Genetics and Genomics for Cardiovascular Disease

"Genome-Wide Association Studies of Coronary Artery Disease in Chinese Han Population"

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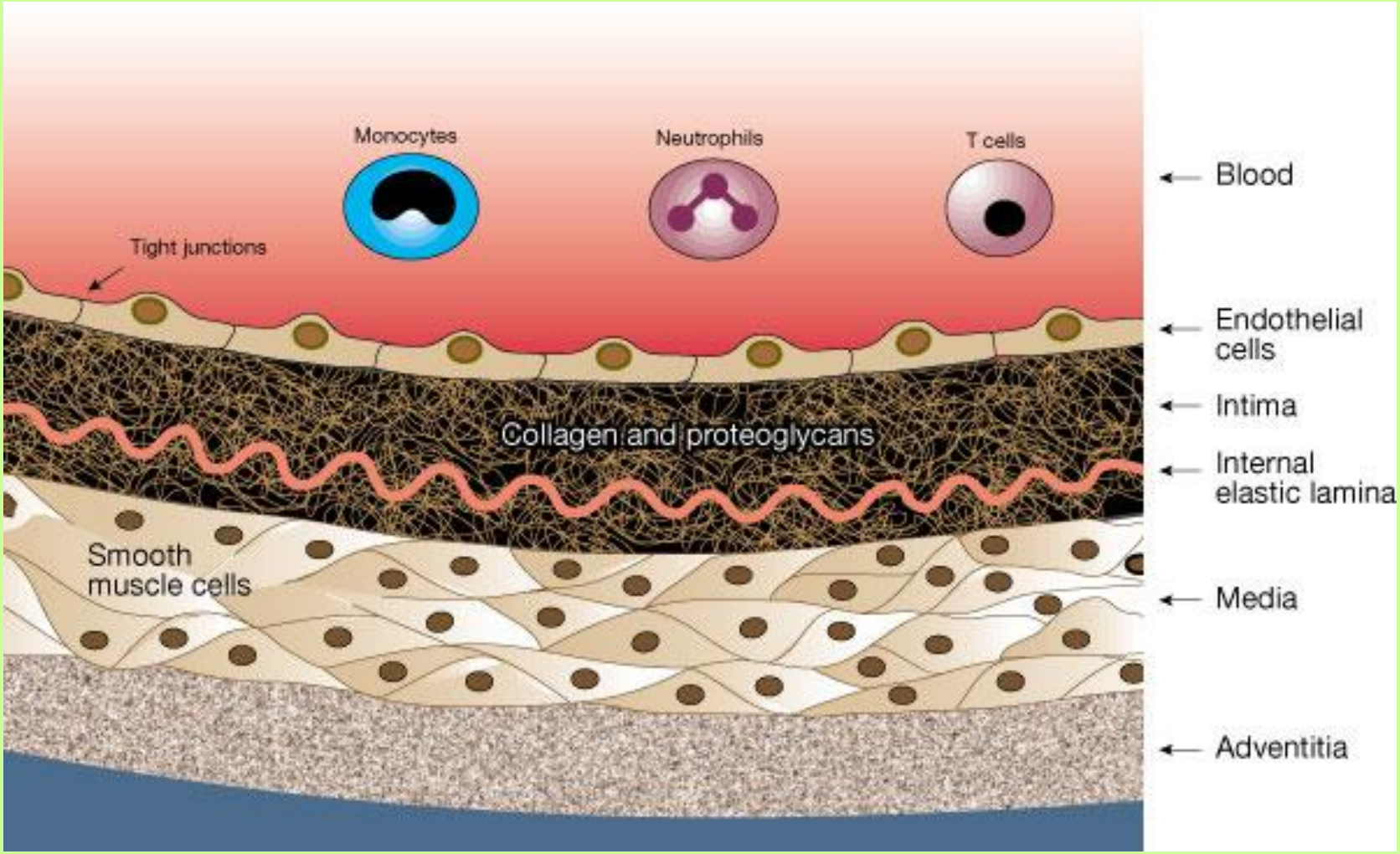
Coronary Artery Disease (CAD) and Myocardial Infarction (MI)

- **U.S. Statistics:**

- **CAD, 16.3 million**
- **MI, 7.9 million**
- **Causes 571 000 deaths each year in the U.S.**
- **Caused 1 of every 5 deaths in the U.S.**
- **Every 25 seconds an American will suffer a coronary event, and about every minute someone will die from one**
- **The estimated cost in 2007: $177.5 billion**

From AHA Heart Disease and Stroke Statistics-2011 Update (*Circulation.* 2011, 123:e18-e209)

