

PHTHISIOLOGY

MOLECULAR GENETIC STRUCTURE OF *MYCOBACTERIUM TUBERCULOSIS* IN KRASNOYARSK REGION

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RESUME

Introduction. Despite the improvement of the general epidemiological situation for tuberculosis (TB) in Krasnoyarsk region, the spread of multiple and pre-extensive drug resistance (MDR and pre-XDR) of the pathogen remains a serious problem that requires a comprehensive analysis of factors, including an assessment of the circulating population of *Mycobacterium tuberculosis*.

Objective. To assess the molecular genetic structure of *M. tuberculosis* strains in Krasnoyarsk region.

Materials and methods. A total of 400 strains were studied for 2024 using SNP- and MIRU-VNTR-24 typing.

Results. High levels of MDR (64.5 %), including pre-XDR (45.0 %) and XDR (1.5 %), were detected in the sample of *M. tuberculosis* strains. The dominance of L2 (Beijing genotype) was found in newly diagnosed cases (72.1 %) and previously treated patients (85.6 %). Non-Beijing strains belonged to the L4 genotypes (LAM, Ural, Haarlem and S). The most common Beijing subtypes were B0/W148 (49.5 %; 198/400) and Central Asian Russian (25.0 %; 99/400), they differed significantly in MDR levels (96.5 % and 36.4 %, respectively, by subtype; $p < 0.001$). Beijing B0/W148 strains had the highest levels of pre-XDR (71.7 %) and XDR (3.0 %). MDR among L4 strains (30.1 %) was significantly lower compared to Beijing (76.4 %) ($p < 0.001$). Strains from HIV-TB patients were more common with an MDR profile (74.4 %) than from patients without HIV infection (60.4 %) ($p = 0.008$) against the background of a higher presence of Beijing B0/W148 in the HIV-TB group (59.8 % versus 45.2 %; $p = 0.008$).

Conclusion. Beijing B0/W148 strains account for about half of the study sample and make a significant contribution to the pre-XDR (78.9 %) and XDR (100 %), which requires further monitoring and enhanced control of treatment effectiveness.

Key words: *Mycobacterium tuberculosis*, Beijing B0/W148, Beijing Central Asian Outbreak, multidrug resistance, tuberculosis, Krasnoyarsk region

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МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКАЯ ХАРАКТЕРИСТИКА ШТАММОВ *MYCOBACTERIUM TUBERCULOSIS* ИЗ КРАСНОЯРСКОГО КРАЯ

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РЕЗЮМЕ

Обоснование. Несмотря на улучшение общей эпидемиологической ситуации по туберкулезу (ТБ) в Красноярском крае, распространение множественной и пре-широкой лекарственной устойчивости (МЛУ и пре-ШЛУ) возбудителя остается серьезной проблемой, требующей комплексного анализа факторов, в том числе и оценки циркулирующей популяции *Mycobacterium tuberculosis*.

Цель исследования. Провести оценку молекулярно-генетической структуры штаммов *M. tuberculosis* из Красноярского края.

Материалы и методы. Изучено 400 штаммов за 2024 год методом SNP-типирования, для идентификации генотипов группы non-Beijing проведено MIRU-VNTR-24 типирование.

Результаты. В выборке штаммов *M. tuberculosis* выявлены высокие уровни МЛУ (64,5 %), в том числе пре-ШЛУ (45,0 %) и ШЛУ (1,5 %). Было обнаружено доминирование изолятов линии L2 (генотип Beijing) как среди впервые выявленных случаев (72,1 %) и ранее леченых пациентов (85,6 %). Штаммы non-Beijing относились к генотипам линии L4 (LAM, Ural, Haarlem и S). Наиболее распространёнными субтипами генотипа Beijing были B0/W148 (49,5 %; 198/400) и Central Asian Russian (25,0 %; 99/400), они значительно отличались по уровням МЛУ (96,5 % и 36,4 % соответственно по субтипам; $p < 0,001$). Штаммы Beijing B0/W148 имели самые высокие уровни пре-ШЛУ (71,7 %) и ШЛУ (3,0 %). МЛУ среди штаммов L4 (30,1 %) была значительно ниже по сравнению с Beijing (76,4 %) ($p < 0,001$). Штаммы больных с ВИЧ-ТБ встречались чаще с профилем МЛУ (74,4 %), чем у пациентов без ВИЧ-инфекции (60,4 %) ($p = 0,008$) на фоне более высокого присутствия Beijing B0/W148 в группе ВИЧ-ТБ (59,8 % против 45,2 %; $p = 0,008$).

