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Comparative Genomics of Multidrug-Resistant Enterobacteriaceae.

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Introduction

The rise of multidrug-resistant (MDR) Enterobacteriaceae represents one of the most pressing challenges in modern medicine. These Gram-negative bacteria, which include *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*, are responsible for a wide range of infections—from urinary tract infections to life-threatening sepsis. Comparative genomics has emerged as a powerful tool to unravel the genetic mechanisms underlying resistance, virulence, and transmission, offering insights that are critical for surveillance and therapeutic innovation [1, 2].

Enterobacteriaceae are facultative anaerobic rods commonly found in the gastrointestinal tract. While many are harmless commensals, others have evolved into formidable pathogens. The emergence of MDR strains—especially those resistant to last-resort antibiotics like carbapenems and polymyxins—has transformed these bacteria into global health threats [3, 4].

Comparative genomics involves analysing and comparing the genomes of different organisms or strains to identify similarities and differences. In the context of MDR Enterobacteriaceae, it helps: Identify resistance genes and their genomic context Track evolutionary relationships and clonal lineages Understand mechanisms of gene acquisition and dissemination. Whole-genome sequencing (WGS) has revolutionized this field, enabling high-resolution analysis of thousands of bacterial isolates across time and geography. Comparative genomics reveals that many resistance genes are located on mobile genetic elements such as plasmids, transposons, and integrons, facilitating horizontal gene transfer (HGT) [5, 6].

Resistance genes are often embedded within genomic islands—large DNA segments acquired via HGT. These islands may carry clusters of resistance and virulence genes, enhancing bacterial fitness in hostile environments like hospitals. Plasmids play a central role in spreading resistance. For example, the blaNDM gene, which encodes New Delhi metallo-β-lactamase, has been found on diverse plasmid backbones across *E. coli*, *K. pneumoniae*, and *Enterobacter spp.*.These clones often harbour multiple resistance determinants and virulence factors, making them particularly difficult to treat and control [7, 8].

Polymyxins (e.g., colistin) are last-resort antibiotics for MDR Gram-negative infections. Resistance to polymyxins is mediated by:Chromosomal mutations in two-component systems like PhoPQ and PmrAB Plasmid-borne mcr genes, which modify lipid A in the bacterial outer membrane. Comparative genomics has traced the spread of mcr-1 and mcr-8 genes across Enterobacteriaceae in both clinical and environmental settings, highlighting the role of mobile elements in resistance dissemination [9, 10].

Conclusion

MDR Enterobacteriaceae are responsible for prolonged hospital stays, increased mortality, and higher healthcare costs. Identifying sources and transmission routes. Monitoring resistance gene prevalence. Targeting conserved resistance mechanisms. For example, genomic analysis of

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Enterobacter cloacae complex has revealed over 1000 sequence types, many associated with nosocomial outbreaks and carbapenem resistance. Advancements in sequencing technologies and bioinformatics are expanding the scope of comparative genomics. Promising areas include: Studying resistance in microbial communities. High-resolution strain differentiation. Predicting resistance phenotypes from genomic data. Integrating genomic data with clinical metadata will enhance our ability to combat MDR pathogens.

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