Published in final edited form as:

Curr Opin Immunol. 2012 October ; 24(5): 538–543. doi:10.1016/j.coi.2012.09.003.

GWAS implicates a role for quantitative immune traits and threshold effects in risk for human autoimmune disorders

Peter K. Gregersen¹, Betty Diamond², and Robert M. Plenge³

¹Robert S. Boas Center for Genomics and Human Genetics, The Feinstein Institute for Medical Research, North Shore-LIJ Health System, Manhasset, New York 1101

²Center for Autoimmune and Musculoskeletal Disorders, The Feinstein Institute for Medical Research, North Shore-LIJ Health System, Manhasset, New York 1101

³Division of Rheumatology Allergy and Immunology, Division of Genetics, Brigham and Women's Hospital, Boston Massachusetts and Broad Institute, MIT and Harvard, Cambridge, Massachusetts

Abstract

Genome wide association studies in human autoimmune disorders has provided a long list of alleles with rather modest degrees of risk. A large fraction of these associations are likely due to either quantitative differences in gene expression or amino acid changes that regulate quantitative aspects of the immune response. While functional studies are still lacking for most of these associations, we present examples of autoimmune disease risk alleles that influence quantitative changes in lymphocyte activation, cytokine signaling and dendritic cell function. The analysis of immune quantitative traits associated with autoimmune loci is clearly going to be an important component of understanding the pathogenesis of autoimmunity. This will require both new and more efficient ways of characterizing the normal immune system, as well as large population resources with which genotype-phenotype correlations can be convincingly demonstrated. Future development of new therapies will depend on understanding the mechanistic underpinnings of immune regulation by these new risk loci.

One of the first reports based on a genome wide association study (GWAS) utilized only 96 cases and identified the association of the *CFH* gene with macular degeneration[1]. At the time, it served as encouraging evidence that the GWAS approach could lead to the identification of relatively common alleles with a strong effect on risk for a common disease, although in this case prior linkage studies had suggested that such strong genetic effects might exist for this disorder. The reality for most common diseases has proven to be far more complex, requiring many thousands, or even tens of thousands of cases and controls to identify common alleles associated with disease. The complexity and low effect

Correspondence to: Peter K. Gregersen MD, The Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, New York, 11030, peterg@nshs.edu, Telephone: 516-562-1542.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

sizes of these associations have led to criticism of the GWAS approach[2], and has certainly highlighted the need to understand the function of these genetic variants.

For autoimmune disorders, there is now a complex menu of hundreds of risk loci with modest or quite weak effects on disease risk. Nevertheless, the study of these risk alleles is in fact beginning to yield a more subtle approach to understanding the underlying biology of autoimmune disorders in humans. This has led to an emphasis on the role of quantitative effects on the immune response and potential role for threshold and staged events in moving from a normal immune system to one that is engaged in mediating full blown clinical autoimmune disease[3]. In this context, one of the major benefits of identifying risk alleles is that it permits the study of immunologic traits in individuals who are clinically normal, but who may exhibit quantitative changes in immune responses that are directly relevant to disease pathogenesis. Fortunately, for immune related diseases, many of the cells engaged in disease pathogenesis are circulating in the blood, and this has permitted investigations in human populations.

In this brief review we will highlight progress on human studies in this area as it relates to understanding the pathogenesis of human autoimmunity.

Simple model of autoimmunity: autoantigen presentation and thresholds of immune activation in the adaptive immune system

Given the diversity of autoantigens that have been identified, many models of autoimmunity understandably emphasize role of autoantigen presentation in the context of a class I or class II MHC molecule to T cells and B cells, as shown in Figure 1. Much of disease specificity (whether a person develops rheumatoid arthritis [RA] or type 1 diabetes) is likely to be determined by this combination of factors. For example, if the autoantigen is gliadin presented in a DQ2 class II MHC molecule, then a patient may be predisposed to develop celiac disease, whereas if the autoantigen is a citrullinated peptide presented in a DR4 class II molecule, then there is a predisposition to RA.

