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Whole-genome sequencing of two clinical strains of *Mycobacterium tuberculosis* with phenotypic susceptibility to rifampicin but predicted resistance by Xpert MTB/RIF

Oleg B. Ogarkov[1]✉, Viacheslav V. Sinkov[1], Tuyana A. Kuhtina[2], Svetlana N. Zhdanova[1], Ilya G. Kondratov[1]

[1]Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russia;
[2]Irkutsk Regional Clinical Tuberculosis Hospital, Irkutsk, Russia

Abstract

Introduction. More than 40% of *Mycobacterium tuberculosis* strains are resistant to rifampicin (RIF) and isoniazid, the first-line drugs. The tuberculosis pathogen becomes resistant to RIF mainly due to mutations in the *rpoB* gene. **The aim** of the study was to search for the most probable compensatory mutations in the *rpoA*, *rpoB* and *rpoC* genes encoding α-, β- and β′-subunits of *M. tuberculosis* RNA polymerase.

Materials and methods. A cross-sectional analysis of phenotypic and genetic resistance to RIF among 2298 clinical strains of *M. tuberculosis* revealed 8 cases in which resistance as determined by the Xpert Ultra MTB/RIF test was not confirmed bacteriologically. In all cases, these were chronic multidrug-resistant or extensively drug-resistant *M. tuberculosis* patients in whom RIF was discontinued due to the detection of resistance to this drug in the isolated strains. Two strains were obtained for genotype testing, Sanger sequencing and whole-genome sequencing.

Results. Repeat Xpert Ultra MTB/RIF test, Sanger sequencing and whole genome sequencing revealed the presence of a single *S450L* mutation in the *rpoB* gene with phenotypic sensitivity in both strains. Phylogenetic analysis revealed that both genomes belonged to the Beijing B0/W148 genotype. The strains were characterized by a higher growth rate than the other isolates. Two potential compensatory mutations *V483G* and *H748P* in the *groC* gene were identified in the absence of other significant changes in the *rpoA* and *rpoB* genes.

Conclusion. It is suggested that the phenomenon of discrepancy between results of bacteriological and molecular genetic tests is associated with the acquisition of compensatory mutations in the *groC* gene during RIF treatment of Beijing B0/W148 strains, and the identified mutations affect the conformation of the β'-subunit, restoring the transcription efficiency of affected by the major *S450L* mutation.

Keywords: *Mycobacterium tuberculosis, Beijing B0/W148, rpoA, rpoB, rpoC, compensatory fitness mutations*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems (protocol No. 2, February 18, 2020).

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Оригинальное исследование
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Полногеномное секвенирование двух клинических штаммов *Mycobacterium tuberculosis* с фенотипической чувствительностью к рифампицину при прогнозируемой Xpert MTB/RIF устойчивости

Огарков О.Б.[1]✉, Синьков В.В.[1], Кухтина Т.А.[2], Жданова С.Н.[1], Кондратов И.Г.[1]

[1]Научный центр проблем здоровья семьи и репродукции человека, Иркутск, Россия;
[2]Иркутская областная клиническая туберкулёзная больница, Иркутск, Россия

Аннотация

Введение. Более 40% штаммов *Mycobacterium tuberculosis* устойчивы к рифампицину (RIF) и изониазиду — препаратам первого ряда. Возбудитель туберкулёза приобретает устойчивость к RIF главным образом за счёт мутаций в гене *rpoB*.

Цель исследования — поиск наиболее вероятных компенсаторных мутаций в генах *rpoA*, *rpoB* и *rpoC*, кодирующих α-, β- и β′-субъединицы РНК-полимеразы *M. tuberculosis*.

Материалы и методы. Перекрёстный анализ фенотипической и генетической устойчивости к RIF среди 2298 клинических штаммов *M. tuberculosis* выявил 8 случаев, когда устойчивость, определённая тестом Xpert Ultra MTB/RIF, не подтверждалась бактериологическим методом. Во всех случаях это были хронические больные туберкулёзом с множественной или широкой лекарственной устойчивостью, у которых был отменён RIF по причине обнаружения устойчивости к этому препарату у выделенного штамма. Для исследования генотипа, секвенирования по Сэнгеру и полногеномного секвенирования были получены 2 штамма.

