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Tuberculosis Exposure With Risk of Behçet Disease Among Patients With Uveitis

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IMPORTANCE Although experimental studies support the hypothesis that exposure of infectious agents may trigger an aberrant immune response and contribute to noninfectious uveitis, the association of a definite pathogen with human noninfectious uveitis conditions appears not to have been well established in a population.

OBJECTIVE To evaluate associations of tuberculosis infection with risk of several noninfectious uveitis conditions.

DESIGN, SETTING, AND PARTICIPANTS These mendelian randomization and observational analyses were conducted with the genetic data of a Chinese cohort enrolled between April 2008 and January 2018 and a Japanese cohort enrolled between January 2002 and June 2009. We recruited participants for T-SPOT.TB (Oxford Immunotec) assays between July and November 2019. The Chinese cohort included patients with uveitis associated with Behçet disease or other uveitis conditions and control participants. The Japanese cohort and the group given T-SPOT.TB assays included individuals with Behçet disease and control participants. Data analyses for this study were completed from July 2019 to January 2020.

EXPOSURES Genetic variants associated with tuberculosis as natural proxies for tuberculosis exposure.

MAIN OUTCOMES AND MEASURES The primary outcome was the odds ratio (OR) for Behçet disease, estimated by an inverse variance weighted mean of associations with genetically determined tuberculosis susceptibility. The T-SPOT.TB positivity rate was examined in individuals with Behçet disease and compared with that of control participants.

RESULTS The Chinese cohort included 999 patients with uveitis associated with Behçet disease, 1585 with other uveitis conditions, and 4417 control participants. The Japanese cohort included 611 individuals with Behçet disease and 737 control participants. The group given T-SPOT.TB assays included 116 individuals with Behçet disease and 121 control participants. Of the Chinese individuals with Behçet disease and control participants, 2257 (41.7%) were female and the mean (SD) age was 35.4 (12.5) years. In the Japanese cohort, 564 (41.8%) were female and the mean (SD) age was 39.1 (12.7) years. Genetically determined tuberculosis susceptibility was associated with an increased risk for Behçet disease. The OR for Behçet disease per 2-fold increase in tuberculosis incidence was 1.26 (95% CI, 1.12-1.43; $P = 1.47 \times 10^{-4}$). Replication using the Japanese cohort yielded similar results (OR, 1.16 [95% CI, 1.08-1.26]). In T-SPOT.TB assays, having a positive result, indicating a history of tuberculosis infection, was found to be an independent risk factor for Behçet disease (OR, 2.26 [95% CI, 1.11-4.60]).

CONCLUSIONS AND RELEVANCE These human genetic and biomarker data demonstrated that tuberculosis exposure was a risk factor for Behçet disease. This study provides novel evidence linking an infectious agent to the risk of a noninfectious uveitis condition.

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Supplemental content

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Uveitis is one of leading causes of visual acuity loss. Its prevalence was estimated to be 38 to 714 cases per 100 000 people.[1] Uveitis can be clinically categorized as infectious or noninfectious. Epidemiological data show that noninfectious uveitis can account for most cases of uveitis in some populations.[2,3] Most noninfectious uveitis conditions are presumed to be immune-mediated disease, driven by autoinflammatory or autoimmune responses, such as Vogt-Koyanagi-Harada disease, uveitis associated with ankylosing spondylitis, and Behçet disease.[4] Although the hypothesis is supported by experimental studies that exposure of infectious agents may trigger an aberrant immune response and contribute to noninfectious uveitis,[5,6] the causal association of a definite pathogen with human noninfectious uveitis conditions has not been well established in a population.[7]

Tuberculosis is currently one of the most prevalent infectious diseases and is caused by *Mycobacterium tuberculosis*. Approximately 25% of the global population may have a latent tuberculosis infection, of which 5% to 10% could progress to an active disease in their lifetime.[8] It has been suggested that *M tuberculosis* could induce inappropriate host responses to self-antigens, thus triggering the subsequent development of an autoimmune or autoinflammatory disorder.[9,10] However, the frequent use of glucocorticoids and immunosuppressive or biologic agents in the treatment of autoimmune or autoinflammatory diseases may also confer an increased risk of tuberculosis infection or reactivation.[11,12] The association between tuberculosis and autoimmune disease is thus not yet clear, since one seems to pose a risk of the other.

