# Hair Loss Update

Curtis T. Thompson, M.D. CTA Pathology and Clinical Professor of Dermatology and Pathology Oregon Health & Sciences University







## Normal Follicular Size

■ 4:1 Terminal:Vellus ♦ Terminal Bulbs in subcutis Thicker than 0.06mm ♦ Vellus or Miniaturized  $\sqrt{\frac{1}{2}}$  diameter of terminal (0.03mm) Inner root sheath as thick as hair shaft Not pigmented

## Normal



## Anatomic site variation in size



Otberg N et al. Variations of Hair Follicle Size and Distribution in Different Body Sites. J Invest Dermatol 122:14-19, 2004.

## Pathologic Miniaturization



Zhou, C., Li, X., Wang, C. *et al.* Alopecia Areata: an Update on Etiopathogenesis, Diagnosis, and Management. *Clinic Rev Allerg Immunol* **61**, 403–423 (2021). https://doi.org/10.1007/s12016-021-08883-0

# Miniaturization ?Pathologic?



TOUTO

Miniaturization Two primary diagnoses

Female/male pattern hair loss
Androgenetic
Senescence
Alopecia areata

## Alopecia areata?



## Alopecia Areata-like Pattern

- Psoriasis
- Lupus erythematosus
- Syphilis
- Permanent chemotherapy induced alopecia (pCIA)
- Systemic amyloidosis
- Linear morphea (en coup de sabre)

> Science. 1998 Jan 30;279(5351):720-4. doi: 10.1126/science.279.5351.720.

## Alopecia universalis associated with a mutation in the human hairless gene

W Ahmad <sup>1</sup>, M Faiyaz ul Haque, V Brancolini, H C Tsou, S ul Haque, H Lam, V M Aita, J Owen, M deBlaquiere, J Frank, P B Cserhalmi-Friedman, A Leask, J A McGrath, M Peacocke, M Ahmad, J Ott, A M Christiano



# Cell cycle phases



## Anagen phase = Hair length





## More catagen = Shorter hair



## Meaning of catagen/telogen

Shorter growth cycleStuck in catagen/telogen





## Evolution toward human hairlessness

Decreased hair cover
Increased eccrine sweat gland density
Increase subcutaneous fat thickness

## Hair density





## Hair density



## Why evolve to less hair cover?

Temperature Regulation
 Changing behavior

 Hunting in the day—safer
 Fire—temperature control better
 Clothing



Brown JG. Ticks, Hair loss, and non-clinging babies: a novel tick-based hypothesis for the evolutionary divergence of humans and chimpanzees. *Life* 11(5):, 135, **2021.** 

## Human Hairless Gene

### Figure 2

From: Molecular evolution of HR, a gene that regulates the postnatal cycle of the hair follicle



#### Molecular evolution of *HR* in primates.

Ka and Ks values were estimated for each branch of the HR tree with the reconstructed sequences at ancestral nodes. Number above the lineage indicates the minimum number of amino acid replacements to explain differences among reconstructed sequences. Ka/Ks ratios are shown below branches. Branch lengths are drawn arbitrarily and do not reflect evolutionary time.

# 2.5x higher density of eccrine glands on forehead



# Follicular density varies with anatomic site



Otberg N et al. Variations of Hair Follicle Size and Distribution in DifferentBody Sites. J Invest Dermatol 122:14-19, 2004.

## Hairlessness = Better cooling

Decreased hair cover—better evaporation
 Increased eccrine sweat gland density

 10x higher than chimpanzee and macaque
 2.5x higher density on forehead

### HR Mutation

CANTÚ ET AL.

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Autosomal recessive inheritance of atrichia congenita

J. M. CANTÚ, J. SÁNCHEZ-CORONA, A. GONZÁLEZ-MENDOZA, R. MARTÍNEZ Y MARTÍNEZ AND D. GARCÍA-CRUZ

Divisiones de Genética y Hematología y de Patología Experimental, Subjefatura de Investigación Científica, Unidad de Investigación Biomédica, Centro Médico de Occidente, Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico

Two families, each with two sibs presenting atrichia congenita, were studied. Histopathological studies of scalp biopsies from affected areas revealed absence of hair follicles. The pedigree data were interpreted as corroborative of a previously postulated autosomal recessive pattern of inheritance.

# Size of hair Anagen/catagen—length Density

Cantu JM et al. 17(3):209-12, 1980



Fig. 1. Family A. Pedigree and facial appearance of the propositi. The girl (left) was more severely affected.

