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MOLECULAR CHARACTERIZATION OF PANTON VALENTINE LEUKOCIDIN GENE AND AGR TYPING IN METHICILLIN RESISTANCE STAPHYLOCOCCUS AUREUS CLINICAL ISOLATES

Gozaiyal Shoeb[1], Prof. (Dr.) Abhineet Mehrotra[2], Dr. Umar Rashid Khan[3], Prof. (Dr.) Khaleel Ahmad Manik[4]

[1]Ph.D Scholar, Department of Microbiology, Integral institute Of Medical Sciences & Research Hospital, Lucknow, Uttar Pradesh, India.
[2]Professor, Department of Microbiology, Integral Institute Of Medical Sciences & Research Hospital, Lucknow, Uttar Pradesh, India.
3Assistant professor, Department Of Microbiology, Integral Institute Of Medical Sciences & Research Hospital, Lucknow, Uttar Pradesh, India.
[4]Professor, Department of Physiology, Integral Institute Of Medical Sciences & Research Hospital, Lucknow, Uttar Pradesh, India.
Corresponding Author: amehrotra@iul.ac.in

ABSTRACT

Methicillin-resistant Staphylococcus Aureus (MRSA) is an important human pathogen associated with multidrug resistance and various virulence factors. Among these, Panton-Valentine Leukocidin (PVL) and the accessory gene regulator (agr) system play significant roles in pathogenicity and disease severity. This review highlights the molecular characterization of the PVL gene and agr typing in MRSA clinical isolates. It summarizes the role of PVL toxins, distribution of agr groups, laboratory detection methods, and their clinical significance based on previously published studies. Understanding the association between PVL genes and agr types may help in better surveillance, infection control, and management of MRSA infections.

KEYWORDS: MRSA, PVL gene, agr typing, molecular characterization, virulence factors.

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INTRODUCTION

Staphylococcus aureus is a major cause of infections in humans, ranging from mild conditions like nasal and skin colonization without symptoms, to serious and life-threatening illnesses such as endocarditis, bloodstream infections (bacteraemia), and necrotizing pneumonia. One of the important harmful substances (virulence factors) it produces is called Panton-Valentine leukocidin (PVL). This is a toxin made up of two parts and is encoded by two genes—lukS-PV and lukF-PV—that are located on the DNA of certain viruses (called temperate bacteriophages) that infect bacteria [1].

In real-world cases, S. aureus strains that produce PVL have been linked to tissue-damaging infections like boils (furunculosis) and serious necrotizing pneumonia [2]. PVL can be found in both methicillin-susceptible S. aureus (MSSA) and methicillin-resistant S. aureus (MRSA). However, PVL is most often associated with a type of MRSA called community-acquired MRSA (CA-MRSA).

On a genetic level, CA-MRSA strains usually carry the SCCmec type IV element and the lukS-PV and lukF-PV genes, which are used as markers to identify CA-MRSA strains found around the world. However, not every CA-MRSA strain has both the PVL genes and SCCmec IV [3].

The rate of infections caused by PVL-positive CA-MRSA differs by region, ranging from less than 5% in some parts of Europe to over 50% in certain areas of the USA [4–6]. Most research shows that PVL-positive CA-MRSA strains tend to come from a limited number of genetic types (a clonal structure), although the types found in Europe are different from those in the USA [7,8].

The most common PVL-producing MRSA types (based on sequence type, or ST) are: ST80 in Europe, ST8-USA300 in the USA, and ST30, known as the Southwest Pacific clone, found more broadly across the world [9,10].
Staphylococcus aureus has shown an increasing trend of resistance towards β-lactam antibiotics along with other classes of drugs like glycopeptides [11].

A unique feature of the USA300 clone is the presence of a genetic element called arginine catabolic mobile element (ACME). This element helps the bacteria grow and survive and may have come from another bacterial species, Staphylococcus epidermidis [12].

Staphylococcus aureus is normally found in the nose and on the skin of healthy people, but it can cause infections if it enters the body through broken skin or damaged tissues [13,14]. A drug-resistant type of this bacteria called methicillin-resistant

Staphylococcus aureus (MRSA) appeared many years ago. This strain has a gene called mecA, which produces a special protein called penicillin-binding protein 2a or 2′ (PBP2a or PBP2′) that makes the bacteria resistant to methicillin [13,14]. The mecA gene is part of a mobile genetic element in the bacteria called the staphylococcal cassette chromosome mec (SCCmec) [15,16].

