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REVIEW ARTICLE

Epidemiology and genetics of CTX-M extended-spectrum β-lactamases in Gram-negative bacteria

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Abstract

CTX-M enzymes, the plasmid-mediated cefotaximases, constitute a rapidly growing family of extended-spectrum β-lactamases (ESBLs) with significant clinical impact. CTX-Ms are found in at least 26 bacterial species, particularly in *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*. At least 109 members in CTX-M family are identified and can be divided into seven clusters based on their phylogeny. CTX-M-15 and CTX-M-14 are the most dominant variants. Chromosome-encoded intrinsic cefotaximases in *Kluyvera* spp. are proposed to be the progenitors of CTX-Ms, while IS*Ecp1*, IS*CR1* and plasmid are closely associated with their mobilization and dissemination.

Keywords: CTX-M, cefotaximase, extended-spectrum β-lactamase (ESBL), IS*Ecp1*, IS*CR1*, plasmid

Introduction

Extended-spectrum β-lactamases (ESBLs) are the most influential mechanism for cephalosporin resistance in Enterobacteriaceae, particularly in *Escherichia coli* and *Klebsiella pneumoniae*. ESBLs confer resistance to penicillins, broad-spectrum cephalosporins with an oxyimino side chain (cefotaxime, ceftriaxone and ceftazidime) and the oxyimino-monobactam aztreonam, but can be inhibited by serine-type β-lactamase inhibitors as sulbactam, clavulanate and tazobactam (Philippon et al., 1989; Bradford, 2001). SHV-2 is the first ESBL, identified in a clinical isolate of *Klebsiella ozaenae* in Germany (Kliebe et al., 1985). To date, over 10 families have been documented to be associated with ESBLs, including CTX-M, SHV, TEM, PER, VEB, BES, GES, TLA, SFO and OXA (Paterson and Bonomo, 2005).

CTX-M enzymes, the plasmid-mediated acquired cefotaximases from a distinct phylogenetic lineage, constitute a rapidly growing family of ESBLs with significant clinical impact (Bonnet, 2004; Cantón and Coque, 2006; Livermore et al., 2007; Naseer and Sundsfjord, 2011). Chromosome-encoded genes of intrinsic cefotaximases in *Kluyvera* spp. are proposed to be the progenitors of CTX-M family (Humeniuk et al., 2002; Olson et al., 2005; Decousser et al., 2011). Most of CTX-Ms exhibit powerful activity against cefotaxime and ceftriaxone but not ceftazidime. However, some CTX-Ms, such as CTX-M-15 (Poirel et al., 2002a), CTX-M-16 (Bonnet et al., 2001) and CTX-M-19 (Poirel et al., 2001), exhibit enhanced catalytic efficiencies against ceftazidime.

This article summarizes the epidemiology of CTX-M-producing Gram-negative bacteria and the genetics of CTX-M ESBLs, with a focus on the phylogeny, origin and genetic platforms including IS*Ecp1*, IS*CR1* and plasmid.

Epidemiology of CTX-M ESBLs

Occurrence and bacterial hosts

A plasmid-mediated cefotaximase was identified from a clinical isolate of *E. coli* in Munich, Germany, and designated CTX-M in reference to its hydrolytic activity and the region where it was found (Bauernfeind et al., 1990). To date, the numbers of CTX-M variants and the recognized organisms harboring the genes have dramatically increased. At least 109 CTX-M variants, CTX-M-1 to CTX-M-124, have been identified (Table 1) and assigned in the Lahey database (Jacoby and Bush, 2012). The amino-acid sequences of CTX-M-14 and

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Table 1. CTX-M ESBLs and their bacterial hosts.

CTX-M (alternate name)	Bacterial host	GenBank accession no.	Reference
CTX-M-1 (MEN-1)	*Escherichia coli*	X92506	Bauernfeind et al., 1996
	Enterobacter cloacae		al Naiemi et al., 2006
	Klebsiella pneumoniae		Komatsu et al., 2001
	Proteus mirabilis		al Naiemi et al., 2006
	Pseudomonas aeruginosa		al Naiemi et al., 2006
	Salmonella enterica		Rodríguez et al., 2009
	Serratia marcescens		Choi et al., 2007
	Stenotrophomonas maltophilia		al Naiemi et al., 2006
CTX-M-2	*Salmonella enterica*	X92507	Bauernfeind et al., 1996
	Acinetobacter baumannii		Nagano et al., 2004
	Citrobacter koseri		al Naiemi et al., 2006
	Escherichia coli		Arduino et al., 2003
	Enterobacter cloacae		Arduino et al., 2003
	Klebsiella pneumoniae		Arduino et al., 2003
	Morganella morganii		Power et al., 2005
	Proteus mirabilis		Bonnet et al., 2000
	Providencia stuartii		Minarini et al. 2009
	Pseudomonas aeruginosa		Arduino et al., 2003
	Serratia marcescens		Arduino et al., 2003
	Vibrio cholerae		Soler Bistué et al., 2006
CTX-M-3	*Citrobacter freundii*	Y10278	Gniadkowski et al., 1998
	Aeromonas caviae		Ye et al., 2010
	Escherichia coli		Yan et al., 2000
	Enterobacter cloacae		De Champs et al., 2000
	Enterobacter aerogenes		Liu et al., 2009
	Klebsiella pneumoniae		Baraniak et al., 2002b
	Klebsiella oxytoca		Baraniak et al., 2002b
	Morganella morganii		Baraniak et al., 2002b
	Proteus mirabilis		Eckert et al., 2006
	Salmonella enterica		Gierczyński et al., 2003
	Sarratia marcescens		Baraniak et al., 2002b
	Shigella flexneri		Galimand et al., 2005
	Shigella sonnei		Acikgoz et al., 2003
CTX-M-4	*Salmonella enterica*	Y14156	Gazouli et al., 1998b
CTX-M-5	*Salmonella enterica*	U95364	Bradford et al., 1998
	Acinetobacter baumannii	AF462635	
CTX-M-6 (renumbered)	*Salmonella enterica*	AJ005044	Gazouli et al., 1998a
CTX-M-7 (renumbered)	*Salmonella enterica*	AJ005045	Gazouli et al., 1998a
CTX-M-8	*Citrobacter amalonaticus*	AF189721	Bonnet et al., 2000
	Enterobacter cloacae		Bonnet et al., 2000
	Enterobacter aerogenes		Bonnet et al., 2000
	Escherichia coli		Minarini et al. 2009
CTX-M-9	*Escherichia coli*	AF174129	Sabaté et al., 2000
	Citrobacter freundii		Minarini et al. 2009
	Enterobacter aerogenes	EF441350	
	Enterobacter cloacae		Chanawong et al., 2002
	Enterobacter hormaechei		Ho et al., 2005b
	Klebsiella pneumoniae		Chanawong et al., 2002
	Klebsiella oxytoca		Alobwede et al., 2003
	Salmonella enterica		García Fernández et al., 2007
	Serratia marcescens		Choi et al., 2007
CTX-M-10	*Escherichia coli*	AF255298	Oliver et al., 2001
	Citrobacter freundii		Valverde et al., 2004
	Enterobacter cloacae		Cantón et al., 2002

(Continued)

Table 1. *(Continued).*

CTX-M (alternate name)	Bacterial host	GenBank accession no.	Reference
	Enterobacter gergoviae		Cantón et al., 2002
	Klebsiella pneumoniae		Coque et al., 2002
	Salmonella enterica		Cartelle et al., 2006
CTX-M-11	*Klebsiella pneumoniae*	AY005110	
CTX-M-12	*Klebsiella pneumoniae*	AF305837	Kariuki et al., 2001
	Escherichia coli		Bae et al., 2006b
	Proteus mirabilis		Song et al., 2011
CTX-M-13	*Klebsiella pneumoniae*	AF252623	Chanawong et al., 2002
	Escherichia coli	DQ058147	
	Enterobacter cloacae	AF462399	
	Enterobacter hormaechei		Ho et al., 2005b
	Proteus mirabilis		Ho et al., 2005a
CTX-M-14	*Escherichia coli*	AF252622	Chanawong et al., 2002
	Citrobacter freundii		Kanamori et al., 2011
	Citrobacter koseri		Kanamori et al., 2011
	Enterobacter cloacae		Chanawong et al., 2002
	Enterobacter hormaechei		Ho et al. 2005b
	Klebsiella pneumoniae		Chanawong et al., 2002
	Proteus mirabilis		Ho et al., 2005a
	Providencia stuartii		Liu et al., 2009
	Salmonella enterica		Romero et al., 2004
	Serratia liquefaciens	AF462398	
	Shigella flexneri	DQ350883	
	Shigella sonnei		Pai et al., 2001
CTX-M-15 (UOE-1) *	*Escherichia coli*	AY044436	Karim et al., 2001
	Acinetobacter baumannii		Shakil & Khan, 2010
	Aeromonas hydrophila		Gómez-Garcés et al., 2011
	Citrobacter freundii	HQ214043	
	Citrobacter koseri		Kanamori et al., 2011
	Enterobacter aerogenes		Kim et al., 2005
	Enterobacter cloacae		Moubareck et al., 2005
	Enterobacter gergoviae	EU118595	
	Klebsiella pneumoniae		Lartigue et al., 2003
	Klebsiella oxytoca		Zhang et al., 2008
	Morganella morganii		al Naiemi et al., 2006
	Pantoea agglomerans		Aibinu et al., 2012
	Proteus mirabilis		Song et al., 2011
	Salmonella enterica		Weill et al., 2004
	Serratia marcescens		Baraniak et al., 2002a
	Shigella flexneri		Zhang et al., 2011
	Shigella sonnei		Hrabák et al., 2008
CTX-M-16 *	*Escherichia coli*	AY029068	Bonnet et al., 2001
CTX-M-17	*Klebsiella pneumoniae*	AY033516	Cao et al., 2002
CTX-M-18[§]	*Klebsiella pneumoniae*	AF325133	Poirel et al., 2001
CTX-M-19 *	*Klebsiella pneumoniae*	AF325134	Poirel et al., 2001
CTX-M-20	*Proteus mirabilis*	AJ416344	Saladin et al., 2002
CTX-M-21	*Escherichia coli*	AJ416346	Saladin et al., 2002
CTX-M-22	*Klebsiella pneumoniae*	AY080894	Yu et al., 2007
	Escherichia coli		Yu et al., 2007
	Enterobacter cloacae		Liu et al., 2007
	Serratia liquefaciens	HM470254	
	Serratia marcescens	DQ309026	
CTX-M-23 *	*Escherichia coli*	AF488377	Stürenburg et al., 2004
	Klebsiella pneumoniae		Stürenburg et al., 2004
CTX-M-24	*Klebsiella pneumoniae*	AY143430	Yu et al., 2007

(Continued)

