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# For the "Genomes and Evolution" Special Issue of *Current Opinion in Genetics and Development*

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## Abstract

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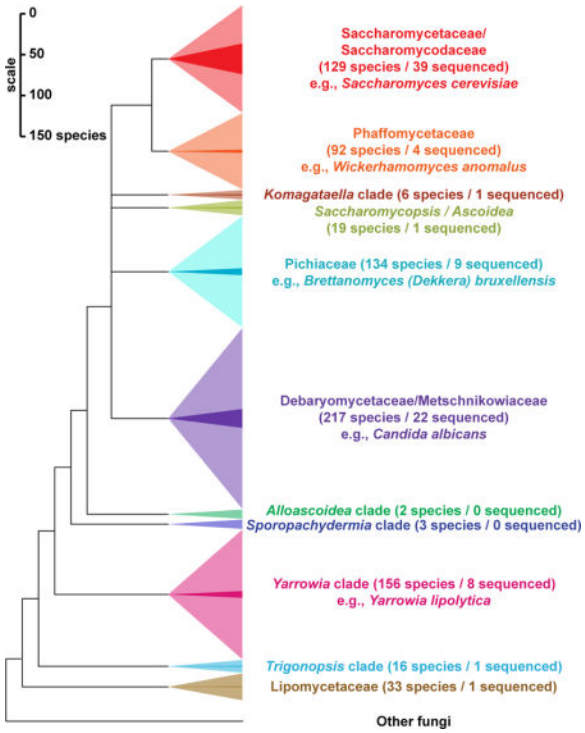
Yeasts are unicellular fungi that do not form fruiting bodies. Although the yeast lifestyle has evolved multiple times, most known species belong to the subphylum Saccharomycotina (syn. Hemiascomycota, hereafter yeasts). This diverse group includes the premier eukaryotic model system, *Saccharomyces cerevisiae*; the common human commensal and opportunistic pathogen, *Candida albicans*; and over 1,000 other known species (with more continuing to be discovered). Yeasts are found in every biome and continent and are more genetically diverse than angiosperms or chordates. Ease of culture, simple life cycles, and small genomes (~10–20 Mbp) have made yeasts exceptional models for molecular genetics, biotechnology, and evolutionary genomics. Here we discuss recent developments in understanding the genomic underpinnings of the making of yeast biodiversity, comparing and contrasting natural and human-associated evolutionary processes. Only a tiny fraction of yeast biodiversity and metabolic capabilities has been tapped by industry and science. Expanding the taxonomic breadth of deep genomic investigations will further illuminate how genome function evolves to encode their diverse metabolisms and ecologies.

## Graphical abstract




## A brief history of yeast evolutionary genomics

The *Saccharomyces cerevisiae* genome was the first eukaryotic genome sequenced [1], a collaborative feat that enabled two decades of innovation and discovery. *C. albicans* soon followed [2], as well as a handful of relatives in both clades and a smattering of taxonomically diverse species [3–8]. *S. cerevisiae* became a proving ground for new genomic technologies, such as deleting and barcoding genes for functional profiling [9]. Early comparative studies pioneered the now commonplace use of genome sequencing to

address specific functional and evolutionary hypotheses, such as using conserved genomic regions to identify functional DNA sequence elements [3,4]. These genomes began to catalyze research in many other fields, resulting in important advances to our understanding of the evolution of genome content and organismal traits [10,11], phylogenetics [12], and cis-regulatory element prediction [13]. By the last comprehensive review of yeast evolutionary genomics in 2010 [14], the genomes of 26 yeast species had been sequenced, still mostly in the two clades containing *S. cerevisiae* and *C. albicans*. With the popularization of next-generation sequencing, the genomes of 40 additional species have been published in the last five years, while 20 more are publicly available but await formal publications (Figure 1). Nonetheless, most yeast biodiversity remains unexplored at the genomic level (Figure 2).

