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Comparative Genomic Analysis of the *mecA* Gene and *agr* Operon in Strains of MRSA

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Abstract

The bacteria species Methicillin-resistant *Staphylococcus aureus* (MRSA) poses many public health risks worldwide due to its shifty abilities that allow it to mutate and become resistant to various antibiotics. Understanding how bacteria have this mechanism to develop resistance and how to create effective antibiotics is not too clear yet, but with MRSA infecting more and more people, there are more sample strains that can be used to analyze the different patterns and genes of these bacteria. This study focuses on a comprehensive genomic analysis surrounding two prominent genes in MRSA strains, the *mecA* gene and *agr* operon. This analysis and comparison will be done through the usage of different MRSA strains from reputed genetic-based databases online, and additionally utilizing different software in order to analyze the different strains to check for gene prominence and nucleotide diversity. The results of this study show that both the *mecA* gene and *agr* operon are prominent in MRSA strains, and since at least the year of 2000 and beyond have been found in these strains. Although, there is no significant judgement that can be made as the strains studied only came from sample dates with year 2000

and after, and earlier sample years would have to be studied in order to identify a proper evolutionary history of these two genes.

Keywords: MRSA; mecA gene; agr operon; Antibiotic resistance; Comparative genomics; Virulence regulation; Gene expression; Genetic variation; Pathogenicity; Phylogenetic analysis.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a type of bacteria that presents several risks worldwide, as it leads to many diseases and infections (Garoy *et al.* 2019). A study reported by the Centers for Disease Control and Prevention (CDC), in the USA alone, displayed that in 2017, 119,000 Americans experienced a MRSA-related bloodstream infection and 20,000 of these infected people had passed away (Kourtis *et al.* 2019). One of the major reasons that MRSA causes a high mortality rate is due to its ability to be well adapted to hosts as well as healthcare industries (Siddiqui & Koirala 2023). MRSA is resistant to several treatments and antibiotics such as methicillin, as stated in its name (Lee *et al.* 2018). Those who have the highest risk of obtaining a colonization of MRSA are infants, the elderly, those who are chronically ill, and cancer patients who receive chemotherapy (Green *et al.* 2012). The risk of MRSA can be minimized by reducing crowding, reducing contact with surfaces, keeping skin clean, and cleaning contaminated items (Green *et al.* 2012). MRSA is a leading cause of bacteremia as well as the infections of the interior heart structure, bone structure, and the skin and soft tissue (Turner *et al.* 2019). Moreover, those infected with bacteremia have a higher risk of being susceptible to further impediments, including sepsis and septic shock (Hassoun *et al.* 2017).

MRSA and bacteria in general develop resistance to various drugs and antibiotics due to gene acquisition. The origin of the first strain of MRSA is unknown, but literature suggests that it

pre-dates methicillin treatment (Harkins *et al.* 2017). The *mecA* gene was acquired in one of these MRSA strains and later passed on (Larsen *et al.* 2022). The presence of *mecA* gene results in phenotypic resistance against β-lactam antibiotics such as methicillin (Stapleton & Taylor 2002). The *mecA* gene is passed on to many more *S. aureus* strains through horizontal acquisition (Vestergaard *et al.* 2019). Essentially, horizontal acquisition is the process allowing bacteria to respond to stimulus in their environment by achieving and being able to pass on DNA sequences to one another (Burmeister 2015). The *mecA* gene is located on a mobile genetic element (MGE) called the *SCCmec*, which is short for staphylococcal chromosomal cassette *mec* (Wielders *et al.* 2002).

