Haplotype Analysis of Genetic Polymorphism in Antisocial Alcoholism

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Background: *A number of studies have reported a possible association between Monoamine oxidase A (MAOA) polymorphisms and alcoholism. MAOA dysfunction appears to be related to a subtype of alcoholism with antisocial impulsive features (type 2: antisocial alcoholism). Functional polymorphisms in the MAOA gene are believed to be good candidates to consider in the inter-individual differences that exist in the susceptibility to alcoholism and/or antisocial personality.*
Objective: *To examine the association between alcoholism and the allele state of 1) 30-bp repeat polymorphism in the promoter region, 2) 941T > G polymorphism in exon 8, and 3) 1460C > T polymorphism in exon 14 of the MAOA gene.*
Material and Method: *Genomic DNA was extracted from venous blood samples of 251 alcoholic subjects and 77 healthy controls. The alcoholic subjects were divided into two groups, type 1 (n = 125) and type 2 (n = 126). All of the subjects were unrelated males of Thai, Thai/Chinese, or Chinese descent.*
Results: *There was no significant difference in the allele frequencies or haplotype distribution between type 1, type 2 antisocial alcoholism, and healthy controls.*
Conclusion: *We are still unable to conclude the association between genetic variation of MAOA locus and antisocial alcoholism in Thai males according to under prevalent condition of the sample size and allele frequency.*

Keywords: *Antisocial alcoholism, MAOA genotyping, Polymorphisms, Alleles, Haplotypes*

J Med Assoc Thai 2017; 100 (6): 679-85
Full text. e-Journal: *http://www.jmatonline.com*

Alcoholism is a multifactorial neuropsychiatric disorder, governed by the combination of genetic, psychological, and social factors[1,2]. The dysfunction of serotonergic neurotransmission system has long been implicated in pathogenesis of alcoholism[3-5]. Among types of alcoholism, type 2 alcoholism patients usually are more severe, which alcohol abuse often begins early in life, and often associate with aggression, are stronger link to genetics and have been found with serotonin deficits. Mutations occurring in the genes in serotonergic pathway might contribute towards the predisposing of alcoholism[6,7]. A mitochondrial enzyme, monoamine oxidase (MAO), plays an important role in the degradation of neurotransmitter amines, including the key neurotransmitters serotonin (5-HT), norepinephrine (NE), and dopamine (DA)[8]. Two MAO genes, monoamine oxidases A and B (*MAOA* and *MAOB*), which are localized in the chromosome region Xp11 control the MAO activity[9]. Decreased levels of platelet MAO activity have been proposed as a marker for predisposition to alcoholism especially type 2 alcoholics[10,11]. In addition, a deficiency in *MAOA* has been associated with aggressive behavior in knockout mice and Dutch men[12,13].

One variant that has been considered associating the susceptibility to antisocial and alcoholism is a 30-bp repeat polymorphism in the *MAOA* gene promoter[14,15]. Additionally, the 941T > G polymorphism in exon 8 (rs1799835) and 1460C > T polymorphism in exon 14 (rs1137070) of the *MAOA* gene have been reported possible role in susceptibility to alcoholism associated with antisocial personality[16]. The association of *MAOA* polymorphism and alcoholism behavior has controversial results[17-25]. In the brain, *MAOB* is expressed in the glia and in serotonergic neurons, whereas *MAOA* predominates in all other neurons[26]. Acetyl- and Butyryl-choline Esterases and *MAOA*/*B* are reported to be targets for Multi-Target Designed Ligands[26]. It was mentioned, that epigenetics may affect *MAOA* activity in alcohol dependence[23]. The expression of *MAOA* is sensitive to adult alcohol

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consumption in outbred rats and the molecular involvement of *MAOA* susceptibility to alcohol and early life stress was proposed[27].

The present study aimed to study genetic variation of *MAOA* polymorphism in antisocial alcoholism individuals.

Objective

The objective of the current research was to evaluate the association of genetic variations in the promoter region, exon 8, and exon 14 of *MAOA* gene and antisocial alcoholism.

