J.Mycopathol.Res. 62(1) : 51-54, 2024, ISSN : 0971-3719 (Print), 2583-6315 (Online) doi.10.57023/JMycR.62.1.2024.051

REVIEW

APOE gene polymorphism and susceptibility to superficial mycoses

KONAD KUNDU[1], SOUMIKA BISWAS[1§], SUBHRAMAY CHATTERJEE[1§], AND SUREKHA KUNDU[2*]
[1]Department of Biochemistry, Medical College Kolkata, 88, College Street, College Square, Kolkata-700073
[2]Molecular and Applied Mycology and Pathology Laboratory, Department of Botany, University of Calcutta, 35 Ballygunge Circular Road, Kolkata-700019

Received : 31.10.2023 Accepted : 25.02.2024 Published : 25.03.2024

Superficial mycoses or superficial fungal infections are diseases of the skin, nails and mucosal layers caused by fungi. In spite of abundance of studies on superficial mycoses, research on genetics of host in relation to susceptibility to these diseases is an emerging field. Amongst the genes that are thought to play important roles, *APOE* gene is one of the least studied. The *APOE* gene codes for Apolipoprotein E which is integral to lipid metabolism. In the general population, there exist three alleles ε2, ε3, and ε4 that result in six genotypes, ε2/2, ε3/3, ε4/4, ε2/3, ε2/4, and ε3/4. Recent research show there is direct link between the status of *APOE* gene polymorphism and susceptibility to superficial mycoses. Although there are mice models for the *APOE* gene of knockout or deficient types, there is no study in mice in regards to susceptibility to superficial fungal infections. In human populational studies there is strong indication that certain allelic *APOE* genotypes are a risk factor for superficial mycoses while other genotypes may be beneficial. Therefore the study of *APOE* gene polymorphism in patients is an important option for better treatment strategies for superficial mycoses.

Keywords: Apolipoprotein gene, cadiovascular disease, diabetes, fungal infections, mycoses, polymorphism.

INTRODUCTION

Fungal infections of the skin and nails are a common global problem. Superficial mycoses or superficial fungal infections are the commonest of fungal infections and about 20-25% of world population suffer from skin mycoses sometime during their life (Havlickova *et al*. 2008). There exists striking disparity in the incidence of dermatophyte infections within and between populations which has elicited numerous investigative researches to decipher whether there lies a link between host genetics and protection against fungal infections (Abdel-Rahman, 2017).

The Apolipoprotein E (APOE) has been shown, through immunohistochemical techniques, to localize into skin cells and *APOE* gene status has been directly implicated in superficial fungal infections.This review discusses the link between *APOE* gene polymorphism and susceptibility to superficial fungal infections.

Superficial mycoses or superficial fungal infections

Superficial mycoses are mostly confined to the external layers of the skin nails and mucosal linings (Tursen *et al.* 2004). These diseases fall under three broad groups; dermatophytic infections, Tinea and superficial candidiasis. Defense against such infections are either immunogenic or non-immunogenic (Tursen *et al*. 2004). The most widespread superficial mycoses are caused by the dermatophytes or ringworm fungi, *Candida*, *Malassezia* species and various groups of pathogenic fungi (Hay, 2010).

*****Correspondence: surekha_kundu@yahoo.com
§ These authors contributed equally

Superficial fungal infections of the skin are commonly designated according to location of the infection. Tinea means fungal infection. Tinea are named as: Tinea pedis (infection of the feet), Tinea cruris (jock itch), Tinea corporis (facial infection), Tinea manuum (tinea of the hand) and Tinea capitis (tinea of the scalp) (Kaushik, *et al*. 2015). These diseases are caused by filamentous fungi belonging to the genera *Trichophyton*, *Microsporum* and *Epidermophyton* spp. (Hay, 2010). Onychomycosis, is the name given to the fungal infection of the toe nails or finger nails caused by the *Trichophyton rubrum* complex, a common human pathogen (Chen *et al*. 2024). Other superficial mycoses include infections by *Candida* sp (Nagi *et al*. 2013), *Malassezia* sp, *Trichosporon* sp and *Hortae* sp. (Ameen, 2010).

Superficial fungal infections tend to be more common in covered moist parts of the body and may later invade various parts of the body. Superficial mycoses include dermatophytes, which infect keratinized epithelial layers of the skin, nail bed and hair follicles (Ameen, 2010).These fungal diseases can be effectively eradicated with simple treatment option in normal immunocompetent people. But in the immunocompromised patients, these can take up serious forms (Kaushik *et al*. 2015).

The link between genetics and proneness to fungal infections

Although fungi are commonly present in the environment, under normal conditions, healthy individuals do not get infected with fungi (Merkhofer and Klein, 2020). Even when present in similar conditions of exposure to fungal inocula, some people get infected while others do not (Maskarinec *et al*. 2016). There is increasing evidence that point to the fact that there is direct correlation between host genetics and susceptibility to dermatophytes (Abdel-Rahman, 2017).

