

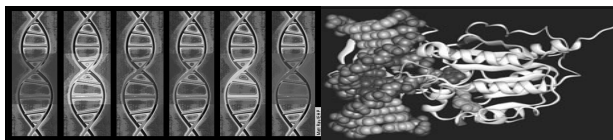


심포지엄 | 제 2 세미나실

유전체학의 개념 및 임상적용(종양유전체학)

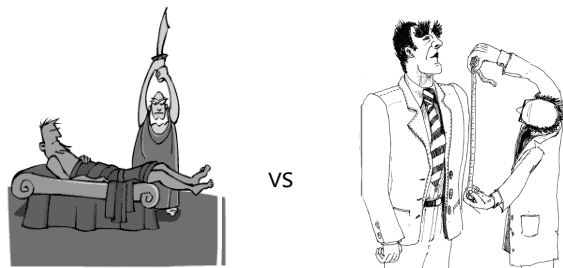
김 경 철

미즈메디병원 가정의학과



- **What's Personalized Medicine?**
 - Significance
 - Clinical application
 - Quick review : Basis of Genomics
- **Whole genome sequencing 연구의 발전 및 DTC**
- **Cancer Genomics의 사례**

What's Personalized Medicine

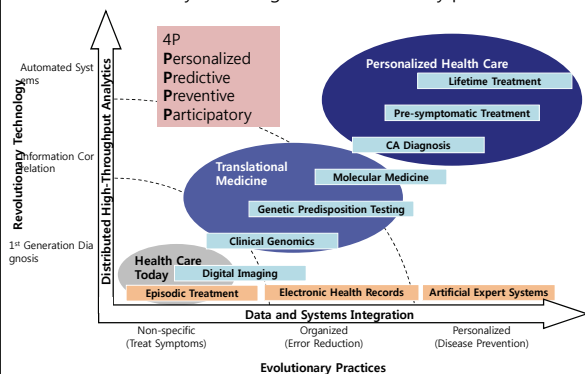


Procrustes (Προκρούστης)

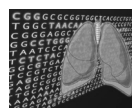
Tailored medicine

Personalized medicine is a medical model that proposes the **customization** of healthcare, with all decisions and practices being **tailored** to the individual patient by use of genetic or other information.

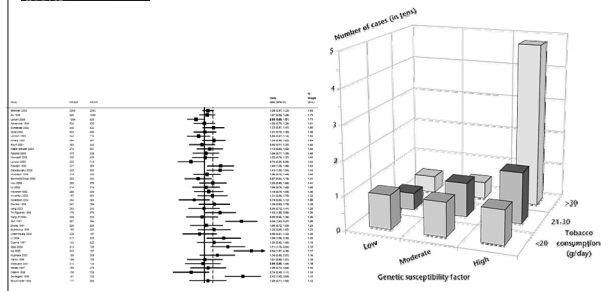
This **transformation** is being accelerated by a combination of revolutionary technologies and evolutionary practices



Page 3



Smoking vs Gene of Lung Cancer



GSTM1 Polymorphisms and Lung Cancer

Genotype of CYP2D6 in 130 cases and 170 control cases

Application of Clinical Genomics

Potential Roles of Genomics in Cancer

- Is my disease still in remission?
- Is my therapy having the desired effect, with acceptable toxicity?
- How do various potential therapies compare with respect to efficacy and safety?
- Compared to other people with my classification, how aggressive is my case and what are the implication for treatment?
- Are my cancer cells malignant, and if so, what is the precise classification of my cancer?
- Do I have cancer cells in my body?
- What is my risk of developing cancer in my lifetime?

Research for the future: Personalized medicine

Goals for personalized medicine:

- Identify genetic differences between people that affect drug response
- Develop genetic tests that predict an individual's response to a drug
- Tailor medical treatments to the individual
 - Increase effectiveness
 - Minimize adverse side effects

Pharmacogenetics
Evaluates how an individual's genetic makeup corresponds to their response to a particular medication.

Pharmacogenomics
Combines pharmacogenetics with genomic studies. Uses large groups of patients to evaluate how candidate drugs interact with a range of genes and their protein products.

