Genomic Islands and the Evolution of Multidrug-Resistant Bacteria

Mario Juhas

Abstract The horizontal gene transfer is crucial for the evolution and adaptation of bacteria. An important part of the horizontal gene transfer is facilitated by the large, discreet DNA segments called genomic islands. Some genomic islands encode means of their own excision, self-transfer and integration into the chromosome, while others can be mobilized by other mobile genetic elements or are stably integrated into the chromosomes of the host bacteria. Genomic islands are involved in the dissemination of a wide variety of genes, including virulence and antibiotic-resistant genes. This review provides an update on the investigation of genomic islands with particular emphasis on their role in the evolution of multidrug-resistant bacteria.

Keywords Horizontal gene transfer · Genomic island · MDR bacteria · ICE · *Escherichia coli* · *Pseudomonas aeruginosa* · *Salmonella enterica* · *Proteus mirabilis* · *Acinetobacter baumannii* · *Staphylococcus aureus*

1 Horizontal Gene Transfer of Resistance Genomic Islands

The horizontal gene transfer is crucial for the evolution and adaptation of bacterial species (Soucy et al. 2015; Koonin 2016). An important part of the horizontal gene transfer is facilitated by the large, discreet DNA segments called genomic islands (GIs) (Carraro et al. 2017b; Juhas et al. 2009). Some GIs are nonmobile and firmly integrated into the chromosomes of the host bacteria. Alternatively, GIs such as SGI/PGI/AGI-like GIs found in *Salmonella enterica*, *Proteus mirabilis*, *Morganella morganii* and *Acinetobacter baumannii* described in this review can be mobilized by other mobile genetic elements that are present in the host genome (Siebor et al. 2016, 2018; Kiss et al. 2015; Murányi et al. 2016; Carraro et al. 2017a, b;

M. Juhas (✉)
Institute of Medical Microbiology, University of Zürich, Zürich, Switzerland
e-mail: mjuhas@imm.uzh.ch

T. G. Villa, M. Viñas (eds.), *Horizontal Gene Transfer*,
https://doi.org/10.1007/978-3-030-21862-1_4

de Curraize et al. 2018; Hawkey et al. 2018; Schultz et al. 2017). Finally, some GIs encode means of their own horizontal transfer into the new host cells. These mobile GIs include a large group dubbed integrative and conjugative elements (ICEs). Although ICEs are often found integrated into the host chromosome, they are capable of excision, transfer into the new host cells by conjugation and reintegration into the chromosome of the new host. ICEs known to be involved in the spread of antibiotic-resistant genes include ICEs found in *Haemophilus* spp. described previously or the recently identified *Pseudomonas aeruginosa* ICEs presented in this review (Juhas et al. 2007a, b, 2008, 2009; Carraro and Burrus 2014; Juhas 2015c; Botelho et al. 2018; Roy Chowdhury et al. 2016, 2017).

In addition to genes crucial for self-propagation, GIs can carry a broad spectrum of accessory open reading frames involved in the virulence (pathogenicity islands), symbiosis (symbiosis islands), metabolism (metabolic islands), fitness (fitness islands) or resistance to antimicrobials (resistance islands) (Juhas et al. 2009). As resistance GIs are capable of carrying large numbers of variable antibiotic-resistant genes, their acquisition can provide the host bacterium with the resistance to the whole array of antimicrobials. The process of the rapid evolution of the multidrug-resistant (MDR) bacteria facilitated by GIs has therefore been dubbed the evolution by "quantum leaps" (Groisman and Ochman 1996; Hacker and Carniel 2001). This review provides an update on the contribution of GIs to the evolution of MDR bacteria, with the particular emphasis on GI3, which contributed to the increased pathogenicity of the *Escherichia coli* O104:H4 2011 outbreak strain and the most recent analyses of SGI/PGI/AGI-like GIs in MDR *S. enterica*, *P. mirabilis*, *M. morganii* and *A. baumannii*, SCC*mec* in MDR *Staphylococcus aureus* and GIs involved in the evolution of MDR *P. aeruginosa*.

2 GI3 in MDR *Escherichia coli* O104:H4

The outbreak of the highly pathogenic *E. coli* strain O104:H4 in 2011 which started in Germany resulted in nearly 5000 cases of severe infections associated with bloody diarrhoea, nearly 1000 cases of haemolytic uremic syndrome and 82 deaths (Rasko et al. 2011). The increased pathogenicity of the *E. coli* O104:H4 2011 outbreak strain was attributed to the acquisition of a battery of mobile genetic elements (Grad et al. 2013). These included Shiga toxin 2 (*stx2*)-encoding prophage typically found in enterohaemorrhagic *E. coli* strains, which in combination with the increased aggregative adherence typical for the enteroaggregative *E. coli* led to the increased absorption of Shiga toxin in the infections caused by the *E. coli* O104:H4 outbreak strain (Juhas 2015a; Rasko et al. 2011).

