Chapter

Insight into the mobilome of *Escherichia coli*

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Abstract

Mobilomes are all mobile genetic elements (plasmids, transposable elements, insertion sequences, gene cassettes, integrons, genomic islands, and bacteriophages) in a genome. Mobilome is one of the responsible agents for the bacterial evolution, virulence, and increasing antibiotic resistance. The mobile genetic elements in the *Escherichia coli* genome can carry antibiotic resistance genes and/or virulence genes. The acquisition of new mobile genetic elements can lead to the emergence of new pathotypes. The aim of this chapter is to gather knowledge about mobile genetic elements in *E. coli* strains. The method in this chapter depends on a literature survey, which scans reviews, research articles, and theses published about transposable elements, plasmids, bacteriophages, and genomic islands in *E. coli* strains.

Keywords: *Escherichia coli*, mobilome, genomic island, plasmid, transposon, bacteriophage

1. Introduction to mobilome and mobile genetic elements

Mobilome encompasses all mobile genetic elements (MGEs) in a genome [1]. Mobile genetic elements are moveable DNA segments, transferring among bacterial genomes. MGEs carry the so-called noncore genes and they have an important contribution to the plasticity of bacterial genomes. Plasmids, transposable elements, insertion sequences, gene cassettes, integrons, genomic islands, and bacteriophages are MGEs. Approximately, 2000 genes from 20 sequenced *E. coli* genomes were found to be noncore genes [2].

The presence and/or absence of MGEs within genomic DNA can lead to variance in *E. coli* pathotypes. Despite the fact that *E. coli* strains have been known as part of the normal microbiota of human gastrointestinal tract among *E. coli,* there are also pathogenic strains, and hence, the strains of *E. coli* are grouped either as (i) commensal, which are nonpathogenic, (ii) intestinal pathogenic strains (IPEC), or (iii) extraintestinal pathogenic (ExPEC) strains [3]. Rearrangements, excision, and integration of the DNA fragments can be the mechanisms behind the rapid evolution of *E. coli* strains and also the emerging pathogenic *E. coli* strains [4].

The most studied MGEs are transposable elements, plasmids, bacteriophages, and genomic islands in *E. coli* strains. Transposable elements are known as DNA sequences that can transfer among different locations in the bacterial genome [5]. Resistance genes can be harbored by a transposon in a genome. Transposons can be integrated and excised from the chromosome by enzymes, called transposases. The simplest version of the transposon is the insertion sequence [6]. Plasmids are self-replicating genetic elements. Different groups of plasmids exist according to

the incompatibility and conjugative features. Plasmids have a big contribution to the bacterial cell in terms of acquiring antibiotic resistance genes and virulence genes [7, 8]. Bacteriophages are viruses that infect bacteria and replicate within bacterial cells. Bacteriophages can transfer genes among bacterial cells with the mechanism, called transduction. Specialized transduction can include only specific genes, however, generalized transduction can transfer any fragment of the bacterial DNA [6]. In a similar manner, some bacteriophages also carry genes, which are advantageous for bacteria such as resistance and virulence-associated genes. Among them, Shiga-toxin coding genes are one of the most significant phage-associated genes that is transferred to *E. coli* O157 : H7 [9]. Important mobile genetic elements are also genomic islands (GIs), which are genomic regions of gene clusters, often acquired by horizontal gene transfer and inserted into tRNA genes [10]. GIs can contain phage- or plasmid-derived sequences. GIs in *E. coli* strains carry genes associated with metabolism, pathogenesis as well as antimicrobial resistance [11].

2. Transposable elements or transposons

Transposable elements (TEs) or transposons have a significant role in the genome evolution and organization [12]. TEs are DNA fragments, which are able to change their position within the genome, in the process called transposition [13]. Bacterial transposable elements or bacterial transposons are divided into three different types: (i) insertion sequence elements, (ii) composite transposons, and (iii) noncomposite transposons. Insertion sequence elements, or in short, insertion sequences (ISs) are the simplest version of the transposable elements. ISs have not genetic information apart from necessary for their mobility. Composite and noncomposite transposons, on the other hand, also they have additional genetic material unrelated with transposition, for example, antibiotic resistance genes [14]. Composite transposons are flanked by the insertion sequences [12]. *E. coli* has various transposable elements carrying antibiotic resistance genes, including Tn*3*, Tn*5*, Tn*7*, Tn*9*, and Tn*10* encoding ampicillin, kanamycin, trimethoprim, chloramphenicol, and tetracycline, respectively [13, 15]. A transposon, Tn*6306*, encoding imipenem-hydrolyzing β-lactamase that mediates dissemination of the $blaIM_I$ among *Enterobacteriaceae* reported in 2017 [16]. The gene conferring resistance

