



The Role of the Skin Microbiome in Eczema

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The human skin is an effective barrier

Epidermal Hydration

Mechanical Barrier

Permeability Barrier

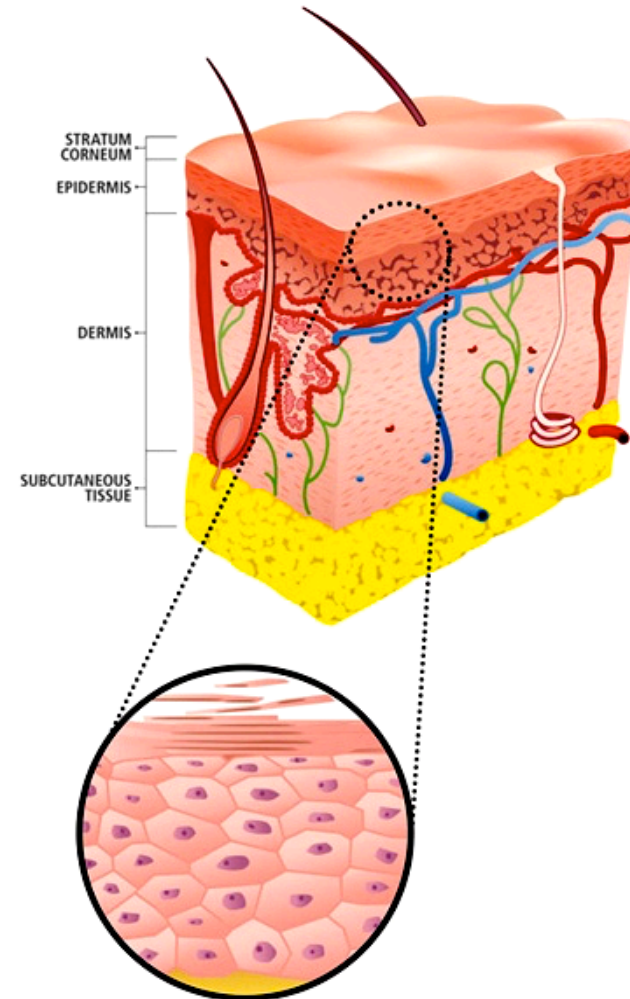
Waterproof Barrier

Anti-microbial Barrier

Anti-oxidant Barrier

Anti-UV Barrier

Initiation of inflammation

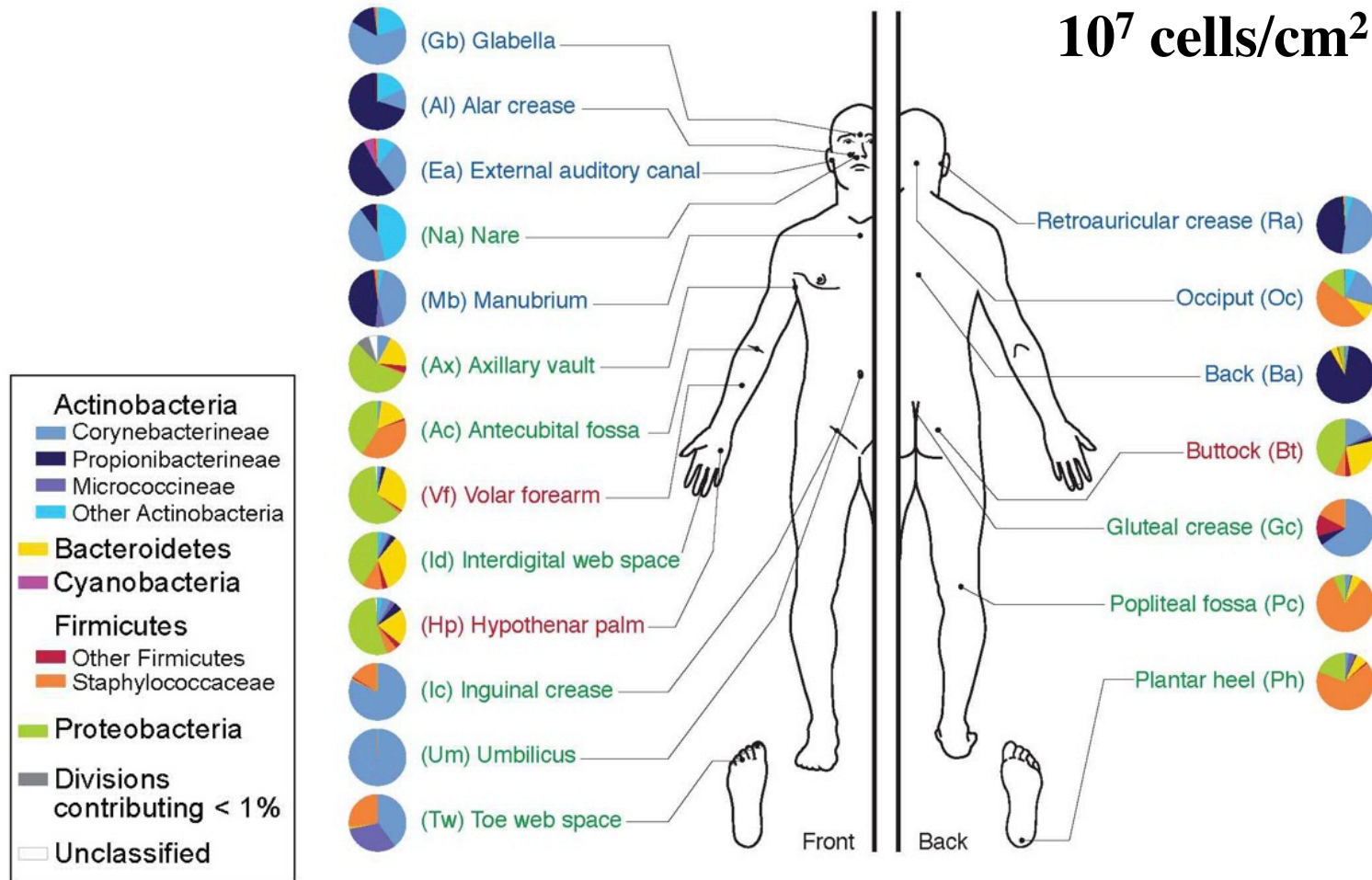


Infection transmission via skin



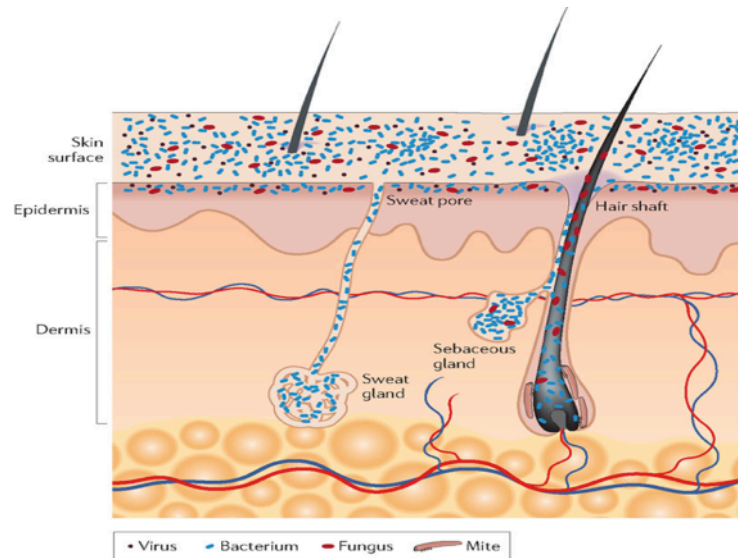
Conjunctivitis, Acne, Staph/Strep infections,
Herpes, Yeast infections, Ebola, RSV, Hand-
foot-mouth disease, Athlete's foot, ...

Microbial Communities on Skin



<http://www.genome.gov/pressDisplay.cfm?photoID=20169>

How do skin bacteria contribute to host health?



Nature Reviews | Microbiology

Skin Microbiome

- Co-evolved with us
- Homeostatic and protective function?



Gut Microbiome

- Nutrient Acquisition
- Drug Metabolism
- Development of Immune System

Credit: Matej Bajzer & Randy J. Seeley. Nature 444, 1009-1010 (21 December 2006)

Disease Phenotype: Atopic Dermatitis (AD)

