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

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A B S T R A C T

Objective: 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.

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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, −174G>C (rs1800795) in IL-6 and −1082G>A (rs1800896) in IL-10 (Bagli et al., 2000; Bhojak et al., 2000; Du et al., 2000;...
Grimaldi et al., 2000; Minster et al., 2000; Nicoll et al., 2000; Rebeck, 2000; Kim 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; Li et al., 2003; Lieto et al., 2003; Ma et al., 2003; McCarron et al., 2003; Sciaccia 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).

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 I² statistic. A random-effects model was used to calculate the pooled OR and 95% CI when I² values > 50% were considered to indicate significant heterogeneity between studies. A fixed-effects model was used when I² 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-
| Study region          | Ethnicity | Criteria | Sample size (case/control) | Genotype distribution (case/control) | HWE (p-value) | Reference |
|----------------------|-----------|----------|---------------------------|-------------------------------------|---------------|-----------|
| **IL-1α (−889C>T)**  |           |          |                           |                                     |               |           |
| Spanish              | Caucasian | NINCDS-ADRDA | 111/89                  | 61/42                               | 41/34         | 9/13      | 0.171      | Clarimon et al. (2003) |
| American             | Caucasian | NINCDS-ADRDA | 298/306                 | 161/195                             | 119/104       | 18/7      | 0.108      | Combarros et al. (2002) |
| British              | Caucasian | NINCDS-ADRDA-CERAD | 235/310                 | 123/111                             | 93/78         | 19/21     | 0.192      | Combarros et al. (2010) |
| Nottingham           | Caucasian | NINCDS-ADRDA | 189/56                  | 87/24                               | 86/29         | 25/3      | 0.125      | Combarros et al. (2010) |
| Slovak               | Caucasian | NINCDS-ADRDA | 83/96                   | 36/46                               | 38/38         | 9/12      | 0.353      | Combarros et al. (2010) |
| American             | Caucasian | NINCDS-ADRDA | 237/262                 | 124/102                             | 80/110        | 29/25     | 0.56       | Combarros et al. (2010) |
| Swedish              | Caucasian | NINCDS-ADRDA | 187/109                 | 95/52                               | 77/50         | 15/7      | 0.269      | Combarros et al. (2010) |
| Dutch                | Caucasian | NINCDS-ADRDA | 391/510                 | 185/2574                            | 162/2111      | 44/425    | 0.789      | Combarros et al. (2010) |
| American             | Caucasian | NINCDS-ADRDA | 302/374                 | 162/220                             | 114/127       | 26/27     | 0.15       | Combarros et al. (2010) |
| Finland              | Caucasian | NINCDS-ADRDA | 129/190                 | 60/90                               | 61/85         | 8/15      | 0.409      | Combarros et al. (2010) |
| American             | Caucasian | NINCDS-ADRDA | 282/312                 | 138/168                             | 118/121       | 26/23     | 0.85       | Deniz-Naranjo et al. (2008) |
| German               | Caucasian | NINCDS-ADRDA | 259/191                 | 141/126                             | 97/62         | 21/3      | 0.131      | Du et al. (2000) |
| Turkish              | Caucasian | DSM-IV    | 104/103                 | 60/45                               | 41/32         | 3/6       | 0.07       | Dursun et al. (2009) |
| USA                  | Caucasian | NINCDS-ADRDA | 142/119                 | 73/50                               | 59/49         | 10/11     | 0.858      | Fidani et al. (2002) |
| UK                   | Caucasian | NINCDS-ADRDA | 294/503                 | 134/221                             | 162/217       | 34/65     | 0.309      | Green et al. (2002) |
| Italian              | Caucasian | NINCDS-ADRDA | 318/335                 | 140/142                             | 125/163       | 53/30     | 0.08       | Grimaldi et al. (2000) |
| UK                   | Caucasian | CERAD     | 68/503                  | 30/221                              | 31/210        | 7/62      | 0.528      | Hayes et al. (2000) |
| Australian           | Caucasian | NINCDS-ADRDA | 221/351                 | 98/153                              | 94/168        | 29/30     | 0.897      | Hedley et al. (2002) |
| Chinese              | Asian     | NINCDS-ADRDA | 172/163                 | 61/44                               | 77/82         | 34/37     | 0.919      | Nishimura et al. (2004) |
| Asian                | Caucasian | NINCDS-ADRDA-DSM-III-R | 335/204            | 131/72                             | 164/112       | 40/19     | 0.009      | Minster et al. (2000) |
| Asian                | Caucasian | NINCDS-ADRDA-DSM-IV | 232/221                | 103/82                             | 99/74         | 30/11     | 0.291      | McCarron et al. (2003) |
| Asian                | Caucasian | NINCDS-ADRDA | 110/73                  | 42/33                               | 39/25         | 29/11     | 0.281      | Mattila et al. (2002) |
| Asian                | Caucasian | NINCDS-ADRDA | 125/93                  | 104/72                              | 104/168       | 20/27     | 0.032      | Kuo et al. (2003) |
| Asian                | Mediterranean | NINCDS-ADRDA-DSM-IV | 145/181               | 103/128                            | 118/121       | 26/23     | 0.85       | Wang et al. (2007) |
| Asian                | Mediterranean | NINCDS-ADRDA-DSM-IV | 131/219               | 152/118                            | 147/85        | 32/16     | 0.897      | Klimkowicz-Mrowiec et al. (2009) |
| Brazilian            | Asian     | NINCDS-ADRDA | 201/260                 | 182/248                            | 46/103        | 17/26     | 0.756      | Wang et al. (2005) |
| Asian                | Mediterranean | NINCDS-ADRDA-DSM-IV | 219/209               | 74/105                            | 118/105       | 38/48     | 0.928      | Wang et al. (2007) |

