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MINIREVIEW

GENETIC IMPLICATIONS IN VITILIGO AND VITILIGO-ASSOCIATED DISEASES

Ana Maria A. STANESCU[1]✉, Ioana V. GRAJDEANU[1], Bogdan SERBAN[1,2], Ovidiu G. BRATU[1,3], Bogdan SOCEA[1,4], Anca PANTEA STOIAN[1], Camelia C. DIACONU[1,5]

[1] University of Medicine and Pharmacy „Carol Davila", Bucharest, Romania
[2] Emergency University Hospital Bucharest, Bucharest, Romania
[3] Emergency Universitary Central Military Hospital, Academy of Romanian Scientists, Bucharest, Romania
[4] Emergency Clinical Hospital „St. Pantelimon", Bucharest, Romania
[5] Clinical Emergency Hospital of Bucharest, Bucharest, Romania

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Abstract

Vitiligo is a chronic, asymptomatic, disease that affects the patient from a cosmetic point of view. It is characterized by the appearance of depigmented areas on the skin or mucous membranes. Depending on the morphology of the lesions, vitiligo can be classified into: segmental, non-segmented or mixed. Vitiligo is associated with a range of autoimmune disorders, most commonly autoimmune thyroid diseases, alopecia areata, halo nevi, psoriasis, diabetes, etc. Etiology is not entirely elucidated, autoimmune theory related to specific genetic mutations being the most studied.

Keywords: vitiligo, genetics, vitiligo-associated diseases, genetic susceptibility.

Résumé

Implications génétiques et associations entre le vitiligo et les maladies associées au vitiligo

Le vitiligo est une maladie chronique, asymptomatique, qui affecte le patient du point de vue esthétique. Elle se caractérise par l'apparition de zones dépigmentées sur la peau ou les muqueuses. Selon la morphologie des lésions, le vitiligo peut être classé en : segmentaire, non segmenté ou mixte. Le vitiligo est associé à une gamme de troubles auto-immuns, le plus souvent de maladies thyroïdiennes auto-immunes, d'alopécie en aires, de nævi halo, de psoriasis, de diabète, etc. L'étiologie est encore trop peu élucidée, la théorie auto-immune liée à des mutations génétiques spécifiques étant la plus étudiée.

Mots-clés: vitiligo, génétique, maladies associées au vitiligo, susceptibilité génétique.

✉ Address for correspondence: Ana Maria A. STANESCU
University of Medicine and Pharmacy „Carol Davila", Bucharest, Romania
Address: Intrarea Pinului no. 34, bl. 6, ap. 10, sector 6, zip code 060564, Bucharest, Romania
E-mail: alexandrazotta@yahoo.com

Introduction

Vitiligo is an acquired depigmentation disorder of the skin of unknown etiology, which is characterized by depigmented areas due to the loss of melanocytes. Prevalence is dependent on ethnicity, gender and age, in Europe being estimated between 0.5% and 1% of the population[1,2]. A multicenter survey estimated the prevalence in Mexico at 0.21%[3]. A meta-analysis has shown a global prevalence of 1.8%, while global distribution tends to Asians and Africans[4]. It may occur at any age, but the onset generally occurs between 10 and 30 years old, affecting both sexes equally[5]. It is an asymptomatic condition, itching may rarely occur and has an increased incidence of sunburn on depigmented areas.

The classification of vitiligo is described in Table 1.

Genetic association between vitiligo and other conditions

The increased incidence of association between vitiligo and other conditions is well-known. The disease, although limited only to the skin, has an increased association with other conditions, such as thyroid disease (hyperthyroidism and hypothyroidism), Addison's disease, alopecia areata, diabetes mellitus, pernicious anemia, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Sjögren's syndrome, dermatomyositis, scleroderma, ocular and auditory abnormalities, psoriasis and atopic dermatitis[7-9]. The quality of life is low in these patients and the incidence of depression is very high. Treatment is not curative, but it aims to improve symptomatology by repigmentation[10].

The association of vitiligo with other diseases (Table 2) led to the hypothesis that common genetic factors may be involved. The possible genetic predisposition and mutations responsible for the appearance of these diseases must be searched.