Dry and itchy skin
Broken skin barrier

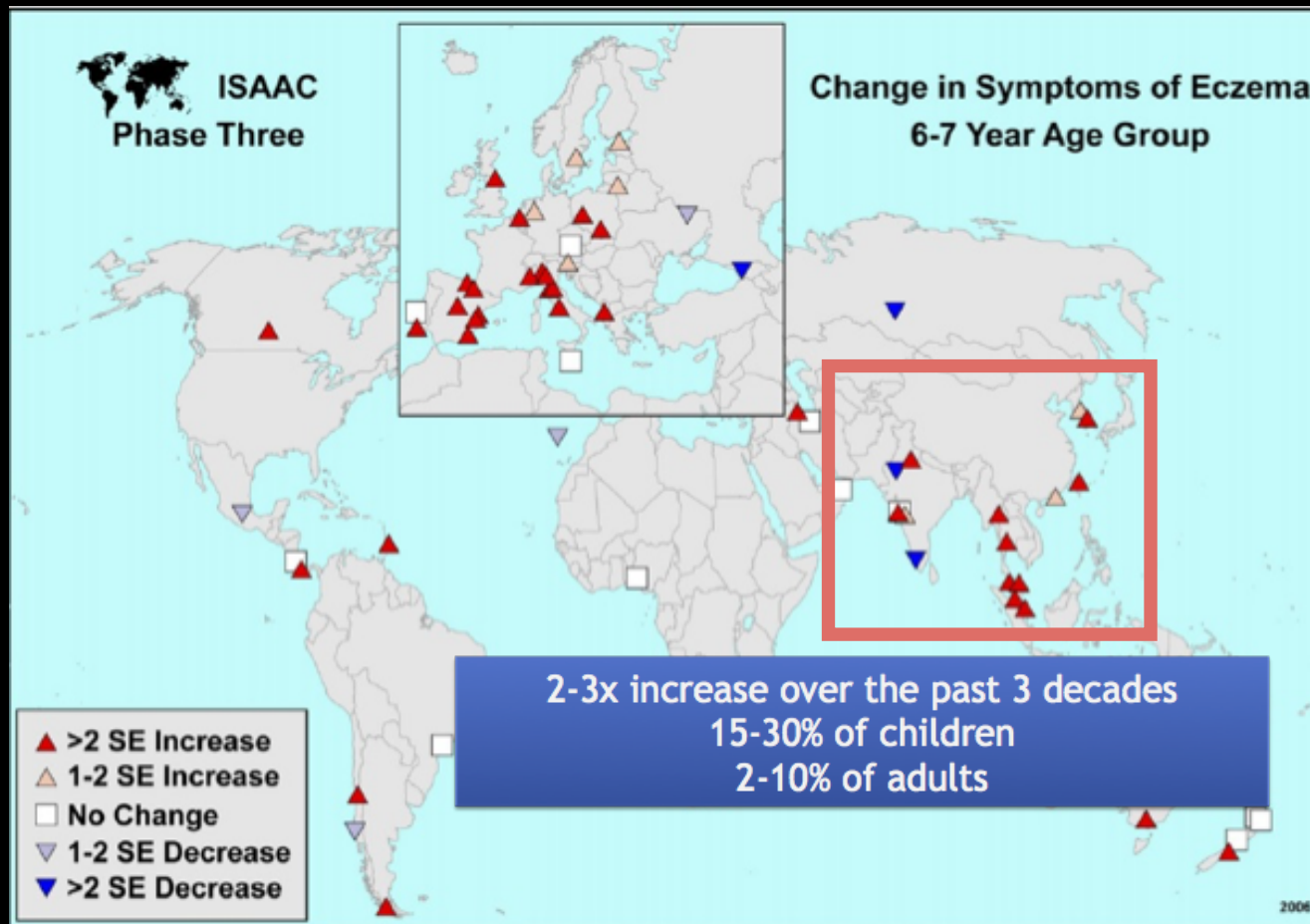


Inflamed lesions that are
prone to bacterial infection

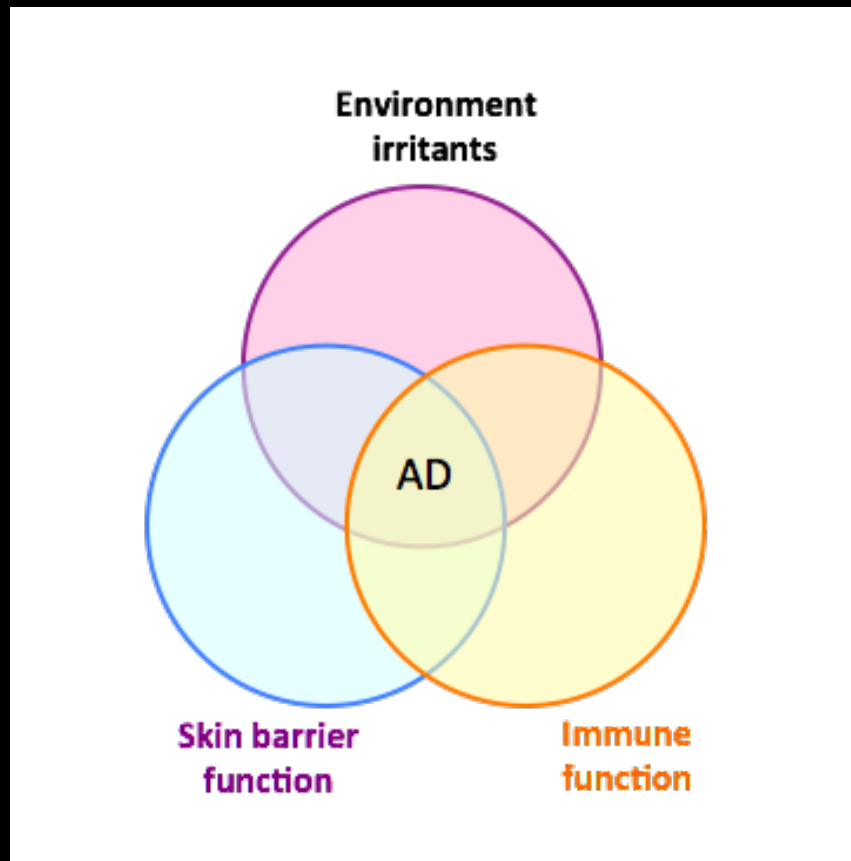


The Atopic Epidemic

International study on Asthma and Allergies in childhood



What causes atopic dermatitis?



