Background: Dermoscopic classification of acquired melanocytic nevi (AMN) is based on the evaluation of 3 main criteria—global pattern, pigment distribution, and color.

Objective: To determine whether these features are different in AMN in white people with different skin types (STs) according to the Fitzpatrick classification.

Design: Digital dermoscopic images of AMN were evaluated, and the correlation of the 3 main dermoscopic criteria with patient ST was analyzed.

Setting: Consecutive patients were recruited from 7 pigmented lesion clinics between June 1, 2004, and June 30, 2005.

Patients: For each patient, the ST (I [always burns, never tans] to IV [rarely burns, tans with ease]) was scored, and 1 representative AMN (defined as the AMN showing a dermoscopic typology that is repeatedly seen in the same patient) was selected and photographed.

Main Outcome Measures: The distribution of the dermoscopic criteria of AMN in patients with different STs was calculated by univariate analysis. Differences in prevalence were tested using the χ² test. The correlation between dermoscopic criteria and ST, adjusted for age, sex, and enrolling center, was evaluated by calculating odds ratios and 95% confidence intervals by logistic regression analysis.

Results: Of 680 included patients, dermoscopic analysis revealed significant differences in the prevalent nevus pattern in the 4 ST groups. Light brown AMN with central hypopigmentation were associated with ST I, and ST IV was associated with the so-called black nevus (P<.001), typified by reticular pattern, central hyperpigmentation, and dark brown coloration. A significant association was also found between multifocal pattern and ST II and ST III.

Conclusions: The dermoscopic nevus type varies according to different ST in white people. This knowledge may have an effect on obtaining for biopsy lesions that exhibit unusual dermoscopic patterns when patient ST is considered.

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pose of the present study was to investigate in a white population whether the prevalent nevus type, as seen at dermoscopy in a given patient, is related to patient ST.

### METHODS

#### STUDY SUBJECTS AND DESIGN

Patients were recruited from 7 specialized pigmented skin lesion clinics in Argentina (Buenos Aires), Austria (Graz), Germany (Konstanz), Italy (Naples), New Zealand (Christchurch), Spain (Barcelona), and the United States (Miami, Fla) between June 1, 2004, and June 30, 2005. The rationale to include 7 centers worldwide was to reduce a possible selection bias from a prevalent ST in a single geographic area and to obtain a balanced representation of individuals from around the world.

Individuals of any age were eligible for inclusion if they had at least 1 AMN, defined as a melanocytic nevus with a macular component and a diameter greater than 2 mm. Individuals were excluded if they had a history of intentional or prolonged sun exposure in the 4 weeks before the examination or were excluded if they had a history of intentional or prolonged sun exposure in the 4 weeks before the examination or dermatitis, or if they were pregnant. All patients were white, and their recruitment centers were obtained.

Data including sex, age, total nevus count and location of nevi, and enrolling center were obtained. For each included nevus, patient demographic data including sex, age, total nevus count and location of nevi, and enrolling center were obtained. All digital images were examined by one of us (I.Z.) with and without the interaction term. ST categories I and II, and III and IV, were combined for the purpose of multivariate analysis, using category 1 as the reference category. When the expected frequency for a given dermoscopic criterion was lower than 5, ST categories I and II, and III and IV, were compared for the purpose of multivariate analysis, using categories I and II as the reference group. Because many comparisons were made, with 33 ORs calculated, we used the Bonferroni correction considering significant ORs with a p-value of .05/15 = .003. The saturated model with age, sex, and enrolling center was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the ST categories II through IV, with ST I as the reference category. When the expected frequency for a given dermoscopic criterion was lower than 5, ST categories I and II, and III and IV, were combined for the purpose of multivariate analysis, using categories I and II as the reference group. Because many comparisons were made, with 33 ORs calculated, we used the Bonferroni correction considering significant ORs with a p-value of .05/15 = .003. The saturated model with age, sex, and enrolling center was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the ST categories II through IV, with ST I as the reference category. When the expected frequency for a given dermoscopic criterion was lower than 5, ST categories I and II, and III and IV, were combined for the purpose of multivariate analysis, using categories I and II as the reference group. Because many comparisons were made, with 33 ORs calculated, we used the Bonferroni correction considering significant ORs with a p-value of .05/15 = .003. The saturated model with age, sex, and enrolling center was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the ST categories II through IV, with ST I as the reference category. When the expected frequency for a given dermoscopic criterion was lower than 5, ST categories I and II, and III and IV, were combined for the purpose of multivariate analysis, using categories I and II as the reference group. Because many comparisons were made, with 33 ORs calculated, we used the Bonferroni correction considering significant ORs with a p-value of .05/15 = .003.

