FEATURE REVIEW

Host Genetics of Tuberculosis Susceptibility[1]

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INTRODUCTION

Tuberculosis, primarily caused by the human pathogen Mycobacterium tuberculosis, continues to be a major global health concern affecting an estimated 8 million people annually and resulting in approximately 2 million deaths. Interestingly, only about 10% of those infected with M. tuberculosis develop clinical disease (1, 2). The disparity in progression from infection to disease points to the possible importance of the host genetic background in susceptibility to tuberculosis. Hence, the identification of host susceptibility genes is important to aid our understanding of tuberculosis pathogenesis and to identify new therapeutic and preventive strategies. New approaches in tuberculosis control are especially relevant now due to the synergistic relationship between tuberculosis and HIV/AIDS making tuberculosis the single biggest killer of people living with HIV/AIDS (3).

Understanding the natural history of M. tuberculosis and distinguishing between infection and disease progression are essential to dissect the genetic basis of tuberculosis. Upon inhalation of the air-borne tubercle bacilli into the lung, two courses of progression are possible. In the majority of individuals, the bacilli are ingested by phagocytic alveolar macrophages and either killed or grow to a limited extent intracellularly. Infrequently, in children and in immuno-compromised individuals, the pathogen disseminates and forms small miliary lesions or life-threatening meningitis. More commonly, within 2 to 6 weeks after infection, a cell-mediated immune response contains the localized, granulomatous lesions, killing most, but not necessarily all of the bacilli. If the cellular immune response is not effective, which occurs in approximately 5% of cases, the primary infection will progress into active disease. In addition, approximately 5% of those 95% who contained the primary infection will develop clinical tuberculosis over the course of their lifetime. In general, M. tuberculosis has a strong predilection for the lungs and the majority of tuberculosis patients develop pulmonary disease. Once an infected individual converts to active pulmonary disease, cavitary lesions develop and the mycobacteria proliferate. If the cavity expands into the alveoli, the patient becomes infectious and spreads the bacilli by speaking, coughing and sneezing (4).

Population variability in susceptibility to tuberculosis

There is significant historical evidence demonstrating the importance of host genetic factors in susceptibility to tuberculosis. Present day resistance to mycobacterial infection is determined in part by a population's history of exposure. Infectious disease outbreaks with high morbidity select for genetic variants that confer resistance (5). Populations with a long history of exposure, such as Europeans, compared with populations only recently exposed, such as North American Natives and sub-Saharan Africans, show greater resistance to tuberculosis (6). Two historical events illustrate population differences in tuberculosis susceptibility and point to variable a resistance pattern in both "resistant" and "susceptible" populations.

The accidental administration to infants of the M. bovis Bacille Calmette-Guérin (BCG) vaccine with a virulent strain of M. tuberculosis in Lübeck, Germany, in 1929 provided an inadvertent experimental opportunity to verify that human individual variation

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exists in response to uniform infectious exposure. Of 251 immunologically naïve infants accidentally inoculated with virulent M. tuberculosis, 4 showed no signs of infection, 72 died of tuberculosis within 1 year of infection, and 175 overcame the infection (7). In contrast to the high survival rate of the immunologically naïve infants in Germany, North American Natives were devastated by tuberculosis upon initial exposure. The death rates during the late 19th century were the highest recorded world-wide and exceeded by 10 times the peak death rate observed in Europe during the 17th century (6).

MOUSE STUDIES

As in many human diseases, studies employing animal models have provided important clues for the mechanisms of susceptibility to tuberculosis and related mycobacteria that could not easily have been obtained from studies in humans alone. Specifically, studies employing mouse models have provided critical insights into the role of host genetics in susceptibility to M. tuberculosis infection. Although M. tuberculosis is not a natural mouse pathogen, inbred strains of mice vary extensively in their susceptibility to tuberculosis (8, 9, 10, 11). Preliminary work involving crosses between susceptible and resistant mice has indicated that, as in humans, susceptibility to the disease is under multigenic control (10). Consequently, mouse models have become powerful tools for the identification of candidate tuberculosis susceptibility genes. One such example is the discovery of the Nramp1 gene, which subsequently led to the identification of NRAMP1 as a susceptibility gene in human tuberculosis, leprosy and HIV (12, 13, 14).