APOE gene polymorphism status and effect on immunity against superficial mycoses

Lipoproteins have been found to play a direct role in preventing fungal infections along with infections caused by other microorganisms (Han, 2010). The *APOE* gene codes for the Apolipoprotein E. It is located on chromosome 19 and has three polymorphisms namely, ε2, ε3, and ε4 (Mustafa *et al*. 2023). These polymorphisms arise due to variation of C or T nucleotide at codons 112 and 158. The resulting three alleles give rise to three isoforms with differences in structural and functional characteristics. The six genotypes are created by different combinations such as (ε2/2, ε3/3, ε4/4, ε2/3, ε2/4, and ε3/4) (Hatters *et al*. 2009). This difference in status of *APOE* gene polymorphism affects the susceptibility to different diseases (Karpouzis, 2009) including superficial fungal infections (Mustafa *et al*. 2023). Since APOE functions both as an immunomodulator as well as antimicrobial agent, identifying the status of *APOE* polymorphism in patients with superficial mycoses is an advantageous option (Tursen *et al*. 2004).

Status of research on superficial mycoses and APOE gene polymorphism

In the recent past, studies on the link between genetic factors and susceptibility to fungal diseases have been active fields of research (Bruno *et al*. 2021). However, reports on research on the link between *APOE* gene polymorphism status on superficial mycoses is scarce; and this remains an unexplored field of research. Studies in this field is discussed under the following two heads:

A. Research on Mice Models

Studies on mice regarding the role of *APOE* polymorphism in susceptibility to particularly superficial mycoses is non-existant; in spite of the fact that mice models are available for *APOE* gene such as *APOE* deficient mice or *APOE* knock-out mice (Lo Sasso *et al*. 2016, Amram and Frenkel, 2017). There are many studies on other functions of *APOE* in mice models. *In vivo* studies with mice models have revealed that APOE protein plays an anti-inflammatory and anti-microbial roles (Petruk *et al*. 2021). There is one report on the effect of *APOE* status on *Candida* infection in mice model. *APOE*-deficient mice were found to be significantly more susceptible

to fungal infections such as systemic candidiasis (Vonk *et al*. 2004). Therefore there may also be a link between *APOE* gene polymorphism status and superficial *Candida* infections.

B. Studies on human populations

A few studies with human populations have shown that the status of *APOE* gene polymorphism can be utilized to assess the risk factor to superficial fungal diseases like dermatophytosis (Tursen *et al*. 2004). However such studies have been limited to only a few ethnicities (Mustafa *et al*. 2023).

Tursen *et al*. (2004), carried out a study with 42 patients in Turkey, where they assessed the *APOE* gene polymorphism status in patients with superficial mycoses. They found that significantly more number of patients had the APOE ε2/3 heterozygosity along with elevated high density lipoprotein. Minimum number of patients presented with the APOE ε3/3 homozygosity. Most of these patients had candidiasis and dermatophytosis. So the conclusion of that study was that the presence of ε 2/3 heterozygosity and the absence of ε3/3 homozygosity along with elevated high density lipoprotein levels were associated with greater risk for superficial mycoses.

Very recently another study was carried out with Egyptian population by Mustafa *et al.*, (2023). In this study, the blood cholesterol levels and the *APOE* status was assessed for 150 patients including males and females with tinea versicolour, cutaneous candidiasis, and dermatophytic lesions. The results showed that the serum total cholesterol, triglycerides, and low-density lipoprotein were higher in the study group compared to the control. The *APOE* gene ε2, ε4 alleles, and ε3/2 and ε3/4 alleles were found to be more significantly represented in the infected patients than in the controls. Moreover, the ε3/4 genotype was found to be more common in patients with candidiasis while the ε3/3 genotype was more abundant in patients with tinea versicolour and dermatophytosis.

CONCLUSION

Research in the area of host genetic make-up and susceptibility to fungal infections has progressed rapidly (Bruno et al, 2021). The hypothesis that APOE plays an important role in modulating immune responses has been amply demonstrated (Laskowitz et al., 2000). There is growing evidence that *APOE* gene polymorphism plays a decisive role in susceptibility to superficial mycoses (Mustafa *et al*. 2023). Therefore the assessment of the status of *APOE* gene polymorphisms in patients with persistent or severe superficial mycoses may help with planning appropriate therapy.

DECLARATIONS

Conflict of interest: Authors declare no conflict of interest.

REFERENCES

Abdel-Rahman, S.M. 2017. Genetic predictors of susceptibility to Dermatophytoses. *Mycopathologia* **182**: 67–76. https://doi.org/10.1007/s11046-016-0046-z

Ameen, M. 2010. Epidemiology of superficial fungal infections. *Clin. Dermatol*.**28**:197-201. doi: 10.1016/j.clindermatol.2009.12.005.

Amram, S., Frenkel D. 2017. Animal models of Alzheimer's disease. Chapter 3. In: *Neuroprotection in Alzheimer's Disease* (Ed.:Illana Gozes), Academic Press, pp. 31-58.

Bruno, M., Matzaraki, V., van de Veerdonk, F.L., Kumar, V., Netea, M.G. 2021. Challenges and opportunities in understanding Genetics of fungal diseases: Towards a Functional Genomics Approach. *Infect. Immun*. **89**:e00005-21. https://doi.org/10.1128/IAI.00005-21.

