

Genetics and Genomics for Cardiovascular Disease

**“Genome-Wide Association Studies of Coronary
Artery Disease in Chinese Han Population”**

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Professor of Molecular Medicine and Genetics
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Dean and Professor (Adjunct)

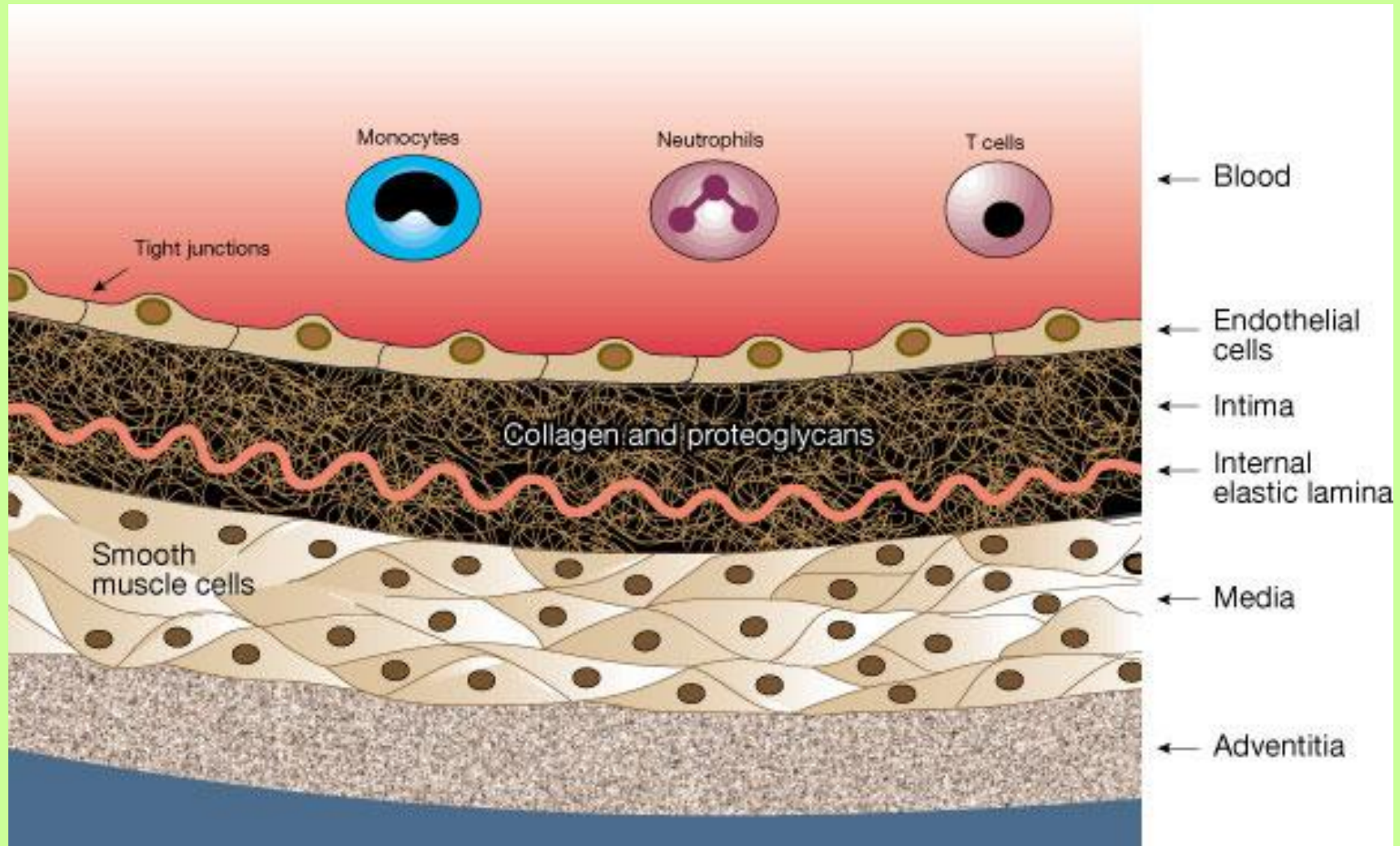
**College of Life Science and Technology
Cardio-X Innovation Team, the Ministry of Education
Huazhong University of Science and Technology
Wuhan, China**

