Clinical Commentary Review

Taxonomy of Allergenic Fungi

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The Kingdom Fungi contains diverse eukaryotic organisms including yeasts, molds, mushrooms, bracket fungi, plant rusts, smuts, and puffballs. Fungi have a complex metabolism that differs from animals and plants. They secrete enzymes into their surroundings and absorb the breakdown products of enzyme action. Some of these enzymes are well-known allergens. The phylogenetic relationships among fungi were unclear until recently because classification was based on the sexual state morphology. Fungi lacking an obvious sexual stage were assigned to the artificial, now-obsolete category, "Deuteromycetes" or "Fungi Imperfecti." During the last 20 years, DNA sequencing has resolved 8 fungal phyla, 3 of which contain most genera associated with important aeroallergens: Zygomycota, Ascomycota, and Basidiomycota. Advances in fungal classification have required name changes for some familiar taxa. Because of regulatory constraints, many fungal allergen extracts retain obsolete names. A major benefit from this reorganization is that specific immunoglobulin E (IgE) levels in individuals sensitized to fungi appear to closely match fungal phylogenetic relationships. This close relationship between molecular fungal systematics and IgE sensitization provides an opportunity to systematically look at cross-reactivity and permits representatives from each taxon to serve as a proxy for IgE to the group. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:375-85)

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The Kingdom Fungi contains diverse eukaryotic organisms including molds, yeasts, mushrooms, bracket fungi, plant rusts, smuts, and puffballs. Fungi have a complex metabolism that differs from animals and plants; they secrete enzymes into their surroundings and absorb the breakdown products of enzyme action. Some of these enzymes are well-known allergens.[1]

True fungi have cell walls that contain chitin (with rare exceptions) and β-(1→3) and β-(1→6) glucans, unlike plant cell walls that contain cellulose, a β-(1→4) glucan, as the structural component.[2] Fungal surfaces have a wide array of molecules that are important targets for recognition by the innate immune system. In addition to β glucans, fungal cell walls contain chitin, mannans and mannoproteins, and galactomannans. Fungi may be unicellular such as yeast, but typically have a thread-like or tube-like body composed of hyphae, which range from 2 to 10 μm in diameter. Hyphae grow at their tips and frequently branch resulting in an interconnected network of hyphae called a mycelium.

Fungi reproduce by producing spores, many of which are adapted for airborne dispersal. Spores may be produced by either meiosis or mitosis. Spores produced by meiosis are associated with sexual reproduction (teleomorphic stage) and are produced in various structures that are characteristic of each fungal phylum. Among allergenic fungi, most spores produced by mitosis are formed on differentiated hyphae or conidiophores and are called conidia. These are associated with the anamorphic (asexual) stage of the life cycle.[3]

FUNGAL TAXONOMY

The phylogenetic relationships among fungi were unclear until recently. Classification was based on the sexual state morphology so fungi lacking an obvious sexual stage were assigned to an artificial, now-obsolete category, called the Deuteromycetes or Fungi Imperfecti. During the last 20 years, DNA sequencing has resolved 8 phyla of fungi, of which 3 are associated with the production of important aeroallergens (Figure 1).[4-7] As a result, the category Deuteromycetes has been discarded, and other fungus-like organisms such as slime molds (myxomycetes) and water molds (oomycetes) moved to other kingdoms.

Advances in classifying fungi have required name changes for some familiar taxa. For example, *Penicillium notatum* is now a defunct name and isolates formerly known by this name are now recognized as closely related species including *P. chrysogenum* and *P. rubens*. Because of regulatory constraints, many fungal allergen extracts have retained obsolete names.

Three phyla Zygomycota, Ascomycota, and Basidiomycota contain most genera of fungi that produce airborne fungal allergens (Figure 2).[4,8] A major benefit from this reorganization is that specific immunoglobulin E (IgE) levels in individuals

Abbreviations used
IgE- Immunoglobulin E
IUIS- International Union of Immunological Societies

sensitized to fungi appear to closely match their phylogenetic relationships. This close relationship between molecular fungal systematics and IgE sensitization to fungal species provides a systematic way to look at cross-reactivity and permits representatives from each taxon to serve as a proxy for IgE to the group.[8,9]

The fungal genera described below each have species that produce substances that can adversely affect humans, causing allergic rhinitis and asthma among other disorders. A number of fungal-derived allergens have been identified from these species (Figure 3, Table E1, available in this article's Online Repository at www.jaci-inpractice.org) and are listed in the International Union of Immunological Societies (IUIS) nomenclature for allergens (see IUIS, Structural Database of Allergenic Proteins database, AllFam database, and Allergome database).[10] The noninfectious role of fungi is emphasized in this review.

Phylum Zygomycota

The phylum Zygomycota contains approximately 1000 species with 4 distinct evolutionary lines.[4] The largest and best studied is the subphylum Mucoromycotina that includes the agents of human mucormycosis (formerly zygomycosis).[11] Most species in the Mucoromycotina are saprobes commonly found in soil, compost, stored grain, fruit, vegetables, and dung. They form sporangia for asexual reproduction. Sporangiospores formed within a sporangium typically become airborne. This group is well known for producing abundant sporangia. Several species are used in food production and biotechnology, especially in cheese making and in the production of fermented foods.

