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Panel of Genetic Variations as a Potential Non-invasive Biomarker for Early Diagnosis of Alzheimer's Disease

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Alzheimer's disease (AD) is the most prevalent form of dementia. Biomarkers such as levels of amyloid beta (Aβ) in cerebrospinal fluid and ApoE genotyping were suggested for the diagnosis of AD, however, the result is either non-conclusive or with invasive procedure. Genome-wide association studies (GWASs) for AD suggested single nucleotide polymorphisms (SNPs) in many genes are associated with the risk of AD, but each only contributed with small effect to the disease. By incorporating a panel of established genetic susceptibility factors, the risk of an individual in getting AD could be better estimated. Further research will be required to reveal if adding to the current well-developed clinical diagnosis protocol, the accuracy and specificity of diagnosis of AD would be greatly improved and if this might also be beneficial in identifying pre-symptomatic AD patients for early diagnosis and intervention of the disease.

KEY WORDS: Alzheimer disease; Genetics; Biomarkers; Diagnosis.

INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of age-related dementia and it is currently affecting more than 30 million people worldwide and the number of people with AD will have doubled to 46 million by 2020.[1)] It has been estimated that delaying the mean age of onset of AD by about 5 years would reduce the number of individuals with this disease by 50% by 2050. Mild cognitive impairment (MCI) is a clinical diagnosis for individuals who have cognitive deficits but do not fulfill the diagnosis of dementia that may represent the early stage of AD.[2-4)] Studies showed that the annual conversion rate for individuals with MCI to AD is 10-12%, compared to the conversion rate of 1-2% in the normal elderly population.[3)] Therefore, early detection of AD and accurate prediction of progression from MCI to AD are the important areas of research in AD.

Over the past decades, basic and clinical research studies provided a lot of knowledge on the molecular mechanism and the clinical progression of the disease. AD is characterized by the deposition of amyloid plaques composed of amyloid beta-peptides (Aβ) derived from amyloid precursor protein (APP) and the formation of neurofibrillary tangles composed of hyperphosphorylated tau.[5)] AD is mainly classified into two groups: (1) early-onset AD, which accounts for 1-6% of all cases and has its onset before the age of 65 years, and (2) late-onset AD, which is responsible for the vast majority (94-99%) of cases and symptoms appear after 65 years old. Several causative mutations on APP, presenilin 1 (PSEN1) and presenilin 2 (PSEN2) have been identified in familial type AD.[6)] On the other hand, late-onset AD is a complex neurodegenerative disease and it is caused by genetic and environmental risk factors.

DIAGNOSIS OF AD

The diagnosis of AD is based on clinical examination using criteria of the National Institute of Neurological and Communicative Disorders and Strokes and the Alzheimer's Disease and Related Disorders Association Work Group (NINCDS-ADRDA).[7)] The diagnostic criteria are well-established and have high reliability and consistency.[8,9)] Definitive diagnosis of AD can only be achieved by postmortem examination based on the histopathologic

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confirmation. Although the diagnostic criteria have good reliability and validity, it is not designed to identify patients with very mild symptoms or to assess the probability of conversion from MCI to AD.

BIOMARKERS

In the past decades, a large number of independent studies were carried out to evaluate the use of biomarkers in facilitating reliable diagnosis of AD, even in the preclinical stage. Based on the pathological importance of amyloid plaques and neurofibrillary tangles on AD, the levels of A β 40, A β 42, total tau and phosphorylated tau (p-tau) in cerebrospinal fluid (CSF) have emerged as the major biomarkers of interest.[10-14] A β 40 and A β 42 are produced from APP cleavage pathway. Based on the observation that increased production of A β 42 in missense mutations in the APP, PS1 and PS2 genes which cause familial AD, suggesting A β 42 plays a central role in the pathogenesis of AD.[15] Studies suggested that the concentration of A β 42 in CSF is significantly lower in AD patients when compared to the age-matched normal controls.[16] On the other hand, total tau in CSF reflects the formation of neurofibrillary tangles in AD. Elevated level of total tau in AD patients have been reported and reviewed in a meta-analysis study.[14,17-19] However, elevated level of total tau in CSF is not a specific marker for AD as it is also observed in fronto-temporal dementia (FTD),[10] vascular dementia[20] and acute ischemic stroke. On the other hand, p-tau is a more specific biomarker for AD as elevated level of p-tau is only detected in AD but not other neurological diseases such as Lewy body dementia and FTD.[21,22]