> Science. 1998 Jan 30;279(5351):720-4. doi: 10.1126/science.279.5351.720.

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## Unintended consequence of evolution?



Advances in Anthropology, 2015, 5, 274-281 Published Online November 2015 in SciRes. <u>http://www.scirp.org/journal/aa</u> http://dx.doi.org/10.4236/aa.2015.54021



## **Evolution of Long Head Hair in Humans**

#### **Peter Frost**

Department of Anthropology, Université Laval, Quebec City, Canada Email: peter\_frost61z@globetrotter.net

Received 26 September 2015; accepted 3 November 2015; published 6 November 2015

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## The Evolution of Beauty

How Darwin's Forgotten Theory of Mate Choice Shapes the Animal World

Richard O. Prum

"Reads like a memoir, argues like a manifesto, and shines with... passion for all things ornithological." —Science

## Conclusion

• What we see in the microscope: ◆ Size--Miniaturization for hairlessness ◆ Density—increase for perspiration (eccrine) ◆ Cell cycle--Short anagen for short hairs Evolution: Temperature control, infestation control, and behavioral change Hypothesis: Some hair loss diseases are unintended consequences of evolution

LPP (FFA) is not unlike Lichen Planus









https://dermnetnz.org/topics/lichen-planus-pathology

Arch Dermatol. 1994 Jun;130(6):770-4.

## Postmenopausal frontal fibrosing alopecia. Scarring alopecia in a pattern distribution.

Kossard S<sup>1</sup>.

Author information 
 Papers

#### Erratum in

Arch Dermatol 1994 Nov;130(11):1407.

#### Abstract

**BACKGROUND:** Recession of the frontal hairline is a common event in postmenopausal women. This has been shown not to be a marker of gross androgenization, and is usually a progressive nonscarring alopecia. Six postmenopausal women, who developed a progressive frontal scarring alopecia, were studied and their clinical and laboratory data, as well as the results of scalp biopsy specimens in all six patients, were analyzed and compared with recognized forms of scarring alopecia and recently described findings in androgenetic alopecia.

**OBSERVATIONS:** The six postmenopausal women developed a progressive frontal hairline recession that was associated with perifollicular erythema within the marginal hairline, producing a frontal fibrosing alopecia extending to the temporal and parietal hair margins. Scalp biopsy specimens from the frontal hair margin showed perifollicular fibrosis and lymphocytic inflammation concentrated around the isthmus and infundibular areas of the follicles. Immunophenotyping of the lymphocytes showed a dominance of activated T-helper cells. Clinical review of all six cases showed a progressive marginal alopecia without the typical multifocal areas of involvement seen in lichen planopilaris or pseudopelade. None of the patients had mucous membrane or skin lesions typical of lichen planus. Hormonal studies, in five patients, showed no elevated androgen abnormalities.

**CONCLUSIONS:** Progressive frontal recession in postmenopausal women may show clinical features of a fibrosing alopecia. The histologic findings are indistinguishable from those seen in lichen planopilaris. However, the absence of associated lesions of lichen planus in all six women raises the possibility that this mode of follicular destruction represents a reaction pattern triggered by the events underlying postmenopausal frontal hairline recession.

## Postmenopausal frontal fibrosing alopecia. Scarring alopecia in a pattern distribution.

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### Fibrosing (scarring) Alopecia in a Pattern Distribution FAPD

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**>** J Eur Acad Dermatol Venereol. 2018 Jun;32(6):e218-e220. doi: 10.1111/jdv.14748. Epub 2018 Jan 15.

### Is there a pathogenetic link between frontal fibrosing alopecia, androgenetic alopecia and fibrosing alopecia in a pattern distribution?

A C Katoulis <sup>1</sup>, K Diamanti <sup>1</sup>, D Sgouros <sup>1</sup>, A I Liakou <sup>1</sup>, E Bozi <sup>1</sup>, G Avgerinou <sup>2</sup>, I Panayiotides <sup>3</sup>, D Rigopoulos <sup>2</sup>



