N-Acetyltransferase 2 gene polymorphism in a group of senile dementia patients in Shanghai suburb[1]

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KEY WORDS *N*-acetyltransferases 2; genotype; Alzheimer disease; polymorphism (genetics)

ABSTRACT

AIM: To investigate the possible association of hereditary polymorphism of *N*-acetyltransferase 2 (*NAT2*) gene with the susceptibility towards senile dementia in farmer population of Shanghai suburb**. METHODS:** *NAT*2 gene genotyping was performed at 7 major polymorphic loci ($G_{191}A$, $C_{282}T$, $T_{341}C$, $C_{481}T$, $G_{590}A$, $A_{803}G$, and $G_{857}A$) with a polymerase chain reaction-based restriction fragment length polymorphism based procedure in 2 groups of farmer subjects in Shanghai suburb. A group of 51 diagnosed dementia patients [comprising 29 sporadic Alzheimer disease (AD) patients and 22 sporadic vascular dementia (VD) patients] and a group of 112 healthy individuals were in the same area. **RESULTS:** The homogenous rapid genotypes (*R/R*, including**4/*4, *13 /*13*, and **4/*13*) was found over-present in both groups of patients, compared with healthy individuals, for all farmer dementia patients, 52.9 % *vs* 33.0 %, *P*=0.016, OR (95 % CI): 2.28(1.16-4.48); for AD group only, 51.7 % *vs* 33.0 %, *P*=0.063, OR (95 % CI): 2.18 (0.95-4.97); for VD group 54.5 % *vs* 33.0 %, *P*=0.055, OR (95 % CI): 2.43 (0.96-2.43). The significant frequency difference of genotype **4/*7B* between farmer dementia patients and healthy individuals, and that of solo-alleles **13*, and **7B* were observed between the healthy individuals and both groups of dementia patients. **CONCLUSION:** Our data suggest the involvement of various *NAT2* rapid-acetylating genotypes in the individual susceptibility to senile dementia. Variant genotypes of *NAT2* might serve as a hereditary risk factor for AD and VD in Chinese population.

INTRODUCTION

The involvement of susceptibility factors in the individual risk to senile dementia has been explored by molecular epidemiological approaches. A variety of genetic factors were identified in different forms of Alzheimer's disease (AD). The rare cases of the early onset familial forms of the disease are linked to 3 different genetic defects found on loci 1q32.1 and 14q24.3, which code for presenlin 2 (PS-2) and presenlin 1 (PS-1), respectively. Locus 21q21.2 codes the amyloid precursor protein (APP). Another gene at locus 19q13.2 codes for apolipoprotein E (ApoE), a protein involved in cholesterol transport and metabolism, which is believed to play a part in the more common late-onset cases. The presence of polymorphic form *ApoE4* seems to increase the deposition of amyloid-protein in the brain and may also increase the number of neurofibrillary

[1] Project supported by the State Key Basic Research and Development Programme of China (973, No 2002CB512900) and German Federal Ministry of Education and Research (BMBF, Project No CHN-112-99).
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Received 2003-09-27 Accepted 2004-02-23

tangles. The single nucleotide polymorphism of the *ApoE* gene was also analyzed in 32 Chinese AD cases and 26 controls, the polymorphism of *ApoE* gene $C_{462}G$ was found associated with AD risk ($P<0.05$)[1].

The genetic polymorphism of xenobiotic-metabolizing enzymes and other genes have also been investigated and taken as hereditary susceptibility factors of senile dementia[2,3]. However, few of the studies on the possible association of *N*-acetyltransferase 2 (*NAT2)* gene polymorphism with senile dementia incidence have been reported[4]. The existence of nerve cell-specific endogenous substrate of NAT2 existing in the brain has been substantiated, and that the exogenous arylamines might be metabolized in ependym was also suggested[5]. It was postulated that the NAT2 activity deviation might have impact on metabolism of exogenous arylamines in the brain. However, the specific mechanism of NAT2 in the brain remains unclear so far.

