

Black patients with cutaneous lupus are associated with positive family history of cutaneous lupus and systemic lupus

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ABSTRACT

Objectives Various genetic polymorphisms have been associated with an increased risk of cutaneous lupus erythematosus (CLE). However, it is not fully known how often positive family histories occur in patients with CLE. The aims of this study are to determine the rate of positive family history among patients with CLE and to identify risk factors associated with positive family history.

Methods A retrospective cohort study was conducted among 338 patients with CLE seen in outpatient dermatology clinics in a tertiary referral centre in Dallas, Texas. The primary outcome was positive family history of CLE and/or SLE, as defined by the presence of self-reported CLE and/or SLE in first-degree or more distant relatives of a patient. Univariate analyses were performed to identify risk factors associated with positive family history of CLE and/or SLE in patients with CLE. Multivariable logistic regression analyses were performed to determine significant predictors of positive family history of CLE and/or SLE.

Results 34% (n=114) of patients reported positive family history of CLE and/or SLE. 7% (n=23) of patients with CLE had relatives with CLE, with 5% (n=18) having a first-degree relative with CLE. 30% (n=102) of patients with CLE had relatives with SLE, and 15% (n=52) had a first-degree relative with SLE. Black patients were more likely to have positive family history of CLE and/or SLE (OR 2.13, 95% CI 1.23 to 3.69, p=0.007).

Conclusions More patients with CLE had positive family history of SLE than CLE. Black patients with CLE were more likely to have a relative with CLE and/or SLE. Providers can use this information to counsel patients with CLE on the risk of other family members having CLE and/or SLE. These data may help identify potentially new genetic polymorphisms associated with positive family history.

INTRODUCTION

While prior studies assessed family histories in patients with SLE, it remains unclear how often patients with cutaneous lupus erythematosus (CLE) have relatives with CLE or SLE.¹ There were previous reports investigating rates of positive family history for discoid lupus erythematosus (DLE) in DLE patient cohorts. However, the rate varied significantly among different studies, ranging from 0% to 20%.²⁻³ The differences in rates were likely

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior family history studies of patients with cutaneous lupus erythematosus (CLE) mostly included those with discoid lupus and were limited by small sample sizes and homogeneous cohorts.

WHAT THIS STUDY ADDS

⇒ In our cohort of 338 patients with CLE, 34% (n=114) of patients reported positive family history of CLE and/or SLE.
⇒ Black patients were more likely to have positive family history of CLE and/or SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Providers can use family history information to guide their history taking and inform at-risk patients to check for family histories of lupus.
⇒ These data can lay the foundation for identifying new genetic polymorphisms associated with positive family history to improve risk analyses for patients with CLE.

due to the populations studied and differences in whether family histories included first-degree relatives and/or more distant relatives. Other limitations were small sample size, homogeneous racial or ethnic populations, and lack of inclusion of other subtypes of CLE. Prior studies on family history of SLE in patients with CLE without SLE faced similar limitations.

Various genetic polymorphisms have been associated with an increased risk of CLE,⁶ but their importance is unclear without further knowledge of frequencies of positive family history in patients with CLE. It is also unknown what type of patients with CLE are more likely to have positive family history of CLE. A better understanding of the rates and risk factors associated with positive family history would help providers counsel patients with CLE on the potential of other family members having this disease. This study aimed to determine the rate of and risk factors associated with a positive family history of CLE or SLE in a



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large, diverse cohort of patients with CLE enrolled in the University of Texas Southwestern (UTSW) CLE Registry.

METHODS

We conducted a retrospective cohort study of patients with CLE seen in dermatology clinics at UTSW Medical Centre and Parkland Health and enrolled in the UTSW CLE Registry from January 2009 to November 2020. Patients diagnosed with CLE by clinicopathological correlation and aged over 18 years were included, while patients with drug-induced CLE were excluded.

The primary outcome was defined as family history of CLE and/or SLE because patients are often unable to distinguish between CLE and SLE. Positive family history of CLE and SLE were subdivided into first-degree relatives and second-degree or more distant relatives. Family histories of CLE and SLE were self-reported by patients or collected from medical records.

We collected demographic and clinical data for predictor variables from medical records and patient questionnaires. The predictor variables included gender, race and ethnicity, type of CLE (acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), chronic cutaneous lupus erythematosus (CCLE)), age at diagnosis of CLE, presence of SLE, smoking and positive history of autoantibodies (ANA, anti-dsDNA, anti-Ro/SSA, anti-La/SSB and anti-Smith).

Statistical analysis

Patient characteristics were summarised as frequencies and percentages for categorical variables, and means and SD for continuous variables. We performed univariate analyses to identify risk factors associated with positive family history with CLE and/or SLE in patients with CLE. For univariate analyses, t-test was used for continuous variables and χ^2 or Fisher's exact tests were used for categorical variables. Two-sided p values of <0.05 was considered significant. Variables significant at a p value of <0.10 from univariate analyses and variables selected a priori (presence of SLE, age at diagnosis and history of positive ANA) were included as predictors in the multivariable logistic regression models for positive history of CLE and/or SLE. ORs with 95% CIs were calculated for each variable in the statistical models. All analyses were performed using SPSS V.25.