Anatomy of Coronary Artery

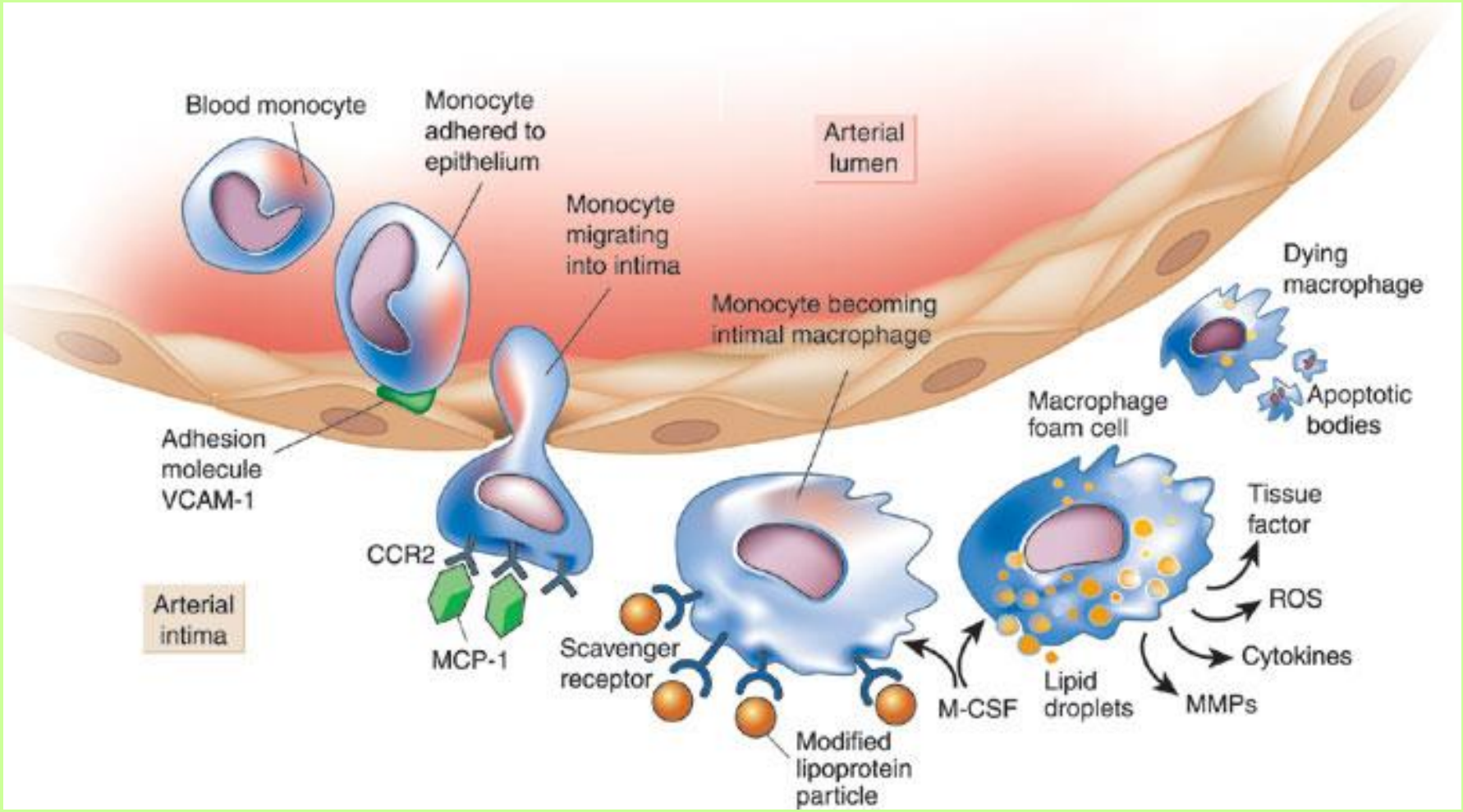


Nature (2000) 407:233

Atherosclerosis

Plaque Formation

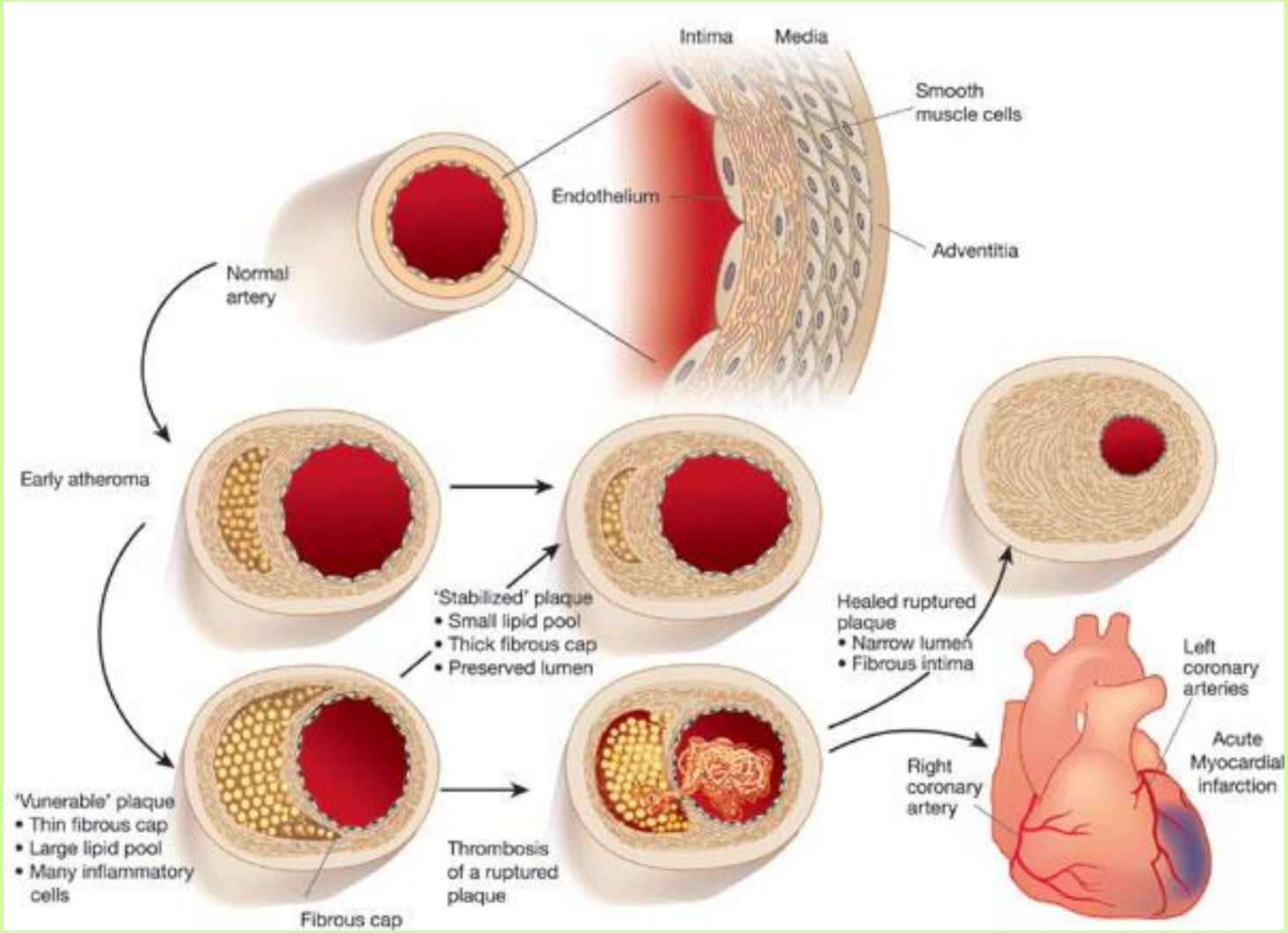
CAD



Nature (2002) 420;869

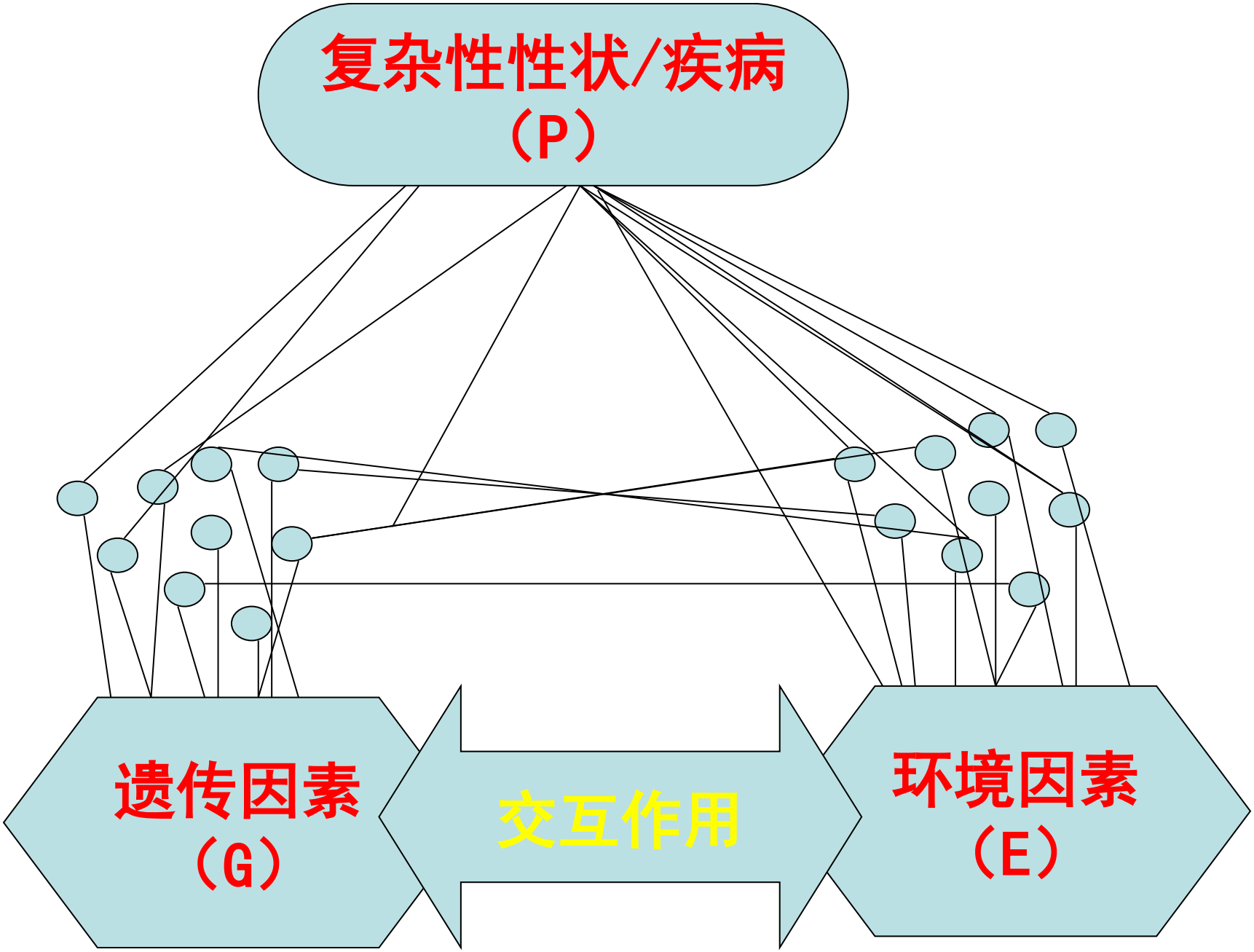
Atherosclerosis

Thrombosis and MI



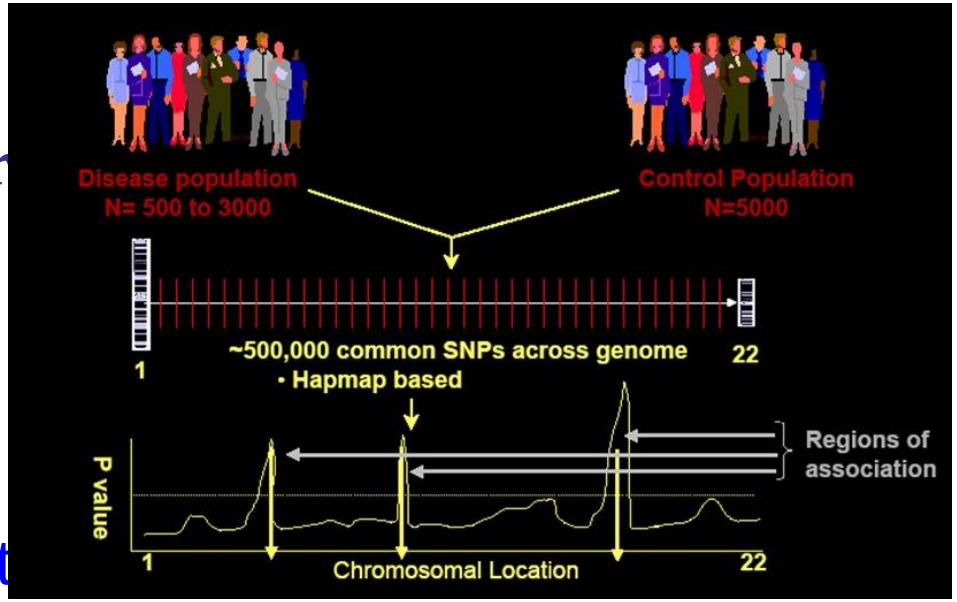
Nature (2002) 420;869

Genetic factors control each step in the development of atherosclerosis and thrombosis


复杂性性状/疾病
（P）
遗传因素
（G）
交互作用
环境因素
（E）

Genome-Wide Association Studies (GWAS)

- **A test for identification of susceptibility variants/loci for human diseases at the whole genome level**
- Through the detection of associations between genotype frequency and trait status



