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# Leprosy and the Human Genome

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## INTRODUCTION

*Mycobacterium leprae* is the etiological agent of human leprosy, an ancient affliction of humankind that has persisted into contemporary times despite the facts that it is not highly transmissible and that chemotherapy has been available for 60 years (215). *M. leprae* produces a broad spectrum of illness, and the host factors that regulate susceptibility to its diverse clinical forms are largely unknown. Studies of human genetic variation and its link to leprosy over the past 35 years strongly suggest that genetic factors influence susceptibility to leprosy and its varied clinical forms (9, 53, 88, 247). Because leprosy's divergent clinical forms reflect two distinct immune responses (Th1 versus Th2) to the same pathogen, human infection with *M. leprae* offers a unique opportunity to link innate and adaptive immune responses to specific host genes. Insight into the genetic determinants of these immune responses has illuminated the immunopathogenesis of leprosy. In addition, this field may broaden our understanding of the host response to *Mycobacterium tuberculosis*, a related but far more virulent and prevalent pathogen.

### Overview of Leprosy

**Epidemiology.** *M. leprae* is a fastidious, acid-fast, intracellular pathogen. In 2008, there were approximately 250,000 new cases reported, predominantly in India, Brazil, and Indonesia (333). Humans were previously thought to be the only important reservoirs of the bacteria, but it is now appreciated that leprosy, or Hansen's disease, may also be acquired from environmental sources (59, 60, 73, 170). A number of reports have linked leprosy to exposure to armadillos (169) or soil exposure (170). Leprosy is likely transmitted by aerosol droplets taken up through nasal or other upper airway mucosa (67, 215), where it has been detected by PCR techniques (148, 221). Large numbers of organisms have been found in the nasal secretions of lepromatous leprosy patients (223, 278, 279). Estimates of the incubation period between exposure and clinically manifest disease vary from months to decades (216), which makes epidemiological assessments of incidence and mechanisms of transmission difficult. Epidemiological studies of leprosy have established several risk factors for the disease, the strongest of which are genetic relatedness (204, 263) and close contact with leprosy patients, especially those with lepromatous disease (128, 204; summarized in reference 203). Other potential risk factors include low education level (156), food insecurity (156), water exposure (156, 167), infrequent changing of bed linen (156), armadillo exposure (59, 60, 73, 169, 311), lack of BCG vaccination (61, 65, 182, 295), and soil exposure (33, 170). Age has been reported to be a risk factor for leprosy or leprosy immune reactions in some studies (204, 243) but not in others (21, 156; see also summary in reference 203). Interestingly, in many, but not all, ethnic groups, there is a 2-to-1 ratio of males to females affected (21, 215; see summary in reference 203).

**Natural history.** Leprosy is primarily a disease of the skin and peripheral nervous system. Less commonly, the eyes, bone, lymph nodes, nasal structures, and testes may also be involved (328). The disease's clinical manifestations fall into two poles, tuberculoid (TT) or "paucibacillary" (PB) and lepromatous (LL) or "multibacillary" (MB), with several intermediate forms (indeterminate, borderline tuberculoid [BT], borderline borderline [BB], and borderline lepromatous [BL]) (249) (Fig. 1). According to the WHO classification, multibacillary leprosy includes the LL, BL, and BB forms, and paucibacillary leprosy encompasses the TT and BT forms (140, 332). In some regions, patients with borderline, as opposed to polar, forms of leprosy (BB, BL, and BT) make up the majority of cases (36, 50, 143). Clinically, patients with lepromatous leprosy have a high burden of leprosy bacilli in skin biopsy specimens ("multibacillary"); multiple skin lesions consisting of macules, papules, plaques, or nodules; and thickened peripheral nerves with anesthesia and may eventually develop keratitis, uveitis, loss of eyebrow hair, ulceration of the nose, bone destruction, and thickened, waxy skin (249) due to infiltration by macrophages, lymphocytes, and plasma cells (328). At the opposite end of the spectrum, patients with tuberculoid (TT and BT) leprosy have a low burden of organisms ("paucibacillary") in skin biopsy specimens and can present with a single, anesthetic skin lesion with or without a thickened peripheral nerve (249). Spontaneous resolution of tuberculoid and indeterminate infections has been observed. In contrast, spontaneous regression of disease does not occur in lepromatous leprosy patients (215).

**Immunology.** The clinicopathological features of leprosy have distinct immunological correlates (44, 249). Immunologically, lepromatous leprosy is characterized by a Th2 T-cell immune response (interleukin-4 [IL-4] and IL-10), antibody complex formation, the absence of granulomas, and failure to restrain *M. leprae* growth. Tuberculoid leprosy features a Th1 T-cell cytokine response (gamma interferon [IFN-$\gamma$] and IL-2), vigorous T-cell responses to *M. leprae* antigen, and containment of the infection in well-formed granulomas (44, 273). Lepromatous leprosy lesions are characterized by a lack of $CD4^+$ T cells, numerous $CD8^+$ T cells, and foamy macrophages, whereas tuberculoid leprosy lesions have a predominance of $CD4^+$ T cells and well-formed granulomas (258, 340, 342). In lepromatous leprosy, robust antibody formation occurs but is not protective, and cell-mediated immunity is conspicuously absent (58, 309). In contrast, in tuberculoid leprosy, cell-mediated immunity is relatively preserved, and there is little evidence of *M. leprae*-specific humoral immunity (44, 258, 340, 342). However, as noted above, the majority of patients are not found at the poles of the leprosy spectrum but in the intermediate categories of BL, BB, and BT disease, which are clinically "unstable." The immunology of these borderline states is poorly understood (273).

**Leprosy reactions.** The Mitsuda reaction is a delayed-type hypersensitivity response (measured 21 to 28 days after inoculation) to intradermally administered leprosy antigens (of which lepromin is one formulation). Patients with tuberculoid leprosy typically have strongly positive Mitsuda reactions, a measure of the presence of functional cell-mediated immunity; in contrast, LL patients commonly have little to no reaction (134, 202, 212, 249, 260, 284). Two types of spontaneous immune reactions, or "reactive states," can also occur in leprosy (Fig. 1). Reversal reactions (RRs), also known as type 1 reactions, represent the sudden activation of a Th1 inflammatory response to *M. leprae* antigens. They occur most frequently, although not exclusively, in borderline categories (BL, BT, or BB categories), often after the initiation of treatment, and

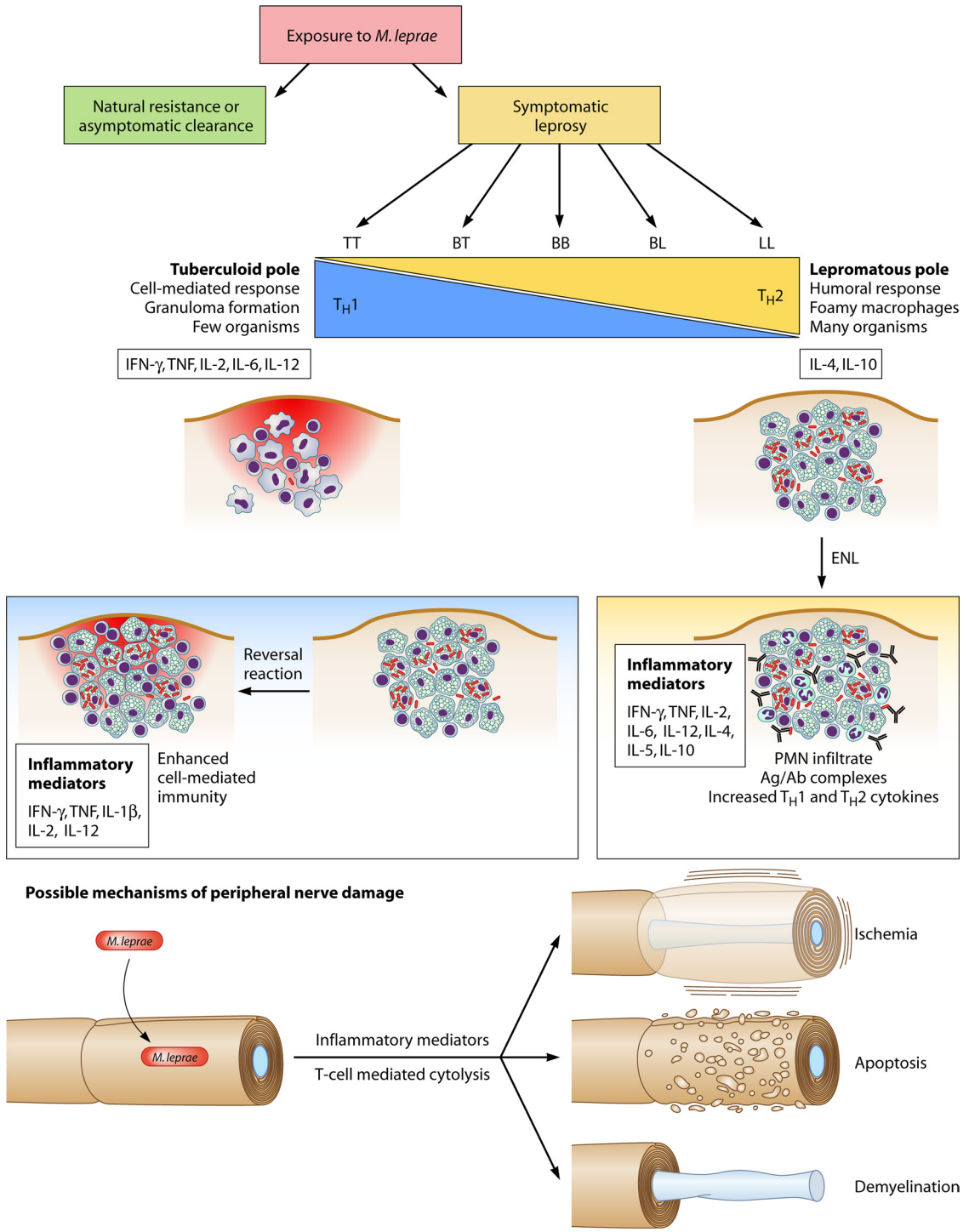


FIG. 1. The leprosy spectrum and possible mechanisms of tissue damage. Leprosy manifestations are classified along a clinical spectrum of tuberculoid (TT), borderline tuberculoid (BT), borderline borderline (BB), borderline lepromatous (BL), and lepromatous (LL) leprosy. Each pole is associated with a characteristic cell-mediated or humoral immune profile. The cell-mediated (Th1) response of the TT pole features the elimination or containment of the organism in granulomas, while the ineffective humoral response at the LL (Th2) pole allows the proliferation of mycobacteria within and around foamy macrophages. Reversal reactions reflect a sudden shift toward the Th1 pole from the BT, BB, or BL state and can lead to irreversible nerve damage (neuritis). Erythema nodosum leprosum (ENL) reactions occur in patients with BL or LL leprosy and reflect an increase in both cell-mediated and humoral responses to *M. leprae*. ENL is associated with the systemic release of TNF and IL-4, a brisk polymorphonuclear leukocyte (PMN) influx, and antigen-antibody (Ag/Ab) complex deposition. The mechanism of nerve damage is unclear but may involve immune injury due to the release of inflammatory cytokines or activity of cytotoxic T cells, ischemia due to edema within the perineural sheath, apoptosis, or demyelination (see discussion in the text).

reflect a switch from a Th2- toward a Th1-predominant response (44, 180, 273, 329). Erythema nodosum leprosum (ENL), also known as a type 2 reaction, is an acute inflammatory condition involving high levels of tumor necrosis factor (TNF) (264), tissue infiltration by CD4 cells and neutrophils (152), and deposition of immune complexes and complement, resulting in immune-complex-associated vasculopathy, panniculitis, and uveitis (44). ENL occurs in LL or BL patients and is more commonly seen in patients with a high bacterial index (249). Numerous investigators have measured intralesional and systemic cytokine production during leprosy reactions (102, 151, 178, 283, 340), but those studies did not consistently show a consistent Th1 versus Th2 cytokine pattern for reversal reaction versus ENL (summarized in references 272 and 273). For example, increased amounts of Th1 cytokines, such as IFN-γ, IL-12, and IL-2, have been demonstrated for both reversal reactions and ENL (summarized in references 44 and 273). A major drawback of these studies is the inability to determine whether the measured cytokine response is the cause or the consequence of inflammation (273). For these reasons, the immune mechanism of these reactions is still poorly understood.

**Cellular and immune pathogenesis.** *M. leprae* is initially recognized by several innate immune receptors, including the Toll-like receptors (TLRs). The TLRs are a family of highly conserved, type 1 transmembrane proteins that orchestrate the innate immune response to microbial motifs, also known as pathogen-associated molecular patterns (PAMPs) (6, 28, 139). The interaction of these ligands with the extracellular domain of TLRs leads to the activation of a signaling pathway and the expression of chemokines and cytokines (6). TLR2 forms a heterodimer with TLR1 to mediate the recognition of several mycobacterial motifs, including the 19-kDa protein and other lipopeptides (26, 123, 233). Functional work by several investigators has shown that TLR2/1 is a critical mediator of the innate immune response to *M. leprae* (34, 163) and that *M. leprae* predominantly activates the TLR2/1 heterodimer (163). Based on data from previous studies with *M. tuberculosis*, several other signaling receptors may also be involved in *M. leprae* recognition. These receptors include TLRs 4, 6, 8, and 9; NOD2; DC-SIGN (dendritic cell [DC]-specific intercellular adhesion molecule 3-grabbing nonintegrin) (or CD209), Dectin-1, and Mincle (19, 20, 23, 49, 68, 75, 189, 190, 220, 255, 269, 299, 300, 314, 346). TLR2 may also act cooperatively with the lectins Dectin-1 and MBL (mannose binding lectin) (72, 101, 137).

*M. leprae* is an obligate intracellular pathogen with a distinct tropism for Schwann cells of the peripheral nervous system and for macrophages (37, 267, 293, 297). The pronounced specificity of *M. leprae* for Schwann cells is related to the tissue-specific expression of laminin-2 on Schwann cells. *M. leprae* contains a phenolic glycolipid (PGL-1) that has been shown to bind to the G domain of the α2 chain of laminin-2 on the membrane of Schwann cells (214). The uptake of *M. leprae* into the Schwann cell is thought to occur when the PGL–laminin-2 complex interacts with α-dystroglycan, the laminin-2 receptor located on the Schwann cell membrane (214, 239, 240). Laminin binding protein 21 (LBP21) also mediates the intracellular entry of *M. leprae* into the Schwann cell (Fig. 2) (238, 281). A variety of other receptors on monocytes and macrophages may also facilitate intracellular entry by *M. leprae*. On monocytes, PGL-1 mediates *M. leprae* phagocytosis via the complement receptor CR3 and serum complement 3 (267). On macrophages, complement receptors 1 and 4 help phagocytose *M. leprae* (266). Another candidate phagocytic receptor on the macrophage is the mannose receptor, which binds mannose and other carbohydrate moieties on mycobacteria (157, 268).

Nerve injury is the hallmark of progressive leprosy infection and involves both myelinated and unmyelinated nerves (115, 146, 147). Biopsy specimens taken from affected nerves of leprosy patients reveal perineural and intraneural inflammation and, in myelinated fibers, eventual demyelination (272). At the tissue level, the influx of immune cells and interstitial fluid (edema) inside inflexible nerve sheaths may cause nerve injury through mechanical compression and ischemia (272). At the cellular level, immunological injury is thought to be a major mechanism of nerve damage. The immune-mediated injury hypothesis has indirect support from *in vitro* studies in which the stimulation of monocytes or macrophages with *M. leprae* induces proinflammatory cytokines such as TNF, IL-12, IL-6, IL-1β, IL-18, and IL-15 (102, 151, 163, 198). For example, the 19-kDa protein of *M. leprae*, which is recognized by the TLR2/1 heterodimer, elicits a robust proinflammatory cytokine response (163) and induces apoptosis in Schwann cells (219). In addition, Schwann cells exposed *in vitro* to necrotic neurons produce TNF and nitric oxide (172), potent inflammatory mediators. In *ex vivo* studies, human Schwann cells loaded with *M. leprae* antigen have been shown to be targeted by cytolytic $CD4^+$ T cells (292). Despite these *in vitro* and *ex vivo* observations, the mechanism of nerve injury remains poorly understood, partly due to the lack of good animal models for leprosy and leprosy-induced nerve damage.

