Hilla University College Journal For Medical Science

Volume 2 | Issue 2 Article 2

2024

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Hayder Ghali Wadi Algawwam
Department of Physiology, College of Medicine, University of Baghdad, Baghdad, Iraq,
Haidar.wadi2208p@comed.uobaghdad.edu.iq

Affan Ezzat Hasan
Department of Physiology, College of Medicine, University of Baghdad, Baghdad, Iraq,
affanezzathasan@comed.uob.edu.iq

How to Cite This Article

Algawwam, Hayder Ghali Wadi and Hasan, Affan Ezzat (2024) "Impact of Genetic Polymorphism on Pulmonary Function and Individualized Treatment Plan in Pulmonary Tuberculosis," *Hilla University College Journal For Medical Science*: Vol. 2: Iss. 2, Article 2.
DOI: https://doi.org/10.62445/2958-4515.1018

REVIEW

Hilla Univ Coll J Med Sci

Impact of Genetic Polymorphism on Pulmonary Function and Individualized Treatment Plan in Pulmonary Tuberculosis

Hayder Ghali Wadi Algawwam *, Affan Ezzat Hasan

Department of Physiology, College of Medicine, University of Baghdad, Baghdad, Iraq

Abstract

Background: Less than 10% of people infected with M. tuberculosis develop the disease, suggesting that there are individual differences in susceptibility to tuberculosis. Defective genes could impact the host's immune response toward any infection, including pulmonary TB. Numerous genetic risk loci like HLA-G, MMP-1, IFN-γ, TLR-2, MCP-1, NRAMP-1 and many others have been discovered by recent genome-wide association studies, which indicate a high polygenic heritability for tuberculosis.

Aim: The aim of this review is to shed light on the potential effect of host genetic polymorphism on the degree of impairment in pulmonary function tests in individuals with pulmonary tuberculosis.

Conclusion: Understanding the complex correlation between genetic variations and disease progression is crucial for improved disease diagnosis, treatment, and control. Genetic testing can help identify patients at risk of severe illness, monitor lung function, and lead to better patient outcomes, and earlier interventions.

Keywords: Genetic polymorphism, Pulmonary function, Pulmonary tuberculosis

1. Introduction

Tuberculosis (TB) is an important health concern leading to disability and death globally; it ranks as the 9th ranking cause of death worldwide, and there are several therapeutic strategies available for its treatment [1, 2]. TB is still one of the most severe infections caused by *M. tuberculosis*. This pathogen is the world's leading cause of death associated with a single pathogen, especially in poor and developing countries [3]. The World Health Organization's (WHO) Global Tuberculosis Report 2021 concludes that approximately 9.9 million people had tuberculosis in 2020 and 1.3 million died from the disease [4] and to the latest WHO estimations about infectious diseases as leading causes of death, TB now ranks second after HIV [5]. Tuberculosis is a disease associated with poor quality of life ratings, especially when linked to low socio-economic status [6]. TB is an airborne, highly contagious disease that commonly affects the lungs leading to the classical symptoms of pulmonary TB: more than two weeks of productive cough, mild fever, night sweats, chest pain, loss of appetite, and weight loss [7].

TB is a significant health problem in Iraq like in other developing countries, especially in the countries of the Eastern Mediterranean region, where the predicted incidence rate in Iraq is about 23 per 100,000 and the detection rate is about 54% [8], and even though tuberculosis remains a public health concern in Iraq, little is known about its genetic background. Therefore, enhancing comprehension of the molecular basis of tuberculosis may lead to a more effective control strategy and a better understanding of the disease's transmission dynamics within the country [9].