Notably, the *E. coli* O104:H4 2011 outbreak strain was found to be resistant to multiple antibiotics. In addition to 90 kb IncI1 plasmid encoding the CTX-M-15 cephalosporinase, which was unique to the 2011 outbreak strain (Künne et al. 2012), comparative whole-genome analyses revealed the presence of the *E. coli* genomic island 3 (GI3) in the chromosomes of the enteroaggregative haemorrhagic *E. coli*

O104:H4 outbreak strains. GI3, considered to be the hotspot for microevolutionary genetic events in the *E. coli* O104:H4 strains, harbours multiple antibiotic-resistant genes, namely, $bla_{\text{TEM-1}}$, *dfrA7*, *strAB*, *sul2* and *tet(A)*A encoding resistance to ampicillin, trimethoprim, streptomycin, sulfamethoxazole and tetracycline, respectively (Roy Chowdhury et al. 2015). The resistance genes in GI3 are located in the complex antibiotic-resistant gene loci (CRL), which also include *ag43* encoding the virulence factor involved in the biofilm formation and *mer* genes encoding the resistance to mercury (Grad et al. 2013). Bioinformatics analysis revealed that the evolution of CRL in GI3 has been mediated by Tn*6029* family of transposons carrying the $bla_{\text{TEM-1}}$-*sul2-strA-strAB* gene cluster flanked by IS*26* (Roy Chowdhury et al. 2015).

The presence of the multiple antibiotic-resistant genes in the genome of *E. coli* O104:H4 contributed to the 2011 outbreak. In addition to limiting the available treatment options, the multiple antibiotic-encoding GI3 in combination with the IncI1 plasmid-encoded CTX-M-15 cephalosporinase played a key role in the ability of the *E. coli* O104:H4 2011 outbreak strain to outcompete the other commensal *E. coli* strains in the guts of patients that were treated with antibiotics (Bielaszewska et al. 2011; Juhas 2015a).

Interestingly, although found to be integrated into the chromosomes of the host *E. coli* O104:H4 strains, GI3 was previously shown to be mobile (Roy Chowdhury et al. 2015). To integrate into the chromosome, GI3 targets a 23 bp genomic sequence found in a broad spectrum of *Enterobacteriaceae*. This highlights the potential risk of GI3 being involved in the emergence of a number of other MDR *Enterobacteriaceae* in the future (Roy Chowdhury et al. 2015).

3 SGI/PGI/AGI-Like GIs in MDR *Salmonella enterica*, *Proteus mirabilis* and *Acinetobacter baumannii*

Salmonella genomic island 1 (SGI1, 42.4 kb), its variants and related GIs, such as SGI2, *Proteus* genomic island (PGI1) and *Acinetobacter* genomic island (AGI1) are frequently found in a broad spectrum of *Enterobacteriaceae* (Siebor et al. 2016; Soliman et al. 2017; Hamidian et al. 2015b, c). Although usually stably integrated into the host cell's chromosome, SGI1 can be mobilized by the helper plasmids of the incompatibility groups A and C (IncA and IncC) (Siebor et al. 2016). It was shown that mobilization of SGI1 is initiated by the helper plasmid-encoded master transcriptional activator complex AcaCD. AcaCD is crucial not only for the expression of genes involved in the excision of SGI1 from the chromosome but also for the expression of the three SGI1-encoded *tra* genes involved in the transfer of SGI1 into a new host cell (Kiss et al. 2015; Murányi et al. 2016). Recent studies showed that SGI1 can reshape the conjugative apparatus of the helper plasmids to promote its own transfer (Carraro et al. 2017a). Besides a conserved backbone comprised of 28 open reading frames involved in the life cycle, excision, transfer and reintegration

Fig. 1 Schematic representation of the SGI/PGI/AGI-like genomic islands. The figure shows the key features of the SGI/PGI/AGI-like genomic islands, which are involved in the evolution of MDR *Salmonella enterica*, *Proteus mirabilis*, *Acinetobacter baumannii* and *Morganella morganii*. SGI/PGI/AGI-like genomic islands are integrated into the chromosome in the 3′ end of the *trmE* gene and are flanked by the *attL* and *attR* attachment sites. In addition to the backbone region carrying open reading frames crucial for the life cycle (excision from the chromosome, transfer and integration into the new host's chromosome), SGI/PGI/AGI-like genomic islands also harbour MDR region encoding resistances to a number of different antibiotics, such as ampicillin (AMP), chloramphenicol (CHLO), sulfamethoxazole (SUL), streptomycin/spectinomycin (STR/SPE) and tetracycline (TET)

of SGI1, SGI1 harbours a complex MDR region conferring resistance to multiple antibiotics, including ampicillin, tetracycline, sulfamethoxazole, chloramphenicol/florfenicol and streptomycin/spectinomycin (de Curraize et al. 2018) (Fig. 1).

