Genetic Characteristics of Dementia in Taiwan

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Abstract- The most common causes of dementia in Taiwan are Alzheimer's disease (AD) followed by vascular dementia (VaD). Several genetic studies have documented an increased risk of AD among apolipoprotein E gene allele 4 (*ApoE4*) carriers in Taiwanese (ethnic Chinese). Although *ApoE4* is considered the most important risk factor for AD, the *ApoE4* allele frequency is lower in Taiwanese (around 7%), than that in most Caucasian populations (over 10%). This phenomenon raises the hypothesis that low *ApoE4* allele frequency contributes to the low prevalence of AD in Taiwanese. Other studies of the genetic impacts on modulation or regulation of manifestations, progression, and treatment response of AD in Taiwan have been inconclusive. Familial AD, which is conferred by *PS1* gene mutation has been identified. There were very few studies of fronto-temporal dementia (FTD) or dementia with Lewy body (DLB) in Taiwan. Genetic studies of VaD remain limited and only *NOTCH3* gene mutation has been detected in a Taiwanese cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) family. Limited data indicated that non- *ApoE4*-associated AD may represent a larger proportion of AD in Taiwanese, suggesting the existence of novel genetic factors which remain to be identified.

Key Words: Genetic study, Dementia, Alzheimer's disease, Vascular dementia, Taiwan

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INTRODUCTION

Dementia is a group of diseases characterized by a decline of cognitive function. Patients with dementia gradually become disabled and dependent in daily activities of life. Dementia is associated with a heavy financial burden for families, society and the economy. In Taiwan and in other countries, the problems caused by dementia are becoming more and more urgent as the life span of the population increases. Reducing the impact of dementia requires a multi-disciplinary approach. From a clinical perspective, correct diagnosis based on an understanding the underlying pathophysiological mechanisms, and the selection of optimal intervention and prevention methods are essential.

The etiology of dementia is various. In most regions of the world including Taiwan, Alzheimer disease (AD) and vascular dementia (VaD) are the two leading causes of cognitive impairment in late life. In Taiwan, AD followed by VaD is the most common cause of dementia[(1)]. There is now compelling evidence that genetic factors are involved in the pathogenesis of dementia. Genetic

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variations among individuals may also be responsible for wide differences in the response to treatment and clinical course of dementia. Thus molecular genetic studies are becoming increasingly important in the clinical diagnosis and prediction of treatment responses. Genetic studies also are providing valuable information which is helping to unravel the pathophysiology of dementia. This article reviews the literature on molecular genetic research in dementia from Taiwan.

Alzheimer disease

The characteristic pathological changes of AD include extracellular senile plaques, intraneuronal neurofibrillary tangles, neuronal and synaptic loss, and neurotransmitter deficits in the brain. The senile plaques and neurofibrillary tangles are pathologic markers for the diagnosis of AD. The pathogenesis of AD is complex and might involve both environmental and genetic factors. Genes linked to early onset, familial AD include beta-amyloid precursor protein gene (*APP*), presenilin-1 (*PS-1*) and presenilin-2 (*PS-2*). Inheritance of the ε4 allele of apolipoprotein E (*ApoE4*) confers a genetic risk for developing late-onset, sporadic AD. Besides, some genes also were found for modulating and regulating the manifestations, progression, and treatment responses of AD.

Apolipoprotein E polymorphisms in Alzheimer disease

Apolipoprotein E (*ApoE*) is one of the proteins constituents of plasma lipoproteins. It transports cholesterol and other lipids to the liver by interaction with the low-density lipoprotein (LDL) receptor on the cell surface of hepatocytes[2]. There are three isoforms of *ApoE*, designated E2, E3, and E4, which are encoded for by three different alleles, *Apo*ε2, ε3, and ε4 respectively. Among the three polymorphisms of *Apo*ε2, 3, and 4, the allele frequency of the *Apo*ε4 allele is increased in AD patients in many ethnic populations in comparison with non-AD controls, whereas *Apo*ε2 allele was considered to have potential protection against AD[3]. ApoE may contribute a final common pathway of neuronal repair and remodeling. It was speculated that ApoE3 and ApoE2 but not ApoE4 function efficiently and effectively in supporting the repair and remodeling of damaged neuronal connections[4].