Illustration by Chris Twichell

Polygenic Determinants of Drug Response

Metabolism genotype	Receptor genotype	Efficacy	Toxicity
+	+	65%	Low (3%)
+	+	32%	Low
+	+	9%	Low
+	+	79%	Moderate (15%)
+	+	40%	Moderate
+	+	10%	Moderate
+	+	80%	High (80%)
+	+	40%	High
+	+	10%	High

3435C → T
11145T

Eribix (Cetuximab)
Developed by Merck, under license from Imclone

The First Targeted Drug For Colorectal Cancer

The Effectiveness Of Eribix Is Determined By The Genetic Makeup Of A Colorectal Tumor.

Eribix and Vectibix, A Similarly-Designed Targeted Effective Only In The Treatment Of Colorectal Tumor And BRAF Genes.

Tumors With Defective K-RAS Genes Did Not Respond (Journal of Medicine In October, 2008)

That Colorectal Tumors With Abnormal BRAF Genes Were Resistant To Both Eribix And Vectibix. (Journal Of Clinical Oncology In 2008)

**히셉틴 - HER2
글리벡 - Philadelphia chromosome
이레사 - EGFR**

각막이영양증(Corneal dystrophy)과 아벨리노 유전자

각막 이영양증은 인간염색체 5q에 위치하는 TGFBI 유전자의 돌연변이가 주 원인으로 알려져 있는 상염색체 우성 유전질환.

한국인은 1300명당 1명에서 발병. 아벨리노(Avellino) 각막이영양증은 라식수술을 시행한 경우 각막 혼탁이 증가되는 것으로 보고되고 있습니다. 따라서 아벨리노(Avellino) 각막이영양증 돌연변이를 갖는 경우, 라식수술은 금기

정상형 돌연변이형



DNA Layers and AlloMap Gene Expression Profiling for Organ Transplant

- Reduce the immune response leading to organ rejection

AlloMap
MOLECULAR EXPRESSION TESTING
A Breakthrough in Heart Transplant Patient Management

Find a Transplant Center and a Doctor Near You. Click here.

Join the AlloMap Family
Join our family and receive a complimentary gift for signing up!
*gift for patients and caregivers only.

AlloMap® The Future IMAGE of Heart Transplant Management

Newsweek Health for Life

Diet and Genes

It isn't just what you eat that can kill you, and it isn't just your DNA that can save you—it's how they interact. Jan 17 2005

Green tea helps silence genes that fuel breast cancer in some women.
Name of gene: HER-2
Function of gene: Triggers growth signals in cells
Long-term effect: Slows HER-2 signaling in aggressive breast tumors

Broccoli boosts genes that protect against heart disease.
Name of genes: GST
Function of gene: Produces the body's master antioxidant, glutathione
Long-term effect: The additional glutathione helps keep arteries healthy

Soybeans affect 123 genes involved in prostate cancer.
Name of gene: p53
Function of gene: Kills mutant cells
Long-term effect: A compound in soy increases activity of the p53 gene, helping to block tumor formation

Turmeric suppresses genes that ratchet up inflammation.
Name of genes: Cox-2
Function of gene: Makes inflammatory compounds
Long-term effect: Could help ward off colon cancer and Alzheimer's

God created us in diversity with his purpose.

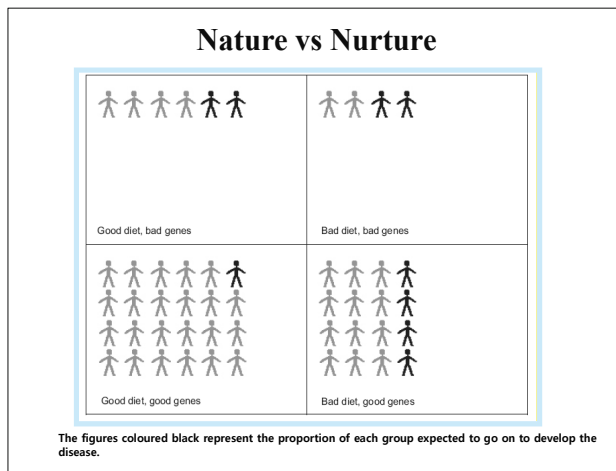
Newsweek Health for Life

Diet and Genes

It isn't just what you eat that can kill you, and it isn't just your DNA that can save you—it's how they interact. Jan 17 2005

Jose Ordovas PhD, HNRCA, Tufts University

10회 심포지움 2005, 인터콘티넨탈 호텔



What's DNA, Chromosome, Genes, Base

Chromosomes
Your genome is divided into 22 pairs of chromosomes that make up the DNA. Most of them hold thousands of genes.

