

# Molecular epidemiology of *Staphylococcus aureus* in asymptomatic carriers

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**Abstract** Microarrays were used to extensively characterise 155 *Staphylococcus aureus* isolates obtained from asymptomatic carriers from Saxony, Germany, in order to determine clonal complex affiliation, as well as the carriage of clinically relevant genes. Isolates belonged to 20 different clonal complexes (CCs). The most common CC was CC8 (18.71%), followed by CCs 15, 30 and 45. Three isolates (1.94%) were methicillin-resistant *S. aureus* (MRSA). Beta-lactamase was common (70.97%), but other resistance genes were found only sporadically. Genes encoding superantigens were abundant. The enterotoxin cluster *egc* was found in 45.81% of isolates. The toxic shock syndrome toxin gene *tst* was detected in 14.84% of isolates and 17.42% harboured enterotoxin A alleles (*sea*, *sea-N315*). Contrarily, Pantone-Valentine leukocidin (*lukS/F-PV*) was rare, being found in only one methicillin-susceptible CC30 isolate. Its low prevalence in asymptomatic carriers might emphasise a

pathogenetic significance in patients with skin and soft tissue infections. Most microbial surface components recognising adhesive matrix molecules of the host (MSCRAMMs) genes were nearly ubiquitously present. However, two MSCRAMM genes, *cna* (collagen adhesin) and *sasG* (surface protein G), were detected in only some CCs. These data provide an insight into its pathogenesis, especially when compared to isolates from patients with defined clinical conditions. They might also be helpful for the design of a future vaccine.

## Introduction

*Staphylococcus aureus* can be found in the anterior nares of a great proportion of a healthy human population. The prevalence is approximately 30% [1]. However, *S. aureus* is also able to cause a variety of skin and soft tissue infections and debilitating or even fatal diseases, such as pneumonia, necrotising fasciitis and septicaemia. It can also produce toxins which cause toxin-mediated conditions such as toxic shock syndrome or food intoxications.

It is a challenge to define which genetic factors determine whether an encounter between a human and *S. aureus* results in asymptomatic carriage or in clinical disease. Recent studies [1–3] indicated that there was no fundamental difference between infecting and colonising *S. aureus* populations. This emphasised the role of host factors, such as immunity or the presence of synthetic implants, and of accidental factors, such as injury.

In the present study, we used microarrays in order to characterise *S. aureus* isolates obtained from asymptomatic carriers. In this way, we determined the presence of a variety of target genes, including resistance determinants, as well as toxin genes and other virulence factors.

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**Table 1** Prevalence rates of clonal complexes (CCs) and of selected genes among *Staphylococcus aureus* from asymptomatic carriers (tr = truncated; these isolates had a truncated *egc* locus)

Clonal complex	Number of isolates	Percent	<i>mecA</i>	<i>blaZ/I/R</i>	<i>ermA</i>	<i>ermC</i>	<i>aacA-aphD</i>	<i>aadD</i>	<i>aphA3</i>	<i>sat</i>	<i>dfrA</i>
CC8	29	18.71		25	2	9		4			
CC15	26	16.77		20							
CC30	25	16.13		21		1		1			
CC45	14	9.03	1	11			1		2	2	
CC101	11	7.10						1			
CC22	8	5.16	1	6		1					
CC25	8	5.16		6							
CC121	7	4.52		4		1					
CC7	6	3.87		5							
CC5	4	2.58	1	3	1			1			
CC12	4	2.58									
CC1	2	1.29		2							
CC20	2	1.29		2							
CC6	1	0.65									
CC9	1	0.65		1			1				1
CC59	1	0.65		1							
CC97	1	0.65									
CC182	1	0.65		1							
CC426	1	0.65									
CC573	1	0.65		1							
Undetermined CC ( <i>agr</i> I)	1	0.65		1							
Undetermined CC ( <i>agr</i> II)	1	0.65									
Total	155	100	3	110	3	12	2	7	2	2	1
Percent			1.94	70.97	1.94	7.74	1.29	4.52	1.29	1.29	0.65

Additionally, the detection of allelic variants of core variable elements, such as *agr* and *hsdS* genes, capsule determinants and genes encoding microbial surface components recognising adhesive matrix molecules of the host (MSCRAMMs), allowed to characterise the overall genetic background of the isolates, i.e. to assign them to clonal complexes (CCs) [4].

