Author's response to reviews

Title: Genetic variation of Glucose Transporter-1 (GLUT1) and albuminuria in 10,278 European Americans and African Americans: a case-control study in the Atherosclerosis Risk in Communities (ARIC) Study

Authors:

Charles C Hsu (cchsu@jhmi.edu)
W.H. L Kao (wkao@jhsph.edu)
Michael W Steffes (steff001@tc.umn.edu)
Tejal Gambir (trami@jhsph.edu)
Frederick L Brancati (fbrancati@jhmi.edu)
Charles W Heilig (cheilig@medicine.bsd.uchicago.edu)
Alan Shuldiner (Ashuldin@medicine.umaryland.edu)
Eric Boerwinkle (Eric.Boerwinkle@uth.tmc.edu)
Josef Coresh (coresh@jhu.edu)

Version: 3  Date: 27 August 2010

Author's response to reviews: see over
Department of Epidemiology

August 15, 2010

Josef Coresh, M.D. Ph.D. and Charles C. Hsu, M.D., Ph.D.
Welch Center for Prevention, Epidemiology and Clinical Research
Department of Epidemiology
Johns Hopkins University
2024 E. Monument St., Suite 2-600
Baltimore, MD 21205
(410) 955-0495 fax 410-955-0476, coresh@jhu.edu

Dr. Hans Zauner
Scientific Editor
BioMed Central Medical Genetics
Tel: +44 (0) 20 3192 2013
e-mail: editorial@biomedcentral.com

MS: 1772243348310353
Version 2
Genetic variation of Glucose Transporter-1 (GLUT1) and nephropathy in 10,278 Caucasian and African-Americans: a case-control study in the Atherosclerosis Risk in Communities (ARIC) Study

Dear Dr. Zauner:

Thank you very much for your most recent comments regarding our manuscript titled “Genetic variation of Glucose Transporter-1 (GLUT1) and nephropathy in 10,278 Caucasian and African-Americans: a case-control study in the Atherosclerosis Risk in Communities (ARIC) Study”.

My co-authors and I would like to submit a revised version (version 3) of our manuscript for your consideration. We appreciate the suggestions from the reviewers and have attempted to address each of the comments (see attached).

The revised manuscript with the most recent changes made as a result of these reviews has been attached.

Thank you. Please do not hesitate to contact us if there are any further questions.

Sincerely,
Reviewer Shiro Maeda:
Comments on Version 2:
Reviewer: Shiro Maeda
Reviewer's report:
The authors have well responded to my previous comments, and I have no further comment on this manuscript.

RESPONSE:
Thank you very much for your review. No changes were made regarding Dr. Maeda’s comments.
Reviewer Samy HADJADJ:
Comments on version 2:
Reviewer's report:
The paper by C. Hsu et al was greatly improved.
However, I feel a little bit concerned. The main positive result relates to type 2 diabetes in European / American subjects.
However, this relationship between GLUT-1 Enh 2 polymorphism and albuminuria was not replicated in the stage2.
In general, the authors are quite permissive with the use of the statistical signification.
The authors should thus clarify if this is a positive result with a lack of replication or negative result with a huge study population. This must be clearly stated in the text.

RESPONSE: Thank you for the response. In order to clarify, we have amended our conclusions to clearly state that this is a positive result in stage 1 and in our combined analysis, however, there is a lack of replication of replication of the stage 1 findings in stage 2.

Edits: We have amended our abstract, results, discussion, and conclusion to reflect this (see below and in text using track changes).

Abstract:
In stage 2(n=7,340), Enh2 risk genotype had slightly increased but non-significant OR among European Americans with diabetes (OR=1.66, [0.77-3.56], P=0.192) and not non-diabetics (OR=0.99, p=0.953), not replicating the findings of stage 1.

The association of Enh2 with albuminuria among European Americans with diabetes found in stage 1 was not replicated in stage 2; however, the risk association was seen after combining all European Americans with diabetes from stages 1 and 2.

Results:
The GLUT1 Enh2 polymorphism was genotyped in a separate stage 2 of European Americans (n=6319; 374 cases) and African Americans (n=1021, 146 cases), and the risk genotype tended towards an increased (but not statistically significant) OR among European Americans with diabetes (OR=1.66, 95% CI: 0.77 – 3.57, p=0.192) but not among non-diabetics (OR=0.99, 95% CI: 0.61 – 1.59, p=0.953). The risk association among European Americans with diabetes from stage 1 was not replicated in stage 2.

Discussion:
Genetic variation of GLUT1 may be associated with the risk of micro- and macroalbuminuria in the general U.S. adult population of European Americans with type 2 diabetes. Though an association was seen when we combined European Americans
with diabetes from stages 1 and 2, the findings of stage 1 were not replicated in stage 2.

By study stage, the Enh2 risk genotype was associated with diabetic albuminuria among European Americans only in stage 1 and in the total study population; these findings were not replicated when we examined stage 2.

Another limitation is that the Enh2 risk genotype was only significantly associated with diabetic albuminuria among European Americans from stage 1 and in the combined analysis. The findings of stage 1 were not replicated in stage 2.

Conclusion:

In summary, GLUT1 genetic variation of Enh2 may predict risk of micro- and macroalbuminuria among European Americans with type 2 diabetes. Though the Enh2 risk genotype was significantly associated with diabetic albuminuria among European Americans from stage 1 and in the combined analysis, the findings of stage 1 were not replicated in stage 2.