Original Investigation

Genetic vs Environmental Factors That Correlate With Rosacea
A Cohort-Based Survey of Twins

Nely Aldrich, MD; Meg Gerstenblith, MD; Pingfu Fu, PhD; Marie S. Tuttle, MD; Priya Varma, BS; Erica Gotow, BS; Kevin D. Cooper, MD; Margaret Mann, MD; Daniel L. Popkin, MD, PhD

IMPORTANCE To our knowledge, this is the first study on rosacea to formally define genetic and environmental contributions.

OBJECTIVES To study a cohort of identical and fraternal twins to determine whether genetic factors contribute to rosacea development and, if genetic factors are present, quantitatively estimate the genetic contribution, as well as to identify environmental factors that correlate with rosacea by controlling for genetic susceptibility.

DESIGN, SETTING, AND PARTICIPANTS Identical and fraternal twins were surveyed regarding risk factors implicated in rosacea. Faculty dermatologists determined a rosacea score for each twin participant according to the National Rosacea Society (NRS) grading system. Data were collected at the annual Twins Days Festival in Twinsburg, Ohio, on August 4-5, 2012, and August 2-3, 2013. Analysis was conducted for several months after each meeting. A cohort of 550 twin individuals, with most from Ohio, Pennsylvania, and the northeastern United States, participated.

MAIN OUTCOMES AND MEASURES The NRS score and rosacea subtype were assessed using the NRS grading system and physical examination by board-certified dermatologists.

RESULTS Among the 275 twin pairs (550 individuals), there were 233 identical twin pairs with a mean rosacea score of 2.46 and 42 fraternal twin pairs with a mean rosacea score of 0.75. We observed a higher association of NRS scores between identical vs fraternal twins ($r = 0.69$ vs $r = 0.46$, $P = .04$), demonstrating a genetic contribution. Using the ACE model (proportion of variance in a trait heritable secondary to additive genetics [A] vs the proportions due to a common environment [C] and unique environment [E]), we calculated this genetic contribution to be 46%. A higher NRS score was also significantly associated with the following factors: age ($r = 0.38$, $P < .001$) and lifetime UV radiation exposure ($r = 0.26$, $P < .001$). These associations remained after use of propensity score matching to adjust for multicollinearity. Other correlated variables included body mass index ($r = 0.21$, $P < .001$), smoking ($r = 0.10$, $P < .02$), alcohol consumption ($r = 0.11$, $P = .01$), cardiovascular comorbidity ($r = 0.17$, $P < .001$), and skin cancer comorbidity ($r = 0.19$, $P < .001$).

CONCLUSIONS AND RELEVANCE The study of twins allows us to separate genetic susceptibility and the influence of environmental factors affecting rosacea. We found that approximately half of the contribution to the NRS score could be accounted for by genetics and the other half by environment. We identified correlations between rosacea and UV radiation exposure, alcohol, smoking, skin cancer history, cardiac comorbidity, and age. These findings may help improve current management and expectations of individuals affected by rosacea.

Published online August 26, 2015.

Copyright 2015 American Medical Association. All rights reserved.
Rosacea is a common and chronic skin disease characterized by facial flushing, papules and/or pustules, and visible blood vessels. The cause of rosacea is poorly understood, although previous studies have suggested both genetic and environmental contributions. A first-degree relative with rosacea, increasing age, photosensitive skin types, sun exposure, and smoking have been implicated as risk factors or triggers for rosacea, suggesting a multifactorial cause with genetic and environmental influences as well as a complex disease process.