#### STATISTICAL ANALYSIS

For each of the 3 dermoscopic criteria (global pattern, pigment distribution, and color), the frequency distribution among the different STs was calculated by univariate analysis. Differences between proportions were tested using the chi² test.

To test the correlation between ST and each of the 3 dermoscopic criteria, considering age, sex, and enrolling center as potentially confounding factors, the likelihood ratio test comparing logistic regression models including age, sex, and enrolling center with and without ST was used. Because 15 comparisons were made, at this stage of inference, we set the statistical significance level at .003 (.05/15 = .003).

The saturated model with age, sex, and enrolling center was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the ST categories II through IV, with ST I as the reference category. When the expected frequency for a given dermoscopic criterion was lower than 5, ST categories I and II, and III and IV, were combined for the purpose of multivariate analysis, using categories I and II as the reference group. Because many comparisons were made, with 33 ORs calculated, we used the Bonferroni correction considering significant ORs with a p-value of .05/15 = .003. The Wald test for trend was performed where appropriate, using ST as the continuous variable (coded I, II, III, or IV). To assess a possible interaction between ST and enrolling center for each dermoscopic criterion, the likelihood ratio test was used, comparing logistic regression models with and without the interaction term. STATA statistical software was used for all analyses.

### RESULTS

#### GENERAL RESULTS

Of 700 AMN included in the study, 680 were eligible for analysis. Table 1 gives the number of study participants assigned to the 4 STs using the Fitzpatrick classification scale. The study population consisted of 367 female subjects (54.0%) and 313 male subjects (46.0%) with a median age of 34 years (age range, 8-88 years). No significant differences in the age of individuals within the different ST groups were observed. The median age of individuals with ST I was 36.7 years (age range, 11-64 years), with ST II was 32.8 years (age range, 8-72 years), with ST III was 35.0 years (age range, 6-88 years), and with ST IV was 36.7 years (age range, 15-64 years).

The most prevalent ST was ST III, followed by ST II, ST I, and ST IV (Table 1). The total nevus count most...
frequently observed was 11 to 50 (57.5%), followed by a nevus count of more than 50 in 189 individuals (27.8%) and fewer than 10 in 100 participants (14.7%). Of the 680 representative nevi selected for dermoscopic evaluation, 592 (87.1%) were located on the trunk and 88 (12.9%) were located on the extremities.

Dermoscopic features scored in our 680 AMN are given in Tables 2, 3, and 4. Among the 3 main categories of dermoscopic features (global pattern, pigment distribution, and color), reticular pattern (39.1%, n=266), uniform pigment distribution (36.2%, n=245), and light brown color (71.6%, n=487) were most frequently seen in the overall sample of AMN. The uniform pigment distribution was most prevalent in patients with a total nevus count of fewer than 50, whereas individuals having more than 50 nevi demonstrated a similar prevalence of the uniform pigment distribution, central hyperpigmentation, multilocal hypopigmentation or hyperpigmentation, or central pigmentation (data not shown). Ten nevi were classified as nonspecific.

Table 2. Morphologic Features of Nevi in 680 Patients by Skin Type*

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>No. of Nevi</th>
<th>Reticular Pattern</th>
<th>Reticular-Homogeneous Pattern</th>
<th>Global-Homogeneous Pattern</th>
<th>Homogeneous Pattern†</th>
<th>Globular Pattern†</th>
<th>Globular-Reticular Pattern†</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>51</td>
<td>127 (24.7)</td>
<td>11 (21.6)</td>
<td>1 (18.5)</td>
<td>30 (9.1)</td>
<td>13 (5.1)</td>
<td>10 (4.1)</td>
</tr>
<tr>
<td>II</td>
<td>278</td>
<td>208 (100.0)</td>
<td>12 (20.1)</td>
<td>7 (15.2)</td>
<td>22 (7.6)</td>
<td>8 (3.0)</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>III</td>
<td>308</td>
<td>245 (100.0)</td>
<td>14 (39.4)</td>
<td>10 (25.6)</td>
<td>15 (3.7)</td>
<td>10 (2.9)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>IV</td>
<td>43</td>
<td>31 (14.0)</td>
<td>1 (0.6)</td>
<td>1 (3.2)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>680‡</td>
<td>266 (39.1)</td>
<td>138 (20.0)</td>
<td>91 (13.4)</td>
<td>70 (10.3)</td>
<td>70 (10.3)</td>
<td>35 (5.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
*Odds ratios were calculated by logistic regression analysis including age, sex, and enrolling center as confounding variables. Significant associations are shown in italics.
†Ten nevi were dermoscopically classified as not specific and are missing in terms of morphology and pigment distribution, but are included in the evaluation of color.
‡Ten nevi were dermoscopically classified as not specific and are missing in terms of morphology and pigment distribution, but are included in the evaluation of color.
§Includes 5 nonspecific nevi.

