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Recent Advances in the Genetics of Autoimmune Disease

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Abstract

Extraordinary technical advances in the field of human genetics over the past few years have catalyzed an explosion of new information about the genetics of human autoimmunity. In particular, the ability to scan the entire genome for common polymorphisms that associate with disease has led to the identification of numerous new risk genes involved in autoimmune phenotypes. Several themes are emerging. Autoimmune disorders have a complex genetic basis; multiple genes contribute to disease risk, each with generally modest effects independently. In addition, it is now clear that common genes underlie multiple autoimmune disorders. There is also heterogeneity among subphenotypes within a disease and across major racial groups. The current crop of genetic associations are only the start of a complete catalog of genetic factors for autoimmunity, and it remains unclear to what extent common variation versus multiple rare variants contribute to disease susceptibility. The current review focuses on recent discoveries within functionally related groups of genes that provide clues to novel pathways of pathogenesis for human autoimmunity.

Keywords

genome-wide association (GWA) study; interferon; NF-κB; autophagy; autoantigen

INTRODUCTION

Over the past several years, there has been an explosion of new information on genetic risk factors for human autoimmune diseases. This progress has resulted from a confluence of remarkable advances in human genetics generally, including the development of commercial genotyping platforms that allow for the production of hundreds of millions of genotypes in a rapid and cost-effective manner. In addition, along with the completion of the finished human genome sequence in 2003, a worldwide effort by the International HapMap Project (1) has provided us with a rich resource for understanding the nature and extent of human genetic diversity that is buttressed by the development of sophisticated statistical tools for analysis. Finally, there has been a renewed appreciation of the genetic complexity of many human diseases, and this has catalyzed collections of very large population data sets for study, thereby providing the required statistical power to find and confirm genetic associations that were previously undetectable. These trends in human genetics have had a major impact on the study of autoimmune diseases, and indeed, the new findings in autoimmunity are a gratifying demonstration that the rigorous application of modern genetic

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tools can lead to exciting new insights and hypotheses about disease pathogenesis, in spite of the extraordinary genetic complexity of these disorders.

Many of the recent genetic discoveries have resulted from the application of genome-wide association (GWA) scans, an approach that is generally geared toward the detection of relatively common genetic risk variants (2). It is important to realize that we are still in the relatively early stages of gene discovery, and even when a putative risk gene has been identified, in most cases the actual causative genetic variants have not been clearly defined. In addition, other forms of genetic variation are emerging as relevant for autoimmunity, including rare variants and copy number variation, and we are still far from understanding the role of epigenetic factors and somatic genetic changes. Therefore, to interpret the significance of present and future genetic findings, an understanding of the strengths and weaknesses of current genetic mapping approaches, as well as those on the horizon, is essential.

Why Map Genes for Human Autoimmunity?

The answer to this question may seem obvious, but it arises surprisingly often, especially in clinical settings. This is because many of the new genetic associations with autoimmunity are extremely modest, often with odds ratios in the range of 1.1–1.5. For the most part, there is no obvious clinical utility to this information, and the predictive value for future development of disease is low. Of course, this may change as knowledge becomes more complete, but currently only the rare autoimmune and inflammatory diseases have a strong genetic component with Mendelian patterns of inheritance. In these cases, knowledge of the underlying genetic defect can be crucial for proper diagnosis and treatment. The periodic fever disorders reviewed in this volume are a good example of this [see the review by Kastner and colleagues (3), in this volume]. However, for most autoimmune diseases this is not the case. Therefore, the most compelling reason for identifying the genetic underpinnings of common autoimmune disorders is to generate new hypotheses about disease mechanisms and pathogenesis. As discussed in this review, the first wave of results has generated a plentiful harvest.

Approaches to Identifying Disease Genes

To evaluate new genetic findings, it is useful to understand some of the conceptual and analytic issues in genetic mapping. Until very recently, three basic approaches have been used to identify genetic variants that may contribute to any human phenotype, including autoimmune disorders. These approaches are (*a*) candidate gene association studies, (*b*) linkage analysis in multiplex families, and (*c*) GWA studies. Candidate gene studies have been a mainstay for human genetic studies for several decades, and they will continue to play an important role. However, early candidate gene case-control studies often suffered from insufficient statistical power owing to inadequate sample sizes and to a lack of appreciation for the importance of careful matching of cases and controls. The strong publication bias for initial positive findings has been clearly documented (4), and reports of candidate gene associations should be viewed with caution until multiple replications have been carried out. Candidate gene studies are usually done to address a plausible hypothesis, but plausibility should not mitigate the requirement for robust and reproducible statistical evidence.

Genetic linkage analysis depends on the cosegregation of chromosomal regions with a phenotypic trait within families, as is typical for highly penetrant Mendelian disorders. For most common autoimmune diseases, familial aggregation is rather modest, and therefore linkage analysis has quite low statistical power to detect chromosomal regions with shared genetic risk within families. Nevertheless, linkage approaches have occasionally contributed

significantly to the identification of new risk genes, for example NOD2 (nucleotide binding and oligomerization domain 2) in Crohn's disease (CD) (5,6), and more recently STAT4 (signal transducer and activator of transcription 4) in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (7).

In the last two years, GWA scans have dominated efforts in gene mapping for autoimmune diseases, and these studies have led to the majority of the new genetic associations discussed in this review. Like candidate gene studies, the analysis is based on association, but in the case of GWA scanning, no particular hypothesis is being addressed. Rather, hundreds of thousands of hypotheses are being addressed simultaneously, without regard to biologic plausibility. This is a purely discovery-driven approach to gene identification, free of the limitations imposed by a priori assumptions about which genes and pathways are likely to be involved in the disease under study. Despite early skepticism, GWA scanning has proved to be a remarkably effective method of gene discovery.

Genome-Wide Association Scans: Design and Interpretation

The GWA scanning approach is critically dependent on knowledge of the extent and patterns of variation in the human genome. Although the initial sequence of the human genome was an important first step, it is really the International HapMap Project that has provided the basis for a rational approach to GWA studies (1). When considering single nucleotide polymorphisms (SNPs), any two unrelated individuals in the population differ by approximately 0.1% across the 3.2 billion base pairs of the genome, or approximately 3 million SNPs. By studying 90 individuals in families from three major racial groups (Caucasian, Asian, and African), the HapMap Project has cataloged the majority of the common SNPs (e.g., SNPs with minor allele frequencies of 5% or greater) in these populations. This has provided a library of millions of SNP markers for use in GWA scans (1).

An important result of the HapMap Project has been the realization that to define most of the common variations among individuals, it is not necessary to genotype all 3 million SNP differences among them, but only a subset of these, on the order of 300,000 to 500,000 SNPs. This is because SNP alleles are distributed non-randomly among individuals, forming blocks of linkage disequilibrium (LD) that may extend from thousands to many hundreds of thousands of base pairs. This results in a kind of bar code that can be used to define the common genetic variation across the genome of a given individual. An illustration of this pattern for the genetic region around the *PTPN22* gene is shown in Figure 1.

This pattern of common variation across genomes has led to the concept of tagging SNPs (8). This involves the use of a single SNP to tag a block of LD formed by many other SNPs, thus allowing for the interrogation of a large section of the genome with a single marker. SNP tagging may be applied in a pairwise fashion, or may also involve using several SNPs to predict the presence of a third. This ability to impute the likely presence of untyped SNPs is based on the information provided by the HapMap on the patterns of LD in the population under study. Although computationally intensive, this approach is applied across the entire genome to generate data on markers that have not been actually typed in the original study (9), which facilitates combining data generated on different typing platforms.

