Global Surface Ultraviolet Radiation Intensity May Modulate the Clinical and Immunologic Expression of Autoimmune Muscle Disease

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Objective. To determine if geoclimatic factors may influence the nature and frequency of dermatomyositis (DM), polymyositis, and associated autoantibodies around the world.

Methods. We assessed, in the first global evaluation of these conditions, the relationship between 13 geoclimatic variables that may modulate disease and the relative proportion of DM and its associated autoantibody anti–Mi-2, directed against an SNF2-superfamily helicase associated with the nucleosome remodeling and histone acetylation and deacetylation complex, in a global myositis population. Altogether, 919 consecutive patients from populations at 15 locations were studied.

Results. Univariate and multivariate analyses demonstrated that of the variables evaluated, surface ultraviolet (UV) radiation intensity (irradiance) most strongly contributed to the relative proportion of DM and was strongly related to the proportion of anti–Mi-2 autoantibodies (weighted \( r = 0.939, P < 4 \times 10^{-7} \) and weighted \( r = 0.69, P = 0.02 \), respectively). Published ethnogeographic immunogenetic allele frequencies imply that the striking differences in the proportion of DM- and DM-specific autoantibodies observed around the world are not the result of inherent global variations in known genetic risk factors.

Conclusion. These data suggest that UV radiation exposure may modulate the clinical and immunologic expression of an autoimmune disease in different populations around the world.

Accumulating evidence suggests that autoimmune diseases result from environmental exposures in genetically predisposed individuals (1). Environmental triggers for most autoimmune disorders are poorly understood, although selected infections, drugs, foods, and occupational exposures have been associated with the onset of certain immune-mediated syndromes (2,3). An environmental exposure of increasing interest in the pathogenesis of immune-mediated disorders is ultraviolet (UV) radiation. UV radiation, beyond inducing accelerated skin aging and skin cancer, has a number of immunomodulatory effects (4). It triggers cytokine production (5), regulates surface expression of adhesion molecules (6), affects cellular mitosis (7), and induces apoptotic cell death (8). UV radiation may also alter the expression of, cellular location of, or immune responses to autoantigens (9,10). Although little is known about the role of UV radiation in the development of autoimmune diseases, it has been anecdotally associated with the development of some disorders (3,11) and is known to increase the clinical expression of conditions characterized by photosensitive rashes, such as lupus and dermatomyositis (DM) (12). The mechanisms by which it has these effects, however, remain poorly understood.

The idiopathic inflammatory myopathies (IIMs) are a group of rare autoimmune muscle diseases characterized by chronic inflammation of muscle that can be divided into 2 major clinicopathologic groups, DM and polymyositis (PM). DM is distinguished clinically from

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PM by the presence of pathognomonic photosensitive rashes (11). These 2 forms of IIM, which share common genetic risk factors (13,14), may differ in pathogenesis. Muscle and skin biopsies from DM patients demonstrate vasculopathy with perivascular inflammation of B cells and CD4+ T cells and possible complement-mediated vascular endothelial cell damage resulting in focal capillary dropout, whereas PM is characterized pathologically by anamnestically activated CD8+ cytotoxic T cells that likely invade and destroy myocytes via perforin-mediated mechanisms (15,16).

Groups of myositis patients can also be defined serologically by the presence or absence of a number of diagnostic autoantibodies, known as the myositis-specific autoantibodies, which are directed against conserved, conformational epitopes on cytoplasmic and nuclear components (17). Myositis-specific autoantibodies include autoantibodies that bind to and inhibit the function of aminoacyl–transfer RNA synthetases (anti-synthetases), those directed against proteins of the signal recognition particle (anti-SRP), and those that react with a 240-kd SNF2-superfamily helicase associated with the nucleosome remodeling and deacetylase complex, known as anti–Mi-2 autoantibodies (18). Myositis-specific autoantibodies define groups of patients that share similar clinical features, responses to therapy, immunogenetics, and prognoses (13). Antisynthetase autoantibodies are found in both DM and PM, while anti-SRP autoantibodies are restricted to PM, and anti–Mi-2 autoantibodies are diagnostic for DM.

