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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, $P = 2 \times 10^{-3}$]. 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 | *TYK2* | monogenic | immunodeficiency | IFN- γ

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 β 1 (IL-12R β 1) 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 $\times 10^{-5}$ 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, $P = 8.37 \times 10^{-8}$) (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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Conflict of interest statement: J.-L.C. and M.L. are coauthors on a 2019 paper [Ahmad L (2019) *J Allergy Clin Immunol* 143:765–769] and a 2017 paper [Israel L (2017) *Cell* 168:789–800] in which they independently provided unpublished reagents/analytic tools. J.-L.C., L.A., and D.K. are coauthors on a 2018 paper [Bolze A (2018) *Proc Natl Acad Sci USA* 115:E8007–E8016] in which they independently provided unpublished reagents/analytic tools.

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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

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

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.

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 (rs34536443) 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 (234/115,093, 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); $P = 2 \times 10^{-3}$] (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, $P = 2 \times 10^{-3}$) 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); $P = 1.8 \times 10^{-3}$]. 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

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

Ethnic background	Cases, %, $n = 620$	Controls, %, $n = 114,473$	Total, %, $n = 115,093$
British	537 (87)	104,752 (91)	105,289 (91)
Irish	25 (4)	2,518 (2)	2,543 (2)
Other white	27 (4)	4,039 (4)	4,066 (4)
Other	31 (5)	3,128 (3)	3,159 (3)

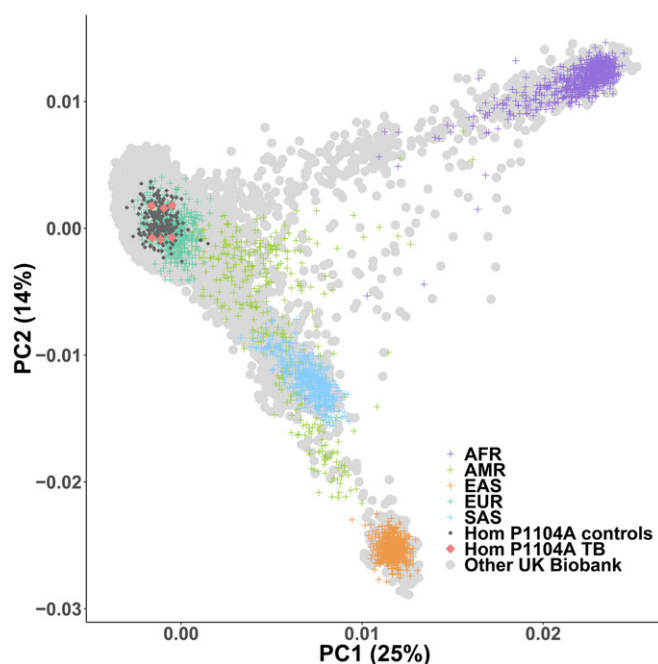


Fig. 1. PCA of the UK Biobank individuals and the 1000 Genome project subjects. The figure shows the PCA (PC1 vs. PC2) conducted on genotyping data for 115,093 individuals with doctor-diagnosed coding from the UK Biobank cohort and 2,504 subjects of the 1000 Genome (1KG) project. The percentages of variance explained by PC1 and PC2 are shown in parentheses. Colored crosses are used to represent the five major ethnic groups from the 1KG project: Africans (AFR, violet), Americans (AMR, light green), East Asians (EAS, orange), Europeans (EUR, dark green), and South Asians (SAS, blue). Light-gray circles are used to represent the individuals from the UK Biobank cohort. Homozygous carriers of the *TYK2* P1104A allele are indicated by red (cases) or dark-gray (controls) diamonds.

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 312 individuals, with only 9 of these codes, in 57 individuals, including bacteriologically and/or histologically confirmed TB (*SI Appendix, Table S2*). Among the 312 individuals, 18 (including 6 with confirmed TB) also had physician-diagnosed TB. This poor correlation is explained by the fact that 581 (89%) physician-diagnosed TB cases occurred before 1996 (*SI Appendix, Fig. S1*), before ICD-10 coding. An additional 20 ICD-10 TB individuals (1 confirmed) belong in the 120,630 individuals with a 0 physician-diagnosis TB code (no TB), representing a proportion of 0.02%, consistent with a low misclassification rate among our controls. Finally, the remaining 274 individuals (50 confirmed) belong in the 381,254 individuals without physician-diagnosed TB information. Importantly, 164 (44%) of the 294 ICD-10 TB cases (33% of the confirmed TB) that do not overlap with physician-diagnosed TB cases have non-European ancestries, whereas a total of only 146 (36 confirmed) were of British origin (*SI Appendix, Table S3*). Accordingly, none of the ICD-10 TB cases were homozygous for the P1104A allele. Another TB-related field extracted from the “Non-cancer illness code, self-reported field” (#20002) was “self-reported TB,” adding up 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 and 101 (32%) of 312 ICD-10 TB (35% for confirmed) had self-reported TB. This is consistent with the poor self-reported stroke information in the UK Biobank (29). Overall, the physician-TB diagnosed field is the most reliable TB information available. The

