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Primary Immunodeficiencies and Inflammatory Disease: A Growing Genetic Intersection

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Abstract

Recent advances in genome analysis have provided important insights into the genetic architecture of infectious and inflammatory diseases. The combined analysis of loci detected by genome-wide association studies (GWAS) in 22 inflammatory diseases has revealed a shared genetic core and associated biochemical pathways that play a central role in pathological inflammation. Parallel whole exome sequencing studies have identified 265 genes mutated in primary immunodeficiencies (PID). Here we examine the overlap between these two datasets, and find that it consists of genes essential for protection against infections and in which persistent activation causes pathological inflammation. Based on this intersection, we propose that although strong or inactivating mutations (rare variants) in these genes may cause severe disease (PIDs), their more subtle modulation potentially by common regulatory/coding variants may contribute to chronic inflammation.

Genomics meet human infectious and inflammatory diseases

The “disease state” results from interactions between intrinsic genetic risks from the host, and extrinsic environmental triggers. The genetic component may be simple, involving powerful mutations that inactivate key physiological pathways, or may be complex and heterogeneous, involving combinations of weak genetic lesions which accumulation phenotypically mimics the effect of a strong mutation. On the other hand, environmental triggers of disease are often complex, heterogeneous and are generally poorly understood. Genetic analysis of susceptibility to infections has proven particularly successful to study how the interface between host and environment causes clinical disease [1–3]. In infectious diseases, exposure to the environmental trigger (e.g. microbial pathogens) is absolutely required to reveal the host genetic diversity and associated risk.. In most extreme cases, selective pressure by lethal microbes has impacted the human genome, and has left identifiable genetic fingerprints in areas of endemic disease and following epidemics. Striking examples include the protective role of hemoglobin (Hb) and ACKR1 (DARC) variants against malaria [4], and of CCR5 deletion against HIV [5]. Dramatic increases in

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performance and affordability of DNA sequencing now permits genome and whole exome sequencing (WES) of unique human patients or families that display unusual susceptibility to infections, including pure or syndromic primary immunodeficiencies (PIDs) [6–8]. The analysis of such patients has generated rich genetic dataset on association of rare variants with this group of diseases.

On the other hand, burns, trauma and environmental insults may disrupt protective tissue barriers and lead to acute or chronic exposure to microbes present at mucosal surfaces and/or to appetizing self-antigens. This triggers an inflammatory response in the host, a normal physiological process that involves initial recognition of tissue damage, elimination of the causative lesion, and restoration of tissue homeostasis. Tight regulation of this response is critical: in presence of persistent tissue injury or sustained microbial insult, over-expression of pro-inflammatory mediators or insufficient production of anti-inflammatory signals results in immuno-pathology, including inflammatory or autoimmune disease or allergy. Genetic analysis of susceptibility to acute (sepsis, encephalitis) or chronic inflammatory diseases with possible microbial, autoimmune, and/or auto-inflammatory etiologies (inflammatory bowel disease, rheumatoid arthritis, psoriasis to name only a few) has offered additional opportunities to identify important elements of host response to microbial and autoimmune stimuli [9]. Population and family studies have long established a strong genetic component to susceptibility to inflammatory diseases.. The recent availability of high-density arrays of polymorphic variants genome-wide (SNP chips) or clustered around “immune” loci (Immunchips) has facilitated the search for genetic determinants (common variants) of susceptibility to inflammatory diseases in humans. Such genome-wide association studies (GWAS) in very large cohorts of human patients (>50,000) from different populations, and subsequent meta-analyses of multiple published GWAS of the same disease have mapped hundreds of genetic loci, each with small effect size, but that together define a rich genetic architecture for several of these diseases [10–18].

This flurry of technology development has produced very detailed genetic maps for susceptibility to infections and to inflammation, and those have been reviewed elsewhere [19–21]. Although these will be briefly cited herein, the specific focus of this review is on the nature and extent of shared genetic risks across both groups of diseases. Specifically, we will discuss how this genetic intersection points to specific genes, and pathways that are required for protection against infections but which sustained engagement in the presence of persistent insult leads to pathological inflammation. We will also review how this intersection may provide information on the etiology of certain inflammatory conditions, and conversely how the two parallel datasets may help identify and validate morbid genes at candidate loci. Finally, this intersection lends support to the hypothesis that strong but rare mutations at specific genes of this overlap may independently cause severe diseases (PIDs), while more subtle modulation by common coding or regulatory variants may contribute to chronic inflammation in the presence of a persistent tissue insult.

Primary Immunodeficiencies

In addition to classical genetic approaches (linkage mapping, immune phenotype-driven candidate gene sequencing, studies from animal models), whole exome sequencing (WES)

has dramatically increased the pace at which causative genes are being discovered for PIDs. WES has been most effective in identifying “morbid” genes in groups of PID patients where presence of homozygosity for deleterious mutations is likely to be high, including (a) familial cases, consanguinity, or cases from isolated populations; (b) patients presenting with particularly severe pathological form of an otherwise more benign condition (unusual pathogenesis); (c) rare early-onset pediatric cases. To date, mutations in 265 genes have been shown to cause PIDs, providing a rich dataset for the systematic characterization of cellular and molecular networks involved in the development, activity and regulation of immune cells during response to infectious or to inflammatory stimuli [Table S1] [22–24]. A clinical classification has recently been provided for PIDs where the genetic etiology is known [25]. It includes (1) combined immunodeficiencies (T and/or B cells), (2) combined immunodeficiencies with syndromic features, (3) humoral deficiencies, (4) diseases of immune dysregulation, (5) defects in phagocytes numbers or function, (6) defects in innate immunity, (7) auto-inflammatory disorders, and (8) deficiencies of the complement system. While the majority of mutations affect the development and function of leukocytes, others are inborn errors of metabolisms (in so-called “house-keeping” proteins) with or without syndromic features [23]. The vast majority of genetic lesions causing PIDs are highly penetrant and inherited in a recessive fashion. However, a fraction are inherited as autosomal dominant (heterozygotes) with variable penetrance, and associated with either haploinsufficiency, with gain-of-function, or with negative dominance [8, 26–29].