The National Institute on Aging Working Group outlined several criteria for an ideal diagnostic biomarker including fundamental relatedness to the disease, validation, high sensitivity and specificity. Also, the biomarkers should be noninvasive, inexpensive and readily available.[23] However, sampling CSF requires the lumbar puncture which is an invasive procedure and the cost for CSF testing is expensive.

IMAGING

Recent advances in functional and molecular neuroimaging provided insights into brain structure and physiology. Imaging techniques such as magnetic resonance imaging (MRI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) provided information on the regional changes of the brain in AD patients when compared to normal age-matched controls. MRI can be used to measure the degree of atrophy and it provided information on the disease state and progression. MRI-based atrophic changes are well matched with the pathological changes of tau deposition.[24-27]

Microstructural changes such as loss in dendrites, myelin and axon in AD can be detected by MRS.[28] Combining the use of radiological-contrast compounds and imaging techniques, some promising diagnostic tool has been studied. One of the widely studied amyloid-binding compounds is ^{11}C-PIB (PIB, Pittsburgh compound B). The uptake of PIB was measured by PET and AD patients showed specific retention of PIB in regions of the brain which is corresponded to the location of amyloid deposition.[29] However, there was also studies reporting elderly subjects without MCI showing increased uptake of ^{11}C-PIB[30,31] but it is uncertain whether this imaging marker has prognostic implications on AD.

GENETIC STUDIES IN AD

ApoE is a widely accepted genetic risk factor for late-onset sporadic AD. Studies showed that ε 4 allele increased AD risk in a dose-dependent manner while ε 2 allele has a protective effect on AD.[32-34] However, bearing ε 4 allele is neither sufficient nor necessary for the development of AD. Many linkage studies were performed to identify the chromosome/loci associated with the risk of AD and identified the ApoE region on chromosome 19 as the risk locus for AD.[35-37] This provided further evidence for the association of ApoE and the risk of AD. On the other hand, several linkage studies identified other regions on chromosome 6,[35,36,38,39] 9,[35,36] 10[35,39,40] and 12[41,42] other than chromosome 19 to be associated with the risk of AD, suggesting genes other than ApoE are involved in the genetics of this complex disease. These linkage studies not only providing further evidence of the involvement of multiple chromosomal regions to the association of the risk of AD, it provided the bases for the individual candidate gene studies. One of the example is tumour necrosis factor- α (TNF α), which is located on chromosome 6p21 and it was identified by several linkage studies to be significantly associated with the risk of AD.[36,38,39,41] Genetic association studies also showed significant association of TNF α polymorphism and the risk of AD.[43-47]

With the advance of genotyping technology and the launching of International HapMap project,[48] many large scale genome-wide association studies (GWASs) were

