The *Candida* Pathogenic Species Complex

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Candida species are the most common causes of fungal infection. Approximately 90% of infections are caused by five species: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*. Three (*C. albicans*, *C. tropicalis*, and *C. parapsilosis*) belong to the CTG clade, in which the CTG codon is translated as serine and not leucine. *C. albicans* remains the most commonly isolated but is decreasing relative to the other species. The increasing incidence of *C. glabrata* is related to its reduced susceptibility to azole drugs. Genome analysis suggests that virulence in the CTG clade is associated with expansion of gene families, particularly of cell wall genes. Similar independent processes took place in the *C. glabrata* species group. Gene loss and expansion in an ancestor of *C. glabrata* may have resulted in preadaptations that enabled pathogenicity.

Candida species are among the most common human fungal pathogens and are responsible for both superficial (mucosal and cutaneous) and systemic infection (reviewed in Papon et al. 2013a). Approximately 8% of nosocomial bloodstream infections are caused by *Candida* species (Pfaller and Diekema 2007). Several international surveys have tracked the incidence of *Candida* infection and the rates of drug resistance over the past decades (Pfaller et al. 2001, 2002, 2008, 2010a,b,c,d, 2011a,b). One of the most comprehensive studies (ARTEMIS), using data from 142 institutions in 41 countries, identified 31 species of *Candida* in clinical samples over a 10-year period (1997–2007) (Pfaller et al. 2010b). Five species are responsible for just over 92% of cases, and 13 species were very rarely identified (incidences of <0.01%) (Pfaller et al. 2010b). The incidence

of some of the intermediate species may also be overestimated. For example, many isolates originally identified as *Candida famata* (*Debaryomyces hansenii*) were subsequently shown to be predominantly *Candida guilliermondii* or *Candida parapsilosis* (Castanheira et al. 2013).

The five species most commonly associated with candidiasis are *Candida albicans* (65.3%), *Candida glabrata* (11.3%), *Candida tropicalis* (7.2%), *C. parapsilosis* (6.0%), and *Candida krusei* (2.4%) (Table 1) (Pfaller et al. 2010b). The number of infections is rising, although there was a slight drop between 2005 and 2007. *C. albicans* remains the most commonly isolated, but the proportion relative to other *Candida* species has decreased over time (from 71% to 65%). This was accompanied by an increasing incidence of *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*.

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Table 1. *Candida* pathogenic species

Name ^a	Common teleomorphs/synonyms	Ploidy ^b	Mating ^c	Incidence ^d (%)
CTG clade species				
<i>C. albicans</i>		Diploid	P	65.3
<i>C. dubliniensis</i>		Diploid	P	0.1
<i>C. tropicalis</i>		Diploid	P	7.20
<i>C. parapsilosis</i>		Diploid	NO	6.00
<i>C. orthopsilosis</i>		Diploid	NO	0.50 ^e
<i>C. metapsilosis</i>		Diploid	NO	<0.1 ^e
<i>C. famata</i>	<i>Debaryomyces hansenii</i>	Haploid	Ho	0.30
<i>C. lusitaniae</i>	<i>Clavispora lusitaniae</i>	Haploid	Het	0.60
<i>C. guilliermondii</i>	<i>Meyerozyma guilliermondii</i> ; <i>Pichia guilliermondii</i>	Haploid	Het	0.70
Other species				
<i>C. krusei</i>	<i>Issatchenkia orientalis</i> ; <i>Pichia kudriavzevii</i>	Haploid	Het	2.40
<i>C. glabrata</i>		Haploid	NO	11.30
<i>C. kefyr</i>	<i>Kluyveromyces marxianus</i>	Haploid	Ho	0.50
<i>C. norvegensis</i>	<i>Pichia norvegensis</i>		Ho	0.10
<i>C. inconspicua</i>	<i>Pichia cactophila</i>		ND	0.20
<i>C. lipolytica</i>	<i>Yarrowia lipolytica</i>	Haploid	Het	0.05

^aSpecies are listed in approximate order of phylogenetic relationship.^bHaploid indicates isolates can exist as stable haploids; diploids may also be formed.^cP, parasexual; NO, not observed; ND, not determined; Ho, homothallic; Het, heterothallic (data from Kurtzman et al. 2011).^dAverage incidence 1997–2007 (Pfaller et al. 2010b), except for *C. metapsilosis* and *C. orthopsilosis*.^eEstimated from Canton et al. 2011; *C. orthopsilosis* isolates are ~8% and *C. metapsilosis* isolates are 1% of isolates identified as *C. parapsilosis*.