Complex interplay between

- Skin Barrier
- Immune system
- Environment
 - Microbiome

Microbiome-wide Association study for AD

On visually normal, undamaged skin

Cohorts



Normals

no history of AD or allergy



SPT+

Allergy, no history of AD



AD

Active AD patients

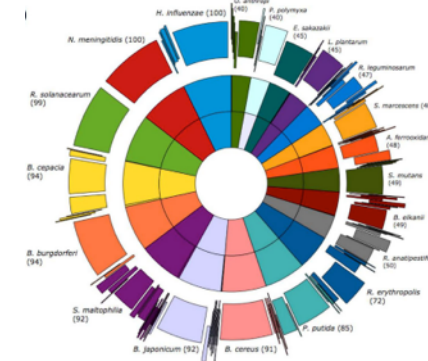
Analysis



Sampling Area:
Antecubital fossa



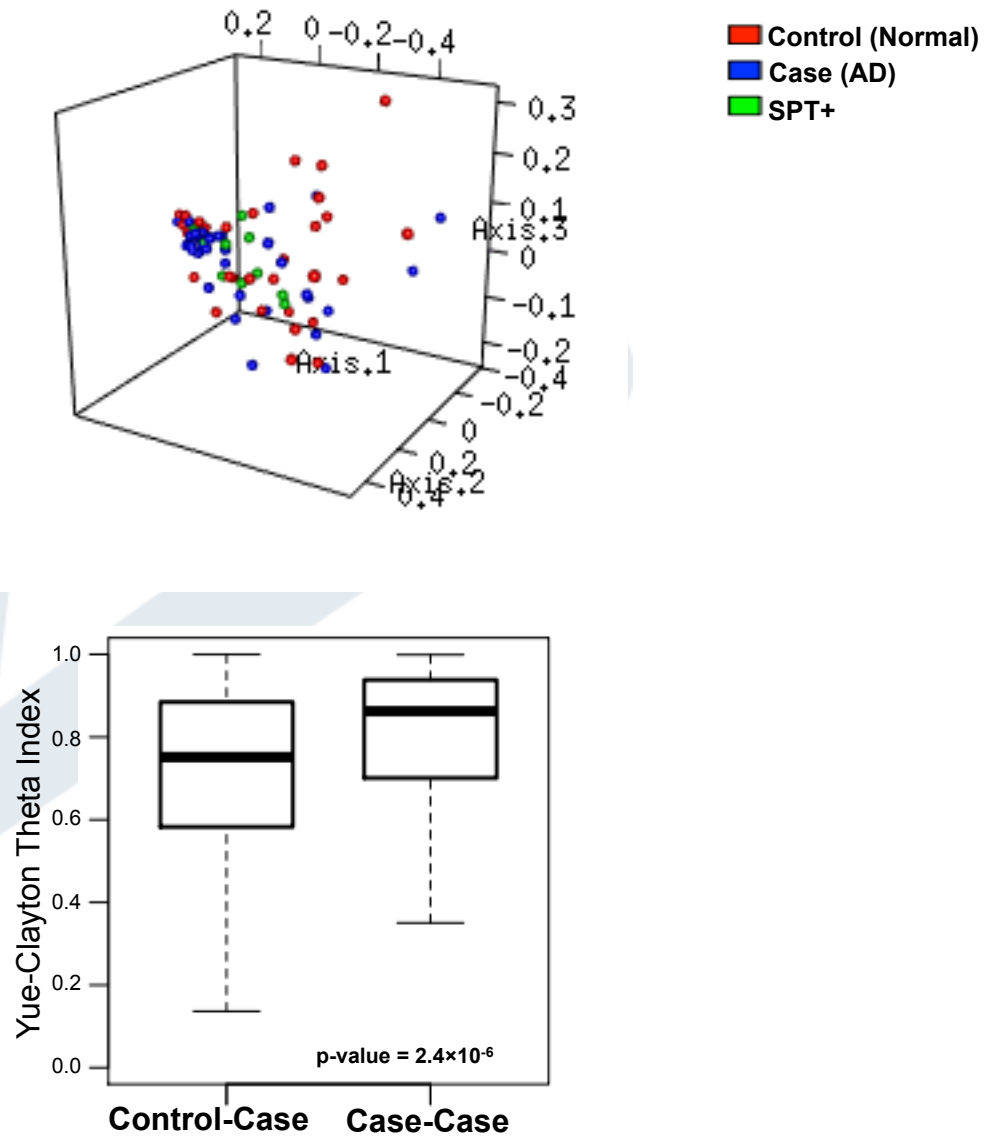
High-throughput
DNA Sequencing



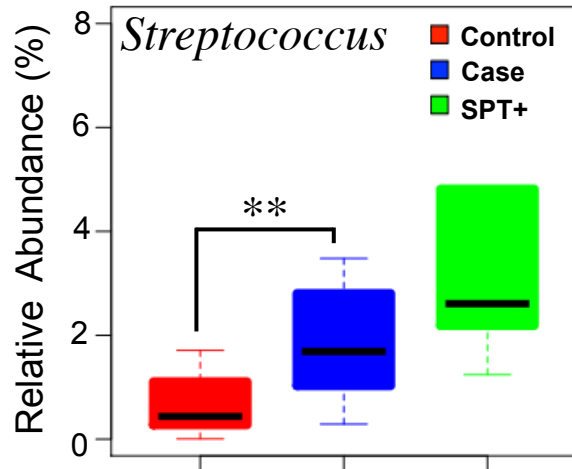
Relative abundance
and statistical analysis

Chng KR, Tay ASL, Li C, Ng AHQ, ..., Lane EB, Chew FT, Common JEA#, Nagarajan N# "Whole metagenome profiling reveals skin microbiome-dependent susceptibility to atopic dermatitis flare"
Nature Microbiology 2016 1:16106 doi:10.1038/nmicrobiol.2016.106

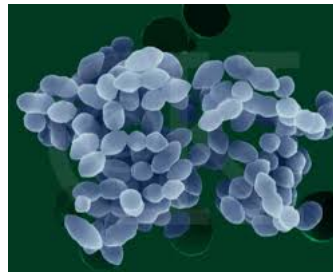
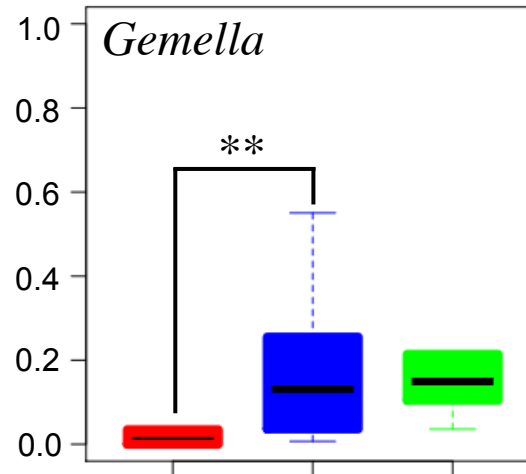
Bacterial Diversity on Normal Skin



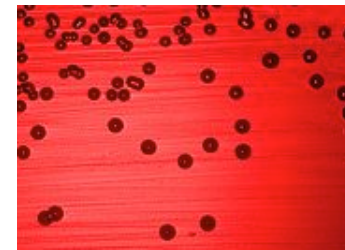
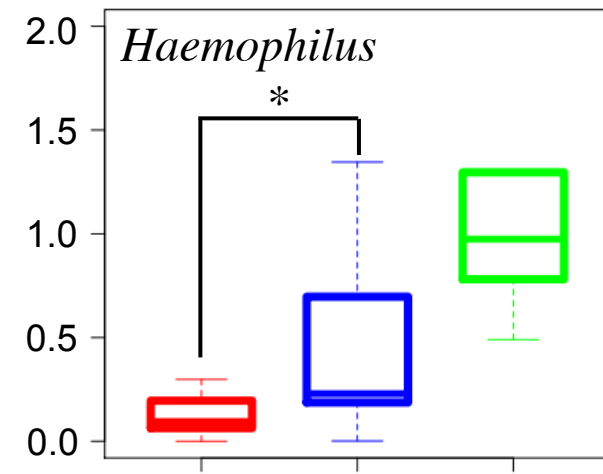
Enrichment of opportunistic pathogens in AD



