Copy number variants in congenital heart disease: A new risk factor impacting outcomes?

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Copy number variants (CNVs) are alterations of genomic DNA in which segments larger than 1000 base pairs are either deleted or duplicated. Through the Human Genome Project and other studies, many of these CNVs have been discovered. Some account for part of the normal genetic variability and are not associated with pathogenic disease states. There is also evidence, however, that larger and in particular de novo CNVs are linked to human disease.¹ The conflicting data on the significance of CNVs may be partially explained by the presence of dosage-dependent genes or regulatory sequences within some of these missing or extra regions.² Multiple deletion and duplication syndromes have been described with congenital heart disease (CHD) among their hallmark features. DiGeorge syndrome, which is a microdeletion of the 22q11.2 region, is one of the best described examples,³ but CNVs have also been reported in nonsyndromic CHD, and as such some have advocated screening for CNVs in all cases.⁴

In this issue of the *Journal*, Kim and colleagues⁵ present results from their study that examined the frequency of large (defined as >300 kilobases) CNVs in children with isolated CHD. In line with previous reports, they similarly found that patients with CHD had an excess of CNVs relative to control subjects (12.2% vs 5.0%; $P = .00016$). But what is perhaps more intriguing is that this study also examined the relationship between CNVs and transplant-free survival after heart surgery. Kim and colleagues found that CNVs conferred a 3.43-fold increased risk of death or transplant after adjustment for known confounders (95% confidence interval, 1.66-7.09; $P = .00009$).

This result is novel and relevant for multiple reasons. Genetic variants have long been known to impact survival. This same group previously published on the impact of *VEGFA* and *SOD2* genetic variants, which are involved in vascular response and oxidative stress pathways, on transplant-free survival.⁶ Previous work

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Central Message

Copy number variants contribute to human genetic variation. They may also impact pediatric cardiac surgery outcomes.

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related to CNVs, however, has largely dealt with the syndromic population or those with extracardiac manifestations. Although there have been adult studies on the relationship between CNVs and mortality, there is little to no literature focusing on the pediatric nonsyndromic CHD population. Thus this study highlights the importance of more subtle underlying genetic variations and their impact on clinical outcomes.

Our current risk stratification systems take into consideration relevant clinical criteria, such as age, weight, prematurity, presence of extracardiac manifestations, genetic syndromes,⁷ and the Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery Risk Stratification system for procedure complexity,⁸ just to cite a few. It is important, however, to recognize that these systems are constantly in need of refinement, refinement that comes from discovering nonobvious sources of risk factors.

Studies like this will be important to help generate the scientific evidence needed to advance toward precision medicine in pediatric cardiac surgery. Moreover, as we better understand the relationship between genetic variation and outcomes, our enhanced knowledge of the underlying pathogenic mechanisms of disease will spur discovery of newer treatments and better preventive strategies.

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