Review Article

Genetic Susceptibility to Fungal Infections

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Abstract

Reports of fungal infections have increased over the past decades, making them a major threat to human health. In this study, we review the effects of genetic defects on susceptibility to fungal diseases. To identify all relevant literature, we searched Google Scholar, PubMed, and Scopus and profiled studies published between 2008 and 2021. The results of several studies conducted on this subject have shown the significant effects of genetic variations such as hyper-IgE syndrome, Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome, dectin-1 deficiency, *CARD9* mutations, *STAT1* mutations, and *IL17* mutationson the host immune system's response, which has an important impact on susceptibility to fungal infections. The underlying immune system-related genetic profile affects the susceptibility of individuals to different fungal infections; therefore, this subject should be further studied for better treatment of fungal diseases.

Keywords: Fungal infections, genetic diseases, immune system

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Introduction

In the past 40 years, cases of invasive fungal infections (IFIs) have increased, and pathogenic fungi are a growing threat to human health.[1] In the fight against fungal diseases, there are important factors such as time of diagnosis, resistance to treatments, and the absence of a vaccine.[2] The incidence of IFIs is increasing, causing annual mortality rates to be the same as malaria and tuberculosis.[3]

Genetic disease is caused by abnormalities in the genome, which are caused either by mutations or passed from parents. Many of these diseases are rare.[4] Fungal infections might be more likely to develop as a result of immune system genetic variations that cause abnormalities in proinflammatory and anti-inflammatory responses. So, it stands to reason that genetic variants affecting key innate and adaptive immune system pathways could play a vital role in susceptibility to fungus infections.[5]

Recent research has shown that genetic variations such as single-nucleotide polymorphisms (SNPs) have a significant influence in determining a host's vulnerability to fungi. The early identification and evaluation of these genetic risk factors will probably make it easier to treat these high-risk individuals.[6]

Fungal diseases have recently been recognized as a major contributor to disease-related mortality, especially in people with immunodeficiency, such as those infected with human immunodeficiency virus (HIV), which further enhances researchers' interest in understanding host resistance mechanisms against these pathogens. As a result, the past few decades have seen a dramatic increase in our knowledge of inherent and adaptive components that underlie the antifungal immune protective and inflammatory mechanisms.[7,8]

Results of previous studies have shown that an individual's genetic affects his/her immune system and is, therefore, an important contributor to the body's response to disease.[9] In the following sections, we focus on some aspects of the association between fungal infections and genetic defects.

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Materials and Methods

To identify all relevant literature, a review was conducted on studies found on online databases such as Google Scholar, PubMed, and Scopus by an Internet-based search on immune system, genetic diseases, and fungal infections studies published between 2008 and 2021. Our search strategy aimed to identify all studies published in English that investigated the association of genetic diseases and susceptibility to fungal infections. The literature search identified 97 potentially relevant articles. After exclusion of irrelevant or duplicate articles by reading titles and abstracts, 54 articles were retrieved for further evaluation.

Results

Most fungal infections are caused by a weakening of the immune system, which causes infections in the skin and mucus membranes.[10] Therefore, the occurrence of chronic mucocutaneous candidiasis (CMC) or IFIs could indicate a genetic impairment that weakens the innate or adaptive immune system.[11]

Various approaches have been proposed to investigate the relationship between fungal infections and genetic defects. Genetic susceptibility to IFIs caused by primary immunodeficiency is being investigated in various ways. Genetic susceptibility to CMCs is associated with a variety of factors and causes various illnesses, including hyper-IgE syndrome (HIES), APECED syndrome, dectin-1 deficiency, caspase recruitment domain-containing protein 9 (*CARD9*) mutations, signal transducer and activator of transcription1 (*STAT1*) mutations, and *IL17* mutations.[11]

