Published in final edited form as:

Trends Microbiol. 2011 November ; 19(11): 564–571. doi:10.1016/j.tim.2011.07.010.

***Cryptococcus gattii*: a resurgent fungal pathogen**

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Abstract

Cryptococcus gattii and *C. neoformans* are causal agents of cryptococcosis, which manifests as pneumonia and meningitis. *C. gattii* has recently received widespread attention due to outbreaks in British Columbia, Canada and the US Pacific Northwest. The biology of this tree-dwelling yeast is relatively unexplored, and there are few clues about how it causes infections in humans and animals. In this review, we summarize recent discoveries about *C. gattii* genetics and its ecological niche and highlight areas ripe for future exploration. Increased focus on epidemiology, ecological modeling, and host-pathogen interactions is expected to yield a better understanding of this enigmatic yeast, and ultimately lead to better measures for its control.

Two etiologic agents of cryptococcosis

Cryptococcus gattii is found as single or budding yeast with round, oval or cylindrical cells enveloped in a polysaccharide capsule. This pathogen causes cryptococcosis that most commonly includes lung and brain infections in healthy as well as immune-compromised individuals (see Glossary). The far better known etiologic agent of cryptococcosis is *C. neoformans*, the sibling species of *C. gattii*. Until recently, these two fungi were classified as varieties of the same species^{1,2}. Cryptococcosis due to *C. neoformans* occurs worldwide and it has received major attention as one of the common complications in HIV⁺ individuals and in AIDS patients. In addition, *C. neoformans* cryptococcosis has been called an ‘awakening giant’ among opportunistic infections in patients with solid tumors³. The pathogen *C. neoformans* comprises two varieties that differ significantly - *C. neoformans* variety (var.) *grubii* is global in distribution while *C. neoformans* var. *neoformans* is more common in Europe^{4,5}. In this review, all references to *C. neoformans* pertain to *C. neoformans* var. *grubii*.

Originally, *C. gattii* was considered to be restricted in distribution to the tropics and sub-tropics⁵. During the past decade, compelling evidence has been accumulated regarding the widespread incidence of *C. gattii* cryptococcosis in Asia, Africa, Australia, South America and outbreaks in parts of North America, which were not previously suspected of harboring this pathogen⁶⁻¹³. Newly presented data also suggests the possibility of a ‘smoldering outbreak’ throughout the Australian continent¹⁴. This emerging information and ongoing

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outbreaks have rekindled interest in *C. gattii* cryptococcosis. This review provides a timely focus on the notable discoveries about population genetics of *C. gattii* and its ecological niche and highlights areas such as disease surveillance, fungal ecology, and host-pathogen interactions that are now ripe for further exploration.

Distinction of *C. gattii* from *C. neoformans*

The available records indicate that a yeast pathogen, initially named *Saccharomyces subcutaneous tumefaciens*, but subsequently identified as *C. gattii*, was documented as far back as 1896^{15, 16}. *Cryptococcus neoformans* var. *gattii* was formally proposed as a new taxonomic entity in 1970 from a clinical case that yielded regular round cells, i.e., R forms, and bacilliform (rod-shaped) cells, i.e., B forms, in culture (Figure 1). The B form phenotype was lost after prolonged culture in the laboratory, but this phenotype could be regained by passage in mice^{1, 15, 17}. This discovery paralleled an earlier characterization of capsular antigens in *C. neoformans* that revealed three serotypes: A, B, and C; B and C serotypes were exclusive to what would eventually become *C. gattii* (Figure 2)¹⁸. Further proof of *C. gattii* being a separate species from *C. neoformans* was provided by the discovery of the sexual form of the former, which was named as *Filobasidiella bacillispora*. The sexual state was observed in the laboratory after mating between compatible strains (*MATa* and *MATa*) led to the production of bacilliform basidiospores or sexual spores¹⁹. Further experiments revealed that interbreeding between *C. gattii* and *C. neoformans* did not yield spores that have an evidence of genetic recombination². Furthermore, biochemical differences were found between *C. gattii* and *C. neoformans* in creatinine, canavanine, and glycine metabolism, which allowed the development of a diagnostic medium to easily differentiate these two pathogens in the laboratory²⁰. Thus, the separation of *C. gattii* from *C. neoformans* met both the morphological and reproductive basis for the recognition of a new species. Further proof of *C. gattii* as a new species resulted from many genetic studies that showed that the two siblings species have evolved into distinct entities 37- 80 million years ago^{21, 22}. These observations satisfied the phylogenetic basis for the formal species status for *C. gattii*². The recent discoveries of rare hybrids of *C. gattii* and *C. neoformans* provides additional proof of a taxonomic proximity, but not similarity between these two species²³.