Known to cause skin and oral infections.
Changes specific to α -hemolytic group

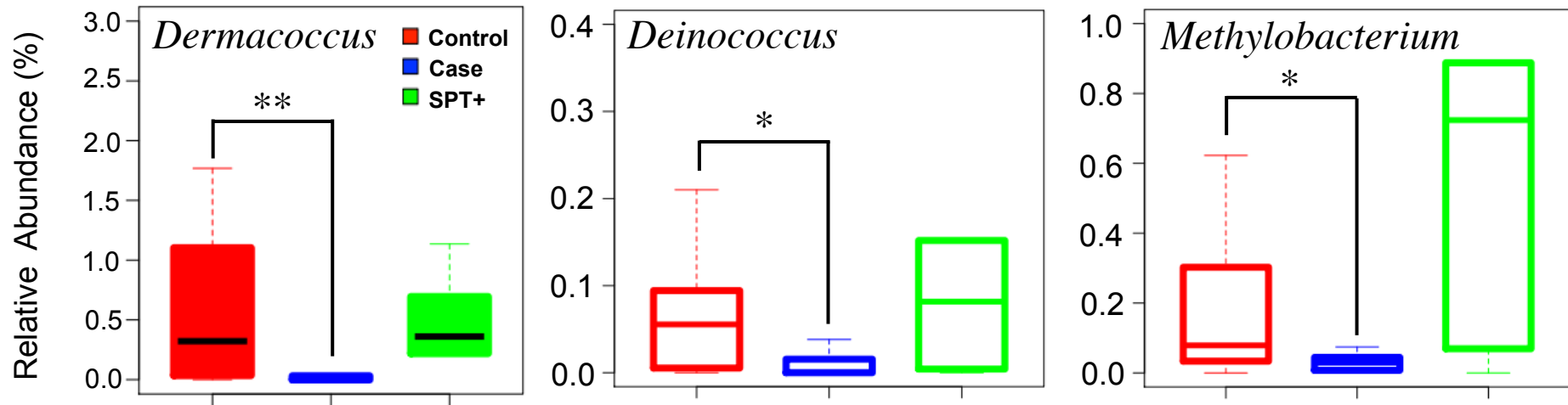


Can aggravate symptoms in Cystic Fibrosis



Staphylococci produce factors that promote the growth of *Haemophilus*

Depletion of metabolically versatile bacteria



Actinomycetales are known for producing secondary metabolites with anti-inflammatory and anti-microbial properties



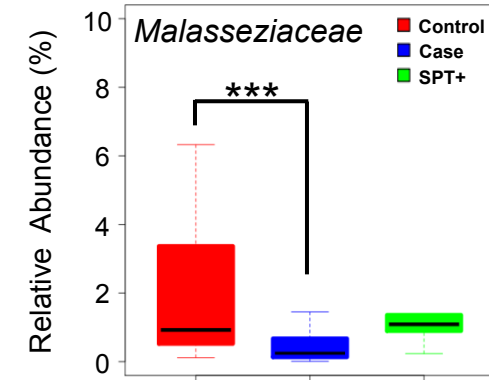
Radiation tolerant and metabolically versatile



Found commonly on human feet

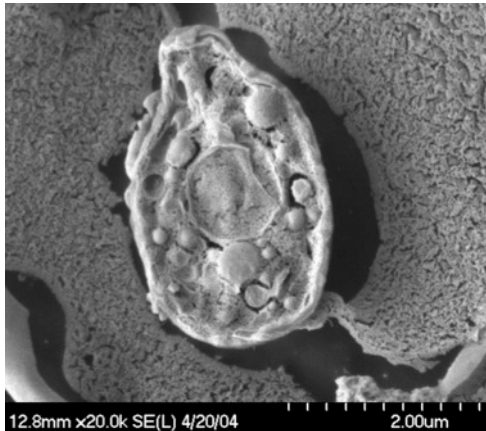
Viruses & Eukaryotes

- No association for Viruses
- Significant depletion of *Malassezia*
 - Lipid dependent and adapted to skin
 - Associated with **Dandruff**, Seborrhoeic dermatitis, Tinea Versicolor



Malassezia Genome Database

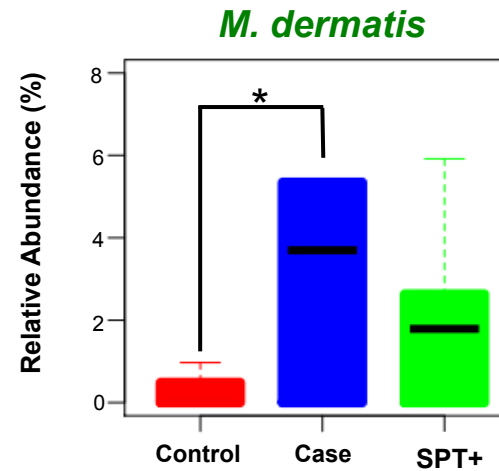
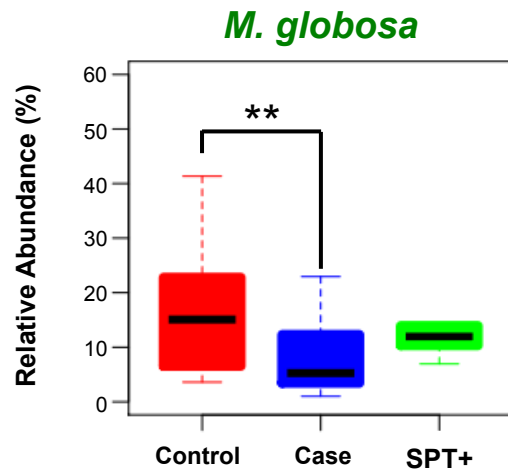
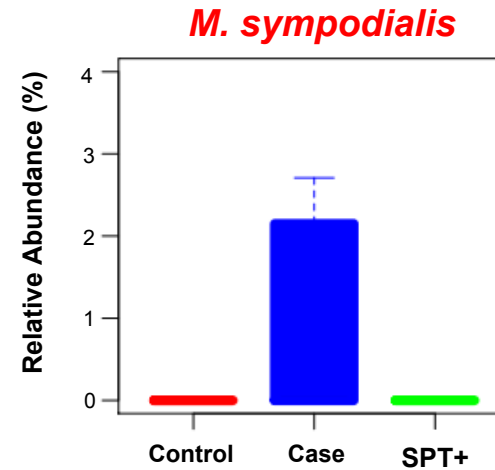
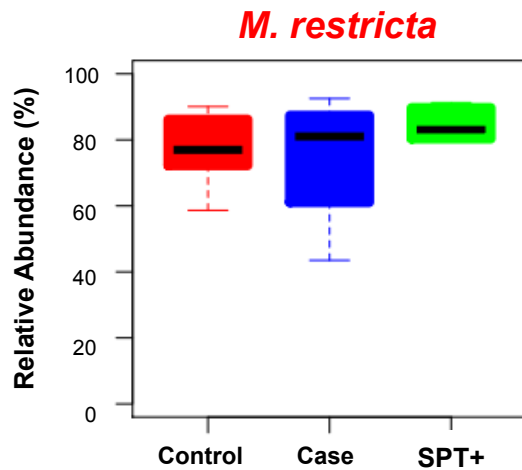
Reference genome and annotation for all **14 species** and **24 strains** of the genus



