



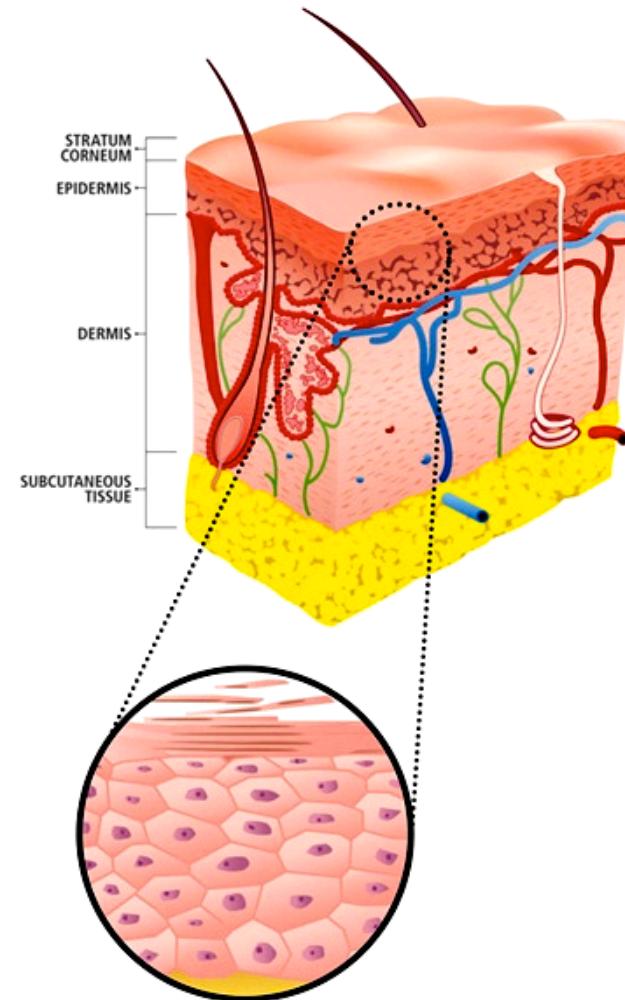
# **The Role of the Skin Microbiome in Eczema**