Currently, it is believed that *C. gattii* comprises four distinct genotypes (VGI – VGIV), which are distinct from *C. neoformans* genotypes (VNI, VNB, VNII and VNIV) as determined by multilocus sequence typing of multiple gene fragments²⁴⁻²⁶. There is considerable genetic divergence among *C. gattii* genotypes, and there is even a proposal to accord strains in these genotypes independent varietal status^{24, 26}. Additional details are expected to emerge when functional analyses of whole genomes are carried out to determine how various *C. gattii* genotypes marshal their cellular processes in response to growth in nature and in animals. Indeed, a recent genome comparison of VGI and VGII strains is a good first step in this direction²⁷.

C. gattii cryptococcosis

The pathogen *C. gattii* is believed to be clinically more virulent than *C. neoformans* given that *C. gattii* causes multiple lesions in the lungs and the brains of affected patients whereas *C. neoformans* does not²⁸⁻³⁰. Similar to other 'primary pathogenic fungi', *C. gattii* causes disseminated skin and lung lesions that can potentially be misdiagnosed as malignancies³¹⁻³³. Brain infections (meningoencephalitis) caused by *C. gattii* are reported to respond slowly to standardized therapy, and they require more diagnostic follow-ups than those seen in *C. neoformans* infections³⁴⁻³⁷. Although the available data are limited, *C.*

gattii isolates susceptible to antifungals in the laboratory can nevertheless cause poor outcomes³⁸⁻⁴⁰.

Other preliminary data suggest that the severity of *C. gattii* infection is due to defective induction of host immune responses, resulting in low levels of the pro-inflammatory cytokines that are crucial for controlling the spread of the fungus in the body⁴¹. One survey in Papua New Guinea, an area highly endemic for *C. gattii*, has shown that significant numbers of people show measurable antibody responses to *C. gattii* protein, but yet they did not develop disease⁴². Surveys conducted in Vancouver Island, British Columbia, have revealed that a small number of cats and dogs in the sampled population could act as asymptomatic carriers of *C. gattii* in their nasal cavity⁴³. These limited observations from humans and animals would support a scenario where some residents and visitors in high-risk areas might be exposed to *C. gattii* and not develop overt illness, but still suffer from reactivation of the disease later in life⁴⁴.

Overall evidence suggests that *C. gattii* cryptococcosis is different from *C. neoformans* cryptococcosis in its manifestations, and it requires accurate diagnosis and careful management. These characteristics have finally caught the attention of physicians, as documented in recently published clinical reports and in the recent guidelines for the treatment of cryptococcosis³⁷. Nevertheless, more systematic surveys are urgently warranted in relevant areas to document the extent of exposure, asymptomatic carriage, and sub-clinical disease among residents and visitors. Similarly, the need for clinical trials to examine if *C. gattii* cryptococcosis requires a more specific therapy and management cannot be overemphasized.

Epidemiology of *C. gattii* cryptococcosis

The epidemiological profile of *C. gattii* cryptococcosis has undergone significant change in the past decade, with the recognition that this disease afflicts the immune-competent as well as immune-compromised patients (including AIDS patients) in areas of the world beyond the tropics and subtropics^{6, 8-11, 45}. Many published reports describe autochthonous cases of human and animal infections from unsuspected areas, thereby providing evidence for the global distribution of *C. gattii* disease. On the other extreme, travel-related *C. gattii* infections have been reported from residents of areas that are considered free of this pathogen^{34, 44}. Overall, epidemiology of this disease is not easily understood because the routine differentiation of *C. gattii* infections from those caused by *C. neoformans* is not a standard practice in many parts of the world. This stems from the fact that the cryptococcosis caused by the two pathogens is not pathognomonic, and that laboratory reagents such as serotyping kits and the specialized culture media, needed to distinguish the two are not easy to commercially obtain. Additionally, many of the genotyping strategies described for the differentiation of two pathogens are only suitable for specialized laboratories. Given these limitations, our understanding of the occurrence and prevalence of *C. gattii* cryptococcosis is expected to remain biased and underestimated unless species differentiation can be integrated into the routine workflow of clinical laboratories.

