Infection and Drug Resistance

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ORIGINAL RESEARCH

# Investigating a rare methicillin-resistant *Staphylococcus aureus* strain: first description of genome sequencing and molecular characterization of CC15-MRSA

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**Purpose:** Methicillin resistant *Staphylococcus aureus* CC15 strains (CC15-MRSA) have only been sporadically described in literature. This study was carried out to describe the genetic make-up for this rare MRSA strain.

**Methods:** Four CC15-MRSA isolates collected in Riyadh, Saudi Arabia, between 2013 and 2014 were studied. Two isolates were from clinical infection and 2 from retail meat products. Whole genome sequencing was carried out using Illumina HiSeq2500 genome analyzer.

**Results:** All the CC15-MRSA isolates had the multilocus sequence typing profile ST1535, 13–13-1–1-81-11-13, which is a single locus variant of ST15. Of the 6 contigs related to the SCC element, one comprised a recombinase gene *ccrAA*, *ccrC-PM1*, *fusC* and a helicase, another one included *mvaS*, *dru*, *mecA* and 1 had *yobV* and *Q4LAG7*. The SCC element had 5 transposase genes, namely 3 identical paralogs of tnpIS431 and 2 identical paralogs of tnpIS256. Two identical copies of a tnpIS256-based insertion element flank the *aacA-aphD* gene. Two copies of this insertion element were present with 1 located in the SCC element and another inserted into the *sasC* gene. A short 3 kb region, which lacks any bacteriophage structural genes and site-specific DNA integrase, was inserted into the *hlb* gene. The *hsdM* and the 5'-part of the *hsdS* gene are replaced by a copy of the *hsdM/hsdS* paralogs from *vSaβ* giving rise to a new chimeric paralog *of hsdS* in *vSaa*.

**Conclusion:** CC15-MRSA shows a novel SCC*mec*V/SCC*fus* composite element. Its variant of *hsdM/hsdS* probably facilitated uptake of foreign mobile genetic elements that promoted emergence of CC15-MRSA. Close surveillance is needed to monitor spread and emergence of further CC15 MRSA strains.

**Keywords:** whole genome sequencing, MRSA, MLST, clonal complex, SCC*mec*, Saudi Arabia

## Introduction

In recent years, the landscape of the molecular epidemiology of methicillin resistant *Staphylococcus aureus* (MRSA) has been characterized by the emergence and dissemination of new strains. Clonal complex 15 (CC15) is ubiquitous and widely described in the literature, but these isolates are mostly methicillin susceptible *S. aureus* (MSSA).[1] CC15-MSSA was recently identified as a predominant nasal colonizer in a report from Saudi Arabia.[2] Previously, methicillin resistant CC15 strains (CC15-MRSA) have only been sporadically described in literature.[3–5] In a large scale genotyping study of MRSA isolates, no CC15-MRSA was identified.[1] Two isolates of CC15-MRSA associated with nasal colonization have been reported in Iran and Saudi Arabia.[3,5] While whole genome sequencing data are available for CC15-MSSA, there are, to the best of our knowledge, no publications on the genomic data for the rare CC15-MRSA. Recently, we reported the first

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identification of CC15-MRSA from clinical infections and retail meat products in the Middle East.[6,7] In light of the emergence of CC15-MRSA in our setting and to provide much-needed insight into the genetic make-up of this rare MRSA clone, we have carried out whole genome sequencing of these isolates.

## Materials and methods

The human isolates were identified as part of a larger MRSA study for which ethical approval was obtained from the Institutional Review Board, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia. Patient consent was waived as the study involved use of archived isolates from specimens submitted for routine diagnostic tests and without use of patient identifiers. Four CC15-MRSA isolates collected in Riyadh, Saudi Arabia between 2013 and 2014 were studied. Two isolates (RUH-2 and RUH-71) were from patients with sepsis and wound infection, respectively, while the other 2 (RUH-98 and RUH-99) were from retail camel meat. *S. aureus* identification and confirmation of methicillin resistance was performed as previously described.[6,7] Genomic DNA was extracted using Qiagen DNA isolation kit (Qiagen, Hilden, Germany) in accordance with manufacturer's instructions. Whole genome sequencing was carried out using the Illumina HiSeq2500 genome analyzer.

