Immunology Taught by Human Genetics

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Human genetic studies are rarely conducted for immunological purposes. Instead, they are typically driven by medical and evolutionary goals, such as understanding the predisposition or resistance to infectious or inflammatory diseases, the pathogenesis of such diseases, and human evolution in the context of the long-standing relationships between humans and their commensal and environmental microbes. However, the dissection of these experiments of Nature has also led to major immunological advances. In this review, we draw on some of the immunological lessons learned in the three branches of human molecular genetics most relevant to immunology: clinical genetics, epidemiological genetics, and evolutionary genetics. We argue that human genetics has become a new frontier not only for timely studies of specific features of human immunity, but also for defining general principles of immunity. These studies teach us about immunity as it occurs under "natural" conditions, through the transition from the almost complete wilderness that existed worldwide until about a century ago to the current unevenly distributed medically shaped environment. Hygiene, vaccines, antibiotics, and surgery have considerably decreased the burden of infection, but these interventions have been available only recently, so have yet to have a major impact on patterns of genomic diversity, making it possible to carry out unbiased evolutionary studies at the population level. Clinical genetic studies of childhood phenotypes have not been blurred by modern medicine either. Instead, medical advances have actually facilitated such studies, by making it possible for children with life-threatening infections to survive. In addition, the prevention and treatment of infectious diseases have increased life expectancy at birth from ~20 yr to ~80 yr, providing unique opportunities to study the genetic basis of immunological phenomena against which there is no natural counterselection, such as reactivation and secondary infectious diseases and breakdown of self-tolerance manifesting as autoimmunity, in populations of adult and aging patients. Recently developed deep sequencing and stem cell technologies are of unprecedented power, and their application to human genetics is opening up exciting and timely possibilities for young immunologists seeking uncharted waters to explore.

Research in humans is increasingly contributing to immunology, not only by defining human-specific features of immunity, but also by revealing general principles of immunity. There are many difficulties inherent to studies of humans, including the great ethical and technical difficulties of experimental approaches, and the tremendous level of inter-individual variability. These obstacles account for the systematic development of experimental approaches in inbred animals from the early 19th century onward. For a long time, human genetics in immunology (i.e., immunogenetics) was almost synonymous with "HLA and transplantation" and "HLA and disease." Major discoveries were made in this area, such as the strong associations of HLA-B27 with spondylarthropathies and of HLA-DQ8 with type 1 diabetes (T1D). However, a few notable discoveries were made outside the realm of HLA, such as the protective role of the sickle-cell trait (HbS) in severe malaria. These and other genetic epidemiological studies have been extended, facilitating the dissection of the seemingly complex basis of phenotypes at the population level (i.e., phenotypes common to large number of patients). The impact of these findings was perhaps more medical than immunological. In the 1970s and the 1980s, when these seminal discoveries on HLA were made, only a few investigators would have predicted that human genetics would soon contribute to immunology in other more spectacular ways.

During the last 30 years, with the emergence of recombinant DNA and molecular genetics, we have witnessed continued and extraordinary progress in the tools of human genetics. This progress has accelerated further during the last 15 years, from Sanger sequencing of the first human genome to the next-generation sequencing (NGS) of countless whole exomes and genomes. These and other achievements, both experimental and statistical, have transformed the genetic variability and phenotypic heterogeneity of human populations from a liability into an asset. They have made it possible to exploit observations of human phenotypes under natural conditions, *in natura*, with an understanding of their germline genetic basis in

each individual. Primary immunodeficiencies (i.e., single-gene inborn errors of immunity) have made a particularly important contribution in this respect, and studies in this field are increasing adding to immunological knowledge. More recently, an older branch of genetics—human evolutionary and population genetics—has reemerged as a powerful molecular approach, following the generation of gigantic data sets cataloging human genetic variation in "healthy" (but nevertheless mortal) individuals (The International HapMap Project, The 1000 Genomes Project, etc.). Evolutionary genetic studies analyze the extent of naturally occurring variations at the level of human populations, transforming the disadvantages of interindividual and interpopulation variation into an advantage, without the need for phenotypic selection.

Clearly, the times when human immunogenetics was synonymous with HLA are long gone. Modern human molecular genetic approaches can be divided into three complementary and overlapping approaches: clinical genetics, epidemiological genetics, and evolutionary genetics. We review here the concepts and methods of these three branches of human genetics, discussing the ways in which they are likely to increase our understanding of immunology in the future. According to Krogh's principle, there is often a "best" species in which to tackle a specific scientific problem experimentally (Krogh 1929; Krebs 1975); implicit within this notion is the assumption that an experimental solution to the problem is required, as suggested by Claude Bernard (1865). However, we can also view "experiments of Nature" in humans as an alternative and complementary way of approaching a wide range of biological problems (McQuarrie 1944), including immunological problems in particular (Good 1991). Now is the ideal time to study such natural experiments, as hygiene, vaccines, antibiotics, surgery, and other features of modern medicine have not yet been around long enough to modify the distribution of genotypes at the scale of human populations. We argue here that human genetics has thrust immunology into a new dimension, and that such studies are complementary to experimental studies in the mouse or even more distant animal models (*Drosophila,* lamprey, zebrafish, etc.). Inspired by insightful papers on what studies of viruses (Zinkernagel 1996), bacteria (Vance 2010), humans (Davis 2012) and even Darwin (Phillips 2002) have taught us about immunology, we will focus on the lessons to be learnt about immunology from human genetics. Owing to space limitations, we will limit ourselves here to genetic studies of infectious and inflammatory diseases.