Influence of immune genetic profile in candidiasis

Infection with *Candida* spp. appears in humans in various ways, such as mucosal or via bloodstream.[12] Genetic sequences have been identified in the human genome, which makes them vulnerable to *Candida* infections. The immunodeficiency associated with genetic factors involved in anti-*Candida* host defense could increase the incidence of CMCs.[13] These congenital genetic errors affect various factors and cause various illnesses. For example, a mutation in the phagocyte reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex (chronic granulomatous disease [CGD]), severe congenital neutropenia, and leukocyte adhesion deficiency type I are associated with aspergillosis and candidiasis, or a mutation in *IFN*-γ causes endemic mycoses. Errors in interleukin-17 (IL-17) and *CARD9* lead to CMC and deep dermatophytosis, respectively.[14]

In a study to identify the genetic factors weakening the immune system, it was found that T helper 17 (Th17) cells play a role in immunity against *Candida* and *Staphylococcus aureus*.[15] Loss of skin or mucus, microbial imbalance, or immune system impairment may increase the sensitivity of mucocutaneous or invasive candidiasis.[16]

Genetics is a decisive factor in the production of IL-17.[17] *Candida* species causes CMC to occur with frequent and persistent infections on the skin and nails or mucus membranes. Genetic abnormalities have the potential to influence the production of IL-17 by Th17 cells in response to Candida.

The Th17 cells produce IL-17 against *Candida* which genetic defects could affect. The IL-17 disorder could develop into CMC disease. Also, the germline mutations involved in IL-17 signaling are seen in CMC patients.[18] IL-17 is a proinflammatory cytokine that activates other proinflammatory cytokines by signaling, including antimicrobial peptides and neutrophil chemokines, which have antifungal activity.[19,20] Secretion of autoantibodies against IL-17A, IL-17F, and/or IL-22, which is seen in patients with autosomal recessive (AR) autoimmune polyendocrine syndrome type 1 (APS-1), may cause CMC.[21]

HIES is linked to impaired salivary function, which increases the susceptibility to oropharyngeal candidiasis.[22]

Between 80% and 90% of patients with APECED are affected by CMC. In a 2021 study, a large cohort of APECED patients and a mouse model of oropharyngeal candidiasis were used to examine oral mucosal immune responses in APECED. The findings supported a theory that exaggerated immunopathology may increase susceptibility to mucosal fungal infection by compromising the integrity of the epithelial barrier, and that abnormal type 1-associated T-cell responses can be harmful to antifungal mucosal immunity.[23]

According to a research on a family with three siblings who had chronic vulvovaginal candidiasis, a full deficiency of dectin-1 resulted in mucosal fungal infections. This is consistent with a previous study that showed dectin-1–knockout mice are susceptible to mucosal candidiasis.[24]

Results from a 2019 study demonstrated that dectin-1 is necessary for the host immune response to *Candida krusei in vitro* and *in vivo*, and also that dectin-1–deficient mice are more susceptible to *C. krusei* infection.[25] Dectin-1–deficient mice were also previously shown to be more susceptible to *Candida glabrata* infection.[26]

de Medeiros *et al.*[27] conducted an experiment on a Turkish family. In this family, there were three patients with CMC. The first patient had a treatment-resistant, cutaneous dermatophytosis, the second one had deep dermatophytosis, and the third patient had CMC with *Candida* encephalitis and endocrinopathy. In the genetic test, R70W *CARD9* mutation was observed on them, and a decrease in IL-17, IL-22, IL-6, and Granulocyte macrophage colony-stimulating factor (GM-CSF) secretion was observed.

IL-23–deficient mice were found to be extremely vulnerable to *Candida albicans*. This occurs due to a decline in all myeloid cell subsets in the infected kidney, which then triggers fungal overgrowth and damages the renal tissue.[28]

