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Polymorphisms in coagulase of Staphylococcus aureus are associated with infection of cardiovascular devices

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Background: *Staphylococcus aureus* is a major cause of bacteraemia and biofilm-associated infections. Candidate gene studies have found polymorphisms in Fibronectin-binding protein A (FnbA) that alter fibrinogen binding are associated with cardiac device infection (CDI). We undertook a genome-wide study for bacterial genetic determinants of CDI by *S. aureus*.

Material/methods: The International *Staphylococcus aureus* Collaboration (ISAC) collated prospectively gathered clinical data and *S. aureus* isolates from several observational studies performed across Europe and Asia between 2006 and 2015. From cases of *S. aureus* bacteraemia, we identified individuals with bacteraemia and an artificial cardiac device (including pacemakers, implantable defibrillators, tissue and mechanical valve prostheses). Local clinical judgment identified those with a device that was infected (cases, n=81) or clearly uninfected (controls, n=141). Centres in Germany, Spain, South Korea and the United Kingdom contributed to the study.

A single isolate from each clinical sample was cultured and underwent whole-genome sequencing on the Illumina MiSeq platform. Single nucleotide polymorphisms (SNPs) were identified after mapping reads against a reference genome (MRSA252) and *de novo* assembly was performed using Velvet. MLST was determined using blast. We examined loci associated with CDI by performing association testing for all SNPs and short sequences (kmers) using Gemma, which controls for bacterial population structure. We applied Bugwas, which identifies bacterial lineages and tests them for association with phenotype.

Results: Phylogeny of *S. aureus* isolates found in the bloodstream of all cases and controls shows a global diversity of lineages, with representatives of clonal complexes (CC) 1, 5, 8, 15, 22, 45, 121 and 398 (Figure). Bugwas showed no lineages were significantly associated with CDI.

The SNP in strongest association with CDI was located in the coagulase gene, encoding an amino acid change in S347N (p=1.7x10^{-5}). An adjacent SNP encoding a further substitution H348Q was also associated with CDI (p=2.4x10^{-4}). This finding is near genome-wide significance threshold (1.7 x10^{-6} adjusted for multiple testing).

Coagulase, a surface bound component of *S. aureus* binds thrombin to facilitate fibrinogen cleavage to form a bacterial fibrin coat. A base call was made for H348Q in 221 of 222 isolates, with the substitution found in 65/140 (46%) controls and 61/81 (77%) cases.

The most significant non-synonymous mutation in FnbA was S432G (after imputation, p=4.2x10^-3). However an allele at this position could only be determined in 24/141 (17%) controls and 13/81 (16%) cases. The presence of glycine at this residue was strongly associated with CDI (p=0.002).

Conclusions: Polymorphism in FnbA is associated with cardiac device infection in a small proportion of isolates from Europe and Asia. We find SNPs associated with cardiac device infection at near-genome wide significance in coagulase, which may affect the binding of bacteria to fibrin-coated cardiac devices.

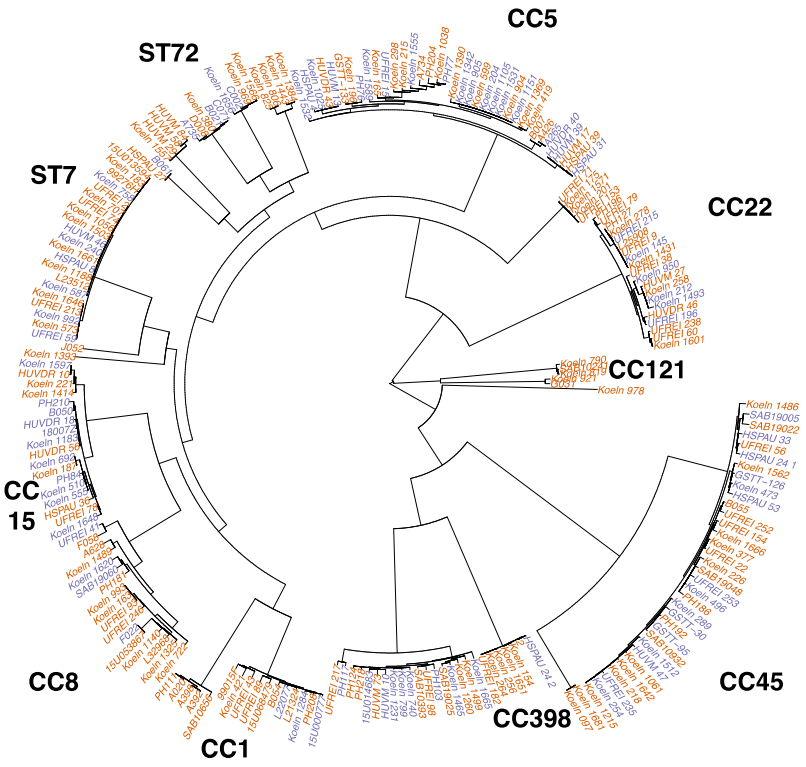

Figure 1: Phylogeny of consensus sequences for all isolates from *S. aureus* bloodstream cardiac device infection (purple) and *S. aureus* bacteraemia with an uninfected cardiac device (orange). Clonal complexes for the major global lineages are marked, as are sequence types (ST) for other major lineages on the tree.