Congenital Heart Disease
Congenital Heart Disease

Molecular Genetics, Principles of Diagnosis and Treatment

Editors

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93 Figures, 49 in color and 43 tables, 2015
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Preface

Congenital heart defects are among the most common birth defects affecting millions of families in all populations around the world. Two factors have had a tremendous impact on our understanding of congenital heart diseases: many details of the molecular mechanisms governing normal cardiac and vascular development have been uncovered using model organisms, and, fortuitously, this increased knowledge of molecular embryology has come at a time when the ability to analyze human genetic abnormalities has expanded exponentially. Together these disciplines are providing unprecedented insights into the causes of cardiac malformations.

Cardiology, as a discrete discipline in pediatric medicine, has also undergone transformative changes in this same era. New methods for imaging and physiological testing have emerged. These methods help to increase our understanding of cardiac growth in the fetal period and begin to pave the way for earlier and more effective interventions. Less invasive management of septal defects and cardiac valve anomalies have become routine practice. Cardiovascular surgery has become safer and more effective for congenital heart diseases. The dramatic improvements in mortality and long-term morbidity rates in this relatively young field are impressive.

Yet, we have to admit that there is still a huge poorly understood terrain ahead of us. Despite the progress in defining the contributions of chromosomal, genomic and single gene disorders to congenital heart diseases, the causes of these defects in most patients remain unknown. The relative contributions of not yet identified genes, gene variations and teratogens are still poorly understood. The likely interactions of individual genetic variation with nutritional factors, maternal metabolic factors, environmental exposures and commonly used medications are only understood abstractly. Whether and how these factors contribute and how they affect individual patients is still speculative. Much more research will be required to advance our understanding of these apparently complex causal mechanisms.

We felt an international team of authors would best represent the state of the art in this very large and diverse field; these authors chosen encompass all the disciplines necessary to unravel questions of etiology and treatments of congenital heart disease. Hence, this is a book intended for students, trainees and colleagues from a wide variety of disciplines. We hope this volume may prove useful irrespective of whether a researcher is devoted to molecular embryology or skilled at mending a mitral valve.
The editors would like to thank all the authors who graciously contributed to this volume and who took the time to share their expertise and explain their most important discoveries to a wide audience. We also would like to extend our deepest gratitude to all the patients and families whom we have met over the course of our careers for their time, generosity and compassionate spirits.

Maximilian Muenke, Bethesda, Md.
Paul S. Kruszka, Bethesda, Md.
Craig A. Sable, Washington, D.C.
John W. Belmont, Houston, Tex.
April 2015
The Editors – Max Muenke, Paul Kruszka, Craig A. Sable, and John W. Belmont – have done a remarkable job assembling international leaders in their respective fields and have created a landmark congenital heart disease volume. After almost 60 years of involvement in pediatric cardiology, I have had the pleasure of watching the field grow into what it is today: an advanced and highly complex discipline. We can make specific genetic diagnoses, identify heritable syndromes, provide genetic counseling, and repair complex heart malformations that would have been previously unimaginable.

Pediatric cardiology began with collections of observations on patients that were made into descriptive studies of congenital heart disease. When I finished my training in the late 1950s, much was known about congenital heart disease associated with Down syndrome, but little was known about other syndromes and noncardiac anomalies associated with congenital heart disease. After starting my first attending physician position at the University of Iowa, I began making 3 × 5 note cards for each patient I saw. After over 800 note cards, I began noticing trends in clinically similar patients. After reporting 9 patients with similar facies and valvular pulmonary stenosis at the Midwest Society for Pediatric Research in 1962 [1], I was able to characterize a syndrome that Dr. Victor McKusick would eventually name ‘Noonan syndrome’. This was the beginning of my interest in cardiovascular genetics. I am still in contact with some of these patients that I have diagnosed and taken care of over the last 5 decades and continue to meet new patients as well. Recently, while at a conference in Sweden, I met a 66-year-old gentleman who had self-diagnosed himself by performing an internet search of his physical findings and he was later found to have a mutation in \textit{PTPN11}. I am happy to see that many children with congenital heart disease are becoming productive adults, and I am excited that long-term
follow-up studies and research in affected adults are progressing [2].

Now, along with important clinical examination techniques developed in the past, we have a new tool in the form of genomic technology. Over the last 20 years, there has been an explosion in the discovery of genes involved in normal cardiac development as well as the genetic mutations that cause cardiac malformations. Animal models and transgenic experiments have given us a better understanding of human cardiac disease, and the completion of the Human Genome Project, cataloguing our entire genetic code, has allowed for further expansion of our knowledge of cardiac genetics.

This volume begins with a historical overview of congenital cardiovascular anomalies and ends with the potential of stem cells and tissue engineering. In between these chapters are explanations of cardiac embryogenesis, epidemiology of congenital heart diseases, descriptions of syndromes associated with cardiovascular anomalies, single-gene disorders, cardiac imaging, surgical and interventional therapies, and ethical considerations. This thorough account of congenital heart diseases is an invaluable reference and learning tool for pediatric cardiologists, geneticists, and primary care providers.

Even with these new technologies at hand, there is much more to learn. As we are now well into the 21st century, much of the genetic basis of cardiac malformations is still unknown. The editors of this book have assembled the most up-to-date information from many of the leaders in the fields of genetics and both pediatric and adult cardiology. I commend the authors and researchers in this field and look forward to the creative energy that will continue to develop our knowledge of cardiac malformations and benefit both affected children and adults.

Jacqueline A. Noonan, Lexington, Ky.
April 2015

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