## Yeast mating systems

Most yeasts have true sexual cycles, but some manifest complex parasexual cycles (non-meiotic processes involving mitotic recombination and chromosome loss), whereas others are thought to be asexual. This multiplicity of forms and sexual cycles led to a byzantine nomenclature system that is undergoing a radical simplification, which will ultimately result in a taxonomy based on phylogeny (Box 1). Although asexual strains achieve higher laboratory fitness [15], they seem not to persist or undergo frequent cladogenesis. Sex may increase the rate of adaptation to novel environments and help purge deleterious alleles [16,17]. Thus, most yeast clades harbor at least some sexual taxa, which likely reflect their ancestral states. Sexual cycles exist in both obligately outcrossing (heterothallic) species, where mating types reside in different individuals, as well as in species that can self-fertilize (homothallic).

Self-fertilization in *S. cerevisiae* and relatives is achieved through the tight regulation of the *HO* gene, which encodes a homing endonuclease co-opted from an intein selfish element [18]. The Ho protein cuts the active mating cassette, allowing for homology repair by one of two silent mating cassettes, thereby switching the mating type and enabling clonal mother-daughter mating. Interestingly, *Kluyveromyces lactis HO* has been replaced by *MATα3*, another selfish element co-opted from a DNA transposon [19,20]. A simpler two-locus system that switches mating types by inversion has evolved in the clade containing *Ogataea (Hansenula) polymorpha* and *Komagataella (Pichia) pastoris* [21]. Here inversion simply switches which of the two mating loci is present in active chromatin, and thus determines which is expressed. These genetic systems have profound effects on maintaining local genetic variation [22] and generating genome instability [23] at the mating-type locus.

The genetic regulatory networks that control the batteries of genes necessary for each mating type have been investigated extensively in several species, establishing a paradigm for both the logic and molecular mechanisms by which such networks evolve. Several genetic changes can facilitate the evolutionary rewiring of regulatory networks, including the duplication of regulators and partitioning of target genes [24], intercalation of new regulators [25], and alteration of binding site specificity [26]. Most such changes are thought to occur through selectively neutral mechanisms, often resulting in the same network output. These studies have established rewiring as a common feature in regulatory network

evolution and have shown how neutral changes can profoundly shape evolutionary outcomes.

## Metabolic diversity, ecology, and biotechnology

Thanks to their diverse metabolisms, yeasts exhibit a remarkable range of ecologies, including methanol consumption in *O. polymorpha* and *K. pastoris*; xylose fermentation in *Scheffersomyces (P.) stipitis* and *Spathaspora passalidarum*; lipid production in *Yarrowia lipolytica* and *Lipomyces starkeyi*; human pathogenesis in *C. albicans* and *C. (Nakaseomyces) glabrata*; and cotton pathogenesis in *Eremothecium (Ashbya) gossypii* [27] (Figure 1). Many of these metabolic capabilities are exploited in various biotechnological, food, and beverage industries. For example, *S. cerevisiae* is the workhorse of the multibillion-dollar brewing, wine-making, baking, and biofuel industries, but other commonly used species include *Kazachstania exigua* (sourdough), *Cyberlindnera jadinii* (syn. *C. utilis*, food additives), *K. pastoris* (heterologous protein production), and *E. gossypii* (riboflavin). Nonetheless, these well-known yeasts represent a scant slice of yeast metabolisms and ecologies, and most species remain unharnessed by industry and only modestly explored by science.

Yeast ecological niches require more study, especially in natural settings, but what limited information exists suggests that yeast niches are partitioned by many parameters, including temperature, pH, radiation, insect and plant hosts, and metabolism [27–29]. For example, *Saccharomyces* and relatives have evolved an extreme preference for fermenting glucose into ethanol, even in the presence of oxygen, a process known as Crabtree-Warburg Effect or aerobic fermentation. This “make-accumulate-consume” strategy provides a powerful ecological advantage by exploiting the rich reserves of simple sugars in sap, fruit, and other sources [30–33]. Other genera, such as *Scheffersomyces* and *Spathaspora*, have adapted to living in the guts of wood-consuming beetles and are capable of fermenting xylose, the second most abundant monosaccharide in woody plant material, which is of critical importance to the lignocellulosic biofuel industry [11,34,35]. Some traits are unique, such as a requirement for carbon dioxide in *Cyniclomyces* [36], while others, such as temperature preferences, evolve quickly [27–29]. A handful of lineages have evolved into commensals and/or pathogens of mammals and birds, exhibiting increased thermophily, the loss of key metabolic functions, increased biofilm-forming ability, and the acquisition of new traits to evade the host immune system [2,7,8,37].

