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Homozygosity for TYK2 P1104A underlies tuberculosis in about 1% of patients in a cohort of European ancestry

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Contributed by Jean-Laurent Casanova, March 22, 2019 (sent for review March 4, 2019; reviewed by Mary Carrington, Dinakantha Kumararatne, and Michael Levin)

The human genetic basis of tuberculosis (TB) has long remained elusive. We recently reported a high level of enrichment in homozygosity for the common TYK2 P1104A variant in a heterogeneous cohort of patients with TB from non-European countries in which TB is endemic. This variant is homozygous in ∼1/600 Europeans and ∼1/5,000 people from other countries outside East Asia and sub-Saharan Africa. We report a study of this variant in the UK Biobank cohort. The frequency of P1104A homozygotes was much higher in patients with TB (6/620, 1%) than in controls (228/114,473, 0.2%), with an odds ratio (OR) adjusted for ancestry of 5.0 (95% confidence interval (CI): 1.96–10.31, P = 2 × 10−5). Conversely, we did not observe enrichment for P1104A heterozygosity, or for TYK2 I684S or V362F homozygosity or heterozygosity. Moreover, it is unlikely that more than 10% of controls were infected with Mycobacterium tuberculosis, as 97% were of European genetic ancestry, born between 1939 and 1970, and resided in the United Kingdom. Had all of them been infected, the OR for developing TB upon infection would be higher. These findings suggest that homozygosity for TYK2 P1104A may account for ∼1% of TB cases in Europeans.

Tuberculosis (TB) remains a major global public health problem. About a quarter of the world’s population is infected with Mycobacterium tuberculosis (1, 2), resulting in ∼10 million new cases and 1.6 million deaths worldwide in 2017 (3). Nevertheless, only ∼5% of infected individuals develop active TB in their lifetime (1, 4). Abundant evidence for the existence of a genetic component of TB in humans has accumulated from classic genetics studies performed from the turn of the 20th century onward, but its molecular architecture has long remained elusive (5–9). From 1996 onward, single-gene inborn errors of IFN-γ immunity have been found to underlie Mendelian susceptibility to mycobacterial disease (MSMD), which is characterized by severe disease caused by poorly virulent mycobacteria (bacillus Calmette–Guérin vaccines and environmental mycobacteria) (10–15). The clinical penetrance for MSMD depends on the genetic etiology and is inversely correlated with the levels of residual IFN-γ immunity (16). From 2001 onward, autosomal recessive interleukin-12 receptor β1 (IL-12Rβ1) and tyrosine kinase 2 (TYK2) deficiencies have also been identified in children with severe TB and without MSMD (17–23). These two deficiencies impair both the IL-12– and IL-23–dependent production of IFN-γ. They are caused by very rare (minor allele frequency, MAF <5 × 10−5 worldwide) or private loss-of-function alleles.

We recently discovered a strong enrichment in homozygosity for the common TYK2 missense variant P1104A in a genetically heterogeneous cohort of patients with TB from countries outside of Europe in which this disease is endemic, relative to ancestry-adjusted controls, with an odds ratio (OR) of 89.3 (95% CI, 14.7–1,725, P = 8.37 × 10−24) (24). Homozygosity for P1104A is also a genetic etiology of MSMD, albeit with much lower estimated penetrance (0.05%, everyone being exposed to poorly virulent mycobacteria) than for TB (80%, upon infection with M. tuberculosis) (24). Homozygosity for this allele had previously been shown to strongly protect against a variety of inflammatory conditions (25). The P1104A TYK2 protein can be phosphorylated but remains catalytically inactive, resulting in a selective impairment of the IL-23–dependent induction of IFN-γ (24, 26). As many as 1/600 Europeans and ∼1/5,000 individuals outside of East Asia and sub-Saharan Africa are homozygous for P1104A (24). The frequency of this variant appears to

Significance

Only ∼5% of individuals infected with Mycobacterium tuberculosis develop clinical TB in their lifetime. We previously reported that homozygosity for the P1104A variant of the TYK2 gene, found in ∼1/600 Europeans and ∼1/5,000 individuals from elsewhere (except East Asians and sub-Saharan Africans), was a monogenic etiology of TB in a genetically heterogeneous cohort of patients from non-European countries endemic for TB. Making use of the UK Biobank cohort, we report a strong enrichment of P1104A homozygotes in a British sample of 620 patients with TB (1%), relative to 114,473 controls (0.2%), 97% of whom were of European descent. Our findings suggest that homozygosity for the P1104A TYK2 variant may underlie TB in ∼1% of European patients.


