Author's response to reviews

Title: Investigation of 95 variants identified in a genome-wide study for association with mortality after acute coronary syndrome

Authors:

Thomas M Morgan (thomas.morgan@vanderbilt.edu)
John House (j1house@saint-lukes.org)
Sharon Cresci (screnci@DOM.wustl.edu)
Phillip Jones (pjjones@saint-lukes.org)
Hooman Allayee (hallayee@usc.edu)
Stanley L Hazen (HAZENS@ccf.org)
Yesha Patel (ypatel@usc.edu)
Riyaz S Patel (rspate5@emory.edu)
Danny J Eapen (deapen@emory.edu)
Salina P Waddy (swaddy@emory.edu)
Arshed A Quyyumi (aquyyum@emory.edu)
Marcus Kleber (Marcus.Kleber@synlab.com)
Winfried März (Winfried.Maerz@synlab.com)
Bernhard R Winkelmann (b.winkelmann@kfsh.de)
Bernhard O Böhm (Bernhard.Boehm@uniklinik-ulm.de)
Harlan M Krumholz (harlan.krumholz@yale.edu)
John A Spertus (spertusj@umkc.edu)

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Author's response to reviews:

Title: Investigation of 95 variants identified in a genome-wide study for association with mortality after acute coronary syndrome

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We again thank the reviewers for their time, expertise, careful reading of our manuscript, and helpful suggestions. Our specific replies to comments appear below.

Reviewer: Jan Bressler

Reviewer's report:

Morgan et al. have submitted a revised version of their manuscript in which they examined the association between 95 polymorphisms identified in a genome-wide association study of premature myocardial infarction and post
acute coronary syndrome (ACS) mortality within 3 years. The report is now framed as a negative result since the statistically significant association between ACS and a MTHFDIL variant (rs6922269) first found in a discovery sample of 811 white individuals was not replicated in 3 additional independent cohorts. My previous concerns have been addressed; some suggestions for minor revisions of the current paper are listed below:

Minor Essential Revisions:

1. Results, fifth paragraph: The association between the A/A genotype and all-cause mortality in the combined group of patients is said to be shown in Figure 2. Figure 2 was not included with the manuscript for review.

We thank Dr. Bressler for noticing the issue with Figure 2, which we believed we had uploaded separately. We have ensured that Figure 2 appears in the revision.

2. Table 4: The abbreviation “IQR” should be defined.

We have defined IQR as interquartile range in the revised Table 4 (N.B., Table 4 now appears as Table 3 in the revised manuscript).

3. Table 5: The referent genotype for the Cox proportional hazards analysis should be indicated.

We have amended the table to indicate the G/G genotype reference (N.B., Table 5 is now Table 4 in the revised manuscript).

4. Appendix: There are several incomplete or missing references which should be provided. Additional information concerning genotyping quality control and call rates for the Cleveland Clinic GeneBank and Emory Cardiology Biobank validation cohorts would be helpful for assessment of these association studies.

We have updated and reviewed the references (24 total) for completeness and found none missing. The call rates for Cleveland Clinic and Emory have been added to the Appendix, as requested.

Reviewer: Aaron Isaacs

Reviewer’s report:
Morgan et al. made numerous substantial improvements to this manuscript and, generally, addressed all of my concerns. A few minor outstanding points:

Minor Essential Revisions

It would be nice to reduce the number of tables. In particular, Table 3 might be better as a supplement. Tables 4, 5, 6, and 7 could be combined into fewer tables plus some text.

We appreciate this suggestion and have reduced the number of tables in the full text from 8 to 5. Table 3 (the largest table) now appears in the Supplement as Supplemental Table 1.

A more informative presentation of the rs6922269 data would be as a meta-analysis and forest plot.

We agree with Dr. Isaacs in principle. However, we stressed in our Discussion that clinical heterogeneity is a limitation of the present study, and while we presented a combined summary of all data, we wish to avoid creating the somewhat misleading impression that our study design was meta-analytic in the strict sense of including all eligible studies that meet certain explicit entry criteria.

The y-axis on Figure 1 is labeled as expected beta, while the figure title says it depicts p-values.

We have changed the title of Figure 1 to avoid confusion.

Discretionary Revisions

The initial data for rs6922269 appears to fit a dominant genetic model. It might be of interest to test such a model.

Although we agree, after our extensive validation attempt we concluded that there is no apparent association, and therefore, we have elected not to imply that there is a promising genetic model to be found in our initial data.