The genetic outlines underlying some of these remarkable innovations are beginning to be understood. Some differences evolve rapidly and can be explained by one or two genes. For example, there is widespread variation in the catabolism of disaccharides, perhaps because extracellular cleavage often sets up a “prisoner’s dilemma” where competitors can consume the monosaccharide intermediates [29]. Other traits, such as galactose catabolism, seem to be lost frequently [10,38] (and potentially regained [39]), correlating with the loss of several genes. Aerobic fermentation is thought to involve many genetic changes in glycolytic and mitochondrial pathways and has evolved only a handful of times [30–33]. Strikingly, many of these pathways underwent parallel evolutionary changes during the acquisition of aerobic

fermentation by the lineage leading to *S. cerevisiae* and the highly divergent lineage leading to *Brettanomyces (Dekkera) bruxellensis* [30,32].

Much remains to be understood about the forces driving most yeast radiations (Figure 2). For example, dozens of species evolved from clades associated with fruit-rot and tree-flux habitats to exploit the diverse chemistries associated with different species of cacti, which, in turn, have been exploited by several different cactophilic *Drosophila* and sap beetle species that feed on these yeasts [27,28]. Most species of the *Starmerella* clade are associated with Hymenoptera species, while yeasts of the genus *Ogataea* frequently inhabit leaf litter where methanol consumption may be beneficial [21,27,40]. Little is known about the genetic underpinnings of these ecological innovations, except that they must rely, at least partly, on metabolism. Metabolic traits, which can be easily studied in the lab and whose genetic basis is often well understood from model organisms, are therefore uniquely suited to provide the thin end of a wedge to open an understanding of yeast diversification.

## Hybridization, introgression, and horizontal gene transfer

One of the most important paradigm shifts catalyzed by broader yeast genome sequencing is a realization of the prevalence of gene sharing through hybridization, introgression, and horizontal gene transfer (HGT), especially among domesticated strains. Perhaps the most iconic examples are the lager-brewing yeasts, which were recently shown to be allopolyploids of *S. cerevisiae* and the recently discovered species *S. eubayanus* [41,42]. Alloploids of *S. cerevisiae x S. kudriavzevii* are also used in brewing, wine fermentation, and cider fermentation [43]. Conversely, strains of *S. uvarum* used in cider and champagne fermentation have acquired genes from several *Saccharomyces* species, but most wild strains lack these introgressions [44].

Fewer alloploids are known outside of the genus *Saccharomyces*, and all are from industrial or clinical settings. In the genus *Zygosaccharomyces*, a miso production strain [45] and a sparkling wine contaminant [46] are allopolyploids. Echoing the recent status of *S. eubayanus*, genome sequencing showed *Millerozyma (P.) sorbitophila*, a sorbitol contaminant, to be an interspecies hybrid of *Millerozyma (P.) farinosa* and a yet-to-be-identified congeneric species [47]. Similarly, genome sequencing of a wine spoilage strain purported to be *B. bruxellensis* revealed it to be allotriploid [48]. Several clinical isolates from the *C. parapsilosis* species complex are also interspecies hybrids [49].

In addition to hybridization, many strains of *S. cerevisiae* used in industry have picked up genes through introgression from various *Saccharomyces* species [44,50,51], as well as from more distantly related yeasts through HGT [52–54]. HGT is not restricted to strains grown in artificial environments but also occurs at a low, but significant, rate across the yeast phylogeny, influencing the content of both the nuclear [55] and mitochondrial genomes [56]. For example, a recent examination of fungal metabolic pathways inferred that 1.8% of yeast metabolic genes have undergone HGT at some point in their history [57]. HGT has influenced individual genes, sometimes repeatedly [33,53,58]; entire metabolic pathways [59]; and larger genomic fragments [52], although the latter has only been observed in industrial strains [52,55]. Although it is thought that conjugation, transformation, and viral

transduction are involved in filamentous fungi [60], less is known about the mechanisms that facilitate yeast HGT. Interestingly, a recent study showed that experimental rates of bacteria-to-yeast HGT can be strongly influenced by gene presence/absence polymorphisms in non-essential yeast genes [61].