In 1996, Hong et al.[5] reported the first results on allele frequencies of *ApoE* in Taiwanese with late-onset sporadic AD. Their data supported the association between *Apo*ε4 and AD[5]. Later, several other studies from Taiwan also confirmed this important finding[3,6-10]. Most studies have found a lower prevalence of AD among ethnic Chinese in comparison with Caucasian populations[1,11-13]. HC Liu and CJ Hong at Taipei Veterans General Hospital first raised the possibility that this phenomenon may be partly attributable to the low *Apoε4* allele frequency in Taiwanese population[5]. The reported *Apoε4* allele frequency in Taiwanese ranged from 4.9 to 11.0%, but was usually higher than approximately 10.0% reported in studies of Caucasian populations[5,6,13-15]. However, the small sample sizes in these studies from Taiwanese might limit their ability to accurately assess this allele frequency. The most importantly, Liu et al.[16] studied the distribution of *ApoE* alleles in a large community and found that the *ApoE4* allele frequency was 8.1%, which is lower than the frequencies reported in most studies of Caucasian populations. Their data support the hypothesis that low *ApoE4* allele frequency contributes to low prevalence of AD in Taiwanese[16]. In addition, their data might also further support an important role of ApoE in AD in Taiwanese population because *ApoE4* allele frequency affects the prevalence of AD[16]. Results from Japanese studies regarding *ApoE* allele frequency are similar to those from Taiwan[17,18] (Table 1). Lung et al.[3] studied the impact of *ApoE2* on AD and the interaction between *ApoE2* and *ApoE4* and found that inheritance of an ε2 allele significantly lowered the risk of ε4-containers for AD.

Many studies have investigated the association between *ApoE4* allele and psychiatric symptoms of dementia (BPSD) in patients with AD. Chang et al.[19] found that AD patients with *ApoE4* allele had an increased incidence of psychotic symptoms, such as delusions and hallucinations. However, Liu et al.[20] found no association between depression and *ApoE4* or

ApoE2 allele in AD. A study of the phenotype of accelerated reduction of cholinergic activity among *ApoE4* allele carriers has suggested that *ApoE4* allele is associated with the treatment response of cholinesterase inhibitors[21]. (Table 2)

A study from Japan found that *ApoE4* allele was associated with both early-onset AD and late-onset AD and that *ApoE4* allele may play a more important role in the early-onset AD than in late-onset AD[22]. The role of *ApoE4* allele has also been demonstrated in familial AD (FAD)[23]. There is still inadequate data from Taiwan to clarify the association between the polymorphisms of *ApoE*, and FAD and early-onset AD.

Genetic risk factors other than *ApoE* in Alzheimer disease

Many genes other than *ApoE* have been associated with AD. Some of these genes are associated with metabolism of amyloid β (Aβ), some with neuro-transmitters and some with inflammation or other mechanisms (Table 3-5).

Amyloid-beta (Aβ) is the most important component of senile plaques and is considered to play a crucial role in neural death in AD. Many enzymes are involved in the metabolism of Aβ, including amyloid precursor protein (APP), presenilin-1 (PS-1), beta-site APP cleaving enzyme (BACE), neprilysin (NEP)[24], and alpha-2 macroglobulin (A2M) (Table 3). BACE and PS-1 digest APP, which consists about 700 amino acids, to produce Aβ, which consists of about 40 amino acids. Extra-cellular Aβ enters the cells through as yet unknown receptors and is degraded by NEP. A2M might compete for the

Table 1. *ApoE4 allele frequencies in different populations*

Authors	Year	*ApoE4* allele frequencies	Populations	Reference
Hong et al.	1996	7.9 %	Taiwanese	5
Hu et al.	1998	7 %	Taiwanese	7
Nakayama et al.	1999	9 %	Japanese	18
Ordovas et al.	1987	13.5 %	Caucasian	14
Davignon et al.	1988	16 %	Caucasian	15
Nunomura et al.	1996	7 %	Japanese	17

