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ORIGINAL RESEARCH

Acquisition and Transmission of *tmexCD1-toprJ1*-Positive Plasmids in Clinical ST17 *Klebsiella pneumoniae*

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Purpose: It is well known that bacteria often acquire drug resistance genes through acquiring exogenous resistant plasmids. The *tmexCD1-toprJ1*-positive plasmid confers tigecycline resistance to bacterial strains.

Methods: Three sequence type (ST) 17 *Klebsiella pneumoniae* strains were isolated from two patients within 5 days. Experimental and comparative genomic analyses were performed to investigate potential transmission routes and antimicrobial resistance phenotype disparities.

Results: Strain HD9931 was tigecycline-sensitive, whereas HD9932 and HD10868 were tigecycline-resistant because of the presence of a *tmexCD1-toprJ1*-positive plasmid. HD10868 exhibited enhanced fitness and greater tigecycline resistance than HD9932 did. Comparative analysis revealed mutations in the AcrAB-TolC efflux pump and *lamb* in HD9932 and HD10868.

Conclusion: Our study highlights the complexity of resistance gene transfer and underscores the need for continued vigilance and research in this field.

Keywords: tigecycline resistance, *tmexCD1-toprJ1*, mutation, plasmids

Introduction

Klebsiella pneumoniae is a gram-negative opportunistic pathogen that causes a wide range of infections, including pneumonia, urinary tract infections, soft tissue infections, and septicemia.[1–3] Owing to its remarkable ability to acquire genetic elements encoding antibiotic resistance genes, multidrug-resistant (MDR) *K. pneumoniae*, particularly carbapenem-resistant *K. pneumoniae* (CRKP), pose serious challenges to clinical treatment.[4] Tigecycline is one of the few remaining options for the treatment of CRKP. However, the emergence of tigecycline resistance further narrows treatment choices and complicating therapy.[5] The prevalence of plasmid-mediated resistance genes, such as *tet(X)*, has exacerbated the difficulty in treating tigecycline-resistant infections.[6–8] In addition, chromosomally encoded factors such as efflux pumps, transcriptional regulators, and porins have also been implicated in tigecycline resistance.[9–12]

The resistance-nodulation-division (RND) family of efflux pumps plays key roles in antimicrobial resistance.[13,14] In 2020, a plasmid-encoded RND efflux pump gene cluster, *tmexCD-toprJ*, was first identified in *K. pneumoniae* and was shown to confer resistance to multiple antibiotics, including tigecycline.[8] Plasmid localization facilitates horizontal gene transfer (HGT) across different bacterial species and introduces new challenges in infection control and treatment. In addition to the MexCD efflux pump, other efflux pump superfamilies are involved in tigecycline resistance, such as AdeABC, AdeFGH, and AdeIJK efflux pumps. The AcrAB-TolC efflux pump, which is also chromosomally encoded, has been linked to tigecycline resistance through overexpression or mutations.[11–13,15] Xu et al[11] reported that the prevalence of a novel of T188A mutation of the AcrA subunit in *K. pneumoniae* was high. In A. baumannii, mutations

