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RESEARCH ARTICLE

# *IN SILICO* MLST, SCC*MEC* AND SPA TYPING OF HUMAN MRSA STRAINS AND DETERMINATION OF ANTIMICROBIAL RESISTANCE GENES

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## ABSTRACT

**Objective:** The incidence of MRSA still remains an important public health problem. The aim of study was to perform in silico analysis of MLST, SCC*mec*, spa type, evolutionary similarity and whole-genome sequencing (WGS) based antimicrobial susceptibility testing by using genomic data of MRSA strains isolated from human infections in different countries.

**Methods:** WGS data of 30 MRSA strains were obtained as etiological agents were download from NCBI. Phylogeny analysis with large data were performed via CSI Phylogeny online software. SCC*mec*, MLST and spa typing were performed using the software at the Center for Genomic Epidemiology. ResFinder 4.0 was used to perform WGS based antimicrobial susceptibility testing.

**Results:** After in silico analysis of 30 MRSA strains, 14 different spa types, 11 different sequence types, and 9 different SCC*mec* types were detected. T037, ST239, and SCC*mec*_type_III(3A) were the most detected spa, MLST, and SCC*mec* types respectively. WGS based antimicrobial susceptibility testing results were analyzed, 28, 27, and 26 out of 30 MRSA strains carried aminoglycoside tetracycline and fluoroquinolone resistance genes respectively.

**Conclusions:** According to our in silico analysis results, we found that similar typing profiles could be observed in the strains in different geographical locations and certain types of spa, MLST, and SCC*mec* can coexist.

**Keywords:** MRSA, MLST, SCC*mec,* in silico analysis, WGS based antimicrobial test

## INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important health problem worldwide due to its multi-drug resistance ability (1). MRSA has been one of the leading pathogens since it was identified in 1960 and is recognized as one of the primary pathogens of nosocomial and community-associated infections globally (2,3). *Staphylococcus aureus* strains carrying the *mecA* gene are defined as MRSA. The *mecA* gene resides on complex mobile genetic elements known as SCC*mec* ("staphylococcal cassette chromosome" or "staphylococcal chromosomal cassette" containing *mecA*). Apart from the *mecA* gene, SCC*mec* also contains additional genes encoding resistance to other antimicrobials such as aminoglycosides or macrolides (4). Different types of SCC*mec* have been reported in association with different infections. For example, SCC*mec* types I, II, and III are generally considered to be MRSA strains associated with healthcare infections, while

types IV and V are considered to be associated with livestock-associated infections (2,4). MRSA epidemiological studies can also be used in methods such as spa typing to investigate nosocomial and community-acquired infections. Spa typing is based on examining the polymorphism of the gene encoding protein A (spa). Protein A is one of the main virulence factors of *S. aureus* (5). It is also successfully used in multilocus sequence typing (MLST) (sequencing for the interior region of seven different housekeeping genes) to distinguish and monitor bacterial species such as MRSA that cause infectious diseases (6). Aim of our study was to perform in silico analysis of SCC*mec*, spa and MLST type, evolutionary similarity and whole genome sequencing (WGS) based antimicrobial susceptibility testing by using genomic data of 30 MRSA strains isolated from human infections in different countries.

## MATERIAL AND METHODS

Whole-genome sequencing (WGS) fasta data of 30 MRSA strains that cause infections in humans and were obtained as etiological agents were included in this study. Genomic data were downloaded from NCBI (www.ncbi.nlm.nih.gov).

