Approaches to Detecting Gene-Environment Interactions in Environmental Adaptability Using Genetic Engineering, Remote Sensing and Geographic Information Systems

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Affects the health of human beings

Human survival requires to understand the essential of an adaptation to UV rays

Skin cancer, a cataract, a viral disease such as AIDS due to a decline in immunity
The formation of environmental adaptability
Could be considered that a stress from the outside
influence a genetic mechanism in mutation form

Gene → Mutation → Environment

Limbic System → Hypothalamus

Endocrine System

Nervous System

Effector Organs

Homeostasis

Physiological functions of each population group can be observed or measured in terms of
phenotype emerged from genotype which is modified by culture and environment
Skin pigmentation phenotype

One of the results of man’s environmental adaptabilities

Results from localized adaptation to UVR conditions

Despite the importance of gene-environment interactions for the complex phenotype, there has been little progress in developing methods that can detect and clarify the interactions involved in skin color variation.

Investigated the evolutionary and adaptation mechanisms involved in skin color variation by detecting gene-environment interactions.
Figure The conceptual framework of new approaches to analyzing the gene-environment interactions
Two approaches to understanding the adaptation

A molecular biological approach

Genome DNA -- SNPs

Genetic engineering was used as a molecular biological approach

To understand the dynamics of the human genome, which encodes the complex human phenotype

An ecological approach

Atmospheric environments -- RS

RS/GIS was used as an ecological approach

To understand how the environment exerts pressures and effects on the genome such that it helps determine human traits
SNPs are DNA sequence variations that occur when a single nucleotide: adenine (A), thymine (T), cytosine (C) or guanine (G) - in the genome sequence is altered. A variation must occur in at least 1% of the population to be considered an SNP.

Variations in DNA sequence

SNPs

Genome DNA
SNPs (single nucleotide polymorphisms)

Definition

Skin color Eye color

Physical constitution: Drug response, Metabolism, etc.

Human diversity
The mechanism of the formation of SNPs

The most case of SNPs that happen is transition; Cytosine (C) is substitute for Thymine (T) when a chemical change called deamination occurs.

C is substitute for T when a chemical change called deamination occurs.

The changes could be influenced by ultraviolet radiation (UVR).

The UV range absorbed by nucleotide is 260～320nm.

It is within the UV range.
SNP genotyping

Based on low-molecular-weight compounds known as tags

Masscode™ system for SNP genotyping

Tagged oligonucleotides are used as primers in an SNP-discrimination assay

SNP specific PCR products are purified to remove unincorporated tagged primers

Presence of a particular tag indicates presence of the corresponding SNP allele in the genomic DNA used as the PCR template
The SNP allele is classified into three types: wild type homo, variant type homo and hetero type.
Alleles were reported using binary nomenclature, in which 1 represented wild-type alleles and 2 represented variant alleles. A homozygous wild-type allele was designated as 1,1 and a heterozygous allele was designated as 1,2.
A molecular biological approach

1. Collected samples of 122 European and 100 East Asian

2. Extract DNA from the collected samples

3. Amplify whole genome

4. PCR to amplify the regions containing the 20 SNPs in the 7 candidate genes, encoding ASIP, TYRP1, TYR, MC1R, OCA2, MITF, MYO5A

5. SNP genotyping: Masscode™ system
Detection natural selection in the human population would have profound implications for the study of human adaptation/evolutionary history and for medicine (Sabeti, 2002).

Conducted Tajima’s D test and Fu and Li’s F test to determine whether any of the SNPs were under natural selection pressures.

Detected natural selection in candidate pigmentation genes in haplotypes revealed by the SNP analyses.

Our results indicate the possibility that the haplotype in the OCA2 gene in the East Asians population has been under selective pressure.
An ecological approach

Atmospheric Remote Sensing data

Earth Probe

The UVR data were derived from readings taken from the NASA Total Ozone Mapping Spectrometer (TOMS), which was flown aboard the Nimbus-7/Earth Probe satellites.

The TOMS sampled single wavelengths representative of long-wave and medium-wave UVR: 324-nm and 380-nm wavelengths for UVA (range, 315-400 nm) and 305-nm and 310-nm wavelengths for UVB (range 280-315 nm).
The original data set for 310-nm UVB (which induces deamination and causes a barely perceptible reddening of light skin) was read as integers into a single integer array of dimensions by using a sample C routine with longitude and latitude.

The data sets were calculated for the average reading for each month from 1979 to 2003.
The processed data were integrated into a GIS and interpolated using inverse distance weighting (IDW) for the values of a raster.

The raster layer was overlaid with the polygon layer, which contained three polygons representing the birthplaces of the human race.
Spatial Analysis in GIS

Each polygon contained and summarized the raster values within its area and reported the results as a table listed below.

Chaplin’s study found that the evolution of skin reflectance could be almost fully modeled as a linear effect of UVR in fall alone.