The study of genotype/phenotype correlations in PIDs has been extremely productive. It has identified not only host cells and pathways that are essential for general protection against microbial pathogens in general but has also recognized pathways that are surprisingly non-redundant and that are required for response to unique groups of pathogens. On the one hand, several PIDs are very severe, and manifest themselves as broad susceptibility to viral, bacterial, and parasitic pathogens. Examples include severe combined immunodeficiency (SCID) (partial or complete loss of T and B cells) that are caused by mutations in > 30 genes, the most frequent being *IL2RG*, *ADA*, *IL7RA*, *JAK3*, *RAG1*, *RAG2* and *CD3* [25, 30]. Likewise, chronic granulomatous disease (CGD) is associated with recurrent bacterial and fungal infections in presence or absence of neutropenia, and linked to impaired production of oxygen radicals by myeloid cells caused by mutations in constituents of the NADPH oxidase (*CYBA*, *CYBB*, *NCF1*, *NCF2*, *NCF4*) [31]. Another example is CD4 lymphopenia, which etiology includes deficiency in *MAGT1*, and which manifests itself by viral and bacterial infections and histoplasma. On the other hand, some PIDs display very restricted infection susceptibility phenotypes. Mutations in *TLR3* cause susceptibility to Herpes Simplex virus and associated encephalitis (HSE) [32], but nothing else. Remarkably, the same restricted HSE phenotype is found in patients harboring mutations in other members of the TLR3-IFN α/β pathways, including *TRIF*, *TRAF3*, *UNC93B1*, and *TBK1* [33]. A similar situation is seen with *IL17* deficiency, *CARD9* deficiency, and some patients with autosomal dominant *STAT1* deficiency who uniformly display a narrow phenotype of chronic mucocutaneous candidiasis (CMC) [34]. Also, defects in the IFN γ /IL12 circuit tend to cause a narrow phenotype of susceptibility to infection with environmental mycobacteria, or disseminated BCG infection post-vaccination, a syndrome named Mendelian Susceptibility

to Mycobacterial Disease (MSMD) [35]. These results highlight the non-redundant nature of the host defense mechanisms against these infections.

Additional insight into different, cell-specific molecular functions of a PID gene product can sometimes be reflected by the heterogeneity of clinical phenotypes associated with different types of mutations in the same gene. For example, heterozygosity for inactivating mutations in *STAT1* cause a decrease in protein phosphorylation and DNA binding, resulting in diminished production of IFN γ which is clinically expressed as susceptibility to mycobacterial infections [36]. Conversely, mutations affecting STAT1 coiled-coil and DNA-binding domains lead to an excess of p-STAT1-driven target gene transcription. These heterozygote *STAT1* mutations impair nuclear dephosphorylation of p-STAT1, causing both increased transcriptional activity and decreased IL17 production by T cells, that is clinically expressed as susceptibility to CMC, and phenotypically mimicking mutations of the *IL17F*, *IL17RA* and *ACT1* genes [37]. Similarly, hemizygosy for loss of function mutations in *WASP* (Wiskott Aldrich Syndrome) cause thrombocytopenia, eczema, decreased T and B cells function and recurrent infections, while activating *WASP* mutations cause neutropenia with no risk of infection [38]. Finally, penetrance and expressivity of a specific PID mutation can be dramatically influenced in different patients by additional, yet to be defined genetic or environmental effects. For example, *GATA2* mutations are associated with a constellation of phenotypes in different patients, including familial myelodysplasia, dendritic cells/monocytes/B and NK cells deficiency, and decreased monocytes counts with susceptibility to mycobacteria [39–41]. Also, patients bearing the same inactivating *TYK2* deletion show different phenotypes with or without Hyper IgE syndrome with associated viral, fungal and BCG infections at clinical presentation in one patient, while another patient with the same mutation had BCGosis and brucellosis with normal IgE level [42, 43].

In conclusion, the rapidly increasing list of PID mutations is identifying critical mechanisms of protection against microbial pathogens [Table S1]. In genotype:genotype comparisons (see below), these mutations can also validate loci and associated gene effects in unrelated diseases with a suspected microbial etiology, and that have been detected as GWAS loci. This is particularly important when the identity of a morbid gene at such GWAS loci remains elusive due, for example, to linkage disequilibrium (LD) near mapped loci. Concordance between PID genes and GWAS disease loci may provide critical new insight into host cells and pathways that play a role in pathogenesis of an unrelated disease, and may even point to a specific pathogen or group of pathogens as participating in the etiology of this unrelated condition.

Inflammatory Diseases

A strong genetic component has long been established (familial clustering, gender effect, segregation analyses, twin studies) for major diseases of inflammation such as inflammatory bowel disease (IBD), multiple sclerosis (MS), rheumatoid arthritis (RA), Celiac disease (CeD), type I diabetes (T1D), systemic lupus erythematosus (SLE), psoriasis (Pso.) and several other such disorders. Over the past 10 years, the genetic architectures of these diseases have been mapped by GWAS in large cohorts of patients and controls (>10,000), and in different populations. In addition, results from independent GWAS studies have been

combined in large “meta-analyses” (>50,000 patients), resulting in the mapping and validation of hundreds of genetic risk loci. Public GWAS databases to which the reader is referred (NHGRI GWAS Catalog, GWASdb, Gen2Phen, GWAS Central, ImmunoBase) provide regular updates; at last count, >600 loci (genome-wide significance threshold $p < 5 \times 10^{-8}$) affecting susceptibility to chronic inflammatory and/or autoimmune diseases had been mapped by this approach [44–47]. As reviewed below, many of these loci are shared between different diseases, while others appear to be disease-specific. The careful scrutiny of the shared genetic risk provides valuable insight into the host mechanisms that underlie the process of pathological inflammation, while disease-specific pathways may reflect specific gene-environment interactions unique to that disease and/or tissue affected. An important caveat of the GWAS datasets is that with the exception of HLA, the effect size of individual loci is small with low odds ratios. This may be caused by a number of factors, including complexity of the genetic determinants, heterogeneity in the disease phenotype which current definition is restricted to a clinical end-point, and complex gene:environment interactions.

The deepest genetic datasets come from IBD [13], MS [17, 18] and RA [14]. IBD encompasses both ulcerative colitis (UC) and Crohn’s disease (CD), two related intestinal inflammatory conditions with distinct clinical and pathological manifestations. The most recent meta-analysis of 75,000 cases and controls detected a total of 163 genetic risk loci, 110 of them being shared in common in both UC and CD, with an additional 23 UC-specific loci, and 30 CD-specific loci, with strong candidate genes identified for 53% of the loci [13]. About one third ($n = 66$) of the loci were also found to be shared in common with other inflammatory and auto-immune diseases. Cell-specific gene expression studies show that the major cell type “hosting” these genetic effects is primarily dendritic cells followed by CD4⁺ T cells and NK cells, while biological network analysis pointed to cytokine production, lymphocytes numbers and activation, and response to bacterial products as the key associated response pathways in these cells [13]. The most recent meta-analysis of MS genetic risk combining GWAS results and independent immuno-chip genotyping (80,000 cases and controls), identified a total of 110 non-MHC loci [18]. Of those, 97 variants fell within 50 kb of genes loosely annotated as immune function (prior annotation, organ and cell-specific expression), with 35 linked to the GO term “immune system process”. Importantly, the genetic architecture solved in this analysis identified a clear overlap with risk loci for IBD (17%), UC (13%), CD (15%), primary biliary cirrhosis (10%) as well as CeD (7%), RA (4.5%), and 3.6% with psoriasis [18]. For RA, a recently published meta-analysis of GWAS and immuno-chip data of >30,000 cases and 73,000 controls identified a total of 101 non-MHC genetic risk loci containing a minimum aggregate number of 377 genes (defined by linkage disequilibrium) [14]. Interestingly, almost 2/3 of the mapped genetic risk loci are shared with other immune-related diseases. Forty four loci show *cis*-regulatory variants (expression QTLs) that are active in CD4⁺ T cells, in CD14⁺ cells or in PBMCs. Pathway and gene expression analysis also shows significant enrichment of T-cell and B-cell dependent pathways and of cytokine signaling pathways [14]. Finally, a recent study defined *cis*-regulatory regions in a variety of hematopoietic cells [48]. It found that ~60% of GWAS loci for inflammatory diseases are associated with *cis*-regulatory regions that display disease-associated and cell type-specific effects (for example, CD and UC hits

have strong association with T cell enhancers; whereas RA, MS and SLE are also linked to B cells).

