

Vitiligo: A comprehensive overview

Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up

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Vitiligo is an acquired pigmentary disorder of unknown etiology that is clinically characterized by the development of white macules related to the selective loss of melanocytes. The prevalence of the disease is around 1% in the United States and in Europe, but ranges from less than 0.1% to greater than 8% worldwide. A recorded predominance of women may reflect their greater willingness to express concern about cosmetically relevant issues. Half of all patients develop the disease before 20 years of age. Onset at an advanced age occurs but is unusual, and should raise concerns about associated diseases, such as thyroid dysfunction, rheumatoid arthritis, diabetes mellitus, and alopecia areata. Generalized vitiligo is the most common clinical presentation and often involves the face and acral regions. The course of the disease is unpredictable and the response to treatment varies. Depigmentation may be the source of severe psychological distress, diminished quality of life, and increased risk of psychiatric morbidity. Part I of this two-part series describes the clinical presentation, histopathologic findings, and various hypotheses for the pathogenesis of vitiligo based on past and current research. (J Am Acad Dermatol 2011;65:473-91.)

Key words: autoimmune; depigmentation; depigmented; hypopigmentation; hypopigmented; leukoderma; macule; melanocyte; melanosome; vitiligo.

Key points

- **Vitiligo is a disorder of pigmentation manifesting as white macules and patches**
- **Vitiligo can occur at any age and affects both sexes equally**
- **Vitiligo is typically asymptomatic**

Vitiligo is an acquired disorder of the skin and mucous membranes that is characterized by well circumscribed, depigmented macules and patches and that occurs secondary to selective destruction of melanocytes.^{1,2} It may appear at any age; cases have been reported as early as 6 weeks after birth.^{1,3,4}

Approximately 0.5% to 1% of the population is affected, and almost half present before 20 years of age. Its prevalence appears to be equal between men and women,^{1,5} and there is no difference in rates of occurrence according to skin type or race.

Vitiligo can be a psychologically devastating disease, especially in darker skinned individuals, in whom it is more easily noticeable. It appears to be transmitted genetically in a polygenic/multifactorial manner. The actual pathogenesis is under debate and has been attributed to autoimmune (AI) causes, oxidative stress, and/or sympathetic neurogenic disturbance.⁶ Vitiligo can be divided into two major classes: nonsegmental (NSV), which is more common, and segmental (SV). The Vitiligo European Task Force (VETF) defines NSV as “an acquired

chronic pigmentation disorder characterized by white patches, often symmetrical, which usually increase in size with time, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes.”⁷ SV occurs in a unilateral distribution that may totally or partially match a dermatome (Fig 1).⁷

Vitiligo lesions may itch and have a propensity to sunburn. The Koebner phenomenon is common (Fig 2).⁶ Vitiligo is a chronic persistent disorder⁸; spontaneous repigmentation is uncommon and occurs in a perifollicular pattern (Fig 3).⁹

Many patients are poorly educated about their illness. In one study, 51.3% of patients believed that their vitiligo was caused by poor medical care, 30% thought personal behavior played a role, 25% diet, 21.3% state of mind, and 20% blamed pollution.¹⁰

EPIDEMIOLOGY

Key points

- **The prevalence of vitiligo is likely less than 1%, but varies based on region**
- **Females usually acquire the disease earlier than males**

The published prevalence of vitiligo is 0.5% to 1%.⁷ Large studies in China, India, and Denmark have found the prevalence to be 0.093%, 0.005%, and 0.38%, respectively.¹¹⁻¹³ Gujarat, India is considered to have the highest prevalence in the world, at about 8.8%.¹⁴ Men and women are equally affected,^{13,15} but women are more likely to seek treatment.^{16,17}

The mean age of onset is earlier in those with a positive family history,^{2,18} which ranges from 7.7% to more than 50%.^{2,17,19-23} Vitiligo is significantly more prevalent in young women (≤ 30 years of age) than young men.^{1,13,24,25} The peak in females occurs in the first decade of life. Male peak prevalence is in the fifth decade of life. Vitiligo is more frequently diagnosed in spring and summer (64.4%).^{1,5}

CAPSULE SUMMARY

- Vitiligo is a pigmentary disorder resulting in white macules which can appear at any time during life and can be psychologically devastating
- It occurs in all skin types and with equal frequencies between men and women
- Though a wide differential exists for disorders with loss of pigment, a biopsy is rarely needed to diagnose vitiligo
- Several theories regarding etiology have been proposed with the most evidence supporting an autoimmune phenomenon associated with underlying genetic predisposition

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Fig 1. Segmental vitiligo of the left abdomen and groin.



Fig 2. Koebner phenomenon occurring at the interface between the metal clasp of a wristwatch and the ventral surface of the wrist.

QUALITY OF LIFE

Key points

- Vitiligo significantly impairs quality of life
- Women are generally more affected by the disorder than men
- It is important to assess a patient's quality of life during encounters

Vitiligo is a psychologically devastating disorder. The fact that it typically occurs in exposed areas (the face and hands) has a major impact on self-esteem and perception of self. In many societies, vitiligo is poorly understood and is believed to be a sign of leprosy or sexually transmitted infection. In these societies, women with vitiligo have difficulty getting married^{8,26} and finding educational and vocational opportunities.²⁷ Many patients worry about the disease worsening, have their social life affected, and feel embarrassment, depression, and shame.²⁸



Fig 3. Spontaneous repigmentation occurs in a follicular pattern.