Twin research has been instrumental during the past 20 years in demonstrating the heritability of diseases such as psoriasis, eczema, and acne. Twin studies are based on the comparison of identical twins and fraternal twins. Identical twins share 100% of their genetic makeup; fraternal twins share 50%, with the latter being equal to siblings of the same biological parents. The value of twin studies is in comparing concordance and discordance in the twin pairs, which can suggest heritability patterns and environmental effects on disease. Twins are considered concordant when both twins express the same phenotype and discordant when only one twin expresses that phenotype. A case report described rosacea affecting 1 of 2 monozygotic twins, raising the hypothesis that environment plays a role in the pathogenesis of the disease. To our knowledge, no studies have investigated concordant and discordant relationships in twins to determine genetic and environmental effects on rosacea. An example of a pair of identical twins discordant for rosacea is shown in Figure 1. Our objective was to determine whether a correlation exists between rosacea and identical or fraternal twin pairs and evaluate any correlating environmental factors.

Methods

The study was approved by the University Hospitals Case Medical Center institutional review board, and participants provided written informed consent. Participants did not receive financial compensation.

Study Design

A questionnaire was administered on August 4-5, 2012, and August 2-3, 2013, at the Twins Days Festival in Twinsburg, Ohio, to 550 twins (233 identical and 42 fraternal twin pairs) aged 18 years or older. Each twin completed the survey separately in the presence of dermatology clinical faculty and residents to obtain information unbiased by the other twin. These metrics included sex, age, personal history of skin disease (ie, skin cancer, eczema, psoriasis), Fitzpatrick skin type, smoking/alcohol history, cardiac comorbidity, lifetime physical activity, and lifetime sun exposure accounting for geographic location. Cardiac comorbidity was defined as any history of congestive heart failure, coronary artery disease, angina pectoris, myocardial infarction, or hypertension. Physical activity was subdivided as intense vs moderate and further subdivided over lifetime years. Twins participated in the study only once (ie, either 2012 or 2013).

All analyses were first performed during several months on the 2012 data set alone. When the 2012 and 2013 data sets were combined, the associations found in 2012 remained across both data sets. This consistency demonstrates the reproducibility of our findings over time, unique twin pairs, and variability of faculty dermatologists determining National Rosacea Society (NRS) scores. The data reported in the present report are from the combined 2012 and 2013 data sets.

Lifetime Sun Exposure and Rosacea Score Assessment

Lifetime sun exposure was calculated using geographic data for each twin during the ages of birth to 13 years, 14 to 19 years, 20 to 29 years, 30 to 39 years, 40 to 64 years, and 65 years or older. We expressed the lifetime sun exposure as UV radiation. For participants with partial information on the lifetime UV radiation exposure, the missing values were imputed using the mean of the data available. This imputation occurred at approximately 5% during any time period of the twin’s life. The data were obtained by asking about hours spent in summer sun between 9 AM and 3 PM during each of these periods, and the mean was then determined. The UV index was then determined for the location of the twin’s residence during the age groups, which is a measurement of the amount of solar radiation on the earth’s surface at 12 PM provided by the National Oceanic and Atmospheric Administration and Environmental Protection Agency. This validated measurement is computed using ozone data, cloud amounts, and ground elevation. The UV index determined for each location during the twin’s lifetime was multiplied by the mean hours spent in the midday summer sun. This product gave us the lifetime sun exposure (UV radiation) value for each individual.

Each twin then received a dermatologist-assessed NRS rosacea grading score based on the scale developed by the National Rosacea Society Expert Committee to rate rosacea as absent, mild, moderate, or severe. This scale includes primary features (ie, flushing, erythema), secondary features (ie, burning, edema, ocular manifestations), physician rating by subtype (ie, erythematotelangiectatic, papulopustular, phymatous, ocular), and patient global assessment of the same subtypes. For the erythematotelangiectatic subtype, attending faculty dermatologists used central vs peripheral telangiectasias, in addition to transient and symptomatic (burning/stinging) clinical features to help distinguish rosacea from telangiectatic photodamage. All twin pairs determined to have rosacea by physician assessment answered a follow-up questionnaire administered on the same day as the first questionnaire on symptoms to obtain the final NRS grading.
score.12 Some dermatology faculty participated in the NRS assessment in both study years; others participated in only one study year.