Currently, it remains unknown whether tuberculosis exposure may contribute to the development of noninfectious uveitis. Interpretations of observational analyses might be biased in assessing associations because of potential reverse causality and residual confounders. A conventional randomized clinical trial of tuberculosis infection cannot be ethical and feasible. In this study, we therefore sought to investigate the potential association based on the principle of mendelian randomization.[13] This approach has been successfully applied to provide evidence that can guide public health interventions.[14-16] The role of host genetic factors in determining susceptibility to tuberculosis has been well established.[17,18] Genome-wide association studies (GWAS) have identified common genetic variants associated with tuberculosis.[17,18] These variants, randomly allocated at birth, could be a natural determinant of tuberculosis risk that may be used for inference on health outcomes.[13] We aim to assess whether tuberculosis is a risk for several noninfectious uveitis conditions, including Behçet disease, Vogt-Koyanagi-Harada disease, uveitis associated with ankylosing spondylitis, and Fuchs uveitis syndrome, by using these genetic variants in the population.

Key Points

Question What is the evidence for tuberculosis exposure in association with noninfectious uveitis in a human population?

Findings In this mendelian randomization and observational cohort study involving 8349 people and a T-SPOT.TB analysis involving 237 participants with a history of uveitis, human genetic and biomarker data demonstrated that tuberculosis was a risk factor for Behçet disease.

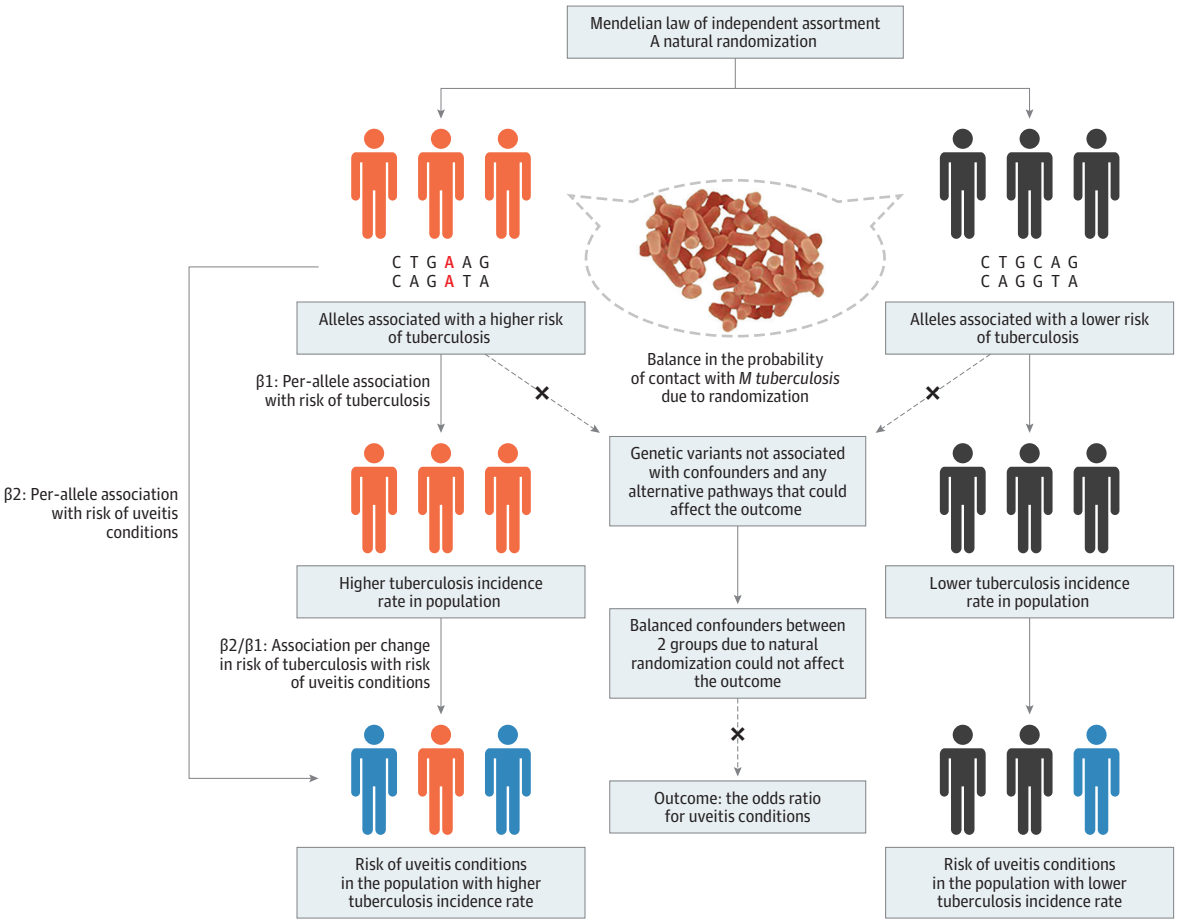
Meaning The present study provides evidence linking tuberculosis exposure with the causative mechanism of a noninfectious uveitis entity, Behçet disease, and may add to knowledge concerning the pathologic consequences of tuberculosis.