**Table 1.** Descriptive information about MRSA strains included in this study

| | Strain | NCBI Accession Numbers | Host | Country |
|---|---|---|---|---|
| **1** | HU-14 | NZ_LR822061.1/LR822061.1 | Human | Argentina |
| **2** | BPH2003 | NZ_LR027878.1/LR027878.1 | Human | Australia |
| **3** | BPH2056 | NZ_LR027874.1/LR027874.1 | Human | Australia |
| **4** | BPH2869 | NZ_LR027869.1/LR027869.1 | Human | Australia |
| **5** | BPH2947 | NZ_LR130515.1/LR130515.1 | Human | Australia |
| **6** | BPH3244 | NZ_LR027877.1/LR027877.1 | Human | Australia |
| **7** | JKD6004 | NZ_CP040622.1/CP040622.1 | Human | Australia |
| **8** | BLR-DV | NZ_CP058312.1/CP058312.1 | Human | Belarus |
| **9** | Be62 | NZ_CP012013.1/CP012013.1 | Human | Brazil |
| **10** | Bmb9393 | NC_021670.1/CP005288.1 | Human | Brazil |
| **11** | Gv51 | NZ_CP012015.1/CP012015.1 | Human | Brazil |
| **12** | Gv69 | NZ_CP009681.1/CP009681.1 | Human | Brazil |
| **13** | Gv88 | NZ_CP012018.1/CP012018.1 | Human | Brazil |
| **14** | HC1335 | NZ_CP012012.1/CP012012.1 | Human | Brazil |
| **15** | HC1340 | NZ_CP012011.1/CP012011.1 | Human | Brazil |
| **16** | CMRSA-3 | NZ_CP029685.1/CP029685.1 | Human | Canada |
| **17** | CMRSA-6 | NZ_CP027788.1/CP027788.1 | Human | Canada |
| **18** | JK3137 | NZ_CP020960.1/CP020960.1 | Human | Canada |
| **19** | 5_3949 | NZ_LT992462.1/LT992462.1 | Human | Germany |
| **20** | 545 | NZ_CP022908.1/CP022908.1 | Human | Germany |
| **21** | MRSA - AMRF 5 | NZ_CP062467.1/CP062467.1 | Human | India |
| **22** | KG-18 | NZ_AP019543.1/AP019543.1 | Human | Japan |
| **23** | KG-22 | NZ_AP019545.1/AP019545.1 | Human | Japan |
| **24** | TUM9463 | NZ_AP019306.1/AP019306.1 | Human | Japan |
| **25** | aureus | NZ_CP029198.1/CP029198.1 | Human | Korea |
| **26** | NCCP14558 | NZ_CP013953.1/CP013953.1 | Human | Korea |
| **27** | V521 | NZ_CP013957.1/CP013957.1 | Human | Korea |
| **28** | P10 | NZ_CP039157.1/CP039157.1 | Human | Pakistan |
| **29** | NCTC9944 | NZ_LS483309.1/LS483309.1 | Human | UK |
| **30** | FDAARGOS_35 | NZ_CP026072.1/CP026072.1 | Human | USA |

**Table 2.** Distribution of similarity, spatype, MLST, SCCmec and WGS based antimicrobial resistance of all MRSA strains included in this study.

