Ascertainment Strategies and Genotype:Phenotype Correlations in Hypertrophic Cardiomyopathy

To the Editor:

Van Driest et al\(^1\) correctly assert that genotype:phenotype correlations in hypertrophic cardiomyopathy (HCM) require continued evaluation. Much of the early literature was built on descriptions of large families ascertained for genetic mapping studies; different referral practices (for example, referral of families with multiple sudden deaths) may have led to ascertainment bias. Unfortunately, the approaches used in this new study carry their own biases and, we believe, further cloud rather than clarify the situation.

The study by van Driest et al\(^1\) is based on unrelated cases referred to the Mayo Clinic for treatment. Focusing on probands will exacerbate patient selection influences. Predictably, their cohort displayed severe disease; 70\% had outflow obstruction (28\% went on to myectomy), and most had symptoms. Thus, it was inevitable that any mutations identified would be in individuals who “had already manifested clinically severe expression of HCM.”

The appropriate study design is to identify mutations in probands and then to disregard genotype:phenotype data in those individuals but to establish this relationship by systematic review of all relatives. In the current study, information on relatives is scanty (only 32\% of probands had a positive family history!). Without systematic data, the only family information available relates to adverse events, exaggerating the impression of a bad prognosis. Information on asymptomatic mutation carriers across the whole pedigree would be needed to know the true impact of the mutation. Indeed, to focus on “the individual patient” in isolation of family history seems misguided in an inherited disorder.

Finally, it is not clear why the authors believed that these particular “benign” mutations would be present at significant frequency. The cumulative experience in the literature from screening many more HCM families than are described in this series resoundingly confirms that all mutations are individually rare; indeed, most families have “private” mutations.\(^2\) Thus, to state that “fewer than 2\% of the subjects harbored a benign mutation” is misleading. In all likelihood a large proportion of their subjects harbor a benign mutation but the strategy used in their study cannot detect these (as most will be novel). To type only for known mutations is unhelpful, firstly because the yield will be very low, and secondly because compound mutations (>1 mutation in an individual gene, or mutations in 2 genes) are surprisingly prevalent.\(^3,4\) The presence of a second mutation is a potent cause of a genuinely benign mutation appearing to cause a more severe phenotype in an individual or family.

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Response

Blair et al insightfully critique our recent publication,\(^1\) highlighting several issues. Foremost is referral/ascertainment bias in our study cohort. Indeed, the hypertrophic cardiomyopathy (HCM) literature is filled with biases, from the breakthrough linkage studies defining HCM as a sarcomeric disease (based on large families with highly penetrant disease) to our study of tertiary referral center HCM. Blair et al emphasize that our cohort is overrepresented by patients with obstructive HCM and myectomy, stating that it was “inevitable” that mutations would be identified in individuals with severe disease. Although the former is true, the average age of our cohort is 41 years, half are asymptomatic, and three fourths have no family history of sudden death, challenging the “inevitability” of severe disease expression. We previously found that only 3 of these 293 patients had a “malignant” mutation,\(^2\) prompting the search for “benign” mutations.

Blair et al recommend analysis of all mutation-positive family members, exclusive of probands. That study design was used to assign mutations as “malignant” or “benign.” However, our goal was to determine whether these previous assignments are predictive in an unrelated cohort of patients who do not share genetic and environmental modifiers.

We agree that to focus on “the individual patient” without considering family history would be misguided. Family history is sought meticulously in our HCM Clinic and was found to be substantial rather than “scanty.” We determined that 32\% of probands had a positive family history of HCM in a first-degree relative (offspring, siblings, and/or parents).

As Blair et al correctly assert, each specific HCM-causing mutation is rare.\(^3\) Our cohort underscores this fact. Although HCM research laboratories clearly understand the implications of this genetic heterogeneity, genetic testing for specific prognostic mutations continues to be advocated, and the notion persists that some mutations are “common.” Here, our work clarifies the situation for those unfamiliar with the field.

Finally, Blair et al highlight the profound effect of compound heterozygosity. Certainly the presence of multiple mutations may contribute to the severe disease seen in these 5 patients. Comprehensive analysis of all HCM-causing genes is underway. However, in 20\% or more cases of HCM, no mutation can be identified in any of the 10 known HCM-causing genes. Until all HCM-causing genes are identified, it may be challenging to determine the precise relative risk contributed by a specific mutation.

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