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Letter to the Editor

Metallo-beta-lactamase *bla*$_{NDM-1}$ in extremely drug-resistant high-risk *Pseudomonas aeruginosa* clone ST235 and non–high-risk clone ST2407 in Brazil

Editor: S. Stefani

Carbapenem-resistant *Pseudomonas aeruginosa* is listed by the World Health Organization as a high-priority pathogen owing to the challenge of treating its infections [1]. This phenotype is often associated with acquired genes, such as metallo-beta-lactamases (MBLs), with the Verona integron-encoded MBL (VIM) being the most disseminated followed by imipenemase (IMP) and New Delhi MBL (NDM). Recently, Fortunato et al. [1] tested the hypothesis that the spread of resistance to carbapenems in *P. aeruginosa* is influenced by phylogenomic features, as they are associated with specific lineages (STs), mainly in high-risk clones. To test this hypothesis, they considered the MBL genes *bla*$_{VIM-2}$ and *bla*$_{NDM-1}$, but the low number of *bla*$_{NDM-1}$+ genomes analysed (n = 27) and the overrepresentation of Asian and European genomes (20/27) may represent a bias [1]. South America was represented by only one Chilean genome (ST654) [1], and in fact, reports of *bla*$_{NDM}$+ *P. aeruginosa* in South America are scarce. Therefore, any data related to this issue is of utmost importance to understanding the forces driving the spread of this gene in this critical pathogen around the world. In this way, we describe, for the first time in South America (Brazil), a *bla*$_{NDM-1}$+ *P. aeruginosa* belonging to the high-risk clone ST235, revealing the genetic context of its *bla*$_{NDM-1}$ gene. Furthermore, in silico surveys of *P. aeruginosa* genomes from Brazil identified the same *bla*$_{NDM-1}$ genetic context in the non–high-risk ST2407 clone.

In 2022, a *P. aeruginosa* strain (PA30N) was discovered in a clinical setting in the southeast region of Brazil (Rio de Janeiro city). PA30N presented resistance to imipenem, doripenem, and meropenem, as well as antibiotics from several other classes, and was classified as extremely drug-resistant (XDR). Whole-genome sequencing was performed on an Illumina HiSeq 2500 FIOCRUZ platform (Illumina, Inc., San Diego, CA, USA), and the reads were filtered using the NGSQCToolkit v.2.3.3 (https://github.com/mjain-lab/NGSQCToolkit) and assembled with SPAdes v3.15.2 (https://github.com/ablab/spades). The in silico survey for Brazilian *bla*$_{NDM}$+ *P. aeruginosa* included all complete and draft genomes (n = 191) from Genbank (accessed October 2023). The STs were determined using mlst v2.22.0 (https://github.com/tseemann/mlst). Antibiotic resistance genes were screened with ABRicate v1.0.1 (https://github.com/tseemann/abricate) using the CARD database.

The PA30N genome was shown to belong to ST235 which, despite being a high-risk clone, is an ST rarely reported in Brazil that carries the *bla*$_{NDM-1}$ gene. Thus far, *bla*$_{NDM-1}$+ ST235 strains have only been reported in Italy, Iran, France, Serbia, Turkey, and Vietnam [2,3]. Interestingly, when searching other Brazilian *P. aeruginosa* genomes in Genbank, we identified a single genome carrying *bla*$_{NDM-1}$: CCBH26428 (GCA_023572735.1). Curiously, this genome was also recovered from a clinical setting in Rio de Janeiro, but it belonged to the rare ST2407 clone, as this ST was only associated with one isolate from Germany in PubMLST (isolate NRZ-31276). These findings showed that in South America, *bla*$_{NDM-1}$+ *P. aeruginosa* is not restricted to one phylogenomic lineage, since *bla*$_{NDM-1}$ is associated with distinct high-risk (ST235 and ST654) and non–high-risk (ST2407) clones. Importantly, based on in vitro and in silico analyses, these *P. aeruginosa* strains displayed an XDR character [4].