Table 1. *(Continued).*

CTX-M (alternate name)	Bacterial host	GenBank accession no.	Reference
	Escherichia coli		Yu et al., 2007
	Enterobacter aerogenes		Ho et al., 2005b
	Proteus mirabilis		Wu et al., 2008
	Shigella sonnei	FN594520	
CTX-M-25 *	*Escherichia coli*	AF518567	Munday et al., 2004
	Klebsiella pneumoniae		Navon-Venezia et al., 2008
	Proteus mirabilis		Navon-Venezia et al., 2008
CTX-M-26	*Klebsiella pneumoniae*	AY157676	Brenwald et al., 2003
CTX-M-27 *	*Escherichia coli*	AY156923	Bonnet et al., 2003
	Salmonella enterica		Bouallègue-Godet et al., 2005
	Shigella sonnei	HM595763	
CTX-M-28	*Escherichia coli*	AJ549244	Galimand et al., 2005
	Enterobacter sp.	EU531513	
	Klebsiella pneumoniae		Yu et al., 2007
	Salmonella enterica		Hasman et al., 2005
CTX-M-29	*Escherichia coli*	AY267213	Yu et al., 2007
CTX-M-30	*Citrobacter freundii*	AY292654	Abdalhamid et al., 2004
CTX-M-31	*Providencia stuartii*	AJ567481	Quinteros et al., 2003
	Escherichia coli		Quinteros et al., 2003
CTX-M-32 *	*Escherichia coli*	AJ557142	Cartelle et al., 2004
	Klebsiella pneumoniae		Mendonça et al., 2009
	Proteus mirabilis		Fernández et al., 2007
CTX-M-33	*Escherichia coli*	AY238472	Galani et al., 2007
CTX-M-34	*Escherichia coli*	AY515297	Miró et al., 2005
CTX-M-35 *	*Klebsiella pneumoniae*	AB176532	
	Citrobacter koseri		Tian et al., 2010
	Escherichia coli	AB176533	
	Klebsiella oxytoca	AB176534	
CTX-M-36	*Escherichia coli*	AB177384	
CTX-M-37 *	*Enterobacter cloacae*	AY649755	
	Salmonella enterica		Govinden et al., 2006
CTX-M-38	*Klebsiella pneumoniae*	AY822595	
CTX-M-39	*Escherichia coli*	AY954516	Chmelnitsky et al., 2005
	Enterobacter cloacae		Navon-Venezia et al., 2008
	Klebsiella pneumoniae		Navon-Venezia et al., 2008
CTX-M-40 *	*Escherichia coli*	AY750914	Hopkins et al., 2006
CTX-M-41	*Proteus mirabilis*	DQ023162	Navon-Venezia et al., 2008
CTX-M-42 *	*Escherichia coli*	DQ061159	Stepanova et al., 2008
CTX-M-43	*Acinetobacter baumannii*	DQ102702	Celenza et al., 2006
	Enterobacter aerogenes		Celenza et al., 2006
	Enterobacter cloacae		Celenza et al., 2006
	Morganella morganii		Celenza et al., 2006
	Pseudomonas aeruginosa		Celenza et al., 2006
CTX-M-44 (Toho-1)	*Escherichia coli*	D37830	Ishii et al., 1995
CTX-M-45 (Toho-2)	*Escherichia coli*	D89862	Ma et al., 1998
CTX-M-46	*Klebsiella pneumoniae*	AY847147	Cheng et al., 2008
CTX-M-47	*Escherichia coli*	AY847143	Cheng et al., 2008
	Klebsiella pneumoniae		Cheng et al., 2008
CTX-M-48	*Klebsiella pneumoniae*	AY847144	Cheng et al., 2008
	Escherichia coli		Cheng et al., 2008
CTX-M-49	*Klebsiella pneumoniae*	AY847145	Cheng et al., 2008
CTX-M-50	*Klebsiella pneumoniae*	AY847146	Cheng et al., 2008
CTX-M-51	*Escherichia coli*	DQ211987	
CTX-M-52	*Klebsiella pneumoniae*	DQ223685	
CTX-M-53 *	*Salmonella enterica*	DQ268764	Doublet et al., 2009

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Table 1. *(Continued).*

CTX-M (alternate name)	Bacterial host	GenBank accession no.	Reference
CTX-M-54 *	*Klebsiella pneumoniae*	DQ303459	Bae et al., 2006a
CTX-M-55 *	*Escherichia coli*	DQ885477	Kiratisin et al., 2007
	Klebsiella pneumoniae		Kiratisin et al., 2007
	Shigella sonnei		Zhang et al., 2011
CTX-M-56	*Escherichia coli*	EF374097	Pallecchi et al., 2007
CTX-M-57[§]	*Salmonella enterica*	DQ810789	Hopkins et al., 2008
	Shigella sonnei	EU086736	
CTX-M-58 *	*Escherichia coli*	EF210159	
CTX-M-59	*Klebsiella pneumoniae*	DQ408762	de Oliveira et al., 2008
CTX-M-60	*Klebsiella pneumoniae*	AM411407	
CTX-M-61	*Salmonella enterica*	EF219142	Brasme et al., 2007
	Klebsiella pneumoniae		Mendonça et al., 2009
CTX-M-62 *	*Klebsiella pneumoniae*	EF219134	Zong et al., 2008
CTX-M-63	*Klebsiella pneumoniae*	AB205197	
	Morganella morganii	EU660216	
	Salmonella enterica		Pornruangwong et al., 2011
CTX-M-64 *	*Shigella sonnei*	AB284167	Nagano et al., 2009
	Escherichia coli		Sun et al., 2010
	Enterobacter cloacae	GQ300937	
CTX-M-65	*Escherichia coli*	EF418608	Doi et al. 2008
	Citrobacter freundii	EF394372	
	Salmonella enterica	FJ907380	
CTX-M-66	*Proteus mirabilis*	EF576988	Wu et al., 2008
CTX-M-67	*Escherichia coli*	EF581888	Oteo et al., 2008
CTX-M-68	*Klebsiella pneumoniae*	EU177100	Heffernan et al., 2009
CTX-M-69	*Escherichia coli*	EU402393	
CTX-M-70[†]		Assigned	
CTX-M-71	*Klebsiella pneumoniae*	FJ815436	Schneider et al., 2009
CTX-M-72	*Klebsiella pneumoniae*	AY847148	Cheng et al., 2009
CTX-M-73[†]		Assigned	
CTX-M-74	*Enterobacter cloacae*	GQ149243	Minarini et al., 2009
CTX-M-75	*Providencia stuartii*	GQ149244	Minarini et al., 2009
c-CTX-M-76[‡]	*Kluyvera ascorbata*	AM982520	
c-CTX-M-77[‡]	*Kluyvera ascorbata*	AM982521	
c-CTX-M-78[‡]	*Kluyvera georgiana*	AM982522	Rodríguez et al., 2010
CTX-M-79	*Escherichia coli*	EF426798	Tian et al., 2008
CTX-M-80	*Klebsiella pneumoniae*	EU202673	Cheng et al., 2010
CTX-M-81	*Klebsiella pneumoniae*	EU136031	Cheng et al., 2010
CTX-M-82 *	*Escherichia coli*	DQ256091	Liu et al., 2009
CTX-M-83	*Salmonella enterica*	FJ214366	Cui et al., 2009
CTX-M-84	*Salmonella enterica*	FJ214367	Cui et al., 2009
CTX-M-85	*Salmonella enterica*	FJ214368	Cui et al., 2009
CTX-M-86	*Salmonella enterica*	FJ214369	Cui et al., 2009
CTX-M-87 (renumbered)	*Escherichia coli*	EU545409	Yin et al., 2009
CTX-M-88	*Salmonella enterica*	FJ873739	Ranjbar et al., 2010
CTX-M-89	*Proteus mirabilis*	FJ971899	McGettigan et al., 2009
	Enterobacter cloacae	FJ966096	
CTX-M-90	*Salmonella enterica*	FJ907381	
	Proteus mirabilis		Song et al., 2011
CTX-M-91	*Proteus mirabilis*	GQ870432	
CTX-M-92	*Escherichia coli*	GU127598	Seputiene et al., 2010
	Klebsiella pneumoniae		Seputiene et al., 2010
CTX-M-93 *	*Escherichia coli*	HQ166709	Djamdjian et al., 2011
CTX-M-94	*Escherichia coli*	HM167760	
c-CTX-M-95[‡]	*Kluyvera ascorbata*	FN813245	

(Continued)

Table 1. *(Continued).*

CTX-M (alternate name)	Bacterial host	GenBank accession no.	Reference
CTX-M-96 (CTX-M-12a)	*Klebsiella pneumoniae*	AJ704396	
CTX-M-97	*Escherichia coli*	HM776707	
CTX-M-98	*Escherichia coli*	HM755448	
CTX-M-99	*Klebsiella pneumoniae*	HM803271	
CTX-M-100†		Assigned	
CTX-M-101	*Escherichia coli*	HQ398214	
CTX-M-102	*Escherichia coli*	HQ398215	
CTX-M-103†		Assigned	
CTX-M-104	*Escherichia coli*	HQ833652	
CTX-M-105	*Escherichia coli*	HQ833651	
CTX-M-106	*Escherichia coli*	HQ913565	
CTX-M-107	*Shigella flexneri*	JF274244	Zhang et al., 2011
CTX-M-108	*Shigella flexneri*	JF274245	Zhang et al., 2011
CTX-M-109	*Shigella flexneri*	JF274248	Zhang et al., 2011
CTX-M-110	*Shigella sonnei*	JF274242	Zhang et al., 2011
CTX-M-111	*Shigella flexneri*	JF274243	Zhang et al., 2011
CTX-M-112	*Shigella sonnei*	JF274246	Zhang et al., 2011
CTX-M-113	*Shigella flexneri*	JF274247	Zhang et al., 2011
CTX-M-114	*Providencia rettgeri*	GQ351346	
CTX-M-115†		Assigned	
CTX-M-116	*Proteus mirabilis*	JF966749	
CTX-M-117	*Escherichia coli*	JN227085	
CTX-M-118		Withdrawn	
CTX-M-119†		Assigned	
CTX-M-120†		Assigned	
CTX-M-121	*Escherichia coli*	JN790862	
CTX-M-122	*Escherichia coli*	JN790863	
CTX-M-123	*Escherichia coli*	JN790864	
CTX-M-124†		Assigned	

*, with enhanced catalytic efficiencies against ceftazidime; †, have been assigned in the Lahey database (Jacoby and Bush 2012); ‡, chromosome-encoded intrinsic cefotaximase identified in *Kluyvera* spp.; §, CTX-M-18 and CTX-M-14, CTX-M-57 and CTX-M-55 are identical in their amino acid sequences.

CTX-M-18 and of CTX-M-55 and CTX-M-57 are identical, and CTX-M-118 has been withdrawn. There is no detailed information available for the assigned members CTX-M-70, -73, -100, -103, -115, -119, -120 and -124 so far. In addition, CTX-M-76, -77, -78 and -95 are chromosome-encoded intrinsic cefotaximases in *Kluyvera* spp., and therefore, they are not counted into the CTX-M family. CTX-M-2, -3 and -37 are plasmid-mediated enzymes but also found on chromosomes in *Kluyvera* spp. To clarify the differences, the term c-CTX-M is used for such chromosome-encoded CTX-Ms in this article. Of the studied CTX-Ms, at least 19 variants display the enhanced catalytic efficiencies against ceftazidime (Table 1).