Recent outbreaks of *C. gattii*

An ongoing outbreak of *C. gattii* cryptococcosis in Vancouver Island, British Columbia, Canada has greatly expanded our understanding of *C. gattii* cryptococcosis¹⁰. This outbreak originated in 1999, suggesting that the fungus has either recently spread or reappeared in a hospitable environment. Vancouver Island has a distinct climate from the rest of Canada (in the temperate climate zone) similar to other *C. gattii* affected areas such as Australia, Spain, South Africa and Southeast Asia, all of which have dry summer subtropical or Mediterranean climates^{46, 47}. Douglas fir and western hemlock trees in Vancouver Island

have a high colonization of *C. gattii* similar to the fungal association with other tree species worldwide^{47, 48}. Moreover, in addition to humans, a number of animals have either been infected or asymptomatically carry the fungus, which suggests that *C. gattii* has a wide host range^{43, 49, 50}. Prior to 2010, there were 218 cases of *C. gattii* cryptococcosis identified in British Columbia, Canada with a rather high human case fatality rate of nearly 9%, which led to a sustained public health effort to increase the awareness among healthcare professionals and the public³⁰.

True to an often repeated maxim 'infectious diseases know no geographical boundaries', the *C. gattii* outbreak has also been recognized in the neighboring Pacific Northwest area of the United States with 52 patients reported between 2004 and 2009^{51, 52}. Unlike Vancouver Island, areas of California and Washington State were already known to harbor *C. gattii* and it is not clear if the recent outbreak represents a spread of the outbreak strain from Vancouver Island or a re-emergence of local strains^{5, 8, 53}. The last point is critical considering that a strain very similar to the Vancouver Island major genotype was isolated from the sputum of a patient from Seattle, WA, in 1970¹⁹. Additional details of the *C. gattii* outbreak in the US are being vigorously investigated considering the high case fatalities (20%) documented so far⁵¹.

There have been no other recent outbreaks reported from parts of the world with documented *C. gattii* cryptococcosis although a recent study raises the possibility of a widespread Australian outbreak¹⁴. Similarly, high incidence of endemic *C. gattii* cryptococcosis has been reported from children in Eastern Amazon areas of Brazil¹³. It would be prudent to plan surveillance studies in relevant geographical areas by means of seroepidemiological and natural surveys to catch early signs of the resurgence of this pathogen.

Ecology of *C. gattii*

Many years after its first recovery from clinical specimens, *C. gattii* was isolated from the environment for the first time by sampling of *Eucalyptus camaldulensis* trees⁵⁴. This tree species was initially thought to be the exclusive natural habitat of *C. gattii* both in its native Australia and around the world given that the tree has been exported extensively. However, after a decade and a half, it became clear that trees beside *E. camaldulensis* also harbor *C. gattii*⁵⁵. A key finding was that the decaying hollows in trunks and branches of a number of tree species are the preferred habitat of the fungus⁵⁶. Tree and tree hollows represent a specialized niche for basidiomycetous yeasts of the genera *Cryptococcus*, and presumably, they offer selective advantages in competition vis-à-vis other microbes⁵⁷. This association with trees has held true worldwide, including the most recent major outbreak in North America that encompasses the Douglas fir-Western Hemlock biogeoclimatic zones^{47, 48}. To date, more than 50 tree species have been reported as harboring the fungus⁴⁸. The fungus has also been found in the air, the soil, and bodies of water in heavily infested areas⁵⁸. An equally important corollary is that the fungus has not been recovered with any regularity from pigeon guano, which is a well-known ecological niche for *C. neoformans*; *C. gattii* has been shown to be unable to complete mating on this substrate⁵⁹.

