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Genetics and evolution of tuberculosis pathogenesis: New perspectives and approaches

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Abstract

Tuberculosis is the most lethal infectious disease globally, but the vast majority of people who are exposed to the primary causative pathogen, *Mycobacterium tuberculosis* (MTB), do not develop active disease. Most people do, however, show signs of infection that remain throughout their lifetimes. In this review, we develop of framework that describes several possible transitions from pathogen exposure to TB disease and reflect on the genetics studies to address many of these. The evidence strongly supports a human genetic component for both infection and active disease, but many of the existing studies, including some of our own, do not clearly delineate what transition(s) is being explicitly examined. This can make interpretation difficult in terms of why only some people develop active disease. Nonetheless, both linkage peaks and associations with either active disease or latent infection have been identified. For transition to active disease, pathways defined as active TB altered T and B cell signaling in rheumatoid arthritis and T helper cell differentiation are significantly associated. Pathways that affect transition from exposure to infection are less clear-cut, as studies of this phenotype are less common, and a primary response, if it exists, is not yet well defined. Lastly, we discuss the role that interaction between the MTB lineage and human genetics can play in TB disease, especially severity. Severity of TB is at present the only way to study putative co-evolution between MTB and humans as it is impossible in the absence of disease to know the MTB lineage(s) to which an individual has been exposed. In addition, even though severity has been defined in multiple heterogeneous ways, it appears that MTB-human co-evolution may shape pathogenicity. Further analysis of co-evolution, requiring careful analysis of paired samples, may be the best way to completely assess the genetic basis of TB.

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Keywords

Tuberculosis; Genetics of pathogenicity; Host-pathogen co-evolution

1. Introduction

Pulmonary tuberculosis (TB) is a major public health problem, as it causes more deaths than any other pathogen[1]. It is also the leading cause of death among people infected with human immunodeficiency virus (HIV)[2]. In Sub-Saharan Africa and Southeast Asia TB is a re-emerging disease, even though incidence is decreasing globally[1]. The bacterium, *Mycobacterium tuberculosis* (MTB), causes most TB, and is transmitted via airborne droplets from coughing and sneezing by people with active disease, meaning that it can be a very mobile pathogen in the age of frequent global travel; hence global exposure is high with between one fourth and one third of the entire global population being infected. However, most people exposed to MTB do not develop active disease. In 2017, only 10 million people developed active disease and 1.6 million people died[1]. These numbers are of interest because they demonstrate that the vast majority of people have resistance to TB. Additionally, some people do not even show signs of having been infected. Examining patterns of resistance to either disease or infection can be extremely useful in developing policies to prevent TB and may be elucidated by understanding the long and complex history of MTB and humans.

Host genetic factors can affect TB risk, and may influence other outcomes that occur between exposure to MTB and development of active TB disease (Figure 1). Following exposure to MTB, a necessary cause of TB, several outcomes or clinical trajectories exist that can be detected using different means (Figure 1). For example, infected individuals are identified with tuberculin skin tests (TST) using purified protein derivative (PPD) and/or interferon-γ release assays (IGRA) (eg. Quantiferon (QFT)). Most exposed individuals will exhibit signs of infection (latent MTB infection or LTBI), but not active disease. However, some individuals never even develop LTBI, even in the face of prolonged and persistent exposure to an infectious TB case and hence MTB[3, 4]. These latter individuals are described as resistant to MTB infection, and have been termed resisters (RSTRs)[5]. Prevalence of RSTR varies as a function of follow-up time and use of TST and/or IGRA, so current estimates of the prevalence of RSTR in high-exposure settings range from 7–25% [5–7]. The path an individual traverses post-exposure is related to differences in immune response and this can have a strong genetic component driven by the long evolutionary co-existence of MTB and humans.

2. Overview from infection to TB

TB is the outward manifestation of the immune response to MTB, and in understanding genetic factors as potential markers and/or therapeutic targets of disease, it is important to understand the natural course from exposure to TB. The progression can manifest via multiple paths. Post exposure to MTB some people exhibit signs of infection (arrow A), while others never become infected (arrow B). Following infection, there is an innate

response by the immune system that, in a small number of people, may lead to early clearance of the bacteria (arrow E)[6, 8, 9]. However, in most people, the bacteria persist, and stimulate an adaptive response to control the bacteria. At this point, mycobacterial antigens are presented, and T and B cells are recruited and utilized to control the infection[10]. In some people, mostly young children or those with immunodeficiencies, primary active disease can develop (arrow C)[11]. If the infection is controlled, a granuloma is formed and the host enters a stage of latent infection (arrow D), with bacteria persisting inside macrophages. If the infection remains in this state, there are neither symptoms nor transmission (as far as is currently understood). If the host immune system is unable to control the bacteria after the primary infection, then the host progresses from LTBI to active TB (arrow F), at which time he/she will experience symptoms and potentially transmit the infection[12]. Those in a state of latent infection can live their entire life in latency or have an activation of disease later in life. However, transition from LTBI to active TB is more likely to occur in the presence of immunosuppression or other stressors on the immune system; this is why HIV co-infection is so perilous. In this review we use this transition map to understand the current genetic literature of host genetics of TB and how it can influence each stage of pathogenesis. We also discuss the pieces of the overall picture that are still missing.

