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# Genetic Susceptibility to Fungal Infections: What is in the Genes?

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## Abstract

The development of severe fungal infections has long been associated with traditional risk factors such as profound immunosuppression, yet it remains challenging to understand why under similar conditions only some patients will develop these infections while others will not. Recent studies have demonstrated the importance of host genetic variation in influencing the severity and susceptibility to invasive fungal infections (IFIs). In this review, we examine selected primary immunodeficiencies characterized by their vulnerability to a narrow range of fungal pathogens, and then focus on recently identified genetic polymorphisms associated with an increased susceptibility to IFIs.

### Keywords

Genetic susceptibility; Single-nucleotide polymorphism; Invasive *Candida* infection; Invasive aspergillosis; Cryptococcus

Author Contributions

All authors contributed to the literature review, writing, reading, and approving the manuscript.

**Compliance with Ethics Guidelines**

**Conflict of Interest**

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**Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by any of the authors.

## Introduction

Invasive fungal infections remain a substantial cause of morbidity and mortality in immunocompromised populations [1, 2]. A significant proportion of these patients will develop an invasive fungal infection despite controlling for classic risk factors. It has been suggested that underlying host genetics may explain some of this discrepancy [3–5]. Recent studies have demonstrated the role of genetic variant single nucleotide polymorphisms (SNPs) to be important in defining a host's susceptibility to IFIs, especially during profound immunosuppression such as that induced by chemotherapy or following organ transplantation [6]. Further identification and evaluation of these genetic determinants will likely facilitate early appropriate prophylaxis and treatment of these high risk patients. In this review, we will highlight the prototypical but rare monogenic diseases that form much of the basis of our understanding of genetic susceptibility to specific fungal pathogens. Then we will review innovative approaches that have advanced our knowledge of the relationship between novel genetic variants of immunity and pathogenesis of selected pathogens within the clinical setting. A review of findings from *in vitro* systems or murine models is beyond the focus of this review and can be found elsewhere [2, 7]. However, data from murine systems of candidiasis can be effectively linked up to human genotypes to identify specific genetic susceptibility genes and SNPs. For example, the dysfunctional CXCR1-M280 and CXCR1-T276 alleles were found to be associated with an increased risk for systemic candidiasis and neutrophil killing of yeasts, respectively, in humans after being identified as important in murine candidiasis [8•, 9•].

## Monogenic diseases

Much of our understanding of the molecular mechanisms underlying anti-fungal immunity was discovered by first investigating primary immunodeficiencies [10, 11]. This unique set of genetic deficiencies confers a predisposition to a narrow range of fungal pathogens, and has often been the presenting clinical manifestation of the immunodeficiency itself.

### Candida

*Candida* species are commensal organisms on the skin and the mucous membranes of healthy individuals, but can become an opportunistic pathogen in the setting of a compromised immune system [12]. *Candida* species are now considered a common pathogen in bloodstream infections, and fungemias are associated with a mortality rate of approximately 40% [10]. Traditional risk factors for invasive infection include recent treatment with broad-spectrum antibiotics, administration of parenteral nutrition, presence of intravascular catheters, prolonged intensive care unit stay and neutropenia. Despite the aforementioned risk factors, only a minority of the population will develop an IFI in these circumstances. The causative etiology for developing an IFI is likely multifactorial; however, several monogenic diseases have been previously described to be associated with an increased susceptibility to infections with *Candida* species.

A notable example of a monogenic disorder, as described by Glocker, et al., involved the identification of a homozygous point mutation in *CARD9* in a consanguineous family with known recurrent IFIs [13]. This mutated gene resulted in a premature stop codon (Q295X)

and loss of function mutation, resulting in the lack of expression of the *CARD9* protein in peripheral mononuclear cells. The mutated sequence was associated with a mean proportional reduction in Th17 cells as well as severe defects in *Dectin-1* triggered *TNF*-α signaling. The activation of this conserved pathway highlights its importance in fungal recognition, stimulation of pro-inflammatory responses, and in Th17-cell differentiation.

Chronic mucocutanous candidiasis (CMC) represents another classic immunodeficiency associated with recurrent fungal infections related to a defect in IL-17 and IL-22 immunity that is required for mucocutaneous anti-fungal host defense [11]. Considered a heterogeneous group of disorders, CMC can be acquired primarily or secondarily; both autosomal dominant (AD) or recessive inheritance patterns can involve the skin, nails, and mucous membranes of affected individuals. Autosomal recessive autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is a rare syndrome caused by a mutation in a thymic transcriptional regulator, AIRE, and manifests clinically in the form of impaired T-cell tolerance, self-reactive autoantibodies and CMC [14]. APECED patients form neutralizing antibodies against important anti-fungal cytokines including IL-17E, IL-17F, and IL-22. Furthermore, Liu et al. investigated the molecular mechanisms underlying *STAT1* gain of function mutations known to characterize the autosomal dominant form of CMC [15]. These mutations increase *STAT1* dependent responses through its impaired nuclear dephosphorylation, affecting cellular response to multiple cytokines and culminating in the curbed differentiation of IL-17 producing T-cells. In a follow-up study, Zheng and coworkers also reported that the negative effects of gain of function *STAT1* mutations on *STAT3* function were secondary to decreased histone acetylation, which affected *STAT3* promoter binding and gene expression [16]. These investigators reported that the reduction in *STAT3* gene expression explains the observed low Th17 responses that are the hallmark of the clinical syndrome of CMC. They noted a reversal in the cellular transcriptional profiles by inhibiting *STAT1* activation or by enhancing histone, suggesting that targeting epigenetic modifiers may offer a unique treatment strategy for AD CMC. More extensive review of the role of genetic variants in the pathogenesis of CMC can be found elsewhere [12, 17–19].

Hyper-IgE syndrome (HIES) is the result of a heterogeneous group of missense mutations or in-frame deletions most commonly in the *STAT3* transcription factor that clinically manifests as a distinct syndrome characterized by extreme elevations in IgE levels, eczema, recurrent pulmonary infections, invasive aspergillosis and cold staphylococcal skin abscesses [14]. Mutations in DOCK8 and Tyk2 have also been associated with HIES [20, 21]. Given the diverse roles of *STAT3* in multiple biological processes, patients with HIES also have a constellation of non-immunologic features such as particular facial features, joint hyperextensibility, pathological fractures, delayed primary tooth exfoliation, pneumatoceles, coronary artery aneurysms, and Chiari's malformation [22]. In 2007, two separate studies determined that mutations in *STAT3* underlie the pathogenesis of HIES. These mutations may be hereditary or spontaneous (de novo), and result in increased levels of pro-inflammatory mediators and defective IL-6 signaling [22, 23]. Approximately 80% of patients with AD-HEIS develop CMC, due to the inability to induce Th17 CD4 differentiation that is crucial to downstream activation of cutaneous defense mechanisms. Patients with AD-HIES have been shown to have a reduced number of circulating Th17 cells

and they generate a decreased amount of IL-17 and IL-22 following *Candida* stimulation. A reduction in these cytokines results in impaired priming of epithelial cells to produce host anti-microbial molecules including β-defensins, histatins, and neutrophil-recruiting chemoattractants important for anti-fungal defense [24, 25]. In addition to CMC, these patients are known to develop IFIs with filamentous molds including *Aspergillus* and *Scedosporium*. Pneumatoceles, parenchymal lung damage, and bronchiectasis resulting from a history of recurrent bacterial infections serve as a medium for these opportunistic mold infections [5, 26].

