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Whole Genome Sequencing of *Klebsiella pneumoniae* Strain Unravels a New Model for the Development of Extensive Drug Resistance in Enterobacteriaceae

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Abstract:

Introduction:

Increased incidence of carbapenem-resistant Enterobacteriaceae (CRE) has been reported worldwide. The WHO warns about the imminent risk to global health if the spread of resistant bacteria is not contained.

Materials and Methods:

Here, single molecule real time sequencing was used to analyse the whole genome and resistome of SKGH01, a strain of *Klebsiella* pneumoniae.

Results and Discussions:

The data showed that SKGH01 was resistant to all commercially available antibiotics. A complete account of extensively drugresistant (XDR) CRE at a genomic level and the entire location map of all antibiotic resistance components are here presented. Additionally, this work proposes a model of XDR acquisition in Enterobacteriaceae.

Keywords: Klebsiella pneumoniae, Extensive drug resistance (XDR), Whole genome sequencing, Antibiotics, WHO, Enterobacteriaceae.

1. INTRODUCTION

Klebsiella pneumoniae of the Enterobacteriaceae family is a non-motile, rod-shaped, Gram-negative bacterium and it is one of the primary causes of hospital-acquired infections globally [1]. *K. pneumoniae* genomes have a strong virulence and a wide array of resistance factors that make them a major source of antimicrobial resistance genes [2]. The *K. pneumoniae* that produce carbapenemase (KPC-KP) are the most challenging pathogens. They exhibit extensive drug-resistant phenotypes and high potential for rapid spread having an overwhelming impact on morbidity and mortality rates [3]. Colistin and polymyxin B are antimicrobial agents that, for the most part, are still active against KPC-KP [4]. However, the emergence of polymyxin-resistant KPC-KP has recurrently been reported [5]. In *K. pneumoniae*, resistance to cationic antimicrobial agents is facilitated via lipopolysaccharide (LPS) sequence alterations driven by the pbgPE operon products, which are highly conserved among Enterobacteriaceae [6, 7]. The PhoQ/PhoP and PmrAB signalling systems positively regulate the pbgPE operon [7]. Activation of the PhoQ/PhoP signalling system induces production of a transmembrane regulatory protein called MgrB. The protein acts as a negative feedback loop on this signalling system by interacting with the PhoQ sensor kinase [8]. The MgrB protein has been shown to have this regulatory function in *Salmonella enterica, Escherichia coli* as well as *Yersinia pestis* and thus might also be conserved in other species, including *K. pneumoniae* [8].

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2. MATERIAL AND METHODS

The Hospital Medical Executive Committee approved the study. The SKGH01 strain was isolated from an 80-yearold man with urinary tract infection. The species was characterised with the VITEK II compact GN system (bioM'erieux, France). For the antimicrobial susceptibility testing the VITEK II N211 system (bioM'erieux) and the Etest method were used. Breakpoints published by the Clinical and Laboratory Standards Institute were applied to determine the susceptibility to the tested antibiotics and the European Committee for Antibiotic Susceptibility Testing breakpoints in the E-test were used to determine the minimum inhibitory concentration of colistin. K. pneumoniae SKGH01 genome was sequenced with the Pacific Biosciences (PacBio, Inc., CA) RS II Single-Molecule Real Time (SMRT) kit. Bell template libraries were prepared using the Template Preparation Kit (PacBio). A single, streamlined protocol was used to create libraries of varying insert lengths, from 250 bp to 20,000 bp. The PacBio SMRT analysis software suite (v. 3.0) and hierarchical genome assembly process were used for *de novo* genome assembly. For the gene calling and automatic functional annotation of SKGH01 chromosome and plasmids the Prokka v1.12b (Vicbioinformatics, Australia) software was used. ResFinder and PlasmidFinder with data from the Center for Genomic Epidemiology (CGE) were employed to analyse the antimicrobial resistance genes and plasmid types. The Antibiotic Resistance Genes Database [9] and the Comprehensive Antimicrobial Resistance Database [10] were compared to all the predicted coding regions in order to screen the outstanding antimicrobial resistance genes. The insertion sequences (IS) in the genome were identified with the online tool, ISfinder 2 (version 2016-05-27). Closely related bacterial genomes were identified with the Microbial Nucleotide BLAST program. The search set consisted of complete genomes of K. pneumoniae (taxid: 573) available in the NCBI database. The BLAST search produced 48 significant hits, with overall similarities between 95% and 99%, and coverages between 85% and 98%. A genome tree was built, which comprised SKGH01 and 40 related strains from NCBI database (accession date: 10/05/16).