Mucor. *Mucor racemosus* is a dimorphic, facultative anaerobic zygomycete, capable of vegetative growth in either a filamentous phase or as spherical yeasts. *M. racemosus* has been shown to induce sensitization in some individuals as demonstrated by skin-prick and provocation tests[9] as well as symptoms of asthma and rhinitis. In addition to homes, *Mucor* has been detected in schools,[12] hospitals,[13] and water-damaged buildings.[14]

Rhizopus. Species of *Rhizopus* are rapidly growing filamentous fungi that are characterized by the presence of rhizoids at the base of the sporangiophores. Colonies appear grayish because of abundant black sporangia.[15] The genus currently contains 10 species.[16] Several species are widely used in preparing fermented foods and in the pharmaceutical industry. Spores of *Rhizopus* tend to disperse in hot, dry weather.[17] *Rhizopus stolonifer*, commonly known as bread mold, is the most common species of *Rhizopus*. This species has been associated with allergy.[18] Allergens of both *R. stolonifer* (syn. *R. nigricans*) and *R. oryzae* have been characterized with both species showing multiple allergenic proteins.[18,19] In addition to IgE sensitization, reported health effects due to *Rhizopus* include rhinitis, asthma, fungal sinusitis, hypersensitivity pneumonitis, and infection.[20] Occupational exposure can occur among food handlers during the storage, transfer, and marketing of strawberries, peaches, cherries, corn, and peanuts.[21]

Phylum Ascomycota

The phylum Ascomycota is estimated to contain 65,000 species. Fungi in this phylum vary from single-celled yeasts to organisms with large fruiting bodies and grow in diverse habitats around the globe as saprobes, pathogens, and mutualistic symbionts. At least 30,000 species occur as the fungal symbionts of lichens.[22] Some cause devastating plant diseases including Dutch elm disease, chestnut blight, powdery mildews, *Alternaria* blight and leaf spot disease, and *Fusarium* head blight.[23] Many human pathogens are also in this phylum including *Aspergillus, Candida, Coccidioides, Histoplasma, Pneumocystis*, and *Trichophyton*.[24]

The defining characteristics are the meiotic ascospores, which are produced within asci (sing, ascus) and often occur in fruiting bodies. Some fruiting bodies are microscopic, whereas others such as morels and truffles are relatively large.[25] In many species, the ascospores are expelled from the asci after rain or during periods of high humidity. As a result, ascospores are often abundant in the air spora after rain. Conidia produced by many members of this phylum are dispersed by wind and often constitute a large component of the air spora; these include many well-known allergenic fungi.

Candida. *Candida albicans* is a yeast and one of the most prominent fungal members of the human microbiome.[26] It is also known to occur in soil and organic debris. *Candida* is known to cause clinically significant opportunistic infections such as thrush in infants, skin infections in diabetic patients, and sepsis in immunocompromised patients.[27,28] Sinonasal polyposis has been associated with hypersensitivity to *C. albicans*.[29] *Candida* is rarely found in surveys of airborne spores. The fungus has a major protein allergen (46 kD) and 15 minor allergens.[30]

Saccharomyces. *Saccharomyces cerevisiae*—baker's yeast or brewer's yeast—ferments sugars, releasing carbon dioxide (CO_2) and alcohol (ethanol) in the process.[31] *S. cerevisiae* exposure is associated with allergic rhinitis, asthma, and atopic dermatitis in sensitized individuals,[32,33] as well as hypersensitivity pneumonitis[34] and baker's asthma.[35] At least 9 allergens have been well characterized from *S. cerevisiae* (www.allergome.org).

Geotrichum. *Geotrichum* species, including *Geotrichum candidum*, can be found worldwide in soil, water, air, and sewage, as well as in plants, cereals, and dairy products. It is also part of the normal human microbiome, particularly in sputum and feces. *Geotrichum* is the causative agent of geotrichosis, an opportunistic infection facilitated by immunocompromised individuals and can present as bronchial, oral, vaginal, cutaneous, and alimentary infections.[36] Along with other molds, *Geotrichum* has been implicated in allergic symptoms in librarians.[37]

***Cladosporium* (obsolete *Fulvia* or *Hormodendrum*).** *Cladosporium* contains more than 750 species; some are the most common indoor and outdoor fungi.[38] Species of *Cladosporium* typically produce olive-green to brown or black colonies, and have pigmented conidia formed in simple or branched chains (Figure 2, *A*). Species of *Cladosporium* are commonly found on living and dead plant material. Many species are plant pathogens, whereas some parasitize fungi.[39]

Spores vary in size (5-40 × 3-13 μm), and they have a variety of shapes and cell numbers. The spores are wind-dispersed and are often extremely abundant in outdoor air. During summer, daily peaks may range from 2000 to 50,000 spores per cubic