NAT2 is one of the important phase II metabolism enzymes which catalyses the conjugation of xenobiotics (mainly of aromatic or heterocyclic amines and hydrazine) with activated acetyl groups. Some of the substrates have been proved as human carcinogens. A series of work suggested the genetic polymorphism of *NAT2* was related with the susceptibility towards various malignant tumors, such as bladder cancer[6], lung cancer[7], and colorectal cancer[8]. *NAT2* polymorphism also served as one of the risk-modifying factors for late-onset AD among non-ApoE epsilon 4 carriers[5]. Other work indicated that *NAT2* was a potential low-penetrance gene in AD pathogenesis, determining an individual susceptibility trait predisposing to this degenerative disease[4]. The present work aimed to verify the correlation between polymorphism of *NAT2* and the risk for senile dementia among Chinese subjects.

In addition to the wild allele *NAT2*4*, 28 point mutations have been detected so far (see http://www.louisville.edu/medschool/pharmacology/NAT2.html). The nucleotide transition or transversion at seven major *NAT2* polymorphic loci ($G_{191}A$, $C_{282}T$, $T_{341}C$, $C_{481}T$, $G_{590}A$, $A_{803}G$, and $G_{857}A$) covers majority of the amino acid substitution in peptide level, which results in the enzyme catalyzing activity changes.

MATERIALS AND METHODS

Subjects A group of senile dementia patients (n=51, including 14 males and 37 females, with an average age of 79.1±9.2, ranging from 53 to 95) in a remote rural area in Shanghai suburb was selected and a group of healthy controls (n=112, 60 males and 52 females with an average age of 65±6, ranging from 55 to 90) in the same area was included in our previous study for α-estrogen receptor (*ER-a*) and aryl hydrocarbon receptor gene (*Ahr*) polymorphism genotyping[9]. At the time of sampling, none of the individuals in the control group has ever been diagnosed to suffer from any kind of cancers, cardiovascular diseases, mental disorders, or any other serious diseases. Within the case group, 29 subjects were diagnosed as sporadic Alzheimer disease (AD), 22 subjects as sporadic non-Alzheimer dementia (non-AD) by neurological/psychiatric examination. The non-AD patients were, mostly, classified as vascular dementia (VD). The diagnosis were conducted by the participants of Shanghai Surveillance Project for Dementia in aged period (supervised by Municipal Mental Health Center of Shanghai) according to the criteria listed in DSM-IIIR (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, revised 3rd ed) and CCMD-3 (Chinese Criteria of Mental Disorders Classifying and Diagnosis, revised 3rd ed)[10]. All of subjects are ethnic Han Chinese (Chinese majority, representing 93 % of the resident population of China) and are farmers or former farmers in this area.

Blood sample collection and DNA extraction Blood samples were collected upon informed consent according to all ethic and safety provisions adopted by the Ethical Committee of District Mental Health Center in the frame of Chinese legal requirement. Blood was taken from each subject by venopuncture. Ethylene diamine tetraacetic acid (EDTA) was used as blood anticoagulant. The blood samples were stored at -80°C. Genomic DNA was extracted from blood with a standard phenol/chloroform procedure as described[11] and kept at -20 ºC for further analysis.

***NAT2* genotyping** A modified polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) procedure[12] was used to determine the mutations on nucleotides 191, 282, 341, 481, 590, 803, and 857. Two sets of primers (for PCR A: forward: 5'-GTC ACA CGA GGA AAT CAA ATG C-3', and reverse: 5'-ACC CAG CAT CGA CAA TGT AAT TCC TGC CCT CA-3'; for PCR B: forward: 5'-AAT TAC ATT GTC GAT GCT GGG T-3' and reverse: 5'-ACA CAA GGG TTT ATT TTG TTC C-3') were employed to amplify two segments in the *NAT2* gene from genomic DNA. Restriction enzymes *Msp* I, *Fok* I, *Dde* I, *Kpn* I, *Taq* I, and *Bam*H I were used to digest PCR

products to determine *NAT2* genotype. The *NAT2*13* allele has a nucleotide substitution at position 282 that does not result in the amino acid change. The genotype carriers of homozygous **4/*4* or **13/*13* were classified as rapid acetylators. Heterozygotes genotype that carried a wild-type allele **4* or **13* and one copy of other variant allele were taken as intermediate acetylators.

