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Genetic Diversity of Human Fungal Pathogens

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Abstract

Purpose of review: Fungi represent a central yet often overlooked domain of clinically relevant pathogens that have become increasingly important in human disease. With unique adaptive lifestyles that vary widely across species, human fungal pathogens show remarkable diversity in their virulence strategies. The majority of these fungal pathogens are opportunistic, primarily existing in the environment or as commensals that take advantage of immunocompromised hosts to cause disease. In addition, many fungal pathogens have evolved from non-pathogenic lifestyles. The extent of genetic diversity and heritability of virulence traits remains poorly explored in human fungal pathogens.

Recent findings: Genetic variation caused by mutations, genomic rearrangements, gene gain or loss, changes in ploidy, and sexual reproduction have profound effects on genetic diversity. These mechanisms contribute to the remarkable diversity of fungal genomes and have large impacts on their prevalence in human disease, virulence, and resistance to antifungal therapies.

Summary: Here, we focus on the genomic structure of the most common human fungal pathogens and the aspects of genetic variability that contribute to their dominance in human disease.

Keywords

fungal genome; *Candida* ; *Aspergillus* ; *Cryptococcus* ; endemic fungal pathogens

Introduction

An estimated 1.5 to 5 million species of fungi are found across diverse environmental conditions [1]. Many fungal species are symbiotic or pathogenic and thrive in close associations with other organisms. Independently evolved from non-pathogens, over 8,000 fungi are plant pathogens and around 200 are pathogenic to humans [2]. Annually, more

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Conflict of Interest

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Human and Animal Rights and Informed Consent

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than one billion people contract a fungal infection, over 300 million people suffer from a serious fungal-related disease, and more than 2 million people die, making them the fifth largest cause of death worldwide [3,4]. While the majority of fungal infections are superficial and relatively easy to cure, invasive fungal infections, commonly caused by *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* are more difficult to diagnose and treat, resulting in a mortality rate that can reach 90% in immunocompromised individuals [5]. The increase in antifungal resistance further challenges our ability to treat these diseases, contributing to high mortality rates [5].

Very few fungal pathogens are dependent on a human host for its life cycle and their pathogenicity is unintended [2]. As opportunistic pathogens, many of the genetic traits required for virulence are likely not specific markers for causing disease and were selected for based on the pathogen's ability to survive in its natural habitat. The adaptability of the fungal pathogen response to their host (i.e., expression of virulence factors, antifungal tolerance) is dependent on their ability to generate genomic variation. Stable and prolonged changes to the genome–gene gain or loss, genomic rearrangements, horizontal gene transfer, changes in ploidy, and sexual reproduction–contribute to the genetic variability, virulence, and antifungal resistance of human fungal pathogens [6].

The first sequenced eukaryotic genome was fungal and fungi have more genomes sequenced than any other eukaryotic group (Table 1). Genome sizes in the fungi are highly variable, ranging from 8.97 Mb to 117.57 Mb with an average genome size of 36.91 Mb in Ascomycota, 46.48 Mb in Basidiomycota, and 74.85 Mb in Oomycota phyla (Table 2). The depth of fungal genome sequencing has enabled direct comparisons between species and lineages, contextualizing the genetic diversity that enables fungi to flourish in disparate habitats and invade plants and animals. This review will focus on the genomic features of the most prevalent human fungal pathogens (*Aspergillus*, *Cryptococcus*, and *Candida*) and endemic fungal pathogens (*Histoplasma, Blastomyces, Coccidioides, Paracoccidioides,* and *Sporothrix*).

Aspergillus

Aspergillus is a genus of widespread and diverse filamentous saprobes with clinical and agricultural significance. Most *Aspergillus* species are not pathogenic, specializing instead in the breakdown of botanical matter. As a genus, the genetic variation in *Aspergillus* is equal to that of the Vertebrate phylum; the close relatives *A. fumigatus* and *A. fischerianus* are as dissimilar as humans and mice [7]. There are hundreds of described *Aspergillus* species, but only a fraction of them are capable of infection humans, with infections primarily caused by *A. fumigatus* and *A. flavus*. Currently, reference genomes are available for 194 *Aspergillus* species through the NCBI Genome Database [8].

