Author's response to reviews

Title: Differential endothelial cell gene expression by African Americans versus Caucasian Americans: A possible contribution to health disparity in vascular disease and cancer

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Editors & Reviewers
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RE: MS 4758905994073540

Dear Doctors:

In our attached revision of our paper entitled “Differential endothelial gene expression…etc”, we have tracked our changes in color. NOTE: different colors have no significance except to indicate when the changes were entered. Also, please be aware that the “track changes” function indicated any paragraphs that were simply moved to a different location as being “deleted.”

CHANGES REQUESTED BY EDITOR

We have taken to heart your request that we ‘broaden the scope of both the background and discussion sections.’ We have extensively revised both sections, with roughly equal proportions of this broadening in each section of the manuscript.

--We have clarified that both intersecting themes of the paper health disparities and cardiovascular disease burden, are enormous problems worldwide and are worldwide medical challenges.

--We emphasize that the present, novel investigational method provides a way to bridge the (wide) gap between information derivable from structural genomics (e.g., association of disease with a genetic locus) and our understanding of
cellular function and disease pathophysiology. In other words, this method offers a new tool to add real functional studies to the field of functional genomics.

--We indicate (in Discussion) the relevance of this study of AA versus CA to the world in general. For example, we now address the role of genetic admixture in the human experience. And we provide an additional example of major admixture: that of European and Asian backgrounds (about a 50/50 mix) in the Uyghur population in western China.

--We have made the presentation less cryptic and reliant on a deep reader understanding of background and context. In other words, we have added much new information so that the presentation will be understandable and of much greater interest to the general medical readership.

--To help walk all readers through the presentation, we have carefully attended to the order with which things are presented, and we have added a number of sub-headings for orientation.

--We have discussed how the present approach relates to other modern approaches (disease association studies, admixture mapping, etc) to help the general reader put this into perspective.

--We have added several new sections, including one on rationale (introduction), one on integration of study results with medical biology (discussion), and one on caveats related to this study (discussion). A number of the Reviewer points are addressed in the latter section.

--We have added a number of new references to provide readers a link to more information, if so desired.

--We have responded below, and in the revised text, to every one of the Reviewer points/comments.

RESPONSE TO REVIEWER (DR. RUNDEK)

“..results if validated may be of important...”

We provide some validation data by way of retrospective analysis of a different group of AA versus CA subjects. This is in the new Caveats section in Discussion.

“clinical characteristics of the subjects”

The clinical data suggested are not available on these subjects. However, this is not important for this specific initial study, for reasons now presented in the new Caveats section (Discussion). It points out that the present experimental approach could easily be applied, for example, to, or to those with versus without specific clinical or biochemical risk factors, or to those with know genomic risk loci profiles. Now that we have established the utility of the method, it can be applied to shed light on many such questions.

“self-identification”
The new Caveats section (Discussion) has a sub-section that presents the hazard versus value of using self-identification as a device for subject group assignment. As noted in Introduction, we chose this because it was the device used for the seminal stroke/hypertension risk studies of AA, and we wanted present results to be relevant to those data.

“no allowance made for admixture”

The new Caveats section (Discussion) points out that this is not a problem for this specific study. In the first place, the impact of admixture would have been to dilute impact of any impact from an African-origin locus, i.e., to weaken results, not to strengthen them. Further, the point of the study was to assess whether a difference could be detected for AA in general. Thus, we wanted the present results to be directly relevant to the seminal studies showing elevated stroke risk and hypertension prevalence amongst AA, studies that were done on the general AA population without knowledge of admixture ratios. We do not have ancestry makers for these subjects, although they could (eventually) be obtained, as could an admixture mapping profile. But that is far beyond the scope of the present report.

“make any connection of their data with a….lipid regulatory…etc”

While we cannot authoritatively link present results to any specific physiologic detail, we have more generally indicated how the present results fit into cardiovascular disease biology. We illustrate a specific, known example which dramatically illustrates the linkage between genetics and environmental factors and blood lipids and oxidative processes, and disease risk. We further note how this relates to the shear responsiveness biology implicated here. This is found in the revised Discussion section on integration of results and vascular biology.

“which journal”

A very strong case can be made for the relevance to BMC medicine rather than BMC genetics, for example. Please see the description of changes made (to make the paper more readable, understandable, and relevant to a much wider, general medical audience. This description is at the top of the document, located in our response to the Editor’s comments.

RESPONSE TO REVIEWER (DR. MA)

“statistical methods”

We have reorganized presentation of statistical methods (Methods section) so that this source of confusion is now eliminated. In addition, we have edited that presentation somewhat. I believe these changes make it clear what was done for what purpose.

Small number of subjects.

We (even the biostatisticians) are not sure what “rationality” means in this context. However, we cannot just increase the n (because a feature of the strict control of culture methods is to use the same lot of chips and of culture medium
for every sample). However, we now provide a form of validation: restrospective application of the analysis to a previous group of control subjects (from an unrelated study, and with no subject overlap with the present study’s subjects). This is now found in the new Caveats section (Discussion).

“Why chose 20-29 year olds; what is the evidence”

A skeletal explanation is found in the subjects sub-section of Methods. However, in the new Caveats section (Discussion) we address—and provide data relevant to—whether ‘young and healthy’ volunteers actually are healthy.

“some references are obsolete”

Most of the original references were specifically chose for one reason or another. However, we have added a large number of references with updated information. And throughout the revised manuscript we discuss the relevance of the present study vis a vis the newer data.

“which journal”

A very strong case can be made for the relevance to BMC medicine rather than BMC genetics, for example. Please see the description of changes made (to make the paper more readable, understandable, and relevant to a much wider, general medical audience. This description is at the top of the document, located in our response to the Editor’s comments.

“language corrections”

The revised manuscript has been scrutinized to be sure all language usage is proper.

Sincerely,

Robert P. Hebbel, M.D.
Professor of Medicine
Vascular Biology Center
University of Minnesota