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Novel Type of Staphylococcal Cassette Chromosome *mec* in a Methicillin-Resistant *Staphylococcus aureus* Strain Isolated in Sweden▽

Carolina Berglund,[1,2]* Teruyo Ito,[2,3] Megumi Ikeda,[2] Xiao Xue Ma,[2] Bo Söderquist,[1,4] and Keiichi Hiramatsu[2,3]

Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden[1]; Department of Infection Control Science, Juntendo University, Postgraduate School, Tokyo, Japan[2]; Department of Bacteriology, Juntendo University, School of Medicine, Tokyo, Japan[3]; and Department of Infectious Diseases, Örebro University Hospital, Örebro, Sweden[4]

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We identified a novel type of staphylococcal cassette chromosome *mec* (SCC*mec*) element carried by methicillin-resistant *Staphylococcus aureus* (MRSA) strain JCSC6082 isolated in Sweden. The SCC*mec* element was demarcated by characteristic nucleotide sequences at both ends and was integrated at the 3′ end of *orfX*. The element carried a novel combination of a type 5 *ccr* gene complex and class C1 *mec* gene complex. The J regions of the element were homologous to those of the SCC*mercury* element of *S. aureus* strain 85/2082, with nucleotide identity greater than 99%. However, the novel SCC*mec* element from JCSC6082 did not carry the *mer* operon nor Tn*554*, suggesting that evolution to SCC*mec* could have been from a common ancestor by acquisition of the class C1 *mec* gene complex. The novel SCC*mec* element from JCSC6082 was flanked by a novel SCC-like chromosome cassette (CC6082), which was demarcated by two direct repeats and could be excised from the chromosome independently of the SCC*mec* element. Our data suggest that novel SCC*mec* elements can be generated on the staphylococcal chromosome through the recombination between extant SCC elements and *mec* gene complexes.

Since the staphylococcal cassette chromosome *mec* (SCC*mec*) was first described as the carrier of the *mecA* gene (9, 13), at least six structural variants have been identified, namely types I, II, III, IV, V, and VI SCC*mec*. They are typically composed of two essential components, the *mec* gene complex (*mec*) and the cassette chromosome recombinase (*ccr*) gene complex (8, 10, 16, 18). In addition, they are integrated at a specific integration site sequence (ISS) of *orfX* on the staphylococcal chromosome (11).

Three major classes of *mec* gene complex have been identified in methicillin-resistant *Staphylococcus aureus* (MRSA) strains. The prototypic *mec* (class A) is composed of *mecA*, its regulatory genes, *mecR1* and *mecI*, and insertion sequence IS*431* downstream of *mecA*. Certain variants of the *mec* gene complex contain insertion of either IS*1272* (class B) or IS*431* (class C1 and C2) at the 3′ portion of *mecR1*. The *ccr* genes are responsible for the chromosomal integration and excision of the SCC*mec*, and there are at least five types of the *ccr* gene complex. The first four types contain two site-specific recombinase genes, *ccrA* and *ccrB*, with surrounding open reading frames (ORFs), while the fifth type contains one site-specific recombinase gene, *ccrC*, with surrounding ORFs. The classification of SCC*mec* is based upon the combination of the *mec* class and the *ccr* type (11).

Recently, SCC*mec* elements with more complex structures have been reported, which contain multiple *ccr* gene complexes (7, 19). In addition, mobile genetic elements that did not themselves carry *ccr* gene complexes have been found integrated downstream of *orfX*, such as the 31-kb arginine catabolic mobile element (ACME). Mobilization of these elements has been suggested to occur by the activity of the recombinases encoded by the *ccrAB* genes located on the adjacent SCC*mec* (4, 5).

In Sweden, the prevalence of MRSA is still below 1%, and MRSA isolates are genetically diverse (1). At present, the community-acquired MRSA strains are more prevalent than the nosocomial MRSA strains (Swedish Institute for Infectious Disease Control; www.smittskyddsinstitutet.se) (1). In addition, several MRSA isolates that were not carrying extant types of SCC*mec* elements have been identified in various regions of Sweden (C. Berglund, unpublished data).

In this work, we describe a novel type of SCC*mec* element from an MRSA strain isolated in Sweden.

MATERIALS AND METHODS

MRSA strain JCSC6082 (p5747/2002) (2) was isolated in 2002 from a subcutaneous abdominal wall abscess of a previously healthy 42-year-old woman. The infection was designated as community acquired; however, the patient had undergone abdominal surgery due to salpingitis 24 years earlier, and in the present abscess cavity the remnants of a suture were found.