Genes
Genes make up 2% of your DNA. The remaining 98% has no known function.

Bases
On the DNA molecule, the bases A and T always face each other, and so do C and G.
 A = Adenine
 T = Thymine
 C = Cytosine
 G = Guanine

• Gene : A part of the DNA that codes for a protein.
 • 30,000 genes in the human genome.

Chromosome, Gene, SNPs

Whole books : 22 Chromosomes
 One book : Chromosomes (Chr 8)
 One page : Chr. region (Chr 8p24)
 One misspelling : SNP (rs2073618)
 One sentence : Gene (TNFRsf11b)
 One misspelling : SNP (rs9594782)

SNP is a single **base** variation in DNA **sequence** that has a **frequency** >=1% in a population.....
Bold represents exons

SNP is a single **vase** variation in DNA **sequence** that has a **frequency** >=1% in a population.....
SNP (rs9594782)

Remember there is another set of encyclopedia in parallel : allele



TNF Chromosomal Location: 6p21.3

```

CGAGCTTCT CAGTCTTCC CCGAGAGAC CTTCTCTGAG GCLTCCAGCC 50
TCCACCAGG CCCCAGCTC CTTCTCCCG CAGGAGCCG AACAGAGCC 100
TCAGACTCA ACAGAGCTT TCCCTCCAC CCGCTTTCT CTTCCCTGAG 150
GACTGACTT TCGAGAGCC CCGAGACTT TACTTATAT TTTTTCGAG 200
ATCTCTCTG GAGTATAGA GGAAGACAG CAGAGACTG GTCCCAAAA 250 | var (214)
CCCCCAGG AAGTATA GCACTTTTG GCACACCG CCGAGAGCC 600
CCTCTCCAC AAGATCTTA GAGAGACAG TAAAGAGAG AAGAGCACT 650
ACAGAGCCC CTTAGAGAG ACTCTCCAG CCGAGTCCG CTAGAGACT 700
CCAGGAGG TTTCTCTTA TCCCTCATCT GACCCAGGC TCCACTCTT 750
CTCTCTTGA AAGATATA TCCACTCTA AAGCATATC CCGAGCTTG 800 | Exon 1 |
Start codon: ATG
AAGTCTCCG CCGAGAGCC CCGAGAGCC CCGAGAGCC CCGAGAGCC 850
E A L P R K R Q H E 27
AAGAGTCTT TTTCTCTCC CTTCTTCCC TTTCTCTAG CCGAGAGCC 900
R R C L F L S L P S P L I V A G A 44
CAGAGACTT TTTCTCTCG TGCATTTTG AGTATGACC CCGAGAGCC 950
T T L F E L D H F S I S P Q R 60
AAGTCTTG TCCCTGACC GACTCTTCC ACTCTCCAG CCGAGAGCC 1000
E E
ATAGAGACC AAGAGAGAG GAGATATAG ATGAGTATA GATTTGCTT 1050 | var
AAGATCTTG CCGAGAGCC GAGAGAGAG AAGAGAGAG ATGAGAGAC 1150 | REPEAT
AAGATCTTG CCGAGAGAG GAGAGAGAG AAGTGTAT GAGTGTATG 1200
AATAGATTA TGAATAGCA AAGATATA TAAATAGAT ATAGAGAGC 1250
CAGTCTCT TTTCTTAGG GAGACTCTT GAGATTAAC CATTCTCTT 1550
CTCCAGAG CTTCCAGAG GACTCTCTC TAAAGAGCC TCGAGAGCC 1600 | Exon 2 |
Start codon: ATG
AAGTCTTG TTTCTCTAG GACTCTCTC TAAAGAGCC TCGAGAGCC 1650
A A V
GGGCTTAG TTAGTACCG TATAGAGCA GTGAGAGAG TTTAAGTTT 1700
GGTCTCTAG GAGATATA TGAATATA AATAGAGAG TATTCTCTC 1750
GAGTCTAG GCTCTACT TTTCTCTT CTTCTCTTG TAAATCATC 1800 | Exon 3 |
CTTCAGAG CCGAGAGCC AAGCTCTAG CCGATTTTG AAGTCTCT 1850
E S T P S D E F V A H V V
TTTCTCTAG TTTCTCTAG CTTAGAGCC TAAATAGAT GATTTAGAT 1900 | var
CAGAGAGCC CCGAGAGCC TTTCTCTCT CTTCTCTCT CTTCTCTCT 2150 | Exon 4 |
ATCATCTCC TTTCTCTAG GACTCTCTC TAAAGAGCC AAGCTCTCT 2400 | UTR |
Start codon: ATG
Stop codon: TGA
CTCCAGAT CATTATTA CCGCTCTT CAGAGACT CACTCTCTC 2450 | var
  
