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Getting personal: understanding how genetic variation affects clinical outcomes in patients with tetralogy of Fallot

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STUDY FINDINGS

Tetralogy of Fallot (TOF) is the most common form of cyanotic heart disease (1). Prior to surgical repair, which usually occurs within the first 6 months of life, affected infants have pressure overload on the right ventricle of the heart and can have episodic or persistent hypoxia. The resulting hypoxic and pressure-induced stress may have lasting effects on the structure and function of the heart. After surgical repair, which involves closing a ventricular septal defect and widening the right ventricular outflow tract to the pulmonary artery, the hypoxia is relieved and the pressure dramatically reduced. Unfortunately, the widened outflow tract leads to leakage of ejected blood back into the right ventricle. Over time, this pulmonary insufficiency causes progressive ventricular dysfunction that will eventually require placement of a competent valve between the right ventricle and the pulmonary artery (2). The rate at which this dysfunction progresses can vary from one patient to the next, and clinical determination of how to time valve replacement to preserve ventricular function and exercise tolerance has been challenging (3). The variable and often unpredictable clinical course suggests that individual differences in how patients with TOF respond to their heart condition or the surgical repair may be important in determining when valve re-

placement will be necessary and how effective the surgery will be in improving a patient's clinical condition.

Therefore, in their paper "Genetic determinants of right ventricular remodeling after tetralogy of Fallot repair," Jeewa *et al.* (4) have made an important contribution to our understanding of what some of those individual differences may be and provide insight into why the progress of the right ventricular dysfunction seems to vary between patients. Given the importance of *Hypoxia Inducible Factor, 1 alpha (HIF1A)*, a hypoxia-inducible transcription factor, in regulating the expression of a broad range of downstream genes in response to hypoxia (5,6), the study team examined the correlation between genetic markers associated with enhanced *HIF1A* expression and (i) the degree of fibrosis at the time of surgical repair and (ii) the right ventricular structure and function during postoperative follow-up. They noted that low-expression *HIF1A* variants were associated with less fibrosis at the time of surgery but enhanced adverse ventricular remodeling after surgical repair. This suggests that individual differences in genetic pathways that govern the hypoxic stress response may have an important role in determining clinical course. Although additional studies will need to be performed to confirm this finding, it raises the important possibility that clinicians may be able,

using focused genetic tests, to identify patients who are at risk for more rapid development of irreversible ventricular dysfunction and treat them patients according to their risk.

IMPORTANCE OF INDIVIDUAL DIFFERENCES

The importance of Jeewa and colleagues' article extends beyond the implications of the findings for patients with TOF. It is an important contribution to the growing body of evidence that genetic variation between patients has an important role in determining outcomes in patients with congenital heart defects. Perhaps the first demonstration of a significant impact of genetic variation on clinical outcomes in this patient population was reported by Gaynor *et al.* (7), who examined the correlation between *Apolipoprotein E (ApoE)* genotype and measures of neurocognitive performance at one year of age in patients who had had cardiac surgery before six months of age. They found a significant effect of the *ApoE* ϵ 2 allele on the Psychomotor Development Index using the Bailey Scale of Infant Development II. The adverse effect of this allele on neurobehavioral function was noted to persist, as was recently demonstrated at the four-year follow-up of this patient cohort (8). At the preschool time point, patients with congenital heart defects who had undergone surgery within the

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first 6 months of life were more likely to demonstrate reduced attention, higher impulsivity, and impaired social skills, all of which were enhanced if the patient harbored the *ApoE* $\epsilon 2$ allele.

The evaluation of the impact of genetic factors on clinical outcomes is now more frequently being incorporated into clinical trials for pediatric cardiac disorders. A recent clinical trial—the Infants with Single Ventricle (ISV) trial, performed by the Pediatric Heart Network with support from the National Heart, Lung, and Blood Institute—examined the effects of enalapril treatment on growth and ventricular function in patients with single-ventricle cardiac defects. A component of that study was an examination of the effect of functional genetic variants in the renin–angiotensin–aldosterone system (RAAS) on these outcome measures. Genotyping of five RAAS-pathway genetic polymorphisms was performed in 154 patients enrolled in the trial (9,10). Genetic variants were categorized as high risk or low risk, according to their effect on RAAS signaling. Patients were then assigned to high- and low-risk groups based on the presence of two or more or fewer than two high-risk variants, respectively. High-risk patients had reduced weight-for-age and height-for-age Z scores prior to entry into the study. The reduced height-for-age persisted at the 14-month follow-up visit and was more pronounced in the high-risk patients treated with enalapril (10). Although beneficial ventricular remodeling (reduction of ventricular mass and volume) is expected after the second-stage operation to palliate single-ventricle-type heart defects, patients with a high-risk RAAS profile did not demonstrate the same level of improvement as the RAAS low-risk group. This study demonstrated that individual genetic variation could affect clinical outcomes and the response to medical therapy.

