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Comparative Genomic Analyses Reveal Core-Genome-Wide Genes Under Positive Selection and Major Regulatory Hubs in Outlier Strains of *Pseudomonas aeruginosa*

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Genomic information for outlier strains of *Pseudomonas aeruginosa* is exiguous when compared with classical strains. We sequenced and constructed the complete genome of an environmental strain CR1 of *P. aeruginosa* and performed the comparative genomic analysis. It clustered with the outlier group, hence we scaled up the analyses to understand the differences in environmental and clinical outlier strains. We identified eight new regions of genomic plasticity and a plasmid pCR1 with a VirB/D4 complex followed by trimeric auto-transporter that can induce virulence phenotype in the genome of strain CR1. Virulence genotype analysis revealed that strain CR1 lacked hemolytic phospholipase C and D, three genes for LPS biosynthesis and had reduced antibiotic resistance genes when compared with clinical strains. Genes belonging to proteases, bacterial exporters and DNA stabilization were found to be under strong positive selection, thus facilitating pathogenicity and survival of the outliers. The outliers had the complete operon for the production of vibrioferrin, a siderophore present in plant growth promoting bacteria. The competence to acquire multidrug resistance and new virulence factors makes these strains a potential threat. However, we identified major regulatory hubs that can be used as drug targets against both the classical and outlier groups.

Keywords: *Pseudomonas aeruginosa*, outliers, environmental genomics, drug targets, positive selection

INTRODUCTION

Pseudomonas aeruginosa is one of the major opportunistic pathogens that has been isolated from a wide range of ecological niches including soil, water and clinical samples (Stover et al., 2000). This opportunistic pathogen is prototypical "multidrug-resistant" (MDR) with intrinsically advanced antibiotic resistance gene clusters (Lambert, 2002; Livermore, 2002). Some of the strains of *P. aeruginosa* have been associated with serious illnesses mainly imparting nosocomial infections (ventilator-associated pneumonia) and various sepsis syndromes (Planquette et al., 2013; Philippart et al., 2015). The pathogenicity of *P. aeruginosa* is attributed to the presence of prominent virulence