

# Preface

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.” This statement has proven remarkably prophetic as microarray analysis and whole exome sequencing technologies have been co-opted for clinical genetic testing, the former now endorsed as a standard of care. The problems that justified survey of heteromorphic regions on chromosomes to help distinguish benign from clinically significant variation have now been extrapolated to high resolution DNA analyses. Just as the previous Atlases did not provide a panacea for such problems, neither does the present volume, but we do now add clinical genetic principles and case examples that help address the polymorphic versus pathogenic dilemma.

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 strove for longer chromosomes with higher band resolution, these advancements did not significantly add new variants or aid 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 did not necessarily improve on the distinction between variants that are clinically significant and those that are not.

Improved chip (array) technologies can detect copy number variants (CNVs) that are widely dispersed throughout the human genome and are not detectable by standard microscopy. CNVs are often produced by unequal crossing over at “hotspots” with flanking repetitive DNA sequences. These submicroscopic microdeletions and microduplications can be specified in exact numbers of

nucleotides since the human genome project has specified the nucleotide sequence for every chromosome (e. g., 1 to ~250 million for chromosome 1). Large scale personalized DNA sequencing defines another type of submicroscopic chromosome change in the form of single nucleotide substitutions, alterations of several nucleotides (like the 3-base pair deltaF508 mutation in cystic fibrosis), or complex repetitive DNA rearrangements like the expanding triplet repeats associated with the fragile site at Xq27. Deciding if these precisely specified CNVs or the single nucleotide changes detected by massive parallel (NextGen) sequencing are polymorphic (benign CNVs or SNPs) or pathogenic remains difficult, and we supplement clinical examples with conceptual criteria and database references to address this problem.

Another example of chromosome change now explained by DNA sequence difference are the “common” and “rare” chromosomal fragile sites, first observed in the 1970s and given renewed interest by clinical relevance. 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. Molecular characterization of the fragile Xq27.3 site associated with X-linked mental retardation provided a new mechanism for genetic disease (expanding DNA repeats), but most fragile sites have no direct clinical association. Common or rare (<5% of individuals) fragile sites can be induced in cultured cells from most people, and it is well known that they occur at sites frequently involved in chromosome rearrangement that arise in people or cancers. More recent molecular characterization has uncovered proto-oncogenes at several such fragile sites, and screening for haplo-insufficient tumor suppressor genes (by microarray) or germline oncogene mutations is an important thrust of modern genetic testing.

Just as the previous volumes changed the title from “Atlas of Human Chromosome Heteromorphism” to “Human Chromosome Variation: Heteromorphism and Polymorphism,” so has this volume morphed to Human Chromosome Variation: Heteromorphism, Polymorphism, and Pathogenesis to consider all levels of chromosomal DNA variation and to provide some examples of clinical correlation. We have retained intact as Part I the core of prior volumes: Pictorial representations of common and not so common heteromorphisms. Part II concerns the advances in molecular cytogenetics and DNA diagnosis, including review of the common and rare fragile sites and discussion of polymorphisms and copy number variations (CNVs) that cannot be detected except at the molecular level, the latter expanded from the previous volume. Part I covers variations seen by routine karyotype or direct analysis of cells and chromosomes by fluorescence in situ hybridization (FISH). Part II includes information on chip-based technologies, and (briefly, as a guide to the future) approaches to genome sequencing, as well as the clinical genetic approach, the latter because discrimination of benign from clinically significant variation is much easier when the genetic test is appropriate to the category of potential genetic disease. Case studies illustrate how the distinction between benign or pathogenic variant, the major objective of this work, is carried out in practice, increasingly challenging as the

resolution of genetic testing extends from chromosome band to the DNA segment and nucleotide level. A summary closes by emphasizing that clinical judgment in ordering and interpreting genetic tests is the fulcrum for balancing variation versus disease.

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