The Nramp1 gene

Segregation analysis in inbred mouse strains led to the identification of a gene on chromosome 1 that controlled the early splenic replication of an attenuated vaccine strain derived from Mycobacterium bovis, bacillus Calmette-Guérin (BCG). This gene, initially designated Bcg (15) and later redefined as Nramp1 (natural resistance-associated macrophage protein 1) (16), had a dominant resistance effect on the multiplication of various mycobacterial species as well as a number of taxonomically unrelated intracellular pathogens including Leishmania donovani and Salmonella typhimurium (17). The Nramp1 gene exists in two allelic forms in inbred mouse strains(17). Resistant Nramp1r strains are able to control microbial proliferation at the initial phase of infection whereas Nramp1s mice are permissive for rapid uncontrolled proliferation of the mycobacteria (15). Susceptibility to infection was determined to be the result of a single, non-conservative, glycine-to-aspartate substitution at position 169 of the Nramp1 protein, a 12-transmembrane divalent cation transporter (16) expressed by professional phagocytes (18). Although the Nramp1 gene is protective against infection with attenuated BCG vaccine strains, its function in modulating infection with fully virulent M. tuberculosis is unclear. In a resistance ranking study, Nramp1r mice appeared to have shorter survival times than Nramp1s strains (9, 19). Furthermore, mice with a functionally deleted Nramp1 gene appeared to be as resistant to virulent M. tuberculosis as their wild-type counterparts (20).

H-2 and non-H-2 genes

The development of cell mediated immunity by preferential induction of the Th1 proliferation pathway has been postulated to be the underlying mechanism of genetic resistance to several intracellular pathogens, including M. tuberculosis. The T helper1 (Th1) phenotype is defined by the profile of type specific cytokines including interferon-gamma (IFN-) and interleukin-12 (IL-12). To understand the significance of specific cytokines in immunity to tuberculosis, numerous gene deletion mouse strains have been generated. Ifn- knockout (GKO) mice are the most susceptible to infection with virulent M. tuberculosis. Since macrophage activation is defective in GKO animals (21), they develop a fatal disseminated infection in response to a sublethal dose of M. tuberculosis (22). Bacterial growth in these mice is virtually unrestricted and, although granulomas develop, they become rapidly necrotic (23). The principal effector mechanism for Ifn- is the production of reactive nitrogen intermediates (RNI) by nitric oxide synthase (Nos2) (24). Important evidence for the role of the Nos2 locus in protection against tuberculosis arose from studies in mice with a targeted Nos2 deletion (Nos2-/-). Infection of Nos2-/- mice with M. tuberculosis produced a severe pathological condition that closely resembled that of GKO mice (25, 26).

The only other gene disruption known to cause such a fulminant M. tuberculosis infection is that of tumor necrosis factor- (Tnf-). Both TNF-deficient (Tnf-/-) (27, 28) and Tnf receptor-1 knockout (Tnfr1 KO) (29) mice are unable to form functional granulomas, have increased bacterial loads and, consequently, succumb quickly to infection. Interestingly, macrophages from both Ifn- receptor and Tnfr1 deficient mice are unable to produce Il-12 in response to mycobacteria (30). Il-12 is pivotal in the eradication of M. tuberculosis since it serves primarily in the induction of Ifn- (31). Direct evidence for the involvement of Il-12 in

antimycobacterial mechanisms was provided by a mouse strain with a genetic disruption in Il-12p40 (Il-12p40-/-) (32). M. tuberculosis-infected Il-12p40-/- mice were shown to develop substantially higher bacterial burdens than control mice and had shorter survival times.

Although Il-18 can potentially induce both a Th1 and Th2 responses (33), its significance in anti-M. tuberculosis immunity lies, as with Il-12, in its ability to stimulate Ifn- production (34). Reduced Ifn- expression in Il-18-gene disrupted mice resulted in a slightly enhanced susceptibility to M. tuberculosis (35, 36). In addition, a reduced production of Ifn- in Il-6 KO animals resulted in an early rise in mycobacterial loads when a low dose of M. tuberculosis was administered (37) but caused rapid mortality with a high dose (38). Furthermore, in Il-1 type I receptor-deficient (Il1r-/-) mice, an increase in susceptibility was the result of defective Il-1 signaling which subsequently led to decreased Ifn- production (39). Thus, gene deletion mouse strains have clearly proven that Ifn- is the key cytokine in the defense against M. tuberculosis.

