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What have we learned from six years of GWAS in autoimmune diseases, and what is next?

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Genome-wide association studies (GWAS) have discovered hundreds of common genetic variants that predispose humans to autoimmune diseases, opening up unprecedented potential for elucidating the pathways and processes of disease. To understand the role of these variants in susceptibility, we need to derive mechanistic insight by integration of genetic results with other biological data types and also with careful functional studies. In many cases, such studies have highlighted coherent biological processes at a high level and elucidated specific mechanisms that contribute to autoimmunity and inflammation. The understanding of the genetic component of autoimmune etiology will become more complete as fine-mapping and sequencing data become readily available. A comprehensive catalog of human immune phenotypes could provide a functional basis for assessing genetic influence on immune function and variation in response to therapeutic interventions, as well as for rationally designing new targeted therapeutics.

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Introduction

Autoimmune diseases are a clinically diverse group of diseases caused by inappropriate or hyperactive immune responses against tissues and substances normally considered 'self.' Although malfunction of the immune system is clearly indicated, the mechanism of autoimmune pathogenesis is still far from elucidated. Family and twin studies have long suggested that genetics contributes

significantly to autoimmunity, and earlier linkage studies identified a handful of strong genetic variants primarily in the major histocompatibility (MHC) region encoding human leukocyte antigens (HLA). Since the completion of the HapMap Project and development of massively parallel array-based genotyping technologies, genome-wide association studies (GWAS) in search for common variants have been extensively carried out in complex diseases. In this review, we examine approaches that have been taken and progress made to understanding of autoimmune genetics through GWAS, with examples of mechanistic insight derived from follow-up studies. We also suggest areas where association studies can be improved to yield further insights.

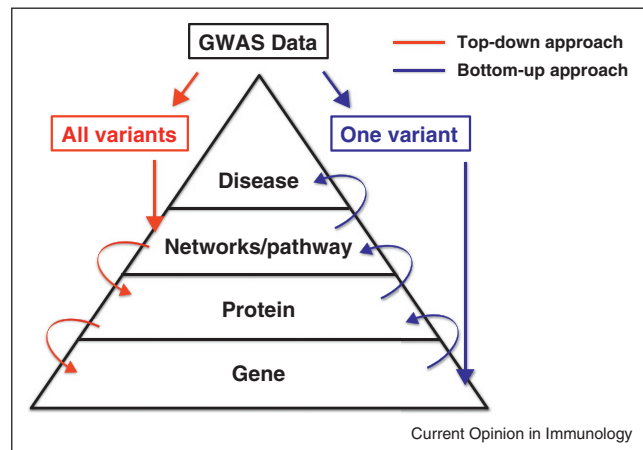
Since 2006, hundreds of single-nucleotide polymorphisms (SNPs) have been associated with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease, ulcerative colitis (UC), type 1 diabetes (T1D), celiac disease, psoriasis and other autoimmune diseases [1]. While a significant accomplishment given the limited historical successes in complex trait genetics, these studies by themselves have limited value without subsequent steps to link emergent genetics to function by pinpointing causal variants, deriving biological relevance, and elucidating pathogenic mechanisms. Although occasionally these risk loci harbor functional coding variants in genes known to be involved in immune processes that alter protein sequences, most others implicate genes with unknown function or are simply non-coding. Furthermore all the currently validated variants have moderate effect sizes and account for only a fraction of the heritability [2]. Therefore, even with an explosion of genetics data, a reasonable question arose: are GWAS results truly useful for either understanding etiology, or for clinical diagnosis and management of autoimmune diseases?

How do we learn about autoimmune diseases from GWAS?

One critical challenge in defining disease biology from associated alleles is the absence of an understanding of the specific genes implicated and the molecular perturbations created by associated alleles. However what GWAS potentially provides is the genetic architecture that underlies autoimmunity, around which the relevant physiological and pathological pathways can be constructed. Following SNP discovery, investigators have devised statistical methods and carried out functional studies to elucidate relevant biology. The approaches taken by these studies

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Figure 1



Two broad approaches taken by GWAS follow-up studies. In a more traditional 'bottom-up' approach, a specific variant/gene is selected from the GWAS results to investigate its functions and the effect of perturbation in the context of the disease. In a 'top-down' approach, the entire list of variants identified by GWAS is analyzed together, often incorporating existing biological data types, to highlight processes and pathways pertinent to disease, which helps to prioritize and focus additional follow-ups such as targeted functional assays and/or discovery of more risk variants.

can be broadly grouped into two major categories, as described in Figure 1: (1) a traditional 'bottom-up' approach in which individual alleles, genes and proteins are examined to gain insight into molecular mechanisms of disease and (2) a 'top-down' approach, where lists of disease-associated regions are examined together to outline relevant biological systems and pathways.

