Genetic predisposition to inflammation: a new risk factor of Alzheimer's disease

Ying WAN^{1*}, Gang WANG^{1*}, Sheng-Di CHEN^{1,2}

¹*Department of Neurology/Neuroscience Institute, Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200025, China*

²*Institute of Health Science, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences/Shanghai Jiaotong University School of Medicine, Shanghai 200025, China*

Abstract: Inflammation has been shown to play an important role in the progression of Alzheimer's disease (AD). Recent epidemical study indicates that the incidence of AD in some populations is substantially influenced by the gene polymorphisms of the inflammation mediators. Meanwhile, an ensured risk factor, the *ApoE* $\epsilon 4$ allele is also reported to directly promote inflammation. Accordingly, it appears that an individual genetic background has partly determined his predisposition for AD by the extent of the inflammation response to the chronic stimulus by β -amyloid peptide ($A\beta$) deposits and other antigen stressor in the elderly. Hence we present a hypothesis that the inflammation genotypes may contribute to AD susceptibility. This may provide a new orientation both for future identification of individuals at risk and for personalized medication.

Keywords: Alzheimer's disease; inflammation; predisposition; polymorphism; inflammation mediators; *ApoE* $\epsilon 4$ allele; identification; personalized medication

1 Introduction

Alzheimer's disease (AD) is one of the most common types of dementia in the world, producing symptoms like progressive memory decline, disordered cognitive function, altered behaviors including paranoia, delusions, loss of social appropriateness, and a progressive decline in language function. Global aging has made the incidence of AD increase at an alarming rate, seriously affecting the quality of life for aged people^[1]. Despite the various theories explaining the etiology of the disease in the past years, none of them cover all the features. It is more likely that AD is a multi-factorial

disease and one factor alone is not sufficient to develop the disease. Therefore, many factors may produce a cumulative effect which increases the likelihood of developing the disease. In recent years, an increasing set of evidence has focused on the role of inflammation in the pathology of AD, with inflammation reactions widely seen in the brain, particularly at the microglia-rich amyloid deposits, where the microglia tend to be activated to release a wide variety of proinflammatory mediators including cytokines, complement components, various free radicals and nitric oxide (NO), all of which potentially contribute to further neuronal dysfunction and eventually result in cellular death^[2]. In addition, apolipoprotein E (*ApoE*) is a risk factor for sporadic AD, and is strongly associated with AD in terms of cognitive decline and disease onset. In addition to its role in causing the β -amyloid peptide ($A\beta$) accumulation, *ApoE*, especially the $\epsilon 4$ allele, has been observed directly promoting an inflammation reaction. This function of $\epsilon 4$ allele may contribute to its close relation with AD, as carrying one $\epsilon 4$ allele nearly doubles the

*These authors contributed equally to this work.

Corresponding author: Sheng-Di CHEN

Tel: 86-21-64457249

Fax: 86-21-64454473

E-mail: chen_sd@medmail.com.cn

Article ID: 1673-7067(2008)-05-0314-09

CLC number: R741.02

Document code: A

Received date: 2008-06-19

lifetime risk of AD, whereas not carrying a $\epsilon 4$ allele decreases this risk. Sufficient epidemiological and genetic evidence show that local and systemic inflammations exist in most patients with AD and have a positive relation with the clinical manifestations of AD, implying that an individual may be more vulnerable to AD if his or her genetic background provides a greater predisposition to inflammation. This idea is supported by the epidemiological finding of reduced incidence of AD in patients who use anti-inflammation drugs compared with controls^[3]. Moreover, the polymorphisms of cytokines have been demonstrated to be genetic risk factor for AD, as genetic variations located within cytokine genes influence AD susceptibility by regulating gene transcription and gene products. Several studies report a significantly different distribution of proinflammatory genes between patients and controls, in which certain alleles are underrepresented in control subjects and overrepresented in patients affected by AD. In conclusion, we propose the hypothesis that a genetic background prone to inflammation may contribute to an individual's risk of suffering from AD. In this article, we will introduce this hypothesis in detail and its potential clinical applications, which may provide us with new tools for identifying the AD-susceptible populations and treating them prior to the severe clinical manifestations of AD.