The *agr* operon is a gene regulatory system that plays a major part in infecting host cells and transmitting bacteria, which leads to many MRSA-based skin infections (Green *et al.* 2012). The *agr* operon is has an important role in regulation. This operon uses toxins, adhesins, and invasins in MRSA (Tan *et al.* 2018). Toxins are responsible for damaging the host cell's tissues and also help disable the immune system in order to prevent the creation of antibodies (Cheung *et al.* 2011). Adhesins are responsible for first recognizing and then attaching themselves to the designated receptors and proteins of the host cells (Cheung *et al.* 2011). Invasins are responsible for mediating the MRSA's genome into the host cell (Cheung *et al.* 2011). The *agr* operon allows MRSA to become lethal as it infects the host cell and then cuts off any sort of communication between the body and the immune system (Tan *et al.* 2018). The *agr* operon has been seen influencing the genomic makeup of the *mecA* gene and vice versa (Tahmasebi *et al.* 2019). The activation of the *agr* operon is negatively correlated with the expression of *mecA* and methicillin resistance. This is because when the *agr* operon is active, the expression of the *mecA* gene is lowered, causing methicillin resistance to decrease (Kirmusaoglu 2017). The same occurs

when the *mecA* gene usage is increased, causing the *agr* operon's expression to be decreased. This implication points toward the fact that there is an inverse relationship between virulence and antibiotic resistance in MRSA (Tan *et al.* 2018). Since these systems are related, it means that the *mecA* gene and agr operon are also tied together in the emergence of MRSA as they played a prominent role in infecting host cells and making this bacterium more deadly. Hence, this allows for the comparison between these two genetic elements.

The primary aims of this paper are the following: Use BLAST sequencing along with alternate bioinformatics utilities in order to compare the *mecA* gene and *agr* operon through fifty various MRSA strains, determining whether or not each of the two genes is present, predicting what the results of several mutations in a gene could be, and examining the gene/protein diversity along with how MRSA has evolved over time. This study seeks to present a thorough examination of these genes' respective roles on the resistance phenotype in MRSA. By comparing these major genes in MRSA, healthcare professionals can gain more insight into how antibiotic resistance mechanisms and virulence factors are connected. This study will shed some on when the *agr* operon and the *mecA* gene fully settled themselves in the MRSA genome. Understanding the this can help to see the creation of more antibiotic resistance mechanisms, which would help predict future evolution in MRSA and create more effective antibiotics.

Methods

All sequences were obtained from the NCBI official website. Their GenBank numbers were used in order to help specify them. There were 50 strains plus an additional 2 strains (the *mecA* and *agr* reference strains) that were downloaded through the NCBI website, in the FASTA format. A variety of different years after the year 2000 were used to have a variety in strain sample dates. Then, the FASTA files containing the nucleotide sequences of the strains were

then uploaded to PathogenWatch. After the upload was complete, each of the strains was checked to see whether or not the *mecA* gene was present. After the checking of the gene presence was complete, the nucleotide diversity was compared through the online BLAST platform on the NCBI website. The sample *mecA* and *agr* sequence downloaded from earlier was uploaded as the query (reference) sequence and the rest of the 50 strains were uploaded as the subject sequences. Then the BLAST program was run, and the percentage identity, E-value, and query coverage were all recorded in order to compare all of the 50 strains with each other, and to see if there were any shifts in the presence and functional changes of the *mecA* and *agr* genes.

Results

In the overall structure of the online strain information, these were the main observations: In GenBank and DDBJ the nucleotide number count is on the left most column while in EMBL it is on the right most column. In GenBank and DDBJ titles such as the locus, definition, accession, version, and keywords are stated while in EMBL they are abbreviated. In GenBank you can analyze the sequence through programs such as BLAST directly through the site, but on EMBL and DDBJ there is only information about the strain but not software to analyze the sequence directly on the page. When downloading each of the files, the overall sequence information is listed in nucleotide bases, and the strain information is the same for all three files formats. Overall, for the downloaded files, the file contents are roughly the same.

