Future direction of cardiovascular genomics

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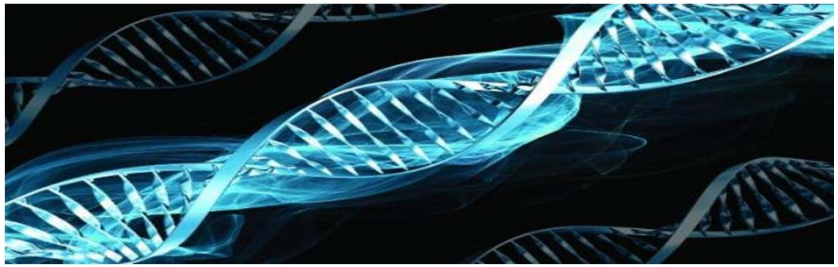
교수 박 정 의

연구간호사 장미자



성공적인 강의

1. 흥미유발
2. 중요한 facts전달
3. 궁금증 풀어줄것

Questions

- 왜 genomics학문이 흥미를 유발하지 못하는가?
- 왜 임상에서 genomics 학문이 유용하게 쓰이지 못하는가?
- 임상에서 genomics 학문이 어떻게 도움이 될 수 있는가?
- 유전질환이 유전자치료로 치료가 가능한 것인가?
- Genomics학문이 다른 어떤 경우에 도움이 될 수 있는가?
- 10년후 genomics는 어떤 상태로 발전할 것인가?

관상동맥질환 가족력

- 관상동맥질환이 있는 환자들에서 가족중(부모, 형제들)에 관상동맥질환이 있는 환자들은 ___ %가 될까?

  – 10,753명중 1,114명(10.4%)

관상동맥질환 가족력

- 관상동맥질환이 있는 환자들에서 가족중 **<u>뇌졸중 병력이</u>** 있는 경우는___ %에서 인가?
  - **총 10,753명 중 940명 (8.7%)**

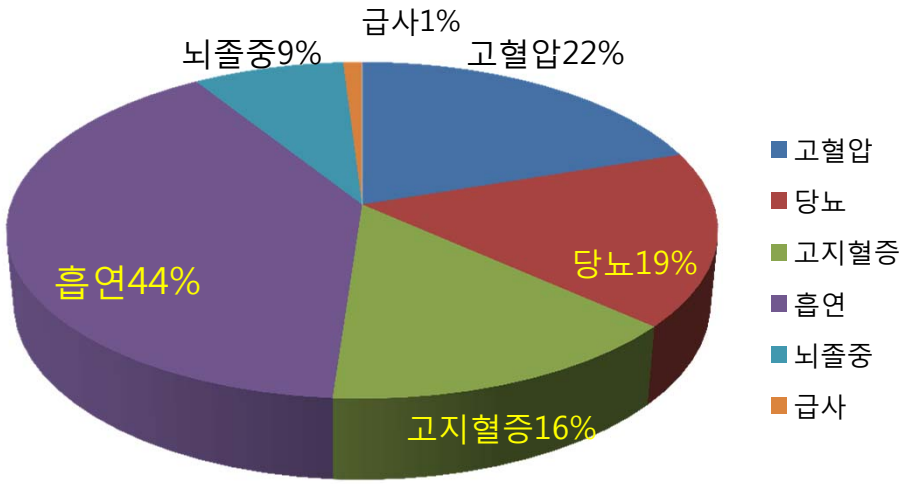
관상동맥질환 가족력유무에 따른

- 연령의 차이

(N=10,753)

Family Hx of CAD	Cases	Age(Yr) Mean ± SD	Median(IQR)	Mann-Whitney test
No	6,487	62.6 ± 10.6	64(56.70)	P<0.001
Yes	4,266	59.8 ± 10.6	60(52.67)	

관상동맥질환의 가족력이 있는 환자들에서 위험요인및 뇌졸중, 급사의 빈도(%)



총 1114명

50세미만 관상동맥질환 환자에서 가족력빈도

➢ 50세미만의 관상동맥질환환자에서 관상동맥질환의 가족력을 지니고있는 경우는?

총 1631명중 278명(17%)

➢50세미만으로 PCI한 환자들중 관상동맥질환의 가족력이 있는 비율은?

총 1171명중 225명(19.2%)

관상동맥질환에서 뇌졸중 가족력

➢50세미만의 관상동맥질환환자에서 뇌졸중의 가족력을 지니고있는 경우는 _____%인가?

총 1631명 중 148명(9.1%)

➢50세미만의 PCI받은 환자들 중 뇌졸중의 가족력이 있는 비율은 _____%인가?

총 1171명중 125명(10.7%)

고혈압과 가족력

- 부모가 모두 정상인 경우 자녀가 고혈압일 경우 4%
- 부모중 한 사람이 고혈압이 있으면 네 자녀중 한 명 고혈압
- 부모가 모두 고혈압이면 두자녀중 한 명에서 고혈압

당뇨와 가족력

- 부모 어느 한쪽이라도 있으면 자녀가 당뇨에 걸릴 확률은 15-20%
- 부모가 모두 당뇨인 경우, 자녀의 30-40%가 당뇨
- 일란성 쌍둥이: 한명이 1형 당뇨인경우 다른 한명에서 1형당뇨 발생할 가능성 50%. 2형당뇨에서는 90%

암과 가족력

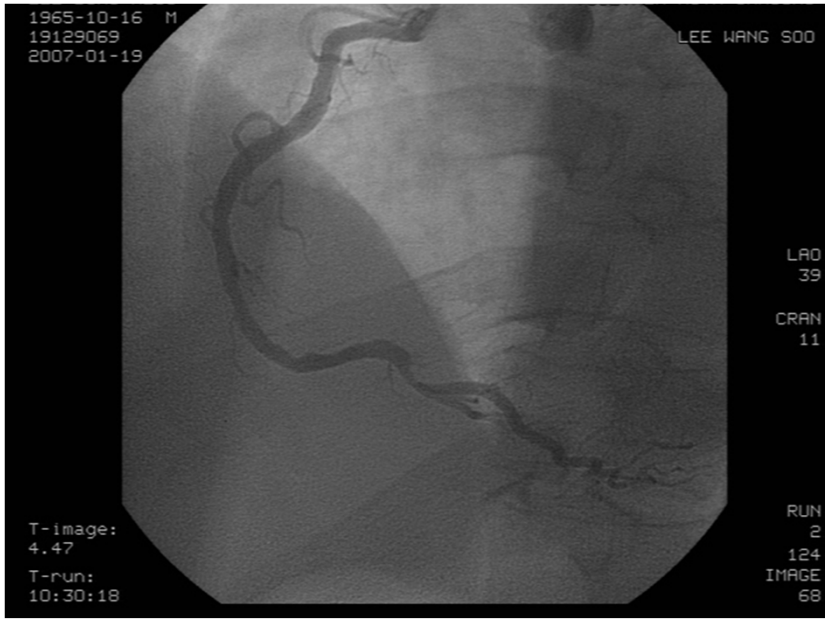
- 대장암, 유방암, 폐암, 난소암, 전립선암, 갑상선암에서 가족중에 발생 높을 수 있다.
- 대장 암 환자의 30%가 가족력 가짐.
- 대장암 가족력이 있는 경우 40세 이후 매년 한번씩 정기적으로 대장내시경 권유

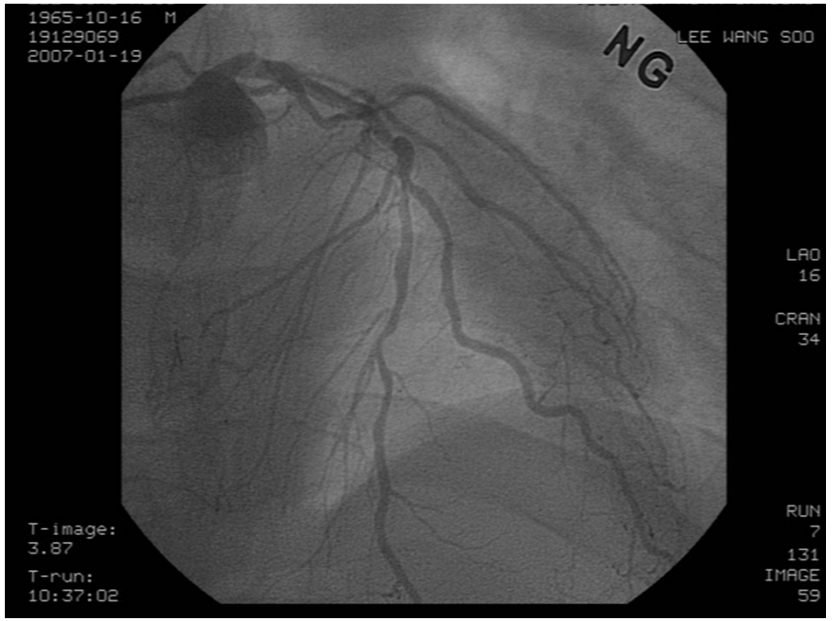
Genomics 의 虛와 實

- 인간 염색체의 모든 유전자를 밝히고, 기능을 알 수 있을 것이다.
- 모든 질병의 원인을 밝힐 수 있을 것이다.
- 유전질환에서 유전자 치료가 가능해 질 것이다.
- 개개인에 맞는 맞춤의학이 전개될 것이다.

