Lack of Association Between Synapsin II (*SYN2*) Gene Polymorphism and Susceptibility Epilepsy: A Case–Control Study and Meta-Analysis

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KEY WORDS epilepsy; *SYN2*; polymorphism; synapsin; meta-analysis

ABSTRACT **Objective:** The *SYN2* rs3773364 A>G polymorphism has been proposed to be involved in susceptibility to epilepsy, but research results have been inconclusive. The aim of this study was to investigate the association between the *SYN2* rs3773364 A>G polymorphism and susceptibility against epilepsy in a case–control study and a meta-analysis. **Methods:** The *SYN2* rs3773364 A>G polymorphism was successfully genotyped in 1182 samples (618 epilepsy patients) of Chinese, Indian, and Malay ethnicities. Meta-analysis of the related studies, including this case–control study, was performed under alternative genetic models. **Results:** Data from the case–control study indicated no allelic and genotypic association of this locus with susceptibility to epilepsy in the tri-ethnic Malaysian population. Similar finding was obtained by stratified analysis by epilepsy syndrome for idiopathic epilepsy. These results were verified by meta-analysis of the related pooled data. **Conclusions:** Our study indicated that *SYN2* rs3773364 A>G polymorphism is not a risk factor for susceptibility to epilepsy. **Synapse 65:1073–1079, 2011.**

INTRODUCTION

Epilepsy is one of the most common neurological disorders with a worldwide prevalence of 1–1.5% (Annegers et al., 1995). It encompasses a heterogeneous group of disorders with a predisposition to recurrent unprovoked seizures, caused by abnormal excessive or synchronous neuronal activity in the brain (Hauser et al., 1993). Genetic analyses have identified a link between synapsins and sporadic seizures (Li et al., 1995). Synapsins are neuronal phosphoproteins that associate with the cytoplasmic surface of synaptic vesicles. These proteins are characterized by multidomain phosphoproteins. They regulate synaptogenesis and synapse maturation and stabilization (Greengard et al., 1993). They also modulate of neurotransmitter release, which suggests their potential role in several neuropsychiatric diseases such as schizophrenia (Hilfiker et al., 1999; Saviouk et al., 2007). Synapsins are encoded by three genes in mammals (*SYN1-3*) with multiple transcripts (Kao et al., 1999).

There is a link between the synapsins with schizophrenia as well as sporadic seizures. Synapsins are involved in the maintenance of the excitability of the neuronal network. Impairment of synapsin function results in unbalanced brain excitability, which can lead to epileptic seizures. Genetic analysis of the different synapsin-deficient mouse lines showed that lack of *SYN1* and *SYN2* function cause susceptibility to epileptic seizures (Etholm and Heggelund, 2009; Li et al., 1995; Cesca et al., 2010). The *SYN2* encodes a neuron-specific phosphoprotein that selectively binds to small synaptic vesicles in the presynaptic nerve terminal (Kao et al., 1999). It is hypothesized that single nucleotide polymorphisms (SNPs) may contribute to susceptibility against epilepsy. SNPs are the

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most frequent form of sequence variations in the human genome (Goldstein and Cavalleri, 2005). The results of a comprehensive study suggested an association of *SYN2* rs3773364 A>G polymorphism with febrile seizure in the UK, Irish, and Finnish cohorts but not in the Australian cohort (Cavalleri et al., 2007). This finding was confirmed by a study in the Indian patients with idiopathic epilepsy (Lakhan et al., 2010). As genetic variation is population specific, we examined the association between the intronic *SYN2* rs3773364 A>G polymorphism and epilepsy susceptibility in a Malaysian tri-ethnic population. Furthermore, we performed a meta-analysis of the previous related data, including this study.