Using BLAST, organisms with similar *mecA* sequences were identified. First, BLASTn was used to find organisms that have similar nucleotide sequences. The organisms other than *S. aureus* with similar *mecA* nucleotide sequences were *Mammaliicoccus lentus* and *Staphylococcus epidermidis.* Then, BLASTx was also used to find organisms that have similar nucleotide sequences. The organisms other than *S. aureus* with similar *mecA* nucleotide

sequences were *Staphylococcus pseudintermedius*, *Staphylococcus epidermidis*, and *Staphylococcus saprophyticus*. This means that, although the nucleotide sequences were the same, BLASTn and BLASTx gave different results for species other than *S. aureus* with similar *mecA* nucleotide sequences.

Next, BLASTp was used to find organisms that have similar amino acid sequences. The organisms other than *S. aureus* with similar *mecA* amino acid sequences were *Staphylococcus pseudintermedius*, *Staphylococcus epidermidis*, and *Staphylococcus saprophyticus*. Then, tBLASTn was also used to find organisms that have similar amino acid sequences. The organisms other than *S. aureus* with similar *mecA* amino acid sequences were *Staphylococcus pseudintermedius*, *Staphylococcus epidermidis*, and *Staphylococcus saprophyticus*. This means that, BLASTp and tBLASTn gave similar results for species other than *S. aureus* with similar *mecA* amino acid sequences.

Using BLAST, organisms with similar *agr* operon sequences were identified. First, BLASTn was used to find organisms that have similar nucleotide sequences. The organisms other than *S. aureus* with similar *agr* operon nucleotide sequences were *Staphylococcus argenteus, Staphylococcus roterodami, Staphylococcus schweitzeri,* and *Staphylococcus sp. MZ.* Then, BLASTx was also used to find organisms that have similar nucleotide sequences. The organisms other than *S. aureus* with similar *agr* operon nucleotide sequences were *Klebsiella pneumoniae*, *Staphylococcus schweitzeri*, *Staphylococcus singaporensis,* and *Staphylococcus argenteus*. This supports the idea that, although the nucleotide sequences were the same, BLASTn and BLASTx gave different results for species other than *S. aureus* with similar *agr* operon nucleotide sequences.

The same prodedure was repeated with the amino acid sequence of the *agr* operon, but unlike the *mecA* gene, the same species were at the top of the highest similarity for both the nucleotide and amino acid sequence. From this analysis, it can be determined that in species other than *S. aureus,* the presence of the *mecA* gene and *agr* operon are located in various species, many of which do not intersect with these two genetic components' presence.

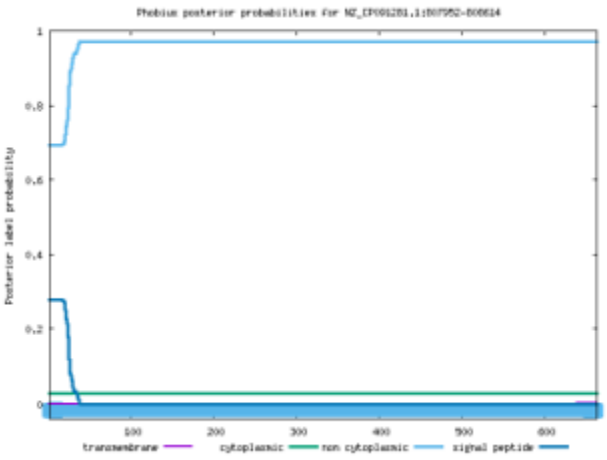
Figure 1

3d Model of mecA Gene from PDB

The crystalline structure of the mecA gene, created and referenced from PDB.

Figure 2

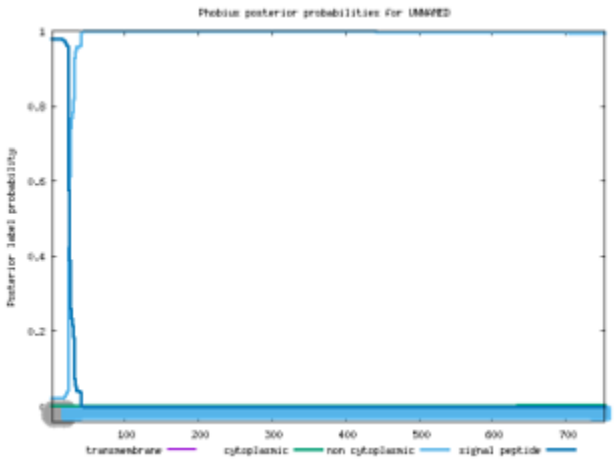
Phobius Prediction of mecA Gene



The presence and activity of the *mecA* gene, when considering the following four conditions: Transmembrane, cytoplasmic, non cytoplasmic, signal peptide.

