Highlights in pathogenesis of vitiligo

Ghada F Mohammed, Amal HA Gomaa, Mohammed Saleh Al-Dhubaibi

Ghada F Mohammed, Amal HA Gomaa, Department of Dermatology and Venereology, Faculty of Medicine, Suez Canal University, Ismailia 41551, Egypt
Mohammed Saleh Al-Dhubaibi, Department of Dermatology, Faculty of Medicine, Qassim University, Buraydah 52571, Saudi Arabia

Author contributions: All authors contributed to this work.
Conflict-of-interest: There are no conflicts of interest. There are no sponsors or fund for the research.
Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
Correspondence to: Ghada F Mohammed, MD, Department of Dermatology and Venereology, Faculty of Medicine, Suez Canal University, El Salam Distric, Ismailia 41511, Egypt. ghada77@hotmail.com
Telephone: +20-11-12518631
Fax: +20-64-3208543
Received: September 27, 2014
Peer-review started: September 28, 2014
First decision: October 28, 2014
Revised: December 27, 2014
Accepted: January 9, 2015
Article in press: January 12, 2015
Published online: March 16, 2015

Abstract

Vitiligo is a common pigmented disorder. Many studies across decades and all over the world have attempted to illustrate the pathogenesis behind it; however, the pathogenesis of vitiligo remains elusive. This review article, we present the findings behind the most and updated theories behind this psychologically debilitating and disfiguring disease. The discussion begun with the role of genetic predisposition followed by neural theory first proposed in the 1950s. We highlight the autoimmune hypothesis, followed by the reactive oxygen species model, zinc-α2-glycoprotein deficiency hypothesis, viral theory, intrinsic theory and biochemical, molecular and cellular alterations accounting for loss of functioning melanocytes in vitiligo. Many theories were elaborated to clarify vitiligo pathogenesis. It is a multifactorial disease involving the interplay of several factors. Future research is needed to clarify the interaction of these factors for better understanding of vitiligo pathogenesis and subsequent successful treatment.

Key words: Etiopathogenesis; Pigmentary disorder; Non-segmental vitiligo; Segmental vitiligo; Vitiligo

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The pathogenesis of vitiligo elaborated by several theory. Future research needed to clarify the interaction of these factors for better understanding of vitiligo pathogenesis and subsequent successful treatment.

Mohammed GF, Gomaa AHA, Al-Dhubaibi MS. Highlights in pathogenesis of vitiligo. World J Clin Cases 2015; 3(3): 221-230
Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i3/221.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i3.221

INTRODUCTION

The pathogenesis is complex and involves the interplay of multiple factors; however, the exact pathogenesis is not well known. Lerner et al(1) in the 1950s firstly proposed the neural theory, and after that, model of reactive oxygen species (ROS), the autoimmune hypothesis and the melanocytorrhagy hypothesis have appeared.
DIFFERENT PATTERNS AND PHYSICAL DISTRIBUTION OF VITILIGO

Pruritus, elevated lesions, and erythematous margins present in inflammatory vitiligo. There are 2 main types: generalized vitiligo (GV) (widespread macules with a symmetrical distribution), whereas focal vitiligo (FV) (1 or few depigmented not elevated areas at a single site). After coalescing of vitiliginous areas in GV, or becomes extensive in the body with remaining of few normal areas, thus called vitiligo universalis. Non-segmental vitiligo enrolled FV and GV, but segmental vitiligo (SV) restricted to one unilateral region(2), (Figure 1). The lesions of vitiligo are asymptomatic except in inflammatory vitiligo, which is associated with pruritus and characterized by elevated lesions, and erythematous margins.

INHERITANCE OF VITILIGO

The inheritance is polygenic[3]. Family history exists in 6.25%-38% of patients with vitiligo[4]. Those who have recessive homozygosity at 3 epistatically interacting autosomal diallelic loci will be affected by vitiligo[5].

Molecular genetics-based studies

Spritz et al[6] (2004) revealed different loci or alleles for GV. Autoimmune susceptibility (AIS)-1, -2 (chromosome 7) and systemic lupus erythematosus vitiligo-related gene (SLEV1) (chromosome 17) both associated loci for GV and concomitant autoimmune diseases. Of 33 tested loci, only (XBP1, TSLP, and FOXP3) were primarily concomitant with GV. FOXP3 associated with X linked recessive multiple autoimmune disease syndrome. In addition, CTLA4 had association secondarily with GV, and the autoimmune diseases[7]. However, patients with GV also linked to AIS3 locus (chromosome 8)[6].

