Presence of Uterine Leiomyomas Has No Significant Impact on Gene Expression Profile in the Scalp of Patients with Central Centrifugal Cicatricial Alopecia

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Central centrifugal cicatricial alopecia (CCCA) is associated with increased expression of genes implicated in fibroproliferative disorders and a higher prevalence of uterine leiomyomas (ULs) among affected individuals. We sought to examine the effect of UL status on the gene expression profile of the lesional scalp in patients with CCCA. Scalp biopsy was obtained from 16 patients with a confirmed diagnosis of CCCA between 2017 and 2020. Microarray analysis was used to identify differential gene expression between patients with CCCA with a history of UL and those without the history. Of more than 20,000 genes analyzed, 23 of 25 genes with the highest expression in patients with CCCA with UL held no statistical significance. No genes previously implicated in fibroproliferative disorders were found among the upregulated transcripts. Of all genes analyzed, only eight upregulated genes and zero downregulated genes had a fold change in expression >2 in patients with CCCA with UL compared with those in patients with CCCA without UL. Our findings highlight similar gene expression patterns in the lesional scalp of patients with CCCA with and without a history of UL. This analysis is key in highlighting no evidence of causational or linked mechanobiology that accounts for the increased prevalence of UL seen in patients with CCCA that previous studies have not addressed.

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INTRODUCTION

Central centrifugal cicatricial alopecia (CCCA) is a predominant form of permanent hair loss in women of Sub-Saharan African descent, typically presenting between the third and fourth decades of life (Ogunleye et al., 2014). This primary, lymphocytic alopecia is characterized by hair breakage or loss at the scalp vertex, progressing insidiously in a centrifugal pattern to involve the surrounding areas of the scalp (Gathers and Lim, 2009). Similar to all cicatricial alopecias, persistent inflammation results in damage to the bulge region of the hair follicle, which contains pluripotent stem cells, eventually leading to loss of follicular ostia and diminished potential for follicular neogenesis (Somani and Bergfeld, 2008).

The understanding of the pathogenesis of CCCA has evolved over the past decade, with studies identifying possible genetic, environmental, and systemic components with a potential role in the disease mechanism (Dlova et al., 2014; Lawson et al., 2017). Importantly, recent evidence has highlighted a higher prevalence of uterine leiomyomas (ULs) (or uterine fibroids) among women with CCCA (Dina et al., 2018). Women with CCCA had five times increased odds of having ULs compared with sex-, age-, and race-matched controls, although there was no association between UL severity and CCCA.

ULs are the most predominant subtype of benign gynecologic tumors found within women in the United States and have approximately a three-fold higher prevalence among black women (Yu et al., 2018). This condition belongs to a class of disorders collectively termed fibroproliferative disorders (FPDs), which include conditions such as systemic sclerosis, sarcoidosis, and keloids (Huang and Ogawa, 2012). These disorders are characterized by impaired wound healing, contributing to persistent fibrosis even in the absence of sustained inflammation (Wynn, 2007).

The potential association of ULs with CCCA prompted further investigation into the expression of gene transcripts implicated in FPDs in patients with CCCA. This study was revealing of the upregulation of several genes implicated in FPDs, including *PDGF* genes; matrix metalloproteinase genes *MMP1*, *MMP2*, *MMP7*, and *MMP9*; and collagen 1 and 3 genes in the lesional scalp of patients with CCCA compared with those of the nonlesional scalp (Aguh et al., 2018). In addition, a significant overlap of the microarrays was seen with hepatic fibrosis and atherosclerosis, two well-known

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Abbreviations: CCCA, central centrifugal cicatricial alopecia; FPD, fibroproliferative disorder; UL, uterine leiomyoma

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Table 1. Demographic and Clinical Characteristics of the 16 Patients with CCCA Analyzed in this Study, Including Clinical Disease Severity, Time from Disease Onset to Study Biopsy, UL Status, and History of Myomectomy or Hysterectomy