A quality of life (QOL) assessment should be made during the first consultation, because there may be a difference between patient and physician assessment of severity, and QOL should be followed during treatment to assess patient satisfaction. The Dermatology Life Quality Index (DLQI) scores range from 4.82 to 14.72,^{23,26,27,29-35} worse than psoriasis patients in certain subscales (feelings, clothing, social, and leisure).^{8,29} Studies suggest that vitiligo imparts a mental and emotional burden comparable to hand eczema or psoriasis,³⁶ and that women tend to suffer more than men.^{3,8,23,27,30,32,36-39} In a study of 158 patients with vitiligo, black or white race did not impact the degree of disturbance by the disorder.³ Vitiligo patients also experience sexual difficulties⁴⁰ and a variety of psychological problems, such as adjustment disorder, sleep disturbance, depression, anxiety, and dysthymia.^{28,31,41-44}

Clinical variables, such as duration, facial or chest involvement, previous treatment, darker skin type, patient-assessed severity, and extent of disease may predict a poorer QOL.^{26,27,32,33,36-39,45}

DIAGNOSIS

Key points

- Vitiligo is classified into localized, generalized, and universal
- Lesions typically develop in areas of friction, reflecting koebnerization
- A Wood's lamp can be helpful in diagnosis; a biopsy is rarely required
- Rare types of vitiligo include ponctué and quadrichrome

Classically, discrete, uniformly white macules or patches with convex borders are surrounded by normal skin (Fig 4).⁴⁶ Though typically asymptomatic, itch has been reported.^{47,48} Vitiligo frequently occurs at sites that are normally hyperpigmented, including the face (periorificial), the dorsal surface of the hands, nipples, axillae, umbilicus, sacrum,



Fig 4. A characteristic vitiligo macule—note the depigmentation and convex borders.

and inguinal/anogenital regions. On extremities, it favors the elbows, knees, digits, and flexor wrists. Koebnerization is typical.^{17,49} Leukotrichia is often-times associated with depigmentation of the surrounding epidermis.

The diagnosis of vitiligo is usually made clinically and with the use of a Wood's lamp, a handheld ultraviolet (UV) irradiation device emitting ultraviolet A (UVA) waves at a wavelength of approximately 365 nm. A Wood's lamp,⁸ photography, and/or in vivo reflectance confocal microscopy⁵⁰ may also facilitate monitoring the progress of lesions over time. Recently, the British Association of Dermatologists drafted recommendations for the diagnosis and evaluation of vitiligo patients (Table I).⁸

Vitiligo usually begins insidiously in sun-exposed areas during the spring and summer months. Severe sunburn,⁵¹ pregnancy,^{51,52} skin trauma,⁵³ and/or emotional stress may precede onset.^{54,55} Vitiligo is generally slowly progressive, either by centrifugal expansion of current lesions and/or the appearance of new lesions. One study found progression in 88.8% of patients, more so with positive family histories, NSV, a longer duration, Koebner phenomenon, and mucous membrane involvement.⁵⁶ A significantly higher incidence of koebnerization and disease progression is seen in NSV.^{57,58}

Vitiligo is divided into three types: localized, generalized, and universal.^{59,60} Localized vitiligo is further subtyped into focal (Fig 5), segmental (dermatomal or Blaschko-linear; Fig 1), and mucosal.⁸ Generalized vitiligo may be acrofacial, vulgaris (Fig 6), or mixed. Universal vitiligo involves more than 80% of the skin. Generalized vitiligo is the most common type, and vulgaris is the most common subtype. The sites of predilection for vitiligo vulgaris are the fingers and wrists, axillae and groin, and body orifices, such as the mouth, eyes, and genitals.^{8,17,61}

SV typically begins in childhood,^{62,63} most commonly in the trigeminal dermatome, with poliosis,

Table I. British Association of Dermatologists recommendations

Vitiligo diagnosis is straightforward when presentation is classical
When presentation is atypical, cases should be referred for expert assessment by a dermatologist
In adults with vitiligo, a blood test to check thyroid function should be considered
A Wood's lamp may be of use in determining extent and activity of vitiligo, as well as monitoring response to therapy
Response to treatment in vitiligo should be considered in context of the natural history, recognizing that spontaneous repigmentation may occur but is uncommon
Clinicians should assess the psychological and quality of life effects of vitiligo on patients
In clinical trials of vitiligo, the patient's improvement in quality of life should be the most important outcome measure

Adapted from Gawkrödger et al.⁸

and tends to be stable.^{17,62} Generalized vitiligo may begin later in life, at sites sensitive to pressure, friction, and/or trauma, and is typically progressive with flare-ups. Hair is affected in later stages. There is often an associated personal or family history of AI disorders.⁶³ The worst QOL is seen in patients with universal vitiligo, who also may have more AI comorbidities and a positive family history.⁶⁴

Vitiligo ponctué is rare; discrete, confetti-like amelanotic macules occur on normal or hyperpigmented skin (Fig 7).⁴⁶ Trichrome vitiligo has a tan zone of varying width between normal and depigmented skin.⁶⁵ On histopathology, this intermediate tan zone has more inflammatory cells, Langerhans cells, and melanophages than vitiliginous or normal skin; the number of melanocytes is greater than in vitiliginous skin but fewer than in normal skin.⁶⁵ Quadrichrome vitiligo has additional marginal or perifollicular hyperpigmentation; it is more common in darker skin types and in areas of repigmentation.^{17,46} Blue vitiligo has a blue-grey hue because of the absence of epidermal melanocytes and the presence of numerous dermal melanophages.⁶⁶ Inflammatory vitiligo (or "vitiligo with raised inflammatory borders") describes erythema at the margins of depigmented macules.^{17,46}

A full body skin examination is necessary to detect genital depigmentation if present. Thyrotropin (thyroid-stimulating hormone) levels, antinuclear antibody titer, and a complete blood count should be considered, especially when prompted by signs or symptoms.¹⁷ Antithyroid peroxidase antibodies and/or



Fig 5. Acrofacial vitiligo in an African American woman affecting the face.



Fig 6. Vitiligo vulgaris on the dorsal forearms and chest.

antithyroglobulin may also be worthwhile, especially if signs of thyroid disease are present.¹⁷

To date, there is no international, universal standardized staging system for vitiligo. The Vitiligo European Task Force (VETF) proposed a system in 2007 that evaluates extent, staging, and spread.⁷ A consistent staging system would allow larger international epidemiologic studies to better characterize the disorder and allow the meaningful comparisons of clinical trials with similar or different treatment modalities.

DIFFERENTIAL DIAGNOSIS

Key points

- The differential diagnosis of vitiligo is broad
- Occupational and iatrogenic causes of depigmentation can present like vitiligo
- Common disorders with similar presentation include nevus depigmentosus, idiopathic guttate hypomelanosis, and tinea versicolor

The differential diagnosis of vitiligo is broad (Table II); however, good history taking, a thorough physical examination, and the judicious use of histopathology generally yields a straightforward diagnosis (Fig 8).



Fig 7. Vitiligo punctuée, a subtype of vitiligo, is characterized by small, discrete, confetti-like amelanotic macules.