Of course, the extent of correlation among SNP alleles in LD is often less than complete, and therefore statistical methods must be applied. Two commonly used measures are a standard correlation coefficient (r2) and D′. D′ is a measure of LD among markers that is normalized to the maximum possible LD, given the allele frequencies, with a D′ = 1 reflecting maximally possible LD. The lower section of Figure 1 illustrates a typical representation of the extent of LD using the D′ measure across a large region around the

PTPN22 locus. Note that a large block of high LD encompasses several genes over a ~200,000 base pair region. Thus, many SNPs in this region are likely to provide evidence of association for diseases that are associated with *PTPN22*, and indeed, this was observed in a recent GWA screen (10) for marker rs6679677 (location shown on Figure 1). Conversely, any association observed with such a SNP may be due to causal variants in any of the genes in this LD block. In the case of *PTPN22*, there is additional functional and biologic evidence that this gene is involved in autoimmunity owing to the effects of a nonsynonymous SNP rs2476601 indicated in the Figure. However, without this additional evidence, it is nearly impossible to prove that *PTPN22* is the relevant risk gene in this region or that the rs2476601 marker used to first detect the association is causative.

Once a SNP association is observed and confirmed, much work remains to be done to establish which genetic variants in the region are actually responsible (e.g., causative) for the association. Furthermore, because many GWA studies employ 500,000 or more SNPs across the genome, each addressing a separate hypothesis, the statistical significance levels must be adjusted for multiple testing. An overall p value of $<5 \times 10^{-7}$ is now widely accepted as compelling evidence of true association, although it is quite clear that lower degrees of statistical significance often reflect real associations. In any case, truly convincing association always requires multiple replications in independent data sets.

A major consideration for GWA scans, as well as any case-control association study, is the issue of proper matching of cases and controls. The availability of genome-wide SNP data across many different populations has now permitted the use of so-called ancestry informative markers (AIMS) to match more precisely cases and controls for their ethnic background. This is quite straightforward for major racial groups, such as Asian, Caucasian, and African, but is more challenging within these groups (11). The pattern of allelic variation observed for the *PTPN22* risk allele in European Caucasian populations nicely illustrates this problem. As shown in Figure 2, the T1858C SNP displays a wide range of allele frequencies in the normal population, generally increasing in frequency going from southern to northern Europe. Therefore, if the cases and controls are taken from different European subpopulations, there is considerable risk of false positive (or negative) results. This phenomenon is generally referred to as population stratification. In the experience of many investigators, self-report by study participants is an unreliable indicator of ancestry, but in the context of GWA studies, it is possible to correct for unknown population stratification using the entire set of SNP markers. This is generally done using a principal components approach (12) or by measures of multidimensional geometric distance among groups of subjects based on allele frequency distributions across the genome (13). More recently, matching of European populations has also been done using selected AIMS (14). One of the advantages of this approach is that it allows for the use of publicly available control data sets in GWA studies, even when the details of ancestry are not known for these control subjects.

Finally, this brief discussion of GWA studies would be incomplete without some mention of statistical power and sample size requirements. Most of the associations with autoimmunity involve the detection of odds ratios between 1 and 2, with many associations on the lower end of this range. The sample sizes required to generate statistical significance in the setting of GWA scan ($p < 5 \times 10^{-7}$) can be very large, depending on the allele frequency in the population and the odds ratios to be detected. For risk ratios on the order of 2 or more, sample sizes of 1000 are generally adequate. However, for risk ratios in the range of 1.2–1.3, even sample sizes of three or four thousand may have low statistical power depending on marker allele frequency (2). This magnitude of a population sample is now considered a minimum for a thorough analysis in the setting of a GWA scan, and truly comprehensive genetic studies will require considerably larger sample sizes to be studied in the future.

GENETIC ASSOCIATIONS WITH AUTOIMMUNITY

We are currently in a period of rapid data accumulation on the variable and complex genetic underpinnings of human autoimmune diseases. Nevertheless, several themes are emerging from the first wave of results. First, some genetic variants clearly predispose to multiple autoimmune diseases, thus providing a gratifying confirmation that many of these diseases share common pathways of pathogenesis, despite their highly heterogeneous clinical manifestations. At the same time, the lack of such overlap for some diseases provides evidence that distinct mechanisms also exist. Second, multiple genes are involved in predisposition to each disease, and typically the genetic associations are quite modest. Third, with a few exceptions, the actual causative genetic variations that explain the associations have not been definitively established. Finally, even the partial data now available suggest that an extraordinarily wide range of different pathways and considerable genetic heterogeneity underlies autoimmunity—some expected, and some entirely unexpected—which offers a rich source of new hypotheses and experimental directions to pursue.

For the purposes of this review, we focus on the most convincing associations reported to date, and our discussion emphasizes the major themes and pathways that are emerging from the new data. Many associations likely to be real but that do not (yet) reach widely accepted levels of statistical significance have not been included because the complete delineation of these genes is a moving target, and in any case a truly comprehensive discussion is impractical given the potentially large number of genes involved.

Table 1 provides a list of leading genetic associations that are proven or highly likely to hold up after further study and that have also provided clues to the underlying mechanisms and pathogenesis of autoimmunity. Most of these findings have been generated from GWA scans, but many also were discovered using candidate gene approaches or linkage analysis. The genes listed in Table 1 are grouped according to their presumed major cellular functions, although it is fair to say that in all cases the exact mechanism by which these genes contribute to risk for autoimmunity is still unknown. The MHC associations with autoimmunity are not included in the Table but are discussed briefly in a separate section. Finally, the list of genes in Table 1 is clearly just the first wave of results that are going to emerge over the next few years. For example, as we were completing this review, convincing evidence for 30 genetic associations with CD was reported (15).

Intracellular Tyrosine Phosphatases

As listed in Table 1, a number of intracellular signaling molecules have been associated with autoimmune disorders. Perhaps the most replicated and broadly relevant of these associations is with the intracellular tyrosine phosphatase PTPN22. The initial association of *PTPN22* with type 1 diabetes (T1D) was reported by Bottini et al. (16), who took a candidate gene approach and focused on a nonsynonymous amino acid polymorphism (R620W) that was judged likely to have functional correlates. In an independent effort, Begovich et al. (17) selected PTPN22 as part of a limited genome-wide screen of likely functional variants in several thousand candidate genes, informed in part by previous linkage results. This led to the association of *PTPN22* with RA. Both associations have now been widely replicated, and the *PTPN22* associations with these and several other autoimmune diseases are among the most robust in the literature. For RA and T1D the PTPN22 620W allele confers a nearly two-fold risk for disease, with odds ratios in the range of 3–4 for homozygous individuals. Thus, in terms of strength of association, *PTPN22* is second in importance only to the MHC for these two diseases.

The patterns of association between the PTPN22 620W allele and autoimmunity are instructive on many levels. First, *PTPN22* was among the first and most convincing

demonstrations that common susceptibility genes underlie diverse autoimmune phenotypes. In addition to T1D and RA, *PTPN22* is associated with Graves' disease (GD) (18–20), Hashimoto thyroiditis (21), myasthenia gravis (22), systemic sclerosis (23), generalized vitiligo (24), Addison's disease (25), and alopecia areata (26). Associations with juvenile idiopathic arthritis (27–29) and SLE (30,31) have generally been weaker than for RA and T1D. Strikingly, there is no evidence of association with multiple sclerosis (MS) (32,33), and the 620W allele actually appears to be protective for CD (15). These contrasting patterns of association are likely to reflect fundamental similarities and differences in the mechanisms underlying the pathogenesis of these disorders. In general, it appears that an important feature of the PTPN22-associated diseases is that they all have a prominent component of humoral autoimmunity.

