Congenital Heart Disease
Molecular Genetics, Principles of Diagnosis and Treatment

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

34 Long-Term View: Lifetime Costs
34 How Critical Are Heart Defects?
34 Prevention: Evidence and Strategies
35 Integrating Interventions
35 When to Start Preventing?
35 What Proportion of Heart Defects Can Be Prevented?
36 Estimating How Many Cases Can Be Prevented
37 Maximizing the Impact
38 Case Study: Maternal Diabetes
39 Case Study: Folic Acid/Multivitamins
40 Putting Everything Together: Healthy Heart, Healthy Child, and Healthy Parents
41 Epidemiology and Prevention: Trends and Future
43 Conclusions
43 References

46 Clinical Epidemiology and Management of Congenital Heart Defects in a Developing Country
Ekure, E.N. (Lagos); Adeyemo, A.A. (Bethesda, Md.)

46 Abstract
47 Types of Congenital Heart Defects Seen in Nigeria
49 Etiology of Congenital Heart Defects in Nigeria
50 Age at Diagnosis
51 Clinical Presentation
52 Management of Congenital Heart Defects in Nigeria
54 Outcome
54 Challenges and Opportunities
55 References

57 Maternal Nongenetic Risk Factors for Congenital Heart Defects
Riehle-Colarusso, T.J. (Atlanta, Ga.); Patel, S.S. (Aurora, Colo.)

57 Abstract
58 Understanding Risk Factors for Congenital Heart Defects
58 Measurements of Associations for Risk Factors with Congenital Heart Defects
59 Challenges of Studying Risk Factors for Congenital Heart Defects
59 Select Risk Factors
60 Maternal Sociodemographic Characteristics
60 Maternal Health Conditions
65 Maternal Therapeutic Medications
66 Maternal Nontherapeutic Drugs
66 Conclusion
67 References

70 Adults with Congenital Heart Disease
Niwa, K. (Tokyo)

70 Abstract
70 Frequency of Adult Congenital Heart Disease
71 Treatment Facilities and Human Resources
72 Current Status and Future Prospects of Adult Congenital Heart Disease
72 Common Problems and Specific Pathophysiological Issues in Adult Congenital Heart Disease
72 Cardiac Failure
73 Arrhythmias
74 Pulmonary Hypertension
75 Pregnancy and Delivery
76 Psychosocial Issues
76 Possibility of Acquired Cardiovascular Disease
77 Aortopathy
77 Conclusion
78 References

3 Chromosomal Disorders

82 Down Syndrome
Kruszka, P.S. (Bethesda, Md.)

82 Abstract
82 Epidemiology
83 Genetics
84 Embryogenesis
85 Clinical Presentation
85 Cardiac Phenotype
87 Treatment
88 Prognosis
88 Gene Therapy for Future Directions
88 References

91 Congenital Cardiovascular Defects in Monosomy X or Turner Syndrome
Bondy, C. (Bethesda, Md.)

91 Abstract
92 Spectrum of Congenital Cardiovascular Malformations in Turner Syndrome
92 Aortic Valve
93 Aortic Dilation
93 Aortic Arch
94 Partial Anomalous Pulmonary Venous Return
94 Other Cardiovascular Defects
94 Theories on the Cause of Congenital Cardiovascular Defects in Turner Syndrome
94 Association with Fetal Lymphedema
95 Neural Crest
95 Parallels with the 22q11.2 Deletion (DiGeorge Syndrome)
96 Genes Implicated in Turner Syndrome
97 X-Chromosome Genomic Imprinting
97 Conclusion
97 References

100 The 22q11.2 Deletion Syndrome
Goldmuntz, E. (Philadelphia, Pa.)

100 Abstract
101 Molecular Characteristics of the 22q11.2 Deletion Syndrome
101 Clinical Characteristics of the 22q11.2 Deletion Syndrome
101 Congenital Heart Disease in the 22q11.2 Deletion Syndrome
166 **Heterotaxy**  

166 Abstract

168 Classification of Heterotaxy: Atrial Isomerisms and Other Laterality Defects

169 Association of Complex Congenital Heart Disease with Heterotaxy

169 Left-Right Patterning and Regulation of Cardiac Looping

171 Genetic Etiology of Heterotaxy

171 Ciliopathies and Heterotaxy

172 Airway Cilium Dysfunction Associated with Primary Ciliary Dyskinesia and Heterotaxy

172 Respiratory Symptoms and Disease in Ciliopathy and Heterotaxy Patients

173 Respiratory Complications and Worse Outcome in Heterotaxy Patients

173 Summary and Future Prospects for Improving Clinical Care and Outcome

175 Acknowledgments

175 References

178 **Molecular Genetics of Isolated Cardiovascular Malformations**  
Lee, T.M.; Chung, W.K. (New York, N.Y.)