## Materials and methods

### Bacterial isolates

For this study, we characterised 155 isolates of *S. aureus* from three different groups of carriers. Isolates were collected between 2005 and 2008 in Dresden in Saxony, Germany.

The first group (77 isolates from nasal swabs) were junior medical students, who had not yet worked with hospitalised patients.

The second group (67 isolates) comprised patients who were admitted because of conditions unrelated to *S. aureus* infection. Nasal swabs of patients suffering from stroke, intracerebral haemorrhage or trauma were taken on admission as part of a methicillin-resistant *S. aureus* (MRSA) screening programme. In case of cataract surgery, conjunctival swabs were taken as pre-operative screening.

The third group (11 isolates from nasal swabs) comprised of employees of a biomedical facility. Samples were

taken as part of a quality control scheme in order to guarantee the absence of pathogenic bacteria from the products of that company.

Cultures were grown (overnight, 37°C) on Columbia blood agar. *S. aureus* was cloned by picking single colonies and re-cultured. Culture material was harvested and lysed using lysostaphin, lysozyme, ribonuclease A and proteinase K (for concentrations and further details, see [4]). DNA was purified using Qiagen EZ1 according to the manufacturer's tissue lysis protocol.

### Array procedures

DNA arrays used for this study, as well as related procedures and protocols, have been previously described in detail [4, 5]. This microarray covers 332 different target sequences, corresponding to, depending on the nomenclature, approximately 185 distinct genes and their allelic variants. It includes species markers, resistance genes, exotoxins, MSCRAMM genes, as well as SCC*mec*, capsule and *agr* group typing markers. The target genes are listed in Supplement 1. The primer and probe sequences have been published previously [4] and are available upon request.

All targets were amplified simultaneously, using a linear primer elongation with one primer per target. Within this step, biotin-16-dUTP was incorporated into the resulting amplicons, which were subsequently hybridised to the array. This was followed by washing and blocking steps.

<i>mupR</i>	<i>tetK</i>	<i>fosB</i>	<i>qacA</i>	<i>qacC</i>	<i>tst</i>	<i>sea</i>	<i>sea-N315</i>	<i>seb</i>	<i>sec/sel</i>	<i>sed/sej/ser</i>	<i>egc</i>	<i>seh</i>
		29	4		2	4		2		23		
1	1	26		1								
		25		1	19	8			3		24+1 tr	2
					1				9		14	
		11		1					3		8	
		8						2			8	
	2	4						1			7	
		4				1	5					
		4					2					
							3		3	1	4	
						1						2
		2									2	
		1				1					1	
		1						1				
					1	1					1	1
		1							1		1	
							1				1	
											1 tr	
1	3	116	4	3	23	16	11	6	19	24	73	5
0.65	1.94	74.84	2.58	1.94	14.84	10.32	7.10	3.87	12.26	15.48	47.10	3.23

Horseradish-peroxidase-streptavidin conjugate was added to the array, followed by incubation and washing. Then, Seramun Green precipitating dye (Seramun, Heidesee, Germany) was added. Finally, an image of the microarray was recorded and analysed using a designated reader and software (ATR01, IconoClust, both by CLONDIAG, Jena, Germany).

The affiliation of isolates to CCs was determined by the comparison of hybridisation profiles to previously typed multilocus sequence typing (MLST) reference strains [4].

## Results and discussion

A complete overview of the microarray hybridisation data is provided as a supplementary file and a simplified summary of the CC affiliations and gene carriage within CCs is provided in Table 1.

Isolates belonged to twenty different CCs. Two isolates were not typeable. The most common CC was CC8, followed by CCs 15, 30 and 45 (Table 1). Fifty-five isolates (35.48%) carried capsule type 5 genes (*capH/I/J/K-5*). This included all isolates of CCs 5, 8, 9, 20, 22, 25, 97, 182 and 573. Another 100 isolates (64.52%) were positive for capsule type 8 (*capH/I/J/K-8*). Eighty-four isolates (54.19%; CCs 6, 7, 8, 20, 22, 25, 45, 59, 97, 101, 182, 426, and one unidentified) belonged to *agr* group I. There

were thirty-six *agr* group II isolates (23.23%; CCs 5, 9, 12, 15 and 573), twenty-eight *agr* group III isolates (18.06%; CCs 1, 30 and one unidentified), as well as seven *agr* group IV isolates (4.52%; exclusively CC121).

