



Nucleotide Polymorphism in the Iron Utilization System Gene *isdB* NEAT Domain Affects Heme-Binding Ability of *IsdB* Protein in Various Human Strains of *Staphylococcus aureus*

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Abstract

Genetic heterogeneity of the *isdB* gene fragment encoding one of two heme-binding NEAr Transporter (NEAT) domains pfam05031 in different isolates of *Staphylococcus aureus* from the healthy carriers and the risk group patients (chronic inflammatory infections of the upper respiratory tract and middle ear) was investigated. All *S. aureus* strains included in the current study differed phenotypically from one another by degree of affinity to polystyrene with immobilized human hemoglobin. The isolates that displayed low affinity to hemoglobin were found to have more mutations within the *isdB* gene fragment which encodes one of the *IsdB* protein domains containing heme-binding sites.

Keywords *Staphylococcus aureus* · *isdB* gene · Affinity · Hemoglobin · Inflammatory upper respiratory tract infections

The *isdB* gene codes for a surface protein adhesin (*IsdB*) which is a part of the *Fe* utilization system in *Staphylococcus* strains [1]. Uncovering molecular mechanisms of a preferential heme Fe^{2+} capture is crucial for understanding virulence in pathogenic *Staphylococcus* species. A system of heme iron acquisition in *Staphylococci* consists of three surface membrane proteins, *IsdA*, *IsdB*, and *IsdH* [2, 3]. The protein *IsdB* plays a key role in human hemoglobin binding by *Staphylococcus aureus*.

The *IsdB* protein functions as the primary receptor for hemoglobin since its inactivation inhibits the ability of *S. aureus* to bind hemoglobin in a dose-dependent way. The *IsdB* protein (iron-regulated surface determinant protein B) consists of 645 amino acid residues. The *IsdB* protein structure is

composed of two NEAT domains and one LPXTG-sorting signal motif. The NEAT domains are heme- and/or hemoprotein-binding modules highly conserved in secondary structure [4]. They have roles in hemoprotein binding, heme extraction, and heme transfer.

Isd proteins are iron-regulated surface proteins found in *Bacillus*, *Staphylococcus*, and *Listeria* species and are responsible for heme scavenging from hemoproteins [5]. The *IsdB* protein is only observed in *Staphylococcus* and consists of an N-terminal hydrophobic signal sequence, a pair of tandem NEAT (NEAr Transporter, IPR006635) domains which confers the ability to bind heme [6] and a C-terminal sortase processing signal which targets the protein to the cell wall. *IsdB* is believed to make a direct contact with methemoglobin facilitating transfer of heme to *IsdB* [7]. The heme is then transferred to other cell wall-bound NEAT domain proteins such as *IsdA* and *IsdC*. It has been shown that *IsdA* and *IsdB* co-localize within the *Staphylococcal* cell wall to discrete sites corresponding to regions of hemoglobin capture [8].

The *IsdB* required for *S. aureus* growth using hemoglobin as the sole iron source is also required for virulence. The *IsdB* promote resistance to hydrogen peroxide and killing by neutrophils. A combined vaccine containing *IsdA* and *IsdB* afforded significant protection in mice against a lethal challenge with *S. aureus* Newman or any of the clinical isolates

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