More than Skin Deep – Understand Skin Biology by Means of Dermatogenomics

Paul Gerson Unna Research Group on Dermatogenomics

Shanghai, 2012.10.1–2015.9.30

Current group members of Paul Gerson Unna Research Group on Dermatogenomics. From left to right: Dr. PENG Qianqian (Research Associate), LI Jinxi (Ph.D. Student), Dr. LI Miaozhu (Postdoc), ZHANG Manfei (Ph.D. Student), Dr. WANG Sijia (Team Leader), DING An'an (Research Assistant), ZHANG Shuimei (Group Secretary).

credit: Photos by courtesy of Prof. WANG Sijia

The Paul Gerson Unna Research Group on Dermatogenomics was founded in October 2012 at the Partner Institute for Computational Biology. The ultimate goal of the group is to understand the biology of skin and skin appendages.

Reported by Group Leader WANG Sijia

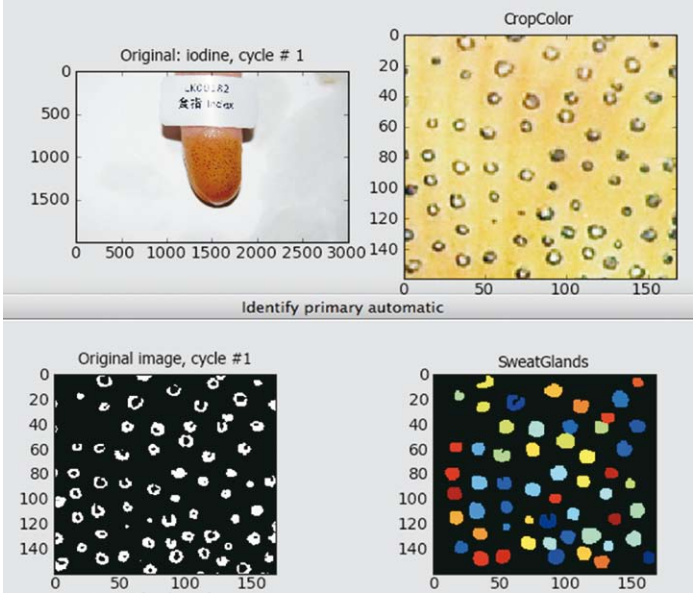

Figure 1: Semi-automatic analysis pipeline for counting active sweat glands using CellProfiler.

OVERVIEW

We approach this goal from a molecular genetics/genomics angle – by developing and integrating the state-of-the-art genomics and computational genetics approaches, and by leveraging available genomic resources from large-scale longitudinal cohorts. We have three research foci:

1. Developing and integrating genomics approaches to identify causal variants underlying normal skin variations.

2. Modeling and evaluating the impact of gene-environment interaction on skin aging.

3. Investigating the adaptation of skin-related traits in the context of human evolution.

MAJOR RESEARCH THEMES

Genes underlying normal skin variations

Skin is the human body's largest organ and the first to contact various environments. Many normal skin characteristics have substantial variations both within and between populations, as a result from adaptation to the local environment through natural selection. These skin characteristics, exemplified by skin pigmentation, have great variations, high heritability, and quantifiable measurements. A well-designed genome-wide mapping should be able to identify genes underlying the variations of these skin characteristics. In this project, we focus on the following skin characteristics with their functionality: 1) eccrine sweat glands and thermoregulation; 2) apocrine sweat glands and body odor; 3) sebaceous glands and skin oiliness; and 4) stratum corneum structure and barrier function.

First, collaborating with other dermatologists' groups, we design quantitative methods to measure these skin characteristics. We then collaborate with longitudinal cohorts to collect data from the individuals with pre-existing genome-wide data. We also develop a novel genome-wide association analysis method that incorporates a selection scan and use this method to scan for candidate genes underlying the skin-related phenotype of interest. We will integrate a range of state-of-the-art genomic tools to prioritize a set of candidate genes, based on both statistical analysis and biological relevance, for further functional validation.

"I most appreciate Max Planck Society's philosophy of 'investing and trusting in people'. The long-term support provided by them has allowed my group to take the risk to target at big questions and to pioneer a new interdisciplinary field."

— Dr. Wang Sijia

We expect to identify multiple novel genes underlying the skin characteristics studied, and provide important clues to understand the molecular biology of the skin characteristics. This project will not only provide an excellent example of incorporating selection scans into phenotype-genotype associations, but also have significant impact in the fields of dermatological sciences, skin diseases, cosmetic sciences, and human evolution.

