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First Report of OXA-181-Producing *Escherichia coli* in China and Characterization of the Isolate Using Whole-Genome Sequencing

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We report the first OXA-181-producing strain in China. $bla_{OXA-181}$ was found in sequence type 410 (ST410) *Escherichia coli* strain WCHEC14828 from a Chinese patient without recent travel history. Genome sequencing and conjugation experiments were performed. $bla_{OXA-181}$ was carried on a 51-kb self-transmissible IncX3 plasmid and was linked with *qnrS1*, a quinolone resistance gene. $bla_{OXA-181}$ was introduced onto the IncX3 plasmid from a ColE2-type plasmid, and IncX3 plasmids have the potential to mediate the dissemination of $bla_{OXA-181}$.

OXA-181 is an OXA-48-type carbapenemase conferring resistance to penicillins and carbapenems, and its encoding gene $bla_{OXA-181}$ originates from *Shewanella xiamenensis*, an environmental bacterium (1). The $bla_{OXA-181}$ gene was initially identified in *Enterobacter cloacae* and *Klebsiella pneumoniae* isolates that were recovered in 2007 at several locations in India (2). Since then, $bla_{OXA-181}$ has been sporadically found in several species of *Enterobacteriaceae* in a few countries, but it has not been identified in China previously. Unlike other major carbapenemase genes, e.g., bla_{NDM} and bla_{KPC}, found in the *Enterobacteriaceae*, the genetic context of $bla_{OXA-181}$ and the plasmid and host strain carrying this gene remain largely uninvestigated. This study characterizes a carbapenem-resistant *Escherichia coli* clinical isolate that was found to carry $bla_{OXA-181}$ in China.

Strain WCHEC14828 was obtained from the blood culture of a leukemia patient receiving stem cell transplantation on 2014. It was identified as *E. coli* and was resistant to imipenem (MIC, 16 μg/ml), meropenem (MIC, 32 μg/ml), ceftazidime (MIC, 128 μg/ml), and ciprofloxacin (MIC, 64 μg/ml) but was susceptible to amikacin (MIC, 16 μg/ml), colistin (MIC, 2 μg/ml), and tigecycline (MIC, 1 μg/ml) as determined using the microdilution method following recommendations of the Clinical and Laboratory Standards Institute (CLSI) (3). Strain WCHEC14828 was also resistant to ampicillin-sulbactam, aztreonam, cefazolin, cefepime, cefotaxime, cefoxitin, ceftriaxone, ertapenem, gentamicin, levofloxacin, nitrofurantoin, piperacillin-tazobactam, tobramycin, and trimethoprim-sulfamethoxazole as determined by Vitek II and to cefoperazone-sulbactam as determined by disk diffusion.

The strain was screened for the acquired carbapenemase-encoding genes bla_{GES}, bla_{KPC}, bla_{IMP}, bla_{NDM}, bla_{OXA-48}-like, and bla_{VIM} using PCR as described previously (4–7). The bla_{OXA-48}-like gene was the only carbapenemase-encoding gene that was detected in strain WCHEC14828. Sequencing the complete coding sequence of the bla_{OXA-48}-like gene amplified with an additional pair of primers (8) revealed the presence of $bla_{OXA-181}$. To our knowledge, this is the first report of OXA-181 in China. Since the identification of OXA-181 in India in 2007, OXA-181-producing *Enterobacteriaceae* has been reported from several other countries in the Indian subcontinent, i.e., Bangladesh (9) and Sri Lanka (10) and potentially Nepal, as a Nepalese patient hospitalized in New Zealand was found to be carrying an OXA-181-producing *K. pneumoniae* (11). Outside the subcontinent, *Enterobacteriaceae* isolates producing OXA-181 have been found in Canada (12), France (13), the Netherlands (14), New Zealand (in a patient from Nepal) (11), Norway (in a patient from Romania) (15), Oman (16), Romania (17), Singapore (9), South Africa (18), and United Kingdom (in a patient from India) (19). In most cases (9, 11–14, 19, 20), the patients from whom OXA-181-producing *Enterobacteriaceae* were recovered had a recent travel history to the Indian subcontinent. In addition, $bla_{OXA-181}$ has been identified in the chromosome of an *S. xiamenensis* isolate recovered in India (1). All of the above findings suggest that the Indian subcontinent is likely the origin place of OXA-181. Nonetheless, the patient in this study had no recent travel history to the Indian subcontinent, and it remains unclear how and where she acquired this OXA-181-producing strain.

