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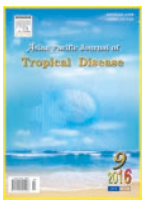

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The genetics of susceptibility to tuberculosis: Progress and challenges

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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.

Table 2
The results of genome-wide studies of predisposition to TB.

Study types	Population	The studied groups	Association with TB	LOD or OR[#]	References
Genome-wide linkage studies	Gambia and South Africa	67 Gambian families with TB (73 independent sib pairs) and 16 Kwa-Zulu-Natal families (19 independent sib pairs)	Xq26	1.82	[12]
			15q11-13	2.18	
	Brazil	16 families with TB (178 individuals) and 21 leprosy families (173 individuals)	10q26.13	1.31	[13]
			11q12.3	1.85	
			20p12.1	1.78	
	Morocco	96 families with TB (227 siblings with TB)	1q22	2.00	[14]
			3q27-q28	1.93	
			8q12-q13	3.38	
	South Africa	81 families with TB (131 sibling pairs) from Cape Town and 24 families with TB (24 sibling pairs) from Malawi	6p21-q23	1.90	[15]
			20q13.31-33	2.00	
	Uganda	803 individuals from 193 TB families (258 full sibling pairs and 175 half sibling pairs)	2q21-q24[**]	$P < 10^{-3}$[*]	[16]
			5p13-q22[**]	$P < 10^{-3}$[*]	
			7p22-p21	$P < 10^{-3}$[*]	
			20q13	$P = 0.002$[*]	
	Thailand	93 TB families (195 individuals)	5q23.2-31.3	2.29	[17]
			17p13.3-13.1	2.57	
			20p13-12.3	3.33	
	South Africa	128 TB families (350 siblings)	11p14	3.81	[18]
			5p15	4.00	
Genome-wide association studies[#]	Ghana and Gambia	11 425 individuals	18q11.2	1.19	[19]
	Thailand and Japan	Thai samples: 433 TB patients and 295 healthy control; Japanese samples: 188 TB patients and 934 healthy control	20q12	1.73	[20]
	Indonesia	125 TB patients and 134 healthy control	*JAG1*	1.14	[21]
			DYNLR	1.18	
			EBF1	0.73	
			TMEFF2	0.89	
			CCL17	0.89	
			HAUS6	1.18	
			PENK	1.14	
			TXNDC4	1.11	
	South Africa	797 TB patients and 91 healthy control	11p13	0.62	[22]
	Russia	6 651 TB patients and 8 472 healthy control	8q24	0.84	[23]

LOD: Logarithm of odds; [#]: For the whole genome linkage analyses, LOD scores were presented, while for associative studies, OR values were presented. [*]: No LOD-scores provided; [**]: loci linked with the resistance to *Mycobacteria* as assessed by the negative tuberculin skin test.

GWAS[24].

In theory, such systematic genome-wide studies should lead to the identification of all major genomic loci that have a significant impact on the risk of the development of a disease, including those shown to be involved by candidate gene studies. However, the results of GWAS contradict with this presumption. By far, GWASs carried out for TB revealed no association with the loci with already proven contribution to TB exposure, such as *NRAMP1, IL12B, TLR2, VDR* and *MCP1*. Also, there are inconsistencies between the results of different GWASs, when the loci identified in one study remain insignificant in another. There are many reasons for that the most important one seems to be the necessity to analyze very large samples to provide sufficient statistical power of the study and obtain associations beyond the accepted statistical threshold of 5×10^{-8}[11].Another issue is that many of the associated polymorphic variants in GWAS are resident in non-coding sequences, which makes it difficult, if possible, to draw mechanistic axis between genotype and phenotype of the disease.

Infectious diseases, including TB, may be a special case for GWAS. The ideology of GWASs of complex diseases assumes the model of common diseases-common polymorphisms according to which frequent phenotypes are caused by frequent polymorphisms with relatively weak effect (OR value is in the range of 1.1–1.5)[24].

With the increasing number of publications on GWAS results, it becomes apparent that a significant proportion of heritability of complex disease cannot be fully explained by the sole influence of common single nucleotide polymorphisms, especially for infectious diseases. Severe selective pressures exerted by infectious diseases suggest that the most important polymorphisms of susceptibility to infection should be characterized by a low frequency[10]. So the model of common disease-rare polymorphisms (with stronger effect) may be more valuable. This is highlighted by the studies of rare Mendelian forms of TB infection.

2.4. The studies of atypical Mendelian forms of mycobacteriosis

A lot of efforts is put to the study of specific immunodeficiency caused by rare mutations in genes coding the components of interleukin-12/interferon-γ-mediated cellular immunity. This line of research has led to important discoveries in the mechanisms of immune defense against specific pathogens including *M. tuberculosis*. In particular, mutations of some genes underlying disorders associated with interleukin-12/interferon-γ-activation were discovered and some of the mutations have led to atypical forms of mycobacterial and other infections in humans with monogenic (Mendelian) form of inheritance. These diseases have been registered in the Online Mendelian Inheritance In Man database as atypical familial mycobacteriosis, formerly known as syndrome of Mendelian susceptibility to mycobacterial diseases (MSMD). These diseases are characterized by the development of generalized infection to non-pathogenic or low pathogenic mycobacteria. The