Statistical Analysis

The ACE model was used to calculate contributions of genetic and environmental factors to the NRS score in twins. The ACE conceptual model, frequently used in twin studies, is a method of determining the influence of genetics vs environment on a certain characteristic or trait. The ACE mathematical model indicates what proportion of variance in a trait is heritable secondary to additive genetics (A) vs the proportion that is due to a common environment (C) and unique environment (E) using structured equation modeling. The core logic requires the assumption that C is the monozygotic (identical twin) correlation minus this estimate of A. The random (unique) factor E is 1 – r_{identical} (ie, identical twins differ only in unique environments).14 Therefore, the variables A, C, and E were solved using the r values of NRS scores within identical and fraternal twins as follows: A = 2(r_{identical} – r_{fraternal}), C = r_{identical} – A, and E = 1 – r_{identical}.14

Statistical analyses were performed using univariate and multivariable regression methods with NRS score as the main outcome measure. The difference between the NRS scores of identical and fraternal twins was examined by a paired, 2-tailed t test. The association of NRS score between twin A and B or 2 continuous variables (eg, rosacea NRS score, age) was estimated for each type of twin using the Pearson correlation coefficient. To account for the possible correlation of NRS scores between each pair of twins, generalized estimating equations were used for inference.15 The generalized estimating equation is used to address an effect specific to paired data. The difference in the association of NRS scores between identical and fraternal twins was tested using Fisher exact test z transformation. All tests were 2-sided and P < .05 was considered statistically significant.

Results

Questionnaires and physical examinations were performed on 275 twin pairs (550 individuals) in 2 years for this study. Participants ranged in age from 18 to 80 years and represented all regions of the United States, with most from Ohio, Pennsylvania, and the northeastern United States. There were 233 identical twin pairs (466 individuals; mean rosacea score, 2.46) and 42 fraternal twin pairs (84 individuals; mean rosacea score, 0.75). Table 1 presents the demographics of our cohort. Identical twins were older, had lighter skin types, and higher UV radiation and NRS scores than the fraternal twins; these differences are addressed below with multivariable and multicollinearity analysis.

Genetic Correlation

As shown in Figure 2A, there was a higher correlation of the NRS scores between 2 identical twin siblings than between fraternal twin siblings (r = 0.69 and r = 0.46, respectively; P = .04). These data provide formal proof for a genetic contribution to rosacea. Using the ACE model, where A = 0.46, it was calculated that C = 0.23 and E = 0.31. Using our data set, we estimated a genetic contribution of approximately 46%, with the remaining 23% and 31% of the NRS score accounted for by common and unique environmental factors, respectively.

Demographic and Comorbidity Correlations

Univariate analysis of comorbidities revealed a correlation between NRS scores with age (r = 0.38; P < .001), UV radiation exposure (r = 0.26; P < .001), body mass index (BMI) (r = 0.21;
A genetic contribution is supported by the higher correlation of the NRS scores between 2 identical twins than 2 fraternal twins. For identical and fraternal twins, each triangle and circle represents a set of twins. Triangle indicates fraternal; circle, identical. B, There was a correlation between NRS score and age, UV radiation exposure, body mass index (calculated as weight in kilograms divided by height in meters squared), skin cancer comorbidity, and cardiovascular comorbidity. Weaker associations included adjusted pack-years and alcohol consumption. All analyses were univariate. 

$P < .001$), skin cancer comorbidity ($r = 0.19; P < .001$), and cardiovascular comorbidity ($r = 0.17; P < .001$) (Figure 2B). Weaker associations included adjusted pack years of smoking ($r = 0.10; P = .02$) and alcohol consumption ($r = 0.11; P = .01$). No correlation was found with eczema comorbidity ($r = -0.03; P = .48$), acne comorbidity ($r = 0.04; P = .37$), or physical activity level ($r = -0.08; P = .06$). The positive correlations with the variables previously described (BMI, UV radiation exposure, cardiovascular comorbidity) remained even after using propensity score matching to adjust for multicollinearity. Ap
proximately 10% of the twin individuals with rosacea reported use of medication. This confounder would likely result in underestimation of the environmental contribution determined by our analysis.