Chemical leukoderma and occupational vitiligo initially present with contact depigmentation but may later spread to other areas. Chemical leukoderma has been induced by dyes, perfume, detergents, cleansers, insecticides, rubber condoms, rubber slippers, black socks and shoes, eyeliner, lip liner, lipstick, toothpaste, antiseptics with phenolic derivatives, and mercuric iodide-containing “germicidal” soap.^{67,68} Occupational vitiligo may occur in those who work with phenolic-catecholic derivatives, including monobenzyl ether of hydroquinone, paratertiary butyl catechol, paratertiary butyl phenol, paratertiary amyl phenol, hydroquinone monomethyl ether, and hydroquinone.⁶⁹ Depigmentation has also been reported in shoemakers⁷⁰ and from contact with arsenic-containing compounds.⁷¹

Nevus depigmentosus is segmental hypopigmentation detectable in the first year of life and stable in size in proportion to the child's growth (Fig 9).⁷² The number of melanocytes may be normal, but the production of melanin pigment is reduced. With a Wood's lamp, the contrast between lesional and normal skin is less marked than in vitiligo.⁶

Piebaldism is an autosomal dominant disease presenting at birth with anterior midline depigmentation and a white forelock (poliosis).⁶⁻⁸ Distribution on the forehead and shins helps confirm the diagnosis.

ASSOCIATIONS AND SYNDROMES

Key points

- Vitiligo may be associated with other autoimmune disorders, including thyroid disease, diabetes, pernicious anemia, and psoriasis
- It may be associated with ophthalmologic and auditory findings
- It can be a part of several syndromes, including autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia and Schmidt syndrome

Table II. Differential diagnosis in vitiligo

Chemically-induced leukoderma (often occupational)
Phenols and other derivatives
Infections
Leishmaniasis
Leprosy
Onchocerciasis
Tinea versicolor
Treponematoses (pinta and syphilis)
Genetic syndromes
Hypomelanosis of Ito
Piebaldism
Tuberous sclerosis
Vogt-Koyanagi-Harada syndrome
Waardenburg syndrome
Postinflammatory hypopigmentation
Atopic dermatitis/allergic contact dermatitis
Nummular dermatitis
Phototherapy- and radiotherapy-induced hypopigmentation
Pityriasis alba
Posttraumatic hypopigmentation (scar)
Psoriasis
Systemic lupus erythematosus
Topical or systemic drug-induced depigmentation
Neoplastic
Amelanotic melanoma
Halo nevus
Melanoma-associated leukoderma
Mycosis fungoides
Idiopathic
Idiopathic guttate hypomelanosis
Lichen sclerosus et atrophicus
Lichen striatus-like leukoderma
Melasma (caused by contrast between lighter and darker skin)
Progressive (or acquired) macular hypomelanosis
Malformations
Nevus anemicus
Nevus depigmentosus/hypopigmentosus

Vitiligo may be associated with many primarily AI disorders (Table III). The link with AI thyroid disorders (hypothyroidism and hyperthyroidism) is the most well established. They may present in as many as 24% of pediatric vitiligo patients,⁷³⁻⁷⁵ although the onset is typically separated by more than a decade.⁷⁶ One study identified thyroid disease in 18.5% of 15,126 vitiligo patients.⁷⁷ A higher incidence of thyroid microsomal antibody is found in vitiligo patients and their family members. Conversely, vitiligo is more common in those with AI thyroid disorders.^{78,79}

Patients with generalized vitiligo, especially when familial, are more likely to have AI disorders than

those with segmental vitiligo.^{2,57} A controlled study of 226 vitiligo patients found an increased incidence of antinuclear (12.4%), antimicrosomal (7.1%), and anti-smooth muscle antibodies (25.7%).⁸⁰

Of 717 vitiligo patients seen at the Mayo Clinic between 1976 and 1981, 29 (4.04%) had concurrent psoriasis that occurred equally on vitiliginous and normal skin.⁸¹ On dermatoscopy, dilated capillaries and red globules of psoriasis against a background of depigmentation have been described as “the red in white sea sign.”⁸²

Up to 20% of patients with vitiligo have hearing loss, which is caused by functional disorders of intermediate cells (melanocytes) of the stria vascularis.^{83,84} Ocular abnormalities present in up to 40% include choroidal anomalies, uveitis,⁸⁵ iritis,^{17,46,86,87} and some degree of fundal pigment disturbance.⁸⁸

There appears to be an interesting association between melanoma and vitiligo, because the development of vitiligo in patients with metastatic melanoma may portend a favorable prognosis.⁸⁹⁻⁹¹ The pathologic mechanism that results in vitiligo may also destroy malignant pigment cells. On the other hand, there is evidence that those with vitiligo have a higher incidence of melanoma and vice versa.⁹² In addition, a slightly higher incidence of nonmelanoma skin cancer has been reported in those with vitiligo but did not reach statistical significance.⁹¹⁻⁹⁴

Vitiligo may be associated with several syndromes (Table III). Autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia (APECED)/autoimmune polyendocrine syndrome type 1 (APS1)/polyglandular autoimmune syndrome, type 1 (PGA1) patients present with a combination of Addison disease, hypoparathyroidism, ectodermal dysplasia, and/or chronic mucocutaneous candidiasis, but may also have alopecia areata, vitiligo, malabsorption syndrome, gonadal failure, pernicious anemia, chronic active hepatitis, corneal dystrophy, and enamel dystrophy.⁹⁵ A study of 68 patients with APECED found that 13 had vitiligo.⁹⁵ Schmidt syndrome/APS2/PGA2 is an autosomal dominant disorder with variable expressivity.⁹⁶ Like APECED, it presents with polyglandular failure (Addison disease, hypothyroidism, and type I diabetes mellitus), and occasionally vitiligo and/or hypogonadism.⁹⁷

Vogt-Koyanagi-Harada disease is a rare systemic T-cell mediated disorder characterized by uveitis, aseptic meningitis, dysacusis, alopecia, poliosis, tinnitus, and vitiligo (8-100%).⁹⁸⁻¹⁰⁴

Kabuki syndrome is a rare multiple malformation disorder that is characterized by developmental delay, distinct facial anomalies, congenital heart defects, limb and skeletal anomalies, and short