Disease Severity	Age	Race	Sex	Time from Disease Onset to Biopsy	UL History	Hysterectomy or Myomectomy History
Focal	27	Black	Female	7 months	No	—
Focal	34	Black	Female	Several y	No	—
Focal	43	Black	Female	20 y	Yes	No
Focal	47	Black	Female	3 y	Yes	Yes, myomectomy
Focal	48	Black	Female	5 y	Yes	No
Focal	50	Black	Female	5 y	No	—
Limited	32	Black	Female	3.5 y	No	—
Limited	35	Black	Female	Unknown	Yes	Yes, myomectomy
Limited	45	Black	Female	Several years	Yes	No
Limited	46	Black	Female	10 y	Yes	No
Limited	50	Black	Female	Unknown (y)	Yes	No
Limited	59	Black	Female	15 y	No	—
Limited	70	Black	Female	1 y	No	—
Diffuse	30	Black	Female	8 y	No	—
Diffuse	32	Black	Female	At least 15 y	No	—
Diffuse	61	Black	Female	7 y	Yes	Yes, hysterectomy

Abbreviations: CCCA, central centrifugal cicatricial alopecia; UL, uterine leiomyoma.

FPDs. Given these associations, we sought to examine the effect of UL status on the gene expression profile in the lesional scalp of patients with CCCA.

RESULTS

Lesional scalp tissue samples from a total of 16 patients with a biopsy-confirmed diagnosis of CCCA were analyzed. Study participant demographics are summarized in Table 1. Eight study participants had a history of ULs confirmed by electronic medical record review, with three patients having undergone hysterectomy or myomectomy for UL burden or symptomatology. The mean age of patients with ULs was 46.9 years, whereas patients without ULs had a mean age of 41.8 years.

Of more than 20,000 genes analyzed, only 8 genes were found to have a fold change in expression >2 in the lesional scalp of patients with CCCA with ULs compared with those in the lesional scalp of patients with CCCA without ULs. Seven of the eight genes held no statistical significance in fold change of gene expression. Importantly, no genes known to be implicated in FPDs were upregulated in patients with CCCA with ULs.

Further analysis of the top 25 genes upregulated in patients with CCCA with ULs based on fold change was revealing of 23 genes without statistical significance in differential gene expression pattern (Table 2). The only two genes with statistical significance in gene expression fold change between patients with CCCA with a history of ULs and patients with CCCA without a history of ULs were *KRTAP19-4* and *LCE3D* genes (2.19, $P = 0.038$ and 1.78, $P = 0.022$, respectively) (Figure 1).

Table 2. Upregulated Transcripts in the Lesional Tissue of Patients with CCCA with a History of ULs

Gene Name	Gene Symbol	Fold Change (History of ULs Versus No History of ULs)	*P*-Value
Cystatin SN	*CST1*	3.11	0.074
Fatty acid desaturase 2	*FADS2*	2.50	0.097
Keratin 2	*KRT2*	2.28	0.318
Small proline rich protein 2G	*SPRR2G*	2.21	0.100
Keratin-associated protein 19-4	*KRTAP19-4*	2.19	0.038[1]
Cystatin S	*CST4*	2.15	0.099
Keratin 1	*KRT1*	2.11	0.411
Serpin family A member 12	*SERPINA12*	2.03	0.448
Keratin-associated protein 16-1	*KRTAP16-1*	1.94	0.255
Lorcin	*LORICRIN*	1.93	0.416
Filaggrin	*FLG*	1.92	0.371
Dermokine	*DMKN*	1.92	0.293
Peptidase M20 domain containing 1	*PM20D1*	1.89	0.269
Desmoglein 1	*DSG1*	1.88	0.388
Keratin 27	*KRT27*	1.88	0.335
Dopachrome tautomerase	*DCT*	1.87	0.185
Defensin beta 4A	*DEFB4A*	1.85	0.143
Small proline rich protein 2E	*SPRR2E*	1.84	0.239
Serum amyloid A1	*SAA1*	1.83	0.187
Diacylglycerol O-acyltransferase 2 like 6	*DGAT2L6*	1.82	0.318
Family with sequence similarity 25 member G	*FAM25G*	1.81	0.102
Keratin 73	*KRT73*	1.81	0.291
ELOVL fatty acid elongase 1	*ELOVL3*	1.79	0.171
Involucrin	*IVL*	1.79	0.204
Late cornified envelope 3D	*LCE3D*	1.78	0.022[1]

