Craniosynostoses
Molecular Genetics, Principles of Diagnosis, and Treatment
Monographs in Human Genetics

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Series Editor

Michael Schmid  Würzburg
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Editorial

It is a great pleasure to introduce volume 19 of the book series *Monographs in Human Genetics* entitled ‘Craniosynostoses: Molecular Genetics, Principles of Diagnosis and Treatment’. The initial idea for this book was born during a workshop on craniosynostoses held at the Academy of Human Genetics in Würzburg (Germany). Hartmut Collmann and Wolfram Kress brought together many seemingly diverse aspects of craniosynostoses, including clinical approaches, genetics, molecular mechanisms and, most importantly, treatments. As that course progressed, they realized how inspiring this subject was to their colleagues and medical students.

Craniosynostoses provide one of the best examples of today’s molecular medicine, connecting simple anatomy and pathology with the structures of molecules that form the relevant signaling pathways. This book truly achieves the aim of *Monographs in Human Genetics* in dealing with the molecular causes of important hereditary diseases, their diagnosis, and their eventual prevention and clinical treatments. The volume has been organized in an exquisite way by Maximilian Muenke, Wolfram Kress, Hartmut Collmann and Benjamin Solomon. I express my gratitude to them for all the time they invested and the efforts they made in processing and refining all 19 chapters of this exciting book. The internationally renowned authors have contributed excellent manuscripts with astonishing illustrations. Their commitment has made the publication of this volume possible. The constant support of Thomas Karger with this ongoing and timely book series is highly appreciated.

Michael Schmid
Würzburg, November 2010
Preface

Craniosynostosis is a challenging and complex condition that has been recognized since the dawn of human history. Our understanding of the clinical manifestations of the disease process has advanced considerably in the last century, with molecular etiologies of many forms of syndromic craniosynostosis emerging in the last two decades. This increased knowledge has in turn enabled researchers and clinicians to probe normal and abnormal sutural biology from the atomic to the population-based level.

Just as important, and in parallel with the recent wave of basic biological understandings of craniosynostosis, advances in clinical diagnosis and treatment have been achieved, which include improvements in prenatal and postnatal imaging and craniofacial surgical techniques. These advances have been important for many reasons, and have allowed functional corrections and achievement of acceptable cosmesis in a broad range of patients.

Thus, given the growth of our knowledge base about craniosynostosis, the editors of this volume feel that the timing of publication comes at a very opportune moment. With the completion of the Human Genome Project and with the more recent availability of high-throughput investigative methods, we are now able to couple knowledge from previous accomplishments to newly emerging genomic technologies. We anticipate that through the critical mass of knowledge achieved to date, we can harness new tools of genome analysis in order to better understand craniosynostosis, both as relates to syndromic and nonsyndromic forms, as well as to normal cranial development more generally. This understanding is critical on many levels, but, most importantly perhaps, may be able to inform modalities of medical and surgical management to help improve the lives of affected patients and families.

We felt an international team of authors would be able to represent this difficult disorder in all its complexity; these are authors of diverse backgrounds, including clinicians and researchers whose careers are intimately involved in understanding the causes, effects, and treatments of craniosynostosis. Hence, this is a book intended for colleagues from a wide variety of disciplines. We hope this volume may prove useful whether a researcher is devoted to basic science at the bench or standing next to an operating table, and at every point in between.

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, their generosity, and their compassionate spirits.

Maximilian Muenke, Wolfram Kress, Hartmut Collmann, and Benjamin D. Solomon
Bethesda and Würzburg, August 2010
The Editors – Max Muenke, Ben Solomon, Hartmut Collmann, and Wolfram Kress – have produced an epic-making volume on craniosynostosis that is a tour de force. They have done a remarkable job of selecting and coordinating many highly respected authorities in the field to write 19 chapters covering a wide range of subjects. It is also remarkable that these four editors have, in addition, written or been coauthors of six excellent articles, so that each one of them is magister mundi of craniosynostosis.

The rate of discovery in the molecular advances in craniosynostosis is very exciting, but it is equally true for the remarkable advances in craniofacial biology, imaging studies, neurosurgical treatment, craniofacial surgical treatment, and therapeutics and it means clearly that the future is now! However, we all know that advances in these fields will continue to flower tomorrow!