**Niranjan Nagarajan**

Associate Director and Group Leader  
Computational & Systems Biology

# 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

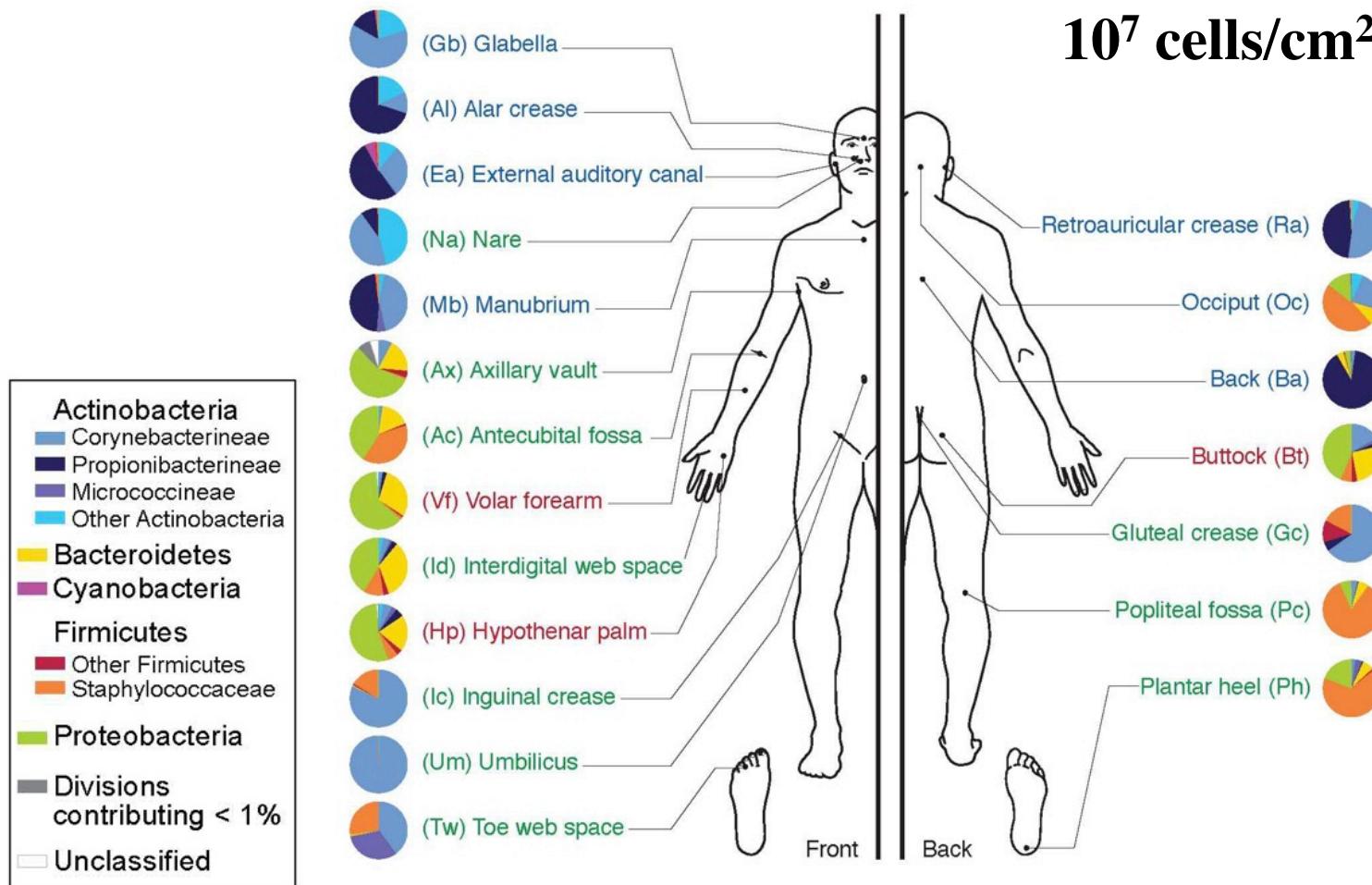


# Infection transmission via skin



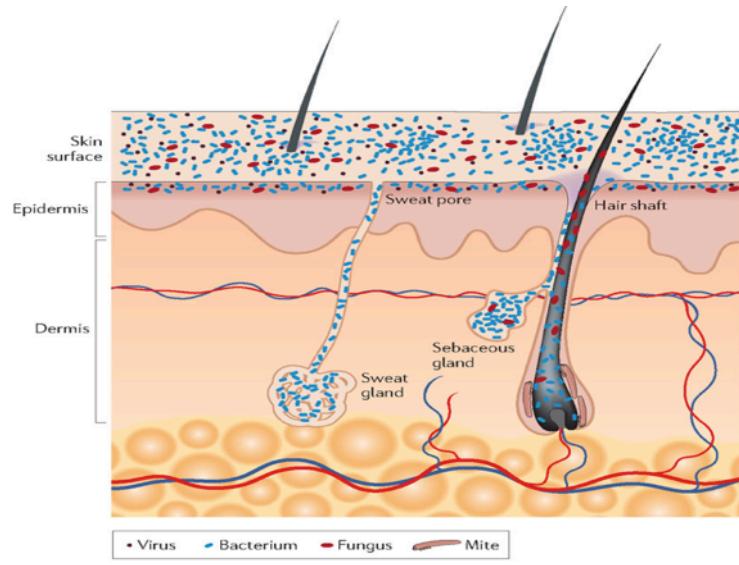
Conjunctivitis, Acne, Staph/Strep infections,  
Herpes, Yeast infections, Ebola, RSV, Hand-  
foot-mouth disease, Athlete's foot, ...

# Microbial Communities on Skin



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

# How do skin bacteria contribute to host health?



## Skin Microbiome

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



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

## Gut Microbiome

- Nutrient Acquisition
- Drug Metabolism
- Development of Immune System

# Disease Phenotype: Atopic Dermatitis (AD)

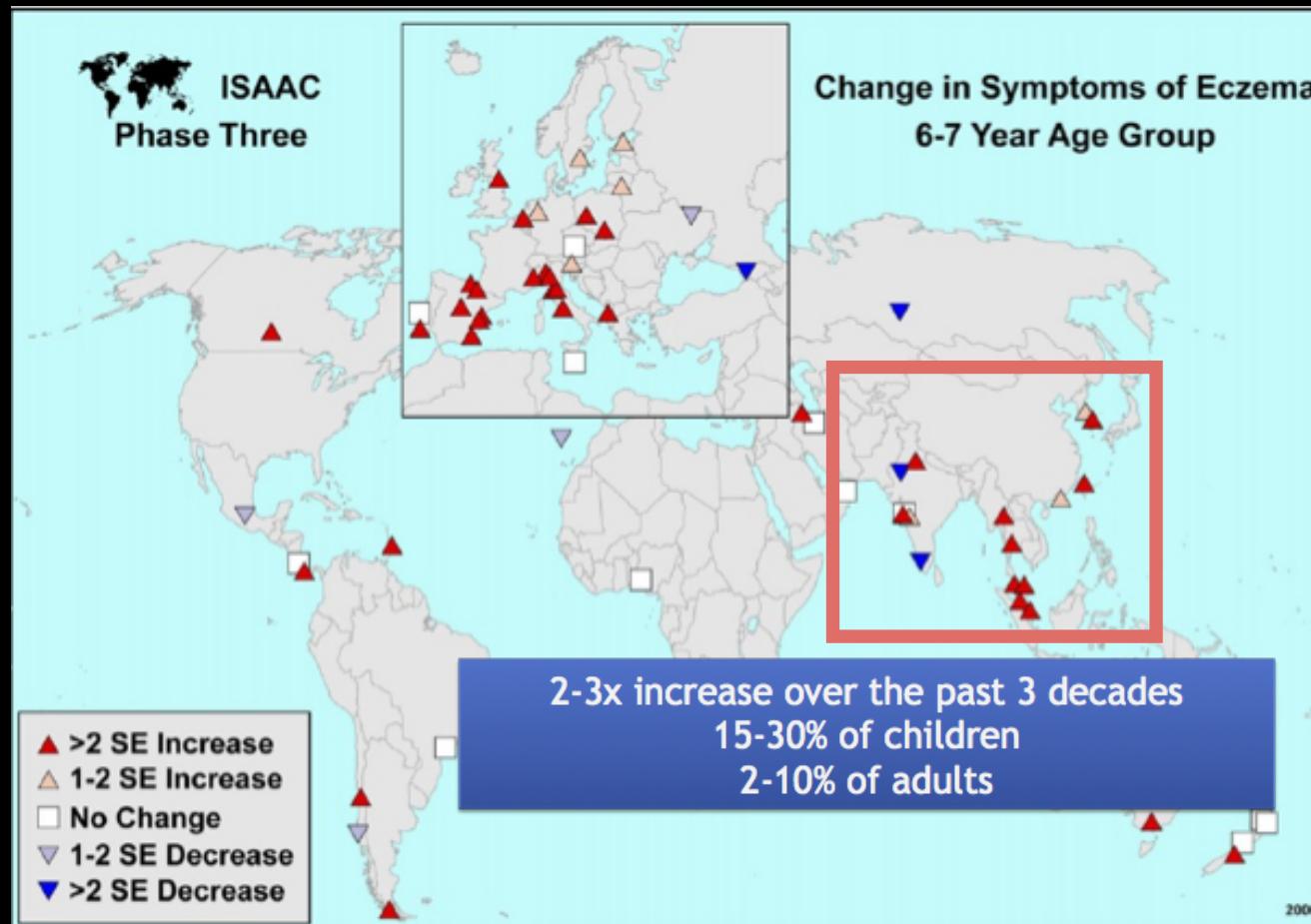
Dry and itchy skin  
Broken skin barrier

