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Genetic Environment of Acquired *bla*$_{ACC-1}$ β-Lactamase Gene in *Enterobacteriaceae* Isolates▽

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We studied the genetic organization of *bla*$_{ACC-1}$ in 14 isolates of *Enterobacteriaceae* from France, Tunisia, and Germany. In a common ancestor, IS*Ecp1* was likely involved in the mobilization of this gene from the *Hafnia alvei* chromosome to a plasmid. Other genetic events involving insertion sequences (particularly IS*26*), transposons (particularly Tn*1696*), or *sulI*-type integrons have occurred, leading to complex genetic environments.

The chromosomally encoded class C β-lactamases confer a natural resistance to β-lactams, which is typical of a number of gram-negative species. Since the 1980s, plasmid-encoded AmpC-type β-lactamases have been found worldwide, most often in organisms lacking inducible chromosomal AmpC enzymes (13). Plasmid-carried *ampC* genes originate from the chromosomal *ampC* genes of organisms such as *Citrobacter freundii* (CMY type), *Enterobacter* spp. (MIR-1 and ACT-1), *Morganella morganii* (DHA type), and *Hafnia alvei* (ACC-1) (13).

ACC-1 was characterized in isolates of several species, such as *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella enterica*, and *Escherichia coli*, from Germany, France, Tunisia, Spain, and The Netherlands (2, 3, 6–9, 11, 12, 15). In France, nosocomial outbreaks following the admission of a patient transferred from Tunisia, a country which seems to be a potential reservoir, were described (11, 12).

The ACC-1-producing rifampin-resistant *K. pneumoniae* SLK54 strain, isolated in Saint-Louis Hospital in Paris, France, was previously studied by cloning experiments, and the genetic organizations of both plasmid-mediated genes, *bla*$_{ACC-1}$ and *arr-2*, were established (1, 11). The presence of IS*26* in both recombinant plasmids suggests that *arr-2* and *bla*$_{ACC-1}$ could be linked in the *K. pneumoniae* SLK54 plasmid. In this study, we have tested this hypothesis, and we have analyzed the genetic environment of the *bla*$_{ACC-1}$ gene in a collection of ACC-1-producing isolates, including 11 *K. pneumoniae*, one *P. mirabilis*, and two *S. enterica* isolates from different settings.

Table 1 lists the 14 clinical isolates and their sources. Most isolates were previously studied (2, 8, 11, 12, 15).

Genomic DNAs from *K. pneumoniae* isolates were prepared as described previously (5), digested with XbaI (New England Biolabs Inc., Saint Quentin en Yvelines, France), and subjected to pulsed-field gel electrophoresis in a CHEF DRIII device (Bio-Rad, Marnes-la-Coquette, France). DNA fragments were separated in a 1% (wt/vol) agarose gel in 0.5× Tris-borate-EDTA buffer at 200 V for 20 h, with pulse times ranging from 5 to 30 s. The pulsed-field gel electrophoresis profiles obtained for isolates C5900 (Tunisia) and KUS (Germany) (profiles C and D, respectively) were different from each other and from those of the nine other *K. pneumoniae* isolates (data not shown). According to the interpretation criteria of Tenover et al. (16), the nine French isolates could be divided into two possibly related clusters, profiles A and B (Table 1).

By mating experiments, *E. coli* K-12 J53-2 or *E. coli* K-12 HB101 transconjugants were obtained with ceftazidime (10 μg/ml) and either rifampin (250 μg/ml) or streptomycin (250 μg/ml) as selective agents. In case of failure, plasmid DNA was used to transform *E. coli* DH10B cells by electroporation (Bio-Rad). Transformants were selected with ceftazidime (10 μg/ml). Fingerprinting analysis was carried out with plasmid DNA purified from transformants or transconjugants by using a plasmid midi kit (QIAGEN, Courtaboeuf, France), digested with EcoRI, and subjected to electrophoresis in a 1.2% agarose gel at 80 V for 3 h. This analysis showed that plasmids present in the 10 French isolates were identical to those in the Tunisian *K. pneumoniae* isolate C5900 (profile A) (data not shown). Each of the other three isolates had unique plasmid profiles (Table 1). It seems that the spread of *bla*$_{ACC-1}$ in three different hospitals in France is linked to the spread of both a clonal strain and a plasmid that likely originated from Tunisia.