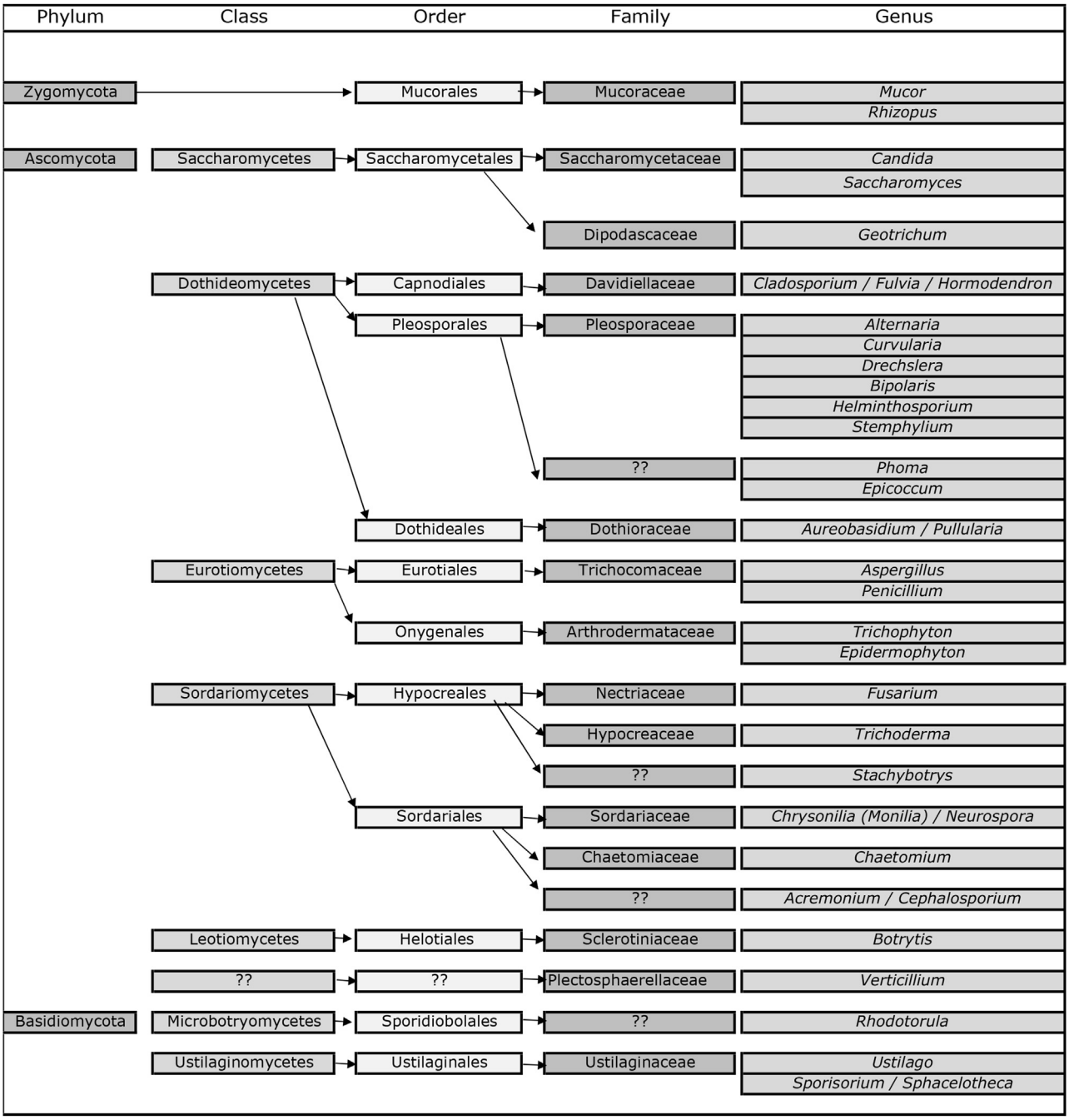

FIGURE 1. Taxonomy of the 3 fungal phyla associated with important aeroallergen production based on DNA sequencing.

meter of air.[40] They are present in the outdoor environment throughout the year in temperate climates; however, concentrations tend to be low during winter.

The concentration of *Cladosporium* spores in indoor air is influenced by outdoor concentrations and, if present, by indoor growth sources. Nonporous surfaces subject to condensation often become colonized by *Cladosporium*. Two species, *Cladosporium spherospermum sensu stricto* and *C. halotolerans*, grow on wet building materials. These are not the same as the familiar species from outdoor air.[41] Other members of the genus prefer cooler growth temperatures and are capable of growth at low water activity[41] such as in non—water-damaged buildings.[42]

Cladosporium spores are known to have a number of allergens that severely affect sensitized people with allergic rhinitis and asthma.[43] The most important *Cladosporium* allergens are Cla h 1 and Cla h 2, both from *C. herbarum*. The allergen of spores varies by strain.[44] *Cladosporium* species also produce volatile organic compounds, which can cause a musty odor.[45]

