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Fibroproliferative genes are preferentially expressed in central centrifugal cicatricial alopecia

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Abstract

Background: Central centrifugal cicatricial alopecia (CCCA) is a primary cicatricial alopecia that most commonly affects women of African descent. Like CCCA, fibroproliferative disorders (FPDs) such as keloids, atherosclerosis, and fibroids are characterized by low-grade inflammation and irritation, resulting in end-stage fibrosis.

Objective: We sought to determine whether fibroproliferative genes were up-regulated in patients with CCCA.

Methods: A total of 5 patients with biopsy-proven CCCA were recruited for this study. Two scalp biopsy specimens were obtained from each patient; 1 from CCCA-affected vertex scalp and 1 from the unaffected occipital scalp. Microarray analysis was performed to determine the differential gene expression patterns.

Results: There was an upregulation of genes implicated in FPDs in patients with CCCA. Specifically, we noted increased expression of platelet derived growth factor gene (*PDGF*), collagen I gene (*COL I*), collagen III gene (*COL III*), matrix metalloproteinase 1 gene (*MMPI*), matrix metalloproteinase 2 gene (*MMP2*), matrix metalloproteinase 7 gene (*MMP7*), and matrix metalloproteinase 9 gene (*MMP9*) in affected scalp compared with in unaffected scalp. Significant overlap in the canonic pathways was noted between patients with CCCA and patients with both atherosclerosis and hepatic fibrosis ($P < .001$).

Limitations: Small sample size and the use of whole skin tissue for analysis.

Conclusion: We have identified the upregulation of critical genes implicated in FPDs in the gene expression profile of patients with CCCA. These findings may help identify future therapeutic targets for this otherwise difficult-to-treat condition. (*J Am Acad Dermatol* 2018;79:904–12.)

Keywords

alopecia; central centrifugal cicatricial alopecia; cicatricial alopecia; fibroproliferative disorders; fibrosis; therapy

INTRODUCTION

Central centrifugal cicatricial alopecia (CCCA) is a lymphocytic primary cicatricial alopecia that most commonly affects women of African descent, and the pathophysiology of this disease remains a mystery.^{1,2} Although a true prevalence rate has yet to be established, some studies estimate that 1 in 15 black women older than 50 years suffer from this condition.³ Hair loss typically begins on the vertex of the scalp and gradually progresses outward centrifugally.^{1,2,4} Although CCCA can display histologic features that overlap with those of other forms of hair loss, unlike patients with primary cicatricial alopecias, in whom appreciable inflammation is the norm, patients with CCCA can often present with minimal to seemingly absent clinical signs of inflammation on examination.^{1,5,6} Eventually, patients develop diffuse fibrosis, which often occurs out of proportion to the clinical and histologic signs of inflammation.^{1,5}

Pathophysiology of FPDs

Fibroproliferative disorders (FPDs) is an umbrella term that encapsulates a variety of conditions characterized by aberrant wound healing and excessive fibrosis. Like CCCA, FPDs such as systemic sclerosis, keloids, atherosclerosis, and uterine fibroids (UFs) are all characterized by persistent low-grade inflammation and irritation that results in end-stage fibrosis.^{7,8} The risk of certain FPDs is increased in people of African descent, and this increased risk is thought to be secondary to the protective effect that profibrotic alleles offer against helminths found in Sub-Saharan Africa.^{8,9}

In normal wound healing, injury to the skin induces a cascade of events that begins with clot formation and hemostasis.¹⁰ The amount of collagen deposited in wounds is controlled by a delicate balance of extracellular matrix (ECM) deposition and degradation. However, in FPDs this equilibrium is disturbed, leading to excess ECM deposition and persistent fibrogenesis that occurs independently of sustained inflammation. Although there is heterogeneity of up-regulated markers between FPDs, a number of genes have been consistently implicated in the pathogenesis of FPDs. These include transforming growth factor beta gene (*TGFB*), platelet derived growth factor gene (*PDGF*), vascular endothelial growth factor gene (*VEGF*), matrix metalloproteinase matrix metalloproteinase gene 1 (*MMP1*), matrix metalloproteinase matrix metalloproteinase gene 2 (*MMP2*), matrix metalloproteinase matrix metalloproteinase gene 7 (*MMP7*), and matrix metalloproteinase matrix metalloproteinase gene 9 (*MMP9*) among others.^{10–14}

Overlap between FPDs and CCCA

This process of excess fibrosis leading to permanent scar tissue formation in FPDs is similar to the process seen in CCCA, in which thick fibrous tracts replace hair follicles.¹ A recent study has shown that UFs are nearly 5 times more common in women with CCCA than in race-and sex-matched controls.⁹ Given that CCCA and FPDs most commonly affect patients of African descent, coupled with the association between CCCA and a common FPD, we sought to determine the overlap in gene expression between CCCA and other FPDs.