RESULTS

Patient characteristics

Of the 339 patients who were initially screened, 338 patients were included. One patient was excluded because there was no family history information available. Demographic and clinical characteristics of these patients are summarised in [table 1](#). More patients were female (84%) than male (16%). The majority of patients were black (51%), Caucasian (33%), Hispanic (11%) and Asian (4%). CCLE was the most common subtype affecting 76% of the patients, followed by SCLE (16%) and ACLE (8%).

Approximately 50% of the patients had concurrent SLE. The age at CLE diagnosis had a mean of 40.43 years old (SD=14.41). The smoking status was approximately equal between those who never and ever smoked in their lives. The follow-up period starting with the time of CLE diagnosis had a mean of 7.16 years (SD=8.93).

Frequencies of positive family histories

34% (n=114) patients reported positive family history of CLE and/or SLE. 7% (n=23) of patients with CLE reported relatives with CLE, with 5% (n=18) reporting a first-degree relative with CLE. 30% (n=102) of patients with CLE reported relatives with SLE, and 15% (n=52) of patients with CLE reported a first-degree relative with SLE. Three per cent (n=11) of patients reported positive family history of both CLE and SLE, and 10 out of these 11 patients reported first-degree relatives with both CLE and SLE.

Factors associated with positive family histories

Univariate analyses demonstrated that Black patients were more likely to report positive family history of CLE and/or SLE than non-Black patients (73/114 (64%) vs 100/224 (45%), $p=0.001$). Positive family history of CLE and/or SLE was more likely to be found in patients with CLE who had history of positive anti-Smith antibodies ($p=0.04$). There were non-significant trends towards younger patients ($p=0.10$), and those with positive ANA ($p=0.11$), or positive dsDNA antibodies ($p=0.11$) with positive family history of CLE and/or SLE. There were no significant differences in follow-up duration in those reporting positive and negative family history of CLE and/or SLE ($p=0.66$) ([table 1](#)).

Multivariable analyses showed that Black patients were more likely to have positive family history of CLE and/or SLE (OR 2.13, 95% CI 1.23 to 3.69, $p=0.007$) after controlling for the additional variables in the statistical models ([table 2](#)).

DISCUSSION

The rate of positive family history of CLE (7%) was similar to prior studies (0%–20.8%), which had fewer patients.^{4,5} This rate is likely conservative because many patients were unable to specify CLE in their family histories. Patients who had family members with 'lupus' were classified as positive family history of SLE instead of CLE, which implies that the gap between positive family histories of CLE and SLE may be smaller than reported. To address the self-reporting bias, we combined the outcomes of family history of CLE and SLE for statistical analyses.

There was a greater percentage of first-degree relatives with positive family history of CLE (78%) than positive family history of SLE (51%). The majority of positive family history of CLE being in first-degree relatives suggests that there could be a substantial genetic contribution to their skin disease in a subset of patients with CLE. There are already known gene polymorphisms associated with CLE, including major histocompatibility complex,

Table 1 Univariate analyses of demographic and clinical features of patients with CLE with and without family history of CLE and/or SLE

Feature	All patients (n=338)	Positive family history of CLE and/or SLE (n=114)	No family history of CLE and/or SLE (n=224)	P value
Sex, n (%)				
Female	283 (84)	98 (86)	185 (83)	0.42
Male	55 (16)	16 (14)	39 (17)	
Race/ethnicity, n (%)				
Black non-Hispanic	173 (51)	73 (64)	100 (45)	0.001
Non-Black*	165 (49)	41 (36)	124 (55)	
Smoking status (No., %) [†]				
Ever	173 (51)	59 (52)	114 (51)	>0.99
Never	163 (49)	55 (48)	108 (48)	
Follow-up duration (years), mean (SD) [‡]	7.16 (8.93)	7.46 (9.21)	7.01 (8.79)	0.66
Age at diagnosis (years), mean (SD) [§]	40.43 (14.41)	38.59 (14.41)	41.37 (14.36)	0.10
Predominant CLE subtype, n (%)				
Acute	27 (8)	11 (10)	16 (7)	0.52
Subacute	53 (16)	15 (13)	38 (17)	
Chronic [¶]	258 (76)	88 (77)	170 (76)	
Concomitant SLE, n (%)				
Yes	171 (51)	66 (58)	105 (47)	0.06
No	167 (49)	48 (42)	119 (53)	
History of positive autoantibody test result ^{**}				
ANA	249 (75)	91 (81)	158 (72)	0.11
Anti-dsDNA	97 (35)	40 (42)	57 (32)	0.11
Anti-Ro/SS-A	129 (48)	49 (51)	80 (47)	0.53
Anti-La/SS-B	41 (16)	15 (16)	26 (16)	>0.99
Anti-Smith	89 (34)	40 (42)	49 (30)	0.04