Knockout animals for *Lyp* (also known as *PEP*, the mouse ortholog of *PTPN22*) exhibit enhanced T cell activation in combination with an increased production of antibodies (34). This is consistent with the ability of PTPN22 to dephosphorylate Lck at the activating phosphotyrosine 394, leading to persistent phosphorylation and Lck activation in knockout animals. Yet somewhat surprisingly, the consequence of the 620W risk allele in humans is apparently a lower degree of T cell activation [an increased threshold for T cell receptor (TCR) signaling] (35,36). One clear biochemical consequence of the 620W polymorphism is to reduce the binding of PTPN22 with the intracellular kinase Csk (16,17). Indeed, amino acid position 620 of PTPN22 is located within one of several SH3 binding sites in the PTPN22 molecule. An important role of Csk is to inhibit Lck activity by phosphorylation of amino acid 505 of the Lck molecule (37). Whether this particular activity is affected by the 620W polymorphism in PTPN22 is unclear. Bottini and coworkers have proposed a model for interactions among Lck, PTPN22, and Csk that may explain the elevation of thresholds for TCR signaling (N. Bottini, personal communication), with the overall implication that reduced, rather than elevated, T cell triggering may be part of the phenotypic predisposition to autoimmunity. A similar tendency to increased thresholds for receptor triggering has also been reported in B cells (36). PTPN22 is widely expressed in many hematopoietic cell types, and several different substrates of PTPN22 have been described (37). However, the overall functions of PTPN22 in non-T cells are largely unknown. PTPN22 is also involved in the activation of endogenous cannabinoids (38). Thus, the exact mechanism for this genetic association is still unresolved, and indeed there could be multiple mechanisms. In this respect, the PTPN22 is an excellent example of how gene discovery is hypothesis generating, and the number of hypotheses can be quite large, even for a single genetic association in which the likely causative variant has been identified.

The disease-associated DNA sequence polymorphism (rs2476601, 1885C>T) resides in a rather large haplotype block encompassing the entire *PTPN22* gene as well as several flanking loci shown in Figure 1. As mentioned in the introduction, in the recent GWA studies reported by the Wellcome Trust, the *PTPN22* association was actually picked up by a marker that is outside of the *PTPN22* gene itself (10). Thus, as with all association studies, the question is whether the polymorphism used to identify the association is actually the causative variant. Resequencing of the *PTPN22* locus by Carlton et al. (39) showed that the 620W allele was the only variant that distinguished the risk haplotype from a second nonassociated haplotype. Modest evidence for associations with additional *PTPN22* haplotypes have not been replicated. The importance of the 620W allele is further supported by the fact that there is no association with *PTPN22* in the Asian populations, and indeed Asian populations rarely carry the 620W variant. Attempts to identify additional *PTPN22* variants that may associate with RA in Asian populations have not been successful (40,41). Thus, although the genetic data are not totally comprehensive across the entire risk haplotype, it is highly likely that the 620W allele is directly responsible for the associations with T1D, RA, and many other autoimmune diseases. But again, proof of causation depends

on combining such genetic evidence with biochemical function and integration of functional differences into a larger pathway of pathogenesis. This has certainly not been fully accomplished for *PTPN22* for any disease, but it is further along toward this goal than most of the other genetic associations discussed in this review.

A second intracellular tyrosine phosphatase, PTPN2, encoded on chromosome 18p11 has also been associated with human autoimmunity; convincing associations have been reported for CD (10,15) and T1D (42), with odds ratios in the range of 1.3. Weaker PTPN2 associations with other autoimmune phenotypes such as RA and GD (42) have not yet been confirmed. *PTPN2* is thought to be the relevant gene on chromosome 18p11 because it is the only known gene located in the associated region over 100 kb, but no clear causative variants have been identified. *PTPN2* is an appealing candidate gene. It is ubiquitously expressed and is clearly involved in immune function. *PTPN2*-knockout animals exhibit a fatal inflammatory wasting syndrome (43), with accompanying abnormalities in multiple cell types. PTPN2 appears to have a negative regulatory role on IL-2R signaling in T cells, consistent with the fact that Jak1 and Jak3 are among its substrates (44). In addition, $PTPN2^{-/-}$ animals have enhanced macrophage Jak1 phosphorylation in response to IFN-γ and increased sensitivity to LPS. Thus, it is reasonable to propose that *PTPN2* variants in humans may alter the thresholds for these, or other, signaling pathways (43).

Susceptibility Genes in Tumor Necrosis Factor Receptor and NF-κB Signaling Pathways

Recently, a number of genetic associations have emerged that implicate molecules in the tumor necrosis factor (TNF) family of molecules as well as NF-κB signaling pathways. Although it is still far from clear if these various observations are related to a common pathway of pathogenesis, we discuss them here together, in part to illustrate how the rapid accumulation of genetic data can generate new hypotheses for exploration.

In late 2007, Plenge et al. (45) reported the association of SNP markers near the *TNFAIP3* locus on chromosome 6q23 with RA. This association has been confirmed (46) and extended to SLE (47,48). The *TNFAIP3* gene encodes a cytoplasmic zinc finger protein known as A20 in the mouse, and A20 is a major negative regulator of TNF-induced NF-κB signaling pathways. Knockout animals for A20 die prematurely from widespread inflammation and cachexia and are hypersensitive to TNF (but not IL-1) with associated inability to downregulate NF-κB (49). The mechanisms by which A20 regulates NF-κB signaling are complex and incompletely defined. A20 possesses dual properties of ubiquitination and deubiquitination, and may act by regulating TNF receptor–associated factors (TRAF)2 and IKKγ, with more recent evidence of regulatory effects on receptor-interacting protein (50). Interestingly, A20 expression is generally low in most cells, but it is induced by NF-κB, consistent with a role in feedback regulation on NF-κB signaling. Several different polymorphisms have been associated with autoimmunity, including a nonsynonymous coding SNP (Phe127Cys) with some evidence of reduced negative regulatory ability for TNF-induced NF-κB signaling by the susceptibility allele (47).

A GWA screen for RA reported in late 2007 also revealed an association with a region on chromosome 9q that contains the *TRAF1* as well as the *C5* locus (51). This has been replicated, and although both *TRAF1* and *C5* are compelling candidate genes, the most recent data strongly suggest that *TRAF1* is likely to be the causative locus (52). TRAFs are a family of cytoplasmic adapter molecules that mediate signaling by a broad array of TNF receptor family members (53). TRAF1 is distinct from all other TRAF family members in that it lacks zinc finger and RING domains that are responsible for mediating downstream signaling directly. Thus, an important function of TRAF1 appears to be the regulation of receptor signaling mediated by other TRAFs. TRAF1 is of interest in the context of this discussion because it interacts with TRAF2 (a molecule regulated by A20) to regulate

signaling through CD40, a TNF receptor family member (TNFRSF5). Both negative and positive effects on CD40 signaling have been ascribed to TRAF1 (54,55), but a recent model proposes that TRAF1 cooperates with TRAF2 to regulate the efficiency of CD40 signaling in B cells, particularly through the NF-κB pathway (56,57). Recently, it has become apparent that CD40 is also an important costimulator in T cells, with predominant activation through NF-κB pathways, again with evidence of dependence on TRAFs for signaling (58). Unlike other TRAFs, the level of expression of TRAF1 is tightly regulated and increases on cell activation, including activation through CD40 (59).