Vitiligo is a condition involving complex genetic factors. Studies regarding the genomic association have described about 50 susceptibility loci for vitiligo, 90% of which confer innate and adaptive immunity, while 10% confer melanocytic antigens and stress response pathways[11]. Among the genes involved in vitiligo are: non-HLA genes (DDR1, XBP1, NLRP1, PTPN22 and COMT) and HLA genes (HLA-A2, HLA-DR4 and HLA-DR7)[12,13]. Linkage and association studies have also provided strong support for vitiligo susceptibility genes on chromosomes 4q13–q21, 1p31, 7q22, 8p12 and 17p13[14].

Glutathione peroxidases (GPX) – their main function is to protect the body against damage caused by free oxygen radicals. There are five forms: GPX1 – cell, GPX2 – gastrointestinal, GPX3 – plasma, GPX4 – phospholipid, and snGPX – sperm. GPX1 is a major intracellular anti-oxidant enzyme, and the Leu200Pro (rs1050450) polymorphism has been reported to be associated with decreased activity in various diseases[15]. For the first time, Mansuri at al confirmed the genetic association of vitiligo with variations in GPX1, which contains at least two independent risk signals, one marked by Arg5Pro SNP and another labeled Leu6Pro[16].

The analysis of haplotype/gene-gene interaction revealed that SOD2 + 47C / T and GPx1 + 599C / T are involved in the imbalance (D: 0.168; r2: 0.10) and individuals with this combination had a 1.273 higher risk [OR; CI (95%)] to develop type II diabetes mellitus[17]. GPX1 deficiency has also been implicated in the promotion of endothelial dysfunction, heart failure and abnormal structural changes in vasculature and myocardium[18]. GPX1 seems to be associated with alopecia areata, coronary heart disease, Addison's disease, psoriasis[19-21].

Catechol-O-methyltransferase (COMT) gene inactivates dopamine, epinephrine and norepinephrine in the nervous system. COMT gene located on the 22q11.1-q11.2 locus, due to its involvement in

Table 1. Vitiligo classification[6].

The type of vitiligo	*Subtype – explanation*
Vitiligo non-segmental	Acrofacial – usually limited to face, head, hands and feet. Generalized – symmetrical macules on hands, fingers, face and trauma areas Mucosal – involves oral and / or genital mucosa, but also involves other areas Universal – depigmentation occurs on 80-90% of body surface area
Vitiligo segmental	Unisegmental – one or more macules on one side of the body Bisegmental – two segmental injuries distributed unilaterally or bilaterally Plurisegmental – multiple lesions distributed unilaterally or bilaterally
Mixed vitiligo	The combination of segmental vitiligo with non-segmental – segmental vitiligo followed by non-segmental vitiligo at least 6 months difference
Vitiligo unclassified	Focal – isolated macules that do not have a segmental distribution, do not evolve in non-segmental vitiligo for at least two years Mucosal – involves only oral or genital mucosa

Table 2. Possible genetic associations between vitiligo and other diseases.

Gene associated with vitiligo	*Other associated conditions*
GPX1	Type II diabetes mellitus Alopecia areata Coronary heart disease Addison's disease Psoriasis
COMT	Schizophrenia Psoriasis Alcoholism Atopic dermatitis
DDR1	Ovarian cancer Malignant melanoma
GZMB	Thyroid disease
PTPN22	Type 1 diabetes Graves' disease Rheumatoid arthritis Juvenile idiopathic arthritis Addison's disease Psoriasis Inflammatory bowel disease
NLRP1	Type 1 diabetes Addison's disease Celiac disease Systemic sclerosis Inflammatory bowel disease Thyroid disease
XBP1	Crohn's disease
VDR	Insulin resistance Colon cancer Depressive symptoms Psoriasis

the catecholamine metabolism, was linked to the increase in oxidative stress in vitiligo[22].

The COMT gene has also been associated with schizophrenia, bipolar disorder and the polymorphisms implicated in schizophrenia; also, the COMT polymorphism contributes significantly to the development of late-onset alcoholism[23,24]. COMT has been found in the skin of patients with psoriasis; Catechol-O-methyltransferase (COMT) 158 polymorphism can reduce the activity of the COMT enzyme, that may trigger defective differentiation of keratinocytes in psoriasis[25].

