

The function and evolution of the *Aspergillus* genome

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Species in the filamentous fungal genus *Aspergillus* display a wide diversity of lifestyles and are of great importance to humans. The decoding of genome sequences from a dozen species that vary widely in their degree of evolutionary affinity has galvanized studies of the function and evolution of the *Aspergillus* genome in clinical, industrial, and agricultural environments. Here, we synthesize recent key findings that shed light on the architecture of the *Aspergillus* genome, on the molecular foundations of the genus' astounding dexterity and diversity in secondary metabolism, and on the genetic underpinnings of virulence in *Aspergillus fumigatus*, one of the most lethal fungal pathogens. Many of these insights dramatically expand our knowledge of fungal and microbial eukaryote genome evolution and function and argue that *Aspergillus* constitutes a superb model clade for the study of functional and comparative genomics.

***Aspergillus*: the 'Dr Jekyll and Mr Hyde' genus of fungi**

There is probably no genus better suited than *Aspergillus*, an important and efficient saprophytic genus found in diverse environments, to illustrate how inextricably intertwined fungi are with human affairs. Its Mr Hyde personality is exemplified by species such as *Aspergillus fumigatus*, responsible for the highest number of deaths from fungi and the second highest number of human infections from fungi [1]; *Aspergillus flavus*, the opportunistic but very destructive agricultural pest that contaminates several crops with the potent carcinogen aflatoxin, causing major crop yield losses and a few deaths per year [2]; or *Aspergillus sydowii*, the opportunistic pathogen of Caribbean gorgonian coral communities, whose recent outbreak of infection threatens the collapse of this fragile ecosystem [3]. By contrast, no species better illustrate its Dr Jekyll side than *Aspergillus niger*, a biotechnological 'cell factory' widely used in the food industry [4,5]; *Aspergillus nidulans*, an important model for eukaryotic genetics and cell biology [6]; or the several *Aspergillus* species that drive production of beverages and sauces in the Far East: among others, *Aspergillus oryzae* is used in the making of sake [7], *Aspergillus sojae* in the production of soy sauce [8], and *Aspergillus kawachii* in the brewing of the spirit shochu [9].

First described nearly 300 years ago by the priest and botanist Antonio Micheli, *Aspergillus* got its name from the resemblance of its asexual spore-forming structure to the

aspergillum, an instrument used to disperse holy water in some Christian liturgical services. *Aspergillus* is thus the name that describes the asexual cycle of the fungus. Because the phenotypic diversity of the sexual fruiting bodies is greater, ten different genera describe the sexual cycles of *Aspergillus* species [10] (Figure 1). For example, *A. nidulans* and *A. fumigatus* describe the asexual cycles of these species, whereas *Emericella nidulans* and *Neosartorya fumigata* are their sexual counterparts. Most commonly, species in the genus are referred to as *Aspergillus* species, which is practical given that only a third of *Aspergillus* species are known to have a sexual cycle [10]. In their classic 1965 treatise on the genus, Raper and Fennell recognized 132 species [11], but the systematic application of a polyphasic approach that uses morphological, physiological, and molecular data to identify and classify new species, including several cryptic ones, has resulted in the present circumscription of more than 250 species [12]. The pace of discovery of new species continues unabated with approximately 50 new species having been described this century [12]. This genomics-enabled systematic revision of the *Aspergillus* taxonomy has dramatically influenced the design and application of molecular techniques to identify medically important *Aspergillus* [13], but also aided the identification of new clinically relevant species [14].

The early decoding of the genomes from some of the species currently available [4,15–18], their widely varying degree of evolutionary affinity [6,18,19], as well as the advent of novel molecular (e.g., [20–22]) and computational (e.g., [23,24–26]) tools, have dramatically accelerated *Aspergillus* 'omics' research and the pace of discovery in genome-wide functional and evolutionary studies (e.g., [7,27–33]). Here, we describe the current status of genomics research on *Aspergillus* and synthesize recent key findings in three key areas, namely genome architecture, secondary metabolism, and virulence, that not only dramatically expand our understanding of the function and evolution of the *Aspergillus* genome, but also argue that *Aspergillus* represents a model clade for the study of eukaryote comparative functional genomics.

A cornucopia of genomes and lifestyles

With the genomes from 14 species already publicly available (Figure 1), *Aspergillus* is the most genome sequenced-rich fungal genus, surpassing even the genome sequenced-rich *Saccharomyces* and *Candida* yeasts [34]. *Aspergillus* is likely to continue holding on to this distinction because the