METHODS

This study was approved by the Johns Hopkins Hospital institutional review board. Informed consent was obtained from all patients with approval from the Johns Hopkins ethics board. A total of 5 patients with biopsy-proven CCCA were recruited for this study. Two scalp biopsy specimens were obtained from each patient; 1 from CCCA-affected vertex scalp and 1 from the unaffected occipital scalp, which served as an intrascap control. No patients had received treatment for CCCA before the skin sampling.

RNA isolation and microarray analysis

Once obtained, fresh tissue samples were immediately submerged in a 2-mL tube containing RNA_{later} (Qiagen, Valencia, CA) stabilization reagent. Tissue was stored at 4°C for 24 hours and then transferred to a freezer for long-term storage at -80°C. Total RNA was extracted by using a Qiagen RNeasy fibrous tissue kit (Qiagen, Valencia, CA). Tissue homogenization and total RNA extraction were performed according to the standard protocols. Bioanalyzer measurements of RNA quality and concentration measurements were performed before microarray analysis.

Samples were analyzed by using the Affymetrix Clariom S microarray (Affymetrix, Santa Clara, CA), which provides transcriptome-wide analysis of more than 20,000 well-annotated human genes, interrogating all known exons. The array data were imported and normalized by using the Robust Multi-Array Averaging protocol with the Partek Genomics Suite analytic platform (version 6.6, Partek, Inc., Chesterfield, MO).

Functional annotation was conducted via gene ontology, which allowed for identification of over-represented gene function categories among up-regulated or down-regulated genes to better understand the gene profile results. Special attention was paid to gene products that have been implicated in FPDs and other cicatricial alopecias.

Differential gene expression between the experimental classes was evaluated with the paired-sample 2-tailed *t* test algorithm to determine the transcripts' fold changes and their statistical significance, as measured by the standard deviation (SD) (from unchanged) and *P* values.

RESULTS

Gene expression patterns between affected scalp and intrascap paired healthy controls were directly compared with each other. More than 21,000 genes were identified and arranged by fold change. A total of 858 genes were noted to have a fold change of more than 2 SDs. Of those, 413 were up-regulated and 445 were down-regulated in affected scalp.

Increased expression of genes that regulate fibrosis and are implicated in FPDs

The genes that were noted to be up-regulated in CCCA-affected scalp tissue include several implicated in FPDs and the regulation of fibroblast proliferation (Fig 1). The largest group of up-regulated genes consisted of those involved in ECM organization. A total of 30 of 188 genes regulating ECM organization were noted to be up-regulated ($P < .001$ [Table I]). These

included fibroblast activation protein alpha gene (*FAP*); collagen I gene (*COL1*), collagen III gene (*COL3*), collagen V gene (*COL5*), collagen XI gene (*COL11*), and fibrillin 1 gene (*FBN1*), as well as genes involved in cell adhesion, such as integrin and laminin subunits. In addition, *MMP1*, *MMP2*, *MMP7*, *MMP9*, matrix metalloproteinase gene 13 (*MMP13*), and matrix metalloproteinase gene 15 (*MMP15*) were all up-regulated more than 2 SDs above the mean based on fold change.

The role of MMPs in FPDs has been studied extensively.^{11,12} Although the role of MMPs is to break down ECM, certain MMPs have been implicated in FPDs such as idiopathic pulmonary fibrosis (IPF) and hepatic fibrosis.¹¹ In particular, *MMP1*, *MMP2*, *MMP7*, matrix metalloproteinase gene 8 (*MMP8*), and *MMP9* have all been associated with increased fibrosis and are up-regulated in certain FPDs.^{11,13} Both *MMP2* and *MMP9* have been associated with fibrocyte migration to healing tissue, which is the source of myofibroblasts implicated in fibrosis.¹¹ *MMP1* and *MMP7* are also consistently up-regulated in IPF and have been suggested as possible biomarkers of disease.¹¹

Of note, 6 of the 50 genes known to regulate fibroblast proliferation showed increased expression in CCCA tissue, including fibronectin 1 (*FN1*), platelet derived growth factor receptor alpha gene (*PDGFRA*), and platelet derived growth factor receptor beta gene (*PDGFRB*) ($P = .024$). *FN1* and *PDGF* have both been implicated in the pathogenesis of FPDs.¹⁰ *PDGF* plays a key role in the migration and proliferation of fibroblasts and also stimulates the recruitment of myofibroblasts, which are a key cell regulator of fibroproliferation.^{11,12} In turn, these myofibroblasts secrete fibronectin, which further encourages excess ECM deposition.