Discoidin domain receptors (DDRs) are a novel class of receptor tyrosine kinases that bind to several collagens and stimulate matrix metalloproteinase production. These discoidin domain receptors are split into two classes, DDR1 and DDR2. The DDR1 gene, located on the 6p21 chromosome region, is involved in the adhesion of melanocytes to the basal layer by CCN3 integrin, mutations in this gene have generated a reduction in melanocytic adhesion in the basal membrane[26]. DDR1 is a susceptibility gene for vitiligo, possibly implicating a defective cell adhesion in vitiligo pathogenesis[26].

The DDR1 was expressed in 63% of serous ovarian cancer tissue, whereas it was undetectable in normal ovarian surface epithelium; DDR1 was expressed significantly more frequently in high-grade (79%) and advanced stage (77%) tumors, compared to low-grade (50%) and early stage (43%) tumors. DDR1 plays a role in the most fatal skin cancer – malignant melanoma[27].

Encoding Granzyme B (GZMB) is a protein coding gene that is located at 14q12 and has 5 exons with a length of 3320 bp. In a recent GWAS study by Jin et al, examining European populations, SNP rs8192917 from GZMB was found to be significantly associated with vitiligo[28]. Xu et al conducted a study on 973 vitiligo patients, based on genetic association, to investigate possible GZMB genetic contributions to the susceptibility of vitiligo. The authors concluded that the GZMB gene has an important site for vitiligo in the Han Chinese population and can be useful in determining the genetic risk for vitiligo in this population[29]. Thyroid disease has a common feature with vitiligo in GZMB gene[30].

The protein tyrosine phosphatase N22 (PTPN22), a gene that regulates activities for both T cells and B cells, located on the 1p13.3-p13.1 locus, has been studied and demonstrated to be an inherited risk factor for generalized vitiligo. Regarding the rheumatoid arthritis and juvenile rheumatoid arthritis in the UK population, studies have shown an increase in the frequency of the PTPN22*T allele in the cases (17.8% in RA; 15% in JIA) compared with controls (10.3%), with an OR for the allele of 1.88 for RA and 1.53 for JIA. It is also associated with: type 1 diabetes, Graves' disease, rheumatoid arthritis, juvenile idiopathic arthritis, Addison's disease, psoriasis, inflammatory bowel disease[31,32].

Nuclear localization leucine-rich-repeat protein 1 (NLRP1) gene is a key regulator of the innate immune system, it is located on the chromosome 17p13 region and has been associated with the risk of generalized vitiligo, but also with several autoimmune diseases associated with vitiligo[33]. NLRP1 was associated with the following diseases: type 1 diabetes, Addison's disease, celiac disease, systemic sclerosis, inflammatory bowel disease, thyroid disease[34,35].

X-box-binding protein 1 (XBP1) gene is a transcription factor located on the 22q12 locus, is involved in the expression of MHC class II genes. There has been an increase in XBP1 expression in the skin of the carriers of a particular XBP1. Concerning genetic influence on early onset, early onset of vitiligo is specifically associated with MHC class II indel rs145954018, which contributes substantially to

the difference in heritability between early onset and late onset subgroups[36]. It has been associated with Crohn's disease[37].

The vitamin D receptor (VDR) gene is located on chromosome 12q12–q14. VDR Apal polymorphism increased the risk of vitiligo susceptibility and there is a positive correlation between serum 25 (OH) D deficiency and the incidence of vitiligo[38,39]. In this regard, the VDR Apal, BsmI, Fokl gene has been found to be associated with insulin resistance, especially in Caucasians and Asians with dark skin pigmentation[40]. Other research has shown that molecular variants of the VDR gene may be related to the development of colon cancer and influences the susceptibility to age-related changes in cognitive function and depressive symptoms[41,42].

Conclusions

A variety of genes are involved in vitiligo, not all of the genetic background being completely elucidated yet. The association of vitiligo with other diseases is known, common genetic factors being involved. More studies are needed on the genetic association between vitiligo and vitiligo-associated diseases.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

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