Human genetics of tuberculosis: a long and winding road

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Only a small fraction of individuals exposed to Mycobacterium tuberculosis develop clinical tuberculosis (TB). Over the past century, epidemiological studies have shown that human genetic factors contribute significantly to this interindividual variability, and molecular progress has been made over the past decade for at least two of the three key TB-related phenotypes: (i) a major locus controlling resistance to infection with M. tuberculosis has been identified, and (ii) proof of principle that severe TB of childhood can result from single-gene inborn errors of interferon-γ immunity has been provided; genetic association studies with pulmonary TB in adulthood have met with more limited success. Future genetic studies of these three phenotypes could consider subgroups of subjects defined on the basis of individual (e.g. age at TB onset) or environmental (e.g. pathogen strain) factors. Progress may also be facilitated by further methodological advances in human genetics. Identification of the human genetic variants controlling the various stages and forms of TB is critical for understanding TB pathogenesis. These findings should have major implications for TB control, in the definition of improved prevention strategies, the optimization of vaccines and clinical trials and the development of novel treatments aiming to restore deficient immune responses.

1. Introduction

Tuberculosis (TB) remains a major public health problem, as Mycobacterium tuberculosis infects an estimated one-third of the world’s population, resulting in approximately 8.6 million new cases of TB and approximately 1.3 million deaths in 2012 [1]. TB bacilli are transmitted by the inhalation of aerosolized droplets generated by the coughing of a patient with active TB. A substantial proportion of subjects do not become infected despite sustained high levels of exposure, as shown by negative tuberculin skin test (TST) and/or interferon (IFN)-γ release assays (IGRAs), and hence never develop disease (figure 1). About 5% of infected individuals develop clinical TB within 2 years of infection, either without latency or after a very short latent phase (figure 1) [2,3]. This ‘primary’ TB is particularly common in children, running an acute course and often associated with extrapulmonary disease owing to dissemination of the bacillus in the bloodstream [4,5]. However, most people infected with M. tuberculosis develop latent TB infection (LTBI). LTBI is characterized by positive TST and/or IGRA and an absence of overt clinical signs (figure 1) [2,6,7]. Most subjects with LTBI (approx. 90–95%) never develop clinical disease. The remaining 5–10% develop clinical TB later in life, typically owing to reactivation of the
original infection. This 'reactivation' TB is predominantly a chronic pulmonary disease of adults, resulting in extensive lung damage and the efficient airborne transmission of bacteria. Hence, individuals susceptible to infection display three clinical presentations: (i) not entering LTBI (primary TB), (ii) remaining with LTBI (silent infection) or (iii) exiting from LTBI (reactivation TB).

Clinical and epidemiological surveys conducted since the 1910s have provided strong evidence that each step underlying infection or disease is controlled by host genetic factors [8–10]. Familial aggregation studies have provided the most convincing evidence [9,10]. In families with an index sputum-positive TB patient, spouses with family histories of TB were found to develop manifest TB more frequently than those without such histories [10]. Twin studies have also shown much higher concordance rates for monogygotic than for dizygotic pairs for clinical TB (combining primary and reactivation TB) [10,11]. In the seminal study conducted by Kallmann and Reissner in New York State, 308 twin pairs in which one of the pair was a confirmed index TB case were studied [11]. In this sample, the percentage of twin siblings of index cases developing manifest TB (defined on the basis of clinical, chest X-ray and sputum examinations) was 66.7% for monogygotic twins (52/78) and 23% (53/230) for dizygotic twins [11]. Interestingly, similar percentages were obtained when the sample was subdivided into groups on the basis of the known history of exposure of the twin siblings to a known active TB patient (table 1). It has long been known that the incidence of TB is particularly high in newly exposed populations [9], such as African populations and native Americans [12]. Similarly, the susceptibility to M. tuberculosis infection of an exposed individual, as measured by the TST, has been shown to be correlated with the region of ancestry of the individual concerned [13,14]. As for clinical TB disease, familial studies, including twin studies, have shown TB infection phenotypes (mostly TST result, considered as a quantitative trait) to be highly heritable (more than 50%, as detailed in §2).

Furthermore, a long series of experimental studies in various animal models, beginning in the 1930s, has also established the importance of host genetic background for determining the outcome of infection with M. tuberculosis (reviewed in [7,15,16]). In mice, a key antimycobacterial molecule is indicative of innate resistance to M. tuberculosis infection. In household studies, 30–50% of contacts with heavy short-term exposure do not become infected [28,29], revealing substantial heterogeneity in susceptibility to infection. We and others have focused on TST and IGRA results as quantitative traits and have shown heritability to be high for the results of both tests following exposure to M. tuberculosis. In Gambia, a study of healthy twins estimated the heritability of TST responsiveness and quantitative IGRA reactivity at 71% and 39%, respectively [30]. The heritability of quantitative TST reactivity in young healthy children exposed to an active TB case has been estimated at 92% in Chile [31]. In a South African familial

Figure 1. A schematic of the natural history of human infection by M. tuberculosis, and the subsequent development of clinical TB. Despite sustained high-level exposure, a substantial proportion of subjects (approx. 10–20%) do not become infected, and hence never develop disease. About 5% of infected individuals develop clinical TB within 2 years of infection; this ‘primary’ TB is particularly common in children, and could be associated with extrapulmonary disease. The remaining persons infected with M. tuberculosis develop latent TB infection (LTBI). Only a minority of subjects with LTBI (approx. 5–10%) develop clinical TB during their lifetime, typically owing to reactivation of the original infection. (Online version in colour.)

