ARTICLE IN PRESS

Frontiers in Laboratory Medicine xxx (2017) xxx–xxx

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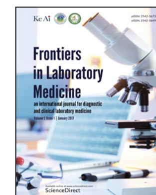
Contents lists available at ScienceDirect

Frontiers in Laboratory Medicine

journal homepage: www.keaipublishing.com/en/journals/frontiers-in-laboratory-medicine



Host genetic effect on tuberculosis susceptibility in Chinese Uyghur

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A R T I C L E   I N F O

Article history:
Received 7 January 2017
Received in revised form 7 February 2017
Accepted 8 February 2017
Available online xxxx

Keywords:
SNPs
Tuberculosis
Susceptibility

A B S T R A C T

Objective: Host genetic factors may play important roles in susceptibility to tuberculosis (TB) infection, and different gene polymorphisms in different ethnicity and genetic backgrounds may lead to different effects on tuberculosis risk. This study aimed to investigate the association of four single nucleotide polymorphisms (SNPs) with susceptibility to tuberculosis in Chinese Uyghur populations.

Methods: Four single nucleotide polymorphisms (SNPs) including rs1524107 in interleukin-6 (IL-6) gene, rs1544410 in vitamin D receptor (VDR) gene, rs9373523 in the syntaxin-binding protein 5 (STXBP5) gene, rs4331426 on chromosome 18q11.2 were genotyped by the improved multiplex ligase detection reaction (iMLDR) method in 258 patients with active TB and 291 geographically and ethnically matched healthy controls.

Results: Logistic regression analysis demonstrated that subjects carrying rs1524107 CT genotype had significantly increased risk for TB than individuals carrying TT genotype (OR: 2.144, 95%CI: 1.134–4.054, $p = 0.017$); Subjects carrying rs1544410 CT genotype had significantly increased risk for TB than individuals carrying CC genotype (OR: 1.612, 95%CI: 1.122–2.315, $p = 0.010$); Subjects carrying rs9373523 GT genotype had significantly increased risk for TB than individuals carrying TT genotype (OR: 1.847, 95%CI: 1.123–3.040, $p = 0.015$). In addition, an age-specific effect in rs1544410 and a sex-specific effect in rs9373523 were detected after stratified by age and sex. Carrying T allele of rs1544410 exhibited increased TB risk (OR: 1.897, 95% CI: 1.070–3.365) in subjects less than 30 years old. Carrying the T allele of rs9373523 exhibited decreased TB risk (OR: 0.888, 95%CI: 0.634–1.242) in female group.

Conclusions: Host genetic factors may play a significant role in susceptibility to TB in Chinese Uyghur population.

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1. Introduction

Tuberculosis (TB) remains a major global health problem by causing ill-health among millions of people each year and ranking as the second leading cause of death from an infectious disease worldwide. The latest estimates were almost 9 million new tuberculosis cases and 1.4 million tuberculosis-related deaths in 2011.[1]

In addition, it seems to be controlled after the improvement of sanitation condition and the development of anti-tuberculosis agent, it becomes a serious healthy matter again and threatens the mankind in the modern society nowadays as the emergency of the multidrug-resistant strains and co-infection between tuberculosis and human immunodeficiency virus.[2]

As one of the areas with high prevalence of TB in the world, China continues to have this major public health problem and it is worthy of note that TB mortality rate in Xinjiang region was 2.9 times the national average. Xinjiang Uygur Autonous Region (Xinjiang) in northwestern of China, has one of the highest rates of incidence and mortality of TB.[3–5] The Chinese Uygur, one of the minority ethnic groups, has higher prevalence of TB than the Chinese Han and other Chinese minorities in Xinjiang, China.[4] TB patients in Xinjiang mainly locate in southern Xinjiang, such as the Kashgar Prefecture, Hotan region, Aksu region, where mainly

Abbreviations: TB, tuberculosis; SNP, single nucleotide polymorphism; IL-6, interleukin-6; VDR, vitamin D receptor; STXBP5, syntaxin-binding protein 5; iMLDR, improved multiplex ligase detection reaction; DBP, vitamin D binding protein; MAF, minor allele frequency; SD, standard deviation; HWE, Hardy–Weinberg equilibrium; PCR, polymerase chain reaction; OR, odds ratio; 95%, CI 95% confidence interval; LOAD, late-onset Alzheimer's disease.

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http://dx.doi.org/10.1016/j.flm.2017.02.003
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Uyghur population reside in, and about 60% of the Uyghur patients are farmers and herdsmen.[6] There are several specific reasons for the higher incidence of TB in Uyghur. Given the special geographical environment of grassland, arid climate, unique customs and lifestyle, poor sanitary conditions of pasturing area, and weak hygiene consciousness of Uyghur further strengthen the prevalence of TB. Besides environmental factors, compelling evidence suggests the involvement of host genetic factors in TB susceptibility, and there is an ethnic difference in the polymorphisms of candidate genes associated with TB susceptibility.[7,8] After a long-time natural selection, Uyghur has developed some genetic features which are different from those populations in other areas. Specific hereditary background may influence the reaction of the host to disease, and there have been several reports demonstrating that host genetic factors play a significant role in susceptibility ofTB.[9–11]

Rs1524107 is a C/T single-nucleotide variation on human chromosome 7. It is single nucleotide polymorphisms in interleukin-6 (IL-6) gene. IL-6 are secreted by Toll-like receptor 2-expressing cells in response to the presence of *Mycobacterium tuberculosis* early in infection and are involved in anti-tuberculosis immunity in the body.[12] High levels of IL-6 cytokine are produced in response to MTB infection,[13,14] and its role seems especially critical when bacterial burden is high.[15] Reports about the involvement of polymorphic variants within IL6 gene and TB susceptibility remain inconsistent.

