

Characterization of an IMP-4-Producing *Klebsiella pneumoniae* ST1873 Strain Recovered from an Infant with a Bloodstream Infection in China

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Purpose: Imipenemase (IMP), an Ambler class B metallo- β -lactamase, is an important carbapenemase that confers resistance to almost all β -lactams. In this study, we characterized the genomic feature of an IMP-4-producing *Klebsiella pneumoniae* ST1873 strain, a rare sequence type (ST) isolated from an infant with a bloodstream infection in China.

Patients and Methods: *K. pneumoniae* strain, BKP19, was collected from a bloodstream infection in an infant who was hospitalized at the department of paediatrics. The whole genome sequence of the strain was sequenced using the Illumina NovaSeq 6000 platform and long-read MinION sequencer. Multilocus sequence typing, antimicrobial resistance gene identification, plasmid and phylogenetic relationship analysis of the strain were analysed by various bioinformatics approaches.

Results: *K. pneumoniae* BKP19 was resistant to multiple antimicrobials, including carbapenems. Eleven antimicrobial resistance genes corresponding to beta-lactam resistance, quinolone resistance, phenicol resistance and fosfomycin resistance could be identified in the genome. The carbapenem resistance gene *bla*_{IMP-4} was located in an IS26-associated class 1 integron of an IncN-type plasmid with 39,033 bp (pIMP-4-BKP19). Sequence alignment revealed that pIMP-4-BKP19 is closely related to the common plasmid carrying IMP-4 in *K. pneumoniae* (pIMP-HZ1-like plasmid) but is smaller, lacking the quinolone resistance gene *qnrS1* and multiple *tra* gene orthologs. Conjugation experiment revealed that pIMP-4-BKP19 is a non-conjugative plasmid. According to in silico MLST analysis, *K. pneumoniae* strain BKP19 belongs to a sporadic clone ST1873.

Conclusion: In summary, our study reports the first genome sequence of a *K. pneumoniae* ST1873 strain harbouring the class B β -lactamase *bla*_{IMP-4} in an IncN-type plasmid recovered from an infant with a bloodstream infection in China. Considering the global emergence of IMP-4 carbapenemase, more attention must be paid to prevent its future prevalence.

Keywords: *Klebsiella pneumoniae*, *bla*_{IMP-4}, IncN plasmid, ST1873, bloodstream infection

Introduction

Klebsiella pneumoniae is an important pathogen of the Enterobacteriaceae family that causes a variety of infectious diseases, including pneumonia, liver abscesses, urinary tract infections and bacteraemia. The emergence of carbapenem-resistant *K. pneumoniae* (CRKP) leaving few therapeutic options available. Imipenemase (IMP), an Ambler class B metallo- β -lactamase, is an important carbapenemase that confers resistance to almost all β -lactams. One of the most commonly observed IMP variants is IMP-4, which was firstly detected in *Acinetobacter* spp. in

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Hong Kong in 2001.¹ Since then, IMP-4-type carbapenemases have spread globally.^{2–5}

The *bla*_{IMP-4} gene is often integrated in broad-host-range conjugative plasmids and is transferred between different Gram-negative bacilli (eg, *Enterobacteriaceae*, *Acinetobacter* spp., *Pseudomonas aeruginosa*).^{1,5–8} The horizontal transfer of *bla*_{IMP-4} in these plasmids is frequently associated with class I integrons.^{9,10} Plasmid-borne *bla*_{IMP-4} has been sporadically reported in different Gram-negative bacilli in China.^{6,11–13} However, only a few studies have reported the complete sequence of *bla*_{IMP-4}-harbouring plasmids,^{6,10,14} which limits our understanding of the transmission mechanism of *bla*_{IMP-4} between different Gram-negative bacilli.

Klebsiella pneumoniae carbapenemase (KPC) has emerged as the predominant carbapenemase in *K. pneumoniae* in China, while there are relatively few IMP-4 producing strains.¹⁵ Carbapenemase IMP is often distributed among multiple STs in *K. pneumoniae*, especially some rare STs.