Additionally, 13 of 45 genes noted to regulate endodermal cell differentiation were up-regulated in affected tissue (including several collagens, cell adhesion molecules such as integrin and laminin subunits, and MMPs) ($P < .001$). Together, these genes reflect the increased collagen turnover and ECM remodeling that form a key component of sustained fibrosis seen in patients with FPDs.^{10,12,14}

Finally, 12 of 39 genes associated with organization of collagen fibril were preferentially expressed in diseased tissue ($P < .001$).

Decreased expression of genes regulating lipid metabolism and biosynthesis of fatty acids

The genes that were down-regulated in CCCA-affected tissue include those with roles in lipid metabolism, the hair cycle, and fatty acid biosynthesis (Table II). In CCCA-affected scalp, 66 of 836 genes that regulate the lipid metabolic process were down-regulated ($P < .001$).^{15–17} This includes genes such as apolipoprotein C1 gene (*APOC1*), apolipoprotein E gene (*APOE*), ELOVL fatty acid elongase 3 gene (*ELOVL3*), ELOVL fatty acid elongase 3 gene (*ELOVL5*), fatty acid 2-hydroxylase gene (*FA2H*), and stearoyl-CoA desaturase 5 gene (*SCD5*). Lipids play an important role in hair follicle homeostasis, and members of the SCD family have been found to play a role in maintaining sebaceous glands.¹⁸ Transgenic mice lacking stearoyl-CoA desaturase 1 gene (*SCD1*) display a depletion of sebaceous lipids and alopecia and are proposed to be a model for scarring alopecia.¹⁸ Similarly, the loss of

FA2H has been linked to altered sebum composition and cyclic alopecia in the mouse model.¹⁹

Of 34 genes that are related to the biosynthesis of unsaturated fatty acids, 7 were down-regulated in scalp tissue affected by CCCA ($P < .001$). *ELOVL3* was notable among these 7 genes, as *ELOVL3*-deficient mice have been found to exhibit a hyper-plastic pilosebaceous system and a sparse hair coat.²⁰ Lastly, 13 of 89 genes associated with the hair cycle process, including leucine-rich repeat-containing G protein coupled receptor 5 gene (*LGR5*), were down-regulated in diseased tissue. *LGR5*-positive cells belong to a stem cell population that is able to generate new hair follicles and maintain hair follicle cell lineages over a long period of time.^{21,22} Additionally, loss of *LGR5* has been found in the affected scalp of men with androgenetic alopecia.²²

Ingenuity pathway analysis

We analyzed our microarray data by using Qiagen's Ingenuity Pathway Analysis (IPA) software. IPA is a robust bioinformatics search tool that utilizes the Ingenuity Knowledge Base to identify the most significant pathways within a data set. Our data showed that of all the canonic pathways analyzed with Qiagen IPA software, the greatest overlap was displayed by the hepatic fibrosis (16.5% overlap) and atherosclerosis signaling (18% overlap) pathways, both of which are PFDs (Table III).

DISCUSSION

To our knowledge, this is the first published study of gene expression patterns in patients with CCCA. In this study, we used DNA microarrays to determine whether there is increased expression of fibroproliferative genes in patients with CCCA by comparing the expression profile of CCCA with that of other known FPDs. Through the use of IPA software, we found that our CCCA microarrays displayed the greatest overlap with hepatic fibrosis and atherosclerosis, which are 2 well-known FPDs. This discovery correlated with our findings revealing that several genes responsible for fibroblast activation, excess collagen deposition, and aberrant wound healing were up-regulated in CCCA-affected scalp compared with in unaffected scalp. A thorough review of the current literature showed a substantial overlap between the expression pattern of fibroproliferative genes in patients with CCCA and that in patients with other known FPDs (Table IV,^{14,23–63}). Of note, CCCA displayed the greatest overlap with IPF and UFs. This finding is supported by a prior study by our group in which we found that patients with CCCA are more likely to develop fibroids than their counterparts are.⁹ Additionally, we noted increased expression of *PDGF*, *COL1*, *COL2*, *COL3*, *MMP1*, *MMP2*, *MMP7*, and *MMP9*, all of which have been implicated in other FPDs.^{13,14,23} The increased expression of these select MMPs is particularly notable. Though MMPs are typically responsible for collagen catabolism, certain MMPs are thought to induce fibrocyte migration, eventually giving rise to myofibroblasts, which are the key cell type responsible for the excess fibrosis seen in FPDs.¹³

