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

Tomohiko Narita¹, Naoki Oiso¹, Kazuyoshi Fukai², Kenji Kabashima³, Akira Kawada¹ and Tamio Suzuki⁴

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

\textbf{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.

\textbf{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).

\textbf{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.\textsuperscript{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,\textsuperscript{5,12,15} including the Chinese and Japanese populations.\textsuperscript{13,14,16} Seven patients (5.3\%) also had alopecia areata, a ratio that is similar to that for generalized vitiligo patients in the African,\textsuperscript{20} Indian,\textsuperscript{21} and Chinese populations,\textsuperscript{14,22} though not in the Caucasian population.\textsuperscript{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,\textsuperscript{8,23} suggesting that these disorders involve shared susceptibility genes, although the specific genes and variants may differ among the populations.\textsuperscript{24-28}

Recent genomewide association studies have identified at least seventeen confirmed vitiligo susceptibility genes.\textsuperscript{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.\textsuperscript{29} However, the initiating process is not well understood to date, because it includes various environmental factors and inflammatory events. Recent epidemiological findings\textsuperscript{5-18} including ours and genomewide association studies\textsuperscript{24-28} support the long-standing hypothesis that generalized vitiligo involves genetic susceptibility loci shared with other autoimmune diseases.\textsuperscript{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

\begin{table}[h]
\centering
\begin{tabular}{lrr}
\hline
\multicolumn{1}{l}{\textbf{Demographics of 133 Japanese generalized vitiligo patients}} & \\
\hline
\textbf{Patients} & \\
\hline
Mean age ± SD (years) & 49.3 ± 19.8 & \\
Age range (years) & 3-89 & \\
Gender (male : female) & 57 : 76 & \\
Age (years) & \\
<20 & 20 & \\
20-59 & 57 & \\
≥60 & 56 & \\
Mean age at onset ± SD (years) & 41.2 ± 20.9 & \\
Range of ages at onset (years) & 3-88 & \\
Age at onset (years) & \\
<20 & 29 & \\
20-59 & 63 & \\
≥60 & 41 & \\
Mean duration ± SD (years) & 8.2 ± 8.6 & \\
Duration range (years) & 0-63 & \\
\hline
\end{tabular}
\caption{Demographics of 133 Japanese generalized vitiligo patients}
\end{table}
Vitiligo and Autoimmune Disease in Japan

Table 2  Autoimmune diseases in patients with generalized vitiligo

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>male</td>
<td>female</td>
<td>total</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>16</td>
<td>5</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves' disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Adult-onset type 1 diabetes mellitus</td>
<td>(1)</td>
<td></td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>Acrodermatitis continua of Hallopeau</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

1 The patient also had Graves' disease.

Table 3  Occurrence of autoimmune diseases in families of generalized vitiligo

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of families</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive family history of generalized vitiligo</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Family member(s) with only generalized vitiligo</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Family member(s) with generalized vitiligo and other family member(s) with rheumatoid arthritis</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>A family member with generalized vitiligo and another family member with alopecia areata</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Positive family history of autoimmune disorders 35

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 inducting generalized vitiligo, autoimmune thyroid disease and other autoimmune disorders.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

REFERENCES


Allergology International Vol 60, No4, 2011 www.jsaweb.jp/ 507
report from vitiligo clinic in Kyoto University Hospital. *Dermatoendocrinol* 2009;**1**:43-5.


27. Quan C, Ren YQ, Xiang LH *et al.* Genome-wide association study for vitiligo identifies susceptibility loci at 6q27 and the MHC. *Nat Genet* 2010;**42**:614-8.

