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The carriage of the serine-aspartate repeat protein-encoding *sdr* genes among *Staphylococcus aureus* lineages



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ABSTRACT

The serine-aspartate repeat proteins (Sdr) are members of a family of surface proteins and contribute to the pathogenicity of *Staphylococcus aureus*. Among 288 *S. aureus* isolates including 158 and 130 associated with skin and soft tissue infections and bloodstream infection, respectively; 275 (95.5%) were positive for at least one of three *sdr* genes tested. The positivity rates for *sdrC*, *sdrD*, and *sdrE* among *S. aureus* isolates were 87.8% (253/288), 63.9% (184/288), and 68.1% (196/288), respectively. 224 (77.8%) of 288 isolates were concomitantly positive for two or three *sdr* genes. There was an association between carriage of *sdrE* and methicillin-resistant *S. aureus* (MRSA) isolates, while the carriage rates of *sdrC* and *sdrD* in MRSA isolates were similar to those in methicillin-sensitive *S. aureus* (MSSA) isolates. The prevalence of co-existence of *sdrC* and *sdrE* among MRSA isolates was significantly higher than that among MSSA isolates ($p < 0.05$). All ST1, ST5, ST7, and ST25 isolates were positive for *sdrD*. While all ST121 and ST398 isolates were negative for *sdrD*. All ST59 and ST88 isolates were positive for *sdrE*. All ST1 isolates were concomitantly positive for *sdrC* and *sdrD*. Concomitant carriage of *sdrC*, *sdrD*, and *sdrE* was found among all ST5, 75.0% (9/12) of ST1, 69.2% (9/13) of ST6, 78.6% (11/14) of ST25, and 90.9% (20/22) of ST88 isolates. *sdrD* was linked to CC5, CC7 and CC88 isolates, especially CC88 isolates. There was a strong association between the presence of *sdrE* and CC59, CC88, and CC5 isolates. A significant correlation between concomitant carriage of *sdrC*, *sdrD*, and *sdrE* and CC88 isolates was found. *sdrC*-positive, *sdrD*-positive and *sdrE*-negative gene profile was significantly associated with CC7 clone. There was an association between *sdrC*-positive, *sdrD*-negative, and *sdrE*-positive gene profile and CC59 isolates. A correlation between *sdrC*-positive, *sdrD*-negative, and *sdrE*-negative gene profile and CC121 clone was found. More CC59 isolates carried *sdrC*-negative, *sdrD*-negative, and *sdrE*-positive gene profile

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relative to other four CCs isolates. All ST1 and ST5, 95.2% (20/21) of ST188 and 95.2% (20/21) of ST630 isolates were positive for *sdrC*. Taken together, our investigation indicated that different *S. aureus* lineages were associated with specific patterns of carriage of *sdr* genes.

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Introduction

Staphylococcus aureus is a frequently encountered human pathogen which is the cause of a wide range of infectious diseases, such as skin and soft tissue infections (SSTIs), foreign-body infections, pneumonia, septic arthritis, osteomyelitis, sepsis, endocarditis, and bloodstream infection (BSI) in both hospital and community settings.¹ The ability of *S. aureus* to successfully persist within the hosts is largely due to a battery of virulence factors which promote adhesion, acquisition of nutrients, and evasion of host immune responses.^{2,3} Many *S. aureus* isolates also produce one or more additional exoproteins including toxic shock syndrome toxin-1 (TSST-1), the staphylococcal enterotoxins (SEs), the exfoliative toxins (ETs), leukocidins, and so on.^{2–4} Most of the adhesins produced by *S. aureus* are cell wall-anchored proteins and are grouped into a single family which is named microbial surface components recognizing adhesive matrix molecules (MSCRAMM). MSCRAMM can bind extracellular matrix proteins such as fibronectin, fibrinogen, collagen, and elastin. The serine-aspartate repeat proteins (Sdr), encoded by the tandemly arrayed *sdrC*, *sdrD*, and *sdrE* genes located in the *sdr* locus, are members of the MSCRAMM family and members of a family of surface proteins with the presence of an R region containing various numbers of the Ser-Asp dipeptides encoded by the *sdr* genes.⁵ Sdr proteins are not closely related, with only 20 to 30% identical amino acid residues, indicating that different Sdr proteins have different roles in *S. aureus* pathogenicity.⁶ There are two, three, or five additional 110- to 113-residue sequences (B motifs) in Sdr proteins. B motifs are followed by segments composed of the SD repeats (R region) and tandemly repeated in SdrC, SdrE, and SdrD, respectively.⁵ The C-terminal end of the Sdr proteins is associated with anchoring the proteins to the bacterial cell wall.⁵ Josefsson et al. reported that at least two *sdr* genes were present in all tested *S. aureus* strains.⁵ The *sdrC* gene is always present in the *sdr* genes, while *sdrD* and *sdrE* are not.^{6,7} However, the correlation between the carriage of *sdr* genes and clonal lineage of *S. aureus* clinical isolates is unknown. The aim of the present study was to investigate the distribution of *sdr* genes among *S. aureus* isolates and the correlation between the carriage of *sdr* genes and clonal lineage of *S. aureus* isolates.