Methylation of deoxyribunucleic acid (DNA) conducted by DNA methyltransferases (DNMT1, -3a, -3b)[8]. Monocytes in vitiliginous patients and normal volunteers showed sensitivity to alterations in methylation and revealed association between IL-10 and reactivity of autoimmune system[9,10]. In comparison with controls, methylation was increased and hypermethylation of the methylation-sensitive region in 11-10 that could alter genes expression in autoimmunity[9]. In a similar way, the role of transforming growth factor beta-receptor II (TGFBR2), which inhibits the inflammatory pathways and lymphocyte activation was revealed[11,12].

The ultraviolet radiation resistance-associated gene (UVRAG), resists photo-damage, and plays a role in autophagy[13]. In 439 controls and 225 NSV patients, UVRAG has 2 SNPs which were significantly different[14].

Both diabetes mellitus type 1 and rheumatoid arthritis with SNPs found beside the insulin-dependent diabetes mellitus 8 locus (IDDM8)[15]. This region contains SMOC2, which enrolled in growth and development[16] and cell matrix interactions[17].

Also, melanocyte proliferating gene 1 (MYG1), is elevated in skin of both vitiliginous patients with activity, and without activity[18].

Human leukocyte antigen

Studies revealed that vitiligo associated with HLA-DRB1*07, HLA-A2, 11, 28, 31, 33, HLA-B17, 35, 40 and 44[16,20].

Susceptibility loci of vitiligo are on chromosome 6 and in the MHC[21]. A study genotyped 6623 patients with vitiligo and 10740 controls for 34 SNPs. At 6q27, 2 SNPS found with 3 unlinked genes. These gene include RNASET2, which responsible for ribonuclease (RNase)[22], The other two genes are the chemokine receptor 6 gene (CCR6)[23], and FGFR10P are imperative to progressing of the cycle of the cell that produce receptor of (FGF)[23]. Genes encode discoidin domain receptor 1 (DDR1)[24], and tyrosine kinase receptor play role in cell's progression and function[25], both were involved in vitiligo.

THEORIES FOR VITILIGO PATHOGENESIS

The neural theory

Early theories: The “neural theory” supposed by Lerner’s (1959) was based on the fact that SV follows the course of the dermatome with exhibiting hyperhidrosis and emotional upset[1-26,27].

The sympathetic nervous system’s role:

Dysfunction of sympathetic nervous system’s role (SNS) activity affect melanin production and lead to depigmentation. With iotophoresis and laser Doppler flowmetry level of microcirculation in lesions with vitiligo assessed to reveal SNS activity[28]. 10 subjects had facial SV, and 2 groups of controls were examined. 1 control group had 10 healthy, unaffected individuals, and the 2nd control group contained 10 non-segmental-type stable vitiligo patients. Patients were matched for gender and age. Approximately, the cutaneous blood flow was higher three times on the lesions vs normal skin in SV. The differences was not revealed in the non-SV.

Neuropeptide and neuronal markers: Neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), and polyclonal general neuronal marker (PGP) tested for their immuno-reactivity in 12 patients with vitiligo and 7 unaffected control subjects[29]. NPY increased in the marginal areas of lesions in half of the patients vs normal, and associated with noradrenaline with exerting a local autonomic effect[29]. Lazarova et al[30] (2000) confirmed this finding; however, they found that CGRP was also non-significantly increased in vitiligo. Precipitating factor, as, stress, produce significant level of neuropeptides such as NPY that induct the disease[30,31]. A cohort study revealed...
The role of humoral immunity: In 2010, tyrosine hydroxylase antibodies checked with radioimmunoassay (RIA) in sera were obtained from 79 non-SV patients, 8 patients with SV, 91 subjects with other autoimmune diseases and 28 healthy subjects. TH antibodies revealed significantly in non-SV. Also, in non-SV, antibodies against MCHR1 (melanin-concentrating hormone receptor 1), tyrosinase [27] and pigment cell-surface antigens [28] were noted.

In 80% of active vitiligo patients, immunoglobulin G (IgG) and immunoglobulin M (IgM) against melanocytes were found. Low levels IgA also found in the inactive and control groups [28].

Furthermore, anti-thyroglobulin antibodies, antithyroid antibodies, anti-thyroid peroxidase, and antithyroid muscle antibody are present. Those are typically related to thyroid disease and other autoimmune diseases [29,40].