**Note:** The table continues on the next page.
analysis. A total of 8641 cases and 14,214 controls from 34 studies (42 subgroup studies) that reported on the association between the IL-1α gene polymorphism (−889C>T) and risk of AD were included in the meta-analysis. A total of 3194 cases and 4621 controls from 18 studies (42 subgroup studies) that reported on the association between the IL-1β gene polymorphism (−511C>T) and risk of AD were included in the meta-analysis. A total of 5755 cases and 12,456 controls from 24 studies (30 subgroup studies) of IL-6 gene polymorphism (−174G>C) were included in the meta-analysis. Seventeen IL-10 gene polymorphism (−1082G>A) studies (23 subgroup studies) involving 4274 cases and 9030 controls were included in the meta-analysis. Most of the studies were performed in Caucasian populations. However, several studies were conducted in Asian populations (nine subgroup studies in IL-1α, six subgroup studies in IL-1β, one subgroup

Table 1 (continued)

| IL-6 (−174G>C) study (author/year) | Study region | Ethnicity | Criteria | Sample size (case/control) | Genotype distribution (case/control) | HWE (p-value) | Reference |
|------------------------------------|--------------|-----------|----------|---------------------------|--------------------------------------|---------------|-----------|
| Arosio et al. (2004)               | Italy        | Caucasian | NINCDS-ADRA-DSM-IV | 59/64 | 17/32 34/27 8/5 | 0.833 | Arosio et al. (2004) |
| Bagli et al. (2000)                | Germany      | Caucasian | NINCDS-ADRA | 102/351 | 33/99 56/208 13/44 | <0.001 | Bagli et al. (2000) |
| Bhojak et al. (2000)              | USA          | Caucasian | NINCDS-ADRA | 464/337 | 178/126 221/155 65/56 | 0.478 | Bhojak et al. (2000) |
| Capurso et al. (2004)             | Italy        | Caucasian | NINCDS-ADRA | 168/220 | 90/129 71/82 7/9 | 0.364 | Capurso et al. (2004) |
| Capurso et al. (2010)             | Italy        | Caucasian | NINCDS-ADRA | 149/298 | 81/172 61/111 7/15 | 0.590 | Capurso et al. (2010) |
| Combarros et al. (2010) (i)       | Bonn         | Caucasian | NINCDS-ADRA-CERAD | 241/224 | 81/77 123/95 37/52 | 0.035 | Combarros et al. (2010) |
| Combarros et al. (2010) (ii)      | Bristol      | Caucasian | NINCDS-ADRA | 189/54 | 66/9 83/29 40/16 | 0.497 | |
| Combarros et al. (2010) (iii)     | Nottingham   | Caucasian | NINCDS-ADRA | 84/95 | 33/32 36/41 15/22 | 0.215 | |
| Combarros et al. (2010) (iv)      | OPTIMA       | Caucasian | NINCDS-ADRA | 243/240 | 88/65 106/141 49/34 | 0.002 | |
| Combarros et al. (2010) (v)       | Oviedo       | Caucasian | NINCDS-ADRA | 190/119 | 89/60 82/51 19/8 | 0.517 | |
| Combarros et al. (2010) (vi)      | Rotterdam    | Caucasian | NINCDS-ADRA | 391/510 | 127/1824 191/246 73/860 | 0.270 | |
| Combarros et al. (2010) (vii)     | Santander    | Caucasian | NINCDS-ADRA | 333/381 | 148/169 137/163 48/49 | 0.328 | |
| Cousin et al. (2011)              | France       | Caucasian | NINCDS-ADRA | 231/470 | 96/171 100/229 35/70 | 0.639 | Cousin et al. (2011) |
