Genetic Susceptibility to Fungal Infections and Links to Human Ancestry

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Over the ages, fungi have associated with different parts of the human body and established symbiotic associations with their host. They are mostly commensal unless there are certain not so well-defined factors that trigger the conversion to a pathogenic state. Some of the factors that induce such transition can be dependent on the fungal species, environment, immunological status of the individual, and most importantly host genetics. In this review, we discuss the different aspects of how host genetics play a role in fungal infection since mutations in several genes make hosts susceptible to such infections. We evaluate how mutations modulate the key recognition between the pathogen associated molecular patterns (PAMP) and the host pattern recognition receptor (PRR) molecules. We discuss the polymorphisms in the genes of the immune system, the way it contributes toward some common fungal infections, and highlight how the immunological status of the host determines fungal recognition and cross-reactivity of some fungal antigens against human proteins that mimic them. We highlight the importance of single nucleotide polymorphisms (SNPs) that are associated with several of the receptor coding genes and discuss how it affects the signaling cascade post-infection, immune evasion, and autoimmune disorders. As part of personalized medicine, we need the application of next-generation techniques as a feasible option to incorporate an individual's susceptibility toward invasive fungal infections based on predisposing factors. Finally, we discuss the importance of studying genomic ancestry and reveal how genetic differences between the human race are linked to variation in fungal disease susceptibility.

Keywords: genetic predisposition, disease susceptibility, invasive, fungal infection, host genetics, genetic polymorphism, SNP, human ancestry

INTRODUCTION

Fungi are eukaryotic organisms that have a tremendous impact on human health. About 5.1 million fungal species are present on the earth (Hawksworth and Rossman, 1997; Blackwell, 2011). They reproduce asexually by sporulation, budding, and fragmentation. Sexual reproduction involves three phases like plasmogamy, karyogamy, and meiosis. In fungi, hyphae are the main mode of vegetative growth and are collectively called the mycelium. They are usually heterotrophic in nature (Carris et al., 2012) and few are commensal, with the human body acting as a host (Ibrahim and Voelz, 2017). Most of the fungi are adapted to the land environments, and during early
episodes of terrestrialization, they had interacted with other organisms having typical parasitic lifestyles (Naranjo-Ortiz and Gabaldón, 2019). Under certain not so well-defined conditions, fungi transform from the non-pathogenic budding yeast to its pathogenic hyphal form, which invades the host tissue (de Pauw, 2011; Underhill and Pearlman, 2015; Kruger et al., 2019; Rai et al., 2021). The fungal species can grow anywhere including plants, animals, and humans. Some enter into our body by inhalation (e.g., Aspergillus) and some are commensal (e.g., Candida, Malassezia) (Underhill and Pearlman, 2015). Commensal like Malassezia is more abundant in sebaceous sites of the host. Since they are lipid dependent, they obtain food sources from the host without harming them and colonization starts immediately after birth, when neonatal sebaceous glands are active (Vijaya Chandra et al., 2021). Studies of the microbiome have emerged to be an important area of research, and more importantly, the spotlight is now to understand less studied fungi that have a tremendous influence on the human microbiome especially among immunocompromised individuals. A dysbiotic microbial population is a general characteristic of any fungal infection affecting the mammalian system (Iliev and Leonardi, 2017). Recent reports point toward the role of fungus in pancreatic ductal adenocarcinoma (PDA), a form of human pancreatic cancer caused directly by the presence of budding yeast Malassezia, which colonizes the human gut (Aykut et al., 2019). The severity of fungal infection depends on factors such as inoculum load, magnitude of tissue destruction, ability of the fungus to multiply in the tissue, ability to migrate to nearby organs, microenvironment, and immunogenetic status of the host. Resistance to fungi externally is based on cutaneous and mucosal physical barriers and internally by the body's immune molecules and the defensins (Aristizabal and González, 2013; Coates et al., 2018; Salazar and Brown, 2018). Immunosuppression and breakdown of anatomical barriers such as the skin are the major factors behind fungal infections (Kobayashi, 1996). In addition to this, malnutrition, poor hygiene, use of antibiotics, genetic predisposition, environmental factors, and host physiological factors (e.g., oily skin) contribute toward disease progression (Figure 1).