## ASSESSING THE GENETIC CONTRIBUTION TO LEPROSY RISK

Leprosy has long been observed to be a disease that aggregates in families (47, 118, 145, 232). In the 19th century, the hereditary versus environmental origins of this illness were vigorously debated (48, 118), driven in part by the social stigma attached to leprosy. The discovery of the *M. leprae* bacillus by Gerhard Henrik Armauer Hansen in 1873 (118, 119) settled the argument for the time being in favor of an environmental etiology. In the modern era it has become clear that while encounter with the *M. leprae* pathogen is necessary for infection, it is not sufficient, since the majority of exposed individuals do not become infected. Host genetic factors may therefore largely determine which exposed individuals develop disease. Evidence that host genes influence susceptibility to leprosy or its various clinical forms is supported by data from a wide variety of sources. These sources include twin studies, segregation analyses, family-based linkage and association studies, candidate gene association studies, and, most recently, genome-wide association studies (GWASs). The most definitive twin study of leprosy by Chackravartti and Vogel (56) enrolled 62 monozygous and 40 dizygous twin pairs from three different regions in India and found a 3-fold-greater concordance rate for the type of leprosy disease in monozygotic twins than in dizygotic twins (56). Segregation analyses determine whether or not there is a segregation of disease among more closely related individuals (evidence of a "major

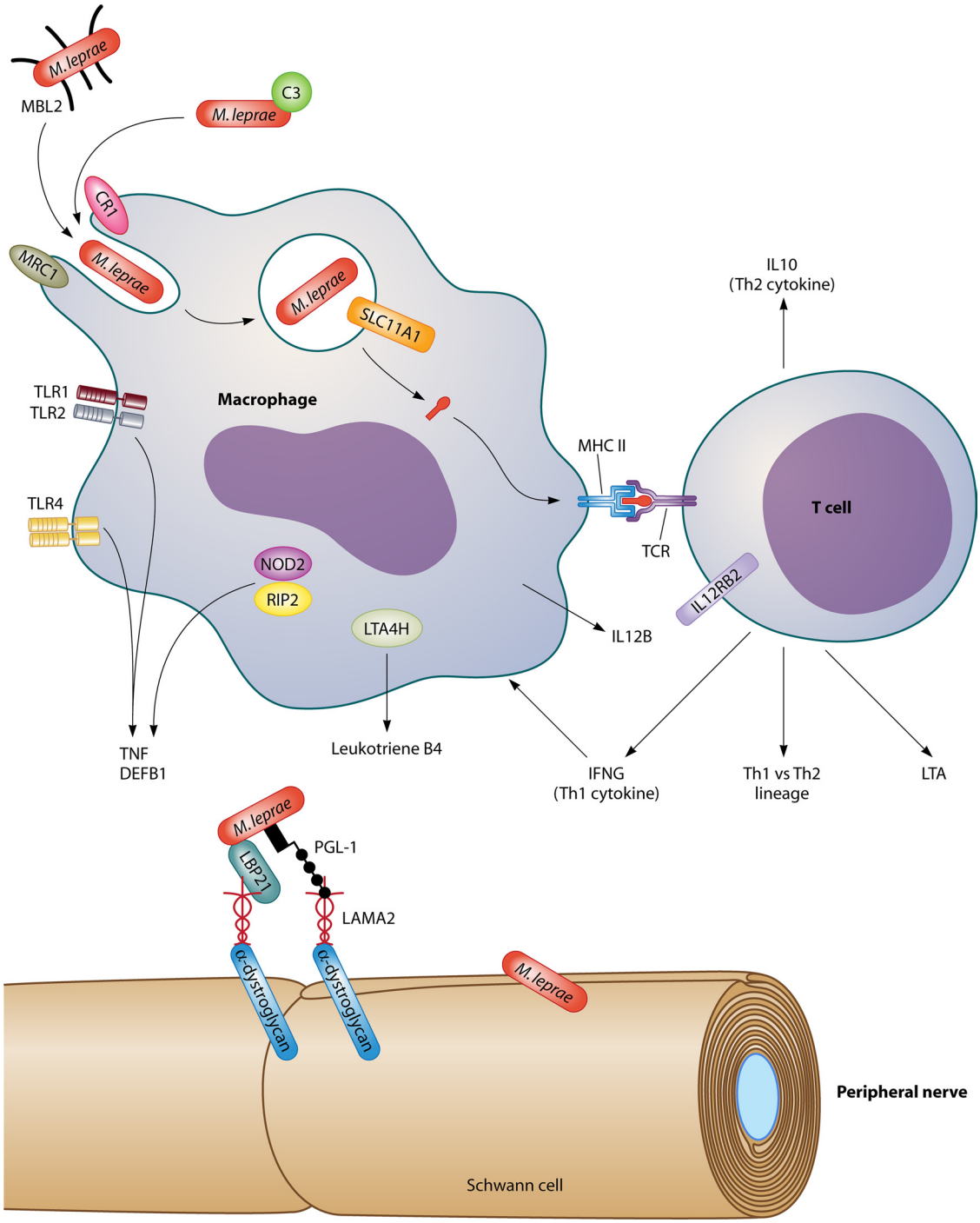


FIG. 2. Genes and gene products involved in the immune response to *M. leprae*. Molecular and cellular interactions known or postulated to play a role in the immune response to *M. leprae* are depicted, as are genes with evidence of an association with susceptibility to leprosy and/or leprosy immune reactions through candidate gene studies, linkage analyses, or genome-wide association studies. Laminin binding protein 21 (LBP21) and phenolic glycolipid 1 (PGL-1) in the *M. leprae* cell wall bind to the α2 chain of laminin-2 (LAMA2) and α-dystroglycan on the Schwann cell membrane. This permits entry and subsequent damage to the peripheral nerve. Abbreviations: C3, complement factor 3; CR1, complement receptor 1; DEFB1, beta defensin 1; IFNG, gamma interferon; IL10, interleukin-10; IL12B, interleukin-12 subunit p40; IL12RB2, interleukin-12 receptor beta 2; LTA4H, leukotriene $A_4$ hydrolase; LTA, lymphotoxin-α; MHC II, major histocompatibility complex class II; MBL2, mannose binding lectin 2; MRC1, mannose receptor; NOD2, nucleotide oligomerization domain 2; RIP2, receptor-interacting kinase; SLC11A1, solute carrier family 11, member 1 (also known as NRAMP); TCR, T-cell receptor; Th1, T-cell helper type 1; Th2, T-cell helper type 2; TLR, Toll-like receptor; TNF, tumor necrosis factor.

gene effect") and what mode of inheritance is at work (dominant, recessive, or additive) (296). A number of segregation studies have been carried out for leprosy (1, 3, 84, 117, 171, 241, 275, 280, 289, 327), several of which have detected the presence of a recessive or codominant mode of inheritance for leprosy overall or for nonlepromatous leprosy (1, 84, 117, 171, 289).

### Study Design for Complex Diseases

It has been widely presumed for many infectious diseases, including leprosy, that susceptibility is governed by polygenic inheritance, or the additive effect of multiple genes, each with a modest effect on the infectious phenotype. Two study designs are typically used to examine diseases with complex inheritance patterns: linkage studies of families and association studies (candidate gene or genome wide). Linkage studies look for evidence of the segregation of a genetic marker and a disease trait within families. Genetic association studies assess whether the frequency of a particular genetic variant differs between individuals with a disease compared to unrelated controls.

**Linkage studies.** Linkage studies often follow up on the results of segregation analyses (discussed above) in the same study population. Several genome-wide linkage studies of leprosy susceptibility have been performed by using a family-based design (197, 282). A major strength of genome-wide linkage studies is the absence of bias: no hypothesis as to which chromosomal loci or genes might be linked to disease status is required. Linkage studies genotype microsatellites or SNPs (single-nucleotide polymorphisms) spaced evenly throughout the genome, typically every 10 centimorgans (cM). Susceptibility loci identified in these studies are then investigated further by higher-resolution mapping of markers or gene alleles and linkage to disease traits (8, 196, 306). Linkage studies have also been used to evaluate candidate regions (142, 330) and candidate genes (2, 261) in leprosy. Significance in these studies is reported via *Z* scores, LOD scores (logarithm of odds), or *P* values (168). The proposed criteria for significance in genome-wide linkage studies are somewhat stringent, given the risk of false positives due to the large number of markers studied. For example, one common genome-wide linkage study design relies on sibling pairs. Suggested threshold levels of significance for "suggestive linkage," "significant linkage," and "highly significant linkage" for individual markers in these sibling pair genome-wide linkage studies are *P* values of $7 \times 10^{-4}$, $2 \times 10^{-5}$, and $3 \times 10^{-7}$, respectively (corresponding to LOD scores of 2.2, 3.6, and 5.4, respectively) (168). The suggested *P* value for validating linkage in replication studies (which typically focus on a candidate region of ~20 cM in size) is a *P* value of 0.01 (168). Linkage studies are also the most powerful study design for identifying rare variants of genes that confer a large risk of disease (18, 296). Conversely, they have reduced statistical power to detect genes with modest or weak effects on disease risk, even when hundreds of families are included (13, 237, 251, 296). Linkage studies that have identified major susceptibility loci or genes for leprosy or leprosy immune reactions are described below.

**Genetic association studies.** In contrast to linkage studies, association studies evaluate whether common polymorphisms in candidate genes are associated with susceptibility to disease, usually in unrelated individuals. These studies are hypothesis driven and often focus on genetic variants that are predicted to alter protein structure or function. The most common study design is a case-control format with comparisons of one or more polymorphism (single nucleotide, insertions, deletions, or microsatellite [MS] markers) frequencies between cases and controls. A major strength of this study design is the power to find relatively modest effects, generally with smaller sample sizes than family-based studies (251, 296). One disadvantage is the problem of population stratification or admixture, where differences in ethnic compositions of the cases and controls can lead to spurious disease associations. Methods to control for population stratification include matching cases and controls for ethnicity and adjusting for ethnicity as a possible confounder in a multivariate logistic regression model. An alternative study design that is robust to population stratification is the transmission disequilibrium test (TDT). This approach looks for evidence of nonrandom transmission of the candidate allele from a heterozygous parent to an affected child and can be used to corroborate findings of either linkage studies or association studies.

It is important to remember that association, even down to the SNP level, is not necessarily causation. Genetic associations at specific loci may derive from neighboring alleles in linkage disequilibrium (LD) with the candidate gene that is being studied. In these situations, the candidate gene SNP serves as a proxy for the association. However, if the haplotype structure of the region surrounding the candidate gene is not explored, the alleles most responsible for the disease association will remain unascertained. The haplotype structures at specific genetic loci often differ between populations (population-specific linkage disequilibrium). This variability can make it difficult to replicate disease associations when the underlying LD structure has not been evaluated for both populations. Both linkage and genetic association study designs are also vulnerable to the generation of false-positive results from multiple comparisons. This problem is especially relevant in the current era of genome-wide linkage scans and high-throughput genotyping strategies, as used in GWASs. As a result, replication and validation of findings in independent populations coupled with investigation of the underlying haplotype structure of each population are an essential part of a careful study design. The candidate gene approach can also be linked to functional studies of the polymorphisms to determine whether there is a biological mechanism relevant to disease pathogenesis.

Finally, although neither association nor linkage studies are designed to detect rare alleles with weak effects (296), adequate power has been a particular problem for candidate gene association studies and probably accounts in part for these studies' rather poor track record for replicating SNP associations. The need to include adequate numbers of cases and controls is particularly important when the frequency of the allele(s) being studied is low (≤5%). Numerous candidate gene association studies have relied on sample sizes of 50 to 100 cases. There is not adequate power to detect a disease association of a variant allele with a population frequency of 5% in these small studies unless the odds ratio (OR) rises to the level of 3.0 to 4.0 (for example, for an $\alpha$ of 0.05 with 100 cases, 100 controls, and a minor allele frequency [MAF] of 0.05, power equals 0.17 for an OR of 1.5, 0.44 for an OR of 2, 0.87 for an OR of 3, and 0.98 for an OR of 4). However, many

candidate genes have disease associations with ORs in the range of 1.5 to 2.5 or lower. To have power to detect associations of low-frequency SNPs with a more modest influence on disease susceptibility, study investigators would need to recruit 300 to 600 cases and an equal number of controls (for example, for an $\alpha$ of 0.05 with 500 cases, 500 controls, and an MAF of 0.05, power equals 0.58 for an OR of 1.5, 0.97 for an OR of 2, and 1.00 for an OR of 3 to 4). Such large numbers have been the exception rather than the rule in candidate gene association studies (Table 1).

Advances in genomic technology and immunology have accelerated the number of candidate gene association studies of infectious diseases. Table 1 summarizes both positive (association found) and negative (no association detected) association studies of leprosy for non-*HLA* candidate genes. A series of linkage and candidate gene studies has demonstrated associations of the major histocompatibility complex (MHC) class I and II loci (especially with *HLA-DR2* alleles) with leprosy susceptibility (30, 39, 277, 305, 316, 317, 331, 347). Those and other studies of the MHC region were extensively reviewed elsewhere previously (108, 315) and will not be included in this review. This review prioritizes a discussion of the genes that have been most thoroughly examined with consistent and validated genetic findings and well-established functional effects. We will first describe family-based linkage studies that have identified regions or genes involved in susceptibility to leprosy. We will then review candidate gene association studies, which typically use a case-control study design with unrelated individuals. Finally, we will summarize findings from two recent genome-wide association studies of leprosy.

## GENOME-WIDE LINKAGE STUDIES

### Chromosome 10p13

The first genome-wide linkage analysis of leprosy was reported by Siddiqui et al. (282) and involved 224 families in India consisting of 245 sibling pairs, all but 4 of whom had exclusively paucibacillary disease. Three hundred eighty-eight microsatellite markers covering the entire genome were used in an initial screen to identify regions associated with leprosy susceptibility (maximum LOD score of $\geq 1$, or $P < 0.10$) in an initial set of 103 sibling pairs (93 families). This screen produced 28 regions of interest (weak suggestive linkage), which were further assessed by using 37 markers in a separate set of 142 sibling pairs (131 families). In the second screen, one region on chromosome 10p showed significant linkage. This region was then fine-mapped, and significant linkage with paucibacillary leprosy was found for marker D10S1661 at 10p13 (LOD score, 4.09; $P < 2 \times 10^{-5}$) (282). Interestingly, this locus was confirmed as a risk factor for paucibacillary leprosy, but not overall leprosy susceptibility, in a separate linkage study by Mira et al. (197). In a follow-up study performed with families from Vietnam and cases and controls from Brazil (see below for details), two SNPs in the mannose receptor 1 gene (*MRC1*), located in the 10p13 region, were found to be associated with multibacillary leprosy and leprosy overall but not with paucibacillary disease (12). The lack of an association with paucibacillary disease in that study suggests that the causative gene at the 10p13 locus has not yet been identified.

### Chromosome 6q25-26: *PARK2* and *PACRG*

To identify genes that control susceptibility to leprosy, Mira and colleagues genotyped 388 microsatellite markers across the entire genome of 86 families in southern Vietnam with either multibacillary (MB) (56.1%) or paucibacillary (PB) (43.9%) disease (197). Chromosomal sites showing preliminary evidence of linkage were then fine-mapped with additional markers, and a region on chromosome 6q25-q27 was linked to leprosy (LOD score, 4.31; $P = 5 \times 10^{-6}$). In a separate group of 208 families, a transmission disequilibrium test (TDT) confirmed that two markers in the 6q25-27 region were strongly linked to leprosy susceptibility. In addition, linkage analysis performed on subsets of the families categorized as having either the PB or MB type of leprosy showed that 6q25-27 was not linked to one particular form of leprosy but seemed to be a determinant of leprosy risk overall (197). Evidence of the linkage of 10p13 with paucibacillary leprosy was also noted in this study (maximum LOD score, 1.74; $P < 0.003$), validating the findings of Siddiqui et al. in India (282). In addition, evidence for linkage at chromosome 6p21, the *HLA* locus, was also found (multipoint maximum likelihood binomial [MLB] LOD score, 2.62; $P = 2.5 \times 10^{-4}$), consistent with data from a previous report (277). Subsequently, that same group examined 81 SNPs in the 6.4-megabase region of 6q25-27 (196) that had been linked to leprosy in their previous study (197). In this scan, 17 SNPs that were associated with leprosy susceptibility were in or near the core promoter region of *PARK2* and *PACRG* and were in strong linkage disequilibrium with each other. *PARK2* (also known as *PARKIN*), a gene associated with Parkinson's disease, encodes an E3 ubiquitin ligase, and *PACRG* (also known as the Parkin-coregulated gene) is a neighboring gene of unknown function. Two SNPs, *PARK2*_e01(−2599) and rs1040079, accounted for the entire association at this locus. These results were validated in a separate set of 975 unrelated individuals in Brazil (587 with leprosy and 388 controls) (Table 1). Nine SNPs were confirmed to be significantly associated with leprosy risk in this population, of which the most highly significant were again the *PARK2*_e01(−2599) and rs1040079 alleles and a third SNP, *PARK2*_e01(2697) (196). In a separate case-control study in India, Malhotra et al. did not find a significant association (after conservative Bonferroni correction) between leprosy and SNPs in the *PARK2* or *PACRG* coregulatory region, including PARK2_e01(−2599) and rs1040079, despite adequate power (184) (Table 1). The identification of *PARK2* and *PACRG* as major leprosy risk genes in two populations, but not a third, highlights the heterogeneity of risk alleles for infectious diseases across different ethnic groups.

