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THE GENOMICS AND GENETICS OF HUMAN INFECTIOUS DISEASE SUSCEPTIBILITY

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■ **Abstract** A genetic basis for interindividual variation in susceptibility to human infectious diseases has been indicated by twin, adoptee, pedigree, and candidate gene studies. This has led to the identification of a small number of strong genetic associations with common variants for malaria, HIV infection, and infectious prion diseases. Numerous other genes have shown less strong associations with these and some other infectious diseases, such as tuberculosis, leprosy, and persistent hepatitis viral infections. Many immunogenetic loci influence susceptibility to several infectious pathogens. Recent genetic linkage analyses of measures of infection as well as of infectious disease, including some genome-wide scans, have found convincing evidence of genetic linkage to chromosomal regions wherein susceptibility genes have yet to be identified. These studies indicate a highly polygenic basis for susceptibility to many common infectious diseases, with some emerging examples of interaction between variants of specific polymorphic host and pathogen genes.

INTRODUCTION

Analysis of the genetic basis of susceptibility to major infectious diseases is potentially the most complex area in the genetics of complex disease. Not only are these highly polygenic diseases with important, if not overwhelming, genetic components, but there is well documented interpopulation heterogeneity; and in all cases, one essential required environmental factor with, almost always, its own genome in play. Nonetheless, steady progress is being made in untangling the complex interplay of host genes and microorganism that results in some striking interindividual variation in susceptibility.

This is one of the oldest areas of complex disease genetics in humans, with one major susceptibility locus for malaria analyzed almost 50 years ago (9). Since the 1930s, several twin studies have supported a substantial role for host genetics in variable susceptibility to tuberculosis (35, 43, 78), leprosy (33), *Helicobacter pylori* infection (93), and hepatitis B virus persistence (88). Early reports in which malaria (71) and tuberculosis microbes (69) were deliberately or accidentally administered to large numbers of nonimmunes have documented clear variation in susceptibility to these pathogens. A large adoptee study has also

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supported the importance of host genetic factors in susceptibility to fatal infectious diseases in Northern Europeans (152). However, good estimates of the increase in risk to siblings of affected individuals compared to the general population (the λ_s value) are generally lacking for infectious diseases; and where available, it may be difficult to dissect the genetic from the environmental contributors to this value.

In the 1980s, HLA analysis was added to hematologic candidate gene studies of malaria; and in the 1990s, more and more non-MHC candidate genes began to be assessed. In recent years, the first genome-wide linkage studies have been reported, and the utility of this approach is now clear. This review begins with consideration of these genetic linkage studies before tackling the large number of reports of association studies with candidate genes. The field has now expanded to the point where no review article of this size can hope to be comprehensive. Priority is given to papers published in the last three years; but even among these, there is inevitably some personal selection. Also excluded from consideration is the large literature on monogenic disorders that give rise to immunodeficiency and infectious disease susceptibility. These disorders, like studies of gene knockout mice and susceptibility gene mapping in other species, may identify important candidate genes for analysis in common infectious diseases; but as these disorders are invariably rare, the analytic approaches involved are different. To date, there is surprisingly little overlap between the loci involved in monogenic immunodeficiencies and those implicated as common susceptibility loci.

Analysis of infectious disease susceptibility has long been of interest to evolutionary biologists, and the debate over the extent to which MHC polymorphism may have been driven by infectious pathogens is well rehearsed. Two further objectives have become more prominent in recent years. The first, in common with much of genomics, is the identification on new pathways of pathogenesis or resistance that may eventually lead to new prophylactic of therapeutic agents for these infections. For examples, industrial interest in blockers of the chemokine receptor, CCR5, has been encouraged by some striking genetic findings, and the design of investigational vaccines for malaria has been influenced by HLA association studies. The second is the potential for genetics studies to facilitate targeting of therapeutic or prophylactic interventions. For example, IL-10 genotypes might be of value in choosing which patients with chronic hepatitis should receive α-interferon therapy (46), or mannose-binding lectin-deficient individuals could be prioritized for pneumococcal vaccination. However, for a more useful assessment of risk profile, many loci will likely need to be evaluated.

GENETIC LINKAGE STUDIES

Some of the first family studies of the genetics of complex disease searched for linkage and association of the HLA region with the mycobacterial diseases leprosy and tuberculosis. Whole genome scans have more recently been undertaken,

initially for the phenotype of parasite burden and subsequently for disease manifestations.

Schistosomiasis

Complex segregation analysis of Brazilian families with *Schistosoma mansoni* infection provided evidence that a major gene could determine susceptibility to high parasite burdens in this region. Careful estimation of the major environmental risk factor, water contact, for this infection allowed this variable to be included in the genetic analysis. A whole genome scan of 11 families with 246 microsatellite markers found a single region of linkage on chromosome 5q31-q33 (96). A parametric linkage analysis in these families revealed a multipoint lod score in excess of 4.5, mainly accounted for by two extended pedigrees (95). This region of chromosome 5q contains a cluster of cytokine and other immunologically important loci, particularly those for the TH2-type cytokines IL-4, IL-9, and IL-13 and also the colony stimulating factor-1 receptor. Immunological studies have suggested a key protective role of TH2-type immune responses and IgE antibodies in protection against this parasitic disease. Further evidence for a role for this chromosomal region in susceptibility to *S. mansoni* was found in a study of West African families, suggesting that the relevant susceptibility loci are not limited to a small number of Brazilian pedigrees (117).