CLINICAL GENETIC STUDIES

General Concepts and Methods

Genetic studies of primary immunodeficiencies (i.e., single-gene inborn errors of immunity) have had a tremendous impact in the field of immunology (Conley et al. 2011; Casanova et al. 2013). These patient-based studies typically aim to investigate the pathogenesis of a relatively rare, specific textbook medical condition, a small group of patients resembling each other but no textbook description, or, even, in some cases, a single patient with a new clinical presentation (Al-Herz et al. 2011; Bousfiha et al. 2013a). These genetic defects have an impact on the population that is individually modest (although their collective impact is greater) (Bousfiha et al. 2013b), but their elucidation has major implications for immunology, as they can connect a morbid genotype to a clinical phenotype. Studies of this kind are the easiest for most immunologists working with animals to understand, as this branch of human genetics is the closest to their own field. Such studies aim to describe the disease-causing genotype, immunological mechanism, and clinical phenotype of patients with a monogenic defect, as in mutant mice discovered by forward genetics or created by reverse genetics approaches. We use the terms monogenic and single-gene defects interchangeably throughout this review. We do not restrict the term "Mendelian" to monogenic defects, as this term implies full clinical penetrance, which is not observed in all cases. Penetrance is the proportion of individuals carrying a given genotype that actually express a disease phenotype. Expressivity is the variability of the phenotype (e.g., in terms of severity) considered among the patients studied who carry a given genotype. An increasing number of single-gene inborn errors of immunity have been described since the 1950s (Casanova and Abel 2007; Pessach et al. 2009). The first such defects to be described were autosomal recessive (AR) or X-linked recessive (XR), but an increasing number of autosomal-dominant (AD) traits have recently been reported (Al-Herz et al. 2011; Bousfiha et al. 2013a). Only in very rare instances the defect is mitochondrial.

Locus, Allelic, and Phenotypic Heterogeneity

The mutant alleles in patients with inborn errors of immunity may be null (i.e., loss-of-function, *sensu stricto*) or hypomorphic (i.e., with residual activity). Interestingly, hypermorphic (i.e., gain-of-function) mutations have also recently been described (Devriendt et al. 2001; Courtois et al. 2003; Liu et al. 2011). The high level of allelic heterogeneity (i.e., diversity of mutant alleles at a given morbid locus, exerting diverse impacts) makes the investigation of human patients with mutations of a given gene particularly rich, due to this diversity (e.g., *RAG1* and *RAG2* mutations underlying different types of T-cell deficits, and *STAT1* mutations underlying different types of infections, of different severity) (Buckley 2004; Boisson-Dupuis et al. 2012; Notarangelo 2013) (Table 1), whereas mutant mice tend to display uniform complete defects, particularly for gene knockout. Even knocked-in and ENU-mutated mice do not display the level of allelic diversity observed in humans. There are no conditional knockouts in humans, but some subtle mutations behave differently in different cell types, being null in some cell types but not in others (e.g., *CYBB* mutations affecting only macrophages in patients with Mendelian susceptibility to mycobacterial disease, MSMD) (Bustamante et al. 2011). Perhaps the greatest surprise of all is the unpredictable impact of AD traits, which may exert their effects

Table 1. Four inborn errors of STAT1 immunity: an illustration of variable inheritance, allelic heterogeneity, variable expressivity, variable penetrance, and locus pleiotropy

Functional impact	Inheritance	Immunological phenotypes	Clinical phenotypes
Complete STAT1 defect	AR	Abolished IFN-α/β, -γ, -λ, IL-27 responses	Severe intracellular bacterial (mycobacteria, salmonella) and viral diseases
Partial STAT1 defect	AR	Impaired IFN-α/β, -γ, -λ, IL-27 responses	Milder intracellular bacterial and viral diseases
Partial STAT1 defect	AD	Selectively impaired IFN-γ responses	Selective intracellular bacterial diseases (MSMD)
Gain of STAT1 activity	AD	Enhanced IFN-α/β, -γ, -λ, IL-27 responses	CMC, other infections, autoimmunity, aneurysms, carcinomas

There is *allelic heterogeneity* at the human *STAT1* locus not only because there are multiple mutant morbid alleles but more importantly because they have different impacts: they can be gain-of-function (GOF) or loss-of-function (LOF), the latter including truly null and hypomorphic alleles. The known GOF alleles are gain of phosphorylation by lack of nuclear dephosphorylation. The *STAT1* mutations actually define two *modes of inheritance*, with two types of AR defects and two types of AD defects. The AR defects are complete (two null alleles) or partial (at least one hypomorphic allele). The AD disorders confer gain (GOF alleles) or loss (LOF and dominant-negative alleles) of activity. In fact, the dominant-negative LOF alleles of STAT1 can be null or hypomorphic and can be further divided into at least three groups, depending on whether they affect the DNA-binding domain, the SH2 domain, or the phosphorylation of Tyr 701. The GOF alleles of STAT1 can also affect the coiled-coil domain or the DNA-binding domain. There is *variable expressivity* as for each of the four types of inborn errors, the clinical severity varies from patient to patient, possibly but not necessarily depending on the specific *STAT1* genotype. There is even *variable penetrance* clinically overall: The clinical penetrance is apparently complete at an early age in patients with complete AR deficiency and AD gain of activity, whereas the disorder may be silent until adulthood and possibly for a lifetime for the partial defects (incomplete penetrance). Finally, the human STAT1 locus is *pleiotropic* because completely different infectious diseases are allelic at the *STAT1* locus, each determined by a specific type of mutant allele (MSMD with dominant-negative alleles and CMC with GOF alleles). These disorders were recently reviewed (Boisson-Dupuis et al. 2012).