2 Inflammation: accelerator in the pathological procession of AD

Neuro-pathological hallmarks of AD are senile plaques and neurofibrillary tangles in the medial temporal lobe structures and cortical areas of the brain, along with a degeneration of the neurons and synapses. However, increasing reports show that A β plaque burden poorly correlates with the progression and severity of dementia in AD. For example, there is no decline in the cognition of the animal models which develop widespread A β plaque deposits^[4]. Moreover, the eventual deposition of A β and neurofibrillary tangles formation may not account for all clinical symptoms of AD, particularly the earliest clinical symptoms arising before neuronal degeneration is evident. In the AD brain, highly insoluble A β deposits and neurofibrillary tangles provide obvious stimuli for inflammation responses, which are associated with reactive astrocytes and microglia. Cytokines like interleukin-1 β (IL-1 β), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and acute phase-proteins are especially up-

regulated in tissues surrounding neuro-pathological lesions in AD brains^[5], but are seldom seen in normal brains^[6]. The induction of microglial-driven inflammation mediators results in a local cytokine-mediated acute-phase response, activation of the complement cascade and inflammation enzyme systems such as the inducible nitric oxide synthase (iNOS) and the prostanoid generating cyclooxygenase-2 (COX-2). All these factors could contribute to neuronal dysfunction and death. Meanwhile, the inflammation mediators also enhance amyloid precursor proteins (APP) production and amyloidogenic processing of APP to generate A β 42 peptide and inhibit the production of the soluble fraction of APP. Thus, A β induces expression of proinflammatory cytokines by glial cells in a vicious circle, which is essential for the pathological progression of AD^[7].

3 Inflammation from the central nervous system (CNS), peripheral or both

It's evident that immunocytes including microglia and astrocytes could be activated by the stimuli in the CNS, which has been described above. Does the activation signal only come from the CNS? Recent study has found the microglia in the brain can also be activated by the remote local infection or systemic inflammation and the peripheral inflammation is linked to the progression of AD. In experimental animals, chronic systemic inflammation response elicited by lipopolysaccharide (LPS) administration induced glial activation. After activation, the microglia modify their morphology and become tissue macrophages producing inflammation mediators. More importantly, elevation of acute-phase proteins in the periphery as markers of systemic inflammation stimuli is supported by epidemiological studies as a risk factor for cognitive decline and dementia. In clinical follow-up of 22 sets of twins, Nee LE^[8] found that five twins with previous serious systemic infection developed AD with earlier onset than their corresponding twin. The brain appears to have the capacity to activate inflammation reactions in response to an immune challenge by releasing cytokines which may be produced by the activated astrocytes and microglia through the proper stimuli either from the local environment, the peripheral immune system or both. Therefore, it may be plausible that gradual accumulation of non-specific inflammation reactions in the natural cycle will trigger and accelerate the neuro-pathological lesions, inducing

Fig. 1 Inflammation enhanced by a variety of factors in the CNS could accelerate the pathologic changes, resulting in the degeneration featuring the neuronal dysfunction and death in AD.

the clinical manifestations at an earlier age.

4 Proinflammatory cytokines and their roles in AD

As reported above, proinflammatory cytokines including IL-1, IL-6 and TNF- α may affect the neuronal function and mediate the pathological changes of AD. This is supported by numerous findings that show abnormally high concentrations of the cytokines around the lesions.

IL-1 is a proinflammatory cytokine that induces other cytokines and is a potent activator of host defense responses to infection and injury both in the periphery and the CNS. In the normal brain, the concentration of IL-1 is very low, but rapidly increases in response to acute and chronic diseases. The increase of IL-1 is followed by neuronal loss, but can be attenuated by adding antibodies to IL-1 prior to the inflammation stimuli^[9]. The negative impact on neuronal survival and function may be partly attributed to the ability of IL-1 to interfere with neurotrophins such as BDNF through suppression of BDNF/neurotrophin signaling^[10]. Recent studies found that IL-1 could decrease BDNF signaling through various pathways, including PI 3-K/Akt and RAS/ERK, which converge at the transcription factor CREB, possibly compromising a broad range of BDNF-mediated functions, ranging