The incidence also varies substantially with geographical location. *C. glabrata* is highest in Asia-Pacific and the European Union (EU), whereas the incidence of *C. tropicalis* infection in Africa and the Middle East is approaching three times that of the EU. *C. parapsilosis* is highest in North America and Latin America. The increase in *C. glabrata* in particular is associated with reduced susceptibility to fluconazole, the most commonly used azole drug (Pfaller and Diekema 2004; Klevay et al. 2008; Chapeland-Leclerc et al. 2010; Alexander et al. 2013).

Candida species have historically been associated with infection of older patients (>64 yr), particularly for *C. glabrata* (Diekema et al. 2002). In contrast, the number of infections caused by *C. parapsilosis* tends to be higher in infants of <1 yr (Diekema et al. 2002). Recent studies suggest that at least in the United States, the incidence of all *Candida* species among neonates is decreasing, which may be related to standardization of central line care (Fridkin et al. 2006; Chitnis et al. 2012; Cleveland et al. 2012).

CLASSIFICATION OF *Candida* SPECIES: THE CTG CLADE AND BEYOND

One of the difficulties in characterizing *Candida* species is that they do not share a single evolutionary origin. The term “*Candida*” was assigned to imperfect fungi (no clearly defined sexual cycle). Many *Candida* species belong to the CTG (or CUG) clade, in which the CTG codon codes for serine, rather than leucine (Table 1) (Santos et al. 1993). The CTG clade includes many of the most important pathogens (*C. albicans*, *C. tropicalis*, and *C. parapsilosis*) as well as rarer causes of disease (*Candida dubliniensis*, *Candida guilliermondii*, and *Candida lusitaniae*) (Fitzpatrick et al. 2006, 2010; Maguire et al. 2013). Some of the species are always, or mostly, diploid (Table 1).

Many of the diploid asexual *Candida* species undergo a parasexual cycle, mating between diploid cells of opposite mating type, followed by loss of chromosomes and reversion to diploid status (reviewed in Sherwood and Bennett 2009; Butler 2010; Heitman 2010). The parasex-

ual cycle has been characterized in *C. albicans* (Bennett and Johnson 2003; Forche et al. 2008) and *C. tropicalis* (Porman et al. 2011), although not in *C. parapsilosis* (Sai et al. 2011). Recently, it has been shown that *C. albicans* cells can form stable haploids, which undergo mating and autodiploidization (Hickman et al. 2013). A full sexual cycle has been described for many of the pathogens with haploid genomes (e.g., *C. lusitaniae* [Reedy et al. 2009] and *C. guilliermondii* [Wickerham and Burton 1954]) and some of the other related rare pathogens or non-pathogens (e.g., *D. hansenii* [van der Walt et al. 1977]).

The gradual discovery of hidden sexual or parasexual cycles in human fungal pathogens led to the hypothesis that limiting sexual reproduction may be important for proliferation in certain niches, particularly during infection of the host (Nielsen and Heitman 2007; Heitman 2010). This is supported by observations that the parasexual cycle in *C. albicans* is induced during stress (Berman and Hadany 2012). The parasexual cycle results in a very high level of aneuploidy (Forche et al. 2008). Aneuploidy also frequently occurs during exposure to antifungal drugs and is likely to be an important adaptive response (Perepnikhatka et al. 1999; Selmecki et al. 2009, 2010; Huang et al. 2011; Hill et al. 2013).

The substitution of serine for leucine at CTG codons is not complete; in *C. albicans* and some other *Candida* species, it is estimated that 97% of CTG codons are translated as serine and 3% as leucine (Suzuki et al. 1997). *C. albicans* has a very high tolerance for misincorporation of leucine at CTG codons, which is induced by stress (Gomes et al. 2007). Misincorporation may affect the function of key signaling molecules involved in pathogenesis (Rocha et al. 2011). Misincorporation also dramatically changes the fungal cell wall, masking β -glucan, and thus interfering with host recognition (Miranda et al. 2013). Altering the genetic code may also reduce the capacity for acquisition of genes by horizontal gene transfer (HGT) (Silva et al. 2007; Fitzpatrick et al. 2008).