by haploinsufficiency (e.g., *RPSA* mutations underlying asplenia and *TBK1* mutations underlying HSE) or by dominant-negative effects (e.g., *STAT1* mutations underlying MSMD and other *TBK1* mutations in herpes simplex encephalitis, HSE). The number of known AD inborn errors of immunity is increasing and constitutes an exciting trend in human studies. Heterozygous mutations may also have different effects on different pathways, being null for all pathways but associated with an AD phenotype in some pathways (e.g., *STAT1* mutations affecting IFN-γ but not IFN-α/β responses in MSMD patients) but not others. Negative dominance accounted for the first AD defects, but haploinsufficiency is increasingly documented, sometimes in the same pathway (e.g., *IFNGR1* and *IFNGR2* underlying MSMD) (Jouanguy et al. 1999; Kong et al. 2013). Both AR and AD disorders may result in partial defects, facilitating the observation of phenotypes not seen with embryonic lethal AR complete defects in mice or humans (e.g., *TRAF3* in HSE and *MCM4* in NK deficiency) (Perez de Diego et al. 2010; Gineau et al. 2012; Hughes et al. 2012). Finally, a particular gene may be subjected to both loss- and gain-of-function mutations (e.g., *WASP* mutations underlying Wiskott–Aldrich syndrome or neutropenia, and *STAT1* mutations MSMD or chronic mucocutanous candidiasis, CMC). This complexity has not been observed in the mouse model. There is also considerable locus heterogeneity (i.e., diversity of mutant loci underlying a given disease phenotype), which can connect hitherto unrelated genes (e.g., agammaglobulinemia and MSMD) (Al-Muhsen and Casanova 2008; Conley et al. 2009). Conversely, there is also pleiotropy at many loci (i.e., apparently unrelated diseases being allelic at the same locus, possibly, but not necessarily, by the same mechanism), potentially connecting hitherto unrelated phenotypes (e.g., *STAT1* heterozygous mutations underlying MSMD or CMC) (Boisson-Dupuis et al. 2012). Finally, it is worth stressing that the diversity of disease phenotypes known to be caused by inborn errors of immunity is steadily increasing. From infections, autoimmunity, allergy, and cancer, which were first recognized as being due to inborn errors of immunity in the 1950s and 1960s, the field has expanded to include phenotypes as diverse as hemophagocytosis, autoinflammation, alveolar proteinosis, and microangiopathies (Casanova and Abel 2007; Kavanagh et al. 2008; Masters et al. 2009; Pessach et al. 2009; Trapnell et al. 2009; Pachlopnik Schmid et al. 2010). There are probably many more relevant phenotypes to be discovered, as the clinical frontiers of this field are relentlessly advancing.

The Discovery of New Genes

So, from an immunological perspective, what should we consider to be the highlights of clinical genetics over the last three decades of gene cloning? First, immunological hypothesis-free, genome-wide (GW) approaches have led to the identification of completely new genes (i.e., previously unknown genes or genes with no known biological function). The cellular complementation of cellular phenotypes led to elucidation of the molecular genetic basis of HLA class II deficiency. This tour de force characterized the nature, diversity, and role of a set of proteins responsible for regulating the transcription of HLA class II loci (e.g., *CIITA*) (Reith et al. 1988; Krawczyk and Reith 2006). This high-risk approach was less fruitful than the much simpler GW linkage (GWL) approach, which has led to the identification of multiple new genes. The first example was the dissection of the gene controlling the phagocytic respiratory burst and mutated in X-linked chronic granulomatous disease, which was made possible by GWL (Royer-Pokora et al. 1986; Teahan et al. 1987). GWL is not unlike forward genetics in mice, which has generated a series of spectacular immunological discoveries (e.g., Nramp, Ly49 H, Tlr4, and Foxp3) (Cook et al. 2006; Beutler et al. 2007; Appleby and Ramsdell 2008; Scalzo and Yokoyama 2008; Vidal

et al. 2008). Examples of human genes identified by GWL include *ATM*, *BTK*, *WASP*, *ARTEMIS*, and *AIRE*, to cite only some of the most interesting (Tsukada et al. 1993; Derry et al. 1994; Savitsky et al. 1995; Consortium, Finnish–German APECED 1997; Nagamine et al. 1997; Moshous et al. 2001). Some of these genetic defects identified molecules as involved in biological processes that had previously been characterized, such as VDJ recombination (e.g., Artemis) (Moshous et al. 2001). Others have revealed the involvement of completely new pathways. Perhaps the most far-reaching success was the discovery of the genetic basis of AR autoimmune polyendocrinopathy type I (APS-1) (Husebye and Anderson 2010) as mutations of *AIRE*. This led to major molecular advances in the field of T-cell tolerance. AIRE controls the thymic expression of peripheral antigens and has also been shown to control tolerance in the periphery (Anderson et al. 2002; Gardner et al. 2008). Patients with APS-1 display multiple autoimmune manifestations, including chronic mucocutaneous candidiasis that is caused, paradoxically, by autoantibodies against IL-17 cytokines (Kisand et al. 2010; Puel et al. 2010). The positional cloning of *AIRE* has opened up an entirely new field in immunology (Abramson et al. 2010). Needless to say, human GWL studies have also had important clinical implications.

The Identification of New Functions for Known Genes

A different, but related situation is the discovery of a new function for a known gene (i.e., a gene to which a different biological function has already been attributed). This discovery may pertain to a novel immunological function or even to the first immunological function of the protein concerned. An example of the former is provided by IL2RG, which was initially identified as a component of the IL-2R. Mutations in children with XR severe combined immunodeficiency (SCID) lacking both T cells and NK cells implied an involvement in other pathways (Noguchi et al. 1993; Puck et al. 1993). Indeed, the lack of T-cell development was later explained by the lack of IL-2RG-dependent IL-7 responses, with the identification of IL-7R deficiency in other SCID patients in whom NK cells were present (Puel et al. 1998). A more recent example is provided by mutations in X-linked *MAGT1*, encoding Magnesium transporter 1, which were surprisingly shown to confer an NK and a T-cell deficiency that results in Epstein-Barr virus (EBV)-driven diseases (Li et al. 2011; Chaigne-Delalande et al. 2013). Mutated individuals display low levels of free Mg^{2+} in their NK and T cells, which accounts for low NKG2D expression and poor control of EBV-infected cells. Strikingly, Mg^{2+} supplementation in vivo complemented the immunological and infectious phenotypes. Another recent example is ISG15, which has been shown to be mutated in patients with mycobacterial disease but normal resistance to viral illnesses (Bogunovic et al. 2012). The known biological and immunological function of ISG15 is as a ubiquitin-like molecule essential for ISGylation, an intracellular process that is dependent on IFN-α/β and contributes to antiviral

immunity in mice (Bogunovic et al. 2013). The discovery that ISG15 is a secreted molecule that also functions as a potent IFN-γ inducer was made by GWL and whole-exome sequencing (WES). A related example is the discovery that patients deprived of linear ubiquitination because of inherited HOIL1 deficiency display a combination of immunodeficiency, autoinflammation, and amylopectinosis (Boisson et al. 2012). A striking example of the discovery of a first immunological function for a known gene is provided by the recent WES-based discovery of heterozygous mutations of the gene encoding the ribosomal protein RPSA in patients with isolated congenital asplenia (ICA) (Bolze et al. 2013). RPSA was not known to play a role in the development or function of the immune system. Over half the patients with ICA carry *RPSA* heterozygous coding mutations and the mechanism underlying the disease involves haploinsufficiency. This is interesting, because RPSA and ribosomes appear to play a specific role in the translation of certain mRNAs controlling spleen development. Another example is provided by the discovery of biallelic *MCM4* mutations in patients with a complex phenotype including a selective NK deficiency in the hematopoietic lineage (Gineau et al. 2012; Hughes et al. 2012). The minichromosome maintenance (MCM) complex was not known to be essential for the final steps of CD56^{bright} cell maturation to generate CD56^{dim} human NK cells.