Genetic variations play an important role in fungal infection (Pana et al., 2014; Maskarinec et al., 2016; Duxbury et al., 2019). Recent studies have shown the importance of host genetic variation in influencing the severity and susceptibility to invasive fungal infections (IFIs) (Maskarinec et al., 2016). Increased incidence of opportunistic fungal diseases has been implicated due to gene polymorphism, and genetic errors are frequently observed in immunodeficient phenotypes (Pana et al., 2014). Along with genetic and environmental factors, lifestyle also contributes toward the variation in the genome, as the presence of toxic chemicals and immunosuppressive drugs in an organism's environment leads to altered immune status and inherited deficiencies, which result in susceptibility toward fungal infection (Kumar et al., 2018; Figure 1). At the molecular level, epigenetic events like alteration of DNA methylation (a key feature that controls gene expression) (Martin and Fry, 2018), modification in the histones (involved in altered gene expression) (Dolino and Jirtle, 2008), and interaction between microbes, genotypes, and environment play a key role in disease progression (Goodrich et al., 2017). Now, challenge for biologists is to identify genetic components that predispose individuals to fungal infection. The study of genes will help to understand the relationship between genetic polymorphism and the cellular phenotype of host and pathogen (Sardinha et al., 2011). Recent research outcomes aided by genomic sequencing point toward an interesting link between genetic predisposition to fungal infections and human ancestry. Single nucleotide polymorphism (SNP) in key immune genes plays an important role in fungal infection affecting particular ancestral populations (Hughes et al., 2008; Dominguez-Andres and Netea, 2019). Thus, with the availability of genetic information, we can study the mechanism behind host defense against the pathogen, susceptibility toward infection (Sardinha et al., 2011), and also have an idea of how the pathogens are evolving and trying to adapt to their host environment through host-pathogen interactions.

**GENETIC PREDISPOSITION AND HOST-PATHOGEN INTERACTION**

An opportunistic fungus causes diseases mostly in immunocompromised individuals, though normal individuals are also affected (Low and Rotstein, 2011; Eades and Armstrong-James, 2019). Host-pathogen communication initiates through the interactions of the fungal ligands and receptors present on the skin and internal organs (Richmond and Harris, 2014). The better fit of the ligand present on the microbes (against the receptors present on the host), the stronger the interaction (Goyal et al., 2018; Patin et al., 2019). Fungal ligands are a
Host susceptibility to fungal infections: predisposing factors and treatment approach. Schematic diagram represents predisposition of the host to certain factors that make them susceptible to fungal infections. Such factors can be genetic as well as non-genetic. Apart from genetic mutations in the host ligand, fungal receptors, and immune genes, human ancestry plays an important role in susceptibility toward invasive fungal infections. The future approaches would be geared toward the investigation (as part of preventive medicine) of the genetic mutations that predispose individuals to fungal infections and offer personalized medicine compared to the more traditional approach that is practiced in the form of antifungal medication.
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TABLE 1 | Genetic mutations, human ancestry, and fungal infections.

