

Generalized Vitiligo and Associated Autoimmune Diseases in Japanese Patients and Their Families

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ABSTRACT

Background: Generalized vitiligo is an acquired disorder in which depigmented macules result from the autoimmune loss of melanocytes from the involved regions of skin. Generalized vitiligo is frequently associated with other autoimmune diseases, particularly autoimmune thyroid diseases (Hashimoto's thyroiditis and Graves' disease), rheumatoid arthritis, adult-onset type 1 diabetes mellitus, psoriasis, pernicious anemia, systemic lupus erythematosus, and Addison's disease.

Methods: One hundred and thirty-three Japanese patients with generalized vitiligo were enrolled in this study to investigate the occurrence of autoimmune diseases in Japanese patients with generalized vitiligo and their families.

Results: Twenty-seven of the patients with generalized vitiligo (20.3%) had autoimmune diseases, particularly autoimmune thyroid disease (sixteen patients, 12%) and alopecia areata (seven patients, 5.3%). Thirty-five patients (26.3%) had a family history of generalized vitiligo and/or other autoimmune diseases. Familial generalized vitiligo was present in fifteen (11.3%), including four families with members affected by autoimmune disorders. Twenty (15.0%) had one or more family members with only autoimmune disorders.

Conclusions: Among Japanese vitiligo patients, there is a subgroup with strong evidence of genetically determined susceptibility to not only vitiligo, but also to autoimmune thyroid disease and other autoimmune disorders.

KEY WORDS

alopecia areata, autoimmune disease, autoimmune thyroid disease, generalized vitiligo, rheumatoid arthritis

INTRODUCTION

Generalized vitiligo is an acquired disorder characterized by progressive, multifocal patches of depigmented skin, overlying hair, and mucous membranes resulting from the autoimmune loss of melanocytes in the involved areas. Generalized vitiligo is the most common hypopigmentation disorder, with a prevalence of approximately 0.4% in most populations,¹⁻³ though in the Chinese population, it is lower, approximately 0.093%.⁴ Studies of generalized vitiligo patients from a number of populations around the world have shown a strong epidemiological association with several other autoimmune diseases, particularly auto-

immune thyroid disease, rheumatoid arthritis, adult-onset type 1 diabetes mellitus, psoriasis, pernicious anemia, systemic lupus erythematosus (SLE), and Addison's disease.⁵⁻¹⁸ The most prevalent autoimmune disease in patients with generalized vitiligo is autoimmune thyroid disease (Hashimoto's thyroiditis and Graves' disease), with a reported overall frequency of 19.4% in Caucasian patients,³ 7.4% in Japanese patients,¹³ and 2.4-5.8% in Chinese patients.^{14,16} In the Caucasian population, family members are predisposed to vitiligo itself, an autoimmune thyroid disease, pernicious anemia, Addison's disease, SLE, and probably inflammatory bowel disease.¹⁹ In Japan, it is still uncertain whether Japanese family members

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Received 13 January 2011. Accepted for publication 9 March 2011.

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have a similar tendency, although affected persons have a predisposed relationship between generalized vitiligo and autoimmune disorders.¹³ The purpose of this investigation was to study the occurrence of concomitant autoimmune diseases in Japanese patients with generalized vitiligo and their families.

METHODS

The study protocol was approved by each institution's ethics committee, and signed informed consent was obtained from each subject. One hundred and thirty-three Japanese patients were enrolled in this study. They were diagnosed with generalized vitiligo at the Dermatology Clinic of Kinki University, Osaka City University, and Yamagata University.

The diagnosis of generalized vitiligo was determined by board-certified dermatologists (N.O., F.K., and T.S.) using standard diagnostic criteria; patients with segmental and localized types of vitiligo were excluded. Subjects were questioned about the age at onset, the duration of the disease, and the personal and familial medical history of generalized vitiligo, autoimmune thyroid diseases, rheumatoid arthritis, type 1 diabetes mellitus, psoriasis, pernicious anemia, SLE, Addison's disease, alopecia areata, and other autoimmune diseases. Multi-specialist medical evaluations were carried out to confirm the diagnoses in some patients and family members.

RESULTS

The characteristics of the one hundred and thirty-three patients are summarized in Table 1. Of these patients, twenty-seven (20.3%) had been diagnosed with other autoimmune disorders (Table 2). Sixteen (12%) had autoimmune thyroid disease, including Hashimoto's thyroiditis in ten (7.5%) and Graves' disease in six (4.5%). Three (two males and a female) had preceding Sutton's nevus. Fifteen (11.3%) reported a positive family history of generalized vitiligo (Table 3), including four families with members affected by autoimmune disorders. Seven (5.3%) had at least one first-degree relative (parent or child) with vitiligo, and four of these (3.0%) had at least one affected sibling. Twenty (15.0%) had a family history of only autoimmune disorders (Table 3).

