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Peer Reviewer of *World Journal of Clinical Cases*, Muhamad Zakaria Brimo Alsaman, MD, Associate Chief Physician, Department of Vascular Surgery, Al-Razi Hospital, Aleppo, Syria; Faculty of Medicine, University of Aleppo, Aleppo 12212, Syria. dr.zakariabrimo@gmail.com

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CASE REPORT

psk1 virulence gene-induced pulmonary and systemic tuberculosis in a young woman with normal immune function: A case report

Fan Wu, Bin Yang, Yan Xiao, Li-Li Ren, Hong-Yi Chen, Xin-Lan Hu, Yan-Yu Pan, Yu-Sheng Chen, Hong-Ru Li

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Fan Wu, Yu-Sheng Chen, Department of Respiratory and Critical Care Medicine, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou 350001, Fujian Province, China

Bin Yang, Yan Xiao, Li-Li Ren, NHC Key Laboratory of Systems Biology of Pathogens and Christophe Mérieux Laboratory, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Hong-Yi Chen, Emergency Department, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou 350001, Fujian Province, China

Xin-Lan Hu, Clinical Microbiology Laboratory, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou 350001, Fujian Province, China

Yan-Yu Pan, Infection Department, The 900th Hospital of the PLA Joint Support Force, Fuzhou 350001, Fujian Province, China

Hong-Ru Li, Department of Infectious Diseases, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou 350001, Fujian Province, China

Corresponding author: Hong-Ru Li, MD, PhD, Chief Doctor, Professor, Department of Infectious Diseases, Shengli Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, No. 134 East Street, Fuzhou 350001, Fujian Province, China. muzi131122@163.com

Abstract

BACKGROUND

Tuberculosis is a chronic infectious disease and an important public health problem. Despite progress in controlling tuberculosis, the incidence of tuberculosis in China is still very high, with 895000 new cases annually. This case report describes the investigation of a case of severe disseminated tuberculosis in a young adult with normal immune function, conducted to ascertain why a *Mycobacterium tuberculosis* (*M. tuberculosis*) strain caused such severe disease.

CASE SUMMARY

A previously healthy 28-year-old woman presented to our hospital with a 1-mo-

nth history of fever and fatigue. She was diagnosed with severe disseminated pulmonary tuberculosis, spinal tuberculosis with paravertebral abscesses, and tuberculous meningitis. *M. tuberculosis* was isolated from bronchoalveolar lavage fluid. She was treated with standard antituberculous therapy and underwent debridement, bone graft, and internal fixation surgery for spinal tuberculosis. She responded to therapy and regained her ability to walk following the surgery. We analysed the whole-genome sequence of the strain and designated it BLM-A21. Additional *M. tuberculosis* genomes were selected from the Virulence Factor Database (http://www.mgc.ac.cn/cgi-bin/VFs/genus.cgi?Genus=Mycobacterium) for comparison. An evolutionary tree of the BLM-A21 strain was built using PhyML maximum likelihood software. Further gene analysis revealed that, except for the *pks1* gene, BLM-A21 had similar virulence genes to the CDC 1551 and H37Rv strains, which have lower dissemination.

CONCLUSION

We speculate that the *pks1* virulence gene in BLM-A21 may be the key virulence gene responsible for the widespread dissemination of *M. tuberculosis* infection in this previously healthy adult with normal immune function.

Key Words: *Mycobacterium tuberculosis*; Disseminated tuberculosis; Spinal tuberculosis; Tuberculous meningitis; Virulence gene; Whole-genome sequencing; Case report

Core Tip: Tuberculosis is an important public health problem that threatens human health that primarily infects the lungs. We report a case of invasive pulmonary tuberculosis in a young woman with normal immune function. Comparison of the genetic characteristics of the patient's strain with those of other disease-causing strains suggests that its virulence and wide dissemination was attributable to the presence of the *pks1* gene, a genotype that can cause meningitis.