Healthcare personnel should carefully consider all demographic, clinical, and histopathological

Received 24 April 2024; accepted 23 June 2024.
Available online 3 September 2024

* Corresponding author.
E-mail addresses: Haidar.wadi2208p@comed.uobaghdad.edu.iq (H. Ghali Wadi Algawwam), affanezzathasan@comed.uob.edu.iq (A. Ezzat Hasan).

https://doi.org/10.62445/2958-4515.1018

characteristics to detect the disease, as early diagnosis may lead to better outcomes [10]

When it comes to determining inter-individual differences in susceptibility or resistance to infectious diseases, such as tuberculosis, host genetic factors are crucial. However, there is still much to learn about the mechanisms that either limit the development of disease in latent infection or cause severe active disease. Research utilizing case-control, twin, candidate gene methodologies, family-based, and genome-wide association studies (GWAS) has demonstrated the correlation between genetic variables and tuberculosis susceptibility or resistance [11, 12].

It is widely recognized that bacterial strains, environmental factors, and host genetic susceptibility collectively play a substantial role in predisposing individuals to tuberculosis and influencing the response to treatment [13].

Pulmonary TB mainly affects the lung parenchyma, leading to structural and functional changes resulting in short-term and long term sequelae. Additionally, TB may result in lungs anatomical changes with a consequence of long-standing complications such as bronchiectasis, bronchial stenosis, lung fibrosis, emphysema, and consequent disturbed lung function, which contribute to permanent injury and an increased risk of mortality, along with a considerable problem of increased medical costs [3].

Here, several crucial research questions arise:

- Why do some individuals infected with M. tuberculosis not develop TB disease?
- Why do not all patients with weakened immune systems and infections develop tuberculosis?
- Why do not all household contacts of PTB patients contract tuberculosis?
- Why do not all medical professionals treating PTB patients develop TB illnesses?
- Why do different geographic regions and ethnic groups have varying rates of the disease?

2. Overview of host genetic polymorphism

Genetic polymorphism is a term that describes the genetic variation existing within a population at a specific point in time. This variation is caused by the presence of different alleles in the genes of the population. An allele is a different form of a particular gene, with each allele having a specific nucleotide sequence at a given gene locus. Genetic polymorphism can manifest in various forms. Firstly, there are single nucleotide polymorphisms, or SNPs. These are the most common type of genetic variation and involve a single base change at a specific position in the DNA sequence. Then, there are insertions and deletions, often referred to as indels [14]. These genetic variations involve the insertion or deletion of a small number of nucleotides in a DNA sequence. Furthermore, there are copy number variations, or CNVs, which represent another type of genetic variation. These variations involve differences in the number of copies of a particular gene found in the DNA sequence [15]. Genetic polymorphism can also manifest as structural variants, encompassing larger genetic variations that may alter the length of the DNA sequence, including inversions, translocations, and gene copy mutations [16].

Many studies have shown that only 33% of the population exposed to M. tuberculosis becomes asymptomatically infected, and less than 10% of these develop tuberculosis, suggesting that there are individual differences in susceptibility to tuberculosis [1]. Even though the underlying pathogenic mechanisms of tuberculosis infection are still unknown, host genetic genes are thought to be one of the reasons for tuberculosis development and may influence pre-tuberculosis disease. In the last few years, genetic variants, e.g.: Toll-like receptors-2 gene [3] and HLA-G gene were demonstrated to be associated with TB susceptibility in Iraqi people [4].

In general, the response to infection by the host immune system varies; while some hosts will develop extensive disease, others can control the infection. What is the mechanism behind these different responses? The answer is still exactly unknown [5]. Many scientists suggest that the genetic background is the logical explanation [6]. Any defective or mutated gene could greatly affect the host immune response towards any infection, including pulmonary TB. Human Leucocyte Antigen-G (HLA-G), a non-classical primary HLA class 1B particle, may be a part of the suppression mechanism of numerous immune cells like natural killer (NK) cells, dendritic cells, CD4+ and CD8+ lymphocytes [4].

HLA is the most polymorphic loci located in chromosome 6 of the human genome. Polymorphisms in Class I and Class II genes might lead to a change in antigen binding affinity which may be a cause in impairment in process of antigenic presentation to CD4+ and CD8+ T-cells [7].

