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Vitamin D Receptor Gene Polymorphisms Differentiated Between Tuberculosis Disease and Infection: Causal Association Study

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Purpose: Latent tuberculosis infection (LTBI) is a critical stage in tuberculosis (TB)control, and few studies have addressed the role of vitamin D receptor(VDR) gene polymorphisms in differentiating between TB and late-onset TB from an immunogenetic perspective.

Patients and Methods: Recruitment of tuberculosis patients and latently infected population in Urumqi, Xinjiang, and use of propensity score matching(PSM) to match the two groups and control confounding to further construct a Bayesian network to analyze causal associations between VDR polymorphisms and tuberculosis disease status.

Results: 137 LTBI and 237 TB were obtained through PSM. Logistic regression showed that the VDR gene BsmI locus, TaqI locus, and ApaI locus were associated with a higher risk of TB in a codominant model ($P<0.05$). Further Bayesian network construction showed that occupation and being a VDR gene BsmI locus were direct influences on TB disease status, and the VDR gene TaqI locus played an indirect role through the BsmI locus, and the probability of TB risk was highest in individuals with manual labour and BsmI locus of the C/T type, which was 84.15%.

Conclusion: Bayesian network modelling intuitively revealed that individuals with a C/T type of BsmI locus and physical labour are at high risk of TB compared with TB infection, and they are key factors between with TB disease, providing reference evidence for controlling TB progression.

Keywords: tuberculosis, disease state, vitamin D receptor, propensity score matching, Bayesian network

Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is the second most deadly infectious disease after new coronavirus pneumonia and the 13th leading cause of death worldwide. The epidemic is still serious, and eradication has become an urgent task. TB is now recognized as a spectrum disease. Disease status changes continuously from the preclinical stage to long-term sequelae.[1] Latent tuberculosis infection (LTBI), the preclinical/subclinical stage of TB, has now been identified as an important TB disease status.[2] Co-morbidities and transmission of Mycobacterium tuberculosis (MTB) can be prevented by controlling and treating LTBI before it progresses to TB disease. Elucidating the potential key factors that distinguish TB infection from TB patients is of paramount importance, as it is difficult to define the boundaries of the disease with current diagnostic techniques and 5–10% of people with LTBI will develop active TB disease during their lifetime.[3] Thus, a greater understanding of which individuals or which immune or genetic factors enable them to resist disease may help develop better biomedical prevention and treatment tools.[4] After inhalation of Mycobacterium tuberculosis, not all people will be infected with Mycobacterium tuberculosis and develop the disease, the pathogenesis of tuberculosis, the medical community has different opinions and has not yet reached a consensus, the mechanism of its occurrence may be closely related to the host's own immune response,[5] and still need to be researched to dig out the real cause of the disease. Vitamin D is known to regulate monocyte-macrophage activity ie and plays an

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important role in the regulation of cellular immunity and innate defence against infectious agents such as Mtb.[6] Vitamin D acts through the vitamin D receptor (VDR), which acts as a transcription factor and regulates a number of vitamin D-responsive genes, including those involved in the immune system. Susceptibility to TB may be caused by vitamin D deficiency, which is influenced by polymorphisms in the VDR gene. However, these findings are not consistent.[7] The four major single nucleotide polymorphism (SNP) loci of the VDR gene are FokI, BsmI, ApaI and TaqI.[8] Despite studies describing an association between polymorphisms in the FokI, BsmI, ApaI and TaqI genes and TB, findings vary widely by region and ethnicity and the relation were found to be contradictory.[9] A case-control study of tuberculosis in Kazakhstan found that T/T polymorphism (BsmI, rs1544410) of VDR genes may act as biomarkers for pulmonary tuberculosis in the Kazakh population and no association was found for other loci.[10] A case-control study found VDR TaqI, BsmI to be significantly associated with tuberculosis susceptibility.[11] The study by Dauren et al found that the A/A polymorphism of VDR ApaI was associated with a reduced risk of TB.[3] A recent meta-analysis found that the FokI polymorphism in the VDR gene increased the risk of TB in HIV-negative populations, both overall and in Asian populations, with no association found for the remaining genes.[7] However, the association of FokI, BsmI, ApaI and TaqI genes with tuberculosis susceptibility was not observed in a Chinese study.[12] VDR genes and their contradictory findings in tuberculosis, the relationship between which continues to be a subject of discussion in the scientific community. In addition, most of the studies are association studies, focusing only on the outcome of whether or not TB occurs, and very few have addressed the question of how useful VDR genetic polymorphisms are in distinguishing between TB and LTBI, which is still an unresolved issue today.