However, the immune response to a presented autoantigen will be influenced by many additional factors, including the developmental timing and underlying thresholds of the various signaling pathways involved in the response, many of which are genetically regulated. A very general overview of the potential threshold effects on B cell and T cell reactivity is summarized in Table. 1. In the case of immune responses in the T cell arm of the adaptive immune system, at least three areas of influence can be identified:

1. early development (central tolerance) – In the thymus, antigens are presented to T cell clones with specific T cell receptors (TCR). If there is a “strong” immune response, then T cell clones are deemed to be autoreactive and undergo negative selection. Genetic predisposition to a high threshold of T cell activation (i.e., less TCR signaling) will lead to less selection against autoreactive clones, thereby predisposing to clinical autoimmunity.
2. activation/apoptosis (peripheral tolerance) – When naïve T cells are exposed to antigen later in life, they respond by a similar mechanism of antigen-MHC-TCR

signaling events. Here, genetic predisposition to a low threshold of T cell activation (i.e., stronger TCR signaling) may lead to an over-exuberant immune response. Alternatively, high thresholds for T cell activation might also predispose to autoimmunity via a reduction of regulatory T cell responses, or a relative deficiency of apoptosis in responding effector cells.

3. polarization – After antigen exposure, a naïve T cell differentiates into a memory T cell of a specific subset (e.g., Th1, Th2, Th17). Polarization into one or another subset is dependent upon the balance of cytokines and transcription factors. Genetic factors may influence the threshold to develop into one subset or another, thereby influencing the relative proportion of memory T cell subsets and predisposing to clinical autoimmune disease.

As discussed below, similar threshold effects are likely to be operating in the regulation of the innate immune response.

Thresholds for TCR and BCR signaling in autoimmunity

The original *PTPN22* associations with type 1 diabetes[4] and rheumatoid arthritis[5], now expanded to many other autoimmune diseases, have emphasized the importance of signaling thresholds in disease predisposition, and, at the same time have demonstrated how difficult it is to conclusively determine how these threshold effects cause disease risk. *PTPN22* encodes an intracellular tyrosine phosphatase that dephosphorylates activating tyrosines on src kinases such as Lck, as well as other molecules involved in TCR signaling such as Zap70 [6]. As expected, knockout of the murine homolog of *PTPN22* results in hyperactivity of T cells[7]. In humans, the disease associated *PTPN22* results in an R to W change at codon 620, a substitution which disrupts the binding of *PTPN22* to its binding partner, the intracellular tyrosine kinase, Csk[5]. However, the consequence of this for T cell activation thresholds remains controversial. Early studies of human carriers of the *PTPN22* risk allele suggested functions consistent with effectively increased phosphatase activity[8], with concomitant reductions in TCR and BCR signaling strength[9]. More recent studies have supported the view that the 620W allele functions analogously to a knockout, with loss of function leading to hyper-responsiveness[10,11]. Beyond the immediate biochemical effects on signaling, a recent report suggests that lack of *PTPN22* results in changes in T cell populations in mice, particularly an expansion of T reg cells[12]. It will be of interest to see whether the human *PTPN22* risk allele 620W has effects on the cell numbers and TCR signaling responses in the Treg population.

B cell receptor signaling also appears to be affected by *PTPN22* alleles, again with somewhat contradictory conclusions in the literature[11,13]. Beyond this however, data from the Meffre lab has suggested that *PTPN22* may have an effect on the diversity and autoreactivity of the human B cell repertoire, presumably as a result of early selection events[14]. This finding could be consistent with relatively low responsiveness (high thresholds for BCR signaling) conferred by the 620W allele in developing B cells, with a relative lack of negative selection. In this context, different lymphocyte populations could have different sensitivities to the regulatory effects of *PTPN22*, and this may explain some of the conflicting data in the literature.

