Meta Gene 8 (2016) 1–10

Contents lists available at ScienceDirect

Meta Gene

journal homepage: www.elsevier.com/locate/mgene

Genetic polymorphisms of interleukin genes and the risk of Alzheimer's disease: An update meta-analysis

Myung-Jin Mun [a,b,c], Jin-Ho Kim [b], Ji-Young Choi [b], Won-Cheoul Jang [b,*]

[a] Department of Nanobiomedical Science and BK21 PLUS NBM Global Research Center for Regenerative Medicine, Dankook University Graduate School, South Korea
[b] Department of Chemistry, School of Natural Science, Dankook University, Cheonan 330-714, South Korea
[c] Institute of Tissue Regeneration Engineering (ITREN), Dankook University, Cheonan 330-714, South Korea

ARTICLE INFO

Article history:
Received 7 September 2015
Revised 30 December 2015
Accepted 7 January 2016
Available online 11 January 2016

Keywords:
Interleukin
Cytokine
Polymorphism
Meta-analysis
Alzheimer's disease

ABSTRACT

Objectives: Recently, several meta-analyses have reported an association between interleukin (IL) gene polymorphisms and the risk of Alzheimer's disease (AD). Several further papers discussing the relationship with the risk of AD have recently been published. The aim of this meta-analysis was to re-evaluate and update the associations between IL gene polymorphisms and the risk of AD.
Methods: The search sources were PubMed, Science Direct, Scopus, and Google Scholar up to July 2015, and the following search terms were used: "interleukin 1 or interleukin 6 or interleukin 10" and "variant or polymorphism or SNP" in combination with "Alzheimer's disease". A meta-analysis using the pooled odds ratios and 95% confidence intervals was carried out to assess the associations between four polymorphisms of IL genes (−889C>T in IL-1α, −511C>T in IL-1β, −174G>C in IL-6 and −1082G>A in IL-10) and the risk of AD under the heterozygous, homozygous, dominant, and recessive models with fixed- or random-effects models.
Results: A total of 21,864 cases and 40,321 controls from 93 individual studies were included in this meta-analysis. Our results indicated that the −889C>T polymorphism was strongly associated with the increased risk of AD. However, three polymorphisms were not associated with the risk of AD.
Conclusions: Similar to previous meta-analyses, our updated meta-analysis suggested that the −889C>T polymorphism may be a factor in AD. However, the results of our meta-analysis of the −174G>C polymorphism differed from those of previous meta-analyses. Consequently, we suggest that the −174G>C polymorphism may not be a risk factor for AD.

1. Introduction

Dementia is an overall term for conditions characterized by a decline in memory, cognitive and other thinking skills that affect a person's abilities. The total number of people with dementia worldwide was estimated at 35.6 million in 2010, and is projected to be 65.7 million in 2030 and 115.4 million in 2050 (WHO, 2012). Among the several types of dementia, Alzheimer's disease (AD) is the most common. AD was first identified more than 100 years ago. However, its symptoms, causes and risk factors were only discovered in the last 30 years (Alzheimer's Association, 2014).

Several cytokines including interleukin 1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) have been reported to be associated with AD (Wilson et al., 2002). Interleukins (ILs) are important components of the immune system, and a deficiency in them may lead to autoimmune disease or immune deficiency. Several studies have suggested that IL-1 is related to the pathogenesis of AD. Griffin et al. reported that IL-1 immunoreactivity was increased in AD compared with non-AD subjects (Griffin et al., 1989). Sheng et al. suggested that overexpression of IL-1 was associated with evolution of neuritic plaques from diffuse amyloid-β (Aβ) deposits in AD (Sheng et al., 1995). In addition, IL-1 promotes the amyloid precursor protein (APP) cleavage pathway (Buxbaum et al., 1992). Similarly, IL-6 has been reported to be involved in AD pathogenesis. Quintanilla et al. reported that IL-6 was associated with increased levels of hyperphosphorylated tau protein in neurons (Quintanilla et al., 2004). Furthermore, Braida et al. suggested that IL-6 deficiency was associated with learning and memory skills in mice (Braida et al., 2004). These findings suggested ILs to be important factors in AD pathogenesis.