The development of causal inference methods provides an effective way of understanding the complex mechanisms involved in the development of disease. Propensity score matching (PSM) is widely used in observational and clinical studies with non-randomised data to reduce bias by matching a control group with a balanced distribution of confounders to the treatment group based on the propensity score. Bayesian networks can qualitatively and quantitatively describe the causal relationship between variables and solve the problem of uncertainty in the real world, and their effectiveness has been demonstrated in many fields.[13] Therefore, in this study, we recruited TB patients and the LTBI population in Xinjiang, matched and controlled for confounding, and constructed a Bayesian network to analyze the causal associations between polymorphisms in the VDR gene and tuberculosis disease status, to provide evidence for the accurate identification of high-risk populations and the prevention and control of tuberculosis disease progression.

Materials and Methods

Study Design

In this study, we selected patients with tuberculosis in treatment who were registered and managed in Urumqi City from 2020 to 2021, and all of them were clinically diagnosed by the designated tuberculosis medical institutions in each district (county). During the same period, close contacts with active tuberculosis infected with Mycobacterium tuberculosis were also recruited for this study. A total of 143 people with TB infection and 709 TB patients were obtained and all the study subjects signed an informed consent form.

Definition and Diagnosis of TB Infection and TB Disease

The patients with TB disease were the patients who had res- piratory specimen culture positivity for MTB. TB contacts were defined as living in the same household or reporting contact with the TB index case for >20 hours weekly for 2 months. For TB infection cases, they were being tested positive for LTBI by tuberculin skin test(TST), a positive TST was defined as ≥5mm induration, and TB disease was excluded by negative chest x-ray and absence of clinical symptoms.

SNP Selection and Genotyping

For the selection of candidate VDR SNPs, we did a systematic review and searched reports investigating VDR SNPs associated with TB and TB infection.[7,14] Four major loci of the vitamin D receptor gene were finally selected: the Fok I (rs2228570) locus, the BsmI (rs1544410) locus, the Apa I (rs7975232) locus and the TaqI (rs731236) locus. After the informed consent of TB patients and TB-infected patients, 5mL of venous blood was collected from the patients by clinical professionals using blood collection tubes containing EDTA anticoagulant, plasma was separated in time, plasma DNA was extracted, and the blood samples of TB patients and TB latent infected patients were tested for typing at four

genetic loci using the iMLDRTM Multiple SNP typing kit provided by Shanghai Tianhao Genetic Analysis Center. The primer sequences of the four SNPs are shown in Table 1.

Methods of Causal Inference

Propensity score matching[15] (PSM) is widely used in observational and clinical non-randomised data studies to match two groups with a balanced distribution of confounders based on propensity scores. In order to achieve balance between the groups of TB patients and TB-infected patients, to improve the comparability of baseline data, to reduce selection bias, and to improve causal efficiency, gender, age and ethnicity were used as matching factors, logistic regression models were constructed and propensity scores were estimated, and the nearest-neighbour matching method of 1:2 was chosen for the matching, resulting in a group of 136 cases of LTBI and a group of 237 cases of TB disease.

The Bayesian network[16] is a probabilistic graphical model used to solve unsolvable problems and to visually describe complex relationships between multiple variables. It is divided into two parts: a directed acyclic graph consisting of multiple nodes representing variables and directed acyclic edges reflecting the causal relationships between different nodes, where directed edges represent dependency or causality and nodes not connected by edges are conditionally independent of each other, thus visually expressing the causal relationships between events; the other is the conditional probability table, which defines for each node the distribution of its variables in the network and allows a more accurate representation of the specific values of the dependencies between variables from a mathematical probability point of view.

Statistical Analysis

Data were collated using Excel software and analyzed using R Studio 4.0.5. In order to reduce heterogeneity between the LTBI group and the TB group, propensity score matching was performed using the "Matchit" package, which matches the two groups on a 1:2 basis, using sex, age and ethnicity as matching factors. Then, the "SNP assoc" package was used to analyze the association between alleles, haplotypes and different genetic patterns (co-dominant, dominant, recessive and super-dominant) at the four VDR loci and TB disease status. Finally, in addition, we used the "bnlearn" package for Bayesian network[17] to infer causal associations between TB disease states and VDR gene polymorphisms with 100X bootstrapping. Only associations which remained statistically significant in >20 of 100X bootstraps were considered significant. A p-value < 0.05 was considered statistically significant.

