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Review

Taxonomy of Pathogenic Yeasts *Candida*, *Cryptococcus*, *Malassezia*, and *Trichosporon*: Current Status, Future Perspectives, and Proposal for Transfer of Six *Candida* Species to the Genus *Nakaseomyces*

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ABSTRACT

This review describes the changes in yeast species names in the previous decade. Several yeast species have been reclassified to accommodate the "One fungus = One name" (1F=1N) principle of the Code. As the names of medically important yeasts have also been reviewed and revised, details of the genera *Candida*, *Cryptococcus*, *Malassezia*, and *Trichosporon* are described in Section 3, along with the history of name changes. Since the phylogenetic positions of *Candida* species in several clades have not been clarified, revision of this species has not been completed. Among the species that remain unrevised despite their importance in the medical field, we propose the transfer of six *Candida* species to be reclassified in the *Nakaseomyces* clade, including *Nakaseomyces glabratus* and *Nakaseomyces nivalensis*.

Key words : *Candida*, *Cryptococcus*, *Malassezia*, *Nakaseomyces glabratus*, nomenclature, taxonomy, *Trichosporon*, yeast, 1F=1N

I. Introduction

"The Yeasts, A Taxonomic Study" (hereafter, "The Yeasts") is a book on yeast classification and identification. Its fifth edition was published in 2011 and included 1,312 strains in the main text (842 ascomycetous yeasts, 464 basidiomycetous yeasts, and 4 *Prototheca* species)[1]. In addition, a list titled "species received too late for inclusion in the chapter" was included for each genus (Table 1).

In the same year, a revision of the International Code of Nomenclature was published in response to the International Botanical Congress held in Melbourne in 2011 (Melbourne Code, https: //www. iapt-taxon. org/melbourne/main. php). While the Code is reviewed and updated every six years, the Melbourne Code included significant items for the taxonomy of fungi, including yeasts[2, 3]. The International Code of Botanical Nomenclature (ICBN) was renamed as the International Code of Nomenclature for algae, fungi, and plants (ICN). The present code is the Shenzhen Code that was published in 2018 (https://www.iapt-taxon.org/nomen/main.php)[4].

Abolition of the dual nomenclature for pleomorphic fungi and the transition to a unified nomenclature called "One fungus = One name (1F=1N)" have had significant effects on the fungal classification system. For example, the principle of priority is equally imposed for both teleomorph and anamorph names in 1F=1N, which is different from the dual nomenclature, wherein teleomorph names has been prioritized.

Since the fifth edition of The Yeasts was published in 2011

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Table 1. Number of species listed in The Yeasts, A Taxonomic Study 5th ed.

Taxa		Number of		Genus estimated drastic name changes due to high polyphyly	Number of species	
		Genera	Species		Listed in the text of chapter	Listed as "Species received too late for inclusion in the chapter"
Ascomycota						
	Anamorphic	14	392	*Candida*	314	51
	Telermorphic	73	452			
Basidiomycota						
	Anamorphic	29	366	*Cryptococcus*	70	25
				Rhodotorula	47	4
	Telermorphic	34	98			
Microalgae						
	Prototheca	1	4			
Total		151	1312			

(before the Melbourne Code), species names were described under the dual nomenclature system. Therefore, they have all been reviewed to implement the 1F=1N nomenclature principle[5, 6]. As most anamorphic genera are phylogenetically polyphyletic, these studies also performed a reclassification based on multigene analyses.

Throughout the decade since the release of the fifth edition of The Yeasts, several species names have changed. Notably, most changes were not due to 1F=1N, but rather to the reclassification of polyphyletic taxa in yeast taxonomy. In this review, we primarily described the changes in species name for approximately 10 years since the publication of the fifth edition of The Yeasts. General progress is described in Section 2, and the current status of medically important yeasts is highlighted in Section 3.

II. Previous decade

1. From 2011

Along with the advances in science and molecular technology and the accumulation of sequence information, identification methods have also been developed[7-10]. Therefore, phylogenetic data based on molecular sequences have become more important at the genus and higher classification levels[11, 12] than those used in the past, such as morphology at sexual and asexual stages and chemotaxonomy, including wall sugar composition and isoprenoid chain length of ubiquinone[13, 14].

In addition, the number of genes used for constructing a phylogenetic tree has increased from only one [e.g., D1/D2 region of large submit ribosomal ribonucleic acid (LSU rRNA) gene, internal transcribed spacer (ITS) including 5.8S gene] to many, in a procedure known as multigene analysis[15-25]. In the multigene analysis of yeasts, *RPB1* (the largest subunit of DNA polymerase II), *RPB2* (the second largest subunit of DNA polymerase II), translation elongation factor 1-α (*TEF1*), and cytochrome b (*CYTB*) are used aside from the ITS and D1/D2 regions of the rRNA gene. The ITS region is known as the "universal DNA barcode marker for fungi"[26]. In yeast taxonomy, the sequence data of both the ITS and D1/D2 regions are used for identification.

With progress in molecular techniques and databases, fungal identification can be performed quickly, and teleomorph and anamorph relationships can also be estimated more easily. The establishment of "barcode genes" has accelerated the study of species diversity. Progress in this area has revealed that yeast taxonomy does not necessarily reflect phylogenetic relationships, and that several anamorphic genera are highly polyphyletic and combined with teleomorphic genera. For example, *Candida* spp. are scattered among 11 of 12 clades in Saccharomycotina, as stated by Kurtzman and Robnett[17], and *Cryptococcus* spp. were found in 3 of the 5 orders of Agaricomycotina, namely Filobasidiales, Tremellales, and Trichosporonales[27]. Because fungi in the environment can be detected using their DNA sequences, the dual nomenclature system was inconvenient for their identification. We presume that all these issues led to changes to the Code[28].

2. Checking of all scientific names

All scientific names in The Yeasts have been checked by various scientists. Special care has been taken for anamorphic species (e.g., *Candida* and *Cryptococcus*) because they are highly polyphyletic. The classification system is also being updated accordingly.