We also noted a decrease in genes that regulate lipid metabolism. Aberrant lipid metabolism has been implicated in other forms of alopecia, namely, lichen planopilaris.^{64,65} Specifically, the decreased expression of peroxisome proliferator associated receptor gamma (*PPARG*) is

thought to incite an inflammatory response that leads to destruction of the pilosebaceous unit in primary scarring alopecias.^{64,65} Interestingly, no difference was noted in *PPARG* expression when CCCA-affected scalp was compared with unaffected scalp; instead, there might be adjustments of protein abundance or modification that were not tested here. This may suggest that the *PPARG* transcriptional changes are not a primary mediator of this phenotype of cicatricial alopecia seen in patients with CCCA.

Although there are no consensus treatments for CCCA, the mainstay of therapy remains anti-inflammatory medications such as topical and intralesional steroids, and the response is often disappointing.^{1,4} However, unlike in patients with other primary cicatricial alopecias, it is not unusual for patients with CCCA to present without appreciable inflammation on the scalp, even as the disease is progressing.^{1,5,6} Patients with early-stage CCCA, however, may exhibit a lymphocytic infiltrate on histology.^{1,4}

In FPDs, though inflammation is often the inciting event that leads to fibrosis, persistent fibrogenesis occurs independent of sustained inflammation.^{10,66} This may partially explain the limited efficacy of anti-inflammatory medications in FPDs.¹⁰ We propose that a similar consideration be made in patients with CCCA. Though the cause of initial irritation to the scalp remains unclear, it may be attributed to 1 of many factors, including hair styling practices, seborrheic dermatitis, and subclinical inflammation due to androgenetic alopecia. Any one of these factors may spur long-term persistent fibrogenesis, even in the absence of continued inflammation. Although anti-inflammatory therapies are helpful to some patients, they may not be sufficient to halt disease progression in all patients, as has been the experience of 2 of our authors (C.A. and L.G.). Investigation of the use of therapies targeting fibrosis in the treatment of CCCA may be warranted, as such therapies have shown some promise in other FPDs.^{67–69} Our data suggest that losartan, atorvastatin, and lovastatin may be reasonable therapeutic targets that are worthy of further investigation in CCCA (Supplemental Fig 1, A–C; available at <http://www.jaad.org>). However, FPDs are notoriously difficult to treat, and further research is required to identify targeted therapies for fibrosis.

This study is limited by the use of a small sample of patients and the use of whole skin tissue for analysis. Future studies may glean more information about the fibroproliferative properties of CCCA by isolating the gene expression patterns of fibroblasts in diseased scalp. Further studies are needed to establish a mechanistic pathway for the development of CCCA. Here, we have identified the upregulation of critical genes implicated in FPDs in the gene expression profile of patients with CCCA. These findings may help identify future therapeutic targets for this otherwise difficult-to-treat condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used:

CCCA	central centrifugal cicatricial alopecia
ECM	extracellular matrix
FPD	fibroproliferative disorder
IPA	Ingenuity Pathway Analysis
IPF	idiopathic pulmonary fibrosis
SD	standard deviation
UF	uterine fibroid

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CAPSULE SUMMARY

- Both central centrifugal cicatricial alopecia (CCCA) and fibroproliferative disorders commonly affect patients of African descent.
- Critical genes implicated in fibroproliferative disorders are up-regulated in CCCA-affected scalp tissue.
- Antifibrotic therapies may play a role in the treatment of CCCA.

Fig 1.

A total of 21,000 genes were analyzed via microarray analysis. Fibroproliferative genes of interest are highlighted. Up-regulated genes (>2 standard deviations [SDs]) are noted in red, unchanged genes (<2 SDs) are noted in gray, and down-regulated genes are noted in blue. *CCCA*, Central centrifugal cicatricial alopecia; *COL1A1*, collagen type I alpha 1 chain gene; *COL1A2*, collagen type II alpha 1 chain gene; *COL3A1*, collagen type III alpha 1 chain gene; *COL5A1*, collagen type V alpha 1 chain gene; *COL5A2*, collagen type V alpha 2 chain gene; *Ctrl*, control; *FAP*, fibroblast activation protein alpha gene; *FC*, fold change; *FN1*, fibronectin 1 gene; *IGF1*, insulin-like growth factor 1 gene; *MMP1*, matrix metalloproteinase 1 gene; *MMP2*, matrix metalloproteinase 2 gene; *MMP7*, matrix metalloproteinase 7 gene; *MMP8*, matrix metalloproteinase 8 gene; *MMP9*, matrix metalloproteinase 9 gene; *PDGFRA*, platelet derived growth factor receptor alpha gene; *PDGFRB*, platelet derived growth factor receptor beta gene; *Pt*, patient; *TGFB1*, transforming growth factor beta 1 gene; *TGFB2*, transforming growth factor beta 2 gene; *VEGFA*, vascular endothelial growth factor A gene; *VEGFB*, vascular endothelial growth factor B gene.

