

Progress and challenges in the genetics of congenital heart disease

Congenital heart disease is often regarded as a chance occurrence affecting only a small number of children. In fact, it affects nearly 1 in 100 newborn infants^{1,2} and is the leading non-infectious cause of death in this age group. A third of those affected will need surgical or catheter-based intervention in the first year of life. In 2002, congenital heart disease accounted for 224 deaths in Australian children.² In the United States there are more than 35 000 new cases each year and over 1 million survivors of congenital heart disease in the community.³

Diagnosis and treatment of congenital heart disease has improved dramatically over the past 15 years. The mortality rate for surgical repair of some common conditions, such as tetralogy of Fallot, is currently less than 3%,⁴ and innovative catheter-based therapies, including closure of certain septal defects, have been developed. Preservation of ventricular function, avoidance of repeat surgery and freedom from arrhythmias are the next goals to be achieved.

The first question affected families usually ask is: "What is the risk of having an affected offspring or another affected sibling?". Population studies suggest that the risk is relatively small (2%, or double the background risk). The reason the risk is relatively modest may be that most congenital heart disease is the result of multiple gene defects and/or an interaction between single or multiple defective genes and the fetal environment. As the genotype and experience of each individual is unique, the occurrence of congenital heart disease in most individuals will not be in the context of a strong familial trait. However, there are many rare examples of families in which congenital heart disease is strongly inherited, and apparently caused by single-gene defects. Even in these families, cardiologic phenotypes can vary enormously, presumably because of the effects of modifier genes and/or influences other than genetic. Such families, if large enough, can be studied using classical genetic techniques (such as linkage analysis), but so far only a small number of clinical cases can be matched to a specific mutation. Thus, family genetic studies are currently not indicated for isolated, non-syndromal cases of congenital heart disease. With the advent of high-throughput genetic screening technology and improved cost benefit, indications for screening may be extended in the future.

Recently, cardiac developmental and molecular biologists and geneticists have started to unravel the molecular circuitry underpinning heart formation. Significant progress has come about partly because we can now dissect the morphological and genetic basis of human congenital heart disease in animal models from zebra fish to mice. Aspects of cardiac development are, in fact, highly conserved through evolution, and many of the regulators that transform embryonic mesoderm to myocardium are similar across species. One example is the cardiac regulatory gene *NKX2.5*, which was first isolated because of its similarity to a gene present

in the fruit fly, a laboratory model for genetic studies. The developmental approach has defined a number of key cardiac regulatory genes subsequently found by conventional linkage studies to underpin familial congenital heart disease.⁵ Mutations in *NKX2.5* itself cause atrial septal defect and conduction abnormalities, while *TBX5* mutations underpin heart and hand malformations of the Holt–Oram syndrome, and mutations in *GATA4* cause atrial septal defect and more complex congenital heart disease. In clear cases of familial inheritance, genetic screening for mutations in these genes may be beneficial.

Studies of gene expression in animal models have provided a window into how the human heart is constructed, and recent insights have led to a revision of traditional concepts of how cardiac chambers and valves develop. The heart begins as a rudimentary vascular tube,⁶ which, cardiologists are taught, is composed of anatomical segments that develop into chambers. Yet mapping of the cardiac precursor cell populations in the embryo has revealed a more complex picture. Gene expression patterns now show us that chambers arise from discrete zones, not segments, and that non-chamber myocardium gives rise to the central conduction system.^{7,8}

