The Complexity of the Host Genetic Contribution to the Human Response to *Mycobacterium leprae*

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Introduction

Prior to the advent of microbiology, infectious diseases had no known etiology and therefore were often qualified as hereditary. With the advances in medicine, the key role of microbes in the etiology of infectious diseases was recognized. However, with the description of latent infections it became clear that in addition to pathogens, unknown host factors are required to establish disease. We know now that a substantial proportion of factors that make a host vulnerable to infectious disease are germline encoded. While much remains to be discovered, in leprosy the role of host genetic factors in disease susceptibility has made remarkable advances over the last 15 years. Genetic epidemiology methods ranging from twin studies to genome wide association studies (GWAS) have helped to unravel the host genetic contribution to leprosy susceptibility. Variants of genes involved in both innate and adaptive immune responses have been identified as key mediators in different stages of leprosy pathogenesis. Here, we present a summary of genetic mediators for leprosy and leprosy-related disease manifestations that have been implicated in susceptibility in multiple studies.

LEPROSY: AN INFECTIOUS DISEASE, A HEREDITARY DISEASE, OR BOTH?

Leprosy is a dermato-neurological infectious disease caused by the intracellular parasite *Mycobacterium leprae* (1). However, this characterization was not always the consensus among scientists. In the mid-nineteenth century, it was believed that leprosy was in truth a hereditary disease that could only be transmitted among family members. The Norwegian physician Daniel Cornelius Danielssen proposed the heredity concept of leprosy in 1857 in the book entitled *Om spedalskhed* (On leprosy). Danielssen implied that leprosy was a congenital dysplasia not caused by a pathogen (2). It was Danielssen's son-in-law Gerhard Armauer Hansen who identified *M. leprae* as the cause of leprosy in 1873 (1). Leprosy is indeed an infectious disease; however, Danielssen also was correct regarding the role of heredity in leprosy. Heredity is an allusion to a genetic component impacting disease outcome. Human genetics was still in its infancy in Danielssen's era, and the limited knowledge about the genetic control of complex traits severely hampered studies of heredity in leprosy (3). It was only in the 1960s that epidemiological studies accumulated convincing data in support of a genetic component in leprosy susceptibility.

THE HEREDITY IN LEPROSY SUPPORTED BY GENETIC EPIDEMIOLOGY DATA

Prior to the advent of DNA-based genetics, epidemiological studies based on observational data and prediction models inferred that there was a genetic component in susceptibility to leprosy. For example, twin studies showed a strong contribution of host genetics to leprosy *per se* susceptibility and clinical leprosy subtype (4, 5). In two independent twin studies, concordance of leprosy in monozygotic twins was 82.6% and 59.7%, while concordance in dizygotic twins was 16.7% and 20.0%, respectively (4, 5). Among the leprosy-affected pairs of monozygotic twins, concordance for leprosy subtype was larger than 85% in both studies (4, 5). Since monozygotic twins share the same germline, while dizygotic twins share only a proportion of their genetic material, these results provided strong support for an important role of host genetics in leprosy. Similarly, analysis of the segregation pattern of leprosy in multiplex families of distinct ethnic background including Caribbean, Brazilian, Vietnamese, and Thai inferred that a genetic component in leprosy susceptibility existed. This approach, termed complex segregation analysis (CSA), estimates the contribution of environmental, familial, and genetic factors that best explain the disease segregation pattern. If a genetic component is inferred, the model of inheritance, the penetrance, and the frequency of the genetic component can also be estimated. Most of the CSA consistently detected evidence of a major gene impacting on leprosy susceptibility with a background of additional genes with milder effects, although there was no consensus for the mode of major gene inheritance (6, 7, 8, 9, 10, 11, 12, 13). Twin studies and CSA provided the rationale for molecular investigations in search of the genetic component in leprosy.

Genetic Control of Host Responses to *M. leprae* at Different Stages of Leprosy Pathogenesis

Leprosy is a complex disease with multiple factors influencing the outcome of exposure to *M. leprae*. Undoubtedly, intensity and length of exposure to *M. leprae* are central for leprosy pathogenesis, albeit little is known about this key step due to our inability to cultivate *M. leprae* in vitro. Following exposure, a combination of environmental and host genetic factors discriminates those who will become infected without clinical signs from those who will progress to clinical disease and commits a subset of patients to adverse immune reactions. In a scenario where environmental factors intervene at all phases of the human/*M. leprae* interaction, the impact of host genetics can be dissected in different stages (Figure 1).

INNATE RESISTANCE

The majority of people exposed to *M. leprae* are innately resistant to clinical leprosy. This conclusion was derived from epidemiological studies in which more than 90% of household contacts of multibacillary leprosy cases did not progress to clinical disease (Figure 1) (14, 15, 16). However, in contrast to tuberculosis (TB), where latent infection is deduced from a positive Tuberculin Skin Test (TST) or by Interferon Gamma Release Assay (IGRA), in leprosy no biological assay for latent infection is available. Therefore, among those who are resistant to clinical disease it is not possible to identify those who are susceptible to infection, and it is not known if humans do become latently infected with *M. leprae*. However, it is likely that innate resistance to infection may account for much of the genetic contribution to leprosy. Possible mechanisms of innate resistance to infection in leprosy are unknown but may represent resistance to host cell infection or rapid clearance of phagocytosed bacilli before the establishment of latent infection (Figure 1). Alternatively, it is possible that a large number of exposed humans are latently infected with *M. leprae* but only few ever progress to clinical disease. There are several notable examples of the inability to invade host cells in other infectious diseases. In HIV, a deletion in the CCR5 gene causes a knockout and obstructs the route of viral invasion (17). In malaria, cell-specific knockouts for the Duffy blood group receptors (FyFy) mediate innate resistance to *Plasmodium vivax* infection (18, 19). The possibility that infection resistance is mediated by early bacterial clearance or the presence of adverse conditions that lead to a decreased ability of parasite survival is supported by TB and HIV infection (Figure 1). In HIV, for example, individual carriers of a combination of KIRDL1/HLA-B*57 present superior and earlier viral clearance (20). In malaria, patients heterozygous for the sickle-cell mutation present premature erytosis of plasmodium infected cells and the accelerated apoptosis delays parasitemia, favoring bacterial clearance (21).