In TB patients, Matrix metalloproteinase-1 (MMP-1) levels will increase in peripheral blood monocytes with 1G genotypes. MMP-1 activity was also detected in the endobronchial TB granuloma from patients with 1G/1G genotype, so 1G genotypes of MMP-1 polymorphism were found to be a strong potential risk factor for the greater risk of TB patients having stenosis in the tracheobronchial tree. Additionally, patients with MMP-1(-1607G) polymorphism are found to be more susceptible to broad and severe lung

fibrosis even after completing the anti-TB treatment course, which could be related to increased activity of MMP-1 which will lead to more powerful damage in lung matrix with consequent fibrosis [17].

3. What are the host genetic polymorphisms associated with pulmonary TB susceptibility?

Numerous genetic polymorphisms of the host have been linked to pulmonary tuberculosis (TB) susceptibility (Table 1). Research has shown that the genetic elements determining tuberculosis susceptibility are caused by particular genes involved in the immune response, such as HLA and non-HLA genes [18]. Notably, correlations between the rs206018 and rs422951 polymorphisms of the Notch4 gene and susceptibility to pulmonary tuberculosis have been demonstrated. The reliability of these results was confirmed by their validation in separate cohorts [19]. Genetic polymorphisms in the host linked to pulmonary tuberculosis susceptibility include those in the genes CCL-2/MCP-1, NRAMP-1/SLC11A1, IRGM-1, IL-8, TLR, and NOD-2. These genes participate in the immune response and encode proteins essential for macrophage function. By altering immunity, polymorphisms in these genes may increase a person's genetic susceptibility to tuberculosis.

Researchers have utilized appropriate statistical techniques and instruments to illustrate the link between tuberculosis and these genetic polymorphisms. Although the significance levels of these genetic polymorphisms may vary, research has indicated that TB susceptibility is more prevalent in certain ethnic groups. Four distinct NRAMP-1 polymorphisms, for example, have been linked to pulmonary tuberculosis susceptibility (5'CA, INT4, D543, and 3'UTR). A homozygous type mutation in the NRAMP-1 gene increases the risk of tuberculosis in those who have it. TAP 1 and TAP 2 polymorphisms have been linked to an increased risk of tuberculosis in the lungs. In general, pulmonary tuberculosis susceptibility is linked to a variety of host genetic polymorphisms, particularly those related to the immune system [20].

Numerous studies have highlighted the host Genetics are important for tuberculosis infection susceptibility, protection, and progression [22, 23]. It has been discovered that the significance of genetic polymorphisms in various genes related to tuberculosis varies [20]. Numerous genetic polymorphisms connected

Table 1. Summary of some genes studied for genetic polymorphism in pulmonary tuberculosis.

Author (s)	Year of publication	Place (Country) of study	Gene studied	No. of patients/control	Association
Ninomiya S, *et al*. [17]	2004	Japan	MMP-1	208/106	Pulmonary Function
Wu F, *et al*. [40]	2008	China	TNF-α	61/122	Susceptibility
Ansari A, *et al*. [41]	2009	Pakistan	IFN-γ	111/188	Pulmonary Function
Martineau AR, *et al*. [42]	2010	South Africa	Vit D receptors	123/140	Susceptibility
Stagas MK, *et al*. [43]	2011	Greece	NRAMP-1	142/144	Susceptibility & Pediatric TB
Morris GA, *et al*. [44]	2011	Argentina	IL-12B	221/144	Susceptibility
Bahari G, *et al*. [45]	2012	Iran	IRGM-1	150/150	Susceptibility
Abhimanyu *et al*. [46]	2012	India	IFNG, TNFB, IL4, IL1RA, IL1B and IL12	110/215	Susceptibility
Singh B, *et al*. [47]	2014	India	MCP-1	303/295	Susceptibility
Wu L, *et al*. [48]	2015	China	TLR-2	109/422	Susceptibility
Awatif H. Issa, *et al*. [49]	2017	Iraq	TLR-2	74/74	Susceptibility
Ibtisam Habeeb Al-Azawi, *et al*. [36]	2018	Iraq	IFN-γ	65/65	Pulmonary Function
Ameen NY, *et al*. [50]	2018	Iraq	IL-17A	80/40	Susceptibility
Ebrahim Alijani, *et al*. [51]	2021	Iran	NOD-2	152/162	Susceptibility
Kim ES, *et al*. [52]	2021	South Korea	SLCO1B1	105	Rifampicin Resistant TB
Entssar S, *et al*. [53]	2021	Iraq	CCL5 –403G/A	50/40	Susceptibility
Bushra J. Al–Tamimi, *et al*. [4]	2022	Iraq	HLA-G	48/42	Susceptibility & Pulmonary Function
Ali ZA, *et al*. [54]	2022	Iraq	IL-37	105/79	Susceptibility
Meng-Rui Lee, *et al*. [55]	2022	Taiwan	TLR1, TLR2, TLR4, MMP1, MMP8, MMP9, MMP12, and tissue inhibitor of MMP2	400/203	Susceptibility
Lu T, *et al*. [56]	2023	China	TAP 1 & TAP 2	449/435	Susceptibility
Mhmoud NA [57]	2023	Sudan	TLR-1,2,4, 6, 8, 9, and 10 (Fig. 2)	160/220	Susceptibility