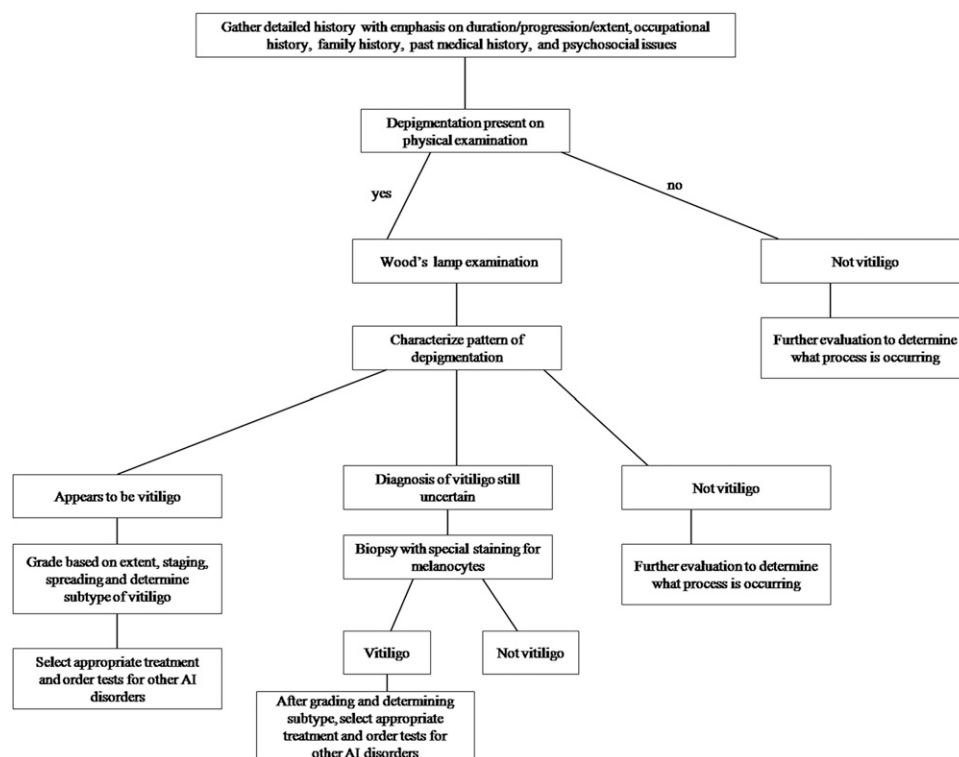


Fig 8. Protocol for the evaluation and diagnosis of vitiligo.



Fig 9. Nevus depigmentosus presents as circumscribed hypopigmentation, usually congenital or detectable in the first year of life.

stature. Associated autoimmune abnormalities are idiopathic thrombocytopenic purpura, hemolytic anemia, thyroiditis, and vitiligo.¹⁰⁵⁻¹⁰⁷

Alezzandrini syndrome presents with unilateral facial vitiligo, poliosis, deafness, and tapetoretinal degeneration.^{17,46,48,108} Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, a mitochondrial disorder, presents with central nervous system abnormalities, neurosensory hearing loss, diabetes mellitus, and cardiomyopathy. One study found vitiligo in 11% (3/28) of MELAS patients.¹⁰⁹

HISTOPATHOLOGY

Key points

- Histopathology can help confirm the diagnosis of vitiligo
- Melanocytes are absent, and there is a scant inflammatory cell infiltrate
- Active lesions may have a lichenoid interface dermatitis
- Immunohistochemical staining verifies the complete absence of melanocytes in skin that may still have melanin granules within keratinocytes

Histopathologic evaluation may help differentiate vitiligo from other disorders in ambiguous cases.¹¹⁰ Vitiligo lesions typically appear unremarkable with only scant cellular infiltrates and few or no melanocytes.⁷² Melanocytes on the pigmented edge of vitiliginous skin are larger, often vacuolated, and with long dendritic processes filled with melanin granules.¹¹¹ Useful special stains include DOPA, which detects active melanocytes, and HMB45 (anti-GP100), Mel-5 (anti-TRP1), and NKI/beteb (anti-pMel-17), which detect both active and dormant melanocytes.^{46,112} A pan-melanoma cocktail (HMB45 + tyrosinase + MART-1; Biocare Medical, Concord, CA) can maximize yield (Fig 10).

A review of 74 vitiligo specimens found: (1) the absence of pigment and suprabasal vacuolization in

Table III. Disorders and syndromes possibly associated with vitiligo (in alphabetical order)

More common associations
Addison disease
Alopecia areata
Atopic dermatitis
Autoimmune thyroid disease
Chronic urticaria
Diabetes mellitus
Halo nevi
Hypoacusis
Hypoparathyroidism
Ichthyosis
Ocular abnormalities
Pernicious anemia
Psoriasis
Rheumatoid arthritis
Less common associations
Acrokeratosis paraneoplastica Bazex
Alezzandrini syndrome
APECED syndrome
Asthma
Ataxia-telangiectasia
Deafness
DOPA-responsive dystonia
Dysgammaglobulinemia
HIV
Inflammatory bowel disease
Kabuki syndrome
Kaposi sarcoma
Melanoma
MELAS syndrome
Morphea
Multiple sclerosis
Myasthenia gravis
Nonmelanoma skin cancer
Pemphigus vulgaris
Sarcoidosis
Schmidt syndrome
Systemic lupus erythematosus
Turner syndrome
Twenty-nail dystrophy
Vogt-Koyanagi-Harada syndrome

APECED, Autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia.

all cases (Fig 11); (2) inflammatory changes, more often in those of short duration; (3) degenerative changes, more prominent in long-standing cases; (4) suprabasal clear cells in perilesional skin in 50% of patients; (5) perivascular mononuclear inflammatory cell infiltrates in 30%; (6) thinned epidermis in 53%; (7) effacement of the dermoepidermal junction in 39%; (8) perivascular inflammatory cell infiltrates in 92%; (9) sweat gland degeneration in 72%; (10) sebaceous gland/hair follicle degeneration in 38%;

(11) dermal nerve degeneration in 78%; and (12) nerve ending degeneration in 91% of cases.¹¹³

In vitiligo, the number of cells expressing c-kit, a transmembrane tyrosine kinase encoded by the c-kit proto oncogene, is markedly decreased at the edge of lesional epidermis compared with nonlesional epidermis and completely absent in the center of the lesion (Fig 12).¹¹⁴ In addition, black hairs within vitiligo patches may contain melanocytes. Disease duration is inversely correlated with the melanocytes' presence within hair follicles. Melanocytes are absent from 100% of white hairs.¹¹⁵

ETIOLOGY

Key points

- The cause of vitiligo is unknown
- The autoimmune hypothesis is the best supported theory
- The neurohumoral, cytotoxic, and oxidative stress theories have moderate evidence
- New theories focus on melanocytorrhagy and decreased melanocyte survival

It remains unclear what causes damage to melanocytes and their subsequent disappearance in affected skin. There are several pathophysiologic theories; the most prominent are autoimmune, neurohumoral, and autocytotoxic. None are mutually exclusive, and it is likely that they each partially contribute.