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have decreased in Europe over the last 4,000 y, perhaps attesting to purging by endemic TB (24). We hypothesized that homozygosity for this variant might underlie TB in a genetically homogeneous European population, and we tested this hypothesis by analyzing the UK Biobank resource.

**Results**

The UK Biobank is a prospective cohort of ~500,000 volunteers between the ages of 40 and 69 y at recruitment, enrolled between 2006 and 2010, from across the United Kingdom (UK) (27). We retrieved genome-wide genotyping data for all participants, together with TB-related phenotype information. Specifically, we used the most relevant field of the resource (#22137), providing “doctor-diagnosed” TB information for 121,284 participants in a binary format. In total, 654 of these individuals were confirmed as TB cases (code 1), whereas the other 120,630 individuals were not (code 0). These nontuberculous individuals were used as controls for subsequent analyses. The TYK2 P1104A variant (rs4536443) was genotyped in 620 of these cases and 114,473 of these controls. There was a slight excess of females among both cases (sex ratio male/female = 0.83) and controls (0.80), consistent with the demographics of the entire UK Biobank cohort (0.84) (SI Appendix, Table S1). Mean age at recruitment was 56.5 y (SD = 7.7) for controls and 61.1 y (SD = 6.5) for patients with TB, who had a mean age of 18.5 y (SD = 16.0) at TB onset. The MAF of P1104A was 4.7% in controls (10,663/228,946 alleles), and a total of 234 individuals (234/110,093, 0.2%) were homozygous for P1104A. The frequency of P1104A homozygotes was much higher in patients with TB (6/620 = 0.97%) than in controls (228/114,473, 0.2%) [OR = 4.90 (95% CI: 1.93–10.10); P = 2 × 10\(^{-3}\)] (Table 1). TB onset occurred before the age of 15 y in three of the six homozygous patients (two born in 1944 and another in 1946), and after the age of 50 y in the others (born in years 1943, 1944, and 1946) (SI Appendix, Table S1). Heterozygous carriers of P1104A, used as controls, were evenly distributed between the two groups (Table 1). Moreover, no association with TB was observed with the other two common TYK2 missense variants genotyped, I684S and V362F; in the heterozygous, homozygous (Table 1), or compound heterozygous with P1104A states (P = 0.82 and P = 0.71, respectively). These findings suggest that homozygosity for P1104A is a strong risk factor for TB in the United Kingdom, possibly accounting for as many as 1% of TB cases.

The participants in the UK Biobank cohort have various ethnic origins, but most are of British European descent (27). We conducted a principal component analysis (PCA) on the 115,093 participants from this cohort and the 2,504 unrelated individuals of the “1000 Genome project” (1KG) database. The resulting PCA and the distribution of P1104A homozygotes are shown in Fig. 1. More than 97% of these UK Biobank participants, including all 234 P1104A homozygotes, are of European ancestry according to this PCA. This finding is consistent with the self-identification of 91% of the participants as British, 2% as Irish, and 4% as having another “white” ethnic background, as defined in field #21000 of the UK Biobank resource. The remaining 3% of individuals, who declared themselves to be of non-European or mixed ethnic background (Table 2), clustered with the other major worldwide ethnic groups present in the 1KG database (Fig. 1). Among the 234 P1104A homozygotes, 212 controls and 5 TB patients claimed to be of British origin, 4 controls and the sixth TB patient declared themselves to be Irish, and the remaining 12 controls were of other white ancestries. We thus performed the association analysis by logistic regression with adjustment for the first three principal components of the PCA (24, 28). The results were very close to those of the unadjusted analysis, with an OR for developing TB of 5.0 (1.96–10.31, P = 2 × 10\(^{-3}\)) in P1104A homozygotes. No significant enrichment was observed for P1104A heterozygotes, and the other two common TYK2 alleles tested did not differ significantly in frequency between the cases and controls (Table 1). Finally, as familial relationships have been reported in the UK Biobank cohort, we searched for all pairs of individuals presenting evidence of relatedness, whether first-degree relatives or monozygous twins. In total, 2,282 pairs were identified, including 26 cases without P1104A homozygosity and 4,338 controls, including 7 homozygotes. We thus performed the association analysis excluding these 4,364 individuals, and obtained very similar results [OR = 5.07 (95% CI: 1.99–10.48); P = 1.8 × 10\(^{-3}\)]. Collectively, these findings establish that homozygosity for the TYK2 P1104A variant is a strong risk factor for TB in the population of European descent living in the United Kingdom.