Although A20 and TRAF1 are involved in a variety of signaling pathways, a renewed focus on their role in CD40 signaling is prompted by the fact that *CD40* itself has been associated with risk for autoimmunity. *CD40* associations were first reported in GD (60), and with few exceptions this finding has been replicated (61,62). A likely risk allele is located in a Kozak sequence (marker rs1883832), and there is evidence for an effect on expression levels of CD40 (63). The possibility that *CD40* may also associate with risk for SLE was raised by fine mapping studies on chromosome 20 (64), but even more compelling evidence comes from a recent large meta-analysis in RA, in which genome-wide levels of significance were achieved using a marker (rs4810485) that is a near perfect proxy for the rs1883832 risk allele associated with GD (65).

Finally, very recent data on a second North American GWA scan in RA (P.K. Gregersen & K. Siminovitch, unpublished data) have provided definitive evidence for an association with the NF-κB family molecule c-Rel. The relevant causative alleles have not been identified, but this association is potentially relevant to the current discussion because CD40 interacts with c-rel in several ways. First, *CD40* transcriptional regulation is influenced by c-rel (66,67). In addition, recent reports suggest that, the CD40 and c-Rel proteins can physically interact and form a heterodimer that is translocated to the nucleus and has transcriptional regulatory activity for known c-rel target genes, including *CD154*, *BLyS/BAFF*, and *Bfl-1/A1* (68). The fact that a membrane protein such as CD40 has a nuclear transcriptional function is surprising, but not entirely novel; similar functions have been reported for other cell surface receptors (67). These genetic data raise the possibility that the genetic associations of A20, TRAF1, CD40, and c-Rel may reflect the involvement of a common cell signaling pathway in autoimmunity (Figure 3). The costimulatory role of CD40 on the APC–T cell interaction has traditionally been viewed as one of its main functions, and indeed a wide range of cells can express CD40 and can be triggered by CD40 ligand expressed on activated T cells. For example, in the synovium of RA patients CD40 is expressed on $CD14^+$ synovial cells, and CD40-CD154 ligation leads to production of TNF-α and IL-1α and -β, thereby contributing to chronic inflammation (69). The CD40 association with GD has likewise been hypothesized to result from overactivity of CD40 on thyrocytes (63).

In contrast to this traditional view, recent studies have emphasized the importance of CD40 in the maintenance of effector T cell populations in autoimmunity. Beginning with early studies in the autoimmunity-prone nonobese diabetic mouse strain (70), evidence has accumulated that a T cell subset expressing low levels of CD4 but high levels of CD40 (designated Th40 cells) is responsible for driving T1D in experimental animals (71). Extending this hypothesis, Waid and coworkers (72) have shown that in the nonobese diabetic mouse the ratio of Treg/Th40 cells is shifted in favor of the autoaggressive Th40 cells. The Th40 cells have a higher resistance to Fas-induced cell death and in fact are protected against Fas-induced cell death if stimulated with CD40. This finding was recently supported by Vaitaitis & Wagner (73), who also showed that Th40 cells not only are protected against Fas-induced cell death but also have increased levels of the anti-apoptotic proteins $Bcl\text{-}X_L$ and $cFLIP_{43}$. Combined with the fact that CD40 costimulation increases

proliferation of Th40 cells, the up-regulation of these antiapoptotic factors might explain the expanded Th40 population in autoimmunity. The relevance of these findings to human autoimmunity is supported by findings that patients with T1D have dramatically increased frequency of $CD4^{lo}CD40^{+}$ T cells in peripheral blood compared with T2D patients or healthy controls (74), and these cells show evidence of reactivity with candidate autoantigens. Another study in humans has recently documented a polymorphism of CD40 that enhances CD40 signaling and is commonly found in subjects of Mexican and South American heritage (75). These ethnic groups are known to be at risk for increased severity of SLE. The relationship of this CD40 polymorphism to clinical outcome in lupus has not been adequately studied.

Clearly, these data mandate further experiments and, particularly, the need to integrate functional studies with the genetic data in humans. They also suggest that it will be fruitful to look at other genes that may be involved in the regulation of TNFR and NF-κB pathways, as well as other facets of immune regulation mediated by CD40.

B Cell–Associated Signaling Molecules

Despite the prominent abnormalities in autoantibody production, a direct role for primary B cell defects has been difficult to prove for the common human autoimmune diseases. This is largely because studies in humans must be conducted after disease has developed, and any B cell abnormalities observed may be secondary to the inflammatory environment accompanying active disease. Although biologic therapies directed at B cells can be effective in some autoimmune disorders such as RA (76) and MS (77), this does not prove a primary B cell defect. Therefore, it should be gratifying to B cell immunologists that genetic associations with B cell–specific genes are emerging from the current studies.

B cell scaffold protein with ankyrin repeats (BANK1) is an adapter protein that was originally identified in 2002 by Yokoyama et al. (78) These investigators also showed that BANK1 is tyrosine phosphorylated as a result of BCR signaling and appears to regulate calcium mobilization mediated by IP3R. More recently, BANK1 has been implicated in negative regulation of CD40 signaling in B cells. BANK1-knockout animals exhibit normal B cell development but have increased germinal center formation and enhanced responses to T cell–dependent antigens (79). Starting with a GWA study in the Swedish population, Marta Alarcon-Riquelme and colleagues (80) provided convincing evidence for an association of *BANK1* with SLE, including several nonsynonymous coding variants and polymorphisms potentially affecting mRNA splicing. However, at this early stage no definitive causative variants have been clearly identified, and so far BANK1 has not been implicated in any other autoimmune diseases.

A second B cell–specific gene, B lymphocyte kinase (*Blk*), has also been associated with risk for SLE (31). This molecule is a member of the src tyrosine kinase family, and little is known about its specific role in B cell biology. Knockout animals do not display any phenotype, which suggests a redundant function, at least in mice. Such redundancy is not necessarily consistent across species, as demonstrated by the fact that deficiency of another B cell tyrosine kinase, Btk, leads to dramatically different phenotypic severity in mice and humans. The genetic associations with Blk have been replicated in a second GWA study in SLE (30), and currently unpublished data suggest that an association with Blk is likely to be present in RA as well (P.K. Gregersen, unpublished data). Blk is one of two possible candidate genes in the region of association, the other being an open reading frame (C8orf13) of unknown function (31). However, the relevant genetic markers are associated with difference in levels of expression of both of these genes, where the risk haplotype confers lower levels of Blk expression (31).

The association of BANK1 and Blk with lupus and possibly other autoimmune disorders raises a number of different mechanistic possibilities. In the case of BANK1, it appears that genetic alterations may affect B-T interactions by virtue of changes in CD40 signaling thresholds. Interestingly, the BANK1 effects on CD40 signaling appear to be primarily mediated through Akt (79), rather than the NF-κB pathways discussed above in the context of TNFR family signaling pathways. In contrast, and consistent with the quantitative changes in expression conferred by the risk alleles, Blk may subtly alter threshold events during early B cell selection. After more genetic studies are carried out to confirm and refine the likely causative variants, the pursuit of these and other hypotheses is clearly in order and may finally permit the detection of intrinsic B cell functional phenotypes that confer risk for human autoimmunity.