Table 1.

Up-regulated transcripts in CCCA-affected tissue

Biological process	Transcripts	No. of genes affected	P value
Positive regulation of fibroblast proliferation	<i>FNI, PDGFRB, PDGFRA, EREG, LIG4, JUN</i>	6/50	.024
Positive regulation of cell proliferation	<i>ATF3, CXCL10, EFN2, EREG, ETS1, ETV5, FNI, FOSL1, HAS2, HGF, HOXC10, IL6, INS, KDR, LYN, NTRK3, PAK1, PDGFRA, PDGFRB, PRAMEF8, PROX1, PTHIR, PTN, SFRP2, SOX9, STOX1, TGFB2, TNFSF13, TN53</i>	29/463	.045
Positive regulation of cell proliferation by VEGF-activated PDGF	<i>PDGFRB, PDGFRA</i>	2/3	.006
Collagen fibril organization	<i>COL11A1, COL12A1, COL14A1, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, LOX, LUM, SFRP2, TGFB2</i>	12/39	<.001
Regulation of immune system process	<i>ADGRF5-B75:B116, AQP3, BTK, BTLA, C12orf4, CCL20, CCL24, CCR7, CD274, CD28, CD96, CEACAM1, COL3A1, CXCL10, CXCL13, DAPK2, EFN2, ETS1, FBN1, FCER1G, FOS, GAL, GATA2, GRAP2, IGLL5, IL36B, IL6, INHBA, JUN, L3MBTL1, LILRB3, LRR17, LTF, LYN, MAFB, NCK1, NCKAP1L, PAK1, PIP, PLA2G7, PPBP, RPK3, SERPINE1, SLC9B2, SNX4, SOX9, TGFB2, THPO, THY1, TMEM176B, TNFRSF21, ZNF675, ZNF683</i>	53/730	<.001
ECM organization	<i>ADAMTS4, COL11A1, COL12A1, COL14A1, COL1A1, COL1A2, COL3A1, COL4A1, COL5A1, COL5A2, COL6A1, COL6A2, COL6A3, CTSK, CTSV, EGFL6, ETS1, FAP, FBN1, FNI, HAS2, ICAM2, ITGA5, ITGA8, KDR, KLKB1, LAMA2, LAMB1, LOX, LUM, MFAP2, MMP13, MMP15, MMP2, MMP7, MMP9, NID1, NID2, POSTN, RAMP2, SERPINE1, SFRP2, SOX9, SPARC, SULF1, TGFB2, VIT</i>	30/188	<.001
Endodermal cell differentiation	<i>COL11A1, COL12A1, COL5A1, COL5A2, COL6A1, FNI, GATA6, INHBA, ITGA5, LAMB1, MMP15, MMP2, MMP9</i>	13/45	<.001