from synaptic plasticity to neuronal survival via the inhibition of multiple pathways. IL-1 is overexpressed within affected cerebral cortical regions of the AD brain at the early stage prior to the detection of A β deposits, which suggests that it may facilitate plaque formation. In addition, our research^[11] has demonstrated that IL-1 promoted the synthesis and processing of APP of neuroglioma cell *in vitro*. Moreover, a positive feedback mechanism is documented through which IL-1-induced release of secreted APP stimulates further microglial IL-1 production. This suggests that IL-1 and APP are involved in a cycle of glia-neuronal interaction which over time can precipitate the neurodegenerative consequences of AD. In addition, IL-1 may be associated with cognitive impairment of AD patients, as it has been shown in a number of studies to selectively target cholinergic basal forebrain neurons by affecting NF κ B and AP-1 DNA binding (the key intracellular cholinergic signal transduction) inducing cholinergic dysfunction in AD^[12].

IL-6 is mainly produced by activated astrocytes and microglia in the CNS. IL-6 and its receptor are expressed in all regions of normal tissue, with various levels of expression in different parts under physiological conditions. Prominent differences between normal brains and AD-affected brains

were found, showing IL-6 expression increased in AD parietal cortex and decreased in occipital cortex. IL-6R expression levels were also strongly increased in AD frontal and occipital cortex but decreased in temporal cortex and cerebellum^[13]. IL-6 can induce the hyperphosphorylation of tau with activation of cdk5/p35 system in hippocampal cells at normal expression level^[14]. Considering the role of IL-6 in AD, several studies of murine models support its association with cognitive impairment and senescence. For example, transgenic mice with over-expression of IL-6 in the brain suffered from severe neurological diseases and a progressive decline in learning. Interestingly, the knockout of *IL-6* gene leads to better spatial learning, working and reference memory in comparison to the wild type. In 10 month old senescence-accelerated prone mice, IL-6 level was markedly increased in the hippocampus and cerebral cortex^[15]. The mechanism still remains unclear. It is known that the neuronal damage in AD has been associated with direct toxicity of A β , excitotoxicity involving NMDA receptors (NMDAR) and altered Ca²⁺ dynamics^[16]. Recent studies show that NMDA-induced cell damage was greatest in cultures chronically exposed to the combined treatment of IL-6 and A β . Also, increased levels of IL-6 alone can affect the physiologic function of cortical neurons by altering Ca²⁺ response produced by activation of NMDARs. In other words, all the information available supports the relation of IL-6 to the cognitive dysfunction in AD, and that NMDARs are involved in numerous neuronal functions including memory and learning.

TNF- α is produced by activated microglia in response to A β , oxidative stress and glutamate. Its neurotoxic effect involves induction of neuronal death and promotion of the A β stimulating synaptic dysfunction as well as A β deposition. For example, TNF- α is significantly higher in AD patients than in mild dementia patients or in healthy controls. However, AD patients exhibit a lower level of serum IGF-I, a neuroprotective factor that is negatively correlated with TNF- α levels, which indicates that increased TNF- α levels might antagonize the neurotrophic activity of IGF-I in these pathologic conditions^[17]. In addition, TNF- α is found to play a key role in inducing extensive microglial glutamate release in an autocrine manner causing excitoneurotoxicity which may contribute to neuronal damage^[18]. This indicates that TNF- α may interfere with the normal signaling transduction, which is necessary for the function and survival of the neurons,

indirectly promoting degeneration of AD. Meanwhile, the anti-TNF- α antibody or the genetic knock-out of the type-I TNF- α receptors (TNF-RI) reduced the inhibition of long-term potential in the hippocampus of the animal model and oxidative alteration promoted by A β 1-40 which occurs in the preclinical stage of AD and this may provide new insight in effective therapy and prevention of the progression of AD^[19].

In addition to the cytokines above, there are a lot of other cytokines recently proven to play a role in the neuro-pathologic changes in AD. For example, transforming growth factor- β 1 (TGF- β 1) and interleukin-18 (IL-18) showed an evident increase in the serum as well as the cerebrospinal fluid (CSF) of the patients with AD, which may indicate their association with AD. TGF- β 1 is a multifunctional cytokine with a pivotal role in tissue injury and repair, regulating the growth and survival of neurons. It is highly expressed in serum and CSF of AD patients, and its increased concentration of TGF- β 1 in CSF of AD patients is negatively correlated with A β levels, indicating a role of this cytokine in affecting amyloid protein metabolism. Recent studies have shown that high levels of TGF- β in the cortex up-regulate APP synthesis in reactive astrocytes and indirectly contribute to A β deposition^[20]. In addition, high levels of TGF- β could also block the proliferation of neural stem and progenitor cells^[21], and enhance neuronal apoptosis caused by A β neurotoxicity in the murine model of AD^[22]. Controversially, a decreased intracellular TGF- β signaling mediated by TGF- β II receptor promotes age-dependent neuro-degeneration, loss of dendrites and A β accumulation in mouse model with AD^[23]. This paradoxical phenomenon may imply that proper concentration of TGF- β is essential in maintaining the normal physical function of neurons in the CNS.

