International Journal of Infectious Diseases 35 (2015) 1–2

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Tuberculosis risk-associated single nucleotide polymorphisms do not show association with leprosy in Chinese population

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ARTICLE INFO

Article history:
Received 17 November 2014
Received in revised form 4 March 2015
Accepted 21 March 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Leprosy
Tuberculosis
Genetic association
Chinese Han population

SUMMARY

Objective: Leprosy and tuberculosis (TB) are chronic granulomatous infectious diseases. As well as pathogen and environmental factors, host genetic factors make a substantial contribution to susceptibility to both diseases. More importantly, leprosy and TB also have pathogenic mechanisms and clinical features in common. In this study, the genetic association between leprosy and TB was investigated in a Chinese Han population.
Methods: A genetic association study that included 46 TB susceptibility single nucleotide polymorphisms (SNPs) was performed, involving 1150 leprosy cases and 1150 controls from the Chinese Han population. The Sequenom MassARRAY system was used.
Results: No significant association was found between the 46 SNPs and leprosy. Therefore, according to the present study, there is no shared susceptibility locus between leprosy and TB in the Chinese Han population.
Conclusions: Although leprosy and TB have a number of similar characteristics, no shared susceptibility loci were found in the Chinese Han population. Thus, this study demonstrated that the genetic basis of the pathogenesis of the two diseases may vary greatly.

1. Introduction

Both leprosy and tuberculosis (TB) are chronic granulomatous infectious diseases caused by human pathogenic bacteria of the genus *Mycobacterium*, which are intracellular, Gram-positive, aerobic, and acid-fast bacilli, characterized by slow multiplication and long incubation periods. These pathogens remain major causes of morbidity and mortality worldwide.[1,2] More than 200 000 new leprosy cases and about nine million new cases of active TB are reported worldwide each year, particularly from developing countries.[3,4]

Although pathogen and environmental factors are important in leprosy and TB, it has been demonstrated through family studies, twin studies, and linkage studies that host genetic factors make a substantial contribution to susceptibility to infectious diseases such as leprosy and TB.[5]

There is some suggestive evidence that leprosy and TB share pathogenic mechanisms and clinical features. For example, both diseases manifest a spectrum of symptoms depending on the host's cell-mediated immune response. In addition, in the initial stages of infection, both *Mycobacterium leprae* and *Mycobacterium tuberculosis* are phagocytosed into the macrophage, resulting in an intracellular form of the bacterium.[6] Moreover, the formation of granulomas is an important clinical hallmark of both leprosy and TB. Furthermore, candidate gene studies have identified several genes with well-defined roles in the immune response to be associated with the pathogenesis of both diseases, including HLA-DRB1 (major histocompatibility complex, class II, DR beta 1), NRAMP1 (natural resistance-associated macrophage protein 1), VDR (vitamin D receptor), interleukin (IL)-12, IL-10, interferon gamma (IFN-γ), and mannose binding protein (MBP).

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http://dx.doi.org/10.1016/j.ijid.2015.03.015

Genome-wide association studies (GWAS) have identified several susceptibility loci for both diseases in the past few years. It was therefore hypothesized that there may be shared susceptibility loci between leprosy and TB. Thus the present comprehensive association study of TB susceptibility loci in Chinese leprosy samples was performed to investigate the common pathogenesis of these two diseases.

2. Materials and methods

All TB GWAS and candidate gene studies published before August 2013, identified through the catalog of published association studies of TB, were reviewed.[7] One hundred and eighty-seven single nucleotide polymorphisms (SNPs) were listed from the previous association studies; a p-value of <0.001 was then applied as the threshold of significance, and finally 56 SNPs were selected. As a result of failed primer design and locus overlap with loci that are also associated with TB, primers were designed for a total of 46 SNPs. The odds ratios, power, and original associated populations of these SNPs are listed in the **Supplementary Material** (Table S2).

After informed consent and approval of the human medical and ethics committee of Shandong Provincial Institute of Dermatology and Venereology had been obtained, genotyping analyses were conducted of the selected 46 SNPs in 1150 leprosy cases and 1150 healthy controls using the Sequenom MassARRAY system (Agena Bioscience, San Diego, CA, USA). All samples were from Chinese Han subjects recruited in northern China (Shandong Province), and were matched for age, gender, and ethnicity. In each replication sample, SNPs with a call rate <95%, low minor allele frequency ($p < 0.01$), or deviation from Hardy–Weinberg equilibrium proportions ($p < 0.01$) in the controls were excluded. Moreover, to test the genotype association, logistic regression was performed for each SNP using Plink v1.07.14 (http://pngu.mgh.harvard.edu/purcell/plink/).

3. Results

No significant association was found between the 46 SNPs and leprosy (**Supplementary Material**, Table S1). Thus, the results of the present study suggest that there may be no shared susceptibility loci between leprosy and TB in the Chinese Han population.

4. Discussion

Leprosy can affect both the skin and peripheral nerves, resulting in sensory and motor impairment with characteristic deformities and disability. Tuberculoid and lepromatous leprosy are two polar forms of the spectrum of leprosy symptoms. The pathogen of TB may infect one third of the world's population, but less than 10% of them will develop the active disease. The polar forms of the spectrum of TB are active and latent TB.

The results of the present study are consistent with those of previous case–control studies. Wang et al.[8] reported that SNP rs2335704, which is a susceptibility locus of TB on chromosome 18q11.2 in the African population, was not associated with the risk of TB in the Chinese population ($p = 0.91$; odds ratios (OR) 0.96, 95% confidence interval (CI) 0.49–1.91). A significant association was found between rs4331426, which is also a TB susceptibility locus on chromosome 18q11.2, and the risk of TB in the Chinese population ($p = 0.011$; OR 0.64, 95% CI 0.45–0.93), but the effect was the opposite. Additionally, Ji et al.[9] found that rs2057178, which has also been identified as a susceptibility locus of TB on chromosome 11p13, was not associated with TB in 600 cases and 618 controls in the Chinese population ($p = 0.15$; OR 1.39, 95% CI 0.89–2.33). Further, SNPs of rs3135499, rs7194886, rs8057341, and rs9302752 in the NOD2 gene, which is the susceptibility gene of leprosy in China, showed no significant association with TB in 1043 cases and 808 controls from the Chinese population (rs3135499: $p = 0.750$; rs7194886: $p = 0.260$; rs8057341: $p = 0.570$; rs9302752: $p = 0.263$).[10]

In conclusion, although leprosy and TB have a number of similar characteristics, including clinical features, pathological mechanisms, and immunity, there may be no shared susceptibility loci between leprosy and TB in the Chinese Han population according to the present association study. Thus it has been demonstrated that the genetic basis of the pathogenesis of the two diseases may vary greatly.

Acknowledgements

This study was supported by the Natural Science Foundation of Shandong Province (grant number HR2013HQ040). We gratefully acknowledge all of the individuals for their participation in this study. This study was approved before its commencement by the Ethics Committee of Shandong Provincial Institute of Dermatology and Venereology.

Conflict of interest: No conflict of interest exists in this study for commercial or other associations.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2015.03.015.

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