CTX-Ms have been detected in at least 26 bacterial species, including *Acinetobacter baumannii*, *Aeromonas caviae, A. hydrophila*, *Citrobacter amalonaticus, C. freundii*, *C. koseri, E. coli*, *Enterobacter cloacae*, *E. aerogenes, E. gergoviae*, *E. hormaechei*, *K. pneumoniae*, *K. oxytoca*, *Morganella morganii*, *Proteus mirabilis*, *Pantoea agglomerans, Providencia rettgeri*, *P. stuartii, Pseudomonas aeruginosa, Salmonella enterica*, *Shigella flexneri*, *S. sonnei*, *Serratia marcescens, S. liquefaciens*, *Stenotrophomonas maltophilia* and *Vibrio cholera* (Table 1).

CTX-M enzymes as the most prevalent ESBLs in *E. coli, K. pneumoniae* and *P. mirabilis*

The high prevalence of CTX-M ESBL genes in Enterobacteriaceae, particularly in *E. coli, K. pneumoniae* and *P. mirabilis,* has been documented worldwide (Bonnet, 2004; Cantón and Coque, 2006), while the CTX-Ms are not prominent in *P. aeruginosa* and *A. baumannii* (Zhao and Hu, 2010, 2012).

A study on the resistance of Enterobacteriaceae to third-generation cephalosporin was undertaken in 16 British hospitals over a 12-week period (Potz et al., 2006). Of 19,252 clinical isolates, CTX-M-producing strains accounted for 1.7%, higher than other ESBLs-producing strains (0.6%) and high-level AmpC-producing strains (0.4%). Particularly, of the resistance isolates of *E. coli* (n = 574) and *Klebsiella* spp. (n = 243), the CTX-M-producing strains accounted for 50.9% and 81.9%, respectively, by contrast with other ESBLs-producing strains (15.3% and 11.1%), high-level AmpC-producing strains (7.1% and 0.8%) and non-β-lactamase-producing strains (26.7% and 3.3%).

A rapid occurrence of CTX-M-producing strains in Enterobacteriaceae was documented by several longitudinal surveillances. Of 20,258 *E. coli* isolates studied in

Italy, the prevalence of ESBL-producing strains increased from 0.2% in 1999 to 1.6% in 2003, of which CTX-M-positive strains increased from 12.5% to 38.2% (Brigante et al., 2005). Of 1574 *P. mirabilis* clinical isolates collected in a Taiwanese hospital during 1999–2005, 44 CTX-M-producing strains were detected at a rate of 0.7% in 1999 and approximately 6% after 2002 (Wu et al., 2008). Of 11,407 *E. coli* isolates from urine samples of outpatients in the USA, 107 CTX-M-producing strains were detected at a rate of 0.07% in 2003 and 1.66% in 2008 (Qi et al., 2010).

CTX-M-producing strains widespread not only in human but also in animals and in environments. Of 240 *E. coli* isolates from health and sick pets during 2007–2008 in China, 97 strains (40.4%) harbored ESBL-encoding genes, of which 96 strains were confirmed to be carriers of $bla_{\text{CTX-M}}$ genes (Sun et al., 2010). Of 16 multi-drug resistant *E. coli* isolates from river water during 2000–2001 in South Korea, 10 strains harbored CTX-M-14 gene (Kim et al., 2008). Of 79 food samples of animal origin in Tunisia, $bla_{\text{CTX-M-1}}$-positive *E. coli* strains were isolated from 10 samples (Ben Slama et al., 2010).

A Japanese group surveyed the spread status of CTX-M genes in nosocomial Gram-negative bacteria collected from 132 geographically distant medical facilities during 2001–2003. Of the 1456 isolates resistant to oxyimino-cephalosporins, 21.8% were found to harbor $bla_{\text{CTX-M}}$ genes. The prevalent rates of CTX-Ms in ESBL-producing *E. coli*, *K. pneumoniae* and *P. mirabilis* were 77% (168/218), 56% (50/90) and 99% (71/72), respectively, while the rates of CTX-Ms in ESBL-producing *A. baumannii* and *S. marcescens* were 4.5% (4/89) and 7% (10/149), respectively (Shibata et al., 2006).

CTX-M-15 and CTX-M-14 as the most dominant variants in CTX-M family

Although the dominant variants of CTX-Ms are geographically different, CTX-M-15 and CTX-M-14 are the most common variants detected worldwide in clinically important pathogens, followed by CTX-M-2, CTX-M-3 and CTX-M-1 (Table 1). Conjugative plasmid-mediated horizontal transfer and clonal spread contributed to the increased prevalence.

Of 171 CTX-M-producing *E. coli* isolates from 11 Canadian medical centers in 2007, the positive rates for CTX-M-15, CTX-M-14, CTX-M-3 and CTX-M-27 were 86.5%, 9.9%, 2.9% and 0.6%, respectively (Peirano et al., 2010). Of 202 CTX-M-producing *K. pneumoniae* isolates from 41 medical centers in Hungary in 2005, 97% were CTX-M-15 producers derived from three genetically distinct clones (Damjanova et al., 2008). Of the CTX-M-producers (288 *E. coli* and 142 *K. pneumoniae* isolates) collected from 6 provinces in China during 1998–2002, CTX-M-14 was predominantly detected in 77.4% and 52.8% of the isolates, respectively, followed by CTX-M-3 (18.4% and 29.6%), CTX-M-24 (5.6% and 14.1%) and CTX-M-15 (0.7% and 1.4%) (Yu et al., 2007). An outbreak of CTX-M-producing *S. enterica* infection occurred in a university hospital in Algeria during 2008–2009, and all of 200 isolates from 138 patients were CTX-M-15 producers, identified to be a single clone (Naas et al., 2011).

Of 44 clinical isolates of CTX-M-producing *P. mirabilis* from a Taiwanese hospital, CTX-M-14 and CTX-M-3 positive strains accounted for 50% and 40.9%, respectively (Wu et al., 2008). Of 71 CTX-M-producing *P. mirabilis* isolates collected from 132 geographically distant hospitals in Japan, however, 100% of the strains carried the $bla_{\text{CTX-M-2}}$-like genes (Shibata et al., 2006). CTX-M-2 was also predominant in *C. koseri*, accounting for 76.7% of ESBL-producing strains (n = 60) collected from 10 areas throughout Japan in a 5-month period between 2009 and 2010 (Kanamori et al., 2011).

Phylogeny, origin and evolution of CTX-M enzymes

Amino-acid identity and phylogeny

The deduced amino-acid sequences of CTX-Ms comprise 291 residues, with the exceptions of CTX-M-11 (282), CTX-M-107 and -108 (288), CTX-M-45 and -109 (289), CTX-M-40, -63 and -106 (290) and CTX-M-110 (292). Based on the phylogenetic tree of amino-acid sequences, CTX-M enzymes may be divided into seven clusters (Figure 1).

CTX-M-3 cluster includes 42 members, sharing 97.6–99.7% identity in amino-acid sequences. The other clusters are as follows: CTX-M-14 cluster, 38 members, 97.3–99.7% identity; CTX-M-2 cluster, 16 members, 95.2–99.7% identity; CTX-M-25 cluster, 7 members, 98.6–99.7% identity; CTX-M-8 cluster, 3 members, 97.9–99.7% identity; CTX-M-64 cluster, 2 members, 95.9% identity. There is only one member in CTX-M-45 cluster. Among CTX-M variants, CTX-M-4 and CTX-M-45 are most divergent with 91 amino-acid substitutions.

Variations of amino-acid sequences

Based on the central positions in phylogenetic tree (Figure 1), CTX-M-2, -3, -8, -14, -25, -45 and -64 are chosen as the representative enzymes in each cluster. The amino-acid sequences of the seven enzymes are aligned, and numbered according to the standard numbering scheme for the class A serine β-lactamases, giving the active site serine residue the Ambler number 70 (Ambler et al., 1991) (Figure 2). The sequences of CTX-M variants are then compared with their representative in each cluster (Table 2). In the CTX-M-3 cluster, for example, a single amino-acid is substituted between CTX-M-3 and CTX-M-15, -22, -42, -54, -62, -66, -72 or -80, while 5 amino-acids are substituted between CTX-M-3 and CTX-M-58.

Origin of CTX-M family

In the family Enterobacteriaceae, the genus *Kluyvera* is a relatively new member, which has been isolated from various clinical specimens and regarded as a potentially virulent pathogen (Sarria et al., 2001). Some *Kluyvera* spp. harbor chromosome-encoded intrinsic genes of

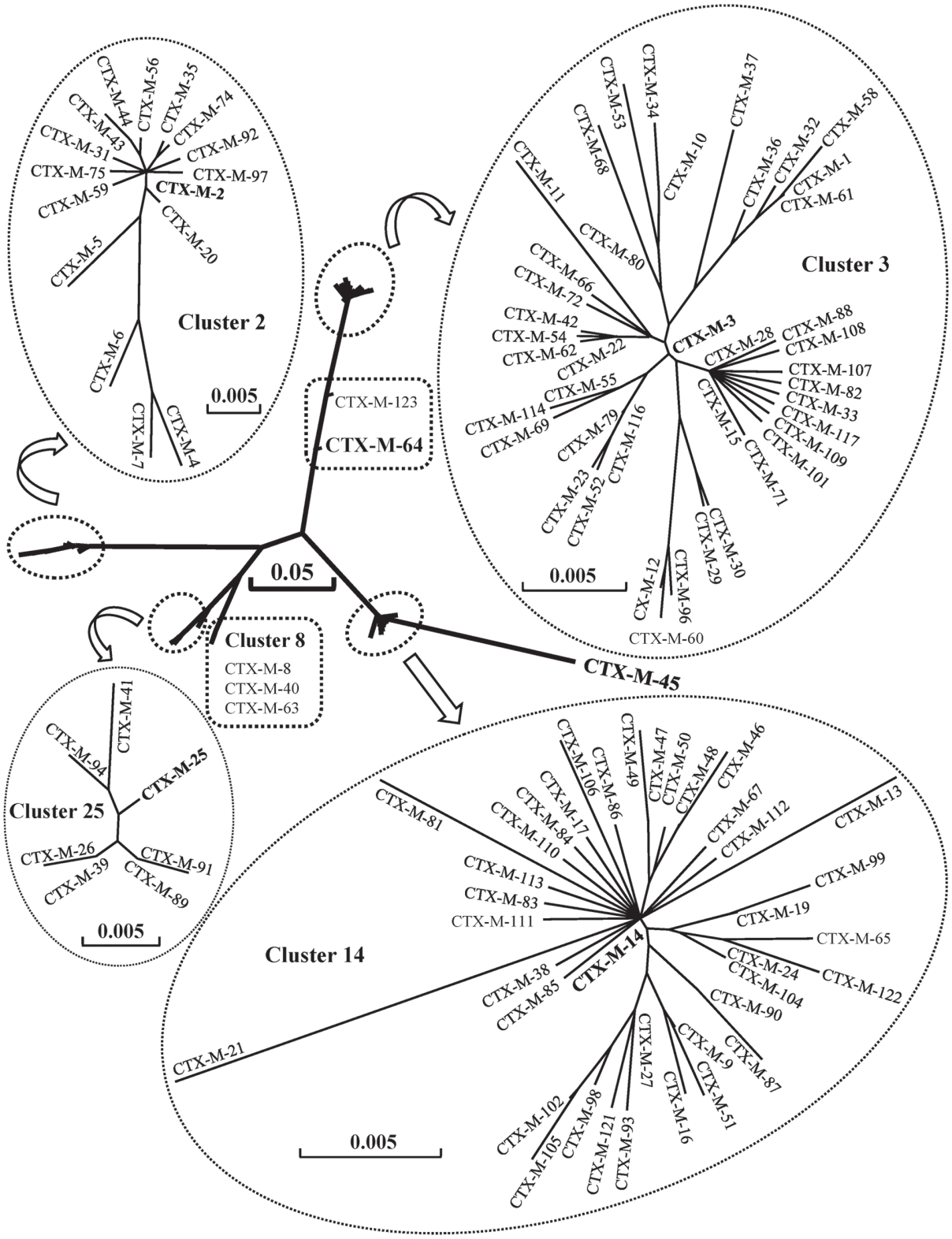

Figure 1. Phylogenetic tree of CTX-M family based on amino-acid sequences. DNASIS Pro v2.10 (Hitachi Software Engineering Co., Tokyo, Japan) was used to align the amino-acid sequences and construct the phylogenetic tree. The amino-acid sequences were downloaded from GenBank under the accession numbers cited in Table 1. The branch lengths are drawn to scale and are proportional to the number of different amino-acid residues. The scale bars of 0.05 and 0.005 represent 5% and 0.5% amino-acid difference, respectively.