Results

Demographic Characteristics of Participants Before and After PSM

A total of 143 LTBI and 709 TB were recruited for the study. 137 LTBI and 237 TB were obtained through PSM. Prior to PSM, there were significant differences between the LTBI and TB groups in terms of age, gender, occupation, and chronic disease status (P<0.05). After PSM, there were no statistically significant differences between the two groups compared to age, gender and ethnicity (P>0.05), Compared to the LTBI group, the TB group had a higher proportion of chronic diseases (20.3%) and a high proportion of physical labour (72.6%), (P<0.05, Table 2).

Table 1 SNPs Sites PCR Primer Design

Gene	Polymorphism	Forward Primer (5´->3´)	Reverse Primer (5´->3´)
VDR	rs7975232	AGGTCGGCTAGCTTCTGGATCA	CACCGGTCAGCAGTCATAGAGG
	rs1544410	CATCATGTCCCCAAGGTCACAA	CGTAGGGGGGATTCTGAGGAAC
	rs2228570	GGCTCACCTGAAGAAGCCTTTG	CTGGCACTGACTCTGGCTCTGA
	rs731236	AGGTCGGCTAGCTTCTGGATCA	CACCGGTCAGCAGTCATAGAGG

Abbreviations: VDR, vitamin D receptor; SNP, single nucleotide polymorphism.

Table 2 Demographic Characteristics of Participants Before and After PSM

Variants		Before PSM			Before PSM		
		LTBI(n=143)	TB(n=709)	*P*	LTBI(n=136)	TB(n=237)	*P*
Age(years)		43.55±19.36	47.09±20.14	0.049	44.64±18.81	48.05±17.62	0.080
Gender	Male	58(40.6%)	423(59.7%)	<0.001	58(42.6)	107(45.1)	0.640
	Female	85(59.4%)	286(40.3%)		78(57.4)	130(54.9)	
Ethnicity	Han	92(65.7%)	495(69.8%)	0.335	92(67.6)	143(60.3)	0.159
	Minority	49(34.3%)	214(30.2%)		44(32.4)	94(39.7)	
Occupation	Mental labour	98(68.5%)	228(32.2%)	<0.001	91(66.9)	65(27.4)	<0.001
	Physical labour	45(31.5%)	481(67.8%)		45(33.1)	172(72.6)	
Chronic disease	Yes	127(88.8%)	569(80.3%)	0.016	16(11.8)	48(20.3)	0.036
	No	16(11.2%)	140(19.7%)		120(88.2)	189(79.7)	

Abbreviation: PSM, propensity score matching.

Association of Different Inheritance Patterns of VDR Gene Polymorphisms with TB Disease Status

After Hardy-Weinberg genetic balance analysis, the frequency distribution of genotypes was found to be representative of the population in accordance with the law of genetic balance ($P > 0.05$).

Compared with the LTBI group, the BsmI was associated with a higher risk of TB in the codominant model (C/T vs C/C, OR=2.328), dominant model (C/T-T/T vs C/C, OR=2.174) and additive model (C/T vs C/C-T/T, OR=2.335); TaqI was associated with a higher risk of TB in the codominant model of inheritance (G/A vs A/A, OR=2.170), and in additive model (GA vs A/A-G/G, OR=2.187); ApaI was associated with higher risk of tuberculosis in codominant mode of inheritance (C/A vs C/C, OR=1.864), dominant model of inheritance (C/A-A/A vs C/C, OR=1.828) and in additive model of inheritance (C/A vs C/C-A/A, OR=1.743). FokI is not yet statistically associated with TB disease status ($P > 0.05$, Table 3).

Table 3 Association Analysis of Different Genetic Models of VDR Loci with TB Disease States

Model		Genotype	LTBI(n,%)	TB(n,%)	*P*	Multifactorial analysis	
						OR(95% CI)	*P*
BsmI	Codominant	C/C	121(89.0)	188(79.3)	0.055	1	
		C/T	14(10.3)	47(19.8)		2.328(1.168,4.638)	0.016
		T/T	1(0.7)	2(0.8)		0.628(0.055,7.109)	0.707
	Dominant	C/C	121(89.0)	188(79.3)	0.017	1	
		C/T-T/T	15(11.0)	49(20.7)		2.174(1.113,4.248)	0.023
	Recessive	C/C-C/T	135(99.3)	235(99.2)	0.910	1	
		T/T	1(0.7)	2(0.8)		0.567(0.050,6.407)	0.646
	Additive	C/C-T/T	122(89.7)	190(80.2)	0.017	1	
		C/T	14(10.3)	47(19.8)		2.335(1.173,4.650)	0.016

(*Continued*)

Table 3 (Continued).