| Dephyo et al. (2004)              | Germany      | Caucasian | NINCDS-ADRA | 113/108 | 33/26 65/64 15/18 | 0.046 | Dephyo et al. (2004) |
| Faltraco et al. (2003)            | Germany      | Caucasian | NINCDS-ADRA | 101/133 | 44/43 47/70 10/20 | 0.326 | Faltraco et al. (2003) |
| Flex et al. (2014)                | Italy        | Caucasian | NINCDS-ADRA | 533/713 | 216/160 241/317 76/216 | 0.192 | Flex et al. (2014) |
| Klimkowis-mrowieic et al. (2010) | Poland       | Caucasian | NINCDS-ADRA | 361/200 | 119/66 185/91 57/43 | 0.271 | Klimkowis-Mrowic et al. (2010) |
| Koivisto et al. (2005)            | Finland      | Caucasian | NINCDS-ADRA | 65/542 | 18/136 32/260 15/146 | 0.349 | Koivisto et al. (2005) |
| Licastro et al. (2003)            | Italy        | Caucasian | NINCDS-ADRA-DSM-IV-R | 332/393 | 137/209 161/165 34/19 | 0.057 | Licastro et al. (2003) |
| Mansorri et al. (2012)            | India        | Caucasian | NINCDS-ADRA | 80/120 | 55/88 24/29 1/3 | 0.743 | Mansorri et al. (2012) |
| Moraes et al. (2013)              | Brazil       | Caucasian | NINCDS-ADRA | 120/412 | 71/260 38/136 11/16 | 0.732 | Moraes et al. (2013) |
| Paradowski et al. (2008)          | Poland       | Caucasian | NINCDS-ADRA | 51/36 | 11/12 31/16 9/8 | 0.549 | Paradowski et al. (2008) |
| Pola et al. (2002)                | Italy        | Caucasian | NINCDS-ADRA | 124/134 | 56/29 51/38 17/47 | 0.170 | Pola et al. (2002) |
| Rasmussen et al. (2013)           | Brazil       | Caucasian | NINCDS-ADRA-DSM-IV | 197/163 | 88/82 91/65 18/16 | 0.557 | Rasmussen et al. (2013) |
| Ravaglia et al. (2006)            | Italy        | Caucasian | NINCDS-ADRA | 105/644 | 50/251 43/304 12/89 | 0.842 | Ravaglia et al. (2006) |
| Shakwatova et al. (2010)          | Slovakia     | Caucasian | NINCDS-ADRA | 50/140 | 23/53 21/66 6/21 | 0.951 | Shakwatova et al. (2010) |
| Shibata et al. (2002)             | Japan        | Asian      | NINCDS-ADRA | 128/83 | 4/7 74/23 50/53 | 0.068 | Shibata et al. (2002) |
| Toral-Rios et al. (2015)          | Mexico       | Caucasian | NINCDS-ADRA | 94/100 | 5/3 23/15 66/82 | 0.040 | Toral-Rios et al. (2015) |
| Vural et al. (2009)               | Turkey       | Caucasian | NINCDS-ADRA | 101/138 | 54/76 43/51 4/11 | 0.556 | Vural et al. (2009) |
| Zhang et al. (2004)               | UK           | Caucasian | NINCDS-ADRA-DSM-III-R | 356/434 | 132/152 171/213 53/69 | 0.095 | Zhang et al. (2004) |

Bonn, Ethics Review Board of the University of Bonn; Bristol, Frenchay Local Research Ethics committee Bristol; Nottingham, Nottingham Research Committee 2 (NHS); OPTIMA, Central Oxford Ethics Committee No 1656; Oviedo, Medical Ethical Committee of the Erasmus MC; Santander, Ethical Committee of the University Hospital “Marqués de Valdecilla”; Santander; NINCDS-ADRA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s disease and Related Disorders Association; CERAD, The Consortium to Establish a Registry for Alzheimer’s Disease; DSM, Diagnostic and Statistical Manual of Mental Disorder. * Zhou et al. data from abstract.
study in IL-6, and one subgroup study in IL-10). The characteristics of the studies are summarized in Table 1.

