Evaluation of the Host Genetic Effects of Tuberculosis-Associated Variants Among Patients With Type 1 and Type 2 Diabetes Mellitus

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Background. Understanding the link between tuberculosis (TB) and diabetes is increasingly important as public health responds to the growing global burden of noncommunicable diseases. Genetic association studies have identified numerous host genetic variants linked to TB; however, potential host genetic mechanisms linking TB and diabetes remain unexplored.

Methods. We used genetic and phenotypic data from the UK Biobank to evaluate the association of 6 previously reported TB-related host genetic variants (genome-wide significant associations from published studies) with diabetes. The study included 409,692 adults of European ancestry including 2177 with type 1 diabetes mellitus (T1DM) and 13,976 with type 2 diabetes mellitus (T2DM), defined by ICD-10 diagnosis codes.

Results. Of the 6 TB-associated single nucleotide polymorphisms (SNPs), 2 were associated with T1DM and 3 with T2DM, after adjusting for age, sex, body mass index, smoking, alcohol use, and population structure. After correction for multiple testing, SNPs rs2894257 and rs3135359 (HLA-DRA-DQA1) were associated with T1DM (rs2894257: odds ratio [OR], 1.32; 95% confidence interval [CI], 1.32–1.34; rs3135359: OR, 1.15; 95% CI, 1.14–1.15) and T2DM (rs2894257: OR, 1.11; 95% CI, 1.08–1.15; rs3135359: OR, 1.06; 95% CI, 1.025–1.096). The associations with T2DM weakened for rs2894257 and rs3135359 after further exclusion of probable T1DM cases defined by International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes. SNP rs4733781 on chromosome 8 (ASAP1 gene) was associated with T2DM after exclusion of T1DM cases.

Conclusions. Our findings suggest that common host genetic effects may play a role in the molecular mechanism linking TB and diabetes. Future large genetic studies of TB and diabetes should focus on developing countries with high burdens of infectious and chronic diseases.

Keywords. tuberculosis; diabetes; host genetics; T1DM; T2DM.

More than 10 million incident cases of tuberculosis (TB) occur around the world each year [1]. In 2017, 1.6 million deaths from TB made it the most common cause of death from infectious disease and 1 of the top 10 causes of death worldwide. TB disease results from either rapid progression of a recently acquired *M. tuberculosis* (*Mtb*) infection or reactivation of a previous latent infection [2]. Rising noncommunicable disease (NCD) incidence is contributing to the profound burden of TB, as NCD comorbidities impact TB susceptibility and TB treatment outcomes. Diabetes mellitus (DM) increases susceptibility to TB, and an estimated 15% of global TB cases may be attributable to DM [3]. New biomedical approaches and technologies that provide insight into mechanisms of TB–diabetes synergy could help inform host-directed therapies for both diseases.

A number of genome-wide association studies (GWAS) have been performed to identify host genetic associations with either susceptibility to *Mtb* infection or the risk of progressing from *Mtb* infection to symptomatic, active TB disease [2]. GWAS studies have identified SNPs associated with susceptibility to active TB. These include rs4331426 (18q11.2; \(P = 6.8 \times 10^{-5}\)) [4] and rs2057178 (\(P = 2.57 \times 10^{-11}\)) [5], identified in African populations, and variants in the ASAP1 gene on chromosome 8q24 (rs4733781: \(P = 2.6 \times 10^{-11}\)), identified in a Russian population [6]. These associations have been replicated in populations of different genetic ancestries such as Asian, European, and African (Supplementary Table 1) [5, 7–9]. Tian et al. conducted a GWAS of 23 common infections and infection-associated procedures and found several SNPs associated with *Mtb* infection in the 6p21.33 HLA region (eg, SNP rs2894257: \(P = 8.16 \times 10^{-36}\); odds ratio [OR], 1.36; 95% confidence interval [CI], 1.33–1.39).
Qi et al. also reported that HLA-DQB1 0201 (OR, 0.47; 95% CI, 0.26–0.69; Bonferroni-corrected $p = 2.80 \times 10^{-3}$), was associated with active TB disease [11]. Few studies have been conducted to evaluate shared host genetic factors between TB and diabetes. With diabetes prevalence increasing rapidly, particularly in countries with a high incidence of TB [12], further exploration of the genetic mechanisms underlying the comorbidity of TB and diabetes could be helpful for identifying vulnerable populations and appropriate interventions. In the present study, we investigated whether host genetic variants previously associated with $Mtb$ infection susceptibility and TB progression were associated with prevalent diabetes mellitus. We used genotypic and phenotypic data from the UK Biobank (UKB) to examine the associations of 6 genetic variants with type 1 and type 2 diabetes [13].