Intracellular Pattern-Recognition Receptors

One of the first successes to come out of genetic mapping efforts in complex disease was the identification of *CARD15* (NOD2) as a risk gene for CD in 2001 (5,6). Following traditional linkage analysis indicating a risk gene on chromosome 16q12 (81), two groups took complementary approaches to gene identification, one pursuing traditional fine mapping (5) and the other focusing on *CARD15* as a compelling candidate gene in the region (6). The associations with *CARD15* are distinct from many of the other genes listed in Table 1 in that the *CARD15* risk alleles are relatively uncommon in the normal population (1–5%), and the risk ratios for CD in heterozygotes are in the range of 2–3, with much higher risk ratios (approaching 20) for homozygotes. The low frequency of these alleles suggests that these risk variants arose fairly recently in the European population, and not surprisingly, they are extremely rare in other major ethnic groups.

CARD15 functions as an intracellular receptor for bacterial-derived peptidoglycans and activates NF-κB pathways in response to these ligands (82). It is expressed in intestinal epithelial cells, as well as in endothelial cells, neutrophils, and monocyte-derived cells such as macrophages and dendritic cells (DCs). Thus, there are potentially both local intestinal and systemic effects of *CARD15* genetic variants. The CARD15 risk alleles involve nonsynonymous changes and frameshift mutations involving the leucine-rich repeat in the C-terminal end of the molecule, a region that is required for signaling responses to peptidoglycans (83). Disease-associated mutations alter the response to peptidoglycan stimulation in terms of cytokine production and gene expression patterns (84). However, despite such functional studies, it is not clear exactly what mechanism(s) explains the CARD15-mediated susceptibility to CD. *CARD15* alleles also appear to influence intestinal location of disease (82), and interestingly, there is also evidence that these alleles influence the severity of graft-versus-host disease in bone marrow transplantation (85). Furthermore, different mutations in the CARD domain of CARD15 are responsible for another inflammatory disorder, Blau syndrome, with a Mendelian dominant pattern of inheritance (86). Thus, similar to PTPN22, although the likely causative alleles in CARD15 have been identified, there is much work to be done to identify the mechanisms by which these alleles cause the various disease phenotypes (82).

Interferon-induced with helicase C domain protein (IFIH1) is another example of an intracellular pattern-recognition receptor that appears likely to associate with autoimmunity. This association was first identified in the context of a GWA study in T1D (87) and has been confirmed in this disease (10,42), with perhaps stronger contributions to risk for GD as well (88). Although there are several other genes in the region of association on chromosome 2q24, a nonsynonymous SNP in IFIH1 is likely to be a causative allele in the region. IFIH1 is one of two well-defined intracellular receptors (the other being RIG-1) for viral dsRNA, and these two intracellular receptors recognize distinct but overlapping forms of dsRNA. In addition, deficiency of IFIH1 or RIG-1 in vivo leads to susceptibility to infection by

different sets of viruses. Thus, on the one hand, this association is consistent with the proposed involvement of viral infection as an environmental risk factor for T1D. On the other hand, this hypothesis has not been advanced for GD, raising the possibility of additional influences of IFIH1 on the innate immune response.

Transcription Factors: Interferon Regulatory Factors 5 (IRF5) and Signal Transducer and Activator of Transcription 4 (STAT4)

The association of SLE with interferon regulatory factor 5 (IRF5) was first reported by Sigurdson et al. (89) in the context of a candidate gene study based on evidence that IFN pathways are involved in the pathogenesis of the disease (90). IRF5 is one of nine IRFs that participate in signaling through Toll-like receptors (TLRs) as well as intracellular pattern-recognition receptors such as RIG-1 and IFIH1 (91). IRF5 is required for induction of inflammatory responses upon triggering through TLR4, 7, and 9 (92). In the context of lupus, TLR7 and TLR9 are of particular interest because their ligands are composed of nucleic acids that are found in the (ribo)nucleoprotein autoantigens that are likely to be driving the disease.

The association of lupus with IRF5 has now been widely replicated and refined (30,31,93–95), with several causative alleles identified that regulate both splicing and levels of expression of the IRF5 gene (94). The IRF5 associations with lupus also hold up in populations of non-European ancestry (96,97). Complementing these genetic results, multiple studies have now shown that increased expression of type 1 IFN–regulated genes are characteristic of the lupus phenotype (98), driven at least in part by self-antigens triggering DCs or other antigen-presenting cells through TLR and Fc receptors (90,99,100). Furthermore, IFN-α levels are heritable (101), and the IRF5 risk haplotype is associated with high serum IFN activity (102). Thus, IRF5 is an example of a genetic discovery that has substantially accelerated progress in an area of disease investigation that was already ongoing, in particular providing support that IFN dysregulation is not simply a secondary abnormality caused by disease activity. Reports of IRF5 associations with other autoimmune diseases, such as ulcerative colitis (103) and perhaps RA in some populations (104), have raised the possibility that this gene may be a general risk factor for autoimmunity. However, these associations need further confirmation in additional populations.

Signal transducer and activator of transcription 4 (STAT4) was first shown to be associated with both RA and SLE by Remmers et al. (7). This finding was driven by prior data in RA showing evidence of linkage to a region on chromosome 2q (105). Gene identification was carried out using a positional fine mapping approach to the region. Interestingly, the GWA scans in RA have not pointed strongly to STAT4 as a risk gene, which undoubtedly relates to the very modest odds ratios for this association [odds ratio (OR) ~1.25]. In contrast, the odds ratios for STAT4 associations with lupus are considerably stronger, and thus STAT4 emerges as a prominent association signal in GWA scans in SLE (30,31). Intriguingly, STAT4 is particularly strongly associated with certain phenotypic subsets of SLE, especially the presence of high titer anti-dsDNA antibody and renal disease (106). The STAT4 associations with both RA and SLE are also observed in Asian populations (107,108), thus confirming STAT4 as an important common risk gene for these two diseases. STAT4 is also associated with Sjögren's syndrome (109); it seems likely that STAT4 is involved in other autoimmune disorders as well, although definitive studies have not yet been published.

Fine mapping and resequencing of the STAT4 risk haplotype continue to support the view that the causative alleles are likely to be located within the third intron of this gene (E.F. Remmers, unpublished data). The risk haplotype is common in the Caucasian populations, with a frequency of ~0.22, and this background population frequency is quite stable across

various European subpopulations. The intronic location of the associated SNPs is consistent with functional changes in either the splice patterns or levels of expression.

STAT4 is a member of a family of transcription factors of which there are six main members, each with distinct roles in cytokine receptor signaling (110). STAT4 is a key molecule for IL-12 signaling in T cells and NK cells, leading to the production of IFN-γ and differentiation of CD4 T cells into a Th1 phenotype (111). Upon IL-12R binding by IL-12, STAT4 is phosphorylated and forms homodimers. These homodimers are translocated to the nucleus, where they initiate transcription of STAT4 target genes, including IFN-γ (112). Thus, $STAT4^{-/-}$ mice do not respond to IL-12, lack Th1 responses, and have a predominantly Th2 immune response phenotype (113).