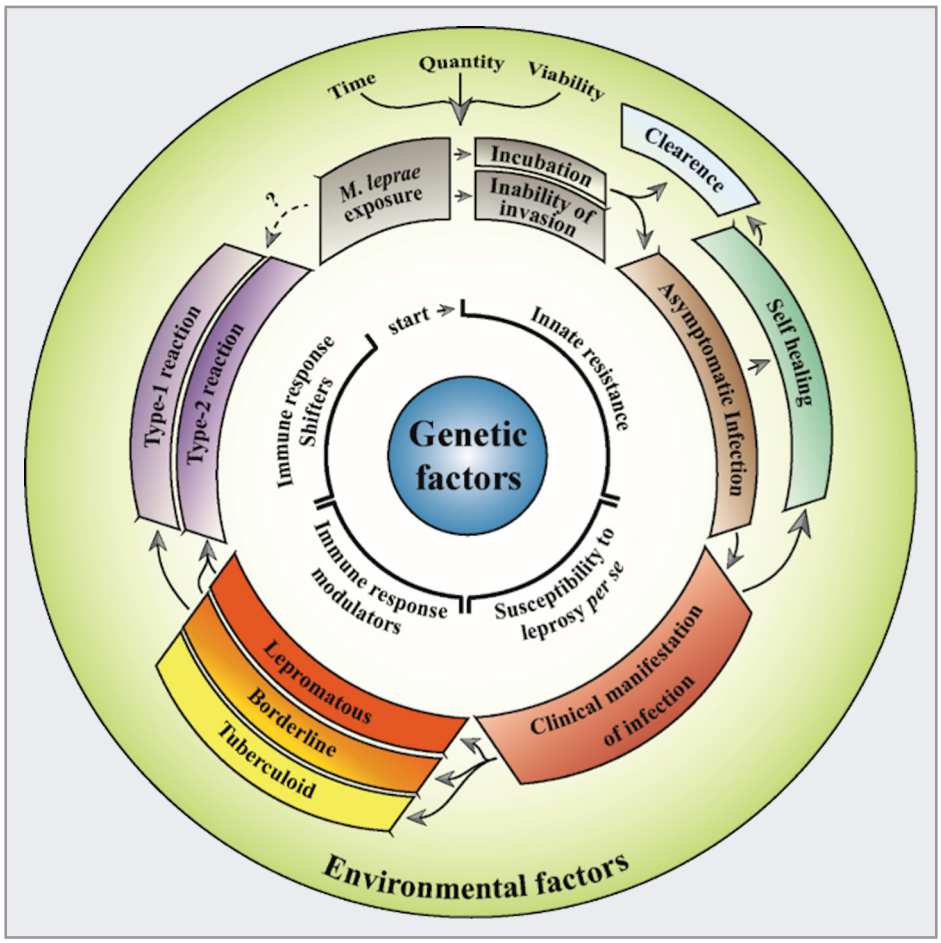

FIG 1 The stages of leprosy pathogenesis and the corresponding phenotypes employed for genetic studies.

Genetic factor may contribute to different stages of leprosy pathogenesis ranging from innate infection resistance to variants modulating host pathological immune responses. Given sufficient exposure to M. leprae, an individual may progress from exposure to infection or present an early resistance phenotype. Innate resistance may be defined by a genetic profile that may impair the ability of bacterial invasion or favor a more efficient bacterial clearance. Persons who are destined to develop clinical leprosy will advance to a pre-clinical stage common to all forms of leprosy that is termed leprosy per se. The genetic factors that contribute to leprosy per se may be different from those that impact the clinical immunological response to M. leprae. Patients with clinical forms of leprosy display a variety of immune responses ranging from a strong cellular immune response (tuberculoid) to a strong humoral immune response (lepromatous). Yet, the majority of leprosy patients display a balance of cellular and humoral responses and are classified as borderline leprosy cases. The specifics of the host immune response are controlled by host genetic variants that modulate the cytokine profile in responses to M. leprae. Certain leprosy patients may experience excessive inflammatory responses known as leprosy

reactions. There are two major types of leprosy reaction Type-1 reaction and Type-2 reaction. Both are characterized by a delayed activation or exacerbation of cellular immune responses which are at least in part controlled by host genetic factors.