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INTRODUCTION

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and is an important public health problem. In 1979, China carried out the first national tuberculosis epidemiological survey, which showed that the prevalence of active tuberculosis was 717/100000[1]. Under the modern tuberculosis control and tuberculosis containment strategy implemented by China in 1992, the prevalence was reduced to 59/100000 by 2020[2]. This was mainly due to active prevention, including vaccination with the bacillus Calmette–Guérin (BCG) vaccine. Despite these achievements, China still has one of the highest burdens of tuberculosis worldwide, with 895000 new cases annually[2].

We report a rare case of disseminated pulmonary tuberculosis with secondary systemic hematogenous dissemination in a young woman with normal immune function and no underlying diseases and discuss the possible underlying causes.

CASE PRESENTATION

Chief complaints

A 28-year-old woman presented with a 1-month history of recurrent fever and lower back pain and a 1-week history of dyspnoea.

History of present illness

The patient had been healthy until the onset of the illness 1 month previously. She was admitted to Fujian Provincial Hospital in August 2021.

History of past illness

None.

Personal and family history

She had no known underlying diseases or family history of hereditary diseases. Her parents and sister did not have similar symptoms. She had not been vaccinated with BCG, although her younger sister had received a BCG vaccination.

Physical examination

On admission her vital signs were as follows: Body temperature, 38.8 ℃; pulse rate, 117 beats/minute; respiratory rate, 40 breaths/minute; blood pressure, 127/64 mmHg; and peripheral oxygen saturation, 80% with an inhaled oxygen concentration of 29%. She had shallow, rapid breathing. Chest auscultation revealed bilateral diffuse moist rales. A lump measuring approximately 3.5 cm × 5.0 cm was present in her lumbosacral region, with slight tenderness, poor mobility, and no redness, swelling, or ulceration of the overlying skin.

Laboratory examinations

Her arterial blood gas results with 29% oxygen supplementation were as follows: PH, 7.483; PCO_2, 34.6 mmHg; PO_2, 44.2 mmHg; and the oxygenation index was 152 mmHg. Haematology revealed a white blood cell count of 5100 cells/μL, with 63.6% segmented neutrophils; a haemoglobin level of 131 g/L; and a platelet count of 273000/μL. Blood biochemistry and immunology revealed the following: Serum albumin, 38 g/L; aspartate aminotransferase, 42 U/L; alkaline phosphatase, 110.6 U/L; lactate dehydrogenase, 548 U/L; procalcitonin, 2.4 ng/mL; C-reactive protein, 67.1 mg/L; and erythrocyte sedimentation rate, 13 mm/h. Immune function tests revealed the following: CD3 cell count, 106 cells/μL; CD4 cell count, 58 cells/μL; CD8 cell count, 43 cells/μL; NK cell count, 35 cells/μL; CD19 cell count, 86 cells/μL; CD45 cell count, 227 cells/μL; serum immunoglobulin G, 9.91 g/L; immunoglobulin A, 2.02 g/L; immunoglobulin M, 0.48 g/L; immunoglobulin E, 165 g/L; complement C3, 0.997 g/L; and complement C4, 0.125 g/L. The antinuclear antibody profile (full set of autoimmunity), antineutrophil cytoplasmic antibody, rheumatoid factor, and anticyclic citrulline polypeptide antibody tests were negative. Hepatitis B antibody, human immunodeficiency virus antibody, and syphilis-specific antibody tests were also negative. Sputum bacterial and fungal cultures were negative.

Imaging examinations

Chest computed tomography showed diffuse lesions in both lungs, bone destruction from the eighth thoracic vertebra to the first lumbar vertebra, and a paravertebral soft tissue mass (Figure 1A and B). Enhanced magnetic resonance imaging (MRI) of the thoracolumbar spine showed abnormal signal shadows from the ninth thoracic vertebral body to the 1st lumbar vertebral body and the surrounding soft tissue (Figure 1C-E). Brain enhanced MRI showed abnormal signals in the right parietal lobe (Figure 1F).