Relatively little is known about how the expression of STAT4 itself is regulated at the transcriptional level. STAT4 is expressed in resting $CD4^+$ T cells and NK cells and in Jurkat cells. STAT4 transcription is regulated in part by Ikaros, a zinc finger transcription factor involved in hematopoietic cell differentiation (114). In contrast, STAT4 is not highly expressed by monocytes or immature DCs but can be induced upon activation and maturation (115). In the case of DCs, NF-κB/Rel proteins upregulate STAT4 transcription during the differentiation into mature human DC in response to LPS, CD40 stimulation, or other activators (116). In this case, the induction of STAT4 transcription in these cells is dependent on the combination of TNF-α and IL-1β. The published work on STAT4 transcriptional regulation is focused on the promoter region 5′ to the gene (116), and there is no information concerning the potential role of intronic regions in the regulation of STAT4. Specifically, the SNPs that are associated with RA and SLE are over 50 kb distant from the 5′ promoter region and show no evidence of LD with SNPs in the promoter region. It is nevertheless intriguing that a recent study reports that a different level of expression of STAT4 in osteoblasts, but not in T cells, is correlated with the STAT4 risk haplotype (95). Thus, intronic variation in STAT4 may influence cell type–specific gene expression through mechanisms that are yet to be defined. Interestingly, Balb/c mice demonstrate significant differences in STAT4 expression from other strains (117), but this difference appears to be restricted to macrophages, again emphasizing the importance of examining the relevant cell type when attempting to correlate changes in expression with genotype.

Targeting STAT4 by inhibitory oligodeoxy-nucleotides or antisense oligonucleotides results in suppression of the disease in arthritis models (118), and STAT4-knockout mice are highly resistant to the induction of proteoglycan-induced arthritis. In RA patients, the high expression of STAT4 in DCs in the synovium disappears after treatment with disease-modifying antirheumatic drugs (119,120). These studies and the association of STAT4 with RA suggest that STAT4 might be a potential therapeutic target.

Several other transcription factors are emerging as important susceptibility genes for autoimmunity. The NKX2-3 is a member of a family of homeodomain containing transcription factors, with a confirmed association with CD (10,15). Mice lacking NKX2-3 are either asplenic or have reduced spleen size, along with a block in formation of Peyer's patches (121); NKX2-3 appears to regulate the differentiation of a fibroblast component of the splenic stromal architecture (122). The mechanism for the CD association is unknown. STAT3 is also associated with CD (15), which is consistent with the likely involvement of cytokine pathways such as IL-23 in this disease, as discussed below.

Cytokines and Cytokine Receptors

One of the first major associations to result from a GWA study of autoimmunity is the association of CD with IL-23 receptor (123). This association has now been confirmed (10,15) and extended to psoriasis (124) and ankylosing spondylitis (AS) (125). These three

disorders exhibit familial aggregation with one another, and thus a common genetic association among them is not unexpected.

The IL-23 receptor is composed of two subunits (p19 and p40), one of which, p40 (IL-12Rb1), is shared with the IL-12 receptor (composed of a p35 and p40 heterodimer). The IL-23 receptor–specific p19 subunit contains a nonsynonymous amino acid change, Arg381Gln, in which the Gln residue provides significant protection against CD. The functional significance of this change has not been elucidated, and it is likely that additional variants in the p19 molecule also contribute to disease risk, perhaps as a result of splicing or regulatory effects on p19 expression. Furthermore, *IL-12RB1* (p40) is located just 3′ to the *IL-23R* (p19) locus. Although there is no direct evidence for genetic associations with p40, regulatory influences on p40 may result from polymorphisms in the *IL-23R* (p19) gene. The additional association of both CD (15) and psoriasis (124,126) with the β subunit of the IL-12 cytokine itself (*IL-12B*) adds to evidence that the balance in activity of IL-23 and IL-12 cytokine pathways is an important component of disease pathogenesis in these disorders.

This genetic evidence for the importance of IL-12 and IL-23 pathways in CD is supported by experimental studies in animal disease models, as well as by recent data on the role of these cytokines in Th17 cell differentiation (127). Both IL-12 and IL-23 are upregulated in the disease, and biologic therapies that block IL-12/IL-23 pathways are emerging as effective therapies (128). In addition to inducing widespread inflammation and colitis (129), IL-23 injection into skin produces psoriatic-like lesions in experimental animals (130), and blockade of IL-12/IL-23 is also showing promise in the clinic as a treatment modality for psoriasis (131). Thus, the biology and genetics of IL-12 and IL-23 pathways are coming together in a way that is likely to alter profoundly the understanding of disease pathogenesis as well as the treatment of these disorders. However, much work needs to be done to fully understand the complexity of the genetic factors, and it remains to be seen whether the identification of genetic subgroups of disease will actually impact the selection of therapy and management of individual patients. It will also be of great interest to see how the genetic findings will improve understanding of AS, a disease whose pathogenesis has an intriguing but still obscure relationship to intestinal abnormalities (132).

A role for IL-2 and IL-2R in susceptibility to autoimmunity has also been reported, although in general the evidence is less clear than for IL-12 and IL-23 pathways. A region on chromosome 4q27 has been unequivocally associated with Celiac disease (133), and there is evidence that this association extends to other autoimmune disorders including T1D (10,42,134), GD (42), and RA (10,134). Associations with psoriasis have also been suggested (135). However, this region contains four genes in strong LD: *KIAA1109-Tenr-IL-2-IL-21*. The first two of these genes have no known relationship to immune function, although both IL-2 and IL-21 are clearly of interest, especially because *IL-2* is a risk gene for T1D in the nonobese diabetic mouse (136). Despite resequencing efforts at the *IL-2* and *IL-21* locus, no obviously functional variants have been identified (42). Additional support for a role for IL-2 comes from the fact that allelic variation in the genetic region encoding the IL-2 receptor is also clearly associated with T1D (10,137,138), again with some evidence for association with GD (139), RA (10), and MS (140,141). Resequencing efforts have failed to identify clearly the causative variants in the *IL-2RA* gene (138), despite being guided by information on the regulatory regions that control the expression of this gene (142). However, risk haplotypes have been correlated with circulating levels of soluble IL-2R (138). Given the obvious functional importance for IL-2 in the growth and differentiation of T cells (142), including regulatory T cells (143,144), it seems likely that IL-2 and/or IL-2R receptor polymorphisms will ultimately be shown to have a direct causative role in disease susceptibility for multiple autoimmune disorders.

Finally, recent genetic studies in MS have focused attention on the gene encoding the IL-7 receptor as a new risk locus for this disease (140,145). A functional SNP that influences splicing and expression has been identified (145), although this finding has not yet been translated into a clear causal relationship to disease pathogenesis. IL-7 appears to play a complex role in T cell development and peripheral T cell homeostasis (146). Interestingly, some evidence for an association of IL-7R with T1D has also been reported (42).

Costimulatory Molecules and Other Cell Surface Receptors

The cytotoxic T lymphocyte antigen 4 (CTLA4) associations with T1D and autoimmune thyroid disease provided one of the first convincing demonstrations that genetic variation in costimulatory molecules is involved in disease susceptibility (147). These associations with T1D have been confirmed in recent GWA scans (10), and a role for CTLA4 in human autoimmunity is widely accepted (148). As with many other associations, the strength of these associations is modest, ranging from OR ~1.15 in T1D to OR ~1.5 in GD. Although the exact mechanisms and causative alleles remain to be proven, these genetic advances have been accompanied by the development of biological therapies targeting CTLA4, and their efficacy provides further confirmation of the importance of this pathway. Other cell surface molecules with negative regulatory effects on T cells, such as PDCD1, have also been associated with autoimmunity, in particular SLE (149). However, the strength and reproducibility of these findings across different populations is still being defined.

