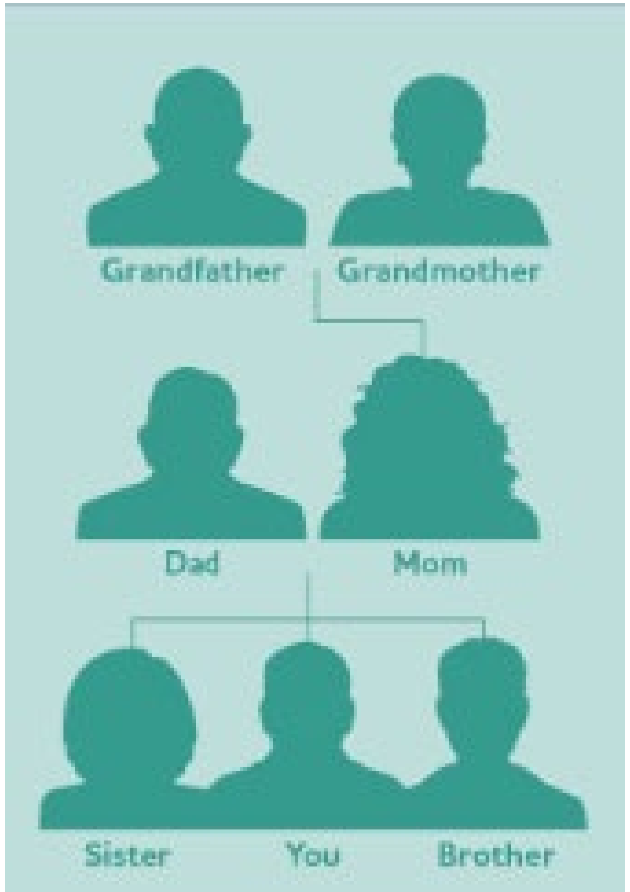
Is Alopecia Areata Genetic?

Leslie Castelo-Soccio, MD, PhD

September 2024

Simple Answer: Yes



- One in five people with AA has a family member with AA
- Certain genes increase risk but doesn’t mean you will get AA

Complete Answer

There are other characteristics that influence autoimmune disease

- environmental factors like diet, smoking, where you were born, where you grew up, infections, medication history, unknown….
- DNA changes are complicated

sunka_art/Shutterstock

Why have we suspected genetic component? Twin Concordance

CosmoDermLetter to the Editor
(2024)4:43
doi:10.25259/CSDM_40_2024

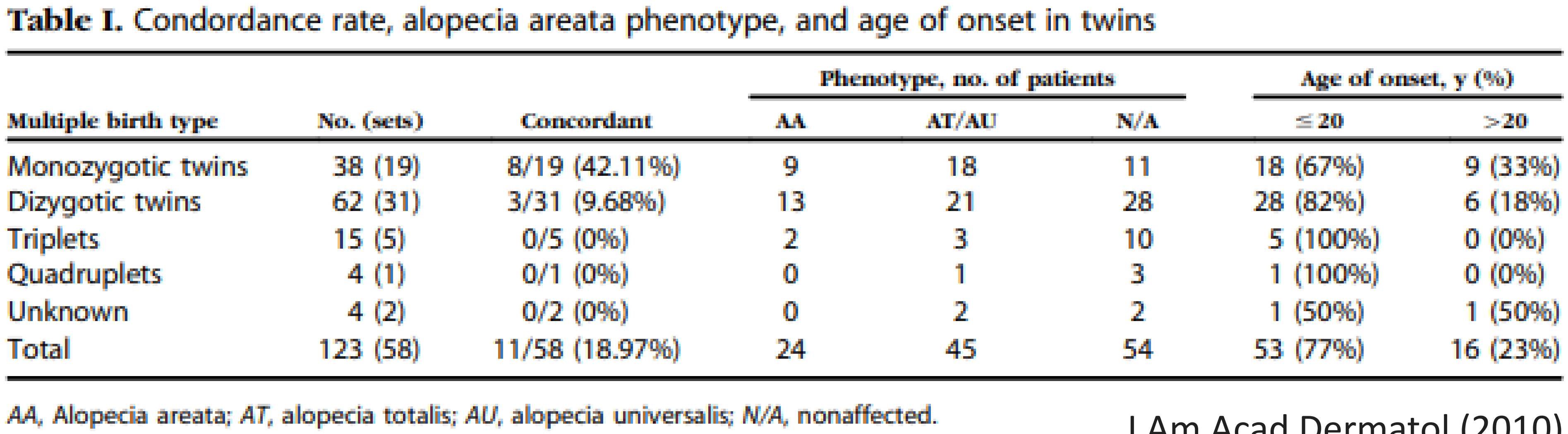


Table I. Condordance rate, alopecia areata phenotype, and age of onset in twins

			Phenotype, no. of patients			Age of onset, y (%)	
Multiple birth type	**No. (sets)**	**Concordant**	**AA**	**AT/AU**	**N/A**	**≤20**	**>20**
Monozygotic twins	38 (19)	8/19 (42.11%)	9	18	11	18 (67%)	9 (33%)
Dizygotic twins	62 (31)	3/31 (9.68%)	13	21	28	28 (82%)	6 (18%)
Triplets	15 (5)	0/5 (0%)	2	3	10	5 (100%)	0 (0%)
Quadruplets	4 (1)	0/1 (0%)	0	1	3	1 (100%)	0 (0%)
Unknown	4 (2)	0/2 (0%)	0	2	2	1 (50%)	1 (50%)
Total	123 (58)	11/58 (18.97%)	24	45	54	53 (77%)	16 (23%)

AA, Alopecia areata; *AT*, alopecia totalis; *AU*, alopecia universalis; *N/A*, nonaffected.

J Am Acad Dermatol (2010) 62(3):525-7.

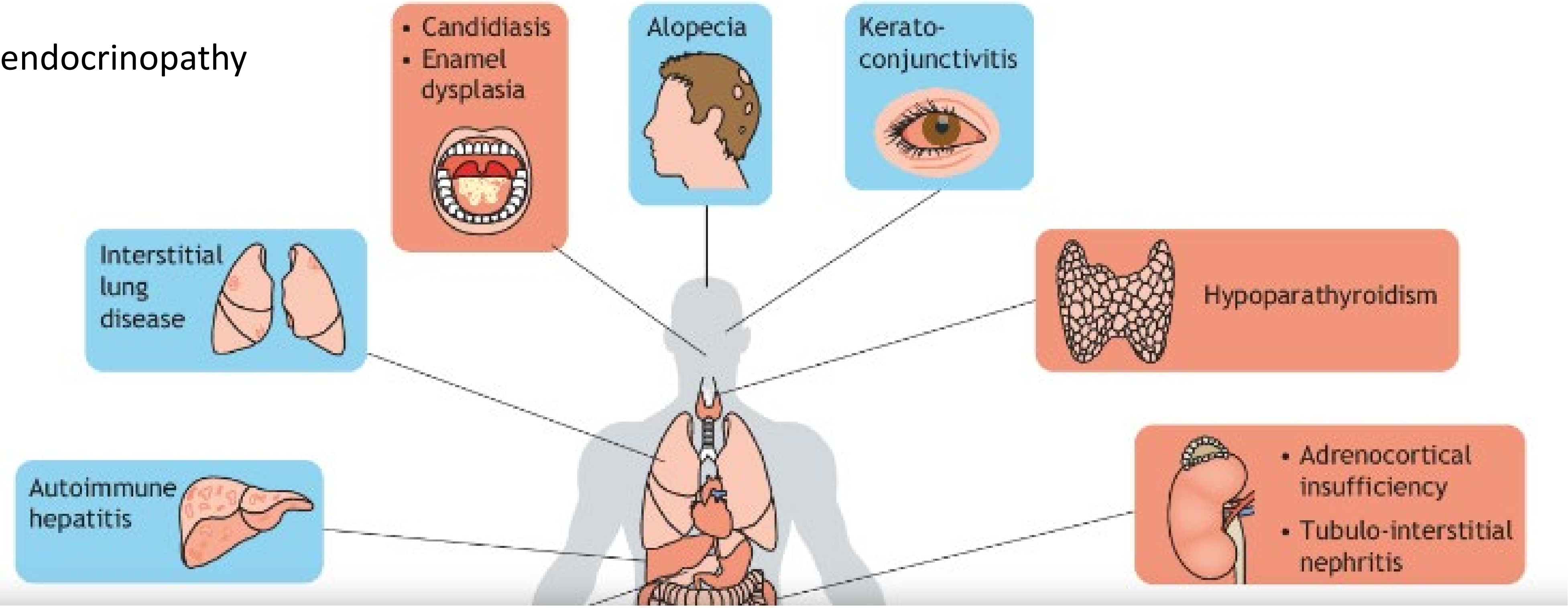
High Rates in some Families of AA and other autoimmune disease

J Dermatol Sci 2015 78:11-20

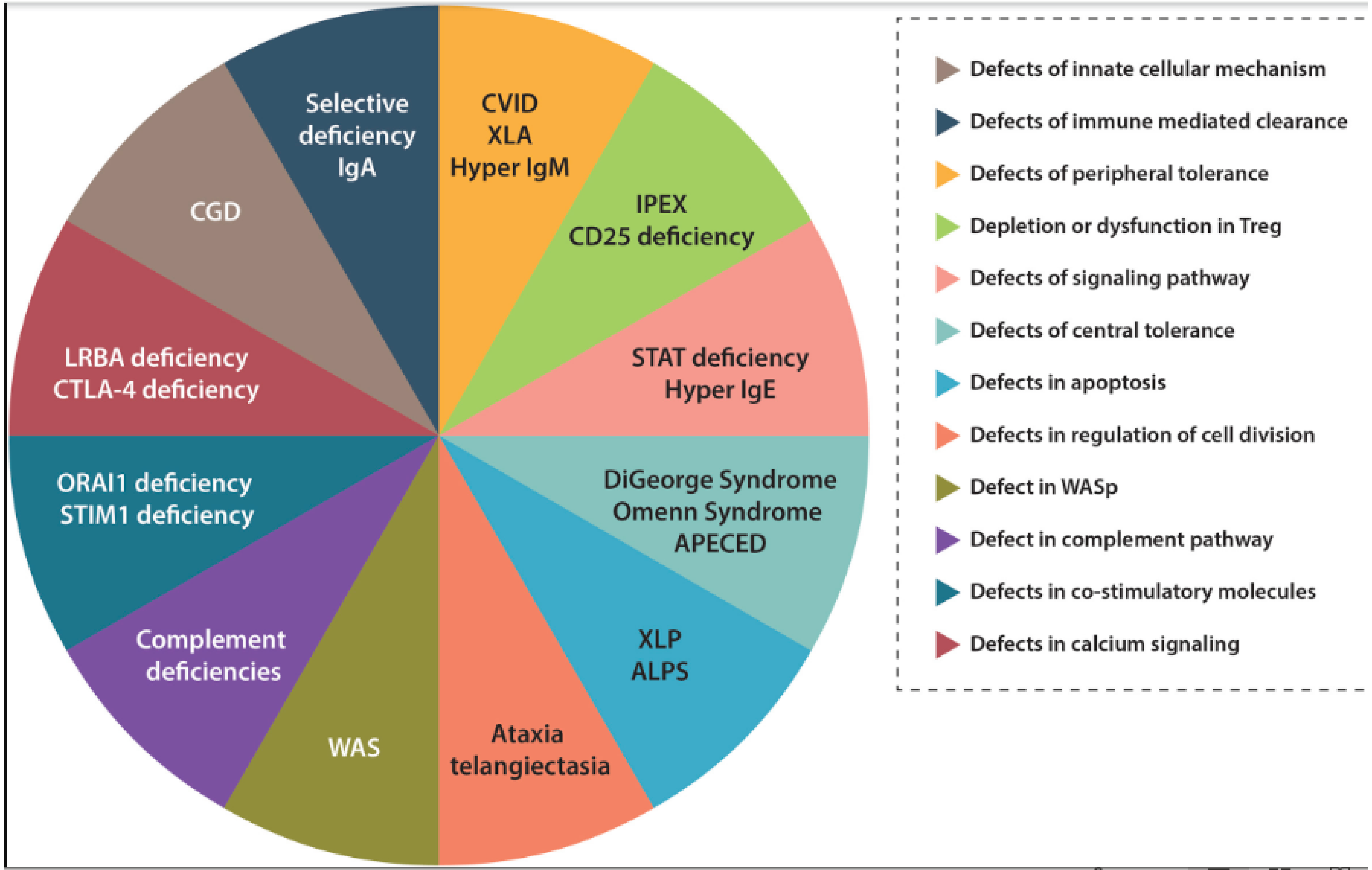
- First-degree relatives of people with AA have estimated 7.8% risk of developing AA, compared to general population prevalence of 2.1%.
- Concept of familial autoimmune disease aggregation

Alopecia areata is seen in some Primary Immunodeficiency syndromes/ Inborn Errors of Immunity (IEIs)

Autoimmune Polyendocrinopathy Syndrome Type 1



Other IEIs and Alopecia Areata



Does this mean that AA is caused by single genes?

