



Advances in paediatric cardiology 2017: the genetics of paediatric cardiovascular disease

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In this issue, we continue our reviews of recent advances and novel approaches in paediatric cardiology, focusing on the amazing advances in understanding the genetics of childhood cardiovascular disease. It has now been 27 years since the initiation of the Human Genome Project, and 14 years since its completion. The major contribution of this project was not only the first sequencing of a single individual's genome but also the development of next-generation technologies for both performing the actual sequencing itself and the highly complex informatics systems required for analysis. As this technology has advanced at a speed-of-light pace, the cost of genome sequencing has plummeted, from the roughly \$300 000 000 required for the Human Genome project (the total cost of which is estimated at \$2.7 billion) to approximately \$1000 today. This has opened the door for the use of whole exome and whole genome sequencing for both research and clinical purposes.

For those who are not full-time geneticists, however, keeping up with this field is a daunting task. As genome sequencing becomes more and more a part of routine paediatric practice, how is the practitioner to determine which test(s) to order, how to interpret the results and how to explain them to patients and their families? As will become evident from several of the articles in this section, these tasks require working in close collaboration with a clinical geneticist and, as importantly, with a trained genetic counsellor. The purpose of the following articles is therefore not to provide the practitioner with the skills to 'go it alone' but to provide a sufficient educational update so that practitioner and geneticist will be speaking the same 'language'.

In the introductory article, James Priest (pp. 000–000), from Packard Children's Hospital at Stanford, provides a comprehensive, yet accessible 'Primer to Clinical Genome Sequencing'. Through this introduction, the methodologies discussed in the following chapters, focused on specific diseases, will be readily understandable. Clinicians considering a genetic diagnosis will learn of the wide array of testing choices available to them, which now includes whole genome sequencing. Although

not a comprehensive test in its current form, genome sequencing offers more information than gene-panel or exome sequencing and in the future may serve as a primary diagnostic test for patients with suspected single-gene disorders.

Next, narrowing our focus to specific childhood cardiovascular disorders, Martina Brueckner and Abigail Simmons from Yale (pp. 000–000) provide an update on advances made possible by next-generation sequencing to the understanding of the cause of congenital heart disease (CHD) as well as to the comorbidities frequently seen in patients with genetic CHD. These comorbidities include neurodevelopmental disability, pulmonary disease, heart failure, renal dysfunction, arrhythmia and an increased risk of malignancy. Identification of the genetic cause of these comorbidities will help physicians to develop treatments to reduce patient morbidity and mortality.

In the next article, Caitlin Rollins, Jane Newburger and Amy Roberts (pp. 000–000), from Boston Children's Hospital, review the state of our current understanding of the link between CHD and neurodevelopmental disorders (NDDs) in the 'Genetic Contribution to Neurodevelopmental Outcomes in Congenital Heart Disease: Are Some Patients Pre-Determined to Have Developmental Delay?' This group has pioneered studies that have changed our appreciation of the risk for neurodevelopmental disabilities in the setting of CHD. This risk is highest in patients with complex CHD such as single ventricle, where up to 90% of patients will require developmental/educational services at some point during childhood. The link between CHD and NDD is multifactorial, including the effect of heart malformations on foetal cerebral blood flow, the effect of hypoxia during infancy before cardiac repair and

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the effects of cardiac surgery. Rollins *et al.* review how advances in genome sequencing technology have recently identified substantial overlap between mutations in children with CHD and those that have previously been associated with NDDs.

Moving from CHD to the cardiomyopathies, Stephanie Ware (pp. 000–000) from Indiana University provides an update on the ‘Genetics of Pediatric Cardiomyopathies’. As with CHD, our understanding of the genetic causes of paediatric cardiomyopathy is rapidly improving and novel causes are identified. However, as we make continued progress in identifying the scope of genetic variation in large population datasets, this has led to a reassessment of our understanding of the significance of rare genetic variation and at times has resulted in a revision of the interpretation of previous mutation results. As our understanding of the basic science of paediatric cardiomyopathies has improved, therapies targeted towards the underlying causes have emerged for syndromes such as Pompe and Noonan, and genome editing provides promise for additional therapeutic approaches in the future.

Greg Enns from Stanford next reviews the complexities of ‘Mitochondrial Disorders and the Heart’ (pp. 000–000). This is perhaps one of the largest differences between the cause of paediatric heart failure and that in adults. Although mitochondrial mutations tend to have effects on multiple organ systems, their effects on the heart are often the

most life-threatening. Mitochondrial proteins are encoded by both nuclear DNA and mitochondrial DNA and mutations in these genes cause both dilated and hypertrophic cardiomyopathies. Currently, most treatments are directed at symptomatic relief; however, recent advances in understanding the pathophysiology of these complex disorders are driving the development of novel approaches directed at correcting the metabolic defects induced by these mutations.

Finally, Gaetano Vacanti, Ricardo Maragna, Silvia Priori and Andrea Mazzanti (pp. 000–000) from Pavia, Italy, review ‘Genetic Causes of Sudden Cardiac Death in Children: Inherited Arrhythmogenic Diseases’. This is an area wherein there have been tremendous advances, especially in unravelling the genes specific for the long QT syndromes. In these cases, confirmation of the specific gene mutation can aid in screening other family members, and in some cases can also provide physicians with guidance to specific drug treatments.

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