Adjustment for Possible Confounders in Identical Twins
As reported in Table 1, higher NRS scores were found in identical twins than in fraternal twins (P = .001). Age (P = .002) and skin type (P = .006) differed significantly between identical twins and fraternal twins, with identical twins being older and having lighter skin types. These findings were investigated to determine the reasons for the higher NRS scores in identical twins. Linear regression was performed to examine the relationship between the NRS score and age, skin type, UV radiation, and other comorbidities. To avoid confounding owing to the multicollinearity between UV radiation exposure and age (ie, older individuals have more sun exposure over lifetime), we excluded either UV radiation exposure or age from the multivariable linear regression models (Table 2). The NRS score remained significantly different between identical twins and fraternal twins even after excluding those 2 variables. Linear regression showed that NRS score positively correlated with age (P = .001) and skin type (P = .003) when excluding UV radiation exposure. Linear regression also positively correlated with UV radiation exposure (P < .007) and skin type (P = .009) when excluding age.

Addressing Confounders and Use of Generalized Estimating Equation
The effect of twin type on NRS score was further assessed after excluding the effects of UV radiation and age. In this analysis, twin type was significant irrespective of age or UV radiation (Table 3). Because older individuals have more lifetime sun exposure, we conducted a matched study to investigate whether UV radiation (low [≤300] vs high [≥600] score) affects the NRS score using propensity-modeling techniques.16,17 The data set was limited to individuals aged 50 to 65 years, and propensity scores were calculated from a logistic model that included the baseline variables (ie, age, sex, skin type) with UV radiation group (low vs high) as the dependent variable. The greedy matching algorithm was applied to match participants between 2 UV radiation exposure groups to the nearest propensity score.18 We observed that both twin type and UV radiation exposure remained significant in this analysis (Table 3).

Discussion
The annual Twins Days festival provides a unique opportunity to study a large number of twins by controlling for genetic susceptibility and examining the influence of environmental factors. A cohort of twins from the 2012 and 2013 Twins Days Festivals

Table 2. Demographic Correlations With NRS Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Excluding UV Radiation</th>
<th>Excluding Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Coefficient</td>
<td>P Value</td>
</tr>
<tr>
<td>Twin type (identical vs fraternal)</td>
<td>0.998</td>
<td>.006</td>
</tr>
<tr>
<td>Skin type (dark vs light)</td>
<td>−0.806</td>
<td>.003</td>
</tr>
<tr>
<td>Age (per 1-y increase)</td>
<td>0.047</td>
<td>.001</td>
</tr>
<tr>
<td>BMI (per 1-U increase)</td>
<td>0.039</td>
<td>.02</td>
</tr>
<tr>
<td>Pack-year smoking/age (per 1-U increase)</td>
<td>1.128</td>
<td>.36</td>
</tr>
<tr>
<td>UV radiation (per 100-UV product increase)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Comorbidity (per 1-disease increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>0.173</td>
<td>.14</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>0.295</td>
<td>.07</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>0.17</td>
<td>.36</td>
</tr>
<tr>
<td>Acne</td>
<td>0.111</td>
<td>.09</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>−0.148</td>
<td>.48</td>
</tr>
<tr>
<td>Lifetime activity/age (per 1-U increase)</td>
<td>0.025</td>
<td>.32</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; NA, not applicable; NRS, National Rosacea Society.