Over time, MRSA has become resistant to many types of antibiotics. Today, only a few antibiotics such as vancomycin (the main treatment), linezolid, tigecycline, daptomycin, and ceftaroline are still effective and used to treat MRSA infections.

Older antibiotics no longer work well because S. aureus causes disease in complex ways. It forms a biofilm and produces many harmful substances (called virulence factors) [12]. The biofilm protects the bacteria from both antibiotics and the body's immune system, helping it survive and cause long-lasting infections [16–18].

The agr system (accessory global regulatory system) is an important control system in S. aureus. It helps break down the biofilm and regulates the production of harmful factors such as MSCRAMMs (proteins that help bacteria stick to host tissues), hemolysins, lipases, leukotoxins, Protein A, exfoliative toxins, staphylococcal enterotoxins (SEs), and toxic shock syndrome toxin-1 (TSST-1) [12,19,20].

Because of its strong resistance and ability to cause serious infections, MRSA is listed as a high priority pathogen by the World Health Organization (WHO) in its 2024 Bacterial Priority Pathogens List [21], and by the Department of Biotechnology (DBT) in India's 2021 Indian Priority Pathogen List [22].

Panton-Valentine leukocidin (PVL) is a potent virulence factor commonly linked to recurrent skin and soft tissue infections (SSTIs) and necrotizing pneumonia caused by Staphylococcus aureus. Necrotizing pneumonia due to PVL-positive strains carries a high mortality rate of 40–60% [23], primarily due to the toxin's pro-inflammatory and cytotoxic effects on immune cells like neutrophils, monocytes, and macrophages. Even at low concentrations (0.04–0.4 µg/mL; 1–10 nM), PVL rapidly activates the inflammasome, triggering massive interleukin-1β release and leading to apoptotic cell death [24].

Although epidemiological evidence supports a role for PVL in disease severity—especially in bone, joint infections, and necrotizing pneumonia—its exact contribution to pathogenesis remains debated. Some clinical trials have found no significant outcome differences in severe SSTIs caused by PVL-positive and PVL-negative strains [26].

PVL is encoded by two co-transcribed genes, lukS-PV and lukF-PV, carried on bacteriophages such as ΦPVL, Φ108PVL, Φ7247PVL, ΦSa2958, ΦSa2MW, ΦSLT, ΦSa2USA, and ΦTCH60
[27]. Though PVL is typically associated with community-acquired methicillin-resistant S. aureus (CA-MRSA), not all CA-MRSA strains harbor the PVL genes [28]. Moreover, PVL-positive hospital-acquired MRSA (HA-MRSA) strains have also been identified [29].

In India, CA-MRSA strains are genetically diverse, with around 75% carrying PVL genes [30]. Major Indian clones include sequence types (ST) 772 and ST22 [31, 32]. The ST772-MRSA-V strain, known as the Bengal Bay clone, is a multidrug-resistant, PVL-positive CA-MRSA variant first reported from India. Indian studies have reported PVL gene prevalence in S. aureus ranging from 16% to 64% [33].

PANTON-VALENTINE LEUKOCIDIN (PVL)

Genetic and Structural Features

Panton-Valentine leukocidin (PVL) is a bicomponent, pore-forming cytotoxin encoded by lukS-PV and lukF-PV genes, which are carried on a lysogenic bacteriophage known as Φ-PVL. The two subunits—LukS-PV (~33 kDa) and LukF-PV (~34 kDa)—assemble into hetero-oligomeric β-barrel pores on the membranes of host immune cells, particularly neutrophils, leading to cell lysis and the release of pro-inflammatory contents, thereby contributing to tissue necrosis and abscess formation [34]. A single nucleotide polymorphism (SNP) within the PVL gene can give rise to two distinct isoforms of the LukS-PV protein: H176 and R176. The R176 variant has been predominantly associated with USA300 (clonal complex 8, or CC8) MRSA strains and may be linked to increased cytotoxic activity, suggesting a possible evolutionary advantage in virulence for certain clones [35].