MATERIALS AND METHODS

Original study

This study was part of an ongoing multicenter collaboration between the University of Malaya Medical Centre, Universiti Kebangsaan Malaysia Medical Centre, and Monash University of Medical Centre. The study protocol was approved by the ethics committees of the centers, and patients were recruited from epilepsy clinics and diagnosed by neurologists who were blinded to the genotype data. Seizures and epilepsy syndromes were classified according to the International League against Epilepsy guidelines (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). Exclusion criteria included unreliable record of seizure frequency, significant psychiatric comorbidity, history of pseudoseizures, alcohol or drug abuse, and presence of progressive or degenerative neurological or systemic disorders. Of 1390 Malaysian Chinese, Indian, and Malay patients with epilepsy, 670 unrelated subjects who met inclusion criteria and 571 healthy individuals with no family history of epilepsy participated in this study. The normal subjects were recruited from blood donors in the Hospital University or from their children. Written informed consent was given by all patients or by their guardians in the case of a child. A standardized extraction template was administered to collect demographic details, information on seizure types and frequency, and relevant family history from the records. Genomic DNA was extracted from either whole blood or buccal swabs by standard methods. The *SYN2* rs3773364 A>G polymorphism was genotyped by using matrix-assisted laser desorption/ionization time of flight mass spectrometry (MassArray, Sequenom, San Diego, CA) at the Genome Research Centre in The University of Hong Kong.

All values were presented either as the mean ± SD for continuous data or as frequency for categorical data. Participants' ages at study entry were normally distributed, as examined by the Kolmogorov–Smirnov test. The difference in continuous (age at study) and categorized data (sex, seizure type, and epilepsy syndrome) between races was calculated by ANOVA or and χ^2-test, respectively. The odds ratios (ORs) with 95% CIs, adjusted for confounders (ethnicity, gender, and age at recruitment), were obtained through binomial logistic regression analysis. The alternative genetic models for the *SYN2* rs3773364 A>G polymorphism included alleles (A vs. G) and genotypes for codominant (A/A vs. G/G and A/G vs. G/G), dominant (A/A+A/G vs. G/G), and recessive (A/A vs. A/G+G/G) models. Two-sided tests of statistical significance were used to determine statistically significant P values ($P < 0.05$) with the SPSS software package (ver. 15.0; SPSS, Chicago, IL).

Meta-analysis

Published studies to November 2010 that determined the distribution of the *SYN2* rs3773364 A>G genotype in epilepsy patients and healthy people were included in this meta-analysis. There was no language limitation. Crude ORs with 95% CIs and P values were calculated from allele and genotypes. Pooled ORs of the *SYN2* rs3773364 A>G polymorphism were performed for allele and alternative genotype models. To measure the strength of genetic association, we used the I^2 test to assess the proportion of statistical heterogeneity and the Q-statistic test with $P \leq 0.10$ to define a significant degree of heterogeneity. Fixed effects were calculated as the inverse variance weighted average of the log OR, if there was no heterogeneity, and random effects were calculated when there was substantial heterogeneity. Statistical analyses were performed by using validated Meta-analysis Made Easy (MIX) version 1.7 (Bax et al., 2006).

RESULTS

Original study

Of 1241 Malaysian participants (670 epilepsy patients) who were enrolled in this study, 1195 samples (643 epilepsy patients) were successfully genotyped and used for the case–control study and meta-analysis. The percentage of Chinese, Indians, and Malays was 40.3, 23.4, and 36.3%, respectively. The control group was adjusted for age, gender, and ethnicity. Males were over-represented, but their frequencies were not significantly different between the Chinese (55%), Indians (56%), and Malays (54%; $P = 0.81$). Partial seizure was significantly more frequent than generalized seizure in the Chinese (57%) and Malays (54%) but less common in the Indians (45%; $P = 0.04$). Symptomatic (39%) and cryptogenic (36%) epilepsies were more often diagnosed in patients than was idiopathic epilepsy. Symptomatic and cryptogenic epilepsies were significantly more common in the Chinese (42 and 39%, respectively) and Malay subjects

TABLE I. Genotypes and allele frequencies of genotyped SYN2 rs3773364 A>G polymorphism in the three ethnicities