**METHODS**

**Study Design and Data Source**

We conducted a cross-sectional genetic association analysis of baseline phenotype data from the UK Biobank. We focused on 452 264 participants of European ancestry with high-quality genetic data from 502 616 adults (aged 37 to 73 years) recruited between 2007 and 2010 [14]. After excluding closely related individuals, the present analysis included an unrelated sample of 342 574 participants of European ancestry with genetic data confirmed (Supplementary Figure 1). Social demographic factors (eg, education level, household income), lifestyle factors (eg, smoking history, alcohol consumption, physical activity), medical history (as documented by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems [ICD-10] codes), and summary information relating to diagnoses were collected during the baseline visit and from hospital records [15]. Written informed consent was obtained from each participant before data collection.

**Outcomes and Covariates**

Study outcomes of interest included type 1 and type 2 diabetes mellitus (Supplementary Figure 1). Cases of type 1 diabetes mellitus (T1DM) were identified by the ICD-10 code “E10 insulin-dependent diabetes” (n = 2177). Cases of type 2 diabetes mellitus (T2DM) were defined by the primary and secondary ICD-10 diagnosis codes of “E11 non-insulin-dependent diabetes mellitus” (n = 13 976). Participants without T1DM or T2DM were considered the non-diabetic control group for this analysis (n = 310 267). Because we identified some participates who had both T1DM and T2DM codes, we created an additional T2DM-only case group (n = 12 502) by excluding those who had primary or secondary T1DM (n = 1474). Body mass index (BMI) was categorized as overweight/obese (BMI $\geq 25$) and normal/underweight (BMI < 25). Self-reported cigarette smoking was dichotomized as current vs noncurrent. Self-reported alcohol consumption was dichotomized as high frequency (daily or almost daily, $\geq 3$ times per week) and low frequency.

**Genetic Data**

Genotyping was performed using Affymetrix UK BiLEVE and UK Biobank Axiom arrays, and quality control and imputation were performed by a collaborative group headed by the Wellcome Trust Centre for Human Genetics, as previously described [15]. In addition to 3 genome-wide significant lead SNPs associated with TB (1 from each of 18q11.2, 11p13, and
ASAP1 loci), we selected 3 SNPs from the human leukocyte antigen (HLA) region for significant and independent associations with positive TB skin test [10]. Collectively, 6 independent TB-related genetic variants from 4 loci were identified through the published GWAS studies and included in this study (Tables 2–4). Details of the studies, including sample size, ethnic group, ORs, and P values, are given in Supplementary Table 1. The summarized 6 TB-related SNPs were the main exposure in this study of prevalent T2DM. Summary information of the candidate TB-related variants is given in Supplementary Table 2, including alleles, gene context, and imputation quality score.

**Statistical Analyses**

To identify common predisposing genetic factors for TB and diabetes, we performed cross-sectional analyses to assess the association of 6 TB-related genetic variants with prevalent T1DM and T2DM. Logistic regression models adjusted for social demographic factors (age, sex), lifestyle (smoke, alcohol consumption), and BMI at enrollment, as well as for population structure, using principal components (PCs) 1–10 from the genome-wide SNP data. PLINK2 ([https://www.cog-genomics.org/plink/2.0/](https://www.cog-genomics.org/plink/2.0/)) was used to calculate genotype distributions, Hardy-Weinberg equilibrium (HWE), and summary statistics for genetic association (P value, odds ratio, with 95% CI). Test statistics comparing the phenotypes between subgroups were calculated using R, version 3.5.0 ([https://www.r-project.org/](https://www.r-project.org/)). For each genetic variant, we performed 2 multivariate logistic regression analyses to calculate ORs and 95% CIs for the prevalence of T1DM/T2DM. The first model was adjusted for age, sex, BMI, and PC1-10. The second model included covariates from the first model, plus current smoking and alcohol consumption. Because multiple genetic associations were tested, we adjusted the statistical significance threshold using Bonferroni correction (.05/number of tested SNPs) to control for false positives.

**RESULTS**

The present study consisted of 310,267 individuals without T1DM or T2DM diagnosis, 2177 participants having T1DM diagnosis, and 13,976 with T2DM.