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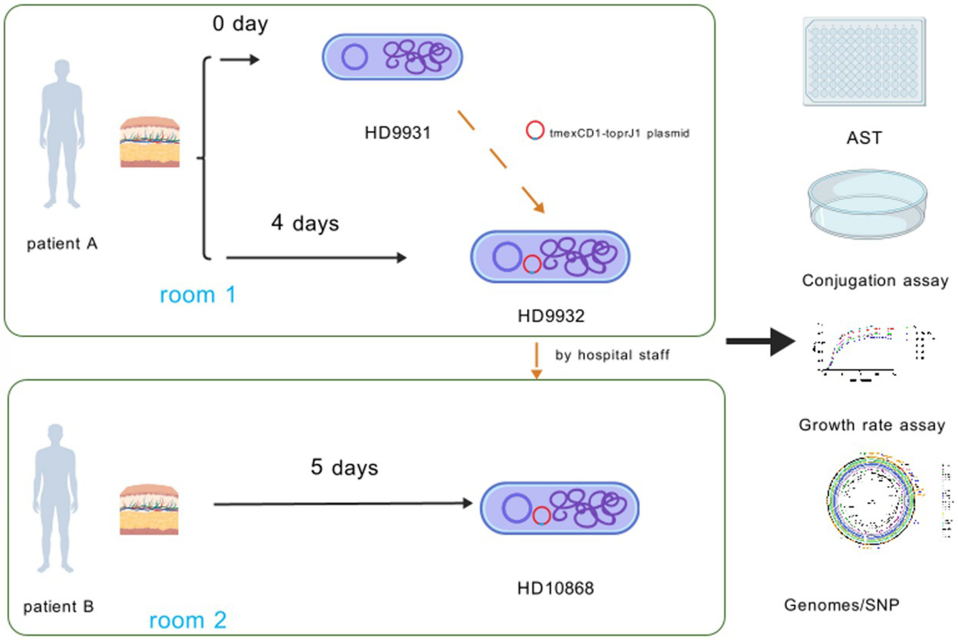
Graphical Abstract



in the *adeS*, *rpoB* and *rrf* are associated with tigecycline resistance in vitro evidence.[12] Xia et al[15] reported both overexpression of *acrAB-tolC* and *tet(A)* gene mutation contributed to the mechanism of tigecycline resistance.

It is well-established that bacteria under antibiotic pressure frequently acquire exogenous resistance genes via HGT to enhance survival.[16] Mobile genetic elements (MGEs), such as plasmids, prophages, transposons, and insertion sequences, enhance bacterial viability and adaptation. Acquirement and mutation of antibiotic resistance genes and virulence genes mediating by MGEs enabled *K. pneumoniae* to gain specific traits to adapt the changing environment. Among the MGEs, plasmids play a central role in mediating the horizontal spread of antibiotic resistance, particularly among gram-negative bacteria.[17] In this study, we characterized HGT of a plasmid harboring the *tmexCD1-toprJ1* gene cluster and investigated the potential determinants of tigecycline resistance in *K. pneumoniae*.

Materials and Methods

Sample Collection, Bacterial Strains Isolation and Identification

This single-center, prospective, observational cohort study was conducted at Zhenjiang First People's Hospital, Jiangsu Province, between January 2020 and December 2020. Strains HD9931 and HD9932 were collected in September 2020, as part of the cohort study. Strain HD10868 was subsequently identified through retrospective screening of the *tmexCD-toprJ* gene cluster in tigecycline-resistant isolates collected from the same ward during the same period. All the strains were obtained from patients as part of routine hospital procedure.

Bacterial identification was performed using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS, Sysmex, France). Basic anonymized metadata, including patient sex and age, specimen collection dates, specimen types, medication history, and length of hospitalization, were collected for analysis.

Antimicrobial Susceptibility Testing (AST)

AST was performed using the broth microdilution method, according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) guidelines. *E. coli* ATCC 25922 was used as the quality control strain. Minimum inhibitory concentrations (MICs) were interpreted based on CLSI guidelines (version 2020), except for tigecycline, which was interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST, version 2020) criteria (http://www.eucast.org).

Conjugation Assay

Conjugative assays were performed using the filter mating method, as previously described.[18] Isolates HD9932 and HD10868 were used as donors separately, whereas *E. coli* J53 (AziR, sodium azide) was used as the recipient to examine the transferability of the *tmexCD-torpJ*-positive plasmids. First, the donor and the recipient strains were cultured to the logarithmic growth phase, mixed at a ratio of 1:1 on a filter paper, and incubated for 3 h at 37°C. Transconjugants were selected on Luria-Bertani (LB) medium containing sodium azide (200 mg/L) and tigecycline (1 mg/L), and the recovered transconjugants were further confirmed by PCR (primer sequences: tmexC-F: TTCCGTGATCTCCTGTTTG, tmexC-R: GATGGCGTTCTGGTTGAG, tmexD-F: CAGCCAGGACTACAACTTC, tmexD-R: TAGAGGAACTTCGGATTGC) and Sanger sequencing. The conjugation frequency was determined using classical plating and CFU counting methods.