Genus-Wide Comparative Genomics of *Malassezia* Delineates Its Phylogeny, Physiology, and Niche Adaptation on Human Skin

Guangxi Wu¹, He Zhao², Chenhao Li¹, Menaka Priyadarsani Rajapakse¹, Wing Cheong Wong³, Jun Xu⁴, Charles W. Saunders⁴, Nancy L. Reeder⁴, Raymond A. Reilman⁴, Annika Scheynius⁵, Sheng Sun⁶, Blake Robert Billmyre⁶, Wenjun Li⁷, Anna Floyd Averette⁶, Piotr Mieczkowski⁸, Joseph Heitman⁶, Bart Theelen⁹, Markus S. Schröder¹⁰, Paola Florez De Sessions¹, Geraldine Butler¹⁰, Sebastian Maurer-Stroh^{3,11}, Teun Boekhout⁹, Niranjan Nagarajan^{1*}, Thomas L. Dawson, Jr.^{12*}

Association with specific *Malassezia* species



HOST-MICROBIOME INTERACTIONS

Cause vs Effect in relation to AD

1. Direct cell-to-cell interactions

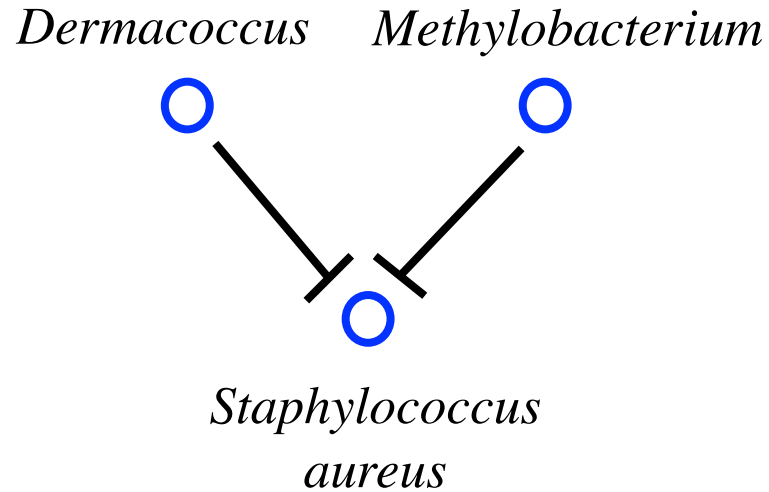
Microbe-human, microbe-microbe

2. By altering the microenvironment

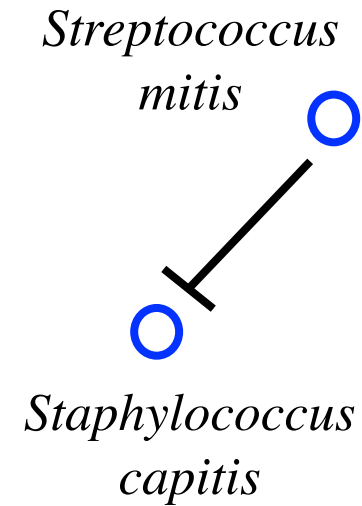
3. Immune-system mediated

AD-associated microbiome inhibits *S. aureus*

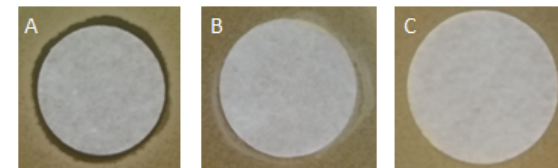
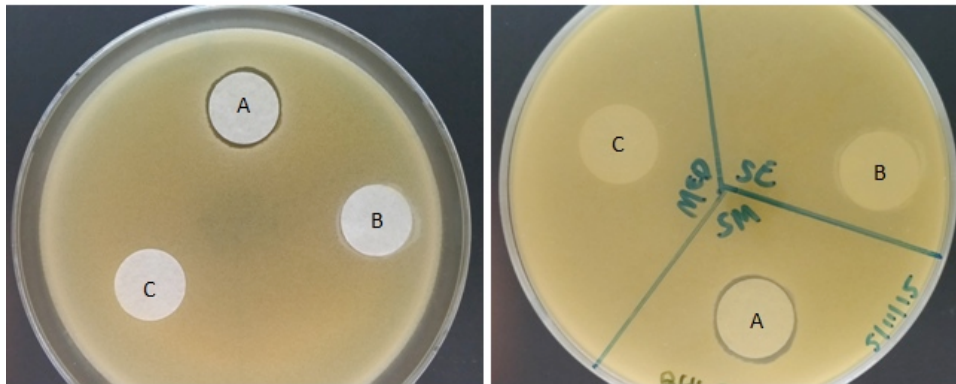
All Subjects



AD Subjects



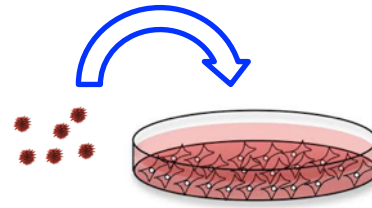
Bacterial Inhibition Assay – *S. aureus* culture