3. Exposure to infection: Who is resistant?

The first process of interest is the transition from exposure to infection. While only a minority of people resist infection (Figure 1, arrow B), studying them is of particular interest as they may be especially useful in elucidating the natural history of TB and knowing their genetic constitutions may be useful in developing prevention and/or treatment strategies. Genetic influences on resistance to infection have been studied in two ways. Some studies have examined LTBI as the trait of interest, using cross-sectional study design, without any long-term follow-up. Other studies have conducted longitudinal follow-up to identify individuals who started as uninfected (TST or IGRA negative), but eventually converted to TST/IGRA positive or LTBI. We contend that RSTRs cannot be defined based on a single assessment without longitudinal follow-up, as conversion to test positivity may occur later [4–7].

It remains to be seen to what extent resistance to infection is driven by genetics. However, PPD reactivity is correlated among siblings, but not among unrelated children who live in the same household who have similar exposures to TB[13]. Such data are indicative of a genetic component for RSTR. In addition, linkage analyses, candidate gene studies, and genome-wide association studies (GWAS) have added to the evidence that genetic variation associates with MTB infection. A genome-wide linkage analysis in Uganda suggested that regions on 2q21–2q24 and on 5p13–5q22 were linked to the RSTR phenotype[14]. The chromosome 2 locus was later fine-mapped to two potential candidate genes, *GTDC1* and *ZEB2* [15]; the locus identified on chromosome 5 was later fine-mapped to a gene, *SLC6A3*[16], and this result was replicated in a candidate gene study of RSTR [17]. A genome-wide linkage study of PPD reactivity as a binary (cross-sectional) trait in South Africa found a locus at 11p14, termed *TST1*[16]. This locus was found in a later study to be identical to a QTL controlling TNF expression and production[18]. When PPD reactivity

was analyzed as a quantitative outcome in the same cross-sectional study, another locus termed *TST2* on 5p15 was identified that is thought to modulate T cell responses[18]. Finally, a genome-wide association study of TST reactivity among HIV-infected individuals from Tanzania and Uganda, defining the trait both as binary and quantitative phenotypes, identified a region on chromosome 5q31 that included the *IL9* gene [19]. This latter study is interesting because in the Tanzanian population, the phenotype was defined cross-sectionally, while in the Ugandan population, the longitudinally-characterized RSTR definition was used. Since this association was replicated across different phenotype definitions, the association with chromosome 5q31 was robust to phenotype definition. This study also examined association with the previously identified loci described above (5p15, 11p14, 2q21-q24, and 5p13–5q22) and observed replication at the $p<0.001$ level with all these loci.

One study in Ghana found a haplotype that associated with low levels of circulating IL-10 with an increased likelihood of PPD positivity (but not with pulmonary disease)[20]. Another study focused on *ULK1*, a gene thought to be important in signal transduction of autophagy effectors, and showed an association with LTBI risk[21, 22]. Autophagy pathways, which are responsible for the destruction of infected cells, are thought to be the most influential host factors in restricting intracellular growth of MTB in macrophages and regulation of the maturation of the mycobacterial phagosome [23].

While the role of antibodies in many infectious diseases is well documented, the role of this response in TB remains unclear. There is likely a role for B cells in susceptibility to MTB infection, but it is likely that the effects go beyond their direct antibody-mediated effector functions[5]. This conclusion is based on the idea that passive transfer of antibodies has not been associated with protection against TB and IgG levels do not appear to be consistently associated with control of bacterial infection. Instead, depletion of B cells is associated with a higher bacterial burden. Furthermore, antibodies, plasma cells, and anti-responsive innate immune cells are found in MTB granulomas[24, 25]. There is even evidence that IgG can “cure” infected macrophages if presented at the right time [26]. A recent study has shown that RSTRs show immunological evidence of exposure to MTB (shown by IgM, class-switched IgG, and non IFN-γ T cell responses to MTB specific proteins) and that these RSTRs show enhanced antibody avidity and IgG F_c profiles specific to MTB. This result indicates that there is an adaptive immune response to MTB exposure that involves antibodies[27]. Overall, these results point to a number of genes and their downstream products that may influence the initial response to MTB exposure and potentially prevent infection.