M,42 Yr

- Age 41, presented with exertional angina
- B.P.: 130/90, BMI: 28
- Never smoked
- FH: Father: 40대 초반 심근경색증, smoker
  Mother: 뇌졸중(65세, 고혈압)
  2남 1녀중 맏,
- Cholesterol 136, Tg 72, HDL 37, LDL 96
  FBS 87, CRP:0.23


1965-10-16 M
19129069
2007-01-19
LEE WANG SOO
LAO
39
CRAN
11
T-image:
4.47
T-run:
10:30:18
RUN
2
124
IMAGE
68


1965-10-16 M
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131
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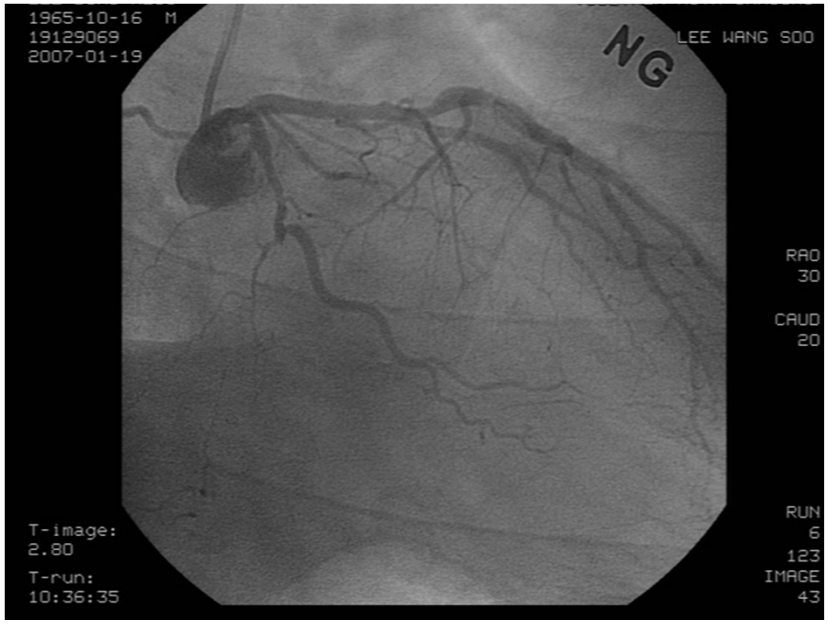
59


1965-10-16 M
19129069
2007-01-19
NG
LEE WANG SOO
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CAUD
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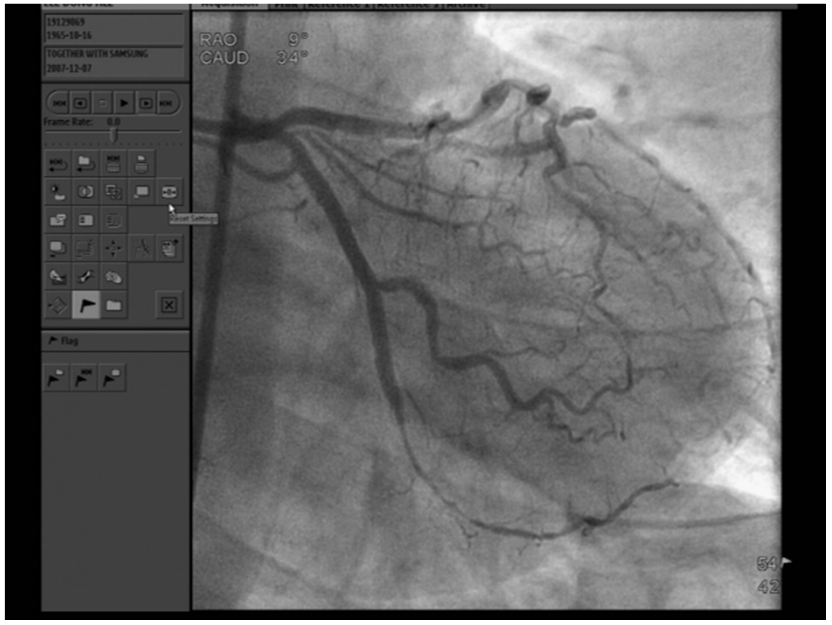
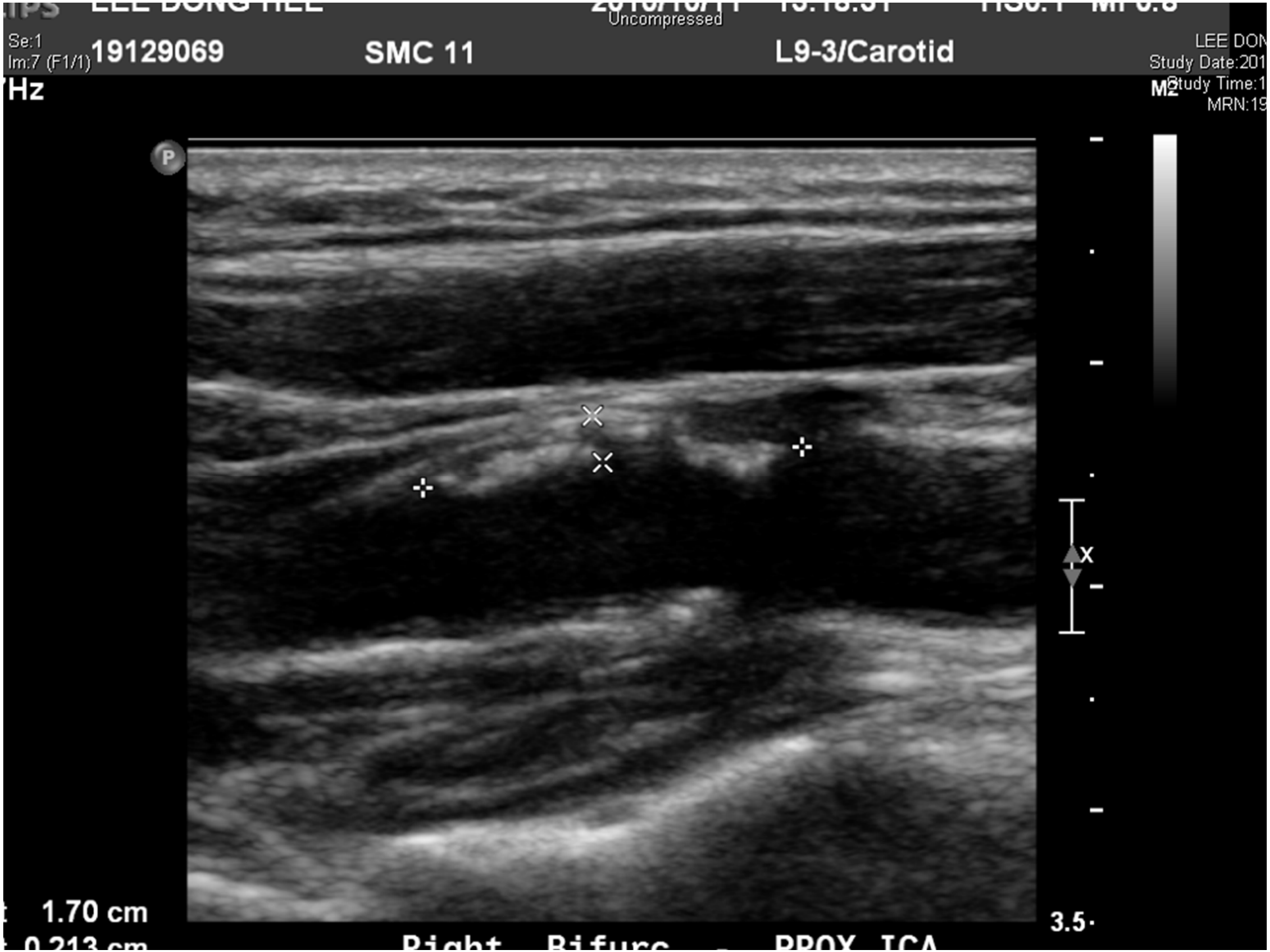
T-image:
2.80
T-run:
10:36:35
RUN
6
123
IMAGE
43


RAO 9°
CAUD 34°


Uncompressed
Se:1
Im:7 (F1/1)
19129069
SMC 11
L9-3/Carotid
LEE DON
Study Date:201
Study Time:1
MRN:19
Hz
M2
P
1.70 cm
3.5

Strong Family Hx

- F,63Yr
  - Resistant HT, HT since 55 yr
  - FHx: 오빠: 뇌졸중, 심근경색, 언니 두분 빼고 형제들 모두 고혈압약 복용, 아버님; 심장마비사
- F,49Yr: HT, migraine
  - 외삼촌 급사,어머니 62세 급사, 외할머니: 뇌졸중, 아버지: 뇌졸중
- F,68 Yr
  - HT, hypercholesterolemia, DM
  - FHx: 언니(50대), 어머니(61세): 심근경색, 식사하다가 갑자기 쓸어져 사망, 아버지: 젊은 나이에 사망, 언니; 고혈압

Human genome

- 3.1 bilion base pair
- 30,000 human genes encode for nearly one million proteins
  - Alternative splicing: 35 to 60% of our genes
  - Multiple transcription start sites
  - Polyadeylation
  - Specific editing of pre-messenger RNA
- Post-translational modification
  - Phosphoryltion
  - Sulphation
  - Glycosylation
  - Hydroxylation
  - N-methylation
  - Carboxymethylation
  - Acetylation
  - Prenylation
  - N-myristylation

