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Molecular Genetics and Epidemiology of Vitiligo: A Minireview

Shahrzad Aghaei1, Masoud Amiri2, Maryam Aghaei3*, Mohammad Ali Nilforoushzadeh4

1Department of Molecular Medicine, School of Advanced Technologies, Shahrekord University of Medical Sciences, Shahrekord, Iran
2Social Determinants of Health Research Center, Shahrekord University of Medical sciences, Shahrekord, Iran
3Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
4Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background and aims: Vitiligo is an acquired, idiopathic, and common depigmentation disorder of the skin that affects people of all ages and both sexes equally worldwide. Although etiology of the disease is unknown, there are theories such as environment and genetic factors.

Methods: In this article, we collected and summarized the appropriate manuscripts regarding the epidemiology and genetics using the terms vitiligo and genetic epidemiology in PubMed and Google Scholar.

Results: Studies showed the highest prevalence of disease in African countries, but with regard to the distribution of disease in different areas, environmental factors were as important as other causes of vitiligo, and 3 genes of FOXP3, XBP1 and TSLP had the most association with the disease.

Conclusion: It seems that recognition of the genetic basis of vitiligo will supply new insight into the therapies for it. Therefore, more genetic studies are needed to discover the genes and causes linked to clinical aspects of this disease.

Keywords: Vitiligo, Molecular epidemiology, Genetics epidemiology

Introduction

Vitiligo is an acquired cutaneous hypopigmentation disorder which affects 1%-4% of the world’s population.1 The clinical symptoms of vitiligo are pale or milk-white macules or patches on different parts of the body skin due to the selective destruction of melanocytes.2 The clinical presentation of vitiligo includes focal, vulgaris, segmental, universal, mucosal and mixed vitiligo.3 The cause of vitiligo is unknown but the interaction of genetic and environmental factors is associated with the disease,3 as there is a positive family history in 30% of the cases.4 There are also other major hypotheses for the pathogenesis of vitiligo such as stress, accumulation of toxic compounds, High H2O2 level, infection, autoimmunity, mutations, altered cellular environment, and impaired melanocyte migration and proliferation.5 The most accepted theory is that vitiligo is an autoimmune disease, as the increased expression of pre-inflammatory and pre-apoptosis cytokines such as IL-6, IL-8, IL-10, IL-12, IFN-γ, TNF-α is associated with vitiligo pathogenesis and cause the death of these cells by changing the pigment of melanocytes.6,7 Moreover, immunohistochemical studies in the skin around the lesion suggests that stimulation of the cytotoxic T-cell CD + 8 detecting MHCI-binding peptides derived from melanocyte proteins may play an important role in the pathophysiology of vitiligo.8

Medical therapy has been an exclusive treatment option for vitiligo during several decades, as re-pigmentation using UV light therapy and corticosteroid creams,9 removing pigment from non-affected skin,10 grafting,11 using an active form of vitamin D (calcitriol) or 1,25 dihydroxyvitamin D3, and the analogue of this hormone (such as calcium poutriol)12 have been used to improve the skin appearance of affected people. In the recent decades, scientists have focused on non-medical treatment options as a first-line or an adjuvant therapy. For instance, Siadat et al compared NB-UVB with oral minocycline in unstable vitiligo treatment and their results showed that NB-UVB was more advantageous than oral minocycline in terms of efficacy and the resulting stability.13
The latest non-medical option in the treatment of vitiligo and management of melanocyte distribution is surgical intervention.\textsuperscript{14-36} Hair follicular transplant is one of these various surgical modalities that are followed to repigment the vitiligo patches. In this case, Aziz Jalali et al used hair follicle autograft transplant in the persistent segmental vitiligo treatment. Their results suggested this method as an effective treatment option.\textsuperscript{17}

**Epidemiology**

Vitiligo has been known for at least 3500 years because of its striking appearance\textsuperscript{19} as was first noted in the Old Testament, the Quran and Buddhist literature in approximately 1400 BC.