Sequencing reads were assembled de-novo with SPAdes and the final assembly was done with SPAdes version 3.10.1 (http://bioinf.spbau.ru/spades).[8] Contigs shorter than 500 nt were dropped. Reads were mapped to the SPAdes contigs but also to the reference sequence (ST15-MSSA strain ST20130938, GenBank: CP012972.1[9]) with the Burrow–Wheeler aligner "bwa" using the local aligning algorithm "mem" ("bwa" version 0.7.12-r1039, https://github.com/lh3/bwa).[10] We also used "bwa-mem" to map the whole SPAdes contigs on the reference sequence (ST15-MSSA strain ST20130938, GenBank: CP012972.1). Read mappings and coverage were visually inspected with "tablet" ("tablet" version 1.14.10.21, https://ics.hutton.ac.uk/tablet/).[11] We manually scaffolded and annotated the contigs from isolate RUH-2, which cover the genomic islands of *vSaβ* and *vSaα*, a 3 kb element inserted into the *hlb* gene and the SCC element. We used the GenomeDiagram module from Biopython to draw sketches from the manually annotated sequences.[12] The reads and the SPAdes contigs were submitted to NCBI sequence database. The manually scaffolded and annotated regions were submitted to Genbank as short sequences.

## Results

For each isolate, a de-novo assembly of the genomic sequence was carried out. The assemblies comprised 73 and 71 contigs for the human isolates RUH-2 and RUH-71, respectively. Isolates RUH-98 and RUH-99 from camel meat had 72 and 66 contigs, respectively. The overall G/C content for the chromosomal contigs was 33%. All the CC15-MRSA isolates had the MLST profile 13–13-1–1-81–11-13. All of the 4 isolates sequenced carried a 30-kb plasmid harboring additional antibiotic resistance genes, namely *cadD*, *cadX*, *blaI*, *blaR*, *blaZ*, *lnuA*, *aadD*. In addition, isolate (RUH-71, from human wound infection) harbored another putative plasmidic contig encoding *tetK*. A comparison of the genomic features of the 4 CC15-MRSA isolates reported in this study (RUH-2, RUH71, RUH-98, RUH-99), with CC15-MSSA sequences in the NCBI GenBank (VCU006, MPROS1797, 08–02119, ST20130938, ST20130940, ST20130941) is given in Table S1.

The 6 contigs related to the SCC element (Figure 1) were identical in all isolates. One contig comprised a recombinase gene "*ccrAA*", *ccrC-PM1*, *fusC* and a helicase; another contig included *mvaS*, *dru*, *mecA* and 1 contig had *yobV* and *Q4LAG7* (putative protein associated with SCC*mec V/VT*, GenBank AM990992.1: 52112 to 54100) (Figure 1). The SCC element presumably comprises 5 transposase genes, namely 3 identical paralogs of tnpIS431 (size 675 nt) and 2 identical paralogs of tnpIS256 (size 1173 nt) (Figure 1). Two identical copies of a tnpIS256-based insertion element flank the bifunctional kanamycin resistance determinant *aacA-aphD*. Two copies of this insertion element were present in the genome with 1 copy located in the SCC element and another copy inserted into the *sasC* gene encoding a surface protein.

The CC15-MRSA isolates had a short 3 kb region inserted into the *hlb* gene (Figure 2). The 3 kb insertion element lacks any bacteriophage structural genes and site-specific DNA integrase. The insertion element comprised 5 genes, including *scn* (staphylococcal complement inhibitor) and *chp* (chemotaxis inhibitor), but *sak* (staphylokinase) was absent (Figure 2).

The CC15-MRSA isolates showed a variant of *hsdM/hsdS* at the major pathogenicity island *vSaα* compared with the reference CC15-MSSA genome (Figure 3). The *hsdM* and the 5'-part of the *hsdS* gene were replaced by a copy of the *hsdM/hsdS* paralogs from *vSaβ*. This gives rise to a new chimeric paralog *of hsdS* in *vSaα* (Figure 3). The chimeric *hsdS* has an intact reading frame. We can see this recombination in all of the 4 CC15-MRSA isolates. Furthermore, a *Sau3AI* restriction system is present in all of the CC15 isolates analyzed, while the type IV restriction system *SauUSI* is absent (Table S1).

## Discussion

All the CC15-MRSA isolates had the MLST profile 13–13-1–1-81–11-13, which is a single locus variant of ST15. This


**Figure 1** CC15-MRSA SCC element.

**Notes:** Six contigs related to the SCC element (MF185204 to MF185209). The first contig comprises the flanking *orfX* gene, and the last contig the flanking *dusC* gene. In between, four contigs are shown carrying genes typically found in SCC elements. Contig 2 has the fusidic acid resistance gene *fusC* and the SCC recombinase genes *ccrAA* and *ccrC*. Contig 3 comprises the *mecA* gene cluster with *mecR1* truncated by tnpIS431. Contig 5 constitutes a true insertion element, where the bifunctional kanamycin resistance determinant *aacAaphD* is flanked by two copies of tnpIS256.

