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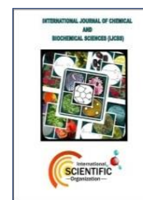

Exploring the Genetic Basis of Tuberculosis Susceptibility in Human Populations

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Abstract

The worldwide morbidity and mortality caused by tuberculosis (TB) continue to be a major problem for public well-being. The underlying processes and causes of failure in a portion of the infected population are still unknown, even though a properly functioning immunological scheme is necessary intended for the management of Mycobacterium tuberculosis (M. TB) infection. To identify biomarkers indicative of susceptibility and obstructions, whole-blood microarray gene expression studies were carried out on tuberculosis patients, hidden infected healthy controls, and uninfected healthy controls. The most differentially expressed gene, Fc gamma receptor 1B (FCGRIB), together with 4 other indicators, provided a great grade of accuracy in separating TB patients from hidden infected donors. We found summaries that linked with tuberculosis susceptibility and resistance and revealed different gene expression patterns specific to the active illness. "The primary distinctive characteristics establishing the success or failure in managing the infection with M. tuberculosis are going to be greater levels of specific gene clusters intricate in apoptosis and "Natural Killer (NK)" cell action in hidden infected donors and greater expression of innate genes associated with immunity in active tuberculosis". The gene communication patterns identified in this work open the door to establishing predictive correlates of protection in tuberculosis and provide insightful hints for an improved sympathy of the transition from latent infection to active illness.

Keywords: Tuberculosis (TB), microarray, mycobacterium tuberculosis (M. tuberculosis), natural killer (NK)

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1. Introduction

M. tuberculosis is the bacterium that causes the infectious illness of TB. Although it often targets the lungs, it may also damage other bodily organs. When a person with TB coughs, sneezes or speaks, small droplets carrying the bacteria are released into the air and may transmit the disease. TB may impact organs other than the lungs, including the kidneys, spine, and brain. This condition, known as extra pulmonary tuberculosis, often affects those with compromised immune systems. Several tests are required to diagnose TB, such as a tuberculin skin test, a blood test, imaging tests, and sputum tests, which are used to identify the bacteria and ascertain their sensitivity to different medications. The cause of tuberculosis is the bacteria M. tuberculosis. The finding of children with Mendelian tendency to disseminate TB provided evidence that TB susceptibility may originate from genetic predisposition [1].

The total amount of members of the Homo sapiens species living in a certain region or on the whole globe is referred to as the human population. Due to elements like birth and death rates, migration, and other demographic processes, these populations are dynamic and continually changing. Sociology, demography, public health, economics, urban planning, and environmental studies are a few examples of disciplines that depend on an understanding of human populations [2]. The infectious disease TB is caused by Mycobacterium tuberculosis. Both human genetic variables and interactions with the virus contribute to TB susceptibility in human populations. It is important to remember that host genetic variables are impartial one part of the puzzle when it comes to TB susceptibility; environmental factors also play a role. In human populations, tuberculosis (TB) host genetic susceptibility is controlled by several genetic variables that modify the immunological response to