Model		Genotype	LTBI(n,%)	TB(n,%)	*P*	Multifactorial analysis	
						OR(95% CI)	*P*
TaqI	Codominant	A/A	123(99.4)	194(81.9)	0.060	1	
		G/A	12(8.8)	42(17.7)		2.170(1.046,4.501)	0.037
		G/G	1(0.7)	1(0.4)		0.312(0.019,5.102)	0.414
	Dominant	A/A	123(99.4)	194(81.9)	0.025	1	
		G/A-G/G	13(9.6)	43(18.1)		1.987(0.979,4.034)	0.057
	Recessive	A/A-G/A	135(99.3)	236(99.6)	1.000	1	
		G/G	1(0.7)	1(0.4)		0.281(0.017,4.597)	0.374
	Additive	A/A-G/G	124(91.2)	195(82.3)	0.019	1	
		G/A	12(8.8)	42(17.7)		2.187(1.055,4.531)	0.035
ApaI	Codominant	C/C	77(56.6)	106(44.7)	0.084	1	
		C/A	50(36.8)	109(46.0)		1.864(1.141,3.043)	0.013
		A/A	9(6.6)	22(9.3)		1.654(0.671,4.074)	0.274
	Dominant	C/C	77(56.6)	106(44.7)	0.027	1	
		C/A-A/A	59(43.4)	131(55.3)		1.828(1.146,2.917)	0.011
	Recessive	C/C- C/A	127(93.4)	215(90.7)	0.369	1	
		A/A	9(6.6)	22(9.3)		1.252(0.524,2.994)	0.613
	Additive	C/C-A/A	86(63.2)	128(54.0)	0.083	1	
		C/A	50(36.8)	109(46.0)		1.743(1.083,2.807)	0.022
FokI	Codominant	G/G	42(30.9)	88(37.1)	0.455	1	
		G/A	71(52.2)	110(46.4)		0.788(0.471,1.320)	0.365
		A/A	23(16.9)	39(16.5)		0.841(0.424,1.668)	0.619
	Dominant	G/G	42(30.9)	88(37.1)	0.223	1	
		G/A-A/A	94(69.1)	149(62.9)		0.801(0.492,1.306)	0.374
	Recessive	G/G-G/A	113(83.1)	198(83.5)	0.909	1	
		A/A	23(16.9)	39(16.5)		0.969(0.526,1.785)	0.920
	Additive	G/G-A/A	65(47.8)	127(53.6)	0.281	1	
		G/A	71(52.2)	110(46.4)		0.836(0.528,1.323)	0.444

Abbreviations: LTBI, latent tuberculosis infection; TB, tuberculosis; VDR, vitamin D receptor; OR, odds ratio; CI, confidence intervals.

Association of Alleles of VDR Gene Polymorphisms with TB Disease Status

As shown in Table 4, Compared with the LTBI group, the TB group had a higher G allele frequency of TaqI, C allele frequency of ApaI, and T allele frequency of BsmI, which was a risk for tuberculosis ($P < 0.05$), and there was no statistically significant difference when comparing the distributions of allele frequencies at the FokI.

Table 4 Association Analysis of Alleles of VDR Loci with TB Disease States

SNP	Allele	LTBI(n,%)	TB(n,%)	χ^2	*P*
TaqI(rs731236)	A	258(94.9)	430(90.7)	4.122	0.042
	G	14(5.1)	44(9.3)		
ApaI(rs7975232)	A	163(44.4)	153(32.3)	12.987	<0.001
	C	204(55.6)	321(67.7)		
BsmI(rs1544410)	C	256(94.1)	423(89.2)	5.029	0.025
	T	16(5.9)	51(10.8)		
FokI(rs2228570)	A	117(43.0)	188(39.7)	0.804	0.370
	G	155(57.0)	286(60.3)		

Abbreviations: LTBI, latent tuberculosis infection; TB, tuberculosis; VDR, vitamin D receptor; SNP, single nucleotide polymorphism.