Proteus genomic island (PGI1) of 81.1 kb, found in *P. mirabilis*, has a gene backbone similar to that of SG1, in addition to the complex MDR region composed of transposons and IS elements and a number of antibiotic-resistant genes, including metallo-β-lactamase-resistant gene $bla_{\text{NDM-1}}$ and extended-spectrum-β-lactamase-resistant gene $bla_{\text{VEB-6}}$ (Siebor and Neuwirth 2014).

Recently, a novel resistance GI, GI*Pm1* of 55.8 kb, was identified in *P. mirabilis* inserted into the chromosome at the *trmE* site, as is typical for other GIs of this subfamily, such as SGI1 and PGI1. GI*Pm1* is composed of the gene backbone similar to GI found in *Enterobacter cloacae* DSM16690 and MDR region conferring resistance to multiple antibiotics (Siebor et al. 2018). The detection of the extra-chromosomal circular form GI*Pm1* suggests that GI*Pm1* is mobile; however, its mobilization is not facilitated by the IncA and IncC helper plasmids but by another, yet unknown mechanism (Siebor et al. 2018).

Recently, two new variants of SGI1 named SGI1-K7 (55.1 kb) and SGI1-*Pm*2CHAMA (53.6 kb) were identified in *P. mirabilis* whose MDR regions carried resistance genes never before identified in this subfamily of GIs, namely, $bla_{\text{CTX-M-15}}$ and $bla_{\text{CARB-2}}$ (de Curraize et al. 2018). Particularly alarming is the identification of $bla_{\text{CTX-M-15}}$ encoding an extended-spectrum-β-lactamase usually found in MDR *E. coli* clinical isolates among the open reading frames of SGI1-K7. Notably, CTX-M-15 was also found in the *E. coli* O104:H4 2011 outbreak strain (Künne et al. 2012; Rasko et al. 2011).

AGI1 with the gene backbone similar to SGI1, PGI1 and their variants was found in the chromosome of *A. baumannii*. AGI1 is integrated into the *A. baumannii* chromosome at the *trmE* site, similar to other GIs from this subfamily. Furthermore, AGI1 carries a MDR region harbouring genes bla_{PER}, *aadB*, *aadA13/2*, *aadA2*, *strAB* and *sul1* conferring resistance to cephalosporins, aminoglycosides and sulphonamides (Hamidian et al. 2015a). Besides AGI1, *A. baumannii* chromosome often harbours other types of resistant GIs, such as *A. baumannii*-resistant island (AbaR). These GIs, together with the plethora of other mobile genetic elements and

the high intrinsic resistance of *A. baumannii* to a number of clinically used antimicrobials, such as the second-generation cephalosporins, aminopenicillins and chloramphenicol, make MDR *A. baumannii* one of the main public threats nowadays (Pagano et al. 2016; Blackwell et al. 2015; Kim et al. 2017; Gallagher et al. 2017; Hawkey et al. 2018).

SGI1-like variant dubbed SGI1-L harbouring $bla_{\text{CARB-2}}$, *dfrA15*, *floR*, *sul1* and *tetA*(G) conferring resistance to amoxicillin, trimethoprim, phenicols, sulphonamides and tetracyclines has been recently identified in a MDR *Morganella morganii* subsp. *morganii* (Schultz et al. 2017).

While the gene backbone region of the SGI/PGI/AGI-like subfamily of GIs is relatively well conserved, their MDR region is very plastic as a result of microevolution events, which include IS element-mediated genome rearrangements and homologous recombination (de Curraize et al. 2018). Taken together with the ability to be mobilized by the helper plasmids, SGI1 and its variants and related GIs, such as PGI1 and AGI1, present a high risk for the dissemination of the clinically relevant antibiotic-resistant genes among other *Enterobacteriaceae* (de Curraize et al. 2018).

4 SCC*mec* in MDR *Staphylococcus aureus*

S. aureus is a highly versatile Gram-positive opportunistic pathogen causing a variety of diseases, ranging from minor skin infections to endocarditis, osteomyelitis, pneumonia and septicaemia. Methicillin-resistant *S. aureus* (MRSA) is considered to be among the main threats to human health nowadays (Juhas 2015a). Alarmingly, MRSA strains have in the meantime acquired resistances to a number of other antibiotics, including β-lactams, lincosamides and macrolides and more recently also vancomycin (Jani et al. 2017). Consequently, MDR MRSA strains are among the leading causes of morbidity and mortality and are among the most significant sources of both nosocomial and community-acquired infections (Anderson et al. 2014).