Two species that are major causes of infection lie outside the CTG clade: *C. glabrata* and

C. krusei (Fig. 1; Table 1). *C. glabrata* is much more closely related to *Saccharomyces cerevisiae* than to *C. albicans* (Fitzpatrick et al. 2006), and it lies within a group of species that have undergone whole-genome duplication (WGD) (Byrne and Wolfe 2007) (Fig. 1). The *C. glabrata* genome contains all the genes required for mating and meiosis (Wong et al. 2003), and mating-type switching has been observed (Brockert et al. 2003; Butler et al. 2004; Edsikes and Wickner 2013). However, a sexual cycle has not yet been described. Recently, two pathogenic species that are closely related to *C. glabrata* have been identified, *Candida bracarensis* and *Candida nivariensis* (Alcoba-Florez et al. 2005; Correia et al. 2006), but these are rarely isolated (Fig. 1) (Lockhart et al. 2009).

C. krusei is less well studied than the other *Candida* species, particularly in relation to virulence. The teleomorph (sexually competent) form of *C. krusei* is known as *Issatchenkia orientalis* (Kurtzman et al. 2011) or *Pichia kudriavzevii*. Most research concentrates on its fermentation ability and potential as a producer of bioethanol (Dandi et al. 2013). The genome sequence was recently reported (Chan et al. 2012). The carriage of *C. krusei* in healthy individuals is usually very low, except in some populations such as Wayampi Amerindians, where it appears to originate from food or the environment (Angebault et al. 2013). The incidence of *C. krusei* in infection is also low, yet the organism is of considerable concern because of its relative resistance to azoles and other antifungal drugs (Drago et al. 2004; Munoz et al. 2005).

Other non-CTG clade *Candida* species that are minor causes of infection include *Candida kefyr* (*Kluyveromyces marxianus*) and two closely related species, *Candida norvegensis* (*Pichia norvegensis*) and *Candida inconspicua* (*Pichia cactophila*) (Pfaller et al. 2010b). *C. kefyr* is related to *Kluyveromyces lactis* and to the *Saccharomyces* group (Lane et al. 2011), and *C. norvegensis* and *C. inconspicua* also belong to a clade within the Saccharomycetales (Diezmann et al. 2004). *Candida lipolytica* (better known as *Yarrowia lipolytica*), a very rare cause of infection (~0.1% of *Candida* infections [Pfaller et al.

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Figure 1. Relationships of the *C. glabrata* species group. The phylogenetic tree is taken from Gabaldón et al. (2013) and was derived from a concatenated alignment of 603 one-to-one orthologs. Genomes sequenced by Gabaldón et al. (2013) are bold. Pathogenic species are shown in red and are indicated with an asterisk. CTG, CTG clade; WGD, whole-genome duplication.

2010b]), is distantly related to both the CTG and *Saccharomyces* clades (Fig. 1) (Fitzpatrick et al. 2006). The remaining non-CTG clade species (e.g., *Candida pelliculosa*/*Pichia anomala*) are even rarer (Pfaller et al. 2010b).

LESSONS FROM THE GENOMES

C. albicans

C. albicans is by far the best-studied species in the CTG clade. Virulence is associated with the transition from yeast growth to filamentous forms such as hyphae and pseudohyphae (reviewed in Liu 2001; Jacobsen et al. 2012) and

also with a phenotypic switch from “white” to “opaque” cells (reviewed in Morschhauser 2010; Huang 2012). Although there is some debate about the relative roles of hyphae and yeast cells in pathogenesis, hyphae are believed to be important because they can invade and damage both epithelial and endothelial cells and because they are required for escape from macrophages following phagocytosis (Thompson et al. 2011; Jacobsen et al. 2012). In addition, a large-scale screen confirmed that many genes required for virulence have no apparent role in morphogenesis and showed that others that are required for morphogenesis have no effect on virulence (Noble et al. 2010).

The switch from round white cells to elongated opaque cells (and vice versa) is strongly correlated with mating (Bennett and Johnson 2005; Lohse and Johnson 2009). Cells that are homozygous at the mating locus switch to the opaque form at a much higher rate than heterozygous cells, and opaque cells are competent for mating. The switching process is highly regulated (Huang et al. 2006; Srikantha et al. 2006; Zordan et al. 2006, 2007; Tuch et al. 2010; Hernday et al. 2013). White and opaque cells have different filamentation programs (Si et al. 2013). White cells are more virulent in systemic infection, whereas opaque cells adhere better to skin (Kvaal et al. 1997, 1999). Opaque cells may be better at evading the host immune response (Geiger et al. 2004; Sasse et al. 2013). The demonstration that strains that are heterozygous at the mating locus can also undergo the white–opaque transition in certain environmental conditions suggests that the switch may be important for virulence of many clinical isolates (Xie et al. 2013).