**Abbreviation:** MRSA, methicillin-resistant *Staphylococcus aureus*.

MLST profile has been assigned to ST1535 (https://pubmlst.org/bigsdb?db=pubmlst_saureus_isolates&page=profiles) and comprises pta-81 instead of pta-12 in canonical ST15. This pta-81 differs from pta-12 by only 1 single-nucleotide polymorphism, which was present in all our isolates. Three of the 4 isolates assigned to ST1535 in the PUBMLST database are MSSA (https://pubmlst.org/bigsdb?db=pubmlst_saureus_isolates&page=profiles). The fourth is MRSA isolate

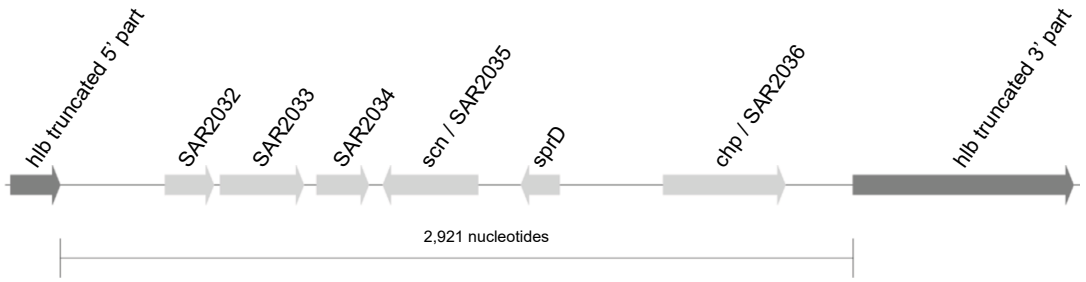


**Figure 2** The *hlb*-3kb-insert in CC15-MRSA.
**Notes:** The hemolysin beta gene (*hlb)* is interrupted by a 3 kb insertion element in CC15-MRSA genomes.
**Abbreviation:** MRSA, methicillin-resistant *Staphylococcus aureus.*