Recent data reports IL-18 may also have association with AD. IL-18, an effective proinflammatory and proapoptosis cytokine, is highly detected in the plasma of patients with AD, and its level is correlated with the severity indexes^[24]. It may be possible that IL-18 accelerates the neuro-degeneration during the AD progression by triggering the Fas/FasL-induced apoptosis cascade under inflammatory conditions.

Proinflammatory cytokines are overexpressed in the serum and CSF of the patients with AD, especially at the preclinical stage. Therefore, it may be plausible to regard these cytokines as biological markers to monitor the treatment and make a prognosis on the degree of pathologic procession of

AD according to the changes in the level of cytokines.

5 The innate immune system in AD

As the first line of host defense, the innate immune system is responsive to a variety of pathogens and injury, which trigger local and systemic inflammation through activation of quiescent macrophages and microglia, the resident phagocytes in the CNS. In addition, Toll-like receptor (TLR) plays a vital role in the initial step of innate immune response. Recently, increasing studies have indicated TLR4 on the microglia has a high affinity to A β peptides and shows a strong action with an additive release of the nitric oxide (NO), TNF- α and IL-6. This strong reaction is evidently inhibited by the spontaneous functional mutation in the *TLR4* gene^[25]. The TLR4 mRNA has a higher level of expression in the mice of AD than in the wide type. As TLR is a first-line host defense receptor against a wide range of exotic and endogenous ligands, such as LPS, it may be possible that the burdens of several infections at various sites may affect the progression of AD, which may be due to remote signaling by inflammation mediators that activate microglia in the neurotic plaques through TLR4 activation. This may be one reason for the deterioration frequently observed in patients with AD during infections. Therefore, it should be biologically plausible that functional variation in the *TLR4* gene could influence the susceptibility to sporadic AD. In particular, recent data report that subjects with the TLR4 Asp 299Gly variant have lower incidence of AD, which may be attributed to an attenuated receptor signaling and a blunted inflammation response of this polymorphism^[26].

6 Polymorphisms of the inflammation mediators contribute to the AD susceptibility

Inflammation mediators constitute a micro-environment where neuropathological lesions are gradually induced, implying that a close relation may exist among the cytokine regulation, disease onset, as well as the severity of AD. Recent genetic studies highlight the relevance of some cytokines in AD pathogenesis, demonstrating that specific polymorphisms in the gene clusters are associated with a greatly increased risk for AD. For example, IL-1 β with the -511TT genotype is associated with early onset of AD and the IL-1 α -889 T/T and C/T genotypes are likely to be susceptible factors for the development of AD^[27,28]. A similar result is ob-

tained with genotype C of an IL-6-174 single nucleotide polymorphism (SNP) through the series of meta-analysis on cytokine polymorphisms showing that the -174 C allele in the promoter region of *IL-6* gene was over-represented in AD patients compared to controls and significantly increased the risk of AD. This was further supported by the increase of IL-6 levels in the blood and brain of patients with AD^[29]. TNF- α -308A/G polymorphism has been related to early onset of AD and aggravation of individual cognition decline in large AD case-control studies^[30]. Conversely there are other reports showing that the TNF- α -863 A allele may be associated with reduced risk of developing AD, and it would be less liable to suffer from AD with TNF- α A/A genotype, as there is a more significant decline in the expression of TNF- α ^[31]. In addition, a recent case-control study showed that both +10C allele and the CC genotype of TGF- β were over-represented in AD when compared to the healthy control, meanwhile this polymorphism appears to be associated with the increase in the level of the expression of TGF- β ^[32]. However, there is always a discrepancy in the association between the polymorphism and AD. The differences may be attributed to the variations in genetic background among different populations and regional variations in allele and genotype frequencies, causing results difficult to replicate.