Material and Method

Subjects

The study protocol was approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University. Written informed consents were obtained from all participants before the start of the study. All subjects were unrelated males of Thai, Thai/Chinese, or Chinese descent.

Control subjects

Male control subjects (n = 77) age more than 18 years old, were passed the screening criteria using the Alcohol Use Disorder Identification Test (AUDIT) (<8) and the Tridimensional Personality Questionnaire (TPQ).

Alcohol-dependent subjects

The present study included 251 alcoholic males, passing the screening criteria using AUDIT (>8), the Mini-International Neuropsychiatric Interview (MINI) (type 1 and type 2), and TPQ. The alcoholic cases then divided into 2 groups: type 1, the alcoholics who started to drink alcohol ≥25 years of age and had no antisocial behavior (n = 125). Type 2 was the alcoholics who started to drink alcohol <25 years of age and had antisocial behavior (n = 126).

DNA analysis

Genomic DNA was extracted from anti-coagulated venous blood samples using a commercial kit, High Pure PCR Template Preparation Kit (Roche, Germany). The *MAOA* 30-bp repeat promoter was amplified by polymerase chain reaction (PCR) with oligonucleotide primers, forward primer FAM-5'-CCCAGGCTGCTCCAGAAAC-3' and reverse primer 5'-GGACCTGGGCAGTTGTGC-3'. Thermal cycling conditions were initial denaturation at 95°C for 10 minutes, followed by 30 cycles of 1 second at 94°C, 1 second at 60°C, 1 minute at 72°C, a final elongation step for 10 minutes at 72°C, and hold at 4°C[15]. Amplification products were separated by ABI Prism 310 Genetic Analyzer (Applied Biosystems, USA).

For exon 8 and exon 14 of *MAOA* gene, the point mutation study was performed using PCR amplification followed by amplicon cutting with restriction enzymes; *Fnu*4HI and *Eco*RV to detect mutation in exon 8 and 14 respectively. *MAOA* exon 8 was amplified using forward primer 5'-GACCTT GACTGCCAAGAT-3' and reverse primer 5'-CTTC TTCTTCCAGAAGGCC-3'[28]. *MAOA* exon 14 was amplified using forward primer 5'-GAAAGCCCAG GCTCTCTC-3' and reverse primer 5'-ATAGTGCCCA GAGTCACCAA-3'[29]. The thermal cycler conditions of these exons were initial denaturation at 95°C for 10 minutes, followed by 30 cycles of 1 second at 94°C, 1 second at 60°C, 1 minute at 72°C, and hold at 4°C.

Data analysis

The frequencies of the alleles, genotypes, and haplotypes at *MAOA* gene were observed and counted directly.

Chi-square was employed to identify any association between alcoholism and either the independent polymorphisms at *MAOA* gene promoter or exon 8 or exon 14 regions. A probability (*p*-value) <0.5 was considered statistically significant.

The haplotype and linkage disequilibrium were calculated using the computer program.

Results

In present study, we recruited 251 alcoholics and 77 normal controls. All subjects were male, because they were hemizygous. The allele and genotype frequencies of polymorphisms in *MAOA* gene in normal controls, type 1, and type 2 alcoholics were presented in Table 1.

Specifically for *MAOA* regulatory polymorphism study in the promoter region, genomic DNA was amplified in vitro, 3 alleles of 30-bp repeat polymorphism were detected for 3, 4, and 5 repeated polymorphisms. Three repeated polymorphisms of *MAOA* promoter in normal control, type 1, and type 2 cases were 54.5%, 53.6%, and 51.6%, respectively. Four repeated polymorphisms of *MAOA* promoter in normal control, type 1, and type 2 cases were 45.5%, 45.6%, and 48.8%, respectively. Five repeated polymorphisms of *MAOA* promoter was detected only in type 1 case (0.8%). The difference in the repeat polymorphism frequencies between type of alcoholics

Table 1. Distribution of allele frequencies of *MAOA* polymorphisms in type 1, type 2 alcoholics, and normal controls