As part of a larger global study of myositis, an international group of specialists, the International Myositis Collaborative Study Group, was established to utilize the natural genetic and environmental variations around the world to investigate differences in the clinical expression of, and risk factors for, these increasingly recognized autoimmune muscle diseases. The initial focus of this group has been to analyze the relationships among a number of geoclimatic factors, the relative proportion of DM and PM at different locales, and the clinical and immunologic phenotypes in each population. Because photosensitive rashes characterize DM and distinguish it from the related disease PM, we have focused our primary efforts on assessing whether such differences may be the result of UV radiation or other climatic exposures that may alter disease expression. This first worldwide analysis of myositis has revealed remarkable geographic variations in the clinical and immunologic expression of disease, which are strongly predicted by the level of UV surface irradiation intensity (irradiance) at different global locations.

**PATIENTS AND METHODS**

**Clinical and serologic evaluations.** As part of the larger framework of the role of geoclimatic variables in the development of myositis, the primary hypothesis we assessed in this study was whether UV irradiance has a significant relationship to the relative proportion of DM compared with PM at referral sites around the world. Therefore, we investigated the proportion of DM and PM patients among the myositis populations at referral centers in 15 cities on 4 continents. International Myositis Collaborative Study Group members at these referral centers who participated in the present study, and the city locations of the centers, are listed in Appendix A. A total of 919 consecutive patients meeting criteria for probable or definite PM or DM (19), with disease onset between 1967 and 1997, were evaluated in the period 1985–1999. DM was distinguished from PM by the presence of Gottron’s papules, Gottron’s sign, or heliotrope rashes (11). Serum samples were collected for autoantibody analyses with ethics committee approval and patient informed consent and were frozen at a temperature of −20°C or lower until use. Sera were not available from all subjects, however, because some centers did not obtain ethics committee permission for such collection or certain subjects did not agree to provide serum for research purposes. Standard immunodiffusion, indirect immunofluorescence, and protein and RNA immunoprecipitation techniques were applied as described previously (20), at a central facility (Oklahoma Medical Research Foundation).

On average, 87% of the patients (range 71%–100%) lived within 100 km of the center where they were evaluated. This distance results in negligible differences in the geoclimatic variables studied (21–23). Based on a query of the investigators and assessment of the catchment areas, there were no known systematic biases in the geographic distribution of or proportion of DM and PM referrals to the centers. However, different numbers of juvenile-onset IIM cases (age at onset <18 years) were seen in different locales (1 case of juvenile DM in Stockholm, 1 in Montreal, 1 in Seoul, 4 in New Delhi, 7 in Mexico City, 24 in Guadalajara, and 7 in Guatemala City; 1 case of juvenile PM in Guatemala City and 1 in Guadalajara), and due to the known propensity for childhood-onset IIM to be DM (24), the data were also analyzed excluding the childhood-onset cases, with no significant change in our findings (see Results). A total of 38 inclusion body myositis (IBM) cases as previously defined (13) (seen in Glasgow [n = 2], Nijmegen [n = 6], Aachen [n = 1], Bethesda [n = 26], Montreal [n = 1], Barcelona [n = 1], and New Delhi [n = 1]) were excluded from the analyses because the primary hypothesis did not include IBM, although including them did not alter the primary findings either (as described in Results). For certain analyses, we assessed the relative contributions of UV intensity and the other geoclimatic variables to the proportion of DM patients at each location, in a combined larger sampling of global sites including data from a recent study of myositis at 9 locations in Europe (25).