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

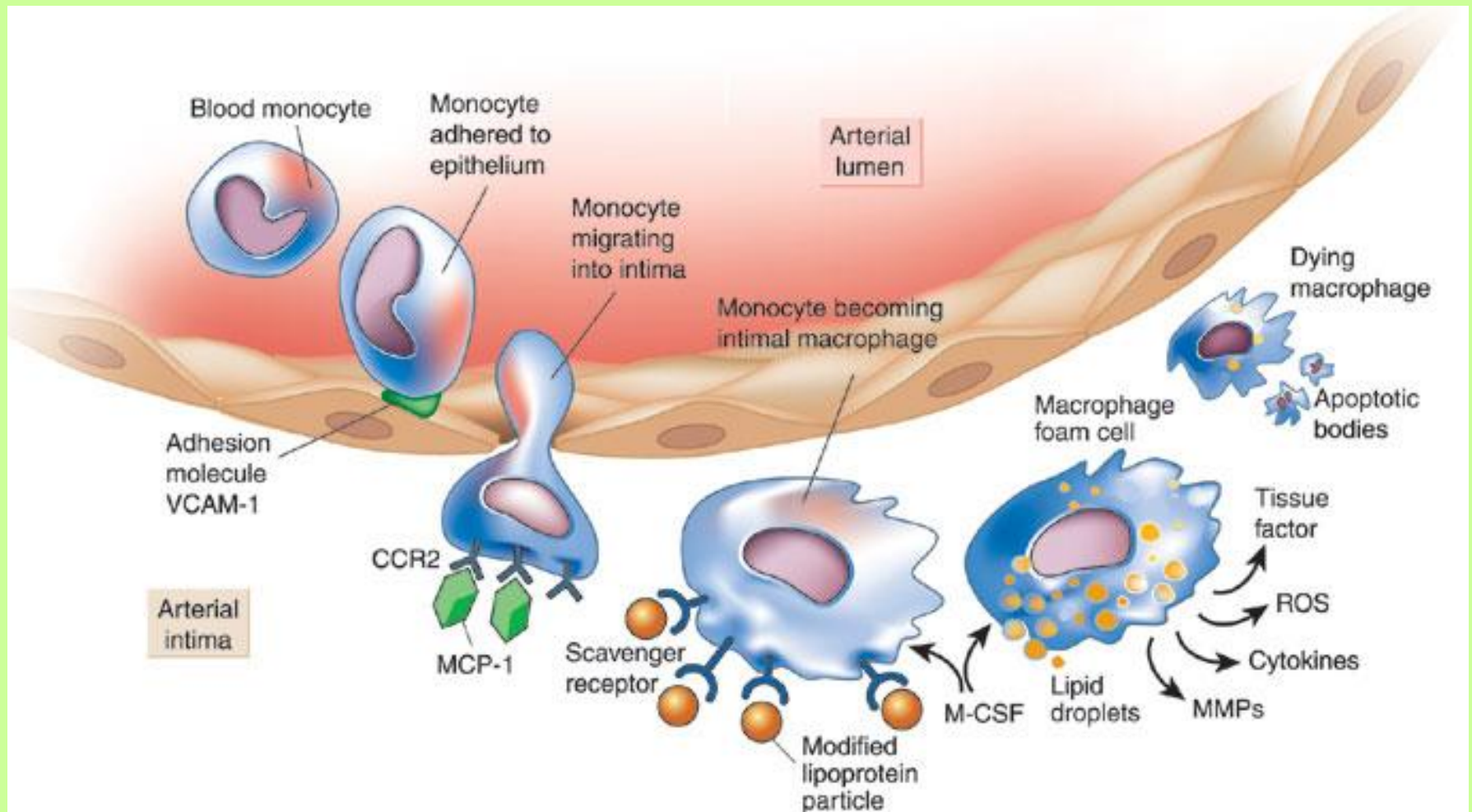
Anatomy of Coronary Artery