The Discovery of Essential Functions of Known Genes

Most monogenic immunodeficiencies were discovered through candidate gene approaches, making use of the known immunological function of various genes. The discovery of humans carrying mutations in these genes was made possible by prior description of the functions of these genes in mice, often by gene targeting but occasionally by forward genetics, or even in humans. In some cases, the candidate gene approach was sufficient, as for the demonstration that IL-7R deficiency is a cause of SCID. In other cases, the candidate gene approach was not used in isolation, instead being combined with GWL, WES, or both. For example, IFN-γR1 deficiency was discovered in patients with MSMD and UNC-93B deficiency was detected in patients with HSE by the combination of GWL with a candidate gene approach (Jouanguy et al. 1996; Newport et al. 1996; Casrouge et al. 2006). In such situations, the morbid gene is chosen for mechanistic studies from a small set of genes selected on the basis of linkage or sequencing. In rare instances, the candidate gene approach is almost nonexistent, as GWL and WES identify a single mutated gene, as illustrated by the discovery of OX40 deficiency in patients with Kaposi sarcoma (Byun et al. 2013). Interestingly, a key lesson to be learnt from these studies is that the human disease phenotype often overlaps, but does not exactly match the phenotype observed in the mouse model. These phenotypic differences are particularly marked when the infectious and autoimmune phenotypes are considered, as seen with inborn errors of IFN-γ, IL-17, TLR3, and TIR immunity (Casa-

nova and Abel 2002; Casrouge et al. 2006; Ku et al. 2007; Zhang et al. 2007, 2013; von Bernuth et al. 2008; Casanova et al. 2011; Liu et al. 2011; Puel et al. 2011, 2012; Bogunovic et al. 2012). In particular, the infectious phenotypes of humans tend to be much narrower than those observed in mice. Surprisingly, a number of severe infections striking otherwise healthy children were shown to be due to single-gene inborn errors of immunity (Casanova and Abel 2005, 2013; Alcais et al. 2010). These and other studies also revealed infectious phenotypes not predicted by the mouse model. For example, the discovery that human IL-21 is essential for protective immunity against *Cryptosporidium parvum* in the liver was surprising (Kotlarz et al. 2013). Likewise, the autoimmune phenotypes of mice and humans do not entirely overlap for Fas, Foxp3, and AIRE deficiencies (Notarangelo et al. 2006; Cheng and Anderson 2012). The development and function of leukocyte subsets may also differ between mice and humans, albeit to a lesser extent and less frequently, as seen, for example, with BTK and IL2RG deficiencies (Buckley 2004; Conley et al. 2009). In any case, human genes display greater redundancy, for both host defense and self-tolerance, than mouse genes, accounting for the narrow infectious or autoimmune phenotype often seen, contrasting with the broader corresponding mouse phenotype. We have explained in detail elsewhere why we believe this is the case, with both differences between species and differences between experimental and natural phenotypes (Casanova and Abel 2004). One issue of key interest in human genetics is the description of immunity *in natura*, in a natural ecosystem governed by natural selection (Casanova and Abel 2007; Quintana-Murci et al. 2007). Finally, it has gradually become apparent that many single-gene inborn errors of immunity do not display full clinical penetrance, particulary, but not exclusively, AD disorders (e.g., *IL12RB1* and *TLR3*) (Fieschi et al. 2003; Zhang et al. 2007; de Beaucoudrey et al. 2010). The search for the germline, somatic, or environmental determinism of health or disease in genetically affected individuals is a major goal in the field, which will also have an immunological impact.

GENETIC EPIDEMIOLOGICAL STUDIES

General Concepts and Methods

Genetic epidemiology involves population-based studies that combine epidemiological and genetic information to identify gene variants with a detectable influence on phenotypes at the population level (Khoury et al. 1993; Alcais and Abel 2004). Before genetic markers became available, many methods were developed for assessing the familial aggregation of a trait. These methods included twin studies (Khoury et al. 1993), which provided strong evidence for the role of genetic factors in both inflammatory diseases, including but not limited to autoimmune diseases (Cooper et al. 1999), and infectious diseases (Alcais and Abel 2004). The most formalized approach in this context is complex segregation analysis, a statistical method in which the familial distribution of a given phenotype results from the combined effects of a "major lo-

cus," a polygenic component and environmental factors (Khoury et al. 1993; Alcais and Abel 2004; Alcais et al. 2009a). A major gene differs from a "Mendelian" effect in displaying incomplete penetrance and its phenotypic expression may be influenced by the environment and other genes (including germline and somatic variants, and both genetic and epigenetic influences) (Alcais et al. 2009a,b). The existence of major genes for various inflammatory (Cooper et al. 1999) and infectious (Alcais et al. 2009a) phenotypes was first suspected in the 1970s. The advent of genetic markers led to the development of the two pillar methods of genetic epidemiology, linkage and association studies, making it possible to identify major genes, as detailed below. Both linkage and association studies can be conducted according to two classical strategies (Casanova and Abel 2004; Alcais et al. 2009a): (1) a "candidate-gene" approach, with the a priori selection of one or a limited number of genes/variants to be tested, based on knowledge obtained from experimental or human studies; (2) a "GW" approach, in which the whole genome is investigated, to generate new hypotheses. All these studies are based on statistical tests and stringent criteria, including replication in independent studies, must be met for the results to be considered convincing. Evidence for a causal role of a polymorphism may also be provided by functional studies, which can be challenging, as the biological impact of the polymorphism may be subtle.