2. Genetic control of tuberculosis infection

There is no direct test for infection with M. tuberculosis and the phenotype of M. tuberculosis infection is inferred exclusively from quantitative measurements of antimycobacterial immunity. These assays cannot distinguish a possible anamnestic response to M. tuberculosis from persistent infection with the bacillus. The TST is the most widely used method [25]. The skin induration generated by the TST is caused by the accumulation of histiocytes and T cells around intradermal deposits of M. tuberculosis antigens. More recently, two in vitro blood assays, measuring either the secretion of IFN-γ by lymphocytes or the frequency of IFN-γ producing blood cells in response to M. tuberculosis antigens (IGRAs), have been developed [26]. TST and IGRAs assess different aspects of antimycobacterial immunity and are not fully concordant in predicting infection with M. tuberculosis [27]. Little or no reactivity in these tests in individuals exposed to M. tuberculosis is indicative of innate resistance to M. tuberculosis infection. In household studies, 30–50% of contacts with heavy short-term exposure do not become infected [28,29], revealing substantial heterogeneity in susceptibility to infection. We and others have focused on TST and IGRA results as quantitative traits and have shown heritability to be high for the results of both tests following exposure to M. tuberculosis. In Gambia, a study of healthy twins estimated the heritability of TST responsiveness and quantitative IGRA reactivity at 71% and 39%, respectively [30]. The heritability of quantitative TST reactivity in young healthy children exposed to an active TB case has been estimated at 92% in Chile [31]. In a South African familiar

findings through demonstrations of an increase in the risk of TB in AIDS patients [20,21], in patients on anti-TNF treatment [22], and in patients with genetic defects impairing IFN-γ immunity [8,23,24]. These studies have clearly demonstrated the critical importance of CD4-mediated immunity and of the interleukin (IL)-12/IFN-γ loop in baseline resistance to M. tuberculosis, but the reasons for which individuals otherwise displaying full immune competence develop TB remain largely unknown. In this context, the identification of genetic variants increasing the risk of TB constitutes a powerful approach to deciphering the mechanistic basis of TB pathogenesis. We provide here an overview of the principal human genes known to underlie the interindividual variability of susceptibility at each of the three main steps in the natural course of M. tuberculosis infection. We also discuss the contribution of genetic research to the development of new approaches to combat TB.
3. Genetic control of severe primary tuberculosis

About 5% of infected individuals develop clinical TB within 2 years of infection (figure 1), either without latency or after a very short latent phase [3]. This ‘primary’ TB is particularly common in children, some of whom develop a haematogenous disseminated form (referred to here as ‘severe primary TB’) [2]. Severe primary TB was, by far, the most frequent form in children in areas of endemic disease before BCG vaccines and antimycobacterial antibiotics became available, resulting in high rates of mortality in children under the age of 2 years [9,23,41]. The risk of severe primary TB remains highly dependent on age at primary infection, decreasing from 10 to 20% for children under the age of 1 year to less than 0.5% for children over the age of 5 years [4,5]. These severe forms are mostly either miliary or affect the central nervous system (causing meningitis, in particular), and they remain life-threatening conditions [4,5]. BCG vaccination provides some protection against severe disseminated TB in childhood, but this protection is incomplete [42]. The development of antibiotics has greatly decreased childhood mortality due to TB, but more than 80,000 children still die from TB each year [43]. One of the fundamental unresolved questions in the field of childhood TB therefore concerns the nature of the predisposition to the development of severe clinical forms in only a minority of infected children. The findings

Table 1. Proportion of monozygotic and dizygotic twins of index cases with TB, as a function of the history of exposure of the co-twin to a known active TB patient, from the study by Kallmann & Reisner [11].

|                          | monozygotic co-twins |                         | dizygotic co-twins |                         |
|--------------------------|----------------------|-------------------------|-------------------|-------------------------|
|                          | number of TB cases   | total number            | % of TB cases     | number of TB cases      | total number            | % of TB cases     |
| history of exposure      |                      |                         |                   |                         |                        |                   |
| without known exposure   | 36                   | 52                      | 69.2              | 46                      | 175                     | 26.3              |
| total                    | 52                   | 78                      | 66.7              | 53                      | 230                     | 23.0              |

sample from an area of hyperendemic TB disease, the heritability of quantitative IFN-γ release responses was estimated to be between 43 and 58%, depending on the nature of the stimulating antigen [32]. Likewise, the heritability of the frequency of antigen-specific IFN-γ−CD4+ and IFN-γ−CD8+ has been estimated at 53–74% [32]. A complex segregation analysis of TST reactivity in related household contacts of TB index cases in a Colombian population provided evidence for a major codominant gene accounting for approximately 65% of TST variability [33]. By contrast, a family study conducted in Uganda reported a lower estimate of heritability for IGRA responses (approx. 17%) [34]. However, as IGRA reactivity was adjusted for TST response in this study, this lower estimate of heritability may reflect genetic components common to the TST and IGRA responses. More recent data from Uganda carefully adjusted for shared environment yielded higher estimates for the heritability of IGRA response (approx. 30%) [35].

Despite the strong evidence in favour of an impact of genetic factors on the assays used for LTBI, only a small number of studies have aimed to identify the genetic variants underlying susceptibility to M. tuberculosis infection. TST reactivity was the phenotype studied in all these studies. Candidate gene association studies have focused on TST response as a binary trait, defined according to various thresholds (0, 5 or 10 mm). In a large study of 3622 TST-positive individuals and 244 TST-negative healthy controls in Ghana, an IL10 promoter haplotype (−2849A/−1082A/−819C) was found to be significantly more frequent in TST-positive than in TST-negative subjects (15.3% versus 9.7%, odds ratio (OR) = 2.09 (1.2–3.5), p = 0.012) [36]. This haplotype was also associated with low levels of circulating IL-10, suggesting a role for IL-10 in the initial host response to M. tuberculosis. However, the similarity of age distribution between TST-negative and TST-positive subjects was not shown. Consistent with the findings for the sample from Ghana, the prevalence of TST negativity was found to be 1.5 times higher in individuals carrying the high-level IL-10-producing genotype GG at single nucleotide polymorphism (SNP) −1082A>G than in individuals carrying the AA and AG genotypes, in an indigenous population from Brazil [37]. Additional associations of cytokine genes with TST reactivity in the Brazilian sample have yet to be replicated.

In Uganda, a genome-wide (GW) linkage analysis reported results suggesting that persistent TST negativity (defined as a TST < 10 or 5 mm, according to age and HIV status) was linked to chromosomal regions 2q21–2q24 and 5p13–5q22 [38]. A study of TST reactivity in a sample of multiplex families from South Africa identified two major loci affecting TST-positivity per se (TST1) and the intensity of TST reactivity (TST2) [39]. TST1 was identified by focusing on the phenotype of TST positivity versus TST negativity (i.e. TST = 0), and maps to chromosome 11p14 (lod score = 3.81, p = 1.4 × 10−5). A second phenotype studied was the size in millimetres of the skin induration in TST-tested subjects. The size of the induration, considered as a quantitative trait, was impacted by a locus on chromosome 15p15 which was termed TST2 (lod score = 4.00, p = 9 × 10−6). The most parsimonious explanation for the role of these two loci is that TST1 reflects innate resistance to infection with M. tuberculosis whereas TST2 reflects T-cell-mediated antimycobacterial immune responses. Unexpectedly, it was subsequently discovered that a locus affecting the production of TNF by blood cells in response to bacillus Calmette–Guerin (BCG) and BCG plus IFN-γ, TNF1, is genetically indistinguishable from TST1 [40]. This raises the exciting possibility that innate resistance to M. tuberculosis infection may involve a TNF-mediated effector mechanism. Such a possibility dovetails neatly with the function of TNF in macrophage activation during early stages of infection. No GW association study (GWAS) has yet been performed for M. tuberculosis infection.
obtained in the last decade have provided the first clue to the riddle, by showing that at least some cases of severe TB can be explained by single-gene inborn errors of immunity.