Chen, J., Yangmin,G., Xiong, S., Peng, Z., Zhan, P. 2024. Expression Profiles of Protease in Onychomycosis-Related Pathogenic Trichophyton rubrum and Tinea Capitis-Related Pathogenic Trichophyton violaceum. *Mycopathologia* **189**:14. doi.org/10.1007/s11046-024-00828-3

Han, R. 2010 Plasma lipoproteins are important components of the immune system. *Microbiol. Immunol.* **54**: 246-253. doi.org/10.1111/j.1348-0421.2009.00203.x

Hatters, D.M., Voss, J.C., Budamagunta. M.S., Newhouse, Y.N., Weisgraber, K.H. 2009. Insight on the molecular envelope of lipid-bound apolipoprotein E from electron paramagnetic resonance spectroscopy. *J. Mol. Biol*. **386**:261–71.

Havlickova, B., Czaika, V.A., Friedrich, M. 2008.Epidemiological trends in skin mycoses worldwide. *Mycoses* **51** Suppl. 4:2-15. doi: 10.1111/j.1439-0507.2008.01606.x.

Hay, R.J. 2010. Superficial and mucocutaneous mycoses. Chapter 59. In: *Antibiotic and Chemotherapy* (Ninth Edition). (Eds. Roger G. Finch, David Greenwood, S. Ragnar Norrby, Richard J. Whitley), W.B. Saunders, pp. 771-776. doi.org/10.1016/B978-0-7020-4064-1.00059-2.

Karpouzis, A., Caridha, R., Tripsianis, G. Michailidis, C., Martinis, G., Veletza, S.V. 2009. Apolipoprotein E gene polymorphism in psoriasis. *Arch Dermatol Res*. **301**: 405–410. doi.org/10.1007/s00403-009-0968-0

Kaushik, N., Pujalte, G.G., Reese, S.T. 2015. Superficial Fungal Infections. *Prim Care*. **42**:501-16. doi: 10.1016/j.pop.2015.08.004. PMID: 26612371.

Laskowitz, D. T., Lee, D. M., Schmechel, D., Staats, H. F. 2000. Altered immune responses in apolipoprotein E-deficient

mice. *J. Lipid Res*. **41**: 613–620. doi.org/10.1016/S0022-2275(20)32409-3.

Lo Sasso, G., Schlage, W.K., Boué, S., Veljkovic, E., Peitsch, M.C., Hoeng, J. 2016.The Apoe(-/-) mouse model: a suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction. *J. Transl. Med*. **20**:14:146. doi: 10.1186/s12967-016-0901-1.

Maskarinec, S.A., Johnson, M.D., Perfect, J.R. 2016.Genetic Susceptibility to Fungal Infections: What is in the Genes? *Curr. Clin. Microbiol. Rep*. **3**:81-91. doi: 10.1007/s40588-016-0037-3.

Merkhofer, R. M., Klein, B. S. 2020. Advances in understanding human genetic variations that influence innate immunity to fungi. *Front. Cell. Infect. Microbiol*. **10**. doi: 10.3389/fcimb.2020.00069.

Mustafa, A.I., Shams, G.M., Fawzy, E.M., Alhusseini, N.F., Khashaba, R.A., El-Shimi, O.S. 2023. Apolipoprotein E Gene Polymorphism, Serum Lipids, and risk of superficial fungal infections in Egyptian patients - A preliminary case-controlled study. *Ind. J. Dermatol*. **68**: 233. doi: 10.4103/ijd.ijd_1001_22.

Nagi, M., Tanabe, K., Nakayama, H., Yamagoe, S., Umeyama, T., Oura, T, Ohno, H., Kajiwara, S., Miyazaki, Y. 2013. Serum cholesterol promotes the growth of *Candida glabrata* in the presence of fluconazole. *J. Infect. Chemother*.**19**:138-143. doi: 10.1007/s10156-012-0531-3. PMID: 23233084.

Petruk, G., Elvén, M., Hartman, E., Davoudi, M., Schmidtchen, A., Puthia, M., Petrlova, J. 2021. The role of full-length apoE in clearance of Gram-negative bacteria and their endotoxins. *J. Lipid Res*. **62**: 100086. doi.org/10.1016/j.jlr.2021.100086.

Tursen, U., Kaya, T.I., Eskandari, G., Bocekli, E., Muslu, N., Camdeviren, H., Ikizoglu, G., Atik, U. 2004. Apolipoprotein E gene polymorphism and serum lipids in patients with superficial fungal disease. *Yonsei Med. J.* **45**: 375-379. doi: 10.3349/ymj.2004.45.3.375.

Vonk, A. G., De Bont, N., Netea, M.G., Demacker, P. N. M., Van Der Meer, J.W.M., Stalenhoef A. F. H., Kullberg, B.J. 2004. Apolipoprotein-E-deficient mice exhibit an increased susceptibility to disseminated candidiasis. *Med. Mycol.* **42**: 341–348. doi.org/10.1080/13693780410001657135.