Materials and methods

Collection of *S. aureus* clinical isolates

A total of 288 non-duplicate *S. aureus* clinical isolates (single isolate per patient), including 158 associated with SSTIs and 130 associated with bloodstream infection (BSI), were

collected for this investigation. The 130 *S. aureus* BSI isolates were identified in patients from four hospitals in eastern China, including the first Affiliated Hospital of Wenzhou Medical University from January 2004 to December 2010 (66 isolates), Lishui Center Hospital in 2010 (10 isolates), Taizhou Center Hospital in 2010 (7 isolates) and Shaoxing Municipal Second Hospital in 2010 (8 isolates) and Jiangxi Provincial Children Hospital in central China in 2010 (39 isolates). The 158 *S. aureus* isolates were identified in patients with SSTIs at the first Affiliated Hospital of Wenzhou Medical University from January 2012 to September 2013 (128 isolates) and Jiangxi Provincial Children Hospital in 2010 (30 isolates). Of 288 *S. aureus* isolates tested, 217 and 71 were isolated from adults and children, respectively. All isolates tested were identified as *S. aureus* using Gram stain, positive catalase and coagulase test results, and Vitek microbiology analyzer (bioMérieux, Marcy l'Etoile, France). All *S. aureus* isolates were tested at the clinical microbiology laboratory, Department of clinical laboratory, the first Affiliated Hospital of Wenzhou Medical University. The Ethics Committee of the first Affiliated Hospital of Wenzhou Medical University exempted this study from review because the present study focused on bacteria.

DNA extraction

S. aureus isolates tested were cultured on blood agar overnight. Three to four bacterial colonies were suspended in 150 μ L sterile distilled water with 10 μ L lysostaphin (1 mg/mL) (Sangon, China) and incubated at 37 °C for 30 min. DNA was extracted using the Genomic DNA Extraction kit in accordance with the manufacturer's instructions (Sangon, China). The extracted DNA was stored at –20 °C and prepared for PCR amplification.

Detection of *sdr* genes

sdrC, *sdrD*, and *sdrE* were detected by PCR assays with primers and conditions previously described.⁸ PCR products were sequenced for the confirmation of *sdrC*, *sdrD* and *sdrE*. *S. aureus* isolates positive for *sdrC*, *sdrD*, and *sdrE* determined by PCR and DNA sequencing were used as control strain for every PCR assay for the detection of *sdrC*, *sdrD*, and *sdrE*.

Multilocus sequence typing (MLST)

MLST typing of *S. aureus* isolates tested was determined using PCR amplification of internal fragments of the seven housekeeping genes of *S. aureus* as described previously, including carbamate kinase (*arcC*), shikimate dehydrogenase (*aroE*), glycerol kinase (*glp*), Guanylate kinase (*gmK*), phosphate acetyltransferase (*pta*), triosephosphate isomerase (*tpi*), and acetyl coenzyme A acetyltransferase (*yqi*).⁹ All PCR productions of seven housekeeping genes tested were

Table 1 – Carriage of *sdrC*, *sdrD*, and *sdrE* among *S. aureus* isolates causing SSTIs and BSI.