The first molecular evidence that childhood TB might reflect a Mendelian predisposition came from the observation of severe TB in children with classical primary immunodeficiencies (PIDs) [44]. In particular, a substantial number of children with chronic granulomatous disease (CGD) were diagnosed with severe TB in several countries [45–49]. In a recent survey investigating the occurrence of mycobacterial diseases in CGD patients, TB was found to be rather common in patients living in countries in which TB is endemic [50]. However, CGD is a rare disorder characterized by a high prevalence of multiple infectious diseases. Further progress towards an understanding of the genetics of severe TB came from the study of the syndrome of Mendelian susceptibility to mycobacterial diseases (MSMDs), which is defined by a selective vulnerability to weakly virulent mycobacterial species, such as BCG and environmental mycobacteria [51]. MSMD patients also often suffer from non-typoidal, extraintestinal salmonellosis. Since 1996, germline mutations in seven autosomal (IFNGR1, IFNGR2, IL12B, IL12RB1, STAT1, IRF8, ISG15) and two X-linked (NEMO, CYBB) genes have been discovered in MSMD patients [8,52–55]. High levels of locus and allelic heterogeneity have resulted in the definition of 17 different disorders, accounting for about half the known cases [56]. These defects are physiologically related, as they all result in an impairment of IFN-γ immunity. Several MSMD patients, particularly those with IFN-γR1 [57,58] and IL-12p40 [59] deficiencies, have been shown to suffer from infections due to both weakly virulent mycobacteria and M. tuberculosis, raising the question as to whether the TB observed in these patients could also be attributed to a monogenic predisposition.

The first answer to this question came when several siblings of MSMD patients carrying the same genetic defect as the index case were found to display severe TB as their sole infectious phenotype. This situation was initially observed in a child with partial IFN-γ-R1 deficiency, who was a sibling of an MSMD patient [60], and was subsequently observed in a male subject from a large multiplex X-linked kindred carrying a specific mutation of CYBB impairing the IFN-γ-dependent respiratory burst in macrophages [53]. However, the most common genetic defect identified in patients with severe TB to date is complete IL-12RB1 deficiency [61]. In one family, an IL-12RB1-deficient sister of a patient with MSMD developed abdominal TB [62]. Several children with severe TB and complete IL-12RB1 deficiency in the absence of a familial history of infections with weakly virulent mycobacteria have been identified [63,64]. In a more systematic search for IL12RB1 mutations in 50 children with severe TB, two patients (4%) with complete IL-12RB1 deficiency were identified [24]. Overall, these results provided proof of principle for monogenic predisposition to severe TB, and raised the possibility that a substantial proportion of children with severe TB carry single-gene inborn errors of immunity. This proportion has been estimated at up to 45% by theoretical calculations [23], and can now be determined experimentally, by whole-exome and whole-genome sequencing. These findings have already paved the way for new treatments based on physiopathology. While until recently it was difficult to envision how point-of-care genotyping could be implemented in TB diagnosis, recent advances in hand-held PCR technology now suggest patient genotyping as a viable tool even in low- and middle-income countries [65,66]. The best example is provided by patients with IL-12RB1 deficiencies presenting TB owing to impaired IFN-γ production, for whom treatment with recombinant human IFN-γ, in addition to antimycobacterial drugs, has been shown to be effective [67].

4. Genetic control of pulmonary tuberculosis

Most people infected with M. tuberculosis present LTBI and do not develop primary TB (figure 1). Epidemiological studies have indicated that approximately 5–10% of individuals with LTBI go on to develop active TB during their lifetime, this risk decreasing with increasing time since infection [7,68]. Molecular epidemiology studies have shown that active TB due to reactivation of the original strain can occur decades after the initial infection [69]. The progression of infection within a subject from LTBI to pulmonary TB (PTB) reflects an impairment of host resistance to M. tuberculosis. This process may be triggered by acquired immunodeficiency, such as HIV infection or anti-TNF treatment. However, in subjects without overt immunodeficiency, the pathogenesis of reactivation remains unclear. As mentioned above, there is strong evidence that the development of PTB is influenced by host genetic factors. This genetic control is also likely to be different from that involved in primary TB [23,70]. Indeed, the study of genetic susceptibility to adulthood PTB has proved more difficult than that of susceptibility to severe childhood TB. In particular, no variants of genes from the IL12/IFN-γ circuit have been convincingly associated with PTB as yet. Current knowledge resulting from attempts to identify the genetic variants associated with PTB points to underlying heterogeneity, possibly due, at least in part, to the long-standing, multistep relationship between M. tuberculosis and its human host, through the natural history of PTB disease [71,72]. In particular, it is possible that specific subgroups of individuals with PTB have certain genetic risk factors, whereas other subgroups have other genetic risk factors. Such subgroups could potentially be defined on the basis of individual factors, such as clinical characteristics, or extrinsic factors, such as pathogen variability.

