

# HLA-CLASS II (DRB & DQB1) IN THAI SUDDEN UNEXPLAINED DEATH SYNDROME (THAI SUDS) FAMILIES (LAI-TAI FAMILIES)

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**Abstract.** Thai Sudden Unexplained Death Syndrome (Thai SUDS), or Lai-Tai, is a major health problem among rural residents of northeastern Thailand. The cause has been identified as a genetic disease. SUDS, a disorder found in Southeast Asia, is characterized by an abnormal electrocardiogram with ST-segment elevation in leads V1-V3, identical to that seen in Brugada Syndrome (Brugada Sign, BS) and sudden death due to ventricular fibrillation and cardiac arrest (represents an arrhythmogenic marker that identifies high-risk for SUDS). SUDS victims have a sleeping disorder (narcolepsy). The HLA-DR locus is tightly associated with narcoleptic Japanese patients and HLA-DR2, DQ haplotypes were also found in Oriental narcoleptic patients. These circumstances prompted us to study the association between the disease and HLA Class II by HLA DNA typing using a PCR-SSO method, with five Thai SUDS families (18 BS-positive subjects as the cases, and 27 BS-negatives as the controls). We found that the HLA-DRB1\*12021 allele was significantly increased in BS-positive subjects ( $p=0.02$ ; OR=4.5), the same as the HLA-DRB1\*12021-DQB1\*0301/09 haplotype ( $p=0.01$ ; OR=7.95). Our data suggests that the HLA-DRB1\*12021 allele associated with BS and the HLA-DRB1\*12021-DQB1\*0301/09 is a haplotype susceptible to arrhythmogenic markers that can identify a high risk for SUDS.

## INTRODUCTION

Sudden Unexplained Death Syndrome (SUDS) is defined as a sudden unexpected death during sleep in previously healthy young adults without clearly defined causes (Parrish *et al*, 1987). It has many local names, such as "Bangungut" in the Philippines, "Pokkuri" in Japan, and "Lai-Tai" in Thailand (Tatsanavivat *et al*, 1992; Tungsanga and Sriboonlue, 1993). In Thailand, most victims come from, or live in northeastern (NE) Thailand (Nimmanit *et al*, 1991; Tatsanavivat *et al*, 1992; Tungsanga and Sriboonlue, 1993). SUDS first attracted Thai public attention when young Thai workers in Singapore suddenly died in their sleep. During

the period 1982-1990, 230 young Thai workers in Singapore suddenly died (Goh *et al*, 1990). Twenty-seven to 40% of their relatives also died in the same manner. In other words, 18% of the victims had brothers who died of SUDS (Tatsanavivat *et al*, 1991). This suggests that SUDS is a genetic disease.

HLA-DR and HLA-DQ antigens are HLA-class II gene products encoded from the short arm of chromosome 6 in the HLA-D region (Franke and Pellegrin, 1977; Trowsdale *et al*, 1985) and play a central role in immune regulation (Unanue and Allen, 1987; Pullen *et al*, 1998) organ transplantation (Carpenter, 1994) and susceptibility to a number of diseases (Tiwari and Terasaki, 1985; Dawkin *et al*, 1993). They are glycoproteins consisting of an alpha ( $\alpha$ ) and a beta ( $\beta$ ) chain as heterodimers on the cell surface of antigen-presenting cells, such as B-lymphocytes and monocytes. HLA-DRB1 ( $\beta$  chain)

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and HLA-DQB1 are highly polymorphic. The allelic polymorphisms are mainly located on the second exon of the genes. An association between HLA-DR antigens and narcolepsy (a sleep disorder) has been reported (Honda *et al*, 1984; 1986; Juj *et al*, 1984; Langdon *et al*, 1984; Matsuki *et al*, 1987). The HLA-DR2, DQ1 haplotype is increased in Oriental narcoleptic patients (sleep disorder *ie*, sleep talking, nightmares, sleep paralysis, etc) but negative in Caucasian and Black narcoleptic patients (Andreas-Zietz *et al*, 1986). SUDS survivors, or patients with SUDS criteria who were successfully resuscitated, have been documented with ventricular fibrillation (VF) cardiac arrest and have ECG patterns like Brugada Syndrome or Brugada Sign (BS), which is right bundle branch block (RBBB) and ST segment elevation in leads V1 to V3 (Sangwatanaroj *et al*, 2001a,b). These clinical signs represent arrhythmogenic markers identified as high risk for SUDS (Sangwatanaroj *et al*, 2001a,b; Nademane *et al*, 1997) and the so-called Brugada sign (BS). Besides clinical signs, sleeping disorders have also been witnessed to occur in SUDS. In this study, the HLA-DRB and HLA-DQB1 alleles were analyzed in 5 Thai families with SUDS (Lai-Tai) and compared with the arrhythmogenic markers of these patients to identify possible associations between the HLA-DRB and HLA-DQB1 alleles and SUDS, and the hereditary transmitted haplotype for this disorder.

