

ARIC Manuscript Proposal #2648

PC Reviewed: 10/13/15
SC Reviewed: _____

Status: A
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Priority: 2
Priority: _____

1.a. Full Title: Cognitive Decline and the PPAR- γ Pro12Ala Genotype

b. Abbreviated Title (Length 26 characters): Cognition and Pro12Ala

2. Writing Group:

Writing group members: Nancy West, Jeannette Simino, Elizabeth Selvin, Jan Bressler, Michael Griswold, Thomas Mosley

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __NW__ [**please confirm with your initials electronically or in writing**]

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3. Timeline: All data is currently available. We plan to submit for publication within 6 months of manuscript proposal approval.

4. Rationale:

An increasing number of reports have linked metabolic dysfunction to cognitive decline and late onset Alzheimer's disease (AD)¹. Impaired glucose metabolism parameters such as hyperglycemia and insulin resistance correlate with the development of AD-related pathology². Further, it is well known that the $\epsilon 4$ allele of the apolipoprotein E (APOE) gene has been identified as a primary genetic determinant of late-onset AD risk³. The APOE gene encodes a glycoprotein involved in the transport of cholesterol and other lipids in the periphery and brain, suggesting a possibility that a dysfunction of the lipid transport system in the brain could play a role in the pathogenesis of AD⁴.

Reports linking metabolic dysregulation to age-related dementia have led to the investigation of genes involved in lipid and glucose metabolism as potential susceptibility loci for cognitive decline. The peroxisome proliferator-activated receptor gamma (PPAR- γ) gene plays a key role in lipid metabolism and insulin sensitivity and has been shown in animal models to regulate components of amyloid β metabolism⁵, a proposed key causative factor in AD. The Pro12Ala (C \rightarrow G, rs1801282) polymorphism in the PPAR- γ gene is responsible for a Pro to Ala transition in codon 12. The Pro12Ala variant has been associated with protection from the development of type 2 diabetes (T2D)⁶, a disorder linked to cognitive impairment. Because of the confirmed association of Pro12Ala with T2D and the link between T2D and cognitive decline, the Pro12Ala polymorphism has been studied in the context of AD and cognitive decline with conflicting results. The absence of consistent results may reflect population differences in the relationship between Pro12Ala and cognitive function. Because PPAR- γ is a master transcriptional regulator involved in the expression of numerous genes, there is potential for complex interactions between the Pro12Ala polymorphism and other genetic and/or environmental factors. Many studies have reported modification of the association between the Pro12Ala polymorphism and cognitive function by sex, T2D status, and/or ethnicity.

Previously reported sex-specific associations between Pro12Ala and cognitive function

An association between male Ala12 carriers and decline in cognitive function has been reported in 3 studies:

- 1) Among a large cohort of older Latinos, an increased rate of dementia/cognitive impairment without dementia was reported among males carriers of the Ala12 allele compared to male non-carriers (adjusted HR=2.7, 95% CI: 1.4-5.2). There was no significant difference in rates of cognitive impairment among female Ala12 carriers compared to female non-carriers (adjusted HR=0.88; 95% CI: 0.47-1.6)⁷.
- 2) Results from a population-based, bi-ethnic cohort study of older adults showed significantly greater cognitive decline, as measured by the Mini-Mental State Examination, among male Ala12 carriers compared to male non-carriers (2.4 points vs 1.2 points, p=0.02) over an average of 22 months follow-up. Decline was not significantly different between female Ala12 carriers and female non-carriers (p=0.41) (West et al, Cognitive decline and the PPAR- γ Pro12Ala genotype: variation by sex and ethnicity, under review).

- 3) A large candidate gene association study reported a gender-specific difference in risk of late-onset AD such that among males there was a trend toward significance for the Ala12 allele to be a risk factor in the dominant model (OR = 1.42, P = 0.08), but among females the Ala12 allele presented as a protective factor in the dominant model (OR = 0.73, P = 0.025)⁸.

Lipid metabolism differs between males and females⁹ and APOE ε4 and lipoprotein receptors appear to play a pivotal role in AD pathogenesis¹⁰, suggesting a possible mechanism that could explain these sex-specific findings relating Ala12 to cognitive decline.

Previously reported associations between Pro12Ala and cognitive function modified by T2D

Two studies have reported an increased risk of cognitive impairment and cognitive decline among Ala12 carriers with T2D^{7,11} compared to diabetic non-Ala12 carriers. In both studies there was no significant difference in cognitive risk between Ala12 carriers and non-carriers among the study participants without T2D. These reports suggest that the Ala12 allele in diabetic individuals may be a prognostic factor for increased diabetes severity that, in turn, may increase the risk of cognitive decline.