Approximately 70% of species names listed in the fifth edition of The Yeasts were expected to change; the whole process had been a huge task. Completion of the name changes before the approval of formal adoption at the International

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Botanical Congress in 2017 was prioritized[29]. Fundamentally, the boundary of a genus was determined based on phylogeny, and the name of the genus was selected according to the Code. If an appropriate genus did not exist, a new genus was proposed.

The investigation and modification of boundaries between genera have been carried out on the basis of phylogenetic trees of several concatenated genes, such as rRNA genes (SSU, LSU D1/D2 domains, and ITS region including 5.8S rRNA) and partial sequences of *RPB1*, *RPB2*, *TEF1*, and *CYTB*.

In ascomycetous yeasts (Taphrinomycotina and Saccharomycotina), species reclassification (mainly teleomorphs) based on such phylogenetic trees had already begun in the decade before the transition to 1F=1N[15, 16, 18, 30-33]. While the reclassification of basidiomycetous yeast species at that time had been delayed, both teleomorphs and anamorphs were reclassified on the basis of phylogenetic relationships to accommodate the requirements of the Code. Three studies have reported such reclassifications for the subphyla Agaricomycotina[27], Pucciniomycotina[23], and Ustilaginomycotina[34]. However, some species names remain unrevised and are treated as *pro tempore*.

In The Yeasts, among the anamorphic ascomycetous yeast species belonging to the genus *Candida*, 314 are listed in the main text and 51 species are listed as "species received too late for inclusion in this chapter"; hence, a total of 365 species are included in The Yeasts. In the decade since the fifth edition was published, approximately half of the *Candida* species have been reclassified into 25 existing genera and 10 proposed novel genera[35-38]; the other half remain unassigned to appropriate genera (see Section 3 and Supplementary Table 1). The major reason for this delay is that the phylogenetic positions for such species are unclear based on multigene analysis; thus, a more robust phylogenetic tree using genome information is needed. Therefore, in this review, we listed the present names of the species listed in Chapter *Candida* by referring to MycoBank and Index Fungorum (365 species, see Supplementary Table 1). NCBI clade names were also included for species that are currently not reclassified.

3. Current status of the transition from dual nomenclature to a unified nomenclature

In the decade since the fifth edition of The Yeast has been published, the names of many yeast species have been changed. However, the transition from dual to unified nomenclature was not completed because of the following:

- Reclassification has not been achieved in some genera for which phylogeny with good resolution has not been obtained (e. g., *Candida* and *Pseudozyma*). The phylogenetic and taxonomic positions of some species near the roots of the clades are unstable.
- Owing to time limitations, the investigation and modification of boundaries between genera were only based on phylogenetics, and phenotypes that characterize and differentiate genera have not been properly taken into consideration.
- In cases where both teleomorph and anamorph species exist in a single genus, it is difficult to use morphological characteristics for delineation. In such cases, the importance of the morphological characteristics of teleomorph species as taxonomic criteria might appear to decrease. However, this is not true because the life cycle is very important in biology. Therefore, the development of new phenotypes that characterize the respective genera is necessary.

Previously, morphological characteristics were mainly used to characterize filamentous fungi at genus and species levels, whereas physiological and biochemical properties have been used in yeasts owing to the lack of morphological characteristics[13]. Since yeasts and filamentous fungi are fungi, it is important to harmonize the taxonomic criteria that can be used for both organisms. Sequence analysis might aid in this effort; however, previous studies have reported differences in the identification thresholds at the genus level and higher taxa[12, 39].

4. Next step: expectations for genome data

Next, we consider yeast species that have not been reclassified, despite requiring revision. Approximately 1,000 species have been described in Saccharomycotina, including 12 clades in one class[17, 40]. Among the 12 clades, only two (Lipomycetaceae and Trigonopsidaceae) do not include *Candida* species; Lachance and Kurtzman[41] reclassified one of the 12 clade species as Trigonopsidaceae. *Candida* is still extremely phylogenetically divergent, and a well-resolved phylogenetic tree cannot be obtained using multigene analyses. Accumulation of genome data not only from *Candida* species but also related species (determined in various genome projects such as the 1000 Fungal Genomes Project, https://mycocosm.jgi.doe.gov/mycocosm/home/, and Y1000 + Project, https: //y1000plus. wei. wisc. edu/) should provide robust phylogenetic data on Saccharomycotina species[42-53].

A recent genomic analysis of fungi reported that Saccharomycotina species diverged earlier and evolved more quickly (~1.6 times faster) than Pezizomycotina[40]. On the other hand, according to the same study, fewer species have been described in Saccharomycotina (1,000 species belonging to 1 class, 12 clades) than in Pezizomycotina (82,000 species in 16 classes). We hypothesize that this limited number of described species might be the reason for the difficult reclassification of *Candida* species. Therefore, it is important to confirm the phylogenetic positions of unrevised species and, if necessary, propose a new taxon for such species even if it becomes a monotypic genus[54, 55].

Although the use of phylogenetic trees to taxonomically

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Table 2. Seven newly reclassified species of *Cryptococcus neoformans* and *Cryptococcus gattii*

Current species name	Before 2015
Cryptococcus neoformans	*Cryptococcus neoformans* var. *grubii*
Cryptococcus deneoformans	*Cryptococcus neoformans* var. *neoformans*
Cryptococcus neoformans × *Cryptococcus deneoformans* hybrid	*Cryptococcus neoformans* intervariety hybrid
Cryptococcus gattii	*Cryptococcus gattii*
Cryptococcus bacillisporus	
Cryptococcus deuterogattii	
Cryptococcus tetragattii	
Cryptococcus decagattii	
Cryptococcus deneoformans × *Cryptococcus gattii* hybrid	*Cryptococcus neoformans* var. *neoformans* × *Cryptococcus gattii* AFLP4/VGI hybrid
Cryptococcus neoformans × *Cryptococcus gattii* hybrid	*Cryptococcus neoformans var. grubii* × *Cryptococcus gattii AFLP4/VGI hybrid*
Cryptococcus neoformans × *Cryptococcus deuterogattii* hybrid	*Cryptococcus neoformans* var. *grubii* × *Cryptococcus gattii* AFLP6/VGII hybrid

classify fungi may be subject to debate[56], utilizing genome data to describe yeast species has been discussed[57, 58]. Therefore, we propose that the fungal classification system should be updated by incorporating genomic data into the present taxonomic system.