The PTPN22 R620W amino acid change clearly influences binding to the intracellular kinase Csk, and Csk itself has recently emerged as a risk gene for various autoimmune disorders including Celiac Disease[15], Scleroderma[16] and Systemic Lupus Erythematosus [17]. The SLE risk haplotype for *Csk* is associated with increased expression of Csk, particularly in transitional and naïve B cells; we have now shown that this results in a relative reduction in BCR signaling strength, mediated in part through changes in the phosphorylation state of Lyn, a target of Csk, as well as alterations in the distribution of early and late transitional B cells[17]. Thus, both PTPN22 and Csk may exert their effect on disease risk through effects on the developing B cell receptor repertoire. Interestingly, an analysis by Raychaudhuri suggested that early transitional and naïve B cell subsets express genes that are preferentially enriched in the group of SLE associated genes by GWAS[18]. In this context, we have recently reported on patterns of expression and allelic regulation of *Blk* (B lymphocyte kinase), a gene which has been associated with both SLE and RA. Although published studies in B cell lines have emphasized the cis-regulation of *Blk* by the autoimmune disease associated haplotypes, we have shown that the cis-regulatory effects on *Blk* expression in native B cells are largely restricted to transitional B cells[19].

Together these data suggest that groups of genes that influence receptor signaling thresholds, including *PTPN22*, *Csk* and *Blk*, may provide risk for autoimmunity either by influencing the selection of an autoimmune repertoire, or the relative abundance of regulatory cell subsets. However, all of these molecules are expressed to some degree in multiple cell types. Both *Csk* and *PTPN22* are widely expressed, and indeed *PTPN22* is most highly expressed in NK cells as well as in a variety of myeloid cells[5]. The functional consequences of allelic variation in these cells clearly need to be investigated. It is likely that no single mechanism will explain the genetic associations for every autoimmune disease.

Quantitative traits in cytokine pathways

Cytokines, their receptors and signaling components are clearly important for regulating a wide variety of immunological activities, and it is therefore not surprising that many of the genetic regions implicated by GWAS contain genes in these pathways. However, relatively few studies in humans have directly demonstrated an effect of disease associated polymorphisms on cytokine function. It is often challenging to identify the exact causative variant(s) that explain a genetic association, especially if such changes are regulatory in nature. But once a risk haplotype is defined, it can be helpful to carry out exploratory genotype-phenotype studies to identify relevant functional effects. A good example of this approach was taken for the *IL2RA* locus, which confers risk for type 1 diabetes[20]. In this study a variety of quantitative traits were explored in normal subjects who carried the risk haplotype, leading to the identification of an extremely robust positive relationship between CD25 levels (CD25 is the protein product of the *IL2RA* gene) on the surface of CD4+ memory T cells and the protective *IL2RA* haplotype. Interestingly, these relationships were not observed on Treg cells, and were in fact reversed in naïve CD4+ T cells[20]. This emphasizes the importance of focusing on the right cell type in order to discover the quantitative trait that is most functionally relevant to disease risk. In this case, the data imply a relative lack of IL2 signaling as being a risk factor for type 1 diabetes, perhaps through alterations in Treg cells. However, the precise functional connection between expression of

IL2RA and immune function is unclear, and thus the exact role in disease susceptibility remains to be clarified.

IL23R provides another example of a quantitative signaling trait that is associated with autoimmunity. *IL23R* was first defined as a risk factor for inflammatory bowel disease in 2006[21]. An amino acid change R381Q located between the transmembrane domain and a putative Jak2 binding site was identified as the likely causative allele. The uncommon 381Q allele has been confirmed to be protective for Crohn's disease[22] and ulcerative colitis[23] as well as ankylosing spondylitis[24] and psoriasis. This polymorphism has now been shown to confer reduced surface expression of IL23R on in vitro T cell lines derived from normal donors, along with a dramatic reduction of signaling by IL23 using phosphorylation of STAT3, STAT1 and STAT5 as a measure of response in these cells[25]. These quantitative changes may be particularly important for regulating Th17 cell effector function[26].

Finally, the regulation of type 1 interferon is clearly altered in systemic lupus and related diseases, and there is substantial evidence that an element of genetic regulation underlies this abnormality[27]. A high interferon state is a quantitative trait that exhibits familial aggregation[28], and this phenotype is independent of autoantibodies that are known to stimulate interferon production through TLR pathways. Of course, familial aggregation could still reflect unknown environmental factors, but the absence of the trait in spouses argues for a genetic basis. *IRF5* and *STAT4* polymorphisms are both associated with SLE, and the *IRF5* risk haplotype is associated with high interferon production[29]; *STAT4* polymorphisms have also been reported to enhance the cellular response to type 1 interferon[30]. Numerous other genes in signaling pathways related to interferon are also associated with SLE and this is consistent with the hypothesis that a "feed forward" mechanism leads to high levels of interferon in SLE that are in part genetically determined[31]. These data, along with the increased prevalence of lupus like phenotypes in patients receiving interferon treatment for unrelated disorders[32] argue for a direct role in disease causation. On the other hand, interferon may have anti-inflammatory effects in some situations[33]. While the exact role of interferon in the pathogenesis of SLE remains to be clarified, it seems clear that genetically regulated quantitative differences in interferon signaling pathways are involved.