Resistance of *S. aureus* to methicillin was acquired via PBP2a-encoding gene *mecA* located on the staphylococcal chromosome cassette methicillin-resistant (SCC*mec*) island. SCC*mec* islands can be highly diverse ranging from 20 to 70 kb. Furthermore, SCC*mec* islands are classified into subtypes based on sequences of serine recombinases *ccrAB* and *ccrC* and regulators *mecI* and *mecR1* (Ray et al. 2016). Recombinases *ccrAB* and *ccrC* play an important role in the excision, circularization and site-specific integration of SCC*mec* into the *S. aureus* chromosome (Smyth et al. 2011; Ray et al. 2016).

The origin of *mecA* in *S. aureus* remains still unclear; however, bioinformatics analyses suggest that it has been acquired horizontally from other staphylococcal species, such as *Staphylococcus epidermidis*, *Staphylococcus fleuretti* or *Staphylococcus haemolyticus* (Juhas 2015a; Xue et al. 2017; Smyth et al. 2011; Ray et al. 2016; Wipf et al. 2015; Tsubakishita et al. 2010; Hosseinkhani et al. 2018). There are several lines of evidence for this claim. First, SCC*mec* subtype IV has been found in

the genome of *S. epidermidis* before it has been reported in *S. aureus* (Smyth et al. 2011). Second, the transfer of SCC*mec* island captured on staphylococcal conjugative plasmid into isogenic *S. aureus* and *S. epidermidis* has been demonstrated in vitro (Ray et al. 2016). Third, SCC*mec* elements have been identified in *S. epidermidis* carrying resistance genes against *β*-lactams, heavy metals and polyamines. It was shown that the resistance genes located on the *S. epidermidis* SCC*mec* elements originated from various bacteria, habitats and geographic regions (Xue et al. 2017). This highlights the role of *S. epidermidis* as a reservoir of resistance genes implicated in the evolution of MDR *S. aureus*. Fourth, *S. fleuretti* naturally harbours *mecA* in its chromosome and is therefore suspected to be the source of the *mecA* in the SCC*mec* island (Wipf et al. 2015; Tsubakishita et al. 2010). Fifth, homology searches showed the presence of the SCC*mec*-borne *ccrB*-encoding recombinase in the genomes of a number of other staphylococci (Fluit et al. 2013). Finally, highly diverse SCC*mec* islands were identified in the genome of *S. haemolyticus* recently, highlighting the role of *S. haemolyticus* in carrying the methicillin-resistant genes (Hosseinkhani et al. 2018).

Interestingly, the gene clustering approach has led to identification of a number of novel GIs which harbour a wide variety of resistance genes in the genome of *S. aureus*, recently. It has been suggested that these yet uncharacterized GIs can shed light on the evolution of MDR in *S. aureus* (Jani et al. 2017).

5 GIs in MDR *Pseudomonas aeruginosa*

P. aeruginosa is an opportunistic Gram-negative human pathogen frequently associated with the chronic nosocomial infections, particularly in immunocompromised individuals (those with AIDS, severe burns and cancer and cystic fibrosis patients) (Oliver et al. 2000; Azam and Khan 2018). The emergence and rapid spread of antibiotic-resistant *P. aeruginosa* led to the classification of the drug-resistant *P. aeruginosa* among the greatest threats to public health by WHO, CDC and ECDC (CDC 2013; ECDC 2015). *P. aeruginosa* infections are notoriously hard to eradicate due to the vast array of intrinsic, adaptive and acquired resistance mechanisms that confer resistances to a number of antimicrobials, including the last-generation carbapenems, which are usually used for the treatment of MDR bacteria (Azam and Khan 2018; Juhas et al. 2004, 2005; Wiehlmann et al. 2007; Juhas 2015b; Potron et al. 2015; Oliver et al. 2015).

Genes encoding resistance to carbapenems are often located on class 1 integrons; however, class 1 integrons are considered to be incapable of self-transfer. Thus for the transfer to the new host, class 1 integrons have to associate with other transferable elements, such as plasmids, transposons or GIs (Roy Chowdhury et al. 2016, 2017). Interestingly, class 1 integrons were found to be carried by the two globally dispersed GIs (GI1 and GI2) that are frequently found in *P. aeruginosa* multidrug-resistant clones ST235, ST253, ST111 and ST175. Both GI1 and GI2 harbour open reading frames conferring resistances to the entire range of antibiotics used to treat

P. aeruginosa infections, including carbapenems (Roy Chowdhury et al. 2016, 2017). Besides resistance to multiple antibiotics, *P. aeruginosa* GI1 and GI2 harbour genes implicated in their conjugative transfer to the new host cells and reintegration into the chromosome, thus suggesting their evolution from a novel, yet uncharacterized ICE. This study also highlights the role GIs play in the capture and dissemination of antibiotic-resistant genes and in the evolution of MDR *P. aeruginosa* (Roy Chowdhury et al. 2017).