- Quick answer: In 10% of cases yes but not in the other 90%

FOXP3 *ICOSSLG*

MICA *MIF*

IL7RA

IL1RN *AIRE*

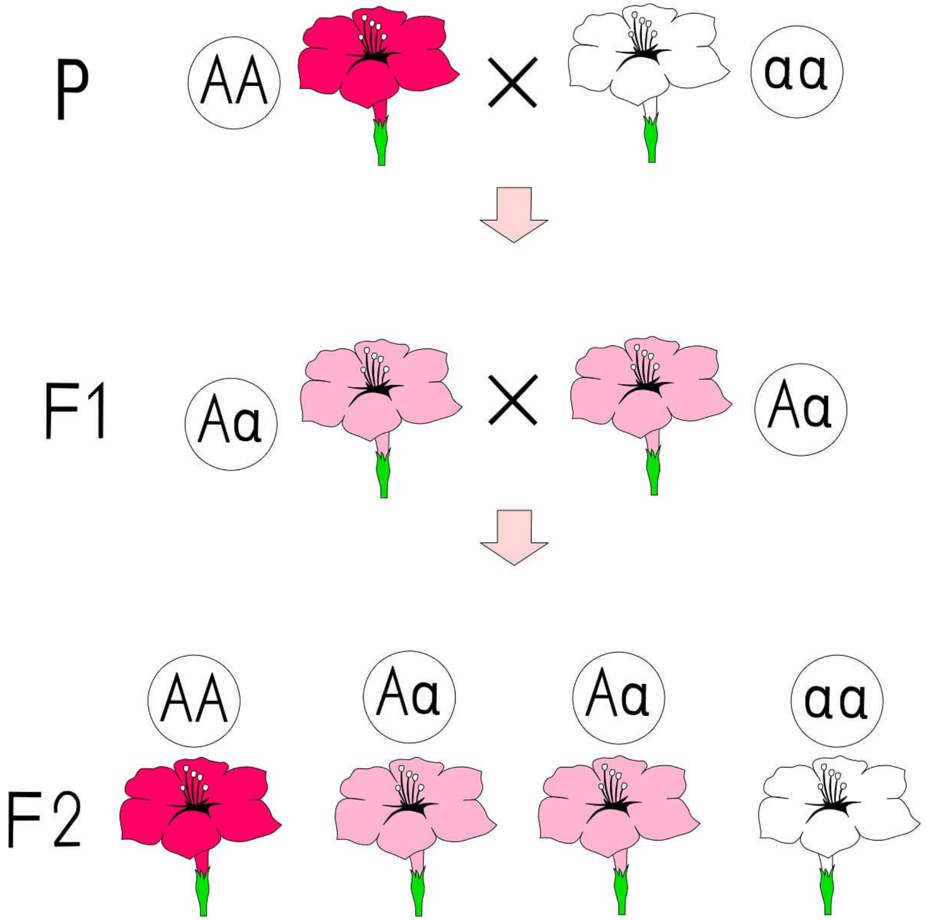
KRT82

SOCS1 *NKFB*

CTLA4 *RAG*

What does it mean if something is monogenic, polygenic or complex?

Mendelian Genetics- Monogenic

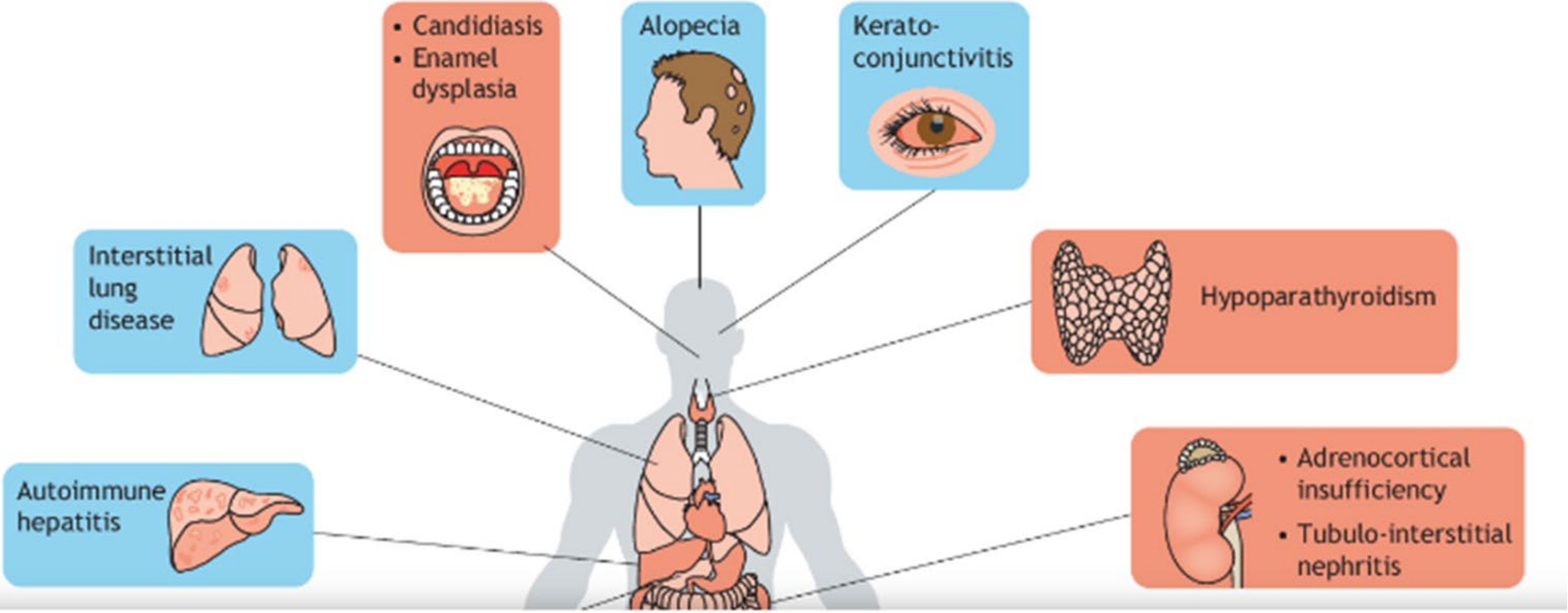


Flower Pigment

Trait is determined by one gene

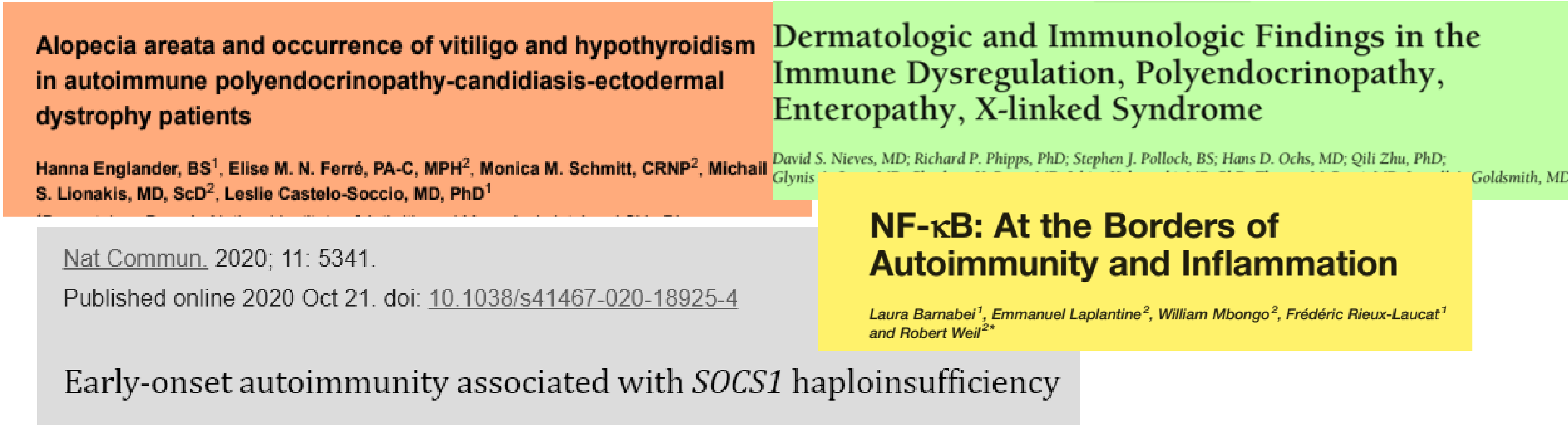
Inborn errors of Immunity

- One gene causes a host of changes e.g. AIRE gene mutation leads to failure of T-cell tolerance



How is Alopecia areata different in IEIs?

- Often occurs in childhood
- Mostly you cannot tell any difference except you may other symptoms
- May have recurrent infections
- May have more than 2 autoimmune diseases



Alopecia areata and occurrence of vitiligo and hypothyroidism in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients

Hanna Englander, BS[1], Elise M. N. Ferré, PA-C, MPH[2], Monica M. Schmitt, CRNP[2], Michail S. Lionakis, MD, ScD[2], Leslie Castelo-Soccio, MD, PhD[1]

Dermatologic and Immunologic Findings in the Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

David S. Nieves, MD; Richard P. Phipps, PhD; Stephen J. Pollock, BS; Hans D. Ochs, MD; Qili Zhu, PhD;
Glynis … Goldsmith, MD

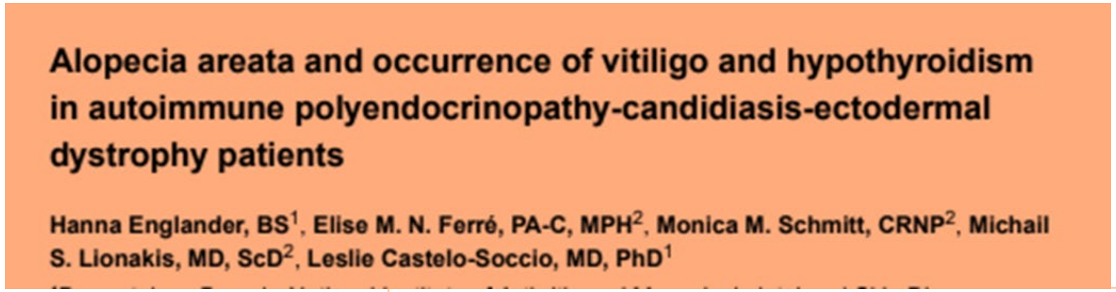
NF-κB: At the Borders of Autoimmunity and Inflammation

Laura Barnabei[1], Emmanuel Laplantine[2], William Mbongo[2], Frédéric Rieux-Laucat[1] and Robert Weil[2]*

Nat Commun. 2020; 11: 5341.

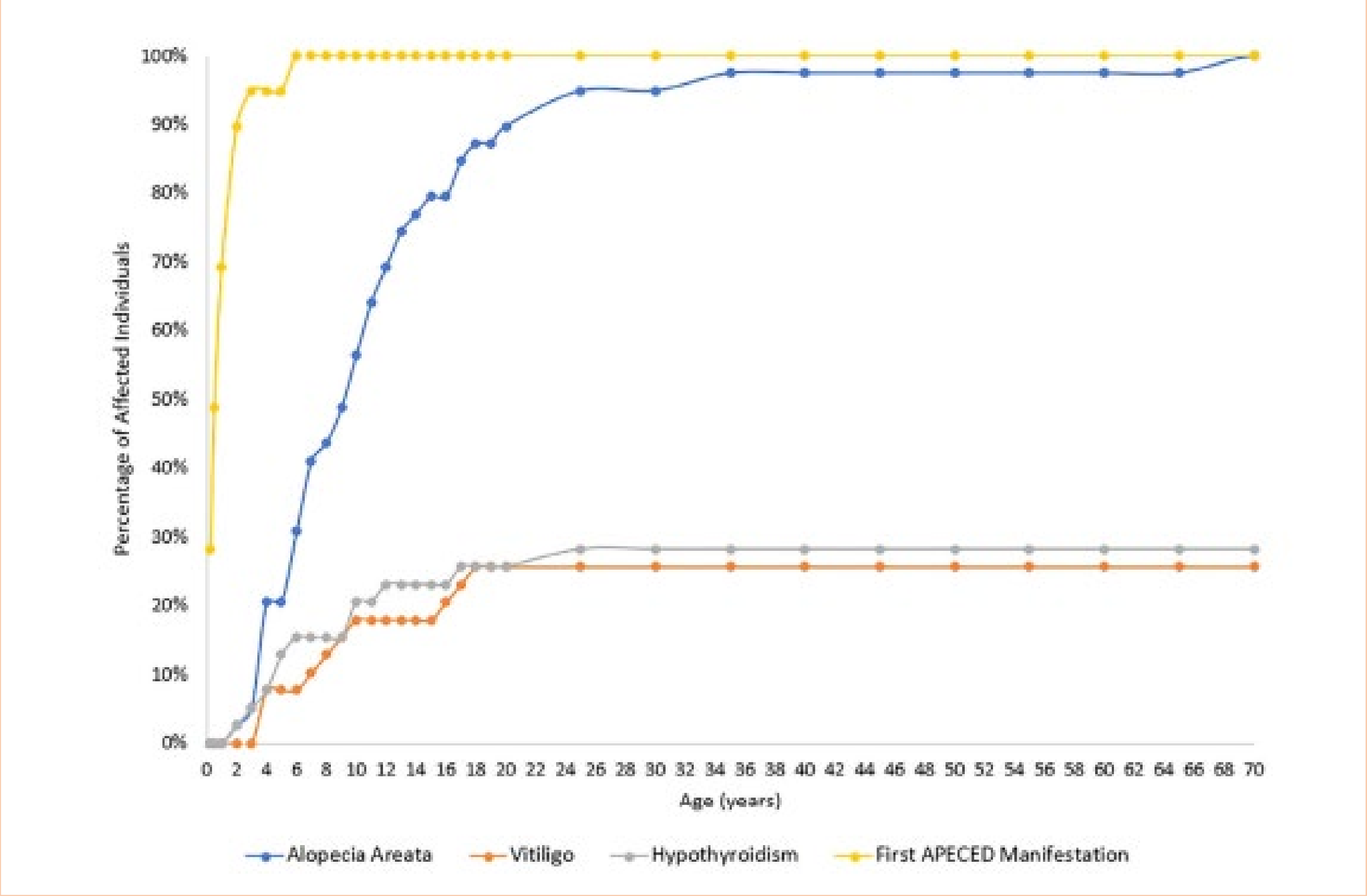
Published online 2020 Oct 21. doi: 10.1038/s41467-020-18925-4