| Immune response | Genes | Ancestry link** | Fungal pathogen | Diseases |
|-----------------|-------|-----------------|-----------------|----------|
| Innate immunity | Cell mediated | DOCK8, MyD88**,CARD9**, NCF1, TLR1, MPO, CYBB, CYBA, NADPH oxidase | Chinese (Han) | Candida | Chronic mucocutaneous candidiasis (CMC), chronic granulomatous disease (CGD), candidiasis |
|                |       | PTX3, NCF1, NCF2, NCF4, DOCK8, TLR4, NADPH oxidase, MPO | African | Aspergillus | Invasive aspergillosis (IA) |
|                |       | CARD9, DOCK8 |               |          |                      |
| Humoral        |       | MBL, MASP-2**, MBL ** | Chinese | Malassezia | Pityriasis versicolor |
|                |       | Ferrooxidase |       | Sporotrix | Sporotrichosis |
|                |       | HLA-B22** |       | Pneumocystis jiroveci | Pneumocystis pneumonia (PCP) |
| Adaptive immunity | Cell mediated | IL-17F, Act1, IL-12R1, IL-17R, IL-17RA, IL-4, IL-12, Tyk2, IL-17RC, ZNF341, IL-17, IL-22, Y238X, CLEC7A, IL-10 | Chinese (Han) | Candida | Recurrent vulvovaginal candidiasis (RVVC) |
|                |       | Dectin 1 **, IL-10 | Dutch | Aspergillus | Invasive pulmonary aspergillosis (IPA) |
|                |       | Y238X **, IL-10 **, TNFα **, IFN-γ **, CLEC7A, CX3CR1 **, ARNT2 ** | European (Dutch, Caucasian) | Pneumocystis jiroveci | Pneumocystis pneumonia (PCP) |
|                |       | Asp299Gly, Thr39Me rs2243250(IL-4) |         | Blastomyces | Blastomycosis |
|                |       | IL-6 |       | Histoplasma | Histoplasmosis |
|                |       | IL-2 |       | Coccidioides | Coccidioidomycosis |
|                |       | STAT1 | Chinese (Han) | Candida | Candidiasis |
|                |       | STAT1, STAT3, AIRE, GATA2, RORC, CYP2C19 **, RAG1, RAG2 | Chilean | Aspergillus | Aspergillosis |
|                |       | NOD2, STAT3, CYP2C19 ** | Chinese (Han) | Pneumocystis jiroveci, Trichophyton | Invasive fungal infection (IFI) |
|                |       | CD40L **, CD50, CD80 | Chinese mainland | Candida | Coccidioidomycosis |
| Humoral |       | IgG, IgA, IgE, IgM, defect in MHC class II molecule |          | Pneumocystis jiroveci, Candida, Aspergillus, Blastomyces, Coccidioides, Cryptococcus, Histoplasma, Paracoccidioides | Pneumocystis pneumonia (PCP), candidiasis, aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis. |

The symbol ** is used for the genes having the ancestry link.

class of evolutionarily conserved structures called the pathogen associated molecular patterns (PAMPs) and are recognized by receptors present on the host surface called pattern recognition receptors (PRRs). Post internalization, fungi are primarily recognized by the innate cells (e.g., macrophages and dendritic cells) of the immune system (Mogensen, 2009). The main receptors that recognize the fungal-derived PAMPs are Toll-like receptor (TLR like TLR2, TLR4, and TLR9), C-type lectin receptor (CLR like Dectin1 and Dectin2), Nod-like receptor (NLR), Rig-like receptor (RLR), complement receptor, and mannose binding lectin (MBL) (Akira et al., 2006; van de Veerdonk et al., 2008; Hatinguais et al., 2020). These receptors are a crucial component of fungal recognition and trigger an innate immune response.

