Genomics analysis of Carbapenem resistance in *Burkholderia cepacia* complex identify PenR E151V subsititution and novel *Burkholderia cepacia* complex specific OXA-1043 subgroup

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Introduction

Burkholderia cepacia complex is an opportunistic pathogen that causes morbidity and mortality, especially in those with cystic fibrosis, chronic granulomatous disease, or immunocompromising host. Mortality of *Burkholderia cepacia* complex bloodstream infections among patients with noncystic fibrosis in a 17-year nationwide study was 16%, 25%, and 36% at 14, 30, and 90 days, respectively. Treatment for *Burkholderia cepacia* complex remain limited due to its intrinsic resistance to most antibiotics. Resistance to carbapenem could be the results of PenB confers β-lactam resistance, and it was established that carbapenem resistance in *B. ubonensis* is due to an inducible class A PenB. However, a recent study did not show significant genomic differences between carbapenem resistance and carbapenem-sensitive strains. The purpose of this study is to provide an answer to the difference in gene expression patterns between imipenem resistance and imipenem-sensitive *Burkholderia cepacia* complex species.

Methods

Ten isolates of carbapenem-resistant *B. cepacia* complex were included in the study. Preliminary identification was performed by MALDI-TOF MS, and all protocols were performed according to the manufacturer's instructions. The antimicrobial susceptibility test was performed using the VITEK 2 system. The genomes of the *Burkholderia cepacia* complex were sequenced using Nanopore GridION. Antibiotic resistant genes were predicted by aligning protein-coding genes with the Comprehensive Antibiotic Resistance Database. The phylogeny of OXA was carried out by Mega and visualized by the interactive Tree Of Life (iTOL).

Flow chart of methods

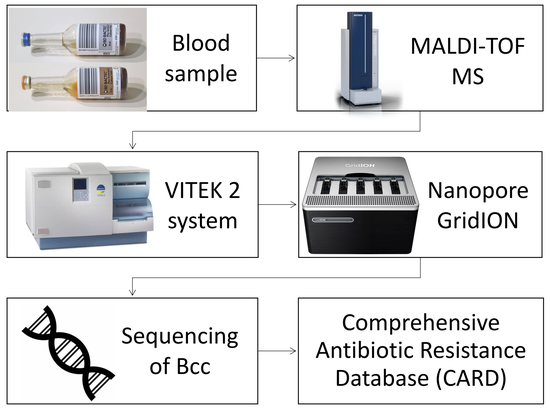


Figure 1. Possible point mutations on *penR*

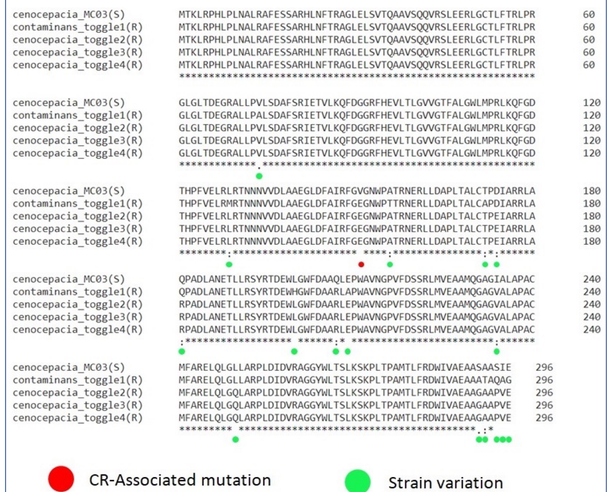
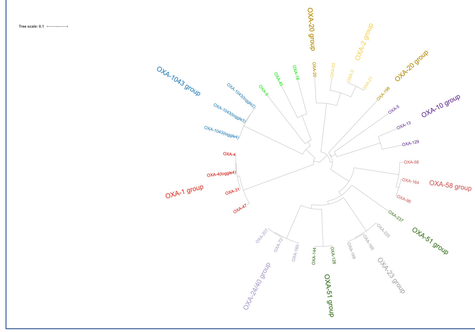


Table 1 PROVEAN of *B. cenocepacia* strain 1103 and strain MC0-3 in PenR

	Strain 1103		Strain MC0-3		
Variant	PROVEAN	Prediction[a]	Variant	PROVEAN	Prediction
E151V	-3.848	Deleterious	V151E	3.848	Neutral
E174D	-0.871	Neutral	D174E	0.871	Neutral
R207Q	0.451	Neutral	Q201R	-0.538	Neutral
V234I	-0.732	Neutral	I234V	0.692	Neutral
Q250L	-0.664	Neutral	L250Q	0.664	Neutral
G291S	0.070	Neutral	S291G	-0.196	Neutral
P294S	0.169	Neutral	S294P	-0.143	Neutral
V295I	-0.162	Neutral	I295V	0.094	Neutral

a. Cut-off of prediction=-2.5

Figure 2. Phylogenetic tree of OXA family



Results

The composition of resistance genes between imipenem-resistance and imipenem-sensitive strains showed no significant differences, which include *penB* and *penR*. Seventeen possible point mutations on *penR* which may be related to imipenem resistance were analyzed (Figure 1), and PROVEAN showed amino acid substitutions at position E151 in *penR* were shown deleterious (Table 1). Hence allele status at V151E of *penR* is critical for the activation of *penB*. A novel *bla*OXA gene is found in stain toggle 2, toggle 3 and toggle 4, which is named *bla*OXA-1043 (Figure 2). Phylogenetic tree and taxonomic ranks also reveal *bla*OXA-1043 is different from the previous OXA family.

Conclusions

Resistance to β-lactam antibiotics of *Burkholderia cenocepacia* was first reported in 1997, and an inducible class A β-lactamase of the Pen family is gradually being explored. The results of this study indicate that antibiotic resistance is related to the amino acid substitutions, which may explain the imipenem-sensitive strain of *Burkholderia cenocepacia.* Besides, a new OXA family is found in *Burkholderia cenocepacia* strain toggle 2, toggle 3 and toggle 4, and is named *bla*OXA-1043.

References

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