**Geographic and climatic data.** A total of 13 geoclimatic variables that describe aspects of the environment that may influence the health of populations, the potential for a variety of diseases, or the likelihood of the spread of disease (surface UV radiation intensity [irradiance], duration of sunshine hours per day, temperature, winter temperature, summer temperature, total annual precipitation, elevation, atmospheric
pressure, vapor pressure, relative humidity, wind speed, longitude, and absolute latitude) were evaluated in relation to the clinical and serologic characteristics of the IIM population at each study site. The list is not inclusive of all geoclimatic factors, but does represent a set of environmental parameters for which accurate data are available on a global basis over the period of interest (21–23).

The UV data were estimated using satellite observations of total column ozone and shortwave reflectivity. A radiative transfer program that takes into account sun angle, altitude, ozone, clouds, and spherical correction was used to estimate surface UV intensity; this approach has been verified at a number of different locations around the world (26). The Total Ozone Mapping Spectrometer, operating on the Nimbus-7 satellite, collected the ozone and reflectivity data; the data collected each year for the entire decade between 1979 and 1989 were used to estimate UV irradiance because they were the most comprehensive and reliable for the locations under investigation. The cloud effect was approximated by the use of reflectivity measurements as proposed (26).

Within the UV region, different wavelengths have varying effects on biologic organisms. To account for this, the UV spectra have been weighted by an artificial action spectrum developed by McKinlay and Diffey (27), which is the standard erythemal action spectrum adopted by the Commission Internationale de l’Eclairage (CIE) to represent the biologic response over the UVB and UVA regions of the spectrum (28). All current evidence suggests that such a weighting can approximate the biologic damage of UV photons more accurately than merely weighting photons by their physical energy (28), and thus this CIE weighting method was used to estimate the UV intensity at each global site. Briefly, the different wavelengths of UV radiation were estimated for each location at 1 nm resolution from 280 nm to 400 nm and then weighted using the CIE weighting function as described (28). For nearly all of the biologic functions that have been assessed, UVB is more damaging than UVA, and the CIE offers the best approximation of this wavelength dependence and is the preferred approach to use when the exact UV spectral weighting function for a given biologic effect is not known.

The other environmental data examined in this study were obtained from standard sources (21–23). In most cases, records were available for the city in question. For 3 cities, Bethesda, Aachen, and Nijmegen, records from the nearest city with available data were used. For all environmental parameters, averages were determined from information collected over at least a 10-year period to estimate climatologic data; current studies suggest minimal variations among the different decades of interest in this investigation (21,22,26,29,30).

Statistical analyses. Statistical analyses of the relationships among the clinical, serologic, and geoclimatic data were performed using Statview (SAS Institute, Cary, NC) and Stata (release 7, Stata Corp., College Station, TX). StatXact 4 (Cytel, Cambridge, MA) was used to compute Monte Carlo approximations of the exact P values for certain contingency tables. The proportions of patients with DM and the proportions with various autoantibodies at each geographic site were correlated with the environmental parameters using weighted correlations, with the weighting proportional to the number of patients in each city to take into account the variation in these numbers. A program was written, using RealBasic (Real Software, Austin, TX), to calculate Monte Carlo–based permutation P values associated with weighted correlations. For each P value, 3 million samples were generated. To further assess the relative usefulness of various environmental parameters in predicting the proportion of patients with DM, forward stepwise, multivariate logistic regression analyses were computed. All P values were 2-sided.

RESULTS

Geographic variation in the clinical and immunologic expression of myositis. Evaluation of the clinical and serologic phenotypes of PM and DM in the 919 patients assessed at the participating centers suggested that there were significant differences in the proportions of DM patients and patients with anti–Mi-2 autoantibodies among the 15 cities (Table 1). The proportion of DM patients seen in Guatemala City (83%), for example, was >3-fold that in Glasgow (27%). The Monte Carlo exact P value for the equality of the proportions was very significant (\(<5 \times 10^{-5}\)). Although DM and PM patients were our defined study group, due to the different proportions of IBM and juvenile-onset IIM cases seen at the centers we performed additional analyses to assess whether these cases might have altered the results of our study. Including the 38 IBM cases in the analyses or excluding the 47 juvenile-onset IIM cases resulted in the same primary finding of important differences in the proportion of patients with DM among myositis patients seen at the centers in the 15 cities (\(P < 5 \times 10^{-5}\)). Similarly, the frequencies of autoantibodies varied greatly at these locations, with anti–Mi-2 autoantibodies found in 60% of the patients in Guatemala City, and in only 3% of the Montreal patients (Monte Carlo exact P value for the equality of the proportions \(<5 \times 10^{-5}\)). As expected, anti–Mi-2 autoantibodies were detected only in DM patients in this study.