Заключение. Штаммы Beijing B0/W148 составляют около половины исследуемой выборки и вносят значительный вклад в пре-ШЛУ (78,9 %) и ШЛУ (100 %), что требует дальнейшего наблюдения и усиления контроля эффективности лечения.

Ключевые слова: *Mycobacterium tuberculosis*, Beijing B0/W148, Beijing Central Asian Outbreak, множественная лекарственная устойчивость, туберкулез, Красноярский край

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INTRODUCTION

Despite progress in tuberculosis (TB) control and improvement in the epidemiological situation in Russia, the prevalence of multidrug-resistant (MDR) *Mycobacterium tuberculosis* continues to be a significant challenge that threatens the goals of the global strategy to reduce TB incidence and mortality [1]. Differences in TB trends across Russian regions [2] highlight the need for a thorough understanding of regional factors that influence infection transmission. Studies of the molecular genetic structure of *M. tuberculosis* allow for the identification of epidemiologically dangerous pathogen variants, which is crucial for the development of effective control and treatment strategies. Data on the genotypic structure of *M. tuberculosis* strains and their association with MDR also contributes to a better understanding of drug resistance development, improvement of diagnostic methods, and optimization of treatment [3]. This is particularly relevant to regions with a high burden of MDR-TB, such as the Krasnoyarsk region, where TB incidence is decreasing, but a large reservoir of infection persists, along with continued high risk of transmission and new cases [4]. Therefore, investigating the molecular genetic structure of *M. tuberculosis* will not only characterize the local pathogen population, but also identify patterns of MDR emergence and spread, which could inform more effective TB management strategies in regions still suffering from a significant TB burden. To date, however, no such studies have been conducted in the Siberian region in question, underscoring the urgency of this study.

AIM

To assess the molecular genetic structure of *M. tuberculosis* strains isolated from the Krasnoyarsk region.

MATERIALS AND METHODS

The study involved 400 clinical *M. tuberculosis* culture samples collected in 2024 from the Krasnoyarsk Regional Tuberculosis Dispensary. The samples represented a consecutive sample (one per patient) from the Löwenstein – Jensen medium. The study was approved by the Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems as part of state assignment No. 121022500179-0 (Protocol No. 2 dated February 18, 2020). Demographic data, including age, sex, district of residence, and information on clinical manifestations of the disease and prior treatment courses, was collected from TB patients. Culturing and drug susceptibility testing of *M. tuberculosis* to anti-TB drugs were conducted using standard methods in accordance with the clinical guidelines for “Tuberculosis in Adults” (2024) [5]. Drug resistance profiles were determined based on these guidelines. Monoresistance

is defined as resistance to a single anti-TB drug. Polyresistance refers to resistance to two or more anti-TB drugs, excluding simultaneous resistance to isoniazid and rifampicin. Multidrug resistance (MDR) is characterized by simultaneous resistance to both isoniazid and rifampicin, regardless of any resistance to other anti-TB drugs. Pre-extensively drug-resistant TB (pre-XDR) encompasses resistance to rifampicin with or without resistance to isoniazid, accompanied by resistance to at least one fluoroquinolone. Extensively drug-resistant TB (XDR) is defined as resistance to rifampicin with or without isoniazid resistance, combined with resistance to any fluoroquinolone and at least to linezolid or bedaquiline.