Influence of immune genetic profile in aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is seen in patients with susceptible immunity, such as those with bronchial asthma and cystic fibrosis.[29] Polymorphism in Toll-like receptor 4 (TLR4) allele G on Asp299Gly was observed to increase susceptibility to pulmonary aspergillosis. Also, the association between allele C on T-1237C and ABPA was observed.[30] SNPs have been identified in TLR3, IL4R, and IL13, which were associated with susceptibility to ABPA.[31] Early endosome antigen 1 (EEA1) plays a role in the phagocytosis of fungi, so it is essential in the process of clearing fungi. Increased phagocytosis and acidification represent overactive monocyte-derived macrophages (MDMs) in patients with ABPA, which causes a high cellular response to *Aspergillus fumigatus* in the airways.[32] The incidence of ABPA is 2%–15% in people with cystic fibrosis. The main treatment, including corticosteroids and itraconazole, has long-term complications, so monoclonal anti-IgE antibody, using agents like omalizumab, has improved asthma control in patients and is a treatment for ABPA in people with cystic fibrosis.[33]

The polymorphisms rs5743611 (R80T) and rs4833095 (N248S) in TLR1 and rs5743810 (S249P) in TLR6 have been linked to invasive pulmonary aspergillosis, according to earlier investigations. The variation rs5743836 in the promoter of TLR9 has been linked to the development of ABPA. The development of invasive pulmonary aspergillosis has been shown to be linked to the presence of SNP leading to an early stop codon (R392X) in TLR5 in Hematopoietic stem cell transplantation (HSCT) recipients.[34] A 2021 study employed a mouse model of invasive pulmonary aspergillosis to validate the involvement of *TREM1* in antifungal host defense against *A. fumigatus*. The immunosuppressed mouse host was more vulnerable to infection when *TREM1* was deficient.[35]

CARD9, a signaling adaptor protein, has an important antifungal effect in people with AR *CARD9* deficiency, as it activates antifungal immune responses.[36] Patients with recurrent fungal infections should be checked for *CARD9* gene mutations in the absence of known immunodeficiencies.[14]

Over the past several years, as human genome sequencing has been recognized, the relationship between fungal infections and *CARD9* deficiency has become more pronounced.[37] *CARD9* contributes to neutrophil accumulation in extrapulmonary tissues infected with *Aspergillus*, but does not play a role in neutrophil-intrinsic chemotaxis and anti-*Aspergillus* effector functions.[38] The function of *CARD9* depends on different receptors, including immunoreceptor tyrosine-based activation motif (ITAM)-bearing or ITAM-coupled receptors in myeloid cells or dectin-1 receptors. It also plays a role in the cytosolic pattern-recognition receptors by activating p38 and JNK kinases.[39] In a rare instance, *CARD9* mutation is also seen in a patient with subcutaneous phaeohyphomycosis caused by *Corynespora cassiicola*, which has various symptoms, including tissue necrosis.[40]

A study published in 2021 showed that patients with *CARD9* deficiency demonstrated selectively impaired innate and adaptive antifungal responses as well as increased vulnerability to *A. fumigatus* infection. Additionally, *CARD9* KO mice were susceptible to pulmonary and cutaneous aspergillosis.[41]

Overton *et al.*[31] conducted an experiment on SNPs in 95 ABPA patients, and 195 tagging SNPs were analyzed for genetic association with ABPA. Seventeen ABPA-associated SNPs (ABPA vatopic asthma) were identified, and three of them, including IL13 rs20541, IL4R rs3024656, and TLR3 rs1879026, remained significant after correction for multiple testing.

In response to proinflammatory signals and microbial moieties, stromal and myeloid cells synthesize the long pentraxin *PTX3*, which is crucial for the host's resistance to *A. fumigatus* infections and is linked with higher susceptibility to invasive aspergillosis. Possible links between invasive mold infections, which are primarily caused by *Aspergillus* species, were discovered in a 2015 cohort study. The results indicated a significant association between invasive mold infection and *PTX3* polymorphisms, including the rs3816527 AA genotype.[42]

Weakened adaptive immune responses to *A. fumigatus* infection are linked to *STAT3* deficiency. Additionally, *STAT3*-deficient patients are more vulnerable to endemic mycosis including cryptococcosis, histoplasmosis, and coccidioidomycosis, as well as other fungal diseases, mainly CMC, and also pneumocystosis and fusariosis. According to an analysis of 74 *STAT3*-deficient patients (HIES) in the French National Cohort, 13 of them experienced at least one episode of pulmonary aspergillosis.[43]

