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Silent mupirocin resistance in methicillin-resistant *Staphylococcus aureus*

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INTRODUCTION

Staphylococcus aureus is a bacterium responsible for many human infections, often resistant to commonly used antimicrobial drugs[1]. There are ongoing reports of the occurrence of silencing of antibiotic resistance by mutation (SARM) when bacteria harbor an antibiotic resistance determinant but remain susceptible to the corresponding antibiotic as a consequence of a genetic defect[2-4]. The presence of bacteria harboring "silent" or "cryptic" antimicrobial resistance genes carries a risk of implementing an ineffective antimicrobial drug in therapy, as the gene would not be activated until infection.

CRYPTIC GENE

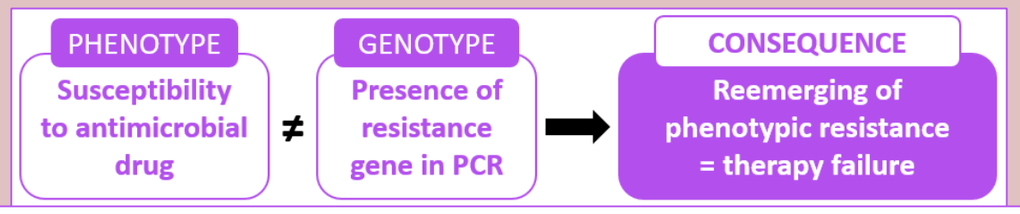

Fig. 1. A graphical representation of a cryptic gene. The Presence of a cryptic gene is usually connected with a mutation causing incorrect protein translation and the lack of expression of antimicrobial resistance.

AIM

The aim of the study was to characterize the genetic mechanism of SARM against mupirocin in methciillin-resistant *Staphylococcus aureus* (MRSA).

MATERIALS & METHODS

In total, 334 *S. aureus* strains were investigated for phenotypic resistance to cefoxitin, erythromycin, tetracycline, gentamycin and mupirocin. PCR was used to screen for the presence of corresponding antibiotic-resistance genes: cefoxitin (*mecA, mecB, mecC*); erythromycin (*ermA, ermB, ermC*); clindamycin (*vga(A)v*); mupirocin (*mupA*); gentamycin (*aacA-aphD*); tetracycline (*tetM, tetK*). Additionally, several virulence genes which presence was attributed to toxin release or biofilm formation was investigated as presented previously[5]. The phenotype was investigated using standard recommended microbiological methods including disc-diffusion method or the determination of minimum inhibitory concentration. The results were interpreted according to the EUCAST. The discrepancies between the genotype and phenotype were investigated. The mupA gene was sequenced as described previously, using Sanger sequencing and six designed pair of primers[6]. The sequences were aligned to create a whole gene sequence, which was then compared with the sequence for mupA gene derived from NCBI database, namely with the reference fully active strain and strain exhibiting non-functional polymorphic mupirocin resistance. For strains exhibiting silenced mupirocin resistance the MLST sequencing was conducted as described elsewhere[5].

RESULTS

Tab. 1. Antimicrobial resistance, the Presence of selected toxin and adhesin genes and epidemiololgical investigation of SARM *S. aureus* isolates.

Antimicrobial resistance	Genes		*SCCmec* type	Genotyping
	Toxins	Adhesins		MLST
Cefoxitin, tobramycin, levofloxacin, ciprofloxacin	-	*eno, fnbA, fnbB, fib, icaA/D/B/C*	VI	ST6295 (CC8)

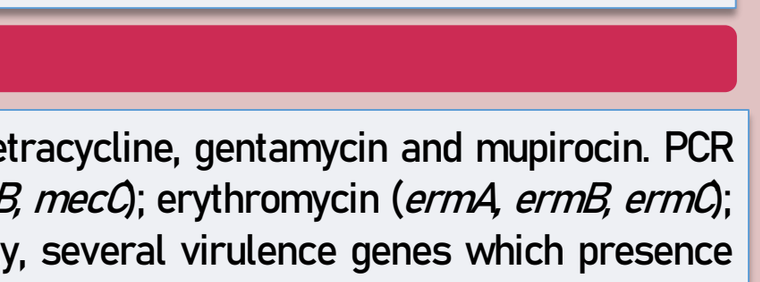

Fig. 2. A fragment of the Sanger chromatogram for *mupA* gene.

