Atlas of Human Chromosome Heteromorphisms

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SPRINGER-SCIENCE+BUSINESS MEDIA, B.V.

Library of Congress Cataloging-in-Publication Data

Atlas of human chromosome heteromorphisms / editors, Herman E. Wyandt and Vijay S. Tonk.
p.; cm.
Includes index.
ISBN 978-90-481-6296-3 ISBN 978-94-017-0433-5 (eBook)
DOI 10.1007/978-94-017-0433-5

1. Human chromosomes – Atlases. 2. Chromosome polymorphism – Atlases. I. Wyandt, Herman Edwin, 1939– II. Tonk, Vijay S.
[DNLM: 1. Chromosomes, Human – Atlases.]

2003051681

ISBN 978-90-481-6296-3

Printed on acid-free paper

DEDICATION

We dedicate this work to our families, to Linda, to Sunita and Sahil, and to Sachi who will not be forgotten.

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Foreword

Critical to the accurate diagnosis of human illness is the need to distinguish clinical features that fall within the normal range from those that do not. That distinction is often challenging and not infrequently requires considerable experience at the bedside. It is not surprising that accurate cytogenetic diagnosis is also often a challenge, especially when chromosome study reveals morphologic findings that raise the question of normality.

Given the realization that modern human cytogenetics is just over five decades old, it is noteworthy that thorough documentation of normal chromosome variation has not yet been accomplished. One key diagnostic consequence of the inability to distinguish a "normal" variation in chromosome structure from a pathologic change is a missed or inaccurate diagnosis.

Clinical cytogeneticists have not, however, been idle. Rather, progressive biotechnological advances coupled with virtual completion of the human genome project have yielded increasingly better microscopic resolution of chromosome structure. Witness the progress from the early short condensed chromosomes to the later visualization of chromosomes through banding techniques, high-resolution analysis in prophase, and more recently to analysis by fluorescent in situ hybridization (FISH).

Pari passu with these advances has been the recognition of normal variation in chromosome morphology with each progressive step in microscopic resolution. Most recently, the advent of analysis by FISH aimed at determination of specific subtelomeric deletions revealed that about 5% of individuals with "idiopathic" mental retardation are accounted for by these submicroscopic telomeric rearrangements. An emerging salutary lesson is that some of the subtelomeric deletions have been observed in entirely normal subjects, and a number of benign familial variants have been documented. Moreover, we now know that demonstration of a subtelomeric deletion in an individual with unexplained mental retardation should nevertheless be followed by the same studies in both parents, before any diagnostic conclusion or phenotypic association is reached. Whether or not observed microdeletions in normal subjects reflect population variation or are not associated with a particular phenotype simply because of gene dosage effects (e.g., trisomy or monosomy) remain unknown. While telomeric imbalances that are not pathogenic have been described (including from 10q and 17p), a full appreciation, size assessment and categorization, is yet to be accomplished. Careful adherence to strict epidemiologic

principles applied to case ascertainment and selection will be necessary to determine definitive associations and delineation of normal variants.

Dr Wyandt and Dr Tonk, in recognizing the need to organize the established data on chromosomal variants, have gathered the important information for this valuable text. Every clinical cytogeneticist engaged in diagnostic or research studies will want to have this reference work in constant reach to assist in the critical distinction between a benign variant and a pathologic chromosomal rearrangement.

AUBREY MILUNSKY, MBBCh, DSc, FRCP, FACMG, DCH

Preface

Standards of care are rapidly changing in clinical cytogenetics. Today's research almost immediately becomes tomorrow's clinical test. What was once unsolvable becomes approachable with new technologies, almost before the overworked clinician or laboratory director may be aware they are available. This book does not provide a panacea for such problems, nor does it try to distinguish between chromosome variants that are clinically significant and those that are not. It does, however, provide the first comprehensive view of perhaps the most neglected regions of the human karyotype – namely, those regions that are the most variable and at the same time can be the most problematic. In almost every case, where striking variants are observed, parental studies are the first order of business, following which new technologies, if available, may be required. There are numerous examples in this volume where this approach has been and should be followed. This volume is intended for those who do cytogenetics daily, as well as for physicians and counselors who must attempt to understand and present sometimes ambiguous results to their patients. A predictable response of the physician, when confronted with a rare or unusual variant that has not been experienced by the cytogeneticist before, is "Well, what do I tell my patient now?"