cefotaximases which are closely associated with CTX-Ms (Decousser, et al., 2001; Humeniuk et al., 2002; Rodríguez et al., 2004). Generally, *Kluyvera* spp. are susceptible to cefotaxime in despite of the presence of naturally occurring cefotaximases. However, the recombinant clones of *E. coli* with *Kluyvera*-derived cefotaximase genes exhibited a significant increase in resistance to cefotaxime (Decousser et al., 2001; Humeniuk et al., 2002;

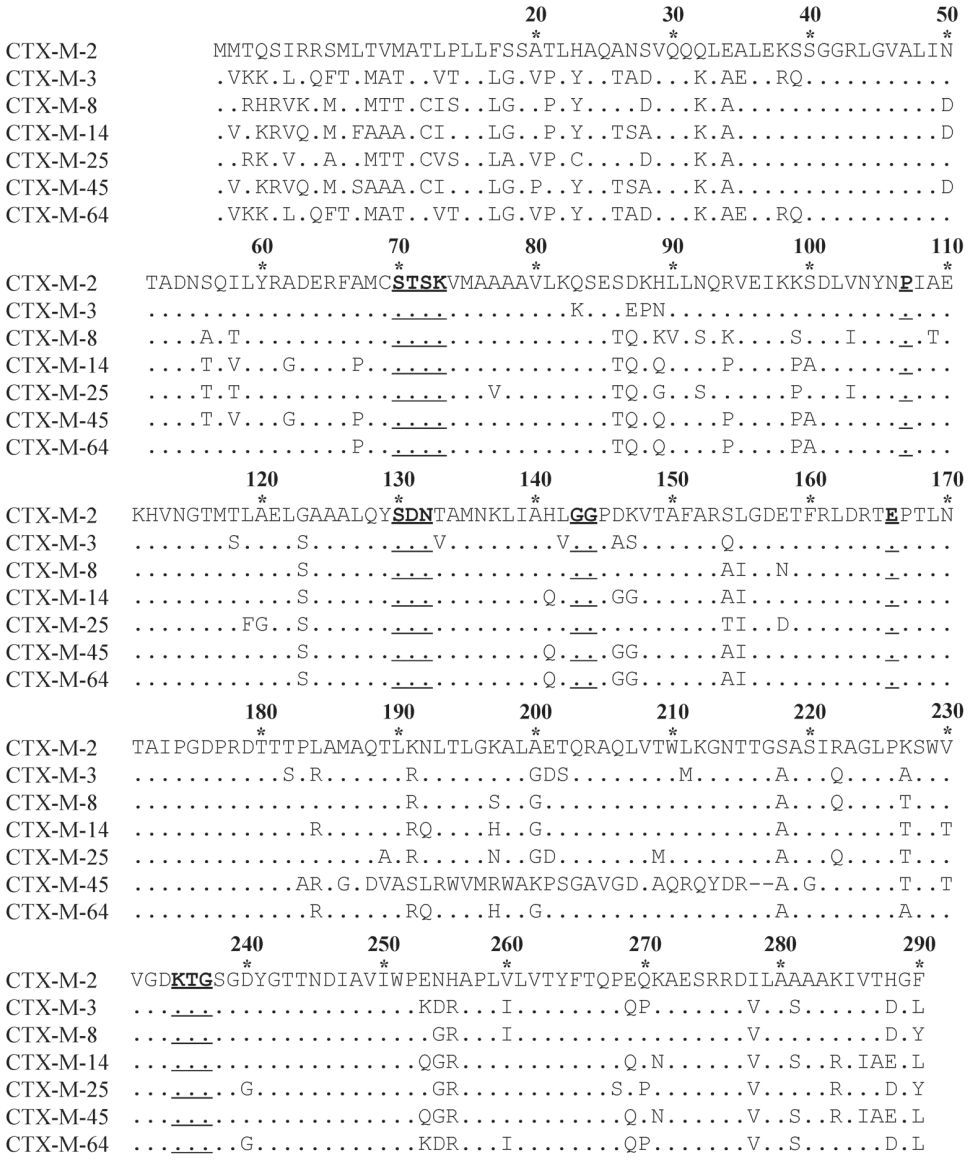

Figure 2. Comparison of amino-acid sequences of seven representative enzymes in the CTX-M family. Amino-acids are numbered according to the standard numbering scheme for the class A serine β-lactamases, giving the active site serine residue the Ambler number 70. Dots indicate identical amino-acids compared to CTX-M-2. Deletion mutations are expressed with short lines. The underlined amino-acids, ^{70}SXXK^{73}, ^{107}P, ^{130}SDN^{132}, ^{143}GG^{144}, ^{166}E and ^{234}KXG^{236}, represent the conserved residues in typical class A serine β-lactamases.

Table 2. Amino acid substitutions of CTX-M variants compared to their representative enzymes.

CTX-M	Amino acid substitution	CTX-M	Amino acid substitution
Cluster 2	**vs. CTX-M-2**	**Cluster 8**	**vs. CTX-M-8**
CTX-M-4	L48Q, R61V, K98R, K99A, A125G, T171S, L225M, V230G	CTX-M-40	K89N, T109A, N158D, N192H
CTX-M-5	A26T, V230G, E253A, I278V	CTX-M-63	K89N, T109A, N158D, N192H, S274N
CTX-M-6	R61L, K99A, A125G, T171S, S228C, I278V	**Cluster 14**	**vs. CTX-M-14**
CTX-M-7	R61V, K98R, K99A, E121Q, A125G, T171S, V230G, I278V	CTX-M-9	V231A
CTX-M-20	I278F	CTX-M-13	V2M, A52K, A154E
CTX-M-31	T159S	CTX-M-16	V231A, D240G
CTX-M-35	P167S	CTX-M-17	E288K
CTX-M-43	D240G, S274R	CTX-M-19	P167S
CTX-M-44	S274R	CTX-M-21	A9G, A10G, C12G, L22F, V29G
CTX-M-56	S274N	CTX-M-24	S274R
CTX-M-59	H89L	CTX-M-27	D240G
CTX-M-74	P167T	CTX-M-38	S220R

(Continued)

Table 2. *(Continued).*

CTX-M	Amino acid substitution	CTX-M	Amino acid substitution
Cluster 2	**vs. CTX-M-2**	**Cluster 14**	**vs. CTX-M-14**
CTX-M-75	P14S	CTX-M-46	S27N, A47P
CTX-M-92	A205T	CTX-M-47	G42R
CTX-M-97	R3G	CTX-M-48	S27N
Cluster 3	**vs. CTX-M-3**	CTX-M-49	G42R, A47P
CTX-M-1	A77V, N114D, A140S, D288N	CTX-M-50	A47P
CTX-M-10	A27V, R38Q	CTX-M-51	A77V, V231A
CTX-M-11	E35G, L119P, D277H, deletion of ^{282}AAKIVTDGL^{290}	CTX-M-65	A77V, S274R
CTX-M-12	T12A, N89S, V278I	CTX-M-67	N106S
CTX-M-15	D240G	CTX-M-81	K82E, K98Q, N132H
CTX-M-22	D288N	CTX-M-83	Q56H
CTX-M-23	A77V, P167T, D288N	CTX-M-84	T209A
CTX-M-28	D240G, D288N	CTX-M-85	L119P
CTX-M-29	T12A, N114D, D240G, D288N	CTX-M-86	I108F
CTX-M-30	T12A, N114D	CTX-M-87	A77V, P167L
CTX-M-32	A77V, N114D, A140S, D240G, D288N	CTX-M-90	A77V
CTX-M-33	N106S, D240G	CTX-M-93	L169Q, D240G
CTX-M-34	A27V, R38Q, G238C	CTX-M-98	A77V, D240G
CTX-M-36	N114D, A140S, D288N	CTX-M-99	P167S, S274R
CTX-M-37	Y23H, R38Q, N114D	CTX-M-102	A205E, D240G
CTX-M-42	P167T	CTX-M-104	S274N
CTX-M-52	A77V, P167S	CTX-M-105	A77V, A205E, D240G
CTX-M-53	A27V, R38Q, A77V, D240G, T263I	CTX-M-106	K234R, R276H, deletion of ^{290}L
CTX-M-54	P167Q	CTX-M-110	K111E, insertion of N before ^{290}L
CTX-M-55	A77V, D240G	CTX-M-111	P145Q
CTX-M-58	A77V, N114D, A140S, P167T, D288N	CTX-M-112	S123G
CTX-M-60	T12A, N89S, V278I, A77V	CTX-M-113	Q83R
CTX-M-61	A77V, N114D, A140S	CTX-M-121	A109T, D240G
CTX-M-62	P167S	CTX-M-122	A154S, S274R
CTX-M-66	S19N	**Cluster 25**	**vs. CTX-M-25**
CTX-M-68	Y23H, A27V, E158D	CTX-M-26	V77A, Q222R, G240D
CTX-M-69	A77V, D240G, K271N, D288N	CTX-M-39	V77A, G240D
CTX-M-71	G238C, D240G	CTX-M-41	V77A, I103V, S123I
CTX-M-72	R164G	CTX-M-89	G240D
CTX-M-79	A77V, D240G, D288N	CTX-M-91	A189S, G240D
CTX-M-80	A27V	CTX-M-94	V77A, F119L
CTX-M-82	A67P, D240G	**Cluster 64**	**vs. CTX-M-64**
CTX-M-88	D240G, R276H	CTX-M-123	P67A, Q83K, T86S, Q87E, K88P, Q89N, P94R, P99K, A100S, T118S, A227T, V230T
CTX-M-96	T12A, N89S, D240G, V278I		
CTX-M-101	S123I, D240G		
CTX-M-107	K234R, D240G, deletion of ^{288}DGL^{290}		
CTX-M-108	V95A, D240G, deletion of ^{288}DGL^{290}		
CTX-M-109	Q56R, D240G, D288K, deletion of ^{289}GL^{290}		
CTX-M-114	V74A, A77V, D240G		
CTX-M-116	A77V, D288N		
CTX-M-117	P174Q, D240G		

Rodríguez et al., 2004), suggesting that a proper genetic platform is necessary for the gene expression. The chromosome-encoded cefotaximases identified in *Kluyvera* spp. include KLUA, KLUG, KLUY, KLUC, c-CTX-M-2, c-CTX-M-3, c-CTX-M-37, c-CTX-M-76, c-CTX-M-77, c-CTX-M-78 and c-CTX-M-95. All of them comprise 291 amino-acid residues. An aspartate aminotransferase-encoding gene is found commonly upstream of these chromosomal *bla* genes, which is replaced by IS*Ecp1* or IS*CR1* in the plasmid-harbored $bla_{\text{CTX-M}}$ genes (see the details under next section).