Inflamed lesions that are  
prone to bacterial infection



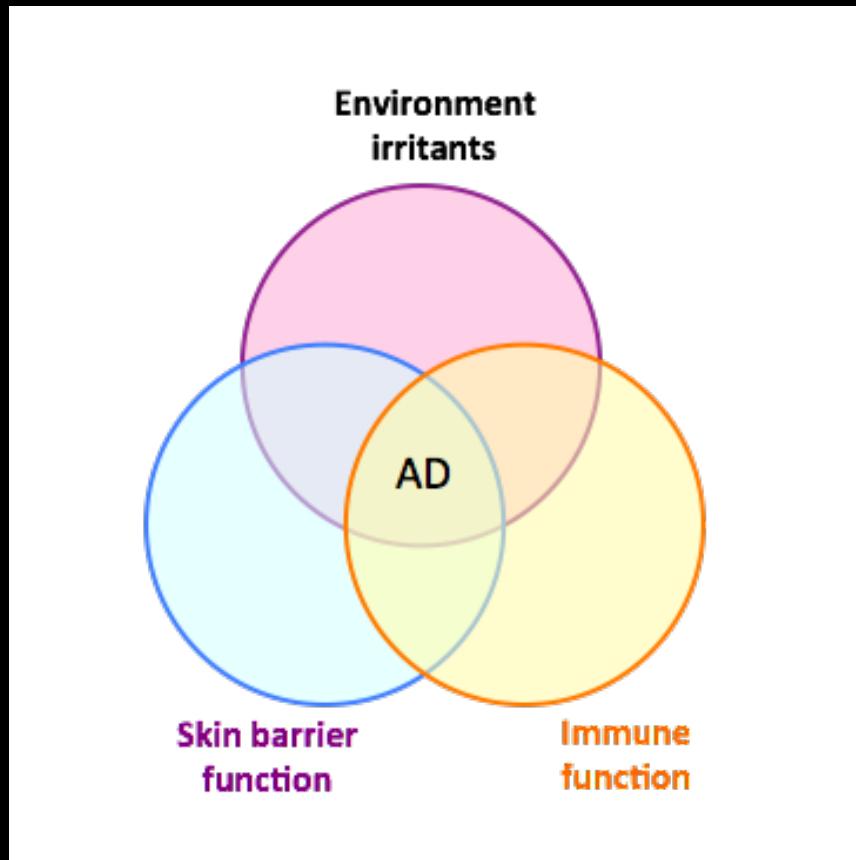
# The Atopic Epidemic

International study on Asthma and Allergies in childhood



# What causes atopic dermatitis?

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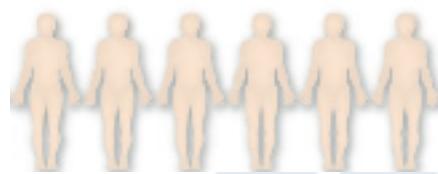
Complex interplay between

- Skin Barrier
- Immune system
- Environment
  - Microbiome

# Microbiome-wide Association study for AD

## On visually normal, undamaged skin

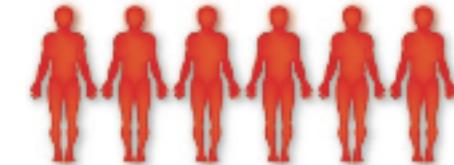
Cohorts



**Normals**  
no history of AD or allergy

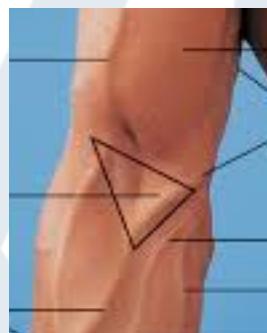


**SPT+**  
Allergy, no history of AD



**AD**  
Active AD patients

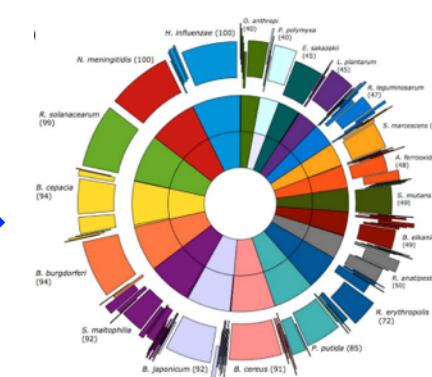
Analysis



**Sampling Area:**  
Antecubital fossa



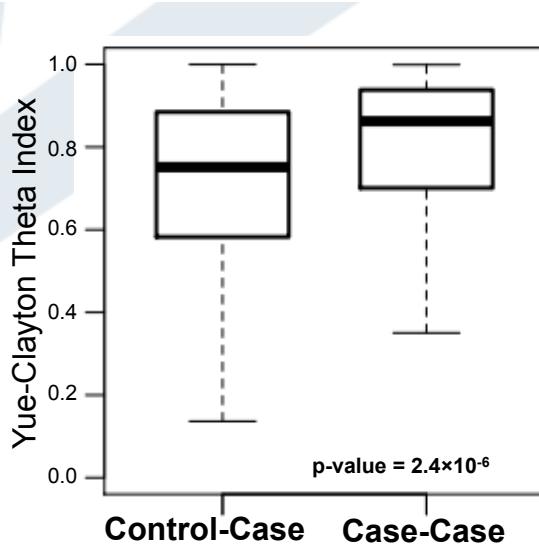
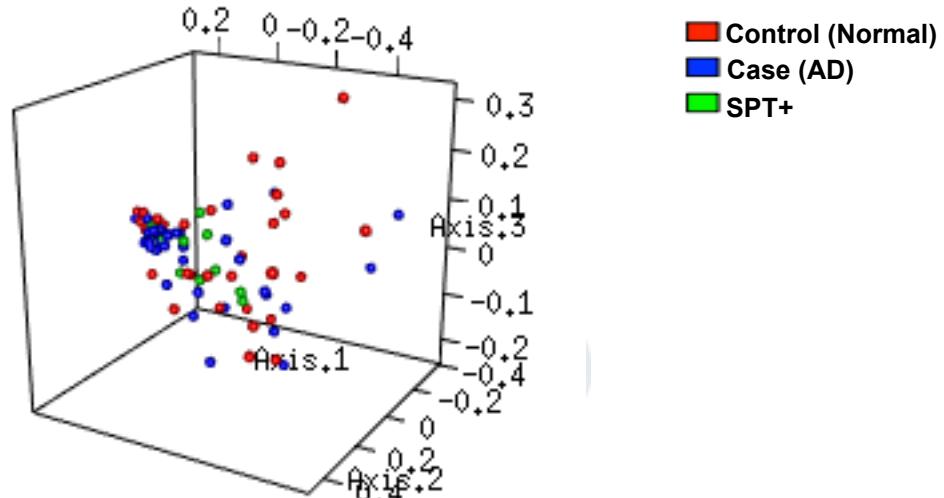
**High-throughput  
DNA Sequencing**