The Dessein and Abel group have also studied disease manifestations resulting from *S. mansoni* infection (42). An analysis of hepatitic periportal fibrosis in Sudanese families employed initially complex segregation analysis that provided evidence of a codominant major gene with a susceptibility allele frequency of 0.16. Subsequent linkage analysis of a subset of these pedigrees assessed four candidate chromosomal regions for evidence of linkage. A lod score of 3.12 was reported for the 6q22-q23 region that includes the interferon-γ-receptor-1 gene. The antifibrogenic role of γ interferon suggests a potential mechanism for the linkage, but association with this gene has not been reported.

Malaria

The success of case-control studies in identifying numerous loci associated with resistance to malaria suggests that this disease is highly polygenic and that genome-wide studies for new susceptibility loci should be worthwhile. Jepson et al. found evidence of linkage of clinical malaria to the MHC in a study of Gambian children (75), and her twin studies indicated a major role for non-MHC loci in determining some cellular immune responses to the malaria parasite (74). Studies in Burkina-Faso, West Africa, have shown consistent parasitological, clinical, and immunological differences between ethnic groups in *Plasmodium falciparum* infection rates, malaria morbidity, and prevalence and levels of antibodies to various *P. falciparum* antigens, and these could not be ascribed to known susceptibility loci (114, 115). Yet, no genome-wide linkage analyses of malarial disease have been reported. This in part reflects operational difficulties. Although hospital-based studies of severe

malaria cases and matched controls have frequently been undertaken in regions of hyperendemic malaria, recruitment of affected sibling pairs with severe malaria is more challenging for an acute infectious disease. Often hospital records will not allow reliable ascertainment of another sibling who has had strictly defined severe malaria in earlier years. Recruitment of sibling pairs with nonsevere clinical malaria is more feasible; but in general, clearer genetic associations have been observed with severe malaria than with the much more prevalent phenotype of clinical malaria.

However, progress has been made in analysis of another malarial phenotype, that of *P. falciparum* parasite density. In highly endemic regions, with age individuals acquire substantial anti-disease immunity to *P. falciparum* that allows them to tolerate high peripheral blood parasite densities with often minimal or no clinical manifestations. Studies have now addressed the genetic regulation of this level of parasite density by frequent sampling of populations in endemic areas and family segregation and genetic linkage analysis. An early complex segregration analysis of 42 Cameroonian families suggested a single strong susceptibility locus (1), but this was not apparent in a larger study of families from Burkina Faso where a marked age effect was noted (131). Linkage analysis of four candidate regions in nine Cameroonian families showed some weak evidence of linkage to the 5q31-33 chromosome regions (53). Analysis of 154 sibs from 34 Burkina Faso families for 5q31-33 markers using nonparametric analysis showed stronger evidence of linkage ($P < 0.001$), supporting the view that a gene or genes in this region may influence parasite density. Together with evidence for linkage to this interval in asthma and atopy (173), the reported linkage studies of both schistosome and malarial parasite density justify further detailed analysis of the chromosome 5q11-13 region to search for associated and potentially causative loci.

Mycobacterial Diseases

Mycobacterial diseases were among the first to show evidence of both linkage and association with the HLA region, and early examples of the use of a variant of the increasingly popular transmission disequilibrium test may be found in these studies (40, 148, 162). More recently, family linkage analysis was used in the identification of the interferon-γ-receptor-1 gene as the susceptibility locus for rare familial susceptibility to usually nonpathogenic atypical mycobacteria and the BCG vaccine (77, 121). Mutations in the IL-12 receptor beta-1 gene have more recently been causally associated with this phenotype and with monogenic susceptibility to *Salmonella* infections (11, 76). In a study of an extended Canadian aboriginal family with unusually marked susceptibility to tuberculosis, linkage to the chromosome 2q35 region was identified (59). However, linkage analysis of this region in families from other regions with other mycobacterial phenotypes has provided mixed and generally negative results (see below) (3, 7, 18, 26, 134, 144, 167).

The first whole genome scan for an infectious disease, tuberculosis, was reported by Bellamy and colleagues (18, 23). In the first stage of this two-stage study,

92 African affected sibling pairs with tuberculosis were studied, mainly families from Gambia (23). Several chromososomal regions, including the MHC, initially showed weak evidence of linkage, and these were reassessed in a second-stage study. In this stage, 81 predominantly South African sibling pairs were studied because of the limited availability of more West African sibling pairs. Nonetheless, two of these chromosomal regions, around bands 15q11 and Xq27, again showed evidence of linkage, with overall lod scores of the order of 2.0 (18). The location of susceptibility genes at these chromosomal regions was further supported by an independent analysis, employing common ancestry using microsatellites mapping. In this variant of homozygosity mapping, chromosomal regions are assessed for increased homozygosity in cases that are compared to controls using Goldstein's genetic distance as a sensitive measure of inbreeding at each locus (18). Several positional candidate genes in these regions are under investigation and linkage disequilibrium mapping is being used to search for the putative susceptibility loci. The X-chromosome linkage may relate to the observation in Africa and other continents that clinical tuberculosis is more frequently found in males than females.