However, in these previous studies it was not possible to concurrently investigate the effect, if any, of genetic variation on individual adaptation at the tissue level. In the study by Jeewa *et al.* (4), there is a very nice chain of evidence linking genetic variation to tissue-based changes in right ventricular (RV) architecture to

Figure 1. Interaction of “environmental” and genetic factors in determining clinical outcomes. Genetic and environmental factors interact to cause disease and to determine the biologic response to the condition and its treatment. In the study by Jeewa *et al.*, *HIF1A* genetic variants affecting its expression influenced the responses of a patient with tetralogy of Fallot (TOF) to the environmental stresses of hypoxia, pressure overload, and surgical repair. Establishing a chain of evidence from underlying genetic variation to observed clinical outcome relies on the integration of biorepository and clinical database resources. RV, right ventricular.

differential effects on RV structure and function. Such studies will be a model for future clinical studies in which there is vertical integration of disease pathogenesis, beginning with the underlying genetic predisposition and culminating with the observed variation in the clinical outcome (Figure 1). In larger studies, it will be possible to go from the observed clinical outcome back to the causative genetic variation using whole-genome genotyping or sequencing to identify novel disease mechanisms.

ROLE OF BIOREPOSITORIES

Jeewa and colleagues’ study (4) depended on careful collection of biologic specimens and linkage of these collected specimens to recorded clinical outcomes. In preparation for this and other studies, the investigative team established the SickKids Heart Centre Biobank Registry (<http://www.heartcentrebibank.ca/home/index.php>), an effort to study the genomic and environmental basis of heart defects in Ontario, Canada. As these types of studies become increasingly prevalent and clinically relevant, the value of prospectively collecting and storing biologic specimens as a means of understanding future clinical outcomes is becoming more widely appreciated.

This has led to a marked increase in the number and scope of biorepositories and biobanks that process and store biologic samples (e.g., blood, DNA, serum, sputum, and tissue) (11). Sample coding preserves patient confidentiality, and parallel clinical databases house the relevant corresponding demographic information, medical records, and outcomes measures. The study by Jeewa *et al.* demonstrates how such a biorepository effort can result in important clinical findings. In the future, it is hoped that biorepositories from many institutions will coordinate the processing and storage of biospecimens using standardized methods and link specimens to specific disorders, outcome measures, and complication and survival data through anonymized (12) and readily searchable clinical databases (13).

THE FUTURE OF PERSONALIZED MEDICINE

Jeewa and colleagues’ study represents an important step in the development of an individual, or “personalized,” approach to the care of patients with congenital cardiac defects. This is not to suggest that our care of the congenital heart patient to date has been impersonal, but we have not had a good understanding of why two patients with very similar heart condi-

tions can respond very differently to the defect itself and to our therapeutic interventions. As more studies identify the genetic variables that affect clinical outcomes, it may become possible to target therapeutic interventions based on each individual's predicted clinical response to the array of treatment options.

SUMMARY

The work by Jeewa *et al.* is an important step toward “personalizing” or individualizing our approach to care of patients with tetralogy of Fallot. Although future studies will need to confirm the potential role of *HIF1A*-mediated signaling in right ventricular remodeling, it raises the possibility that modulation of the *HIF1A* signaling pathway or its downstream effectors such as TGF- β may allow better preservation of ventricular function in patients with TOF. Furthermore, directed genotyping for *HIF1A* and other genetic variants may help identify patients at risk for adverse outcomes. This study demonstrates the potential for genetics-of-outcomes studies to evaluate novel

therapeutic targets and to identify at-risk populations that may require specific therapeutic considerations.

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REFERENCES

1. Hoffman JL, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J* 2004;147:425–39.
2. Geva T. Indications and timing of pulmonary valve replacement after tetralogy of Fallot repair. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2006;11–22.
3. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *Am J Cardiol* 2005;95:779–82.
4. Jeewa A, Manickaraj AK, Mertens L, *et al.* Genetic determinants of right ventricular remodeling after tetralogy of Fallot repair. *Pediatr Res* 2012;72:407–413.
5. Miyata T, Takizawa S, van Ypersele de Strihou C. Hypoxia. 1. Intracellular sensors for oxygen

and oxidative stress: novel therapeutic targets. *Am J Physiol Cell Physiol* 2011;300:C226–31.

6. Dekanty A, Romero NM, Bertolin AP, *et al.* *Drosophila* genome-wide RNAi screen identifies multiple regulators of HIF-dependent transcription in hypoxia. *PLoS Genet* 2010;6:e1000994.
7. Gaynor JW, Gerdes M, Zackai EH, *et al.* Apolipoprotein E genotype and neurodevelopmental sequelae of infant cardiac surgery. *J Thorac Cardiovasc Surg* 2003;126:1736–45.
8. Gaynor JW, Nord AS, Wernovsky G, *et al.* Apolipoprotein E genotype modifies the risk of behavior problems after infant cardiac surgery. *Pediatrics* 2009;124:241–50.
9. Hsu DT, Zak V, Mahony L, *et al.* Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation* 2010;122:333–40.
10. Mital S, Chung WK, Colan SD, *et al.* Renin-angiotensin-aldosterone genotype influences ventricular remodeling in infants with single ventricle. *Circulation* 2011;123:2353–62.
11. Baker M. Biorepositories: building better biobanks. *Nature* 2012;486:141–6.
12. Tamersoy A, Loukides G, Nergiz ME, *et al.* Anonymization of longitudinal electronic medical records. *IEEE Trans Inf Technol Biomed* 2012;16:413–23.
13. Shublaq NW, Coveney PV. Merging genomic and phenomic data for research and clinical impact. *Stud Health Technol Inform* 2012;174:111–5.