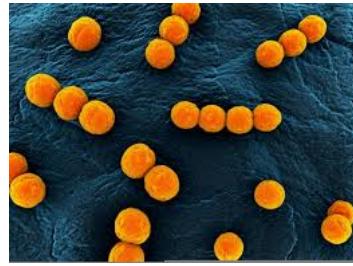
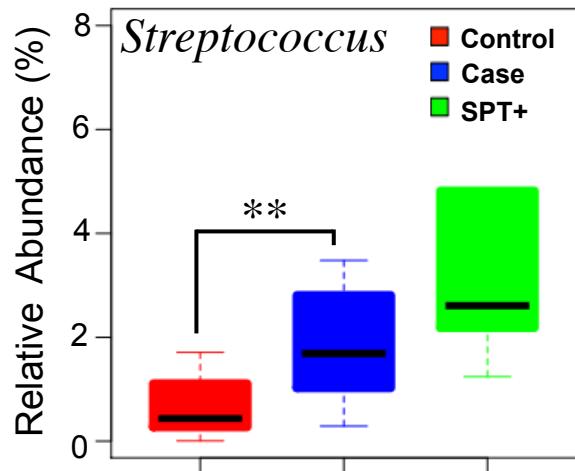
**Relative abundance  
and statistical analysis**

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

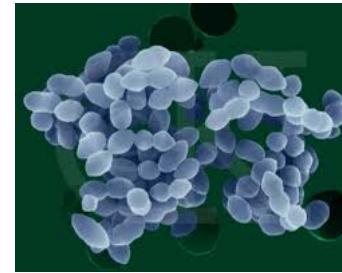
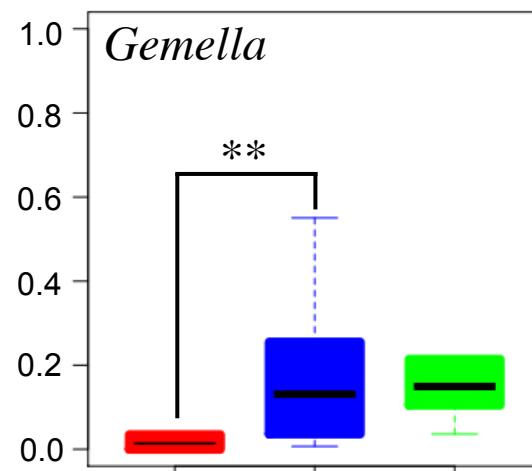
# Bacterial Diversity on Normal Skin



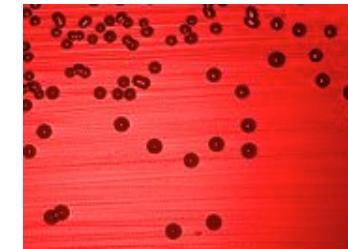
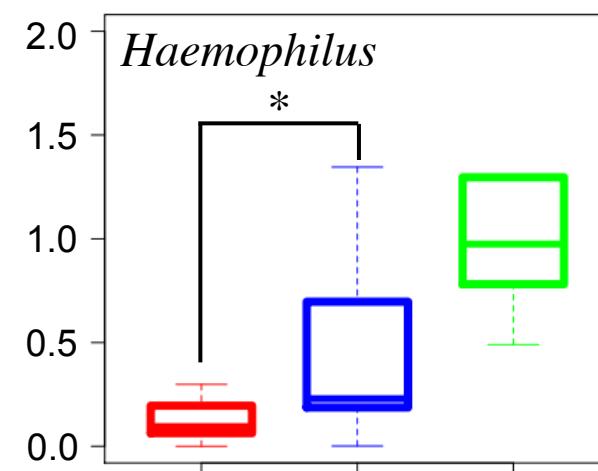
# Enrichment of opportunistic pathogens in AD



Known to cause skin and oral infections.  
Changes specific to  $\alpha$ -hemolytic group

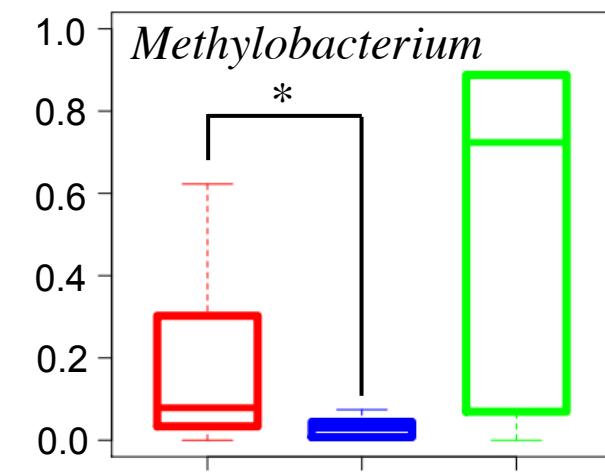
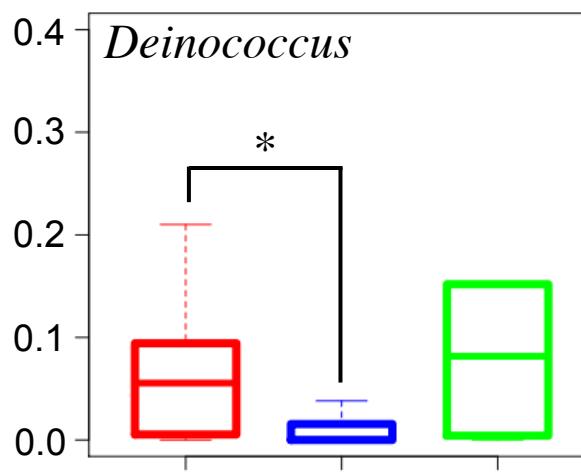
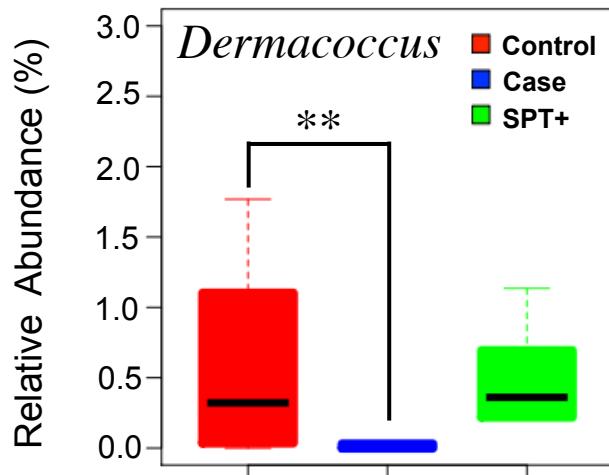