Growth Rate Assay

Bacteria were inoculated into 2 mL LB broth and incubated at 150 rpm, 37 °C to the logarithmic growth phase. The cultures were adjusted to the same optical density (OD600 = 0.3), diluted 1:100 in fresh LB broth, incubating the cultures for 24 hours at 37 °C with shaking. Bacterial growth was monitored by automatically measuring the OD density of the cultures at 600 nm at hourly intervals. Growth curves were generated using GraphPad Prism version 8.3.0. Two-way analysis of variance (ANOVA) was used to evaluate the differences between means, with a significant probability at a P-value ≤ 0.05. Growth curves were obtained in triplicates.

Whole-Genome Sequencing and Bioinformatics Analysis

The genomic DNA of the strains was obtained using the Omega Bio-Tek Bacterial DNA Kit (Doraville, GA, USA). Draft-genome sequencing of the three strains was conducted using a paired-end library with an average insert size of 350 bp on a NovaSeq 6000 sequencer (Illumina, CA, USA), and quality-filtered reads were assembled de novo utilizing SPAdes 3.11 (https://cab.spbu.ru/software/spades). To obtain complete genome sequences of the three strains, we conducted Nanopore PromethION long-read sequencing (Oxford Nanodrop Technologies, OX, UK). High-quality complete genome sequences were automatically annotated using the RAST annotation server (http://rast.nmpdr.org/) and were manually modified. Acquired resistance genes, plasmid replicon types, and multi-locus sequence typing (MLST) of the strains were determined using the ResFinder 4.1, Plasmid Finder 1.3 and MLST 2.1 servers, which are available at the Center for Genomic Epidemiology (http://www.genomicepidemiology.org/). Virulence genes were identified using ABRicate (https://github.com/tseemann/abricate/). BRIG was used for genetic comparisons.

Statistical Analysis

Statistical analysis was conducted using two-way ANOVA to compare the bacterial growth curve. Result was considered statistically significant at $p \leq 0.05$.

Nucleotide Sequence Accession Numbers

The complete genome sequences of the three strains were deposited in GenBank under BioProject PRJNA1212054, PRJNA1212314, and PRJNA1212320, respectively.

Results

Clinical Information of the Three *Klebsiella pneumoniae* Strains

The three strains were isolated from wound secretion samples collected from two male patients in an Orthopedic Ward. HD9931 was isolated from a 79-year-old male patient, and HD9932 was isolated from the same patient four days later. Strain HD10868 was derived from a 30-year-old male patient one day after collection of HD9932. Notably, both patients were hospitalized in the same ward, but in different rooms during the same period, and were cared for by the same medical team. The patient demographics, clinical presentations, outcomes, and microbiological features of the three strains are summarized in Table 1.

Antimicrobial Resistance Profiles

Antimicrobial susceptibility testing (AST) results (Table 2) revealed that HD9931 was susceptible to ceftazidime, aztreonam, imipenem, meropenem, tobramycin, levofloxacin, tigecycline, colistin, and sulfamethoxazole. In contrast, HD9932 was resistant to aztreonam, tobramycin, and tigecycline, and showed intermediate susceptibility to ceftazidime and levofloxacin. In HD9932, the MICs of the antibiotics aztreonam, tobramycin and tigecycline increased 4 to 64-fold compared with those of HD9931. However, HD9932 remained susceptible to imipenem, meropenem, colistin, and sulfamethoxazole. Notably, HD10868 exhibited a resistance profile similar to that of HD9932, except for a 4-fold increase in tigecycline MIC.

Genome Feature of the Three Strains

The complete genomes of the three strains were obtained and deposited in the NCBI database (accession numbers SAMN46290449, SAMN46297288, and SAMN46297523). Specific information on these strains is presented in Table 3.

