Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Exploring IFN-γ +874T/A gene polymorphisms among suspected tuberculosis cases in Ouagadougou, Burkina Faso

Tani Sagna[1,2,3*], Wendbenedo Yasmine Astrid Sana[2], Lassina Traore[2,3], Tegwinde Rebeca Compaore[1,2,3], Serge Théophile Soubeiga[1,2,3], Ifono Kekoura[2], Pierre Zabre[2], Sanata Nadine Kiemde[2], Sylvie Zida[1], Kadari Cisse[1], Dinanibé Kambire[1], Oumarou Ouedraogo[1], Ina Marie Angèle Traore[1,2,3], Absatou Ky Ba[3], Adjima Combary[4], Henri Gautier Ouedraogo[1], Seni Kouanda[1], Jacques Simpore[2,3*]

[1] *Health Sciences Research Institute (IRSS), Ouagadougou, Burkina Faso*
[2] *Pietro Annigoni Biomolecular Research Center / Laboratory of Molecular Biology and Genetics (CERBA/LABIOGENE), Ouagadougou, Burkina Faso*
[3] *Université Joseph Ki-Zerbo (UJKZ), Ouagadougou, Burkina Faso*
[4] *National Tuberculosis Control Program (PNT), Ouagadougou, Burkina Faso*

Article Info

Article history:

Received: October 27, 2024
Accepted: January 03, 2025
Published: February 28, 2025

Use your device to scan and read the article online

Abstract

Interferon-gamma (IFN-γ) plays a crucial role in resistance to mycobacterial infections, as it is a regulatory cytokine that acts as a pro-inflammatory mediator. Consequently, variants in the gene encoding this cytokine may be associated with a high risk of contracting pulmonary tuberculosis. The present study aimed to investigate the genetic susceptibility of polymorphisms in the gene coding for IFN-γ to infection by *Mycobacterium tuberculosis* in Burkina Faso. This cross-sectional study was conducted from May 2023 to January 2024. Venous blood was collected from suspected cases. Tuberculosis was confirmed by GeneXpert (CEPHEID). Human genomic DNA was extracted using the salting-out extraction technique, followed by the amplification and genotyping of IFN-γ gene polymorphisms,through the conventional PCR. Statistical analyses were performed using the SPSS and Epi info software. A total of 168 participants were included in the study, with an average age of 38.58 ±14.88, the majority of whom were men (76.19%). In our study population, 73.2% (123/168) were confirmed positive for tuberculosis. Some 46.4% (78/168) of the previous cases were contacts. Of these contact cases, 82.05% (64/78) were GeneXpert positive. The genotypic frequencies of the IFN-γ gene were distributed as follows: 73.3% (AA), 21.8% (AT) and 4.9% (TT), with a frequency of 84.2% for the A allele versus 15.8% for the mutated T allele. No statistically significant association was found between IFN-γ gene polymorphisms and M. tuberculosis infection in Burkina Faso. IFN-γ gene polymorphisms (IFN +874T/A) do not appear to be associated with *M. tuberculosis* infection in Burkina Faso.

Keywords: Active tuberculosis, Genetic susceptibility, Gene, IFN-γ, Burkina Faso.

1. Introduction

Tuberculosis (TB) remains a global health problem. It is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis (M. tuberculosis)*, and that 5-10% of these infected people develop active TB during their lifetime [1, 2]. Around two million people die from the disease every year [2, 3]. Tuberculosis can be transmitted from person to person via the micro secretions emitted by a sick person, through coughing or sneezing for instance. Cases of intra- or inter-species transmission have been reported [4]. Preventing tuberculosis means protection against it; actively seeking out and screening cases and treating sick individuals to block progression. Close and prolonged contact with tuberculosis cases facilitates transmission. However, some individuals, in spite of exposure, escape by managing to control *M. tuberculosis* infection and progression to tuberculosis [5]. This could be exploited to help achieve the WHO's End TB target [2].