4. Primary Active Disease

While the vast majority of healthy individuals who become infected enter a state of latent infection, a small portion of people (~5%) develop active tuberculosis either right away or after a relatively brief period of latency[11](Figure 1, arrow C). This state is known as primary active tuberculosis and is most common in adults with immunodeficiencies or children, especially those who are very young (less than 2 years old) and/or have inherited a primary immunodeficiency (such as chronic granulomatous disease or Mendelian

susceptibility to mycobacterial disease)[28]. These children often manifest a severe disseminated form of TB that can infect the central nervous system and is extremely life-threatening. Prior to the widespread use of the BCG vaccine and increased availability of antibiotics, this form of TB was common among children in endemic areas[28, 29]. While these advances have decreased mortality, 230,000 children died from TB in 2018 (including those infected with HIV) and there remains a strong correlation between younger age and death from TB[1, 30].

There are different types of evidence pointing to the influence of host genetics on susceptibility to TB, and these genetic influences may affect timing of transition to active TB. Twin and Mendelian Susceptibility to Mycobacterial Disease (MSMD) studies together support the conclusion that TB susceptibility is influenced by genetic variation. MSMD is an immunodeficiency disorder in children characterized by mutations in the IFN-γ and IL-12 signaling pathways[31–33]. Children with MSMD are extremely vulnerable to weakly virulent mycobacterial species and can even get sick from the BCG vaccine. These children often suffer from a number of other bacterial infections as well[34]. MSMD associates with a number of different genotypes, including mutations in seven autosomal and two X-linked genes (*IFNGR1/2, STAT1, IRF8, CYBB, IL12B, IL12RB1, NEMO, and ISH15* genes), all of which lead to impairment of IFN-γ immune function. [28, 34, 35]. However, these loci only account for about half of known MSMD cases. Many siblings of children with MSMD often get severe primary TB (but are not susceptible to weak environmental mycobacteria). Defects in the IFN-γ response have also been shown to be present in the siblings, but the most common characteristic is a complete IL-12Rβ1 deficiency[36, 37]. Taken together, these deficiencies point to the importance of the IFN-γ response in controlling the initial TB infection and leading to a state of latency, rather than a severe primary disease. The response appears to be affected by multiple genes.

Genetic association studies of children with active TB have not been common, but there are some associations reported in the literature. There have been two studies, one in China and one in the USA, that have associated variants in *SLC11A1* with pediatric disease[38, 39]. Another study in Turkey found that *TLR8* polymorphisms are associated with pediatric TB[40]. Two studies have also examined the association between genetic variants and BCG vaccine induced production of cytokines that are known to be an important part of the response to BCG vaccination. One study found that *SIGLEC14* variants were associated with increased BCG-induced IL-2 and IL-17 production in South African children[41]. The other found that variants in *HSP90B1* (a chaperone protein for multiple toll-like receptors) were associated with higher BCG-induced IL-2 production in South African children[42].

4.1 Delayed transition from latent infection to active TB

Most people infected with MTB enter a state of latency. However, a portion of these people (~5–10%) will go on to develop active pulmonary tuberculosis later in life. This transition can happen many decades later, but likelihood of transition to TB decreases the longer a person remains in a latent state [11, 28]. States of immunodeficiency have been observed to trigger reactivation, such as HIV or the use of immunosuppressant drugs (especially anti-TNF drugs), but reactivation can also happen in people without known immunodeficiency.

The transition in seemingly healthy individuals is not well understood but it is generally thought to be distinct from that of children who have severe primary TB[43]. As many healthy adults who develop active TB and are included in genetic epidemiology studies will likely have been latently infected prior to activation, most case-control studies on susceptibility probably capture host genetic variation related to reactivation of TB. Unfortunately, based on the design of current TB susceptibility studies that usually do not explicitly test for LTBI, we have not been able to say with certainty which variants are related directly to progression from LTBI to TB as opposed to primary active disease.