Genomics 학문의 영역

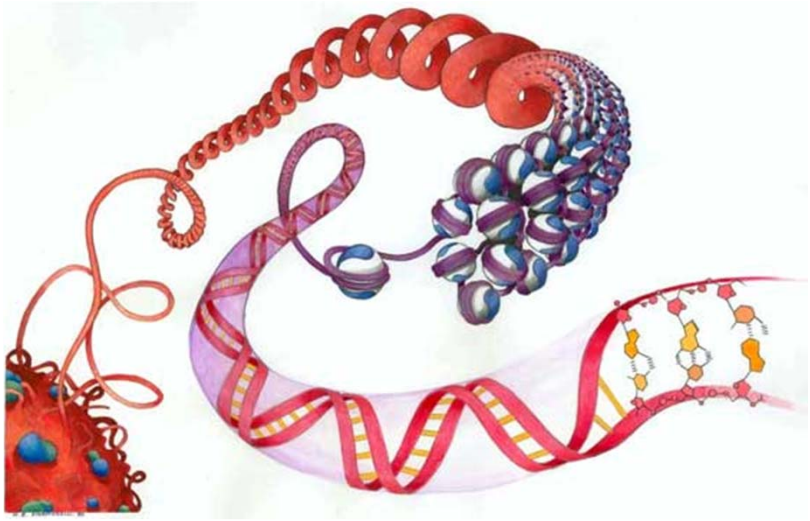
- Genetic predisposition:
  - Risk prediction and disease prevention
- Genetic cause찾기
  - Monogenic disease
  - Polygenic disease
- Drug target발굴
- Gene therapy

Heritability of traits

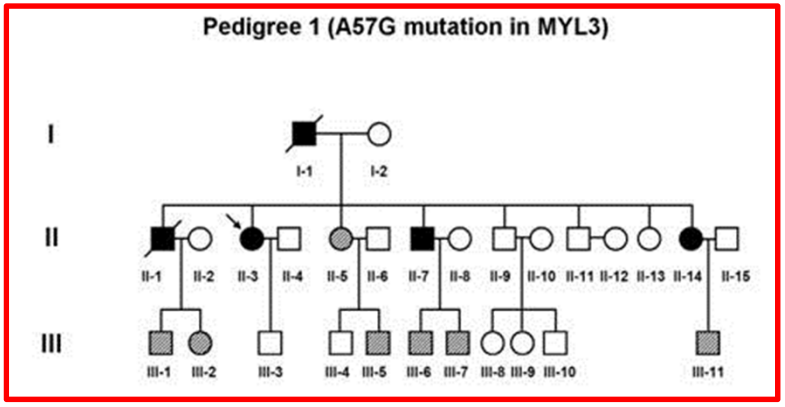
- "simple" Mendelian traits:
  - Familial HCM
  - Marfan's syndrome
  - Long QT syndrome
- Complex traits
  - Myocardial infarction
  - Type 2 diabetes mellitus
  - Age-related macular degeneration

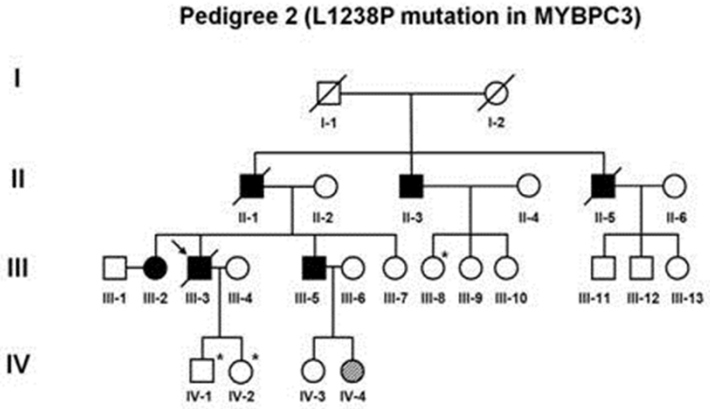
Challenges of genomics

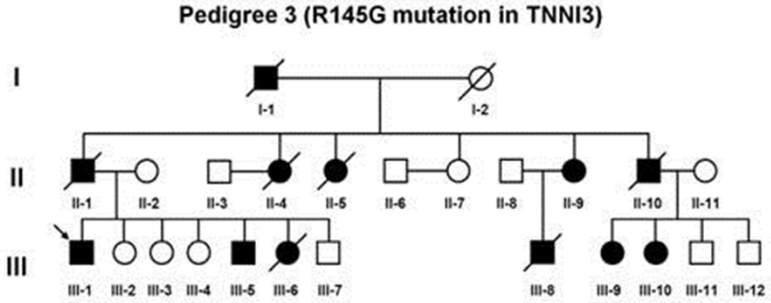
- Variable penetrance
- Low allele frequencies
- Epigenetic variation

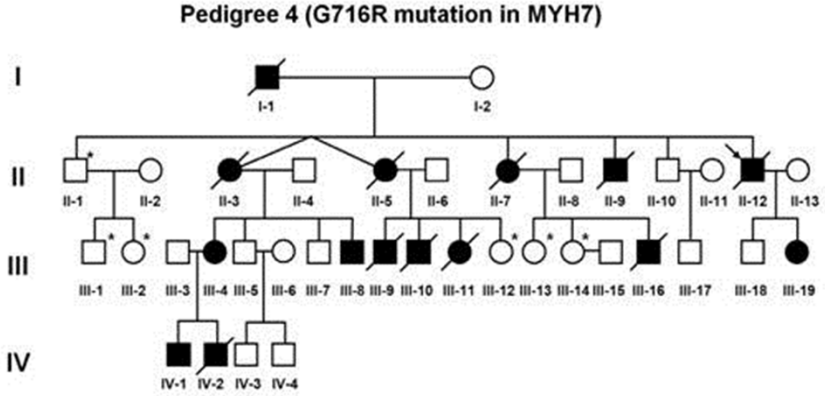


Variable penetrance and expression
HCM family

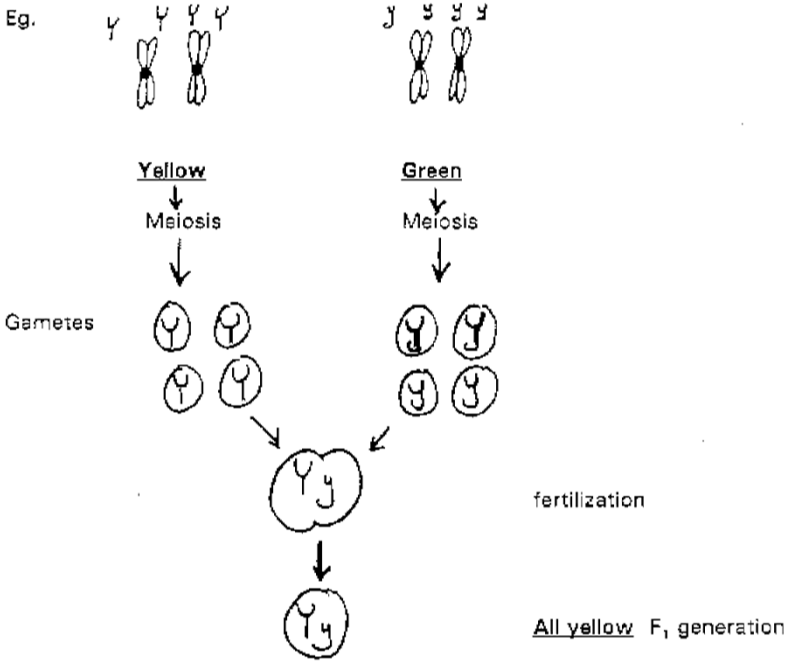








Gregor Johann Mendel
(July 20,1822-Jan 6,1884)



9p21

- 9p21 locus spans 58,000 base pairs
- 9p21 variant is extremely common with approximately 50% of the popultion posessing 1 copy and a further 20% to 25%posessing 2 copies of the risk variant.
- One copy of 9p21 increased risk for CAD by approximately 20% whereas 2 copies augment risk by 40%

Four SNPs on Chromosome 9p21 in a South Korean Population Implicate a Genetic Locus That Confers High Cross-Race Risk for Development of Coronary Artery Disease

Shen, Gong-Qing; Li, Lin; Rao, Shaoqi; Abdullah, Kalil G.; Ban, Ji Min; Lee, Bok-Soo; Park, Jeong Euy; Wang, Qing K.

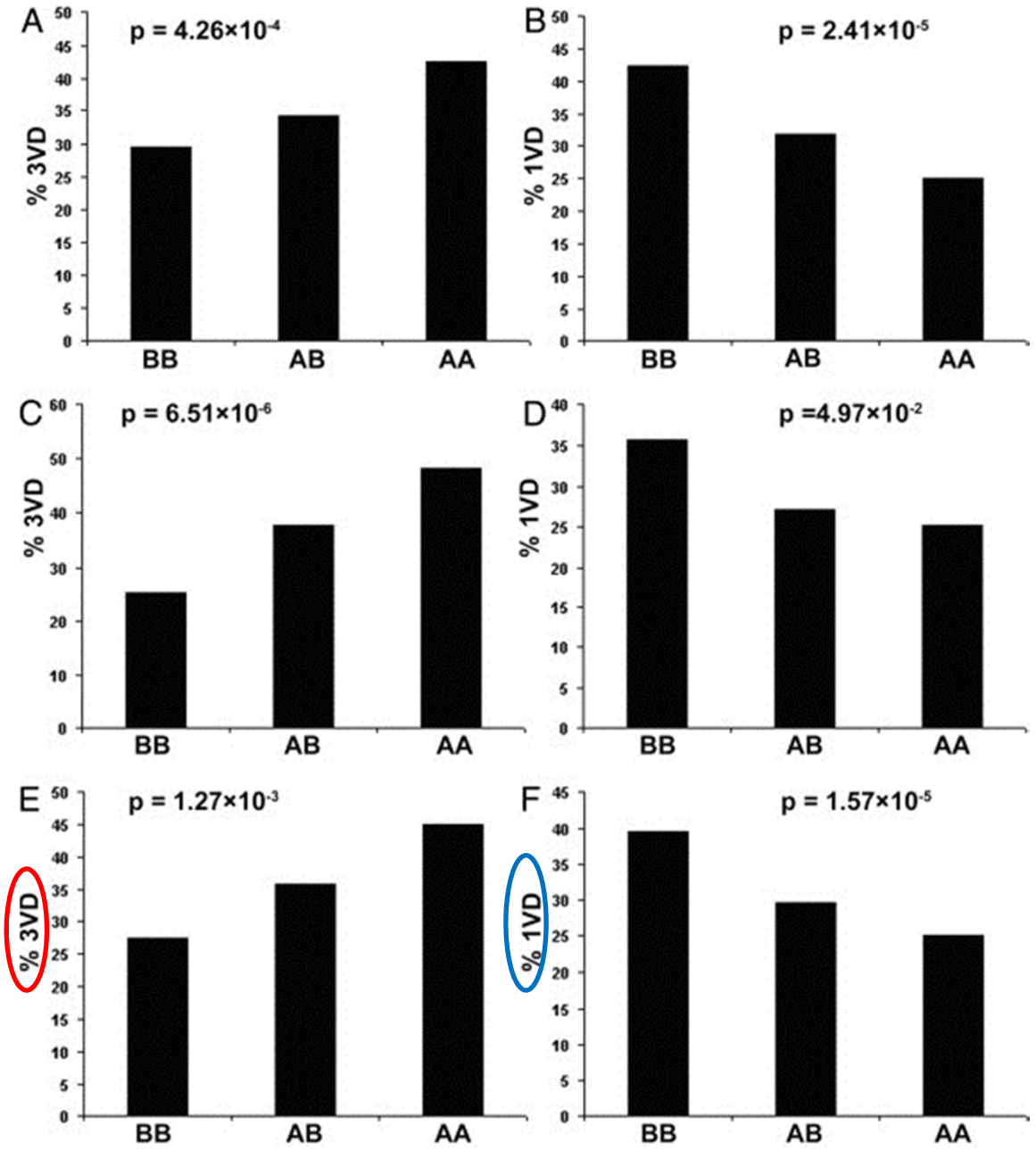
Arterioscler Thromb Vasc Biol 28(2008),pp.360-365

