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Investigating the Mutations in *atpE* and *Rv0678* Genes in *Mycobacterium Tuberculosis* Clinical Isolates

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ABSTRACT

Introduction: Tuberculosis (TB) caused by the bacterium *Mycobacterium tuberculosis* remains a critical global public health concern due to the high morbidity and mortality rates. Mutation in *atpE* and *Rv0678* genes contributes to drug resistance in *M. tuberculosis.* This study investigates the antibiotic resistance patterns and mutations in *atpE* and *Rv0678* genes in 22 *M. tuberculosis* clinical isolates. **Methods:** Drug susceptibility testing (DST) for rifampin, isoniazid, streptomycin, capreomycin, ofloxacin, kanamycin, and ethambutol was conducted using the proportional method. This was followed by determining the minimum inhibitory concentration (MIC) for bedaquiline (BDQ) via the microplate Alamar blue assay (MABA). Genomic regions encompassing *atpE* and *Rv0678* genes were amplified and sequenced for mutation analysis. Data analysis was performed using SPSS software to interpret mutation patterns concerning drug susceptibility profiles. **Results:** Of 22 isolates, 5 (27.8%) were extensively drug-resistant tuberculosis (XDR-TB), and 13 (72.2%) were multi-drug resistant tuberculosis (MDR-TB). Resistance rates to kanamycin, ofloxacin, capreomycin, and streptomycin were 40.6%, 46.3%, 85%, and 74.6%, respectively. Additionally, phenotypic resistance to bedaquiline was observed in 12 (54.5%) isolates. Sequencing revealed no resistance-conferring mutations in the *atpE* or *Rv0678* genes among the isolates. **Conclusion:** Our findings showed substantial resistance to first- and second-line drugs in *M. tuberculosis* clinical isolates. This highlights the necessity for ongoing, comprehensive studies to elucidate the evolving drug resistance patterns and understand the underlying mechanisms in clinical isolates.

INTRODUCTION

Tuberculosis (TB) remains a pervasive global health challenge, causing substantial morbidity and mortality [1, 2]. According to The World Health Organization (WHO) report, about 10.6 million people are diagnosed with TB annually, and 1.6 million die from this infection, of which 87.5% belong to HIV-negative individuals and 11.7% to HIV-positive patients [3]. Geographically, the majority of TB cases in 2022 occurred in South-East Asia (45%), Africa (23%), and the Western Pacific (18%), followed by the Eastern Mediterranean (8.1%), the Americas (2.9%) and Europe (2.2%) [3].

The growing drug-resistant TB, especially MDR-TB and XDR-TB, poses a formidable obstacle to global TB control efforts. MDR-TB is characterized by resistance to at least isoniazid and rifampicin, the two main first-line anti-TB medications. XDR-TB involves resistance to isoniazid, rifampin, fluoroquinolones, and at least one of the three injectable second-line drugs, including but not limited to bedaquiline (BDQ) or linezolid [4]. Inappropriate treatment of drug-resistant TB, such as wrong drug choice or inadequate treatment duration, often results in higher treatment costs and increased side effects [5].

BDQ is an oral diarylquinoline medication with antituberculosis activity. This medication has been approved by the US Food and Drug Administration

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(FDA) specifically for treating multidrug-resistant tuberculosis. The FDA's approval, which marked the first new TB drug in 40 years, is notable for the unique BDQ mechanism of action— the inhibition of mycobacterial ATP synthase [6]. BDQ is part of the combination therapy, particularly when treatment options are limited, and has been shown to reduce treatment durations [7]. It is effective against a variety of pathogenic mycobacteria, including *M. tuberculosis*, *Mycobacterium leprae*, and *Mycobacterium Avium* complex, as well as against the non-pathogenic *Mycobacterium smegmatis*, commonly used as a model organism in research [8]. The antimycobacterial mechanism of BDQ is thought to be related to its cationic amphipathic properties, predominately through its inhibitory effects on the mycobacterial ATP synthase [9].