5. Studies of Susceptibility to Pulmonary TB

Susceptibility to TB is distinct from resistance to MTB infection and is central in understanding genetic factors underlying TB pathogenesis. From a design standpoint, there are problems with the approach taken in many case-control studies of active TB. Not all studies have ensured that exposure status is similar between cases and controls, and in some studies controls could contain the unexposed, the exposed and infected (LTBI), and RSTRs[44, 45]. Assuming the study participants are adults, most cases probably were latent prior to active disease in endemic areas. In the context of Figure 1 and our understanding of TB pathogenesis, susceptibility studies do not neatly fit into a single biological process. The number of potential steps and paths to active TB may affect our ability to detect meaningful results, as we often do not determine *a priori* which of the steps we are assessing in a given study. Nonetheless, the most likely scenario of the progression to active disease in adults is that they have had a (re)activation of latent infection. Confirming this scenario may substantially improve power to detect genetic actors in TB risk, if studied explicitly.

Hundreds of candidate gene studies have been published focusing on pulmonary TB as the phenotype. A recent review summarized 15 genes with robust, replicable associations, although many other variants have been reported[19]. The majority of these 15 genes variants code for human leukocyte antigen (HLA) (with variants in *HLA-DRB1* especially well represented), but multiple studies have also reported associations for variants in *IFNG, IFNGR1, IL10, MBL2, MCP1, SLC11A1, TLR2, TLR4, TLR9, TNF, and VDR*[19]. Pathway analysis of these genes revealed multiple canonical pathways to be significantly associated with TB susceptibility. The most significant pathway was in altered T and B cell signaling in rheumatoid arthritis and T helper cell differentiation[19]. Other pathways include the innate and adaptive immune responses, and helper T cell cytokine responses. Since the vast majority of candidate gene studies have examined one gene at a time, and often only a few variants within each gene, pathway analysis may provide clearer insight into the biological mechanisms underlying TB risk. Considering most candidate genes were studied due to their suspected role in the immunological response, it can help us better match our understanding of genetic variation in susceptibility studies to the pathophysiology of TB, if we discuss these 15 results (which are also found in Table 1 of Stein et al. [19]) in the context of their role within the immunological response to TB and the rest of this section will focus on the genes listed in this paragraph.

HLA is an important type of protein for recognition of both foreign and host cells by the immune system and represents the major system by which “self” is distinguished from

"other" in the human body. As stated above, many variants related to TB susceptibility are associated with polymorphisms in various HLA genes and these have a wide-ranging impact on regulating the immune system and host response to infection[46].

VDR codes for the vitamin D receptor and *MBL2* codes for mannose binding lectin 2, both are which found throughout cells of the innate immune system. The MBL2 protein functions by binding to sugars found on the surface of many pathogens. This serves as a signal to activate the complement system, which is a host immune response that can destroy invading pathogens and trigger inflammation[47]. The role of vitamin D in infection is still being examined but it is known that vitamin D can activate transcription and studies have indicated that it can regulate the expression of many genes in the immune system, including genes coding for important components of the innate immune response[48].

When MTB enters the lung, it must contend with the resident alveolar macrophages. And as stated above, LTBI is an intracellular infection of macrophages and active TB disease can occur when macrophages do not adequately contain the mycobacterium. Thus, macrophage related variants are thought to be important in TB risk. There have been a number of associations reported that pertain to this response (including those above), which is part of the innate immune system (the initial response to infection) and variants pertaining to the macrophage response may contribute to resistance and susceptibility. *MCP1* (also known as *CCL2)* codes for monocyte chemoattractant protein 1 (known as CCL2), and functions to recruit immune cells to a site of infection (such as MTB in the lungs). The immune cells recruited to the site of the infection including monocytes, precursor cells that may eventually become macrophages[49]. *TNF* codes for tumor necrosis factor, a cytokine that is a key driver of the inflammatory response, which is important to fighting a myriad of pathogens and is chiefly produced by activated macrophages.

SLC11A1 (previously called *NRAMP1*), is one of the most well studied genes for association with pulmonary TB susceptibility and a large number of studies have found associations between *SLC11A1* and susceptibility[19]. It is an important regulator of macrophage responses to MTB [19, 50, 51]. *SLC11A1* functions within macrophages, regulating changes in iron transport and the transport of other cations in response to infection, thus depriving MTB of the iron it needs to replicate and spread within the body [50–53].

One of the most well studied pathways in genetic susceptibility to TB in humans is that of toll-like receptors (TLRs). TLRs are part of the innate immune system, found primarily on macrophages and other antigen presenting cells such as dendritic cells, and function to recognize conserved ligands in microbes. In essence, they help mount a proper immune response to specific microbes, including MTB. There are a number of polymorphisms that have associated with TB susceptibility in the pathways for toll-like receptors (TLRs) and other genes that affect TLR function[22, 54–60]. Unfortunately, with the exception of *TLR2*, *TLR4*, and *TLR9* (as reported above and in Table 1 of Stein et al. [19]), not all of these polymorphisms have an obvious functional role and some lack adequate replication in the literature[5]. However, toll-like receptors, as a family, show a clear role in both immunological and genetic studies of TB.

