Preface

Uncovering Recurrent Submicroscopic Rearrangements As a Cause of Disease

For five decades since Fred Sanger's *(1)* seminal discovery that proteins have a specific structure, since Linus Pauling's *(2)* discovery that hemoglobin from patients with sickle cell anemia is molecularly distinct, and since Watson and Crick's *(3)* elucidation of the chemical basis of heredity, the molecular basis of disease has been addressed in the context of how mutations affect the structure, function, or regulation of a gene or its protein product. Molecular medicine has functioned in the context of a genocentric world. During the last decade it became apparent, however, that many disease traits are best explained not by how the information content of a single gene is changed, but rather on the basis of genomic alterations. Furthermore, it has become abundantly clear that architectural features of the human genome can result in susceptibility to DNA rearrangements that cause disease traits. Such conditions have been referred to as genomic disorders *(4,5)*.

It remains to be determined to what extent genomic changes are responsible for disease traits, common traits (including behavioral traits), or perhaps sometimes represent benign polymorphic variation. The widespread structural variation of the human genome, alternatively referred to as large-copy number polymorphisms, large-scale copy number variations, or copy number variants has begun only recently to be appreciated *(6–9)*. High-resolution analysis of the human genome has enabled detection of genome changes heretofore not observed because of technology limitations. Whereas agarose gel electrophoresis enables detection of changes of the genome up to 25–30 kb in size, and cytogenetic banding techniques can resolve deletion rearrangements only greater than 2–5 Mb in size, alterations of the genome between more than 30 kb and less than 5 Mb defied detection until pulsed-field gel electrophoresis and fluorescence *in situ* hybridization became available to resolve changes in the human genome of such magnitude *(10–12)*. Those methods were limited to detection of specific genomic regions of interest and could not evaluate genomic rearrangements in a global way.

The availability of a "finished" human genome sequence *(13)* and genomic microarrays *(14)* have enabled approaches to resolve changes in the genome heretofore impossible to assess on a global genome scale (i.e., simultaneously examining the entire genome rather than discreet segments). Array comparative genome hybridization (aCGH) is one powerful approach to high-resolution analysis of the human genome. The CGH determines differences by comparisons to a reference "normal genome," whereas the array enables detection of such changes at essentially any resolution that is desired, limited only by imagination and cost. Furthermore, the application of bioinformatic analyses to the finished human genome sequence and comparative genomic analysis enable information technology approaches to identify key architectural features throughout the entire genome that are associated with known recurrent rearrangements causing genomic disorders.

An increasing number of human diseases are recognized to result from recurrent DNA rearrangements involving unstable genomic regions. A combination of high-resolution

genome analysis with informatics capabilities to examine individuals with well-characterized phenotypic traits is a powerful approach to address the question: To what extent are constitutional DNA rearrangements in the human genome responsible for human traits? Such approaches may also yield insights into recurrent somatic rearrangements *(15)*.

Genomic Disorders: The Genomic Basis of Disease attempts to survey the subject area of genomic disorders in the beginning of the postgenomic era. After a short historical presentation (Part I) describing the trials and tribulations involved in uncovering the recurrent submicroscopic duplication associated with Charcot-Marie-Tooth disease type 1A, the book is organized into parts on genome structure (II), genome evolution (III), genomic rearrangements and disease traits (IV), functional aspects of genome structure (V), and modeling and assays for genomic disorders (VI). Finally, Part VII includes appendices that delineate disease traits and genomic features (listed in tabular form) for well-characterized genomic disorders as well as clinical phenotypes for which chromosome microarray analysis may be used to detect the responsible rearrangement mutation. We believe that the topics chosen for individual chapters illustrate the genomic basis of disease.

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