Table 3. Results From Linear Regression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Excluding UV Radiation</th>
<th>Excluding Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Coefficient</td>
<td>P Value</td>
</tr>
<tr>
<td>Age (per 1-y increase)</td>
<td>−0.03</td>
<td>.61</td>
</tr>
<tr>
<td>UV radiation (per 100-UV product increase)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Skin type (dark vs light)</td>
<td>−1.25</td>
<td>.14</td>
</tr>
<tr>
<td>Twin type (identical vs fraternal)</td>
<td>2.61</td>
<td>.006</td>
</tr>
<tr>
<td>UV radiation exposure score (≤300 vs ≥600)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

* Propensity modeling was used to account for age, sex, skin type, and twin type.

60 Matched Twins (Aged 50-65 y)

| Characteristic                              | Excluding UV Radiation | Excluding Age/VU Radiation | 60 Matched Twins (Aged 50-65 y)
|--------------------------------------------|------------------------|---------------------------|-------------------------|
|                                            | β Coefficient | P Value | β Coefficient | P Value | 60 Matched Twins (Aged 50-65 y)
|                                            | β Coefficient | P Value | β Coefficient | P Value | 60 Matched Twins (Aged 50-65 y)
| Age (per 1-y increase)                     | −0.04        | .52     | NA            | NA      | NA
| UV radiation (per 100-UV product increase) | NA           | NA      | 0.001         | .007    | 2.28
| Skin type (dark vs light)                  | −1.42        | .13     | NA            | NA      | NA
| Twin type (identical vs fraternal)         | 2.36         | .05     | NA            | NA      | NA
| UV radiation exposure score (≤300 vs ≥600) | NA           | NA      | NA            | NA      | 2.28

Abbreviation: NA, not applicable.

60 Matched Twins (Aged 50-65 y)

The greedy matching algorithm was applied to match participants between 2 UV radiation groups.
was examined for the presence of rosacea and the possible associated environmental factors. Using the criterion standard for genetic associations (ACE), we found that genetic and environmental factors each contributed to approximately half of the NRS score in our cohort. Previous studies have found that rosacea is associated with familial predisposition, photosensitive skin types, and history of smoking. Although alcohol has been found to be a trigger for rosacea flares, it has not been identified as a risk factor for development of the disease.

We believe that the genetic contribution we identified may be an overestimate given the older age, amount of UV radiation exposure, and lighter skin type of identical vs fraternal twins in our cohort. We attempted to account for these confounders in our analyses and found the same associations, albeit with a decreased magnitude of association.

Adjustments were made for confounders in multivariable and multicollinearity analyses as well as using UV radiation-restricted and age-restricted data sets with our primary endpoint: NRS score. We understand the limitations of our study regarding unappreciated effects that can bias any human study. Nevertheless, we submit that by studying twins, we are better able to discern environmental factors that contribute to rosacea given the shared genetics and relatively common environment shared by twins. Given this special group, we used generalized estimating equations to account for whether any variable was significantly correlated with NRS score between each twin pair given the unique pairing of our dataset compared with data from other groups. Rosacea subtypes were not separated in our study because it was not powered to accurately do subtype analysis.

We provide confirmatory evidence that age and UV radiation exposure positively correlate with rosacea as measured by the NRS score with this unique cohort. In addition, our data indicate that a positive association may exist between BMI and rosacea. We do not know whether this association is the result of unique behavior patterns in individuals with a high BMI. However, this finding provides a starting point for addressing this unexpected association. Another unexpected association with the NRS score was cardiovascular disease. Finally, identical vs fraternal twin status was significantly associated with a higher NRS score. If confirmed in other studies, monogyosity may correlate with rosacea severity as it does with having other health problems, including primary infertility and potentially increased risk of testicular cancer.

Conclusions

To our knowledge, this study is the first to formally define genetic vs environmental contributions to rosacea. Moreover, we have confirmed the importance of UV radiation as the single most important environmental variable as well as uncovering other unexpected associations, such as BMI.