## Aspergillus

*Aspergillus* spp are a group of filamentous environmental molds commonly found in soil and decaying vegetation. The spore form of these molds often enters the human host through inhalation and deposits into the bronchioles or alveolar spaces [14]. Without a robust host immune response, these spores can germinate and the hyphae invade local tissues, leading to established infection [6, 27]. *Aspergillus fumigatus* remains the most common and lethal species in most areas of the world and is thus responsible for approximately 90% of reported cases of invasive aspergillosis (IA) with a one-year survival rate as low as 20% in certain patient populations [28, 29]. Among the known primary immunodeficiencies, chronic granulomatous disease (CGD) has been associated with infections due to *Aspergillus* spp.; these mold infections can be lethal and are particularly persistent despite appropriate anti-fungal therapy [11, 30, 31]. In many cases, this inability to completely eliminate the fungus requires indefinite anti-fungal secondary suppression. These patients may also experience other fungal infections such as candidiasis as well as infection with the rare mold *Rasamsonia* (*Geosmithia*) *argillacea* species [32, 33]. CGD is a rare disorder characterized by specific defects in the NADPH subunits in phagocytes, resulting in defective superoxide production and compromised oxygen-dependent microbicidal activity [34]. It was initially thought that CGD had an X-linked (XL) pattern of inheritance, but later autosomal recessive (AR) forms of the disease were also recognized. Both forms involve primarily defects in the NADPH oxidase in either its membrane-associated (XL form) or cytosolic (AR form) components [35]. The sex-linked gene encodes for the gp 91 protein. The autosomal/recessive forms are transmitted through Neutrophil Cytosol Factor 1 (NCF1) encoding the p47 protein, and Cytochrome B-245 light chain (CYBA) encoding for the p22 protein. The types of mutations in these genes are varied and may include deletions, frameshifts, and nonsense and missense mutations. The inability of recruited macrophages and neutrophils to deploy oxidative killing mechanisms in response to inhaled conidia predisposes these patients to recurrent and/or persistent invasive fungal infections. While *A. fumigatus* has been the most commonly reported fungal pathogen in CGD, other *Aspergillus* spp., including *A. nidulans* may also cause infections in afflicted patients [11, 36]. The introduction of new triazole agents and the use of prophylactic anti-fungal regimens have substantially reduced the incidence and associated mortality of fungal infections in this population [37].

IFIs have also been reported among patients with a syndrome of monocytopenia, B-cell and NK-cell lymphopenias (known as MonoMAC) and further susceptibility to mycobacteria, papillomaviruses and myelodysplasia. The incidence of IFIs and specifically IA in this

population has been estimated at 18–43% and 17%, respectively [5]. Cryptococcal and *Histoplasma* spp. infections have also been reported [38]. MonoMAC results from specific mutations in the transcription factor, *GATA2*, which affects a number of genes important in the proliferation and growth factor responsiveness of early hematopoietic cells [39]. Although these patients have a complex hematopoietic clinical syndrome including lymphocytopenia, they still have evidence of immune cells in tissue compartments at sites of inflammation and normal immunoglobulin levels. This histopathology could represent local persistence of previously produced cells or possibly local proliferation from tissue resident macrophages. Functionally, affected neutrophils exhibit a spectrum of defects including uncharacteristic surface antigen expression, abnormal granule contents and even frank dysplasia; monocytopenia and monocyte dysfunction appear to be linked through an undefined mechanism to this susceptibility profile.

## Polygenic diseases

Over the past decade, there has been substantial progress in understanding the role of the numerous genes that mediate host-pathogen interactions in fungal infections. We have begun to appreciate the sophisticated interplay between innate and adaptive immune cells along with numerous other key effector cells that constitute the host immune response to fungal invasion, and how certain genetic defects in these pathways can lead to increased susceptibility to infection [19]. *In vitro* and murine models have been paramount in generating the framework of this exchange; however, we are only recently able to begin to explore the application of these genetic findings in humans (Table 1). The ability to identify additional genetic risk factors would likely prove to be very beneficial during times of profound immunosuppression in that such information might personalize prophylactic anti-fungal regimens or augment therapeutic management plans in high risk patients.

### Candida

Toll-like receptors (TLRs) are known to be key players in fungal immune recognition and have been well studied in models of *Candida* infection [2]. An increased susceptibility to *Candida* bloodstream infections was found to be associated with TLR4 D299G and T399I polymorphisms in non-neutropenic patients, but this finding was not supported in a study involving a larger patient cohort [40, 41]. Instead, Plantinga and coworkers found three SNPs in TLR1 were significantly associated with an increased susceptibility to candidemia in a population of hospitalized Caucasian subjects, while no appreciated associations were noted in other TLRs including 2, 4, 6, 9 and the adaptor molecules MyD88 and TIRAP [42]. Moreover, there was no association between any of the SNPs analyzed and outcomes of infection including dissemination, persistence of infection, or mortality, implying that TLR1 may be more important in early host immune response rather than determining the outcome of an established infection. However, this finding was in contrast to a prior report, which demonstrated that TLR1 knock-out (TLR1 −/−) mice did not show increased susceptibility to infection in a model of disseminated candidiasis [43]. Explanations that may account for the anti-fungal role of TLR1 in humans have been related to possible alterations in the signaling profiles of other TLRs such as TLR2 or TLR6 or through downstream effector molecules such as beta-defensin-3, which activates immune cells through TLR1/TLR2 [17].

Lastly, patients with polymorphisms in TLR2 were shown to have decreased IFN-γ and IL-8 plasma levels during *Candida* sepsis [44].

Johnson et al. examined the role of cytokine gene polymorphisms in a cohort of candidemia patients, and discovered that none of the cytokine SNPs examined (IFNG, IL10, IL12B, IL18, IL1B, IL8) was associated with an increased susceptibility to candidemia [45]. Of the cytokines tested, the persistence of candidemia was found to be associated with SNPs in cytokine genes, IL-12B and IL-10, but no association was appreciated between polymorphisms in cytokine genes and disseminated disease or 30-day mortality. Follow-up *in vitro* studies using peripheral blood mononuclear cells (PBMCs) demonstrated lower cytokine transcription compared to healthy individuals in response to *Candida* stimulation. Sun and coworkers found a similarly increased risk for invasive *Candida* infections with a polymorphism in IL-10, and demonstrated that increased IL-10 production may be a predisposing factor for prolonged candidemia [46].

Using a candidate gene approach, Choi and coworkers investigated genetic variations that contribute to the risk of developing chronic disseminated candidiasis (CDC) in patients with acute leukemia [47]. A common haplotype of IL4 (-1089T/-589C/-33C) was found to be associated with a greater risk of developing CDC, whereas no association with the other investigated variant genotypes of IL10, IL12A, TGFB1, and TNF was appreciated. Another interesting finding of the study was that a different haplotype (-1089T/-589T/-33T), which corresponds to individuals that are heterozygous for the IL4-589 polymorphism, was protective against CDC.

