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Negative results

Functional effects of genetic polymorphism in inflammatory genes in subjective memory complainers

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Abstract

A number of genetic risk factors have been identified for Alzheimer's disease (AD) including genes involved in the inflammatory response (interleukin 1A, [IL-1α (-889)], interleukin 1B (IL-1β [+3953]), and tumor necrosis factor (TNF [-308 and -850]). We investigated the prevalence and functional consequences (baseline cognitive performance, plasma cytokine levels) of possession of these putative genetic risk factors within a group of subjective memory complainers (SMC, n = 226) and age and sex matched noncomplainers (NMC, n = 167). We observed no effect of any of the genetic factors investigated on cognitive performance. Further, there was no difference in the frequency of the disease-associated alleles, or cytokine levels between subjective memory complainers and noncomplainer participants. There was no relationship between TNF polymorphisms and TNF levels. There was a significant increase in plasma IL-1β levels in those homozygous for the disease-associated allele (i.e., IL-1β +3953 TT). Follow-up longitudinal assessments on this cohort will provide insight as to how these polymorphisms may affect the risk of cognitive decline over time.
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1. Introduction

We investigated the prevalence of the following polymorphisms associated with increased risk and reduced age of onset of Alzheimer's disease (AD): interleukin 1A (IL-1α -889 C/T) (Du et al., 2000), interleukin 1B (IL-1β +3953 C/T) (Nicoll et al., 2000), tumor necrosis factor (TNF -850 C/T) (Laws et al., 2005), and TNF -308 G/A (Kroeger et al., 1997) in a group of individuals who may represent a preclinical at-risk group for the incidence of AD (subjective memory complainers; SMC) (Jonker et al., 2000). Our hypotheses were that the prevalence of these functional variants would be increased in SMC compared with noncomplainers (NMC), and that these risk polymorphisms would be associated with impaired global cognitive performance and increased plasma cytokine levels. Apolipoprotein Eε4 (APOE) was included in the analysis as the major genetic risk factor identified to date for AD (Corder et al., 1993), to determine any

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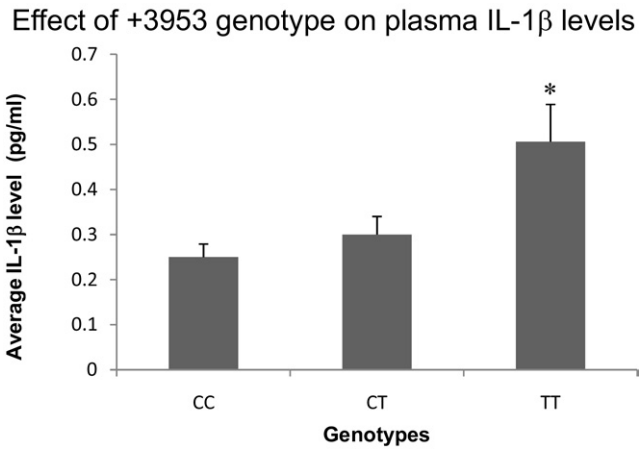

Figure 1. Effect of IL-1β +3953 genotype on IL-1β plasma levels. The TT genotype was associated with significantly higher plasma IL-1β compared to the CC genotype ($p \leq 0.05$). The difference in plasma IL-1β between CT and CC participants neared statistical significance ($p = 0.054$). (Data are presented as mean + SEM; asterisk denotes statistical significance).

synergistic effect between inflammatory genes and possession of the APOEε4 allele.

2. Methods

Cognitive assessments (see supplementary material) and venous blood sampling occurred on the same day. The scores obtained from participants at baseline (i.e., entry into the study) were analyzed (see supplementary material). DNA was isolated from leukocytes for polymerase chain reaction (PCR) (supplementary material Table 1), and enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems Quantikine HS® Kits; R&D Systems, Minneapolis MN, USA) were used to measure plasma cytokine levels.

3. Results

No SMC effect was found with respect to age, gender, or cognitive scores (supplementary material Table 2), and frequency of disease associated alleles and cytokine levels (supplementary material Table 3). All participants were cognitively normal and there was no effect of any of the genetic factors investigated on cognitive performance (supplementary material Table 4). No significant associations were observed between the polymorphisms of interest and the APOEε4 allele. The AD risk genotype IL-1β +3953 TT was associated with elevated plasma IL-1β levels (0.51 pg/mL $\pm$ 0.03) compared with the CC genotype (0.25 pg/mL $\pm$ 0.08) ($p \leq 0.05$) (supplementary material Fig. 1).

4. Discussion

The lack of association between the genetic markers of interest and SMC observed here could be due to a number of factors. SMC may be a poor indicator of presymptomatic AD, with little predictive power. Furthermore, our method of determining SMC may have been too crude (i.e., based on a single question from the Cambridge Examination for Mental Disorders in the Elderly-Revised (CAMDEX-R). Alternatively, the cross-sectional design in a healthy cohort may not have the statistical power to detect minor preclinical changes and the inflammatory gene single nucleotide polymorphisms (SNPs) investigated have a relatively small effect size, even amongst case-control studies of AD. Finally, while the specific genetic variants of the TNF and IL-1β genes analyzed in this study show no evidence to support an association with SMC, we cannot categorically rule out the possibility that a significant association, through an untyped variant, was missed as a whole gene approach was not implemented in this study.

To our knowledge this is the first report of a significant effect of the IL-1β +3953 TT genotype on plasma IL-1β levels compared with CC genotype ($p < 0.05$) in an "at-risk" group for AD. The TT genotype has been previously associated with increased plasma IL-1β in AD patients (Licastro et al., 2000) and IL-1β has been shown to increase the production of beta-amyloid (Aβ) (Rogers et al., 1999). These findings warrant confirmation in follow up studies, as longitudinal assessments on this cohort may provide greater insight as to how these polymorphisms and their cytokines affect the risk of cognitive decline over time.

Disclosure statement

The authors have no actual or potential conflicts of interest to declare.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2010.09.003.

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