	Chinese (n = 484)			Indian (n = 277)			Malay (n = 434)			Total (1195)		
	Epilepsy (n = 260)			Epilepsy (n = 152)			Epilepsy (n = 231)			Epilepsy (n = 643)		
Allele/genotype	E (%)	I (%)	Control (%)	E (%)	I (%)	Control (%)	E (%)	I (%)	Control (%)	E (%)	I (%)	Control (%)
A	191 (36.7)	33 (36.7)	187 (41.7)	148 (48.7)	59 (54.6)	112 (44.8)	171 (37.0)	44 (43.1)	149 (36.7)	510 (39.7)	136 (45.3)	448 (40.6)
G	329 (63.3)	57 (63.3)	261 (58.3)	156 (51.3)	49 (45.4)	138 (55.2)	291 (63.0)	58 (56.9)	257 (63.3)	776 (60.3)	164 (54.7)	656 (59.4)
A/A	38 (14.6)	5 (11.1)	36 (16.1)	38 (25.0)	18 (33.3)	24 (19.2)	35 (15.2)	9 (17.6)	22 (10.8)	111 (17.3)	32 (21.3)	82 (14.9)
A/G	115 (44.2)	23 (51.1)	115 (51.3)	72 (47.4)	23 (42.6)	64 (51.2)	101 (43.7)	26 (51.0)	105 (51.7)	228 (44.8)	72 (48.0)	284 (51.4)
G/G	107 (41.2)	17 (37.8)	73 (32.6)	42 (27.6)	13 (24.1)	37 (29.6)	95 (41.1)	16 (31.4)	76 (37.4)	244 (37.9)	46 (30.7)	186 (33.7)

Abbreviations: E, all type epilepsy; I, idiopathic epilepsy; C, control.

TABLE II. Genotypes and allele frequencies of genotyped SYN2 rs3773364 A>G polymorphism in the three ethnicities under alternative genetic models

	Ethnicity															
	Chinese (n = 484)				Indian (n = 277)				Malay (n = 434)				Total (1195)			
Genotype	E	C	P	OR (CI 95%)	E	C	P	OR (CI 95%)	E	C	P	OR (CI 95%)	E	C	P	OR (CI 95%)
A vs. G	520	448	0.11	1.23 (0.95–1.60)	304	250	0.36	0.85 (0.61–1.19)	462	406	0.90	0.98 (0.74–1.30)	1286	1104	0.67	1.04 (0.88–1.22)
A/A vs. G/G	145	109	0.25	1.37 (0.79–2.37)	80	61	0.30	0.70 (0.35–1.38)	130	98	0.51	0.81 (0.44–1.51)	335	268	0.81	0.96 (0.68–1.35)
A/G vs. G/G	222	188	0.05	1.48 (1.00–2.20)	114	101	0.96	1.01 (0.58–1.77)	196	181	0.20	1.30 (0.87–1.96)	532	470	0.04	1.30 (1.01–1.68)
A/A+A/G vs. G/G	260	224	0.05	1.45 (1.00–2.11)	152	125	0.71	0.90 (0.53–1.53)	231	203	0.45	1.16 (0.79–1.71)	643	552	0.13	1.20 (0.95–1.53)
A/A vs. A/G+G/G	260	224	0.70	1.10 (0.67–1.81)	152	125	0.25	0.71 (0.40–1.27)	231	203	0.18	0.67 (0.38–1.20)	643	552	0.24	0.83 (0.61–1.13)

Abbreviations: E, epilepsy; C, control.

TABLE III. Meta-analysis of genotyped SYN2 rs3773364 A>G polymorphism in the related studies under alternative genetic models

	Susceptibility to epilepsy (n = 1766)									
	All type of epilepsy (n = 1766)					Idiopathic epilepsy (n = 1108)				
	E (n = 1015) vs. C (n = 751)					I (n = 357) vs. C (n = 751)				
Allele/genotype	OR	CI	P	I^2 (%)	P	OR	CI	P	I^2 (%)	P
A vs. G	1.10	0.96–1.27	0.16	35	0.20	0.97	0.70–1.34	0.85	61	0.05
A/A vs. G/G	1.09	0.81–1.46	0.57	30	0.23	0.88	0.46–1.66	0.69	55	0.08
A/G vs. G/G	1.10	0.86–1.41	0.46	0	0.48	0.89	0.64–1.23	0.48	0	0.94
A/A+A/G vs. G/G	1.00	0.67–1.49	0.99	63	0.04	0.92	0.46–1.82	0.81	73	0.01
A/A vs. A/G+G/G	1.05	0.84–1.32	0.67	36	0.20	0.95	0.69–1.30	0.74	0	0.67

Abbreviations: E, all type epilepsy; I, idiopathic epilepsy; C, control.

