Göteborg, 2020

IDENTIFICATION OF NOVEL ANTIBIOTIC RESISTANCE GENES THROUGH THE EXPLORATION OF MOBILE GENETIC ELEMENTS

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligt försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, Sverige, torsdagen den 11 juni, klockan 13.00.

av Mohammad Razavi

Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten

I. **Discovery of the fourth mobile sulfonamide resistance gene**.
Mohammad Razavi, Nachiket P. Marathe, Michael R. Gillings, Carl-Fredrik Flach, Erik Kristiansson, and D. G. Joakim Larsson. *Microbiome*; 5:160. (2017)

II. **Discovery of a novel integron-borne aminoglycoside resistance gene present in clinical pathogens by screening environmental bacterial communities**.
Maria-Elisabeth Böhm, Mohammad Razavi, Nachiket P. Marathe, Carl-Fredrik Flach, and D. G. Joakim Larsson. *Microbiome*; 8:41. (2020)

III. **A Novel, Integron-Regulated, Class C β-Lactamase**.
Maria-Elisabeth Böhm, Mohammad Razavi, Carl-Fredrik Flach, and D. G. Joakim Larsson. *Antibiotics*, 9(3), 123. (2020)

IV. **Can the association with insertion sequences guide the discovery of novel antibiotic resistance genes?**
Mohammad Razavi, Erik Kristiansson, Carl-Fredrik Flach, and D. G. Joakim Larsson. *Manuscript*.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

Identification of novel antibiotic resistance genes through the exploration of mobile genetic elements

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ABSTRACT

Backgrounds and aims: The evolution of multi-resistant pathogens is seriously threatening our ability to provide modern healthcare. Many of the mobile resistance factors in clinics appear to originate from environmental bacteria. In this thesis, strategies are developed and applied to explore and identify novel antibiotic resistance genes (ARGs) captured and carried by different mobile genetic elements on a large-scale. The primary aim is to identify novel, mobile ARGs that could become, or that already are, a threat to the public health.

Methods: We used targeted amplicon sequencing (Paper I) and functional metagenomics of amplified gene cassettes (Papers II and III) that were recovered from two polluted environments. In Paper IV, we studied the associations between insertion sequences (ISs) and ARGs by analyzing all sequenced bacterial genomes. Moreover, several thousand metagenomic runs were analyzed to estimate the abundance of ARGs (including novel ARGs) and ISs.

Results and discussion: In Paper I, we found a novel mobile sulfonamide resistance gene providing a high level of resistance when expressed in *E. coli*. By using functional metagenomics (Papers II and III), we identified a completely new integron-borne aminoglycoside resistance gene that was already present, but previously not identified, in multi-resistant clinical isolates collected from patients in Italy, as well as in two food-borne *Salmonella enterica* isolates from the USA. Moreover, we described and characterized the first *ampC*s encoded as integron gene cassettes with increased transmission opportunities to move between different bacterial species. Metagenomic analysis showed that all three genes are spread in different geographical locations and were abundant in wastewater environments. In Paper IV, ISs and tentative composite transposons with strong associations with ARGs were identified, and we proposed that these could be explored further to discover novel ARGs, for example with an amplicon sequencing approach. Finally, metagenomic analyses shed light on the environments that potentially contain such ISs.

Conclusions: Targeted amplicon sequencing and its integration with functional metagenomics were successful in finding novel resistance gene cassettes that have already accumulated in pathogens or have the potential to do so. With a well-designed strategy, the content of ISs could be explored to identify unknown mobile ARGs in addition to those associated with integron gene cassettes. Finally, the information produced in this thesis is the initial seed for an accessible web application useful in studying the association between ISs and ARGs.

Keywords: Antibiotic resistance, resistome, integron, insertion sequences, metagenomics, environment

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