Table 1 Clinical Characteristics of Two Patients Infected with ST17 *K. Pneumoniae*

Characteristic	**Value or Information for Patient from Whom Indicated Isolate was Obtained**	
	Patient A	**Patient B**
Age(yr)	79	30
Sex	Male	Male
Hospital ward	Orthopedic Ward 1	Orthopedic Ward 2
Type of specimen	Wound secretion	Wound secretion
Date of isolation	HD9931 2020/9/4 HD9932 2020/9/8	HD10868 2020/9/9
Clinical characteristic	Lumbar Spinal Stenosis	Open Fracture of the Tibia
Temp(°C)	38.5°C	38.1°C
White blood cell count/ L	7.0 x 10^9	4.3 x 10^9
Outcome	Discharged	Discharged

Table 2 MIC Profiles of the Strains in This Study

Isolation ID	**MIC (mg/liter)**								
	CAZ	**ATM**	**IPM**	**MEM**	**TOB**	**LEV**	**TGC**	**COL**	**SXT**
Clinical strains									
HD9931	<= 0.12	<= 1	<= 0.25	<= 0.25	<= 1	<= 0.12	<=0.25	<= 0.5	<= 20
HD9932	8	16	<= 0.25	<= 0.25	≥ 16	1	1	<= 0.5	<= 20
HD10868	8	16	<= 0.25	<= 0.25	≥ 16	1	4	<= 0.5	<= 20
Recipients									
E. coli J53	<=0.12	<=1	<= 0.25	<= 0.25	<= 1	<= 0.12	<=0.25	<= 0.5	<= 20
Transconjugants									
HD9932-J53	8	16	<= 0.25	<= 0.25	≥ 16	0.5	1	<= 0.5	<= 20
HD10868-J53	8	16	<= 0.25	<= 0.25	≥ 16	0.5	1	<= 0.5	<= 20

Abbreviations: CAZ, ceftazidime; ATM, aztreonam; IPM, imipenem; MEM, meropenem; TOB, tobramycin; LEV, levofloxacin; TGC, tigecycline; COL, colistin; SXT, Sulfamethoxazole/Trimethoprim.

Table 3 Microbiological Characteristics of the Three Strains

Characteristic	**HD9931**		**HD9932**			**HD10868**		
	Chromosome	**pHD9931-1**	**Chromosome**	**pHD9932-1**	**pHD9932-2**	**Chromosome**	**pHD10868-1**	**pHD10868-2**
Size (bp)	5173744	226421	5172707	226396	282547	5329347	226394	282400
ST	17	-	17	-	-	17	-	-
GC content	58%	52%	58%	52%	47%	58%	52%	47%
Replicon type	-	IncFIB(K)	-	IncFIB(K)	IncFIB(K)	-	IncFIB(K)	IncFIB(K)
		IncHI1B		IncHI1B	IncHI1B		IncHI1B	IncHI1B
Resistance gene(s)	$bla_{SHV\text{-}172/96/94}$	-	$bla_{SHV\text{-}172/96/94}$	-	*aph(4)-Ia*	$bla_{SHV\text{-}172/96/94}$	-	*aph(4)-Ia*
	fosA6		*fosA6*		*aph(6)-Id*	*fosA6*		*aph(6)-Id*
	OqxB		*OqxB*		*aph(6)-Id*	*OqxB*		*aph(6)-Id*
	OqxA		*OqxA*		*aph(3')-Ia*	*OqxA*		*aph(3')-Ia*
					aph(3'')-Ib			*aph(3'')-Ib*
					aph(3'')-Ib			*aph(3'')-Ib*
					aadA1			*aadA1*
					aadA2b			*aadA2b*
					aac(3)-IV			*aac(3)-IV*
					armA			*armA*
					$bla_{DHA\text{-}1}$			$bla_{DHA\text{-}1}$
					$bla_{CTX\text{-}M\text{-}55}$			$bla_{CTX\text{-}M\text{-}55}$
					msr(E)			*msr(E)*
					mph(E)			*mph(E)*
					cmlA1			*cmlA1*
					qnrB4			*qnrB4*
					sul1			*sul1*
					sul3			*sul3*
					tmexD1			*tmexD1*
					TOprJ1			*TOprJ1*
					tmexC1			*tmexC1*

Note: Plasmids >10 kb were demonstrated here.