Recent whole-genome sequencing analyses of the high-risk *P. aeruginosa* clone ST235 revealed the presence of a novel GI, ICE*Pae690* carrying $bla_{\text{GES-6}}$ carbapenemase gene (Botelho et al. 2018). $bla_{\text{GES-6}}$ was found on a class 1 integron In1076 located within ICE*Pae690*. Besides In1076 integron, ICE*Pae690* carried gene-encoding integrase, type IV secretion system, relaxase and type IV coupling protein involved in the excision, conjugation and reintegration of ICE*Pae690* and other genes encoding maintenance functions. ICE*Pae690* was integrated into the chromosome next to a tRNA^{Gly} gene and flanked by 16 bp ICE*clc*-like *attL* and *attR* sequences. The flanking *attL* and *attR* sequences are probably a result of recombination between the attachment sites *attB* and *attP* on the chromosome and ICE*Pae690*, respectively. This study also demonstrated that ICE*Pae690* is capable of the self-transfer by conjugation from the original *P. aeruginosa* clone ST235 to *P. aeruginosa* standard laboratory strain PAO1. It has been suggested that In1076 integron harbouring $bla_{\text{GES-6}}$ "hitch-hiked" ICE*Pae690* to promote its own propagation to other host cells through ICE-mediated conjugation (Botelho et al. 2018).

Recent whole-genome sequencing analyses led to the identification of a number of novel GIs (PAGIs) in the genomes of *P. aeruginosa*, namely, PAGI-13, PAGI-14, PAGI-15 and PAGI-16 carrying a broad spectrum of resistance genes, including $bla_{\text{IMP-6}}$, $bla_{\text{IMP-10}}$ and $bla_{\text{GES-24}}$. In PAGI-13, PAGI-14, PAGI-15 and PAGI-16, these resistance genes are located on the class 1 integrons and confer resistance to carbapenems (Hong et al. 2016; Silveira et al. 2016).

6 Conclusions

Work over the last years, in particular the recent bioinformatics and whole-genome sequencing analyses, highlighted the diversity of GIs and shed new light on the GI-mediated genome plasticity (Botelho et al. 2018).

It is now widely accepted that GIs play an important role in the evolution of a broad spectrum of bacterial species, including MDR bacteria, such as MDR *E. coli*, *S. enterica*, *P. mirabilis*, *M. morganii*, *A. baumannii* and *P. aeruginosa*, presented in this review but also in a number of other clinically relevant MDR pathogens. For instance, the master transcriptional activator complex AcaCD of the IncA/C helper plasmids originally found in the GIs of the SGI/PGI/AGI-like subfamily was shown to be involved in the mobilization of other unrelated resistance GIs, such as MGI*Vch*Hai6 of *Vibrio cholerae* which confers resistance to β-lactams, tetracycline,

sulfamethoxazole, trimethoprim, streptomycin/spectinomycin and chloramphenicol (Carraro et al. 2016).

Furthermore, recent analyses revealed that GIs are undergoing constant micro-evolution and continue to accumulate novel resistance genes within their sequences (e.g. by capturing other resistance gene-harbouring integrons and transposons) (Roy Chowdhury et al. 2016, 2017). This development is alarming particularly in connection with the ability of some GIs to self-transfer into the new host as the acquisition of such multi-resistance GIs can provide the host bacterium with the resistances to the whole array of antimicrobials.

Future studies will be required to elucidate the molecular mechanisms involved in the life cycle of some GIs, in particular the role the GIs-borne regulatory genes play in their propagation. Furthermore, additional analyses will be needed to elucidate the details of the process of acquisition of accessory genes, such as novel antibiotic-resistant genes, by GIs. Additional analyses are also required to assess the prevalence of the recently identified GIs, such as SGI/PGI/AGI-like GIs and their variants, PAGI-13, PAGI-14, PAGI-15, PAGI-16 and ICE*Pae690* in other bacterial species. This will contribute to the better understanding of GIs and their role in the spread of antimicrobial-resistant genes and the evolution of MDR bacteria.