CLINICAL DISEASE AND LEPROSY SUBTYPES

Leprosy *per se*, which is leprosy irrespective of the clinical subtype, is a widely used phenotype (Figure 1). It is not known what stage of leprosy pathogenesis is captured by the *per se* phenotype. Given that all clinical subtypes are governed by the *per se* definition, the most parsimonious explanation is that leprosy *per se* reflects an early stage of non-symptomatic pathogenesis. If this explanation is correct, leprosy *per se* genes and mechanisms would determine the transition from a latent infection to clinical disease (Figure 1). This interpretation is supported by reports of high rates of self-healing leprosy in the absence of antibiotic intervention (Figure 1) (22, 23). Self-healing is most pronounced if clinical symptoms are mild and has been reported to occur in up to 70% of non-lepromatous cases, demonstrating the continuum of leprosy pathogenesis (22, 23, 24). Hence, *per-se* genes likely impact on different stages of latent infection and, as the infection progresses and manifests itself as clinical disease, different sets of genes impact on leprosy subtype. Patients with self-healing—before or after the emergence of clinical symptoms—could be a reservoir for ongoing transmission of leprosy. However, independently of late bacterial clearance or not, patients suffering from leprosy *per se* share a common genetic component that is fundamental for the clinical manifestation of disease (Figure 1).

Leprosy presents a good opportunity to evaluate the host genetic contribution to clinical symptoms of an infectious disease, since *M. leprae* is essentially monoclonal (Figure 1) (25). Hence, susceptibility is mainly influenced by environmental factors and by host genetics. Following the first signs of clinical infection, each leprosy patient will develop a particular adaptive immune response. Some patients have the capability to develop granuloma and contain the infection. These patients are characterized as tuberculoid and present a cytokine profile of an effective cellular immune response (Figure 1). On the opposite side of the spectrum are patients with lepromatous leprosy, who are permissive for extensive bacillary replication. These patients develop a humoral immune response that is not effective for bacterial containment (Figure 1). The majority of leprosy cases will present a balance between cellular and humoral immune responses and are commonly referred to as borderline leprosy patients (Figure 1). The host genetic control of different leprosy subtypes is a largely understudied area of leprosy pathogenesis (26).

ADVERSE IMMUNE RESPONSES

An interesting aspect of leprosy pathogenesis is that protective immune reactions can be clearly separated from those that cause host tissue damage. In leprosy, up to 50% of patients develop excessive inflammatory responses know as leprosy reactions (LR) (27). LR afflict leprosy patients during the course of the disease or even after microbiological cure and are a major cause of tissue damage and disabilities (28, 29). There are two major types of LR: the type-1 reactions (T1R) and

the type-2 reactions (T2R). T1R are more frequent and mostly affect individuals classified in the borderline spectrum of leprosy (28). T2R affect only patients of the lepromatous and borderline subtype who display strong humoral immune responses. LR are characterized by a shift towards a cell-mediated immune response with a strong and rapid boost in TNF and IFN-γ production (30). LR present a unique opportunity to study the modulatory factors in the host immune response to pathogens. A dysregulated pro-inflammatory response to a pathogen is an immune characteristic in Crohn's disease (CD) and a main cause of tissue damage in dengue (31, 32, 33, 34).

Genetic Approaches Applied to the Study of Human Susceptibility to Leprosy

Different approaches have been applied to identify the host genetic factors uncovered by epidemiological studies and CSA. From a candidate gene approach to hypothesis-free genome wide testing, multiple factors have been connected with clinical disease or subtypes. The research efforts since the beginning of the century have resulted in a better picture of the host contribution to disease outcome (Figure 2). Nevertheless, we are still far from explaining the strong genetic component reported by twin studies.

CANDIDATE GENE APPROACHES

The candidate gene approach was the first strategy used to describe the molecular identity of the genetic component in leprosy. It is a powerful strategy if the biological process contributing to disease pathogenesis is well known. Focusing on genes most likely to be relevant to a disease reduces the risk of false positive findings due to multiple comparisons. There are several examples in leprosy in which candidate gene associations have been successfully replicated in independent populations.

Studies of the ABO system

The first reports of a specific gene associated with leprosy pathogenesis focused on the ABO blood type, with many studies performed since the 1920s (35, 36). The ABO gene is located on chromosome region 9q34.2, where amino acid changes in exons 6 and 7 differentiate the AB blood groups while the O blood group represents a frame shift mutation. Individual studies of the ABO system in leprosy have reported no correlation of blood types and disease susceptibility (37, 38, 39). In 1967, compiled information of 27 independent population from 14 countries indicated