Negative findings in this genome-wide analysis are also of interest. Despite speculation on the potential role of NRAMP1 as a major susceptibility locus for tuberculosis in humans, no support has been found for this possibility in the linkage analysis of these African families. Although there is a clear association of clinical tuberculosis with the HLA class II region in several Asian studies, significant linkage to the MHC was not found in the final analysis of these African families. Although this lack of linkage does not exclude susceptibility genes in these chromosomal regions, it does limit the potential magnitude of their effects. Finally, placed alongside the estimates of the magnitude of a host genetic effect suggested for tuberculosis by early twin studies (35,43,78), the lack of a clear major locus for tuberculosis in these African families suggests that much or most of the genetic component, at least in Africans, may be dispersed among many loci, with no locus or chromosomal region sufficiently important to show clear linkage. This inference, together with the evidence from candidate gene studies of malaria (63) that show that susceptibility to this disease is also highly polygenic, raised the possibility that, in general, susceptibility to major infectious disease might be too polygenic for major loci to be mapped convincingly using the available genome-wide linkage strategies. Fortunately, other data soon contradicted this negative view.

Leprosy is one of the infectious diseases most amenable to genetic linkage analysis. In a study of approximately 250 affected sibling pairs from South India, it was possible to recruit almost all the parents in these families, and a genome scan using almost 400 microsatellite markers was undertaken (146). One area of strong linkage with a lod score over 4.0 was identified on chromosome 10p13. In contrast, the MHC showed only weak evidence of linkage, despite evidence of association with HLA-DR2 within these families. There are several positional candidate genes within the chromosome 10 region of linkage, and further fine mapping studies are in

progress. Estimation of the locus-specific sibling risk in these families suggested that this region may account for a substantial proportion of the overall genetic component in this geographic region. The latter was estimated indirectly in a different South Indian population (60, 132). Nonetheless, this study provides the clearest indication yet that genome scans can provide a useful approach to major gene identification in a major infectious disease, despite the polygenic nature of these diseases.

Viral Diseases

HIV infection is now frequently investigated by human geneticists, but the rarity of multicase families has generally prevented useful linkage analyses. An exception is an HLA study of 95 HIV-infected hemophiliac brother-pairs where HLA concordant sibling pairs and those sharing one but not zero HLA haplotypes were significantly concordant in their rate of CD4 T-cell number decline (85).

One of the clearest dichotomies in the response to an infectious pathogen is the ability of most, but not all, individuals infected by the hepatitis B virus to clear this infection. In most populations, 5%–20% of individuals fail to clear the virus and develop a chronic carrier state that substantially increases their risk of chronic liver disease and hepatocellular carcinoma. A small Taiwanese twin study provided some evidence of a host genetic influence of viral clearance (88). Whole genome scans to examine the phenotype of persistent HBV infection have now been undertaken in both Gambian and Italian populations. In the European families, there was evidence of linkage to chromosome 6q (50). The West African study assessed almost 200 Gambian sibling pairs and identified a linkage (lod score > 3.5) to a region on chromosome 21 that encodes numerous cytokine receptor genes (L. Zhang, A. Frodsham, U. Dumpis, S. Best, A. Hall, H. Whittle, B. Hennig, S. Hellier, M. Thursz, H. Thomas, & A. Hill, unpublished data). Preliminary evidence of association with a variant of one of these genes has been found in these families, and the availability of a full sequence of this chromosome should facilitate further analysis. Interestingly, it has been recognized for over 30 years that individuals with trisomy 21 have a higher prevalence of chronic HBV infection (28), suggesting that the same gene or genes on chromosome 21 may underlie this finding and the linkage result.

CANDIDATE GENE STUDIES

Human Leukocyte Antigens

Studies of HLA and malaria in Gambia helped to establish the view that natural selection by infectious disease has contributed to the maintenance of the remarkable allelic diversity of HLA class I and II loci (64, 65). Gilbert et al. (57) have extended these studies to assess association of malaria parasite variants with HLA class I type. When parasites were divided into strains according to allelic types

of an HLA class I restricted epitope in the major coat protein of the sporozoite, an association was observed between parasite type and the relevant HLA class I molecule, HLA-B*35. A remarkable nonrandom distribution of parasite allelic type, termed cohabitation, was documented in which parasite types that could mutually antagonize CD8 T-cell responses in primary (129) and effector T-cell assays (57) were found together more frequently than expected in mixed parasite infections. A mathematical model was employed that supported the inference that the immunological mechanisms documented in vitro may be maintaining the nonrandom distribution of parasite types through HLA class I restricted T-cell antiparasite responses. This study of coevolution provides insight into the potentially powerful influences that HLA restricted responses may exert on pathogen diversity and population structure and suggests that further analyses of host HLA and pathogen diversity in the same sample sets should be instructive.

Some further evidence of HLA association with the rate of progress of HIV infection has been provided by several recent studies. HLA-B*5701 was found in 11 of 13 long-term nonprogressors with low viral loads, but only 10% of controls (111). In a study of large U.S. cohorts, HLA-B*35 and Cw*04 were associated with rapid progression to AIDS-defining illnesses (32). In a powerful study of 75 rapid progressors and 200 long-term nonprogressors, representing the extremes of this spectrum, a variety of alleles were associated with protection and susceptibility (60a). HLA-A29 and -B22 were significantly associated with rapid progression; whereas B14, C8, and, though less strongly, B27, B57, and C14 were protective. Interestingly, in contrast to other chronic viral diseases, such as persistent hepatitis B and C infection, HLA class II associations have been less evident in these studies of HIV/AIDS. In contrast, in a rare study of susceptibility to HIV/AIDS in Africans (92), HLA-A2 related subtypes were associated with resistance to disease progression, and the class II type HLA-DR1 was associated with resistance to HIV infection in Nairobi commercial sex workers.