Linkage Studies

Linkage studies are used to search for chromosomal regions that segregate in a nonrandom manner with the phenotype of interest within families (Khoury et al. 1993; Alcais and Abel 2004). Initially, the regions identified were limited to those for which markers were available, such as the HLA region in particular. The development of GWL screens in the 1990s extended the use of the major gene concept to loci identified in this context (Alcais et al. 2009a,b). HLA-linked major loci were identified by these approaches in a number of inflammatory disorders (Forabosco et al. 2009), such as T1D (Concannon et al. 2005), multiple sclerosis (MS) (Sawcer et al. 2005), and ankylosing spondylitis (AS) (Zhang et al. 2004). Several non-HLA major loci have also been mapped in GWL screens (Goris and Liston 2012). Unfortunately, in contrast to the situation for more penetrant monogenic diseases, fine mapping of the genes of interest cannot be achieved by linkage alone. The next step is investigating the role of variants located within the identified region in comprehensive association studies. One of the most remarkable instances of the identification of a non-HLA locus in an immunological disorder was the discovery of *NOD2*/*CARD15* variants in patients with Crohn's disease (CD), within the chromosome 16 region (Hugot et al. 2001; Ogura et al. 2001) previously identified by GWL analysis (Hugot et al. 1996). This positional cloning strategy also led to the identification of variants at two major loci mapped in a GWL study on leprosy (Mira et al. 2003). The first of these variants, on chromosome 6q25, concerned the regulatory region shared by *PARK2*, a

gene encoding an E3-ubiquitin ligase called Parkin, and *PACRG* (Parkin coregulated gene) (Mira et al. 2004). The second, on chromosome 6p21, was a single functional polymorphism of the lymphotoxin-α (*LTA*) gene (Alcais et al. 2007). More recently, *TOX* variants have been shown to be associated with pulmonary tuberculosis (TB) (Grant et al. 2013), following the identification of a major locus on chromosome 8q12 (Baghdadi et al. 2006). The association observed in these studies was much stronger in patients who developed early-onset leprosy or pulmonary TB, consistent with the general concept that a younger age at onset of the disease reflects a stronger individual genetic effect (Alcais et al. 2010; Casanova and Abel 2013).

Candidate Gene Association Studies

Association studies aim to assess the contribution of genetic variants to the disease studied by comparing the distribution of these variants between affected (cases) and unaffected (controls) subjects (Khoury et al. 1993; Alcais and Abel 2004). Family-based designs can also be used for association studies (Laird and Lange 2006). Until the advent of high-throughput genotyping, such studies investigated a limited number of variants of candidate genes. The first and, probably, the most remarkable association was that identified by Anthony Allison, who discovered in the early 1950s that HbS was protective against severe forms of *P. falciparum* malaria (Allison 1954). However, the candidate genes most frequently studied in inflammatory and infectious diseases since the 1970s have been those of the HLA region. Consistent with the linkage results, the most interesting findings have been obtained for inflammatory disorders, with a number of impressive associations (Thorsby and Lie 2005; Cho and Gregersen 2011; Goris and Liston 2012). Interestingly, most HLA associations seem to be specific to a given disease, and in many diseases the presence of a given HLA molecule is almost necessary, but not sufficient for disease. One of the most emblematic examples is the association of HLA-B27 with AS. Almost all AS patients carry this HLA antigen, but most HLA-B27 subjects do not develop AS (Uchanska-Ziegler et al. 2012). HLA genes appear to play a much less striking role in infectious diseases, as most of the many associations reported have not been confirmed (Martin and Carrington 2005; Blackwell et al. 2009). There may be a number of reasons for this, such as considerable heterogeneity (e.g., in terms of ethnic origin, phenotype definition, HLA typing, microbial strains) of the samples tested for a given disease. The most consistent results obtained with HLA variants have been those for leprosy (Zhang et al. 2009a) and, particularly, for HIV infection (Goulder and Watkins 2008; Leslie et al. 2010), with some HLA class I alleles being associated with relatively successful control of viral replication and slow disease progression (Migueles et al. 2000; Kiepiela et al. 2004), and others being associated with relatively ineffective control of viral replication and rapid disease progression (Carrington et al. 1999; Kiepiela et al. 2004). Finally, a recent study reported that autoantibodies against IFN-γ conferring a predisposition to mycobacterial infec-tions and mimicking MSMD (Puel and Casanova 2013) are strongly associated with two linked HLA class II alleles (Chi et al. 2013).

Genome-Wide Association Studies

A breakthrough occurred in the mid-2000 with the advent of GW association studies (GWASs), following the development of high-throughput genotyping. The first spectacular finding obtained in a GWAS was the identification, in 2005, of complement factor H polymorphisms in patients with age-related macular degeneration (Klein et al. 2005) providing new insight into the immune-related pathogenesis of this disease (Ambati et al. 2013). The same result was however obtained following a linkage approach (Edwards et al. 2005; Haines et al. 2005). GWAS also confirmed that the HLA region contained the common variants with the greatest impact on inflammatory disorders, and identified more than 250 additional loci associated with one or more of these diseases (Cho and Gregersen 2011; Visscher et al. 2012). A number of the non-HLA loci have been implicated in multiple diseases, defining common pathways and suggesting similar underlying mechanisms for these diseases (Cho and Gregersen 2011; Cotsapas et al. 2011; Goris and Liston 2012; Voight and Cotsapas 2012). For example, 70% of the 163 loci for which involvement in CD and ulcerative colitis (UC) has been confirmed (Jostins et al. 2012) have also been implicated in other inflammatory diseases (such as AS and psoriasis in particular), and there is also an interesting overlap with loci conferring susceptibility to mycobacterial infection. These 163 loci include five MSMD-related loci (*IL12B*, *IFNGR2*, *STAT1*, *IRF8*, *TYK2*), and seven of the eight loci identified in the leprosy GWAS (including *NOD2*/*CARD15*) (Zhang et al. 2009b, 2011) have also been implicated in CD and UC (Jostins et al. 2012). The effects of CD/UC and mycobacterial risk alleles on gene function and expression include effects operating in opposite (e.g., *NOD2*/*CARD15*) and similar (e.g., *IFNGR2*) directions (Jostins et al. 2012). GWASs have identified fewer loci involved in infectious diseases. Some of the findings of these studies have confirmed previously reported associations with HLA variants in leprosy (Zhang et al. 2009b), and chronic viral infections (Fellay et al. 2007; Dalmasso et al. 2008; Kamatani et al. 2009; Pereyra et al. 2010). However, the most remarkable achievement of GWAS in infectious diseases has been the identification of *IL28B* variants associated with the clearance of HCV either in response to treatment (Ge et al. 2009; Suppiah et al. 2009; Tanaka et al. 2009) or spontaneously (Thomas et al. 2009; Duggal et al. 2013). The molecular mechanisms underlying this association remained elusive until the recent identification of a new dinucleotide variant (TT vs. ΔG) in the *IL28B* region (Bibert et al. 2013; Prokunina-Olsson et al. 2013). The ΔG allele associated with poorer clearance of the virus is a frameshift variant that apparently generates a new gene, *IFNL4*, encoding a putative IFN-λ4 protein (Prokunina-Olsson 2013). The mechanisms by which IFN-λ4 may impair HCV clearance remain to be deciphered.