MULTIDISCIPLINARY EXPERT CONSULTATION

Further diagnostic workup

The patient underwent immediate endotracheal intubation and bronchoscopy. A bronchoalveolar lavage fluid (BALF) smear was positive for acid-fast bacilli, and a Gene X-pert MTB/RIF assay was positive for *M. tuberculosis* DNA. Next-generation sequencing of blood and BALF, and BALF culture confirmed *M. tuberculosis* infection.

To ascertain why this *M. tuberculosis* strain had caused such a severe infection in a young adult with normal immune function, we analysed the strain using whole-genome sequencing. We designated the strain, which had a total of 4155 genes, BLM-A21. We selected other *M. tuberculosis* genomes from the virulence factor database (VFDB) (http://www.mgc.ac.cn/cgi-bin/VFs/genus.cgi?Genus=Mycobacterium) [3], developed by the bioinformatics research team of the institute of Pathogenic Biology, Chinese Academy of Medical Science. We then performed phylogenetic analysis using PhyML maximum likelihood software[4] to build an evolutionary tree (Figure 2). We found that BLM-A21 had a close evolutionary relationship to CCDC5079, CCDC5180, and Beijing NTR203. Therefore, we analysed the whole genomes of several strains, including CCDC5079, CCDC5180, Beijing NTR203, CDC1551, and classic H37Rv and H37Ra, for subsequent genome comparison, as these strains have previously shown strong dissemination ability[5,6]. We used the BLASTP performance comparison algorithm[7] and the virulence factor protein reference sequence of the VFDB to annotate genes of these species (covering reference genes ≥ 85%, similarity ≥ 80%), and mapped the virulence gene classification and genome position information using CGView[8] (Figure 3). We identified high-virulence genes in BLM-A21 which we displayed in a heat map (Figure 4). Compared with the high-dissemination strains HN878 and W4 of the W/Beijing strain series, CDC 1551 has lower dissemination ability owing to the absence of the genes *pks1–15*. In our study, we found that BLM-A21 had similar virulence genes to CDC 1551 and H37Rv, except for the *pks1* gene, and thus hypothesized that *pks1* was the key virulence gene responsible for the widespread dissemination of the BLM-A21 strain of *M. tuberculosis* in this patient.

FINAL DIAGNOSIS

The patient was diagnosed with severe pulmonary tuberculosis and secondary systemic disseminated tuberculosis, including spinal tuberculosis with a paravertebral abscess, and tuberculous meningitis.

TREATMENT

After receiving isoniazid, rifampicin, ethambutol, and pyrazinamide, the patient's temperature dropped; her cough and