Polymorphisms in TNF-α and β-defensin 1 were shown to be associated with an increased susceptibility to intra-abdominal candidiasis (IAC) among a cohort of high-risk surgical intensive care unit (ICU) patients [48•]. Prevalence of “heavy” Candida colonization was associated with the TLR4 D229G SNP, but no such correlation was found for this SNP with IAC. Interestingly, the SNPs found to be linked with fungal colonization varied from those associated with IAC in this population. This finding suggests that although colonization is considered a predisposing risk factor to invasive infection, there are likely distinct mechanisms that contribute to this pathogenic transition [48•].

Recent studies have utilized functional genomics coupled to case-control association studies and genome-wide associated studies (GWAS) as a comprehensive method for the identification of the genetic variants affiliated with increased susceptibility to invasive *Candida* infections exclusively in human studies. Smeekens and colleagues were able to compare the transcriptional profile produced after stimulating primary leukocytes with *Candida albicans* as compared to other unrelated inflammatory stimuli thereby identifying an expression signature of 101 transcripts (95 genes) that described a distinct molecular response to *C. albicans* [49•]. Analysis revealed an overrepresentation of the IFN signaling pathway. Using genotyping results from a cohort of patients with candidemia, several genes were identified from the transcripts analyzed and were found to have a significant association with susceptibility to systemic candidiasis in four genes (*CCL8, STAT1, PSMB8, and SP110*). To further validate the role of IFN-related genes in the anti-*Candida* immune response, correlation between cytokine production with SNP variants showed a

significant association at both *IRF1* and *STAT1* regions. Immunological studies showed that type I IFNs, induced in the setting of *Candida*-induced inflammation, modulate the cytokine profile from a Th17 to a Th1 response, underscoring the role of this pathway in anti-*Candida* host response in humans.

The first GWAS evaluating genetic susceptibility to candidiasis was performed using the largest patient cohort to date [50]. This analysis revealed significant association between novel SNPs in the *CD58, LCE4A-C1orf68*, and *TAGAP* loci. This risk of candidemia was increased 19.4-fold in those individuals carrying two or more risk alleles. Mechanistically, *CD58* was found to inhibit fungal germination at the level of the phagosome as well as modulate *Candida*-specific cytokine production, findings that highlight a new role for this molecule in mediating host responses. Investigations into the role of *TAGAP* in fungal infection demonstrated the inability of *TAGAP* (−/−) mice to eradicate the fungus from the liver and kidney at later stages of infection, underscoring its role in anti-fungal host defense. An interesting conclusion of this study is the observation that the genes identified as novel risk factors for candidemia are also noted to be associated with autoimmune diseases such as rheumatoid arthritis, psoriasis, and Crohn's disease, suggesting that some consideration be given to the notion that a predisposition to such conditions may have been evolutionarily driven by exposure to pathogens [50].

## Aspergillus

The estimated incidence of IA in the hematopoietic stem cell transplant (HSCT) population is approximately 10–12%, and despite significant advances in anti-fungal therapy, the 1-year mortality related to these infections remains high at 50–80%. IA is the leading cause of infection-related deaths among patients with allogeneic hematopoietic-stem cell transplants [51]. Several studies have demonstrated that specific SNPs associated with genes governing the immune system have affected the course and outcome of patients with *Aspergillus* infections [52].

Most notable of these was the study published by Bochud and coworkers, suggesting an association between allelic variations in *TLR4* haplotype S4 among donors and the risk of IA among recipients of HSCT [51]. The *TLR4* S4 haplotype (6% haplotype frequency) was discovered to be present in carriers of two SNPs (1063 A/G and 1363 C/T) in strong linkage disequilibrium, and was subsequently confirmed by the investigators in a companion validation study. Additional subgroup analysis also revealed that the association between IA and the S4 haplotype was most significant in unrelated donors as compared to related donors, for which the underlying explanation for this difference is unknown. Moreover, the cumulative incidence of IA as well as the incidence of death not related to relapse were increased in patients with seropositivity for CMV, donor positivity for the S4 haplotype, or both, as compared to patients who were negative for CMV or the S4 haplotype. The authors postulated that the observed SNPs affect *TLR4* function thereby explaining the observed clinical phenotype, as studies have demonstrated *TLR4* involvement in fungal ligand recognition, detection of lipopolysaccharide, and innate immune activation [53–55]. The genetic susceptibility to IA found to be associated with polymorphisms at 1063A/G and 1363C/T was further confirmed by Koldehoff and coworkers, who demonstrated that either

probable or proven IA in transplant recipients occurred if either recipients or donors harbored one of the aforementioned *TLR4* variants [56•]. However, investigations into the functional consequences of the Asp299Gly (1063 A/G) polymorphism have yet to find a consistent signaling response following TLR4 stimulation [57–59]. Increased risk for IA after allogeneic HSCT has been shown to be associated with polymorphic variants in *CXCL10, TLR1,* and *TLR6* [52, 60, 61].

Genetic variation in inflammatory cytokines has also been shown to be associated with susceptibility to IA. Sainz and coworkers examined the influence of IL-1 gene cluster polymorphisms on the susceptibility profile of hematological patients, and found that certain haplotypes were associated with an increased risk of developing IA (VNTR2/-889C/-511T) while other haplotypes were associated with resistance to infection (VNTR2/-889C/-511C) [62]. Genetic variation in the promoter region of IL-10 have also be shown to be associated with differential susceptibilities to IA in hematological patients; more specifically, the IL-10 -1082A allele was associated with increased susceptibility to IA while the -1082(AA) genotype was associated with resistance to develop IA [63]. Seo and coworkers investigated the association between three SNPs in the IL-10 promoter and the risk for IA following allogeneic HSCT. The risk for IA was variable among the different haplotypes, with the most striking finding that the ACC haplotype reduced the risk of IA approximately 9-fold [64].

A recent study published by Cunha et al. revealed HSCT recipients who received a donor with a homozygous haplotype (h2/h2) in *PTX3* were found to have an associated increased risk of infection with Aspergillus as well as defective expression of *PTX3*, a soluble pattern recognition receptor shown to have a non-redundant role in modulating host response to fungal infection [65•]. The genetic deficiency of *PTX3* was suggested to affect the anti-fungal capacity of neutrophils, presumably due to messenger RNA instability and altered regulation of *PTX3* expression, ultimately resulting in impaired phagocytosis and clearance of the fungus. Exogenous addition of *PTX3* to isolated *PTX3*-deficient neutrophils reversed the observed functional deficit, illustrating that the innate anti-fungal mechanisms of these cells are compromised by a lack of sufficient *PTX3*. This association was found regardless of HLA status of the door, T cell manipulation, acute GVHD and prophylaxis. Moreover, the h2/h2 haplotype was consistently associated with a defect in *PTX3* expression in BAL fluid, lung biopsy specimens, and innate immune cells. These findings could not be replicated, however, in a small group of patients from a case-control study that previously confirmed the role of TLR4 mutations [3].