ADAMTS4, ADAM metalloproteinase with thrombospondin type 1 motif 4 gene; *ADGRF5*, adhesion G protein-coupled receptor F5 gene; *AQP3*, aquaporin 3 (Gill blood group) gene; *ATF3*, activating transcription factor 3 gene; *BTK*, Bruton tyrosine kinase gene; *BTLA*, B and T lymphocyte associated gene; *C12orf4*, C12ORF50 chromosome 12 open reading frame 4 gene; *CCCA*, central centrifugal cicatricial alopecia; *CCL20*, C-C motif chemokine ligand 20 gene; *CCR7*, C-C motif chemokine receptor 7 gene; *CD274*, CD274 molecule gene; *CD28*, CD28 molecule gene; *CD96*, CD96 molecule gene; *CEACAM1*, carcinoembryonic antigen related cell adhesion molecule 1 gene; *COL11A1*, collagen type XI alpha 1 chain gene; *COL12A1*, collagen type XII alpha 1 chain gene; *COL14A1*, collagen type XIV alpha 1 chain gene; *COL1A1*, collagen type I alpha 1 chain gene; *COL1A2*, COL1A1 collagen type I alpha 1 chain gene; *COL3A1*, collagen type III alpha 1 chain gene; *COL4A1*, collagen type IV alpha 1 chain gene; *COL5A1*, collagen type V alpha 1 chain gene; *COL5A2*, collagen type V alpha 2 chain gene; *COL6A1*, collagen type VI alpha 1 chain gene; *COL6A2*, collagen type VI alpha 2 chain gene; *COL6A3*, collagen type VI alpha 3 chain gene; *CTSK*, cathepsin K gene; *CTSV*, cathepsin V gene; *CXCL10*, C-X-C motif chemokine ligand 10 gene; *CXCL13*, C-X-C motif chemokine ligand 13 gene; *DAPK2*, death associated protein kinase 2 gene; *ECM*, extracellular matrix; *EFNB2*, ephrin B2 gene; *EGFL6*, EGF like domain multiple 6 gene; *EREG*, epiregulin gene; *ETS1*, ETS proto-oncogene 1 transcription factor gene; *ETV5*, ETS variant 5 gene; *FAP*, fibroblast activation protein alpha gene; *FBN1*, fibrillin 1 gene; *FCER1G*, F fragment of IgE receptor Ig gene; *FNI*, fibronectin 1 gene; *FOS*, Fos proto-oncogene, AP-1 transcription factor subunit gene; *FOSL1*, FOS like AP-1 transcription factor subunit gene; *GAL*, galanin and GMAP prepropeptide gene; *GATA2*, GATA binding protein 2 gene; *GRAP2*, GRB2 related adaptor protein 2 gene; *HAS2*, hyaluronan synthase 2 gene; *HGF*, hepatocyte growth factor gene; *HOXC10*, homeobox C10 gene; *ICAM2*, intercellular adhesion molecule 2 gene; *IGLL5*, immunoglobulin lambda like polypeptide 5 gene; *IL6*, interleukin 6 gene; *IL36B*, interleukin 36 beta gene; *INHBA*, inhibin subunit beta A gene; *INS*, insulin gene; *ITGA5*, integrin subunit alpha 5 gene; *ITGA8*, integrin subunit alpha 8 gene; *JUN*, Jun proto-oncogene, AP-1 transcription factor subunit gene; *KDR*, kinase insert domain receptor gene; *KLKB1*, kallikrein B1 gene; *L3MBTL1*, L3MBTL1, histone methyllysine binding protein gene; *LAMA2*, laminin subunit alpha 2 gene; *LAMB1*, laminin subunit beta 1 gene; *LIG4*, DNA ligase 4 gene; *LILRB3*, leukocyte immunoglobulin like receptor B3 gene; *LOX*, gene; *LRR17*, leucine rich repeat containing 17 gene; *LTF*, lactoferrin gene; *LUM*, lumican gene; *LYN*, LYN proto-oncogene, Src family tyrosine kinase gene; *MAFB*, MAF bZIP transcription factor B gene; *MFAP2*, microfibril associated protein 2 gene; *MMP13*, 2, 7, 9, 13, and 15, matrix metalloproteinase 1, 2, 7, 9, 13, and 15 genes; *NCK1*, NCK adaptor protein 1 gene; *NCKAP1L*, NCK associated protein 1 like gene; *NID1*, nidogen 1 gene; *NID2*, nidogen 2 gene; *NTRK3*, neurotrophic receptor tyrosine kinase 3 gene; *PAK1*, p21 (RAC1) activated kinase 1 gene; *PDGF*, platelet-derived growth factor; *PDGFRA*, platelet derived growth factor receptor alpha gene; *PDGFRB*, platelet derived growth factor receptor beta 1 gene; *PPBP*, pro-platelet basic protein gene; *PRAMEF8*, PRAME family member 8 gene; *PROX1*, prospero homeobox 1 gene; *PTHIR*, parathyroid hormone 1 receptor group VII gene; *POSTN*, periostin gene; *PPBP*, pro-platelet derived growth factor; *PDGFRA*, platelet derived growth factor receptor alpha gene; *PIP*, prolactin induced protein gene; *PLA2G7*, phospholipase A2 frizzled related protein 2 gene; *SLC9B2*, solute carrier family 9 member B2 gene; *SNX4*, sorting nexin 4 gene; *SNX9*, sorting nexin 9 gene; *SPARC*, secreted protein acidic and cysteine rich gene; *STOX1*, storkhead box 1 gene; *SULF1*, sulfatase 1 gene; *TGFB2*, transforming growth factor beta 2 gene; *THPO*, thrombopoietin gene; *THY1*, Thy-1 cell surface antigen gene; *TMEM176B*, transmembrane protein

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176B gene; *TNFRSF21*, TNF receptor superfamily member 21 gene; *TNFSF13*, TNF superfamily member 13 gene; *TNS3*, tensin 3 gene; *VEGF*, vascular endothelial growth factor; *VIT*, vitrin gene; *ZNF675*, zinc finger protein 675 gene; *ZNF683*, zinc finger protein 683 gene.