The current thought is that vitiligo represents a group of heterogeneous pathophysiologic disorders with a similar phenotype. The convergence theory states that stress, accumulation of toxic compounds, infection, autoimmunity, mutations, altered cellular environment, and impaired melanocyte migration can all contribute to pathogenesis.¹¹⁶ Autoimmune mechanisms likely underlie generalized vitiligo, while a more localized phenomenon (ie, the neurohumoral hypothesis) may be responsible for segmental or focal vitiligo.⁶²

Genetics

Although most cases of vitiligo are sporadic, familial clustering is not uncommon, and up to 20% of patients report an affected relative.^{18,117} In whites, the lifetime frequency of vitiligo among patients' siblings is 6.1%, an 18-fold increase over the studied population.¹⁸ The frequency of vitiligo among first-degree relatives in white, Indo-Pakistani, and Hispanic populations is 7.1%, 6.1%, and 4.8%, respectively,¹⁸ compared to an estimated worldwide frequency of 0.14% to 2%.¹¹⁸

Epidemiologic studies indicate that vitiligo is inherited in a non-Mendelian, multifactorial, and

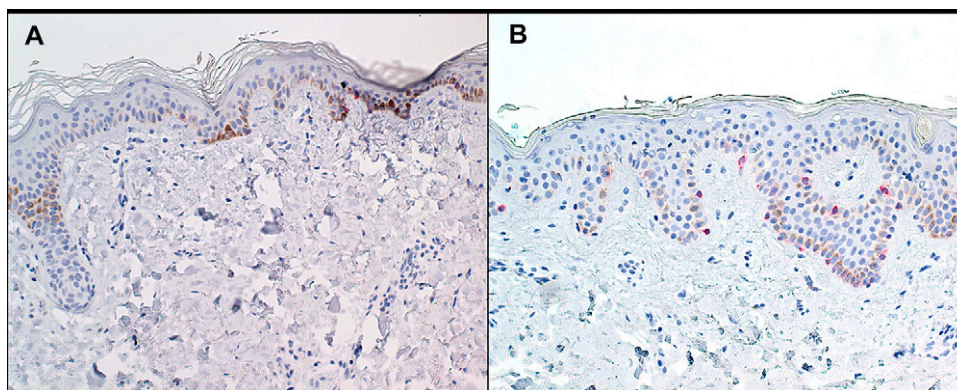


Fig 10. Vitiliginous skin (**A**) houses only two panmelanoma positive cells (red) in contrast to the normal number of melanocytes in unaffected skin (**B**). Many of the basal keratinocytes still have abundant melanin pigment within them, a common finding in early evolving lesions of vitiligo that have not yet completely depigmented. (Panmelanoma cocktail stain [HMB45 + tyrosinase + MART-1; Biocare Medical, Concord, CA].)

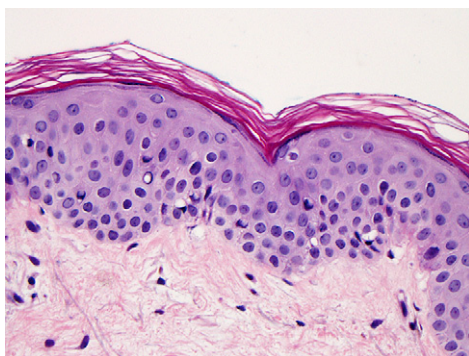


Fig 11. There is a slightly effaced rete ridge pattern with suprabasal vacuolization and occasional suprabasal clear cells. The dermis contains scant inflammatory cells. No melanin pigment is visible. (Hematoxylin–eosin stain; original magnification: $\times 30$.)

polygenic pattern, with incomplete penetrance.^{18,119} Recessive alleles at multiple unlinked loci may act epistatically in the development of vitiligo.¹¹⁷ Monozygotic twins with identical DNA have only a 23% concordance in developing vitiligo,¹⁸ suggesting a significant nongenetic component. Lastly, different phenotypes are associated with different genetic susceptibility genes and environmental exposures.¹²⁰

Familial clustering of generalized vitiligo with other autoimmune diseases is compelling evidence for an autoimmune diathesis, a common underlying genetic susceptibility to an immunologic aberrancy. Among vitiligo patients, 20% report thyroid disease (an 8-fold increase over the general population), particularly hypothyroidism.¹⁸ Similarly, there is an increased frequency in other forms of autoimmune disease and autoimmune polyendocrine syndromes (Table III).

Genetic association studies

Human leukocyte antigen (HLA) haplotypes may contribute to vitiligo susceptibility. HLAs-A2, -DR4, -DR7, and -DQB1*0303 are most frequent.^{121,122} Different ethnicities have different HLA-associated susceptibilities (Table IV). The strongest associations of vitiligo with particular HLA haplotypes appear to be in patients and families with various vitiligo-associated autoimmune/autoinflammatory syndromes,¹²³ further supporting an autoimmune diathesis.