MSMD syndrome is a rare congenital syndrome formally described for the first time in 1951 as disseminated disease caused by bacillus Calmette-Guerin vaccine[25]. In about half the reported cases, MSMD is characterized by a concomitant severe infection caused by non-typhoid or, rarer typhoid *Salmonella* serotypes. Mutations that cause the development of MSMD have been found in seven autosomal genes (*IFNGR1, IFNGR2, IL12B, IL12RB1, STAT1, ISG15, IRF8*) and two X-chromosome genes (*IKBKG, CYBB*)[25-29]. There is a significant allelic heterogeneity in MSMD syndrome with more than 140 causal mutations described in these genes. Both dominant and recessive alleles are known as well as null alleles, accompanied and not accompanied by protein products, and alleles affecting different parts of the functional domains of the same protein. Overall, the mutations can be grouped into 18 genetic diseases associated with the MSMD syndrome[30]. Due to such a genetic heterogeneity, the MSMD syndrome is characterized by varying degree of severity of clinical manifestation. Therefore, a knowledge of the genetic etiology of the MSMD allows predicting the disease effectively and correct therapeutic tactics, including substitution treatment.

Of note, in many countries, the study of the MSMD and a search for mutations in the genes that lead to its development has never been carried out. In addition, approximately half of the clinical cases with MSMD genetic etiology remains unknown suggesting the possibility of identifying new genes that lead to the development of this syndrome[31,32].

A hypothesis has been put forward that the role of the genes responsible for the development MSMD in the development of TB is much wider than expected. High genetic heterogeneity of MSMD and incomplete penetrance of a number of causative mutations served as the basis for an assumption that some polymorphisms of these genes with strong effects are the significant causes of TB in general population, in particular for primary TB in children. The proportion of Mendelian disseminated TB was estimated to potentially vary from 3% to 45%[33]. This suggestion was supported by the results of the study which showed that rare mutations in *TLR4* gene cause susceptibility to meningococcal infection[34]. However, no known MSMD mutations or rare polymorphisms with strong effect were found in TB patients from Siberia using direct sequencing[35]. Thus, the hypothesis on the impact of MSMD causing genetic variants on TB predisposition requires further verification.

3. Issues and challenges

Despite the fact that the rapid development of molecular genetic techniques identified a large number of genes and polymorphisms that affect susceptibility to TB, a comprehensive understanding of the factors of genetic susceptibility to the disease remains an important, complex and yet unsolved problem.

Most studies of genetic susceptibility of TB are focused on the study of pulmonary TB and they are carried out by a simple comparison with healthy persons in order to find and association between the studied polymorphisms and the disease. Only in a limited number of studies, the analysis was carried out for such phenotypes as disease severity or individual clinical forms[36,37]. The study of individual clinical parameters may lead to the discovery of a fundamentally new and important aspects of pathophysiology of TB. Genes and polymorphisms associated with TB may also be associated with certain clinical features that characterize the clinical course of the disease and, therefore, exhibit important prognostic value.

The issue of differentiated genetic susceptibility to various stages of tuberculous infection is discussed including primary interaction of the host with mycobacteria cells, the primary TB, latent TB and secondary forms of the disease (reactivation)[5]. Possibly, different genes control these different stages of TB infection as highlighted by recent studies. In most cases, the genes and their polymorphic variants associated with infection or primary TB exhibit no connection with pulmonary TB and vice versa. One genome-wide linkage study identified locus 11p14 (called *TST1*) linked (LOD = 3.81, P = 1.4e-5) to positive Mantoux test[2]. The development of primary TB was suggested to be associated with the polymorphisms of genes responsible for the development of the MSMD syndrome[5,33,38]. An association of secondary TB with a number of different genes was found[4,39].

Thus, despite the remarkable research achievements in the field of genetics of TB, there are still unresolved issues. Furthermore, currently, there are no examples of actual implementation of the results of these studies in clinical practice.

4. Conclusion

Over the past decades, immunogenetic studies progressed evidently, largely due to the successful development of molecular genetic technologies for simultaneous analysis of millions of genetic variants. The studies of genetic susceptibility to TB allowed identifying new associations of various genes and their polymorphisms with the disease, thus contributing to the understanding of the molecular mechanisms of protective immune response against *M. tuberculosis*. The existing arsenal of technologies and approaches to the study of genetic susceptibility to complex disease is now quite diverse, but each approach has the limitations. Thus, an integrated approach to the study of the genetic susceptibility to TB with a parallel study of both polygenic and Mendelian susceptibility to disease is required.

No less important is the aspect of the use of the data on the genetic markers of susceptibility/resistance to TB in clinical medicine. In this context, it is important to understand that success in revealing the genetic basis of susceptibility to TB must not be seen as the end itself, instead it must serve as the basis for the creation of fundamentally new, innovative approaches for patient care. Nowadays, doctors actually have no sensitive and specific clinical predictive markers of the risk of TB and its clinical course. The existent methods of preventing the spread of TB are limited to bacillus Calmette-Guerin-vaccination (the effectiveness of which has recently been challenged), tuberculin skin test, X-ray screenings and prescription of nauseating anti-TB drugs.[40-42]. Therefore, it is crucially important to focus on the translation of the knowledge on genetic mechanisms of susceptibility to TB to the development of new and effective prevention strategy to combat TB. Genetic markers of susceptibility to TB may serve as a basis for the development of genotypic risk prediction tests for the disease, while mechanistic models of expansion of genetic predisposition to clinical phenotype will help identify new drug targets and develop vaccines.

Conflict of interest statement

We declare that we have no conflict of interest.

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