Melanin concentrating hormone (MCH) binds MCHR1 thus increase calcium influx and acting as an agonist of α-melanocyte-stimulating hormone (α-MSH) [31-33].

The role of cell-mediated immunity: Immunohistochemical examination of the inflammatory infiltrates in perilesional vitiligo skin using single and double immunostaining for melanocytes, Langerhans cells, T-cells, and macrophages revealed higher densities of melanocytes in normal skin, vs non-affected skin in subjects with vitiligo. These T cell had dramatic production of (IL-2R), and increased CD8:CD4 ratio. Thus, melanocytes destruction may be cytotoxic CD8 T-cell mediated. Perilesional HLA-DR production (MHC class II receptor) exhibited in all of the patients with vitiligo, especially along suprabasal and basal keratinocytes, due to local T cell reactivity. In addition, macrophages were numerous in vitiligo vs controls, whereas the CD36 subset of macrophages were higher in the later [44].

The role of cytokines in vitiligo: Beyond lymphocytes and antibodies, the immune system has a complex interplay of many cytokines. There are significantly increased expression of tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and IL-10 [45]. As IFN-γ and TNF-α are T helper cell-1 (Th1) cytokines, so vitiligo is mediated by the Th1 response [46].

IL-17 plays role with macrophages, keratinocytes, and fibroblasts. In addition, it activates the expression of others, as IL-1 and IL-6, and TNF-α [47,48]. Examination of sera and tissue of 30 vitiliginous subjects and 20 normal subjects showed significant higher levels of IL-17 toward vitiliginous subjects and disease duration [47].

The biochemical Theory- reactive oxygen species model Oxidative stress hypothesis suggests that imbalanced redox (reduction-oxidation) state of the vitiliginous skin. This results in the dramatic production of reactive oxygen species (ROS), as H2O2. ROS oxidize components of the cell leading to melanocytes destruction and creating the depigmented macules [49].

The redox status of vitiligo patients: Sera of
thirty-six patients with vitiligo (18 with inactive and 18 with unstable disease), and 40 normal subjects were examined for main factors of redox status involving selenium, malondialdehyde (MDA), vitamins A and E, and glutathione peroxidase (GPx) in the erythrocyte activities, catalase (CAT) and superoxide dismutase (SOD). Superoxide radicals are scavenged and their toxicity is reduced with SOD which transforms O₂⁻ to H₂O₂ and O₂, and catalase transforms (H₂O₂) to (H₂O) and (O₂)[50]. As MDA results from lipid peroxidation, it is a marker of oxidative stress[51,52]. Selenium is required for GPx activity and vitamins A and E are important in antioxidative activity. Serum selenium, SOD and MDA are prominent in both unstable and inactive types. By enhancing SOD activity, the H₂O₂ accumulates. In addition, GPx detoxifies H₂O₂ (downstream enzyme). Therefore, GPx levels decreased in patients with vitiligo[50,53].

Increased SOD activity in patients with vitiligo is a response to oxidative stress; thus, H₂O₂ elevate as could not be eradicated by low level of CAT[53,54].

The role of tetrahydrobiopterin recycling in vitiligo: Another cellular pathway affected by accumulating H₂O₂ involves tetrahydrobiopterin. Tyrosinase is an imperative enzyme in formation of melanin[55]. L-tyrosine synthase from L-phenylalanine by the phenylalanine hydroxylase (PAH). The 5, 6, 7, 8-tetrahydrobiopterin or 6BH₄ is essential cofactor for this process is. Defective recycling of 6BH₄ lead to excess 7BH₄ that is an inhibitor of enzyme in formation of melanin. Haase et al[53] (1996) also found that 7BH₄ production yields H₂O₂. Haase et al[53] (2004) studied the enzyme dihydropteridine reductase (DHPR) (imperative to end the normal 6BH₄ recycling). They assessed whole blood samples from 27 untreated vitiligo subjects and 8 normal subjects. The results showed that DHPR activity decrease with high concentrations of H₂O₂ and vice versa.

Effect of H₂O₂ on acetylcholinesterase (AchE) decrease in patients with vitiligo vs healthy controls[59,60]. Thus, AchE dependent on H₂O₂ concentration levels, i.e., low H₂O₂ concentrations (approximately 10-6M or mol/L) activate AchE whereas high concentrations (10-3M or mol/L) deactivate AchE[60]. Butyrylcholinesterase (BchE) mediates the hydrolysis of acetylcholine. The hydrolysis reaction is one of the rate-limiting steps in cholinergic signal transduction[61,62].

