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The discovery of innate immune genes, such as those encoding Toll-like receptors (TLRs), nucleotide-binding oligomerisation domain-like receptors (NLRs), and related signal-transducing molecules, has led to a substantial improvement of our understanding of innate immunity. Recent immunogenetic studies have associated polymorphisms of the genes encoding TLRs, NLRs, and key signal-transducing molecules, such as interleukin-1 receptor-associated kinase 4 (IRAK4), with increased susceptibility to, or outcome of, infectious diseases. With the availability of high-throughput genotyping techniques, it is becoming increasingly evident that analyses of genetic polymorphisms of innate immune genes will further improve our knowledge of the host antimicrobial defence response and help in identifying individuals who are at increased risk of life-threatening infections. This is likely to open new perspectives for the development of diagnostic, predictive, and preventive management strategies to combat infectious diseases.

Introduction

Environmental and host factors are important determinants of susceptibility to infection. In recent years, a rapidly growing body of evidence has underscored the importance of host genetic factors. The effect of genetic and environmental factors on the risk of death was assessed in a study of 960 adoptees. Death of a biological parent (but not of an adoptive parent) from infection before the age of 50 years resulted in a six times increase in the relative risk of dying from infection in the adoptee, strongly suggesting that susceptibility to infection aggregates in families. Individuals who are heterozygous for haemoglobin S are known to be protected against malaria, whereas homozygous individuals have sickle-cell anaemia. The high frequency of sickle-cell anaemia and other red blood cell disorders in regions where malaria is highly prevalent suggests that infectious agents (eg, Plasmodium falciparum) can exert quite substantial selective pressure on human populations. Although natural immunity ensures survival of the species as a whole, individuals themselves are not likely to be immunocompetent to all pathogens, and individual differences in susceptibility to specific pathogens are quite common. The development of the Human Genome Project in 1990 propelled the scientific community into a new era, allowing genetic mapping and the development of large-scale gene identification that has greatly facilitated the study of gene polymorphisms.

We review recent advances in the field of innate immunogenetics of host defences and show how an interdisciplinary approach of combining genetic epidemiology, genetics, genomics, and molecular and cellular biology will improve our understanding of the pathogenetic basis of infectious diseases, and help the development of new preventive and therapeutic treatment strategies.

Genetic variation and human diseases

Little inter-individual variation exists within the human genome. In fact, all genetic differences between individuals are estimated to be caused by variability in 3 million bp, which represent about 0.01% of the human genome. Since the mutation rate in mammalian genomes is low (10^-9 per bp per year), most inter-individual variations are inherited. The most frequent variation is the single nucleotide polymorphism (SNP), which occurs on average every 1300 bp. Another type of genetic mutation is the variable number of tandem repeat (VNTR); VNTRs consist of repeats of sequences ranging from a single basepair to thousands of basepairs. The term microsatellite is used for repeats of one to six nucleotides, whereas repeats of longer units are called minisatellites (seven to 100 nucleotides) or, in the extreme case, satellite DNA (more than 100 nucleotides). Since the number of repeats varies among individuals, VNTRs have been widely used as genetic markers.
Within a coding region of a gene, an SNP can either induce an aminoacid change (non-synonymous SNPs) or not (synonymous SNPs). SNPs may be located in the promoter region of a gene and therefore influence gene expression or splicing. Similarly, different lengths of VNTR regions have been associated with differential gene expression.7 Certain SNPs or VNTR alleles, or both, may be linked together in a coding region of a gene. The functions of nearly all SNPs that are located outside gene-coding or regulatory regions are unknown.

Genotyping techniques
In recent years, SNP genotyping technologies with high throughput and affordable costs have become available. These technologies are based on a few basic biochemical reactions (hybridisation, PCR with differential primer extension, specific ligation, and differential cleavage), which are used on different support media and can be detected by different methods (figure 1).6 Recent high-throughput technologies allow genotyping at low cost (ie, a few cents per SNP per sample).9

Haplotypes and minimum haplotype tagging SNPs
Once markers have been typed, two main approaches can be used to analyse them: single marker analysis or haplotype analysis. A haplotype refers to the arrangement of two or more alleles on the same chromosome. Currently, there is much debate about which approach is the most appropriate. Studies have proposed that the underlying structure of the human genome can be described by use of a relatively simple framework in which the data are parsed into a series of discrete haplotype blocks.10,11 This observation has led to the development of haplotype tagging methods that aim to capture the haplotype structure in a candidate region.12 Haplotype tagging refers to the concept that most of the haplotypic structure in a particular chromosomal region can be captured by genotyping a smaller number of markers than all of those that constitute the haplotypes. The crucial markers to type would be the minimum set of markers that unambiguously identify each possible haplotype.