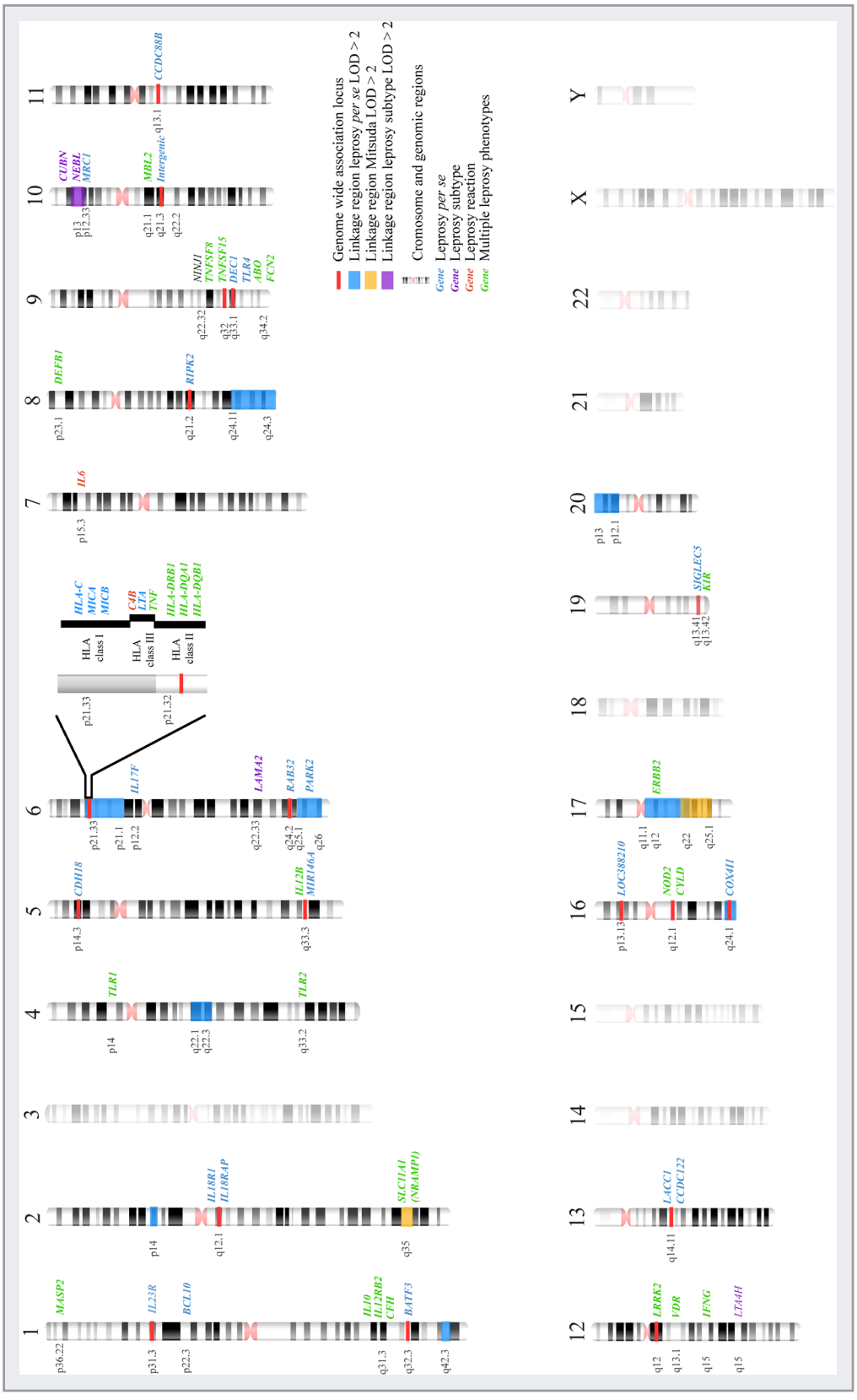

FIG 2 Ideogram presenting the genomic regions and genes reported in linkage of association with leprosy phenotypes.

no correlation of ABO and Rh with leprosy *per se* or its clinical forms (35). Subsequent work employing an alternative statistical approach and increased sample size detected a loose association between leprosy *per se* and ABO blood groups (36). Individuals with the A blood type were more susceptible to leprosy *per se* in a dominant model than the B or O blood types. Moreover, the O blood type was more frequent among lepromatous cases (36, 40, 41, 42). The effect of the ABO system in leprosy is likely very subtle, since almost half a million samples were needed to capture the weak association signal with the disease. Therefore, the ABO gene explains very little of the genetic susceptibility to leprosy.

The Toll-like receptor family

The Toll-like receptors (TLRs) are an important class of pattern recognition receptors (PRP) involved in the host defense against a broad spectrum of pathogens (43). In leprosy, cell surface expressed heterodimers of TLR1, TLR2, and TLR6 mediate cell activation by recognizing *M. leprae* antigen (44, 45). Two amino acid substitutions in TLR1, I602S (rs5743618) and N248S (rs4833095), were associated with leprosy phenotypes (46, 47, 48). The 602S allele of TLR1 was associated with protection for leprosy *per se* in Indian and Turkish populations, but this association was not validated in Brazilian and Chinese populations (46, 47, 49). Moreover, the 602S allele was associated with protection from T1R in Nepalese (48). TLR1 carrying the 602S allele inhibits surface trafficking of the TLR1/TLR2 dimer, resulting in hypo-responsiveness to *Mycobacteria* (50, 51). The 248S allele of TLR1 was associated with susceptibility to leprosy *per se* in independent samples from Brazil and a sample from Bangladesh (47, 52). The S248 allele alters the electrostatic surface potential of TLR1, influencing protein interaction affinity (47). Both I602S and S248N polymorphisms have been associated with susceptibility to intracellular pathogens, suggesting an important role for these two variants that is not exclusive to leprosy (53, 54).

Variants in TLR2 and TLR4 have been associated with leprosy phenotypes. A synonymous amino acid substitution N299N (rs3804099) and a microsatellite in the TLR2 gene region were associated with T1R in Ethiopians (55). In leprosy lesions, TLR2 was shown to mediate in vivo apoptosis of Schwann cells contributing to nerve injury, which is a hallmark of T1R (56). TLR4 is mostly known as a lipopolysaccharides (LPS) receptor but it can also bind other microbial molecules. Two TLR4 missense polymorphisms, D299G (rs4986790) and T399I (rs4986791), were associated with leprosy *per se* (57, 58). The 299G and 399I alleles of TLR4 were risk factors for leprosy *per se* in Ethiopians and Indians (57, 58).