Other studies have investigated the association of a premature stop codon polymorphism in *Dectin-1*, a C-type lectin receptor present on human immune cells that recognizes the β-1,3 glucan motif on fungal species including *Candid*a and *Aspergillus*, and the risk and clinical course of IA in both non-HSCT and post-HSCT patients [1]. Cunha and et al. found that the Y238X polymorphism in *Dectin-1* increased susceptibility to IA among HSCT patients, with the high risk occurring when the polymorphism was present in both donors and recipients [66]. Similarly, in a hematological population, genotypic variation in *Dectin-1* and DC-SIGN were associated with a significantly increased risk for IA [67]. Chia and coworkers discovered that the Y238X allele frequency was higher in non-HSCT patients with IA, and

that heterozygosity for the polymorphism in HSCT recipients only showed a limited trend toward IA susceptibility but did not influence the clinical course of IA [1]. This was in contrast to the non-HSCT population, in which there was a stronger association towards enhanced susceptibility. Although this study demonstrated that *Dectin-1* had limited influence on the susceptibility to IA in HSCT patients, thought to be partially attributable to redundancy in the innate immune system, this polymorphism may prove to be important in non-HSCT patients. Larger studies are needed to further clarify the relevance of this finding. Multiple *in vitro* studies and murine models have also demonstrated the requisite role of *Dectin-1* in the host defense to *Aspergillus* [68, 69].

A novel method to identify candidate gene polymorphisms associated with an increased risk of IA following HSCT was conducted by Zaas and coworkers [70]. In this approach, the authors developed an exogenously suppressed murine model and investigated host genetic differences following pulmonary aspergillosis infection using computational haplotype genetic analysis. A SNP (Asp472Asn) in the gene encoding plasminogen was shown to be associated with an increased susceptibility to IA in the developed mouse model that was subsequently identified in the human homolog (PLG; Gene ID 5340). An association study of a cohort of allogeneic HSCT patients was then pursued, demonstrating that recipients that were homozygous or heterozygous for the Asn472 (AA or AG genotype) were at a significantly increased risk of developing IA following transplant. Interestingly, they also detected an apparent “gene-dosage effect,” in that heterozygous individuals were at a 3.0-fold increased risk while homozygous individuals were at a 5.6-fold risk of developing IA. Follow-up *in vitro* experiments showed that human plasminogen is able to directly bind to both swollen conidia and hyphal forms of *Aspergillus*, implicating the fibrinolytic pathway in the pathogenesis of IA.

## Cryptococcus

*Crytococcus neoformans* is considered an opportunistic fungal pathogen and is the leading cause of fungal meningitis in the world [10, 71]. This infection remains the fourth leading cause of death in HIV-infected patients for which the burden of *Cryptococcus* infection remains high. An estimated 1 million cases of cryptococcal meningitis occur annually in these patients worldwide [72]. Other risk factors for cryptococcosis include solid organ transplantation, hematological malignancy, and prolonged immunosuppression or chemotherapy. Previous studies have shown that inhalation of basidiospores or desiccated yeast cells can cause an initial pulmonary infection that has the predilection for dissemination to the central nervous system manifesting as meningoencephalitis [73]. Multiple studies have demonstrated an increased propensity for cryptococcal infection in patients with CD4 lymphopenia. Netea and coworkers analyzed *ex vivo* cytokine production from stimulated whole blood isolated from two patients with idiopathic CD4 lymphopenia and refractory cryptococcal meningitis [74]. They noted defective production of IFN-γ and TNF-α, two cytokines known to be involved in stimulation of anti-cryptoccocal mechanisms in phagocytes, suggesting that the deficiency of these pro-inflammatory mediators plays a crucial role in the development of IFIs in these patients. This concept was further supported when recombinant IFN-γ was administered as an adjunctive therapy to one of the progressively deteriorating patients that led to clinical recovery. Additionally, anti-IFN-γ

antibodies have been isolated from a series of patients with crytococcosis and even the presence of auto-antibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) have been linked to cryptococcal infections [75, 76]. A prospective population study from Australia and New Zealand analyzed the host response and the epidemiological incidence of both *C. neoformans* and *Cryptococcus gattii* infection and found an increase in both types of infection in a predominately immunocompetent Aboriginal population in rural and semirural locations [77]. The authors noted that although the disease secondary to *C. gattii* was disproportionately high in this population suggesting an environmental exposure as the dominant risk factor, the increased incidence of *C. neoformans* was similarly increased, prompting the need for other risk factors such as genetic susceptibility to be further investigated.

Recent investigations into the genetic susceptibility of cryptococcosis have begun to identify potential human genes associated with cryptococcosis. Interestingly, a common theme has been polymorphisms in the Fc gamma receptors linked to cryptococcal disease [78–80•]. This work has emphasized the importance of B–cell immunology in the control of this encapsulated yeast. There has also been an association with genetic variability in the mannose-binding lectin complex and cryptococcosis, and we are starting to see reports of affected patients with mutations in cytokine genes for adaptive immunity such as IL12 [81, 82]. Thus both by phenotype and genotype, the search is underway for a detailed understanding of the genetic susceptibility to cryptococcosis, especially in the apparently immunocompetent host.

## Conclusions

These studies continue to highlight the important role of the host's underlying genetic profile in determining susceptibility to IFIs. Advances in knowledge about the human genome and vast improvements in genome technologies have facilitated this, and will continue to launch the field forward towards a better understanding of genetic risk to IFIs. However, the integration and subsequently translation of the aforementioned genetic findings are still very much in their infancy, as we have only begun to appreciate the complex and interwoven factors that govern host-pathogen interactions [34]. Studies involving large cohorts of patients are needed and outcomes analyses are mandatory to correlate the relative contribution of genetic findings to specific clinical outcomes. This is particularly important given the multiple challenges of genetic association studies including population heterogeneity and insufficient replication power [83]. The ability to stratify "at-risk" patients with selective genetic immunodeficiencies for susceptibility to specific pathogens has the great potential to dramatically alter clinical care in the future [84]. Dissecting the contribution that host genetic variation has on the susceptibility to fungal infection will be principal for personalizing medicine in infectious diseases. It will also serve as a catalyst for future research into the significance of genetics in other infectious phenotypes and population outcomes amid various management strategies.

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## References


Papers of particular interest, published recently, have been highlighted as:

•Of importance

••Of major importance

1. Chai LY, de Boer MG, van der Velden WJ, Plantinga TS, van Spriel AB, Jacobs C, et al. The Y238X stop codon polymorphism in the human beta-glucan receptor dectin-1 and susceptibility to invasive aspergillosis. J Infect Dis. 2011; 203(5):736–43. [PubMed: 21242599]
2. Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL. Immune defence against Candida fungal infections. Nat Rev Immunol. 2015; 15(10):630–42. [PubMed: 26388329]
3. de Boer MG, Jolink H, Halkes CJ, van der Heiden PL, Kremer D, Falkenburg JH, et al. Influence of polymorphisms in innate immunity genes on susceptibility to invasive aspergillosis after stem cell transplantation. PLoS One. 2011; 6(4):e18403. [PubMed: 21483748]
4. Delsing CE, Bleeker-Rovers CP, Kullberg BJ, Netea MG. Treatment of candidiasis: insights from host genetics. Expert Rev Anti Infect Ther. 2012; 10(8):947–56. [PubMed: 23030333]
5. Lionakis MS. Genetic Susceptibility to Fungal Infections in Humans. Curr Fungal Infect Rep. 2012; 6(1):11–22. [PubMed: 23087779]
6. Zaas A. Host genetic affect susceptibility to invasive aspergillosis. Medical Mycology. 2006; 44:S55–S60.
7. Plato A, Hardison SE, Brown GD. Pattern recognition receptors in antifungal immunity. Semin Immunopathol. 2015; 37(2):97–106. [PubMed: 25420452]
8•. Lionakis MS, Swamydas M, Fischer BG, Plantinga TS, Johnson MD, Jaeger M, et al. CX3CR1-dependent renal macrophage survival promotes Candida control and host survival. J Clin Invest. 2013; 123(12):5035–51. This study revealed the direct interaction of macrophages with fungus at the site of infection as well as showed that the dysfunctional CX3CR1 SNP is associated with susceptibility to infection in both mice and humans. [PubMed: 24177428]
9•. Swamydas M, Gao JL, Break TJ, Johnson MD, Jaeger M, Rodriguez CA, et al. CXCR1-mediated neutrophil degranulation and fungal killing promote Candida clearance and host survival. Sci Transl Med. 2016; 8(322):322ra10. This study identified CXCR1 as a critical factor in innate host immune defense against systemic *Candida* infection in both mice and humans, and that variation at CXCR1 in humans is associated with impaired neutrophil effector function.
10. Lanternier F, Cypowyj S, Picard C, Bustamante J, Lortholary O, Casanova JL, et al. Primary immunodeficiencies underlying fungal infections. Curr Opin Pediatr. 2013; 25(6):736–47. [PubMed: 24240293]
11. Antachopoulos C, Walsh TJ, Roilides E. Fungal infections in primary immunodeficiencies. Eur J Pediatr. 2007; 166(11):1099–117. [PubMed: 17551753]
12. Smeekens SP, van de Veerdonk FL, Kullberg BJ, Netea MG. Genetic susceptibility to Candida infections. EMBO Mol Med. 2013; 5(6):805–13. [PubMed: 23629947]
13. Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med. 2009; 361(18):1727–35. [PubMed: 19864672]
14. Casadevall, A.; Mitchell, AP.; Berman, J.; Kwon-Chung, KJ.; Perfect, JR.; Heitman, J. Human Fungal Pathogens. Vol. 2015. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 2015.
15. Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med. 2011; 208(8):1635–48. [PubMed: 21727188]
16. Zheng J, van de Veerdonk FL, Crossland KL, Smeekens SP, Chan CM, Al Shehri T, et al. Gain-of-function STAT1 mutations impair STAT3 activity in patients with chronic mucocutaneous candidiasis (CMC). Eur J Immunol. 2015; 45(10):2834–46. [PubMed: 26255980]

17. Plantinga TS, Johnson MD, Scott WK, Joosten LA, van der Meer JW, Perfect JR, et al. Human genetic susceptibility to Candida infections. Med Mycol. 2012; 50(8):785–94. [PubMed: 22662758]
18. van der Meer JW, van de Veerdonk FL, Joosten LA, Kullberg BJ, Netea MG. Severe Candida spp. infections: new insights into natural immunity. Int J Antimicrob Agents. 2010; 36(Suppl 2):S58–62. [PubMed: 21129931]
19. Lionakis MS. New insights into innate immune control of systemic candidiasis. Med Mycol. 2014; 52(6):555–64. [PubMed: 25023483]
20. Bittner TC, Pannicke U, Renner ED, Notheis G, Hoffmann F, Belohradsky BH, et al. Successful long-term correction of autosomal recessive hyper-IgE syndrome due to DOCK8 deficiency by hematopoietic stem cell transplantation. Klin Padiatr. 2010; 222(6):351–5. [PubMed: 21058221]
21. Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity. 2006; 25(5):745–55. [PubMed: 17088085]
22. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007; 357(16):1608–19. [PubMed: 17881745]
23. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007; 448(7157):1058–62. [PubMed: 17676033]
24. Mogensen TH. STAT3 and the Hyper-IgE syndrome: Clinical presentation, genetic origin, pathogenesis, novel findings and remaining uncertainties. Jakstat. 2013; 2(2):e23435. [PubMed: 24058807]
25. Conti HR, Baker O, Freeman AF, Jang WS, Holland SM, Li RA, et al. New mechanism of oral immunity to mucosal candidiasis in hyper-IgE syndrome. Mucosal Immunol. 2011; 4(4):448–55. [PubMed: 21346738]
26. Vinh DC, Sugui JA, Hsu AP, Freeman AF, Holland SM. Invasive fungal disease in autosomal-dominant hyper-IgE syndrome. J Allergy Clin Immunol. 2010; 125(6):1389–90. [PubMed: 20392475]
27. Dagenais TR, Keller NP. Pathogenesis of Aspergillus fumigatus in Invasive Aspergillosis. Clin Microbiol Rev. 2009; 22(3):447–65. [PubMed: 19597008]
28. Fukuda T, Boeckh M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood. 2003; 102(3):827–33. [PubMed: 12689933]
29. Schmitt HJ, Blevins A, Sobeck K, Armstrong D. Aspergillus species from hospital air and from patients. Mycoses. 1990; 33(11–12):539–41. [PubMed: 2129435]
30. Martire B, Rondelli R, Soresina A, Pignata C, Broccoletti T, Finocchi A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. Clin Immunol. 2008; 126(2):155–64. [PubMed: 18037347]
31. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000; 79(3):155–69. [PubMed: 10844935]
32. De Ravin SS, Challipalli M, Anderson V, Shea YR, Marciano B, Hilligoss D, et al. Geosmithia argillacea: an emerging cause of invasive mycosis in human chronic granulomatous disease. Clin Infect Dis. 2011; 52(6):e136–43. [PubMed: 21367720]
33. Giraud S, Favennec L, Bougnoux ME, Bouchara JP. Rasamsonia argillacea species complex: taxonomy, pathogenesis and clinical relevance. Future Microbiol. 2013; 8(8):967–78. [PubMed: 23902144]
34. Lionakis MS, Netea MG. Candida and host determinants of susceptibility to invasive candidiasis. PLoS Pathog. 2013; 9(1):e1003079. [PubMed: 23300452]
35. Bortoletto P, Lyman K, Camacho A, Fricchione M, Khanolkar A, Katz BZ. Chronic Granulomatous Disease: A Large, Single-center US Experience. Pediatr Infect Dis J. 2015; 34(10): 1110–4. [PubMed: 26181896]

