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The Genetic Relationship between Interleukin Genes in Alzheimer's Disease

Myung-Jin Mun[1,2,3], Sue Kyung Kim[1], Jin-Ho Kim[1], Ji-Young Choi[1] and Won-Cheoul Jang[1,2,*]

[1]Department of Chemistry, School of Natural Science, Dankook University, Cheonan 330-714, South Korea;
[2]Institute of Tissue Regeneration Engineering (ITREN), Dankook University, Cheonan 330-714, South Korea
[3]Department of Nanobiomedical Science, Dankook University, Cheonan 330-714, South Korea

The contribution of genetics to Alzheimer's disease (AD) risk and the pathological mechanisms of AD have been extensively investigated. Genetic polymorphisms in causative genes, including *Amyloid precursor protein* (*APP*), *Presenilin 1* (*PSEN1*) and *Presenilin 2* (*PSEN2*), are associated with the risk of early-onset AD (EOAD) [1] and *Apolipoprotein E* (*APOE*) has been linked to an increased risk of late-onset AD (LOAD) [2]. These genes all share a common function and affect amyloid beta (Aβ) production and clearance in the brain, which is an important factor in the pathogenesis of AD. AD is characterized by two neuropathological hallmarks: senile plaques and neurofibrillary tangles comprised of Aβ proteins, and the hyper phosphorylation of tau [3]. However, there is a strong correlation between neuroinflammation and the production of cytokines by immune cells. Interleukins (ILs), a group of cytokines, may actively participate in AD pathogenesis since they mediate a self-perpetuating cycle of neuroinflammation in AD [4]. Clinically, several cytokines including IL-1, IL-6, tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) have been shown to associate with AD [5]. In addition, ILs is associated with many autoimmune diseases [6]. Therefore, there have been extensive studies on the genetic association between ILs and AD [7-10].

IL gene polymorphisms, including -889C>T in IL-1α, -511C>T in IL-1β, -174G>C in IL-6, and -1082G>A in IL-10, may be associated with risk of AD. However, the results of these studies are controversial due to inconsistencies [11-15]. Performing a meta-analysis is one of the best ways to re-evaluate the involvement of these polymorphisms in AD. A recent meta-analysis of 25 studies showed that the -889C>T polymorphism in IL-1α is associated with an increased risk of LOAD in Caucasians [11]. In contrast, the -511C>T polymorphism in IL-1β was found to have no association with AD risk in the overall population in a subgroup analysis using age at onset from 16 studies [12]. Interestingly, this polymorphism may be linked to a modest increase in AD risk in non-European populations. The -174G>C polymorphism in IL-18 was found to be associated with a decreased risk of AD in the overall population using 18 studies (3,101 cases and 3,860 controls), with a particularly strong effect in both Europeans and non-Europeans. Therefore, the -174G>C polymorphism could be a useful marker for the clinical evaluation of AD [13]. Similar results for this polymorphism have been observed in additional studies (4,280 cases and 8,788 controls) [14]. However, no relationship between IL-10 polymorphisms, including-1082G>A, -819T>C and -592C>A, and AD was found using data from 15 studies [15]. The cumulative number of publications for -889C>T, -511C>T, -174G>C and -1082G>A IL polymorphisms is 34, 18, 24 and 17, respectively. Most of these studies and observations considered the finding that ILs is associated with the risk of AD [16]; however, meta-analyses using larger sample sizes to support the involvement of ILs in AD risk are needed.

In our previous meta-analysis, we included a total of 93 individual studies to evaluate four IL polymorphisms for AD risk [17]. These studies included a total of 22,855 (8,641 cases and 14,214 controls) -889C>T IL-1α participants, 7,815 (3,194 cases and 4,621 controls) -511C>T IL-1β participants, 18,211 (5,755 cases and 12,456 controls) -174G>C IL-6 participants, and 13,304 (4,274 cases and 9,030 controls) -1082G>A IL-10 participants. These results confirmed that the -889 C>T IL-1α polymorphism is significantly associated with an increased risk of AD in both overall and Caucasian populations, and confirmed that the other three polymorphisms, -511C>T, -174G>C and -1082G>A, were not associated with AD risk. Griffin et al. suggested that elevated expression of the proinflammatory cytokine IL-1 surrounding amyloid plaques is associated with AD pathogenesis [18]. In addition, increased expression of IL-1 has been detected in other neurodegenerative disorders such as multiple sclerosis, Parkinson's disease and Creutzfeldt-Jakob disease [19]. However, the results for the -174 G>C polymorphism in IL-6 differed from those of previous meta-analyses, potentially due to differences in sample size. In this study, eight additional studies were included and four studies were excluded from Qi et al. [14] of which three had insufficient genotype data, and one overlapped with van Oijen et al. and Combarros et al. [20,21].

It is difficult to confirm whether IL polymorphisms are associated with an increased risk of AD through meta-analyses alone. However, there is *in vivo* evidence from animal models that ILs contribute to AD pathogenesis [22]. IL expression can be affected by cardiovascular disease due to its association with chronically elevated plasma concentrations of IL-1β, IL-6, TNF-α and IL-18 [23]. Although the precise mechanisms underlying IL involvement in AD are not yet completely understood, our meta-analysis has strengthened the association between ILs and AD by demonstrating that the IL-1α -889 C>T polymorphism is significantly associated with an increased risk of AD in both overall and Caucasian populations. Furthermore, as most studies have been performed using Caucasian populations, future studies should be performed to determine the association between the four main polymorphisms and AD risk in Asian populations because race and ethnicity are considered to be related to ethnicity or country of origin.

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***Corresponding author:** Won-Cheoul Jang, Department of Chemistry, School of Natural Science, Dankook University, Cheonan 330-714, South Korea, Tel: +82-41-529-6256; E-mail: wcjang@dankook.ac.kr

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