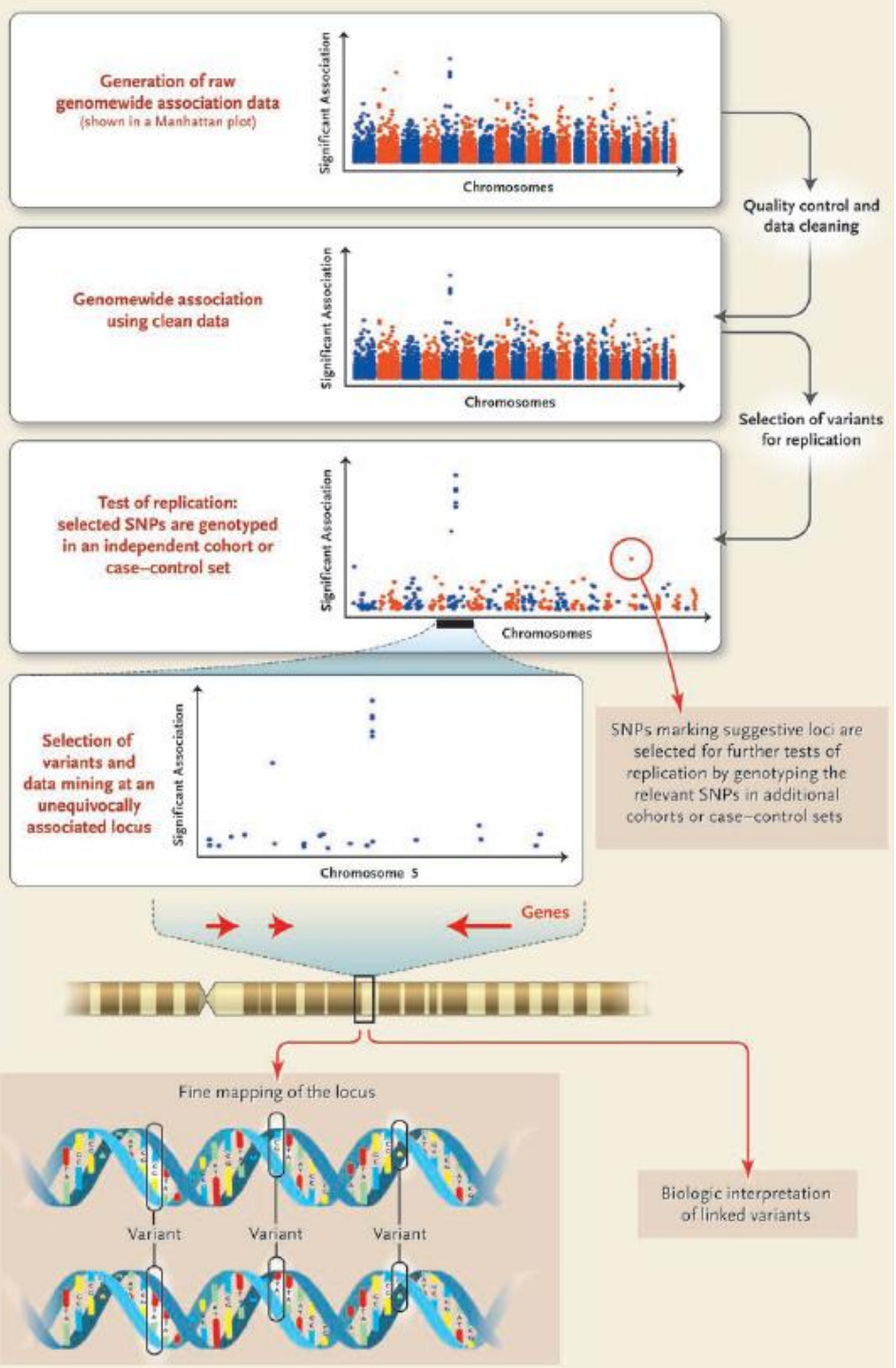
➢A test of the association between markers, called single-nucleotide polymorphisms (SNPs), across the genome and disease, usually involving 500,000 or more markers that are reasonably polymorphic and are spread across the genome fairly evenly

➢This approach is hypothesis free.

Genome-Wide Association Study（GWAS）

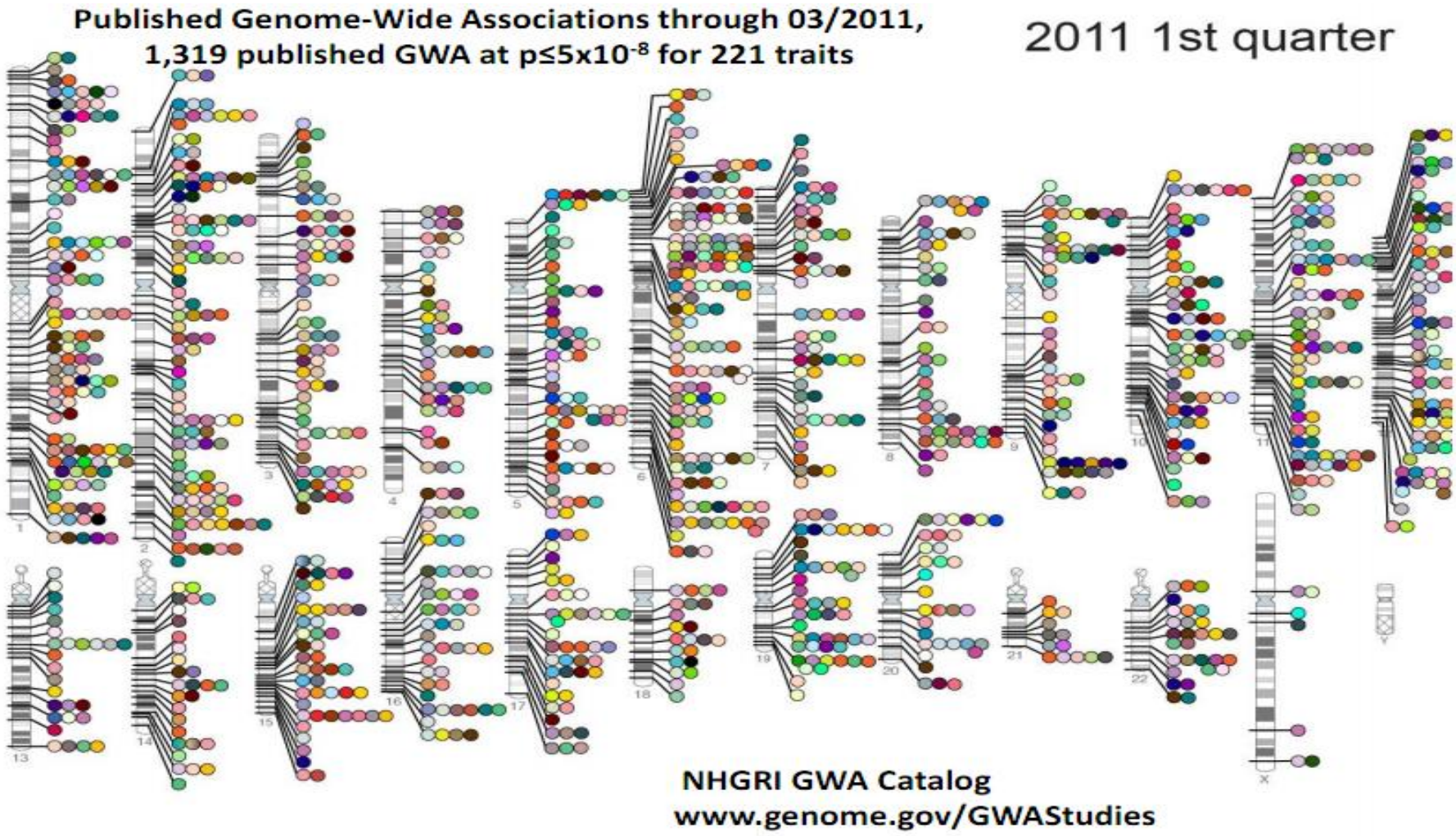
- **Most effective method at the present time**
- **Need high throughput genotyping platforms (e.g. Affymetrix or Illumina Chips)**

- **Need more than 2 large, independent case control populations**
- **Some risk variants may be used for personalized medicine in the future**



GWAS

- Accurate phenotyping
- Strict quality control
- Multi-stage replication
- Multiple genotyping methods
- Consideration of geographical areas, ethnicity, individual differences
- Effective statistical analysis
- Functional SNPs
- Functional studies



GWAS: A test of the association between markers, called single-nucleotide polymorphisms (SNPs), across the genome and disease, usually involving 500,000 or more markers that are reasonably polymorphic and are spread across the genome fairly evenly

Summary of GWAS for CAD/MI by 2010

NO.	Locus	SNP	Nearby Gene
1	***9p21***	***rs1333048***	***CDKN/B-ANRIL***
2	***1p13***	***rs646776***	***CELSR2-PSRC1-SORT1***
3	***21q22***	***rs9982601***	***SLC3-MRPS6-KCNE2***
4	***1q41***	***rs17465637***	***MIA3***
5	***10q11***	***rs1746048***	***CXCL12***
6	***6p24***	***rs12526453***	***PHACTR1***
7	***19p13***	***rs1122608***	***LDLR***
8	***2q33***	***rs6725887***	***WDR12***
9	***1p32***	***rs11206510***	***PCSK9***
10	***12q24***	***rs2259816***	***HNF***
11	***12q24***	***rs3184504***	***SH2B3***
12	***3q22***	***rs9818870***	***MRAS***
13	***6q26-27***	***rs3798220***	***LPA***
		rs10455872	***LPA***

1. Peden, J.F., et al., *A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease.* Nature Genetics, 2011.
2. Schunkert, H., et al., *Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease.* Nature Genetics, 2011.
3. Wang, F., et al., *Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population.* Nature Genetics, 2011.