### Table 2. Genetic Associations of T1DM With TB-Related SNPs in the UK Biobank (2177 T1DM Cases, 310,267 Controls)

| Chromosome | POS  | SNP ID   | Alleles | Freq | Model 1 | Model 2 |
|------------|------|----------|---------|------|---------|---------|
|            |      |          |         |      | OR (95% CI) | P Value | OR (95% CI) | P Value |
| 6          | 31629397 | rs148844907 | T/A    | 0.01 | 0.771 (0.555–1.073) | .123 | 0.768 (0.552–1.088) | .117 |
| 6          | 32390578 | rs3156539 | T/C    | 0.73 | 1.722 (1.573–1.886) | 5.85×10⁻⁹ | 1.721 (1.572–1.884) | 7.15×10⁻⁹ |
| 6          | 32433276 | rs2894257 | G/C    | 0.51 | 1.320 (1.205–1.445) | 1.97×10⁻⁸ | 1.315 (1.201–1.440) | 3.27×10⁻⁸ |
| 8          | 131296767 | rs4733781 | C/A    | 0.69 | 1.037 (0.972–1.105) | .272 | 1.037 (0.992–1.165) | .261 |
| 11         | 32368187 | rs2057178 | A/G    | 0.84 | 1.075 (0.992–1.165) | .076 | 1.073 (0.992–1.165) | .084 |
| 18         | 20190795 | rs4331426 | G/A    | 0.97 | 0.907 (0.773–1.065) | .234 | 0.906 (0.772–1.063) | .226 |

### Table 3. Genetic Associations of T2DM With TB-Related SNPs in the UK Biobank (13,976 T2DM Cases, 310,267 Controls)

| CHROM | POS  | SNP ID   | Alleles | Freq | Model 1 | Model 2 |
|-------|------|----------|---------|------|---------|---------|
|       |      |          |         |      | OR (95% CI) | P Value | OR (95% CI) | P Value |
| 6     | 31629397 | rs148844907 | T/A    | 0.01 | 0.974 (0.875–1.084) | .633 | 0.977 (0.887–1.088) | .67 |
| 6     | 32390578 | rs3156539 | T/C    | 0.73 | 1.061 (1.026–1.096) | .001 | 1.060 (1.025–1.096) | .001 |
| 6     | 32433276 | rs2894257 | G/C    | 0.51 | 1.111 (1.077–1.145) | 1.42×10⁻¹¹ | 1.106 (1.073–1.140) | 1.14×10⁻⁹ |
| 8     | 131296767 | rs4733781 | C/A    | 0.69 | 1.030 (1.003–1.058) | .026 | 1.031 (1.004–1.058) | .024 |
| 11    | 32368187 | rs2057178 | A/G    | 0.84 | 0.988 (0.956–1.022) | .488 | 0.986 (0.954–1.020) | .427 |
| 18    | 20190795 | rs4331426 | G/A    | 0.97 | 0.973 (0.909–1.041) | .421 | 0.970 (0.906–1.037) | .371 |

**Abbreviations:** CHROM, chromosome number; CI, confidence interval; Freq, frequency of effect allele; OR, odds ratio; POS, base pair position (GRCh37/hg19); SNP, single nucleotide polymorphism.

*The 2 alleles represent reference/effect alleles.

*Freq: frequency of effect allele.

*Model 1: basic adjusted model with age, sex, body mass index, principal components 1–10.

*Model 2: full adjusted model with age, sex, body mass index, smoking, alcohol, principal components 1–10.

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**Table 2. Genetic Associations of T1DM With TB-Related SNPs in the UK Biobank (2177 T1DM Cases, 310,267 Controls)**

**Table 3. Genetic Associations of T2DM With TB-Related SNPs in the UK Biobank (13,976 T2DM Cases, 310,267 Controls)**
diagnosis codes, and 13,976 participants having T2DM diagnosis codes from the UK Biobank cohort from 2006 to 2010 (Supplementary Figure 1). Table 1 summarizes the distributions of age, sex, BMI, smoking, and alcohol consumption in the 2 case groups and controls at enrollment. Overall, members of the T1DM and T2DM case groups were older than the control group and included higher proportions of males, overweight or obese individuals, current smokers, and frequent consumers of alcohol.

Summarized in Table 2, the C alleles of rs2894257 and rs3135359 at the HLA-DRA-DQA1 locus were associated with increased odds of T1DM after adjusting for age, sex, BMI, and top 10 PCs (model 1: rs2894257: OR, 1.32; 95% CI, 1.21–1.45; rs3135359: OR, 1.72; 95% CI, 1.57–1.89) and after adjusting for these variables in addition to smoking status and alcohol consumption (model 2: rs2894257: OR, 1.32; 95% CI, 1.20–1.44; rs3135359: OR, 1.72; 95% CI, 1.57–1.88). Associations with both SNPs remained statistically significant after Bonferroni correction for multiple testing.