M. tuberculosis. Variations in susceptibility to illness, its manifestations, and its course may all be influenced by such genetic variables [3]. Studies on the genetics of tuberculosis (TB) susceptibility have implicated both the host and the pathogen. Innate and adaptive immune responses, cellular processes, and the metabolism of medications used to treat tuberculosis may all be affected by a person's genetic makeup. Although our knowledge of the genetic variables that influence TB susceptibility is expanding, many genes and genetic variations have been identified as possible contributors to TB susceptibility. Genome-wide association studies (GWAS), candidate gene investigations, and functional analysis are only a few of the methods used to investigate the genetics of tuberculosis susceptibility. Against discovering genetic variations linked with elevated risk, these approaches compare the genetic profiles of those with TB susceptibility against those without. Researchers in the field of functional genomics are interested in the effects of genetic variations on immunological responses and medication metabolism [4]. M. tuberculosis causes tuberculosis (TB), a chronic infectious illness that poses a significant danger to human health and is among the top 10 leading causes of mortality worldwide. Statistics show that roughly one-third of the global population is infected with MTB, however only about one-tenth of those people become ill; additionally, few of those people have identifiable risk factors like HIV infection, diabetes, alcoholism, advanced age, or the use of corticosteroids, suggesting that a sizable portion of them may be certainly resistant to TB infection. Numerous genetic variants are associated with the development and prognosis of tuberculosis, as shown by applicant gene education and genome-wide association studies (GWAS) [5].The study [6] evaluated the diagnostic efficacy of several TB screening methods and approaches in this group. World Health Organization (WHO) recommended four symptom screens (W4SS) as the first step in the screening and diagnosis of tuberculosis in ambulatory HIV-positive individuals, and if favorable, a WHO-recommended molecular rapid diagnosis. The study [7] established the limit of detection of genotypic tests for gatifloxacin-resistant mutant identification in artificially combined populations. M. tuberculosis often displays heteroresistance, defined as the coexistence of drug-susceptible and -resistant cells. The paper [8] determined about the pathways of metabolism used by different bacterial pathogens to provide energy and their relationship to the physiological activities of Adenosine Triphosphate (ATP) synthesis. The ATP synthase is necessary for the growth of numerous species of obligate aerobes, obligatory anaerobes, and aerotolerant anaerobes, in contrast to the majority of facultative anaerobic pathogens. Combination therapy may take advantage of the physiological implications, including membrane hyperpolarization, of interfering with the ATP synthase in facultative anaerobes. The study [9] observed at the effects of metformin on people both in the lab and in the wild. Metformin is the most extensively used diabetic medication, and it has been suggested that it might be used as an additional host-directed treatment for TB; nevertheless, its effects on human host responses to M. tuberculosis are little understood. The study [10] determined the immunological response to tuberculosis and its clinical effects are influenced by the genetic variety of the causative organism, M. tuberculosis. It is unclear, however, how the variety of bacteria controls the immunological responses that lead to varying degrees of TB severity. They analyze data from 681 individuals with pulmonary TB and demonstrate that, notwithstanding the severity of the illness, Across several donors, M. TB isolates from patients with intermediate illness consistently elicit potent cytokine responses in macrophages. The study [11] determined the presence of either latent or active TB increases susceptibility to SARS-COVID-19 infection, worsens the severity of sickness, and hastens the development of COVID-19 pneumonia. Clarification of risk factors for COVID-19, the viral pneumonia first identified in Wuhan, China in December 2019, is necessary to ensure that individuals most at risk of developing severe COVID-19 sequelae get the attention and care they need.

The research [12] contrasted the results of phenotypic drug susceptibility testing and the line probe assay with those acquired from whole-genome sequencing to make a genotypic prediction of the first-line drug susceptibility profile. The review [13] addressed the relevant literature and focus on the function of a few miRNAs and SNPs that have been linked to tuberculosis. The human genetic factors influencing susceptibility or resistance to TB pathogenesis have been investigated in high-throughput and low-throughput association studies. In the experiment, predictions based on whole-genome sequencing data were compared with the results of phenotypic drug susceptibility testing for 266 M. tuberculosis isolates. The research [14] showed that reduced electron transport chain activity and suboptimal growth of M. tuberculosis on multiple carbon sources are both caused by defects in succinate oxidation. They also demonstrate that a lack of proper succinate oxidation might have both beneficial and deleterious effects on the efficacy of different antituberculosis medications. Insights into mycobacterial physiology and medication sensitivity gained from these studies will be invaluable to the ongoing quest to perfect bioenergetics inhibitors. The research [15] compared the long-term effects of therapy for drug-sensitive and drug-resistant tuberculosis patients in Mexico and Italy. There is a lack of data about how tuberculosis therapy affects lung function. Once their TB treatment was finished, patients underwent a thorough clinical assessment that included a functional assessment of respiratory mechanics, gas exchange, and a 6-minute walking test. The treatment protocols and terminology used were those suggested by the WHO.

