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Review

Recent findings on genes associated with inflammatory disease

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Abstract

Inflammatory diseases encompass a variety of medical conditions. In this chapter, autoimmune diseases and allergic disorders will be our focus. The autoimmune diseases include organ-specific autoimmunities, such as type I diabetes mellitus and autoimmune thyroiditis (AITD), and organ non-specific disorders such as systemic lupus erythematosus (SLE). All of them seem to share aspects of aberrant immunologic tolerance toward self-antigens. Asthma and atopic diathesis are among the allergies. Crohn disease and SLE are relatively rare with a prevalence of 10–50 per 100,000, and rheumatoid arthritis (RA), psoriasis, AITD and asthma are commoner with a prevalence of 500 per 100,000 or much higher. The difference among ethnic groups is not prominent for rheumatoid arthritis, psoriasis, AITD or asthma, but Crohn disease and SLE affect some ethnic populations more than others. Although all of these disorders have some environmental component, asthma and atopy seem most affected by environmental factors, as is suggested by the significant increase in their incidence over the last several decades with changes in various environmental factors, especially in developed countries. Over the last 10 years, multiple linkage studies revealed many disease-linked loci throughout the genome with various consistencies. As implicated by some pathophysiological studies of inflammatory immune system related disorders, certain loci are involved in multiple disorders. In the following sections, reports on the identification of disease-associated genes or markers will be summarized for individual diseases (cytotoxic T lymphocyte-associated 4 (CTLA4), CARD15, DLG5, SLC22A4/A5, programmed cell death 1 (PDCD1), RUNX1, SLC9A3R1/NAT9, PADI4, ADAM33, DPP10, PHF11 and GPRA), followed by a discussion of the genes that have been implicated in multiple disorders.

Keywords: Inflammatory disease; Autoimmune disease; Allergic disease; Case-control study; TDT

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Contents

1. Introduction

There are many medical disorders or phenotypes that have a genetic contribution. Of note, infectious diseases that had been believed to represent environmental factor-oriented disorders are now known to be influenced by genetic factors [1]. It would not be an exaggeration to say that almost all medical conditions are affected by genetic factors. Although any disorder with genetic components is a potential target of SNP-based genetic evaluation, current technologies for SNPs seem to be oriented toward investigations of so-called common disorders with multiple susceptibility genes. Therefore, this chapter will focus on recent progress in gene-identification research to identify disease-susceptible genes using multiple SNPs for autoimmune or allergic disorders and characterize their approaches and findings so that insight into the future direction of high-throughput genetics in the inflammatory diseases can be obtained. Since the strategy to evaluate genetic contribution of HLA locus is different from other regions due to the extreme variations in *HLA* genes, this topic will not be discussed much, although the majority of inflammatory disorders are linked to the HLA locus somehow and SNPs seem to be beneficial tools for understanding the complicated genetic factors in the region [2].

2. Identification of disease-associated genes or genetic markers

Here, reports on 12 genes will be introduced (Fig. 1). A report on cytotoxic T lymphocyte-associated 4 (CTLA4) in the 1990s was based on a candidate approach. The rest of the reports were based on the whole genome survey at its beginning. The majority of them identified susceptible gene(s) with or without functionally relevant variant(s) to a disease by positional cloning strategy. In those cases, a locus was identified by a whole genome linkage survey(s) using microsatellites, followed by detailed evaluations of the locus with an increased number of genetic markers, including tens to hundreds of SNPs. In this strategy, the locus of link-