Table 3. Pigment Distribution of Nevi in 680 Patients by Skin Type*

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>No. of Uniform Pigment Distribution, No. (%)</th>
<th>Adjusted OR (95% CI)</th>
<th>Central Hypopigmentation</th>
<th>Adjusted OR (95% CI)</th>
<th>Multilocal Hypopigmentation or Hyperpigmentation</th>
<th>Adjusted OR (95% CI)</th>
<th>Central Hypopigmentation</th>
<th>Adjusted OR (95% CI)</th>
<th>Eclectic Hypopigmentation</th>
<th>Adjusted OR (95% CI)</th>
<th>Eclectic Hypopigmentation</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>51</td>
<td>141§</td>
<td>1 (7.8)</td>
<td>0.27 (0.17-2.18)</td>
<td>11 (6.4)</td>
<td>1.03 (0.61-1.77)</td>
<td>15 (8.8)</td>
<td>1.09 (0.57-2.19)</td>
<td>1 (3.1)</td>
<td>0.48 (0.17-0.99)</td>
<td>0.45 (0.14-1.43)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>278</td>
<td>145§</td>
<td>1 (7.8)</td>
<td>0.30 (0.25-1.35)</td>
<td>10 (5.9)</td>
<td>1.06 (0.62-1.80)</td>
<td>15 (8.8)</td>
<td>1.09 (0.57-2.19)</td>
<td>1 (3.1)</td>
<td>0.48 (0.17-0.99)</td>
<td>0.45 (0.14-1.43)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>308</td>
<td>145§</td>
<td>1 (7.8)</td>
<td>0.30 (0.25-1.35)</td>
<td>10 (5.9)</td>
<td>1.06 (0.62-1.80)</td>
<td>15 (8.8)</td>
<td>1.09 (0.57-2.19)</td>
<td>1 (3.1)</td>
<td>0.48 (0.17-0.99)</td>
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<td></td>
</tr>
<tr>
<td>IV</td>
<td>43</td>
<td>145§</td>
<td>1 (7.8)</td>
<td>0.30 (0.25-1.35)</td>
<td>10 (5.9)</td>
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<td>15 (8.8)</td>
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<td>1 (3.1)</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>680‡</td>
<td>145§</td>
<td>1 (7.8)</td>
<td>0.30 (0.25-1.35)</td>
<td>10 (5.9)</td>
<td>1.06 (0.62-1.80)</td>
<td>15 (8.8)</td>
<td>1.09 (0.57-2.19)</td>
<td>1 (3.1)</td>
<td>0.48 (0.17-0.99)</td>
<td>0.45 (0.14-1.43)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
*Odds ratios were calculated by logistic regression analysis including age, sex, and enrolling center as confounding variables. Significant associations are shown in italics.
†Because of the small number of observations, comparisons were performed combining skin types I and II, and III and IV.
‡Ten nevi were dermoscopically classified as not specific and are missing in terms of morphology and pigment distribution, but are included in the evaluation of color.
§Includes 5 nonspecific nevi.

SPECIFIC RESULTS

Tables 2 through 4 give the absolute numbers, percent prevalences, and ORs adjusted by age, sex, and enrollment center.

Global Pattern in Relation to ST

Of the 6 global patterns, the reticular pattern was the most frequent in all STs (Table 2). Its prevalence increased with increasing darkening of the skin (OR, 2.80; 95% CI, 1.08-7.26; P=.03, for ST IV compared with ST I). No significant differences were found between the other 5 global patterns and the 4 STs.