2. Materials and methods

A variety of techniques and methodologies are used to investigate the genetic causes of TB susceptibility in human populations.

2.1 Subject Enrolment and sample collection

The research described here has received ethics committee approval from Uttar Pradesh and Karnataka, and each participant has provided written informed permission.This investigation comprised 34 healthy donors with "latent tetanus toxin infection (LTBI)", 33 tuberculosis patients, and 9 healthy non-infected controls (NIDs) from a group of TB patients and their family members who were gathered in Karnataka (Table 1 and Figure 1 show the age and sex distribution of donors among groups). Within the last three months, domestic contacts were classified as the immediate family of a TB patient who had at least three hours of daily contact. Established on M. tuberculosis sputum

culture findings, chest radiography, and tuberculin skin tests, TB patients and controls were identified. The entire group were HIV-negative, and TB patients' samples were collected before treatment. 2.6 ml of peripheral complete blood from each donor was drawn into PAXgene pipes and kept there at 80 degree Celsius until being processed.

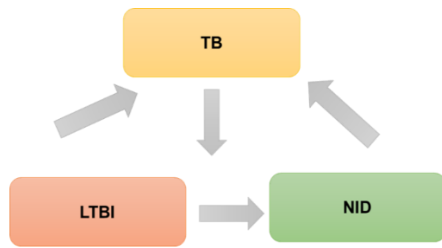

Figure 1: Pair wise gene expression comparisons

Table 1: The study groups and gene expression profile comparisons

Number of donors		LTBI 34	ND 9	TB 33
Characteristics				
	Male	13	15	4
Sex	Female	23	20	7
	Range	18-55	15-56	1-64
Age	Mean (SD)	27.6	27.0	27.5

2.2 The Microarray and RNA Extraction Process

The the company's guidelines and the PAXgene blood RNA technology were used to harvest "RNA 2.6 ml of nearby whole plasma mixed in PAXgene tubes". The RNA and integrity were assessed using Agilent 2100 Bioanalyses. The Fluorescent Linear Amplification Kit was used for marking the RNA by the instructions supplied by the manufacturer. Before the specimens were hybridized to the whole-genome oligonucleotide microarray, the material's amount and labeling effectiveness was checked. In this experiment, they employed two-color microarray plates that has RNA from every group in the study were hybridized with RNA of individuals with the same sex and age of the other categories. To prevent possible dye-specific bias, dye colors are modified within the different groups. Due to the limited quantity of NID that could be obtained for the investigation, individual RNA sample from the particular category was co-hybridized with a collection of RNA of 3 related individuals from the added couple of categories.

2.3 Data analysis

An Agilent scanner was used to prepare and scan microarray chips at a 5 µm resolution. Software called Feature Extraction was used to analyze the images. The Bioconductor R package limma's read. The images function was used to handle the raw microarray data, and the norm-exp approach was used to background-correct the intensity of the spots that were not marked out. Red or green ratios were lowness adjusted using background-corrected data to get as impartial results as feasible. The information of entire arrays was quantile standardized for cross-country comparison. Additionally, features with mean log intensities of <7 were excluded since the accidental noise in the information would provide erroneous signals for these low-intensity areas. They used a grouping of t-tests and the following wrong innovation amount rectification constructed on the method of "Efron and Tibshirani" using three alternative opposites across NID, LTBI, and TB patients, significantly verify difference expression. Data were log converted, and by using a 2-sample t-test with a q value of <.01, genes with significantly different expression levels relative to one another were identified using a log-fold-difference method. With the aid of the dataset for an explanation, revelation, and "Integrated Discovery Bioinformatics Resources 2008", functional annotation exploration and clustering were carried out. Liaw and Wiener's technique was used to do the random forest analysis.