Autophagy is the process by which the immune system clears out infected cells (including macrophages). Although polymorphisms in autophagy pathways are not included in the 15 robust associations described above, immunological studies have strongly suggested a role for autophagy variants in the host response to MTB infection and TB disease. And polymorphisms in *ATG5* and *IRGM*, both of which are involved in autophagy, have been associated with TB susceptibility [61–64].

T cells also play an important role in regulating the host response to infection by MTB. HIV-positive individuals (who have low CD4+ cell counts) are more likely to progress to active disease than those without HIV. Consistent with this observation, mouse studies have shown that IFN-γ production by T-cells is important in controlling MTB replication, survival, and the formation of the granulomas that sustain latency[65–73]. Several of the robust associations are key players in the IFN-γ response (e.g., *IFNG* and *IFNGR1*). There may also be IFN-γ independent T cell responses that play a role in TB pathogenesis; for example SNPs in *IL10* that have shown strong association with TB [5, 19, 27]. Another important T-cell response associated with TB is the recognition of non-protein mycobacterial antigens. CD1 and MR1 proteins function in this capacity and the genes coding for these (*CD1* and *MR1*) both have polymorphisms that may be associated with TB susceptibility, although these findings are not considered as robust as some other genes [74, 75].

In addition to candidate gene studies, six linkage studies have identified loci that influence TB susceptibility (Table 2). These studies, performed in Southeast Asia, South America and both West and East Africa, identified several putatively linked loci, but the linkage regions differed across studies. One study in Thailand identified suggestive evidence of linkage at loci on chromosomes 5q23.2–31.3, 17p13.3–13.1, and 20p13–12.3 [76]. A study in West Africans found evidence of putative linkage with TB on 6p21–23 and 20q13.31–33 that were later mapped to the *CTSZ* and *MC3R* [77]. A study of TB in Brazilians identified loci on chromosomes 10q26.13, 11q12.3, and 20p12[78]. A different study of TB in Brazil found a cluster of four genes (*NOS2A, CCL18, CCL4*, and *STAT5B*) on 17q11–21 that showed linkage with TB[79]. This chromosome 17 region was chosen as the syntenic region in mice had been shown to affect intra-macrophage infections in mice[79]. A study performed in The Gambia and South Africa provided evidence of linkage with TB on chromosome 15q and Xq[80]. Finally, a study in Uganda identified linkage with TB on 7p22–21, and nominal linkage for *IL1* and *IL12A*[14]. Of note, these linkage signals generally differ among populations leaving many unanswered questions about universal versus population specific effects. One limitation of interpreting these studies is that linkage peaks are wide, and in most cases these significantly linked chromosomal regions do not contain any established TB candidate genes.

Genome-wide association studies (GWAS) studies have also yielded valuable insights into TB susceptibility, with 9 case-control studies finding associations with pulmonary TB[19] (Table 2). *WT1* was originally identified on chromosome 18q11.2 and found to be associated with susceptibility in a cohort of Ghanaians, Gambians, and Malawians[81]. It was then replicated in Russians, Indonesians, admixed South Africans, and a different cohort of Gambians [82, 83]. The study in South Africa also identified loci on chromosomes 14q24.2 and 11q21–22[82]. Loci on chromosomes 11 and 18 were found in a Russian cohort that

replicated the locus on chromosome 11 but not 18. This study did, however, identify a novel gene, *ASAP1* [84]. When researchers examining a Moroccan cohort attempted to replicate the results on chromosomes 11 and 18, they failed to do so at a level of genome-wide significance (but did so at a nominal significance, p=0.05)[85]. HLA variants showed associations in Russian, Icelandic, and Croation cohorts, but these same studies did not replicate the aforementioned loci on chromosomes 11 and 18[86]. A study of a Japanese cohort identified a locus on chromosome 20q12 that was significantly associated with younger age of TB onset[87]. A cohort of HIV-positive subjects showed a significant association at 5q33.3 and a subsequent haplotype analysis was consistent with this association being caused by variation in *IL12B* [88]. In summary, GWAS studies have yielded a number of insights. These are in need of replication and may differ with respect to populations, which may be due to different frequencies of certain polymorphisms in these populations[19] (Table 2). Furthermore, none of the linkage peaks or associating loci replicated with genome-significance across studies. However, in at least one GWAS it was shown that 8 of 22 previously associating candidate genes did replicate at a nominal p-value ($p < 0.05$)[84]. This is unlikely to have occurred by chance alone.