Linkage versus association studies
The detection and estimation of familial aggregation is usually the first step in the genetic analysis of a trait. Once familial aggregation has been documented, the traditional approach has been to narrow down the genetic region of interest by use of linkage analysis, followed by fine mapping and association studies (table 1). Linkage and association studies are based on the same underlying principle: once a mutation occurs on a particular chromosome, it is subsequently transmitted to offspring together with nearby loci. This association is broken down at each successive generation by recombination (ie, homologous chromosomes pair during the meiotic cell division and exchange genetic material). When two loci are close enough on the same chromosome that their alleles cosegregate when passed on to the next generation, we say that the two loci are linked.12 Linkage disequilibrium refers to allelic association that is caused by linkage, or in other words, that has not yet been broken up by recombination.13 An association between two loci, such as the non-independence of alleles at these loci, may be caused not only by linkage, but also to factors such as population stratification or chance. Population stratification refers to the situation in which study participants are selected from genetically different subpopulations. Population stratification will only lead to a spurious association (and hence be a confounder) if both the allele and disease frequencies differ across subpopulations.14 Some researchers have argued that too much emphasis has been put on this issue and surprisingly few examples can be found that unequivocally show that population stratification has led to a spurious association.14

Whereas linkage and association studies can be done in families, only association studies can be done in unrelated cases and controls (table 1). The main difference between related and unrelated cases is the number of meiotic events that separate them, so that unrelated cases share a much shorter chromosomal segment around a particular causative mutation than related cases. Linkage and association can be obscured by incomplete penetrance (ie, there is no one-to-one correspondence between genotype and phenotype), misdiagnoses, genetic heterogeneity (several genes can produce a similar phenotype), phenocopies (ie, environmental factors mimicking the effect of certain genes), and disease
heterogeneity (ie, several subgroups with different genetic causes exist within a specific disease).

An important advance toward enabling efficient whole-genome-scan association studies is the determination of linkage disequilibrium patterns on a genome-wide scale through the HapMap project.8 Because most diseases are likely to be influenced by several genes and environmental factors, the analysis of gene–gene interactions (epistasis) and gene–environment interactions will represent an important task in the future, but this is, and will remain, a challenging issue for the years to come.

**Innate immunity**

The innate immune system assumes an essential role in the natural host defences against microbes. The recognition of microbial pathogens, either in tissue in contact with the host’s environment or in the systemic circulation after invasion of the bloodstream, is done by macrophages, dendritic cells, natural killer cells, granulocytes, and monocytes, which act as sentinels of the innate immune system (figure 2). This process involves coordinated action of several families of proteins, such as Toll-like receptors (TLRs),9 nucleotide-binding oligomerisation domain (NOD)-like receptors (NLRs),10,11 RNA helicase-containing proteins,12 and the C-type lectins.13

**TLRs**

TLRs are essential components of the innate immune system.14 TLRs are type I transmembrane proteins that function as homodimers or heterodimers. The extracellular domain comprises multiple leucine-rich repeat structures that vary among different TLRs and are implicated in the selective recognition of a vast range of microbial-associated molecular patterns (MAMPs).14 So far, 12 members of the TLR family have been identified in mammals. Several molecules, including CD14,15 CD36,16 and MD2,17 have also been shown to participate in the sensing of microbial products and are therefore integral components of these receptor complexes. Binding of microbial products to microbial-recognition molecules activates signal transduction pathways and the transcription of immune genes that code for costimulatory molecules activates signal transduction pathways, leading to the production of cytokines and expression of costimulatory molecules. Cytokines induce and regulate the inflammatory response and orchestrate the adaptive immune response. By contrast with other TLRs, TLR3, TLR7, TLR8, and TLR9 are expressed mainly in the endosomal compartment (2), where local acidification is required for recognition of microbial products by their cognate receptors. Intracellular pathogens or microbial products released intracellularly after lysis of ingested microorganisms may also interact with intracytoplasmic receptors, such as nucleotide-binding oligomerisation domain-like (NLR) proteins (3), or the RNA helicase-containing molecules (4: RIG-I or MDA5). TLR–T-cell receptor.

