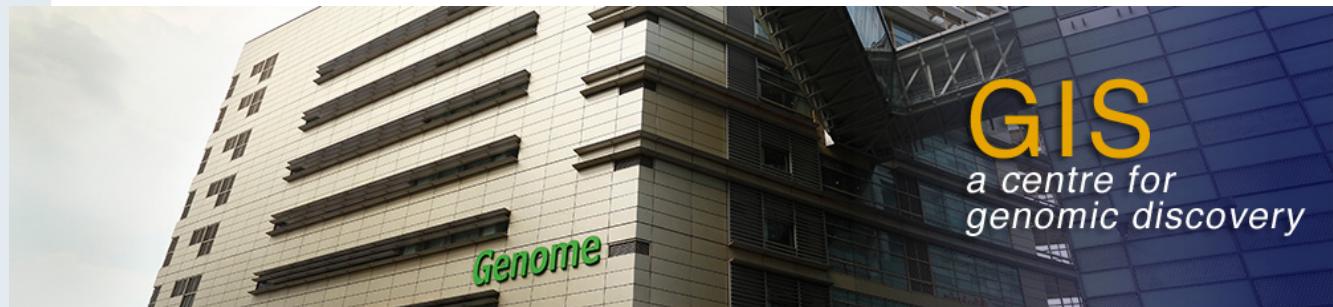


# The Role of the Skin Microbiome in Eczema

Niranjan Nagarajan

Associate Director and Group Leader  
Computational & Systems Biology



# The human skin is an effective barrier

Epidermal Hydration

Mechanical Barrier

Permeability Barrier

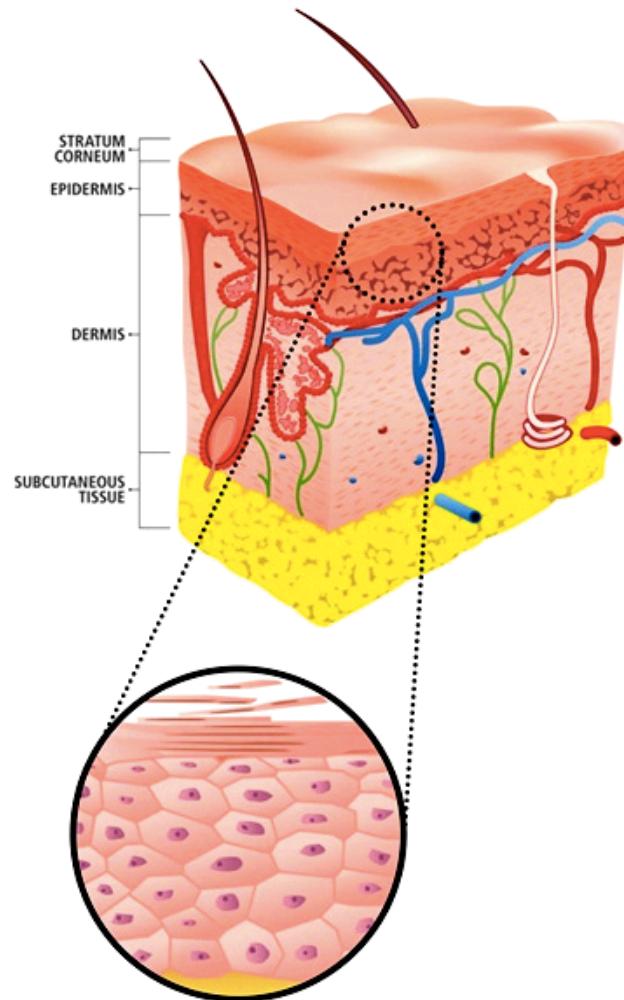
Waterproof Barrier

**Anti-microbial Barrier**

Anti-oxidant Barrier

Anti-UV Barrier