One of the more intriguing and robust associations to emerge from the recent GWA scans in SLE is with integrin α_M (ITGAM or CD11b) (30,31). ITGAM has also been the focus of extensive candidate gene analyses, driven by the results of previous linkage studies (150). Thus, like STAT4 and CARD15, this demonstrates that linkage information can lead to gene identification even in a genetically complex disease. It is highly likely that the major causative allele in ITGAM is a nonsynonymous amino acid change in the extracellular portion of the molecule. ITGAM encodes the α chain of the $\alpha_M\beta_2$ integrin known variously as Mac1, CR3, or CD11b/CD18. This molecule binds a range of different ligands including ICAM1 and ICAM2, certain complement components (C3bi), fibrinogen, and GPIbα (150). It is unclear which of these functions explains the associations with lupus, although changes in neutrophil expression of ITGAM (151) have been described, and abnormalities of immune complex clearance are characteristic of the disease. Indeed, Fc receptor polymorphisms have long been associated with SLE (152,153), and genetic evidence for involvement of other genes in this family have recently been reported (154). These new genetic findings will surely catalyze a renewed effort to understand the details of these pathways in SLE (155).

Genes Involved in Autophagy

One of the more unexpected findings to emerge from the recent GWA scans has been the identification of genes that function in autophagy as risk factors for CD—an example of how genetic findings can catalyze new perspectives on disease pathogenesis. Autophagy is a phylogenetically ancient mechanism by which the cell can degrade and dispose of intracellular constituents in a regulated manner, and also provides a way of disposing of intracellular infectious agents without destroying the cell itself (156). Two genes in the autophagy pathway, *ATG16L1* (157,158) and *IRGM* (10,159), have been associated with CD. In the case of *ATG16L1*, a potentially causative nonsynonymous variant (A197T) has been associated with disease, and an upstream insertion deletion polymorphism in *IRGM* that is associated with disease has recently been shown to affect expression (160). It was further shown that expression levels of IRGM have an influence on the efficiency of antibacterial autophagy (160). Because the host response to intestinal bacteria is important for the pathogenesis of CD, a role for autophagy in this process is clearly a leading

hypothesis to explain these genetic associations. However, autophagy may also play a role in other aspects of the immune response, particularly with regard to the antigen presentation (161), including within thymic epithelium, where high levels of autophagy have been observed (162).

Genes with Novel Enzymatic Functions

Two novel associations of genes with enzymatic functions have emerged from recent genetic data. One of these, *PADI4*, is a member of a family of peptidyl arginine deiminases encoded on chromosome 1p35–36 (163). The function of these enzymes is the conversion of arginine residues to citrulline in mature proteins, and such posttranslational modification appears to be important for a variety of structural molecules, such as keratin, histones, and myelin basic protein. Citrullination also accompanies inflammation, and in the case of RA, local citrullination of fibrin and other proteins is observed in the inflamed synovium (164). Over the past decade, it has become apparent that antibodies to citrullinated peptides are quite specific to RA, and therefore the discovery in 2003 of an association between PADI4 and RA emphasized the importance of citrullinated antigens in this disease (165), and also contributed to the current view that anticitrulline antibodies define a distinct subset of RA. Interestingly, the associations with RA of PADI4 have only been convincingly replicated in Asian populations (166), and the causative alleles have not been defined. Although there are hints of association in non-Asian populations, a role for PADI4 in disease risk in Caucasians has been difficult to demonstrate (167). This difficulty may relate to population differences in environmental exposures, such as smoking, that are risk factors for the development of anticitrulline antibodies (168). Thus, the PADI4 associations with RA offer an opportunity to explore gene-environment interactions in the setting of an autoimmune disease.

A second enzyme of interest is the aminopeptidase regulator of TNFR1 shedding 1 (ARTS1). As implied by the name, ARTS1 has a role in the cleavage of cell surface receptors for proinflammatory cytokines including IL-1R2 and IL-6Ra, as well as TNFR1. Genetic alterations that affect cell surface receptor shedding are clearly important for susceptibility to inflammatory disease, as demonstrated by the TNF receptor–associated periodic syndrome (TRAPS) (169), a Mendelian disorder associated with defects in receptor shedding [see review by Masters et al. (3), this volume]. Thus, defects in ARTS1 cleavage functions could have proinflammatory effects. Interestingly, ARTS1 is also active in the endoplasmic reticulum and is involved in trimming peptides for MHC class I presentation. Given the strong associations of AS with HLA-B27, this is another potential explanation for the involvement of ARTS1 in risk for AS.

Autoantigens as Susceptibility Genes

The discovery over a decade ago that regulatory polymorphisms in the insulin gene are associated with T1D (170,171) has fostered the view that alterations in tolerance for specific autoantigens may underlie susceptibility to autoimmune disease. In the case of T1D, this is further supported by the demonstration of insulin-specific T cells in the pancreas of affected individuals (172), and by the fact that autoantigens under the control of the *Aire* gene are presented to developing thymocytes during thymic selection (173,174). Furthermore, there is considerable variation of thymic expression of potential tissue autoantigens among individuals (175), obviously raising the possibility of genetic regulation of these phenotypes. This has led to the exploration of autoantigens as candidate genes for genetic association. Other than insulin, the only compelling genetic support for this hypothesis in humans is the association of the TSH receptor (TSHR) with GD (125,176,177). Interestingly, even comprehensive genome-wide SNP screens may miss such associations for technical reasons, as was the case for insulin in the Wellcome Trust study (10). Thus, it seems likely that further examples of risk alleles in autoantigens will emerge in the future.

The Major Histocompatibility Complex

The MHC is the predominant genetic region of importance for many autoimmune disorders; a basic unresolved issue is still the precise role of the various associated HLA alleles in disease pathogenesis. However, the recent availability of dense SNP marker sets that span the MHC has also revealed evidence that loci in addition to the well-established HLA class II associations are relevant in several autoimmune diseases. For example, in a recent detailed analysis in T1D, risk is conferred by the HLA-B locus (178), in addition to the known class II risk alleles. By performing analyses that condition upon the known risk alleles, similar evidence of genetic complexity has emerged for other disorders such as RA (179,180), MS (181), and myasthenia gravis (182). Because of the extensive LD of some common autoimmune risk haplotypes, such as A1-B8-DR3, it will be challenging to fully dissect these issues using a purely genetic approach. Deep resequencing will likely be required, along with functional studies on newly defined candidate polymorphisms. Thus, the current data suggest that the MHC still contains valuable genetic insights that have yet to be fully mined.

Copy Number Variation and Rare Genetic Variants: The Next Frontier

This review has focused on the recent genetic associations of autoimmunity with common genetic variants, generally SNPs. However, it is now apparent that variation in copy number of genes or DNA sequences is an extremely common form of genetic difference among individuals in the population (183,184). Some of these have been associated with autoimmunity (154), but we are still in the early stages of establishing the overall extent of this variability. In addition, it is now clear that copy number change can arise de novo (185), and this may explain the sporadic appearance of complex disorders such as autism (186) and schizophrenia (187,188). The extent to which this type of somatic genetic change contributes to autoimmunity is unknown, but it is striking that even twins commonly exhibit copy number differences between them (189). Could this contribute to the relatively high rate of discordance for autoimmunity among monozygotic twin pairs?