The genome sequence of *C. albicans* was first reported in 2004 (Jones et al. 2004) and further curated in 2005 (Braun et al. 2005). Assembly of the diploid genome was partially addressed in 2007 (van het Hoog et al. 2007), and a “phased” diploid genome was reported in 2013 (Muzzey et al. 2013). *C. albicans* SC5314 plus eight related strains, which were known to be homozygous for one chromosome each, were sequenced using high-coverage next-generation sequencing. This enabled unambiguous determination of the phasing of single-nucleotide polymorphisms (SNPs) in the parent strain. The analyses supported previous observations from SNP/CGH arrays that loss of heterozygosity (LOH) events are common in *C. albicans* (Abbey et al. 2011). Indeed, LOH is induced by stress such as exposure to antifungal drugs or growth in a mammalian host (Forche et al. 2009, 2011). However, some chromosomes or chromosomal regions are never observed to become homozygous, probably because they contain lethal alleles (Hickman et al. 2013).

Allele-specific gene expression was detected even in *C. albicans* grown in rich media (Muzzey et al. 2013). Almost 200 genes have premature

termination codons in one allele, and in the majority, expression is biased toward the intact allele. Muzzey et al. (2013) found that indels are enriched in regulatory (promoter) regions, although there was no obvious correlation with allele-specific gene expression. Interestingly, the net effect of indels is to increase repeat length over evolutionary time, which may result from selective forces on nucleosome positioning.

Early comparisons of the *C. albicans* genome with that of the nonpathogenic model yeast *S. cerevisiae* led to the identification of several gene families that are expanded in the pathogen and are associated with virulence (Calderone and Fonzi 2001; Jones et al. 2004; Braun et al. 2005). These include the ALS (agglutinin-like sequence) adhesins, secreted aspartyl proteases and lipases, and proteins involved in oligopeptide and iron transfer. Subsequent analysis showed that many gene families are expanded in other species in the CTG clade (Butler et al. 2009). Twenty-one gene families are enriched in the pathogens.

The ALS family of adhesins is expanded in all the CTG pathogens, and its members have been particularly associated with virulence in *C. albicans* (Hoyer 2001; Hoyer et al. 2008). ALS genes encode GPI-anchored proteins located at the cell wall and are required for adhesion. *ALS3* in particular has multiple roles. It is required for adherence to plastic and for subsequent biofilm development (Nobile and Mitchell 2005; Nobile et al. 2006). Als3 binds to N-cadherin and E-cadherin on host endothelial and epithelial cells and, together with the invasion Ssa1, is required for endocytosis of *C. albicans* (Phan et al. 2007; Moreno-Ruiz et al. 2009; Wachtler et al. 2012). Als3 and Ssa1 also bind to the EGF (epidermal growth factor) receptor and to HER2 in epithelial cells, inducing autophosphorylation of the receptors and endocytosis of the fungus (Zhu et al. 2012). Finally, Als3 is required for acquisition of iron from ferritin in the host (Almeida et al. 2008).

Somewhat surprisingly, Als3 appears to be restricted to *C. albicans* (Jackson et al. 2009), which may partially explain the dominance of *C. albicans* as an infectious organism. Recom-

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binant vaccines directed against *C. albicans* have mostly been generated using the amino terminus of Als3 (Spellberg et al. 2006; Ibrahim et al. 2013). However, the vaccine is also protective against infection with *Staphylococcus aureus*, suggesting that it has a broad range (Spellberg et al. 2008).

Many of the gene families that are expanded in pathogenic species encode components of the cell wall, which may influence interaction with the host (Butler et al. 2009). Some have been experimentally associated with pathogenesis such as the Hyr/IFF family (Bates et al. 2007; Kempf et al. 2009). However, other families, such as the leucine-rich IFA family of putative transmembrane proteins, remain understudied.

To date, most characterizations of *C. albicans* isolates have been carried out using molecular fingerprinting methods, such as the Ca3 fingerprinting probe, multilocus sequence typing (MLST), multilocus microsatellite typing (MLMT), and SNP array analysis (Soll 2000; Bougnoux et al. 2002; Odds 2010; L'Ollivier et al. 2012). MLST is probably the most widely applied and has been used to type >2000 *C. albicans* isolates (Bougnoux et al. 2002, 2008; Odds et al. 2007; Odds 2010; Butler et al. 2012). The population structure is mostly clonal, with the majority of isolates falling into five major clades and more than 10 minor clades (Odds et al. 2007; Odds 2010). A small number of "atypical" isolates, mostly isolated from the genitals of Africans and Europeans, fall into MLST clade 13, which is the most different from the other clades (Odds 2010; Butler et al. 2012). There is evidence that there is a low level of recombination within and between the clades (Bougnoux et al. 2008).