**Figure 2: Recognition of microbial pathogens by the innate immune system**

Microbial-associated molecular patterns are recognised by transmembrane receptors (1: eg, Toll-like receptors [TLRs]), which trigger the activation of several signal-transducing pathways, leading to the production of cytokines and expression of costimulatory molecules. Cytokines induce and regulate the inflammatory response and orchestrate the adaptive immune response. By contrast with other TLRs, TLR3, TLR7, TLR8, and TLR9 are expressed mainly in the endosomal compartment (2), where local acidification is required for recognition of microbial products by their cognate receptors. Intracellular pathogens or microbial products released intracellularly after lysis of ingested microorganisms may also interact with intracytoplasmic receptors, such as nucleotide-binding oligomerisation domain-like (NLR) proteins (3), or the RNA helicase-containing molecules (4: RIG-I or MDA5). TCR–T-cell receptor.

**Figure 3: Toll-like receptors (TLRs), cognate ligands, and the main signalling pathways**

TLR4 detects lipopolysaccharide (LPS), mannan (Candida albicans), and the fusion protein of the respiratory syncytial virus. TLR2 forms a heterodimer with either TLR1 to detect triacyl lipopeptide or TLR6 to detect diacyl lipopeptide and zymosan. TLR2 is also involved in the recognition of lipoteichoic acid (LTA), peptidoglycan (PG), lipooligosaccharide (LPS), mannan (Candida albicans), and the haemaglutinin protein (HA, measles virus). TLR3, TLR7, TLR8, and TLR9 are located in the endosomal compartment and detect nucleic acids and/or haemozoin (Plasmodium spp, TLR9). Through their intracellular domain, TLRs interact with specific adaptors, including MyD88, the TIR domain-containing adaptor protein (TRIF), and the TRIF-related adaptor molecule (TRAM). These adaptors lead to the activation of several transcription factors such as the nuclear factor κB (NFκB), the activating-protein 1 (AP1), and/or the interferon regulatory factors 3 and 7 (IRF3/7) that ultimately induce the production of pro-inflammatory mediators.
the TLR4 specificity of some of these putative TLR ligands.30 TLR2 and TLR6 heterodimers detect diacyl lipopeptides, whereas TLR2 and TLR1 heterodimers recognise triacyl lipopeptides.17 TLR2 has also been proposed to sense lipoteichoic acid, peptidoglycan, lipoarabinomannan, phospholipomannan (C. albicans), zymosan (Saccharomyces cerevisiae), porins (Neisseria spp), glycosylphosphatidylinositol mucin (Trypanosoma spp), and the haemaglutinin protein of the measles virus.30 TLR3, TLR7, TLR8, and TLR9, which are mainly expressed in endosomes, serve to detect viral or bacterial nucleic acids. TLR3 detects double-stranded RNA and TLR8 detects single-stranded RNA.9 TLR9 senses DNA containing the unmethylated CpG motifs found in bacteria and viruses and the malaria pigment haemozoin.7 Compartimentalisation of TLR3, TLR7, TLR8, and TLR9 thus allows the detection of pathogenic DNA and RNA within the endosomal compartment, while avoiding the detection of self-DNA and mRNA.23

On binding of cognate ligands, the intracellular Toll-interleukin-1 receptor (TIR) domain of TLRs recruits and activates different adaptor proteins, including myeloid differentiation primary response protein 88 (MyD88), TIR domain-containing adaptor protein, TIR domain-containing adapter-inducing interferon β (TRIF; also known as TICAM), and TRIF-related adapter molecule, ultimately leading to the activation of several specific signal-transducing pathways and transcription factors such as nuclear factor κB (NFκB) and activating protein 1 (API; figure 3 and figure 4).40 MyD88-dependent signalling pathways (NFκB and API) are activated by all TLRs, whereas MyD88-independent, TRIF-dependent signalling pathways (interferon regulatory factor [IRF] 3) are activated only by some TLRs (such as TLR3 and TLR4). The observation that different TLRs may activate different signalling pathways with different biological consequences shows that the innate immune system can produce pathogen-specific defensive responses.