- A – *Streptococcus mitis*
- B – *Staphylococcus epidermidis*
- C – BHI Media

AD associated bacteria elicit distinct immune responses

BF: *Bacillus firmus*



Bacteria

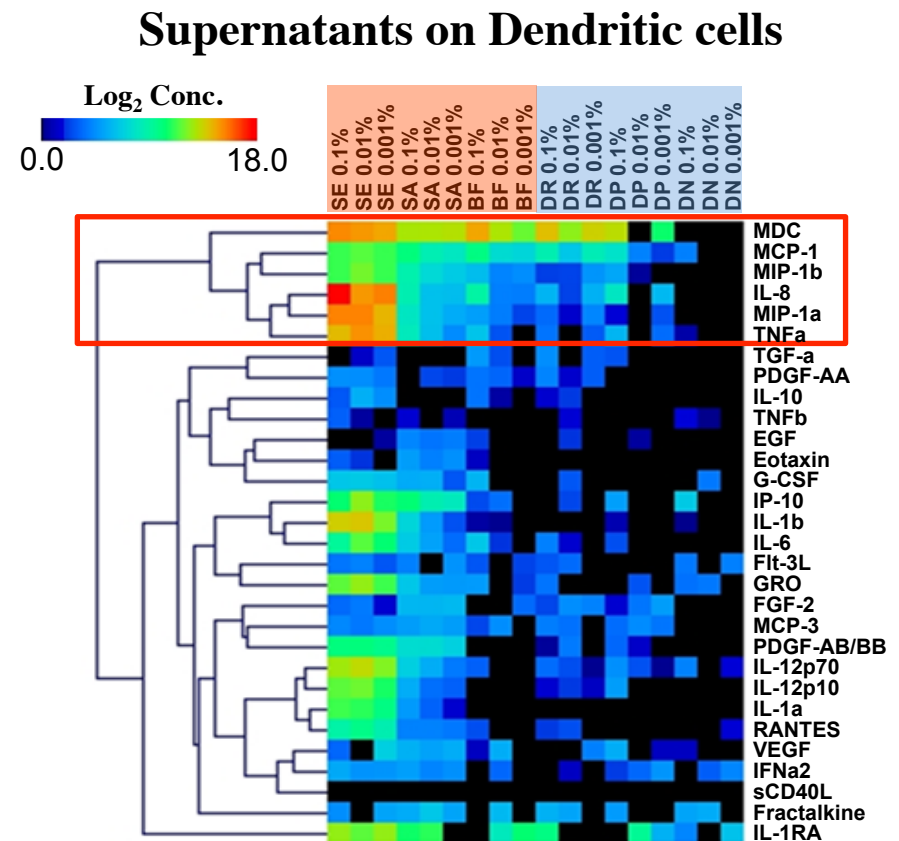
Human cells
(NHEKs, MoDCs)

DP: *Dermaococcus profundus*

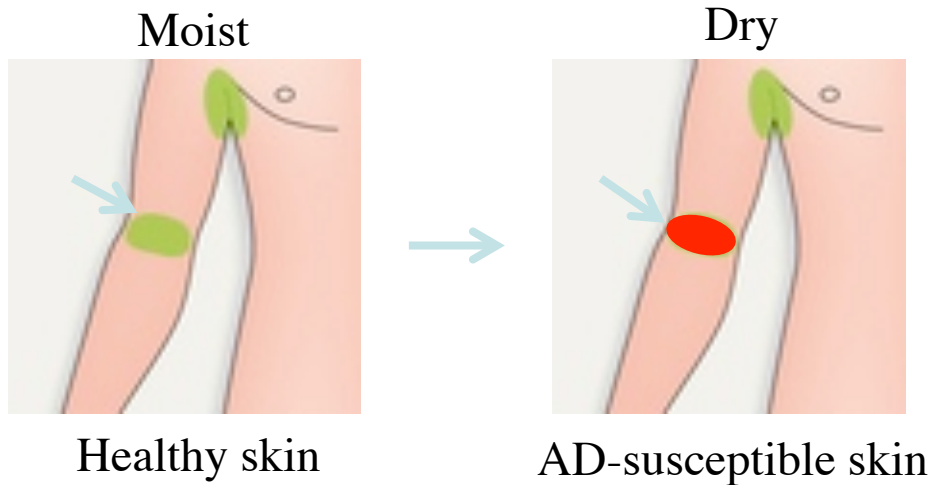
- ## 1. Flare associated bacteria (*S. epidermidis* and *S. aureus*) induce strong immune response

- TNF-driven myeloid activating and Th1 polarizing cytokine signature

- ## 2. Depleted bacteria (*D. nishinomiyaensis* and *D. radiodurans*) elicit minimal response



AD skin selects for *S. aureus* strains



geh gene - Lipase gene
(glycerol ester hydrolase) is
important for virulence.