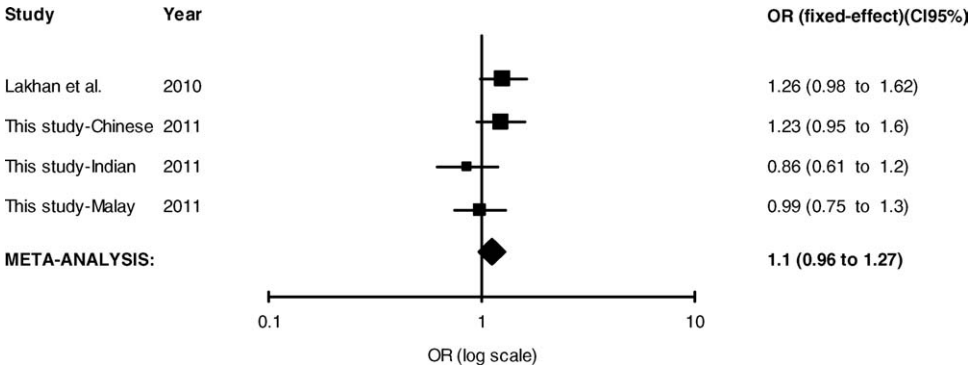

Fig. 1. Forest plot presenting the meta-analysis of the related studies for the *SYN2* rs3773364 A>G polymorphism and epilepsy susceptibility. The area of each square is inversely proportional to the variances of the log ORs. The horizontal lines represent 95% CI on estimating the outcome of the A allele versus the G allele in the meta-analysis. The overall effect estimate is plotted as a diamond. The lateral points of that diamond indicate the 95% CI of this estimate.

(38 and 36%, respectively) than in Indian subjects (35 and 30%, respectively; $P < 0.01$).

Table I lists the allele and genotype percentages of the *SYN2* rs3773364 A>G polymorphism for the 643 epilepsy patients and 552 controls in this study. The G-allele was significantly more common in the Chinese (61%) and Malays (63%) than Indians (53%; $P < 0.01$). No allelic association was observed with susceptibility against epilepsy in the overall or in every ethnicity. Subanalysis by epilepsy syndrome showed no allelic association with susceptibility to cryptogenic, idiopathic, and symptomatic epilepsies.

The genotype distribution of the *SYN2* rs3773364 A>G polymorphism was consistent with the Hardy–Weinberg equilibrium in each ethnic subgroup of epilepsy patients and controls. Overall, the G/G genotype (38%) was more common than the A/A genotype (17%). Association of genotype with susceptibility to epilepsy was significant in the overall patients under the codominant (A/G vs. G/G: adjusted OR 1.30, CI = 95%, 1.01–1.68, $P = 0.04$) model (Table II). Stratified analysis by ethnicity showed significant genotypic association between this variant and susceptibility to epilepsy in the Chinese at the marginal level under codominant (A/G vs. G/G: adjusted OR 1.48, CI = 95%, 1.00–2.20, $P = 0.05$) and dominant (adjusted OR 1.45, CI = 95%, 1.00–2.11, $P = 0.05$) models. In these patients, the G/G genotype was more common than the controls under codominant (48 and 39%, respectively) and dominant (41 and 33%, respectively) models. However, after correction of multiple comparisons with Bonferroni's method, these significant association was lost. Stratified analysis by epilepsy syndrome showed no genotypic association with susceptibility to cryptogenic, idiopathic, and symptomatic epilepsies. Taken together, the *SYN2* rs3773364 A>G polymorphism was not a risk factor for susceptibility to epilepsy in the Malaysian patients.