Replication of the association between a chromosome 9p21 polymorphism and coronary artery disease in Japanese and Korean populations

Kunihiko Hinohara Æ Toshiaki Nakajima Æ Megumi Takahashi Æ Shigeru Hohda Æ Taishi Sasaoka Æ
Ken-ichi Nakahara Æ Kouji Chida Æ Motoji Sawabe Æ Takuro Arimura Æ Akinori Sato Æ
Bok-Soo Lee Æ Ji-min Ban Æ Michio Yasunami Æ Jeong-Euy Park Æ Toru Izumi Æ Akinori Kimura

J Human Genet 53(4)(2008), PP 357-359

9p21



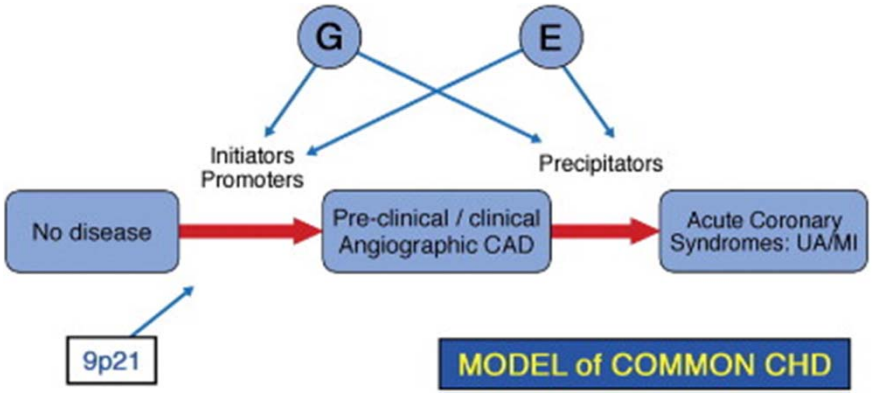
Early onset

Late onset

Whole patients

J Am Coll Cardiol 2010,Aug3,56(6):479-486

Genetic model of CAD.



J Am Coll Cardiol 2010,Aug 3,56(6):487-489

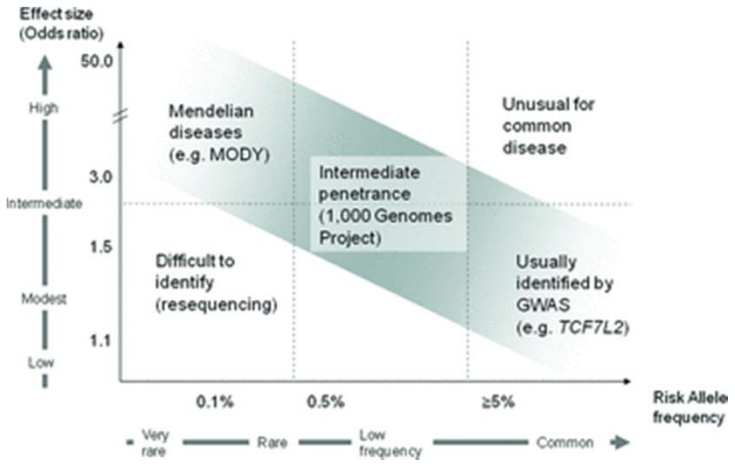
DM

- GWAS
- PPARG, KCNJ11
- 44 loci by GWAS
- Can explain 10%

AMD

- Common variants in two genes implicated in the complement pathway have shown to contribute to over half of the heritability of AMD

Detection of gene by GWAS: depends on allele frequency and effect size.

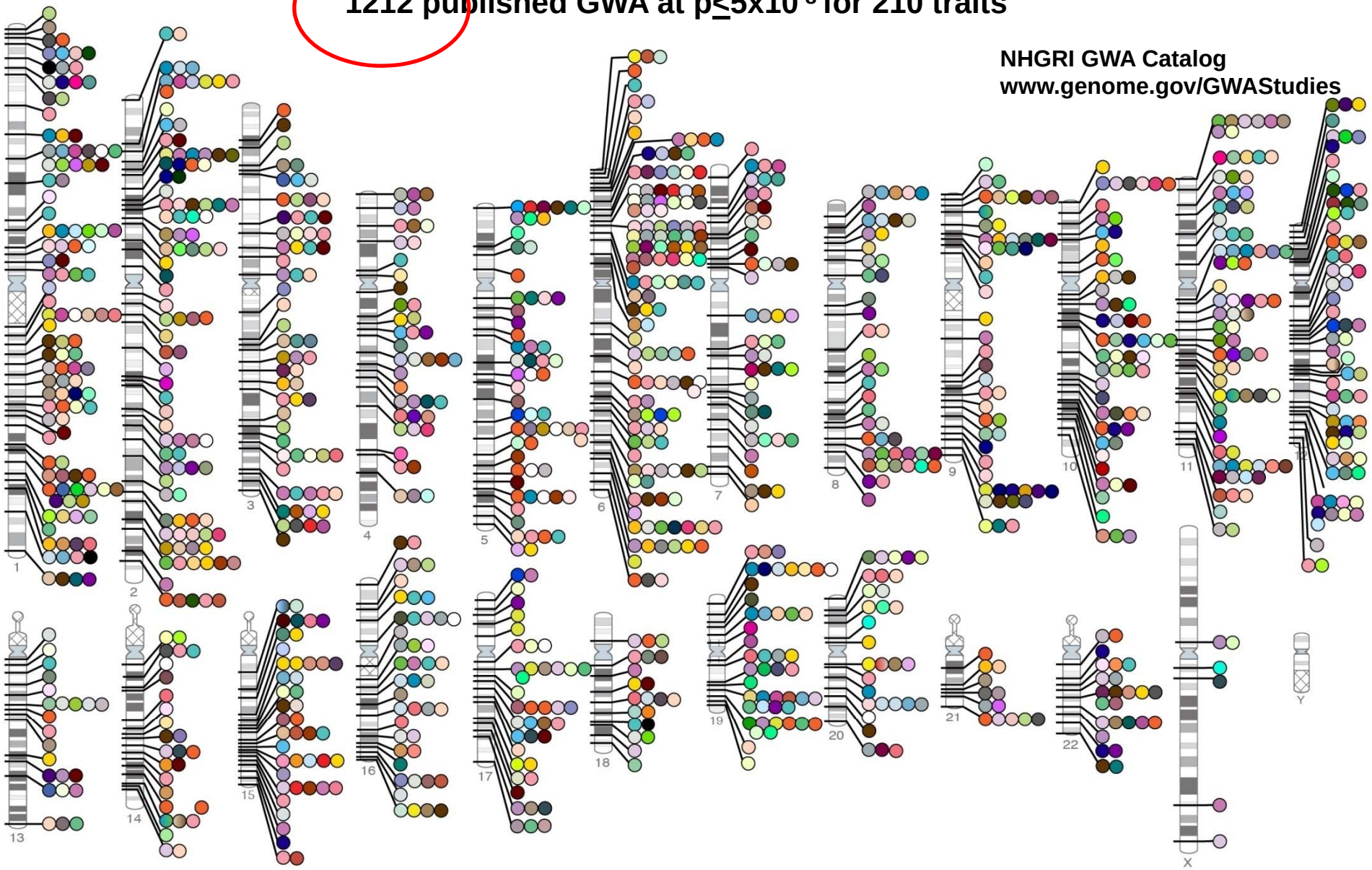


ANNALs of NYAS,2010;1212:59-77

Genome-Wide Linkage Scans	SNP Association Studies
Affected and unaffected sibling pairs of "multiplex" families	Sporadic cases and controls
Utilizes microsatellite markers	Utilizes SNPs
Laborious accrual of families	Rapid accrual of cases and control subjects
Less power to detect common genotypic variants	Increased power to detect common genotypic variants
	Easier replication in independent studies

Published Genome-Wide Associations through 12/2010, 1212 published GWA at $p \leq 5 \times 10^{-8}$ for 210 traits

