)	30 (46)	-	-	120 (56)	84 (50)	-	-
		CT	24 (37)	18 (33)	0.8 (0.4-1.8)	0.6	25 (32)	24 (50)	2.2 (1.0-4.6)	0.04	31 (41)	32 (49)	1.2 (0.6-2.4)	0.6	80 (37)	74 (44)	1.3 (0.9-2.0)	0.2
		TT	5 (8)	4 (8)	0.9 (0.2-3.5)	0.9	2 (3)	2 (4)	2.3 (0.3-17.2)	0.4	9 (12)	3 (5)	0.4 (0.1-1.6)	0.2	16 (7)	9 (6)	0.8 (0.3-1.9)	0.6
		C	94 (73)	82 (76)	-	-	125 (81)	68 (71)	-	-	101 (67)	92 (71)	-	-	320 (74)	242 (73)	-	-
		T	34 (27)	26 (24)	0.9 (0.5-1.6)	0.7	29 (19)	28 (29)	1.8 (1.0-3.2)	0.1	49 (33)	38 (29)	0.9 (0.5-1.4)	0.5	112 (26)	92 (27)	1.1 (0.8-1.5)	0.6
9	*CALHM1*	rs11191692																
		GG	25 (39)	28 (51)	-	-	18 (24)	17 (35)	-	-	33 (44)	29 (45)	-	-	76 (36)	74 (44)	-	-
		GA	32 (50)	25 (45)	0.7 (0.3-1.5)	0.3	44 (59)	20 (42)	0.5 (0.2-1.1)	0.1	31 (41)	29 (45)	1.1 (0.5-2.2)	0.9	107 (50)	74 (44)	0.7 (0.5-1.1)	0.1
		AA	7 (11)	2 (4)	0.3 (0.05-1.3)	0.1	13 (17)	11 (23)	0.9 (0.3-2.5)	0.8	11 (15)	7 (10)	0.7 (0.2-2.1)	0.6	31 (14)	20 (12)	0.7 (0.3-1.3)	0.2
		G	82 (64)	81 (74)	-	-	80 (53)	54 (56)	-	-	97 (65)	87 (67)	-	-	259 (61)	222 (66)	-	-
		A	46 (36)	29 (26)	0.6 (0.4-1.1)	0.1	70 (47)	42 (44)	0.9 (0.5-1.5)	0.7	53 (35)	43 (33)	0.9 (0.6-1.5)	0.7	169 (39)	114 (34)	0.8 (0.6-1.1)	0.1
10	*KCNAB1*	rs2280032																
		TT	12 (19)	9 (16)	-	-	19 (26)	7 (15)	-	-	24 (31)	18 (28)	-	-	55 (26)	34 (20)	-	-
		TG	34 (52)	30 (55)	1.2 (0.4-3.2)	0.7	40 (54)	27 (56)	1.8 (0.7-5.0)	0.2	34 (44)	28 (44)	1.1 (0.5-2.4)	0.8	108 (50)	85 (51)	1.3 (0.8-2.1)	0.4
		GG	19 (29)	16 (29)	1.1 (0.4-3.3)	0.8	15 (20)	14 (29)	2.5 (0.8-7.9)	0.1	19 (25)	18 (28)	1.3 (0.5-3.1)	0.6	53 (24)	48 (29)	1.5 (0.8-2.6)	0.2
		T	58 (45)	48 (44)	-	-	78 (53)	41 (43)	-	-	82 (53)	64 (50)	-	-	218 (51)	153 (46)	-	-
		G	72 (55)	62 (56)	1.0 (0.6-1.7)	0.9	70 (47)	55 (57)	1.5 (0.9-2.5)	0.1	72 (47)	64 (50)	1.1 (0.7-1.8)	0.6	214 (49)	181 (54)	1.2 (0.9-1.6)	0.2
		rs992353																
		GG	13 (20)	9 (16)	-	-	19 (26)	7 (15)	-	-	29 (38)	19 (29)	-	-	61 (28)	35 (21)	-	-
		GA	33 (51)	30 (55)	1.3 (0.5-3.5)	0.6	39 (53)	29 (60)	2.0 (0.7-5.4)	0.2	33 (43)	28 (43)	1.3 (0.6-2.8)	0.5	105 (49)	87 (52)	1.4 (0.9-2.4)	0.2
		AA	19 (29)	16 (29)	1.2 (0.4-3.6)	0.7	15 (21)	12 (25)	2.2 (0.7-6.9)	0.2	15 (19)	18 (28)	1.8 (0.7-4.5)	0.2	49 (23)	46 (27)	1.6 (0.9-2.9)	0.1
		G	59 (45)	48 (44)	-	-	77 (53)	43 (45)	-	-	91 (59)	66 (51)	-	-	227 (53)	157 (47)	-	-
		A	71 (55)	62 (56)	1.1 (0.6-1.8)	0.8	69 (47)	53 (55)	1.4 (0.8-2.3)	0.2	63 (41)	64 (49)	1.4 (0.9-2.2)	0.2	203 (47)	179 (53)	1.3 (1.0-1.7)	0.1
11	*ASIC1*	rs844347																
		AA	46 (73)	42 (79)	-	-	53 (70)	37 (77)	-	-	49 (68)	31 (49)	-	-	148 (70)	110 (67)	-	-
		AC	16 (25)	10 (19)	0.7 (0.3-1.7)	0.4	21 (28)	10 (21)	0.7 (0.3-1.6)	0.4	20 (28)	29 (45)	2.3 (1.1-4.7)	0.03	57 (27)	49 (30)	1.2 (0.7-1.8)	0.5
		CC	1 (2)	1 (2)	1.1 (0.1-18.1)	0.9	2 (2)	1 (2)	0.7 (0.1-8.2)	0.8	3 (4)	4 (6)	2.1 (0.4-10.1)	0.4	6 (3)	6 (3)	1.3 (0.4-4.3)	0.6
		A	108 (86)	94 (89)	-	-	127 (84)	84 (88)	-	-	118 (82)	91 (71)	-	-	353 (84)	269 (82)	-	-
		C	18 (14)	12 (11)	0.8 (0.4-1.7)	0.5	25 (16)	12 (12)	0.7 (0.3-1.5)	0.4	26 (18)	37 (29)	1.8 (1.0-3.3)	0.04	69 (16)	61 (18)	1.2 (0.8-1.7)	0.4
12	*SCN8A*	rs11169883																
		CC	60 (92)	46 (85)	-	-	59 (78)	36 (75)	-	-	65 (85)	51 (79)	-	-	184 (85)	133 (80)	-	-
		CT	5 (8)	7 (13)	1.8 (0.5-6.1)	0.3	15 (20)	10 (21)	1.1 (0.4-2.7)	0.8	11 (14)	12 (18)	1.4 (0.6-3.4)	0.5	31 (14)	29 (17)	1.3 (0.7-2.3)	0.4
		TT	0 (0)	1 (2)	-	-	2 (2)	2 (4)	1.6 (0.2-12.2)	0.6	1 (1)	2 (3)	2.5 (0.2-28.9)	0.5	3 (1)	5 (3)	2.3 (0.5-9.8)	0.3
		C	125 (96)	99 (92)	-	-	133 (88)	82 (85)	-	-	141 (92)	114 (88)	-	-	399 (92)	295 (88)	-	-
		T	5 (4)	9 (8)	2.3 (0.7-7.0)	0.2	19 (12)	14 (15)	1.2 (0.6-2.5)	0.6	13 (8)	16 (12)	1.5 (0.7-3.3)	0.3	37 (8)	39 (12)	1.4 (0.9-2.3)	0.1