Rs1544410 is a C/T single-nucleotide variation on human chromosome 12. It is single nucleotide polymorphisms in vitamin D receptor (VDR) gene. Case control studies have previously reported independent associations between vitamin D deficiency and susceptibility to active TB.[16] The case for vitamin D deficiency playing a causal role in enhancing disease susceptibility is supported by findings of genetic studies reporting that polymorphisms in the VDR and the vitamin D binding protein (DBP) genes modify the influence of vitamin D status on susceptibility to active disease in the UK.[17,18] A prospective study in Pakistan has previously reported that vitamin D deficiency precedes onset of active disease,[19] and laboratory studies have reported that vitamin D metabolites induce antimycobacterial activity in vitro.[20]

Rs9373523 is single nucleotide polymorphism in the syntaxin-binding protein 5 (STXBP5). STXBP5, also known as tomosyn-1, is a novel candidate for affecting platelet secretion. STXBP5 is a 130-kDa protein that was originally identified as a STX1-binding partner in neuronal tissue.[21] STXBP5 belongs to a family of WD40 repeat-containing proteins associated with exocytosis and with the actin cytoskeleton: Sro7/Sro77 in yeast, Tom1 in *Caenorhabditis elegans*, and STXBP5 in mammals.[22–27] Our preliminary experiment showed that genotype distribution of rs9373523 between case and control group is different, so we further extend the sample size to investigate the association of rs9373523 with TB susceptibility.

Rs4331426 is single nucleotide polymorphism on chromosome 18q11.2. Chromosome 18q11.2 is a gene-desert region that is punctuated by evolutionarily conserved domains with regulatory potential, and rs4331426 has been associated with TB by genome wide association studies in Ghana and Gambia.[28] There is no data regarding the effect of this variant on TB risk in Uyghur populations. Thus, the present study discusses the possible association of rs4331426 genotypes with susceptibility to TB in Uyghur population.

In the current case control study, by using a candidate gene-based approach, we evaluated the association of four single nucleotide polymorphisms (SNPs), including rs1524107 in the interleukin-6 (IL-6) gene, rs1544410 in the vitamin D receptor (VDR) gene, rs9373523 in the syntaxin-binding protein 5 (STXBP5) gene, rs4331426 on chromosome 18q11.2, with TB susceptibility in China Uyghur population.

2. Subjects and methods

2.1. Population

All of the subjects are Chinese Uygur, coming from Hotan area of Xinjiang province. The ethnicity recording of all the participants as Chinese Uygur were derived from their self-declaration and checked by their identity (ID) card. We recruited 258 patients with active TB as case group and 291 healthy volunteer as control group. The detailed clinical characteristics of the study subjects were summarized in Table 1. All patients satisfied the inclusion criteria for established TB: smear positive for TB and/or culture positive for TB and/or clinical TB with the diagnostic criteria of TB.[29] In addition, patients with human immunodeficiency virus or other causes of infections or immunodeficiency were excluded. The Ethic Committee of the first affiliated hospital of Xinjiang medical university approved the present study with written assent forms. All subjects were provided written informed consent for sample collection and subsequent analysis after the study was clearly explained.

2.2. Snps selection

Through an extensive scanning of the databases of the International HapMap Project (http://www.hapmap.org), dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/), we identified potential functional polymorphisms. TB-related genes were screened with bioinformatics according to previously reported literature. Some SNPs were selected according to our preliminary experiment. Only SNPs with minor allele frequency (MAF) > 10% reported in the Asian population in SNP database (National Center for Biotechnology Information) were selected as candidates.

2.3. Genotype and allelic analysis of SNPs

Peripheral blood samples (3 ml/individual) from patients and healthy controls were stored in aseptic anticoagulants tubes at 70 °C for experiment. Genomic DNAs were extracted from blood samples using Qiagen DNA blood kit (Qiagen, Hilden, Germany) under the producer's instructions. Briefly, blood samples were digested and further purified with proteinase K and phenolchloroform, respectively. The genotyping of SNPs were analyzed by Center for Genetic & Genomic Analysis, Genesky Biotechnologies Inc., Shanghai. The genotype method was improved multiplex ligase detection reaction (iMLDR) method. The condition for polymerase chain reaction (PCR): a final reaction volume of 10 μl which contained GC-I buffer-Takara(1×), 3.0 mM Mg^{2+}, 0.3 mM dNTP, 1 U HotStarTaq polymerase (Qiagen Inc), 1 μl sample DNA and 1 μl PCR primer. The procedure for PCR cycle: 1 step: 95 °C for 2 min → 2 step: 11 cycles of 92 °C for 20 s, 65 °C for 40 s and finally 72 °C for 1.5 min → 3 step: 24 cycles of 94 °C for 20 s, 59 °C for 30 s and finally 72 °C for 1.5 min → 4 step: 72 °C for 2 min, then 4 °C forever. The system for DNA ligase reaction: 1 μl ligase buffer (10×), 0.25 μl ligase enzyme, 0.4 μl 5′primer (1 μM), 0.4 μl 3′primer (2 μM), 2 μl PCR production and 6 μl ddH_2O. The procedure for DNA ligase reaction: 1 step: 94 °C for 1 min and 56 °C for

Table 1
Epidemiologic data of enrolled subjects.

	Controls (291)	Cases (258)
Gender		
Male	153 (52.6)	111 (43.0)
Female	138 (47.4)	147 (57.0)
Age(±SD)	29.62 ± 13.907	56.26 ± 16.717

Please cite this article in press as: Rong H., et al. Host genetic effect on tuberculosis susceptibility in Chinese Uyghur Frontiers in Laboratory Medicine (2017), http://dx.doi.org/10.1016/j.flm.2017.02.003

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