Methods

Study Design

We performed a mendelian randomization in which genetic variants strongly associated with tuberculosis were used as natural indicators of risk or likelihood in tuberculosis infection, to test potential association with the risk of noninfectious uveitis conditions (**Figure 1**). In the mendelian randomization design, we selected genetic variants directly associated with tuberculosis, not associated with confounders and any alternative pathways that could affect the outcome. Under the assumption that the randomly inherited genotype of individuals determines an assignment for tuberculosis susceptibility at birth, the outcome of genetically determined tuberculosis susceptibility can be analogous to the intention-to-treat effect in a randomized clinical trial.[13] This mendelian randomization study was designed in June 2019, and data were analyzed during July 2019 and January 2020 based on the Chinese and Japanese GWAS data sets. In the Chinese cohort, a total of 2584 patients with uveitis and 4417 healthy control participants of Chinese ancestry were enrolled at 5 centers in China from April 2008 through January 2018 for the genome-wide genotyping and association study (Peizeng Yang, MD, PhD; written communication; July 15, 2019). Among Chinese patients with uveitis, diagnosis of Behçet disease, Vogt-Koyanagi-Harada disease, and ankylosing spondylitis was made according to international standardized criteria.[19-21] A diagnosis of Fuchs uveitis syndrome was principally clinical, based on the description of classic literature.[22,23] In the Japanese cohort, 611 individuals with Behçet disease and 737 healthy control participants were enrolled at 8 centers in Japan between January 2002 and June 2009, after which the main GWAS results were published elsewhere.[24] Our primary analysis was based on the Chinese GWAS data set, and the Japanese data set was used as a replication. In addition, we performed a prospective observational study in which we examined the T-SPOT.TB positivity rate in individuals with Behçet disease compared with control participants. Consecutive participants with a history of uveitis were screened at the First Affiliated Hospital of Chongqing Medical University according to predefined exclusion criteria. Individuals were excluded if any of the following criteria were met: they were aged 50 years or older (this criterion was based on the consideration that the age of onset of Behçet disease is about 20 to 40 years old,[25] while tuberculosis infection can occur in older individuals; the observation may be associated with inversion of cause and effect, if elderly individuals are involved); were HIV positive; had serous effusion; or had used systemic corticosteroids of more

Figure 1. Study Design of the Mendelian Randomization Study



Mendelian randomization tests indicate an association by first establishing via linear regression that tuberculosis-associated genetic variants increase the risk of tuberculosis (β1). These variants are then tested for a linear association with the risk of uveitis conditions (β2). An assessment of association with the risk of uveitis conditions per change in the risk of tuberculosis can be obtained by β2/β1.

than 20 mg per day in the last 3 months and had other serious medical conditions, such as hepatic failure, kidney failure, and heart failure. A total of 237 participants were enrolled for this investigation between July and November 2019.

