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Evidence of cat-to-human transmission of *Staphylococcus felis*

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Abstract

Introduction. *Staphylococcus felis* is a coagulase-negative staphylococcal species that is commonly isolated from healthy cats. Like other commensal staphylococci, *S. felis* can cause opportunistic infections, e.g. otitis externa, skin and urinary tract infections, in cats.

Gap Statement. Several studies have reported within-household transmission between humans and pets and human infections caused by coagulase-positive staphylococci. However, human infections with coagulase-negative staphylococci of zoonotic origin are relatively rare.

Methodology. Culture of a surgical site infection in a 58-year-old woman who underwent a laminectomy revealed dominant growth of *S. felis*. The three cats owned by the patient were sampled to investigate potential within-household transmission. *S. felis* isolates were sequenced to investigate the relatedness of the isolates and to look for virulence factors and host specific genes.

Results. All cats were colonized with *S. felis*. Comparative genomics of the isolates showed that each cat was colonized with a distinct genotype. The patient's isolate clustered with isolates of one of the cats. Sequence analysis of the studied isolates together with 29 publicly available *S. felis* genomes detected putative virulence factors that can be crucial in potential interspecies transmission.

Conclusion. The current case is the first reported human infection caused by *S. felis* and highlights the zoonotic potential of this bacterial species. Evidence of cat-to-human transmission was shown by comparative genomics of isolates from the patient with isolates of her cats.

INTRODUCTION

Several staphylococcal species colonize the skin and mucous membranes of humans and animals. The close contact between companion animals and humans poses a potential risk of transmission of pathogens. Several studies have reported within-household transmission between humans and pets and human infections caused by (methicillin-resistant) *Staphylococcus pseudintermedius* and *Staphylococcus aureus*, both coagulase-positive staphylococci [1]. Coagulase-negative staphylococci (CoNS) originating from animals might also pose a zoonotic risk and constitute a potential reservoir for virulence and resistance genes, but studies on within-household transmission of CoNS are scarce. CoNS, a heterogenous group of species, are opportunistic pathogens frequently encountered in nosocomial infections, especially in immunosuppressed patients and in prosthetic implants. *S. epidermidis, S. hominis, S. haemolyticus, S. capitis, S. saprophyticus* and *S. lugdunensis* are the most common species in human CoNS

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Abbreviations: bpm, beats per minute; CoNS, Coagulase-negative staphylococci; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; WBC, white blood cells; WGS, whole-genome sequencing.

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Sequencing reads and genome assemblies are deposited in the European Nucleotide Archive (ENA) under project number PRJEB45765. List of genome assemblies with assigned accessions: Genome | Accession Number, 19S01889-1 | GCA_910592845, 19S01890-1 | GCA_910592785, 19S01891-1 | GCA_910592665, 19S01892-1 | GCA_910592825, 19S01893-1 | GCA_910593715, 19S01894-1 | GCA_910593635, 19S01895-1 | GCA_910593895, 19S01932-1 | GCA_910593665.