Further studies of Europeans (156, 166) have supported previous findings (10, 113, 126, 175) that the linked HLA class II alleles, HLA-DRB1*11 and HLA-DQB1*0301, are associated with resistance to persistent HCV infection; this is now probably the most consistently documented HLA association with a viral disease. In a cohort study of infection with the HTLV-1 retrovirus, HLA-A2 was strongly associated with a reduced risk of developing HTLV-associated myelopathy, and viral load also reduced in individuals with this class I type (73). Other types, HLA-B*54, Cw*08, and DRB1*0101, showed less strong associations (72). In this study and the Carrington et al. study of HIV infection in American cohorts (32), the influence of HLA heterozygosity was examined. A graded protective effect of HLA-A, -B, and -C heterozygosity against disease progression to AIDS and death was found with heterozygotes at all three loci showing the slowest progression (32). In the study of HTLV-1 infection, individuals heterozygous at all three HLA class I loci had significantly reduced viral load compared to other genotypes (72). Together with an association of HLA class II heterozygosity in HBV infection (157), these data provide important support for the proposal (44)

that heterozygote advantage against viral infectious disease plays some part in maintaining the polymorphism of HLA loci.

Two studies have analyzed further the well-established association of HLA-DR2 with susceptibility to tuberculosis as well as to leprosy in Indian populations (107, 130). Analysis of HLA-DR2 subtypes showed that the HLA-DRB1*1501, but not the *1502 allele, is associated with susceptibility to tuberculosis, but the HLA-DQB1*0601 allele in strong linkage disequilibrium with HLA-DRB1*1501 is also strongly associated. In a small study of tuberculosis in Vietnam, a susceptibility association with the rare HLA-DQB1*0503 allele was reported (58). Intriguingly, an HLA-DR2 association has now been reported with a third mycobacterial disease. In North American AIDS patients, HLA-DRB1*1501 was associated with an accelerated onset of disseminated *Mycobacterium avium* complex disease (86), suggesting a common mechanism underlying these three mycobacterial disease associations.

Cytokines and Their Receptors

Since the initial report of a TNF polymorphism association with cerebral malaria by Kwiatkowski & colleagues (105), there have been several studies of polymorphism in cytokines and infectious diseases. The promoter variant allele at position -308 has now been associated with cerebral malaria, mucocutaneous leishmaniasis, leprosy type, and scarring trachoma in various populations (31, 36, 105, 138). Some, but not all, of these studies analyzed flanking HLA polymorphisms to allow independent assessment of the relevance of the TNF promoter variant. Some functional analyses have found evidence of increased transcription (170) by the rarer TNF2 allele at this -308 position, but this remains controversial (4). Analysis of the other common clinical presentation of severe malaria in African children, severe malarial anemia, has demonstrated an association of the variant allele at position -238 of the TNF promoter with this phenotype (106), suggesting that these different complications of malaria infection are influenced by separate genetic factors near the TNF gene. The -238 variant has also been associated with chronic hepatitis B virus infection in Europeans (67).

Another TNF promoter variant has recently been associated with cerebral malaria (80). In this case, the polymorphism at position -376 altered binding of a transcription factor, identified as OCT-1, to that region of the promoter and resulted in altered gene expression in a human monocytic cell line. Although relatively uncommon, this variant was associated with a fourfold increase in risk of cerebral malaria after allowing for flanking polymorphisms.

Interleukin (IL)-1 genetic variation has been investigated in several autoimmune diseases, and evidence of its relevance to infectious disease susceptibility has been recently reported. A twin study has demonstrated that host genetic factors influence susceptibility to *H. pylori* infection (93), and a study of IL-1 beta polymorphisms has now found association with complications of this chronic gastric infection. Two polymorphisms in near-complete linkage disequilibrium were

associated with both *H. pylori*–induced hypochlorhydria and increased risk of gastric cancer, and one of these variants is a TATA box promoter polymorphism that was found to alter DNA-protein interactions (47). Two studies have also reported preliminary evidence that polymorphism in the IL-1 beta and the flanking IL-1 receptor antagonist genes may affect either risk or clinical presentation of tuberculosis (20, 169).

Three single nucleotide polymorphisms (SNPs) in the promoter of the IL-10 gene and two flanking microsatellite polymorphisms have been investigated in several autoimmune disorders. The variants at position -1082, -819, and -592 are G to A changes, and assays of IL-10 production suggest that the GGA haplotype is associated with higher IL-10 levels (37, 159). The variants associated with higher IL-10 production are associated with clearance, rather than persistence, of hepatitis B virus in both West Africans and Europeans (L. Zhang, A. Frodsham, S. Knapp, H. Thomas, M. Thursz, & A. Hill, unpublished). A study of response to α-interferon therapy in hepatitis C infected patients also suggested that the A allele at -592, associated with lower IL-10 production, is a marker of good response to this intervention (46). In American HIV-infected cohorts, the presence of the -592 A allele was associated with more rapid disease progression, particularly late in the course of infection (145).