Physician-diagnosed TB (#22137) is not the only TB-related field in the UK Biobank resource. Data on hospital episode statistics (#41202 and #41204), with International Classification

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**Table 1. Distribution of P1104A, I684S, and V362F TYK2 variants among cases and controls and OR estimation for the dominant and recessive models of inheritance**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Genotype</th>
<th>Cases, %</th>
<th>Controls, %</th>
<th>OR, 95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1104A</td>
<td>GG</td>
<td>567 (91)</td>
<td>104,038 (91)</td>
<td>0.93 0.94  4.90 5.00</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>47 (8)</td>
<td>10,207 (9)</td>
<td>(0.69–1.22) (0.71–1.24) (1.93–10.10) (1.96–10.31)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>6 (1)</td>
<td>228 (0.2)</td>
<td>P = 0.62 P = 0.71 P = 0.002 P = 0.002</td>
</tr>
<tr>
<td>I684S</td>
<td>AA</td>
<td>525 (82)</td>
<td>96,158 (82)</td>
<td>1.01 1.03  0.89 0.82</td>
</tr>
<tr>
<td></td>
<td>CA</td>
<td>113 (18)</td>
<td>20,463 (18)</td>
<td>(0.82–1.22) (0.84–1.25) (0.32–1.92) (0.32–1.96)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>5 (0.8)</td>
<td>1,028 (0.9)</td>
<td>P = 0.96 P = 0.80 P = 0.79 P = 0.90</td>
</tr>
<tr>
<td>V362F</td>
<td>CC</td>
<td>318 (49)</td>
<td>60,050 (51)</td>
<td>1.07 1.06  1.01 1.00</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td>275 (43)</td>
<td>48,434 (41)</td>
<td>(0.91–1.25) (0.91–1.24) (0.75–1.33) (0.74–1.31)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>53 (8)</td>
<td>9,580 (8)</td>
<td>P = 0.41 P = 0.43 P = 0.93 P = 0.97</td>
</tr>
</tbody>
</table>

Data were retrieved from the UK Biobank genotyped resource.

*Logistic regression was used to obtain ORs and P values (using a likelihood ratio test), and the first three principal components of the PCA were added for the adjusted (adj) ORs and P values.

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**Table 2. Self-reported ethnic background of 115,093 P1104A genotyped individuals of the UK Biobank database with doctor-TB-diagnosed information**

<table>
<thead>
<tr>
<th>Ethnic background</th>
<th>Cases, %, n = 620</th>
<th>Controls, %, n = 114,473</th>
<th>Total, %, n = 115,093</th>
</tr>
</thead>
<tbody>
<tr>
<td>British</td>
<td>537 (87)</td>
<td>104,752 (91)</td>
<td>105,289 (91)</td>
</tr>
<tr>
<td>Irish</td>
<td>25 (4)</td>
<td>2,518 (2)</td>
<td>2,543 (2)</td>
</tr>
<tr>
<td>Other white</td>
<td>27 (4)</td>
<td>4,039 (4)</td>
<td>4,066 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>31 (5)</td>
<td>3,128 (3)</td>
<td>3,159 (3)</td>
</tr>
</tbody>
</table>
of Diseases (ICD)-10 coded diagnosis information, are available for patients of the UK Biobank database hospitalized after 1996. A total of 47 TB-related ICD-10 codes for main or secondary diagnoses are reported in at least one individual, aggregating to a total of 2,629 patients. We noted a very poor overlap with the other TB-related fields, as only 308 (47%) of 654 physician-diagnosed TB cases have a reported age at onset, and a specific number of 120,630 individuals have an entered 0 code (no TB) in this field.