In 2008, showed that xanthine oxidase (XO) is a source of H₂O₂. High concentrations of H₂O₂ inhibit the activity of XO, and vice versa[63]. Briefly, there are at least 5 important pathways enrolled in H₂O₂ overproduction in vitiligo: (1) Defective recycling of 6BH₄[55,64,65], (2) Catecholamine formation increased as levels of monoamine oxidase A (MAO) increased[34,66,67], (3) Inhibition of thioredoxin/thioredoxin reductase by calcium[68,70], (4) NADPH oxidase activities increased by the cellular infiltrate[71]; and (5) Nitric oxide synthase (NOS) activities increased[72].

Oxidative stress affects calcium homeostasis at the cellular level in melanocytes and keratinocytes in vitiliginous patients[69].

Zinc-α2-Glycoprotein deficiency hypothesis
For the first time, Bagherani et al[73] and Yaghoobi et al[74] pointed the probable association which might be present between ZAG and vitiligo[73,74]. It was suggested that the pathogenesis of vitiligo could be attributed to decrease in ZAG as follows: (1) Studies have demonstrated that ZAG is acting as a keratinocyte-derived factor influencing melanocyte proliferation and dendritic[75,76]. So, ZAG could be considered as a marker of cells differentiation and maturation[78]; (2) A chronic detachment of melanocytes is an imperative pillar in the pathogenesis of vitiligo[74,77,78]. Thus, melanocyte adhesions to the other cells in epidermis will be impaired in the lack of ZAG; (3) Topical steroids are the most safest and effective forms of treatment for vitiligo, especially for the localized one[74,79], because of their ability to increase ZAG expression[80,81]; (4) Some studies have shown that zinc can precipitate ZAG[74,82]. Thus, the effectivity of zinc in treating this disease is related to its ability to precipitate circulating ZAG at the site of vitiligo[73]; and (5) The linkage signals on chromosome 7 in patients with GV and associated autoimmune diseases have been reported[73,83]. Surprisingly, ZAG gene is located on the chromosome 7[80].

Viral theory
There is a strong association between vitiligo and chronic hepatitis C virus (HCV) infection and autoimmune hepatitis[84]. Akcan et al[85] in 2006 reported a low hepatitis B virus (HBV) sero-positivity in vitiliginous patients. Previous or concurrent cytomegalovirus (CMV) infections may induce the etio-pathogenesis or deterioration of vitiligo[85,86].

Furthermore, other viruses as Epstein-Barr virus, hepatitis E virus, herpes virus and the human immunodeficiency virus (HIV) also have suspicious association with vitiligo[86,87].

Intrinsic theory
Melanocytes in vitiligo have an intrinsic defect leading to their death. They demonstrate different abnormalities, including abnormal rough endoplasmic reticulum or deficiency of unidentified melanocyte growth factors such as basic fibroblast growth factor (bFGF) and decrease in the number of melanocytes expressing the c-kit receptor in lesional skin[88,89]. Melanocytes require a constant keratinocyte-derived c-Kit stimulation for their maintenance[90], thus weak expression of keratinocyte-derived factors, as stem cell factor (SCF), may lead to passive melanocyte death and might explain the Koebner phenomenon[91].
Cellular, molecular and biochemical alterations and melanocytes loss of in vitiligo

Recently, malfunctioning melanocytes found in vitiliginous lesions[92]. Electron microscopy, reverse transcription PCR (polymerase chain reaction) and southern blotting experiments revealed sporadic survival of melanocyte in vitiliginous lesions[93,94]. Thus, this points to presence of immature melanocyte precursors/stem cells[95,96]. Now, 2 pathways have been supposed for melanocytes loss: highly programmed death by apoptosis[77,91,97,98] and accelerated cell senescence[99].

Apoptosis and accelerated cell senescence:

Melanocytes from non-lesional skin of vitiligo patients have abnormalities as cytoplasm vacuolization, rough endoplasmic reticulum dilatation, DNA marginalization in the nucleus, loss of dendrites and detachment[88,99,100].

Regarding keratinocytes, apoptosis occurs at least in the traumatized vitiligo skin[101]. Thus, basal and suprabasal epidermal cells in the depigmented and normally pigmented skin show degeneration due to swelling of the membrane-bound organelles, formation of vacuoles and cytoplasm condensation[102].