In contrast to Ifn- however, the function of Th2 cytokines such as Il-4 and Il-10 in host defence against M. tuberculosis has not yet been defined. Targeted gene disruption of either Il-4 or Il-10 on a tuberculosis resistant C57BL6/J background did not appear to drastically alter susceptibility to M. tuberculosis-triggered disease (37, 40). In fact, a study employing Il-10 deficient animals observed enhanced antimycobacterial immunity in the absence of this cytokine (41). In yet another study however, M. tuberculosis-infected Il-4 KO mice had an increased pulmonary bacterial burden compared to wild-type mice (42), suggesting a subtle but protective role for this immune mediator.

A role for H-2 genes in susceptibility to tuberculosis has also been established in the mouse. Carriers of the H-2k haplotype appear more susceptible to M. tuberculosis than H-2b and H-2d haplotype carriers on the basis of response phenotypes such as the bacterial burden in the lung (43) and median survival times (9). In contrast, Apt and colleagues (44) observed that I-Ab/Db allele combinations were associated with shorter survival times compared to I-Ak/Dd combinations. This discrepancy may be partially explained by the differences in the infectious doses administered. In this same study, Apt and colleagues also determined that expression of the H-2f haplotype did not confer protective immunity by BCG vaccination. Furthermore, although H -2 genes have been implicated in the antibody response to mycobacterial antigens (45, 46), the generation of a granulomatous inflammatory response to M. tuberculosis does not appear to be under H-2 control (47). Hence, although the H-2 genes exert some influence on susceptibility to tuberculosis, other more significant genes are yet to be identified.

Quantitative trait locus analysis

Due to the multigenic control of host resistance to tuberculosis, an alternative strategy to identifying susceptibility genes has been adopted. Quantitative trait locus (QTL) analysis entails performing a genome-wide scan employing mice generated by experimental crosses between inbred mouse strains that represent polar ends of a resistance/susceptibility spectrum. QTLs are then assigned to specific chromosomal regions by the use of sophisticated analytical tools (48, 49) and high-density genome-wide maps.

Using different murine models, three groups have identified various genetic loci of yet unknown molecular identities that are implicated in tuberculosis susceptibility. In the first of these studies, Lavebratt et al (50) investigated M. tuberculosis-triggered body weight loss in a panel of [(A/Sn I/St)F1 I/St] backcross animals derived from "resistant" A/Sn mice and "susceptible" I/St mice. QTLs impacting on M. tuberculosis induced weight loss were identified on distal chromosome 3 and proximal chromosome 9 in females only, and suggestive linkages were observed on chromosomes 8 and 17 in females and chromosomes 5 and 10 in males. Recently, linkage of the aforementioned chromosomal regions to loss of body weight and duration of survival was studied in M. tuberculosis-infected (A/Sn I/St)F2 mice (51). The QTLs on chromosomes 3 and 9, designated tbs1 (tuberculosis severity 1) and tbs2 respectively, were only suggestively linked to postinfection body weight loss in F2 mice of both sexes. In addition, the previously identified QTL on chromosome 17, located in the proximity of the H-2 complex, was also involved in the control of tuberculosis and appeared to interact with tbs1.

Another important tuberculosis susceptibility locus was recently mapped to a 9-cM interval on mouse chromosome 1 using an F2 informative population derived from C57BL/6J (resistant) and C3HeB/FeJ (susceptible) progenitor strains (52). This locus, termed sst1 for susceptibility to tuberculosis, controls progression of lung disease, specifically lung-specific granuloma formation, caused by virulent M. tuberculosis. Although the sst1 locus is located only 10 cM of the Nramp1 gene, these loci appear mutually exclusive given that the C57BL/6J strain carries both the resistant allele of sst1 (sst1r) and the susceptible

allele of Nramp1 (Nramp1s). It is important to note, however, that Nramp1s strains are known to be more resistant to M. tuberculosis than their Nramp1r counterparts.

Using survival time as an expression of tuberculosis susceptibility, Mitsos and colleagues (53) performed a genome-wide QTL analysis in a panel of F2 mice derived from "susceptible" DBA/2J and "resistant" C57BL6/J parental strains. These authors identified two significant linkages on the distal portion of chromosome 1 and the proximal portion of 7, termed Tuberculosis resistance locus-1 (Trl-1) and Trl-3 respectively. Trl-2 was the designation given to the third suggestive linkage detected on the proximal portion of chromosome 3. Together, Trl-1, Trl-2 and Trl-3 accounted for approximately half of the phenotypic variance observed between the two progenitors with respect to duration of survival. Furthermore, homozygosity for the parental C57BL/6J allele at each of the three loci was associated with a significantly longer survival time.