Can aggravate symptoms in Cystic Fibrosis



*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



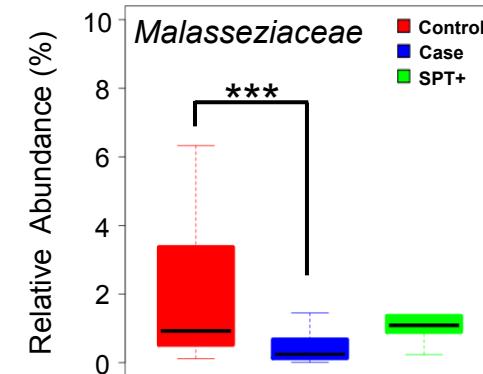
Radiation tolerant and metabolically versatile



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

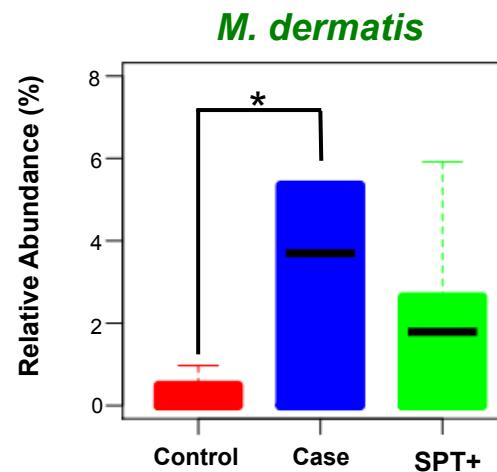
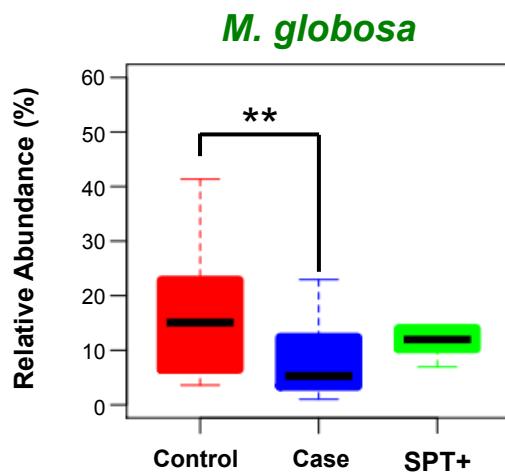
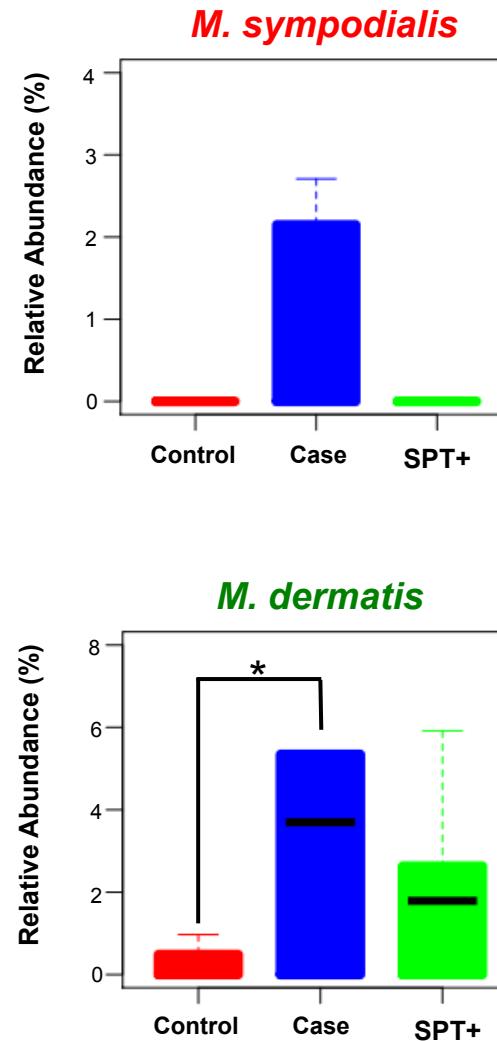
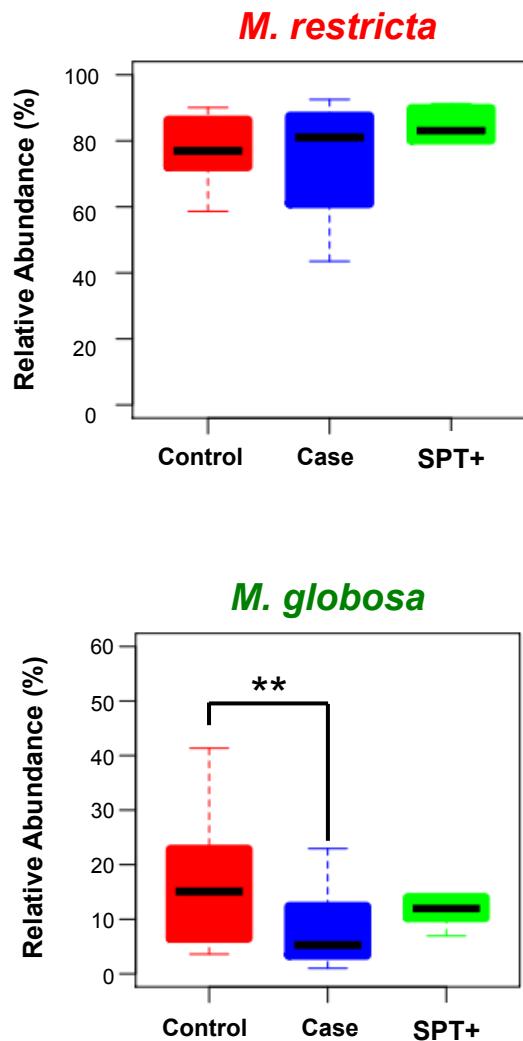
Reference genome and annotation for all **14 species** and **24 strains** of the genus