As vitiligo could inducted by trauma (Koebner’s phenomenon). Lee et al[97] revealed the lower expression levels of the antiapoptotic Bcl-2 and FLIP proteins in vitiliginous skin vs the normally pigmented skin. On the other hand, there was dramatic levels of the proapoptoticBax and p53 proteins and of the active forms of caspase-3, 8 and 9[97].

Apoptosis triggered by normal developmental program, UV light, H2O2, staurosporine and other stimuli[93,103]. NALP1 gene that stimulates cellular apoptosis[102,104], is associated with vitiligo susceptibility[105,106].

Epidermal melanocytes from epidermal melanin unit produce growth factors (GF) for melanocytes[107]. Therefore, its damage have imperative effects on melanocyte survival[91]. Thus, low levels of GF as SCF, endothelin-1 (ET-1) or high levels of melanocyte inhibiting cytokines, as TNF-α and IL-6 may lead to keratinocyte apoptosis, and then apoptosis of melanocytes[108].

Life span of lesional keratinocytes is greatly shortened when compared to the life span of normal and non-lesional vitiligo keratinocytes. It also shows modification of proliferation and senescence marker expression (p16, p53, p21), when compared to keratinocytes from clinically noninvolved skin[109].

Although apoptosis and senescence of epidermal keratinocytes is a response to various stimuli, they also share some cellular mechanisms and controlled by similar molecular regulators[109]. Both apoptosis and aging induced by stress signals as ROS accumulation and DNA damage[101]. The paradigmatic proapoptotic factor p53[111], is also a guard keeper of DNA integrity which triggers cell cycle arrest in DNA damaged cells[109].

Melanocytorrhagy theory: Gauthier et al[78] in 2003 mentioned that NSV occurs due to “melanocytorrhagy”, or a chronic melanocytes detachment and loss caused by trauma and other stressors include catecholamines, ROS, or autoimmune elements. This theory combined the concepts from other theories mentioned before to elaborate a single integrated explanation of vitiligo pathogenesis[78].

A study done by Tobin et al[92] in 2000 proposed loss of melanocytes in vitiligo. They explained these findings because of oxidative stress caused by H2O2. Gauthier et al[78] (2003) also reported that impaired cell adhesion plays a role in vitiligo pathogenesis as the synthesis of extracellular matrix components by keratinocytes may be defective, the presence of focal gaps in the basement membrane and impaired formation of basement membrane. These abnormalities weaken the basal attachment of melanocytes. Trauma could aggravate this susceptibility with subsequent chronic melanocyte loss, known as melanocytorrhagy.

Le Poole et al[112] mentioned that the protein tenasin may play a role in decreasing melanocytes adhesion in vitiligo. This protein was highly expressed in patients with vitiligo than the controls[112]. This can explain the development of vitiligo by Koebner phenomenon, which represent “transdermal migration”[78,113].

Integrated theory (Conversion theory)

Despite all the mentioned theories are attractive, it is likely that vitiligo is a result of the convergence of these pathological pathways. Most experts agree that vitiligo may be a syndrome with a multi-factorial etiology rather than a single entity[114] (Figure 2).

TREATMENT

The disfigurement associated with vitiligo could cause serious emotional stress for the patient and affect his quality of life[115]. Sun protection of vitiliginous areas with sun blocks is imperative[115,116] to prevent sunburn, photodamage and occurrence of Koebner phenomenon. In addition, sun blocks decrease tanning of the uninvolved skin and thus lessen the contrast with vitiliginous lesions[117].

There is no treatment ensures complete cure of vitiligo. Therefore, there is a plethora of modalities, such as topical corticosteroids, vitamin-D derivatives, calcineurin inhibitors, photochemotherapy [psoralen plus UV-A (PUVA)], psoralen with sunlight (PUVASOL), phototheraphy (UV-A, narrowband UV-B), surgical techniques[117-123], excimer laser[115,117,118-123], topical prostaglandin E (PGE2)[118], and combinations of topical therapies and light treatment[79]. Complementary and integrative therapies are also used, as ginkgo biloba[79], and levamisole[124], because of their immune-modulating properties[117].

Pseudocatalase cream with Dead Sea climatotherapy can also promote repigmentation[117]. Topical fluor-
levels and antioxidant enzymes\textsuperscript{[134]} and inhibiting pro-inflammatory cytokines as TNF-α\textsuperscript{[135]}.