The careful delineation of the shared genetic risk in inflammatory and other immune related diseases is of particular interest to understand the basic mechanisms of pathological inflammation, and to identify possible novel drug targets of broad therapeutic value. A combined analysis of these GWAS datasets for 22 most common inflammatory diseases identified a total of 439 unique genetic risk loci; of these 203 (46%) are shared with at least one other inflammatory disease, 88 loci are shared by 2 diseases, 39 by 3 diseases, 34 by 4 diseases, while a surprising 42 loci (9.6% of the loci tested) were shared in common by 5 or more diseases [Figure 1, Table S2]. The Circos plot shown in Figure 1 illustrates the genetic loci shared by 4 or more inflammatory diseases. In comparing the extent of overlap in genetic risk loci across the different diseases, it is important to remember that this overlap will be affected by the number of loci mapped in each disease, which is in part determined by the number of patients analyzed in each study (statistical power), and the strength of the genetic component in each disease. [To maximize the capture of shared genetic loci across different inflammatory diseases, we used a reduced statistical threshold and p value $< 1 \times 10^{-5}$]. Hence, the overlaps identified in Figure 1 [Table S2] are likely to be underestimates, negatively influenced by the relative smaller size of certain GWAS studies. Conversely, the bias for informative SNPs at “immune genes” in the Immunochip [49] used in a few of the GWAS may positively affect the size of the genetic overlap between mapped loci in different diseases. Amongst these 76 ubiquitous genetic loci (detected in 4 or more diseases) [Figure 1], the HLA-DQ/HLA-DR region of the MHC (or specific portions of it) was most prominent, being positive for association in all of the 22 diseases tested. Other shared loci in this group related to cell types, responses and pathways already known for relevance to pathogenesis, including a) pattern recognition receptors of the innate immune system and associated signalling cascades; b) antigen processing and presentation, production of cytotoxic species, and secretion of pro-inflammatory mediators by myeloid cells; c) T and B lymphocyte maturation, including control of auto-reactive T and B cells; d) antigen receptors of T and B cells for recognition in the context of Class I or Class II MHC; e) production of pro-inflammatory cytokines, and associated regulation of Th1, Th17, Treg polarization of the immune response. Interestingly, about a quarter of these 76 most commonly shared loci do not show a clear biological candidate.

Genetic Intersections between Primary Immunodeficiencies and Inflammatory Diseases

The selective pressure imposed by pathogens during human evolution has shaped the host defense gene repertoire, but this has been suggested to have a fitness cost predisposing to inflammatory diseases (reviewed in [50]). Interestingly, we note a significant overlap between GWAS loci for inflammatory diseases (LD regions from the GWAS Catalog) and genes mutated in PIDs, with 80 of the 265 identified PID genes (30%) falling within boundaries of GWAS loci [Table 1]. This overlap is statistically highly significant, when using 10 independent training sets of 250 genes as controls (p value compared to random expectations = 3.5×10^{-12} ; Fisher's exact test). In addition, over half of these PID genes

(44/80) are associated with susceptibility to more than one inflammatory disease. The greatest overlap is with CD (34), UC (30), RA (24) and MS (23) possibly due to the greater number of loci mapped in these diseases. Interestingly, of the 24 PID genes associated with RA loci, 8 are specific for RA. Globally, most of the genes in these overlaps represent a “who’s who” of immune genes (see Figure 2). This list contains master transcription factors (*STAT1*, *STAT2*, *STAT3*, *STAT4*, *STAT5B*, *AIRE*, *IRF7*, *IRF8*, *NFκB*, *IKZF1*, *CIITA*) and regulatory proteins (*ATM*, *CASP8*, *CASP10*) involved in ontogeny, and maturation of myeloid cells and lymphoid cells; proteins participating in antigen recognition, processing, and presentation (Class I MHC, Class II MHC, *NOD2*, *TAP1*, *TAP2*, *CD40*), inflammasome activation platforms (*CARD9*, *CARD11*, *TYK2*), and anti-microbial function (*NCF2*, *NCF4*) of myeloid cells. The list also includes a number of pro- and anti-inflammatory cytokines (*IL10*, *IL12*, *IL21*) as well as cytokine receptors expressed by lymphoid and myeloid cells (*IL2R*, *IL7R*, *IL10R*, *IL12R*, *IFNGR1*, *IFNGR2*, *CXCR4*), and protective serum molecules from the complement system (*C2*, *C3*, *C5*, *CFB*, *CFH*, *ITGAM*). Therefore, it is obvious that the same cellular and molecular mechanisms that are required for protection against infections may also be involved, through sustained engagement, in onset or progression of inflammatory diseases. Figure 3 illustrates some of these proteins and associated pathways in the immune pathogenesis of IBD, MS and RA.

Although many of the genes at the PID/GWAS interface are associated with general and severe immunodeficiencies, others are associated with narrower immunodeficiency phenotypes, perhaps pointing at specific host responses and unique host:microbe interactions that may be relevant to the inflammatory diseases where they behave as genetic risks. For example, mutations in *STAT1* (IBD, SLE, RA, PBC, SS), *IFNGR1* (MS), *IFNGR2* (CD, RA), *IL12B* (IBD, MS, PSo., AS), *IL12R* (MS), *IRF8* (IBD, MS, RA, SLE, PBC, SS) and *TYK2* (many diseases including MS) are associated with Mendelian Susceptibility to Mycobacterial Diseases (MSMD), a fairly narrow form of immunodeficiency revealed after BCG vaccination and associated with impaired Th1 response (IFN γ /IL12 circuit). Interestingly, the detected overlap between MSMD genes and MS loci, with unique association of *IFNGR1* and *IL12R*, is supporting a role of IFN γ /IL12 loop in the etiology of this debilitating auto-immune disorder. Likewise, mutations in *TRAF3IP2* (UC/CD, psoriasis), and *CARD9* (UC/CD, AS) cause a narrow invasive fungal infection phenotype in humans. Finally, *TICAM1* mutations lead to herpes simplex encephalitis caused by natural HSV infection, while this gene is associated with vitiligo in GWAS studies. It is tempting to speculate that coincidence between a) gene mutations causing narrow immunodeficiencies restricted to one group of pathogens, and b) GWAS loci for one or several inflammatory diseases, may point to gene:environment interaction possibly with the same group of microbes involved in the etiology of inflammatory diseases.