```

Within a gene, mutations can occur in either coding or non-coding regions. Coding regions are called **exons** and non-coding regions are **introns**.

SNP Mutations

- These may change phenotype
- rSNP regulatory SNP
- iSNP intron SNP
- cSNP amino acid substitution
- cSNP no amino acid substitution
- gSNP

SNPs are the smallest possible change in DNA. Most changes do not change an organism's phenotype, though some do. On an individual level, a mutation may cause an inherited disease.

What's SNP

SNP: DNA sequence variations That occur when a single nucleotide (A,T,C, or G) in the genome sequence is altered with frequency >1% in a population.

SNPs: Single Nucleotide Polymorphisms

ARG
GTACC**G**CGGCGC Allele 1 (M)
GTACC**C**GGGCGC Allele 2 (F)

HIS
Human *ApoE* gene segment, rs1542035 SNP

Three Genotypes

- Homozygous wild type : GG
- Heterozygous mutant type : GA
- Homozygous mutant type : AA

Genotype: PP (Homozygous for the dominant allele), AA (Homozygous for the recessive allele), Bb (Heterozygous)

Central dogma

The diagram illustrates the central dogma of molecular biology. It starts with DNA containing a promoter, TSS, and exons/introns. Transcription produces a primary transcript with introns and exons. Splicing removes introns and joins exons to form a mature mRNA with a 5' cap, 5'UTR, CDS, 3'UTR, and polyA tail. Translation of the mature mRNA produces a protein.

Non-synonymous SNPs

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Table 15.1 The Genetic Code

First Letter	Second Letter				Third Letter
U	UUU UCU UCA UUG	UUC UCC UCA UUG	UAU UAC UAG UAA	UUA UUC UUG UAA	U C A G
C	CUU CUC CUA CUG	CCU CCC CCA CCG	CAU CAC CAA CAG	CUU CUC CUG CUA	U C A G
A	AUU AUC AUA AUG	AUU AUC AUA AUG	AUU AUC AUA AUG	AUU AUC AUA AUG	U C A G
G	GUU GUC GUA GUG	GUU GUC GUA GUG	GUU GUC GUA GUG	GUU GUC GUA GUG	U C A G

Example

TTT → TTA/G
Phe → Leu

ACT → ATT
Thr → Ile

GTC → TTC
Val → Phe

"Non-synonymous"

Genome wide association (GWA) study

- The first major GWAS was published in Nature in February 2007 by Robert Sladek *et al.* in a study searching for type II diabetes variants
- Numerous genome-wide association studies for the diseases **coronary heart disease**, **type 1 diabetes**, **type 2 diabetes**, **rheumatoid arthritis**, **Crohn's disease**, **bipolar disorder**, and **hypertension** has studied.
- One of the challenges for a successful GWAS in the future will be to apply the findings in a way that accelerates drug and diagnostics development

A WTC study in coronary artery disease (Samani, NEJM 2007)

Published Genome-Wide Associations through 07/2012

Published GWA at $p < 5 \times 10^{-8}$ for 18 trait categories

SNP-associated trait categories

- Digestive system disorder
- Cardiovascular disorder
- Metabolic disorder
- Immune system disorder
- Neurological disorder
- Liver enzyme measurement
- Lipid or lipoprotein measurement
- Inflammatory marker measurement
- Hematological measurement
- Body measurement
- Cardiovascular measurement
- Other measurement
- Response to drug
- Biological process
- Cancer
- Other disease
- Other trait
- Trait mapping in progress

NHGRI GWA Catalog
www.genome.gov/GWASStudies
www.ebi.ac.uk/fgpt/gwas/ EMBL-EBI

