UDC 579.852.1:575.113:577.21 *https://doi.org/10.31861/biosystems2025.02.216*

PHYLOGENETIC ANALYSIS OF THE EVOLUTIONARY STABILITY OF THE *icaA* GENE WITHIN THE GLOBAL STAPHYLOCOCCUS AUREUS POPULATION

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Staphylococcus aureus is one of the most significant opportunistic pathogens affecting humans and animals. A key factor in its virulence is its ability to form biofilms, which is mediated by the biosynthesis of the polysaccharide intercellular adhesin and encoded by the icaA gene. However, the evolutionary dynamics and degree of conservatism of this gene within the global S. aureus population are not well understood. This study aimed to elucidate evolutionary relationships and assess genetic diversity of the icaA gene among different S. aureus isolates. Twenty-three nucleotide sequences, representative of 14 countries and various ecological niches (clinical, veterinary and environmental), isolated between 2004 and 2025, were analysed. Phylogenetic analysis of the icaA gene (using the maximum likelihood method MEGA 12, GTR+G model) confirmed its conservatism, as all isolates studied formed a dense cluster with short branches, indicating low nucleotide divergence. A main cluster was identified that united isolates from Europe and North America. This cluster has been circulating for over 20 years, indicating the global spread of clones with a stable icaA sequence. The analysis showed that isolates of animal origin from Pakistan did not form a statistically significant subclade, suggesting an absence of local adaptation of the icaA gene in these populations. While some strains from Asia show minor local divergence, the overall tree structure highlights the gene's high stability. The results confirm that the icaA gene is a highly conserved functional gene subject to strong negative selective pressure due to its critical function. This gene's stability may be pivotal to S. aureus' success as a global pathogen.

Keywords: Staphylococcus aureus, tonsillitis, icaA, biofilm, phylogenetic analysis, Maximum Likelihood, conservatism.

Introduction. Tonsillitis is a common disease, particularly prevalent among children and young adults. It is mainly caused by infectious agents, with viral pathogens accounting for approximately 70-95 % of cases. While bacterial causes of tonsillitis are less common, they are clinically significant due to their potential to cause complications (Nimmana & Paterek, 2025). When diagnosing tonsillitis, it is important to consider infection caused by group A beta-haemolytic streptococcus. However, numerous other bacteria (including *Staphylococcus aureus* and *Haemophilus influenzae*), viruses and other infectious and non-infectious causes should also be considered. Identifying the causative agent is crucial for choosing the appropriate therapy, ensuring rapid recovery and preventing complications (Brook, 2005).

Although bacterial causes of tonsillitis are less common than viral causes, they are of key clinical importance due to the high risk of complications. The leading bacterial pathogen capable of causing tonsillitis as a monoinfection is group A beta-haemolytic streptococcus (*Streptococcus pyogenes*), which is most commonly found in children aged 5 to 15 years (Pallon et al., 2021; Miller et al., 2024). However, the course of the disease is often complicated by the formation of polymicrobial associations, which may include such opportunistic and pathogenic microorganisms as *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Fusobacterium necrophorum* (especially in adolescents and young adults), and *Streptococcus dysgalactiae*. Recurrent tonsillitis is often polymicrobial, with biofilm-forming organisms such as *S. aureus* and *H. influenzae* contributing to its persistence (Klagisa et al., 2022). Changes in the tonsil microbiota and reduced microbial diversity (dysbiosis) are also associated with recurrence.

In the context of the microbiology of acute tonsillitis, it has been demonstrated that *S. aureus*

frequently colonises the tonsils of patients (Andersen et al., 2023). The dynamics of observation are particularly revealing: in 12 % of patients, the bacterium persisted, remaining present during and after infection. This ability to persist for extended periods is directly related to one of the key factors of staphylococcal pathogenicity: the capacity to form biofilms. *S. aureus* is a common component of the tonsil microbiota, as evidenced by its presence in 15 % of patients with pharyngotonsillitis (Pallon et al., 2021).

The intracellular persistence of *S. aureus* in tonsil tissue is a key factor in recurrence (Zautner et al., 2010). The ability to survive for extended periods and evade the immune system and antibiotics is closely linked to biofilm formation. A key characteristic of biofilms is their increased tolerance to antibiotics, making infections caused by these microorganisms particularly difficult to treat. The protective matrix slows down the diffusion of antibiotics, and the low-metabolic environment deep within the biofilm renders bacteria less susceptible to drugs that target actively dividing cells (Hall & Mah, 2017). Therefore, understanding the mechanisms of biofilm formation in *S. aureus* is essential for effectively treating recurrent and chronic tonsillitis.