Comparing 13,976 participants with T2DM diagnosis codes with non-DM controls, the TB risk alleles—2 SNPs in the HLA region (rs3135359 and rs2894257) and 1 in the ASAP1 gene (rs4733781)—were associated with increased odds of T2DM (Table 3). After Bonferroni correction for multiple testing \((P = .05/6 = .0083)\), the associations of both rs2894257 and rs3135359 remained significant.

To remove potential misclassification of T2DM as T1DM, we further excluded any T2DM patients who also had primary or secondary T1DM diagnosis from the T2DM case group \((n = 12,502)\). As shown in Table 4, the OR for the association of rs2894257 with T2DM was reduced from 1.11 to 1.08 (model 1: 95% CI, 1.05–1.12; \(P = 8.65 \times 10^{-7}\); 95% CI, 1.05–1.12; \(P = 3.60 \times 10^{-6}\)). None of the other 5 tested genetic associations were significant after Bonferroni correction for multiple testing. The SNP in the ASAP1 gene, rs4733781, was marginally associated with T2DM at the nominal threshold \((raw \ P < .05)\) with an OR of 1.03 (95% CI, 1.002–1.06).

Phenome-wide association studies (PheWAS) offer a complementary framework to investigate genetic associations across many disease traits simultaneously [16]. We examined genetic associations between target SNPs and clinical phenotypes using the GeneATLAS browser (http://geneatlas.roslin.ed.ac.uk/phewas/) [17]. Although PheWAS results for rs2894257 (C/G) were not available, we identified numerous diseases and traits associated with rs3135359. Phenome-wide associations for the T1DM-associated rs3135359 in the European ancestry subset of the UK Biobank data are summarized in Table 5. The TB-associated C allele of rs3135359 increased the risk of noncancer thyroid conditions by 81%. The top-ranked disease traits (ie, the lowest \(P\) values) associated with rs3135359 included thyroid conditions, neurological problems, blood cell traits, and other autoimmune diseases.

### DISCUSSION

Based on >300,000 Caucasian participants from the UK Biobank, we found that a TB-related variant in the HLA-DRA-DQA1 region (rs2894257) was associated with both T1DM (OR, 1.31; 95% CI, 1.21–1.45) and T2DM (OR, 1.08; 95% CI, 1.05–1.12). A second variant in this region, rs3135359, was also associated with T1DM but not T2DM after exclusion of T2DM cases who also had a T1DM diagnosis code. A third variant, rs4733781 (ASAPI), was moderately associated with T2DM (OR, 1.03; 95% CI, 1.00–1.06) but not T1DM.

The closest gene to SNP rs3135359 is BTNL2, which belongs to the butyrophilin-like B7 family of immunoregulators (proteins involved in immune surveillance) [18]. It mainly works as a negative T-cell regulator that decreases T-cell proliferation and cytokine release [19]. The naturally occurring mutations in BTNL2 are associated with several diseases, including

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**Table 4. Genetic Associations of T2DM (Excluding T1DM) and TB-Related SNPs in the UK Biobank (12,502 Non-T1DM T2DM Cases, 310,267 Controls)**

| Chromosome | POS   | SNP ID       | Alleles | Freqa | Model 1b | OR (95% CI) | PValue   | Model 2c | OR (95% CI) | PValue   |
|------------|-------|--------------|---------|-------|----------|-------------|----------|----------|-------------|----------|
| 6          | 31628397 | rs148844907 | T/A     | 0.01  | 0.942    | 0.843–1.053 | .296     | 0.945     | 0.845–1.056 | .319     |
| 6          | 32390578 | rs3135359   | T/C     | 0.73  | 1.024    | 0.990–1.061 | .170     | 1.024     | 0.989–1.060 | .187     |
| 6          | 32433276 | rs2894257   | G/C     | 0.51  | 1.084    | 1.050–1.119 | .147     | 1.079     | 1.045–1.114 | .506     |
| 8          | 131296767 | rs4733781   | C/A     | 0.69  | 1.030    | 1.002–1.059 | .036     | 1.031     | 1.003–1.060 | .033     |
| 11         | 32364187 | rs2057178   | A/G     | 0.84  | 0.972    | 0.938–1.007 | .115     | 0.970     | 0.936–1.005 | .096     |
| 18         | 20190795 | rs4331426   | G/A     | 0.97  | 0.981    | 0.914–1.054 | .608     | 0.979     | 0.911–1.051 | .552     |

Abbreviations: CHROM, chromosome number; CI, confidence interval; Freq, frequency of effect allele; OR, odds ratio; POS, base pair position (GRCh37/hg19); SNP, single nucleotide polymorphism.