PCR experiments and DNA sequencing were carried out with the clinical isolates to detect *bla*$_{TEM}$, as previously described (17), and *bla*$_{ACC}$ (Table 2 PCR A). The sequence analysis showed that, except for *S. enterica* serovar Mbandaka MMAS$_{40}$, all isolates were TEM-1 positive (data not shown), and it confirmed that all isolates and transformants or transconjugants were ACC-1-positive.

The genetic context of *bla*$_{ACC-1}$ was explored by PCR mapping using the *bla*$_{ACC-1}$-carrying plasmids from transconjugants or transformants. First, we tested whether *bla*$_{ACC-1}$ and *arr-2* in *K. pneumoniae* SLK54 were linked on the same plasmid. Primers were designed to amplify the region between *bla*$_{ACC-1}$ and *intI* (PCR F) (Table 2). As expected, the 2.3-kb segment (PCR F) overlapped with both sequences of SLK54

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TABLE 1. Origin, epidemiological features, and PCR mapping of clinical isolates

Species and strain	Reference	Collection yr	Country (city, hospital) of origin[a]	ACC-1 plasmid transfer[b]	PFGE type	ACC-1 plasmid fingerprint	Resistance cotransferred[c]	Result of PCR:									
								A	B	C	D	E	F	G	H	I	J
Klebsiella pneumoniae																	
KUS	2	1997	Germany (Kiel, H1)	Tc, *E. coli* J53	D	C	TMP	+	+	−	−	−	−	−	−	−	−
C5900	15	1997	Tunisia (Sfax, H2)	Tc, *E. coli* J53	C	A	GM	+	+	+	+	+	−	−	−	+	+
SLK54	11	1998	France (Paris, H3)	Tc, *E. coli* HB101	A1	A	GM, TM, NET, SSS, RA	+	+	+	+	+	+	+	+	+	−
SLK55	11	1998	France (Paris, H3)	Tc, *E. coli* J53	A1	A	GM	+	+	+	+	+	−	−	−	+	+
SLK56	11	1998	France (Paris, H3)	Tc, *E. coli* HB101	A1	A	GM, TM, NET, SSS, RA	+	+	+	+	+	+	+	+	+	−
RP2	12	1999	France (Garches, H4)	Ep, *E. coli* DH10B	B2	A	GM, TM, NET, SSS, RA	+	+	+	+	+	+	+	+	+	−
RP4	12	1999	France (Garches, H4)	Ep, *E. coli* DH10B	B3	A	GM, TM, NET, SSS, RA	+	+	+	+	+	+	+	+	+	−
RP6	12	1999	France (Garches, H4)	Tc *E. coli* HB101	A1	A	GM, TM, NET, SSS, RA	+	+	+	+	+	+	+	+	+	−
RP22	12	1999	France (Garches, H4)	Ep, *E. coli* DH10B	B3	A	GM, TM, NET, SSS, RA	+	+	+	+	+	+	+	+	+	−
RP27	12	1999	France (Garches, H4)	Tc, *E. coli* HB101	A2	A	GM, TM, NET, K, SSS, RA	+	+	+	+	+	+	+	+	−	−
VIL	This study	2000	France (Paris, H6)	Ep, *E. coli* DH10B	B1	A	GM, TM, NET, SSS, RA	+	+	+	+	+	+	+	+	+	−
Proteus mirabilis SLP57	This study	1999	France (Paris, H3)	Tc, *E. coli* J53	ND	A	GM, TM, NET, SSS, RA	+	+	+	+	+	+	+	+	+	−
Salmonella enterica																	
Serovar Mbandaka $MMAS_{40}$	8	1999	Tunisia (Tunis, H5)	Ep, *E. coli* DH10B	ND	B	GM, TM, NET, K, SSS, TMP	+	+	−	−	−	+	−	−	−	−
Serovar Livingstone B952	15	2000	Tunisia (Sfax, H2)	Tc, *E. coli* J53	ND	D	TMP	+	+	−	−	−	−	−	−	−	−
Hafnia alvei HAF TN01	11							+	+	−	−	ND	ND[d]	ND	ND	ND	ND