M. tuberculosis DNA was isolated using previously described protocols [6]. Genotyping of strains based on specific SNPs using real-time PCR was performed according to the following protocol: (I) differentiation of major genetic families, L2 (Beijing) and L4; (II) identification of Beijing sublineages, including ancient (Proto-Beijing) and modern (Modern); (III) and Beijing subtypes that are common in the Russian Federation [7], such as B0/W148, Central Asian Russian, Early Ancient 1, and Central Asian Outbreak (CAO)) (Table 1). Beijing strains that were not identified by these markers were classified as “other Beijing”. After identifying L4 strains, MIRU-VNTR typing was performed at 24 loci as previously described [6]. Statistical analysis and assessment of the reliability of the results were performed using normal distribution tests (Shapiro – Wilk and Kolmogorov – Smirnov tests). Quantitative data were presented as median (Me) and interquartile range [IQR]. Categorical data were described in terms of absolute numbers and percentages. Differences were assessed using the Fisher’s exact test and the χ^2 test, with appropriate degrees of freedom (df). Statistical significance was determined at a level of at least 95%.

RESULTS

A total of 400 clinical *M. tuberculosis* isolates were obtained from 233 newly diagnosed patients (199 samples prior to chemotherapy initiation and 34 during treatment), as well as 167 patients who had previously been treated, with no significant differences in age or sex between the groups (Table 2). One hundred seventeen samples (29.3 %) were obtained from HIV-infected patients. The clinical structure was represented by infiltrative (44.0 %), disseminated (48.5 %), fibro-cavernous (3.0 %) tuberculosis, and 12 cases (4.5 %) of other forms.

Regarding drug resistance distribution, susceptible strains accounted for 21.5 % (86 out of 400), while monoresistant and polyresistant strains accounted for 5.3 % (21 out of 400) and 8.7 % (35 out of 400), respectively. MDR was present in 64.5 % (258 out of 400), including pre-XDR in 45 % (180 out of 400) and XDR in 1.5 % (6 out of 400) of strains. As expected, considering

TABLE 1
PRIMER AND PROBE STRUCTURES DESIGNED FOR IDENTIFICATION

Genetic lineage	Genomic position / Mutation / Gene	Sequence 5'→3'
L2 [8]	811753/C→T/Rv0715	L2F; CCGGAGGTGTTGTAGATGA L2R; CAATACCCGGTTGCGGTC nL2; R6G/-ACGGGTGTCGCCTTT[G-LNA]TGG-/BHQ-1/ L2; /FAM/-ACGGGTGTCGCCTTT[A-LNA]TGG-/BHQ-1/
L2.1 (Proto-Beijing) [8]	4165481/G→C/Rv3721	L2.1F; TCGGCCACATGGACCGAA ; L2.1R; TGCCGAGCCGAAACACCA; nL2.1; /R6G /-CTCGAGGCCGGTGT[G-LNA]GG-/BHQ-1/ L2.1; / FAM /-CTCGAGGCCGGTGT[C-LNA]GG-/BHQ-1/
L2.1 Early ancient 1 [9]	2423040/A→G/Rv2161c	L2.1ea1F ; ACGGCGTGCTCCTGCTGA L2.1ea1R ; GTTCGTACCGACCTGAC nL2.1ea1; /R6G/-TGCGTCTTCTCCGGC[A-LNA]CAT-/BHQ-1/ L2.1ea1; /FAM/-TGCGTCTTCTCCGGC[G-LNA]CAT-/BHQ-1/
L2.2 (ancient and modern) [10]	195682/C→G/Rv0166	L2.2amF; CGATGACCGCGCTCTACA; L2.2amR; GTCAGCATGTTGCCGATTC; nL2.2am; /R6G/-GCGACGTCGGTTTCGT[C-LNA]GG-/BHQ-1/ L2.2am; /FAM/-GCGACGTCGGTTTCGT[G-LNA]GG-/BHQ-1/
L2.2 (modern) [10]	542514/C→G/Rv0452	L2.2mF; GATCTGCTTGCCAATCTGC; L2.2mR; CGCGTCGACGAGCGCTA; nL2.2m; /R6G/-CACCTCTGCTCGAGAT[G-LNA]CAG-/BHQ-1/ L2.2m; /FAM/-CACCTCTGCTCGAGAT[C-LNA]CAG-/BHQ-1/
L2.2.1 (Central Asia) [10]	1887060/C→G/Rv1663	L2.2.1caF; TTGCGGGCCAAGGTCGAT L2.2.1caR; GCTGCAGCATAATTGGCCT nL2.2.1ca; /R6G/-GAATTTGCATGAGCTCAC[C-LNA]CGG-/BHQ-1/ L2.2.1ca; / FAM/-GAATTTGCATGAGCTCAC[G-LNA]CGG-/BHQ-1/
L2.2.1 (CAO) [10]	1884305/T→G/Rv1662	L2.2.1caoF ; CGATGATGCGTAGAGAGCA L2.2.1caoR ; TCGACCCGACTGCCAAA nL2.2.1cao /R6G/-GGGCACCCGAGTGA[A-LNA]CAA-/BHQ-1/ L2.2.1cao /FAM/-GGGCACCCGAGTGA[C-LNA]CAA-/BHQ-1/
L2.2.1 B0/W148 [11]	1149144-1149145/GT→del/Rv1028c	kdpDF; CGGCACGATTTCGGCTAC kdpDR; CGTCGTCAATACCAAGAC nW148 R6G-ATCACCAGTGT[T-LNA]G[A-LNA]GC-/BHQ-1/ W148 FAM-ATCACCAGTGT[A-LNA]G[C-LNA]CC-/BHQ-1/
L4 [8]	2825466/G→A/Rv2509	L4F 5'-GCTCCGCGCGCCATCGT L4R 5'-GAAGTGATGCCTAGCTGCC L4 5'-FAM-CGTGGGTGCCTTTTACAA[G-LNA]AGG-BHQ1 nL4 5'-R6G-TCGTGGGTGCCTTTTACAA[A-LNA]AGG-BHQ1

