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Relationship between toll-like receptor 2 R753Q and T16934A polymorphisms and *Staphylococcus aureus* nasal carriage

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Abstract

Background: The association among specific single-nucleotide polymorphisms (SNPs) in TLR2 R753Q (rs5743708) and T16934A (rs4696480) and the nasal carriage of *Staphylococcus aureus* was studied in adults before CABG.

Methods: The TLR2 polymorphisms were genotyped in 299 consecutive patients prepared for a CABG operation. Genotyping was performed using restriction fragment length polymorphism (RFLP) analysis of PCR-amplified fragments. Two nasal swab cultures were taken within 2 weeks before the operation. Subjects were classified as *Staphylococcus aureus* carriers if at least one culture was positive while those patients with both cultures found to be negative were classified as non-carriers.

Results: The prevalence of nasal *S. aureus* carriage in the final cohort was 22.1% (66/299), while no MRSA was detected in our study group. No significant differences in the TLR2 polymorphisms were observed between the study and the control groups. No associations were found between *TLR2* haplotypes and the covariates of age, sex, NYHA, weight, height, BMI, CAD, smoking status and ESlog score. No differences were found between carriers and non-carriers regarding the allelic distribution of the TLR2 T-16934A SNP. Almost 93% of the patients who were screened for the presence of the TLR2 Arg753Gln (rs5743708) were GG wild type homozygous. Twenty one subjects from the study group (7.1%) were GA heterozygous, while no patient in either group was homozygous for the TLR2 Arg753Gln (rs5743708) mutation. TLR2 Arg753Gln genotyping showed that GA heterozygous patients were detected more frequently in the group of *Staphylococcus aureus* nasal carriers than in non-carrier adults.

Conclusion: Our results suggest that the carrier status for the GA variant of the TLR2 Arg753Gln (rs5743708) polymorphism may be a risk factor for *Staphylococcus aureus* carriage.

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Key words: TLR 2, polymorphism; *Staphylococcus aureus*, carriage; cardiac surgery

Postoperative nosocomial infections are a considerable problem in cardiac surgery patients associated with increased morbidity, mortality and prolonged hospitalization [1–3]. *Staphylococcus aureus* (*S. aureus*) nasal carriage is a major risk factor for postoperative infections in cardiac surgery patients [4]. Undoubtedly, many factors, both environmental and the host's immune status, are thought to play a crucial role in determining the *S. aureus* nasal carrier state [5]. Toll-like receptors (TLRs) are transmembrane proteins that play an important role in the activation of the

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immune system by regulating the production of antimicrobial peptides and inflammatory cytokines. Toll-like receptors (TLRs) are a class of pattern recognition molecules with unique functions in the innate immune response to microbial pathogens. TLR2 has been shown to be involved in the innate immune response to Gram-positive bacteria, an immune sensor for Gram-positive bacterial cell wall components. Polymorphisms of TLR2 deteriorate the immune response of the body, and may be associated with certain diseases, such as infective vitiligo, endocarditis and atopic dermatitis [6–8]. The common single nucleotide polymorphism (SNP) in the TLR2 gene that is translated into an amino acid substitution of arginine for glutamine at position 753 (R753Q also described as Arg753Gln [rs5743708]) results in a defective response to peptidoglycan, lipopeptides, and other known ligands, and may increase a patient's predisposition to microbial infections [9–13]. In another study, the authors have suggested that spontaneous bacterial peritonitis was significantly more frequent in patients with the TLR2 T16934A (rs4696480) polymorphism [14]. Therefore, the present study aimed to investigate the frequencies of TLR2 gene polymorphisms R753Q (rs5743708) and T16934A (rs4696480) in cardiac surgery patients and to explore the association between the polymorphisms and the nasal carriage of *Staphylococcus aureus* in patients undergoing cardiac surgery operations.