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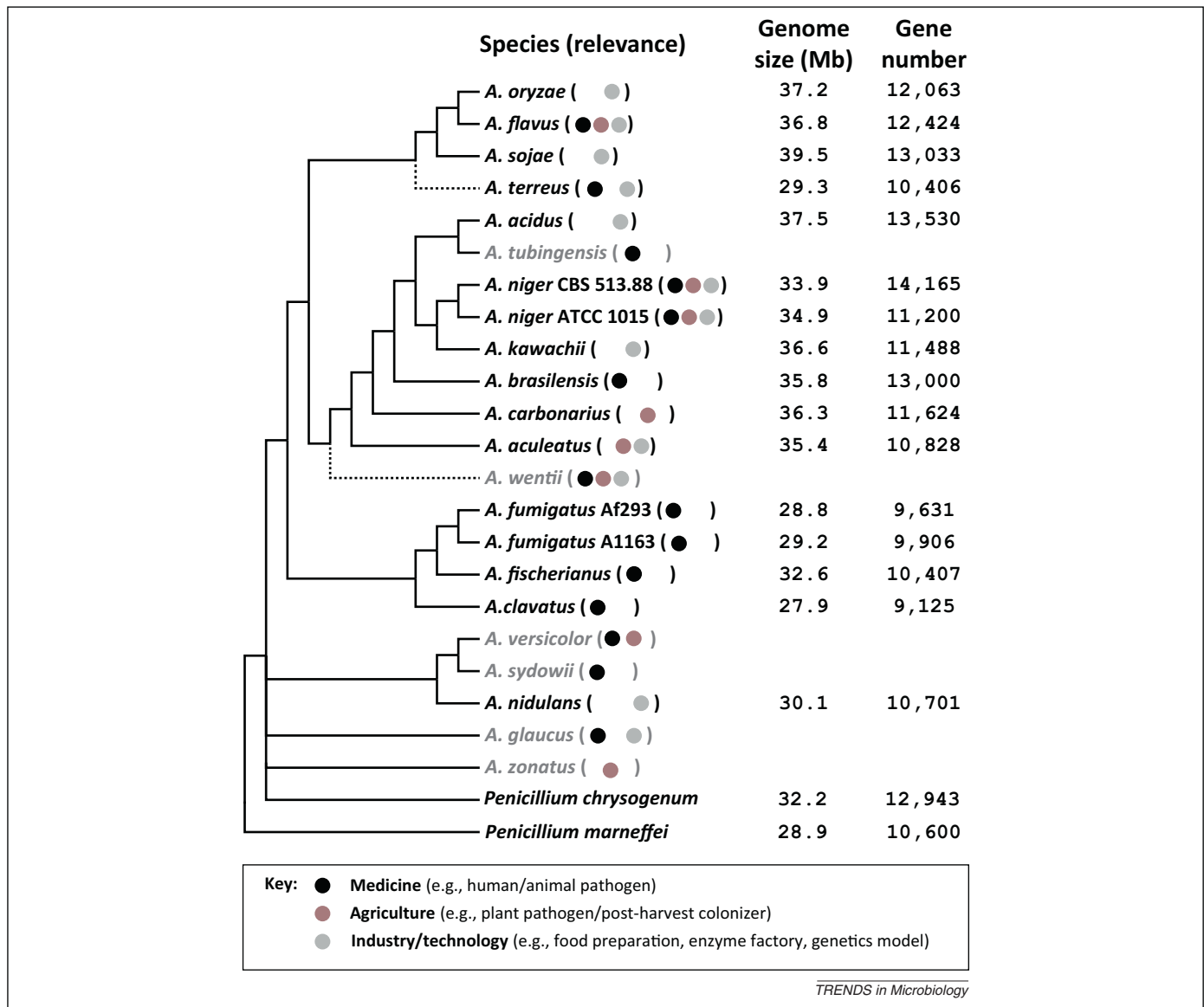


Figure 1. Evolutionary relationship, relevance, and content of available and in progress *Aspergillus* genomes. The phylogeny of *Aspergillus* genomes was synthesized from the phylogenies described by Houbraken and Samson [37], Geiser and coworkers [35], Peterson [36], and Rokas and Galagan [6]. Broken line branches indicate uncertainty about their placement on the phylogeny. Genome size and gene number data are from the published genome analyses [4,8,9,15–18,42,94]; for unpublished genomes, these values were obtained from the Joint Genome Institute (JGI) genome portal [41] (*A. acidus*, *A. aculeatus*, *A. brasiliensis*, *A. carbonarius*, and *A. tubingensis*) or the Broad Institute's *Aspergillus* Comparative Database (*A. flavus* and *A. terreus*).

US Department of Energy Joint Genome Institute (JGI), as part of its 2011 community sequencing proposal mechanism, approved a multi-investigator proposal and is currently sequencing the genomes of eight additional species (Figure 1), including the coral pathogen *A. sydowii* and the xerophile *Aspergillus glaucus*. The panel of currently available genomes includes a good sample of the diversity of the fungi comprising *Aspergillus*: the model organism *A. nidulans*, the 'cell factory' *A. niger*, the human pathogens *A. fumigatus* and *Aspergillus terreus*, the human pathogen and agricultural pest *A. flavus*, as well as the fermenters *A. oryzae*, *A. sojae*, and *A. kawachii*. Importantly, there appears to be no association between lifestyle and evolutionary affinity. For example, *A. oryzae* is a domesticated ecotype of *A. flavus* and their genomes share 99.5% identity, yet the first is used in the making of several traditional Far Eastern sauces and beverages and has a Generally

Regarded as Safe label by the US Department of Agriculture, whereas the second is a destructive agricultural pest and potent mycotoxin producer [7,19]. Similarly, the top three most common human pathogens, *A. fumigatus*, *A. flavus*, and *A. terreus*, do not group together in the *Aspergillus* family tree and all possess relatives that rarely, if ever, infect humans (Figure 1) [35–37]. This lack of association between lifestyle and evolutionary affinity is probably because many of the traits render fungi into potent pathogens, agricultural pests, or cell factories, are generally associated with the saprophytic lifestyle and selected for survival in conditions independent of their current roles in pathogenesis, pestilence, or biotechnology.

Although no database contains all 14 available *Aspergillus* genomes, most are available from several, including the *Aspergillus* Genome Database (AspGD) [25], FungiDB [38], Central *Aspergillus* Data REpository (CADRE) [39],

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