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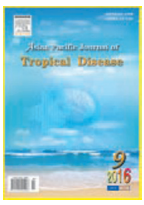

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The genetics of susceptibility to tuberculosis: Progress and challenges

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ABSTRACT

Tuberculosis is a global pressing healthcare issue in the modern world. Host genetics is an important modifier of the disease risk. Genetic and genomic studies aim to reveal key inherited variants of the human genome associated with the susceptibility to tuberculosis. Much attention is given to the study of differential genetic susceptibility to various stages of tuberculous infection, particularly latent tuberculosis, the detection of which is most challenging. Susceptibility genes have been identified and most of which exhibit a relatively small effect on the disease risk. On the other hand, a proportion of children suffer from Mendelian susceptibility to tuberculosis associated with rare mutations with deterministic effect in genes for the components of cellular immunity against intra-cellular infections. This review focuses on the current achievements in genomic studies devoted to the identification of genes important for the implementation of the immune response and protection against the development of the infection in different populations in the world.

1. Introduction

Tuberculosis (TB) remains one of the most common and dangerous infections despite all the measures taken to combat the disease. Approximately one-third of the world population is infected by *Mycobacterium tuberculosis* (*M. tuberculosis*) and each year about 9 million new TB cases in the world arise and more than 2 million people die from the disease[1,2]. TB is the second leading infectious disease in the number of deaths. On the background of the rising proportion of multiresistant forms of the disease, TB infection becomes more difficult to control and cure, thus urging the development of innovative strategies and approaches for the prevention, diagnosis and treatment of TB.

TB as well as many other infections, is a complex disease. While, its development is dependent on social factors (overcrowding, poverty and migration) and environmental factors, and properties of the pathogen (*e.g.* antibiotic resistance), genetically determined ability of the host organism to give an adequate immune response to the pathogen is crucial[3-5]. The analysis of the inherited basis of complex diseases, many of which are widespread and socially important, including some infections, is one of the priorities of contemporary human genetic research[4,6]. Among other infectious disease, TB is one of the most actively studied by geneticists and this is due to several reasons: proven influence of heredity in its development, the prevalence of the disease and its high social significance.

The current paper reviews the main directions in the study of genetic basis of susceptibility to TB and the latest achievements in this area.

2. Approaches to the study of the genetic susceptibility to TB

By now, the electronic database HuGE Navigator accumulated data for more than 380 genes examined for association with TB and believed to be controlling the development of the disease. A number of different approaches were used to identify these genes including experiments in animal models, the analysis of polymorphisms of candidate genes and the agnostic search for new candidate genes using genome-wide association studies[7]. The use of these approaches over the past decades led to significant progress in understanding the genetic basis of susceptibility to TB.

2.1. Animal models

A considerable role in human genetic research belongs to the study

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of mutant and genetic knockout lines of animals. Investigations of the influence of genetic factors on the susceptibility and resistance to TB were initially conducted on laboratory animals. In these studies, it has been clearly determined that the susceptibility to TB is inherited in complex, polygenic fashion[8,9]. Inbred laboratory mice were the main object in the studies of experimental TB due to similarity of basic characteristics of immune response to mycobacteria in mouse and human and wide variety of mouse lines with differential sensitivity to mycobacterial infection. Using the model mouse lines and gene knock-out technology allowed discovering a number of new candidate genes of TB predisposition in humans, *e.g. SLC11A1* (formerly, *NRAMP1*), the most actively investigated gene in TB and other infectious diseases, and *SP110*, encoding the closest homolog of the mouse Ipr1 protein in humans. The Ipr1 protein increases the ability of macrophages to induce apoptosis in mice, infected by *M. tuberculosis*. In later years, this led to the active studies of the human homologue *SP110* in terms of its associations with TB in different populations.

2.2. Candidate gene studies

Genetic studies of TB built on the assumption of a polygenic genetic basis of the disease and carried out over the past 30–40 years in many populations of the world showed the association of the disease with many genes described in detail in numerous reviews[3]. The genes for the study have been chosen based on their possible involvement to pathogenesis of TB or its clinical features. Some of the candidate genes have also been discovered in experimental animals (Table 1).

