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Origin of *Candida albicans* in Human Oral Cavity

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Abstract

Purpose: *Candida albicans* is regarded as a part of normal flora in the human oral cavity. However, it remains unclear whether the genus *Candida*, especially *C. albicans*, is an oral resident microorganism and causes marital infection or not. The purpose of the present study was to elucidate the origin of oral *C. albicans* by investigating the colonization and infection route to oral cavities of this organism with arbitrarily primed polymerase chain reaction (AP-PCR). **Methods:** After *C. albicans* was isolated from four subjects (average age: 42.2, range: 33 - 56), the isolations of this organism from them were performed six months later again. To investigate whether *C. albicans* is an oral resident microorganism, the genotype homology of each *C. albicans* isolates that were isolated twice from the same subjects was compared. Moreover, *C. albicans* was isolated from five pairs of married couples (average period of cohabitation: 12.4 years, range: 5 - 31). To investigate whether *C. albicans* causes marital infection, the genotype homology of *C. albicans* isolates that were isolated from each pair of married couples was compared. **Results:** AP-PCR patterns of *C. albicans* that were isolated from each subject at o month and after 6 months showed the identical genotypes among each individual. *C. albicans* isolates from five pairs of married couples showed the identical genotypes between a husband and wife of each pair on AP-PCR. **Conclusion:** These results indicated that *C. albicans* was an oral resident microorganism and caused the marital infection.

Keywords

Candida albicans, Oral Cavity, AP-PCR, Genotyping

1. Introduction

As oral *Candida* is often isolated from the oral cavity of healthy humans, this organism is regarded as a part of the normal oral flora [1] [2] [3]. The most common *Candida* species that harbors the oral cavity is *Candida albicans*. Although oral *Candida* remains dormant under physiologic conditions; however, under opportunistic conditions, this organism may transform into contagious pathogens and induce oral diseases such as oral candidiasis [4] [5]. Results from a recent clinical study reported that the subgingival oral biofilm was a reservoir for increased *Candida* colonization [6]; and in susceptible patient groups (such as individuals with poor oral hygiene status), oral *Candida* growth can contribute to the progression of periodontal diseases such as chronic periodontitis [7].

It is difficult to derive a precise oral carriage rate for *C. albicans*, since it depends on the age and health of the research population. A compilation of data from a number of reports showed that the mean carrier rate of *C. albicans* in healthy individuals (no known underlying disease) was 17.7% (range: 1.9% - 62.3%), whereas the mean carrier rate in hospitalized individuals (without clinical candidiasis) was 40.6% (range: 6.0% - 69.6%) [8]. These data indicate that the health of an individual is a predisposing factor for *C. albicans* colonization. A large number of sites in the oral cavity can be colonized; in healthy individuals, *C. albicans* is most commonly isolated from the mid-line of the middle and posterior thirds of the tongue, the cheek, or the palatal mucosa [9] [10] [11]. It is of interest that only a proportion of the population is colonized by *C. albicans*, and only a subset of these individuals develops candidiasis. Few longitudinal studies have been carried out on healthy individuals to see if *Candida* colonization was continuous. However, daily sampling has shown that *C. albicans* carriage persisted in a proportion of healthy people and that colonization recurred in a majority of the remaining subjects [12] [13]. In a study of 163 neonates in an intensive care and surgical unit, 21 of the neonates initially carried *C. albicans* in their mouths, but only five yielded 6 or more yeast-positive cultures over the 17-week study period [14]. These neonates were colonized by *C. albicans* for periods of between 7 and 63 days. The biotypes of *C. albicans* strains were investigated, and there was unequivocal evidence that more than two biotypes were detected in only 8.1% of colonized neonates. In immune-compromised hosts, candidiasis is often caused by a resident strain [15] [16], and the same strain can cause recurrent infections [17]. Some of the factors involved in the development of candidiasis have been reviewed previously [18]. However, little is known about the transmission of the isogenic *C. albicans* strain within a married couple.

Arbitrarily primed polymerase chain reaction (AP-PCR) is a polymerase chain reaction-based method developed for genetic analysis of eukaryotic and prokaryotic cells [19] [20]. This method has been used for fingerprinting individual strains of pathogenic microorganisms and has been proven to be a useful tool for distinguishing microorganism strains.

Candida albicans is regarded as a part of normal flora in the human oral cavity; however, it remains unclear whether the genus *Candida*, especially *C. albi-*

cans, is an oral resident microorganism and causes marital infection or not. The purpose of the present study was to elucidate the origin of oral *C. albicans* by investigating the colonization and infection route to oral cavities of this organism with AP-PCR.