The UK Biobank individuals of European ancestry were born between 1939 and 1970, when the mean annual incidence of TB was declining from ∼75 per 100,000 in the 1950s to less than 20 per 100,000 in the 1970s (30). The prevalence of TB infection is not known for the controls enrolled in the UK Biobank, but it was reported to be below 10%, according to IFN-gamma release assays, in other individuals at higher risk of exposure to \( M. tuberculosis \) living in the United Kingdom, such as nurses (31) and prisoners (32). The prevalence of TB infection was found to be 6.9% in prisoners over the age of 45 y (32). These findings are consistent with the lower annual incidence of TB in the UK-born population, which was 3.2 per 100,000 in 2016, than in the non-UK-born population, which was 49.4 per 100,000, giving an overall incidence of 10.2 per 100,000 (33). All these observations indicate that the vast majority (>90%) of UK Biobank controls of European ancestry living in the United Kingdom are unlikely to have been exposed to and infected with \( M. tuberculosis \). As noninfected controls are not at risk for developing TB, the previously calculated OR for developing TB for P1104A homozygotes is a major underestimate of the true risk of TB upon infection. We thus simulated the distribution of P1104A homozygotes in the control group assuming that all individuals were infected. We conservatively estimated the probability of infected individuals not homozygous for P1104A developing TB at 5% in the general population. In our previous study, we used this general TB risk value, together with the observed OR for TB development in P1104A subjects to estimate the probability of P1104A homozygotes developing TB upon infection, i.e., the penetrance (SI Appendix, Supplementary Information Text); we obtained an estimate for this penetrance of 82% (44–99%) (24). We therefore removed from the control group the proportion of individuals who would have developed TB upon infection: 5% of those not homozygous and a proportion of homozygotes ranging from 40 to 80% (a conservative range of values with respect to penetrance estimates). The resulting ORs for developing TB upon infection are shown in SI Appendix, Fig. S2, and are estimated at 7.7 and 23.0 for a penetrance of 40% and 80%, respectively. In other words, compared with the global risk of 5%, one can estimate the relative risk of TYK2 homozygotes developing TB between 8 (for a penetrance of 40%) and 18 (for a penetrance of 80%). Despite the use of crude estimates for this simulation, it demonstrates a very strong effect of P1104A homozygosity on the risk of TB upon infection.

Another point of interest is the proportion of TB cases homozygous for P1104A. In our previous study, the seven patients homozygous for P1104A originated from Brazil, Chile, Algeria, Morocco, and Turkey, countries with an annual incidence of TB ranging from 17 per 100,000 (Chile) to 99 per 100,000 (Morocco). Based on a mean MAF for P1104A of ∼1.4% in these countries, and on the probabilities of developing TB upon infection for homozygotes and nonhomozygotes, as described above, we estimated that ∼0.33% (95% CI: 0.17–0.40%) of TB cases might be due to homozygosity for P1104A (24). Here, we obtained a more reliable estimate by focusing on a population with a homogeneous European genetic background. For this estimation, we used only the 589 TB cases and 111,345 controls of self-reported British, Irish, and other white ancestry of the UK Biobank cohort, corresponding to 97% of our initial sample (Table 2). P1104A homozygotes accounted for 1.02% of these cases of European origin (6/589), but only 0.2% of controls (228/111,345). The overall MAF of P1104A in European controls was 4.7%, consistent with the value obtained for the remaining 357,710 UK Biobank individuals without TB information (4.5%), slightly higher than for Europeans in the gnomAD database (4%) (https://gnomad.broadinstitute.org/contact). Overall, these results indicate that homozygosity for the P1104A TYK2 allele is a
common monogenic etiology of TB, accounting for about 1% of TB cases in Britain and, by inference, probably in other populations of European ancestry.

**Discussion**

We have shown that homozygosity for TYK2 P1104A confers a strong predisposition to TB in individuals of European ancestry originating from and living in the United Kingdom after World War II. This result is consistent with our previous findings for a genetically heterogeneous cohort of patients with TB from various non-European countries in which TB is endemic (24). The results presented here were obtained using a population of homogeneous ancestry exposed to similar environmental pressures, with more than 97% of cases and controls having European ancestry, and all living in the United Kingdom between 1939 and 2010. Importantly, the participants of this study were all living in a country of low endemicity for TB, as it is unlikely that more than 10% of Britons after World War II were infected by *M. tuberculosis*. This implies that the estimated OR of P1104A homozygotes developing TB upon infection (OR = 5) is underestimated. It is more likely to be >10, as shown by the data for the infected control simulation, corresponding to a lifetime risk of TB between 40 and 80%. This OR is higher than those reported for the few SNPs identified by genome-wide association studies (GWAS) in TB (34-46). These 12 GWAS did not detect the effect of P1104A, as they did not report testing a recessive model. This is also the case for the UK Biobank GWAS conducted on the self-reported TB phenotype (47). In addition, most of these studies, in particular the 10 studies in Latin America (n = 1), Africa (n = 5), and Asia (n = 4), for which the frequency of the P1104A allele is lower, would have been underpowered.