III. Current taxonomical status of pathogenic yeasts

1. *Cryptococcus neoformans*/*Cryptococcus gattii* and related *Cryptococcus* species

Cryptococcosis is an infectious disease caused by a fungus belonging to the genus *Cryptococcus*. *Cryptococcus* species mainly infect the lungs and skin to form lesions[59-61]. Pulmonary cryptococcosis is the most common type of the disease; however, disseminated cryptococcosis can also develop. In particular, *Cryptococcus* species spread to the central nervous system, causing cerebral meningitis. Renal disease, malignant tumors, diabetes, and steroid administration are risk factors for cryptococcosis, and people with human immunodeficiency syndrome virus infection are at a high risk for cryptococcal meningitis. *Cryptococcus* species have thick capsules composed of polysaccharides on the outside of the cell wall. *Cryptococcus neoformans* and *Cryptococcus gattii* are the main causative agents of cryptococcosis.

The species epithet "*Cryptococcus neoformans*" was described in 1901[62] and was modified to "*Cryptococcus neoformans* var. *gattii*" in 1970[63], creating two recognized varieties (var. *neoformans* and var. *gattii*). Subsequently, *C. neoformans* var. *gattii* was classified as *C. gattii*[64]. Since the anamorphic names *C. neoformans* and *C. gattii* correspond to the teleomorphic names *Filobasidiella neoformans* and *Filobasidiella bacillisporus*, respectively[65], the genus name "*Cryptococcus*" is currently being used[66, 67]. Cryptococcal capsules are serologically divided into five serotypes: A, B, C, D, and AD (a hybrid of A and D types), which not only provide epidemiological information but have also been applied to the taxonomical identification of *C. neoformans*/*C. gattii*. Serotypes A, D, and AD correspond to *C. neoformans*, whereas B and C correspond to *C. gattii*, and serotypes A and D further correspond to the varieties *grubii* and *neoformans* of *C. neoformans*[65, 68]. However, there was a conflict regarding the taxonomy of *C. neoformans*. The type strain *C. neoformans* CBS 123 belongs to serotype AD[69], which was revealed to be a natural hybrid between the A and D serotypes[70]. Thus, this strain is impossible to classify as *C. neoformans* var. *grubii* and var. *neoformans*. Therefore, each variety was proposed to be a single species: *C. neoformans* for serotype A, *Cryptococcus deneoformans* for serotype D, and *C. neoformans*/*C. deneoformans* hybrid for serotype AD (described later in detail).

Genotyping studies based on amplified fragment length polymorphisms, PCR-fingerprinting using restriction fragment length polymorphisms, and multilocus sequence typing have revealed the genetic diversity within *C. neoformans* and *C. gattii*. The two varieties of *C. neoformans* were reclassified as *C. neoformans* and *C. deneoformans* (Table 2). Infection due to *C. neoformans* occurs worldwide and is a major causative agent of invasive cryptococcosis, whereas infection due to *C. deneoformans* is observed mainly in Europe and causes cutaneous infection[67]. *C. gattii* has been reclassified into five distinct species: *C. gattii*, *Cryptococcus bacillisporus*, *Cryptococcus decagattii*, *Cryptococcus deuterogattii*, and *Cryptococcus tetragattii*. The first four species belong to serotype B, whereas *C. tetragatii* belongs to serotype C. An outbreak of *C. gattii* VGII first occurred in Vancouver[71] and then has spread to North and South America[72]. *C. gattii* VGII

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is known as *C. deuterogattii*. On the other hand, Kwon-Chung et al.[73] claimed that nomenclatural instability will continue because the seven new species names for each clade were proposed on the basis of genetic diversity, while biological differences between the genetic clades are absent. Alternatively, they recommended the use of "*Cryptococcus neoformans* species complex" and "*Cryptococcus gattii* species complex". However, molecular phylogenetic analyses have resolved the taxonomic problems of many yeast species complexes, elucidating the correlation between each newly recognized species and epidemiological characteristics, virulence, and drug susceptibility, such as the *Candida parapsilosis* species complex[74], *Candida guilliermondii* species complex[75], *Malassezia furfur* species complex[76], and *Trichosporon cutaneum* species complex[77].

Although *Cryptococcus albidus*, *Cryptococcus diffluens*, *Cryptococcus curvatus*, *Cryptococcus humicola*, and *Cryptococcus laurentii* are rarely isolated from immunocompromised hosts, these species are now reclassified as *Naganishia albida*, *Naganishia diffluens*, *Cutaneotrichosporon curvatum*, *Vanrija humicola*, and *Papiliotrema laurentii*, respectively (Table 3, Supplementary Table 2).

2. *Trichosporon*

Trichosporon is one of the largest genera of basidiomycetous yeasts and is morphologically characterized by the production of arthroconidia. This genus was described from a strain isolated from an infected mustache hair from Germany in 1890 (named *Trichosporon ovoides*)[78], and the fungi was known to be the causative agent of superficial infection, particularly white piedra. To date, few cases of white piedra have been reported due to the improvement in hygiene; however, microorganisms have been newly recognized as opportunistic pathogens capable of causing life-threatening infection (trichosporonosis) in immunocompromised hosts. The first report was from a patient with brain abscess as an underlying disease in 1970[79]. Additionally, breakthrough infections in patients receiving echinocandins are associated with high mortality rates[80, 81]. Furthermore, *Trichosporon* spp. are capable of inducing summer-type hypersensitivity pneumonitis (SHP), which is a type III or IV allergy[82]. During the hot and humid season, the fungus inhabiting the environment spreads and grows in the household, and SHP is induced by repeatedly inhaling the hyphae or arthroconidia of the fungus. Until 30 years ago, two species, namely *Trichosporon cutaneum* and *Trichosporon beigelii*, coexisted as causative agents of trichosporonosis, and their taxonomy has a complicated history[83].