Table 2. *Genetic studies of ApoE in dementia*

Alleles	Authors	Year	Cohort	Association Positive (Y) / Negative (N)	Ref
ApoE4	Hong et al.	1996	56 late-onset sporadic AD 57 controls	AD (Y)	5
ApoE4	Hu et al.	1998	55 late-onset sporadic AD 93 controls	AD (Y)	7
ApoE4	Lai et al.	2003	30 VaD patients 112 normal controls	VaD (N)	10
ApoE4	Lin et al.	2004	49 VaD patients 112 normal controls	VaD (N)	48
ApoE2	Lung et al.	2005	428 AD 807 control	AD (N/Y) Part of the protective effect of ApoE2 against AD	3
ApoE2	Lin et al.	2004	49 VaD patients 112 normal controls	VaD (Y) Protective effect	48

VaD: vascular dementia; AD: Alzheimer's disease.

receptors with Aβ. BACE is the rate-limiting enzyme in A-beta formation. Liu et al's[25] study of all of the exons of *BACE* gene by single strand conformation polymorphism (SSCP) revealed a novel polymorphism in this gene, but it showed no significant association with the occurrence of AD. The *PS-1* gene is one of the genetic loci linked to early onset familial AD. Two previous studies showed no association between the intronic polymorphism of the *PS-1* gene and late-onset sporadic AD in the Taiwanese population[7,8]. A2M is a serum panprotease inhibitor which binds tightly to Aβ peptide and attenuates fibrillogenesis and neurotoxicity of Aβ by interfering with degradation of Aβ. Previous studies showed no association between *A2M-2* (a polymorphism of *A2M* gene) and AD, and that *A2M-2* was not a significant risk factor for AD among Taiwanese[8,26]. Studies of neurotransmitters in AD patients have led to the development of the current standard treatment for AD (Table

Table 3. *Genetic studies of the association of dementia with amyloid metabolism in Taiwan*

Gene	Authors	Year	Cohort	Association Positive / Negative	Ref
PS-1	Hu et al.	1998	55 late-onset AD patients 93 controls	AD (N)	7
A2M	Hu et al.	1999	65 AD 84 controls	AD (N)	26
BACE	Liu et al.	2003	25 AD patients 100 controls	AD (N)	25
MMEL2	Liu et al.	2004	107 AD 118 controls	AD (N)	24

PS-1: presenilin-1; A2M: Alpha-2 macroglobulin; BACE: Beta-site APP cleaving enzyme; MMEL2: Neprilysin-like 2.

Table 4. *Genetic studies of the association of neurotransmitters with dementia in Taiwan*

Gene	Authors	Year	Cohort	Association Positive / Negative	Ref
5-HT6	Tsai et al.	1999	92 AD 104 controls	AD (Y)	30
BuChE	Lee et al.	2000	89 AD 101 controls	AD (N)	27
nAChR	Liou et al.	2001	120 AD 98 controls	AD (N)	29
5-HTTLPR	Tsai et al.	2001	136 AD 83 older controls 92 younger controls	AD (N)	33
NR2b	Tsai et al.	2002	132 AD 114 controls	AD (N)	34
Alpha2a-adrenoceptor	Hong et al.	2001	142 AD 98 controls	AD (N)	36
A2aAR	Liu et al.	2005	174 AD 141 controls	AD (N)	35
CHRM1	Liu et al.	2005	232 AD 169 controls	AD (N)	28

BuChE: butyrylcholinesterase; nAChR: nicotinic acetylcholine receptor; 5-HTTLPR: 5-HTT gene-linked promoter region; NR2b: NMDA receptor 2b subunit; A2aAR: adenosine A2a receptor; CHRM1: cholinergic receptor muscarinic 1.