The host immune response mainly consists of two types, innate and adaptive immunity (Chaplin, 2010; Aristizabal and Gonzalez, 2013; Netea et al., 2019). Cell-mediated innate immunity is through antigen-presenting cells (APC), which recognize the fungal antigen and process and present it to the T cells. The T cells that participate in antifungal immunity involve...
Th (helper T cells), Tc (cytotoxic T cells), and Treg (regulatory T cells) cells (Hamad et al., 2018). As soon as the body’s immune cells see the foreign fungus, a chain reaction is initiated. Phagocytosis of the fungal pathogen is mediated by neutrophils, macrophages, and dendritic cells, and the oxidative burst kills fungal pathogen by the activity of NADPH oxidase (Rosales and Uribe-Querol, 2017; Warris and Ballou, 2019). The deficiency of this enzyme disrupts the formation of reactive oxygen species (ROS) and makes an individual more susceptible to fungal infection (Hamad et al., 2018). The non-oxidative killing of the fungal pathogen is enhanced by antimicrobial peptides (AMPs) that disrupt the fungal cell wall and also produce neutrophil extracellular traps (NETs) consisting of calprotectin, which induces antifungal activity (Pathakumari et al., 2020; Ulfieg and Leichert, 2021). Calprotectin released from NET is an antimicrobial heterodimer that helps in clearing fungus like Candida, and its deficiency leads to increased fungal burden (Urban et al., 2009). Innate immune response activates adaptive immunity, which is enhanced by both humoral and cell-mediated immune response, aiding in recognizing fungal antigen, generating inflammation, activating the complement cascade, and further leading to opsonization and neutralization of fungal pathogen (Drummond et al., 2014).

Characterization of single gene defects that predispose individuals to fungal infections needs urgent attention. Monogenic causes for susceptibility of invasive fungal infections have unmasked novel molecules and key signaling pathways in defense against mucosal and systemic antifungal threats (Lionakis et al., 2014; Constantin and Lionakis, 2020). Genetic changes in some key genes play a crucial role in host-pathogen recognition (Kumar et al., 2018; Cunha and Carvalho, 2019; Merkhofer and Klein, 2020). Fungal β-glucan (PAMP) activity can be masked through a change in cell wall components and thus prevent target recognition (Plato et al., 2015). A genetic defect in the different types of PRR families makes the host susceptible to fungal infection (Netea et al., 2012). Defect in the CLR Dectin1, encoded by CLEC7A (C-type lectin domain containing 7A) predisposes humans to invasive aspergillosis (IA), chronic mucocutaneous candidiasis (CMC), and recurrent vulvovaginal candidiasis (RVVC) (Reid et al., 2009; Plantinga et al., 2012; Cunha et al., 2018). The CLEC7A intronic SNPs rs3901533 and rs7309123 are associated with susceptibility to invasive pulmonary aspergillosis (IPA) in patients with hematologic diseases (Taylor et al., 2007; Sainz et al., 2012). Dectin-1 Y238X polymorphism leading to diminished Dectin-1 receptor activity plays a role in RVVC and IA (Plantinga et al., 2009; Cunha et al., 2010; Zachedi et al., 2016). Dectin-1 gene variant also contributes susceptibility to coccidioidomycosis (del Pilar Jiménez-A et al., 2008). Another receptor MBL interacts with pathogens, helps in triggering an immune response, and plays an important role in innate immunity. Deficiency in MBL expression is associated with susceptibility to RVVC (Carvalho et al., 2010) and pneumocystis pneumonia (PCP) (Yanagisawa et al., 2020). Polymorphism in MBL is also associated with chronic cavitary pulmonary aspergillosis and Candida infection (Vaid et al., 2007).

SNPs in TLR lead to genetic variation that results in susceptibility to Candida and Aspergillus infections (Cunha et al., 2010; Table 1). Mutation in TLR1 is associated with candidemia (Ferwerda et al., 2009; Plantinga et al., 2009, 2012). Genetic variation in the PRR TLR4 can also make an individual susceptible to diseases like IPA (Cunha and Carvalho, 2019). Polymorphism in Asp299Gly and Thr399Ile present in the TLR4 impacts hyporesponsiveness to lipopolysaccharide signaling in epithelial cells or alveolar macrophages and results in chronic cavitary pulmonary aspergillosis (Arbour et al., 2000; Carvalho et al., 2008). In addition, polymorphism in immune response NOD2 (nucleotide binding oligomerization domain containing 2) gene results in IPA. Variation in another receptor type RLR is also associated with Candida infection (Gresnigt et al., 2018; Jaeger et al., 2019). Thus, a mutation in the gene coding for a receptor is an important susceptibility factor for CMC and plays a central role in host immune response (Glocker et al., 2009).