## MATERIALS AND METHODS

### Subjects

The study was carried out on five Thai families with SUDS from Nakhon Phanom and Sakhon Nakhon Provinces. They were coded as families A, B, C, D and E. Eleven members of family A (2 were BS-positive) were investigated, 9 members of family B (3 BS-positive), 8 members of family C (3 BS-positive), 8 members of family D (4 BS-positive) and 9 members of family E (6 BS positive) (see also Figs 1 to 5).

These 5 Thai SUDS (Lai-Tai) families (Table 1) consisted of 18 subjects (14 males and 4 females) with BS. Of these, 16 were affected with SUDS and 2 were near SUDS or survivors of

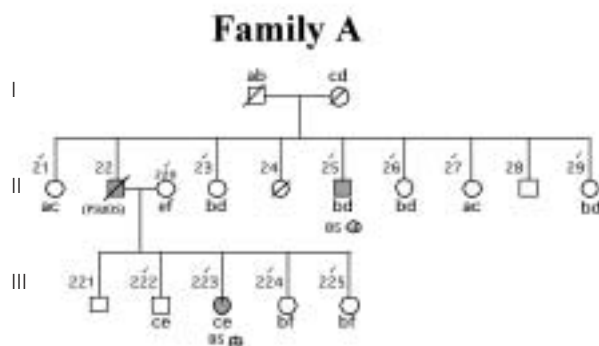


Fig 1—A pedigree of one presumptive Sudden Unexplained Death Syndrome (PSUDS) victim (family A). Circles indicate females; squares males; open symbol, negative Brugada sign (BS) by post procainamide infusion; open symbol with slash, death of unknown or other causes; not PSUDS, stippled; positive BS stippled with slash; PSUDS; a, b, c, d, e and f are letters coded for the HLA-DR - DQB haplotypes:

- a = HLA-DRB1\*1502/08, DRB5\*0102/08 N, DQB1\*06011/013 (R2-Q4)
- b = HLA-DRB1\*09012, DRB4\*0101/03/04/05, DQB1\*03032/033 (R15-Q7)
- c = HLA-DRB1\*1501/09, DRB5\*01011, DQB1\*06011/013 (R1-Q4)
- d = HLA-DRB1\*1504, DRB5\*0102/08 N, DQB1\*06011/013 (R3-Q4)
- e = HLA-DRB1\*0701/03/04, DRB4\*01011/03/05, DQB1\*0201/02 (R13-Q5)
- f = HLA-DRB1\*1101/04, DRB3\*0202/10/12-15, DQB1\*0301/09 (R6-Q6)
- ✓ = studied cases

SUDS (N-SUDS). Twenty-seven subjects without BS (12 males and 15 females) were used as controls. All subjects were willing to participate in the family studies. After obtaining informed consent, blood samples were collected.

### HLA-DRB, DQB-DNA typing by PCR-SSO

The polymorphisms of HLA-DRB and HLA-DQB1 were investigated by polymerase chain reaction sequence-specific oligonucleotide (PCR-SSO) typing. The DNA was amplified by polymerase chain reaction (PCR), and the amplified products were hybridized with sequence-specific oligonucleotide probes.

In this study, genomic DNA was extracted from white blood cells by a salting out technique (Miller *et al*, 1988; Bein *et al*, 1992). The second

