Letters to the Editor

Candidate gene association analysis of thoracic aortic aneurysm and dissection

To the Editor:

In their recent article, Chen and colleagues¹ have described the association of three single-nucleotide polymorphisms of the matrix metalloproteinase 9 gene, with thoracic aortic aneurysm and dissection. One of the three single-nucleotide polymorphisms (A-8202G) was found to be associated with the disease phenotypes of aortic aneurysm and aortic dissection. Such genetic association studies are based on the presence of linkage disequilibrium in the human genome and can be a powerful tool to dissect the genetic basis of diseases. A fundamental aspect of this approach, however, is the meticulous selection and matching of unrelated study subjects (case and control subjects). We believe that this study has some basic weaknesses; hence the results should be viewed with caution.

First, Chen and colleagues¹ compared the prevalence of alleles and genotypes at the three loci between patients recruited from the United States and their control subjects from Australia. In our opinion, the case and control subjects belong to two very distinct populations, and their comparison cannot yield any meaningful evidence. It is a common observation in genetic association studies that genetic markers have diverse, and in some cases even opposite, associations in different ethnic groups.²⁻⁴ The strength of linkage disequilibrium between any two loci will not be equal in any two different ethnic groups, hence the importance of ethnicity-matched control subjects.

Second, Chen and colleagues¹ should comment on the presence of Hardy-Weinberg equilibrium in the genotype distributions at the three loci separately for the case and control groups. Hardy-Weinberg equilibrium in the genotype distributions provides evidence of random selection of subjects, which is an important pillar of the case-control genetic association study design. Furthermore, if the genotypes at the

three loci are in Hardy-Weinberg equilibrium in case and control subjects, then it will be interesting to see the prevalence of the various haplotypes in the study population and also their associations with the diagnoses under study. This may provide additional information about the role of matrix metalloproteinase polymorphisms in thoracic aortic aneurysm and dissection.

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References

1. Chen L, Wang X, Carter SA, Shen YH, Bartsch HR, Thompson RW, et al. A single nucleotide polymorphism in the matrix metalloproteinase 9 gene (-8202A/G) is associated with thoracic aortic aneurysms and thoracic aortic dissection. *J Thorac Cardiovasc Surg*. 2006;131:1045-52.
2. Cao K, Hollenbach J, Shi X, Shi W, Chopek M, Fernandez-Vina MA. Analysis of the frequencies of HLA-A, B, and C alleles and haplotypes in the five major ethnic groups of the United States reveals high levels of diversity in these loci and contrasting distribution patterns in these populations. *Hum Immunol*. 2001;62:1009-30.
3. Sanghera DK, Saha N, Aston CE, Kamboh MI. Genetic polymorphism of paraoxonase and the risk of coronary heart disease. *Arterioscler Thromb Vasc Biol*. 1997;17:1067-73.
4. Wang X, Fan Z, Huang J, Su S, Yu Q, Zhao J, et al. Extensive association analysis between polymorphisms of PON gene cluster with coronary heart disease in Chinese Han population. *Arterioscler Thromb Vasc Biol*. 2003;23:328-34.

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Reply to the Editor:

We appreciate the comments by Ahmad and colleagues regarding our initial investigation of single nucleotide polymorphisms (SNPs) involving the matrix metalloproteinase 9 gene (*MMP9*) in patients

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with thoracic aortic pathology.¹ Selection of a control group that is perfectly matched for ethnic ancestry with a group of affected individuals is indeed a major challenge in studying the associations between candidate genes and diseases. Not surprisingly, most published studies have imperfectly matched case-control populations. Nevertheless, the substantial geographic difference between our control and study populations clearly warrants discussion.

Although geographically diverse, white populations from Australia and the United States are genetically similar. The majority of the white Australian population has ancestors who, within only a few generations, originated from the European continent. Previous studies of other genetic polymorphisms have demonstrated great similarities between the white Australian population and white subjects residing on other continents.^{2,3} Our American patients with thoracic aortic disease were classified as white with European origin and therefore share a similar genetic origin with white Australians. Although the Australian and American populations have resided on two different continents for a number of generations, the migration and constitutive establishment for both countries date back only approximately 200 years. The founder effect is generally small within such a short period. Still, even within a given white population, genetic admixture can be large for certain genes. Because of this and other inherent limitations, studies in separate populations are required to confirm any significant genetic associations observed from one particular population.

