Genetics and genomics of infectious disease susceptibility

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Human genetic variation is a major determinant of susceptibility to many common infectious diseases. Malaria was the first disease to be studied extensively and many susceptibility and resistance loci have been identified. However, genes for other diseases such as HIV/AIDS and mycobacterial infections are now being identified using a variety of approaches. A large number of genes appear to influence susceptibility to infectious pathogens and defining these can provide insights into pathogenic and protective mechanisms and identify new molecular targets for prophylactic and therapeutic interventions. Immunogenetic associations with infectious diseases have considerable potential to guide immunomodulatory interventions and vaccine design.

Although it has been clear for many years that individuals may differ markedly in their susceptibility to infectious diseases, recent advances in genomics have led to a dramatic increase in the power of techniques available to identify the relevant genes. Some infectious diseases were once regarded as familial before the identification of the causative micro-organism[1] and early twin studies found that there was a substantial host genetic influence on susceptibility to diseases such as tuberculosis and polio. Today, it is clear that human genetic variation exerts a major influence on the course of disease caused by many infectious micro-organisms. Such host–pathogen gene interactions are of general biological interest as they underlie the maintenance of much genetic diversity and such co-evolutionary interplay is often best studied in human infectious diseases where both the pathogen and the host genome are well characterised.

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In this short chapter, I shall first review some of the powerful approaches to analysing the host genetic contribution to infectious disease susceptibility that are now available and in use as a result of recent dramatic progress in characterising the human genome. Secondly, I shall attempt to summarise briefly the state of knowledge on genetic factors influencing susceptibility to some major infectious diseases. This selection is a personal one and not at all comprehensive, but may

illustrate the great potential of new molecular genetic approaches to characterising the human genetic basis of variable susceptibility to infection. Although outside the scope of this review, in parallel with progress in host genetics important strides are being made in the genomics of many micro-organisms and, together, these complementary genetic approaches hold considerable promise for explaining variability in the outcome of host–pathogen encounters.

Mapping and identifying the relevant genes

The most frequently adopted approach in the human genetics of infectious disease has been the assessment of candidate genes in case-control studies. However, a variety of different approaches to gene mapping and identification may now be employed in studies of susceptibility to complex disease and most of these have been applied to at least one infectious disease. In general, two distinct approaches may be used. Either a genetic linkage study may be undertaken to search for co-segregation of a genetic marker with disease in families, or a genetic association study is used to determine whether an allele is found more or less frequently in individuals with the disease than in unaffected controls. There are advantages and disadvantages to each approach and ideally both should be employed.

For association studies, large sample sizes are generally required, particularly to assess rare alleles or multi-allelic genes. Control populations need to be carefully matched to the cases to avoid false-positive or false-negative associations due to population stratification. The most important variables to match are ethnic group and locality of birth and residence. Matching for age and sex is usually less important as gene frequencies change little with age and autosomal alleles seldom show sex differences in frequency. Parental controls may be used to avoid the possibility of unknown confounding variables differing between case and controls[2]. A large number of candidate genes are now available for study and these have been suggested by a variety of approaches. The geographic distribution of haemoglobin gene variants in the Mediterranean first suggested that they might play a role in malaria resistance[3]. More recently, some loci, such as the Mx influenza resistance gene, have been found to affect susceptibility to infection in different strains of mice leading to assessment of their human homologues[4]. However, a much larger number of candidate genes have now been suggested by studies of the susceptibility of various gene knockout mice to infectious pathogens. Perhaps the largest class of candidate genes includes those implicated by a knowledge of the

Table 1 A selection of susceptibility and resistance genes implicated in infectious diseases.

