

Genetic Cardiovascular Conditions – It's All About Family



Jonathan R. Skinner, MD, FRACP, FHRS^{a,b,*},
John J. Atherton, MBBS, PhD, FRACP^{c,d,e,f},
Christopher Semsarian, MBBS, PhD, MPH^{g,h,i}

^aGreen Lane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand

^bDepartment of Paediatrics Child and Youth Health, The University of Auckland, Auckland, New Zealand

^cDepartment of Cardiology, Royal Brisbane and Women's Hospital, Brisbane, Qld, Australia

^dFaculty of Medicine, University of Queensland, Brisbane, Qld, Australia

^eFaculty of Science, Health, Education and Engineering, University of Sunshine Coast, Brisbane, Qld, Australia

^fFaculty of Health, Queensland University of Technology, Brisbane, Qld, Australia

^gAgnes Ginges Centre for Molecular Cardiology at Centenary Institute, University of Sydney, Sydney, NSW, Australia

^hFaculty of Medicine and Health, University of Sydney, NSW, Australia

ⁱDepartment of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia

Keywords

Genetic cardiology • Family history • Multidisciplinary care • Genetic testing

For most of us, our lives revolve around our family. Māori elders (Kaumatua) advise us that, when we see an individual in front of us, we should see behind them, like a giant wedge, the parents and grandparents going way back into antiquity, and we should acknowledge their presence and their spirit. All of us are the product of our parents and their parents before them. We inherit their strengths and their vulnerabilities. So, it should come as no surprise that a properly taken family history during a medical consultation has the potential to reveal vulnerability to disease in the patient before us.

Yet, cardiologists tend to be poor at taking family histories. A recent study in New Zealand, with its relatively enlightened and cohesive national health service, revealed that cardiology teams on medical wards rarely take a proper family history. In a cohort of adult patients with non-coronary conditions, (mostly cardiomyopathy and unexplained cardiac arrest) a three-generation family history taken by a trained nurse revealed a familial diagnosis in 32% of the cases, compared to 8% detected by the admitting team [1].

Genetic cardiology has now come of age. The reason for this lies mostly with the increasing availability and relevance of genetic testing. Over 20 years we have gone from waiting

years for a single gene to be screened to sequencing an entire human genome in a matter of a few weeks.

This special edition of *Heart Lung and Circulation* brings together much collective wisdom from the new Australasian multidisciplinary family of clinicians and allied professionals who lead the way in this exciting field. They have drawn expertise from their international colleagues and coauthors, and present summaries and novel perceptions to assist the general cardiologist to come to grips with this rapidly advancing area of medical science.

A recurring theme is the significance of family history. There is no blood test for this, it cannot be ordered on a laboratory form, yet it is of huge diagnostic importance. To diagnose long QT syndrome, Brugada syndrome, familial hypercholesterolaemia (FH), familial dilated cardiomyopathy, familial hypertrophic cardiomyopathy and arrhythmogenic cardiomyopathy, the family history is essential. Family history is even incorporated into scoring systems to make the diagnosis, or in guiding risk stratification for sudden death, as in hypertrophic cardiomyopathy (HCM).

Many of the articles in this special edition also highlight the importance of detailed examination of first-degree relatives of the patients with a possible inherited condition. A firm diagnosis of familial cardiomyopathy or cardiac ion

*Corresponding author at: Green Lane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, PCCS, Level 3, Building 32, Grafton, Auckland 1142, New Zealand; Email: j.skinner@adhb.govt.nz

channelopathy in a child may only be made possible after detailed cardiological assessment of the parents reveals the condition in them. The same also applies in adults. A 40-year-old man who presents with suspected arrhythmogenic cardiomyopathy may receive a certain diagnosis when one of his parent's cardiac magnetic resonance imaging (MRI) findings are diagnostically abnormal. A 40-year-old woman with syncope and a suspiciously prolonged QT interval, may receive a certain diagnosis if her child has definitive QT prolongation. A single cardiologist is not likely to be able to arrange all this family testing, so services for children and adults need to learn to work together. Dedicated multidisciplinary cardiac genetic clinics need to be encouraged and supported to facilitate this. They provide more comprehensive and co-ordinated family screening for familial cardiac conditions than isolated genetic or cardiology services [2], and families like them [3].

Such dedicated services are especially vital in the investigation of young, sudden unexpected death. Bagnall *et al.* review the data in this special edition of the Journal [4]. Pathologists become part of the service in helping direct the investigation of the surviving family members and a high-quality autopsy and DNA preservation are essential. Contrary to the impression gained from many previous publications focussing on sudden death in athletes, population-based studies show that sudden death in the young occurs during rest or sleep in over 85% of cases [5], so they largely go unnoticed by media.