Cell membranes enriched with omega-3 polyunsaturated fatty acids have elevated activity of glutathione peroxidase (GSH)\textsuperscript{[136]}. In addition, omega-3 fatty acids contain indole-3-carbinol which activates CYP1A1 that is responsible for hydroxylation of estrogens to 2-hydroxyestrone\textsuperscript{[137]}. Furthermore, omega-3 fatty acids have a vital role in the function of the central nervous system and affect the susceptibility and prognosis of depression\textsuperscript{[138]}. Twenty percent of patients with vitiligo are found to have depression. This highlights the benefits of these lipids in vitiligo\textsuperscript{[137]}.

In conclusion, many theories were elaborated to clarify vitiligo pathogenesis. It is a multifactorial disease involving the interplay of several factors. Future research is needed to clarify the interaction of these factors for better understanding of vitiligo pathogenesis and subsequent successful treatment.

REFERENCES

1. Lerner AB. Vitiligo. J Invest Dermatol 1959; 32: 285-310 [PMID: 13641799 DOI: 10.1038/jid.1959.49]
2. Wolff K, Johnson RA, Suurmond D. Section 13: Pigmentary Disorders-VITILIGO. In: Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York: McGraw-Hill, 2009 Available from: URL: http://www.accessmedicine.com/login. ezproxy.library.ualberta.ca/content.aspx?aid=5187746
3. Njoo MD, Westerhof W. Vitiligo. Pathogenesis and treatment. Am J Clin Dermatol 2001; 2: 167-181 [PMID: 11705094 DOI: 10.2165/0128071-200102030-00006]
4. Nath SK, Majumder PP, Nordlund JU. Genetic epidemiology of vitiligo: multilocus recessivity cross-validated. Am J Hum Genet 1994; 55: 981-990 [PMID: 7977362]
5. Kim SM, Chung HS, Hann SK. The genetics of vitiligo in Korean patients. Int J Dermatol 1998; 37: 908-910 [PMID: 9888330 DOI: 10.1046/j.1365-4362.1998.00540.x]
6. Spritz RA, Gowan K, Bennett DC, Fain PR. Novel vitiligo susceptibility loci on chromosomes 7 (AIS2) and 8 (AIS3), confirmation of SLEV1 on chromosome 17, and their roles in an autoimmune diathesis. Am J Hum Genet 2004; 74: 188-191 [PMID: 14691733 DOI: 10.1086/381134]
7. Birlea SA, Jin Y, Bennett DC, Herbstman DM, Wallace MR, McCormack WT, Kemp EH, Gawkrodger DJ, Westman AP, Ricardo M, Leone G, Taib A, Jouary T, Ezzedine K, van Geel N, Lambert J, Overbeck A, Fain PR, Spritz RA. Comprehensive association analysis of candidate genes for generalized vitiligo supports XBP1, FOXP3, and TSLP. J Invest Dermatol 2011; 131: 371-381 [PMID: 21085187 DOI: 10.1038/jid.2010.337]
8. Li E. Chromatin modification and epigenetic reprogramming in mammalian development. Nat Rev Genet 2002; 3: 662-673 [PMID: 12209141]
9. Zhao M, Gao F, Wu X, Tang J, Lu Q. Abnormal DNA methylation in peripheral blood mononuclear cells from patients with vitiligo. Br J Dermatol 2010; 163: 736-742 [PMID: 20560952 DOI: 10.1111/j.1365-2133.2010.09919.x]
10. Szalmás A, Bánáti F, Koroknai A, László B, Fehér E, Salamon D, Gergely I, Minárovits J, Kónya J. Lineage-specific silencing of human IL-10 gene expression by promoter methylation in cervical cancer cells. Eur J Cancer 2008; 44: 1030-1038 [PMID: 18378443]
11. Yun JY, Uhm YK, Kim HJ, Lim SH, Chung JH, Shin MK, Yim SV, Lee MH. Transforming growth factor beta receptor II (TGFB2R) polymorphisms and the association with nonsegmental vitiligo in the Korean population. Int J Immunogenet 2010; 37: 289-291
Nogoceke E, Mira MT. Genetic variants of the DDR1 gene are associated with vitiligo. *J Invest Dermatol* 2010; 134: 225-230 [PMID: 20025221 DOI: 10.1038/jid.2009.347]