	<i>S. aureus</i> SSTIs isolates (n = 158) (%)	<i>S. aureus</i> BSI isolates (n = 130) (%)	p-Values
<i>sdrC</i>	136 (86.1)	117 (90.0)	>0.05
<i>sdrD</i>	101 (63.9)	83 (63.8)	>0.05
<i>sdrE</i>	112 (70.9)	84 (64.6)	>0.05
<i>sdrC</i> +, <i>sdrD</i> + and <i>sdrE</i> +	75 (47.4)	59 (45.4)	>0.05
<i>sdrC</i> +, <i>sdrD</i> + and <i>sdrE</i> -	17 (10.8)	20 (15.4)	>0.05
<i>sdrC</i> +, <i>sdrD</i> - and <i>sdrE</i> +	26 (16.5)	21 (16.2)	>0.05
<i>sdrC</i> -, <i>sdrD</i> + and <i>sdrE</i> +	5 (3.2)	1 (0.9%)	>0.05
<i>sdrC</i> +, <i>sdrD</i> - and <i>sdrE</i> -	18 (11.4)	17 (13.1)	>0.05
<i>sdrC</i> -, <i>sdrD</i> + and <i>sdrE</i> -	4 (2.5)	3 (2.3)	>0.05
<i>sdrC</i> -, <i>sdrD</i> - and <i>sdrE</i> +	6 (3.8)	3 (2.3)	>0.05

sequenced. The DNA sequences were compared with the existing sequences available on the MLST website for *S. aureus* (<http://saureus.mlst.net>), and STs were determined according to the allelic profiles. Novel STs were deposited in the MLST database (<http://saureus.mlst.net>). Clonal complexes were analyzed using eBURST v3 available on the MLST website for *S. aureus* (<http://saureus.mlst.net>).

Statistical analysis

Differences between groups were assessed by using the chi-square test.

Analyses were carried out with the statistical software SPSS 13.0. *p*-values <0.05 were considered a statistically significant.

Results and discussion

Prevalence of *sdr* genes among *S. aureus* clinical isolates

SdrC promotes both bacterial adherence to surfaces and biofilm formation.¹⁰ The expression of *SdrC* and *SdrD* each contributed to the ability of *S. aureus* to adhere to human desquamated nasal epithelial cells, while the expression of *SdrE* did not promote adhesion.¹¹ However, Peacock et al. found a strong correlation between *S. aureus* invasiveness and the presence of one of the allelic variants of the *sdrE* gene.⁷ Presence of *sdrD* gene in *S. aureus* isolates was significantly more prevalent in bone infections.¹² Sitkiewicz et al. reported that *SdrD* played a role in the interactions between *S. aureus* and human immune system.¹³ In the present study,

275 (95.5%) of 288 *S. aureus* isolates were positive for at least one *sdr* genes tested. The positivity rates of *sdrC*, *sdrD*, and *sdrE* among *S. aureus* isolates were 87.8% (253/288), 63.9% (184/288), and 68.1% (196/288), respectively. The carriage of *sdrC*, *sdrD*, and *sdrE* among *S. aureus* isolates are shown in Table 2. Previous investigations showed that *sdrC* was present in all *S. aureus* isolates tested.^{6,7} However, 12.2% (35/288) of *S. aureus* isolates tested were negative for *sdrC* in the present study. The positivity rates of *sdrD* and *sdrE* in the present study were higher than in the previous study that showed positivity rates of *sdrD* and *sdrE* in *S. aureus* isolates of 48% and 56%, respectively.⁷ Out of 288 isolates, 134 (46.5%) were concomitantly positive for *sdrC*, *sdrD* and *sdrE*; 31.2% (90/288) were concomitantly positive for two of the three *sdr* genes tested. While 17.4% (51/288) of the isolates were only positive for one of the three *sdr* genes tested.