In this study, the IMP-4-producing *K. pneumoniae* strain BKP19 was collected from a bloodstream infection in an infant who was hospitalized at the department of paediatrics. The isolate was preliminarily identified using the VITEK MS system (bioMérieux, France) and was further confirmed by 16S rRNA gene sequencing. The whole genome of the strain was sequenced. The *bla*_{IMP-4}-harbouring plasmid and genetic characteristics of the strain were analysed to gain a better understanding of the transmission mechanism of *bla*_{IMP-4}.

Materials and Methods

Patient and Isolate

A female neonate with a birth weight of 1.13 kg was hospitalized at the department of paediatrics half an hour after preterm delivery at a tertiary hospital in Hangzhou, Zhejiang Province, China. During her hospitalization, the neonate received multiple antimicrobial treatments, including cefotaxime, erythromycin, vancomycin and meropenem. Carbapenem-resistant *K. pneumoniae* was isolated from a blood sample from the patient one month later after her hospitalization. The isolate was preliminarily identified using the VITEK MS system (bioMérieux, France) and was further confirmed by 16S rRNA gene sequencing.

Antimicrobial Susceptibility Test

Antimicrobial susceptibility testing was conducted using the VITEK 2 system (bioMérieux, France) with Gram-

negative antimicrobial susceptibility testing cards (AST-GN16) and the Etest method following the guidelines of the Clinical and Laboratory Standards Institute (CLSI). Antimicrobial susceptibility was determined using the breakpoints approved by the CLSI.¹⁶

Whole-Genome Sequencing

The genomic DNA of the isolate was extracted using a QIAamp DNA Mini Kit (Qiagen, USA). The Illumina NovaSeq 6000 platform (Illumina Inc., San Diego, CA, USA) and a long-read MinION sequencer (Nanopore, Oxford, UK) were used for whole-genome sequencing. The de novo hybrid assembly of both short Illumina reads and long MinION reads were performed using Unicycler.¹⁷ The whole-genome sequence was automatically annotated by the NCBI Prokaryotic Genome Annotation Pipeline (PGAP) server.

Multilocus Sequence Typing and Antimicrobial Resistance Gene Identification

Multilocus sequence typing (MLST) and the identification of antimicrobial resistance genes and plasmid replicons were performed using the BacWGSTdb server.¹⁸

Plasmid Analysis

The graphical circular map of the *bla*_{IMP-4}-carrying plasmid was converted by the CGView Server.¹⁹ The comparisons between the *bla*_{IMP-4}-carrying plasmid and similar plasmids were conducted by using the BLAST Ring Image Generator (BRIG) in concentric rings.²⁰ The comparison of the *bla*_{IMP-4}-carrying plasmid with the most closely related plasmid was performed by EasyFig 2.2.3.²¹

Conjugation Experiment

The transfer capacity of the *bla*_{IMP-4}-harbouring plasmid was investigated in a conjugation experiment.²² Rifampicin-resistant *E. coli* EC600 was used as the recipient, and strain BKP19 was used as the donor. The donor and recipient bacteria were cultured in MH broth for 4 hrs. Aliquots of 100 µL of each cultured donor and recipient bacterium were mixed together. A 40 µL aliquot of the mixture was spotted on a sterile filter membrane, which was placed on a Muller-Hinton (MH) agar plate, followed by incubation at 35°C for 18 h. The bacteria were washed from the filter membrane, and *bla*_{IMP-4}-positive *E. coli* transconjugants were selected on MH agar plates supplemented with rifampicin (800 mg/L) and imipenem (8 mg/L).

Phylogenetic Analysis

The phylogenetic relationship between BKP19 and other *K. pneumoniae* strains retrieved from the NCBI GenBank database was analysed using the BacWGSTdb server.^{18,23} The BacWGSTdb server offers core genome Multilocus Sequence Typing (cgMLST) and single nucleotide polymorphism (SNP) approaches to investigate the phylogenetic relationship of the uploaded genome sequence with sequences deposited in the database. The database currently contains 7480 *K. pneumoniae* strains.

