Comparative Genomics and Phenomics Reveal Genetic and Functional Diversity within *Pseudomonas Aeruginosa* Isolates

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Abstract Text:

Pseudomonas aeruginosa is a leading cause of infections in immunocompromised individuals and in healthcare settings. The treatment of these infections is complicated by the presence of a variety of antimicrobial resistance and virulence mechanisms. However, the mechanisms of the specific metabolic functions that are modulated across diverse *P. aeruginosa*phenotypes during human infection are poorly understood. To better understand the metabolic links and facilitate innovative treatment strategies against this versatile pathogen, we obtained 971 clinical isolates of *P. aeruginosa* from 590 patients at the UVA Health System Clinical Microbiology Laboratory, with corresponding patient metadata, bacterial morphological phenotypes, and antimicrobial susceptibility profiles. We selected a set of 25 phenotypically representative isolates for whole genome sequencing from the entire isolate collection through stratified random sampling. The genome sequence data was used for comparative genomic analysis using the PA14 strain as the reference genome. A dissimilarity matrix was enumerated from the output of multiple local alignment searches and was used to develop a phylogenetic cluster of the isolates. The genotypic clustering was compared to the phenotypic clustering generated from a multi-parametric analysis to assess the genotype-phenotype correlation. Each of the complete genomes of the isolates was annotated based on the KEGG biochemical database and a genome-scale metabolic reconstruction was developed for each isolate through extensive amendment to an existing PA14 reconstruction, *i*Pau21, from our group. With approximately 33-47% of unique metabolic landscape across the isolates compared to the reference PA14 strain, these models show diverse metabolic capability and substrate dependencies, as further validated by substrate consumption and fitness profiles from Biolog Phenotype Microarray of 192 substrates.