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

Guangxi Wu<sup>1</sup>, He Zhao<sup>2</sup>, Chenhao Li<sup>1</sup>, Menaka Priyadarsani Rajapakse<sup>1</sup>, Wing Cheong Wong<sup>3</sup>, Jun Xu<sup>4</sup>, Charles W. Saunders<sup>4</sup>, Nancy L. Reeder<sup>4</sup>, Raymond A. Reilmann<sup>4</sup>, Annika Scheynius<sup>5</sup>, Sheng Sun<sup>6</sup>, Blake Robert Billmyre<sup>6</sup>, Wenjun Li<sup>7</sup>, Anna Floyd Averette<sup>6</sup>, Piotr Mieczkowski<sup>8</sup>, Joseph Heitman<sup>6</sup>, Bart Theelen<sup>9</sup>, Markus S. Schröder<sup>10</sup>, Paola Florez De Sessions<sup>1</sup>, Geraldine Butler<sup>10</sup>, Sebastian Maurer-Stroh<sup>3,11</sup>, Teun Boekhout<sup>9</sup>, Niranjan Nagarajan<sup>1\*</sup>, Thomas L. Dawson, Jr.<sup>12\*</sup>

# Association with specific *Malassezia* species



# HOST-MICROBIOME INTERACTIONS

## Cause vs Effect in relation to AD

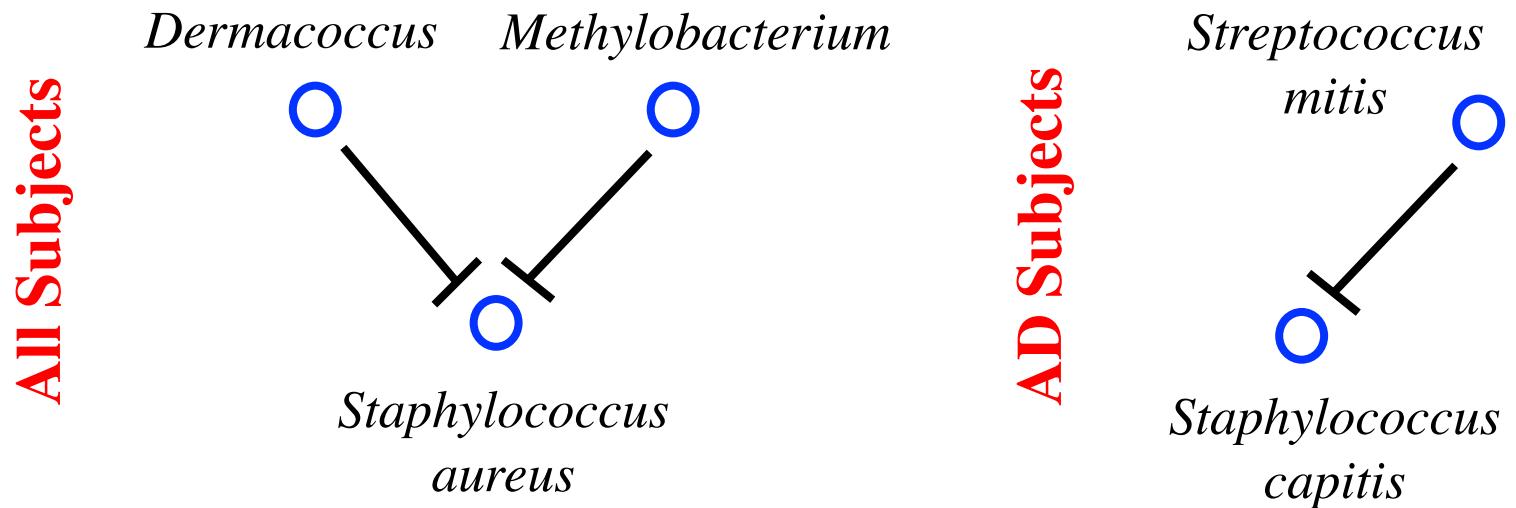
### 1. Direct cell-to-cell interactions

Microbe-human, microbe-microbe

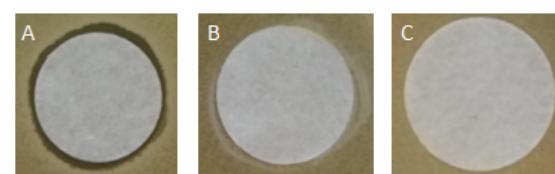
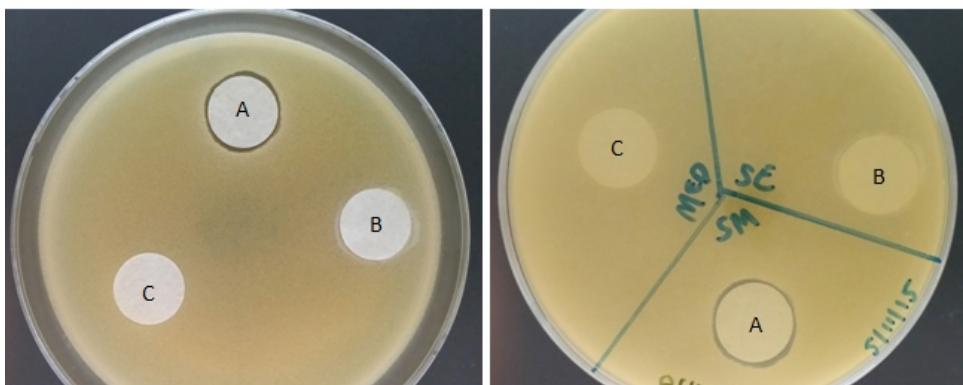
### 2. By altering the **microenvironment**

### 3. Immune-system mediated

# AD-associated microbiome inhibits *S. aureus*



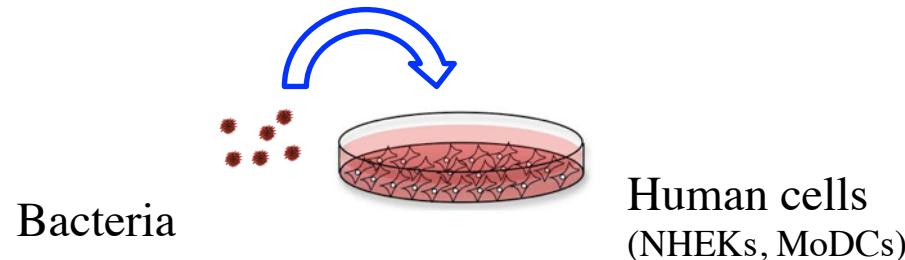
Bacterial Inhibition Assay – *S. aureus* culture