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Sciencexpress Report

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,[1]* Gudmar Thorleifsson,[1]* Andrei Manolescu,[1]* Solveig Gretarsdottir,[1] Thorarinn Blondal,[1] Aslaug Jonasdottir,[1] Adalbjorg Jonasdottir,[1] Asgeir Sigurdsson,[1] Adam Baker,[1] Arnar Palsson,[1] Gisli Masson,[1] Daniel Gudbjartsson,[1] Kristinn P. Magnusson,[1] Karl Andersen,[2] Allan I. Levey,[3] Valgerdur M. Back
Steinunn
Christop
Gulcher,

[1]deCODE
Medicine,
University

*These au

†To whom

9p21.3

Sciencexpress Report

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPher
Hinds,[3] Len A
Cohen[2,8]†

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Science Cent
University of

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Vol 447|7 June 2007|doi:10.1038/nature05911 nature

ARTICLES

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The nature genetics

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Myocardial Infarction Genetics Consc

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 2, 2007 VOL. 357 NO. 5

Genomewide Association Analysis of Coronary Artery Disease

1st Replication of 9p21.3 CAD Locus in a Non-Caucasian Population (Korean Population)

Arteriosclerosis, Thrombosis, and Vascular Biology
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
Learn and Live℠

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

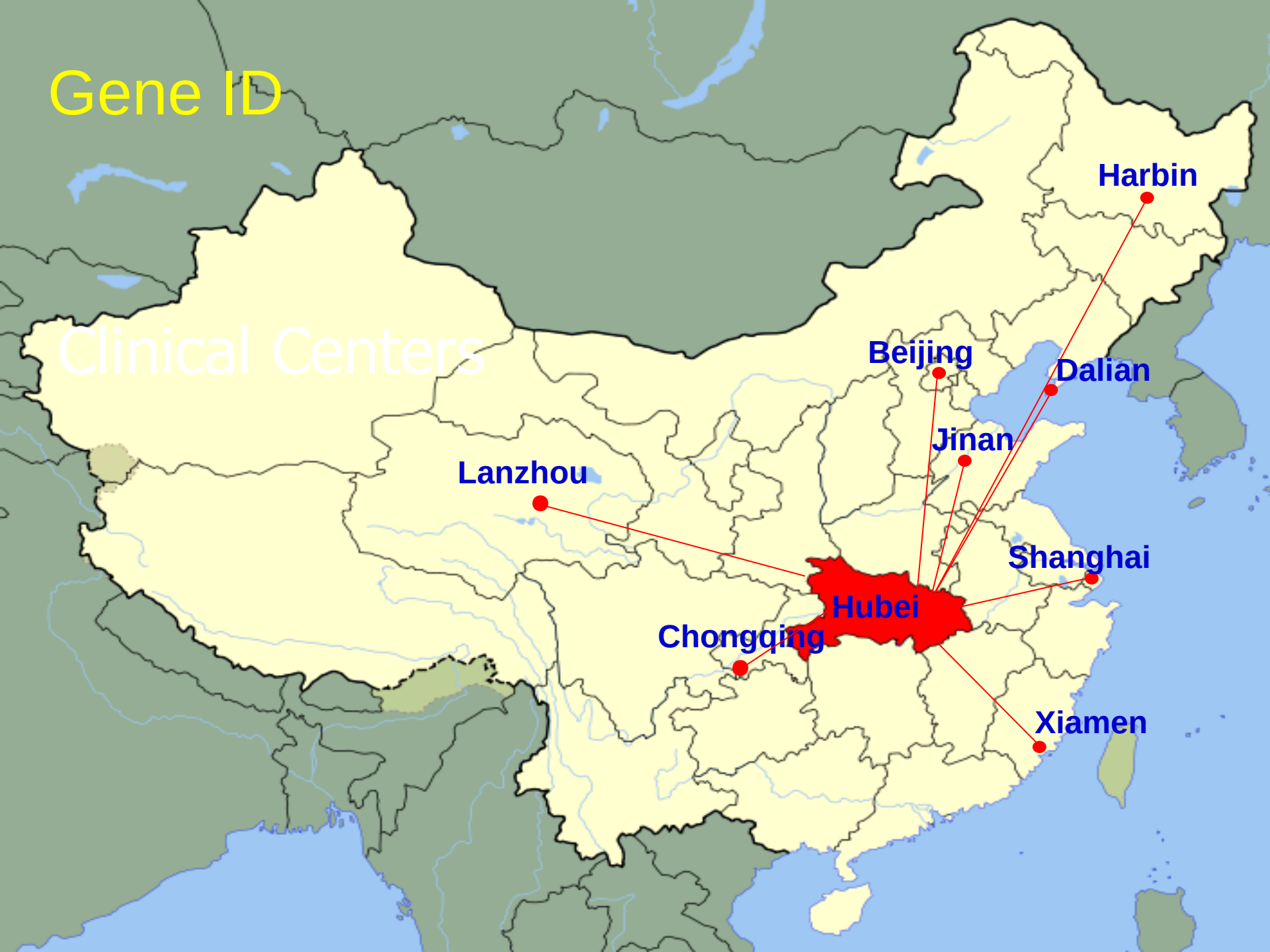
Gong-Qing Shen, Lin Li, Shaoqi Rao, Kalil G. Abdullah, Ji Min Ban, Bok-Soo Lee, Jeong Euy Park and Qing K. Wang

CAD/MI GWAS **in the Chinese Population?**

Gene ID

Bio-bank of Chinese

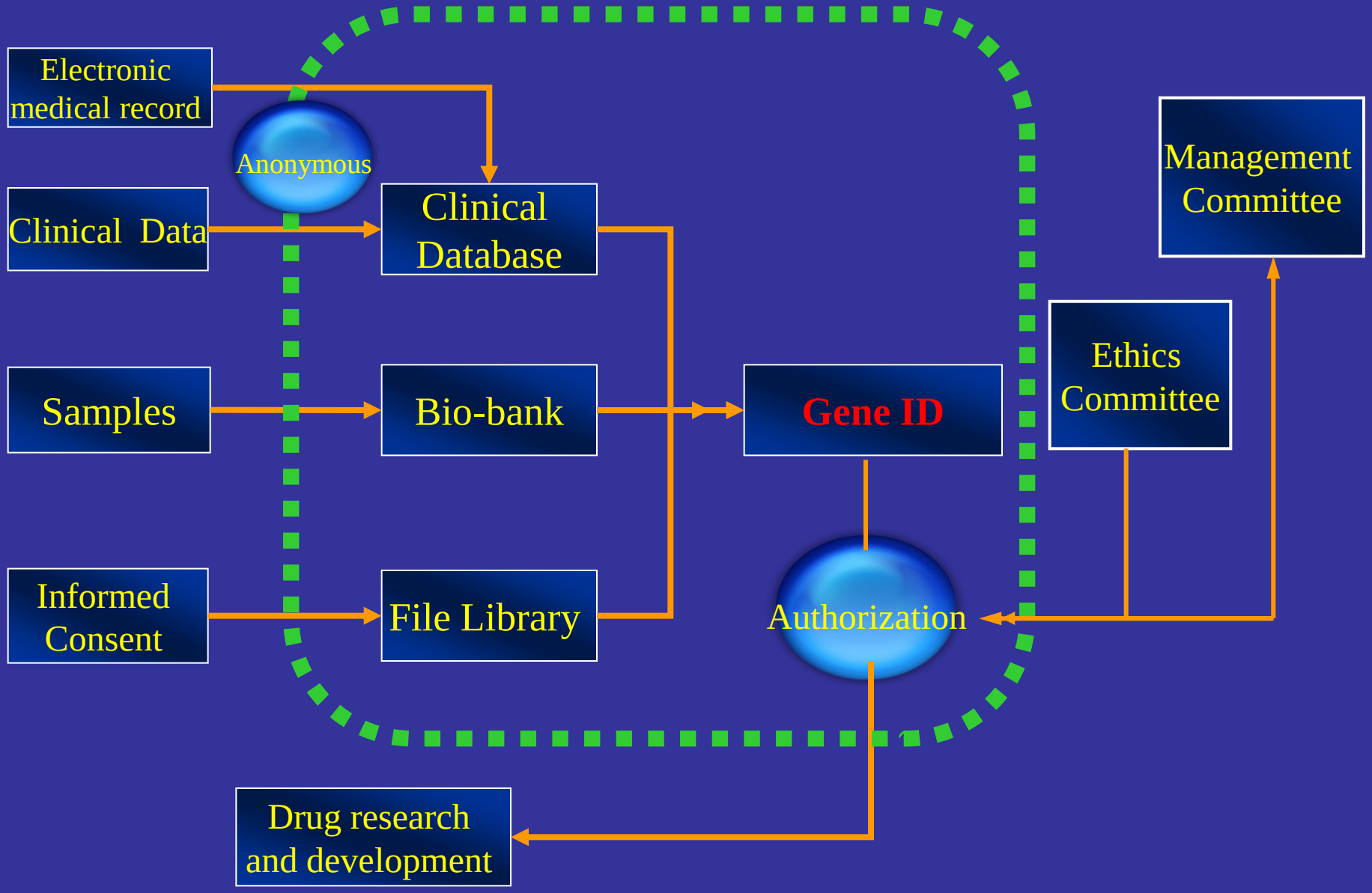
Cardiovascular Disease


Gene ID
Clinical Centers
Harbin
Beijing
Dalian
Jinan
Lanzhou
Shanghai
Hubei
Chongqing
Xiamen