Less than 25% of the global population infected with *M. tuberculosis* will develop latent tuberculosis [6], and around 10% of these people will progress to active tuberculosis [7]. What distinguishes those who can control the infection from those who cannot? Beside, environmental factors such as nutrition, immunity, co-infection and differences between bacterial strains, the genetics of the human host are likely to play a role [8]. Specific gene polymorphisms that may predispose individuals to tuberculosis are not fully elucidated [9, 10]. Several antigen-presenting molecules, including interferon-gamma (IFN-γ) and major histocompatibility complex, are encoded by polymorphic genes. Some polymorphisms affect susceptibility to tuberculosis [11]. IFN-γ and its receptors, which are of great interest in tuberculosis research [11], is a regulatory cytokine that participates in immune response by acting as a

* Corresponding author.
E-mail address: stanilinda@gmail.com (T. SAGNA).
Doi: http://dx.doi.org/10.14715/cmb/2025.71.2.10

pro-inflammatory mediator [12, 13]. IFN-γ plays a crucial role in resistance to mycobacteria. Consequently, variants in the gene encoding this cytokine could be associated with a high risk of developing pulmonary tuberculosis.

The main objective of this study was to investigate polymorphisms of the gene encoding IFN-γ among suspected cases and their association with *M. tuberculosis* infection in Burkina Faso. The specific objectives were to identify variants of the gene encoding IFN-γ (IFN +874T/A) and to assess a possible association between this gene and *M. tuberculosis* infection in Burkina Faso.

2. Materials and methods

2.1 Type, period, site and study population

This was a cross-sectional study conducted from May 2023 to January 2024. The study population consisted of patients with suspected tuberculosis sent to the "Diagnosis and Treatment Centre (CDT)" of the "Bogodogo University Hospital (CHU-B)", in Ouagadougou, Burkina Faso. Inclusion was performed consecutively at the CDT of the CHU-B. All patients were included during the study period, except those who did not consent or brought samples of their sick relatives. Diagnosis of *M. tuberculosis* was performed at the CHU-B laboratory by real-time PCR on the GeneXpert (CEPHEID) from sputum samples. IFN-γ genotyping was carried out in the molecular biology and genetics laboratory (LaBioGene) and the biomedical research laboratory of the Health Sciences Research Institute (IRSS).

Data were collected from participants through questionnaire administered to them. A blood sample (4 mL) was collected from each participant on EDTA tube for DNA extraction, followed by genotyping, using Gene Amp 9700 (Applied Biosystem).

2.2. Molecular confirmation of suspected cases by real-time PCR

Tuberculosis was confirmed by PCR using the GeneXpert device (CEPHEID) and its commercial kit Xpert MTB/RIF. This test allows for molecular diagnosis of tuberculosis and at the same time identifies cases of rifampicin resistance. To carry out the test, 4mL of diluent was added to 2 mL of coughed-up sputum, mixed vigorously and incubated at room temperature for 15 min. Two (02) mL of this mixture were then used to load the cartridge prior to insertion and analysis in the GeneXpert module. Target detection and characterization are performed in real time using a six-color laser device.

2.3. DNA extraction and genotyping of the IFN-γ gene

Genomic DNA was extracted using the rapid Salting-Out technique (Miller et al. 1988), based on cell lysis, protein digestion and precipitation, as well as impurity washing and DNA elution. After DNA extraction, the amount was estimated using a BioDrop, and solely over 7-200µg/mL concentrations were considered, with adjustment for high concentrations (over 200µg/mL). Other samples were re-extracted prior to genotyping. Both negative and positive controls were used at each stage. These included water for the extraction steps, together with human growth hormone for genotyping.

For genotyping of the IFN-γ gene (IFN +874T/A), a classical allele-specific PCR was used with specific primers (Table 1) (Araujo *et al.)* A pair of primers targeting the human growth factor (HGF) gene was included as an internal control. For each sample, a total reaction volume of 20 µL consisting of 0.6 µL of sense primer; 0.6 µL of antisense primer; 4 µL of Hot FIREPol® Master Mix (5X) and 8.6 µL of PCR water was used.

2.4. Statistical analysis

Data were entered using Excel 2016 and analyzed using R version 1.4.1717 and SPSS version 20. The chi-square test, Fisher's exact test, Odds ratios (OR) and 95% confidence intervals (95% CI) were also calculated to assess associations between interferon gamma polymorphisms and tuberculosis. Hardy-Weinberg Equilibrium (HWE) was used in this genetic association study to predict the distribution of genotypes in this population; if $p< 0.05$ - not HWE compliant.