654 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 underestimation 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 16 (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 ancestries of the UK Biobank cohort, corresponding to 97% of our initial sample (Table 2). P1104A homozygotes accounted for 1.02% of TB 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 accessible in Gene Atlas (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 ($P = 2 \times 10^{-3}$) 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^{-8} . 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 $< 2 \times 10^{-6}$ in our GWAS, 121 variants with a more significant P value than P1104A ($< 2 \times 10^{-3}$) and with a 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 auto-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 ancient DNA time transects should attempt to track 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 travel 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 IL-12R β 1 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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1. Esmail H, Barry CE, 3rd, Young DB, Wilkinson RJ (2014) The ongoing challenge of latent tuberculosis. *Philos Trans R Soc Lond B Biol Sci* 369:20130437.
2. Houben RMGJ, Dodd PJ (2016) The global burden of latent tuberculosis infection: A re-estimation using mathematical modelling. *PLoS Med* 13:e1002152.
3. WHO (2018) Global tuberculosis report 2018. Available at https://www.who.int/tb/publications/global_report/en/. Accessed March 1, 2019.

4. Borgdorff MW, et al. (2011) The incubation period distribution of tuberculosis estimated with a molecular epidemiological approach. *Int J Epidemiol* 40:964–970.
5. Puffer R (1944) *Familial Susceptibility to Tuberculosis: Its Importance as a Public Health Problem* (Harvard Univ Press, Cambridge, MA).
6. Abel L, et al. (2018) Genetics of human susceptibility to active and latent tuberculosis: Present knowledge and future perspectives. *Lancet Infect Dis* 18:e64–e75.