The Search for Missing Heritability

GWAS has made it possible to identify common variants with modest effects at hundreds of loci, for a number of common diseases, including inflammatory and autoimmune diseases (Visscher et al. 2012). However, even at its most successful, such as when applied to CD and to inflammatory diseases in general, the loci identified by this approach account for only a small proportion of the variance of disease risk (e.g., 13.6.% in CD [Casanova and Abel 2009; Smith et al. 2009; Jostins et al. 2012]). This has led to the concept of "missing heritability" (Manolio et al. 2009) and to the development of several non-mutually exclusive hypotheses that might account for this phenomenon (Table 2). One of these explanations, the existence of rare disease-causing variants, is appealing for at least two reasons: (1) conceptually, as rare variants bridge the gap between Mendelian and complex inheritance and largely correspond to the major gene notion (Alcais et al. 2009a, 2010), and (2) experimentally, as these variants can now be tested by NGS (Cirulli and Goldstein 2010). One recent study reported a negligible impact of rare variants located in the exons of 25 risk genes previously identified by GWASs in ~25,000 patients with six autoimmune and/or inflammatory diseases (Hunt et al. 2013). A more successful use of this approach resulted in the demonstration that the *DCTN4* gene influenced *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (Emond et al. 2012). This discovery was based on WES in patients with "extreme phenotypes" (43 patients with the earliest onset of infection vs. 48 patients with the latest onset of infection). The search for missing heritability is, undoubtedly, a major challenge in this field.

Table 2. A selection of genetic hypotheses possibly accounting for missing heritability in inflammatory and infectious diseases

Masked genetic effect	Methods of investigation
Causal common variants not identified	Dense targeted sequencing of disease-associated regions and functional studies
Other common variants with weaker effect not identified	Increase population sample size and conduct large meta-analyses
Rare variants with stronger effect not identified	Next-generation sequencing focusing on specific kindreds (multiplex) and phenotypes (extreme).
"Structural" variants not identified (e.g., copy number variants)	Specific analysis of high-throughput genotyping and sequencing data
Gene × gene interaction and epistasis	Development of specific methods of analysis
Gene × environment interaction	Assessment of environmental risk factors (e.g., microbiome), study of specific subpopulations (e.g., early age of onset)

The missing heritability may also be a consequence of confounding factors, such as phenocopies (i.e., a patient falsely attributed a disease phenotype), undetermined environmental triggers (i.e., apparent concordance resulting from a shared environmental trigger), and epigenetic influences (e.g., parental imprinting).

EVOLUTIONARY GENETICS IN HUMANS

General Concepts and Methods

Evolutionary or population genetics is another approach that provides invaluable immunological information and involves analysis of the distribution, in human populations, of alleles at loci known or presumed to be involved in host defense and/or self-tolerance, and the comparison of this distribution with that in other species, including primates in particular. If we wish to understand immunological heterogeneity, both between individuals and between populations, we can investigate the way in which natural selection has acted on host genes over time, by determining the current patterns of variability in the general population (individuals not chosen for study on the basis of a particular disease phenotype) (Sabeti et al. 2006; Quintana-Murci et al. 2007; Barreiro and Quintana-Murci 2010; Quintana-Murci and Clark 2013). Contemporary humans are the descendants of people who survived multiple threats, including those posed by microbes (a greater threat than war, predation, and famine) (Cairns 1997). "Natural" conditions have changed, particularly in western countries, but modern medicine, introduced at the start of the 20th century ("yesterday" from an evolutionary standpoint), has not yet had time to affect the pattern of population genetic diversity. If human adaptation to microbial pressure has a genetic basis, it will be engraved in our genomes, so evolutionary genetics can quantify the action of selection on host genes (Sabeti et al. 2006; Nielsen et al. 2007). Numerous studies have searched for the footprints of selection at the GW level and identified immunity-related genes among those most strongly targeted by selection, in its different forms and intensities (Bustamante et al. 2005; Voight et al. 2006; Sabeti et al. 2007; Barreiro et al. 2008; Pickrell et al. 2009; Grossman et al. 2013). Purifying selection removes deleterious alleles from the population, whereas positive and balancing selection favor increases in the population frequency of advantageous variants and the maintenance of polymorphism, respectively (Table 3). Each type of selection leaves a distinctive molecular signature around the genomic region targeted, and these signatures can be detected by various statistical approaches (Nielsen 2005; Sabeti et al. 2006; Nielsen et al. 2007). On the basis of these signatures, population genetics theory can be used to infer the relative biological contributions of different classes of immunity genes to host defense *in natura*.

