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REVIEW

# *Klebsiella pneumoniae* with Two Carbapenemases: Where Molecular Research Stands Now

Qian Yu[1], Gaosha Li[1], Qianqian Xu[2], Yijun Zhu[1]

[1]Department of Clinical Laboratory, Affiliated Jinhua Hospital, Zhejiang University School of Medicine (Jinhua Municipal Central Hospital), Jinhua, Zhejiang, People's Republic of China; [2]Jinhua Prefectural Center for Disease Control and Prevention, Jinhua, Zhejiang, People's Republic of China

Correspondence: Yijun Zhu, Department of Clinical Laboratory, Affiliated Jinhua Hospital, Zhejiang University School of Medicine (Jinhua Municipal Central Hospital), No. 365 Renmin East Road, Jinhua, Zhejiang Province, 321000, People's Republic of China, Tel +8657982553839, Email zhuyijunwz@sina.com



**Abstract:** *Klebsiella pneumoniae* is a significant pathogen causing various infections. Since the 1990s, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has threatened global health. Its main resistance mechanism is producing carbapenemases like KPC, NDM, OXA, IMP and VIM, which have different prevalent isoforms and resistance features. In China, KPC is the most common carbapenemase in CRKP, followed by metallo-β-lactamase (MBL). Alarmingly, an increasing number of *K. pneumoniae* strains carry two or more types of enzymes, making resistance more complex. This review summarizes the major carbapenemases carried by *K. pneumoniae*, their global spread, and plasmids of CRKP enzyme type combinations reported in existing studies. Common combinations such as KPC + metalloenzyme, bimetallic enzyme, and metalloenzyme + OXA-48 are discussed in detail, including their genetic environments and transfer characteristics. Whole genome sequencing technology plays a crucial role in studying drug resistance genes of *K. pneumoniae*, facilitating in - depth identification and analysis of bacteria, and being useful for outbreak investigation and epidemiological surveillance. In conclusion, resistance genes in *K. pneumoniae* are often located on mobile elements. Different resistance genes tend to be carried by specific plasmids, which have high transformation rates and little impact on host growth. In order to prevent the emergence of Klebsiella pneumoniae carrying multiple drug-resistant genes, several measures such as the rational use of antibiotics, earlier monitoring of the transmission trajectory of strains, and the prediction of the development direction of drug resistance as much as possible are particularly important in the world today.

**Keywords:** *Klebsiella pneumoniae*, two carbapenemases, whole genome sequencing

## Introduction

*Klebsiella pneumoniae* is a crucial pathogen causing hospital- and community-acquired infections, including pneumonia, septicaemia, urinary tract infections, bacteraemia, meningitis and pyogenic liver abscesses.[1] Since the 1990s, the increasing frequency of infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has posed a tremendous threat to worldwide public health, with mortality rates as high as 37.2%.[2,3] In the United States and Europe, carbapenem-resistant Klebsiella pneumoniae is mainly of the ST258 type, while in China, it is mainly of the ST11 type.[4] The primary resistance mechanism is the synthesis of carbapenemases, which include enzymes A, B, and D. B enzymes, also known as metallo β-lactamases, catalyze the breakdown of β-lactam antibiotics, whereas A and D enzymes target serine. In China, the primary carbapenemase prevalent in CRKP is *Klebsiella pneumoniae* carbapenemase (KPC), which accounts for about 70% of the total. This is followed by MBL, which accounts for around 10% of CRKP isolates.[5] However, an alarming trend is emerging, with a growing number of cases of *Klebsiella pneumoniae* harboring two or more enzyme types, indicating that with the introduction of new enzyme-inhibiting medicines, resistance to *Klebsiella pneumoniae* is becoming more complex. As a result, there is an urgent need for further understanding and investigation of *Klebsiella pneumoniae*, which currently produces two or more enzyme kinds.

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## Major Carbapenemases Carried by Klebsiella Pneumoniae

The main carbapenemases carried by carbapenem-resistant *Klebsiella pneumoniae* include KPCase, NDMase,[6] OXAase, IMPase[7] and VIMase.[8] Through summarizing the literature, it was found that the main prevalent subtypes of these classes of carbapenemases are KPC-2, NDM-1, OXA-48, NDM-5 and IMP-4. Also, the resistance generated by various types of enzymes differs and can be better explored through research results from throughout the world:

### KPC

Of all the carbapenemases, KPC is the most common. KPC-1 quickly spread to the east coast of the United States after being first identified and found there in 1996. Previously, it was considered endemic to the New York region.[9] In 2007, a clonal expansion of KPC-2-producing CRKP strains caused an outbreak in Crete, Greece, and these strains were clonally related to those from New York.[10,11] This strain has been referred to as the "super-popular Greek clone" and has been the primary infecting clone in Greece ever since.[12] According to data from the Centers for Disease Control and Prevention (CDC), type ST258 accounts for about 70% of CRKP strains that produce KPC.[13] Additionally, there was a high association between ST258-type strains and the emergence of antibiotic multi-drug resistance.[14] However, investigations have shown that only a tiny fraction of individuals have been colonized by the KPC-2-producing ST258 strain of CRKP and subsequently become sick, indicating that this strain is an opportunistic pathogen of low virulence. These CRKP strains simultaneously constitute an expansion group with comparatively low rates of pathogenicity and death.[15] Since 2009, Chinese researchers[16] have found that Chinese strains carrying the $bla_{\text{KPC-2}}$ gene have a different genetic environment around their resistance genes than the classical " Tn4401" of the American isolate. A novel genetic environment in the $bla_{\text{KPC-2}}$ gene from pKP048 contains a complete structure based on a Tn*3* transposon and a partial Tn*4401* fragment in the gene order of Tn*3* transposase, Tn*3* catabolism enzyme, IS*Kpn8,* $bla_{\text{KPC-2}}$ and IS*Kpn6*-like elements. Subsequent studies identified two more genetic structures containing $bla_{\text{KPC-2}}$: Tn*1721*-$bla_{\text{KPC-2}}$-Tn*3* and Tn*1721*-$bla_{\text{KPC-2}}$-ΔTn*3*-IS*26*.[17,18] After obtaining *Klebsiella pneumoniae* with the complete $bla_{\text{KPC-2}}$ gene sequence from the NCBI database and analyzing it, it was discovered that non-Tn*4401* elements contained the majority of the $bla_{\text{KPC-2}}$ gene of ST11CRKP.[19] Meanwhile, the epidemic spread of ST11-type *Klebsiella pneumoniae* carrying $bla_{\text{KPC-2}}$ in China is mainly associated with horizontal transfer mediated by incompatible group F plasmids.[20–24] The Tn*1721*-$bla_{\text{KPC-2}}$-carrying IncFII plasmids appear to be interchangeable with several ST11-type *Klebsiella pneumoniae* strains. Horizontal transfer of Tn*1721* and IncFII plasmids appears to be an important factor driving molecular diversification among ST11CRKP strains, as inferred by Fu et al. Additionally, the ST39CRKP, which produces KPC-2, appears. This serves as a reminder that strains of bacteria are constantly developing medication resistance mutations.[25]

