REVIEW

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Genetic susceptibility to dermatophyte infections: a review

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ABSTRACT

Dermatophytes infect people of all ages, races, genders, and socioeconomic statuses. However, some groups of individuals tend to be more susceptible. Several risk factors have been described, particularly in immunocompromised individuals and patients with severe illnesses. Unfortunately, this still does not explain why only some immunocompetent individuals experience infections. Some studies have concluded that genetic susceptibility is associated with defects in Toll-like receptors involved in the inflammatory response and pathogen clearance mechanisms, C-type lectin receptors, nucleotide-binding and oligomerization domain (NOD)-like receptors, and defects in soluble pattern recognition receptors, which can lead to impaired phagocytosis and pathogen elimination by neutrophils. The purpose of this article is to highlight how the human body reacts to fungal exposure and a number of genetic changes that may be the cause of fungal infections, even in immunocompetent people.

Keywords: dermatophytes, genetic, susceptibility.
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INTRODUCTION

There are approximately 5.1 million species of fungi on Earth. These eukaryotic organisms have a significant impact on human health. Fungi can grow anywhere, including on the human body.[1] Fungi can cause various symptoms in humans, from skin lesions to pulmonary manifestations, which can resolve spontaneously in immunocompetent individuals, while life-threatening conditions may occur in immunocompromised individuals.[2]

Dermatophytes infect people of all ages, races, genders, and socioeconomic statuses. However, some groups of individuals tend to be more susceptible.[3] Several risk factors have been described, particularly in immunocompromised individuals and patients with severe illnesses. Unfortunately, this still does not explain why only some immunocompetent individuals experience infections.[4]

These risk factors are divided into three groups by Gnat et al.: 1) environmental conditions of the host and pathogen; 2) host characteristics; and 3) dermatophyte species and ecological groups. Environmental conditions relate to climate, while host characteristics determine the body's ability to fight pathogen exposure.[3] Patients immunocompetent with fungal infections are often affected by genetic alterations in several key genes, and most reported genetic defects are related to the failure of the innate immune system to recognize fungal components.[1,4]

For years, clinicians have studied the molecular interactions between pathogens and pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs). The identification of mutations or polymorphisms in patients and experimental animals has furthered clinicians' understanding of the mechanisms and functions of PRRs that underlie antifungal immunity in various aspects, such as intracellular signaling, induction and/or regulation of cellular responses, and the formation of adaptive immunity.[2] Based on this finding, clinicians are required to broaden their understanding of the role of genetics in fungal infections. In this regard, this article aims to emphasize the human body's response to fungal exposure and several genetic alterations that may underlie fungal infections, particularly in immunocompetent individuals.

ROLE OF GENETIC SUCEPTIBILTY

Understanding the role of genetics in susceptibility to infection is crucial for improving diagnostic accuracy, genetic counseling, and the discovery of novel therapies.[5,6] One key to understanding susceptibility to infectious diseases is the study of inborn errors in the immune system that can compromise host defense against infection. This analysis will be invaluable in elucidating the mechanisms of infectious disease pathogenesis. One advancement in this era is the recognition that disease-related genes do not always cause immune system abnormalities, but sometimes contribute to a distinct clinical picture of infection. However, several challenges remain in genetic studies, including determining the genetic variation of the host and pathogen. This requires larger sample sizes.[6]

Genetic Susceptibility to Fungal Infections

Genetic variation plays a role in fungal infections. Recent studies have shown that it is associated with the severity and susceptibility of fungal infections. The increased incidence of opportunistic infections is also related to genetic polymorphisms and genetic errors, which are often found in immunocompromised phenotypes. Along with genetic and environmental factors, lifestyle also contributes to genomic variation, such as exposure to toxic chemicals and immunosuppressive medications.[1]

A familial susceptibility, characterized by a high frequency of dermatophyte infections within a family, is currently being observed.[3] The symptoms of dermatophytosis are not limited to the appearance of acute or chronic lesions, but involve a broad spectrum, ranging from individuals who have never experienced infection to those who experience inflammatory, non-inflammatory, and therapy failure, as well as invasive, disseminated, and life-threatening conditions. Exposure of the stratum corneum to infectious dermatophyte elements does not always result in symptoms of infection.[3]

The host's health condition influences the course of the disease and the relationship with dermatophytes, and the same genetic strain of dermatophyte can cause different infection patterns in humans living in the same environment. Furthermore, several coexisting health conditions, such as eczema, psoriasis, ichthyosis, atopic dermatitis, and seborrheic dermatitis, can influence susceptibility to dermatophytes. Different fungal strains with varying infective capacities, combined with the host's genetic susceptibility, determine the type of infection that will occur. Thus, the host's genetic predisposition is as important as the pathogen's virulence and adaptation. In clinical practice, both factors must be considered.[3]