As the data shown above, SNPs involved in differential production of cytokines is associated with susceptibility or resistance to AD by influencing gene transcription and in turn cytokine production. Therefore, an individual's genetic background has partly determined his or her predisposition for AD by the extent of the inflammation response to the chronic stimuli throughout life. It would make a profound influence to draw a risk profile for the early identification of individuals susceptible to disease and the appropriate mediation.

7 The variant of *ApoE* alleles and inflammation

As previously stated, a well known genetic risk factor in late-onset AD is represented by *ApoE*, which is the gene encoding apolipoprotein E, a constituent of the low density lipoprotein (LDL) particle. In human population, there are three variants of the gene with the difference of a change in a single amino acid, which are *ApoE* ϵ 2, ϵ 3 and ϵ 4, with different impact on the concentration of the blood lipoprotein. Many studies have demonstrated a strong association be-

tween $\epsilon 4$ allele and late-onset familial as well as sporadic forms of AD, and its effect is dose-dependent. The risk for AD increases from 20% to 90% and the mean age of onset decreases from 84 to 68 years as the number of $\epsilon 4$ allele increase. $\epsilon 4$ allele is strongly related to clinical symptoms of AD, especially cognitive decline. For example, compared to AD patients without the $\epsilon 4$ allele, the group with the $\epsilon 4$ allele represented a significant decline in cognitive tasks as well as immediate memory, exhibiting increased errors in a battery of computerized cognitive tests which incorporate speed-of-processing components into measures of verbal, spatial and working memory, attention, and visual-spatial ability^[33]. The mechanisms underlying these manifestations are not clearly known. It reported that $\epsilon 4$ had a strong association with cerebral amyloid deposition in cholesterol rich lipid rafts, enhancing aggregation into senile plaques, causing neuronal dysfunction and neuronal loss, which is consistent with the findings that $\epsilon 4$ may accelerate thinning in areas due to aging (medial prefrontal and pericentral cortex), initiate thinning in areas associated with AD and accelerate amyloid- β aggregation (occipitotemporal and basal temporal cortex)^[34]. In addition to its role in the classical neuro-pathological changes, $\epsilon 4$ allele has been described to promote inflammation. Actually, numerous studies have demonstrated the association between the ApoE and the immune system. For example, ApoE and other plasma lipoproteins were originally found to suppress the DNA synthesis and reduce phospholipid turnover in T cells, indicating the impairment of the lymphocyte function. Researchers further found that ApoE regulated macrophage function in the mouse model which experienced a large increase in pro-inflammatory cytokines for the lack of an *ApoE* gene and ApoE protein^[35]. As a positive relation with the AD has been supported, increasing research focused on *ApoE* variants and achieved numerous important findings. Compared with $\epsilon 3$ allele, the murine macrophages transfected with $\epsilon 4$ allele secrete more pro-inflammatory mediators, with a higher production of superoxide radicals^[36]. The $\epsilon 4$ allele carriers have a predisposition to inflammation, their monocytes release more NO and IL-10 and anti-inflammation cytokines are less expressed in the periphery^[37] than in the carriers with $\epsilon 3$. Similar results were found in another mouse model transfected with *ApoE4* that microglia derived from the model demonstrate a pro-inflammatory phenotype including altered cell morphology, increased NO production

and higher release of the pro-inflammatory cytokines, compared to microglia from mice carrying *ApoE 3/3*^[38]. And the effect was gene dose-dependent and increased with the number of *ApoE4* gene alleles. The higher production of cytoactive agents by *ApoE4/4* microglia showed an increasing injury to neighboring cultured neurons^[39]. In addition, LPS was injected into peritoneum of three different models *ApoE3/3*, *ApoE3/0*, and *ApoE4/4* to detect the difference of the response among them^[40]. Interestingly, it showed that the *ApoE* genotype-specific immune profile was observed in the cortex of aged mice of the three phenotypes. The *ApoE4/4* phenotype showed a significant inflammation response at the strongest level of the three whereas the *ApoE3/0* was the slightest. These data was consistent to the previous finding that *ApoE 4* allele actively promoted inflammation in the CNS. The *ApoE 3* allele may inhibit the inflammation and the impact may depend upon the dose of *ApoE 3* protein. Actually, the ancestral allele $\epsilon 4$ enhanced host defense to the areas of high rate of infectious disease by its pro-inflammatory properties in the past. However, the pro-inflammatory trait has been amplified in the present with increasing aging, resulting into detrimental effects in terms of chronic inflammation. This increased inflammation reaction with *ApoE* $\epsilon 4$ is possibly due to an increased activation of NF- κ B which is central to a series of signaling pathways involved in the regulation of inflammation responses^[37].