Interleukins

Interleukins are secreted by leukocytes and play an important role in cell-cell communication and in the modulation of host defense against infection (59). In leprosy, interleukins are essential for an effective cellular immune response and to develop infectious granuloma to contain *M. leprae*

dissemination (60). A key modulatory cytokine in the cellular immune response is IL12. The IL12 cytokine is formed by two subunits, 12p35 and 12p40, that are encoded by the IL12A and IL12B genes, respectively. IL12 exerts its function through the interaction with its receptor, which consists of two subunits encoded by the IL12RB1 and IL12RB2 genes. The IL12B gene is expressed by macrophages to induce the differentiation of Th1 cells (61). Variants near the IL12B gene have been associated with leprosy phenotypes in multiple populations. A variant in the IL12B 3' UTR was associated with a risk for leprosy *per se* and TB in India and with leprosy subtypes in Mexico (62, 63). Common variants located in the vicinity of the IL12B gene were also associated with leprosy *per se* and multibacillary leprosy in Indian and Chinese patients (64, 65, 66). Variants in the promoter region of the IL12RB2 gene were associated with a leprosy subtype in a Japanese population but not in a Brazilian study (67, 68). No association was reported for the IL12RB1 gene in leprosy (69). The 12p40 subunit is part of IL23 and therefore interacts with the IL23 receptor. Copy number variants in the IL23R gene region have been shown to be associated with a leprosy clinical subtype (65).

IL10 is the most studied interleukin in leprosy (70). IL10 inhibits the production of pro-inflammatory cytokines by effector cells such as macrophages and Th1 cells. IL10 activates the humoral immune response and induces antibody production in leprosy patients. The SNP rs1800890 located at -819 bases upstream to the IL10 transcription starting site (TSS) was associated with leprosy *per se* in multiple populations (71). The most common association with leprosy *per se* and clinical subtypes was the haplotype containing the three TSS polymorphisms at positions -1082 (1800896), -819 (rs1800871), and -592 (rs1800872) in Brazilian, Colombian, and Indian populations (71, 72, 73, 74, 75). A recent meta-analysis of ten studies of the IL10 gene in leprosy phenotypes confirmed the association of the TSS promoter variants with leprosy *per se* (70). Interestingly, a meta-analysis of TB cases also reported the haplotype of the -819 and -592 SNPs associated with susceptibility to TB in the same direction as observed in leprosy *per se*. However, the association was limited to individuals with an Asian ethnic background (76, 77). An IL10 promoter haplotype—which included SNPs associated with leprosy—impacted on IL10 expression, providing a possible mechanism for the modulation of IL10 function by genetic risk factors (78).

Other associations of interleukin genes have been reported for leprosy phenotypes. A study in an Indian population detected an association of the IL17F missense H161R polymorphism (rs763780) with leprosy *per se* (79). However, a subsequent study in a Mexican population failed to validate the IL17F association (80). A Brazilian study focused on LR showed the independent association of two IL6 polymorphisms with T2R (81). The IL6 variants -174 (rs1800795) and +6804 (rs2069840) associated with T2R influenced IL6 gene expression and were correlated with circulation levels of IL6, respectively (81, 82). Variants near the IL18 receptors have been associated with leprosy *per se* in Chinese patients (66). The IL18RAP and IL18R1 genes are clustered with the IL1RL1 gene on chromosomal region 2q12.1. The associated signal observed in the Chinese population extended across these three genes and did not differentiate which gene(s) in the locus was (were) the cause of association with leprosy *per se*.

The lectin pathway

The mannose binding lectin (MBL) is involved in pathogen recognition and clearance by the innate immune response (83). A haplotype overlapping the MBL2 gene (encoding MBL) was associated with susceptibility to leprosy *per se* and clinical subtypes in Brazilian and Chinese populations (84, 85). Moreover, association of the missense G54D polymorphism (rs1800450) in MBL2 exon 1 was validated for a leprosy clinical subtype in a population sample from Nepal but not in an independent Brazilian sample (86, 87). MBL activates the complement pathway by co-opting MBL-associated serine proteases (MASPs) (88). Two genes, MASP1 and MASP2, encode MASP proteins. Five polymorphisms near the MASP2 gene were associated with susceptibility to leprosy *per se* in a Brazilian sample (89). The complex formed by MBL with MASP1 and MASP2 can cleave complement proteins C2 and C4 and induce pathogen opsonisation (88). Alleles of the C4B gene were associated with lepromatous leprosy and susceptibility to T2R (90). The ficulin-2 protein encoded by the FCN2 gene is a complement activating lectin that forms a complex with MASPs (91). Variants near the promoter region of the FCN2 gene have been associated with leprosy *per se* and clinical subtypes in Brazilian and Chinese populations (85, 92). Finally, variants near the CFH gene, encoding the complement regulating factor H, were associated with leprosy in a Chinese population (85). Taken together, these results demonstrate the participation of the lectin pathway in leprosy *per se* and clinical subtype susceptibility.

Additional candidate genes

The active form of vitamin D modulates innate and adaptive immune responses (93). The VDR gene encodes the vitamin D receptor and is expressed by macrophages in response to TLR1/2 stimulation (94). Two functional VDR polymorphisms were associated with leprosy phenotypes. A VDR synonymous SNP I352I (rs731236 alias Taq1) located in a splicing site was associated with leprosy subtypes and granuloma formation (95, 96). A missense M1T polymorphism (rs2228570 alias Fok1) at the first amino acid of a VDR isoform showed a trend for association with T1R (86). Interestingly, VDR expression has been associated with progression to leprosy reaction (97). A forward genetic screen in zebrafish identified the lta4h gene as a hyper susceptibility factor (98). Two non-coding SNPs (rs1978331 and rs2660898) at the human LTA4H gene were associated with multibacillary leprosy in a population from Nepal (98). Due to the role of beta-defensin 1 in epithelial innate immunity, a study evaluated the association of the DEFB1 gene in leprosy. The DEFB1 5' UTR variant rs1800972 was associated with leprosy *per se* and a clinical subtype in a Mexican population (99). *M. leprae* was shown to invade myelinating Schwann cells by recognizing and binding laminin alpha 2, which in humans is encoded by the LAMA2 gene (100). A missense V2587A variant (rs2229848) of LAMA2 was associated with a leprosy subtype in a Brazilian population (101). Type II interferon (IFN-γ) is a critical cytokine of the innate and adaptive immune response against intracellular pathogens (102). A promoter polymorphism at position +874 (rs2430561) of the IFNG gene was associated with leprosy *per se* in independent Brazilian populations (103, 104). A lower expression of BCL10 was reported in lesions of leprosy patients when compared to healthy controls (105, 106). The SNP (rs2735591) near the BCL10 gene was