Another significant advance is the discovery of a second distinct pool of cardiac precursor cells in the embryo that migrate into the forming heart tube from the region of the developing pharyngeal arches. These

cells, the so-called "secondary heart field", contribute importantly to the right ventricle, outflow tracts and atria.⁹ Characterisation of the secondary heart field has unified genetic, developmental and clinical observations in congenital heart disease. Abnormal development and/or deployment of the secondary heart field cells causes underdevelopment and malpositioning of the outflow tracts over the ventricles. This occurs in velocardiofacial syndrome (VCFS, incorporating DiGeorge syndrome), which is caused by microdeletions in chromosome 22q11.¹⁰ The *TBX1* transcription factor gene is expressed in the secondary heart field and is deleted in VCFS. Its loss in mice has been causally related to abnormalities of the outflow tract that can arise in VCFS. One such abnormality is tetralogy of Fallot, in which unequal partitioning of the rudimentary outflow vessel produces a large aorta and a right ventricular outflow tract obstruction, with subsequent complications. Malalignment of the outflow vessels over the interventricular septum causes a large ventricular septal defect. Although fewer than a third of cases of tetralogy of Fallot are associated with the 22q11 microdeletion, single-gene mutations may prove to be a significant cause. In the case of interrupted aortic arch type B and truncus arteriosus, however, more than 50% of cases are associated with the 22q11 microdeletion. Recent developments in genome-wide screening technology have the power to detect microdeletions in individual patients on an unprecedented scale. This may revolutionise the detection of congenital heart disease genes.

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Pathological circumstances also provide deep insights into development. In the fetus, even simple primary structural disease (eg, a pulmonary valve that fails to develop) can cause complex secondary disorders as a result of disturbed blood-flow patterns. In heart development, function (flow) dictates form, and loss of normal blood-flow patterns can contribute to underdevelopment of chambers. In these circumstances, it is often difficult to predict from primary lesions the extent to which abnormal development and remodelling will occur as the fetus grows — this is one of the challenges of fetal echocardiography. Now, surgical correction during fetal life, long taboo, is being explored experimentally for valve correction,¹¹ as this would allow more time for normal ventricular development.

While only a small proportion of congenital heart lesions currently have identifiable gene markers, the number is growing rapidly. The next decade of research into congenital heart disease will see an exciting convergence of the disciplines of developmental biology, genetics and paediatric cardiology, and, we hope, will not only go further towards answering the question “Why did this happen to us?”, but also provide more secure grounds for genetic counselling and intervention.

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- 1 Hoffman JI. Incidence of congenital heart disease: I. Postnatal incidence. *Pediatr Cardiol* 1995; 16: 103-113.
- 2 Australian Institute of Health and Welfare (AIHW) 2004. Heart, stroke and vascular diseases — Australian facts 2004. Canberra: AIHW and National Heart Foundation of Australia, 2004. (AIHW Catalogue No. CVD 27. Cardiovascular Disease Series No. 22.)
- 3 American Heart Association. Heart disease and stroke statistics — 2005 update. Dallas, Tex: American Heart Association, 2005.
- 4 Aylin P, Bottle A, Jarman B, et al. Paediatric cardiac surgical mortality in England after Bristol: descriptive analysis of hospital episode statistics 1991-2002. *BMJ* 2004; 329: 825.
- 5 Gruber PJ, Epstein JA. Development gone awry: congenital heart disease. *Circ Res* 2004; 94: 273-283.
- 6 Harvey RP. Patterning the vertebrate heart. *Nat Rev Genet* 2002; 3: 544-556.
- 7 Christoffels VM, Habets PE, Franco D, et al. Chamber formation and morphogenesis in the developing mammalian heart. *Dev Biol* 2000; 223: 266-278.
- 8 Anderson RH, Webb S, Brown NA, et al. Development of the heart: (3) Formation of the ventricular outflow tracts, arterial valves, and intrapericardial arterial trunks. *Heart* 2003; 89: 1110-1118.
- 9 Kelly RG, Buckingham ME. The anterior heart-forming field: voyage to the arterial pole of the heart. *Trends Genet* 2002; 18: 210-216.
- 10 Yagi H, Furutani Y, Hamada H, et al. Role of *TBX1* in human del22q11.2 syndrome. *Lancet* 2003; 362: 1366-1373.
- 11 Huhta J, Quintero RA, Suh E, et al. Advances in fetal cardiac intervention. *Curr Opin Pediatr* 2004; 16: 487-493. □