Table 1. Summary of results of genome-ide association study in AD

Studies	AD	Normal	Gene	*p* value	Odds ratio
Grupe *et al.*[190]	1808	2062	TOMM40, ApoE, GALP, TNK1, APOC2, PCK1, LMNA, PGBD1, THEMS, MYH13, CTSS, UBD, BCR, AGC1, TRAK2, EBF3	0.001 to 1.0×10^{-8}	1.07 to 2.73
Li *et al.*[128]	753	736	GOLPH2	9.82×10^{-3}	0.51
Abraham *et al.*[191]	1082	1239	LRAT	3.4×10^{-6} to 6.1×10^{-7}	1.2 to 1.3
Bertram *et al.*[192]	1376		chr 14q31, chr19q13	6.0×10^{-6} to 2.0×10^{-6}	1.1 to 1.4
Beecham *et al.*[193]	730	718	chr 12q13	3.4×10^{-7}	—
Feulner *et al.*[194]	491	479	MAPT, SORL1, CHRNB2, CH25H, GAB2, PGBD1, PCK1, LMNA	0.05 to 6.8×10^{-3}	—
Harold *et al.*[50]	4957 (Stage 1) 2023 (Stage 2)	9682 (Stage 1) 2340 (Stage 2)	CLU, PICALM	1.3×10^{-9} to 8.5×10^{-10}	0.86
Lambert *et al.*[51]	2032 (Stage 1) 3978 (Stage 2)	5328 (Stage 1) 3297 (Stage 2)	CLU, CR1	3.7×10^{-9} to 7.5×10^{-9}	0.86 to 1.21
Seshadri *et al.*[87]	3006 (Stage 1) 2032 (Stage 2)	14642 (Stage 1) 5328 (Stage 2)	BIN1, EXOC3L2/BLOC1S3/ MARK4, CLU, PICALM	0.007 to 0.03	0.82 to 1.26

AD, Alzheimer's disease; CLU, clusterin.

performed to investigate the genes associated with the risk of AD. GWASs simultaneously genotyped a large number of genetic markers in a unbiased setting as the single nucleotide polymorphisms (SNPs) to be genotyped were chosen to cover the common variations in human genome.[49] Until now, more than 10 AD GWASs were performed and a number of candidate genes for the risk of AD were identified. The results from the GWASs of AD were summarized in Table 1. Individual genetic association studies were also performed to follow-up and validate the findings from GWASs in different populations. Interestingly, these GWASs identified different candidate genes for the risk of AD but they consistently resulted in significant association of Apolipoprotein E (ApoE) and the risk of AD. Recent GWASs identified three genes including CLU, CR1 and phosphatidylinositol binding clathrin assembly protein (PICALM) as the susceptibility genes for AD.[50,51]

Since the identification of the association of ApoE and the risk of AD, it remains to be the most widely studied gene in AD. AlzGene website (http://www.alzgene.org)[33] is a database with continuously updated list of genes associating with AD. The database provided the results of allele-based meta-analyses for all polymorphisms with sufficient genotype data and ranked the genes based on the genetic variant with the strongest association (HuGENet/Venice criteria, *p*-value and effect size) to AD. In the database, there is a "Top Results" list showing the "most promising" AD candidate genes and it could help in choosing the genes in high priority for future studies. However, there is unavoidable limitation of the database such as possibility in overlooking the studies, allele analysis instead of genotype analysis (less powerful in revealing the underlying mode of inheritance), lack of haplotype data or consideration of co-variates such as age or gender. According to the statistics of AlzGene as of October 2010, the top ten genes showed the strongest association in AD are ApoE, CLU, PICALM, EXOC3L2, BIN1, CR1, SORL1, GWA_14q32.13, TNK1 and IL8.

GENETIC VARIATIONS AS MARKERS FOR ALZHEIMER'S DISEASE

Results from GWASs and linkage studies in AD identified several genes/SNPs conferring to the risk of AD. In addition, twin studies suggested that the additive genetic effects contributed 37% to 75% to the variance in age-at-onset of AD.[52] On the other hand, it is uncommon to have large implication of a single gene in common diseases such as AD. For most genes or SNPs, they only conferred a modest risk to the disease. It is unlikely that any single genetic polymorphism would be sufficient to be a reliable marker as diagnostic and prognostic tool, but a panel of genetic variation markers might serve this purpose. Recently, a study reporting 95 loci associated with lipid traits was based on analyzing the result of 59 GWAS,[53] which made the idea of developing a panel of genetic marker as diagnostic and prognostic tool for AD promising. In this review, the relatedness and usefulness of using genetic variations in AD susceptibility genes as diagnostic tool and markers will be discussed.