'Bottom-up' approach: focused follow-up studies directly shed light on molecular mechanisms of pathogenesis

In traditional Mendelian genetics, the identification of disease causing mutations in a single gene would be immediately followed by targeted follow-up efforts to understand the function of the gene and how its alteration precipitates disease. Similarly, conducting focused functional and statistical follow-up studies in well-validated loci have quite directly suggested specific molecular mechanisms through which allelic variants confer risk or protection in autoimmune diseases [3–7,8*,9–13]. For example, Pidascheva *et al.* determined that the R381Q (rs11290926) variant in *IL23R*, which is associated with reduced risk of inflammatory bowel disease, results in a loss of function which reduces T-cell activation in response to IL-23, lending evidence that the IL-23 pathway is pathogenic [5]. Leucine-rich repeat kinase 2 (*LRRK2*) is another major risk gene for Crohn's disease. Liu *et al.* [6] investigated the molecular mechanisms by which *LRRK2* negatively regulates NFAT1 which mediates T-cell activation as well as cytokine production in

antigen presenting cells, and showed that *LRRK2*-deficiency conferred increased risk to colitis in mouse model. And in one of the clearest examples of novel insights gained from GWAS, the role of autophagy in Crohn's disease, previously unsuspected before the first GWAS studies, has now become a major therapeutic target in disease owing to the elucidation of the role of variation at *ATG16L1* and *IRGM* [described in detail by Garder and Xavier in this issue]. In these follow-up studies that characterize specific candidate genes that emerged from GWAS, the functional effect of variants on immune response has been clearly illustrated.

In other examples, using detailed statistical approaches Raychaudhuri *et al.* [8*] delved into one of the longest-known susceptibility loci associated with anti-CCP-positive rheumatoid arthritis, namely the MHC region. They imputed alleles in the region including *HLA-DRB1* using existing GWAS genotypes, followed by conditional analysis, and successfully fine-mapped the causal variants to sequences of five amino acids located the binding groove of three MHC molecules. This analysis improved upon the 'shared epitope' theory that had existed for more than 30 years [14], and is a successful example of delineating the causal variants from GWAS data. Okada *et al.* focused on the HLA-Cw*1202-B*5201-DRB1*1502 haplotype and were able to tease apart its opposite effects on the two closely-related inflammatory bowel diseases in the Japanese population, specifically increasing susceptibility to ulcerative colitis but reducing risk of Crohn's disease [7]. This observation supports the hypothesis that Crohn's disease is a Th1-like disease (preferentially producing a repertoire of Th1 cytokines such as interferon- γ) whereas UC is more Th2-like; and susceptibility difference between the two are manifestations of Th1/Th2 imbalance in immune response induced by differential helper T-cell responses to specific pathogens.

'Top-down' approaches: examining GWAS results in aggregate outlines coherent biological processes

While the bottom-up approach is more tractable and traditional, the realization emerging from GWAS that autoimmune diseases are the result of many, probably hundreds, of simultaneously contributing genes and variants has borne an alternate approach to the problem by considering all associations together. Many analytic methods have therefore been developed to interpret GWAS results by examining groups of risk regions or implicated genes in aggregate, incorporating information from other biological data types such as gene and protein expression [15–19,20*,21,22,23*,24]. Encouragingly, these analyses have often convincingly shown that disease-associated regions implicate coherent biological processes and molecular pathways. For example, for many autoimmune diseases, significant enrichment of physical interactions among genes in associated risk loci has been demonstrated, implicating organized networks of

biological pathways [23^{••}]. Similarly, the evaluation of cell-specific expression of autoimmune SNPs-implicated genes showed enrichment in particular immune cells, providing an unbiased method for using raw GWAS results to identify likely pathogenic cell types [19]. Such analyses must be undertaken with care – biases in both the genetic discovery data (e.g. GWAS arrays preferentially discover associations that are both gene and SNP rich, certain gene families are systematically much larger than others) and in the biological data to be integrated (e.g. certain families of genes are more well-studied in protein interaction experiments and more well-represented on expression arrays) require careful attention in the evaluation of statistical significance.

If managed properly, these issues can be overcome, and when GWAS results are shown to implicate regions that contain genes that are compellingly non-randomly drawn from specific pathways or which are unusually closely related in the context of independent functional data, such relationships clearly indicate a convincing biological insight into disease has emerged from the collective GWAS results set. In one study, Lee *et al.* constructed a genome-scale human gene network using genomic and proteomic data. Studying genes regions associated with Crohn's disease, they observed the interaction of genes in the TNF pathway, the Th17-differentiation network, as well as genes involved in autophagy. Moreover, they were able to combine this approach to boost the detection power of GWAS, and suggest more candidate genes based on their interaction partners in highlighted pathways, such as *GRB2* and *SHC1* [20[•]].

A number of overlapping HLA and non-HLA risk alleles have emerged across autoimmune diseases, implicating shared pathogenic pathways among phenotypically heterogeneous diseases. It is intuitive that immune response pathways would be broadly involved in all autoimmune diseases; as well as diverging pathways should eventually lead to variation in clinical presentations. Systematically examining the shared alleles provides one means for comparing and contrasting autoimmune diseases in terms genetic backgrounds and implications on shared pathogenic mechanisms [25–31]. As one example, Ramos *et al.* investigated the genetic connections across 17 autoimmune diseases, and noted the strongest correlations between RA and T1D as well as between Crohn's disease and UC, suggesting common pathogenic mechanistic pathways. They also noted that SLE possesses a distinct genetic background, supporting partial pleiotropy among autoimmune diseases [28].

The 'top-down' approach often does not directly yield validated risk genes and variants, however it is powerful in highlighting coherent biological processes relevant to the diseases, and in turn providing guidance to focus

statistical and functional follow-ups on the most interesting candidate genomic regions and the most relevant molecular and cellular models.

How can autoimmune GWAS be improved?

Identifying the remaining genetic architecture

It is estimated that all the validated SNPs in aggregate explain a fraction hovering around 10–40% of total heritability in most complex-trait diseases [32,33], making missing heritability a glaring issue with existing GWAS results. There are several oft-discussed possible sources for what has been termed this 'missing heritability', including the potentially large-effect rare and structural variants, gene–gene interactions (epistasis), gene–environment interactions, as well as many more common variants that simply have not been discovered owing to the lack of power as limited by sample size [34,35]. Stahl *et al.* modeled the polygenic architecture based on Bayesian inference in several complex-trait diseases, and suggested that thousands of undiscovered common SNPs could explain an additional 20% and 43% of disease risk in RA and celiac disease, respectively [36^{••}]. Similarly Park *et al.* predicted that for Crohn's disease, more than 140 risk loci with effect sizes comparable to the first 32 validated loci together would account for 20% of the heritability [37].

Next-generation deep sequencing in candidate regions has been successful in discovering a handful of rare variants associated with several diseases [38–42]. Examples include a splice variant in *CARD9* (OR = 0.29) associated with reduced risk of Crohn's disease [40], four protective rare variants in *IFIH1* in T1D [41], as well as several rare variants contributing to the risk of celiac disease discovered by Trynka *et al.* using data from pilot 1000 Genome Project studies and other resequencing data [42]. Much more than increasing heritability explained by identifying rare variation missed by GWAS, such studies can provide clearer functional insights into the roles of individual genes and in the case of strongly protective variants, articulate clear therapeutic hypotheses that can be pursued.

Harnessing the value of genetics: profiling the human immunophenotypes is necessary to link genetics to function in autoimmune diseases

The value of genetic knowledge we have gathered through GWAS is one piece of the puzzle for elucidating normal physiology and disease mechanisms of autoimmunity. One major hindrance to delineating the functional role of genetic variants as well as in autoimmune research in general lies in the lack of a comparable functional catalog of the human immune system [43]. Much of the current immunological knowledge has come from mouse models. While it has been a valuable source, the mouse immune system only emulates the human system partially. Without clear definitions and comprehensive descriptions of the normal immune

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system, it will be difficult for sporadic and focused manipulative assays to capture patterns of functional variance with respect to genetic or environmental changes in such a complex system. Also clinically, diagnosis of autoimmune diseases is largely descriptive with few reliable biomarkers, and it is difficult to design, assess, and improve efficacy of therapeutic agents. It is therefore crucial to establish the phenotypes and functional profiles of the components of the human immune system. Then, the relationship between function and genetics can be systematically assessed, and therapeutic interventions can be designed and modified accordingly.

Conclusion

For years the primary bottleneck in understanding autoimmune disease was the inability of genetics to provide genuine, replicable insights – this has been overcome, but simply places the emphasis now on challenges greater than expected, the interpretation of hundreds of contributing genetic risk factors into a coherent and actionable biological insights. Now a large volume of statistical and functional follow-up studies to GWAS results is starting to emerge. But, despite the amount of raw data and follow-up statistical and functional studies, many mechanisms of genetic contribution to autoimmune diseases remain unclear.

It is important to keep in mind that in the effort to ultimately understand disease mechanisms, GWAS and other statistical approaches do not replace *in vitro* or *in vivo* functional studies. Rather, GWASs have proven to serve as a powerful first step to guide and complement functional studies, as they (1) outline relevant and coherent systems and processes involved in disease pathogenesis; (2) suggest specific molecular pathways and appropriate cellular/organismal models for focused functional studies; and (3) offer a promising path to discovering potential leads of targeted therapy. It is particularly encouraging that progress is being made beyond GWAS via the integration of many different types of biological data such as gene expression, immunophenotypes, epigenetics, protein interactions and clinical data. These efforts are helping to elucidate the complex biology that association studies outline and make further progress towards realizing the promise of human genetics.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
 - of outstanding interest
- Hindorf LA, MacArthur J, Wise A, Jenkins HA, Hall PN, Klemm AK, Manolio TA: **A Catalog of Published Genome-Wide Association Studies**. Available at: www.genome.gov/gwastudies. Accessed [22.08.12].
 - Anderson CA, Soranzo N, Zeggini E, Barrett JC: **Synthetic associations are unlikely to account for many common disease genome-wide association signals**. *PLoS Biol* 2011, **9**:e1000580.
 - Gorlatova N, Chao K, Pal LR, Araj RH, Galkin A, Turko I, Moul J, Herzberg O: **Protein characterization of a candidate mechanism SNP for Crohn's disease: the macrophage stimulating protein R689C substitution**. *PLoS ONE* 2011, **6**:e27269.
 - Guerini FR, Cagliani R, Forni D, Agliardi C, Caputo D, Cassinotti A, Galimberti D, Fenoglio C, Biasin M, Asselta R *et al.*: **A functional variant in ERAP1 predisposes to multiple sclerosis**. *PLoS ONE* 2012, **7**:e29931.
 - 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.
 - Liu Z, Lee J, Krummey S, Lu W, Cai H, Lenardo MJ: **The kinase LRRK2 is a regulator of the transcription factor NFAT that modulates the severity of inflammatory bowel disease**. *Nat Immunol* 2011, **12**:1063-1070.
 - Okada Y, Yamazaki K, Umeno J, Takahashi A, Kumasaka N, Ashikawa K, Aoi T, Takazoe M, Matsui T, Hirano A *et al.*: **HLA-Cw*1202-B*5201-DRB1*1502 haplotype increases risk for ulcerative colitis but reduces risk for Crohn's disease**. *Gastroenterology* 2011, **141**:864-871 e861-865.
 - Raychaudhuri S, Sandor C, Stahl EA, Freudenberg J, Lee HS, Jia X, Alfredsson L, Padyukov L, Klareskog L, Worthington J: **Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis**. *Nat Genet* 2012, **44**:291-296.
- In this study, the authors used GWAS SNP data and imputed alleles in the HLA region and discovered five amino acid polymorphisms in the peptide-binding grooves of three MHC molecules that may completely explain the MHC association to rheumatoid arthritis.
- Rossi F, Bellini G, Tolone C, Luongo L, Mancusi S, Papparella A, Sturgeon C, Fasano A, Nobili B, Perrone L *et al.*: **The Cannabinoid Receptor type 2 Q63R variant increases the risk of celiac disease: implication for a novel molecular biomarker and future therapeutic intervention**. *Pharmacol Res* 2012, **66**:88-94.
 - Tejasvi T, Stuart PE, Chandran V, Voorhees JJ, Gladman DD, Rahman P, Elder JT, Nair RP: **TNFAIP3 gene polymorphisms are associated with response to TNF blockade in psoriasis**. *J Invest Dermatol* 2012, **132**:593-600.
 - Wang S, Adrianto I, Wiley GB, Lessard CJ, Kelly JA, Adler AJ, Glenn SB, Williams AH, Ziegler JT, Comeau ME *et al.*: **A functional haplotype of UBE2L3 confers risk for systemic lupus erythematosus**. *Genes Immun* 2012, **13**:380-387.
 - Wiede F, Shields BJ, Chew SH, Kyparissoudis K, van Vliet C, Galic S, Tremblay ML, Russell SM, Godfrey DI, Tiganis T: **T cell protein tyrosine phosphatase attenuates T cell signaling to maintain tolerance in mice**. *J Clin Invest* 2011, **121**:4758-4774.
 - Zhou J, Wu R, High AA, Slaughter CA, Finkelstein D, Rehg JE, Redecke V, Hacker H: **A20-binding inhibitor of NF-kappaB (ABIN1) controls Toll-like receptor-mediated CCAAT/enhancer-binding protein beta activation and protects from inflammatory disease**. *Proc Natl Acad Sci USA* 2011, **108**:E998-E1006.
 - Stastny P: **HLA-D and Ia antigens in rheumatoid arthritis and systemic lupus erythematosus**. *Arthritis Rheum* 1978, **21**:S139-S143.
 - Bakir-Gungor B, Sezeran OU: **A new methodology to associate SNPs with human diseases according to their pathway related context**. *PLoS ONE* 2011, **6**:e26277.
 - Chen M, Cho J, Zhao H: **Incorporating biological pathways via a Markov random field model in genome-wide association studies**. *PLoS Genet* 2011, **7**:e1001353.
 - Cleynen I, Juni P, Bekkering GE, Nuesch E, Mendes CT, Schmied S, Wyder S, Kellen E, Villiger PM, Rutgeerts P *et al.*: **Genetic evidence supporting the association of protease and protease inhibitor genes with inflammatory bowel disease: a systematic review**. *PLoS ONE* 2011, **6**:e24106.
 - Nakaoka H, Cui T, Tajima A, Oka A, Mitsunaga S, Kashiwase K, Homma Y, Sato S, Suzuki Y, Inoko H *et al.*: **A systems genetics**

approach provides a bridge from discovered genetic variants to biological pathways in rheumatoid arthritis. *PLoS ONE* 2011, **6**:e25389.

19. 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.

20. Lee I, Blom UM, Wang PI, Shim JE, Marcotte EM: **Prioritizing candidate disease genes by network-based boosting of genome-wide association data.** *Genome Res* 2011, **21**: 1109-1121.

The authors devised a modified guilt-by-association algorithm, and analyzed GWAS data in conjugation with a functional network for human genes, which showed significant power to discover candidate genes.

21. Bergholdt R, Brorsson C, Palleja A, Berchtold LA, Floyel T, Bang-Berthelsen CH, Frederiksen KS, Jensen LJ, Stirling J, Pociot F: **Identification of novel type 1 diabetes candidate genes by integrating genome-wide association data, protein-protein interactions, and human pancreatic islet gene expression.** *Diabetes* 2012, **61**:954-962.

22. Akula N, Baranova A, Seto D, Solka J, Nalls MA, Singleton A, Ferrucci L, Tanaka T, Bandinelli S, Cho YS *et al.*: **A network-based approach to prioritize results from genome-wide association studies.** *PLoS ONE* 2011, **6**:e24220.

23. Rossin EJ, Lage K, Raychaudhuri S, Xavier RJ, Tatar D, Benita Y, **Cotsapas C, Daly MJ: Proteins encoded in genomic regions associated with immune-mediated disease physically interact and suggest underlying biology.** *PLoS Genet* 2011, **7**:e1001273.

The authors built a protein-protein interaction network, and used a permutation-based methods to show that protein products of genes implicated in GWAS results of autoimmune diseases have abundant physical interaction, and participate in common molecular processes.

24. Fehrmann RS, Jansen RC, Veldink JH, Westra HJ, Arends D, Bonder MJ, Fu J, Deelen P, Groen HJ, Smolonska A *et al.*: **Trans-eQTLs reveal that independent genetic variants associated with a complex phenotype converge on intermediate genes, with a major role for the HLA.** *PLoS Genet* 2011, **7**:e1002197.