The vast majority of studies conducted to date to determine the molecular basis of PTB susceptibility have been association studies investigating the role of specific candidate genes. Most classical genetic association studies investigating PTB have focused on candidate genes, and a number of common risk variants have been reported in particular in immunity-related genes such as those encoding DC-SIGN, Toll-like receptors 1 and 2, vitamin D receptor, TNF, IL-1β or some HLA class II molecules [73]. However, there has been a lack of consistency between most of the reported results of independent studies [73,74]. One of the most convincing findings was the identification of associated polymorphisms of the NRAMP1 gene (alias SLC11A1), the human orthologue of the murine Nramp1 gene [17]. Following the initial association reported in a Gambian population [75], a meta-analysis of a large number of studies showed that several NRAMP1 polymorphisms were significantly associated with PTB in African and Asian populations, but not in populations of European descent [76]. Two studies also provided evidence of a role for NRAMP1 in early-onset TB. The first showed significant linkage to the NRAMP1 gene in a large aboriginal Canadian family in which an
outbreak of TB occurred [77]. In a follow-up study, common polymorphic alleles of NRAMP1 were shown to be strong risk factors for TB (OR = 3.13 (1.54–6.25)) in children living in Texas, mostly of Hispanic and African origin, resulting in an allelic association acting in the opposite direction to that observed in adults [78]. These observations are consistent with the hypothesis that NRAMP1 polymorphisms affect the speed of progression from infection to TB disease, accounting for the high frequency of some common alleles in patients with pediatric disease and the paucity of patients with the same alleles among TB cases with disease onset during adulthood. Overall, these studies provide strong support for a role of NRAMP1 in TB, with an effect that is heterogeneous across populations, epidemiological settings and clinical phenotypes. They also highlight the importance of considering age at TB onset in these analyses. Generally, in the field of infectious diseases, stronger genetic effects are more pronounced in early-onset cases than in late-onset cases [70]. For example, in leprosy the association of genetic variants with disease has been shown repeatedly to be highly age-dependent [79,80].

The concept of stronger genetic effects associated with early-onset disease was further supported by the positional cloning of the first major locus conferring predisposition to PTB, which was found to be linked to chromosome region 8q [81]. Refined association mapping of the linked region identified variants of the TOX gene as strongly associated (OR = 3.09 (1.99–4.78)) with the development of early-onset PTB (before 25 years of age) in populations from Morocco and Madagascar [82]. TOX encodes a nuclear factor involved in the development of T cells [83], particularly the CD4+ T cells [84,85], critical for immunity to mycobacteria [20]. Conversely, GWASs on PTB, considered as a single phenotype, have met with limited success to date. A first GWAS performed on a large sample from Gambia and Ghana identified a single SNP with a weak effect (OR = 1.19 (1.12–1.26)) located in a ‘gene desert’ on chromosome 18 as a risk factor for PTB [86]. Further imputation of the original Ghanaian data identified a second locus on chromosome 11p13 as protective against TB [87]. The main protective SNP allele was well replicated in the Gambian sample but displayed only borderline associations in Indonesian patients and in a very large sample (more than 10,000 subjects) from subjects from Russia [87]. Another GWAS recently conducted in a South African population confirmed the protective effect of the chromosome 11p13 factor but identified no new risk loci of GW significance [88]. Finally, a GWAS in Asian populations identified an independent TB risk locus in chromosome region 20q12, only in patients defined as ‘young cases’ (OR = 1.73 (1.42–2.11)) [89]. Based on the observed age distribution of this latter study, young cases were defined as having an onset of TB before the age of 45 years, although more refined analyses with lower age thresholds showed that higher deviations of p-values from the null hypothesis were observed with younger age cut-offs despite the lower number of cases in each subset [89]. Overall, a striking feature of these GWASs is the lack of replication of the PTB susceptibility factors previously detected in candidate gene analyses [8,73,74]. Overall, the GWAS results suggest that common variants may have a limited impact on predisposition to adult PTB, at least when considered as a single phenotype, and point to underlying heterogeneity, possibly in phenotype definition.

5. Perspectives

TB was long considered to be purely infectious, but there is increasing evidence to suggest that this disease also reflects host genetic vulnerability. However, the precise nature of the genetic factors involved remains largely unknown. Several non-mutually exclusive explanations can account for the difficulties experienced in identifying the causal variants, especially in GWASs. Genetic heterogeneity may play a role, together with a complex mode of inheritance involving incomplete penetrance and modifier genes [90,91]. Likewise, the contribution of rare variants to TB pathogenesis is attracting attention for two main reasons: (i) conceptually, rare variants bridge the gap between Mendelian and complex inheritance, and may account for the major loci identified through linkage studies [56,70,92]; (ii) experimentally, these variants abound in the genome and can now be studied by whole-exome and whole-genome sequencing [93,94]. However, the phenotypic heterogeneity of TB-related traits causes more serious problems. For example, three measurements of immune reactivity are currently used to detect infection with M. tuberculosis. However, the results of these tests display limited concordance, and each assay captures a different aspect of the antimycobacterial response [27]. MSMD probably provides the best example of the critical interplay between phenotype and genetic control. The syndromic phenotype is MSMD, but the identification of the underlying genetic defects was greatly facilitated by establishing endophenotypes (e.g. specific patterns of cytokine production such as IL-12 and IFN-γ [95]), guiding subsequent genetic analysis. Endophenotypes are more closely related to gene function and are likely to be generally useful for the dissection of TB phenotypes. In PTB, the most commonly used phenotype-defining characteristic is the presence of M. tuberculosis in the sputum of patients, regardless of the other clinical, microbiological and demographic covariables. This approach completely ignores the dynamic nature of pulmonary TB, the likelihood of different stages of this process being under different genetic controls, as shown in a mouse model of BCG infection [96], and the possible impact of the M. tuberculosis strain on LTBI and clinical outcome [97–99]. The need for improvements in the definition of a more homogeneous and more refined TB phenotype for genetic studies is also demonstrated by the strong impact of age at onset of disease on our ability to detect genetic effects in clinical TB [78,82].

Traditional genetic approaches will also benefit from a better understanding of the molecular mechanisms of TB pathogenesis throughout the infectious cycle. For example, transcriptomic studies, including the search for loci involved in the expression of genes and/or microRNAs (expression quantitative trait loci, eQTL) in cell- or tissue-specific studies [100], based on RNA-seq in particular [101], are of major importance. A transcriptomic analysis of peripheral blood cells identified a neutrophil-driven IFN-α/β-inducible transcript signature in individuals with active PTB [102]. This blood signature was validated in independent studies [103–105], and was shown to be different from that of several infectious and pulmonary diseases [102,106], providing new insights into the most relevant pathways and candidate biomarkers for investigation in TB [107]. Some eQTLs associated with variation in gene expression levels in dendritic cells infected with M. tuberculosis [108] have also provided
interesting candidate loci that remain to be tested for association with TB infection phenotypes. It is also possible that somatic mutations and epigenetic effects have a substantial impact on clinical susceptibility to TB, particularly in patients with late-onset disease [70]. Epigenetic mechanisms play a critical role in the immune system [109], and their investigation, particularly through GW analyses of the methylome [110,111], should provide new insight into the genetic basis of infection and clinical TB [112]. These epigenetic factors may be influenced by environmental and/or other host factors, such as diet, vitamin status or ageing [113,114], leading to additional possible gene × environment interaction effects. One of the main challenges in the next few years will be the integrated analysis of all these different sources of genomic information [115,116]. Finally, studies of various animal models, including zebrafish [90,91], rodents [15,16,117] and non-human primates [117,118], will be essential to provide critical information complementary to that obtained in human studies [7].