The MRSA strain belonged to the epidemic and widespread sequence type 5 (ST5) and clonal complex 5 (CC), and carried neither the genes for Panton-Valentine leukocidin (PVL) nor exfoliative toxin A or B. The results of susceptibility testing using the agar dilution method according to Clinical and Laboratory Standards Institute guidelines showed that it was resistant to oxacillin, tetracycline, and erythromycin, with MICs of 48, 32, and 8 mg/liter, respectively (1).

Construction of fosmid libraries. Genomic DNA of JCSC6082 was prepared using ISOPLANT (Nippon Gene Co., Tokyo, Japan) and was subsequently used as insert DNA in the fosmid library. The fosmid libraries were created using the

* Corresponding author. Mailing address: Department of Clinical Microbiology, Örebro University Hospital, SE-701 85 Örebro, Sweden. Phone: 46 19 602 15 20. Fax: 46 19 12 74 16. E-mail: carolina.berglund@orebroll.se.

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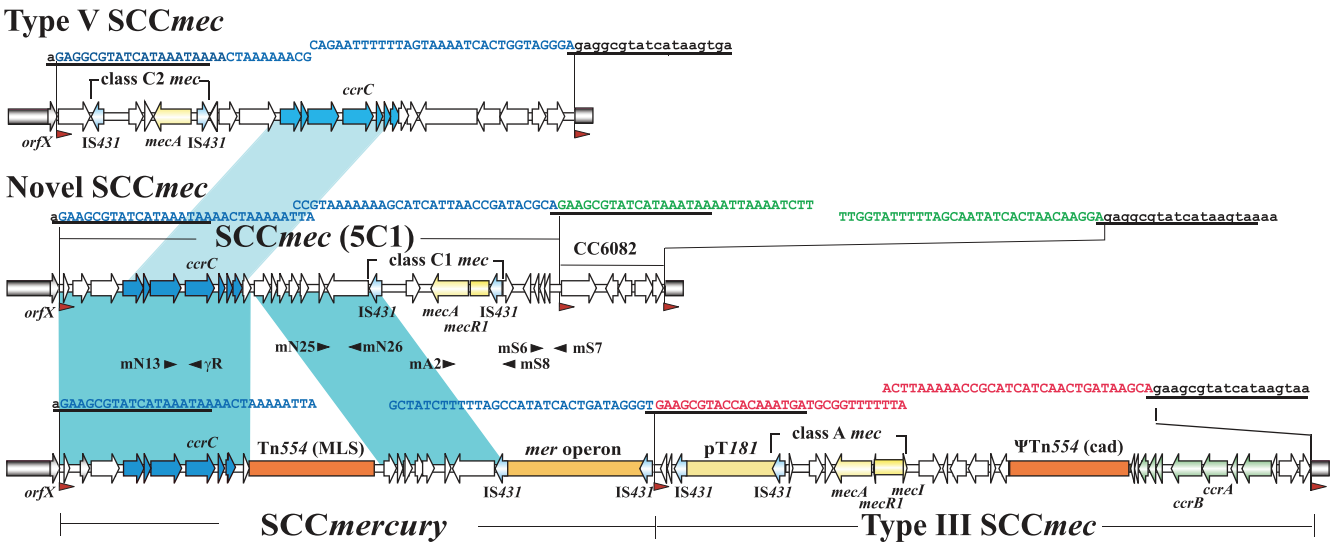

FIG. 1. Structural comparisons of the novel SCC*mec* element and a chromosome cassette identified from JCSC6082 isolated in Sweden, SCC*mercury*, and type III SCC*mec* carried by 85/2082 and the type V SCC*mec* carried by WIS. The structures of these elements are illustrated based on the nucleotide sequence deposited in the DDBJ/EMBL/GenBank database under accession no. AB373032, AB037671, and AB121219. Conserved regions are indicated in blue: more than 99% homology is in dark blue and 19.1% to 93.6% homology is in light blue. Red arrowheads indicate integration site sequence of SCC*mec* (ISS) that comprises DR sequences, and black arrowheads indicate the positions and directions of primers used for detection of the novel type of SCC*mec*.

