Journal of Autoimmunity xxx (2015) 1–12

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

The genetics of human autoimmune disease: A perspective on progress in the field and future directions

Michael F. Seldin [a, b, *]

[a] Department of Biochemistry and Molecular Medicine, University of California, Davis, Tupper Hall Room 4453, Davis, CA 95616, USA
[b] Division of Rheumatology and Allergy, Department of Medicine, University of California, Davis, Tupper Hall Room 4453, Davis, CA 95616, USA

ARTICLE INFO

Article history:
Received 23 June 2015
Accepted 23 August 2015
Available online xxx

Keywords:
Genetics
Autoimmune diseases
HLA
Susceptibility loci
Functional variants
Immunoregulation

ABSTRACT

Progress in defining the genetics of autoimmune disease has been dramatically enhanced by large scale genetic studies. Genome-wide approaches, examining hundreds or for some diseases thousands of cases and controls, have been implemented using high throughput genotyping and appropriate algorithms to provide a wealth of data over the last decade. These studies have identified hundreds of non-HLA loci as well as further defining HLA variations that predispose to different autoimmune diseases. These studies to identify genetic risk loci are also complemented by progress in gene expression studies including definition of expression quantitative trait loci (eQTL), various alterations in chromatin structure including histone marks, DNase I sensitivity, repressed chromatin regions as well as transcript factor binding sites. Integration of this information can partially explain why particular variations can alter proclivity to autoimmune phenotypes. Despite our incomplete knowledge base with only partial definition of hereditary factors and possible functional connections, this progress has and will continue to facilitate a better understanding of critical pathways and critical changes in immunoregulation. Advances in defining and understanding functional variants potentially can lead to both novel therapeutics and personalized medicine in which therapeutic approaches are chosen based on particular molecular phenotypes and genomic alterations.

Contents

* Department of Biochemistry and Molecular Medicine, University of California, Davis, Tupper Hall Room 4453, Davis, CA 95616, USA
E-mail address: mfseldin@ucdavis.edu.

http://dx.doi.org/10.1016/j.jaut.2015.08.015
0896-8411/

1. Introduction

Our understanding of which genes predispose to different autoimmune diseases has expanded rapidly over the last decade. This progress has been mostly due to genome-wide association studies (GWAS) and the development of various technical and analytic tools. However, despite this progress less than half of the heritability of most autoimmune diseases can be explained and nearly half of this identified genetic risk is due to variations within HLA. The actual functional variants that underlie statistically significant associations are with some notable exceptions are still largely unknown. In the following perspective, I will review some of the more salient advances in the field, provide examples to illustrate specific points, indicate where knowledge is sparse, and discuss the potential for future advances that I believe could further define the pathogenesis and perhaps enable application to diagnoses and therapy. More detailed aspects of the genetics for a variety of autoimmune diseases is presented by experts in the field in other sections of this special issue of the journal. A general paradigm for GWAS and sequence variant studies is shown in Fig. 1 and discussed in subsequent sections.

1.1. Heritability

Epidemiological studies of most autoimmune diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), multiple sclerosis (MS), and primary biliary cirrhosis (PBC) show that there is strong heritability. These include studies showing increased concordance in monozygotic compared to dizygotic twin as well as studies showing increased risk to siblings of proband cases compared to the general population.

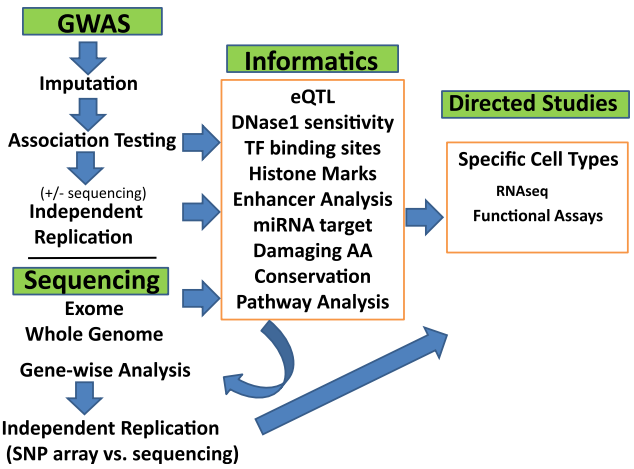

Fig. 1. Diagram of general scheme for genetic studies of complex autoimmune diseases. GWAS studies can greatly benefit from imputation and replication studies for loci suggested in the discovery phase. For some studies, replication is limited to those loci (genes) that are also part of pathways for genes previously identified as significantly associated with the disease. This is also proposed for sequencing studies to identify less common variants in which power issues may be partially addressed by limiting replication analyses based on prior pathway information.

Although most of these studies are not truly population based and may have biased results, there are some caveats worth noting. First, some autoimmune diseases have much higher sibling relative risk rates than other diseases (e.g. SLE [1,2], T1D [3], celiac disease [4], and PBC [5,6] compared to others e.g. RA [2], and MS [7]). Second, although concordance of disease is much higher in monozygotic compared with dizygotic twins for many autoimmune diseases, the overall monozygotic concordance of disease is usually substantially less than 50% [8]. This indicates that stochastic factors including environmental variables are a strong component and although genetics can be very useful in identifying important factors in etiopathogenesis it can only partially predict phenotype. Although some specific environmental factors have been identified (e.g. smoking and rheumatoid arthritis [9,10]) it is also possible that most of the incomplete concordance is simply chance or indefinable events.

1.2. General considerations for identifying genetic loci for autoimmune disease susceptibility

The major advance in identifying genetic loci that predispose to autoimmune diseases has been GWAS. Although some non-major histocompatibility (HLA in humans) loci were identified prior to GWAS using linkage or candidate gene studies, and other methodologies including admixture mapping have also enabled identification of a modicum of risk loci, the exponential increase in loci (over 200 for some autoimmune diseases) has been the direct result of GWAS. The basis of GWAS is the technology enabling efficient and accurate genotyping of single base polymorphisms (SNPs) and large collaborative studies such as HapMap [11,12] defining large numbers (hundreds of thousands) of SNPs in different populations. The success of GWAS is in large part due to practical advantage in conducting case/control design, namely the ability to recruit large numbers of cases and population controls as opposed to the difficulty in recruiting families: power for any association study is largely based on numbers. A critical aspect for these studies has been the ability to adequately control for population substructure differences using statistical methodology. Most commonly this is done by logistic regression using relevant principal components defined by principal component analyses or similar methods [13–15]. In some studies only continental population differences are accounted for, but for the most part type 2 errors (false positives) due to unrecognized stratification differences in case and control populations have been minimized. In fact, many studies have used publically available control genotypes rather than specific matched collections of controls. It is also worth noting that it may be possible to increase power (decrease Type 1 errors, false negatives) to ascertain risk variants by limiting studies to more homogenous populations and additional considerations of population substructure is discussed in subsequent sections (see sections 3.3 and 4). However, GWAS is largely applicable to those loci that fulfill the common variant (>0.05 minor allele frequency) common disease hypothesis since this methodology relies on linkage disequilibrium (LD) between the marker (SNP) detected and the actual disease causing variant(s). The commonly used genotyping platforms (Illumina and Affymetrix chip arrays) and

Please cite this article in press as: M.F. Seldin, The genetics of human autoimmune disease: A perspective on progress in the field and future directions, Journal of Autoimmunity (2015), http://dx.doi.org/10.1016/j.jaut.2015.08.015