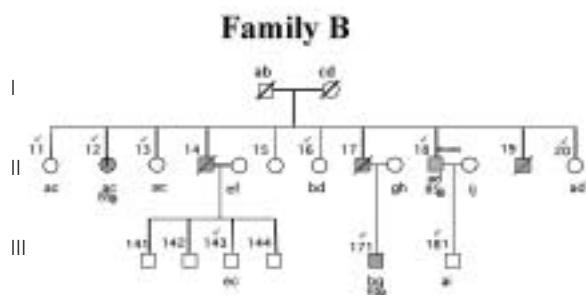


Fig 2—A pedigree of one Near Sudden Unexplained Death Syndrome (NSUDS, No.18) and three presumptive Unexplained Death Syndrome (PSUDS, No. 14,17,19) victim (family B). Circles indicate females; squares males; open symbol, unaffected status; closed symbol, NSUDS; stippled, positive Brugada sign; stippled with slash; PSUDS; a, b, c, d, e, f, g, h, i and j are letters coded for the HLA-DR-DQB haplotypes:

a = HLA-DRB1\*12021, DRB3\*0301, DQB1\*0502(R8-Q2)  
 b = HLA-DRB1\*09012, DRB4\*0101/03/04/05, DQB1\*03032/033(R15-Q7)

c = HLA-DRB1\*140, DRB3\*0207, DQB1\*05031(R11-Q3)

d = HLA-DRB1\*1502/08, DRB5\*0102/08 N, DQB1\*0502(R2-Q2)

e = HLA-DRB1\*1502/08, DRB5\*0102/08N, DQB1\*0501(R2-Q1)

f = -

g = HLA-DRB1\*1501/09, DRB5\*01011, DQB1\*06011/013(R1-Q4)

i = HLA-DRB1\*0301/06/18, DRB3\*0202/10/12-15, DQB1\*0201/02(R4-Q5)

✓ = studied cases

exon of the DRB and DQB locus were amplified and tested by PCR-SSO (Saiki *et al*, 1985, 1988; Millus and Faloon, 1987; Buyse *et al*, 1993). For DRB typing, the reaction mixture included a set of primer DRB1+3+4+5, 86G, 86V and DRB1 using a high resolution kit (INNO-LiPA HLA-DRB decoder amplification, Abbott Laboratories). Fifty nanograms genomic DNA and PCR reagents were placed in a Perkin Elmer 480 thermal cycler at 95°C for 5 minutes, and 95, 58 and 72°C for 20, 30, and 30 seconds, respectively, and for 35 cycles at 72°C for 10 minutes each cycle. The quality of the amplified products was checked by 2% agarose gel electrophoresis. After allelic amplification, hybridization against 62 sequence-specific oligonucleotide probes (SSOP) was performed. The probe-bound am-

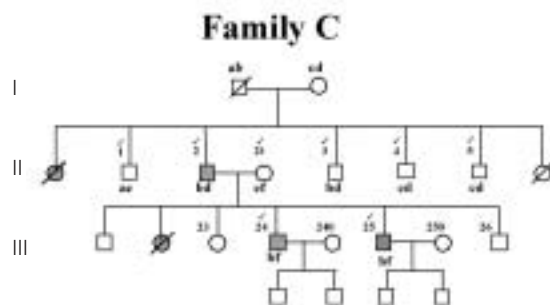


Fig 3—A pedigree of Sudden Unexplained Death Syndrome (SUDS) victim (family C). Circles indicate females; squares males; open symbol, negative Brugada Sign (BS); open symbol with slash; death of unknown or other causes, not presumptive SUDS (PSUDS); stippled, positive BS (No. 2, 24); stippled with slash, PSUDS; closed symbol = NSUDS (No. 25, BS positive); a, b, c, d, e and f are letters coded for the HLA-DRB-DQB1 haplotypes:

a = HLA-DRB1\*1502/08, DRB5\*0102/03/08N, DQB1\*0501(R2-Q1)

b = HLA-DRB1\*12021, DRB3\*0202/10/12-15, DQB1\*0301/09(R8-Q6)

c = HLA-DRB1\*0405/29/30, DRB4\*0101/02-05,0201N, DQB1\*0401(R5-Q8)

d = HLA-DRB1\*09012, DRB4\*0101/02-05 0201N, DQB1\*03032/033(R15-Q7)

e = The same as (a)

f = HLA-DRB1\*1404, DRB3\*01011/014/04, DQB1\*05031(R11-Q3)

✓ = studied cases

plified products were detected by color formation (Saiki *et al*, 1989) which were positive on the HLA-DRB decoder strips. The DRB types were obtained from the LiPA-HLA-DRB decoder typing table or the LiPA-Expert-HLA-DRB, DQ, DP interpretation software program. For the DQB1, the reaction mixture, including DQB1 primers (DynaL RELI™ SSO HLA-DQB1 from Dynal Biotech, UK), 200 ng genomic DNA and PCR reagent mixture, were incubated in a Perkin-Elmer 480 thermo cycler at 95°C for 5 minutes, and at 95, 60, and 72°C for 45 minutes, 60 seconds and 60 seconds, respectively for 35 cycles, and 72°C for 5 minutes for one cycle. After allelic amplification, hybridization against 24 sequence-specific oligonucleotide (SSO) probes was performed and typing was assigned by