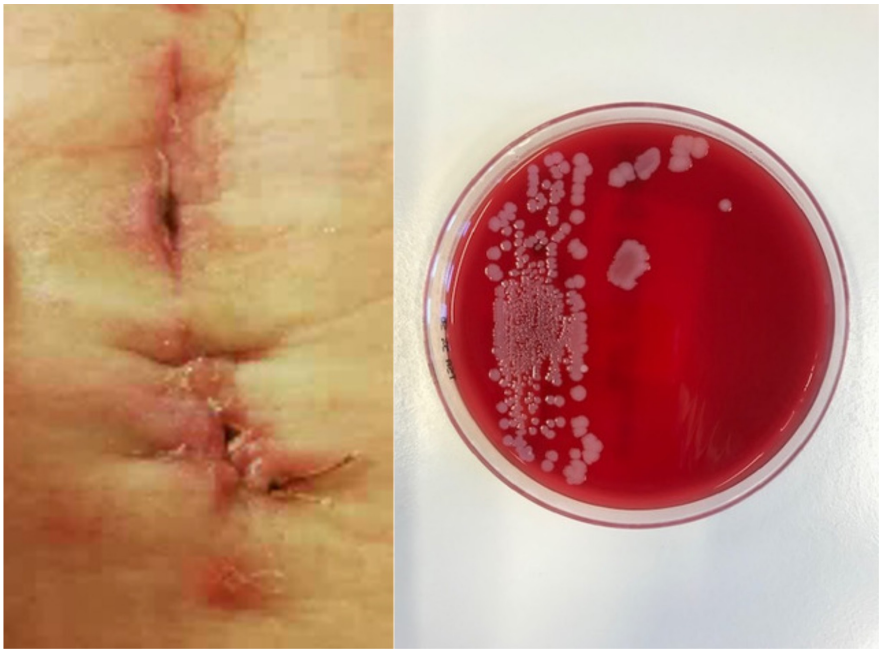

Fig. 1. Dorsal wound with signs of inflammation (left) and wound culture with dominant growth of white non-hemolytic colonies identified as *S. felis* on a sheep blood agar plate (right).

infections [2]. Infections with CoNS originating from an animal source are relatively rare. *S. felis* is a common cat commensal, which can cause opportunistic infections in cats as well [3]. Reports on human *S. felis* infections are lacking, which might be due to misidentification or underreporting but might also reflect host specificity. Analysis of whole-genome sequencing (WGS) data can be helpful in identifying host-specific genes, but until now only sequence data from feline isolates are publicly available [4].

METHODS AND RESULTS

A 58-year-old woman presented to the outpatient emergency department with symptoms of dorsal wound leakage. Two weeks previously she had undergone a laminectomy at the L2-L3 level because of spinal stenosis. Visual inspection of the surgical site revealed wound leakage and mild redness without other signs of inflammation (Fig. 1). The patient was afebrile and presented with a heart rate of 66 beats per minute (bpm) and blood pressure of 128/83 mm Hg. Laboratory parameters showed a leukocytosis of 10.6×10^9 WBC/L. Wound culture revealed growth of skin flora with dominance of white non-hemolytic colonies on sheep blood agar (Fig. 1), which were identified as *Staphylococcus felis* by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Billerica, MA, USA). The isolate was susceptible to all tested antibiotics (Vitek2, bioMérieux SA, Marcy l'Étoile, France) with MICs of flucloxacillin<=0.25 μg ml^{-1}; gentamicin<=0.5 μg ml^{-1}, trimethoprim/sulfamethoxazole<=0.5 μg ml^{-1}, levofloxacin<=0.12 μg ml^{-1}, erythromycin 1 μg ml^{-1}, clindamycin 0.25 μg ml^{-1}, vancomycin<=0.5 μg ml^{-1}, rifampicin<=0.03 μg ml^{-1}, tetracyclin<=1 μg ml^{-1}, fusidic acid<=0.5 μg ml^{-1}, linezolid 1 μg ml^{-1} and teicoplanin 1 μg ml^{-1}. The wound was surgically closed, and the patient was discharged in good condition with an antibiotic regimen of oral flucloxacillin.

The unexpected finding of *S. felis* prompted further investigation, which revealed that the patient owned three cats. Swabs were taken from the three cats (showing no overt clinical signs) from multiple body sites (perineum, oral mucosa and axilla) by a veterinarian. The swabs were submitted to the Veterinary Microbiological Diagnostic Center of Utrecht University. All samples were first enriched in Mueller–Hinton broth with 6.5% NaCl followed by culturing on sheep blood agar (Biotrading, Mijdrecht, The Netherlands). Suspected colonies were confirmed as *S. felis* using MALDI-TOF MS (Bruker Daltonics, Billerica, MA, USA). Cat A tested positive at all three sites, the other two cats at two sites each (cat B: axilla/oral mucosa and cat C: perineum/oral mucosa). All isolates (seven feline and one human) were sequenced with Illumina Nextseq sequencing to investigate the relatedness of the isolates and genomes were assembled using SPAdes v3.14.1 [5]. Genome sequences have been deposited in the European Nucleotide Archive (www.ebi.ac.uk) under project number PRJEB45765. Twenty-nine publicly available *S. felis* genomes were included in the analysis. A core-genome alignment using Parsnp v1.2 [6] and filtering of recombination regions using Gubbins v2.3.4 [7], resulted in a core genome of 1.86 Mbp. The phylogenetic tree was visualized with FigTree (http://tree.bio.ed.ac.uk/