associated with leprosy *per se* in three independent population samples from China (106). A common outcome in leprosy is nerve injury, which frequently leads to permanent disabilities (27). The NINJURIN1 protein encoded by the NINJ1 gene has been implicated in the cellular repair mechanism in Schwann cells after nerve injury (107). A NINJ1 missense A110D polymorphism (rs2275848) has been associated with protection from disabilities in two independent Brazilian samples (108, 109).

A newly recognized class of endogenous controllers of gene expression are named microRNAs (miRNAs). Alterations in miRNAs structure may influence their ability to exert their function properly. In leprosy, the polymorphism rs2910164 in the seed region of Pre-miR-146a encoded by the MIR146A gene has been associated with susceptibility to leprosy *per se* in independent populations from Brazil (110). Functionally, it was shown that *M. leprae* induced MIR146A expression in THP-1 cells. Moreover, nerve biopsies of leprosy cases exhibited a higher expression of MIR146A compared to nerve biopsies from pathologies not related to leprosy (110). However, there was no evidence of a direct impact of the leprosy *per se* risk variant on MIR146A activity. An independent study implicated microRNA-21 in a clinical subtype of leprosy via the vitamin D antimicrobial pathway (111).

Summary of candidate genes studies

Resistance or susceptibility to *M. leprae* invasion relies on different stages of host immunity. The first line of defense against external pathogens is provided by sentinel cells, such as macrophages and dendritic cells, of the innate immune response. These cells express PRP that belong to the toll-like receptor family and components of lectin pathways. Candidate gene approaches have helped to identify key genes in this early phase of host-pathogen interaction. Associations of TLR1, MBL2, and FCN2 with leprosy have been confirmed in independent populations, suggesting that alterations in these genes are critical to facilitate *M. leprae* invasion. In response to pathogen recognition, host sentinel cells kick-up the production of interleukins. Indeed, candidate gene approaches showed that the IL23R, IL12B, and IL17F genes are associated with leprosy susceptibility. These genes are important regulators that direct the adaptive immune response towards Th1 and Th17 cells. Patients with an efficient cellular immune response are more likely to contain *M. leprae* dissemination.

GENOME WIDE LINKAGE APPROACHES TO GENE DISCOVERY IN LEPROSY

Genome wide linkage studies (GWLS) are hypothesis-free analytical approaches that investigate the non-random transmission of a genomic region among affected individuals in a family-based approach. A series of GWLS have identified host genomic regions as likely locations of leprosy susceptibility genes. However, among the chromosomal regions identified by GWLS, only a few have led to the identification of leprosy susceptibility genes via the fine-mapping of the linked regions.

Region 2q35

The murine Slc11a1 (alias Nramp1) gene located on chromosome 1 in mice controls susceptibility to a variety of intracellular pathogens (112, 113, 114, 115). The human SLC11A1 gene has been implicated in leprosy risk by multiple studies. An extended haplotype overlapping the SLC11A1 gene was linked with leprosy *per se* in Vietnamese patients (116). A SNP located in intron 4 (rs3731865) was associated with paucibacillary leprosy in Indonesia (117). Heterozygosity for a 3' untranslated insertion/deletion of the SLC11A1 gene was a risk factor for multibacillary leprosy in Mali (118). The SLC11A1 exon 3 UTR variant -274C/T (rs2276631) was reported as associated with both T1R and T2R with opposite risk effects in Brazilians (119). Interestingly, two GWLS in Vietnamese samples linked chromosomal region 2q35, which in humans harbors the SLC11A1 gene, with the capacity to mount an in vivo granulomatous response to lepromin (a so-called Mitsuda reaction) (120, 121). Subsequent studies identified an SLC11A1 promoter variant in association with the extent of the Mitsuda reaction in Brazilians (122).

Region 10p13

The first GWLS in leprosy described the chromosomal region 10p13 in linkage with paucibacillary leprosy in an Indian sample of multiplex families (123). A subsequent GWLS in Vietnamese families confirmed the initial report (124). The linked chromosomal segment harbored the MRC1 gene. This gene encodes a mannose receptor present in macrophages and immature dendritic cells, where it is involved in phagocytosis of bacteria. Hence, the MRC1 gene was tested as a positional candidate leprosy gene. A SNP G396S (rs1926736) in exon 7 of the MRC1 gene was found to be associated with leprosy *per se* and multibacillary leprosy in Vietnamese and Brazilian, but not Chinese, patients (125, 126). Two non-coding variants of MRC1 located in intron 5 and intron 7 were associated with paucibacillary leprosy in Chinese but not Vietnamese patients (126, 127). The differences between the risk markers across studies suggest that more than one variant of MRC1 may play a role in leprosy pathogenesis. Subsequently, high density association mapping of the 10p13 region evaluated 39 genes for association with leprosy *per se* and clinical manifestation of the disease (127). In these experiments, the Cubin (CUBN) and Nebulette (NEBL) genes were found to be associated with multibacillary leprosy in two independent Vietnamese populations (127). Hence, contrary to expectations, the majority of associations of genetic polymorphisms in the 10p13 region were either with leprosy *per se* or multibacillary leprosy, but not with paucibacillary leprosy. The reason(s) for this unexpected observation is (are) not known.