Genome DNA of strain WCHEC14828 was prepared using the QIAamp DNA minikit (Qiagen, Hilden, Germany) and was subjected to whole-genome sequencing with a ca. 100× coverage using the HiSeq 2500 Sequencer (Illumina, San Diego, CA, USA) following the manufacturer's protocol at the Beijing Genomics Institute. A total of 6,051,062 clean reads were obtained from the genome sequencing for strain WCHEC14626. The GC content was 50.24%. Reads were assembled to 154 contigs, of which 98 were ≥500 bp in length using the SPAdes program (21). The Prokka program (22) was employed for annotating the genome sequence.

Strain WCHEC14828 was assigned to sequence type 410

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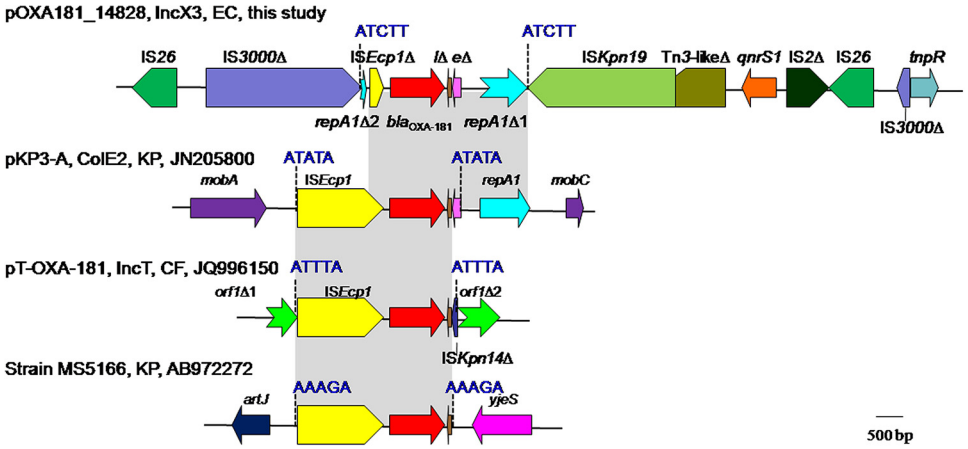

FIG 1 Genetic contexts of $bla_{OXA-181}$. The name, the type, the host strain, and the GenBank accession number of plasmids carrying $bla_{OXA-181}$ are shown. In strain MS5166, it remains unknown whether $bla_{OXA-181}$ is on a plasmid, as only a partial sequence is available. EC, *E. coli*; KP, *K. pneumoniae*; CF, *C. freundii*; Δ, Incomplete; *l*Δ, *lysR*Δ; *e*Δ, *ereA*Δ. The 5-bp AT-rich DRs due to the transposition of IS*Ecp1* are blue. Identical regions of different contexts are gray. On plasmid pOXA181_EC14828, *repA1* (encoding the ColE2-type replication initiation protein) is interrupted into two parts, which are shown as *repA1*Δ1 and *repA1*Δ2 here. *repA1*Δ2 was originally at the 3′ end of *repA1*, i.e., downstream of *repA1*Δ1 but is located close to $bla_{OXA-181}$ on pOXA181_EC14828. On plasmid pKP3-A, *mobA* and *mobC* are genes encoding proteins for plasmid mobilization. On plasmid pT-OXA-181, a gene of unknown function, which is shown as an open reading frame (ORF) here, is interrupted into two parts by the insertion of IS*Ecp1* and the neighboring sequences ($bla_{OXA-181}$, *lysR*Δ, and a truncated IS*Kpn14*). In strain MS5166, *artJ* is a lysine-arginine-ornithine-binding periplasmic protein-encoding gene, and *yjeS* encodes an Fe-S electron transport protein.