3.2. IL genes polymorphisms and risk of AD

Forty-two subgroup studies involving 8641 cases and 14,214 controls identified an association between the −889C>T polymorphism and risk of AD. The distributions of the genotypes in the control groups followed HWE. Our comprehensive meta-analysis indicated that the −889C>T polymorphism was significantly associated with an increased risk of AD by three genetic models. The ORs of the homozygote (CC vs. TT), dominant (TT/CT vs. CC) and recessive (TT vs. CC/CT) models were 1.32, 1.09 and 1.32, respectively (95% CI: 1.18–1.49, 1.03–1.16 and 1.18–1.45, respectively) using a fixed-effects model (Fig. 2). However, the heterozygote model (CC vs. TC) was not associated with risk of AD (OR: 1.05, 95% CI: 0.98–1.12).

Our meta-analysis suggested that the −889C>T polymorphism was not related to risk of AD. Thirty subgroup studies on the −174G>C polymorphism included 5755 cases and 12,456 controls. Of them, five studies deviated from HWE (p < 0.05) (Bagli et al., 2000; Depboylu et al., 2004; Combarros et al., 2010; Toral-Rios et al., 2015). The tendency of our meta-analysis indicated that the −174G>C polymorphism was related to a decreased risk of AD. However, this polymorphism was statistically not associated with risk of AD (homozygote: OR = 0.85, 95% CI = 0.64–1.13; heterozygote: OR = 0.99, 95% CI = 0.85–1.13; dominant: OR = 0.95, 95% CI = 0.80–1.13; recessive: OR = 0.83, 95% CI = 0.67–1.03) by a random-effects model. Consequently, our results suggested that the −174G>C polymorphism was not associated with risk of AD.

Twenty-three subgroup studies involving 4274 cases and 9030 controls identified an association between the −1082G>A polymorphism and risk of AD. Two studies of the association between the −1082G>A polymorphism and AD risk were conducted in Asian populations. Among previous studies, the results of four studies departed from HWE (p < 0.05) (Lio et al., 2003; Ma et al., 2003; Heun et al., 2012). Our meta-analysis results showed that the −1082G>A polymorphism of IL-10 was not related to risk of AD. The ORs of four genetic
models (homozygote, heterozygote, dominant and recessive) were 1.04, 1.12, 1.10 and 0.97, respectively, using a random-effects model (95% CIs: 0.85–1.28, 0.94–1.33, 0.93–1.29 and 0.83–1.14, respectively). The results of the meta-analysis are summarized in Tables 2 and 3. The results by sequentially deleting each subgroup study from the meta-analysis (Tables 2 and 3). We also performed a sensitivity test to assess the stability and reliability of the results by sequentially deleting each subgroup study from the meta-analysis. The sensitivity test results indicated that none of the subgroup studies altered the pooled OR, suggesting that our meta-analysis was stable and reliable.

4. Discussion

Our meta-analysis summarizes the evidence to date regarding the association between four polymorphisms (−889C>T, −1082G>A, −172G>C and −1082G>A) and the risk of AD. The results indicate that −889C>T was significantly associated with an increased risk of AD. However, three polymorphisms (−511C>T, −172G>C and −1082G>A) were statistically not related to the risk of AD.