2.5. Ethical considerations

The protocol was approved by the Burkina Faso Health Research Ethics Committee under number 2022-02-023. Subjects recruited were those who agreed to participate in the study and gave their free and informed consent for blood sampling. We guaranteed the confidentiality of our database by storing it on a password-protected computer.

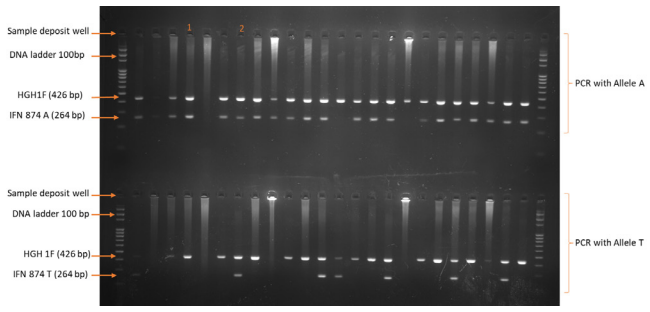

Fig. 1. Overview of the gel after amplification and agarose gel migration of the DNA sample. The genotype of each individual (+874A/T) was analyzed using the refractory amplification-mutation-PCR technique. A primer pair based on the nucleotide sequence of human growth hormone (HGH 1F) was added to amplify a 426 bp product (Control +) to assess PCR success; negative control (second well of the gel), 1: Sample AA; 2: Sample AT; DNA ladder 100pb: base-pair marker (first well); HGH 1F: Human growth hormone.

Table 1. Primers and amplicon sizes used in the study.

	IFNG gene primers	Size (bp)
Primer T of IFN gamma+874T (Forward)	5'-TTC TTA CAA CAC AAA ATC AAA TCT-3	
Primer A of IFN gamma+874A (Forward)	5'-TTC TTA CAA CAC AAA ATC AAA TCA-3'	
Primer of IFN gamma +874T/A (Reverse)	5'-TCA ACA AAG CTG ATA CTC CA-3'	264
Primer oh Gh1f-F (Forward)	3'-CAG TGC CTT CCC AAC CAT TCC CTT A- 5'	
Primer oh Gh1f-R (Reverse)	5'-ATC CAC TCA CGG ATT TCT GTT GTG TTT C 5'	426

3. Results

3.1. Socio-demographic characteristics of the study population

The 168 participants ranged between 15 and 73 years, with an average age of 38.58 ±14.88 years. Women represented 23.81% (40/168) of the population, compared with 76.19% (128/168) men. Majority of the participants already had some knowledge of tuberculosis prior to the request for examination. In our study population, 73.2% (123/168) were confirmed positive for tuberculosis by GeneXpert. No cases of resistance to treatment were found with the GeneXpert test. Socio-demographic characteristics are shown in Table 2. The results showed that the majority of GeneXpert positive participants had no education (73.58%).

3.2. Amplification and polymorphism detection

After conventional PCR amplification of a fragment of the gene encoding IFN-γ, we obtained amplicons at 264 bp, the wild-type allele (A). Mutated homozygotes (T) were characterized by a band size of 264 bp. In our study population, some heterozygotes (AT) were found.

3.3. Genotypic and allelic frequencies of the gene encoding IFN-γ

Genotypic frequencies conformed to Hardy-Weinberg equilibrium (HWE) in the group of negative cases in our study population with $p = 0.0898$ but did not conform to Hardy-Weinberg equilibrium (HWE) in the group of positive cases in our study population with $p = 0.007$ ($p < 0.05$) (Table 3).

3.4. Distribution of genotypic and allelic frequencies

In females, genotype frequencies were 80% for AA homozygotes, 16.67% for AT heterozygotes and 3.33% for TT mutated homozygotes. The frequency of mutated alleles was 11.7% (Table 4).

In males, genotype frequencies were 71.43% for AA homozygotes, 23.21% for AT heterozygotes and 5.36% for TT wild-type homozygotes. The frequency of mutated alleles was 17.0% (Table 4).

Table 4 shows the proportion of two age groups at diagnosis of tuberculosis, before and after the age of 40, in our study population. Before the age of 40, genotype frequencies were 60.58% for AA homozygotes, 67.74% for AT heterozygotes and 28.57% for TT mutated homozygotes. After 40 years, genotype frequencies were 39.42% for AA homozygotes, 32.26% for AT heterozygotes and 71.43% for TT wild-type homozygotes.

