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1 **Earliest case of *Candida auris* infection imported in 2007 in Europe from India prior to**  
2 **the 2009 description in Japan**

3

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17

18 **Abstract (47 words)**

19 *Candida auris* is an emerging pathogen frequently associated with multidrug resistance and  
20 involved in many worldwide outbreaks. We here report the first European imported case in  
21 France due to isolate belonging of the South Indian clade I and the importance of prevention  
22 measure to avoid fungal spreading.

23 **Keywords:**

24 *Candida auris*, Europe, India, whole genome sequencing, short tandem repeat

25

## 26 **Case report (793 words)**

### 27 **Introduction**

28 *Candida auris* has been under scrutiny because of several outbreaks reported in intensive care  
29 units (ICUs) [1, 2]. *Candida auris* was first described in a Japanese patient in 2009 [3],  
30 raising the hypothesis that the species was unnoticed before. Indeed, the earliest isolate of *C.*  
31 *auris* was found in 1996 in the Korean isolate collection [4]. However, the first European  
32 outbreaks date from spring 2015 [5, 6]. The French National Reference Center for Invasive  
33 Mycoses & Antifungals (NRCMA) provides expertise for difficult to identify isolates. We  
34 regularly review the isolates for which identification failed for lack of homology in the  
35 databases. This is how we discovered the oldest European isolate of *C. auris*, to date.

### 36 **Clinical case**

37         The patient, a 54-year-old male, had a long medical history with splenectomy in 1971  
38 after traumatic shock and liver transplantation in 2004 followed by persistence of hepatitis C.  
39 He visited India in February 2007 for vacation. He was hospitalized in ICU for septic shock  
40 on April 11<sup>th</sup> in Delhi. Ultrasound investigation revealed a large liver abscess. Drainage  
41 yielded turbid bile but no germ. The patient was treated with (meropenem, ofloxacin,  
42 metrodinazole, and teicoplanine) and inotrope support (noradrenaline). The patient was  
43 repatriated in France on April 24<sup>th</sup> where antibiotics were pursued (imipenem, ciprofloxacin,  
44 teicoplanine and metronidazole in the hospital, followed by amoxicilline and metronidazole  
45 for a month at home). He was re-hospitalized in ICU on June 8<sup>th</sup> with cholestasis, renal  
46 insufficiency but without rejection on liver biopsy. Imaging showed several intrahepatic  
47 collections with arterial thrombosis. Cyclosporine was stopped and replaced by prednisone (5  
48 mg/d) and mycophenolate mofetil. Caspofungin was added on June 10<sup>th</sup> on an empiric basis.  
49 On June 16<sup>th</sup>, a first extended-spectrum  $\beta$ -lactamase (ESBL) producing *Escherichia coli* was  
50 isolated from surveillance swabs leading to physical measures to prevent dissemination.

51 Hepatic drainage on June 28<sup>th</sup> yielded purulent liquid without bacteria but with an  
52 unidentified *Candida* sent to the NRCMA. Blood cultures were negative. Standardized  
53 EUCAST broth microdilution method for susceptibility testing of yeast revealed high  
54 minimum inhibitory concentrations (MIC) of fluconazole ( $\geq 64$  mg/L) with lower values for  
55 voriconazole (0.5mg/L), posaconazole (0.125mg/L), amphotericin B (0.5mg/L), caspofungin  
56 (0.06mg/L) and micafungin (0.5mg/L) [2]. Caspofungin was stopped on July 7<sup>th</sup> The patient  
57 was given posaconazole 400 mg twice a day. The patient died 50 days after intensive cares.

### 58 **Identification**

59         Based on phenotypical identification (ID32C carbon assimilation pattern:  
60 55671503151; bioMérieux, Marcy-l'Etoile, France) and internal transcribed spacers (ITS) of  
61 DNA ribosomal sequencing (Genbank accession number KP131674.1), using universal  
62 primers (V9D/LS266), the clinical isolate (CNRMA7.797), recovered from liver, was first  
63 identified as belonging to the *Candida haemulonii* complex. Recently, species identification  
64 was confirmed as *C. auris* upon ITS sequencing compared to sequence of the type strain  
65 (CBS 10913). Short tandem repeat (STR) genotyping, based on the 12 markers described by  
66 de Groot *et al.*, placed the isolate in the Indian clade I (STR genotype 17), the main genotype  
67 observed in the South Asian clade (Figure 1) [7, 8]. Whole genome of the clinical isolate was  
68 sequenced at the Mutualized Platform for Microbiology (P2M, Institut Pasteur, Paris, France),  
69 using an Illumina NextSeq 500 sequencer. Libraries were constructed using Nextera® DNA  
70 Library Preparation Kit and sequenced using a 2 × 150 nucleotide paired-end strategy. All  
71 reads were preprocessed with AlienTrimmer v0.4.0. Genome was mapped to genome  
72 reference of each clade using the Burrows-Wheeler Alignment tool, BWA version 0.7.13 with  
73 the BWA-mem algorithm and SAMtools version 1.9. Single nucleotide polymorphism (SNP)  
74 positions were determined using vcftools version 0.1.13. Genome analysis showed only 1,165  
75 SNPs difference between the genome of the CNRMA7.797 isolate and that of the

76 representative strains of the clade I (B8441), while 51,935 SNPs, 36,353 SNPs, and 130,749  
77 SNPs were found for clade II (strain B11220), clade III (strain B11221) and clade IV (strain  
78 B11243), respectively. These results were comparable to those available in the literature,  
79 confirming the belonging of the CNRMA7.797 isolate to clade I [9].

## 80 **Discussion**

81 The present case shows that *C. auris* existed in 2007 in India before the first  
82 description [3] and highlights the importance of international travel in its spreading [7]. A  
83 recent study demonstrated that majority of patients with *C. auris* colonization, no longer had  
84 detectable *C. auris*, 12 months after discharge of the community setting. This confirms that  
85 isolation of the patient is useful as long as the carriage of *C. auris* lasts [10]. It is therefore of  
86 utmost importance to quickly identify infected patients and carriers by systematic  
87 identification of uncommon yeasts recovered from patients returning from endemic countries,  
88 and specially if ESBL-producing bacteria have been identified. Protecting measures to  
89 prevent ESBL-producing bacteria dissemination probably also prevented secondary *C. auris*  
90 cases in 2007 since no case was reported in France before 2018 [11]. More studies in endemic  
91 countries are warranted to assess the current prevalence of *C. auris* in patients but also in the  
92 environment.

93

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100 **Figure 1:** Minimum spanning tree of 40 representative STR genotypes described by de Groot

101 *et al.*[8], constructed using Bionumerics v6.1 (Applied Maths, Kortrijk, Belgium). Each circle  
102 represents a STR genotype with a clade-specific color (orange for clade I South Asia, yellow  
103 for clade II East Asia, blue for clade III Africa, green for clade IV South America, purple for  
104 clade IV Iran). The black circle corresponds to the clinical isolate CNRMA7.797, reported in  
105 the present study. The number of the STR genotype is indicated in each circle. The branch  
106 lengths indicate the similarity between isolates with the number of markers differing between  
107 genotypes.

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