Initiation of inflammation

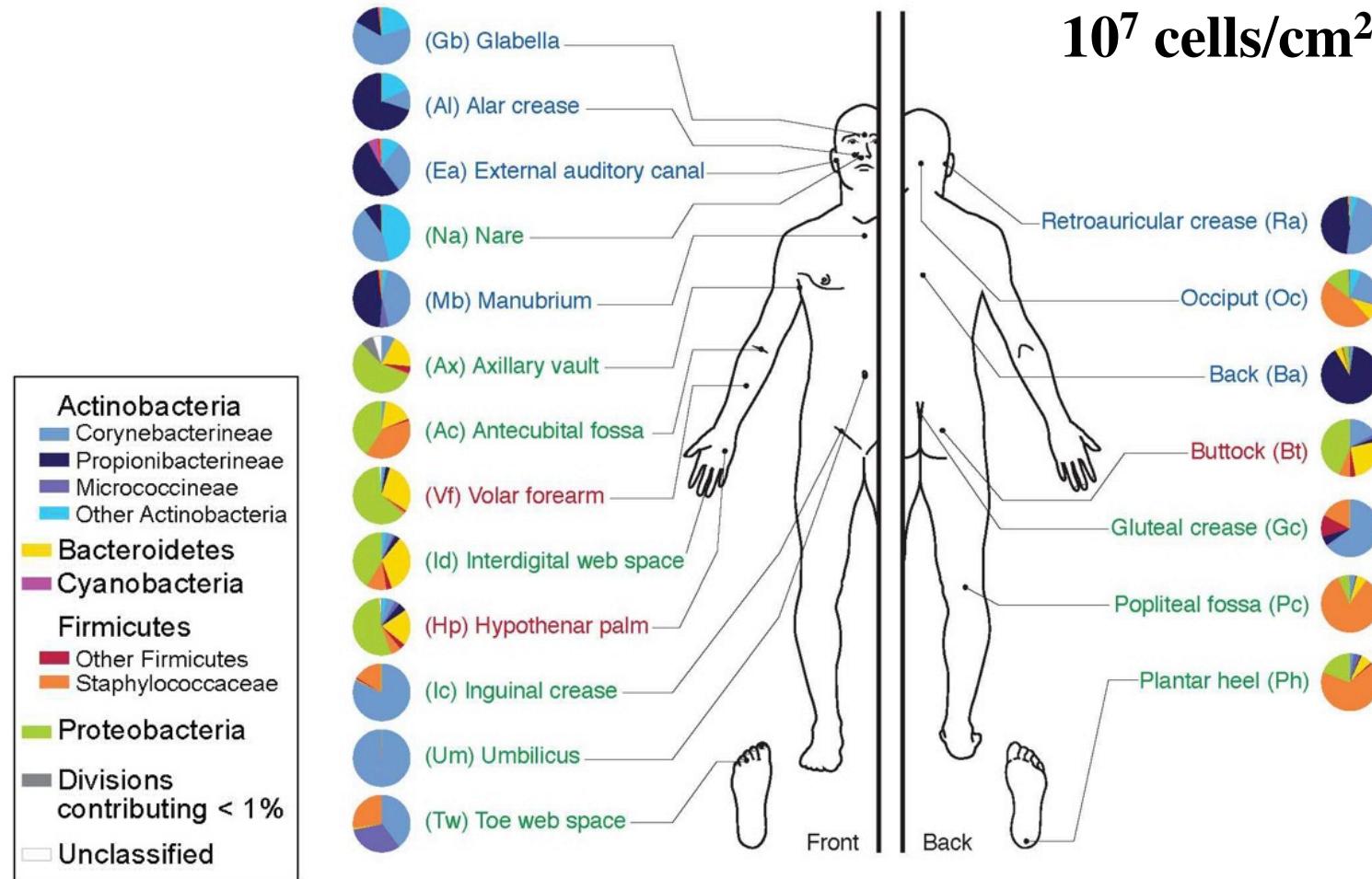


# Infection transmission via skin



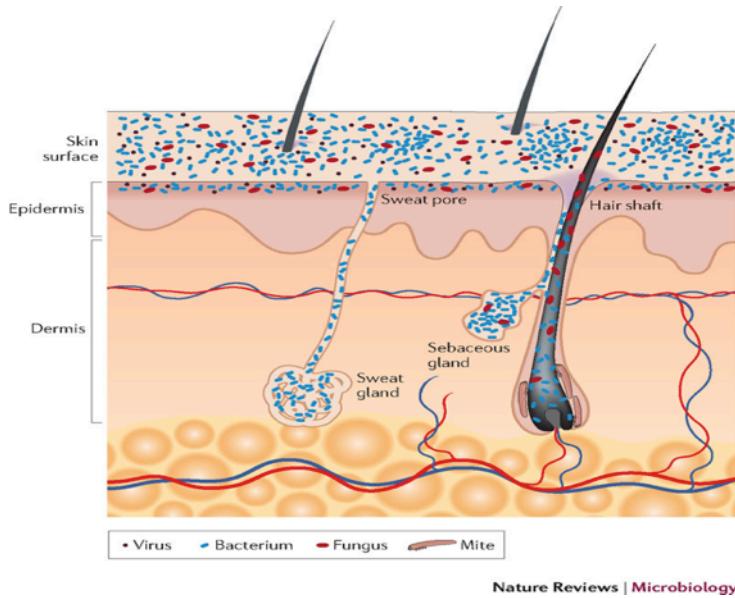
Conjunctivitis, Acne, Staph/Strep infections,  
Herpes, Yeast infections, Ebola, RSV, Hand-foot-mouth disease, Athlete's foot, ...

# 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)

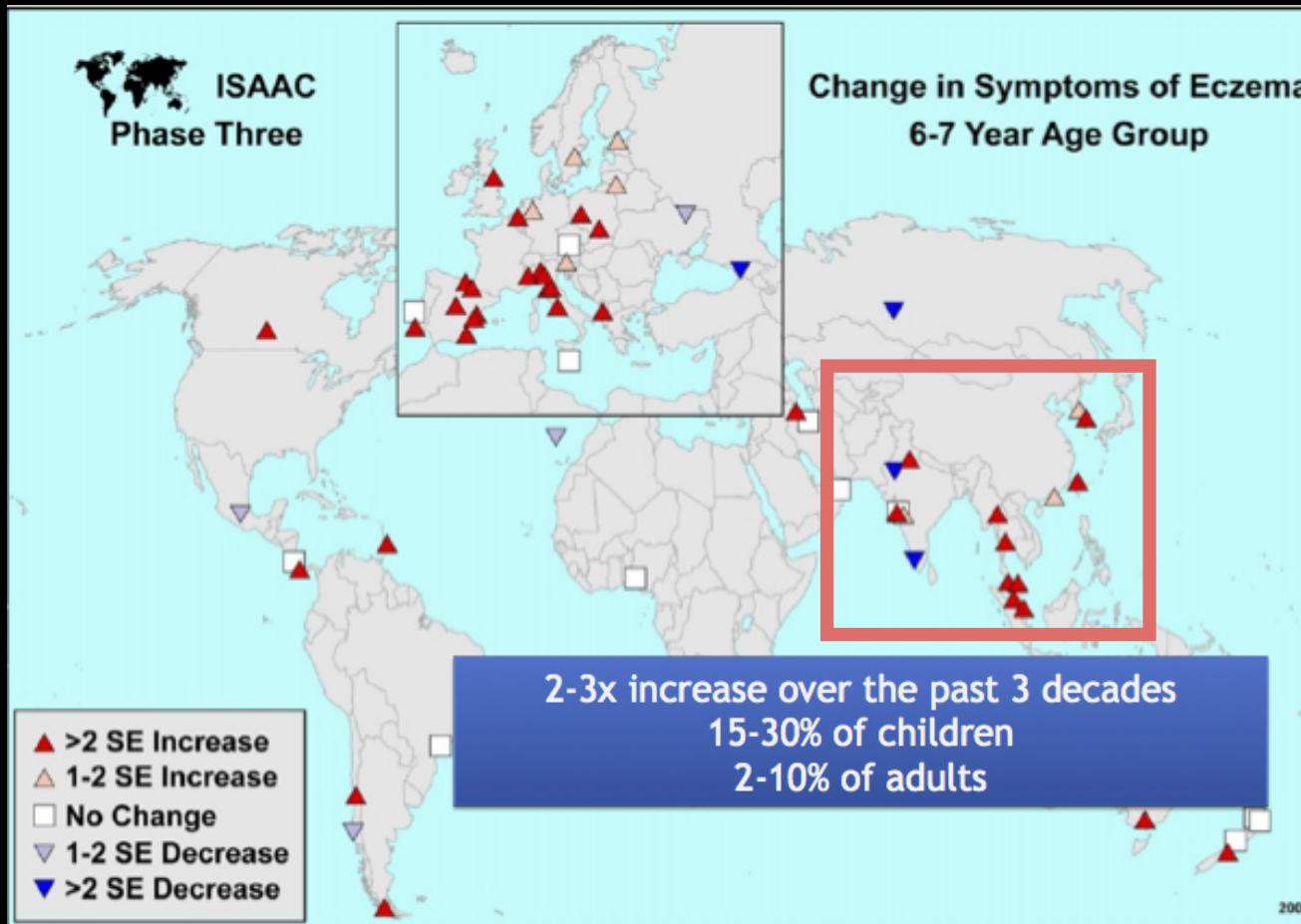
Dry and itchy skin  
Broken skin barrier