Table 4 also shows the distribution of interferon-γ variant (IFN +874T/A) genotypes and alleles in relation to the GeneXpert results. In the study population, the genotype frequencies of mutated homozygotes (AA), heterozygotes (AT) and wild-type homozygotes (TT) were 73.3%, 21.8% and 4.9% respectively.

These same genotypes in particular (AA, AT and TT) accounted for 75.0%, 19.23% and 5.77% respectively in positive cases, and 68.42%, 28.95% and 2.63% in negative cases. No significant association was found between the variants of this polymorphism and tuberculosis.

Furthermore, the frequency of the mutated [A] allele was 84.6% in positive cases and 82.9% in negative con-

Table 2. Socio-demographic characteristics of study participants linked to GeneXpert results

Socio-demographic characteristics		GeneXpert results	
		Negative	Positive
Age	<40 (97)	25.77% (25/97)	74.23% (72/97)
	≥40 (71)	28.17% (20/71)	71.83% (51/71)
Gender	Female (40)	35% (14/40)	65.0% (26/40)
	Male (128)	24.22% (31/128)	75.78% (97/128)
Marital status	Single (72)	25.0% (18/72)	75.0% (54/72)
	Married (96)	28.13% (27/96)	71.87% (69/96)
Level of formal education	None (53)	26.42% (14/53)	73.58% (39/53)
	Local language (12)	33.33% (4/12)	66.67% (8/12)
	Primary (38)	21.05% (8/38)	78.95% (30/38)
	High school and up (65)	29.23% (19/65)	70.77% (46/65)
Profession	Unemployed (38)	28.95% (11/38)	71.05% (27/38)
	Informal (54)	24.07% (13/54)	75.93% (41/54)
	Employed (76)	27.63% (21/76)	72.37% (55/76)
Total (168)		26.8% (45/168)	73.2% (123/168)

Table 3. Comparison of expected and observed IFN-γ genotype frequencies.

	Genotypes	Positive		Negative	
		Observed	Calculated	Observed	Calculated
GeneXpert IFN +874T/A	AA	78	74.5	26	26.1
	AT	20	27.1	11	10.8
	TT	6	2.5	1	1.1
χ^2		***7.10***		***0.016***	
HWE		p = 0.007		p = 0.898	

χ^2 :chi-square; HWE : Hardy Weinberg equilibrium; p : p-value

Table 4. Interferon-γ (IFN +874T/A) variants in relation to gender, age and GeneXpert results.

		Gender				
		Total	**Female**	**Male**	**OR (95% CI)**	**p-value**
		N=142(%)	**N=30(%)**	**N=112(%)**		
Genotype	**AA**	104 (73.3)	24 (80.0)	80 (71.43)	**Reference**	
	AT	31 (21.8)	5 (16.67)	26 (23.21)	0.64(0.20-185)	0.68
	TT	7 (4.9)	1 (3.33)	6 (5.36)	0.55(0.06-4.84)	0.29
	AT+TT	38 (26.8)	6 (20.65)	32 (28.57)	0.63(0.23-1.67)	0.89
Allele	**A**	239 (84.2)	53 (88.3)	186 (83.0)	**Reference**	
	T	45 (15.8)	7(11.7)	38 (17.0)	0.65(0.27-1.53)	1.00
		Age ranges				
		Total	**<40**	**≥40**	**OR (95% CI)**	**p-value**
		142 (100.0)	**N(%)**	**N(%)**		
Genotype	**AA**	104 (73.3)	63 (60.58)	41 (39.42)	**Reference**	
	AT	31 (21.8)	21 (67.74)	10 (32.26)	1.37(0.58-3.20)	0.52
	TT	7 (4.9)	2 (28.57)	5 (71.43)	0.26(0.04-1.40)	2.77
	AT+TT	38 (26.8)	23 (26.7)	15 (27.8)	1.00(0.46-2.13)	<0.001
Allele	**A**	239 (84.2)	147 (85.5)	92 (82.1)	**Reference**	
	T	45 (15.8)	25 (14.5)	20 (17.9)	0.78(0.42-1.41)	0.56
		GeneXpert Results				
		Total	Positive	Negative		
		142 (100.0)	**N=104(%)**	**N=38(%)**	**OR (95% CI)**	**p-value**
Genotype	**AA**	104 (73.3)	78 (75.0)	26 (68.42)	**Reference**	
	AT	31 (21.8)	20 (19.23)	11 (28.95)	1.65(0.69-3.89)	0.25
	TT	7 (4.9)	6 (5.77)	1 (02.63)	0.50(0.05-4.34)	0.52
	AT+TT	40 (28.2)	26(25.0)	12(31.58)	1.38(0.61-3.12)	0.43
Allele	**A**	239 (84.2)	176 (84.6)	63 (82.9)	**Reference**	
	T	45 (15.8)	32 (15.4)	13 (17.1)	0.44(0.05-3.79)	0.44
		Contacts Case				
		Total	GeneXpert Positive	GeneXpert Negative		
		142 (100.0)	**N=56(%)**	**N=11(%)**	**OR (95% CI)**	**p-value**
Genotype	**AA**	104 (73.3)	39 (69.64)	9 (81.82)	**Reference**	
	AT	31 (21.8)	14 (25.0)	2 (18.18)	0.61(0.11-3.22)	0.56
	TT	7 (4.9)	3 (5.36)	0 (0)	0.00	0.41
	AT+TT	40 (28.2)				
Allele	**A**	239 (84.2)	53	11	**Reference**	
	T	45 (15.8)	3	0	0.00	0.43