Briefly, the HD9931 genome was assembled into one chromosome (5173 kb) and a plasmid (226 kb) designated as pHD9931-1. Strains HD9932 and HD10868 were assembled into one chromosome and two plasmids. HD9932 contains two plasmids (pHD9932-1 (226 kb) and pHD9932-2 (282 kb)), similar to HD10868 (pHD10868-1 and pHD10868-2). The genetic structures of the chromosomes and plasmids were highly similar between HD9932 and HD10868. An IncFIB (Mar)/IncHI1B hybrid plasmid carrying the *tmexCD*1-*toprJ1* cluster was identified in both pHD9932-2 and pHD10868-2 plasmids. In addition, the hybrid plasmid replicon type IncFIB (Mar) /IncHI1B was found in three other plasmids: pHD9931, pHD9932-1, and pHD10868-1.

Several plasmids carrying the *tmexCD1-toprJ1* cluster were retrieved from GenBank for comparative analysis (Figure 1). These *tmexCD1-toprJ1*-positive strains were isolated from clinical samples or animals, and showed relatively high similarity. Notably, pSYCC1_tmex_287k (BioProject PRJNA904099), isolated from a live poultry market in a neighboring city in 2022, exhibited significant similarity to pHD9932-2.

Subsequently, we analyzed the genetic structure of the *tmexCD1-toprJ1* region in pHD9932-2 and pSYCC1_tmex_287k using Tn6855 (GenBank accession number MK347425) as a reference. The two 14.7 kb *tmexCD1-toprJ1* region in pHD9932-2 and pSYCC1_tmex_287k displayed the typical structure IS26–*strB*–*strA*–*tnpR*–*tnpA*–*hp*–*toprJ1*–*tmexD1*–*tmexC1*–*nfxB*–*hp*–IS26 with 100% coverage and 99.99% identity (Figure 2).