Another informative dataset to consider are genes mutated in unique cases of very early onset pediatric IBD (VEO-IBD), the list of which shows significant intersection with genes mutated in PIDs [Table 1]. This group includes diverse proteins that play a critical role not only in sensing of microbial products at the mucosal barrier, but also in microbial activity, as well as in activation and amplification of pro-inflammatory responses (illustration in Figure 2). Selected examples include a) *ADAM17* (metalloprotease that cleaves TNF α , L-

selectin, EGFR ligands), a gene mutated in patients with neonatal onset of IBD [51]; b) *IKBKG* encoding nuclear KB essential modulator protein (NEMO) associated with enterocolitis with villous atrophy and epithelial cell shedding [52, 53]; c) hemizygote mutation for X-linked inhibitor of apoptosis protein gene (*XIAP*) in pediatric IBD [54–57]; d) a homozygote mutations in the *PIK3R1* gene in a patient with colitis and B cell deficiency [58, 59]; e) *TTC7A* mutations in patients with intestinal atresia, enterocolitis and combined immunodeficiency [60, 61]; f) *FOXP3* variants in individuals of European ancestry presenting with an early-onset and atypical form of IBD [62]; g) multiple variants in subunits of the NADPH oxidase complex [63]; h) hypermorphic *PLCG2* allele in a familial form of dominant inflammatory disease including enterocolitis [64]; i) *CTLA4* missense mutation (CTLA-4 Y60C) have been associated with severe, early-onset Crohn's disease (CD) with increased T cell activation and an increased ratio of memory to naive T cells [65] and finally, rare variants in *IL10* and its receptors *IL10RA* and *IL10RB*, and *IL21* genes associated with chronic intestinal inflammation in early childhood [59, 66–69].

Furthermore, the coincidence between gene mutations identified in PIDs and risk loci mapped by GWAS, provides valuable information for the identification of the morbid gene in GWAS risk loci showing LD. [LD is defined by the co-segregation (and absence of recombination) of markers linked to disease on so-called “haplotype blocks”; The causative genetic lesion may map within the boundaries or be physically linked to the LD segment (see Box and Glossary)]. For example the Chr1 locus at position 1.1–1.3Mb associated with CD and UC contains 17 genes in LD, with limited annotation for several of the genes; hence the identification of *TNFRSF4* in this interval as mutated in patients with OX40 deficiency provides a testable hypothesis that this gene is responsible for the effect in IBD. Similar situations occur for loci on Chr2 [204Mb, 3 genes in LD group, association with 7 diseases; *ICOS*], and Chr12 [63–66Mb, 9 genes in LD, 4 diseases; *TNFRSF1A*]. Interestingly, certain PID genes map to GWAS loci for which a different positional candidate had been previously proposed based on general ontology annotation. A locus on Chr21 (45Mb) was associated with disease risk in CD, UC, CeD and RA; from the list of 9 genes in LD at this locus, *ICOSLG* was previously identified as the best candidate based to its co-stimulatory function in T-cells. However, the discovery that this Chr21 locus contains the PID gene and transcription factor *AIRE* [Table 1] suggests an additional candidate gene to be considered for the effect. The same situation arises for other GWAS loci: i.e. the Chr15 locus (91Mb; identified in CD, UC, RA, T2D), where the PID gene *BLM* must be considered in addition to the current leading candidate *CRTC3*, and the Chr20 locus (62Mb; CD, UC, MS) which contains both the PID gene *RTEL1* and the published candidate *TNFRSF6B*, and finally the Chr8 locus (91Mb; CD) where the PID gene *NBN* gene must be considered along with *RIPK2*. Finally, an interesting situation emerges from the analysis of a locus on Chr12 (109–113Mb; 6 diseases), and that contains a total of 57 genes in LD, including the *UNG* (low level of circulating IgG and IgA) and the *MVK* (auto-inflammatory disorder caused by mevalonate kinase deficiency) genes which inactivation causes PIDs. Hence the GWAS hit at this location in 6 diseases may be due to the independent effect of each gene in specific diseases, an effect that cannot be segregated due to LD; alternatively, it is interesting to consider the possibility that alterations at both genes (either coding variants, or regulatory modulation/eSNPs) may be required to impact inflammatory pathologies.

Box 1**The *IFIH1* gene and pathway at the intersection of inflammatory diseases and primary immunodeficiencies**

The study of tens of thousands of patients by genome-wide association (GWAS) and using SNP arrays of increasing density and informative content, have identified a rich genetic architecture in inflammatory diseases. Of the >400 unique risk loci discussed in our review, identifying the causative gene is limited in part by the presence of linkage disequilibrium (LD) near the mapped loci. LD occurs when chromosomal segments containing several disease-linked contiguous markers (SNPs) are inherited together as a block (haplotype blocks), with the lack of recombination making it difficult to narrow down the exact position of the causative genetic lesion. On the other hand, the rapid identification of rare coding mutations in PID patients by whole exome sequencing is providing a deep dataset for genes that are essential for protection against infections. Merging the 2 datasets may help identify morbid genes at or near GWAS loci.

In the example shown (Figure I), multiple SNPs on human 2q24.2 are associated with inflammatory or autoimmune diseases: 1- rs2111485 is associated with Crohn's and ulcerative colitis [13], lupus [70] and vitiligo [71]; 2- rs1990760 with type 1 diabetes [72], IgA antibody deficiency [73] and Grave's diseases [74] and 3- rs17716942 with psoriasis [75]. LD in this region defines an interval that contains 5 or 6 candidate genes, two of them are expressed in peripheral blood cells and associated with immune function. Interestingly, rs2111485 behaves as a *cis*-acting eQTL that affects *IFIH1* mRNA expression [70]. In addition, application of a "Myeloid Inflammatory Score" (MIS) [76] that considers DNA binding and transcriptional activation by pro-inflammatory transcription factors points to *Ifih1* as the top positional candidate in the LD interval (Figure IB). Interestingly, mice carrying a gain-of-function mutation in *IFIH1* develop spontaneous lupus-like symptoms [77]. Moreover, rare *IFIH1* variants have been associated with risk of type 1 diabetes and Lupus (SLE) [78–81].