trols. No statistically significant difference was observed between this allele and the occurrence of tuberculosis (OR = 0.44; CI (95%) = 0.05-3.79; p = 0.52).

The genotypic and allelic frequencies of the interferon-γ (IFN +874T/A) variants in relation to the GeneXpert results for Contact Cases are presented in Table 4. After analysis, the distribution of genotypes and alleles showed no specific pattern or correlation between TB patients and negative controls.

4. Discussion

This study aimed to investigate polymorphisms of the gene encoding IFN-γ among suspected cases and their association with *Mycobacterium tuberculosis* infection in Burkina Faso. It revealed the presence of the AA, AT and TT genotypes of interferon gamma. The respective proportions were 73.24%, 21.83% and 4.93%.

Analysis of the data according to sociodemographic characteristics showed that the age range of our study population varied from 15 to 73 years, with an average of 38.58 ±14.88 years. Our results showed that majority of the infected participants were not educated (73.58%).

Analysis of the genotypic and allelic frequencies of the study population showed that the different genotypes and alleles in the group of negative cases were in Hardy Weinberg equilibrium, while those in the positive sample were not. Indeed, Hardy Weinberg's law states that within a population, allelic and genotypic frequencies remain

constant from one generation to the next [14, 15]. Thus, this leads us to believe that the genotypic and allelic distribution of the polymorphism of the gene encoding IFN-γ in our study is not fully representative of that of the population of Burkina Faso. This suggests that the polymorphism is not constant from one generation to the next.

In this study, 73.2% of participants had laboratory-confirmed tuberculosis. AA, AT and TT variants were identified, with AA genotypes predominant in 75%, 19.23% and 5.77% of the study population respectively. Previous studies have also shown a predominance of AA genotypes in cases of pulmonary tuberculosis in Argentina [16]. Indeed, the AA genotype leads to low expression of interferon-gamma and consequently a predisposition to tuberculosis after infection with *Mycobacterium tuberculosis* [17]. These will not be the only interferon variants, as several others that may be involved in TB susceptibility have been described [18, 19]. In addition to those of Interferon-gamma, authors have identified other genetic or epigenetic variants that could be involved through their role in the regulation of interferon-gamma [20-22]. Contrary to the results of Wu and collaborators [23], the polymorphism associated with tuberculosis (AA genotype for this case) was found predominantly in women (80% vs. 71.43%), but they were the least affected by tuberculosis (65% vs. 75.78%). This could be explained by the fact that the group with the highest awareness of the existence of TB were women (85% vs. 75%), and therefore more inclined to protect themselves. The under-40 age group was the most representative of the AA genotype, in contrast to the results obtained by Naz and collaborators [24], who found that younger people were more predisposed to contracting the disease. But by taking genetic and epigenetic variants into account [16], exposure effects could be reduced.