Rabenhorst[84] described *Pleurococcus beigelii*, a strain isolated from the clinical specimens of a patient with chignon disease in 1867. Subsequently, Vuillemin[85] reclassified the fungus to the genus *Trichosporon* because he considered *P. beigelii* identical to *T. ovoides* (type species). On the other hand, *Oidium cutaneum* was originally described as a strain isolated from a lesional region of skin, then was transferred into the genus *Trichosporon* by Ota in 1926[86]. Puntoni[87] suggested that *T. cutaneum* might be a synonym of *T. beigelii* because the characteristics of the species are similar, but the name *T. beigelii* is considered doubtful and consequently cannot be maintained according to the nomenclatural rule[83].

T. cutaneum is taxonomically considered a heterogeneous species based on the coenzyme Q molecule type, cell wall structure, mol% G + C content, or serological characteristics. Phylogenetic analysis revealed that *Trichosporon* consisted of 14 distinct species (*Trichosporon asahii*, *Trichosporon asteroides*, *Trichosporon coremiiforme*, *T. cutaneum*, *Trichosporon dulcitum*, *Trichosporon faecale*, *Trichosporon gracile*, *Trichosporon jirovecii*, *Trichosporon laibachii*, *Trichosporon loubieri*, *Trichosporon moniliiforme*, *Trichosporon montevideense*, *Trichosporon mucoides*, and *Trichosporon sporotrichoides*)[77]. A large-scale comprehensive analysis of clinical isolates revealed that *T. asahii* was the major causative agent of both trichosporonosis and SHP, and *T. cutaneum* had little involvement in any disease[88-91]. The species epithet "*asahii*" was derived from Professor Kenkichi Asahi, Professor of Dermatology in Kyushu University, Japan, and was named by Akagi in 1929[92]. Unfortunately, the paper that published *T. asahii* as a new species did not meet the taxonomic criteria for the proposal of a new species, so it was treated as *nomen dubium*. Sugita et al.[93] maintained the epithet by validating the name of *T. asahii*.

In 2015, the genus *Trichosporon* was taxonomically revised. *Trichosporon* has been re-established into five genera: *Apiotrichum*, *Cutaneotrichosporon*, *Effuseotrichosporon*, *Haglerozyma*, and *Trichosporon* (Fig. 1, Table 3, and Supplementary Table 3)[20]. *T. asahii*, the causative agent of trichosporonosis, and *Trichosporon inkin* and *T. ovoides*, the causative agents of white piedra, were retained. The historically important species *T. cutaneum* has been transferred to the genus *Cutaneotrichosporon*. *T. faecale* and *T. coremiiforme* are phylogenetically closely related to *T. asahii* and are rarely isolated from human clinical specimens. Because the DNA sequences of the ITS and D1/D2 regions of the rRNA gene of these three species are very similar, analysis of the intergenic spacer (IGS) 1 sequence is recommended for the accurate identification of these microorganisms[88]. By analyzing the IGS sequences, molecular epidemiological information can also be obtained; genotype 1 is predominant in clinical isolates from infections, whereas genotype 3 is predominant in environmental isolates from the homes of SHP patients[89].

3. *Malassezia*

Malassezia species inhabit the skin of humans and non-human mammals; however, these species are not found in the environment. Except for one species (*Malassezia*

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Table 3. Reclassification of pathogens previously classified as *Candida*, *Cryptococcus*, and *Trichosporon*