# Hair Root Touch-up Dye

## **5A/MEDIUM ASH BROWN**

WATER, C12-15 PARETH-3, AMMONIUM HYDROX-IDE, OLETH-10, DILINOLEIC ACID, COCAMIDE MEA, LINOLEAMIDOPROPYL DIMETHYLAMINE DIMER DILINOLEATE, STEARETH-21, BEHENTRIMONIUM CHLORIDE, POLYQUATERNIUM-22, SODIUM SULFATE, FRAGRANCE, RESORCINOL, ERYTHORBIC ACID, p-PHENYLENEDIAMINE, CARAMEL, p-AMINOPHENOL, m-AMINOPHENOL, IRON OXIDES, MICA, SODIUM SULFITE, N,N-BIS(2-HYDROXYETHYL)-p-PHENYLENE-DIAMINE SULFATE, 1-NAPHTHOL, SODIUM METASILI-CATE, EDTA, SARGASSUM FILIPENDULA EXTRACT, HY-PNEA MUSCIEORMIS EXTRACT, GELLIDIELA ACEROSA EXTRACT TITANIUM DIOXIDE.

Fibrosing alopecia in a pattern distribution (FAPD)

# Older women with FPHL/senescence and diffuse LPP



#### Fibrosing alopecia in a pattern distribution

Jacob Griggs, BA\_A 🖾 ● Ralph M. Trüeb, MD ● Maria Fernanda Reis Gavazzoni Dias, MD ● Maria Hordinsky, MD ● Antonella Tosti, MD

Published: January 08, 2020 • DOI: https://doi.org/10.1016/j.jaad.2019.12.056
# Fibrosing alopecia in a pattern distribution (FAPD)

Older women with FPHL/senescence and diffuse LPP



Case Reports > Int J Trichology. 2013 Oct;5(4):217-9. doi: 10.4103/0974-7753.130420.

# Frontal fibrosing alopecia and lupus overlap in a man: guilt by association?

Sabrina Khan<sup>1</sup>, David A Fenton<sup>2</sup>, Catherine M Stefanato<sup>1</sup>



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<u>Skin Appendage Disord.</u> 2017 Jan; 2(3-4): 162–165. Published online 2016 Nov 12. doi: <u>10.1159/000452925</u> PMCID: PMC5264358 PMID: <u>28232926</u>

#### Frontal Fibrosing Alopecia Coexisting with Lupus Erythematosus: Poor Response to Hydroxychloroquine

Letícia Arsie Contin, Elisa Raquel Martins da Costa Marques, and Leandro Noriega\*













# Fibromyxoid scarring



# CD123 "Clusters"



# Vitiligo and FFA

De Souza B, Burns L, Senna MM. Frontal fibrosing alopecia preceding the development of vitiligo: A case report. JAAD Case Rep 6(2):154-55, 2020.





# Pigment incontinence in FFA



#### Lichen Planus Pigmentosus/FFA

#### Mostly skin type >IV

Verzi AE et al. Association of frontal fibrosing alopecia with facial papules and lichen planus pigmentosus in a Caucasian woman. Skin Appendage Disord 6:379-83, 2020.



#### Depression of the frontal veins: A new clinical sign of frontal fibrosing alopecia

Sergio Vañó-Galván, MD, PhD 🛛 🙁 • Ana Rita Rodrigues-Barata, MD • Marta Urech, MD • ...

John Paoli, MD, PhD • Jesús Cuevas, MD, PhD • Pedro Jaén, MD, PhD • Show all authors

DOI: https://doi.org/10.1016/j.jaad.2015.02.1129



#### Prominent veins

Forehead has most follicles on body
292 versus 29 follicles/cm2 on the back
Loss of follicles=Major architectural change



Otberg N et al. Variations of hair follicle size and distribution in different body sites. J Invest Dermatol 122:14-19, 2004.

Salido-Vallejo R, Garnacho-Saucedo G, Moreno-Gimenez JC, Camacho-Martinez FM. Beard involvement in a man with frontal fibrosing alopecia. Indian J Dermatol Venereol Leprol. 2014 Nov-Dec;80(6):542-4. doi: 10.4103/0378-6323.144183. PMID: 25382516.