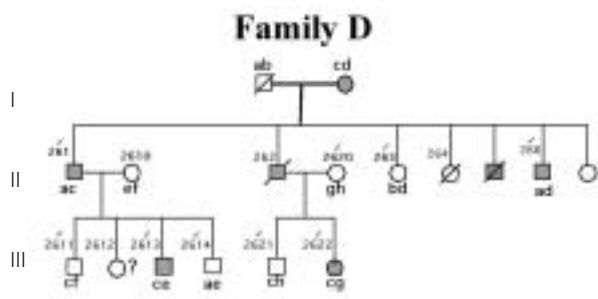


Fig 4—A pedigree of Sudden Unexplained Death Syndrome (SUDS) victim (Family D). Circles indicate females; squares males; open symbol, negative Brugada Sign open symbol with slash; death of unknown or other causes not presumptive SUDS (PSUDS); open symbol with question mark, ECG data not available; stippled, positive Brugada Sign (No. 261, 266, 2613, 2622); a, b, c, d, e, f, g and h are letters coded for the HLA-DRB-DQB1 haplotypes:

- a = HLA-DRB1\*12021, DRB3\*0202/10/12-15, DQB1\*0502(R8-Q2)
- b = HLA-DRB1\*1307, DRB3\*0202/10/12-15, DQB1\*0301/09(R9-Q6)
- c = HLA-DRB1\*0301/06/18, DRB3\*0202/10/12-15, DQB1\*0201/02(R4-Q5)
- d = HLA-DRB1\*1502/08, DRB5\*0101/05/09, DQB1\*0501(R2-Q1)
- e = HLA-DRB1\*1401/26/39, DRB3\*0301, DQB1\*05031 (R10-Q3)
- f = HLA-DRB1\*1404, DRB3\*01011/014/04, DQB1\*05031(R11-Q3)
- g = The same as C
- h = HLA-DRB1\*1401/26/39, DRB3\*0202/10/12-15, DQB1\*0502(R10-Q2)
- ✓ = studied cases

reading the pattern on the HLA-DQB1 typing strip to determine the positive HLA-DQB1-alleles of the DNA samples. This analysis can be done manually using the HLA-DQB1 overlying the score sheet and interpretation table, or the Dgnal RELI™ SSO pattern-matching software program.

**Statistical analysis**

Allelic frequencies and haplotype associations were estimated by direct counting. Data were analyzed statistically using the chi-square test and Fisher's exact test. The p-values were corrected by Yates' correction. The relative risks

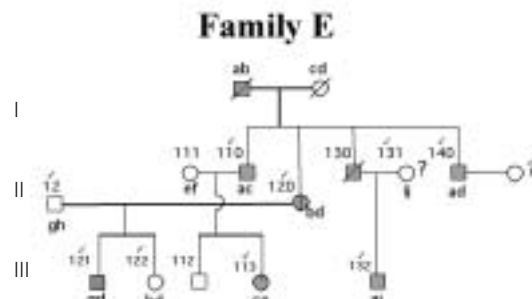


Fig 5—A pedigree of Sudden Unexplained Death Syndrome (SUDS) Victim (family E). Circles indicate females; squares; males; open symbol, negative Brugada Sign. Open symbol with slash, death of unknown or other causes; not presumptive SUDS (PSUDS), open symbol with question mark, ECG data not available/stippled; positive Brugada Sign (No 110, 120, 140, 132, 113), closed symbol; NSUDS (No. 121); a, b, c, d, e, f, g, h, i, j, are letters coded for the HLA-DRB-DQB1 haplotypes:

- a = HLA-DRB1\*12021, DRB3\*0301, DQB1\*0301/09(R8-Q6)
- b = HLA-DRB1\*1501/09, DRB5\*01011/09, DQB1\*0502(R1-Q2)
- c = HLA-DRB\*0701/03/04, DRB4\*0101/04/05,0201N, DQB1\*0201/02(R13-Q5)
- d = HLA-DRB1\*0801/16, DQB1\*06011/013(R14-Q4)
- e = HLA-DRB1\*1101/24/39, DRB3\*0202/10/12-15, DQB1\*0301/09(R7-Q6)
- f = -
- g = the same as a
- h = HLA-DRB1\*1422, DRB3\*0202/10/12-15, DQB1\*06011/013(R12-Q4)
- i = HLA-DRB1\*0701/03/04, DQB1\*0301/09(R13-Q6)
- ✓ = studied cases

(RR) or odds ratios were determined according to the Woolf method (Woolf, 1995).