Aspergillus fumigatus

Disease and Diversity: *A. fumigatus* causes the greatest number of deaths, the second highest number of human infections, and is responsible for up to 90% of aspergillosis cases [9]. The global distribution of *A. fumigatus* and its ability to grow well at 37°C results in 11 million allergic reactions and over 3 million chronic and invasive lung infections annually

[9]. Phylogenetic analyses separating *A. fumigatus* into clades have been inconclusive with no significant variation found between clinical and environmental isolates [10,11]. However, the subdivision of *A. fumigatus* into two broad clades is supported by the uneven distribution of *cyp51* (*erg11*) alleles, the target for azoles [12].

Genome: *A. fumigatus* was first sequenced in 2005 (strain Af293), with recent genomes providing telomere-to-telomere coverage for strains CEA10 and A1160 [13]. Comparisons of the A1160, CEA10, and Af293 genome assemblies revealed several chromosomal rearrangements, the most significant occurring between chromosomes 1 and 6 [13]. Pan-genome analysis identified a core set of orthologs (69%), with 16% to 22% of the genome varying between strains [10]. Variation is primarily found in accessory genes affiliated with transmembrane transporters, iron-binding activity, and carbohydrate and amino acid metabolism, which may explain the wide range in virulence observed in *A. fumigatus* isolates [10]. Chronic disease isolates are more genetically diverse than strains from invasive aspergillosis or the environment and are more likely to engage in parasexual or sexual recombination, contributing to the development of azole resistance [10,14].

Aspergillus flavus

Disease and Diversity: A common plant pathogen, *A. flavus* produces several aflatoxins, causes pulmonary and systemic infections in humans and can be up to 50 times more virulent than *A. fumigatus* [15]. However, infection by *A. flavus* is less common than *A. fumigatus*, responsible for less than 10% of pulmonary aspergillosis cases [16]. *A. flavus* forms a single monophyletic clade but whole genome analysis breaks *A. flavus* isolates from the United States into 3 populations, with population C more closely related to *A. oryzae* [17]. Populations A and B are widely distributed and have similar geographic distribution while Population C is often isolated from Iowa, Indiana, and Pennsylvania [17]. Notably, populations B and C have lower diversity than population A [17].

Genome: Several *A. flavus* isolates have been sequenced [18–20] with the nearly complete assembly of isolate NRRL3357 being released in 2021 [21]. This 37.75 Mb genome assembly completed 7 of the 8 chromosomes from telomere-to-telomere and is considerably larger than other *Aspergillus* genomes [21].

Compared to *A. fumigatus* there is significantly less genetic diversity among the clinical isolates of *A. flavus*. Remarkably similar to that of its closest relative, *A. oryzae,* only 43 genes are unique to *A. flavus* [22]. *A. flavus* produces carcinogenic secondary metabolites known as aflatoxins, absent from its close relatives. Furthermore, the regulatory proteins of aflatoxin biosynthesis are necessary for *A. flavus* asexual development [23].

Cryptococcus

A basidiomycete, *Cryptococcus* yeasts are found worldwide in soil, bird-droppings, decaying wood, and trees. *Cryptococcus* is the etiological agent of one of the most lethal fungal infections, cryptococcosis and fungal meningoencephalitis [24]. The vast majority of infections, up to 95%, are caused by the globally distributed *C. neoformans* although cases caused by *C. gattii* are increasing annually [24]. *C. gattii* is a primary human pathogen,

causing disease in both immunocompetent and immunocompromised individuals [24]. *C. gattii* is endemic in tropical climates, with climate change likely playing a role in the Pacific Northwest outbreaks [25].