Abbreviation: R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.12: Association tests of selected gene polymorphisms between nonresponders and responders to CBZ or VPA monotherapy in Malaysian symptomatic epilepsy patients.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
1	*ABCC2*	rs2273697																
		CC	57 (86)	70 (86)	-	-	18 (45)	27 (69)	-	-	42 (84)	59 (80)	-	-	117 (75)	156 (80)	-	-
		CT	9 (14)	11 (13)	1.0 (0.4-2.6)	1.0	19 (48)	11 (28)	0.4 (0.1-1.0)	0.1	7 (14)	15 (20)	1.5 (0.6-4.1)	0.4	35 (22)	37 (19)	0.8 (0.5-1.3)	0.4
		TT	0 (0)	1 (1)	-	-	3 (7)	1 (3)	0.2 (0.0-2.3)	0.2	1 (2)	0 (0)	-	-	4 (3)	2 (1)	0.4 (0.1-2.1)	0.3
		C	123 (93)	151 (92)	-	-	55 (69)	65 (83)	-	-	91 (91)	133 (90)	-	-	269 (86)	349 (89)	-	-
		T	9 (7)	13 (8)	1.2 (0.5-2.8)	0.7	25 (31)	13 (17)	0.4 (0.2-0.9)	0.03	9 (9)	15 (10)	1.1 (0.5-2.7)	0.8	43 (14)	41 (11)	0.7 (0.5-1.2)	0.2
2	*GJD2*	rs3743123																
		CC	36 (54)	42 (51)	-	-	12 (30)	21 (55)	-	-	22 (44)	45 (62)	-	-	70 (45)	108 (56)	-	-
		CT	25 (38)	37 (45)	1.3 (0.6-2.5)	0.5	18 (45)	14 (37)	0.4 (0.2-1.2)	0.1	26 (52)	26 (35)	0.5 (0.2-1.0)	0.1	69 (44)	77 (40)	0.7 (0.5-1.1)	0.2
		TT	5 (8)	3 (4)	0.5 (0.1-2.3)	0.4	10 (25)	3 (8)	0.2 (0.04-0.7)	0.02	2 (4)	2 (3)	0.5 (0.1-3.7)	0.5	17 (11)	8 (4)	0.3 (0.1-0.7)	0.01
		C	97 (74)	121 (74)	-	-	42 (53)	56 (74)	-	-	70 (70)	116 (80)	-	-	209 (67)	293 (76)	-	-
		T	35 (26)	43 (26)	1.0 (0.6-1.7)	1.0	38 (47)	20 (26)	0.4 (0.2-0.8)	0.01	30 (30)	30 (20)	0.6 (0.3-1.1)	0.1	103 (33)	93 (24)	0.6 (0.5-0.9)	0.01
3	*OPRM1*	rs1799971																
		AA	24 (36)	31 (38)	-	-	10 (25)	10 (26)	-	-	18 (36)	20 (28)	-	-	52 (33)	61 (31)	-	-
		AG	29 (44)	38 (46)	1.0 (0.5-2.1)	1.0	24 (60)	20 (51)	0.8 (0.3-2.4)	0.7	19 (38)	36 (49)	1.7 (0.7-4.0)	0.2	72 (46)	94 (49)	1.1 (0.7-1.8)	0.7
		GG	13 (20)	13 (16)	0.8 (0.3-2.0)	0.6	6 (15)	9 (23)	1.5 (0.4-5.8)	0.6	13 (26)	17 (23)	1.2 (0.4-3.1)	0.7	32 (21)	39 (20)	1.0 (0.6-1.9)	0.9
		A	77 (58)	100 (61)	-	-	44 (55)	40 (51)	-	-	55 (55)	76 (52)	-	-	176 (56)	216 (56)	-	-
		G	55 (42)	64 (39)	0.9 (0.6-1.4)	0.6	36 (45)	38 (49)	1.2 (0.6-2.2)	0.6	45 (45)	70 (48)	1.1 (0.7-1.9)	0.6	136 (44)	172 (44)	1.0 (0.8-1.4)	0.8
4	*NR1I2*	rs6785049																
		GG	21 (32)	27 (33)	-	-	10 (25)	11 (28)	-	-	15 (31)	33 (45)	-	-	46 (30)	71 (37)	-	-
		GA	36 (54)	37 (45)	0.8 (0.4-1.7)	0.5	20 (50)	16 (41)	0.7 (0.2-2.1)	0.6	26 (53)	29 (40)	0.5 (0.2-1.1)	0.1	82 (53)	82 (42)	0.6 (0.4-1.0)	0.1
		AA	9 (14)	18 (22)	1.6 (0.6-4.2)	0.4	10 (25)	12 (31)	1.1 (0.3-3.6)	0.9	8 (16)	11 (15)	0.6 (0.2-1.9)	0.4	27 (17)	41 (21)	1.0 (0.5-1.8)	1.0
		G	78 (59)	91 (56)	-	-	40 (50)	38 (49)	-	-	56 (57)	95 (65)	-	-	174 (56)	224 (58)	-	-
		A	54 (41)	73 (44)	1.2 (0.7-1.8)	0.5	40 (50)	40 (51)	1.1 (0.6-2.0)	0.9	42 (43)	51 (35)	0.7 (0.4-1.2)	0.2	136 (44)	164 (42)	0.9 (0.7-1.3)	0.7
5	*SLC6A11*	rs2304725																
		TT	22 (33)	18 (22)	-	-	9 (23)	12 (32)	-	-	17 (34)	22 (30)	-	-	48 (31)	52 (27)	-	-
		TC	31 (47)	43 (52)	1.7 (0.8-3.7)	0.2	21 (52)	16 (42)	0.6 (0.2-1.7)	0.3	26 (52)	41 (55)	1.2 (0.5-2.7)	0.6	78 (50)	100 (51)	1.2 (0.7-1.9)	0.5
		CC	13 (20)	21 (26)	1.0 (0.8-5.0)	0.2	10 (25)	10 (26)	0.8 (0.2-2.6)	0.6	7 (14)	11 (15)	1.2 (0.4-3.8)	0.7	30 (19)	42 (22)	1.3 (0.7-2.4)	0.4
		T	75 (57)	79 (48)	-	-	39 (49)	40 (53)	-	-	60 (60)	85 (57)	-	-	174 (56)	204 (53)	-	-
		C	57 (43)	85 (52)	1.4 (0.9-2.2)	0.1	41 (51)	36 (47)	0.9 (0.5-1.6)	0.6	40 (40)	63 (43)	1.1 (0.7-1.9)	0.7	138 (44)	184 (47)	1.1 (0.8-1.5)	0.4
		rs2272394																
		GG	51 (79)	51 (62)	-	-	31 (78)	30 (79)	-	-	39 (78)	53 (72)	-	-	121 (78)	134 (69)	-	-
		GA	14 (21)	29 (36)	2.1 (1.0-4.4)	0.1	8 (20)	7 (18)	0.9 (0.3-2.8)	0.9	10 (20)	21 (28)	1.5 (0.7-3.6)	0.3	32 (21)	57 (29)	1.6 (1.0-2.6)	0.1
		AA	0 (0)	2 (2)	-	-	1 (2)	1 (3)	1.0 (0.1-17.3)	1.0	1 (2)	0 (0)	-	-	2 (1)	3 (2)	1.4 (0.2-8.2)	0.7
		G	116 (89)	131 (80)	-	-	70 (88)	67 (88)	-	-	88 (88)	127 (86)	-	-	274 (88)	325 (84)	-	-
		A	14 (11)	33 (20)	2.1 (1.1-4.1)	0.03	10 (12)	9 (12)	0.9 (0.4-2.5)	0.9	12 (12)	21 (14)	1.2 (0.6-2.6)	0.6	36 (12)	63 (16)	1.5 (1.0-2.3)	0.1
6	*CAMSAP2*	rs2292096																
		AA	46 (71)	61 (75)	-	-	32 (80)	31 (80)	-	-	36 (72)	59 (80)	-	-	114 (74)	151 (77)	-	-
		AG	19 (29)	19 (23)	0.8 (0.4-1.6)	0.5	8 (20)	8 (20)	1.0 (0.3-3.1)	1.0	14 (28)	14 (19)	0.6 (0.3-1.4)	0.3	41 (26)	41 (21)	0.8 (0.5-1.2)	0.3
		GG	0 (0)	2 (2)	-	-	0 (0)	0 (0)	-	-	0 (0)	1 (1)	-	-	0 (0)	3 (2)	-	-
		A	111 (85)	141 (86)	-	-	72 (90)	70 (90)	-	-	86 (86)	132 (89)	-	-	269 (87)	343 (88)	-	-
		G	19 (15)	23 (14)	1.0 (0.5-1.8)	0.9	8 (10)	8 (10)	1.0 (0.4-2.9)	1.0	14 (14)	16 (11)	0.7 (0.3-1.6)	0.5	41 (13)	47 (12)	0.9 (0.6-1.4)	0.6