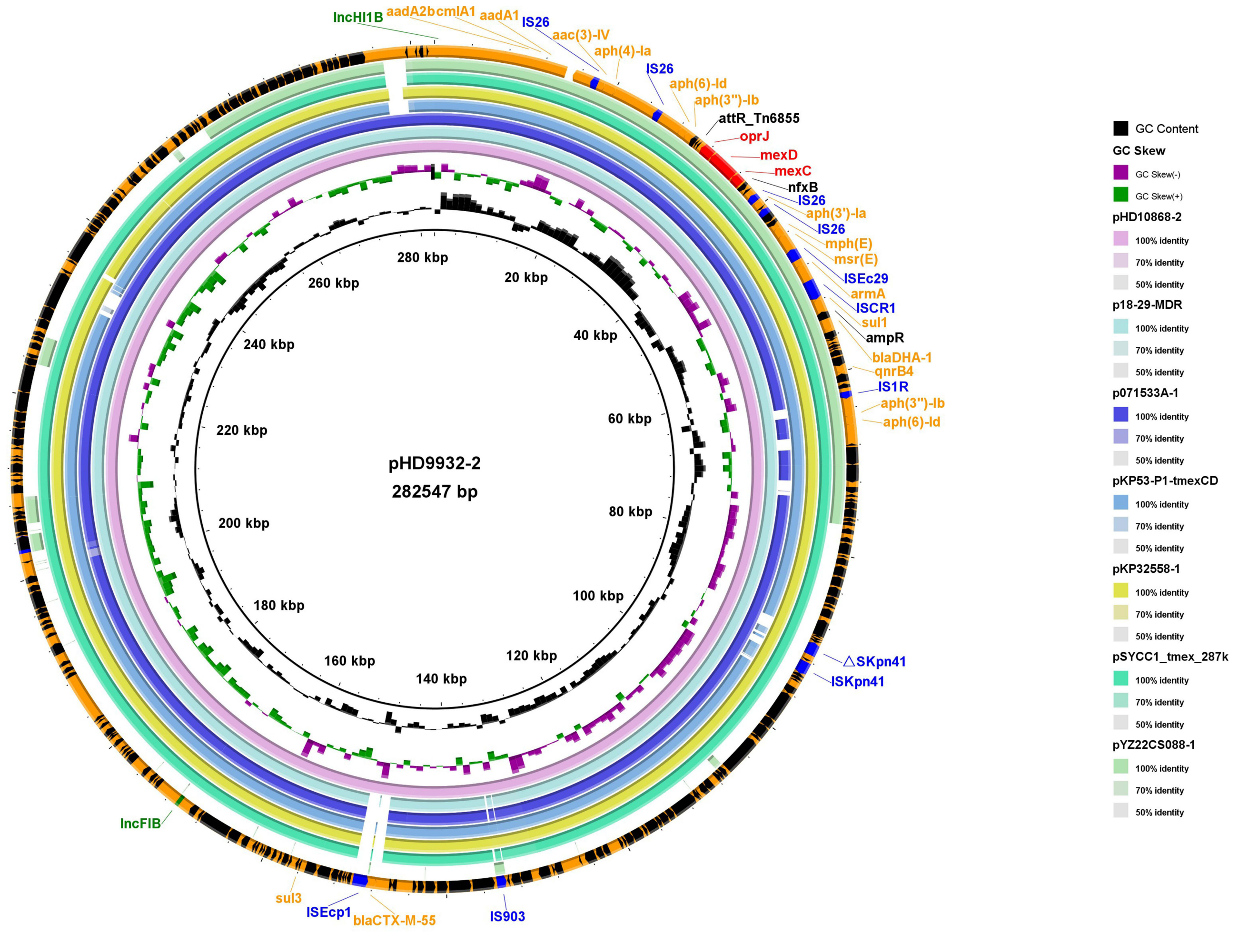


Figure 1 Alignment analysis of *tmexCD1-toprJ1*-bearing plasmid sequences among pHD9932-2, pHD10868-2 in this study, and similar plasmids downloaded from NCBI database, including p18-29-MDR (accession no. MK262712), p071533A-1 (accession no. CP138747), pKP53-P1-tmexCD (accession no. CP087670), pKP32558-1 (accession no. CP076031), pSYCC1_tmex_287k (accession no. CP113179), and pYZ22CS088-1 (accession no. CP110154).