**RESULTS**

Fifteen HLA-DRB1 alleles, 8 HLA-DQB1 alleles and 21 HLA-DRB1-DQB1 haplotypes were detected in our series (Tables 2, 3). Of the 15 detectable HLA-DRB1 alleles, HLA-DRB1\*12021 was the most common type in the BS-positive cases. This was significantly different from the controls (BS-negative cases) (p=0.02). For the HLA-DQB1, the most common type was HLA-DQB1\*0301/09 (33.3%), but this was not sig-

nificantly different from the control group. Twenty-one HLA-DRB1-DQB1 haplotypes were observed in these 5 Thai families with SUDS. Two interesting patterns of HLA-DRB1-DQB1 were shared in 2/5 Thai SUDS families; HLA-DRB1\*12021-DQB1\*0502 was found in 2/3 of BS-positive members in family B (12,20) and 2/4 members in family D (261,266); HLA-DRB1\*12021-DQB1\*0301/09 was found in all 3 BS-positive members in family C (2,24,25) and 4/6 of BS-positive members in family E (110,140,121,132). It is noteworthy that a combination of the two alleles (HLA-DRB1\* 12021-DQB1\*0301/09 haplotype) can clearly discriminate between the two groups, since this haplotype gave an odds ratio of up to 7.95, higher than in persons without BS. The HLA-DRB1\* 12021-DQB1\*0301/09 was the susceptible haplotype in the BS-positive cases (OR=7.95, p-value=0.010).

In conclusion, the HLA-DRB1\*12021 allele and the HLA-DRB1\*12021-DQB1\* 0301/09 haplotype have significant associations with BS-

positive or arrhythmogenic markers that identify a high risk group for SUDS, as summarized in Table 4. Specifically, the frequencies of HLA-DRB1\*12021 and HLA-DRB1\*12021-DQB1\*0301/09 haplotypes were significantly increased in BS-positive cases, with p-values of 0.02 and 0.01, respectively.

## DISCUSSION

In the present study, 15 HLA-DRB1 alleles and 8 HLA-DQB1 alleles were detected in Thai SUDS families. The analysis included 18 members (14 males, 4 females) with Brugada signs (BS-positive) and 27 controls (12 males, 15 females) without BS (BS-negative). The HLA-DRB1\*12021 allele was the most frequently observed in cases compared to the controls, with a significant difference. It was distributed in 4 of 5 Thai SUDS (Lai-Tai) families. The HLA-DQB1 allele failed to reach a significant difference when compared to the control, although one type (DQB1\*0301/09) was relatively frequent in BS-

Table 1  
Family codes, members and number of BS-positive and -negative subjects in 5 Thai SUDS families.

Family codes	Codes for family members	Total	No. BS-positive	No. BS-negative	Other
A	(21, 23, 26, 27, 29, 220) (F) 25 (M), 222 (M) (223, 224, 225) (F) (9 Females, 2 Males)	11	2 (25, 223)	9	NSUDS = 1 (No. 25) PSUDS = 1 (No. 22)
B	(11, 12, 13, 16, 20) (F) 18 (M) (143, 171, 181) (M) (5 Females, 4 Males)	9	3 (12, 18, 171)	6	NSUDS = 1 (No. 18) PSUDS = 3 (No. 14, 17, 19)
C	(1, 2, 3, 4, 5) (M), 20 (F) (24, 25) (M) (1 Female, 7 Males)	8	3 (2, 24, 25)	5	NSUDS = 1 (No.25)
D	(261, 266) (M), (263, 2620) (F) (2611, 2613, 2614, 2621) (M) (2622) (F) (3 Females, 6 Males)	9	4 (261, 266, 2613, 2622)	5	PSUDS = 1 (No. 262)
E	(110, 140) (M), 120 (F), (12, 121, 132) (M) (113, 122) (F) (3 Females, 5 Males)	8	6 (110, 120, 140, 121, 113, 132)	2	PSUDS = 1 (No. 130) NSUDS = 1 (No. 121)
A+B+C+D+E	21 Females, 24 Males	45	18 (5 F, 13 M)	27 (16 F,11M)	

Table 2  
Frequencies of HLA-DRB1, DQB1 alleles in BS-positive cases and controls (BS-negative).