Immune regulation by dendritic cells

Highlighted by the 2011 Nobel Prize, dendritic cells have taken center stage as potent initiators of immune responses as well as mediating immune tolerance, both central and peripheral[34]. Many of the peripheral tolerance mechanisms appear to depend on Treg cells as well as the production of TGF β . A deficiency of TGF β signaling in DC leads to experimental autoimmune colitis. DC specific knockout of genes associated with human autoimmunity on GWAS, such as *Blimp1* and *TNFAIP3*, leads to autoimmune phenotypes in experimental animals. This includes disease mimics of inflammatory bowel disease and ankylosing spondylitis in the case of dendritic cell deficiency of TNFAIP3[35], while dendritic cell specific knockout of *Blimp1* leads to the presence of humoral autoimmunity with a lupus like serology[36]. Interestingly, the recent analysis of Raychaudhuri points to

genes specifically expressed in dendritic cells as being especially enriched in the GWAS results for Crohn's Disease, and to a lesser degree in the list of genes implicated in SLE[18]. Human GWAS studies have implicated *Blimp1* in risk for both inflammatory bowel disease[22,23] as well as lupus, while *TNFAIP3* has been primarily associated with SLE and rheumatoid arthritis[37].

We have recently investigated the phenotypic consequences of the disease associated *Blimp1* alleles on dendritic cell function in human subjects (unpublished data; S-J Kim, manuscript submitted). These studies were carried out on normal individuals who differed with respect to *Blimp1* genotype, with a focus on dendritic cell phenotypes. Subjects carrying the SLE risk allele exhibited lower Blimp1 expression and strikingly increased production of proinflammatory cytokines. We have made similar observations related to the Blimp1 risk allele for Crohns Disease (unpublished data). These data suggest that polymorphisms related to human autoimmunity specifically alter quantitative traits in human dendritic cells.

Population resources for genotype-phenotype studies of quantitative immune traits

These results suggest that many GWAS discoveries in autoimmune diseases will be associated with rather subtle changes in immune responsiveness and/or immune regulatory differences that are quantitative in nature. This may be due to the presence of structural amino acid changes, as in *PTPN22*, or changes in gene regulation that are specific to particular cells and stages of differentiation. In order to dissect these relationships, a large population resource of human subjects carrying the various polymorphisms of interest is required. The study of patients is clearly not desirable, at least for initial investigations, since phenotypic variation may be affected by active inflammation and drug treatment; the phenotypic consequences of common polymorphisms may therefore be obscured or substantially confounded by the presence of disease. Similar to the Cambridge Biobank in the UK that was utilized for the IL2RA studies cited above[20], a large population resource of over 5,000 subjects – the Genotype and Phenotype (GaP) Registry - is also available to investigators across the United States. All subjects in the GaP Registry have been typed with the immunochip, providing a ready resource of subjects with genotypic information relevant to autoimmune disorders. Information can be found at www.gapregistry.org. In addition to this, there is an obvious need to develop high-throughput methods to assess quantitative phenotypes in large numbers of subjects in the population. It is likely that emerging technologies such as single cell mass spectrometry [38] will streamline analysis and reduce costs, allowing for a more global approach to defining immune quantitative traits in populations. Focusing these resources on genetic variants implicated in GWAS for autoimmunity is likely to be especially fruitful.

Conclusion

GWAS and related gene discovery approaches have revealed the importance and complexity of identifying and understanding the functional consequences of genetic variation on biological systems. As described in this review for immune-mediated traits, we are beginning to unravel the quantitative effects of risk alleles on the immune response. The

examples provided here, together with the unique resources such as repositories of healthy controls and patients, offer hope that new avenues for therapy will soon emerge from these investigations.

