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Human Genetics: Conceptual and Practical Advances in the Post-Genome Era

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The pace of advances in the 21st century has made this a remarkable time for Human Genetics and Genomics, coinciding with the publication of the draft versions of the human genome in 2001 and publication of a more detailed version of the human genome in 2004. The rapid pace of technological advances in sequencing, the use of a variety of genomic tools, as well as progress in cell biology and biochemistry have led to a number of conceptual advances that have had practical applications. A number of these advances will be highlighted in this review issue. The conceptual advances include the identification of important new class of segmental duplication and deletion that lead to copy number variation, the importance of non-coding RNAs in disease and development, the genetics/genomics of gene expression changes and the role of common or rare variation in complex genetic diseases. These and other conceptual advances that include a greater understanding of pathways in gene function and the role of cell biology in providing a framework for understanding gene function in health and disease have led to important insights into single gene and complex disorders as well as the application of these insights to treatment of human genetic disease.

The first three chapters discuss our current insights into novel genetic mechanisms responsible for genetic variation and disease. The article by **Mefford and Eichler** examines the recently recognized importance of segmental duplications and deletions in the human genome. Some of Copy number variants are ubiquitous and wide-spread. Some variants are common and heritable, but some occur de novo. Common variants appear to be important for normal variation, but both types of variation have recently been recognized to play important roles in common genetic disease, especially neuropsychiatric disorders, as will be discussed below.

Micro-RNAs and other non-coding RNAs were discovered based on their important roles in the normal regulation of gene expression. More recently, these classes of RNAs were found play important roles in human diseases. **Wang and Olson** discuss the role of these micro-RNAs in endothelial cell function and angiogenesis, and have termed these angiomiRs. They discuss the general role of these angiomiRs in angiogenesis, including their targets, in vivo functions, and describe their potential as targets for therapeutics.

The HapMap project was based on the “common disease, common variant” model of genetic variation, which argues that genetic variations with appreciable frequency in the population at

large, but relatively low ‘penetrance’ (or the probability that a carrier of the relevant variants will express the disease), are the major contributors to genetic susceptibility to common diseases. The ‘common disease, rare variant’ hypothesis, on the other hand, argues that multiple rare DNA sequence variations, each with relatively high penetrance, are the major contributors to genetic susceptibility to common diseases. **Schork, Murray, Frazier and Topol** review these hypotheses from an historical and contemporary perspective. They feel that most, if not all, diseases are very likely to have components of both of these two extreme hypotheses, with both forms of variation making contributions to disease susceptibility at some level.

The next four articles describe recent insights into several single gene disorders and families of disorders. The primary cilium has recently been recognized as an important organelle for modulating subcellular signaling cascades during development and in the adult, possibly acting as a cellular antennae. **Lancaster and Gleeson** discuss this organelle, its role in signaling, and its role in disease. In particular, mutations affecting the primary cilium in both humans and animal models lead to a variety of phenotypes including retinal degeneration, kidney cysts, and brain malformations. This review underscores the importance of cell biology in providing a framework for the understanding of normal human development and human genetic disorders.

As we learn more about gene function and conserved genetic/developmental pathways, it is clear that using this pathway information provides another important framework for understanding normal human development and disease. **Tidyman and Rauen** discuss the Ras pathway and how the understanding of this important signal transduction pathway ties together a seemingly disparate group of human genetic disorders into a common pathway. They have termed this group of disorders “RASopathies.”

This chapter and the following two chapters show how the study of single gene disorders is revealing insights into more complex diseases. **Foster and colleagues** describe how the study of sleep is leading to novel insights into psychiatric disorders and neurodegenerative disease both of which are associated with disturbances in sleep patterns. The study of mutant mouse models has been particularly fruitful in revealing key genes associated with abnormal circadian rhythms and the physiology of sleep such as the link between sleep and neurotransmitter genes.

Orr and colleagues give an overview of how the 17 known genes which cause autosomal dominant spinocerebellar ataxias reveal a range of cellular processes involved in neurodegeneration of the spinocerebellum. Many of these pathways are interconnected and may be relevant not only to the understanding of cerebellar function, but also to the understanding of key aspects of neurodegenerative processes in general.

A bridge between single gene and complex genetic disorders is provided by the chapter on Parkinson's disease by **Hardy and colleagues**. They discuss that initial clues for multifactorial and more common forms of Parkinson' disease can come from those rarer families where the disease shows Mendelian inheritance. They give a critical overview of association studies have revealed candidate genes but where the evidence for involvement in disease pathology is weaker. The challenge in the future will be to determine whether it is possible to group these genes in relation to pathogenesis. Is there a Lewy body or mitochondrial group for example?

In the following chapter, **Owen and colleagues** report how the analysis of schizophrenia presents its own challenges because the phenotype is complex resulting from common alleles of small effect as well as rare alleles of large effect. There is a real need to analyse very large, well phenotyped patient samples. Many candidate genes have been reported but there are no replicated findings. More recently, compelling evidence has emerged that CNVs play a role in some cases. The rapid advances in genomics are finally bearing fruit in this clinically important disorder.

The autism spectrum disorders are another example of the types of challenges that a heterogeneous set of developmental disorders presents, but there has been some important recent progress. **Bill and Geschwind** review the autism spectrum disorders and describe the role that phenotypic classification and hypothesis based genetic studies are playing in sorting through the genetic complexities of this common but enigmatic disorder. Of note, the use of pathway-based approaches provides promise for this complex genetic disorder, much as it has for Mendelian disorders such as the RASopathies.

The chapter by **Weiss and colleagues** summarises how these various genetic association methodologies have been used to identify 43 new genes associated with asthma. There are more genes to be discovered but those already reported are providing valuable insights into the disease pathobiology. The challenge in the future, will be to consider epistatic interactions (gene-gene interactions).

In the final two reviews, the progress toward therapy of two disorders are considered. **Stone** describes how genetic studies have revealed dozens of genes that cause photoreceptor degeneration. These genes have provided valuable insights into the pathogenesis of retinal diseases and have accelerated the development of a variety of different types of therapy for these disorders. He argues that the remaining challenge is to use appropriate genetic testing to identify those individuals who will likely benefit from different types of therapy. This underscores the promise and remaining challenges that remain as we attempt to translate our greater understanding of human genetic and genomic disease to devise and apply treatments to those disorders.

This review issue ends with a chapter by **Arlett et al** on the neuromuscular disease where the potential for therapy has progressed very rapidly in recent years. There are a several approaches for a wide range of neuromuscular diseases which are providing paradigms for other disorders.

These last two chapters underscore that finally, the genetic studies of more than two decades are resulting in clinical trials for Mendelian genetic disorders based on knowledge of the genetic pathways. There is hope that in the future, as similar insights into the mechanisms of other Mendelian disorders and even complex genetic disorders are found, we will continue to see progress in the treatment of all types of human genetic diseases.

Biographies

Kay Davies studies the molecular basis of movement disorders. Her group has a particular interest in Duchenne muscular dystrophy and is currently developing approaches to an effective therapy for the disease. Her group also uses animal models to gain insights into motor neuron disease (SMA and ALS) and cerebellar ataxias.

Anthony Wynshaw-Boris studies the pathways and mechanisms important for normal human brain development and the pathogenesis of human neurogenetic diseases by studying mouse models of human genetic diseases such as neuronal migration defects and neural tube closure. His laboratory has used these models and insights into these disorders to study autism and other neuropsychiatric diseases in the human.