Precision medicine and tuberculosis.

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Abstract

The era of molecular medicine begun after the completion of the Human Genome Project in 2003 (NHGRI). The availability of the data base of approximately 3 billion base pairs and 30,000 genes in human DNA has led to a better understanding of physiological and pathological changes in the human body.

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Precision Medicine

After US President Barack Obama proposed in 2015 the "Precision Medicine Initiative" and provided US$215 million for the program in obtaining the breach of human genome in associated with diseases, the Genome-Wide Association Studies (GWAS) started.

GWAS is considered the most powerful available tool to study the association between phenotypes and genotypes and also to identify common low-penetrance susceptibility loci in a particular disease. Each person gave a sample of DNA, from which millions of genetic variants are read using SPN arrays. If one type of variant (one allele) is more frequent in people with the disease, the variant is said to be associated with that disease [1].

Tuberculosis

Tuberculosis is an infectious disease generally caused by inhaling the acid-fast *Mycobacterium tuberculosis* (*Mtb*). It is a disease that anyone can contract at any age - anywhere in the world, although it is only about 90% of those infected with *Mtb* have asymptomatic, latent TB infection, with only a 10% lifetime chance of progression to clinically active TB. Those are particular groups of individuals with insufficient innate immunity or suppressed immune systems, such as infants, foreign-born individuals in TB-prevalent countries, HIV/AIDS patients, diabetics, alcoholics, long-standing users of immune-suppression drugs, such as corticosteroids, and people living in countries with poor sanitation and crowded conditions, such as had been the case in South Asia and South-East Asia among other regions of the world [2].

Formerly, tuberculosis was prevented, as well as diagnosed and treated by circumstantial and various clinical means. Such achievements depended largely on the variable potentiality of the attention paid by and the ambiguity of the humans responsible, which left behind a large pool of infective sources.

In the current era of advanced genomic technology, however, human genetic study is a novel approach to understanding the molecular basis of this and other diseases. Medical practice is adapting to comprehensive "precision medicine", but the question remains: "Is it possible for precision medicine ever to lead to control of tuberculosis?" [3].

In responding to such a question, one must precisely understand the molecular basis of tuberculosis and its causative organism. In recent years, human genetics has achieved tremendous progress in its approach to understanding the molecular basis of human diseases. The theme of human genetics involves genes and genetic variations. The diversity of genetic susceptibility to common diseases in the human population enables researches to understand the molecular mechanisms of tuberculosis pathogenesis by the genetic approach [4].

Unfortunately, our extensive literature review of available reports indicated that most hypothesis-free efforts on world-wide research to revamp the traditional idea of TB genetic susceptibility have not identified candidate genes playing an important role in limiting *Mtb* infection in association with active tuberculosis. Further, TB-association loci in the genome-wide association study (GWAS) found no gene that functions in *Mtb* infection. Nevertheless, hope remains based on a few findings cited in the following papers, although it should be mentioned that controversy continues [5].

• A few loci worthy of attention, i.e. *2q35* (Greenwood CM, et al. Am J Hum Genet 2000; 67: 405-16), *8q12313* (Baghdadi JE, et al. J Exp Med 2006; 203: 1679-84), and *20q13* reported in African populations (Stein CM, et al. PLoS One 2008; 3:e4094. PubMed: *19116662*), and *5p15* in linkage with delayed type *hypersensitivity* (Cobut A, et al. J Exp Med 2009; 206: 2583-91).

• The linkage locus at *chr2q35* contains a candidate gene *SLC11A1*. The gene associated with TB is a solute carrier family 11 member 1 gene *(SLC11A1)* at *Chr2q35*, which is the natural resistance-associated macrophage protein 1 gene *(NRAMP1);* the genetic effect is absolutely unrelated to DTH response (Forget A, et al. Infect Immun 1981; 32: 42-47).

• *NRAMP1* is a proton acting as a divalent-metal efflux pump at the phagosomal membrane of macrophage; it depletes divalent metal as Zn^{2+}, CU^{2+}, FE^{2+} and Mn^{2+} from bacteria-containing phagosomes. Deletion of these divalent metals may render the *MTB* more sensitive to the killing by oxygen radicals (Forbes JR, et al. Trends Microbiol 2001; 9: 397-403).