GENETIC POLYMORPHISM OF THE IMMUNE SYSTEM LINKED TO FUNGAL INFECTIONS

Genetic variants leading to immunological susceptibility have long been recognized with a few immunodeficiencies characterized by their vulnerability to IFIs (Pana et al., 2014; Maskarinenc et al., 2016; Merkhofer and Klein, 2020). Deficiency in PTX3 (Pentraxin 3), which is involved in innate immunity, leads to susceptibility toward IA (Garlanda et al., 2002). Recently, downregulation of cluster of differentiation molecules CD50 and CD80 has been shown to make an individual susceptible to Trichophyton infection (Hamad et al., 2018). Polymorphism in the CX3CR1 gene (C-X3-C motif chemokine receptor 1, encoding chemokine receptor) is associated with fungal infection in the gut, and it plays an important role in antifungal activity through activation of Th17 cells and IgG antibody response (Kumar et al., 2018). Candida infections (ranging from mucosal to bloodstream, including deep-seated infections) are influenced by genetic variants in the human genomes like polymorphism in signal transducer and activator of transcription protein-coding genes STAT1 and STAT3 (Plantinga et al., 2012; Smeekens et al., 2013). The important adaptor protein CARD9 (caspase recruitment domain-containing protein 9) is involved in signal transduction from a variety of receptors, and mutation in this gene not only leads to mucosal infection but also is associated with IFIs, development of autoimmune diseases, inflammatory bowel disease (IBD), and cancer (Glocker et al., 2009; Drummond et al., 2018). CARD9 plays an important role in Th17 cell differentiation and helps in the release of cytokines (Vautier et al., 2010; Speakman et al., 2020; Vornholz and Ruland, 2020). Recently, defects in CARD9 and STAT3 have been found to cause IFI with gastrointestinal manifestations (Vinhal, 2019) and mutation in STAT3 results in reduced Th17 cells causing candidiasis (Engelhardt and Grimbacher, 2012). A heterozygous missense mutation in STAT1 is associated with coccidioidomycosis and histoplasmosis (Sampaio et al., 2013). Mutation in another transcription factor GATA2 (GATA-binding
factor 2) makes patients vulnerable to myeloid malignancy who have a high risk for treatment-associated IFIIs involving aspergillosis and candidiasis (Spinner et al., 2014; Donadieu et al., 2018; Vedula et al., 2021). ZNF341 (zinc finger protein 341) is a transcription factor that resides in the nucleus and regulates the activity of STAT1 and STAT3 genes. ZNF341-deficient patients lack Th17 cells and have an excess of Th2 cells and low memory B cells. Upon Candida infection, individuals with STAT3 mutation result in hyper–immunoglobulin E syndrome (HIES) associated with defective Th17 cell differentiation and characterized by elevated serum IgE (Béziat et al., 2018; Frey-Jakobs et al., 2018; Egri et al., 2021). Patients with AIRE (autoimmune regulator) gene mutations are also susceptible to Candida albicans infection and present themselves with autoimmune disorders (Pedroza et al., 2012; de Albuquerque et al., 2018). Genes encoding immune molecules of the adaptive immune system play an important role in controlling fungal invasion (Kawai and Akira, 2007). Immunoglobulins (Igs) IgG, IgA, IgE, and IgM as part of the humoral adaptive immunity mediate protection through direct actions on fungal cells, and classical mechanisms such as phagocytosis and complement activation are affected in case of mutations in genes coding for those Igs (Kaufman, 1985; Lionakis et al., 2014; Table 1). MHC class II defects lead to primary immunodeficiency disease (PIDD) and make individuals susceptible to a high rate of fungal infection like Candidiasis and PCP (Lanternier et al., 2013; Abd Elaziz et al., 2020). Mutation in CARD9 and DOCK8 (dedicator of cytokinesis 8) among PIDD individuals makes them susceptible to Malassezia infection, and deficiency in STAT3 leads to IPA (Abd Elaziz et al., 2020). Summary of the immune-related genes responsible for susceptibility to fungal infection is highlighted in Table 1.