Inflamed lesions that are  
prone to bacterial infection



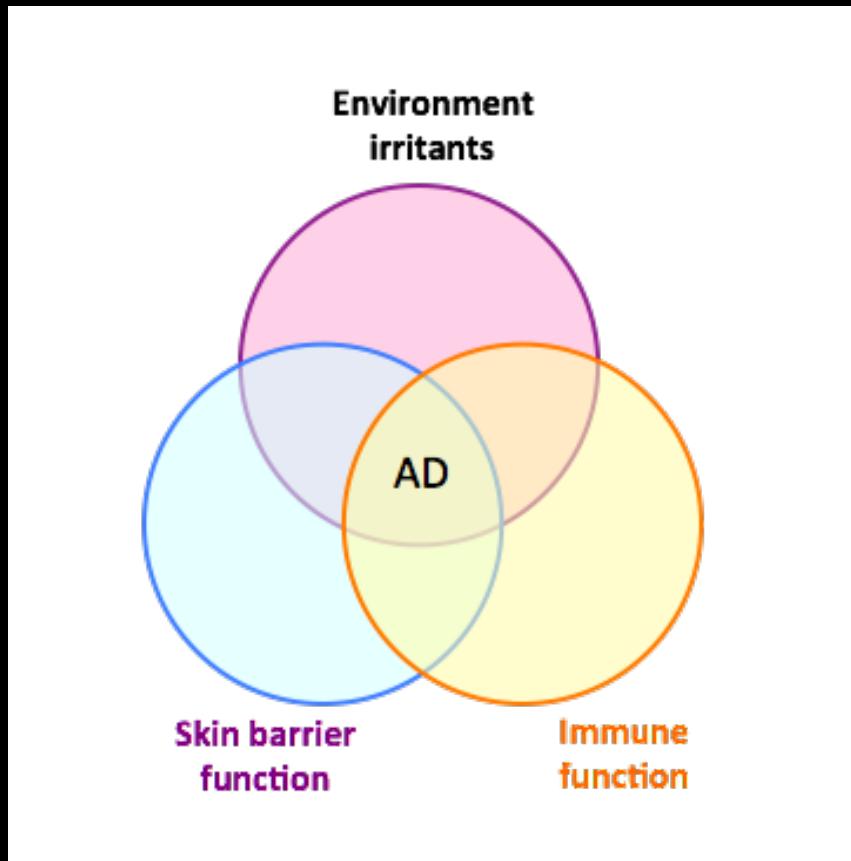
# The Atopic Epidemic

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



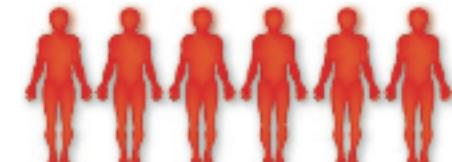
**Normals**

no history of AD or allergy



**SPT+**

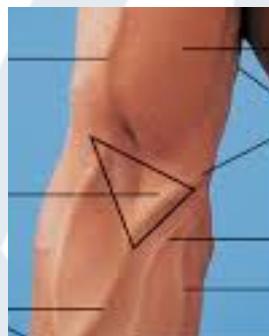
Allergy, no history of AD



**AD**

Active AD patients

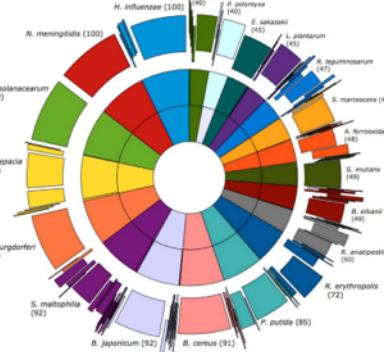
Analysis



Sampling Area:  
Antecubital fossa



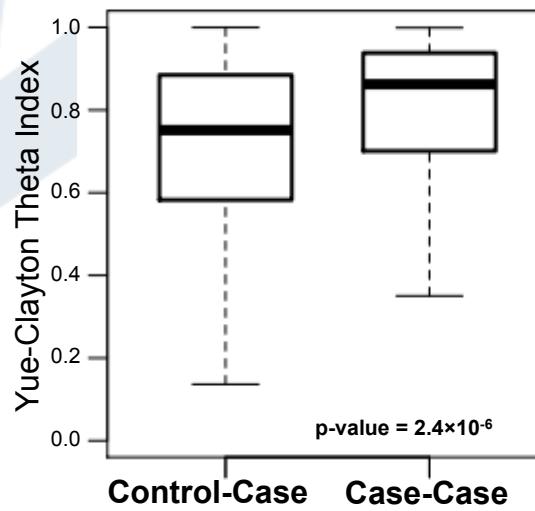
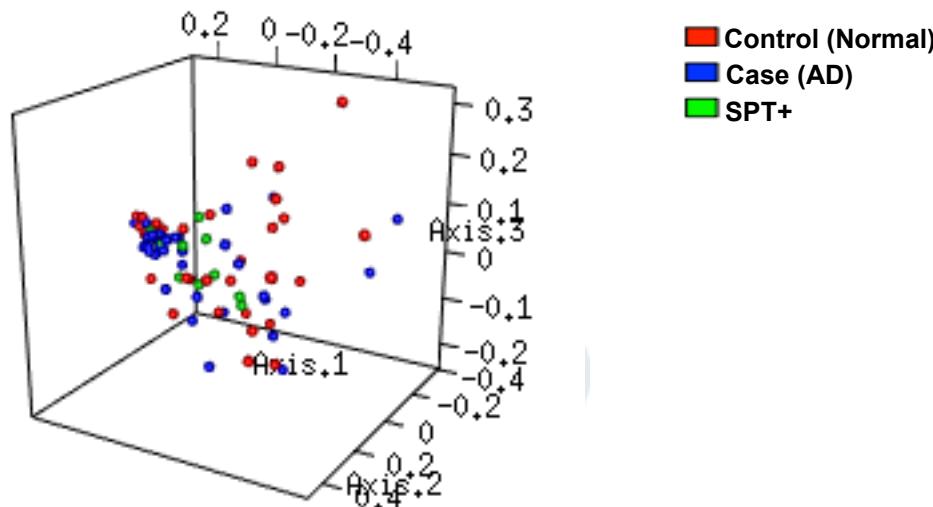
High-throughput  
DNA Sequencing