Hubei Province

Tertiary referral centers

Union Hospital
Tongji Hospital
Renmin Hospital
Zhongnan Hospital
1st Hospital of Wuhan


Electronic medical record
Anonymous
Clinical Data
Clinical Database
Management Committee
Samples
Bio-bank
Gene ID
Ethics Committee
Informed Consent
File Library
Authorization
Drug research and development

Gene ID Database

- **Nearly 40,000 samples by August, 2011**

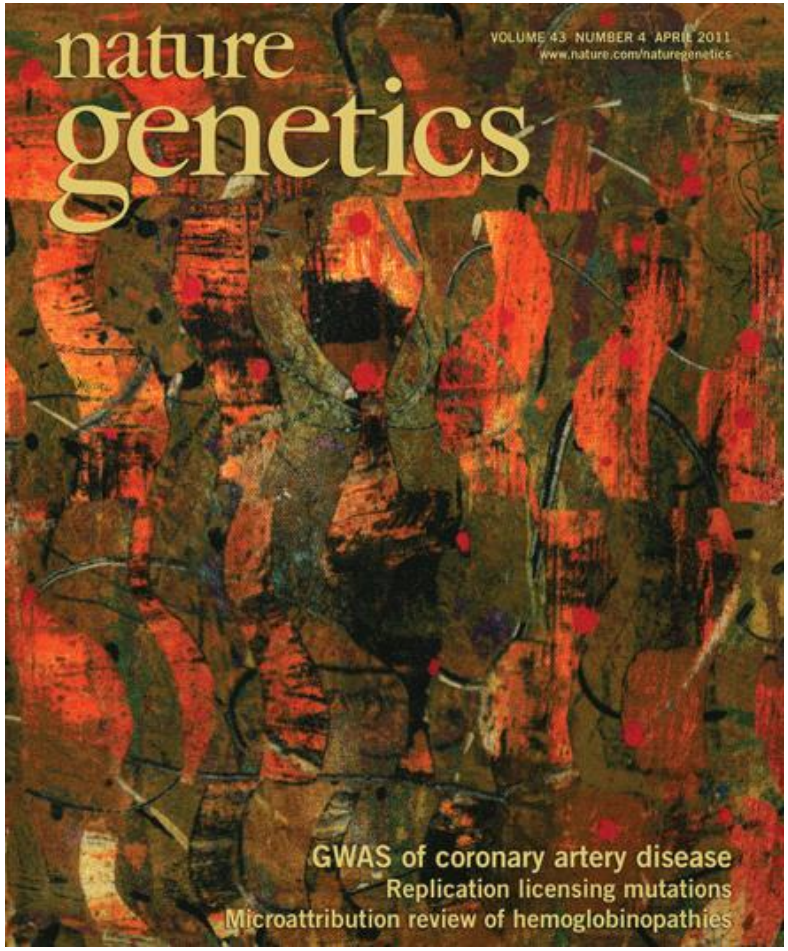
  - **>9,000 CAD**
  - **>1,450 AF （lone AF=230 cases)**
  - **>800 VT/VF**
  - **>2,000 stroke**
  - **>12,000 Others (heart failure, congenital heart disease, hypertension, etc)**
  - **>14,550 controls**

First genome-wide association in the Chinese Han population identifies a susceptibility locus for coronary artery disease

--Wang et al

By Huazhong University of Science and Technology and Other Chinese Collaborators

2011-4



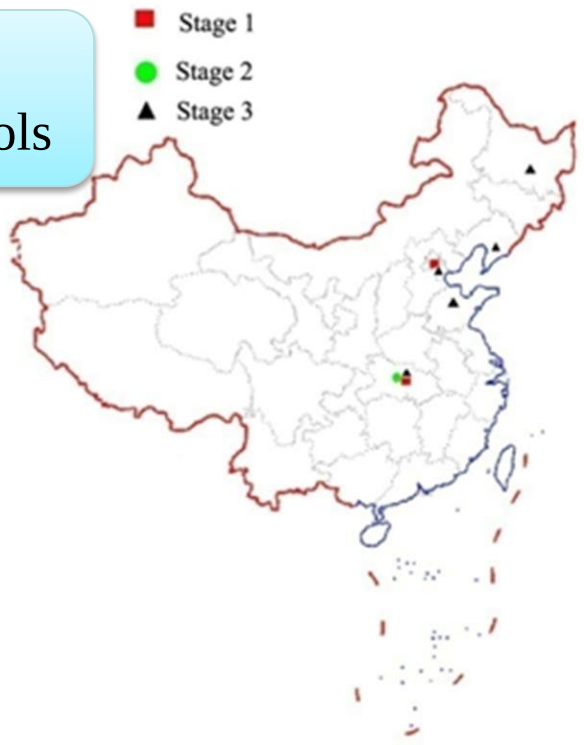
GWAS of CAD in the Chinese Population (Overall Study Design)

Stage 1 Dis-Hubei
100 cases vs. 100 controls

Stage 1 Dis-Beijing
130 cases vs. 130 controls

P<0.01 in both discovery cohort

Stage 2 validation cohort
572 cases vs. 436 controls

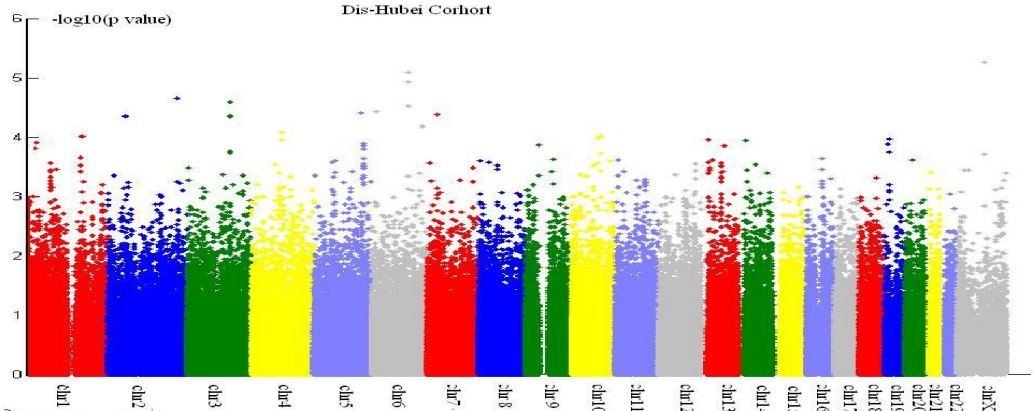


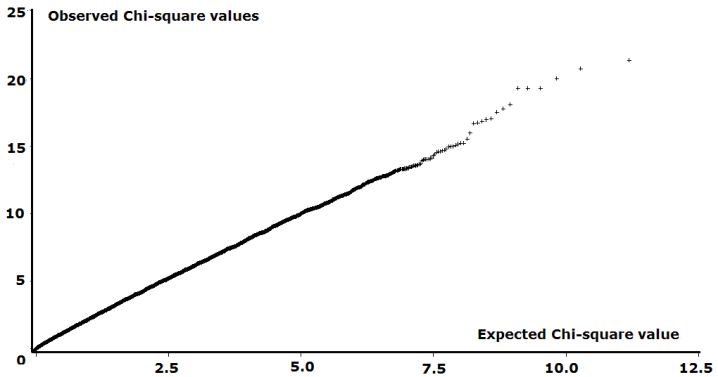
Stage 3 Rep-Shandong
811 cases vs. 818 controls