Previously reported ethnic-specific associations between Pro12Ala and cognitive function

The reported effects of the Pro12Ala polymorphism on cognitive function are inconsistent across race-ethnic populations, suggesting possible gene-gene and/or gene-environment interactions. A significant decline in cognitive function, as measured by the Modified Mini-Mental State Examination after 4 years of follow-up, was reported among non-Ala12 carriers in a biracial (Blacks and Whites) cohort of older individuals; however the results were attenuated after adjustment for race, suggesting a complex-interrelationship among Pro12Ala, race/ethnicity, and cognitive decline.¹² Further, results from a bi-ethnic cohort of older Mexican- and European-Americans in Colorado showed no significant difference in cognitive decline, as measured by the Mini-Mental State Exam, between Ala12 carriers and non-carriers among the European-American population (p=0.90) but significantly greater decline in MMSE score among the Mexican-American carriers of the Ala12 allele compared to Mexican-American non-carriers (p=0.02) [West et al, Cognitive decline and the PPAR-γ Pro12Ala genotype: variation by sex and ethnicity, under review].

Summary of gaps in literature

Given the heterogeneity in the magnitude and direction of associations reported between Pro12Ala and cognitive function within different populations, an important next step is to identify specific sub-populations of Pro12Ala genotype carriers that may be at increased risk for cognitive impairment.

5. Main Hypothesis/Study Questions:

- i. Investigate the association between the Pro12Ala polymorphism in the PPAR- γ gene and performance on cognitive function and decline across ARIC study visits (V2 through V5).
- ii. Investigate whether these relationships are modified by sex, diabetes status, and/or race.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design

Cohort study using longitudinal data across study visits 2-5.

Exclusions

Participants with race other than black or white.

Participants with RES_DNA = "CVD Research" or RES_DNA = "No use/storage DNA".

Participants with no cognitive function scores during visits 2-5.

Participants without Pro12Ala genotyping.

Exposure

Because of the low frequency of the Ala12Ala genotype, genotypes will be categorized as Ala12 allele carriers (Ala12Ala or Pro12Ala) and non-Ala12 carriers (Pro12Pro). The allele and genotype frequencies for the Pro12Ala polymorphism will be determined by race and whether they meet Hardy-Weinberg equilibrium expectations in each group.

Outcomes

The outcome variables will be the repeated measures of 3 cognitive tests as well as a 4th summary measure of the 3 tests:

1. Delayed word recall test (DWRT)
2. Digit symbol substitution test (DSST)
3. Word Fluency Test (WFT)
4. Composite score derived from the DWRT, DSST, and WFT ("Global-Z")

For each test, a Z-score will be calculated by subtracting the test mean and dividing by the standard deviation. To create the "global-Z", the Z-score from each test will be averaged.

Statistical Analysis

The analytic population will be characterized using means (standard deviation) or N (%) for all covariates. Mixed models will be used to perform longitudinal analysis of the relationship between Ala12 carriers and cognitive decline across study visits. Analyses will adjusted for standard risk factors for cognitive decline including age,

education, and APOE ε4 carrier status. If there is no evidence of effect modification by sex and/or race, these covariates will be added to the model. In the final model, variables that may lie in the causal pathway between Ala12 carrier status and cognitive decline (body mass index/waist circumference at baseline, systolic blood pressure at baseline, and baseline stroke history) will be added. If there is no evidence of effect modification by baseline diabetes status, this covariate will also be included in the final model.

Model 1: Crude/unadjusted

Model 2: Model 1 + age, education, and APOE ε4 carrier status, (and sex and race if no evidence of effect modification)

Model 3: Model 2 + baseline BMI (and separately waist circumference at baseline), baseline systolic blood pressure, and baseline stroke history (and baseline diabetes status if no evidence of effect modification)

Effect Modification

Interactions between Ala12 carrier status and sex, baseline diabetes status, and race/ethnicity status will be tested by including product terms in the models. Stratified analysis will also be performed to investigate effect modification.

Sensitivity Analysis

As sensitivity to the Missing At Random (MAR) assumptions inherent in the mixed models, we will examine Missing Not At Random (MNAR) approaches such as shared parameter model (SPM) formulations, inverse probability of weighting for attrition (IPAW) models and Multiple Imputation (MICE) strategies incorporating additional known information.

Challenges/Limitations

Ala12 carrier rates in African American populations are relatively low (~5%) compared to European American (~20%). This will likely reduce the statistical power to identify a relationship with cognitive decline among this race/ethnic population. However, this limitation may be mitigated by the relatively large sample of African Americans in the ARIC cohort.

Sensitivity analysis (see above) will be performed to assess possible violations of the ‘missing at random’ assumption.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
 No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? Yes
 No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?

Yes No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>

Yes No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

There are 3 manuscript proposals related to the Pro12Ala genotype and diabetes but none related to the Pro12Ala genotype and cognition:

MSP #1280 Interactions between diabetes, diabetes genes, and the androgen receptor gene on risk of prostate cancer (Meyer)

MSP #1072 Peroxisome Proliferator-Activated Receptor (PPARG) and Neuropeptide Y (NPY) Polymorphism and Retinal Vessel Diameters In African-Americans (Wong)

MSP #1237 Association between genetic variants conferring risk for type 2 diabetes mellitus and incident chronic kidney disease (Kottgen)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2008.06)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does

not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.

Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

References

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