## Resequencing dynamic genomes

Yeast genomics has greatly enhanced our understanding of the evolutionary dynamics of natural populations, among domesticated strains, during infections, and during laboratory experiments. Aside from *S. cerevisiae* [51], population genomic studies have characterized the metabolic, genetic, and biogeographic diversity of *S. paradoxus* [62], *S. kudriavzevii* [38], and *S. uvarum* [44], making this genus one of the few where population genomic datasets exist for the majority of known species [63]. Large-scale population genomic studies in other yeasts remain rare, but a recent investigation of the stability of the unusual GC content of a chromosome-arm in *Lachancea kluyveri* is an undeniable harbinger of the future [64]. Remarkably, estimates of the frequency of outcrossing ($\sim 10^{-5}$) in *L. kluyveri* are similar to *Saccharomyces* [22], suggesting that key lifestyle parameters may be conserved across vast timespans, different ecologies, and different mating-type control systems.

Genome resequencing has allowed experimental evolution studies in *S. cerevisiae* to rapidly move from identifying specific adaptive mutations [15,65,66] to examining pools of variants undergoing clonal interference [67,68] to massively parallelized tracking of individually tagged lineages [69]. Although the most advanced genetic tricks are not available for other yeasts, some of these approaches have even been extended to study the evolution of clinical isolates of *C. albicans* during the course of infection [70,71]. Collectively, these studies paint the portrait of a dynamic genome that can be pushed easily toward evolving a variety of traits. Indeed, a provocative corollary is that the trillions of scattered cells belonging to each yeast species are being exposed to potentially quite different selective pressures, ultimately engendering different genomic outcomes that must be reconciled.

## Which microevolutionary processes explain macroevolutionary patterns?

Juxtaposing data from laboratory evolution and population genomic studies to the data from comparisons of distantly related genomes raises an interesting paradox: rapid, radical, and sometimes irreversible changes regularly occur across microevolutionary timescales, and yet, relative stability persists over macroevolutionary ones. Some common types of mutations, such as aneuploidy [66], are unlikely to be fixed in a species because these low frequency polymorphisms are easily reversed. Others, such as interspecies hybridization and the loss of mating pathways, can expose lineages to Muller's Ratchet and eventual extinction. Many of the most readily acquired mutations are further predicted to reduce or eliminate gene activity, especially in regulatory genes [15,65,66,71].

Certainly, many lineages have lost specific genes, networks, and traits, but even when they arise as conditionally advantageous mutations, several forces likely act to limit the impact of the most radical changes over geological timescales. First, species are seldom exposed to static environments that allow conditionally useful genes to be tossed aside. Rather, they must be able to thrive and complete their life cycles in fluctuating environments. Second,

individuals exchange genes with other members of their species, which may exist across a range of environments, allowing genes to be reintroduced if a loss was only transiently beneficial. Third, although the mutations may be rarer than nonsense or frameshift mutations, more specific regulatory mutations are likely to arise eventually [72]. Fourth, horizontal gene transfer (HGT) may allow genes to be reacquired from other organisms [55,59]. Finally, lineages that have lost key functions may be less likely to undergo cladogenesis or be more susceptible to extinction.

Given the currently limited sampling of yeast genomes, one might justly ask whether we are missing a trend of widespread, but undetected, gene loss and gene sharing that will be revealed as all the branches of the phylogeny are filled in. Many additional congeneric hybrids at the tips of the phylogeny will undoubtedly be discovered. Nonetheless, as with most gene loss events, hybridization events are generally neutral or short-lived adaptations to extreme conditions. Allopolyploidization results in whole genome duplications (WGDs) [73], which are relatively easy to detect, thanks to pioneering work that inferred the WGD in the lineage leading to *S. cerevisiae* by comparing this genome to itself [74]. Although that solitary WGD event had a tremendous and lasting impact on duplicate gene function and genome structure in over 50 species of Saccharomycetaceae, including *S. cerevisiae* [75], the frequency with which yeast WGD descendants persist is clearly much lower than in angiosperms, where most lineages have undergone multiple rounds of WGD [76]. Finally, HGT is responsible for a non-trivial number of yeast adaptations, but the rate remains much lower than in bacteria [57].