NHGRI GWA Catalog
www.genome.gov/GWAStudies

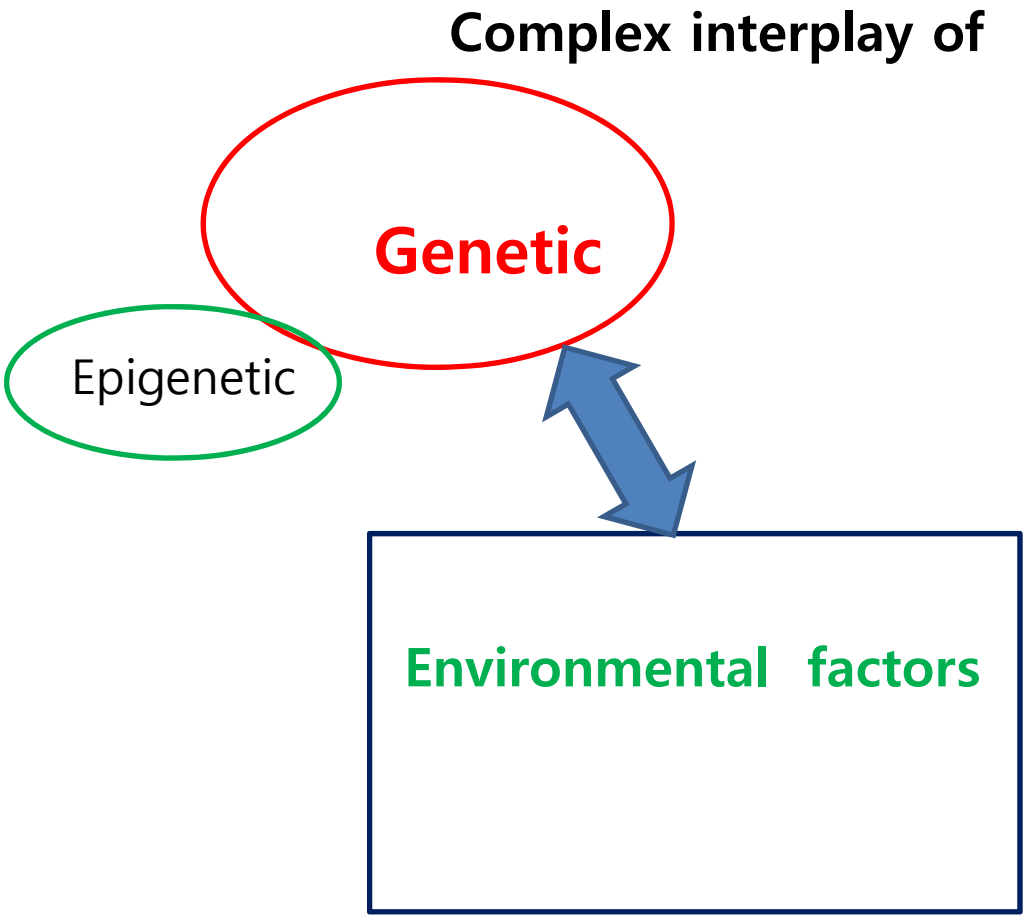


Pandora's Box

Nutrigenomics

- how genetic variation interacts with the diet to influence CVD risk
- study of the interaction between diet and an individual's genetic makeup

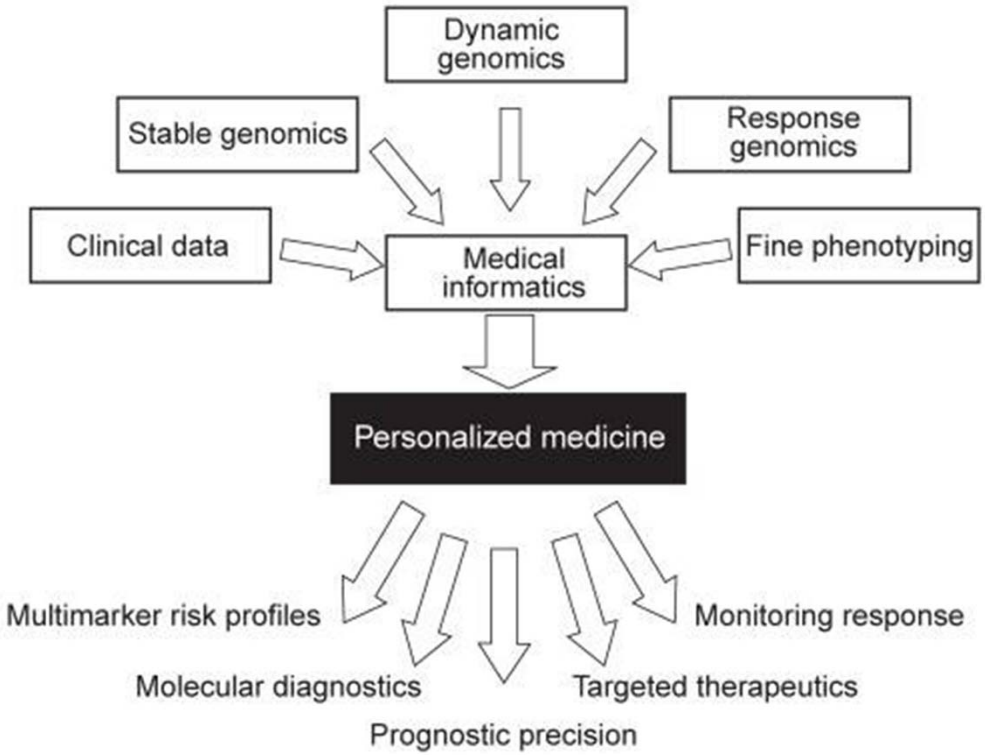
Human cardiovascular diseases



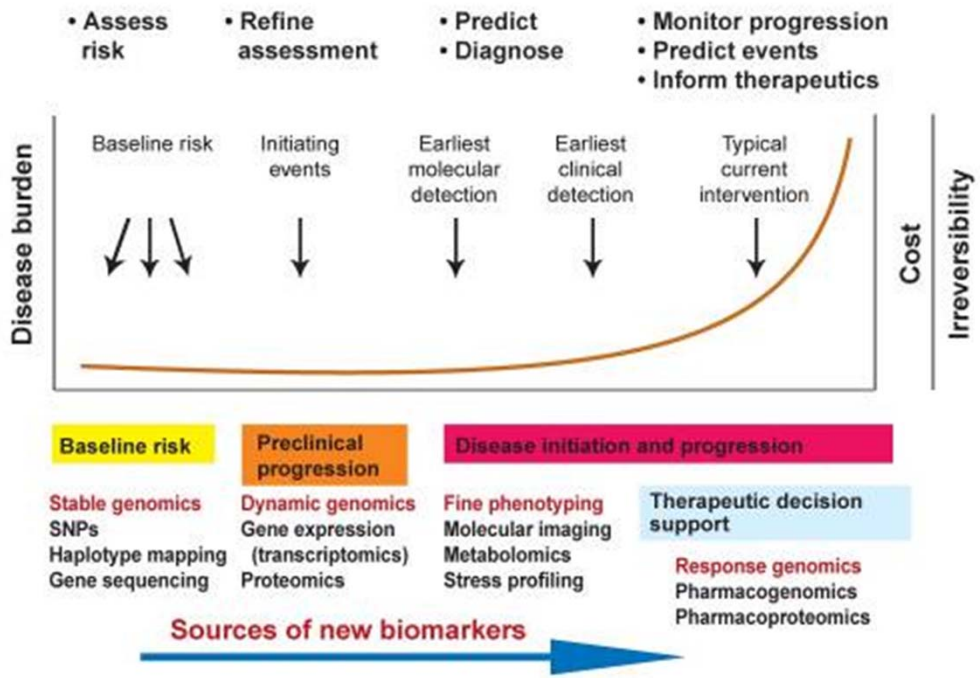
Personalized medicine

- defined by Francis Collins, head of the Human Genome Project, as “using information about a person’s genetic makeup to tailor strategies for the detection, treatment, or prevention of disease”

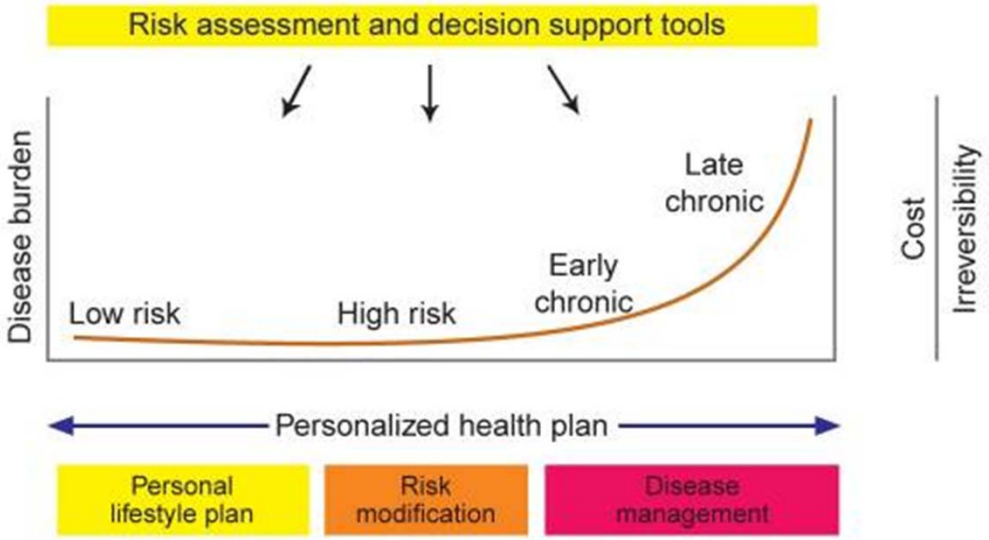
Personalized Medicine



Gene-based presymptomatic assessment of diesease prediction.