(ST410) using the assembled genome sequence (see below) to query the seven alleles of the multilocus sequence typing scheme for *Escherichia coli* (http://mlst.warwick.ac.uk/mlst/dbs/Ecoli) (23). ST410 is of the ST23 clonal complex, and it has been proposed as the founder ST of the ST23 complex (24). *E. coli* of ST410 has a worldwide distribution, as it has been recovered from humans and animals in Europe (Belgium, France, Germany, Greece, Ireland, Italy, Norway, Portugal, Spain, Switzerland, and United Kingdom), Africa (Congo, Ghana, Mauritania and Tunisia), Asia (Taiwan and Vietnam), North America (Canada), and South America (Brazil) (http://mlst.warwick.ac.uk/mlst/dbs/Ecoli) (25–27). In addition, strain WCHEC14828 belonged to the phylogenetic group A as determined by phylogenetic group (A, B1, B2, and D) typing performed as described previously (28).

In strain WCHEC14828, $bla_{OXA-181}$ was carried on a 51-kb plasmid, pOXA181_EC14828, which was completely circularized with intervals between contigs being filled by PCR with primers designed based on available sequences and Sanger sequencing. pOXA181_EC14828 was a self-transmissible plasmid, as it was able to be transferred to the recipient strain, azide-resistant *E. coli* strain J53, in the conjugation experiment and belonged to the IncX3 type. $bla_{OXA-181}$ has not been found on an IncX3 plasmid before but has been detected on a 84-kb IncT plasmid (29) or on a 7.6-kb ColE2-type plasmid (1). The presence of $bla_{OXA-181}$ on a self-transmissible IncX3 plasmid is of significance, as IncX3 plasmids have been found as a common vehicle mediating the dissemination of bla_{NDM-1} and bla_{NDM-5} among the *Enterobacteriaceae* in China (30, 31). Although this is the first case of $bla_{OXA-181}$, IncX3 plasmids have the potential to facilitate the wide dissemination of this carbapenemase gene.

The IncX3 plasmid backbone (26 kb in size) of pOXA181_EC14828 was nearly identical (with only two nucleotide differences) to those of two IncX3 plasmids carrying bla_{NDM-1}, of which one was recovered from another local ST3835 (the ST10 complex) *E. coli* strain (unpublished data), and the other was plasmid pNDM-HF727 from an *E. cloacae* strain from Guangdong, another province in China (31). The presence of $bla_{OXA-181}$ on an IncX3 plasmid with a nearly identical backbone to IncX3 plasmids carrying bla_{NDM-1} suggests that $bla_{OXA-181}$ might have coexisted with bla_{NDM-1} in the same host strain. Indeed, the coexistence of $bla_{OXA-181}$ and bla_{NDM-1} has been found in a few strains previously (9, 10, 12, 15–17, 29). However, plasmids within almost all of those strains carrying bla_{NDM-1} and $bla_{OXA-181}$ have not been characterized in previous studies, and therefore it remains largely unclear whether bla_{NDM-1} and $bla_{OXA-181}$ have been carried by a single plasmid or by different ones in those strains. The only exception was in a *Citrobacter freundii* strain; bla_{NDM-1} was not detected on the plasmid carrying $bla_{OXA-181}$, suggesting that bla_{NDM-1} is likely located on a different plasmid. It would be interesting to explore whether bla_{NDM-1} was located on an IncX3 plasmid within those strains carrying bla_{NDM-1} and $bla_{OXA-181}$ (9, 10, 12, 15–17, 29). On the other hand, as WCHEC14828 has no bla_{NDM-1}, it may also be possible that an IncX3 plasmid carrying $bla_{OXA-181}$ has replaced the IncX3 plasmid carrying bla_{NDM-1} due to plasmid incompatibility.