CGD is a primary immune disease that is an inherited disorder of NADPH oxidase that may be associated with fungal infections and the fungi that cause the disease are mostly *Aspergillus* species. Hematopoietic stem cell transplantation is the most common way to treat CGD. Antibacterial and antifungal prophylaxis and recombinant interferon-γ are other suggested ways.[44,45] In the examination of white cells of people with CGD, especially granulocytes and monocytes, it has been shown that the infection is caused by a defect of these cells in killing bacterial or fungal microbes.[46] In one patient with CGD, pulmonary infection was seen with *Arthrographis kalrae,* a hyaline fungus, which was not treated with antibacterial and antifungal medicines and posaconazole was needed. In this regard, new experiments have been performed on lung computed tomography (CT) scans for early diagnosis of pulmonary fungal infection in CGD. Pulmonary nodules smaller than 30 mm are the first signs of pulmonary fungal infection.[47,48] The genetic factors found to interfere with the production and function of T cells that produce IL-17 are *STAT3*-deficiency and *AD-STAT1* gain-of-function mutations, which are seen in patients with autosomal dominant (AD) HIES.[21] IFIs, including *Pneumocystis*, *Cryptococcus*, and other endemic dimorphic fungi, as well as CMC, have been

linked to *STAT1* gain-of-function and *STAT3* loss-of-function mutations.[49] CGD and HIES are most frequently associated with Invasive fungal diseases. Fungal infections are common among 28% of HIES patients, which are chiefly *Aspergillus* species. Invasive aspergillosis is crucial among these patients and could be located in the aspirate of the lymph node.[50,51]

It has been previously shown that *IL-1* gene cluster polymorphisms are linked to an increased risk of developing invasive pulmonary aspergillosis.[52] In a 2014 research, it was also demonstrated that SNPs in IL-1B, IL-1RN, and IL-15 were associated with chronic cavitary pulmonary aspergillosis (CCPA), supporting a role for the *IL-1* pathway and implicating the *IL-15* gene in CCPA susceptibility.[53]

Mannose-binding lectin (MBL) has been shown to be more prevalent in invasive aspergillosis patients. Surfactant protein A2 (SP-A2) has also been linked to susceptibility to CCPA and ABPA.[54,55]

Cryptococcus

Cryptococcus neoformans can cause life-threatening infections in immunosuppressed individuals, including those with acquired immunodeficiency syndrome (AIDS) and other underlying conditions such transplantation and cancer. One of the primary causes of death in people with HIV continues to be *Cryptococcus* infection. In Chinese patients without HIV, MBL deficiency caused by polymorphisms in the *MBL2* gene was linked to an increased vulnerability to cryptococcosis.[56]

MBL contributes significantly to innate immunity as the body's initial line of defense against pathogens. The modulation of a wide range of immune and inflammatory responses is aided by Fc-receptors (FCGR). In individuals who were HIV uninfected, Meletiadis *et al.*[57] found a correlation between the polymorphisms FCGR2A 131R and FCGR3A 158V and cryptococcosis.

Dermatophytes

Dermatophytes with surface invasion and with the help of external factors like immunosuppression, environmental factors, and so on cause skin, hair, and nail infections. However, different individuals have different sensitivities to dermatophyte infection due to different genetic backgrounds.[58] The most common causes of human dermatophytes are two types of *Trichophyton rubrum* on the glabrous skin and nails and *Trichophyton violaceum* on the scalp.[59] Decreased *DEFB4 CN*, elevated *hBD-2*, and *IL-22* have been found to interact with patients' susceptibility to dermatophytosis.[60] Susceptibility to invasive dermatophytosis is related to *CARD9* deficiency. Several studies have reported various *CARD9* mutations in patients with dermatophyte infection (c.184 + 5 G > T, c.951G > A, c.271T > C, and c.1269 + 18G > A).[61-63] Other genetic variations such as those of the major histocompatibility complex (MHC) class II gene (*HLA-DR4* and *HLA-DR8*) and dectin-1 have also shown an effect against dermatophytosis susceptibility.[58]