Abbreviation: R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value

Table 4.12: continued.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
7	*GRIK2*	rs4840200																
		TT	19 (29)	21 (26)	-	-	21 (53)	24 (62)	-	-	16 (32)	18 (25)	-	-	56 (36)	63 (32)	-	-
		TC	35 (53)	46 (56)	1.2 (0.6-2.5)	0.7	17 (42)	11 (28)	0.6 (0.2-1.5)	0.2	29 (58)	37 (51)	1.1 (0.5-2.6)	0.8	81 (52)	94 (49)	1.0 (0.6-1.6)	0.9
		CC	12 (18)	15 (18)	1.1 (0.4-3.0)	0.8	2 (5)	4 (10)	1.8 (0.3-10.5)	0.5	5 (10)	17 (24)	3.0 (0.9-10.1)	0.1	19 (12)	36 (19)	1.7 (0.9-3.3)	0.1
		T	73 (55)	88 (54)	-	-	59 (74)	59 (76)	-	-	61 (61)	73 (51)	-	-	193 (62)	220 (57)	-	-
		C	59 (45)	76 (46)	1.1 (0.7-1.7)	0.8	21 (26)	19 (24)	0.9 (0.4-1.9)	0.8	39 (39)	71 (49)	1.5 (0.9-2.6)	0.1	119 (38)	166 (43)	1.2 (0.9-1.7)	0.2
8	*LGI1*	rs3758532																
		CC	35 (53)	49 (60)	-	-	25 (63)	26 (67)	-	-	25 (50)	37 (51)	-	-	85 (54)	112 (58)	-	-
		CT	28 (42)	29 (35)	0.7 (0.4-1.5)	0.4	13 (32)	11 (28)	0.8 (0.3-2.2)	0.7	21 (42)	31 (42)	1.0 (0.5-2.1)	1.0	62 (40)	71 (36)	0.9 (0.6-1.4)	0.5
		TT	3 (5)	4 (5)	1.0 (0.2-4.5)	1.0	2 (5)	2 (5)	1.0 (0.1-7.4)	1.0	4 (8)	5 (7)	0.8 (0.2-3.5)	0.8	9 (6)	11 (6)	0.9 (0.4-2.3)	0.9
		C	98 (74)	127 (77)	-	-	63 (79)	63 (81)	-	-	71 (71)	105 (72)	-	-	232 (74)	295 (76)	-	-
		T	34 (26)	37 (23)	0.8 (0.5-1.4)	0.5	17 (21)	15 (19)	0.9 (0.4-1.9)	0.8	29 (29)	41 (28)	1.0 (0.5-1.7)	0.9	80 (26)	93 (24)	0.9 (0.6-1.3)	0.6
9	*CALHM1*	rs11191692																
		GG	29 (45)	37 (45)	-	-	16 (40)	13 (34)	-	-	17 (34)	37 (51)	-	-	62 (40)	87 (45)	-	-
		GA	29 (45)	32 (39)	0.9 (0.4-1.7)	0.7	15 (38)	17 (45)	1.4 (0.5-3.8)	0.5	24 (48)	29 (40)	0.6 (0.3-1.2)	0.1	68 (44)	78 (40)	0.8 (0.5-1.3)	0.4
		AA	7 (10)	13 (16)	1.5 (0.5-4.1)	0.5	9 (22)	8 (21)	1.1 (0.3-3.6)	0.9	9 (18)	7 (9)	0.4 (0.1-1.1)	0.1	25 (16)	28 (15)	0.8 (0.4-1.5)	0.5
		G	87 (67)	106 (65)	-	-	47 (59)	43 (57)	-	-	58 (58)	103 (71)	-	-	192 (62)	252 (65)	-	-
		A	43 (33)	58 (35)	1.1 (0.7-1.8)	0.7	33 (41)	33 (43)	1.1 (0.6-2.1)	0.8	42 (42)	43 (29)	0.6 (0.3-1.0)	0.04	118 (38)	134 (35)	0.9 (0.6-1.2)	0.4
10	*KCNAB1*	rs2280032																
		TT	9 (14)	21 (26)	-	-	14 (35)	10 (26)	-	-	15 (30)	15 (20)	-	-	38 (24)	46 (24)	-	-
		TG	33 (50)	36 (44)	0.5 (0.2-1.2)	0.1	19 (48)	17 (45)	1.3 (0.4-3.6)	0.7	28 (56)	42 (57)	1.5 (0.6-3.5)	0.4	80 (52)	95 (49)	1.0 (0.6-1.7)	0.9
		GG	24 (36)	25 (30)	0.4 (0.2-1.2)	0.1	7 (17)	11 (29)	2.2 (0.6-7.7)	0.2	7 (14)	17 (23)	2.4 (0.8-7.6)	0.1	38 (24)	53 (27)	1.2 (0.6-2.1)	0.6
		T	51 (39)	78 (48)	-	-	47 (59)	37 (49)	-	-	58 (58)	72 (49)	-	-	156 (50)	187 (48)	-	-
		G	81 (61)	86 (52)	0.7 (0.4-1.1)	0.1	33 (41)	39 (51)	1.5 (0.8-2.8)	0.2	42 (42)	76 (51)	1.5 (0.9-2.4)	0.1	156 (50)	201 (52)	1.1 (0.8-1.4)	0.6
		rs992353																
		GG	10 (15)	21 (26)	-	-	15 (38)	10 (26)	-	-	16 (32)	15 (21)	-	-	41 (26)	46 (24)	-	-
		GA	30 (46)	36 (44)	0.6 (0.2-1.4)	0.2	17 (42)	17 (45)	1.5 (0.5-4.3)	0.4	28 (56)	41 (56)	1.6 (0.7-3.7)	0.3	75 (48)	94 (49)	1.1 (0.7-1.9)	0.7
		AA	26 (39)	25 (30)	0.5 (0.2-1.2)	0.1	8 (20)	11 (29)	2.1 (0.6-6.9)	0.2	6 (12)	17 (23)	3.0 (0.9-9.7)	0.1	40 (26)	53 (27)	1.2 (0.7-2.1)	0.6
		G	50 (38)	78 (48)	-	-	47 (59)	37 (49)	-	-	60 (60)	71 (49)	-	-	157 (50)	186 (48)	-	-
		A	82 (62)	86 (52)	0.7 (0.4-1.1)	0.1	33 (41)	39 (51)	1.5 (0.8-2.8)	0.2	40 (40)	75 (51)	1.6 (0.9-2.7)	0.1	155 (50)	200 (52)	1.1 (0.8-1.5)	0.6
11	*ASIC1*	rs844347																
		AA	51 (79)	61 (75)	-	-	29 (74)	29 (76)	-	-	28 (56)	55 (75)	-	-	108 (70)	145 (76)	-	-
		AC	13 (20)	18 (22)	1.2 (0.5-2.6)	0.7	10 (26)	8 (21)	0.8 (0.3-2.3)	0.7	18 (36)	17 (23)	0.5 (0.2-1.1)	0.1	41 (27)	43 (22)	0.8 (0.5-1.3)	0.3
		CC	1 (1)	2 (3)	1.7 (0.1-19.0)	0.7	0 (0)	1 (3)	-	-	4 (8)	1 (2)	0.1 (0.0-1.2)	0.1	5 (3)	4 (2)	0.6 (0.2-2.3)	0.4
		A	115 (89)	140 (86)	-	-	68 (87)	66 (87)	-	-	74 (74)	127 (87)	-	-	257 (83)	333 (87)	-	-
		C	15 (11)	22 (14)	1.2 (0.6-2.4)	0.6	10 (13)	10 (13)	1.0 (0.4-2.6)	1.0	26 (26)	19 (13)	0.4 (0.2-0.8)	0.01	51 (17)	51 (13)	0.8 (0.5-1.2)	0.2
12	*SCN8A*	rs11169883																
		CC	56 (84)	66 (81)	-	-	26 (67)	29 (76)	-	-	43 (86)	63 (86)	-	-	125 (80)	158 (82)	-	-
		CT	11 (16)	16 (19)	1.2 (0.5-2.9)	0.6	13 (33)	9 (24)	0.6 (0.2-1.7)	0.4	7 (14)	10 (14)	1.0 (0.3-2.8)	1.0	31 (20)	35 (18)	0.9 (0.5-1.5)	0.7
		TT	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	-
		C	123 (92)	148 (90)	-	-	65 (83)	67 (88)	-	-	93 (93)	136 (93)	-	-	281 (90)	351 (91)	-	-
		T	11 (8)	16 (10)	1.2 (0.5-2.7)	0.6	13 (17)	9 (12)	0.7 (0.3-1.7)	0.4	7 (7)	10 (7)	1.0 (0.4-2.7)	1.0	31 (10)	35 (9)	0.9 (0.5-1.5)	0.7