Prevalence of *sdr* genes among MRSA and MSSA isolates

In the United States, MRSA isolates from patients with complicated SSSI were more likely than MSSA isolates to carry *sdrC*, *sdrD* and *sdrE* genes.⁸ Carriage of *sdrC*, *sdrD*, and *sdrE* among *S. aureus* isolates causing SSTIs and BSI is shown in Table 1. There were no significant differences in frequencies of *sdrC*, *sdrD*, and *sdrE* between *S. aureus* isolates from SSTIs and BSI. Carriage of *sdrC*, *sdrD*, and *sdrE* among MRSA and MSSA isolates is shown in Table 2. In the present study, although the positivity rates of three *sdr* genes tested among MRSA isolates were higher than among MSSA isolates, the significant difference was only found in the prevalence of *sdrE* (*p* < 0.05). Previous study found a strong association between

Table 2 – Carriage of *sdrC*, *sdrD*, and *sdrE* among *S. aureus*, MRSA and MSSA isolates.

	<i>S. aureus</i> isolates (n = 288) (%)	MRSA isolates (n = 109) (%)	MSSA isolates (n = 179) (%)	p-Values
<i>sdrC</i>	253 (87.8)	101 (92.7)	152 (84.9)	0.063
<i>sdrD</i>	184 (63.9)	70 (64.2)	114 (63.7)	>0.05
<i>sdrE</i>	196 (68.1)	85 (78.0)	111 (62.0)	0.013
<i>sdrC</i> +, <i>sdrD</i> + and <i>sdrE</i> +	134 (46.5)	56 (51.4)	78 (43.6)	0.274
<i>sdrC</i> +, <i>sdrD</i> + and <i>sdrE</i> -	37 (12.8)	12 (11.0)	25 (14.0)	>0.05
<i>sdrC</i> +, <i>sdrD</i> - and <i>sdrE</i> +	47 (16.3)	25 (22.9)	22 (12.3)	0.032
<i>sdrC</i> -, <i>sdrD</i> + and <i>sdrE</i> +	6 (2.1)	1 (0.9)	5 (2.8)	0.4141
<i>sdrC</i> +, <i>sdrD</i> - and <i>sdrE</i> -	35 (12.2)	8 (7.3)	27 (15.1)	0.063
<i>sdrC</i> -, <i>sdrD</i> + and <i>sdrE</i> -	7 (2.4)	1 (0.9)	6 (3.4)	0.086
<i>sdrC</i> -, <i>sdrD</i> - and <i>sdrE</i> +	9 (3.1)	3 (2.7)	6 (1.7)	>0.05

+, positive; -, negative.

Table 3 – Carriage of *sdrC*, *sdrD* and *sdrE* among five major CCs *S. aureus* isolates.

	CC5 (n = 146) (%)	CC7 (n = 34) (%)	CC59 (n = 26) (%)	CC88 (n = 23) (%)	CC121 (n = 27) (%)	p-Values
<i>sdrC</i>	137 (93.8)	29 (85.3)	20 (76.9)	22 (95.7)	21 (77.8)	0.067
<i>sdrD</i>	109 (74.7)	28 (82.4)	5 (19.2)	22 (95.7)	4 (14.8)	0.000
<i>sdrE</i>	116 (79.5)	9 (26.5)	26 (100)	23 (100)	5 (18.5)	0.000
<i>sdrC</i> +, <i>sdrD</i> + and <i>sdrE</i> +	85 (58.2)	8 (23.5)	5 (19.2)	21 (91.3)	1 (3.7)	0.000
<i>sdrC</i> +, <i>sdrD</i> + and <i>sdrE</i> -	18 (12.3)	18 (52.9)	0 (0)	0 (0)	0 (0)	0.000
<i>sdrC</i> +, <i>sdrD</i> - and <i>sdrE</i> +	24 (16.4)	1 (2.9)	15 (57.7)	1 (4.3)	3 (11.1)	0.000
<i>sdrC</i> -, <i>sdrD</i> + and <i>sdrE</i> +	5 (3.4)	0 (0)	0 (0)	1 (4.3)	0 (0)	0.519
<i>sdrC</i> +, <i>sdrD</i> - and <i>sdrE</i> -	10 (6.8)	2 (0.59)	0 (0)	0 (0)	17 (63.0)	0.000
<i>sdrC</i> -, <i>sdrD</i> + and <i>sdrE</i> -	1 (0.7)	2 (0.59)	0 (0)	0 (0)	0 (0)	0.103
<i>sdrC</i> -, <i>sdrD</i> - and <i>sdrE</i> +	2 (1.4)	0 (0)	6 (23.1)	0 (0)	1 (3.7)	0.000

