Increased Prevalence of Autoimmunity in Patients With White Spot Syndromes and Their Family Members

Robert B. Pearlman, MD; Pamela R. Golchet, MD; Marni G. Feldmann, MD; Lawrence A. Yannuzzi, MD; Michael J. Cooney, MD; Jennifer E. Thorne, MD, PhD; James C. Folk, MD; Edwin H. Ryan, MD; Anita Agarwal, MD; Kathleen C. Barnes, PhD; Kevin G. Becker, PhD; Lee M. Jampol, MD

**Objective:** To determine whether there is an increased prevalence of systemic autoimmune diseases in both patients with white spot syndromes (WSS) and their family members.

**Methods:** Patients with WSS at participating institutions were asked to complete a questionnaire reporting their own medical histories as well as any autoimmune diseases among their first- and second-degree relatives.

**Results:** As of January 1, 2008, 114 questionnaires had been collected, providing medical histories of 114 patients with WSS and 1098 family members. The number of patients with WSS with self-reported systemic autoimmune diseases was 26 (23%). Of 1098 relatives, 106 (10%) had at least 1 autoimmune disease. Systemic autoimmunity was more prevalent in female relatives (13%) as compared with male relatives (6%). In addition, the prevalence of autoimmunity was significantly higher among first-degree relatives (13%) than second-degree relatives (8%). Patients who themselves had systemic autoimmune diseases showed a greater prevalence of systemic autoimmunity among their families as compared with the families of patients without systemic autoimmune diseases.

**Conclusions:** Our data indicate that there is an increased prevalence of systemic autoimmunity in both patients with WSS and their first- and second-degree relatives. This suggests that WSS occur in families with inherited immune dysregulation that predisposes to autoimmunity.

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Author Affiliations:
Department of Ophthalmology, Northwestern University, Chicago, Illinois (Drs Pearlman, Golchet, Feldmann, and Jampol); Manhattan Eye and Ear Infirmary, New York, New York (Drs Yannuzzi and Cooney); Wilmer Eye Institute (Dr Thorne), Department of Epidemiology, Johns Hopkins University (Dr Barnes), and National Institutes of Health (Dr Becker), Baltimore, Maryland; Department of Ophthalmology, University of Iowa, Iowa City (Dr Folk); Department of Ophthalmology, University of Minnesota, Minneapolis (Dr Ryan); and Department of Ophthalmology, Vanderbilt University, Nashville, Tennessee (Dr Agarwal).

The white spot syndromes (WSS) are a group of disorders characterized by multiple whislike-yellow inflammatory lesions at the level of the outer retina, retinal pigment epithelium, or choroid. These syndromes include multifocal choroiditis/punctate inner choroidopathy (MFC/PIC), acute zonal occult outer retinopathy (AZOOR), birdshot chorioretinopathy, multiple evanescent white dot syndrome, serpiginous choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPE), acute macular neuroretinopathy, and relentless placoid chorioretinitis. The syndromes of AZOOR and acute macular neuroretinopathy do not have white lesions per se but are included because of an association with the other entities.

The etiology of these diseases is unclear. Jampol and Becker hypothesized that the origin of these WSS may be explained by Becker's common genetic hypothesis of autoimmune/inflammatory diseases. Persons with WSS may have systemic immune dysregulation. Relatively common, non-disease-specific loci that predispose to systemic autoimmunity may be involved in the WSS. Environmental factors or other genes including major histocompatibility antigens (such as HLA-A29 in birdshot chorioretinopathy) may help explain the variations in clinical course. This hypothesis is consistent with the observation that these disorders often occur in young females, as do many autoimmune diseases.

Previous studies have suggested that patients can concurrently have WSS and systemic autoimmune diseases. If this association between WSS and systemic autoimmune diseases exists, one would expect to find systemic autoimmune diseases in the family members of patients with WSS because patients and their family members share common genes. The purpose of this study is to examine whether there is an increased prevalence of systemic autoimmunity in the patients with WSS and their family members.
Of these, 114 agreed to participate. These patients were identified and recruited by the primary investigators at 6 institutions across the United States: Northwestern University, the Manhattan Eye and Ear Infirmary, the Wilmer Eye Institute, Vanderbilt University, the University of Minnesota, and the University of Iowa. Permission to conduct the study was obtained from the institutional review board at each institution.