The analysis showed the presence SARM in 0.6% of *S. aureus* strains (2/334). In both cases, they were strains harboring the ***mupA gene*** (resistance to mupirocin). Sequencing showed the presence of a deletion, resulting in incorrect translation of the nucleotide into an amino acid sequence, shortening the amino acid chain and inhibiting the synthesis of the protein responsible for mupirocin resistance.

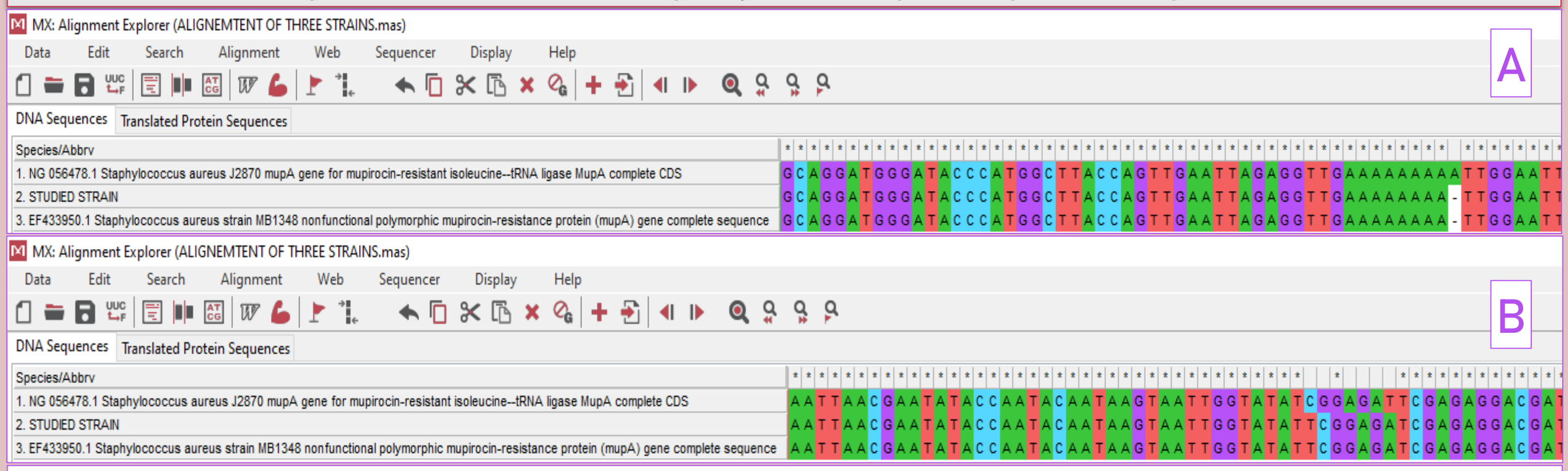

Fig. 3. (A) An alignment representing the single nucleotide deletion in poly(A) tract in the studied MRSA isolate and the reference strain with nonfunctional polymorphic mupirocin-resistance protein vs. the reference *S. aureus* Strain with normal *mupA* expression; (B) an alignment showing the frameshift in amino-acid sequence.

CONCLUSIONS

Mupirocin is an antibiotic applied in the treatment of staphylococcal infection of the skin, including the eradication (the removal of a microorganism from the body) of *S. aureus* from the nasal cavity. Despite the analysis showed a low share of *S. aureus* strains exhibiting silenced antimicrobial resistance (<1%), there is still a risk of antimicrobial therapy failure and reinfection. Further studies should also focus on determining factors that increase the probability of activation of "silent" genes responsible for the resistance to mupirocin.

REFERENCES: [1] https://doi.org/10.1080/21505594.2021.1878688 ; [2] https://doi.org/10.15374/PwAil0201601 ; [3]. https://doi.org/10.1016/j.bioorg.2019.103252 ; [4] https://doi.org/10.3389/fmicb.2020.01744; [5] https://doi.org/10.3390/pathogens10040427; [6] https://doi.org/10.1128/AAC.00241-07

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