In the principal countries in which TB is endemic, disease control is based largely on passive case identification and drug treatment. This approach has proved effective for decreasing case mortality and human suffering, but the impact of current TB control on global TB trends is less clear [119–121]. The emergence and spread of extremely drug resistant strains resistant to the antibiotics currently available are warning signs that additional approaches will be required to halt endemic TB [122]. The availability of an effective vaccine against post-primary TB would provide us with a useful tool for decreasing TB transmission. Unfortunately, recent vaccine trials have yielded disappointing results [123,124], possibly reflecting our incomplete understanding of intrinsic vulnerability to TB as (i) mice that are genetically more resistant to M. tuberculosis infection benefit more from BCG vaccination than their susceptible counterparts [125], (ii) antimycobacterial immunity in humans is highly heritable and, thus, has a strong genetic component [30–32] and (iii) TB patients are more likely to suffer subsequent episodes of TB than would be expected on the basis of population incidence, strongly suggesting that TB patients have a susceptibility that cannot be overcome by conventional vaccination and/or antibiotics [126]. The strong positive selection of T-cell epitopes by M. tuberculosis across clinical strains presents an additional hurdle for vaccine development [127]. Taken together, these experimental data and observations in natura suggest that any effective TB vaccine must take into account the genetic susceptibility of patients if it is to trigger a protective response. Likewise, new therapeutic approaches based on the complementation of a specific immunodeficiency identified by human genetics should also have a positive complementary impact on the classical treatment of TB. For example, young patients developing disseminated TB during primary infection owing to the impaired production of IFN-γ (such as those with IL12RBI mutations) would benefit from targeted treatment with recombiant IFN-γ [67]. Finally, the recent discovery of TST1 as a locus with an impact on intrinsic resistance to infection with M. tuberculosis provides another example for the usefulness of human genetics in TB control [39]. Once identified, the molecular mechanisms underlying TST1 might constitute attractive targets for the prevention of infection by drug-based or vaccine interventions. The prevention of infection is the gold standard for stopping the TB endemic and studies of host genetics are an important weapon in the war against TB.

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References

1. WHO. 2013 Global tuberculosis report. Geneva, Switzerland: World Health Organization.
2. Stewart GR, Robertson BD, Young DB. 2003 Tuberculosis: a problem with persistence. Nat. Rev. Microbiol. 1, 97 – 105. (doi:10.1038/nrmicro749)
3. Zuma A, Raviglione M, Halter R, von Reyn CF. 2013 Tuberculosis. N Engl. J. Med. 368, 745 – 755. (doi:10.1056/NEJMra1200894)
4. Cruz AT, Starke JR. 2007 Clinical manifestations of tuberculosis in children. Pediatr. Respir. Rev. 8, 107 – 117. (doi:10.1016/j.prrv.2007.04.008)
5. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. 2006 Childhood pulmonary tuberculosis: old wisdom and new challenges. Am. J. Respir. Crit. Care Med. 173, 1078–1090. (doi:10.1164/rccm.200511-180950)
6. Ernst JD. 2012 The immunological life cycle of tuberculosis. Nat. Rev. Immunol. 12, 581 – 591. (doi:10.1038/nri3259)
7. O’Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP. 2013 The immune response to tuberculosis. Annu. Rev. Immunol. 31, 475 – 527. (doi:10.1146/annurev-immunol-030711-073827)
8. Casanova JL, Abel L. 2002 Genetic dissection of immunity to mycobacteria: the human model. Annu. Rev. Immunol. 20, 581 – 620. (doi:10.1146/annurev.immunol.20.081501.125831)
9. Dubos RJ, Dubos J. 1952 The white plague; tuberculosis, man and society, 1st edn, p. 277. Boston, MA: Little Brown.
10. Puffer R. 1944 Familial susceptibility to tuberculosis; its importance as a public health problem, p. 106. Cambridge, MA: Harvard University Press.
11. Kilman J, Reiser D. 1943 Twin studies on the significance of genetic factors in tuberculosis. Am. Rev. Tuberc. 47, 549 – 574.
12. Stead WW. 1997 The origin and erratic global spread of tuberculosis. Am. Rev. Respir. Dis. 155, 1651 – 1655. (doi:10.1164/00024854.155.5.1651)
13. Stead WW. 1992 Genetics and resistance to tuberculosis. Could resistance be enhanced by genetic engineering? Ann. Intern. Med. 116, 937 – 941. (doi:10.7326/0003-4819-116-11-937)
14. Stead WW, Senner JW, Reddick WT, Lofgren JP. 1990 Racial differences in susceptibility to infection by Mycobacterium tuberculosis. N. Engl. J. Med. 322, 422 – 427. (doi:10.1056/NEJM199002223220702)
15. Di Pietrantonio T, Schurr E. 2005 Mouse models for the genetic study of tuberculosis susceptibility. Brief Funct. Genomics Proteomics 4, 277 – 292. (doi:10.1016/j.bfgp.2004.12.001)
16. Fortin A, Abel L, Casanova JL, Gros P. 2007 Host genetics of mycobacterial diseases in mice and men: forward genetic studies of BCG-osis and tuberculosis.
30. Jepson A, Fowler A, Banya W, Singh M, Bennett S, Marks SM, Taylor Z, Qualls NL, Shrestha-Kuwahara L. 2006 An update on the diagnosis of Mycobacterium tuberculosis. Am. J. Respir. Crit. Care Med. 174, 399–422. (doi:10.1164/ajrccm.174.4.20060000)

31. Sepulveda RJ, Heiba IM, King A, Gonzalez B, Elston RC, Sorensen RU. 1994 Evaluation of tuberculin reactivity in BCG-immunized siblings. J. Am. Respir. Crit. Care Med. 149, 620–624. (doi:10.1164/ajrccm.149.3.8118628)

32. Cobat A et al. 2010 High heritability of antitymocytobacterial immunity in an area of hyperendemicity for tuberculosis disease. J. Infect. Dis. 201, 15–19. (doi:10.1086/646611)