7. Kallmann FJ, Reiser D (1943) Twin studies on the significance of genetic factors in tuberculosis. *Am Rev Tuberc* 47:549–571.
8. von Verschuer F (1939) Twin research from the time of Francis Galton to the present-day. *Proc R Soc Lond B Biol Sci* 128:62–81.
9. Pearson K (1909) Discussion on the influence of heredity on disease, with special reference to tuberculosis, cancer, and diseases of the nervous system: Introductory address. *Proc R Soc Med* 2:54–60.
10. Altare F, et al. (1998) Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. *Science* 280:1432–1435.
11. Altare F, et al. (1998) Inherited interleukin 12 deficiency in a child with bacille Calmette-Guérin and Salmonella enteritidis disseminated infection. *J Clin Invest* 102:2035–2040.
12. de Jong R, et al. (1998) Severe mycobacterial and Salmonella infections in interleukin-12 receptor-deficient patients. *Science* 280:1435–1438.
13. Jouanguy E, et al. (1996) Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guérin infection. *N Engl J Med* 335:1956–1961.
14. Newport MJ, et al. (1996) A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. *N Engl J Med* 335:1941–1949.
15. Bustamante J, Boisson-Dupuis S, Abel L, Casanova J-L (2014) Mendelian susceptibility to mycobacterial disease: Genetic, immunological, and clinical features of inborn errors of IFN- γ immunity. *Semin Immunol* 26:454–470.
16. Dupuis S, et al. (2000) Human interferon-gamma-mediated immunity is a genetically controlled continuous trait that determines the outcome of mycobacterial invasion. *Immunol Rev* 178:129–137.
17. Altare F, et al. (2001) Interleukin-12 receptor beta1 deficiency in a patient with abdominal tuberculosis. *J Infect Dis* 184:231–236.
18. Boisson-Dupuis S, et al. (2011) IL-12R β 1 deficiency in two of fifty children with severe tuberculosis from Iran, Morocco, and Turkey. *PLoS One* 6:e18524.
19. Boisson-Dupuis S, et al. (2015) Inherited and acquired immunodeficiencies underlying tuberculosis in childhood. *Immunol Rev* 264:103–120.
20. Caragol I, et al. (2003) Clinical tuberculosis in 2 of 3 siblings with interleukin-12 receptor beta1 deficiency. *Clin Infect Dis* 37:302–306.
21. Kreins AY, et al. (2015) Human TYK2 deficiency: Mycobacterial and viral infections without hyper-IgE syndrome. *J Exp Med* 212:1641–1662.
22. Ozbek N, et al. (2005) Interleukin-12 receptor beta 1 chain deficiency in a child with disseminated tuberculosis. *Clin Infect Dis* 40:e55–e58.
23. Tabarsi P, et al. (2011) Lethal tuberculosis in a previously healthy adult with IL-12 receptor deficiency. *J Clin Immunol* 31:537–539.
24. Boisson-Dupuis S, et al. (2018) Tuberculosis and impaired IL-23-dependent IFN- γ immunity in humans homozygous for a common TYK2 missense variant. *Sci Immunol* 3:eaau8714.
25. Dendrou CA, et al. (2016) Resolving TYK2 locus genotype-to-phenotype differences in autoimmunity. *Sci Transl Med* 8:363ra149.
26. Martínez-Barricarte R, et al. (2018) Human IFN- γ immunity to mycobacteria is governed by both IL-12 and IL-23. *Sci Immunol* 3:eaau6759.
27. Bycroft C, et al. (2018) The UK Biobank resource with deep phenotyping and genomic data. *Nature* 562:203–209.
28. Belkadi A, et al.; Exome/Array Consortium (2016) Whole-exome sequencing to analyze population structure, parental inbreeding, and familial linkage. *Proc Natl Acad Sci USA* 113:6713–6718.
29. Woodfield R, Sudlow CL; UK Biobank Stroke Outcomes Group; UK Biobank Follow-up and Outcomes Working Group (2015) Accuracy of patient self-report of stroke: A systematic review from the UK Biobank stroke outcomes group. *PLoS One* 10:e0137538.
30. Glaziou P, Floyd K, Raviglione M (2018) Trends in tuberculosis in the UK. *Thorax* 73:702–703.
31. Khanna P, Nikolayevskiy V, Warburton F, Dobson E, Drobniowski F (2009) Rate of latent tuberculosis infection detected by occupational health screening of nurses new to a London teaching hospital. *Infect Control Hosp Epidemiol* 30:581–584.
32. Gray BJ, Perrett SE, Guddeon B, Shankar AG (January 4, 2019) Investigating the prevalence of latent Tuberculosis infection in a UK remand prison. *J Public Health (Oxf)*, 10.1093/pubmed/fdy219.
33. Public Health England (2017) Tuberculosis in England. Available at <https://www.gov.uk/government/organisations/public-health-england>. Accessed October 24, 2017.
34. Schurz H, et al. (2019) A sex-stratified genome-wide association study of tuberculosis using a multi-ethnic genotyping array. *Front Genet* 9:678.
35. Zheng R, et al. (2018) Genome-wide association study identifies two risk loci for tuberculosis in Han Chinese. *Nat Commun* 9:4072.
36. Qi H, et al. (2017) Discovery of susceptibility loci associated with tuberculosis in Han Chinese. *Hum Mol Genet* 26:4752–4763.
37. Sobota RS, et al. (2016) A locus at 5q33.3 confers resistance to tuberculosis in highly susceptible individuals. *Am J Hum Genet* 98:514–524.
38. Sveinbjornsson G, et al. (2016) HLA class II sequence variants influence tuberculosis risk in populations of European ancestry. *Nat Genet* 48:318–322.
39. Grant AV, et al. (2016) A genome-wide association study of pulmonary tuberculosis in Morocco. *Hum Genet* 135:299–307.
40. Curtis J, et al. (2015) Susceptibility to tuberculosis is associated with variants in the ASAP1 gene encoding a regulator of dendritic cell migration. *Nat Genet* 47:523–527.
41. Chimusa ER, et al. (2014) Genome-wide association study of ancestry-specific TB risk in the South African coloured population. *Hum Mol Genet* 23:796–809.