2.4 Quantitative RT-PCR

Quantitative real-time polymerase sequence reactions were used to verify the varied expression of multiple genes. Superscript II and oligo-dT primers were used for reverse transcription to produce cDNA. SYBR Green incorporation-based quantitative RT-PCR was used to quantify transcript levels. Table 2 displays primers and the basis of the target genes.

3. Results and discussions

3.1 Analysis of gene expression in LTBI and NID associations and patients with TB

Microarray chips with ~45000 distinct characteristics were used to create genome-wide transcriptional patterns in blood samples after 34 LTBI, 33 TB patients, and 9 NIDs from a region where tuberculosis is widespread. TB against LTBI, TB versus NID, and LTBI against NIDs are the 3 analyses that will be analyzed as part of our method to find gene expression differences across the study populations. The ultimate goal is the discovery of specific characteristics connected to active TB. They concentrated on LTBI and NID comparability with the initial objective, which was to uncover disease-related gene patterns. They suggested that such contrasts identify patterns that isolate the presence of current TB illness from overall health. To find patterns that coincide with resistance and susceptibility, they focused on genes whose activity varied among TB and LTBI as opposed to between TB and NID. This strategy removed broad disease-related designs. The difference in gene expression among LTBI and patients with TB was found at 2048 in total. A total of 988 transcripts in all, and their expression was varied in TB patients as well as NIDs. A fold-change criterion of <.2 or <-.2 using <.01 has been applied in this study. To determine if those who participated in this research might have been categorized into various categories according to their gene expression patterns, a clustering approach was carried out. FCGR1B was the gene with the greatest amount of pronounced variation in expression between the TB and control groups in this investigation. Important variations in this gene's expression across research groups were validated by RT-PCR. To determine if this collection of genes might distinguish between LTBI and TB patients from the South Indian inhabitants analyzed here, the RT-PCR analysis also includes those genes previously used as biomarkers. In line with these previous findings, we found that RAB33A degrees of expression matched in TB and LTBI, but CD64 and LTF shows important distinction in gene regulation across the study categories (Figure 2).

3.2 RT-PCR confirms differential gene expression

The classifying ability of each of these genes to discriminate among TB contributors and LTBI was calculated using randomized forest analysis. A combination of each of the indicators produced an accuracy and specificity of 88 and 91 percent, accordingly, to detect patients with TB, and CD64 served as a particularly potent distinguishing gene (figure 3). After performing the same analysis on each of the thirteen genes, RT-PCR communication assessments revealed that a combination of the 5 most powerful differentiated genes CD64,FCGR1B, LTF, guanylate attaching proteins 5 and Granzyme provided the highest degree of accuracy in differentiating between LTBI and TB. A biosignature that increased sensitivity and specificity to 94% and 97%, accordingly, was created using this intriguing group of genes (figure 3).

3.3 Functional classification of genes with variable expression

They utilized the online tool dataset for Visualization, Annotation, and Interactive research to classify alternatively controlled genes. A substantial amount of genes related to protein binding, cell communication, and transmission of signals were found when annotation for functional grouping of genes associated with analyses of TB against LTBI and TB against NID was performed (Figure 4). In the gene ontological study, genes implicated in various immunological responses, apoptosis, and stress responses have been elevated. The 792 to 988 transcripts (744 to 927 genes) that exhibited either more or less activity in the two separate TB vs LTBI or TB against NID studies responded equally to the genes that were differentially regulated in the two comparisons. These genes had a primary role in regulating the immune system and apoptosis, and they had extremely substantial enrichment in gene ontology keywords. The results we obtained support the idea that systemic alterations in immune system function serve as a reliable sign of a developing TB illness. Similarities in gene regulation between the two kinds of comparisons between TB patients and healthy Inflammation of the system are common in persons with LTBI or NID due to M. tuberculosis exposure.