The GWAS study received ethical approval from the local institutional ethics committees (eMethods in the Supplement). All the participants provided written informed consent to use their genetic data for any investigation, and this investigation was designed in June 2019 and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. All the procedures adhered to the Declaration of Helsinki. There was no financial compensation for participants.

Genetic Variants

Five genetic variants (rs4240897, rs2269497, rs41553512, rs12437118, and rs6114027) associated with tuberculosis at genome-wide significance ($P < 5.0 \times 10^{-8}$) in the Chinese population were used as the instrumental variable for tuberculosis exposure (eTable 1 in the Supplement).[17,18] We obtained the summary estimates of associations between genetic variants and tuberculosis from 2 previously published GWAS, which finally included 4310 patients with tuberculosis vs 6386 healthy control participants[17] and 2949 patients with tuberculosis vs 5090 control participants.[18] The exposure allele for each single-nucleotide variant (SNV) was the allele associated with higher risk of tuberculosis. To our knowledge, there has been only 1 GWAS and replication study[26] reported on tuberculosis in the Japanese population, involving 393 young Japanese and Thai individuals with tuberculosis and 1255 healthy control participants, in which 1 SNV reached the significance at a P value less than 5.0×10^{-8}. To obtain sufficient power by multiple SNVs, we used a significance threshold of $P < 5.0 \times 10^{-6}$ to select genetic variants and obtained 3 eligible SNVs as proxies for tuberculosis in the Japanese population: rs6071980, rs4604310, and rs10792563. In the Chinese cohort, genome-wide genotyping was performed using the HumanOmniZhongHua-8 BeadChip (Illumina), and association analyses of SNV genotype with uveitis conditions were performed using logistic regression adjusted for sex, age, and testing additive, per-allele genetic outcomes. To perform 2-sample mendelian randomization analyses, we obtained summary statistics of these ge-

netic variants from the Chinese and Japanese GWAS results. There was no sample overlap between each data set that we used. All SNVs in respective data sets are located on different chromosomes and are not in pairwise linkage disequilibrium. We evaluated each SNV and its relevant proxy SNVs with linkage disequilibrium (r^2 >0.80) for pleiotropic associations with potential confounders or other traits, except tuberculosis, by searching the PhenoScanner database (University of Cambridge; http://www.phenoscanner.medschl.cam.ac.uk/), which contained more than 65 billion genotype-phenotype association results from large-scale, published GWAS.[27] The genetic variant associated with other traits or having a proxy SNV associated with other traits at genome-wide significance ($P < 5.0 \times 10^{-8}$) was likely to be pleiotropic and was excluded in sensitivity analyses. All computations of pairwise linkage disequilibrium were based on the East Asia population in 1000 Genomes Project.[28]

T-SPOT.TB Test

The T-SPOT.TB test is a diagnostic assay for past or present tuberculosis infection, by measuring effector T cells reactive to stimulation with *M tuberculosis* antigens ESAT-6 and CFP-10.[29] Samples were assayed using the T-SPOT.TB kit (Oxford Immunotec Ltd) according to the manufacturer's instructions. The results were defined as positive when there was a positive response to ESAT-6 and/or CFP-10 antigens.

Statistical Analyses

The *F* statistics were calculated to evaluate the association strength.[30] For individual SNVs, mendelian randomization estimates of the association with outcomes were determined by the Wald-type ratio.[31] We combined the associations of individual SNVs to produce an inverse variance–weighted mean of the associations in multiplicative random-effects and fixed-effects models.[31] To avoid the potential heterogeneity bias, the estimates obtained by multiplicative random-effects inverse variance weighting were considered the primary outcome. All estimates were described as odds ratios (ORs) with 95% CIs per 2-fold increase in tuberculosis incidence.[32] Heterogeneity was tested using the Cochran Q and I^2 statistics. An MR Egger regression was performed, whereby an intercept statistically different from null (0) could demonstrate the presence of directional pleiotropy ($P < .05$).[33] We performed a leave-1-out sensitivity analysis by excluding each SNV in turn to examine the outcome influenced by each genetic variant. Sensitivity analyses based on maximum likelihood, MR Egger regression, and weighted median and contamination mixture models were conducted under different assumptions about potential bias and pleiotropy.[31,33-35] Comparison of the results of sensitivity analyses with the primary analysis was performed using Fisher *z* scores.[36] We used logistic regression analysis to estimate the OR of T-SPOT.TB positivity for individuals with Behçet disease, whereby ORs were further adjusted for sex, age, body mass index, smoking history, drinking history, (urban or rural) residence, and education level. For the primary mendelian randomization estimate in the Chinese cohort, a 2-sided $P < .0125$ (by Bonferroni correction, [$P < .05$] / 4 entity outcomes) was considered to indicate statistical significance. This study did not plan for multiple-comparison adjustments for sensitivity analyses, so the results are reported with point estimates and 95% CIs only. The statistical analyses were performed using Stata version 15.0 (StataCorp) and R version 3.5.0 (R Foundation for Statistical Computing).