KLUA-1 to -5 and -8 to -12 (GenBank accession no. AJ272538, AJ251722, AJ427461, AJ427462, AJ427463, AJ427465, AJ427466, AJ427467, AJ427468, AJ427469) are a group of chromosomal cefotaximases identified in *K. ascorbata*, with minor variations (<5%) in their

amino-acid sequences (Humeniuk et al., 2002). KLUA-2 shares 100% identity with plasmid-mediated CTX-M-5. CTX-M-2 and CTX-M-3 originally identified on plasmids were also found on the chromosomes of *K. ascorbata* (Rodríguez et al., 2004; Lartigue et al., 2006). The immediate upstream- and downstream-sequences of $bla_{\text{KLUA-1}}$ and plasmid-mediated *bla genes in* CTX-M-2 cluster ($bla_{\text{CTX-M-2, -4, -5, -6, -7, -44}}$) share 85 to 100% identities (Di Conza et al., 2002; Humeniuk et al., 2002). The architectures of the flanking regions corresponding to c-CTX-M-3 and plasmid-mediated CTX-M-3 are identical, including a 128 bp immediate upstream region and the first 373 bp of the downstream region of the *bla* gene (Rodríguez et al., 2004). The c-CTX-M-76, -77 and -95 (AM982520, AM982521, FN813245) identified in *K. ascorbata* also share high identities with the enzymes in CTX-M-2 cluster.

KLUY-1 to -4 (AY623932, AY623935, AY623934, AY623933) are a group of chromosomal cefotaximases identified in *K. Georgiana* (Olson et al., 2005). They share high homology with the enzymes in CTX-M-14 cluster. Typically, KLUY-1 exhibits 100% amino-acid identity with CTX-M-14. The upstream- and downstream-sequences of bla_{KLUY} and $bla_{\text{CTX-M-9, -13, -14}}$ also share consistent identity. A 42 bp upstream region of $bla_{\text{CTX-M-14}}$ is identical to the corresponding region of bla_{KLUY} genes. A 347 bp downstream region of $bla_{\text{CTX-M-9}}$ and $bla_{\text{CTX-M-13}}$ shares 95.7–98.6% identities with the corresponding region of bla_{KLUY} genes (Olson et al., 2005).

KLUG-1 (AF501233) and c-CTX-M-78 (AM982522) are the chromosomal cefotaximases identified in *K. Georgiana*. KLUG-1 shares 99% amino-acid identity with the plasmid-mediated CTX-M-8 (Poirel et al., 2002b). The c-CTX-M-78 possesses high homology with the known members of CTX-M-25 cluster, sharing 95.2–96.2% identities (Rodríguez et al., 2010).

CTX-M-37 was also found on the chromosome of *K. cryocrescens* (FN813246), suggesting the c-CTX-M-37 as an origin of CTX-M-3 cluster. KLUC-1 (AY026417) and KLUC-2 (EF057432), with a single amino-acid substitution, are two chromosome-encoded cefotaximases identified in *K. cryocrescens* (Decousser et al., 2001). KLUC-1 and -2 are diverse from the known CTX-Ms, sharing only 87.6% identity with CTX-M-3. Notably, KLUC-2 was also identified on a plasmid carried by a clinical isolate of *E. cloacae*, indicating the transfer of bla_{KLUC} from chromosome to the plasmid (Petrella et al., 2008). We would like to suggest the plasmid-mediated KLUC-2 as a novel cluster or member of CTX-M family.

CTX-M-64 shows a chimeric sequence of both CTX-M-14 (central portion) and CTX-M-15 (N- and C-terminal moieties), suggesting an origination owing to homologous recombination between the $bla_{\text{CTX-M-14}}$ and $_{\text{-15}}$ genes (Nagano et al., 2009).

Taken together, the origins of the acquired CTX-Ms in various clusters can be traced back to the intrinsic cefotaximase genes harbored by *Kluyvera* spp., of which the CTX-M-2 cluster appears to be derived from *K. ascorbata*, the CTX-M-14, CTX-M-8 and CTX-M-25 clusters from *K. georgiana*, while the CTX-M-3 cluster from both *K. ascorbata* and *K. cryocrescens* (Figure 3).

Genetic platforms of CTX-M enzymes

IS*Ecp1*

Insertion sequences (ISs) are the smallest transposable elements (<2.5 kb) capable of independent transposition in an organism, thereby causing insertion mutations and genome rearrangements (Mahillon and Chandler, 1998). ISs play three basic roles in bacteria: encoding a transposase which makes a genetic element mobile; providing promoters to activate silent genes or enhance expression of downstream determinants; moving IS-mobilized genes among integrons, transposons, plasmids and chromosomes, thereby greatly increasing the opportunity a resistance determinant becomes transferable.

Of the genetic platforms associated with CTX-Ms, IS*Ecp1* is one of the most important elements (Table 3). IS*Ecp1* was first identified on the plasmid pST01 in *E. coli* strain 79 (AJ242809), hence its name (Stapleton, 1999). IS*Ecp1* is composed of an *orf* encoding a transposase with 420 amino-acids and two imperfect and inverted

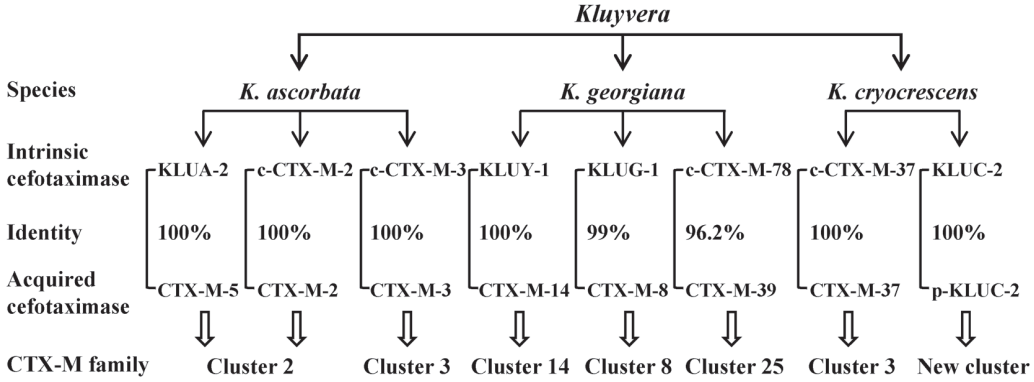

Figure 3. Identification of intrinsic cefotaximase genes in *Kluyvera* spp. as the original sources of acquired CTX-Ms based on their amino-acid identities and the homologies of neighboring sequences of the associated genes. c-CTX-M, CTX-M identified on chromosome of *Kluyvera* spp.; p-KLUC-2, KLUC-2 identified on plasmid in a clinical isolate of *Enterobacter cloacae.*

Table 3. Genetic platforms of CTX-M enzymes.

CTX-M	Genetic platform	Bacterial host	Reference/GenBank accession no.
CTX-M-1	IS*Ecp1*–$bla_{CTX-M-1}$–*orf477*	*E. coli*	Eckert et al., 2006
	IS*Ecp1Δ*----IS*26*–IS*Ecp1Δ*–$bla_{CTX-M-1}$	*K. pneumoniae*	Diestra et al., 2009
	IS*26*–IS*Ecp1Δ*–$bla_{CTX-M-1}$– *orf477Δ*	*E. coli*	Cullik et al., 2010
	intI1–dfrA17–aadA5–qacEΔ1–sul1–IS*CR1*–$bla_{CTX-M-1}$–*orf3*–IS*3000–qacEΔ1–sul1*-like–*orf5*	*E. coli*	Su et al., 2008
CTX-M-2	*intI1–aacA4–*bla_{OXA-2}*–orfD–qacEΔ1–sul1*–IS*CR1*–$bla_{CTX-M-2}$–*orf3Δ–qacEΔ1–sul1*	*P. mirabilis*	Arduino et al., 2002
	intI1–aacA4–bla_{OXA-2}*–orfD–qacEΔ1–sul1*–IS*CR1*–$bla_{CTX-M-2}$–*orf3Δ–qacEΔ1–sul1–orf5*	*V. cholera*	Soler Bistué et al., 2006
	intI1–aacA4–bla_{OXA-2}*–orfD–qacEΔ1–sul1*–IS*CR1–dfrA10–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1–sul1–orf5–tniBΔ*–IS*1326*	*S. enterica*	AJ311891
	intI1–dfrA12–orfF–aadA2–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1–sul1–orf5*–IS*1326*	*K. pneumoniae*	EU780013
	intI1–estX–aadA1–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1–sul1–orf5*–IS*1326*	*E. coli*	Valverde et al., 2006
	intI1–aac(6')-Iq–aadA1–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1*	*K. pneumoniae*	EU622037
	intI1–aadA1–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1*	*K. pneumoniae*	EU622040
	intI1–aadA2–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1*	*K. pneumoniae*	EU622038
	intI1–dhfrh1–aadA2–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1–sul1*	*E. coli*	Eckert et al., 2006
	intI1–dfrA1–aadA1–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1*–sul1	*S. enterica*	EF592570
	intI1–dfrA12–orfF–aadA2–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1*–sul1	*S. enterica*	EF592571
	intI1–dfrA21–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1*	*K. pneumoniae*	EU622039
	intI1–dfr22–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1*	*K. pneumoniae*	EU622041
	intI1–orf1–cat–orf2–aadA1–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-2}$*–orf3Δ–qacEΔ1*–sul1	*P. mirabilis*	Song et al., 2011
	IS*Ecp1–*$bla_{CTX-M-2}$	*P. mirabilis*	Harada et al., 2012
CTX-M-3	IS*Ecp1–*$bla_{CTX-M-3}$*–orf477*	*K. pneumoniae*	Eckert et al., 2006
	IS*Ecp1–*$bla_{CTX-M-3}$*–orf477–mucA*	*K. pneumoniae*	Eckert et al., 2006
	IS*Ecp1*-like–$bla_{CTX-M-3}$*–orf477*-like	*P. mirabilis*	Wu et al., 2008
	IS*Ecp1–*$bla_{CTX-M-3}$	*E. coli*	Diestra et al., 2009
	IS*Ecp1*–IS*1–*$bla_{CTX-M-3}$*–orf477–mucA*	*K. pneumoniae*	Eckert et al., 2006
	IS*Ecp1–*$bla_{CTX-M-3}$*–orf–mucA*	*C. freundii*	Lartigue et al., 2004
	IS*26*–IS*Ecp1Δ–*$bla_{CTX-M-3}$	*E. coli*	Diestra et al., 2009
	IS*26*–IS*Ecp1–*$bla_{CTX-M-3}$*–orf477–mucA*	*P. mirabilis*	Eckert et al., 2006
CTX-M-9	*intI1–aadB–qacEΔ1*–sul1–IS*CR1–*$bla_{CTX-M-9}$*–orf3*-like–IS*3000*	*E. cloacae*	DQ108615
	intI1–dhfr12–orfX–aadA8–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-9}$*–orf3–orf339Δ*	*E. coli*	Eckert et al., 2006
	intI1–dfrA16–aadA2–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-9}$*–orf3*-like–IS*3000–qacEΔ1–sul1*	*E. coli*	Sabaté et al., 2002
	IS*CR1–*$bla_{CTX-M-9}$	*E. coli*	Diestra et al., 2009
	IS*Ecp1–*$bla_{CTX-M-9}$	*C. freundii*	Minarini et al. 2009
CTX-M-10	Tn*1000-like–orf2–orf3–orf4*–DNA-invertase-gene–$bla_{CTX-M-10}$*–orf7–orf8*–IS*4321–orf10–orf11*–IS*5*	K. pneumoniae	Oliver et al., 2005
	IS*Ecp1–*$bla_{CTX-M-10}$*–orf*–Tn*5396*	*E. coli*	Lartigue et al., 2004
CTX-M-12	IS*Ecp1–*$bla_{CTX-M-12}$	*P. mirabilis*	Song et al., 2011
CTX-M-13	IS*Ecp1B–*$bla_{CTX-M-13}$	*E. coli*	DQ058147
CTX-M-14	IS*Ecp1–*$bla_{CTX-M-14}$–IS*903*	*E. coli*	Lartigue et al., 2004
	IS*Ecp1*-like–$bla_{CTX-M-14}$–IS*903*-like	*P. mirabilis*	Wu et al., 2008
	IS*Ecp1*–IS*10–*$bla_{CTX-M-14}$–IS*903*	*E. coli*	Eckert et al., 2006
	IS*Ecp1*–IS*10–*$bla_{CTX-M-14}$–IS*903D*	*E. coli*	EU136400
	IS*26*–IS*Ecp1–*$bla_{CTX-M-14}$	*K. pneumoniae*	Eckert et al., 2006
	IS*26*–IS*Ecp1–*$bla_{CTX-M-14}$–IS*903*	*K. pneumoniae*	GQ385317
	IS*26–*$bla_{CTX-M-14}$–IS*903D*	*S. enterica*	Izumiya et al., 2005
	IS*Ecp1B–*$bla_{CTX-M-14}$	*E. coli*	Billard-Pomares et al., 2011
	intI1–dfrA12–orfF–aadA2–qacEΔ1–sul1–IS*CR1–*$bla_{CTX-M-14}$–IS*903*-like	*E. coli*	Bae et al., 2007
	intI1–dfrA12–orfF–aadA2–qacEΔ1–sul1–orf5–IS*6100*–IS*CR1–ISEcp1Δ–*$bla_{CTX-M-14}$–IS*903D*	*E. coli*	Bae et al., 2008