3.4 Individualized expression patterns in LTBI and TB Illness

The following restricted the search to just those genes that differed in regulation between LTBI and TB to find shapes of gene expression suggestive the development from LTBI to dynamic TB disease. A gene region associated with regulating apoptotic was discovered by comparative research to have less action in TB than LTBI (Table 3). This specific gene group had identical amounts of activity in TB and NID since genes included across the two comparisons had been filtered away. Similar to how LTBI generated differently from TB and NID, a collection of genes associated with host defense reactions that are primarily engaged in granulocyte and macrophage-impacting activity and division were additionally expressed at a reduced level in LTBI (Table 3). These gene subgroups that show a decline in apoptosis and an increase in innate host defense are thought to be indicators of the development of TB illness from LTBI.

3.5 Expression patterns related to various functions and cell types

Myeloid differentiation primary response protein88 (MyD88) and interferon regulatory factor 7 (IRF7), two genes linked with Toll-like receptors, were significantly up regulated when the functional classification of variations between expression genes specific to TB vs LTBI was performed. The results also reveal greater levels of “several interferon-inducible genes, including 2', 5'-oligoadenylate synthase 1 and 2, guanylate binding proteins 1 and 2, interferon alpha-inducible proteins 6 and 27, and ISG15 ubiquitin-like modifier (in Table 4), When comparing the activity of specific subsets of genes linked with macrophages and NK cells, it was found that TB and LTBI had different gene expression profiles”. TB increased the expression of genes related to macrophages. As opposed to LTBI patients, TB patients had decreased NK cell related genes. Comparably, although B cell associated genes was mostly downregulated in TB patients, response and inflammasome-associated gene activity was raised. It should be emphasized that there were no differences in the level of expression among TB and NID for any of those operational and cellular type-associated genes. They can't explicitly rule out the possibility that the observed variances in genes expressed are due to different overall numbers of various cell categories in LTBI patients as opposed to TB patients and NIDs. The gene that has the greatest gradation of variation in countenance across each of the donation groups during this research was found to be FCGR1B. CD64 represented one of the genes with the greatest ranked variation in expression among TB-diseased vs latently infected Caucasian participants, according to a previous investigation from the lab. Despite having various comments, the coding regions of such genes are extremely comparable. The sequences of the probes containing oligonucleotides on the matrix chips utilized in both investigations were 100% equivalent to one another. Thus, transcripts from the two genes were the focus of the microarray chips in the two trials. As a result, they created primers for the RT-PCR analysis that precisely address the mRNA responsible for CD64 synthesis. Significantly more genes that are differentially regulated among people in each of the three research groups have been included in the profiles that were developed in this investigation. Independent of M. tuberculosis infection, these changes were particularly noticeable between sick donors. The genes' annotations of function grouping revealed a significant frequency of elements associated with the transmission of signals, gene expression, immunological regulation, protein and metal ion binding, and gene expression activity. The expression patterns found in this research need to be further validated by extensive gene expression studies in other geographical and racial populations. These investigations are presently being conducted in populations from other African nations to confirm the gene profiles used as biomarkers, find the characteristics of gene expression unique to TB, and identify patterns of expression shared by TB and other chronic infectious illnesses. Consequently, to finally develop a distinct biosignature for TB, further thorough investigations into expression patterns that might be perilous for understanding resistance and susceptibility in M. tuberculosis-infected individuals.