Результаты. Повторный тест Xpert Ultra MTB/RIF, секвенирование по Сэнгеру и полногеномное секвенирование выявили наличие единственной мутации *S450L* в гене *rpoB* при наличии фенотипической чувствительности у обоих штаммов. При филогенетическом анализе выяснено, что оба генома принадлежали к генотипу Beijing B0/W148. Штаммы отличались более высокой скоростью роста, чем другие изоляты. Выявлены две потенциальные компенсаторные мутации *V483G* и *H748P* в гене *rpoC* при отсутствии других значимых изменений в генах *rpoA* и *rpoB*.

Заключение. Высказано предположение, что феномен расхождения бактериологических и молекулярно-генетических результатов связан с приобретением в процессе лечения RIF штаммами Beijing B0/W148 компенсаторных мутаций в гене *rpoC,* а выявленные мутации влияют на конформацию β'-субъединицы, восстанавливая эффективность транскрипции, вызванную мажорной мутацией *S450L*.

Ключевые слова: *Mycobacterium tuberculosis, Beijing B0/W148, rpoA, rpoB, rpoC, компенсаторные фитнес-мутации*

Этическое утверждение. Исследование проводилось при добровольном информированном письменном согласии пациентов. Протокол исследования одобрен Этическим комитетом Научного центра проблем здоровья семьи и репродукции человека (протокол № 2 от 18.02.2020).

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Introduction

Multidrug-resistant (MDR) tuberculosis develops in patients treated with rifampicin (RIF) and isoniazid, the most effective anti-tuberculosis drugs, also called first-line drugs. Globally, more than 40% of *Mycobacterium tuberculosis* (MBT) strains become MDR or at least RIF resistant[1]. RIF binds close to the active site in the β subunit (*rpoB* gene) of the bacterial RNA polymerase enzyme [1] in the RIF resistance determining region (RRDR). The binding of RIF to RRDR sterically impedes the elongation of newly synthesized RNA, which ultimately blocks protein synthesis by the microbial cell. MBT has no known mechanism of horizontal gene transfer; RIF resistance mainly arises from chromosomal mutations within the RRDR [2]. The impact of RIF resistance is significant and is often reflected in MBT in terms of a reduced growth rate and the decreased competitiveness of RIF-resistant mutants compared to ancestral susceptible forms [3]. However, it has been observed that MBT forms with low adaptability can partially or completely restore phenotypic properties over time, in particular, increase growth rate due to the appearance of so-called compensatory mutations [4]. The identification of compensatory mutations is very difficult and depends on the methodology used.

Molecular epidemiologic studies of Beijing B0/W148 genomes belonging to the L2 genetic lineage [5, 6] indicate that more than 95% of clinical strains of this genotype contain mutations in RRDR and is one of the key factors in the epidemic spread of primary drug-resistant tuberculosis with RIF in Russia [6, 7]. Almost 90% of these strains carry the most common amino acid substitution *S450L* (nucleotide substitution C→T in 761155 position of the genome) [6], and it was noted that the genetic cost of this substitution in the RRDR of the *rpoB* gene for mutants is the lowest [2].

The aim of the study: to search for the most probable compensatory mutations in *rpoA*, *rpoB* and *rpoC* genes encoding α-, β- and β′-subunits of RNA polymerase of MBT, causing the phenomenon of phenotypic sensitivity to RIF.

Materials and methods

A retrospective cross-analysis of Xpert Ultra MTB/RIF and phenotypic bacteriological results for 2022 obtained in the laboratory department of the Irkutsk Regional Tuberculosis Hospital was performed. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems (protocol No. 2, February 18, 2020).