DISCUSSION

We assessed the occurrence of autoimmune diseases in one hundred and thirty-three Japanese patients with generalized vitiligo. Generalized vitiligo is associated with higher prevalence of other autoimmune diseases in both the patients and their close relatives.^{8,11,13-18} In the present study, twenty-seven patients (20.3%) with generalized vitiligo had other autoimmune disorders. These results are similar to those for other populations,^{5-12,15} including the Chinese and Japanese populations.^{13,14,16} Seven patients (5.3%) also had alopecia areata, a ratio that is similar to that

Table 1 Demographics of 133 Japanese generalized vitiligo patients

	Patients
Mean age \pm SD (years)	49.3 \pm 19.8
Age range (years)	3-89
Gender (male : female)	57 : 76
Age (years)	
<20	20
20-59	57
\geq 60	56
Mean age at onset \pm SD (years)	41.2 \pm 20.9
Range of ages at onset (years)	3-88
Age at onset (years)	
<20	29
20-59	63
\geq 60	41
Mean duration \pm SD (years)	8.2 \pm 8.6
Duration range (years)	0-63

for generalized vitiligo patients in the African,²⁰ Indian,²¹ and Chinese populations,^{14,22} though not in the Caucasian population.⁸ Thirty-five patients (26.3%) had a positive family history of generalized vitiligo or other autoimmune diseases, which is again similar to the ratio reported in other populations,^{8,23} suggesting that these disorders involve shared susceptibility genes, although the specific genes and variants may differ among the populations.²⁴⁻²⁸

Recent genomewide association studies have identified at least seventeen confirmed vitiligo susceptibility genes.²⁴⁻²⁸ Many of these genes have also been implicated in other autoimmune diseases, particularly those that are epidemiologically associated with generalized vitiligo, such as autoimmune thyroid disease, rheumatoid arthritis, type 1 diabetes mellitus, and others. These shared immune related disease susceptibility genes may underlie our observed associations in patient with generalized vitiligo and their close relatives.

Hashimoto's thyroiditis is a fairly common disease in Japanese generalized vitiligo patients as shown in this study. This disease is characterized by the destruction of thyroid cells by various cell- and antibody-mediated immune processes.²⁹ However, the initiating process is not well understood to date, because it includes various environmental factors and inflammatory events. Recent epidermological findings⁵⁻¹⁸ including ours and genomewide association studies²⁴⁻²⁸ support the long-standing hypothesis that generalized vitiligo involves genetic susceptibility loci shared with other autoimmune diseases.³⁰ Similar to autoimmune thyroid disease, generalized vitiligo is now believed to be caused by the damage of melanocytes by various cell- and antibody-mediated immune mechanisms. Nevertheless, the initiating process has

Table 2 Autoimmune diseases in patients with generalized vitiligo

	Number of patients			Number of patients		
	total	male	female	total	male	female
Autoimmune thyroid disease	16	5	11			
Hashimoto's thyroiditis				10	2	8
Graves' disease				6	3	3
Alopecia areata	7	3	4			
Psoriasis	2	2	0			
Pernicious anemia	1	1	0			
Adult-onset type 1 diabetes mellitus	(1 [†])	(1 [†])	0			
Acrodermatitis continua of Hallopeau	1	1	0			
Total	27	12	15			

[†]The patient also had Graves' disease.

Table 3 Occurrence of autoimmune diseases in families of generalized vitiligo

	Number of families	Number of families
Positive family history of generalized vitiligo	15	
Family member(s) with only generalized vitiligo	11	
Family member(s) with generalized vitiligo and other family member(s) with rheumatoid arthritis	3	
A family member with generalized vitiligo and another family member with alopecia areata	1	
Positive family history of only autoimmune disorders	20	
Autoimmune thyroid disease	13	
Hashimoto's thyroiditis		5
Graves' disease		5
Unknown		3
Alopecia areata	4	
Rheumatoid arthritis	1	
Psoriasis	1	
Adult-onset type 1 diabetes mellitus	1	
Total	35	

not well been elucidated. Further study is needed to identify the initiating factors inducing generalized vitiligo, autoimmune thyroid disease and other autoimmune disorders.

ACKNOWLEDGEMENTS

This work was supported by a grant-in-aid from Health Sciences Research grants from the Ministry of Health, Welfare and Labour of Japan.

CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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