GENETIC POLYMORPHISM OF THE NF-KB1 P105/P50 PROCESSING REGION IN PULMONARY TUBERCULOSIS

Meyer AV ✉, Thorenko BA, Imekina DO, Dutchenko AP, Pyanzova TV, Karabchukov KB, Lavryashina MB

Kemerovo State Medical University, Kemerovo, Russia

Pulmonary tuberculosis (TB) is a socially significant disease and a global challenge faced by public health. The NF-kB signaling pathway is involved in differential expression of the genes involved in immune responses and regulation of inflammation in response to infection. The study aimed to assess associations of the *NFKB1* allelic variants with TB based on the panel of SNPs (rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993) located within the NF-kB1 p105→p50 processing region. Total DNA was extracted from blood samples (phenol-chloroform extraction) of patients with TB (n = 93) and the population control group (n = 96) consisting of residents of the Kemerovo Region. Genotyping was performed by real-time PCR, and the results were processed using the resources of the Statictica, SNPStats, Arlequin software packages. Ethnic features ($p < 0.05$) of the Russian population of Siberia (population control group) were demonstrated based on the rs4648050 and rs4648051 allele frequencies. Differences ($p < 0.05$) of the genetic profile of the sample of patients with pulmonary tuberculosis throughout the entire SNP complex, except for rs1609993, were noted. We showed differences ($p < 0.05$) in the rs4648068 allelic frequencies between the population control sample and patients with pulmonary tuberculosis. The association with susceptibility to pulmonary tuberculosis was determined for genotypes AA*rs4648055 (OR = 2.51; p = 0.05) and GG*rs4648068 (OR = 2.16; p = 0.03). The findings are indirect evidence of modifying effects of the SNP located within the processing zone in the gene *NFKB1* and its possible contribution to the NF-kB1 p105/p50 protein balance and immune response to mycobacterial infection.

Keywords: *NFKB1*, genetic polymorphism, pulmonary tuberculosis, transcription factors, inflammation

Funding: the study was conducted within the framework of the basic budgetary funding source for project of the State Assignment of the Ministry of Health of the Russian Federation (agreement No. 056-03-2023-050 dated 17.01.2023).

Author contribution: Meyer AV, Lavryashina MB — developing the study concept and design, manuscript writing and final approval; Thorenko BA — genotyping, statistical analysis, working with the database; Imekina DO — genotyping, statistical analysis, technical editing; Dutchenko AP — search for literature, manuscript writing; Pyanzova TV — research management, clinical and biological material collection, final approval of the manuscript; Karabchukov KB — clinical history taking.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Kemerovo State Medical University (protocol No. 301 dated 08 February 2023) and conducted in accordance with the ethical principles stated in the WMA Declaration of Helsinki; the written informed consent to participation in the study was obtained from all patients.

✉ **Correspondence should be addressed:** Alina V. Meyer
Voroshilov, 22a, Kemerovo, 650056, Russia; shapo-alina@yandex.ru

Received: 23.12.2024 **Accepted:** 06.02.2025 **Published online:** 19.02.2025

DOI: 10.24075/brsmu.2025.004

ГЕНЕТИЧЕСКИЙ ПОЛИМОРФИЗМ ОБЛАСТИ ПРОЦЕССИНГА P105/P50 NF-KB1 ПРИ ТУБЕРКУЛЕЗЕ ЛЕГКИХ

А. В. Мейер ✉, Б. А. Тхоренко, Д. О. Имекина, А. П. Дутченко, Т. В. Пьянзова, К. Б. Карабчуков, М. Б. Лавряшина

Кемеровский государственный медицинский университет, Кемерово, Россия

Туберкулез легких (ТБ) — социально значимое заболевание, общемировая проблема здравоохранения. NF-kB-сигнальный путь вовлечен в дифференциальную экспрессию генов, задействованных в иммунных реакциях и регулирующих воспаление в ответ на инфицирование. Целью исследования было изучить ассоциации с ТБ аллельных вариантов гена *NFKB1* по панели SNP (rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993), локализованных в зоне процессинга NF-kB1 p105→p50. Тотальную ДНК выделяли из образцов крови (метод фенол-хлороформной экстракции) пациентов, больных ТБ (n = 93), и группы популяционного контроля (n = 96) жителей Кемеровской области. Генотипирование проводили методом ПЦР в режиме реального времени, обработку результатов — с использованием ресурсов программ Statictica, SNPStats, Arlequin. Продемонстрированы этнические особенности ($p < 0,05$) русского населения Сибири (группа популяционного контроля) по частотам аллелей rs4648050 и rs4648051. Отмечено отличие ($p < 0,05$) генетического профиля выборки пациентов с туберкулезом легких от общемировой и европейской популяций по всему комплексу SNP, за исключением rs1609993. Показано различие ($p < 0,05$) аллельных частот rs4648068 между выборкой популяционного контроля и пациентов с туберкулезом легких. Установлена ассоциация с подверженностью туберкулезу легких для генотипов AA*rs4648055 (OR = 2,51; p = 0,05) и GG*rs4648068 (OR = 2,16; p = 0,03). Полученные результаты косвенно свидетельствуют о модифицирующем влиянии SNP, локализованных в зоне процессинга, в гене *NFKB1* и его возможном вкладе в баланс белков NF-kB1 p105/p50 и иммунный ответ на микобактериальную инфекцию.