Causal Association of VDR Gene Polymorphisms with TB Disease Status

VDR gene polymorphisms, occupation and chronic disease were used as exposures, and TB disease status was used as an outcome to construct a Bayesian network model, and network learning was performed using a hill-climbing algorithm and combined with bootstrap method to obtain an average network, and the structure of the network obtained after inverse and deletion adjustment retained four nodes and three edges, as shown in Figure 1. The BDe score of the Bayesian network obtained by the greedy search algorithm is −1431.45, and the conditional independence test shows that all the directed edges have significance test (P <0.05), indicating that the network structure is credible.

The results of Bayesian network show that TB disease status has 2 parent nodes, which are occupation and VDR BsmI locus, they are the direct influences on TB disease status, meanwhile, VDR TaqI locus is indirectly influencing TB disease status by influencing VDR BsmI locus.

The conditional probabilities of each network node obtained by parameter learning are shown in Table 5. Depending on the combination of four different value levels for the parent node (occupation, VDR BsmI locus), the child node (TB

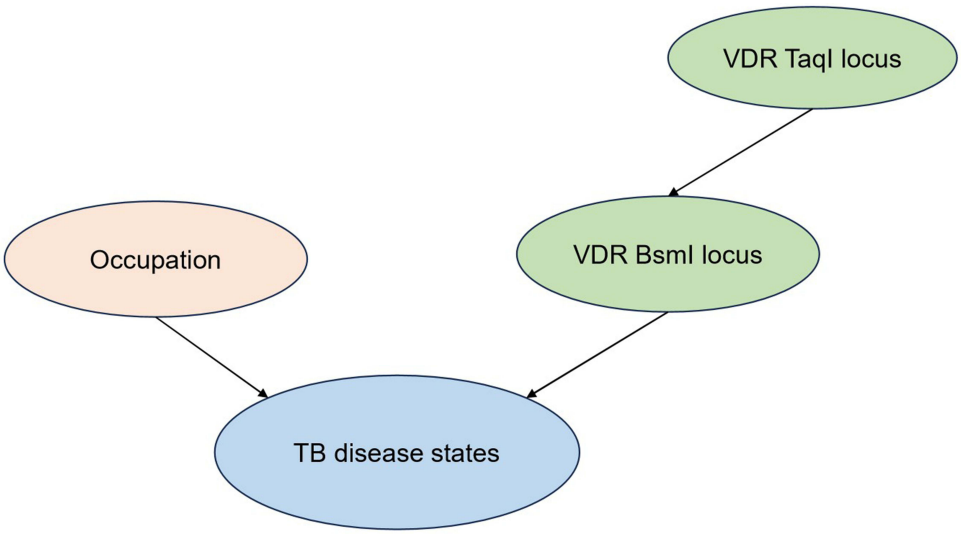

Figure 1 Bayesian network topology of TB disease states and influencing factors.
Abbreviations: TB, tuberculosis; VDR, vitamin D receptor.

Table 5 Conditional Probability Distribution of Tuberculosis Disease States

Occupation	VDR BsmI locus	LTBI(%)	TB(%)
Physical labour	C/C-TT	23.39	76.66
	C/T	15.85	84.15
Mental labour	C/C-TT	61.14	38.60
	C/T	41.67	58.33

Abbreviations: LTBI, latent tuberculosis infection; TB, tuberculosis; VDR, vitamin D receptor.

disease status) will correspond to six different conditional probability values. Among them, the highest probability of TB risk was 84.15% for individuals with physical labour and C/T type of vitamin D gene BsmI locus.

Discussion

The occurrence and development of tuberculosis is the result of the interaction between Mycobacterium tuberculosis and host immunogenetics, and the association between host immunity and genetic polymorphisms and tuberculosis has been a hot topic of discussion both nationally and internationally,[18,19] However, the role of host immunogenetics in TB remains controversial and is unknown in LTBI.

