Dear Sir/Madam,

We would like to submit this revised manuscript entitled "Aging Syndrome Genes and Premature Coronary Artery Disease" for consideration for publication in BMC Medical Genetics. This manuscript was originally submitted earlier this year and attributed the number MS: 1615729018612709. We appreciate the Reviewers' helpful comments and have addressed each of them in turn as detailed below.

Reviewer #1:
1. Our study is of comparable size to other published work on the genetics of CAD. Most previous studies have contained 300-500 subjects and are typically more heterogeneous than our cohort. We have deliberately tried to combine a high-resolution phenotype (acute coronary syndromes confirmed on angiography) with a sample size large enough to detect sizeable effects, so as to minimize the dilutional effects of phenotypic heterogeneity which have complicated the interpretation of many studies of CAD.

We have highlighted the estimated power of the study and its overall limitations so as to offer the reader an objective assessment of the magnitude of effect we have excluded, and to prevent over-interpretation of the results. Using case-control association methodology, false negative findings are a priori considerably less likely than false positive findings. Of note, this study in essence also is a replicate cohort for the findings of Arking et al. but with higher resolution phenotyping.

2. As these are young patients presenting with an initial acute coronary syndrome, the incidence of coronary calcification is expectedly very low. There was no discernible calcification in our patient cohort on standardized diagnostic coronary angiography.

3. We have extensively rewritten the manuscript as suggested. Specifically, we have substantially trimmed the background section, and discussion. We also have included more primary references as space allows, including the twin study by Marenberg.

4. Spelling errors have been rectified.

Reviewer #2:
1. We have removed the final sentence from the background section as advised.

2. The methods section is placed at the end of the manuscript.

3. We have added definitions of the cardiovascular risk factors. We have also reiterated our relatively small sample size as a limitation of the study.

4. The discussion section has been shortened as suggested and the discretionary revisions acted on.

Reviewer #3:
1. We did not undertake covariate analyses in our original study to avoid the issues related to multiple
testing. However, when analyses were conducted using age, BMI, gender, hypertension, diabetes mellitus, statin-use, and smoking history as covariates no significant associations were detected. We have added this to the manuscript.

2. The power calculation has been modified as suggested by the reviewer. Taking a priori a 1.8 fold difference in allele frequency between the 2 groups and an allele frequency of 0.2, our study has a 93% power to detect the differences assuming an alpha of 0.05.

3. There were no significant differences with regards to the use of statins or other common medications among both populations.

4. We have only selected a single SNP for Klotho because this was reported previously to be positively associated with a family history of CAD among siblings of probands with coronary artery disease.

5. The haplotype blocks were assigned the modified estimation-maximization algorithm as implemented in the Haploview software package and described in the Methods section.

6. Linkage disequilibrium is certainly a possible explanation for the previously observed associations, and this has been added to the discussion.

7. We also have addressed each of the minor essential revisions as detailed in the review. Of note, we removed references to the MEF2A gene, but discuss the related novel CAD locus which is statistically robust, and not associated with any evidence of dyslipidemia. In addition, while homozygosity of LMNA is not yet accepted as a disease mechanism, the high frequency of homozygosity in HGPS patients is well documented and somatic mutations have been documented in other human diseases, so this mechanism seemed a reasonable a priori hypothesis to test.

All the authors have contributed to the research as described and have read and approved the final manuscript. None of the authors have any conflicts of interest to declare. Please address all correspondence to Dr. MacRae at the above address. We hope that you will find this paper to be of interest to your readership. Thank you for your consideration of this manuscript.

Sincerely,