### NDM

NDM is a carbapenemase that is extremely resistant to drugs and has a high rate of dissemination.[26] Studies on the $bla_{\text{NDM-1}}$ gene were first found on a Swedish resident of New Delhi in late 2007, from whom the first isolation of carbapenem-resistant *Klebsiella pneumoniae* carrying $bla_{\text{NDM}}$ was made.[27] Since then, there has been significant alarm over its quick global spread.[28] Following then, reports of $bla_{\text{NDM}}$ genes have come from Pakistan, India, and the UK.[29,30] In China, the initial $bla_{\text{NDM-1}}$ gene epidemic was caused by the transmission assistance provided by the IncX3-type plasmid in *Klebsiella pneumoniae* ST11.[6,31] The sequence consistently occurred in the 100 bp upstream area of $bla_{\text{NDM-1}}$, according to Toleman et al's analysis of all available NDM-1-related sequences. They also showed that the $bla_{\text{NDM-1}}$ gene initially emerged in A*cinetobacter baumannii* chimeras mediated by IS*Aba125*.[32] Others have also identified a new gene ($ble_{\text{MBL}}$, the *ble* gene associated with the metallolactamase NDM-1) by analysing the direct genetic environment of $bla_{\text{NDM-1}}$ in a range of NDM-1-producing Enterobacteriaceae bacteria. $ble_{\text{MBL}}$ is able to encode a novel bleomycin-resistant protein (BRP), named BRPMBL, which bears weak similarity (less than 60% amino acid identity) to known BRPs. BRPMBL expression confers resistance to bleomycin and bleomycin-like molecules in Enterobacteriaceae and A*cinetobacter baumannii*. Co-expression of $bla_{\text{NDM-1}}$ and $ble_{\text{MBL}}$ genes under the control of the same promoter located upstream of the $bla_{\text{NDM-1}}$ gene and at the end of the insertion sequence IS*Aba125*. Most NDM-producing strains have the $ble_{\text{MBL}}$ gene. This study shows that the carbapenemase NDM-1 is subject to selection by bleomycin-like molecules and

that strains capable of producing BRPMBL are better adapted to various environments. Thus, it has been hypothesized that the usage of antibiotics, anticancer medications, and naturally occurring bleomycin molecules in the environment (such as in seepage samples) may all be contributing factors to the proliferation of strains that produce NDM.[33,34] Since NDM-1, other mutants of various kinds have been discovered. *bla*$_{\text{NDM-5}}$ was initially identified from Escherichia coli type ST648 from the throat and perineum of a British patient who had been admitted to the hospital in India. Mutations in Val3Leu at position 88 and Met3Leu at location 154 distinguish NDM-5 from NDM-1. In contrast, *bla*$_{\text{NDM-7}}$ was discovered in Germany in 2013, and sequencing showed that the *bla*$_{\text{NDM-7}}$ gene has two point mutations at loci 388 (GA) and 460 (AC), corresponding to amino acid substitutions in Asp130Asn and Met154Leu, respectively.[35]

## IMP

IMP was originally discovered in Japan in 1988 from an imipenem-resistant strain of *Pseudomonas aeruginosa* and was named after this phenotype because of its resistance to imipenem.[36] In the CRKP strain, the first MBL found was from IMP-1 in Singapore in 1996.[37] Since then, IMP-producing CRKP strains have been isolated and discovered globally, but mainly in South and Southeast Asia.[38–40] *bla*$_{\text{IMP-4}}$ was isolated and reported in the mid-1990s from A*cinetobacter baumannii* in Hong Kong, China, and *Citrobacter yangtzeii* in mainland China.[41,42] Over the past 15 years, *bla*$_{\text{IMP-4}}$ has been described in at least seven different Inc-type broad-spectrum plasmids (A/C, A/C-Y, HI2, HI2-N, I1, L/M, and N1),[43,44] and it is always present in class I integrons, but it can be found as part of single gene cassettes or cassette arrays. It is most commonly found in a four-gene cassette array: *bla*$_{\text{IMP-4}}$*-qacG-aacA4-catB3*, and this four-gene cassette array has been found in Australia,[43,45] Hong Kong,[46] Singapore,[47] Japan[48] and Malaysia.

