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On the Origins of mobile Antibiotic Resistance Genes

A comparative genomics approach

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 09.06.2021 klockan 13:00

Av **Stefan Ebmeyer**

Fakultetsopponent:
Gerry Wright, Professor
McMaster University, Kanada

Avhandlingen baseras på följande delarbeten

I. Ebmeyer S, Kristiansson E & Larsson D. G. J. **PER extended-spectrum β-lactamases originate from Pararheinheimera spp**. *Int. J. Antimicrob. Agents* **53**, 158–164 (2019).

II. Ebmeyer S, Kristiansson E & Larsson D. G. J. **CMY-1/MOX-family AmpC β-lactamases MOX-1, MOX-2 and MOX-9 were mobilized independently from three *Aeromonas* species**. *J. Antimicrob. Chemother.* (2019) doi:10.1093/jac/dkz025.

III. Ebmeyer S, Kristiansson E. & Larsson D. G. J. **The mobile FOX AmpC beta-lactamases originated in Aeromonas allosaccharophila.** *Int. J. Antimicrob. Agents* **54**, 798–802 (2019).

IV. Kieffer N, Ebmeyer S & Larsson D. G. J. **The Class A Carbapenemases BKC-1 and GPC-1 Both Originate from the Bacterial Genus Shinella.** *Antimicrob. Agents Chemother.* **64**, (2020).

V. Ebmeyer S, Kristiansson E & Larsson D. G. J. **A framework for identifying the recent origins of mobile antibiotic resistance genes.** *Commun. Biol.* **4**, 1–10 (2021).

VI. Ebmeyer S, Kristiansson E, Larsson DGJ. **GEnView: A gene-centered, phylogeny-based comparative genomics pipeline for bacterial genomes and plasmids.** Manuscript

SAHLGRENSKA AKADEMIN
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Abstract

Mobile antibiotic resistance genes (ARGs), transferable between bacterial cells, are major contributors to the antibiotic resistance crisis we are facing today. From which organisms pathogens acquired these genes is mostly unknown, yet knowledge about their origin is needed in order to limit the emergence and spread of novel ARGs in the future. Increasing the number of known origins of mobile resistance genes would allow us to investigate potential patterns that may hint towards the conditions that potentially promote the emergence of mobile ARGs. This thesis aims to identify from which taxa ARGs have been mobilized into pathogens, so that this knowledge may aid mitigations to limit the emergence of novel ARGs in the future.

We used comparative genomic methods on the large amount of publicly available sequenced bacterial genomes in order to identify bacterial taxa from which certain ARGs have been mobilized (paper I-IV). A literature review and the development of a computational pipeline (paper VI) to compare hundreds of genomic loci allowed us to scrutinize previously reported origins and analyze patterns among to-date identified ARG origins (paper V).

In this thesis, we have identified the recent origins of PER-type class A beta-lactamases as *Pararheinheimera* spp. (Paper I), the recent origin of CMY-1/MOX-1, MOX-2 and MOX-9 class C beta-lactamases as *Aeromonas sanarellii, Aeromonas caviae* and *Aeromonas media* respectively (Paper II), the recent origin of FOX-type class C beta-lactamases as *Aeromonas allosaccharophila* (Paper III), and the recent origin of GPC-1/BKC-1 carbapenemases as *Shinella* spp (Paper IV). In paper V, based on the amended and curated data from the literature, five criteria allowing for the confident identification of recent origins of mobile ARGs were identified. Of all recent origins identified on species level, all were Proteobacteria, >90% were identified as potential pathogens of humans and/or domestic animals, none of them known antibiotic producers themselves. However, all curated recent origins account for only about 4% of known mobile ARGs, indicating that environmental bacteria may represent a significant source of resistance genes. Finally, Paper VI presents a bioinformatics pipeline, GEnView, for comparative genomic analysis of gene loci among hundreds of genomes, developed throughout this thesis.

This thesis further elucidates the recent origins of several mobile resistance genes, identifies previously unrecognized patterns about their emergence and provides other researchers with the tools to investigate the origins of other resistance genes. This knowledge may prove valuable to guide future efforts trying to mitigate the emergence of additional ARGs in the clinics.

Keywords: antibiotic resistance, origin, comparative genomics

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