Results

Study Population and Genetic Variants

In the Chinese cohort, 999 were diagnosed with Behçet disease, 608 had Vogt-Koyanagi-Harada disease, 477 had uveitis associated with ankylosing spondylitis, and 500 had Fuchs uveitis syndrome; 4417 were control individuals. A Japanese cohort of 611 individuals with Behçet disease and 737 control participants was included as a replication; 509 of 611 patients (83.3%) in this cohort had uveitis.[24] Of the Chinese individuals with Behçet disease and control participants, 2257 (41.7%) were female and the mean (SD) age was 35.4 (12.5) years. In the Japanese cohort, 564 individuals (41.8%) were female and the mean (SD) age was 39.1 (12.7) years. All 5 genetic variants had sufficient association strength with tuberculosis in the Chinese population, as reflected by *F* statistics greater than 10.0 (rs4240897: $F_{10\,694}$, 97.12; rs2269497: $F_{10\,694}$, 62.39; rs41553512: $F_{10\,694}$, 91.68; rs12437118: F_{8037}, 57.83; rs6114027: F_{8037}, 55.35; eTable 1 and eTable 2 in the Supplement). Additionally, a total of 116 individuals with Behçet disease and 121 control participants underwent T-SPOT.TB tests and were included in the observational analysis.

Primary Outcome

Estimates for the associations of individual variants with the risk of Behçet disease as well as other 4 conditions are shown in eTable 3 in the Supplement. Across all 5 tuberculosis-associated SNVs, a given genetic increase in the risk of tuberculosis was correlated with a concomitant increase in the risk of Behçet disease (rs4240897: OR, 1.27 [95% CI, 1.20-1.33]; $P = 1.41 \times 10^{-11}$; rs2269497: OR, 1.51 [95% CI, 1.35-1.68]; $P = 3.37 \times 10^{-8}$; rs41553512: OR, 2.14 [95% CI, 1.78-2.57]; $P = 7.93 \times 10^{-11}$; rs12437118: OR, 1.28 [95% CI, 1.19-1.37]; $P = 1.72 \times 10^{-11}$; rs6114027: OR, 1.34 [95% CI, 1.23-1.47]; $P = 2.37 \times 10^{-11}$; **Figure 2**; eFigure 1 and eTable 1 in the Supplement). The genetically determined tuberculosis susceptibility was associated with an increased risk of Behçet disease (**Table 1**); in the Chinese cohort, the odds ratio of Behçet disease per 2-fold increase in tuberculosis incidence was 1.26 (95% CI, 1.12-1.43; $P = 1.47 \times 10^{-4}$). No associations were detected for Vogt-Koyanagi-Harada disease (OR, 0.94 [95% CI, 0.65-1.38]; $P = .77$), uveitis associated with ankylosing spondylitis (OR, 0.99 [95% CI, 0.81-1.22]; $P = .95$), and Fuchs uveitis syndrome (OR, 1.03 [95% CI, 0.86-1.24]; $P = .72$).

No heterogeneity was detected in the inverse variance weighted estimate for Behçet disease ($I^2 = 0\%$; $P = .51$; eTable 4 in the Supplement). Nevertheless, there was a certain degree of heterogeneity detected in estimates for Vogt-Koyanagi-Harada disease ($I^2 = 88.8\%$), uveitis associated with ankylosing spondylitis ($I^2 = 57.0\%$), and Fuchs uveitis syndrome ($I^2 = 47.1\%$; eTable 4 in the Supplement). In addition, the MR

Egger intercept test demonstrated no evidence of pleiotropy in the estimates for Behçet disease as well as the 3 other conditions (eTable 5 in the Supplement).