Abbreviation: R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value

4.4.2 Haplotypes

4.4.2.1 *KCNAB1* rs2280032-rs992353 and *SLC6A11* rs2304725-rs2272394

Haplotype analyses were performed for *KCNAB1* rs2280032 and rs992353 and *SLC6A11* rs2304725 and rs2272394 polymorphisms (Table 4.13, Figure 4.4 and 4.5). Only haplotypes with frequencies above 3% were included in the analysis. Following 1000 permutation test performed for correction of multiple comparisons, the significant results were lost. Therefore, haplotypes of these genes are not risk factors for epilepsy drug responsiveness in Malaysia. There was a strong LD were observed between *KCNAB1* rs2280032 and rs992353 (D' > 80%, Figure 4.4), but it was very weak between the *SLC6A11* rs2304725 and rs2272394 (D' < 80%, Figure 4.5).

Table 4.13: Haplotype frequencies of *KCNAB1* and *SLC6A11* polymorphisms between nonresponders and responders to CBZ or VPA monotherapy in Malaysian epilepsy patients.

No.	Gene	Polymorphism	Chinese				Indians				Malays				Total			
			R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p	R	NR	OR (95% CI)	p
1.	*KCNAB1*	rs2280032-rs992353																
		Total epilepsy																
		GA	234 (56)	222 (53)	0.8 (0.6-1.1)	0.2	129 (45)	152 (53)	1.5 (1.1-2.0)	0.02	196 (46)	196 (46)	1.0 (0.8-1.3)	1.0	559 (49)	570 (50)	1.0 (0.9-1.2)	0.9
		TG	175 (42)	197 (47)	1.2 (0.9-1.6)	0.2	161 (55)	129 (45)	0.7 (0.5-0.9)	0.02	212 (49)	225 (53)	1.1 (0.9-1.5)	0.4	548 (48)	551 (49)	1.0 (0.8-1.2)	0.9
		Other**	9 (2)	3 (0)	-	-	2 (0)	7 (2) (1)	-	-	20 (5)	3 (1)	-	-	31 (3)	13 (1)	-	-
		Cryptogenic epilepsy																
		GA	84 (53)	73 (51)	0.9 (0.6-1.4)	0.6	26 (42)	59 (52)	1.6 (0.9-3.1)	0.1	94 (56)	59 (40)	0.5 (0.3-0.8)	0.01	204 (53)	191 (48)	0.8 (0.6-1.1)	0.2
		TG	68 (43)	66 (47)	1.1 (0.7-1.8)	0.6	36 (58)	50 (44)	0.6 (0.3-1.1)	0.1	73 (43)	86 (59)	1.9 (1.2-2.9)	0.01	177 (46)	202 (50)	1.2 (0.9-1.6)	0.2
		Other**	6 (4)	3 (2)	-	-	0 (0)	5 (4)	-	-	1 (1)	1 (1)	-	-	7 (1)	9 (2)	-	-
		Idiopathic epilepsy																
		GA	71 (55)	62 (56)	1.1 (0.6-1.8)	0.8	69 (47)	53 (55)	1.4 (0.9-2.4)	0.2	61 (40)	62 (48)	1.4 (0.9-2.3)	0.2	201 (47)	177 (53)	1.2 (0.9-1.7)	0.1
		TG	58 (44)	48 (44)	0.9 (0.6-1.6)	0.8	77 (53)	41 (43)	0.7 (0.4-1.2)	0.2	80 (52)	64 (50)	0.9 (0.6-1.4)	0.7	215 (50)	153 (46)	0.8 (0.6-1.1)	0.1
		Other**	1 (1)	0 (0)	-	-	0 (0)	2 (2)	-	-	13 (8)	2 (2)	-	-	14 (3)	4 (1)	-	-
		Symptomatic epilepsy																
		GA	79 (61)	86 (52)	0.7 (0.4-1.1)	0.1	32 (40)	39 (51)	1.5 (0.8-2.9)	0.2	38 (38)	75 (51)	1.7 (1.0-2.8)	0.1	149 (48)	200 (52)	1.1 (0.8-1.5)	0.6
		TG	49 (37)	78 (48)	1.5 (0.9-2.3)	0.1	46 (58)	37 (49)	0.7 (0.3-1.2)	0.2	56 (56)	71 (49)	0.7 (0.4-1.2)	0.2	151 (49)	186 (48)	0.9 (0.7-1.2)	0.6
		Others**	2 (2)	0 (0)	-	-	2 (2)	0 (0)	-	-	6 (6)	0 (0)	-	-	10 (3)	0 (0)	-	-
2.	*SLC6A11*	rs2304725-rs2272394																