Stage 3 Rep-Hubei
1012 cases vs. 1732 controls

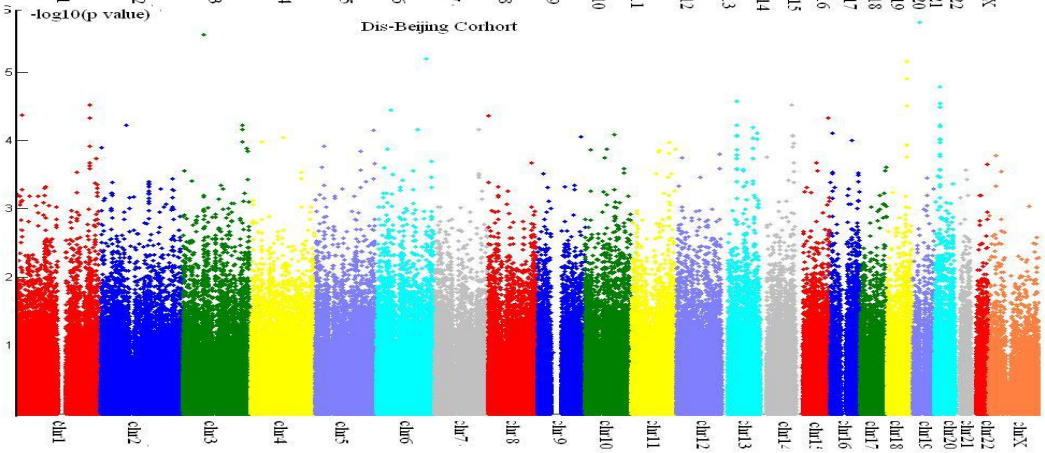
Stage 3 Rep-North
845 cases vs. 1367 controls

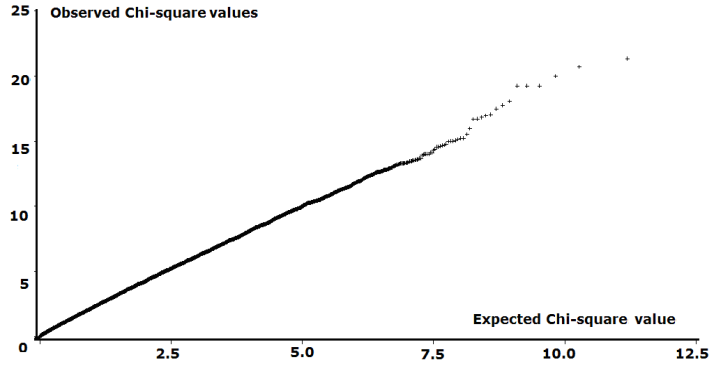
Stage I –Discovery GWAS QQ plot





Discovery Set Dis-Hubei, Genomic Control Inflation factor lambda=1.02





Discovery Set Dis-Beijing, Genomic Control Inflation factor lambda=1.04

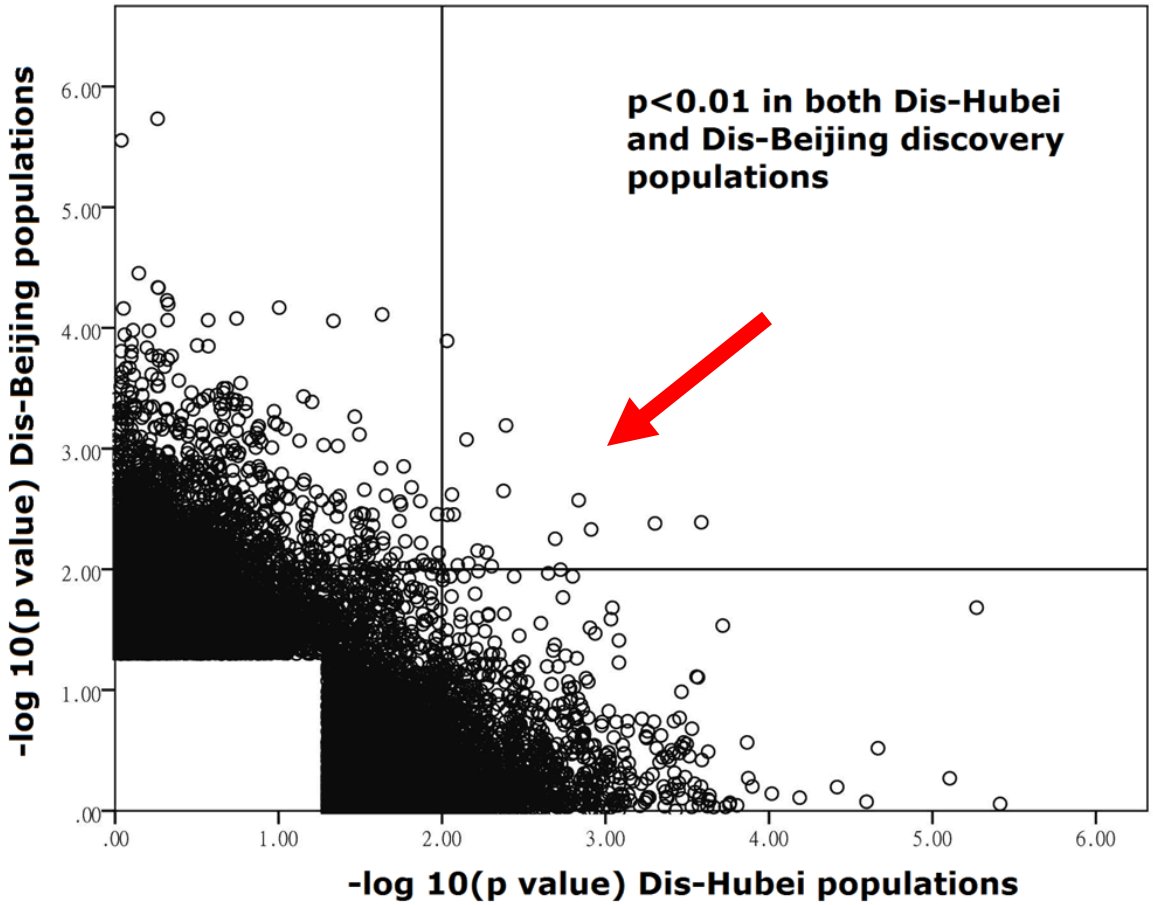
Wang, F., et al.,*Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population.* Nature genetics, 2011. **43**(4): p. 345-349.

9p21.3 CAD Locus in GeneID

Locus	dbSNP	RA	Cohort	Case /Control	*P* value	*OR(95%CI)*	Genes Near by
9 p21.3	rs1333048	G	Wuhan	0.57/0.41	0.001	1.93(1.29-2.89)	*MTAP, ANRIL*
			Beijing	0.54/0.41	0.005	1.65(1.16-2.33)	
	rs1333049	C	Wuhan	0.58/0.40	0.0006	2.00(1.34-2.99)	
			Beijing	0.54/0.43	0.008	1.60(1.13-2.26)	

Although the two discovery cohorts are small, two SNPs at the 9p21.3 CAD locus showed positive association with CAD, suggesting that the study design is appropriate.

Stage II- Validation of 9 SNPs



Wang, F., et al.,*Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population.* Nature Genetics, 2011. **43**(4): p. 345-349.

GWAS for CAD/MI in the Chinese Han Population

- **SNP rs6903956 on chromosome 6p24.1**

Stage	Population (*n*, case/control)	A allele frequency (case/control)	P_{HWE}	Without adjustment		After adjustment	
				P_{obs}	OR (95%CI)	P_{adj}	OR (95%CI)
Stage I	Dis-Hubei (100/100)	0.10/0.04	1.00	8.00×10^{-3}	3.07 (1.27–7.45)	0.04	2.89 (1.04–8.00)
	Dis-Beijing (130/130)	0.15/0.06	0.40	2.00×10^{-3}	2.59 (1.41–4.78)	0.02	2.16 (1.14–4.11)
Stage II	Validation population (572/436)	0.08/0.05	0.64	5.00×10^{-3}	1.71 (1.18–2.48)	0.02	1.69 (1.10–2.63)
Stage III	Rep-Shandong (811/818)	0.09/0.06	0.49	3.00×10^{-3}	1.47 (1.14–1.91)	0.01	1.41 (1.07–1.85)
	Rep-Hubei (1,012/1,732)	0.11/0.07	0.24	1.19×10^{-8}	1.74 (1.44–2.11)	9.00×10^{-9}	1.81 (1.47–2.21)
	Rep-North (845/1,367)	0.10/0.07	0.34	4.00×10^{-3}	1.36 (1.10–1.69)	1.00×10^{-3}	1.90 (1.32–2.73)
Combined	Combined all replication populations (3,240/4,353)	0.10/0.07	0.28	4.87×10^{-12}	1.51 (1.34–1.70)	2.55×10^{-13}	1.65 (1.44–1.90)

P_{HWE}, *P* value from Hardy-Weinberg equilibrium tests; P_{obs}, observed *P* value; P_{adj}, *P* value after adjustment for covariates; OR, odds ratio.

Wang, F., et al.,*Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population.* Nature genetics, 2011. **43**(4): p. 345-349.

GWAS for CAD/MI in the Chinese Han Population

- Association of rs6903956 with CAD

Population (*n*, cases/controls)	A allele frequency (case/control)	Without adjustment		After adjustment	
		P_{obs}	OR (95% CI)	P_{adj}	OR (95% CI)
CAD in male 2,095/2,766	0.10/0.07	9.84×10^{-7}	1.44 (1.24–1.67)	1.21×10^{-7}	1.58 (1.33–1.87)
CAD in female 1,145/1,587	0.10/0.07	7.46×10^{-7}	1.63 (1.34–1.98)	3.17×10^{-7}	1.82 (1.47–2.29)
CAD with MI 646/4,353	0.09/0.07	2.00×10^{-3}	1.40 (1.14–1.72)	1.00×10^{-3}	1.48 (1.18–1.87)
CAD without MI 2,594/4,353	0.10/0.07	7.31×10^{-12}	1.54 (1.36–1.74)	1.90×10^{-13}	1.71 (1.48–1.97)

P_{obs}, observed *P* value; P_{adj}, *P* value after adjustment for covariates; MI, myocardial infarction.