***Alternaria*.** The genus *Alternaria* contains more than 270 species many of which are important plant pathogens and

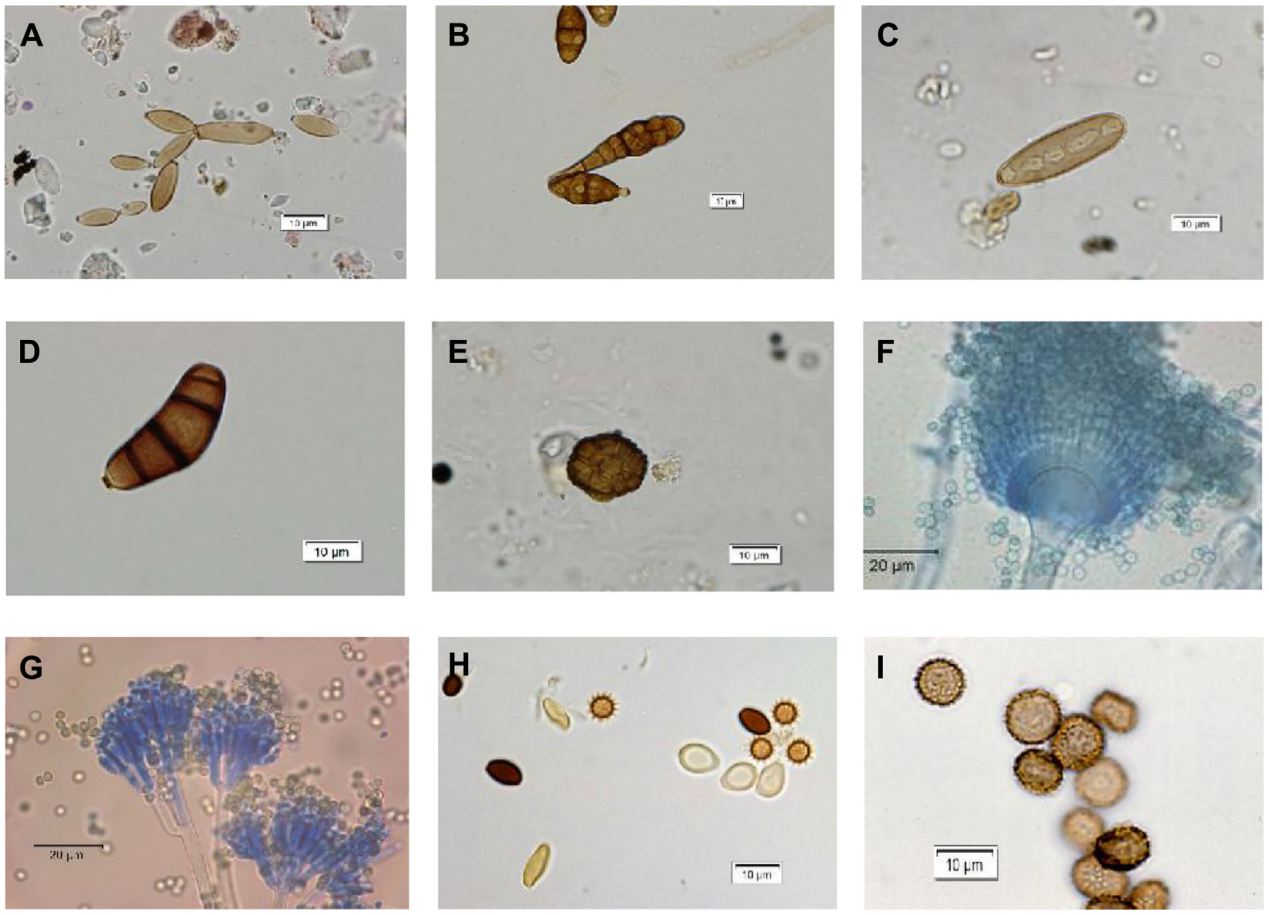

FIGURE 2. Common allergenic fungi **A)** *Cladosporium* conidia in the air sample, **B)** *Alternaria* conidia, **C)** *Bipolaris* conidium in the air sample, **D)** *Curvularia* conidium, **E)** *Epicoccum* conidium in the air sample, **F)** *Aspergillus fumigatus* conidiophore from culture, **G)** *Penicillium solitum* conidiophore from culture, **H)** mixed basidiospores, and **I)** *Ustilago maydis* teliospores.

saprotrophs that occur on a great diversity of wild and cultivated plants worldwide.[46] *Alternaria* conidia are among the most common spore types in the outdoor environment; however, these fungi are also commonly found indoors growing on damp building materials. Outdoor concentrations of *Alternaria* spores tend to be highest on dry, windy days, and typically range from 500 to 1000 spores per cubic meter. Although they can be found in the air year-round, peak levels usually occur in the late summer to fall.[47]

Alternaria spores are multicellular and club shaped (Figure 2, *B*), and are produced in chains borne on vegetative mycelium. They are usually dispersed in the air as individual spores. Multiple allergens from *Alternaria* have been characterized and are discussed by Williams et al.[48]

***Bipolaris* complex.** This is a group of closely related genera in the Pleosporaceae that have been a source of confusion in the literature. *Bipolaris, Drechslera, Helminthosporium*, and *Exserohilum* all produce morphologically similar conidia (pigmented, cylindrical, and generally pseudoseptate), so were originally "lumped" together, and then split into different anamorphic genera and also are at times named by their sexual states. By the 1980s, these genera were separated on the basis of spore morphology, spore germination, and other features.[49]

***Drechslera*.** Most species of *Drechslera* are plant pathogens and saprobes. The pseudoseptate conidia are pigmented, cylindrical, and capable of germinating from every cell. The basal attachment scar does not protrude, and the attachment area is rounded.[50] *Drechslera* species produce allergens,[51] and some can cause infections in immunocompromised patients[52] as well as fungal sinusitis[53] and bronchopulmonary mycosis.[54]

***Bipolaris*.** The genus *Bipolaris* contains approximately 45 species, which are plant pathogens and saprobes. The pigmented conidia are pseudoseptate and cylindrical, fusiform, or curved (Figure 2, *C*). The attachment scar at the base of the conidium protrudes slightly, and unlike *Drechslera*, the spores germinate only from the end cells. Colonies are fast growing and produce abundant conidia.[24,49,50] Several species, including *Bipolaris australiensis, B. hawaiiensis,* and *B. spicifera,* are also known to be human pathogens. At least 4 IgE-binding proteins have been identified from the extracts of *Bipolaris*.[55]

***Helminthosporium*.** *Helminthosporium* species tend to be pathogens and saprobes that are responsible for leaf spot diseases

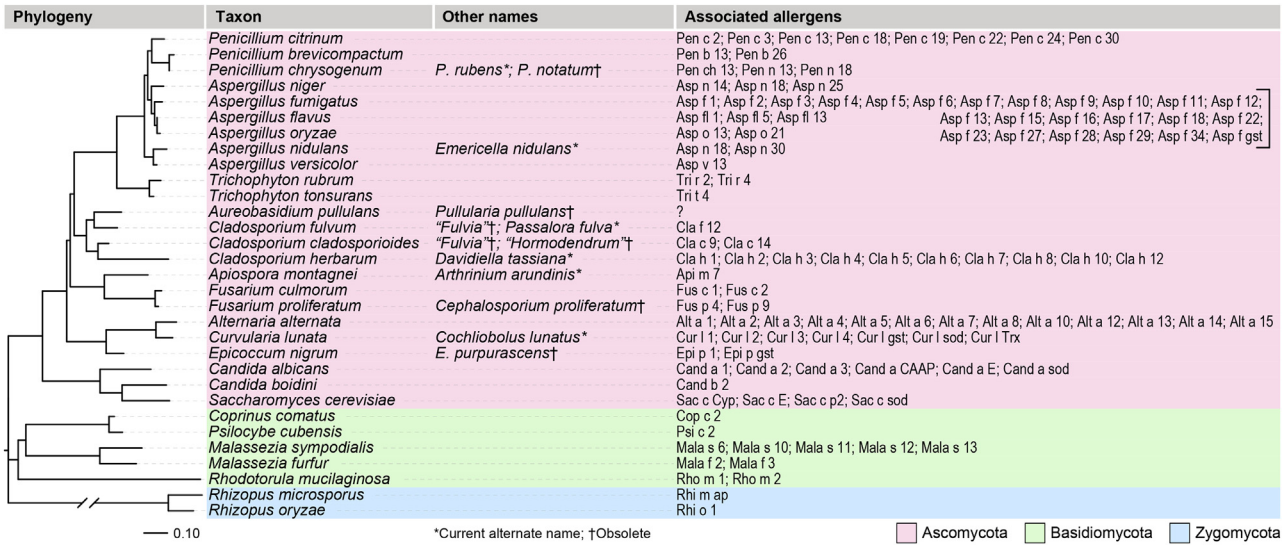

FIGURE 3. Phylogeny of common allergenic fungi and the relationship of allergenic taxa with associated allergens. Phylogenetic tree based on the alignment of partial nucSSU sequences using ClustalX2 and generated using the neighbor-joining algorithm in TreeView v1.6.6. Reference sequences are provided in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