to the incidence and prognosis of tuberculosis have identified through candidate gene and genome-wide association studies [18]. Variations in genes that regulate immune response and function could affect a person's susceptibility to tuberculosis in the lungs [23]. For example, the polymorphisms rs206018 and rs422951 in the Notch4 gene were linked to an increased risk of developing pulmonary tuberculosis [19].

Researchers investigated the genetic polymorphisms that affect host susceptibility to pathogens, such as tuberculosis [24], in a different population-based case-control study. Although there is ample evidence suggesting that host genetic factors influence susceptibility/resistance to MTB infection and TB disease [25], further studies are necessary to find novel treatments like host-directed therapy. It has confirmed the genetic susceptibility to tuberculosis (TB) following a thorough review of the literature and research results [20]. Consequently, the genetic component should be considered in all future functional research or studies on PTB.

4. How might host genetic polymorphisms impact the individualized treatment plans of pulmonary tuberculosis patients'?

Treatment strategies are formulated based on an analysis of data from the drug susceptibility and resistance survey as well as the prevalence of anti-TB medication use. Drug susceptibility-resistance trends and various subsets of different cases (failures, relapse, return after default, and chronic cases). The WHO recommends the use of fixed-dose combinations of drugs for treating all TB patients. The four essential medications classified as "first line" in the standardized regimens for anti-TB treatment are isoniazid, rifampicin, pyrazinamide and ethambutol. WHO recommends a standardized regimen of two phases for treating new cases of pulmonary or extrapulmonary tuberculosis: four drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) are administered in the initial (intensive) phase for two months, followed by two drugs (rifampicin and isoniazid) in the continuation phase for four months. It is advised that all new cases undergo supervised daily medication administration during the initial phase of treatment [26].

Recent research has investigated the correlation between host genetic polymorphisms and individualized treatment for patients with pulmonary tuberculosis (TB) has been examined in recent research. Several studies have shown that specific haplotype combinations and alleles may provide protection against tuberculosis (TB) in various populations. However, finding a reliable genetic marker for tuberculosis disease has proven difficult due to research design heterogeneity and limitations in sample size. Nonetheless, studies suggest that host genetics may be important for tuberculosis treatment, and newer methods to reduce the duration of tuberculosis treatment are required.

Furthermore, due to ethnic variation, genetic markers found in one population might not be consistent with other populations [21]. Several allelic variants of the NRAMP-1 gene have been strongly linked to tuberculosis in pediatric patients, and polymorphisms in this gene identified as risk factors for pediatric TB disease. This suggests that host genetic polymorphism might influence the way pediatric pulmonary tuberculosis patients receive individualized care [20]. Furthermore, it has been discovered that variations in the SLCO1B1 gene affect the bioavailability of lower rifampicin concentrations and bioavailability in TB patients from South African populations has been linked to TB drugs and specific SNPs [21].