36. Segal BH, DeCarlo ES, Kwon-Chung KJ, Malech HL, Gallin JI, Holland SM. Aspergillus nidulans infection in chronic granulomatous disease. Medicine (Baltimore). 1998; 77(5):345–54. [PubMed: 9772923]
37. Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM. Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore). 2000; 79(3):170–200. [PubMed: 10844936]
38. Vinh DC, Patel SY, Uzel G, Anderson VL, Freeman AF, Olivier KN, et al. Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. Blood. 2010; 115(8):1519–29. [PubMed: 20040766]
39. Tsai FY, Keller G, Kuo FC, Weiss M, Chen J, Rosenblatt M, et al. An early haematopoietic defect in mice lacking the transcription factor GATA-2. Nature. 1994; 371(6494):221–6. [PubMed: 8078582]
40. Van der Graaf CA, Netea MG, Morre SA, Den Heijer M, Verweij PE, Van der Meer JW, et al. Toll-like receptor 4 Asp299Gly/Thr399Ile polymorphisms are a risk factor for Candida bloodstream infection. Eur Cytokine Netw. 2006; 17(1):29–34. [PubMed: 16613760]
41. Wang X, van de Veerdonk FL, Netea MG. Basic Genetics and Immunology of Candida Infections. Infect Dis Clin North Am. 2016; 30(1):85–102. [PubMed: 26897063]
42. Plantinga TS, Johnson MD, Scott WK, van de Vosse E, Velez Edwards DR, Smith PB, et al. Toll-like receptor 1 polymorphisms increase susceptibility to candidemia. J Infect Dis. 2012; 205(6): 934–43. [PubMed: 22301633]
43. Netea MG, van de Veerdonk F, Verschueren I, van der Meer JW, Kullberg BJ. Role of TLR1 and TLR6 in the host defense against disseminated candidiasis. FEMS Immunol Med Microbiol. 2008; 52(1):118–23. [PubMed: 18036178]
44. Woehrle T, Du W, Goetz A, Hsu HY, Joos TO, Weiss M, et al. Pathogen specific cytokine release reveals an effect of TLR2 Arg753Gln during Candida sepsis in humans. Cytokine. 2008; 41(3): 322–9. [PubMed: 18249133]
45. Johnson MD, Plantinga TS, van de Vosse E, Velez Edwards DR, Smith PB, Alexander BD, et al. Cytokine gene polymorphisms and the outcome of invasive candidiasis: a prospective cohort study. Clin Infect Dis. 2012; 54(4):502–10. [PubMed: 22144535]
46. Sun RT, Tian WJ, Xing XW, Gao SH, Wang SB. Association of cytokine gene polymorphisms with susceptibility to invasive candidiasis. Genet Mol Res. 2015; 14(2):6859–64. [PubMed: 26125894]
47. Choi EH, Foster CB, Taylor JG, Erichsen HC, Chen RA, Walsh TJ, et al. Association between chronic disseminated candidiasis in adult acute leukemia and common IL4 promoter haplotypes. J Infect Dis. 2003; 187(7):1153–6. [PubMed: 12660931]
48•. Wojtowicz A, Tissot F, Lamoth F, Orasch C, Eggimann P, Siegemund M, et al. Polymorphisms in tumor necrosis factor-alpha increase susceptibility to intra-abdominal Candida infection in high-risk surgical ICU patients*. Crit Care Med. 2014; 42(4):e304–8. The authors identified that genetic variations in tumor necrosis factor-alpha are associated with susceptibility to intra-abdominal Candida infection in a cohort of high risk, non-neutropenic patients. [PubMed: 24557424]
49•. Smeekens SP, Ng A, Kumar V, Johnson MD, Plantinga TS, van Diemen C, et al. Functional genomics identifies type I interferon pathway as central for host defense against Candida albicans. Nat Commun. 2013; 4:1342. By integrating transcriptional analysis and functional genomics, these authors demonstrated that the type I interferon pathway has a critical role in anti-Candida defense in humans. [PubMed: 23299892]
50. Kumar V, Cheng SC, Johnson MD, Smeekens SP, Wojtowicz A, Giamarellos-Bourboulis E, et al. Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia. Nat Commun. 2014; 5:4675. [PubMed: 25197941]
51. Bochud PY, Chien JW, Marr KA, Leisenring WM, Upton A, Janer M, et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med. 2008; 359(17):1766–77. [PubMed: 18946062]
52. Ok M, Einsele H, Loeffler J. Genetic susceptibility to Aspergillus fumigatus infections. Int J Med Microbiol. 2011; 301(5):445–52. [PubMed: 21550849]

53. Braedel S, Radsak M, Einsele H, Latge JP, Michan A, Loeffler J, et al. Aspergillus fumigatus antigens activate innate immune cells via toll-like receptors 2 and 4. Br J Haematol. 2004; 125(3): 392–9. [PubMed: 15086422]

54. Meier A, Kirschning CJ, Nikolaus T, Wagner H, Heesemann J, Ebel F. Toll-like receptor (TLR) 2 and TLR4 are essential for Aspergillus-induced activation of murine macrophages. Cell Microbiol. 2003; 5(8):561–70. [PubMed: 12864815]

55. Netea MG, Warris A, Van der Meer JW, Fenton MJ, Verver-Janssen TJ, Jacobs LE, et al. Aspergillus fumigatus evades immune recognition during germination through loss of toll-like receptor-4-mediated signal transduction. J Infect Dis. 2003; 188(2):320–6. [PubMed: 12854089]

56•. Koldehoff M, Beelen DW, Elmaagacli AH. Increased susceptibility for aspergillosis and post-transplant immune deficiency in patients with gene variants of TLR4 after stem cell transplantation. Transpl Infect Dis. 2013; 15(5):533–9. This paper demonstrated an association between specific TLR4 halpotypes and the risk for invasive aspergillosis in recipients of hematopoietic stem cell transplants, implicating the need for optimized prevention and screening strategies in this population. [PubMed: 23890253]

57. Imahara SD, Jelacic S, Junker CE, O'Keefe GE. The TLR4 +896 polymorphism is not associated with lipopolysaccharide hypo-responsiveness in leukocytes. Genes Immun. 2005; 6(1):37–43. [PubMed: 15565173]

58. Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, et al. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat Genet. 2000; 25(2):187–91. [PubMed: 10835634]

59. van der Graaf C, Kullberg BJ, Joosten L, Verver-Jansen T, Jacobs L, Van der Meer JW, et al. Functional consequences of the Asp299Gly Toll-like receptor-4 polymorphism. Cytokine. 2005; 30(5):264–8. [PubMed: 15927851]

60. Mezger M, Steffens M, Beyer M, Manger C, Eberle J, Toliat MR, et al. Polymorphisms in the chemokine (C-X-C motif) ligand 10 are associated with invasive aspergillosis after allogeneic stem-cell transplantation and influence CXCL10 expression in monocyte-derived dendritic cells. Blood. 2008; 111(2):534–6. [PubMed: 17957030]

61. Kesh S, Mensah NY, Peterlongo P, Jaffe D, Hsu K, MVDB, et al. TLR1 and TLR6 polymorphisms are associated with susceptibility to invasive aspergillosis after allogeneic stem cell transplantation. Ann N Y Acad Sci. 2005; 1062:95–103. [PubMed: 16461792]

62. Sainz J, Perez E, Gomez-Lopera S, Jurado M. IL1 gene cluster polymorphisms and its haplotypes may predict the risk to develop invasive pulmonary aspergillosis and modulate C-reactive protein level. J Clin Immunol. 2008; 28(5):473–85. [PubMed: 18484169]

63. Sainz J, Hassan L, Perez E, Romero A, Moratalla A, Lopez-Fernandez E, et al. Interleukin-10 promoter polymorphism as risk factor to develop invasive pulmonary aspergillosis. Immunol Lett. 2007; 109(1):76–82. [PubMed: 17321603]

64. Seo KW, Kim DH, Sohn SK, Lee NY, Chang HH, Kim SW, et al. Protective role of interleukin-10 promoter gene polymorphism in the pathogenesis of invasive pulmonary aspergillosis after allogeneic stem cell transplantation. Bone Marrow Transplant. 2005; 36(12):1089–95. [PubMed: 16247433]

65•. Cunha C, Aversa F, Lacerda JF, Busca A, Kurzai O, Grube M, et al. Genetic PTX3 deficiency and aspergillosis in stem-cell transplantation. N Engl J Med. 2014; 370(5):421–32. Hematopoetic stem cell transplant recipients who received a donor with a homozygous haplotype in PXT3 were associated with an increased risk of invasive aspergillosis, which was linked to a deficiency in PTX3 and diminished anti-fungal capabilities of neutrophils. [PubMed: 24476432]