		Total epilepsy																
		CG	167 (40)	176 (42)	1.1 (0.8-1.4)	0.6	144 (48)	148 (51)	1.1 (0.8-1.5)	0.5	174 (41)	168 (39)	0.9 (0.7-1.2)	0.6	486 (42)	492 (43)	1.0 (0.9-1.2)	0.8
		TG	191 (45)	166 (39)	0.8 (0.6-1.0)	0.1	123 (41)	108 (37)	0.8 (0.6-1.2)	0.3	188 (45)	207 (49)	1.2 (0.9-1.5)	0.3	501 (44)	482 (42)	0.9 (0.8-1.1)	0.4
		CA	24 (6)	38 (9)	1.6 (1.0-2.8)	0.1	15 (5)	20 (7)	1.4 (0.7-2.8)	0.3	26 (6)	25 (6)	0.9 (0.5-1.6)	0.7	64 (6)	83 (7)	1.3 (0.9-1.8)	0.1
		TA	38 (9)	42 (10)	1.1 (0.7-1.8)	0.7	16 (6)	14 (5)	0.9 (0.4-1.9)	0.8	34 (8)	28 (6)	0.8 (0.5-1.3)	0.4	89 (8)	83 (8)	0.9 (0.7-1.3)	0.7
		Cryptogenic epilepsy																
		CG	69 (43)	51 (36)	0.7 (0.5-1.2)	0.2	30 (45)	60 (52)	1.3 (0.7-2.4)	0.4	70 (42)	63 (43)	1.0 (0.7-1.6)	0.8	169 (43)	174 (43)	1.0 (0.7-1.3)	1.0
		TG	63 (40)	62 (44)	1.2 (0.8-1.9)	0.4	29 (44)	39 (34)	0.6 (0.3-1.2)	0.2	76 (46)	61 (42)	0.8 (0.5-1.3)	0.5	168 (43)	162 (40)	0.9 (0.7-1.2)	0.5
		CA	10 (6)	10 (7)	1.2 (0.5-2.8)	0.8	5 (8)	13 (11)	1.5 (0.5-4.3)	0.5	8 (5)	8 (5)	1.1 (0.4-3.1)	0.8	23 (6)	31 (8)	1.4 (0.8-2.4)	0.3
		TA	18 (11)	19 (13)	1.2 (0.6-2.4)	0.6	2 (3)	4 (3)	1.3 (0.2-7.7)	0.8	12 (7)	14 (10)	1.4 (0.6-3.1)	0.4	32 (8)	37 (9)	1.1 (0.7-1.8)	0.7
		Idiopathic epilepsy																
		CG	48 (37)	54 (49)	1.6 (1.0-2.7)	0.1	75 (51)	53 (55)	1.2 (0.7-2.0)	0.5	62 (42)	50 (39)	0.9 (0.5-1.4)	0.6	187 (44)	156 (47)	1.1 (0.8-1.5)	0.4
		TG	62 (47)	39 (36)	0.6 (0.4-1.0)	0.1	60 (40)	35 (37)	0.9 (0.5-1.4)	0.6	60 (39)	71 (54)	1.8 (1.1-2.9)	0.01	180 (42)	146 (43)	1.1 (0.8-1.4)	0.7
		CA	8 (6)	9 (8)	1.5 (0.5-4.0)	0.4	6 (4)	5 (5)	1.4 (0.4-4.8)	0.6	17 (11)	8 (6)	0.5 (0.2-1.2)	0.1	29 (7)	23 (7)	1.0 (0.6-1.8)	1.0
		TA	12 (10)	8 (7)	0.7 (0.3-1.8)	0.5	7 (5)	3 (3)	0.6 (0.2-2.4)	0.5	11 (8)	1 (1)	0.1 (0.0-0.8)	0.01	32 (7)	11 (3)	0.4 (0.2-0.9)	0.01
		Symptomatic epilepsy																
		CG	50 (38)	67 (41)	1.1 (0.7-1.8)	0.7	38 (48)	35 (45)	0.9 (0.5-1.7)	0.7	40 (40)	55 (37)	0.9 (0.5-1.5)	0.7	127 (41)	157 (41)	1.0 (0.7-1.3)	0.9
		TG	66 (51)	64 (39)	0.6 (0.4-1.0)	0.04	32 (40)	32 (43)	1.1 (0.6-2.2)	0.7	48 (48)	72 (49)	1.0 (0.6-1.7)	0.9	147 (48)	168 (43)	0.8 (0.6-1.1)	0.3
		CA	6 (5)	18 (11)	2.5 (1.0-6.6)	0.05	3 (3)	1 (2)	0.6 (0.1-4.8)	0.6	0 (0)	8 (5)	526.5 (30.8-8996.8)	0.03	10 (3)	27 (7)	2.1 (1.0-4.4)	0.04
		TA	8 (6)	15 (9)	1.5 (0.6-3.8)	0.3	7 (9)	8 (10)	1.1 (0.4-3.1)	0.9	12 (12)	13 (9)	0.7 (0.3-1.6)	0.4	26 (8)	36 (9)	1.1 (0.7-1.9)	0.6

Abbreviation: No.: number; R: drug responder; NR: drug nonresponder; OR: odds ratio; CI: 95% confidence interval; p: p-value

** Haplotypes with frequency less than 3% were excluded from analysis

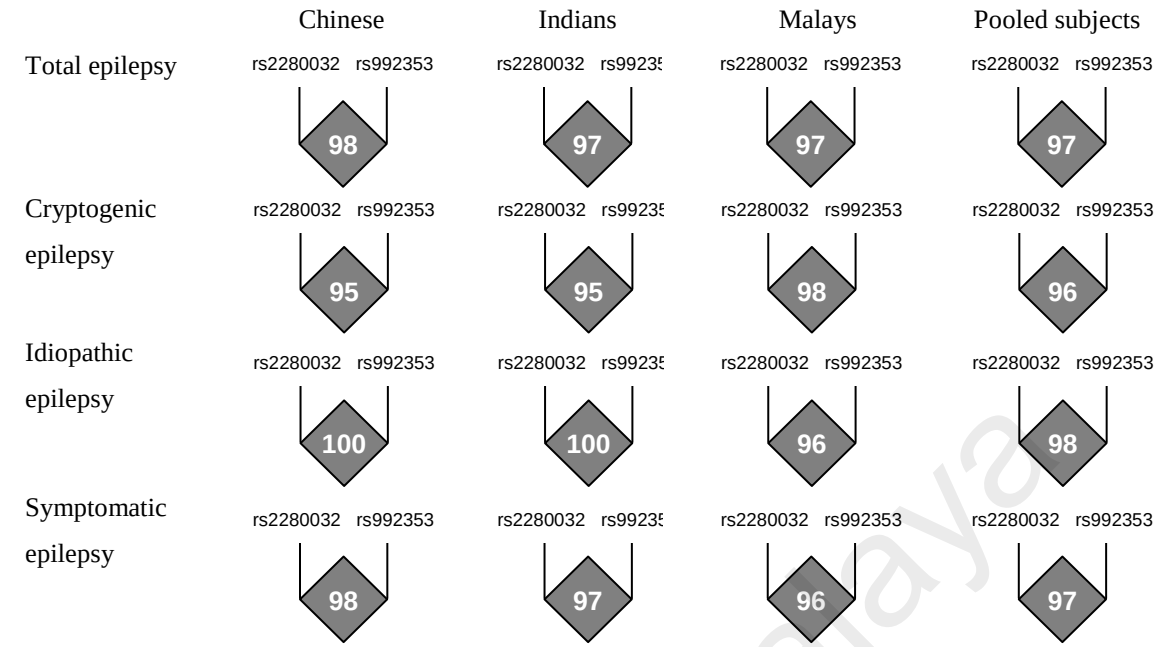

Figure 4.4: Pattern of linkage disequilibrium (D') between two SNPs of *KCNAB1* gene (rs2280032-rs992353) among the nonresponders and responders to CBZ or VPA monotherapy from the Chinese, Indians and Malays in each epilepsy syndrome.