the TB treatment history, there was a significant decrease in the proportion of drug-susceptible strains (3 % vs. 34.8 %; $p < 0.001$) and an increase in MDR (92.8 % vs. 44.6 %; $p < 0.001$), due to pre-XDR (75.4 % vs. 23.2 %; $p < 0.001$), in the previously treated group compared to the newly diagnosed cases (Fig. 1a). *M. tuberculosis* strains from the newly diagnosed patients, before and during TB treatment, differed in terms of the frequency of susceptibility (38.7 %; 77 out of 199 vs. 11.8 %; 4 out of 34, $p = 0.006$) and pre-XDR samples (20.6 %; 41 out of 199 vs. 41.2 %; 14 out of 34, $p = 0.006$). Among HIV-infected individuals, MDR was detected more frequently (74.4 %; 87 out of 117), compared to TB patients without HIV infection (60.4 %; 171 out of 283)

($p = 0.008$) (Fig. 1b). Primary MDR was present in 41.7 % (83 out of 199) of *M. tuberculosis* strains obtained from patients prior to treatment initiation, with half of these being pre-XDR samples (20.6 %; 41 out of 199). XDR was detected in a single newly diagnosed patient one year following treatment initiation.

The strain collection from the Krasnoyarsk region was represented by only two genetic families, L2 and L4. All strains belonging to the L2 family were of the modern Beijing lineage (L2.2 modern). The Beijing genotype was found in 77.8 % (311 out of 400) of *M. tuberculosis* strains, with a significantly higher proportion in the previously treated group (85.6 %; 143 out of 167) compared to the newly diagnosed

TABLE 2

GENERAL CHARACTERISTICS OF CLINICAL DATA OF TB PATIENTS AND *M. TUBERCULOSIS* STRAINS

Parameter	Newly diagnosed TB cases, <i>n</i> =233	Newly diagnosed TB ^a cases, <i>n</i> =167	<i>p</i>
Men, %	172; 73.8	136; 81.4	0.07
HIV-positive status ^c , %	72; 30.9	45; 26.9	0.39
	Median age at TB diagnosis (Me [IQR]), years		
Men	44[37–52]	47[40–54]	0.89
Women	43[35–50]	43[35–50]	0.77
	Clinical forms of pulmonary TB, %		
Infiltrative	110; 47.2	66; 39.5	0.01
Disseminated	109; 46.8	85; 50.9	
Fibro-cavernous	2; 0.9	10; 6.0	
Fibro-cavernous	12; 5.2	6; 3.6	
	Genotypic groups, %		
L2	168; 72.0	143; 85.6	<0.01
of which: Beijing B0/W148	80; 34.3	118; 70.7	<0.01
Beijing Central Asian Russian including:	80; 34.3	19; 11.3	<0.01
Beijing CAO	10; 4.3	3; 1.8	0.27
other Beijing	8; 3.4	6; 3.6	0.93
L4	65; 28.0	24; 14.4	<0.01
of which: LAM	27;11.6	9; 5.4	0.05
Ural	13;5.6	6; 3.6	0.49
Haarlem	6;2.7	3; 1.8	0.74
S	1;0.4	1; 0.6	0.81
other L4	18;7.7	5; 3.0	0.07