Chapter 1 by Ben Solomon, Hartmut Collmann, Wolfram Kress, and Max Muenke provides a historical review of craniosynostosis. The authors take us on a tour of ancient times, later historical developments, the advent of modern classifications, and the evolution of the molecular causes of craniosynostosis, and management. In Chapter 2, Ulrich Müller discusses Boston-type craniosynostosis and its molecular mutation on MSX2 (p.Pro148His).

Some basic biological and molecular studies are grouped next. In Chapter 3 Douglas Benson and Lynne Opperman focus on the molecular regulation of calvarial bone growth by Ephrins, FGFs, and TGFβ. In Chapter 4, Jeanette Connerney and Douglas Spicer raise the question of how different signaling transduction pathways integrate with one another to regulate the formation and morphogenesis of craniofacial structures, which is only starting to be understood. In Chapter 5, Andrew Beenken and Moosa Mohammadi address the molecular mechanisms of FGFR activation in craniosynostosis and in some of the skeletal dysplasias, and discuss ligand-independent gain-of-function mutations, and also ligand-dependent gain-of-function mutations for those few disorders in the linker region between IgII and IgIII. In Chapter 6, Norman Arnheim and Peter Calabrese discuss recurrent germline mutations in FGFR2 and FGFR3, which are paternally derived and age-dependent. The process is driven by a selective advantage of spermatogonial cells, as demonstrated in Apert syndrome.

Several chapters deal with various syndromes. Each of these is remarkably extensive and very thorough, analyzing both clinical and molecular aspects of the disorders. I have dealt with Apert syndrome, Crouzon syndrome, and Pfeiffer syndrome in Chapter 7. Ben Solomon and Max Muenke have analyzed the condition named after Max, namely Muenke syndrome in Chapter 8. Wolfram Kress and Hartmut Collmann have Saethre-Chotzen syndrome as their subject in Chapter 9. Ilse Wieland writes about craniofrontonasal syndrome in Chapter 10.

In Chapter 11, Manu Raam and Max Muenke tackle a large group of uncommon syndromes.

In Chapter 12, Donna McDonald-McGinn, Elaine Zackai and their colleagues present two patients with trigonocephaly, one with postaxial polydactyly, the other with polysyndactyly. Both were shown to have GLI3 mutations.

Chapters 13–17 deal with general problems of various kinds. In Chapter 13, Maria Rita Passos-Bueno and her colleagues deal with the difficult problems of analyzing chromosomal alterations associated with craniosynostosis. In Chapter 14, Hartmut Collman and his colleagues review non-syndromic craniosynostoses. In Chapter 15, Ute Hehr discusses the molecular genetic testing of patients with craniosynostosis, and in Chapter 16, Thomas Schramm discusses prenatal ultrasonography, pointing out that there are no data on the validity of prenatal ultrasound screening for craniosynostosis, although to a certain degree, syndromic forms of craniosynostosis with craniofacial and limb involvement may allow ultrasonic differentiation between syndromes. Karen Gripp in Chapter 17 provides a wonderful clinical approach to craniosynostosis and distinguishes isolated synostosis from the more complicated search for the causes of the craniosynostosis associated with other anomalies together with their more complicated medical needs.

The final two chapters discuss surgical treatment in the craniosynostoses. In Chapter 18, Hartmut Collmann and his colleagues deal with imaging studies and neurosurgical treatment. They indicate that the diagnosis of craniosynostosis is primarily a matter of careful clinical examination with the use of imaging to verify the clinical diagnosis, to detect other possible sutures involved, to look for signs of intracranial hypertension, and to assess possible associated anomalies. The earlier craniectomy techniques used have now been partially replaced by plastic surgical techniques. Long term postoperative surveillance is mandatory. In Chapter 19, Hartmut Böhm and his colleagues discuss maxillofacial treatment. Procedures developed have included Le Fort III distraction, frontoorbitomaxillary advancement, monobloc frontofacial advancement, and orbital transposition.

Finally, let me say that all these highly respected authorities have written remarkably excellent chapters, which are so provocative that this volume will be read by many clinicians, many residents, many craniofacial biologists, many molecular geneticists, and many students. This will be the definitive volume on craniosynostosis for many years to come!

M. Michael Cohen Jr.
Halifax (Canada), July 2010