CopyControl fosmid library production kit (Epicentre Biotechnologies, Madison, WI) according to the manufacturer's recommendation. The clones were screened by PCR with primer pairs to identify *orfX*, *mecA*, and the chromosomal region located downstream of SCC*mec*.

DNA manipulations. PCRs for screening of fosmid clones and identification of specific genes, long-range PCR for amplification of DNA fragments covering the entire SCC*mec*, and nested PCR experiments for identification of precise excision of the novel SCC*mec*, SCC*mec* and CC6082 together, and CC6082 alone were carried out as described previously (9). The sequences and locations of the PCR primer pairs used to amplify DNA fragments covering the entire SCC*mec* region are shown in Fig. 1 and Table 1.

Nucleotide sequencing was performed as described previously (15), and the sequences were analyzed and assembled using the BioEdit sequence alignment editor.

Analysis of ORFs. ORFs longer than 100 bp were identified with the GenomeGambler v.1.5 software Japan (Marine Science and Technology Center and Xanagen, Inc., Kawasaki, Japan) and were compared with sequence databases at the National Center for Biotechnology Information with the basic local alignment search tool BLAST (National Library of Medicine, Bethesda, MD) for annotation and prediction of functions. The *ccr* genes were investigated using the ClustalW (1.83) multiple alignment program available at http://www.staphylococcus.net.

Nucleotide sequence accession number. The nucleotide sequence reported in this paper has been deposited in the DDBJ/EMBL/GenBank database under accession no. AB373032.

RESULTS AND DISCUSSION

Identification of a new member of the SCC*mec* family. We identified an MRSA strain, JCSC6082, which carried an unknown type of SCC*mec* element according to PCR detection of the extant types of SCC*mec* (10, 14, 17). The MRSA strain JCSC6082 was considered to be community acquired, although the patient had a history of hospitalization 24 years previously. It may be that the patient had acquired the MRSA strain recently and that it was a true community-acquired infection. However, the specific location of the infection in addition to a difficult-to-treat infection 24 years earlier makes it tempting to consider the possibility of a dormant infection or at least persistence of MRSA, adherent to foreign material (e.g., a suture)

TABLE 1. Oligonucleotide primers employed for PCR detection of the novel type of SCC*mec*

Primer for identification of type 5C1 SCC*mec*	Nucleotide sequence (5′→3′)	Nucleotide position[a]	Expected size of product (kbp)
mN13	ACAACTTGCGAATTATGACGA	6132–6152	1.9
γR	CCTTTATAGACTGGATTATTCAAAATAT	8071–8044	
mN25	TCCGCTTGTACAATTAATATTGAGCGT	14310–14336	2.5
mN26	ACGAAACGACCATGTCTGCTCTAACA	16848–16823	
mA2	AACGTTGTAACCACCCCAAGA	21149–21169	3.5
mS8	CAAAATTGAGCGGAATCGTT	24693–24674	
mS6	TGTTTTCGAGTATCGCTTTGA	26080–26100	1.8
mS7	GAAAGTGCGTTTATATCTGCAAAA	27870–27847	

[a] Nucleotide positions based on the nucleotide sequence in the DDBJ/EMBL/GenBank database (accession no. AB373032) are indicated.