Cryptococcus species are typically haploid with a 19 Mb genome on 14 chromosomes. However, changes in ploidy, hybrid genomes, and chromosome duplications are not uncommon and karyotype variation has occurred in strains over the course of infection [26]. *C. neoformans* and *C. gattii* share a genetic identity of ~85%, however hybrids between the two species have been reported, increasing the genetic variability of the genus [27]. Multilocus sequence typing has identified 5 major molecular types of *C. neoformans* and 4 major molecular types of *C. gattii* [28]. Genomic rearrangements and changes in chromosome length in *Cryptococcus* likely contribute to chronic infection, adaptation to the host, and antifungal resistance [29,30].

Cryptococcus neoformans

Genome: Both the reference strain H99 and a recently completed ungapped genome of *C. neoformans* VNII spanned 19 Mb across 14 chromosomes [31,32]. Comparisons between *C. neoformans* and *C. gattii* genomes found 2 large inversions, 3 translocations, and extensive rearrangements in *C. neoformans* [30,33].

C. neoformans undergoes ploidy changes during sexual development and in response to various environmental and host cues [26]. During infection the haploid *C. neoformans* can form polyploid titan cells [34] and form diploid blastospores during unisexual reproduction [26]. These genomic variations correspond with phenotypic differences and alter transcriptional regulation, signal transduction, and glycolysis pathways, impacting the course of infection [35]. Segmental aneuploidy has been detected on multiple chromosomes, which conferred azole resistance in some isolates during host infection [26]. Aneuploidy formation in *C. neoformans* may be related to an increased rate of transposon movement [29].

Cryptococcus gattii

Genome: The most complete *C. gattii* assembly contains 14 chromosomes and 18.4 Mb with eight internal gaps [36]. A number of other strains and variants have been sequenced, but they remain incomplete scaffolds. The genome structure is highly conserved across *C. gattii* variants, on average only a 7% sequence divergence among *C. gattii* VGI and VGII genomes [36]. Between all four *C. gattii* variants, ~87% of the genome has been identified as a core set of genes [37]. The limited genome evolution of *C. gattii* has not changed genome size or structure but instead acted on conserved gene families, like drug transporters, and gene expansions that likely facilitate survival in the human host [37].

Candida

Candida encompasses non-pathogenic species, harmless commensals or endosymbionts, and pathogens of humans and plants. Several *Candida* species can cause superficial infections, systemic fungemia, or invasive candidiasis. *C. albicans*, a normal constituent of the human skin, gastrointestinal, and genitourinary tracts, causes the majority of *Candida* bloodstream

infections but other non-*albicans Candida* species, including *C. glabrata, C. parapsilosis, C. tropicalis, C. krusei,* and *C. auris* are responsible for an increasing number of cases [38]. Resistance to commonly used antifungals may explain the rise in cases caused by other *Candida* species [39].

A polymorphic fungus, *Candida* is able to express several different morphologies. Generally, the environmental yeast-phase of *Candida* species switches to a multicellular filamentous form during infection [40]. The highest genetic diversity is observed in species that are most frequently human commensals–*C. albicans, C. tropicalis,* and *C. glabrata* [41]. Below we discuss the genome characteristics of *C. albicans*, non-*albicans Candida,* and the emerging pathogen *C. auris*.

Candida albicans

Disease and Diversity: *C. albicans* is the most prevalent human fungal pathogen. It is the fourth most common hospital acquired infection in the United States and responsible for nearly half a million life-threatening infections annually, primarily in immunocompromised individuals [42]. Multi-locus sequence typing split *C. albicans* into 17 predominantly clonal populations that separate independent of geography [43]. In *C. albicans*, *C. tropicalis* and *C. parapsilosis*, the CUG codon is translated to serine instead of leucine [44]. *C. albicans* demonstrates a wide range of morphological forms–yeast, true hyphae, pseudohyphae, and chlamydospores–that likely aid in its survival, growth, and dissemination throughout their mammalian host as a commensal and pathogen.

Genome: Multiple sequencing efforts have assembled the diploid *C. albicans* genome [45–47]. Long-read sequencing generated a haploid assembly of pathogenic *C. albicans* [48] and a diploid assembly for environmental *C. albicans* [49]. *C. albicans* is naturally diploid with a 14 to 16 Mb haploid genome organized into eight pairs of chromosomes [45]. However, *C. albicans* can maintain stable ploidy states ranging from haploid to tetraploid [50].