Early-onset autoimmunity associated with *SOCS1* haploinsufficiency



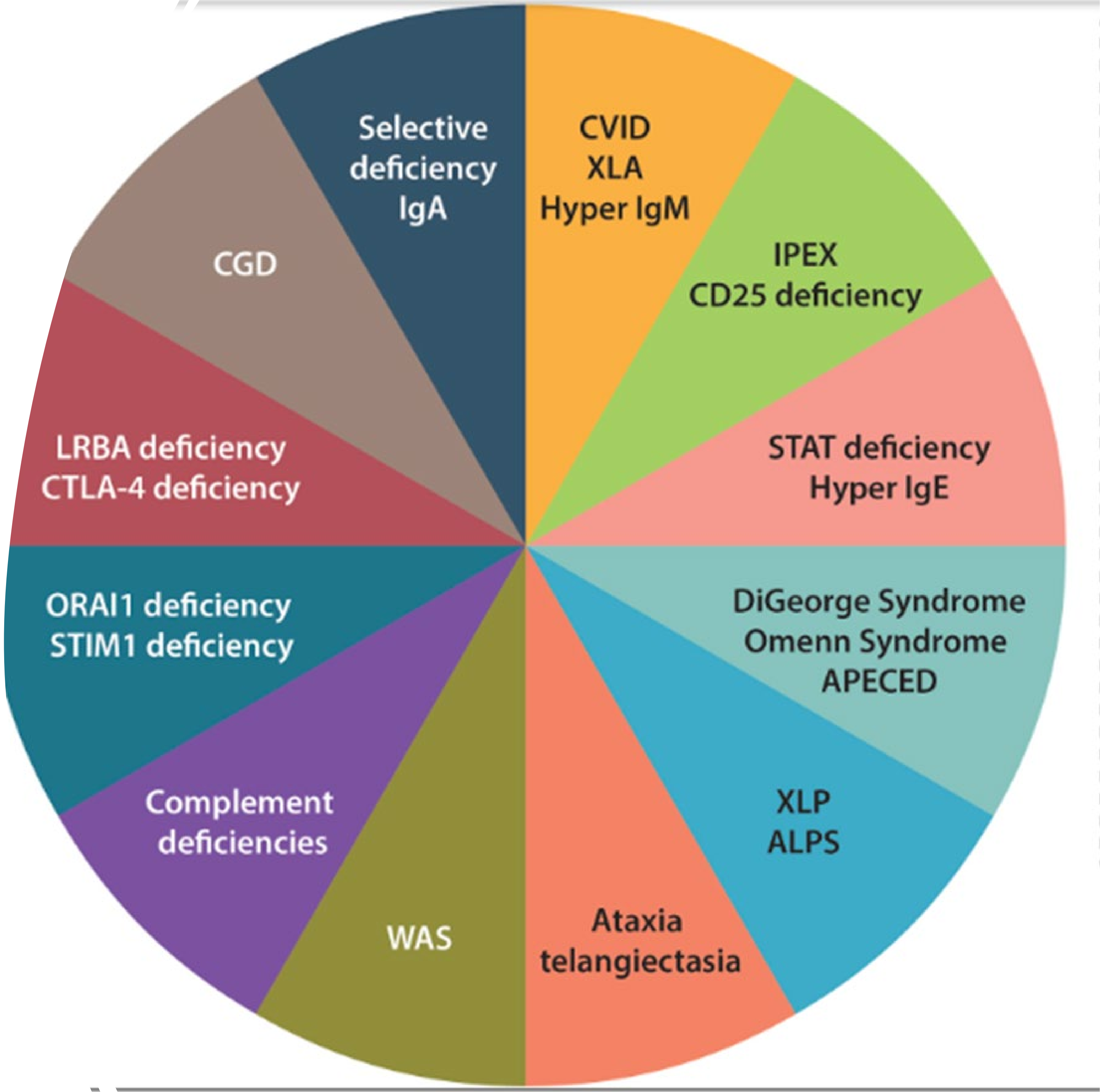
Alopecia areata and occurrence of vitiligo and hypothyroidism in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients

Hanna Englander, BS[1], Elise M. N. Ferré, PA-C, MPH[2], Monica M. Schmitt, CRNP[2], Michail S. Lionakis, MD, ScD[2], Leslie Castelo-Soccio, MD, PhD[1]



Monogenic disease can teach us a lot about why a disease might happen

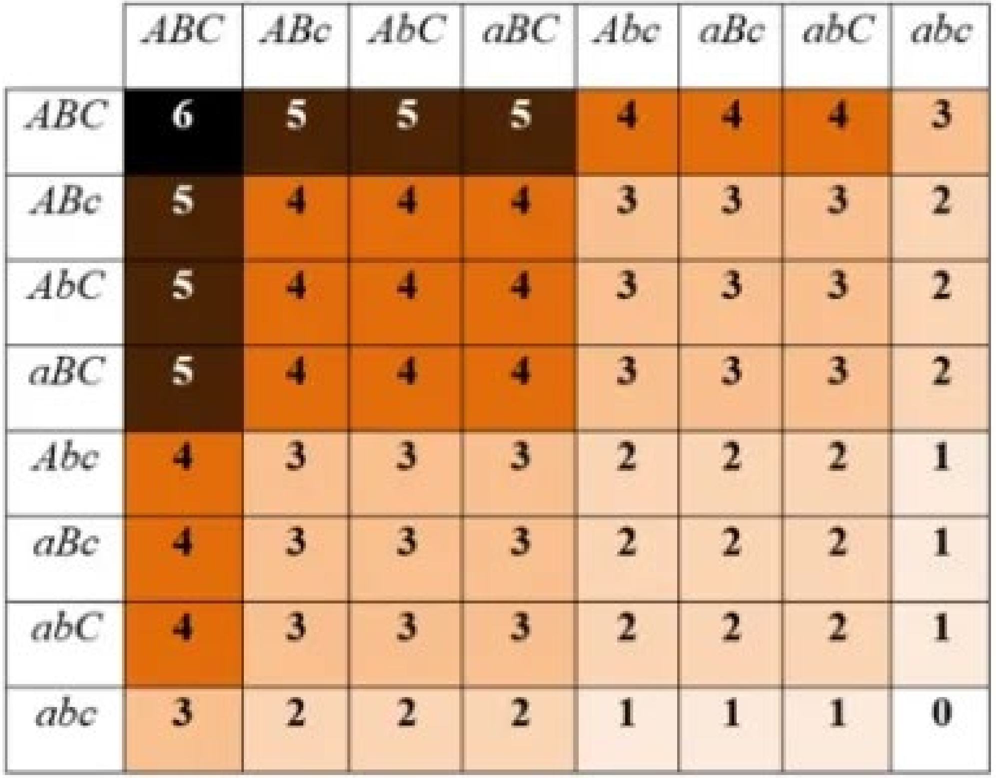
- Importance of T Regulatory cells
- Infection and other stressors may impact AA



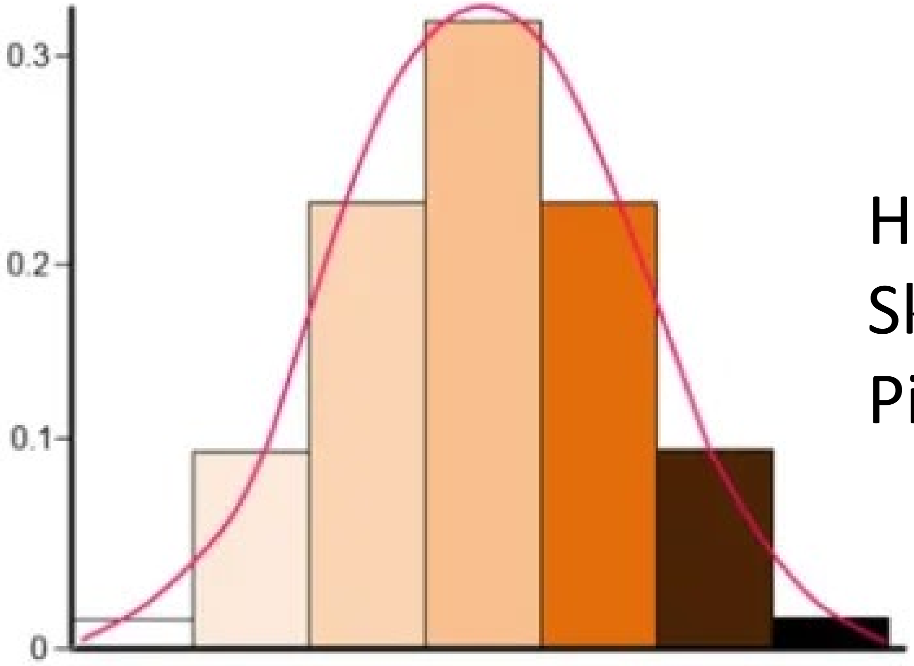
Polygenic: Multiple genes contribute to trait

https://www.express.co.uk/news/uk/561472

Non-Mendelian Genetics- Polygenic



	ABC	*ABc*	*AbC*	*aBC*	*Abc*	*aBc*	*abC*	*abc*
ABC	6	5	5	5	4	4	4	3
ABc	5	4	4	4	3	3	3	2
AbC	5	4	4	4	3	3	3	2
aBC	5	4	4	4	3	3	3	2
Abc	4	3	3	3	2	2	2	1
aBc	4	3	3	3	2	2	2	1
abC	4	3	3	3	2	2	2	1
abc	3	2	2	2	1	1	1	0

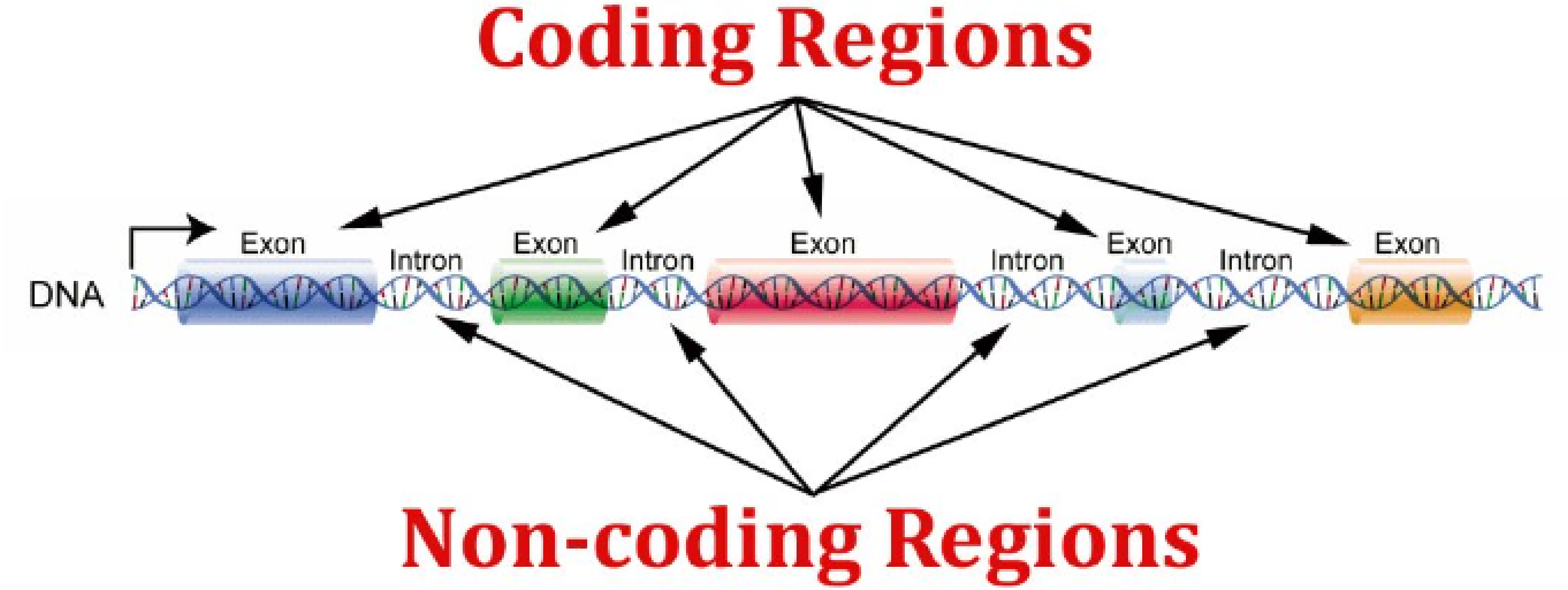


Human
Skin
Pigment

https://www.khanacademy.org/

Trait is determined by more than one gene
and some of these genes may not be coding genes