Gene expression studies have also yielded insights into host genomics of TB. Most of these studies have focused on transcripts that are unique to TB cases and found in peripheral blood [89–96]. However, one study used cells stimulated with MTB after isolation from circulating blood[97]. These studies varied greatly with respect to control groups and the transcripts they studied, making it difficult to draw generalizable conclusions [19]. Some studies reported differential expression of type I and II interferon pathways in TB cases [90, 94, 95]. One study showed differential expression for *CCL1*[96]. Interestingly, the transcriptomic signatures in some of these studies normalized during or after treatment, indicating that these signatures may be specific to active disease[90, 95, 96].

6. Genetics of Severity of TB disease

Studies examining severity are less common than those studying association or linkage with disease. And those that do study TB severity use a wide variety of severity definitions, making comparisons difficult. Phenotypes utilized include TBscore (a validated outcome based on 11 clinically relevant symptoms), disease progression, cavitary disease, lung lesions, bacterial load, or parenchymal involvement as markers of severity [98–109] (Table 3). In these studies of phenotypes related to clinical severity, the MCP-1/MMP-1/PAR-1 pathway was associated with more severe disease based on the Bandim TBscore[99]. A recent study also found an association between SNPs in *IL12B* and the Bandim TBscore[109]. Variants in *TLR4* were correlated with bacillary load and lung involvement on radiological examination[105], *TLR8* variants were associated with bacterial load in one study[98]. One study found a *CTLA4* haplotype was less common in patients with larger chest opacities[108]. *HLA-DRB1* variants associated with more advanced lung lesions[102]. Variants in both *SLC11A1* and *IL23R* have been associated with cavitary disease[100, 106].

In transcriptomic studies, greater expression of genes in the *SOCS* family were associated with more lung parenchymal involvement upon radiological examination[104]. Higher expression of *IL17* and *IFNG* in peripheral blood was associated with radiological and

clinical parameters that describe disease severity in patients with active disease compared to healthy BCG-vaccinated controls[101].

In summary, severity as a phenotype is understudied, and it is not obvious how the different phenotype definitions are related. Notably, some of the severity associating genes (i.e., *IFNG, SLC11A1, MCP1*, *TLR* variants, and *HLA* variants) are similar or identical to those implicated in previous studies of susceptibility or resistance to TB. How TB risk and severity relate will require more work to better define how the genetics of risk and progression do or do not correlate across severity definitions. This will be useful in understanding functional aspects TB genetics.

7. MTB Lineage, Human Disease, and Co-evolution

There are seven currently described lineages of MTB that cause disease in humans. Two are ancient and 5 are modern. In addition, there are numerous sub-lineages that are often highly limited in their geographical distribution, some to a single country. Many of these sub-lineages are thought to be recently diverged and many of them are thought to have come from lineage, L4, that is the most widespread lineage of MTB. L4 was originally found in Europe, and potentially moved to other continents with Europeans [110]. Studies have indicated that MTB lineage can affect the probability of developing TB disease [111–114]. However, two studies in Uganda have shown no association between an MTB sub-lineage unique to Uganda and severity of disease, as measured by presence of cavitary disease and extent of lung involvement[115, 116]. A major question arises when trying to assess the diversity of MTB, namely, whether pathogenicity or virulence is a function of the host, MTB, or both. This is especially pertinent to TB, as most infections do not cause disease.

7.1 Human-MTB interaction and TB

Although it is clear that both human and MTB genetic variants can affect TB risk, it is also possible that combinations of the two impact risk. Such a model posits that human-MTB co-evolution exists and that risk and/or severity is determined by the exact combination of human genes and MTB genes[117]. Studies examining possible interaction between host genotype and MTB lineage are sparse. It is especially difficult for the study of TB susceptibility as it is virtually impossible to know what MTB lineages a specific host has been exposed to prior to enrollment in a study. One way to circumvent this problem is to study how interaction affects disease severity.

TB severity in the context of co-evolution is especially important as evolutionary theories hypothesize that long-term coexistence between the human genome and MTB lineage may decrease risk of developing active TB or minimize the severity of disease, if disease is present[117]. This concept is referred to as co-evolution. Co-evolution implies concordant genetic variation of both MTB lineages and human variation as a product of long term coexistence that promotes mutual adaptation and thereby modulates the effects of infection. Co-evolution has been hypothesized to lead to prudent exploitation or covert infection, such that exposure and latent infection does not necessarily lead to active disease and will cause less virulent disease, when present[118, 119]. A pathogen that is prudently exploiting the human host would be evolutionarily incentivized to persist and be transmitted, but not cause

disease severe enough to cause rapid death that could lead to the extinction of the host population and ultimately the MTB population. [120]. Under the co-evolution model, a newly divergent MTB lineage that did not historically co-exist with the human population in question is more likely be associated with disease and also more likely to cause severe disease [121]. In practice, only the latter can be explicitly studied as exposure histories are impossible to know in the absence of disease. Consistent with this possibility and the conditions that could lead to co-evolution, humans and MTB have a very long history and most people exposed to MTB do not progress to active disease, making MTB a likely prudent exploiter [122].