Abbreviations: CCCA, central centrifugal cicatricial alopecia; UL, uterine leiomyoma.

KRTAP19-4 and *LCE3D* are the only two identified genes with statistical significance in fold change between patients with CCCA with and without a history of ULs among the top upregulated gene transcripts in CCCA. These genes do not have a known role in fibrosis or impaired wound healing.

[1]Indicates statistical significance at $P < 0.05$.

Evaluation of the gene transcripts downregulated in the lesional scalp of patients with CCCA with ULs compared with those in patients with CCCA without ULs was revealing of an overall very similar expression pattern, with no genes noted to have a fold change in expression < -2 (Table 3). Of the top genes downregulated in the patients with fibroid, only three genes held statistical significance in fold change: *KRBOX1* gene (−1.54, $P = 0.041$), *PALS2* gene (−1.48, $P = 0.001$), and *PTGR2* gene (−1.47, $P = 0.007$).

The top 2% of gene transcripts as measured by fold change with increased expression in the lesional scalp of patients with CCCA with ULs had identified roles in epidermis development, keratinocyte differentiation, keratinization,

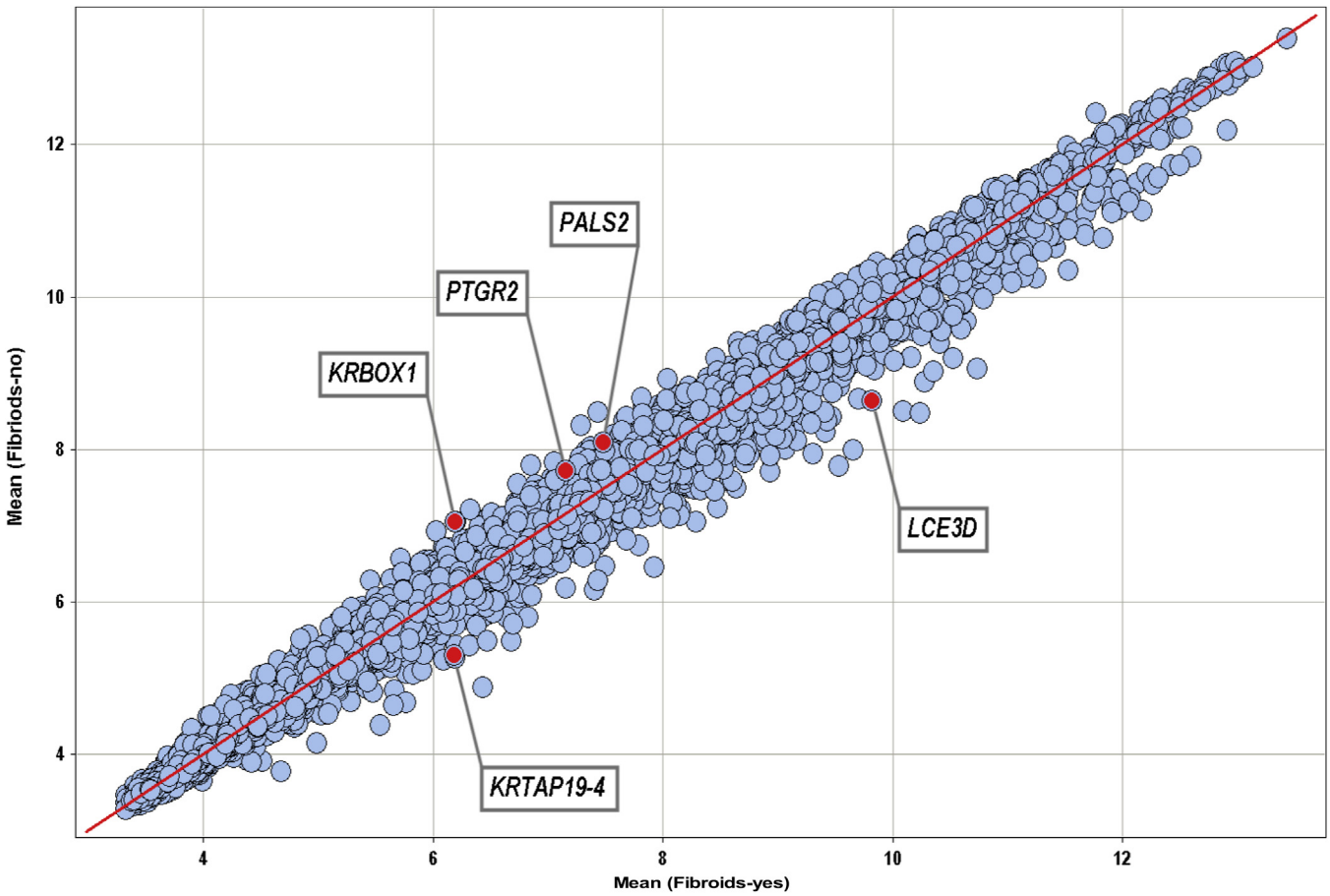

Figure 1. Comparison of mean fold change in patients with CCCA with a history of uterine leiomyomas with that in patients with CCCA without the history. Of more than 20,000 genes analyzed in patients with CCCA with and without a history of uterine leiomyomas, the top upregulated (*LCE3D, KRTAP19-4*) and downregulated (*KRBOX1, PTGR2, PALS2*) genes with statistical significance in patients with CCCA with uterine leiomyomas compared with those in patients with CCCA without a history of uterine leiomyomas are highlighted in red. CCCA, central centrifugal cicatricial alopecia.

oxidation–reduction process, peptide cross-linking, and proteolysis (Table 4). The primary functional pathways identified in the top 2% of the genes transcripts downregulated in patients with CCCA with ULs were cell adhesion, defense response to virus, cell surface receptor signaling pathway, and blood coagulation (Table 5).