33. Cobat A, Barraza LF, Henao H, Arebelaez P, Abel L, Garcia LF, Schurz E, Alcais A. 2012 Tuberculin skin test reactivity is dependent on host genetic background in Colombian tuberculosis household contacts. Clin. Infect. Dis. 54, 968–971. (doi:10.1093/cid/cis972)

34. Stein CM, Guwatudde D, Nakaketo M, Peters P, Elston RC, Twian HI, Mugwera R, Whalen CC. 2003 Heritability analysis of cytokines as intermediate phenotypes of tuberculosis. J. Infect. Dis. 187, 1679–1685. (doi:10.1086/375249)

35. Tao L, Zulwango S, Cheruvak S, Thiel B, Malone LL, Qui F, Mayan-Koza H, Boom WH, Stein CM. 2013 Genetic and shared environmental influences on interferon-gamma production in response to Mycobacterium tuberculosis antigens in an Ugandan population. Am. J. Trop. Med. Hyg. 89, 169–173. (doi:10.4269/ajtmh.12-0670)

36. Thye T et al. 2009 IL10 haplotype associated with tuberculin skin test response but not with pulmonary TB. PLoS ONE 4, e5420. (doi:10.1371/journal.pone.0005420)

37. Zembrzuski VM, Basta PC, Coligang-Jacques SM, Santos RV, Coimbra CE, Salzano FM, Hutz MH. 2010 Cytokine genes are associated with tuberculin skin test response in a native Brazilian population. Tuberculosis (Edinb) 90, 44–49. (doi:10.1016/j.tube.2009.11.002)

38. Stein CM et al. 2008 Genome scan of M. tuberculosis infection and disease in Iranians. PLoS ONE 3, e4094. (doi:10.1371/journal.pone.0004094)

39. Cobat A et al. 2009 Two loci control tuberculin skin test reactivity in an area of hyperendemicity for tuberculosis. J. Exp. Med. 206, 2583–2591. (doi:10.1084/jem.200908692)

40. Cobat A et al. 2013 Identification of a major locus, INFI, that controls BCG-triggered tumor necrosis factor production by leukocytes in an area hyperendemic for tuberculosis. Clin. Infect. Dis. 57, 963–970. (doi:10.1093/cid/cit338)

41. Banke T. 1910 Diagnose und epidemiologie des Tuberkel. Lancet 75, 279–306.

42. Marks SM, Taylor Z, Qualls NL, Shrestha-Kuwahara RJ, Wilce MA, Nguyen CH. 2000 Outcomes of contact investigations of infectious tuberculosis patients. Am. J. Respir. Crit. Care Med. 162, 2033–2038. (doi:10.1164/ajrccm.162.6.20000422)

43. Jepson A, Fawer A, Banya V, Singh M, Bennett S, Whittle H, Hill AV. 2001 Genetic regulation of acquired immune responses to antigens of Mycobacterium tuberculosis: a study of twins in West Africa. Infect. Immun. 69, 3989–3994. (doi:10.1128/IAI.69.6.3989-3994.2001)

44. Reichenbach J, Rosenzweig S, Doffinger R, Dupuis S, Whalen CC. 2001 Tuberculosis associated with chronic granulomatous disease in two of fifty children with severe tuberculosis infection living in a region endemic for tuberculosis. Clin. Infect. Dis. 34, S384–S390. (doi:10.1086/517036)

45. Bustamante J et al. 2007 BCG-osis and tuberculosis in a child with chronic granulomatous disease. J. Allergy Clin. Immunol. 120, 32–38. (doi:10.1016/j.jaci.2007.04.034)

46. Lau YL, Chan GC, Ha SY, Hui YF, Yuen KY. 1998 The role of phagocytic respiratory burst in host defense against Mycobacterium tuberculosis. Clin. Infect. Dis. 26, 226–227. (doi:10.1086/517036)

47. Lee PP et al. 2008 Susceptibility to mycobacterial infections in children with X-linked chronic granulomatous disease: a review of 17 patients living in a region endemic for tuberculosis. Pediatr. Infect. Dis. J. 27, 224–230. (doi:10.1097/INF.0B013e318159f945)

48. Marotte B et al. 2008 Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. Clin. Immunol. 126, 155–164. (doi:10.1016/j.clim.2007.09.008)

49. Mohammedi M et al. 2004 Chronic granulomatous disease: a clinical survey of 41 patients from the Iranian primary immunodeficiency registry. Int. Arch. Allergy Immunol. 134, 253–259. (doi:10.1159/000078774)

50. Conti et al. Submitted. Mycobacterial diseases in 71 patients with chronic granulomatous disease.

51. Al-Muhsem S, Casanova JL. 2008 The genetic heterogeneity of Mendelian susceptibility to mycobacterial diseases. J. Allergy Clin. Immunol. 122, 1043–1051; quiz 1052–1043. (doi:10.1016/j.jaci.2008.10.037)

52. Bogunovic D et al. 2012 Mycobacterial disease and impaired IFN-gamma immunity in humans with inherited ISG15 deficiency. Science 337, 1684–1686. (doi:10.1126/science.1224026)

53. Bustamante J et al. 2011 Germline CYBB mutations that selectively affect macrophages in kindreds with X-linked predisposition to tuberculous mycobacterial disease. Nat. Immunol. 12, 213–221. (doi:10.1038/ni.1992)

54. Filip-Santos D et al. 2006 Inborn errors of IL-12/23- and IFN-gamma-mediated immunity; molecular, cellular, and clinical features. Semin. Immunol. 18, 347–361. (doi:10.1016/j.smim.2006.07.010)

55. Hambleton S et al. 2011 IRF8 mutations and human dendritic-cell immunodeficiency. N. Engl. J. Med. 365, 127–138. (doi:10.1056/NEJMoa1100666)

56. Casanova JL, Abel L. 2013 The genetic theory of infectious diseases: a brief history and selected illustrations. Annu. Rev. Genomics Hum. Genet. 14, 215–243. (doi:10.1146/annurev-genom-091212-153448)

57. Dorman SE et al. 2004 Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. Lancet 364, 2113–2121. (doi:10.1016/S0140-6736(04)68752-1)

58. Sasaki Y, Nomura A, Kusuhara K, Takada H, Ahmed S. 2007 IL12B deficiency as a predominant type. Annu. Rev. Immunol. 25, 227–257. (doi:10.1146/annurev.immunol.25.020706.092315)