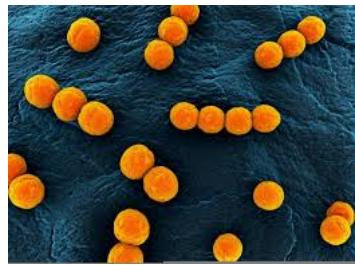
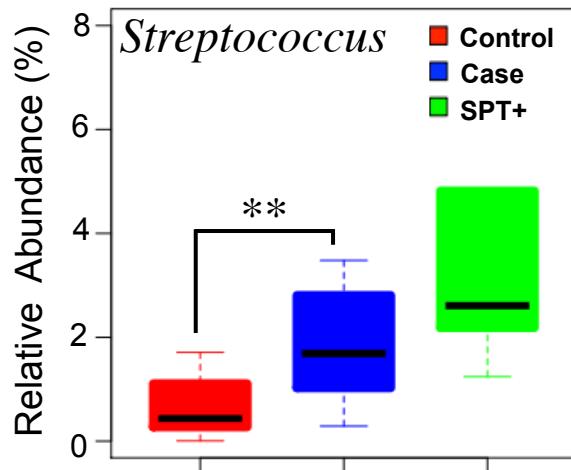
Relative abundance  
and statistical analysis

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

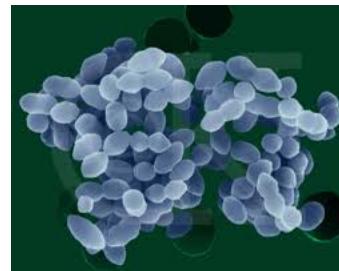
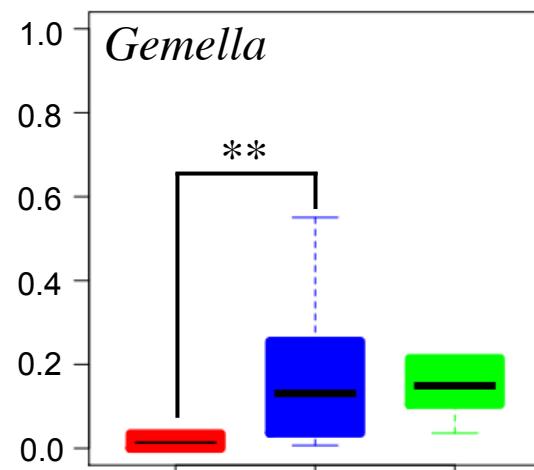
# Bacterial Diversity on Normal Skin



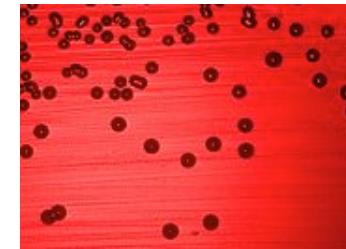
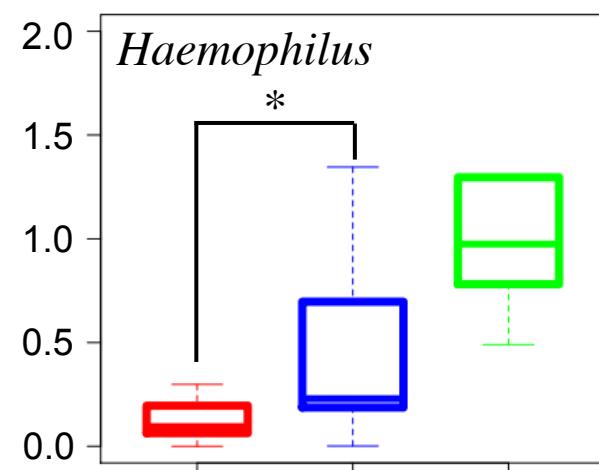
# Enrichment of opportunistic pathogens in AD