Rosacea is a chronic and common disease with few studies investigating the genetics or environmental factors involved. We aimed to define a genetic vs environmental contribution for rosacea and assess any related comorbidities. The unique cohort found at the Twins Days Festival allowed us to start answering these questions, just as twin research has been instrumental for other diseases. We hope this twin study will serve as a foundation to confirm and pursue the mechanism for specific genetic and environmental contributions to rosacea.

**REFERENCES**


13. Heflich YR, Maier LE, Cui Y, et al. Clinical, histologic, and molecular analysis of differences...
JAMA Dermatol. 2014.4728.

NOTABLE NOTES

Streaks of White Hair in Popular Culture
Not as Simple as Black and White
Patricia M. Richey, BS; Scott A. Norton, MD, MPH, MSc

Characters with white-streaked hair appear throughout popular entertainment, from classic literature to movies to comics (Figure). Some characters are born with white streaks; others acquire them—although precisely how differs greatly. An acquired white streak usually signifies something momentous in the character’s history: exposure to magic, a turn to evil or goodness, or most often, physical or psychological trauma.

In Disney’s film Frozen (2014), Princess Elsa possesses cryokinetic powers to generate ice, frost, and snow. She struggles to control her wintery powers but, alas, she accidentally injures her sister, Princess Anna, whose hair then acquires a white streak. Years later, Elsa, with powers still untamed, flees her kingdom, afraid that she will continue to hurt loved ones. Anna pleads with her to return but Elsa, distraught, again loses control of her powers, piercing Anna’s heart. As Anna’s health wanes, her hair whitens. Ultimately, Anna is saved by her sister’s true love, the only cure for her ailment, and her hair regains its original shade of red.

In X-Men, superheroine Rogue absorbs powers of other mutants. As she acquires the ability control magnetic fields from Magneto, villain supreme of X-Men comics, her hair becomes white-streaked with his waning life force. Another Marvel superhero, Reed Richards, encounters a similar situation, when a burst of cosmic radiation turns his hair streaky white—but also gives him the power of limitless corporeal elasticity. Thus, he embarks on a new career as Mister Fantastic, one of Marvel’s Fantastic Four.

White hair is also symbolic of encounters with the paranormal. In A Nightmare on Elm Street (1984), serial killer Freddy Krueger, rather than succumb to death, makes a devil’s deal to continue his murderous spree in victims’ dreams. Nancy Thompson, the protagonist and one of these victims, develops a white streak after encountering Krueger. Another sci-fi film, The Sixth Sense (1999) tells the story of Cole and Vincent, boys who share an ability to communicate with the dead, along with their identical patches of white hair.

The popular imagery appears in more than just movies and comics. In Victor Hugo’s Les Misérables, the color white signifies a righteous act by protagonist, Jean Valjean. He surrenders to police in order to save a man falsely accused of crimes that Valjean committed. As he watches the court proceedings and prepares to save the innocent man, Valjean’s entire head of hair turns completely white.

Then there is the Marie Antoinette Syndrome or canities subita: a sudden whitening of the hair. The term was coined during the French Revolution, after the observation that the queen’s hair turned white overnight before her execution. Whether this was from fright or simply the absence of her coiffeur, well, we can’t be sure.

Figure. Cruella De Vil
One of the most famous white streaks is that of the antagonist of Dodie Smith’s The Hundred and One Dalmatians, later adapted by Disney. Although the origin of her white hair is not revealed, it certainly commands a powerful presence. Copyright 1961 Disney.

Author Affiliations: Georgetown University School of Medicine, Washington, DC (Richey); Department of Dermatology, Children’s National Medical Center, Washington, DC (Norton).

Corresponding Author: Patricia Richey, 3900 Reservoir Rd NW, Washington, DC 20007 (pmr35@georgetown.edu).

Figure. Cruella De Vil
One of the most famous white streaks is that of the antagonist of Dodie Smith’s The Hundred and One Dalmatians, later adapted by Disney. Although the origin of her white hair is not revealed, it certainly commands a powerful presence. Copyright 1961 Disney.