NLRs

In addition to the TLRs, the family of proteins comprising NOD proteins and the NALPs (neuronal apoptosis inhibitor [like] proteins), also known collectively as NLRs or NACHT-leucine-rich-repeat-containing proteins, have been shown to have a crucial role in the sensing of microbial products, invasive pathogens, and endogenous host proteins. NLRs are cytosolic proteins composed of three different structural domains, a carboxy-terminal ligand-binding domain consisting of leucine-rich repeats, a nucleotide oligomerisation domain, and an amino-terminal effector domain consisting of various caspase-recruitment domains (CARD), a pyrin domain, or a baculoviral inhibitor-of-apoptosis repeat.17,41 NOD1 and NOD2 have been shown to recognise specific bacterial peptidoglycan motifs,42 and to interact with TLR signalling pathways.19,42 NOD2 detects muramyl-dipeptide, a peptidoglycan fraction of Gram-positive and Gram-negative bacteria,43 whereas NOD1 detects

| Comment | Consequence | References |
|----------|-------------|------------|
| Human TLR4 B96A/G (D299G) | SNP in extramembrane domain | Impairs lipopolysaccharide recognition | 31,32 |
| Human TLR5 1174C/T (392 stop) | Stop codon in extramembrane domain | Absence of TLR5, no flagellin detection | 33 |
| Human TLR2 microsatellite polymorphism | Microsatellite in promoter region | Lower TLR expression, modified signalling? | 7 |
| C3 H/HeJ mouse TLR4 2342A/T (P781H) | SNP in TIR signalling region | No signalling | 29 |
| Human IRAK4 620-1AC/del (21B stop) | Stop codon in kinase domain | Abolished gene expression, no signalling | 34, 35 |
| Human IKKγ 1259A/G (K420W) | Elongated protein, probably impairing molecule stability | Impaired NFκB activation | 36 |
| Human IκBα 94G/T (S321) | Increased inhibitory capacity of IκBα, no phosphorylation by IKK on serine 32, no ubiquitination and no degradation | Impaired NFκB activation | 37–40 |

Figure 4: Example of genetic variants that impair the host innate immune response

SNP = single nucleotide polymorphism.

Targeting these variants may be a therapeutic strategy for improved innate immune function.
RNA helicases

A series of fascinating articles have provided strong evidence implicating the innate immune system in the host defence against viruses. Two intracytoplasmic molecules have been implicated in the detection of viral RNA. Retinoic-acid-inducible protein I (RIG-I)\(^{54}\) and melanoma differentiation-associated gene 5 (MDA5)\(^{55-57}\) possess a CARD domain and RNA helicase domains that function as sensors of double-stranded RNA.\(^{58}\) RIG-I and MDA5 signal through the adaptor molecule MAVS (mitochondrial antiviral signalling protein; also known as CARDIF or VISA)\(^{18,59,60}\) and interact with several other molecules, including ASC (apoptosis-associated speck-like protein containing a CARD domain), caspase 1, and caspase 5, and are essential for the activation of interleukin 1B (IL-1\(\beta\))\(^{49}\). The NALP-related protein CARD12 (also known as CEM15 or APOBEC3G) is implicated in the detection of ATP,\(^{51}\) bacterial RNA,\(^{52}\) and uric acid crystals.\(^{35}\) However, most NALPs are orphan recognition proteins with no known ligands.

Intrinsic immunity

A newly described form of innate immunity, termed intrinsic immunity, ensures protection by providing a constitutive, always-on line of defence, relying on intracellular obstacles to hinder the replication of pathogens.\(^{46}\) This component of the immune system has gained much attention as a cornerstone of the resistance of mammals against several classes of retroelements and retroviruses.\(^{20}\) Among the best studied proteins are the family of apolipoprotein B mRNA-editing enzyme catalytic polypeptide 3 (APOBEC3) proteins, which interfere with the viral lifecycle by incorporating themselves into viral particles, leading to viral DNA hypermutation on the next round of infection.\(^{62,63}\) A series of studies involving infection of human CD4+ T cells and macrophages with wild-type HIV-1 and HIV-1 deficient in the vif gene showed that the antiviral effect of ABC3G (also known as CEM15 or APOBEC3G) is counteracted by Vif.\(^{44}\) Interestingly, in non-human primates, ABC3G orthologues provide antiviral activity against wild-type HIV-1,\(^{20}\) but not their cognate simian immunodeficiency viruses, suggesting that virus permissiveness in different primates results from species-specific differences within vif.\(^{45}\) One human variant of ABC3G has been associated with rapid HIV-1 disease progression.\(^{46}\)