ApoE

ApoE gene is mapped to chromosome 19q13.2 and it is expressed in liver, brain and cells such as macrophages and monocytes.[54] There are three isoforms of ApoE coded for by ε 2, ε 3 and ε 4 alleles. A dose-dependent effect of ApoE ε 4 and the risk of AD was reported in late-onset AD[34] and the finding was replicated by differ-

ent groups in different populations.[32,55-58] It is by far the most widely studied and replicated genetic polymorphism conferring to the risk of AD, up to 20-50%.[59] Bearing ε4 allele increased the risk for AD from 20% to 90% and decreased the age-at-onset from 84 to 68 years with an increased dose of ApoE ε4 alleles.[34,60] Moreover, biochemical data showed ApoE was associated with amyloid in senile plaques[61] and neurofibrillary tangles.[62,63] Different isoforms of ApoE bind Aβ in different rate and ε4 binds to Aβ at a faster rate when compared to ε3.[64] On the other hand, both ApoE ε2 and ε3 bind to tau protein but not ε4, suggesting the interaction between ApoE and tau may serve as a protective function and this might explain the biological significance of ε4 as a risk factor for AD. Until now, almost all GWASs in AD identified ApoE as a susceptibility locus and the association of ApoE ε4 and the risk of AD was replicated and confirmed in large number of studies in different populations.

There is a dose-dependent effect of ApoE and the risk of AD where 55% of ApoE ε4/ε4 group developed AD, compared with 27% of ApoE ε3/ε4 and 9% of ApoE ε3/ε3 groups.[65] The frequency of ε4 is less than 20% compared to ε3, with a frequency of over 65%,[66] therefore it is unlikely the genotype of ApoE alone is sensitive enough to diagnose AD. It is clear that bearing ApoE ε4 allele increased the risk of AD but not essential for the development of AD. Several studies assessed the specificity and sensitivity of ApoE genotyping in the diagnosis of AD. The sensitivity of ApoE genotyping for the diagnosis of AD varied and it ranged from 19% to 75%.[67-70] Mayeux *et al.*[68] assessed the specificity and sensitivity of ApoE genotyping, clinical diagnosis and the combination of both techniques in more than 2000 AD patients. They reported the specificity of clinical diagnosis and ApoE genotyping alone were 55% and 68% respectively, although the sensitivity of clinical diagnosis was much higher than ApoE genotyping, with 93% versus 65%. They further analysed the specificity of combining both techniques and it increased to 84%, suggesting the combination of clinical diagnosis and ApoE genotyping would greatly reduce the false positive rate. Overall, the specificity of clinical diagnosis and ApoE genotyping were 50-55% and 68-71% respectively[68,71] but the sensitivity of ApoE genotyping was much lower than clinical diagnosis, with only 59-65% compared to clinical diagnosis yielding up to 93%. The specificity of diagnosis with both clinical diagnosis and ApoE genotyping was greatly increased to 84%, which was higher than either method alone. A study examining the predictive value of ApoE genotyping in 69 patients who had been clinically diagnosed with probable AD and 85% of them were confirmed to have AD at autopsy. No non-AD demented patients were found to carry ApoE ε4 allele and 75% autopsy-confirmed AD patients carried at least one ε4 allele, which gave a 100% specificity of ApoE genotyping in predicting AD.[67] However, there was also study showing that 50% of individuals carrying at least one ε4 allele did not develop AD in their lifetime.[72] Therefore, ApoE genotyping alone does not have sufficient specificity and sensitivity for the diagnosis of AD but it might be used as a adjutant test to improve the accuracy of clinical diagnosis of AD.

CLU

Clusterin (CLU), also named as apolipoprotein J, is mapped on chromosome 8. Like ApoE, it is a lipoprotein that widely expressed in most tissues, with higher levels in brain, liver, ovary and testis.[73] Owing to its functional relationship with ApoE, it is a candidate gene for the risk of AD. In addition, several lines of evidence suggested its role in the pathogenesis of AD. It was shown that the CLU expression was elevated in hippocampus, both in AD patients and animal models.[74-76] CLU has a regulatory role in Aβ metabolism, that it binds to soluble Aβ,[77-80] prevents aggregation of Aβ[79,80] and suppresses Aβ deposition and modifies Aβ clearance together with ApoE.[81-83] Studies also showed that reduced levels of ApoE and increased levels of CLU were associated with the number of ApoE ε4 allele, suggesting a compensatory effect of CLU on the reduced level of ApoE.[84] The association of CLU polymorphism rs11136000 and the risk of AD was recently identified by two lately published large scale GWASs.[50,51] These two papers were followed by other individual genetic association studies, including meta-analysis studies from different cohorts of different populations confirming the association.[85-88] A recent study showed association of disease progression and severity of AD and the plasma concentration of CLU, although they showed no association of the SNP rs11136000 and the risk of AD.[89] Polymorphism of CLU has also been reported to be associated with serum HDL cholesterol.[90] With the similarities of the function of CLU and ApoE and their significant association to the risk of AD, the importance of lipid metabolism and trafficking in brain became an area for research in AD.