2298 samples were examined, of which 529 were sensitive to RIF, while 363 were resistant; sensitivity to RIF using Xpert Ultra MTB/RIF was not determined in 90 samples. The main reason for the lack of positive PCR results is the low concentration of the target substance when Xpert Ultra MTB/RIF was performed. In 8 cases, resistance determined by Xpert Ultra test in sputum was not confirmed by bacteriologic methods. All cases were chronic MDR or extensively drug-resistant TB patients who had been discontinued from RIF due to the presence or acquisition of resistance to the drug in a previously isolated strain.

Two strains were obtained for repeat Xpert Ultra MTB/RIF, genotype testing, Sanger sequencing, and whole genome sequencing (WGS) (**Table 1**). DNA isolation, library preparation, WGS and bioinformatics, phylogenetic and statistical analyses were performed as described previously [6]. Primary nucleotide sequences were deposited in the NCBI bioproject PRJNA1215569. Resistance to anti-tuberculosis drugs was determined on a BD Bactec bacteriological analyzer (Becton Dickinson) and on Löwenstein–Jensen medium according to the Order of the Ministry of Health of Russia from 21.03.2003 No. 109 (ed. 05.06.2017). Genetic heteroresistance in individual genome positions was determined by the number of alternative short reads during WGS as described previously [8].

Amino acid substitution probability in detected mutations was investigated using two approaches: PAM matrices (Point Accepted Mutation matrices) — PAM30 and PAM250 [9] and SIFT (Sorting Intolerant From Tolerant) algorithm for predicting amino acid substitutions affecting protein function [10].

Results

Repeated Xpert Ultra MTB/RIF test, Sanger sequencing and WGS revealed the presence of a single *S450L* mutation in the *rpoB* gene with phenotypic sensitivity in both strains. Phylogenetic analysis revealed that both genomes belonged to the Beijing B0/W148 genotype. The strains were characterized by a higher growth rate than the other isolates. After elucidation of the genotypic affiliation of the studied strains to the Beijing B0/W148 genotype, 513 complete B0/W148 genomes from the Short Read Archive (NCBI) online service published between 1995 and 2020 for strains from Northern Eurasia were used as reference genomes.

A total of 34 missense mutations in the *rpoB* gene were detected for this genome set [11]. Level 1 missense mutations were in 9 variants; level 2 — in 2; and level 3 — in 20 (**Table 2**). Furthermore, 3 mutations were found in the *rpoB* gene that were absent in the WHO catalog description: *E82G, I90M, R219G*. 45 missense mutations were detected in the *rpoC* gene, all of them belonged to mutations of level 2 significance (Table 1). Only 5 missense mutations were detected in

[1] WHO. Global tuberculosis report 2024. Geneva: World Health Organization; 2024. URL: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024

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Table 1. Characterization of *M. tuberculosis* isolates

No.	Patient record group	HIV	Drug resistance	Genotype
Irk1	Ineffective course of tuberculosis treatment	+	To isoniazid, RIF*, capreomycin, pyrazinamide, prothianamide, bedaquiline, linezolid	Beijing B0/W148
Irk2	Tuberculosis relapse	_	To isoniazid, RIF*, ethambutol, capreomycin, pyrazinamide, levofloxacin, bedaquiline, linezolid	Beijing B0/W148

Note. *Based on the Xpert Ultra MTB/RIF results, but not the microbiological test.

Table 2. Presence of mutations of the 1st, 2nd and 3rd levels of significance [11]

Gene	Mutations of level 1 significance	Mutations of level 2 significance	Mutation of level 3 significance
rpoB	*L430P; Q432P; D435V; D435Y; H445D; H445L; S450L; L452P; H723D*	T427A; S431R	*P45S; G79S; V305I; G376V; T400A; P454S; I491M; V496A; L554P; Y564H; S672Y; L731P; V800A; R827C; R827L; H835P; G836S; K891E; Q980K; R1008C*
rpoC	None	*E187G; G311R; G332S; G433C; P434A; P434L; K445R; L449R; F452C; V483G; D485N; E488Q; I491V; I491T; L507V; L516P; V517L; G519S; A521D; Q523E; H525N; L527V; L558L; Y586H; Q693H; N698H; N698S; N698K; E702K; D735N; D735E; D747A; H748P; E757A; R770H; T812I; S838C; D943N; D943G; M983I; P1040S; P1040R; I1046M; V1147A; K1152N*	None
rpoA	None	*G31C; R153R; T187P; V183A; R182Q*	None

the *rpoA* gene, also belonging to mutations of the 2nd level of significance (Table 1).