Pigment Distribution in Relation to ST

Central hypopigmentation was the most frequent type of pigment distribution of nevi in patients with STI (41.2%; P=.001) (Table 3). Its prevalence gradually decreased with increasing darkening of the skin (Figure 1), and decreased to 7.0% in ST IV (test for trend, P=.001).
Central hyperpigmentation showed an opposite trend, gradually decreasing with increasing lightening of the skin (Figure 1) (test for trend, \( P < .001 \)), with higher prevalence observed in ST III (OR, 4.45; 95% CI, 1.44-13.74) and ST IV (OR, 13.37; 95% CI, 3.67-48.63), compared with ST I. Although most nevi in ST II and III exhibited uniform pigment distribution (32.4% and 40.3%, respectively), multifocal hyperpigmentation or hypopigmentation was significantly associated with ST II (OR, 5.92; 95% CI, 1.96-17.87) and ST III (OR, 7.24; 95% CI, 2.28-22.92), compared with ST I.

**Table 4. Color of Nevi in 680 Patients by Skin Type**

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>No. of Nevi</th>
<th>Light Brown (95% CI)</th>
<th>Dark Brown (95% CI)</th>
<th>Other, Including White, Red, Blue, Gray, and Black† (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>51</td>
<td>47 (92.2)</td>
<td>2 (3.9)</td>
<td>16 (4.9)</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>278</td>
<td>225 (80.9)</td>
<td>39 (14.0)</td>
<td>3.70 (0.84-16.31)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>308</td>
<td>197 (64.0)</td>
<td>100 (32.5)</td>
<td>9.32 (2.08-41.71)</td>
<td>16 (4.6)</td>
</tr>
<tr>
<td>IV</td>
<td>43</td>
<td>18 (41.9)</td>
<td>20 (46.5)</td>
<td>16.72 (3.34-83.63)</td>
<td>32 (4.7)</td>
</tr>
<tr>
<td>Total</td>
<td>680‡</td>
<td>487 (71.6)</td>
<td>181 (23.7)</td>
<td>32 (4.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

*Odds ratios were calculated by logistic regression analysis including age, sex, and enrolling center as confounding variables. Significant associations are shown in italics.

†Because of the small number of observations, comparisons were performed combining skin types I and II, and III and IV.

‡Ten nevi were dermoscopically classified as not specific and are missing in terms of morphology and pigment distribution, but are included in the evaluation of color.

**Figure 1.** Changing dermoscopic profiles of nevi for prevalence of pigment distribution and color for the 4 skin types (I [always burns, never tans] to IV [never burns, tans very easily]).

Color in Relation to ST

Light brown and dark brown showed remarkable differences in the 4 ST groups (Table 4). Light brown gradually decreased with increasing darkening of the skin (test for trend, \( P < .001 \)), and dark brown gradually increased with increasing darkening of the skin (test for trend, \( P < .001 \)) (Figure 1). Most nevi were light brown in ST I and II, whereas dark brown was more frequent in ST III (adjusted OR, 9.32; 95% CI, 2.08-41.71) and ST IV (adjusted OR, 16.72; 95% CI, 3.34-83.63) than in ST I and II.

**COMMENT**

The most striking result of our study is that individuals with different STs are prone to different nevus types in terms of pigment distribution, color, and, to some extent, global dermoscopic pattern. In ST I, the prevalent nevus type was characterized by central hypopigmentation and light brown color (Figure 2), whereas in ST IV, nevi exhibited central hyperpigmentation and dark brown color (Figure 3). In ST II and III, a significant association was seen with nevi exhibiting multifocal hyperpigmentation or hypopigmentation (Figure 4). Although the pigment network showed higher prevalence in darker STs, this global pattern was the most frequent in all ST groups. This is not surprising given the median age of our patients (34 years). As previously demonstrated, the reticular pattern is the most frequently seen at this age.\(^1\)

In Figure 1, the changing dermoscopic profile for pigment distribution and color is shown for the various STs. The changes are represented by a gradual increasing or decreasing trend among the 4 STs.

The observed differences in pigment distribution and color among the 4 ST groups might be explained by the
different dispersion or activation levels of melanosomes in melanocytes and their ratio of pheomelanin to eumelanin production in the various STs. In general, melanosomes in fair STs are clustered and small, less activated, and produce higher levels of pheomelanin (ie, red to yellow pigment). In contrast, in dark STs, melanosomes are homogeneously dispersed, large and activated, and produce higher levels of eumelanin, which is responsible for the dark brown to black coloration.