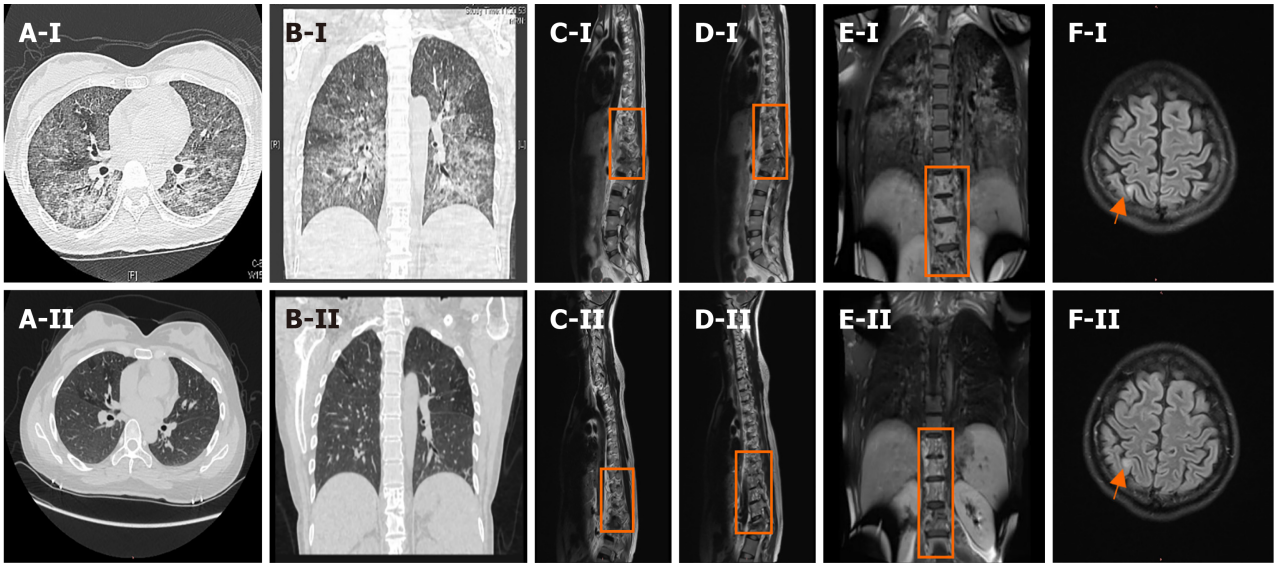

Figure 1 Chest computed tomography and enhanced magnetic resonance imaging of the thoracolumbar spine and brain. A-I and B-I: Chest computed tomography scans showing diffuse lesions in both lungs on admission; C-I, D-I, and E-I: Enhanced magnetic resonance imaging (MRI) of the thoracolumbar spine performed on day 13, showing abnormal signal shadows from the ninth thoracic vertebral body to the first lumbar vertebral body and the surrounding soft tissues; F-I: Enhanced MRI of the brain performed on day 12, showing an abnormal right parietal lobe signal. A-II and B-II: The chest computed tomography scan performed 6 ½ months after admission, showing an improvement in the diffuse lesions in both lungs. C-II, D-II, and E-II: Enhanced MRI of the thoracic spine performed 6 ½ months after admission, showing improved signal shadows from the ninth thoracic vertebral body to the first lumbar vertebral body and the surrounding soft tissues; F-II: Enhanced MRI of the brain performed 6 ½ months after admission, showing similar signal intensities in the right parietal lobe and the frontal lobe.