Bekdash A, Mebazaa A, Gravel P, Cibert M, Zouali H. Autoimmune thyroiditis in children and adolescents with vitiligo. *J Dermatol Sci* 2006; 43: 226-230 [PMID: 16682119 DOI: 10.1016/j.jdermsci.2006.02.009]

Kemp EH, Emheimad S, Akhtar S, Watson PF, Gawkrodger DJ. Autoantibodies against thyroid-stimulating hormone receptor and TSH receptor in children and adolescents with vitiligo. *J Invest Dermatol* 2007; 127: 2068-2072 [PMID: 17518096 DOI: 10.1038/sj.jid.5501425]

Lepe V, Moncada B, Castanedo-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003; 139: 581-585 [PMID: 12756094 DOI: 10.1001/archderm.139.5.581]

Kemp EH, Emhemad S, Akhtar S, Watson PF, Gawkrodger DJ. Autoantibodies against thyroid-stimulating hormone receptor and TSH receptor in children and adolescents with vitiligo. *J Invest Dermatol* 2007; 127: 2068-2072 [PMID: 17518096 DOI: 10.1038/sj.jid.5501425]

Lepe V, Moncada B, Castanedo-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003; 139: 581-585 [PMID: 12756094 DOI: 10.1001/archderm.139.5.581]

Kemp EH, Emhemad S, Akhtar S, Watson PF, Gawkrodger DJ. Autoantibodies against thyroid-stimulating hormone receptor and TSH receptor in children and adolescents with vitiligo. *J Invest Dermatol* 2007; 127: 2068-2072 [PMID: 17518096 DOI: 10.1038/sj.jid.5501425]

Lepe V, Moncada B, Castanedo-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003; 139: 581-585 [PMID: 12756094 DOI: 10.1001/archderm.139.5.581]

Kemp EH, Emhemad S, Akhtar S, Watson PF, Gawkrodger DJ. Autoantibodies against thyroid-stimulating hormone receptor and TSH receptor in children and adolescents with vitiligo. *J Invest Dermatol* 2007; 127: 2068-2072 [PMID: 17518096 DOI: 10.1038/sj.jid.5501425]

Lepe V, Moncada B, Castanedo-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003; 139: 581-585 [PMID: 12756094 DOI: 10.1001/archderm.139.5.581]

Kemp EH, Emhemad S, Akhtar S, Watson PF, Gawkrodger DJ. Autoantibodies against thyroid-stimulating hormone receptor and TSH receptor in children and adolescents with vitiligo. *J Invest Dermatol* 2007; 127: 2068-2072 [PMID: 17518096 DOI: 10.1038/sj.jid.5501425]

Lepe V, Moncada B, Castanedo-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003; 139: 581-585 [PMID: 12756094 DOI: 10.1001/archderm.139.5.581]

Kemp EH, Emhemad S, Akhtar S, Watson PF, Gawkrodger DJ. Autoantibodies against thyroid-stimulating hormone receptor and TSH receptor in children and adolescents with vitiligo. *J Invest Dermatol* 2007; 127: 2068-2072 [PMID: 17518096 DOI: 10.1038/sj.jid.5501425]
Pattern in a vitiligo patient: a clue to an epidermal stem-cell feature in vitiligo. Davids LM, Kim YJ, Kang HY, Sohn S, Lee ES. Histopathologic KU. Melanocytes are not absent in lesional skin of long duration Tobin DJ. Fitzpatrick's Dermatology in General Medicine. 7th ed, Vol. I. Philadelphia, USA: Mosby Elsevier, 2006: 683-687

Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I. Treatment of Skin Disease: Comprehensive Therapeutic Strategies. 2nd ed. Philadelphia, USA: Mosby Elsevier, 2006: 683-687

Burns T, Breathnach S, Cox N, Griffiths C. Rook's Textbook of Dermatology. 7th ed, Vol. II. Oxford: Blackwell Science, 2004: 52-57

Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ. Fitzpatrick's Dermatology in General Medicine. 7th ed, Vol. I. USA: Mac Graw Hill, 2007: 616-621

Lotti T, Gori A, Zanieri F, Colucci R, Moretti S. Vitiligo: new and emerging treatments. Dermatol Ther 2008; 21: 110-117 [PMID: 18394085 DOI: 10.1111/j.1600-0749.2008.00178.x]

Szczurko O, Boo HS. A systematic review of natural health product treatment for vitiligo. BMC Dermatol 2008; 8: 2 [PMID: 18498646 DOI: 10.1186/1471-5945-8-2]