The majority of isolates associated with superficial infection and commensal carriage fall into Clade 1 and have a truly global distribution, suggesting that they may be better adapted for colonization (Schmid et al. 1999; Odds et al. 2007; Odds 2010). However, isolates from the different clades do not differ in virulence in animal models (MacCallum et al. 2009). Clade 1 isolates are generally resistant to the antifungal drug flucytosine (a fluorinated

analog of cytosine), because of a mutation in the *FUR1* gene (uridine phosphoribosyl transferase) (Dodgson et al. 2004). Clade 1 isolates are also resistant to terbinafine (Odds 2009). Few other traits are clade specific, and there is a wide variation in the phenotypes of the individual isolates (MacCallum et al. 2009).

Molecular typing methods have been used to type microevolution events during infection, to follow the transition from commensal to infectious organism, and to look for evidence of nosocomial transmission (Odds 2010). However, it is not possible to distinguish between closely related isolates, nor to follow small changes that occur during infection. In the near future, we expect to see whole-genome sequencing replacing MLST analysis, both for population studies and for following the course of infection.

C. albicans and *C. dubliniensis*

C. dubliniensis is the closest relative of *C. albicans* with a fully sequenced genome, and until the mid-1990s, it was not recognized as a distinct species (Sullivan et al. 1995). However, *C. dubliniensis* is a rare cause of disease in man and is also less virulent in animal models (Gillfillan et al. 1998; Stokes et al. 2007; Pfaller et al. 2010b). Comparison of the genomes of the two species revealed that there has been widespread gene loss in *C. dubliniensis*. Some genes have been deleted, such as members of the serine protease SAP family and *HYR1* (one of the IFF gene family). Others have undergone pseudogenization, including many of the filamentous gene regulator (FGR) family. In contrast, some genes have been specifically amplified in *C. albicans*, such as the *TLO* family, which encode components of the mediator complex (Zhang et al. 2012a).

Several of the genomic differences between *C. albicans* and *C. dubliniensis* are related to the ability to switch to hyphal growth. Within the CTG clade, only *C. albicans* and *C. dubliniensis* form true hyphae. However, the conditions that induce hyphal growth are significantly different, and *C. dubliniensis* makes much fewer hyphae. It is very likely that this is caused by underlying

differences in transcriptional networks as well as in genome content. This question was thoroughly addressed by Grumaz et al (2013), who characterized the transcriptional profile of both species during the yeast to hyphal transition. They found that there is a shared core hyphal response, which includes increased expression of cell wall genes and of genes associated with iron metabolism. Expression of the transcription factors *FCR1*, *NRG1*, and *RME1* is reduced in both species. However, under some conditions, such as following phagocytosis by macrophages, *NRG1* is down-regulated in *C. albicans* and not in *C. dubliniensis*, at least partly explaining inefficient hyphal production by the latter (Moran et al. 2007).

Grumaz et al. (2013) found that expression of the regulators *UME6*, *SFL2*, *SET3*, and *ZCF39* is induced during hyphal growth of *C. albicans* only. However, other studies showed that *UME6* is also induced in hyphal growth of *C. dubliniensis* Wu284 (O'Connor et al. 2010). Specific repression of *SFL2* in *C. albicans* was identified by Spiering et al. (2010). *SFL2* is a major regulator of morphogenesis in *C. albicans* and acts together with a homolog *SFL1* to regulate expression of hyphal- and yeast-specific genes (Znaidi et al. 2013).

Further comparative transcriptional profiling of *C. albicans* and *C. dubliniensis* is likely to yield further insights into the evolution of virulence and other characteristics. For example, these are the only CTG clade species known to form chlamydospores (large, thick-walled spherical cells, usually found at the end of pseudohyphae) under certain growth conditions. The biological function of chlamydospores is not known, but production is induced in nutrient-poor media and in *nrg1* deletion strains in *C. albicans*, and during growth of *C. dubliniensis* on Staib media (reviewed in Staib and Morschhauser 2007). Comparing the transcriptional response of the two species revealed that at least two cell wall proteins (*CSP1* and *CSP2*) are specifically expressed and localized in chlamydospores in both (Palige et al. 2013). Future research is needed to elucidate the biological role of this unusual morphogenic pathway.