The first study analyzing genetic linkages for dermatophyte infection susceptibility was conducted by Bonifaz et al. In their study, they examined cases of tinea imbricata caused by Trichophyton concentricum, and genetic susceptibility with an autosomal dominant pattern was found in nine of 16 family members. In addition to inherited susceptibility, an ineffective immune response may explain the high recurrence rate and the widespread infection.[7] Several other researchers have reported a high prevalence of tinea imbricata in several races living in a country with similar environmental conditions.[3] The link between genetics and infection has also been studied in a cohort study. The study found that more than 65% of the variability in infection incidence was influenced by sequence variations in 21 genes. These genes are involved in leukocyte recruitment, activation, and migration (SEMA6A, ROBO1, SLIT3, cd99L2, CSMD1, GAB2), extracellular matrix formation, integrity, and remodeling (FBLN5, FBN2, MFAP4, SMOC2, PCDH7, MMP3, ADAM 12), epidermal development, maintenance, and wound healing (FGF1, MAPK8, IGF1R), and skin homeostasis and host-pathogen interactions (LASS4, GALP, KAL1, FibCD1).[3,8]

Abdel-Rahman and Preuett have identified genes responsible for host-pathogen interactions and their association with increased susceptibility to dermatophyte infections. They studied cases of tinea capitis over several years. The study included 20 children with a *T. tonsurans* infection frequency of ≥ 90% (i.e., always or almost always infected) and 20 children with an infection rate of ≤ 10% (i.e., never or rarely infected). Twenty-one genes significantly differed in infection rates between genotypes. The majority of genes contributing to variability were genes with multiple functions, including leukocyte function, extracellular matrix remodeling, wound healing, and skin permeability. These findings indicate that the adaptive immune response influences predisposition to dermatophyte infections.[9] Literature studies have also highlighted the possibility of an interaction between innate immune defects and the adaptive response.[10] Jaradat et al. examined the relationship between dermatophytosis caused by *T. rubrum* and the expression of genes encoding interleukin (IL)-22, human beta defensin-2 (hBD-2), and beta-defensin-4 (DEFB4). There was a relationship between variations in the number of DEFB4 mRNA copies and the appearance of superficial dermatophytosis caused by *T. rubrum*. Low copies are a risk factor for dermatophytosis. In addition, increased levels of IL-22 are also implicated in its pathogenesis.[11] Other genes, such as Fc receptor gamma, which is used by the recognition receptor dectin-2 to induce an innate immune response against *T. rubrum*, are also involved in increased susceptibility to dermatophyte infections. This gene also exhibits variable copy numbers in individuals with and without infection and may contribute to the pathogenesis of dermatophyte infections.[3]

The major histocompatibility complex (MHC) and human leukocyte antigen (HLA) systems are considered important for antigen presentation and activation of T cell-mediated responses in the course of fungal infections.[12] In a Brazilian Ashkenazi Jewish population with *T. rubrum* onychomycosis, HLA-DR4 was found in 100% of asymptomatic individuals and in 25% of cases, suggesting a protective effect on disease susceptibility. Conversely, in a Mexican mestizo population with onychomycosis caused by the same dermatophyte species, HLA-DR8 frequencies tended to be higher in affected families, suggesting that this haplotype may confer susceptibility.[3] Furthermore, Carrillo-Mele'ndrez et al. demonstrated an association of HLA-DR8 with genetic susceptibility to onychomycosis in patients with nail psoriasis. Their study also revealed a possible association between HLA-DR1 and a genetic predisposition to the development of onychomycosis.[12]

Another candidate gene for predisposition to superficial dermatophytosis is CLEC7A-Y238X, an early stop codon variant that affects the recognition of fungal beta-glucan by the dectin-1 receptor. Defects in dectin-1 surface expression associated with the Tyr238 polymorphism lead to impaired beta-glucan recognition and impaired cytokine responses by monocytes and macrophages. This polymorphism is frequently identified in African populations.[3] This genetic defect was found in a family of Dutch descent, and all family members had onychomycosis.[13]

Toll-like Receptor Defects

Toll-like receptors are predominantly expressed by immune system cells, such as monocytes, neutrophils, basophils, eosinophils, and natural killer cells. They are also expressed by epithelial, endothelial, and stromal cells.[4] Genetic defects in TLRs can affect adaptive immune responses, in addition to fungal recognition and innate immunity. Although not yet widely available, clinicians should consider a patient's genetic profile during diagnostic approaches based on measuring fungal-specific adaptive immune responses.[14] The same applies to immunotherapeutic strategies focused on direct or indirect cytokine manipulation, as there are numerous examples of genetic variants that influence cytokine production and function.[15]

C-Type Lectin Receptor Defects

The major class of CLRs includes dectin-1, dectin-2, mannose receptor, dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN), macrophage inducible C-type lectin (Mincle), macrophage C-type lectin (MCL), and MelLec.[16] These receptors are highly implicated in the activation and regulation of antifungal immune responses.[2] Among CLRs, dectin-1 is the most prominent receptor capable of regulating the activation of the adaptive immune response to fungi. Dectin-1 recognizes beta-glucan and triggers intracellular signaling pathways that, either synergistically or through cross-regulatory mechanisms, lead to NF-κB activation and cytokine gene expression.[4]