METHODS

The study was approved by the Bioethics Committee of the Pomeranian Medical University while informed consent was obtained from all subjects. This was a prospective observational cohort study. The study group consisted of 299 consecutive adults. Therefore, 222 male and 77 female patients, with an age range from 32 to 85 years (mean 63.2 years) who had qualified for their first coronary artery bypass grafting were included in this study. The distribution of TLR2 SNPs in the study group was compared with that observed in 167 healthy newborns identified from the same area. The demographic and clinical data were assessed during the pre-assessment visit. Two nasal swab cultures were performed within 2 weeks before the planned operation. All swabs (CITOSWAB, Collection Swab Stuart Medium, CellPath Ltd., Newtown Powys, UK) were inoculated on blood agar and, in parallel, on MRSA chrome agar plates (BD Diagnostics, Heidelberg, Germany). The plates were incubated at 37° C for no more than 48 hours. The appearance and growth score on blood agar were recorded. Colonies suspected to be *S. aureus* were characterized further with the slide coagulase test. We obtained complete bacteriological results in 299 patients. Subjects were classified as carriers if at least one of the cultures were positive, while those with both cultures found to be negative were classified as non-carriers. All participants were genotyped for 2 known functional TLR2 gene polymorphisms. During hospital admission 2 mL of the whole blood samples were collected from each subject by the standard venipuncture method. In the control group, 5 mL of cord blood was collected after birth. Genomic DNA was isolated from the peripheral blood leukocytes using the QIA DNA Mini Kit (Qiagen). Subsequently, the polymerase chain reaction (PCR)-restriction fragment length polymorphism method to investigate the R753Q (rs5743708) and T16934A (rs4696480) polymorphisms was applied. The primers were as follows: forward 5′-CCAAATTTAAAAGAGGGCAAGAA-3′ and reverse 5'-GGTGATTAGGTTATGAAGGCTGTA-3′ for the rs4696480 polymorphism, and for the rs5743708 polymorphism: forward 5'-TATGGTCCAGGAGCTGGAGA-3′ and reverse 5'-TGACATAAAGATCCCAACTAGACAA-3′13. Forward and reverse primers for the rs4696480 T16934A polymorphism were designed using Lasergene (DNA Star) software. Optimal PCR conditions (temperature-time profile, number of cycles) for given primer pairs and conditions for restriction analyses of formed amplicons were identified in the initial experiments. All amplifications were performed in a thermocycler Mastercycler gradient (Eppendorf). PCR conditions were as follows: 5 min of initial denaturation at 94ºC, followed by 38 cycles of 94º C for 20 s, 56º C/52º C (rs4696480/rs5743708) for 40 s and 72º C for 40 s. The TLR2 amplicons were subsequently digested with 5 units of HphI (rs4696480) and *Pst*I (rs5743708) restriction enzymes (MBI Fermentas, Lithuania). After digestion, 10 µL of the products was electrophoresed in ethidium bromide-stained 3% agarose gel (Sigma-Aldrich, Germany). The results were observed under UV light and recorded with photographs of the gels. For the T (-16934)A polymorphism, the T(-16934) allele was cleaved into 209, 47, 71, 27 and 14 bp restriction fragments, while the A(-16934) allele was cleaved into 256, 71, 27 and 12 bp restriction fragments. For the Arg-753Gln polymorphism, the Gln753 allele was cleaved into 285 and 145 bp restriction fragments, while the Arg753 allele remained uncleaved. The final stage of analysis was an assessment of the possible relationship between the R753Q (rs5743708) and T16934A (rs4696480) TLR2 gene polymorphisms and the *Staphylococcus aureus* carriage in patients undergoing CABG procedures.

