Title: Investigating the Complex Genetic Architecture of Ankle-Brachial Index, a Measure of Peripheral Arterial Disease, in non-Hispanic Whites

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Version: 3 Date: 22 April 2008

Author's response to reviews: see over
April 22, 2008

Dear Editor-in-Chief,

Please find enclosed our revised manuscript titled ‘Investigating the Complex Genetic Architecture of Ankle-Brachial Index, a Measure of Peripheral Arterial Disease, in non-Hispanic Whites’ which we would like to re-submit for publication in BMC Medical Genomics as an original research article. As part of our re-submission process, we have gone through the reviewer comments and provide our point-by point responses below.

All authors have read and approved re-submission of the manuscript and the manuscript has not been published nor is not being considered for publication elsewhere.

None of the authors have any conflict of interest to declare.

Thank you very much for your consideration of the manuscript.

Sincerely,

Sharon L. Kardia, PhD

Reviewer 1 report
Title: Investigating the Complex Genetic Architecture of Ankle-Brachial Index, a Measure of Peripheral Arterial Disease, in non-Hispanic Whites
Version: 2 Date: 24 March 2008
Reviewer: Marylyn Ritchie
Reviewer's report:
I am pleased with all of the revisions. I do not see any additional areas for improvement.
What next?: Accept without revision
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests.

We thank the reviewer for her comments and suggestions. Incorporating them has improved the overall quality of our manuscript.

Reviewer 2 report
Title: Investigating the Complex Genetic Architecture of Ankle-Brachial Index, a Measure of Peripheral Arterial Disease, in non-Hispanic Whites
Version: 2 Date: 10 March 2008
Reviewer: Andreas Ritsch
Reviewer's report:
Sharon et al. investigated the relationship of 435 SNPs in 112 candidate genes with ABI in 1046 non-Hispanic white hypertensive patients from the GENOA study. As stated within the abstract, the main effects are found for two SNPs of the NOS3 gene.
Presentation of these data in the Abstract and in section Results suggest that this is a novel finding. However, this association has been described in a recent publication by the same group in the same patients (Kullo et al., Association of polymorphisms in NOS3 with the ankle-brachial index in hypertensive adults, Atherosclerosis 2007), which is exclusively acknowledged within the Discussion. After the reviewer’s opinion, presentation of 25 SNP-SNP interactions including corresponding statistical data does not warrant publication in BMC Medical Genomics.

**What next?:** Reject because too small an advance to publish

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** I declare that I have no competing interests.

We thank the reviewer for his comments.

As indicated in our first point-by-point response, submitted on Feb. 19, 2008, we do acknowledge, and report in our manuscript, that the main effect associations reported here between the NOS3 SNPs and ABI were reported in the above referenced publication. It is not our intention to present this as a novel independent finding. Rather, we present the single gene main effects in order to fully represent our findings across the multidimensional framework that we investigated.

Many studies to date that have investigated the genetic nature of PAD have only looked at single gene effects and a limited number of genes have been studied. By contrast, our study utilizes a candidate gene approach to investigate multiple variants across 112 candidate genes. The main goal of this paper was to extend beyond the single gene approaches that have previously been employed, in order to begin to develop a deeper and more realistic understanding of the complex genetic nature of PAD.

Under the advice of the BMC Medical Genomics editorial staff, we have revised the Background section of our manuscript with the hopes of placing our present study in better context with respect to this main goal. Specifically, the 3rd paragraph of the Background section in our revised manuscript is new and minor additions have been included in the 4th and 5th paragraphs of this section. We have also slightly revised the Discussion section in our revision, with the hopes of specifically drawing attention to the importance of the interactive effects detected. Revisions in the Discussion section are captured in the first four paragraphs of the section.

While our study includes the investigation and reporting of main effects by necessity, we report on a number of SNP-Covariate and SNP-SNP interactions in the present study, which we feel highlight the multi-factorial and polygenic nature of complex, common diseases such as PAD. While our results may be preliminary, we believe they advance previous literature by extending beyond the previously reported main effect understanding of this complex phenotype.