DISCUSSION

This study identifies similar gene expression patterns in the scalp of patients with CCCA with and without ULs, suggesting that there are no pathophysiologic changes in the lesional scalp of patients with CCCA associated with a clinical history of ULs. This finding is consistent with our previously published data inversely highlighting that although UL prevalence was higher among patients with CCCA, there was no correlation with increased severity of ULs in affected individuals (Aguh et al., 2018). In this small subset of patients with CCCA, ULs were present across a range of CCCA disease severities, further emphasizing no direct clinical association between these conditions. Three patients analyzed in this study had severe enough leiomyoma burden or symptomatology requiring myomectomy or hysterectomy; yet, this was seen across mild (stages 1A through 2B), moderate (stages 3A through 4B), and severe (stages 5A and 5B) CCCA (Olsen et al., 2008).

We previously identified an overlap in the upregulation of *PDGFB*, *PDGFC*, *COL1A1*, *COL1A2*, *COL3A1*, *FN1*, and matrix metalloproteinase genes *MMP1*, *MMP2*, *MMP7*, and *MMP9* genes in the affected scalp of patients with CCCA and separately in patients with ULs (Aguh et al., 2018). We find no significant upregulation of these genes in patients with CCCA with a history of ULs compared with the genes in patients with CCCA without a history of ULs and instead find increased expression of *KRTAP19-4* and *LCE3D*, genes without a known role in fibrosis or aberrant fibrogenesis (Marshall et al., 2001; Sack et al., 2018). *KRTAP19-4* is instead a protein-encoding gene involved in the formation of disulfide bonds between hair keratins and cysteine residues (Ramroach et al., 2020; Yahagi et al., 2004), and *LCE3D* encodes stratum corneum proteins and belongs to a gene cluster located on human chromosome 1 in the epidermal differentiation complex (Marshall et al., 2001).