Note. ^a Previously treated cases included: tuberculosis relapse, treatment after failure of a chemotherapy course, treatment after interruption of a chemotherapy course, and transfer for treatment continuation.

group (72 %; 168 out of 233) ($p = 0.001$). Strains belonging to family L4 (89 out of 400) included LAM (9 %; 36 out of 400), Ural (4.8 %; 19 out of 400), Haarlem (2.3 %; 9 out of 400), and S (0.5 %; 2 out of 400), as well as 23 strains (5.8 %) that were not identified and designated as “other L4”. The most prevalent Beijing subtypes were B0/W148 (49.5 %; 198 out of 400) and Central Asian Russian (25 %; 99 out of 400). In the previously treated group, the proportion of strains with the B0/W148 genotype increased to 70.7 % (118 out of 167) compared to the newly diagnosed cases (34.3 %; 80 out of 233) (Table 2). In the group of strains collected prior to chemotherapy initiation, the frequency of B0/W148 was even lower (31.7 %; 63 out of 199) compared to those collected from newly diagnosed patients during treatment (50.0 %; 17 out of 34) ($p = 0.01$). Other Beijing subtypes analyzed did not differ significantly in frequency

between newly diagnosed cases prior to and after treatment initiation. The Central Asian Russian subtype was 35.7 % (71 out of 199) vs. 26.5 % (9 out of 34) ($p = 0.46$), and other Beijing was 3 % (6 out of 199) vs. 5.9 % (2 out of 34) ($p = 0.70$). The frequency of L4 did not significantly differ between newly diagnosed patients prior to and after treatment initiation – 29.6 % (59 out of 199) vs. 17.6 % (6 out of 34) ($p = 0.14$). In the previously treated patients, there was a significant reduction in the total number of L4 strains (16.8 %; 24 out of 143 vs. 27.9 %; 65 out of 233, $p = 0.001$) when compared to newly diagnosed patients. Analysis of individual L4 genotype distributions showed a significant decrease in LAM strains among previously treated patients (9 out of 167 vs. 27 out of 233 newly diagnosed patients; $p = 0.05$), but this was not the case for other variables due to their low frequency in the sample.

The distribution of genotypic groups according to drug resistance status showed its own characteristics (Fig. 2a). In total, among 258 MDR isolates, 235 were of the Beijing genotype and 23 were of L4. The MDR level differed significantly between the Beijing (75.6 %; 235 out of 311) and L4 genotypes (25.8 %; 23 out of 89) ($p < 0.001$). The highest MDR frequency was found in the Beijing B0/W148 subtype (96.5 %; 191 out of 198), including pre-XDR (71.7 %) and XDR (3 %).

In the Beijing Central Asian Russian strains, the MDR rate was 36.4 % (36 out of 99), of which the Beijing Central Asian Outbreak subtype (a subgroup of Beijing Central Asian Russian) carried MDR significantly more frequently (62 %) than other representatives of this subtype (13.3 %) ($p = 0.003$). L4 isolates were drug-sensitive in 59.6 % of cases (31 out of 52). MDR was represented by LAM (9, including 3 pre-XDR), Ural (6), S (2, including 1 pre-XDR), Haarlem (3 pre-XDR), and other L4 strains



FIG. 1. Drug resistance of *M. tuberculosis* strains of patients at different phases of TB treatment (a); with HIV-negative (1) and HIV-positive (2) status (b) in Krasnoyarsk region (abs.)