IFIH1 encodes the cytosolic viral RNA receptor MDA5, member of the RIG-I-like receptor family, that mediates the induction of a type I interferon for anti-viral immunity (reviewed in [10]). The binding of long dsRNA to MDA5 helicase domain (Figure IC) stimulates signalling through the CARD domain-associated adaptor molecule IPS-1/MAVS, itself a risk locus for asthma [82]; MDA5-IPS-1 signalling is kept under control by the negative regulator ADAR1 [83]. The activated signalling cascade includes several genes implicated in inflammatory diseases by GWAS or mutated in PID (genes in blue and red; Figure ID, Table S2). MDA5 helicase domain sequence variants have been found in Aicardi-Goutières syndrome (AGS) patients (elevated type I IFN levels and signalling) [84, 85]. All identified mutations are autosomal dominant and cause a stabilisation of the helicase domain with dsRNA. MDA5 variants have also been detected in SLE patients, consistent with the fact that some of these AGS patients develop lupus-like symptoms [81].

Figure I. *IFIH1*: a novel PID gene associated with multiple immune-related diseases
 (A) Genome browser representation of genes at a locus bearing SNPs (black bars) associated with several immune-related diseases (labeled in red over the associated SNP). The SNP rs2111485 has been shown to behave as a *cis*-eQTL for expression of *IFIH1* mRNA in response to IFN γ [86]. The mRNA expression of genes in the interval in PBMC is shown (RNA-seq tracks density) over individual exons [87]. (B) Illustration of the corresponding mouse locus, including the position of the genes, the myeloid inflammation score [76] calculated for each gene for presence and activity of pro-inflammatory transcription factors, the binding sites for these transcription factors and histone marks were identified by ChIP-seq, and the levels of expression of each gene in

macrophages in response to IFN γ (**C**) Domain structure of MDA5 (*IFIH1*). The variants associated with immune-related diseases by GWAS (blue) and the missense mutations recently identified in PID patients (red) are shown. (**D**) The signalling pathway activated by MDA5 and RIG-I is critical for host defense against viral infections and alterations in this pathway are associated with various immune-related diseases (blue) and with PIDs (red).

Concluding Remarks

In conclusion, the explosion of genome technologies has dramatically increased our understanding of the genetic architecture of human susceptibility to infections and to inflammatory conditions. Combined analysis of these two datasets identifies a significant overlap composed of genes and proteins that are required for protection against infections but which engagement is associated with pathological inflammation. The genes/proteins identified at this interface may represent valuable new targets for drug discovery. This genetic intersection additionally suggests that although strong mutations and/or inactivation (rare variants) of intersecting genes may independently cause severe diseases (PIDs), their more subtle modulation through the action of common variants in the presence of a persistent tissue insult may contribute to chronic inflammation. Because these two datasets (whole exome sequencing in PIDs; GWAS of inflammatory diseases) continue to expand, it is likely that the intersection between them will continue to grow, increasing its informative content. Likewise, combined analysis of GWAS and PID datasets may help prioritize and/or validate candidate genes identified by sequencing or mapping. These analyses may also point to signal transduction pathways, protein products that physically interact, genes sharing the same expression pattern, and/or regulated by *cis* or *trans* eQTL, and which further modulation may be associated with disease. Finally, the emergence of novel methods for high efficiency genome editing (CRISPR-Cas9) opens the door to the creation of informative animal models where the immunological and biochemical basis of these genes function can be studied in well-defined environments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary Box

Complex disorders

Diseases that are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors

eQTL	Expression Quantitative Trait Loci are loci that affect mRNA expression levels of a specific gene or group of genes
Genome-Wide Association Study (GWAS)	A genome-wide study that aims to associate disease phenotypes with specific genetic markers or loci (SNPs), and that is generally conducted in large populations.
Immunochip	Custom genotyping array containing genetic markers associated with immune-related gene(s)
Linkage disequilibrium (LD)	Situation when multiple physically linked genetic markers (and associated genes) associated with disease are inherited together as “haplotype blocks”, due to absence of recombination events between them in the population studied. The disease-causing genetic lesion may map within the boundaries of the haplotype block or may be physically linked outside the limits of the haplotype block.
Mendelian disorders	Genetic diseases that follows simple mendelian patterns of inheritance
Meta-analysis	A combined analysis of multiple published GWAS to provide additional statistical power to identify disease loci.
Polygenic disease	A disease with a genetic component that involves c several genes
Primary immunodeficiency (PID)	Disorders resulting from inherited defects of the immune system characterized by an increased susceptibility to infections and, in some cases, increased incidence of autoimmunity and malignancies
Quantitative Trait Loci (QTL)	Part of the genome (locus) that modulates a quantitative phenotype
Single nucleotide polymorphism (SNP)	Single nucleotide difference in the DNA sequence of individual members of a given species
SNP array (SNP chips)	An array of single nucleotide polymorphisms that allows genome-wide assignment and is used for association studies

BIBLIOGRAPHY

1. Newport MJ, Finan C. Genome-wide association studies and susceptibility to infectious diseases. *Brief Funct Genomics*. 2011; 10(2):98–107. [PubMed: 21436306]
2. Khor CC, Hibberd ML. Host-pathogen interactions revealed by human genome-wide surveys. *Trends Genet*. 2012; 28(5):233–43. [PubMed: 22445588]
3. Vannberg FO, et al. Human genetic susceptibility to intracellular pathogens. *Immunol Rev*. 2011; 240(1):105–16. [PubMed: 21349089]
4. Aidoo M, et al. Protective effects of the sickle cell gene against malaria morbidity and mortality. *Lancet*. 2002; 359(9314):1311–2. [PubMed: 11965279]