Candida species	Current species name	Class	Order	Family/Lineage
Candida africana	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida albicans	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida auris	1)	Saccharomycetes	Saccharomycetales	Metschnikowiaceae
Candida blankii	1)	Saccharomycetes	Saccharomycetales	2)
Candida bracarensis	*Nakaseomyces bracarensis* 3)	Saccharomycetes	Saccharomycetales	Saccharomycetaceae
Candida catenulata	*Diutina catenulata*	Saccharomycetes	Saccharomycetales	2)
Candida colliculosa	*Torulaspora delbrueckii*	Saccharomycetes	Saccharomycetales	Saccharomycetaceae
Candida dubliniensis	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida duobushaemuloni	1)	Saccharomycetes	Saccharomycetales	Metschnikowiaceae
Candida fabianii	*Cyberlindnera fabianii*	Saccharomycetes	Saccharomycetales	Phaffomycetaceae
Candida famata	*Debaryomyces hansenii*	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida fermentati	*Meyerozyma caribbica*	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida freyschussii	1)	Saccharomycetes	Saccharomycetales	2)
Candida glabrata	*Nakaseomyces glabratus* 3)	Saccharomycetes	Saccharomycetales	Saccharomycetaceae
Candida guilliermondii	*Meyerozyma guilliermondii*	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida haemuloni	1)	Saccharomycetes	Saccharomycetales	Metschnikowiaceae
Candida haemuloni var. *vulneris*	1)	Saccharomycetes	Saccharomycetales	Metschnikowiaceae
Candida inconspicua	1)	Saccharomycetes	Saccharomycetales	Pichiaceae
Candida infanticola	*Wickerhamiella infanticola*	Saccharomycetes	Saccharomycetales	Trichomonascaceae
Candida kefyr	*Kluyveromyces marxianus*	Saccharomycetes	Saccharomycetales	Saccharomycetaceae
Candida krusei	*Pichia kudriavzevii*	Saccharomycetes	Saccharomycetales	Pichiaceae
Candida lambica	*Pichia fermentans*	Saccharomycetes	Saccharomycetales	Pichiaceae
Candida lipolytica	*Yarrowia lipolytica*	Saccharomycetes	Saccharomycetales	Dipodascaceae
Candida lusitaniae	*Clavispora lusitaniae*	Saccharomycetes	Saccharomycetales	Metschnikowiaceae
Candida maltosa	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida melibiosica	1)	Saccharomycetes	Saccharomycetales	2)
Candida mesenterica	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida mesorugosa	*Diutina mesorugosa*	Saccharomycetes	Saccharomycetales	2)
Candida metapsilosis	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida mogii	1)	Saccharomycetes	Saccharomycetales	Metschnikowiaceae
Candida molischiana	*Kuraishia molischiana*	Saccharomycetes	Saccharomycetales	2)
Candida mucifera	1)	Saccharomycetes	Saccharomycetales	Trichomonascaceae
Candida neorugosa	*Diutina neorugosa*	Saccharomycetes	Saccharomycetales	2)
Candida nivariensis	*Nakaseomyces nivariensis* 3)	Saccharomycetes	Saccharomycetales	Saccharomycetaceae
Candida norvegensis	*Pichia norvegensis*	Saccharomycetes	Saccharomycetales	Pichiaceae
Candida orthopsilosis	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida palmioleophila	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida parapsilosis	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida pararugosa	*Wickerhamiella pararugosa*	Saccharomycetes	Saccharomycetales	Trichomonascaceae
Candida pelliculosa	*Wickerhamomyces anomalus*	Saccharomycetes	Saccharomycetales	Phaffomycetaceae
Candida pulcherrima	*Metschnikowia pulcherrima*	Saccharomycetes	Saccharomycetales	Metschnikowiaceae
Candida rugosa	*Diutina rugosa*	Saccharomycetes	Saccharomycetales	2)
Candida sake	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida sojae	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida tropicalis	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida tunisiensis	1)	Saccharomycetes	Saccharomycetales	2)
Candida utilis	*Cyberlindnera jadinii*	Saccharomycetes	Saccharomycetales	Phaffomycetaceae
Candida viswanathii	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida zeylanoides	1)	Saccharomycetes	Saccharomycetales	Debaryomycetaceae
Candida pseudohaemuloni	1)	Saccharomycetes	Saccharomycetales	Metschnikowiaceae
Cryptococcus species	Current species name	Class	Order	Family
Cryptococcus adeliensis	*Naganishia adeliensis*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Cryptococcus albidus	*Naganishia albida*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Cryptococcus curvatus	*Cutaneotrichosporon curvatum*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Cryptococcus diffluens	*Naganishia diffluens*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Cryptococcus flavescens	*Papiliotrema flavescens*	Tremellomycetes	Tremellales	Rhynchogastremataceae
Cryptococcus gastricus	*Goffeauzyma gastrica*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Cryptococcus humicola	*Vanrija humicola*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Cryptococcus laurentii	*Papiliotrema laurentii*	Tremellomycetes	Tremellales	Rhynchogastremataceae
Cryptococcus liquefaciens	*Naganishia liquefaciens*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Cryptococcus luteolus	*Hannaella luteola*	Tremellomycetes	Tremellales	Bulleribasidiaceae
Cryptococcus macerans	*Cystofilobasidium macerans*	Tremellomycetes	Cystofilobasidiales	Cystofilobasidiaceae
Cryptococcus magnus	*Filobasidium magnum*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Cryptococcus uniguttulatus	*Filobasidium uniguttulatum*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Cryptococcus uzbekistanensis	*Naganishia uzbekistanensis*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Cryptococcus vishniacii	*Naganishia vishniacii*	Tremellomycetes	Filobasidiales	Filobasidiaceae
Trichosporon species	Current species name	Class	Order	Family
Trichosporon asahii	*Trichosporon asahii*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon asteroides	*Trichosporon asteroides*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon coremiiforme	*Trichosporon coremiiforme*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon cutaneum	*Cutaneotrichosporon cutaneum*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon debeurmannianum	*Cutaneotrichosporon debeurmannianum*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon dermatis	*Cutaneotrichosporon dermatis*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon domesticum	*Apiotrichum domesticum*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon faecale	*Trichosporon faecale*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon inkin	*Trichosporon inkin*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon japonicum	*Trichosporon japonicum*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon loubieri	*Apiotrichum loubieri*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon mucoides	*Cutaneotrichosporon mucoides*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon mycotoxinovorans	*Apiotrichum mycotoxinovorans*	Tremellomycetes	Trichosporonales	Trichosporonaceae
Trichosporon ovoides	*Trichosporon ovoides*	Tremellomycetes	Trichosporonales	Trichosporonaceae