Mouse models have helped uncover numerous genes involved in the control of host response to infection with human bacterial pathogens. In terms of tuberculosis susceptibility, the H-2 major histocompatibility genes as well as several non-H-2 genes such as Nramp1, Tnfa and Infg genes have been clearly implicated in susceptibility. The creation of novel and improved analytical and experimental tools will further facilitate the study of complex diseases such as tuberculosis and consequently lead to the discovery of new tuberculosis candidate genes.

HUMAN STUDIES

For human populations, Abel and Casanova (54) have described the genetic control of tuberculosis as a continuous spectrum of genetic complexity, with simple Mendelian disease at one extreme, and complex polygenic disease control at the other. Presently, mutations involved in Mendelian susceptibility to mycobacterial infections are very rare and cannot account for the global burden of disease. In contrast, numerous polymorphisms contributing moderately to susceptibility have been identified but their functional relevance and their impact at the population level remains elusive. There is evidence suggesting major gene control of susceptibility in certain populations or epidemiologic contexts where gene-environment interactions can be modeled (54, 55). It seems likely that the molecular genetic dissection of tuberculosis will depend on studying all aspects of the spectrum, on distinguishing susceptibility to infection versus susceptibility to disease progression, on distinguishing primary and reactivation infection, and on using both mouse and human models.

Several different but complementary study designs can be used to identify human host genetic factors involved in disease susceptibility. These methods include: the study of individuals displaying extreme phenotypes (or Mendelian inheritance of susceptibility); case-control, candidate gene studies; and family-based, genome-wide linkage studies.

Mendelian susceptibility to mycobacterial disease

Recently, specific mutations conferring susceptibility to mycobacteria and occasionally salmonella species have been grouped under the genetic syndrome Mendelian susceptibility to mycobacterial disease (MIM 209950). Individuals with the syndrome are unable to produce or respond to interferon- (IFN-) and are therefore highly vulnerable to weakly virulent non-tuberculous mycobacteria, such as ubiquitous environmental mycobacteria and live-attenuated M. bovis BCG vaccine strain. Several individuals with the syndrome have been diagnosed with clinical tuberculosis but it is unclear to what extent the mutations are important in M. tuberculosis infection or disease progression (56, 57, 58, 59).

The mutations resulting in Mendelian susceptibility to mycobacteria are present in genes essential in host cellular immunity, or more specifically, the type-1 cytokine cascade. The genes include those encoding interleukin 12 subunit p40 (IL12B), interleukin 12 receptor beta-1 subunit (IL12RB1), interferon gamma receptor 1 (IFNGR1), interferon gamma receptor 2 (IFNGR2) and signal transducer and activator of transcription 1 (STAT1) (60, 61, 62, 63, 64, 65). The mutations result in three classes of alleles and several corresponding clinical, immunological and histopatholgical outcomes: recessive or non-functional alleles; recessive, partially functional alleles; and dominant-negative alleles resulting in partial functionality (66, 67). The identification of individuals with infections to otherwise avirulent pathogens has helped dissect and identify essential pathways crucial for immunity to mycobacteria.

An important but unanswered question is whether more common polymorphisms of the type-1 cytokine cascade genes contribute at a population level to susceptibility to tuberculosis (66, 68). Recently, two studies showed an association between a genetic defect involved in decreased production of IFN- with increased risk of developing tuberculosis (69,70). In addition, specific IL12RB1 polymorphisms are associated with increased tuberculosis risk in a Japanese population (71). Although the importance of IFN- in host response to mycobacteria is well

established, more studies are needed to understand the importance of common type-1 cytokine polymorphisms in anti-mycobacterial immunity.

Candidate tuberculosis susceptibility genes

Candidate genes, identified by their known or suspected involvement in disease pathogenesis, are tested by association using population or family-based case-control designs (72). "Major" susceptibility genes that account for a significant proportion of the genetic contribution to disease at the population level have not been identified. However, numerous "moderate" effect genes are associated with tuberculosis. Several of these genes will be reviewed briefly.