Table 2: qRT-PCR primer sequence

Gene name	Sequence (5^0–3^0)	Amplicon size	Primer	Accession no.
B2M	ATGCTGCGCGCGTGCGCTGCT GCTGC	19	Forward	NM_004048
	ATGCTGCGC		Reverse	
CASP1	TAGATGCAGGTTCCATAGCG	53	Forward	NM_033292
	TACAGAGCTGGAGGCATTTG		Reverse	
CD64	ATGCTGAGCTGACATCCAGG	13	Forward	NM_000566
	TACGACTCGACTGTAGGTC		Reverse	
CEACAM1	ATGCTAGCTAGCTAGCTAGCT AGCTAGCTAGCTAGCTAGCTA GCTAG	43	Forward	NM_001024912
	CTAG		Reverse	
DEFA3	ATGAGCTGAGCTGAGCTGAGC TGAGCTGAGCT	306	Forward	NM_005217
	TAGATGCAGGTTCCATAGCG		Reverse	
FCGR1B	GGGTTAACATTAGGCTGGGA	85	Forward	NM_001017986
	CCGAACTGAGTATTGGTGGA		Reverse	
GZMA	GCTCGCGCTACTCTCTCTTT	82	Forward	NM_006144
	CTCTGCTGGATGACGTGAGT		Reverse	
HP	TGCAGGAAATGCAAAGAAAG	110	Forward	NM_005143
	AACTGGACCCTGTCGTTCTC		Reverse	
IFI27	GAAGAGACTCGTGCAATGGA	92	Forward	NM_005532
	ACATTAGGCTGG		Reverse	
LTF	AGAGAGACTCCCCCATCCAGT	60	Forward	NM_002343
	AGGCCTGGTTTGCAGCTTT		Reverse	
Rab33A	GGTGACTTCCATCCAGGACT	58	Forward	NM_004794
	ACAGTGGAGCAAAGGTGTGG		Reverse	
S100A12	TGGCAAATCCTACCTGATGA	96	Forward	NM_005621
	CCATATCCAAATTCCCTTGG		Reverse	