Over the past decades, many genetic studies and meta-analyses have been performed to investigate the relationship between IL gene polymorphisms and the risk of AD. The most recent meta-analyses of the association between the four IL gene polymorphisms (−889C>T, −511C>T, −172G>C and −1082G>A) and the risk of AD were reported in 2012 and 2013 (Dai et al., 2012; Di Bona et al., 2012; Hua et al., 2012; Qi et al., 2012; Li et al., 2013; Yuan et al., 2013). A previous meta-analysis of −889C>T polymorphism had included twenty-eight studies and a total 12,817 subjects (Li et al., 2013). Their results indicated that −889C>T polymorphism was significantly associated with increased risk of AD. Furthermore, Caucasian studies revealed that this polymorphism was associated with increased risk of AD. However, most genetic models (dominant, recessive and T allele vs. C allele) showed that −889C>T polymorphism was not associated with risk of AD in Asian. Similarly, our results showed that −889C>T polymorphism was associated with increased risk of AD in overall and Caucasian subgroup studies. In −511C>T polymorphisms, Yuan et al. reported that −511C>T polymorphism was not associated with risk of AD. Furthermore, subgroup studies demonstrated that −511C>T polymorphism was not related with AD in Europe, non-Europe, Caucasian and non-Caucasian. In addition, many genetic models showed that heterogeneity (Yuan et al., 2013). Similar to previous meta-analysis, our results indicated that −511C>T polymorphism was not associated with risk of AD in overall and Caucasian subgroup studies. In 2012, Bona et al. suggested that GG vs. AG/AA model of −1082G>A polymorphism was modestly associated with risk of AD (OR: 0.82, 95% CI: 0.65–1.02). In addition, results of meta-analysis showed that moderate degree of heterogeneity between studies (Di Bona et al., 2012). In contrast, our
results suggested that −1082G>A polymorphism was statistically not associated with risk of AD. However, degree of heterogeneity was similar to previous meta-analysis. As mentioned above, meta-analysis results of three polymorphisms (−889C>T, −511C>T and −1082G>A) were similar to previous meta-analysis. However, the results of the −174C>T polymorphism were different. In 2012, Dai et al. reported an association between the −174C>T polymorphism and the risk of AD in a meta-analysis including 3101 cases and 3860 controls. The overall analysis showed that the −174C>T polymorphism was significantly associated with a decreased risk of AD using a recessive model (OR: 0.70, 95% CI: 0.54–0.90). In addition, the heterozygote model revealed that the −174C>T polymorphism was strongly associated with a decreased risk of AD (OR: 0.83, 95% CI: 0.60–0.96) (Dai et al., 2012). Similarly, Qi et al.’s meta-analysis (4280 cases and 8788 controls) suggested that the recessive model (CC vs. GC/GG) was significantly associated with a decreased risk of AD (OR: 0.65, 95% CI: 0.52–0.82) (Qi et al., 2012). However, our meta-analysis (5755 cases and 12,456 controls) shows that all genetic models (homozygote, CC vs. GC; heterozygote, CC vs. GG; dominant CC/GC vs. GC; recessive models, CC vs. GC/GG) were significantly not associated with the risk of AD. The conflicting results between Qi et al. and our meta-analysis may be due to the included studies. Our meta-analysis contains an additional eight studies (Ravaglia et al., 2006; Combarros et al., 2010; Shawkatova et al., 2010; Cousin et al., 2011; Moraes et al., 2013; Rasmussen et al., 2013; Flex et al., 2014; Toral-Rios et al., 2015). In addition, we deleted four studies (Infante et al., 2004; Combarros et al.,

Table 3

| SNP          | Gene models                  | Fixed effect model OR (95% CI) | Random effect model OR (95% CI) | Heterogeneity I² value | Publication bias P-value | Departed from the HWE |
|--------------|------------------------------|--------------------------------|--------------------------------|------------------------|--------------------------|-----------------------|
| rs1800587 (IL-10; −889C>T) | Homozygote model (TT vs. CC) 1.32 (1.18–1.49) | 1.31 (1.13–1.51) | 22% | 0.110 | 0.900 | / |
|              | Heterozygote model (CT vs. CC) 1.05 (0.98–1.12) | 1.04 (0.97–1.13) | 24% | 0.080 | 0.174 | |
|              | Dominant model (CT/CT vs. CC) 1.09 (1.03–1.16) | 1.08 (1.00–1.17) | 31% | 0.030 | 0.164 | |
|              | Recessive model (TT vs. CC/CT) 1.32 (1.18–1.45) | 1.30 (1.14–1.49) | 18% | 0.160 | 0.897 | |
| rs16544 (IL-1; −511C>T) | Homozygote model (TT vs. CC) 0.95 (0.81–1.12) | 0.94 (0.75–1.18) | 42% | 0.040 | 0.284 | Ma et al. (2003) and Minster et al. (2000) |
|              | Heterozygote model (CT vs. CC) 0.94 (0.84–1.06) | 0.94 (0.82–1.08) | 32% | 0.130 | 0.924 | |
|              | Dominant model (CT/CT vs. CC) 0.95 (0.86–1.06) | 0.94 (0.82–1.08) | 32% | 0.100 | 0.528 | |
|              | Recessive model (TT vs. CC/CT) 0.96 (0.82–1.11) | 0.98 (0.75–1.28) | 63% | <0.001 | 0.475 | |
| rs1800795 (IL-6; −174C>G) | Homozygote model (GG vs. CC) 0.79 (0.70–0.88) | 0.85 (0.64–1.13) | 78% | <0.001 | 0.670 | Bagli et al. (2000), Combarros et al. (2010) (I), |
|              | Heterozygote model (GG vs. GC) 0.97 (0.89–1.05) | 0.99 (0.85–1.15) | 64% | <0.001 | 0.953 | Combarros et al. (2010) (IV), |
|              | Dominant model (GG/GC vs. GC) 0.93 (0.86–1.01) | 0.95 (0.80–1.13) | 76% | <0.001 | 0.917 | Combarros et al. (2010) (IV), |
|              | Recessive model (GG vs. GC/GC) 0.79 (0.71–0.88) | 0.83 (0.67–1.03) | 70% | <0.001 | 0.616 | Depboylu et al. (2004), and Toral-Rios et al. (2015) |
| rs1800896 (IL-10; −1082G>A) | Homozygote model (AA vs. GG) 0.98 (0.86–1.12) | 1.04 (0.85–1.28) | 51% | <0.005 | 0.158 | Heun et al. (2012) (II), |
|              | Heterozygote model (GA vs. GG) 1.07 (0.96–1.20) | 1.12 (0.94–1.33) | 51% | <0.006 | 0.631 | Lio et al. (2003), Ma et al. (2005) and Toral-Rios et al. (2015) |
|              | Dominant model (AA/GA vs. GG) 1.04 (0.94–1.16) | 1.10 (0.93–1.29) | 51% | <0.005 | 0.353 | |
|              | Recessive model (AA vs. GG/GA) 0.93 (0.84–1.03) | 0.97 (0.83–1.14) | 55% | <0.002 | 0.144 | |