Ключевые слова: *NFKB1*, генетический полиморфизм, туберкулез легких, транскрипционные факторы, воспаление

Финансирование: работа выполнена в рамках базового бюджетного источника финансирования работ государственного задания Минздрава РФ (Соглашение № 056-03-2023-050 от 17.01.2023).

Вклад авторов: А. В. Мейер, М. Б. Лавряшина — разработка концепции и дизайна исследования, подготовка и окончательное утверждение рукописи; Б. А. Тхоренко — генотипирование, статистический анализ, работа с базой данных; Д. О. Имекина — генотипирование, статистический анализ, техническое редактирование; А. П. Дутченко — поиск литературы, подготовка рукописи; Т. В. Пьянзова — организация исследования, сбор клинического и биологического материала, окончательное утверждение рукописи; К. Б. Карабчуков — сбор клинического анамнеза.

Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГБОУ ВО КемГМУ Минздрава России (протокол № 301 от 08 февраля 2023 г.), проведено согласно этическим принципам, изложенным в Хельсинкской декларации ВМА; от всех пациентов получено добровольное письменное согласие на участие.

✉ **Для корреспонденции:** Алина Викторовна Мейер
ул. Ворошилова 22а, г. Кемерово, 650056, Россия; shapo-alina@yandex.ru

Статья получена: 23.12.2024 **Статья принята к печати:** 06.02.2025 **Опубликована онлайн:** 19.02.2025

DOI: 10.24075/vrgmu.2025.004

Pulmonary tuberculosis (TB) is a pressing global issue of theoretical medicine and practical healthcare [1]. High incidence and mortality rates persist in a number of countries, which are caused by drug resistance of the pathogen, high prevalence of HIV infection among tuberculosis patients, low patient adherence to treatment, and the genetically determined features of the response to infection and treatment [2–5].

Diverse studies, including the analysis of genomes of *Mycobacterium tuberculosis* (*M. tuberculosis*) and the host, are conducted in order to investigate the genetic component value. One avenue in this field is the search for associations between the fact of carrying certain genotypic and allelic variants of genes and the specifics of human body's response to *M. tuberculosis* infection and anti-tuberculosis therapy. Despite a significant amount of data accumulated [6–9], there is still ambiguity and even some inconsistency of the results obtained, which determines the need for further research in this field.

Considering current ideas about the key immune mechanisms ensuring recognition of *M. tuberculosis* and subsequent destruction of the pathogen [10, 11], intracellular signaling pathways and molecular cascades involved in differential expression of the genes engaged in immune responses and ensuring regulation of inflammation as the body's systemic protective response are of great interest for scientific community [12–14]. These include the NF-kB signaling pathway, activation of which results in stimulation of inflammation via enhanced biosynthesis of TNFα, IFNγ, IL6, IL8 pro-inflammatory factors and other cytokines [15].

The NF-kB1 transcription factor (nuclear factor kappa-light-chain-enhancer of activated B cells) is represented in the cell by the full-length precursor protein (p105) and its processed form (p50). NF-kB1/p50 as part of the complex with p65 (RelA) is a transcription activator, while NF-kB1/p105 in the form of homodimers (or together with IkB, the NF-kB inhibitor) functions as a suppressor of this process. Therefore, the p105→p50 processing modification can affect the NF-kB pathway direction and effectiveness, while intracellular p105/p50 balance can determine adequacy of the cellular response to activation signals, thereby contributing to the tuberculosis pathogenesis.

The Ub-independent p105→p50 posttranslational processing involving the 20S proteosome is currently considered as the main mechanism underlying generation of NF-kB1/p50 [16]. The endoproteolysis region is long enough and includes amino acid bases (AA) 430–530. At the gene level this region covers the exon region (E) E13 (403–433 AA) — E15 (499–546 AA) with the overall length of 2771 bp. The study aimed to assess associations with tuberculosis of the light *NFKB1* gene allelic variants localized within the NF-kB1 p105→p50 processing zone based on the SNP panel.