PICALM

PICALM, encodes the phosphatidylinositol-binding clathrin assembly protein and is mapped on chromosome 11.[91] It is ubiquitously expressed and it is highly expressed in neurons. PICALM is involved in clathrin-mediated endocytosis[92] and in the fusion of synaptic vesicles to the presynaptic membrane by directing the trafficking of VAMP2 involved in neurotransmitter release.[93] The association of genetic variation in PICALM and the risk of AD was first identified through GWAS by Harold *et al.*[50] and the result was further replicated and confirmed by other individual groups and meta-analysis.[85,87,88] The SNP rs3851179, 88.5kb 5' to PICALM was associated to the risk of AD. The polymorphism might alter the function of PICALM in synaptic vesicle cycling or endocytic pathways resulting in changes in APP processing and Aβ levels.[50] Meta-analysis study by Jun *et al.*[85] showed there was synergistic effects of ApoE and PICALM on AD risk and such synergistic effect was also identified by previous studies investigating interaction of ApoE with PSEN1,[94] PSEN2[95] and APP.[95,96] In addition, PICALM SNP rs3851179 was associated with hippocampal volume and entorhinal cortex thickness (ECT).[97] Biochemical studies showed that PICALM is localized at the endothelial cell of brain and this facilitates the transportation of Aβ across the blood vessel wall as the major pathway for Aβ removal. Polymorphisms of PICALM might increase the expression of PICALM and impaired the Aβ removal mechanism, which ultimately causing the development of AD.[98]

CR1

CR1 encodes complement component (3b/4b) receptor 1 and is mapped to chromosome 1q32. The hypothesis on the relationship between inflammation/immune response and the development of AD was proposed for decades. Several lines of evidence including activated microglia surrounding Aβ deposits as phagocytic response activated by Aβ in microglia in a dose- and time-dependent manner,[99] the release of various inflammatory mediators after microglia activation,[100,101] recruitment of astrocytes to enhance the inflammatory response against Aβ, activation of complement cascade and induction of other inflammatory components such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2),[102,103] suggested microglia and astrocytes are the major players involved in the inflammation process leading to the development of AD.[101,104]

CR1 plays an important role in the regulation of complement cascade and clearance of complement components C3b and C4b.[105] Several lines of evidence including activation and bounding of Aβ by C3b,[106-108] inverse relationship between C3b expression and Aβ deposition[109,110] and C3b deficiency in APP transgenic mice resulted in Aβ accumulation and neurodegeneration[109] suggested the involvement of C3b in the pathogenesis of AD. Since CR1 is the receptor for C3b and a protective role for CR1 in AD through the binding of C3b and subsequent Aβ clearance was suggested.[51,111] A recently published GWAS of AD showed significant association of CR1 polymorphism rs3818361 and the risk of AD[51] and it was replicated and confirmed by other independent studies.[85,88] In addition, another CR1 SNP rs1408077 was associated with ECT,[97] suggesting the biological relevance of this gene and the risk of AD.

SORL1

SORL1 encodes sortilin-related receptor 1 and is mapped on chromosome 11q23. SORL1 is a member of the low density lipoprotein receptor family of ApoE receptors in human brain.[112] Studies showed that reduced SORL1 expression in AD patients[113,114] and human brain cells,[115] suggesting the possible relationship of SORL1 and the pathogenesis of AD. It was identified that SORL1 is involved in the processing and trafficking of APP, by binding directly to APP and sorting it into endocytic or recycling pathways, thus influencing Aβ generation.[116,117] In the absence of SORL1, APP entered the endosomal pathway and subjected to β- and γ-secretases cleavage and resulted in Aβ production.