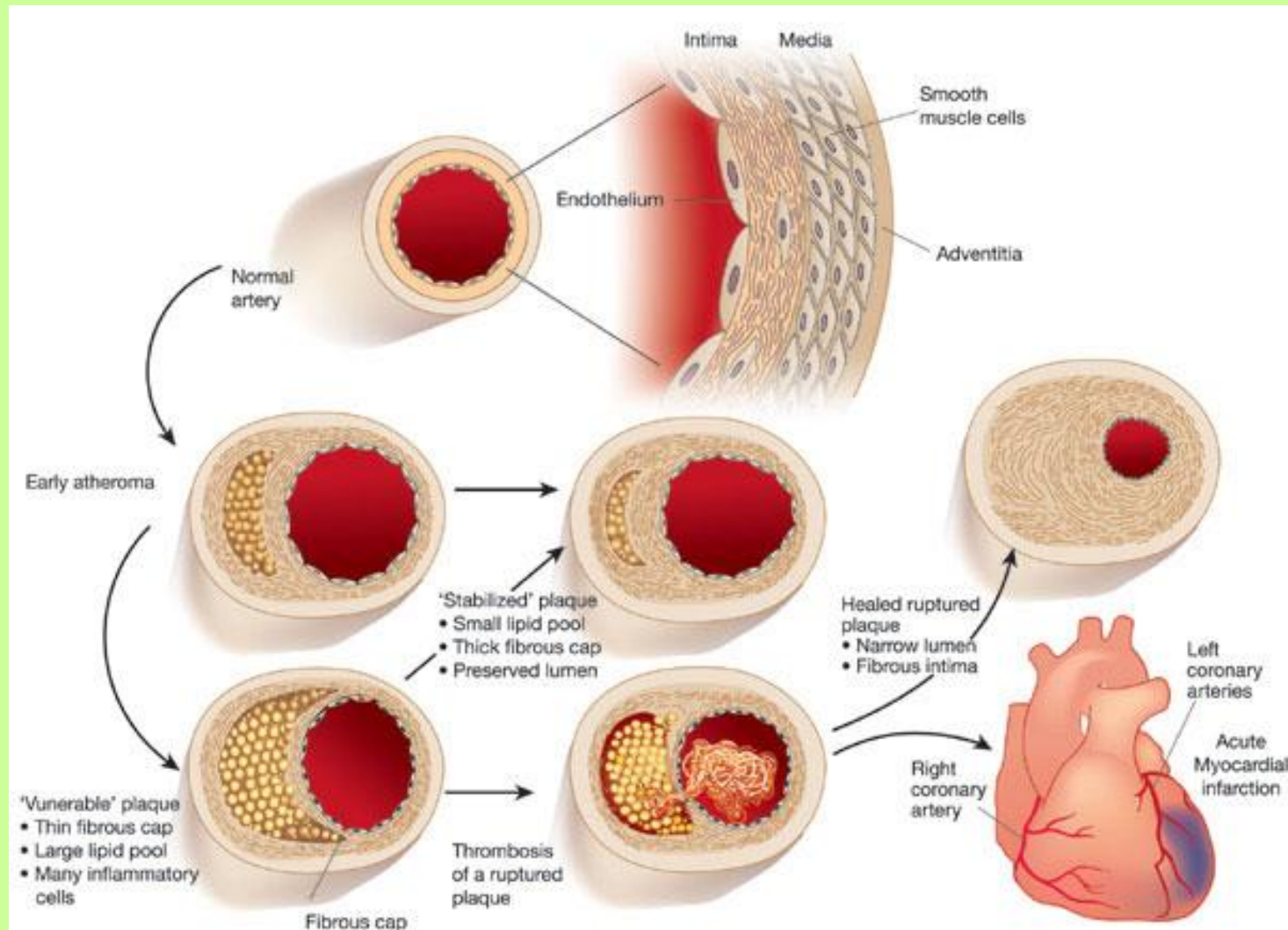


Atherosclerosis

CAD

Plaque Formation

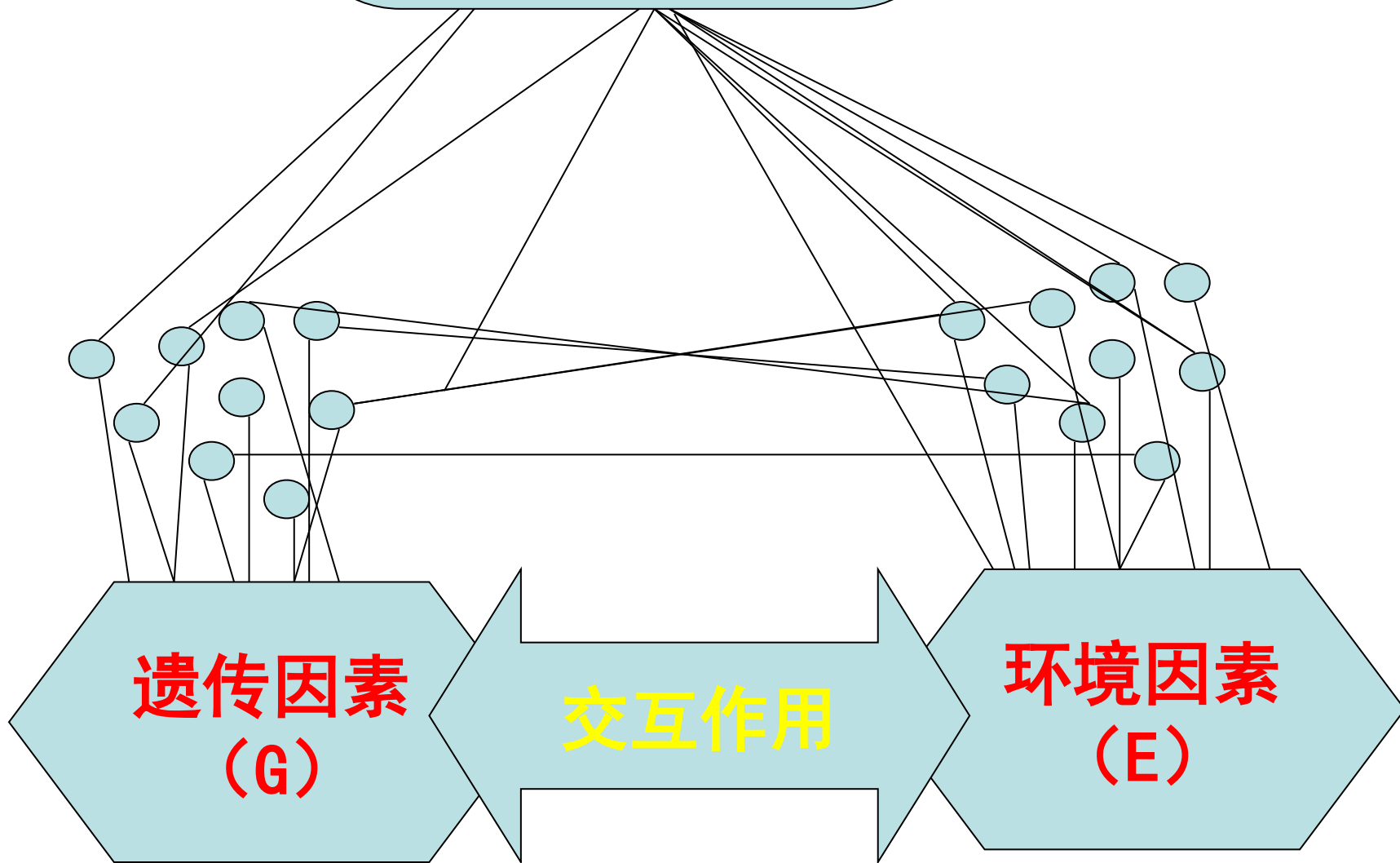




Nature (2002) 420;869