Patient participation was accomplished either in person or via telephone by the investigator at each site. Inclusion criteria included being aged at least 18 years, willingness to participate in the study, and a definitive diagnosis of 1 or more WSS. Twenty-five patients declined to participate. One patient initially could not be enrolled in the study as she was 17 years old at the initiation of enrollment. When she turned 18 years old, we enrolled her in the study. Once the patients consented, a questionnaire requesting information on both the patient and his or her family members was provided. Each patient was asked for his or her sex, race, and date of birth if allowed by each center’s institutional review board. A history of systemic autoimmunity was also asked of each patient. The systemic autoimmune diseases in question included atopic dermatitis, alopecia areata, ankylosing spondylitis, pemphigoid, dermatomyositis, Graves disease, Hashimoto thyroiditis, type 1 (insulin-dependent) diabetes mellitus, inflammatory bowel disease (IBD), juvenile rheumatoid arthritis (JRA), multiple sclerosis (MS), psoriasis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and vitiligo. These were the autoimmune diseases that Prahalad et al listed in their study, which found increased systemic autoimmunity in families of patients with WSS.

Each patient was also asked to contact each of his or her living first- and second-degree relatives, including children, siblings, parents, grandparents, aunts, uncles, and cousins. Decedent family members were not included in the study. Each living relative was asked by the patient whether he or she had at any time been diagnosed with any of the earlier-mentioned systemic autoimmune diseases. Specifically, the patients were asked to write one of the following responses for each family member: the name of the autoimmune disease (if applicable), “no” if the family member did not have any of the autoimmune diseases, or “NA” if the information about the family member was not available. If any medical history provided in the questionnaire was unclear, the patient was contacted by the primary investigator via telephone or e-mail to clarify the history. If the relative was unable or unwilling to be contacted to provide the needed information, that individual’s history was not included in the study. There were 319 such family members who were not included in the study.

The completed questionnaires were submitted to the investigators at the sites. The investigators then faxed the questionnaires to Northwestern University. The data collected from the completed questionnaires were used to develop a master database. The data were also used to form family pedigrees. The master database was used for the statistical analyses of this study. Descriptive statistics were used to determine the prevalence of systemic autoimmune diseases in patients with WSS and their family members. Specifically, the prevalence of autoimmunity was summarized using frequencies and percentages. The Pearson χ² test was used to test the difference in prevalence of autoimmunity between groups. We used SAS version 9 statistical software (SAS Institute, Inc, Cary, North Carolina) for statistical analyses. Patients who had a diagnosis of 2 different autoimmune diseases were counted separately when calculating the overall prevalence of systemic autoimmunity among the patients. Each autoimmune disease was counted separately when calculating the overall prevalence of each systemic autoimmune disease among the patients.

### RESULTS

One hundred fourteen questionnaires containing histories of systemic autoimmune diseases of patients with WSS and their relatives were completed. Fifty-four (47%) of those patients had MFC/PIC, 21 (18%) had AZOOR, 16 (14%) had birdshot chorioretinopathy, 11 (10%) had multiple evanescent white dot syndrome, 5 (4%) had serpiginous choroiditis, 4 (4%) had APMPPPE, 3 (3%) had acute macular neuroretinopathy, and 1 (1%) had relentless plaid choriorioretinitis (Table 1).

The mean age of the 114 patients at the time of entry was 46 years (range, 18-84 years). The mean age of the patients in each subgroup was as follows: MFC/PIC, 44 years; AZOOR, 51 years; birdshot chorioretinopathy, 41 years; multiple evanescent white dot syndrome, 39 years; serpiginous choroiditis, 43 years; APMPPPE, 42 years; acute macular neuroretinopathy, 47 years; and relentless plaoid choriorioretinitis, 36 years. Eighty-two of the 114 patients (72%) were female.