and blights on a number of grasses, cereal grains, and fruit trees.[56] Conidia are pigmented, pseudoseptate, elongate, and characteristically taper toward the apex. Health effects of *Helminthosporium* species have included allergic rhinitis and asthma[56,57] as well as keratitis.[58]

Exserohilum. *Exserohilum* species are also plant pathogens, soil saprobes, and human pathogens. Conidia are pigmented and greatly elongated, with some spores 100 μm in length. The conidial apex often tapers and may appear beak-like. Spores are generally pseudoseptate although distinct septa may occur at the base and apex, and the attachment scar strongly protrudes.[24,49] Several species of *Exserohilum* are human pathogens, and *Exserohilum rostratum* was responsible for fungal meningitis in many patients during a multistate outbreak linked to contaminated methylprednisolone used for epidural injections.[59] Allergens from *E. rostratum* have been detected using a halogen immunoassay with pooled patient sera.[60] This species has previously been named *Helminthosporium rostratum, B. rostrata*, and *Drechslera rostrata*.

Curvularia. *Curvularia* includes species that are facultative plant pathogens and saprobes. The conidia are frequently seen in air samples although seldom are abundant. Species in this genus are characterized by thick-walled conidia with transverse septa and a prominent attachment scar at the base. The central cell is characteristically swollen on one side giving the condium a curved appearance (Figure 2, *D*).[24] *Curvularia lunata* is also an opportunistic human pathogen. It has been associated with infections related to catheters, prosthetic heart valves, and pacemakers. Being closely related taxonomically, *Curvularia* shares some IgE cross-reactivity with *Alternaria* and *Stemphylium*.[61] It is also closely related to the genera in the *Bipolaris* complex.

Stemphylium. *Stemphylium* species including *S. herbarum, S. solani, S. botryosum*, and *S. vesicarium* are plant pathogens that grow on a wide range of vegetables including tomato, lettuce, beans, and pea.[62] Several allergens of *Stemphylium* (Ste h 1 and Ste b 1) appear to be highly cross-reactive with *Alternaria* Alt a 1.[63] *S. herbarum* is associated with allergic asthma and hypersensitivity pneumonitis.[64]

Phoma. *Phoma* species are ubiquitous with more than 270 taxa currently recognized.[65] They can be found in soil, as saprobes on plants, and both human and plant pathogens.[66] *Phoma* species also occur indoors in carpet dust and on damp surfaces.[67] Allergen cross-reactivity has been reported between *Phoma betae* and *Alternaria alternata*.[68]

Epicoccum. *Epicoccum nigrum* (synonym *E. purpurascens*) is a common plant pathogen, soil and litter saprobe, and leaf surface epiphyte. This fungus is also known from indoor dust and damp materials.[67] The genus contains asexual fungi within the order Pleosporales. The conidia, which are easily recognized in air samples, are subglobose, rough-walled, dark brown, and randomly multicellular, ranging in size from approximately 15 to 20 μm in diameter (Figure 2, *E*). *Epicoccum* is a cause of allergy-mediated upper and lower respiratory tract disease[69] including hypersensitivity pneumonitis[70] and allergic fungal sinusitis.[71] Airborne spores of *Alternaria* and *Epicoccum* tend to display a similar temporal pattern, with the peak daily counts occurring in late summer to early fall, particularly in agricultural regions.[72]

IgE cross-reactivity has been demonstrated between *E. nigrum, C. lunata, A. alternata, C. herbarum*, and *P. citrinum*.[73] Immunoglobulin G cross-reactivity has also been demonstrated between *Epicoccum* and *Alternaria*.[74] The major allergen Epi p 1 is a serine protease.[75] Another 12 kD allergen has also been isolated.[76] The cell walls have been shown to contain epiglucan that is a highly side-chain/branched (1→3;1→ 6)-β-glucan.[77]

***Aureobasidium* (obsolete *Pullularia*).** *Aureobasidium pullulans* (previously known as *Pullularia pullulans*) is a black yeast-like fungus found in temperate and tropical climates. It is commonly found on the surface of leaves or flowers and may also

grow in many types of soil.[78] It occurs indoors on a wide range of materials in the presence of excessive moisture[79] and is commonly isolated from house dust.[67,80] It is an exclusively asexual genus in the Dothideales. In outdoor air, conidial release has been reported to peak at night and during rain.[81]

Historically *Aureobasidium* has not been considered a major allergen source; however, recent reports have linked elevated levels of *Aureobasidium* in house dust to both rhinitis in children and sinusitis in adults.[80] Studies have also implicated *A. pullulans* exposure in both upper and lower airways disease,[81] and bronchial challenges have been positive.[82] Hypersensitivity pneumonitis has been reported with saunas, damp buildings, and contaminated humidification systems.[83] Sensitization to *A. pullulans* has been linked to increased asthma severity.[84] It has been associated with problems relating to occupational exposure in sawmills.[85]

Aspergillus. The name *Aspergillus* refers to the microscopic spore-bearing structures that resemble an aspergillum (a liturgical instrument used for sprinkling holy water).[86] More than 250 species occur in soil and as agents of food spoilage worldwide.[87] Four species *Aspergillus fumigatus* (Figure 2, *F*), *A. terreus, A. nidulans*, and *A. niger* are common agents of human and animal disease. Of these, *A. fumigatus* is perhaps the most frequently encountered and virulent of all opportunistic fungal pathogens.[88] Sensitivity to *A. fumigatus* is associated with severe persistent adult asthma, although the precise immunological mechanism is not known.[89] This species is also an important agent of allergic bronchopulmonary aspergillosis.[90]