The most common resistance gene was the beta-lactamase gene *blaZ* (accompanied by *blaR* and *blaI*), which was detected in 110 (70.97%) isolates. The details, as well as the data on other resistance genes are provided in Table 1 and in Supplement 1.

Only three isolates (1.94%) proved to be MRSA. One isolate sampled from a 30-year-old male patient belonged to ST22-MRSA-IV (UK-EMRSA-15/Barnim epidemic strain). Another MRSA isolate was sampled from a 62-year-old female patient with underlying haematological condition and history of hospitalisations. This isolate was a ST45-MRSA-IV (Berlin epidemic strain). The third MRSA isolate was sampled from a 52-year-old male haematology patient who also had a history of repeated hospitalisations; it belonged to ST5-MRSA-II (UK-EMRSA-3/Rhine-Hesse epidemic strain). Additionally, five isolates harboured genes usually belonging to SCC*mec* elements without being positive for *mecA* and associated genes (*mecR*, *mecI*, *ugpQ*). These included four CC8 isolates carrying *ccrA/B-4* genes and the ST182 isolate which was positive for *ccrA/B-2* and the *kdp*-operon.

Apparently, common MRSA strains do not necessarily derive from common CCs. The most abundant CCs in this

**Table 1** (continued)

Clonal complex	<i>sek/seq</i>	<i>lukF/S-PVL</i>	<i>lukD</i> and/or <i>lukE</i>	<i>hIII</i>	<i>sak</i>	<i>chp</i>	<i>scn</i>	<i>eta</i>	<i>etb</i>	<i>etd</i>	<i>edinB</i>
CC8	2		29	29	28	4	28				
CC15			26	26		26	26				
CC30		1		25	14	12	15				
CC45				14	13	13	13				
CC101			11	11	10		10				
CC22					8	8	8				
CC25			7	8	8	8	8			8	8
CC121			7	7	7	2	7	2	1		
CC7			6	6	5		5				
CC5			4	4	4	4	4				
CC12			4	4	3		3				
CC1	1		2	2	2		2				
CC20			2	2	2	2	2				
CC6			1	1	1		1				
CC9				1	1	1	1				
CC59	1			1		1	1				
CC97			1	1	1		1				
CC182				1	1	1	1				
CC426			1	1	1	1	1				
CC573				1			1				
Undetermined CC ( <i>agr</i> I)			1	1	1		1				
Undetermined CC ( <i>agr</i> II)					1	1	1				
Total	4	1	102	146	111	84	140	2	1	8	8
Percent	2.58	0.65	65.81	94.19	71.61	54.19	90.32	1.29	0.65	5.16	5.16

study were CC8, 15 and 30. To our knowledge, there is no description of a MRSA strain from, e.g. CC15, while CC8 and CC30 produced several widespread and clinically important MRSA clones. This suggests that the abundance of a CC, i.e. the probability for it to come into contact with a potential donor of a mobile genetic element, was not the only factor influencing its chance to evolve into MRSA. Thus, further studies should investigate whether there were functional differences between different CCs, affecting, e.g. the ability to integrate SCC*mec* elements.

Some genes encoding superantigens were common. An example is the enterotoxin cluster *egc* (*seg*, *sei*, *sem*, *sen*, *seo* and *seu*), which was detected in 71 isolates (45.81). In another two isolates (1.29%), it was truncated (*seo* and *sem+seo*). Enterotoxin A (*sea*) was found in 17 isolates (10.32%), and an allele of it, designated *sea-N315* or *sep*, was present in another 11 isolates (7.10%). The gene encoding toxic shock syndrome toxin (*tst*) was detected in 23 isolates (14.84%) that belonged to CCs 8, 30, 45 and 426, with CC30 being predominant.