The association of genetic polymorphisms of SORL1 and the risk of AD was identified[118,119] and confirmed in different populations.[120-124] In addition, SORL1 was identified in GWAS of AD[125] and provided further evidence of its role in the risk of AD. The first study reporting the association of SORL1 SNPs and the risk of AD was performed in multi-centers setting and they included four different ethnic groups. The authors identified two sets of haplotypes: SNPs in the 5'end and SNPs in the 3' end and their biological study suggested that the genetic variants might modulate the cell-type specific transcription or translation of SORL1 in neurons.[119] The association of SNPs in SORL1 and the risk of AD was further confirmed in autopsy-confirmed AD patients.[121] Groups using different populations to examine the relationship between SORL1

and the risk of AD, with four supported the initial findings[120,121,126,127] but the other three showed either negative or weak results.[122,124,128] One of the studies showed significant association of the SORL1 haplotypes and the risk of AD and also abstract reasoning ability as measured by Similarity test.[126] This finding suggested that polymorphisms in SORL1 might be useful in predicting the risk of AD, as well as the severity of the disease or the preclinical symptoms of the disease.

INFLAMMATION-RELATED GENES

As mentioned in previous section, there is hypothesis for the important role of inflammation in the pathogenesis of AD and genes involved in the inflammatory pathway are therefore of high interest as the susceptibility genes for AD. Studies showed that microglia surrounding plaques was positive for markers related to inflammation such as MHC class II, COX-2, MCP-1, TNF-α, IL-1β and IL-6.[104] In addition, elevated levels of chemokines and cytokines and their receptors including IL-1α, CXCR2, CCR3, CCR5 and TGF-β were found in post-mortem AD brains.[129] Epidemiological studies suggested non-steroidal anti-inflammatory drugs (NSAIDs) might be beneficial in preventing or delaying the onset of AD,[130,131] but not reversing the pathology.[132] Based on these observations and the on-going studies investigating the relationship between inflammation and AD, it is hypothesized that Aβ aggregates trigger microglia and astrocytes, leading to local inflammation and further activate the immune response. This resulted in the activation of inflammatory mediators such as TNF-α, IL-1β and IL-6, causing neuronal cell death and further activates microglia and astrocytes, formed a vicious cycle of inflammatory response.[133-135]

There were many genetic association studies investigating the relationship of polymorphisms of inflammatory-related genes including TNF-α, IL-1β, IL-6, IL-10, TLR-4 and COX-2 and the risk of AD. In addition, among the top 10 genes as listed in AlzGene, two of them are involved in the inflammatory pathway (CR1 and IL-8), suggesting the possible implication of inflammation in the pathogenesis of AD. Different TNF-α SNPs (-238, -308, -850, -863 and -1031) were investigated in genetic association studies and TNF-238, -863 and -1031 were reported to modulate the transcriptional activity of TNF-α gene and to be associated with risk of AD, with population specificity.[46,47,136-141] AlzGene meta-analysis showed that TNF-1031 was significantly associated with the risk of AD, giving odds ratio of 1.35 (95% CI: 1.04-1.77). IL-1β-511 and IL-1β-3953 were the most widely studied SNPs in IL-1β for the risk of AD. However, the results of the published genetic association studies on the relationship between IL-1β and the risk of AD are still inconclusive.[142-158] AlzGene meta-analysis showed that both SNPs were significantly associated with the risk of AD and another meta-analysis study confirmed the association of IL-1β-3953 but not IL-1β-511.[33,159] Di Bona *et al.*[44] showed a remarkable heterogeneity among studies for IL-1β-511, therefore sub- group (Caucasians) meta-analysis was performed and yielded significant association to the risk of AD, with OR of 1.32 (95% CI: 1.03-1.69).[44] This finding suggested that there is hidden population stratification for some SNPs in the association to the risk of the trait and it is important to control for these variants for the data analysis.