C. tropicalis and *C. parapsilosis*

C. tropicalis is a common cause of infection in intensive care units and is a particular problem in neutropenic patients (Negri et al. 2012; Silva et al. 2012). The organism has a diploid genome and, like *C. albicans*, has a parasexual cycle (Porman et al. 2011; Seervai et al. 2013). In addition, *C. tropicalis* switches from white to opaque cells (Porman et al. 2013; Xie et al. 2013). However, there are also significant differences between the species. White–opaque switching in *C. tropicalis* is independent of mating type, whereas in *C. albicans*, isolates that are heterozygous at the mating locus only switch in very defined conditions (Xie et al. 2012; Porman et al. 2013). The *Wor1* transcription factor regulates the white–opaque switch in both species, but other transcription factors appear to be specific to *C. albicans* (Porman et al. 2011, 2013). The role of the white–opaque switch in determining virulence of *C. tropicalis* is not yet known.

C. parapsilosis is particularly associated with infection of neonates (Chow et al. 2012; Pammi et al. 2013). Drug resistance is a problem; isolates are inherently less susceptible to echinocandins because of amino acid substitutions in the β -(1,3)-D-glucan synthase *FKS* gene (Garcia-Effron et al. 2008). The species is more distantly related to *C. albicans* than is either *C. dubliniensis* or *C. tropicalis* (Fitzpatrick et al. 2006). Close relatives include *C. orthopsilosis* and *C. metapsilosis*, once characterized as belonging to the same species (Tavanti et al. 2005). *C. orthopsilosis* and *C. metapsilosis* are much less frequent causes of infection than *C. parapsilosis* (Table 1) and are less virulent in animal models (Nemeth et al. 2013). Comparing the genomes of *C. parapsilosis* and *C. orthopsilosis* suggests that amplification of gene families, in particular of cell wall genes, is associated with increased virulence of *C. parapsilosis* (Riccombeni et al. 2012).

C. parapsilosis has a diploid genome, but the level of heterozygosity is much lower than the other diploid CTG species (Butler et al. 2009). All isolates characterized to date have *MTLa* idiomorphs at the mating-type locus, and mat-

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ing has not been observed in either *C. parapsilosis* or *C. orthopsilosis* (Sai et al. 2011). Some characteristics, such as secretion of lipases, are important for virulence in both *C. albicans* and *C. parapsilosis* (Trofa et al. 2011). There are, however, other species-specific traits. Biofilm formation is an important for virulence in both, and the Bcr1 transcription factor is a major regulator (Nobile et al. 2006; Ding and Butler 2007). However, the functions and/or targets may be different; whereas Bcr1 regulates expression of the CFEM cell wall family in both species, the family is required for biofilm development only in *C. albicans* (Ding et al. 2011).

White–opaque switching has not been observed in *C. parapsilosis* isolates. However, colonies do undergo several types of morphological switching (Lott et al. 1993; Laffey and Butler 2005; Kim et al. 2006). The transcription factor Efg1 is a major regulator of switching from concentric to smooth colonies, and the switching rate is dramatically increased when *EFG1* is deleted (Connolly et al. 2013). Efg1 regulates filamentation, white–opaque switching, and many other phenotypes in *C. albicans* (reviewed in Liu 2002). Many of the targets are shared in *C. parapsilosis*, suggesting that Efg1 is an ancient regulator of morphology (Connolly et al. 2013). Notably, however, *EFG1* is missing from *C. tropicalis* (Fig. 2) (Porman et al. 2011). A second transcription factor, *UME6*, is required for filamentation (pseudohyphal growth) in *C. parapsilosis*, *C. tropicalis*, and *C. guilliermondii*, indicating that it is also a core regulator of morphology in the CTG clade (Lackey et al. 2013).

OTHER CTG CLADE SPECIES

C. guilliermondii and *C. lusitaniae* are relatively rare causes of human infection. *C. guilliermondii* is of general interest to the biotechnology sector, as a producer both of riboflavin and of xylitol (Papon et al. 2013b), and several molecular tools have been developed (Papon et al. 2012). The species is haploid and fully sexual, which may facilitate genetic analysis. Resistance to antifungal drugs is a growing problem (Savini et al. 2011).

C. lusitaniae has historically been associated with reduced susceptibility to amphotericin B, which may be related to altered expression of ergosterol synthesis genes (Merz 1984; Hadfield et al. 1987; Young et al. 2003). However, azole therapies are effective (Hawkins and Baddour 2003). *C. lusitaniae* isolates are haploid and heterothallic; the mating pathway has been characterized (Reedy et al. 2009), and gene disruption tools have been developed (El-Kirat-Chatel et al. 2011; Zhang et al. 2012b). Molecular characterization is therefore likely to increase in the near future.