While BDQ treatment is aimed at preventing the emergence of resistance and tuberculosis recurrence, resistance and relapse may still occur [10]. Notably, increased BDQ resistance among *M. tuberculosis* isolates has been reported, even in settings where BDQ is not widely prescribed [11]. Therefore, the WHO has recommended careful surveillance and investigation of BDQ resistance patterns. Specific mutations in the genes that regulate target sites of antibiotics are among this bacterium's most substantial resistance mechanisms [12]. The *atpE* gene codes for the F1/F0-ATPase synthase, an enzyme complex essential for cellular energy production in *M. tuberculosis*. Mutations in this gene have been identified in approximately 30% of BDQ-resistant clinical isolates. Resistance due to mutations in the *atpE* gene is primarily associated with alterations in the C subunit of the enzyme [13]. Another gene associated with BDQ resistance, Rv0678, regulates the expression of the MmpS5-MmpL5 efflux pump [14]. Mutations in both *atpE* and *Rv0678* genes are associated with BDQ resistance [15].

Numerous mechanisms that contribute to developing resistance to antituberculosis drugs have been identified in mycobacteria, specifically *M. tuberculosis*. These mechanisms include various cellular adaptations, such as mutations in target genes, reduced cell wall permeability to anti-tubercular drugs, and the active expulsion of drugs through efflux pumps [16]. Despite the significance of the *atpE* and *Rv0678* genes in conferring drug resistance, limited studies from Iran provide a detailed analysis of mutations and associated resistance patterns in *M. tuberculosis* clinical isolates. This study investigated antibiotic resistance patterns and mutations in the *atpE* and *Rv0678* genes in *M. tuberculosis* clinical isolates from Iran.

MATERIAL AND METHODS

Bacterial strains. We investigated 22 *M. tuberculosis* clinical isolates collected by the Department of Mycobacteriology and Pulmonary Research at the Pasteur Institute of Iran from 2016 to 2021. Written informed consent was obtained from all individual participants included in the study. The Ethics Committee of the Pasteur Institute of Iran approved the study under the code IR.PII.REC.1399.055.

Drug susceptibility testing (DST). DST was conducted per the World Health Organization (WHO) guidelines using the proportional method with the following antibiotics at specified concentrations: rifampicin (RIF 40.0 µg/mL), isoniazid (INH; 0.2 µg/mL), kanamycin (KAN; 20 µg/mL), ofloxacin (OFX; 4 µg/mL), capreomycin (CAP; 20 µg/mL), streptomycin (STR; 4 µg/mL) and ethambutol (EMB; 2.0 µg/mL). Resistance was determined by bacterial growth equal to or exceeding 1% compared to growth in a drug-free Löwenstein-Jensen (LJ) medium used as a negative control for background growth. The M. tuberculosis H37Rv strain (ATCC 27294) was employed for DST quality control. DST results were recorded after 28 and 42 days of incubation.

Determination of BDQ MIC. A microplate Alamar blue assay (MABA) was performed to determine the BDQ MIC values for all 22 clinical isolates. Alamar Blue reagent was obtained from AbD Serotec (Oxford, UK), and BDQ was sourced from Sigma-Aldrich (St. Louis, MO, USA). The MIC was defined as the lowest BDQ concentration that prevented the colorimetric change in the assay. Isolates were considered resistant with BDQ MIC values ≥ 0.25 µg/mL. The initial BDQ stock solution was prepared in dimethyl sulfoxide (DMSO) and stored as the manufacturer recommended. Fresh bacterial clones were picked from the Löwenstein–Jenson medium for the assay. The turbidity of each bacterial suspension was adjusted to a 1.0 McFarland standard (3×10^8 CFU/mL). The suspensions were then diluted with Middlebrook 7H9 medium (Sigma-Aldrich, St. Louis, MO, USA), supplemented with 10% albumin dextrose catalase (Becton Dickinson, Oxford, UK). Amounts of 100 µl of the inoculum were added into wells of a 96-well plate containing the respective concentrations of BDQ. Each microplate was designed with a positive control well containing only the H37Rv strain suspension to ensure typical growth. The negative control well included the medium and antibiotic without bacteria. A color change in the wells was indicative of bacterial growth. Each test was conducted in duplicate for every isolate to ensure reproducibility and to calculate an accurate average MIC.