66. Cunha C, Di Ianni M, Bozza S, Giovannini G, Zagarella S, Zelante T, et al. Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. Blood. 2010; 116(24):5394–402. [PubMed: 20807886]

67. Sainz J, Lupianez CB, Segura-Catena J, Vazquez L, Rios R, Oyonarte S, et al. Dectin-1 and DC-SIGN polymorphisms associated with invasive pulmonary Aspergillosis infection. PLoS One. 2012; 7(2):e32273. [PubMed: 22384201]

68. Steele C, Rapaka RR, Metz A, Pop SM, Williams DL, Gordon S, et al. The beta-glucan receptor dectin-1 recognizes specific morphologies of Aspergillus fumigatus. PLoS Pathog. 2005; 1(4):e42. [PubMed: 16344862]
69. Werner JL, Metz AE, Horn D, Schoeb TR, Hewitt MM, Schwiebert LM, et al. Requisite role for the dectin-1 beta-glucan receptor in pulmonary defense against Aspergillus fumigatus. J Immunol. 2009; 182(8):4938–46. [PubMed: 19342673]
70. Zaas AK, Liao G, Chien JW, Weinberg C, Shore D, Giles SS, et al. Plasminogen alleles influence susceptibility to invasive aspergillosis. PLoS Genet. 2008; 4(6):e1000101. [PubMed: 18566672]
71. Perfect JR, Bicanic T. Cryptococcosis diagnosis and treatment: What do we know now. Fungal Genet Biol. 2015; 78:49–54. [PubMed: 25312862]
72. Centers for Disease Control. C. neoformans Infection Statistics. 2015. Available from: http://www.cdc.gov/fungal/diseases/cryptococcosis-neoformans/statistics.html
73. Chen Y, Litvintseva AP, Frazzitta AE, Haverkamp MR, Wang L, Fang C, et al. Comparative analyses of clinical and environmental populations of Cryptococcus neoformans in Botswana. Mol Ecol. 2015; 24(14):3559–71. [PubMed: 26053414]
74. Netea MG, Brouwer AE, Hoogendoorn EH, Van der Meer JW, Koolen M, Verweij PE, et al. Two patients with cryptococcal meningitis and idiopathic CD4 lymphopenia: defective cytokine production and reversal by recombinant interferon- gamma therapy. Clin Infect Dis. 2004; 39(9):e83–7. [PubMed: 15494899]
75. Browne SK, Burbelo PD, Chetchotisakd P, Suputtamongkol Y, Kiertiburanakul S, Shaw PA, et al. Adult-onset immunodeficiency in Thailand and Taiwan. N Engl J Med. 2012; 367(8):725–34. [PubMed: 22913682]
76. Saijo T, Chen J, Chen SC, Rosen LB, Yi J, Sorrell TC, et al. Anti-granulocyte-macrophage colony-stimulating factor autoantibodies are a risk factor for central nervous system infection by Cryptococcus gattii in otherwise immunocompetent patients. MBio. 2014; 5(2):e00912–14. [PubMed: 24643864]
77. Chen S, Sorrell T, Nimmo G, Speed B, Currie B, Ellis D, et al. Epidemiology and host- and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000; 31(2):499–508. [PubMed: 10987712]
78. Meletiadis J, Walsh TJ, Choi EH, Pappas PG, Ennis D, Douglas J, et al. Study of common functional genetic polymorphisms of FCGR2A, 3A and 3B genes and the risk for cryptococcosis in HIV-uninfected patients. Med Mycol. 2007; 45(6):513–8. [PubMed: 17710620]
79. Hu XP, Wu JQ, Zhu LP, Wang X, Xu B, Wang RY, et al. Association of Fcgamma receptor IIB polymorphism with cryptococcal meningitis in HIV-uninfected Chinese patients. PLoS One. 2012; 7(8):e42439. [PubMed: 22879986]
80•. Rohatgi S, Gohil S, Kuniholm MH, Schultz H, Dufaud C, Armour KL, et al. Fc gamma receptor 3A polymorphism and risk for HIV-associated cryptococcal disease. MBio. 2013; 4(5):e00573–13. This study demonstrated a significant association between the FCGR3A 158V allele and cryptococcal disease risk in HIV-infected individuals, which extends previous studies that show the same association in HIV-uninfected patients. [PubMed: 23982074]
81. Ou XT, Wu JQ, Zhu LP, Guan M, Xu B, Hu XP, et al. Genotypes coding for mannose-binding lectin deficiency correlated with cryptococcal meningitis in HIV-uninfected Chinese patients. J Infect Dis. 2011; 203(11):1686–91. [PubMed: 21592999]
82. Jirapongsananuruk O, Luangwedchakarn V, Niemela JE, Pacharn P, Visitsunthorn N, Thepthai C, et al. Cryptococcal osteomyelitis in a child with a novel compound mutation of the IL12RB1 gene. Asian Pac J Allergy Immunol. 2012; 30(1):79–82. [PubMed: 22523911]
83. Cunha C, Kurzai O, Carvalho A. PTX3 deficiency and aspergillosis. N Engl J Med. 2014; 370(17): 1666–7. [PubMed: 24758632]
84. Chapman SJ, Hill AV. Human genetic susceptibility to infectious disease. Nat Rev Genet. 2012; 13(3):175–88. [PubMed: 22310894]
85. Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med. 2009; 361(18):1760–7. [PubMed: 19864674]

86. Plantinga TS, van der Velden WJ, Ferwerda B, van Spriel AB, Adema G, Feuth T, et al. Early stop polymorphism in human DECTIN-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2009; 49(5):724–32. [PubMed: 19614557]

87. Wojtowicz A, Gresnigt MS, Lecompte T, Bibert S, Manuel O, Joosten LA, et al. IL1B and DEFB1 Polymorphisms Increase Susceptibility to Invasive Mold Infection After Solid-Organ Transplantation. J Infect Dis. 2015; 211(10):1646–57. [PubMed: 25398456]

88. Jurevic RJ, Bai M, Chadwick RB, White TC, Dale BA. Single-nucleotide polymorphisms (SNPs) in human beta-defensin 1: high-throughput SNP assays and association with Candida carriage in type I diabetics and nondiabetic controls. J Clin Microbiol. 2003; 41(1):90–6. [PubMed: 12517831]

89. Nahum A, Bates A, Sharfe N, Roifman CM. Association of the lymphoid protein tyrosine phosphatase, R620W variant, with chronic mucocutaneous candidiasis. J Allergy Clin Immunol. 2008; 122(6):1220–2. [PubMed: 19084113]

90. Nahum A, Dadi H, Bates A, Roifman CM. The L412F variant of Toll-like receptor 3 (TLR3) is associated with cutaneous candidiasis, increased susceptibility to cytomegalovirus, and autoimmunity. J Allergy Clin Immunol. 2011; 127(2):528–31. [PubMed: 21093032]

91. Nahum A, Dadi H, Bates A, Roifman CM. The biological significance of TLR3 variant, L412F, in conferring susceptibility to cutaneous candidiasis, CMV and autoimmunity. Autoimmun Rev. 2012; 11(5):341–7. [PubMed: 22024499]