Chromosomal rearrangements, aneuploidy, point mutations, and loss of heterozygosity (LOH) contribute to *C. albicans* genome plasticity and have been extensively reviewed [51–53]). *C. albicans* is heterozygous with more than 1% nucleotide divergence between isolates [54]. Excessive polymorphisms are present on chromosomes 5 and 6 with low instances of polymorphism found on chromosomes 3 and 7 [45]. Host pressures and other stressors, like exposure to antifungals, can result in a temporary increase in *C. albicans* ploidy, driving diploid cells up to 16N [55]. In patients treated with azoles, *C. albicans* aneuploidy frequency increased over time [56]. Additional stressors may also lead to non-disjunction events as *C. albicans* often loses chromosome 5 when forced to grow on sorbose and strains that are resistant to fluconazole have frequently lost chromosome 4 or gained chromosome 3 [57].

Although the vast majority of mutational events occur somatically, mating and parasexual mating are strong drivers of genetic diversity in *C. albicans* [58]. *C. albicans* primarily reproduces through asexual clonal division, but the machinery needed for mating and meiosis has been retained [59]. However, the products of diploid *C. albicans* mating are

tetraploid and carry out “concerted chromosome loss” by losing chromosomes at random until they reach a near-diploid genome [60,61].

Non-*albicans Candida* (NAC) species

The non-*albicans Candida* (NAC) species *C. glabrata,, C. tropicalis, C. parapsilosis,* and *C. krusei* are increasingly responsible for candidiasis globally [39]. *C. glabrata* and *C. krusei* were recently renamed as *Nakaseomyces glabrata* and *Pichia kudriavzeveii*, respectively, however we have maintained the former naming scheme in this review article to align with previously published literature. Their prevalence varies with geographical location, with *C. glabrata* infections highest in Asia-Pacific and Europe, whereas *C. tropicalis* are the top infection in Africa and the Middle East, and *C. parapsilosis* is the predominant cause of infection in North American and Latin America [38].

Candida glabrata (Nakaseomyces glabrata)—Typically a harmless commensal, *C. glabrata* can cause superficial mucosal and serious disseminated infections in older, immunosuppressed patients, and those with diabetes [62,63]. Phylogenetically, *C. glabrata* is more closely related to *Saccharomyces cerevisiae* than *C. albicans* [64]. A haploid fungus, the completed genome of *C. glabrata* has 13 chromosomes with a total size of 12.3 Mb [65,66]. Most of the genomes sequenced recover between 97.3% and 98.7% of the genes annotated in the reference genome, showing little variation in gene content [67]. Genetic variation in *C. glabrata* results from changes in copy number variation, aneuploidy, or single nucleotide polymorphisms and affects biofilm formation, GPI-anchored cell wall adhesins, and protease expression [65,68].

Candida tropicalis—*C. tropicalis* is a globally distributed opportunistic fungal pathogen found in numerous ecological environments [69]. Primarily infecting neutropenic patients, *C. tropicalis* is the most common cause of candidiasis in Southeast Asia and Africa and second most common species in Central and South America [69]. *C. tropicalis* isolates are genetically diverse and have arisen from disparate environments, with no clear geographic separation [70]. First sequenced in 2009, the diploid *C. tropicalis* genome is 14.6 Mb across seven pairs of chromosomes [71]. Interestingly, early research identified 12 chromosomes in *C. tropicalis* with chromosomal length polymorphisms between three strains, suggesting that chromosomal rearrangements occur frequently in *C. tropicalis* [72]. Like *C. albicans*, *C. tropicalis* has a known parasexual cycle that often results in a high level of aneuploidy [73]. Single nucleotide polymorphisms and copy number variants, including *ERG11* and *TAC1*, were present in fluconazole-resistant isolates, indicating that stress and selection pressure are mechanisms through which *C. tropicalis* may acquire resistance [70].