Autoimmune Disease: Complex inheritance Multiple Genes can be altered plus other



Autoimmune disease- 90% Complex

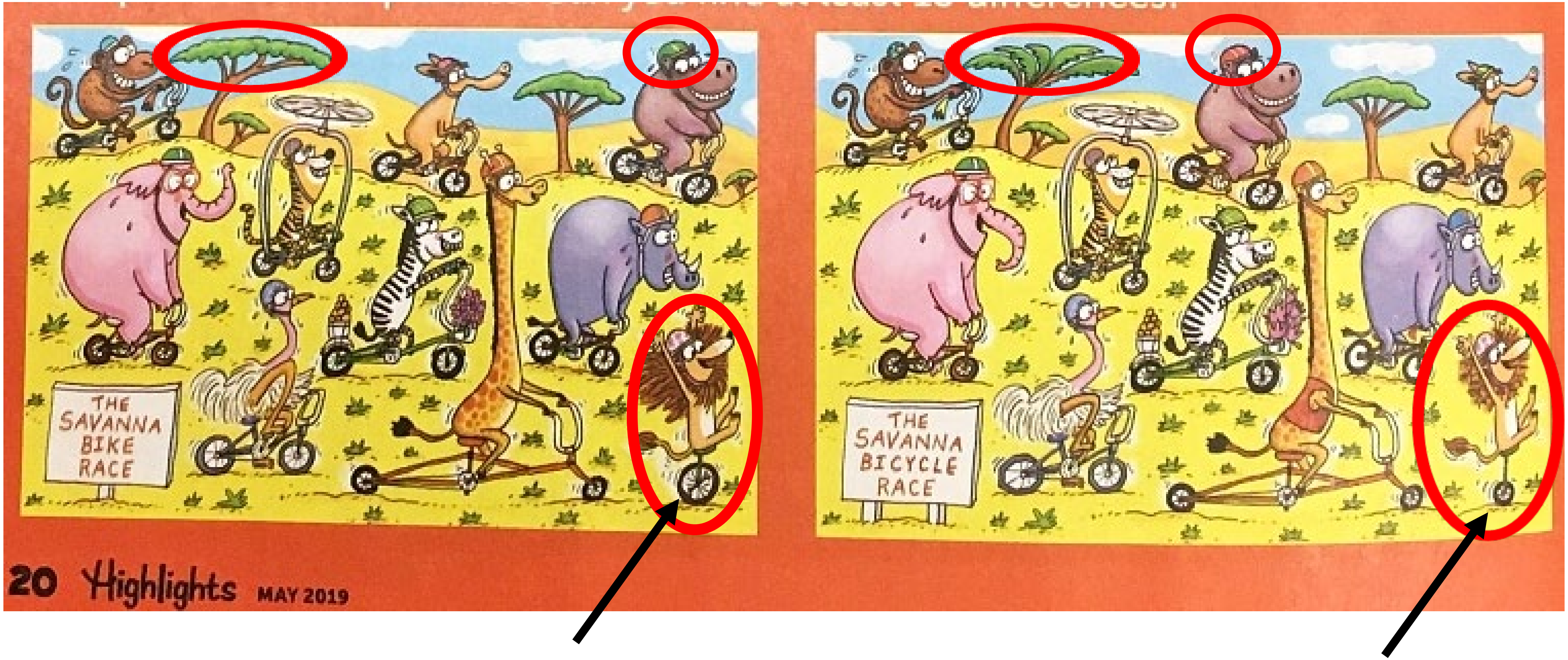
Additive effects of multiple susceptibility genes

Single nucleotide polymorphisms (SNPs) exert small impact and in noncoding regions but can add up

SNPS can lead to variable expression of a gene rather than a different protein product

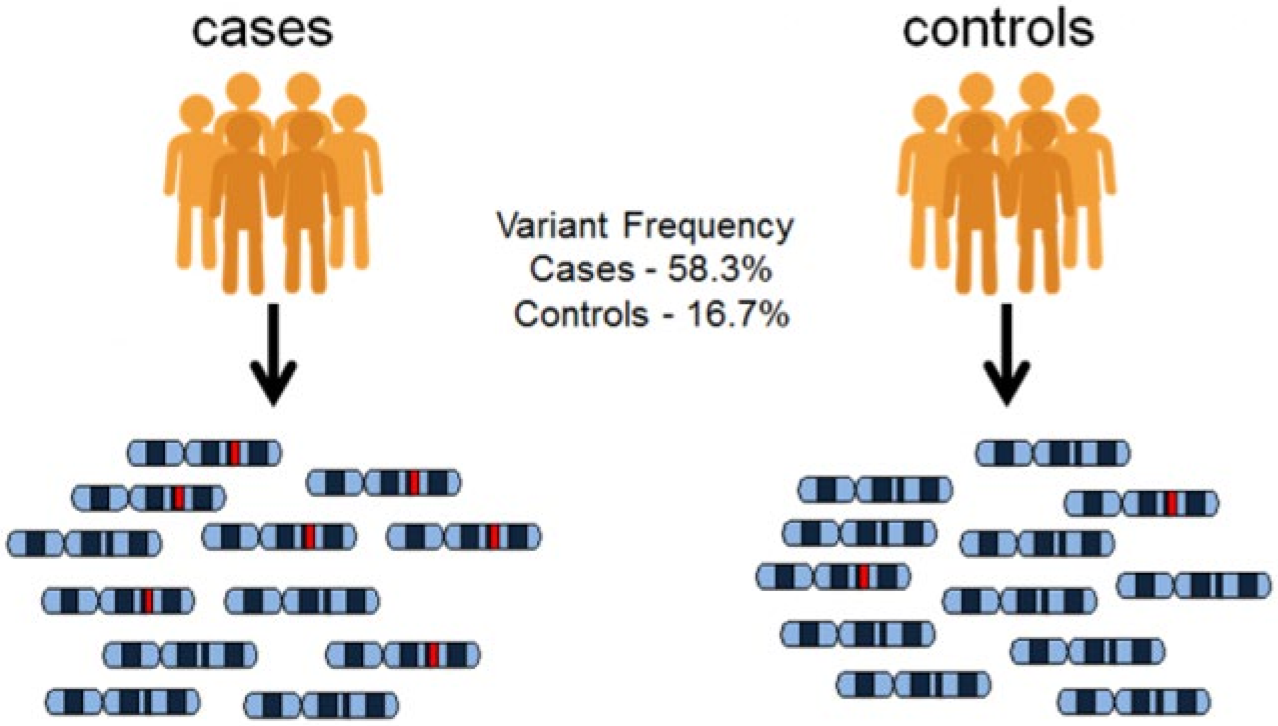
Environment can change expression

Single Nucleotide Polymorphisms

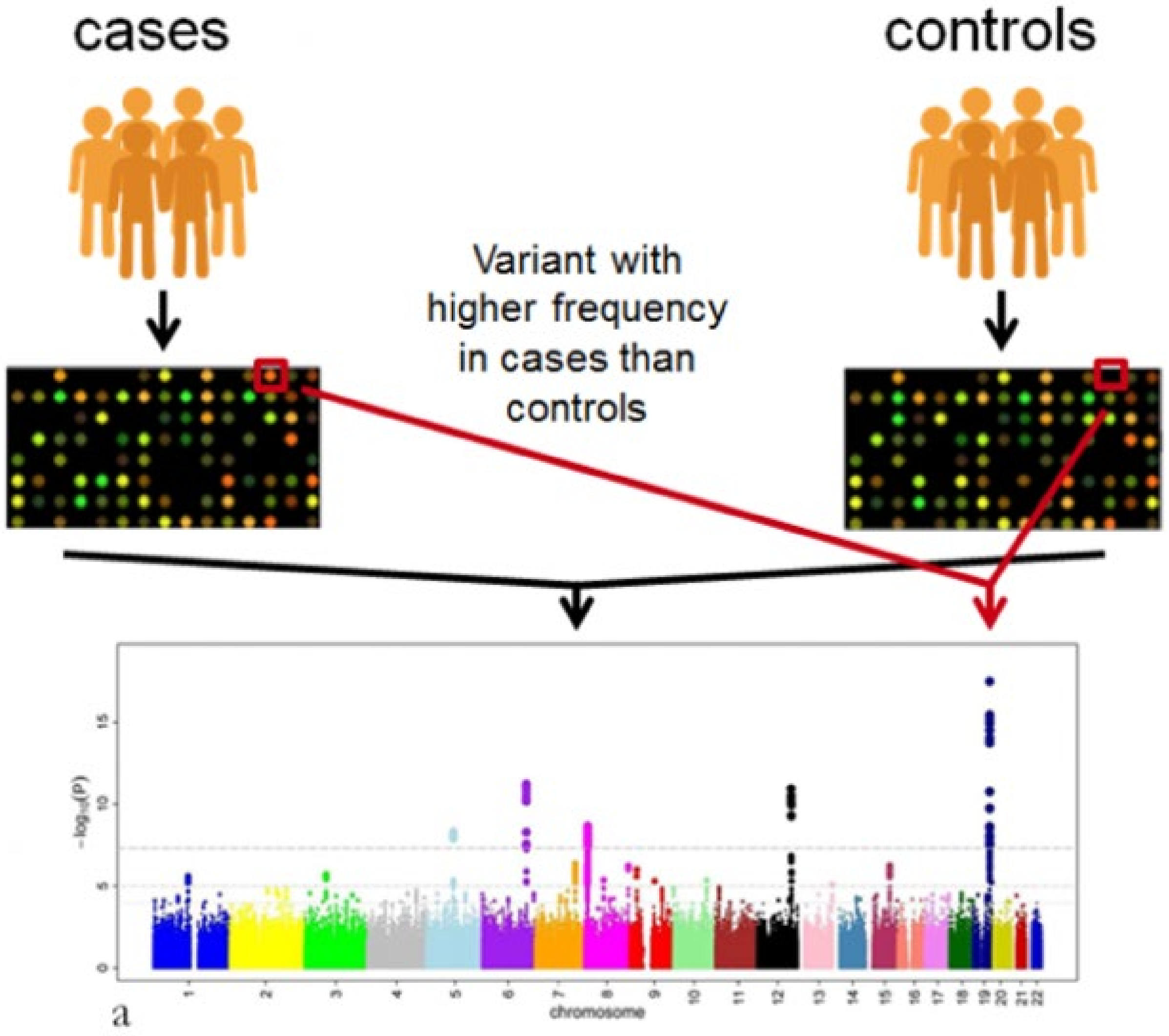


Genome Wide Association Studies

- Research method that compares the DNA of many people to identify genetic markers that may be associated with a disease or trait.



https://www.ebi.ac.uk/training/online/courses/gwas

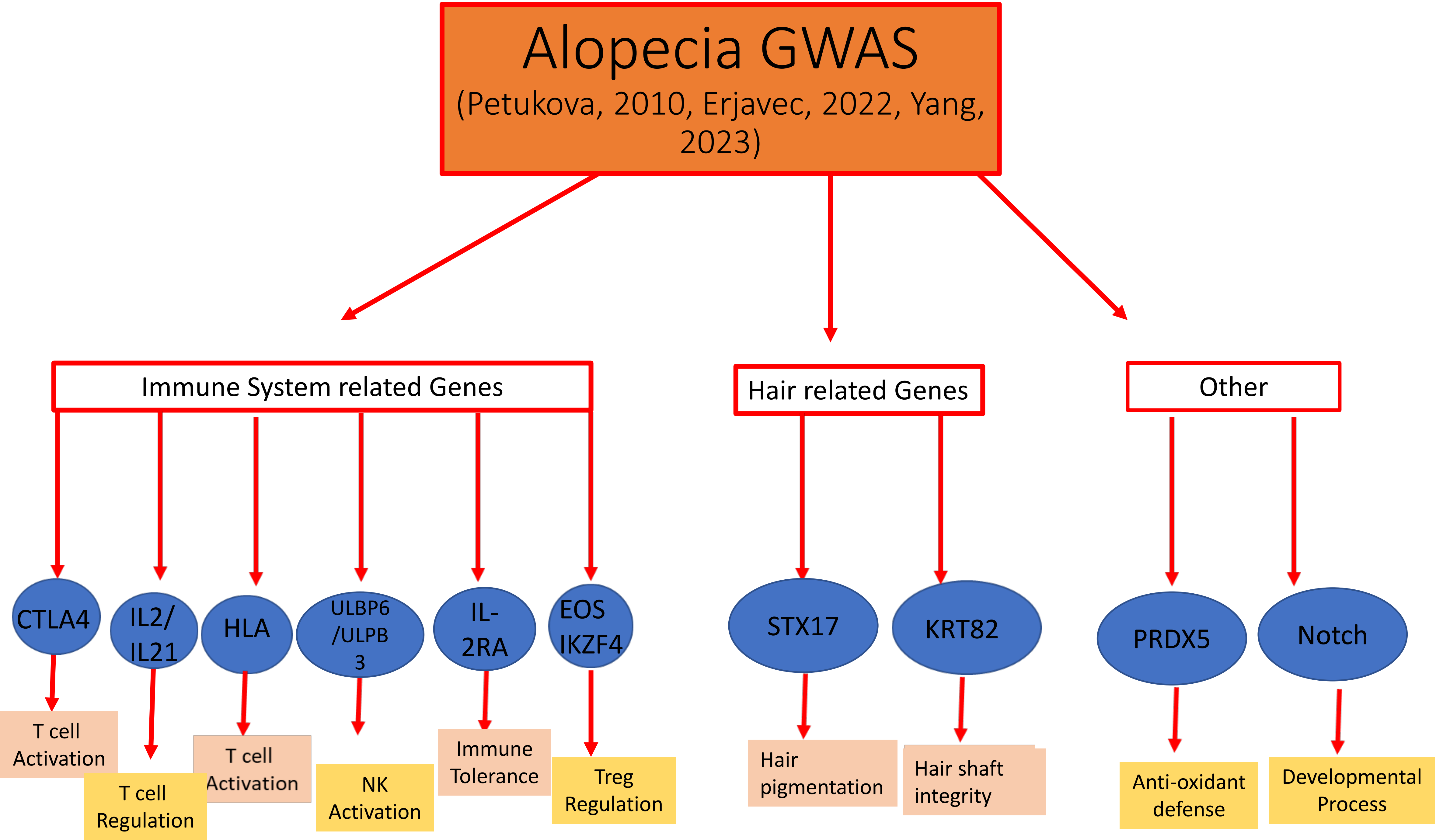


cases

controls

Variant with higher frequency in cases than controls

Statistical analysis is carried out to indicate how likely a variant is to be associated with a trait.