| Strain | Similarity (%) | SpaType | MLST | SCCmec | ResFinder |
|---|---|---|---|---|---|
| **HU-14** | 92,64 | t149 | 5 | SCCmec_type_I (1B) | gyrA, grlA, aac(6')-aph(2''), aph(3')-III, ant(6)-Ia, ant(9)-Ia, erm(A), mecA |
| **BPH2003** | 93,94 | t037 | 239 | SCCmec_type_III (3A) | gyrA, grlA, aph(3')-III, ant(6)-Ia, aac(6')-aph(2''), ant(9)-Ia, erm(A), dfrG, blaZ, mecA, tet(K), tet(M) |
| **BPH2056** | 92,99 | t037 | 239 | SCCmec_type_III (3A) | aac(6')-aph(2''), ant(6)-Ia, aph(3')-III, ant(9)-Ia, erm(A), dfrB, blaZ, mecA, tet(K), tet(M) |
| **BPH2869** | 93,77 | t037 | 239 | SCCmec_type_III (3A) | gyrA, grlA, qacA, aac(6')-aph(2''), aadD, ant(9)-Ia, erm(A), dfrB, blaZ, mecA, tet(M) |
| **BPH2947** | 93,80 | t037 | 239 | SCCmec_type_III (3A) | gyrA, grlA, grlB, aph(3')-III, aac(6')-aph(2''), ant(6)-Ia, ant(9)-Ia, ermA, dfrG, blaZ, mecA, tet(K), tet(M) |
| **BPH3244** | 93,61 | t1155 | 239 | SCCmec_type_III (3A) | gyrA, grlA, qacA, aac(6')-aph(2''), aadD, ant(9)-Ia, erm(A), dfrB, tet(M), blaZ, mecA |
| **JKD6004** | 93,71 | t1959 | 239 | SCCmec_type_III (3A) | grlA, ant(9)-Ia, erm(A), dfrB, tet(M), blaZ, mecA |
| **BLR-DV** | 93,20 | t037 | 239 | SCCmec_type_III (3A) | grlA, gyrA, ant(6)-Ia, aac(6')-aph(2''), aph(3')-III, dfrG, blaZ, mecA, rpoB, tet(M), tet(K) |
| **Be62** | 95,04 | t037 | 239 | SCCmec_type_III (3A) | grlA, gyrA, ant(6)-Ia, aac(6')-aph(2''), aph(3')-III, ant(9)-Ia, erm(A), dfrB, blaZ, mecA, rpoB, tet(M) |
| **Bmb9393** | 94,28 | t138 | 239 | SCCmec_type_III (3A) | grlA, gyrA, ant(6)-Ia, ant(9)-Ia, aac(6')-aph(2''), aph(3')-III, erm(A), dfrG, blaZ, mecA, rpoB, tet(M) |
| **Gv51** | 94,63 | t037 | 239 | SCCmec_type_III (3A) | grlA, gyrA, ant(6)-Ia, ant(9)-Ia, aac(6')-aph(2''), aph(3')-III, erm(A), dfrB, blaZ, mecA, rpoB, tet(M) |
| **Gv69** | 94,99 | t037 | 239 | SCCmec_type_III (3A) | gyrA, ant(6)-Ia, ant(9)-Ia, aac(6')-aph(2''), aph(3')-III, erm(A), dfrB, blaZ, mecA, rpoB, tet(M), ileS |
| **Gv88** | 95,01 | t037 | 239 | SCCmec_type_III (3A) | grlA, gyrA, ant(6)-Ia, ant(9)-Ia, aac(6')-aph(2''), aph(3')-III, erm(A), dfrB, blaZ, mecA, rpoB, tet(M) |
| **HC1335** | 94,50 | t138 | 239 | SCCmec_type_III (3A) | grlA, gyrA, ant(6)-Ia, ant(9)-Ia, aph(3')-III, erm(A), dfrB, blaZ, mecA, rpoB, tet(M), ileS |