(3, including 1 pre-XDR). These strains were predominantly isolated from patients who had been previously treated (16 out of 23).

Primary MDR (based on drug susceptibility testing prior to TB treatment initiation) was most prevalent in Beijing B0/W148 (90.5 %; 57 out of 63) and Beijing Central Asian Outbreak (75 %; 6 out of 8) strains. Among other Beijing representatives, it did not exceed one-third of cases (Beijing Central Asian Russian – 17.5 %; 11

out of 63; “other Beijing” – 33.3 %; 2 out of 6), and among L4 – 11.7 % (7 out of 60). The two Beijing subtypes, B0/W148 and Central Asian Outbreak, together accounted for more than two-thirds (75.9 %; 63 out of 83) of the detected primary MDR, indicating their significant role in the development and spread of multidrug-resistant strains. Conversely, half of the L4 strains (54.2 %; 32 out of 59) were drug-sensitive, and only 7 strains (11.9 %) exhibited MDR (Ural – 2, LAM – 4, and S – 1).

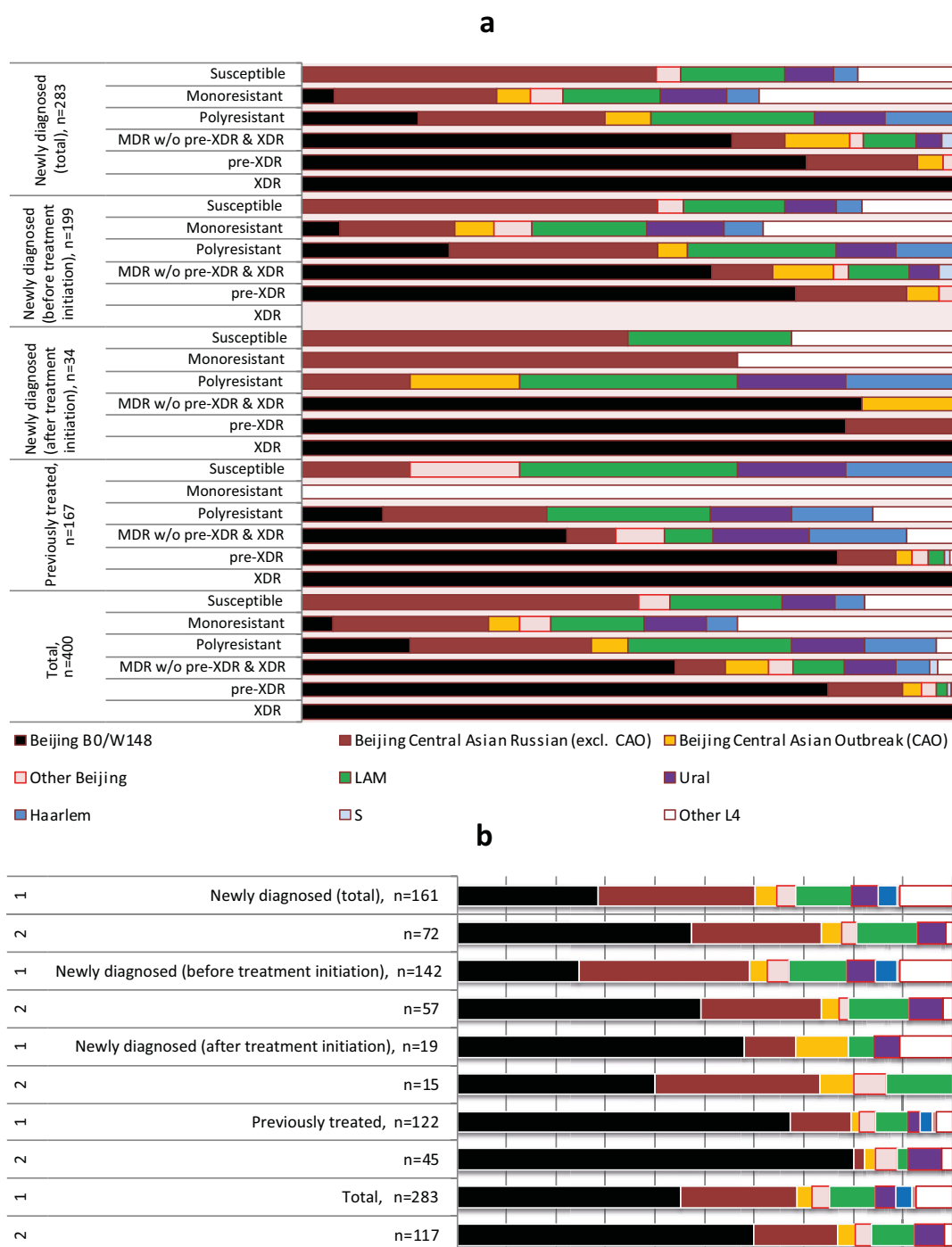


FIG. 2. Genotypic structure of *M. tuberculosis* strains of patients at different phases of TB treatment (**a**); with HIV-negative (1) and HIV-positive (2) status (**b**) in the Krasnoyarsk region (abs.)

The genotypic structure of *M. tuberculosis* from HIV-infected patients was characterized by a predominance of the Beijing B0/W148 genotype (59.8 %; 70 out of 117 compared to 45.2 %; 128 out of 283 in HIV-negative patients, $p = 0.008$). In the group of strains collected from HIV-positive patients prior to TB treatment initiation, the proportion of Beijing B0/W148 was significantly higher (49.1 %; 28 out of 57) compared to that from HIV-negative patients (24.6 %; 35 out of 142) ($p = 0.003$). Other cases from different stages and episodes of TB treatment demonstrated an increasing proportion of Beijing B0/W148, but there were no statistically significant differences between HIV-negative and HIV-positive cases. At the same time, comparing the distribution of L4 genotypes in subgroups of newly diagnosed and previously treated patients based on HIV status revealed no significant differences ($p > 0.05$ in all cases) (Fig. 2b).