Candida parapsilosis—In contrast to most other *Candida* species, *C. parapsilosis* cases are higher in neonates [63]. *C. parapsilosis* infections are increasing because of its global distribution, broad range of virulence factors, and antifungal resistance. The completed diploid genome of *C. parapsilosis* has 8 chromosome pairs spanning 13 Mb [74]. With low levels of heterozygosity, there is little evidence for significant diversity among *C. parapsilosis* isolates [74,75]. Multi-locus sequence typing divided *C. parapsilosis* into three distinct species: *C. parapsilosis*, *C. orthopsilosis,* and *C. metapsilosis* [76].

Additional sequencing of clinical strains discovered hybrids between these species with major translocations occurring between *C. parapsilosis* and *C. orthopsilosis* chromosomes [77]. In both *C. parapsilosis* and *C. orthopsilosis*, expansion of cell wall gene families for the creation of biofilms have been associated with increased virulence [78].

Candida krusei (Pichia kudriavzeveii)—*C. krusei* is an opportunistic fungal pathogen of high medical importance because of its natural resistance to fluconazole [79]. Causing invasive candidiasis in immunocompromised individuals, *C. krusei* responds poorly to antifungal therapies and has a mortality rate up to 58% [79]. While genetically split into two clusters, different populations of *C. krusei* co-exist in the same geographic environment [79]. A diploid, highly heterozygous yeast, the first assembly of *C. krusei* contained 626 contigs covering 10.4 Mb [80]. PFGE analysis estimates that *C. krusei* has 4 to 6 chromosomes and a genome size of 11.4 Mb [81]. Compared to other *Candida* species, *C. krusei* is understudied and the genomic mechanisms supporting its high genetic diversity have not been investigated. Exposure to antifungal agents is believed to act as a selection factor and may play a role in the evolution of *C. krusei* biofilm formation [79].

Candida auris

Disease and Diversity: *C. auris* represents a newly emerging human fungal infection that poses a significant threat as it rapidly develops resistance to antifungals and spreads easily through hospital environments on skin and surfaces. *C. auris* mainly manifests as a bloodstream infection, but it is also found in wound and ear infections [82]. Diagnosing a *C. auris* infection requires molecular methods, which is not always feasible, contributing to an underestimation of the global spread of *C. auris* [82]. *C. auris* is a thermotolerant, multidrug-resistant ascomycete, with 80.8% of strains showing resistance against fluconazole, 38.1% against voriconazole, and 26.2% against amphotericin B [83].

First described in 2009, *C. auris* has spread across six continents with outbreaks occurring in more than 30 countries [82,83]. Genomic analyses have confirmed a near-simultaneous evolution of *C. auris* in multiple areas around the world [84]. *C. auris* has been separated into 5 genetically distinct, geographically distributed clades: South Asian (Clade I), East Asian (Clade II), African (Clade III), South American (Clade IV), and Iranian (Clade V) [84,85].

Genome: The majority of *C. auris* assemblies remain highly fragmented and inconsistently annotated. A haploid ascomycete, *C. auris* has a 12.1 to 12.7 Mb genome spread across five to seven chromosomes [86]. Each clade differs from the other four by tens of thousands of single nucleotide polymorphisms, but exhibits a highly clonal population structure within the clade; on average less than 70 single nucleotide polymorphisms within each geographic cluster, even in isolates thousands of miles apart [84,87]. Comparisons of Clades I through IV (comparisons with Clade V have not been reported) show a high level of similarity, with a shared 98.7% nucleotide identity [86]. Clade II is the most rearranged with two inversions and nine translocations but is most similar to Clade III with a 99.3% shared identity [86]. Conservation of *C. auris* as a species complex is supported by their more distant relationship

to other *Candida* species; on average 88% similar to its closest relatives, *C. haemulonii*, *C. duobushaemulonii*, and *C. pseudohaemulonii* [86].

