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EDITORIAL COMMENT

Towards Understanding the Impact of Sarcomeric Gene Mutations*

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> *With this profound new knowledge, humankind is on the verge of gaining immense, new power to heal. Genome science will have a real impact on all our lives—and even more, on the lives of our children. It will revolutionize the diagnosis, prevention, and treatment of most, if not all, human diseases.*
>
> —President Bill Clinton during the announcement of the completion of the draft sequences of the human genome, June 26, 2000 (1)

One of the promises in the era of genomics is the ability to predict potential adverse cardiovascular events in specific patient populations. This is certainly a goal for individuals who have hypertrophic cardiomyopathies and left ventricular hypertrophy. The genetic predisposition to underlying cardiomyopathies represents the evolution of our understanding of the molecular underpinnings of these diseases (2). Studies of hypertrophic cardiomyopathy have progressed

See page 459

from the initial mapping of genes responsible for familial hypertrophic cardiomyopathies in large kindreds, testing candidate genes in patient populations, conducting genome-wide association studies, and validating candidate gene associations using transgenic animal models (3–6). In fact, the ability to rapidly sequence DNA using next-generation platforms represents a significant advance toward analyzing patient genomes. For example, recent investigations have shown that truncating mutations in the sarcomeric protein titin are common causes of dilated cardiomyopathy, occurring in ~25% of familial cases and in ~18% of sporadic cases of idiopathic dilated cardiomyopathy (7).

The wealth of information derived from these approaches requires further investigations to understand how the results of initial study groups can be extrapolated to broader patient populations. In this issue of the *Journal*, Fujita et al. (8) report the results of a multicenter registry in Japan in which they examined sarcomere gene mutations in individuals who had left ventricular hypertrophy or hypertrophic cardiomyopathy. Over a 3-year period, 257 individuals with left ventricular hypertrophy (defined as maximal left ventricular wall thickness ≥13 mm) with or without hypertensive heart disease (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) were enrolled and underwent direct DNA sequencing of all translated exons for 9 of the most common genes associated with hypertrophic cardiomyopathy. These included MYBPC3-encoding myosin binding protein C, MYH7-encoding myosin heavy chain, MYL2- and MYL3-encoding regulatory and essential myosin light chains, TNNI3-encoding troponin I, TNNT2-encoding cardiac troponin T, TPM1-encoding tropomyosin, TTN-encoding titin, and ACTC1-encoding cardiac actin. The cohort was divided into 3 groups: patients with hypertensive heart disease without sarcomere gene mutation, those with hypertrophic cardiomyopathy with sarcomere gene mutation, and those with hypertrophic cardiomyopathy without hypertensive heart disease or sarcomeric gene mutation. The cohort was followed for 1 year to determine differences in cardiovascular events. The authors examined sudden cardiac death, ventricular tachycardia/ventricular fibrillation, admission for heart failure, and atrial fibrillation. Interestingly, individuals who had sarcomere gene mutations had more total cardiovascular events than individuals who had hypertensive heart disease without sarcomere gene mutation or neither hypertensive heart disease nor sarcomeric gene mutation. Moreover, individuals who were 50 years of age or older and had sarcomere gene mutations showed a high incidence of admission for heart failure or atrial fibrillation.

The results provide evidence of left ventricular hypertrophy with sarcomere gene mutation and the incidence of cardiac events in the study cohort. However, several cautions should be noted. First, this was a small study with 1-year follow-up to date and a high number of patients who did not complete the study (~25%) for unclear reasons. The indolent progression of left ventricular hypertrophy can take years before cardiac events occur, and thus longer term follow-up is required.

Second, significant differences were present among the baseline characteristics of the groups including age, blood pressure, brain natriuretic peptide levels, left ventricular posterior wall thickness, maximal left ventricular wall thickness, left ventricular end-diastolic dimension, left ventricular outflow tract pressure gradient, and the presence of mitral regurgitation. These differences in baseline characteristics represent potential confounders in the interpretation of the study results.

Third, previous studies reported the distributions of sarcomere gene mutations in hypertrophic cardiomyopathy as follows: *MYH7* mutation in ~25% to 35%, *MYBPC3* mutation in ~20% to 30%, *TNNT2* mutation in ~3% to 5%, *TNNI3* mutation in <5% (9). The prevalence of *TNNI3*

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JACC: Heart Failure Vol. 1, No. 6, 2013
December 2013:467–8

was 29.7% (11 of 37 patients) and 45.9% (17 of 37 patients) of *MYBPC3* reported by Fujita et al. (8) was higher than other general epidemiological data. This may represent a difference in the study population or a limitation in the sample size of the cohort. Although a higher prevalence of *MYBPC3* mutations was observed, stratifying individuals who had sarcomere gene mutations according to the presence or absence of *MYBPC3* mutation did not reveal a difference in cardiovascular events between the 2 groups. Thus, the authors concluded that the higher prevalence of *MYBPC3* mutations is unlikely to confound the results by increasing the incidence of heart failure in the elderly population. However, the small sample size may explain the investigators' observations that there was no significant relationship between the type of disease-causing gene and the occurrence of cardiovascular events in their cohort.

Fourth, some of the cardiac event endpoints may have been underrepresented, particularly nonsustained ventricular tachycardia because Holter monitoring or continuous electrocardiography was not performed in all study patients. Interestingly, individuals who were 50 years of age and older and had sarcomere gene mutations were found to have a higher incidence of atrial fibrillation. However, there was also a higher prevalence of mitral regurgitation and larger atrial dimensions in this age group, and these factors are known to contribute to higher occurrences of atrial fibrillation.

Despite these limitations, the study by Fujita et al. (8) highlights the continued need to understand the potential impact of sarcomere gene mutations on cardiac diseases. Genetic testing provides diagnostic information but currently does not reliably predict prognosis. However, studies like that of Fujita et al. (8) have the potential to delineate how sarcomere gene mutations may someday predict clinical outcomes. Furthermore, new information pertaining to epigenetic mechanisms of gene regulation will add complexity to the existing models of how the genome functions in health and disease. Alterations in DNA methylation, histone modifications, long noncoding RNAs, and microRNAs are among the factors that may also influence the architecture of genome in disease states. This is an exciting time in science and medicine. Continued investigations are necessary to fulfill the promise to improve our ability to predict potential adverse cardiovascular events based on genomic information.

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Key Words: heart failure ■ left ventricular hypertrophy ■ prognosis ■ sarcomere gene mutations.