The numbers of patients with WSS who had systemic autoimmune diseases were as follows: 8 with Hashimoto thyroiditis, 4 with psoriasis, 4 with alopecia areata, 3 with Graves disease, 3 with atopic dermatitis, 3 with RA, 2 with SLE, 2 with vitiligo, 1 with IBD, 1 with MS, and 1 with insulin-dependent diabetes mellitus (Table 2). Six patients had a history of 2 different systemic autoimmune diseases; these combinations included the following: Graves disease and Hashimoto thyroiditis, IBD and insulin-dependent diabetes mellitus, Hashimoto thyroiditis and atopic dermatitis, Hashimoto thyroiditis and vitiligo, Hashimoto thyroiditis and SLE, and atopic dermatitis and alopecia areata.

The overall prevalence of systemic autoimmunity among the patients was 23%. Although a higher prevalence of systemic autoimmunity has been reported in female patients, there was generally no difference in prevalence when comparing the overall autoimmunity among male and female patients with WSS (25% and 22%, re-

### Table 1. Total Number of Patients With Each White Spot Syndrome and Total Number of Systemic Autoimmune Diseases for Those Patients

<table>
<thead>
<tr>
<th>WSS</th>
<th>Patients With Systemic Autoimmunity for Given WSS, No. (%), n = 114</th>
<th>Patients With WSS, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFC/PIC</td>
<td>54 (47)</td>
<td>14/54 (26)</td>
</tr>
<tr>
<td>AZOOR</td>
<td>21 (18)</td>
<td>5/21 (24)</td>
</tr>
<tr>
<td>Birdshot chorioretinopathy</td>
<td>16 (14)</td>
<td>4/16 (25)</td>
</tr>
<tr>
<td>MEWDS</td>
<td>11 (10)</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Serpiginous choroiditis</td>
<td>5 (4)</td>
<td>1/5 (20)</td>
</tr>
<tr>
<td>APMPPPE</td>
<td>4 (4)</td>
<td>0/4</td>
</tr>
<tr>
<td>AMN</td>
<td>3 (3)</td>
<td>0/3</td>
</tr>
<tr>
<td>RPC</td>
<td>1 (1)</td>
<td>1/1 (100)</td>
</tr>
</tbody>
</table>

Abbreviations: AMN, acute macular neuroretinopathy; APMPPPE, acute posterior multifocal plaidoid pigment epitheliopathy; AZOOR, acute zonal occult outer retinopathy; MEWDS, multiple evanescent white dot syndrome; MFC/PIC, multifocal choroiditis/punctate inner choroidopathy; RPC, relentless plaid choriorioretinitis; WSS, white spot syndrome.
The prevalence of systemic autoimmune disorders among the different age groups of patients was as follows: 20% among those aged 18 to 25 years, 15% among those aged 26 to 35 years, 27% among those aged 36 to 45 years, 31% among those aged 46 to 55 years, 20% among those aged 56 to 65 years, 29% among those aged 66 to 75 years, and 0% among those older than 75 years.

The overall prevalence of systemic autoimmunity among those with each of the more frequent WSS was as follows: 26% of patients with MFC/PIC, 25% of patients with birdshot chorioretinopathy, and 24% of patients with AZOOR (Table 1).

A total of 1098 family members were included in this study. The numbers of relatives with systemic autoimmune diseases were as follows: 24 with RA, 19 with IBD, 18 with Hashimoto thyroiditis, 14 with psoriasis, 8 with atopic dermatitis, 7 with alopecia areata, 6 with insulin-dependent diabetes mellitus, 5 with Graves disease, 5 with SLE, 5 with MS, and 1 with JRA (Table 3).

Six relatives had a history of 2 different autoimmune diseases, with the following combinations: IBD and MS, RA and IBD, IBD and alopecia areata, Graves disease and alopecia areata, psoriasis and IBD, and RA and SLE. The overall prevalence of systemic autoimmunity among family members was 10%.

Among all of the living parents of patients with WSS (69 mothers and 48 fathers), the overall prevalence of systemic autoimmunity was 21%. However, this was significantly higher among mothers as compared with fathers (26% vs 12%, respectively). The prevalence of autoimmunity was 11% among siblings and 15% among grandparents (Table 4 and Table 5). In both of these categories, more females than males were affected. Table 5 provides the prevalence of autoimmunity for other relatives as well.