The potential for human-MTB co-evolution has been explored in human and model systems, but studies have not yet identified a clear effect at the population level[111, 114, 123–127]. Studying co-evolution in TB risk can be problematic because even within a household the strain to which an individual is predominantly exposed may not match that of the index case, since community exposure can be the major source of exposure[128]. Thus, due to the idea that co-existence would decrease severity over time and prolong the co-existence of the two species, one way to approach possible co-evolution is to study TB severity. Another limit to studying people with only TB compared to LTBI is that those who are latently infected cannot usually be examined for MTB strain. Hence, all existing studies of host-MTB genome interaction have been case-only studies that at best examine association between lineage and host genotypes, but not explicit interactions [53, 124, 126, 129]. However, a recent study of ours has shown that interaction between host variants in *SLC11A1* and MTB lineage can affect severity of TB, measured by the Bandim TBscore[109]. Specifically, we found that the recently diverged Ugandan L4 sub-lineage caused more severe disease, but only in individuals with an ancestral *SLC11A1* genotype; those with the ancestral genotype and the older MTB lineages did not have as severe disease. In general, the combinations of host genotype and MTB lineage that had co-existed longer had less severe disease, lending support to the model of co-evolution and prudent exploitation of humans by MTB. Relevant to *SLC11A1,* this gene has bene a well-studied candidate gene for TB susceptibility but not all studies found an association. It is possible that failure to replicate was a function of MTB lineage among those with disease. Given how lineage can affect the relationship between host genotype and TB, and that interactions between the two genomes may drive disease processes, it will be important to improve our understanding of the role that the MTB lineage - human genome interaction plays.

Beyond examination of MTB genetics classified by lineage, it will be important to understand how the MTB genome and specific variants can affect severity and susceptibility in humans. Some work has indicated that there may genetic diversity of MTB within a given host and that MTB can evolve within the host it has infected, affecting both transmission and drug resistance[130]. Elucidating the evolutionary process of MTB both within a host and on a population level will allow for a deeper biological understanding of the interaction between the host and MTB than examining lineages or human genomes alone. Future work should be done in this area as it may elucidate what makes MTB pathogenic.

8. Conclusions

Previous study of human genetics in the context of TB has been extensive, but there are still important gaps in the existing literature. Resistance to MTB infection has great relevance for TB research, but has been relatively understudied with respect to human genetic influences. Susceptibility has been the most extensively studied phenotype and there are a number of robust associations reported. However, there is still variation between populations and inconsistency in many results, with many associations not replicating across distinct study populations. Severity is a field of study with little to no consistency in phenotype and only a few studies in the context of genetics. We are beginning to recognize and understand the role of MTB lineage and MTB genotypes but there is a need for population level studies looking at the interaction between human genetic variants and the lineage and/or genotype of MTB. This will at present need to be assessed in the context of severity. All of these factors are important considerations and should help us better understand TB pathogenesis in a way that helps to control disease or improve treatment.

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Highlights

- Tuberculosis usually requires several steps from exposure to disease
- Human genetic variation associates with most transitions among TB related phenotypes
- Mycobacterium-human coevolution can affect TB severity and likely risk