2. Materials and Methods

2.1. Subjects

Eighteen volunteers participated in the present study. The volunteers consisted of five pairs of married couples (average period of the cohabitation: 12.4 years; range: 5 - 31) and other eight volunteers (average age: 42.2; range: 33 - 56). They had no systemic disease and received no antibiotic therapy for at least 3 months, and also none wore a denture. All participants were asked not to brush, rinse, or smoke immediately prior to the assessment and not to eat or drink for at least 2 h beforehand. The present study was approved by the Ethics Committee of Nihon University School of Dentistry at Matsudo, Japan (EC 20-022). Informed consent was obtained from all volunteers.

2.2. Clinical Samples

Paraffin-stimulated whole saliva samples were collected in a sterile microcentrifuge tube. All samples were dispersed by sonication for 30 s in an ice bath (50 W, 20 kHz, Astrason® System model XL 2020, NY., USA). Portions (100 µl) of appropriate dilutions of these samples were inoculated on CHROMagar™ Candida (CHROMagar, Paris), a commercial selective medium for the genus *Candida*. Selective medium plates were cultured at 30˚C for 2 days under aerobic conditions. After the cultivation, *C. albicans* was isolated from five pairs of married couples. Likewise, after *C. albicans* was isolated from other eight subjects, the isolations of this organism from four of them were performed six months later again.

2.3. Identification of *C. albicans* Isolated from Clinical Samples

Ten of the approximately 50 green colonies that grew on the selective medium plate per subject were randomly isolated and subcultured, and their species identifications were then confirmed by a multiplex PCR analysis [21]. Subcultured isolates were suspended in 1.0 McFarland standard in 100 µl of distilled water, and 5.6 µl of the suspension was used as a template for AP-PCR. The multiplex PCR condition and PCR primers used in this study were performed as described previously [21]. Briefly, the multiplex PCR mixture contained 0.2 µM of each primer, 10 µl of 2 × MightyAmp Buffer Ver.3 (Takara Bio Inc., Shiga, Japan), 0.4 µl of MightyAmp DNA Polymerase (Takara), and 5 µl of the template in a final volume of 20 µl. PCR reactions were performed in a DNA thermal cycler (Applied Biosystems 2720 Thermal Cycler; Applied Biosystems, CA, USA). PCR conditions included an initial denaturation step at 98˚C for 2 min, followed by 30 cycles consisting of 98˚C for 10 s and 68˚C for 1 min. PCR products were analyzed by 2.0% agarose gel electrophoresis before being visualized by electro-

phoresis in 1 × Tris-borate-EDTA on a 2% agarose gel stained with ethidium bromide. A 100-bp DNA ladder (Takara Biomed, Shiga, Japan) was used as a molecular size marker. When the amplicon of 1009 bp was detected, the isolate was identified with *C. albicans*.

2.4. Genotyping by AP-PCR Analysis

AP-PCR analysis for genotyping of *C. albicans* isolates was performed as follows. Subcultured *C. albicans* isolates were suspended in 1.0 McFarland standard in 100 µl of distilled water, and 7.6 µl of the suspension was used as a template for AP-PCR. AP-PCR was performed as described previously [22]. Briefly, the PCR mixture contained 0.2 µM of OPG-19 primer (5'-GTCAGGGCAA-3'), 10 µl of 2 × MightyAmp Buffer Ver.3 (Takara Bio Inc., Shiga, Japan), 0.4 µl of MightyAmp DNA Polymerase (Takara), and 7.6 µl of the template in a final volume of 20 µl. AP-PCR was carried out in a DNA thermal cycler (Applied Biosystems 2720 Thermal Cycler). AP-PCR conditions included an initial denaturation step at 98˚C for 2 min, 50˚C for 2 min, and 35˚C for 1 min, followed by 30 cycles consisting of 72˚C for 2.5 min, 92˚C for 1.5 min, and 35˚C for 1 min and final extension period of 72˚C for 5 min. PCR products were analyzed by 2.0% agarose gel electrophoresis and visualized by gel staining with ethidium bromide. A 100-bp DNA ladder was used as a molecular size marker (Takara Biomed).