All who wish to come to grips with cardiac genetics should start with the article on genetic testing by Ingles *et al.* [6]. In plain language, they introduce and clarify the nomenclature and many important concepts in this field. Waddell-Smith *et al.* also discuss when to order a genetic test and how to interpret the result [7]. They take long QT syndrome as an example and demonstrate the importance of pre-test probability in interpreting a genetic result. Genetic test results are probabilistic and rarely definitive, and therefore must be interpreted in the light of a fully evaluated clinical phenotype; a single electrocardiograph (ECG) just doesn't cut it.

Cardiomyopathies can result directly from genetic risk as well as from our behaviour and lifestyle. This interplay between acquired and inherited risk is studied in a paper by Prior and La Gerche [8]; does endurance exercise cause arrhythmogenic cardiomyopathy on its own, or is it all down to genetics? Similarly, it turns out that the patient with an apparent post-partum or alcoholic cardiomyopathy may carry genetic risk factors for their cardiomyopathy, particularly truncating Titin (TTN) variants. Peters *et al.* discuss this [9]; and, also show the increasing number of genotypes which dictate specific management strategies for dilated cardiomyopathies.

Another emerging area of genetic testing, which may ultimately bypass the cardiac genetic clinics due to the size of the population involved, is that of polygenic risk scores (PRS) for coronary artery disease and atrial fibrillation [10]. Presented here by Gladding *et al.*, PRS may become like genetic testing for FH, which is expertly reviewed by Pang

et al. in this edition [11]. Such tests have enormous potential in targeting when more detailed cardiological screening and treatments are indicated for these common conditions, over and above that currently indicated by (for example) family history and blood lipids alone. And these genetic tests will be relatively inexpensive.

Curative treatments are rare for inherited cardiac conditions, but gene therapies are coming. Some of the targets for this are illustrated beautifully by Winbo *et al.* in their enlightening discussion of neurocardiac modulation in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT) [12]. Flecainide is not a cure for CPVT, but its protective effect in CPVT is extraordinary, such that, in combination with a beta blocker, an implantable cardioverter defibrillator (ICD) may not be required, even after cardiac arrest [13,14]. However, Pflaumer *et al.* discuss CPVT further and take us to the "dark side of the moon" to remind us that there is still much to learn. Radiofrequency ablation of the epicardial surface of the right ventricular outflow tract in Brugada syndrome is getting close to a cure. Such ablations can eliminate the signature Brugada ECG and, it seems likely, risk of sudden cardiac death. Brugada syndrome seems to be a channelopathy which has turned partly into a cardiomyopathy. Isbister *et al.* describe the problems associated with this most difficult and complex condition over which experts dispute the pathophysiology while clinicians grapple with the impossibility of accurate prognostication [15]. Bennett *et al.* describe how such ablations can be done and indicate other conditions, particularly Lamin cardiomyopathy, where catheter ablation plays a significant role [14]. They also emphasise that prevention of sudden cardiac death in inherited heart conditions is not just about implanting a defibrillator, and in most cases for most conditions they are not needed at all.

Dennis *et al.* detail the role of cardiac MRI, particularly in the genotype positive-phenotype negative patient with familial cardiomyopathies [16]. They describe how the distribution of fibrosis in cardiomyopathies has a role in both diagnosis and predicting risk of sudden cardiac death. The prediction of risk of sudden death in hypertrophic cardiomyopathy (HCM), and the knowledge of the changing genetic architecture and epidemiology of HCM, is expertly reviewed by Younger *et al.*, who also describe how HCM presents and behaves quite differently in the older patient [17].

Multisystem disorders may have significant cardiovascular components. Zentner *et al.* bring us up to speed with syndromes and the genetics underlying aortopathies [18]. Wider knowledge of these conditions, more than just aortic dimensions, is vital in determining appropriate management. Amyloid cardiomyopathy, long recognised as the great mimicker of other cardiomyopathies, is now known to be an inherited condition itself in some cases. Bart *et al.* walk us through what is known of the inheritance and genetics of this condition which is commonly associated with neuropathy or carpal tunnel syndrome [19]. The autosomal dominant inheritance and the emergence of effective and specific drug therapies means that the condition can not only be treated

better, but possibly also prevented in pre-symptomatic family members.