Finally, the contribution of multiple rare variants to autoimmune phenotypes must be considered. A compelling recent example involves the association of multiple rare alleles in TREX1 with lupus (190). TREX1 is a DNA exonuclease that was originally implicated in a Mendelian disorder, Aicardi-Goutieres syndrome (AGS1), that is accompanied by some clinical manifestations reminiscent of lupus (191). Multiple rare variants in TREX1 are associated with sporadic lupus, several with distinct functional consequences for cellular localization of this enzyme (190). Beyond the fascinating biology of this finding, TREX1 is a beautiful example of how multiple rare alleles in unexpected places can contribute to autoimmunity. It is highly likely that more such associations will be discovered as the technology for resequencing large sections of the genome becomes more financially accessible.

CONCLUSION

In this review, we have attempted to give a broad overview of the fast moving field of human genetics as it applies to the problem of human autoimmunity. It is virtually certain that by the time of publication numerous additional risk genes will be identified and that some genetic associations that we have chosen to pass over in discussion will be revealed as critically important. For example, we have not discussed various genes of unknown function, some of which have compelling associations with disease (192). However, we think it unlikely that any of the genes discussed here will be shown to be false positives. Thus, although the details will change, it should be quite obvious that the recent outpouring of genetic data is producing a rich harvest of new avenues for investigation.

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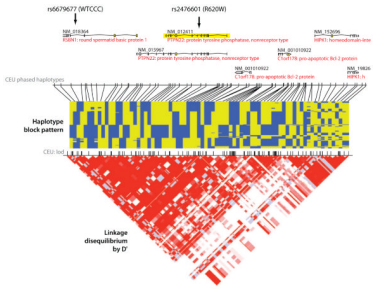

Figure 1.

A map of the region around the *PTPN22* locus on chromosome 1p13 covering approximately 200,000 base pairs. The genes in the region are shown at the top of the figure. The blue and yellow haplotype block pattern was generated by looking at combinations of single nucleotide polymorphisms (SNP) alleles in 90 Caucasian subjects from the HapMap Project. Note that a limited number of patterns are observed, generating a kind of bar code for each subject. The lower portion of the figure shows a heat map in which the intensity of red color reflects the degree of correlation [linkage disequilibrium (LD) measured by D′] among SNPs across the region (indicated by *tick marks*). Note that widely separated SNPs are highly correlated. Two markers associated with type 1 diabetes (and other autoimmune diseases) are shown at the top. Marker rs2476601 is likely to be the causative variant in this region. Note that another marker (rs6679677) nearly a distance of 100 kb also strongly associates with diabetes. This emphasizes that it is difficult to assign the causative locus on the basis of associations alone, as discussed in the text.

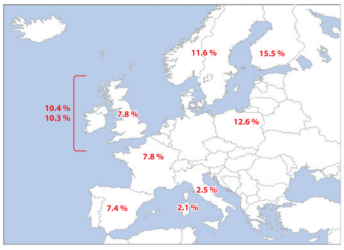

Figure 2.
The allele frequencies of the *PTPN22* risk allele (T) across Europe. Note that there is a gradient of increasing frequency of this allele moving from southern to northern geographic regions. This gradient emphasizes the importance of carefully matching case and control subjects for association studies, even within European populations.

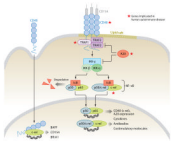

Figure 3.
Genes associated with autoimmunity regulate the CD40/NF-κB signaling pathway. The CD40/NF-κB pathway regulates numerous immune-related functions, such as T and B cell proliferation and activation. After association with its ligand, CD40 trimerizes and translocates to lipid rafts, where it interacts with intracellular mediators, including TNF receptor–associated factors (TRAF)1 and 2, which mediate activation of the I κB kinase (IKK) complex. Through phosphorylation, IKK targets the I κB molecule for destruction, which releases NF-κB to translocate into the nucleus and bind to promoter regions of target genes. The NF-κB pathway is regulated by the inhibitor A20 (encoded by *TNFAIP3*) and by TRAF1, both found to be associated with autoimmune disorders. Interestingly, CD40 has also been detected in the nucleus of B cells, where it interacts with c-rel and initiates transcription of target genes. Both CD40 and c-rel are recently discovered candidate genes for rheumatoid arthritis (RA) (see text).

Table 1

Genetic loci with confirmed associations with human autoimmune disorders

Gene	Location	Function	Diseases[a]	Selected references
Intracellular signaling molecules and receptors				
PTPN22	1p13.3	TCR and BCR signaling and other?	RA, SLE, AITD, T1D	16,17,21,167,193,194
BANK1	4q22	B cell activation/BCR signaling	SLE	80
TNFAIP3	6q23	Ubiquitin editing enzyme; inhibitor of TNFR signaling/NF-κB pathway	RA, SLE, CD	45_48
BLK	8p23	B cell activation	SLE	31
PTPN2	8p11.3	Negative regulator of T cell activation	CD, T1D	10,15
TRAF1	9q33	Regulates TNFR signaling/NF-κB pathway	RA	51,195
Intracellular pattern-recognition receptors				
IFIH1	2q24	Receptor for viral dsRNA	T1D, GD	10,42,87,88
NOD2/CARD15	16q12	Intracellular receptor for bacteria, signals via NF-κB	CD	5,6
Transcription factors				
REL	2p13	Member of NF-κB	RA	P.K. Gregersen & K. Siminovitch, unpublished data
STAT4	2q32.2	Regulates IFN-γ pathway	RA, SLE	7,108
IRF5	7q32	Regulates type 1 IFN pathway	SLE	89,93
NKX2-3	10q24.2	Regulates development of intestinal and secondary lymphoid organs and B and T cell homing	CD	10,15,159
Cytokines and cytokine receptors				
IL2/Il21	4q26	T cell regulation	T1D, RA, Celiac disease	133,134
IL23R	1p31.1	Th17 homeostasis	PSA, PSO, CD, AS	10,15,123_125
IL7RA	5p13	Memory T cell homeostasis	MS	140,141,145
IL2RA	10p15.1	T cell/Treg homeostasis	MS, T1D, GD	137_141,196
IL12B	15q31.1	Development of T cell subsets, Th1 and Th17	PSO, CD	15,124,135
Membrane receptors and costimulatory molecules				
CTLA4	2q33	T cell costimulation inhibitory	T1D, RA	10,147,167
ITGAM	16p11.2	Immune complex clearance/leukocyte adhesion	SLE	30,31,150
CD40	20q12	B/T cell costimulation	RA	65
		Production of IgM, TNF-α, IL-2 via NF-κB pathway		
Autophagy related				
ATG16L1	2q37.1	Autophagy	CD	15,157,158
IRGM	5q33.1	Autophagy	CD	10,15,159,197
Enzymes				

Gene	Location	Function	Diseases[a]	Selected references
ARTS1	5q15	Peptide trimming for MHC I	AS	125
PADI4	1p36.13	Enzymatic peptide citrullination	RA	165,167
Autoantigens				
INS	11p15.5	Target autoantigen	T1D	170,171
TSHR	14q31	Target autoantigen	AITD	125,176,177

[a] Abbreviations: AITD, autoimmune thyroid disease; AS, ankylosing spondylitis; CD, Crohn's disease; GD, Graves' disease; MS, multiple sclerosis; PSA, psoriatic arthritis; PSO; psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes.