Cytokine Gene Polymorphisms and Human Autoimmune Disease in the Era of Genome-Wide Association Studies

Koen Vandebroek^{1,2}

Cytokine (receptor) genes have traditionally attracted great interest as plausible genetic risk factors for autoimmune disease. Since 2007, the implementation of genome-wide association studies has facilitated the robust identification of allelic variants in more than 35 cytokine loci as susceptibility factors for a wide variety of over 15 autoimmune disorders. In this review, we catalog the gene loci of interleukin, chemokine, and tumor necrosis factor receptor superfamily and ligands that have emerged as autoimmune risk factors. We examine recent progress made in the clarification of the functional mechanisms by which polymorphisms in the genes coding for interleukin-2 receptor alpha (*IL2RA*), *IL7R*, and *IL23R* may alter risk for autoimmune disease, and discuss opposite autoimmune risk alleles found, among others, at the *IL10* locus.

Introduction

AUTOIMMUNE DISEASES are caused by an aberrant immune response against innocent substances normally present in the body. As multifactorial diseases, they are hallmarked by modest genetic risk heritability and multifaceted interactions with a range of differing environmental influences (Oksenberg and Rioux 2006). A constant shared by the full spectrum of autoimmune disorders is the genetic association with the *HLA* class II region on chromosome 6p21, though the precise composition of associated haplotypes differs from one disease to another and will not be discussed in this review. While the *HLA* region explains a significant portion of the associated genetic risk, identification of additional non-*HLA* risk factors has posed major challenges. The approaches to track down such factors range from candidate gene studies to genome-wide association studies (GWAS). Candidate genes are defined as genes of which the products are likely to play a role in the etio-pathogenesis of the disease based on immunological or biological knowledge. GWAS, in contrast, are “agnostic,” that is, model independent, in view of the fact that they cover the full genome thus avoiding gene selection bias.

Cytokine and cytokine receptor genes have traditionally attracted great interest as candidate genes for autoimmune diseases (see Vandebroek 2006). This interest was largely driven by the finding that it was possible to significantly alter disease outcome in animal models of autoimmune disease by means of either monoclonal antibodies against specific cytokines, administration of recombinant cytokines, or silencing of cytokine genes, and numerous examples of such successful interventions are available in the scientific

literature. In 2007, the first GWAS in autoimmune diseases were published, and these revealed for the first time the real genetic size effects of non-*HLA* risk factors. What emerged was the finding that non-*HLA* risk factors have weak-to-modest effects, with odds ratios rarely exceeding 1.3. To robustly validate these genes with genome-wide significance (normally set at $P=10^{-7}$), huge sample collections of carefully ascertained patients and controls are needed. With the benefit of hindsight, we now know that most pre-GWAS cytokine candidate gene studies did not have sufficient statistical power to reliably determine whether or not cytokine genes were autoimmune risk factors as the required thresholds for genome-wide significance were only very rarely met. Even if successful, the genomic context of multiple associated loci cannot be ascertained by candidate gene studies.

It should therefore not surprise that more than candidate gene studies, it is the GWAS approach that has facilitated the robust identification of those cytokine/receptor gene loci that act as clear-cut genetic risk factors for autoimmune disease. The aim of this review was to examine cytokine/receptor loci that have emerged as autoimmune risk factors mainly from GWAS but also, wherever relevant, from well-powered candidate gene studies performed after 2007 (Table 1, Figure 1). Cytokine/receptor loci emerging from GWAS were identified via the NHGRI GWAS catalog by means of the GWAS Integrator bioinformatics tool (Hindorff and others 2009; Yu and others 2011). A total of 17 autoimmune diseases were surveyed (Figure 1), that is, alopecia areata (AA), ankylosing spondylitis (AS), asthma, atopic dermatitis, Behçet's disease (BD), celiac disease (CeD), crohn's disease (CD), graves' disease (GD), multiple sclerosis (MS), primary biliary cirrosis (PBC), psoriasis, psoriatic arthritis, rheumatoid

¹Neurogenomiks Group, Universidad del País Vasco (UPV/EHU), Zamudio, Spain.

²IKERBASQUE, Basque Foundation for Science, Bilbao, Spain.

TABLE 1. MOST FREQUENTLY SHARED AND VALIDATED AUTOIMMUNE DISEASE-ASSOCIATED INTERLEUKIN (RECEPTOR) GENE LOCI IDENTIFIED IN GENOME-WIDE ASSOCIATION STUDIES

Chr	Gene or gene cluster	Associated SNP risk allele	Position	Context	P value	OR [95% CI]	Disease	Reference
1p31.3	IL23R	rs11209026-G rs11209026-G rs11209026-G rs11209026-? rs11209026-? rs1495965-G rs3024505-T rs3024505-T rs3024505-C rs1518111-? rs6897932-C rs6897932-C rs3194051-G rs860413-A rs2546890-A rs2546890-A rs10045431-C rs6556416-C rs6871626-A rs12188300-T rs706779-A rs706778-T rs2104286-T rs3118470-G rs12722489-C rs12251307-?	67478546 67478546 67478546 67478546 67478546 67526096 205006527 205006527 205006527 205011268 35910332 35910332 35912031 35978799 158692478 158692478 158747111 158751323 158759370 158762105 6138830 6138955 6139051 6141719 6142018 6163501	R381Q R381Q R381Q R318Q R318Q 28 kb 3' 1 kb 3' 1 kb 3' 1 kb 3' Intron 2 T244I T244I I356V 66 kb 3' 2.4 kb 5' 2.4 kb 5' 57 kb 5' 61 kb 5' 69 kb 5' 72 kb 5' Intron 1 Intron 1 Intron 1 Intron 1 Intron 1 19 kb 5'	2×10^{-17} 5×10^{-28} 1×10^{-64} 7×10^{-7} 7×10^{-11} 2×10^{-11} 6×10^{-17} 2×10^{-14} 2×10^{-9} 4×10^{-18} 3×10^{-7} 8×10^{-6} 4×10^{-8} 1×10^{-11} 1×10^{-20} 1×10^{-11} 4×10^{-13} 2×10^{-8} 1×10^{-21} 7×10^{-17} 3×10^{-9} 1×10^{-11} 9×10^{-8} 2×10^{-12} 3×10^{-9} 1×10^{-13}	N.A. 1.74 [1.57-1.92] 2.66 [2.36-3.00] 1.49 [1.27-1.74] 2.56 [1.92-3.45] 1.35 [1.24-1.47] 1.25 [1.19-1.32] 1.12 [1.07-1.17] 1.19 [1.10-1.30] 1.45 [1.34-1.58] 1.18 [1.11-1.26] 1.12 [1.06-1.19] 1.07 [1.02-1.12] 1.30 [1.21-1.40] 1.54 [1.32-1.79] 1.15 [1.09-1.22] 1.11 [N.A.] N.A. 1.17 [1.12-1.22] 1.7 [1.50-1.93] 1.27 [1.17-1.37] 1.14 [N.A.] 1.15 [1.04-1.27] 1.41 [1.27-1.56] 1.11 [1.05-1.16] N.A.	AS UC CD Ps IBD ^a BD UC CD T1D BD MS T1D UC PBC Ps MS CD AS UC PsA V RA MS AA CD T1D	Evans and others (2011) Anderson and others (2011) Franke and others (2010) Strange and others (2010) Kugathasan and others (2008) Mizuki and others (2010) Anderson and others (2011) Franke and others (2010) Barrett and others (2009) Remmers and others (2010) Hafler and others (2007) Todd and others (2007) Anderson and others (2011) Mells and others (2011) Ellinghaus and others (2010) IMSGC and WTCCC2 (2011) Barrett and others (2008) Evans and others (2011) Anderson and others (2011) Hüffmeier and others (2010) Jin and others (2010) Stahl and others (2010) De Jager and others (2009) Petukhova and others (2010) Franke and others (2010) Barrett and others (2009)

Included are only bona fide interleukin genes and their receptors.

Studies were selected from the NHGRI Catalog of Published GWAS, and from additional published GWAS. For loci that emerged more than once from independent GWAS on the same disease, only one representative study is included.

^aPediatric onset form of the disease.

AA, alopecia areata; AS, ankylosing spondylitis; BD, Behçet's disease; CD, Crohn's disease; IBD, inflammatory bowel disease; MS, multiple sclerosis; PBC, primary biliary cirrhosis; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; T1D, type 1 diabetes; UC, ulcerative colitis; V, vitiligo; "?," risk allele was not reported; GWAS, genome-wide association studies; IL2RA, interleukin-2 receptor alpha.

Gene or gene cluster	Chromosome	Alopecia Areata	Ankylosing Spondylitis	Asthma	Atopic Dermatitis	Behçet's disease	Celiac Disease	Crohn's Disease	Graves' Disease	Multiple Sclerosis	Primary Biliary Cirrhosis	Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Systemic Lupus Erythematosus	Type 1 Diabetes	Ulcerative Colitis	Vitiligo
<i>CCL2</i> → <i>CCL8</i> ⁽¹⁾	17q12							1										
<i>CCL21</i>	9p13.3													2				
<i>CCR1</i> – <i>CCR3</i>	3p21.31						2											
<i>CCR4</i>	3p22.3						1											
<i>CCR6</i>	6q27							2	1					2				1
<i>CXCR1</i> – <i>CXCR2</i>	2q35																1	
<i>CXCR4</i>	2q22.1									1								
<i>CXCR5</i>	11q23.3									1	1							
<i>IFNG</i> – <i>IL26</i> – <i>IL22</i>	12q15																3	
<i>IL1R2</i> → <i>IL18RAP</i> ⁽²⁾	2q12.1		1	2			2	1									1	
<i>IL2</i> – <i>IL21</i>	4q27	1					3							1		1	1	
<i>IL2RA</i>	10p15.1	1						1		3				1		2		1
<i>IL2RB</i>	22q12.3			1														
<i>IL7R</i>	5p13.2									3	1					1	1	
<i>IL10</i>	1q32.1					2		1							1	1	5	
<i>IL12A</i>	3q25.33						2			2	3							
<i>IL12B</i>	5q33.3		1					3		1		4	1				1	
<i>IL12RB2</i>	1p31.1										3							
<i>IL13</i>	5q31.1			1								1						
<i>IL17REL</i>	22q13.33																2	
<i>IL22RA2</i>	6q23.3									1								
<i>IL23A</i>	12q13.3												2					
<i>IL23R</i>	1p31.3		2			2		7				2					4	
<i>IL27</i>	16p11.2							1								1		
<i>IL28RA</i>	1p36.11											1						
<i>IL33</i>	9p24.1				2													
<i>LTBR</i>	12p13.31		1															
<i>TNFSF4</i>	1q25.1														2			
<i>TNFSF11</i>	13q14.11							1										
<i>TNFSF14</i>	19p13.3									1								
<i>TNFSF15</i>	9q32							2									1	
<i>FASLG</i> – <i>TNFSF18</i>	1q24.3						1											
<i>TNFRSF1A</i>	12p13.31									1	1							
<i>TNFRSF6B</i>	20q13.33				1			1									1	
<i>TNFRSF9</i>	1p36.23						1										1	
<i>TNFRSF14</i>	1p36.32						1							2			1	

FIG. 1. GWAS-based identification of cytokine gene loci as risk factors for 17 autoimmune/chronic inflammatory disorders. Included are chemokine and cytokine (receptor) and ligands/receptors of the TNF superfamily. Genes are considered to be associated with a disease, if they contain an associated SNP in the coding/intronic/3' or 5' regulatory sequences, or in the surrounding region within reach of linkage disequilibrium with the gene. Only GWAS and meta-analyses of GWAS that include validation of the associated variant through independent replication were examined. GWAS were accessed via the NHGRI Catalog of Published GWAS (www.genome.gov/gwastudies), and additional searches were performed in PubMed (up to August 2011). Black squares denote association of the gene locus with genome-wide significance, white numbers refer to the times the gene locus has turned up in independent GWAS, be it not necessarily with the same SNPs. Notes: ¹Gene cluster on chr17q12 (pos 29606409–29672532) containing the following contiguous chemokine genes: *CCL2*–*CCL7*–*CCL11*–*CCL8*. ²Gene cluster on chr2q12.1 (position 101974738–102435458) containing the following contiguous cytokine genes: *IL1R2*–*IL1R1*–*IL1RL2*–*IL1RL1*–*IL18R1*–*IL18RAP*. GWAS, genome-wide association studies.

arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), ulcerative colitis (UC), and vitiligo. Figure 1 provides a snapshot of a rapidly changing landscape of identified interleukin and chemokine (receptor) genes and members of the TNF receptor and ligand superfamily. Even if the functional implications of most of these associations are not yet clarified, we are beginning to understand the mechanisms by which associated polymorphisms in interleukin-2 receptor alpha (*IL2RA*), *IL7R*, cytokines belonging to the *IL12* family, and *IL10* may affect immune regulation in autoimmune disease. This review attempts to outline these emerging concepts.

IL2RA

The *IL2RA* and beta (*IL2RB*) chains, in conjunction with the common gamma chain (*IL2RG*), form the heterotrimeric high-affinity cell surface receptor for IL-2, a cytokine with pronounced effects on proliferation of B and T lymphocytes. The *IL2RA* locus was one of the first to emerge from early GWAS as autoimmune risk factor. Thus far, this gene locus

has been ascertained as risk factor for a diverse series of autoimmune diseases including MS (Hafler and others 2007; De Jager and others 2009), T1D (Barrett and others 2009), AA (Petukhova and others 2010), CD (Franke and others 2010), RA (Stahl and others 2010), and vitiligo (Jin and others 2010). Substantial progress has been made toward the characterization of *IL2RA*-associated susceptibility effects, and this has facilitated the elucidation of the discordant association patterns observed across different diseases. Lowe and others (2007) identified within the *IL2RA*-*RBM17* region associated with T1D two independent groups of single nucleotide polymorphisms (SNPs), which were localized to a 40-kb region enclosing intron 1 and the intergenic region located upstream from *IL2RA*. None of the disease-associated SNPs appear to be located in known regulatory regions. Interestingly, T1D-associated allelic variants in both these regions were found to correlate with reduced levels of sIL-2RA, a soluble form of the IL-2RA chain (Lowe and others 2007). Building upon these observations, Maier and others (2009) discovered a third, novel group of SNPs at the *IL2RA* locus associated with T1D, and confirmed the extended

degree of allelic heterogeneity at this autoimmune risk locus. Using a large collection of DNA samples from healthy controls, MS patients, and T1D patients, they found that Group I SNPs are associated with risk for T1D but not risk for MS, Group II SNPs confer susceptibility to T1D but protection from MS, and Group III SNP susceptibility alleles are shared between T1D and MS. The presence of two independent *IL2RA* allelic association signals for MS risk was also observed in an independent study (Cavanillas and others 2010). In addition, serum sIL-2RA levels appeared to be independently associated with SNPs belonging to each of the 3 groups (Maier and others 2009)—indicative for incongruence between sIL-2RA level and *IL2RA*-conferred susceptibility. Dendrou and others (2009) documented a series of phenotypic changes conferred by the different common haplotypes that account for most of the genetic diversity at the *IL2RA* locus. Essentially, *IL2RA* haplotype-specific expression patterns of the IL-2RA receptor showed pronounced differences between the different immune cell subsets analyzed. For rs2104286, a Group III SNP (Maier and others 2009), the protective genotype reduced the likelihood for CD4⁺-naïve T cells to express IL-2RA, thus limiting the extent of activation. On the other hand, the rs12722495 protective Group I genotype led to expression of higher IL-2RA levels on CD4⁺ memory T cells, which may increase their likelihood of activation by IL-2 (Dendrou and others 2009). Simultaneously, IL-2 secretion was observed by a higher proportion of stimulated CD69⁺ CD4⁺ memory T cells from homozygotes for the protective rs12722495 allele than from homozygotes for the susceptible allele. This is consistent with known defects in the production of IL-2 by individuals suffering from T1D (Zier and others 1984). Possibly, IL-2 produced by CD4⁺ memory T cells is required for FOXP3⁺ Treg homeostasis and competitive fitness, but alternatively, a higher expression level of IL-2RA on anti-self effector T cells may be beneficial and protect against MS and T1D through a reinforced sensitivity to activation-induced apoptosis (Willerford and others 1995).

Thus, multiple, complex phenotypic effects are conferred by autoimmune-associated allelic variants at the *IL2RA* locus, and some findings point to previously unrecognized differences and similarities between IL-2/IL-2RA-centered immune pathways in T1D and MS (Dendrou and others 2009). In fact, from a network-based analysis of shared susceptibility genes, *IL2RA* emerged as a powerful factor linking MS to T1D (Baranzini 2009). At any rate, full elucidation of the ultimate molecular basis of these effects is as yet largely unexplored. It is of interest to note that several autoimmune-associated *IL2RA* SNPs disrupt or create CpG dinucleotides, methylation of which may possibly affect transcriptional regulation (Lowe and others 2007). Lastly, epigenetic modifications such as acetylation of promoter nucleosomes are known to modify gene transcription activity, and this process maybe affected by SNPs that influence histone remodeling. Since transcription and chromatin regulatory elements in *IL2RA* are correlated with acetylation islands (Roh and others 2005), the extent to which SNPs may disrupt chromatin modifications and gene activity deserves further scrutiny.

IL7R

The IL-7 receptor alpha-chain is instrumental in V(D)J recombination during lymphocyte development, and regu-

lates access of the TCR γ locus by STAT5. Furthermore, evidence from knockout studies in mice indicates that IL7R blocks apoptosis during differentiation of T lymphocytes. These, and additional, biological activities position IL-7R α as a crucial mediator of naïve and memory T cell homeostasis (Surh and Sprent 2008). A nonsynonymous missense SNP, rs6897932, located in the 6th exon of the *IL7R* gene that changes T244 in I has emerged from GWAS as risk factor for MS (Hafler and others 2007; De Jager and others 2009) and T1D (Todd and others 2007). Haplotype analysis of *IL7R* has shown that rs6897932, or haplotypes including this marker, constitutes the most strongly associated determinant for susceptibility to MS at this locus (Lundmark and others 2007; O'Doherty and others 2008; Vandembroeck and others 2011), suggesting that in contrast to *IL2RA*, susceptibility to MS conferred by *IL7R* is less likely to be driven by complex patterns of allelic heterogeneity. Gregory and others (2007) demonstrated that the presence of the C risk allele of rs6897932 resulted in a 2-fold increase in the skipping of exon 6 in *IL7R* transcripts when compared with transcripts containing the alternate T allele. Exon-6-free transcripts code for a soluble form of the protein (Goodwin and others 1990). The ratio of membrane-bound to soluble IL-7R α is likely to affect T cell responses to myelin proteins in MS via neutralization of IL-7 (Traggiai and others 2001). Analysis of the effect of *IL7R* haplotypes on transcript isoform ratios in different immune cell subsets showed that maximal differences were found in dendritic cells, in which the MS-protective haplotype produced a marked decline in the ratio of soluble to membrane-bound receptor (Hoe and others 2010). Possibly, this altered balance may make dendritic cells more responsive to thymic stromal lymphopoietin (TSLP), a cytokine employing the IL-7R α receptor chain. TSLP-activated dendritic cells regulate the positive selection of regulatory T cells (Ziegler and Liu 2006). TSLP activation of either myeloid or plasmacytoid dendritic cell subsets via IL-7R α is associated with the generation, as well as altered IL-10 and TGF- β cytokine production potential, of FOXP3⁺ regulatory T cells (Hanabuchi and others 2010). Haas and others (2011) found evidence for reduced IL-7R α expression on conventional T cells, increased plasma IL-7 levels, and reduced myeloid dendritic cell TSLPR expression in MS, which may contribute to inhibition of Treg neogenesis in MS, even though these effects seemed not to be associated with rs6897932.

Neither TSLP nor TSLPR has emerged from GWAS as genetic risk factors for MS. However, a large-scale analysis of genes functionally related to the IL-7R α pathway identified *IL7* and *SOCS1* as novel MS risk genes (Zuvich and others 2010). *IL7* was also identified in a recent GWAS in MS (IMSGC and WTCCC2 2011). While *IL7* did not emerge from another independent large-scale study in a Spanish-Basque cohort, *SOCS1* appeared as the single most strongly MS-associated gene out of 44 cytokine/receptor genes scrutinized by means of a haplotype-tagging approach (Vandembroeck and others 2011). IL-7 is crucial in the regulation of expansion of effector Th17 cells in experimental autoimmune encephalomyelitis as well as of Th17 cells in subjects with MS, but has no effect on Th17 differentiation (Liu and others 2010b). Moreover, IL-7R antagonism induced apoptosis of differentiated Th17 cells, but less so of Th1 and regulatory T cells, and these effects were correlated with low levels of IL-7R α presentation on Treg cells and high level of *SOCS1* in Th1 cells (Liu and others 2010b). Importantly, *SOCS1* was

recently found to be required for Treg cell integrity by upholding FOXP3 expression, and this process was associated with suppression of both STAT1-driven IFN- γ expression and STAT3-driven IL-17 production (Takahashi and others 2011). Thus, from these studies has appeared a functional link between IL-7, IL-7R α , and SOCS1 in the regulation and homeostasis of Th17/Th1/Treg cells of relevance to autoimmunity, which seems to be vindicated by the identification of “hard-wired” polymorphisms in the 3 corresponding gene loci that act as susceptibility factors for MS (Zuvich and others 2010; Vandenberg and others 2011). The decipherment of how these polymorphisms potentially intersect to change the phenotypic behavior of helper and regulatory T cell function in MS remains for now an important and exciting challenge.

Autoimmune Risk Factors Belonging to the IL-12 Family of Heterodimeric Cytokines: IL12A, IL12B, IL12RB2, IL23A, IL23R, and IL27

IL-12, a heterodimeric cytokine composed of disulfide-bonded p35 (coded for by *IL12A*) and p40 subunits (coded for by *IL12B*), is of crucial relevance to cell-mediated immunity and Th1 differentiation (Collison and Vignali 2008). IL-12 has been implicated in the pathogenesis of a multitude of diverse autoimmune diseases (reviewed by Kastelein and others 2007; and by Paunovic and others 2008) and exerts its biological effects via binding to a heterodimeric receptor consisting of IL-12R β 2 and IL-12R β 1 subunits. Three of the genes coding for proteins involved in the initial stages of the IL-12 binding and signaling cascade, that is, *IL12A*, *IL12B* and *IL12RB2*, have emerged as risk factors from GWAS on a variety of autoimmune disorders (Figure 1, Table 1), though the precise patterns of diseases associated with each of the 3 genes overlap only partially. For *IL12A*, the MS-associated risk allele was reported to be protective in CeD (De Jager and others 2009; IMSCG 2010). The MS- and CeD-associated *IL12A* risk SNPs are located 5' from the gene in the same haplotype block, and show only limited correlation with the PBC-associated risk SNPs located 3' from the gene in a distinct haplotype block (Hunt and others 2008; IMSCG 2010; Liu and others 2010a). To date, *IL12RB2* has emerged only as risk factor for PBC, with the reported top associated SNPs mainly located in intronic sequences (Hirschfield and others 2009; Liu and others 2010a; Mells and others 2011). *IL12B* has been identified in GWAS on 6 autoimmune conditions, and the majority of reported risk SNPs are located 5' from the *IL12B* gene at varying positions (Table 1). Whereas alternative splice variants for both *IL12RB2* and *IL12A* are documented in the Ensembl database (www.ensembl.org), no such variants are recorded for *IL12B*. However, promoter polymorphisms of the *IL12B* gene that influence its regulation of expression have been reported (Müller-Berghaus and others 2004). Very recently, a distal enhancer located at 10 kb 5' from the transcription start of *il12b* was found to be targeted for transcriptional repression by the basic leucine zipper protein, nuclear factor interleukin-3 regulated (NFIL3) (Smith and others 2011; Kobayashi and others 2011). *Nfil3*-knockout mouse spontaneously transcribe *il12b* mRNA in colonic lamina propria mononuclear cells (Kobayashi and others 2011), and myeloid cells lacking NFIL3 produce higher amounts of both the p40 subunit and IL-12 (Smith and others 2011). Of interest, NFIL3 expression levels were lower

in lamina propria mononuclear cells from CD and UC patients respective to control subjects (Kobayashi and others 2011). The *NFIL3* gene has not been reported as risk factor for autoimmunity. However, the NFIL3 regulatory pathway may present a promising target for analysis of the potential effects of autoimmune risk SNPs located 5' to the *IL12B* gene on expression regulation mediated by NFIL3.

Like IL-12, IL-23 is a heterodimeric cytokine that shares the former's p40 subunit, this time covalently linked to a p19 subunit (coded for by *IL23A*). It is mainly produced by dendritic cells and macrophages, and, in conjunction with IL-6 and TGF- β 1, plays a pivotal role in the induction of Th17 cells and secretion of lineage-specific IL-17A (Betelli and others 2008). These effects are initiated via the engagement of IL-23 with a heterodimeric receptor consisting of IL-23R and IL-12R β 1 subunits, which leads to phosphorylation of STAT3 and further downstream signaling events (Paunovic and others 2008). Silencing of the *il23a* gene or selective targeting of IL-23 inhibits inflammation in experimental animal models of MS (Cua and others 2003), RA (Murphy and others 2003), IBD (Hue and others 2006), as well as psoriasis development in a clinically relevant xenotransplant mouse psoriasis model (Tonel and others 2010). Set against this background of immunological evidence, the identification of the *IL23R* gene locus as risk factor for 5 autoimmune conditions based on 17 GWAS is, perhaps, not entirely unexpected (Table 1, Figure 1). The most frequently encountered peak SNP at this locus is rs11209026, which is associated with 4 autoimmune diseases. The rs11209026 is a non-synonymous G>A SNP that changes R381, located in the cytoplasmic domain of IL-23R, into Q. The Q allele is much less common than the R allele and has an allele frequency <9% in each of the 10 HapMap reference populations analyzed to date. The R and Q alleles function, respectively, as risk and protective factors for AS, UC, CD, and psoriasis (Table 1). Recent attempts at elucidating the functional repercussions of this amino acid substitution have revealed that the 381Q variant does not affect Th17 cell differentiation, but reduces Th17 effector response by limiting IL-23-induced IL-17A production and STAT3 phosphorylation (Di Meglio and others 2011). Sarin and others (2011) found that the 381Q variant impaired IL-23-dependent CD8+ T cell expansion and STAT3 activation, and reduced IL-17 and IL-22 levels in CD4+ and CD8+ T cells. In general, these observations are reconcilable with a role for *IL23R* R381Q in IL-17A-induced peripheral tissue pathology rather than systemic inflammation (Di Meglio and others 2011).

The *IL23R* gene has also been implicated in BD based on both Japanese and Turkish GWAS (Mizuki and others 2010; Remmers and others 2010). The R381Q SNP, rs11209026, appeared monomorphic in the Japanese population, and did not emerge from the Turkish GWAS. However, both studies coincided in locating the peak association signal at around 30 kb 3' from the *IL23R* gene on the *IL23R* side of a recombination hotspot separating the *IL23R* and *IL12RB2* haplotype blocks. Of relevance to this finding is the observation that noncoding *IL23R* SNPs that are not or only weakly correlated with rs11209026 have been reported to constitute residual, independent risk variants for other autoimmune disorders including IBD/UC (Duerr and others 2006; Silverberg and others 2009; McGovern and others 2010), psoriasis (Nair and others 2009), and AS (Evans and others 2011). Possibly, the functional implications of these secondary

signals maybe related to the complex splicing strategies utilized by the *IL23R* gene. At least six alternatively spliced naturally occurring mRNA isoforms of *IL23R* have been reported, that can result in premature termination producing a different receptor ectodomain or a frame shift that modifies the lengths of the endodomain (Zhang and others 2006). Kan and others (2008) reported up to 24 different *IL23R* transcripts in activated human leukocytes, including 4 prematurely terminated isoforms. Exon-9 deletion transcripts have been identified that code for a truncated receptor containing the complete ectodomain. This soluble variant is secreted and functions as IL-23 antagonist by intercepting the cytokine and inhibiting IL-23-mediated STAT3 phosphorylation and production of the Th17 cytokines IL-17A and IL-17F (Yu and Gallagher 2010).

Notwithstanding functional indications for a role of the IL-23/Th17 axis in neuroinflammation (Becher and others, 2011), *IL23R* polymorphisms appear not to be associated with overall risk for MS (Begovich and others 2007; Roos and others 2008; Vandenbroeck and others 2011), even though two studies have suggested a modest, although differential, impact on clinical course of the disease (Illes and others 2008; Núñez and others 2008). Taken in conjunction with the lack of efficacy in a phase II trial of RR MS of ustekinumab (Segal and others 2008), an antibody neutralizing the p40 subunit shared by IL-23 and IL-12 that was shown to be highly effective in psoriasis (Leonardi and others 2008) and promising in CD (Sandborn and others 2008), this data sheds doubt on the pathogenetic role of IL-12 and IL-23 in MS (Martin 2008). Though the final verdict will depend on further mechanistic studies, the validated association of the *IL12A* and *IL12B* genes with risk for MS (De Jager and others 2009; IMSGC and WTCCC2 2011) seems to affirm the IL-12 pathway in MS. However, as the *IL12A*-encoded p35 subunit can associate with EBI3 (coded for by *IL27B*) to form the T cell regulatory cytokine IL-35 (Collison and others 2007), the currently undocumented role of IL-35 in neuroinflammation and MS will have to be resolved so as to factor it in into the overall phenotypic manifestation of *IL12A*-conferred genetic risk. In addition, the *IL12B*-encoded p40 subunit can homodimerize to form a cytokine with both antagonistic and agonistic activities mediated by binding to the IL-12Rβ1 chain only (reviewed by Brombacher and others 2003). While only limited data are available on the agonist role of (p40)₂ in neuroinflammation, the observation that (p40)₂ induces expression of iNOS and lymphotoxin-α in microglia is suggestive for a causative role in the pathogenesis of neuroinflammatory processes (Jana and others 2009; Jana and Pahan 2009). There are no records as to whether ustekinumab binds and neutralizes the (p40)₂ homodimer. Consequently, the ascertainment of *IL12A* and *IL12B* as genetic risk factors for MS could well point to IL-35- and (p40)₂-associated effector processes that work beyond the classical IL-12 (Th1)/IL-23 (Th17) paradigms and that are reconcilable with both the observed lack of therapeutic benefit of ustekinumab in MS and of evidence for a role of *IL23R* in genetic risk.

An SNP located in an intronic sequence of the *STAT2* gene located 3.7kb downstream from *IL23A* was found to be associated with risk for psoriasis (Nair and others 2009). Though its functional effects are as yet unknown, highly significant differences in *IL23A* expression levels between involved and uninvolved skin biopsies, and between normal

skins from controls and uninvolved skin from cases were observed (Nair and others 2009). Taken in conjunction with the identification of *IL23R* and *IL12B* as additional risk genes for this disease, psoriasis appears to come forth as the single autoimmune disease with the clearest genetic impact of the IL-23 pathway on its pathogenesis. Finally, SNPs located in the region of the *IL27* gene that codes for the p28 subunit known to heterodimerize with the EBI3 subunit to form the highly pleiotropic regulatory cytokine IL-27 (Collison and Vignali 2008) were found to be associated with risk for T1D (Barrett and others 2009) and CD (Franke and others 2010). Since this region is very gene dense, it remains to be seen whether these SNPs impact *de facto* upon IL-27 regulation or biology.

***IL10*, and Opposite Autoimmune Risk Alleles**

Polymorphisms within or near many other cytokine and chemokine gene loci have been implicated in a wide array of different autoimmune diseases through GWAS (Table 1). Of these, a few stand out with reproducible patterns of association. A potent antiinflammatory cytokine, IL-10, is known to be an essential immunoregulator of inflammatory processes in the intestinal tract (Steidler and others 2000) and inhibits the costimulatory activity of macrophages on T cell activation. In two GWAS on BD, promoter and intronic variants in *IL10* emerged with genome-wide significance (Remmers and others 2010; Mizuki and others 2010). The associated rs1518111 variant was associated with altered mRNA transcription and protein expression (Remmers and others 2010). BD was not associated with rs3024505, an SNP that has been linked to various autoimmune diseases (see next paragraph), indicating a different IL-10-related causative pathway (Remmers and others 2010) substantiated by the absence of correlation between the BD-associated SNPs and rs3024505 ($r^2 \cong 0.07$).

The T allele of the rs3024505 SNP, which is located close to the 3' untranslated region of *IL10*, has emerged as a risk factor for UC (Franke and others 2008), CD (Franke and others 2010), and SLE (Gateva and others 2009). Interestingly, the T allele of rs3024505 protects against T1D (Wang and others 2010). This sharing of opposite risk alleles across a spectrum of autoimmune diseases is not restricted to *IL10* and extends to other well-documented autoimmune risk loci such as the MHC region, the R602W variant in *PTPN22*, as well as other cytokine loci (Wang and others 2010). For instance, rs4788084 located 5' from *IL27* and rs917997 located 3' from *IL18RAP* show opposite patterns of association with IBD versus T1D (Wang and others 2010), and similarly, opposite association patterns have been recorded for rs11594656 located 5' from *IL2RA* with MS versus T1D (discussed in the section on *IL2RA*; Maier and others 2009), and for an intronic SNP in *IL23R*, rs2201841, in susceptibility to psoriasis versus UC (Nair and others 2009; McGovern and others 2010). This data raises the question as to the evolutionary forces and selection pressures that have driven maintenance of these alleles in the human population. Indeed, as either of both alleles at these risk loci is unfavorable by predisposing to a different disease, the question arises under which circumstances they do confer evolutionary advantages. Since gene variants associated with complex traits contribute only little to overall disease risk, autoimmune disease itself is unlikely to have acted as selective pressure

(Barreiro and Quintana-Murci 2010). Susceptibility loci for autoimmune diseases have been suggested to occur under a balancing selection, by which multiple alleles are actively perpetuated in the gene pool at high frequencies through interactions with heterogeneous environmental factors (Wang and others 2010). This does not necessarily reflect heterozygosity advantage but could be the result of competition between diverse immune pathways to control distinct infectious pathogens. A signature for balancing selection was identified at the *IL10* promoter locus (Wilson and others 2006). A seminal population genetics study analyzing 91 cytokine/receptor genes demonstrated that five IL genes, including the established autoimmune risk genes *IL7R* and *IL18RAP*, have been possible targets of pathogen-driven balancing selection (Fumagalli and others 2009). Allelic variation at these loci may have been maintained by balancing selection achieved through antagonistic pleiotropic effects. However, analysis of 11 autoimmune risk loci with opposite risk alleles confined balancing selection largely to the extended MHC region, and suggested that the observed level of nucleotide diversity at most of these loci, including *IL10*, is consistent with evolutionary neutrality (Cagliani and others 2011). According to this theory, evolutionary changes are caused by random drift of neutral allelic variants that impact little or not upon fitness. In some cases, opposite patterns of allelic association maybe brought about by underlying complex haplotype structures in gene areas with pronounced genetic diversity (Cagliani and others 2011).

Other Cytokine Risk Loci

Of the large family of chemokine and their receptors, the *CCR6* gene region in particular leaps out through multiple associations with risk for RA (Stahl and others 2010), CD (Barrett and others 2008), vitiligo (Quan and others 2010), and GD (Chu and others 2011). In a Japanese population, Kochi and others (2010) identified a triallelic dinucleotide polymorphism in strong LD with the RA-associated *CCR6* promoter risk variant rs3093024 that affects transcription regulation and is correlated with *CCR6* expression levels and IL-17+ status of RA cases. The rs3093024 is in virtually perfect LD with the nearby SNP rs3093023 ($r^2=1$), that is, the *CCR6* RA risk variant identified in a GWAS based on patients and controls of European ancestry (Stahl and others 2010). *CCR6* is a cell surface marker for Th17 cells (Annunziato and others 2007). Synovial cells from arthritic joints of mice and humans secrete large amounts of the chemokine CCL20, the ligand of *CCR6*, which controls the migration of arthritogenic *CCR6*+ Th17 cells to the inflamed tissues (Hirota and others 2007). Though other additional mechanisms may pertain to *CCR6*-associated risk for autoimmune disease, *CCR6*-driven Th17 cell recruitment to inflammatory lesions constitutes an attractive working model that is worthy of further scrutiny in CD (Brand 2009) and vitiligo (Wang and others 2011).

Finally, a multitude of SNPs in regions encompassing more than 8 genes belonging to the tumor necrosis factor receptor (TNFR) superfamily and its ligands has emerged from GWAS in 7 autoimmune diseases (Figure 1). However, so far little mechanistic information is available explaining the functional consequences of the genetic basis of these associations. Interactions between TNF superfamily receptors expressed on T cells and TNF-like ligands have wide-ranging implications on

inflammatory processes by affecting T cell stimulation, communication between T cell subsets, and amplification of inflammatory responses via non-T cells (Croft 2009).

Concluding Remarks

Since 2007, a rapidly expanding series of GWAS diseases has identified and validated numerous cytokine/receptor gene loci as autoimmune risk factors. It is important to note that the majority of the associated DNA variants are unlikely to constitute the ultimate causative risk factors of disease, but have probably emerged as a consequence of linkage disequilibrium with the actual causative variant. One of the main challenges for the near future therefore will be the fine mapping of each associated locus with dense panels of markers. Through linkage disequilibrium, some autoimmune-associated variants located within or close to cytokine gene loci may, as well, impact upon the functional genomics of neighboring, noncytokine genes located in the same haplotype block. In addition, uncommon variants with large effect size could explain part of the hidden heritability of autoimmune diseases. Rare variants tend to be underrepresented in current databases as well as in commercially available genome-wide SNP arrays (Oksenberg and Baranzini 2010) and their identification may require deep sequencing of DNA from patients, an option that is rapidly becoming a cost-effective perspective. Further understanding of causality will be dependent on functional studies that link allelic variants with biological processes, which will help to explain disease-specific pathophysiological manifestations.

For the purpose of this review, literature survey was confined to cytokine/receptor genes. The phenotypic effects of polymorphisms in these genes cannot be uncoupled from those of other autoimmune risk loci if we wish to gain comprehensive insights. Epistatic interactions will need to be addressed and may refine and expand current concepts of cytokine-centered pathways. One of the most important findings from current GWAS, which is particularly true with regard to cytokine/receptor genes, is the sharing of cytokine genes and allelic variants across a wide spectrum of autoimmune diseases. Whereas this clearly indicates that common underlying pathogenetic mechanisms exist, the reality might be more complex. For many of the gene loci covered in this review including, but not limited to, *IL2RA*, *IL10*, *IL23R*, and *IL7R*, association signals for one autoimmune disease appear not to be correlated with those found for other such conditions at the same locus. For some autoimmune diseases, secondary association signals are found within a cytokine gene locus that are uncorrelated with the primary signal at the same locus. Opposite risk alleles are documented to occur at the *IL10*, *IL23R*, *IL2RA* and *IL18RAP* loci. This global picture may reflect the complex genetic architecture and modularity of human autoimmune diseases, and several strategies have already been developed to define the unique and shared gene assortments for autoimmune diseases (Baranzini 2009; Sirota and others 2009).

Traditional pre-GWAS candidate gene approaches have highlighted numerous genetic associations between cytokine genes and risk for, or clinical parameters of, autoimmune diseases, and many of these associations may remain valid even if their effects are modest (for review see Goris and Vandenbroeck 2003; Vandenbroeck 2006). However, GWAS rather than candidate gene approaches have provided the

power and resolution to unequivocally pin down those cytokine/receptor genes that affect susceptibility with genome-wide significance. For the cytokine biologist, a treasure trove of new information is now available that may act as a powerful guide to further research into the functional and immunological ramifications of these associations.

Author Disclosure Statement

No competing financial interests exist.

References

- Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, Lee JC, Goyette P, Imielinski M, Latiano A, Lagacé C, Scott R, Amininejad L, Bumpstead S, Baidoo L, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Colombel JF, Denson LA, De Vos M, Dubinsky M, Edwards C, Ellinghaus D, Fehrmann RS, Floyd JA, Florin T, Franchimont D, Franke L, Georges M, Glas J, Glazer NL, Guthery SL, Haritunians T, Hayward NK, Hugot JP, Jobin G, Laukens D, Lawrance I, Lémann M, Levine A, Libioulle C, Louis E, McGovern DP, Milla M, Montgomery GW, Morley KI, Mowat C, Ng A, Newman W, Ophoff RA, Papi L, Palmieri O, Peyrin-Biroulet L, Panés J, Phillips A, Prescott NJ, Proctor DD, Roberts R, Russell R, Rutgeerts P, Sanderson J, Sans M, Schumm P, Seibold F, Sharma Y, Simms LA, Seielstad M, Steinhart AH, Targan SR, van den Berg LH, Vatn M, Verspaget H, Walters T, Wijmenga C, Wilson DC, Westra HJ, Xavier RJ, Zhao ZZ, Ponsioen CY, Andersen V, Torkvist L, Gazouli M, Anagnou NP, Karlsen TH, Kupcinskas L, Sventoraityte J, Mansfield JC, Kugathasan S, Silverberg MS, Halfvarson J, Rotter JI, Mathew CG, Griffiths AM, Gearry R, Ahmad T, Brant SR, Chamaillard M, Satsangi J, Cho JH, Schreiber S, Daly MJ, Barrett JC, Parkes M, Annesse V, Hakonarson H, Radford-Smith G, Duerr RH, Vermeire S, Weersma RK, Rioux JD. 2011. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet* 43: 246–252.
- Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, Parente E, Fili L, Ferri S, Frosali F, Giudici F, Romagnani P, Parronchi P, Tonelli F, Maggi E, Romagnani S. 2007. Phenotypic and functional features of human Th17 cells. *J Exp Med* 204:1849–1861.
- Baranzini SE. 2009. The genetics of autoimmune diseases: a networked perspective. *Curr Opin Immunol* 21:596–605.
- Barreiro LB, Quintana-Murci L. 2010. From evolutionary genetics to human immunology: how selection shapes host defence genes. *Nat Rev Genet* 11:17–30.
- Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, Julier C, Morahan G, Nerup J, Nierras C, Plagnol V, Pociot F, Schuilenburg H, Smyth DJ, Stevens H, Todd JA, Walker NM, Rich SS; Type 1 Diabetes Genetics Consortium. 2009. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet* 41:703–707.
- Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bittan A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhart AH, Targan SR, Xavier RJ; NIDDK IBD Genetics Consortium, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P, Van Gossum A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E; Belgian-French IBD Consortium; Wellcome Trust Case Control Consortium, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghorri J, Bumpstead S, Gwilliam R, Tremelling M, Deloukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ. 2008. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 40:955–962.
- Becher B, Segal BM. 2011. T(H)17 cytokines in autoimmune neuroinflammation. *Curr Opin Immunol* 23:707–712.
- Begovich AB, Chang M, Caillier SJ, Lew D, Catanese JJ, Wang J, Hauser SL, Oksenberg JR. 2007. The autoimmune disease-associated IL12B and IL23R polymorphisms in multiple sclerosis. *Hum Immunol* 68:934–937.
- Betelli E, Korn T, Oukka M, Kuchroo VK. 2008. Induction and effector functions of T(H)17 cells. *Nature* 453:1051–1057.
- Brand S. 2009. Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. *Gut* 58:1152–1167.
- Brombacher F, Kastelein RA, Alber G. 2003. Novel IL-12 family members shed light on the orchestration of Th1 responses. *Trends Immunol* 24:207–212.
- Cagliani R, Riva S, Pozzoli U, Fumagalli M, Comi GP, Bresolin N, Clerici M, Sironi M. 2011. Balancing selection is common in the extended MHC region but most alleles with opposite risk profile for autoimmune diseases are neutrally evolving. *BMC Evol Biol* 11:171.
- Cavanillas ML, Alcina A, Núñez C, de las Heras V, Fernández-Arquero M, Bartolomé M, de la Concha EG, Fernández O, Arroyo R, Matesanz F, Urcelay E. 2010. Polymorphisms in the IL2, IL2RA and IL2RB genes in multiple sclerosis risk. *Eur J Hum Genet* 18:794–799.
- Chu X, Pan CM, Zhao SX, Liang J, Gao GQ, Zhang XM, Yuan GY, Li CG, Xue LQ, Shen M, Liu W, Xie F, Yang SY, Wang HF, Shi JY, Sun WW, Du WH, Zuo CL, Shi JX, Liu BL, Guo CC, Zhan M, Gu ZH, Zhang XN, Sun F, Wang ZQ, Song ZY, Zou CY, Sun WH, Guo T, Cao HM, Ma JH, Han B, Li P, Jiang H, Huang QH, Liang L, Liu LB, Chen G, Su Q, Peng YD, Zhao JJ, Ning G, Chen Z, Chen JL, Chen SJ, Huang W, Song HD. 2011. A genome-wide association study identifies two new risk loci for Graves' disease. *Nat Genet* 43:897–901.
- Collison LW, Vignali DAA. 2008. Interleukin-35: odd one out or part of the family? *Immunol Rev* 226:248–262.
- Collison LW, Workman CJ, Kuo TT, Boyd K, Wang Y, Vignali KM, Cross R, Sehy D, Blumberg RS, Vignali DA. 2007. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. *Nature* 450:566–569.
- Croft M. 2009. The role of TNF superfamily members in T-cell function and diseases. *Nat Rev Immunol* 9:271–285.
- Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, Lucian L, To W, Kwan S, Churakova T, Zurawski S, Wiekowski M, Lira SA, Gorman D, Kastelein RA, Sedgwick JD. 2003. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* 421:744–748.
- De Jager PL, Jia X, Wang J, de Bakker PI, Ottoboni L, Aggarwal NT, Piccio L, Raychaudhuri S, Tran D, Aubin C, Briskin R, Romano S; International MS Genetics Consortium, Baranzini SE, McCauley JL, Pericak-Vance MA, Haines JL, Gibson RA, Naeglin Y, Uitendhaag B, Matthews PM, Kappos L, Polman A, McArdle WL, Strachan DP, Evans D, Cross AH, Daly MJ, Compston A, Sawcer SJ, Weiner HL, Hauser SL, Hafler DA, Oksenberg JR. 2009. Meta-analysis of genome scans and replication identify CD6, IRF8 and TNFRSF1A as new multiple sclerosis susceptibility loci. *Nat Genet* 41:776–782.

- Dendrou CA, Plagnol V, Fung E, Yang JH, Downes K, Cooper JD, Nutland S, Coleman G, Himsworth M, Hardy M, Burren O, Healy B, Walker NM, Koch K, Ouwehand WH, Bradley JR, Wareham NJ, Todd JA, Wicker LS. 2009. Cell-specific protein phenotypes for the autoimmune locus IL2RA using a genotype-selectable human bioresource. *Nat Genet* 41:1011–1015.
- Di Meglio P, Di Cesare A, Laggner U, Chu CC, Napolitano L, Villanova F, Tosi I, Capon F, Trembath RC, Peris K, Nestle FO. 2011. The IL23R R381Q gene variant protects against immune-mediated diseases by impairing IL-23-induced Th17 effector response in humans. *PLoS One* 6:e17160.
- Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhardt AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barmada MM, Rotter JI, Nicolae DL, Cho JH. 2006. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 314:1461–1463.
- Ellinghaus E, Ellinghaus D, Stuart PE, Nair RP, Debrus S, Raelson JV, Belouchi M, Fournier H, Reinhard C, Ding J, Li Y, Tejasvi T, Gudjonsson J, Stoll SW, Voorhees JJ, Lambert S, Weidinger S, Eberlein B, Kunz M, Rahman P, Gladman DD, Gieger C, Wichmann HE, Karlsen TH, Mayr G, Albrecht M, Kabelitz D, Mrowietz U, Abecasis GR, Elder JT, Schreiber S, Weichenthal M, Franke A. 2010. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. *Nat Genet* 42:991–995.
- Evans DM, Spencer CC, Pointon JJ, Su Z, Harvey D, Kochan G, Oppermann U, Dilthey A, Pirinen M, Stone MA, Appleton L, Moutsianas L, Leslie S, Wordsworth T, Kenna TJ, Karaderi T, Thomas GP, Ward MM, Weisman MH, Farrar C, Bradbury LA, Danoy P, Inman RD, Maksymowych W, Gladman D, Rahman P; Spondyloarthritis Research Consortium of Canada (SPARCC), Morgan A, Marzo-Ortega H, Bowness P, Gaffney K, Gaston JS, Smith M, Bruges-Armas J, Couto AR, Sorrentino R, Paladini F, Ferreira MA, Xu H, Liu Y, Jiang L, Lopez-Larrea C, Díaz-Peña R, López-Vázquez A, Zayats T, Band G, Belenguez C, Blackburn H, Blackwell JM, Bramon E, Bumpstead SJ, Casas JP, Corvin A, Craddock N, Deloukas P, Dronov S, Duncanson A, Edkins S, Freeman C, Gillman M, Gray E, Gwilliam R, Hammond N, Hunt SE, Jankowski J, Jayakumar A, Langford C, Liddle J, Markus HS, Mathew CG, McCann OT, McCarthy MI, Palmer CN, Peltonen L, Plomin R, Potter SC, Rautanen A, Ravindrarajah R, Ricketts M, Samani N, Sawcer SJ, Strange A, Trembath RC, Viswanathan AC, Waller M, Weston P, Whittaker P, Widaa S, Wood NW, McVean G, Reveille JD, Wordsworth BP, Brown MA, Donnelly P; Australo-Anglo-American Spondyloarthritis Consortium (TASC); Wellcome Trust Case Control Consortium 2 (WTCCC2). 2011. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nat Genet* 43:761–767.
- Franke A, Balschun T, Karlsen TH, Sventoraityte J, Nikolaus S, Mayr G, Domingues FS, Albrecht M, Nothnagel M, Ellinghaus D, Sina C, Onnie CM, Weersma RK, Stokkers PC, Wijmenga C, Gazouli M, Strachan D, McArdle WL, Vermeire S, Rutgeerts P, Rosenstiel P, Krawczak M, Vatn MH; IBSEN Study Group, Mathew CG, Schreiber S. 2008. Sequence variants in IL10, APRC2 and multiple other loci contribute to ulcerative colitis susceptibility. *Nat Genet* 40:1319–1323.
- Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, Anderson CA, Bis JC, Bumpstead S, Ellinghaus D, Festen EM, Georges M, Green T, Haritunians T, Jostins L, Latiano A, Mathew CG, Montgomery GW, Prescott NJ, Raychaudhuri S, Rotter JI, Schumm P, Sharma Y, Simms LA, Taylor KD, Whiteman D, Wijmenga C, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Cohen A, Colombel JF, Cottone M, Stronati L, Denson T, De Vos M, D'Inca R, Dubinsky M, Edwards C, Florin T, Franchimont D, Garry R, Glas J, Van Gossom A, Guthery SL, Halfvarson J, Verspaget HW, Hugot JP, Karban A, Laukens D, Lawrance I, Lemann M, Levine A, Libioulle C, Louis E, Mowat C, Newman W, Panés J, Phillips A, Proctor DD, Regueiro M, Russell R, Rutgeerts P, Sanderson J, Sans M, Seibold F, Steinhardt AH, Stokkers PC, Torkvist L, Kullak-Ublick G, Wilson D, Walters T, Targan SR, Brant SR, Rioux JD, D'Amato M, Weersma RK, Kugathasan S, Griffiths AM, Mansfield JC, Vermeire S, Duerr RH, Silverberg MS, Satsangi J, Schreiber S, Cho JH, Annesse V, Hakonarson H, Daly MJ, Parkes M. 2010. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet* 42:1118–1125.
- Fumagalli M, Pozzoli U, Cagliani R, Comi GP, Riva S, Clerici M, Bresolin N, Sironi M. 2009. Parasites represent a major selective force for interleukin genes and shape the genetic predisposition to autoimmune conditions. *J Exp Med* 206:1395–1408.
- Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X, Ortmann W, Kosoy R, Ferreira RC, Nordmark G, Gunnarsson I, Svenungsson E, Padyukov L, Sturfelt G, Jönsen A, Bengtsson AA, Rantapää-Dahlqvist S, Baechler EC, Brown EE, Alarcón GS, Edberg JC, Ramsey-Goldman R, McGwin G Jr., Reveille JD, Vilá LM, Kimberly RP, Manzi S, Petri MA, Lee A, Gregersen PK, Seldin MF, Rönnblom L, Criswell LA, Syvänen AC, Behrens TW, Graham RR. 2009. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. *Nat Genet* 41:1228–1233.
- Goodwin RG, Friend D, Ziegler SF, Jerzy R, Falk BA, Gimpel S, Cosman D, Dower SK, March CJ, Namen AE, et al. 1990. Cloning of the human and murine interleukin-7 receptors: demonstration of a soluble form and homology to a new receptor superfamily. *Cell* 60:941–951.
- Goris A, Vandenbroeck K. 2003. Cytokine gene polymorphisms in multifactorial diseases: gateways to novel targets for immunotherapy? *Trends Pharmacol Sci* 24:284–289.
- Gregory SG, Schmidt S, Seth P, Oksenberg JR, Hart J, Prokop A, Caillier SJ, Ban M, Goris A, Barcellos LF, Lincoln R, McCauley JL, Sawcer SJ, Compston DA, Dubois B, Hauser SL, Garcia-Blanco MA, Pericak-Vance MA, Haines JL; Multiple Sclerosis Genetics Group. 2007. Interleukin 7 receptor alpha chain (IL7R) shows allelic and functional association with multiple sclerosis. *Nat Genet* 39:1083–1091.
- Haas J, Korporal M, Schwarz A, Balint B, Wildemann B. 2011. The interleukin-7 receptor α chain contributes to altered homeostasis of regulatory T cells in multiple sclerosis. *Eur J Immunol* 41:845–853.
- Hafler DA, Compston A, Sawcer S, Lander ES, Daly MJ, De Jager PL, de Bakker PI, Gabriel SB, Mirel DB, Ivinson AJ, Pericak-Vance MA, Gregory SG, Rioux JD, McCauley JL, Haines JL, Barcellos LF, Cree B, Oksenberg JR, Hauser SL. 2007. Risk alleles for multiple sclerosis identified by a genome-wide study. *N Eng J Med* 357:851–862.
- Hanabuchi S, Ito T, Park WR, Watanabe N, Shaw JL, Roman E, Arima K, Wang YH, Voo KS, Cao W, Liu YJ. 2010. Thymic stromal lymphopoietin-activated plasmacytoid dendritic cells induce the generation of FOXP3+ regulatory T cells in human thymus. *J Immunol* 184:2999–3007.
- Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS, Manolio TA. 2009. Potential etiologic and func-

- tional implications of genome-wide association loci for human diseases and traits. *Proc Natl Acad Sci U S A* 106:9362–9367.
- Hirota K, Yoshitomi H, Hashimoto M, Maeda S, Teradaira S, Sugimoto N, Yamaguchi T, Nomura T, Ito H, Nakamura T, Sakaguchi N, Sakaguchi S. 2007. Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. *J Exp Med* 204:2803–2812.
- Hirschfield GM, Liu X, Xu C, Lu Y, Xie G, Lu Y, Gu X, Walker EJ, Jing K, Juran BD, Mason AL, Myers RP, Peltekian KM, Ghent CN, Coltescu C, Atkinson EJ, Heathcote EJ, Lazaridis KN, Amos CI, Siminovitch KA. 2009. Primary biliary cirrhosis associated with HLA, IL12A and IL12RB2 variants. *N Eng J Med* 360:2544–2555.
- Hoe E, McKay FC, Schibeci SD, Gandhi K, Heard RN, Stewart GJ, Booth DR. 2010. Functionally significant differences in expression of disease-associated IL-7 receptor alpha haplotypes in CD4 T cells and dendritic cells. *J Immunol* 184:2512–2517.
- Hue S, Ahern P, Buonocore S, Kullberg MC, Cua DJ, McKenzie BS, Powrie F, Maloy KJ. 2006. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. *J Exp Med* 203:2473–2483.
- Hüffmeier U, Uebe S, Ekici AB, Bowes J, Giardina E, Korendowycz E, Juneblad K, Apel M, McManus R, Ho P, Bruce IN, Ryan AW, Behrens F, Lascorz J, Böhm B, Traupe H, Lohmann J, Gieger C, Wichmann HE, Herold C, Steffens M, Klareskog L, Wienker TF, Fitzgerald O, Alenius GM, McHugh NJ, Novelli G, Burkhardt H, Barton A, Reis A. 2010. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. *Nat Genet* 42: 996–999.
- Hunt KA, Zhernakova A, Turner G, Heap GA, Franke L, Bruinenberg M, Romanos J, Dinesen LC, Ryan AW, Panesar D, Gwilliam R, Takeuchi F, McLaren WM, Holmes GK, Howdle PD, Walters JR, Sanders DS, Playford RJ, Trynka G, Mulder CJ, Mearin ML, Verbeek WH, Trimble V, Stevens FM, O'Morain C, Kennedy NP, Kelleher D, Pennington DJ, Strachan DP, McArdle WL, Mein CA, Wapenaar MC, Deloukas P, McGinnis R, McManus R, Wijmenga C, van Heel DA. 2008. Newly identified genetic risk variants for celiac disease related to the immune response. *Nat Genet* 40:395–402.
- Illes Z, Safrany E, Peterfalvi A, Magyari L, Farago B, Pozsonyi E, Rozsa C, Komoly S, Melegh B. 2008. 3'UTR C2370A allele of the IL-23 receptor gene is associated with relapsing-remitting multiple sclerosis. *Neurosci Lett* 431:36–38.
- IMSGC. 2010. IL12A, MPHOSPH9/CDK2AP1 and RGS1 are novel multiple sclerosis susceptibility loci. *Genes Immun* 11:397–405.
- IMSGC, WTCCC2. 2011. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* 476:214–219.
- Jana M, Dasgupta S, Pal U, Pahan K. 2009. IL-12 p40 homodimer, the so-called biologically inactive molecule, induces nitric oxide synthase in microglia via IL-12R beta 1. *Glia* 57:1553–1565.
- Jana M, Pahan K. 2009. Induction of lymphotoxin-alpha by interleukin-12 p40 homodimer, the so-called biologically inactive molecule, but not IL-12 p70. *Immunology* 127:312–325.
- Jin Y, Birlea SA, Fain PR, Gowan K, Riccardi SL, Holland PJ, Mailloux CM, Sufit AJ, Hutton SM, Amadi-Myers A, Bennett DC, Wallace MR, McCormack WT, Kemp EH, Gawkrödger DJ, Weetman AP, Picardo M, Leone G, Taïeb A, Jouary T, Ezzedine K, van Geel N, Lambert J, Overbeck A, Spritz RA. 2010. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. *N Eng J Med* 362:1686–1697.
- Kan SH, Mancini G, Gallagher G. 2008. Identification and characterization of multiple splice forms of the human interleukin-23 receptor alpha chain in mitogen-activated leukocytes. *Genes Immun* 9:631–639.
- Kastelein RA, Hunter CA, Cua DJ. 2007. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. *Annu Rev Immunol* 25: 221–242.
- Kobayashi T, Matsuoka K, Sheikh SZ, Elloumi HZ, Kamada N, Hisamatsu T, Hansen JJ, Doty KR, Pope SD, Smale ST, Hibi T, Rothman PB, Kashiwada M, Plevy SE. 2011. NFIL3 is a regulator of IL-12 p40 in macrophages and mucosal immunity. *J Immunol* 186:4649–4655.
- Kochi Y, Okada Y, Suzuki A, Ikari K, Terao C, Takahashi A, Yamazaki K, Hosono N, Myouzen K, Tsunoda T, Kamatani N, Furuichi T, Ikegawa S, Ohmura K, Mimori T, Matsuda F, Iwamoto T, Momohara S, Yamanaka H, Yamada R, Kubo M, Nakamura Y, Yamamoto K. 2010. A regulatory variant in CCR6 is associated with rheumatoid arthritis susceptibility. *Nat Genet* 42:515–519.
- Kugathasan S, Baldassano RN, Bradfield JP, Sleiman PM, Imielinski M, Guthery SL, Cucchiara S, Kim CE, Frackelton EC, Annaiah K, Glessner JT, Santa E, Willson T, Eckert AW, Bonkowski E, Shaner JL, Smith RM, Otieno FG, Peterson N, Abrams DJ, Chiavacci RM, Grundmeier R, Mamula P, Tomer G, Piccoli DA, Monos DS, Annesse V, Denson LA, Grant SF, Hakonarson H. 2008. Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. *Nat Genet* 40:1211–1215.
- Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB; PHOENIX 1 study investigators. 2008. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 371:1665–1674.
- Liu X, Invernizzi P, Lu Y, Kosoy R, Lu Y, Bianchi I, Podda M, Xu C, Xie G, Macciardi F, Selmi C, Lupoli S, Shigeta R, Ransom M, Lleo A, Lee AT, Mason AL, Myers RP, Peltekian KM, Ghent CN, Bernuzzi F, Zuin M, Rosina F, Borghesio E, Floreani A, Lazzari R, Niro G, Andriulli A, Muratori L, Muratori P, Almasio PL, Andreone P, Margotti M, Brunetto M, Coco B, Alvaro D, Bragazzi MC, Marra F, Pisano A, Rigamonti C, Colombo M, Marziani M, Benedetti A, Fabris L, Strazzabosco M, Portincasa P, Palmieri VO, Tiribelli C, Croce L, Bruno S, Rossi S, Vinci M, Prisco C, Mattalia A, Toniutto P, Picciotto A, Galli A, Ferrari C, Colombo S, Casella G, Morini L, Caporaso N, Colli A, Spinzi G, Montanari R, Gregersen PK, Heathcote EJ, Hirschfield GM, Siminovitch KA, Amos CI, Gershwin ME, Seldin MF. 2010a. Genome-wide meta-analyses identify three loci associated with primary biliary cirrhosis. *Nat Genet* 42:658–660.
- Liu X, Leung S, Wang C, Tan Z, Wang J, Guo TB, Fang L, Zhao Y, Wan B, Qin X, Lu L, Li R, Pan H, Song M, Liu A, Hong J, Lu H, Zhang JZ. 2010b. Crucial role of interleukin-7 in T helper type 17 survival and expansion in autoimmune disease. *Nat Med* 16:191–197.
- Lowe CE, Cooper JD, Brusko T, Walker NM, Smyth DJ, Bailey R, Bourget K, Plagnol V, Field S, Atkinson M, Clayton DG, Wicker LS, Todd JA. 2007. Large-scale genetic fine mapping and genotype-phenotype associations implicate polymorphism in the IL2RA region in type 1 diabetes. *Nat Genet* 39:1074–1082.
- Lundmark F, Duvefelt K, Iacobaeus E, Kockum I, Wallström E, Khademi M, Oturai A, Ryder LP, Saarela J, Harbo HF, Celius EG, Salter H, Olsson T, Hillert J. 2007. Variation in interleukin

- 7 receptor alpha chain (IL7R) influences risk of multiple sclerosis. *Nat Genet* 39:1108–1113.
- Maier LM, Lowe CE, Cooper J, Downes K, Anderson DE, Sevrerson C, Clark PM, Healy B, Walker N, Aubin C, Oksenberg JR, Hauser SL, Compston A, Sawcer S; International Multiple Sclerosis Genetics Consortium, De Jager PL, Wicker LS, Todd JA, Hafler DA. 2009. IL2RA genetic heterogeneity in multiple sclerosis and type 1 diabetes susceptibility and soluble interleukin-2 receptor production. *PLoS Genet* 5:e1000322.
- Martin R. 2008. Neutralisation of IL12 p40 or IL23 p40 does not block inflammation in multiple sclerosis. *Lancet Neurol* 7: 765–766.
- McGovern DP, Gardet A, Törkvist L, Goyette P, Essers J, Taylor KD, Neale BM, Ong RT, Lagacé C, Li C, Green T, Stevens CR, Beauchamp C, Fleshner PR, Carlson M, D'Amato M, Halfvarson J, Hibberd ML, Lördal M, Padyukov L, Andriulli A, Colombo E, Latiano A, Palmieri O, Bernard EJ, Deslandres C, Hommes DW, de Jong DJ, Stokkers PC, Weersma RK; NIDDK IBD Genetics Consortium, Sharma Y, Silverberg MS, Cho JH, Wu J, Roeder K, Brant SR, Schumm LP, Duerr RH, Dubinsky MC, Glazer NL, Haritunians T, Ippoliti A, Melmed GY, Siscovick DS, Vasilias EA, Targan SR, Annese V, Wijnga C, Pettersson S, Rotter JI, Xavier RJ, Daly MJ, Rioux JD, Seielstad M. 2010. Genome-wide association identifies multiple ulcerative colitis susceptibility loci. *Nat Genet* 42:332–337.
- Mells GF, Floyd JA, Morley KI, Cordell HJ, Franklin CS, Shin SY, Heneghan MA, Neuberger JM, Donaldson PT, Day DB, Ducker SJ, Muriithi AW, Wheeler EF, Hammond CJ, Dawwas MF; UK PBC Consortium; Wellcome Trust Case Control Consortium 3, Jones DE, Peltonen L, Alexander GJ, Sandford RN, Anderson CA. 2011. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. *Nat Genet* 43:329–332.
- Mizuki N, Meguro A, Ota M, Ohno S, Shiota T, Kawagoe T, Ito N, Kera J, Okada E, Yatsu K, Song YW, Lee EB, Kitaichi N, Namba K, Horie Y, Takeno M, Sugita S, Mochizuki M, Bahram S, Ishigatsubo Y, Inoko H. 2010. Genome-wide association studies identify IL23R-IL12RB2 and IL10 as Behçet's disease susceptibility loci. *Nat Genet* 42:703–706.
- Müller-Berghaus J, Kern K, Paschen A, Nguyen XD, Klüter H, Morahan G, Schadendorf D. 2004. Deficient IL-12p70 secretion by dendritic cells based on IL12B promoter genotype. *Genes Immun* 5:431–434.
- Murphy CA, Langrish CL, Chen Y, Blumenschein W, McClanahan T, Kastelein RA, Sedgwick JD, Cua DJ. 2003. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. *J Exp Med* 198:1951–1957.
- Nair RP, Duffin KC, Helms C, Ding J, Stuart PE, Goldgar D, Gudjonsson JE, Li Y, Tejasvi T, Feng BJ, Ruether A, Schreiber S, Weichenthal M, Gladman D, Rahman P, Schrod SJ, Prahalad S, Guthery SL, Fischer J, Liao W, Kwok PY, Menter A, Lathrop GM, Wise CA, Begovich AB, Voorhees JJ, Elder JT, Krueger GG, Bowcock AM, Abecasis GR; Collaborative Association Study of Psoriasis. 2009. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet* 41:199–204.
- Núñez C, Dema B, Cénit MC, Polanco I, Maluenda C, Arroyo R, de las Heras V, Bartolomé M, de la Concha EG, Urcelay E, Martínez A. 2008. IL23R: a susceptibility locus for celiac disease and multiple sclerosis? *Genes Immun* 9:289–293.
- O'Doherty C, Kantarci OH, Vandenbroeck K. 2008. IL7RA polymorphisms and susceptibility to multiple sclerosis. *N Eng J Med* 358:753–754.
- Oksenberg JR, Baranzini SE. 2010. Multiple sclerosis genetics—is the glass half full, or half empty? *Nat Rev Neurol* 6:429–437.
- Oksenberg JR, Rioux JD. 2006. Genetics of multifactorial disorders. In: Vandenbroeck K, ed. *Cytokine gene polymorphisms in multifactorial conditions*. Boca Raton: CRC Press, Taylor & Francis Group (FL), pp 35–46.
- Paunovic V, Carroll HP, Vandenbroeck K, Gadina M. 2008. Signalling, inflammation and arthritis: crossed signals: the role of interleukin (IL)-12, -17, -23 and -27 in autoimmunity. *Rheumatology* 47:771–776.
- Petukhova L, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, Kim H, Singh P, Lee A, Chen WV, Meyer KC, Paus R, Jahoda CA, Amos CI, Gregersen PK, Christiano AM. 2010. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature* 466: 113–117.
- Quan C, Ren YQ, Xiang LH, Sun LD, Xu AE, Gao XH, Chen HD, Pu XM, Wu RN, Liang CZ, Li JB, Gao TW, Zhang JZ, Wang XL, Wang J, Yang RY, Liang L, Yu JB, Zuo XB, Zhang SQ, Zhang SM, Chen G, Zheng XD, Li P, Zhu J, Li YW, Wei XD, Hong WS, Ye Y, Zhang Y, Wu WS, Cheng H, Dong PL, Hu DY, Li Y, Li M, Zhang X, Tang HY, Tang XF, Xu SX, He SM, Lv YM, Shen M, Jiang HQ, Wang Y, Li K, Kang XJ, Liu YQ, Sun L, Liu ZF, Xie SQ, Zhu CY, Xu Q, Gao JP, Hu WL, Ni C, Pan TM, Li Y, Yao S, He CF, Liu YS, Yu ZY, Yin XY, Zhang FY, Yang S, Zhou Y, Zhang XJ. 2010. Genome-wide association study for vitiligo identifies susceptibility loci at 6q27 and the MHC. *Nat Genet* 42:614–618.
- Remmers EF, Cosan F, Kirino Y, Ombrello MJ, Abaci N, Satorius C, Le JM, Yang B, Korman BD, Cakiris A, Aglar O, Emrence Z, Azakli H, Ustek D, Tugal-Tutkun I, Akman-Demir G, Chen W, Amos CI, Dizon MB, Kose AA, Azizlerli G, Erer B, Brand OJ, Kaklamani VG, Kaklamanis P, Ben-Chetrit E, Stanford M, Fortune F, Ghabra M, Ollier WE, Cho YH, Bang D, O'Shea J, Wallace GR, Gadina M, Kastner DL, Gül A. 2010. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behçet's disease. *Nat Genet* 42: 698–702.
- Roh TY, Cuddapah S, Zhao K. 2005. Active chromatin domains are defined by acetylation islands revealed by genome-wide mapping. *Genes Dev* 19:542–552.
- Roos IM, Kockum I, Hillert J. 2008. The interleukin 23 receptor gene in multiple sclerosis: a case-control study. *J Neuroimmunol* 194:173–180.
- Sandborn WJ, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, Johans J, Blank M, Rutgeerts P; Ustekinumab Crohn's Disease Study Group. 2008. A randomized trial of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 135:1130–1141.
- Sarin R, Wu X, Abraham C. 2011. Inflammatory disease protective R381Q IL23 receptor polymorphism results in decreased primary CD4+ and CD8+ human T-cell functional responses. *Proc Natl Acad Sci U S A* 108:9560–9565.
- Segal BM, Constantinescu CS, Raychaudhuri A, Kim L, Fidelus-Gort R, Kasper LH; Ustekinumab MS Investigators. 2008. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. *Lancet Neurol* 7: 796–804.
- Silverberg MS, Cho JH, Rioux JD, McGovern DP, Wu J, Annese V, Achkar JP, Goyette P, Scott R, Xu W, Barmada MM, Klei L, Daly MJ, Abraham C, Bayless TM, Bossa F, Griffiths AM, Ippoliti AF, Lahaie RG, Latiano A, Paré P, Proctor DD, Regueiro MD, Steinhart AH, Targan SR, Schumm LP, Kistner EO,

- Lee AT, Gregersen PK, Rotter JI, Brant SR, Taylor KD, Roeder K, Duerr RH. 2009. Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat Genet* 41:216–220.
- Sirota M, Schaub MA, Batzoglu S, Robinson WH, Butte AJ. 2009. Autoimmune disease classification by inverse association with SNP alleles. *PLoS Genet* 5:e1000792.
- Smith AM, Qualls JE, O'Brien K, Balouzian L, Johnson PF, Schultz-Cherry S, Smale ST, Murray PJ. 2011. A distal enhancer in *il12b* is the target of transcriptional repression by the STAT3 pathway and requires the basic leucine zipper (B-ZIP) protein NFIL3. *J Biol Chem* 286:23582–23590.
- Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, Li Y, Kurreeman FA, Zernakova A, Hinks A, Guiducci C, Chen R, Alfredsson L, Amos CI, Ardlie KG; BIRAC Consortium, Barton A, Bowes J, Brouwer E, Burtt NP, Catanese JJ, Coblyn J, Coenen MJ, Costenbader KH, Criswell LA, Crusius JB, Cui J, de Bakker PI, De Jager PL, Ding B, Emery P, Flynn E, Harrison P, Hocking LJ, Huizinga TW, Kastner DL, Ke X, Lee AT, Liu X, Martin P, Morgan AW, Padyukov L, Posthumus MD, Radstake TR, Reid DM, Seielstad M, Seldin MF, Shadick NA, Steer S, Tak PP, Thomson W, van der Helm-van Mil AH, van der Horst-Bruinsma IE, van der Schoot CE, van Riel PL, Weinblatt ME, Wilson AG, Wolbink GJ, Wordsworth BP; YEAR Consortium, Wijmenga C, Karlson EW, Toes RE, de Vries N, Begovich AB, Worthington J, Siminovitch KA, Gregersen PK, Klareskog L, Plenge RM. 2010. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis loci. *Nat Genet* 42:508–514.
- Steidler L, Hans W, Schotte L, Neirynck S, Obermeier F, Falk W, Fiers W, Remaut E. 2000. Treatment of murine colitis by *Lactococcus lactis* secreting interleukin-10. *Science* 289:1352–1355.
- Strange A, Capon F, Spencer CC, Knight J, Weale ME, Allen MH, Barton A, Band G, Bellenguez C, Bergboer JG, Blackwell JM, Bramon E, Bumpstead SJ, Casas JP, Cork MJ, Corvin A, Deloukas P, Dilthey A, Duncanson A, Edkins S, Estivill X, Fitzgerald O, Freeman C, Giardina E, Gray E, Hofer A, Hüffmeier U, Hunt SE, Irvine AD, Jankowski J, Kirby B, Langford C, Lascorz J, Leman J, Leslie S, Mallbris L, Markus HS, Mathew CG, McLean WH, McManus R, Mössner R, Moutsianas L, Nalau AT, Nestle FO, Novelli G, Onoufriadi A, Palmer CN, Perricone C, Pirinen M, Plomin R, Potter SC, Pujol RM, Rautanen A, Riveira-Munoz E, Ryan AW, Salmhofer W, Samuelsson L, Sawcer SJ, Schalkwijk J, Smith CH, Stähle M, Su Z, Tazi-Ahnini R, Traupe H, Viswanathan AC, Warren RB, Weger W, Wolk K, Wood N, Worthington J, Young HS, Zeeuwen PL, Hayday A, Burden AD, Griffiths CE, Kere J, Reis A, McVean G, Evans DM, Brown MA, Barker JN, Peltonen L, Donnelly P, Trembath RC. 2010. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet* 42:985–990.
- Surh CD, Sprent J. 2008. Homeostasis of naive and memory T cells. *Immunity* 29:848–862.
- Takahashi R, Nishimoto S, Muto G, Sekiya T, Tamiya T, Kimura A, Morita R, Asakawa M, Chinen T, Yoshimura A. 2011. SOCS1 is essential for regulatory T cell functions by preventing loss of Foxp3 expression as well as IFN- γ and IL-17A production. *J Exp Med* 208:2055–2067.
- Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V, Bailey R, Nejentsev S, Field SF, Payne F, Lowe CE, Szeszeko JS, Hafler JP, Zeitels L, Yang JH, Vella A, Nutland S, Stevens HE, Schuilenburg H, Coleman G, Maisuria M, Meadows W, Smink LJ, Healy B, Burren OS, Lam AA, Ovington NR, Allen J, Adlem E, Leung HT, Wallace C, Howson JM, Guja C, Ionescu-Tirgoviste C; Genetics of Type 1 Diabetes in Finland, Simmonds MJ, Heward JM, Gough SC; Wellcome Trust Case Control Consortium, Dunger DB, Wicker LS, Clayton DG. 2007. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. *Nat Genet* 39:857–864.
- Tonel G, Conrad C, Laggner U, Di Meglio P, Grys K, McClanahan TK, Blumenschein WM, Qin JZ, Xin H, Oldham E, Kastelein R, Nickoloff BJ, Nestle FO. 2010. Cutting edge: a critical functional role for IL-23 in psoriasis. *J Immunol* 185:5688–5691.
- Traggiai E, Biagioli T, Rosati E, Ballerini C, Mazzanti B, Ben Nun A, Massacesi L, Vergelli M. 2001. IL-7-enhanced T-cell response to myelin proteins in multiple sclerosis. *J Neuroimmunol* 121:111–119.
- Vandenbroeck K. 2006. Cytokine gene polymorphisms in multifactorial conditions. Boca Raton: CRC Press, Taylor & Francis Group (FL), p 459.
- Vandenbroeck K, Alvarez J, Swaminathan B, Alloza I, Matesanz F, Urcelay E, Comabella M, Alcina A, Fedetz M, Ortiz MA, Izquierdo G, Fernandez O, Rodriguez-Ezpeleta N, Matute C, Caillier S, Arroyo R, Montalban X, Oksenberg JR, Antigüedad A, Aransay A. 2011. A cytokine gene screen uncovers SOCS1 as genetic risk factor for multiple sclerosis. *Genes Immun*, doi: 10.1038/gene.2011.44.
- Wang CQ, Cruz-Inigo AE, Fuentes-Duculan J, Moussai D, Gulati N, Sullivan-Whalen M, Gilleaudeau P, Cohen JA, Krueger JG. 2011. Th17 cells and activated dendritic cells are increased in vitiligo lesions. *PLoS One* 6:e18907.
- Wang K, Baldassano R, Zhang H, Qu HQ, Imielinski M, Kugathasan S, Annese V, Dubinsky M, Rotter JI, Russell RK, Bradfield JP, Sleiman PM, Glessner JT, Walters T, Hou C, Kim C, Frackelton EC, Garriss M, Doran J, Romano C, Catassi C, Van Limbergen J, Guthery SL, Denson L, Piccoli D, Silverberg MS, Stanley CA, Monos D, Wilson DC, Griffiths A, Grant SF, Satsangi J, Polychronakos C, Hakonarson H. 2010. Comparative genetic analysis of inflammatory bowel disease and type 1 diabetes implicates multiple loci with opposite effects. *Hum Mol Genet* 19:2059–2067.
- Willerford DM, Chen J, Ferry JA, Davidson L, Ma A, Alt FW. 1995. Interleukin-2 receptor alpha chain regulates the size and content of the peripheral lymphoid compartment. *Immunity* 3:521–530.
- Wilson JN, Rockett K, Keating B, Jallow M, Pinder M, Sisay-Joof F, Newport M, Kwiatkowski D. 2006. A hallmark of balancing selection is present at the promoter region of interleukin 10. *Genes Immun* 7:680–683.
- Yu RY, Gallagher G. 2010. A naturally occurring, soluble antagonist of human IL-23 inhibits development and *in vitro* function of human Th17 cells. *J Immunol* 185:7302–7308.
- Yu W, Yesupriya A, Wulf A, Hindorff LA, Dowling N, Khoury MJ, Gwinn M. 2011. GWAS Integrator: a bioinformatics tool to explore human genetic associations reported in published genome-wide association studies. *Eur J Hum Genet* 19:1095–1099.
- Zhang XY, Zhang HJ, Zhang Y, Fu YJ, He J, Zhu LP, Wang SH, Liu L. 2006. Identification and expression analysis of alternatively spliced isoforms of human interleukin-23 receptor gene in normal lymphoid cells and selected tumor cells. *Immunogenetics* 57:934–943.
- Ziegler SF, Liu YJ. 2006. Thymic stromal lymphopoietin in normal and pathogenic T cell development and function. *Nat Immunol* 7:109–114.

- Zier KS, Leo MM, Spielman RS, Baker L. 1984. Decreased synthesis of interleukin-2 (IL-2) in insulin-dependent diabetes mellitus. *Diabetes* 3:552–555.
- Zuvich RL, McCauley JL, Oksenberg JR, Sawcer SJ, De Jager PL; International Multiple Sclerosis Genetics Consortium, Aubin C, Cross AH, Piccio L, Aggarwal NT, Evans D, Hafler DA, Compston A, Hauser SL, Pericak-Vance MA, Haines JL. 2010. Genetic variation in the IL7RA/IL7 pathway increases multiple sclerosis susceptibility. *Hum Genet* 127:525–535.

Address correspondence to:
Koen Vandenbroeck
Neurogenomiks (UPV/EHU)
Parque Tecnológico de Bizkaia
Edif 205, planta -1
48170 Zamudio
Bizkaia
Spain

Email: k.vandenbroeck@ikerbasque.org

Received 3 October 2011/Accepted 4 November 2011