4). Changes in the brain cholinergic system are critical for the development of AD as has been shown by studies of the pathophysiology of cognitive dysfunction, post-mortem pathological findings, animal studies and results of clinical studies using current standard treatments. Cholinesterase inhibitors are now widely used for the treatment of mild to moderate AD. Acetylcholine is degraded by two enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Increased BuChE activity has been reported to be associated with the formation of amyloid plaques and neurofibrillary tangles and may consequently be involved in the pathogenesis of AD. The genes encoding AchE, BuChE and cholinergic receptors are all candidates for genetic study of AD. Lee et al.[27] found no association between *BuCHE-K* and either early or late onset (age > 65 years) AD in Taiwanese. They also found no synergistic effect between the *BuCHE-K* variant and *ApoE4*. Liu et al.[28] tested the allelic variant (C267A) of the cholinergic receptor muscarinic 1 (*CHRM1*) and found that the *CHRM1* C267A polymorphism did not confer susceptibility to AD. Changes in the nicotinic acetylcholine receptors (nAChRs) have been demonstrated in patients with AD. Liou et al.[29] tested the association between the allelic variant, 2bp deletion, of the partially duplicated alpha7 *nAChR* gene and AD. They found that this genetic polymorphism of partially duplicated alpha7 *nAChR* contributed no major effect on AD. A role of serotonergic dysfunction in the pathogenesis of AD has been supported by studies of serotonin and its metabolite in post-mortem specimens and CSF. Tsai et al.[30] found that the 267C allele of one of the serotonin receptor genes, *5-HT6* gene, is a risk factor for AD. Two recent studies have demonstrated an association between deletion/insertion polymorphism on the promoter region of the serotonin transporter gene (*5-HTTLPR*) and AD[31,32].

Table 5. *Genetic studies of the association of inflammation with dementia in Taiwan*

Gene	Authors	Year	Cohort	Association Positive / Negative	Ref
Alpha1-antichymotrypsin	Wang et al.	1999	157 AD 114 controls	AD (N)	45
TPH	Wang et al.	2001	150 AD 100 controls	AD (N)	43
nNOS	Liou et al.	2002	134 AD 101 controls	AD (N)	39
ACE	Cheng et al.	2002	173 AD 286 controls	AD (Y)	40
IL-1A	Tsai et al.	2003	234 AD 170 controls	AD (N)	37
IL-1A	Kuo et al.	2003	125 AD 93 controls	AD (N)	38
IL-1A	Kuo et al.	2003	70 VaD 93 controls	VaD (N)	38
BDNF	Tsai et al.	2004	163 AD 89 controls	AD (N)	46
COMT	Wang et al.	2005	66 AD 86 controls	AD (N/Y) A synergistic effect of the COMT HH genotype and APOE 4 allele	44

TPH: tryptophan hydroxylase, nNOS: neuronal NO synthase, ACE: angiotensin-converting enzyme, IL-1A: Interleukin 1A, BDNF: brain-derived neurotrophic factor, COMT: catechol-O-methyltransferase.

However, this finding was not confirmed in Tsai et al's study[30]. The study just showed no significant differences of genotype distribution or allele frequencies between AD patients and normal controls. Their results suggested that *5-HTTLPR* polymorphism is unlikely to play a substantial role in conferring susceptibility to AD in Taiwanese[33]. N-methyl-D-aspartate (NMDA) receptor dysfunction has been implicated in the pathogenesis of AD. The NMDA receptor is composed of several subunits, of which the receptor 2b subunit (*NR2b*) is of particular significance for AD. Tsai et al.[34], however, demonstrated no significant association between the *NR2b* C2664T polymorphism and AD.

Adenosine functions as a neuromodulator in the brain and it is widely distributed throughout the central nervous system. There is compelling evidence supporting the involvement of adenosine A2a receptor (*A2aAR*) in the pathogenesis of AD. Liu et al.[35] found no significant difference in *A2aAR* T1976C genotype distribution or allelic frequency between AD patients and controls, indicating that the *A2aAR* T1976C polymorphism is unlikely to play an important role in the occurrence of AD. There exists considerable evidence implicating abnormalities of the alpha-adrenergic system in the development of AD. Hong et al.[36] studied the relationship between alpha1a/alpha2a-adrenoceptor gene polymorphism and AD. Their results indicate that none of the alpha1a/2a-adrenoceptor polymorphisms is associated with increased risk to AD.