Acknowledgments

PKG is supported by grants from the National Institutes of Health (RO1-AR-44422; RO1-AI-68759; RC2AR059092-01) and the Alliance for Lupus Research, in addition to support from Eileen Ludwig Greenland and the Boas family. BD is supported by the Alliance for Lupus Research. RMP is supported by grants from the NIH (RO1-AR057108, RO1-AR056768, U01-GM092691, RO1-AR059648), and holds a Career Award for Medical Scientists from the Burroughs Wellcome Fund.

References

1. Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST, et al. Complement factor H polymorphism in age-related macular degeneration. *Science*. 2005; 308:385–389. [PubMed: 15761122]
2. Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. *Am J Hum Genet*. 2012; 90:7–24. [PubMed: 22243964]
3. Cho JH, Gregersen PK. Genomics and the multifactorial nature of human autoimmune disease. *N Engl J Med*. 2011; 365:1612–1623. [PubMed: 22029983]
4. Bottini N, Musumeci L, Alonso A, Rahmouni S, Nika K, Rostamkhani M, MacMurray J, Meloni GF, Lucarelli P, Pellicchia M, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet*. 2004; 36:337–338. [PubMed: 15004560]
5. Begovich AB, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Alexander HC, Ardlie KG, Huang Q, Smith AM, Spoeke JM, et al. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *Am J Hum Genet*. 2004; 75:330–337. [PubMed: 15208781]
6. Rhee I, Veillette A. Protein tyrosine phosphatases in lymphocyte activation and autoimmunity. *Nat Immunol*. 2012; 13:439–447. [PubMed: 22513334]
- *7. Hasegawa K, Martin F, Huang G, Tumas D, Diehl L, Chan AC. PEST domain-enriched tyrosine phosphatase (PEP) regulation of effector/memory T cells. *Science*. 2004; 303:685–689. The original mouse knockout of PTPN22 suggests lowered thresholds for T cell activation. [PubMed: 14752163]
8. Vang T, Congia M, Macis MD, Musumeci L, Orru V, Zavattari P, Nika K, Tautz L, Tasken K, Cucca F, et al. Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant. *Nat Genet*. 2005; 37:1317–1319. [PubMed: 16273109]
- *9. Rieck M, Arechiga A, Onengut-Gumuscu S, Greenbaum C, Concannon P, Buckner JH. Genetic variation in PTPN22 corresponds to altered function of T and B lymphocytes. *J Immunol*. 2007; 179:4704–4710. One of the first reports providing evidence of a “gain of function” by the PTPN22 620W risk allele. [PubMed: 17878369]
10. Zikherman J, Hermiston M, Steiner D, Hasegawa K, Chan A, Weiss A. PTPN22 deficiency cooperates with the CD45 E613R allele to break tolerance on a non-autoimmune background. *J Immunol*. 2009; 182:4093–4106. [PubMed: 19299707]
- *11. Zhang J, Zahir N, Jiang Q, Miliotis H, Heyraud S, Meng X, Dong B, Xie G, Qiu F, Hao Z, et al. The autoimmune disease-associated PTPN22 variant promotes calpain-mediated Lyp/Pep degradation associated with lymphocyte and dendritic cell hyperresponsiveness. *Nat Genet*. 2011; 43:902–907. This is detailed analysis of the PTPN22 in a mouse model, suggesting that that PTPN22 risk alleles is functionally analogous to the mouse knockout phenotype. [PubMed: 21841778]
12. Maine CJ, Hamilton-Williams EE, Cheung J, Stanford SM, Bottini N, Wicker LS, Sherman LA. PTPN22 alters the development of regulatory T cells in the thymus. *J Immunol*. 2012; 188:5267–5275. [PubMed: 22539785]