[a] H1, Kiel University Hospital; H2, Habib Bourguiba University Hospital; H3, Saint-Louis University Hospital; H4, Raymond Poincaré University Hospital; H5, La Rabta University Hospital; H6, University Hospital Saint-Antoine.

[b] Tc, transconjugant; Ep, transformant.

[c] Resistance cotransferred to transconjugants or electroporants: GM, gentamicin; TM, tobramycin; NET, netilmicin; K, kanamycin; SSS, sulfonamides; TMP, trimethoprim; RA, rifampin.

[d] ND, not determined.

TABLE 2. Sequences of oligonucleotides used for PCR mapping

PCR	Primer[a]	Primer sequence (5′→3′)	Position in published sequences (bp)	Target	PCR product length (kb)
A	A^F	CACCGAAGCCGTTAGTTGAT	2,749[b]	bla_{ACC-1}	0.9
	A^R	GACACCGTTGATGACCTGAT	3,688[b]	bla_{ACC-1}	
B	B^F	GCTCGTATGGGCTGGAAAG	2,382[b]	*gdha*	1.3
	B^R	GACACCGTTGATGACCTGAT	3,688[b]	bla_{ACC-1}	
C	C^F	TGGGTGTCGCTCGCATAAA	1,212[b]	*orf1*	1.3
	C^R	GTAGTGGGTTTGCTTATCTT	2,492[b]	*gdha*	
D	D^F	TGCTCATCTGGTCAATACTG	5[b]	*tnpR*	1.3
	D^R	CTGCCCTTTTGATTCCACTC	1,287[b]	*orf1*	
E	E^F	TAGCAGCCAGAGCACCTTG	3,712[b]	bla_{ACC-1}	0.6
	E^R	AGCCGTTTTTCCATTTCAG		IS*26*	
F	F^F	CACCGAAGCCGTTAGTTGAT	2,749[b]	bla_{ACC-1}	2.3
	F^R	CTTCCCGACGCCCTTGAGC	265[c]	*intI1*	
G	G^F	AGGAGATGCTGGCTGAACG	4,251[b]	IS*26*	1.8
	G^R	AGGCTGAAAAGTAGATGTGCT	1,236[c]	*arr-2*	
H	H^F	GCTCAAGGGCGTCGGGAAG	247[c]	*intI1*	1.0
	H^R	AGGCTGAAAAGTAGATGTGCT	1,236[c]	*arr-2*	
I	I^F	GACATCCATTACGATTGATA	558[d]	IS*Ecp1*	2.0
	I^R	CTGCTACTGTTCGCTCACGA	161[b]	*tnpR*	
J	J^F	TGGTACTGGCGTAACCCTTC	6,724[d]	IS*26*	1.9
	J^R	CCGATGACCAGTTGGAAAAT	8,558[d]	*tniBD1*	

[a] F, forward primer; R, reverse primer.
[b] Accession number AJ270942.
[c] Accession number AJ277027.
[d] Accession number AJ870922.

previously submitted to the sequence databases; the first comprises bla_{ACC-1} (GenBank accession number AJ270942), and the second comprises *arr-2* (GenBank accession number AJ277027) (Fig. 1). We then used several PCRs (PCRs B to H) to characterize the genetic context of bla_{ACC-1} in the other 13 isolates (Fig. 1; Table 2). Eight isolates other than SLK54 (seven *K. pneumoniae* isolates and one *P. mirabilis* isolate) were positive in these PCRs (Table 1). Two aliquots of the PCR products were totally digested, one with TacI (New England Biolabs) and the other with HaeIII (New England Biolabs). The restriction profiles obtained from these PCR products were the same for each isolate (data not shown), suggesting that the genetic environments of bla_{ACC-1} were at least similar, if not identical, in the plasmids from these nine isolates.