C. auris genome variation results from changes in copy number and gain or loss of chromosomes as there is no evidence for alterations in ploidy states [87]). These mutations contribute to differences in antifungal resistance between *C. auris* clades and increased virulence. Compared to other *Candida* species, *C. auris* has higher resistance to cationic, cell wall, and oxidative stressors and can maintain viability and higher proteinase and phospholipase activity at 42°C [88].

C. auris genomes have conserved mating loci, but only one of the two mating types, MTLa or MTLα, have been detected in each clade [83]. Mating between clades has not yet been reported, but in countries where multiple clades have been identified, mating may occur where MTLa and MTLα strains are no longer geographically separated [83,88].

Endemic Fungal Pathogens

Thermally dimorphic fungal pathogens, which alter their morphology and virulence in response to temperature, are responsible for hundreds of thousands of infections and deaths annually [89]. Globally distributed, but geographically and ecologically restricted, these organisms exist in the environment as saprotrophic hyphae that transition to parasitic forms (yeasts or spherules) in mammalian hosts [90]. These pathogens are all found within the phylum *Ascomycota*, but are spread across a number of orders, exemplifying the convergent evolution of dimorphism and pathogenesis in fungi [90]. Assessing the global burden of these diseases is difficult, but mortality rates can reach up to 70% for infected individuals [89]. Below we discuss the genome characteristics of the thermally dimorphic fungi: *Histoplasma*, *Blastomyces, Coccidioides, Paracoccidioides,* and *Sporothrix*.

Histoplasma

The fungal pathogen *Histoplasma* is found on every continent. It causes mild flu-like symptoms in most people but the infection may develop into a life-threatening systemic disease, especially for immunocompromised individuals. Previously, *Histoplasma* was divided into three varieties based on clinical presentation, morphology, and geographic distribution: *H. capsulatum var. Capsulatum*, responsible for pulmonary histoplasmosis; *H. capsulatum var. duboisii*, responsible for African histoplasmosis; and *H. capsulatum var. Farciminosum*, responsible for equine histoplasmosis [91]. *H. capsulatum* associates with river valleys, particularly in the Central and Eastern United States and Central and South America, while *H. duboisii* is primarily found in Africa [92].

Phylogenetic analyses have revealed at least eight clades that are tightly associated with specific geographical regions: North American classes 1 and 2 (NAm 1 and NAm 2), Latin American groups A and B (LAm A and LAm B), Eurasian, Netherlands, Australian, African [93,94] and a recently identified Indian lineage [95]. The LAm groups were later divided into six phylogenetic groups [96]. Speciation and admixture have been shown between *Histoplasma* isolates [97–99]. Comparative genetic analyses have suggested new nomenclature for *H. capsulatum* as four new subspecies: *H. capsulatum* (Panama or H81

lineage), *H. mississippiensis* (NAm 1), *H. ohiensis* (NAm 2), and *H. suramericanum* (LAm A) [97].

Early studies identified 5-7 chromosomes [100]. The original genome assembly contained >3000 contigs spanning 43.5 Mb across the highly repetitive *Histoplasma* genome (strain G217B) [101]. Completed assemblies of 5 *Histoplasma* strains revealed genomes ranging in size from 31 to 40 Mb due to differences in repeat content with extensive synteny among geographically segregated isolates [102]. The observation of transposon and transposon-embedded gene upregulation in the yeast phase of strain G217B suggests that repetitive DNA may play a role in the dimorphic lifestyle [102].

Blastomyces dermatitidis

Blastomyces dermatitidis and *Blastomyces gilchristii* are the etiological agents of blastomycosis, an invasive fungal infection in humans. Identifying the environmental niche that *Blastomyces* inhabits has proven elusive, but epidemiological data suggests that *Blastomyces* species live in soil and wet, decaying wood [103]. *B. gilchristii* is primarily found in Canada and the northern United States [104]. *B. dermatitidis* is endemic to Eastern North America, found throughout northern Ontario to the Mississippi and Ohio River Valleys, but its range is expanding towards the Appalachian mountains and the Eastern United States [103]. The genome of *B. dermatitidis* is incompletely sequenced, with four strains represented by up to ~4,000 scaffolds. Only one isolate of *B. gilchristii* has been sequenced with a genome scaffold of ~1,800 contigs. Compared to other fungi, the gene content of *Blastomyces* species is highly conserved, but the genome contains large, highly variable repetitive long terminal repeat transposon regions [102,105]. An increase in gene copy number is likely associated with gene expression changes in proteases, antioxidants, and trace metal acquisition which are involved in host interactions and virulence [105].