Maintaining the Status Quo: Essentiality

Selection often results in maintenance of the status quo, by eliminating genetic variants with an impact on protein function that may compromise organism fitness. Genes subject to strong purifying selection, for which mutations are highly deleterious for the carrier, generally display a major deficit of amino-acid altering mutations. This is the case, for example, for a number of genes encoding innate immunity molecules, such as endosomal TLRs and most of the NALP members of the NLR family (Barreiro et al. 2009; Wlasiuk and Nachman 2010; Vasseur et al. 2012),

Table 3. Different forms of natural selection and their relation to immunity and disease

Form of selection	Molecular signatures	Immunological function/relevance	Expected phenotype
Purifying/negative selection	Low functional (nonsynonymous) diversity Overall reduction in diversity Excess of rare alleles	Essential, nonredundant	Rare, severe disorders
Positive selection	High functional (nonsynonymous) diversity Overall reduction in diversity Long-range haplotypes/homozygosity Increased population differences	Advantage for a new (improved) function Flexible immunological mechanisms	Rare or common disorders Mostly complex predisposition
Balancing selection	Maintenance of polymorphism Increased heterozygosity Decreased population differences	Advantage for protein variability Flexible immunological mechanisms	Rare or common disorders Mostly complex predisposition

Each form of selection leaves a specific molecular signature around the genomic region targeted, which can be detected by an increasing number of statistical methods (Nielsen et al. 2007, for a thorough review). Depending on the intensity and form of selection in place, population genetics can provide useful information about the function and relative biological relevance of immunity-related genes as well as predict the mode in which these genes may contribute to disease. The expected phenotypes represent the general trends observed, but note that they are not exclusive (e.g., positive selection can also increase the frequency of mutations exerting a protective and almost Mendelian effect against infections) (Quintana-Murci and Barreiro 2010).

adaptors such as MYD88 and TRIF (Nakajima et al. 2008; Fornarino et al. 2011), or effector molecules, such as a subset of IFN-α/β and IFN-γ (Manry et al. 2011). This attests to the unique, essential nature of the mechanisms—immunological or otherwise—involved. Furthermore, variation in genes evolving under strong purifying selection would be expected to lead to severe, highly penetrant and even Mendelian disorders. This prediction is supported by GW population studies, as genes associated with Mendelian disease are enriched in signs of purifying selection (Bustamante et al. 2005; Barreiro et al. 2008; Blekhman et al. 2008), particularly when the disease-causing alleles are dominant by haploinsufficiency (e.g., *RPSA* mutations in patients with congenital asplenia) (Bolze et al. 2013). Clinical genetic studies also support this notion, as rare mutations underlying life-threatening diseases have been found in highly constrained genes and pathways. For example, mutations in the TLR3-TRIF, TIR-MYD88, and IFN-γ pathways have been associated with life-threatening infections during childhood: HSV-1 encephalitis (Zhang et al. 2007, 2013; Guo et al. 2011; Sancho-Shimizu et al. 2011), pyogenic bacterial infections (Picard et al. 2003, 2010; Ku et al. 2007; von Bernuth et al. 2008), and MSMD (Jouanguy et al. 1996; Newport et al. 1996; Casanova and Abel 2002; Bogunovic et al. 2012), respectively. Similarly, mutations of the *NALP3* and *RPSA* genes have been associated with severe inflammatory disease (Hoffman et al. 2001; Aganna et al. 2002; Strowig et al. 2012) and invasive bacterial disease due to congenital asplenia (Bolze et al. 2013), respectively.

Relaxing the Constraints: Immunological Redundancy

Purifying selection acts less strongly on mildly deleterious mutations, which can be tolerated and may even increase in frequency in the population, depending on the extent to which they are deleterious to host survival. Genes evolving under weaker selective constraints (i.e., weak negative selection) tend to be involved in more re-

dundant mechanisms than strongly constrained genes (those under strong purifying selection) (Quintana-Murci and Clark 2013). For example, among the innate immunity sensors responsible for detecting nucleic acids, the weaker constraints characterizing the three members of the RIG-I-like receptor (RLR) family than endosomal TLRs suggest that there is some degree of redundancy for RLR-mediated antiviral immunity (Barreiro et al. 2009; Wlasiuk and Nachman 2010; Vasseur et al. 2011). Furthermore, variation in genes evolving under relaxed constraints would be expected to have milder effects on host phenotype. At the GW level, purifying selection tends to be weaker for "complex" disease genes than for "Mendelian" disease genes (Di Rienzo 2006; Kryukov et al. 2007; Blekhman et al. 2008; Alcais et al. 2010). In some cases, the constraint may be relaxed completely, and the population frequency of mutations with an impact on protein function can increase freely under conditions of strict neutrality, demonstrating the highest levels of immunological redundancy. This is the case for genes such as *MBL2*, *TLR5*, and *TLR10*, for which the frequency of loss-of-function mutations is high at population level (up to 25%, depending on the population), indicating that distinct immunological mechanisms may confer sufficient protection against infection in the absence of these genes (Verdu et al. 2006; Walsh et al. 2006; Barreiro et al. 2009; Wlasiuk et al. 2009). In other cases, gene loss may even be advantageous to the host (MacArthur et al. 2012; Quintana-Murci 2012), according to the "less-is-more" hypothesis, as illustrated by the high population frequencies of loss-of-function mutations of genes such as *DARC*, *CASP12*, or some leukocyte Ig-like receptor genes (Hamblin et al. 2002; Xue et al. 2006; Hirayasu et al. 2008), owing to their protective effects against infection.