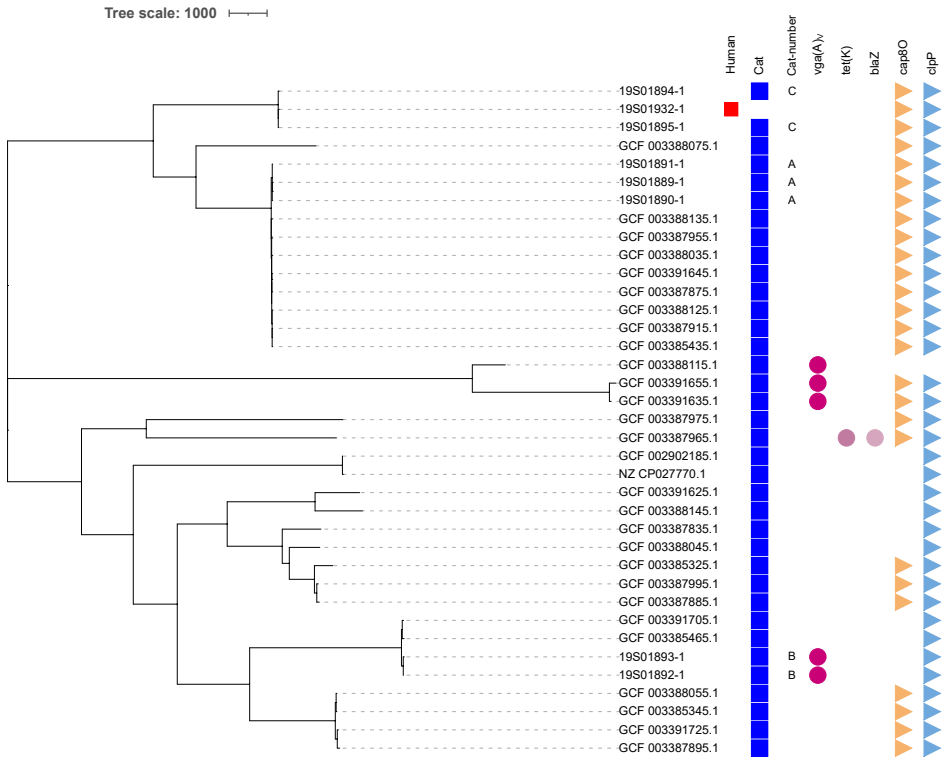

Fig. 2. Phylogenetic tree of core genomes of *S. felis* isolates; one human isolate (red) and 36 feline isolates (blue), seven from three cats (*n*=7; cat A–C) combined with 29 publicly available *S. felis* isolates. Shown are resistance and virulence genes.

software/figtree/). Comparison of the *S. felis* core genomes showed that the isolates from each individual cat clustered separately, and that the human isolate clustered with the cat C isolates, demonstrating evidence of cat-to-human transmission (Fig. 2).

ResFinder [8] (using a cut-off identity >75% and coverage >90%) identified resistance gene *vga*(A)$_V$ conferring resistance to Streptogramine A/lincosamide in isolates from cat B and in three publicly available feline isolates; resistance genes *tet*(K) and *blaZ* were uniquely found in one publicly available feline isolate. VirulenceFinder [9] (using a cut-off identity >75% and coverage >90%) identified putative homologues of *clpP*, encoding for a proteolytic enzyme, in all isolates from the patient and the three cats. Isolates from cat A, cat C and the patient harboured a putative gene *cap8O*, involved in capsule production. Both genes seem quite abundant in *S. felis; clpP* was found in all but one publicly available isolates as well and *cap8O* was present in 20/29 publicly available isolates (Fig. 2).