Paracoccidioides

Paracoccidioides brasiliensis and *P. lutzii* are responsible for paracoccidioidomycosis, a disease that forms granulomas in the nose, sinuses, and skin. Up to 80% of cases occur in Brazil with the severity of disease increasing in HIV and immunocompromised patients [106]. Four genomes of *P. brasiliensis* and one genome of *P. lutzii* have been sequenced and assembled to the scaffold-level with ~2,000 contigs [106,107]. Paracoccidioides species have haploid genomes that vary from 29.1 to 32.9 Mb and are highly divergent [107–110]. Gene family expansions specific to *Paracoccidioides* include the fungal-specific kinase family and genes encoding secreted proteins, with gene losses in cell wall and carbohydrate metabolism detected across dimorphic fungal pathogens [107,111].

Coccidioides

Coccidioides immitis and *C. posadasii* are the etiological agents of coccidioidomycosis, also known as valley fever. Endemic to the southwestern United States and Mexico, it is estimated that 60% of infections are asymptomatic with less than 1% of patients developing disseminated disease [112]. Morphologically identical, *C. immitis* and *C. posadasii* are genetically distinct [112,113]. There are 5 scaffold genome sequences with at most ~4,000

contigs available for *C. immitis* and 13 genome sequences available for *C. posadasii* with one recent chromosome-level reference genome released [112,114]. Genomes for both *C. immitis* and *C. posadasii* are ~28 Mb organized into 9 chromosomes [114]. Hybridization has occurred between the two species, mainly from *C. posadasii* to *C. immitis,* transferring coding genes that likely function in immune evasion and cell wall biosynthesis [112,115]. *C. posadasii* is divided into two main clades: Clade I isolates are found in Arizona and Clade II isolates are found in Texas and South America [116]. Phylogenetic analyses of *Coccidioides* species have proven useful in molecular epidemiology studies [117].

Sporothrix

The common route of *Sporothrix* infection introduces spores through a cut or wound in the skin, as opposed to pulmonary routes. *S. brasiliensis, S. schenckii* and *S. globosa* are found worldwide, but are endemic in Peru and Asia, which experience a higher incidence of disease [118]. There is a high level of similarity between *Sporothrix* genomes with an average sequence identity of 97.5% between *S. schenckii* and *S. brasiliensis* [119]. There is one assembly for *S. brasiliensis* with 13 contigs spanning 33.2 Mb [106,119]. The *S. globosa* genomes have only been assembled to the scaffold-level with at most 571 contigs for the 33.5 Mb genome [120]. The *S. schenckii* genome has been assembled to 16 contigs, covering 32.8 Mb [121,122]. *S. schenckii* has the greatest genetic variation and evidence of genetic recombination, but all *Sporothrix* species have lost polysaccharide lyase genes suggesting that they have switched from plant to animal hosts [119].

Conclusion

Fungal genomics has been gaining importance in recent years. More than 50% of research articles cited in this review were published within the last five years, underlining the attainability of fungal genome sequencing and analysis tools. Accordingly, the next steps that will expand upon our understanding of fungal genetic diversity are to 1) generate complete telomere-to-telomere sequences for all notable pathogens and their non-pathogenic relatives, 2) expand the number of strains and isolates sequenced by carrying out clinical and environmental population level analyses, and 3) establish a system for identifying and detecting emerging pathogens. With our current understanding of genetic diversity in the fungi, a single or few reference genomes is insufficient for describing the full range of variation present in the population. With the reduction in cost of long-read sequencing, the number of complete fungal genome assemblies will continue to increase. The subsequent limiting factor will be characterizing the impacts of genetic variability on gene expression, translational efficiency, and function, which may shed light onto the molecular mechanisms of fungal pathogenesis.