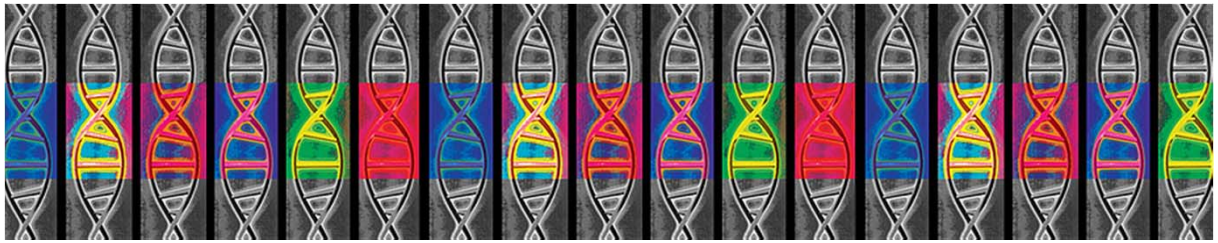


Risk assessment and decision support tools

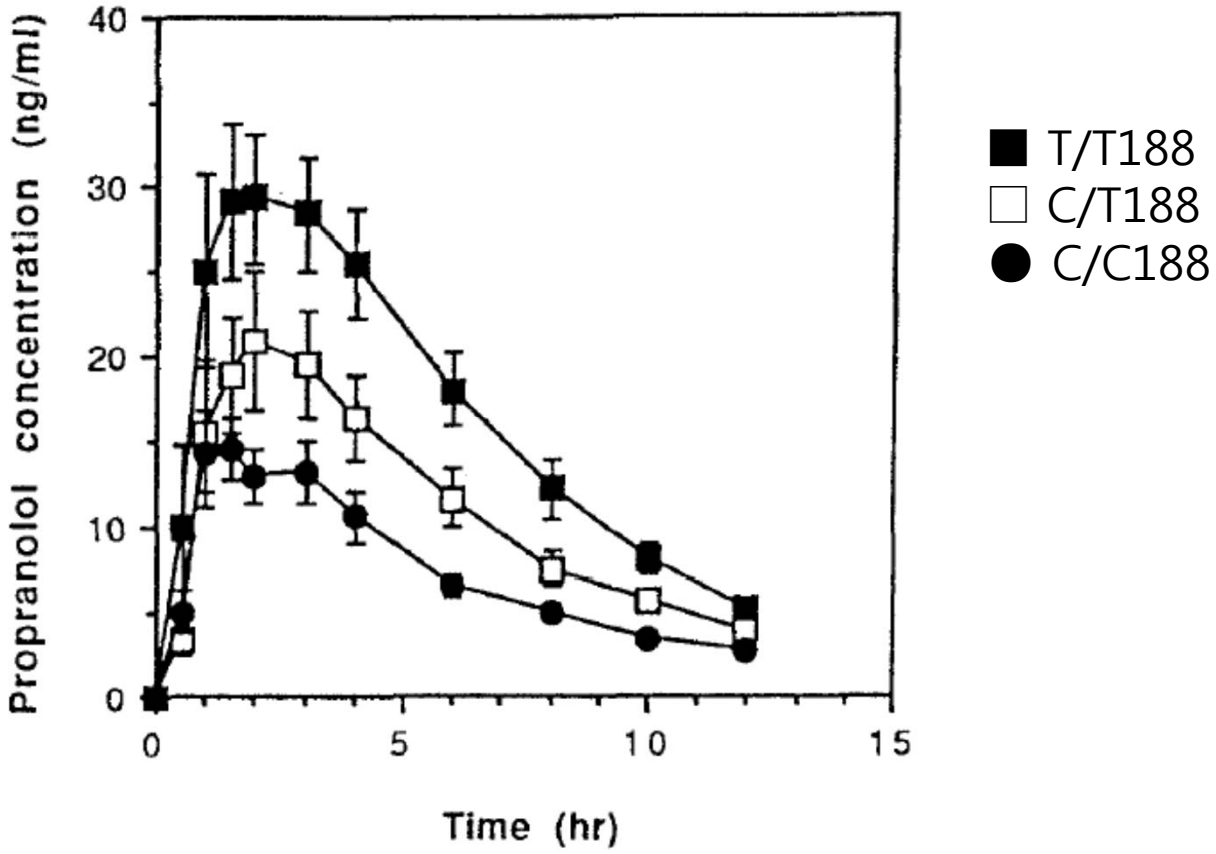


Pharmacogenomics

- Maximize response
- Minimize toxicity
- 'one drug fits all' → 'right drug for the right patient at the right dose and time'



Propranolol disposition in Chinese subjects of different CYP2D6 genotypes: 188C>T

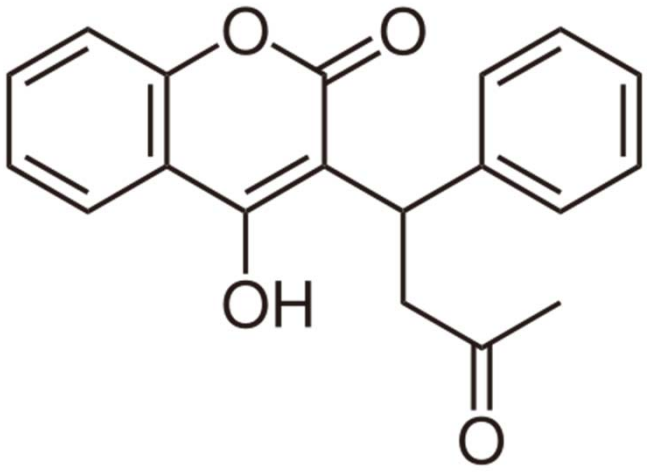


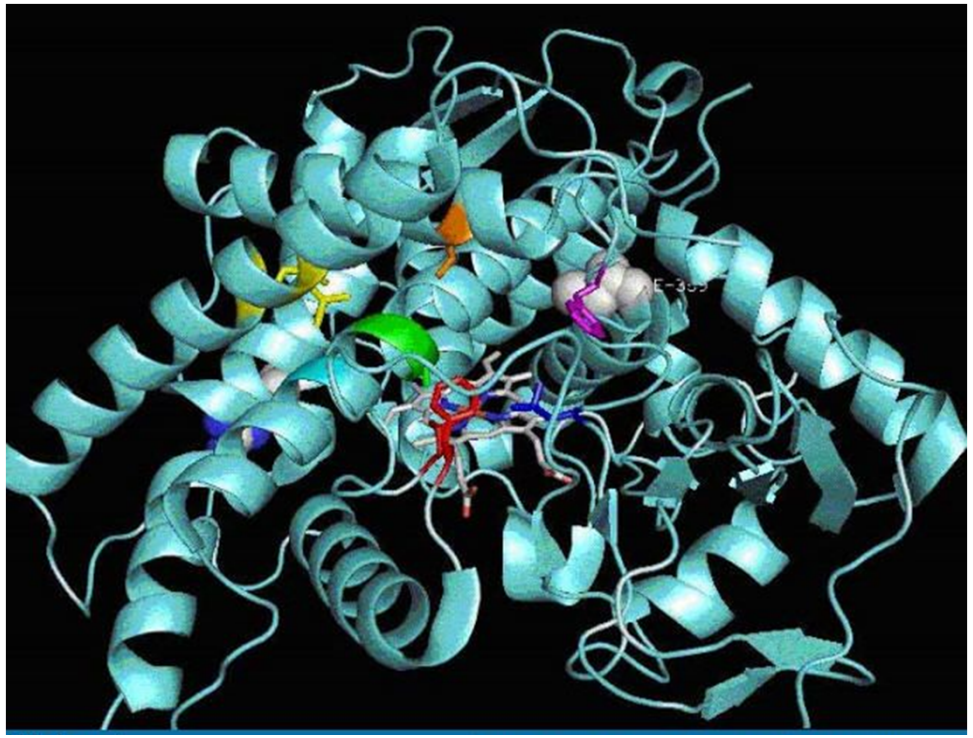
Lai ML, et al. Clin Pharmacol Ther. 1995; 58(3): 264-8.

Beta-blockers in Hypertension: Personalized medicine

- Can the effects be predicted?
- Metoprolol shows wide variation in pharmacokinetics according to CYP2D6*10 genotypes – common in Chinese populations