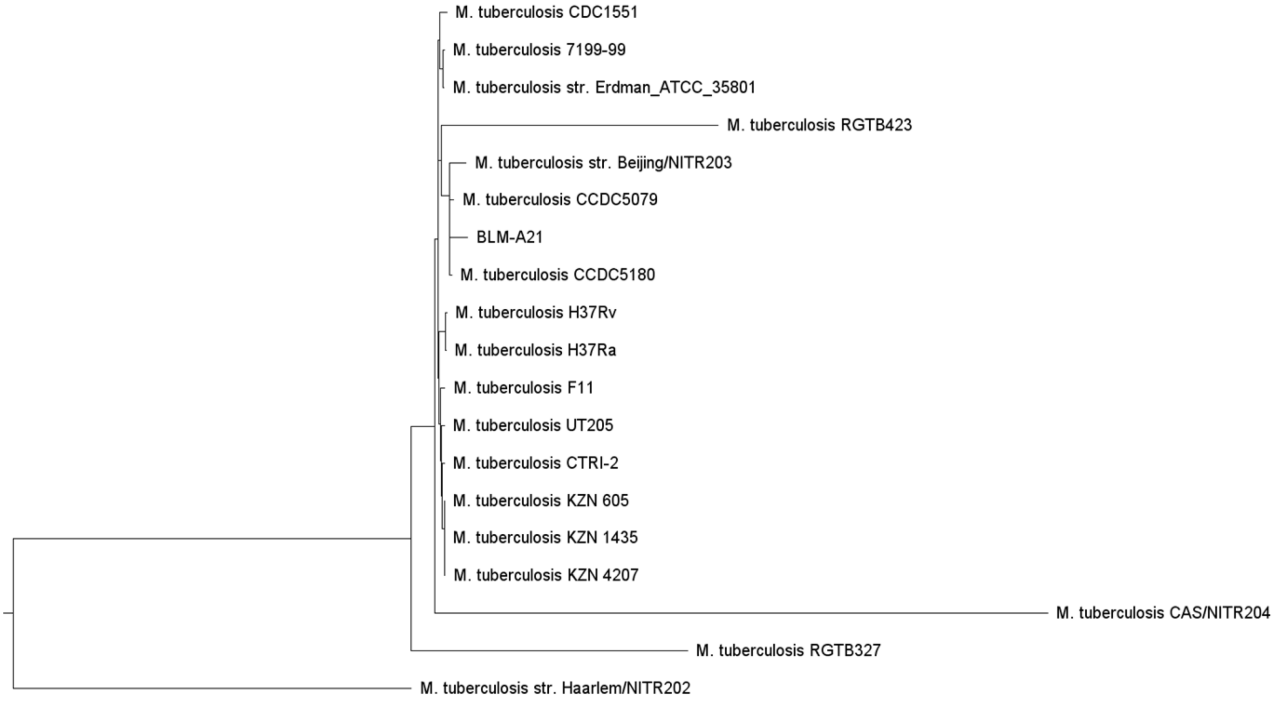

Figure 2 Whole-genome evolutionary tree of *Mycobacterium tuberculosis*. Additional *Mycobacterium tuberculosis* genomes were selected from the Virulence Factor Database (VFDB) (http://www.mgc.ac.cn/cgi-bin/VFs/genus.cgi?Genus=Mycobacterium), developed by the bioinformatics research team of the Institute of Pathogenic Biology, Chinese Academy of Medical Science, and a phylogenetic tree was built using the PhyML (maximum likelihood) software. The whole genomes of several strains, including CCDC5079, CCDC5180, Beijing NTR203, CDC1551, and classic H37Rv and H37Ra, were analysed for subsequent genome comparison, as these strains have previously shown strong dissemination ability. The patient's strain (BLM-A21) was closer to CCDC5079, CCDC5180, and Beijing NTR203 as shown on the evolutionary tree.