Natural resistance associated macrophage protein 1 (NRAMP1)

The human homologue to murine Nramp1 has been tested in numerous association studies. Most notably, NRAMP1 variants were found to be strongly associated to tuberculosis susceptibility in a West African population (12). Individuals with tuberculosis were four-times as likely to have a disease-associated NRAMP1 genotype compared with healthy controls. Additional associations have also been detected in smaller studies of patients from Japan, Korea, Guinea-Conakry and Cambodia (73, 74, 75, 76). The independent replication of NRAMP1 association with tuberculosis in multiple studies across different populations provides very strong evidence for NRAMP1 as a tuberculosis susceptibility gene. The modest genetic impact of the gene on susceptibility has been interpreted to suggest that the gene accounts for only a small proportion of the total genetic contribution to susceptibility (77). However, an alternative explanation is provided by a recent genetic study of tuberculosis susceptibility in an Aboriginal Canadian community. In this study, it was possible to detect a very strong genetic effect (relative risk = 10) of NRAMP1 on tuberculosis. Of note, this strong genetic effect was only detected when essential gene-environment interactions were introduced into the analysis. Despite substantial genetic evidence implicating NRAMP1 in tuberculosis susceptibility, a causal relationship between NRAMP1 variants and increased susceptibility has not been established.

Vitamin D Receptor (VDR)

During the 19th century, cod-liver oil and sunlight, both important sources of vitamin D, were prescribed as treatment for tuberculosis. It has since been discovered that the biologically active metabolite form of vitamin D, 1,25 dihydroxyvitamin D3 (1,25(OH)2D3), interacting with the vitamin D receptor (VDR), is an important immunomodulatory hormone (78). It plays a role in activating monocytes as well as suppressing lymphocyte proliferation, immunoglobin production and cytokine synthesis (79, 80, 81). In vitro, 1,25(OH)2D3 has been shown to enhance the ability of human monocytes to restrict M. tuberculosis growth (82, 83). Alveolar macrophages from tuberculosis patients produce large quantities of the vitamin (84) suggesting a role in restricting mycrobacterial growth within granulomas (77). In addition, results from epidemiologic studies point to a link between vitamin D deficiency and a higher risk of tuberculosis. This is demonstrated by seasonal variation of tuberculosis incidence, lower vitamin D serum levels in untreated tuberculosis patients, and a higher incidence of tuberculosis in individuals with relatively low serum vitamin D levels, such as the elderly, uremic patients and Asian immigrants in the United Kingdom (85).

Given that vitamin D exerts its effects via the vitamin D receptor (VDR), and that the receptor is present on monocytes and on T and B lymphocytes (86, 87), several studies have investigated the association between VDR gene variants and tuberculosis. In a Gambian population, the VDR genotype "tt" at codon 352, associated with increased levels of 1,25(OH)2D3, was found to be over-represented in healthy controls, supporting the hypothesis that vitamin D protects against tuberculosis (88). A study investigating the interaction between serum vitamin D concentrations and VDR genotype in a Gujarati population living in London, England, failed to show a significant association between VDR genotype and increased risk of tuberculosis. However, a strong association was between undetectable vitamin D serum levels and tuberculosis was observed. Moreover, the study was able to detect evidence for gene-environment interaction between the TT/Tt genotype and vitamin D deficiency and susceptibility to tuberculosis (89). In contrast, no association was found when testing for the effect of VDR on tuberculosis in a Cambodian population (76).

Major histocompatibility complex (MHC)

Reports of association between highly polymorphic class II human leukocyte antigen (HLA) alleles and tuberculosis susceptibility are conflicting and vary among populations. Studies in different populations show an association with HLA-DR2 alleles (90, 91, 92, 93, 94) and with HLA-DQB1*0501 (94) and DQB1*0503 alleles (95). Other studies failed to detect the HLA-DR2 or DQB1/DQA1 associations (96). One of the earlier studies reported HLA-DR3 specificities enriched in healthy controls suggesting a protective

role of the antigen (97). The functional significance of these associations is not known. Given the complexity of the MHC, and the large number of immunomodulatory genes within it, a greater understanding of the role of MHC in tuberculosis pathogenesis, whether in infection, progression, or response to chemotherapy, is necessary before any real conclusions can be made.

