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Hypertrophic Cardiomyopathy: How Far Should We Go With Genetic Testing?

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TO THE EDITOR

We would like to respond to Dr. Kim L. McBride's comments regarding our manuscript "A RASopathy phenotype with severe congenital hypertrophic obstructive cardiomyopathy associated with a *PTPN11* mutation and a novel variant in *SOST*", in which we describe a patient with severe congenital hypertrophic cardiomyopathy (HCM), and two abnormalities in the RAS–MAPK pathway, including a previously well-described *PTPN11* mutation known to cause Noonan syndrome–multiple lentigines (NS–ML; previously referred to as LEOPARD syndrome) and a novel, likely pathogenic variant in *SOS1* [Fahrner et al., 2012]. We appreciate Dr. McBride's suggestion to pursue sequencing of genes encoding sarcomeric proteins involved in HCM [McBride, 2012]. As geneticists, we recognize that there are likely many modifier genes encoding proteins with diverse functions outside of the RAS–MAPK pathway, which could potentially contribute to our patient's severe HCM. We agree that even after identifying two mutations in the RAS–MAPK pathway, ideally we would want to sequence the sarcomeric protein genes to search for additional contributing mutations/variants. Such an analysis on a research basis could certainly prove to be fruitful and interesting. However, the standard of care in the clinical setting traditionally has been to stop looking for additional etiologies of a phenotype once a molecular diagnosis (particularly one that fits as well as this one) has been made. The reasons for this have been mostly financial and practical. Insurance companies would likely refuse to pay for what they might refer to as unnecessary and expensive tests. Furthermore, the testing of additional gene panels would likely identify variants of uncertain significance and potentially create more questions than answers for the family.

Having said that, the trend in genetics, especially in research settings, is now moving away from sequencing of limited gene panels and toward whole exome sequencing, which would identify countless potential modifier mutations/variants. This is a potentially reasonable option for our patient as well, although this too would not be covered by the patient's medical insurance.

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In this particular case, the parents have been extensively counseled about targeted parental testing and recurrence risk if one or both harbor a pathogenic mutation. In addition, they have been made aware that in all cases reported to date of two abnormalities in the RAS–MAPK pathway, one was inherited from a parent who may or may not have exhibited phenotypic features [Fahrner et al., 2012]. However, to date they have declined testing, and thus it is very likely that they would also deny sequencing of the sarcomeric protein genes.

As Dr. McBride points out, we obtained a careful family history and emphasized the sudden death of a maternal grand-father [McBride, 2012]. We did in fact inform the proband's mother that HCM, whether associated with an abnormality in the RAS–MAPK pathway or not, can be familial and could certainly present with sudden death. The mother was unaware of individuals in her family with known cardiac arrhythmias or congestive heart failure. We performed an echocardiogram on the mother (age 30) and documented that she had normal myocardial function and cardiac anatomy. The father declined echocardiogram.

In summary, we agree that sequencing of the sarcomeric protein genes known to cause HCM could potentially identify other contributing mutations/variants, some of which may be novel, and academically interesting. However, given the issues of cost, difficulties in interpretation of variants of unknown significance, and the priorities of the patient's parents, in this situation where we found two abnormalities in the RAS–MAPK pathway in a child whose phenotype fits with a RASopathy, pursuing this additional testing was not feasible as a part of clinical care. Ideally, then, further analysis would take place on a research basis. This, however, would require obtaining informed consent from a family who seems weary of genetic testing.

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