Nucleotide Sequence Accession Numbers

The results of this whole-genome shotgun project have been deposited at DDBJ/EMBL/GenBank under accession number VWRO00000000. The version described in this paper is the first version.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Zhejiang Provincial People's Hospital. Written informed consent from the patient was exempted by the Ethics Committee of Zhejiang Provincial People's Hospital because the present study only focused on bacteria. The clinical isolate *K. pneumoniae* BKP19 was part of the routine hospital laboratory procedure.

Results and Discussion

The MICs of the antibiotics tested are presented in Table 1. *K. pneumoniae* BKP19 was resistant to multiple antimicrobials, including cefazolin, ceftriaxone, cefepime, ceftazidime, imipenem, meropenem, ciprofloxacin and levofloxacin. This

Table 1 MICs of the Antibiotics Tested in *K. pneumoniae* BKP19

Antibiotics	MIC (mg/L)	
	BKP19	Interpretive Categories
Cefazolin ^a	≥64	R
Ceftriaxone ^a	≥64	R
Cefepime ^a	≥64	R
Ceftazidime ^a	≥64	R
Aztreonam ^a	≤1	S
Imipenem ^b	>32	R
Meropenem ^b	16	R
Amikacin ^a	≤2	S
Gentamicin ^a	≤1	S
Tobramycin ^a	≤1	S
Ciprofloxacin ^a	≥4	R
Levofloxacin ^a	≥8	R
Tigecycline ^b	1	S
Colistin ^b	0.25	S

Notes: ^aTested by AST-GN16. ^bTested by Etest method.

Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; R, resistant.

strain was susceptible to aminoglycosides, aztreonam, tigecycline and colistin.

The genome of *K. pneumoniae* strain BKP19 consists of five contigs that comprise 5,600,093 bp. Among them, contig 1 (2,265,448 bp), contig 2 (1,983,649 bp) and contig 3 (1,049,807 bp) belong to the chromosome, and the others belong to two plasmids (contig 4: 262,156 bp and contig pIMP-4-BKP19: 39,033 bp). The PGAP server predicted a total of 5,262 protein-coding sequences, 88 tRNA genes and 25 rRNA operons. Three plasmid replicons were identified: IncFIB(K) and IncHI1B on plasmid 4 and IncN on plasmid pIMP-4-BKP19.

The antimicrobial resistance genes present in the genome of the isolate are presented in Table 2. We identified the aminoglycoside resistance genes *aph(6)-Id* and *strA*;

Table 2 Antimicrobial Resistance Genes in *K. pneumoniae* BKP19

Antimicrobial Resistance Gene	Contig	Identity (%)	Position	Antimicrobial Resistance Category
<i>bla</i> _{SHV-2}	1	100	1835313.1836173	Beta-lactam
<i>oqx</i> A	2	99.06	941409.942584	Quinolone
<i>oqx</i> B	2	99.02	938233.941385	Quinolone
<i>fos</i> A	3	99.76	132010.132429	Fosfomycin
<i>aph(6)-Id</i>	4	100	214820.215656	Aminoglycoside
<i>str</i> A	4	100	214017.214820	Aminoglycoside
<i>bla</i> _{SHV-11}	4	99.88	204854.205714	Beta-lactam
<i>cat</i> A1	4	99.55	4680.5339	Phenicol
<i>dfr</i> A5	4	100	210580.211053	Trimethoprim
<i>sul</i> 2	4	100	220320.221135	Sulphonamide
<i>bla</i> _{IMP-4}	pIMP-4-BKP19	100	5188.5928	Beta-lactam

the beta-lactam resistance genes *bla_{SHV-2}*, *bla_{SHV-11}* and *bla_{IMP-4}*; the quinolone resistance genes *oqxA* and *oqxB*; the phenicol resistance gene *catA1*; the sulphonamide resistance gene *sul2*; the trimethoprim resistance gene *dfrA5* and the fosfomycin resistance gene *fosA*. *bla_{SHV-2}*, *oqxA*, *oqxB* and *fosA* were located in the chromosome. *aph (6)-Id*, *strA*, *bla_{SHV-11}*, *catA1*, *dfrA5* and *sul2* were located in plasmid 4. The carbapenem-resistant gene *bla_{IMP-4}* was located in plasmid pIMP-4-BKP19.