An SNP at position -589 of the IL-4 promoter has been investigated in several diseases, in view of its potential relevance to TH1-TH2 switching of the cellular immune response. In a study of Japanese HIV-infected individuals, homozygotes for the T allele were more likely to develop syncytium-inducing strains of HIV than other genotypes (120). These strains use the CXCR4 coreceptor, appear later in HIV infection, and their emergence represents a marker of more rapid disease progression. In this study, no association of this viral phenotype with RANTES or IL-10 promoter variants was observed.

There have been fewer reported studies of variation in cytokine receptors than cytokine genes in common infectious diseases. However, it is clear that rare inactivating mutations in the interferon-γ-receptor-1 and the IL-12Rβ1 genes are associated with susceptibility to usually nonpathogenic mycobacteria and *Salmonella* species (11, 76, 77, 121). There is, to date, no evidence from population studies that common variants in the interferon-γ-receptor genes affect susceptibility to tuberculosis, although several groups have addressed this question.

Chemokines and Their Receptors

The discovery in 1996 of the resistance to HIV infection of Caucasian homozygotes for a 32-base pair deletion in CC chemokine receptor 5 (CCR5) (41, 90, 140) has led to numerous studies of chemokine receptors, and more recently chemokine polymorphisms, in HIV infection and disease. It soon became apparent that this variant is not significantly protective against infection in the heterozygous state, but that heterozygotes manifest slower disease progression to AIDS and death, at least among homosexuals but possibly not among hemophiliacs (39, 41, 68, 109, 177).

Rare homozygotes infected by HIV-1 have been described so protection is not absolute (16). Sadly, in regions of Africa and Asia where the epidemic is most marked, the variant is essentially absent (100).

A valine-to-isoleucine change in the first transmembrane region of the flanking CCR2 gene is also associated with delayed disease progression but not altered susceptibility to HIV infection (151). This protective effect has now been confirmed in another U.S. cohort and in Swiss and British studies (45, 81, 133). In a large Texas-based study, this association was observed in African Americans, but not Caucasians, with HIV infection (118). The lack of association in another published study (110) may be due to analyses of a seroprevalent rather than a seroincident cohort (150), as this CCR2 polymorphism may be most relevant early in HIV infection. In a study of the genetics of susceptibility to HIV or AIDS in Africans, Anzala et al. found an increased frequency of the protective CCR2 allele in Kenyan long-term nonprogressors (14). A possible molecular mechanism underlying this association was suggested by the finding that in vitro CCR2 can heterodimerize with CCR5 but that the CCR2 isoleucine variant, unlike the wild type, cannot heterodimerize with CXCR4 (108).

Several studies have now found that variants in the promoter region of CCR5 also influence the rate of disease progression. An A to G change at position 59029 [in the numbering of Genbank clone U95626, equivalent to position 303 as numbered in the study by Martin & colleagues (99) as well as 2459 as numbered in the report by An et al. (13)] of the CCR5 promoter region was associated with reduced promoter activity in Jurkat cells (104). G/G homozygotes progressed to AIDS more slowly than A/A homozygotes, particularly in the absence of the 32-bp CCR5 deletion and CCR2-isoleucine variants (104). In parallel, haplotypes of eight other SNPs in the CCR5 promoter region were defined, and one of these, termed P1, was significantly associated with accelerated progression to AIDS (99). The P1 haplotype and the 59029 A allele are in very strong linkage disequilibrium in both Caucasisans and African Americans (13). An Australian study found that 59029 A/A homozygotes were less frequent among long-term nonprogressors (34), consistent with the U.S. datasets. Among African Americans, the 59029 A association with rapid progression was also observed, but in contrast to Caucasians, the effect was dominant rather than recessive (13). Evidence of further complexity in the CCR5 promotor and possible population differences in haplotypic associations was provided by an evolutionary analysis of extended haplotypes among a Texas cohort (119). Analysis of another promoter variant, a C to T change at position 590356 that is more prevalent in African Americans, showed increased perinatal transmission of HIV-1 from mothers to 21 African American offspring who were homozygous for the variant T allele (82). In a study of French HIV-infected individuals who were homozygotes for a coding change at position 280 of the fractalkine receptor, CX_3CR1, showed increased rates of progress to AIDS (48). However, analysis of U.S. cohorts failed to replicate this association and instead suggested that heterozygotes for this change might have a reduced rate of disease progression (103).

Variation in the regulatory regions of two chemokine genes has now been associated with HIV infection or disease progression. The promoter of the gene for RANTES, one of the ligands for CCR5, was sequenced in Japanese subjects and two promoter variants at positions -28 and -403 were identified. The G allele at position -28 showed increased expression in transfection assays and was associated with delayed disease progression in Japanese (89). The -403 position change has also been found to be of functional significance in in vitro assays and has been associated with atopic dermatitis, atopy, and asthma (51, 122). In the U.S. Multicenter AIDS Cohort Study, the A allele at -403 of the RANTES promoter was associated with an increased risk of HIV infection but with a slower rate of disease progression to AIDS (102). Clearly, further studies of these RANTES promoter variants are required to address this complexity. More heterogeneous results have been reported for a 3′-UTR variant in the gene for stromal-derived factor-1, SDF-1, the principal ligand for CXCR4. Winkler et al. initially reported that homozygotes for a variant A SNP were highly significantly protected from disease progression to AIDS (172). Five studies have now failed to replicate this strong protective effect, and four of them find evidence of greater disease susceptibility of 3′-UTR A/A homozygotes at this locus (15, 29, 45, 118, 163). A London cohort study showed no SDF association (45), but a Texas cohort showed that A/A homozygotes had faster progression to death (118). Balotta et al. (15) associated A/A homozygosity with low CD4 T-cell counts, Brambilla et al. (29) observed a more rapid late progression of A/A homozygotes; and in a Dutch cohort (163), homozygotes progressed more rapidly to AIDS but not to death.