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

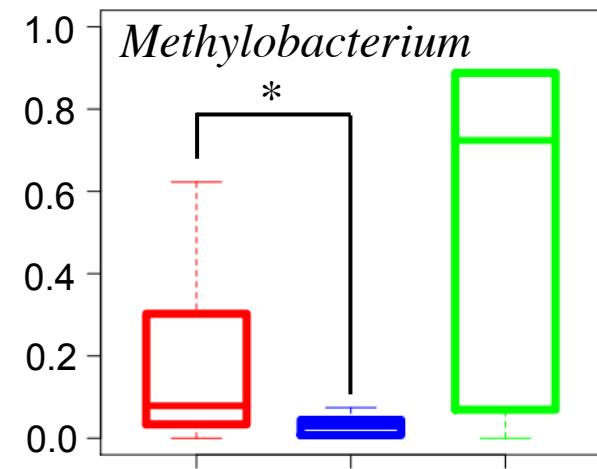
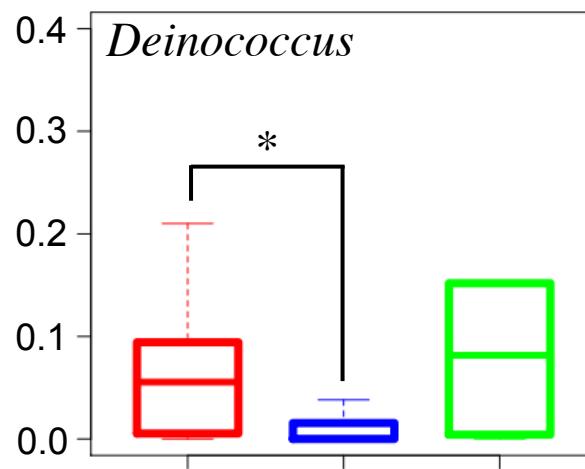
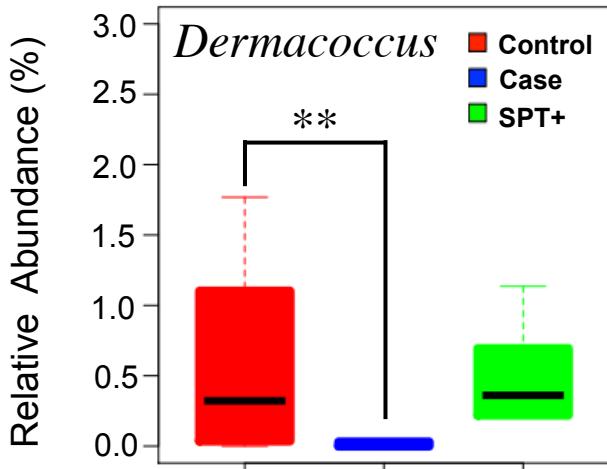


Can aggravate symptoms in Cystic Fibrosis

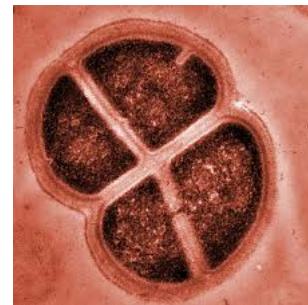


*Staphylococci* produce factors that promote the growth of *Haemophilus*

# Depletion of metabolically versatile bacteria



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



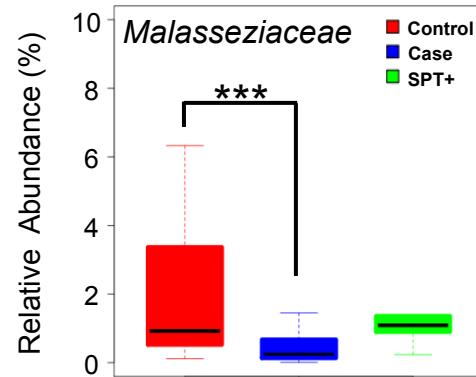
Radiation tolerant and metabolically versatile



Found commonly on human feet

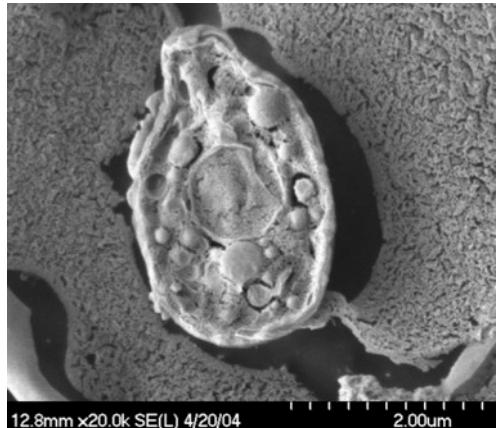
# Viruses & Eukaryotes

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



## Malassezia Genome Database

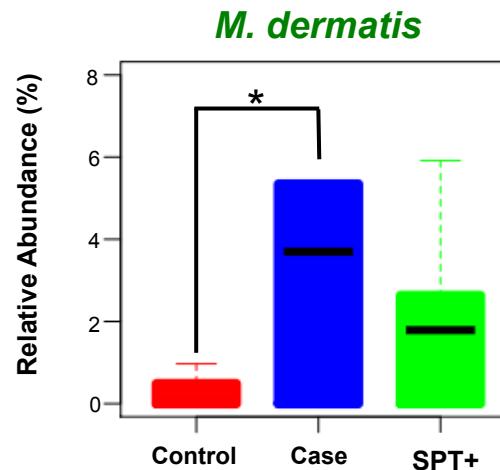
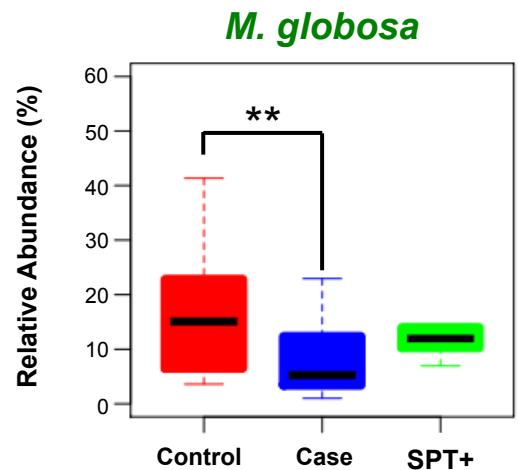
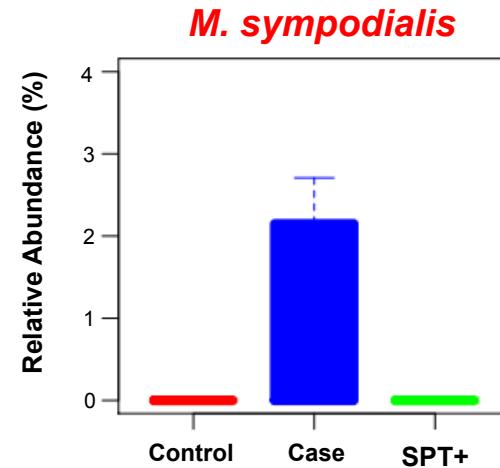
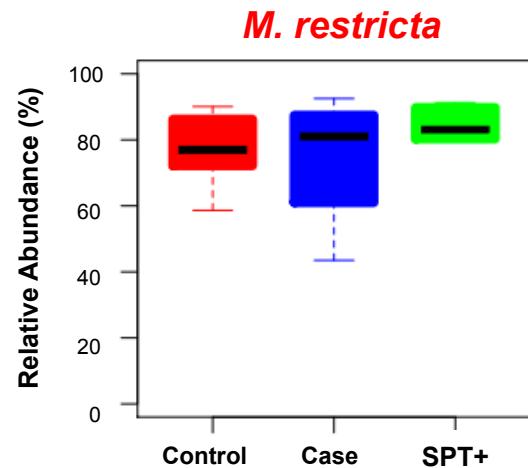
Reference genome and annotation for all **14 species** and **24 strains** of the genus