Name	Description	Reference
Transposon-like element	bla_{CMY-2}-carrying element	[22]
Tn*21*-type transposon	*dfrA* trimethoprim resistance	[18]
Tn*1999*-like element	bla_{OXA-48} gene encoding OXA-48 carbapenem	[23]
Tn*6306*	bla_{IMI}	[16]
ISApl1	*mcr-1*	[17]
In*53*	bla_{VEB-1}	[21]
Tn*3*	Ampicillin resistance	[24]
Tn*5*	Kanamycin resistance	[25]
Tn*7*	Trimethoprim resistance	[26]
Tn*9*	Chloramphenicol resistance	[27]
Tn*10*	Tetracycline resistance	[28]

Table 1.
Transposable elements in E. coli *strains.*

to colistin, *mcr-1* gene is carried by the ISApl1 transposon [17]. Moreover, trimethoprim resistance gene *dfrA* was rapidly disseminated in Nigeria and Ghana via Tn*21*-type transposon in *E. coli* [18]. In **Table 1**, the most important transposable elements of *E. coli* are listed.

Sometimes transposable elements comprise integrons, which are genetic elements that can capture genes including antibiotic resistance from different sources [19]. And integrons can be located on transposons, but also on plasmids, and in the bacterial chromosome [20]. Integrons are genetic elements that include the gene for the enzyme integrase together with gene cassettes encoding antibiotic resistance genes. A study reported a novel integron, In*53*, which is located on transposon inserted into a self-transferable plasmid [21].

3. Plasmids

Plasmids are extrachromosomal DNA elements, which are self-replicating. Apart from the genetic information needed for the autonomous replication, they can also carry additional genetic information like antibiotic resistance genes and the genes encoding resistance to heavy metals, virulence, and other metabolic functions [22, 29]. Thanks to their specific functions, certain plasmids are used as cloning vectors in the recombinant DNA technology [30]. Plasmids are grouped into different Inc families/groups. Inc groups are based on the inability of two plasmids to co-exist together in a bacterial cell [31]. Inc plasmids of the same Inc group have same type of replication region and thus have incompatible replication and partition mechanisms and hence cannot co-exist in a bacterial cell [32]. Plasmids belonging to the IncX family encode various resistance genes, mainly distributed among members of *Enterobacteriaceae* [33]. For example, recently, an emerging IncX plasmid, which is encoding bla_{SHV-12} β-lactamase gene was reported in *E. coli*. The bla_{IMI-2} gene, encoding an imipenem-hydrolyzing β-lactamase, is carried by pRJ18, an IncFIB plasmid [16]. The ESBL-encoding plasmids belonging to the Inc F, A/C, N, H12, 11 and K type were reported from The European Union. And one of the significant ESBL enzyme genes, CTX-M-1, is generally located on the Inc1 or IncN plasmids. For instance, CTX-M-1 ß-lactamase originated from an animal is transmitted via Inc1 ST3 plasmid [34].

The paradigm F plasmid, found among members of *Enterobacteriaceae,* is an IncF plasmid [35]. F-like plasmids can be detected in pathogenic as well as in non-pathogenic *E. coli* strains of different origins. The whole genome sequencing data of *E. coli* ST131 indicated that the acquisition of the CTX-M resistance gene was transferred via the conjugative F plasmid [36]. However, with the F plasmid, another significant antibiotic resistance gene is transferred, the *mcr-1* gene conferring resistance to colistin. Moreover, this *mcr-1* gene was found to be carried by 13 different plasmid incompatibility groups, among them are the Incl2, IncX4, and IncHI2 [37]. Although it has been reported that *mcr-1* gene has been carried by a transposon, it was shown that the *mcr-1* gene was transported via the plasmid, firstly. Moreover, it was found that the other *mcr* genes including *mcr-2, mcr-3, mcr-4, mcr-5,* and variants are carried by plasmids [38–40]. Recently, a new international outbreak was reported in Denmark. This outbreak was caused by *E. coli* ST410, an extraintestinal pathogenic *E. coli* resistant to fluoroquinolones, third-generation, cephalosporins, and carbapenems. This strain has acquired an IncX3 plasmid carrying $bla_{OXA-181}$ gene and also an IncFII plasmid carrying bla_{NDM-5} [41].