Meta-analysis

Out of the two association studies that have been reported of *SYN2* rs3773364 A>G polymorphism in susceptibility to epilepsy (Cavalleri et al., 2007; Lakhan et al., 2010), only the data of one study (Lakhan et al., 2010) was extractable and hence included in this meta-analysis. A total of 1195 Malaysian samples (643 epilepsy patients) from Chinese (n = 484), Indian (n = 277), and Malay (n = 434) cases and controls from this study were included with the 571 subjects from an Indian report (Lakhan et al., 2010) in the meta-analysis. We meta-analyzed the pooled data into two categories: (1) genetic susceptibility to all types of epilepsy and (2) genetic susceptibility to idio-

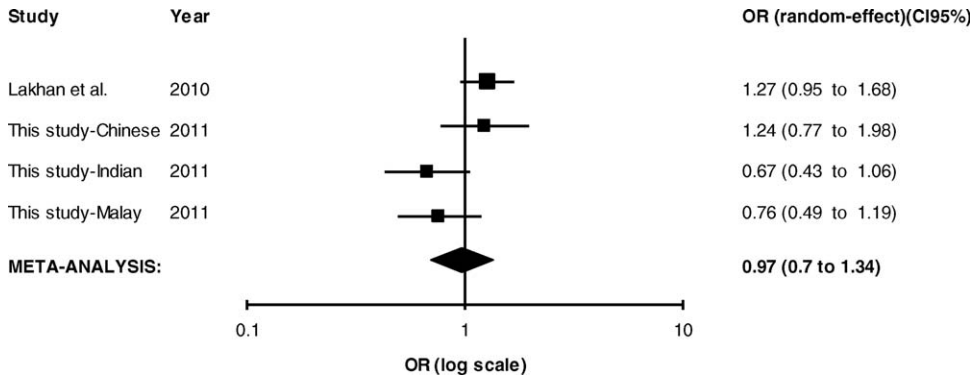

Fig. 2. Forest plot presenting the meta-analysis of the related studies for the *SYN2* rs3773364 A>G polymorphism and idiopathic epilepsy susceptibility. The area of each square is inversely proportional to the variances of the log ORs. The horizontal lines represent 95% CI on estimating the outcome of the A allele versus the G allele in the meta-analysis. The overall effect estimate is plotted as a diamond. The lateral points of that diamond indicate the 95% CI of this estimate.

pathic epilepsy (Table III; Figs. 1 and 2). Allelic and genotypic meta-analyses of these studies showed no association of this locus with susceptibility to epilepsy or idiopathic epilepsy. Therefore, this variant was not a risk factor for susceptibility to epilepsy or idiopathic epilepsy. A wide heterogeneity was observed among the studies performed on patients with epilepsy (0–63%) or idiopathic epilepsy (0–73%) versus healthy individuals. In the idiopathic epilepsy group, allelic heterogeneity of studies was significant (I^2 = 61%, P = 0.05). A significant heterogeneity was observed in all types of epilepsy categories under dominant models (I^2 = 63%, P = 0.04) as well as in the idiopathic epilepsy category under codominant (A/A vs. G/G: I^2 = 55%, P = 0.08) and dominant (I^2 = 73%, P = 0.01) models. This heterogeneity was contributed mainly by the Indian report and by the Malaysian Indian study in the overall epilepsy syndromes as well as in idiopathic epilepsy. In the category of idiopathic epilepsy, both studies were equally affected. Removal of either Indian study or Malaysian Indian data from allelic meta-analysis gave 46% (P = 0.16) and 47% (P = 0.15) heterogeneity, respectively, however the results were still not significant. This finding showed that these two data have the highest effect on allelic association of *SYN2* rs3773364 A>G polymorphism with susceptibility to epilepsy. Similar results were observed in the genetic models.

DISCUSSION

In this study, we found no association between *SYN2* rs3773364 A>G polymorphism and susceptibility to epilepsy or idiopathic epilepsy in the Malaysian epilepsy patients as indicated by the meta-analysis of pooled data. Therefore, this variant was not a risk factor for susceptibility to epilepsy or idiopathic epilepsy. These results were inconsistent with a Caucasian study for epilepsy and an Indian report for idiopathic epilepsy but not for epilepsy (Lakhan et al., 2010). This discrepancy may be caused by some factors such as small sample size and ethnicity.