**Table 2. Continue**

| | | | | | |
|---|---|---|---|---|---|
| **HC1340** | 95,08 | t037 | 239 | SCCmec_type_III (3A) | grlA, gyrA, ant(6)-Ia, ant(9)-Ia, aac(6')-aph(2''), aph(3')-III, erm(A), dfrB, blaZ, mecA, rpoB, tet(M), ileS |
| **CMRSA-3** | 93,30 | t037 | 241 | SCCmec_type_III (3A) | grlA, gyrA, ant(9)-Ia, erm(A), dfrG, blaZ, mecA, rpoB, tet(K), tet(M) |
| **CMRSA-6** | 93,96 | t037 | 239 | SCCmec_type_III (3A) | grlA, gyrA, ant(6)-Ia, ant(9)-Ia, aac(6')-aph(2''), aph(3')-III, erm(A), dfrG, blaZ, mecA, rpoB, tet(K), tet(M) |
| **JK3137** | 96,13 | t008 | 8 | SCCmec_type_IV a (2B) | grlA, gyrA, mecA |
| **5_3949** | 89,30 | t034 | 398 | SCCmec_type_Vc (5C2&5) | dfrG, blaZ, mecA, tet(K), tet(M) |
| **545** | 95,60 | t009 | 254 | SCCmec_type_IV (2B) | grlA, gyrA, ant(6)-Ia, aac(6')-aph(2''), aph(3')-III, dfrB, mecA, tet(K), tet(M) |
| **MRSA - AMRF 5** | 90,80 | t657 | 772 | SCCmec_type_V (5C2) | grlA, gyrA, ant(6)-Ia, aac(6')-aph(2''), aph(3')-III, erm(A), msr(A), mph(C), dfrG, blaZ, mecA |
| **KG-18** | 92,58 | t17639 | 5 | SCCmec_type_II (2A) | gyrA, grlA, grlB, aaD, aac(6')-aph(2''), ant(9)-Ia, erm(A), mecA, tet(M) |
| **KG-22** | 92,92 | t17639 | 5 | SCCmec_type_II (2A) | gyrA, grlA, grlB, aaD, aac(6')-aph(2''), ant(9)-Ia, erm(A), mecA, tet(M) |
| **TUM9463** | 94,54 | t539 | 2389 | SCCmec_type_II (2A) | gyrA, grlA, aac(6')-aph(2''), ant(9)-Ia, erm(A), dfrB, mecA, tet(M), |
| **aureus** | 94,10 | t002 | 5 | SCCmec_type_II (2A) | gyrA, grlA, aac(6')-aph(2''), ant(9)-Ia, erm(A), rpoB, mecA, tet(M), fusC |
| **NCCP14558** | 94,20 | t045 | 5 | SCCmec_type_II (2A) | gyrA, grlA, aadD, ant(9)-Ia, erm(A), mecA, tet(M) |
| **V521** | 94,64 | t037 | 239 | SCCmec_type_III(3A) | gyrA, grlA, aph(3')-III, ant(6)-Ia, aac(6')-aph(2''), ant(9)-Ia, erm(A), dfrG, tet(K), tet(M), blaZ, mecA |
| **P10** | 94,68 | t064 | 113 | SCCmec_type_IV c (2B) | grlA, gyrA, ant(6)-Ia, ant(9)-Ia, aac(6')-aph(2''), aph(3')-III, dfrG, blaZ, mecA, rpoB, tet(K), fusA, mupA |
| **NCTC9944** | 93,14 | t037 | 240 | SCCmec_type_III (3A) | aac(6')-aph(2''), ant(9)-Ia, erm(A), dfrG, blaZ, mecA, tet(K), tet(M) |
| **FDAARGOS_35** | 100,00 | t064 | 507 | SCCmec_type_IV d (2B) | gyrA, grlA, aadD, blaZ, mecA, tet(M) |

Descriptive information about all these MRSA strains were shown in Table 1.

All in silico analysis with fasta files were performed on Center for Genomic Epidemiology (CGE) website (https://www.genomicepidemiology.org/) with related softwares. Phylogeny, alignment or similarity analysis with large data were performed via CSI Phylogeny online software (7). SCCmec, spa and MLST typing were performed using with softwares at Center for Genomic Epidemiology (CGE) website (8,9,10). ResFinder 4.0 softwares were used to performe whole genome sequencing (WGS) based antimicrobial susceptibility testing (AST) (11).