A controlled study provided direct evidence of the role of biofilms in tonsillitis. It showed that biofilms on the tonsil surface are significantly more prevalent in patients with recurrent tonsillitis (80 %) than in healthy individuals (45 %), and are at a significantly higher stage of development. This indicates their causal role in the development of the disease (Woo et al., 2012). Given the ability of *S. aureus* to form biofilms and its frequent colonisation of the tonsils, targeted research into this pathogenicity factor is necessary to advance our understanding of the mechanisms of recurrent tonsillitis development and treatment. The main mechanism of biofilm formation in *S. aureus* is the synthesis of polysaccharide intercellular adhesion (PIA), which is determined by the *ica*ADBC operon genes (Peng et al., 2022). While the entire operon functions as a single system, the *ica*A gene, which encodes the catalytic subunit of N-acetylglucosaminyltransferase, is considered the most critical for initiating matrix synthesis. Modern molecular studies confirm the importance of this genetic determinant in the development of persistent infections, demonstrating a high frequency of *ica*A among clinical isolates of S. aureus and emphasising its key role in pathogenesis (Hammoudi & Mohammed, 2025).

In addition to studying prevalence, it is important to conduct a phylogenetic analysis of the *ica*A gene in order to trace its evolution and molecular variability among different *S. aureus* isolates. Recent studies confirm that the *ica* operon is under significant evolutionary pressure and remains unchanged among pathogenic strains (Pizauro et al., 2021). For instance, a phylogenetic analysis of *S. aureus* isolates from patients with urinary tract infections revealed a high degree of identity (99.0–99.8 %) in the *ica*A gene sequences between local isolates and reference strains, forming dense monophyletic groups (Abbas & Hamim, 2020). This conservatism suggests that the *ica*A gene plays a pivotal role in the pathogenesis and survival of the bacterium, making it a promising target for further research. However, the pathogenic significance of *S. aureus* extends beyond acute upper respiratory tract infections. Its ability to form biofilms is a key virulence factor, ensuring chronic persistence and resistance to antibiotics. Biofilm formation complicates a wide range of infectious processes, from recurrent tonsillitis (Kravets et al., 2022) to severe nosocomial infections such as implant-related infections and diabetic foot ulcers, in which *S. aureus* is a common pathogen (Volch et al., 2025).

The aim of this study was to assess the evolutionary stability and genetic diversity of the *ica*A gene in the global population of *S. aureus* using phylogenetic analysis. To this end, isolates of different geographical and ecological origins, collected over the last two decades, were used for comparison.

Materials and methods. The study focused on the nucleotide sequences of the *ica*A (intercellular adhesion A) gene in *Staphylococcus aureus* strains. These sequences were obtained from the NCBI (National Centre for Biotechnology Information) GenBank database. The BLASTN tool was used to search for and select sequences with high homology to the reference *ica*A gene. Records that met the following criteria were included in the subsequent analysis: the annotation ‘gene=*ica*A’, a length of at least 800 bp (to avoid fragmented sequences) and metadata on the source, geographical origin and year of isolation of the strain (Table 1.). Multiple alignment of nucleotide sequences was performed using the MUSCLE algorithm in the MEGA 12 software package. Low-quality regions (those with a large number of gaps or uncertainties) were then removed from the initial alignment using the Trim Alignment tool, in order to minimise noise and improve the accuracy of phylogenetic reconstruction. Evolutionary relationships were then reconstructed using the maximum likelihood method in MEGA 12 (Kumar et al., 2018). The optimal nucleotide substitution model was selected using the Find Best DNA/Protein Models module in MEGA 12, based on AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) criteria.

The General Time Reversible (GTR) model, adjusted for gamma distribution of substitution rates and a proportion of invariable sites (G+I), was determined to be the most appropriate. The analysis took the coding nature of the gene into account, including all three codon positions. Gaps were handled using the partial deletion method with a 95 % cut-off threshold. The search for the optimal tree was performed using the Nearest-Neighbour-Interchange (NNI) heuristic method.

Table 1.