A genome-wide association study of patients with drug-induced liver injury in Ethiopia also demonstrated the possibility of tailoring treatment based on host genetic polymorphisms, with certain SNPs linked to anti-TB drug-induced hepatotoxicity in China. These results emphasize how crucial it is to take host genetic factors when developing individualized treatment programs for tuberculosis patients [25]. Relationship between rs206018 and the Notch4 gene,rs422951 polymorphisms, as well as pulmonary tuberculosis susceptibility and immune response-related genes like HLA and non-HLA genes, has been identified. These findings emphasize how crucial it is to take host genetic variables into account when creating individualized treatment programs for tuberculosis patients. The discovery of four distinct NRAMP-1 polymorphisms (5'CA, INT4, D543, and 3'UTR) linked to pulmonary tuberculosis susceptibility raises the possibility that pediatric pulmonary tuberculosis patients may require individualized care. Future studies should consider constraints and investigate the potential for creating individualized treatment plans and forecasting treatment outcomes based on host genetic polymorphisms [19].

5. Pulmonary function test

Pulmonary function test (PFT)-Spirometry is an essential test in any patient with respiratory pathology that requires evaluation and monitored. PFT provides significant data in relation to respiratory airways, both large and small, the lungs' parenchyma and also the size and integrity of the pulmonary capillary bed

[27]. Chronic obstructive pulmonary disease (COPD) is a common respiratory disease with episodes of exacerbation that can be evaluated by spirometry [28]. The prevalence of COPD is commonly reported in many countries; especially developed countries, there are large differences in reported prevalence rates across countries due to differences in methodology, diagnostic criteria, and the demographics of the populations studied [29].

Even though spirometry does not provide a clear-cut diagnosis, it reveals various abnormalities present in different pulmonary diseases, which aids in confirming a diagnosis [27]. Spirometry can monitor the progression the respiratory diseases and assess how the lungs respond to the treatment for these conditions. An obstructed airways pattern is assumed when the ratio of forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) is decreased. Low forced vital capacity is defined as a value below the 5th percentile in adults or less than 80% of predicted in children and adolescents five to 18 years. The two parameters FEV_1/FVC ratio and FVC are used together for the identification of obstruction pattern,restriction pattern, or mixed patterns of both obstructive and restrictive. FEV_1 is used to determine the intensity of obstructive and restrictive disease patterns [30].

The link between pulmonary tuberculosis and pulmonary function impairment is recognized. Pulmonary tuberculosis can cause irreversible pulmonary damage that is visible as scars, fibrosis, cavitation or other types of damage exposed by radiological examinations. Frequently, patients with different levels of pulmonary function impairment, which can cause a decrease in quality of life [31].

Symptoms related to airflow obstruction consist of dyspnea, reduced exercise capacity and chronic bronchitis. The extent of the obstruction of the airway is usually calculated by measuring the forced expiration volume in 1st second (FEV1). FEV1 is reported as an absolute volume and as a percentage of the predicted normal volume, with a reduction of 100 mL of FEV1 considered clinically significant [27]. Many studies have shown that there is a decrease in FEV1 during and after TB treatment. Decrease in FEV1 may be related to different primary pathological mechanisms like cavitation, which is frequently associated with pulmonary TB may destroy respiratory airways, resulting in airflow obstruction. In a study of sequential changes in the structure of lung tissues and changes in respiratory function, patients having lung cavities had meaningfully lower FEV1 at baseline and at 1month after starting tuberculosis treatment compared to the patients who do not have those cavities [31].

Restriction models in spirometry are characteristic of restrictive lung diseases and have been reported as a consequence of tuberculosis since the late 1910s. Recent epidemiological studies conducted for cases among miners and hospital attenders in South Africa have suggested that a history of TB infection and an increase in the frequency of this disease may lead to restrictive lung diseases in lung function tests. However, there is no population data supporting the relationship between tuberculosis history and spirometry restrictions [32].