3. RESULTS AND DISCUSSION

The data showed that SKGH01 is a true extensively Drug-Resistant (XDR) strain to ampicillin, ampicillinclavulanic acid, piperacillin-tazobactam, cefotaxime, ceftazidime, cefepime, aztreonam, meropenem, cotrimoxazole, amikacin, gentamicin, and colistin. A total of 6 contigs representing 6,088,457 bases (GC content 56.54%, N50=10,230) were obtained from assembled sequences of strain SKGH01 (Table S1). 6,034 genes (total), 5,907 CDS (total), 5,777 genes (coding), and 127 tRNAs genes were annotated for final contigs. The complete genome of K. pneumoniae SKGH01 consists of a circular chromosome 5,490,611 base-pairs in length with an average G-C content of 56.4%, four circular plasmids. The complete genome of strain SKGH01 consisted of a circular chromosome (5,490,611 base-pairs long) with an average G-C content of 56.4%, and four circular plasmids. Most of the genes for acquired resistance to antibiotics were positioned on the chromosome. The complete resistomes of strain SKGH01 are presented in Table 1. The insertion sequence, ISEcp1 (synonym, ISEc9) was found in four and blaOXA-181 in three places on the SKGH01 chromosome. The search for the (partial) protein sequence encoded by mgrB was performed. The most significant tblast match was a 42-amino acid, 5' partial sequence of mgrB, which corresponded to the first ISEcp1 position identified on the SKGH01 chromosome. The remaining 3' partial sequence of mgrB was identified with a manual search. Another manual search identified left- and right-flanking, inverted repeats (IRL and IRR, respectively) located at the first ISEcp1 position on the chromosome. We also found two alternative IRRs (IRRalts), which produced the insertions ISEcp1-blaOXA-181-IRRalt1 and ISEcp1-blaOXA-181-IRRalt2. One of these insertions led to the inactivation of the mgrB gene (Fig. S1). ISEcp1-like insertion sequences are the most common genetic element associated with blaCTX-M, blaCMY and blaACC genes and have more recently been associated with blaOXA-181 [11].

START	STOP	Gene	Identity %*	Associated Resistance	
2637986	2638846	shv-11	100	beta-lactam resistance gene	
1544531	1545253	baeR	91	aminocoumarin resistance gene; aminoglycoside resistance gene;	
2009887	2010294	h-ns	94	macrolide resistance gene; fluoroquinolone resistance gene; tetracycline resistance gene; beta-lactam resistance gene	
253419	254558	acrE	75	beta-lactam resistance gene; fluoroquinolone resistance gene	
489403	490224	bacA	89	peptide antibiotic resistance gene	
1546725	1548140	mdtD	84	efflux pump conferring antibiotic resistance	
95184	95666	dfrA14	99	trimethoprim resistance gene	

Table 1.	Resistome	analysis for	r the SKGH01	strain of K.	pneumoniae.

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(Table 1) contd.....

START	STOP	Gene	Identity %*	Associated Resistance
987867	991019	oqxB	98.5	Quinolone resistance
991043	992218	oqxA	99.5	Quinolone resistance

* Percentage given by the Antibiotic Resistance Genes Database (ARDB) and the Comprehensive Antimicrobial Resistance Database (CARD) when compared with known resistance genes database.

CONCLUSION

Here, using the long-read sequencing technology multiple, identical, carbapenem-resistance elements in the *K. pneumoniae* strain SKGH01 genome were identified. Based on the data, a new model explaining how XDR in this *K. pneumoniae* isolate developed via colistin resistance by mgrB gene disruption by ISEcp1. In this model, new resistance was driven by the existing mobile resistance determinants. Additionally, the data showed that ISEcp1 sequence interrupted the negative feedback regulator of the PhoQ-PhoP signalling system, namely the *mgrB* gene. Interestingly, this disruption was previously shown to drive the KPC-KPs acquired colistin resistance. Indeed, interruption of the *mgrB* gene caused upregulation of PhoQ-PhoP signalling; in turn, this upregulation activated the Pmr system, which was responsible for modifying the LPS target of polymyxin [12].

NUCLEOTIDE SEQUENCE ACCESSION NUMBER

The nucleotide sequence data are available in the GenBank nucleotide database, under accession numbers CP015500.1 to CP015505.1.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the hospital Medical executive committee.

HUMAN AND ANIMAL RIGHTS

Animals did not participate in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008.

CONSENT FOR PUBLICATION

Consent for publication is obtained.

CONFLICT OF INTEREST

The author declare that they have no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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