Among the candidate genes, the most actively studied are *SLC11A1, VDR, IFNG*, and *TNF*; for each more than 50 papers published on the association with TB included meta-analyses for separate polymorphisms. Of note, the association of genetic markers with TB is not always replicated in different populations, possibly due to population and ethnic specificity of susceptibility to TB[1,3]. Other issues can also underline the lack or reproducibility, such as small sample sizes (causing the lack of statistical power), inconsistent inclusion/exclusion criteria for cases and control groups in different studies and genetic heterogeneity[1,10].

2.3. Genome-wide association studies (GWAS)

On the background of the progress in the study of the human genome and with the advancement of molecular genetic techniques, genome-wide association studies have become increasingly popular[11]. The GWAS has high capacity to identify novel candidate genes based on their genomic localization without prior knowledge of the pathogenic effect of these genes. To date, more than a dozen GWAS have been completed for TB (Table 2). They identified a number of new loci and genes associated with the disease, but in all cases, the effect size measured by the value of the OR was not high and did not exceed the value of 2, though this is typical for

Table 1

The most frequently studied candidate genes of predisposition to TB.

Genes	MIM	Chromosomal localization	Protein	Effects on antimycobacterial immunity
SLC11A1 (*NRAMP1*)	600266	2q35	Solute carrier family 11, member 1	Transport of divalent metal ions and inhibition of the intracellular growth of mycobacteria
IFNG	145570	12q14	interferon-γ	Activation of macrophages and immunoregulation
VDR	601769	12q12-q14	Vitamin D receptor	Stimulation of cellular immunity, immunoglobulin production and synthesis of cytokines
TNF	191160	6p21.3	Tumor necrosis factor	The regulation of cell proliferation, differentiation, apoptosis, lipid metabolism and induction of granuloma formation
IL10	124092	1q31-q32	Interleukin 10	Pleiotropic effects on immunoregulation and inflammation
HLA	142830 142860 146880	6p21.3	Major histocompatibility complex	Determination and presentation of antigens to immune cells
TLR2	603028	4q32	Toll-like receptor 2	Reception of bacterial components and activation of cytokine gene expression
MBL2	154545	10q11.2-q21	Mannose-binding lectin	Opsonisation of bacterial antigens and activation of the complement system
CCL2 (*MCP1*)	158105	17q11.2-q12	Chemokine, CC motif, ligand 2	Immunoregulation and the inflammatory process and the most powerful factor of monocyte chemotaxis
TLR4	603030	9q32-q33	Toll-like receptor 4	Reception of bacterial components and activation of cytokine gene expression
CD209	604672	19p13.3	CD209 antigen	Initiation of the immune response
IFNGR1	107470	6q23.3	Interferon-gamma receptor 1	Immunoregulation, activation of dendritic cells and phagocytes
IL12B	161561	5q31.1-q33.1	Interleukin 12	Activation of the cellular immune response
P2RX7	602566	12q24.31	Purinergic receptor p2x, ligand-gated ion channel, 7	Participation in the process of apoptosis
IL1B	147720	2q14	Interleukin 1	Proinflammatory response and stimulation of cellular immunity
TIRAP	606252	11q24.2	TIR-domain-containing adaptor protein	Signal transmission from the toll-like receptors
CD14	158120	5q31.3	Monocyte differentiation antigen CD14	Receptor complex component recognizing *Mycobacterium*
TLR9	605474	3p21.2	Toll-like receptor 9	Reception of bacterial components and activation of cytokine gene expression
TGFB	190180	19q13.1	Transforming growth factor, β-1	Inhibition of proinflammatory response and suppression of cell-mediated immunity
IL4	147780	5q31.1	Interleukin 4	Activation of humoral and suppression of cellular immunity
SP110	604457	2q37.1	Nuclear body protein *SP110*	Limitation of intracellular growth and multiplication of the *Mycobacteria*. Switching the death of infected macrophages from necrosis to apoptosis
IL6	147620	7p15.3	Interleukin 6	Synthesized by activated macrophages and T-cells and stimulating an immune response
CCL5 (*RANTES*)	187011	17q12	Chemokine, CC motif, ligand 5	Immune regulation and inflammation and leukocyte chemotactic factor to the inflammatory focus

MIM: Mendelian Inheritance in Man Database Code.