These negative findings are important in establishing no direct association between CCCA and ULs that previous studies have not addressed. Rather than a causative or linked mechanism of occurrence of these conditions among black women, it is more likely that CCCA and ULs occur

Table 3. Downregulated Transcripts in the Lesional Scalp of Patients with CCCA with a History of ULs

Gene Name	Gene Symbol	Fold Change (CCCA with ULs Versus CCCA without ULs)	*P*-Value
Hemoglobin subunit gamma 2	*HBG2*	−1.90	0.247
Zinc finger and BTB domain containing 16	*ZBTB16*	−1.78	0.081
Mucin 7	*MUC7*	−1.67	0.334
Interferon induced protein 44 like	*IFI44L*	−1.67	0.065
Polycomb group ring finger 5	*PCGF5*	−1.63	0.075
Four and a half LIM domains 5	*FHL5*	−1.61	0.139
Aspartoacylase	*ASPA*	−1.60	0.056
Osteoglycin	*OGN*	−1.57	0.101
Hemoglobin subunit alpha 2	*HBA2*	−1.56	0.324
Calponin 1	*CNN1*	−1.56	0.156
Hemoglobin subunit alpha 1	*HBA1*	−1.56	0.336
Interferon induced protein with tetratricopeptide repeats 2	*IFIT2*	−1.54	0.155
KRAB box domain containing 1	*KRBOX1*	−1.54	0.041[1]
Fibroblast growth factor binding protein 2	*FGFBP2*	−1.53	0.096
Interferon induced protein with tetratricopeptide repeats 3	*IFIT3*	−1.51	0.132
Circadian associated repressor of transcription	*CIART*	−1.50	0.083
Myosin heavy chain 11	*MYH11*	−1.50	0.285
G kinase anchoring protein 1	*GKAP1*	−1.50	0.070
Coagulation factor X	*F10*	−1.49	0.084
ATP binding cassette subfamily A member	*ABCB5*	−1.49	0.104
Interferon induced protein 44	*IFI44*	−1.49	0.073
Protein associated with LIN7 2, MAGUK family member	*PALS2*	−1.48	0.001[1]
HORMA domain containing 1	*HORMAD1*	−1.47	0.350
Protocadherin 8	*PCDH8*	−1.47	0.058
Prostaglandin reductase 2	*PTGR2*	−1.47	0.001[1]

Abbreviations: CCCA, central centrifugal cicatricial alopecia; UL, uterine leiomyoma.

KRBOX1, *PALS2*, and *PTGR2* were found to have a decreased expression in the lesional scalp of patients with CCCA with a history of ULs compared with those in patients with CCCA with no known history of ULs.

[1]Indicates statistical significance at $P < 0.05$.