## OXA - 48

The first discovery of OXA-48 originated from *Klebsiella pneumoniae* isolated and found in Turkey in 2003.[49] This was followed by reports from all over the world, including countries in Europe, the southern and eastern Mediterranean, and Africa.[50–53] *bla*$_{\text{OXA-48}}$ has been reported mainly on IncL-incompatible plasmids, which are characterised by their small size (60–70kb), self-passaging, and not carrying additional resistance genes.[54] *bla*$_{\text{OXA-48}}$ is usually present on Tn*1999* transposons with two copies of IS*1999* or on Tn*1999.2* transposons with one of the two IS*1999* copies truncated by IS*1*R.[55,56] At the end of 2013, the *bla*$_{\text{OXA-48}}$ genes found in *Klebsiella pneumoniae* type ST11 in Taiwan[57,58] were identical to those in other countries in that they were all on the IncL/M plasmid scaffold, but most of the OXA-48-encoding genes on the Tn*1999.2* composite transposon of *Klebsiella pneumoniae* type ST11 in Taiwan could be carried by the IncA/C plasmid as well.[59] Also, *bla*$_{\text{OXA-48}}$ has been occasionally detected on other incompatible plasmids such as IncA/C2,[60] IncFIIk[61] and indistinguishable plasmids[62] or there is also integration within Tn*6237* on the Escherichia coli chromosome (Tn*6237* is a composite transposon composed of two IS*1R* sequences).[62] In terms of transmission effects, the *bla*$_{\text{OXA-48}}$ gene can affect not only plasmid transmission, but also transmission of ST11-type *Klebsiella pneumoniae* carrying *bla*$_{\text{OXA-48}}$ in the chromosome.

## VIM

In France in 2004, an outbreak caused by the production of VIM-1 CRKP occurred right after the hospitalisation of a Greek patient.[63] Since then, several more VIM subtypes have been discovered, such as VIM-12, VIM-19, VIM-4, VIM-27, VIM-26 and VIM-39. At the same time these VIM variants are genetically interrelated, and they can be altered by small genetic factors that cause them to appear one after the other. In March 2005, CRKP carrying the VIM-12 gene, whose sequence differs from that of the VIM-1 gene by 18 base pairs, was isolated for the first time. Comparison with *bla*$_{\text{VIM-1}}$ and *bla*$_{\text{VIM-2}}$, the nucleotide changes in *bla*$_{\text{VIM-12}}$ have led to speculation that this novel variant may be recombinant from *bla*$_{\text{VIM-1}}$ and *bla*$_{\text{VIM-}}$2.[64] And in 2008, the VIM-19 gene was found in a single CRKP isolated from a hospital in Ceres.[65] Shortly after, in 2010 at the University Hospital of Larissa, researchers isolated and described for the first time a new MBL variant, VIM-27, from another patient treated. Through a series of experimental studies, researchers also concluded that the *bla*$_{\text{VIM}}$ gene is usually integrated in class I integrons.[66]

In summary, the major carbapenemases carried by *Klebsiella pneumoniae*, such as KPC, NDM, IMP, OXA and VIM, present different prevalence characteristics and transmission patterns globally (Figure 1, The figure only show the

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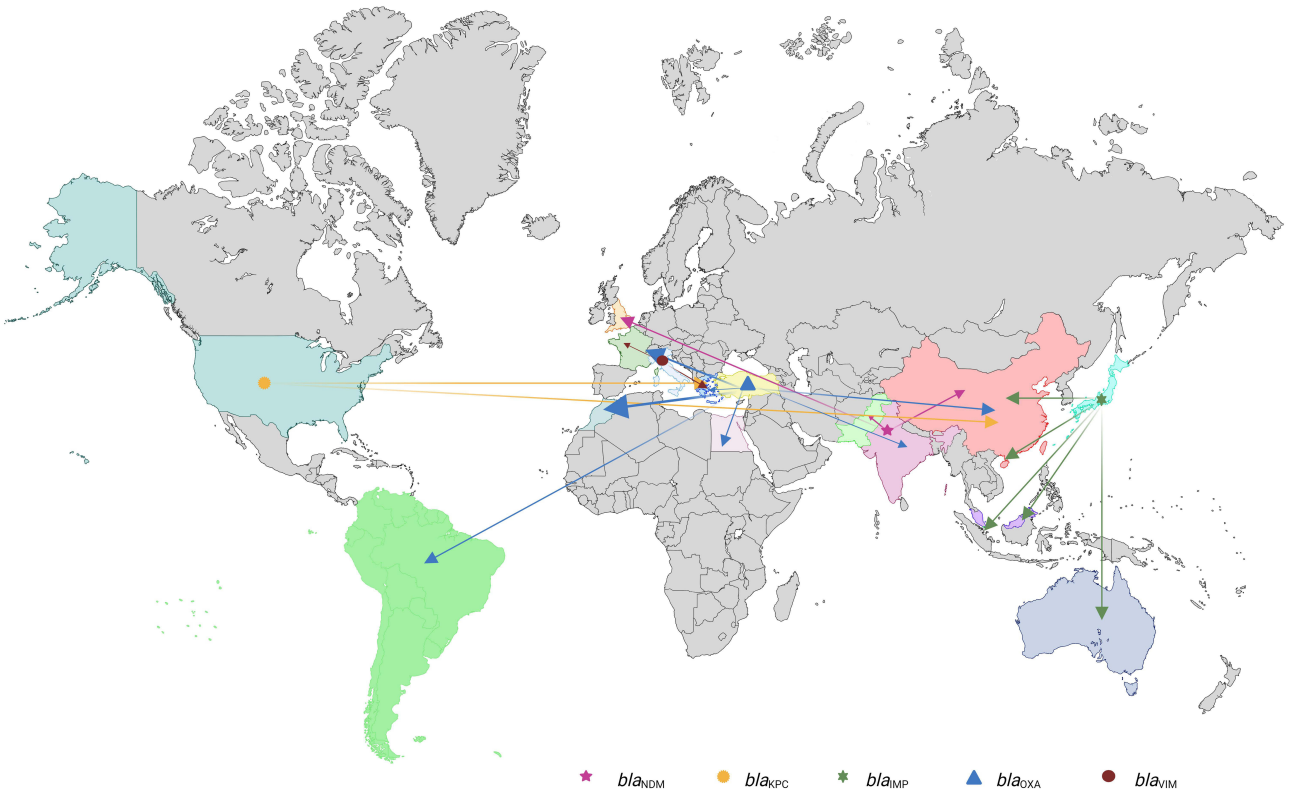


**Figure 1** The picture shows the detection of five carbapenemases, KPC, NDM, IMP, OXA, and VIM, carried by Klebsiella pneumoniae worldwide based on literature and the subsequent main diffusion areas. Purple represents NDM, yellow represents KPC, green represents IMP, blue represents OXA, and brown represents VIM. Created in BioRender. Yu, Q. (2025) https://BioRender.com/1d6fhxw.

transmission routes of some countries), as well as their genetic environments and mutations. These enzymes are the key factors of drug resistance in *Klebsiella pneumoniae*, which lays the foundation for the subsequent study of enzyme combinations and drug resistance mechanisms.