Although all investigators were queried regarding possible referral biases relating to the proportion of DM versus PM cases, asymmetric catchment areas, or other explanations that might have accounted for the specific myositis phenotypes among patients presenting to each clinic, we were unable to identify any systematic biases that could account for these data.

Geographic and environmental associations with myositis phenotypes. We investigated for correlations between the distribution of clinical and immunologic phenotypes and the 13 geoclimatic variables, which were hypothesized to influence the development of different forms of myositis at each location. These weighted correlation analyses revealed strong positive correlations between the proportion of DM in the total myositis population at each center and a number of parameters,
<table>
<thead>
<tr>
<th>City</th>
<th>No. of patients studied (DM + PM)</th>
<th>No. with DM</th>
<th>No. with PM</th>
<th>DM/PM, %</th>
<th>No. with autoantibodies tested</th>
<th>No. with anti-Mi-2+</th>
<th>No. with anti-synthetase+</th>
<th>No. with anti-SRP+</th>
<th>No. with no myositis-specific autoantibodies</th>
<th>Mi-2+/autoantibodies tested, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow, Scotland</td>
<td>15</td>
<td>4</td>
<td>11</td>
<td>26.7</td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>12</td>
<td>6.7</td>
</tr>
<tr>
<td>Stockholm, Sweden</td>
<td>38</td>
<td>12</td>
<td>26</td>
<td>31.6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Warsaw, Poland</td>
<td>27</td>
<td>9</td>
<td>18</td>
<td>33.3</td>
<td>27</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>25</td>
<td>3.7</td>
</tr>
<tr>
<td>Nijmegen, The Netherlands</td>
<td>97</td>
<td>37</td>
<td>60</td>
<td>38.1</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Aachen, Germany</td>
<td>147</td>
<td>57</td>
<td>90</td>
<td>38.8</td>
<td>147</td>
<td>20</td>
<td>59</td>
<td>0</td>
<td>68</td>
<td>13.6</td>
</tr>
<tr>
<td>Tokyo, Japan</td>
<td>50</td>
<td>20</td>
<td>30</td>
<td>40.0</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bethesda, Maryland, US</td>
<td>186</td>
<td>84</td>
<td>102</td>
<td>45.2</td>
<td>186</td>
<td>10</td>
<td>48</td>
<td>7</td>
<td>121</td>
<td>5.4</td>
</tr>
<tr>
<td>Montreal, Quebec, Canada</td>
<td>31</td>
<td>15</td>
<td>16</td>
<td>48.4</td>
<td>31</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>28</td>
<td>3.2</td>
</tr>
<tr>
<td>Seoul, Korea</td>
<td>51</td>
<td>26</td>
<td>25</td>
<td>51.0</td>
<td>51</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>36</td>
<td>7.8</td>
</tr>
<tr>
<td>Santiago, Chile</td>
<td>13</td>
<td>8</td>
<td>5</td>
<td>61.5</td>
<td>13</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>7</td>
<td>23.1</td>
</tr>
<tr>
<td>Barcelona, Spain</td>
<td>64</td>
<td>40</td>
<td>24</td>
<td>62.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>New Delhi, India</td>
<td>60</td>
<td>44</td>
<td>16</td>
<td>73.3</td>
<td>47</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>32</td>
<td>19.1</td>
</tr>
<tr>
<td>Mexico City, Mexico</td>
<td>52</td>
<td>41</td>
<td>11</td>
<td>78.8</td>
<td>36</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>18</td>
<td>36.1</td>
</tr>
<tr>
<td>Guadalajara, Mexico</td>
<td>58</td>
<td>46</td>
<td>12</td>
<td>79.3</td>
<td>38</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>33</td>
<td>13.2</td>
</tr>
<tr>
<td>Guatemala City, Guatemala</td>
<td>30</td>
<td>25</td>
<td>5</td>
<td>83.3</td>
<td>30</td>
<td>18</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>60.0</td>
</tr>
</tbody>
</table>