Statistical analysis Chi-square test was used to compare the distribution of *NAT2* genotype and single allele in AD group and VD group with control group. An odd ratio (OR) and 95 % confidence interval (95 % CI) were also calculated. Hardy-Weinberg equilibrium was used to calculate the expected heterozygote genotype frequency.

RESULTS

Population frequencies of *NAT2* genotypes in the dementia patients and in the healthy individuals Eleven genotypes, **4/*4, *4/*13, *13/*13, *4/*5B, *4/*5D, *4/*6A, *4/*7B, *5B/*6A, *6A/*6A, *6A/*7B,* and **7B /*7B*, were found in the community control group. Allele **4/*4* was the most frequent genotype (representing 31.3 % of the subjects), which was also the most dominant genotype in both groups of dementia patients (27.6 % and 40.9 % for AD and VD patients, respectively). In AD groups, 13 different kinds of *NAT2* genotype carriers were recorded as: **4/*4, *4/*13, *13/*13, *4/*6A, *4/*7B, *6A/*6A, *6A/*7B,* and **4/*7A, *4/*11, *4/*12B, *13/*6A, *6A/*11, *11/*7A*, the last 6 genotypes were missing among the healthy control group. Only 9 genotypes were found in relatively smaller group of VD dementia patients: **4/*4, *4/*13, *13/*13, *4/*6A, *4/*7A, *4/*7B, *4/*11, *13/*6A,* and **6A/*6A* (Tab 1).

The distribution of *NAT2* genotypes in community control group was in agreement with Hardy-Weinberg equilibrium, which indicated that the control group was chosen randomly (data not shown).

The distribution of variant acetylating status in all dementia patients, AD and VD groups The distribution of intermediate (heterozygous) rapid acetylators (*R/S*) and rapid (homozygous) acetylators (*R/R*) and slow acetylators (*S/S*) in dementia group were compared with community control group. The comparison showed the overrepresentation of *R/R* acetylator in all dementia patients, 52.9 % *vs* 33.0 %, OR 2.28, 95 % CI: 1.16-4.48, *P*=0.016. However the intermediate rapid acetylator (*R/S* genotype carriers) showed higher prevalence in healthy individuals than all dementia groups (54.5 % *vs* 35.3 %, OR 0.46, 95 % CI: 0.23-0.90, *P*=0.023). Furthermore, the population frequency of rapid acetylator (*R/R* genotypes) in AD and VD group displayed marginal significant differences over community control group, (OR 2.18, 95 % CI: 0.95-4.97, *P*=0.063 and OR 2.43, 95 % CI: 0.96-2.43, *P*=0.056) respectively. The presence of intermediate rapid acetylator (*R/S* genotypes) in 31.0 % of the AD group (OR 0.38, 95 % CI: 0.16-0.90, *P*= 0.025) and in 40.9 % in non-AD group (OR 0.58, 95 % CI: 0.23-1.46, *P*=0.245) was recorded (Tab 2). The prevalence of slow acetylator (*S/S* genotypes) showed no statistically significant difference between three groups of the subjects tested (data not shown).

Tab 1. The various *NAT2* genotypes represented in 3 investigated groups.

Genotype	Controls (*n*=112)	AD patients (*n*=29)	VD patients (*n*=22)
**4/ *4*	35 (31.3 %)	8 (27.6 %)	9 (40.9 %)
**4/*13*	1 (0.9 %)	5 (17.2 %)	2 (9.1 %)
**13/*13*	1 (0.9 %)	2 (6.9 %)	1 (4.5 %)
RR	37 (33.0 %)	15 (51.7 %)	12 (54.5 %)
**4/*5B*	3 (2.7 %)	0	0
**4/*5D*	1 (0.9 %)	0	0
**4/*6A*	30 (26.8 %)	4 (13.8 %)	4 (18.2 %)
**4/*7A*	0	1 (3.4 %)	1 (4.5 %)
**4/*7B*	27 (24.1 %)	1 (3.4 %)	1 (4.5 %)
**4/*11*	0	1 (3.4 %)	1 (4.5 %)
**4/*12B*	0	1 (3.4 %)	0
**13/*6A*	0	1 (3.4 %)	2 (9.1 %)
RS	61 (54.5 %)	9 (31.0 %)	9 (40.9 %)
**5B/*6A*	1 (0.9 %)	0	0
**6A/*6A*	3 (2.7 %)	2 (6.9 %)	1 (4.5 %)
**6A/*7B*	9 (8.0 %)	1 (3.4 %)	0
**6A/*11*	0	1 (3.4 %)	0
**7B/*7B*	1 (0.9 %)	0	0
**11/*7A*	0	1 (3.4 %)	0
SS	14 (12.5 %)	5 (17.2 %)	1 (4.5 %)
Total	112 (100 %)	29 (100 %)	22 (100 %)