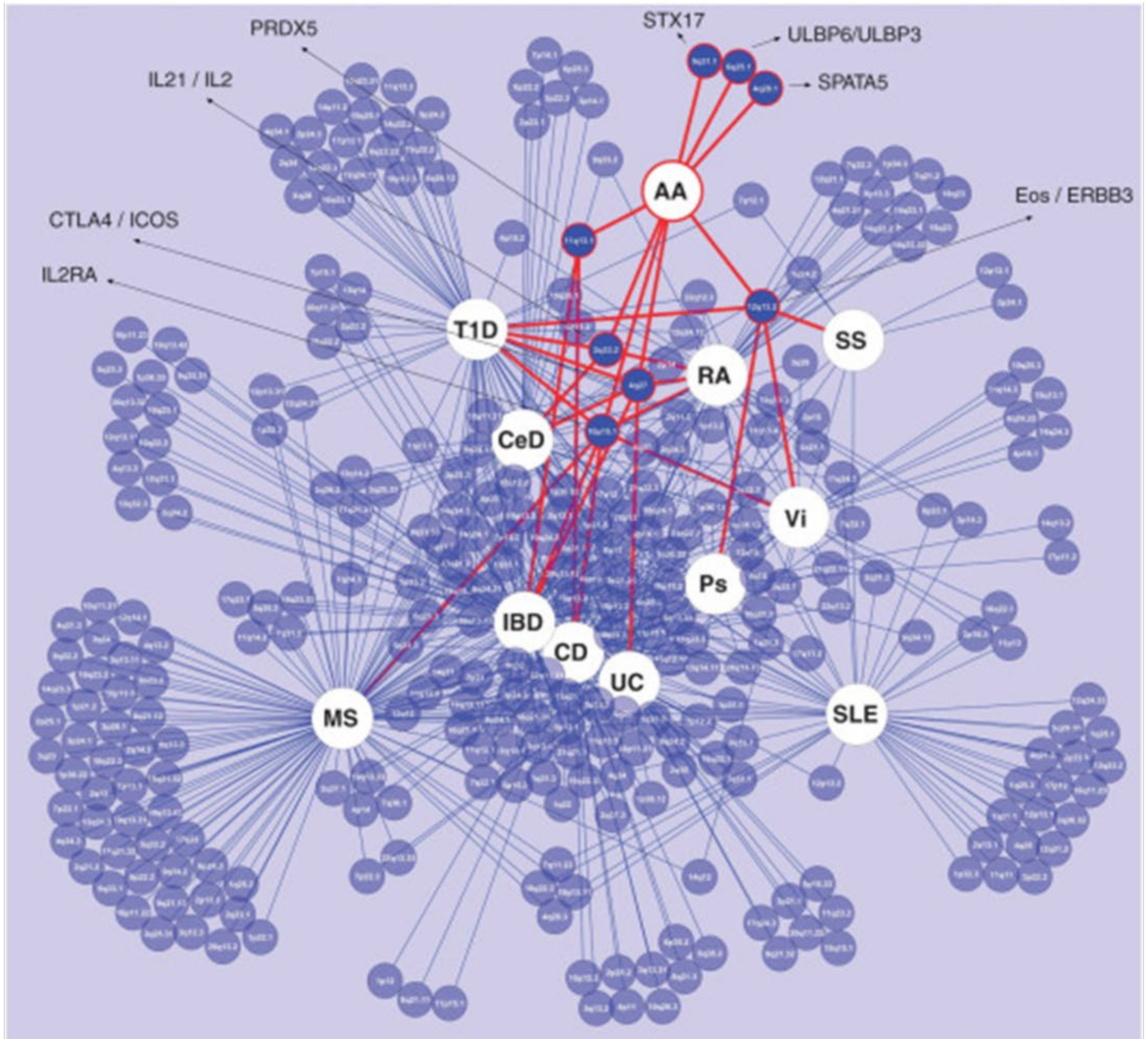


Alopecia GWAS

(Petukova, 2010, Erjavec, 2022, Yang, 2023)

- Immune System related Genes
  - CTLA4
    - T cell Activation
  - IL2/ IL21
    - T cell Regulation
  - HLA
    - T cell Activation
  - ULBP6 /ULPB 3
    - NK Activation
  - IL- 2RA
    - Immune Tolerance
  - EOS IKZF4
    - Treg Regulation
- Hair related Genes
  - STX17
    - Hair pigmentation
  - KRT82
    - Hair shaft integrity
- Other
  - PRDX5
    - Anti-oxidant defense
  - Notch
    - Developmental Process

Comparing GWAS For multiple autoimmune Diseases



Journal of Investigative Dermatology Symposium Proceedings Volume 16, Issue 1, December 2013 Pages S16-S22

Recognition of these variants led to testing of JAK inhibitors first in mice and then humans

Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata

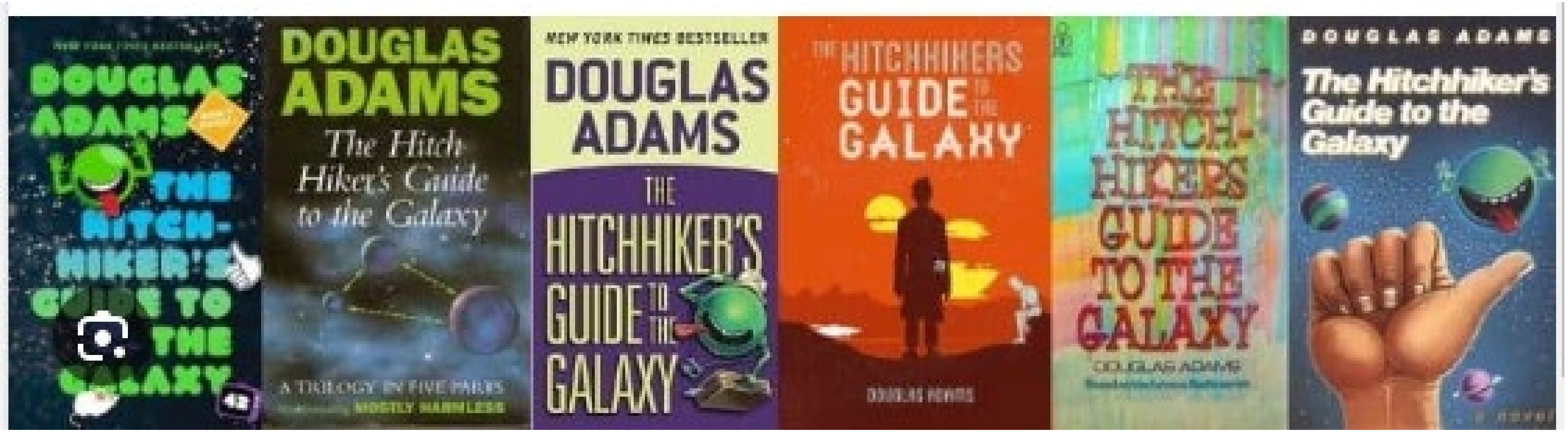
Julian Mackay-Wiggan,[1] Ali Jabbari,[1] Nhan Nguyen,[1] Jane E. Cerise,[1] Charlotte Clark,[1] Grace Ulerio,[1] Megan Furniss,[1] Roger Vaughan,[2] Angela M. Christiano,[1,3] and Raphael Clynes[1]

Authorship note: J. Mackay-Wiggan, A. Jabbari, A.M. Christiano, and R. Clynes contributed equally to this work.

Published September 22, 2016 - More info

Can you easily test genetics of AA in clinic?

- Whole exome sequencing will identify monogenic disease but usually not the polymorphisms/SNPs
- Whole genome sequencing can identify polymorphisms but not practically used and difficult to know if it is cause (coding and noncoding regions)



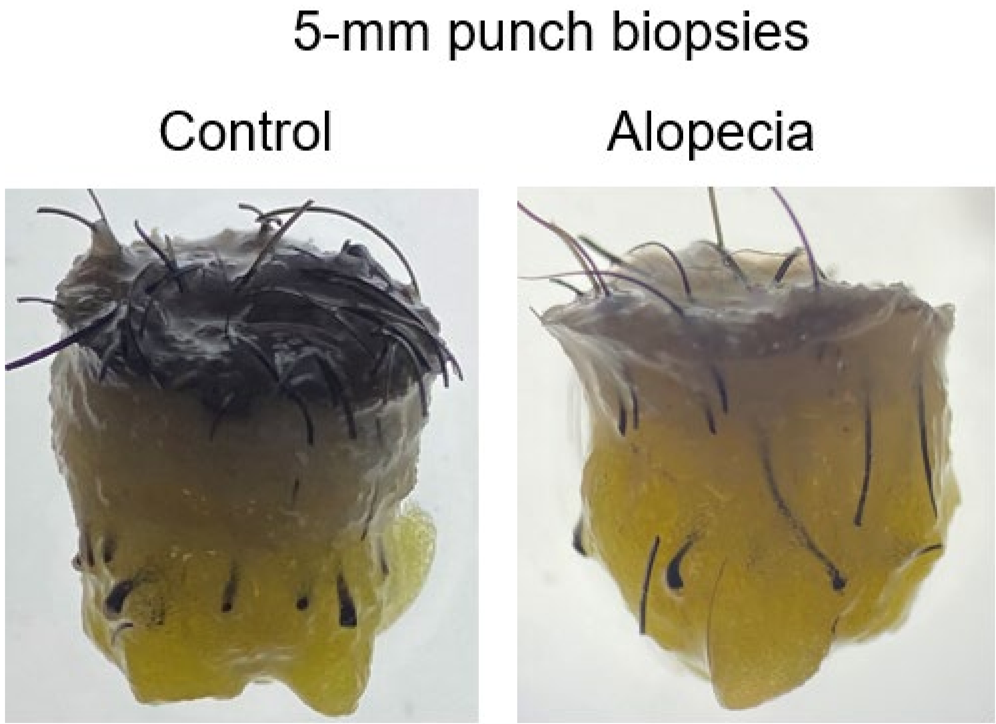
Erjavec, …Christiano
Nat Commun. 2022 Feb 10;13(1):800.

