



Genome Sequences and Antifungal Susceptibility of *Candida auris* from a Patient with Atopic Dermatitis

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Abstract The whole-genome sequencing of two *Candida auris* isolates from the skin lesions of a Korean head and neck atopic dermatitis patient classified them within clade II. The isolates were susceptible to common antifungals. This study provides valuable genomic data for understanding the

epidemiology and antifungal response of this emerging pathogen.

Keywords Antifungal susceptibility · Atopic dermatitis · *Candida auris* · Clade II · Genomes

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Candida auris, an ascomycete yeast, is an emerging fungal pathogen posing serious threats in healthcare environments due to its multidrug resistance, which makes infections difficult to treat. *C. auris* was first isolated in Korea in 1996, misidentified as *C. haemulonii*, and later correctly identified after its description as a novel species by Japanese researchers in 2009 [1–3]. *C. auris* has since spread globally and is now recognized by the World Health Organization as a critical priority fungal pathogen [4]. It colonizes human skin and persists on hospital surfaces, enabling human-to-human transmission and outbreaks [5]. Six distinct clades, each corresponding to a geographic origin, have been defined by whole-genome sequencing and SNP analysis: South Asia (clade I), East Asia (clade II), South Africa (clade III), South America (clade IV), Iran (clade V), and Singapore (clade VI) [6]. Fluconazole resistance is common in some clades, typically due to clade-dependent point mutations in the *ERG11* gene, such as Y132F and K143R in clade I, F126L in clade III, and Y132F/K143R in clade IV, while clade II, V, and VI isolates are generally susceptible to fluconazole [7].

A 33-year-old immunocompetent male presented with waxing and waning pruritic, erythematous, scaly, and lichenified patches on the face and neck. He had a history of severe atopic dermatitis (AD) and allergic conjunctivitis, which had been treated with bi-weekly subcutaneous injections of dupilumab (IL-4/IL-13 receptor monoclonal antibody) along with topical corticosteroids, tacrolimus ointment, and intermittent applications of antibiotic ointments. He reported no other history of systemic disease or ongoing medication. Laboratory findings were unremarkable except for mild eosinophilia ($0.51 \times 10^3/\mu\text{L}$) and markedly elevated total serum IgE levels (8,257 IU/mL). A multiple allergen simultaneous test revealed elevated allergen-specific IgE levels in response to *Dermatophagoides farinae* (class 6), *Dermatophagoides pteronyssinus* (class 4), *Candida albicans* (class 3), baker's yeast (class 2), and *Cladosporium* species (class 2).

Two skin swab samples were aseptically collected from lesional sites on the neck and the cheek, respectively. Each swab was cultured on a yeast extract peptone dextrose (YPD) agar medium containing chloramphenicol, kanamycin, and gentamycin. Two yeast colonies were isolated from each culture. Microscopically, small, round or ovoid, single or budding yeast-like cells were observed, without any filamented structures (Supplementary Fig. S1). Colony PCR using ITS4 and ITS5 primers, followed by Sanger sequencing, was used to characterize the isolates' internal transcribed spacer regions. Alignments showed that both isolates were *C. auris*, with 100% nucleotide identity. The isolates from the neck and the cheek were then deposited in the National Culture Collection for Pathogens (NCCP) in the Korea Disease Control and Prevention Agency as *C. auris* NCCP 32832 and NCCP 32833, respectively.

The whole genomes of the *C. auris* isolates NCCP 32832 and NCCP 32833 were sequenced for further characterization. Two additional strains, *C. auris* NCCP 32684 and NCCP 32789 were provided by the NCCP, and their genomes were also sequenced to serve as reference strains throughout the current study. Genomic DNA was extracted using the Wizard® Genomics DNA Purification Kit (Promega, Madison, WI, USA), and a paired-end DNA library for next-generation sequencing was constructed using

the NEBNext® Ultra™ DNA Library Prep Kit (NEB, Ipswich, MA, USA). Sequencing was then performed on the Illumina NovaSeq 6000 platform using 100 bp paired-end sequencing, yielding 7.93 Gbases of raw data (78,526,478 reads). Adapter sequences and low-quality data trimming were performed using Trimmomatic (v0.39) with the parameters “ILLUMINACLIP:Adapter.fa:2:30:10:8:TRUE,” “SLIDINGWINDOW:4:20,” and “MINLEN:50” [8]. The resulting high-quality sequences were assembled using SPAdes (v4.0.0) [9]. QUAST (v5.3.0) was employed to calculate the genome assembly statistics [10].