(Continued)

Table 3. *(Continued).*

CTX-M	Genetic platform	Bacterial host	Reference/GenBank accession no.
CTX-M-15	IS*Ecp1*–$bla_{\text{CTX-M-15}}$	*A. hydrophila*	Gómez-Garcés et al., 2011
	IS*Ecp1*–$bla_{\text{CTX-M-15}}$–*orf477*	*E. coli*	Eckert et al., 2006
	IS*Ecp1*–$bla_{\text{CTX-M-15}}$–*orf477Δ*–Tn3	*A. baumannii*	JN788267
	Tn3*Δ*–IS*Ecp1*–$bla_{\text{CTX-M-15}}$–*orf*–Tn3*Δ*	*E. coli*	Lartigue et al., 2004
	IS*26*–IS*Ecp1*–$bla_{\text{CTX-M-15}}$–*orf477*	*E. coli*	Eckert et al., 2006
	IS*26*–IS*Ecp1*–$bla_{\text{CTX-M-15}}$–*orf477Δ*	*S. enterica*	Fabre et al., 2009
	$bla_{\text{TEM-1}}$–*tnpR*–*tnpA*–IS*Ecp1*–$bla_{\text{CTX-M-15}}$–*orf477*	*E. coli*	Eckert et al., 2006
CTX-M-16	IS*Ecp1*–$bla_{\text{CTX-M-16}}$–IS*903*	*E. coli*	Brasme et al., 2007
	IS*Ecp1*–$bla_{\text{CTX-M-16}}$–*orf3*–*orf339*–*orf477*	*E. coli*	AM910790
CTX-M-17	IS*Ecp1*-like–$bla_{\text{CTX-M-17}}$–IS*903C*	*K. pneumoniae*	Cao et al., 2002
CTX-M-19	*intI1*-like–*aacA4*–*cmlA1*–*qacEΔ1*–*sul1*–Tn*1721*–IS*Ecp1B*–$bla_{\text{CTX-M-19}}$–IS*903D*	*K. pneumoniae*	Poirel et al., 2003
CTX-M-20	IS*Ecp1*–$bla_{\text{CTX-M-20}}$	*P. mirabilis*	AJ416344
CTX-M-21	IS*Ecp1*–$bla_{\text{CTX-M-21}}$	*E. coli*	AJ416346
CTX-M-22	IS*Ecp1Δ*–IS*26*–$bla_{\text{CTX-M-22}}$–*orf477*–IS*Ecp1Δ*	*S. liquefaciens*	HM470254
CTX-M-24	IS*Ecp1*–$bla_{\text{CTX-M-24}}$–IS*903*	*E. coli*	Eckert et al., 2006
	IS*Ecp1*-like–$bla_{\text{CTX-M-24}}$–IS*903*-like	*P. mirabilis*	Wu et al., 2008
CTX-M-25	*intI1*–*aacA4*–$bla_{\text{OXA-2}}$–IS*Ecp1*–$bla_{\text{CTX-M-25}}$–*qacEΔ1*–*sul1*	*P. mirabilis*	Navon-Venezia et al. 2008
	IS*Ecp1Δ*–*IS50-A*–IS*Ecp1Δ*–$bla_{\text{CTX-M-25}}$–*orfX*	*E. coli*	Munday et al. 2004
CTX-M-26	*intI1*–*dhfr7*–IS*Ecp1*–$bla_{\text{CTX-M-26}}$–*qacEΔ1*–*sul1*	*K. pneumoniae*	Navon-Venezia et al. 2008
	IS*Ecp1*–$bla_{\text{CTX-M-26}}$–*orfX*	*K. pneumoniae*	Munday et al. 2004
CTX-M-27	IS*Ecp1*–$bla_{\text{CTX-M-27}}$	*S. enterica*	Bouallègue-Godet et al., 2005
	IS*Ecp1*–$bla_{\text{CTX-M-27}}$–*IS903*	*E. coli*	Sun et al., 2010
CTX-M-32	IS*Ecp1Δ*–IS*5*–IS*1A*–IS*Ecp1Δ*–$bla_{\text{CTX-M-32}}$–*orf477*	*E. coli*	Fernández et al., 2007
	IS*Ecp1Δ*–IS*5*–IS*Ecp1Δ*–$bla_{\text{CTX-M-32}}$	*E. coli*	Diestra et al., 2009
CTX-M-39	*intI1*–*dhfr7*–IS*Ecp1*–$bla_{\text{CTX-M-39}}$–*qacEΔ1*–*sul1*	*E. coli*	Navon-Venezia et al. 2008
	intI1–*aadA1*–IS*Ecp1*–$bla_{\text{CTX-M-39}}$–*qacEΔ1*–*sul1*	*E. coli*	Navon-Venezia et al. 2008
CTX-M-40	IS*Ecp1*-like–$bla_{\text{CTX-M-40}}$	*E. coli*	Hopkins et al., 2006
CTX-M-42	IS*Ecp1*–$bla_{\text{CTX-M-42}}$	*E. coli*	DQ061159
CTX-M-53	IS*Sen2*---$bla_{\text{CTX-M-53}}$–*orf477Δ*–IS*26*	*S. enterica*	Doublet et al., 2009
CTX-M-54	IS*Ecp1*–$bla_{\text{CTX-M-54}}$–IS*903*-like	*K. pneumoniae*	Bae et al., 2006a
CTX-M-55	IS*Ecp1*–$bla_{\text{CTX-M-55}}$–*orf477*	*E. coli*	Sun et al., 2010
	IS*Ecp1Δ*–IS*1294*–$bla_{\text{CTX-M-55}}$–*orf477*	*E. coli*	JN977127
CTX-M-59	*intI1*–*dfr15b*–*cmlA4*-like–*aadA2*–*qacEΔ1*–*sul1*–IS*CR1*–$bla_{\text{CTX-M-59}}$–*orf3Δ*–*qacEΔ1*	*K. pneumoniae*	EU622856
CTX-M-62	IS*Ecp1*–$bla_{\text{CTX-M-62}}$–IS*Ecp1Δ1/Δ2*	*K. pneumoniae*	Zong et al., 2010
CTX-M-64	IS*Ecp1*–$bla_{\text{CTX-M-64}}$–*orf477*	*S. sonnei*	Nagano et al., 2009
CTX-M-65	IS*Ecp1*–$bla_{\text{CTX-M-65}}$–IS*903*	*E. coli*	Sun et al., 2010
CTX-M-66	IS*Ecp1*-like–$bla_{\text{CTX-M-66}}$–*orf477*-like	*P. mirabilis*	Wu et al., 2008
CTX-M-74	IS*CR1*–$bla_{\text{CTX-M-74}}$–*orf3Δ*–*qacEΔ1*–*sul1*	*E. cloacae*	Minarini et al. 2009
CTX-M-75	IS*CR1*–$bla_{\text{CTX-M-75}}$–*orf3Δ*–*qacEΔ1*–*sul1*	*P. stuartii*	Minarini et al. 2009
CTX-M-79	IS*Ecp1*–$bla_{\text{CTX-M-79}}$	*E. coli*	FJ169498
CTX-M-82	IS*Ecp1*–$bla_{\text{CTX-M-82}}$	*E. coli*	GU477621
CTX-M-89	IS*Ecp1*-like–$bla_{\text{CTX-M-89}}$–*orf477*-like	*E. cloacae*	FJ966096
CTX-M-90	IS*Ecp1*–$bla_{\text{CTX-M-90}}$–IS*903*-like	*P. mirabilis*	Song et al., 2011
	IS*Ecp1*–$bla_{\text{CTX-M-90}}$	*P. mirabilis*	Song et al., 2011
CTX-M-93	IS*Ecp1*–$bla_{\text{CTX-M-93}}$–IS*903*	*E. coli*	Djamdjian et al., 2011
CTX-M-98	IS*Ecp1*–$bla_{\text{CTX-M-98}}$–IS*903*	*E. coli*	HM755448
CTX-M-101	IS*Ecp1*–$bla_{\text{CTX-M-101}}$	*E. coli*	HQ398214
CTX-M-102	IS*Ecp1*–$bla_{\text{CTX-M-102}}$–IS*903*	*E. coli*	HQ398215
CTX-M-104	IS*Ecp1*–$bla_{\text{CTX-M-104}}$–IS*903*	*E. coli*	HQ833652
CTX-M-105	IS*Ecp1*–$bla_{\text{CTX-M-105}}$–IS*903*	*E. coli*	HQ833651
CTX-M-116	IS*Ecp1*–$bla_{\text{CTX-M-116}}$	*P. mirabilis*	JF966749
CTX-M-121	IS*Ecp1*–$bla_{\text{CTX-M-121}}$–IS*903*	*E. coli*	JN790862
CTX-M-122	IS*Ecp1*–$bla_{\text{CTX-M-122}}$–IS*903*	*E. coli*	JN790863
CTX-M-123	IS*Ecp1*–$bla_{\text{CTX-M-123}}$	*E. coli*	JN790864

repeats. IS*Ecp1* can mobilize the downstream-located bla_{CTX-M} gene and provide a promoter for its expression (Karim et al., 2001; Cao et al., 2002; Poirel et al., 2003, 2005; Dhanji et al., 2011b).