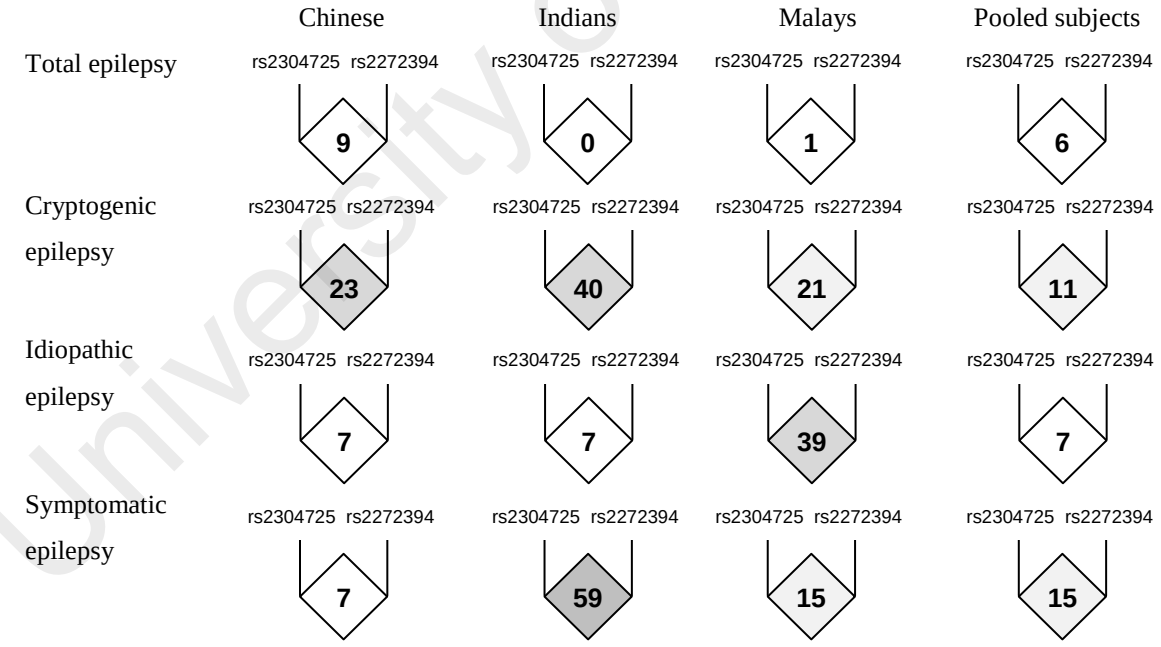

Figure 4.5: Pattern of linkage disequilibrium (D') between two SNPs of *SLC6A11* gene (rss2304725-rs2272394) among the nonresponders and responders to CBZ or VPA monotherapy from the Chinese, Indians and Malays in each epilepsy syndrome.

CHAPTER 5

DISCUSSION

5.0 DISCUSSION

5.1 Genetic association studies

The aims of these genetic association studies were to determine whether certain genetic polymorphisms are associated with susceptibility to epilepsy or to drug responsiveness in the Malaysian Malay, Chinese and Indian subgroups.

5.1.1 *BDNF* gene polymorphisms and susceptibility to epilepsy

BDNF protein encoded by the *BDNF* gene, plays an important role in the growth and differentiation of new neurons and synapses as well as in survival of existing neurons of the central and peripheral nervous system (Fargali et al., 2012; Ichim et al., 2012). The *BDNF* gene has a complex structure with multiple regulatory elements and four promoters that are differentially expressed in the neurons (Tapia-Arancibia et al., 2004; Binder and Scharfman, 2004). This gene initially produces a prodomain form (pro-BDNF) which is cleaved and generates mature BDNF (mBDNF) (Nagappan et al., 2009; Yang et al., 2009). Cleavage of the pro-BDNF is a fundamental step for regulation of BDNF function in the brain (Je et al., 2012; Chen et al., 2005a).

Our results of *BDNF* gene polymorphisms showed that the rs6265, rs7103411 and rs7127507 and their haplotypes were risk factors for susceptibility to cryptogenic and symptomatic epilepsy in the Malaysian Indians. In this ethnicity, the $rs6265_T$, $rs7103411_c$, and $rs7127507_T$ loci and their haplotype were risk variants for epilepsy. However, these loci and their haplotypes were not associated with drug responsiveness in Malaysian epilepsy patients. Therefore, *BDNF* genetic polymorphisms may play a remarkable role in susceptibility to epilepsy in the Malaysian Indian ethnic subgroup, but not to drug responsiveness in epilepsy patients. Previous association studies of *BDNF* gene

polymorphisms have mostly focused on the rs6265 in epilepsy and psychiatric conditions such as bipolar disorders, schizophrenia and addiction (Chang et al., 2013; Li et al., 2013; Wang et al., 2012; Sears et al., 2011; Kim et al., 2008; Cheah et al., 2014; Su et al., 2014; Haerian, 2013). Table 5.1 is a summary of results of previous reports and this study in epilepsy.

Table 5.1: Comparison of MAF distributions of the *BDNF* gene polymorphisms in the cases and controls with different types of epilepsy in various populations, including Malaysians.

No.	Locus	Author	Year	Origin	Epilepsy	Minor allele frequency		Association
						Case	Control	
1	rs6265	Lohoff et al.	2005	European American	TLE	0.16	0.19	No
		Bragatti et al.	2010	European Brazilian	TLE	0.22	0.14	No
		Tondo et al.	2011	Spanish	TLE	0.79	0.21	No
		Chou et al.	2004	Taiwanese	FS_1	0.50	0.58	No
		This study	2014	Malaysian Malay	Epilepsy	0.41	0.43	No
				Malaysian Chinese	Epilepsy	0.50	0.46	No
				Malaysian Indian	Epilepsy	0.32	0.23	Yes[1]
2	rs7103411	This study	2014	Malaysian Malay	Epilepsy	0.44	0.44	No
				Malaysian Chinese	Epilepsy	0.50	0.45	No
				Malaysian Indian	Epilepsy	0.40	0.29	Yes[2]
3	rs7127507	This study	2014	Malaysian Malay	Epilepsy	0.20	0.19	No
				Malaysian Chinese	Epilepsy	0.11	0.11	No
				Malaysian Indian	Epilepsy	0.31	0.37	Yes[3]

Abbreviations: TLE, temporal lobe epilepsy; FS_1, febrile seizure; 1, with cryptogenic epilepsy; 2, with cryptogenic epilepsy and symptomatic epilepsy; 3, with cryptogenic epilepsy

The rs6265 polymorphism is located in the 5' pro-region, which encodes a pro-BDNF (Egan et al., 2003). Reports from Taiwan, China, New Zealand and Korea found association between rs6265 and susceptibility to mental disorders (Chang et al., 2013; Li et al., 2013; Wang et al., 2012; Sears et al., 2011; Kim et al., 2008; Cheah et al., 2014), whereas other studies from North America, Brazil, Spain and Taiwan identified no association between this locus and temporal lobe epilepsy, epilepsy in with fragile X, and febrile seizure (Lohoff et al., 2005; Bragatti et al., 2010; Tondo et al., 2011; Chou et al., 2004). To the best of our knowledge, there is no report from India for the role of this

polymorphism in epilepsy. Moreover, there is no report of rs7103411 and rs7127507 in association wit susceptibility to epilepsy. Thus, it is plausible that these low penetrance variants of *BDNF* gene synergistically modulate the risk of epilepsy in the Malaysian Indians.