METHODS

The study involved total DNA extracted from blood samples of the patients of the Kopylova Kuzbass Clinical Phthisiopulmonology Medical Center (Kemerovo) with pulmonary tuberculosis (TB group, n = 93) and the population control group (PC group, n = 96) represented by the sample of residents of the city of Kemerovo and Kemerovo Region. The group of patients with pulmonary tuberculosis included 74 males and 19 females aged 26–88 years diagnosed for the first time (n = 78) and having relapses (n = 15). Clinical forms were represented by infiltrative (n = 49), disseminated (n = 23), focal (n = 6), fibrous-cavernous (n = 5) pulmonary tuberculosis, tuberculoma (n = 7), pleurisy (n = 3). Both groups were formed considering ethnicity (based on self-determination), demographic and medical history data.

Inclusion criteria for the TB group: established diagnosis of incident tuberculosis or tuberculosis relapse; age over 18 years. Exclusion criteria: HIV infection; fact of detecting antibodies against hepatitis C virus (HCVAg) and hepatitis B virus (HBsAg) in blood serum; refusal of participation in the study. All the patients were assessed in accordance with the standard regulated by current clinical guidelines. A complex of clinical, laboratory, and instrumental testing data was used to verify the diagnosis. The diagnosis of tuberculosis was established by the central medical board of the Kopylova Kuzbass Clinical Phthisiopulmonology Medical Center. DNA was extracted from biological samples by the phenol-chloroform extraction method. Genotyping based on rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993 was performed by real-time PCR in the Applied Biosystems QuantStudio 5 Real-Time PCR System (Thermo Fisher Scientific, USA) using the commercially available kits (DNA-Synthesis, Russia). According to the manufacturer's instruction, the amplification programs had the following settings: initial denaturation for 3 min at a temperature of 95 °C; 40 cycles of primer annealing at a temperature specific for each polymorphism (54–59 °C); chain elongation at a temperature of 72 °C, and denaturation at a temperature of 95 °C. The amplification reagent mixture composition was as follows: DNA of the studied sample — 1 μL, Taq DNA polymerase — 0.5 μL, 10× buffer for Taq DNA polymerase — 2.5 μL, primer mixture (forward F, reverse R) — 2.5 μL, solution of four dNTP — 1 μL, fluorescent labeling probes TaqMan (FAM, VIC) — 1 μL each, deionized water — to the total mixture volume of 25 μL. Primary results were subjected to standard analysis using the resources of the Statictica, SNPStats, Arlequin software packages. Genotypic and allelic frequencies were calculated. The Hardy–Weinberg equilibrium was assessed using the Pearson's chi-squared (χ^2) test ($\chi^2_{X\text{-}W}$). The analysis of associations of the candidate genes' polymorphic variants was conducted based on the odds ratio (OR) considering the confidence interval (CI) for the odds ratio (95% CI). The null hypothesis was rejected when p-value was below 0.05.

RESULTS

The *NFKB1* gene (HGNC:7794) located in 4q24 with the length of 115.973 kbp (GRCh38: CM000666.2 – 4: 102,501,330-102, 617,302) contains 27 exons (E). The SNP (Single Nucleotide Polymorphism) panel for the study was generated considering the following: 1) SNP location within the processing zone — the region of exons E13-E15 was used as a target, together with the adjacent introns (I) — I12, I15; 2) minor allele frequency (MAF) in the population of at least 0.1. Information was taken from the Ensembl genome browser (http://www.ensembl.org), and the NCBI data were used (https://www.ncbi.nlm.nih.gov/).

The total number of SNPs in the *NFKB1* gene is 41,781. The number of SNPs found in the populations with the minor allele frequency (MAF) exceeding 0.1 was 152. After selecting polymorphic variants in the target region I12-E13-I13-E14-I14-E15-I15 with the length of 7325 bp (102,593,569–102,600,894 bp) a total of five variants located in introns were identified, along with one exonic variant. The characteristics of the SPN panel generated are provided in Table 1.