Co-existence of IS*Ecp1* and bla_{CTX-M} at a high rate in CTX-M-producing *E. coli* isolates is well documented. IS*Ecp1* was identified upstream of bla_{CTX-M} genes in 86.9% of the isolates (93/107) recovered from health and sick pets in China, and no major clonal relatedness was observed (Sun et al., 2010). Similarly, IS*Ecp1* was identified upstream of $bla_{CTX-M-14}$ in 91.4% of the clinical isolates (32/35) in Korea (Kim et al., 2011), and upstream of $bla_{CTX-M-1}$ in 69.2% of the isolates (9/13) from food samples in Tunisia (Ben Slama et al., 2010). In addition, variations of IS*Ecp1* were also observed. IS*Ecp1B*, originally identified upstream of a $bla_{CTX-M-19}$ gene cassette (AF458080), differs from IS*Ecp1* by three nucleotide substitutions (Poirel, et al., 2003). Of the 174 IS*Ecp1*-like and $bla_{CTX-M-15}$ complex from *E. coli* isolates, the intact IS*Ecp1*, truncated IS*Ecp1* with various lengths and a 24 bp remnant of IS*Ecp1* accounted for 62%, 33.3% and 4.6%, respectively (Dhanji et al., 2011b). Notably, IS*Ecp1* was also detected upstream of chromosomal $bla_{CTX-M-2}$ genes in 4 *P. mirabilis* isolates in Japan (Harada et al., 2012), highlighting the IS*Ecp1*-mediated movement of bla_{CTX-M} genes between plasmids and chromosomes.

IS*Ecp1*-bla_{CTX-M}-IS*903* (Figure 4A) and IS*Ecp1*-bla_{CTX-M}-*orf477* (Figure 4B) are two major genetic platforms. In some cases, IS*Ecp1*-mobilized bla_{CTX-M} is inserted in a class 1 integron (Figure 4C). IS*903* (V00359) encodes a transposase with 307 amino-acids and was originally found on a kanamycin resistance transposon Tn903 (Oka et al., 1981). IS*903* and IS*903*-like elements, such as IS*903C* and IS*903D*, are located downstream of bla_{CTX-M} genes (Table 3), including $bla_{CTX-M-14}$-like genes ($bla_{CTX-M-14,\ -16,\ -17,\ -19,\ -24,\ -27,\ -65,\ -90,\ -93,\ -98,\ -102,\ -104,\ -105,\ -121,\ -122}$) and $bla_{CTX-M-3}$-like gene ($bla_{CTX-M-54}$). *orf477* encodes a protein of 158 amino-acids with unknown function and the *orf477* and *orf477*-like elements were found downstream of plasmid-harbored $bla_{CTX-M-3}$-like genes

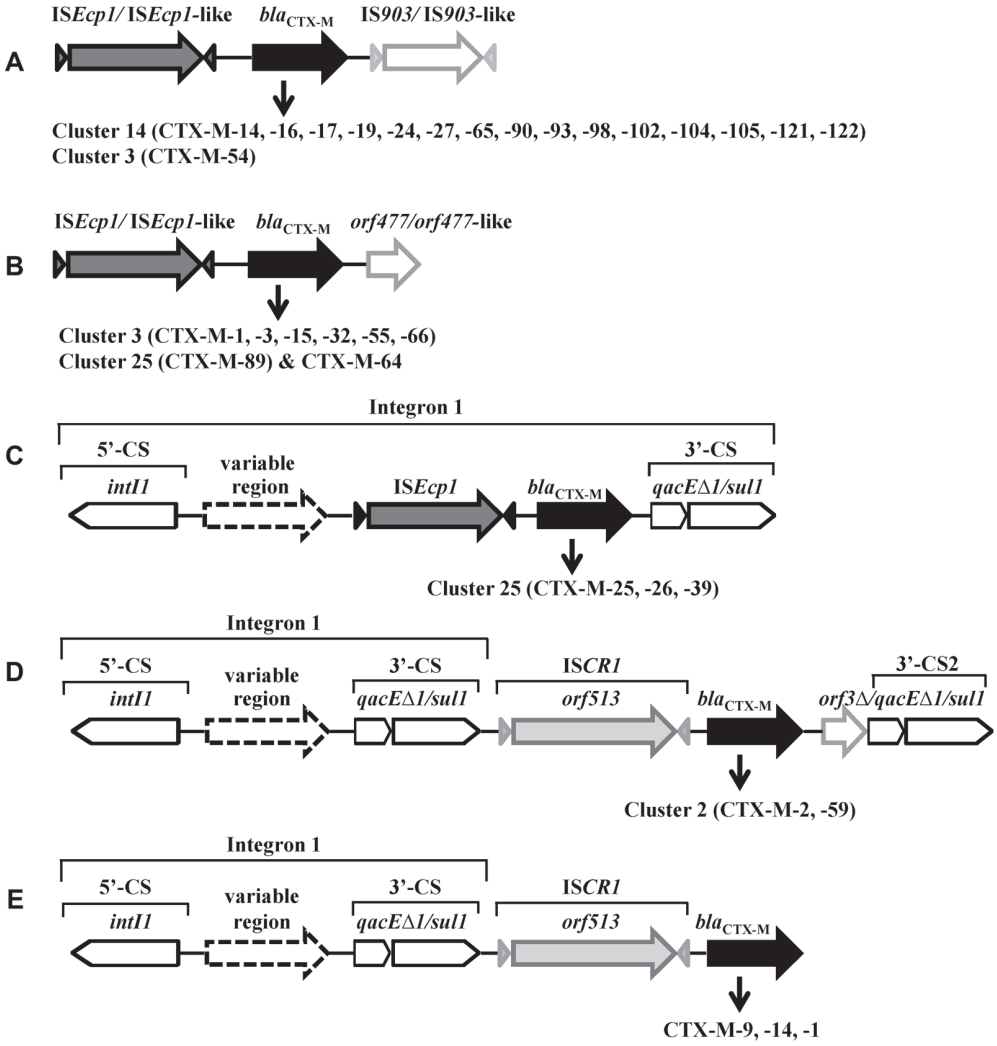

Figure 4. Typical genetic platforms of CTX-M enzymes. A & B: the bla_{CTX-M} gene cassettes bracketed upstream by IS*Ecp1*/IS*Ecp1*-like and downstream by IS*903*/IS*903*-like (A) or *orf477*/*orf477*-like (B); C: bla_{CTX-M} genes associated with class 1 integron-IS*Ecp1*; D & E: bla_{CTX-M} genes associated with class 1 integron-IS*CR1* complex. CS, conserved segment; *intI*, integrase gene; *qacEΔ1,* quaternary ammonium resistance gene; *sul1,* sulphonamide resistance gene; 3′-CS2, the second copy of 3′-conserved segment.

($bla_{CTX\text{-}M\text{-}1,\ -3,\ -15,\ -22,\ -32,\ -53,\ -55,\ -66}$), $bla_{CTX\text{-}M\text{-}89}$ and $bla_{CTX\text{-}M\text{-}64}$ (Table 3). The *orf477* was also identified downstream of the chromosomal $bla_{CTX\text{-}M\text{-}3}$ in *K. ascorbata*, of the chromosomal $bla_{KLUY\text{-}1,\ -2,\ -3,\ -4}$ in *K. georgiana*, and of the chromosomal $bla_{CTX\text{-}M\text{-}37}$ (FN813246) in *K. cryocrescens* (Rodriguez et al., 2004; Olson et al., 2005), footnoting the IS*Ecp1*-mediated transfer of $bla_{CTX\text{-}M}$ genes together with the *orf477* from the chromosomes of *Kluyvera* spp. to plasmids.

Class 1 integron-IS*CR1* complex

Integrons are defined as mobile DNA elements that can capture genes by site-specific recombination (Stokes and Hall, 1989). A typical class 1 integron consists of a 5′ conserved segment (5′-CS), a variable region and a 3′ conserved segment (3′-CS). The 5′-CS consists of the gene encoding integrase (*intI1*), the site adjacent to *intI1* for the insertion of captured genes (*attI*), and a promoter region (Pc). The 3′-CS often consists of a partially deleted *qac* gene (*qacEΔ1*) fused to a *sul1* gene, and confers resistance to antiseptics and sulfonamide, respectively. Class 1 integrons play a critical role in acquiring and spreading metallo-β-lactamases (Mazel, 2006; Zhao and Hu, 2011a,b). The role of integrons in CTX-M gene acquisition and dissemination, however, is still unclear. The physical link of some $bla_{CTX\text{-}M}$ genes with class 1 integron-IS*Ecp1* complex (Figure 4C) and class 1 integron-IS*CR1* complex (Figure 4D, 4E) indicates a possible association among the three genetic elements.

IS*CR1* is another important element in the genetic platforms associated with the mobilization and dissemination of CTX-M genes (Rodriguez-Martinez et al. 2006; Toleman et al., 2006). Common region 1 (CR1) was first found as element associated with but distinct from class 1 integrons (Stokes et al., 1993). The CR1 element was renamed IS*CR1* because it possesses the key motifs of IS*91*-like element and accommodates *orf513* gene which codes a putative transposase of 513 amino-acids (Toleman et al., 2006). IS*CR1* is particularly important for CTX-M-2 and CTX-M-9 genes (Table 3). In most instance, the IS*CR1*-$bla_{CTX\text{-}M\text{-}2}$ is located between a typical class 1 integron and a fuse type of *orf3Δ* and *qacEΔ1/sul1* (Table 3, Figure 4D). Notably, the genes harbored by class 1 integrons in their variable regions, such as $bla_{OXA\text{-}2}$, *aacA4*, *cmlA* and *dfr*, are also associated with bacterial resistance to β-lactam, aminoglycoside, chloramphenicol and trimethoprim, respectively.

Molecular epidemiological study performed in Argentine during 1993–2000 showed that class 1 integron-IS*CR1* complex was adjacent to $bla_{CTX\text{-}M\text{-}2}$ in all the CTX-M-2 producers ($n = 35$), including *Acinetobacter* spp., *E. cloacae*, *E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, S. enterica* and *S. marcescens*, while only 1.5% of the $bla_{CTX\text{-}M\text{-}2}$-negative isolates ($n = 65$) harbored IS*CR1* (Arduino et al., 2003). These data strongly implicate the association of IS*CR1* with the emergence and dissemination of $bla_{CTX\text{-}M\text{-}2}$ gene. In addition, IS*CR1* is also related to $bla_{CTX\text{-}M\text{-}59,\ -74,\ -75}$ (members of CTX-M-2 cluster) and $bla_{CTX\text{-}M\text{-}1,\ -9,\ -14}$ (Table 3).