In terms of allelic distribution, the wild-type A allele had a frequency of 84.6%, compared with 15.4% for the mutated allele. Our allelic frequencies were similar to those of [17], which showed that the A allele was clearly over-represented among individuals compared with the T allele. This could be explained by the fact that there is a similarity in the population of the two studies. The genotype distribution (OR T: 0.50 [95% CI = 0.05-4.34] $P < 0.43$) and allelic distribution (OR T: 0.44 [95% CI = 0.05-3.79] $P < 0.44$) of the gene encoding INF-γ, were not statistically significant. Our results differ from those of Al-Rashidi et al, 2021, who indicated that the distribution of the INF-γ T + 874A gene polymorphism reveals a strong and significant association between the INF-γ + 874 T/A TT genotypes in BC patients (ORTT: 6 [95% CI = 2.72-15.1] $P < 0.0001$) and a strong and significant association with the T allele (ORT: 1.99 [95% CI = 1.43-2.76] $P < 0.0001$), compared with the screening of healthy persons. This could be explained by the different genotypes of the two populations studied, black versus European.

Genotype A/T, which is very often associated with extra-pulmonary tuberculosis [25], was predominant in the under-40s (67.74%). However, none of the participants in our study had ever been diagnosed with extra-pulmonary tuberculosis. The TT genotype was predominant among those aged 40 and over (71.43%), but in a very small proportion of TB cases.

Although the genetic profile of the host can influence disease susceptibility as much as treatment resistance [26], for this study population, no cases of treatment resistance were found.

The broader implications for understanding tuberculosis susceptibility in different populations include :

- Building up a pathogen-specific and country-specific database on high-risk alleles. Indeed, the risk of developing tuberculosis increases with the number of risk alleles [27]. Our study will also serve as a motivation for other studies that will enrich this database.
- Identifying high-risk individuals, so that diagnosis and personalized treatment strategies might be tailored to the individual and the country.

4.1. Study limitations

This study provides important information on the proportion of interferon-gamma genotypes in a population with presumed tuberculosis. This is a preliminary study with limitations, such as the small sample size and the number of parameters available. It will however, guide further studies into a clear definition of the association between risk alleles, epigenetics and tuberculosis disease in Burkina Faso.

This study carried out in Ouagadougou, Burkina Faso, revealed the presence of gamma interferon AA, AT and TT genotypes in the respective proportions of 73.24%, 21.83% and 4.93% within a population with presumed tuberculosis. However, no association was established between polymorphisms in the gene encoding INF-γ + 874 T/A and tuberculosis infection. This is a preliminary study that will guide further studies with larger sample sizes that should help ease the identification of the association between the polymorphisms found and tuberculosis disease in Burkina Faso. Studies on at-risk alleles will help direct the public health strategy of Burkina Faso towards personalized care. Taking human genetics into account would be an asset in the fight against tuberculosis.

Conflict of interest

The authors declare that they have no conflict of interest.

Consent for publications

All authors have read and approved the manuscript.

Ethical approval and consent to participate

This study was approved by the Health Research Ethics Committee (reference: deliberation N° 2022-02-023). Written informed consent was obtained from patients and donors. We have guaranted the confidentiality of our database by storing it on a password-protected computer.

Informed Consent

All participants gave their free, informed and written consent after being informed of the study's objectives and implications.

Availability of data and material

All the necessary data have been integrated into the manuscript. Datasets used and/or analyzed during the present study are available from the corresponding authors upon reasonable request.

Authors' contributions

Conceptualization: TS. Preparation of original project TS, WYAS, LT, STS, TRC, IF, PZ, SNK, SZ, DK, OO. WYAS,

TS, PZ, IK performed laboratory analyses. KC, LT, SNK performed statistical analysis. Writing: TS. Revision and editing: TS, WYAS, LT, STS, TRC, IF, PZ, SNK, SZ, DK, OO, IMAT, AKB, AC, HGO, SK, JS. All authors contributed to data interpretation and discussions and approved the final manuscript.

Funding
This work was carried out with the aid of a grant from UNESCO-TWAS and the Swedish International Development Cooperation Agency (Sida) n°21-127 RG/BIO/AF/AC_I-FR3240319483. The views expressed herein do not necessarily represent those of UNESCO-TWAS, Sida or its Board of Governors.