Analyzing the resistance profile to anti-TB drugs among different genotypes/subtypes, it can be concluded that Beijing B0/W148 strains exhibit a higher frequency of MDR compared to other strains. This, in turn, contributes to the lower treatment effectiveness for patients infected with the B0/W148 strain compared to other genotypes. It is evident that the B0/W148 genotype is a significant contributor to unsatisfactory treatment outcomes for tuberculosis in the region. Among previously treated patients with pre-XDR strains, B0/W148 isolates accounted for 80.2 % of cases (101 out of 126).

DISCUSSION

Genotypic identification of *M. tuberculosis* strains, as an integral part of genomic epidemiological surveillance, is likely to become a key tool for TB monitoring and control in the near future [12, 13]. Our study is believed to be the first to analyze the diversity and distribution of *M. tuberculosis* genotypes within the Krasnoyarsk region. Analysis of data from 400 strains revealed that this sample represents a cross-section of the current *M. tuberculosis* population. The distribution of strain resistance profiles and frequency of cases among HIV-infected individuals is comparable to official statistics from the Krasnoyarsk region for 2023, where 67.5 % of patients had MDR-TB, and one-third (32.5 %) were infected with HIV [14]. The widespread increase in the prevalence of MDR strains and progression towards pre-XDR and XDR strains [15] is also evident in the analyzed *M. tuberculosis* sample. Our results suggest that MDR strains of *M. tuberculosis* are predominant in the studied region (64.5 %).

Analysis of isolates from all regions of the area revealed the predominance of genetic lineage L2 (Beijing), which is represented by its modern sublineage. This finding is consistent with previous studies conducted in the Siberian and Far Eastern Federal Districts [7, 16–18]. Isolates from the Krasnoyarsk region were primarily (74.3 %) composed of two subtypes. There was