Even though the airflow obstructive pattern in pulmonary TB had the utmost consideration, the mixed obstructive-restrictive disease patterns were the most common form of respiratory malfunction in a review of population based and observational studies conducted in South Africa. Structural changes in the lungs resulting from abnormal repair of lung tissue (broncho-vascular distortion, fibrotic bands, and thickening of the pleura) may explain the limitation of air flow in TB patients [33].

6. Impact of host genetic polymorphism on pulmonary function in pulmonary tuberculosis

Tests for pulmonary function, like spirometry, gauge how well the lungs can exchange gases. These tests offer important information about the extent of tuberculosis-related lung damage. Various genetic polymorphisms have been linked to particular changes in pulmonary function parameters, such as peak expiratory flow (PEF), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1).

Polymorphisms in Tumor Necrosis Factor Alpha (TNF-α): One essential cytokine that aids the host in combating mycobacterial infections is TNF-α. Unbalanced immune responses have been linked to specific TNF-α polymorphisms that are linked to altered TNF-α production levels. In patients with pulmonary tuberculosis, these polymorphisms have been correlated with reduced pulmonary function [34].

Polymorphisms of Interferon-Gamma (IFN-γ) (Fig. 1): One cytokine that elicits a robust response is IFN-γ immunity against Mycobacterium tuberculosis. It has been proposed that genetic variations in the IFN-γ gene and its receptor contribute to the development of pulmonary tuberculosis. These polymorphisms could influence IFN-γ synthesis, signaling, and function, which may ultimately result in compromised lung function [35].

Variations in the Human Leukocyte Antigen (HLA): Human leukocyte antigen-G (HLA-G) is a

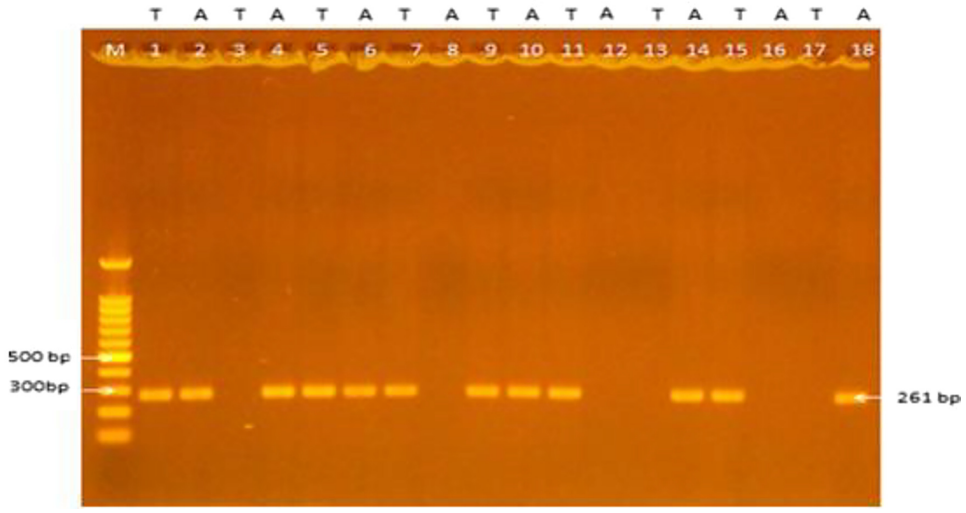

Fig. 1. Agarose gel electrophoresis of IFN-γ genotypes [36].