## Prospects for the future

As with all organisms, yeast genome sequences comprehensively describe their genetic makeups, but historical and genetic processes that have sculpted their evolution are best understood through a comparative lens. Remarkably, several ambitious projects promise to enhance dramatically the genome sampling of fungal biodiversity at both the population and species levels, including the 1KFG Project surveying the entire spectrum of fungal diversity (http://1000.fungalgenomes.org), the 1002 Yeast Genomes Project focusing on *S. cerevisiae* (http://1002genomes.u-strasbg.fr), the Dikaryome Consortium (http://dikaryome.org), the iGénolevures Consortium (http://gryc.inra.fr), and the Y1000+ Project focusing on the subphylum Saccharomycotina (http://y1000plus.org).

At least for the yeasts, these projects stand a chance of saturating two key dimensions of known biodiversity: genetic depth and taxonomic breadth. Just as a genome sequence definitively describes what genes are present in an organism, only a complete clade of genomes can fully chronicle their evolution and enable the study of genetic and functional diversification across taxa, niches, and time. With these projects underway and with perhaps the most advanced armamentarium for functional dissection at hand, the genetic features that cause some species to make beer, others to inhabit cacti, and still others to cause lethal blood infections are finally coming into focus. The yeasts are rising to the challenge to create an unparalleled model of eukaryotic genome evolution.

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**Box 1**

### One Fungus, One Name (1F1N) and the Phylogenomic Future of Yeast Taxonomy

Despite the considerable progress made classifying yeasts using multi-locus DNA sequence data, critical gaps remain. Many genera are paraphyletic or polyphyletic, while many taxonomic circumscriptions at or above the family level are poorly supported or completely lacking. Further complicating matters, many species are assigned to large, polyphyletic, anamorphic (no known sexual state) genera (e.g. *Candida*), rather than to allied teleomorphic (sexual) genera. Due to a recent revision in the International Code of Nomenclature for algae, fungi, and plants (formerly the International Code of Botanical Nomenclature), anamorphs and teleomorphs can now, for the first time, be reassigned to monophyletic genera that contain species both with and without known sexual cycles. This long-overdue change presents a timely opportunity to formulate a comprehensive and stable yeast taxonomy based on complete genetic data. Well-circumscribed monophyletic genera (and higher order taxa) will finally provide evolutionary geneticists, mycologists, biotechnologists, and clinicians with phylogenetically informative names to aid in the design of experiments and the interpretation of data. In this review, the current, formally recognized genus names are shown first with alternative names in parentheses. In some cases, such as the affinity of *C. glabrata* with *Nakaseomyces*, there is strong phylogenomic support and a virtual certainty that the species will be ultimately reassigned to a particular genus; in other cases, phylogenomic analyses and further taxonomic consensus will be required.