In addition, there are numerous candidate genes and genetic loci associated with vitiligo (Table V). These genes have been implicated in a number of autoimmune diseases and likely function as general autoimmune/autoinflammatory susceptibility loci similar to HLA. A recent metaanalysis revealed that specific small nucleotide polymorphisms in cytotoxic T lymphocyte antigen 4, a critical negative feedback regulator of T cell activation and proliferation, were associated with vitiligo only in those with concomitant autoimmune disease.¹²⁴

Protein tyrosine phosphatase, nonreceptor type 22 encodes the gene for lymphoid protein tyrosine phosphatase, which negatively regulates T cell activation. One particular allele is associated with generalized vitiligo that occurs without other concomitant autoimmune diseases.¹²⁵ Mannose-binding lectin is a calcium dependent lectin that, when aberrant, predisposes to infections and autoimmune diseases.¹²⁶ There was an increased frequency of one allele in vitiligo patients, suggesting that it contributes to susceptibility.¹²⁶ NACHT leucine-rich-repeat protein 1 (NALP1) is a key regulator of the immune system that stimulates inflammatory pathways to unknown antigens. It is also a major susceptibility gene that is epidemiologically linked

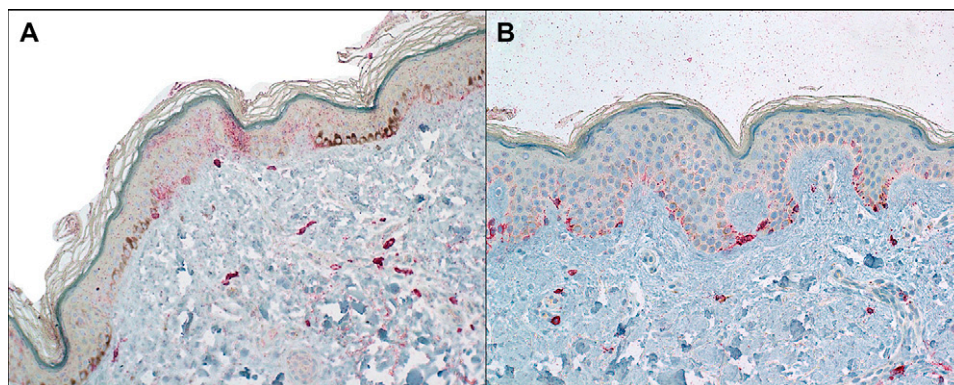


Fig 12. A single c-kit positive cell (red) is present in the basal layer of vitiliginous skin (**A**) as opposed to the normal number seen in unaffected skin (**B**). Also, there is notable patchy loss of melanin pigment in vitiligo (**A**) whereas normal skin (**B**) shows homogenous distribution of melanin granules in the lower epidermis. (c-kit stain [DAKO, Glostrup, Denmark]; original magnification: $\times 20$.)

to generalized vitiligo and other autoimmune diseases, such as autoimmune thyroid disease, pernicious anemia, systemic lupus erythematosus, and Addison disease.¹²⁷

Lastly, one study revealed that variant promoter regions of X-box binding protein 1 (XBP1) were associated with vitiligo in the Chinese Han population and that XBP1 was elevated in vitiligo lesions.¹²⁸ The XBP1 gene product, a DNA-binding protein, may interact with HLA-DR, thereby contributing to the development of vitiligo.¹²⁸

Genetic linkage studies

The first genome-wide linkage analysis uncovered a locus termed AI susceptibility 1 (AIS1) located in chromosome 1p31.3-p32.2 that was associated with vitiligo in a large, multigenerational family with vitiligo and other autoimmune diseases.¹²⁹ The AIS1 locus has been confirmed in subsequent studies.¹³⁰ Within the AIS1 region, there is a promoter variant in FOXD3, which is a gene for an embryonic transcription factor that regulates melanoblast differentiation and development.¹²⁹

Additional studies identified other susceptibility genes, including linkage signals on chromosomes 7 (AIS2), 8 (AIS3), and 17p.⁹⁶ The locus on chromosome 17 likely corresponds to SLEV1, which is associated with systemic lupus erythematosus and vitiligo.⁹⁶ AIS1, AIS2, and SLEV1 linkages occur in families with vitiligo and other autoimmune disease, while AIS3 links to a nonautoimmune family subgroup.⁹⁶

Very recently, linkage studies identified loci on chromosomes 7 and 9 that were significantly associated with vitiligo and that also interact with NALP1.¹³¹

Autoimmune hypothesis

There is substantial evidence for the immune-mediated destruction of melanocytes. Melanoma patients who develop hypopigmentation have a better prognosis,^{90,132} indicating that a common immune response to melanocytes is responsible for both hypopigmentation and tumor control. New-onset vitiligo has followed bone marrow transplants or lymphocyte infusions for the treatment of leukemias and lymphomas.¹³³⁻¹³⁶ Finally, the severity of hypopigmentation in the vitiligo animal model, the Smyth chicken, is lessened by suppressing T cell activity with cyclosporine A,¹³⁷ and B cell activity through neonatal bursectomy.¹³⁸

Humoral immunity. Antibodies in the sera of vitiligo patients are categorized as antibodies to cell surface pigment cell antigens, intracellular pigment cell antigens, and nonpigment cell antigens (common tissue antigens).¹³⁹

The first antigens were cell surface antigens of molecular weights 35, 40 to 45, 75, 90, and 150 kDa.¹⁴⁰ The more common antigens are VIT 40/75/90; less frequent are antibodies to the 35- and 150-kDa molecules.¹⁴¹ The former are present in 83% of vitiligo patients compared to 7% of controls.¹⁴¹ Only VIT 90 is found exclusively on pigment cells, while VIT 40 and VIT 75 are considered common tissue antigens because they are found on both pigment and nonpigment cells.¹⁴¹ Although these antibodies are nonspecific, melanocytes are much more sensitive to toxic or immune-mediated injury than are keratinocytes or fibroblasts,¹⁴² and so minimal injury from nonspecific antibodies may induce lethal harm to melanocytes, but not to the surrounding cells.

Table IV. Human leukocyte antigen haplotypes elevated among vitiligo patients of different ethnicities

HLA	Population	Reference
DR4, DQw3	African American	187
Allelic microsatellite loci at HLA D6	Columbian	188
DRB1*04- DQB1*0301	White	189
DR4	Caucasian American	190
DRB4*0101, DBQ1*0303	Dutch	191
DR4, DR53	Dutch	192
Cw7, DR6	Dutch	193
A*30, Cw*06, DRB1*07, DQB1*0201	Han Chinese	194
A2, A30, A31, B13, B46, Cw4, Cw6	Han Chinese	195
DQA1*0302, DQA1*0601, DQB1*0303, DQB1*0503	Han Chinese	196
DQA1*0302, DQB1*0303, DQB1*0503	Han Chinese	197
A*2501, A*30, B*13, B*27, Cw*0602	Han Chinese	195
DR1	Hungarian	198
A31, B46, Cw4	Japanese	199
B13	Jewish Moroccan	200
BW35	Jewish Yemenite	200
B21, Cw6, DR53	Kuwaiti	201
DRB1*04	Mexicans with thyroid disease	202
A30, Cw6, DQw3	Northern Italian	203
DRW12	Northern German	204
Bw6, DR7	Omani	205
B7, B15, Bw6, Cw6, Cw7, DRB4*010101	Saudi	206
A2, Dw7	Slovak	207
DRB1*0701, DQB1*0201, DPB1*1601	Slovak	208
DRB1*03, DRB1*04, DRB1*07	Turkish	209

Different ethnicities have associations with specific human leukocyte alleles with resultant variations in susceptibility. Major histocompatibility complex class I (A, B, and C) and class II (D) alleles are implicated, supporting roles for both cellular and humoral immunity, respectively.