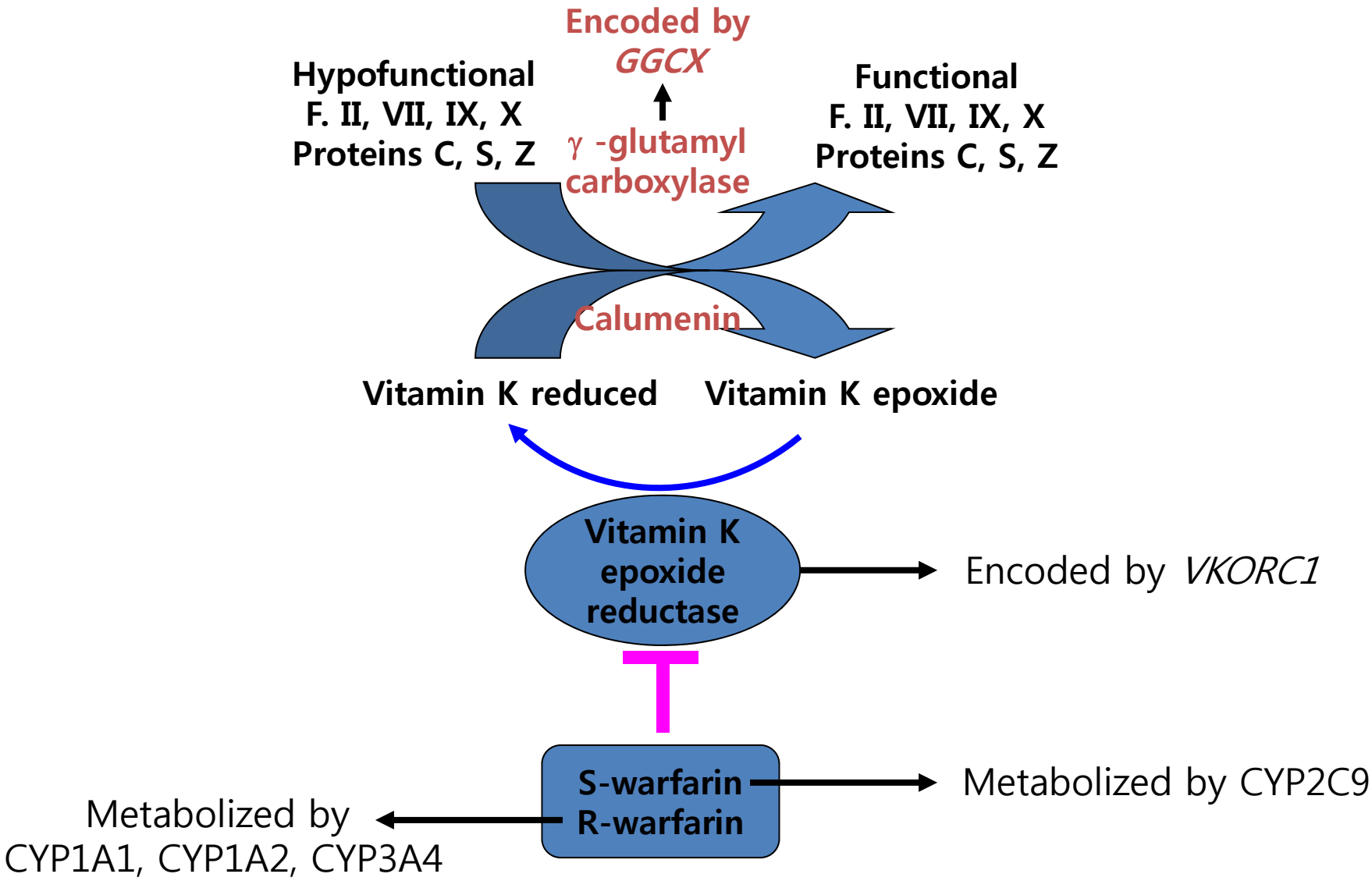
Pharmacology of Warfarin





Cytochrome P450 2C9 (CYP2C9)

Pharmacology of Warfarin



Warfarin Sensitivity

Mutations in *VKORC1* cause warfarin resistance and multiple coagulation factor deficiency type 2

Simone Rost[1,2]*, Andreas Fregin[1]*, Vytautas Ivaskevicius[3], Ernst Conzelmann[4], Konstanze Hörtnagel[2], Hans-Joachim Pelz[5], Knut Lappegard[6], Erhard Seifried[3], Inge Scharrer[7], Edward G. D. Tuddenham[8], Clemens R. Müller[1], Tim M. Strom[2,9] & Johannes Oldenburg[1,3]

Nature 2004;427:537-41.

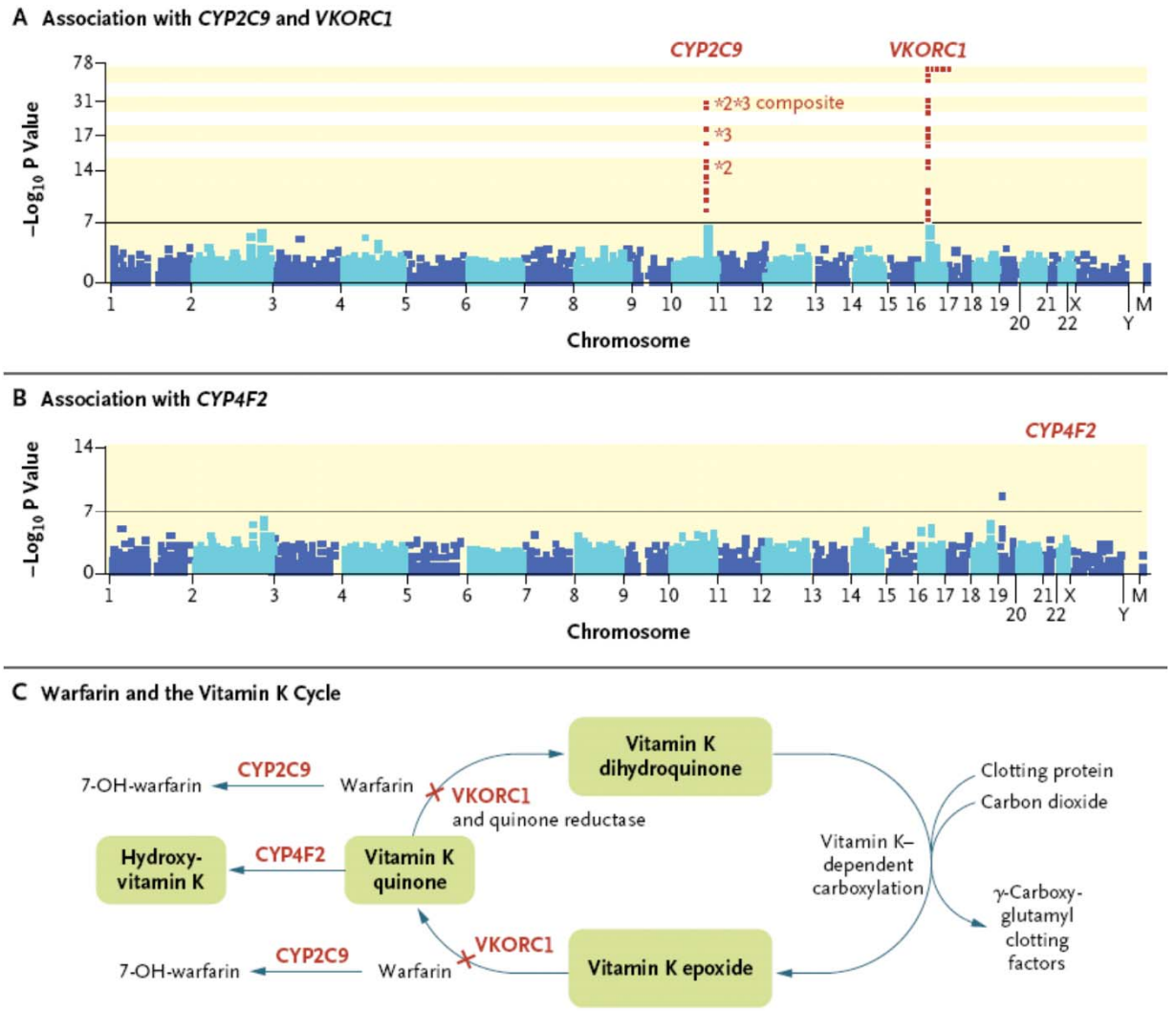
Identification of the gene for vitamin K epoxide reductase

Tao Li[1], Chun-Yun Chang[1], Da-Yun Jin[1], Pen-Jen Lin[1], Anastasia Khvorova[2] & Darrel W. Stafford[1]

[1]*Department of Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA*
[2]*Dharmacon, Inc., 1376 Miners Drive 101, Lafayette, Colorado 80026, USA*

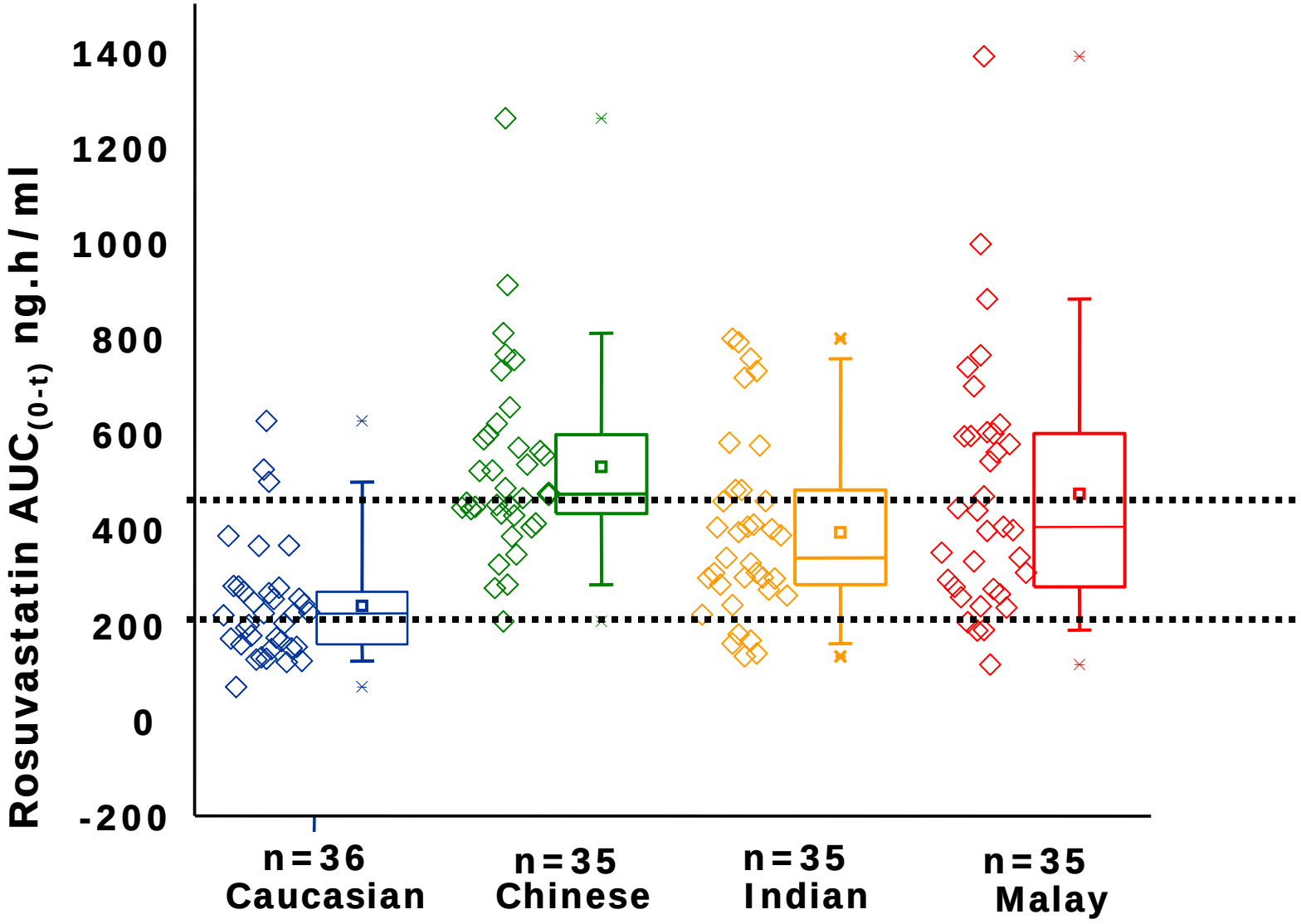
Nature 2004;427:541-4.