Prevalence and Clonal Distribution

The prevalence of PVL among S. aureus isolates varies geographically and is closely associated with specific clonal types. In the United States, approximately 36% of S. aureus clinical isolates harbor PVL genes, with 97% of the R176 isoform found in CC8 (USA300) MRSA strains, a predominant CA-MRSA lineage [36]. In India, PVL genes are commonly found in community-associated MRSA (CA-MRSA); a tertiary-care hospital study reported a 70.4% PVL-positivity rate, primarily in isolates carrying SCCmec type IV or V, which are typical of community strains [37]. Several Indian studies have observed similar high PVL prevalence ranging from 56.9% to 85.1% in clinical CA-MRSA isolates. In Uganda, CA-MRSA isolates also show a strong association with PVL carriage and SCCmec IV/V, alongside a diverse clonal structure that includes ST121 and ST88, both of which are linked to skin and soft tissue infections [38]. Interestingly, in Indonesian hospitals, the overall MRSA prevalence was relatively low (~6.6%), and no PVL-positive MRSA was detected. However, PVL-positive methicillin-susceptible S. aureus (MSSA) was more frequent (~18.5%), with ST121 clones being the dominant lineage among them—highlighting the role of PVL in MSSA virulence as well.

agr Typing and Regulatory Role

The accessory gene regulator (agr) locus in Staphylococcus aureus encodes a well-characterized quorum-sensing system that plays a crucial role in regulating virulence gene expression. It comprises four genes—agrA, agrB, agrC, and agrD—which together control the production of an effector RNA molecule, RNAIII, the primary regulator of exotoxin and enzyme expression. As bacterial cell density increases, agr signaling transitions the organism from expressing surface-associated adhesion proteins to secreting toxins and enzymes that facilitate tissue invasion and immune evasion. This regulatory switch enables the pathogen to effectively adapt from colonization to invasive disease. There are four known agr specificity groups (I–IV), each defined by the sequence of its autoinducing peptide (AIP). These groups are mutually inhibitory and typically conserved within clonal complexes, thereby contributing to lineage-specific regulation and virulence patterns [39].

agr Types and Clinical Associations

Different agr groups are frequently associated with specific clonal lineages and can influence the pathogenicity of S. aureus strains. Although agr typing is less commonly performed than PVL detection, accumulating evidence links certain agr groups with PVL-positive S. aureus clones. For example, agr group IV has been associated with ST121 MSSA strains in Uganda, a lineage known for causing severe skin and soft tissue infections. Similarly, agr group III is commonly observed in ST88 MRSA isolates, which have been reported across sub-Saharan Africa and Asia and often carry the PVL genes [40]. In studies from Iran and South Asia, agr groups I and III were frequently found among PVL-positive MRSA isolates, suggesting a potential association between these regulatory backgrounds and enhanced virulence, though detailed molecular epidemiological data remain sparse and inconsistent [41]. Understanding the agr-PVL interplay could provide deeper insight into strain behavior and help refine clinical risk stratification and outbreak tracking.

MOLECULAR TYPING METHODS

Conventional and multiplex polymerase chain reaction (PCR) assays remain the cornerstone for initial molecular characterization of Staphylococcus aureus. Routine diagnostic panels include detection of mecA (conferring methicillin resistance), nuc (species-specific thermonuclease gene), and pvl genes (lukS-PV and lukF-PV), with PVL detection typically targeting a ~433 bp fragment spanning both toxin subunit genes. Multiplex PCR protocols have been standardized for typing SCCmec elements (types I–V), allowing differentiation between community- and hospital-associated MRSA strains. Similarly, agr typing is commonly conducted using allele-specific PCR assays, which identify agr groups I to IV based on the sequence variation in their autoinducing peptide-encoding regions. These molecular tools are rapid, cost-effective, and widely implemented in both clinical and surveillance contexts [42].

HIGH-RESOLUTION GENOTYPING

For finer epidemiological resolution and phylogenetic analysis, high-resolution genotyping methods are essential. Multilocus sequence typing (MLST) categorizes S. aureus strains into specific sequence types (STs) based on the allelic profiles of seven housekeeping genes. This method has helped define widely studied clones such as ST8 (USA300), ST30, ST22 (EMRSA-15), ST121, and ST88, which are often linked with specific PVL and agr profiles. spa typing, based on the polymorphic X region of the protein A gene, provides single-locus discrimination and is often used in conjunction with MLST. Pulsed-field gel electrophoresis (PFGE), although labor-intensive, has historically been the gold standard for outbreak investigations due to its high discriminatory power. More recently, whole-genome sequencing (WGS) and single nucleotide polymorphism (SNP)-based pipelines have emerged as the most comprehensive approaches, offering unparalleled resolution for tracking strain microevolution, horizontal gene transfer events (e.g., PVL phage acquisition), and hospital- or community-based transmission dynamics [43].