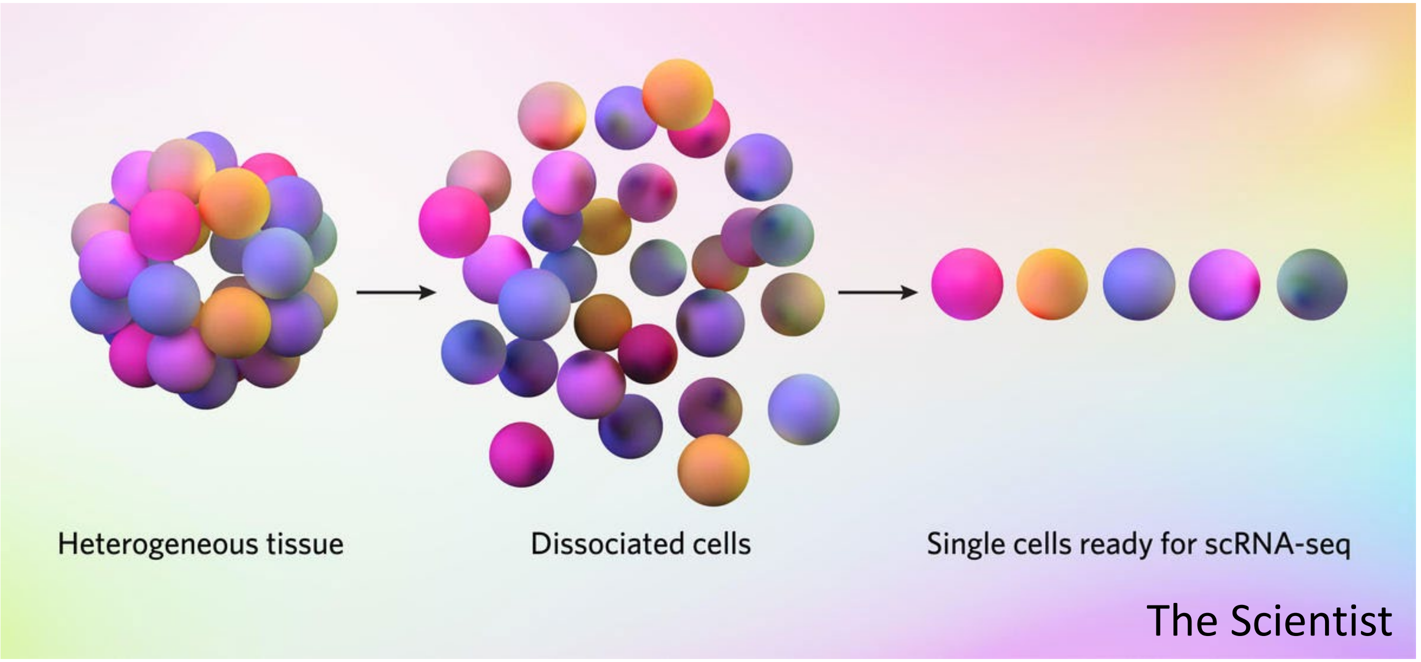
There have been identification of a meaningful proportion of genetic variants associated with alopecia areata but:

- <u>Need</u> better and more meaningful clinical tests/panels
- <u>Need</u> to look at the level of the hair follicle and what genes are up or down during AA and after treatment
- <u>Need</u> to elucidate environmental factors and their interactions with gene function (global and cell level)

What are we doing to assess genes in tissues affected by AA? Single cell RNA sequencing

Single Cell RNA sequencing

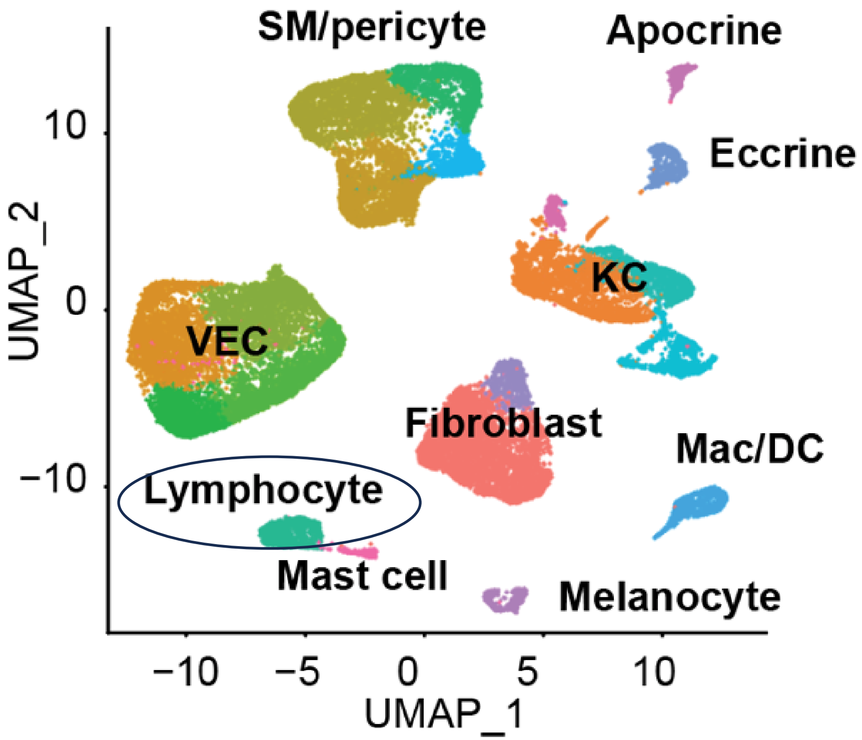




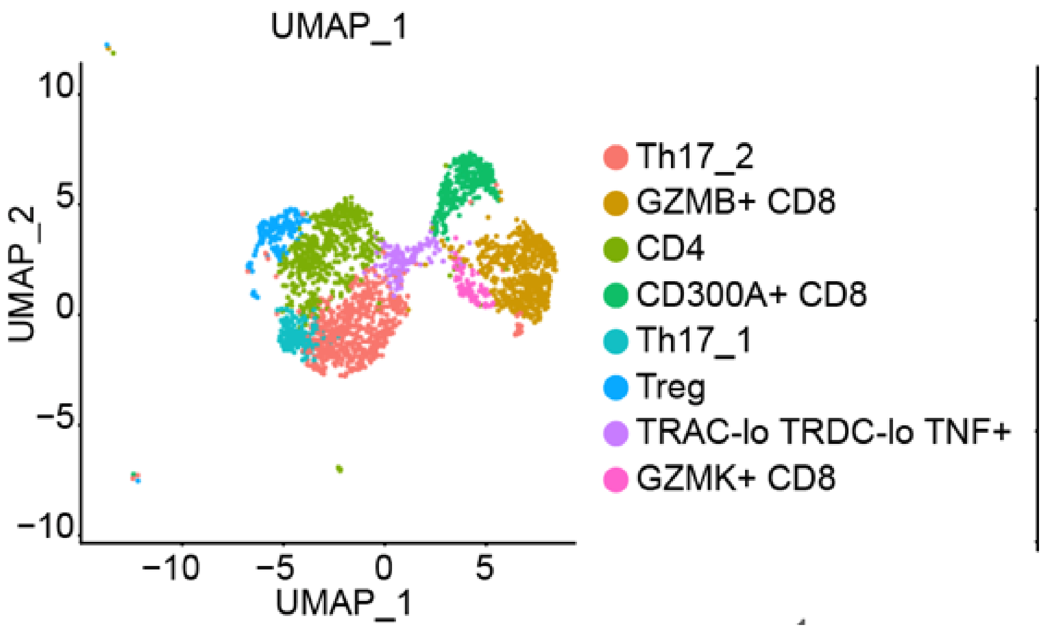
The Scientist

Can look at specific populations of cells in biopsy

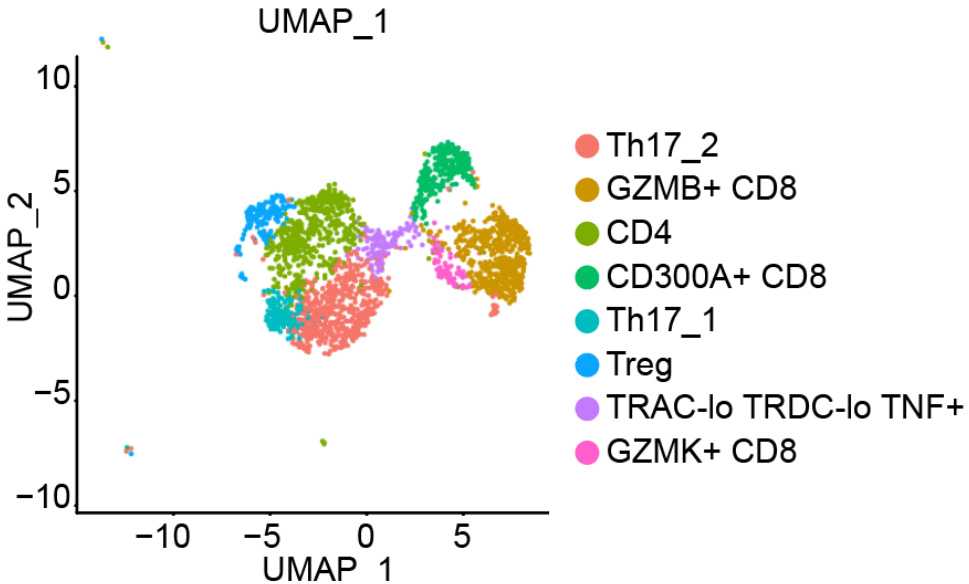
Whole Biopsy

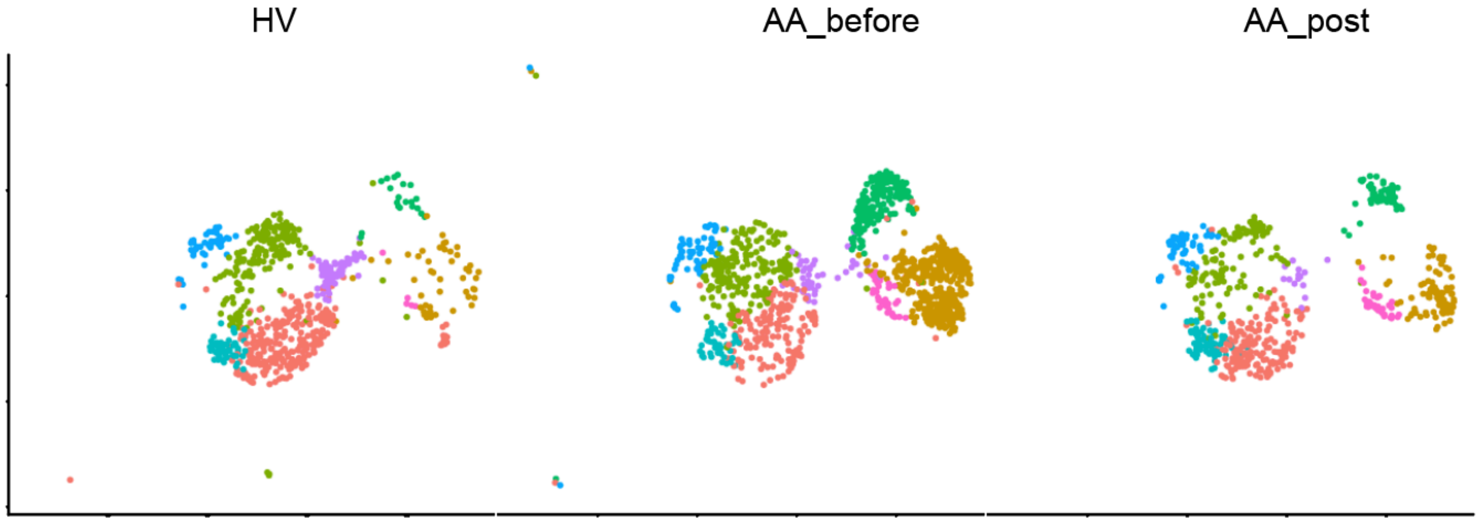


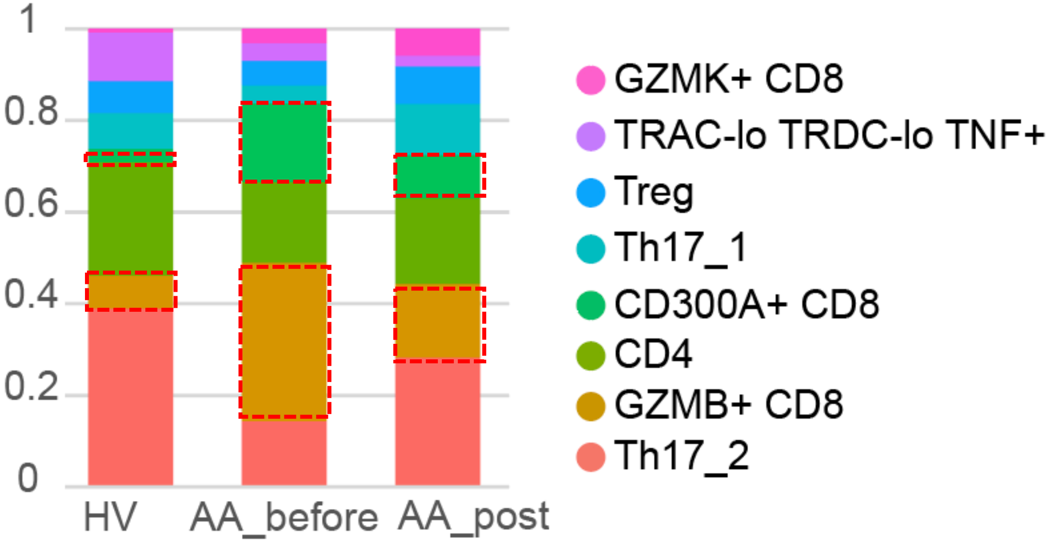
Lymphocytes



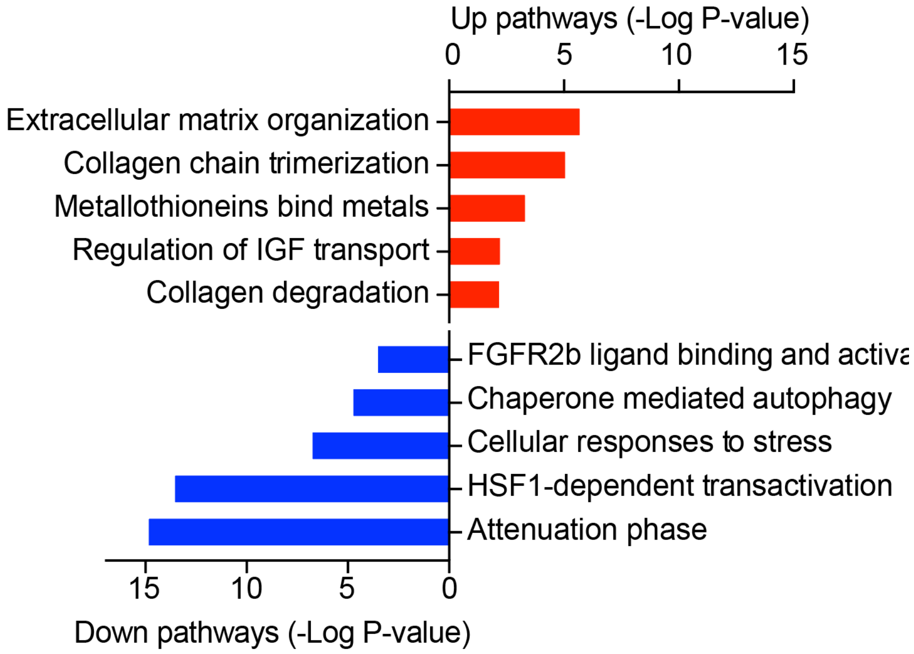
Significant changes in specific clusters