*DM = dermatomyositis; PM = polymyositis; anti-SRP = anti-signal recognition particle; NA = not available.
particularly UV surface irradiation intensity (irradiance), temperature, and elevation (Table 2). Conversely, latitude, atmospheric pressure, and relative humidity had strong negative correlations with the proportion of subjects with DM at each location.

One difficulty in assessing the relative importance of many geoclimatic parameters in relation to health risks is that a number of these parameters are strongly dependent upon and related to each other. For example, there are strong correlations (in the range of 0.8–0.9) of temperature, pressure, elevation, relative humidity, and UV radiation with latitude. Therefore, multivariate logistic regression analyses were performed to dissect which geoclimatic parameters were most important in predicting DM or PM, once other parameters were already in the model. With the multivariate logistic analyses, the relative ranking of the 5 parameters most predictive of DM was the same as that with the weighted correlations: UV intensity was the strongest predictor, followed by latitude, with other strong predictors being temperature, pressure, and elevation. If we began with the UV parameter in the model, then none of the other 12 environmental parameters added significantly to the ability to predict the proportion of DM patients at each location (P > 0.20 in likelihood ratio tests for each of the added parameters). On the other hand, if we began with latitude, the second strongest univariate predictor in the model, adding UV did add a significant predictive ability (P = 0.005 in the likelihood ratio test).

These multivariate results, coupled with the lack of biologic plausibility for an effect of the non-UV variables, provide strong evidence that of the geoclimatic variables studied, differences in UV surface radiation intensity are primarily responsible for the differences in the proportion of patients with DM at the various sites, and that the other environmental variables derive their association with the DM proportions largely from their correlation with UV intensity. Including the 38 IBM cases or excluding the 47 juvenile-onset IIM cases in the analyses resulted in the same primary findings that there is a strong correlation between the proportion of DM cases and UV irradiance (weighted r = 0.929, P = 7 × 10^{-7} and weighted r = 0.898, P = 4 × 10^{-6}, respectively) and that UV irradiance is primarily responsible for the different proportions of patients with DM at the different sites.

The possible effect of these environmental factors on myositis-specific immune responses in the populations from which serum samples were obtained was also assessed. The primary autoantibodies evaluated were antisynthetase and anti-Mi-2 autoantibodies, since the small number of subjects with anti-SRP autoantibodies (Table 1) prohibited appropriate analysis. There were no significant correlations between the proportion of IIM patients without any myositis-specific autoantibodies and any of the environmental factors studied (smallest P value was 0.11). For the proportion of patients with antisynthetase autoantibodies, the weighted correlations with latitude and UV intensity were marginally significant (P = 0.036 and P = 0.032, respectively), but the tests for correlations with all other environmental factors studied yielded P values >0.10. In contrast, the proportion of subjects at each center who had the DM-associated anti-Mi-2 autoantibody correlated with atmospheric pressure, winter temperature, elevation, UV intensity, and latitude (P = 0.0080, P = 0.0084, P = 0.015, P = 0.02, and P = 0.035, respectively) (Table 2). The limited autoantibody and environmental

Table 2. Correlations between the geoclimatic variables studied and the proportion of subjects with dermatomyositis (DM) and with anti–Mi-2 autoantibodies at each study site