5. Dean M, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the *CKR5* structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science*. 1996; 273(5283):1856–62. [PubMed: 8791590]
6. Picard C, Fischer A. Contribution of high-throughput DNA sequencing to the study of primary immunodeficiencies. *Eur J Immunol*. 2014; 44(10):2854–61. [PubMed: 25154746]
7. Chou J, et al. Use of whole exome and genome sequencing in the identification of genetic causes of primary immunodeficiencies. *Curr Opin Allergy Clin Immunol*. 2012; 12(6):623–8. [PubMed: 23095910]
8. Conley ME, Casanova JL. Discovery of single-gene inborn errors of immunity by next generation sequencing. *Curr Opin Immunol*. 2014; 30:17–23. [PubMed: 24886697]
9. Delogu LG, et al. Infectious diseases and autoimmunity. *J Infect Dev Ctries*. 2011; 5(10):679–87. [PubMed: 21997935]
10. Parkes M, et al. Genetic insights into common pathways and complex relationships among immune-mediated diseases. *Nat Rev Genet*. 2013; 14(9):661–73. [PubMed: 23917628]
11. Anderson CA, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet*. 2011; 43(3):246–52. [PubMed: 21297633]
12. Franke A, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet*. 2010; 42(12):1118–25. [PubMed: 21102463]
13. Jostins L, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012; 491(7422):119–24. [PubMed: 23128233]
14. Okada Y, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*. 2014; 506(7488):376–81. [PubMed: 24390342]
15. Tsoi LC, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nat Genet*. 2012; 44(12):1341–8. [PubMed: 23143594]
16. Ellinghaus E, et al. Genome-wide association study identifies a psoriasis susceptibility locus at *TRAF3IP2*. *Nat Genet*. 2010; 42(11):991–5. [PubMed: 20953188]
17. International Multiple Sclerosis Genetics, C., et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*. 2011; 476(7359):214–9. [PubMed: 21833088]
18. International Multiple Sclerosis Genetics, C., et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet*. 2013; 45(11):1353–60. [PubMed: 24076602]
19. Chapman SJ, Hill AV. Human genetic susceptibility to infectious disease. *Nat Rev Genet*. 2012; 13(3):175–88. [PubMed: 22310894]
20. Karlsson EK, et al. Natural selection and infectious disease in human populations. *Nat Rev Genet*. 2014; 15(6):379–93. [PubMed: 24776769]
21. Abel L, et al. The dissection of complex susceptibility to infectious disease: bacterial, viral and parasitic infections. *Curr Opin Immunol*. 2014; 30:72–8. [PubMed: 25083600]
22. Milner JD, Holland SM. The cup runneth over: lessons from the ever-expanding pool of primary immunodeficiency diseases. *Nat Rev Immunol*. 2013; 13(9):635–48. [PubMed: 23887241]
23. Parvaneh N, et al. Inborn errors of metabolism underlying primary immunodeficiencies. *J Clin Immunol*. 2014; 34(7):753–71. [PubMed: 25081841]
24. Itan Y, Casanova JL. Novel primary immunodeficiency candidate genes predicted by the human gene connectome. *Front Immunol*. 2015; 6:142. [PubMed: 25883595]
25. Al-Herz W, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol*. 2014; 5:162. [PubMed: 24795713]
26. Casanova JL, et al. Guidelines for genetic studies in single patients: lessons from primary immunodeficiencies. *J Exp Med*. 2014; 211(11):2137–49. [PubMed: 25311508]
27. Rieux-Laucat F, Casanova JL. Immunology. Autoimmunity by haploinsufficiency. *Science*. 2014; 345(6204):1560–1. [PubMed: 25258064]

28. Boisson B, et al. Immunological loss-of-function due to genetic gain-of-function in humans: autosomal dominance of the third kind. *Curr Opin Immunol.* 2015; 32:90–105. [PubMed: 25645939]
29. Anderson MS, Casanova JL. More than Meets the Eye: Monogenic Autoimmunity Strikes Again. *Immunity.* 2015; 42(6):986–8. [PubMed: 26084018]
30. Fischer A, et al. Severe combined immunodeficiency. A model disease for molecular immunology and therapy. *Immunol Rev.* 2005; 203:98–109. [PubMed: 15661024]
31. Song E, et al. Chronic granulomatous disease: a review of the infectious and inflammatory complications. *Clin Mol Allergy.* 2011; 9(1):10. [PubMed: 21624140]
32. Zhang SY, et al. TLR3 deficiency in patients with herpes simplex encephalitis. *Science.* 2007; 317(5844):1522–7. [PubMed: 17872438]
33. Zhang SY, et al. Inborn errors of interferon (IFN)-mediated immunity in humans: insights into the respective roles of IFN-alpha/beta, IFN-gamma, and IFN-lambda in host defense. *Immunol Rev.* 2008; 226:29–40. [PubMed: 19161414]
34. Puel A, et al. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. *Curr Opin Allergy Clin Immunol.* 2012; 12(6):616–22. [PubMed: 23026768]
35. Bustamante J, et al. Mendelian susceptibility to mycobacterial disease: Genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. *Semin Immunol.* 2014; 26(6):454–470. [PubMed: 25453225]
36. Dupuis S, et al. Impairment of mycobacterial but not viral immunity by a germline human STAT1 mutation. *Science.* 2001; 293(5528):300–3. [PubMed: 11452125]
37. Liu L, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med.* 2011; 208(8):1635–48. [PubMed: 21727188]
38. Devriendt K, et al. Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia. *Nat Genet.* 2001; 27(3):313–7. [PubMed: 11242115]
39. Hahn CN, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. *Nat Genet.* 2011; 43(10):1012–7. [PubMed: 21892162]
40. Hsu AP, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. *Blood.* 2011; 118(10):2653–5. [PubMed: 21670465]
41. Dickinson RE, et al. Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency. *Blood.* 2011; 118(10):2656–8. [PubMed: 21765025]
42. Minegishi Y, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity.* 2006; 25(5):745–55. [PubMed: 17088085]
43. Kreins AY, et al. Human TYK2 deficiency: Mycobacterial and viral infections without hyper-IgE syndrome. *J Exp Med.* 2015; 212(10):1641–62. [PubMed: 26304966]
44. Hindorff LA, et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proc Natl Acad Sci U S A.* 2009; 106(23):9362–7. [PubMed: 19474294]
45. Li MJ, et al. GWASdb: a database for human genetic variants identified by genome-wide association studies. *Nucleic Acids Res.* 2012; 40(Database issue):D1047–54. [PubMed: 22139925]
46. Webb AJ, et al. An informatics project and online “Knowledge Centre” supporting modern genotype-to-phenotype research. *Hum Mutat.* 2011; 32(5):543–50. [PubMed: 21438073]
47. Thorisson GA, et al. HGVbaseG2P: a central genetic association database. *Nucleic Acids Res.* 2009; 37(Database issue):D797–802. [PubMed: 18948288]
48. Farh KK, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature.* 2015; 518(7539):337–43. [PubMed: 25363779]
49. Cortes A, Brown MA. Promise and pitfalls of the Immunochip. *Arthritis Res Ther.* 2011; 13(1):101. [PubMed: 21345260]
50. Siddle KJ, Quintana-Murci L. The Red Queen’s long race: human adaptation to pathogen pressure. *Curr Opin Genet Dev.* 2014; 29:31–8. [PubMed: 25170983]

