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Genetics of Human Infertility

Volume Editor

Peter H. Vogt Heidelberg

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Editorial

It is my great pleasure to introduce volume 21 of the book series *Monographs in Human Genetics*, entitled "Genetics of Human Infertility." The concept of this book emerged in the summer of 2014 during a telephone call with my colleague of many years, Peter Vogt, from the University of Heidelberg. From a demographic point of view, it appears that in endlessly and exponentially growing world populations that can account for hunger crises, diseases, epidemics, and even war conflicts between nations, any concerns about possibly overcoming infertility or subfertility factors in the human genome are unnecessary. However, it is a well-established fact that many individual couples who have faced a personal battle with involuntary childlessness have journeyed through an immense burden in the form of social, emotional, and psychological strain. Fortunately, the past decades have been witness to remarkable advances in human infertility treatments that include assisted reproductive technologies. In parallel, genetic aetiologies of female and male infertility have been unravelled by a variety of genetic disciplines and different techniques. These landmark discoveries call for a timely and thorough overview of this area with the assistance of expert investigators.

The present volume has been organized in an exquisite way. I am very thankful to Peter Vogt for all the time he invested and the efforts he made in processing the 11 chapters of this captivating book. In addition to 9 chapters on the genetic aspects of human infertility, 2 chapters focus on germ cell development in mice and primates. Internationally renowned authors have contributed superb articles that are well prepared and flawlessly illustrated. Finally, I am grateful to Karger Publishers for their enduring support of this book series.

Michael Schmid, Würzburg

Preface

The cover picture of this volume is the first drawing of a severe human sperm pathology, termed teratozoospermia. It was prepared 340 years ago in 1677 by Antoni van Leeuwenhoek, who is considered to be the world's first microbiologist. He gazed through a tiny lens set into a brass holder, looked into the sun, and by this simple construction achieved the magnification of nearly 300 times normal vision. This picture was never published in an original paper or book, but came to light through his correspondence with the Royal Society of England in London, which published these letters in their *Philosophical Transactions* (vol. 12, pp. 1040–1046). It remains unclear whether such human sperm dysmorphologies have some genetic origin despite their high incidence in human males with distinct infertility problems.

Today we know that human male and female infertility affects nearly 15–20% of all couples worldwide and that this condition presents with highly heterogeneous pathologies. Sometimes they are only visible in the germ line, but often they are also affecting the common health condition. Their aetiology often, but not always, includes genetic factors besides anatomical defects, immunological interference, and environmental aspects. Nearly 30% of infertility cases are probably due primarily to only genetic defects. Experimental animal knockout models mainly performed with mouse and *Drosophila* convincingly show that male or female infertility can be caused by single or multiple gene defects. However, translating these findings into the practice of an infertility clinic is challenging because human is not an experimental species. Genetic causes for human infertility therefore often remain unexplained – also called "idiopathic" – for the vast majority of male or female infertility patients. Nevertheless, a large number of human candidate genes have been identified by sophisticated molecular methods. However, since also many structural polymorphism and polymorphic sequence variants have been identified in the human genome in different populations, it remains a major challenge to select those gene and genome mutations causing infertility unless one has the chance to also analyse the patient's genetic family background.

At present, there are therefore only a handful of genetic defects that have been shown to cause, or to be strongly associated with, primary male or female infertility. This situation may change in the near future since sophisticated molecular diagnostic test systems are now also becoming available in the infertility clinic, including tools like CGH (comparative genomic hybridization) array analyses and genomic sequencing with NGS (next-generation sequencing) machines.

With this background in mind, I would like to thank all of the authors of this volume who have contributed to an actual comprehensive overview on what is known today about the ma-

jor genetic conditions causing male or female infertility in humans. All authors have focused their papers on finding answers to the basic question of how to translate their results into the clinical practice as soon as possible. The authors are also thanked for their willingness to incorporate some future insights into their chapters, including the presentation of diagnostic tools for the analysis of the epigenetic equipment required for fertility, and putative experimental systems for the imminent generation of male or female germ cells from pluripotent stem cells. I also highly appreciate the discussions concerning the heterogeneity of somatic pathologies, including infertility caused by distinct genetic defects due to chromosome aneuploidies like the Klinefelter syndrome (47,XXY) or single gene mutations in the *CFTR* and *AR* gene, respectively. Special thanks also go to my colleagues who critically compared the genetic and epigenetic control of male germ cell development in mice and primates with that in humans. A critical description of the putative functional and nonfunctional aspects of mutations in the azoospermia factor locus (AZF) located on the long arm of the human Y chromosome reveals the importance of chromosome studies and family studies in all sporadic cases of human infertility.

Peter H. Vogt
Heidelberg, March 2017