In addition to $bla_{OXA-181}$, strain WCHEC14828 had a few resistance genes, including $bla_{CTX-M-15}$ (an extended-spectrum β-lactamase [ESBL] gene widely distributed in the world), bla_{CMY-2} (a plasmid-borne AmpC gene), bla_{OXA-1} (a non-ESBL oxacillinase gene), bla_{TEM-1b} (a non-ESBL β-lactamase gene), bla_{ampC} (a chromosome-based AmpC gene), *aac(6′)-Ib-cr* (encoding an aminoglycoside acetyltransferase with low-level activity against fluoroquinolones), *qnrS1* (conferring low-level resistance to fluoroquinolones), and *tetA* (a tetracycline resistance gene). The vast majority of these genes were bounded by IS elements, making their positioning very difficult. Among these resistance genes, only *qnrS1* was located on pOXA181_EC14828 (Fig. 1). *qnrS1* was flanked by an IS*2*-like insertion sequence upstream, which was truncated by IS*26*, and by a Tn*3*-like transposon downstream, which was truncated by IS*Kpn19*. The IS*26*-*qnrS1*-

IS*Kpn19* region is also present on several plasmids carrying the carbapenemase genes bla_{NDM-1} and bla_{KPC-2} in China (GenBank accession numbers KC958437 and KF914891) (32) but none was of the IncX3 type. The *qnrS1* region on pOXA181_EC14828 was, therefore, introduced from another plasmid, which was likely due to the action of a transposable element.

Based on the limited currently available data, $bla_{OXA-181}$ is always adjacent to IS*Ecp1*. It is known that a single copy of IS*Ecp1* is able to mobilize neighboring resistance genes including $bla_{OXA-181}$ by misidentifying various sequences as its alternative right-hand inverted repeat (IR) (1, 33). Indeed, in all of three contexts of $bla_{OXA-181}$ available in the GenBank, the 5-bp AT-rich direct target repeats (DRs) that are the characteristics of the transposition of IS*Ecp1* have always been identified flanking the left-hand IR and downstream of $bla_{OXA-181}$ (Fig. 1). This suggests that the mobilization of $bla_{OXA-181}$ resulted from the action of IS*Ecp1* in the three cases. However, unlike those in previous contexts of $bla_{OXA-181}$, IS*Ecp1* was truncated on pOXA181_EC14828. On plasmid pKP3-A, a ColE2-type replication initiation protein-encoding gene *repA1* is located downstream of $bla_{OXA-181}$. The presence of *repA1* on pOXA181_EC14828 suggests that $bla_{OXA-181}$ was introduced from a ColE2-type plasmid onto the IncX3 scaffold and formed the plasmid pOXA181_EC14828. Surprisingly, *repA1* was interrupted into two parts on pOXA181_EC14828 with the small part present upstream of $bla_{OXA-181}$ instead (Fig. 1). A 5-bp AT-rich duplicate sequence (ATCTT) was identified at the end of the large part and the beginning of the small part of the interrupted *repA1* gene. This suggests that the interruption of *repA1* was likely due to the insertion of an additional IS*Ecp1*. The truncation of the IS*Ecp1* abutting $bla_{OXA-181}$ and translocation of a part of *repA1* from the downstream of $bla_{OXA-181}$ to the upstream might be explained by subsequent homologous recombination between two copies of IS*Ecp1* as proposed before (34). $bla_{OXA-181}$ was on pOXA181_EC14828, and the generation of such a complicated context of $bla_{OXA-181}$ is likely a result of the direct insertion and subsequent recombination of multiple transposable elements. In addition, the two copies of IS*26* in the region containing $bla_{OXA-181}$ and *qnrS1* can form a composite transposon, which has the potential to mobilize $bla_{OXA-181}$ independent of the action of IS*Ecp1*.

In conclusion, we report here the first OXA-181-producing strain in China, which was an ST410 *E. coli* strain causing blood stream infection (BSI) in a patient with leukemia. $bla_{OXA-181}$ was likely introduced from a ColE2-type plasmid onto the IncX3 scaffold. The association of $bla_{OXA-181}$ and an IncX3 plasmid is worrying as the IncX3 plasmid has the potential to serve as a common vehicle for mediating the further dissemination of $bla_{OXA-181}$ among the *Enterobacteriaceae* like it is currently doing for bla_{NDM-1} in China.

Nucleotide sequence accession number. Reads of WCHEC14828 genome sequence were deposited into the NCBI database under BioProject number PRJNA270793 and BioSample number SAMN03268883. The complete sequence of pOXA181_EC14828 was deposited into GenBank under the accession number KP400525.

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