Sometimes, plasmids are transferred among bacteria with conjugation, a genetic transfer that occurs between donor and recipient cell that is in a direct cell-to-cell contact [42]. Conjugative plasmids can carry integrons and/or transposons, and such genetic information can be transferred then horizontally via conjugation [43].

Therefore, the spreading of multiresistant genes is promoted [44]. For example, a conjugative *E. coli* plasmid from a swine incorporated a *cfr* gene, which conferred resistance to phenicol, lincosamides, oxazolidinones, pleuromutilins, streptogramin A, and also the $bla_{CTX\text{-}M\text{-}14b}$ ESBL gene [45]. Moreover, a colV plasmid (pCERC3) from a commensal *E. coli* ST95 carried virulence and antibiotic resistance genes including sulfonamide resistance encoded by sul3-associated with a class 1 integron [46]. The pE80 plasmid from a foodborne *E. coli* strain encodes multiple resistance determinants *oqxAB*, *fosA3*, *blaCTX-M-55*, and *blaTEM-1* and hence confers resistance to tetracycline, streptomycin, olaquindox/quinolone, and kanamycin [47].

In addition to carrying antibiotic resistance genes, plasmids have a major role in the transfer of virulence-associated genes. One of the most significant *E. coli* outbreaks was the hybrid enterohemorrhagic *E. coli* (EHEC)-enteroaggregative *E. coli* (EAEC) O104:H4 strain in Germany. This strain possesses three different plasmids: pAA (7.4 kb), pESBL (89 kb), and pG (1.5 kb) [48, 49]. pAA plasmid carries virulence factors including fimbriae for adherence, surface protein dispersion, Aat

Name or class	Description/gene carried	Reference
IncA/C plasmids	Multiple antibiotic resistance	[29]
IncX3 plasmid	$bla_{SHV\text{-}12}$	[33]
IncA/C or IncI1 plasmid	$bla_{CMY\text{-}2}$-like genes	[52]
pRJ18	$bla_{IMI\text{-}2}$	[16]
Incl2, IncX4, and IncHI2 plasmid	*mcr-1*	[37]
MOBP131/IncL plasmids	$bla_{OXA\text{-}48}$	[23]
IncX3 plasmid	$bla_{OXA\text{-}181}$	[41]
IncFII plasmid	$bla_{NDM\text{-}5}$	[41]
pEC26	*mcr-1.9*	[53]
pCERC3	A colV plasmid carrying Sul3-related integron	[46]
pAA	Encoding aggregative adherence fimbriae variant	[48]
	aap gene encoding the surface protein dispersin	[50]
	aatPABCD operon encoding Aat secretion system	[50]
	Protease SepA	[50]
	aggR gene is encoding EAEC master virulence gene regulator AggR	[50]
	Support of the translocation of the Stx2a across the epithelial cell	[54]
pS88	Encoding virulence genes $ompT_p$, *sitA*, *cia*, *iss*, *iroN, hlyF*, *cvaA*	[55]
pO157	Encoding enterohemolysin, serine protease, type II secretion protein, catalase, peroxidase, toxinB	[8]
pED1169	Encoding F4-like fimbriae	[7]
pGXEC3	Conjugative plasmid harboring *cfr* gene	[45]
pE80	Conjugative IncFII plasmid encoding *oqxAB*, *fosA3*, $bla_{CTX\text{-}M\text{-}55}$, and *blaTEM-1*	[47]
Inc1 ST131	$bla_{CTX\text{-}M\text{-}1}$	[34]

Table 2.
Plasmids in E. coli *strains.*

secretion system, protease, and the virulence regulator AggR [50]. Since the pAA plasmid is in the same cell as the pESBL, it increases both virulence and antibiotic resistance of this bacterium. Further, an EHEC O104:H7 strain that was isolated from cattle feces possessed IncB/O/K/Z and IncFIB plasmids carrying principal virulence genes, including, enterohemolysin and autotransporter [51]. Another significant serotype *for E. coli* is the O103 serotype, which is the second most common serogroup among the human foodborne illness. This serogroup has a pO157 plasmid encoding various virulence factors including enterohemolysin and type II secretion protein [8]. Recently, a characterized novel plasmid in a shiga-toxin-producing ETEC harbored *fae* locus encoding ETEC F4 fimbriae [7]. Some more examples of important *E. coli* plasmids are given in **Table 2**.