The *C. glabrata* Species Group

C. glabrata is one of only two of the major *Candida* pathogens that falls outside of the CTG clade. The species is a common cause of candidiasis in immunosuppressed patients including those suffering from HIV/AIDS, diabetes, cancer patients undergoing chemotherapy, and the elderly (Fidel et al. 1999). *C. glabrata*–associated candidiasis largely occurs in the oral cavity, and its incidence in older members of the population has been linked to its ability to attach to the acrylic surface of dentures as well as increased suppression of the immune response (Lockhart et al. 1999; Bagg et al. 2003; Li et al. 2007).

Increasing incidence of *C. glabrata* infection also results from the increased use of prophylactic antifungal treatment in immunosuppressed patients (Chakrabarti et al. 2009; Lee et al. 2009). *C. glabrata* exhibits low-level resistance to the antifungal agent fluconazole; prophylactic exposure to fluconazole can induce resistance, as well as lead to cross-resistance to other related azoles (Panackal et al. 2006). Most resistant isolates have gain-of-function mutations in the *PDR1* transcription factor, which regulates expression of the multidrug transporters' *CDR* genes (Vermitsky and Edlind 2004; Tsai et al. 2006; Vermitsky et al. 2006). *PDR1* is also required for adherence and for virulence (Ferrari et al. 2011; Vale-Silva et al. 2013). Resistance to echinocandins is associated with mutations in the *FKS1* and *FKS2* genes (Garcia-Effron et al. 2009; Alexander et al. 2013).

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Figure 2. Visualization of *EFG1* orthologs in the *Candida* Gene Order Browser. The diagram shows a screenshot from CGOB (cgob.ucd.ie; Fitzpatrick et al. 2010; Maguire et al. 2013) around the *EFG1* gene in CTG clade species. Each horizontal line shows a chromosomal region, and each pillar indicates orthologs. All genes are shown at the same size. Breaks in synteny are indicated by changes in color. *EFG1* lies between a tRNA gene (white) and orthologs of orf19.607 in most species (*C. albicans* isolates have an additional gene). In *C. tropicalis*, there has been an inversion adjacent to the tRNA relative to *C. albicans* (indicated by gray lines with orange tips), and *EFG1* has been lost.

Sequencing the *C. glabrata* genome in 2004 revealed that there was widespread gene loss relative to *S. cerevisiae*, including the galactose, phosphate, and nicotinic acid metabolism (BNA) pathways (Dujon et al. 2004). There was also a significant expansion of the EPA family of glycolipid proteins and of the YPS family of GPI-linked aspartyl proteases, which are required for virulence (De Las Penas et al. 2003; Kaur et al. 2007). Expression of the subtelomeric EPA adhesins is usually silenced, except during infection of the urinary tract (Domergue et al. 2005). Limitation of nicotinic acid in urine (and lack of the BNA pathway) leads to a reduction in NAD⁺, required for activity of the histone deacetylase Sir2. The resulting change in chromatin structure induces expression of the EPA genes, leading to increased adherence.

The evolution of pathogenicity in *C. glabrata* is of particular interest because, until recently, it was believed to be the only pathogenic

yeast species belonging to the WGD group of the Saccharomycetaceae (Fig. 1). It has now, however, been joined by *C. bracarensis* and *C. nivariensis* (Alcoba-Florez et al. 2005; Correia et al. 2006). Gabaldón et al. (2013) recently sequenced the genomes of *C. bracarensis* and *C. nivariensis* and of three related but nonpathogenic species, *Nakaseomyces bacillisporus*, *Candida castellii*, and *Nakaseomyces delphensis* (Fig. 1). Interestingly, *C. bracarensis* and *C. nivariensis* are more closely related to the nonpathogenic *N. delphensis* than they are to *C. glabrata*. *N. bacillisporus* and *C. castellii* form a separate and more distantly related group (Fig. 1).

One of the first observations was that loss of the nicotinic acid pathway is common to all of the sequenced genomes and is not unique to *C. glabrata*, as previously assumed (Domergue et al. 2005). This is also true for the galactose, phosphate, and other gene clusters. In addition, there is evidence for accelerated evolution in

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the lineage leading to the *glabrata* group (the three pathogens plus *N. delphensis*). Gabaldón et al. (2013) suggested that some of these changes may be “preadaptations” that enabled pathogenicity, rather than direct adaptations to the human host. These findings highlight the importance of sequencing the genomes of multiple species to avoid erroneous conclusions from, for example, simply comparing *C. glabrata* to *S. cerevisiae*.