## Combinations of CRKP Enzyme Types Reported in Existing Studies

The major carbapenemases carried by *Klebsiella pneumoniae*, which play a key role in the process of bacterial drug resistance, have been described in detail above. With further research, it has been found that multiple enzymes are increasingly common in *Klebsiella pneumoniae*, and the combination of different enzyme types makes the resistance mechanism more complex. In the next section, we will focus on the combinations of CRKP enzymes reported in existing studies. CRKPs carrying bicarbocyanine resistance genes have been increasingly widely reported and the combinations are becoming more diverse. A tabular summary of the combinations mentioned in the wider literature is shown in Table 1.

Literature references more often mention KPC + metalloenzyme combinations. For example, Huang et al identified *Klebsiella pneumoniae* carrying $bla_{\text{NDM-5}}$ and $bla_{\text{KPC-2}}$, with $bla_{\text{KPC-2}}$ (IncFII/IncR) and $bla_{\text{NDM-5}}$ (IncX3) located on different plasmids.[67] Also Dong et al identified *Klebsiella pneumoniae* type ST852 carrying $bla_{\text{KPC-2}}$ and $bla_{\text{IMP-4}}$ with serotype KL18, a spliced hybrid plasmid consisting of an IncHI5 plasmid-like region, an IncFII(YP)/IncFIA plasmid-like region and a KPN1344 chromosome-like region.[68] Whereas *Klebsiella pneumoniae* carrying $bla_{\text{NDM-1}}$ and $bla_{\text{KPC-2}}$ have likewise been mentioned several times,[69–72,86] there are *Klebsiella pneumoniae* belonging to the ST15 phenotype with the $bla_{\text{NDM-1}}$ gene located on the IncX3 plasmid, and the double copy of the $bla_{\text{KPC-2}}$ gene located on IncX6 and IncFII, respectively. Others have also found that $bla_{\text{KPC-2}}$ and/or $bla_{\text{NDM-1}}$ plasmids are successfully transferred by splicing, whereas $bla_{\text{KPC-2}}$ and/or $bla_{\text{NDM-1}}$ are usually carried on IncFII plasmids. There have also been large-scale screening studies that have identified the presence of both *Klebsiella pneumoniae* carrying $bla_{\text{NDM-1}}$ and $bla_{\text{KPC-2}}$, and *Klebsiella pneumoniae* carrying $bla_{\text{NDM-7}}$ and $bla_{\text{KPC-2}}$ in a group of strains.[73] Compared to the combination of KPC+metalloenzyme, bimetalloenzyme has not been as abundantly reported, with reports mentioning *Klebsiella pneumoniae* carrying $bla_{\text{NDM-1}}$ and $bla_{\text{IMP}}$-4,[76–78] which includes about the CRKP with ST20 type and

**Table 1** Summary of Common CRKP Enzyme Type Combinations

| CRKP Enzyme Type | Genotype Combinations | Sequences Type | Types of Plasmids Hosted by Carbapenemases | Country |
|---|---|---|---|---|
| KPC+ metalloenzyme | $bla_{NDM-5}$+ $bla_{KPC-2}$ | ST11 | ColRNAI, IncFII (pHN7A8), IncHI1B, IncR, IncX3 | China[67] |
| | $bla_{KPC-2}$+ $bla_{IMP-4}$ | ST852 | IncHI5, IncFII (Yp) /IncFIA, KPN1344 chromosome | China[68] |
| | $bla_{NDM-1}$+ $bla_{KPC-2}$ | ST11 | ColRNAI, IncFIB (pB171), IncFII (K), IncFII (Yp) IncR | China[69] |
| | $bla_{NDM-1}$+ a couple $bla_{KPC-2}$ | ST15 | IncX3, IncX6, IncFII | China[70] |
| | $bla_{NDM-1}$+ $bla_{KPC-2}$ | Not mentioned | Inc FIIK, IncFII, | Egypt[71] |
| | $bla_{NDM-1}$+ $bla_{KPC-2}$ | ST3493, ST11, ST15 | IncFII, IncN, IncX, IncHI1B | China[72] |
| | $bla_{NDM-7}$+ $bla_{KPC-2}$, $bla_{NDM-1}$+ $bla_{KPC-2}$ | ST11 | Not mentioned in detail in the text | Brazil[73] |
| | $bla_{NDM-1}$+ $bla_{KPC-3}$ | ST307 | IncA/C | Argentina[74] |
| Bimetallic enzyme | $bla_{VIM-1}$+ $bla_{KPC-2}$ | ST39 | Tn*125* derivatives, In-e541-like | Greece[75] |
| | $bla_{NDM-1}$+ $bla_{IMP-4}$ | ST20 | IncFIB (K) /IncHI1B/IncX3 | China[76] |
| | $bla_{NDM-1}$+ $bla_{IMP-4}$ | ST273 | ST7 IncN, IncHI5 | China[77] |
| | $bla_{NDM-1}$+ $bla_{IMP-4}$ | ST17 | Not mentioned in detail in the text | China[78] |
| | $bla_{NDM-1}$+ $bla_{IMP-26}$ | ST290 | IncHI2A | China[79] |
| | $bla_{NDM-1}$+ $bla_{VIM-1}$ | ST11 | Tn*125* derivatives, In-e541-like | Greece[80] |
| Metalloenzyme +OXA-48 | $bla_{NDM-1}$+ $bla_{OXA-48}$ | ST101 | IncL/M, IncA/C | Switzerland[81] |
| | $bla_{NDM}$+ $bla_{OXA-48}$ | ST14 | Not mentioned in detail in the text | United Arab Emirates[82] |
| | $bla_{NDM-1}$+ $bla_{OXA-48}$ | Not mentioned | Not mentioned in detail in the text | Egypt[83] |
| | $bla_{NDM-1}$+ $bla_{OXA-48}$ | ST11 | ColRNAI,IncA/C2, IncFIB(K),IncFIB(Mar), IncFII(K),IncFII (pKPX1), IncHI1B and IncR, | Greece[84] |
| | $bla_{NDM-1}$+ $bla_{OXA-48}$ | ST307 | IncL/M and IncA/C2 | China[85] |

