Chapter 17
Role of Genetics and Genomics in Clinical Trials in Osteoarthritis and Rheumatoid Arthritis

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Introduction

Identifying the genetic variants that contribute to the pathogenesis of common diseases and the variation in therapeutic response to drugs is an important goal of biomedical research. With completion of the Human Genome Project, researchers have open access to high-quality databases that contain extensive information on gene structure and on polymorphic variation within genes. Other developments such as the Haplotype Mapping Project provide powerful tools for rapid identification of informative variants in candidate genes without the need for extensive resequencing. These developments are likely to make a major impact on all common diseases but are particularly relevant to conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA), which have a strong genetic component. The application of genetics and genomics to clinical trials in arthritis has so far been limited, but this is certain to change in the future as our knowledge about the molecular-genetic basis of these conditions increases and new drugs are developed that target specific molecular pathways.

This chapter will review some basic principles relevant to the genetic dissection of complex traits; briefly review the role of genetic factors in the pathogenesis of OA and RA, and discuss the current status of genetics and pharmacogenetics as applied to these diseases with particular emphasis on the potential application to clinical trials.

Approaches to the Identification of Complex Disease Genes

The approaches that have been used to identify genes that predispose to common diseases are illustrated in Figure 17.1 and are discussed in detail below.
Fig. 17.1 The figure illustrates the four main approaches used in the identification of genes for complex diseases. See the text for more details of each approach.

**Linkage Analysis**

The classic approach used for gene identification is linkage analysis in families. This involves identifying a model of inheritance for the disease (e.g., autosomal dominant) and looking for evidence of segregation of the disease within a family according to that model, in relation to the inheritance of a panel of genetic markers. If specific genetic markers are inherited by individuals within a family who have the disease, but not by unaffected individuals, this provides evidence of linkage. Because the chromosomal location of genetic markers is known, successful linkage studies can localize susceptibility genes to a specific chromosomal region, allowing positional candidate genes to be screened for disease-causing mutations. The results of linkage analysis are reported in lodscore units. The lodscore is defined as the logarithm of the odds that the disease and the genetic marker are inherited together within a family (linked) compared with being inherited independently (unlinked). By convention, linkage is considered significant when the lodscore exceeds about +3.0, whereas linkage is considered suggestive when the lodscore exceeds +1.9. Conversely, linkage can be excluded by the finding of a lodscore below −2.0. Linkage studies are usually performed on a genome-wide basis, with a panel of 300 to