Table 4. Functional Pathways Represented among the Upregulated Gene Transcripts

Biological Process	Transcripts	No. of Genes Affected	*P*-Value
Epidermis development	*ACER1, CASP14, CDSN, COL17A1, C1orf68, DSP, DCT, EMP1, GRHL1, GRHL3, KLK5, KRT2, KRT5, KRT14, KRT15, KRT16, KRT17,KRT31, KRT32, KRT34, KRT83, KRT85, KRTAP5-9, LCE2B, LCE3D, SPRR1A, SPRR1B, SPRR2A, SPRR2B, SPRR2D, SPRR2E, SPRR2F, SPRR2G, S100A7, TGM5, ZNF750*	36 of 500	<0.001
Keratinocyte differentiation	*ACER1, CDSN, CERS3, CRCT1, C1orf68, DSG4, DSP, FLG, IVL, KRT10, KRT16, LCE1D, LCE2A, LCE2B, LCE2C, LCE3C, LCE3D, LCE3E, PRR9, SPRR1A, SPRR1B, SPRR2A, SPRR2B, SPRR2D, SPRR2E, SPRR2F, SPRR2G, S100A7, TGM3, TP63*	30 of 500	<0.001
Keratinization	*ABCA12, CASP14, CNFN, HRNR, IVL, KRT2, KRT16, KRT17, LCE1D, LCE2A, LCE2B, LCE2C, LCE3C, LCE3D, LCE3E, SPRR1A, SPRR1B, SPRR2A, SPRR2B, SPRR2D, SPRR2E, SPRR2F, SPRR2G, SFN, TGM3, TCHH*	26 of 500	<0.001
Oxidation–reduction processes	*ALDH1L1, ALOX15B, BMP2, CYP2B6, CYP2S1, CYP4F22, DHRS9, DCT, DUOX1, FA2H, FADS1, FADS2, FASN, FAR2, BBOX1, HEPHL1, HGD, HSD11B1, HSD3B1, MGST1, NDUFA4L2, SCD, SDR16C5, SORD, SURF1*	25 of 500	0.004
Peptide cross-linking	*CRCT1, C1orf68, DSP, FN1, IVL, LCE1D, LCE2A, LCE2B, LCE2C, LCE3C, LCE3D, LCE3E, PRR9, SPRR1A, SPRR1B, SPRR2A, SPRR2B, SPRR2D, SPRR2E, SPRR2F, SPRR2G, TGM3, TGM5*	23 of 500	<0.001
Proteolysis	*ADAM12, CAPN8, CPA4, CASP14, CLCA2, ERAP2, FAP, IDE, KLK5, KLK10, MMP1, MMP7, MMP10, MMP12, MMP13, MMP19, PM20D1, PRSS3, TMPRSS11E, TMPRSS11F*	20 of 500	0.018

Abbreviations: CCCA, central centrifugal cicatricial alopecia; No., number; UL, uterine leiomyoma.

The top functional pathways among the top 2% of the upregulated transcripts in patients with CCCA with a history of ULs were epidermis development, keratinocyte differentiation, keratinization, oxidation–reduction processes, peptide cross-linking, and proteolysis.

Table 5. Functional Pathways Represented among the Downregulated Gene Transcripts

Biological Process	Transcripts	No. of Genes Affected	*P*-Value
Cell adhesion	*APC, NUAK1, SPG7, CTNNAL1, CSF3R, FEZ1, IGSF11, ITGA8, ITGB3BP, ITGB6, LSAMP, MMRN1, OMD, PLXNC1, SSPN, SELL, THBS4*	17 of 500	0.095
Defense response to virus	*CXCL10, GBP1, HERC5, IFIT1, IFIT2, IFIT3, IFI44L, IFNAR1, IL33, ISG15, MX1, MX2, OAS2*	13 of 500	0.001
Cell surface receptor signaling pathway	*ADGRA3, ADGRE3, BIRC3, CALCRL, CDA, CXCL10, KLRB1, LIFR, LY96, TSPAN15, TSPAN8, UPK1A*	12 of 500	0.098
Blood coagulation	*DOCK8, ENPP4, FGG, F10, HBB, HBG2, MMRN1, NFE2, PRKAR2B, RAD51B, TFPI*	11 of 500	0.021
IFN-1 signaling pathway	*GBP2, IFIT1, IFIT2, IFIT3, IFNAR1, ISG15, MX1, MX2, OAS2*	9 of 500	<0.001
Response to virus	*ACTA2, IFIT1, IFIT2, IFIT3, IFI44, IFNAR1, MX1, MX2, OAS2*	9 of 500	0.008
Bicarbonate transport	*CA1, CA6, CFTR, HBA1, HBA2, HBB, SLC4A1, SLC26A2*	8 of 500	<0.001

Abbreviations: CCCA, central centrifugal cicatricial alopecia; No., number; UL, uterine leiomyoma.

