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Inhibitory Fcγ Receptor and Paired Immunoglobulin Type 2 Receptor Alpha Genotypes in Alzheimer's Disease

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Abstract

We investigated whether *FCGRIIB* (rs1050501 C/T) and *PILRA* (rs1859788 A/G) genotypes contributed to the development of Alzheimer's disease (AD). We genotyped 209 African American (AA) and 638 European American (EA) participants for the *FCGRIIB and PILRA* alleles. In the AA cohort, subjects homozygous for the C allele of *FCGRIIB* were more than 4 times as likely to develop AD as those homozygous for the alternative T allele. This SNP also interacted with *PILRA*: participants who were the carriers of the *FCGRIIB* C allele and *PILRA* A allele were 3 times as likely to develop AD as those who lacked these alleles.

Keywords

Amyloid-β; *FCGRIIB* ; neurotoxicity; *PILRA*

INTRODUCTION

The heritability of late-onset Alzheimer's disease (AD) has been estimated to be about 80%, using data from monozygotic and dizygotic twins [1]. Although genomic studies have identified hundreds of putative susceptibility genes for AD, most disease heritability remains unexplained, suggesting the involvement of additional genes in its etiology. Inhibitory Fcγ receptor IIB (*FCGRIIB*) and paired immunoglobulin type 2 receptor alpha (*PILRA*) are excellent candidate genes for involvement in AD etiology. *FCGRIIB* has been shown to mediate amyloid-β (Aβ) neurotoxicity, and in animal models of AD, it is associated with neuronal uptake and inter-neuronal accumulation of Aβ, a hallmark of AD [2, 3]. Particular *FCGRIIB* genotypes have been reported to be associated with IgG3 antibody responses to herpes simplex virus type 1 (HSV1) in patients with mild cognitive impairment, but not AD,

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in an Italian population [4]. Its role in AD pathogenesis in people of African descent has not been examined. *PILRA* is a co-receptor for the cell entry of HSV1, which has been implicated in AD pathogenesis [5, 6].

The aim of the present investigation was to determine whether particular SNPs of *FCGRIIB* (rs1050501 C/T) and *PILRA* (rs1859788 A/G) genes—individually and/or epistatically—contribute to the development of AD.

MATERIALS AND METHODS

Study design and DNA samples

We used a prospective cohort study design and archived DNA from three longitudinal cohorts on aging led by the Rush Alzheimer's Disease Center: The Minority Aging Research Study (MARS), the Rush Memory and Aging Project (MAP), and the Religious Orders Study (ROS) [7, 8]. Participants undergo a uniform, structured, clinical evaluation performed annually by examiners blinded to previously collected information. AD diagnoses conform to the criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [9]. For this study, African American (AA) participants from all three cohorts were included (n = 209). A subset of European American (EA) participants, matched on age and sex, was selected from the two cohorts that are predominantly EA (N = 638). All studies were approved by an Institutional Review Board of Rush University Medical Center. All participants signed an informed consent and a repository consent allowing their data to be shared. MARS, MAP, and ROS data can be requested https://www.radc.rush.edu.

Genotyping

FCGRIIB (rs1050501 C/T) and *PILRA* (rs1859788 A/G) genotyping was done by real-time PCR detection, using custom-designed TaqMan® genotyping assays from Applied Biosystems Inc. (Foster City, CA). The primers and probes used have been described previously [4, 10]. For technical reasons, some samples could not be genotyped. Thus, statistical analyses involved *PILRA* rs1859788 data from N = 634 and *FCGRIIB* rs1050501 data from N = 632 EA participants. For AA participants, analyses involved N = 205 for both genotypes.

Statistical analyses

The associations between *FCGRIIB* rs1050501 C/T and *PILRA* rs1859788 A/G genotypes and time to development of AD were assessed using Cox proportional hazards (PH) models, separately for EA and AA participants. Participants who were not diagnosed with AD or who were lost to follow-up were considered censored at death or last date of contact, respectively. Time to development of AD was modeled as a function of covariates (baseline age, sex, years of education, *APOE* ε4 carrier status [yes/no]). Both main and interactive effects of the two genes on the development of AD were investigated. Because of the relatively small number of minor allele homozygotes for the *PILRA* rs1859788 gene (especially among AA participants), the A/A and A/G groups were combined, thus reflecting whether or not the participant was an A-carrier. For gene × gene interactions,

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a backwards model selection process was used. No adjustment was made for multiple comparisons, as this was largely a hypothesis generating exercise. Analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

FCGRIIB rs1050501 and *PILRA* rs1859788 genotype frequencies were in Hardy-Weinberg equilibrium. In AA participants, both main and interactive effects of *FCGRIIB* rs1050501 were noted. Participants homozygous for the C allele of *FCGRIIB* rs1050501 were more than 4 times as likely to develop AD as those homozygous for the alternative T allele of this SNP (HR 4.2, CI 1.5, 11.6, Table 1). Participants who were the carriers of *FCGRIIB* rs1050501 C allele (i.e., CC and CT participants) and *PILRA* rs1859788 A allele (i.e. AA and AG participants) were 3 times as likely to develop AD as those who lacked these alleles (HR 3.0, CI 1.3, 7.0, Table 2). These associations were independent of the *APOE* ε4 allele status and other covariates. No significant associations were found in EA participants (Table 1).