42. Mahasirimongkol S, et al. (2012) Genome-wide association studies of tuberculosis in Asians identify distinct at-risk locus for young tuberculosis. *J Hum Genet* 57:363–367.
43. Png E, et al. (2012) A genome wide association study of pulmonary tuberculosis susceptibility in Indonesians. *BMC Med Genet* 13:5.
44. Thye T, et al. (2012) Common variants at 11p13 are associated with susceptibility to tuberculosis. *Nat Genet* 44:257–259.
45. Thye T, et al.; African TB Genetics Consortium; Wellcome Trust Case Control Consortium (2010) Genome-wide association analyses identifies a susceptibility locus for tuberculosis on chromosome 18q11.2. *Nat Genet* 42:739–741.
46. Luo Y, et al. (2018) Progression of recent Mycobacterium tuberculosis exposure to active tuberculosis is a highly heritable complex trait driven by 3q23 in Peruvians. *bioRxiv*:10.1101/401984. Preprint, posted August 28, 2018.
47. Canela-Xandri O, Rawlik K, Tenesa A (2018) An atlas of genetic associations in UK Biobank. *Nat Genet* 50:1593–1599.
48. Diogo D, et al. (2015) TYK2 protein-coding variants protect against rheumatoid arthritis and autoimmunity, with no evidence of major pleiotropic effects on non-autoimmune complex traits. *PLoS One* 10:e0122271.
49. Cortes A, et al.; International Genetics of Ankylosing Spondylitis Consortium (IGAS); Australo-Anglo-American Spondyloarthritis Consortium (TASC); Groupe Française d'Etude Génétique des Spondylarthrites (GFEGS); Nord-Trøndelag Health Study (HUNT); Spondyloarthritis Research Consortium of Canada (SPARCC); Wellcome Trust Case Control Consortium 2 (WTCCC2) (2013) Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet* 45:730–738.
50. Beecham AH, et al.; International Multiple Sclerosis Genetics Consortium (IMSGC); Wellcome Trust Case Control Consortium 2 (WTCCC2); International IBD Genetics Consortium (IBDGC) (2013) Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet* 45:1353–1360.
51. Jostins L, et al.; International IBD Genetics Consortium (IBDGC) (2012) Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 491:119–124.
52. Tsoi LC, et al.; Collaborative Association Study of Psoriasis (CASP); Genetic Analysis of Psoriasis Consortium; Psoriasis Association Genetics Extension; Wellcome Trust Case Control Consortium 2 (2012) Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nat Genet* 44:1341–1348.
53. Fodil N, Langlais D, Gros P (2016) Primary immunodeficiencies and inflammatory diseases: A growing genetic intersection. *Trends Immunol* 37:126–140.
54. Langlais D, Fodil N, Gros P (2017) Genetics of infectious and inflammatory diseases: Overlapping discoveries from association and exome-sequencing studies. *Annu Rev Immunol* 35:1–30.
55. Gadina M, et al. (2018) Translational and clinical advances in JAK-STAT biology: The present and future of jakinibs. *J Leukoc Biol* 104:499–514.
56. He X, Chen X, Zhang H, Xie T, Ye X-Y (2019) Selective Tyk2 inhibitors as potential therapeutic agents: A patent review (2015–2018). *Expert Opin Ther Pat* 29:137–149.
57. Papp K, et al. (2018) Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. *N Engl J Med* 379:1313–1321.
58. Kaya FO (2017) Anti-TNF treatment and tuberculosis. *Austin J Pulm Respir Med* 4:1055.
59. Dubos RJ, Dubos J (1987) *The White Plague: Tuberculosis, Man, and Society* (Rutgers Univ Press, New Brunswick, NJ).
60. Murray JF (2015) The Industrial Revolution and the decline in death rates from tuberculosis. *Int J Tuberc Lung Dis* 19:502–503.
61. Olalde I, et al. (2018) The Beaker phenomenon and the genomic transformation of northwest Europe. *Nature* 555:190–196.
62. Fieschi C, et al. (2003) Low penetrance, broad resistance, and favorable outcome of interleukin 12 receptor β 1 deficiency: Medical and immunological implications. *J Exp Med* 197:527–535.
63. Holland SM (2001) Immunotherapy of mycobacterial infections. *Semin Respir Infect* 16:47–59.
64. Udawadia ZF, Amale RA, Ajbani KK, Rodrigues C (2012) Totally drug-resistant tuberculosis in India. *Clin Infect Dis* 54:579–581.
65. Daley CL, Caminero JA (2018) Management of multidrug-resistant tuberculosis. *Semin Respir Crit Care Med* 39:310–324.
66. Dheda K, et al. (2017) The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med*, S2213-2600(17)30079-6.
67. Casanova J-L (2015) Human genetic basis of interindividual variability in the course of infection. *Proc Natl Acad Sci USA* 112:E7118–E7127.
68. Casanova J-L (2015) Severe infectious diseases of childhood as monogenic inborn errors of immunity. *Proc Natl Acad Sci USA* 112:E7128–E7137.
69. Cohen JC, Hobbs HH (2013) Genetics. Simple genetics for a complex disease. *Science* 340:689–690.
70. Chakravarti A, Clark AG, Mootha VK (2013) Distilling pathophysiology from complex disease genetics. *Cell* 155:21–26.
71. Florez JC, Hirschhorn J, Altshuler D (2003) The inherited basis of diabetes mellitus: Implications for the genetic analysis of complex traits. *Annu Rev Genomics Hum Genet* 4:257–291.
72. Katsanis N (2016) The continuum of causality in human genetic disorders. *Genome Biol* 17:233.
73. McLaren PJ, Carrington M (2015) The impact of host genetic variation on infection with HIV-1. *Nat Immunol* 16:577–583.
74. McClellan J, King M-C (2010) Genetic heterogeneity in human disease. *Cell* 141:210–217.
75. Casanova J-L, Abel L (2002) Genetic dissection of immunity to mycobacteria: The human model. *Annu Rev Immunol* 20:581–620.
76. Lifton RP (2004) Genetic dissection of human blood pressure variation: Common pathways from rare phenotypes. *Harvey Lect* 100:71–101.