Statistical analysis was performed using Statistica software (StatSoft, Tulsa, USA). The concordance with the Hardy-Weinberg equilibrium was evaluated with the chi-square test. The distribution of genotypes in *Staphylococcus aureus*-carrying patients and non-carrying individuals was examined using Fisher's exact test. The Mann-Whitney U-test, paired and unpaired Student's t- tests were used for comparison between the groups. A logistic regression analysis was performed to obtain the odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between specific SNPs and *Staphylococcus aureus* carriers using

Table 1. Baseline characteristics of the study group

	S. aureus **non-carriers (n = 233)**	***S. aureus*** **carriers (n = 66)**	***P***
Age (years, mean ± SD)	63.3 ± 10.9	63.3 ± 9.1	0.1497
Male n (%)	175 (75.1)	47 (71.2)	0.3298
Height (cm, mean ± SD)	167.1 ± 9.2	165.9 ± 9.2	0.3789
Body mass (kg, mean ± SD)	79.2 ± 13.5	76.1 ± 13.9	0.1220
BMI (kg m^{-2}, mean ± SD)	28.3 ± 3.9	27.6 ± 4.3	0.2311
NYHA Class n (%)			
0	112 (48.1)	41 (62.1)	
I	20 (8.6)	2 (3.0)	
II	42 (18.0)	8 (12.1)	0.1844
III	50 (21.5)	14 (21.3)	
IV	9 (3.8)	1 (1.5)	
CAD time (month, mean ± SD)	64.9 ± 119.1	47.7 ± 86.7	0.2999
Smoking n (%)	98 (42.1)	28 (42.4)	0.8467
ESlog	6.7 ± 7.9	5.5 ± 4.8	0.2498

BMI — body mass index; NYHA — New York Heart Association, CAD — coronary artery disease, ESlog — logistic EuroSCORE

Table 2. Associations between *TLR2* haplotypes and covariates.

	T16934A*			**R753Q***		
	TA	**TT**	**AA**	**GG**	**GA**	**AA**
Age (years, mean ± SD)	63.7 ± 9.8	63.2 ± 10.4	64.0 ± 9.4	63.6 ± 9.5	63.2 ± 13.6	–
Male n (%)	117 (74.1)	59 (80.8)	46 (67.6)	207 (74.2)	15 (75.0)	–
Height (cm, mean ± SD)	167.5 ± 9.2	167.2 ± 8.4	165.1 ± 9.6	166.8 ± 9.1	167.3 ± 9.9	–
Body mass (kg, mean ± SD)	79.7 ± 13.1	78.3 ± 13.0	76.3 ± 15.2	78.6 ± 13.7	78.2 ± 12.6	–
BMI (kg m^{-2}, mean ± SD)	28.3 ± 3.8	27.9 ± 3.9	27.9 ± 4.4	28.2 ± 4.1	27.8 ± 3.1	–
NYHA Class n (%)						
0	77 (48.7)	40 (54.8)	35 (51.5)	140 (50.2)	12 (60.0)	–
I	15 (9.5)	3 (4.1)	5 (7.4)	23 (8.2)	0 (0.0)	–
II	27 (17.1)	10 (13.7)	12 (17.7)	44 (15.8)	5 (25.0)	–
III	32 (20.3)	19 (26.0)	14 (20.5)	62 (22.2)	3 (15.0)	–
IV	7 (4.4)	1 (1.4)	2 (2.9)	10 (3.6)	0 (0.0)	–
CAD time (month, mean ± SD)	64.9 ± 130.5	63.4 ± 93.7	47.9 ± 79.8	61.2 ± 114.8	43.7 ± 62.9	–
Smoking n (%)	100 (59.2)	31 (42.4)	22 (32.4)	163 (58.4)	13 (65.0)	–
ESlog	6.2 ± 9.8	5.7 ± 6.9	7.9 ± 9.8	6.5 ± 7.6	5.1 ± 3.6	–

BMI — body mass index; NYHA — New York Heart Association; CAD — coronary artery disease; ESlog — logistic EuroSCORE; *No associations between TLR2 haplotypes and the covariates were found

unadjusted and adjusted multivariate models (SPSS Inc., Chicago, IL, USA). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

In the study group the mean age was 63 years, 74% were male, 42% were current smokers, and more than half of the patients were in the 0 NYHA class. These baseline characteristics were not significantly different between *S. aureus* carriers and non-carrier groups (Table 1).