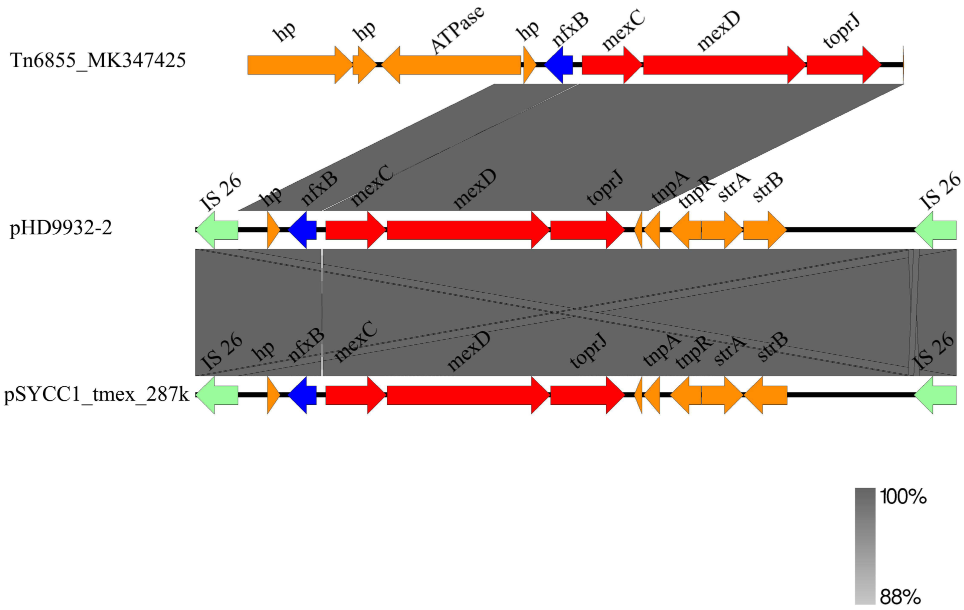


Figure 2 Genetic contexts of *tmexCD1-toprJ1* gene cluster in pHD9932-2, pSYCC1_tmex_287k, and Tn6855_MK347425.

Multi Locus Sequence Typing (MLST)

MLST classified all the isolates as sequence type 17 (ST17). Pairwise SNP comparisons revealed 11–35 SNPs on the chromosomes, indicating clonal relatedness (Table S1). Additionally, the backbones of pHD9931-1, pHD9932-1, and pHD10868-1 were highly similar with 99% coverage and 99.99% homology. Moreover, the three plasmids were nearly identical, sharing 7, 10, and 13 SNPs, respectively (Table S2). In addition, pHD9932-2 and pHD10868-2 shared almost 100% similarity with 18 SNPs. These findings strongly suggest that the three isolates belong to the same clone, indicating the possibility of nosocomial transmission.

Transmissibility and Effect on Growth of *tmexCD1-toprJ1*-Bearing Plasmids

Conjugation experiments were performed to evaluate the transmissibility of *tmexCD1-toprJ1*-bearing plasmids from *K. pneumoniae*. Two *tmexCD1-toprJ1*-bearing plasmids, pHD9932-2 and pHD10868-2, were successfully transferred from host strains into recipient E. *coli* J53. The conjugation transfer efficiency of the two plasmids was comparable at 37°C in LB (pHD9932-2: 1.1×10-6 transconjugants per donor cell, pHD10868-2: 2.5×10-6 transconjugants per donor cell). Notably, the AST results of the transconjugants (Table 2) revealed that the MIC of tigecycline in transconjugants HD9932-J53 and HD10868-J53 was significantly higher than that in E. *coli* J53, because both carried *tmexCD1-toprJ1*.

To assess the effect of the *tmexCD1-toprJ1*-bearing plasmid on the growth of the strain, growth curves were compared among six strains (HD9931, HD9932, HD10868, HD9932-J53, HD10868-J53, and E. *coli* J53). No statistically significant differences in growth were observed ($p > 0.05$; Figure 3), indicating that the acquisition of the *tmexCD1-toprJ1*-bearing plasmid had a minimal impact on the growth of both the parental strains and *E. coli* J53.

Discussion

Emerging tigecycline resistance poses a critical challenge in treating *K. pneumoniae* infections, particularly when tigecycline is used as a salvage therapy.[19] We identified a *K. pneumoniae* strain, HD9932, carrying the *tmexCD1-toprJ1* gene cluster, along with another strain, HD9931, isolated from the same patient a few days earlier. To further investigate the prevalence of *tmexCD1-toprJ1* within the hospital during the same period, we conducted a retrospective PCR screening of tigecycline-resistant Enterobacteriaceae clinical isolates. Isolate HD10868 were identified and sequenced. Although two of the three strains in this study carried this gene cluster, the overall prevalence of *tmexCD1-*

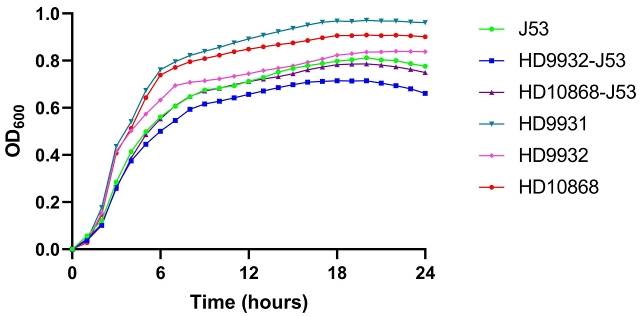


Figure 3 Growth curve comparison. The growth curves of the six strains showed no statistically significant differences (p>0.05).