The genome assemblies of *C. auris* NCCP 32832, NCCP 32833, NCCP 32684, and NCCP 32789 ranged from 12.06 to 12.40 Mb (Supplementary Table S1), which were comparable to the 12.37 Mb genome of the type strain *C. auris* B8441, obtained from the Candida Genome Database [11]. To taxonomically characterize the isolates, we randomly selected the genomes of 27 *C. auris* strains, collectively representing each known clade, from NCBI, and average nucleotide identities (ANIs) were computed using fastANI (v1.33) [12]. The results revealed that the genomes of isolates NCCP 32832 and NCCP 32833 had overall similarities of 99.93% with clade II *C. auris* strains (Supplementary Figs. S2 and S3).

Since antifungal resistance in *C. auris* is an issue, we characterized the antifungal susceptibility of isolates NCCP 32832 and NCCP 32833, comparing them to reference strains NCCP 32684 and NCCP 32789 using the CLSI broth microdilution method [13]. Isolates NCCP 32832 and NCCP 32833 were susceptible to fluconazole, itraconazole, amphotericin B, flucytosine, and caspofungin (Supplementary Table S2). In contrast, NCCP 32789, identified as clade III in this study, exhibited relatively high minimum inhibitory concentrations (MICs) for fluconazole, itraconazole, and caspofungin: > 64, > 256, and > 8 $\mu\text{g/mL}$, respectively.

Genome analysis identified two nonsynonymous mutations, V125A and F126L, in the *ERG11* gene of *C. auris* NCCP 32789. These mutations are a well-documented determinant of azole resistance in clade III strains [6, 7, 14]. Strain NCCP 32684 showed slightly higher resistance to azole antifungal agents than other clade II strains, which appears to be due to a nonsynonymous P213L mutation in the *TAC1B*

gene (Supplementary Tables S3 and S4). Notably, this is a novel mutation, existing only in NCCP 32684, that is distinct from the *TAC1B* mutation previously associated with azole resistance, F214S [15]. Given that the P213L mutation is structurally very close to the F214S mutation, it is highly likely to be associated with antifungal resistance. Additionally, NCCP 32684, the clade II reference strain, exhibited a high MIC for flucytosine (16 µg/mL, Supplementary Table S2). While flucytosine resistance in *C. auris* is typically linked to mutations in *FCY1*, *FCY2*, or *FUR1*, which encode cytosine deaminase, purine-cytosine permease, and uracil phosphoribosyl transferase, respectively [16–18], no such variants were detected in NCCP 32684, suggesting novel mechanisms underlie its resistance (Supplementary Tables S3 and S4).

The colonization of lesional skin by *C. auris* in AD patients has not yet been reported in the literature, and the current study is the first whole-genome analysis of *C. auris* clinical isolates from such a case. Thus, our data show that colonization of the face and neck by *C. auris* is possible in individuals with AD. In predisposed individuals, *C. auris* colonization could contribute to AD development or exacerbate the condition (e.g., through skin barrier disruption, immune dysregulation, and/or antigen-driven inflammation), but proving a causal relationship will require additional research, including comprehensive epidemiological, immunological, and longitudinal cohort studies. Regardless, as *C. auris* infections continue to emerge globally, our genomic data will help provide critical insights into the epidemiology and antifungal resistance of this important fungus.

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Data Availability The whole genome sequencing data of *C. auris* strains NCCP 32832, NCCP 32833, NCCP 32684, and NCCP 32789 have been deposited in the NCBI Sequence Read Archive under the BioSample accession numbers SAMN46897839, SAMN46897840, SAMN46897841, and SAMN46897842, respectively.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval This study was performed after obtaining written informed consent from the volunteers, following the ethical committee approval process of the Institutional Review Board of Jeonbuk National University Hospital (IRB No. JNUH 2022–09–066).

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