Sensitivity Analyses

Searching the 5 SNVs in the PhenoScanner for associations with other traits except tuberculosis indicated that SNV rs4240897 or its relevant SNVs that were in strong linkage disequilibrium were likely to have a pleiotropy ($P = 1.91 \times 10^{-34}$ for association with plateletcrit; $P = 3.77 \times 10^{-22}$ for association with platelet count; eTable 6 in the Supplement). Nevertheless, excluding the SNV rs4240897 in the sensitivity analysis showed a similar result with that of the primary analysis (OR, 1.25 [95% CI, 1.07-1.46]; eFigure 2 in the Supplement). In addition, the leave-1-out sensitivity analysis did not suggest that a single SNV was driving the association (eFigure 2 in the Supplement). A concordant association of increased tuberculosis susceptibility with higher risk of Behçet disease was observed in analyses using maximum likelihood (OR, 1.27 [95% CI, 1.11-1.46]), MR Egger (OR, 1.60 [95% CI, 1.09-2.34]), weighted median (OR, 1.27 [95% CI, 1.06-1.51]), and contamination mixture (OR, 1.37 [95% CI, 1.08-1.75]) models (eFigure 3 and eFigure 4 in the Supplement).

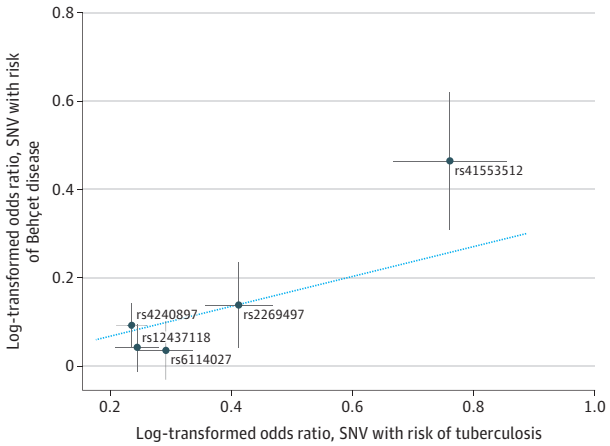
Replication and Observational Analysis

In the Japanese cohort (eTable 7 in the Supplement), genetically determined tuberculosis susceptibility scaled per 2-fold increase in tuberculosis incidence conferred a 1.16-fold change in the odds ratio for Behçet disease (95% CI, 1.08-1.26; $P = 9.13 \times 10^{-5}$ in the random-effects model). No heterogeneity and pleiotropy were detected in the estimate (eTable 4 and eTable 5 in the Supplement). In the observational analysis, a positive T-SPOT.TB test result, indicating past or present tuberculosis infection, was observed in 38 individuals with Behçet disease (32.8%) and 19 control participants (15.7%) (eFigure 5 in the Supplement). After adjustment for covariables, T-SPOT.TB-positive status was an independent risk factor for having Behçet disease among patients with uveitis (OR, 2.26 [95% CI, 1.11-4.60]; $P = .03$; **Table 2**).

Discussion

This mendelian randomization study showed that an increased risk or likelihood of tuberculosis infection was associated with a higher risk of Behçet disease among individuals with a history of uveitis. Clinical biomarker data also suggested that tuberculosis infection was an independent risk factor for developing Behçet disease. The present study provides evidence in people linking infectious agents to the risk of noninfectious uveitis and may also add to our knowledge concerning the pathologic consequences of tuberculosis. The study did not provide sufficient evidence showing the association of tuberculosis with the risk of Vogt-Koyanagi-Harada disease, uveitis associated with ankylosing spondylitis, and Fuchs uveitis syndrome, which warrants further investigations.