Gene	Variant	Disease	Effect
ABO	Blood group O	Cholera	Susceptibility
α-Globin	Thalassaemias	Malaria (Pf)	Resistance
β-Globin	Sickle, thalassaemias	Malaria (Pf)	Resistance
Erythrocyte band 3	27 bp deletion	Malaria (Pf, Pv)	Resistance
G6PD	Deficiency variants	Malaria (Pf)	Resistance
HLA-B	HLA-B53	Malaria (Pf)	Resistance
HLA-DR	HLA-DRB1*1302	Malaria (Pf)	Resistance
HLA-DR	HLA-DR2	Tuberculosis	Susceptibility
HLA-DR	HLA-DR2	Leprosy	Susceptibility
HLA-DR	HLA-DRB1*1302	HBV persistence	Resistance
HLA-DR	HLA-DRB1*11	HCV persistence	Resistance
TNF	Promoter 308	Malaria (Pf)	Susceptibility
FUT2	Non-secretors	UTI	Susceptibility
NRAMP1	5′ and 3′ variants	Tuberculosis	Susceptibility
Interferon-γ receptor	Various mutations	Disseminated BCG	Susceptibility
IL-12 receptor	Various mutations	Intracellular bacteria	Susceptibility
CCR5	32 bp deletion	HIV infection/progression	Resistance
CCR2	codon 64	HIV progression	Resistance
Duffy receptor	Promoter variant	Malaria (Pv)	Resistance
PRP	Codon 129	Creutzfeldt-Jakob Disease	Susceptibility

Pf, *Plasmodium falciparum*; Pv *Plasmodium vivax.*

pathophysiology and immunology of the particular disease. For many infectious diseases this list would include genes such as HLA, tumour necrosis factor and mannose-binding lectin variants which have been studied frequently because of their known functions (Table 1).

A newer approach in human infectious disease genetics is to search for genetic linkage to, rather than association with, a disease in family studies. With the completion of a genetic map of the human genome and the identification of thousands of very variable microsatellite markers it has become possible to search the whole genome efficiently for regions linked to disease susceptibility. Thus, identification of a genetic marker convincingly linked to susceptibility indicates that there is a susceptibility gene somewhere in that chromosomal region[5]. Typically, hundreds of families with two affected siblings need to be studied to provide compelling evidence of linkage. Chromosomal regions identified in this way are initially very large, and contain some hundreds of genes distributed over several megabases, so that much further work is usually required to actually identify the causative gene. However, the attraction of this relatively laborious approach is that unknown genes may be mapped and identified without prior information on their function. The main concern about the applicability of this approach to common infectious diseases is that the statistical power of this approach is generally lower than that of case-control studies, in part because fewer multi-case families than random cases can be recruited. Thus, if the

genetic contribution to susceptibility is accounted for by a large number of genes with modest or small effects, they may not be picked up on linkage analysis. Nonetheless, this approach does allow a comprehensive screen of the whole genome to be undertaken to search for any major susceptibility genes, and major genes may be those of most biological interest. Similar linkage approaches have been used in mice to map the locations of many susceptibility genes[6] and one of these, termed *Nramp1*, a susceptibility gene for *BCG, Leishmania* and *Salmonella* in mice, was isolated by positional cloning[7]. The human homologue of this gene, *NRAMP1*, has recently been found to affect susceptibility to pulmonary tuberculosis[8] in West Africans and may also be involved in susceptibility to diseases caused by other intracellular pathogens.

Diseases

Mycobacterial diseases

Leprosy and tuberculosis have been frequently studied by human geneticists for several reasons. Both show familial clustering and, being chronic diseases which require a protracted period of treatment, it is relatively easy to recruit large numbers of cases and even multi-case families. Also, there have been twin studies of both diseases that found substantially higher concordance rates in monozygotic than dizygotic twins[9,10], and thus provided an estimate of the magnitude of the host genetic component to variable susceptibility. Early studies of HLA variation in India and Surinam found associations with both tuberculosis and leprosy[11,12]. HLA-DR2 (particularly the HLA-DR15 subtype) was associated with susceptibility to tuberculoid leprosy in India and more recent data show an association of this HLA type with susceptibility to both tuberculoid and lepromatous forms of leprosy as well as to tuberculosis in several Asian populations[13–16]. However, in other continents no clear HLA association has been identified and HLA-DR2 appears not to be associated with susceptibility. Recently, in a study of leprosy in Calcutta variation in the promoter of the tumour necrosis factor gene was associated with susceptibility to lepromatous but not tuberculoid leprosy[17]. A variant of the vitamin D receptor has also been associated with the type of leprosy developed in the same study population (Roy *et al.* manuscript submitted).