References

Anderson DJ, Moehring RW, Sloane R, Schmader KE, Weber DJ, Fowler VG, Smathers E, Sexton DJ (2014) Bloodstream infections in community hospitals in the 21st century: a multicenter cohort study. PLoS One 9:e91713

Azam MW, Khan AU (2018) Updates on the pathogenicity status of *Pseudomonas aeruginosa*. Drug Discov Today 24(1):350–359

Bielaszewska M, Mellmann A, Zhang W, Köck R, Fruth A, Bauwens A, Peters G, Karch H (2011) Characterisation of the *Escherichia coli* strain associated with an outbreak of haemolytic uraemic syndrome in Germany, 2011: a microbiological study. Lancet Infect Dis 11:671–676

Blackwell GA, Nigro SJ, Hall RM (2015) Evolution of AbGRI2-0, the progenitor of the AbGRI2 resistance island in global clone 2 of *Acinetobacter baumannii*. Antimicrob Agents Chemother 60:1421–1429

Botelho J, Grosso F, Peixe L (2018) Unravelling the genome of a *Pseudomonas aeruginosa* isolate belonging to the high-risk clone ST235 reveals an integrative conjugative element housing a blaGES-6 carbapenemase. J Antimicrob Chemother 73:77–83

Carraro N, Burrus V (2014) Biology of three ICE families: SXT/R391, ICEBs1, and ICESt1/ICESt3. Microbiol Spect 2(6). https://doi.org/10.1128/microbiolspec.MDNA3-0008-2014

Carraro N, Rivard N, Ceccarelli D, Colwell RR, Burrus V (2016) IncA/C conjugative plasmids mobilize a new family of multidrug resistance islands in clinical *Vibrio cholerae* non-O1/non-O139 isolates from Haiti. MBio 7:e00509

Carraro N, Durand R, Rivard N, Anquetil C, Barrette C, Humbert M, Burrus V (2017a) Salmonella genomic island 1 (SGI1) reshapes the mating apparatus of IncC conjugative plasmids to promote self-propagation. PLoS Genet 13:e1006705

Carraro N, Rivard N, Burrus V, Ceccarelli D (2017b) Mobilizable genomic islands, different strategies for the dissemination of multidrug resistance and other adaptive traits. Mob Genet Elem 7:1–6

CDC (2013) Multidrug-resistant Pseudomonas aeruginosa. In: Antibiotic resistance threats in the United States, 2013, pp 69–71. https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

de Curraize C, Neuwirth C, Bador J, Chapuis A, Amoureux L, Siebor E (2018) Two new Salmonella genomic islands 1 from Proteus mirabilis and description of blaCTX-M-15 on a variant (SGI1-K7). J Antimicrob Chemother 73(7):1804–1807

ECDC (2015) Pseudomonas aeruginosa. In: Antimicrobial resistance surveillance in Europe 2015, pp 34–47. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf

Fluit AC, Carpaij N, Majoor EA, Bonten MJ, Willems RJ (2013) Shared reservoir of ccrB gene sequences between coagulase-negative staphylococci and methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 68:1707–1713

Gallagher LA, Lee SA, Manoil C (2017) Importance of core genome functions for an extreme antibiotic resistance trait. MBio 8(6):e01655–e01617

Grad YH, Godfrey P, Cerquiera GC, Mariani-Kurkdjian P, Gouali M, Bingen E, Shea TP, Haas BJ, Griggs A, Young S, Zeng Q, Lipsitch M, Waldor MK, Weill FX, Wortman JR, Hanage WP (2013) Comparative genomics of recent Shiga toxin-producing *Escherichia coli* O104:H4: short-term evolution of an emerging pathogen. MBio 4(1):e00452–e00412

Groisman EA, Ochman H (1996) Pathogenicity islands: bacterial evolution in quantum leaps. Cell 87:791–794

Hacker J, Carniel E (2001) Ecological fitness, genomic islands and bacterial pathogenicity. A Darwinian view of the evolution of microbes. EMBO Rep 2:376–381

Hamidian M, Holt KE, Hall RM (2015a) Genomic resistance island AGI1 carrying a complex class 1 integron in a multiply antibiotic-resistant ST25 *Acinetobacter baumannii* isolate. J Antimicrob Chemother 70:2519–2523

Hamidian M, Holt KE, Hall RM (2015b) The complete sequence of Salmonella genomic island SGI1-K. J Antimicrob Chemother 70:305–306

Hamidian M, Holt KE, Hall RM (2015c) The complete sequence of Salmonella genomic island SGI2. J Antimicrob Chemother 70:617–619

Hawkey J, Ascher DB, Judd LM, Wick RR, Kostoulias X, Cleland H, Spelman DW, Padiglione A, Peleg AY, Holt KE (2018) Evolution of carbapenem resistance in *Acinetobacter baumannii* during a prolonged infection. Microb Genom 4(3):e000165