pIMP-4-BKP19 is an IncN-type plasmid that comprises 39,033 bp. The circular map of pIMP-4-BKP19 is presented in Figure 1. It contains conserved IncN-type backbone regions that contain a replication gene and its accessory structure for plasmid replication. The *tra* genes (*traB*, *traK* and *traM*) for conjugal transfer, the *stbABC* operon for plasmid maintenance, the *ardA*, *ardK* and *ardR* genes with an antirestriction function and the *mucAB* operon for UV protection were identified in the plasmid backbone. The *bla_{IMP-4}*

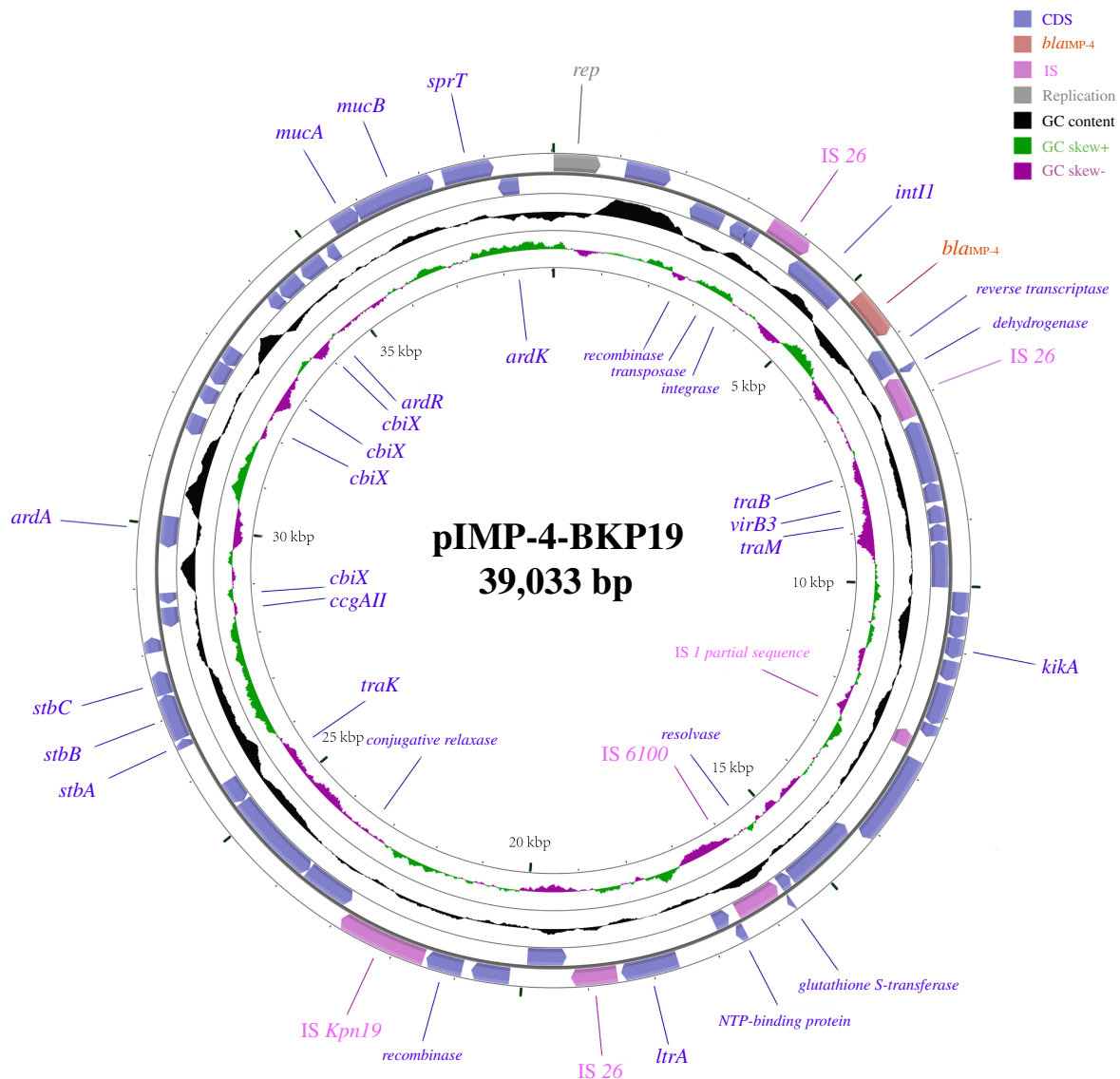


Figure 1 Backbone structure of the *bla_{IMP-4}*-encoding plasmid pIMP-4-BKP19.