Figure 3

Phobius Prediction of agr Operon



The presence and activity of the *agr* operon, when considering the lookating at the following four conditions: Transmembrane, cytoplasmic, non cytoplasmic, signal peptide.

As seen from figures 2 and 3, the mecA gene and agr operon's activity in each of the 4 different places was similar. Both transmembrane activity was 0 and cytoplasmic activity was 0 for agr operon and very close to 0 for the mecA gene. Non cytoplasmic regions' activity was 1 for both genetic components and dropped to 0 for the signal peptide. This shows that the activity in different regions was similar for both the mecA gene and agr operon, meaning that there is a higher chance of evolutions in these areas for both genetic components.

A study was conducted using 50 MRSA strains, that were determined based on various factors. Main factors for strain selection was to optimize for a variety of geographical locations while also trying to keep the strain collection date within the past 20 years. All of the strains are shown in the table below. The 50 MRSA strains were put into PathogenWatch to determine if

they had the *mecA* gene, and then blasted against an example *agr* operon to check for both genetic components' prevalence. The 50 MRSA genes and information about name, geographic location, host, sample collection date, sequence type, and GenBank assembly number are displayed in the table below.

Table 1

MRSA Strain Information Data Table

Strain	Country	Host	Year	ST	Assembly #
MRSA - AMRF 5	India	Human	2020	772	GCA_015219905.1
NRS384	USA	Human	2018	8	GCA_002993865.1
MRSA107	China	Human	2016	239	GCA_002895385.1
V521	Korea	Human	2016	239	GCA_001641025.1
TUM9463	Japan	Human	2018	2389	GCA_003945425.1
BPH2003	Australia	Human	2019	239	GCA_900607265.1
CC239-MRSA-III	Trinidad&Tobago	Human	2023	239	GCA_030252735.1
M48	China	Human	2019	239	GCA_004136255.1
CMRSA-6	Canada	Human	2018	239	GCA_003264815.1
HC1340	Brazil	Human	2016	239	GCA_001515745.1
Gv69	Brazil	Human	2014	239	GCA_000769575.1
BPH2947	Australia	Human	2019	239	GCA_900620245.1
CC239-MRSA-III(var.)	Trinidad&Tobago	Human	2023	239	GCA_030252695.1
CC239-MRSA-III	Trinidad&Tobago	Human	2023	239	GCA_030252755.1
Taliyah	Taiwan	Human	2022	239	GCA_026625305.1
Zed	Taiwan	Human	2022	239	GCA_026625265.1
Akali	Taiwan	Human	2022	239	GCA_026625365.1

Ryze	Taiwan	Human	2022	239	GCA_026625225.1
Galio	Taiwan	Human	2022	*df10	GCA_026625205.1
NY2491	China	Human	2022	239	GCA_022832755.1
M92	Canada	Human	2018	5354	GCA_002097595.2
Gv88	Brazil	Human	2016	239	GCA_001515705.1
Gv51	Brazil	Human	2016	239	GCA_001515665.1
Be62	Brazil	Human	2016	239	GCA_001515685.1
BPH2056	Australia	Human	2019	239	GCA_900607305.1
SA0907	China	Human	2023	45	GCA_029625375.1
HC1335	Brazil	Human	2016	239	GCA_001515765.1
Bmb9393	Brazil	Human	2013	239	GCA_000418345.1
HU-14	Argentina	Human	2020	5	GCA_903932605.1
P3.1	Argentina	Human	2020	5	GCA_903932595.1
BPH2869	Australia	Human	2019	239	GCA_900607295.1
Orianna	Taiwan	Human	2022	*df10	GCA_026625245.1
PartE-Saureus-RM8376	Japan	Human	2022	247	GCA_022870005.1
BLR-DV	Belarus	Human	2020	239	GCA_013389715.1
aureus	South Korea	Human	2019	5	GCA_006088835.1
FDAARGOS_766	USA	Human	2019	247	GCA_006364775.1
CMRSA-3	Canada	Human	2018	241	GCA_003264775.1
AR_0470	USA	Human	2018	30	GCA_003193745.1
FDAARGOS_35	USA	Human	2018	507	GCA_001019485.2
2395 USA500	USA	Human	2014	8	GCA_000746505.1