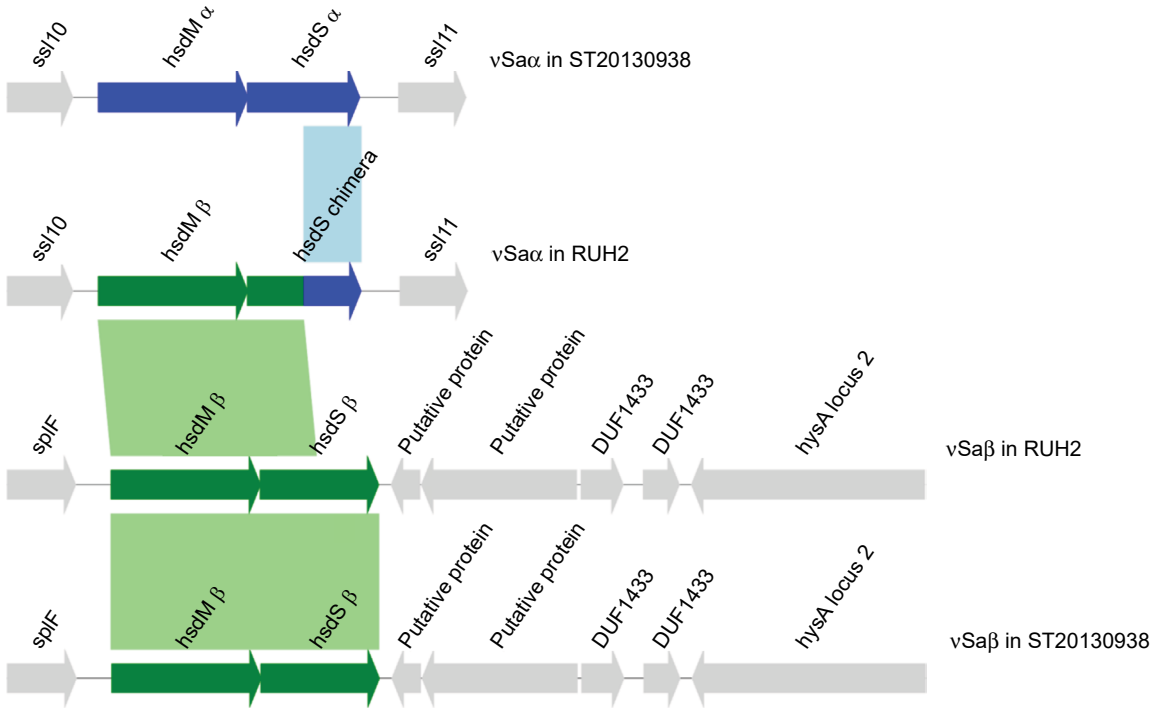


**Figure 3** *hsdM*/*hsdS* recombination in CC15-MRSA.
**Notes:** The Figure shows the contents of genomic islands *νSaα* and *νSaβ* in isolate RUH-2 (ST1535/CC15, MF185202, MF185203) and in ST20130938 (ST15/CC15, Genbank accession CP012972.1). The reference genome CP012972.1 comprises two distinct paralog of *hsdM*/*hsdS* in genomic islands alpha and beta. The mapping of the sequencing reads from isolate RUH-2 onto the reference sequence CP012972.1 reveals, that *hsdM-alpha* and the 5'-end of *hsdS- alpha* are missing in RUH-2, while the coverage of *hsdM-beta* and the 5'-end of *hsdS-beta* is doubled with respect to other chromosomal genes, indicating that this stretch of DNA is duplicated in RUH-2. We extracted the duplicated region of *νSaβ* from the SPAdes contigs and were able to link it to contigs mapping to *νSaα*.
**Abbreviation:** MRSA, methicillin-resistant *Staphylococcus aureus.*

MPROS1797, which has a similar SCC element as the CC15 MRSA in this study (https://www.ncbi.nlm.nih.gov/biosample/SAMEA2664415; Table S1). Due to the presence of repeats, the SCC element could not be scaffolded into a single contiguous sequence. The overall constellation of the SCC element as shown in Figure 1 was interpreted as a novel SCC*mec*V/SCC*fus* composite element. A very similar element has also been found by microarray hybridization in CC97-MRSA from Saudi Arabia.[13] Furthermore, reports from Saudi Arabia have described MRSA isolates from other lineages that also harbored SCC*fus* in addition to SCC*mec* IV or V elements.[6,13] Insertion elements flanked by 2 antiparallel copies of a transposase are common in bacteria, and often found in association with antibiotic resistance genes. The *sasC* gene, which is interrupted by insertion of another copy of the tnpIS256-based insertion element, has been linked with biofilm production in *S. aureus*.[14]

In *S. aureus*, an insert in the *hlb* gene is typically a prophage comprising several structural genes encoding the capsule, head and tail of the phage alongside an integrase at the terminus. It also frequently carries virulence associated genes like *sea, sep* (N315), *see, chp, sak* and *scn* in

various combinations. [15] The Riyadh CC15-MRSA isolates (as well as other published CC15 genomes) had a short 3 kb region inserted into the *hlb* gene (Figure 2). The absence of bacteriophage structural genes and site-specific DNA integrase suggests that it is no longer mobile but blocking the *hlb* insertion site. This insertion element seems to be a remnant of a bacteriophage as it is homologous to the terminus of the *hlb* converting phage in MRSA252 (Genbank accession BX571856.1, genes SAR2032 to SAR2036). In MRSA252, the *hlb* converting phage has a size of about 44 kb. However, we did not find any resemblance between the putative SCC elements in our CC15-MRSA isolates and the SCC element in MRSA252. MRSA252 has a full *mec* gene cluster comprising *mecA/mecR1/mecI/mecR2*, while the *mec* cluster is truncated in *mecR1* in the CC15-MRSA isolates. MRSA252 has cassette recombinase *ccrA-2/ccrB-2*, while we find *ccrC* in the CC15-MRSA isolates. The *sak* gene is associated with tissue invasion.[16,17] Its absence could be the reason why most CC15 isolates are associated with carriage rather than invasive infection.