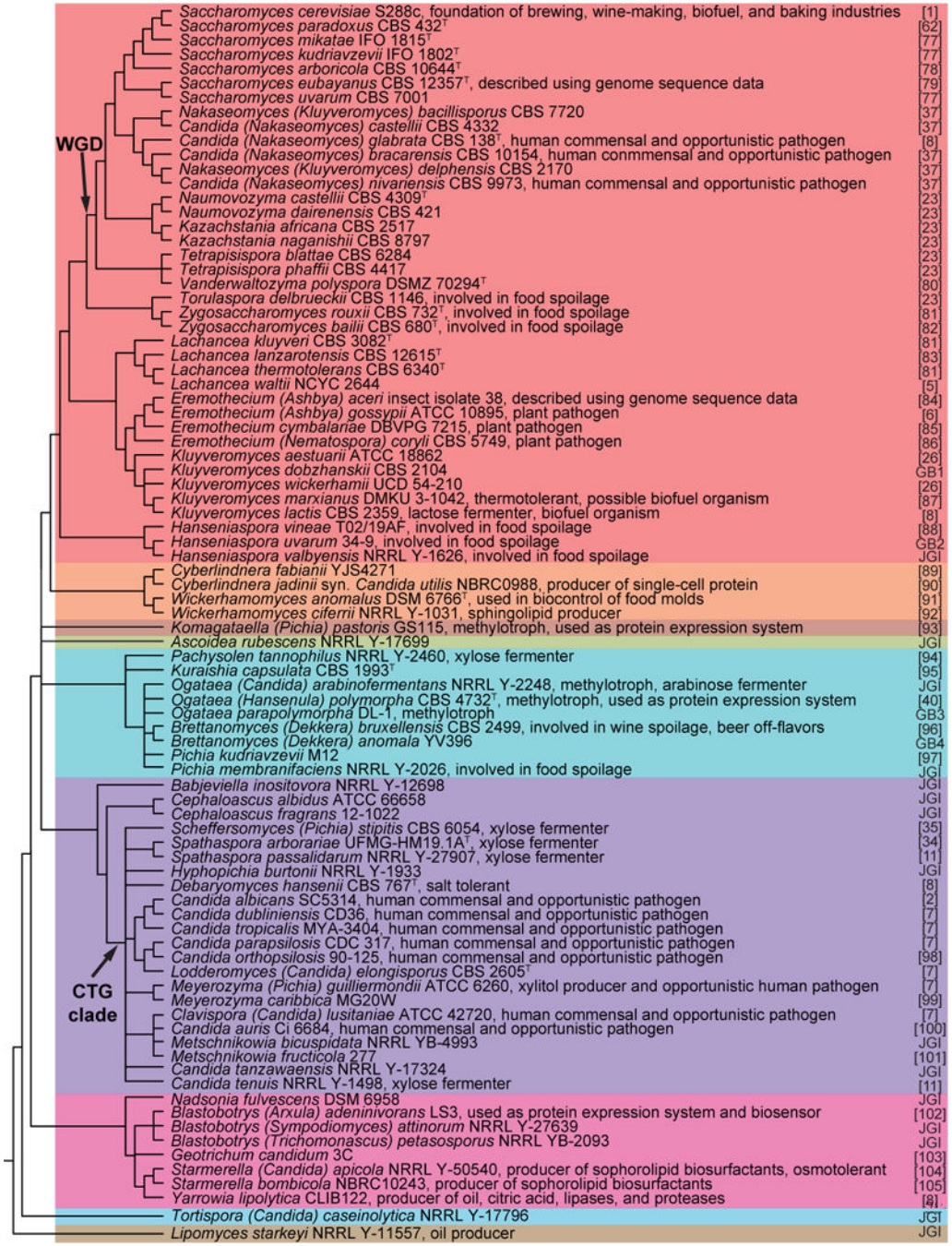


**Figure 1. Key traits and phylogenetic relationships of the 86 yeasts of the subphylum Saccharomycotina whose genomes have been sequenced**

The topology of the cladogram has been estimated conservatively from previous analyses using genome [12,23] or multi-locus sequence data [27,36]. Major clades [36] are color-coded (clade names are shown in Figure 2). Only one reference genome per species is included with preference given to the highest quality and/or most widely used reference genome. Only publicly available genome assemblies are included. Interspecies hybrids are discussed in the text but are not shown here. WGD, whole genome duplication; recent work has shown that the WGD was caused by an allopolyploidization event that occurred between

an early member of the *Zygosaccharomyces*/*Torulaspora* clade and an early member of the *Kluyveromyces*/*Lachancea*/*Eremothecium* clade, thus making this part of the phylogeny a network, rather than a tree [73]. CTG clade, yeasts using an alternate codon table where CTG encodes serine, instead of leucine. JGI, genomes publicly available on MycoCosm at http://genome.jgi-psf.org/programs/fungi/index.jsf, which are subject to the usage terms of the DOE Joint Genome Institute until formal publication. GB1, GenBank Accession CCBQ000000000; GB2, Genbank Accession JPPO00000000; GB3, GenBank Accession AEOI00000000; GB4, GenBank Accession LCTY00000000.