Gene-environment interaction and extrinsic skin aging

Extrinsic skin aging is mostly affected by environmental factors. It has been linked to chronic exposure to solar radiation and cigarette smoke, and most recently, to industrial and traffic-related airborne particles in a Caucasian popu-

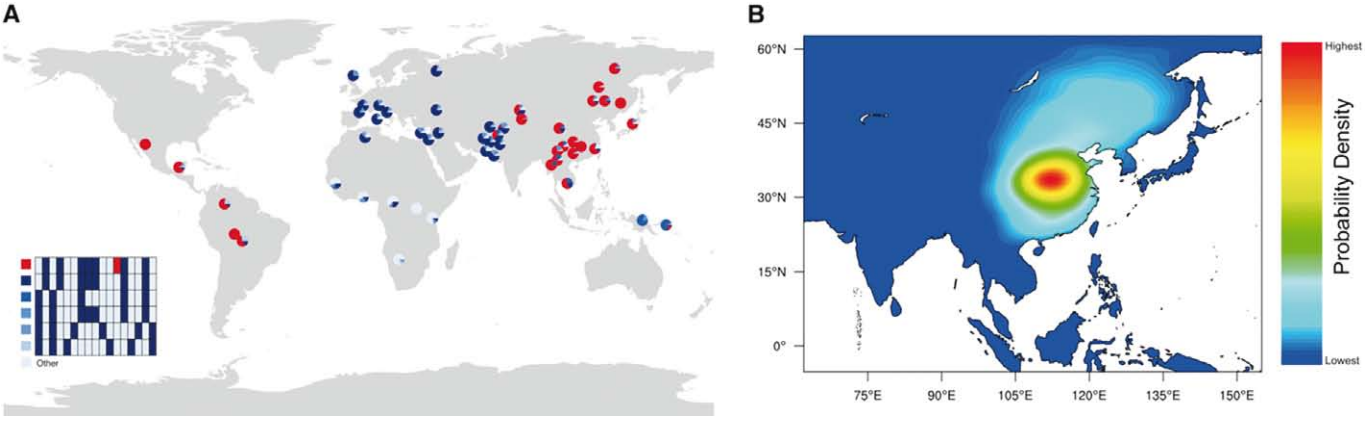

Figure 2: **Population distribution and the origin of EDARV370A.** A) Haplotype analysis around *EDARV370A* showed that the haplotype with the derived allele (red) only appear in East Asia and America. B) The most likely origin of *EDARV370A* simulated by approximate Bayesian computation.

lation. However, extrinsic skin aging varies strikingly among individuals and among ethnic populations. The biological mechanism behind extrinsic skin aging could be complicated and involves interactions between genes and environments. In order to obtain a clear picture of the environmental impact on extrinsic skin aging in Chinese populations, we have launched a multidisciplinary effort – in collaboration with Fudan University, China and the Leibniz Research Institute for Environmental Medicine (IUF), Germany – to perform this project involving 3,000 Chinese individuals in a longitudinal cohort.

Specifically, we are collecting data on extrinsic skin aging, lifestyle environmental factors, industrial and traffic-related air pollution exposure, indoor air pollution exposure, and genes. By combining these data with those available from collaborators, we will be able to rigorously test whether: 1) there is an ethnic difference in the manifestation of extrinsic skin aging between Chinese and Caucasian, and the impact of environmental factors like sun exposure and smoking on extrinsic skin aging may vary between Chinese and Caucasian; 2) industrial and traffic-related air pollution exposure is associated with more pronounced extrinsic skin aging manifestation in Chinese populations, and if the associations are different from those found in Caucasian populations; 3) indoor air pollution exposure is associated with more pronounced extrinsic skin aging; and 4) functional relevant genetic markers are affecting the association between environmental exposure and extrinsic skin aging.

The anticipated outcomes of this project will make significant contribution in improving our knowledge of the environmental exposures and genetic risk factors for extrinsic skin aging, and shed important light on its biological mechanism.

Adaptation of skin-related traits in human evolution

Having originated from Africa more than 100 thousand years ago, modern humans quickly occupied different environmental niches all over the world in a relatively short period of time. Local adaptation has been shaping us into an extremely diverse species with a great deal of phenotypic variations. Skin, as the first contact to the environment has experienced extensive adaptive selection in the past tens of thousands years.

Several interesting genes associated with skin-related traits show clear signatures of selection. We first focus on a derived coding variant of the Ectodysplasin A Receptor, *EDARV370A*, one of the most compelling candidate adaptive alleles from genome-wide scans in humans. *EDARV370A* is associated with several phenotypic changes of epidermal appendages, including an increased density of sweat glands. This could be a crucial feature in human evolution, as superior thermoregulation is thought to be one of the main advantages in prehistoric hunting. To follow up the interesting results revealed by *EDARV370A* association studies, we will carry out several projects to test two key hypotheses: 1) whether there is a direct association between sweating ability (*e.g.* sweating amount and rate during exercise) and *EDARV370A*; and 2) which environmental variable is most relevant to *EDARV370A*.

We will also investigate the case of *ABCC11*, another gene under strong selection. A derived variant of *ABCC11* is associated with earwax type, body odor, as well as apocrine colostrum secretion. Apart from *EDAR* and *ABCC11*, there are many other causal genes – discovered or undiscovered – responsible for variation in skin-related traits. We will further our understanding of the genes and the relevant skin-related traits by studying them in an evolutionary context. ◂