serotype K28, which carries two resistance genes, $bla_{NDM-1}$ and $bla_{IMP-4}$, which are being found to be simultaneously localised on a 296-kb IncFIB(K)/IncHI1B/IncX3 plasmid (pAZS099NDM-IMP). Also in a strain study screening for a hospital district, Hu et al identified *Klebsiella pneumoniae* carrying $bla_{NDM-1}$ and $bla_{IMP-2}$6,[79] and the strain had multiple copies of $bla_{NDM-1}$ due to multiple insertion sequences. For cases combining metalloenzymes and OXA-48, relatively more cases have been reported abroad than in China, which may be related to the different levels of prevalence of resistance genes in different regions.[81–85]

Overall, a variety of CRKP enzyme combinations have been reported in existing studies, with more KPC + metalloenzyme combinations reported, relatively few dual-metalloenzyme combinations reported, and metalloenzyme + OXA-48 combinations reported differently in China and abroad. The emergence and spread of these combinations reflect the complexity and severity of the drug resistance situation of *Klebsiella pneumoniae*.

## Molecular Characterisation of Common Combinations

Having understood the CRKP enzyme-type combinations reported in existing studies, in-depth molecular characterization of these combinations is essential to unravel the mechanisms of resistance. Based on this, this chapter will provide a detailed molecular characterization of common enzyme-type combinations.

### KPC + Metalloenzyme

#### Combinatorial Studies of $bla_{NDM-5}$ and $bla_{KPC-2}$

Among the clinical strains in China, more and more reports have appeared on the ability of *Klebsiella pneumoniae* to produce both KPC-2 and NDM-1 enzyme phenotypes,[69,87,88] and Huang et al showed that *Klebsiella pneumoniae*


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harboured *bla*$_{KPC-2}$ (IncFII/IncR) and *bla*$_{NDM-5}$ (IncX3) located in two differentplasmids. Genetic environmental studies of the *bla*$_{KPC-2}$ gene, which is located upstream of the Tn*1331* element. In addition, an IS*Kpn6*-like element is located downstream of the *bla*$_{KPC-2}$ gene, followed by the korC gene (a gene encoding a transcriptional repressor protein), a gene encoding a hypothetical protein, and the klcA gene. For *bla*$_{NDM-5}$, an IS*26* element, a gene encoding a protein in the signal sequence domain of the double arginine translocation (TAT) pathway, a gene encoding a hypothetical protein, and a trpF gene, a gene encoding a phosphorosilicon aminobenzoic acid isomerase gene, were localised upstream of *bla*$_{NDM-5}$ and inserted between them. In addition, an IS*5* element is located downstream of *bla*$_{NDM-5}$.

The IncX3 plasmid is often found in bacteria carrying *bla*$_{NDM-5}$ in Chinese clinics.[89,90] BLAST results showed that the plasmid containing the *bla*$_{NDM-5}$ gene had >99% sequence homology to the region corresponding to other plasmids isolated from different hosts in other countries, indicating that the plasmid has been widely disseminated worldwide. Meanwhile, many studies have also presented the genetic environment of *bla*$_{NDM-5}$ and found that various mobile genetic elements play a key role in the rapid spread of *bla*$_{NDM-5}$.[91,92] Remarkably, such genetic environments have been found in different plastids in China, which may indicate a common origin.[89,93] Furthermore, the genetic environment of *bla*$_{NDM-5}$ is also similar to that of *Klebsiella pneumoniae* previously reported in India and Spain.[91,94]

### Combinatorial Studies of bla$_{KPC-2}$ and bla$_{IMP-4}$

Dong et al reported in the literature that they detected a splice hybrid plasmid containing *bla*$_{KPC-2}$ and *bla*$_{IMP-4}$ from a clinical isolate of *Klebsiella pneumoniae*-like ST852-KL18, which was composed of a plasmid region similar to IncHI5, a plasmid region similar to IncFII(YP)/IncFIA and a chromosome-likeKPN1344 region. The paper also mentions that one of the more important plasmids, pKP18-31-IMP, may have been derived from recombination of IncHI5 with another plasmid, and together, these findings highlight that the IncHI5 plasmid possesses a strong evolutionary capacity. This could lead to the formation of new multi-drug resistant plasmids and further expand the range of hosts they can carry.

In their study, a novel class I integron carrying *bla*$_{IMP-4}$-4-K1pnI3 was also described. It has been previously reported and mentioned that *bla*$_{IMP-4}$-4-K1pnI3 is considered to be the most common structure in IMP-4-producing Chinese strains.[95] It was also shown that transposons such as Tn*6017*and Tn*1696* are important vectors mediating *bla*$_{IMP}$ transmission in Enterobacteriaceae.