### Chromosome 6p21: Lymphotoxin-α

In a study published in 2007 (8), the original *PARK2* investigators (196, 197) revisited a second linkage peak that was found in the 6p21 chromosomal region on the initial genome-wide scan performed with Vietnamese families. This second peak fine-mapped to lymphotoxin-α (*LTA*), a T-cell cytokine

TABLE 1. Summary of non-HLA leprosy candidate gene association studies[c]

| Gene | Reference(s) (yr) | Population | Sample size | Variant(s)[a] | Phenotype | OR (95% CI), rel. risk, or $\chi^2$ value | *P* value[b] |
|---|---|---|---|---|---|---|---|
| *CFB* (B factor, Bf) | 114 (1980) | Thailand (Chinese) | 24 controls, 38 leprosy | Bf S allele | NE: lep | | |
| | | Thailand (Thai) | 184 controls, 198 leprosy | Bf S allele | NE: lep | | |
| | 69 (1993) | Brazil | 172 controls, 109 leprosy (73 LL [46 with ENL], 36 non-TL) | Bf F allele ("Bf-F1") | S: ENL | ND | <0.03 |
| *C2* | 114 (1980) | Thailand Chinese | 24 controls, 38 leprosy | C2 C allele | NE: lep | | |
| | | Thailand (Thai) | 184 controls, 198 leprosy | C2 C allele | NE: lep | | |
| *C3* | 83 (1972) | Angola | 439 controls, 468 leprosy (97 LL, 180 TL, 191 IL) | S (major allele) vs F (minor allele) | NE: lep or lep type | | |
| | 15 (1973) | Angola | 439 controls, 470 leprosy (97 LL, 182 TL, 191 IL) | S (major allele) vs F (minor allele) | NE: lep or lep type | | |
| | 4 (1974) | Ethiopia and Mali | 66 controls, 152 leprosy | S (major allele) vs F (minor allele) | S: lep | [OR, 2.33 (0.19–0.98) (dom)] | [0.041] |
| | | | | | | [OR, 2.43 (0.17–0.98) (het)] | [0.041] |
| | 294 (1975) | Ethiopia | 55 related controls, 91 leprosy | S (major allele) vs F (minor allele) | NE: lep | | |
| *C4A* | 114 (1980) | Thai and Chinese individuals combined | 123 controls, 201 leprosy (27 TT, 103 BL, 71 LL) | C4A F1 allele ("functionally inactive") | S: con vs. TT vs BB vs LL (4 × 2 chi square) | $\chi^2$ = 13.7 (ND) | <0.01 |
| | | | | | S: LL vs con | $\chi^2$ = 12.6 (ND) | <0.001 |
| *C4B* | 69 (1993) | Brazil | 172 controls, 109 leprosy (36 non-LL, 73 LL [46 ENL, 27 no ENL]) | C4B*Q0 absent allele | S: lep vs con | ND | $4.4 \times 10^{-5}$ |
| | | | | | S: ENL vs no ENL | Rel. risk = 5.3 | [0.017] |
| | | | | | S: ENL | ND | $3.6 \times 10^{-7}$ |
| | | | | C4B*1 | S: ENL | ND | $3.9 \times 10^{-3}$ |
| *CR1* | 93 (2004) | Malawi | 166–252 controls, 186–399 leprosy (>90% PB) | G3093T | NE: lep | | |
| | | | | A4795G "McCoy" | R: lep | OR, 0.3 (0.1–0.8) (rec) | 0.02 |
| | | | | G4828A "Swain-Langley" | NE: lep | | |
| | | | | A4870G | NE: lep | | |
| | | | | C5507G | NE: lep | | |
| *DEFB1* (β-defensin 1) | 230 (2009) | Mexico | 151 controls, 75 leprosy (46 LL) | G668C | S: lep | OR, 2.42 (1.37–4.28) (dom) | 0.009 |
| | | | | | S: LL vs con | OR, 3.06 (1.47–6.04) (dom) | 0.024 |
| | | | | A692G | NE: lep or lep type | | |
| | | | | A1836G | NE: lep or lep type | | |
| | | | | Haplotype (668/692/1836) CGA | S: LL | 2.25 (1.23–4.03) | 0.009 |
| *FCN2* | 70 (2009) | Brazil, mixed ethnicity | 210 controls, 158 leprosy (92 LL, 14 TT, 22 BL, 27 IL) | 20 SNPs | NE: lep | | |
| | | | | Haplotype AGA (−986/−602/−4) | R: lep | OR, 0.13 (0.03–0.43) | <0.013 |
| | | | | Haplotype AGAG (−986/−602/−4/+6424) | R: lep | OR, 0.10 (0.11–0.43) | <0.011 |
| *IFNG* | 248 (2003) | Brazil | 98 controls, 96 leprosy (10 TT, 59 BL, 27 LL) | Intron 1 CA repeat (short [fewer than 122 bp]→long [122–126 bp]) | S: lep | [OR, 2.62 (1.29–5.32)] | 0.01 |
| | 93 (2004) | Malawi | 236 controls, 402 cases | Intron 1 T874A | NE: lep | | |
| *IL10* | 262 (2002) | Brazil | 62 controls, 202 leprosy (143 MB, 59 PB) | C−819T | S: PB vs MB | OR, 2.28 (1.1–4.5) (allele) | <0.01 |
| | | | | | S: PB vs con | OR, ↑ [ND] (allele) | <0.05 |
| | | | | | S: lep | OR, 2.64 (0.93–8.04) (rec) | 0.04 |
| | | | | C−592A | NE: lep or lep type | | |
| | 206 (2004) | Brazil | 283 controls, 297 leprosy (131 PB, 166 MB) | C−819T | NE: lep or lep type | | |
| | | | | A−1082G | NE: lep or lep type | | |
| | | | | C−2763A | NE: lep or lep type | | |
| | | | | G−2849A | NE: lep or lep type | | |
| | | | | T−3575A | NE: lep or lep type | | |
| | | | | Haplotype −3575A/−2849G/−2763C | R: lep | OR, 0.35 (0.13–0.91) | 0.005 |
| | | | | | R: lep vs PB vs MB | OR, 0.32 (0.12–0.83) (ordinal trait) | 0.006 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Haplotype −3575T/−2849A/−2763C | S: lep | OR, 2.37 (1.04–5.39) | 0.027 |
| | 93 (2004) | Malawi | 191–215 controls, 349–362 leprosy (>90% PB) | C−819T | NE: lep | | |
| | | | | C−592A | NE: lep | | |
| | | | | A−1082G | NE: lep | | |
| | 185 (2005) | India | 266 controls, 282 leprosy (144 MB, 142 PB) | C−819T | S: lep | OR, ↑ (ND) (allele) | "Significant" [ND] |
| | | | | | S: lep | OR, 2.50 (1.49–4.00) (rec) | <0.001 |
| | | | | | S: MB vs con | OR, 2.63 (1.51–4.76) (rec) | 0.001 |
| | | | | | S: PB vs con | OR, 2.32 (1.29–4.16) (rec) | 0.005 |
| | | | | C−592A | S: lep | OR, ↑ [ND] (allele) | "Significant" [ND] |
| | | | | | S: lep | OR, 2.43 (1.47–4.00) (rec) | <0.001 |
| | | | | | S: MB vs con | OR, 2.56 (1.44–4.54) (rec) | 0.001 |
| | | | | | S: PB vs con | OR, 2.32 (1.29–4.16) (rec) | 0.005 |
| | | | | G−1082A | NE: lep or lep type | | |
| | | | | C−2763A | NE: lep or lep type | | |
| | | | | G−2849A | NE: lep or lep type | | |
| | | | | T−3575A | NE: lep or lep type | | |
| | | | | Haplotype −3575T/−2849G/−2763C/−1082A/−819C/−592C | R: lep | OR, 0.58 (0.37–0.89) | 0.01 |
| | | | | Haplotype −3575T/−2849G/−2763C/−1082A/−819T/−592A | S: MB > PB > con; NE: lep | ND (ordinal trait) | 0.0002 |
| | | | | Diplotype of proximal promoter SNPs G−1082A, C−819T, and C−592A (ACC/ACC) | R: lep | [OR, 0.35 (0.19–0.63)] | 0.001 |
| | | | | | R: MB vs con | [OR, 0.26 (0.11–0.60)] | 0.002 |
| | | | | | R: PB vs con | [OR, 0.44 (0.22–0.88)] | 0.02 |
| | | | | Diplotype of proximal promoter SNPs, G−1082A, C−819T, and C−592A (ATA/ATA) | S: lep | [OR, 1.82 (1.05–3.23)] | 0.03 |
| | | | | | S: MB vs con | [OR, 1.96 (1.03–3.85)] | 0.04 |
| | 225 (2008) | Brazil | 368–380 controls, 321–369 leprosy | C−819T | S: lep | OR, 1.60 (ND) (TT vs CC) | 0.05 |
| | | | | | | OR, 1.44 (ND) (dom) | 0.026 |
| | | | | A−1082G | ND (not in HWE) | | |
| | | | | C−2763A | NE: lep | | |
| | | | | G−2849A | NE: lep | | |
| | | | | T−3575A | NE: lep | | |
| | | | | Haplotype −3575T/−2849G/−2763C/−819T | S: lep | OR, 1.35 (ND) | 0.03 |
| | 225 (2008) | Meta-analysis[e] | 1,347 controls, 1,355 leprosy | C−819T | S: lep | OR, 1.30 (1.13–1.49) (allele) | 0.0003 |
| | | | | | S: lep | OR, 1.28 (1.03–1.60) (dom) | 0.0237 |
| | | | | | S: lep | OR, 1.66 (1.29–2.15) (rec) | 0.0001 |
| | 96 (2009) | Brazil | 240 controls, 156 leprosy | Diplotype G−1082A/C−819T/C−592C | NE: lep | | |
| *IL12B* (IL-12p40) | 207 (2007) | India | 89 controls, 80 leprosy | 3′ UTR TaqI site SNP (genotype 2.2 vs 1.1 or 1.2) | R: lep | [OR, 0.13 (0.03–0.58) (rec)] | 0.002 |
| | | | | | NE: lep type | | |
| | 14 (2008) | Mexico | 51 controls, 44 LL | 3′ UTR 1188 A/C (TaqI site) | S: lep | [OR, 7.2 (2.38–21.61) (rec)] | <0.05 |
| *IL12RB2* | 218 (2005) | Japan | 68 controls, 176 leprosy (130 LL, 46 TL) | A−1035G | S: LL vs TL | OR, 3.97 (ND) (allele) | <0.001 |
| | | | | A−1023G | S: LL vs TL | OR, 2.95 (ND) (allele) | <0.01 |
| | | | | −650delG | S: LL vs TL | OR, 3.74 (ND) (allele) | <0.001 |
| | | | | A−464G | S: LL vs TL | OR, 3.64 (ND) (allele) | <0.01 |
| | | | | Haplotype −1035A/−1023A/−650G/−464A | R: LL vs TL | ND | 0.0002 |
| | | | | | R: LL vs con | ND | 0.039 |
| | | | | 4 other haplotypes tested | NE: lep or lep type | | |
| *KIR* | 97 (2008) | Brazil | 289 controls, 165 leprosy (65 LL, 49 BB, 42 TT) | KIR2DL1-5 | NE: lep or lep type | | |
| | | | | KIR3DL1-3 | NE: lep or lep type | | |
| | | | | KIR2DS3 | NE: lep type | | |
| | | | | | S: TT vs LL | 2.72 (1.12–6.58) | 0.04 |
| | | | | KIR2DS1-2, KIR2DS4-5 | NE: lep or lep type | | |
| | | | | KIR2DP1 | NE: lep or lep type | | |
| | | | | KIR3DP1 | NE: lep or lep type | | |

*Continued on following page*

TABLE 1—*Continued*

| Gene | Reference(s) (yr) | Population | Sample size | Variant(s)[a] | Phenotype | OR (95% CI), rel. risk, or $\chi^2$ value | *P* value[b] |
|---|---|---|---|---|---|---|---|
| *LAMA2* (laminin α-2) | 334 (2002) | Indonesia | 58 controls, 53 leprosy (26 TL, 27 LL) | T7809C | S: TL vs LL | $\chi^2$ = 8.07 (genotype)<br>OR, 6.73 (1.94–23.36) (TC vs. TT) | <0.025<br><0.005 |
| *LTA* (lymphotoxin-α) | 93 (2004) | Malawi | 333 controls, 184 leprosy (85% PB) | 5′ UTR microsatellite $(AC/GT)_n$ at −3.5-kb 105-bp allele | S: lep | OR, 1.6 (1.1–2.4) | 0.03 |
| | | | | 5′ UTR microsatellite $(AC/GT)_n$ at −3.5-kb 101-bp allele | S: MB vs con | $\chi^2$ = 11.7 (ND) | 0.003 |
| | 8 (2007) | India | 371 controls, 364 leprosy | LTA−294 univariate analysis | S: lep | 1.78 (1.29–2.45) | 0.0004 |
| | | | | LTA−294 multivariate analysis | NE: lep | | |
| | | | | LTA−293 | NE: lep | | |
| | | | | LTA+10 | NE: lep | | |
| | | | | LTA+80 (A allele) univariate analysis | NE: lep | | |
| | | | | LTA+80 (A allele) multivariate analysis | S: lep | 1.60 (1.10–2.33) (dom) | 0.01 |
| | | | | LTA+80 (A allele) subgroup ages 16-25 yr | S: lep | 2.95 (1.32–6.58) (dom) | 0.006 |
| | | | | LTA+252 | NE: lep | | |
| | | | | LTA+368 | NE: lep | | |
| | | | | MCCD1 rs2259435 (A allele) univariate analysis | S: lep | 1.59 (1.24–2.04) | 0.0002 |
| | | | | MCCD1 rs2259435 (A allele) multivariate analysis | S: lep | 1.82 (1.38–2.41) | 0.0004 |
| | | Vietnam[d] | 194 simplex leprosy families | LTA−294 | NE: lep | | |
| | | | | LTA−293 univariate analysis | S: lep | 1.97 (1.30–2.99) | 0.0009 |
| | | | | LTA−293 multivariate analysis | S: lep | 1.97 (1.30–2.99) | 0.0009 |
| | | | | LTA+10 | NE: lep | | |
| | | | | LTA+80 univariate analysis | S: lep | 1.74 (1.16–2.60) | 0.007 |
| | | | | LTA+252 | NE: lep | | |
| | | | | LTA+368 univariate analysis | S: lep | 1.63 (1.09–2.43) | 0.02 |
| | | Brazil | 192 controls, 209 leprosy | LTA−294 | NE: lep | | |
| | | | | LTA−293 | NE: lep | | |
| | | | | LTA+10 | NE: lep | | |
| | | | | LTA+80 (A allele) | NE: lep | | |
| | | | | LTA+80 (A allele) subgroup ages 16-25 yr | Trend: lep | 2.76 (0.74–10.32) | NS [ND] |
| | | | | LTA+252 | NE: lep | | |
| | | | | LTA+368 | NE: lep | | |
| *LTA4H* | 304 (2010) | Nepal | 899 leprosy (443 MB without ENL, 335 PB) | rs1978331 T/C | R: MB vs PB | OR, 0.62 (0.46–0.82) (het) | 0.001 |
| | | | | rs2660898 T/G | R: MB vs PB | OR, 0.70 (0.52–0.95) (het) | 0.021 |
| *MBL2* | 93 (2004) | Malawi | 261 controls, 231 leprosy | G239A | NE: lep | | |
| | 71 (2007) | Brazil | 214 controls, 264 leprosy (150 LL, 36 TL, 37 BL, 17 IL) | Haplotype LYPA (−550L/221Y/+4P/ exon 1 A) | S: lep | OR, 2.25 (1.31–3.88) | 0.020 |
| | | | | | S: LL vs con | OR, 2.22 (1.21–4.05) | 0.060 |
| | | | | | S: BL vs con | OR, 2.98 (1.29–6.87) | 0.060 |
| | | | | "Low"-MBL-producing genotypes | R: LL vs TL | OR, 0.31 (0.13–0.71) | 0.012 |
| *MICA/MICB* | 331 (1999) | China | 112 controls, 69 leprosy | MICA-A5 | R: lep | Rel. risk, 0.62 (allele) | 0.06 |
| | | | | | R: MB vs con | Rel. risk, 0.56 (allele) | <0.05 |
| | | | | Haplotype MICA-A5 with HLA-B46 | R: lep | Rel. risk, 0.37 | <0.03 |
| | | | | | R: MB vs con | Rel. risk, 0.22 | <0.01 |
| *MRC1* | 12 (2010) | Vietnam[d] | 490 simplex families (53% MB) + 90 multiplex families (55% MB) for a total of 704 leprosy patients (325 PB, 374 MB) | rs1926736 G/A A allele (396S) | R: lep | OR: 0.76 (0.60–0.96) (best dom) | 0.035 |
| | | | | | R: MB | OR: 0.71 (0.51–0.99) (best dom) | 0.034 |
| | | Brazil | 384 leprosy (~162 MB, ~167 PB), 399 controls, | rs1926736 A/G G allele (396G) | S: lep | OR, 1.34 (1.06–1.70) (additive) | 0.016 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | S: MB | OR, 1.42 (1.05–1.93) (additive) | 0.023 |
| | | | | rs2437257 C/G (407L) | NE: lep | | |
| | | | | | R: MB | OR, 0.63 (0.41–0.97) (dom) | 0.04 |
| | | | | Haplotype G396-F407 | S: lep | OR, 1.41 (1.13–1.76) | 0.003 |
| | | | | | S: MB | OR, 1.61 (1.21–2.14) | 0.001 |
| | | | | Haplotype S396-F407 | R: lep | OR, 0.75 (0.59–0.95) | 0.019 |
| | | | | | R: MB | OR, 0.68 (0.50–0.93) | 0.015 |
| *NOD2* | 93 (2004) | Malawi | ND | C802T<br>C2104T<br>G2722C<br>3020insC 1007fs | Not present in population | | |
| | 27 (2010) | Nepal | 101 controls, 933 leprosy | rs12448797 T/C (C allele) | S: lep | OR, 2.18 (1.06–5.23) (allele) | 0.031 |
| | | | | | | OR, 2.47 (1.12–6.44) (dom) | 0.021 |
| | | | | rs2287195 A/G (G allele) | S: lep | OR, 1.51 (1.08–2.14) (allele) | 0.013 |
| | | | | | | OR, 1.85 (1.19–2.88) (dom) | 0.004 |
| | | | | rs8044354 A/G (G allele) | S: lep | OR, 1.53 (1.11–2.10) (allele) | 0.006 |
| | | | | | | OR, 2.07 (1.33–3.22) (dom) | 0.0006 |
| | | | | rs13339578 G/A (A allele) | S: lep | OR, 1.71 (1.10–2.68) (dom) | 0.012 |
| | | | | rs4785225 C/G (G allele) | S: lep | OR, 1.67 (1.07–2.60) (dom) | 0.017 |
| | | | | rs751271 A/C (C allele) | S: lep | OR, 1.65 (1.07–2.58) (dom) | 0.016 |
| | | | | rs1477176 T/C (C allele) | R: lep | OR, 0.44 (0.28–0.71) (allele) | <0.001 |
| | | | | | | OR, 0.43 (0.26–0.73) (dom) | 0.0005 |
| | | | 124 ENL | rs2287195 A/G (G Allele) | S: ENL vs no ENL | OR, 1.82 (1.12–3.00) (dom) | 0.011 |
| | | | 428 no ENL | rs8044354 A/G (G Allele) | S: ENL vs no ENL | OR, 1.34 (0.99–1.82) (allele) | 0.046 |
| | | | | | | OR, 2.17 (1.26–3.88) (dom) | 0.003 |
| | | | | rs7194886 C/T (T allele) | S: ENL vs no ENL | OR, 1.66 (1.07–2.57) (dom) | 0.016 |
| | | | | rs6500328 A/G (G allele) | S: ENL vs no ENL | OR, 1.69 (1.09–2.62) (dom) | 0.012 |
| | | | | rs17312836 A/C (C allele) | S: ENL vs no ENL | OR, 1.43 (1.00–2.04) (allele) | 0.039 |
| | | | | | | OR, 1.70 (1.09–2.64) (dom) | 0.013 |
| | | | | rs1861759 A/C (C allele) | S: ENL vs no ENL | OR, 1.42 (1.00–2.01) (allele) | 0.037 |
| | | | | | | OR, 1.78 (1.15–2.73) (dom) | 0.006 |
| | | | | rs1861758 C/T (T allele) | S: ENL vs no ENL | OR, 1.41 (0.99–1.99) (allele) | 0.047 |
| | | | | | | OR, 1.69 (1.09–2.63) (dom) | 0.014 |
| | | | 240 RR | rs2287195 A/G (G allele) | R: RR vs no RR | OR, 0.74 (0.58–0.95) (allele) | 0.013 |
| | | | 693 no RR | | | OR, 0.69 (0.50–0.96) (dom) | 0.023 |
| | | | | rs8044354 A/G (G allele) | R: RR vs no RR | OR, 0.74 (0.59–0.92) (allele) | 0.005 |
| | | | | | | OR, 0.69 (0.49–0.96) (dom) | 0.021 |
| | | | | rs8043770 C/G (G allele) | R: RR vs no RR | OR, 0.73 (0.57–0.94) (allele) | 0.012 |
| | | | | | | OR, 0.67 (0.49–0.92) (dom) | 0.010 |
| | | | | rs7194886 C/T (T allele) | R: RR vs no RR | OR, 0.74 (0.55–0.98) (allele) | 0.032 |
| | | | | | | OR, 0.69 (0.49–0.96) (dom) | 0.023 |
| | | | | rs1861759 A/C (C allele) | R: RR vs no RR | OR, 0.75 (0.57–0.99) (allele) | 0.041 |
| | | | | | | OR, 0.69 (0.49–0.95) (dom) | 0.019 |
| | | | | rs4785225 C/G (G allele) | R: RR vs no RR | OR, 0.71 (0.52–0.97) (dom) | 0.027 |
| | | | | rs751271 A/C (C allele) | R: RR vs no RR | OR, 0.73 (0.53–0.99) (dom) | 0.038 |
| *PARK2/PACRG* | 196 (2004) | Brazil | 388 controls, 587 leprosy (38% PB, 62% MB) | rs2803104 (A allele) | NE: lep | | |
| | | | | 10 kb_target_5_2 (T allele) | S: lep | ND | 0.019 |
| | | | | PARK2_e01(−697) (G allele) | S: lep | ND | 0.001 |
| | | | | PARK2_e01(−2599) (T allele) | S: lep | ND | 0.003 |
| | | | | PARK2_e01(−3024) (C allele) | NE: lep | | |
| | | | | PARK2_e01(−3800) (G allele) | S: lep | ND | 0.009 |
| | | | | 28 kb_target_2_1 (T allele) | NE: lep | | |
| | | | | 28 kb_target_4_1 (A allele) | S: lep | ND | 0.003 |
| | | | | rs1514343 (T allele) | S: lep | ND | 0.045 |
| | | | | rs1333955 (C allele) | S: lep | ND | 0.034 |
| | | | | rs1040079 (C allele) | S: lep | ND | 0.001 |
| | | | | 40 kb_target_8_F60 (A allele) | S: lep | ND | 0.032 |
| | | | | 40 kb_target_8_F706 (G allele) | NE: lep | | |