Table II.

Down-regulated transcripts in CCCA-affected tissue

Biological process	Transcripts	No. of genes affected	P value
Lipid metabolic process	<i>ACSM3, ACSM6, ADGRF5, AGPAT1, AGTRI, ALOX15B, APOC1, APOE, AWAT2, CCR7, CEACAM1, CH25H, DECR2, EGRI, ELOVL3, ELOVL5, ESYT3, FABP9, FADS1, FADS2, FAR2, FAXDC2, GAL, HAO2, HMGCS2, HRASLS2, IDI1, INPP4B, INS, INSIG1, ISPD, LIPH, LIPK, LRP8, LYN, MOGAT2, MOGAT3, NR1D1, OLAH, PDGFRB, PDGFRB, PIGL, PLA2G2A, PLA2G2E, PLA2G3, PLA2G4C, PLA2G7, PLAU, PLBD1, PLD6, PLTP, PM20D1, PNPLRP3, PNPLA5, PPARGC1A, PRKAA2, PROX1, PTGDS, SC5D, SIRT4, SLC44A5, STS, TECRL, TRPV1, UGT2B7</i>	66/836	<.001
Unsaturated fatty acid biosynthetic process	<i>ALOX15B, DECR2, ELOVL3, ELOVL5, FADS1, FADS2, PTGDS</i>	7/34	<.001

ACSM3, Acyl-CoA synthetase medium chain family member 3 gene; *ACSM6*, acyl-CoA synthetase medium chain family member 6 gene; *ADGRF5*, adhesion G protein-coupled receptor F5 gene; *AGPAT1*, 1-acylglycerol-3-phosphate O-acyltransferase 1 gene; *AGTRI*, angiotensin II receptor type 1 gene; *ALOX15B*, arachidonate 15-lipoxygenase, type B gene; *APOC1*, apolipoprotein C1 gene; *APOE*, apolipoprotein E gene; *AWAT2*, acyl-CoA wax alcohol acyltransferase 2 gene; *CCCA*, central centrifugal cicatricial alopecia; *CCR7*, C-C motif chemokine receptor 7 gene; *CEACAM1*, carcinoembryonic antigen related cell adhesion molecule 1 gene; *CH25H*, cholesterol 25-hydroxylase gene; *DECR2*, 2,4-dienoyl-CoA reductase 2 gene; *EGRI*, early growth response 1 gene; *ELOVL3*, ELOVL fatty acid elongase 3 gene; *ELOVL5*, ELOVL fatty acid elongase 5 gene; *ESYT3*, extended synaptotagmin 3 gene; *FABP9*, fatty acid 2-hydroxylase gene; *FABP9*, fatty acid binding protein 9 gene; *FADS1*, fatty acid desaturase 1 gene; *FADS2*, fatty acyl-CoA reductase 2 gene; *FAXDC2*, fatty acid hydroxylase domain containing 2 gene; *GAL*, galanin and GMAP prepropeptide gene; *HAO2*, hydroxyacid oxidase 2 gene; *HMGCS2*, 3-hydroxy-3-methylglutaryl-CoA-synthase 2 gene; *HRASLS2*, HRAS like suppressor 2 gene; *IDI1*, isopentenyl-diphosphate delta isomerase 1 gene; *INPP4B*, inositol polyphosphatase type 1 B gene; *INS*, insulin gene; *INSIG1*, insulin induced gene 1 gene; *ISPD*, isoprenoid synthase domain containing gene; *LIPH*, lipase H gene; *LIPK*, lipase family member K gene; *LRP8*, LDL receptor related protein 8 gene; *LYN*, LYN proto-oncogene, Src family tyrosine kinase gene; *MOGAT2*, monoacylglycerol O-acyltransferase 2 gene; *MOGAT3*, monoacylglycerol O-acyltransferase 3 gene; *NR1D1*, nuclear receptor subfamily 1 group D member 1 gene; *OLA*, oleoyl-ACP hydrolase gene; *PDGFRB*, platelet derived growth factor receptor alpha gene; *PDGFRB*, platelet derived growth factor receptor beta gene; *PIGL*, phosphatidylinositol glycan anchor biosynthesis class L gene; *PLA2G2A*, phospholipase A2 group IIA gene; *PLA2G2E*, phospholipase A2 group IIE gene; *PLA2G3*, phospholipase A2 group IVC gene; *PLA2G7*, phospholipase A2 group VII gene; *PLAUR*, plasminogen activator, urokinase receptor gene; *PLBD1*, phospholipase B domain containing 1 gene; *PLD6*, phospholipase D family member 6 gene; *PLTP*, phospholipase D family member 6 gene; *PM20D1*, peptidase 20 domain containing 1 gene; *PNLIPRP3*, pancreatic lipase protein related protein 3 gene; *PNPLA5*, patatin like phospholipase domain containing 5 gene; *PPARGC1A*, PPARG coactivator 1 alpha gene; *PRKAA2*, protein kinase AMP-activated catalytic subunit alpha 2 gene; *PROX1*, prospero homeobox 1 gene; *PTGDS*, prostaglandin D2 synthase gene; *SC5D*, sterol-C5-desaturase gene; *SIRT4*, sirtuin 4 gene; *SLC44A5*, solute carrier family 44 member 5 gene; *STS*, steroid sulfatase gene; *TECRL*, trans-2,3-enoyl-CoA reductase like gene; *TRPV1*, transient receptor potential cation channel subfamily V member 1 gene; *UGT2B7*, UDP glucuronosyltransferase family 2 member B7 gene.