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

# AD associated bacteria elicit distinct immune responses

**SE:** *Staphylococcus epidermidis*  
**SA:** *Staphylococcus aureus*  
**BF:** *Bacillus firmus*

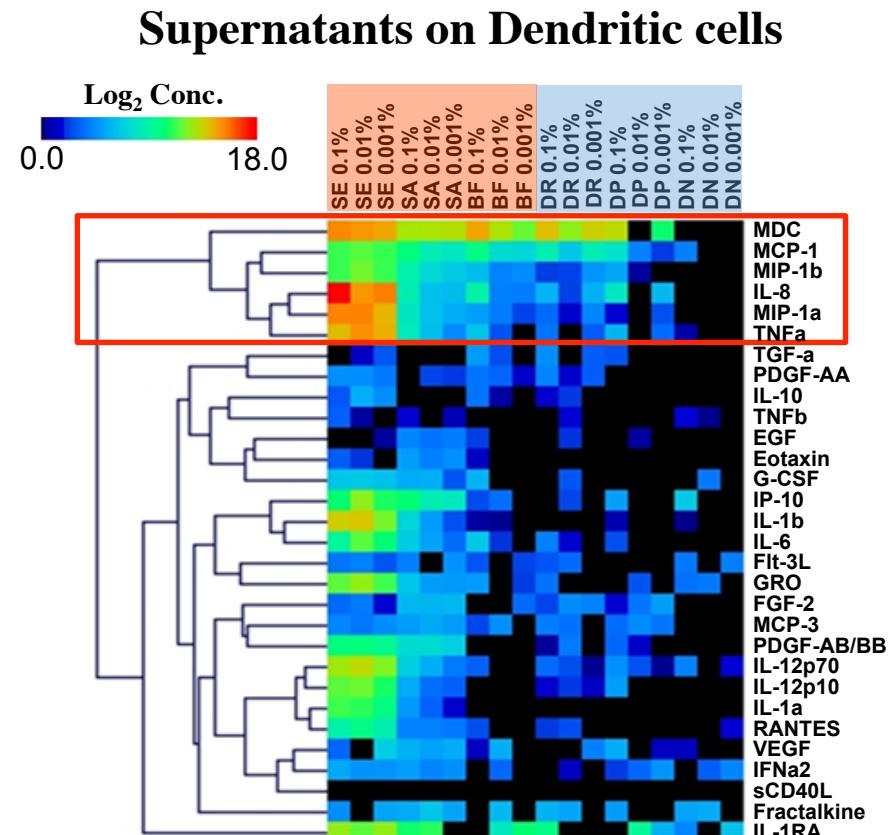


**DR:** *Deinococcus radiodurans*  
**DN:** *Dermacoccus nishinomiyaensis*  
**DP:** *Dermacoccus profundi*

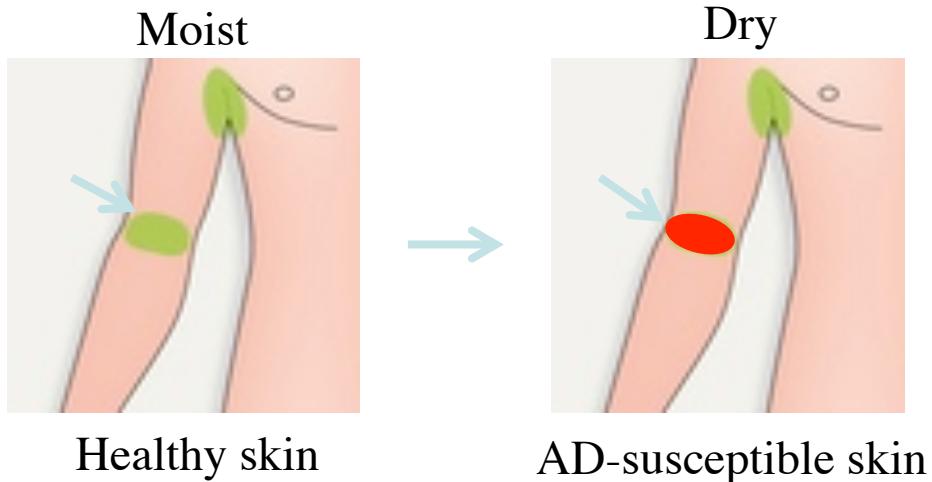
## 1. Flare associated bacteria (*S. epidermidis* and *S. aureus*) induce strong immune response

- 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<sup>373</sup>  
 Normal skin = *geh* Thr<sup>373</sup>

Dry skin sites = *geh* Arg<sup>373</sup>  
 Moist skin sites = *geh* Thr<sup>373</sup>