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TABLE 1—*Continued*

| Gene | Reference(s) (yr) | Population | Sample size | Variant(s)[a] | Phenotype | OR (95% CI), rel risk, or $\chi^2$ value | *P* value[b] |
|---|---|---|---|---|---|---|---|
| | 184 (2006) | India | 350 controls, 286 leprosy (144 MB, 142 PB) | PARK2_e01(−2599) | NE: lep or lep type | | |
| | | | | PARK2_e01(−697) | NE: lep or lep type | | |
| | | | | 28 kb_target_2_1 | NE: lep or lep type | | |
| | | | | 10 kb_target_5_2 | NE: lep or lep type | | |
| | | | | rs1040079 | NE: lep or lep type | | |
| *SLC11A1* (*NRAMP*) | 256 (1999) | India | 165 controls, 227 leprosy (105 TL, 122 LL) | 5′ MS [$(GT)_n$ or $(CA)_n$] | NE: lep or lep type | | |
| | | | | 3′ UTR TGTG del/ins | NE: lep or lep type | | |
| | | | | (469 + 14 G/C) intron 4 SNP | NE: lep or lep type | | |
| | | | | Exon 2 polymorphism | NE: lep or lep type | | |
| | 191 (2001) | Mali | 201 controls, 273 leprosy (92 PB, 181 MB) | 3′ UTR TGTG deletion | S: MB vs PB (het vs del/del) | OR, 5.79 (1.46–24.61) | 0.003 |
| | 89 (2004) | Brazil | 61 controls (30 positive for MR, 24 negative for MR), 90 leprosy (45 MB, 45 PB, 18 positive for MR, 64 negative for MR) | Alleles of 5′ promoter microsatellite [$(GT)_n$ or $(CA)_n$] polymorphisms | NE: lep, lep type, MR | | |
| | 321 (2007) | Thailand | 140 controls, 37 leprosy (13 PB, 24 MB) | (469 + 14 G/C) intron 4 SNP | NE: lep or lep type | | |
| | | | | D543N SNP | NE: lep or lep type | | |
| | | | | 3′ UTR TGTG del/ins | NE: lep or lep type | | |
| | 93 (2004) | Malawi | 283–429 controls, 244–258 leprosy (>90% PB) | Promoter microsatellite$(GT)_n$ genotypes 199/201, 199/199, 201/201 | NE: lep | | |
| | | | | Other promoter microsatellite$(GT)_n$ genotypes | NE: lep | | |
| | | | | Exon 2, 9-bp del | NE: lep | | |
| | | | | 3′ UTR TGTG del/ins | NE: lep | | |
| | | | | 3′ UTR CAAA del/ins | NE: lep | | |
| *TLR1* | 149 (2007) | Turkey | 90 controls, 57 leprosy | T1805G G allele (602S) | R: lep | OR, 0.48 (0.29–0.80) | 0.004 |
| | | | | T1805G GG genotype (602SS) | R: lep | ND | 0.02 |
| | 198 (2008) | Nepal | 933 leprosy (311 TL, 490 LL) | T1805G G allele (602S) | NE: lep | | |
| | | | | | NE: TL vs LL | | |
| | | | | | R: RR | OR, 0.51 (0.29–0.87) (allele) | 0.01 |
| | 271 (2009) | Bangladesh | 543 controls, 842 leprosy (702 PB, 140 MB) | T1805G G allele (602S) | NE: lep | | |
| | | | | A743G GG genotype (248SS) | S: lep | OR, 1.34 (1.06–1.70) (rec) | [0.016] |
| | | | | A743G G allele (248S) | R: ENL | OR, 0.40 (0.16–0.99) (allele) | [0.04] |
| | | | | A743G GG genotype (248SS) | Trend: RR | OR, 1.57 (0.97–2.55) (rec) | NS |
| *TLR2* | 93 (2004) | Malawi | 379 controls, 210 cases (26 MB, 184 PB) | Intron 2 microsatellites 216 bp, 222 bp, 224 bp, 226 bp | NE: lep | | |
| | | | | Intron 2 microsatellite 224 bp | MB vs PB | $\chi^2 = 6.3$ (ND) | 0.042 |
| | 35 (2008) | Ethiopia | 197 controls, 441 leprosy (298 LL, 138 TL, 5 uncharacterized, 66 RR, 150 no RR) | Microsatellite (280 bp) | S: RR | OR, 5.83 (1.98–17.15) (rec) | 0.001 |
| | | | | Microsatellite (288 bp) | R: LL vs. TL | OR, 0.49 (0.27–0.90) (dom) | 0.02 |
| | | | | Microsatellite (290 bp) | R: lep | OR, 0.62 (0.41–0.93) (additive) | 0.02 |
| | | | | Other microsatellites | NE: lep, lep type, RR | | |
| | | | | C597T (N199N) | R: RR | OR, 0.34 (0.17–0.68) (dom) | 0.002 |
| | | | | T1350C (S450S) | NE: lep, lep type, RR | | |
| | | | | "280 C-T haplotype" (280 bp, 297C, 1350T) | S: RR | OR, 6.39 (2.14–19.07) (rec) | 0.001 |
| *TLR4* | 36 (2009) | Ethiopia | 197 controls, 441 leprosy (298 lepromatous [199 BL, 81 LL, 18 MB], 138 tuberculoid [128 BT, 3 TT, 7 PB], 5 uncharacterized, 133 neuritis, 66 RR, 17 ENL) | G896A | R: lep | OR, 0.34 (0.20–0.57) (additive) | <0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | T1196C | R: lep | OR, 0.15 (0.06–0.39) (dom) | <0.001 |
| | | | | G1530T | R: lep | OR, 0.38 (0.14–1.01) (dom) | 0.05 |
| | | | | A1976G | NE: lep or lep type | | |
| | | | | Haplotype 896G/1196T/1530G/1976A | R: lep | OR, 0.12 (0.05–0.34) | <0.001 |
| | | | | Haplotype 896G/1196C/1530T/1976A | R: lep | OR, 0.23 (0.08–0.69) | 0.008 |
| | 93 (2004) | Malawi | 288 controls, 235 leprosy | G896A | NE: lep | | |
| *TNF* | 257 (1997) | India | 160 controls, 228 leprosy (121 LL, 107 TT) | G−308A | S: LL vs con | Rel. risk, 2.5 (1.1–6.5) (allele) | 0.03 |
| | 261, 262 (2000 and 2002, respectively) | Brazil | 92 controls, 300 leprosy (MB [70 LL, 85 BL, 55 BB], PB [63 BT, 2 TT], 10 indeterminant, 15 pure neuritis) | G−308A | R: lep | [OR, 0.63 (0.39–1.0) (allele)] | <0.05 |
| | | | | | R: MB vs con | [OR, 0.53 (0.30–0.91) (allele)] | <0.01 |
| | | | | | S: PB vs MB | OR, 1.65 (0.9–2.9) (allele) | <0.05 |
| | | | | G−238A | NE: lep or lep type | | |
| | 93 (2004) | Malawi | 258–283 controls, 216–243 leprosy (>90% PB) | G−238A | NE: lep | | |
| | | | | G−308A | NE: lep | | |
| | | | | G−376A | NE: lep | | |
| | | | | C−863A | NE: lep | | |
| | 321 (2007) | Thailand | 140 controls, 37 leprosy (13 PB, 24 MB) | G−308A | S: MB vs con (het) | OR, 2.69 (ND) | 0.04 |
| | | | | G−238A | NE: lep or lep type | | |
| *VDR* | 256 (1999) | India | 166 controls, 231 leprosy (107 TL, 124 LL) | TaqI T→C ("T"→"*t*") | S: TL vs con | OR, 3.22 (1.47–7.13) (rec) | 0.001 |
| | | | | | R: LL vs con | [OR, 0.60 (0.37–0.96) (dom)] [OR, 0.54 (0.33–0.86) (het)] | [0.03] [0.01] |
| | 93 (2004) | Malawi | 328–398 controls, 168–247 leprosy (>90% PB) | TaqI T→C ("T"→"*t*") | Controls violate HWE | | |
| | | | | ApaI G→T ("a"→"A") | NE: lep | | |
| | | | | BsmI C→T ("b"→"B") | NE: lep | | |
| | 113 (2006) | Brazil | 68 controls, 102 leprosy (55 PB, 47 MB) | TaqI T→C ("T"→"*t*") genotypes alone | NE: lep or lep type | | |
| | 85 (2009) | Mexico | 144 controls, 71 LL | TaqI T→C ("T"→"*t*") | R: lep (LL) | OR, 0.55 (0.31–0.98) (dom) [OR, 0.50 (0.27–0.92) (het)] | 0.04 [0.03] |

[a] By convention, the variant SNP (a) is designated second (e.g., "A→a," "A/a," or "A[nucleotide position]a").

[b] When present, corrected *P* values are reported.

[c] Abbreviations: con, controls, lep, leprosy (multiple forms or unspecified forms); MB, multibacillary; PB, paucibacillary; BL, borderline (depending on the study, this may indicate BB, BL, BT, or any combination of these); IL, indeterminate leprosy; LL, lepromatous leprosy (depending on study, this may indicate LL only or LL plus BL or plus BB); TL, tuberculoid leprosy (depending on the study, this may indicate TT or TT plus BT); ENL, erythema nodosum leprosum; RR, reversal reaction; MR, Mitsuda reaction; S, susceptible; R, resistant; dom, dominant model of genetic analysis (compares aa plus Aa versus AA); rec, recessive genetic model (compares aa versus AA plus Aa); het, heterozygotes or heterozygous model of analysis (Aa versus AA plus aa); HWE, Hardy-Weinberg equilibrium; del, deletion; ins, insertion; ND, no data (data not shown or not available); NE, no effect (no association found); NE: lep or lep type, phenotypes investigated and relevant variant not associated with either phenotype (i.e., not with leprosy overall or a specific type of leprosy, such as MB, PB, TT, or LL); NS, not significant; rel risk, relative risk. Data in brackets indicate where *P* values, ORs, or 95% confidence intervals were calculated by these reviewers or where ORs have been inverted to simplify comparison of the same risk allele across different studies.

[d] The Vietnamese component of this study was a family-based association study.

[e] See references 93, 185, 206, 225, and 262.

gene located in the *HLA* class III region. Eight SNPs in this gene region (*LTA*−293, rs3131628, rs2523500, *LTA*+80, *LTA*+368, rs2516479, rs2844484, and rs2256965) showed linkage to leprosy. Notably, 7 of 8 SNPs were in strong linkage disequilibrium (LD) with each other, and the causative SNP could not be conclusively identified (8). Since the *LTA*+80 polymorphism was known to have a functional effect, it was considered to be the most likely candidate SNP. The *LTA*+80 polymorphism is located in a regulatory E2 box motif, C(A/C)GCAG, of the gene (8). The A allele allows the binding of the activated B-cell factor 1 transcriptional repressor and is associated with decreased *LTA* expression. The C allele alters the binding site of the transcriptional repressor (158). The abrogation of the *LTA* signaling pathway in mice is associated with increased susceptibility to intracellular pathogens (38, 116). Attempts to validate *LTA* SNP associations were made in two additional case-control studies in India (364 patients with leprosy and 371 controls) and Brazil (209 leprosy patients and 192 healthy controls) (Table 1). In addition, a second Vietnam sample set was studied (104 families). In these populations, no consistent association was seen between disease status and the SNPs *LTA*+80, *LTA*−294, or *LTA*−293 in unadjusted analyses. However, in all three ethnic groups, the risk conferred by the *LTA*+80 allele showed age dependence, with the highest ORs seen for the youngest age group. For example, the association of the *LTA*+80[A] allele with leprosy risk in Vietnam was almost entirely due to the effect on patients under 16 years of age (OR, 5.76; $P = 4 \times 10^{-5}$) (8). Since the *LTA*+80 variant is within 200 to 1,000 kb from neighboring *HLA* class I and II loci, theoretically, the susceptibility effect of this variant could be due to linkage disequilibrium with alleles in the *HLA* class I or II loci (108, 305, 339). However, there was no evidence of LD between alleles in *HLA* classes I and II and *LTA*+80 in Vietnamese and Indian subjects (8), strong evidence that the *LTA* gene is an independent risk factor. Subsequently, Fitness et al. used a candidate gene approach to investigate several alleles of a 5′ untranslated region (UTR) microsatellite polymorphism of *LTA* in Malawi (184 leprosy cases and 333 controls) and found one allele with an association with leprosy (93) (Table 1).