Acknowledgements
The authors would like to thank all the participants of this study, the CDT of the Bogodogo university hospital, the biomedical research laboratory of the of Health Sciences Research Institute (IRSS), and the Molecular Biology and Genetics Laboratory (LABIOGENE) of Joseph KI-ZERBO University, Ouagadougou, Burkina Faso. The authors would also like to thank Mr. James AMEDEKER for his assistance with English-language editing.

References

1. Small PM and Fujiwara PI (2001) Management of tuberculosis in the United States. N Engl J Med 345:189-200. doi: 10.1056/NEJM200107193450307
2. WHO (2023) Global Tuberculosis Report 2023. 75p. Geneva:World Health Organization.
3. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC and Dye C (2003) The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med 163:1009-21. doi: 10.1001/archinte.163.9.1009
4. Cooke DM, Goosen WJ, Burgess T, Witte C and Miller MA (2023) Mycobacterium tuberculosis complex detection in rural goat herds in South Africa using Bayesian latent class analysis. Vet Immunol Immunopathol 257:110559. doi: 10.1016/j.vetimm.2023.110559
5. Emery JC, Richards AS, Dale KD, McQuaid CF, White RG, Denholm JT and Houben R (2021) Self-clearance of Mycobacterium tuberculosis infection: implications for lifetime risk and population at-risk of tuberculosis disease. Proc Biol Sci 288:20201635. doi: 10.1098/rspb.2020.1635
6. Houben RM and Dodd PJ (2016) The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med 13:e1002152. doi: 10.1371/journal.pmed.1002152
7. Jilani TN, Avula A, Zafar Gondal A and Siddiqui AH (2024) Active Tuberculosis. StatPearls, Treasure Island (FL): StatPearls Publishing; January 26, 2023 . https://www.ncbi.nlm.nih.gov/books/NBK513246/
8. Cooke GS and Hill AV (2001) Genetics of susceptibility to human infectious disease. Nat Rev Genet 2:967-77. doi: 10.1038/35103577
9. Bellamy R (2005) Genetic susceptibility to tuberculosis. Clin Chest Med 26:233-46, vi. doi: 10.1016/j.ccm.2005.02.006
10. Hill AV (1998) The immunogenetics of human infectious diseases. Annu Rev Immunol 16:593-617. doi: 10.1146/annurev.immunol.16.1.593
11. Cooke GS, Campbell SJ, Sillah J, Gustafson P, Bah B, Sirugo G, Bennett S, McAdam KP, Sow O, Lienhardt C and Hill AV (2006) Polymorphism within the interferon-gamma/receptor complex is associated with pulmonary tuberculosis. Am J Respir Crit Care Med 174:339-43. doi: 10.1164/rccm.200601-088OC
12. Boisson-Dupuis S (2020) The monogenic basis of human tuberculosis. Hum Genet 139:1001-1009. doi: 10.1007/s00439-020-02126-6
13. Bibova I, Linhartova I, Stanek O, Rusnakova V, Kubista M, Suchanek M, Vasakova M and Sebo P (2012) Detection of immune cell response to M. tuberculosis-specific antigens by quantitative polymerase chain reaction. Diagn Microbiol Infect Dis 72:68-78. doi: 10.1016/j.diagmicrobio.2011.09.024
14. Hartl DL and Clark AG (2007) Principles of Population Genetics. Third Edition. Sinauer Associates, Sunderland.
15. Garant D (2007) "Hartl, D. L. & A. G. Clark, 2007. Principles of Population Genetics." Ecoscience 14 (4):544-545. doi: 10.2980/1195-6860
16. Alvarez GI, Hernandez Del Pino RE, Barbero AM, Estermann MA, Celano J, Musella RM, Palmero DJ, Garcia VE and Pasquinelli V (2023) Association of IFN-gamma +874 A/T SNP and hypermethylation of the -53 CpG site with tuberculosis susceptibility. Front Cell Infect Microbiol 13:1080100. doi: 10.3389/fcimb.2023.1080100