CORRELATION BETWEEN PVL AND agr TYPES

PVL-positive Staphylococcus aureus clones often exhibit specific agr types that correspond to their clonal lineage, suggesting a degree of evolutionary co-selection between virulence regulation and genetic background. For instance, the USA300 clone (CC8)—a dominant community-associated MRSAstrain in North America—is typically characterized by the R isoform of PVL and agr group I. In other regions, particularly South Asia and sub-Saharan Africa, different PVL-positive clones dominate. ST121 (often MSSA, occasionally MRSA), typically associated with agr group IV, and ST88 MRSA, linked with agr group III, are commonly found to harbor PVL genes and are associated with skin and soft tissue infections (SSTIs) and other invasive diseases. While these patterns suggest clonal linkages between PVL carriage and agr type, exceptions exist, and agr associations can vary depending on regional clone dynamics and horizontal gene transfer events [44].

REGULATORY INTERPLAY AND VIRULENCE

The agr system plays a central role in modulating S. aureus virulence by controlling the expression of numerous toxins and secreted enzymes, including PVL. The timing and magnitude of PVL expression are believed to be influenced by the functionality of the agr system, with some studies suggesting that agr groups I and III are particularly effective in driving high levels of PVL expression. Additionally, integration of PVL-carrying phages, agr activity, and SCCmec type may collectively shape the virulence profile of a given strain. For example, CA-MRSA clones with agr I or III backgrounds and SCCmec IV/V elements tend to be more virulent and better adapted to cause SSTIs and community outbreaks. Moreover, strains with intact agr function are more likely to produce robust biofilms and secrete cytolytic toxins. However, direct evidence linking specific agr types to differential PVL gene expression remains limited, highlighting a need for further functional studies that examine the interplay between agr signaling, PVL regulation, and clinical outcomes [45].

CLINICAL AND EPIDEMIOLOGICAL IMPLICATIONS

The combined molecular detection of PVL, mecA/SCCmec, agr types, and genotyping tools such as MLST and spa typing provides significant diagnostic utility by enabling differentiation between community-associated (CA-MRSA) and hospital-associated (HA-MRSA) strains, which is critical for effective infection control and timely outbreak responses. Clinically, PVL-positive S. aureus strains—whether methicillin-resistant or susceptible—are often associated with severe disease manifestations such as necrotizing pneumonia and skin and soft tissue infections (SSTIs), although pathogenicity is influenced by multiple virulence factors beyond PVL alone. Furthermore, there is a pressing need for structured molecular surveillance in regions like South Asia and Africa to systematically map agr and PVL gene distributions, monitor emerging MRSA clones, and implement targeted public health and infection control measures [46].

FUTURE DIRECTIONS

Future research should prioritize expanded molecular epidemiological surveillance in underrepresented regions such as India, Africa, and Southeast Asia to accurately map the association patterns between PVL genes and agr types, which remain poorly characterized in these high-burden areas. Integrating advanced genomic tools like whole-genome sequencing (WGS) and phage typing will be essential to unravel the microevolution of MRSA, particularly the mechanisms and dynamics of PVL-encoding phage acquisition and dissemination across different clonal backgrounds. Additionally, functional studies on the agr regulatory system are crucial to determine how specific agr alleles influence PVL gene expression, biofilm formation, antibiotic resistance profiles, and clinical disease severity, offering insight into potential targets for therapeutic intervention and infection control strategies.

CONCLUSION

Comprehensive molecular characterization of Staphylococcus aureus, particularly methicillin-resistant strains (MRSA), is critical for unraveling the complex interplay between virulence, resistance, and clonal dissemination. Key genetic markers—including PVL gene status, agr typing, SCCmec classification, and clonal markers such as spa types and MLST profiles—provide valuable insights into the epidemiology and pathogenic potential of circulating strains. In particular, PVL-positive MRSA is predominantly linked to community-associated (CA-MRSA) lineages and is frequently implicated in severe clinical conditions such as necrotizing pneumonia and skin and soft tissue infections. Meanwhile, agr typing helps delineate strain-specific regulatory patterns that influence toxin production, biofilm formation, and disease severity. The integration of whole-genome sequencing (WGS) enhances resolution for outbreak investigations and microevolution tracking. Given the ongoing global spread of hypervirulent and resistant MRSA clones, expanded genomic surveillance and functional studies are urgently needed—especially in underrepresented regions—to guide infection control, therapeutic strategies, and public health interventions.

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