HLA alleles	Allelic code	BS +ve cases N = 18 (%)	Controls (BS -ve) n = 27 (%)	OR	p-value
DRB1* 1501/09	R1	3	3		
DRB1* 1502/08	R2	2	8		
DRB1* 1504	R3	1	3		
DRB1* 0301/06/18	R4	4	4		
DRB1* 0405/29/30	R5	0	3		
DRB1* 1101/04	R6	0	3		
DRB1* 1101/24/39	R7	1	0		
DRB1* 12021	R8	11 (61.1)	7 (25.9)	4.5	0.02
DRB1* 1307	R9	0	1		
DRB1* 1401/26/39	R10	1	3		
DRB1* 1404	R11	3	5		
DRB1* 1422	R12	0	2		
DRB1* 0701/03/04	R13	4 (22.2)	2 (7.4)	3.6	0.16
DRB1* 0801/16	R14	3 (16.7)	1 (3.7)	5.2	0.14
DRB1* 09012	R15	3 (16.7)	9 (33.3)		
DQB1* 0501	Q1	1	4		
DQB1* 0502	Q2	6	9		
DQB1* 05031	Q3	4	6		
DQB1* 06011/013	Q4	6	11		
DQB1* 0201/02	Q5	7 (38.9)	6 (22.2)	2.2	0.44
DQB1* 0301/09	Q6	9 (50)	6 (22.2)	3.3	0.10
DQB1* 03032/033	Q7	3	9		
DQB1* 0401	Q8	0	3		

positive cases. The extended analysis of the HLA-DRB1\* 12021-DQB1\*0301/09 haplotype revealed this combination in 7 of 18 BS-positive cases, and showed a significant association with BS, a characteristic of high risk.

The Thai SUDS or Lai-Tai families were of autosomal dominant inheritance. The ratio of BS-positive males to females in this study was 2.6:1, which is similar to the ratio for the HLA-DRB1\*12021 positive alleles in males and females. The combined HLA-DRB1\*12021-DQB1\*0301/09 haplotype was observed only in BS males and accounted for 38.9% of all BS-positive cases.

We believe the SUDS-associated haplotypes can be inherited from a presumptive SUDS (PSUDS) father, persons carrying these haplotypes are susceptible to the syndrome. For instance, one PSUDS in family A (No 22, Fig 1) possessed HLA-DRB1\*1501/09-DQB1\*06011/

013 and HLA-DRB1\*09012-DQB1\*03032/033 haplotype, and passed them to his four children. PSUDS No.17 in family B carried HLA-DRB1\*09012-DQB1\*03032/033 haplotype and passed it to his child, No. 171. Child No. 171 received the maternal haplotype, HLA-DRB1\* 1501/09-DQB1\* 06011/013. Child No.171 carried the same HLA-DRB1-DQB1 haplotype as PSUDS No. 22. Interestingly, this observation suggests the possibility of a common ancestor in these two families, and may imply a founder effect of SUDS in the community. In addition, No. 171 carried the BS phenotype, which is prone to be Lai-Tai.

Although an ECG was not available for PSUDS No. 22, he had some symptoms compatible with SUDS: age 20-50 years, event taking place during sleep or a short nap, victims known to be healthy until immediately before the event, difficulty breathing, difficulty waking or

Table 3

Comparison of HLA-DRB1-DQB1 haplotype in BS-positive cases and controls (BS-negative cases).