Group	Allele (frequency)							Total
	Promoter repeat*			T941G**		C1460T***		
	3-repeat	4-repeat	5-repeat	1	2	1	2	
Type 1 alcoholics	67 (0.536)	57 (0.456)	1 (0.008)	57 (0.456)	68 (0.544)	58 (0.464)	67 (0.536)	125
Type 2 alcoholics	65 (0.516)	61 (0.484)	0 (0.000)	59 (0.468)	67 (0.532)	56 (0.444)	70 (0.556)	126
Normal control	42 (0.545)	35 (0.455)	0 (0.000)	40 (0.519)	37 (0.481)	39 (0.506)	38 (0.494)	77

* Comparisons of genotype frequencies between type 1 alcoholics and normal control: X^2-test = 0.62, df = 2, p = 0.73; between type 2 alcoholics and normal control: X^2-test = 0.17, df = 1, p = 0.68; between type 1 alcoholics and type 2 alcoholics: X^2-test = 1.16, df = 2, p = 0.56

** Comparisons of genotype frequencies between type 1 alcoholics and normal control: X^2-test = 0.77, df = 1, p = 0.38; between type 2 alcoholics and normal control: X^2-test = 0.50, df = 1, p = 0.48; between type 1 alcoholics and type 2 alcoholics: X^2-test = 0.04, df = 2, p = 0.85

*** Comparisons of genotype frequencies between type 1 alcoholics and normal control: X^2-test = 0.34, df = 1, p = 0.56; between type 2 alcoholics and normal control: X^2-test = 0.74, df = 1, p = 0.39; between type 1 alcoholics and type 2 alcoholics: X^2-test = 0.10, df = 1, p = 0.76

and between alcoholics and controls were non-significant. For exons 8 and 14 of *MAOA* gene, the point mutation study was performed using PCR and amplicon cutting of exons 8 and 14 with *Fnu*4HI and *Eco*RV, respectively (Fig. 1, 2). Comparison of allele frequency for T941G polymorphism between type 1 alcoholics and controls (p = 0.38), type 2 alcoholics and controls (p = 0.48), type 1 and type 2 alcoholics (p = 0.85) were non-significant. The T allele was a slightly more frequent in controls group (51.9%) compared to alcoholics (46.2%). Comparison of allele frequency for C1460T polymorphism between type 1 alcoholics and controls (p = 0.56), type 2 alcoholics and controls (p = 0.39), type 1 and type 2 alcoholics (p = 0.76) were also non-significant. Similarly, the wild type C allele was a slightly more frequent in controls group (50.6%) when compared to alcoholics (45.4%).

Comparisons of allele and genotype frequencies of three polymorphisms were non-significant between type 1, type 2 alcoholics, and control groups.

Table 2-4 presented the haplotypes frequencies of three polymorphic markers in type 1, type 2 alcoholics, and normal controls.

In our alcoholics and healthy control samples, 9 haplotypes were detected using three polymorphism sites. Two of nine haplotypes were more common and represented in all alcoholics, type 2 alcoholics, and healthy controls. We compared overall haplotypes frequency distribution between type 1 alcoholics and controls (X^2 = 6.73, p = 0.57), type 2 alcoholics and controls (X^2 = 8.54, p = 0.20) and type 1 and type 2 alcoholics (X^2 = 6.44, p = 0.60), which no significant difference in haplotype frequency was found (Table 5).

Discussion

Alcoholism is a complex heterogeneous disorder. While social and environmental factors are relevant to alcoholism, many studies have shown that there is a major genetic component, suggesting a heritability of at least half of the cases[30,31]. The polymorphic variation in *MAOA* gene including

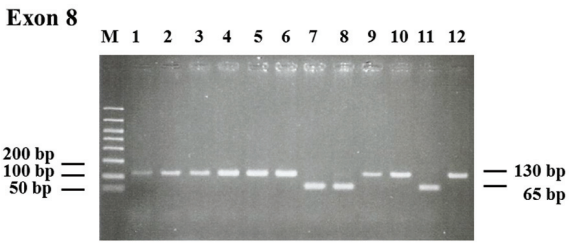

Fig. 1 T941G polymorphism is detected by gel electrophoresis after Fnu4HI digestion. Lane M ladder marker; lane 1-6, 9, 10, 12 wild type alleles; lane 7, 8, 11 mutant alleles.