The prevalence of the nasal *S. aureus* carriage in the final cohort was 22.1% (66/299), while MRSA was not detected in our study group.

No associations were found between *TLR2* haplotypes and the covariates of age, sex, NYHA, weight, height, BMI, CAD, smoking status and ESlog (Table 2).

Table 3. The relationship between R753Q (rs5743708) and T16934A (rs4696480) TLR2 gene polymorphisms and *Staphylococcus aureus* carriage

TLR2 Polymorphism	Hardy-Weinberg equilibrium p	Carrier status, n (%)		*P**	Total n (%)
		carrier	non-carrier		
R753Q					
GG (wild type)		54 (81.8)	224 (96.1)		278 (92.9)
GA	0.549	12 (18.2)	9 (3.9)	0.0005	21 (7.1)
AA		0	0		0
Total		66 (100)	233 (100)		299 (100)
T16934A					
TA		37 (56.1)	122 (52.3)		159 (53.1)
TT	0.288	16 (24.2)	58 (24.9)	0.8553	74 (24.8)
AA		13 (19.7)	53 (22.8)		66 (22.1)
Total		66 (100)	233 (100)		299 (100)

* Fisher's exact test

The distributions of genotypes were consistent with the Hardy-Weinberg equilibrium for each single nucleotide polymorphism in the TLR2 gene (rs4696480, rs5743708), in patients with positive nasal swab cultures and non-carriers. Of the 299 patients who were screened for the presence of the TLR2 T-16934A SNP (rs4696480), more than half of the patients (158/299 52.8%) were TA heterozygous without this polymorphism. The TT genotype was detected in 74 patients (24.8%), while, in contrast, the AA genotype was detected in 66 subjects (22.1%). No differences were found between carriers and non-carriers regarding the allelic distribution of the TLR2 T-16934A SNP. Almost 93% of the patients who were screened for the presence of the TLR2 Arg753Gln (rs5743708) were GG wild type homozygous. Twenty one subjects of the study group (7.1%) were GA heterozygous, while no patient in either group was homozygous for the TLR2 Arg753Gln (rs5743708) mutation. TLR2 Arg753Gln genotyping showed that GA heterozygous patients were detected more frequently in the group of *Staphylococcus aureus* nasal carriers than in non-carriers (Table 3).

DISCUSSION

Several major randomized double-blind placebo-controlled trials have shown that *Staphylococcus aureus* carrier status is a risk factor both for surgical site infection and non-surgical site infection [15, 16]. We determined the prevalence of *S. aureus* carriage in a cohort study of cardiac surgery patients in one department of cardiac surgery in north-western Poland. Every fifth participant of our study was colonized with *S. aureus*. In Europe, two studies from the UK have shown similar results to our study [17, 18]. Gamblin *et al.* [17] found 28% nasal *S. aureus* colonization in Southampton, which is close to the previous estimate of 23% by Abudu *et al.* [18] in Birmingham. In our study, we identified genetic polymorphisms in the TLR2 gene as novel susceptibility factors for *Staphylococcus aureus* carriage in cardiac surgery patients. In detail, we observed an increased incidence of *S. aureus* nose colonization in patients with the TLR2 gene variants GA of the R753Q (rs5743708) polymorphism. To the best of our knowledge, this is the first report to demonstrate that the GA variant of the TLR2 Arg753Gln SNP is significantly associated with a higher risk of *Staphylococcus aureus* carriage in adults. An analogous result was not observed for the T16934A (rs4696480) polymorphism. Since the discovery of the TLR receptor polymorphisms, many scientists have tried to prove their clinical significance. In the case of the TLR2 receptor, it seemed that the proof that its polymorphism correlates with the development of infections, especially Gram (+) infections, was only a matter of time. TLR2 is expressed on the cell surface of macrophages and other immune competent cells and recognizes bacterial PAMPS (patogen associated molecular patterns), in particular constituents of the Gram-positive organisms, such as peptidoglycans. The TLR2 triggers innate immune responses, i.e. the production of pro-inflammatory cytokines [19–22]. In the year 2000, Lorenz published a study that proved that the TLR2 R753Q mutation decreases the TLR2 response to bacterial peptides *in vitro* [13]. A similar effect was shown *in vivo* in an animal model [23]. Since then, reports have been published that showed a correlation between TLR2 polymorphism carrier status and cases of infection caused by *Bacillus tuberculosis*, *Bacillus anthracis* and *staphylococci*. Unfortunately, all of these studies were performed in small groups and none of them have reached any statistical significance [24–29]. When studying the mechanism of TLR2 receptor activation and its potential