NRAMP1

Genetic linkage studies in mice led to the mapping of a gene, initially termed *Lsh/Ity/Bcg*, that influences early resistance to several intramacrophage pathogens, *Leishmania donovani*, *Salmonella typhimurium*, and some strains of *M. bovis* BCG (25). This gene was positionally cloned by Gros and colleagues in Montreal and termed Nramp1 (natural-resistance–associated macrophage protein-1) (165). Cellular and molecular studies have now indicated that Nramp1 is expressed in both macrophages and neutrophils, is a transporter of divalent cations, and is localized to the phagolysosomal membrane (149). Recent studies from the Gros laboratory have suggested that Nramp1 can pump manganese ions out of the phagolysosomal space in a pH-dependent manner (70), although inward pumping has also been advocated (27). Iron and other ions may also be pumped out (17), thereby perhaps modifying mycobacterial viability.

The susceptibility allele of Nramp1 in mice bears a glycine-to-arginine substitution at position 105, leading effectively to a null phenotype (164). The clear effect of this change on susceptibility to BCG Montreal infection (149), together with some complex segregation analysis of human mycobacterial disease that suggested a major gene effect (2), led to speculation that the human homologue, NRAMP1,

might be a major gene for human mycobacterial disease. It is now increasingly clear that this speculation is generally incorrect.

Recent linkage studies in mice have shown that the major gene effect evident in studies of BCG strains is not observed in challenge with *M. tuberculosis* (123), and other loci have now been mapped that do affect tuberculosis susceptibility in mice (84). Whole genome scans for tuberculosis in West and South Africans (18) and for leprosy in India (146) have not found significant linkage to the chromosome 2 region encoding the human NRAMP1 gene. However, linkage to leprosy has been reported in a small number of Vietnamese families (3) and in analyses of skin test responses (Mitsuda reactions) to leprosy antigens in Vietnamese (7). No evidence of association with NRAMP1 variants was reported in these studies. Furthermore, in a large aboriginal Canadian family with multiple affected individuals significant linkage to the NRAMP1 locus has been found (59). Interpretation of such positive linkage data is complicated by the finding that in mice a locus termed Sst1 has been mapped near to the NRAMP1 locus on chromosome 1 as a tuberculosis susceptibility locus (84).

However, several studies have now found evidence for association of NRAMP1 polymorphisms with mycobacterial disease. The largest study, undertaken in Gambians, found association with several variants, in particular a 4-bp insertion-deletion polymorphism in the 3′ untranslated region (21). Recently the same variants have been associated with tuberculosis in independent studies of Koreans (139) and Japanese (52). In Bengal (136) and Mali (107a), no association was found with leprosy per se; but in the latter study, there was evidence of a possible association with leprosy type.

How may these apparently heterogeneous reports be reconciled? With the exception of the Canadian aboriginal family (59), there appears to be no evidence of a major effect of NRAMP1 or a flanking gene on general tuberculosis susceptibility. Evidence of genetic association in several tuberculosis studies exists, but the magnitude of these effects is modest and compatible with the absence of significant linkage in family studies. Indeed, the man-mouse difference may be more apparent than real, in that small differences in susceptibility to tuberculosis between the susceptible and resistant mouse strains might be missed in linkage studies. It remains possible that the associations observed, like the positive linkage data, result from linkage disequilibrium with variation in some flanking gene (97). However, similar allelic associations in Japanese and Africans and the known function of NRAMP1 make this gene still the most parsimonious culprit. A different issue is whether the associations result from a primary effect of the NRAMP1 gene on *M. tuberculosis* susceptibility. Variable degrees of exposure to environmental mycobacteria may underlie the variable efficacy of BCG vaccine against tuberculosis in different populations, and a primary effect of NRAMP1 variation on other mycobacterial infections might conceivably result in altered tuberculosis susceptibility.

Recently, associations have been reported with other diseases, including HIV infection in Columbians (98), juvenile arthritis in Latvians (142), and sarcoidosis in African Americans (94).

Vitamin D and Other Receptors

Polymorphism in the vitamin D receptor gene was initially extensively investigated in osteoporosis and other bone disorders (116). Although there are many apparently conflicting reports of associations with SNPs in the 3′ region of this gene, overall it appears that, at least in some populations, variation at a Taq I site in codon 352 (with alleles denoted T and t) and at flanking sites is associated with susceptibility to reduced bone mineral density. Several studies have now suggested that this and perhaps other variants of the VDR gene may be associated with susceptibility to various infectious diseases. In a case-control study of pulmonary tuberculosis in Gambia, homozygotes for the rarer tt genotype were reduced in frequency in the cases, suggesting a protective effect (19). Some support for this conclusion was provided by a study of a Gujarati tuberculosis patient in West London where both the T allele and deficiency of 25-hydroxycholecalciferol were associated with tuberculosis (168). In vitro studies have reported that dihydroxy vitamin D is one of the few mediators identified that can lead to a reduction in the growth of *M. tuberculosis* in human macrophages (135).