Combarros et al. (2010) (I), Bonn, Ethics Review Board of the University of Bonn; Combarros et al. (2010) (IV), OPTIMA, Central Oxford Ethics Committee No 1656; Heun et al. (2012), Nottingham, Nottingham Research Committee 2 (NHS).

−889C>T polymorphism of IL-10x studies were not departed from HWE.

⁎ Statistically significant (p < 0.05).

Fig. 3. Funnel plot for the association between the −889C>T polymorphism and Alzheimer's disease.
Many studies have reported the association between several gene polymorphisms and the risk of AD. Coon et al., suggested that c2/e4, ε3/ε4 and ε4/ε4 variant types of ApoE significantly increased the risk of AD (odds ratios: 3.49, 4.32 and 25.31, respectively) compared with c3/e3 (Coon et al., 2007). In addition, meta-analysis data suggested that ApoE ε4/ε4 type was significantly associated with the prevalence of AD. Interestingly, meta-analyses indicated that the highest estimates were in Northern Europe and the lowest estimates were in Asia (prevalence: 14.1%, 95% CI: 12.2–16.0 in Northern Europe; prevalence: 7.70%, 95% CI: 5.84–9.55 in Asia) (Ward et al., 2012). In addition, it is known that mutations in the presenilin-1 (PSEN-1) and presenilin-2 (PSEN-2) genes are related to AD. Manotas-Rodriguez et al. reported that the PSEN-1 polymorphism (rs165932) was probably associated with the risk of AD in the European sub-group (fixed effect model). OR: 1.19, 95% CI: 1.02–1.37, p-value < 0.05) (Rodrigue-Manotas et al., 2007). In addition, a meta-analysis by Chen et al. suggested that the rs8383 polymorphism of PSEN-2 was associated with an increased risk of AD (OR: 1.16, 95% CI: 1.00–1.33, p-value: 0.043; CC vs. TT, OR: 1.37, 95% CI: 1.02–1.84, p-value: 0.037) (Chen et al., 2012). Furthermore, genome-wide association studies have provided several polymorphisms of candidate genes and loci for AD (Li et al., 2008; Harold et al., 2009). However, the associations between several polymorphisms of candidate genes and the risk of AD are still unclear. To better understand the genetic risk factors for AD, large scale studies are needed to validate the associations and further investigations should consider the effects of environmental factors and genetic interactions.

5. Conclusions

In summary, our updated meta-analysis of 93 studies showed that the results of --889C>T polymorphism was statistically associated with the risk of AD. In contrast, three other polymorphisms were not associated with the risk of AD. In addition, our results of three polymorphisms (~889C>T, ~511C>T and 1082G>A) were similar to those of previous meta-analyses. However, our results for the ~174G>C polymorphism differed from those of previous meta-analyses. Consequently, our results suggested that the ~889C>T polymorphism may be a potential risk factor in AD. However, the other three polymorphisms may not be a risk factor for AD.

Conflict of interest statement

The authors declare that they have no conflict of interest.
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