*Non-Black patients included 111 White non-Hispanic (33%), 13 Asian (4%), 37 White Hispanic (11%) and four other (1%) patients.
[†]Smoking status was unavailable for two patients.
[‡]Follow-up duration was calculated as the time between CLE diagnosis and the last study visit. Six patients whose CLE diagnosis date was unavailable were excluded.
[§]Age of CLE diagnosis was unknown for six patients.
[¶]Patients with chronic CLE included 221 patients with DLE (65%), 28 with LE tumidus (8%), 8 with LE panniculitis (2%) and 1 with Chilblain's lupus (1%).
^{**}ANA test result was unavailable for 7 patients, anti-dsDNA antibody test for 64 patients, anti-Ro/SS-A antibody test for 72 patients, anti-La/SS-B for 79 patients and anti-Smith antibody test for 77 patients.
.anti-dsDNA, anti-double-stranded DNA antibody; CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; LE, lupus erythematosus.

tyrosine kinase 2 and interferon regulatory factor 5.^{6–8} While further studies can be done to see how commonly these gene polymorphisms show up in patients with CLE, there are likely others that have yet to be discovered.

The rate of positive family history of SLE was 30%, which was higher than those of prior studies (2%–14%). Of note, these studies investigated patients with CLE without SLE. Excluding patients with CLE with SLE in our cohort did not greatly change the rate of positive family history; 42 out of 125 (34%) patients without SLE had positive family history of SLE. Given that prior studies primarily investigated patients with DLE, the inclusion of other patients

with CLE, particularly ACLE and SCLE, which comprised 23% of our cohort, may have contributed to the higher rate of positive family history of SLE, given their higher association with SLE.⁹

We found that Black patients with CLE were more likely to have a family member with CLE or SLE. Our study further supports that there may be a genetic component in some Black patients developing CLE. For example, on the short arm of chromosome 11 (11p13), a genetic linkage was found in Black families with SLE and DLE, but not in European families.¹⁰ Furthermore, Black race being a risk factor of positive family history of CLE

Table 2 Multivariable logistic regression analysis of patient factors associated with positive family history of CLE and/or SLE

	Positive family history of CLE and/or SLE*	
	OR (95% CI)	P value
Black versus non-Black	2.13 (1.23 to 3.69)	0.007
Concomitant SLE	0.95 (0.46 to 2.00)	0.90
Age at diagnosis	1.00 (1.00 to 1.00)	0.25
History of positive ANA	1.10 (0.46 to 2.61)	0.83
History of positive anti-Smith	1.77 (0.92 to 3.38)	0.09
History of positive anti-dsDNA	1.00 (0.52 to 1.90)	0.99

*A total of 244 patients were included in the multivariable model for family history of CLE and/or SLE; 94 patients were excluded due to missing data.
 .CLE, cutaneous lupus erythematosus; dsDNA, double-stranded DNA antibody.;

may explain prior epidemiological studies showing that Black patients have a higher prevalence and incidence of chronic CLE.^{11 12}

Study strengths included having a large cohort with diverse CLE subtypes and racial and ethnic backgrounds. Limitations include patients self-reporting of family history data that could not be independently verified, and incomplete autoantibody patient profiles in many patients. The multivariable analyses did not include patients with missing data and did not find any autoantibody to be significantly significant. The study cohort was recruited from a tertiary care centre that may not reflect patients seen in other outpatient clinics. Future larger multicentre prospective studies are planned to confirm our findings and potentially identify new genetic polymorphisms associated with CLE.

In conclusion, most patients with CLE with positive family history of CLE had affected first-degree family members. Positive family histories of SLE were more common than positive family histories of CLE in patients with CLE. Black patients were more likely to have another family member with CLE and/or SLE. Thus, we recommend asking patients with CLE about their family history of CLE and SLE, particularly Black patients, and raising awareness to prompt their family members to seek evaluation and workup. Robust family history data will be helpful to identify potentially new genetic polymorphisms associated with a strong positive family history and improve risk analyses for patients with CLE.

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Competing interests BFC is an investigator for Daavlin Corporation, Biogen and Pfizer. He is a consultant for Bristol Meyers Squibb, EMD Serono, Horizon Therapeutics and Biogen. BFC receives royalties from MAPI Research Trust. The other authors have no conflicts of interest.

Patient consent for publication Not applicable.

Ethics approval This study was approved by University of Texas Southwestern Medical Center's institutional review board (STU #082010-241).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Deidentified participant data are available upon reasonable request from skinlupusregistry@utsouthwestern.edu. Data sharing agreement would be required per institution policy.

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