The following combinations of mutations were detected in the 2 strains studied: in the Irk1 strain, *rpoB — S450L*; *rpoC — H748P*; in the Irk2 strain, *rpoB — S450L*; *rpoC — V483G*. Interestingly, a similar case of drug sensitivity in the presence of a combination of *rpoB — S450L*; *rpoC — V483G* mutations was described in 2024 in the strain of Euro-American lineage (4.2.2.2.2.1) [12]. However, the authors suggested that the result obtained was a laboratory error due to the use of inflated concentrations of RIF during testing. The *H748P* mutation in the *rpoC* gene is not considered compensatory in the final version of the article, although it was described as such in the original manuscript by the same authors[2] [12].

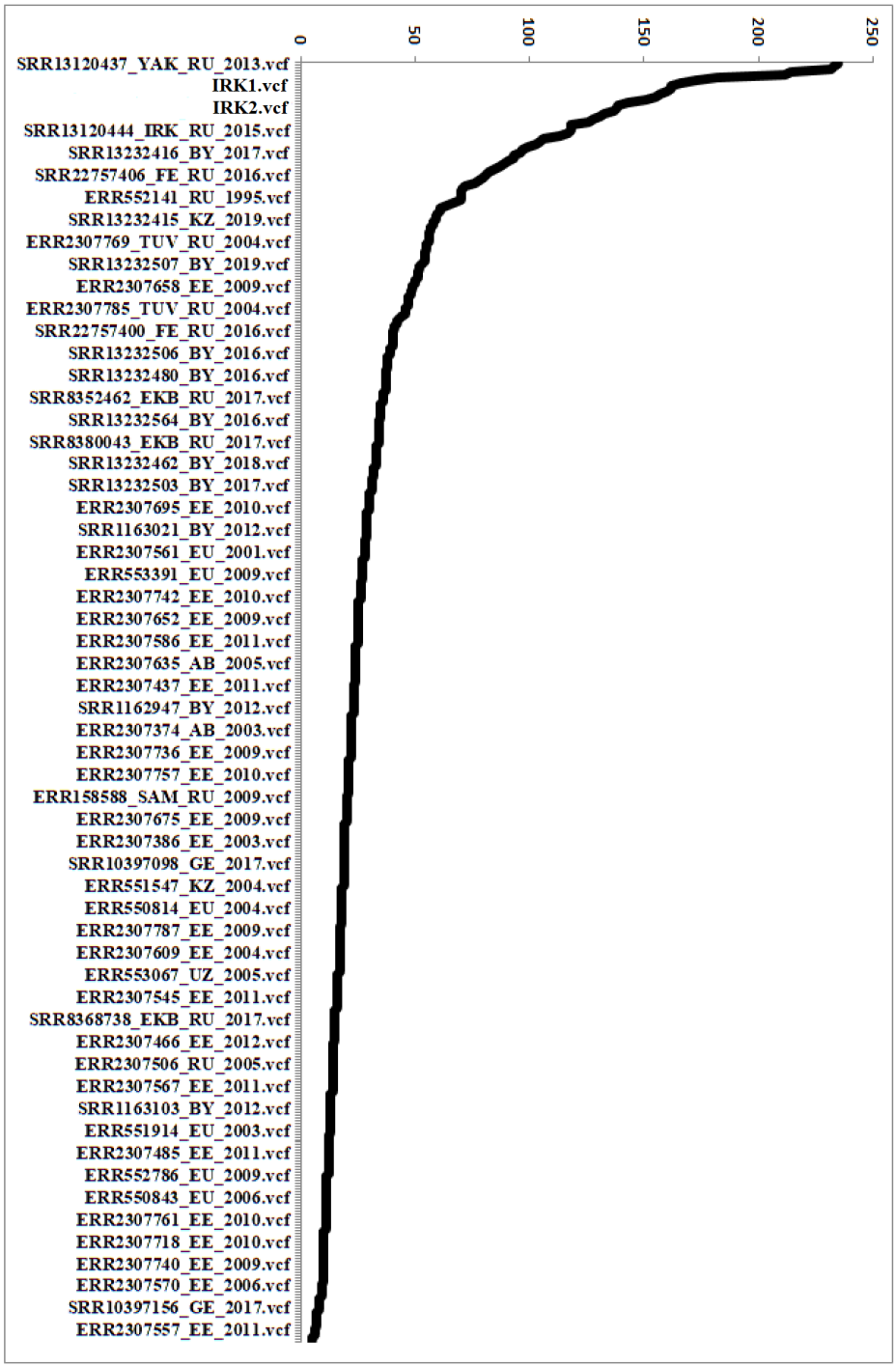
The Irk1 and Irk2 genomes tested occupy the highest positions in terms of heteroresistance values (214 and 212) at position 761155 (*rpoB* nucleotide substitution — *S450L*; **Figure**). The highest heteroresistance (235), expressed as the presence of alternative short reads at WGS at the position under study, was observed in only one genome from Yakutia isolated in 2013. We investigated the probability of occurrence of detected amino acid substitutions in the *rpoC* gene using two approaches: PAM (Point Accepted Mutation) matrices — PAM30 and PAM250 [9] and the SIFT (Sorting Intolerant From Tolerant) algorithm [10]. To predict amino acid substitutions affecting protein function, PAM matrices were used to estimate the probability of amino acid substitutions during evolution [9]. The SIFT algorithm was used to determine whether amino acid substitutions affect protein function using evolutionary information and homologous sequence alignments [10].