The data characterizing frequencies of the alternative allele based on the panel of six SNPs (rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993) in the gene *NFKB1* in patients with TB and in the PC group, along with the indicators of the genotypic frequency equilibrium ($\chi^2_{X\text{-}W}$), as well as the data on the alternative allele frequencies in the

Table 1. Characteristics of the studied *NFKB1* SNP complex (according to Ensembl, http://www.ensembl.org)

RefSec	Localization	Type of variant	Position of variant (GRCh38)	Ancestral allele	Alternative variants
rs4648050	I 12	SNV	102593584	T	A, C*, G
rs4648051	I 12	SNV	102593836	A	G*
rs4648055	I 12	SNV	102594156	G	A*, C
rs4648058	I 12	SNV	102594434	G	C*
rs4648068	I 14	SNV	102597148	A	G*
rs1609993	E 12	SNV	102593501	T	A, C*, G

Note: I — intron, E — exon, * — alternative variants analyzed in the study.

global (Global) and European (EUR) populations are provided in Table 2.

Determination of the state of genotype frequency equilibrium in the studied samples has shown the following. Values of the $\chi^2_{X\text{-}W}$ parameter in the PC group suggest that there was no significant deviation from the Hardy–Weinberg equilibrium throughout the entire studied SNP panel in the gene *NFKB1*. In the sample of TB patients, genotypic frequency deviation ($p < 0.05$) was reported based on two SNPs (rs4648068 and rs1609993): $\chi^2_{X\text{-}W}$ was 5.06 and 9.15, respectively.

To analyze specifics of the gene pool of Russians of Siberia, we performed pairwise comparison of the rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993 allele frequencies in the gene *NFKB1* in the studied sample of Russians of the Kemerovo Region (Kuzbass; PC group) with the available data on the global and European populations. The results obtain reflect the features of the genetic profile of the Russian population of Siberia compared to global frequencies and the frequencies typical for populations of Europe based on rs4648050 ($p < 0.05$), as well as in terms of matching with the global population based on rs4648051 ($p < 0.05$). As for other studied SNPs, there were no significant differences in allelic frequencies in the PC group.

Comparison of the nature of allelic frequency distribution in the TB sample and PC group revealed a significant difference ($p < 0.05$) based on rs4648068, for which the χ^2 value was 3.86. The fact attracts attention that comparison of allelic frequencies in the sample of TB patients with the frequencies in the global and European populations demonstrates specifics throughout the entire SNP complex, except for rs1609993. This suggests that the increase in sample size with make it possible to reveal a broader range of associations between the studied SNPs and TB in the future.

Frequencies of the rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993 genotypes in the gene *NFKB1* and the results of assessing the association of the generated SNP panel with TB are provided in Table 3.

Comparison of genotypic frequencies revealed significant differences for two SNPs: rs4648068 ($p = 0.03$) and rs4648055 ($p = 0.05$). As for rs4648068, as mentioned above, we have shown significant differences based on the data of comparing the allelic frequencies as well. The study demonstrates the increased frequency of the homozygous GG variant comprising the alternative allele. As for rs4648055, in this case the sample of TB patients also shows higher frequency of the homozygous genotype comprising the alternative allele, AA. Both genotypes, GG *rs4648068 and AA*rs4648055, are considered as the etiological fraction genotypes, i.e. the genotype carrier state is associated with the increased susceptibility to developing TB in case of mycobacterial infection. The study has determined a significant correlation with TB of the genotypic variants AA*rs4648055 (OR = 2.51; $p = 0.05$) and GG*rs4648068 (OR = 2.16; $p = 0.03$).

DISCUSSION

The results of matching the alternative allele frequencies to the cumulative data by projects (ALFA dataset, https://ncbiinsights.

Table 2. Frequencies of the rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993 alternative alleles in the gene *NFKB1* in the studied sample, global and European populations

SNP	Samples	$\chi^2_{X\text{-}W}$	Alt	χ^2_{TB}	MAF «ALFA»		χ^2_{GLOBAL}	χ^2_{EUR}
					Global	EUR		
rs4648050	PC	1.41	0.531	0.001	0.278	0.293	**28.26**	**24.21**
	TB	1.43	0.528				**27.59**	**23.61**
rs4648051	PC	0.47	0.389	1.24	0.274	0.309	**6.27**	2.96
	TB	0.01	0.471				**16.86**	**10.61**
rs4648055	PC	0.83	0.338	2.96	0.291	0.304	1.02	0.52
	TB	0.07	0.461				**12.82**	**10.64**
rs4648058	PC	2.49	0.411	1.14	0.324	0.331	3.29	2.75
	TB	0.27	0.489				**11.24**	**10.17**
rs4648068	PC	2.85	0.395	**3.86**	0.339	0.321	1.34	2.4
	TB	**5.06**	0.538				**16.22**	**19.8**
rs1609993	PC	0.35	0.942	0.58	0.924	0.916	0.44	0.84
	TB	9.15	0.913				0.15	0.01

Note: $\chi^2_{X\text{-}W}$ — criterion for estimation of the Hardy–Weinberg equilibrium; χ^2 — criterion for pairwise comparison of frequencies; Alt — alternative allele frequency; MAF — minor allele frequency in the global population (Global) and European population (EUR), the χ^2 indices represent variants of pairwise comparison: TB — of population control with the group of TB patients; GLOBAL — of both studied samples with frequencies in the global population; EUR — with frequencies in the European population. Statistically significant values are highlighted in bold.