In a study in The Gambia, West Africa, allelic variation in both the 3′ untranslated region and in the promoter region of the natural resistance-associated macrophage protein-1 (*NRAMP1*) gene was associated with susceptibility to sputum-positive pulmonary tuberculosis[8]. A genome-wide linkage analysis of tuberculosis in Africans has now been

undertaken and this has suggested that there may be genes with relatively major effects on susceptibility located on chromosomes 15 and X (Bellamy *et al.* manuscript submitted). However, much further work will be required to identify these putative susceptibility genes. Analyses of rare individuals with marked susceptibility to atypical mycobacterial disease has recently revealed several interesting molecular defects. Some such children who are homozygous for mutations in the interferon-γ receptor gene are remarkably susceptible to weakly pathogenic mycobacteria, including the BCG vaccine, and have a poor prognosis[18,19]. But whether these children have increased susceptibility to tuberculosis and leprosy is not known. Similarly, 'knockout' mutations in the IL-12 receptor beta-1 gene produce a phenotype of marked susceptibility to atypical mycobacterial disease[20,21] and, in one family, to *Salmonella* infections. Although such mutations that have major effects on mycobacterial susceptibility must be rare, it is possible that milder defects in these cytokine and receptor genes might explain some general variation in susceptibility to tuberculosis.

Malaria

Malaria provides the classic examples of infectious disease resistance genes and more genes have been implicated in differential susceptibility to malaria than to any other infectious disease. In the 1930s, studies of the use of malaria therapy in the management of syphilis suggested some marked interindividual differences in susceptibility to malaria in non-immunes[22]. The subsequent identification of the major effect of sickle haemoglobin heterozygosity on malaria resistance[23] and the emerging picture of the geographical distribution of some haemoglobin variants provided the incentive for genetic investigations in a diversity of populations. Such studies of sickle haemoglobin and G6PD deficiency have provided clear-cut evidence of their protective relevance against *Plasmodium falciparum* malaria[24,25], but it is still uncertain whether haemoglobin C, which is common in parts of West Africa, and haemoglobin E, widely distributed in Southeast Asia, are protective. A few studies have demonstrated protection associated with either heterozygosity for β-thalassaemia or, more recently, various α-thalassaemia genotypes, but the mechanisms of protection remain uncertain[26,27]. Interestingly, it has recently been suggested that some of this protection may have an immune basis and that interactions between susceptibility to *Plasmodium vivax* and *P. falciparum* may be relevant in populations where both are prevalent[28].

Despite the geographical variation in frequencies of many malaria resistance alleles, there have been few useful interpopulation comparisons

of malaria susceptibility. However, a study of different ethnic groups in Mali, West Africa has found significant differences in immune responses to *P. falciparum* and in malaria susceptibility between these groups that appear to be genetic in origin[29]. These differences could not be explained by the known malaria resistance alleles.

Both HLA class I and II alleles have been found to influence malaria susceptibility in Africa in large case-control studies[30,31]. In the largest study in The Gambia, HLA-B53 was associated with resistance to both cerebral malaria and severe malarial anaemia, whereas the class II allele, HLA-DRB1*1302, was associated with resistance only to the latter. Subsequent immunological investigations in this population have suggested a possible molecular basis for these HLA associations through the identification of peptide epitopes in the parasite restricted by these HLA types (see below)[32]. In a study in Kenya, a different HLA class II type was associated with protection, and interpopulation heterogeneity in HLA associations appears to be fairly common in infectious diseases. This can have many causes but a prominent one in malaria is likely to be the marked polymorphism of immunodominant malaria antigens. HLA has recently been found to influence the strain of malaria parasite associated with clinical malaria and complex interactions between malaria parasite strains may lead to further variability in HLA associations[33]. Geographical heterogeneity in association may also be found for other genes. For example a polymorphic host receptor involved in parasite sequestration, intercellular adhesion molecule-1 (ICAM-1), may influence susceptibility to cerebral malaria[34]. Homozygotes for an African-specific variant, ICAM-Kilifi, were found significantly more frequently amongst cases of cerebral malaria in Kenya, but in The Gambia no effect of this variant on malaria susceptibility was detected (Bellamy *et al.* 1998 in press).