The population frequencies of various *NAT2* genotypes distributed in healthy individuals and both groups of dementia patients The significant lower overall distribution of **4/*7B* genotype was found in both groups of the dementia patients, for AD group (OR 0.12, 95 % CI: 0.146-0.186, *P*=0.013), and for VD group (OR 0.15, 95 % CI: 0.02-1.17, *P*=0.039).

However, a higher frequency of *NAT2**4/*13 was found in both dementia groups than that in control group (Tab 3).

Various *NAT2* alleles represented in dementia patient groups and healthy group The wild-type **4* allele was the most dominant allele in all groups, with 58.9 % in control group and 50.0 % in AD group and 61.4 % in VD group, showing no statistically significant difference among three groups of the subjects. The allele of *NAT2*11* was only detected in AD and non-AD group. The allele of *NAT2*13* notably represents more in AD group (P<0.01) and in VD group (P<0.01). However, *NAT2*7B* was more frequent in community control group than in AD group (17.0 % *vs* 3.5 %) (Tab 4).

DISCUSSION

NATs can catalyze intermediate reactions leading to DNA reactive metabolites, such as *O*-acetylations of *N*-hydroxyarylamines stemming from previous P450-catalyzing-metabolism[13], and DNA damage may conduce to neuronal cell death and neuron degeneration[14, 15]. So it was possible that the polymorphism of *NAT2* might affect the individual susceptibility to AD and VD. Our data visualized the overrepresentation of rapid acetylator *R/R* genotype, including *4*/*4, 4*/*13, 13*/*13* in senile dementia patients as a whole and in either AD or VD patients, though in late cases only marginal statistic significance was reached (P=0.016, P=0.056, P=0.063, respectively). The data are in line with the frequency of rapid acetylator phenotype increased in the non-apoE epsilon 4 carriers of late-onset AD in Japanese[5]. In contrast with present study, there was no role for the polymorphism of *NAT2* in the etiology of AD in a group of 23 Caucasian AD patients[16]. The result suggests that rapid acetylator of *NAT2* is a risk factor for senile dementia in East Asian, but not a decisive factor.

No *NAT2*6/*5B* represented in senile dementia group, but only 1 case (0.9 %) appeared in control group in present study. Other work showed that *NAT2*6/*5B* completely absented in a group of 53 Portuguese AD patients, while 22.5 % represented in the control group[4]. This discrepancy might be due to the racial difference between Caucasian and East Asian. There were significant differences between Caucasian and Chinese in the distribution of variant *NAT2* genotype[17].

Subsequent analysis showed a statistically higher prevalence intermediate rapid acetylator genotypes (*R/S*) in community group than in AD group (P=0.025), however no notable difference was found, compared

Tab 2. The distribution of rapid and slow acetylators in total dementia group, AD and VD group, and compared with that of healthy group.

	R/R	*P*	OR (95 % CI)	*R/S*	*P*	OR (95 % CI)	*S/S*
Controls (n=112)	37 (33.0 %)	Ref	/	61 (54.5 %)	Ref	/	14 (12.5 %)
Total dementia patients (n=51)	27 (52.9 %)	0.016	2.28 (1.16-4.48)	18 (35.3 %)	0.023	0.46 (0.23-0.90)	6 (11.8 %)
AD (n=29)	15 (51.7 %)	0.063	2.18 (0.95-4.97)	9 (31.0 %)	0.025	0.38 (0.16-0.90)	5 (17.2 %)
VD (n=22)	12 (54.5 %)	0.056	2.43 (0.96-2.43)	9 (40.9 %)	0.245	0.58 (0.23-1.46)	1 (4.5 %)

Tab 3. The frequencies of major *NAT2* genotypes distributed in control individuals and compared with two groups of patients.