3. Results

3.1. Comparison of Genotype of Each *C. albicans* Isolate at 0 Month and after 6 Months

Figure 1 shows the results of genotyping by AP-PCR using OPG-19 primer of each *C. albicans* isolate from subject A and B. Figure 2 shows the results of those from subject C and D. Oral *C. albicans* isolates of each subject were classified as one genotype among each individual; however, the AP-PCR patterns of oral *C. albicans* isolates were not identical among each subject. Figure 3 shows the results of genotyping by AP-PCR using OPG-19 primer of each *C. albicans* isolate from subject E, F, G and H at 0 month and after 6 months. The AP-PCR patterns of *C. albicans* that were isolated from each subject at o month and after 6 months showed identical genotypes among each individual.

3.2. Comparison of Genotypes of *C. albicans* Isolates between Husband and Wife of Each Pair of Married Couples

C. albicans isolates from five pairs of married couples showed the identical genotypes between a husband and wife of each pair on AP-PCR (Figure 4).

4. Discussion

The genetic diversity among clinical *C. albicans* isolates is investigated by molecular typing techniques amenable to high-throughput capability for epidemiological purposes. These studies have occasionally identified small outbreaks in-

side hospitals which escaped identification by routine hospital infection control measures [23] [24].

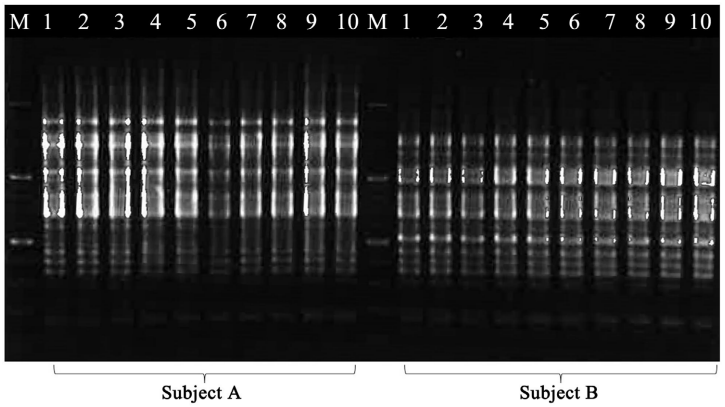

Figure 1. Genetic differences among *C. albicans* isolates from subject A and B with AP-PCR. Left lanes: 1 - 10, *C. albicans* isolates from subject A; right lanes: 1-10, *C. albicans* isolates from subject B; M, molecular size marker (100-bp DNA ladder).

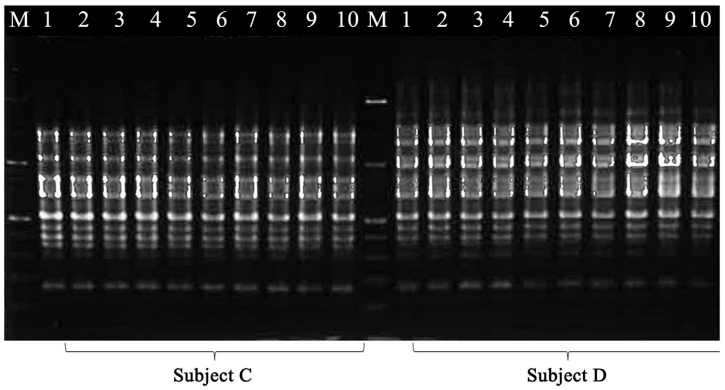

Figure 2. Genetic differences among *C. albicans* isolates from subject C and D with AP-PCR. Left lanes: 1 - 10, *C. albicans* isolates from subject C; right lanes 1-10, *C. albicans* isolates from subject D; M, molecular size marker (100-bp DNA ladder).

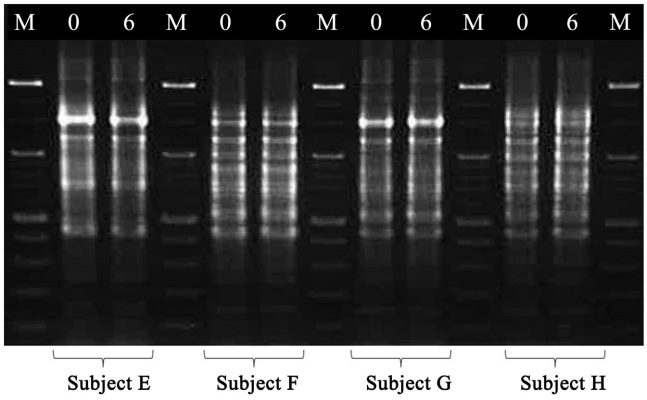

Figure 3. Genetic differences among *C. albicans* isolates from each subject at 0 month and after 6 months with AP-PCR. Lane: 0, *C. albicans* isolates from each subject at 0 month; Lane 6, *C. albicans* isolates after 6 months; Lane M, molecular size maker (100 bp DNA ladder).