Interleukins (ILs) play a crucial role during fungal infection and help in the maturation of B cells and antibody secretion, which helps fight fungal infections (Antachopoulos and Rolides, 2005; Verma et al., 2015; Sparber and LeibundGut-Landmann, 2019; Griffiths et al., 2021). Mutations in genes encoding for members of the IL-1 family are associated with acute and chronic inflammation and are essential for the innate response to infection (Caffrey et al., 2015; Griffiths et al., 2021). Genetic variation in IL-6 results in blastomycosis (Merkhofer et al., 2019), and defect in IL-10 and IL-6 signaling affects STAT3, a key immune response molecule. Genetic variation in IL-10 has also been found to be the underlying cause of susceptibility toward fungal infections like IA (ZaaS, 2006). IL-10 mutation makes an individual susceptible to Candida and Coccidoides immitis infection (Fierer, 2006), and IL-4 polymorphism resulted in susceptibility toward Candida infection (Babula et al., 2005; Choi et al., 2005). SNP in rs2243250, known to influence IL-4 production, is associated with susceptibility to PCP in HIV-positive patients (Wójcieszczuk et al., 2019). In addition, deficiency of interleukin IL-17 and IL-22 production as a result of genetic mutation has been reported to be the cause of RVVC (Sobel, 2016). IL-2 mutation too predisposes individuals to invasive fungal infection like histoplasmosis by affecting T cell functions (Smeekens et al., 2013; Lionakis et al., 2014; Kumareshan et al., 2017; Pathakumari et al., 2020). The emerging role of the IL-12 family of cytokines in the fight against candidiasis has been reported (Ashman et al., 2011; Thompson and Orr, 2018). IL-12RB1 (interleukin receptor subunit beta 1) impairs the development of human IL-17 producing T cells (Huppler et al., 2012; Johnson et al., 2012; Thompson and Orr, 2018), and mutations inherited might be responsible for histoplasmosis (León-Lara et al., 2020). RAR-related orphan receptor C (RORC) encoding transcription factors play an integral role in both IL-17 and IFNγ pathways in CMC (De Luca et al., 2007; Constantine and Lionakis, 2020). Deficiency of tyrosine kinase 2 (Tyk2) that participates in signal transduction for various cytokine receptors leads to impaired helper T cell type 1 (Th1) differentiation and accelerated helper T cell type 2 (Th2) differentiation in candidiasis (Minegishi et al., 2006). Mutation in the main inflammasome NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3), associated with fungal infection, leads to susceptibility toward RVVC or IPA (Kasper et al., 2018; Wang et al., 2020; Briard et al., 2021). Also, mutations in key recombination activating genes (RAG1 and RAG2) lead to loss of T and B cells, making individuals susceptible to CMC and a broad spectrum of pathogens (Schuetz et al., 2008; Delmonte et al., 2018). Genetic polymorphism in the IL-17 family genes, which encode for the Th17 cellular differentiation, results in an individual's susceptibility toward fungal infection (Hamad et al., 2018). One of the key signaling molecule pathways, the IL-17R signaling is dependent on Act1 (Actin1—a conserved protein that helps in key cellular processes), and mutation in the gene coding for Actin1 leads to defect in IL-17R signaling pathway, which ultimately fails to provide immunity against CMC (Boisson et al., 2013). IL-17RA binds to homo- and heterodimers of IL-17A and IL-17F, and its deficiency or genetic mutation in any of the gene coding for receptors IL-17RA or IL-17RC leads to CMC (Puel et al., 2011; Sawada et al., 2021).

