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GUIDING THE MOLECULAR DIAGNOSIS OF HYPERTROPHIC CARDIOMYOPATHY

To the Editor:

With interest, we read the recent guideline for hypertrophic cardiomyopathy (HCM) and highly appreciate the useful clinical information.¹ HCM is a pathophysiologically heterogeneous condition. We agree with the authors that there is comprehensive evidence that mutations in 8 genes encoding proteins of, or associated with, the sarcomere can cause HCM. These are, as stated in chapter 6 of the guideline, the genes encoding β myosin heavy chain, myosin binding protein C, troponin T, troponin I, α -tropomyosin, actin, regulatory light chain, and essential light chain. However, only about 40% to 60% of HCM cases can be attributed to these 8 genes.^{2,3}

More recently, a ninth gene was convincingly linked to HCM after a genome-wide linkage analysis. Mutations in *CSRP3* encoding muscle LIM protein were shown to cosegregate with HCM in several families in whom gene mutations in the 8 incriminated sarcomeric proteins had been previously excluded.⁴ All these mutations affected highly conserved residues and were not found in the control genomes. Linkage analysis with a highly significant 5.9 logarithm of the odds score in a single large family provided additional genetic evidence. Physicians and geneticists unaware of the mutation status ensured an unbiased attribution of disease

status and an unbiased genome-wide linkage analysis in that family.⁵ Furthermore, functional data supported the genetic results. Cardiomyocyte disarray was observed in *CSRP3* mutation-positive cardiac tissue from patients with HCM. The findings indicate that *CSRP3* mutations cause "true" HCM and not merely a HCM phenocopy.

Although *CSRP3* mutations in patients with HCM are not common (<5%), we believe that there is convincing, scientific evidence that the gene should be included in the list of confirmed HCM disease genes. *TPM1* and *ACTC* (encoding α -tropomyosin and actin) mutations occur at a frequency not much different than *CSRP3* mutations. The prevalence of HCM disease genes is also related to ethnicity. Such patterns require active surveillance of disease genes and *CSRP3* should be included. To learn more about the ethnic spectrum of disease genes and specific founder mutations we propose including all well-established disease genes into scientific genetic screening analyses. Muscle LIM protein is not confined solely to sarcomeric localizations but can be localized to the sarcolemma and to the cell nucleus. Mechanistically, there is much to be learned about this protein, its gene, and their contributions to HCM. We therefore wish to draw attention to *CSRP3*.

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RE: SIMPLIFIED PERFUSION STRATEGY FOR REMOVING RETROPERITONEAL TUMORS WITH EXTENSIVE CAVOATRIAL INVOLVEMENT

To the Editor:

The authors compare beating heart cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA) for removing retroperitoneal tumors with extensive cavoatrial involvement.¹ They included in their series retroperitoneal renal tumors with level III-IV tumor thrombus