Experimental studies provide further proof of a *C. gattii* ecological niche in trees: the fungal cells can survive and proliferate on inoculated almond seedlings (*Terminalia catappa*) and on plant derived-substrates, such as leaves and wood^{60, 61}. *C. gattii* can complete its sexual cycle on experimentally inoculated *Arabidopsis thaliana* plants (Thale cress or mouse ear cress), and the fungus makes special structures (extracellular fibrils) that are hypothesized to be important for plant colonization and animal virulence^{62, 63}.

The use of sophisticated modeling tools has revealed that drier coastal areas at an elevation of approximately 100 meters, January temperatures of 2.8°C, and the predominance of Douglas fir (*Pseudotsuga menziesii*) and western hemlock (*Tsuga heterophylla*) trees were characteristics of a *C. gattii* ecological niche in outbreak areas of British Columbia⁴⁷. Future studies should focus on how *C. gattii* colonizes trees and what role this colonization plays in the fitness of the fungus for mammalian virulence. This ecological knowledge will be valuable in clarifying certain epidemiological aspects of *C. gattii* cryptococcosis such as the likely natural reservoirs of this pathogen and the role that outdoor occupations or recreational activities might play in exposure to *C. gattii* (Figure 3).

***C. gattii* virulence mechanisms**

We know a great deal about the different structural and regulatory elements of *C. neoformans* that help to make it a successful pathogen. Capsular polysaccharide, melanin pigment, thermal tolerance, cellular signaling pathways, strategies to parasitize host phagocytes and mechanisms to breach the blood-brain barrier are all critical for *C. neoformans* virulence³⁶. It is safe to extrapolate that these attributes are equally critical for virulence in *C. gattii* due to the close proximity of these sibling species. However, distinctions in these traits or some yet unrecognized virulence factors must exist to explain unique features of cryptococcosis caused by *C. gattii*.

Published studies have indicated that some *C. gattii* virulence attributes subtly differ from those seen in *C. neoformans*. The clues to these distinctions resulted from the finding that *C. gattii* is able to arrest migration of neutrophils under laboratory conditions and in infected animals; such an effect on neutrophils would explain why healthy people could fall victim to this infection⁶⁴. Further investigations in animal models revealed that *C. gattii* metabolites especially acetoin and dihydroxyacetone, elicit less pro-inflammatory responses than do *C. neoformans* metabolites thereby promoting fungal survival and multiplication in the infected host^{65, 66}. The prominent antioxidant superoxide dismutase (SOD1p) in *C. gattii* protects the functional integrity of a number of virulence factors. Further experiments showed that SOD1p is required for infection in an animal model and for protection from killing by human phagocytes; some of these cellular functions differ remarkably from a homologous protein in *C. neoformans*^{67, 68} (Table 1). The mitochondrial superoxide dismutase (SOD2p) was equally critical for growth at 37°C and virulence (inhalation model) for both *C. gattii* and *C. neoformans*^{69, 70}. Trehalose is another important antioxidant and stress protectant in fungi. Two genes encoding the key biosynthetic enzyme trehalose-6-phosphate (T6P) synthase (TPS1p, and TPS2p), were found to be critical for thermotolerance, virulence and the integrity of various virulence factors such as the capsule and melanin of *C. gattii*. The homologous proteins in *C. neoformans* were essential for thermotolerance, but not for expression of capsule and melanin^{71, 72}. Functional divergence was again seen in transcription factor Ste12α, which regulated mating, melanin, virulence and ecological fitness in *C. gattii*, but only mating and capsule size in *C. neoformans*^{61, 73}. Thus, there is a closer link between some important cellular processes and virulence in *C. gattii*, which is not the case for similar processes in *C. neoformans*.

An interesting evolutionary switch in functions has been documented for *C. gattii* and *C. neoformans* Gα protein cAMP-protein kinase A (Pka1p and Pka2p). Pka1p controls mating, capsule, melanin and virulence in *C. neoformans*, but only influences capsule production in *C. gattii*. Pka2p regulates mating, capsule and melanin in *C. gattii* while the corresponding protein has no such role in *C. neoformans*^{74, 75}. These studies have elegantly connected *C. gattii* – *C. neoformans* speciation to ‘rapid re-wiring’ of a key cellular signaling pathway⁷⁵.