Figure 2. Scatterplot of per-Allele Effect of Each Single-Nucleotide Variant (SNV)



Per-allele association (log-transformed odds ratio) with the risk of Behçet disease is shown against the per-allele association with the risk of tuberculosis infection. Error bars show 95% CIs for each SNV. The regression line represents the outcome estimated by the inverse variance weighting.

Previous studies have shown that the 65-kD heat shock protein (HSP65) from *Mycobacterium* is highly homologous to human 60-kD heat shock protein, which might provide a role for antigenic mimicry in the development of Behçet disease.[37] Several reports documented that tuberculosis was complicated with Behçet disease and that antituberculosis chemotherapy could relieve the symptoms of Behçet disease.[38,39] Nevertheless, these studies were case reports or case series with small sample sizes. The major strength of this study was the use of naturally randomly inherited variants to indicate the tuberculosis exposure from the perspective of the time of birth, which might minimize the possibility of reverse causality and provide nearly randomized evidence in this population. Our mendelian randomization estimates were consistent with the T-SPOT.TB observations as well as previous experimental and clinical reports, implying that tuberculosis could be a risk factor for Behçet disease. Elucidation of the precise mechanisms involved, however, requires further studies.

Our study may provide several implications for clinical practice. First, there might be a need to carry out screening of Behçet disease for tuberculosis. We report here that the T-SPOT.TB positivity rate was 32.8% in individuals with Behçet disease, which is similar with a previous study.[40] Second, in terms of the frequent use of glucocorticoids and immunosuppressive or biologic agents, especially tumor necrosis factor inhibitors, for the treatment of Behçet disease, special attention should be paid to the risk of reactivation or progression of tuberculosis, especially in patients with positive T-SPOT.TB assays. Third, understanding the role of infectious agents in the development of Behçet disease may be helpful for the prevention and treatment of the disease. Together with existing clinical observations,[38,39] our results support the need for randomized clinical trials to evaluate the benefits of antituberculosis intervention for patients with Behçet disease associated with tuberculosis infection.

Table 1. Estimated Association of Genetically Determined Tuberculosis Susceptibility With the Risk of Uveitis Conditions

Outcome	Random-effects inverse-variance weighting[a]		Fixed-effects inverse-variance weighting	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Behçet disease	1.26 (1.12-1.43)	1.47×10^{-4}	1.26 (1.11-1.44)	5.37×10^{-4}
Vogt-Koyanagi-Harada disease	0.94 (0.65-1.38)	.77	0.94 (0.79-1.13)	.54
Uveitis associated with ankylosing spondylitis	0.99 (0.81-1.22)	.95	0.99 (0.82-1.20)	.95
Fuchs uveitis syndrome	1.03 (0.86-1.24)	.72	1.03 (0.86-1.25)	.72

[a] A random-effects inverse-variance weighted estimate was considered the primary outcome in this study.

Table 2. Multivariable Logistic Regression Analysis of Factors Associated With Behçet Disease

