Guidelines for Reporting Novel mecA Gene Homologues


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Methicillin-resistant staphylococci are disseminated all over the world and are frequent causes of health-care- and community-associated infections. Methicillin-resistant strains typically carry the acquired mecA gene that encodes a low-affinity penicillin-binding protein (PBP), designated PBP2a or PBP2b. In most strains, mecA is part of a chromosomally integrated mobile genetic element called staphylococcal cassette chromosome mec (SCCmec). The mecA gene is widely disseminated among Staphylococcus aureus and other staphylococcal species, and its expression is essential for the methicillin-resistant phenotype.

Recently, mecA gene homologues that are only distantly related to mecA have been identified in the genomes of staphylococci and some related bacterial species (Table 1). So far, four groups of mecA homologues have been described based on their degree of homology to the earliest identified mecA gene.

We believe that this diversity warrants a new naming system which can also serve as a guideline for the reporting of additional novel mecA homologues that may be identified in the future.

OVERVIEW OF mecA GENE HOMOLOGUES

The mecA gene originally identified in methicillin-resistant S. aureus (MRSA) (2, 9, 12) encodes a PBP of 668 amino acid residues which is responsible for beta-lactam resistance (8, 13, 17, 19). The mecA gene is carried by SCCmec and has been identified in various staphylococcal species, such as S. aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus saprophyticus, and Staphylococcus aureus (18). The mecA genes present in these species have >98% sequence identity with the mecA carried by the first fully sequenced prototype MRSA strain N315 (10). The first divergent mecA gene homologues were identified on the chromosomes of Staphylococcus sciuri subsp. sciuri, S. sciuri subsp. rodentius, and S. sciuri subsp. carnaticum. These homologues are very similar to each other and have approximately 80% nucleotide sequence identity to mecA of N315 (3, 20, 21). A second group of mecA gene homologues identified in Staphylococcus vitulinus have about 90% nucleotide identity to mecA of N315 (15).

A third group of mecA gene homologues are located on the chromosome and plasmids of Macroccus caseolyticus, a member of a genus that is phylogenetically closely related to Staphylococcus.

TABLE 1 List of mecA homologues

<table>
<thead>
<tr>
<th>Strain</th>
<th>Reported gene name</th>
<th>Proposed new name</th>
<th>Size (bp)</th>
<th>% identity with the mecA gene in S. aureus N315</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus N315a</td>
<td>mecA</td>
<td>mecA</td>
<td>2,007</td>
<td>100</td>
</tr>
<tr>
<td>Staphylococcal strains that carry mecA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. sciuri K11a</td>
<td>mecA (mecA1)</td>
<td>mecA1</td>
<td>2,001</td>
<td>79.1</td>
</tr>
<tr>
<td>S. sciuri ATCC 700061</td>
<td>mecAs</td>
<td>mecA</td>
<td>2,001</td>
<td>80.2</td>
</tr>
<tr>
<td>S. vitulinus CSBO8a</td>
<td>mecA</td>
<td>mecA2</td>
<td>2,007</td>
<td>91</td>
</tr>
<tr>
<td>M. caseolyticus JCSC5402a</td>
<td>mecAm</td>
<td>mecB</td>
<td>2,025</td>
<td>61.6</td>
</tr>
<tr>
<td>S. aureus LGA251¢</td>
<td>mecA, LGA251</td>
<td>mecC</td>
<td>1,998</td>
<td>68.7</td>
</tr>
</tbody>
</table>


The mecA homologues carried by these strains have 62% nucleotide sequence identity to mecA of N315 (1). The fourth mecA gene homologue most recently identified in S. aureus strain LGA251 shows 69% identity to mecA of N315 (5, 16). The phylogenetic relationship of these genes is illustrated in Fig. 1. A detailed comparison of nucleotide sequences is shown in Tables S1 and S2 in the supplemental material.

PROPOSED SCHEME OF CLASSIFICATION

Several of the best-studied antimicrobial resistance genes have been classified based on differences in deduced amino acid sequences (e.g., tetracycline resistance, macrolide resistance, and...
β-lactamase genes), and the breakpoint for classification is 80% amino acid identity (11, 14). Based on extensive discussion within the International Working Group on the Classification of Staphylococcal Cassette Chromosome (SCC) Elements (IWG-SCC) (http://www.sccmec.org), especially including the authors who first described and reported the four mecA gene homologues described above, we herein propose a classification and naming system for mecA and its homologues based on a combination of nucleotide sequence similarity and the chronological order of their discovery, i.e., the date of publication. In this way, we can more easily discern phylogenetic relationships among mecA genes which have been identified in various bacterial species of human as well as animal origin. This method will also help to identify the transfer of the methicillin resistance genes among human and animal commensals, independent of their antimicrobial resistance phenotype.

The mec gene is defined as a determinant that encodes a PBP similar to PBP2a or PBP2’ that is composed of three structural domains, a characteristic N-terminal structure, a transpeptidase domain, and a nonbinding domain.

A mec gene type encompasses mec genes sharing ≥70% nucleotide sequence identity with their respective prototype. The types are referred to as mecA, mecB, mecC, etc., which reflects the chronological order of their discovery. We suggest that the following prototype mec genes should be used in the definition of new types: mecA of S. aureus N315, mecB of M. caseolyticus, and mecC of S. aureus LGA251. Sequence identities among mecA homologues should be determined by creating a similarity matrix and a phylo-
genetic tree. Since mecA and most of its homologues are associated with mobile DNA elements, they are likely to be found across barriers of species or genera. Therefore, we do not limit the mec nomenclature system to the genus Staphylococcus.

The mec gene types are divided into allotypes, where each allotype encompasses a group of mec genes that share \( \geq 70\% \) but \( < 95\% \) nucleotide sequence identity to mecA of S. aureus N315, mecB of M. caseolyticus JCSC5402, or mecC of S. aureus LGA251. The allotypes for the class mecA, for example, are referred to as mecA1, mecA2, mecA3, etc., with the numeral based on the chronological order of discovery. The same applies for the classes mecB, mecC, etc.

According to the proposed new nomenclature, the mecA gene homologues described to date are renamed as follows (Table 1).

(i) The mecA homologues formerly called mecAm in M. caseolyticus and mecA\(_{G251}\) of S. aureus strain LGA251 are renamed chronologically as mecB and mecC, respectively, to reflect the order of publication.

(ii) mecA genes that have nucleotide sequence identities to the original mecA gene of \( \geq 95\% \) are referred to as mecA, signifying that they are members of the allotype represented by the original mecA gene. Those with nucleotide sequence identities to the original mecA of \( \geq 70\% \) but \( < 95\% \) are regarded as belonging to other allotypes of mecA. Accordingly, the mecA homologues detected in S. sciuri, which have a nucleotide sequence identity to the original mecA gene of approximately 80\%, are designated mecA1. The mecA homologues in S. vitulinus that have nucleotide sequence identities to the original mecA gene of approximately 90\% are designated mecA2.

With the continued selective pressure of beta-lactam use and the increasing number of whole-bacterial-genome sequences becoming available, many more mecA gene homologues may be discovered in the future. We hope that the proposed classification and naming system will help to facilitate a better understanding of the transfer of methicillin resistance determinants among commensal and pathogenic bacteria.

REFERENCES