Limitation of sample size and power is a common problem in genetic association studies. Small sample size leads to underpowered results (Tan et al., 2004; Otto, 2004). Cavalleri et al. found positive results for *SYN2* rs3773364 A>G polymorphism in the overall 1528 Caucasian samples with a history of febrile seizures, recruited from UK, Ireland, Australia, and Finland. Unlike the Australian samples, subanalysis by population confirmed this finding in the British, Irish, and Finnish cohorts. This variant was also associated with all epilepsy phenotype only in the British cohort (810 cases and 359 controls) (Cavalleri et al., 2007). However, this may be false positive due to heterogenous population with a small sample size. On the other hand, it is possible that our negative results of this cohort and meta-analysis study or Indian report for epilepsy (Lakhan et al., 2010) be false-negative due to smaller sample size and less statistical power than previous report. Thus, further studies with much more sample size and homogeneous subjects are required to realize the association of this variant with susceptibility against epilepsy.

Ethnicity is another factor that may confound results. Evidence indicated that the modern humans migrated from Africa within 100,000 years ago. Europeans were the initial immigrants to out of Africa and then Asians diverged from Europeans (Jorde and Wooding, 2004; Witherspoon et al., 2006). Absence of mutated G-allele of the *SYN2* rs3773364 A>G polymorphism in the African population and its low frequency in the Europeans (0.22) indicate a recent emergence of this polymorphism, probably after expansion of Europeans from Africa. Under the migration, genetic drift, and selection processes, G-allele tended to differentially distributed in the Asians such as Han Chinese (0.54) and Japanese (0.51), as well as in the African American (0.07; Fig. 3; NCBI, HapMap; Sabeti et al., 2006). The G-allele frequency in the Malaysian Indians (53%) was less

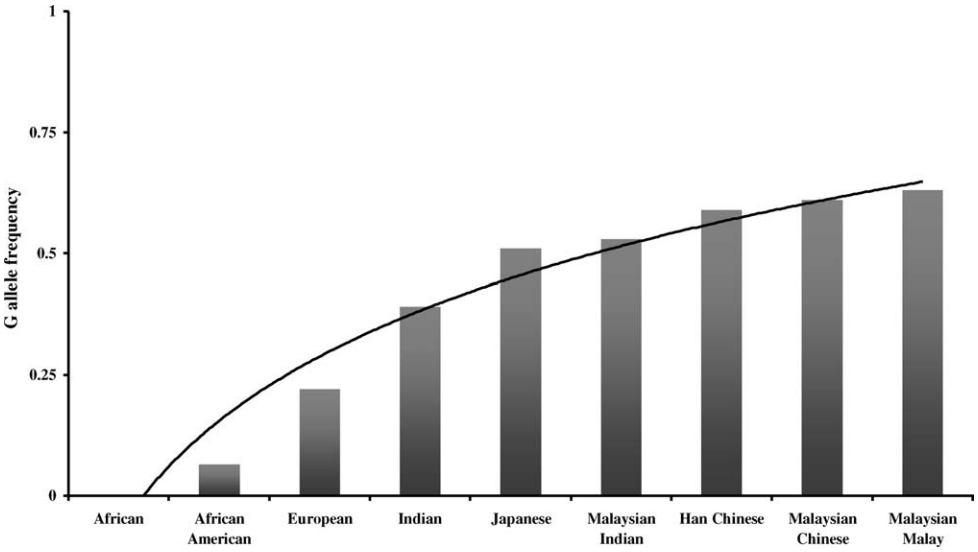

Fig. 3. Trend of G allele frequency of *SYN2* rs3773364 A>G polymorphism among different populations including Malaysians (HapMap; Lakhan et al., 2010; NCBI).

common than Malaysian Chinese (61%) and Malays (63%), while it was higher than a previous report from India (39%; Lakhan et al., 2010). G-allele frequency among populations might be influenced by distinct environmental or cultural (language and religion) pressures. Diversity of G-allele prevalence in populations may affect on susceptibility to common disease such as epilepsy and differential drug response (Sabeti et al., 2006; Campbell and Tishkoff, 2008; Rotimi and Jorde, 2010).

A major limitation of this study was the small sample size obtained by stratified analysis by ethnicity in the case–control study. Another limitation was small number of studies in the meta-analysis produced less reliable results and made it impossible to perform stratified analysis by ethnicity.

CONCLUDING REMARKS

In conclusion, the present case–control study and meta-analysis showed no evidence for contribution of *SYN2* rs3773364 A>G polymorphism to susceptibility to epilepsy or idiopathic epilepsy. Further larger, preferably LD studies are suggested.

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