Although functional differences among four *C. gattii* genotypes are not yet fully known, a good beginning was recently made when a group of highly virulent strains was found to differ from other *C. gattii* strains in their ability to parasitize phagocytes more effectively via increased activity of their mitochondria⁷⁶. Most recently, *C. gattii* was found to make extracellular fibrils on plant surfaces that impart an increased ability to evade killing by human neutrophils in laboratory tests⁶³. This mechanism could possibly allow the fungus to more readily colonize lungs in infected individuals by avoiding initial attack by phagocytes. The emerging theme from molecular pathogenesis is that the two sibling pathogens have evolved to use similar genes for different purposes tailored to different environments and pathogenic modes. Less progress has been made to find *de novo* virulence traits in *C. gattii*; this could be either because such factors do not exist, or, more likely, is due to the lack of incisive experiments attempted so far. In either case, basic experimental tools are now available to carry out detailed host-pathogen analyses of *C. gattii* cryptococcosis to discover the reason for its unique virulence.

Hypervirulent clone(s) in North America?

C. gattii genotypes have been co-opted as tools for tracking down strains from recent outbreaks and for the determination of the ancestry of virulent strains. A rare *C. gattii* genotype (VGII) was found among clinical and environmental strains collected in connection with the outbreak of *C. gattii* cryptococcosis on the Vancouver Island^{77, 78}. It was further suggested that *C. gattii* strains from Vancouver Island comprised two sub-genotypes (VGIIa and VGIIb)^{77, 78}. The *C. gattii* VGIIa strains were abundant in the outbreak, tested hypervirulent in mice and presented genetic evidence of spread from Australia to Canada by means of clonal expansion⁷⁸. A more recent analysis along similar lines suggested that a *C. gattii* outbreak in the Pacific Northwest included the Vancouver Island outbreak major sub-genotype VGIIa, as well as a new hypervirulent sub-genotype VGIIc, which possibly emerged by recombination events in the VGIIa strains¹¹. Thus, there is strong analytical evidence to suggest that reassortment of genetic information either by asexual or sexual processes could lead to the emergence and rapid expansion of hypervirulent *C. gattii* strains in a new locale.

The insightful discoveries on the emergence of hypervirulent clones cannot be fully reconciled with other published data. The type strain of Vancouver Island outbreak R265, is very similar in genotype and virulence attributes of a clinical strain NIH444, which was reported from Seattle, WA, in 1970^{19, 79}. Furthermore, the hypervirulence trait is shared by many VGIIa strains collected from clinical and environmental sources in different parts of the world⁸⁰. Paradoxically, the hypervirulence trait documented by mouse experiments seems to have no bearing on the course of human disease as both VGIIa and VGIIb strains cause similar morbidity and mortality among patients in the Vancouver Island outbreak³⁰. Clearly, much more remains to be done to elucidate if the *C. gattii* genotypes are uniform predictors of hypervirulence and emergence of outbreak strains, and if genotypes have important bearing on the course of cryptococcosis.

Concluding remarks

With the recent outbreaks in North America, *C. gattii* has finally caught the attention of healthcare professionals in its own right. While it might take awhile for reagents and diagnostic procedures to catch up with the clinical need for rapid and routine differentiation of *C. neoformans* from *C. gattii*, this is an important challenge for clinical laboratories to address. In addition, the new guidelines for *C. gattii* disease will hopefully mean that clinicians can better treat cryptococcosis and that they will look for clusters of *C. gattii* cases, which suggest a common origin. A parallel awareness in veterinary medicine would

ensure prompt diagnosis and treatment of domestic animals. The recent rise in the incidence of infections in North America and Australia promises that biomedical researchers will devote greater resources to investigations of the host-pathogen factors that underlie *C. gattii* disease (Box 1). Such efforts would benefit greatly by the expected rapid expansion of knowledge on the genomics of this pathogen.