Overall, data from several different study populations provide good evidence that the *LTA* gene is implicated in leprosy susceptibility in some populations (Vietnam and India), although it is less clear which specific SNP accounts for the association. The *LTA*+80 SNP, for example, appears to exert its effect mostly on younger subjects. Its association with leprosy in older individuals or age-unspecified individuals is inconsistent (findings for a Brazilian population were negative). Interestingly, the age-specific incidence rates for leprosy in countries where the disease is endemic, such as India, show a peak in incidence in children aged 10 to 14 years, followed by a decline and then a second rise at around the age of 30 years that levels off (215). The reasons for this variable incidence are unknown but suggest that distinct risk factors may operate for individuals in different age groups.

### Chromosomes 20p12 and 20p13

Two studies have reported linkage between chromosomal regions 20p12 and 20p13 and leprosy susceptibility (195, 306). The first study (306) was an extension of the genome-wide scan by Siddiqui et al. (282) that had identified a major susceptibility locus on chromosome 10p13 and a second region of weaker linkage on chromosome 20. In the initial screen, 388 microsatellite markers were genotyped in 93 families (103 sibling pairs) from Tamil Nadu, India, to identify regions associated with leprosy susceptibility (306). In the follow-up study, 11 markers in the chromosome 20 region with suggestive evidence of linkage (maximum LOD score of ≥1, or $P < 0.10$) in the initial scan were examined for a second set of 82 families in Tamil Nadu and 58 families in the neighboring state of Andhra Pradesh (140 families total). Except for 10 families, all siblings had paucibacillary leprosy. One marker (D20S115) showed strong evidence for linkage, with a multipoint maximum logarithm of odds score (MLS) of 2.17, although the effect was seen only within the Tamil Nadu families. To confirm these results, transmission disequilibrium testing of D20S115 and eight flanking markers was carried out for the families from Tamil Nadu. A microsatellite marker flanking D20S115 (D20S835) was associated with leprosy ($P = 0.021$) (306).

The second study to find an association with leprosy susceptibility in the chromosome 20 region was reported by Miller et al. for a Brazilian population (195). In the first stage, 21 families were genotyped for 405 markers, and nine regions with preliminary linkage to leprosy susceptibility were identified. In a second stage examining 50 new families, a linkage peak was found at marker D20S889, located on chromosome 20p13. This marker also showed linkage (LOD score, 1.51; $P = 0.004$) in the combined analysis (stage 1 and stage 2). The 20p13 site is about 3.5 megabases distal to the 20p12 linkage peak at D20S115 discussed above for paucibacillary leprosy susceptibility in India (306). Interestingly, among the families with tuberculoid leprosy, there was a nonsignificant linkage peak near marker D20S115 that was associated with the D20S835 allele (195). This study also replicated the finding of linkage with the chromosome 6p21 region (*HLA* and *LTA* loci) but failed to find linkage with chromosome 6q25 or 10p13. In addition, the authors noted evidence of a linkage at chromosome 17q22 (195).

## CANDIDATE REGION LINKAGE STUDIES

### Chromosome 17q11-21

A study by Jamieson and coworkers (142) selectively explored linkage between loci on chromosome 17 and leprosy susceptibility in a Brazilian population. Human chromosome 17q is syntenic to mouse chromosome 11, a region previously associated with increased susceptibility to cutaneous leishmaniasis in the mouse (31, 201, 253). Jamieson and colleagues therefore genotyped 16 microsatellite markers across chromosome 17q11.1-21.31 in 72 multicase leprosy families (208 affected individuals) and observed a broad region of linkage with two peaks at markers D17S250 (maximum *Z* score for likelihood ratio [$Z_{lr}$], 2.34; $P = 0.01$) and D17S1795 ($Z_{lr}$, 2.67; $P = 0.02$) (142). No data are presented for SNPs in regional candidate genes, which include multiple innate immune genes such as *NOS2A*, *MCP-1*, *MIP1*-α, *MIP1*-β, *RANTES*, *CCR7*, *STAT3*, *STAT5A*, and *STAT5B*.

### Chromosome 21q22

Wallace and coworkers performed a search for genes associated with tuberculoid or lepromatous leprosy on chromosome 21 using an identity-by-descent (IBD) regression analysis (330). This method of analysis compares the likelihood of linkage for a given allele in type-concordant sibling pairs (both siblings have the same form of leprosy) to that in type-discordant sibling pairs (those in which siblings have different forms of leprosy). In the first stage of the analysis, 83 families in Malawi were genotyped for markers for the selected region. Makers for regions showing preliminary evidence of linkage ($P < 0.05$) were genotyped in 185 extended pedigrees. In the first stage of the analysis, regions on chromosomes 10q23, 15q21, and 21q22 were singled out for further study. In the second stage of the analysis, only the region on chromosome 21q22 retained a suggestive association with leprosy susceptibility ($P \sim 0.001$) that did not meet genome-wide linkage study criteria for significance (330). Those authors speculated that the most likely candidate gene for this region is *ITGB2*, a gene that encodes the β2 subunit of leukocyte integrins (330). Interestingly, the 21q22 region was more likely to be shared by type-concordant pairs and less likely to be shared by type-discordant sibling pairs, suggesting that this locus affects susceptibility to a specific form of leprosy rather than leprosy overall.

## SUMMARY OF LINKAGE STUDIES

The strongest evidence for the linkage of non-*HLA* genes with leprosy and/or leprosy type susceptibility exists for chromosome 6q25, subsequently linked to the *PARK2/PCRG* gene regulatory region (196, 197); chromosome 6p21, subsequently mapped to the lymphotoxin-α gene (8, 195, 197); and chromosome 10p13, for which the candidate gene has not yet been identified (197, 282). Each of these regions has been validated for separate populations and/or alternate ethnic groups studied by the same or other investigators, and in two of the three cases, a causative gene has been identified. While the causative gene has not been identified for chromosomal region 10p13, this region's specific association with paucibacillary leprosy was validated in a subsequent study (197).

## CANDIDATE GENE ASSOCIATION STUDIES

### Innate Immune Receptors

***TLR1.*** Toll-like receptor 1 (TLR1) forms a heterodimer with TLR2 to mediate the recognition of *M. leprae* (163). A *TLR1* polymorphism, T1805G (I602S), encodes a nonsynonymous SNP in the transmembrane domain of TLR1 that regulates signaling in response to $Pam_3CysK_4$, a synthetic ligand of TLR1 (121, 302, 338). Individuals homozygous for the 1805G variant are functionally TLR1 deficient (121). In previous work, we and others have observed that the T1805G SNP strongly regulates NF-κB signaling via the TLR1/2 receptor such that leukocytes from 1805G homozygous donors have a 2-fold-or-greater reduction in responses to $Pam_3CysK_4$ compared to 1805T homozygous donors (121, 149, 198, 338). In HEK293 cells stimulated with $Pam_3CysK_4$, NF-κB signaling was deficient in 1805G compared to 1805T transfectants (121). Additionally, we found that the T1805G SNP regulates *in vitro* responses to whole irradiated *M. leprae* bacteria and to cell wall extracts of *M. leprae* (198). Both Johnson et al. (149) and Wurfel et al. (338) demonstrated that leukocytes from individuals with the 1805GG genotype lack surface expression of TLR1, in contrast to leukocytes from 1805TT individuals. Therefore, the 1805G variant of human *TLR1* confers a state of functional TLR1 deficiency in which hyporesponsiveness to TLR1 ligands appears linked to a TLR1 trafficking defect. Interestingly, this polymorphism has extreme variation in frequency among different populations worldwide and suggests that *TLR1* could have different impacts on susceptibility to leprosy and other diseases depending on the population studied (22, 121). The 1805G SNP has been shown to be under positive selection, suggesting that this allele, which confers a hyporesponsive immune response to *M. leprae* and possibly other bacterial pathogens, offers a selective advantage in certain populations (22, 79).

Johnson and coworkers examined the role of the *TLR1* T1805G SNP in modulating leprosy susceptibility in 57 patients and 90 controls in Turkey and found that the 1805G SNP was associated with protection from leprosy (OR, 0.48; $P = 0.004$) (149). We examined the relationship of *TLR1* T1805G with tuberculoid versus lepromatous leprosy and two leprosy immune reactions, erythema nodosum leprosum (ENL) and reversal reaction (RR), in 933 leprosy cases in Nepal, including 238 cases of RR (198). *TLR1* 1805G was not associated with leprosy risk overall, nor was it associated with tuberculoid or lepromatous leprosy, although there was a trend toward an association with lepromatous leprosy (OR, 4.76; $P = 0.11$). However, the 1805G SNP was significantly associated with protection from a reversal reaction, a Th1-mediated event (OR, 0.51; $P = 0.01$). The frequency of 1805G was low in this population and decreased the overall power to detect associations.

A third group examined another *TLR1* SNP, A743G (N248S), for leprosy associations using a large group of 842 patients and 543 controls in Bangladesh. The 248SS genotype and S allele were associated with an increased risk of leprosy (OR, 1.34; $P = 0.02$, recessive model) and a decreased risk of ENL (OR, 0.40; $P = 0.04$), respectively, although the subgroup analysis for ENL had a sample size of only 11 (271). In addition, the 248S allele was associated with a trend toward an increased risk of RR (subgroup of 75 cases), but this was not statistically significant. Interestingly, in our prior functional studies of *TLR1* (121), we found that SNP 248S (743G) was in strong LD with 602I (1805T), a hyperfunctional variant of *TLR1* associated with increased signaling in response to triacylated lipopeptide and *M. leprae* (198). The T1805G SNP was also investigated in this Bangladeshi population and was found to have no association with leprosy susceptibility (271). In summary, these studies suggest that *TLR1* influences susceptibility to leprosy immune reactions and leprosy susceptibility, with slightly more evidence in favor of T1805G, rather than A743G, as the causative SNP. In addition, the T1805G SNP was recently investigated in a GWAS in India, and the G allele was associated with protection against leprosy (336).

***NOD2.*** The Nod-like receptors (NLRs) are a family of cytosolic receptors that detect microbial cell wall products. Nucleotide oligomerization domain 2 (NOD2) recognizes muramyl dipeptide (MDP) (98) as well as mycobacteria (90, 91).

The cell wall from *M. leprae* contains a unique MDP structure, which differs from that seen for *M. tuberculosis* and most Gram-negative organisms, and may elicit distinct NOD2-mediated immune responses (64, 183). To our knowledge, no functional studies of the role of NOD2 in the immune response to *M. leprae* have been reported. However, in mouse models of *M. tuberculosis* infection, the deletion of *NOD2* is associated with impaired *in vivo* and *in vitro* immune responses (75, 220, 344). Human mutations in *NOD2* have been associated with altered susceptibility to tuberculosis (TB) in African-Americans (19), inflammatory bowel disease (131), and Blau's disease (192), the latter two of which are diseases with dysregulated granuloma formation. Three recent genetic association studies (including two genome-wide association studies [GWASs]) have also examined the role of NOD2 polymorphisms in leprosy (27, 337, 348).

A recent GWAS identified two polymorphisms in *NOD2*, rs9302752 and rs7194886, associated with susceptibility to leprosy (348). That group also reported associations with polymorphisms in RIP2 kinase, a molecule in the NOD2 signaling pathway (see below for a full discussion of this GWAS). In contrast, Wong et al. did not note associations with NOD2 pathway genes (NOD2 and Rip2K) in an association study in India and Mali (337). When those authors fine-mapped the *NOD2* gene region, they identified five polymorphisms in the *NOD2* gene region, including rs7194886, with leprosy associations that became insignificant after correction for multiple comparisons (337). In a separate study by Fitness and colleagues, several uncommon *NOD2* polymorphisms associated with Crohn's disease were examined in leprosy cases from Malawi, but no association was observed (93). In a recent case-control study of 933 leprosy patients (124 with ENL and 240 with RR) and 101 controls from Nepal, we identified common noncoding polymorphisms in the region around *NOD2* by searching a region on chromosome 16q12 from 50 kb upstream to 50 kb downstream of the *NOD2* and *CYLD* genes for haplotype-tagging SNPs. Eight SNPs were associated with increased susceptibility to leprosy (odds ratios ranging from 1.7 to 2.5) (27) (Table 1). Ten of these SNPs were also associated with leprosy reactions (see Table 1 for details), especially ENL. Of note, some polymorphisms included in this study were in genes adjacent to *NOD2* (*SLIC-1* [or *SNX20*] and *CYLD*) and may therefore implicate these genes in the host response to *M. leprae*.

Taken together, those studies provide evidence that the *NOD2* gene region and intracellular immunity may be important in the host response to *M. leprae*. However, a number of questions remain. First, strong associations in the *NOD2* gene in one population have been marginal or absent in other populations (337). This result could be due to population-specific linkage disequilibrium, which occurs when the true causative SNP is in LD with the identified SNP in one population but not in another (11). Second, *NOD2* polymorphisms may be important for different aspects of the disease in different ethnicities. Ethnic variation in the *NOD2* association, for example, also occurs for Crohn's disease (343). This result can arise for diseases governed by complex or polygenic inheritance patterns, where susceptibility is a cumulative effect of epistatic interactions among several or many genes. Last, the mechanism by which these noncoding region SNPs might alter the innate immune response to leprosy is unclear. Overall, therefore, data from *NOD2* genetic studies suggest that this gene may play a role in leprosy. However, the lack of consistency among genetic association studies in different populations and the absence of a functional mechanism for these SNPs require further exploration.

***TLR2.*** Bochud et al. studied a number of Toll-like receptor 2 gene (*TLR2*) variants in an Ethiopian case-control study (441 cases and 197 controls) (35). A 290-bp microsatellite (MS) polymorphism composed of two adjacent variable-number tandem repeats (VNTRs) in the TLR2 promoter region was less frequent in cases than in controls (OR, 0.62; $P = 0.02$, additive model). When comparing lepromatous and tuberculoid patients, another MS variant (288 bp) was less frequent in those with lepromatous leprosy (OR, 0.49; $P = 0.02$, dominant model). In a small subgroup of patients ($n = 216$) monitored for 8 years to assess leprosy reactions, the 288-bp MS variant was also strongly associated with an increased risk of RR (OR, 5.83; $P = 0.001$, recessive model). In addition, a synonymous-coding-region SNP, C597T, was associated with protection from RR (OR, 0.34; $P = 0.002$, dominant model). The C597T association with RR remained significant even after a conservative Bonferroni adjustment (e.g., $0.002 \times 21 = 0.042$) (35).

Fitness and colleagues also investigated an intron 2 MS polymorphism previously associated with altered receptor function (322, 345) in a Malawi population (~210 leprosy patients and ~379 controls), but no association was found with disease (93). They identified a borderline significant ($P = 0.042$) difference in the genotype frequency of the 224-bp microsatellite between PB and MB patients, although the small number of MB patients ($n = 26$) makes this result possibly due to sampling error.

One study reported the association of a putative *TLR2* polymorphism, C2029T (R677W), with leprosy susceptibility in a South Korean population (154). Subsequent investigators convincingly demonstrated that R677W is an artifact that arises when genotyping primers amplify both *TLR2* and a nearby *TLR2* pseudogene and that this SNP does not exist in the authentic *TLR2* gene (186, 194).

***TLR4.*** Toll-like receptor 4 (TLR4) is present on many cell types, including macrophages, monocytes, and dendritic cells, and recognizes lipopolysaccharide (LPS) from Gram-negative bacteria (228). While *M. leprae* signals predominantly through TLR1/2 heterodimers (163), there is evidence that live *M. tuberculosis* may signal through TLR4 (190). Several polymorphisms have been described for the coding region of *TLR4* (G896A, C1196T, G1530T, and A1976G), and some (G896A and C1196T) have been shown to impair signaling through TLR4, as evidenced by decreased cytokine production in patients given inhaled LPS (17). The G896A (D299G) and C1196T (T399I) polymorphisms have been extensively studied and are associated with many bacterial illnesses, including Gram-negative infections and Legionnaires' disease (5, 109, 122, 270). Functional studies of these polymorphisms have suggested a possible signaling defect, although this was not validated by other groups and remains unclear (17, 52, 80, 82, 193, 222, 265, 313, 326).

In an Ethiopian population (441 cases and 197 controls), we identified two *TLR4* SNPs, G896A and C1196T, that were associated with protection from leprosy (OR of 0.34 [$P < 0.001$, additive model] and OR of 0.16 [$P < 0.001$, dominant

model], respectively) (36). Additionally, we found that signaling in monocytes through TLR4 by endotoxin was inhibited by heat-killed *M. leprae* (36). In another study in Malawi of 235 patients and 88 controls, Fitness et al. found no association of the G896A polymorphism with leprosy (93). Overall, the association of *TLR4* with leprosy is inconclusive, since the associations in Ethiopia were not validated in Malawi, and requires further investigation in other populations. For example, the different conclusions of these two studies regarding the association of *TLR4* with leprosy overall could be due to different patterns of linkage disequilibrium between the two populations or to a true lack of an effect of *TLR4* (and/or causative genes in LD with TLR4) on leprosy susceptibility. Alternatively, it is possible that *TLR4* is associated predominantly with lepromatous leprosy, since 298 of 441 (67.5%) of the Ethiopian cases were at the lepromatous pole (classified as BL, LL, or multibacillary), compared to only 26 of 270 (9.6%) cases in Malawi. In fact, the authors of the Malawi study stated that the results for most SNPs studied did not change when the 28 multibacillary patients were excluded. From this, it can be inferred that the Malawi study likely lacked the power to detect genetic associations specific to multibacillary disease.