<table>
<thead>
<tr>
<th>Geoclimatic variable</th>
<th>Subjects with DM</th>
<th>Subjects with anti–Mi-2 autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted correlation coefficient</td>
<td>P</td>
<td>Weighted correlation coefficient</td>
</tr>
<tr>
<td>Surface ultraviolet radiation intensity</td>
<td>0.939</td>
<td>&lt;0.0000004</td>
</tr>
<tr>
<td>(irradiance), joules/meter²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latitude, degrees</td>
<td>−0.902</td>
<td>0.0000003</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>0.830</td>
<td>0.0001</td>
</tr>
<tr>
<td>Winter temperature, °C</td>
<td>0.817</td>
<td>0.0002</td>
</tr>
<tr>
<td>Atmospheric pressure, millibars</td>
<td>−0.771</td>
<td>0.0007</td>
</tr>
<tr>
<td>Elevation, meters</td>
<td>0.756</td>
<td>0.0010</td>
</tr>
<tr>
<td>Sunshine, hours/day</td>
<td>0.683</td>
<td>0.021</td>
</tr>
<tr>
<td>Relative humidity, %</td>
<td>−0.737</td>
<td>0.023</td>
</tr>
<tr>
<td>Summer temperature, °C</td>
<td>0.340</td>
<td>0.21</td>
</tr>
<tr>
<td>Vapor pressure, hectopascals</td>
<td>0.356</td>
<td>0.26</td>
</tr>
<tr>
<td>Longitude, degrees</td>
<td>−0.309</td>
<td>0.26</td>
</tr>
<tr>
<td>Wind speed, meters/second</td>
<td>−0.069</td>
<td>0.85</td>
</tr>
<tr>
<td>Annual precipitation, millimeters</td>
<td>−0.032</td>
<td>0.91</td>
</tr>
</tbody>
</table>
data at many sites precluded the application of appropriate multivariate logistic likelihood regression model analyses. Among the climatic variables, however, UV intensity was the only one with a reasonable biologic plausibility for an association with the DM-associated anti–Mi-2 autoantibodies.

Of interest, there was no evidence for either combinatorial effects of the geoclimatic data tested or nonlinear association effects (data not shown). There was also little evidence to support the notion of a threshold level above which UV intensity might be particularly damaging; rather, the data suggested that increases in UV radiation consistently increase the odds of a higher proportion of DM- and anti–Mi-2–positive patients, without evidence of clear upper or lower bounds (Figure 1).

Because a recent study identified a correlation between latitude and the proportion of patients with DM among myositis patients at 9 locations in Europe (25), we analyzed our data together with data from that study, to assess the relative contributions of UV intensity and the other geoclimatic variables to the proportion of DM patients at each location in this combined larger sampling of global sites. Because that study and the present study had 2 sites in common (Nijmegen and Stockholm), only the data from the study with the larger number of patients from each location were used. Again, UV surface radiation intensity was found to have the strongest univariate association, among all the geoclimatic variables assessed, with the proportion of DM patients at each center (weighted correlation coefficient 0.856, \( P \approx 0.04 \)). In this combined population, the multivariate logistic analyses resulted in the same finding as that obtained with the weighted correlations: UV intensity was the strongest predictor of the proportion of DM patients at each site, and with UV intensity in the model, only 1 of the remaining geoclimatic variables, precipitation, was even marginally statistically significant (\( P = 0.04 \)). In summary, this combined analysis of data from 1,152 DM and PM patients at 22 global locations also suggests that, of the geoclimatic variables studied, UV surface radiation intensity is primarily responsible for the different proportions of patients with DM at the different sites and that the other environmental variables derive their association with the DM proportions largely from their correlation with UV intensity.

Analyses of possible global gradients in genetic risk factors for myositis autoantibodies. Certain polymorphic immune response genes, known as human leukocyte antigens (HLA) and Gm/Km markers on immunoglobulins, have been associated with myositis and some myositis-specific autoantibody groups (13,14,17,31), and there is increasing evidence that such genetic risk factors may differ in certain ethnographic populations (31). The strongest known genetic risk factors for both DM and PM in Caucasians are the HLA–DRB1*0301 and HLA–DQA1*0501 alleles, which are in linkage disequilibrium (13,14), while the strongest known risk factors for DM and PM in Mesoamericans are Gm 1, Gm 17, Gm 21, and Km 3 (31). Since genetic risk factors are the same for both DM and PM in all populations that have been studied, inherent differences in the frequencies of these alleles in different ethnic groups cannot explain the wide variations in the proportion of DM around the world seen in our study.