## RESULTS

After phylogeny analysis, according to FDAARGOS_35 strain from USA, similarity percentage of strains were shown in Table 2. The evolutionary tree of these strains were shown in Figure 1. Strain 5_3949 from Germany was the most distant similarity to FDAARGOS_35 strain and similarity was found 89.3%. FDAARGOS_35 strain was found SCCmec_type_IVd(2B), on the other hand, Strain 5_3949 was found SCCmec_type_Vc(5C2&5). Strain JK3137 from Canada was found the most similar strain to FDAARGOS_35 and similarity was found 96.13%. Strain JK3137 was also found SCCmec_type_IVa(2B). Strains 545 from Germany and HC1340 from Brazil similarities were found 95.60% and 95.08% respectively. When the spa types were analysed, 14 different spa types were detected of all MRSA strains. Spa type t037 was most detected. 14 (46.6%) out of 30 MRSA strains were found spa type t037. Spa type t064, t138 and t17639 were found 2 MRSA strains. 10 MRSA strains showed unique spa types. (Table 2). When the MLST were analysed, 11 different sequence types were found via MLST. ST239 was most detected 16 (53.3%) out of 30 MRSA strains. ST5 was found the second one at 5 out of 30 strains. The other 9 nine ST were found unique strain (Table 2). When the SCCmec type were analysed, 9 different SCCmec types were found. 18 (60%) out of 30 MRSA strains were found SCCmec_type_III(3A). 5 MRSA strains were found SCCmec_type_II(2A). 7 strains showed unique SCCmec types. When the WGS based antimicrobial susceptibility testing results were analysed, 28 out of 30 MRSA strains were carrying aminoglycoside resistance gene such as aac(6')-