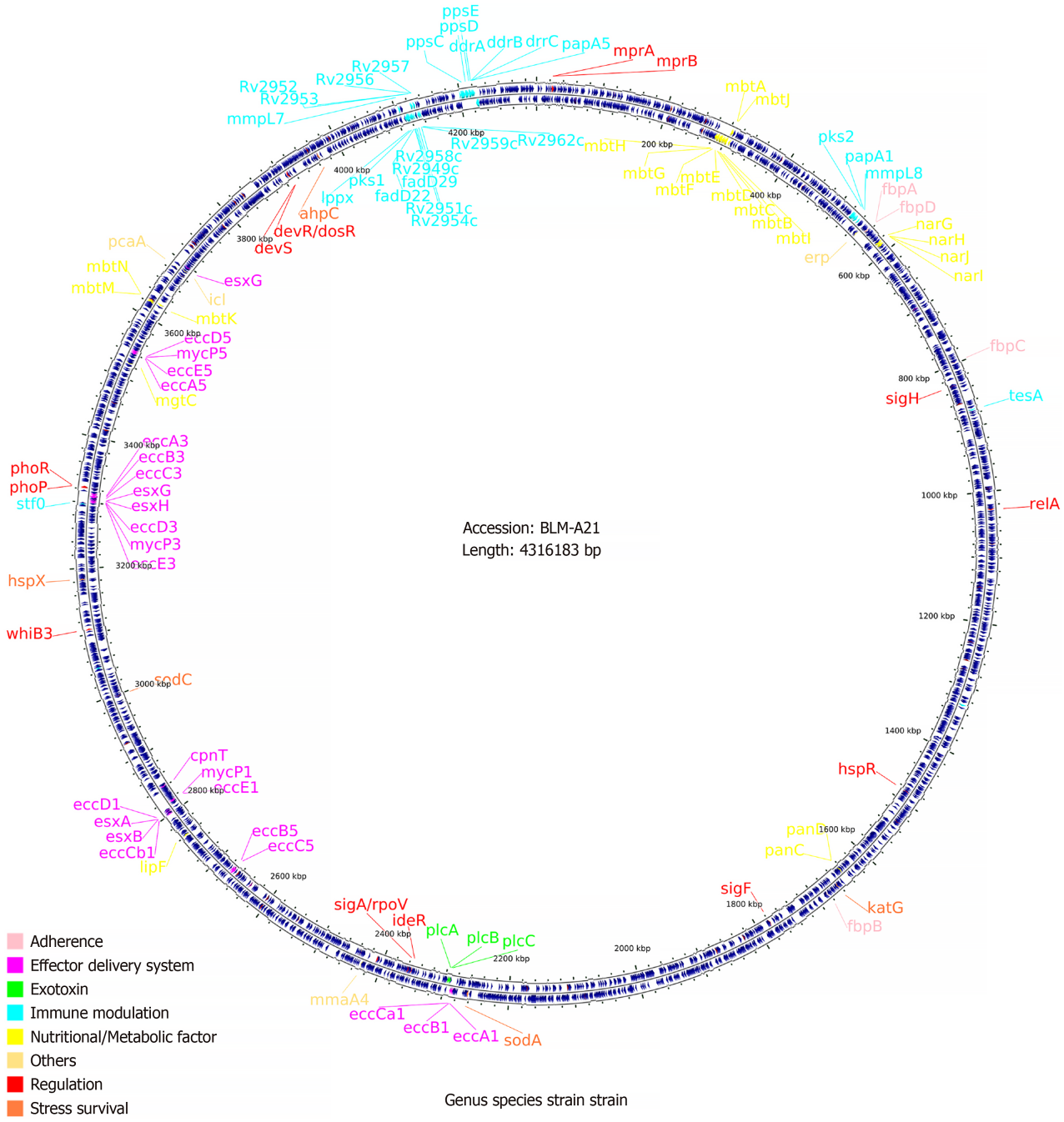

Figure 3 Chromosome genome circle map and virulence factor annotation of *Mycobacterium tuberculosis* strain BLM-A21. The BLASTP performance comparison algorithm and the virulence factor protein reference sequence of the Virulence Factor Database was used to annotate genes of these species, and the virulence gene classification and genome position information was mapped using CGView.

shortness of breath improved, and the tracheal intubation was removed. Imaging of the patient's brain, chest, and vertebral body performed 6 months after starting treatment showed that her condition had greatly improved (Figure 1A-F). Eight months after starting antituberculous treatment, the patient underwent debridement, bone graft, and internal fixation surgery for spinal tuberculosis, and left psoas abscess debridement.

OUTCOME AND FOLLOW-UP

After the surgery the patient has recovered the ability to walk unaided. Pain was evaluated using a visual analogue scale (VAS), with pain intensity graded on a scale of 0 (no pain) to 10 (most severe pain). The Oswestry Disability Index (ODI), which consists of 10 questions with a total score of 100 points, was used to evaluate the degree of lumbar functional impairment. A higher score indicates more severe the functional impairment. Both the VAS and ODI improved markedly after treatment. The VAS and ODI results before, and 6 ½ months after, treatment are shown in Table 1.