The genetic organization of bla_{ACC-1} in five isolates (SLK55, C5900, KUS, $MMAS_{40}$, and B952) seemed to be different from that in SLK54. Therefore, we used cloning experiments to explore the region surrounding bla_{ACC-1}. The plasmid DNA was partially digested with SauIIIA, and the fragments were ligated into the BamHI site of pACYC184. Recombinant plasmids introduced into *E. coli* DH10B were then selected with ceftazidime (10 μg/ml) and chloramphenicol (50 μg/ml). Several clones with an insert encompassing bla_{ACC-1} were obtained from each of the five isolates. The largest of these were selected, and their sequences were analyzed on both strands. Finally, overlapping inserts of recombinant plasmids together with PCR mapping segments (PCRs I and J) allowed us to map the unknown region surrounding bla_{ACC-1} for these five isolates (Fig. 1). The genetic organizations of bla_{ACC-1} from the 14 isolates of this study and from *Salmonella enterica* serovar Bareilly 60.50, isolated in The Netherlands (7), are shown in Fig. 1.

Common structures. The ACC-1-producing isolates all have the same genetic organization of plasmid-encoded bla_{ACC-1} in the proximity of the β-lactamase gene. In each isolate, a 1,318-bp region originating from the *H. alvei* chromosome, comprising *ampC* but lacking *ampR* (which is consistent with the high level of β-lactamase production), was present. The total length of the sequence mobilized from *H. alvei* is unknown, as the previously sequenced region surrounding the *ampC* and *ampR* genes from *H. alvei* (accession number AF180952) is too short, with only the final 18-bp segment of *gdha* being present in this sequence. Nevertheless, *gdha* is present downstream from bla_{ACC-1} in *H. alvei* (PCRs A and B) (Table 1) and in the six plasmid-carried bla_{ACC-1} genetic organization profiles. Moreover, *gdha*, which encodes a glutamate dehydrogenase, is a very common housekeeping gene among proteobacteria, and its presence on the *H. alvei* genome would be expected. Thus, the *gdha* sequence present downstream from bla_{ACC-1} is presumed to have been mobilized from the *H. alvei* chromosome together with bla_{ACC-1}.

The insertion sequence IS*Ecp1* upstream from bla_{ACC-1} is always present in the same orientation but has variable dele-