Wang, F., et al.,*Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population.* Nature genetics, 2011. **43**(4): p. 345-349.

GWAS for CAD/MI in the Chinese Han Population

- SNP rs6903956 risk allele A is associated with deceased expression of putative gene *C6orf105* mRNA

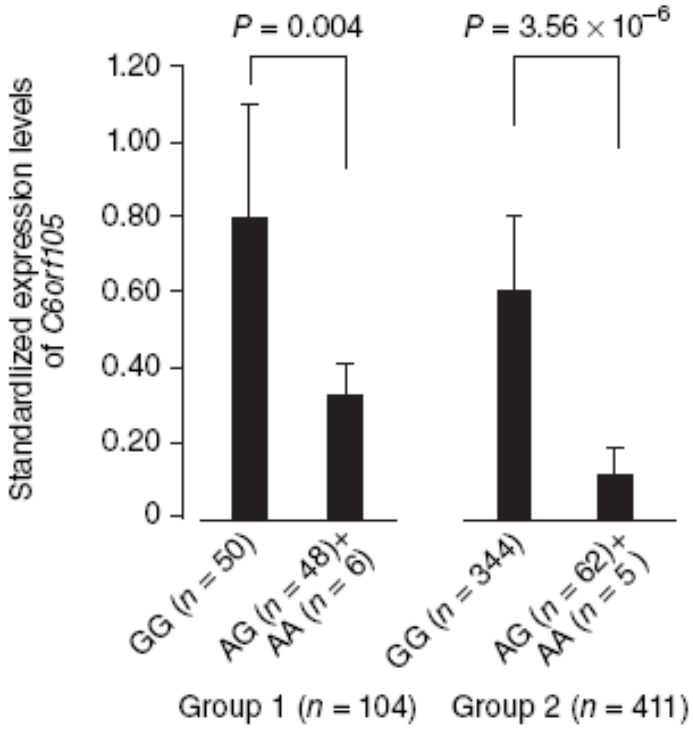


Figure 1 Association of the risk allele A of rs6903956 with decreased expression of *C6orf105* mRNA assuming a dominant model. Error bars, ± 2 s.e.

GWAS for CAD/MI in the Chinese Han Population

- SNP rs6903956 is located within an intron of putative gene *C6orf105*
- Risk allele A associated with decreased C6orf105 expresison
- *C6orf10*5
  - homologous to androgen-inducible protein 1 （AIG1）
  - Expressed in endothelial cells

A Potential Mechanism for CAD/MI by SNP rs6903956 in C6orf105

Androgen (雄性激素)

\+

C6orf105

\+

Tissue Factor Pathway Inhibitor (TFPI)

\-

TF-FXa

TF-FVIIa

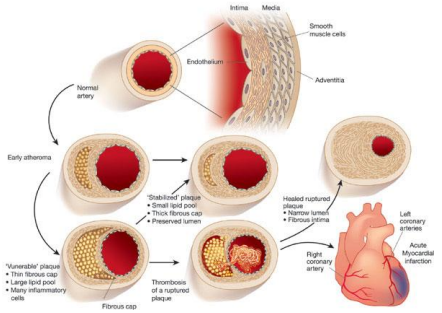
\+

Coagulation

\+

Thrombosis and MI

SNP Allele A



Lupu et al. *Blood*, 2011

Research Highlights

Subject Categories: Genetics Clinical medicine

Published online: 4 May 2011 | doi:10.1038/nchina.2011.35

Medical genetics: Follow your heart

Felix Cheung

A three-stage genome-wide association study in China has identified a novel genetic variant associated with coronary artery disease

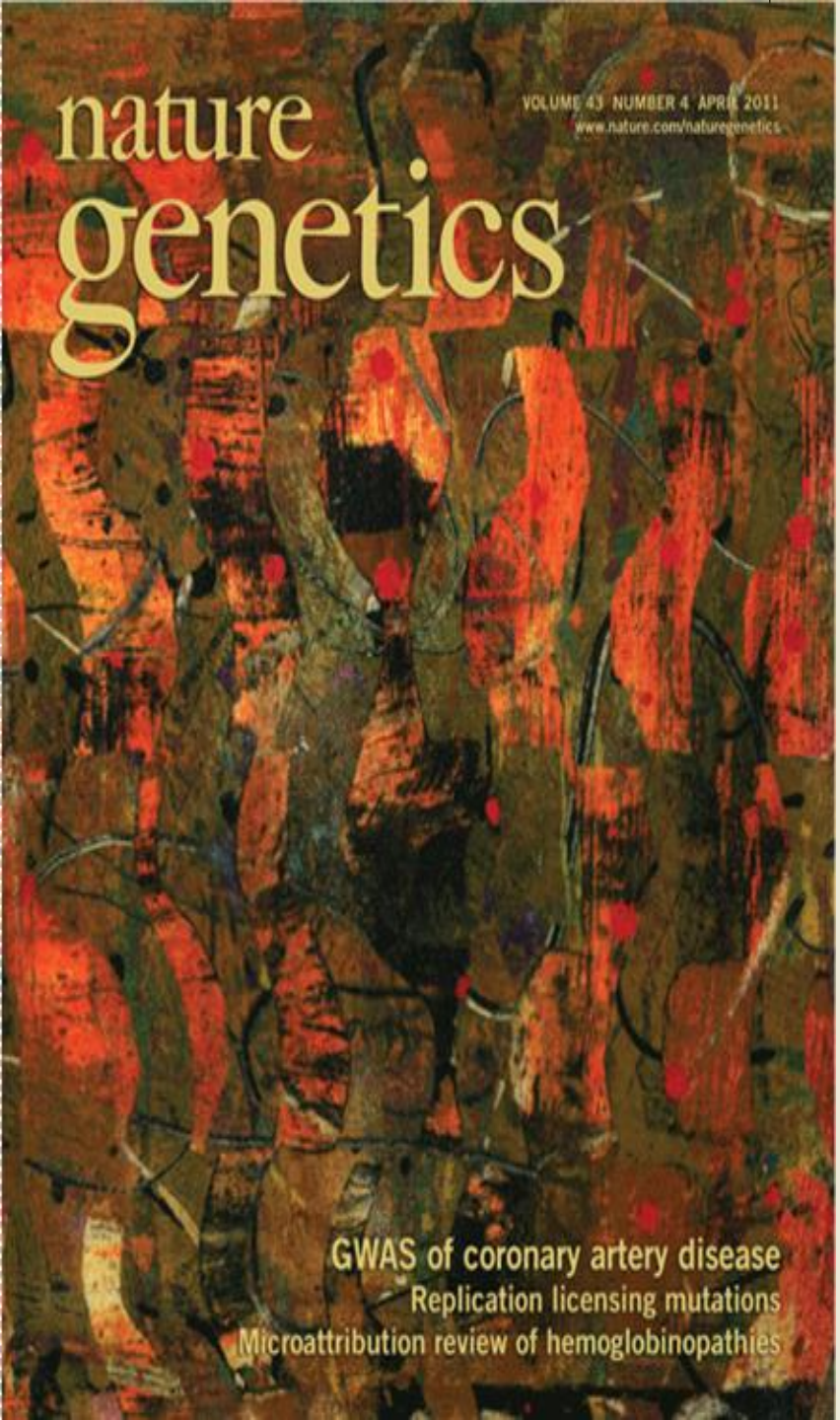
Original article citation
Wang, F. *et al.* Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population. *Nature Genet.* **43**, 345–351 (2011).

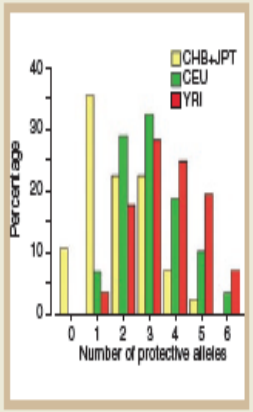
Full text article available for download

Coronary artery disease (CAD) is the leading cause of death in western countries. In China, CAD causes more than 700,000 people die every year.

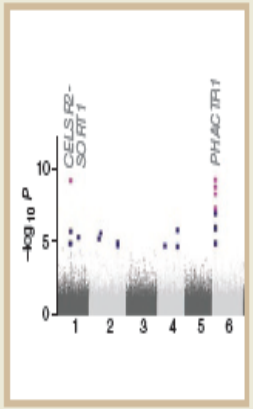
Previous genome-wide association studies on European populations have identified several genetic variants, or single-nucleotide polymorphisms (SNPs), associated with CAD. Kenneth Qing Wang and Xin Tu at Huazhong University of Science and Technology in Wuhan and co-workers[1] have now performed a genome-wide association study on a Chinese population and identified a new SNP associated with CAD.

The researchers carried out the study in three stages. In the 'discovery' stage, they analysed the genetic makeup of 460 people from Beijing and Hubei province and identified nine SNPs that appear frequently in CAD-affected individuals but not in healthy individuals. In the 'validation' stage, they repeated the same genetic analysis on 1,008 people from Hubei province by focusing on eight of the nine previously identified SNPs, and found that only one SNP — rs6903956 in the gene *C6orf105* — had a significant association with CAD.