TABLE 2. ORFs of the novel SCC*mec* and chromosome cassette CC6082 in JCSC6082

ORF	Value for coding sequence[a]			Gene	Description of product	Data indicating homology to ORF in SCC*mec* or SCC*mercury* of			
						85/2082		WIS (JCSC3624)	
	Location[b]	Gene size (bp)	Length (aa)			% Identity[c]	Corresponding ORF(s) (size in bp)	% Identity[c]	Corresponding ORF(s) (size in bp)
SCC*mec*									
Sw01	135–614	480	159	*orfX*	Conserved hypothetical protein OrfX	99.4	CZ080 (480)	99.4	V001 (480)
Sw02	860–1165	306	101		Hypothetical protein	100	CZ078 (306)		
Sw03	1363–2226	864	287		Hypothetical protein	100	CZ077 (870)		
Sw04	2334–3809	1476	491		Hypothetical protein	100	CZ076 (1500)	19.1	V011 (1989)
Sw05	4036–5136	1101	366		Hypothetical protein	100	CZ075 (1101)	77.1	V012 (1110)
Sw06	5129–5500	372	123		Hypothetical protein	100	CZ074 (372)	84.4	V013 (369)
Sw07	5497–7140	1644	547		Hypothetical protein	100	CZ073 (1644)	82.1	V014 (1644)
Sw08	7365–9041	1677	558	*ccrC*	Cassette chromosome recombinase C	99.9	CZ072 (1544)	93.6	V015 (1623)
Sw09	9144–9485	342	113		Hypothetical protein	100	CZ070 (342)	48.6	V016 (339)
Sw10	9581–9892	312	103		Hypothetical protein	100	CZ069 (312)	49.1	V017 (327)
Sw11	9908–10414	507	168		Hypothetical protein	100	CZ068 (507)	67.1	V019 (504)
Sw12	10435–10881	447	148	*radC*	DNA repair protein RadC	100	CZ067 (318)		
Sw13	11051–11923	873	290		Hypothetical protein	100	CZ059 (873)		
Sw14	11962–12270	309	102		Hypothetical protein	100	CZ058 (309)		
Sw15	12286–12774	489	162		Hypothetical protein	100	CZ057 (489)		
Sw16	12909–13436	528	175		Hypothetical protein	98.9	CZ056 (528)		
Sw17	13498–13941	444	147		Membrane protein homologue	99.3	CZ055 (489)		
Sw18	14505–14828	324	107		Hypothetical protein	100	CZ053 (324)	98.1	V020 (567)
Sw19	(17134–14906)	2229	742	*hsdR*	Truncated type I restriction modification system endonuclease homologue	100	Z059 (2244)	98.2	V021 (3120)
Sw20	(17855–17181)	675	224	*tnp*	Transposase of IS*431*	100, 99.6, 99.1, 99.1	Z035 (675), Z041 (675), Z046 (675), Z058 (675)	99.1, 97.8	V003 (675), V008 (675)
Sw21	19157–19900	744	247		Glycerophoshoryl diester phophodiesterase	99.6	CZ030 (744)	99.6	V004 (744)
Sw22	19997–20425	429	142		MaoC domain protein homologue	100	CZ029 (429)	100	V005 (429)
Sw23	(22477–20471)	2007	668	*mecA*	Penicillin binding protein, PBP2′	99.8	Z030 (2007)	99.7	V006 (2007)
Sw24	22577–23575	999	332	*mecR1*	Truncated signal transducer protein MecR1	86.4	CZ028 (114)	80.9	V007 (111)
Sw25	(24277–23603)	675	224	*tnp*	Transposase of IS*431*	100, 100, 99.1, 98.6	Z046 (675), Z058 (675), Z035 (674), Z041 (675)	98.2, 97.8	V003 (675), V008 (675)
Sw26	24321–24875	555	184		Hypothetical protein, similar to glutathione synthase				
Sw27	(25834–25403)	432	143	*tnp*	Truncated transposase IS*1296* homologue				
Sw28	(26236–25973)	264	87	*tnp*	Truncated transposase IS*1296* homologue				
Sw29	(26565–26287)	279	92	*tnp*	Truncated transposase homologue				
Sw30	(26830–26534)	297	98	*tnp*	Truncated transposase IS*3*/IS*911* homologue				
CC6082									
Sw31	27446–29311	1866	621		Hypothetical protein similar to reverse transcriptase				
Sw32	(30451–29804)	648	125		Membrane protein homologue				
Sw33	(31197–30472)	726	241	*hsdM*	Type I restriction modification system DNA methylase			87.9	V023 (1515)
Sw34	31369–32343	975	324		Hypothetical protein				
Sw35	32312–32884	573	190		Hypothetical protein				

[a] Nucleotide positions are determined based on nucleotide sequences deposited under DDBJ/EMBL/GenBank accession no. AB373032, AB037671, and AB121219, and they correspond to the 5′→3′ direction.
[b] Parentheses indicate complement.
[c] Identity of the amino acid sequence to each ORF.

and embedded in biofilm, for more than 20 years until it was reidentified by the presentation of the abscess in 2002.

The structure of the SCC*mec* element from JCSC6082 was further investigated by construction of fosmid libraries and determination of the entire nucleotide sequence. The overall structure of the 33,261-bp region encompassing the SCC*mec* element from JCSC6082 is illustrated in Fig. 1, and the ORFs carried by this region are listed in Table 2.

The sequenced region included three ISSs comprising directly repeated (DR) sequences typical of SCC-like cassettes,

suggesting that JCSC6082 carried two SCC-like elements, including an SCC*mec* element and an SCC-like chromosome cassette lacking *ccr* recombinase genes (Fig. 1).