The main allergen of *A. fumigatus*, Asp f1, is an 18 kD IgE-binding protein that shows extensive sequence homology (95%) with mitogillin, which is a cytotoxin also produced by *A. restrictus*. It has been suggested that Asp f1 could play a dual role in the pathogenesis of disease by promoting colonization through cytotoxic activity and by causing inflammatory reactions involving IgE antibodies.[91] Allergens of *A. fumigatus* have not been found in indoor air.[92]

A. versicolor is commonly found in damp buildings. Specific IgE was found in 2% of 1800 children in one study.[93] It produces the allergen Asp v 13, a subtilisin-like serine protease.[94]

Penicillium. The genus is named for the conidiophore that resembles an artist's paintbrush, or penicillus in Latin (Figure 2, *G*). Members of *Penicillium* are among the most commonly occurring, economically important, and taxonomically difficult of all fungi. *Penicillium* includes species that are frequent contaminants of foods and colonizers of damp building environments.[26] Species of *Penicillium* are ubiquitous in soil; preferring cool conditions, *Penicillium* species are common wherever organic material is available and some can grow under conditions with very little water. Saprobic species of *Penicillium* live mainly on organic biodegradable substances and are among the main causes of food spoilage.[95] Some *Penicillium* species commonly grow on old bread, giving it a blue fuzzy texture.

Penicillium is one of the most common airborne allergenic fungi, along with *Cladosporium* and *Alternaria*.[96] In addition, *Penicillium* exposure in damp homes is a risk factor for asthma.[97,98] Multiple *Penicillium* allergens have been characterized.[48]

The most common species, *P. chrysogenum*, has recently been shown to consist of 4 species, only 1 of which apparently is common on damp building materials. This species aligned with the penicillin-producing strains first isolated by Sir Alexander Fleming.[99] Based on molecular and other evidence, this species was recently reassigned its original name, *P. rubens*.[100]

Trichophyton* and *Epidermophyton. The genera *Trichophyton* and *Epidermophyton* are closely related members of the ascomycete order Onygenales (family Arthrodermataceae). They are filamentous fungi many of which lack known sexual forms. Accordingly, the agents of human tinea are found in this group—the so-called dermatophytes. Current taxonomic treatments recognize more than 20 human-infecting species with many formerly described species representing morphologically variant forms of single phylogenetic lines.[101] Allergic reactions to *Trichophyton* have been observed.[102]

Dermatophyte infection may be associated with so-called id or dermatophytid reactions in which distant, secondary, T-lymphocyte—mediated or antibody-mediated inflammatory changes arise after exposure to circulating fungus-specific antigen.[103] Commonly, these reactions manifest as follicular, lichenoid, or papulosquamous lesions on the face, neck, trunk, or extremities, and resolve after the elimination of the underlying infection.

Fusarium. *Fusarium* is a large genus of anamorphic fungi, which can be soil saprobes, devastating plant pathogens, and human pathogens. The plant pathogens have been especially well studied because several produce potent mycotoxins, including deoxynivalenol, fumonisins, and zearalenone. Ingestion of grain contaminated with these mycotoxins has been implicated in disorders of livestock and humans.[104]

Fusarium spores can become airborne, especially during wet weather. The genus has been frequently isolated from both outdoor air and indoor environments.[105] Although various spore types are produced, the most easily recognized *Fusarium* spores are the macroconidia, which are typically sickle-shaped, hyaline, and multicellular.

Fusarium species can cause sinusitis, allergic bronchopulmonary mycosis, keratitis, onchymycosis, and other infections. Several studies have shown skin test reactivity to *Fusarium* extracts.[106] These fungi produce multiple allergens.[48]

Isolates of *Fusarium venenatum* are the source of the mycoprotein, Quorn, which is used as a meat substitute for people following vegetarian diets or those looking for nonmeat options. There are several reports of allergic reactions to Quorn as well as reports of other adverse reactions.[107]

Trichoderma. *Trichoderma* is a ubiquitous genus of anamorphic fungi commonly isolated from soil, decaying vegetation, wood, other plant material, and other fungi. *Trichoderma* species are serious pathogens of cultivated mushrooms. Although typically soil-borne, *Trichoderma* has been reported from air samples using culture-based methods,[108] and indoor *Trichoderma* has been frequently isolated from wet building materials.[109]

There are at least 75 species of *Trichoderma* with the majority associated with a *Hypocrea* sexual stage.[110,111] Members of the genus are known to be allergenic with studies showing positive skin tests and specific IgE.[112] *Trichoderma longibrachiatum* has been shown to cause allergic fungal sinusitis.[113]

Stachybotrys. *Stachybotrys chartarum* and *S. chlorohalonata* are 2 closely related and cooccurring species (formerly lumped together as *S. chartarum*, obsolete *S. atra*) that are commonly found on paper-faced gypsum wallboard. These species produce either simple and/or macrocyclic tricothecene mycotoxins.[114]

Stachybotrys has been colloquially referred to as "toxic" or "black" mold even though not all strains are toxic or black.

Extremely high indoor exposure to *Stachybotrys* associated with handling fungus-contaminated building materials has been associated with adverse health effects[115]; however, the clinical relevance of less extreme exposures is controversial. This fungus is found only when the building materials have been wet for a sustained period, and consequently, it never occurs by itself making it difficult to identify *Stachybotrys*-specific health effects.