We performed GWAS for the “doctor-diagnosed” TB phenotype in the UK Biobank data under a recessive model and P1104A (P = 2 × 10⁻⁶) remained below the genome-wide significance threshold (5 × 10⁻⁸) (SI Appendix, Fig. S3). A limitation of our study is the relatively small number of physician-diagnosed TB cases (n = 620). Assuming 1% of homozygotes among cases and 0.2% among controls in a balanced case-control study, 5,550 cases and 5,550 controls would be needed to reach a genome-wide significant P value of 5 × 10⁻⁶. It will be important to test whether homozygosity for P1104A is associated with TB in other, larger cohorts of European ancestry. While no variants reached a P value < 2 × 10⁻⁶ in our GWAS, 121 variants with a more significant P value than P1104A (<2 × 10⁻⁶) and with an MAF > 2% gave ORs higher than 5, suggesting that there may be other recessive etiologies of TB in this cohort. Interestingly, GWAS performed on other, larger population samples for phenotypes other than TB have shown that homozygosity for TYK2 P1104A has a strong protective effect (ORs ranging from 0.1 to 0.3) against various auto-inflammatory or autoimmune conditions (25, 48-54). In light of these results, the potential pharmacological benefits of TYK2 inhibitors for treating autoimmune inflammatory or autoimmune conditions are currently being evaluated (55-57). Our findings indicate that if such treatments were to be introduced into widespread use, then it would be important to assess the risk of TB before and during treatment, as is currently done for anti-TNF immunotherapy (58).

Homozygosity for the TYK2 P1104A variant apparently underlies a sizable proportion of TB cases, perhaps accounting for ~1% of TB cases in Europeans and ~0.33% of cases in most other regions of the world (i.e., outside Europe, sub-Saharan Africa, and Eastern Asia). While this small percentage is estimated from a small number of patients, in this (95% CI: 0.2–1.8%) and in our previous study (95% CI: 0.17–0.40%, ref. 24), it corresponds to millions of individuals over the last 10,000 y. An estimate of 1 billion deaths from TB in Europe over the last 2,000 y (SI Appendix, Supplementary Information Text; refs. 59, 60) would imply that about 10 million of these people died due to TYK2 P1104A homozygosity. Future studies based on ancestral time trajectories and the allele frequency trajectories of the P1104A allele across time and in different regions of the world, following up our initial observations for a small population of ancient Europeans (24, 61). Our findings suggested that the frequency of P1104A had decreased from 9 to 4.2% over the last 4,000 y in Europe, which was consistent with a purge operated by TB (24). These studies should be interpreted in light of other population-based studies of the contribution of P1104A homozygosity to the development of TB across modern-day human populations. The lower frequency of P1104A in populations of non-European ancestry, including in particular its very low frequency in East Asia and sub-Saharan Africa, will require unusually large population-based studies. A large number of P1104A-related TB cases would have major implications for the prevention and treatment of TB. It should make it easier to target individuals at high risk of TB when defining optimal cohorts for trials of TB candidate vaccines. Indeed, vaccination strategies should aim at protecting the 5% of individuals who are not naturally, genetically resistant to *M. tuberculosis*. Genetic testing for this variant may also be warranted before traveling to countries highly endemic for TB. The vast majority of P1104A homozygotes living in the most developed countries are asymptomatic, as they have not been exposed to *M. tuberculosis* and the penetrance for MSMD is very low (24). The diagnosis of P1104A homozygosity in patients with TB could also pave the way for genetic counseling in their families. Moreover, injections of recombinant IFN-γ would probably be beneficial in these patients, as in patients with IL12Rβ1 deficiency (15, 62, 63). This is of particular importance in the current context of increasing drug resistance in *M. tuberculosis* strains (64-66). Finally, the notion that 0.5–1% of TB is autosomal recessive and accounted for by homozygosity for a common TYK2 variant has far-reaching implications for the genetic study of TB and other common, severe infectious diseases (67, 68). This discovery further blurs the dichotomy between rare monogenic etiologies (rare variants with a large effect) and common risk factors (common variants with a modest effect) (69-76). It should prompt searches for other monogenic but common causes of TB and other severe infections.

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