5.1.2 *CALHM1* gene polymorphism and susceptibility to epilepsy

CALHM1 is a transmembrane glycoprotein encoded by *CALHM1* gene, plays an important role in development and maintenance of epilepsy. This protein regulates calcium homeostasis and amyloid β (Aβ) function as well as in mediates cortical neuronal excitability (Delorenzo et al., 2005; Ma et al., 2012). The *CALHM1* gene contains four hydrophobic domains and two *N*-glycosylation motifs that are conserved across at least 20 species, including mouse and *C.elegans* (Siebert et al., 2013; Dreses-Werringloer et al., 2008). This gene was identified with five human homologs which are expressed in brain regions. It is the most critical ion channel for neuronal signaling and function in the neurons (Siebert et al., 2013; Dreses-Werringloer et al., 2008; Dreses-Werringloer et al., 2013).

Our results of *CALHM1* gene polymorphism showed that the rs11191692 was a risk factor for susceptibility to cryptogenic epilepsy in the Malaysian Indians. In this ethnicity, the rs11191692 was a risk variant for epilepsy. However, this locus was not associated with drug responsiveness in the Malaysian epilepsy patients. Therefore, *CALHM1* genetic polymorphism may plays a remarkable role in susceptibility to epilepsy in the Malaysian Indian ethnic subgroup. Previous association studies of *CALHM1* gene polymorphisms have mostly focused on the rs2986017 in epilepsy, Alzheimer's disease and sporadic Creutzfeldt-Jakob disease (Koppel et al., 2011; Shibata et al., 2010; Cui et al., 2010; Calero et al., 2012). Table 5.2 is a summary of results of previous reports and this study on epilepsy.

Table 5.2: Comparison of MAF distributions of the *CALHM1* gene polymorphism in the cases and controls with different types of epilepsy in various populations, including Malaysians.

No.	Locus	Author	Year	Origin	Epilepsy	Minor allele frequency		Association
						Case	Control	
1	rs11191692	Lv et al	2011a	Han Chinese	TLE	0.32	0.26	Yes
		Li et al.	2014	Han Chinese	MTLE	0.30	0.29	No
		This study	2014	Malaysian Malay	Epilepsy	0.35	0.27	No
				Malaysian Chinese	Epilepsy	0.32	0.34	No
				Malaysian Indian	Epilepsy	0.42	0.47	Yes[1]

Abbreviations: TLE, temporal lobe epilepsy; MTLE, mesial temporal lobe epilepsy; 1, with cryptogenic epilepsy

The rs11191692 polymorphism located at the 3'UTR of the *CALHM1* gene, is associated with susceptibility to TLE patients (Lv et al., 2011a), but showed no association with MTLE in Han Chinese population (Li et al., 2014). A recent study suggested that some genetic predisposition shared similar functions in epilepsy and Alzheimer's disease (Chin & Scharfman, 2013). Studies from North America, Japan, China and Spain found an association between the *CALHM1* gene polymorphisms and susceptibility to Alzheimer's disease (Koppel et al., 2011; Shibata et al., 2010; Cui et al., 2010; Rubio-Moscardo et al., 2013), however, others studies from Belgium, Hungary and Italy reported no association between those loci and this disorder (Sleegers et al., 2009; Fehér et al., 2011; Nacmias et al., 2010). Yet, there is no report from Malaysia or from India for association of rs11191692 with susceptibility to epilepsy. Thus, it is plausible that this low penetrance variant of *CALHM1* gene synergistically modulate the risk of epilepsy in the Malaysian Indians.

5.1.3 *ASIC1* gene polymorphism and susceptibility to epilepsy

ASIC1 is an acid-sensing ion channel 1a encoded by *ASIC1* gene, plays an important role in the generation and maintenance of epileptic seizures through regulating the brain pH (Chen et al., 2005b). The *ASIC1* gene may possibly disrupt the neuroplasticity

which then can contribute to synchronized activities underlying epileptic seizures (Wemmie et al., 2002; Xiong, et al., 2004). This gene is widely expressed in the neurons of the peripheral sensory and the central nervous system (Alvarez de la Rosa et al., 2003; Wemmie et al., 2002). The ASIC1 protein is irreversibly modulated by extracellular trypsin, a serine protease, through proteolytic cleavage (Vukicevic et al., 2006). Modification of ASIC1 in the brain is fundamental step for shiffing the pH dependence of the channel activation and inactivation to more acidic pH (Poirot et al., 2004).

Our results of *ASIC1* gene polymorphism showed that the rs844347 was a risk factor for susceptibility to idiopathic epilepsy in the Malaysian Malays. However, this locus was not associated with drug responsiveness in the Malaysian epilepsy patients. Therefore, *ASIC1* genetic polymorphism may play a remarkable role in susceptibility to epilepsy in the Malaysian Malay. Our finding is consistent with one study from China which identified an association between rs844347 with susceptibility to temporal lobe epilepsy in the Han Chinese (Lv et al., 2011b). There are some reports of *ASIC1* gene polymorphisms associated with insulin resistance or with blood pressure levels (Lv et al., 2011b; Wu et al., 2010; Ko et al., 2008). Thus, it is plausible that the *ASIC1* rs844347 involved in susceptibility to idiopathic epilepsy in the Malaysian Malays.

5.1.4 *GRIK2* gene polymorphism and susceptibility to epilepsy

GRIK2 as type of glutamate receptor encoded by *GRIK2* gene, is also known as glutamate receptor 6 (GluR6). This receptor plays an important role in reducing the synaptic concentration of glutamate (Maragakis and Rothstein, 2001; Shigeri et al., 2004). It is widely expressed on the neurons and on glial membranes (Hollman and Heinemann, 1994; Dingledin et al., 1999). Glutamate is the principal excitatory neurotransmitter that could produce excessive excitability during development as some of the mechanisms in

epilepsy are shared by the mature brain and the developing brain (Sanchez and Jensen, 2001). Occasionally, in animal models, exposure to chronically elevated extracellular glutamate is reported to promote epileptogenesis and excitotoxicity (Vazquez-Lopez et al., 2005; Sierra-Paredes et al., 2001), possibly via cellular reorganization and increased expression of the extrasynaptic NMDA receptors (Vasquez-Lopez et al., 2005).

Our results of *GRIK2* gene polymorphism showed that the rs4840200 was a risk factor for susceptibility to symptomatic epilepsy in the Malaysian Malays. This locus was not associated with drug responsiveness in the Malaysian epilepsy patients. Previous association studies of *GRIK2* gene polymorphisms reported data from epilepsy, obsessive-compulsive disorder (OCD) and autism disorders (Guo et al., 2012; Mattheisen et al., 2014; Sampaio et al., 2011; Cai et al., 2013; Jamain et al., 2002; Shuang et al., 2004). Amongst these studies, a GWAS report from China found an association between the rs9390754, rs4840200 and rs9390790 and susceptibility to epilepsy in Han Chinese, but, these SNPs showed no association in the replication cohort (Guo et al., 2012). Nonetheless, one study from German suggests that allelic variants of *GRIK2* are not involved in the expression of common familial IGEs (Sander et al., 1995). To sum up, it is plausible that the *GRIK2* rs4840200 polymorphism modulate the risk of epilepsy in the Malaysian Malays.