We then conducted nested PCR experiments in order to investigate whether these elements could be excised from the chromosome independently. DNA fragments, indicating that these elements have been excised from the chromosome, were successfully amplified by PCR, and nucleotide sequencing confirmed that excision had occurred precisely at the DR sites (data not shown).

The SCC*mec* element was 26,733 bp in size, i.e., as small as type IV and V SCC*mec* elements that are prevalent among community-acquired MRSA (3). It carried a class C1 *mec* complex, which was different from class C2 *mec* since the orientation of the IS*431* inserted downstream of *mecA* and disrupting the *mecR1* gene was opposite to that found in class C2 *mec*. The class C1 *mec* complex was first identified in methicillin-resistant *Staphylococcus haemolyticus* strain SH631 (12). To our knowledge, this is the first description of a class C1 *mec* complex in an MRSA strain. Interestingly, in the SCC*mec* element from JCSC6082 the deletion of Δ*mecR1* was not the same as that found in the previously described C1 *mec* complex (12).

The SCC*mec* element from JCSC6082 carried a type 5 *ccr* gene complex, in common with the type V SCC*mec* and SCC*mercury* elements (8, 10). In this case, however, *ccrC* was 1,677 bp in size: i.e., larger by 133 bp than the *ccrC* gene carried by SCC*mercury* in 85/2082 (accession no. AB037671). Since the region of SCC*mercury* corresponding to the entire 1,677 bp of the *ccrC* gene had a nucleotide identity of 99.9%, it was considered that a premature stop codon had been introduced in the *ccrC* of SCC*mercury*. The *ccrC* genes appear to be more diversified in comparison with *ccrA* and *ccrB*, since several variants of this recombinase have been described (6, 19).

Consequently, we regarded the region between the first ISS and the second ISS in JCSC6082 as a novel type of SCC*mec* element, since it carried a type 5 *ccr* gene complex (*ccrC*) and a class C1 *mec* gene complex. No additional resistance gene other than the *mecA* was identified in the element.

Interestingly, the nucleotide sequence of this novel SCC*mec* element had 99% homology with the SCC*mercury* element of 85/2082 (11) but in contrast carried the *mec* complex instead of the *mer* operon and Tn*554*. SCC*mercury* has been reported to be similar to SCC*cap1* carrying a type 1 capsule operon in the same manner (11). These three SCC elements might have been generated in a similar way, with incorporation of mercury resistance operon and Tn*554* to generate SCC*mercury*, a capsule gene cluster to make SCC*cap-1*, or the *mec* gene complex to create SCC*mec*. We also suspect that the class C1 *mec* complex present in this novel SCC*mec* may be a composite transposon itself, since it is demarcated by two copies of IS*431*, which further strengthens the hypothesis that an SCC element might evolve into an SCC*mec* element by acquiring a *mec* gene complex. However, so far, there is no evidence of transposition ability of the *mec* gene complex.

Characteristics of chromosome cassette CC6082. The SCC-like chromosome cassette CC6082 was 5,617 bp in length and was located between the second and third ISSs, downstream of the SCC*mec* element. CC6082 carried an *hsdM* gene encoding a type I restriction modification system DNA methylase, a gene encoding a membrane protein homologue, a gene encoding a hypothetical protein similar to a reverse transcriptase, and two additional ORFs of unknown function. Neither *ccr* genes nor a *mec* complex was identified in this region. This region may be a remnant of a previously active SCC element.

Naming of novel SCC elements. The SCC*mec* element should be defined by a specific combination of the class of *mec* and *ccr* gene complex, and it should be indicated in Roman numerals. We considered that atypical elements e.g., carrying two *ccr* gene complexes or non-*mecA*-carrying SCC, at first should be analyzed by determining the entire nucleotide sequences. In the case of a composite of SCC and SCC*mec*, the elements should be described separately and primarily be categorized into the type of SCC*mec* as determined by the *ccr* and *mec* carried on the element demarcated by ISS and subsequently given the Roman numeral. Here, we designated the novel SCC*mec* element in JCSC6082 carrying a type 5 *ccr* gene complex (*ccrC*) and a class C1 *mec* gene complex as type 5C1. However, we suggest that this novel SCC*mec* should receive a Roman numeral as type VII. To avoid confusion on the naming of SCC*mec* elements, we await a decision from the International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements.

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