The dectin-1 defect caused by the early stop codon polymorphism rs16910526 (Y238X) results in a truncated form of dectin-1 missing several amino acids in the carbohydrate recognition domain. Consequently, there is decreased expression on the surface of myeloid cells and defective cytokine production, particularly IL-17. This condition is strongly implicated in fungal colonization in the mucosal and gastrointestinal tract. Furthermore, another dectin-1 variant, rs16910527, is associated with low interferon-γ levels and an increased risk of oropharyngeal candidiasis in human immunodeficiency virus (HIV) patients.[4]

Several conditions can lead to recurrent severe infections, one of which is caspase recruitment domain-containing protein 9 (CARD9) deficiency. This component is an adaptor molecule that controls the antifungal activity of macrophages and neutrophils in the skin. The CARD9 protein is also crucial for the activity of T-helper 17 (Th17) cells, particularly through signaling by dectin-2, dectin-1, and macrophage-inducible C-type lectin. The deficiency is inherited in an autosomal recessive manner.[3] Neutrophils from these patients exhibit impaired phagolysosomal killing of unopsonized C. albicans, a phenotype independent of dectin-1 and NADPH oxidase activity. This explains the varied clinical presentation of fungal infections in patients with dectin-1 and CARD9 deficiencies.[4]

Various CARD9 loss-of-function mutations have been associated with autosomal recessive susceptibility to invasive fungal infections, including *Candida spp*., dermatophytes, and fungal growth.[5] Glocker et al. presented a pedigree analysis for a family with multiple members affected by chronic fungal infections associated with a possible autosomal recessive inheritance pattern of CARD9. In their study, recurrent fungal infections were clinically diagnosed in eight family members, three of whom died in early adolescence. None of these patients had bacterial or viral diseases, indicating normal host defenses against pathogens.[17] Nazarian et al. described a case of tinea profunda caused by *Trichophyton rubrum* and *Trichophyton violaceum* in a 31-year-old man who had bi-allelic mutations in CARD9.[18] Additionally, Vaezi et al. reported that deep dermatophytosis accounted for 37.3% of reported cases of fungal infections associated with CARD9 deficiency due to autosomal recessive mutations. *Trichophyton violaceum*, *T. rubrum*, and *T. mentagrophytes* were the pathogens in these dermatophytosis cases. Interestingly, analysis of the characteristics, distribution, frequency, and association between CARD9 gene mutation genotypes and fungal infections in reported cases revealed that 75% of cases were found in Africa.[19] These data suggest that mutations may be specific to certain populations or geographic regions.[3,19,20]

Defects in Soluble Pattern Recognition Receptors

In addition to the PRRs described previously, several soluble molecules also have the ability to interact with microbial polysaccharides without inducing intracellular signals. These components function as opsonins that facilitate phagocytosis. Mannose-binding lectin (MBL) is a CLR that binds microbial carbohydrates and activates the lectin pathway. Genetic variation is responsible for differences in MBL levels and function in at least 8% of the global population. They do not exhibit a clear clinical phenotype, indicating that MBL deficiency can be compensated for by the humoral immune system. Although it does not cause a clear immunodeficiency, defects in MBL function are an important risk factor for infection.[4]

Another water-soluble pattern recognition receptor is long pentraxin-3 (PTX3). This molecule binds to a number of microorganisms, such as bacteria, viruses, and fungi. The resulting polymorphism does not cause immunodeficiency, but it does disrupt neutrophil function (phagocytosis and pathogen elimination). Pentraxin-3 is a molecule that links neutrophil and B-cell functions, including switching, plasma blast expansion, and antibody production. PTX3 binding to myeloid differentiation protein 2, an adaptor of the TLR4 signaling complex, is essential for the immune system. Restoring PTX3 to normal levels in vitro with the aid of a recombinant protein can restore the antifungal efficacy of neutrophils.[4]

CONCLUSION

Fungal infections are quite common. Their severity depends on several factors, such as environmental conditions, fungal virulence, and the host's immunogenetic status. Numerous studies have implicated genetic variations in the risk of contracting fungal infections. Some studies have concluded that genetic susceptibility is associated with defects in Toll-like receptors involved in the inflammatory response and pathogen clearance mechanisms, C-type lectin receptors, and defects in Soluble Pattern Recognition receptors, which can lead to impaired

phagocytosis and pathogen elimination by neutrophils. However, further studies are needed to determine the causative alleles and their exact functional consequences. Understanding the role of genetics is crucial because identifying high-risk families allows for education about their potential risk of fungal infections. In clinical practice, this information can also lead to faster and more appropriate diagnosis and therapy.

Conflict of Interest

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