It tends to occur or recur in spring and/or summer\textsuperscript{2,19} and disease severity is inversely proportional to distance from the equator.\textsuperscript{20} It occurs mostly in dark-skinned individuals and its distribution differs in various geographical areas depending on skin types, ethnic groups, environmental conditions, genetic factors, ethnical and cultural diversity.\textsuperscript{21} Vitiligo is more frequent in females and 50% of cases appear before 20 years of age and shows an inverse trend with age increment.\textsuperscript{21,22}

The reports on vitiligo epidemiology are based on population surveys and patients referred to dermatology clinics.\textsuperscript{19}

In population-based studies, the lowest prevalence was related to Asia and Atlantic (0.1%), the second rank was related to Africa and Europe (0.4%), and the highest frequency was seen in Oceania (1.2%). According to hospital-based studies, the lowest prevalence was related to America (1.5%) and Asia (1.6%) and the highest was in Africa (2.5%).\textsuperscript{21}

Publications were arranged based on the year, from 1997 to 2015. Some covered areas included India (9.98%), China (0.15%), Saudi Arabia (0.32%), Sri Lanka (1.22%), Turkey (1.44%), Nepal (0.91%), Iran (1.82%), Korea (0.13%), Japan (1.68%) in Asia, Tanzania (0.71%), Egypt (0.06%), Nigeria (2.8%) in Africa, Brazil (0.04%), the United States (2.42%), Mexico (2.6%) in America, Denmark (0.38%), Italy (0.17%), Germany (0.57%), France (0.28%) in Europe, and Australia (1.2%).\textsuperscript{21}

In Asia, except for Saudi Arabia (18-45 years old), in Europe except for Italy (only 18 years old) and Germany (14-86 years old) and in America except for USA (1-60 years old), all age groups were equally affected. In Australia the prevalence of vitiligo was found among adults (15-21 years old).\textsuperscript{21}

**Genetic Epidemiology**

Despite a long history of this dermatosis, the exact pathogenesis of vitiligo is still unknown. Although environmental factors are important, several genetic epidemiological studies on twins and families have also demonstrated that genetic factors play an important role in the pathogenesis of vitiligo.\textsuperscript{23} Probably the earliest evidence on the genetic basis of vitiligo was described by Addison in 1855 in the patients with Addison’s disease, vitiligo, and pernicious anemia.\textsuperscript{24} Familial aggregation of vitiligo was noted as early as 1933\textsuperscript{25} and a positive family history was obtained in 56.8% of families studied, 57.1% of them having two or more affected relatives.\textsuperscript{26} Moreover, Alkhateeb et al found that the concordance for vitiligo in monozygotic twins was 23%, supporting the roles for both genetic and non-genetic factors in disease pathogenesis.\textsuperscript{27} Furthermore, studies on the genetic bases of vitiligo in the United States and India revealed genetic model of autosomal recessive for vitiligo with 3 or 4 loci controlling the disease.\textsuperscript{28,29}

To date, approximately 33 vitiligo susceptibility loci have been identified. Almost 90% of them encode immunoregulatory proteins and about 10% encode melanocyte proteins.\textsuperscript{30} The candidate genes include \textit{ACE, AIRE, CAT, CD4, CLEC11A, COMT, CTLA-4, C1orf10, DDR1, EDN1, ESRI, E45, FBXO11, FOXD3, FOXP3, GATM1, GSTT1, IL1RN, IL10, KITLG, MBL2, NFE2L2, PDGFRA-KIT, PTGS2, STAT4, TAPI-P, PSMB8, TGFB2, TNI, TSLP, TXNDC5, UV3AG, VDR, and XBP1}. Only 3 genes of \textit{FOX3, XBP1} and \textit{TSLP} showed an association with the disease.\textsuperscript{31}