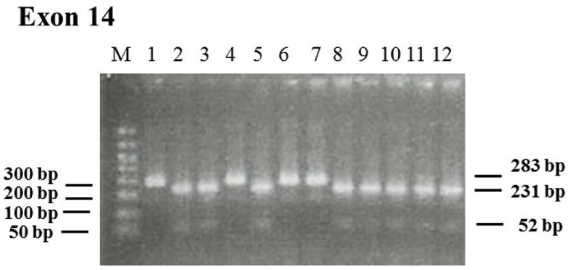

Fig. 2 C1460T polymorphism is detected by gel electrophoresis after EcoRV digestion Lane M ladder marker; lane 1, 4, 6, 7 wild type alleles; lane: 2, 3, 5, 8-12 mutant alleles.

Table 2. Haplogroup distribution of 3 markers in healthy control males

Haplogroup	Type of polymorphisms			n	Frequency (x)	% frequency (x)	X^2	X^3
	Promoter	T941G	C1460T					
H1	3	1	1	6	0.0779	7.7922	0.0061	0.0005
H2	3	1	2	0	0.0000	0.0000	0.0000	0.0000
H3	3	2	1	0	0.0000	0.0000	0.0000	0.0000
H4	3	2	2	36	0.4675	46.7532	0.2186	0.1022
H5	4	1	1	33	0.4286	42.8571	0.1837	0.0787
H6	4	1	2	1	0.0130	1.2987	0.0002	2.1904E-06
H7	4	2	1	0	0.0000	0.0000	0.0000	0.0000
H8	4	2	2	1	0.0130	1.2987	0.0002	2.1904E-06
H9	5	1	1	0	0.0000	0.0000	0.0000	0.0000
Total				77	1.0000	100	0.4087	0.1814

Sum $(X^2)^2 = 0.167011$, 1 - sum $X^2 = 0.5913$, Haplotype diversity = 0.59911

Table 3. Haplogroup distribution of 3 markers in type 1 alcoholics

Haplogroup	Type of polymorphisms			n	Frequency (x)	% frequency (x)	X^2	X^3
	Promoter	T941G	C1460T					
H1	3	1	1	3	0.0240	2.4000	0.0006	0.00001382
H2	3	1	2	1	0.0080	0.8000	0.0001	0.00000051
H3	3	2	1	1	0.0080	0.8000	0.0001	0.00000051
H4	3	2	2	62	0.4960	49.6000	0.2460	0.12202394
H5	4	1	1	51	0.4080	40.8000	0.1665	0.06791731
H6	4	1	2	1	0.0080	0.8000	0.0001	0.00000051
H7	4	2	1	2	0.0160	1.6000	0.0003	0.00000410
H8	4	2	2	3	0.0240	2.4000	0.0006	0.00001382
H9	5	1	1	1	0.0080	0.8000	0.0001	0.00000051
Total				125	1.0000	100	0.4141	0.18997504

Sum $(X^2)^2 = 0.171515$, 1 - sum $X^2 = 0.5859$, Haplotype diversity = 0.590581

Table 4. Haplogroup distribution of 3 markers in type 2 alcoholics

Haplogroup	Type of polymorphisms			n	Frequency (x)	% frequency (x)	X^2	X^3
	Promoter	T941G	C1460T					
H1	3	1	1	2	0.0159	1.5873	0.0003	0.00000400
H2	3	1	2	0	0.0000	0.0000	0.0000	0.00000000
H3	3	2	1	2	0.0159	1.5873	0.0003	0.00000400
H4	3	2	2	61	0.4841	48.4127	0.2344	0.11346917
H5	4	1	1	51	0.4048	40.4762	0.1638	0.06631303
H6	4	1	2	6	0.0476	4.7619	0.0023	0.00010798
H7	4	2	1	1	0.0079	0.7937	0.0001	0.00000050
H8	4	2	2	3	0.0238	2.3810	0.0006	0.00001350
H9	5	1	1	0	0.0000	0.0000	0.0000	0.00000000
Total				126	1.0000	100	0.4016	0.17991218