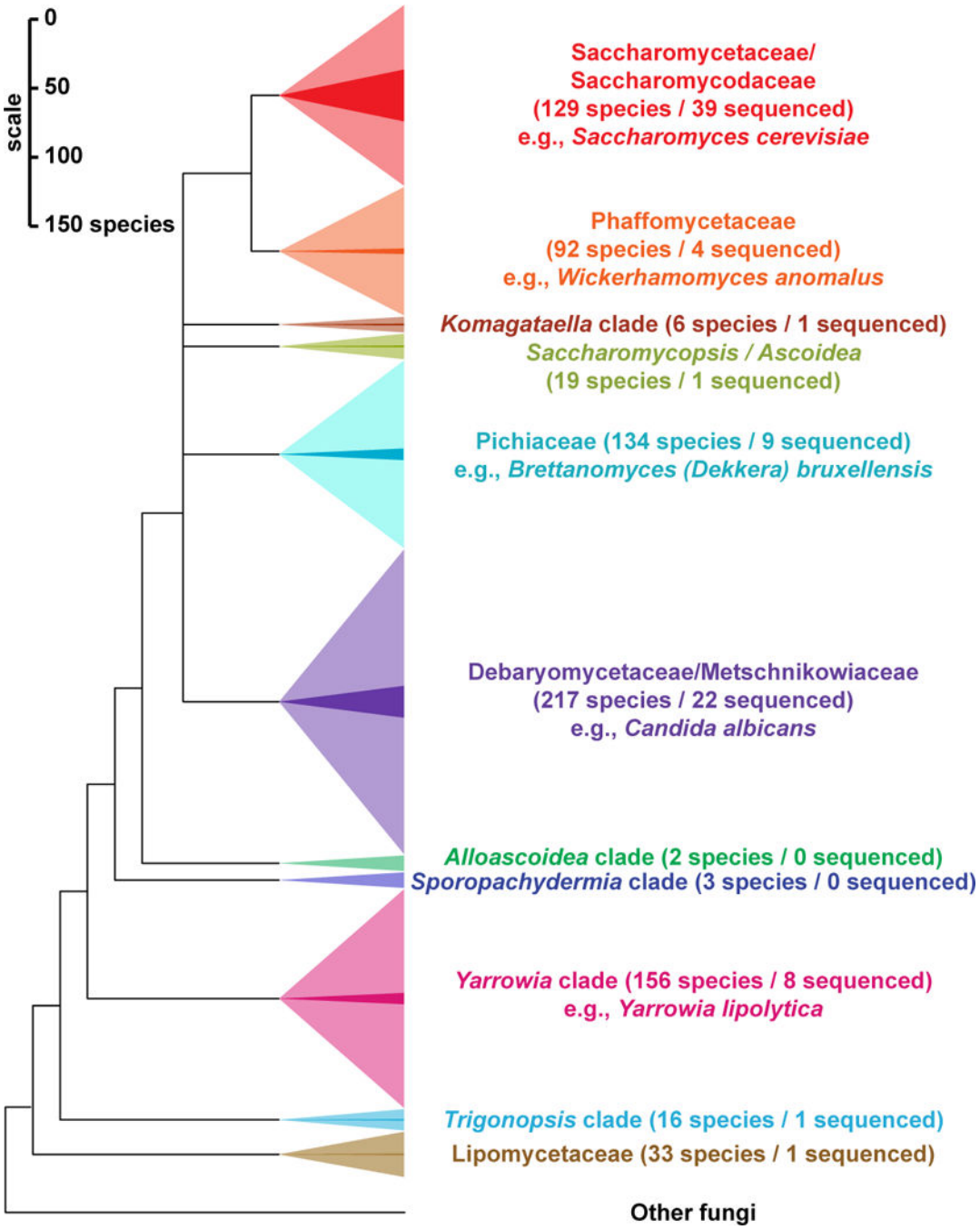


**Figure 2. Most yeast clades remain underrepresented by genome sequence data**

Estimated species counts for each major yeast clade [36] (light colors) are compared with the number of publicly available genomes from each clade (dark sliver within larger triangles). In addition to the 807 species shown, approximately 400 anamorphic species (e.g. *Candida* spp.) currently lack a clear phylogenetic placement. As the phylogeny is resolved, these species will be reassigned to genera and higher taxonomic ranks consistent with their phylogeny (Box 1). Color codes are the same as in Figure 1.