### Combinatorial Studies of bla$_{NDM-1}$ and bla$_{KPC-2}$

A study by Sun et al reported that[70] found the ST15-type CRKP which carries the *bla*$_{NDM-1}$ gene is located on the 53096-bp IncX3 plasmid, whereas the two-copy *bla*$_{KPC-2}$ gene is located on the 103807-bp IncX6 plasmid and the 88164-bp IncFII plasmid, respectively. The *bla*$_{NDM-1}$ gene is preceded by two sockets, IS*3000*and IS*5*. Comparison of the genetic environments of the two plasmids of the *bla*$_{KPC-2}$ gene reveals a similar core structure flanked by IS*Kpn19*-*bla*$_{KPC-2}$-IS*Kpn6*. The ORF-*ydaA*-IS*Kpn19* fragment is located in the upstream region of the pKP46_2_kpc *bla*$_{KPC-2}$ gene, whereas the highly conserved IS*Kpn6*-ORF1-*KLcA*-ORF2refB fragment is located in the downstream region. In pKP46_1_KPC, three transposase genes (Tn*3*-tnpR-IS*Kpn27*) were inserted upstream of *bla*$_{KPC-2}$ and the ORF-*ydaA*-IS*Kpn19* fragment was flipped. Mohamed et al found that INCFIK and INCFII plasmids predominated in strains carrying *bla*$_{KPC-2}$ and/or *bla*$_{NDM-1}$ and their transposons, suggesting that this type of plasmid predominantly mediates the horizontal transmission of such resistance genes.

In the study by Gao et al they observed increased morbidity due to infection with KPC-2-NDM-1-CRKP. And based on whole genome sequencing analyses, it was proposed that KPC-2-NDM-1-CRKP was produced from a KPC-2-CRKP precursor that was later transformed into a strain carrying *bla*$_{KPC-2}$ and *bla*$_{NDM-1}$ as a result of the acquisition of another highly transferable *bla*$_{NDM-1}$ plasmid. This was followed by a plasmid disaffinity study of the splicer C2974T-3 carrying both *bla*$_{KPC-2}$ and *bla*$_{NDM-1}$ plasmids. It was found that both *bla*$_{KPC-2}$ and *bla*$_{NDM-1}$ plasmids were present in 58 out of 94 single clones (61.7%, 58/94), indicating that the two plasmids are compatible. And the plasmid stability test also showed that the plasmid was stable in transmission. The cost of adaptation test also showed that the strain carrying the dual-resistance gene was not different from other strains, and the carrying of the dual-resistance gene did not cause a huge growth cost to the host itself. Like previous reports, they also concluded that *bla*$_{KPC-2}$ tends to be on the IncFII plasmid, whereas *bla*$_{NDM-1}$ is located in a different context and can be on, for example, IncN, IncX and IncHI1B. Thus, the

restriction of a particular plasmid to a particular bacterial host may help *bla*$_{KPC-2}$ and *bla*$_{NDM-1}$ to adapt to different ST patterns. For example, certain plasmids favour specific host mechanisms (the relationship between IncFII and ST11-type CRKPs is unclear). It has also been proposed that certain high-risk CRKP clones are associated with specific narrow host range IncF plasmids.[96]

### Combinatorial Studies of bla$_{VIM-1}$ and bla$_{KPC-2}$

CRKPs producing both VIM-1 and KPC-2 are usually classified as ST147-type, implying that ST147-type CRKPs are usually associated with VIM-1.[97] A flow-conditioning study by Monika et al identified the ST147 *Klebsiella pneumoniae* clone that produces both KPC-2, VIM-1, and OXA48. The gene encoding the KPC carbapenemase is located on the Tn*440* transposon, which is located on plasmids with different replicon types (IncF, IncL/M, ColE1, IncR and IncX3). These plasmids show the ability to bind the *bla*$_{KPC}$ gene and spread it to new bacterial populations.[98] Recently, however, CRKP strains carrying both *bla*$_{VIM-1}$ and *bla*$_{KPC-2}$ have been included in the ST39 phenotype, implying that the typing of this strain is somehow linked to the *bla*$_{KPC-2}$ resistance gene.[75] In a newly published study in 2024, Maria et al isolated KPC-2 and VIM-1-producing high-risk clones of *Klebsiella pneumoniae* ST39 from clinical samples in Greece, from which they identified several replicons by whole genome sequencing including CoIRNA, IncC, IncFIB(K), IncFIB(pQiL) and IncFII(K).[99] It can be seen that the combination of *bla*$_{VIM-1}$ and *bla*$_{KPC-2}$ *Klebsiella pneumoniae* has become prevalent in Europe and elsewhere, and it is extraordinarily important to take precautions.

## Bimetallic Enzyme Combinations

### Combinatorial Studies of bla$_{NDM-1}$ and bla$_{IMP-4}$

Jia et al identified a novel hybrid plasmid carrying both *bla*$_{NDM-1}$ and *bla*$_{IMP-4}$ in ST20-K28 carbapenem-resistant *Klebsiella pneumoniae* (CRKP) AZS099. It was shown that *bla*$_{NDM-1}$ and *bla*$_{IMP-4}$ were simultaneously located on the 296-kb IncFIB(K)/IncHI1B/IncX3 plasmid (pAZS099NDM-IMP), a large plasmid composed of four different types of small plasmids. The *bla*$_{IMP-4}$-containing region is located in a class I integron named In0, which is located in the IS*6100*-IS*26* transposon-like structure and is approximately 5 kb in length. The region carrying the *bla*$_{NDM-1}$ gene is located in the Tn*125* transposon residue region. And the splicing experiments showed that pAZS099-NDM-IMP had a high transformation rate (>95%) and good horizontal transfer ability. The growth curve assay, on the other hand, confirmed that the presence of pAZS099-NDM-IMP was not growth stressful to the host itself. *bla*$_{NDM-1}$ is derived from an IncX3-type plasmid similar to pA575-NDM, and *bla*$_{IMP-4}$ integrates into this region. Previous studies have identified that IncX3-type plasmids are widely distributed in a variety of species in different regions of China and the UAE and may be associated with the spread of *bla*$_{NDM-}$1.[6]