Table 3. Distribution of the rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993 genotypes in the gene *NFKB1* and indicators of association with TB

SNP	Genotype	Frequency %		X^2 test value with the Yates's correction (significance level *p*)	Odds ratio OR (95% confidence interval)
		PC (*n* = 96)	TB (*n* = 93)		
rs4648050	TT	25	19.1	0.62 (*p* = 0.43)	0.70 (0.35–1.42)
	TC	43.75	56.18	2.37 (*p* = 0.12)	1.64 (0.92–2.94)
	CC	31.25	24.72	0.67 (*p* = 0.41)	0.72 (0.37–1.37)
rs4648051	AA	38.94	27.58	2.14 (*p* = 0.10)	0.59 (0.32–1.11)
	AG	44.22	50.58	0.50 (*p* = 0.47)	1.26 (0.70–2.25)
	GG	16.84	21.84	0.44 (*p* = 0.50)	1.38 (0.65–2.89)
s4648055	GG	41.66	28.27	3.14 (*p* = 0.07)	0.552 (0.30–1.01)
	GA	48.96	51.08	0.02 (*p* = 0.88)	1.08 (0.61–1.92)
	AA	9.38	20.65	**3.86 (*p* = 0.05)**	**2.51 (1.07–5.89)**
rs4648058	GG	38.54	27.47	2.10 (*p* = 0.14)	0.60 (0.32–1.12)
	GC	40.62	47.25	0.58 (*p* = 0.44)	1.30 (0.73–2.33)
	CC	20.84	25.28	0.30 (*p* = 0.58)	1.28 (0.64–2.54)
rs4648068	AA	40.62	27.17	3.21 (*p* = 0.07)	0.54 (0.29–1.00)
	AG	39.58	38.05	0.004 (*p* = 0.94)	0.93 (0.52–1.68)
	GG	19.8	34.78	**4.60 (*p* = 0.03)**	**2.16 (1.11–4.18)**
rs1609993	TT	0	3.27	1.44 (*p* = 0.23)	0
	TC	11.46	10.87	0.01 (*p* = 0.91)	0.942 (0.38–2.33)
	CC	88.54	85.86	0.10 (*p* = 0.74)	0.786 (0.33–1.85)

ncbi.nlm.nih.gov/2020/03/26/alfa/) (Table 2) indicate the differences between the values obtained in this study for the population groups of the Siberian region relative to both global values (Global) and Caucasoid populations (EUR) throughout the range of studied SNPs, except for rs1609993. This suggests the features of the "genetic portrait" of the Russian population of Siberia related to the studied complex, which should be considered when conducting meta-analysis, arranging association studies, and determining the range of informative TB biomarkers.

In this study, significant associations with the risk of developing TB were reported for intronic variants rs4648055, rs4648068 (Table 3). In case of variant rs4648055, the alternative allele A in homozygous state increases the risk of disease 2.5-fold, while the 2-fold increased disease risk reported for rs4648068 results from the presence of alternative variant of allele G in homozygous state in the genotype. The trend towards statistical significance for protective effects of the major genotypes GG*rs4648055 (OR = 0.55; p = 0.07) and AA*rs4648068 (OR = 0.54; p = 0.07) can also be noted.

It should be noted that to date the literature data on the rs4648055 and rs4648068 contribution to the development of disorders are scarce, and the results are ambiguous. A number of papers report that there are no significant associations of rs4648055 and rs4648068 with the development of such disorders, as lung cancer [17] and coronary artery disease [18]. At the same time, when studying head and neck cancer in residents of Pakistan infected with HPV, the role of allele G in heterozygous and homozygous states in the increased risk of developing cancer was reported for rs4648068 [19]. When studying the risk factors of developing gastric cancer in the population of Han Chinese, significant results were reported for allele G of rs4648068 (OR = 1.43; p = 0.0001) [20]. Frequencies of genotype distribution in the control group were as follows: AA — 27.71%, AG — 53.58%, GG — 18.71%; in the group of patients — 22.94%, 45.64%, 31.42%. The alternative allele G frequency in the comparison group was 0.455, and in the cancer group it was 0.542, which is similar to the data obtained in our study for the TB group (0.538). Similar results were reported when studying the rs4648055 and rs4648068 contribution to ovarian cancer development in the Chinese population, and significant associations were also reported only for allele G of rs4648068 (OR = 1.38; p = 0.001), frequency of which in the group of patients was 0.532, and in the comparison group it was 0.454 [21].