Hong JS, Yoon EJ, Lee H, Jeong SH, Lee K (2016) Clonal dissemination of *Pseudomonas aeruginosa* sequence type 235 isolates carrying blaIMP-6 and emergence of blaGES-24 and blaIMP-10 on novel genomic islands PAGI-15 and -16 in South Korea. Antimicrob Agents Chemother 60:7216–7223

Hosseinkhani F, Tammes Buirs M, Jabalameli F, Emaneini M, van Leeuwen WB (2018) High diversity in SCCmec elements among multidrug-resistant Staphylococcus haemolyticus strains originating from paediatric patients; characterization of a new composite island. J Med Microbiol 67:915–921

Jani M, Sengupta S, Hu K, Azad RK (2017) Deciphering pathogenicity and antibiotic resistance islands in methicillin-resistant. Open Biol 7(12):170094

Juhas M (2015a) Horizontal gene transfer in human pathogens. Crit Rev Microbiol 41:101–108

Juhas M (2015b) *Pseudomonas aeruginosa* essentials: an update on investigation of essential genes. Microbiology 161:2053–2060

Juhas M (2015c) Type IV secretion systems and genomic islands-mediated horizontal gene transfer in Pseudomonas and Haemophilus. Microbiol Res 170:10–17

Juhas M, Wiehlmann L, Huber B, Jordan D, Lauber J, Salunkhe P, Limpert A, von Gotz F, Steinmetz I, Eberl L, Tummler B (2004) Global regulation of quorum sensing and virulence by VqsR in *Pseudomonas aeruginosa*. Microbiology 150:831–841

Juhas M, Wiehlmann L, Salunkhe P, Lauber J, Buer J, Tummler B (2005) GeneChip expression analysis of the VqsR regulon of *Pseudomonas aeruginosa* TB. FEMS Microbiol Lett 242:287–295

Juhas M, Crook DW, Dimopoulou ID, Lunter G, Harding RM, Ferguson DJP, Hood DW (2007a) Novel type IV secretion system involved in propagation of genomic islands. J Bacteriol 189:761–771

Juhas M, Power P, Lunter G, Harding R, Thomson N, Dimopoulou ID, Elamin ARE, Hood DW, Crook DW (2007b) Sequence and functional analyses of seven representative genomic islands of Haemophilus spp. Abstr Gen Meeting Am Soc Microbiol 107:253–254

Juhas M, Crook DW, Hood DW (2008) Type IV secretion systems: tools of bacterial horizontal gene transfer and virulence. Cell Microbiol 10:2377–2386

Juhas M, van der Meer JR, Gaillard M, Harding RM, Hood DW, Crook DW (2009) Genomic islands: tools of bacterial horizontal gene transfer and evolution. FEMS Microbiol Rev 33:376–393

Kim DH, Jung SI, Kwon KT, Ko KS (2017) Occurrence of diverse AbGRI1-type genomic islands in *Acinetobacter baumannii* global clone 2 isolates from South Korea. Antimicrob Agents Chemother 61(2):e01972–e01916

Kiss J, Papp PP, Szabó M, Farkas T, Murányi G, Szakállas E, Olasz F (2015) The master regulator of IncA/C plasmids is recognized by the Salmonella genomic island SGI1 as a signal for excision and conjugal transfer. Nucleic Acids Res 43:8735–8745

Koonin EV (2016) Horizontal gene transfer: essentiality and evolvability in prokaryotes, and roles in evolutionary transitions. F1000Res 5:1805

Künne C, Billion A, Mshana SE, Schmiedel J, Domann E, Hossain H, Hain T, Imirzalioglu C, Chakraborty T (2012) Complete sequences of plasmids from the hemolytic-uremic syndrome-associated *Escherichia coli* strain HUSEC41. J Bacteriol 194:532–533

Murányi G, Szabó M, Olasz F, Kiss J (2016) Determination and analysis of the putative AcaCD-responsive promoters of Salmonella genomic island 1. PLoS One 11:e0164561

Oliver A, Cantón R, Campo P, Baquero F, Blázquez J (2000) High frequency of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis lung infection. Science 288:1251–1254

Oliver A, Mulet X, López-Causapé C, Juan C (2015) The increasing threat of *Pseudomonas aeruginosa* high-risk clones. Drug Resist Updat 21–22:41–59

Pagano M, Martins AF, Barth AL (2016) Mobile genetic elements related to carbapenem resistance in *Acinetobacter baumannii*. Braz J Microbiol 47:785–792

Potron A, Poirel L, Nordmann P (2015) Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: mechanisms and epidemiology. Int J Antimicrob Agents 45:568–585