Sensitivity to *S. chartarum* is potentially more widespread than previously appreciated. In one study, 13 of 139 (9.4%) blood donor sera contained *S. chartarum*—specific IgE.[116] At least 2 allergenic proteins from *S. chartarum* have been sequenced.[117]

***Chrysonilia* (obsolete *Monilia*)/*Neurospora*.** *Neurospora* is an ascomycete genus in the Sordariaceae with dark ascospores and *Chrysonilia* anamorphs. Although some older texts referred to *Chrysonilia* as *Monilia*, these are now recognized as unrelated. *Neurospora* species (as the teleomorph) occur throughout the world and in nature fruiting of ascomata is typically associated with burnt plant materials especially grasses and woody shrubs.[118]

Neurospora crassa is widely used as a model species in genetics research on a par with *Drosophila* and *Saccharomyces*.[119] The narrow asci of *Neurospora* preserve the physical arrangement of meiosis products resulting in "ordered tetrads" that are useful for attributing effects to either the first or second division during meiosis. *Chrysonilia* states grow rapidly and sporulate profusely on multibranched conidiophores.

Chrysonilia sitophila is known as pink bread mold and is a serious problem if it becomes established in bakeries because of difficulty in eradication and because it can be a serious occupational allergen. It can also be a serious nuisance if contamination becomes established in microbiology laboratories. Occupational lung diseases due to *Neurospora* (*Chrysonilia*) exposure are known among coffee,[120] bakery, sawmill,[121] and cork workers.[122] Although recognized as sources of allergens in multiple environments, currently there are no well-characterized allergens.

***Chaetomium*.** *Chaetomium* is an ascomycete genus of approximately 400 species with wide distribution in tropical and temperate zones. Some species are facultative pathogens; others are sources of cytochalasins[123] and industrial enzymes. Many species of *Chaetomium* are well-recognized decomposers of cellulosic materials, and *Chaetomium globosum* commonly occurs indoors on water-damaged building materials. Ascomata of *Chaetomium* are scattered on the mycelium and are flask-shaped, darkly pigmented, and typically covered with short to long hairs that may be simple or branched, and straight or coiled. The single-celled brown lenticular spores are often microscopically distinguishable because of an evident germ pore at one end. To date, no allergens from *Chaetomium* have been well characterized.

***Acremonium*.** The genus *Acremonium* includes some of the most structurally simple of all anamorphic fungi, reproduced by the production of phialides often with little differentiation of the conidium-bearing cells. The genus *Cephalosporium* was previously applied to many species; however, in the modern sense, *Cephalosporium* is restricted to only a few taxa of agricultural importance.[124] Recent investigations on the taxonomy of *Acremonium* have revealed that the genus, as traditionally conceived, is highly polyphyletic, with affiliations to at least 12 variously unrelated orders of the Ascomycota.[125]

Positive skin tests have been reported in the context of indoor building investigations,[112] and several reports have linked this fungus to hypersensitivity reactions relating to home humidifiers.[126]

***Botrytis*.** Conidiophores of *Botrytis* resemble a cluster of grapes (botryose). *Botrytis* species are mostly necrotrophic plant pathogens that cause significant blight of greenhouse ornamentals and postharvest decay of fresh fruits and vegetables. Approximately 20 species are described; most are rather specific to a few host plants, whereas *Botrytis cinerea* has a broad host range.[127] The familiar gray mold of strawberries is the result of infection by *B. cinerea*. These are anamorphic stages of fungi in the family Sclerotiniaceae. Sensitivity to *B. cinerea* based on skin prick testing was demonstrated in 18% of severe asthmatics and always in combination with sensitization to at least 1 other fungal allergen.[128]

Phylum Basidiomycota

Basidiomycota is the second largest phylum of fungi with more than 30,000 species. There is tremendous morphological diversity in this phylum ranging from yeasts and other microscopic fungi to organisms forming large conspicuous fruiting bodies such as mushrooms, bracket fungi, and puffballs.[96] Basidiomycetes can be found in terrestrial, aquatic, and marine habitats throughout the world. The phylum includes saprobes, pathogens, and mutualistic symbionts. Many woodland mushrooms are produced by the fungal partners of mycorrhizae, which are mutualistic relationships between fungi and the roots of trees. Rust fungi and smut fungi are important plant pathogens in this phylum,[96] whereas notable human pathogens include *Cryptococcus, Trichosporon*, and *Malassezia*.[129]

Basidiomycetes are characterized by the production of sexual spores called basidiospores (Figure 2, *H*). These are produced externally on club-shaped structures called basidia (sing basidium), and there are generally 4 basidiospores produced on each basidium. The basidia line the gills of mushrooms and the pores of bracket fungi. Asexual reproduction is by the formation of conidia in many basidiomycetes; additionally, highly specialized spores are produced by the rust and smut fungi. The basidiomycete yeasts reproduce by budding.

The basidiospores from mushrooms, bracket fungi, and related organisms are actively released into the atmosphere during periods of high humidity. As a result, basidiospores often dominate the air spora during late night and early morning hours.[130] Basidiospores have been associated with spikes in emergency department visits for asthma in New Orleans in what has been recognized as one of the strongest asthma-environmental connections.[131] A number of major basidiospore allergens have been identified.[132] In addition, shared allergenic determinants exist between select species of basidiomycetes and ascomycetes.

***Rhodotorula*.** *Rhodotorula* is included in the Basidiomycota and is most often recognized as a yeast collected from air, soil, lakes, ocean water, and milk products. *Rhodotorula* can be strongly pigmented and is easily identifiable when grown on Sabouraud dextrose agar by its distinctive orange, pink, or red colonies. The taxonomy of the genus has undergone some reorganization with 3 species commonly recognized (*Rhodotorula glutinis, R. minutis*, and *R. mucilaginosa*). The formerly recognized *R. rubra* has been reclassified as *R. mucilaginosa*[24], and, the extract formerly available

under that name is actually a strain of *R. mucilaginosa*. The extract currently available under the name *R. mucilaginosa* is the same extract that was formerly available under *R. rubra*.