5_3949	Germany	Human	2018	398	GCA_900324235.1
NY2010	China	Human	2022	239	GCA_022832835.1
KG-22	Japan	Human	2019	5	GCA_009176875.1
KG-18	Japan	Human	2019	5	GCA_009176785.1
NCTC13140	United Kingdom	Human	2018	8	GCA_900474725.1
NCTC9944	United Kingdom	Human	2018	240	GCA_900474575.1
JK3137	Canada	Human	2019	8	GCA_004614315.1
NCCP14558	South Korea	Human	2016	5	GCA_001640905.1
HL21008	South Korea	Human	2021	5	GCA_019551095.1
KG-03	Japan	Human	2019	5	GCA_009176765.1

The descriptions of the strain, country, host cell, sample date, sequence type, and the assembly number for each of the 50 strains. *Note:* The strains are in no specific order.

After checking Pathogen Watch to ensure that both *agr* and *mecA* genes were present in each of the 50 strains, each one of the strains was blasted against a query sequence of the *mecA* gene and the *agr* operon. Then, the query cover (how much of the query sequence was fully covered), the E value, and percentage identity were determined for each of the strains after being blasted with *mecA* gene and *agr* operon. The results are shown in the data table below:

Table 2

The Query Cover, E value, and Percentage Identity that Each of the 50 Strains had as the Results from BLAST.

Assembly #	Query Cover (mecA)	E Value (mecA)	Percent Identity (mecA)	Query Cover (agr)	E Value (agr)	Percent Identity (agr)
GCA_015219905.1	100%	0	99.72%	100%	0	99.87%
GCA_002993865.1	100%	0	100%	100%	0	100%