The tripartite motif (TRIM) family is a well-conserved family of proteins characterised by a structure comprising a ring-finger domain, one or two B-box motifs, and a predicted coiled-coil region.\(^{67}\) Additionally, most TRIM proteins have additional carboxy-terminal domains. Members of the TRIM protein family are involved in various cellular processes, including cell proliferation, differentiation, development, oncogenesis, and apoptosis.\(^{68,69}\) Some TRIM proteins exert antiviral properties. TRIM5\(\alpha\) is reported to restrict retroviral infection by specifically recognising the viral capsid and promoting its premature disassembly.\(^{23}\) Human TRIM5\(\alpha\) has limited efficacy against HIV-1, whereas some primate TRIM5\(\alpha\) orthologues can potently restrict this particular lentivirus.\(^{54,55}\) Substantial interspecies sequence diversity characterises TRIM5\(\alpha\) and may underlie differences in the pattern and breadth of restriction of multiple lentiviruses. Human TRIM5\(\alpha\) variants do not modify susceptibility to HIV-1; however, they change susceptibility to other retroviruses, such as N-tropic murine leukaemia virus.\(^{70}\) Polymorphisms found in TRIM5\(\alpha\) might conceivably have been selected in past epidemics by viruses unrelated to HIV-1.

Comparative innate immunogenetics

The increasing availability of genomic data allows comparative analyses of genetic sequences involved in innate and intrinsic immunity. This approach, also described as evolutionary genomics, identifies the role of adaptive forces on protein-encoding genes by determining signs of positive (diversifying) or negative (purifying) selection. For example, positive selection in the human genome indicates shifts in living conditions experienced by modern human populations, such as different habitats, food sources, population densities, and exposure to pathogens.\(^{25}\)

Several families of innate immunity genes have been investigated by use of comparative genomics. Vertebrate TLRs are an example of evolutionary conservation that...
indicate the difficulty for the microbes to mutate genes that encode MAMPs.73,74 The CD209 (DC-SIGN) proteins, a family of C-type lectins that participate in the recognition of various pathogens, display a complex pattern of evolution. Whereas CD209 has been under a strong selective constraint that prevents accumulation of aminoacid changes, CD209L (also known as DC-SIGNR or DC-SIGNR) exhibits greater variation across human populations.75 Such variations may be tolerated because of the potentially redundant functional activities of the molecules encoded by these genes.76 The killer-cell immunoglobulin-like receptor (KIR) genes encode a family of receptors expressed by natural killer cells, which participate in early responses against infected or transformed cells through production of cytokines and direct cytotoxicity.77,78 By contrast with TLRs and CD209, only a small proportion of KIR alleles are conserved among primates, showing a rapid species-specific diversification of the KIR gene family members and a plasticity of the genomic region that parallels that of the MHC loci.79 Thus, the evolutionary forces driving the genesis of natural killer receptors and their HLA ligands represent a concerted response to pathogens. Finally, a remarkable success of evolutionary genomics in infectious diseases is the identification of protein regions relevant to host–pathogen interactions in HIV-1 infection. Comparative analysis of the primate antiretroviral cellular defence genes encoding for ABC3G and TRIM5α has revealed the powerful selective pressures emerging from a long-standing battle between retroviruses and their hosts.80–82 Singular aminoacids or regions (patches) contain key residues that confer primates the ability to combat HIV-1.

### Innate immunogenetics

Given that the innate immune system is at the interface between the host and the pathogen, polymorphisms of innate immune genes are very likely to affect the host susceptibility to infections. Since the innate immune system senses only a limited number of highly conserved microbial-associated molecular patterns (MAMPs) via a limited number of receptors and signalling molecules, as anticipated, several polymorphisms have been found to confer an increased susceptibility to specific pathogens (table 2, table 3, and figure 4).

### Common polymorphisms in TLRs (complex inheritance)

A study from Turkey revealed an association between susceptibility to tuberculosis and an SNP (R753Q) in the TLR2 gene.14 14 (9.3%) of 151 tuberculosis patients were homozygous for the minor allele compared with two (1.3%) of 116 healthy controls (odds ratio 6.0, 95% CI 1.3–3.9, p=0.009). Of note, R753Q was associated with decreased responsiveness to bacterial lipopeptides.95
Mendelian disorders in TLR adaptors (monogenic inheritance)