Discussion

Several risk factors have been associated with fungal infections. However, only certain patients develop these infections in similar circumstances. These findings questioned whether the genetic variation is associated with susceptibility to fungal infections. CMC, invasive candidiasis, invasive aspergillosis, deep dermatophytosis, pneumocystosis, and endemic mycoses are diseases caused by genetic variations leading to primary immunodeficiencies.[64]

New antifungal drugs have only partially succeeded in improving the prognosis of patients. Investigating the interactions between fungi and host has led to the design and exploration of new therapeutic strategies like cytokine therapy, vaccines, and cellular immunotherapy. Sensitivity to fungal infections increases for several reasons, including immune regulation, gene polymorphisms, and other non-genetic predisposing factors. Therefore, by determining the genetic status of patients, it is possible to determine the type of treatment, that is, prophylactic antifungal treatment or adjunctive immunotherapy.[65,66]

Extensive studies have focused on the effects of immune cells on fungal infections. For example, mast cells can increase host resistance to infections such as bacteria and fungi In general, these studies demonstrate the ability of immune cells in altering the immune responses to fungal infections by multiple mechanisms.[67,68]

As discussed in numerous studies, the immune system is strongly influenced by the individual's genetics.[69] The individual's genetics, due to its close relationship with the immune system, should be investigated and analyzed as an effective factor in the detection, prevention, and treatment of fungal infections.[70,71]

Over the past few decades, the epidemic of immunodeficiency, such as AIDS, and significant advances in the medical management of people with fungal infectious diseases have led to the identification of immune-related genes that affect human allergens to opportunistic infections.[34] This has significantly increased our understanding of the theory of the impact of immune system components on fungal infections.[72]

In recent studies, researchers have been trying to investigate the effects of genetic engineering on the treatment of fungal diseases. Many of these investigations showed positive results due to the fact that many fungal infections are resistant to modern treatments and recombinant DNAs can be utilized in the treatment of these diseases, which indicates another link between fungal infection and host's genetic.[73]

In an experiment that Vicencio *et al.*[74] performed on six children with severe asthma and fungal susceptibility, all six patients were heterozygous for a 24-base pair duplication in the *CHIT1* gene, which was proven with reduced levels of circulating chitotriosidase and susceptibility to fungal infection.

The extensive research on fungal infections and their relationship with genetics has expanded our knowledge of various diseases, such as IFIs and CMCs, and the importance of controlling or treating these diseases should be taken into consideration in medical centers.[11] In similar articles, it has been concluded that the analysis of genetic causes of immunodeficiencies and molecular and cognitive immune mechanisms that affect the susceptibility to fungal disease may address new goals for gene therapy.[75]

Conclusion

Overall, in this study, we collected data from various studies that examined the effects of genetic variation on the susceptibility to fungal infections. The results of these studies show the direct impact of different genetic factors on different fungal infections, which shows this view as an important light in the pathway for treatment and diagnosis of these diseases and can be a factor in the development of drugs, vaccines, and therapies against fungal infections and as a known agent in ineffective treatments. Immune system gene variations are effective in susceptibility to aspergillosis and candidiasis. IL-17 disorder could be associated with the development of CMC disease. *CARD9* deficiency is closely associated with the defect in antifungal immune responses. CGD and HIES have been repeatedly linked with IFIs. Several gene variations such as *IL-22*, *CARD9*, and MHC class II genes (*HLA-DR4* and *HLA-DR8*) were shown to be correlated with dermatophytosis. Previously, the effects of genetic factors on the immune system and mechanisms of their effect on fungal infections have been less studied. But today, with the spread of positive results in various articles on similar topics, it is hoped that the doors of the science of treatment and prevention will be open to the progress of these factors.

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Conflicts of interest

There are no conflicts of interest.

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