DISCUSSION

The current case seems to be the first reported human infection caused by *S. felis*. Evidence of cat-to-human transmission was shown by comparative genomics of isolates from the patient with isolates of the cats.

S. felis was described in 1989 as a new species from clinical samples from cats [10]. The description was based on 39 isolates that were isolated from different infections in cats, but not from infections in dogs. *S. felis* isolates are coagulase-negative, produce urease, may display very weak hemolytic activity and are typically susceptible to most antimicrobial agents [10]. Traditional phenotypic tests like the Gram stain, catalase testing and coagulase testing will not distinguish between *S. felis* and other CoNS. Additional biochemical tests will lead to correct identification in most cases, however biochemical characteristics of *S. felis* and *S. simulans* are very similar. As CoNS maybe considered less clinically relevant, further identification may not always be routinely performed. This has potentially led to an underestimation of *S. felis,* especially in early studies. By using current methods for identification, e.g. MALDI-TOF MS and molecular typing, rapid and reliable identification is much easier.

The diversity of staphylococcal species on skin and mucosa from healthy and sick cats is high. *S. felis* is a common cat commensal, which was confirmed by the isolation of *S. felis* from all three healthy cats in the current case. A study on the prevalence of staphylococcal colonization in 520 healthy and 67 sick cats revealed that *S. felis* was the most frequently isolated staphylococcal species in both groups of cats; 63% of the cats was colonized with *S. felis* [3]. Like other commensal staphylococci, e.g. *S. aureus*

in humans, *S. felis* might act as an opportunistic pathogen in cats. Otitis externa, skin and urinary tract infections are the most reported infections associated with *S. felis* in cats [11–13]. The exact pathogenicity of *S. felis* is not well-established yet, but several genes showing high homology with putative virulence factors in other staphylococcal species have been identified in *S. felis*. These virulence genes have been shown to be associated with adhesion, immune evasion, biofilm formation and production of toxin and proteolytic enzymes in other staphylococcal species. Interestingly, based on species characteristics, it was already previously concluded that *S. felis* can harbour a range of virulence genes that can be crucial in potential interspecies transmission [4, 14]. This was confirmed by the detection of virulence genes *clpP* and *cap8O* in most isolates included in our analysis. Additional *in vitro* analyses are important to confirm the functional capacities of these genes.

The population structure of *S. felis* is hardly studied. One characterization study on 37 *S. felis* isolates from cats suggested a multiclonal population structure [4], which was confirmed in the current case, where isolates from each cat clustered separately (Fig. 2). We detected only a few antimicrobial resistance genes in a minority of the isolates. This is in line with other studies where just a few resistance genes and/or low levels of phenotypic antimicrobial resistance were found in *S. felis* isolates [4, 12]. The low levels of antimicrobial resistance contrast with *S. pseudintermedius*, a coagulase-positive staphylococcal species often found in companion animals, as well as with other CoNS, which are often multidrug-resistant. Next to methicillin-resistance conferred by SSC*mec*, other mobile genetic elements conferring resistance are frequently found in *S. pseudintermedius* as well as in other CoNS [2, 15].

The current study provides evidence of pet-to-human transmission from staphylococcal species other than the more frequently reported (methicillin-resistant) *Staphylococcus pseudintermedius* and *Staphylococcus aureus*. Transmission of pathogens may occur following close contact between pets and humans. From a One Health perspective, awareness of these transmission routes is of relevance.

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Author contribution
Conceptualization: G.S., M.W., E.B. Resources: G.S., M.D., M.W., E.B. Formal analysis: L.G., B.D. Writing original draft: G.S., M.W., B.D. E.B. Writing review and editing: G.S., M.D., M.W., L.G., B.D., E.B.

Conflicts of interest
The authors declare no conflicts of interest.

Ethical statement
The cats were sampled for diagnostic purposes with consent from the owner. The study was exempt from ethical approval as no animal experiments were involved.

Consent to publish
Informed consent for publication was obtained from the patient.

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