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Application of Genomic Approaches to Bacterial Pathogenesis and Mechanisms of Antimicrobial Resistance

Project Number
1ZIAAI001249-01

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Awardee Organization
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Description

Abstract Text

The emergence of MDR gram-negative bacterial pathogens has been recognized as a critical threat to public health. Many important classes of bacterial AMR undergo selection and evolution in the natural context of antibiotic treatment in a human host, though important features of host context are not commonly included in studies of AMR. One of the main areas of focus of this work is the application of genomic techniques to understand the evolutionary mechanisms by which resistance emerges in this natural context. The approaches applied include sequencing of current and historical clinical bacterial isolates in combination with in vitro models of adaptive evolution to characterize pathways by which present day resistance to specific antimicrobial drug classes has evolved. Population genomics approaches are applied in combination with molecular genetic analysis to understand selection dynamics and host-pathogen interactions in the context of defined genetic immunodeficiency diseases. Work completed during the 2019 fiscal year focused on how P. aeruginosa hypermutator phenotypes may facilitate the emergence of resistance to antibiotics in vivo. P. aeruginosa is an important pathogen responsible for significant morbidity and mortality among hospitalized patients, and the mechanisms underlying the emergence of MDR P. aeruginosa phenotypes within patients receiving antibiotic therapy is critical to developing approaches to treat these infections. Using a combination of whole genome sequencing of clinical isolates and in vitro adaptive evolution experiments, we have demonstrated that evolved mismatch repair (MMR) deficiencies may be exploited by P. aeruginosa to facilitate rapid acquisition of antibiotic resistance in acute infection, and we have directly documented rapid clonal succession by such a hypermutating lineage in a patient. These results suggest a possibly underappreciated role for evolved MMR deficiency in facilitating rapid adaptive evolution of P. aeruginosa in the context of acute infection, with potential diagnostic and treatment implications. Other work initiated during the 2019 fiscal year involves comprehensive whole genome sequencing of a historical collection of clinical Bacteroides fragilis group (BFG) isolates covering a period of five decades to understand how mechanisms of resistance have arisen. Members of the BFG are important constituents of the human microbiota, but they can also behave as significant pathogens in certain contexts. Historically, antimicrobial susceptibility patterns in BFG isolates were largely predictable, allowing effective use of empiric treatment regimens. Alarming increases in antimicrobial resistance have recently necessitated reconsideration of empiric strategies. While genes conferring resistance to clinically utilized antibiotics in anaerobic bacteria have been the subject of extensive research, a broader understanding of the historical evolutionary processes governing their acquisition is lacking. In this work, we seek a comprehensive genomic characterization of clinical BFG isolates spanning 52-years from the early antibiotic era to the present with the primary goal of studying the acquisition of genes mediating antibiotic resistance. Ongoing research with this genomic archive will provide valuable information concerning the genetic basis, acquisition, and evolution of antimicrobial resistance in anaerobic bacteria.

Public Health Relevance Statement

Thank you for your feedback!

Data not available.

NIH Spending Category

Antimicrobial Resistance Biodefense Biotechnology

Emerging Infectious Diseases Genetics Infectious Diseases

Project Terms

Anaerobic Bacteria Antibiotic Resistance Antibiotic Therapy Antibiotics

Antimicrobial Resistance Antimicrobial susceptibility Archives Area

Bacteria Bacterial Infections Bacteroides fragilis Clinical Collection

Diagnostic **Disease** Evolution Genes Genetic Genomic approach

Genomics Goals Human Immunologic Deficiency Syndromes In Vitro

Infection Mediating Mismatch Repair Molecular Genetics

Morbidity - **disease** rate Multi-Drug Resistance Pathogenesis

Pathway interactions Patients Pattern Phenotype Plasmids Population

Process Pseudomonas aeruginosa Public Health Research Resistance

Details

No information available for 1ZIAAI001249-01

Sub Projects

No Sub Projects information available for 1ZIAAI001249-01

Publications

No Publications available for 1ZIAAI001249-01

Patents

No Patents information available for 1ZIAAI001249-01

Outcomes

The Project Outcomes shown here are displayed verbatim as submitted by the Principal Investigator (PI) for this award. Any opinions, findings, and conclusions or recommendations expressed are those of the PI and do not necessarily reflect the views of the National Institutes of Health. NIH has not endorsed the content below.

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