Several studies have shown associations between mutations in genes encoding several proteins of the TLR signalling pathways (IRAK4,13,14 IKBKG,96–98 and IκBα129,130) and rare inherited immunodeficiencies. Complete recessive interleukin-1 receptor-associated kinase 4 (IRAK4) deficiency is characterised by recurrent infections with pyogenic bacteria at an early age that tend to disappear over time. By contrast, mutations affecting the other genes result in X-linked (IKBKG) or autosomal-dominant (IκBα) anhidrotic ectodermal dysplasia, which is characterised by increased susceptibility to a broader range of pathogens, such as atypical mycobacteria or Pneumocystis jirovecii and a complex disorder involving impaired development of skin appendages, conical teeth, and hypotrichosis.123–125

Taken together, these data clearly show that mutations in the genes encoding TLRs and downstream signal-transducing molecules influence innate immune responses and increase susceptibility to many infectious diseases. Similarly, polymorphism of cytokines and cytokine receptor genes, which are key effector molecules, have also been associated with altered susceptibility to invasive pathogens.110

NLRs

Polymorphisms in genes encoding NLRs have been shown to influence susceptibility to inflammatory diseases. Polymorphisms in NOD2 have been associated with susceptibility to Crohn’s disease,111,112

| (Continued from previous page) | 896A/G(D299G) and 1196C/T(T399I) | Bacterial vaginosis | No evidence for association |
| Newport et al107 | 896A/G(D299G) and 1196C/T(T399I) | Tuberculosis | No evidence for association |
| Szebeni et al115 | 896A/G(D299G) and 1196C/T(T399I) | Necrotising enterocolitis | No evidence for association |
| Rivera-Chavez et al15 | 896A/G(D299G) and 1196C/T(T399I) | Acute appendicitis | No evidence for association |
| Morre et al105 | 896A/G(D299G) and 1196C/T(T399I) | Chlamydia | No evidence for association |
| Smirnova et al106 | 896A/G(D299G) and 1196C/T(T399I) | Meningococcal sepsis | No evidence for association |

| Hawn et al105 | Rare mutations | Legionellosis | High |
| Smirnova et al106 | 896A/G(D299G) and 1196C/T(T399I) | Meningococcal sepsis | Decreased |

**TLR5**

Hawn et al105

**TLR6**

Kesh et al111

**TLR9**

Bochud et al106

Muckenheupt et al106

Lammers et al111

Muckenheupt et al106

**NOD2**

Meier et al111

Szebeni et al115

Necrotising enterocolitis | No evidence for association |

Increased* |

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Table 3: Association between innate immune gene polymorphisms and susceptibility to infectious diseases: monogenic inheritance

| Polymorphisms | Type of infection | Effect of polymorphism on susceptibility in individuals with genetic variant |
|---------------|------------------|--------------------------------------------------------------------------|
| IRAK4         | 620–1AC/del (218stop); 821Tdel (287stop); 877C/T (293stop) | Pyogenic bacterial infections Increased |
| Picard et al34 |                  |                                                                          |
| IL10          | 946GT (532I)     | Bacterial infections Increased                                             |
| Courtois et al35 |               |                                                                          |
| IL13          | 1217A/T (D406V); 1249C/T (C417R); 1259A/G (X420W); other mutations | Bacterial and mycobacterial infections Increased |
| Zonana et al36, Jain et al,37 | |                                                                     |
| Jain et al,38 Doffinger et al39 | |                                                                    |

Table 4: Common limitations in genetic association studies

| Comments |
|----------|
| Internal validity |
| Confounding |
| Population stratification | Limited information on ethnicity |
| Failure to account for known confounders | Cohort not established in view of genetic study; insufficient clinical data; failure to adjust for multiple confounders in the analyses |
| Selection biases | No or insufficient attempt to ensure that cases and controls come from the same source population |
| Information biases | Information on exposure or study endpoints is gathered differently for cases and controls |
| Statistical analyses |
| Limited power | No sample size calculation; insufficient sample size to detect a small effect; difficult and costly to collect large cohorts |
| Absence of a priori specified hypotheses | Investigators rarely distinguish between hypothesis-testing and hypothesis-generating studies |
| No correction for multiple testing | Multiple endpoints and genetic markers are analysed, but only significant associations are reported |
| Causality |
| Biological plausibility | Biological systems not sensitive enough to illustrate functional association |
| Simplistic measure of genetic variability | Studies often limited to a few SNPs per gene |
| Failure to account for gene-gene and gene-environment interactions | Genetic and environmental background can be expected to influence most associations |
| Strength of the association | Any single genetic variant usually only has a small effect |
| Consistency of the association | Results are rarely replicated across studies |
| Dose-response effect | Alleles do not always display an additive mode of action |

SNP = single nucleotide polymorphisms.