17. Araujo Z, Palacios A, Biomon R, Rivas-Santiago B, Serrano CJ, Enciso-Moreno L, Lopez-Ramos JE, Wide A, Jimenez JC, Larrea CF and Enciso-Moreno JA (2017) Concordance between IFN-gamma gene +874 A/T polymorphism and interferon-gamma expression in a TB-endemic indigenous setting. Rev Soc Bras Med Trop 50:199-207. doi: 10.1590/0037-8682-0398-2016
18. Thada S, Ponnana M, Sivangala R, Joshi L, Alasandagutti M, Ansari MS, Schumann RR, Valluri V and Gaddam S (2016) Polymorphisms of IFN-gamma (+874A/T) and IL-12 (+1188A/C) in tuberculosis patients and their household contacts in Hyderabad, India. Hum Immunol 77:559-65. doi: 10.1016/j.humimm.2016.04.016
19. Wei Z, Wenhao S, Yuanyuan M, Yang L, Daming Z, Jiangchun X and Jijun J (2017) A single nucleotide polymorphism in the interferon-gamma gene (IFNG +874 T/A) is associated with susceptibility to tuberculosis. Oncotarget 8:50415-50429. doi: 10.18632/oncotarget.17304
20. Liu Z, Deligen B, Han Z, Gerile C and Da A (2024) Integrated sequence-based genomic, transcriptomic, and methylation characterization of the susceptibility to tuberculosis in monozygous twins. Heliyon 10:e31712. doi: 10.1016/j.heliyon.2024.e31712
21. Martinez-Barricarte R, Markle JG, Ma CS, Deenick EK, Ramirez-Alejo N, Mele F, Latorre D, Mahdaviani SA, Aytekin C, Mansouri D, Bryant VL, Jabot-Hanin F, Deswarte C, Nieto-Patlan A, Surace L, Kerner G, Itan Y, Jovic S, Avery DT, Wong N, Rao G, Patin E, Okada S, Bigio B, Boisson B, Rapaport F, Seeleuthner Y, Schmidt M, Ikinciogullari A, Dogu F, Tanir G, Tabarsi P, Bloursaz MR, Joseph JK, Heer A, Kong XF, Migaud M, Lazarov T, Geissmann F, Fleckenstein B, Arlehamn CL, Sette A, Puel A, Emile JF, van de Vosse E, Quintana-Murci L, Di Santo JP, Abel L, Boisson-Dupuis S, Bustamante J, Tangye SG, Sallusto F and Casanova JL (2018) Human IFN-gamma immunity to mycobacteria is governed by both IL-12 and IL-23. Sci Immunol 3. doi: 10.1126/sciimmunol.aau6759
22. Poyhonen L, Kroger L, Huhtala H, Makinen J, Nuolivirta K, Mertsola J, He Q and Korppi M (2017) Association of MBL2, TLR1, TLR2 and TLR6 Polymorphisms With Production of IFN-gamma and IL-12 in BCG Osteitis Survivors R1. Pediatr Infect Dis J 36:135-139. doi: 10.1097/INF.0000000000001375
23. Wu S, Wang Y, Zhang M, Wang M and He JQ (2019) Genetic variants in IFNG and IFNGR1 and tuberculosis susceptibility. Cytokine 123:154775. doi: 10.1016/j.cyto.2019.154775
24. Naz A, Ali M, Aslam MA, Khan AUH, Manzoor H, Iqbal R, Shehzad MA, Ahmad S, Shaheen Z and Rasul S (2019) Influence

of single-nucleotide polymorphisms in the IFNG towards susceptibility to tuberculosis in a Pakistani population. Ann Hum Genet 83:426-433. doi: 10.1111/ahg.12325

25. Wani BA, Shehjar F, Shah S, Koul A, Yusuf A, Murtaza M, Singh R, Althobaiti F, Aldhahrani A and Afroze D (2021) Association of IFN-gamma and IL-10 gene variants with the risk of extrapulmonary tuberculosis. Saudi J Biol Sci 28:4210-4216. doi: 10.1016/j.sjbs.2021.06.029
26. Moller M, Kinnear CJ, Orlova M, Kroon EE, van Helden PD, Schurr E and Hoal EG (2018) Genetic Resistance to Mycobacterium tuberculosis Infection and Disease. Front Immunol 9:2219. doi: 10.3389/fimmu.2018.02219
27. Luo F, Zou P, Liao Y, Luo J, Luo D, Hu K, Zhang K and Wang B (2022) Association between TAP gene polymorphisms and tuberculosis susceptibility in a Han Chinese population in Guangdong. Mol Genet Genomics 297:779-790. doi: 10.1007/s00438-022-01885-3