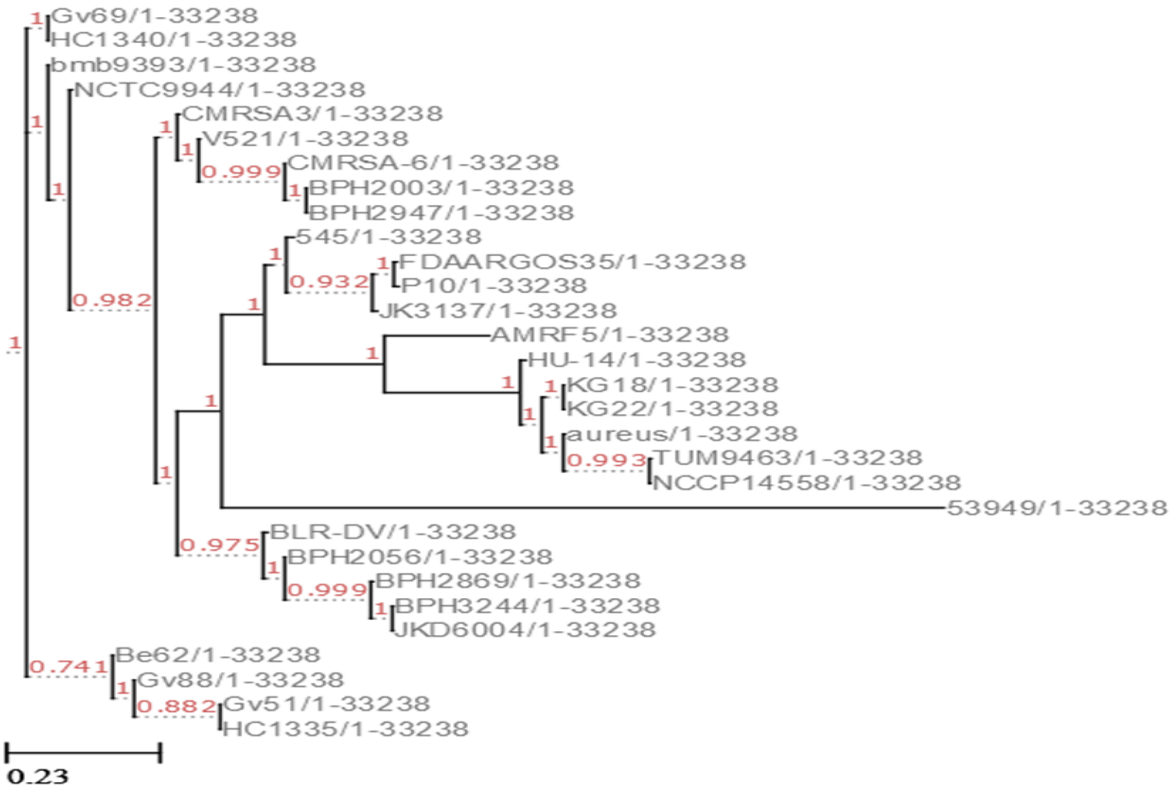


**Figure 1.** Maximum-likelihood trees for large alignments of MRSA strains.

aph(2''), aph(3')-III and ant(6)-Ia. 27 strains were carrying tetracycline resistance genes such as tet(K) or tet(M). 26 strains were carrying fluoroquinolone resistance genes and single nucleotide polymorphisms (SNPs) such as gyrA (p.S84L) or grlA (p.S80F). 24 out of 30 strains were carrying macrolide and folate pathway antagonist resistance genes such as erm(A) or dfrB respectively (Table 2).

## DISCUSSION

The incidence of MRSA is still increasing and remains an important public health problem (1,12). The increase in resistant strains creates serious difficulties in the treatment. In order to develop new drugs, it is important to detect virulence and resistance genes in multi-resistant strains such as MRSA. In recent years, big data obtained with WGS technologies have provided tremendous developments. It can be used for typing strains such as MRSA, detecting antibiotic resistance and virulence genes, and examining their genomic materials (12).

Zhou et al, in their study, reported that when they examined the phylogenetic tree of different MRSA strains, they thought that the strains from different geographies were similar to each other and that the strains could migrate frequently between geographic regions (13). We found a similar result in the strains we examined in our study.

Asadollahi et al. reported spa types detected in different geographical regions in their study. It has been reported that t037 is the most detected spa type in Asia and Africa (14). Neela et al. also reported in their study that 83% of the strains in Malaysia were spa type t037 (15). Stańkowska et al. reported that they detected spa type t037 with high prevalence in Poland (16). These data showed us that as Zhou et al (13) stated, the strains migrated seriously and these strains could be encountered in different geographical regions.

In our study, ST239 was most detected 16 (53.3%) out of 30 MRSA strains. Neela et al. also reported in their study that 83% of the strains in Malaysia were ST239 (15). Asadollahi et al. reported some spa types constantly associated with some STs such as ST5 or ST239 (14). Dai et al., in their study in China, reported that the prevalence of ST239 and t037 types was decreased in MRSA isolates, whereas ST5 and t2460 types were seen in isolates. They also stated that there was an increase in the prevalence of ST398 type. They said that they did not know exactly what the reason was (17). Although not all of our strains originate from Asia, we found that the frequency of ST239 and ST5 was high after our in silico analysis.

Gostev and Siderenko reported in their study that SCCmec I, II and III were detected together with hospital-acquired epidemic strains such as ST5 and ST8, and SCCmec IV began to be detected in different geographical locations (18). Neela et al. also reported in their study that ST5-SCCmec type II and ST239-SCCmec type III appeared mostly together (15). We detected SCCmec_type_III(3A) in our study after our in silico analysis. Although we included strains from different countries in the in silico analysis, we obtained results similar to those reported by Neela et al. (15).

Mohammadi et al. reported that SCCmec type III strains contained aminoglycoside resistance genes in MRSA isolates they examined in their study. They also reported that they contain especially the ermA gene for erythromycin (19). Ebrahim-Saraie et al. reported that the resistance rates of SCCmec type III MRSA isolates they examined in their study were lower than the resistance rate of SCCmec type I and II strains, but they had serious antimicrobial resistance (20). In our study, we observed that MRSA strains carry genes associated with severe antimicrobial resistance after wgs-based antimicrobial resistance testing, and that although there may be slight differences in different geographical locations, the rates of resistance to major antimicrobial classes may be very high.

## CONCLUSION

As a conclusion, after our in silico analysis results, we found that similar typing profiles could be observed in the strains in different geographical locations. we realized that certain types of spa, MLST and SCC*mec* can coexist. We believe that these types and their antimicrobial resistance profiles should be continuously followed up with these new techniques.

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