Bolognia JL, Jorizzo JL, Rapini R. Dermatology. 2nd edn, Vol. I. USA: Mosby Elsevier, 2008: 913-920

Forscher T, Buchholtz S, Stockfleth E. Current state of vitiligo therapy—evidence-based analysis of the literature. J Dtsch Dermatol Ges 2007; 5: 467-475 [PMID: 17537039]

Grimes PE. New insights and new therapies in vitiligo. JAMA
Mohammed GF et al., Pathogenesis of vitiligo

2005; 293: 730-735 [PMID: 15701915]

123 Ostovari N, Passeron T, Zakaria W, Fontas E, Larouy JC, Blot JF, Lacour JP, Ortonne JP. Treatment of vitiligo by 308-nm excimer laser: an evaluation of variables affecting treatment response. *Lasers Surg Med* 2004; 35: 152-156 [PMID: 15334620 DOI: 10.1002/lsm.20057]

124 Pasricha JS, Khera V. Effect of prolonged treatment with levamisole on vitiligo with limited and slow-spreading disease. *Int J Dermatol* 1994; 33: 584-587 [PMID: 7960359]

125 Tsuji T, Hamada T. Topically administered fluorouracil in vitiligo. *Arch Dermatol* 1983; 119: 722-727 [PMID: 6614958]

126 van den Wijngaard R, Wankowicz-Kalinska A, Pals S, Weening J, Das P. Autoimmune melanocyte destruction in vitiligo. *Lab Invest* 2001; 81: 1061-1067 [PMID: 11502857]

127 Michaëllson G, Juhlin L, Vahlquist A. Effects of oral zinc and vitamin A in acne. *Arch Dermatol* 1977; 113: 31-36 [PMID: 137693]

128 Hillström L, Pettersson L, Hellbe L, Kjellin A, Leczinsky CG, Nordwall C. Comparison of oral treatment with zinc sulphate and placebo in acne vulgaris. *Br J Dermatol* 1977; 97: 681-684 [PMID: 146511 DOI: 10.1111/j.1365-2133.1977.tb14277.x]

129 Burrows NP, Turnbull AJ, Punchard NA, Thompson RP, Jones RR. A trial of oral zinc supplementation in psoriasis. *Cutis* 1994; 54: 117-118 [PMID: 7956335]

130 Kim YJ, Chung BS, Choi KC. Depigmentation therapy with Q-switched ruby laser after tanning in vitiligo universalis. *Dermatol Surg* 2001; 27: 969-970 [PMID: 11737134]

131 Koshevenko IU. [alpha-Tocopherol in the combined treatment of vitiligo]. *Vestn Dermatol Venereol* 1989; 10: 70-72 [PMID: 2609752]

132 Mandel AS, Haberman HF, Pawlowski D, Goldstein E. Non PUVA nonsurgical therapies for vitiligo. *Clin Dermatol* 1997; 15: 907-919 [PMID: 9404694 DOI: 10.1016/S0738-081X(97)00132-6]

133 Bickers DR, Athar M. Oxidative stress in the pathogenesis of skin disease. *J Invest Dermatol* 2006; 126: 2565-2575 [PMID: 17108903 DOI: 10.1038/sj.jid.5700340]

134 Fernandes G. Dietary lipids and risk of autoimmune disease. *Clin Immunol Immunopathol* 1994; 72: 193-197 [PMID: 8050192 DOI: 10.1006/clim.1994.1129]

135 Logan AC. Omega-3 fatty acids and major depression: a primer for the mental health professional. *Lipids Health Dis* 2004; 3: 25 [PMID: 15535884 DOI: 10.1186/1476-511X-3-25]

136 Joulain C, Prigent AF, Némoz G, Lagarde M. Increased glutathione peroxidase activity in human blood mononuclear cells upon in vitro incubation with n-3 fatty acids. *Biochem Pharmacol* 1994; 47: 1315-1323 [PMID: 8185640 DOI: 10.1016/0006-2952(94)90329-8]

137 Namazi MR. Prescribing cyclic antidepressants for vitiligo patients: which agents are superior, which are not? *Psychother Psychosom* 2003; 72: 361-362 [PMID: 14526142]

P- Reviewer: Kaliyadan F, Kostoglou-Athanassiou I S- Editor: Ji FF L- Editor: A E- Editor: Lu YJ