59. Picard C et al. 2001 Genetic basis of patients with bacille Calmette-Guerin osteomyelitis in Japan: identification of dominant partial interferon-gamma receptor 1 deficiency as a predominant type. J. Infect. Dis. 185, 706–709. (doi:10.1086/339011)

60. Pickard C et al. 2002 Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. Am. J. Hum. Genet. 70, 336–348. (doi:10.1086/338625)

61. Josangy E et al. 1997 Partial interferon-gamma receptor 1 deficiency in a child with tuberculoid
bacillus Calmette-Guérin infection and a sibling with clinical tuberculosis. J. Clin. Invest. **100**, 2656–2664. (doi:10.1172/JCI119810)

61. de Beaucoudrey L et al. 2010 Revisiting human IL-12beta1 deficiency: a survey of 141 patients from 30 countries. Medicine (Baltimore) **89**, 381–402. (doi:10.1097/MD.0b013e31816dd832)

62. Altare F et al. 2001 Interleukin-12 receptor beta1 deficiency in a patient with abdominal tuberculosis. *J. Infect. Dis.* **184**, 231–236. (doi:10.1086/321999)

63. Caragol I et al. 2003 Clinical tuberculosis in 2 of 3 siblings with interleukin-12 receptor beta1 deficiency in a child with disseminated tuberculosis. *Clin. Infect. Dis.* **37**, 302–306. (doi:10.1086/375587)

64. Ozbek N, Fieschi C, Yilmaz BT, de Beaucoudrey L, et al. 2000 Linkage of tuberculosis to chromosome 2q35 loci, including *NRAMP1*, in a large aboriginal Canadian family. *Am. J. Hum. Genet.* **67**, 405–416. (doi:10.1086/303102)

65. Myers FB, Henrikson RH, Bone J, Lee LP. 2013 A novel polymorphism in the human IRGM gene and susceptibility to tuberculosis. *FEMS Immunol. Med. Microbiol.* **67**, 274–277. (doi:10.1016/j.femsim.2013.03.013)

66. Roberts JD et al. 2012 Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID trial). *Eur. J. Clin. Pharmacol.* **68**, 1052–1060. (doi:10.1007/s00228-012-1405-3)

67. Aliahmad P, Seksenyan A, Kaye J. 2012 The many roles of TOX in the immune system. *J. Exp. Med.* **205**, 245–256. (doi:10.1084/jem.20071944)

68. Thye T et al. 2010 Genome-wide association analyses identifies a susceptibility locus for tuberculosis on chromosome 18q11.2. *Nat. Genet.* **42**, 739–741. (doi:10.1038/ng.639)

69. Comas I et al. 2013 Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans. *Nat. Genet.* **45**, 1176–1182. (doi:10.1038/ng.2744)

70. Alcais A, Quintana-Murci L, Thaler DS, Schurr E, Abel L, Casanova JL. 2010 Life-threatening infectious diseases of childhood: single-gene inborn errors of immunity? *Ann. N Y Acad. Sci.* **1214**, 18–33. (doi:10.1111/j.1749-6632.2010.05834.x)

71. Azad AK, Sadee W, Schlesinger LS. 2012 Innate immune gene polymorphisms in tuberculosis. *Infect. Immun.* **80**, 3343–3359. (doi:10.1128/IAI.00443-12)

72. Bellamy R, Ruwende C, Cornah T, McAdam KP, Whittle HC, Hill AV. 1998 Variations in the NRAMP1 gene and susceptibility to tuberculosis in West Africans. *N Engl. J. Med.* **338**, 640–644. (doi:10.1056/NEJM199903303380102)

73. Malik S et al. 2005 Alleles of the NRAMP1 gene are risk factors for pediatric tuberculosis disease. *Proc. Natl. Acad. Sci. USA* **102**, 12183–12188. (doi:10.1073/pnas.0503368102)

74. Alcas A et al. 2007 Stepwise replication identifies a low-producing lymphotoxin-alpha allele as a major risk factor for early-onset leprosy. *Nat. Genet.* **39**, 517–522. (doi:10.1038/ng0000)

75. Herb F et al. 2008 ALOX5 variants associated with susceptibility to human pulmonary tuberculosis. *Hum. Mol. Genet.* **17**, 1052–1060. (doi:10.1093/hmg/ddm378)

76. Pirofski LA et al. 2005 Autophagy gene variant IRGM6–261T contributes to protection from tuberculosis caused by *Mycobacterium tuberculosis* but not by *M. africanum* strains. *PLoS Pathog.* **5**, e1000577. (doi:10.1371/journal.ppat.1000577)

77. Intemann CD et al. 2008 Common variants at 11p13 are associated with susceptibility to tuberculosis in Asians identify distinct at-risk locus for young tuberculosis. *J. Hum. Genet.* **57**, 363–367. (doi:10.1038/jhg.2012.23)

78. Behr M, Schurr E, Gross P. 2010 TB: screening for responses to a vile visitor. *Cell* **140**, 615–618. (doi:10.1016/j.cell.2010.02.030)

79. Miotto DM et al. 2010 The Ita4 locus modulates susceptibility to mycobacterial infection in zebrafish and humans. *Cell* **140**, 717–730. (doi:10.1016/j.cell.2010.02.013)

80. Behr M, Casanova JL. 2000 Genetic predisposition to clinical tuberculosis: bridging the gap between simple and complex inheritance. *Am. J. Hum. Genet.* **67**, 274–277. (doi:10.1086/360303)

81. Herb F et al. 2008 ALOX5 variants associated with susceptibility to human pulmonary tuberculosis. *Hum. Mol. Genet.* **17**, 1052–1060. (doi:10.1093/hmg/ddm378)

82. Herb F et al. 2008 ALOX5 variants associated with susceptibility to human pulmonary tuberculosis. *Hum. Mol. Genet.* **17**, 1052–1060. (doi:10.1093/hmg/ddm378)

83. Intemann CD et al. 2008 Autophagy gene variant IRGM6–261T contributes to protection from tuberculosis caused by *Mycobacterium tuberculosis* but not by *M. africanum* strains. *PLoS Pathog.* **5**, e1000577. (doi:10.1371/journal.ppat.1000577)

84. Intemann CD et al. 2008 Autophagy gene variant IRGM6–261T contributes to protection from tuberculosis caused by *Mycobacterium tuberculosis* but not by *M. africanum* strains. *PLoS Pathog.* **5**, e1000577. (doi:10.1371/journal.ppat.1000577)