Most previous studies have compared TB with healthy controls, and previous studies have found no association between VDR gene polymorphisms (ApaI, BsmI, FokI and TaqI) and tuberculosis and a positive second acid-fast bacilli smear.[20,21] A Chinese study finds that allelic variants in the VDR genes rs58379944, rs12581281 and rs11574012 are strongly associated with tuberculosis risk.[22] A study in Kazakhstan found that T/T polymorphism (BsmI, rs1544410) of VDR genes may act as biomarkers for pulmonary tuberculosis in the Kazakh population.[10] It's worth noting that TB and LTBI are two distinct disease states and a recent cohort study suggests a protective role of vitamin D against the development of active TB in close household contacts of TB patients[23].The present study differs from related studies in the selection of TB patients and LTBI as endpoints, By comparing the variability of the VDR gene BsmI (rs1544410), TaqI (rs731236), FokI (rs2228570), and ApaI (rs7975232) in the TB group with the LTBI group, it was found that higher TB risk was associated with the BsmI, the TaqI, and the ApaI (P<0.05). Yu et al in 2023 reported that the allele and genotype frequencies of Fok I, Taq I, Apa I and Bsm I in the VDR were not associated with TB susceptibility.[12] The meta-analysis[14] found ApaI, BsmI, TaqI and FokI gene polymorphisms in patients with pulmonary TB. However, the effects of these genes should be evaluated in a larger sample size. Meanwhile, the relationship between VDR polymorphism and susceptibility to pulmonary TB may be moderated by the vitamin D status of the host. Vitamin D deficiency in the body may increase the risk of developing pulmonary TB.

The Bayesian network causal association study revealed that the BsmI of VDR gene directly affects TB disease status, meanwhile, the TaqI locus of vitamin D gene is indirectly affecting tuberculosis disease status through the BsmI locus. A study of TB patients and contacts in Kazakhstan showed that BsmI and TaqI loci may influence TB susceptibility.[24] A study of TB patients and their household contacts in northern India found no significant differences in the FokI gene in the tuberculosis group compared with the group with latent infection in close contacts.[25] Similarly, Taq I-TT was also found to be a risk factor in the population of Andhra Pradesh in India.[26] The above studies are similar to the results of this study. In terms of mechanisms, BsmI (rs1544410), and TaqI (rs731236) may be able to influence the stability and transcriptional activity of mRNA encoding the vitamin D gene, thereby affecting TB susceptibility.[27] Particular attention needs to be paid to individuals with the BsmIC/T genotype, who are at higher risk of TB. Studies suggest that the vitamin D gene enhances the expression of various antimicrobial peptides and mediates the innate immune response to eliminate Mycobacterium tuberculosis.[28,29]

The main task of biomedical research is to identify the causal mechanisms of disease and to target interventions to prevent, control and treat disease in order to promote the health of populations.[16] However, in practice, randomized controlled trials are difficult to implement due to the problems of medical ethics, subject compliance and so on;[30] Observational studies are susceptible to confounding factors that make it difficult to determine both causal direction and causal effects.[31] The development of causal inference methods provides an effective way to explore complex mechanisms in disease development for observational studies. The present study was conducted as a real-world study to conduct a field survey, and the study aimed to obtain reliable and rigorous results, taking into account the heterogeneity and other confounding factors in the tuberculosis and latent infection groups in addition to polymorphisms in the VDR gene. Propensity score matching are precisely the method used to balance the baseline characteristics, match control confounds, and manifest cause and effect.[32,33] Bayesian networks can be used to describe causal relationships between variables qualitatively and quantitatively and to solve real-world problems in terms of uncertainty, with an intuitive form, clear semantics, and comprehensibility, and their validity has been verified in many fields.[34,35] This study explores the causal association between vitamin D receptors and tuberculosis disease status using propensity score tuberculosis Bayesian networks, which is feasible from a methodological point of view.

In conclusion, this study elucidated the causal network pathway between the VDR gene and TB disease status based on propensity score matching controlling for heterogeneity and confounding factors to ensure network stability. The study expresses in an intuitive manner that individuals with a C/T type of BsmI locus and physical labour are at high risk of TB compared to TB infection, and they are key factors between with TB disease. However, there are some limitations to this study. The population selected for this study was TB patients and TB-infection, excluding the healthy control population, which was too small to be considered in this study. In addition, the study did not have a follow-up study of household contacts, as well as not analysing immune factors such as serum vitamin D levels in the study population. In order to validate our findings, further in-depth studies with larger sample sizes, preferably prospective follow-up studies to follow up LTBI and observe the progression of TB and the role of associated immune factors and genes in disease progression.

Abbreviations

LTBI, latent tuberculosis infection; TB, tuberculosis; MTB, mycobacterium tuberculosis; VDR, vitamin D receptor; PSM, propensity score matching; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence intervals.

Data Sharing Statement

All data contained in this study can be obtained from the corresponding author under reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Ethics Review Board of the First Affiliated Hospital of Xinjiang Medical University (No. K202103-22). All study subjects signed an informed consent form in accordance with the Declaration of Helsinki.

Consent for Publication

Consent for publication was obtained from the all the authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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