Article

Current Biology

Patterns of Genomic Variation in the Opportunistic Pathogen *Candida glabrata* Suggest the Existence of Mating and a Secondary Association with Humans

Highlights

- *Candida glabrata* strains can be clustered into highly genetically divergent clades
- Genetic structure suggests a recent global spread of previously isolated populations
- The existence of sex in *C. glabrata* is supported by genomic footprints of selection
- Mating-type switching occurs in *C. glabrata* natural populations but is error prone

Authors

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In Brief

Genome analyses of globally distributed isolates of the emerging fungal pathogen *Candida* point to a recent global spread of previously isolated populations, and suggest that humans are most likely a secondary niche for this yeast. Carreté et al. find evidence for the existence of recombination and mating in this purported "asexual" pathogen.

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Patterns of Genomic Variation in the Opportunistic Pathogen *Candida glabrata* Suggest the Existence of Mating and a Secondary Association with Humans

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SUMMARY

Candida glabrata **is an opportunistic fungal pathogen that ranks as the second most common cause of systemic candidiasis. Despite its genus name, this yeast is more closely related to the model yeast *Saccharomyces cerevisiae* than to other *Candida* pathogens, and hence its ability to infect humans is thought to have emerged independently. Moreover, *C. glabrata* has all the necessary genes to undergo a sexual cycle but is considered an asexual organism due to the lack of direct evidence of sexual reproduction. To reconstruct the recent evolution of this pathogen and find footprints of sexual reproduction, we assessed genomic and phenotypic variation across 33 globally distributed *C. glabrata* isolates. We cataloged extensive copy-number variation, which particularly affects genes encoding cell-wall-associated proteins, including adhesins. The observed level of genetic variation in *C. glabrata* is significantly higher than that found in *Candida albicans*. This variation is structured into seven deeply divergent clades, which show recent geographical dispersion and large within-clade genomic and phenotypic differences. We show compelling evidence of recent admixture between differentiated lineages and of purifying selection on mating genes, which provides the first evidence for the existence of an active sexual cycle in this yeast. Altogether, our data point to a recent global spread of previously genetically isolated populations and suggest that humans are only a secondary niche for this yeast.**

INTRODUCTION

The prevalence of infections by opportunistic pathogens (i.e., candidiasis) is increasing, partly owing to recent medical progress enabling the survival of susceptible individuals [1]. Main prevalent agents of candidiasis comprise three *Candida* species: *Candida albicans*, *Candida glabrata*, and *Candida parapsilosis*, generally in this order [2]. Phylogenetically, these species are only distantly related. *C. glabrata* belongs to the *Nakaseomyces* clade, a group that is more closely related to the baker's yeast *Saccharomyces cerevisiae* than to *C. albicans* or *C. parapsilosis* [3]. Furthermore, both *C. glabrata* and *C. albicans* have closely related non-pathogenic relatives, and hence the ability to infect humans in these two lineages must have originated independently [4, 5]. Genome sequencing of non-pathogenic and mildly pathogenic relatives of *C. glabrata* has enabled tracing the genomic changes that correlate with the evolutionary emergence of pathogenesis in the *Nakaseomyces* group [3]. These analyses revealed that the ability to infect humans has most likely emerged at least twice independently in the *Nakaseomyces*, coinciding with parallel expansions of the encoded repertoire of cell-wall adhesins. Thus, increased—or more versatile—adherence may be implicated in the evolutionary emergence of virulence potential toward humans. In contrast, other virulence-related characteristics had a more ancient origin within the clade, and were also found in environmental relatives.

Our understanding of the evolution of *C. glabrata* at the species level is limited to analyses of natural variation in a few loci [6–8]. These studies have shown the existence of genetically distinct clades and generally suggested clonal, geographically structured populations. Geographically structured populations are also found in *C. albicans*, which is tightly associated with humans and which can undergo a parasexual cycle [9–11], and *S. cerevisiae*, for which some strains have been domesticated and which can undergo a full sexual cycle, usually involving self-mating [12, 13]. *C. glabrata* has been described as an asexual species despite the presence of homologs of *S. cerevisiae* genes involved in mating [14]. Here we undertook a genomics approach to shed light on several fundamental open questions on the recent evolution of this important opportunistic pathogen: namely (1) what is the genetic structure of the global *C. glabrata* population? (2) Does *C. glabrata* show patterns of co-evolution with human populations indicating an