4. Bacteriophages

Viruses that are infecting bacteria are called bacteriophages. They have a significant impact on the dissemination of antibiotic resistance and virulence-associated genes among foodborne pathogens, as they can transfer genes among bacteria in the process called phage-mediated transduction. Hence, they not only shape the bacterial evolution, but also cause the emergence of new pathogenic bacteria. On the other hand, in a good sense, phages protect against bacterial colonization of mucosal surfaces [56]. Moreover, viruses can be found everywhere in the world including soils, oceans, sewage, and different microbial communities [57, 58]. Transduction can be mediated via virulent or temperate phages. In the case of virulent phages, essentially any region of the bacterial DNA can be transferred (generalized transduction), while temperate phages can transfer only certain genes that are close to the attachment site of the lysogenic phage in the bacterial chromosome (specialized transduction). Specialized transduction happens when the prophage excision is inaccurate and some bacterial DNA co-excised with the prophage DNA [57]. Transduction is a significant process in terms of transferring antimicrobial resistance genes among bacterial cells [59]. For example, the phage called 933E transferred tetracycline resistance gene from the *E. coli* O157:H7 strain to the laboratory *E. coli* K12 AB1157 strain [60]. Similar to plasmids, phages have a crucial role in the acquisition of β-lactamase genes such as $bla_{CTX\text{-}M}$, bla_{SHV}, bla_{TEM}, *qnrA*, *qnrB*, and *qnrS* [61]. A well-characterized P1-like bacteriophage, which lysogenizes bacteria, was reported, and it has encoded SHV-2 resistance in its genomic structure [62].

Furthermore, phages also have the ability to disseminate virulence factors such as staphylokinase, phospholipase or DNase, and superantigens [58]. Phages, which have been known for several years including bacteriophage λ, have been found to carry not only bacterial adhesion genes but also bacterial survival genes [63, 64]. Additionally, *E. coli* phage Ayreon carries the *cdt* gene cluster encoding the CdtA, CdtB, and CdtC subunits of the cdtI holotoxin [65]. Another significant toxin encoded by a temperate phage is the Shiga Toxin 2, which is a virulence factor in *E. coli* O157:H7 [9]. Moreover, some other Shiga Toxin variants including Shiga Toxin 2c can be encoded by phages of the pathogenic *E. coli* O157 strain [66]. However, some bacteriophages, for example, phiC119 can be used as biological control agents, as they can infect and lyse their bacterial hosts (phage therapy) [67]. Interestingly, genetic elements encoded by bacteriophages can also regulate gene expression in the bacterial host cell. For instance, transcription factor Cro has an effect on the regulation of virulence genes in enterohemorrhagic *E. coli* [68]. **Table 3** shows some well-known phages involved in the transduction of virulence or resistance genes.

Name	Description/gene carried	Reference
Bacteriophage 933W	*tet*	[60]
P1-like bacteriophage (RCS47)	bla_{SHV-2}	[62]
Phage ayreon	*cdt* gene cluster	[65]
Phage 2851	*Stx2c*	[66]
Phage λ	*lom* gene encoding K12 adhesion to human buccal epithelial cells	[64]
Phage λ	*bor* gene homologous to *iss* serum resistance locus	[63]
Phage PP01	Two tail fiber genes- 37 and 38 responsible for host-cell recognition	[69]

Table 3.
Bacteriophages of E. coli.

5. Genomic islands

Genomic island (GI) is a large region of genomic DNA, more than 10 kb length, which can be frequently exchanged between bacterial isolates. GIs are encoding proteins for transfer, recombination, and restriction/modification or other proprieties, for example, gene clusters for metabolic adaptation, virulence, and or resistance of bacteria [11]. GIs involving virulence-associated genes are called pathogenicity islands (PAIs) [70]. PAI generally encodes genes related to virulence factors (VFs) including adhesins, toxins, invasins, capsule biosynthesis machinery, iron uptake system, and type III, IV, VI and or VII secretion apparatus [71]. Generally, the size of PAIs more than 10 kb and their GC content differs from the average genome. Their integration site is located in tRNA genes and repeated sequences, which is containing at least one mobile genetic element including remnants of plasmids, insertion sequences (ISs), and integrons, and associated gene cassettes [72]. tRNA-encoding genes are known as the hot spot for the integration of foreign DNA [71]. Several PAIs can be excised from bacterial chromosome by site-specific recombination [73].