178 Abstract

179 Monogenic Cardiovascular Malformations

179 Atrial Septal Defects

181 Ventricular Septal Defects

181 Bicuspid Aortic Valves

181 Supravalvar Aortic Stenoses

181 Additional Lesions

182 Recent Advances

182 Copy Number Variants

182 De novo Variants

182 Genome-Wide Association Studies

182 Clinical Genetic Evaluation and Testing

183 Conclusion

183 References

186 **Other Single-Gene Disorders Causing Congenital Heart Disease**  

186 Abstract

186 VACTERL Association

187 Diagnosis/Evaluation

187 The Kabuki Syndrome

188 Diagnosis/Evaluation

188 The Ellis-van Creveld Syndrome

189 Diagnosis/Evaluation

189 The Cornelia de Lange Syndrome

190 Diagnosis/Evaluation

190 The Mowat-Wilson Syndrome

190 Diagnosis/Evaluation

190 The Smith-Lemli-Opitz Syndrome

191 Diagnosis/Evaluation

191 Treatment

191 The Rubinstein-Taybi Syndrome

192 Diagnosis/Evaluation

192 The Char Syndrome

193 Diagnosis/Evaluation

193 The Goldenhar Syndrome

193 Diagnosis/Evaluation

193 Conclusion

193 Acknowledgments

194 References

5 **Arrhythmias, Cardiomyopathies, and Connective Tissue Disorders**

198 **Genetic Arrhythmias (Channelopathies)**  
Mazzanti, A.; Ng, K. (Pavia); Priori, S.G. (Pavia/New York, N.Y.)

198 Abstract

199 Long QT Syndrome

199 Epidemiology

199 Genetic Variants

199 Diagnosis

201 Clinical Manifestations

201 Risk Stratification

202 Management

202 Short QT Syndrome

202 Epidemiology

202 Genetic Variants

203 Diagnosis

203 Clinical Manifestations

203 Risk Stratifications and Management

204 Brugada Syndrome

204 Epidemiology

204 Genetic Variants

204 Diagnosis

204 Clinical Manifestations

205 Risk Stratification

205 Management

206 Catecholaminergic Polymorphic Ventricular Tachycardia

206 Epidemiology

206 Genetic Variants

206 Diagnosis

206 Clinical Manifestations

206 Risk Stratifications

206 Treatment

208 Conclusions

208 References

210 **Genetic Cardiomyopathies**  
Towbin, J.A. (Memphis, Tenn.)

210 Abstract

211 Final Common Pathways

211 Dilated Cardiomyopathy

212 Genetics of Dilated Cardiomyopathy

216 Muscle Is Muscle: Cardiomyopathy and Skeletal Myopathy Genes Overlap

216 Hypertrophic Cardiomyopathy
Contents

6 Evaluation

238 The Genetic Workup for Congenital Structural Heart Disease: From Clinical to Genetic Evaluation
Kruszka, P.S. (Bethesda, Md.); Sable, C.A. (Washington, D.C.); Belmont, J.W. (Houston, Tex.); Muenke, M. (Bethesda, Md.)

238 Abstract
240 Genetic Testing Algorithm
248 Aneuploidy
248 Copy Number and Structural Variants
250 Targeted Gene Sequencing
252 Whole Genome and Whole Exome Sequencing
254 Genetic Counseling
254 Concluding Remarks
254 References

257 Imaging of Congenital Heart Defects for the Noncardiologist
Sable, C.A. (Washington, D.C.)

257 Abstract
257 Types of Imaging
257 Ultrasound Physics
259 Echocardiography Examination
260 Indications
260 Timing of Imaging
260 Where/Who Does the Echocardiography
261 Common Lesions
261 Atrial Septal Defects

260 Ventricular Septal Defects
264 Atrioventricular Septal Defects
265 Tetralogy of Fallot
266 Pulmonary Valve Stenosis
267 Concluding Remarks
268 References

269 Prenatal Evaluation of Congenital Heart Defects and Fetal Intervention
Weinberg, J.G.; Krishnan, A. (Washington, D.C.)

269 Abstract
269 Indications for Fetal Cardiac Evaluation
270 Timing and Performance of Fetal Echocardiography
271 Prenatal Diagnosis of Congenital Heart Defects Associated with Specific Genetic Defects
271 Fetal Intervention
275 Importance of Fetal Diagnosis and Outcomes following Prenatal Detection of Congenital Heart Defects
276 References

7 Treatment

280 Surgical Management

280 Abstract
280 Trisomy 21 – Down Syndrome
283 The 22q11.2 Deletion – DiGeorge Syndrome
284 Trisomy 13 (Patau Syndrome) and Trisomy 18 (Edwards Syndrome)
285 Marfan Syndrome
285 Turner Syndrome
285 Noonan Syndrome
286 Other Syndromes
286 Special Considerations
287 References

289 Interventional Cardiology
Morgan, G.J.; Qureshi, S.A. (London)

289 Abstract
289 Interventional Cardiac Catheterisation in Paediatric Cardiology
289 Neonatal Intervention
290 Atrial Septostomy
290 Aortic Valvoplasty
291 Pulmonary Valvoplasty
292 Infant and Paediatric Procedures
292 Atrial Septal Defect Occlusion
293 Ventricular Septal Defect Occlusion
294 Transcatheter Pulmonary Valve Implantation
294 Coarctation Stent Implantation
295 Stent Technology
295 Fetal Interventions
295 Hybrid Techniques
296 Hybrid Palliation of Hypoplastic Left Heart Disease
296 Muscular Ventricular Septal Defect Closure
297 Paravalvar Leak Occlusion
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 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.

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Foreword

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 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

References