What Can Genetic Studies of Left Ventricular Mass Tell Us?

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Left ventricular hypertrophy (LVH), whether measured by electrocardiography, echocardiography, or at autopsy, is associated with increased risk of cardiovascular morbidity and mortality.1,2 Although LVH has been associated with several clinical characteristics such as age, sex, body mass index, and hypertension, the effects and their directionality have varied according to the criteria for LVH.3 Aggregation within families suggests a heritable component due to genetics,4 although a recent study of echocardiographic left ventricular mass in a large sample was unable to identify common genetic factors.5 Treatment of hypertensives with LVH can lead to its regression and with it reduction in risk of cardiovascular disease.6 Thus, it appears to be a modifiable risk factor, although LVH induced by exercise training is thought to be benign. Thus, LVH is a complex trait with diverse definitions, has multiple clinical and genetic contributors and is a modifiable risk factor in some but not all settings.

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It is not surprising therefore that the (patho-) physiological mechanisms that underlie LVH remain incompletely characterized. Human genetics offers one opportunity to expose mechanisms not previously recognized to play a role in the development of LVH. Shah et al report in this issue of Circulation Cardiovascular Genetics a genetic screen to identify common genetic variants related to electrocardiographic correlates of left ventricular mass (ECG LVM): 2 reflecting simple voltage measures—Sokolow-Lyon voltage and 12-lead QRS voltage sum—and 2 incorporating QRS duration—Cornell product and QRS voltage product.7

The investigators genotyped gene-focused single-nucleotide polymorphisms (SNPs) found on the ITMAT-Broad-CARE (IBC) array, marketed by Illumina as the HumanCVD BeadChip 50K array, with ~35 000 SNPs passing quality control. The array includes SNPs at 2100 candidate genes selected for being implicated in processes thought to be involved in cardiovascular disease as well as some genes identified through genome-wide association studies (GWAS).8 However, it is really a hybrid between a candidate gene study and a GWAS (it includes 10% of the genome), because many genes will have minimal plausible candidacy for involvement in any one specific physiological process.

Shah’s study included 10 526 individuals of European ancestry and attempted to strengthen statistical support for 12 SNPs by genotyping them in an additional 11 777 individuals. In total, SNPs at 4 loci passed the study’s threshold for replication and achieved joint association in discovery plus replication with P-values <2x10⁻⁷, a reasonable threshold considering the number of SNPs and phenotypes tested. The lead SNPs demonstrated association with Cornell product at 3p22.2 near SCN5A and with 12-lead QRS voltage sum at 12q13.3 near PTGES3, 15q25.2 near NMB, and 15q26.3 near IGFIR.

The P-values tell us that these findings are unlikely to be due to chance and thus that there is bona fide genetic variation in the 4 loci that influence the traits studied. However, the biological meaning of the findings requires consideration of the specific traits, variants, and genes at the loci and annotations of their potential functions. Only then can their possible clinical relevance be understood.

The SNP on 3p22.2 lies in an intron of SCN5A, encoding the α-subunit of the voltage-gated cardiac sodium channel, which is obviously an excellent candidate to mediate the association. Rare mutations in the gene have been associated with congenital long-QT syndrome, Brugada syndrome, dilated cardiomyopathy, heart block caused by conduction system disease, and sudden cardiac death. Common polymorphisms at the locus have been related to QT interval,9 QRS duration,10 and PR interval,11 although some appear more likely to act through the nearby gene SCN10A, based on proximity, by physical or genetic distance, and observations in murine models.12 In fact, the lead SNP rs6797133 that is related to Cornell product is correlated to a SNP 2 kb away (r²=0.37 in HapMap CEU) found to be associated with QRS duration,10 raising the possibility that the association with Cornell product is in fact driven by association with QRS duration, a cardiac conduction phenotype, rather than LVM. Imputation of unmeasured SNPs with reference to HapMap or other samples was not conducted in the current report, so it is unclear whether the SNP with the strongest association with Cornell product is also a lead SNP for QRS. More work will be needed to refine the phenotype and genotype that drive the association detected in the Shah study.

The SNP on 12q13.3 associated with 12-lead voltage sum lies in an intron of PTGES3, encoding prostaglandin E synthesis.3 The SNP was perfectly correlated with a SNP
associated with myocyte and fibroblast transcript levels of \textit{RBMS2}, encoding a protein with possible RNA-binding motifs, and with monocyte transcript level of \textit{PRIM1}, encoding primase 1 polypeptide involved in DNA replication. Neither of these are a priori biological candidates to influence ECG LVM, but the strong eQTL relationships of the lead SNP must now put these genes on the short list to mediate the association. The fact that a SNP is associated with transcripts of multiple genes at a locus is now commonplace across many of the larger GWAS. Whether more than 1 gene is the source of association for any given trait requires much more work. Examples of coordinated regulation of multiple genes, only 1 of which is sufficient to influence a phenotype, are now accruing.\textsuperscript{12} Clearly, the monocyte or fibroblast is unlikely to mediate the association of the 12q13.3 association with ECG LVM; eQTL analysis of heart tissue could point more specifically to 1 gene at the locus (or in fact others). Such databases are only now being developed in large scale.