gene was located in an IS26-associated class 1 integron, preceded by IS26-*intI1* in the upstream region and followed by another IS26 sequence in the downstream region. The similarity of pIMP-4-BKP19 to other *bla*_{IMP-4}-carrying plasmids was analysed with the Basic Local Alignment Search Tool (BLASTN). Several similar *bla*_{IMP-4}-carrying plasmids were found in the NCBI GenBank database (Figure 2). The most common type of plasmid carrying IMP-4 in *K. pneumoniae* that has been reported to date is a pIMP-HZ1-like IncN-type plasmid with a size of approximately 50 kb (eg, *K. pneumoniae* strain Kp1 plasmid pIMP-HZ1,

accession no. KU886034, 51,599 bp; *K. pneumoniae* strain 24,854 plasmid p24854-IMP, accession no. MH909341, 51,393bp),¹⁴ these plasmids also carry the quinolone resistance gene *qnrS1*. The structural characteristics of pIMP-4-BKP19 compared to pIMP-HZ1 and p24854-IMP are presented in Figure 3. The structure of the pIMP-4-BKP19 plasmid is very similar to these two plasmids, with >99% query coverage and >99% nucleotide identity, but pIMP-4-BKP19 is smaller than the other plasmids (only 39,033 bp). There are three major genetic differences between the backbones of pIMP-4-BKP19 and the