A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose



Takeuchi F et al. PLoS Genet 2009;5(3):e1000433

Rosuvastatin Pharmacokinetics: Plasma Levels in Asians 2x Caucasians



Lee E *et al*. Clin Pharmacol Ther 2005;78:330-41.

Association of HLA-B*1502 with Carbamazepine-induced SJS/TEN in different populations

Country/region	Major population	HLA-B*1502 allele frequency (%)	Association with SJS/TEN
Taiwan	Han-Chinese	5.9	Strong association
Hong Kong	Han-Chinese	10.2	Strong association
Thailand	Thai	8.5	Strong association
China	Northern Han-Chinese	1.9	Data not available
	Southern Han-Chinese	7.1	Strong association
Japan	Japanese	0.1	No association
Korea	Korean	0.2	No association
Germany	European	0	No association
France	European	0	No association

Lee MT et al., Expert Opin. Pharmacother. 2010;11:2153-2162.

Personalized medicine

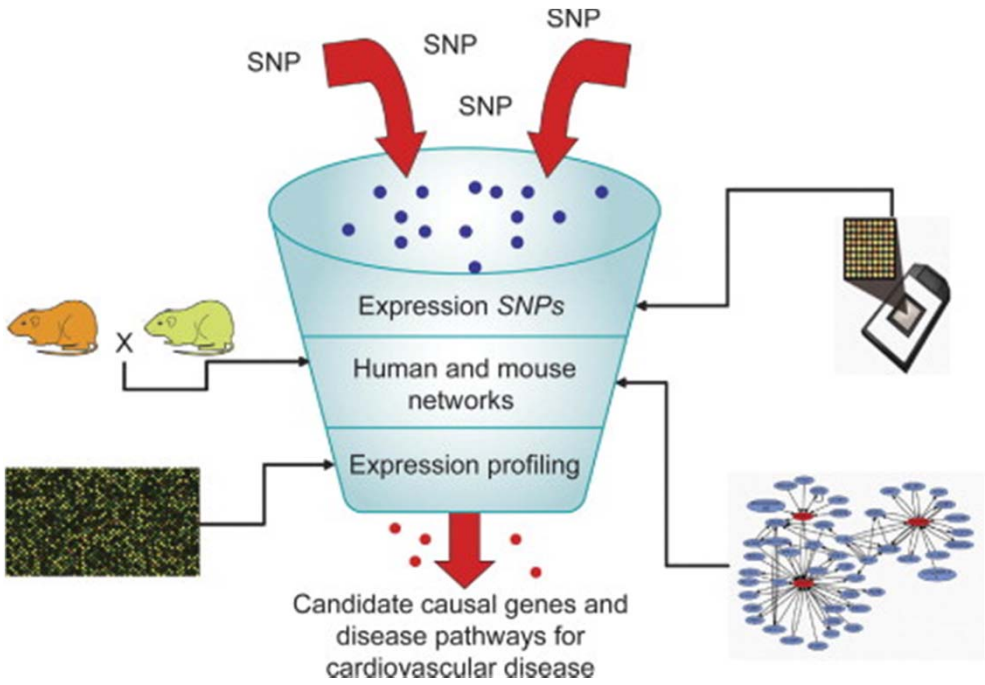
by David Goldstein

- Two striking findings will define the study of disease for the decade to come. First, common genetic variation seems to have only a limited role in determining people's predisposition to many common diseases.
- Second, gene variants that are very rare in the general population can have outsized effects on predisposition.

Future eras

- Massive advances in
  - Technology
  - Information handling
  - Computational power

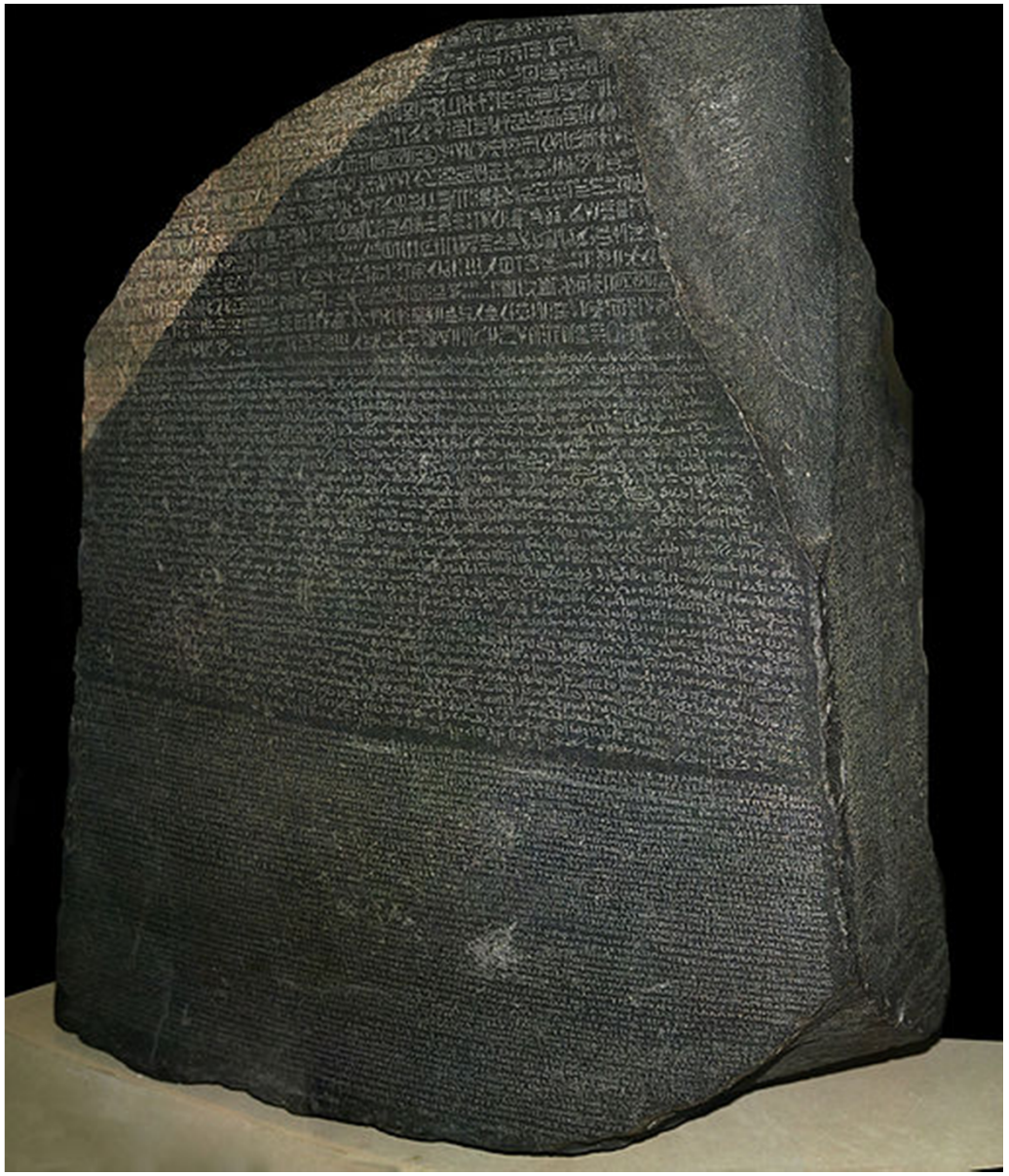
- Need for comprehensive biobanks
  - Repositories for biological samples
    - United Kingdom Biobank: 500,000 patients
    - Reykjavik Heart Study: deCode Genetics
    - Japanese Biobank: started in 2003,DNA, serum and information from 300,000 patients



Systems biology: to find the drug target from the causal genes found from GWAS study.

Questions

- 왜 genomics학문이 흥미를 유발하지 못하는가?
- 왜 임상에서 genomics 학문이 유용하게 쓰이지 못하는가?
- 임상에서 genomics 학문이 어떻게 도움이 될 수 있는가?
- 유전질환이 유전자치료로 치료가 가능한 것인가?
- Genomics학문이 다른 어떤 경우에 도움이 될 수 있는가?
- 10년후 genomics는 어떤 상태에 있을 것인가?



Rosetta stone