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#### Frontal Fibrosing Alopecia Involving the Limbs Shows Inflammatory Pattern on Histology: A Review of 13 Cases

Miteva, Mariya MD Author Information 😒

The American Journal of Dermatopathology: March 2020 - Volume 42 - Issue 3 - p 226-229 doi: 10.1097/DAD.000000000001500



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#### Summary of FFA Lesions

**FAPD**—Likely same chemical cause in hair product (touch up dye) Lupus may present alone as FFA or in conjunction with LPP-like FFA Pigmentary alteration—multiple causes Beard FFA follows limb loss Limb/body biopsies are challenging

#### Colloidal Iron finds subtle scarring



#### Colloidal Iron finds subtle scarring in FFA





# FFA always has a low follicular count/density







# Alopecic lupus vs LPP





# Alopecic lupus vs LPP





# Hyperkeratosis (not parakeratosis) is a clue to seborrheic dermatitis on the scalp









## Folliculitis decalvans vs LPP




### Folliculitis decalvans vs LPP

Folliculitis decalvans Men under age 40 Lichen Planopilaris Women over age 40

## Folliculitis decalvans vs LPP









## Tufted compound follicles





#### Lymphocytic

Chronic cutaneous lupus erythematosus Lichen planopilaris Classic lichen planopilaris Frontal fibrosing alopecia Graham-Little syndrome Classic pseudopelade (Brocg) Central centrifugal cicatricial alopecia Alopecia mucinosa Keratosis follicularis spinulosa decalvans Neutrophilic Folliculitis decalvans Dissecting cellulitis/folliculitis (perifolliculitis capitis abscedens et suffodiens) Mixed Folliculitis (acne) keloidalis Folliculitis (acne) necrotica

Erosive pustular dermatosis

Nonspecific

Summary of North American Hair Research Society (NAHRS)sponsored Workshop on Cicatricial Alopecia, Duke University Medical Center, February 10 and 11, 2001

Elise A. Olsen, MDa • Wilma F. Bergfeld, MDb • George Cotsarelis, MDc • Vera H. Price, MDd • Jerry Shapiro, MDe • Rodney Sinclair, MDf • Alvin Solomon, MDg • Leonard Sperling, MDh • Kurt Stenn, MDi • David A. Whiting, MDj the members of the Workshop on Cicatricial Alopecia<sup>\*</sup> • Show less

DOI: https://doi.org/10.1067/mjd.2003.68

## Absence of catagen/telogen with lymphocytes is a clue to LPP/CCCA



## Melanin/Pigment casts are mostly associated with dark hair



### Colloidal iron for perifollicular fibrosis



# Allows for correlation of special stains to H&E (identical sections)





## Normal scalp has a lot of mucin



## For practical purposes CCCA = LPP



## For practical purposes CCCA = LPP



#### CCCA is not related to folliculitis devalvans

CCCA--women of African descent over age 40

Folliculitis decalvans--men under age 40

### Solar elastosis—clue to female pattern hair loss (androgenetic alopecia)



#### Demodex Cause of inflammation and pruritus



#### Lack of yeast (seborrheic dermatitis) with lymphocytes present is a clue to LPP/CCCA/FFA and to Folliculitis decalvans





 Case Reports
 > JAAD Case Rep. 2022 Mar 11;23:46-48. doi: 10.1016/j.jdcr.2022.02.036.

 eCollection 2022 May.

## Three-dimensional imaging of a peripilar cast and compound follicle in frontal fibrosing alopecia

Curtis T Thompson <sup>1</sup><sup>2</sup>, Maria Abril Martinez Velasco <sup>3</sup>, Antonella Tosti <sup>4</sup>



## In vivo confocal microscopy



## 2mm transverse H&E sections









## LSC clue to trichotillomania



## LSC clue to trichotillomania



## FPHL versus alopecia areata







## CD3 subacute alopecia areata





Kolivras A and Thompson CT. Distinguishing diffuse alopecia areata from pattern hair loss using CD3+ T-cells. JAAD. 74:937-44, 2016.





6 slides total with 18 cross sections; 3 sections per slide

- 1. Tissue is embedded epidermis-down
- 2. Step through entire block on initial H&E stains
- 3. Obtain unstained slides

A method for more precise sampling of the scalp and eyebrows in frontal fibrosing alopecia

Curtis T. Thompson, MD 🛛 A 🖾 • Antonella Tosti, MD

Published: December 23, 2018 • DOI: https://doi.org/10.1016/j.jaad.2018.12.033 • 🦚 Check for updates

# Allows for correlation of special stains to H&E (identical sections)





## A few more pearls on alopecia:

- Most important clinical information: Patch vs diffuse
- Be careful with biopsies from the hairline (where large meets small)
- Telogen effluvium is ~15% catagen/telogen and generally a +hair pull test or complaint of significant shedding

## Merci beaucoup!

- Miami and Bologna--Antonella Tosti and Colombina Vincenzi and Betty Nguyen
- Brussels--Athanassios Kolivras
- Oregon--Janet Roberts and Nisha Desai
- Contact: curtisinportland@gmail.com