Other IS and phage-related sequences

Besides IS*Ecp1*, IS*903* and IS*CR1* described above, IS*1*, IS*5*, IS*10,* IS*26*, IS*50A,* IS*1294*, IS*1326,* IS*3000*, IS*4321* and IS*6100* were also found to be adjacent to $bla_{CTX\text{-}M}$ genes (Table 3). In some cases, several IS elements co-existed in a gene complex, for example, *intI1-dfrA12-orfF-aadA2-qacEΔ1-sul1*-IS*CR1*-IS*6100*-IS*CR1-ISEcp1Δ-*$bla_{CTX\text{-}M\text{-}14}$-IS*903D* (Bae et al., 2008). Such heterogeneity may be explained by a continuously recombinatorial exchange of gene cassettes, denoting the sophisticated genetic rearrangement strategies that organisms acquire and dispense resistance genes.

A 12.2-kb DNA fragment containing $bla_{CTX\text{-}M\text{-}10}$ gene in plasmid pRYCE21 was cloned from *K. pneumoniae*, and further detected in other bacterial species including *E. coli, E. cloacae* and *E. gergoviae. A*nalysis of the sequence showed a phage-related 3.5-kb element immediately upstream of the $bla_{CTX\text{-}M\text{-}10}$ gene cassettes. This phage-related fragment corresponds to four *orfs*, of which *orf2*, *orf3* and *orf4* display homology to the genes of conserved phage tail proteins (Oliver et al., 2005). Although there is a limited report on phage-related CTX-M genes, this finding indicates that phages may also function as a tool for $bla_{CTX\text{-}M}$-associated genetic elements to become transferable.

Plasmids

The movement of IS-mobilized genes between chromosomes and plasmids greatly increase the opportunity a resistance determinant becomes transferable. Particularly, conjugative plasmid is one of the most important mechanisms for intra-species, inter-species and inter-genus gene transfers.

Plasmids are usually classified on their incompatibility (Inc), defined as the inability of two plasmids to be propagated stably in the same bacterial strain; thus, only compatible plasmids can be rescued in transconjugants (Novick et al., 1976). At least 29 Inc groups have been recognized among plasmids of enteric bacteria, including IncFI, IncFII, IncFIII, IncFIV, IncFV, IncFVI, IncI1, IncI2, IncIy, IncHI1, IncHI2, IncHI3, IncA/C, IncB, IncD, IncJ, IncK, IncL/M, IncN, IncO, IncP, IncS, IncT, IncU, IncV, IncW, IncX, IncY and com9 (Novick et al., 1976; Couturier et al., 1988). The IncFII, IncA/C, IncL/M, and IncI1 plasmids show the highest occurrence among the typed resistance plasmids (Carattoli, 2009).

Molecular epidemiological studies have revealed a close and significant linkage of $bla_{CTX\text{-}M}$ genes to plasmids, mainly belonged to IncF, IncI, IncN, IncHI2, IncL/M and IncK groups (Table 4). The IncF group (FIA, FIB and FII) is the most prevalent in transmitting $bla_{CTX\text{-}M\text{-}15}$ genes, while IncF, IncK and IncI1 are closely related to the widespread of $bla_{CTX\text{-}M\text{-}14}$ genes. In addition, the $bla_{CTX\text{-}M\text{-}1}$ gene is dominantly harbored by IncN and IncI1, $bla_{CTX\text{-}M\text{-}3}$ gene by IncL/M and IncI1, and $bla_{CTX\text{-}M\text{-}9}$ gene by IncHI2.

Unlike the plasmids with broad host range, such as IncP, IncA/C and IncQ, IncF plasmids are limited by host range to the genera of Enterobacteriaceae (Toukdarian,

Table 4. Plasmids associated with the spread of CTX-M genes.

CTX-M gene (No. of isolates)	Inc group (No. of isolates)	Rate*	Resource	Reference
$bla_{CTX-M-1}$ (119)	N (119)	100%	*E. coli* from bovine on a dairy farm with high consumption of cephalosporins in Czech Republic, 2008	Dolejska et al., 2011
$bla_{CTX-M-1}$ (10)	I1 (10)	100%	*S. enterica* from poultry and humans in France, 2003–08	Cloeckaert et al., 2010
$bla_{CTX-M-3}$ (14)	L/M (13)	92.9%	Enterobacteriaceae from Bulgaria, Poland and France	Galimand et al., 2005
$bla_{CTX-M-9}$ (41)	HI2 (24)	58.5%	Enterobacteriaceae from a university hospital in Spain, 1996–03	Novais et al., 2006
	P1-α (10)	24.4%		
	FIB (4)	9.8%		
	HI2, F1 (2)	4.9%		
	I1 (1)	2.4%		
$bla_{CTX-M-14}$ (40)	K (27)	67.5%	*E. coli* from patients and healthy volunteers in Spain, 2000–05	Valverde et al., 2009
	I1 (11)	27.5%		
	HI2 (2)	5%		
$bla_{CTX-M-14}$ (25)	F (8)	32%	*E. coli* from 20 hospitals in 15 provinces in China, 2007–08	Cao et al., 2011
	I1 (5)	20%		
	F, I1 (3)	12%		
	N (1)	4%		
	Q (1)	4%		
$bla_{CTX-M-14}$ (23)	FII (13)	56.5%	*E. coli* from outpatients in Hong Kong, 2002–04	Ho et al., 2011
	I1-Iγ (4)	17.4%		
	FIB (2)	8.7%		
	FII, I1-Iγ (1)	4.3%		
	K (1)	4.3%		
$bla_{CTX-M-15}$ (18)	FII (17)	94.4%	*E. coli* from a hospital in Turkey, 2002–04	Gonullu et al., 2008
	FI (1)	5.6%		
$bla_{CTX-M-15}$ (36)	FI (36)	100%	*E. coli* from a university hospital in Germany, 2006–07	Mshana et al., 2009
$bla_{CTX-M-15}$ (55)	FIIA (41)	74.5%	*K. pneumoniae* from patients in 9 Asian countries, 2008–09	Lee et al., 2011
	A/C (3)	5.5%		
	FIIA, A/C (4)	7.3%		
$bla_{CTX-M-1}$ (11)	N (8)	72.7%	*E. coli* from different areas in France, 1997–02	Marcadé et al., 2009
	I1 (3)	27.3%		
$bla_{CTX-M-14}$ (15)	F (9)	60%		
	K (2)	13.3%		
$bla_{CTX-M-15}$ (19)	F (12)	63.2%		
	I1 (1)	5.3%		
	L/M (1)	5.3%		
	N (1)	5.3%		
$bla_{CTX-M-1}$ (7)	N (5)	71.4%	*E. coli* and *K. pneumoniae* from 11 hospitals in Spain, 2004	Diestra et al., 2009
	FII (2)	28.6%		
$bla_{CTX-M-9}$ (14)	I1 (4)	28.6%		
	I1, P (3)	21.4%		
	HI2 (4)	28.6%		
	FIB (2)	14.3%		
$bla_{CTX-M-14}$ (13)	K (12)	92.3%		
$bla_{CTX-M-15}$ (4)	F (4)	100%		
$bla_{CTX-M-32}$ (3)	N (3)	100%		
$bla_{CTX-M-2}$ (16)	A/C (11)	68.8%	*E. coli* from a survey among 3193 healthy children in Peru & Bolivia, 2005	Pallecchi et al., 2007
	FVII (1)	6.3%		
	I1 (1)	6.3%		
$bla_{CTX-M-14}$ (8)	I1 (6)	75%		
$bla_{CTX-M-3}$ (49)	I1 (36)	73.5%	*E. coli* from faeces of residents in16 nursing homes in the UK, 2004–06	Dhanji et al., 2011a
	FI (8)	16.3%		
	Y (3)	6.1%		
	N (2)	4.1%		
$bla_{CTX-M-15}$ (11)	FI (11)	100%		

*Rate = (No. in the 2nd column/No. in the 1st column) × 100%.

2004), footnoting the high prevalence and widespread of CTX-M genes in Enterobacteriaceae, but not in *Acinetobacter* and *Pseudomonas*.

Various resistance genes frequently co-exist on a plasmid, facilitating the dissemination of resistance determinants and the survival of bacteria under the pressure of various antibiotics. For example, plasmid pEK499 (a fusion of type FII and FIA replicons) identified in a UK variant of the internationally prevalent *E. coli* O25:H4-ST131 lineage is confirmed to harbor 10 resistance genes, conferring resistance to seven antibiotic classes, β-lactams ($bla_{\text{CTX-M-15,}}$ $bla_{\text{OXA-1,}}$ $bla_{\text{TEM-1}}$), aminoglycoside (*aac6'-Ib-cr, aadA5*), macrolides (*mph(A)*), chloramphenicol (*catB4*), tetracycline (*tet(A)*), trimethoprim (*dfrA7*) and sulfonamide (*sul1*) (Woodford et al., 2009).

Secondary chromosomal integration

Most of the $bla_{\text{CTX-M}}$ genes are harbored by plasmids and the secondary chromosomal insertions of $bla_{\text{CTX-M}}$ genes are also confirmed, particularly in *P. mirabilis*. Of 25 clinical isolates of CTX-M-producing *P. mirabilis* collected in Korea, 21 strains harbored $bla_{\text{CTX-Ms}}$ on their chromosomes (Song et al., 2011). The genes of $bla_{\text{CTX-M-25}}$ and $_{\text{-41}}$ were also found on the chromosomes of *P. mirabilis* in Israel (Navon-Venezia et al., 2008).

In addition, chromosomal integration of $bla_{\text{CTX-M-15}}$ gene was reported in *E. coli*, *K. pneumoniae* and *S. enterica* (Coque et al., 2008; Coelho *et al., 2010*; Fabre et al., 2009). Chromosomal $bla_{\text{CTX-M-9}}$ was observed in one strain of 30 *E. coli* isolates collected in Barcelona during 1996–1999 (García et al., 2005).

Conclusion

Plasmid-mediated CTX-M enzymes are the most prevalent ESBLs, particularly in *E. coli, K. pneumoniae* and *P. mirobilis.* At least 109 members in CTX-M family are identified and can be divided into seven clusters based on their phylogeny. CTX-M-15 and CTX-M-14 are the most dominant variants in the family, followed by CTX-M-2, CTX-M-3 and CTX-M-1.

The CTX-M genes can be traced back to the chromosome-encoded cefotaximas genes in *Kluyvera* spp., strongly indicating that the plasmid-mediated CTX-M enzymes are originally from *Kluyvera*. Multiple genetic elements, especially IS*Ecp1* and IS*CR1*, are involved in the mobilization of $bla_{\text{CTX-M}}$ genes from the chromosomes to plasmids. Conjugative plasmids are responsible for the transfer of the $bla_{\text{CTX-M}}$ genes to new hosts, while the properties of plasmid incompatibility and host range are closely associated with the high prevalence and widespread of the CTX-M genes in Enterobacteriaceae, but not in *Acinetobacter* and *Pseudomonas*.

Declaration of interest

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