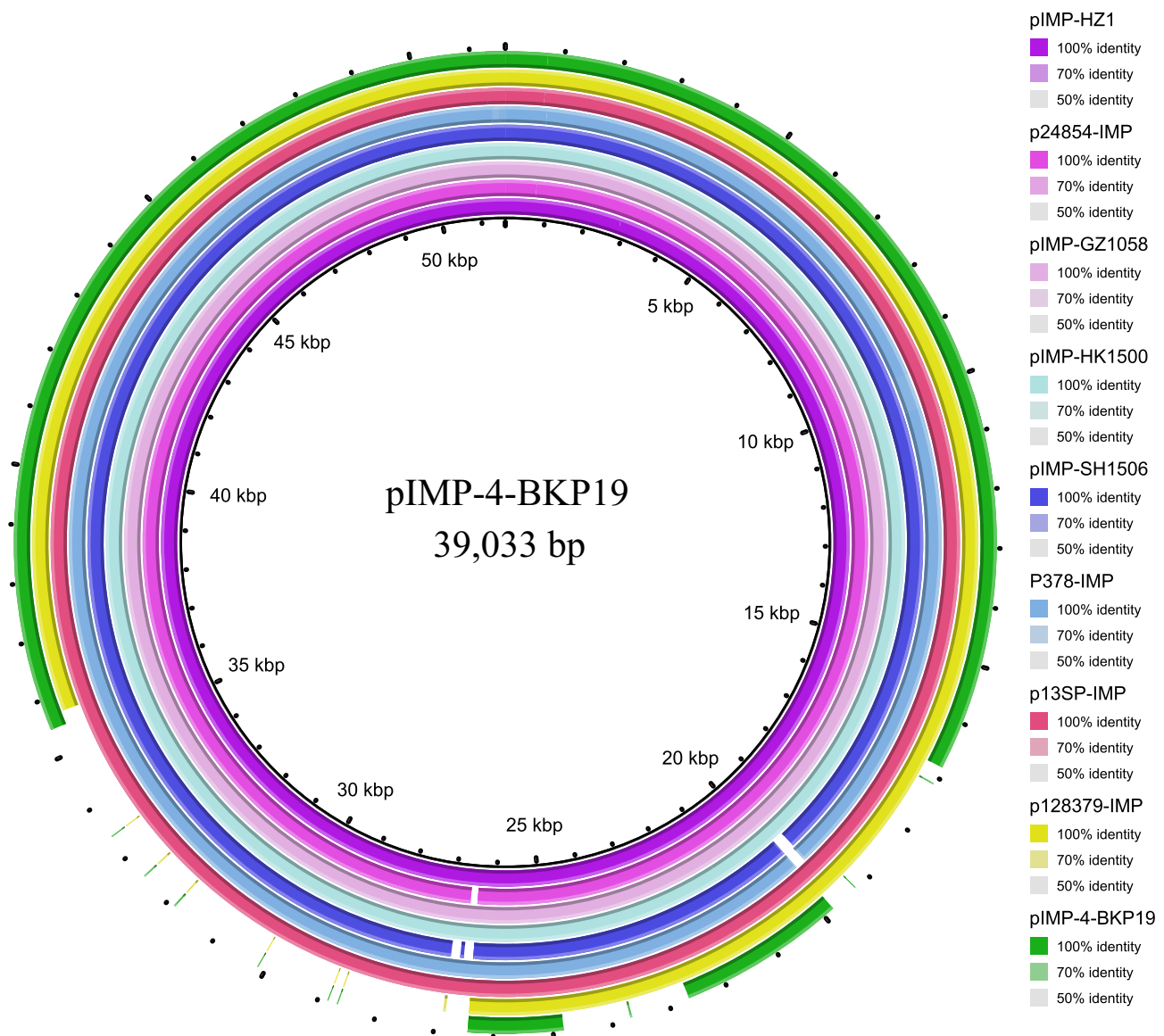


Figure 2 Sequence alignment of the pIMP-4-BKP19 plasmid from *Klebsiella pneumoniae* strain BKP19 with data in the NCBI GenBank database revealed several highly identical plasmids from different Gram-negative bacillus strains, including pIMP-HZ1 (*K. pneumoniae* strain Kp1, accession no. KU886034), p24854-IMP (*K. pneumoniae* strain 24854, accession no. MH909341), pIMP-GZ1058 (*Escherichia coli* strain CRE1058, accession no. KU051709), pIMP-HK1500 (*Citrobacter freundii* strain CRE1500, accession no. KT989599), pIMP-SH1506 (*Enterobacter cloacae* strain CRE1506, accession no. KT989598), p13SP-IMP (*Klebsiella pneumoniae* strain 13-sp, accession no. MH909334), P378-IMP (*Pseudomonas aeruginosa* strain P378, accession no. KX711879), and p128379-IMP (*Enterobacter hormaechei* strain 128379, accession no. MF344559).