51. Blaydon DC, et al. Inflammatory skin and bowel disease linked to ADAM17 deletion. *N Engl J Med*. 2011; 365(16):1502–8. [PubMed: 22010916]
52. Cheng LE, et al. Persistent systemic inflammation and atypical enterocolitis in patients with NEMO syndrome. *Clin Immunol*. 2009; 132(1):124–31. [PubMed: 19375390]
53. Mizukami T, et al. Successful treatment with infliximab for inflammatory colitis in a patient with X-linked anhidrotic ectodermal dysplasia with immunodeficiency. *J Clin Immunol*. 2012; 32(1): 39–49. [PubMed: 21993693]
54. Aguilar C, et al. Characterization of Crohn disease in X-linked inhibitor of apoptosis-deficient male patients and female symptomatic carriers. *J Allergy Clin Immunol*. 2014; 134(5):1131–41 e9. [PubMed: 24942515]
55. Dziadzio M, et al. Symptomatic Males and Female Carriers in a Large Caucasian Kindred with XIAP Deficiency. *J Clin Immunol*. 2015
56. Yang X, et al. Clinical and genetic characteristics of XIAP deficiency in Japan. *J Clin Immunol*. 2012; 32(3):411–20. [PubMed: 22228567]
57. Zeissig Y, et al. XIAP variants in male Crohn's disease. *Gut*. 2015; 64(1):66–76. [PubMed: 24572142]
58. Conley ME, et al. Agammaglobulinemia and absent B lineage cells in a patient lacking the p85alpha subunit of PI3K. *J Exp Med*. 2012; 209(3):463–70. [PubMed: 22351933]
59. Salzer E, et al. Early-onset inflammatory bowel disease and common variable immunodeficiency-like disease caused by IL-21 deficiency. *J Allergy Clin Immunol*. 2014; 133(6):1651–9 e12. [PubMed: 24746753]
60. Avitzur Y, et al. Mutations in tetratricopeptide repeat domain 7A result in a severe form of very early onset inflammatory bowel disease. *Gastroenterology*. 2014; 146(4):1028–39. [PubMed: 24417819]
61. Chen R, et al. Whole-exome sequencing identifies tetratricopeptide repeat domain 7A (TTC7A) mutations for combined immunodeficiency with intestinal atresias. *J Allergy Clin Immunol*. 2013; 132(3):656–664 e17. [PubMed: 23830146]
62. Okou DT, et al. Exome sequencing identifies a novel FOXP3 mutation in a 2-generation family with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2014; 58(5):561–8. [PubMed: 24792626]
63. Dhillon SS, et al. Variants in nicotinamide adenine dinucleotide phosphate oxidase complex components determine susceptibility to very early onset inflammatory bowel disease. *Gastroenterology*. 2014; 147(3):680–689 e2. [PubMed: 24931457]
64. Zhou Q, et al. A hypermorphic missense mutation in PLCG2, encoding phospholipase Cgamma2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. *Am J Hum Genet*. 2012; 91(4):713–20. [PubMed: 23000145]
65. Zeissig S, et al. Early-onset Crohn's disease and autoimmunity associated with a variant in CTLA-4. *Gut*. 2014
66. Glocker EO, et al. Infant colitis--it's in the genes. *Lancet*. 2010; 376(9748):1272. [PubMed: 20934598]
67. Glocker EO, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med*. 2009; 361(21):2033–45. [PubMed: 19890111]
68. Kotlarz D, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. *Gastroenterology*. 2012; 143(2):347–55. [PubMed: 22549091]
69. Moran CJ, et al. IL-10R polymorphisms are associated with very-early-onset ulcerative colitis. *Inflamm Bowel Dis*. 2013; 19(1):115–23. [PubMed: 22550014]
70. Bentham J, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. *Nat Genet*. 2015
71. Jin Y, et al. Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. *Nat Genet*. 2012; 44(6):676–80. [PubMed: 22561518]
72. Todd JA, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. *Nat Genet*. 2007; 39(7):857–64. [PubMed: 17554260]

73. Ferreira RC, et al. Association of IFIH1 and other autoimmunity risk alleles with selective IgA deficiency. *Nat Genet.* 2010; 42(9):777–80. [PubMed: 20694011]
74. Sutherland A, et al. Genomic polymorphism at the interferon-induced helicase (IFIH1) locus contributes to Graves' disease susceptibility. *J Clin Endocrinol Metab.* 2007; 92(8):3338–41. [PubMed: 17535987]
75. Genetic Analysis of Psoriasis, C., et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet.* 2010; 42(11):985–90. [PubMed: 20953190]
76. Kennedy JM, et al. CCDC88B is a novel regulator of maturation and effector functions of T cells during pathological inflammation. *J Exp Med.* 2014; 211(13):2519–35. [PubMed: 25403443]
77. Funabiki M, et al. Autoimmune disorders associated with gain of function of the intracellular sensor MDA5. *Immunity.* 2014; 40(2):199–212. [PubMed: 24530055]
78. Nejentsev S, et al. Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. *Science.* 2009; 324(5925):387–9. [PubMed: 19264985]
79. Cen H, et al. Association of IFIH1 rs1990760 polymorphism with susceptibility to autoimmune diseases: a meta-analysis. *Autoimmunity.* 2013; 46(7):455–62. [PubMed: 23734776]
80. Gateva V, et al. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. *Nat Genet.* 2009; 41(11):1228–33. [PubMed: 19838195]
81. Molineros JE, et al. Admixture mapping in lupus identifies multiple functional variants within IFIH1 associated with apoptosis, inflammation, and autoantibody production. *PLoS Genet.* 2013; 9(2):e1003222. [PubMed: 23441136]
82. Loo YM, Gale M Jr. Immune signaling by RIG-I-like receptors. *Immunity.* 2011; 34(5):680–92. [PubMed: 21616437]
83. Pestal K, et al. Isoforms of RNA-Editing Enzyme ADAR1 Independently Control Nucleic Acid Sensor MDA5-Driven Autoimmunity and Multi-organ Development. *Immunity.* 43(5):933–944. [PubMed: 26588779]
84. Rice GI, et al. Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. *Nat Genet.* 2014; 46(5):503–9. [PubMed: 24686847]
85. Oda H, et al. Aicardi-Goutieres syndrome is caused by IFIH1 mutations. *Am J Hum Genet.* 2014; 95(1):121–5. [PubMed: 24995871]
86. Fairfax BP, et al. Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. *Science.* 2014; 343(6175):1246949. [PubMed: 24604202]
87. Salem S, et al. Functional characterization of the human dendritic cell immunodeficiency associated with the IRF8(K108E) mutation. *Blood.* 2014; 124(12):1894–904. [PubMed: 25122610]

Trends

- Alterations in numbers and activity of immune cells and associated responses result in infectious and inflammatory diseases, which are two of the most common disease areas in humans.
- Complex genomic datasets involving hundreds of genes are emerging from genome-wide association studies of susceptibility to common inflammatory diseases, and from whole exome sequencing of patients suffering from primary immuno-deficiencies.
- Combined analysis of risk loci for 22 common human inflammatory diseases, and of all primary immunodeficiencies with a known genetic lesion identifies a highly significant genetic overlap between the two groups of diseases
- The cellular and molecular pathways anchored around these genes are therefore required for protection against infections, but their persistent or dysregulated engagement for pathological inflammation in humans.