13. Arechiga AF, Habib T, He Y, Zhang X, Zhang ZY, Funk A, Buckner JH. Cutting edge: the PTPN22 allelic variant associated with autoimmunity impairs B cell signaling. *J Immunol.* 2009; 182:3343–3347. [PubMed: 19265110]
- *14. Menard L, Saadoun D, Isnardi I, Ng YS, Meyers G, Massad C, Price C, Abraham C, Motaghedi R, Buckner JH, et al. The PTPN22 allele encoding an R620W variant interferes with the removal of developing autoreactive B cells in humans. *J Clin Invest.* 2011; 121:3635–3644. This paper links PTPN22 polymorphisms to the regulation of the humoral autoimmune repertoire. [PubMed: 21804190]
15. Trynka G, Hunt KA, Bockett NA, Romanos J, Mistry V, Szperl A, Bakker SF, Bardella MT, Bhaw-Rosun L, Castillejo G, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. *Nat Genet.* 2011; 43:1193–1201. [PubMed: 22057235]
16. Martin JE, Broen JC, Carmona FD, Teruel M, Simeon CP, Vonk MC, van't Slot R, Rodriguez-Rodriguez L, Vicente E, Fonollosa V, et al. Identification of CSK as a systemic sclerosis genetic risk factor through Genome Wide Association Study follow-up. *Hum Mol Genet.* 2012; 21:2825–2835. [PubMed: 22407130]
- **17. Manjarrez-Orduño N, Marasco E, Chung S, Katz MS, Kiridly JF, Simpfendorfer KR, Freudenberg J, Ballard D, Nashi E, Hopkins TJ, et al. CSK regulatory polymorphism is associated with systemic lupus erythematosus and influences B cell signaling and activation. *Nature Genetics.* 2012 in press. This report links detailed genetic analysis of Csk to quantitative differences in expression and lymphocyte signaling using population resources or normal subjects to establish genotype-phenotype correlations.
- *18. Hu X, Kim H, Stahl E, Plenge R, Daly M, Raychaudhuri S. Integrating autoimmune risk loci with gene-expression data identifies specific pathogenic immune cell subsets. *Am J Hum Genet.* 2011; 89:496–506. This paper uses a bioinformatic analysis of GWAS associated genes and gene expression to propose a cellular localization of disease risk pathways. [PubMed: 21963258]
19. Simpfendorfer KR, Olsson LM, Manjarrez Orduno N, Khalili H, Simeone AM, Katz MS, Lee AT, Diamond B, Gregersen PK. The autoimmunity-associated BLK haplotype exhibits cis-regulatory effects on mRNA and protein expression that are prominently observed in B cells early in development. *Hum Mol Genet.* 2012
- **20. Dendrou CA, Plagnol V, Fung E, Yang JH, Downes K, Cooper JD, Nutland S, Coleman G, Himsworth M, Hardy M, et al. Cell-specific protein phenotypes for the autoimmune locus IL2RA using a genotype-selectable human bioresource. *Nat Genet.* 2009; 41:1011–1015. This study is the first comprehensive functional examination of a GWAS risk haplotype on IL2R expression utilizing a large resource of normal human subjects. [PubMed: 19701192]
21. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhardt AH, Abraham C, Regueiro M, Griffiths A, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science.* 2006; 314:1461–1463. [PubMed: 17068223]
22. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet.* 2010; 42:1118–1125. [PubMed: 21102463]
23. Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, Lee JC, Goyette P, Imielinski M, Latiano A, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet.* 2011; 43:246–252. [PubMed: 21297633]
24. Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouwehand WH, Samani NJ, et al. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. *Nat Genet.* 2007; 39:1329–1337. [PubMed: 17952073]
25. Pidasheva S, Trifari S, Phillips A, Hackney JA, Ma Y, Smith A, Sohn SJ, Spits H, Little RD, Behrens TW, et al. Functional studies on the IBD susceptibility gene IL23R implicate reduced receptor function in the protective genetic variant R381Q. *PLoS ONE.* 2011; 6:e25038. [PubMed: 22022372]
26. Di Meglio P, Di Cesare A, Laggner U, Chu CC, Napolitano L, Villanova F, Tosi I, Capon F, Trembath RC, Peris K, et al. The IL23R R381Q gene variant protects against immune-mediated