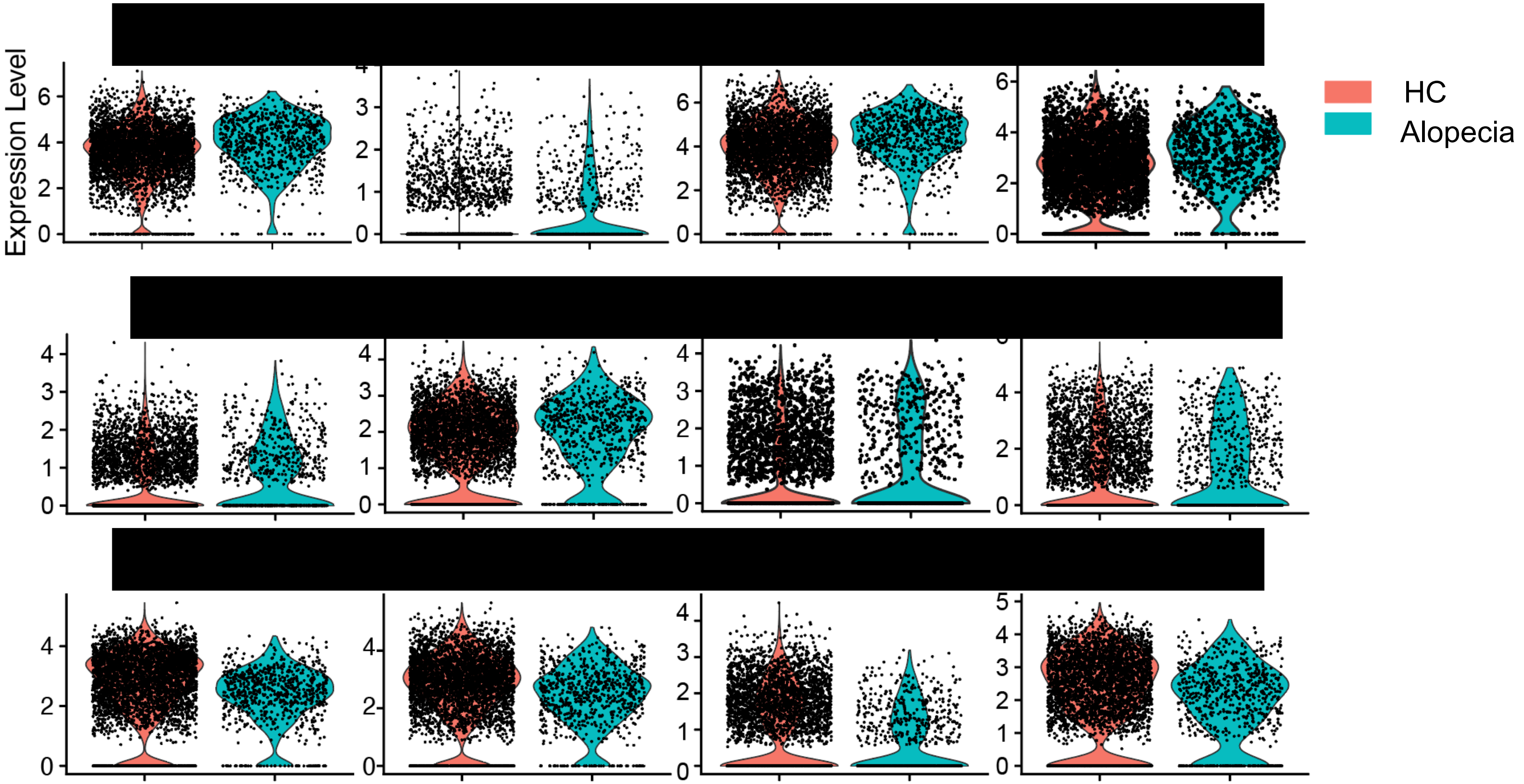






Can look at specific genes that are upregulated or downregulated




[redacted]

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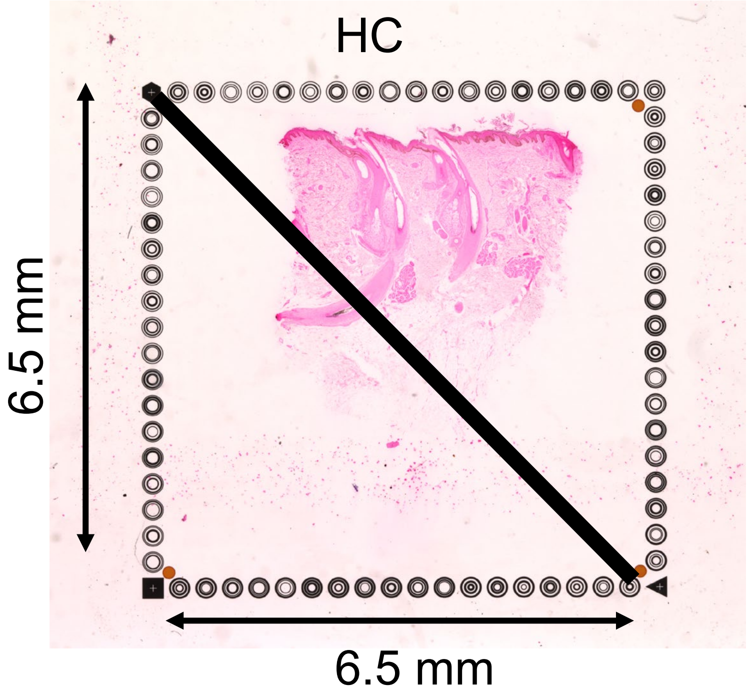
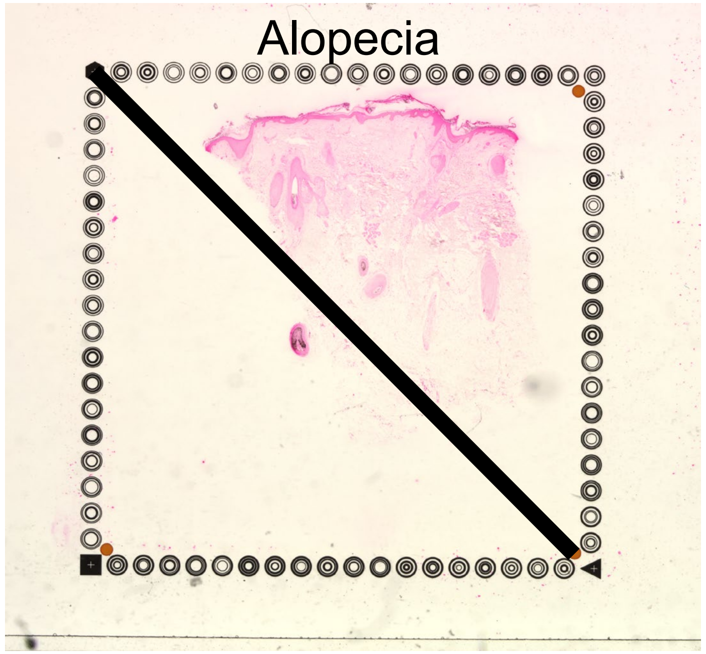
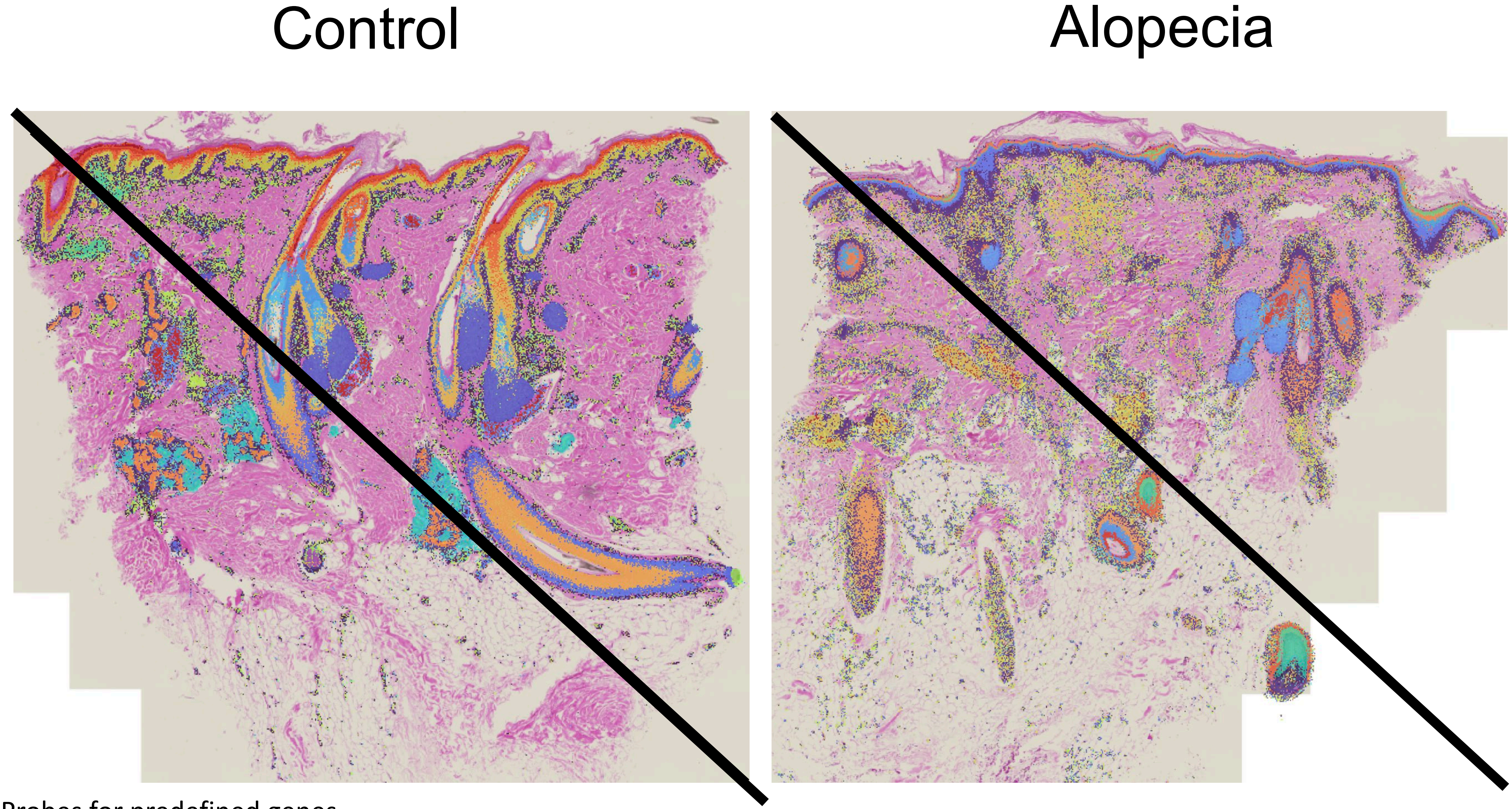
Spatial transcriptomics