Expansion of the *EPA* genes is mostly restricted to the pathogens and appears to have occurred in a lineage-specific manner. *C. bracarensis* and *C. nivariensis* share many *EPA* duplications, suggesting they may have occurred in the common ancestor and were subsequently lost (or possibly pseudogenized) in the non-pathogen *N. delphensis*. Amplification in *C. glabrata* occurred independently. Correlation of *EPA* expansion with pathogenesis and the observation that they are required for adherence in *C. glabrata* suggest that this family is important for virulence. The *C. glabrata* genome also has expanded *YPS* and *MNT3* arrays, predicted to be involved in carbohydrate metabolism. It is therefore likely that *C. glabrata* has undergone species-specific gene amplification, which may explain why it is significantly more virulent than the other pathogenic species within the *Nakaseomyces* group.

One difficulty with this analysis is the definition of pathogenesis: *C. bracarensis* and *C. nivariensis* are rare, but their emergence is likely a result of improved detection methods due to sequence analysis. Another important factor is opportunity. Species defined as nonpathogenic, because they are not isolated from clinical settings, may cause infection if they came into contact with a human host. Interpretations may also change as additional genomes are sequenced. Gabaldón et al. (2013) postulated that the *Nakaseomyces* group evolved from an ancestral environmental yeast; gene loss and amplifications enabled growth as commensals in humans, and some species independently evolved into opportunistic pathogens. Similar to yeasts of the CTG clade, the evolution of pathogenicity is associated with changes in genes involved in cell adhesion, carbohydrate metabolism, the

hypoxic response, and phosphate starvation, enhancing the ability of the yeasts to survive in the host environment.

CONCLUDING REMARKS: THE FUTURE OF GENOMICS IN *Candida*

Improvements in genome sequencing have been paralleled by improvements in genome annotation, particularly for *C. albicans* and other species in the CTG clade. Use of RNA-seq and high-resolution tiling arrays has led to the correction of many open reading frames (ORFs) and the identification of hundreds of novel transcriptionally active regions that may represent structural or regulatory RNAs (Bruno et al. 2010; Sellam et al. 2010; Tuch et al. 2010). Strand-specific RNA sequencing has revealed that the 5' end of transcripts that are differentially expressed between white and opaque cells are particularly long (Tuch et al. 2010). RNA-seq data has provided experimental evidence for the presence of introns and identified several that had not been predicted computationally (Mitrovich et al. 2007).

RNA-seq analysis has also been important for annotation of other genomes, such as *C. parapsilosis* (Guida et al. 2011) and *C. dubliniensis* (Grumaz et al. 2013). In *C. parapsilosis*, several hundred new genes were identified, and approximately 900 gene models were corrected (Guida et al. 2011). It is becoming increasingly clear that the high level of unknown transcripts, or even antisense transcripts, in *Candida* species is indicative of a layer of regulation that is at present almost completely unexplored and is likely to be an important focus in the future. Even in the absence of transcriptional data, however, comparative genomics applications are very useful for identifying protein-coding regions. For example, comparing the genomes of six species in the CTG clade led to the identification of 91 novel ORFs in *C. albicans* (Butler et al. 2009). A more detailed analysis uncovered more than 1500 previously unannotated ORFs in 13 genomes (Maguire et al. 2013) (Fig. 2).

Tools pioneered in *S. cerevisiae* are now being applied to *C. albicans* and hopefully to other *Candida* species also. Several collections of gene

disruptions and gene knockouts have been generated in *C. albicans* and, together with gene expression profiling and chromatin immunoprecipitation, have been applied to identifying networks involved in adhesion, biofilm formation, virulence, and more (Chen et al. 2011; Finkel et al. 2012; Nobile et al. 2012; Pande et al. 2013; Perez et al. 2013). The developments of an overexpression library and constitutively activated transcription factors are also exciting (Chauvel et al. 2012; Schillig and Morschhauser 2013). Characterization of stable haploids of *C. albicans* will open up huge new areas of research and may allow the application of methods such as synthetic genetic arrays, although a meiotic cycle is required to fully exploit these approaches (Baryshnikova et al. 2010). We will no doubt see a major increase in sequencing individual isolates from a single species, which will facilitate analysis of clade-specific traits (Engel and Cherry 2013). The future will bring an explosion in data availability, and the challenges that come with dealing with it.

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