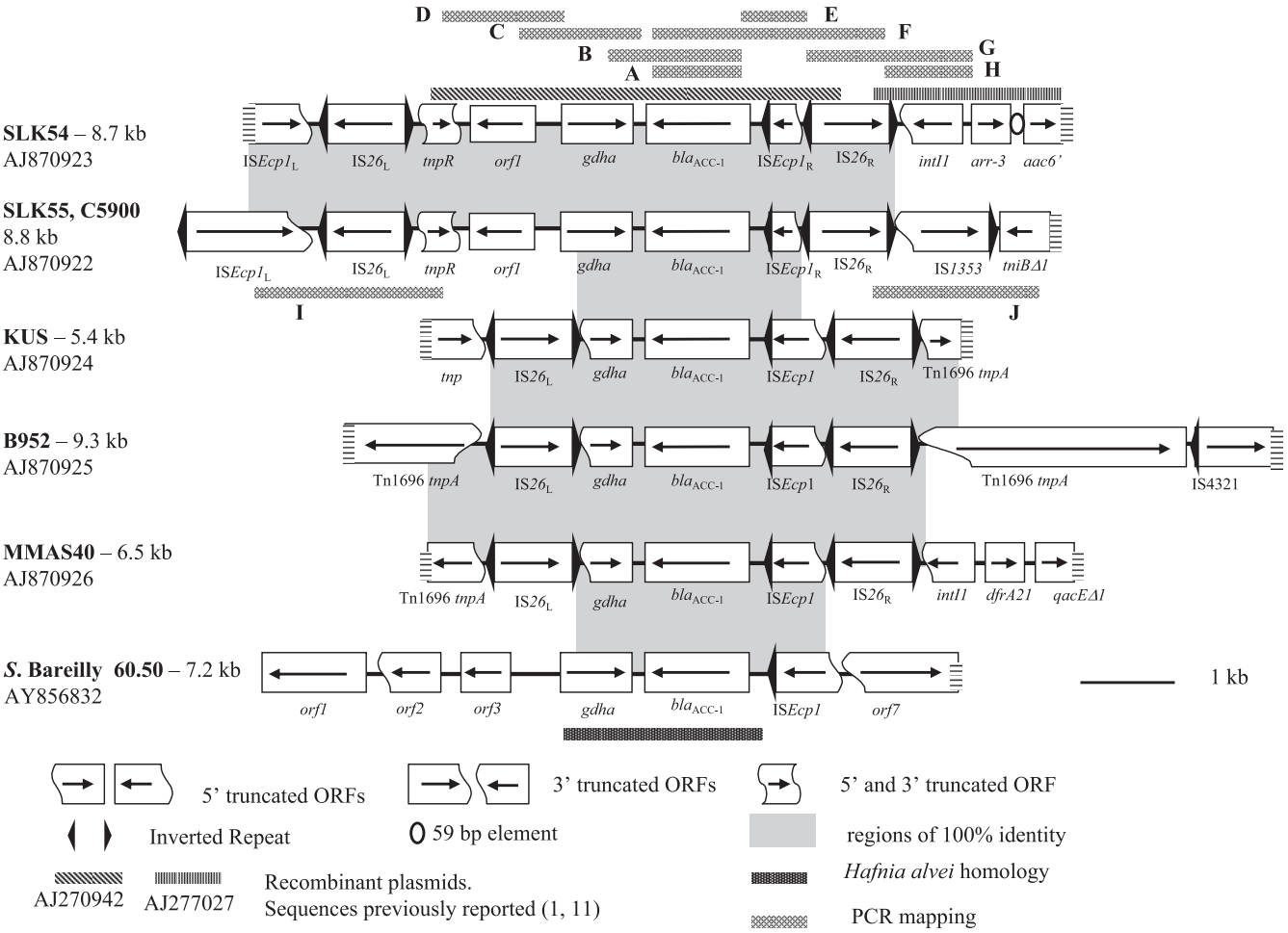

FIG. 1. Comparison of regions surrounding bla_{ACC-1}. ORF, open reading frame.

tions in the 5′ part: a 1,433-bp deletion for SLK54 and SLK55; a 1,101-bp deletion for KUS, B952, and $MMAS_{40}$; and a 988-bp deletion for *S. enterica* serovar Bareilly 60.50. Nevertheless, the length between the end of IS*Ecp1* and the ATG codon of bla_{ACC-1} is constant, which suggests that only one genetic recombination event has occurred. IS*Ecp1* is known to be involved in both the mobilization and expression of bla_{CTX-M} β-lactamase genes (14). Although IS*Ecp1* is always truncated in the 5′ part and can no longer function in transposition events, we cannot rule out the possibility that it was involved in the initial mobilization of bla_{ACC-1} in an ancestor common to the six different profiles described here. Indeed, IS*Ecp1* transposase may recognize a wide range of DNA sequences as inverted right repeats and use them as ends in a mobilization process involving its adjacent sequences (14). The −35 and −10 regions corresponding to putative promoter sequences for acquired *bla* were different for the chromosomal bla_{ACC} type of *H. alvei*. Indeed, whatever the deletion of IS*Ecp1*, the promoter is likely provided by ISEcp1, as reported with bla_{CTX-M} (4).