A SIFT value of 0.00 was obtained for *V483G* (IRK2) indicating low tolerance, which may indicate a significant effect of this substitution on the function of the β'-subunit of RNA polymerase. However, the moderate values of PAM10 (0) and PAM250 (–1) suggest that this mutation does not lead to a complete loss of function and may stabilize the RNA polymerase complex, compensating for the destabilization caused by *S450L*. In turn, the *H748P* (IRK1) mutation with SIFT 0.05 and PAM250 (-3) shows moderate tolerance, indicating a slightly negative effect on the protein. It can be hypothesized that the above mutations affect the conformation of the β'-subunit, restoring the transcription efficiency caused by the major *S450L* mutation, where *V483G* may play a more pronounced compensatory role.

Discussion

The phenomenon of the emerging sensitivity in strains has been observed earlier in two international projects [8] when the minimum inhibitory concentration of MBT strains from the same patient was determined sequentially. It has been repeatedly observed (data not published) that withdrawal of certain anti-tuberculosis drugs, including RIF, leads to a decrease in the minimum inhibitory concentration down to the values of the borderline sensitivity defined by the manufacturer of the Sensititre MYCOTB kits (TREK Diagnostics). The main hypothesis that could explain this phenome-

[2] URL: https://www.biorxiv.org/content/10.1101/2022.02.22.481565v1.full.pdf



Heteroresistance assessment of a sample of 515 genomes at position 761155 (*rpoB* nucleotide substitution — *S450L*).