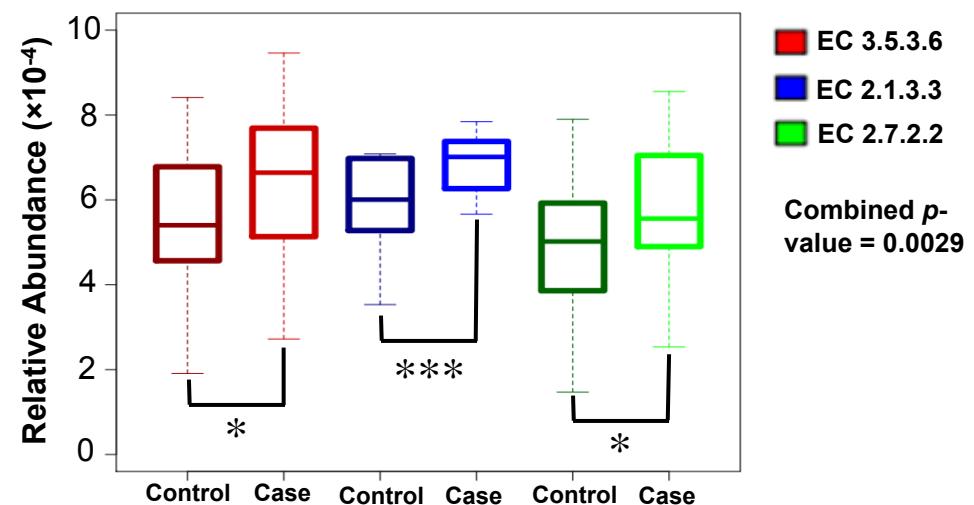
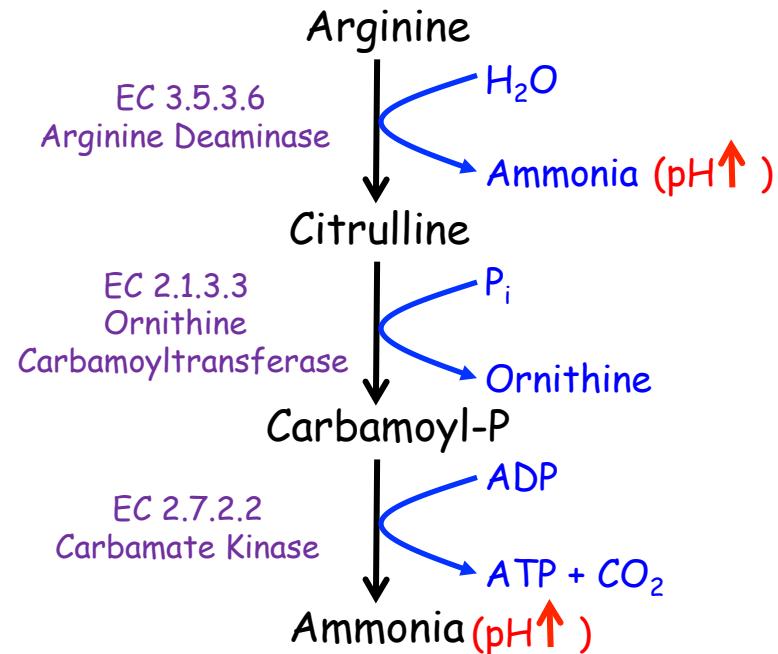
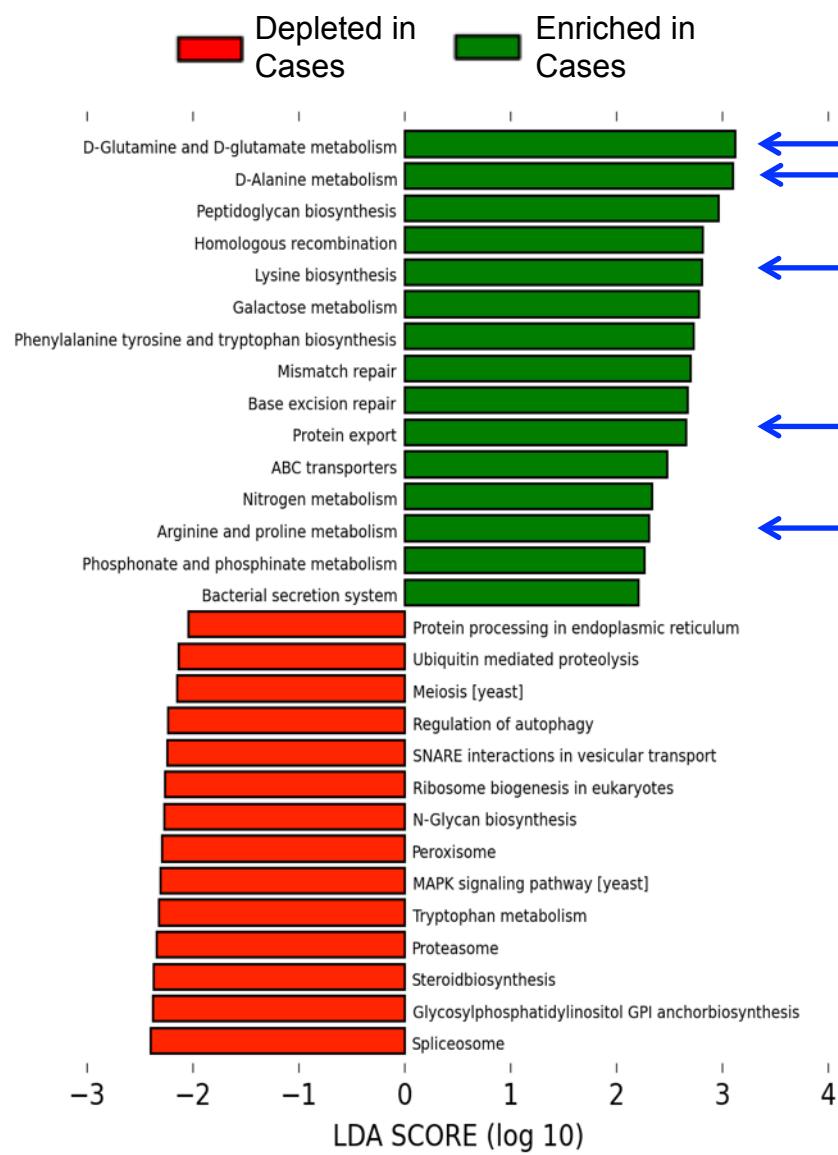
## Cases vs Controls in our study

Control	Threonine	100.00%	100.00%	100.00%	49.00%	33.00%	25.00%	20.00%	0.00%	0.00%	0.00%			
	Arginine	0.00%	0.00%	0.00%	51.00%	67.00%	75.00%	60.00%	100.00%	100.00%	100.00%			
Case	Threonine	25.00%	22.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
	Arginine	75.00%	78.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

## Dry vs Moist sites in Oh et al, Nature 2014

Ac (Moist)	Threonine	100.00%	100.00%	60.00%	54.00%	38.00%	4.00%	0.00%	0.00%	0.00%	0.00%			
	Arginine	0.00%	0.00%	40.00%	46.00%	62.00%	95.00%	100.00%	100.00%	100.00%	100.00%			
Vf (Dry)	Threonine	18.00%	0.00%	0.00%	0.00%	0.00%	0.00%							
	Arginine	82.00%	100.00%	100.00%	100.00%	100.00%	100.00%							

# Perturbed microbial metabolism on AD skin



# Summary