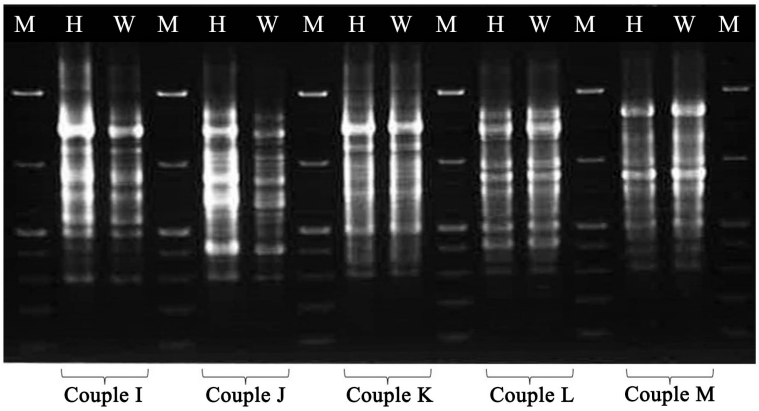

Figure 4. Genetic differences among *C. albicans* isolates from five pairs of married couples with AP-PCR. Lane: H, *C. albicans* isolate from each husband; Lane: W, *C. albicans* isolate from each wife; Lane M, molecular size maker (100 bp DNA ladder).

AP-PCR is distinct from classical PCR in the use of a single primer and low annealing temperature and has been to detect genomic polymorphisms at the strain level [19] [20] [25] [26]. AP-PCR has several advantages over phenotyping and other genotyping methods: it is universally applicable, as it requires no prior knowledge of DNA sequence, and it yields fast and reliable results at a low cost. Slots *et al.* [25] and Pres *et al.* [26] suggested the usefulness of AP-PCR in fingerprinting bacterial strains. In this study, AP-PCR using OPG-19 primer was performed to compare the genetic differences among *C. albicans isolates* of each subject.

Candida albicans is regarded as a part of normal flora in the human oral cavity; however, it remains unclear whether the genus *Candida*, especially *C. albicans*, is an oral resident microorganism and causes marital infection or not. The purpose of the present study was to elucidate the origin of oral *C. albicans* by investigating the colonization and infection route to oral cavities of this organism with AP-PCR. In this study, oral *C. albicans* isolates of each subject were classified as one genotype among each individual; however, the AP-PCR patterns of oral *C. albicans* isolates were not identical among each subject. Because plural genotypes were detected from each individual, there may not be many opportunities to be infected with *C. albicans*, in daily life. Also, AP-PCR using OPG-19 primer was useful to compare the genetic differences among *C. albicans isolates* of each subject. In this study, the AP-PCR patterns of *C. albicans* that were isolated from each subject at o month and after 6 months showed identical genotypes among each individual. This result indicated that *C. albicans* was an oral resident microorganism. Our result was similar to that of the previous studies [12] [13] reporting that *Candida* colonization in the healthy individuals was continuous. In this study, *C. albicans* isolates from five pairs of married couples showed the identical genotypes between a husband and wife of each pair on AP-PCR. This result indicated that *C. albicans* caused the marital infection. Our results support several previous studies [27] [28] [29] demonstrating that indirect and direct human-to-human transmission of *Candida* species was possible.

However, because unfortunately the mechanisms and preventions of transmission still remain unclear, it was considered that further exploration would be needed in the future.

5. Conclusion

The present study focused on the origin of oral *C. albicans* by investigating the colonization and infection route to oral cavities of this organism with AP-PCR. Our results indicated that *C. albicans* was an oral resident microorganism and caused the marital infection. The finding of the present study might contribute toward taking preventive measures for in-home infection.

Authors' Contributions

Akira Fukatsu, Mana Fuchigami, Yoshinori Ono, Satoshi Uchibori, Yuji Takahashi, Chiaki Komine, Koji Umezawa, Sachiyo Hayashi, Taira Kobayashi and Hiroshi Murakami corrected the data. Akira Fukatsu, Osamu Tsuzukibashi, Masanobu Wakami and Masahiko Fukumotodrafted wrote the manuscript. The concept of this manuscript was devised by Akira Fukatsu. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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