Genotype	Controls	AD group	*P* value [OR, 95 % CI]	VD group	*P* value [OR, 95 % CI]
**4/*4*	35 (31.3 %)	8 (27.6 %)	0.703 [0.84 (0.34,2.08)]	9 (40.9 %)	0.378 [1.52 (0.60,3.90)]
**4/*13*	1 (0.9 %)	5 (17.2 %)	0.0001 [23.13 (2.58,207.03)]	2 (9.1 %)	0.017 [11.1(0.96,128.78)]
**4/*6A*	30 (26.8 %)	4 (13.8 %)	0.145 [0.44 (0.14,1.36)]	4 (18.2 %)	0.397 [0.61 (0.19,1.94)]
**4/*7B*	27 (24.1 %)	1 (3.4 %)	0.013 [0.01 (0.15,0.87)]	1 (4.5 %)	0.039 [0.15 (0.02,1.17)]
**6A/*7B*	9 (8.0 %)	1 (3.4 %)	0.391 [0.41 (0.05,3.36)]	0	/
**13/*13*	1 (0.9 %)	2 (6.9 %)	/	1 (4.5 %)	/

Tab 4. The comparison of major *NAT2* allele distribution in healthy individuals and both groups of dementia patients.

Allele	Controls	AD group	P_1 value [OR, 95 % CI]	VD group	P_2 value [OR, 95 % CI]
**4*	132 (58.9 %)	29 (50.0 %)	0.221 [0.70 (0.39, 1.24)]	27 (61.4%)	0.764 [1.11 (0.57, 2.15)]
**5B*	4 (1.8 %)	0	/	0	/
**6A*	46 (20.5 %)	10 (17.2 %)	0.575 [0.81 (0.38, 1.71)]	8 (18.2 %)	0.722 [0.86 (0.37, 1.98)]
**7B*	38 (17.0 %)	2 (3.5 %)	0.009 [0.17 (0.04, 0.74)]	1 (2.3 %)	0.012 [0.11 (0.02, 0.85)]
**11*	0	3 (5.2 %)	/	1 (2.3 %)	/
**13*	3 (1.3 %)	10 (17.2 %)	<0.01 [15.35 (4.07, 57.88)]	6 (22.7 %)	0.019 [11.63 (2.79, 48.51)]

with non-AD group (P=0.245). The data postulated that the same acetylator had different effect on susceptibility to VD and AD. No significant frequency difference of total *NAT2* slow acetylator genotypes was found between AD and healthy controls in present study, which was in line with the research in Japanese[18].

It has been reported that some of the amino acid substitutions change the affinity of the NAT2 enzyme. The catalysing activity towards hazard xenobiotics is pre-determined by wide range of polymorphic alleles and their combinations. *NAT2* alleles with nucleic acid substitution *G857A* (*NAT2*7A, *7B*) expressed recombinant NAT2 allozymes with the smallest but yet significant reductions[19]. However, the catalyzing ability of *NAT2*13* was equaled to that of wild genotype *NAT2*4*[20]. It is interesting to notice that the *NAT2*7B* allele represented more in control group than AD and VD group, and besides, *NAT2*13* allele have a marked decrease in control group (Tab 3). Therefore, it is possible that *NAT2*7B* allele might serve a protective role resulting from change in expression ability. But no difference was observed about the distribution of other rapid and slow genotypes. The sample volume in present study was not sufficient for multi-stratification. It was technically impossible at the moment to further expand the sample volume in a restricted population. Further work with more samples collected from surrounding rural area would be of promising.

In conclusion, rapid acetylator contributed to develop AD and VD, and variant genotypes of *NAT2* were correlated with risk for senile dementia in Chinese.

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