DNA extraction. The isolates were cultured in Lowenstein-Jensen (LJ) slants. Visible colonies from isolates were harvested using a sterile loop, transferred into 500 µl of Tris-EDTA buffer (pH 8.0), and heated at 80 °C for 20 min. Lysozyme was added to samples in a final 1 mg/mL concentration, followed by incubation at 37 °C for 2 h. Then, 10% sodium dodecyl sulfate (to achieve a final concentration of 1.1%) and proteinase K (to a final concentration of 0.2 mg/mL) were added, and the tubes were incubated at 65°C for an additional 20 min. Amounts of 100 µl of NaCl (5M) were added to the mixtures to achieve the desired ionic strength. Then 100 µl of a

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mixture of N-acetyl-N, N, N, -trimethylammonium bromide (CTAB), and NaCl was added to tubes, vortexed, and incubated at 65 °C for 10 min. Amounts of 750 µl of chloroform/isoamyl alcohol (24:1) were added to each tube and centrifuged at the corresponding g-force for 13,000 rcf for 5 min at room temperature. Genomic DNA was precipitated from the aqueous phase using ethanol, and the resulting DNA pellet was resuspended in 30 µl of nuclease-free water. The purified genomic DNA was immediately stored at -20 °C until further molecular analysis was performed [17].

PCR amplification and mutation detection. The *atpE* and *Rv0678* genes were amplified using specific primers listed in Table 1 [18]. The 25 µL PCR reactions included 12.5 µL master mix (SinaClon Co., Iran), 1µL (10 pmol/µl) of each primer, 2 µL of DNA template, and deionized water to the final volume. The PCR amplification involved an initial denaturation at 94 °C for 5 min, followed by 30 cycles of denaturation at 94 °C for 30 s, annealing for 30 s, and extension at 72 °C for 30 s, and a final extension at 72 °C for 10 min. Bidirectional sequencing of the PCR products was performed by MacroGen Company (South Korea).

Table 1. The primers used in PCR amplification of *Rv0678* and *atpE* genes of *M. tuberculosis*

Gene	Primer	Nucleotide sequence	Tm (°C)	Amplicon size (bp)
Rv0678	F	5' -GCTTGAGAGTTCCAATCAT-3'	56 °C	674
	R	5' -CGCATCAACAAGGAGTGA-3'		
atpE	F	5' -CCAAGCGATGGAGCTCGAAGAGG-3'	58 °C	439
	R	5' -GGGAATGAGGAAGTTGCTGGACTCG-3'		

Statistical analysis. Data was analyzed using the statistical package for the social sciences (SPSS) (version 20). Chi-square and Fisher tests were used to evaluate the relationship between data. Statistical significance was defined as *P*-value <0.05.

RESULTS

Demographic distribution of clinical isolates. The study examined 22 clinical isolates: 14 (63.7%) from Iranian patients and 8 (36.3%) from Afghan patients. Six isolates (27.3%) belonged to females and 16 (72.7%) to males.

Antibiotic resistance patterns. Of the 22 isolates, 4 (18.2%) were fully susceptible to first-line anti-tuberculosis drugs, 5 (27.8%) were XDR-TB, and 13 (72.2%) were MDR-TB. All the resistant isolates (n=18, 100%) demonstrated resistance to isoniazid ethambutol and rifampin, and the lowest resistance rate (n=8, 44.4%) was to Kanamycin. The proportion of isolates resistant to second-line drugs, such as kanamycin, ofloxacin, and capreomycin, was 44.4%, 50%, and 83.3%, respectively. Resistance to streptomycin, typically classified as a first-line drug, was observed in 72.2% of isolates (Table 2).

Table 2. Drug susceptibility profile for first-line and second-line anti-tuberculosis drugs in 18 MDR and XDR isolates compared to 4 isolates susceptible to all tested medications

No	BDQ MICs	INH	RIF	STR	EMB	KAN	OFX	CAP
1	0.25	R	R	S	R	R	R	R
2	0.25	R	R	R	R	S	R	R
3	0.0312	R	R	S	R	S	S	R
4	1	R	R	R	R	S	R	R
5	0.5	R	R	R	R	R	R	S
6	2	R	R	R	R	R	S	R
7	0.5	R	R	R	R	S	S	R
8	1	R	R	R	R	S	S	R
9	0.25	R	R	S	R	R	R	R
10	0.0625	R	R	R	R	S	S	S
11	0.125	R	R	S	R	S	S	R
12	8	R	R	R	R	R	R	R
13	0.5	R	R	R	R	S	R	R
14	16	R	R	R	R	R	R	R
15	0.125	R	R	R	R	R	S	S
16	0.0312	R	R	S	R	S	S	R
17	4	R	R	R	R	R	R	R
18	0.0625	R	R	R	R	S	S	R
19	0.125	S	S	S	S	S	S	S
20	0.0312	S	S	S	S	S	S	S
21	0.125	S	S	S	S	S	S	S
22	0.0625	S	S	S	S	S	S	S

BDQ resistance. MABA test yielded BDQ MIC values for 22 clinical isolates ranging from 0.0312 to 16 µg/mL, suggesting 12 (54.5%) resistant isolates based on the defined resistance threshold of MIC ≥0.25µg/mL (Table 2).