CONCLUSIONS

The following aspects can be considered as the main findings of the study. First, new research data on the frequencies of rs4648050, rs4648051, rs4648055, rs4648058, rs4648068, rs1609993 in the gene *NFKB1* in Russians of Siberia were obtained. These data make it possible to draw a conclusion about the specifics of genetic structure of the Russian population that should be considered when conducting association studies. Second, the statistically significant differences of the rs4648050, rs4648051, rs4648055, rs4648058, rs4648068 allelic frequencies in the sample of tuberculosis patients from the global frequencies and frequencies typical for populations of Europe suggest potential informational value of the generated SNP panel, which requires further research. Third, the detection of associations between susceptibility to TB and homozygous genotypes based on the alternative allele for rs4648055 and rs4648068 is indirect evidence in favor of modifying effects of genetic polymorphism, SNPs located within the processing zone in the gene *NFKB1*, and its possible contribution to the p105→p50 processing effectiveness, balance of the NF-kB1 gene products (p105/p50), and regulation of target gene expression. This assumption requires further research based on the analysis of the p105 and p50 levels with parallel assessment of transcription activity of the target genes of this transcription factor. Identification and analysis of the features of molecular mechanisms at the population and individual

levels not only provide detailed understanding of molecular mechanisms underlying the TB pathogenesis, but also contribute to improvement of diagnostic procedures, including those involving prediction of disease progression, as well as to improvement of therapeutic strategies and the search for the ways to develop new drugs.