5.1.5 *KCNAB1* gene polymorphisms and susceptibility to drug responsiveness

Potassium channels structurally and functionally represent the most complex class of voltage-gated ion channels. They are involved in various functions in the body, including regulating neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction, and cell volume. There are four sequence-related potassium channel genes, namely shaker, shaw, shab, and shal. *KCNAB1* gene encoding subunit beta-1 of these channels is from shaker type. This gene is highly

expressed in brain and heart and produces protein with a complex structure. This protein plays an important role in shaping the action potential, and in neuronal excitability and plasticity (Tempel et al., 1988; Attali et al., 1992). Because alternative splicing, there are various isoforms of KCNAB1, some express six transmembrane domains and some express two transmembrane domains including the voltage-gated (Kv) channels, the KCNQ channels, the EAG-like K+ channels, and three types of calcium (Ca)-activated K+ channels (BK, IK and SK) (Miller, 2000).

Our results of *KCNAB1* gene polymorphisms showed that only rs2280032 was a risk factor for drug resistance after at least a year of AED treatment in the Malaysian Malays with cryptogenic epilepsy. This locus was not associated with susceptibility to epilepsy in the Malaysian patients. The rs2280032 is a synonymous that does not results in amino acid change. This finding was consistent with a report from a multicentre study (in the UK, Ireland, Finland and Australia) and also from Italy. The multicentre study showed an association between the *KCNAB1* gene polymorphisms and susceptibility to lateral temporal epilepsy (Busolin et al., 2011: Cavalleri et al., 2007b). This SNP is a synonymous mutation that will not results in amino acid change. However, no previous study has been performed on this locus in drug responsiveness in epilepsy. Thus, it is plausible that this low penetrance variant of *KCNAB1* gene be a risk factor for drug resistance in the Malaysian Malay with crptogenic epilepsy patients.

5.1.6 *ABCC2* gene polymorphism and susceptibility to drug responsiveness

The ATP-binding cassette, sub-family C, member 2 (ABCC2) as a member of the ATP-binding cassette (ABC) transporter superfamily, is the most abundant transporters in the epilepsy brain tissues compared to normal human brain (Dombrowski et al., 2001; Nies et al., 2004). The ABCC2 encoded by *ABCC2* gene, plays an important role in the

formation of multidrug resistance protein 2 (MRP2) that involved in the transporter of many AEDs at the blood-brain barrier (BBB) (Potschka et al., 2003). Overexpression of *ABCC2* gene on BBB cells may increase efflux AEDs to the capillary lumen, leading to reduction of the AED concentration in the brain to a level which may be inadequate to control seizures (Löscher and Potschka, 2005; Schmidt and Löscher, 2009). Some polymorphisms in this gene may alter its expression and function which then resulting in resistance to AEDs.

Our results of *ABCC2* gene polymorphism showed that the rs2273697 was a risk factor for drug resistance after at least a year of AED treatment in the Malaysian Chinese with idiopathic epilepsy. However, this locus was not associated with susceptibility to epilepsy in the Malaysian patients. Previous association studies of *ABCC2* gene polymorphisms have mostly focused on the rs2273697 in epilepsy (Ufer et al., 2011; Kwan et al., 2011; Hilger et al., 2012; Sporis et al., 2013; Seo et al., 2008; Kim et al., 2009). Table 5.3 is a summary of results of previous reports and this study on epilepsy.

Table 5.3: Comparison of MAF distributions of the *ABCC2* gene polymorphism in the drug nonresponders and drug responders with different types of epilepsy in various populations, including Malaysians.

No.	Locus	Author	Year	Origin	Epilepsy	Minor allele frequency		Association
						NR	R	
1	rs2273697	Ufer et al.	2011	European Germany	CE_1	0.19	0.31	Yes
		Kwan et al.	2011	Han Chinese	Epilepsy	0.13	0.11	No
		Hilger et al	2012	European Austrian	Epilepsy	0.21	0.20	No
		This study	2014	Malaysian Malay	Epilepsy	0.11	0.11	No
				Malaysian Chinese	Epilepsy	0.23	0.22	Yes[1]
				Malaysian Indian	Epilepsy	0.11	0.08	No

Abbreviations: NR, drug nonresponder; R, drug responder; CE_1, childhood epilepsy; PE, partial epilepsy; 1, with idiopathic epilepsy

Studies from German, North India and China found an association between rs2273697 and drug responsiveness in epilepsy patients (Ufer et al., 2011; Grover et al.,

2012; Qu et al., 2012; Ma et al., 2014), but, other reports from Austria, Japan , China, South Korea and Croatia reported no association between this locus and drug responsiveness in their populations (Hilger et al., 2012; Seo et al., 2008; Kwan et al., 2011; Kim et al., 2009; Sporis et al., 2013). Yet, there has been only one previous study which looked at the association of rs2273697 with drug responsiveness in the Malaysian epilepsy patients (Subenthiran et al., 2013). Thus, it is plausible that this low penetrance variant of *ABCC2* gene synergistically modulate the risk of drug resistance in the Malaysian Chinese with idiopathic epilepsy patients.

5.1.7 Other candidate genes polymorphisms

The present study also investigated a number of SNPs in various candidate genes, including *GJD2*, *OPRM1*, *NR1I2*, *SLC6A11*, *CAMSAP2*, *LGI1*, and *SCN8A*. None of the SNPs in these genes were found to be associated with susceptibility to epilepsy or to drug responsiveness in this study population.

5.2 Study limitations

In this study, we acknowledge the following limitations that may have influenced our results:

1. Small sample size after stratification of the subjects into the different ethnic groups, and epilepsy patients into cryptogenic, idiopathic and symptomatic epilepsy. This strategy reduced heterogeneity between study samples.
2. Confounders effect size which may bias of results. Therefore, by application of adjusted regression the effect of these variables were controlled.

3. AED polytherapy or combination of both monotherapy and polytherapy treatments. Interaction of drugs when used in combination (polytherapy) may change drug efficacy.

Hence, further study which covers larger sample size should be carried out and more functional study especially involving animal work are needed.

CHAPTER 6

CONCLUSION AND FUTURE STUDIES

6.0 CONCLUSION AND FUTURE STUDIES

6.1 Conclusion

Genetic association study of susceptibility to epilepsy indicate a positive association between the candidate genes *BDNF, CALHM1*, *ASIC1*, and *GRIK2* with susceptibility to epilepsy in a Malaysian population consisting of the Chinese, Indians, and Malay subgroups. Results of this study showed plausible association between the *BDNF* rs6265, rs7103411 and rs7127507 and their haplotype, *CALHM1* rs11191692, *ASIC1* rs844347, and *GRIK2* rs4840200 and susceptibility to epilepsy. The results also show plausible association between the *KCNAB1* rs2280032 and *ABCC2* rs2273697 polymorphisms and drug responsiveness in Malaysians. Therefore, these variants might be risk factors for susceptibility to epilepsy or for drug responsiveness in this disorder. A larger sample size and more ethnically diverse samples are needed to replicate these findings.

6.2 Future studies

The findings described in this thesis expand our knowledge on the association of genetic polymorphisms with susceptibility to epilepsy and drug responsiveness to carbamazepine or valproate monotherapy treatment in Malaysian population. This approach will be useful in future in order to minimize the genotyping cost yet presenting the information that could reflect the role of the other relevant SNPs within the gene. The study fuels the notion that genetic polymorphisms could potentially be used as risk markers or as therapeutic targets in epilepsy treatment. We also provide further data that considering the three major ethnic groups in Malaysian population, namely the Chinese, Indians, and Malay subgroups. The population effect of the Chinese, Indians, and Malay subjects used in this association study may be different from the future report from

Western studies, or even another Asian studies. Having said that, the present study associating particular genes and their variants with susceptibility to epilepsy or drug responsiveness to carbamazepine or valproate monotherapy might already be something to be gained from new discoveries, and holds promise that diagnostic tests might be even more useful in the future.

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