CytAssist

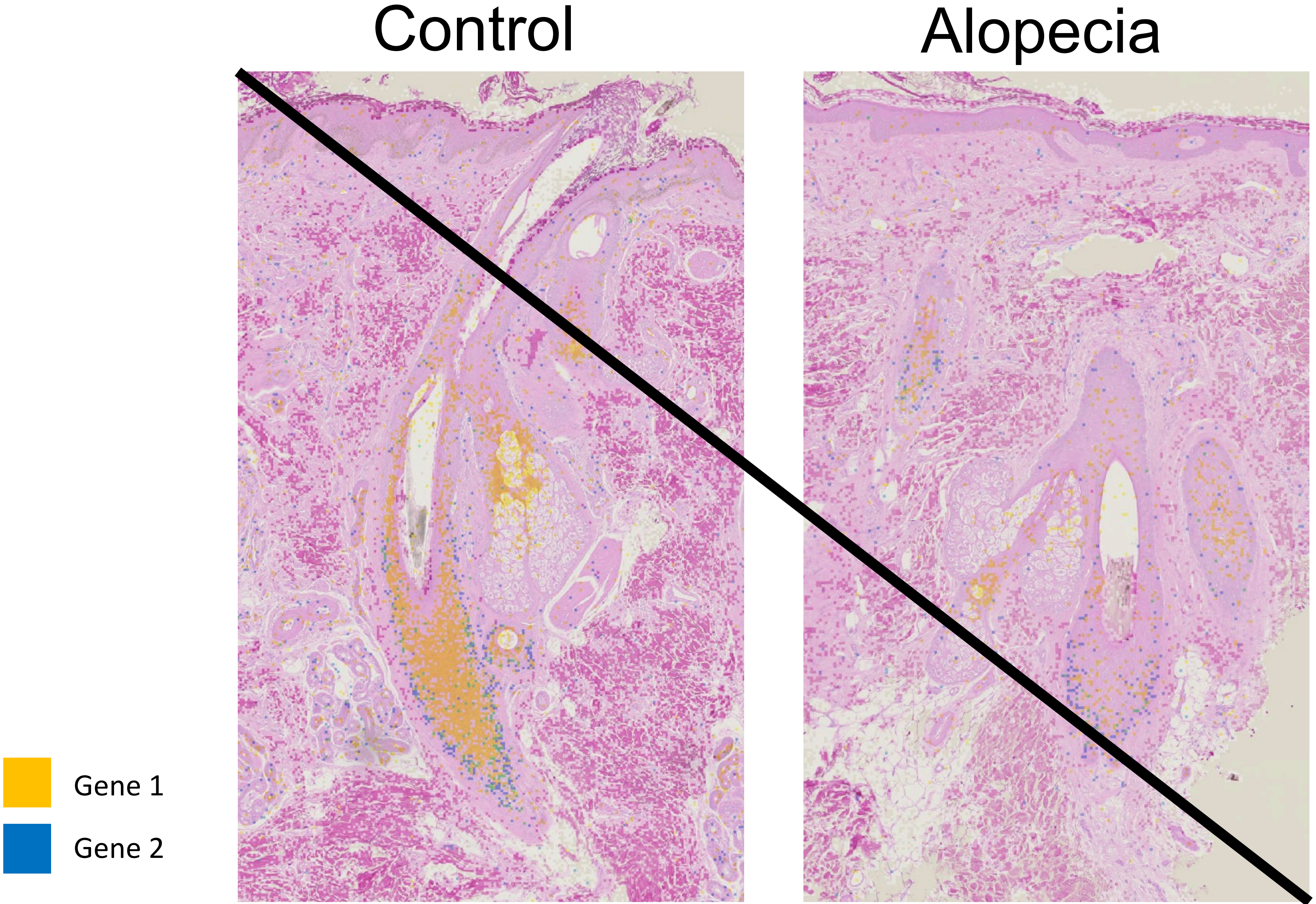




Allows incubation of tissue with specific gene probes to ask where are these Genes up or down in the context of the hair and surrounding skin



Probes for predefined genes



Control

Alopecia

Problems with this approach

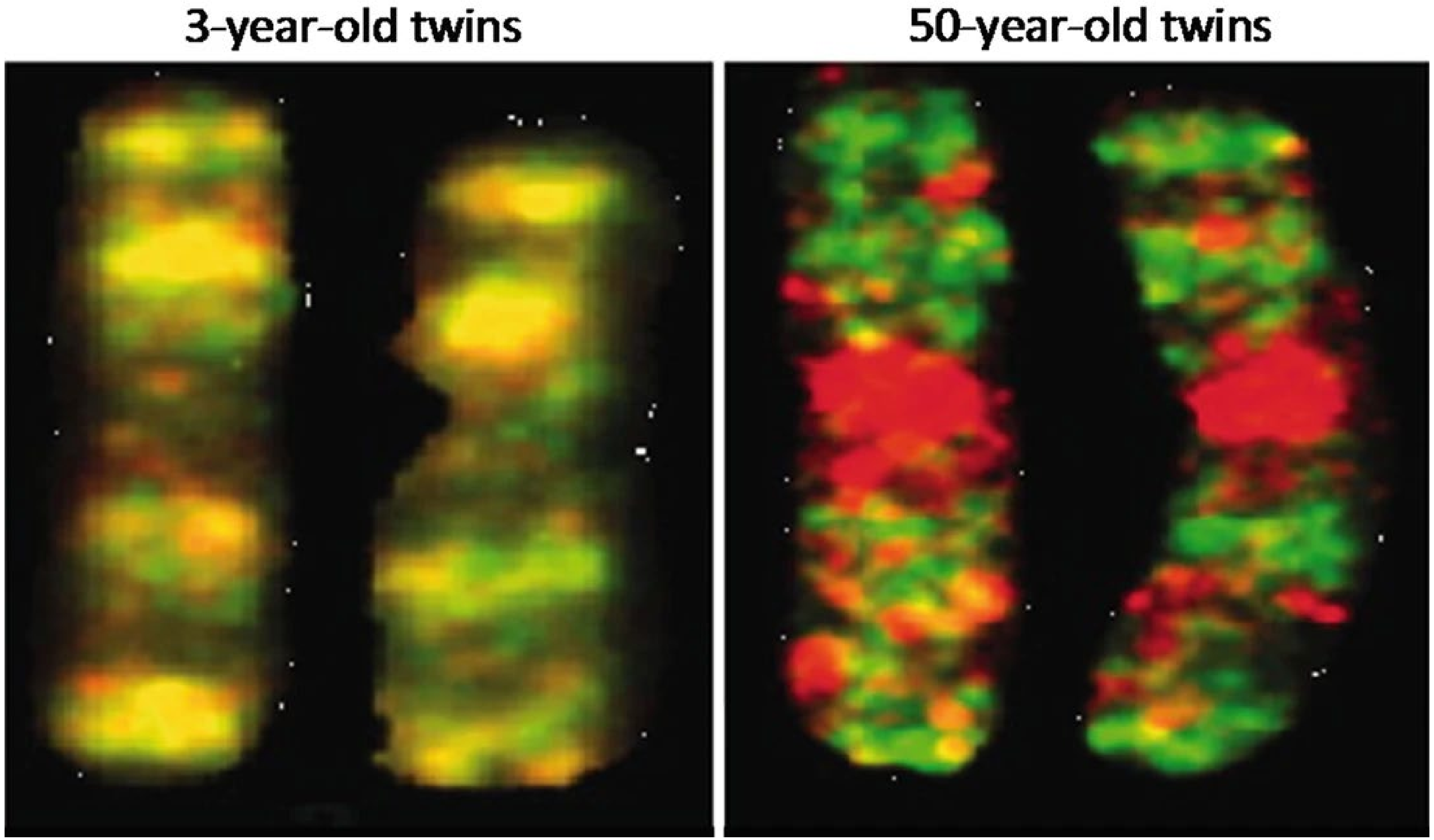
- Takes a lot of time and costs a lot of money
- Now being used mostly as a research test
- Not the complete answer
- We know about non-coding genes and we know environmental factors plays a role

Twin studies again

- The over ten-fold increase in AA concordance in siblings with identical DNA sequence compared to siblings sharing 50% genetic identity indicates a large genetic component to disease risk
- But also suggest other things play a role

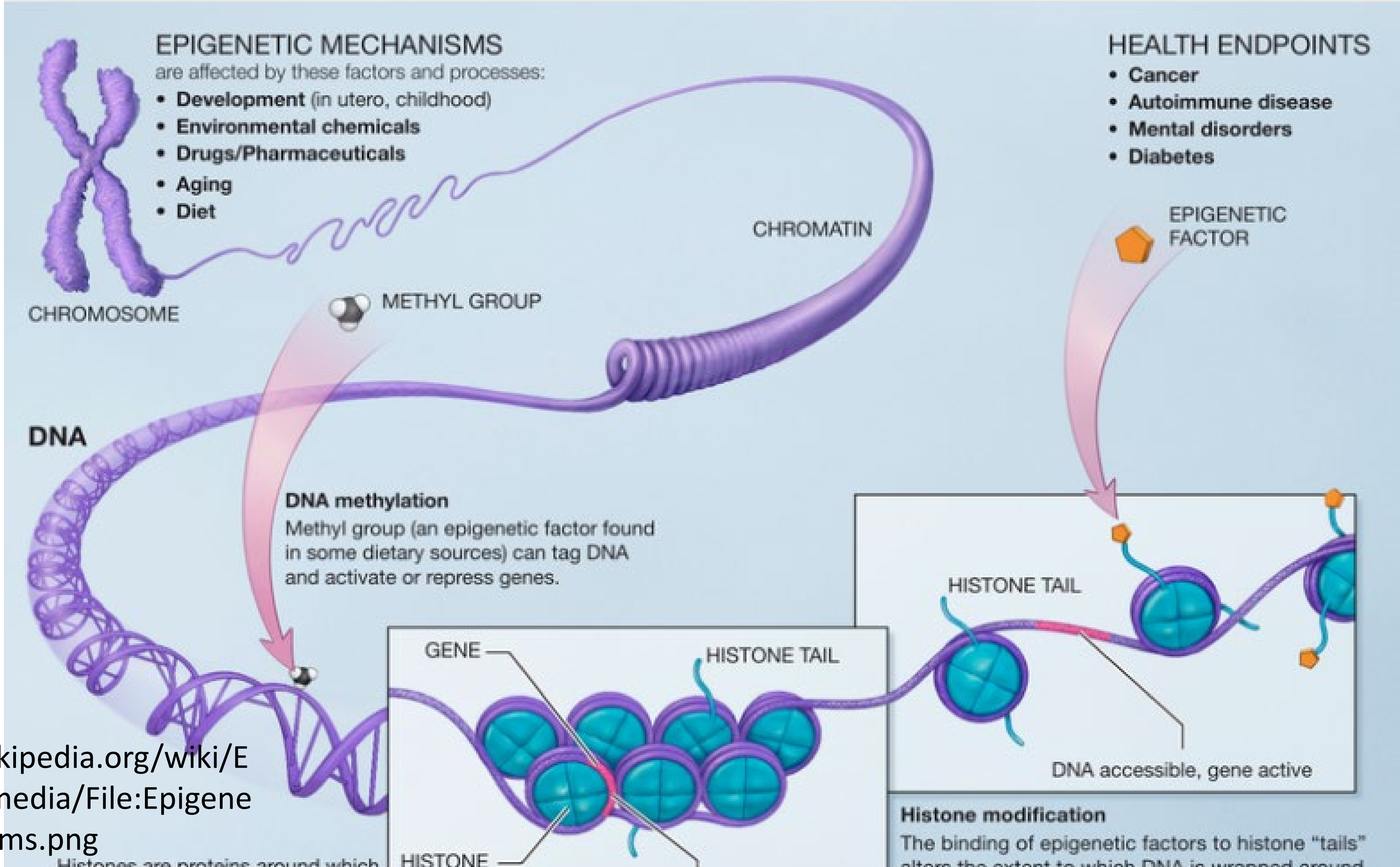
Factors contributing to the facial aging of identical twins"
B Guyuron, DJ Rowe et al., 2009, *Plast Reconstr Surg, 123(4)*, p. 1322.

Chromosome 3 methylation in 3-year-old twins vs. 50-year-old twins



"Epigenetic differences arise during the lifetime of monozygotic twins."
M.F. Fraga, E. Ballestar et al., 2005, *Proc Natl Acad Sci U.S.A.*, *102 (30)*, p. 10607

Epigenetics: **changes in DNA** that do not involve alterations to the underlying sequence



are affected by these factors and processes:

- **Development** (in utero, childhood)
- **Environmental chemicals**
- **Drugs/Pharmaceuticals**
- **Aging**
- **Diet**

HEALTH ENDPOINTS

- **Cancer**
- **Autoimmune disease**
- **Mental disorders**
- **Diabetes**

DNA methylation

Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histone modification

The binding of epigenetic factors to histone "tails"

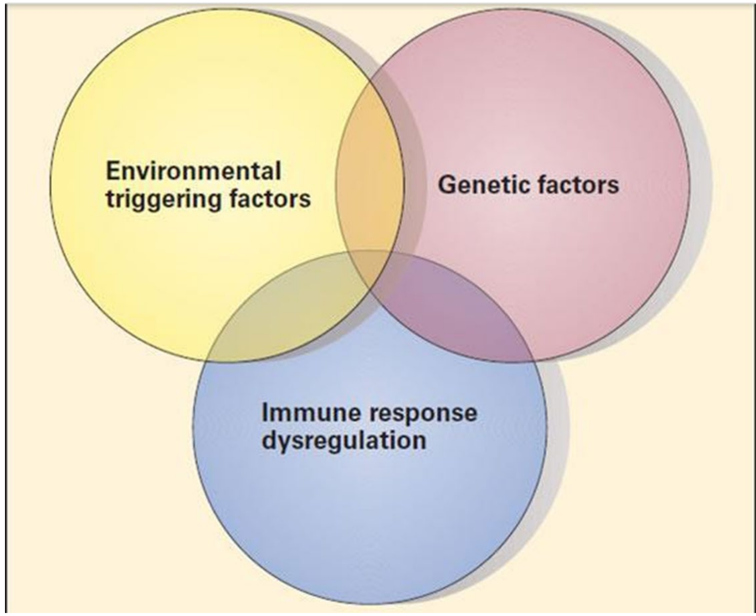
https://en.wikipedia.org/wiki/Epigenetics#/media/File:Epigenetic_mechanisms.png

Can these be targets of therapy?

- Targeting epigenetic factors may be more specific than targeting the immune system pathways
- If we know a specific gene expression is up or down in an individual’s tissue can we use epigenetic therapeutics to do the opposite.
- This is happening for other diseases: histone modifying enzymes for Colorectal Cancer

So is Alopecia Areata Genetic?

Summary



- Progress has been made
- Combined effects of risk alleles important
- The more we learn about genetics, the more we need to know
- Transcriptional variation at the tissue level is happening
- Spatial Transcriptomics tell us about tissue gene expression changes
- Epigenetics of alopecia is an area that may lead to additional therapeutics and potentially enable understanding of environmental factors impact on autoimmune disease

Thank you!

Questions?

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Final Disclosure

- This talk represents my own views of the science and not necessarily my employer, The National Institutes of Health