Two *R. mucilaginosa* allergens, an enolase and a serine protease, have been described.[133,134] Specific IgE antibodies against *Rhodotorula* have been identified in a study of yeast sensitivity, and cross-reactivity with other allergens including dust mite[135] and other yeasts[136] has been reported.

***Ustilago* and other smut fungi.** The smut fungi are a group of plant pathogens in the Basidiomycota. There are approximately 1500 species of smut fungi, and more than 4000 species of plants are affected. *Ustilago* is one of the largest genera of these pathogens with more than 200 species, and it is perhaps the best studied in terms of its importance to allergic disease. *Sporisorium* and *Sphacelotheca* are 2 other genera of smut fungi considered allergenic.

The main dispersal phase for smut fungi is teliospores, which are thick-walled spores that give rise to basidia and basidiospores. Teliospores are typically produced in a sorus (pl. sori), which consist of a spore mass along with host tissue.[137] The unicellular teliospores are globose to subglobose in shape with yellow to brown pigmentation. Spore walls may be smooth, but more commonly have spiny or reticulate ornamentation (Figure 2, *I*).

Smut teliospores are wind-dispersed, and numerous studies have documented their presence in the atmosphere at locations around the world.[138-140] The occurrence of specific airborne smut spores is typically seasonal and related to the phenology of the host plant. Some smut species produce and release spores when the host plant pollinates; however, in other smuts, spores are released when the grain on the host plant is mature.[138] In addition to their common occurrence in the atmosphere, smut teliospores have also been isolated from various indoor environments because of the intrusion of outdoor air.[141,142]

As early as 1937, Wittich and Stakman[143] reported on a patient with respiratory allergy and asthma that was sensitive to grain smuts. In a study of mill dust allergens, Wittich[144] subsequently found that 103 of 135 patients were clinically sensitive to smuts. Later studies confirmed these early observations. In one study, 61% of patients with asthma and 15% of patients with rhinitis had positive intradermal reactions to *Ustilago maydis* (corn smut) extract.[145]

CONCLUSION

The Kingdom Fungi contains diverse eukaryotic organisms with a complex metabolism that differs from animals and plants. They secrete enzymes, some of which are well-known allergens, into their surroundings and absorb the breakdown products.

The phylogenetic relationships among fungi only became clear recently due in part to the large number of fungi lacking sexual states that are the basis of classification. This lack of information on the sexual state morphology was confounded by relying on an artificial, now-obsolete category called Deuteromycetes or Fungi Imperfecti, which gained inappropriate recognition as a valid grouping rather than a contrivance of convenience. Based on DNA sequencing, 8 phyla of fungi are now recognized. Most fungal genera relevant to clinical allergy—due to the production of airborne spores—are in 3 of these phyla: Zygomycota, Ascomycota, and Basidiomycota. Clarifying the relationships of fungal groups incurred name changes for some familiar fungi, but regulatory constraints often preclude using current names and many fungal allergen extracts retain obsolete names.

Evident from this reorganization is that specific IgE levels in individuals sensitized to fungi generally reflect the newly resolved phylogenetic relationships of fungi. These parallels between molecular fungal systematics and IgE sensitization to fungal species provides a systematic way to look at cross-reactivity among fungi. With further research, this new classification should provide new insights into the role of fungal allergy in human disease.

GLOSSARY

Anamorph: An asexually reproducing form of a fungus (restricted to phyla Ascomycota and Basidiomycota).

Ascospore: A sexually produced fungal spore formed within an ascus of ascomycetes.

Ascus (pl. Asci): A sac, typically cylindrical in shape, in which the spores of ascomycete fungi develop.

Conidium (pl. Conidia): An asexually produced fungal spore, formed on a conidiophore.

Gametangium (pl. Gametangia): An organ or a cell in which gametes are produced.

Hypha (pl. Hyphae): Long slender tubes that develop from germinated spores and form the structural parts of the body of a fungus.

Mycelium: A mass of hyphae that form the vegetative part of a fungus.

Saprobe, Saprophyte, Saprotroph: A fungus that lives on decaying organisms or nonliving organic matter.

Sorus (pl. Sori): A small, pustular mass of spores.

Sporangium (pl. Sporangia): A single-celled or many-celled structure in which spores are produced.

Spore: A reproductive unit capable of giving rise to a new individual without sexual fusion.

Symbiont: Two dissimilar organisms living in a mutually beneficial relationship.

Teleomorph: The sexually reproducing form of a fungus (restricted to phyla Ascomycota and Basidiomycota).

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TABLE E1. Sequences used to construct phylogenetic tree

Taxon name	GenBank number
Alternaria alternata	U05194.1
Apiospora montagnei	JN546134.1
Aspergillus flavus	KP893281.1
Aspergillus fumigatus	KsJ809565.1
Aspergillus nidulans	U77377.1
Aspergillus niger	GQ338836.1
Aspergillus oryzae	D63698.1
Aspergillus versicolor	KM096191.1
Aureobasidium pullulans	EU682923.1
Candida albicans	AF114470.1
Candida boidinii	AB054551.1
Cladosporium cladosporioides	EU375523.1
Cladosporium fulvum	AY251109.2
Cladosporium herbarum	JN546121.1
Coprinus comatus	NG016488.1
Curvularia lunata	KJ909964.1
Epicoccum nigrum	KM096239.1
Fusarium culmorum	AF548073.1
Fusarium proliferatum	JN236216.1
Malassezia sympodialis	KF706460.1
Malassezia furfur	KF706457.1
Penicillium brevicompactum	KP981369.1
Penicillium citrinum	KC960012.1
Penicillium chrysogenum	AF548086.1
Psilocybe cubensis	KF830074.1
Rhizopus microsporus	AF548092.1
Rhizopus oryzae	AF113440.1
Rhodotorula mucilaginosa	KP233783.1
Saccharomyces cerevisiae	AF548094.1
Trichophyton rubrum	X58570.1
Trichophyton tonsurans	AY083229.1