Table III.

Top canonic pathways displaying overlap with CCCA

Pathway	Overlap (%)	P value
Hepatic fibrosis/hepatic stellate cell activation	16.5	<.001
Atherosclerosis signaling	18	<.001
Granulocyte adhesion and diapedesis	14.2	<.001
Agranulocyte adhesion and diapedesis	12.8	<.001
GP6 signaling pathway	13.8	<.001

CCCA, Central centrifugal cicatricial alopecia; GP6, glycoprotein VI platelet.

Table IV.

Up-regulated and down-regulated genes in various fibroproliferative disorders

Gene symbol	CCCA*	Keloids	Hypertrophic scar	Systemic sclerosis	Idiopathic pulmonary fibrosis	Uterine fibroids
<i>TGFBI</i>	Unchanged	↑14,23	↑14	↑24	↑25	↑26
<i>PDGFB, PDGFC</i>	↑	↑14	↑14	↑27	↑28	↑29
<i>IGF1</i>	Unchanged	↑14	↑14	↑30	↑31	↑32
<i>COL1A1</i>	↑	↑33	↑34	↑35	↑36	↑37
<i>COL1A2</i>	↑	↑38	↑14	↑39	↑40	↑41
<i>COL3A1</i>	↑	↑42	↑14	↑43	↑44	↑41
<i>FN1</i>	↑	↑14	↑45	↑46	↑47	↑48
<i>VEGF</i>	Unchanged	↑49	↑50	↑51	↓52	↑33
<i>PTEN</i>	Unchanged	↓53	↓54	↓55	↓56	↑57
<i>MMP1</i>	↑	↓33,58	↓33,58	↓43	↑59	↑37
<i>MMP2</i>	↑	↑58	↓58	↓60	↑13	↑37,48
<i>MMP7</i>	↑	Unchanged ³³	↓61	↑62	↑59	↑37
<i>MMP9</i>	↑	↓33,58	↓33,58	↑63	↑59	↑37

Upward arrows indicate upregulation, and downward arrows indicate downregulation.

COL1A1, Collagen type I alpha 1 chain gene; *COL1A2*, collagen type II alpha 1 chain gene; *COL3A1*, collagen type III alpha 1 chain gene; *FN1*, fibronectin 1 gene; *IGF1*, insulin-like growth factor 1 gene; *MMP1*, matrix metalloproteinase 1 gene; *MMP2*, matrix metalloproteinase 2 gene; *MMP7*, matrix metalloproteinase 7 gene; *MMP8*, matrix metalloproteinase 8 gene; *MMP9*, matrix metalloproteinase 9 gene; *PDGFB*, platelet derived growth factor subunit B gene; *PDGFC*, platelet derived growth factor subunit C gene; *PTEN*, phosphatase and tensin homolog gene; *TGFBI*, transforming growth factor beta 1 gene; *VEGF*, vascular endothelial growth factor gene.

* Upregulated genes are based on fold change of more than 2 standard deviations compared with unaffected scalp.