***MRC1.*** Mannose receptor 1 (MRC1) is a phagocytic receptor that recognizes mannose, fucose, *N*-acetylglucosamine (GlcNAC) (157), and mannose-capped lipoarabinomannan, a mycobacterial cell wall lipoprotein (144, 268). *MRC1* localizes to chromosome 10p13 (77), a previously identified leprosy susceptibility locus (282). A study by Alter and colleagues examined polymorphisms in exon 7 of the *MRC1* gene in a family-based association study of 580 Vietnamese families and a case-control study of 783 Brazilians (12). Exon 7 was the focus of investigation, since unpublished reports implicated this region of the *MRC1* gene as a risk factor for PB leprosy (Tosh et al., unpublished data cited in reference 127 and referenced in reference 12). Of three previously described nonsynonymous SNPs in *MRC1*, only one, G396S, was found after sequencing healthy individuals in Vietnam. In Vietnamese families, weak evidence for an association of the 396S variant was observed with protection against leprosy (OR, 0.76; $P = 0.035$) and against MB disease (OR, 0.71; $P = 0.034$). To replicate these findings, exon 7 SNPs were then investigated in a genetic association study of 384 leprosy patients and 399 controls in Brazil. In Brazil, the 396S allele was again associated with protection from leprosy overall (OR, 0.75; $P = 0.016$) and from MB disease (OR, 0.70; $P = 0.023$). When *MRC1* haplotypes containing the 396G or 396S SNP were ectopically expressed in HEK293 cells, no differences in the phagocytosis of zymosan or ovalbumin were observed between the two variants (12). Interestingly, the transfected HEK cells were unable to bind *M. leprae* or BCG, suggesting that the mannose receptor may cooperate with an unknown second receptor to internalize *M. leprae* (12).

Although only one genetic study has been performed on *MRC1* and leprosy, the concordant findings for the two different ethnic groups are encouraging and suggest a possible role for *MRC1* variants in leprosy susceptibility. However, functional studies of the *MRC1* SNPs are inconclusive. This gene was considered to be the strongest candidate gene at the chromosome 10p13 locus, a region that has been linked to susceptibility to PB leprosy. The lack of an association between *MRC1* and PB leprosy in the current study suggests that an alternate candidate gene specific for PB leprosy may exist in the 10p13 region.

***VDR.*** Vitamin D modulates diverse effects on the immune system, which can be inhibitory or stimulatory depending on the cell type and the nature of the immune response. In dendritic cells, vitamin D inhibits maturation by blocking the expression of MHC class II, CD40, CD80, and CD86 (208) and reducing the expression of IL-12 (224). In macrophages, vitamin D also downregulates IL-12 expression (66). However, in monocytes and macrophages infected with *M. tuberculosis*, vitamin D augments the TLR1/2-stimulated expression of cathelicidin and thereby enhances intracellular killing (179). In contrast, the net effect of vitamin D on the adaptive immune response is an enhancement of Th2 T-cell responses at the expense of Th1 responses (208). Vitamin D blocks Th1 responses by inhibiting the expression of the Th1 cytokines IL-2, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (29, 246, 308) and suppressing lymphocyte proliferation (174, 250). Vitamin D also enhances the generation of nonspecific T suppressor cells, inhibits the induction of $CD8^+$ T cells, and reduces class II antigen expression in mixed-lymphocyte reactions (174, 208).

Several polymorphisms located near the 3′ UTR of the vitamin D receptor gene (*VDR*) (BsmI, ApaI, and TaqI) have been reported to regulate the stability or transcriptional activity of *VDR* mRNA (209). The TaqI C (or *t*, as it is sometimes represented) polymorphism has been associated with higher mRNA transcript levels of *VDR* (209), although this finding is controversial (200, 323).

The TaqI *VDR* polymorphism was studied in a population in Kolkata, India, in a case-control genetic association study involving 231 patients with leprosy (107 with tuberculoid disease and 124 with lepromatous disease) and 166 controls matched for ethnicity (256). No differences were seen in the distribution of TaqI genotypes between all leprosy patients and controls. However, the CC (*tt*) genotype was found significantly more frequently in tuberculoid leprosy than in controls (OR, 3.22; $P = 0.001$, adjusted), and conversely, the TT genotype was enriched for patients with lepromatous leprosy compared to controls (OR, 1.67; $P = 0.04$, adjusted) (256). Interestingly, although not reported by those authors, individuals with TC genotypes were protected from lepromatous leprosy, suggesting a heterozygous advantage (Table 1).

A second study in Malawi examining ~247 leprosy cases and ~398 controls also found a significant association of the TaqI CC (*tt*) genotype with an increased risk of leprosy (OR, 4.3; $P = 0.004$, unadjusted) (93). All but 26 of the leprosy cases were PB or tuberculoid leprosy. However, as those authors pointed out, the controls were not in Hardy-Weinberg equilibrium (HWE) for this polymorphism, suggesting that this finding may be due to population stratification or genotyping error rather than a bona fide association.

TaqI receptor polymorphisms were also investigated in a study of 71 Mexican patients with lepromatous leprosy compared to 144 healthy blood bank donor controls. The TC (T*t*) or CC (*tt*) genotypes combined were associated with protection from leprosy (in this case, lepromatous leprosy), with marginal significance (OR, 0.55; $P = 0.04$) (85), an effect similar in direction and magnitude to that reported in the Kolkata study

(256). Of note, the patients included in that study appeared to have lepromatous leprosy exclusively. In another study in Brazil of 102 Brazilian patients (55 with PB and 47 with MB) and 68 nonconsanguineous household contacts, no association was found between TaqI genotypes and overall leprosy susceptibility or leprosy subtype (113). It is quite likely that this study lacked the power to find an association of TaqI with either PB or MB disease, given 1.5- to 2.5-fold-higher numbers of patients with lepromatous or tuberculoid leprosy in other studies reporting an association for this SNP (85, 256). This negative study illustrates the problem of comparing genetic association studies carried out with populations with different ratios of multibacillary to paucibacillary disease, which could be circumvented by carrying out replication studies of populations with a similar bias along the leprosy clinical spectrum or by ensuring the recruitment of adequate numbers of patients in the relevant categories.

The somewhat contradictory findings with respect to the effect of the CC (*tt*) genotype or C (*t*) allele on leprosy susceptibility in different studies could be due to differences in ethnic background, variations in sample size affecting study power to investigate associations with different types of leprosy, or other aspects of study design. Another consideration is that the 3′ end of the *VDR* gene also contains several polymorphisms in various degrees of linkage disequilibrium in different populations (135, 256). As a result, the effect of a TaqI polymorphism might be attributable not to TaqI *per se* but to other alleles (including ApaI or BsmI) that are in population-specific linkage disequilibrium with the TaqI SNP. It is interesting that of the two studies that reported an association of this SNP, both displayed a dominant protective effect of the *t* allele against lepromatous leprosy as well as a heterozygous advantage (85, 256).

**Summary of association studies of innate immune receptors.** The most consistent findings among the different studies of receptors are for the effect of *TLR1* (SNP T1805G) on leprosy susceptibility and/or an altered risk of a reversal reaction and for *NOD2* associations with leprosy. The most clear functional effect is that of *TLR1* 1805G, which has been shown by several groups to impart a signaling defect for ligands operating through the TLR1/2 heterodimer (121, 149, 198, 338).

## Cytokines

***TNF*.** TNF is a multifunctional proinflammatory cytokine produced by monocytes and macrophages and is important for the control of mycobacterial and other infectious diseases. Treatment with TNF inhibitors may be associated with the development of leprosy, and the withdrawal of TNF inhibitor treatment in leprosy patients may also enhance the formation of a type I reversal reaction (274). There is also evidence that TNF inhibitors may be effective for the treatment of recurrent erythema nodosum leprosum (81). While some studies have documented the association of the *TNF* promoter region polymorphisms with susceptibility to different infections, the validity of these findings is unclear due to a lack of reproducible data in reports from other populations (24, 51, 187).

The first association study of the *TNF* promoter region SNP G-308A was carried out by Roy et al. in a population in Kolkata, India (257). In that study, the *TNF* −308A allele was noted to be significantly increased for patients with LL ($n = 121$) compared to TT ($n = 107$ patients) (RR = 2.5; $P = 0.03$) (257). This finding was not replicated in a linkage study of six French Polynesian families (176). In a Brazilian population of 300 leprosy cases and 92 controls, the −308A allele was associated with paucibacillary disease (OR, 1.65; $P < 0.05$) (261, 262), a finding opposite of that seen for the Indian population (257). In addition, the −308A allele was associated with protection from leprosy acquisition (OR, 0.63; $P < 0.05$) and MB leprosy (OR, 0.53; $P < 0.01$). These findings were more pronounced for the female subgroup, where the *TNF* −308A allele was associated with protection from leprosy overall (OR, 0.4; $P = 0.01$) and from MB leprosy (OR, 0.21; $P < 0.01$). In this Brazilian study, a second SNP, G−238A, was not associated with leprosy overall or leprosy type. A separate TDT analysis in Brazil found that the −308G allele was more frequent for patients with leprosy or lepromatous leprosy (277). In a case-control association study in Thailand, the −308A allele was associated with multibacillary leprosy (OR, 2.69; $P = 0.04$) (321). A linkage study of 223 families and 230 sibling pairs in southern India also demonstrated associations of a *TNF* MS polymorphism with leprosy, but the associations failed the bootstrapping test used in this study ($P = 0.089$ after bootstrapping) (307). In this Indian study, the G−308A polymorphism was also not associated with susceptibility to leprosy. Last, in a case-control study of 933 patients with leprosy and 101 control patients in Nepal, we found that the −308A allele was associated with protection against leprosy (OR, 0.52; $P = 0.016$) (W. R. Berrington, unpublished data).

The biological mechanism of action of G−308A and other promoter variants remains uncertain. Overall, functional investigations of the −308A and the −238A promoter SNPs through a variety of approaches (*in vitro*, *in vivo*, and *ex vivo*) have not shown a consistent association of either variant with increased or decreased TNF production (40, 87, 104, 165, 181, 291, 301, 303). The *TNF* −308A allele, for example, has been shown to have increased transcriptional activity in some studies in which this variant has been cloned upstream of a reporter construct (162, 335) but not in others (43, 159). Knight et al. investigated the transcriptional activity of the *TNF* −308A and −308G variants *in vivo* in Epstein-Barr virus (EBV)-transformed human B-cell lines and did not find differences in TNF transcription (by levels of phosphorylated RNA polymerase II) between the two alleles (159). The variable results of these functional studies of the −308A variant may be due partly to different experimental approaches, such as the reliance on *in vitro* assays of plasmid reporter gene expression versus *in vivo* assays with human cell lines, the use of specific cell lines, or variable stimulation conditions (335). Even if it were clear which TNF alleles were associated with altered gene transcription or cytokine production, the role of TNF (and other cytokines) in the pathogenesis of leprosy and leprosy immune reactions is still not well understood (272, 273).

Collectively, the genetic association data for *TNF* are also inconsistent. While some studies support an association of the SNP G−308A with altered susceptibility to leprosy overall or leprosy type, the SNP appears to have opposite effects on leprosy polarity (tuberculoid versus lepromatous) in different populations. The *TNF* gene is located on chromosome 6q23-12 in a region in close linkage with *HLA-DR* (51, 187, 213), a gene

locus that has also been associated with leprosy (39, 40, 108, 315, 317). Similarly, the *TNF* −308 SNP is in LD with the *LTA* gene, and a haplotype containing the −308A allele and *LTA* SNPs +10A, +252G, and +723A has been shown to be associated with increased *LTA* transcriptional activity (159). Population-specific differences in the LD between *TNF* and either or both of these two candidate gene regions, if unaccounted for, could potentially confound the results of association studies of this candidate gene.

***IL10*.** Interleukin-10 (IL-10) is an anti-inflammatory cytokine that inhibits the production of IL-1, IL-6, and TNF in LPS- and IFN-γ-activated macrophages (92, 129, 138, 166, 205). IL-10 also impairs the host response to mycobacteria, as shown for IL-10-overexpressing mice that failed to clear mycobacterial infection (211). In humans, elevated mRNA expression levels of the Th2 cytokines IL-4, IL-5, and IL-10 has been demonstrated for LL lesions in contrast to TT lesions, where the Th1 cytokines gamma interferon and IL-2 predominate (341). Data from clinical studies suggest that higher levels of IL-10 and lower TNF-to-IL-10 ratios correlate with multibacillary leprosy, T-cell anergy in patients with lepromatous leprosy, and progression from leprosy exposure to symptomatic illness (177, 199).

Santos et al. investigated SNPs in the *IL10* promoter region in 143 patients with MB leprosy, 59 patients with PB leprosy, and 62 healthy controls (262). A greater frequency of the −819TT genotype was found among leprosy patients (MB and PB combined) than controls (OR, 2.64; $P = 0.04$, recessive model) (262). The promoter polymorphism −819T was also more frequent for patients with PB leprosy (262). Those investigators also studied the association between haplotypes of five promoter polymorphisms in *IL10* and multibacillary or paucibacillary leprosy in a separate group of approximately 297 patients from Rio de Janeiro, Brazil (206). No association was found between any of the individual polymorphisms, including C−819T, and leprosy susceptibility, although there were some haplotype associations. In addition, one haplotype was more strongly associated with PB leprosy (Table 1) (206). Franceschi and colleagues also investigated promoter SNPs A−1082G, C−819T, and C−592A in 156 leprosy patients (65 LL, 49 TT, and 45 BB patients) and 240 controls in Brazil (Parana state) and found a lower frequency of the *IL10* promoter haplotype −1082G/−819C/−592C among patients with lepromatous leprosy. However, this finding lost significance after correction for multiple comparisons (96).

Malhotra and colleagues also studied *IL10* SNPs and haplotypes for 282 leprosy patients and 266 controls in India and found associations for both the C−819T and the C−592A polymorphisms (185). Individuals with the −819TT genotype were at a significantly increased risk of leprosy (OR, 2.50; $P < 0.001$), and individuals with the −592CC genotype were significantly protected from leprosy (OR, 0.60; $P = 0.006$) (185). That group also examined the effect of the individual *IL10* SNPs T−3575A, G−2849A, C−2763A, A−1082G, C−819T, and C−592A and haplotypes of these SNPs on leprosy type (185). In contrast to the report by Santos et al., they found that the −819TT genotype was more frequent in patients with multibacillary (MB) leprosy than in controls (OR, 2.63; $P = 0.001$). In addition, the −592CC genotype was associated with protection from MB leprosy (OR, 0.48; $P = 0.002$) (185) (Table 1).

Fitness et al. examined three *IL10* proximal promoter polymorphisms, A−1082G, C−819T, and C−592A, in a Malawian population (~362 leprosy cases and ~215 controls) (93). No association was found between any of these *IL10* variants and leprosy risk, although there was a trend toward an association of the −592CC genotype with leprosy resistance compared to AA homozygotes (OR, 0.58; $P = 0.06$) (93).

In a large case-control study (~369 leprosy patients and ~380 controls), Pereira et al. investigated the C−819T SNP and four other *IL10* promoter SNPs (225). Carriers of the −819T allele and individuals with the −819TT genotype were found to be at an elevated risk of leprosy compared to controls (OR, 1.44 for the comparison of TT/CT versus CC; $P = 0.026$, adjusted analysis) (225). Those authors subsequently performed a meta-analysis of that study and four prior studies performed in Brazil, India, and Malawi (93, 185, 206, 262). A fifth, negative study from Brazil was not included (96). The meta-analysis showed that the −819T allele and the TT genotype were both significantly associated with an elevated risk of leprosy ($P = 0.0001$ to 0.024), although the magnitude of the risk was modest (OR, 1.28 to 1.66) (225).

A number of functional studies have been carried out on disease-associated polymorphisms or haplotypes of *IL10*, with inconsistent results. A high-frequency *IL10* haplotype containing SNP −819T has been described for healthy Dutch Caucasians and African-Americans and was associated with elevated levels of IL-10 production (110). However, other studies found lower IL-10 levels associated with the −819T SNP or in haplotypes containing this SNP (225, 312). In one study, cytokine responses of peripheral blood mononuclear cells (PBMCs) from healthy donors with differing genotypes were examined. Donors with the −819 TT or CT genotypes produced significantly less IL-10 in response to stimulation with high doses of *M. leprae* than did individuals with the CC genotype (225).

Elevated IL-10 production in individuals with the −819T SNP is a biologically plausible mechanism to account for enhanced leprosy susceptibility but leads to the prediction that this SNP would be enriched in MB rather than PB leprosy. Consistent with this expectation, elevated IL-10 production has been associated with MB or lepromatous forms of leprosy in clinical studies (199, 341). In the genetic association studies reviewed here, one group reported an association of −819T with MB leprosy (185), and another reported an association with PB leprosy (262). One potential explanation for these conflicting data could be that "distal" promoter SNPs closer to the 5′ end of the promoter than −819T may be the actual regulatory SNPs for IL-10 production (110).