There was a statistically significant difference in systemic autoimmunity among female and male relatives (13% and 6%, respectively; \( P = .001 \)). Similarly, first-degree relatives had a significantly higher prevalence (13%) than second-degree relatives (8%) (\( P = .007 \)). However, there was no statistical significance in the prevalence of systemic autoimmunity between maternal and paternal relatives (8% and 7%, respectively) (Table 6).

Patients with systemic autoimmune diseases showed a greater prevalence of family members with a history of autoimmunity (65%) compared with family members of patients without systemic autoimmune diseases (41%) (\( P = .03 \)).

The combined prevalence of systemic autoimmunity for the families of those patients with the 3 most common diagnoses, which were MFC/PIC, AZOOR, and birdshot chorioretinopathy, was also analyzed. The prevalence of systemic autoimmunity among parents in this category was 24%, including 30% of mothers and 16% of fathers; the prevalence in this category was 13% among...
siblings, 21% among grandparents, 14% among first-degree relatives, and 9% among second-degree relatives (Tables 4-6).

The results of this study support our hypothesis that there is an increased prevalence of systemic autoimmunity among patients with WSS as well as their relatives. Patients with WSS had an overall systemic autoimmunity prevalence of 23%, while their family members had an overall autoimmunity prevalence of 10%. Such values are significantly higher than the 4% to 5% overall prevalence of systemic autoimmunity in the United States. The overall prevalence of autoimmunity among the first-degree relatives of our patients was higher than that among the second-degree relatives (13% vs 8%, respectively). This is logical as first-degree relatives have a 50% greater chance of sharing genes with the patients than do second-degree relatives. The families of patients with WSS with systemic autoimmune diseases also had a higher likelihood of having systemic autoimmune diseases (65%) compared with families of patients without systemic autoimmune diseases (41%).

The difference in prevalence of systemic autoimmunity between maternal and paternal relatives was not statistically significant. Systemic autoimmunity was, however, more prevalent in female relatives as compared with male relatives (13% vs 6%, respectively). Female first- or second-degree relatives also showed higher prevalence of systemic autoimmunity compared with male relatives. Siblings showed an overall systemic autoimmunity prevalence of 11%. As the siblings share 50% of the genetic makeup of the patients, we might have expected an even higher prevalence of systemic autoimmunity. As previously mentioned, second-degree relatives had less systemic autoimmunity than did first-degree relatives (8% vs 13%, respectively). However, 8% possibly suggests a higher rate of autoimmunity than the public at large even in these more distant relatives. Of the second-degree relatives, aunts showed the highest rate of autoimmunity.

When examining prevalence of systemic autoimmunity for individual WSS, we found a high prevalence among the patients with MFC/PIC, AZOOR, and birdshot chorioretinopathy (26%, 24%, and 25%, respectively). These rates of autoimmunity are significantly higher than the national average of 4% to 5%.

Table 5. Prevalence of Systemic Autoimmunity Among Patients’ Individual Family Members

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Relatives, No. With Systemic Autoimmunity/Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mothers/Fathers/Sisters/Brothers/Grandmothers/Grandfathers/Aunts/Uncles</td>
</tr>
<tr>
<td>All WSS</td>
<td>18/69 (26)/6/48 (12)/13/91 (14)/9/101 (9)/7/34 (21)/1/18 (6)/12/129 (9)/6/119 (5)</td>
</tr>
<tr>
<td>MFC/PIC, AZOOR, or birdshot chorioretinopathy only (n = 854)</td>
<td>16/53 (30)/6/36 (18)/12/69 (17)/8/84 (10)/7/27 (26)/1/12 (6)/10/97 (10)/5/92 (5)</td>
</tr>
<tr>
<td>MFC/PIC (n = 557)</td>
<td>9/33 (27)/5/29 (17)/7/38 (18)/6/45 (13)/6/22 (27)/1/9 (11)/8/73 (11)/1/61 (2)</td>
</tr>
<tr>
<td>AZOOR (n = 163)</td>
<td>4/11 (36)/1/4 (25)/1/17 (6)/2/25 (8)/0/1/NA/1/14 (7)/2/29 (10)</td>
</tr>
<tr>
<td>Birdshot chorioretinopathy (n = 134)</td>
<td>3/9 (33)/0/5/4/14 (29)/0/14/1/4 (25)/0/9/1/10 (10)/2/11 (18)</td>
</tr>
<tr>
<td>MEWDS (n = 128)</td>
<td>1/8 (12)/0/5/1/5 (7)/1/5 (20)/0/4/0/6/2/22 (9)/1/13 (8)</td>
</tr>
<tr>
<td>APMPPPE (n = 48)</td>
<td>0/3/0/3/0/2/0/6/0/2/0/1/0/4/0/7</td>
</tr>
<tr>
<td>Serpiginous choroiditis (n = 37)</td>
<td>1/3 (33)/0/1/0/4/0/3/0/1/0/1/0/4/0/4</td>
</tr>
</tbody>
</table>