- diseases by impairing IL-23-induced Th17 effector response in humans. *PLoS ONE*. 2011; 6:e17160. [PubMed: 21364948]
27. Niewold TB, Clark DN, Salloum R, Poole BD. Interferon alpha in systemic lupus erythematosus. *J Biomed Biotechnol*. 2010; 2010:948364. [PubMed: 20652065]
 28. Niewold TB, Hua J, Lehman TJ, Harley JB, Crow MK. High serum IFN-alpha activity is a heritable risk factor for systemic lupus erythematosus. *Genes Immun*. 2007; 8:492–502. [PubMed: 17581626]
 29. Niewold TB, Kelly JA, Flesch MH, Espinoza LR, Harley JB, Crow MK. Association of the IRF5 risk haplotype with high serum interferon-alpha activity in systemic lupus erythematosus patients. *Arthritis Rheum*. 2008; 58:2481–2487. [PubMed: 18668568]
 30. Kariuki SN, Kirou KA, MacDermott EJ, Barillas-Arias L, Crow MK, Niewold TB. Cutting edge: autoimmune disease risk variant of STAT4 confers increased sensitivity to IFN-alpha in lupus patients in vivo. *J Immunol*. 2009; 182:34–38. [PubMed: 19109131]
 31. Hall JC, Rosen A. Type I interferons: crucial participants in disease amplification in autoimmunity. *Nat Rev Rheumatol*. 2010; 6:40–49. [PubMed: 20046205]
 32. Ioannou Y, Isenberg DA. Current evidence for the induction of autoimmune rheumatic manifestations by cytokine therapy. *Arthritis Rheum*. 2000; 43:1431–1442. [PubMed: 10902743]
 33. Axtell RC, Raman C. Janus-like effects of type I interferon in autoimmune diseases. *Immunol Rev*. 2012; 248:23–35. [PubMed: 22725952]
 34. Mayer CT, Berod L, Sparwasser T. Layers of dendritic cell-mediated T cell tolerance, their regulation and the prevention of autoimmunity. *Front Immunol*. 2012; 3:183. [PubMed: 22783257]
 35. Hammer GE, Turer EE, Taylor KE, Fang CJ, Advincula R, Oshima S, Barrera J, Huang EJ, Hou B, Malynn BA, et al. Expression of A20 by dendritic cells preserves immune homeostasis and prevents colitis and spondyloarthritis. *Nat Immunol*. 2011; 12:1184–1193. [PubMed: 22019834]
 36. Kim SJ, Zou YR, Goldstein J, Reizis B, Diamond B. Tolerogenic function of Blimp-1 in dendritic cells. *J Exp Med*. 2011; 208:2193–2199. [PubMed: 21948081]
 37. Plenge RM, Cotsapas C, Davies L, Price AL, de Bakker PI, Maller J, Pe'er I, Burtt NP, Blumenstiel B, Defelice M, et al. Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. *Nat Genet*. 2007
 - *38. Bendall SC, Simonds EF, Qiu P, Amir el AD, Krutzik PO, Finck R, Bruggner RV, Melamed R, Trejo A, Ornatsky OI, et al. Single-cell mass cytometry of differential immune and drug responses across a human hematopoietic continuum. *Science*. 2011; 332:687–696. This paper points the way to new more comprehensive methods of defining immune diversity. [PubMed: 21551058]

Highlights

A large number of associations for autoimmunity have been identified, generally involving common variants of modest effect

Many associations defined by GWAS are in non-coding regions and appear to regulate quantitative effects on gene expression

A large fraction of the common variants act through quantitative changes in thresholds for immune signaling and activation.

Figure 1. A simplified model for autoimmunity reflects the role of HLA polymorphisms in regulating the response of the adaptive immune system to specific disease-related autoantigens. Additional factors summarized in Table 1 are required for the development of clinical autoimmunity.

Table 1

General consequences of altered signaling thresholds on functional immune phenotypes in the adaptive immune system

	Weak Signal (high threshold)	Strong Signal (low threshold)
B cell arm - immature	Bone marrow and transitional B cells; reduced counterselection with escape of autoreactive B cells, leading to expanded autoimmune repertoire	
B cell arm - mature		Increased responsiveness to (auto)antigens
T cell arm - immature	Thymus – reduced negative selection, escape of autoreactive T cells	
T cell arm - mature	Reduced activity of Treg cells with relative loss of peripheral tolerance; Altered polarization	Relative increase in peripheral effector T cell responses. Altered polarization