A study by Liu et al identified ST273 carbapenem-resistant *Klebsiella pneumoniae* carrying *bla*$_{NDM-1}$ and *bla*$_{IMP-4}$. The *bla*$_{NDM-1}$ in this study was carried by the ST7-type IncN self-propagating plasmid, while *bla*$_{IMP-4}$ was located on the IncHI5-type self-propagating plasmid. Meanwhile, Liu et al learnt from the literature that in China, the ST7-type IncN plasmid is also equipped to mediate the spread of *bla*$_{IMP-4}$ in different Enterobacteriaceae bacteria from different regions. Plasmid pNDM1_LL34 carrying *bla*$_{NDM-1}$ was found to be closely related to plasmid pNDM-BTR by database comparison (99% coverage, 99% identity). Plasmid pNDM-BTR is also a ST7-type IncN plasmid carrying *bla*$_{NDM-1}$. *bla*$_{IMP-4}$ is carried by a class I integron in the *bla*$_{IMP-4}$-qacG2-aacA4 cassette array on pIMP4_LL34. The best match to pIMP4_LL34 by BLAST comparison was p13190-VIM. pIMP4_LL34 has a replicon that is thought to be IncHI5. Using the 885-bp replication protein-coding gene of the IncHI5 replicon, they found 15 more IncHI5 plasmids in GenBank. And these 15 IncHI5 plasmids were from the strains of *Klebsiella pneumoniae, Klebsiella acidophilus*, and *Raoultia ornithinolytica*, and all of them were in China. This indicates that the IncHI5 plasmids have become popular in China.

## Metalloenzyme + OXA – 48

### Combinatorial Studies of bla$_{NDM-1}$ and bla$_{OXA-48}$

Seiffert et al identified a XDR *Klebsiella pneumoniae* during routine pathogen screening of patients in a Swiss hospital. The bacterium also carries *bla*$_{NDM-1}$, *bla*$_{OXA-48}$, *bla*$_{CTX-M-15}$ and *bla*$_{CMY-16}$ resistance genes. This causes it to be resistant to most antibiotics, with only tigecycline, polymyxin and fosfomycin being sensitive. Examining the genetic information

of the strains, they found that IS*Ab125* was found upstream of $bla_{NDM-1}$, but $ble_{MBL}$encoding bleomycin was not detected downstream,[100] and $bla_{OXA-48}$ was carried by Tn*1999*.2.[101] Meanwhile, they also further studied and confirmed that $bla_{OXA-48}$ is located on IncL/M plasmid; $bla_{CTX-M-15}$ is located on IncR plasmid; and IncA/C plasmid carries drug-resistant genes such as $bla_{NDM-1}$ and $bla_{CMY-16}$. As a result of this discovery, they believe that an epidemic of this type of *Klebsiella pneumoniae* is likely to occur very soon, and that the only measures that can be taken at this time are early screening and early isolation and treatment to prevent widespread epidemics of drug-resistant bacteria.

Shi et al identified five ST307-type CRKPs in a study that contained $bla_{CMY-6}$, $bla_{OXA-48}$ and truncated $bla_{NDM-1}$. The plasmid replicon types for pNDM-1 and pOXA-48 were IncA/C2 and IncL/M, respectively. Studies have also shown that IncL/M-type plasmids are more likely to associate with $bla_{OXA-48}$ than with any other ARGs.[102] In addition, $bla_{NDM-1}$ has been found on different types of plasmids, such as IncF in the narrow host incompatibility group and IncA/C, IncL/M, IncH and IncN in the wide host incompatibility group.[103] And the important finding in that study was that $bla_{NDM-1}$was disrupted by IS*10*, which belongs to the IS*4*family.Their experiments also coincide with the study of Vila et al. The native signal peptide is associated with NDM-1 anchored to the outer membrane, which affects the concentration of soluble NDM-1 in the peripheral plasma, whereas IS inserted in the $bla_{NDM-1}$ signal peptide abolishes the carbapenemase function of NDM-1.[104]

In conclusion, molecular characterization of common enzyme-type combinations has shown that different combinations have different gene localization, genetic environments and transfer characteristics. These features not only affect the transmission of drug-resistant genes, but also provide an important basis for understanding the resistance mechanism of *Klebsiella pneumoniae*, which helps to target prevention and control strategies.

## Whole Genome Sequencing Technology: Lighting the Way for Studying Drug Resistance Genes

The enzyme-type combinations of *Klebsiella pneumoniae* and their molecular characterization have been discussed previously, and the accurate study of these drug resistance-related information cannot be achieved without the support of advanced technologies. Whole-genome sequencing technology has an unique advantage in the study of drug resistance genes in *Klebsiella pneumoniae*, and its important role in this field is described in detail below. Whole genome sequencing enables in-depth identification and analysis of bacteria and can also be a powerful tool for studying outbreaks of intranasal infections[105] as well as for epidemiological surveillance.[106] Brisse et al developed a free BIGSdb-KP database to facilitate researchers' understanding of the virulence and prevalence of *Klebsiella pneumonia*e,[107] which helps researchers to quickly extract medical and epidemiological information from the genome sequence of *Klebsiella pneumoniae*. Some researchers have also used high-throughput sequencing to access and analyse the genomes of an endemic high virulence strain (CG23) and an almost non-virulent MDR strain (CG258). Bialek-Davenet et al found that the CG258 strain was almost non-virulent, but had a variety of genes associated with resistance, such as mutations in the gyrA and parc genes, the resistance-determining regions for quinolones. It was also found that most of the genes of the MDR strain and the strongly virulent strain did not overlap with each other.[107]