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Table 1:

Summary of the most common human fungal pathogens and their distribution

Genus	Phylum	Human Disease Caused	Distribution
Aspergillus	Ascomycota	Aspergillosis, allergic bronchopulmonary aspergillosis, allergic *Aspergillus* sinusitis, aspergilloma, chronic pulmonary aspergillosis, invasive aspergillosis, cutaneous aspergillosis	Global
Cryptococcus	Basidiomycota	Cryptococcal meningitis, cryptococcosis	Primarily Sub-Saharan Africa, Asia and the Pacific. Notably fewer cases occur in North/South America, the Caribbean, North Africa, the Middle East, and Europe.
Candida	Ascomycota	Candidiasis, vaginal candidiasis, invasive candidiasis, oropharyngeal candidiasis (thrush), candidemia	Global
Histoplasma	Ascomycota	Histoplasmosis	Central and Eastern United States, Central and South America, Africa, Asia, and Australia
Blastomyces	Ascomycota	Blastomycosis	Primarily Eastern United States and Candida with fewer cases reported from Africa, the Middle East, India, and western North America
Coccidioides	Ascomycota	Coccidioidomycosis	Southwestern United States, parts of Mexico and Central and South America
Paracoccidioides	Ascomycota	Paracoccidioidomycosis	Mexico and Central and South America
Sporothrix	Ascomycota	Sporotrichosis	Global, endemic in Latin America

Table 2:

A summary of the sequenced genomes for the most common human fungal pathogens

Genus	Species	Genome Sequence Status	Genome Size	Chromosomes/Contigs	Plody	References
Aspergillus	*fumigatus*	Complete	29 Mb	8 chromosomes	haploid	[13]
	flavus	Chromosome	37 Mb	8 chromosomes	haploid	[18,19,21]
Cryptococcus	*neoformans*	Chromosome	19 Mb	14 chromosomes	haploid	[32]
	gattii	Chromosome	17.5 Mb	14 chromosomes	haploid	[25,36]
Candida	*albicans*	Chromosome	14 Mb (haploid assembly)	8 chromosomes (haploid assembly)	diploid	[45–47,49]
	glabrata (now *Nakaseomyces glabrata*)	Chromosome	12.3 Mb	13 chromosomes	haploid	[65,66]
	tropicalis	Chromosome	14.6 Mb	7-12 chromosomes	diploid	[71,72]
	parapsilosis	Scaffold	13 Mb	8 chromosomes	diploid	[74]
	krusei (now *Pichia kudriavzeveii*)	Chromosome	10.4-11.4 Mb	4-6 chromosomes	diploid	[80,81]
	auris	Chromosome	12 Mb	5-7 chromosomes	haploid	[85]
Histoplasma	*capsulatum*[*]	Chromosome	31-40 Mb	6-12 chromosomes	haploid	[102]
Blastomyces	*dermatitidis*	Scaffold	66.6 Mb	25 scaffolds/591 contigs	haploid	[105]
	gilchristii	Scaffold	75.3 Mb	100 scaffolds/1791 contigs	haploid	[105]
Coccidioides	*immitis*	Scaffold	27 Mb	6 scaffolds/10 contigs	haploid	[112]
	posadasii	Chromosome	28 Mb	9 chromosomes	haploid	[114]
Paracoccidioides	*brasiliensis*	Scaffold	29 Mb	57 scaffolds/556 contigs	haploid	[108]
	lutzii	Scaffold	33 Mb	110 scaffolds/672 contigs	haploid	[109]
Sporothrix	*brasiliensis*	Scaffold	33 Mb	13 contigs	haploid	[119]
	schenckii	Contig	32 Mb	16 contigs	haploid	[121,122]

[*] Speciation of *Histoplasma capsulatum* has been studied and new naming for the subspecies has been suggested by Sepulveda et al. [97]