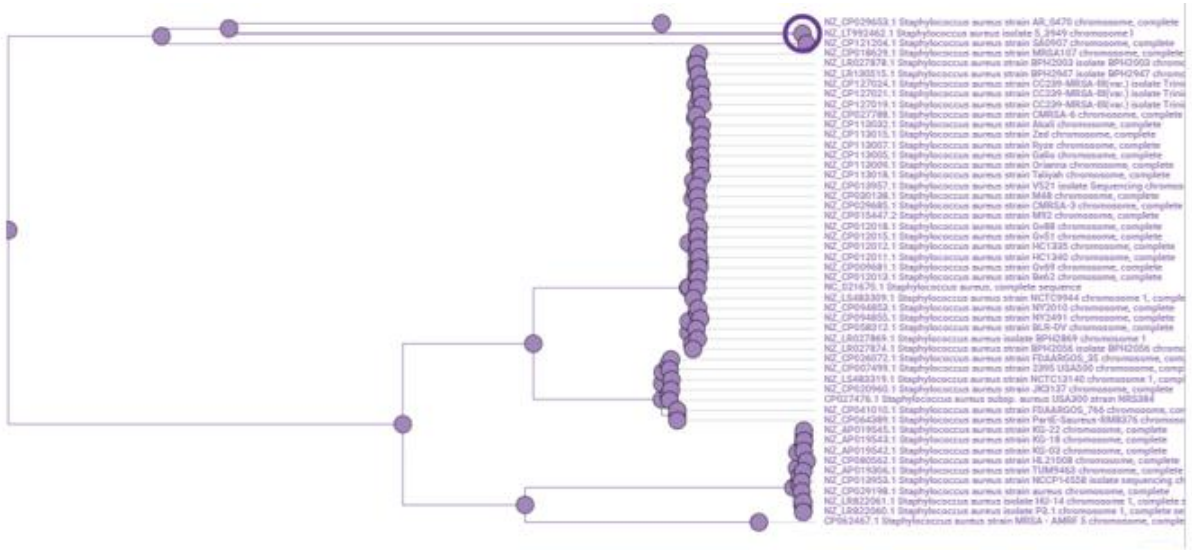
GCA_002895385.1	100%	0	100%	100%	0	99.20%
GCA_001641025.1	100%	0	100%	100%	0	99.20%
GCA_003945425.1	100%	0	99.72%	100%	0	99.87%
GCA_900607265.1	100%	0	100%	100%	0	99.20%
GCA_030252735.1	100%	0	100%	100%	0	99.20%
GCA_004136255.1	100%	0	100%	100%	0	99.20%
GCA_003264815.1	100%	0	100%	100%	0	99.20%
GCA_001515745.1	100%	0	100%	100%	0	99.20%
GCA_000769575.1	100%	0	100%	100%	0	99.20%
GCA_900620245.1	100%	0	100%	100%	0	99.20%
GCA_030252695.1	100%	0	100%	100%	0	99.20%
GCA_030252755.1	100%	0	100%	100%	0	99.70%
GCA_026625305.1	100%	0	100%	100%	0	99.20%
GCA_026625265.1	100%	0	100%	100%	0	99.20%
GCA_026625365.1	100%	0	100%	100%	0	99.20%
GCA_026625225.1	100%	0	100%	100%	0	99.20%
GCA_026625205.1	100%	0	100%	100%	0	99.20%
GCA_022832755.1	100%	0	100%	100%	0	99.20%
GCA_002097595.2	100%	0	100%	100%	0	99.20%
GCA_001515705.1	100%	0	100%	100%	0	99.20%
GCA_001515665.1	100%	0	100%	100%	0	99.20%
GCA_001515685.1	100%	0	100%	100%	0	99.20%
GCA_900607305.1	100%	0	100%	100%	0	99.20%
GCA_029625375.1	100%	0	100%	100%	0	99.20%
GCA_001515765.1	100%	0	100%	100%	0	99.20%

GCA_000418345.1	100%	0	100%	100%	0	99.20%
GCA_903932605.1	100%	0	100%	100%	0	99.20%
GCA_903932595.1	100%	0	100%	100%	0	99.20%
GCA_900607295.1	100%	0	100%	100%	0	99.20%
GCA_026625245.1	100%	0	100%	100%	0	99.20%
GCA_022870005.1	100%	0	100%	100%	0	99.20%
GCA_013389715.1	100%	0	100%	100%	0	99.20%
GCA_006088835.1	100%	0	100%	100%	0	99.20%
GCA_006364775.1	100%	0	100%	100%	0	99.20%
GCA_003264775.1	100%	0	100%	100%	0	99.20%
GCA_003193745.1	100%	0	100%	100%	0	99.20%
GCA_001019485.2	100%	0	100%	100%	0	99.20%
GCA_000746505.1	100%	0	100%	100%	0	99.20%
GCA_900324235.1	100%	0	100%	100%	0	99.87%
GCA_022832835.1	100%	0	100%	100%	0	99.87%
GCA_009176875.1	100%	0	100%	100%	0	99.87%
GCA_009176785.1	100%	0	100%	100%	0	99.20%
GCA_900474725.1	100%	0	100%	100%	0	99.87%
GCA_900474575.1	100%	0	100%	100%	0	99.87%
GCA_004614315.1	100%	0	100%	100%	0	99.20%
GCA_001640905.1	100%	0	99.72%	100%	0	99.87%
GCA_019551095.1	100%	0	99.72%	100%	0	99.87%
GCA_009176765.1	100%	0	99.72%	100%	0	99.87%

All of these values were influenced and determined by each of the strain's similarity with respect to the model sequence for both the *mecA* gene and *agr* operon.