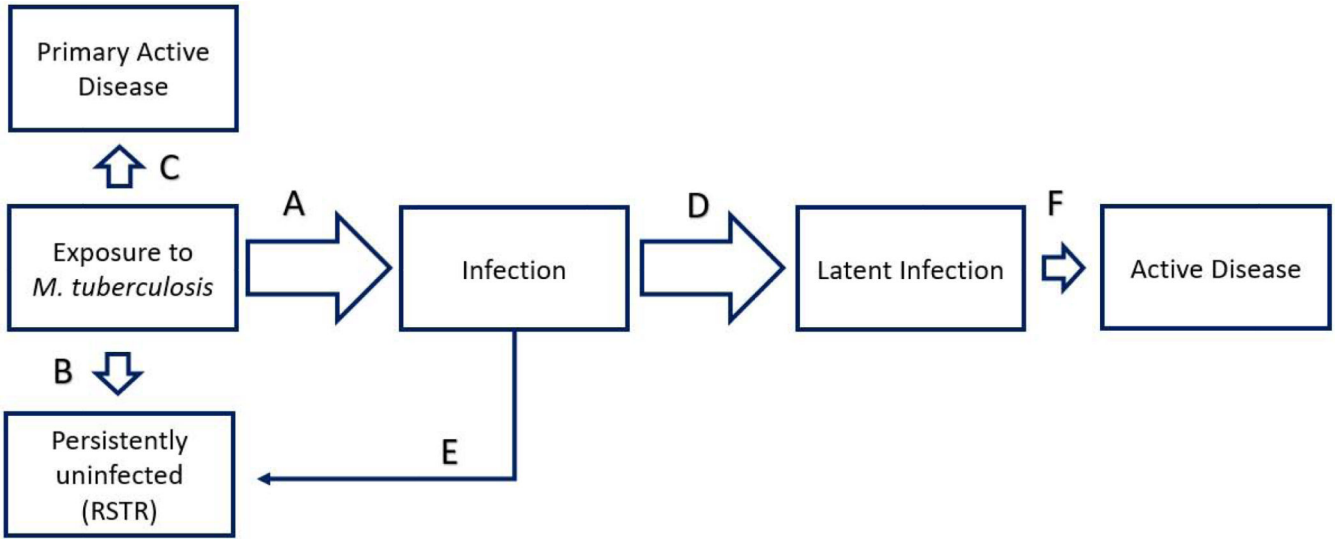

Figure 1. Tuberculosis Disease Progression.

Possible paths from exposure to disease. A: Transition from Exposure to Infection (usually leading to LTBI); B: RSTRs or those who never become infected (a minority of those exposed); C: Development of primary active disease (usually in children or individuals who are immunocompromised, rare or non-existent in others); D: Transition from infection to a state of latency (LTBI, presumably the most common transition post exposure and infection); E: Early clearance of infection, manifested as reversion of TST/QFT; F: Re-activation of disease following a period of latency. Arrow sizes are proportional to likelihood of transition.

Table 1.

Summary of findings for resistance to MTB infection, by phenotype definition and approach

Type of study	Gene/Locus	Phenotype	Population	References
Candidate gene	*ULK1*	TST positivity	Seattle	[21, 22]
	SLC6A3	RSTR	Uganda	[17]
	IL10	TST positivity	Ghana	[20]
Genome-wide	2q21-q24 (*GTDC1* and *ZEB2*) 5p13-q22	RSTR (longitudinal)	Uganda	[14] [16] [15]
	11p14 (*TST1*)	TST positivity (cross-sectional)	South Africa	[16]
	5p15 (*TST2*)	Reactivity (quantitative)		[18]
	5q31 (including *IL9*)	TST positivity and reactivity	Tanzania and Uganda	[19]

Table 2.

Summary of findings from genome-wide scans of TB disease

Approach	Locus (nearby gene)	Population	References
Linkage			
	5q23.2–31.3, 17p13.3–13.1, 20p13–12.3	Thais	[76]
	6p21–23 and 20q13.31–33	West Africans	[77]
	15q and Xq	Gambia and South Africa	[80]
	10q26.13, 11q12.3, and 20p12	Brazilians	[78]
	17q11–q21	Brazilians	[79]
	7p22–7p21	Uganda	[14]
Association			
**3 studies replicating same locus*	18q11.2 (*WT1*)	Ghana, Gambia, Malawia, Indonesia, South Africa, Russia	[81] [82, 83]
	14q24.2 11q21-q22	South Africa	[82]
	ASAP1	Russia	[84]
	HLA Variants	Russia, Iceland, Croatia	[86]
	20q12	Japan (young onset TB)	[87]
	5q33.3 (*IL12B*)	Uganda and Tanzania (HIV+)	[88]

Table 3.

Genes associated with severity

Gene	Definition of severity	Population	References
MCP1/MMP1/PAR1	Bandim TBscore	Peru	[99]
IL12B	Bandim TBscore	Uganda	[109]
SOCS	Parenchymal Involvement	Pakistan	[104]
IL17 & IFNG	Radiological/Clinical Severity	Argentina	[101]
TLR4	Bacillary load & Lung Involvement	India	[105]
CTLA4	Chest opacity size	Ghana	[108]
HLA-DRB1	Advanced nature of lung lesions	Korea	[102]
IL23R	Cavitary Disease	China (Uygur)	[100]
SLC11A1	Cavitary Disease	East India	[106]
TLR8	Bacterial Load	Pakistan	[98]