92. van Till JW, Modderman PW, de Boer M, Hart MH, Beld MG, Boermeester MA. Mannose-binding lectin deficiency facilitates abdominal Candida infections in patients with secondary peritonitis. Clin Vaccine Immunol. 2008; 15(1):65–70. [PubMed: 17978009]

93. Babula O, Lazdane G, Kroica J, Linhares IM, Ledger WJ, Witkin SS. Frequency of interleukin-4 (IL-4) -589 gene polymorphism and vaginal concentrations of IL-4, nitric oxide, and mannose-binding lectin in women with recurrent vulvovaginal candidiasis. Clin Infect Dis. 2005; 40(9): 1258–62. [PubMed: 15825027]

94. Babula O, Lazdane G, Kroica J, Ledger WJ, Witkin SS. Relation between recurrent vulvovaginal candidiasis, vaginal concentrations of mannose-binding lectin, and a mannose-binding lectin gene polymorphism in Latvian women. Clin Infect Dis. 2003; 37(5):733–7. [PubMed: 12942410]

95. Giraldo PC, Babula O, Goncalves AK, Linhares IM, Amaral RL, Ledger WJ, et al. Mannose-binding lectin gene polymorphism, vulvovaginal candidiasis, and bacterial vaginosis. Obstet Gynecol. 2007; 109(5):1123–8. [PubMed: 17470593]

96. Lev-Sagie A, Prus D, Linhares IM, Lavy Y, Ledger WJ, Witkin SS. Polymorphism in a gene coding for the inflammasome component NALP3 and recurrent vulvovaginal candidiasis in women with vulvar vestibulitis syndrome. Am J Obstet Gynecol. 2009; 200(3):303, e1–6. [PubMed: 19254587]

97. Cunha C, Giovannini G, Pierini A, Bell AS, Sorci G, Riuzzi F, et al. Genetically-determined hyperfunction of the S100B/RAGE axis is a risk factor for aspergillosis in stem cell transplant recipients. PLoS One. 2011; 6(11):e27962. [PubMed: 22114731]

98. Crosdale DJ, Poulton KV, Ollier WE, Thomson W, Denning DW. Mannose-binding lectin gene polymorphisms as a susceptibility factor for chronic necrotizing pulmonary aspergillosis. J Infect Dis. 2001; 184(5):653–6. [PubMed: 11474427]

99. Granell M, Urbano-Ispizua A, Suarez B, Rovira M, Fernandez-Aviles F, Martinez C, et al. Mannan-binding lectin pathway deficiencies and invasive fungal infections following allogeneic stem cell transplantation. Exp Hematol. 2006; 34(10):1435–41. [PubMed: 16982337]

100. Carvalho A, De Luca A, Bozza S, Cunha C, D'Angelo C, Moretti S, et al. TLR3 essentially promotes protective class I-restricted memory CD8(+) T-cell responses to Aspergillus fumigatus in hematopoietic transplanted patients. Blood. 2012; 119(4):967–77. [PubMed: 22147891]

101. Sainz J, Salas-Alvarado I, Lopez-Fernandez E, Olmedo C, Comino A, Garcia F, et al. TNFR1 mRNA expression level and TNFR1 gene polymorphisms are predictive markers for susceptibility to develop invasive pulmonary aspergillosis. Int J Immunopathol Pharmacol. 2010; 23(2):423–36. [PubMed: 20646338]

102. Sainz J, Perez E, Hassan L, Moratalla A, Romero A, Collado MD, et al. Variable number of tandem repeats of TNF receptor type 2 promoter as genetic biomarker of susceptibility to develop invasive pulmonary aspergillosis. Hum Immunol. 2007; 68(1):41–50. [PubMed: 17207711]

## Table 1

SNPs associated with *Candida*, *Aspergillus*, and *Cryptococcus* infections

| Pathogen/Disease | Gene | Molecular Phenotype | Refs |
|---|---|---|---|
| ***Candida*** | | | |
| Candidemia, invasive candidiasis | CCL8 | Defective type I IFN pathway | [49] |
| | CXCR1 | Impaired neutrophil effector function | [9] |
| | IL-10 | ↑ Candida-induced IL-10 production | [45] |
| | IL-12B | ↓ Candida-induced IFN-γ production | [45] |
| | PSMB8 | Defective type I IFN pathway | [49] |
| | SP110 | Defective type I IFN pathway | [49] |
| | STAT1 | Defective type I IFN pathway | [49] |
| | TLR1 | ↓ IL-1β, IL-6, IL-8 after stimulation | [42] |
| | TLR2 | ↓ IFN-γ and IL-8 | [44] |
| | TLR4 | ↑ IL-10 production | [40] |
| *Candida* colonization, *Candida* carriage | Dectin-1 | ↓ IL-1β and TH17 responses | [85, 86] |
| | DEFB1 | Unknown | [87, 88] |
| CDC | IL-4 | Unknown | [47] |
| CMC | PTPN22 | Unknown | [89] |
| | TLR3 | ↓ IFN-γ levels | [90, 91] |
| IAC | MBL | ↓ MBL levels | [92] |
| RVVC | IL-4 | ↑ vaginal IL-4, ↓ NO and MBL levels | [93] |
| | MBL | ↓ vaginal MBL levels | [94, 95] |
| | NLPR3 | Impaired IL-1β production | [96] |
| ***Aspergillus*** | | | |
| IA | AGER | Enhanced expression of RAGE | [97] |
| | CLEC7A | Defective cytokine production<br>Defective expression of dectin-1 | [1, 66, 67] |
| | CXCL-10 | Impaired expression of CXCL-10 | [60] |
| | Dectin-1 | Unknown | [1, 66] |
| | IL-10 | Unknown | [63, 64] |
| | MBL | Variable MBL levels | [98, 99] |
| | PLG | Unknown | [70] |
| | PTX3 | ↓ PTX3 levels | [65] |
| | S100B | Enhanced secretion of S100B | [97] |
| | TLR1 | Unknown | [61] |
| | TLR3 | Defective antigen presentation and activation of CD8 T-cell responses | [100] |
| | TLR4 | Unknown | [51, 56] |
| | TLR6 | Unknown | [61] |

| Pathogen/Disease | Gene | Molecular Phenotype | Refs |
|---|---|---|---|
| | TNFR1 | Impaired expression of TNFR1 mRNA | [101] |
| | TNFR2 | Unknown | [102] |
| ***Cryptococcus*** | | | |
| Cryptococcosis | FCGR(2A/3A) | Unknown | [79, 80] |
| | IL12RB1 | Defective IL-12 signaling<br>↓ IL-12Rβ1 expression on cell surface | |
| | MBL | ↓ MBL levels | [81] |

CDC – chronic disseminated candidiasis; CMC – chronic mucocutaneous candidiasis; CXCL – chemokine (C-X-C motif) ligand; DC – disseminated candidiasis; IA – invasive aspergillosis; IAC – intra-abdominal candidiasis – IAC; IFN – interferon; IL – interleukin; MBL – mannose-binding lectin; PLG – plasminogen; RAGE – receptor for advanced glycation end products; RVVC – recurrent vulvovaginal candidiasis; SNP – single nucleotide polymorphism; TLR – Toll-like receptor; TNFR – tumor necrosis factor receptor.