25. Corona E, Dudley JT, Butte AJ: **Extreme evolutionary disparities seen in positive selection across seven complex diseases.** *PLoS ONE* 2010, **5**:e12236.

26. Eyre S, Hinks A, Bowes J, Flynn E, Martin P, Wilson AG, Morgan AW, Emery P, Steer S, Hocking LJ *et al.*: **Overlapping genetic susceptibility variants between three autoimmune disorders: rheumatoid arthritis, type 1 diabetes and coeliac disease.** *Arthritis Res Ther* 2010, **12**:R175.

27. Suzuki A, Kochi Y, Okada Y, Yamamoto K: **Insight from genome-wide association studies in rheumatoid arthritis and multiple sclerosis.** *FEBS Lett* 2011, **585**:3627-3632.

28. Ramos PS, Criswell LA, Moser KL, Comeau ME, Williams AH, Pajewski NM, Chung SA, Graham RR, Zidovetzki R, Kelly JA *et al.*: **A comprehensive analysis of shared loci between systemic lupus erythematosus (SLE) and sixteen autoimmune diseases reveals limited genetic overlap.** *PLoS Genet* 2011, **7**:e1002406.

29. Menon R, Farina C: **Shared molecular and functional frameworks among five complex human disorders: a**

comparative study on interactomes linked to susceptibility genes. *PLoS ONE* 2011, **6**:e18660.

30. Lewis SN, Nsoesie E, Weeks C, Qiao D, Zhang L: **Prediction of disease and phenotype associations from genome-wide association studies.** *PLoS ONE* 2011, **6**:e27175.

31. Cotsapas C, Voight BF, Rossin E, Lage K, Neale BM, Wallace C, Abecasis GR, Barrett JC, Behrens T, Cho J *et al.*: **Pervasive sharing of genetic effects in autoimmune disease.** *PLoS Genet* 2011, **7**:e1002254.

32. So HC, Li M, Sham PC: **Uncovering the total heritability explained by all true susceptibility variants in a genome-wide association study.** *Genet Epidemiol* 2011, **35**:447-456.

33. Visscher PM, Brown MA, McCarthy MI, Yang J: **Five years of GWAS discovery.** *Am J Hum Genet* 2012, **90**:7-24.

34. Gibson G: **Hints of hidden heritability in GWAS.** *Nat Genet* 2010, **42**:558-560.

35. Lee SH, Wray NR, Goddard ME, Visscher PM: **Estimating missing heritability for disease from genome-wide association studies.** *Am J Hum Genet* 2011, **88**:294-305.

36. Stahl EA, Wegmann D, Trynka G, Gutierrez-Achury J, Do R, Voight BF, Kraft P, Chen R, Kallberg HJ, Kurreeman FA *et al.*: **Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis.** *Nat Genet* 2012, **44**:483-489.

The authors examined the genetic architecture based on existing GWAS data for rheumatoid arthritis, and estimated the contribution of yet-undiscovered SNPs that could additional disease risk in RA, celiac disease, and other diseases, lending evidence that GWAS will continue to be productive.

37. Park JH, Wacholder S, Gail MH, Peters U, Jacobs KB, Chanock SJ, Chatterjee N: **Estimation of effect size distribution from genome-wide association studies and implications for future discoveries.** *Nat Genet* 2010, **42**:570-575.

38. Feng T, Zhu X: **Genome-wide searching of rare genetic variants in WTCCC data.** *Hum Genet* 2010, **128**:269-280.

39. Lehne B, Lewis CM, Schliitt T: **Exome localization of complex disease association signals.** *BMC Genomics* 2011, **12**:92.

40. Rivas MA, Beaudoin M, Gardet A, Stevens C, Sharma Y, Zhang CK, Boucher G, Ripke S, Ellinghaus D, Burt N *et al.*: **Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease.** *Nat Genet* 2011, **43**:1066-1073.

41. Nejentsev S, Walker N, Riches D, Egholm M, Todd JA: **Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes.** *Science* 2009, **324**:387-389.

42. 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.

43. Blumberg RS, Dittel B, Hafler D, von Herrath M, Nestle FO: **Unraveling the autoimmune translational research process layer by layer.** *Nat Med* 2012, **18**:35-41.