The particular nevus type we found in ST IV, known as black or hypermelanotic nevus, is a lesion representing the Ugly Duckling sign because it usually draws the clinician’s attention because of its dark color. Dermoscopically, this nevus is characterized by a central black blotch (black lamella), corresponding histopathologically to a pigmented parakeratosis, that covers the underlying dermoscopic structures and, thus, may sometimes cause diagnostic difficulty. However, the central black lamella can be easily removed with tape or plaster, enabling visualization of a typical network (reticular pattern) and the diagnosis of a black nevus with increased confidence.

The prevalence of black nevi in dark-skinned individuals might be interpreted as a peculiar biologic mechanism of nevi to protect the melanocytes against UV irradiation, with the black lamella representing a sort of natural sunshade. The sunshade theory of black nevi might be further supported by previous observations regarding UV-dependent dermoscopic changes in melanocytic nevi. The UV-induced changes constitute a significant darkening of color, increased fading of borders, increase or decrease of a prominent pigment network, reduction of hypopigmentation, and development of new black dots or blotches. At electron microscopy, the black dots or blotches correspond to melanosomes in keratinocytes, and at histopathologic analysis to pigmented parakeratosis (ie, transepidermal pigment transfer and elimination), which can be explained by UV-induced increased melanin synthesis of melanocytes, resulting in a subsequent increased pigment transfer between melanocytes and keratinocytes (melanocyte-keratinocyte unit). However, because irregular black dots and blotches may also be associated with melanoma, it is generally recommended that nevi not be examined after intense UV exposure to avoid unnecessary excision of benign nevi. Because we included only individuals without sun exposure before the examination, it seems remarkable that the predominant nevus type in dark-skinned individuals exhibits the same basic dermoscopic patterns as UV-irradiated nevi, such as dark brown color, prominent pigment network, and the central black blotch. This observation allows, to some extent, the theoretical conclusion that UV exposure may neither cause nor significantly influence the dermoscopic profile of the prevalent nevus type in individuals with a dark ST, but this finding may be explained by an intrinsic genetic or racial/ethnic background.

A possible limitation of our study is the prevalence of nevus patterns in our study population, which might have been biased by the inclusion of a single representative nevus in each individual. We cannot rule out that some study participants might have exhibited additional dermoscopic types of nevi. However, the literature has repeatedly addressed the concept that the predominant nevus type is valid and reliable for the management of individuals with multiple nevi. In this context, our
study was not based on a previously established and well-defined hypothetical consideration but had a purely descriptive-investigative purpose. The risk that the investigators were prone to select representative nevi to prove or disprove an underlying hypothesis seems to be low. Furthermore, that a single observer analyzed these data might introduce a certain risk of misclassification bias. In the field of morphologic diagnosis, there is always the intrinsic problem related to the human subjective evaluation of criteria, and this problem is difficult to resolve even if more independent observers are involved.

In conclusion, our study demonstrates that individuals with different STs exhibit significant differences in their prevalent dermoscopic nevus type. Our results could be the basis for further research into the cellular mechanisms of UV protection, with particular interest in the black nevus. In addition, further studies are needed to better clarify the role of UV irradiation on nevogenesis and its influence on dermoscopic nevus patterns.

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Author Contributions: Dr Argenziano had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Zalaudek, Malvehy, Puig, and Soyer. Acquisition of data: Zalaudek, Argenziano, Mordente, Moscarella, Blum, Cabo, Di Stefani, Hofmann-Wellenhof, Langford, Johr, Malvehy, Kolm, Sgambato, and Puig. Analysis and interpretation of data: Zalaudek, Corona, Sera, Blum, Cabo, Malvehy, and Puig. Drafting of the manuscript: Zalaudek and Sera. Critical revision of the manuscript for important intellectual content: Zalaudek, Argenziano, Mordente, Moscarella, Corona, Sera, Blum, Cabo, Di Stefani, Hofmann-Wellenhof, Malvehy, Kolm, Sgambato, Puig, and Soyer. Statistical analysis: Corona and Sera. Obtained funding: Cabo. Administrative, technical, and material support: Zalaudek, Argenziano, Mordente, Moscarella, Cabo, Hofmann-Wellenhof, and Sgambato. Study supervision: Zalaudek, Blum, Cabo, Di Stefani, Malvehy, Puig, Soyer, and Kerl.

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