Figure 1. Correlations between the weighted surface ultraviolet (UV) intensity (irradiance) at each of the global locations and the proportion of patients with dermatomyositis (DM) among all patients with DM or polymyositis (PM) (weighted \( r = 0.939, P < 4 \times 10^{-5} \)) and the proportion of patients with anti–Mi-2 autoantibodies among all patients tested for myositis-specific antibodies (MSA) (weighted \( r = 0.69, P = 0.02 \)) at each center. The size of the circle representing each site is proportional to the number of patients evaluated at that location. Autoantibodies were not assessed at some locations (see Table 1).
Because myositis-specific autoantibodies may be associated with different DRB1 and DQA1 alleles (17,31), however, it is possible that the observed serologic variations might be due to differences in the frequency of associated genetic risk factors in different ethnogeographic populations. In an attempt to address this possibility, we analyzed the frequency of the major genetic risk factors for antisynthetase autoantibodies (HLA–DRB1*0301 and the linked DQA1*0501) and those for anti–Mi-2 autoantibodies (HLA–DRB1*07 and the linked DQA1*0201 in Caucasians, and DRB1*04 and the linked DQA1*03 in Mesoamericans) in the ethnogeographic groups studied. Based on analyses using published HLA allele distributions in ethnic populations from the 15 global locations assessed (31–33), however, there was no evidence of any significant correlation between the proportion of these genetic risk factors in the populations and the observed frequency of the myositis autoantibodies (P > 0.4 for all). Thus, the striking differences around the world in frequencies of DM and the DM-specific autoantibodies do not appear to be the result of inherent variations in the known genetic risk factors among ethnogeographic populations at different locations.

DISCUSSION

In this first evaluation of the phenotypes of myositis in patients around the world, dramatic geographic differences in clinical and serologic expression were noted and were found to strongly correlate with the intensity of surface UV irradiation (irradiance) at each global location. Such a correlation is biologically plausible given the known immunomodulatory effects of UV radiation and evidence of its possible association with some autoimmune diseases. While explanations for the strong associations observed in the present study require further investigation, the epidemiologic evidence clearly demonstrates that a high degree of the variability in the clinical and serologic data can be explained in terms of the variability in UV surface radiation intensity among the participating sites. These data are consistent with the results of a study of DM and PM in Europe, in which a latitudinal gradient in the relative proportion of DM was observed (25). When the data from both studies were combined in multivariate analyses, UV irradiance again showed the strongest correlation with the relative proportion of DM at each center, implying that UV intensity is primarily responsible for the different proportions of patients with DM and that the other environmental variables, including latitude, derive their association with the DM proportions largely from their correlation with UV intensity.

These findings raise the interesting question of whether UV radiation may induce DM in individuals who would otherwise be healthy or whether, rather, it shifts disease expression from PM to DM among subjects in whom some form of myositis is developing. Unfortunately, since we do not have information on the true incidence rates of either PM or DM in any of these populations, we are currently not able to determine which of these possibilities is more likely.

Although attempts were made to avoid possible confounding in all aspects of the study, there are limitations to the approaches used in this investigation. For example, an ideal study would have assessed the population-based proportion of DM and PM at each location to avoid the possibility that the groups of myositis patients seen at each center might not be representative of those from the entire myositis population; however, the rarity of the disease and the lack of coordinated health care systems in most countries make this approach infeasible. The use of data from referral centers that evaluate a large proportion of the myositis patients in a given catchment area is the only practical approach for such a study, and we are not aware of any systematic referral biases to these centers that could account for our findings. Another limitation of the study is that we did not capture all the locations in which the subjects lived prior to and after development of myositis, so relocations of subjects from areas with different levels of UV radiation may have altered the correlations observed.