The monthly mean values by the human racial population were organized for the seasonal mean values for winter, spring, summer, and fall.
With the data obtained from these analyses based on genetic engineering/RS/GIS data, we conducted spatial statistical analysis to evaluate G×E interactions while assessing the relationship between the SNPs at candidate genes involved in human skin pigmentation and seasonal UVR exposure in the three regions denoted using polygons.
To perform spatial statistical analysis, we used the following data:

● 20 SNPs in seven candidate genes for human skin pigmentation obtained in our previous study

● 553 SNPs in the OCA2 gene (a common gene in both European and East Asian populations in our previous study) from the HapMap database

● Seasonal UVR exposure in the three regions denoted using polygons
Calculated the mean values for the heterozygous genotype frequency for every allele pattern in each population
Conducted PCA using the correlation matrix to determine the relationships between **SNP frequencies** for **heterozygous subjects** and the **seasonal UVR data**. The following four kinds of PCA analyses were conducted:

(I) 20 SNPs in seven candidate genes from our previous study + UVR data for the fall;
(II) 20 SNPs in seven candidate genes from our previous study + UVR data for all four seasons;
(III) 553 SNPs in the OCA2 gene from the HapMap database + UVR data for the fall; and
(IV) 553 SNPs in the OCA2 gene from the HapMap database + UVR data for all four seasons
The results showed more significant correlations in the mean G/T SNP frequencies for heterozygous alleles for the SNPs identified in our previous study than in those from the HapMap database.
The mean 310-nm UVR levels in fall and winter were more highly correlated with the G/T SNP than were the mean seasonal 310-nm UVR levels in spring and summer.

The correlation matrix results showed very high correlations between the G/T SNP and the mean seasonal 310-nm UVR levels.

<table>
<thead>
<tr>
<th></th>
<th>UVR (Autumn)</th>
<th>UVR (Summer)</th>
<th>UVR (Winter)</th>
<th>UVR (Spring)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UVR (Autumn)</td>
<td>1.00000</td>
<td>0.90878</td>
<td>0.99078</td>
<td>0.99573</td>
</tr>
<tr>
<td>UVR (Summer)</td>
<td>0.90878</td>
<td>1.00000</td>
<td>0.84387</td>
<td>0.94341</td>
</tr>
<tr>
<td>UVR (Winter)</td>
<td>0.99078</td>
<td>0.84387</td>
<td>1.00000</td>
<td>0.97405</td>
</tr>
<tr>
<td>UVR (Spring)</td>
<td>0.99573</td>
<td>0.94341</td>
<td>0.97405</td>
<td>1.00000</td>
</tr>
<tr>
<td>SNP (C/T)</td>
<td>-0.99905</td>
<td>-0.88973</td>
<td>-0.99574</td>
<td>-0.99076</td>
</tr>
<tr>
<td>SNP (A/G)</td>
<td>-0.27792</td>
<td>0.14828</td>
<td>-0.40549</td>
<td>-0.18807</td>
</tr>
<tr>
<td>SNP (G/T)</td>
<td>0.99023</td>
<td>0.84172</td>
<td>0.99999</td>
<td>0.97314</td>
</tr>
<tr>
<td>SNP (A/T)</td>
<td>0.70147</td>
<td>0.34009</td>
<td>0.79156</td>
<td>0.63270</td>
</tr>
<tr>
<td>SNP (A/C)</td>
<td>0.42726</td>
<td>0.76556</td>
<td>0.30084</td>
<td>0.50888</td>
</tr>
</tbody>
</table>
The points of the principal component scores of each distinct population were distributed separately, dividing the data into two groups: one group of Africans and another group of Europeans and East Asians for the cases I, II, and IV.
The principal component loading results showed a high first principal component loading of 0.98 for the G/T SNP, which was positively correlated to the G/T SNP variable in case I.

The other principal component loadings were low for the other SNPs and did not correlate with other SNPs for cases II, III and IV.

This indicates a strong relationship between the G/T SNP and fall.
Our results suggest the possibility that genes involved in skin pigmentation might be subject to UVR-induced mutations.

Available data also indicate that mutations possibly occurred due to modification of bases, i.e. 8-oxoG (8-oxoguanine).

8-oxoG is a potent premutagenic lesion because it can pair with adenine as well as cytosine during DNA replication and can thus cause a G:C→T:A transversion mutation.

It is thus possible that 8-oxoG formation, which is involved in active oxygen through UV exposure, may contribute to G:C→T:A transversion mutations.
The mutations may then be passed on to the next generation, leading to skin pigmentation mutations and resulting in skin pigmentation variations.

This supports the theory that depigmented and tannable skin may have evolved numerous times in hominin evolution via independent genetic pathways under natural selection.
Conclusions

It is important to investigate human adaptability to UVR exposure to enable better prediction of the health risks caused by extreme environmental conditions and to develop preventive interventions.

Understanding human adaptability to UVR may allow us to predict the impact of environmental changes on health risks, particularly regarding high UV exposure secondary to ozone depletion.

Given the newly developed RS technologies that capture more detailed, higher resolution UV wavelength measurements and the emerging approaches to G×E interactions, it would clarify the mechanism underlying human adaptability to varying levels of UVR.