Abbreviations: APMPPPE, acute posterior multifocal placoid pigment epitheliopathy; AZOOR, acute zonal occult outer retinopathy; MEWDS, multiple evanescent white dot syndrome; MFC/PIC, multifocal choroiditis/punctate inner choroidopathy; NA, not applicable; WSS, white spot syndromes.

Table 6. Prevalence of Systemic Autoimmunity Among Stated Categories

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>First-Degree Relatives</th>
<th>Second-Degree Relatives</th>
<th>Female Relatives</th>
<th>Male Relatives</th>
<th>Maternal Relatives</th>
<th>Paternal Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>All WSS</td>
<td>57/450 (13)/49/646 (8)</td>
<td>73/578 (13)/65/450 (14)</td>
<td>33/519 (6)</td>
<td>31/380 (8)</td>
<td>18/266 (7)</td>
<td></td>
</tr>
<tr>
<td>MFC/PIC, AZOOR, or birdshot chorioretinopathy only (n = 854)</td>
<td>51/361 (14)/43/493 (9)</td>
<td>62/490 (14)/29/404 (7)</td>
<td>27/292 (9)</td>
<td>16/201 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFC/PIC (n = 557)</td>
<td>30/211 (14)/30/346 (9)</td>
<td>42/299 (14)/18/288 (7)</td>
<td>16/192 (8)</td>
<td>14/154 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZOOR (n = 163)</td>
<td>12/85 (14)/8/78 (10)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birdshot chorioretinopathy (n = 134)</td>
<td>9/65 (14)/5/69 (7)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APMPPPE (n = 48)</td>
<td>0/15</td>
<td>0/33</td>
<td>0/20</td>
<td>0/29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serpiginous choroiditis (n = 37)</td>
<td>1/20 (5)</td>
<td>0/17</td>
<td>1/18 (6)</td>
<td>0/19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APMPPPE, acute posterior multifocal placoid pigment epitheliopathy; AZOOR, acute zonal occult outer retinopathy; MEWDS, multiple evanescent white dot syndrome; MFC/PIC, multifocal choroiditis/punctate inner choroidopathy; NA, not applicable; WSS, white spot syndromes.
We performed a subset analysis for the combined families of patients with MFC/PIC, AZOOR, and birdshot chorioretinopathy. These 3 most common WSS also had the highest prevalence of systemic autoimmunity. For patients with MFC/PIC, AZOOR, or birdshot chorioretinopathy, the overall prevalence of systemic autoimmunity among each type of family member (eg, among all mothers with any of the 3 diseases) was significantly higher than the national prevalence of systemic autoimmunity. The highest prevalence of 30% was found among mothers in this subgroup. Fathers and siblings with any of the 3 syndromes showed prevalences of 16% and 13%, respectively. The rates of systemic autoimmunity among first- and second-degree relatives for these diseases were 14% and 9%, respectively (Table 6).

When examining the prevalence of individual systemic autoimmune diseases in our patients with WSS, we found Hashimoto thyroiditis, psoriasis, and alopecia areata to be the most common (Table 2). Among the patients’ relatives, the most common systemic autoimmune diseases were RA, IBD, Hashimoto thyroiditis, and psoriasis. Interestingly, in a recent study of family members of patients with MS, the most common coexisting systemic autoimmune diseases were RA, IBD, Hashimoto thyroiditis, and psoriasis. This correlates with previous studies showing that individuals with one systemic autoimmune disease are more likely to have another.