Several epidemiological studies have investigated the association between genetic polymorphisms of IL genes and the risk of AD, including −889C>T (rs1800587) in IL-1α, −511C>T (rs16944) in IL-1β, −174C>G (rs1800795) in IL-6 and −1082G>A (rs1800896) in IL-10 (Bagli et al., 2000; Bhojak et al., 2000; Du et al., 2000;

Abbreviations: OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; SNP, sing nucleotide polymorphism; AD, Alzheimer's disease; IL, Interleukin.

* Corresponding author at: 119, Dandae-ro, Dongnam-gu, Cheonan-si, Chungnam 330-714, South Korea.
E-mail address: wcjang@dankook.ac.kr (W.-C. Jang).

http://dx.doi.org/10.1016/j.mgene.2016.01.001

Grimaldi et al., 2000; Minster et al., 2000; Nicoll et al., 2000; Rebeck, 2000; Ki et al., 2001; Prince et al., 2001; Combarros et al., 2002; Fidani et al., 2002; Green et al., 2002; Hedley et al., 2002; Mattila et al., 2002; Pirskanen et al., 2002; Pola et al., 2002; Shibata et al., 2002; Clarimon et al., 2003; Depboylu et al., 2003; Faltraco et al., 2003; Kuo et al., 2003; Licastro et al., 2003; Lio et al., 2003; Ma et al., 2003; McCarron et al., 2003; Sciacca et al., 2003; Tsai et al., 2003; Arosio et al., 2004; Capurso et al., 2004; Depboylu et al., 2004; Hayes et al., 2004; Li et al., 2004; McCulley et al., 2004; Nishimura et al., 2004; Scassellati et al., 2004; Zhang et al., 2004; Koivisto et al., 2005; Ma et al., 2005; Seripa et al., 2005; Wang et al., 2005; Culpan et al., 2006; Ramos et al., 2006; Ravaglia et al., 2006; Zhou et al., 2006; Bagnoli et al., 2007; Wang et al., 2007; Combarros et al., 2008; Deniz-Naranjo et al., 2008; Paradowski et al., 2008; Dursun et al., 2009; Hu et al., 2009; Klimkowicz-Mrowiec et al., 2009; Serretti et al., 2009; Vural et al., 2009; Capurso et al., 2010; Combarros et al., 2010; Klimkowicz-Mrowiec et al., 2010; Ribizzi et al., 2010; Shawkatova et al., 2010; Cousin et al., 2011; Vendramini et al., 2011; Heun et al., 2012; Mansoori et al., 2012; Payao et al., 2012; Moraes et al., 2013; Rasmussen et al., 2013; Torres et al., 2013; Flex et al., 2014; Kang et al., 2014; Tian et al., 2015; Toral-Rios et al., 2015). However, these epidemiological studies have reported inconsistent results. In addition, several previous meta-analyses have assessed the associations between four polymorphisms of the IL genes and the risk of AD. However, several further papers regarding this relationship between IL gene polymorphisms and the risk of AD have been published recently. It is thus necessary to update the data regarding the association between IL gene polymorphisms and the risk of AD.

Therefore, we have re-evaluated and updated the associations between the polymorphisms of four IL genes and the risk of AD using published studies.

2. Materials and methods

2.1. Search strategy

Two clinical researchers independently searched and reviewed the literature. We conducted a meta-analysis of the published literature to analyze the associations between IL gene polymorphisms and Alzheimer's disease. The search sources were the PubMed, Science Direct, Scopus, and Google Scholar databases, the search was conducted up to July 2015, and the following search terms were used: “interleukin 1 or interleukin 6 or interleukin 10” and “variant or polymorphism or SNP” in combination with “Alzheimer's disease”. The reference lists in the published articles were reviewed to identify any studies missing from the database search. The workflow of the literature search is shown in Fig 1.