In summary, the majority of studies of the *IL10* promoter SNP C−819T support a role for its association with leprosy susceptibility, and functional studies of this SNP in human primary cells suggest that it mediates IL-10 production in response to *M. leprae*. However, there is no consistent evidence that the C−819T SNP is associated with any particular form of leprosy. There is suggestive evidence that the *IL10* SNP C−592A alters leprosy risk, with significance found in one study (185) and a consistent trend found in another study (93). For the *IL10* polymorphisms T−3575A, G−2849A,

C−2763A, and A−1082G, different haplotype combinations have been studied for different ethnic groups, and the data are difficult to evaluate.

***IFNG.*** Gamma interferon (IFN-γ) is a prototypic Th1 cytokine produced by activated $CD4^+$ T cells or $CD8^+$ T cells that is essential for the effective control of intracellular pathogens. IFN-γ from T cells stimulates a mycobactericidal response in macrophages involving the production of NO and other reactive species (94). IFN-γ produced by dendritic cells, macrophages, and NK cells also upregulates the expression of the signaling subunit of the IL-12 receptor on T cells, allowing T cells to respond to IL-12 from innate immune cells, undergo Th1 differentiation, and produce additional IFN-γ (130, 310). Mice deficient in IFN-γ develop disseminated *M. tuberculosis* after aerosol or intravenous challenge (63, 95). Similarly, in an experimental leprosy infection model using mouse footpads, macrophages from heavily infected tissue are refractory to gamma interferon activation and fail to kill unrelated intracellular pathogens or to produce normal levels of superoxide (160).

Gamma interferon gene (*IFNG*) polymorphisms have been extensively investigated in tuberculosis association studies, and several common SNPs are associated with TB susceptibility (62, 99, 325). The *IFNG* gene contains a microsatellite polymorphism in intron 1 with a variable number of CA repeats. Pravica and coworkers have shown that certain alleles of this MS repeat are associated with elevated levels of IFN-γ production in healthy individuals (231). Seven alleles at the intron 1 MS polymorphic site were investigated in an association study of 192 leprosy patients and 196 controls (248). Although no allele was individually associated with an altered risk of leprosy or leprosy subtypes, there was a significant difference in the distribution of short versus long CA repeats among tuberculoid leprosy patients ($P = 0.013$) compared to controls. In addition, when individuals were divided into groups of those with longer alleles and those with shorter alleles, a significantly higher percentage of leprosy patients had the longer alleles (17.1% versus 6.5%; $P = 0.01$) (248). Another *IFNG* intron 1 polymorphism, T874A, had no association with leprosy in Malawi (93).

## Transport Molecules

***SLC11A1.*** The solute carrier family 11 member 1 gene (*SLC11A1*), also known as *NRAMP1* (natural resistance-associated macrophage protein 1), was first described as a gene known as *Ity/Lsh/Bcg* that controlled the susceptibility of inbred mice to intracellular pathogens, including *M. leprae*, *Mycobacterium bovis* (BCG), *Leishmania donovani*, and *Salmonella enterica* serovar Typhimurium (41, 42, 46, 226, 227, 286, 287). *SC11A1* has since been shown to have diverse effects on macrophage function, but the mechanism by which this gene regulates the killing of intracellular pathogens remains unsettled. Ity/Lsh/Bcg has been shown to control macrophage activation and to reside in the endosome and lysosome, where it functions as an iron transporter (285, 288). SLC11A1 removes iron essential for the survival of intracellular bacteria from the phagolysosome, where these organisms reside, into the cytoplasm (32). Mice with a mutation in Nramp1 are also deficient in other aspects of innate immune function, including antigen presentation, the oxidative burst, NOS expression and NO production, TNF production, and IL-1β production. These diverse effects may or may not be linked to iron and free-radical metabolism (32). In addition, the adaptive immune phenotype of NRAMP-mutated mice is biased toward Th2, rather than Th1, T-cell responses (32). An *SLC11A1* promoter polymorphism has also been associated with increased susceptibility to tuberculosis in two different studies (25, 31).

Meisner and colleagues studied several *SLC11A1* variants in 273 (181 MB and 92 PB) leprosy patients and 201 controls in Mali (191). A 4-allele CA microsatellite in the 5′ region of the gene, an SNP in intron 4 (469 + 14 G/C), and a TGTG deletion/insertion in the 3′ UTR (1729 + 55del4) were examined. Homozygotes for the TGTG 3′ UTR deletion were much more commonly found in the PB group than in the MB group in comparison to heterozygotes (OR, 5.79; $P = 0.003$) (191). Ferreira et al. investigated the frequency of the CA (=GT) repeat promoter polymorphism in Brazil in 90 cases (45 MB and 45 PB cases) compared to 61 nonconsanguineous household contacts but found no association with PB or MB disease (89).

Two other candidate gene studies also failed to detect any associations between *SLC11A1* polymorphisms and leprosy. Vejbaesya and colleagues examined three polymorphisms in *SLC11A1*; a polymorphism in intron 4 (469 + 14G/C); a coding SNP, G1627A (D543N); and the TGTG deletion in the 3′ UTR (1729 + 55del4) in a very small study (24 MB, 13 PB, and 140 controls) and found no association with leprosy in a Thai population (321). A second study in India (107 tuberculoid versus 124 lepromatous patients) examined the 4-allelic CA repeat promoter polymorphism and several other variants and found no associations with leprosy (256).

A number of investigations of the linkage between leprosy and *SLC11A1* have been reported. Abel et al. examined the evidence for linkage between polymorphisms in *SLC11A1* and neighboring genes and leprosy in 16 Vietnamese and 4 Chinese families (2). They found evidence of linkage of both the *SLC11A1* intragenic haplotypes and the extended haplotypes (formed from SNPs in *SLC11A1* and flanking genes) with leprosy in the Vietnamese families and all families combined but not in the Chinese families. That study also looked for associations of *SLC11A1* haplotypes with leprosy among unrelated affected and unaffected parents but was not able to identify a haplotype associated with altered leprosy risk, likely due to the small sample size (2). The number of individuals with tuberculoid or lepromatous leprosy was not provided.

Subsequently, that same group used a segregation analysis to investigate genetic determinants of the Mitsuda reaction in 168 Vietnamese and Chinese families (89 lepromatous versus 159 nonlepromatous cases). Those authors found that the quantitative Mitsuda reaction is under the control of a second major gene distinct from *SLC11A1* that operates as a recessive trait (241). In a follow-up genome-wide scan to identify chromosomal regions in linkage with quantitative Mitsuda reactivity in 19 families (25 tuberculoid versus 29 lepromatous cases) in Vietnam, two regions of linkage were identified (242). One was located on chromosome 2q35 and corresponded to the *SLC11A1* locus, while the second was found on chromosome 17q21-25 and corresponded to a diverse group of immune genes. Of interest, chromosome 17q11-21 was also iden-

tified in an unrelated linkage study in Brazil (195) (see above). Other groups have reported no evidence of linkage between *SLC11A1* and the Mitsuda reaction and/or leprosy (120, 175, 254, 276).

Despite an *in vitro* biological mechanism linking *SLC11A1* to critical host defenses against mycobacteria, the *SLC11A1* genetic data overall are inconsistent with respect to the effects of specific *SLC11A1* polymorphisms, such as the TGTG 3′ UTR deletion. Nonetheless, a subset of these data derived from linkage studies (2, 241, 242) suggests that *SLC11A1* may modulate either leprosy susceptibility or the immune recognition of *M. leprae* (Mitsuda reaction) in some populations. Given the observation that *Slc11a1* mutations in mice create a bias toward Th2 immune responses (32), it is possible that human *SC11A1* polymorphisms alter susceptibility to leprosy type rather than leprosy overall. The lack of an association with *SLC11A1* in some genetic studies might then arise from a lack of power due to the failure to include enough individuals with polar disease (TT or LL).

### Tissue-Specific Markers

***LAMA2.*** Wibawa et al. investigated three polymorphisms in the coding region of the G3 domain of the laminin α-2 gene (*LAMA2*), T7809C, C7879G, and G7894A, in a small study with 53 leprosy cases and 58 controls (334). Only the T7809C variant encoded an amino acid substitution (V2587A). Genotypes for T7809C did not differ between leprosy patients and healthy contacts (defined as those with daily exposure to an individual with leprosy and presumably not family members). However, among patients with tuberculoid leprosy, 19/26 (73%) had the TC genotype, compared to 8/27 (30%) of those with lepromatous leprosy. Conversely, the TT genotype was enriched in patients with lepromatous leprosy (63%) compared to patients with tuberculoid leprosy (23.1%). Those authors noted that patients with tuberculous leprosy tended to experience peripheral nerve damage (neuritis) earlier than those with lepromatous leprosy (140) and speculated that the valine-to-alanine substitution at position 7809 in laminin α-2 allows the enhanced binding of *M. leprae*, facilitating rapid intracellular entry in hosts with the TC genotype and earlier peripheral nerve damage. The major difficulty with this hypothesis is the fact that the nerve lesions of lepromatous leprosy also contain an abundance of bacilli inside Schwann cells (272), suggesting that the peripheral nerve damage seen for tuberculoid leprosy requires more than the mere invasion of Schwann cells. It is also unclear how homozygosity versus heterozygosity at the C allele would affect the ability of laminin α-2 to bind *M. leprae*, since no functional data were presented. Nonetheless, this is an intriguing association detected in a small group of cases and controls that awaits replication in future leprosy studies.

### Innate Immune Effector Molecules and Serum Proteins

***LTA4H.*** Leukotriene $A_4$ hydrolase ($LTA_4H$) is an enzyme that converts leukotriene $A_4$ ($LTA_4$) into the proinflammatory leukotriene $B_4$ ($LTB_4$). $LTB_4$ serves as a potent leukocyte chemoattractant and promotes the production of TNF (100, 111), a cytokine critical to *M. tuberculosis* control. $LTA_4$ production is closely tied to the activation of the eicosanoid pathway, whereas $LTA_4H$ expression is fairly ubiquitous (reviewed in reference 259). Interestingly, the chemical inhibition of $LTA_4H$ diverts the pathway toward an alternative $LTA_4$ product, the anti-inflammatory lipoxin $A_4$ ($LXA_4$) (244), suggesting that the regulation of the pro- and anti-inflammatory effects of this pathway may be $LTA_4H$ dependent (57, 74). In mice, infection with virulent *M. tuberculosis* strain H37Rv is associated with higher levels of $LXA_4$ than an attenuated strain and promotes necrosis in an $LXA_4$-dependent manner (57, 74). Mice deficient in 5-lipooxygenase are unable to make $LXA_4$ and are resistant to *M. tuberculosis* infection (57).

In an unbiased genetic screen for susceptibility to *Mycobacterium marinum* in zebrafish, we identified *lta4h* as a hypersusceptible mutant (304). Additional characterization showed that increased lipoxins in these mutants blocked the $LTB_4$-induced TNF production critical for mycobacterial resistance (304). Using SNPs derived from a haplotype previously associated with altered $LTB_4$ production and risk of myocardial infarction (124), we next explored associations with a case-control study of 899 Nepalese leprosy patients. Two intronic SNPs in the $LTA_4H$ gene (*LTA4H*), rs1978331 and rs2660898, were associated with protection from multibacillary leprosy (ENL excluded) in a heterozygous model only (OR, 0.62 [$P = 0.001$] and OR, 0.70 [$P = 0.021$], respectively). The same SNPs were also associated with protection from tuberculosis in a heterozygous advantage model in a second association study in Vietnam (304).

The fact that *LTA4H* is a susceptibility locus for three distinct mycobacterial diseases (infection with *M. marinum*, *M. tuberculosis*, and *M. leprae*) in two divergent vertebrates (zebrafish and humans) is compelling evidence that this gene influences susceptibility to mycobacterial disease via a broad and common mechanism, such as the regulation of eicosanoids. The additional finding of an apparent heterozygous advantage in TB and leprosy is intriguing, since it is consistent with the hypothesis that $LTA_4H$ regulation is critical to balancing the potentially destructive effects of an unrestrained $LTB_4$-mediated inflammatory response on host tissues versus the hypersusceptibility of an unrestrained $LXA_4$-mediated response in which TNF production is blocked.

***MBL2.*** Mannose binding lectin (MBL) is a pattern recognition receptor, but unlike the TLRs, it is a soluble serum protein that binds sugar groups on bacteria. A complex containing MBL, MASP-I (mannose binding lectin-associated serine protease I), and MASP-II bound to a pathogen cleaves C2 and C4, leading to complement activation and opsonization (136). MBL may also cooperate with TLR2 in pathogen recognition (137). Baseline levels of MBL can vary between individuals by 2 to 3 logs, and lower levels have been associated with heightened susceptibility to extracellular pathogens, such as *Streptococcus pneumoniae* and *Neisseria meningitidis* (78, 298). However, variation in response to infection is minimal, perhaps suggesting that baseline rather than induced MBL levels influence host defense. Paradoxically, while lower levels of MBL are associated with susceptibility to extracellular pathogens, they may also confer resistance to intracellular pathogens like mycobacteria that rely on complement opsonization for cellular entry (290). In some studies, higher levels of MBL have been associated with an increased risk of lepromatous leprosy

(105, 112), while frank MBL deficiency (defined as serum levels <100 ng/ml or ~10-fold lower than average) is associated with protection from lepromatous leprosy (76, 105, 112). Those studies measured MBL levels in patients with active disease, an approach vulnerable to confounding if MBL levels are modulated by leprosy-associated inflammation (105, 324).

MBL deficiency was previously correlated with homozygosity or compound heterozygosity for six well-described SNPs of the *MBL2* gene: two promoter SNPs (at positions −550 [*H*/*L*] and −221 [*Y*/*X*]), a 5′ untranslated region SNP (position +4 [*P*/*Q*]), and three nonsynonymous SNPs in exon 1 (allele *D*, R52C; allele *B*, G54D; and allele *C*, G57E) (106). These loci are in strong linkage disequilibrium, resulting in only seven common haplotypes from combinations of these six alleles (71, 76, 106, 136).

To date, one of two studies has reported an association between *MBL2* gene polymorphisms and clinical leprosy (71). de Messias-Reason and colleagues investigated haplotypes of the three upstream polymorphisms (*H*/*L*, *Y*/*X*, and *P*/*Q*) and the exon 1 polymorphisms (*D*, *B*, *C*, or *A* [wild type]) in 264 leprosy cases and 214 controls in Brazil (71). Haplotypes were identified by the direct sequencing of a single PCR product covering all the variant alleles. In a subset of individuals, MBL levels were measured, allowing the correlation of genotypes with MBL expression. Three haplotypes were associated with higher levels of MBL (HYPA, LYPA, and LYQA). Consistent with previous reports that higher MBL expression is a risk factor for mycobacterial disease, the "high"-expressing haplotype LYPA was also more frequent in patients than in controls (OR, 2.25; $P = 0.02$, adjusted analysis). There was also a nonsignificant association of this haplotype with lepromatous and borderline leprosy (71). In a second study, Fitness et al. analyzed a single exon 1 polymorphism but found no association in Malawi (93).

The association of "high" MBL levels with increased susceptibility to leprosy observed by de Messias-Reason et al. was previously reported (76, 106). What is novel in this study is the strong and direct association of specific MBL haplotypes with altered leprosy susceptibility, where previous studies reported either associations of haplotypes with MBL levels or MBL levels with leprosy only.

***FCN2*.** The ficolin-2 (also known as "L ficolin") gene (*FCN2*) encodes a soluble receptor with structural resemblance to MBL that binds to pathogen molecular motifs (PAMPs), such as lipoteichoic acid, acetyl groups, peptidoglycan, and lipopolysaccharide, and enhances opsonization and phagocytosis of microbes (133, 161). Three promoter polymorphisms of *FCN2* have been associated with alterations in levels of circulating ficolin-2, A−986G, G−602A, and A−4G (132). In addition, a fourth polymorphism in exon 8, G6424T (A258S) has been shown to have greater binding capacity for the *N*-acetylglucosamine (GlcNAC) motif in peptidoglycan than wild-type ficolin-2 and to be associated with lower levels of protein (126, 132, 210).

de Messias-Reason and colleagues investigated *FCN2* haplotypes in 158 individuals with leprosy in southern Brazil compared to 210 matched controls (70). A haplotype containing the −986A, −602G, and −4A polymorphisms was associated with a significant decrease in the risk for leprosy (OR, 0.13; $P < 0.013$, adjusted analysis) (70). In addition, when the −6424G allele was included, the resultant haplotype, AGAG, was also associated with a significantly reduced risk of leprosy (OR, 0.10; $P < 0.011$, adjusted analysis). Preceding functional studies by another group showed that the AGAG haplotype is associated with normal circulating levels of ficolin-2, while the GGAT and GGAG haplotypes are associated with lower levels of ficolin-2 (210). de Messias-Reason et al. therefore proposed that the mechanism for reduced susceptibility to leprosy in carriers of the AGA or AGAG haplotype in this Brazilian population is due to normal, as opposed to low, levels of the ficolin-2 protein. An additional mechanism conferred by the inclusion of the +6424G allele in the AGAG haplotype may be normal, as opposed to reduced, binding activity of ficolin-2 to a specific PAMP on *M. leprae*.