Other studies have taken this idea of shared susceptibility to autoimmunity a step further and suggested an association between systemic autoimmune diseases and specific WSS. Gass et al found that 28% of patients with AZOOR had a concurrent systemic autoimmune disease, of which Hashimoto thyroiditis was the most common. They reported a positive autoimmune history in 6% of family members. A recent study of patients with PIC showed a prevalence of systemic autoimmunity in 26% of families.

Latkany et al reported MFC in patients with familial juvenile systemic granulomatosis. Vianna et al reported a case of MFC in a patient with Crohn disease. Similarly, Ugarte and Wearne described a patient who had both serpiginous chorioretinitis and Crohn disease. They hypothesized that activation of T lymphocytes in patients with Crohn disease may lead to infiltration of these cells in the choroid, choroid, and retinal pigment epithelium, triggering serpiginous chorioretinitis.

Bridges et al described a patient with JRA who developed APMPPPE. The syndrome of APMPPPE has also been associated with other systemic autoimmune diseases such as necrotizing vasculitis.

Wegener granulomatosis, cerebral vasculitis, polyarteritis nodosa, and ulcerative colitis. Some authors have hypothesized that a delayed hypersensitivity reaction may cause damage to the retinal pigment epithelium, thus triggering APMPPPE.

Although there have been associations made between specific autoimmune diseases and WSS, it was Jamjol and Becker who first hypothesized a genetic link between systemic autoimmune diseases and WSS. They suggested that non-disease-specific genes predispose patients to both systemic autoimmune diseases and WSS. Although genetic markers do exist for some WSS, no genetic link has yet been found between them and systemic autoimmune diseases. Some gene varieties lead to immune dysregulation. Environmental factors (eg, infections, immunizations, or stress) in such patients may predispose to systemic autoimmune diseases and/or WSS.

Using a similar concept of a familial predisposition toward autoimmunity, Prahalad et al found an increased prevalence of systemic autoimmunity in both first- and second-degree relatives of patients with JRA. They concluded that different autoimmune diseases may share common genes that predispose patients to autoimmunity.

Our study uses medical histories of autoimmunity obtained from patients and their family members, including both first- and second-degree relatives. We found a higher prevalence of systemic autoimmunity among female family members. This is not surprising as both systemic autoimmunity and WSS occur more frequently in women.

It may be helpful in the future for patients with WSS to be checked for concurrent systemic autoimmune diseases. The WSS have a variable time course; some are self-limited to a few weeks of activity, such as APMPPPE, and some are chronic with exacerbations, such as MFC. As many of the systemic autoimmune diseases are also chronic with exacerbations, we may be able to suggest specific systemic autoimmune workups in the future for these patients with WSS.

Limitations of this study include a lack of control participants and only a moderate number of patients. Without the advantage of control probands, we used epidemiology studies detailing rates of autoimmunity in the United States for comparison. In regard to the number of patients in this study, it is difficult to obtain large sample sizes given the rarity of WSS. We will be adding more patients over time. It is important to note that the small number of patients with the rarer WSS limits our ability to report meaningful associations of these diseases with systemic autoimmunity; for example, this study included only 1 patient with relentless placoid chorioretinitis.

Another potential weakness of the study is that we did not contact the family members directly to obtain data regarding systemic autoimmune diseases. Although interviews and review of medical records would have been ideal, we based our study on data collected from the patients detailing their relatives’ autoimmune histories. This allowed us to acquire the needed institutional review board approval for our study. As such, it is possible that our findings regarding family members are an underestimate of the actual prevalence of autoimmunity. In addition, our patients and some of their family members are still young, and further systemic autoimmune diseases may manifest as these individuals age.

In conclusion, we report an increased prevalence of systemic autoimmunity among patients with WSS as well as their family members. This association was strongest among first-degree relatives. The prevalence of systemic autoimmunity was found to be greatest in female members of the families. In addition, the patients who themselves had systemic autoimmune diseases showed a greater prevalence of systemic autoimmunity among their own families as compared with the families of patients without systemic autoimmune diseases.
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Correspondence: Lee M. Jampol, MD, Department of Ophthalmology, Northwestern University, 645 N Michigan Ave, Ste 440, Chicago, IL 60611 (l-jampol@northwestern.edu).

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REFERENCES


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