+, positive; -, negative.

the presence of the *sdrD* gene and MRSA isolates, while the prevalence of *sdrE* among MRSA and MSSA isolates was not different.⁶ Conversely, there was an association between carriage of *sdrE* and MRSA isolates, while the prevalence of *sdrD* in MRSA isolates was similar to that in MSSA isolates in the present study. A previous study also found that all MRSA isolates were positive for two or the three *sdr* genes.⁶ Our investigation showed that the prevalence of co-existence of *sdrC* and *sdrE* among MRSA isolates was significantly higher than among MSSA isolates ($p < 0.05$). However, there was no significant difference between the concomitant carriage of *sdrC*, *sdrD*, and *sdrE* among MRSA and MSSA isolates ($p < 0.05$). In 35.8% (39/109) of MRSA isolates and in 29.1% (52/179) of MSSA isolates there were concomitant positivity for two genes tested. Compared with MRSA isolates (11.0%, 11/109), more MSSA isolates (22.3%, 40/179) were only positive for one *sdr* locus. The *sdrC*-positive, *sdrD*-negative, and *sdrE*-negative gene profile was exclusively found among 29 MSSA isolates.⁶ In contrast, this gene profile was found both in MRSA and MSSA isolates in the present study. All gene profiles of *sdr* genes were found among MSSA isolates. However, *sdrC*-negative, *sdrD*-positive, and *sdrE*-negative gene profile was not found among MRSA isolates except one isolate.

Prevalence of *sdr* genes among different clonal complexes

A total of 59 STs were identified among 288 *S. aureus* isolates tested. Five clonal complexes (CCs) accounting for more than 20 isolates, including CC5, CC7, CC59, CC88, and CC121 were identified by clustering analysis using eBURST v3 available on the MLST website for *S. aureus* (<http://saureus.mlst.net>). CC5, CC7, CC59, CC88, and CC121 accounted for 146, 34, 26, 23 and 27 *S. aureus* isolates, respectively. Among 146 CC5 isolates 27 STs were identified, including ST188 (21 isolates), ST630 (21 isolates), ST25 (14 isolates), ST239 (13 isolates), ST6 (13 isolates), ST1 (11 isolates), ST5 (11 isolates), and ST965 (9 isolates). Five STs including ST7, ST774, ST789, ST943, and ST2833 were found among 34 CC7 isolates, among which ST7 was the predominant ST accounting for 30 isolates. Among 26 CC59 isolates, 23, 1, 1, and 1 belonged to ST59, ST749, ST2201, and ST2832, respectively. Only two STs, ST88 (22 isolates), and ST1219 (one isolate) were identified among CC88 isolates. A total of seven STs were found among 27 CC121 isolates, including ST121 (11 isolates), ST120 (10 isolates), ST946 (two isolates), ST2209 (one isolate), ST2210 (one isolate), ST2213

(one isolate), and ST2213 (one isolate). These data indicate that included *S. aureus* isolates exhibited considerable genetic heterogeneity.