Interleukin-1 and Interleukin-1Ra (IL1B and IL1RN)

The cytokines interleukin-1 (IL-1 encoded by IL1B) and interleukin-1 receptor antagonist (IL-1Ra encoded by IL1RN), produced by monocytes, macrophages and neutrophils, are involved in the regulation of immunological and inflammatory responses and are thought to be important regulators of tuberculosis disease progression (98, 89). Both cytokines interact with and compete for the IL-1 receptor: IL-1 induces a strong pro-inflammatory response whereas IL-1Ra, as a receptor antagonist, inhibits it. Although an initial pro-inflammatory response is important in host defense, sustained expression of IL-1 can lead to tissue destruction (98). Therefore, the ratio of IL-1Ra to IL-1 may be important in M. tuberculosis infection since overproduction of IL-1Ra may block the anti-microbial activity of IL-1 during the early stages of infection (or early in the establishment of lung granulomas). Increased serum levels of IL-1Ra, and a high ratio of IL-1Ra to IL-1 in bronchoalveolar lavage, were found in patients with active pulmonary tuberculosis (99, 100). In the same Gambian population tested for associations in NRAMP1 and VDR, a weak association was found between IL1RN and tuberculosis susceptibility (101). However, when corrected for multiple testing these associations are no longer significant. Finally, IL1RN was tested in a Cambodian population for association with tuberculosis but no association was found (76). Taken together, these results suggest a modest contribution at best of IL1 and IL1RN polymorphism to tuberculosis susceptibility.

Tumor Necrosis Factor (TNF)

TNF plays an important role in host immune response to M. tuberculosis and the immunopathology of tuberculosis. TNF is pro-inflammatory cytokine and is produced mainly by monocytes and macrophages. In-vitro studies show that the cytokine increases the ability of macrophages to phagocytose and kill mycobacteria (102, 103). TNF is also required for the formation of granulomas which sequester and contain the mycobacteria. The importance of the pro-inflammatory cytokines TNF and IL-1 in tuberculosis is demonstrated by the increased risk of reactivation in rheumatoid arthritis patients receiving anti-TNF and anti-IL-1 therapy (104, 105). Despite its importance in immunity and its association to leprosy, another mycobacterial disease, few studies have evaluated TNFA polymorphisms in tuberculosis susceptibility (106, 107). Studies in two populations showed conflicting results: there was no association between a polymorphism linked to TNF production and tuberculosis in Cambodian patients whereas the opposite was found in an Italian population (95, 108). Further investigation in different populations is needed to clarify the importance of TNF polymorphisms in modulating disease susceptibility.

Linkage studies

Complementary to candidate-gene studies are genome-wide scans, a powerful approach to identify major susceptibility loci. Genome scans, a linkage-based study method, evaluate the significance of excess-allele sharing among affected pairs of offspring. A large study was performed in 92 sib-pairs with tuberculosis from Gambia and South Africa. Weak evidence for linkage was detected on chromosome regions 15q and Xq. Given that linkage analysis are more powerful to detect disease-susceptibility loci conferring high risk, the two loci identified in this study are probably different, and might have substantially larger effects than previously identified loci (109). Unfortunately, this expectation was not borne out in a follow-up association study of the chromosome 15q region (110).

Two linkages studies have assessed the role of NRAMP1 in tuberculosis susceptibility. An analysis of families with multiple cases of tuberculosis in Brazil did not show significant linkage to NRAMP1, but two markers tightly linked to the gene were weakly linked to disease susceptibility (111). A linkage study of a large Aboriginal Canadian family took into account gene-environment interactions, such as vaccination status, tuberculin skin-test result, age and previous disease, and showed significant linkage between tuberculosis susceptibility and a marker just distal to NRAMP1 (55). In this study, NRAMP1 appeared to modulate the progression from infection to active disease.

CONCLUSION

There is clear and unambiguous evidence that human genetic variability is an important modulator of susceptibility to tuberculosis. Several tuberculosis risk variants have already been described and it is likely that others will follow. The methodological challenge for the future will be to properly capture, and to

incorporate into the analysis, gene-gene and gene-environment interactions. However, the biggest challenge will be to advance the basic genetic findings into the arena of public health and tuberculosis control. How this will happen is difficult to predict. Given the present efforts in generating better tuberculosis vaccines, a potentially fruitful application of tuberculosis genetics is the exploitation of host genetics for vaccine development. At any rate, to what extent modern genetics will be able to facilitate disease control will be an important measure to judge the benefits of the human genome project for medicine and human health.

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