In *P. aeruginosa*, the *bla*$_{NDM-1}$ gene has been associated with a class 1 integron bearing the insertion sequence (IS) common region 1/3/5 (ISCR1/3/5) [5], IS91, and Tn21- and Tn402-like transposons including ISAba125/*bla*$_{NDM-1}$/*ble*$_{MBL}$ (Fig. 1) [1]. Therefore, we explored this issue in the two Brazilian *bla*$_{NDM-1}$+ *P. aeruginosa* genomes. Interestingly, despite belonging to different STs, both genomes carried the same *bla*$_{NDM-1}$ genetic context, characterised by the ISAba125 and *ble*$_{MBL}$ genes, and flanked by the *trp*F, *dsb*D, *aph*(3′)-VI, and ISAba14 genes (Fig. 1). In fact, a core segment (~3.2-kbp) comprising the *ble*$_{MBL}$/*bla*$_{NDM-1}$/ISAba125/*aph*A genes is shared by PA30N, CCBH26428, and other *bla*$_{NDM-1}$+ *P. aeruginosa* genomes (Fig. 1) [1]. However, the flanking genes of this core segment of both Brazilian genomes (*trp*F, *dsb*D, and ISAba14) are unique to other *bla*$_{NDM-1}$+ *P. aeruginosa* genomes, suggesting the acquisition of *bla*$_{NDM-1}$ through a different mobile element compared with other *bla*$_{NDM-1}$+ *P. aeruginosa* genomes. This synteny has already been described in *Enterobacteriacea* and *Acinetobacter* spp. [5], but not yet in *P. aeruginosa*, which may represent the potential for dissemination of this element. Interestingly, the entire *bla*$_{NDM-1}$ region of PA30N and CCBH26428 showed approximately 100% identity and coverage with several plasmid sequences from different species (*Acinetobacter baumannii, Klebsiella pneumoniae, Escherichia* spp., *Provincia* spp., *Enterobacter hormaechei*, and *Citrobacter* spp.) (Fig. 1), which could explain the broad phylogenetic diversity of *bla*$_{NDM-1}$+ hosts pointed out by Fortunato et al. [1]. Indeed, the *bla*$_{NDM-1}$ carried by *P. aeruginosa* in Chile (ST654) was associated with a plasmid, where *bla*$_{NDM-1}$ was flanked by ISCR3 and ISCR5-like elements [4].

In conclusion, our study adds original information on *bla*$_{NDM-1}$+ *P. aeruginosa* in South America, slightly expanding on the previous epidemiological scenario revealed by Fortunato et al.. This is because we observed *bla*$_{NDM-1}$ occurring in the same genetic context in high- and non–high-risk clones in the same city on the continent. Taken together, these findings contribute to the genomic surveillance of this WHO's critical priority pathogen, allowing for greater control and preventive actions.

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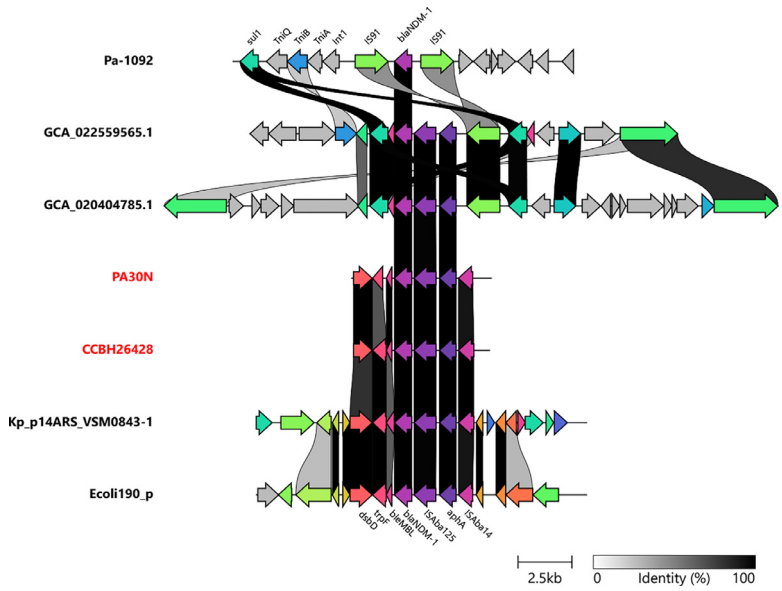

Fig. 1. Genetic environment of bla_{NDM-1} in *Pseudomonas aeruginosa*. The bla_{NDM-1} gene has already been described as being associated with IS91 (Pa-1092), and Tn21-(GCA_020404785.1) and Tn402-like (GCA_022559565.1) transposons. PA30N and CCBH26428 (highlighted in red) share a core comprising the ble_{MBL}/bla_{NDM-1}/ISAba125/*aph*A genes with Tn21- and Tn402-like transposons. In addition, PA30N and CCBH26428 also share these core genes and the *dsb*D, *trp*F, and ISAba14 genes with plasmids from different species.

Competing interests

None declared.

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Sequence information

The PA30N genome is available at Genbank under accession number JAYSJR000000000.

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