Editorial

Four-Generation Family With Ebstein Anomaly Highlights Future Challenges in Congenital Heart Disease Genetics

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Mercer et al[1] describe a family in which a missense variant in Filamin A (*FLNA*) segregates with Ebstein anomaly. This is a syndromal form of congenital heart disease (CHD) in that affected individuals have craniofacial and musculoskeletal anomalies, as well as keloid scarring and oligodontia. Clinically, affected family members had no apparent neurological involvement, although cranial imaging was not reported. Overall, the phenotype is clearly in a continuum with other *FLNA*-associated disorders including otopalatodigital syndrome (OPD1 and OPD2) and Melnick–Needles syndrome. However, this represents a new addition to the stable phenotypes linked to *FLNA*, with the cardiac features being particularly noteworthy.

See Article by Mercer et al

Such families are a unique resource in expanding our knowledge of causal genes and mechanisms in CHD. The unfolding of this story (some of the family had previously been screened for *NKX2-5* and *MYH7* mutations in a previous era) over some 25 years, and 4 generations are testament to the persistence of the authors, as well as the effectiveness of modern sequencing technology. It also illustrates the power of the phenotype to illuminate the genotype. Previously, *FLNA* had been associated with cardiac valvular disease (not including Ebstein anomaly) in families lacking extracardiac features.[2] Kyndt et al[2] had access to multiple families, including 1 very large family, enabling them to use linkage data to confidently associate cardiac features and genetic variants. By contrast, Mercer et al[1] had only 6 affected individuals available for testing, insufficient for linkage to provide much support for pathogenicity, even with an X-linked gene. The rarity of the variant and in silico support for pathogenicity are suggestive but would not constitute conclusive evidence. However, the clinical overlap between the features of their patients and other *FLNA*-associated phenotypes is the clincher, leaving no real doubt about the result—even while this family extends our knowledge of the role of *FLNA* in the heart.

This study exemplifies a further dimension of current investigations into the genetic causation of CHD. Association of structural heart disease with other conditions, in this case musculoskeletal disorders, but also a wide spectrum of neurodevelopmental and behavioral anomalies, is an emerging theme. It is possible that these associations are because of the disruption of common progenitor cell populations by mutation. Common progenitors to the heart and the musculoskeletal system, for example, exist in nascent mesoderm. However, because all mesodermal structures are derived from this germ layer, one might expect a greater number of associations extending beyond the musculoskeletal system. For neurodevelopmental and behavioral anomalies, it is even less likely that disruption of common progenitors would be the cause of association with structural heart disease. A more plausible explanation relies on overlapping gene expression profiles with mutation disrupting gene expression/function in the developing heart and other tissues. Evidence in support of this exists with respect to the association between structural heart disease and neurodevelopmental and behavioral anomalies, with the identification of mutations in many genes that are expressed in both the developing heart and brain.[2,3]

With a range of conditions and potentially causal genes clustering around what might be a structurally simple cardiac defect evident on antenatal echocardiography, it is just a small jump to the application of massively parallel sequencing to assess fetal DNA in amniotic fluid of affected fetuses. Given the gravity of decisions stemming from provision of this information on continuation of pregnancy and later surgical management, there is an urgent need to develop our knowledge of genotype–phenotype relationships across multiple organ systems and to ensure the robustness of advice provided. *FLNA* presents a particular challenge here, given the enormous variability of associated phenotypes—from cardiac valvular disease to intestinal pseudo-obstruction, in addition to the syndromes mentioned above and at least one more, FG syndrome. Even within families, variability can be considerable—as seen in the family reported by Mercer et al.[1] The potential benefits of an accurate antenatal diagnosis are real, but so are the risks. It would be all too easy to over- or misinterpret the significance of a variant in *FLNA* in a fetus, about whom the only phenotypic information is sonographic evidence of cardiac valvular disease.

Where affected children have already been born, a unifying genetic diagnosis brings some certainty about diagnosis and quantification of recurrence risk in future offspring. The cost of achieving such diagnoses remains significant. It

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is reasonable to question how such families should be selected for the initial genetic evaluation in a publicly funded system. There are many such families in general CHD clinics with less exotic diagnoses, who could expect a genetic diagnosis in 15% to 35% in familial cases.[4] The value of such information needs to be evaluated alongside the combined cost of massively parallel sequencing and the numerous expert hours of bioinformatics time, reporting, and genetic counseling.

Interest in Ebstein anomaly is growing. Clinical approaches are evolving as the natural history of this condition is established. In this study, the full spectrum from neonatal presentation to adult surgery and compensated disease is illustrated. There are fundamental differences between those requiring neonatal[5] and later management,[6] and thresholds for surgical intervention are changing.[7] Newer approaches to repair the tricuspid valve achieve better early results than previous iterations, although long-term outcomes are yet to be established. The role of surgery in asymptomatic patients is not agreed, although it is understood that the development of left-sided pathology and arrhythmia is likely over time.

As the authors conclude, *FLNA* variants are unlikely to explain sporadic, nonsyndromal cases of Ebstein anomaly. Nevertheless, in families with multiple affected members, a significant proportion of cases solved tend to be mild phenotypes of previously undetected syndromes (for example, Holt–Oram, Char Syndrome) and at the very least, *FLNA* is another gene to add to the list of CHD candidates in the screening workflow.

Disclosures

None.

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