Sum $(X^2)^2 = 0.161293$, 1 - sum $X^2 = 0.5984$, Haplotype diversity = 0.603175

Table 5. Haplotype frequency distributions of *MAOA* polymorphisms in male type 1, type 2 alcoholics, and healthy controls

Haplogroup	Controls (%)	Type 1 (%)	Type 2 (%)
H1	6 (7.8)	3 (2.4)	2 (1.6)
H2	0 (0.0)	1 (0.8)	0 (0.0)
H3	0 (0.0)	1 (0.8)	2 (1.6)
H4	36 (46.8)	62 (49.6)	61 (48.4)
H5	33 (42.9)	51 (40.8)	51 (40.5)
H6	1 (1.3)	1 (0.8)	6 (4.8)
H7	0 (0.0)	2 (1.6)	1 (0.8)
H8	1 (1.3)	3 (2.4)	3 (2.4)
H9	0 (0.0)	1 (0.8)	0 (0.0)
Total	77 (100.0)	125 (100.0)	126 (100.0)

MAOA = monoamine oxidase A
Type 1 alcoholics and controls: $X^2 = 6.73$, $p = 0.57$
Type 2 alcoholics and controls: $X^2 = 8.54$, $p = 0.20$
Type 1 and type 2 alcoholics: $X^2 = 6.44$, $p = 0.60$

promoter, exon 8, and 14 was widely used to study an association with antisocial alcoholism behavior[16,23,32,33]. The phenotypes and physiology studies evidence that the *MAOA* gene might relate to alcoholism.

Although significant association exists between alcoholics and *MAOA* polymorphisms in Euro-Americans, Taiwanese Han Chinese and German[17,18,21,22]. However, several lines of evidences reported controversial results of no association of *MAOA* polymorphism and alcoholic phenotype[19,20,25]. One report concluded that the phenotypic description of alcohol dependent disease was too complex for a simple genetic analysis[23]. These different results regarding association studies could be due to ethnic and genetically different populations, sample size as well as the tool for phenotype assessment[19,20].

A haplotype is a particular combination of allele within defined molecular region. It is suggested that haplotype analysis should provide more information than single allele variation especially for complex heterogeneous diseases. However, from the present study, we could not prove a positive or negative relationship between alcoholism, types of alcoholism and 3 known *MAOA* polymorphisms. The findings in present study agreed with several works that showed negative reports of *MAOA* gene polymorphisms and alcoholism among different ethnic groups[21,23,24]. Therefore, the genetic heterogeneity would regulate alcoholism among different ethnic background.

Conclusion

According to under prevalent condition of the sample size and allele frequency, therefore, it is still unable to conclude the association between genetic variation of *MAOA* locus and antisocial alcoholism in Thai males. Prospective analysis of a family based association would be necessary to test whether these results are consistent. Furthermore, it might be useful to examine the levels of *MAOA* activity also the metabolite levels of DA, 5-HT, and NE in blood and urine of different genetic background groups.

What is already known on this topic?

MAOA dysfunction appears to be related to a subtype of alcoholism with antisocial impulsive features. The significant association was reported between alcoholics and *MAOA* polymorphisms in Euro-Americans and Taiwanese Han Chinese.

What this study adds?

No significant difference in the allele frequencies or the haplotype distribution of promoter, exons 8 and 14 of *MAOA* gene between type 1, type 2 alcoholics and healthy controls in Thai individuals.

Acknowledgements

We would like to thank Dr. Chayapath Chayupong, Samitivej Hospital for sample collection, Dr. Teerapong Siriboonpiputtana and Miss Janpen Thanakitkosate, Department of Pathology, Faculty of Medicine Ramathibodi Hospital for performing laboratory process. This work was supported by research grant from the Faculty of Medicine Ramathibodi Hospital (FY2004).