References

1. Global Tuberculosis Report 2023. Available from: https://www,who,int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023 (30.11.2024).
2. Khan PY, Yates TA, Osman M, Warren RM, van der Heijden Y, Padayatchi N, et al. Transmission of drug-resistant tuberculosis in HIV-endemic settings. Lancet Infect Dis. 2019; 19 (3): e77–e88. DOI: 10.1016/S1473-3099(18)30537-1.
3. Liebenberg D, Gordhan BG, Kana BD. Drug resistant tuberculosis: Implications for transmission, diagnosis, and disease management. Front Cell Infect Microbiol. 2022; 12: 943545. DOI: 10.3389/fcimb.2022.943545.
4. Dohal M, Porvaznik I, Solovič I, Mokry J. Advancing tuberculosis management: the role of predictive, preventive, and personalized medicine. Front Microbiol. 2023; 14: 1225438. DOI: 10.3389/fmicb.2023.1225438.
5. Shabani S, Farnia P, Ghanavi J, Velayati AA, Farnia P. Pharmacogenetic Study of Drugs Affecting Mycobacterium tuberculosis. Int J Mycobacteriol. 2024; 13 (2): 206–12. DOI: 10.4103/ijmy.ijmy_106_24.
6. Aravindan PP. Host genetics and tuberculosis: Theory of genetic polymorphism and tuberculosis. Lung India. 2019; 36 (3): 244–52. DOI: 10.4103/lungindia.lungindia_146_15.
7. Abhimanyu Bose M, Giri A, Varma-Basil M. Comparative Genetic Association Analysis of Human Genetic Susceptibility to Pulmonary and Lymph Node Tuberculosis. Genes (Basel). 2023; 14 (1): 207. DOI: 10.3390/genes14010207.
8. Murugesan H, Sampath P, A VK, R S, Veerasamy A, Ranganathan U, et all. Association of CYP27B1 gene polymorphisms with pulmonary tuberculosis and vitamin D levels. Gene. 2024; 927: 148679. DOI: 10.1016/j.gene.2024.148679.
9. Samimi R, Hosseinpanahi A, Zaboli R, Peymani A, Rouhi S, Ahmadi Gooraji S, et all. Prevalence of Vitamin D Receptor Genes Polymorphisms in People with Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis. Med J Islam Repub Iran. 2024; 38: 32. DOI: 10.47176/mjiri.38.32.
10. Ferluga J, Yasmin H, Al-Ahdal MN, Bhakta S, Kishore U. Natural and trained innate immunity against Mycobacterium tuberculosis. Immunobiology. 2020; 225 (3): 151951. DOI: 10.1016/j.imbio.2020.151951.
11. Wang Y, Shi Q, Chen Q, Zhou X, Yuan H, Jia X, et all. Emerging advances in identifying signal transmission molecules involved in the interaction between Mycobacterium tuberculosis and the host. Front Cell Infect Microbiol. 2022; 12: 956311. DOI: 10.3389/fcimb.2022.956311.
12. Stutz MD, Clark MP, Doerflinger M, Pellegrini M. Mycobacterium tuberculosis: Rewiring host cell signaling to promote infection. J Leukoc Biol. 2018; 103 (2): 259–68. DOI: 10.1002/JLB.4MR0717-277R.
13. Gallant J, Heunis T, Beltran C, Schildermans K, Bruijns S, Mertens I, et all. PPE38-Secretion-Dependent Proteins of M. tuberculosis Alter NF-kB Signalling and Inflammatory Responses in Macrophages. Front Immunol. 2021; 12: 702359. DOI: 10.3389/fimmu.2021.702359.
14. Bullen CK, Singh AK, Krug S, Lun S, Thakur P, Srikrishna G, et all. MDA5 RNA-sensing pathway activation by Mycobacterium tuberculosis promotes innate immune subversion and pathogen survival. JCI Insight. 2023; 8 (20): e166242. DOI: 10.1172/jci.insight.166242.
15. Mitchell S, Vargas J, Hoffmann A. Signaling via the NFκB system. Wiley Interdiscip Rev Syst Biol Med. 2016; 8 (3): 227–41. DOI: 10.1002/wsbm.1331.
16. Moorthy AK, Savinova OV, Ho JQ, Wang VYa-F, Vu D, Ghosh G. The 20S proteasome processes NF-kappaB1 p105 into p50 in a translation-independent manner. EMBO J. 2006; 25 (9): 1945–56. DOI: 10.1038/sj.emboj.7601081.
17. Liu CW, Wu LS, Lin CJ, Wu HC, Liu KC, Lee SW. Association of tuberculosis risk with genetic polymorphisms of the immune checkpoint genes PDCD1, CTLA-4, and TIM3. PLoS One. 2024; 19 (5): e0303431. DOI: 10.1371/journal.pone.0303431.
18. Guo XL, Liu XC, Su GB, Zhou CY, Cui QT. Association of NF-κB1 gene polymorphisms with coronary artery disease in a Han Chinese population. Genet Mol Res. 2016; 15 (3). DOI: 10,4238/gmr,15038072.
19. Sarwar S, Tareen MU, Sabir M, Sultan A, Malik SA. NF-κB1 Intronic Region Polymorphisms as Risk Factor for Head and Neck Cancer in HPV-Infected Population from Pakistan. Curr Mol Med. 2022; 22 (1): 74–82. DOI: 10.2174/1566524021666210302144344.
20. Hua T, Qinsheng W, Xuxia W, Shuguang Z, Ming Q, Zhenxiong L, et all. Nuclear factor-kappa B1 is associated with gastric cancer in a Chinese population. Medicine (Baltimore). 2014; 93 (28): e279. DOI: 10.1097/MD.0000000000000279.
21. Chen LP, Cai PS, Liang HB. Association of the genetic polymorphisms of NFKB1 with susceptibility to ovarian cancer. Genet Mol Res. 2015; 14 (3): 8273–82. DOI: 10.4238/2015.July.27.15.

Литература

1. Global Tuberculosis Report 2023. Available from: https://www,who,int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023 (30.11.2024).
2. Khan PY, Yates TA, Osman M, Warren RM, van der Heijden Y, Padayatchi N, et al. Transmission of drug-resistant tuberculosis in HIV-endemic settings. Lancet Infect Dis. 2019; 19 (3): e77–e88. DOI: 10.1016/S1473-3099(18)30537-1.
3. Liebenberg D, Gordhan BG, Kana BD. Drug resistant tuberculosis: Implications for transmission, diagnosis, and disease management. Front Cell Infect Microbiol. 2022; 12: 943545. DOI: 10.3389/fcimb.2022.943545.
4. Dohal M, Porvaznik I, Solovič I, Mokry J. Advancing tuberculosis management: the role of predictive, preventive, and personalized medicine. Front Microbiol. 2023; 14: 1225438. DOI: 10.3389/fmicb.2023.1225438.
5. Shabani S, Farnia P, Ghanavi J, Velayati AA, Farnia P. Pharmacogenetic Study of Drugs Affecting Mycobacterium tuberculosis. Int J Mycobacteriol. 2024; 13 (2): 206–12. DOI: 10.4103/ijmy.ijmy_106_24.
6. Aravindan PP. Host genetics and tuberculosis: Theory of genetic polymorphism and tuberculosis. Lung India. 2019; 36 (3): 244–52. DOI: 10.4103/lungindia.lungindia_146_15.
7. Abhimanyu Bose M, Giri A, Varma-Basil M. Comparative Genetic Association Analysis of Human Genetic Susceptibility to Pulmonary and Lymph Node Tuberculosis. Genes (Basel). 2023; 14 (1): 207. DOI: 10.3390/genes14010207.
8. Murugesan H, Sampath P, A VK, R S, Veerasamy A, Ranganathan U, et all. Association of CYP27B1 gene polymorphisms with pulmonary tuberculosis and vitamin D levels. Gene. 2024; 927: 148679. DOI: 10.1016/j.gene.2024.148679.
9. Samimi R, Hosseinpanahi A, Zaboli R, Peymani A, Rouhi S, Ahmadi Gooraji S, et all. Prevalence of Vitamin D Receptor Genes Polymorphisms in People with Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis. Med J Islam Repub Iran. 2024; 38: 32. DOI: 10.47176/mjiri.38.32.
10. Ferluga J, Yasmin H, Al-Ahdal MN, Bhakta S, Kishore U. Natural and trained innate immunity against Mycobacterium tuberculosis. Immunobiology. 2020; 225 (3): 151951. DOI: 10.1016/j.imbio.2020.151951.