However, this gene may also, or alternatively, influence the type of cellular immune response evoked by pathogens. In a case-control study of leprosy in Bengalis, the TT and tt genotypes were associated with the two polar forms of leprosy, lepromatous and tuberculoid (136). As the latter form is associated with a stronger cellular immune response to *M. tuberculosis*, the tt genotype here and in the tuberculosis studies may be modulating the predominant type of cellular immune response evoked. 1,25-dihydroxy vitamin D has been found to affect IL-12 production by macrophages and to modulate dendritic cell maturation (38, 127). In Gambians, the tt genotype was also associated with a greater rate of viral clearance in those infected by the hepatitis B virus (19), again consistent with a stronger cellular immune response. However, vitamin D stores are influenced by both diet and sunlight exposure, providing opportunities for important gene-environment interactions and suggesting that there may be substantial heterogeneity in VDR infectious disease associations between populations. Variation in the VDR gene has also been associated with susceptibility to *Mycobacterium malmoense* pulmonary disease (56), localized early-onset peridontitis (61), and, which is intriguing, to Crohn's disease (147), a granulomatous disease of the intestine for which a possible mycobacterial or other infectious etiology has been mooted.

The immunoglobulin receptor FcγRIIa, CD32, has a common dimorphism at position 131 where the variant with histidine has higher opsonic activity for IgG2 antibodies than the arginine 131 variant. In 1994, small clinical studies by the van de Winkel group suggested that children homozygous for the arginine variant may be at increased risk of recurrent bacterial infection (141) and meningococcal septic shock (30). An association with meningococcal disease has now been reported in a small study of Slavic children over 5 years of age (128). A possible increased risk of bacteremic pneumococcal disease associated with homozygosity for the arginine variant has also been suggested (174; S. Segal, K. Knox, D. Crook, &

A. Hill, unpublished data). If this genotype is associated with susceptibility to disease caused by several encapsulated bacteria, this would suggest that some other fairly strong positive selective pressure has been maintaining the arginine variant at high frequencies.

A proposed role for the class B scavenger receptor CD36 in the downregulation of dendritic cell activation following malaria parasite clearance raised the possibility that some common deficiency variants of this gene observed in Africans might have been selected through enhanced malaria resistance (161). However, African case-control study data have not, so far, supported this idea (6).

Mannose-Binding Lectin

Mannose-binding lectin (MBL) (also known as mannose-binding protein) is a serum collagenous lectin that has a remarkably high prevalence of alleles and genotypes that produce little or no protein as a result of mutations in codons 52, 54, or 57 of the gene (160). Heterozygotes for one or other of these variant alleles are found at frequencies in the order of 0.33 in major population groups. Homozygotes or compound heterozygotes for the variant alleles (collectively sometimes termed functional mutant homozygotes) produce very little or no MBL and, thus, have impaired opsonization of some pathogens and lack the ability to activate complement through MBL-associated serine proteases. This manifestly functional genetic variation has led to searches for MBL association with many infectious diseases.

Although initially it was proposed that MBL deficiency led to susceptibility to recurrent infections in young children, evidence supporting this is weak. Studies of children in London suggested that both heterozygotes and homozygotes may be susceptible to a variety of infections and to menigococcal disease (62, 153), but the ethnic complexity of these study populations and the unusual distribution of specific genotypes in the groups raises the possibility of significant confounding by population stratification (154). A Danish study suggested that functional mutant homozygotes show increased susceptibility to HIV infection and progress to death more rapidly following diagnosis of AIDS (55). A difficulty with these and some other studies in the literature is the surprisingly low frequency of functional mutant homozygotes in the control groups employed, sometimes as low as 1%, when the expectation from the frequency of heterozygotes is about 5%. However, a Finnish study also reported a higher frequency of MBL homozygotes in HIV-infected individuals than controls (125), and a small study of Italian children found an association of codon 54 heterozygotes with an increased rate of progression to AIDS but not with infection (12). A study in London of HIV disease progression failed to find any genotypic association (101). Finally, in an Amsterdam cohort, there was a suggestion that MBL heterozygotes might progress more slowly to AIDS and death. Overall, this heterogeneous literature fails to provide convincing evidence, as yet, that MBL genotype really influences any of these phenotypes.

Several groups have studied MBL genotypes and tuberculosis, following a suggestion that MBL deficiency might have been maintained evolutionarily by

a reduced capacity of mycobacteria to invade macrophages in the absence of MBL, leading to resistance to tuberculosis (54). Small studies in India and South Africa suggested that homozygotes may be susceptible to tuberculosis (143) and that codon 54 heterozygotes may be protected from tuberculous meningitis (66), but a larger study in Gambia (22) found no genotypic association. Recently, a Mexican study of surfactant genes expressing collectins that are evolutionarily and functionally related to MBL has suggested that variation in these genes may influence tuberculosis susceptibility (49).

Evidence from a study in London that MBL codon 52 heterozygotes may be susceptible to hepatitis B virus persistence (155) was not supported by data from Gambia (22), and a weak association of MBL heterozygotes with severe malaria susceptibility seen in Gabon (91) was not found in a larger study of Gambians (22).

In an Oxford-based study of Caucasian hospital patients with invasive pneumococcal disease, we have recently found a significantly increased frequency of MBL functional mutant homozygotes in cases, suggesting a protective role for MBL in this disease (S. Roy, K. Knox, D. Crook, & A. Hill, unpublished). But protective associations with MBL deficiency genotypes have yet to be identified. Thus, the enigma of why multiple MBL deficiency alleles are so prevalent remains.