2.2. Selection criteria

All articles reporting the genotype frequencies of the following IL gene single-nucleotide polymorphisms (SNPs) were included: −889C>T, −511C>T, −174C>G and −1082G>A. As the studies were heterogeneous in terms of the number of cases and controls, racial composition, and the polymorphisms analyzed, we used the following inclusion criteria: hospital-based or population-based case–control studies on the associations of IL gene polymorphisms with AD, genotype frequencies of each polymorphism provided for cases and controls, genotype distribution in the control group confirmed by Hardy–Weinberg equilibrium (HWE), and English-language articles only. If overlapping cases and controls between studies were identified, only the most-complete study was included in this meta-analysis.

2.3. Data extraction

Data extraction was performed by two reviewers. The following data were extracted from each study: last name of the first author, publication year, study region, participants' ethnicity, sample size, genotype distribution of the polymorphisms of four interleukin genes in both cases and controls, and *p*-values for the HWE of genotype distribution of controls (p value less than 0.05 of HWE was considered to indicate significance).

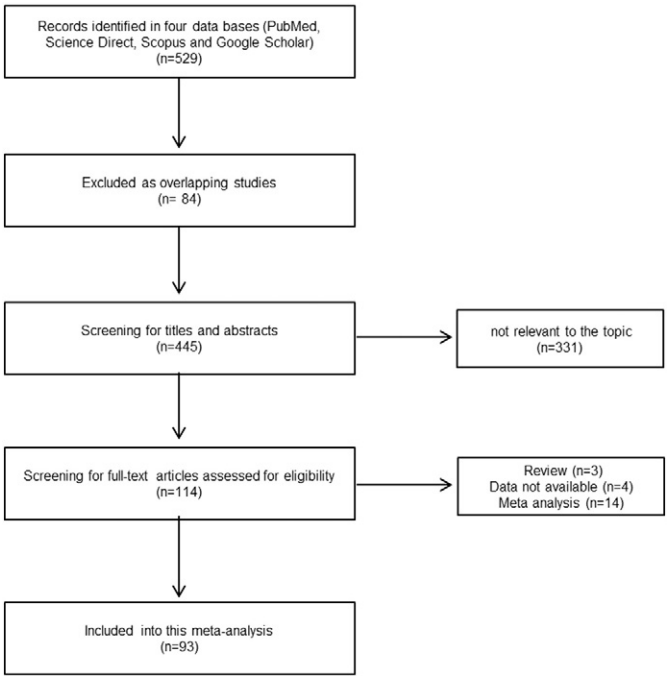

Fig. 1. Flow chart of the selection of studies for inclusion in our meta-analysis.

2.4. Statistical analysis

The chi-squared test was used to determine whether the distribution of genotypes in the control group was in agreement with HWE. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the associations between four IL gene polymorphisms (−889C>T, −511C>T, −174C>G and–1082G>A) and AD risk under the heterozygous, homozygous, dominant, and recessive models with fixed-effects (Mantel–Haenszel method) and random-effects models (Mantel–Haenszel method). Statistical heterogeneity between studies was evaluated using the I^2 statistic. A random-effects model was used to calculate the pooled OR and 95% CI when I^2 values > 50% were considered to indicate significant heterogeneity between studies. A fixed-effects model was used when I^2 values <50% were considered to indicate low heterogeneity between studies. We also performed subgroup analyses by ethnicity (Caucasian and Asian). The risk of small study bias, such as publication bias, was measured using funnel plots and further evaluated with Egger's linear regression test. It was assumed that large-sized studies would plot close to the mean in the absence of publication bias, whereas small-sized studies would be spread smoothly on both sides of the mean. All meta-statistical analyses were performed using the RevMan ver. 5.1 software (Cochrane Collaboration, Copenhagen, Denmark) and confirmed using the Comprehensive Meta-Analysis trial version. Two-sided *p*-values < 0.05 were considered to indicate significance.

3. Results

3.1. Characteristics of the included studies

A total of 529 papers published before July 2015 was identified in the search of the four databases. Of them, a total of 21,864 cases and 40,321 controls from 93 individual studies were included in our meta-