Inflammation is a characteristic change in the brain of AD patients. Interleukin 1A (*IL-1A*), a potent proinflammatory cytokine, has been implicated in the pathogenesis of AD. Several recent studies have shown that a polymorphism in the *IL-1A* locus -889 was associated with occurrence and early onset AD, however, other studies did not support these findings. Studies of the *IL-1A* C (-889)T polymorphism in the Taiwanese population by at least two groups revealed no association with AD[37,38]. Neuronal nitric oxide synthase (nNOS) has been implicated in the pathogenesis of AD. Liou et al.[39] examined the role of the polymorphisms of neuronal NOS (*nNOS*) gene in AD and found no association between AD and *nNOS* polymorphism. Genetic background might affect the metabolism of neuro-transmitters and drugs. Mutations or defects of genes result in decrease of efficiency of enzymes which participate in the metabolism of drugs. The pharmacogenetics of this machinery could be directly involved in the response of treatment or even occurrence of AD.

Angiotensin-converting enzyme (ACE) has been shown to be involved in cognition and memory. Several studies of the association of polymorphisms of *ACE* gene with susceptibility to AD have yielded inconsistent results. Cheng et al.[40] demonstrated the association of *ACE* gene polymorphism with AD in Taiwanese patients. Two recent meta-analysis reports revealed ACE gene could be another important gene for AD other than *ApoE4*[41,42]. ACE might be a potential target for genetic study of AD in the near future.

Wang et al.[43] found that tryptophen hydrolase gene (*TPH*) polymorphism was not a major genetic factor for AD.

A few studies showed an interaction between estrogen and ApoE in AD. Estradiol promoted synaptic sprouting via an ApoE-dependent pathway. The neuroprotective effect of estradiol was seen only in *ApoE*-bearing mice. Wang et al.[44] identified a synergistic effect of the estrogen-metabolizing gene, COMT, and *ApoE4* on occurrence of AD. It is possible that a high metabolism rate of estrogen by COMT enzyme reduces the protective effect of estrogen against AD in carriers of *COMT HH* genotype.

Recent studies have shown that a common polymorphism in alpha-1-antichymotrypsin (*ACT*) confers a significant risk for AD. Furthermore, the *ApoE4* allele effect associated with AD risk is modified by *ACT* polymorphisms. Association studies of *ACT* polymorphisms in Taiwanese AD patients by Wang et al.[45] and Hu et al.[8], however, indicated that the *ACT* polymorphisms had no effect on the development of AD either alone or in combination with the *ApoE4* allele. An association study showed no association between brain-derived neurotrophic factor gene (*BDNF*) Val66Met polymorphism and AD[46]. (Table 5)

In summary, the *ApoE4* allele is currently the only widely accepted genetic risk for AD. The genetic studies

of AD other than *ApoE4* in Taiwan remain inconclusive. *ACE* appears to be the candidate gene with the most potential involvement but confirmation of its role requires further investigation.

Vascular dementia

VaD is the second leading cause of dementia in Taiwan[1]. Genetic factors have been found for cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), a rare inherited autosomal dominant disease characterized by migraine, recurrent strokes, dementia, and psychiatric disorders. Mutations of the *NOTCH3* gene have been identified in many CADASIL families. Tang et al.[47] first reported the *NOTCH3*, Arg332Cys mutation at exon 6 in Asian patients. They emphasized the importance of genetic analysis of *NOTCH3* for Asians with a phenotype consistent with CADASIL. This condition may be overlooked in Asia because of the higher prevalence for vascular dementia.

A few studies have documented changes in levels of plasma lipoproteins as risk factors for cerebral arteriosclerosis. The association between the allele frequency of *ApoE4* and VaD is controversial. In Taiwan, several studies have attempted to clarify whether the *ApoE4* is associated with VaD [9,10,48]. But, all of them concluded that *ApoE4* played no significant role in the development of VaD. On the other hand, *ApoE4* was demonstrated to be an important risk factor for ischemic cerebrovascular disease in a Taiwanese cohort of uremic patients[49]. By contrast, *ApoE2* was shown to have a protective effect against the development of intracranial vascular diseases (ICVD) and VaD in Taiwanese aged below 65 years [48].

Kao et al.[38] examined polymorphism of *IL-1a* in Taiwanese patients with VaD and found no difference in allele frequencies of C-889T polymorphism on *IL-1a* between VaD and non-VaD controls[38]. In summary, there has been limited studies of the genetics of VaD in Taiwan. *NOTCH3* gene mutation, which has been identified in CADASIL families, is the only gene mutation which has been well established as a risk factor for VaD in this population.

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