Variables	Participants, No. (%)		Unadjusted		Multivariable adjusted	
	With Behçet disease (n = 116)	Control (n = 121)	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
T-SPOT.TB test positivity	38 (32.8)	19 (15.7)	2.62 (1.40-4.88)	.003	2.26 (1.11-4.60)	.03
Male	99 (85.3)	66 (54.5)	4.85 (2.59-9.08)	<.001	4.66 (2.25-9.67)	<.001
Age, y						
<20	8 (6.9)	21 (17.4)	0.27 (0.10-0.72)	.009	0.73 (0.22-2.37)	.60
20-29	31 (26.7)	22 (18.2)	1 [Reference]	NA	1 [Reference]	NA
30-39	50 (43.1)	31 (25.6)	1.15 (0.57-2.32)	.71	1.42 (0.64-3.17)	.40
40-49	27 (23.3)	47 (38.8)	0.41 (0.20-0.84)	.02	0.55 (0.24-1.28)	.17
BMI						
<18.5 (Underweight)	11 (9.5)	16 (13.2)	0.58 (0.25-1.34)	.20	0.63 (0.23-1.72)	.36
18.5-23.9 (Normal weight)	68 (58.6)	57 (47.1)	1 [Reference]	NA	1 [Reference]	NA
≥24 (Overweight and obesity)	37 (31.9)	48 (39.7)	0.65 (0.37-1.13)	.12	0.70 (0.36-1.38)	.30
Smoking history						
Never	76 (65.5)	75 (62.0)	1 [Reference]	NA	1 [Reference]	NA
Formerly	9 (7.8)	9 (7.4)	0.99 (0.37-2.62)	.98	1.11 (0.38-3.29)	.85
Currently occasionally	6 (5.2)	1 (0.8)	5.92 (0.70-50.37)	.10	5.12 (0.52-51.02)	.16
Currently regularly	25 (21.6)	36 (29.8)	0.69 (0.38-1.25)	.22	0.66 (0.33-1.34)	.25
Drinking history						
Never	77 (66.4)	98 (81.0)	1 [Reference]	NA	1 [Reference]	NA
Formerly	28 (24.1)	11 (9.1)	3.24 (1.52-6.92)	.002	1.91 (0.78-4.66)	.16
Currently occasionally	8 (6.9)	7 (5.8)	1.46 (0.51-4.19)	.49	0.85 (0.25-2.86)	.79
Currently regularly	3 (2.6)	5 (4.1)	0.76 (0.18-3.30)	.72	0.38 (0.07-2.01)	.25
Urban resident	77 (66.4)	88 (72.7)	0.74 (0.43-1.29)	.29	0.66 (0.33-1.31)	.23
Education level						
Primary school and less	7 (6.0)	21 (17.4)	1 [Reference]	NA	1 [Reference]	NA
Middle school	36 (31.0)	30 (24.8)	3.60 (1.35-9.62)	.01	2.69 (0.85-8.50)	.09
High school	21 (18.1)	32 (26.4)	1.97 (0.71-5.44)	.19	1.89 (0.58-6.20)	.29
College and higher	52 (44.8)	38 (31.4)	4.11 (1.58-10.64)	.004	4.33 (1.36-13.73)	.01

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.

Limitations

This study has some limitations. First, although the SNVs were strongly associated with tuberculosis in the Chinese population, because of the lack of data, the actual tuberculosis infection status and the prevalence of tuberculosis could not be assessed in our population. Therefore, our mendelian randomization estimates only suggested that an increased risk or likelihood of tuberculosis infection was associated with a higher risk of Behçet disease, rather than that tuberculosis exposure directly increased the risk of Behçet disease. To address this issue, we examined the T-SPOT.TB positivity rate in another group of individuals with Behçet disease compared with control participants, which provided further evidence on the association between the history of tuberculosis and the risk of Behçet disease. Second, our study was based on a 2-sample mendelian randomization. This approach may lead to reduced precision in calculating effect sizes compared with 1-sample mendelian randomization analysis by using individual-level data. Because of power concerns, we did not perform a secondary 1-sample mendelian randomization test using the individual-level data of T-SPOT.TB cohort. Thus, these results may just indicate a positive association between the risk

of tuberculosis infection and that of Behçet disease, but the estimated association could not be directly translated into the effect size in the real world. Third, the strength of the association between genetic variants and tuberculosis in the Japanese population was not as strong, and the analysis was liable to weak instrument bias.[41] Therefore, the results from the Japanese population may not be reproducible and require further validation. Moreover, although much effort was made to address potential bias in the T-SPOT.TB analysis, because of the observational design, some unmeasured confounders may not have been completely excluded. Fourth, we did not detect a significant association for Vogt-Koyanagi-Harada disease, uveitis associated with ankylosing spondylitis, and Fuchs uveitis syndrome, which may be because of the small sample size and insufficient statistical power. In addition, we strictly followed international standardized criteria for the diagnosis of Behçet disease.[21] Nevertheless, these criteria principally rely on clinical manifestations but not laboratory tests. To overcome this, we have introduced a multidisciplinary approach and specialist experience, especially the recommendations by rheumatologists, in the diagnosis of the disease.

Conclusions

In conclusion, human genetic and biomarker data demonstrated that an increased risk of tuberculosis infection was associated with a higher risk of Behçet disease among individuals with a history of uveitis. Our study provides novel evidence linking an infectious agent to the risk for noninfectious uveitis.

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