Figure 1. Genome-Wide Association Studies of Inflammatory Diseases: Major Shared Genetic Loci

Graphical representation of the genetic architecture of susceptibility to major inflammatory diseases (Circos plot). The outside rim identifies the 22 human chromosomes in individual colors. The inflammatory diseases surveyed are identified and depicted by concentric circles onto which the mapped loci shared by 2 or more diseases are positioned (blue dots). Two genetic risk loci are considered overlapping when the most significant SNP at a given locus maps <50kb from another locus (Table S2). Red intersecting lines identify loci that are shared in common by 4 or more of the diseases surveyed. An abbreviated list of genes in linkage disequilibrium (the number of genes in LD are in brackets) at each locus radiates to the outer part of the plot. Abbreviations: CD (Crohn's Disease); UC (ulcerative colitis); CeD (celiac disease); MS (multiple sclerosis); RA (rheumatoid arthritis); Pso. (psoriasis); SLE (systemic lupus erythematosis); Vit. (vitiligo); T1D (type 1 diabetes); AS (Ankylosing spondylitis); Asth. (asthma); AD (Atopic dermatitis); PBC (primary biliary cirrhosis); AA (Alopecia areata); Behc. (Behcet's disease); Grav. (Graves' disease); Hypoth. (hypothyroidism); Kawa. (Kawasaki disease); Narc. (narcolepsy); Neph. (Nephropathy); SS (Systemic sclerosis); T2D (type 2 diabetes).

Figure 2. Signalling Pathways Altered in Primary Immunodeficiencies and Detected as Genetic Risks of Major Inflammatory Diseases

Components of cytokine signalling pathways and associated transcriptional responses affected in PIDs and detected as genetic risk loci for common inflammatory diseases (**red lettering**). Upon binding of type I IFNs to their receptor (IFNAR), the canonical signal transducer (JAK1/TYK2), and activator of transcription 1 (STAT1)–STAT2–IFN-regulatory factor 9 (IRF9) signalling complex binds to IFN-stimulated response elements leading to induction of a large number of IFN-stimulated antiviral genes such as OAS and MX1. Binding of Type II IFNs can also signal through STAT1 homodimers, inducing antimicrobial responses. The engagement of different interleukin receptors (IL-2R, IL-7R, IL-10R, IL-12R, IL-21R) induces the transcription of target genes through several signalling pathways, including the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, all of which induce several immune gene responses.

Figure 3. Illustration of Selected Proteins and Associated Pathways mutated in PIDs and detected as Risk Factors in Inflammatory Diseases

Proteins (from Table 1; **red lettering**) involved in the functional cross-talk between myeloid and lymphoid cells including antigen recognition, capture, processing, and presentation to T cells, and associated responses are represented. Impaired regulation in monogenic disorders can affect adaptive immune responses (such as CD45, OX40, ICOS and CD40 deficiencies) by effector cells, peptide presentation by APC (such as PSMB8, TAP1/2 deficiencies) or bacterial sensing (NOD2, CARD9) exemplify the interaction network between PID and inflammatory diseases (for further details refer to text).

Table 1
Genes Mutated in Primary Immunodeficiencies and Detected as Risk Loci in Genome-Wide Association Studies of Major Inflammatory Diseases.

PID Genes	CD	UC	CeD	MS	RA	Pso.	SLE	Vit.	T1D	AS	JIA	Asth.	AD	PBC	AA	Behc.	ATD	Kawa.	Narc.	Neph.	SS	T2D	VEO-IBD
1. Combined immunodeficiencies																							
ADA																							
BCL10																							
CARD11																							
CD247																							
CD27																							
CD40																							
CIITA																							
IL21																							
IL7R																							
MALT1																							
MAP3K14																							
PTPRC																							
RAG1																							
RAG2																							
RHOH																							
TAP1																							
TAP2																							
TNFRSF4																							
2. Well-defined syndromes with immunodeficiencies																							
ATM																							
BLM																							
DCLRE1B																							
DNMT3B																							
IKZF1																							
NBN																							

PID Genes	CD	UC	CeD	MS	RA	Pso.	SLE	Vit.	T1D	AS	JIA	Asth.	AD	PBC	AA	Behc.	ATD	Kawa.	Narc.	Neph.	SS	T2D	VEO-IBD
NFKBIA																							
RTEL1																							
SP110																							
STAT3																							
STAT5B																							
3. Predominantly antibody deficiencies																							
CD19																							
CR2																							
ICOS																							
NFKB2																							
PRKCD																							
UNG																							
4. Diseases of immune dysregulation																							
AIRE																							
CASP10																							
CASP8																							
CTLA4																							
FAS																							
FASLG																							
IFIH1																							
IL10																							
IL10RB																							
IL2RA																							
LYST																							
RNASEH2C																							
5. Congenital defects of phagocyte number, function, or both																							
NCF2																							
NCF4																							
RAC2																							

PID Genes	CD	UC	CeD	MS	RA	Pso.	SLE	Vit.	T1D	AS	JIA	Asth.	AD	PBC	AA	Behc.	ATD	Kawa.	Narc.	Neph.	SS	T2D	VEO-IBD
6. Defects in intrinsic and innate immunity																							
CARD9																							
CXCR4																							
FCGR3A																							
IFNGR1																							
IFNGR2																							
IL12B																							
IL12RB1																							
IRF7																							
IRF8																							
RORC																							
STAT1																							
STAT2																							
TICAM1																							
TRAF3																							
TRAF3IP2																							
TYK2																							
7. Autoinflammatory disorders																							
CARD14																							
LPIN2																							
MVK																							
NOD2																							
PSMB8																							
SLC29A3																							
TNFRSF1A																							
8. Complement deficiencies																							
C2																							
C3																							
C5																							

PID Genes	CD	UC	CeD	MS	RA	Pso.	SLE	Vit.	T1D	AS	JIA	Asth.	AD	PBC	AA	Behc.	ATD	Kawa.	Narc.	Neph.	SS	T2D	VEO-IBD
CFB																							
CFH																							
ITGAM																							
Newly identified genes (PMID)																							
STAT4 (25492914)																							
	34	30	8	23	24	10	18	7	13	6	5	1	3	6	5	2	5	5	1	4	4	2	12

CD, Crohn’s disease; UC, Ulcerative colitis; CeD, Celiac disease; MS, Multiple colitis; RA, Rheumatoid arthritis; Pso., Psoriasis; SLE, Systemic lupus erythematosus; Vit., Vitiligo; T1D, Type 1 diabetes; AS, Ankylosing spondylitis; JIA, Juvenile idiopathic arthritis; AD, Atopic dermatitis; PBC, Primary biliary cirrhosis; AA, Alopecia areata; Behc., Behcet’s disease; ATD, Autoimmune thyroid disease (including Graves’ disease and hypothyroidy); Kawa., Kawasaki disease; Narc., Narcolepsy; Neph., Nephropathy; SS, Systemic sclerosis; T2D, Type 2 diabetes; VEO-IBD, Very early onset inflammatory bowel disease; PMID, PubMed ID number.

* N.B.: light gray boxes represent GWAS *p* value <10^{−5}, and dark gray boxes are for *p* values <10^{−8}.