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PPAR-γ Pro12Ala genotype and risk of cognitive decline in elders

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Abstract

Background: The Pro12Ala polymorphism of peroxisome proliferator-activated receptor-gamma (PPAR-γ) has been associated with decreased risk of diabetes and obesity, both disorders linked to cognitive impairment. We tested whether this polymorphism is associated with cognition.
Methods: Two thousand nine hundred sixty-one participants (mean age, 74.1; 41% Black; 52% women) were administered the Modified Mini-Mental State Examination (3MS) and Digit Symbol Substitution Test (DSST) at baseline and 4 year follow-up. Test scores were adjusted for age, sex, education, cerebrovascular disease, depression and APOE genotype and additionally for race. We determined the association between Ala allele and development of cognitive decline (3MS decline of ≥5 points).
Results: At baseline, unadjusted scores on both cognitive tests were higher for Ala carriers compared to non-carriers (3MS, 94.2 versus 92.5, $p < 0.001$; DSST, 40.2 versus 34.5, $p < 0.001$). Similarly, follow-up scores were higher for Ala carriers. Multivariable adjustment led to similar results; additional adjustment for race attenuated the baseline 3MS results. After 4 years, 17.5% of Ala carriers developed cognitive decline compared to 25% among non-carriers (unadjusted OR = 0.61; 95%CI, 0.46–0.82; adjusted OR = 0.75; 95%CI, 0.55–1.02). Further adjustment for metabolic variables including fasting blood glucose and lipid level did not change the results.
Conclusions: The PPAR-γ Ala12 allele carriers may have less risk of developing cognitive decline.

Keywords: Cognitive function; PPAR-γ; Cognitive impairment; Dementia; Metabolism

1. Introduction

The peroxisome proliferator-activated receptor-gamma (PPAR-γ) is a critical transcription factor in the development and function of adipose tissue. PPAR-γ plays an important role in several age-associated changes in body composition and metabolism, including obesity, insulin resistance and type 2 diabetes. It is well recognized as the molecular target of the thiazolidinediones class of insulin-sensitizing class [18]. The Pro12Ala PPAR-γ2 variant was first identified in 1997 and is relatively common in White populations [29]. The Ala allele has been associated with higher body mass index (BMI) [21] but also a reduced risk of type 2 diabetes [1,24].

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PPAR-γ is also expressed in the central nervous system in microglial cells and monocytes [4]. PPAR-γ activation has been shown to inhibit microglial mediated neurotoxicity and cytokine expression in both in vitro [7] and in vivo [13] experiments. A recent trial that tested the effects of PPAR-γ agonists on patients with early Alzheimer disease (AD) and mild cognitive impairment (MCI) yielded favorable short-term results [26]. No studies to date have determined whether common polymorphisms of PPAR-γ are associated with cognitive function. However, obesity, insulin resistance and diabetes are increasingly recognized as important risk factors for dementia and cognitive decline [8,12,19,27,28,11].

We examined the relationship between Ala allele carrier status in the Pro12Ala polymorphism of PPAR-γ with performance on two tests of cognitive function at baseline and after approximately 4 years of follow-up in a large biracial cohort of older adults. Since the Ala allele has been associated with decreased risk of diabetes in several populations [1], we hypothesized a priori that the Ala allele would be associated with better cognitive test performance and less cognitive decline over time. Moreover, we postulated that an association between PPAR-γ polymorphisms and cognitive function might be mediated by metabolic variables including obesity, diabetes and dyslipidemia.

2. Methods

2.1. Study population

Participants enrolled in the Health, Aging and Body Composition study (Health ABC) were well-functioning men and women between the ages of 70 and 79 years who were recruited from April 1997 to June 1998 from a random sample of Medicare beneficiaries residing in the areas surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. To be eligible for inclusion in the study, participants had to report no difficulty in walking 1/4 mile, climbing 10 steps or performing basic activities of daily living. Individuals requiring assistive devices for ambulation, subjects with difficulty performing activities of daily living or life-threatening cancers, and those planning to leave the area within 3 years were excluded from the study.

We first performed a cross-sectional study using the baseline medical history, physical exam measurements, laboratory tests and cognitive function tests gathered in 1997–1998. We then performed a prospective analysis for change in cognitive function with a mean length of follow-up of 3.7 ± 0.9 years. Of the 3075 participants enrolled in Health ABC, we excluded 100 who were missing PPAR-γ genotype information and another 14 who did not have cognitive testing at the baseline examination. Thus, our analytic sample included 2961 participants.

The study was approved by the institutional review boards of the University of California, San Francisco, University of Pittsburgh and University of Tennessee. All of the study participants provided written informed consent to participate in the study.

2.2. Measurements

2.2.1. PPAR-γ genotype

From genomic DNA, the Pro12Ala PPAR-γ2 variant was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis as previously described [2,29]. Briefly, genomic DNA was subjected to PCR using upstream primer 5′-GCCAATTCAAGCCCA-GTC-3′ and mutagenic downstream primer 5′-GATATGTTT-GCAGACAGTGTATCAGTGAAGGAATCGCTTTCCG-3′ using standard reagents and cycling conditions to yield a 270 base pair product. If the C→>G substitution at nucleotide 34 of the PPAR-γ gene was present, the mutagenic downstream primer introduced a BstU-I restriction site (CG||CG). Digestion with BstU-I was performed, followed by electrophoresis on a 2.5% agarose gel, staining with ethidium bromide and visualization by UV transillumination.

2.3. Cognitive function tests

The Modified Mini-Mental State Examination (3MS) was administered to all participants during the baseline visit and repeated at the third and fifth annual follow-up examinations. This test is a brief general cognitive battery with components for orientation, concentration, language, praxis and immediate and delayed memory with a maximum score of 100 [25]. The 3MS test is more sensitive than the 30-point Mini-Mental State Examination, especially for mild cognitive change [25]. We examined the change in 3MS score from the baseline examination to the 4-year follow-up, and clinically significant cognitive decline was defined as a 3MS decline of 5 or more points over time as has been previously recommended [17].

The Digit Symbol Substitution Test (DSST) measures attention, psychomotor speed and executive function. The DSST score was calculated as the total number of test items correctly coded in 90 s, with a higher score indicating better cognitive function [3]. The DSST was administered at baseline and at Year 5.

2.4. Covariates and explanatory factors

Racial group, age, sex and education were assessed by self-report during the baseline interview. Participants reported smoking history as never, former or current smoker. Each participant had seated systolic and diastolic blood pressures measured by a manual sphygmomanometer. Hypertension was defined by self-report of a diagnosis, use of an anti-hypertensive medication, or if systolic blood pressure $\geq$140 mmHg or if diastolic blood pressure $\geq$90 mmHg. Diabetes was defined by self-report of diabetes diagnosis, use of diabetes drug or if fasting plasma glucose $\geq$126 mg/dl or 2-h post-challenge glucose $\geq$200 mg/dl. Cerebrovascular disease