Human Chromosome Variation: Heteromorphism and Polymorphism

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Springer

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ISBN 978-94-007-0895-2 e-ISBN 978-94-007-0896-9
DOI 10.1007/978-94-007-0896-9
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2011930400

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

Foreword

Clinical experience in virtually all fields of diagnostic medicine confirms the not infrequent enigma of distinguishing an observation of suspected pathology from normal variation. This inherent difficulty becomes even more pronounced by increasing the depth of diagnostic inquiry, exemplified by the stepwise progression from light microscopy, to electron microscopy, to high-resolution chromosome study and finally to molecular analysis. In all of these endeavors, accurate diagnosis followed by clinical decision-making depends on delineating normal variation from pathologic change.

For the clinical cytogeneticist to incorrectly certify a result as purely a heteromorphism may have critical consequences, including recurrence of mental retardation, a major congenital malformation, or the birth of another affected child. The obverse is, of course, also seriously problematic. Heteromorphisms depend upon the technique used such as the type of chromatin stain or molecular methodology. While the determination that a heteromorphic change is a normal variation and not clinically significant, other vitally important uses are well known. Use of heterochromatin blocks, satellite or repeat sequence regions, or inversions, have proved valuable in paternity evaluation, forensic investigation, following bone marrow transplantation, linkage analysis, genotyping, and for the diagnosis of uniparental disomy.

The advent of microarrays has brought even greater emphasis on the need to determine normal variation. Mental retardation and congenital malformations are frequently due to structural chromosomal rearrangements. Such rearrangements that are larger than 5–10 Mb in size are detectable by conventional cytogenetic examination. However, clinically significant smaller rearrangements may be detectable by FISH or where possible by genomic microarrays. The difficulty in determining whether a ~5 Mb rearrangement is present or significant, would lead to an array-based evaluation. However, CNVs confounding the effort to distinguish a polymorphism from a clinically significant rearrangement, can be equally challenging. While studies of CNVs are ongoing using platforms with increasing genomic coverage, current estimates indicate that a single individual has over 1,000 CNVs. Moreover, many and probably the vast number of the CNVs are inherited. The logistic and economic issue that flows from that realization is the need to analyze parental samples before concluding about clinical significance. Systematic checking

of parental samples has enabled the elucidation of dozens of newly recognized de novo microdeletion/duplication disorders, some of which are emerging as phenotypically recognizable syndromes. To what degree somatic or germ line mosaicism may complicate continuing studies, remains to be established. Moreover, unanimity has not always been reached for some observed changes. For example, pericentric inversion of the Y chromosome with breakpoints at p11.2 and q11.2 is not considered by some as a heteromorphism. An important limitation of microarrays is the inability to recognize balanced alterations (such as translocations and inversions) that influence risks of abnormality in future or present offspring.

Notwithstanding the demonstration of an inherited or novel CNV, the question of clinical importance may remain hard or impossible to answer, despite a careful assessment of genes within or proximate to the CNV. This consideration is made more difficult given that the CNVs have an important role in genetic susceptibility for many different genetic disorders.

The authors have thoroughly reviewed what is known about human heteromorphisms and presented a succinct and authoritative guide that will surely influence diagnostic cytogenetic reporting for years to come. It would be wise for every clinical cytogeneticist engaged in diagnostic or research studies to have this reference work at hand to assist in the critical distinction between a benign variant and a pathologic chromosomal rearrangement.

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Preface to Human Chromosome Variation: Heteromorphism and Polymorphism

In the Atlas of Human Chromosome Heteromorphisms, we emphasized the rapid change in standards of care in clinical cytogenetics—"that today's research almost immediately becomes tomorrow's clinical test. What was once unsolvable becomes approachable with new technologies, almost before the … clinician or laboratory director may be aware they are available." The Atlas did not provide a panacea for such problems, nor does the present volume. It did not distinguish between chromosome variants that are clinically significant and those that are not. The present volume, likewise, falls short of such an endeavor. In the Atlas, we spoke of the problematic nature of heteromorphic regions of the human karyotype, and of the necessity of performing parental studies whenever a striking variant was observed. This approach needs to be emphasized even more strongly for new technologies that are revealing ever more detailed knowledge of variable regions throughout the genome.

