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Estrogen receptor polymorphisms and incident dementia: The prospective 3C study

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Abstract

Background: Genetic variation in the estrogen receptor (*ESR*) may be associated with the incidence of Alzheimer's disease (AD), but this association could be modified by genetic and environmental factors.

Methods: The association between five *ESR* α (*ESR1*) and β (*ESR2*) polymorphisms with 7-year dementia incidence was examined among 6959 older men and women from the Three City Study using multivariate-adjusted Cox regression models with delayed entry. Gender, the apolipoprotein E (*APOE*) ε4 allele, and hormone treatment were considered as potential effect modifiers of this association.

Results: Among women, the CC genotype of *ESR1 rs2234693* was specifically associated with a small increased risk of AD (adjusted hazard ratio [HR]: 1.54, 95% confidence interval [CI]: 1.03–2.28, $P = .03$). However, women with this genotype had a substantially increased risk of AD associated with the *APOE* ε4 allele (adjusted HR: 3.24, 95% CI: 1.81–5.79 for women *rs2234693* CC; compared with HR: 1.87, 95% CI: 1.37–2.56 for all women). There was also evidence of a nominally significant interaction between the *ESR1* and *ESR2* polymorphisms on the risk of all dementias ($P = .04$). Hormone treatment did not modify these associations, and there were no significant associations in men.

Conclusions: Although there was only weak support for a gender-specific association between the common *ESR1 rs2234693* polymorphism and AD, this polymorphism may act as an effect modifier, modifying the association between an *ESR2* polymorphism and dementia, as well as the risk of AD associated with the *APOE* ε4 allele.

Keywords: Alzheimer's disease; Dementia; Estrogen receptor polymorphisms; ESR1; ESR2; Gender-specific; *APOE*; Epidemiology; Cohort study

1. Background

Dementia is a multifactorial disease that has been associated with many interacting environmental, biological, and genetic risk factors. Recent genome-wide association studies (GWAS) have identified a few candidate genes for Alzheimer's disease (AD) [1,2]; however, together these genes only explain a small amount of the underlying genetic component of the disease [3]. This may be accounted for in part by the interplay between genetic and environmental factors, in complex gene-gene and gene-environment interactions that cannot be identified through GWAS.

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Epidemiological studies have reported that women have a higher incidence of dementia, and in particular AD, compared with men [4], which suggests the potential involvement of steroid hormones such as estrogen. In support of this, estrogen is synthesized in the brain by the aromatization of androgens, with estrogen receptors (ESRs) being present in limbic brain regions known to be implicated in dementia [5], and there is considerable experimental evidence indicating that estrogen has neuroprotective and neurotrophic effects [6]. Furthermore, several cohort and case-controlled studies have found that the risk of dementia and especially AD was reduced in postmenopausal women using estrogen-containing hormone treatment, although this was not supported by the findings of a large randomized controlled trial (see for review [7]). It is plausible that genetic variants that modify estrogen signaling, such as polymorphisms in the estrogen receptors α (*ESR1*) and β (*ESR2*), could be candidate risk genes for dementia.

Indeed, several case-control studies have examined differences in the frequency of *ESR1* polymorphisms between patients with late-onset AD and controls, but the exact association remains unclear. Some of these studies have reported that AD patients had a significantly higher frequency of the minor C and G alleles of *rs2234693* and *rs9340799*, respectively [8–11]; however, other studies have found no significant associations [12–14] or even reverse associations [15,16]. Meta-analyses conducted a few years ago found a small but significant association between the minor alleles of these polymorphisms and an increased risk of AD (odds ratio [OR] ~1.2) [17,18]; however, this is not supported by the most recent meta-analysis on the Alzheimer's Research Forum (http://www.alzgene.org). Gender-specific effects have not been examined in these analyses, nor have gene-gene interactions been considered. However, there are limitations to case-control studies, which are inherently more prone to selection bias and a greater risk of population stratification, which is of particular concern for genetic association studies. The only prospective study to be undertaken [19], the Rotterdam study of 2483 men and 3573 women aged at least 55 years, failed to find a significant association between the two common *ESR1* variants and the 6-year risk of all-cause dementia or AD [19]. This finding is yet to be replicated in another cohort. Furthermore, very few studies overall have investigated associations between *ESR2* polymorphisms and dementia despite evidence from animal studies suggesting it plays a key neuroprotective role [20].

The present study examines the association between *ESR1* polymorphisms and the risk of all-cause dementia or AD in the elderly general population. As only the second prospective study to be undertaken, we aim to help clarify previous findings while also investigating prospectively for the first time potential associations with *ESR2* polymorphisms. On the basis of previous findings from relatively small case-control studies, we also investigated a priori interactions between *ESR1* and *ESR2* receptors on the risk of dementia [21] and the possibility that ESR polymorphisms could further increase the risk of AD associated with the apolipoprotein E (*APOE*) ε4 allele [9,11].

2. Methods

2.1. Study participants

The Three City (3C) Study is a multicenter longitudinal study of community-dwelling elderly aged 65 years and over from three French cities [22]. Recruitment of the study cohort from the electoral rolls took place between 1999 and 2001. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre (France). Written informed consent was obtained from all participants in the study. At baseline and the 2-, 4-, and 7-year follow-ups, participants were administered standardized questionnaires by trained staff and underwent clinical examinations. Of the 9080 dementia-free participants recruited to the 3C Study, 644 refused to provide blood samples for genotyping analysis and 670 had no follow-up data. A further 474 had incomplete genotyping data and 333 had missing data for at least one of the covariates considered in this analysis. Thus, these data are based on 6959 men and women. Compared with the analyzed sample, participants not included in this analysis were more likely to be older and have a lower education level, physical incapacities, depressive symptoms, and comorbidity (P values $<.005$) at baseline, and they were more likely to be diagnosed with dementia during the follow-up period ($P < .001$). There was no significant difference between excluded and included participants in terms of the frequency of the *APOE*-ε4 allele or of the *ESR1* and *ESR2* genotypes, with the exception of *rs4986938*, in which excluded participants were more likely to carry the variant A allele ($P = .02$).

2.2. Dementia diagnosis

Dementia diagnosis was based on a three-step procedure [22], the first of which involved a thorough neuropsychological examination by trained psychologists, including the assessment of different aspects of cognitive function. The severity of cognitive disorders, activities of daily living, and, when possible, magnetic resonance images or computed tomography scans were also collected. A neurologist then examined all participants suspected of having dementia. The final step of the diagnosis involved a review of all potential cases of dementia by a national panel of independent neurologists who were experts in the field of dementia. Cases were reviewed using all of the existing information, and a consensus on the diagnosis of dementia was obtained according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV),* revised criteria and etiology. AD was classified according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria [23]. This current study