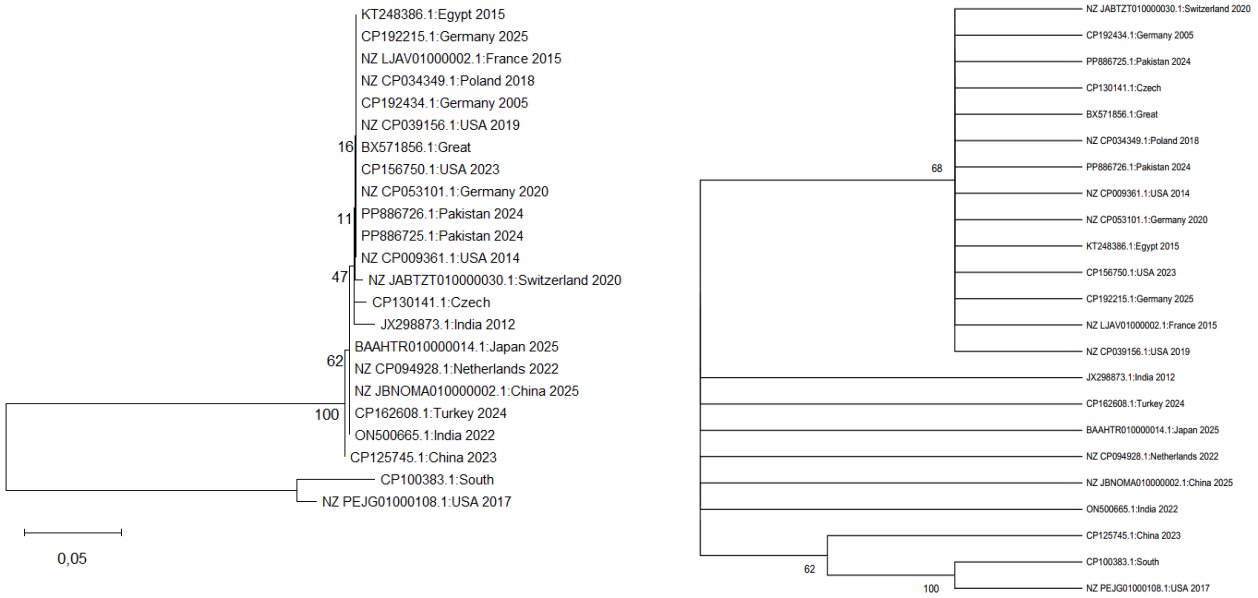
Characteristics of the nucleotide sequences of the icaA gene of Staphylococcus spp. used in the phylogenetic analysis

№	Identifier in GenBank	Strain	Source of isolation	Country	Year of isolation
1	NZ_CP009361.1	*Staphylococcus aureus* ATCC 25923 (ref.)	Clinical (Human) (Treangen et al., 2014)	USA	2014
2	JX298873.1	*S.aureus* KVAFSU-15	Veterinary (Bovine mastitis) (Akshatha et al., 2012; Akshatha et al., 2020)	India	2012
3	KT248386.1	*S.aureus* Bendary IC4	Clinical (Human) (Bendary et al., 2015)	Egypt	2015
4	PP886725.1	*S.aureus* C5I	Veterinary (Camel mastitis) (Ijaz et al., 2024)	Pakistan	2024
5	PP886726.1	*S.aureus* C23I	Veterinary (Camel mastitis) (Ijaz et al., 2024)	Pakistan	2024
6	NZ_CP053101.1	*S.aureus* EDCC5398	Clinical (Bone infection) (Mannala & Alt, 2020)	Germany	2020
7	BAAHTR010000014.1	*S.aureus* JMUB7492	Clinical (Intra-hospital) (Suzuki et al., 2025)	Japan	2025
8	NZ_JABTZT010000030.1	*S.aureus* 18SBCL678	Animal origin (Ready to eat food) (Schwendimann et al., 2020)	Switzerland	2020
9	CP162608.1	*S.aureus* MetB16	Clinical (Human) (Ozbek et al., 2024)	Turkey	2024
10	CP156750.1	*S.aureus* R8015	Clinical (Blood infection) (Berti et al., 2023)	USA	2023
11	BX571856.1	*S.aureus* MRSA252	Clinical (Hospital) (Holden et al., 2004)	Great Britain	2004
12	NZ_CP039156.1	*S.aureus* WCUH29	Clinical (Bone infection) (Silverstein & Yang, 2019)	USA	2019
13	CP192434.1	*S.aureus* IL-060T	Clinical (Nasopharyngeal colonization) (Grebe et al., 2025)	Germany	2025
14	NZ_CP094928.1	*S.aureus* 08	Veterinary (Bovine mastitis) (Vera Murguia, 2022)	Netherlands	2022
15	NZ_JBNOMA010000002.1	*S.aureus* 24J2506	Animal origin (Raw milk (Zhou, 2025)	China	2025
16	NZ_CP034349.1	*S.aureus* 80wphwpl	Unidentified (Collection) (Lobocka et al., 2018)	Poland	2018
17	NZ_LJAV01000002.1	*S.aureus* chock11	Clinical (Blood infection) (Sassi et al., 2015)	France	2015
18	CP125745.1	*S.aureus* IVRI_FBI_635	Animal origin (Products) (Mirsab et al., 2023)	China	2023
19	CP130141.1	*S.aureus* MHD60_8	Environmental (Public transport) (Smelikova, 2023)	Czech Republic	2023
20	ON500665.1	*S.aureus* RM3	Unidentified (Collection) (Khodabux & Mariappan, 2022)	India	2022
21	CP192215.1	*S.aureus* DSM 110898	Biobank (Collection) (Swiderski & Bunk, 2025)	Germany	2025
22	CP100383.1	*S.epidermidis* sep6 (outgroup)	Unidentified (Collection) (Lee & Son, 2022)	South Korea	2022
23	NZ_PEJG01000108.1	*S.epidermidis* SCH-17 (outgroup)	Clinical (Neck/axilla) (Greninger et al., 2017)	USA	2017