toprJ1 remained relatively low in our sample collection (1/132, 0.76%; 1/78, 1.3%), which is consistent with previous reports.[20,21]

It is well known that bacteria often acquire mobile genetic elements (such as plasmids) to better adapt to changing environments. HD9931 and HD9932 exhibited a high degree of genetic similarity, differing only in 11 chromosomal and 10 plasmid SNPs. However, HD9932 harbored an additional plasmid, pHD9932-2, which carried multiple drug resistance genes, including *tmexCD1-toprJ1* and conferred resistance to several antibiotics compared with HD9931. HD10868 also showed high genetic similarity to HD9932 but differed by 35 chromosomal SNPs and 13/18 plasmid SNPs. HD10868 was isolated from a different patient who was cared for by the same medical team in the same ward, just one day after HD9932. This temporal and spatial proximity, combined with genetic evidence, suggests a possible intra-hospital clonal transmission. Conjugation experiments confirmed that *tmexCD1-toprJ1*-carrying plasmids from both HD9932 and HD10868 can be transferred to the recipient *E. coli* J53 strain with comparable efficiency. These findings highlight the importance of monitoring plasmid-mediated resistance mechanisms and implementing strict infection control measures to prevent the spread of resistant clones in health care settings.

Compared to J53, the tigecycline MICs in the transconjugants HD9932-J53 and HD10868-J53 increased by at least 4-fold, suggesting that *tmexCD1-toprJ1* played a significant role in the increase in the MIC of tigecycline. However, there was still a 4-fold difference in tigecycline MICs between HD9932 and HD10868. Other factors likely contributed to the observed differences in the donor strain HD10868. Genomic analysis revealed that HD10868 harbored a chromosomally encoded porin, lamB with a 40–amino acid truncation at the N-terminus, as well as a missense mutation (N389D) in the AcrA component of the AcrAB-TolC efflux pump. Deng et al[9] reported that *lamB* overexpression in *E. coli* ATCC25922 reduced tigecycline MIC, whereas *lamB* knockout caused an 8-fold increase in tigecycline MIC. Several studies have documented the role of AcrAB-TolC in tigecycline resistance.[15,22,23] Whether these mutations contributed to tigecycline resistance in our strains remains to be experimentally confirmed.

The IncFIB-HI1B hybrid plasmid carrying *tmexCD1-toprJ1* has been identified in *K. pneumoniae* from flies, food production chains, and clinical sources and is considered a dominant vehicle for transmitting this resistance gene cluster.[20,24] The plasmid pSYCC1_tmex_287k, which belongs to the IncHI-type hybrid plasmid family and exhibits significant similarity to pHD9932-2, was isolated from *K. pneumoniae* in a live poultry market in Yangzhou City, an area neighboring the researchers' location. These findings support previous reports and raise the possibility of interspecific transmissions.

Although our results suggest plasmid acquisition by clinical strains and possible transmission routes within the hospital, the original source of the plasmid remained unidentified. Further research is needed to clarify the mechanisms underlying the higher tigecycline resistance observed in HD10868 than in HD9932.

Conclusion

In summary, our study described the evolutionary trajectory of *K. pneumoniae* under clinical antibiotic pressure. The acquisition of a plasmid carrying multiple resistance genes, including *tmexCD1-toprJ1*, combined with chromosomal mutations, collectively contributed to tigecycline resistance. This highlights the complexity of resistance gene transfer and underscores the need for continued vigilance and research in this field.

Ethics Statement

This study was approved by the Medical Ethics Committee of The Affiliated People's Hospital of Jiangsu University (K-20220149-Y). This study was retrospective and associated with bacterial drug susceptibility and the genetic information of the specimens. Written informed consent has been obtained from all study participants prior to study commencement for the collection of the isolates. All the patient's data in this study were collected anonymously and ensured the confidentiality of their information. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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