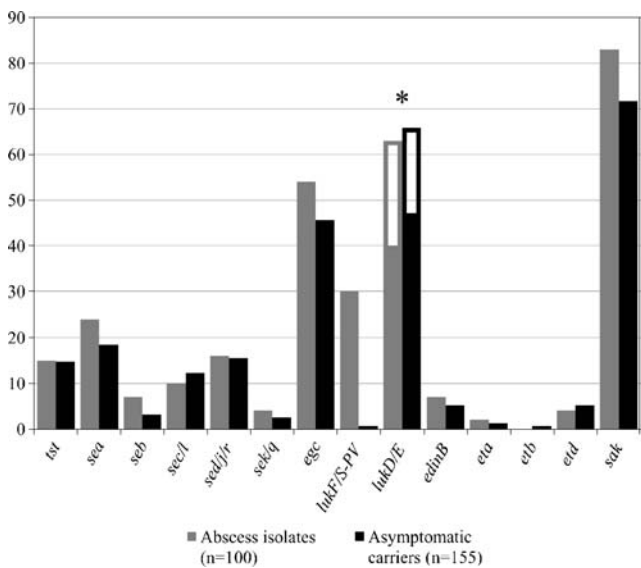
Other studies also found similar prevalence rates for enterotoxins and *tst* in carriage isolates [2, 3], and a similar high rate of *tst*-positive *S. aureus* among carriers (9%) has been noted in Japan [6]. The abundances of most virulence markers (except for PVL, see below) are also very similar (Fig. 1) to the frequencies of these markers in previously tested abscess isolates [7]. There are different possible

interpretations for this observation. Enterotoxins and *tst* might simply not play any significant pathogenetic role in skin and soft tissue infections, and their prevalence in patients merely reflected the situation in healthy carriers. Alternatively, they could have the *same* function in carriers as well as in patients, e.g. to trigger the apoptosis of leucocytes on intact mucous membranes or within minor foci of inflammation, helping the bacteria to persist. This might also explain why superantigens are abundant, while superantigen-mediated disease, such as toxic shock syndrome is rare. The latter could then be attributed to host factors such as the absence of antibodies, to massive systemic effect of the toxin and, in the case of menstrual toxic shock, to non-physiological conditions created by the presence of hyper-absorbent tampons.

On the other hand, Pantone-Valentine leukocidin genes (*lukF/S-PV*) were found only once (0.65%) in a methicillin-susceptible CC30 isolate which additionally carried *tst*, enterotoxins C and L, and the *egc* cluster. This is essentially the same prevalence as found for carriers in a recent Dutch study [8]. In abscess patients, PVL was much more common (30% [7] to 38.9% [8]). Thus, the presence of PVL more reliably corresponds to a clinical condition, while the detection of other virulence factors did not allow drawing a distinction between infecting and colonising strains. Because of the low rate of asymptomatic PVL carriage, PVL-positive *S. aureus* should be regarded as

<i>edinC</i>	<i>bbp</i>	<i>clfB</i>	<i>cna</i>	<i>fib</i>	<i>fnbA</i>	<i>fnbB</i>	<i>map</i>	<i>sasG</i>	<i>sdrC</i>	<i>sdrD</i>
	29	29		29	29	29	29	29	29	29
	26	26		26	26	26	26	26	26	22
	24	25	22	25	24	6	25		23	25
	13	14	14	13	14	14	14		14	12
	10	9		11	11	11	11		11	10
	7	8	8	8	8	5	5	8	8	8
	6	8		8	8	7	8		8	6
1	7	7	6	7	7	5	7		7	5
	6	6		6	6	6	6		6	6
	4	4		4	4	4	4	4	4	4
	4	3	4	4	4	4	4		4	4
	2	2	2	2	2	2	1	2	2	2
	2	2		2	2	2	1	2	2	1
	1	1	1	1	1	1	1	1	1	1
	1	1		1	1	1	1		1	1
	1	1		1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1	1
1	147	152	62	154	154	127	149	77	153	140
0.65	94.84	98.06	40.00	99.35	99.35	81.94	96.13	49.68	98.71	90.32

obligatory pathogens rather than as occasional or accidental pathogens. Whether this was due to PVL itself or to another co-expressed factor [9], or to a combination of both, still needs to be clarified experimentally.



**Fig. 1** Comparison of the prevalence rates of virulence factors found in this study (black) to abscess isolates from a previous study ([7], grey). \*For *lukD/E*, the percentage of isolates being positive for both components is indicated (solid bar), as well as the proportion of isolates in which only one out of the two components was detectable

Some virulence factors always clustered together. This included enterotoxin genes *sec+sel*, *sed+sej+ser* and *sek+seq*, as well as genes encoding the epithelial cell differentiation inhibitors B (*edinB*) and the exfoliative toxin *etd*.