Two distinct copies of the *hsdM* and *hsdS* genes are present in most genomes of *S. aureus*. These genes encode components of a type I restriction-modification (R-M) system (*hsdM* encodes a DNA methylase, *hsdS* encodes the specificity determinate). One pair of *hsdM/hsdS* is typically located in the genomic island *vSaα* between the superantigen-like genes *ssl10* and *ssl11*. A second pair of *hsdM/hsdS* genes resides in genomic island *vSaβ*. The CC15-MRSA isolates showed a different variant of *hsdM/hsdS* at the major pathogenicity island *vSaα* compared with the reference CC15-MSSA genome. This has arisen presumably due to intrachromosomal recombination, resulting in a repertoire of *hsdM/hsdS* restriction enzymes that deviate from the CC15 parent. This might have played a role in acquiring an SCC element as bacteria use the type I R-M system to control uptake of foreign DNA. In the type I R-M system, the *hsdM/hsdS* gene products are required in this process.[18] Usually, the composition of the genomic island *vSaα* and *vSaβ* is highly conserved within clonal complexes. It has been shown that the type I R-M system has facilitated the evolution of distinct *S. aureus* lineages and controls the horizontal transfer of mobile genetic elements.[18] The *Sau3A* is a type II system that digests DNA at GATC sites and that was first described by Seeber *et al.* [19] Interestingly, *Sau3AI* is present in all CC15 isolates, while *SauUSI* is absent (Table S1). This is rather unusual as *Sau3AI* is uncommon in *S. aureus*. Indeed, most *S. aureus* isolates harbor the *SauUSI* (type IV) at the DNA locus for *Sau3AI*.[19,20] Therefore, based on our findings, we suggest that changes in the *hsdM/hsdS* system and the type II R-M locus facilitated uptake of foreign mobile genetic elements, that is, of SCC*mec*/SCC*fus* by the ancestral CC15-MSSA promoting emergence of CC15-MRSA.

The limitation of our work is that the gaps between the contigs, which are presumably caused by repeated sequence elements, could not be resolved since the average fragment size of the Illumina library was only about 250 nt. Also, we were unable to determine the spa type reliably from our assembly since spa is a highly repetitive locus of a variable number of imperfect repeats. This genomic arrangement typically provokes artifacts in read assembly.

## Accession numbers

The raw read sequences have been deposited in the Sequence Read Archive database (Bioproject PRJNA386092) with accession numbers: SAMN06925301, SAMN06925302, SAMN06925303, SAMN06925304.

De-novo assembled contigs have been deposited at DDBJ/ENA/GenBank under the accession NHZU00000,000, NHZV00000000, NHZW00000000, NHZX00000000. The version described in this paper is version NHZU01000000, NHZV01000000, NHZW01000000, NHZX01000000.

The manually scaffolded sequences for *hlb*_3kb_insert, *vSaα*, *vSaβ* and the 6 SCC element contigs have been submitted to the GenBank under the following accession numbers: MF185201, MF185202, MF185203, MF185204, MF185205, MF185206, MF185207, MF185208, MF185209

## Conclusion

We provide the molecular characterization of a MRSA strain from a common lineage that until recently gave rise only to very few MRSA. The findings indicate that CC15-MRSA has a novel SCC*mecV*/SCC*fus* composite element. Changes in the *hsdM/hsdS* system and the type II R-M locus probably played role in the emergence of this rare MRSA strain. Close surveillance is needed, especially with regard to spread among humans and livestock in the Middle East and emergence of further CC15 MRSA strains.

## Acknowledgment

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## Disclosure

The authors report no conflicts of interest in this work.