*The 2 alleles represent reference/effect alleles.

bFreq: frequency of effect allele.

Model 1: basic adjusted model with age, sex, body mass index, principal components 1–10.

Model 2: full adjusted model with age, sex, body mass index, smoking, alcohol, principal components 1–10.
sarcoidosis, ulcerative colitis, inflammatory bowel disease, T1DM, and prostate cancer [20].

The ASAP1 gene (also known as AMAP1 and DDEF1) encodes a multidomain ADP-ribosylation factor GTPase-activating protein, which is involved in the regulation of cytoskeletal dynamics, receptor recycling, and intracellular vesicle trafficking [6, 21]. Its expression is associated with poor prognosis for a variety of cancers and promotes cell migration, invasion, and metastasis. Although the functional role of ASAP1 in diabetes is unclear, elevated expression of ASAP1 mRNA was reported in adipose tissue isolated from obese mice and mice with diabetes compared with tissue isolated from wild-type mice [22]. Loss of ASAP led to delayed adipocyte development and reduced fat depot formation in mice [23]. Using the Genotype-Tissue Expression (GTEX) database to search for the functional links of genetic variants to gene expression levels, we found that rs4733781 is strongly associated with ASAP1 expression in whole blood \((P = 6.5\times10^{-10})\), thyroid \((P = 1.5\times10^{-7})\), skin \((P = 1.7\times10^{-7})\), and lung \((P = 2.5\times10^{-6})\) tissues. The association we found between ASAP1 and T2DM offers a clue to potential mechanisms underlying the comorbidity of TB and T2DM.

Several published studies have investigated the relationship between TB and diabetes, motivated by observed comorbidity between the 2 diseases [24–26], although very little is known about underlying molecular mechanisms [27]. Our study is another step toward understanding host genetic variants that could be related to both TB and diabetes. Although the relationship between TB and T2DM is suspected to be bidirectional, it is challenging to study the genetic risk of T2DM among people who have active TB or Mtb infection without large cohort studies that include host genetics. Most such studies, as well as PheWAS, have been conducted in US and European populations. Countries with high TB prevalence, which are best suited for studying factors underlying TB–diabetes comorbidity, are generally underrepresented in large genetics studies. Additional studies, particularly with a longitudinal design, will be needed to further explore relationships among host genetic risk factors for TB and diabetes.

In the present study, diabetes phenotypes were extracted from the baseline visit and from routine clinical health care follow-up records collected in the UK Biobank. Using ICD-10 codes from primary and secondary diagnoses, we were able to identify both T1DM and T2DM patients and examine specific genetic associations with each disease. The wide spectrum of phenotypes available in the UK Biobank study facilitates the PheWAS approach, which we used to search for additional disease phenotypes associated with HLA-DRA-DQAI.

This study had limitations. First, we identified T1DM and T2DM using diagnosis codes from the UK Biobank study. Although such disease definitions in large biobank studies permit efficient analysis of human genomics and diseases (including diabetes [28–30]), there is likely misclassification due to screening practices within the population. Potential underdiagnosis of diabetes may reduce the power of identifying genetic associations. Second, as some TB-associated genetic variants were identified in non-European populations, the underlying functional variants tagged by observed common variants may not exist or have low frequency in European ancestry (eg, UK Biobank Europeans). Such a difference in genetic ancestry may lead to negative associations using lead variants from previous GWAS. Ideally, we would repeat such association analyses in large genomic epidemiological studies of TB and DM with matching genetic ancestry (eg, Africans and South Asians). However, no large population studies with both phenotypic and genomic data in non-European ancestry are currently available to investigate the human genetics of TB and DM. Future human genetic and genomic studies need to establish large diverse cohorts representing global ancestries [31–33], which is particularly critical for TB—a global public health burden mostly in populations having non-European ancestries.

Our results support the hypothesis that TB-associated host genetic factors are also associated with T1DM and T2DM via immunologic functions. Moreover, common genetic factors and pathways may exist more broadly between other infectious and metabolic diseases, particularly via molecular mechanisms.
associated with defense against infectious pathogens. A better understanding of the underlying relationships between infectious and chronic diseases may be particularly important for developing countries with a high prevalence of both.

**Supplementary Data**

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. Y.V.S. was responsible for the conception, organization, and execution of the research project. Y.V.S., H.Z., Y.H., and Q.H. were responsible for the design and execution of the statistical analysis. The first draft was written by Z.H. and Y.V.S. and developed further by M.J.M., M.G., and N.R.G. All co-authors contributed to critical review and editing of the manuscript.

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