• A number of studies have reported the genetic association of *HLA* class II polymorphisms with TB susceptibility. The DQbeta1Asp57 allele was associated with increased risk of progressive pulmonary tuberculosis. The DQbeta1Asp57 demonstrates reduced ability to bind to the immunogenic peptides of *MTB*, which may weaken the Th1 response. (Delgado JC, et al. J Immunol 2006; 176:1090-7).

• Increased TB susceptibility was associated with the DR2allele in Indonesian (Bothamley GH, et al. J Infect Dis 1989; 159: 549-55) and Asian Indian (Brahmajothi V, et al. Tubercle 1991; 72: 123-32), the DQB1*0503 allele in Cambodian (Goldfeld AE, et al. JAMA 1998; 279: 226-8).

• Genome-wide SNP-based linkage in tuberculosis patients in Thais (Mahasirimongkol S, et al. Genes Immun 2008; 10: 77-83) [6].

• Toll-like receptors (TLRs) play an essential role in the activation of innate immunity against microbial infection (Takeda K, et al. Semin Immunol 2004; 16: 3-9). Davila S, et al. identified the TB association of the TLR7 and TLR8 locus in Indonesian cohort. This study highlights the potential function of the TLRs in anti TB immunity (PLOs Genet 2008; 4:e1000218; PubMed: 18927625).

• The DNA variations of the IFN-y gene *(IFNG)* were associated with TB susceptibility (Dorman SE, et al. The Lancet 2004; 364: 2113-21).

• MSMD mutations of the IL-12 signaling gene which have the phenotypes with low penetrance and better prognosis (Fieschi C, et al. J Exp Med 2003; 197: 527-35; Picard C, et al. Am J Hum Genetics 2002; 70: 336-48).

• Identification of a novel association tagged by a single-nucleotide polymorphism (SNP) *rs4331426* at *18q11.2.* (Thye T, et al. Nat Genet 2010; 42(9):739-41).

• Findings suggesting that host genetic risks for TB are affected by age at onset of TB (Mahasirimongkol S, et al. J Hum Genet 2012; 57:363-7) [7].

Addendum

Diagnosis of tuberculosis nowadays can be made by a molecular test which detects the DNA in TB bacteria. It uses a sputum sample and gives result in less than two hours; Or by a urine test for detecting glycan antigen lipoarabinomannan (LAM), a marker of active TB. Both provide broad implications for pulmonary TB scanning and early treatment.

TB Vaccine

BCG vaccine has been in practice for preventing primary TB infection for almost a century (97 years). A new generation of vaccines intended to suppress the transition from infection to disease on person already infected (tuberculin-positive persons). Presumably they already have implants containing dormant bacilli [8].

Discussion and Conclusions

Knowledge about the molecular mechanisms underlying immunity to TB is critical for the development of effective strategies to control tuberculosis. However, genetic studies of TB susceptibility have not been so successful because of the serious confounding effects of environmental factors. Currently, the risk of MTB infection remains routinely determined by the combined effect of a number of factors, such as the virulence of *Mtb*, exposure, the infectious dose, and route of infection. A number of non-genetic factors, such as AIDS, aging, and socioeconomic conditions, may contribute to the host's susceptibility to *Mtb* infection. The risk of developing active TB from latent TB infection is influenced by a number of non-genetic factors, including AIDS, diabetes, smoking, alcoholism, malnutrition, aging, immunosuppressive treatment (e.g. antitumor necrosis factor alpha therapy), and multiple environmental confounding factors, particularly the intensity of exposure [9,10].

For the above reasons, our opinion at this point is that precision medicine would not be amenable as an effective strategy to control tuberculosis, not until the molecular mechanisms underlying immunity to TB are exactly known. Although, it is possible that in the near future new generation vaccines, such as those of Lowrie DB, et al. would become available for use in suppressing the transition from infection to disease in tuberculin-positive persons.

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