The top functional pathways among the top 2% of downregulated transcripts in patients with CCCA with a history of ULs were cell adhesion, defense response to virus, cell surface receptor signaling pathway, blood coagulation, IFN-1 signaling pathway, response to virus, and bicarbonate transport.

independent of one another and may belong to a similar class of conditions, FPDs. As seen with other FPDs that can exist concurrently such as atherosclerosis and keloids, these conditions are mechanistically independent. This study is limited by the small sample size at a single academic institution; the use of whole-scalp tissue in the microarray analysis; the use of electronic medical record review to confirm UL status; and the small possibility of asymptomatic, undiagnosed ULs in patients with no reported history. Further investigation into the classification of CCCA as an FPD is needed owing to the significant overlap in gene expression with other FPDs, although the simultaneous presence of both ULs and CCCA does not appear to have any impact on disease features. Future studies on potential associations between CCCA and FPDs should primarily focus on the shared molecular signature (e.g., cytokine or chemokine expression) across FPDs rather than a causative or linked relationship of CCCA to any FPD in particular.

MATERIALS AND METHODS

This study was approved by the Johns Hopkins Hospital (Baltimore, MD) institutional review board. All patients underwent written informed consent with authorization from the Johns Hopkins ethics board. A total of 16 patients with CCCA were recruited between 2017 and 2020. The clinical severity of CCCA in these patients was staged using a six-point photographic scale developed by Olsen et al. (2008), with gradation ranging from normal hair density without hair loss (stage 0) to end-stage, fibrotic scalp with permanent hair loss (stage 5) (Olsen et al., 2008). Patients were grouped into the following disease severity categories on the basis of the extent of clinical disease involvement at the time of tissue sample collection: focal (stage 1A through 2B), limited (stage 3A through 4B), and diffuse (stages 5A and 5B) disease involvement.

A 4-mm punch biopsy was obtained from the peripheral, hair-bearing areas of the affected vertex of the scalp in each patient. All patients were either treatment naive or had not received treatment for at least 1 year at the time of tissue specimen collection. History of UL status was documented in each study participant and confirmed through electronic medical record review. Eight patients had a confirmed history of ULs, and eight patients had no history of ULs.

RNA isolation and microarray analysis

Immediately after collection, scalp tissue samples were submerged in a 2-ml tube containing RNAlater (Qiagen, Santa Clarita, CA) stabilization reagent. Samples were subsequently stored at 4 °C for 24 hours and then transferred to a −80 °C freezer for long-term storage. Total RNA was extracted using a Qiagen RNeasy fibrous tissue kit (Qiagen). Standard protocols were followed for total RNA extraction and tissue homogenization. Before microarray analysis, RNA concentration and quality were measured with a bioanalyzer. Gene-level expression through a transcriptome-wide analysis of more than 20,000 well-annotated human genes was measured using Clariom S Assays (Affymetrix, Santa Clara, CA). The first 5 of the final 16 samples were obtained through our previously published microarray study in 2018 (Aguh et al., 2018). Batch effect was corrected for using a two-way ANOVA, with a batch date as the second degree of freedom.

Functional annotation through gene ontology (Database for Annotation, Visualization and Integrated Discovery, version 6.8) was conducted to identify over-represented gene function categories among the top 500 upregulated and downregulated gene transcripts as measured by fold change. Differential gene expression between patients with CCCA with and without ULs was evaluated with the paired-sample two-tailed *t*-test to assess fold changes in gene transcript expression and statistical significance, as measured by *P*-values. Statistical significance was determined at $P < 0.05$.

Data availability statement

The data discussed in this publication have been deposited in National Center for Biotechnology Information's Gene Expression Omnibus and is accessible through Gene Expression Omnibus Series accession number GSE179054 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE179054).

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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