Region 6q25-q26

A second linkage hit for leprosy was located on chromosome region 6q25-q26 (124). High resolution association mapping of 43 genes located in the 6q25-q26 locus pointed to the co-regulatory region of the PARK2 and PACRG genes as the main association signal with leprosy *per se* (128). The association of PARK2/PACRG variants was confirmed in independent samples from Vietnam, India, and Brazil (64, 128, 129, 130, 131). Specifically, the PARK2 promoter variant rs9356058

was shown to be a global risk factor in leprosy *per se* (130). A second independent signal of association in the PARK2/PACRG locus was represented by the SNP rs10400079 but was only observed in early onset cases of leprosy (130). Interestingly, the same polymorphisms associated with susceptibility to leprosy *per se* were also risk factors for infection with *Salmonella typhi* and *S. paratyphi A* in Indonesia (132). PARK2 is a key regulatory element in the production of IL6 and CCL2 by human macrophages, and stimulation of whole blood with *M. leprae* sonicate triggers the transcriptional activation of both immune mediators (133). Interestingly, in the latter assay, transcript levels of both IL6 and CCL2 were significantly correlated with the presence or absence of PARK2 leprosy susceptibility alleles (130, 133). PARK2 encodes the E3-ligase Parkin, which is the cause of a small number of cases with early onset Parkinson's disease (134, 135). Parkin ubiquitinates phagosomes containing an intracellular macrophage pathogen, which destines the tagged vesicles and their microbial content for destruction by autophagy (136, 137, 138). While these findings identify PARK2 as an effector gene of innate immunity, the mechanistic details of how genetic leprosy risk variants modulate the Parkin function and its microbicidal activity are unknown.

Region 6p21

Independent studies have reported a linkage peak for leprosy *per se* on chromosome region 6p21.3 in the human leukocyte antigen (HLA) complex (124, 139, 140). High-resolution linkage disequilibrium mapping of the 6p21.3 locus led to the identification of the LTA gene in HLA class III and the HLA-C gene in HLA class I as independent signals of association with leprosy *per se* (141, 142). Lymphotoxin alpha (LTA) is an important mediator for lymphocytes recruitment in response to infection (143, 144). The LTA +80 SNP (rs2239704) was identified as a risk factor for leprosy *per se* in India, Vietnam, and Brazil, with a stronger risk effect before the age of 25 (141). The leprosy *per se* risk allele "A" of LTA +80 disrupts an ABF1 binding site, resulting in lower LTA expression (145). Fine mapping of the HLA class I locus identified an SNP variant tagging the HLA-C*15:05 allele in association with leprosy *per se* in two population samples, one from Vietnam and one from India (142). The variants associated with leprosy correlated with higher HLA-C expression (142).

Candidate gene approaches have long reported genes in the HLA region associated with leprosy (146). In the HLA class III region, the promoter polymorphisms located at -238 (rs361525), -308 (rs1800629), and -1031 (rs1799964) of the TNF gene were associated with leprosy *per se* and/or a clinical subtype in different ethnic groups (11, 139, 147, 148, 149, 150, 151). The TNF gene encodes a potent inflammatory mediator that is essential for granuloma formation in response to *Mycobacteria* (152). Moreover, variants tagging the BAT1, NFKB1L1, LTA, TNF, and BTNL2 genes were associated with leprosy *per se* in unrelated samples from India (153). In the HLA class I region, the truncated allele *5A5.1 of the MICA gene was associated with leprosy *per se* in India (154). The HLA-B*13:01 allele was identified as a risk factor for Dapsone hypersensitivity syndrome, a condition that affects 1% to 1.5% of leprosy cases with an estimated 10% chance of mortality (155). In addition, a combination of killer cell immunoglobulin receptor (KIR) and its respective HLA class I ligands was associated with leprosy *per se* in a population from Brazil (156, 157). In the HLA class II region, different alleles of the HLA-DRB1 gene were identified as risk factors for leprosy *per se* and clinical subtypes (46, 158, 159, 160, 161, 162, 163, 164). The HLA class

II molecules are expressed on antigen-presenting cells (APC) such as dendritic cells and macrophages, and they play an important role in the communication between APC and CD4+ T-cells during the early phase of the inflammatory response (165). Taken together, the HLA locus is the genomic region with the highest concentration of leprosy risk factors.

Additional chromosomal regions

Additional chromosomal regions have been shown to be linked to leprosy phenotypes by independent GWLS. The chromosome regions 20p13 and 20p12 were linked to leprosy *per se* in Brazilian and Indian families, respectively (140, 166). Chromosome region 17q11-q21 was linked to leprosy *per se* in Brazilian patients, while the region 17q21-q25 was linked to Mitsuda reactivity in Vietnamese families (121, 167). The ERRB2 gene located on chromosome region 17q12 has been selected as a positional candidate gene for leprosy *per se* in the 17q11-q21 locus. The ERBB2 gene encodes a surface receptor in the Schwann cell that is used by *M. leprae* for cellular invasion (168). ERRB2 alleles were associated with susceptibility to leprosy *per se* in some, but not all, Brazilian samples (169, 170). A GWLS reported a linkage hit for leprosy *per se* on chromosome regions 2p14, 8q24, 4q22, and 16q24 in Chinese families (171). The leprosy susceptibility genes underlying these linkage hits are not known.