Favoring Advantageous Variation: Improving Gene Function

The detection of positive and balancing selection makes it possible to define more dynamic immunological

mechanisms, variations of which have been beneficial to the host over different evolutionary timescales. Recent data indicate that long-term balancing selection (i.e., a heterozygote advantage that has persisted across species) has occurred not only at the well-known *HLA* locus, but also at other immunity-related loci, such as the membrane glycoprotein, ABO blood group, or *TRIM5* genes (Klein et al. 1993; Cagliani et al. 2010; Segurel et al. 2012; Leffler et al. 2013). Humans may also have acquired advantageous variants through admixture with other hominids, such as Neandertals or Denisovans, as reported for some HLA alleles (Abi-Rached et al. 2011). Human populations maintain unexpectedly high levels of genetic diversity at some immunity-related loci, due to the effects of balancing selection (Parham and Moffett 2013). A striking example is provided by Amerindian populations, which, despite presenting the lowest level of GW genetic diversity worldwide, have retained high levels of diversity for the *HLA* and *KIR* genes, attesting to the advantage of variation at these loci for survival (Gendzekhadze et al. 2009; Parham et al. 2012). In cases of more recent selection or of selection restricted to specific populations, the advantage conferred depends on more recent environmental variables, which may be pathogen-related. Indeed, several studies have shown that pathogen-driven selection has shaped local adaptation of the HLA, blood group antigen and interleukin genes, and the genes encoding their receptors (Prugnolle et al. 2005; Fumagalli et al. 2009a,b, 2011). Selection can increase the frequency of some mutations exerting a protective, strong, in some cases almost Mendelian effect against various infections (Quintana-Murci and Barreiro 2010). Notable examples are provided by the HbS heterozygotes in Africa, independent G6PD-deficiency variants worldwide, the *DARC* null allele in Africa, and the various FUT2 deficiency alleles in different populations (Allison 1954; Tishkoff et al. 2001; Hamblin et al. 2002; Saunders et al. 2002; Ferrer-Admetlla et al. 2009; Louicharoen et al. 2009). Selection can also increase the frequency of alleles associated with complex traits or diseases, such as the *TLR1* I602S hyporesponsiveness mutation in Europe (Hawn et al. 2007; Johnson et al. 2007; Barreiro et al. 2009; Pickrell et al. 2009), suggesting that there may be an advantage associated with weak TLR1-mediated responses, or with various mutations of the four type III IFN genes in Europeans and Asians (Manry et al. 2011), some of which have been associated with the clearance of HCV infection (Ge et al. 2009; Thomas et al. 2009; Prokunina-Olsson et al. 2013). The match between the selected variants of some genes and their known associations with phenotypic variation provides proof-of-concept for the predictive value of population genetics, particularly for evaluating the disease implications of other, uncharacterized variants targeted by selection.

Side Effects of Past Selection

Past selection, leading to higher resistance to infection, may, in some cases, result in maladaptation and immune dysfunction, such as autoimmunity and inflammation.

The introduction of hygiene and medical interventions has decreased the pathogen pressure exerted on modern human societies. In this context, the controversial "hygiene hypothesis" states that a decrease in the diversity of microbes we are exposed to (both pathogens and commensals) has led to an imbalance in the immune response, potentially promoting chronic inflammation (Sironi and Clerici 2010). It has been suggested that the underlying mechanism may involve an imbalance between helper T cells of the "Th1" and "Th2" classes (Szabo et al. 2003; Pulendran and Artis 2012). Population genetics has provided additional support for this hypothesis, as several immunity-related genes, variants of which confer a higher risk of inflammatory bowel disease, celiac disease, T1D, MS, or psoriasis, have been targeted by positive selection (Fumagalli et al. 2009a; Barreiro and Quintana-Murci 2010; Sironi and Clerici 2010; Raj et al. 2013). The higher frequency of alleles conferring greater susceptibility to some of these diseases in populations exposed to high microbial/viral loads, as documented for risk alleles of *IL18RAP*, *IL18R1*, *IL23*, or *IL18R1* for inflammatory bowel disease or celiac disease, suggests that these variants play an otherwise beneficial protective role in host defense (Sironi and Clerici 2010). Perhaps the most straightforward example is that of celiac disease. Population genetic and functional analyses have shown that several celiac disease risk alleles of genes such as *IL12A*, *IL18RAP*, and *SH2B3* have been subjected to positive selection and that individuals carrying these alleles benefit from protection against some infections (Barreiro and Quintana-Murci 2010; Zhernakova et al. 2010; Abadie et al. 2011). Further clinical and epidemiological genetic studies are required, but, overall, population genetic studies support the notion that the current increase in the incidence of autoimmune and inflammatory disorders may be at least partly due to past adaptation, strengthening immune responses to combat infectious agents (Sironi and Clerici 2010).

CONCLUSION

Human genetic studies make use of experiments of Nature. The scale is impressive, with the world population steadily increasing and having already reached seven billion individuals, all of whom are genetically unique and exposed to a tremendously variable and changing environment. The depth is also impressive, as these individuals are constantly "phenotyped" by clinicians and can be studied in much more detail in the course of a study, if required. This approach is particularly powerful in immunology, especially as concerns immunity to infection and self-tolerance, the two pillars of immunology. With only about 20,000 protein-encoding genes, many more isoforms, and about 20,000 RNA-encoding genes, and mutation rate for nucleotide substitution in the germline of 10^{-9} (on top of other types of mutation), complete dissection of the function of most, if not all of the genes involved in immunity is feasible. Whereas WES can detect variations in only 1%–2% of the genome, WGS has the potential to detect mutations in the remaining,

intergenic space, which may possibly enlighten its functions. We will undoubtedly witness a flurry of discoveries of single-gene inborn errors of immunity in the coming years. In genetic epidemiology, studies aiming to increase phenotypic homogeneity will probably identify genetic contributions that are stronger than those usually found in GWASs. Population genetics, which has mostly followed a gene-centered approach, with the examination of genes in isolation, will adopt an interactome approach, trying to determine how multiple genes, each contributing modestly to the study phenotype (benign or disease-related), interact with each other and contribute to phenotypic variation (e.g., the Human Gene Connectome) (Itan et al. 2013). One major challenge will be the integrated analysis of all these different sources of genomic information, carefully taking into account context (tissue)-specific effects (Hawkins et al. 2010; Knight 2013). In this context, the iPSC technology can be used to study almost any human cell type from any patient, including nonhematopoietic cells not otherwise studied in humans (Lafaille et al. 2012; Takahashi and Yamanaka 2013). The study of tissue-specific immunity, which is probably altered in tissue-specific infection or autoimmunity, is particularly appealing. As shown here, human genetics has already taught us a great deal about immunology. We firmly believe that, in the era of NGS and iPSC, human genetics is an exciting frontier that is bound to teach us much more about immunology.

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