ligands, infections caused by Gram (+) and Gram (–) bacteria were analyzed. No statistical significance was reported between TA, TT and AA polymorphisms T16934A (rs4696480) of the TLR2 receptor and the frequency of Gram (+) and Gram (–) infections. The above-mentioned polymorphism is one of the least studied genetic variants of TLR2. Its relevance has been discussed in the pathogenesis of asthma, atopic dermatitis or hepatic cancer [14, 27, 28]. The only study that showed any potential correlation between the TT polymorphism variant of the T16934A (rs4696480) TLR2 receptor and the frequency of spontaneous peritonitis was performed by Nischalke in a group of 150 patients with liver cirrhosiss [14]. In the study published by Lee in the year 2011, the relationship between the R753Q polymorphism and postoperative infections was analyzed in a group of 694 patients after liver transplantation [29]. This study showed no difference between the frequency of Gram (+) infections among all infections in patients with genetic variants GG and GA R753Q. The frequency of Gram (+) infections in the group with GA variant carrier status was higher than in the GG variant carrier group (27.8% vs. 11.8%), with a borderline statistical significance $P = 0.07$ [29]. The concept of the relationship between TLR2 receptor polymorphisms and the frequency of infections is very difficult to prove due to multiple co-existing risk factors in both study groups. Only studies performed in large patient populations can lead to a conclusive answer, confirming or denying any potential relationship.

The main part of the study was the analysis of the relationship between different variants of inheritance of the studied polymorphisms and the occurrence of *Staphylococcus aureus* carrier status in the study group. No correlation was found for the T16934A (rs4696480) polymorphism of the TLR2 receptor. The percentage of carriers was 21.5% for TA, 20.5% for TT and 19.2% for AA, which is consistent with the previous reports of *Staphylococcus aureus* carrier status in the population of Western Pomerania [30]. Different results were obtained for R753Q (rs5743708) polymorphisms. In 55% of patients with the GA polymorphism variant of the R753Q TLR2 receptor, carrier status for *Staphylococcus aureus* was confirmed. For comparison, the percentage for the GG variant was 19.7%, a difference that reached statistical significance ($P = 0.0004$). In the available literature, no studies have been found to support this observation. In our opinion, unlike the problem of postoperative infections which is influenced by many variables, it seems that the carrier status for a given pathogen is fully dependent on the susceptibility of that organism. The genetic factors influencing the identification and eradication of micro-organisms by the host's immune response system may play a key role in identifying groups with increased risk for infection. Given the fact that the carrier status for *Staphylococcus aureus* is a widely recognized risk factor for postoperative infections after cardiac surgery, proving a relationship between the R753Q polymorphism and the carrier state is potentially of clinical importance. However, since *Staphylococcus aureus* carriage can be treated successfully with mupirocine, the utility of the TLR2 polymorphisms as prognostic genetic markers should be further evaluated prospectively in a broader range of patients.

CONCLUSIONS

The GA variant of the TLR2 Arg753Gln (rs5743708) polymorphism predisposes one for nasal *Staphylococcus aureus* carriage.

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