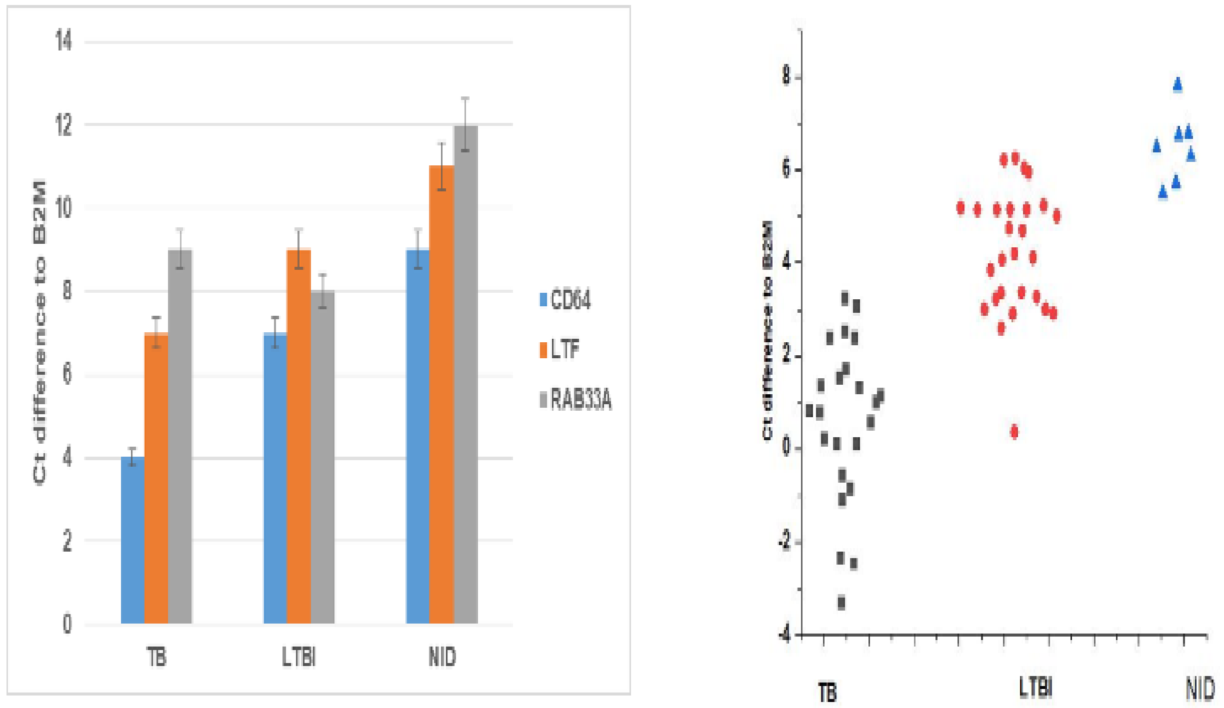

Figure 2: TB, LTBI, and NID gene expression levels in the Indian group

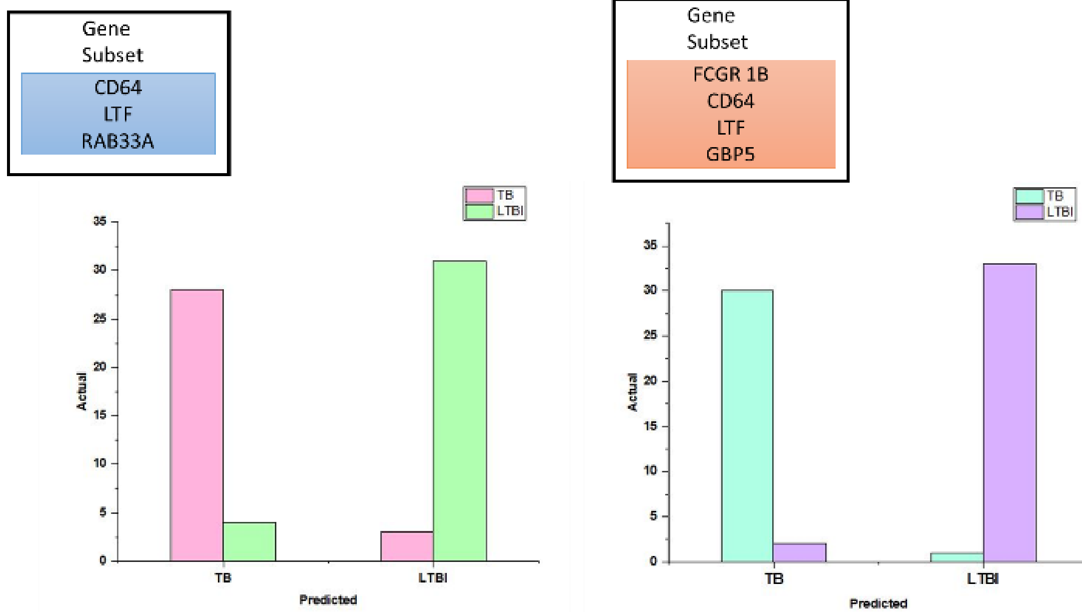

Figure 3: Gene subsets separating TB and LTBI were subjected to random forest analysis.