Figure 4

This Dendrogram Shows the Relationships Between each of the 50 Strains.



The similarity between these 50 strains in this dendrogram is determined by the date of the sample collection. This diagram helps model how different strains are correlated with each other with respect to year and can help determine if there are any connections between *S. aureus* evolution.

Discussion

From data Table 2 in the results section, it can be determined that all of the strains (subject sequences) were extremely similar to the query sequences (*mecA* gene and *agr* operon). This can be determined, as the E value for all the results is 0, which is the lowest possible and defines the highest similarity. The query coverage for all 50 of the strains was also 100%, which means that the entirety of the *mecA* gene and *agr* operon original nucleotide sequences were present in each of these respective strains. The percentage identity was also above 99% for all 50

of the strains, meaning that the overall similarity between the query sequence and these subject sequences was extremely high and had little to no differences in nucleotide base pairs.

Based on these results, since all of the 50 strains tested had extremely high similarities with the sample *mecA* gene and *agr* operon reference strain, it can be said that the *mecA* gene prevalence and *agr* operon prevalence are both extremely high in recently identified MRSA strains. Although earlier strains that did not have the *mecA* in them were tested too, many of those strains still had a similar percentage identity to the *agr* operon reference strain. This suggests that there is a possibility that the *agr* operon's prevalence can be traced back to a time much before S. aureus became resistant to methicillin and developed the *mecA* gene and has been a virulence factor for a very long time. After noting that the *mecA* gene and *agr* operon are present in all 50 of the strains and that their prevalence is equally high in all of these strains, it is also worth noting that, while *mecA* has not always been present in *S. aureus* and has developed through mutations and resistance, the *agr* operon could have been present *S. aureus* since the time it was first discovered. But this is the opposite perspective than was found in the article Methicillin-resistant Staphylococcus aureus emerged long before the introduction of methicillin into clinical practice, as it was found that methicillin antibiotics were not responsible for the resistance and formation of the *mecA* gene, rather it came from the usage of first-generation beta-lactams, including penicillin, which is many years before the introduction of methicillin (Harkins et al. 2017). As seen in this paper, the *agr* operon is a key part in the virulence of S. aureus and would have to be studied further to determine its impact on the evolution of virulence (Cheung et al. 2011).

These findings are consistent with existing literature indicating that both the mecA gene and agr operon contribute significantly to MRSA's evolutionary stability and adaptability

(Vestergaard et al., 2019). The high conservation observed across diverse strains reinforces prior evidence that these genes are integral to MRSA's survival under antibiotic pressure and to its capacity to regulate virulence. Furthermore, the inverse relationship between mecA expression and agr activity (Kirmusaoglu 2017), supports the notion that antibiotic resistance and virulence are dynamically interconnected mechanisms within MRSA's genome.

However, several limitations must be acknowledged. The analysis included only strains collected after the year 2000, which restricts evolutionary inferences regarding the historical emergence of mecA and agr. In addition, reliance on publicly available databases such as NCBI and PathogenWatch introduces potential sampling bias, as strain representation may be geographically uneven. The methodology also focused primarily on nucleotide identity through BLAST, without incorporating gene expression, protein function, or environmental interactions, which could further elucidate the genes' biological impact.

Future research should address these gaps by examining earlier MRSA isolates and expanding comparative analyses to include transcriptomic and proteomic datasets. Integrating functional genomics approaches, such as RNA sequencing, protein structure modeling, and machine learning–based phylogenetic tracking, could help reveal how mecA and agr interact to influence MRSA's pathogenic potential. Additionally, experimental studies exploring these genes' regulation under antibiotic stress may provide valuable insights for the development of novel therapeutic strategies that target both antibiotic resistance and virulence pathways simultaneously.

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