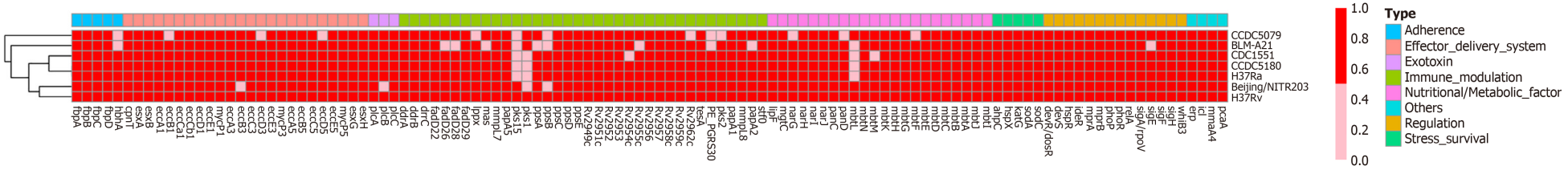

Figure 4 Virulence genes of *Mycobacterium tuberculosis* strains and their related genomes. The red color indicates that the presence of the virulence gene, whereas the pink color indicates the absence of the virulence gene in the genome. As the figure shows, CDC1551 Lacks genes *pks1–15*. BLM-A21 carries the *pks1* gene but lacks *pks15*; nevertheless, the number of other virulence genes is essentially consistent with that of CDC1551 and H37Rv.

DISCUSSION

BCG is an attenuated form of *Mycobacterium bovis* that provides immune protection and has been the only vaccine available against tuberculosis in China since the 1930s. In 2000, the BCG vaccination coverage in newborns reached 90%, effectively preventing miliary tuberculosis and tuberculous meningitis in children, and reducing the risk of *M. tuberculosis* infection in adults[9]. The patient, who had not received BCG vaccination suffered from severe *M. tuberculosis* infection, whereas her sister, who had received BCG vaccination, did not become ill.

Previous studies have shown that most children with hematogenous disseminated pulmonary tuberculosis had not received BCG vaccination[10], suggesting that the risk of severe tuberculosis is higher in individuals without BCG vaccination.

Severe pulmonary tuberculosis is very rare, accounting for approximately 3%-7% of cases[11]. Most patients with severe tuberculosis have had previous contact with an individual with tuberculosis, have weakened cellular immune function, or have other conditions such as anaemia, malnutrition, and a delay in seeking medical treatment[12-15]. However, this patient had none of these predisposing factors. Therefore, we hypothesised that the *pks1* virulence gene of BLM-A21 may have been the reason for the severity of the patient's disease.

A previous study showed that, compared with strains with a high risk of dissemination, strains that lack *pks1–15*, a phenol glycolipid (PGL)-related synthesis gene, have weak ability to disseminate to the central nervous system[16]. We found that BLM-A21 carried the *pks1* gene, but lacked the *pks15* gene, whereas the number of other virulence genes was consistent with that of other low-dissemination strains such as CDC 1551 and H37Rv. Based on an *in vitro* live bacterial transcriptome experiment, *pks1* has been reported to have a greater effect than *pks15* on regulating *fadD22*, *Rv2949c*, *lppX*, *fadD29*, and other genes, thus promoting PGL synthesis. PGL is related to several cell functions, particularly the impermeability of the cell wall, phagocytosis, the defence mechanism against nitroso compounds, oxidative stress, and the ability of mycobacteria to form biofilms, allowing strains to grow rapidly and invade the host[17].

CONCLUSION

We hypothesize that the *pks1* virulence gene of the BLM-A21 *M. tuberculosis* strain, induced severe pulmonary tuberculosis and secondary systemic disseminated tuberculosis in this unvaccinated patient with normal immune function. The mechanism whereby the *pks1* gene causes highly invasive tuberculosis needs further study.

Table 1 The visual analogue scale and Oswestry Disability Index results before, and 6 ½ months after, treatment

	Before treatment	6 ½ months after treatment
VAS score	6	1
ODI score	44	12

VAS: Visual analogue scale; ODI: Oswestry Disability Index.

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FOOTNOTES

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