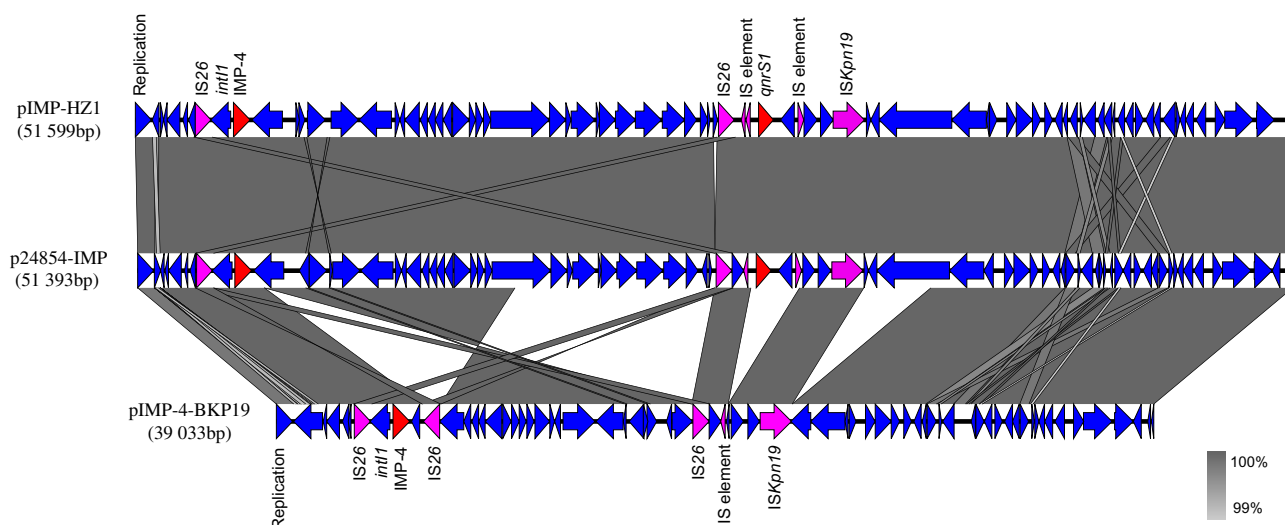


Figure 3 Comparative analysis of the homologous regions shared by three IncN-type plasmids (pIMP-4-BKP19, p24854-IMP and pIMP-HZ1). The plasmids were annotated by Rapid Annotation using Subsystem Technology (RAST) server. The figure was produced using EasyFig v. 2.2.3, and BLASTN was used to compare sequence homology with the following threshold parameters: minimum length of 100 bp accompanied by 90% identity. Antimicrobial resistance genes are indicated in red, IS elements are indicated in purple, and all other genes are indicated in blue.

pIMP-HZ1-like plasmids. First, a segment downstream of *bla*_{IMP-4} is shortened and reversed, with an IS26 mobile element occurring on each side of the segment. The reduced sequence mainly includes genes encoding the *tra* gene orthologs (*traC*, *traE*, *traF* and *traG*). Second, the quinolone resistance gene *qnrS1* is absent. There are insertion elements on both sides of the *qnrS1* gene in the pIMP-HZ1-like plasmid. It is likely that the *qnrS1* gene was introduced into the IncN plasmid through these insertion elements. Third, some nucleotide sequences downstream of *ISKpn19* are absent. Conjugation experiment revealed that pIMP-4-BKP19 is a non-conjugative plasmid.

According to the *in silico* MLST analysis, *K. pneumoniae* strain BKP19 belongs to sequence type (ST) 1873, which is a very rare ST. IMP often appears in some rare STs (eg, ST476, ST2270, ST37, ST107, ST133, ST323, ST686, ST1114) in *K. pneumoniae*.^{6,10,12,24} We analysed the genome data in the NCBI GenBank database (accessed on 10 December 2019) and found that no ST1873 *K. pneumoniae* sequences are currently available in the database. We then further analysed the similar isolates with the threshold of 2000 (based on the cgMLST strategy) in BacWGSTdb. Fifteen phylogenetically related *K. pneumoniae* strains could be found in the database (Table S1). The strain closest to BKP19 was *K. pneumoniae* PN089E1 (ST2958) isolated from Cameroon in 2016 with 1610 different alleles.

Here, we report the first genome sequence of a *K. pneumoniae* ST1873 strain harbouring the class

B β-lactamase *bla*_{IMP-4} recovered from an infant with a bloodstream infection in China. Comprehensive analysis of the *bla*_{IMP-4}-carrying plasmid revealed that it was an IncN-type plasmid that has variant region within the integron mediated by IS26. Plasmids belonging to the IncN type commonly exhibit a broad host range and high transmission efficiency.⁶ It seems that the IS26-associated class 1 integron contributes to the dissemination of IMP-4 in different plasmids and that the IS26 mobile element plays an important role in the recombination of plasmid backbones. Our data may help to understand the genomic features of this bacterial pathogen. The genome sequence of *K. pneumoniae* BKP19 can be used as a reference sequence for comparative genomic analysis to obtain a better understanding on the transmission mechanism of *bla*_{IMP-4}.

Conclusion

Our study reports the first genome sequence of a *K. pneumoniae* ST1873 strain harbouring the class B β-lactamase *bla*_{IMP-4} in a IncN-type plasmid recovered from an infant with a bloodstream infection in China. Considering the global emergence of IMP-4 carbapenemase, more attention must be paid to prevent its future prevalence.

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Disclosure

The authors report no conflicts of interest in this work.

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