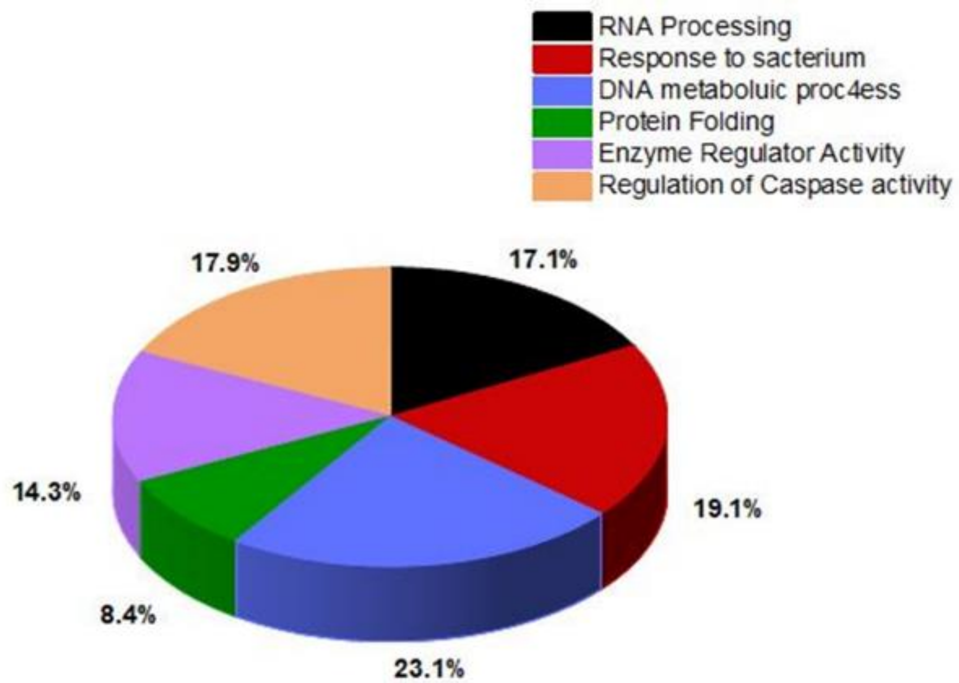

Figure 4: The connection between cells and the transmission of signals

Table 3: Apoptosis and defense genes variation

Transcript ID	M (log 2)	Gene symbol
NM_014061	—0.42	MAGEH1
NM_001731	—0.51	BTG1
NM_001316	—0.28	CSE1L
NM_014739	—0.31	BCLAF1
NM_016542	—0.83	RP6-213H19.1
NM_001637	0.34	AOAH
NM_001725	0.31	BPI
NM_172313	0.52	CSF3R
NM_021175	0.39	HAMP
NM_000634	0.36	IL8RA

Table 4: TB and LTBI gene expression

Gene sign	M (log 2)	q
Complement-associated genes		
SERPING1	2.13445	1.5E—00
C3AR1	2.37222	1.2E—04
C1QB	2.35989	7.2E—09
C1QA	2.02992	1.0E—07
Macrophage-associated genes		
STAB1	.26	3.7E—06
NOD2	.78	8.1E—05
MARCO	.86	6.3E—06
IFI16	.27	4.9E—03
CD68	.24	1.9E—03
CD36	.33	1.7E—03
NK cell-associated genes		
PRF1	- .46	7.8E05
NCR3	- .58	2.4E06
KLRsa	- .73 to -.26	2.0E03
KIR2DL2	- .26	4.3E—03
GZMK	-.90	9.5E—09
GZMB	-.44	1.5E—03
GNLY	-.46	4.0E—03
CD160	-.27	4.4E—05
Inflammasome-associated genes		
CASP5	CASP5	CASP5
IL1B	IL1B	IL1B
PYCARD	PYCARD	PYCARD
B cell-associated genes		
POU2AF1	-.57389	7.7E04
PIK3AP1	.45888	4.9E07
CD19	-.45888	3.2E05
BANK1	-.82986	1.8E08
IFN-induced and TLR-associated genes		
WARS	WARS	WARS
TLR6	TLR6	TLR6
RF7	RF7	RF7
OASL	OASL	OASL

4. Conclusion

In conclusion, a complex interaction between host genetic traits, pathogen virulence, and environmental variables underlies the genetic foundation of TB susceptibility in human populations. Although several genes and genetic variants have been discovered as possible TB susceptibility factors, additional study is required to completely understand the underlying processes and to provide more specialized strategies for tuberculosis prevention, diagnosis, and treatment. The patterns of gene expression discovered in this study open the way to developing predictive correlates of protection against TB as well as offering incisive insights for a better comprehension of the change from latent infection to active sickness. Integrating genetic, epigenetic, environmental, and host-pathogen variables into studies of TB susceptibility in human populations is an area that needs further attention in the future. A better knowledge of TB susceptibility and successful ways for its diagnosis and treatment may emerge from such a collaborative effort including experts from a variety of fields.

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