It is also possible, despite the strong correlation of global UV irradiance with the clinical and immunologic expression of autoimmune muscle disease, that alternative explanations might be responsible for our findings. First, environmental exposures other than those we studied, possibly relating to socioeconomic status, such as industrial or agricultural pollutants or certain infections, may vary in similar geographic gradients as does UV radiation intensity. Although there are no published data to address this issue, some of these exposures might be important environmental risk factors for DM or PM and could be another explanation for our data. Second, a variety of factors, in addition to the local climate, can affect an individual’s personal UV exposure. These include differences in the use of photoprotective measures, such as clothing styles and sunscreens, as well as occupations, avocations, and travel. Although it seems unlikely that consistent global gradients in any of these factors that parallel UV exposure could explain our results, they were not assessed in this study and are
possible confounders. Finally, although we excluded inherent ethnogeographic variations in frequencies of known genetic risk factors for myositis and myositis-specific autoantibodies as an explanation for our findings, it is possible that as-yet-unidentified genetic risk factors—which also might vary in similar geographic gradients as UV radiation intensity does—could account for our findings. Future investigations should address the limitations in this study and these possible alternative explanations for the findings.

In summary, although we cannot exclude the role of these limitations and alternative possibilities in our results, the very strong correlations noted in this study of many centers in areas with a wide range of UV exposure, and the biologic relevance of UV radiation in the possible induction and exacerbation of DM and autoantibody formation (12,34), suggest it is unlikely that such limitations or alternative explanations alone could account for the present findings.

The mechanisms by which UV radiation may modulate the clinical and immunologic expression of an autoimmune disease remain unknown. Although UV radiation has important effects on the skin, it has been strongly associated with systemic immunomodulation as well, with evidence, in a number of systems, of both immunosuppression and promotion of autoimmunity (34–36).

Different wavelengths within the UV range (middle-wave UV [called UVB; 290–315 nm] and long-wave UV [called UVA; 316–400 nm]) result in different UV effects in different autoimmune diseases (37). UVA and UVB also differ in their effects on cytokine-induced migration of Langerhans cells and antigen-presenting dendritic cells (10). Irradiation with low dosages of UVB decreases antigen presentation and allografting by antigen-presenting cells, resulting in decreased T cell responses that are further modified by the induction of T cells with suppressor activity (38,39). UV-induced alterations of cellular and humoral immunity may modulate the outcomes of infections (40,41), which have been hypothesized to play a role in certain forms of myositis (11) and which differ in type and frequency among different global regions (42). Moreover, UV radiation induces apoptosis of keratinocytes, alters the localization, processing, and presentation of certain signaling molecules and autoantigens, and may result in selected immune targeting of these proteins or their proteolytic fragments (43,44). Furthermore, UV radiation is strongly absorbed by DNA, resulting in the formation of DNA photoproducts that have been associated with selected gene activation (45). Thus, UV radiation may promote autoimmune disease and immune responses to autoantigens by multiple independent mechanisms.

The strong associations of UV radiation with DM and with a disease-specific autoimmune response directed against an SNF2-family helicase have implications for prevention strategies as well as for new avenues of research into the pathogenesis and treatment of inflammatory muscle disease. Given our present findings as well as previously known information on the pathology of DM and the effects of UV radiation, we speculate that sunlight could play a role in the development of DM and anti–Mi-2 autoantibodies via mechanisms involving immune dysregulation and alterations in the expression, subcellular distribution, and/or metabolism of components of the nucleosome remodeling and histone acetylation and deacetylation complex in skin and muscle vascular endothelium. This hypothesis suggests a number of experimental approaches to understand these associations more fully.

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REFERENCES

11. Miller FW. Inflammatory myopathies: polymyositis, dermatomyo-
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APPENDIX A: INTERNATIONAL MYOSITIS COLLABORATIVE STUDY GROUP

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