HIV and AIDS

There has been considerable interest in investigating genetic susceptibility to HIV and AIDS over the last few years. This has been encouraged by studies of cohorts in which a small proportion of individuals remain HIV seronegative despite repeated exposure to HIV from infected sexual partners[35]. Immunological assays have confirmed that some such resistant sex workers have been exposed to the virus. Individuals also vary in their rate of disease progression to AIDS once infected and several genes have now been identified that appear to influence this rate. HLA studies have shown that in several populations HLA-B35 and the HLA-A1-B8-DR3 haplotype are associated with more rapid disease progression[36,37] and HLA-B27 and HLA-B57 with a lower

rate of progression[38]. Some combinations of HLA class I and II alleles and variants of the transporter associated with antigen processing (TAP) genes have also been implicated[39] in north American cohorts. A genetic linkage study of haemophiliac brothers also demonstrated an effect of major histocompatibility complex variation on rate of CD4+ T cell decline[40]. Thus, despite the variability of HIV between and within individual infections, HLA type has been found to be a significant if minor determinant of the rate of disease progression.

Recently, there have been numerous genetic analyses of chemokine receptors that are coreceptors with CD4 for viral entry into macrophages and lymphocytes. Homozygotes for a 32 bp deletion in the gene encoding CC chemokine receptor-5 (CCR5), the coreceptor for macrophage-tropic HIV, are very markedly resistant to HIV infection and heterozygotes display lower rates of disease progression[41]. Variants of the flanking gene for the CCR2 chemokine receptor and of the stromal-derived factor (SDF-1) gene encoding the ligand for CXCR4, the coreceptor for lymphocyte-tropic strains, have also been associated with some alteration in rate of disease progression[42,43]. However, several other resistance genes must exist as the known variants of CCR5 account for only a minority of Caucasians and none of the African individuals found to be markedly resistant to HIV infection.

Other infectious diseases

Many genetic associations with other infectious diseases have been reported and will probably turn out to be important in multiple populations. For example, genetic variation in the mannose-binding ligand gene[44] is likely to influence susceptibility to several bacterial pathogens. A codon 129 polymorphism in the host prion protein (PRNP) gene is strongly associated with susceptibility to both iatrogenic Creutzfeldt-Jakob Disease (CJD) in US and French series and to new-variant CJD in UK cases[45,46]. The genetic linkage approach has recently been successfully applied to map a gene affecting susceptibility to the helminth, *Schistosomiasis mansoni*, in Brazilian families[47]. The chromosome 5 region identified encodes numerous cytokine genes such as IL-4 and IL-13 and this gene cluster has also been linked to atopy and asthma, consistent with the speculation that a gene selected to provide resistance to helminthic infections might predispose to asthma or atopy. Finally, the recent finding that the cystic fibrosis transmembrane conductance regulator (CFTR) is the intestinal receptor for *Salmonella typhi*[48] raises the possibility that common cystic fibrosis mutations may have been selected in Caucasians to provide resistance to typhoid.

Applications

We are only beginning to uncover what will probably turn out to be a huge number of genes involved in variable susceptibility to infectious disease. There are many reasons for continuing to define these genetic factors and elucidate their mechanisms.

Risk assessment

One application will be in risk prediction and this genetic information will probably influence behaviour, travel patterns, and the use of prophylactic anti-microbials and immunisations. Genetic profiling to estimate individual susceptibility will have a place and already screening for mannose-binding ligand deficiency alleles has been advocated, but the most useful risk profiling will probably involve typing of numerous genetic loci.

Mechanisms in pathogenesis and protection

Genetic associations have already provided numerous insights into the pathogenesis of infectious disease and the relevance of particular defence mechanisms. Association of polymorphisms in cytokines and chemokines or their receptors has led to attempts to modulate the activity of these mediators in particular diseases. For example, the up-regulatory variant of the polymorphism at position –308 of the TNF promoter[49] was associated with susceptibility to severe malaria[50] and agents that may reduce the activity of this cytokine are under assessment[51,52].