Summary of linkage studies

Linkage studies have been successfully used in the analysis of host susceptibility to leprosy. Linkage peaks led to the subsequent identification of two of the most replicated associations with leprosy. A linkage peak on chromosome region 6q25 led to the identification of the PARK2 gene as the first gene identified by positional cloning in a common infectious disease. The linkage peak on the 6p21.3 chromosomal region led to the identification of variants near the HLA-C, LTA, and HLA-DR / HLA-DQ genes as leprosy risk factors. Interestingly, these findings were later confirmed by GWAS. While linkage analysis was superseded by GWAS, with the advent of next generation sequencing, linkage analysis is now increasingly used to identify rare variants causally associated with disease susceptibility.

THE GENOME WIDE ASSOCIATION APPROACH

GWAS in infectious diseases have not been as successful as in other phenotypes (172). Compared to other common infectious diseases, leprosy has the advantage that the genetic variability of the *M. leprae* is extremely low and essentially worldwide cases of leprosy are infected by a monoclonal bacterium (25, 173). To what extent the monoclonality of *M. leprae* underlies the success in mapping host genetics factors in leprosy is not known. The first GWAS performed in leprosy reported six genomic loci near the HLA-DR-DQ, RIPK2, TNFSF15, LRRK2, CCDC122/LACC1, and NOD2 genes associated with leprosy *per se* in a Chinese population (174). The associations of HLA-DR alleles with leprosy had been well documented previously; however, the other GWAS loci

pointed to new susceptibility genes. Studies in population samples from Vietnam, India, West-Africa, and Brazil validated the association of variants near the RIPK2, CCDC122/LACC1, and NOD2 genes with leprosy *per se,* supporting the robustness of the GWAS results in leprosy (175, 176, 177, 178). The LRRK2 gene was tagged by a suggestive hit in the initial GWAS and was not consistently associated with leprosy *per se* or a clinical subtype in independent populations (175, 176, 179, 180). Conversely, the association of the TNFSF15 locus with leprosy *per se* was not replicated in follow-up studies (175, 176, 177). Unexpectedly, variants near the TNFSF15 region were associated with T1R but not leprosy *per se* in a Vietnamese sample (181). Moreover, the TNFSF15 variants belonged to a larger group of highly correlated SNP that extended from the TNSF15 locus to the neighboring TNFSF8 gene. The role of TNFSF8 in T1R was further strengthened by the observation that all of the T1R SNPs, including those located within TNFSF15, were expression quantitative trait loci (eQTL) for TNFSF8 (181). The detection of eQTL signifies that the genotypic constellation at a given set of SNPs is correlated with the expression levels of a given gene. The variants overlapping TNFSF8 were validated for the association with T1R in independent Brazilian samples (181). A similar situation was observed for the LRRK2 gene. In a Vietnamese sample, a missense M2397T polymorphism (rs3761863) previously reported as a leprosy *per se* risk factor was significantly associated with T1R but not leprosy *per se* (182). Most of the leprosy susceptibility genes identified by the GWAS also were associated with inflammatory bowel disease (IBD), suggesting an overlap in the pathogenesis between the two diseases (183). However, the demonstration that a subset of these genes predisposes to T1R rather than leprosy *per se* suggested that the overlap between IBD and leprosy not only may be found in the response to mycobacteria but also may be an innate predisposition of some hosts to undergo excessive inflammatory responses that lead to tissue damage.

The number of subjects enrolled in the first leprosy GWAS was expanded twice (49, 184). The first expansion resulted in the discovery of two additional leprosy *per se* loci near the IL23R and RAB32 genes, respectively (49). The variants in the IL23R region were validated in a Vietnamese population (185). An association of the RAB32 variants and leprosy *per se* was also observed in a Vietnamese population. However, the most significant SNPs in the Vietnamese sample were not the same as those observed in the Chinese GWAS, suggesting that the true causal variant remains to be established (49, 185). Six additional GWAS loci were associated with leprosy *per se* in the second subject expansion of the Chinese GWAS population (184). However, these findings are yet to be validated. Interestingly, one of the new GWAS loci near the COX4I1 gene falls within a previous linkage peak for leprosy *per se* on chromosome region 16q24.1 (171).

Conclusion

Studies of the host genetic component in leprosy have discovered new genes and candidate pathways that contribute to disease pathogenesis. Many of the findings were confirmed by studies in ethnically distinct populations, thereby demonstrating the fundamental importance for leprosy susceptibility of the pathways tagged by host genetic studies. Despite the progress made in deci-

phering the contribution of host genetic variants to leprosy pathogenesis, a comprehensive picture has not yet emerged. Notably, the lack of diagnostics for latent infection and our continued ignorance of the mode of dissemination of *M. leprae* prevent a study of the genetic controllers of these important stages of leprosy pathogenesis. Following the impressive success in identifying genetic modulators of leprosy susceptibility, additional contributions will depend on the study of more refined phenotypes such as early onset cases or subgroups of the generalized leprosy *per se* phenotype. For example, recent studies have indicated that the genetic contribution to leprosy susceptibility differs between children/adolescents and adults. Moreover, the contribution of epigenetic processes and the role of rare genetic variants impacting on the primary protein structure and biological function in leprosy are largely unknown. An important feature derived from recent data was the genetic overlap of leprosy with IBD and Parkinson's disease. Perhaps by restricting our investigations to the commonalities between these apparently unrelated phenotypes, we will be able to identify novel pathways and regulators of host immune responses in leprosy.

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