Tyrosinase and tyrosinase-related proteins 1 and 2 (TRP-1 and TRP-2) are key enzymes in melanin synthesis located within melanosomes. The percentage of vitiligo patients with antibodies to these

antigens has varied greatly¹⁴³⁻¹⁴⁸—therefore, their role remains undefined.

Lastly, antibodies to SOX9 and SOX 10 (transcription factors involved in the differentiation of cells derived from the neural crest) were detected in patients with APS1 and in vitiligo patients without concomitant disease,¹⁴⁹ which suggests a potential general role in vitiligo.

There is a direct correlation between antibody levels and disease activity.^{144,150-152} Vitiligo patient sera are able to damage melanocytes in vitro both by complement activation and by antibody-dependent cellular cytotoxicity,^{150,153} and associated antibodies may also be able to damage melanocytes in vivo.¹⁵⁴

Cellular immunity. It is clear that altered cellular immunity is present in vitiligo, in addition to and perhaps in combination with a humoral response.¹⁵⁵ Normal-appearing perilesional skin has degenerative changes in melanocytes, vacuolization of basal cells, lymphocytic infiltrates, and melanophages in the upper dermis, all more prominent in actively spreading lesions.¹⁵⁶ Epidermotropic T cells in perilesional skin have an increased CD8/CD4 ratio, many express the skin-homing cutaneous lymphocyte antigen, and they frequently juxtapose the remaining melanocytes.^{157,158} These T cells also express activation molecules interleukin-2 (CD25), major histocompatibility complex II (specifically HLA-DR), and secrete interferon-gamma, which promotes T cell migration to the skin by increasing intracellular adhesion molecule-1 expression.^{157,158}

The peripheral blood of vitiligo patients shows high frequencies of Melan-A specific CD8⁺ T cells with cutaneous lymphocyte antigen, and their number may correlate with disease extent.¹⁵⁹⁻¹⁶¹ Clonally expanded cytotoxic T cells from a vitiligo-like halo surrounding a melanoma were identical to T cells within the tumor.¹⁶² Moreover, immunization with Melan-A peptide to augment the immune response to melanoma induced vitiliginous areas and regression of the melanoma associated with an oligoclonal expansion of Melan-A/MART-1 specific CD8⁺ T cells in both the serum and lesions in one patient.¹⁶³

Neurohumoral hypothesis

Dysregulation of the nervous system, either at a local or systemic level, may damage melanocytes in vitiligo. In support of this, both melanocytes and nerves arise from neural crest cells, and some vitiligo is segmental, follows the distribution of nerves, and shows alterations in perspiration and changes in nerve structure.¹⁶⁴

Immunohistochemical stains show an increase in neuropeptide Y intralesionally and perilesionally.¹⁶⁵ Vitiligo lesions may also exhibit increased levels of

Table V. Candidate genes for vitiligo

Chromosome	Gene or locus	Method	Comments	Reference
1p31.3-p32.2	AIS1 (FOXD3)	Linkage	Rare autosomal dominant	129
1p13	PTPN22	Association	Associated with autoimmune disorders	125
2p21	VIT1 (FBXO11)	Expression analysis	No evidence for causal involvement in vitiligo	210
2q33	CTLA4	Association	Associated with autoimmune disorders	124
3p14.1-p12.3	MITF	Study shows no linkage	Candidate gene only	211
6p21.3	MHC, and genes involved in cellular processing of antigens (LMP/TAP)	Association, linkage	Associated with autoimmune disorders	212 (see Table V)
6q25.1	ESR1	Association		213
7	AIS2	Linkage	Associated with autoimmune disorders	96
8	AIS3	Association	Associated with families without concurrent autoimmune disorders	96
10q11.2-q21	MBL-2	Association		126
11p13	CAT	Association	Questionable validity	179
12q12-q14	VDR	Association	Associated with autoimmune disorders	214
12q13	MYG1	Gene expression studies		215
14q22.1-q22.2	GCH1	DNA sequencing	Proven unrelated	216, 217
17p13	NALP1 (SLEV1)	Association, linkage	Associated with autoimmune disorders	96
21q22.3	AIRE	Linkage	Associated with APECED	218
22q12	XBP1	Association		128

AIRE, Autoimmune regulator gene; *AIS1*, autoimmune susceptibility 1; *APECED*, autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia; *CAT*, catalase; *CTLA4*, cytotoxic T lymphocyte antigen 4; *ESR1*, estrogen receptor 1; *GCH1*, GTP-cyclohydrolase; *MBL*, mannose-binding lectin; *MITF*, microphthalmia-associated transcription factor; *MYG1*, melanocyte proliferating gene 1; *NALP1*, NACHT leucine-rich-repeat protein 1; *PTPN22*, protein tyrosine phosphatase, nonreceptor type 22; *VDR*, vitamin D receptor; *XBP1*, X-box binding protein 1. The numerous susceptibility genes show the variety of etiologies and pathways that may contribute to vitiligo. This supports the view that vitiligo is a spectrum of heterogeneous disorders presenting with a common phenotype.

norepinephrine,¹⁶⁶ and a decrease in parasympathetic acetylcholine esterase activity.¹⁶⁷ The increased neurotransmitters may be directly cytotoxic to the cells, or may have an indirect effect through local vasoconstriction leading to hypoxia and subsequent stress-generated hydrogen peroxide (H₂O₂).¹⁶⁸

There is evidence that this neural dysregulation is systemic and that vitiligo often emerges during periods of increased stress. Changes in serum levels of epinephrine and norepinephrine (NE) are present,^{169,170} but their significance is unclear.¹⁷¹ Compelling evidence comes from 24-hour urine levels of homovanillic acid and vanilmandelic acid, which were significantly increased in patients with recent onset or progressive disease.¹⁶⁸

The source of excess neurotransmitters is uncertain, because both terminal nerve endings and keratinocytes are capable of synthesizing and secreting

them.¹⁶⁴ A high local concentration of NE has been related to a decrease in phenylethanolamine-N-methyl transferase activity and increased activity in tyrosine hydroxylase.¹⁷² High levels of catecholamines likely explain the increased intralesional enzymatic activity of catechol-o-methyltransferase, which normally neutralizes the neurotransmitters and generates toxic byproducts.¹⁷³ These byproducts can then damage the cell.