Another application is in the understanding of specific immune defences used in host resistance to infection or disease. For example, the enhanced susceptibility to non-virulent mycobacteria in children with mutations in the interferon-γ receptor has highlighted the importance of this pathway in controlling these mycobacteria. But the finding that these children appear to have little or no alteration in their susceptibility to other common pathogens has also been informative. Studies of mannose-binding ligand deficiency have demonstrated that this molecule plays a key role in resistance to some but not to other infectious agents[53]. A major goal in the field is the identification of genetic loci that influence the predominant type of cellular immune response to infectious pathogens and potential allergens. Substantial progress has been made in mapping genes affecting atopy and allergy[54] and these may also be relevant to infectious disease. Candidates for influencing the TH1–TH2 shift of the cellular immune responses are

numerous and include IL-4, its receptor, several other cytokines and the vitamin D receptor.

Vaccine design

Immunogenetic associations with infectious diseases may facilitate vaccine design. For example the association between the HLA class I molecule, HLA-B53, and resistance to severe malaria in African children[30] has been analysed in detail. This association was not secondary to known variation in flanking HLA class II or class III region genes[30,50]. This suggested that the association resulted from the action of HLA class I restricted T cells. A search for such cells in Africans exposed to malaria employed a strategy known as reverse immunogenetics[32,55]. Peptides are eluted from the groove of the disease-associated HLA molecule and sequenced to identify the characteristics of peptides that bind to that HLA type. This sequence information is then used to scan protein sequences from the relevant micro-organism to identify candidate epitopes for T cells restricted by that HLA molecule[56]. Application of this approach in malaria led to the identification of an epitope restricted by HLA-B53 in the *P. falciparum* liver-stage antigen-1[32]. This was the first short epitope for CD8+ cytotoxic T cells to be defined in the malaria parasite and it is very substantially conserved across different strains of this very variable pathogen. These findings provided support for efforts to develop vaccines against malaria that would induce protective CD8+ T cells against liver-stage antigens[57]. This vaccine strategy has come up against the problem of the weak immunogenicity of most conventional vaccines for CD8+ T cell induction. However, recently a new prime-boost immunisation strategy may have overcome this difficulty and clinical trials of a new generation of CD8+ T cell-inducing vaccines against malaria are in progress[58]. Animal models of malaria infection have also provided support for this vaccination approach against liver-stage antigens. However, because the pathogen of humans, *P. falciparum*, does not infect rodents or most primates, the immunogenetic data on human malaria have been of particular value.

Several HLA class II associations with infectious diseases have also been defined[59]. These likely reflect an important role for particular CD4+ T cells in immune defence and a similar reverse immunogenetic approach has been taken for the HLA-DR13 association with resistance to chronic hepatitis B virus infection[60]. However, there is additional complexity in analysing these class II associations because of the considerable functional diversity of CD4+ T cells. Definition of associations with other immunoregulatory genes as well as HLA class II

type may be valuable in defining the particular type of CD4+ T cell that is of protective relevance.

New pharmacological targets

Perhaps the most important application in future will be the identification of new molecules and pathways which may become targets for pharmacological intervention. A recent illustration of the rapid application of a finding in host genetics comes from the HIV field. Demonstration of the very substantial resistance to HIV infection of homozygotes for a deletion in the CCR5 gene has underpinned ongoing attempts to develop pharmacological blockers of this viral coreceptor. Other potential coreceptors for HIV, such as CCR2, are now the subject of detailed genetic studies[61] as are potential receptors and coreceptors for many other infectious pathogens. Newer techniques of genome-wide analysis using association analysis[62] as well as the established linkage approaches offer the prospect of many new target molecules in these highly polygenic diseases. The power of these new tools has generated considerable excitement in this field and it is likely that what has been discovered so far is only the tip of an iceberg of informative genetic information on disease aetiology.

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