Currently, areas of research in *Klebsiella pneumoniae* by whole genome sequencing also include the exploration of *Klebsiella pneumoniae* virulence at the genomic level, the formation of the biofilm and the development of related resistance mechanisms. It was through genome mapping that Rimoldi et al found the $bla_{KPC}$ gene to be associated with carbapenem resistance and found an association between *Klebsiella pneumoniae* type 3 bacterial hairs and iron carrier genes.[108] Meletis et al, on the other hand, found that the coat serotype of NDM-1-producing *Klebsiella pneumoniae* is determined by the nucleotide sequence of the wzc gene, while its genome includes 16 resistance genes, 12 of which are located in the plasmid and 4 on the chromosome.[109] Funou et al sequenced the whole genome of ESBL-producing *Klebsiella pneumoniae* using the Illumina MiSeq platform, and found that it contained a variety of β-lactamase genes, including $bla_{OXA-1}$, $bla_{TEM-1b}$, $bla_{SHV-1}$ and $bla_{CTX-M-15}$ resistance genes, and the type of replicon plasmid it carried was also detected.[110] Whole genome sequencing has been applied in various fields of bacterial research and it is believed that it will become a major tool for bacterial research in the future.

In summary, whole genome sequencing technology plays an important role in the study of *Klebsiella pneumoniae* for in-depth identification and analysis of the bacteria, outbreak investigation and epidemiological surveillance, as well as for

exploring bacterial virulence, biofilm formation and drug resistance mechanisms. It provides a powerful tool for research in this field and promotes a deeper knowledge of *Klebsiella pneumoniae*.

## Discussion

Through the study of the main carbapenemases, enzyme type combinations, molecular characterization, and the application of whole genome sequencing technology in *Klebsiella pneumoniae*, we have gained a more comprehensive understanding of *Klebsiella pneumoniae*, which produces two carbapenemases. On this basis, this chapter will summarize the whole study and propose strategies to deal with it. The whole genome of *Klebsiella pneumoniae* is about 5–6 Mbp in size and this contains 5,000–6,000 genes to be coded.From these codable genes, about 1700 genes are considered to be core genes. The core genome of *Klebsiella pneumoniae* is relatively conserved between strains. Typically, for a species, 95% of the genes are core genes. The remainder of the genome is auxiliary genes. An auxiliary genome is a flexible, adaptable or complementary genome.[111,112] Resistance genes are generally found in mobile elements such as plasmids, transposons and integrons. Antimicrobial resistance (AMR) has become an urgent global public health threat, and CRKP carrying dual carbapenemases is a more intractable upgraded version in antimicrobial resistance. The article has previously mentioned that single carbapenemases (such as KPC, NDM) have rendered CRKP resistant to carbapenem antibiotics, and the combination of two enzymes (such as KPC+NDM, NDM+OXA-48) will further expand the resistance spectrum. For example, strains carrying $bla_{\text{NDM-1}}$ and $bla_{\text{OXA-48}}$ are resistant to the vast majority of antibiotics and are only sensitive to a few drugs such as tigecycline and polymyxin. This "pan-drug resistance" characteristic greatly limits clinical treatment options and may also lead to a sharp increase in the treatment failure rate. The introduction also mentioned that the mortality rate of CRKP infections is as high as 37.2%. Due to the more complex drug resistance mechanisms of double-enzyme strains, the mortality rate may be further increased, directly exacerbating the threat of AMR to patients' lives. At the same time, double carbapenemase strains are key carriers of the "co-diffusion" of drug resistance genes and have a "multiplier effect" on the population transmission of AMR. Section 4.2.1 mentioned that drug resistance genes are mostly located on mobile elements such as plasmids and transposons, and plasmids carrying double enzymes (such as IncFII/IncX3 composite plasmids) have a high conversion rate (>95%) and have minimal impact on host growth. Section 4.1.1 also mentioned that plasmids carrying both $bla_{\text{KPC-2}}$ and $bla_{\text{NDM-5}}$ can be rapidly transmitted between different strains through horizontal transfer, causing originally sensitive strains to acquire double drug resistance in a short period. This characteristic of "transferring two drug resistance genes in one transfer" is more efficient than the transmission of a single gene and may accelerate the outbreak of drug-resistant strains in hospitals, communities, and even the environment, upgrading AMR from "individual drug resistance" to a "population drug resistance crisis". The presence of dual enzymes significantly increases the difficulty of monitoring, tracing, and intervening in AMR, exposing the weaknesses of the existing prevention and control system. Traditional detection methods may miss the detection of dual enzymes (for example, reagent kits relying on single - enzyme detection cannot identify the KPC + VIM combination). This diagnostic lag may lead to the failure to isolate drug - resistant strains in a timely manner, accelerating the spread within the hospital. In addition, the geographical distribution of different dual - enzyme combinations varies significantly, and their transmission patterns are different from those of single - enzyme strains. Therefore, targeted prevention and control strategies need to be adjusted (for example, for OXA - 48+NDM strains carrying IncL/M plasmids, port monitoring needs to be strengthened). If the particularity of dual enzymes is ignored, the existing AMR prevention and control measures may become ineffective.

Studying double-enzyme strains is at the core of understanding the "evolutionary logic" of AMR, providing a scientific basis for addressing AMR. The combination of double enzymes is not random: the paper found that specific enzyme combinations (such as KPC + metalloenzymes) are more common, and their genetic environment (such as the Tn1721 transposon, IS26 insertion sequence) has characteristics of co-evolution. This "preferential combination" reveals the interaction rules of drug-resistant genes, providing ideas for designing inhibitors that target and inhibit the synergistic effect of double enzymes (such as small molecule drugs that simultaneously block the activities of KPC and NDM). At the same time, research on the stability of plasmids carrying two enzymes can provide targets for the development of "plasmid eliminators" (such as drugs that interfere with the replication of IncFII plasmids), blocking the spread of drug-resistant genes at the source, which is an innovative direction for combating AMR.

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## Disclosure

The authors report no conflicts of interest in this work.

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