Rasko DA, Webster DR, Sahl JW, Bashir A, Boisen N, Scheutz F, Paxinos EE, Sebra R, Chin CS, Iliopoulos D, Klammer A, Peluso P, Lee L, Kislyuk AO, Bullard J, Kasarskis A, Wang S, Eid J, Rank D, Redman JC, Steyert SR, Frimodt-Møller J, Struve C, Petersen AM, Krogfelt KA, Nataro JP, Schadt EE, Waldor MK (2011) Origins of the *E. coli* strain causing an outbreak of hemolytic-uremic syndrome in Germany. N Engl J Med 365:709–717

Ray MD, Boundy S, Archer GL (2016) Transfer of the methicillin resistance genomic island among staphylococci by conjugation. Mol Microbiol 100:675–685

Roy Chowdhury P, Charles IG, Djordjevic SP (2015) A role for Tn6029 in the evolution of the complex antibiotic resistance gene loci in genomic island 3 in enteroaggregative hemorrhagic *Escherichia coli* O104:H4. PLoS One 10:e0115781

Roy Chowdhury P, Scott M, Worden P, Huntington P, Hudson B, Karagiannis T, Charles IG, Djordjevic SP (2016) Genomic islands 1 and 2 play key roles in the evolution of extensively drug-resistant ST235 isolates of *Pseudomonas aeruginosa*. Open Biol 6(3):150175

Roy Chowdhury P, Scott MJ, Djordjevic SP (2017) Genomic islands 1 and 2 carry multiple antibiotic resistance genes in *Pseudomonas aeruginosa* ST235, ST253, ST111 and ST175 and are globally dispersed. J Antimicrob Chemother 72:620–622

Schultz E, Barraud O, Madec JY, Haenni M, Cloeckaert A, Ploy MC, Doublet B (2017) Multidrug resistance Salmonella genomic island 1 in a *Morganella morganii* subsp. morganii human clinical isolate from France. mSphere 2:1–5

Siebor E, Neuwirth C (2014) Proteus genomic island 1 (PGI1), a new resistance genomic island from two *Proteus mirabilis* French clinical isolates. J Antimicrob Chemother 69:3216–3220

Siebor E, de Curraize C, Amoureux L, Neuwirth C (2016) Mobilization of the Salmonella genomic island SGI1 and the Proteus genomic island PGI1 by the a/C2 plasmid carrying blaTEM-24 harboured by various clinical species of Enterobacteriaceae. J Antimicrob Chemother 71:2167–2170

Siebor E, de Curraize C, Neuwirth C (2018) Genomic context of resistance genes within a French clinical MDR *Proteus mirabilis*: identification of the novel genomic resistance island GIPmi1. J Antimicrob Chemother 73(7):1808–1811

Silveira MC, Albano RM, Asensi MD, Carvalho-Assef AP (2016) Description of genomic islands associated to the multidrug-resistant *Pseudomonas aeruginosa* clone ST277. Infect Genet Evol 42:60–65

Smyth DS, Wong A, Robinson DA (2011) Cross-species spread of SCCmec IV subtypes in staphylococci. Infect Genet Evol 11:446–453

Soliman AM, Ahmed AM, Shimamoto T, El-Domany RA, Nariya H (2017) First report in Africa of two clinical isolates of *Proteus mirabilis* carrying Salmonella genomic island (SGI1) variants, SGI1-PmABB and SGI1-W. Infect Genet Evol 51:132–137

Soucy SM, Huang J, Gogarten JP (2015) Horizontal gene transfer: building the web of life. Nat Rev Genet 16:472–482

Tsubakishita S, Kuwahara-Arai K, Sasaki T, Hiramatsu K (2010) Origin and molecular evolution of the determinant of methicillin resistance in staphylococci. Antimicrob Agents Chemother 54:4352–4359

Wiehlmann L, Munder A, Adams T, Juhas M, Kolmar H, Salunkhe P, Tuemmler B (2007) Functional genomics of *Pseudomonas aeruginosa* to identify habitat-specific determinants of pathogenicity. Int J Med Microbiol 297:615–623

Wipf JR, Schwendener S, Nielsen JB, Westh H, Perreten V (2015) The new macrolide-lincosamide-streptogramin B resistance gene erm(45) is located within a genomic island in *Staphylococcus fleurettii*. Antimicrob Agents Chemother 59:3578–3581

Xue H, Wu Z, Qiao D, Tong C, Zhao X (2017) Global acquisition of genetic material from different bacteria into the staphylococcal cassette chromosome elements of a *Staphylococcus epidermidis* isolate. Int J Antimicrob Agents 50:581–587