Hemoglobins and Blood Groups

There has been evidence for many years that heterozygotes for sickle hemoglobin and for β thalassemia enjoy protection from severe malaria, but data on the other common hemoglobin variant in Africa, hemoglobin C, have been lacking. This is distributed more focally than hemoglobin S in West Africa, and a Dogon population from Mali has now been studied (5). Substantial protection against severe cerebral malaria was documented with an odds ratio of 0.14, suggesting that the level of protection afforded by hemoglobin C may be very substantial.

Lack of the Duffy blood group on red blood cells, manifest as the FY (a-b-) phenotype, is associated with complete protection against *Plasmodium vivax* malaria (112). This chemokine receptor gene that encodes the Duffy antigen has a point mutation in its promoter, which prevents erythroid expression (158), and this FY*A null allele is present at frequencies of almost 100% in most sub-Saharan African populations but is rare or absent in Caucasians. Zimmerman et al. (178) have now identified a FY*A null allele at low frequencies in Papua New Guinea and present preliminary evidence that the rate of *P. vivax* infection may be lower in heterozygotes for this variant.

The inability to secrete blood groups' substances into saliva and at other mucosal surfaces was one of the earliest human genetic markers studied and is determined by null alleles of the fucosyltransferase-2 gene (79). Nonsecretors make up 15%–25% of major population groups and may be at increased risk of bacterial urinary tract infections. A study of Senegalese commercial sex workers has found that nonsecretors were at lower risk of HIV-1 infection (8), supporting a previous study of a heterosexual HIV transmission (24).

Prion Protein Gene

One of the strongest genetic associations described with an infectious disease is for the prion protein gene (PRNP). About 50% of Caucasians are heterozygous for methionine and valine at position 129 of this gene, and these individuals are strongly protected against sporadic Creutzfeld-Jacob disease (CJD) (124) and new-variant CJD (176), which resulted from the bovine spongiform encephalopathy epidemic. Methionine homozygotes are at greater risk of sporadic CJD than valine homozygotes (171), and these two genotypes are associated with subtly different clinicopathologic phenotypes (83). Recently, it has been possible to genotype kuru cases and matched controls from the Fore tribe of the New Guinea highlands where the original epidemic of this transmissible spongiform encephalopathy was described. Methionine homozygotes show the highest risk of disease and manifest a shorter incubation period than other genotypes, raising the possibility that more heterozygotes will be identified in the current British new variant CJD epidemic as time progresses (87).

CONCLUDING REMARKS

There has been a clear upturn in the amount of activity in this field in recent years, driven by the greater ease of genotyping and new analytical approaches. Larger and more realistic sample sizes are becoming common because of technical improvements. Although, as ever, there are apparently inconsistent reports from different laboratories, usually studying very different populations, some important areas of consensus are clear. There are some clear and repeatable genetic associations with particular diseases. The existence of HLA associations with several infectious diseases now appears beyond dispute, particularly with leprosy, tuberculosis, persistent hepatitis, HIV and HTLV-1, and malaria. Evidence for the importance of heterozygote advantage in maintaining HLA polymorphism is growing. The associations of variation in the chemokine receptor genes, CCR5 and CCR2, and altered rate of HIV disease progression are now very well supported, but evidence of chemokine associations is more preliminary. Several other loci are credibly associated with malaria, tuberculosis, and pneumococcal disease manifestations. But the great majority of these associations to date are of modest effect.

The exceptions are worth noting. Hemoglobin S and possibly hemoglobin C provide a very substantial reduction in risk of severe malaria in the heterozygous state. The absence of the Duffy blood group on red blood cells is associated with complete resistance to vivax malaria. Homozygosity for the CCR5 32-bp deletion is very substantially protective against HIV infection, and heterozygotes at position 129 of the prion protein gene hardly ever develop Creutzfeld-Jacob disease. Interestingly, these strong associations are all disease specific, whereas the many immunogenetic loci that have smaller more modulatory effects (e.g., HLA,

VDR, CD32) are often associated with multiple infectious diseases. All four of these loci were identified as candidate genes, but increasing use of genome-wide linkage analysis of multicase families suggests that new major susceptibility loci should soon emerge from this approach. Although this is clearly a more demanding approach than candidate gene analysis, progress, so far, with linkage studies of several infectious diseases has been encouraging.

In the near future, two new approaches will become of increasing importance. The first will be the rise of detailed linkage disequilibrium mapping, resulting from the availability of huge numbers of new SNPs in all areas of the genome. This will initially allow much more precise mapping of known associations and linkages and eventually lead to genome-wide association studies. The potential of the latter has been extensively discussed in the field of complex disease in general, and the apparently highly polygenic nature of common infectious disease suggests that this approach may be particularly fruitful in this arena. The other approach that is already attracting more interest, that of combined host-parasite genetic analysis, is also fuelled by genomic information. Viral genome sequences have been available for some years, bacterial genomes, such as that of *M. tuberculosis* and the meningococcus, are newly available, and those of larger parasites, such as *P. falciparum*, will be available in the near future. In diseases where it is readily possible to sample the genomes of both host and pathogen simulataneously, such as for HIV, malaria, and many other infections, this should lead to new combined analytical approaches that may reveal much about the nature of evolutionary driving forces for host and parasite genetic diversity.

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