The distribution of some virulence genes was correlated with the different MRSA lineages.^{14,15} All ST1 and ST5, 95.2% (20/21) of ST188 and 95.2% (20/21) of ST630 isolates were positive for *sdrC*. All ST1, ST5, ST7, and ST25 isolates were positive for *sdrD*. While all ST121 and ST398 isolates were negative for *sdrD*. All ST59 and ST88 isolates were positive for *sdrE*. All ST1 isolates were concomitantly positive for *sdrC* and *sdrD*. Concomitant carriage of *sdrC*, *sdrD*, and *sdrE* was found among all ST5, 75.0% (9/12) of ST1, 69.2% (9/13) of ST6, 78.6% (11/14) of ST25, and 90.9% (20/22) of ST88 isolates. However, five of seven ST39 isolates were negative for *sdrC*, *sdrD*, and *sdrE*.

Carriage of *sdrC*, *sdrD*, and *sdrE* among five major CCs isolates is shown in Table 3. In addition to CC59 isolates with an *sdrC* prevalence of 76.9%, the prevalence of *sdrC* among CC5, CC7, CC88, and CC121 isolates were more than 85.0%, among which CC88 isolates had the highest prevalence of *sdrC* (95.7%). There were no differences in the positivity rates of *sdrC* among five major *S. aureus* clones ($p = 0.067$). However, the positivity rates of *sdrD* among CC5, CC7, and CC88 isolates were high to 74.7%, 82.4%, and 95.7%, respectively, while the rates among CC59 and CC121 isolates were only 19.2% and 14.8%, indicating that *sdrD* was linked to CC5, CC7, and CC88 isolates, especially CC88 isolates. Compared with CC59 and CC88 isolates with an *sdrE* prevalence of 100% and CC5 isolates with an *sdrE* prevalence of 79.5%, the prevalence of *sdrE* among CC7 (26.5%) and CC121 isolates (18.5%) were significantly lower ($p < 0.05$). There was a strong association between presence of *sdrE* and CC59, CC88, and CC5 isolates. Surprisingly, 91.3% of CC88 isolates were concomitantly positive for *sdrC*, *sdrD* and *sdrE*, followed by CC5 isolates (58.2%), while concomitant carriage of the three *sdr* genes tested among CC7 (23.5%), CC59 (19.2%), and CC121 (3.7%) isolates was much lower, indicating a significant correlation between concomitant carriage of *sdrC*, *sdrD*, and *sdrE* and CC88 isolates. The prevalence of *sdrC*-positive, *sdrD*-positive, and *sdrE*-negative gene profile among CC7 isolates (52.9%) was higher than in other CCs isolates, especially CC59, CC88, and CC121 isolates where this gene profile was not found, indicating that such profile was significantly associated with the CC7 clone. *sdrC*-positive, *sdrD*-negative, and *sdrE*-positive gene profile was found in 57.7% of CC59 isolates, which was significantly higher than that in other CCs isolates ($p < 0.05$). There

was an association between *sdrC*-positive, *sdrD*-negative, and *sdrE*-positive gene profile with CC59 isolates. The positivity rates of *sdrC*-negative, *sdrD*-positive, *sdrE*-positive gene profile among five major clones were very low, and absent among CC7, CC59, and CC121 isolates. The prevalence of *sdrC*-positive, *sdrD*-negative, and *sdrE*-negative gene profile among CC121 isolates (67.3%) was much higher than in other CCs isolates ($p < 0.05$), indicating a correlation between *sdrC*-positive, *sdrD*-negative, and *sdrE*-negative gene profile with CC121 clone. Sabat et al. reported that *S. aureus* isolates with *sdrC*-positive, *sdrD*-negative, and *sdrE*-negative gene profile belonged to ST1, ST12, ST25, ST30, ST34, ST39, ST47, and ST49.⁶ More CC59 isolates (23.1%) carried *sdrC*-negative, *sdrD*-negative, and *sdrE*-positive gene profile relative to other four CCs isolates.

S. aureus infections usually result from the combined action of a variety of virulence factors. However, the contribution of particular virulence factors to *S. aureus* infection is unclear. To further cast light on the role of *sdr* genes in *S. aureus* infections caused by different clones, a larger number of *S. aureus* clinical isolates with specific clones should be investigated.

In conclusion, our investigation indicated that different *S. aureus* lineages were associated with specific patterns of carriage of *sdr* genes.

Conflicts of interest

The authors declare no conflicts of interest.

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