Potential conflicts of interest

None.

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การวิเคราะห์แฮพโพลไทป์ของความหลากหลายทางพันธุกรรมในผู้ติดสุราที่มีบุคลิกภาพผิดปกติแบบต่อต้านสังคม

รณชัย คงสกล, นวลกันยา สถิรพงษะสุทธิ, บุษบา ฤกษ์อำนวยโชค

ภูมิหลัง: *การศึกษาจำนวนมากรายงานเกี่ยวกับความสัมพันธ์ที่อาจเป็นไปได้ระหว่างความหลากหลายของจีนโมโนเอมีนออกซิเดส เอ (MAOA) กับสภาวะการติดสุรา การทำงานที่ผิดปกติของจีน MAOA มีความสัมพันธ์กับสภาวะการติดสุราชนิดย่อยของลักษณะบุคลิกภาพผิดปกติแบบต่อต้านสังคมที่มีอารมณ์วู่วาม (ชนิดที่ 2: ผู้ติดสุราที่มีบุคลิกภาพผิดปกติแบบต่อต้านสังคม) โดยเชื่อว่าความหลากหลายของการทำงานของจีน MAOA ซึ่งมีความแตกต่างกันในมนุษย์แต่ละคน เกี่ยวข้องกับการคงสภาพในความไวต่อสภาวะการติดสุรา และ/หรือ บุคลิกภาพผิดปกติแบบต่อต้านสังคม*

วัตถุประสงค์: *เป็นการตรวจสอบความเกี่ยวข้องระหว่างสภาวะการติดสุราและสภาพของแอลลีลของจีน MAOA ได้แก่ 1) ความหลากหลายของจำนวนซ้ำของดีเอ็นเอขนาด 30 คู่เบส ในบริเวณโปรโมเตอร์ 2) การเปลี่ยนแปลงเบส T เป็น G ในตำแหน่งนิวคลีโอไทด์ที่ 941 ของเอกซอนที่ 8 และ 3) การเปลี่ยนแปลงเบส C เป็น T ในนิวคลีโอไทด์ที่ 1460 ของเอกซอนที่ 14 ซึ่งเคยมีรายงานว่าสภาพของแอลลีลเหล่านี้อาจมีบทบาทต่อความไวของสภาวะการติดสุราที่สัมพันธ์กับบุคลิกภาพผิดปกติแบบต่อต้านสังคม*

วัสดุและวิธีการ: *การศึกษาครั้งนี้ได้ตัวอย่างจากผู้ติดสุราจำนวน 251 คน ซึ่งแบ่งเป็นผู้ป่วย 2 กลุ่ม คือ ชนิดที่ 1 (จำนวน 125 คน) ชนิดที่ 2 (จำนวน 126 คน) และคนปกติสุขภาพดี (จำนวน 77 คน) ตัวอย่างที่ใช้ในการศึกษานี้เป็นตัวอย่างจากชายอาสาสมัครทุกคนที่ไม่ใช่ญาติกัน มีการสืบเชื้อสายจากชาวไทย ไทย-จีน หรือ จีน*

ผลการศึกษา: *ถึงแม้ว่ามีรายงานความสัมพันธ์อย่างมีนัยสำคัญระหว่างสภาวะการติดสุรา และความหลากหลายของจีน MAO ในชาวยูโร-อเมริกัน และชาวไต้หวันเชื้อสายจีนฮั่น แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญของความถี่แอลลีลหรือการกระจายตัวของแฮพโพลไทป์ ระหว่างสภาวะการติดสุราที่สัมพันธ์กับบุคลิกภาพผิดปกติแบบต่อต้านสังคมชนิดที่ 1 และชนิดที่ 2 กับคนปกติ*

สรุป: *พบว่าไม่มีความสัมพันธ์ระหว่างความผันแปรทางพันธุกรรมของตำแหน่ง MAOA ในชายไทยที่ติดสุราซึ่งมีบุคลิกภาพผิดปกติแบบต่อต้านสังคม*