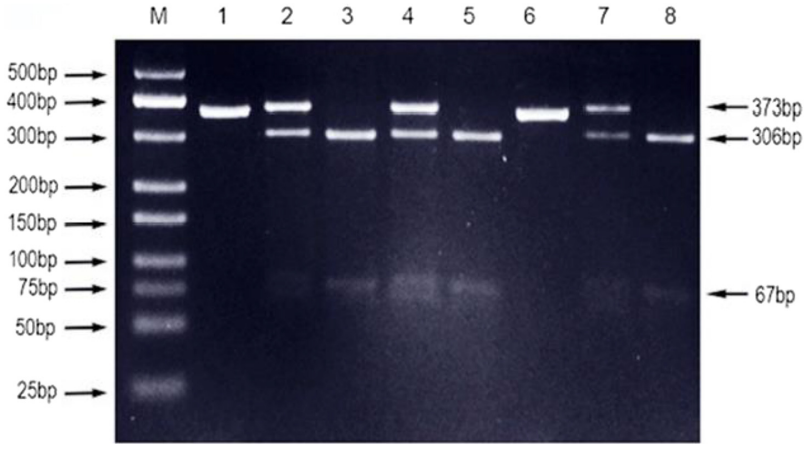

Fig. 2. PCR-RFLP assay for analyzing the TLR4 polymorphisms in Sudanese pulmonary Tuberculosis patients [57].

non-classical class IB-HLA molecule, it has an immunomodulatory and tolerogenic properties [37], when it comes to introducing antigens to the immune system, HLA molecules are essential. Research has indicated a correlation between particular alleles of the HLA gene and compromised lung function in patients with pulmonary tuberculosis. These differences in HLA alleles can impact the immune response against Mycobacterium tuberculosis, resulting in a range of clinical manifestations and changes in lung function [21, 38].

Neutrophils predominate in the respiratory secretions of patients with pulmonary tuberculosis, neutrophils predominate. In comparison to controls, MMP-8, neutrophil myeloperoxidase (MPO), and neutrophil gelatinase associated lipocalin (NGAL) concentrations were higher in TB patients. MMP-8 showed a strong correlation with MPO and NGAL, both indicators of neutrophil activation, indicating that sputum MMP-8 likely originates from neutrophils. In addition to supporting earlier findings that neutrophils are the predominant phagocytic cells in TB patients' respiratory secretions, MMP-8-expressing neutrophils have been found in the inner walls of tuberculous cavities and may further erode the lung matrix.

Furthermore, TB patients displaying cavities on their chest radiographs exhibit elevated MMP-8 levels compared to patients without cavities. These findings highlight the significance of collagenases, including MMP-1 and MMP-8, as the only enzymes that, at neutral pH, can break down the triple helix of collagen. Neutrophils are important players in tissue destruction in tuberculosis (TB) and subsequently in altering spirometry findings, as evidenced by the consistent elevation of MMP-8 levels across different patient groups [39].

Understanding the influence of host genetic polymorphisms on pulmonary function in patients with pulmonary tuberculosis could facilitate the

development of tailored treatment approaches. thorough analysis of the genetic influences in addition to suitable pulmonary function assessments can help in making more accurate treatment and prognosis decisions. Further research is essential to validate the findings and establish standardized procedures for integrating this genetic data into clinical practice.

7. Conclusion

In conclusion, tuberculosis remains a serious global health concern, especially in developing countries like Iraq. The illness has a significant influence on people's quality of life, mortality rates, and financial burdens. It also has an impact on communities, healthcare systems, and individuals. Genetic polymorphisms are crucial for determining the severity, treatment response, and susceptibility of tuberculosis. The discovery of genetic variations linked to tuberculosis susceptibility has created new opportunities for understanding the illness, creating individualized treatment regimens, and predicting treatment results.

Notable genetic factors linked to pulmonary function and tuberculosis susceptibility include MMP-1, TNF-α, IFN-γ, HLA and many other genes. Additionally, pulmonary function test-spirometry is important for assessing and tracking lung damage related to tuberculosis and provide important information about the course and management of the disease. Despite significant advancements in the identification of genetic markers and the comprehension of their influence on pulmonary tuberculosis, additional investigation is required to effectively integrate this knowledge into clinical practice. Understanding the interplay between genetics and pulmonary function in tuberculosis patients presents opportunities for customized, more effective therapeutic approaches. This information also emphasizes how important it is to carry out more research, particularly on diverse populations, to fully utilize the potential of genetic insights in TB management. Understanding the genetic basis of tuberculosis susceptibility and its impact on pulmonary function, treatment strategies, and protocol is a critical matter in improving tuberculosis management and outcomes, providing hope for more specialized and effective interventions in combating this disease.

Conflict of interests

None declared.

Funding

The authors received no funding for this study.

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