This editorial ends where it should begin – in considering the impact that all these varied conditions have upon our many and varied patients of all ages, and their families. In striving to keep our patients alive, we must not destroy their lives in the process. O'Donovan et al. remind us that too little is known about how we should nurture our patients and families through all of this [20]. As the proverbial sword of Damocles hangs over them, we restrict their activities, impose sometimes unpleasant life-long therapies, while they risk possible adverse discrimination by schools, employers and insurance companies and we ask them to spread the news of a lethal condition through their families. One third of our patients have clinically significant levels of psychological distress expressed as anxiety or depression. This of itself is bad enough, but these factors may also contribute to non-adherence. Psychological expertise to guide clinicians and support our patients must be central to our care and O'Donovan et al. propose a framework to help us understand and improve our holistic care.

References

- [1] Waddell-Smith K, Donoghue T, Graham M, Oates S, Crawford J, Li J, et al. The inpatient cardiology visit: missing the opportunity to detect inherited heart conditions. *Heart Lung Circ* 2014;23(Suppl 2):e18–9.
- [2] Knight LM, Miller E, Kovach J, Arscott P, von Alvensleben JC, Bradley D, et al. Genetic testing and cascade screening in pediatric long QT syndrome and hypertrophic cardiomyopathy. *Heart Rhythm* 2020;17:106–12.
- [3] Ingles J, Lind JM, Phongsavan P, Semsarian C. Psychosocial impact of specialized cardiac genetic clinics for hypertrophic cardiomyopathy. *Genet Med* 2008;10:117–20.
- [4] Bagnall RD, Sinder ES, Tfelt-Hansen J. Sudden cardiac death in the young. *Heart Lung Circ* 2020;29:498–504.
- [5] Bagnall RD, Weintraub RG, Ingles J, Dufflou J, Yeates L, Lam L, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med* 2016;374:2441–52.
- [6] Ingles J, Maccioca I, Morales A, Thomson K. Genetic testing in inherited heart diseases. *Heart Lung Circ* 2020;29:505–11.
- [7] Waddell-Smith KE, Skinner JR, Bos JM. Pre-test probability and genes and variants of uncertain significance in familial long QT syndrome. *Heart Lung Circ* 2020;29:512–9.
- [8] Prior D, La Gerche A. Exercise and arrhythmogenic right ventricular cardiomyopathy. *Heart Lung Circ* 2020;29:547–55.
- [9] Peters S, Johnson R, Birch S, Zentner D, Hershberger RE, Fatkin D. Familial dilated cardiomyopathy. *Heart Lung Circ* 2020;29:566–74.
- [10] Gladding PA, Legget M, Fatkin D, Larsen P, Doughty R. Polygenic risk scores in coronary artery disease and atrial fibrillation. *Heart Lung Circ* 2020;29:634–40.
- [11] Pang J, Sullivan DR, Brett T, Kostner KM, Hare DL, Watts GF. Familial hypercholesterolaemia in 2020: a leading Tier 1 genomic application. *Heart Lung Circ* 2020;29:619–33.
- [12] Winbo A, Paterson DJ. The brain-heart connection in sympathetically triggered inherited arrhythmia syndromes. *Heart Lung Circ* 2020;29:529–37.
- [13] Pflaumer A, Wilde AAM, Charafeddine F, Davis AM. 50 years of catecholaminergic polymorphic ventricular tachycardia (CPVT) – time to explore the dark side of the moon. *Heart Lung Circ* 2020;29:520–8.
- [14] Bennett R, Campbell T, Kumar S. Catheter and device management of inherited cardiac conditions. *Heart Lung Circ* 2020;29:594–606.
- [15] Isbister JC, Krahn AD, Semsarian C, Sy RW. Brugada syndrome: clinical care amidst pathophysiological uncertainty. *Heart Lung Circ* 2020;29:538–46.
- [16] Dennis M, Ugander M, Kozor R, Puranik R. Cardiovascular magnetic resonance imaging of inherited heart conditions. *Heart Lung Circ* 2020;29:584–93.
- [17] Younger J, Lo A, McCormack L, McGaughan J, Prasad S, Atherton J. Hypertrophic cardiomyopathy: challenging the status quo? *Heart Lung Circ* 2020;29:556–65.
- [18] Zentner D, James P, Bannon P, Jeremy R. Familial aortopathies – state of the art review. *Heart Lung Circ* 2020;29:607–18.
- [19] Bart NK, Thomas L, Korczyk D, Atherton JJ, Stewart GJ, Fatkin D. Amyloid cardiomyopathy. *Heart Lung Circ* 2020;29:575–83.
- [20] O'Donovan C, Ingles J, Broadbent E, Skinner JR, Kaskarian NA. How patient perceptions shape responses and outcomes in inherited cardiac conditions. *Heart Lung Circ* 2020;29:641–52.