Loci associated with susceptibility to IgA nephropathy (p 321)



GWAS of coronary artery disease in European and Asian populations (pp 333, 339, 345)

Summary: GWAS for CAD/MI

- CARDIoGram Consortium performed a meta-analysis of 14 independent CAD GWAS data and identified 13 new risk variants/loci for CAD in the European ancestry populations

- The Coronary Artery Disease (C4D) Genetics Consortium analyzed 8,424 European patients and 6,996 South Asian patients and found 5 new variants/loci for CAD

Summary: GWAS for CAD/MI

- To date, there are more than 10 CAD/MI GWAS, which identified about 30 risk variants/loci for CAD and MI

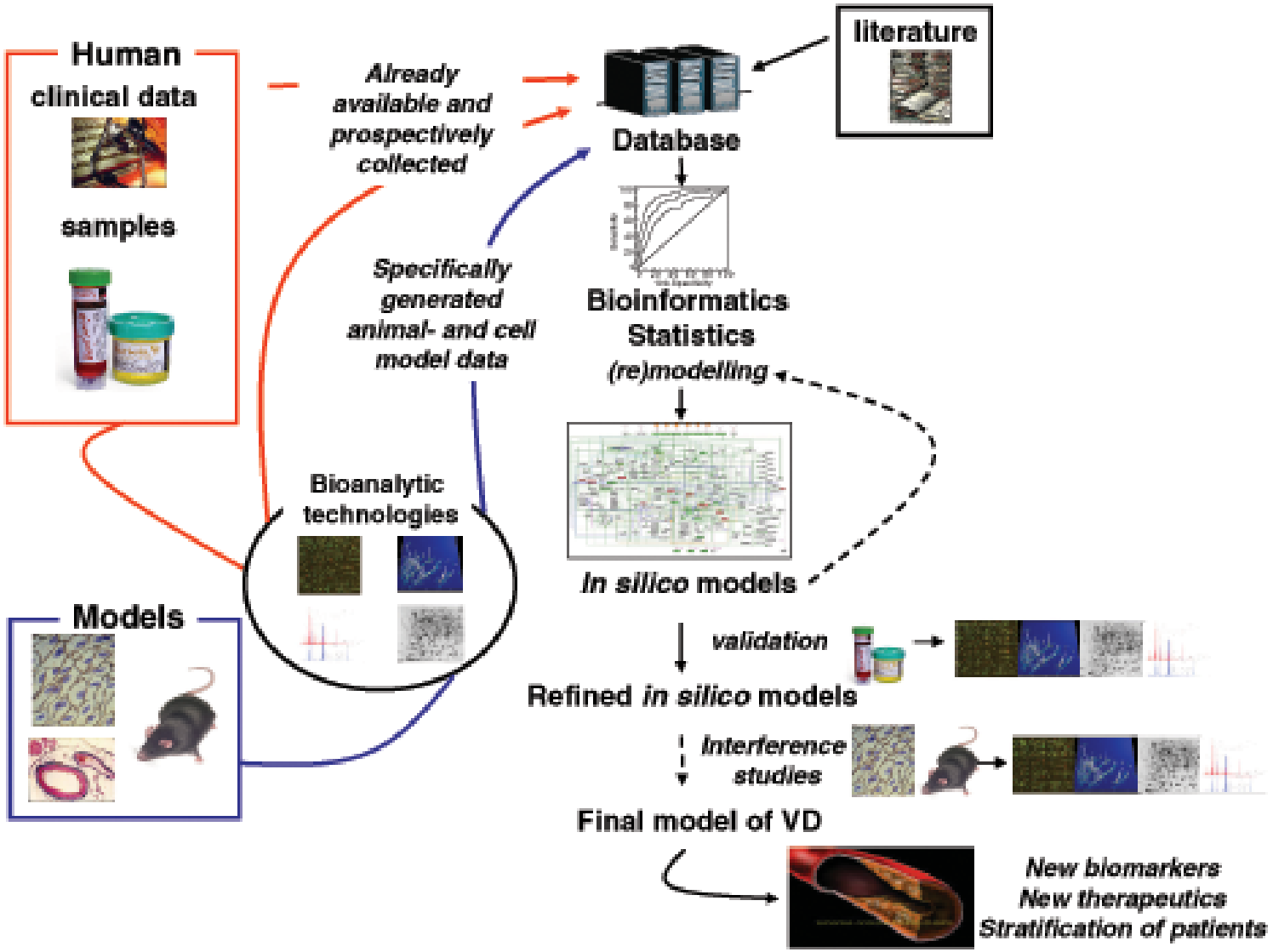
- Provide novel biological insights into the pathogenic mechanisms of atherosclerosis

- The 30 loci/variants discovered by GWAS are thought to explain about 8%-13% of the genetic risk
  - (Peden JF and Farrall M Hum Mol Genet 2011; 20:R198-R205)

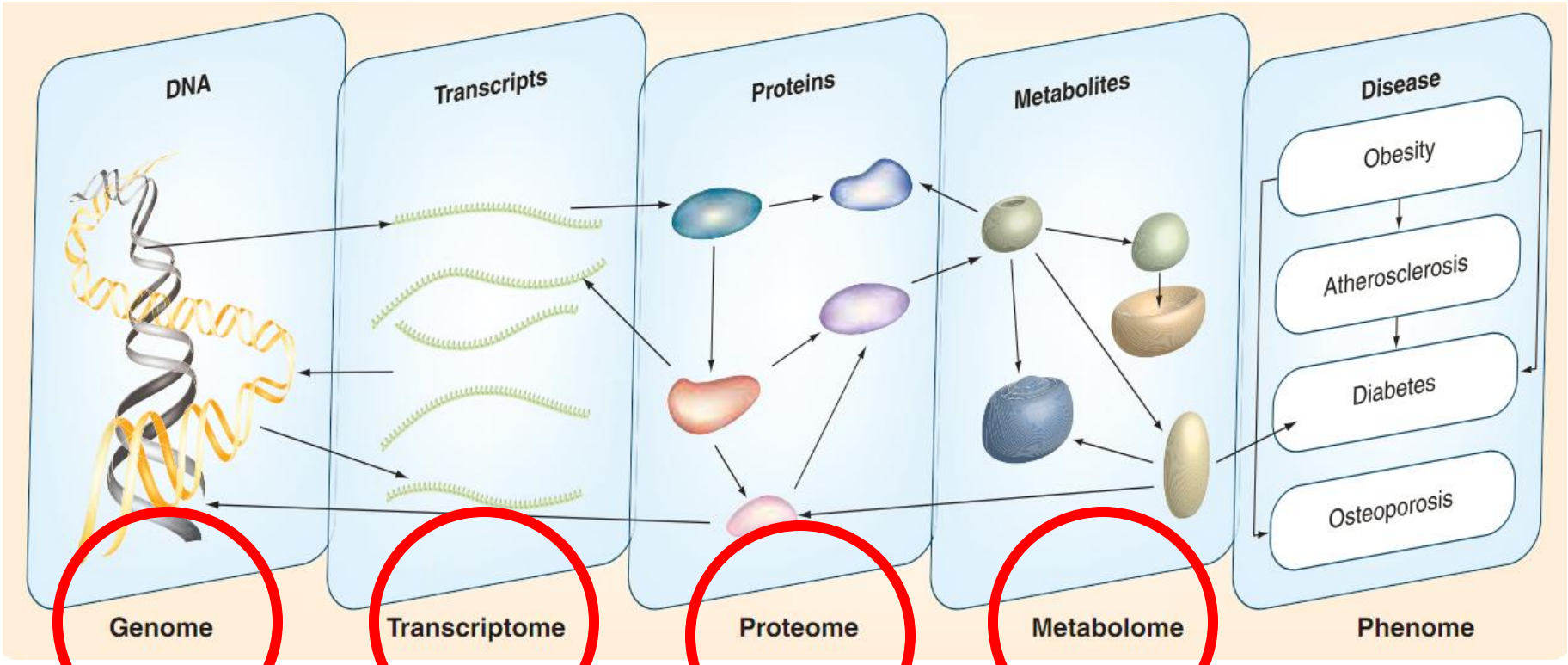
Future

- (1) Identification of new genomic variants for CAD and MI by further GWAS and next generation whole genome sequencing
  - "Rare variants, common disease" theory
    - Whole genome sequencing, whole exome sequencing
    - Life after linkage: the future of family studies
  - GWAS in non-Caucasian populations
  - GWAS in populations with diverse geographical ancestries
- (2) Identifying the specific genes at each GWAS locus
- (3) Identifying genetics, cellular and molecular mechanisms at each GWAS locus
- (4) Developing methods for CAD risk prediction and personalized risk assessment based on GWAS data
- (5) Translating basic discoveries into novel therapeutic and preventive strategies

Systems Biology in Coronary Artery Disease



Systems Biology of CAD and MI



Beside those methods, a system approach is needed to comprehend the existing findings, to discover new genes for and to finally illustrate the molecular mechanism of CVD

Expert Rev. Cardiovasc. Ther. 2007 5(6):1095-1103

These studies highlight a dilemma often faced by those attempting to apply genomics to medical practice

A First Step in a Long Journey!

Future: Systems Biology


谢谢!