Blau syndrome,133 early-onset sarcoidosis,134 and graft-versus-host disease.135 Genetic variations in NALP3 have been linked to three autosomal dominant diseases: Muckle-Wells syndrome,136 familial cold auto-inflammatory syndrome, and chronic infantile neurological cutaneous and articular syndrome (also known as neonatal onset multisystemic inflammatory disease).137 Loss-of-function mutations in the gene encoding another NLR-related protein, the class II transactivator, decrease expression of MHC II, resulting in type II bare lymphocyte syndrome.138 So far, there are no data on mutations of NLR genes and susceptibility to, or outcome of, infectious diseases. However, in view of the part played by these molecules in inflammation, this area undoubtedly deserves further clinical investigation.

Limitations of genetic studies

Common limitations of genetic association studies are shown in table 4. Genetic studies done to date often fail on the following factors: (1) to properly account for confounding factors (such as lack of information on ethnicity), and selection and information biases (insufficient data on the source population of cases and controls or study endpoints); (2) to present appropriate statistical analyses (such as lack of sample size calculation and correction for multiple testing); and (3) to provide convincing information about biological plausibility. As an example, among five studies that assessed the effect of TLR4 polymorphisms on susceptibility to, and outcome of, severe infections, only two included more than 100 patients,395 two provided information about patient’s ethnicity,391,396 and only one limited the analysis to a specific ethnic group.397

Comparison of data is often impaired by the fact that apparently similar studies used markedly different controls groups and endpoints.398–400 Proving causality is never trivial.Associations are likely to occur when non-causal markers are in linkage disequilibrium with the true disease locus. Although the replication of a finding in an independent sample decreases the risk of a false-positive result, the functional significance of the genetic variant should ultimately be shown in biological studies. However, proving biological plausibility may be difficult in view of the limitations of in-vitro studies used as proxy of complex in-vivo biological processes. For example, use of gene-silencing techniques often reduces the biological observation to that of an on/off system, which does not allow the detection of quantitative variations (ie, a dose-response effect) of gene expression or discrete functional alterations. With the increasing use of high-throughput genotyping techniques, the number of genetic associations that will be reported in the years to come will most probably exceed our capacity to do proper functional studies and hence to provide convincing evidence for biological plausibility.401
Future perspectives
In recent years, innate immunogenetic studies of inherited genetic disorders have provided researchers and clinical investigators with crucial information that has improved our understanding of the host defenses against microbial pathogens. Table 5 shows examples of the effect of recent discoveries in the field of innate immunogenetics with foreseeable applications for the short, middle, and long term in areas such as vaccine development and predictive and preventive medicine. The persistence or emergence of potentially devastating infectious diseases, such as tuberculosis, malaria, HIV/AIDS, and, most recently, severe acute respiratory syndrome or avian influenza, underscore the need to develop new vaccines and therapeutic treatment strategies. A better understanding of microbial genomics and genetics and host innate immunogenetics is likely to provide important information for the development of new vaccines. Vaccine immunogenicity is determined not only by the chemical and physical nature of microbial antigens and adjuvants, but also by the genetic make-up of vaccine recipients. Analyses of polymorphisms of innate immune genes may also help understand why some individuals exhibit suboptimum responses to vaccination.109 Immunosuppression as a result of myeloablative chemotherapy, solid organ or hematological stem-cell transplantation, or corticosteroid therapy for autoimmune diseases represent other clinical conditions for which immune gene polymorphisms may help to predict the risk of life-threatening infectious complications.

The recent discoveries of genes encoding TLRs, NLRs, and the related signal-transducing molecules has markedly improved our understanding of innate immunity. The availability of high-throughput genotyping techniques opens new perspectives to further improve our understanding of the pathogenesis of infectious diseases and for the development of new diagnostic, predictive, and preventive treatment strategies. Clinicians and researchers should be aware of the results and far-reaching implications of recent innate immunogenetic studies that have associated genetic polymorphisms with susceptibility to, or outcome of, infectious diseases. Collecting DNA should now be an integral part of epidemiological or clinical infectious disease studies. National and international consortia should be created to put together large cohort studies to promote and facilitate research in the field.
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