DISCUSSION

We found significant associations between *FCG RIIB* rs1050501 genotypes and time to development of AD in our AA, but not EA, cohort. It is possible that homozygosity for the C allele, which is associated with the development of AD, causes uptake and inter-neuronal accumulation of Aβ as shown in the animal models of AD [3], resulting in neurodegeneration. Notably, the frequency of the C allele in AA participants is higher than in EA participants, 45.4 versus 20.6%, suggesting the genotype is under positive selection in Africa for reasons unknown at this time.

Racial differences in linkage disequilibrium (LD) may be a contributory factor to the observed differences in *FCGRIIB* rs1050501 associations between the AA and EA groups. For instance, there may be other putative risk-conferring genes for AD on chromosome 1 in LD with *FCGRIIB* rs1050501. Any differences in the strength of LD between the two groups could contribute to the observed differences in associations. Substantial population differences in LD patterns are well established [11]. To our knowledge, this is the first report assessing the role of *FCGRIIB* in the development of AD in people of African descent. The lack of association between the *FCGRIIB* rs1050501 genotypes and AD in our EA sample is consistent with the results obtained in an Italian cohort [4].

We found no associations between *PILRA* rs1859788 genotypes and time to development of AD in our prospective study of EA participants. This is in contrast to the results of a case-control study which found a significant association between the arginine-coding allele (A) of this SNP and protection from AD in patients of European ancestry [12]. The differences in study designs of the two studies—prospective cohort versus case-control—may have contributed to this discrepancy. Another contributory factor could be the divergent allele frequencies and the differences in putative environmental factors relevant to AD pathogenesis in the two study populations. Differences in sample size— N = 634 (prospective cohort) versus N = 8,060 (case-control)—could also have contributed to the

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discrepant results between the two studies. Thus, our study may have been under-powered to detect an association between *PILRA* rs1859788 and AD. However, it is noteworthy that the case-control study derived the *PILRA* rs1859788 data from a subset of a genome-wide association study (N = 85,133), which did not show an association with this SNP and AD [13].

The putative mechanisms underpinning the epistatic effects of *PILRA* rs1859788 and *FCGRIIB* rs1050501 on the development of AD observed here are not clear. One could, however, speculate on a mechanism involving neuroinflammation. *PILRA*, expressed on microglia, has been shown to be associated with neuroinflammation [14]. It is possible that the expression of the A allele of *PILRA* rs1859788 in microglia causes a higher degree of neuroinflammation, which, coupled with inter-neuronal accumulation of Aβ associated with the C allele of *FCGRIIB* rs1050501, could result in neurodegeneration associated with the development of AD.

AD is a polygenic disease, and it would be of interest to investigate possible epistatic interactions of *PILRA* and *FCGRIIB* genes with other candidate genes, especially those involved in the type I interferon pathway, which is integral to neuropathology, as demonstrated in the animal models of AD [15]. To our knowledge, this is the first report of an interactive effect of *PILRA* and *FCGRIIB* SNPs on the development of AD. It needs confirmation by independent investigations and in larger datasets.

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Table 1

Distribution of *FCGRBIIB* (rs1050501 C/T) and *PILRA* (rs1859788 A/G) genotypes and association with AD, stratified by race

	European Americans (*n* = 634)				African Americans (*n* = 205)			
Genotype	***N***	**%**	**HR for AD**	**95% CI**	***N***	**%**	**HR for AD**	**95% CI**
FCGRIIB								
C/C	12	1.9	1.3	0.6–2.9	12	5.9	4.2	1.5–11.6
C/T	118	18.7	0.9	0.7–1.3	81	39.5	1.2	0.6–2.3
T/T	502	79.4	reference		112	54.6	reference	
PILRA								
A-carriers	339	53.5	0.9	0.7–1.2	60	29.3	1.7	0.9 to 3.2
NonA-carriers	295	46.5	reference		145	70.7	reference	

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Table 2

Interactive effects of *FCGRIIB* (rs1050501 C/T) and *PILRA* (rs1859788 A/G) genotypes on AD development among African American subjects

Genotype Combinations	*N*	%	HR for AD	95% CI
FCGRIIB-C+, PILRA-A+	25	12.2	3.0	1.3 to 7.0
FCGRIIB-C−, PILRA-A+	35	17.1	0.7	0.2 to 2.0
FCGRIIB-C+, PILRA-A−	68	33.2	0.8	0.4 to 1.8
FCGRIIB-C− and PILRA-A−	77	37.6	reference	