1) Under reclassification

2) Family to be assigned

3) Proposed in this study

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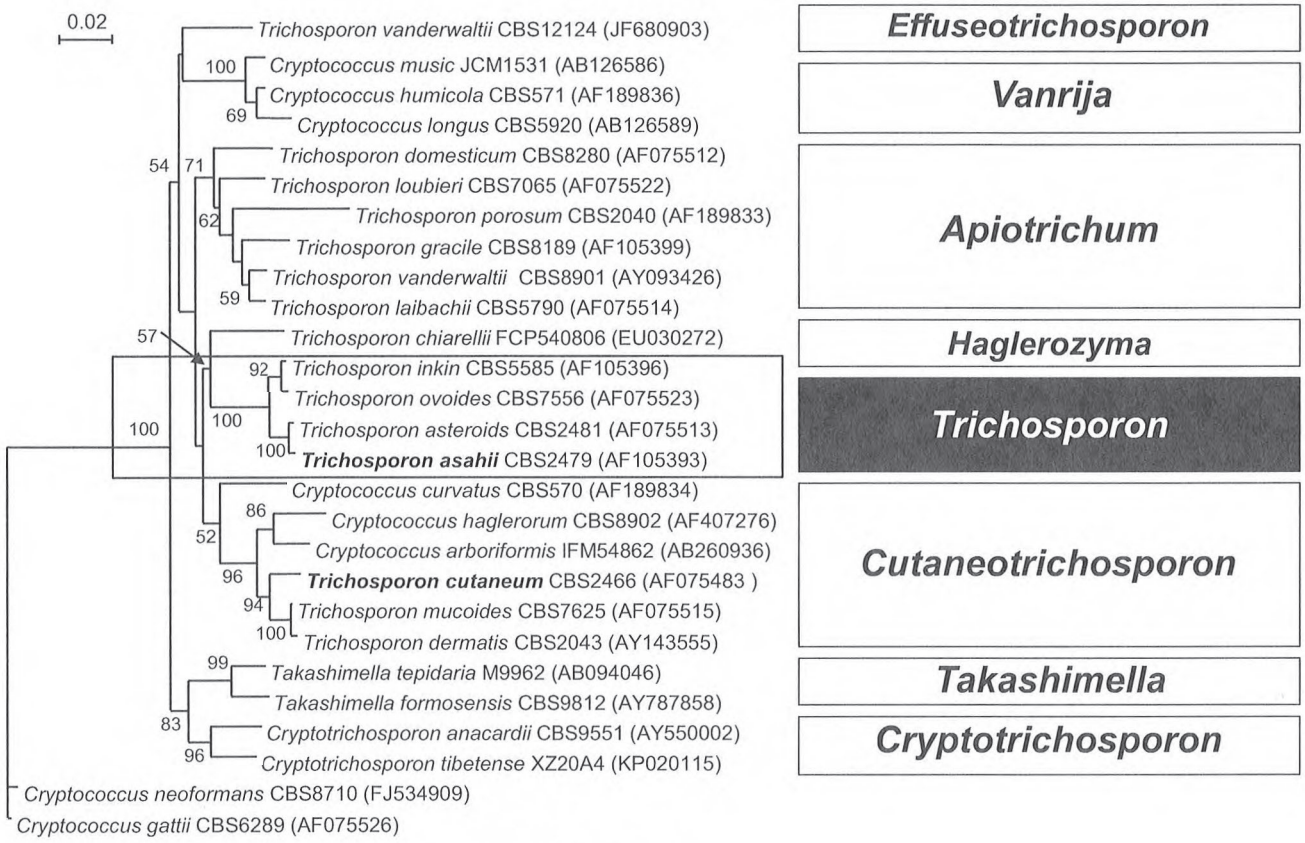


Fig. 1. Phylogenetic tree of the genus *Trichosporon* and related genera.
The tree was generated using the sequences of the D1/D2 domain of the LSU rRNA gene.

pachydermatitis), the fungi colonize sebum-rich areas of the skin surface because they require several types of fatty acids for their growth. Therefore, to cultivate *Malassezia* species, Tween, oleic acid, and bile salts were added to the medium[94-96].

Eichstedt[97] observed hyphae in scale specimens of patients with pityriasis versicolor, and Robin[98] named the culture *Microsporon furfur*. Baillon[99] established the new genus *Malassezia* with *Microsporon furfur*. On the other hand, Sabouraud[100] also described the new genus *Pityrosporum* with a fungus associated with dandruff. However, the genera *Pityrosporum* and *Malassezia* are taxonomically identical. Because *Malassezia* was published earlier than *Pityrosporum*, *Malassezia* has the nomenclatural priority[101]. Although *Malassezia furfur* is a clinically important species, it was considered a taxonomically heterogeneous species. In 1996, molecular phylogenetic analysis revealed that *M. furfur* consisted of five distinct species: *M. furfur*, *Malassezia globosa*, *Malassezia obtusa*, *Malassezia restricta*, and *Malassezia slooffiae*[76]. No sexual stage of *Malassezia* species has been discovered, and the genus is phylogenetically monophyletic. Therefore, its taxonomy has been retained. Eighteen species are listed in the genus *Malassezia*; ten show affinity to human skin, whereas the remaining eight have affinity to the skin of non-human animals (Table 4). The last discovery of a new species derived from humans was *Malassezia yamatoensis*, which was isolated from the skin of a patient with seborrheic dermatitis in 2004[102]. *Malassezia* species described as new species in recent years have been isolated from non-human animals such as bats and parrots[103, 104]. Although *Malassezia* species are commensal yeasts in healthy humans, they can cause pityriasis versicolor, seborrheic dermatitis, *Malassezia* folliculitis, and exacerbate atopic dermatitis[94, 95]. Both *M. restricta* and *M. globosa* are predominant in the skin of healthy individuals and in *Malassezia*-associated skin diseases[94, 105-109]. However, their colonization ratios are different for each skin disease: *M. restricta* is more predominant than *M. globosa* in seborrheic dermatitis, whereas *M. globosa* is more predominant than *M. restricta* in ptyriasis versicolor[105]. The historically important species, *M. furfur*, was rarely detected in clinical specimens.

4. *Candida*

The fifth edition of The Yeasts reports more than 300 species of the genus *Candida*. Around 20 to 30 years ago, approximately 10 species were pathogenic, including *Candida albicans*, *Candida dubliniensis*, *Candida glabrata*, *C. guilliermondii*, *Candida kefyr*, *Candida krusei*, *Candida lusitaniae*, *C. parapsilosis*, and *Candida tropicalis*; however, several dozen

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Table 4. List of *Malassezia* species