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

复杂性性状/疾病
(P)



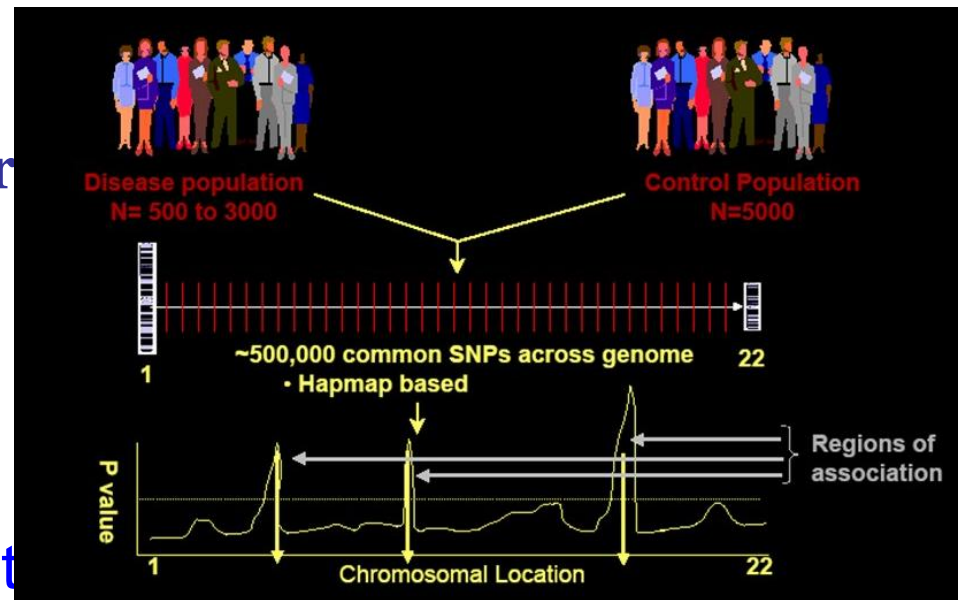
遗传因素
(G)