Statistical support for branches was assessed using bootstrap analysis with 1,000 replications. Clusters were considered statistically supported at the following bootstrap values: > 90 % – high support; 70–90 % – moderate support; and < 70 % – low support. The tree was rooted using *Staphylococcus epidermidis ica*A gene sequences as an outgroup. The MEGA Tree Explorer tool was used for visualisation, editing and annotation of the phylogenetic tree (with indication of strain code, country of origin and year of isolation).

Results and discussion. To elucidate the evolutionary relationships between different strains of S. aureus, a phylogenetic analysis was performed on 23 *ica*A gene nucleotide sequences obtained from the NCBI GenBank database (Table 1.). The analysis included isolates from 14 countries, ensuring representative geographical coverage. The sample covered isolates collected over a period of more than 20 years (from 2004 to 2025) from various sources, including humans, farm animals, and the environment. This allowed for a comprehensive assessment of the evolutionary dynamics of the gene.

The phylogenetic tree was constructed using the maximum likelihood method (ML) in the MEGA 12 programme. The General Time Reversible (GTR) model with a correction for the gamma distribution of substitution rates in five categories (+G) was determined to be the best model of nucleotide substitutions. The final dataset contained 458 positions. The statistical support for the branches was assessed using bootstrap analysis with 1000 replications. The dendrogram confirmed the extremely high conservatism of the *ica*A gene among the studied *S. aureus* isolates, as evidenced by the short branches and dense grouping of sequences within the main cluster (Fig. 1).



A ***B***

Fig. 1 Phylogenetic tree (cladogram) showing the evolutionary relationships between Staphylococcus spp. strains. This was constructed based on a comparative analysis of the nucleotide sequences of the icaA gene, using the maximum likelihood method.

Note: phylogenetic reconstruction was performed in MEGA 12 based on 458 nucleotide positions, using the GTR+G substitution model. Outgroup: S. epidermidis (GenBank numbers NZ_PEJG01000108.1 and CP100383.1).

Part A reflects evolutionary distances (the number of nucleotide substitutions per site), and part B reflects bootstrap support values (1000 replications; values ≥50 % are shown).

The tree was rooted using *S. epidermidis* sequences (NZ_PEJG01000108.1 and CP100383.1), which formed a distinct outgroup with maximum bootstrap support (100 %), thus confirming the phylogenetic distance from *S. aureus*.

All *S. aureus* isolates formed a compact main cluster with very short branch lengths, indicating low nucleotide divergence of the *ica*A gene. Most of the internal branches were characterised by low bootstrap support values (less than 70 %), which is typical of highly conserved genes for which the number of informative sites is insufficient to form stable subclades (Suzuki et al., 2012).

The largest cluster included the majority of the isolates from Europe (Germany, the Czech Republic, Poland and France) and North America (the United States), as well as the reference strain (NZ_CP009361.1). This suggests that clones with virtually identical *ica*A sequences have been circulating for a long period of time (2004–2025),

which is consistent with the concept of the global spread of key *S. aureus* clones (Azarian et al., 2021).