an atypical prevalence of Beijing B0/W148 (49.5 %) over Beijing Central Asian Russian (25 %) among Siberian samples. A more significant difference in the distribution of these subtypes was observed in the group of patients who had previously received treatment. In this group, 70.7 % of strains were of the Beijing B0/W148 subtype and 11.3 % were of the Beijing Central Asian Russian subtype. One possible explanation for this difference may be related to the different frequencies and profiles of drug resistance among these subtypes. The Beijing B0/W148 strain is characterized by an extremely high level of MDR, which was also observed in this study. The MDR, which can affect treatment efficacy [5], was detected in 96.5 % of the Beijing B0/W148 strains, including pre-XDR strains (71.7 %). Moreover, the majority (68.7 %) of primary MDR cases were also attributed to Beijing B0/W148, which can be explained by the fact that this strain is the most prevalent with low-cost mutations and a rapidly expanding drug resistance profile [19–21]. In contrast, strains from the Beijing Central Asian Russian (excluding Beijing CAO) group showed lower MDR rates in our sample (overall 30.2 %, and 17.5 % for new TB cases), falling within the range reported for this subtype from other regions [14–16, 22–24].

When comparing the major Russian Beijing subtypes identified in our study to their frequencies in other Siberian and Far Eastern regions, a difference was observed in the proportion of Beijing B0/W148. In our study, this subtype accounted for 49.5 %, compared to 9.5 % in Buryatia [16], 32.6 % in the Kemerovo region [7], 34 % in Sakha (Yakutia) [24], 38.8 % in the Irkutsk region [16], but closer to data from three Western Siberian regions at 45.6 % [22, 23] (in collections from the current decade). Although most of these studies were population-based, some were based on strain collections from large TB hospitals primarily treating MDR-TB and may therefore have had selection bias. Therefore, caution should be exercised when interpreting the higher prevalence of Beijing B0/W148 in the Krasnoyarsk region.

The diversity of *M. tuberculosis* in the studied region includes not only the heterogeneous Beijing genotype, but also LAM, Ural, Haarlem, and S genotypes from the Euro-American lineage (L4). These genotypes were detected in 22.3 % of samples. This lineage is found in all Russian samples and has been described in studies with significant regional variability [25]. In our study, 9 % of isolates were from the LAM genotype. The proportion of the Haarlem genotype in studied Russian cohorts varies significantly [26], but does not exceed 5 % [7, 18, 24, 26]. According to our data, it was 2.3 % in the studied isolates. Overall, the results of our study are consistent with previous research, which has shown that L4 genotypes have lower MDR levels compared to the Beijing genotype [3, 19–21].

The methods used were not able to provide a detailed identification of certain clinical isolates, requiring their separate grouping. The “other Beijing” group likely includes minor representatives of this genotype that are

rarely found in Russian collections [8, 10]. Cross-border transmission of epidemiologically dangerous strains from other regions and countries, similar to that seen with Beijing CAO [7, 18], cannot be ruled out. Therefore, these atypical strains require further analysis using additional molecular epidemiology techniques, including whole-genome sequencing, in order to gain a better understanding of their epidemiology. These unique strains could indicate both recently imported TB cases and persistent sources of infection in the Krasnoyarsk region.

Due to the frequent association of elevated MDR-TB levels with HIV-infected individuals [27], we conducted a comparative analysis of the *M. tuberculosis* structure in this patient group, given that the Krasnoyarsk region has a higher burden of the HIV epidemic [12]. The study found that the predominance of Beijing B0/W148 strains was associated with both patient HIV status and *M. tuberculosis* MDR. On the other hand, there is no conclusive evidence that specific strains have an advantage in people living with HIV. However, in the group of newly diagnosed HIV-infected individuals, the Beijing B0/W148 genotype was seen almost twice as frequently (48.3 % vs. 24.6 % in HIV-negative individuals). Several studies have linked TB-HIV co-infection with specific, epidemiologically prevalent strains, suggesting recent infection in this patient population [28]. At the same time, the similarity in genotypic distributions during TB treatment among HIV-infected and HIV-negative individuals supports the overall increase in patients requiring repeated TB treatment courses, the selection for which is driven by MDR strains. Nevertheless, the extremely high detection rate of Beijing B0/W148 suggests its successful endemic spread, given that the studied region borders areas where fewer of these strains have been reported.

CONCLUSION

Therefore, the identification of a set of *M. tuberculosis* genotypes and subtypes that are characteristic of Siberia in the Krasnoyarsk region provides a basis for the successful future application of molecular genetic methods in a genomic epidemiological surveillance system.

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Conflicts of interest

The authors declare no conflicts of interest.

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