85. Nicol MP, Wilkinson RJ. 2008 The clinical consequences of strain diversity in *Mycobacterium tuberculosis* transmission. *Res. Soc. Trop. Med. Hyg.* **102**, 955–965. (doi:10.1611/lsrtm.2008.03.025)

86. Gregersen PK. 2012 Cell type-specific eQTLs in the human immune system. *Nat. Genet.* **44**, 478–480. (doi:10.1038/ng.2588)

87. Pickrell JK et al. 2010 Understanding mechanisms underlying human gene expression variation with RNA sequencing. *Nature* **464**, 768–772. (doi:10.1038/nature08872)

88. Berry MP et al. 2010 An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature* **466**, 973–977. (doi:10.1038/nature09247)

89. Clif JM et al. 2013 Distinct phases of blood gene expression pattern through tuberculosis treatment reflect modulation of the humoral immune response. *J. Infect. Dis.* **207**, 18–29. (doi:10.1093/clinfects/jis499)
and resistance in tuberculosis. Genes Immun. 12, 15–22. (doi:10.1038/geni.2010.51)

105. Ottenhoff TH et al. 2012 Genome-wide expression profiling identifies type 1 interferon response pathways in active tuberculosis. PLoS ONE 7, e45839. (doi:1371/journal.pone.0045839)

106. Bloom CI et al. 2013 Transcriptional blood signatures distinguish pulmonary tuberculosis, pulmonary sarcoidosis, pneumonias and lung cancers. PLoS ONE 8, e70630. (doi:1371/journal.pone.0070630)

107. Berry MP, Blankley S, Graham CM, Bloom CI, O’Garra A, et al. 2013 Systems approaches to studying the immune response in tuberculosis. Curr. Opin. Immunol. 25, 579–587. (doi:10.1016/j.coi.2013.08.003)

108. Barreiro LB, Taillieux L, Pai AA, Gicquel B, Marioni JC, Gilad Y. 2012 Deciphering the genetic architecture of variation in the immune response to Mycobacterium tuberculosis infection. Proc. Natl Acad. USA 109, 1204–1209. (doi:10.1073/pnas.1115761109)

109. Suarez-Alvarez B, Rodriguez RM, Fraga MF, Lopez-Lamea C. 2012 DNA methylation: a promising landscape for immune system-related diseases. Trends Genet. 28, 506–514. (doi:10.1016/j.tig.2012.06.005)

110. Knueger F, Kneck B, Franke A, Andrews SR. 2012 DNA methyline analysis using short bisulfite sequencing data. Nat. Methods 9, 145–151. (doi:10.1038/nmeth.1828)

111. Laird PW. 2010 Principles and challenges of genomewide DNA methylation analysis. Nat. Rev. Genet. 11, 191–203. (doi:10.1038/nrg2732)

112. Esterhuysen MM, Linhart HG, Kaufmann SH. 2012 Can the battle against tuberculosis gain from epigenetic research? Trends Microbiol. 20, 220–226. (doi:10.1016/j.tim.2012.03.002)

113. Chiachiera F, Piunti A, Pasini D. 2013 Evolutionarily conserved epigenetic methylations and their connections with metabolism. Cell Mol. Life Sci. 70, 1495–1508. (doi:10.1007/s00018-013-1293-5)

114. Kaelin Jr WG, McKnight SL. 2013 Influence of metabolism on epigenetics and disease. Cell 153, 56–69. (doi:10.1016/j.cell.2013.03.004)

115. Hawkins RD, Hon GC, Ren B. 2010 Next-generation DNA methylome analysis using short bisulfite sequencing data. Nat. Methods 7, 1179–1186. (doi:10.1038/nrmicro2795)

116. Knight JC. 2013 Genomic modulators of the immune response. Trends Genet. 29, 74–83. (doi:10.1016/j.tig.2012.10.006)

117. O’Toole R. 2010 Experimental models used to study human tuberculosis. Adv. Appl. Microbiol. 71, 75–89. (doi:10.1016/S0065-2164(10)71003-0)

118. Flynn JL. 2006 Lessons from experimental Mycobacterium tuberculosis infections. Microbes Infect. 8, 1179–1188. (doi:10.1016/j.micinf.2005.10.033)

119. Raviglione M. 2006 Lessons from experimental Mycobacterium tuberculosis infections. Microbes Infect. 8, 1179–1188. (doi:10.1016/j.micinf.2005.10.033)

120. Oxlade O, Schwartzman K, Behr MA, Benedetti A, Pai M, Heymann J, Menzies D. 2009 Global tuberculosis trends: a reflection of changes in population health. Int. J. Tuberc. Lung Dis. 13, 1238–1246.

121. Oxlade O, Schwartzman K, Benedetti A, Pai M, Heymann J, Menzies D. 2011 Developing a tuberculosis transmission model that accounts for changes in population health. Med. Decis. Making 31, 53–68. (doi:10.1177/0272989X10369001)

122. Lienhardt C, Glaziou P, Uplekar M, Lonnoth K, Getahun H, Raviglione M. 2012 Global tuberculosis control: lessons learnt and future prospects. Nat. Rev. Microbiol. 10, 407–416. (doi:10.1038/nrmmicro2797)

123. Ota MO et al. 2011 Immunogenicity of the tuberculosis vaccine MV85A is reduced by coadministration with EPI vaccines in a randomized controlled trial in Gambian infants. Sci. Transl. Med. 3, 88ra56. (doi:1126/scitranslmed.3002461)

124. Tameris MD et al. 2011 Safety and efficacy of MV85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. Lancet 381, 1021–1028. (doi:10.1016/S0140-6736(13)60177-4)

125. Medina E, North RJ. 1999 Genetically susceptible mice remain proportionally more susceptible to tuberculosis after vaccination. Immunology 96, 16–21. (doi:10.1046/j.1365-2567.1999.00663.x)

126. Verver S et al. 2005 Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. Am. J. Respir. Crit. Care Med. 171, 1430–1435. (doi:1164/rcrcc.200409-12000C)

127. Comas I, Chakavartti J, Small PM, Galagan J, Niemann S, Kremer K, Ernst JD, Gagneux S. 2010 Human T cell epitopes of Mycobacterium tuberculosis are evolutionarily hypervaried. Nat. Genet. 42, 498–503. (doi:1038/ng.590)