PAIs have been reported firstly in the genome of uropathogenic *E. coli*, later also in other pathogenic bacteria [74]. PAIs are now found to be widely distributed among animal- and plant-associated bacterial pathogens and PAIs that can be horizontally transferred have great impact on the rapid evolution of virulent and antibiotic-resistant strains [71].

Enterocyte effacement locus (LEE) is one of the best known PAIs in *E. coli*. LEE is a 35-kb cluster of genes associated with bacterial adherence to intestinal epithelial cells and the formation of attaching and effacing lesions [75]. High-pathogenicity island (HPI), a PAI originally found in *Yersinia* species, but also widely spread among other *Enterobacteriaceae* including *E. coli*, encodes a siderophore iron uptake system (the *fyuA-irp* gene clusters), the so-called yersiniabactin. HPI was found among enteroaggregative *E. coli*, enteropathogenic *E. coli*, enteroinvasive *E. coli*, and enterotoxigenic *E. coli* (ETEC) [76]. HPI was also found in genomes of certain non-O157 STEC clonal lineages [77] (**Table 4**).

It was reported that UPEC strain 536 has at least four PAIs located on the chromosome. The sizes of the first two PAI I536 and PAI II536 are 70 and 120 kb. The significant virulence-associated genes encoded on these PAIs are hemolysin and P fimbriae. PAI III536 and PAI IV536 have S fimbriae and HPI analog gene clusters [78]. It was reported that an ExPEC strain causing neonatal meningitis possessed the HPI, suggesting that HPI was associated with the development of neonatal meningitis [79]. Moreover, capsule synthesis-associated genes can be

Name	Description	Reference
LEE	PAI locus of enterocyte effacement	[75]
Yersiniabactin-HPI	Encoding an siderophore iron uptake system	[77]
PAI I536 and PAI II536	Hemolysin and P fımbriae	[78]
PAI III536 and PAI IV536	S fimbriae and HPI	[78]
PAI V536	K15 capsule determinant	[80]
Vat-encoding PAI	Adjacent to the 3′ terminus-thrW tRNA gene	[82]
EPAI1	RTX family exoprotein	[85]
EPAI2	O-antigen polysaccharide (OPS)	[85]
EPAI3	EPAI3	[85]
EPAI4	T3SS	[85]
EPAI5	O122	[85]
EPAI6	LEE	[85]
AGI-3 PAI	SelC-associated GI involved in carbohydrate uptake and virulence	[86]
GI OI-29	Transcriptional activator GmrA	[83]

Table 4.
Genomic islands and pathogenicity islands in E. coli.

located on different PAIs in ExPEC [80]. Furthermore, it was shown that HPI in general contributes to ExPEC virulence [81]. Another novel PAI was found in an APEC strain integrated adjacent to the thrW tRNA gene encoding vacuolating autotransporter toxin. This PAI is known as Vat-encoding pathogenicity island and may contribute to APEC pathogenicity [82]. A novel function carried by a GI was reported recently—a GI located in the EHEC chromosome included the transcriptional activator GmrA that controls the motility of EHEC O157:H7 [83]. In addition, GIs have a role not only in virulence but also in the metabolic process of the bacterial cell. The *dnd* operon, which is a DNA modification system cluster encoding and catalyzing phosphorothioation of DNA in *E. coli* was found to be located on diverse GIs in *E. coli* [84]. **Table 4** shows some well-known GIs and PAIs.

6. Conclusion

E. coli is one of the most studied bacteria all around the world. There are various pathotypes and subclones of *E. coli* as well as commensal strains. One of the most important reasons of emerging numerous pathotypes of *E. coli* is MGEs, including transposons, plasmids, bacteriophages, and genomic islands. MGEs are significant drivers of the horizontal gene transfer. Therefore, in order to understand the genome evolution, virulence and antibiotic resistance genes acquisition among *E. coli* strains from various sources is important to study MGEs and the mobilome.

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Conflict of interest

The author has no conflict of interest.

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