8 Conclusion

Due to the lack of specific parameters in diagnosis, most patients diagnosed with AD are at a moderate or severe stage with an evident decline in their cognitive function, seriously affecting their life quality. In addition, there is still no definitive treatment or cure for AD. Disease interventions only provide short-lived improvement, with no effect on the progression of the disease. Therefore, identification of susceptible populations and prophylactics would have a profound implication on disease treatment. Inflammation may play a role in the initiation and progression of AD, and the inflammation genotypes have been showed in large numbers of epidemical studies to influence the incidence of patients with AD. Based on the previous studies, here we present a hypothesis that an individual genetic background prone to inflammation may contribute to this risk of suffering from AD as well as the deterioration of the disease. With respect to it,

the aberrant inflammatory status can not be ignored in the treatment of AD. Therefore, the hypothesis may provide us with a new orientation to the effective intervention of AD, in particular at the preclinical stage. Moving it into practice, a series of new strategies to treat individuals at risk of AD, as well as the patients with AD, could be carried out as follows: (1) A more comprehensive risk profile should be detected and utilized. In addition to the established risk factors like *ApoE4*, the alleles that favor the increased expression of the immunological mediators should be also considered on large scale epidemiological screening on the purpose of future prediction and individual therapy. (2) Appropriate prophylactics. Susceptible populations with dangerous proinflammatory genotypes might be given anti-inflammation medicine such as NSAID and antibiotics at a particular dosage for the prophylaxis of AD by relieving the inflammatory burdens in senescence. The aged people with systemic infection might be treated with appropriate intervention since the microglia may be activated by systemic stimuli. (3) Personalized therapy. This might be possible in treating AD patients in terms of retrieving the aberrant immune response. For example, high levels of proinflammatory cytokines produced by high-risk genotypes may suggest the usage of specific antibodies directed against the cytokine. The drugs that interfere with the inflammation signaling pathway could be an alternate way to block inflammation-inducing impairment to the brain. (4) Assisting monitoring the condition. These cytokines in the serum and the CSF could be potential biomarkers in monitoring and prognosis of AD, which indirectly reflect the progression of neuronal damage.

Acknowledgements: This work was supported by the National Basic Research Development Program of China (No. 2006cb500706), the National Natural Science Foundation of China (No. 30700251), Shanghai Key Project of Basic Science Research (No. 04DZ14005), and the Program for Outstanding Medical Academic Leader (No. LJ 06003). We thank Ms. Tess EIDEM and Prof. Jia-lin ZHENG at the University of Nebraska Medical Center and Dr. Yong-Bin CHI from Department of Immunology, Shanghai Jiaotong University School of Medicine for critical reading of the manuscript.

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遗传基因的趋炎症性：阿尔茨海默病的又一危险因素

万赢^{1*}，王刚^{1*}，陈生弟^{1,2}

¹上海交通大学附属瑞金医院神经内科 / 神经病学研究所，上海 200025

²中国科学院上海生命科学研究院 / 上海交通大学医学院健康科学研究所，上海 200025

摘要：炎症反应在阿尔茨海默病的进展中发挥着重要的作用。近来流行病学研究显示炎症介质的基因多态性可以影响阿尔茨海默病在人群中的发病率。另有报道，ApoE ϵ 4，阿尔茨海默病的危险因子，可直接增强炎症反应。因此，在老龄化过程中，个体是否容易罹患阿尔茨海默病，可能与对A β 斑块和其他免疫原的长期刺激引发的炎症反应强度有关，其反应强度取决于其遗传基因。炎症相关的基因可能影响个体对阿尔茨海默病的易感性，并可能为将来的阿尔茨海默病危险人群的筛选和个体化治疗提供新的研究方向。

关键词：阿尔茨海默病；炎症；易感性；多态性；炎症介质；ApoE ϵ 4 等位基因；诊断；个体化治疗