The haemolysin gamma cluster (*lukS*, *lukF* and *hlgA*) was detected in all isolates, although isolates from CCs 22 and 45 harboured deviant alleles, as indicated by reactivity with a probe derived from GenBank sequence EF672356 [4]. Other haemolysin genes *hl* (SACOL0921 in COL, SA0780 in N315), *hla* and *hld* were detected in all isolates, and *hIII* (SACOL2160, SA1973) was found in 146 isolates (94.19%). This could be an indication for a divergent allele, most notably in CC22. Leukocidin genes *lukD/lukE* were both present in 73 isolates (47.10%). In another 29 isolates-belonging to CCs 6, 15, 20, 101, 121 and 426-only one out of the two components were detectable. This could also be indicative of the presence of deviant alleles.

The ACME locus (*arcA/B/C/D*) was found in four isolates (2.58%) which belonged to CC8 as the USA300 epidemic strain (ST8-MRSA-IV) where this gene cluster has originally been detected [10]. Genes of the *ssl/set* clusters were present in all isolates, yielding hybridisation patterns specific for the respective CCs (Supplement 1, [4]).

Biofilm genes *icaA/icaC/icaD* were present in all isolates; *bap* (biofilm-associated protein) was always

absent. MSCRAMM genes *clfA* (clumping factor gene A), *ebh* (endothelial cell binding protein), *ebpS* (cell surface elastin binding protein), *eno* (enolase/laminin binding protein) and *vwb* (von Willebrand factor binding protein) were ubiquitous. MSCRAMM genes, which were not always present, are listed in Table 1. While the absence of most of these genes was probably due to random deletions and not related to CC affiliations (e.g. *bbp*, which was absent from two out of eight CC25 isolates), two MSCRAMM genes, *cna* (collagen adhesin) and *sasG* (surface protein G), were present only in isolates of certain CCs. The latter gene was found in 77 isolates (49.68%). This is remarkable as its *S. epidermidis* homologue *aap* appears to be more prevalent (around 90%, [11]). Possible explanations are a truly different functionality in *S. aureus* or the presence of a divergent, currently unsequenced and undetectable, allele of *sasG* in some CCs. One strain (Sanger MRSA 252) from such a CC (CC30) has been fully sequenced, and it did not harbour such a *sasG* allele. Since a single strain might not be representative, more genome data from the apparently *sasG*-negative CCs are needed.

Generally, MSCRAMM genes, genes of the *ssl/set* clusters, as well as *agr* and capsule genes yield results specific for CCs (allowing to assign a given isolate to a CC, [4]). Whether a CC affiliation (reflecting the actual allelic variant of the core genome) in itself is of pathogenetic significance is not yet clear, although allelic variations of core genome markers such as MSCRAMMs may result in different functionalities. On the other hand, superantigens, PVL, genes associated with beta-haemolysin converting phages (*sak*, *scn*, *chp*), as well as resistance genes, are apparently randomly distributed across diverse CCs. This can, of course, be explained by their usual location on mobile genetic elements (phages, plasmids, transposons, SCC- or 'pathogenetic island'-like elements). Thus, a molecular epidemiology of *S. aureus* infection needs to take into account not only two co-evolving populations (humans and *S. aureus*), but three (humans, *S. aureus* core genome and, separately, *S. aureus* mobile elements). Screening for toxin genes by polymerase chain reaction (PCR) avoids the issue of CC affiliation, while MLST is not able to determine toxin gene carriage. For practical purposes, the multitude of relevant factors requires a DNA array approach, and the proposed technology allows the rapid screening of significant numbers of clinical isolates.

While our study provides insight into the epidemiology of *S. aureus* in asymptomatic carriers in southeastern Germany, further work should focus on carriers from other regions, as the epidemiological situation might be different in different locations. This is indicated by a study on *S. aureus* carriage in remote Australian communities [12]. In this setting, CCs 1, 5 and 45 predominated. CCs 8, 15, 25,

101 and 121, as well as some others, were also found in smaller numbers.

Data on the epidemiology of *S. aureus* carriage might provide an insight into its pathogenesis, especially when compared to isolates from clearly defined pathological conditions. Knowledge of the relative abundances of virulence factors and surface molecules might also be helpful for the design of a future vaccine.

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