Given the genetic similarities between white Australians and white Americans (despite the geographic difference), we chose our control population for the absence of angiographic evidence of proximal thoracic aortic aneurysms or dissection. This reduced the likelihood that control subjects had thoracic aortic disease, which would have confounded the comparisons with our patient groups. To address at least somewhat the issue of geographic diversity in our study, we demonstrated that the frequencies of the three *MMP9* SNPs in our control group were not significantly different from those previously described by Applied Biosystems (Foster City, Calif) in a white population from the United States.¹ The presence of Hardy-Weinberg equilibrium in the control group is also reassuring; there was no significant deviation from Hardy-

Weinberg equilibrium for the three *MMP9* polymorphisms in the control group ($P = .81$ for -8202A/G; $P = .98$ for IVS4 + 3G/T; $P = .93$ for 2003A/G). No significant deviation from Hardy-Weinberg equilibrium was observed for IVS4+3G/T and 2003A/G in patients with thoracic aortic aneurysms or dissection; a significant deviation from Hardy-Weinberg equilibrium was observed for -8202A/G in our case patients.

Recent publications have suggested the existence of haplotype blocks. Haplotypes at these blocks could serve as multiallelic markers in disease-association studies.⁴ Examining all observed haplotypes for associations, rather than just those that are proxies for known SNPs, increases power to detect rare causal alleles, but at the cost of reduced power to detect common causal alleles. Furthermore, the haplotype-SNP-based approach does not always have higher power than the single-SNP-based study, as is supported by theoretic considerations. With the data collected in our population, some linkage analysis can be conducted for haplotype construction. Estimated haplotype frequencies cannot be treated as observed data, however, and therefore there is no valid statistical test for evaluating the possible contribution of individual haplotypes. Although testing haplotype blocks of the *MMP9* locus and surrounding regions by including more SNPs might provide additional information, the most effective way to validate the findings reported in our study is to confirm the association in other case-control populations.

As with all genetic association studies, our study has limitations and the findings should be interpreted cautiously. Studies in separate populations will be required to confirm the association that we observed between the *MMP9* -8202A/G polymorphism and thoracic aortic aneurysms and dissection. We hope that our data will stimulate expanded research regarding the genetic aspects of thoracic aortic disease, particularly in patients who do not have archetypal heritable disorders such as Marfan syndrome. Our participation in the newly established Specialized Center of Clinically Oriented Research in Thoracic Aortic Aneurysms and Dissection will provide exciting opportunities to perform such studies and expand our understanding of the genetic determinants that underlie thoracic aortic disease.

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References

1. Chen L, Wang X, Carter SA, Shen YH, Bartsch HR, Thompson RW, et al. A single nucleotide polymorphism in the matrix metalloproteinase 9 gene (-8202A/G) is associated with thoracic aortic aneurysms and thoracic aortic dissection. *J Thorac Cardiovasc Surg*. 2006;131:1045-52.
2. Wang XL, Wang J. Endothelial nitric oxide synthase gene sequence variations and vascular disease. *Mol Genet Metab*. 2000;70:241-51.
3. Wang XL, Raveendran M, Wang J. Genetic influence on cigarette-induced cardiovascular risk. *Prog Cardiovasc Dis*. 2003;45:361-82.
4. de Bakker PI, Yelensky R, Pe'er I, Gabriel SB, Daly MJ, Altshuler D. Efficiency and power in genetic association studies. *Nat Genet*. 2005;37:1217-23.
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Placement of the Impella Recover LD microaxial blood pump through a bioprosthesis is technically feasible To the Editor:

We read with great interest the article of Strauch and colleagues¹ regarding their experience with Impella Recover LD support for postcardiotomy low-output syndrome in a patient undergoing aortic valve replacement with a bioprosthesis. In our initial experience² we reported the use of the Impella Recover LD to support a patient with valvular cardiomyopathy who underwent conventional mitral valve repair and aortic valve replacement with a 21 mm Carpentier-Edwards bioprosthesis. Despite maximal inotropic support (epinephrine dose, $0.2 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$), the patient could not be weaned from extracorporeal circulation, with hypotension, increased filling pressure (left atrial pressure, 28 mm Hg), and oliguria (urine output, $<30 \text{ mL/h}$). The calculated intra-aortic balloon pump (IABP) score for the patient was 2, which predicts a 52% 30-day mortality according to Hausmann and coworkers.³ The Impella LD was then implanted with the standard technique and advanced in the left ventricle through the prosthesis under echocardiographic guidance. In our experience passing the biologic valve was not immediate