11. Wang Y, Shi Q, Chen Q, Zhou X, Yuan H, Jia X, et all. Emerging advances in identifying signal transmission molecules involved in the interaction between Mycobacterium tuberculosis and the host. Front Cell Infect Microbiol. 2022; 12: 956311. DOI: 10.3389/fcimb.2022.956311.
12. Stutz MD, Clark MP, Doerflinger M, Pellegrini M. Mycobacterium tuberculosis: Rewiring host cell signaling to promote infection. J Leukoc Biol. 2018; 103 (2): 259–68. DOI: 10.1002/JLB.4MR0717-277R.
13. Gallant J, Heunis T, Beltran C, Schildermans K, Bruijns S, Mertens I, et all. PPE38-Secretion-Dependent Proteins of M. tuberculosis Alter NF-kB Signalling and Inflammatory Responses in Macrophages. Front Immunol. 2021; 12: 702359. DOI: 10.3389/fimmu.2021.702359.
14. Bullen CK, Singh AK, Krug S, Lun S, Thakur P, Srikrishna G, et all. MDA5 RNA-sensing pathway activation by Mycobacterium tuberculosis promotes innate immune subversion and pathogen survival. JCI Insight. 2023; 8 (20): e166242. DOI: 10.1172/jci.insight.166242.
15. Mitchell S, Vargas J, Hoffmann A. Signaling via the NFκB system. Wiley Interdiscip Rev Syst Biol Med. 2016; 8 (3): 227–41. DOI: 10.1002/wsbm.1331.
16. Moorthy AK, Savinova OV, Ho JQ, Wang VYa-F, Vu D, Ghosh G. The 20S proteasome processes NF-kappaB1 p105 into p50 in a translation-independent manner. EMBO J. 2006; 25 (9): 1945–56. DOI: 10.1038/sj.emboj.7601081.
17. Liu CW, Wu LS, Lin CJ, Wu HC, Liu KC, Lee SW. Association of tuberculosis risk with genetic polymorphisms of the immune checkpoint genes PDCD1, CTLA-4, and TIM3. PLoS One. 2024; 19 (5): e0303431. DOI: 10.1371/journal.pone.0303431.
18. Guo XL, Liu XC, Su GB, Zhou CY, Cui QT. Association of NF-κB1 gene polymorphisms with coronary artery disease in a Han Chinese population. Genet Mol Res. 2016; 15 (3). DOI: 10,4238/gmr,15038072.
19. Sarwar S, Tareen MU, Sabir M, Sultan A, Malik SA. NF-κB1 Intronic Region Polymorphisms as Risk Factor for Head and Neck Cancer in HPV-Infected Population from Pakistan. Curr Mol Med. 2022; 22 (1): 74–82. DOI: 10.2174/1566524021666210302144344.
20. Hua T, Qinsheng W, Xuxia W, Shuguang Z, Ming Q, Zhenxiong L, et all. Nuclear factor-kappa B1 is associated with gastric cancer in a Chinese population. Medicine (Baltimore). 2014; 93 (28): e279. DOI: 10.1097/MD.0000000000000279.
21. Chen LP, Cai PS, Liang HB. Association of the genetic polymorphisms of NFKB1 with susceptibility to ovarian cancer. Genet Mol Res. 2015; 14 (3): 8273–82. DOI: 10.4238/2015.July.27.15.