Two animal-origin isolates from Pakistan (PP886725.1 and PP886726.1) tend to cluster together. However, bootstrap analysis did not provide statistical support for this subclade, indicating its instability. Therefore, the available data do not confirm the formation of a distinct local genetic lineage linked to veterinary sources; rather, they suggest the random grouping or accumulation of a few common mutations.

Some strains, such as JX298873.1 (India), CP162608.1 (Turkey) and ON500665.1 (India), are positioned more distantly from the main cluster and form separate branches. This is probably because they have accumulated unique point mutations that have distanced them from the central group of strains, but not led to the formation of stable regional subclades.

The results of the maximum likelihood (ML) phylogenetic analysis confirm that the *ica*A gene is a highly conserved genetic locus, which is consistent with its critical role in biofilm formation (Beenken et al., 2004). The lack of a clear correlation between geographical origin and position within the main cluster of the tree confirms the hypothesis of the global circulation of *S. aureus* clones. The slight differences observed in individual subclades may be attributed to local adaptation or sporadic recombination events; however, these do not significantly impact the functionality of this pivotal gene. The data indicate strong negative evolutionary pressure on the *ica*A gene due to its vital role in synthesising the intercellular adhesion polysaccharide (PIA) (Silva-de-Jesus et al., 2025). Thus, the results demonstrate that *ica*A is a highly stable functional gene, with a conserved sequence even among isolates of different ecological origins. The presence of several weakly supported subclades may reflect local microevolutionary changes; however, they do not affect the overall conservative structure of this functionally important gene.

Conclusions. Phylogenetic analysis of the *ica*A gene sequence revealed extremely high conservation among *Staphylococcus aureus* strains of different geographical and ecological origins. A large cluster was identified that united isolates from Europe and North America, which were collected over a period of more than 20 years. This indicates the circulation of clones with virtually identical gene sequences. The presence of minor microevolutionary differences is indicated by separate branches formed by isolates of animal origin and some Asian strains. The obtained data confirm that the *ica*A gene is a highly stable functional gene under significant selective pressure due to its critical role in biofilm biosynthesis.

Interests' disclosure. *The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.*

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ФІЛОГЕНЕТИЧНИЙ АНАЛІЗ ОЦІНКИ ЕВОЛЮЦІЙНОЇ СТАБІЛЬНІСТЬ ГЕНА *icaA* В ГЛОБАЛЬНІЙ ПОПУЛЯЦІЇ *STAPHYLOCOCCUS AUREUS*

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Staphylococcus aureus є одним з найважливіших опортуністичних патогенів людини та тварин. Ключовим фактором вірулентності є здатність утворювати біоплівку, що залежить від біосинтезу полісахариду міжклітинної адгезії, за синтез якого відповідає ген icaA. Однак еволюційна динаміка та ступінь консервативності цього гена в глобальній популяції S. aureus залишаються недостатньо вивченими. Метою цієї роботи було з'ясування еволюційних взаємозв'язків та оцінка генетичного різноманіття гена icaA серед різних ізолятів S. aureus. Було проаналізовано 23 нуклеотидні послідовності, репрезентативні для 14 країн світу та різних екологічних ніш (клінічні, ветеринарні, навколишнє середовище), виділені протягом 2004–2025 рр. Філогенетичний аналіз гена icaA (методом максимальної правдоподібності MEGA 12, модель GTR+G) підтвердив його консервативність, оскільки всі досліджені ізоляти утворили щільний кластер із короткими гілками, що свідчить про низьку нуклеотидну дивергенцію. Виявлено основний кластер, що об'єднує ізоляти з Європи та Північної Америки, котрий циркулював протягом понад 20 років, що вказує на глобальне поширення

клонів зі стабільною послідовністю icaA. Аналіз показав, що ізоляти тваринного походження з Пакистану не утворюють статистично підтриманої окремої субклади, що свідчить про відсутність специфічної локальної адаптації гена icaA в цих популяціях. Деякі штами з Азії демонструють незначну локальну дивергенцію, однак загальна структура дерева підкреслює високу стабільність гена. Результати підтверджують, що ген icaA є висококонсервативним функціональним геном, що перебуває під сильним негативним селективним тиском, зумовленим його критичною функцією. Стабільність цього гена може бути ключовим фактором успіху S. aureus як глобального патогена.

Ключові слова: золотистий стафілокок, тонзиліт, icaA, біоплівка, філогенетичний аналіз, Maximum Likelihood, консервативність.

Отримано редколегією 16.11..2025 р.

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