Autocytotoxic hypothesis

Toxic metabolites, either from environmental exposures, such as phenol or quinones, or from intrinsic melanin synthesis pathways, may accumulate and damage melanocytes of genetically susceptible individuals.¹⁷⁴ Chemical leukoderma is thought to occur through the inhibition of enzymes in the melanin pathway. As tyrosine, itself a phenol, enters into the pathways which eventually produce melanin,

electrically unstable byproducts are generated with the potential to damage other cellular substrates.¹⁷⁴ A defect in the melatonin receptor may result in toxic byproducts without a concomitant increase in melanin synthesis, leading to cellular damage.¹⁷⁴ Although plausible, there is no scientific evidence for functional melatonin receptors on melanocytes.

The biochemical theory of vitiligo

This theory states that the dysregulation of biop-terin pathways predisposes to melanocyte cytotoxicity and vitiligo. Pteridines (6R)-L-erythro 5,6,7,8 tetrahydrobiopterin (6BH4) and (7R)-L-erythro 5,6,7,8 tetrahydropterin (7BH4) are elevated in vitiligo.¹⁷⁵ 6BH4 is an essential cofactor for phenylalanine hydroxylase, the enzyme that converts dietary phenylalanine to tyrosine. Increased 6BH4, either from overactivity of its synthesizing enzyme GTP-cyclohydrolase I or reduced activity of recycling enzyme 4a-hydroxy BH4 dehydratase,¹⁷⁵ drives the metabolic pathway forward leading to an accumulation of byproducts 7BH4 and H₂O₂. Increased 7BH4 inhibits phenylalanine hydroxylase, further contributing to an increase in 6BH4. 6-biopterin is cytotoxic at high concentrations.¹⁷⁶

Oxidative stress hypothesis

It is unclear why both lesional and nonlesional skin from vitiligo patients has abnormally low levels of catalase enzyme,¹⁷⁷ which correlates with high H₂O₂ levels throughout the epidermis.¹⁷⁸ A single nucleotide polymorphism in the catalase gene may interfere with the enzyme's subunit assembly and function, and is more frequent among vitiligo patients.¹⁷⁹ H₂O₂ accumulation also degrades the active site of catalase, reducing its function.¹⁸⁰ The deranged melanin synthesis pathways involving 6-biopterin produce high levels of H₂O₂.¹⁷² Other possible explanations include increases in NE and monoamine oxidase, H₂O₂ generation as a byproduct,¹⁶⁶ and reduced glutathione peroxidase activity.¹⁸¹ Lastly, defective calcium uptake could alter the thioredoxin/thioredoxin reductase activities and oxidative balance.¹⁸²

Melanocytorrhagy hypothesis

This theory may explain the Koebner phenomenon because it proposes that melanocytes are weakly anchored and therefore minor friction and/or other stress can induce upward migration and loss.¹⁸³ Four minutes of light friction on the nonlesional skin of NSV patients produced melanocyte detachment after 4 and 24 hours.¹⁸⁴ Tenascin, an extracellular matrix molecule which inhibits adhesion of melanocytes to fibronectin, is elevated in

vitiliginous skin, and may contribute to loss of melanocytes or ineffective repopulation.¹⁸⁵

Decreased melanocyte survival hypothesis

Yet another theory questions if a deficiency in survival signals leads to melanocyte apoptosis. Keratinocyte-derived stem cell factor regulates melanocyte growth and survival by binding to membrane tyrosine kinase receptor c-kit. The significantly decreased number of c-kit receptors in perilesional melanocytes¹¹⁴ and the lower expression of stem cell factor from surrounding keratinocytes¹⁸⁶ may contribute to vitiligo pathogenesis.

SUMMARY OF ETIOLOGIC THEORIES

The cause of vitiligo still remains unknown, although it is clear that several different pathophysiologic processes may be involved. The autoimmune hypothesis is best supported because of the numerous genetic association and genetic linkage studies, in combination with humoral and cellular immune aberrancies. The neurohumoral, cytotoxic, and oxidative stress theories have moderate evidence. Newer theories, such as melanocytorrhagy and decreased melanocyte survival, are just beginning to accrue data. Because all of these theories are plausible, it seems likely that vitiligo may indeed include a spectrum of disorders that manifest as a common phenotype.

WORK-UP RECOMMENDATIONS

In a patient with new-onset depigmentation, a thorough history and physical examination will usually establish the diagnosis of vitiligo; examination with a Wood's lamp will help determine true extent of involvement regardless of skin type (Fig 8). In cases where the diagnosis is less obvious, histopathologic evaluation is typically diagnostic. Specimens should be obtained both from lesional and normal skin if possible, because comparing the two may yield a higher diagnostic accuracy. Screening for thyroid function abnormalities with a thyroid-stimulating hormone test, and for autoimmune disease with an antinuclear antibody test should be considered in all patients. Any additional serologic studies and ophthalmologic and audiologic examinations are of value in those who are symptomatic or have a positive family history of such involvement. Patients in whom vitiligo is part of a systemic syndrome typically have multisystem organ dysfunction that will present accordingly and is likely to be discovered at birth or during infancy; evaluation by a medical geneticist and appropriate specialists is recommended. A QOL assessment is necessary for all patients presenting with vitiligo. If it is

determined that there is considerable psychosocial impact—as is often present—a referral to a social worker or counseling services is very helpful and much appreciated by the patient.

Vitiligo is inherited in a non-Mendelian, multifactorial, and polygenic pattern, with incomplete penetrance. Different pathogenetic concepts have been put forward and supported by scientific evidence. Recently, the so-called “convergence theory” proposed that no single mechanism suffices to explain the pathogenesis. Although vitiligo does not produce direct physical impairment, it poses a significant psychosocial burden, and QOL improvement should be the most important outcome measure in future clinical trials.

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Answers to CME examination

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