## 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>, Nirajan 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

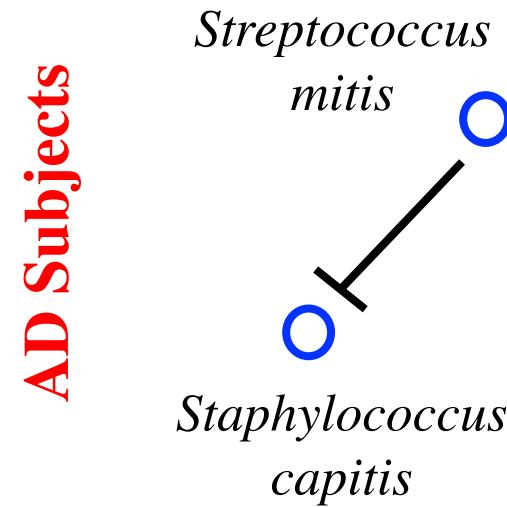
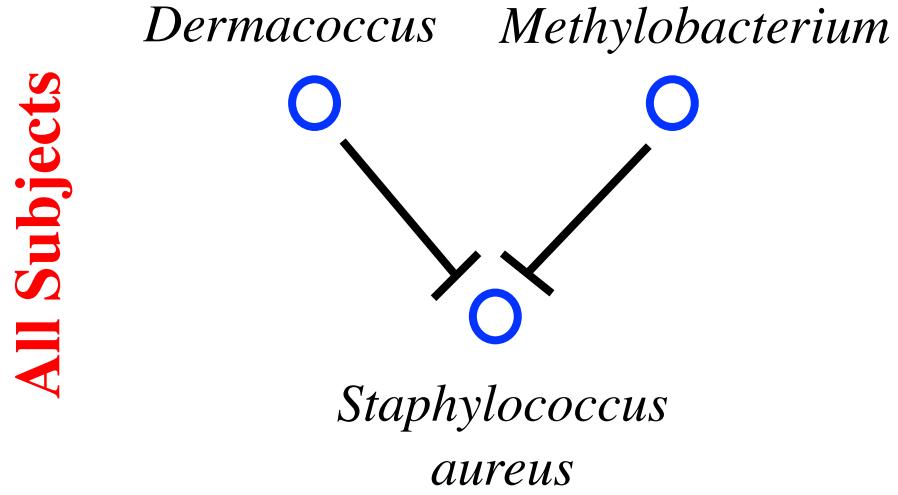
### 1. Direct cell-to-cell interactions

Microbe-human, microbe-microbe

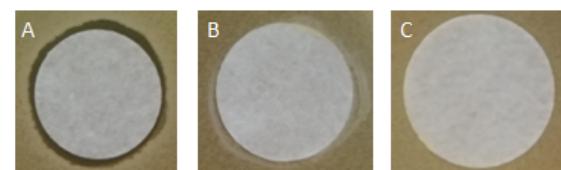
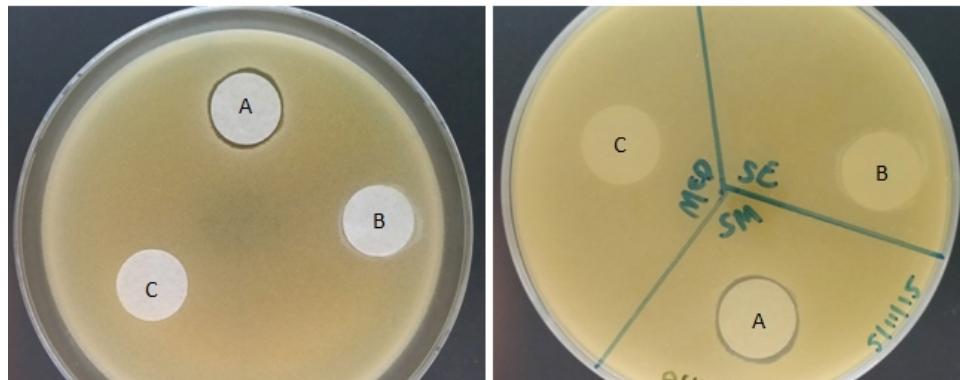
### 2. By altering the **microenvironment**

### 3. Immune-system mediated

# AD-associated microbiome inhibits *S. aureus*



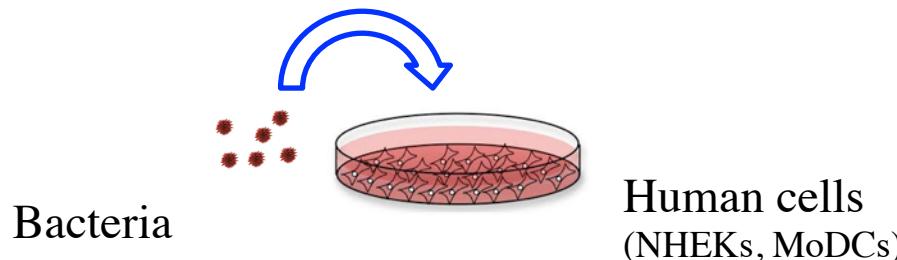
## Bacterial Inhibition Assay – *S. aureus* culture