Mutation in DOCK8 characterized by elevated IgE level is also known to be responsible for recurrent fungal infections like IA and mucocutaneous candidiasis (Biggs et al., 2017; Nahum, 2017). During Aspergillus infection, tumor necrosis factor-alpha (TNFα) enhances the phagocytic activity and the polymorphic site in TNF promoter predisposes individuals to IA (Rolides et al., 1998; Sainz et al., 2007). Neutrophil cytotoxic factors (NCFs) are part of the group of proteins that form the enzyme complex called NADPH oxidase, and mutation in any of the key genes NCF1, NCF2, and NCF4 leads to impaired fungal eradication (as in aspergillosis) due to non-functional NADPH oxidase (Panday et al., 2015; Giardino et al., 2017; Dinauer, 2019; Wu et al., 2019). Decreased myeloperoxidase (MPO) activity (inability to produce hypochlorous acid) in neutrophils leads to delayed killing of pathogen and makes an individual susceptible to invasive Candida infection (Aratani et al., 1999; Merkhofer and Klein, 2020). Myeloperoxidase mutants lead to impaired ROS production, making the host susceptible to infection, and thus, both MPO and NADPH oxidase mutants are unable to eradicate fungal threats like chronic granulomatous disease (CGD) and IA (Lehrer and Cline, 1969; Aratani et al., 2004; Segal and Romani, 2009; Ren et al., 2012). Cytochrome b-245 is a primary component of the microbicidal oxidase system of phagocytes encoded by the alpha and beta chains CYBA and CYBB/Nox2 (NADPH oxidase 2), respectively (Stasia, 2016), and cytochrome...
b deficiency is also linked to CGD (Clark, 1999; Stasia et al., 2003; Kutukculer et al., 2019). Recently, it has been reported that mutants in the ferroxidase gene make individuals susceptible to mucormycosis (Navarro-Mendoza et al., 2018), an infection that has been affecting COVID-19 patients (Raut and Huy, 2021). Thus, mutations of key genes of the immune system play an important role in fungal resistance, and interestingly, genetic polymorphisms in these genes have revealed some links with human ancestry.

HUMAN ANCESTRY AND GENETIC PREDISPOSITION TO FUNGAL INFECTIONS

There is limited research investigating the link between genetic polymorphism in key immune genes, human ancestry, and susceptibility toward fungal infection (Figure 1). But recent research outcomes aided by genomic sequencing point toward an interesting fact. Infection with the fungus *Coccidioides immitis* among Filipino ancestry was found to be common among men and non-white persons causing coccidioidomycosis (van Burik and Magee, 2001). Studies on DNA, which provides genetic information transferred from ancestors to their family members and relatives, indicate that the Hmong ancestry are more susceptible to fungal infection (Xiong et al., 2013). In another report, genetic differentiation among the Hmong ancestry originating from Wisconsin makes them more susceptible to blastomycosis. The Chinese Han population was found to suffer due to poor metabolism as a result of *Hlm* ancestry originating from Wisconsin makes them more susceptible to fungal infection (Figure 1). Recently, it has been reported that mutants in the ferroxidase gene make individuals susceptible to mucormycosis (Navarro-Mendoza et al., 2018), an infection that has been affecting COVID-19 patients (Raut and Huy, 2021). Thus, mutations of key genes of the immune system play an important role in fungal resistance, and interestingly, genetic polymorphisms in these genes have revealed some links with human ancestry.