Human-associated species	Species associated with non-human animals
Malassezia arunalokei	*Malassezia brasiliensis*
Malassezia dermatis	*Malassezia caprae*
Malassezia furfur	*Malassezia cuniculi*
Malassezia globosa	*Malassezia equina*
Malassezia japonica	*Malassezia nana*
Malassezia obtusa	*Malassezia pachydermatis*
Malassezia restricta	*Malassezia psittaci*
Malassezia slooffiae	*Malassezia vespertilionis*
Malassezia sympodialis	
Malassezia yamatoensis	

species have been isolated from clinical materials (Table 3)[110]. The increasing number of pathogens was attributed to species reclassification as yeast taxonomy progressed, and the diversification of causative agents as the number of immunocompromised hosts increased. An example of the former is that *C. parapsilosis* is divided into three species: *C. parapsilosis*, *Candida metapsilosis*, and *Candida orthopsilosis*[74]. Reclassification of microorganisms advanced medical mycology, as each species was found to have different pathogenicity and susceptibility to antifungal agents. *Candida rugosa*, *Candida sake*, and *Candida zeylanoides* were isolated from the environment as nonpathogens 70–100 years ago, but have been isolated from immunocompromised hosts in the last decade. In some cases, *Candida* has been isolated from clinical materials and described as a new species, such as *Candida auris*[111], *Candida nivariensis*[112], and *Candida bracarensis*[113]. *C. auris* was originally isolated from the external ear canal of an inpatient; however, it has been recognized as an emerging pathogen associated with outbreaks in clinical settings over the last decade[114, 115].

Recent multigene phylogenetical analyses have revealed that species belonging to the genus *Candida* can be divided into more than ten clades, and reclassification of the genus is underway. Among the major pathogens, *C. guilliermondii*, *C. kefyr*, *C. krusei*, and *C. lusitaniae* were reclassified as *Meyerozyma guilliermondii* (Debaryomycetaceae), *Kluveromyces marxianus* (Saccharomycetaceae), *Pichia kudriavzevi* (Pichiaceae), and *Clavispora lusitaniae* (Metschnikowiaceae), respectively. The history of nomenclatural changes in *C. krusei* is interesting. The teleomorphic name of the yeast was *Issatchenkia orientalis* in the fourth edition of The Yeasts; however, it was changed to *Pichia kudriavzevii* in the fifth edition. The taxonomy of *Issatchenkia* was revised to the genus *Pichia*; thus, the name *I. orientalis* should have been changed to *Pichia orientalis*. However, as *Pichia orientalis* was already listed as an illegitimate name, the new name "*kudriavzevii*" was alternatively assigned for *I. orientalis*.

Although the number of *Candida* pathogens is limited, the taxonomy of several species has not yet been established. *C. albicans*, *C. dubliniensis*, *C. parapsilosis*, and *C. tropicalis* are phylogenetically monophyletic and are classified as *Lodderomyces*/*C. albicans* clade[30] (Fig. 2). *Candida vulgaris* is the type species of *Candida*; however, this microorganism has been recognized to be synonymous with *Candida tropicalis*. Therefore, *C. tropicalis* is used to refer to the type species of the genus *Candida*. With this consideration, the species belonging to *Lodderomyces*/*C. albicans* clade, including *C. tropicalis*, may be newly redefined as the genus *Candida*.

The emerging pathogen *C. auris* is clinically problematic worldwide, and *Candida haemuloni*, *Candida pseudohaemuloni*, and *Candida doubushaemulonis* are phylogenetically closely related to *C. auris*. Multidrug-resistant strains of these fungi have been previously isolated[116-118] and may be assigned to the genus *Clavispora* (Metschnikowiaceae). Although the main causative agent of candidiasis is *C. albicans*, the isolation rate of *C. glabrata* from patients with candidiasis has increased over the last two decades. Kurtzman[15] created a new genus, *Nakaseomyces* (Saccharomycetaceae), with two teleomorphic species, *Kluyveromyces bacillisporus* and *Saccharomyces delphensis*. Several anamorphic species such as *C. glabrata*, *C. bracarensis*, *Candida castellii*, *C. nivariensis*, *Candida kungkrabaensis*, and *Candida uthaithanina* also belong to the *Nakaseomyces* clade.

We propose that the following six anamorphic *Candida* species be assigned to the genus *Nakaseomyces*. "*Nakaseomyces*" was named in honor of Dr. Takashi Nakase, former Director of the Japan Collection of Microorganisms of RIKEN, for his many contributions to yeast systematics, including the early application of molecular methods to the study of relationships among yeasts[15, 119].

1. *Nakaseomyces bracarensis* (A. Correia, P. Samp., S.A. James & C. Pais) Sugita & Takashima comb. nov., MycoBank no. MB#843852.

Synonym:

≡ *Candida bracarensis* A. Correia, P. Samp., S.A. James, and C. Pais, Int. J. Syst. Evol. Microbiol. 56 (1): 315 (2006).

2. *Nakaseomyces castellii* (Capr.) Sugita & Takashima comb. nov., MycoBank no. MB#843853.

Synonyms:

≡ *Candida castellii* (Capr.) S.A. Mey. & Yarrow, Yarrow & Meyer, Int. J. Syst. Bacteriol. 28 (4): 612 (1978).

≡ *Torulopsis castellii* Capr., J. gen. Microbiol. 26: 42 (1961).

3. *Nakaseomyces glabratus* (H. W. Anderson) Sugita & Takashima comb. nov., MycoBank no. MB#843854.

Synonyms:

≡ *Candida glabrata* (H.W. Anderson) S.A. Mey. & Yarrow,

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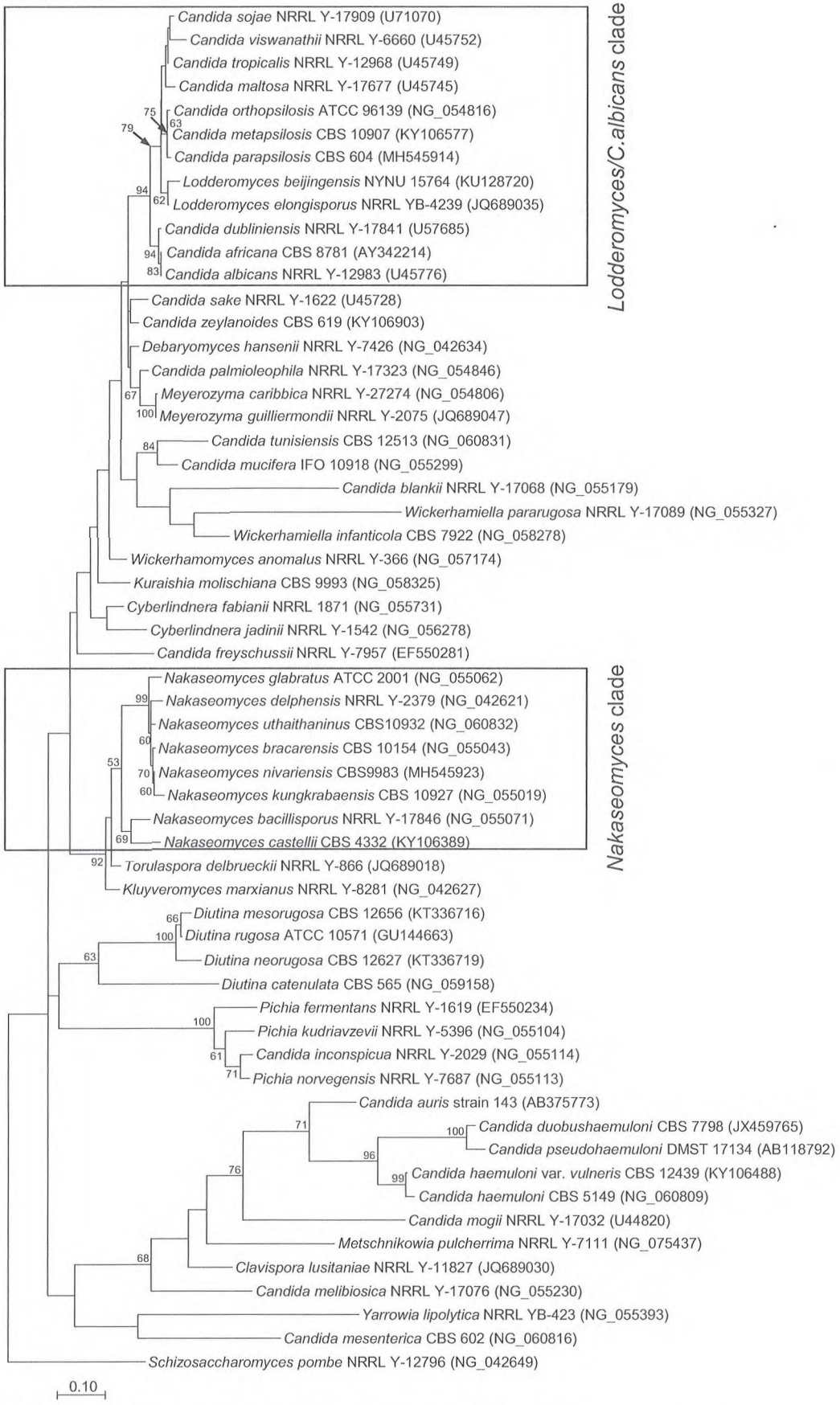


Fig. 2. Phylogenetic tree of medically important yeasts in Saccharomycotina.

The tree was generated using the maximum-likelihood method based on the sequences of the D1/D2 domain of the LSU rRNA gene.

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Yarrow & Meyer, Int. J. Syst. Bacteriol. 28 (4): 612 (1978).
≡ *Cryptococcus glabratus* H.W. Anderson, J. Infect. Dis. 21: 379 (1917).
4. *Nakaseomyces nivariensis* (Alcoba-Flórez, Méndez-Álv., Cano, Guarro, Pérez-Roth & Arévalo, J.) Sugita & Takashima comb. nov., MycoBank no. MB#843855.
Synonym:
≡ *Candida nivariensis* Alcoba-Flórez, Méndez-Álv., Cano, Guarro, Pérez-Roth & Arévalo, J. Clin. Microbiol. 43(8): 4111 (2005).
5. *Nakaseomyces kungkrabaensis* Limtong & Yongman. ex Sugita & Takashima sp. nov. MycoBank no. MB#843856. For a description, see Antonie Van Leeuwenhoek 98(3), 379-388 (2010).
Holotype: BCC 23060 (preserved in a metabolically inactive state).
Synonym: *Candida kungkrabaensis* Limtong & Yongman., Antonie Van Leeuwenhoek 98 (3): 385 (2010) nom. inval., Art. 40.7 (Shenzhen).
6. *Nakaseomyces uthaithaninus* Limtong, Jindam, Am-in, Kaewwich, Nitiyon, Yongman. & Nakase ex Sugita & Takashima sp. nov. MycoBank no. MB#843857.
For a description, see Antonie van Leeuwenhoek 99 (4): 865-871 (2011).
Holotype: BCC 29899 (preserved in a metabolically inactive state).
Synonym: *Candida uthaithanina* Limtong, Jindam, Am-in, Kaewwich, Nitiyon, Yongman. & Nakase, Antonie van Leeuwenhoek 99(4): 869 (2011) nom. inval., Art. 40.7 (Shenzhen).

IV. Conclusion

Over the last decade, several yeast names have changed, including those that are important in the field of medical mycology. Anamorphic taxa, such as *Candida* and *Cryptococcus*, were found to be highly polyphyletic. Thus, they were reclassified on the basis of their phylogenetic relationships to accommodate the requirements of the Code. Therefore, the introduction of molecular techniques in taxonomical identification has advanced the field and has led to a new classification system. However, reclassification has not been concluded in some genera, such as *Candida*, for which a well-resolved phylogeny has not been obtained. This indicates that the transition to a unified nomenclature is incomplete. To resolve this problem, going forward, we will introduce genomic data into the taxonomy and investigate a classification method using such data. With the use of these new methods, we will transfer the presently unrevised species, such as *Candida auris*, to an appropriate genus after determining the delineation and delimitation between related genera.

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Conflicts of interest

None.

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