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*

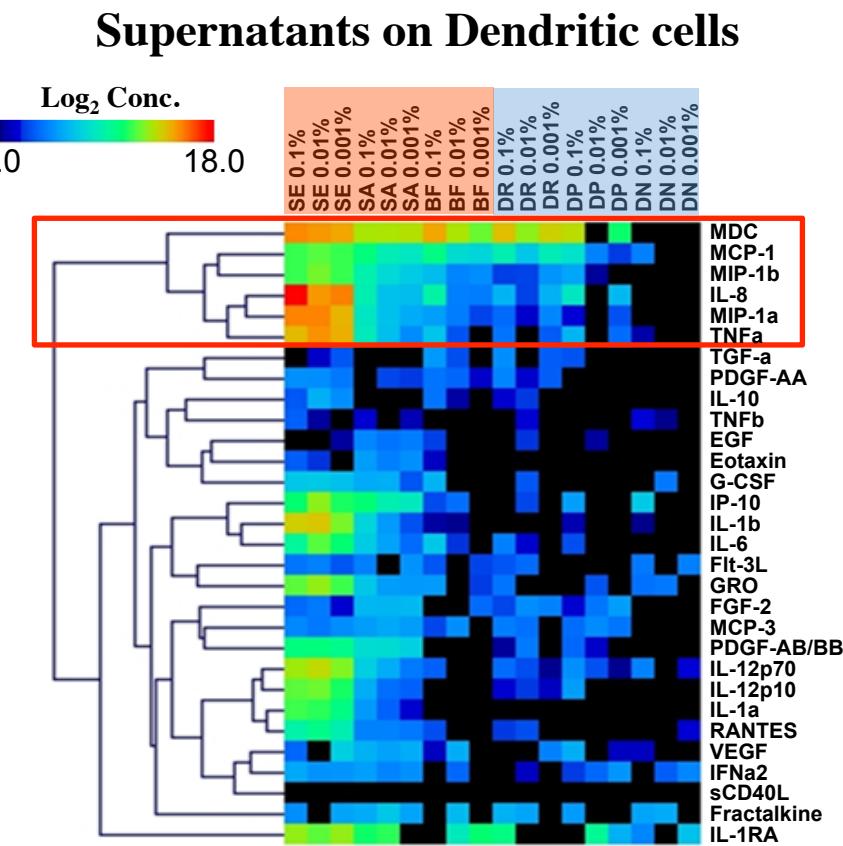


**DR:** *Deinococcus radiodurans*  
**DN:** *Dermacoccus nishinomiyaensis*  
**DP:** *Dermacoccus profundi*

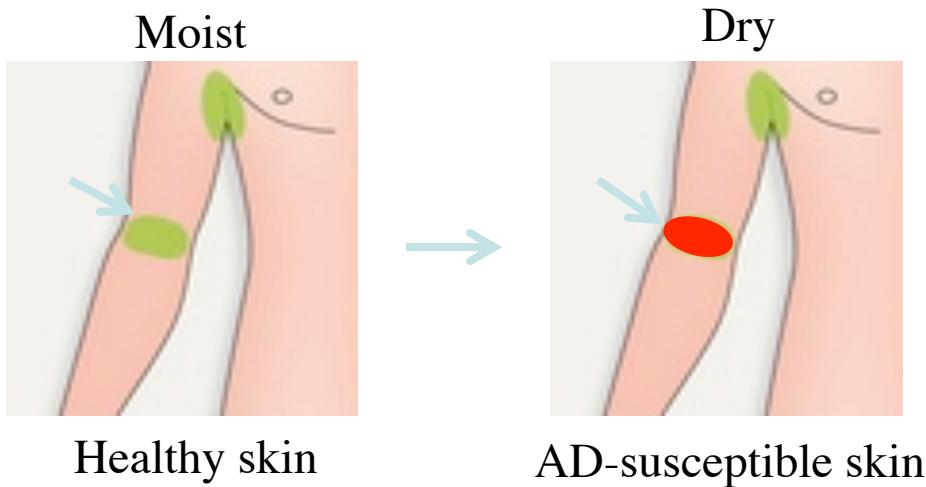
1. Flare associated bacteria (*S. epidermidis* and *S. aureus*) induce strong immune response

- 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 =  $geh^{\text{Arg 373}}$   
 Normal skin =  $geh^{\text{Thr 373}}$