DISCUSSION

Fungi play an important role in the human microbiome (Huseyin et al., 2017; Perez et al., 2021; Tiew et al., 2021). In this review, we have focused on genetic predisposition to human fungal infections and discussed the link that exists between ancestry and susceptibility to IFIs. Among those fungi that are commensal with the warm-blooded host, few turn pathogenic under not so well-defined conditions (Hall and Noverr, 2017; Jacobsen, 2019; Limon et al., 2017). Such conversion to pathogenic forms is aided by external factors like environment, immunological status, and most importantly host genetics (Kobayashi, 1996; Kumar et al., 2018; Figure 1). As we learn more about fungal biology, we also understand genetic signatures in the host that make them prone to fungal infections. This is explained by the term genetic predisposition, and external players like the environment also play a role in triggering an autoimmune, inflammatory, or allergic reaction to fungal infections (Figure 1). Identification of fungal allergens has become challenging because most of the allergens mimic immune molecules (Pavia et al., 2020). We have seen how mutations in key recognition molecules (Table 1) play a trigger for several fungal infections. We looked into variations introduced by SNPs that are present in the immune response genes (Table 1) critical for fungal infections. The polymorphism in the immune genes (PTX3, CX3CR1, CARD9, STAT3, and others, Figure 1) make the host susceptible (Garlanda et al., 2002; Kumar et al., 2018; Vinh, 2019), and defect in interleukins (e.g., IL-4, IL-10) leads to genetic predisposition toward fungal infection (Babula et al., 2005; Choi et al., 2005; Zaa, 2006; Table 1). The study of these genes helps us to understand the relationship between genetic polymorphism and the cellular
phenotype of host, pathogen, and associated defense mechanisms (Sardinha et al., 2011). Thus, the composition of both host and pathogen plays important role in disease progression, and the challenge is to identify the genetic components involved in pathogenesis.

A few studies point toward a link between human ancestry and genetic predisposition to fungal infections (van Burik and Magee, 2001; Ferwerda et al., 2009; Xiong et al., 2013; Chen et al., 2019; Du et al., 2019; Espinoza et al., 2019; Table 1). Mutations in several components of the immune system make certain human ancestral descendants more prone to fungal infections. Few studies have looked into genetic associations and human ancestry. This aspect is an important and emerging research area in terms of population genetics (Hirschhorn et al., 2002; Gnat et al., 2021). Mutation in key genes relating to the immune system of the host makes certain ancestral descendants susceptible to fungal infections as we observe in the case of certain European, African, and Caucasian individuals (Larcombe et al., 2002; Gnat et al., 2021). Mutation in key genes relating to the immune system makes certain ancestral descendants more susceptible to fungal infections (Figure 1). Such fungi are a threat to global public health and can colonize the skin, spread from person to person, and cause many high-risk diseases (Lamoth and Kontoyiannis, 2018). To deal with such organisms, we require better surveillance methods, rapid and accurate diagnostics, and decolonization protocols that include administration of antimicrobial or antiseptic agents and new antifungal drugs (Jeffery-Smith et al., 2018; Jackson et al., 2019; Chowdhary et al., 2020; Fisher et al., 2020; Steenwyk et al., 2020). Genome-wide association studies (GWAS) would help us to evaluate the difference in the DNA sequences and understand heritability, disease risk, and susceptibility to antifungals (Bloom et al., 2019; Guo et al., 2020; Figure 1). From genome sequencing, genomic variations like SNPs, variable number tandem repeats (VNTRs), and insertion/deletions (Indels) can be identified. Structural genome variations like aneuploidy and copy number variations (CNVs) also provide important clues to fungal virulence (Tsai and Nelliat, 2019). During fungal microevolution, many of these events like insertion/deletion of genes, loss of heterozygosity (LOH), and genome plasticity help fungus to adapt against antifungal drugs and harsh host environment (Beekman and Ene, 2020). Thus, as part of preventive medicine, a better understanding of host genetics behind fungal infection will help us to study infectious diseases through modern genomic approaches and offer personalized therapy against invasive fungal diseases.

**AUTHOR CONTRIBUTIONS**

SD conceptualized, reviewed, and approved the manuscript. BN drafted the manuscript, revised the article critically, and provided critical suggestions. SA contributed toward artwork and reviewed the manuscript. SL provided critical review and revised intellectual content. All authors contributed to the article and approved the submitted version.

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