Acknowledgments

We are grateful for the contributions of the following individuals: Andrew J. Hamilton, Birgit Stein (née Rodeghier), Brian L. Wickes, the late Charles Lowry, Ping Ren, Srinivas D. Narasipura, Soumitra K. Saha, Jinjiang Fan, Madhu Dyavaiah, Deborah J. Springer, Manoj Iyer, Guan Zhu, Melissa J. Behr, and William A. Samsonoff. We also thank an anonymous reviewer for many suggestions for the improvement of this manuscript. Investigations in our laboratories were supported with funds from the National Institutes of Health (AI-41968, AI-48462, AI-05887701 and AI-053732), Pfizer Inc., and the Clinical Laboratory Reference Systems of the Wadsworth Center. The authors apologize to those whose studies could not be included as the citation of published literature is selective due to space limitations.

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Box 1. Outstanding questions

- In some parts of the world, *C. gattii* cryptococcosis has been reported, but there have been no isolations of the fungus; or, the converse is true. What causes these disconnect between ecology and epidemiology?
- Do forested or semi-forested areas pose higher risks for *C. gattii* infection?
- Are some trees species particularly prone to *C. gattii* colonization? Do interactions with plants make *C. gattii* more pathogenic?
- Do *C. gattii* genotypes other than VGII have hypervirulent strains? Are hypervirulent strains clonal or undergo asexual or sexual assortment of characters?
- Are current genotyping methods sufficient or are more refined typing methods are needed based on whole genome analyses?
- How common are asymptomatic infections, especially in people and animals living in areas of high incidence, and what triggers re-activation of the infection?
- Do neutrophils fight or flee in response to *C. gattii* infection? Are some phagocytes more important than others?
- Are *C. gattii* cells evolving in response to antifungals and are instances of clinical or laboratory resistance not currently recognized?
- What are the intricate details of the capsular material and its organization in *C. gattii*?

Figure 1.

C. gattii under the microscope. Some photographs courtesy of Ping Ren and Sunanda S. Rajkumar. (a) Yeast cells are round (R form) or rod-shaped (B form) in fungal culture [NIH444 (ATCC 32609), Serotype B, *MAT α* , *VGIIa*] grown on yeast-peptone dextrose agar at 30°C for 24-hrs and imaged by differential interference contrast (DIC) microscopy (Bar = 6.25 μ m). (b) More details of yeast cells seen with a scanning electron microscope [scanning electron microscopy (SEM), Bar = 2.0 μ m]. (c) When two sexually compatible yeast cultures (NIH444 {*MAT α* } X NIH198 {*MATa*}) are grown under dry conditions and nitrogen limitation, they produce characteristic slender thread-like structure (hypha) with bulb-like head (basidium) bearing sexual spores (basidiospores, thick arrow); also seen is a clamp connection (thin arrow) between two hyphal segments. Some yeast cells (gray arrow) can also be seen in the same field (Bar = 6.25 μ m). (d) SEM image of hyphal segment (arrow) with clamp connection (Bar = 2.0 μ m). (e) Further SEM images highlighting basidium and basidiospores (Bar = 1.0 μ m). (f) Yeast cells make large capsules when they are in tissues as seen here in a DIC image of lung tissue from an infected mouse (Bar = 6.25 μ m).

Figure 2.

Serotypes and genotypes of *C. gattii* and *C. neoformans*. *C. gattii* strains are either serotype B or C; BC serotype strains have been rarely reported. *C. neoformans* variety *grubii* strains are serotype A while *C. neoformans* variety *neoformans* strains are serotype D; the taxonomic status of AD serotype strains is not clear. *C. gattii* and *C. neoformans* genotypes are based upon multilocus sequence typing of various gene fragments. *C. gattii* outbreaks in North America are variably linked to VGII sub-genotypes. Details of *C. neoformans* VNI sub-genotypes are not shown.

Figure 3.