Standard methods of identifying most human chromosome abnormalities and variants (heteromorphisms) have been in use for more than four decades. The benign nature of heteromorphism of certain chromosomal regions was established in early population studies and information has not been much improved since. Although laboratories strive for longer chromosomes with higher band resolution, these advancements have not significantly added new variants or aided in interpretation of known variants detectable by standard light microscopy. Fluorescence *in situ* hybridization (FISH) in the 1990s allowed better characterization of some variants and revealed a few new variants that were not detectable by standard cytogenetic methods. Likewise, however, they do not necessarily improve on the distinction between variants that are clinically significant and those that are not.

Improved chip (array) technologies and movement toward large scale personalized DNA sequencing have resulted in the routine detection of large variable copy number DNA sequences (CNVs) that are widely dispersed throughout the human genome. Such DNA sequences (not detectable by standard microscopy) typically flank "hotspots" for duplications and deletions that are associated with genetic disease, many of which are now routinely tested for by high resolution array technology. Whether or not CNVs themselves can be disease causing remains uncertain and

may depend on their specific location, but they certainly can result in false-positive or false-negative test interpretations. Hence, a number of CNV data bases have been developed to record information about CNVs that over time will hopeful improve the interpretation of test results.

An additional class of chromosomal variant that was first observed and characterized in the early and mid 1970s, and in which there is now renewed interest, is that of the "common" and "rare" chromosomal fragile sites. Fragile sites on chromosomes have been observed to occur in specific bands, under a variety of *in vitro* conditions, including low folic acid, inhibition of folic acid metabolism, etc. With the exception of the fragile X site at band q27.3, associated with X-linked mental retardation, common fragile sites and most rare fragile sites have no direct clinical association. Common fragile sites can be induced in cultured cells from most people. Rare fragile sites (occurring in less than 5% of people) can also be enhanced in cell culture, some by different conditions than common fragile sites. It is well known that both common and rare fragile sites are sites that are frequently recurrent in chromosome rearrangement, and that there is a strong correlation for a significant number with breakpoints involved in cancer rearrangements. More recent molecular characterization has in fact revealed that several such sites are the co-locations of proto-oncogenes.

In contrast to the previous work entitled "Atlas of Human Chromosome Heteromorphism", the current volume has been titled, "Human Chromosome Variation: Heteromorphism and Polymorphism" to more accurately reflect normal chromosome variants at both the microscopic and submicroscopic levels. While we have retained much of the old "Atlas" as a pictorial representation of common and not so common heteromorphisms, we have eliminated chapters, as wells as material in some chapters that seemed less relevant, while hopefully retaining material that is more applicable. Topics previously treated in separate chapters are now condensed as headings under the general title, "Human Chromosome Methods and Nomenclature", comprising Part I. Part II is an updated pictorial section on chromosome heteromorphisms and FISH variants. At the same time, we have added two new sections (previously not covered in the Atlas): Part III is a review of the common and rare fragile sites, with photographs of many of the most common aphidicolin-induced sites; Part IV is a discussion of polymorphisms and copy number variations (CNVs) involving micro- and minisatellites, oligos and SNPs that cannot be detected except at the molecular level, with references to relevant websites for identifying CNVs.

Acknowledgments

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. Müller, S. Patil, P. Pearson, M. Shaw, and many others who perceived the need to study heteromorphisms in populations and who attempted to give order to 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 respective laboratories. The cytogenetic technologists and associates who helped provide additional examples from these sources include: Xin Li Huang, Alex Dow, Agen Pan, Zhen Kang, Xiao Wu, and Hong Shao in the Center for Human Genetics at Boston University, and Caro E. Gibson, Manju G. Jayawickrama, Eun Jung Lee, Jee Hong Kyhm, Eun-Hee Cho, Pam Nye and Chung-Hwan Yuk in the Cytogenetics Laboratory at Texas Tech University. Sun Han Shim (former post-doctoral fellow), in the Center for Human Genetics, also helped provide 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 help of our respective departments and support staff. 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. We are similarly grateful to the following individuals in the Center for Human Genetics, Boston University School of Medicine, Boston, MA: 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 owe specials thanks for critical review of the manuscript to: Golder Wilson, M.D, Professor of Pediatric Genetics at Texas Tech University Medical Center, and to Caro Gibson for screening of the manuscript for clerical errors.

We must also thank Peter Butler, Marlies Vlot, and staff at Springer Science+Business Media for taking a personal interest, both in the Atlas of Human Chromosome Heteromorphisms (Kluwer Academic Publishers) and in present version of Human Chromosome Variation: Heteromorphism and Polymorphism. We are also grateful to Max Haring, publishing editor at Springer SBM/Biomedicine for his help with the present volume.

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