The SNP on 15q26.3 associated with 12-lead voltage sum lies in an intron of \textit{IGF1R}, encoding the insulin-like growth factor 1 receptor, which, as pointed to by the authors, has been well established to mediate insulin-like growth factor effects on myocardial cell growth through ERK 1/2, Akt, and myostatin.\textsuperscript{13,14} \textit{IGF1R} appears quite likely, therefore, to be the source of association at this locus.

The SNP on 15q25.3 associated with 12-lead voltage sum lies in an intron of \textit{NMB}, encoding neurenomedin B, which is not known to be involved in myocardial hypertrophy. It showed correlation ($r^2=0.48$) to an amino acid–altering SNP rs1051168 (Pro73Thr) in \textit{NMB} but at statistical significance about an order of magnitude less than the lead SNP. Whether this SNP mediates the association is unknown, and thus which gene at the locus is involved in the processes leading to ECG LVM remains unclear. In fact, the lead SNP is associated in monocytes with expression of \textit{WDR73} and \textit{NMB}. In the latter case it is not clear whether the correlated missense SNP in \textit{NMB} may have interfered with detection of transcripts with one of the alternate coding sequences, thus inducing spurious association.

Without regard to the causal SNP or gene, one can consider the ability of SNPs to predict clinical outcomes. Given the small proportion of variation of the ECG LVM traits measured in the current studies, 0.28\% or less, the impact on clinical outcomes such as cardiovascular disease or mortality would be modest if at all detectable in subsequent studies. Shah et al have considered the ability of the SNPs identified to increase the risk of being in the top decile of each ECG LVM trait, but this is likely overestimated as a result of probable “winner’s curse” in the observed effect estimates and of unclear clinical relevance. Association with risk of exceeding ECG LVH thresholds were not reported. Such thresholds have been proposed for Cornell product; they are less well established for 12-lead voltage sum. Clearly, what one cares most about is hard cardiovascular outcomes, and it seems unlikely that there will be much effect.

What may have been missed in this study? Such studies often have modest power to find variants of similar effect to those found, suggesting that other common variants of similar effect, whether in the associated genes or in other genes without association signals, could have been found if equally powered independent studies were conducted. Moreover, the coverage of the genome was focused on genes—some common variant loci are intergenic—and on just $\approx 10\%$ of genes in the genome. These other genes and nongenic regions have thus not yet been interrogated.

Why were none of the findings replicated in EchoGen? The authors examined the 4 SNPs in a GWAS of echocardiographic LVM and found no association, even at a nominal value of $P<0.05$. Although this could reflect the play of chance, this seems less likely, given the roughly similar sample sizes of the 2 studies (a significance threshold closer to $P<0.05$ would be sufficient for the 4 SNPs).\textsuperscript{5} In retrospect, the nonreplication may not be so unexpected. As the authors cite, there is evidence of independent relationships to cardiovascular outcomes of echo LVM and ECG LVM\textsuperscript{15} as well as differing heritability of echo and ECG LVM.\textsuperscript{4} Coupled with the variable covariate relationships among different ECG LVM measures,\textsuperscript{5} it is quite likely that distinct mechanisms may be at play in different measures of what is broadly called LVM or LVH when defined in diverse ways. We recently identified 29 SNPs related to blood pressure, which, in aggregate, were positively related to increased echo LVM (weakly) and LV wall thickness (more strongly) in the EchoGen study,\textsuperscript{16} consistent with a model in which blood pressure is causally related to echo LVM. Whether a similar relationship exists with ECG LVM remains to be tested.

We must better understand the physiology that underlies adaptive hypertrophy in the athlete versus the pathophysiology that underlies maladaptive hypertrophy in hypertensives, diabetics, and others at increased risk of LVH and cardiovascular disease. Interventional studies such as the LIFE study represent one opportunity to examine the modifiability of the various LVH measures. Identifying novel proteins and pathways involved in LVM, as in the study by Shah et al, represents another foot in the door to an expanded understanding of these heterogeneous processes. Ultimately, more precise phenotypes and genotypes will be needed to resolve etiologic heterogeneity into distinct mechanisms of LVH.

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\textbf{Disclosures}

None.

\textbf{References}


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