\textit{FOX3} gene (Xp11.23 region) encodes protein – scurfine (SFN). Dysregulation of regulatory T cells (Tregs), specifically CD\textsuperscript{4+}CD\textsuperscript{25+} and Forkhead box P\textsuperscript{3} (FoxP\textsuperscript{3}) Tregs may be one of the factors that can break tolerance to melanocyte self-antigens and contribute to vitiligo pathogenesis.\textsuperscript{32,35} Birlea et al in a meta-analysis screening 37 SNPs of \textit{FOX3} gene found the greatest significance with a promoter SNP rs3761547 and valid linkage disequilibrium with rs11798415 and rs5906843 block.\textsuperscript{36} Song et al also screened 3 promoter SNPs of \textit{FOX3} gene (rs3761548, rs2232365, and rs5902434) in Han Chinese populations (in 682 vitiligo patients and 682 vitiligo -free age- and sex-matched controls) and found significant association of rs3761548 and rs2232365 with vitiligo risk.\textsuperscript{37} At the same time, Jahan et al determined \textit{FOX3} gene rs3761548 in the genomic DNA isolated from blood samples of 303 Indian patients and 305 controls.\textsuperscript{38} Moreover, Elela et al found lower levels of FoxP3 in skin biopsies from 84 non-segmental vitiligo patients and 80 controls.\textsuperscript{39} In order to study the role of Tregs in vitiligo pathogenesis, Hegab and Attia evaluated FoxP\textsuperscript{3} peripheral Tregs (CD\textsuperscript{4+}CD\textsuperscript{25+}) in 80 Egyptian patients and 60 healthy controls. Results revealed low numbers of both peripheral CD\textsuperscript{4+}CD\textsuperscript{25+} and FoxP\textsuperscript{3} T cells in the vitiligo patients compared to the control subjects.\textsuperscript{40}
The next gene, XBP1 (X-box binding protein 1) is localized on chromosome 22 and plays the role of a transcription factor through recognition of the X2 promoter element of both HLA DR-α and HLA DP-β. In 2009, Ren et al surveyed sequences of XBP1 in 319 cases and 294 controls of Han Chinese and showed an elevated expression of XBP1 in the lesional skins of patients carrying the risk-associated C allele of rs2269577. Tarlé et al also studied 596 affected children and both parents in Southern Brazilian population and found a positive association between marker rs2239815 and vitiligo and the relation of rs2269577 with 2 SNPs in strong linkage disequilibrium. In order to investigate the association between oxidative stress (as a vitiligo trigger) and disease progression, Toosi et al demonstrated that phenols indeed up-regulated the expression of unfolded protein response in melanocytes, including XBP1 in melanocytes.

The third gene, TSLP (thymic stromal lymphopoietin, 5q22.1) induces naive CD+ T cells to produce Th2 cytokines. The blockade of TSLP or TSLP receptor induces low production of Th2 cytokines and strong Th1 response that play an important role in vitiligo development. In 2009, Cheong et al examined the relation between 4 SNPs of TSLP gene and vitiligo in 160 Korean vitiligo patients and 568 healthy individuals and showed C allele at the TSLP-847C>T polymorphism may increase susceptibility to vitiligo through decreasing TSLP expression. Moreover, many studies determined the localization of alleles and antigens predisposing vitiligo within the HLA. For instance, in the study of Jin et al, clinical features of vitiligo patients with HLA-DRB1*07 positive and negative were compared among the Han Chinese population. Patients with HLA-DRB1*07 positive showed an earlier disease onset, higher frequency in the family, and coexistence of autoimmune diseases compared with DRB1*07 negative patients. In Caucasians, in the MHC I region, the major association signal was in strong linkage disequilibrium among the Han Chinese population. Patients with HLA-DRB1*07 positive showed an earlier disease onset, higher frequency in the family, and coexistence of autoimmune diseases compared with DRB1*07 negative patients. In Caucasians, in the MHC I region, the major association signal was in strong linkage disequilibrium with HLA-A*02. In the MHC II region, the major association signal was located between HLA-DRB1 and HLA-DQA1, in moderate linkage disequilibrium with HLA-DRB1*04.

**Conclusion**

Altogether, the common studies revealed the highest prevalence rate of vitiligo in African countries, but with regard to the distribution of disease in different areas, environmental factors are as other causes of vitiligo. In addition, some polymorphisms of three genes of FOXP3, XBP1 and TSLP showed the most relation with vitiligo and thus can be potential therapeutic targets. Therefore, more genetic studies are needed to discover genes and causes linked to clinical aspects of the disease. It is hoped that investigation of biological pathways involved in vitiligo pathogenesis will introduce new methods for the treatment, diagnosis, and prevention of the disease in individuals with inherited susceptibility.

**Ethical Approval**

Not applicable.

**Conflict of Interest Disclosures**

None.

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