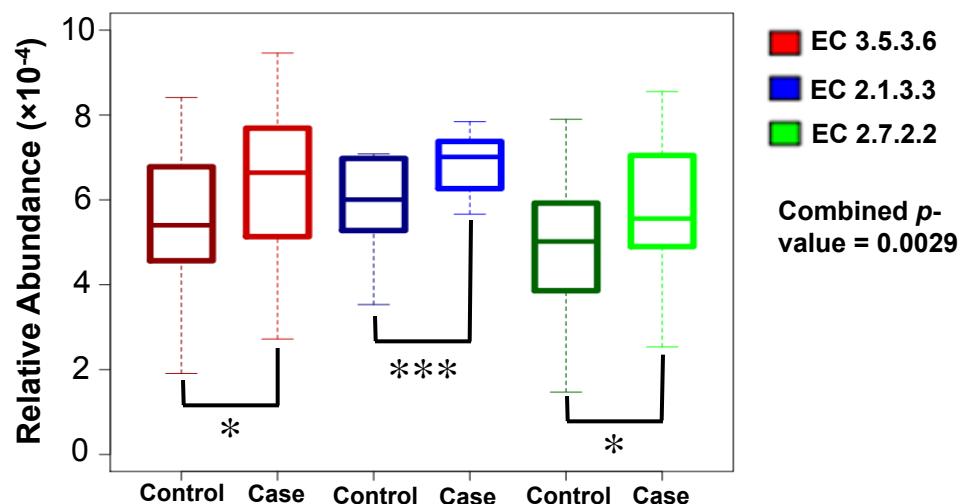
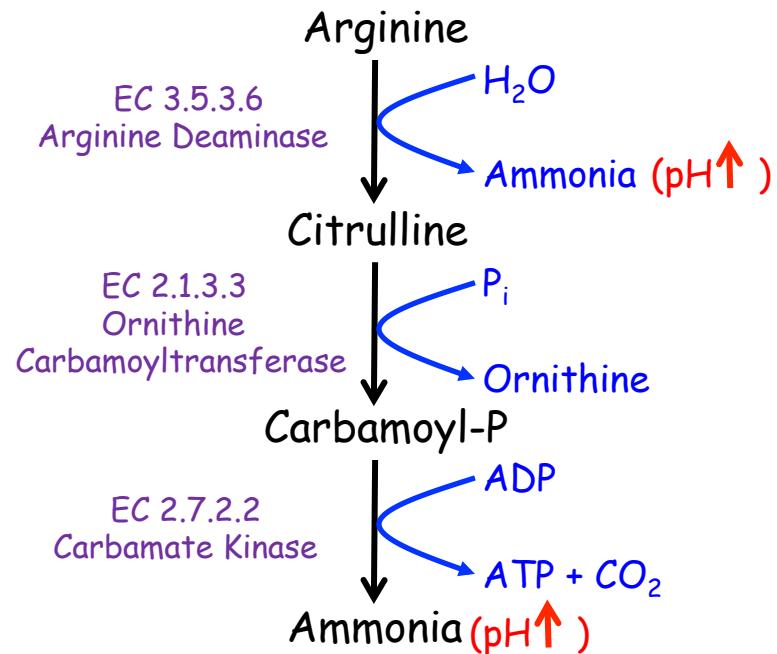
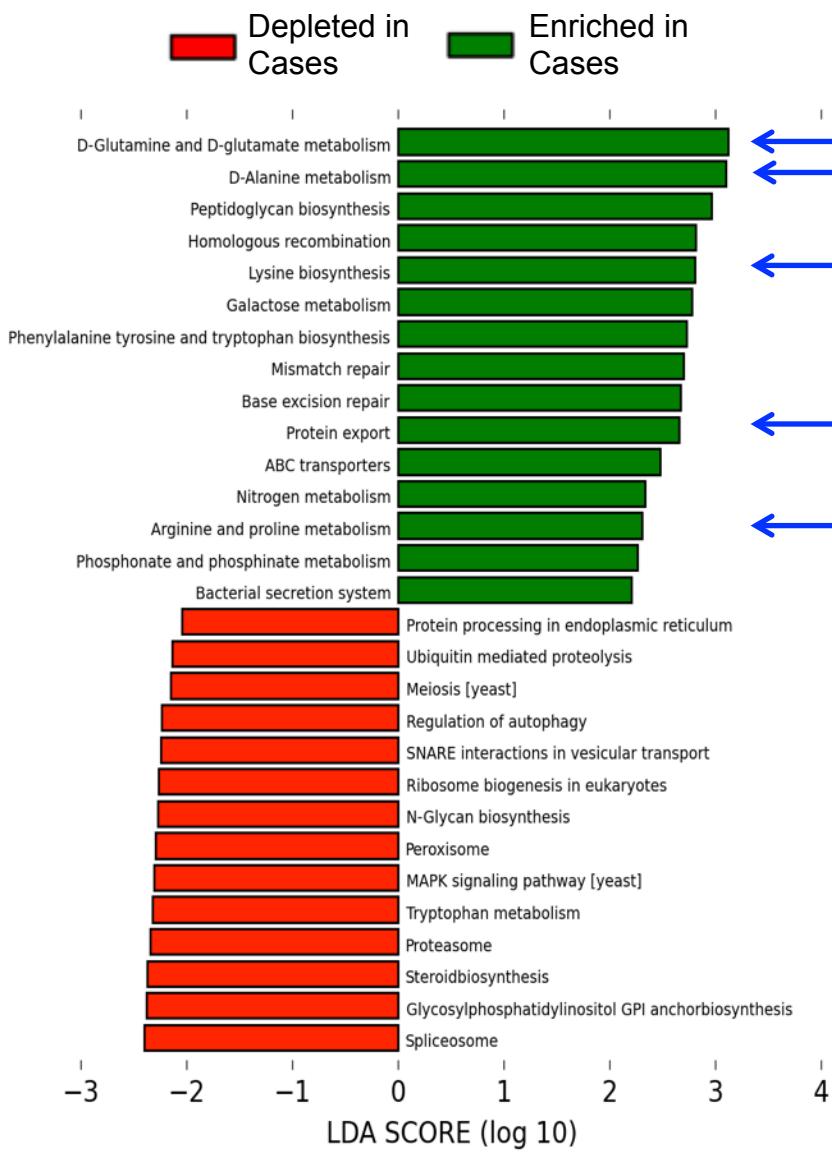
Dry skin sites = *geh*<sup>Arg 373</sup>  
Moist skin sites = *geh*<sup>Thr 3</sup>

### **Cases vs Controls in our study**

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

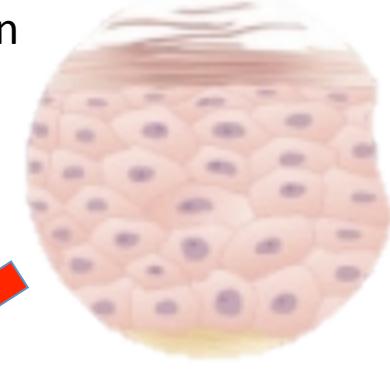
Ac (Moist)	Threonine	100.00%	100.00%	60.00%	54.00%	38.00%	4.00%	0.00%	0.00%	0.00%
	Arginine	0.00%	0.00%	40.00%	46.00%	62.00%	95.00%	100.00%	100.00%	100.00%
Vf (Dry)	Threonine	18.00%	0.00%	0.00%	0.00%	0.00%	0.00%			
	Arginine	82.00%	100.00%	100.00%	100.00%	100.00%	100.00%			

# Perturbed microbial metabolism on AD skin



# Summary

Normal Skin

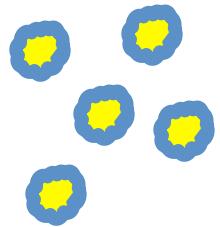


Risk factors

1. Predisposing microbiome

Altered microenvironment

2. pH change



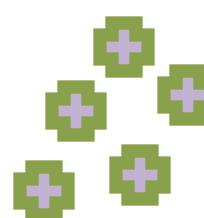
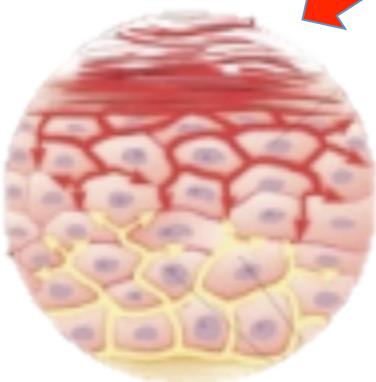
3. Increase in pathobionts

Loss of Homeostasis

4. Loss of Immune Damping

Immune activation, Inflammation

AD flare Skin



Colonization by opportunistic pathogens



Genome Institute  
of Singapore



Genome