Different structures. The genetic organization of plasmid-carried bla_{ACC-1} differs beyond IS*Ecp1* and *gdha*, and it can be divided into three main patterns.

(i) the first pattern was found in SLK54 and in the related isolates SLK55 and C5900. In this pattern, IS*Ecp1* has a 1,433-bp deletion due to an insertion of an IS*26* in the opposite orientation. A second copy of IS*26* ($IS26_L$) is present 4,210 bp upstream from the first copy, $IS26_R$. The two copies of IS*26* are in opposite orientations, with the 3′ ends facing outwards (Fig. 1). Another copy of IS*Ecp1* ($ISEcp1_L$) is present downstream from $IS26_L$ and is 3′ truncated, with the deletion being exactly complementary to that of $ISEcp1_R$ upstream from bla_{ACC-1}. This and the presence of two copies of IS*26* suggest that a composite transposon with two directly repeated IS*26*s was inserted in IS*Ecp1* with the duplication of a 8-bp target site (characteristic of IS*26* transposition) GACATTTT (10). However, we are still unsure as to how $ISEcp1_L$ and $IS26_L$ could have been secondarily inverted and moved elsewhere, downstream from bla_{ACC-1}.

(ii) The second pattern was found in KUS, B952, and $MMAS_{40}$. In this group, IS*Ecp1* has a 1,101-bp deletion due to the insertion of an IS*26* in the same orientation. A second copy of IS*26* ($IS26_L$) is present 2,742 bp downstream from bla_{ACC-1} (Fig. 1). The two copies of IS*26* are in opposite orientations, with the 3′ ends facing inwards. The DNA sequence between the two copies of IS*26* is 100% identical in KUS, B952, and $MMAS_{40}$. Beyond IS*26*, the DNA sequence was different in the three structures (Fig. 1). Thus, the structures from the

KUS, B952, and MMAS40 isolates are likely derived from a common ancestor different from that of the first pattern, with a shorter deletion of IS*Ecp1* due to the insertion of IS*26* in the opposite direction. After this event, several different genetic events seem to have occurred, mainly involving Tn*1696* but also involving a class 1 integron carrying a *dfrA21* gene cassette.

(iii) The third pattern was observed in *S. enterica* serovar Bareilly only (Fig. 1). This has an IS*Ecp1* deleted by 988 bp due to the insertion of the previously described *orf7* (7). The 309-amino-acid protein encoded by *orf7* is 99% identical to a transposase described for *Yersinia enterocolitica* strain 29979 (GenBank accession number CAA73750). Upstream from *gdha*, the three previously described open reading frames encode proteins, the first identical to a transposase from *K. pneumoniae* CG43 (accession number NP_943502), the second identical to a protein from the *Y. enterocolitica* plasmid p29930 (GenBank accession number CAD58550), and the third identical to a recombinase from the same plasmid (GenBank accession number CAE46772).

Studies of the molecular mechanisms of *ampC* gene transfer from chromosome to plasmids are in progress. It seems that several different DNA-mobilizing elements, such as common regions associated to integrons and insertion sequences, are involved in the movement of the *ampC* gene and the adjacent region (13, 17). Although IS*26* has been found in the genetic organization of bla_{ACC-1} in several clinical isolates, it is likely that this structure is not directly involved in the translocation of the *ampC* gene from the *H. alvei* chromosome to different plasmids. Nevertheless, its presence seems to be linked with recombination events occurring after the insertion of IS*Ecp1* upstream from bla_{ACC-1} that lead to the deletion of the 5′ end of IS*Ecp1* (Fig. 1). In all cases, IS*Ecp1* was never complete, and its deletion may have led to the stabilization of bla_{ACC-1} on different plasmids.

Nucleotide sequence accession numbers. The nucleotide sequences in strains SLK54, SLK55, KUS, B952, and $MMAS_{40}$ have been submitted to GenBank and have been assigned accession numbers AJ870923, AJ870922, AJ870924, AJ870925, and AJ870926, respectively.

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