In fact, this is a work in progress. Often there is not an easy answer to the question. Ultimately, if the specific question cannot be answered, the query becomes "Where is it reasonable to stop?" In prenatal cases, time and the resources at hand may be the constraints. In other cases it is the goal to answer the question as completely as possible to satisfy the need of the individual or family to know or plan what to expect. In such cases there may not be an immediate endpoint. However, there is always the obligation to present the facts and their limitations to the extent these are known. This is the normal process in genetics. The purpose of this volume is to summarize the known facts about regions of the human karyotype, which have not been summarized in one place before.

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Editors

Acknowledgements

This is a review of the work of many investigators spanning more than five decades of cytogenetic research. It is not possible to adequately represent the early efforts of investigators such as A. Craig-Holms, J.P Geraedts, P. Jacobs, H Lubs, W. H. MacKenzie, R.E. Magenis, A.V.N. Mikelsaar, H.J. Muller, S. Patil, P. Pearson, M. Shaw, and many others who perceived the need to study heteromorphisms in populations and who attempted to make order of a complicated topic. We have tried to be thorough in our review but, because of the great volume of literature that has accumulated over time, worldwide, we have inevitably made significant omissions. We regret these oversights and anticipate that our colleagues will inform us of the most serious ones. We also acknowledge the contributions to the literature on the topic by the late Ram S. Verma.

For specific examples of common and rare heteromorphisms, we are grateful for the individual contributions from colleagues around the world. These are acknowledged throughout the book and hopefully will encourage additional contributions of a similar nature in future editions. In this regard, we owe special thanks to Lauren Jenkins at Kaiser Permanente Medical Group (San Jose), who provided us with a significant number of examples of chromosome heteromorphisms without which we may never have started. We must also acknowledge the use of archived material from our laboratories. The cytogenetic technologists and technicians who helped in providing additional examples from these sources include: Xin Li Huang (supervisor), Alex Dow, Agen Pan, Zhen Kang, Xiao Wu, Xiuqi Li, Xiaoli Hou, Hong Shao and Yan Li in the Center for Human Genetics at Boston University, and Manju G. Jayawickrama, Caro E. Gibson, Ken L. Futrell, Eun Jung Lee and Amantia S. Kennedy in the Cytogenetics Laboratory at Texas Tech University. Sun Han Shim (cytogenetics fellow, CHG) also provided key examples of FISH variants. For the remainder, we would be remiss if we did not acknowledge the large amount of published material for which we obtained permission to reproduce in this volume.

This project would not have been completed without the support of our respective departments. In this regard, we are grateful to the following individuals in the Department of Pediatrics, Texas Tech University Health Sciences Center in Lubbock, TX: Richard M. Lampe, M.D., Chairman; Surendra K. Varma, M.D., Vice Chairman; John A. Berry, Administrator; Rebecca L. Timmons and Stephanie S. Stephens, Medical Secretaries; and Leandra Gomez, Coordinator. We are similarly grateful to the following individuals in the Center for Human Genetics, Boston University School of Medicine, Boston, MA: Marilyn McPhail,

Medical Secretary; Judy Heck, Administrator; Aubrey Milunsky, MB.B.Ch., D.Sc., Professor of Human Genetics, Pediatrics, Pathology and Obstetrics & Gynecology and Director of the Center for Human Genetics and Jeff Milunsky, M.D., Associate Professor of Pediatrics, Genetics and Genomics and Associate & Clinical Director of the Center for Human Genetics.

We also owe specials thanks for critical review of the manuscript to: David Morgan, M.D., Associate Professor of Pathology and Pediatrics, Texas Tech University; Shafiq A Khan, Ph.D., Associate Professor, Clinton C. MacDonald, Ph.D., Associate Professor and Simon C. Williams, Ph.D., Associate Professor, Department of Cell Biology and Biochemistry, Texas Tech University; and Golder Wilson, M.D, Professor of Pediatric Genetics, Texas Tech University.

We must also thank Peter Butler and staff at Kluwer Academic Publishers for taking a personal interest in this project and Phil Johnstone and staff at Lancaster Publishing Services Ltd. for remarkable compliance with our suggestions in nearly all aspects of the organization and printing of this volume. Any deficiencies or failings, therefore, are our own.

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Numbers in parentheses with a "c" prefix represent specific atlas contributions. Some variants that were submitted were not able to be included because of redundancy. Nevertheless, those individuals or institutions are listed, but are not followed by "c" number(s). In other instances, submissions were of published material so that appropriate citations have been made accordingly in the text, figure or plate where used, but have not been given "c" number(s). We encourage continued submission of variants, or useful data, which have not already been included in this volume, for possible inclusion in future editions.

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