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Analysis of *atpE* and *Rv0678* genes. Sequencing the *atpE* and *Rv0678* genes, followed by BLAST analysis, revealed no mutation, suggesting that resistance in the assayed clinical isolates was not associated with changes in these target regions.

DISCUSSION

Previous studies have documented the emergence of drug-resistant tuberculosis, including both MDR and XDR forms [19]. Given that effective treatment regimens are crucial for managing tuberculosis [20], particularly for strains resistant to isoniazid (INH) and rifampicin (RIF), our study targeted drugs critical for treating such resistant strains. In our study, the resistance rates of isolates to kanamycin, ofloxacin, capreomycin, and streptomycin were 44.4%, 50%, 83.3%, and 72.2%, respectively. Comparatively, a similar study in Latvia in 2023 reported higher resistance rates to these drugs, i.e., 82.5% to kanamycin, 93.3% to ofloxacin, 81% to capreomycin, and 95.4% to streptomycin [21].

In our study, MDR and XDR rates were 72.2% and 27.8%, respectively, which agree with those reported by Mansoor *et al*. (2023), highlighting a similar distribution of drug-resistant tuberculosis [22]. In Ecuador, among 21 isolates investigated in 2023, 15 (71.4%) were MDR, and 2 (9.5%) were XDR, rates that almost match our findings [23]. In a 2023 study in India, of 64 isolates, 43 (67.1%) were identified as MDR and 2 (3.1%) as XDR [24].

BDQ is in use in over 50 countries and represents a significant advancement in treating MDR-TB and XDR-TB, bringing hope to patients with limited therapeutic options previously available [25]. In our study, 54.5% (n=12) of the isolates exhibited resistance to BDQ, a concerning observation given the BDQ's critical role in current MDR-TB treatment regimens. This resistance level suggests potential challenges for BDQ efficacy in the long-term management of tuberculosis. A similar study in Iran reported a 60% (15 out of 24) resistance rate to BDQ [25], reaffirming the need for vigilant drug resistance surveillance [26]. In 2022, 24 out of 51 isolates (47%) were resistant to BDQ in Cape Town, Africa, highlighting the geographical variability of resistance patterns [27]. Meanwhile, a study from China identified a 16.7% resistance rate to BDQ among XDR-TB isolates – the highest documented in the country [28]. A survey in China in 2021 indicated a reduction in mortality rates among drug-resistant tuberculosis cases treated with BDQ [29]. In our current study, like findings from an earlier report in Iran [26], we observed no mutations in the *atpE* and *Rv0678* genes among the isolates tested. Further research could elucidate the implications of these genetic profiles on BDQ resistance. In China, among 245 isolates, five were BDQ-resistant, and no mutations in the *atpE* gene were found [30]. Similarly, another study in China reported the absence of *atpE* gene mutations among ten BDQ-resistant isolates [28]. In Korean isolates, no mutations were found to correlate with BDQ resistance [31]. Contrastingly, in a large-scale study of 1025 isolates in China in 2022, 168 isolates exhibited mutations in the *Rv0678* gene, a finding divergent from our results [32].

Given the observed BDQ resistance and the absence of mutations in the *atpE* and *Rv0678* genes in our isolates, the results suggest that other factors might contribute to resistance. The mechanisms might include the efflux pump action or the presence of resistance-conferring mutations in genes not investigated in this study [26, 33]. One of the limitations of this study was the relatively small number of isolates examined, which may not represent all the strains circulating in Iran and Afghanistan. Another limitation was the lack of access to the whole genome sequencing (WGS) method, which could help identify potential genes involved in BDQ resistance.

In conclusion, the clinical isolates examined in this study exhibit a notable resistance to first and second-line drugs, underscoring the need for targeted long-term epidemiological studies and molecular research to elucidate drug resistance patterns and the underlying resistance mechanisms in *M. tuberculosis*.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

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