DNA Sequence data

AD susceptible skin = *geh*^{Arg 373}
 Normal skin = *geh*^{Thr 373}

Dry skin sites = *geh*^{Arg 373}
Moist skin sites = *geh*^{Thr 373}

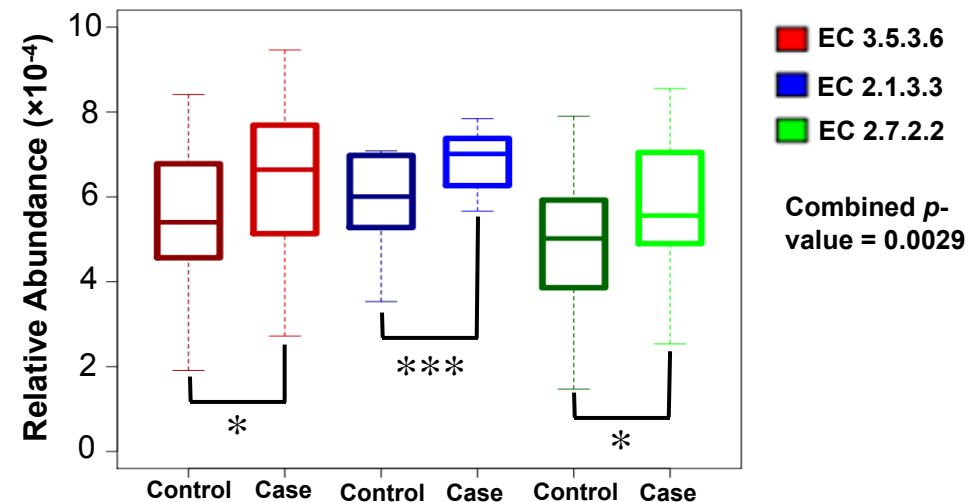
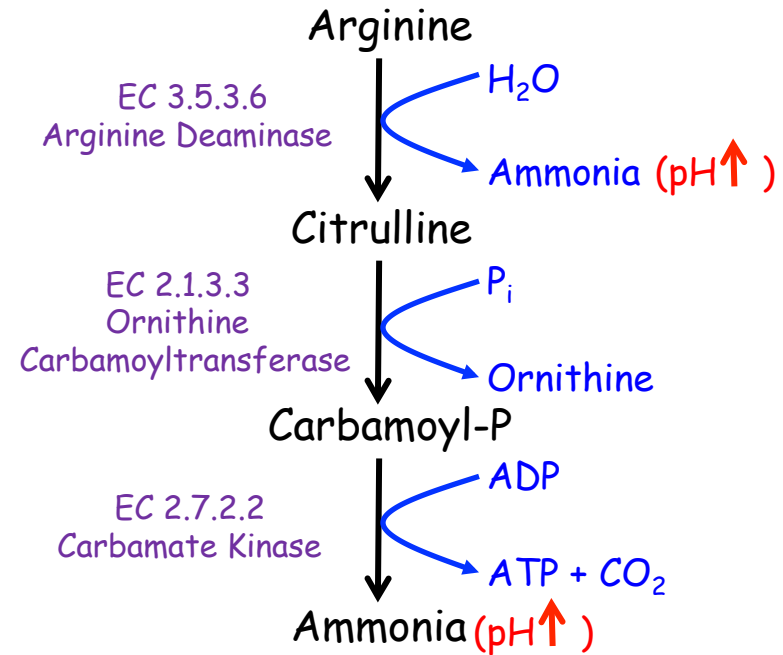
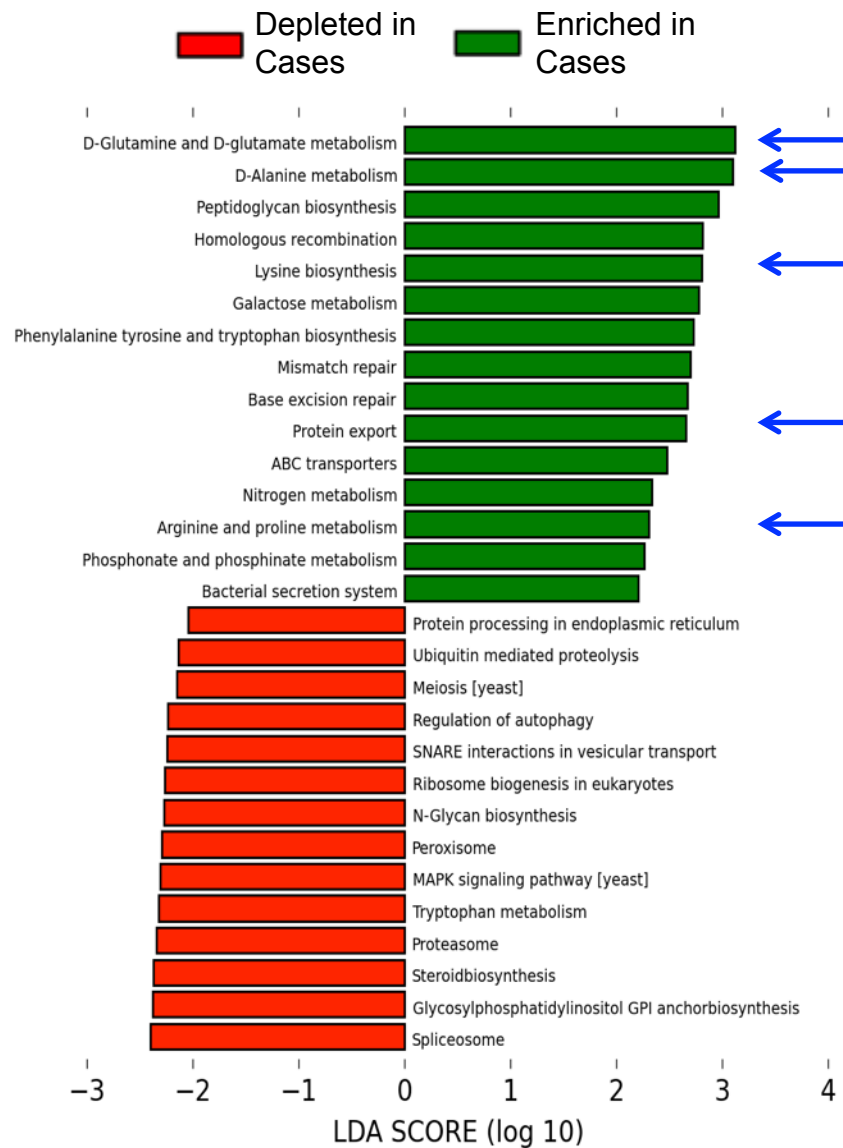
Cases vs Controls in our study

[illegible]

Dry vs Moist sites in Oh et al, Nature 2014

[illegible]

Perturbed microbial metabolism on AD skin



Summary