HLA-DRB1-DQB1 haplotype	Haplotype code	BS- positive cases N = 18 (%)	BS- negative cases N = 27 (%)	OR	p-value
DRB1*1501/09-DQB1*06011/013	R1-Q4	2 (11.1)	3 (11.1)		
DRB1*1501/09-DQB1*0502	R1-Q2	1 (5.5)	0		
DRB1*1502/08-DQB1*0501	R2-Q1	1 (5.5)	4 (14.8)		
DRB1*1502/08-DQB1*0502	R2-Q2	1 (5.5)	2 (7.4)		
DRB1*1502/08-DQB1*06011/013	R2-Q4	0	2 (7.4)		
DRB1*1504-DQB1*06011/013	R3-Q4	1 (5.5)	3 (11.1)		
DRB1*0301/06/08-DQB1*0201/02	R4-Q5	4 (22.2)	4 (14.8)		
DRB1*0405/29/30-DQB1*0401	R5-Q8	0	3 (11.1)		
DRB1*1101/04-DQB1*0301/09	R6-Q6	0	3 (11.1)		
DRB1*1101/24/39-DQB1*0301/09	R7-Q6	1 (5.5)	0		
DRB1*12021-DQB1*0502	R8-Q2	4 (22.2)	5 (18.5)		
DRB1*12021-DQB1*0301/09	R8-Q6	7 (38.9)	2 (7.4)	7.95	0.01
DRB1*1307-DQB1*0301/09	R9-Q6	0	1 (3.7)		
DRB1*1401/26/39-DQB1*0502	R10-Q2	0	2 (7.4)		
DRB1*1401/26/39-DQB1*05031	R10-Q3	1 (5.5)	1 (3.7)		
DRB1*1404-DQB1*05031	R11-Q3	3 (16.6)	5 (18.5)		
DRB1*1422-DQB1*06011/013	R12-Q4	0	3 (11.1)		
DRB1*0701/03/04-DQB1*0201/02	R13-Q5	3 (16.6)	2 (7.4)		
DRB1*0701/03/04-DQB1*0301/09	R13-Q6	1 (5.5)	0		
DRB1*0801/16-DQB1*06011/013	R14-Q4	3 (16.6)	1 (3.7)		
DRB1*09012-DQB1*03032/033	R15-Q7	3 (16.6)	9 (33.3)		

Table 4

Allelic and haplotypic association with BS-positive cases.

HLA	BS-positive n = 18 (%)	BS-negative n = 27 (%)	OR	p-value
Allelic				
HLA-DRB1* 12021	11 (61.1)	7		
Haplotypic association		(25.9)	4.5	0.02
HLA-DRB1* 12021-DQB1* 0301/09	7 (38.9)	2 (7.4)	7.95	0.01

death. Factors other than genetic that may be involved are environmental factors, psychological factors (stress due to socioeconomic problems) and potassium deficiency, which may trigger malignant ventricular arrhythmias and cause sudden death. Since BS is common in SUDS or NSUDS, it represents an arrhythmogenic marker that clinically identifies patients at risk for Sudden Death Syndrome.

In our preliminary study, HLA-DRB1\*09012-DQB1\*03032/033 and HLA-DRB1\*12021-DQB1\*0502 seemed to be susceptible risk

haplotypes. However, after all of the 5 Lai-Tai families were investigated, the SUDS associated haplotype was demonstrated as HLA-DRB1\*12021-DQB1\*0301/09. We found that HLA-DRB1\*12021 was a moderate risk allele with an odds ratio of 4.5. The combined HLA-DRB1\*12021-DQB1\*0301/09 haplotype discriminates a high risk for SUDS from a lower risk and non-risk group (OR=7.95, p=0.010).

Haplotype HLA-DRB1\*12021-DQB1\*0301/09 is a HLA-type SUDS associate which has not been previously reported. Accumulating evi-



dence indicates that Lai-Tai is a multifactorial disorder. Multiple genes may participate in a single individual, triggered by environmental factors. Mutation of R367H and A735V of the SCN5A gene (the gene that controls the cardiac sodium channel kinetics) in Lai-Tai has been reported (Vatta *et al*, 2000). There may be other candidate genes for SUDS, such as genes for other potassium and calcium current in the action potential, such as *Ica*, *Ikr*, etc. In this study, the HLA-DRB1\*12021 allele, and the HLA-DRB1\*12021-DQB1\*0310/09 haplotype are SUDS-associated HLA types. Further molecular-genetic investigations should improve our understanding of this syndrome and lead to accurate identification of those at high risk for SUDS.

#### ACKNOWLEDGEMENTS

This study was supported by a grant from the Department of Medical Services, Ministry of Public Health. The authors are grateful to Phon Sawan Community Hospital, Tha Uthen Community Hospital, Pla Pak Community Hospital, Nakhon Phanom Province and the director of Sawang Daen Din Community Hospital, Sakon Nakhon Province for their assistance in investigating the family members. The authors are also indebted to the Thai SUDS (Lai-Tai) families. Special thanks also to Assoc Prof Virapong Prachayasittikul, for his valuable suggestions for the project.

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