Many groups performed genetic association studies on IL-6 and the risk of AD. The common SNPs for IL-6 being studied included -572, -174 and variable number tandem repeat (VNTR) polymorphism but there was no confirmed association.[160-167] Interestingly, some studies showed no association of genetic polymorphisms on IL-6 and the risk of AD alone, but observed significantly increased risk of AD when combined with certain genotypes at other genes such as TNF-α and IL-10, suggesting there might be interaction effect between genes in modulating the risk of AD.[168-170] IL-10 is an anti-inflammatory gene and several groups reported association of IL-10 polymorphisms and the risk of AD[171-175] but the association is inconclusive with some studies reporting negative results.[47,128,139,176-178] IL-10 polymorphisms were associated with IL-10 levels[175,179] and clinical progression of AD,[180] suggesting its possible function as genetic marker for predicting disease progression. COX-2 is also at the top list of the inflammation-related genes implicating in the risk of AD, based on its important role in the pathophysiological process of inflammatory disease. Polymorphisms of COX-2 (-2319, -765, Ex10+837) were associated with the risk of AD[181-183] and the use of COX-2 inhibitors has been suggested for treatment of AD.[184,185]

The advantage of using genetic marker for inflammatory genes in determining the risk of AD over measuring the level of inflammatory cytokines such as IL-1, IL-6, IL-10 or TNF-α, is the measurement will be less likely to be affected by the daily fluctuation. Several studies suggested that the increased level of inflammatory cytokines is associated with increased risk of AD. On the other hand, several genetic markers were associated with

the predisposition of increased inflammatory cytokine levels. Therefore, it might be possible to predict one's risk of getting AD by genotyping those inflammatory genetic markers.

As observed in other common diseases, the SNPs associated with the risk of AD conferred a small effect to the risk of AD, giving the relative risk of the disease to the order of 1.1 to 2.0 and odds ratio rarely exceeding 3.[33,186] For example, it is estimated the attributable fraction for ApoE was 25.5%, CLU was 8.9% and CR1 was 4%.[51,111] Since AD is a complex disease and it is expected to be affected by multiple genes and polymorphisms, with each contributing a small effect on the disease risk. On the other hand, gene-gene interaction effect for the risk of AD was observed in a number of genes such as IL-1, IL-10 and TNF-α,[168-170] testing multiple SNPs that were associated with the risk of AD might provide more information in the prediction.[187] Studies in other common diseases such as diabetes also suggested the use of multiple gene loci to predict disease risks.[188] Genetic profiling, by incorporating a panel of established genetic susceptibility factors to estimate one's risk to a disease might be useful in providing a more accurate diagnosis.[189] Each susceptibility locus contributed to the genetic risk score can be added up and weighed differently based on its prevalence and relative risk to the disease. For example, the genotype of ApoE is expected to be weighted more in the risk score. A cut-off score can then be determined base on the results of previous studies and algorithm to estimate the risk of the disease. In AD, genes showing significant association in GWASs of AD, inflammatory genes and ApoE will be promising candidate genes for the panel in genetic profiling for diagnosis of AD or predicting one's risk of conversion from MCI to AD. However, this approach is limited by the restricted predictive value of genetic markers in complex disease and by the interaction effect of environmental influences such as exposure to different environmental factors and epigenetic changes on the onset and progression of the disease. At this stage, genetic profiling will not be adequate for the diagnosis of AD but it might improve the accuracy and specificity of diagnosis in addition to the present clinical diagnosis and imaging techniques and possibly applied in the identification of pre-symptomatic AD patients.

In conclusion, a large collaborative efforts will be required to explore the genetic variations, including structural variation and epigenetic, in addition to the statistical algorithms to estimate the contribution of each susceptibility polymorphism to the overall disease risk of AD. Further research efforts are necessary to find out if in the future, genetic profiling in addition to the current clinical diagnosis might be useful in identifying subjects with high risk of AD predisposition and ultimately lead to early diagnosis and intervention of the disease.

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