Suggested natural cycle of *Cryptococcus gattii* and events leading to cryptococcosis. The available information indicates the pathogen can cycle through plants, soil, air and water without any intermediate live hosts (solid line with arrows). Yeast cells of either mating type (*MATa* or *MATα*) have been repeatedly isolated from trees especially hollows (solid circle); it is not yet known if cells of *C. gattii* complete their sexual cycle in nature as has been shown in the laboratory (dotted circle). Humans and animals (domestic and wildlife) coming in contact with fungal propagules (yeast cells or sexual spores) mostly remain asymptomatic (dotted lines with arrows), but a small number of infected humans and animals develop serious infections of the lungs and brain. These drawings are not to exact scale. Graphic artist: Andrew Bentley.

Table 1

The evolution of cell functions in similar proteins as revealed by gene knockout mutants of *C. gattii* (Cg) and *C. neoformans* (Cn)^a

Target gene	Cellular function	Fungus	Fungal features examined ^b					Ref.
			37°C growth	Capsule	Melanin	Mating	Virulence	
<i>SOD1</i>	Cytoplasmic antioxidant	Cg Cn	↔ ↔	↓ ↔	↓ ↔	↔ ND	↓ ↓	67, 68
<i>SOD2</i>	Mitochondrial antioxidant	Cg Cn	↓ ↓	↔ ND	↔ ND	↔ ND	X X	69, 70
<i>TPS1</i>	Trehalose biosynthesis pathway	Cg Cn	↓ ↓	↓ ↔	↓ ↔	↓ ND	↓ X	71, 72
<i>TPS2</i>	Trehalose biosynthesis pathway	Cg Cn	X ↓	↓ ↔	↓ ↔	↔ ND	↓ ↔	71, 72
<i>PKA1</i>	Regulation of cellular pathways	Cg Cn	ND ND	↓ X	↔ X	↔ X	ND X	74, 75
<i>PKA2</i>	Regulation of cellular pathways	Cg Cn	ND ND	↓ ↔	↓ ↔	↑ ↔	ND ND	74, 75
<i>STE12a</i>	Regulation of mating	Cg Cn	ND ↔	↔ ↓	↓ ↔	↓ ↓	↓ ↔	61, 73

^a *C. neoformans* refers to *C. neoformans* var. *grubii*.

^b Abbreviations: ND, not done; ↔, no change; ↓, reduced; ↑, enhanced; X, absent.

Glossary	
Antioxidant	A molecule or compound that prevents or neutralizes oxidative stress caused by reactive oxygen species.
Autochthonous	Indigenous or native in origin; not imported.
Bacilliform	Shaped like a <i>Bacillus</i> bacterium, rod-shaped.
Clamp connection	A tube-like connection between two segments of a hypha to ensure that differing nuclei are equally distributed during the cell division.
Clonal	Derived from mother cell by asexual reproduction.
Cryptococcosis	Lung and brain infections caused by fungi <i>Cryptococcus gattii</i> or <i>Cryptococcus neoformans</i> .
Ecological niche	The specialized space in the environment where an organism lives and interacts with living and non-living objects in its surroundings.
Endemic	Native to or originating from a geographical area.
Genotype	The genetic makeup revealed by a biological assay.
Hybrids	Offspring resulting from crossing of dissimilar parent cells
Immunocompetent	Possessing a functioning immune system that mounts effective host defense to infection.
Immunocompromised	Unable to mount effective host defense to infection due to underlying immunodeficiency or immunosuppressive treatment.
Mating type	Genetic characteristics that distinguish two sexually compatible cells that appear similar in morphology.
Meningoencephalitis	Inflammation of the brain and surrounding membrane.
Neutrophils	Abundant white blood cells that play important role in immune defense via their ability to engulf and destroy pathogenic microbes.
Opportunist pathogen	A fungus that is only able to cause disease in an immunocompromised host.
Outbreak	A sudden increase in the incidence of an infection not expected in an area or at a particular period of time.
Pathogenicity	The ability of a fungus to produce disease in a given host.
Primary pathogen	A pathogen that is able to cause disease in apparently healthy host.
Phagocytosis	The process of engulfment of a pathogenic microbe by immune response cells or phagocytes.
Recombination	An assortment of genes or characteristics in offspring that distinguish the offspring from their parents.
Serotype	Characteristic surface antigens that permit closely related microbes to be distinguished by means of antibodies.
Virulence	The degree of pathogenicity of a fungus in a given host.