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# Supplementary material

**Table S1** Comparison of CC15-MRSA and CC15-MSSA

| Isolate name | RUH-2 | RUH-71 | RUH-98 | RUH-99 | VCU006 | MPROS1797 | 08–02,119 | ST2,01,30,938 | ST2,01,30,940 | ST2,01,30,941 |
|---|---|---|---|---|---|---|---|---|---|---|
| Biosample accession | SAMN06925302 | SAMN06925301 | SAMN06925303 | SAMN06925304 | SAMN00138234 | SAMEA2664415 | SAMN04939716 | SAMN04166246 | SAMN04166494 | SAMN04166543 |
| Collection date | 07-Nov-2013 | 04-Apr-2014 | 26-Oct-2014 | 26-Oct-2014 | | | | | | |
| Collection place | Saudi Arabia: Riyadh | Saudi Arabia: Riyadh | Saudi Arabia: Riyadh | Saudi Arabia: Riyadh | | | | | | |
| Host | *Homo sapiens* | *Homo sapiens* | *Camelus dromedarius* | *Camelus dromedarius* | | | | | | |
| Host disease | Sepsis | Wound infection | | | | | | | | |
| Isolation source | | | Retail meat, neighborhood meat shop | Retail meat, neighborhood meat shop | | | | | | |
| MLST | 1535 | 1535 | 1535 | 1535 | 15 | 1535 | 582 | 15 | 15 | 15 |
| Clonal complex | 15 | 15 | 15 | 15 | 15 | 15 | CC15/CC20 chimera | 15 | 15 | 15 |
| SCC element | SCCmecV / SCCfus | SCCmecV / SCCfus | SCCmecV / SCCfus | SCCmecV / SCCfus | None | SCCmecV / SCCfus | None | None | | |
| Paired end sequencing | 2×51 | 2×51 | 2×51 | 2×51 | | 2×100 | | | | |
| Average insert size | 260 | 270 | 290 | 310 | | 260 | | | | |
| Fragments sequenced | 10461449 | 9646853 | 8433245 | 7667462 | | 2852668 | | | | |
| Total number of bases | 1067067798 | 983979006 | 860190990 | 782081124 | | 570533600 | | | | |
| Estimated coverage | 360 | 330 | 290 | 260 | | 190 | | | | |
| WGS accession | SAMN06925302 NHZU00000000 | SAMN06925301 NHZV00000000 | SAMN06925303 NHZW00000000 | SAMN06925304 NHZX00000000 | AGTZ00000000.1 | | CP0156451 | CP012972.1 | CP012979.1 | CP012978.1 |
| Number of contigs | 73 contigs | 71 contigs | 72 contigs | 66 contigs | | | | | | |
| capsular genotype (assembly) | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| agr type (assembly) | II | II | II | II | II | II | II | II | II | II |
| RIDOM spa type (assembly) | t328, uneven coverage | t328, uneven coverage | t328, uneven coverage | t328, uneven coverage | t393 | t084 | t084 | t385 | t084 | t084 |
| RIDOM spa profile | 07–23-12–34-34–12-12–23-02–12-23–02-12–23 | 07–23-12–34-34–12-12–23-02–12-23–02-12–23 | 07–23-12–34-34–12-12–23-02–12-23–02-12–23 | 07–23-12–34-34–12-12–23-02–12-23–02-12–23 | 07:23:12:34:12:12:12:23:02:12:23 | 07:23:12:34:34:12:12:23:02:12:23 | 07:23:12:34:34:12:12:23:02:12:23 | 07–23-12–34-34–12-12–23-12–23 | 07:23:12:34:34:12:12:23:02:12:23 | 07:23:12:34:34:12:12:23:02:12:23 |
| RIDOM spa repeat count | 14 | 14 | 14 | 14 | 11 | 11 | 11 | 10 | 11 | 11 |

(*Continued*)

**Table S1** Comparison of CC15-MRSA and CC15-MSSA

| Isolate name | RUH-2 | RUH-71 | RUH-98 | RUH-99 | VCU006 | MPROS1797 | 08–02,119 | ST2,01,30,938 | ST2,01,30,940 | ST2,01,30,941 |
|---|---|---|---|---|---|---|---|---|---|---|
| cna (assembly) | Missing | Missing | Missing | Missing | Missing | Missing | Missing | Missing | Missing | Missing |
| sarT/sarU (assembly) | Present | Present | Present | Present | Present | Present | Present | Present | Present | Present |
| sasC | Truncated | Truncated | Truncated | Truncated | Intact | Truncated | Intact | Intact | Intact | Intact |
| tetK | Missing | Present | Missing | Missing | Missing | Missing | Missing | Missing | Missing | Missing |
| blaZ | Present | Present | Present | Present | Present | Present | Present | Present | Present | Missing |
| fusC | Present | Present | Present | Present | Missing | Present | Missing | Missing | Missing | Missing |
| mecA | Present | Present | Present | Present | Missing | Present | Missing | Missing | Missing | Missing |
| hlb | Truncated | Truncated | Truncated | Truncated | Truncated | Truncated | Truncated | Truncated | Truncated | Truncated |
| scn | Present | Present | Present | Present | Present | Present | Present | Present | Present | Present |
| chp | Present | Present | Present | Present | Present | Present | Present | Present | Present | Present |
| 3 kb hlb insert | Present | Present | Present | Present | Present | Present | Present | Present | Present | Present |
| sau3AI | Present | Present | Present | Present | Present | Present | Present | Present | Present | Present |
| sauUSI | Missing | Missing | Missing | Missing | Missing | Missing | Missing | Missing | Missing | Missing |

**Notes:** Comparison genome properties of CC15-MRSA from this study with those of CC15-MSSA/MRSA from the NCBI GenBank.

**Abbreviations:** MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin susceptible *S. aureus*; MLST, multilocus sequence typing; WGS, whole genome shotgun.