### Other Candidate Gene Studies

**Miscellaneous candidate genes.** A number of other candidate genes not discussed above have reported associations with leprosy (Table 1). These genes include *DEFB1*, encoding β-defensin 1 (230); *MICA* and *MICB* (307, 331), *KIR* (killer immunoglobulin-like receptor) (97); IL-12 subunit p40 (*IL12B*) (14, 207); IL-12 receptor β2 (*IL12RB2*) (218); complement receptor 1 (*CR1*) (93); and a number of complement factors (*C2*, *C3*, *C4A*, *C4B*, and *CFB* [also known as properdin]) (4, 15, 69, 83, 114, 252, 294). A number of complement factor polymorphisms were investigated in the 1970s and 1980s in small groups of patients using older techniques (e.g., migration of DNA fragments on electrophoretic gels) to identify genetic variants (4, 15, 69, 83, 114, 252, 294). *C2*, *C4*, and *CFB* are located on chromosome 6 in close linkage to *HLA-B* loci (229). Those early studies did not adequately address the possible effects of linkage disequilibrium with nearby MHC loci, and future studies of this region will need to address the potential confounding impact of LD with MHC variants.

**Genes with insufficient data to assess.** A number of genes and polymorphisms have been analyzed in single studies with very small sample sizes or using a control population that is not in HWE for the SNP of interest. Due to the limited amount of data on these genes, it is difficult to assess these findings with any certainty. These genes include procollagen IIIα1 (*COL3A*) (one study with 26 patients and 14 controls) (155), heat shock protein A1A (*HSPA1A* [formerly *HSP70-1*]) (one study with 49 patients and 38 controls) (235), transporter associated with antigen processing 2 (*TAP2*) (one study with 57 patients and 40 controls) (236), beta-2 glycoprotein I (*APOH*) (one study with 113 patients and 113 controls [control group not in HWE for SNP with disease association]) (45), and cytotoxic-T-lymphocyte-associated antigen (*CTLA4*) (one study with 26 patients and 14 controls) (155). In addition, there are a small number of genes for which single studies suggested no effect. For example, *DC-SIGN* (dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin), encoding a C-type lectin that binds to pathogens displaying surface carbohydrate moieties (16, 107, 318), is a promising candidate gene because of functional studies demonstrating this receptor's ability to bind *M. leprae* (23) as well as other studies showing an enrichment of DC-SIGN$^+$ macrophages and an absence of CD1b$^+$ DCs in lepromatous compared to tuberculoid lesions (164). However, *DC-SIGN* polymorphisms were recently investigated in 194

leprosy cases (109 lepromatous and 85 tuberculoid cases) and 78 controls in a Pakistani population, and no associations with leprosy overall or with polar disease were detected (23). Other genes with a reported lack of association include *BTNL2*, a candidate costimulatory molecule (one study with 72 families and 208 affected individuals; association was attributed to LD with the *HLA-DR* region) (150), IL-12 receptor β1 (*IL12RB1*) (one study with 93 patients and 94 controls) (173), and gamma interferon receptor 1 (*IFNGR1*) (one study with 93 patients and 94 controls) (173).

## GENOME-WIDE ASSOCIATION STUDIES

Genome-wide association studies (GWASs), to date, have been uncommon in infectious diseases (86, 125, 141, 153, 188, 245). These studies typically include thousands of unrelated individuals and genotype hundreds of thousands of polymorphisms spaced across the genome to look for associations with disease using commercially available platforms. Typically, a "discovery sample set" is genotyped, and areas of association are then more finely mapped with specific polymorphisms covering candidate genes in regions with the greatest association in the discovery set analysis. The advantage of such studies is the ability to combine the breadth of unbiased discovery previously unique to family-based genetic linkage studies with the resolution of associations down to the SNP level. In addition, GWASs apply to large populations, rather than family pedigrees or small case-control studies, and so are designed to capture gene effects that may be entirely missed by the narrow focus and smaller sample sizes of candidate gene studies. The disadvantage of these studies is the need for large sample sizes, driven by the need to correct for multiple comparisons for hundreds of thousands of SNPs.

Recently, the first leprosy GWAS was reported for a population in China (348). This large, seminal study relied on a discovery set of 706 patients, 1,225 controls, and three independent replication sets that together comprised 3,254 patients and 5,955 controls (348). For genotyping, Zhang and coinvestigators used an Illumina Human 610-Quad BeadChip containing 500,000 SNPs. The initial discovery analysis found strong associations within the MHC region on chromosome 6p21 at both the *HLA-B*/*HLA-C* locus (MHC class I) and the *HLA-DR-DQ* locus (MHC class II) that were independently significant; additional associations were also found for chromosome 16q21 and chromosome 13q14. Ninety-three SNPs from the 60 top non-MHC regions of association (defined as having a *P* value of $<5.0 \times 10^{-4}$) were then genotyped in the replication sets.

Interestingly, the replication studies failed to show an association with the MHC class I region but strongly confirmed the association for an SNP in the *HLA-DR-DQ* locus, rs602875 (OR, 0.67; $P = 5.35 \times 10^{-27}$, combined analysis). Among the non-MHC genes, nine SNPs in five different genes were replicated. Two polymorphisms (rs42490 and rs40457) in *RIPK2* (receptor-interacting serine-threonine kinase 2), a gene in the *NOD2* signaling pathway, were associated with protection from leprosy (OR, 0.76 [$P = 1.38 \times 10^{-16}$] and OR, 0.77 [$P = 1.34 \times 10^{-12}$], respectively [combined analysis]). SNP rs42490 was more strongly associated with MB leprosy than PB leprosy. Two SNPs in the *NOD2* region (rs9302752 and rs7194886) lying in the intergenic region between *NOD2* and its 5′ upstream neighbor, *SNX20*, were both associated with elevated leprosy risk (OR of 1.59 [$P = 3.77 \times 10^{-40}$] and OR of 1.63 [$P = 1.77 \times 10^{-30}$], respectively [combined analysis]). These two SNPs were more strongly associated with leprosy than two other SNPs within the *NOD2* gene, rs8057341 ($P = 5.22 \times 10^{-2}$) and rs3135499 ($P = 9.21 \times 10^{-2}$). The effect of SNP rs9302752 was also stronger for MB than PB leprosy (348). In addition, three polymorphisms (rs4574921, rs10114470, and rs6478108) in *TNFSF15* (tumor necrosis factor [ligand] superfamily member 15), two SNPS (rs3764147 and rs10507522) in *C13orf31* (chromosome 13, open reading frame 31), and two SNPs (rs9533634 and rs3088362) in *CCDC122* (coiled-coil domain containing 122) were associated with increased or decreased leprosy susceptibility (348). Those investigators also analyzed the haplotype blocks surrounding the risk-associated variants and analyzed any gene associated with this block. For all genes except for those in the MHC, only one gene was found per haplotype block.

This GWAS confirmed the previous long-standing association of the MHC class II region with leprosy risk but failed to validate the association of leprosy with the *PARK2*/*PACRG* (196, 197) and *LTA* (8) genes or the association of PB leprosy with chromosome 10p13 region (282). Notably, although those authors investigated 13 SNPs in the *PARK2*/*PACRG* regulatory region, they did not evaluate PARK2_e01(−2599) and rs1040079, the two SNPs found to capture all of the associations of the chromosome 6q25 region with leprosy risk (196). Similarly, eight SNPs in the *LTA* gene were examined, but not *LTA*+80, the SNP identified as the causative variant for *LTA*'s association with leprosy (8). In addition, the mean age at the onset of diagnosis of all participants in this study was 23.3 years. In the previous linkage study reporting an association of the *LTA* gene with leprosy, the risk was highest for patients under the age of 16 years or between the ages of 16 and 25 years (8). In the 10p13 region, more than 10 SNPs were investigated, none of which had an association with paucibacillary leprosy in the GWAS. The identity of the causative variant at this locus remains elusive. In addition, two new candidate genes of unknown function were identified: *C13orf31* and *CCDC122* (348).

Following the study by Zhang et al. in China, another group reported a second genome-wide association study for leprosy that was carried out in India and Mali (336, 337). That study used a gene-centric 50,000-SNP microarray to assess associations for >2,000 genes across the genome (10-fold-lower SNP density than the GWAS performed in China). A primary-association analysis was performed with 258 leprosy cases and 300 controls in New Delhi, India. SNPs with significant associations ($P < 1 \times 10^{-4}$) in this initial screen were investigated in two or three different replication studies: a separate case-control study in Bengal, India (220 cases and 162 controls); a TDT study in Tamil Nadu, India (161 families); and a case-control study in Mali (336, 337). In the *HLA-DRB1*/*DQA1* region, two SNPs with strong associations with leprosy susceptibility were identified (rs1071630 and rs9270650 [$P = 3.1 \times 10^{-11}$ and $4.9 \times 10^{-14}$, respectively, combined allelic analysis]) (336). In addition, the *TLR1* I602S (T1805G) SNP was strongly associated with protection from leprosy in the New Delhi and Bengal populations (OR, 0.27 to 0.40; $P = 1.3 \times 10^{-4}$ to 0.02, allelic analysis) but was borderline in the TDT study (OR, 0.61; $P = 0.09$). Nonetheless, this SNP association remained highly

significant in the combined analysis ($P = 5.7 \times 10^{-8}$) (336). This GWAS also confirmed the association of two other SNPs identified in the Chinese GWAS, rs3764147 (*C13orf31*) and rs9533634 (*CCDC122*), with leprosy susceptibility (OR, 1.59 [95% confidence interval {CI}, 1.34 to 1.89]; $P = 6.11 \times 10^{-8}$, combined analysis) and leprosy resistance (OR, 0.70 [95% CI, 0.59 to 0.82]; $P = 1.12 \times 10^{-5}$, combined analysis), respectively (337).

The finding of an association of the *TLR1* SNP T1805G (I602S) replicates previous reports of an association of this SNP with protection from leprosy or type 1 reactions (149, 198). All three studies also showed the same direction of effect, strongly supporting a role for *TLR1* in leprosy immunopathogenesis. *TLR1* has widely varying frequencies across different ethnic groups (121, 149, 336, 338). The lack of an association of *TLR1* with leprosy in the China GWAS likely stems from the very low frequency of the 602S allele in this population (1.7%) (336) and the resultant lack of power to detect associations at this locus.

For *NOD2*, in contrast to the GWAS findings in China (348), no associations with leprosy were found in the second leprosy GWAS (337). As mentioned above, we recently found associations of *NOD2* polymorphisms with leprosy in Nepal (27), consistent with data from the China study. Although the polymorphisms examined in our study and the study by Zhang et al. were mostly nonoverlapping and there is no known functional mechanism for any of these variants, these two studies support a role for the *NOD2* pathway in leprosy pathogenesis (27). The reason for the lack of an association in the Indian and Malian populations is unclear but could reflect different underlying LD (haplotype) structures in these gene regions or the presence of alternate susceptibility loci that mask or reduce the effect of *NOD2* alleles. Other associations that were not replicated in the second leprosy GWAS by Wong et al. included *LTA*, *NOD2*, *PARK2* and *PACRG*, *RIPK2*, *SLC11A1*, *TLR2*, *TLR4*, *TNFSF15*, and *VDR* (337).

## CONCLUSIONS

In this review, we have presented a detailed view of the field of leprosy genetics and commented on the quality of evidence that exists for each gene or susceptibility locus. Of the many reports of genes associated with leprosy, relatively few have been replicated in additional study populations. Among those that have been validated, genes with a potential or demonstrated biological mechanism form an even smaller subset. There are several reasons for this rather modest track record. In the first place, many of the candidate gene studies are simply underpowered to detect risk alleles of modest effect. Sufficient power to detect modest effects (OR of ~1.5) requires large sample sizes (thousands) and/or polymorphisms present at high frequencies. Linkage studies require even greater numbers to have sufficient power to uncover modest effects in complex diseases (251) and are best at detecting rare alleles with large effects (296). The effect of risk alleles could also be modified by the preponderance of certain clinical forms of leprosy in one geographic region compared to another (195, 215). If 10p13 is associated with PB leprosy exclusively, the effect may be more difficult to demonstrate in a region where MB disease predominates, for example. Second, there is likely to be a heterogeneity of genetic effects across populations. The 10p13 region is a risk factor for leprosy in India (282) but not in Brazil (195), and conversely, the *HLA* region is a risk factor for leprosy in Brazil (277) but not in India (282). This phenomenon can arise from alterations in the linkage structures of alleles between populations (population-specific linkage disequilibrium) (11), differences in the polymorphisms or genes that confer disease risk in different ethnic groups, variability in penetrance, or epistatic interactions. Third, differences in leprosy case ascertainment or categorization of leprosy type could also exist. Finally, failure to correct for population stratification between cases and controls may also confound study results.

Traditionally, common infectious diseases, such as leprosy, are thought to have a complex or polygenic pattern of inheritance. In this model, the disease trait arises out of the additive effect of multiple genes, each with a modest effect on the phenotype (one disease and many genes). Conversely, the inheritance pattern of primary immunodeficiency syndromes, such as SCID (severe combined immunodeficiency) or Bruton's agammaglobulinemia, are monogenic. Primary immunodeficiency syndromes in this traditional sense are the consequence of the Mendelian transmission of single mutations producing a severe phenotype, often with multiple infections of different microbial etiologies (one highly penetrant gene and many infections) (54, 217, 234). This view has recently been challenged by some experts in the field, who point to the narrow impact of some Mendelian mutations that unexpectedly alter susceptibility to single rather than multiple pathogens (7, 234). For example, herpes simplex encephalitis was shown to be due to rare, highly penetrant Mendelian mutations in TLR3 or Unc93B (7, 55). Could some common infectious diseases be determined by monogenic or oligogenic inheritance as well? In the case of leprosy, data from genome-wide linkage studies might suggest that rather than being a disease of complex or polygenic inheritance, susceptibility to leprosy or forms of leprosy may be controlled mostly by a few major genes (8, 196, 197, 234). However, even for this well-studied disease, some large effects from linkage studies have not been replicated in alternate populations, while candidate gene association studies have uncovered modest-risk genes, such as *NOD2*, that have not been detected by linkage studies. Further studies are needed to assess whether leprosy susceptibility is governed by oligogenic or polygenic inheritance patterns.

Which genomic regions and which genes have the best data to support a role in leprosy susceptibility? The strongest evidence from linkage analysis exists for chromosome 10p13 (two separate linkage studies, one in India and one in Vietnam) (197, 282), the *PARK2*/*PACRG* promoter region (three populations [two from Vietnam {linkage} and one from Brazil {case-control SNP association study}]) (196, 197), and chromosome 6p21 and the *LTA* gene (two populations [one from Vietnam {linkage} and one from India {case-control}]) (8). Each of these studies involved large numbers of families, sibling pairs, and/or unrelated cases and controls and contained an internal replication set. Reasonable evidence also exists for the linkage of *SLC11A1* (*NRAMP*) with the Mitsuda reaction (2, 10, 241, 242). The putative disease-associated SNPs have been identified for *PARK2*/*PACRG* [PARK2_e01(−2599) and rs1040079] and for chromosome 6p21 (*LTA*+80) but not for

10p13. Subsequent studies of these *PARK2*/*PACRG* SNPs in alternate ethnic groups have not validated these specific variants. The *PARK2* gene encodes an E3 ubiquitin ligase, which facilities the proteosomal degradation of proteins, but was also recently reported to regulate cyclin E (319, 320). Cyclin E is a tumor suppressor protein that is normally suppressed by PARK2. The release of this negative control causes neuronal apoptosis (319), which could be a mechanism by which *M. leprae* causes nerve damage, although this is speculative.

Among the candidate gene studies, the best-quality evidence exists for *TLR1* SNP T1805G or A743G (four studies, including a GWAS) (149, 198, 271, 336), the *NOD2* gene (two positive studies, including data from a GWAS, with associations in nonoverlapping SNPs) (27, 337, 348), and the *IL10* promoter SNP C−819T (five studies, including one meta-analysis) (93, 96, 185, 206, 225). In addition, the first leprosy GWAS (348) identified SNPs in two genes of unknown function, *CCDC122* (rs9533634) and *C13orf31* (rs3764147) (348), which were validated in a second GWAS (337). Functionally, the *TLR1* variant T1805G has been shown to regulate the surface expression of TLR1 (149), which is a major receptor for *M. leprae*, and to regulate the recognition of *M. leprae* by human monocytes (198). The *IL10* promoter SNP −819T has been associated with decreased IL-10 levels (225), although it remains unclear if this mechanism is related to the SNP's variable association with leprosy type. The mechanisms underlying *NOD2* polymorphisms are not known.

Over the last decade there has been an enormous expansion in both the methodology and affordable technology available to perform sophisticated genetic studies of disease associations. It is now financially and technically possible to scrutinize over 1 million SNPs in thousands of samples and identify allelic variants associated with disease. Our understanding of the genetic risk factors for specific infections is quickly expanding, to cover more populations and more genes, and deepening, to discover more SNPs per gene and better understand how risk alleles might be modified, appear, or disappear in different populations. A small but growing number of genome-wide association studies have been carried out for infectious diseases, including malaria (141), HIV (86, 125), Creutzfeldt-Jakob disease (188), hepatitis B and C (153, 245), and now leprosy (336, 337, 348). Information on new types of genetic variation, including copy number variants, is just emerging. These new tools promise an era of rapid acquisition of data describing genetic variation in diverse populations and the elaboration of fresh theories of infectious pathogenesis, novel means of immunomodulation, and improvements in drug design. In the case of leprosy and tuberculosis, diseases for which our pharmaceutical armamentarium is underdeveloped, such new insights from the human genome could make large contributions to global health.

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