Author's response to reviews

Title: The contribution of a 9p21.3 variant, a KIF6 variant, and C-reactive protein to predicting risk of myocardial infarction in a prospective study

Authors:

Dov Shiffman (dov.shiffman@celera.com)
Ellen S O'Meara (omeara.e@ghc.org)
Charles M Rowland (Charles.Rowland@celera.com)
Judy Z Louie (judy.louie@celera.com)
Mary Cushman (Mary.Cushman@uvm.edu)
Russell P Tracy (Russell.Tracy@uvm.edu)
James J Devlin (james.devlin@celera.com)
Bruce M Psaty (psaty@u.washington.edu)

Version: 3 Date: 22 February 2011

Author's response to reviews: see over
Dear Dr. Shipley,

We are submitting our second revision to the manuscript entitled “The contribution of a 9p21.3 variant, a KIF6 variant, and C-reactive protein to predicting risk of myocardial infarction in a prospective study” for your consideration.

Specifically, we have now addressed point 5 in the report of reviewer number 1. We have indicated below how we addressed his comment, and indicated in red font the changed text in the manuscript.

We hope that you find this revised manuscript suitable for publication in BMC Cardiovascular Disorders.

Sincerely,

Dov Shiffman, PhD
Point 5 in Reviewer 1 report:

5. Are the discussion and conclusions well balanced and adequately supported by the data?

There is insufficient explanation of both how the markers were selected, and what the benefit of a genetic biomarker may be over a non-genetic biomarker. The discussion may benefit from looking at what numbers of participants were positive for the KIF6719Arg variant and had a raised CRP, as this will have an impact upon important metrics such as the NNS/NNT.

We have revised the Discussion to explain how the markers were selected, and to discuss the relative merits of genetic and non-genetic biomarkers.

Genetic and non-genetic biomarkers offer different benefits in the assessment of CHD risk. Non-genetic biomarkers could change over time, and therefore, repeat measurements may be necessary because of day-to-day variation in the level of these biomarkers. However, repeat measurements of non-genetic biomarkers may also provide an indication of successful medical therapy or life-style modification. Genetic biomarkers do not change and thus need only be measured once to obtain information about the lifelong exposure to that biomarker. The 9p21.3 and KIF6 gene variants were chosen for investigation because they have both been reported to be associated with CHD in multiple prospective studies and are common variants. For example, in the white population about 75% of carry at least one risk allele of 9p21.3 and about 65% carry at least one KIF6 719Arg risk allele. CRP was chosen because of the well-established association between CRP levels and risk of CHD and because of continuing interest in whether it should be added to risk prediction algorithms. Elevated CRP is also common. For example, although CRP was analyzed as a continuous variable in this study in order to increase the power of the study, others have reported that in CHS, 26% of the population have elevated CRP (>3mg/dL) [31]. Thus, ~17% of the CHS white population have both elevated CRP and carry the 719Arg allele of KIF6.