non was the assumption that antibiotic-sensitive clones begin to multiply more actively in the pathogen population after anti-tuberculosis drug withdrawal from the persister pool [8]. The Beijing B0/W148 genotype carries resistance to RIF in more than 95% of cases upon primary infection, i.e. it has already acquired all the compensatory mutations necessary for survival outside the organism in the process of evolution. The key question of the study is what fitness mutations lead to the emergence of the sensitivity phenomenon in the presence of the major *rpoB* mutation — *S450L*. The detected missense mutations *V483G* and *H748P* in the *groC* gene in the absence of other significant changes in the *rpoA* and *rpoB* genes may indicate that the withdrawal of certain anti-tuberculosis drugs may lead to the emergence of compensatory fitness mutations, manifested as sensitivity to anti-tuberculosis drugs in the presence of the major substitution, identified in PCR test. It can also be assumed that against the background of high heterogeneity on the *rpoB* gene in the pathogen population,

the described combination of *S450L* mutations together with *V483G/H748P* undergoes stabilizing selection only during RIF treatment. The abolition of RIF leads to a gradual return of the pathogen population to a more stable model in which clones containing *V483G/H748P* and other fitness mutations are eliminated. The source of this is persisters harboring *S450L* but lacking mutations in the *rpoC* gene.

Conclusion

It can be assumed that the phenomenon of discrepancy between results of bacteriological and molecular genetic tests is associated with the acquisition of compensatory mutations in the *groC* gene during RIF treatment of Beijing B0/W148 strains. The identified mutations affect the conformation of the β'-subunit, restoring the transcription efficiency caused by the major *S450L* mutation. Further studies of the phenomenon of decreased resistance to anti-tuberculosis drugs in the tuberculosis pathogen after its withdrawal are necessary.

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Information about the authors

Oleg B. Ogarkov✉ — Dr. Sci. (Med.), Director, Institute of Epidemiology and Microbiology, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russia, obogarkov@mail.ru, https://orcid.org/0000-0002-3168-1983

Viacheslav V. Sinkov — Cand. Sci. (Med.), senior researcher, Laboratory of epidemiologically and socially significant infections, Institute of Epidemiology and Microbiology, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russia, vsinkov@gmail.com, https://orcid.org/0000-0003-3396-9590

Tatyana A. Kuhtina — bacteriologist, Head, Bacteriological laboratory, Irkutsk Regional Clinical Tuberculosis Hospital, Irkutsk, Russia, tuyanatsta@mail.ru

Svetlana N. Zhdanova — Dr. Sci. (Med.), leading researcher, Laboratory of epidemiologically and socially significant infections, Institute of Epidemiology and Microbiology, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russia, svetnii@mail.ru, https://orcid.org/0000-0001-7160-9700

Ilya G. Kondratov — Cand. Sci. (Biol.), researcher, Laboratory of epidemiologically and socially significant infections, Institute of Epidemiology and Microbiology, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russia, kondratovig@mail.ru, https://orcid.org/0000-0002-2631-4724

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Информация об авторах

Огарков Олег Борисович✉ — д-р мед. наук, директор Института эпидемиологии и микробиологии Научного центра проблем здоровья семьи и репродукции человека, Иркутск, Россия, obogarkov@mail.ru, https://orcid.org/0000-0002-3168-1983

Синьков Вячеслав Владимирович — канд. мед. наук, с. н. с. лаб. эпидемиологически и социально значимых инфекций Института эпидемиологии и микробиологии Научного центра проблем здоровья семьи и репродукции человека, Иркутск, Россия, vsinkov@gmail.com, https://orcid.org/0000-0003-3396-9590

Кухтина Туяна Анандуевна — врач-бактериолог, зав. бактериологической лабораторией Иркутской областной клинической туберкулёзной больницы, Иркутск, Россия, tuyanatsta@mail.ru

Жданова Светлана Николаевна — д-р мед. наук, в. н. с. лаб. эпидемиологически и социально значимых инфекций Института эпидемиологии и микробиологии Научного центра проблем здоровья семьи и репродукции человека, Иркутск, Россия, svetnii@mail.ru, https://orcid.org/0000-0001-7160-9700

Кондратов Илья Геннадьевич — канд. биол. наук, н. с. лаб. эпидемиологически и социально значимых инфекций Института эпидемиологии и микробиологии Научного центра проблем здоровья семьи и репродукции человека, Иркутск, Россия, kondratovig@mail.ru, https://orcid.org/0000-0002-2631-4724

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