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

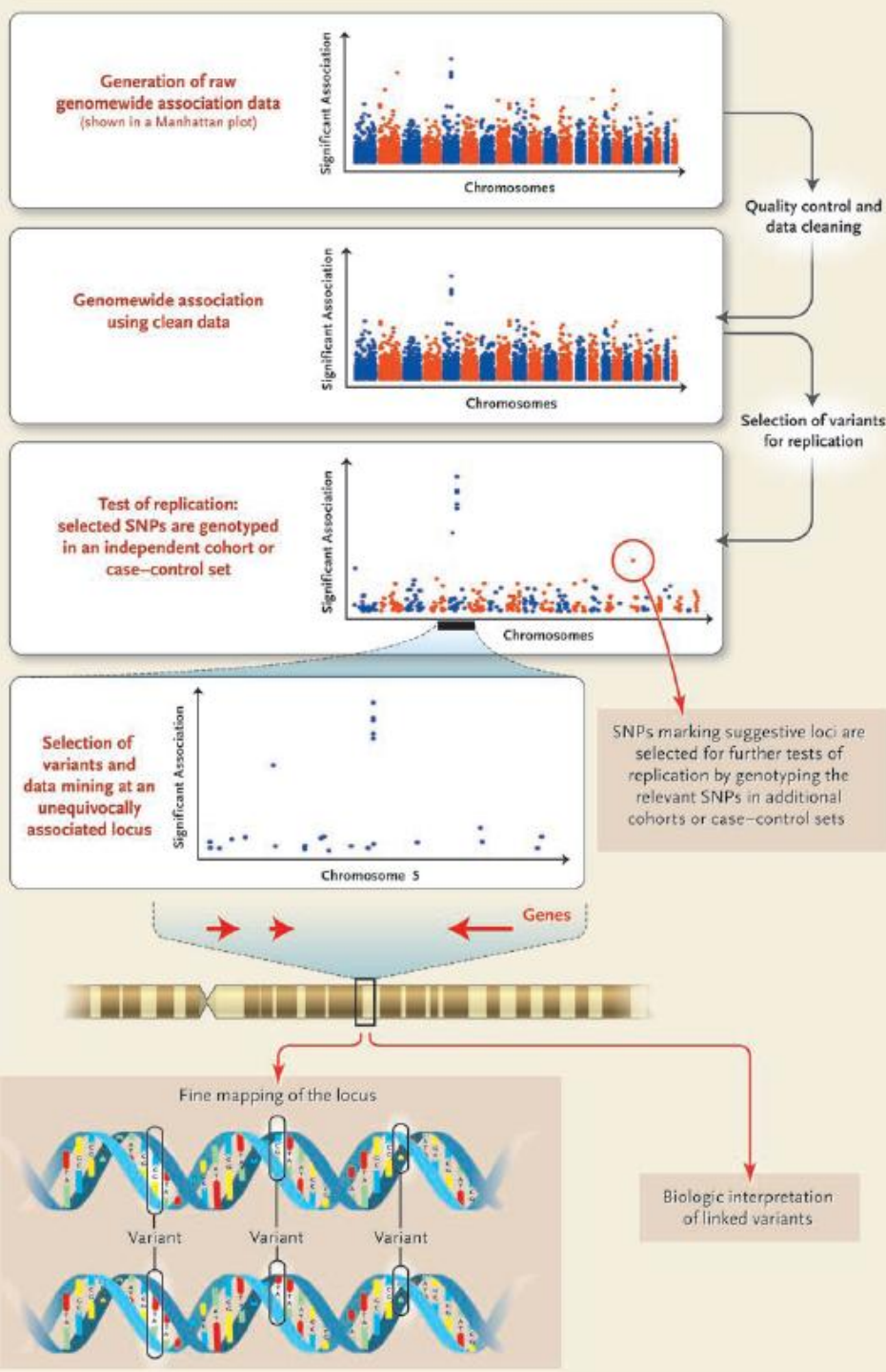


- A test of the association between markers, called single-nucleotide polymorphisms (SNPs), across the genome and disease, usually involving 500,000 or more markers that are reasonably polymorphic and are spread across the genome fairly evenly
- This approach is hypothesis free.

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**

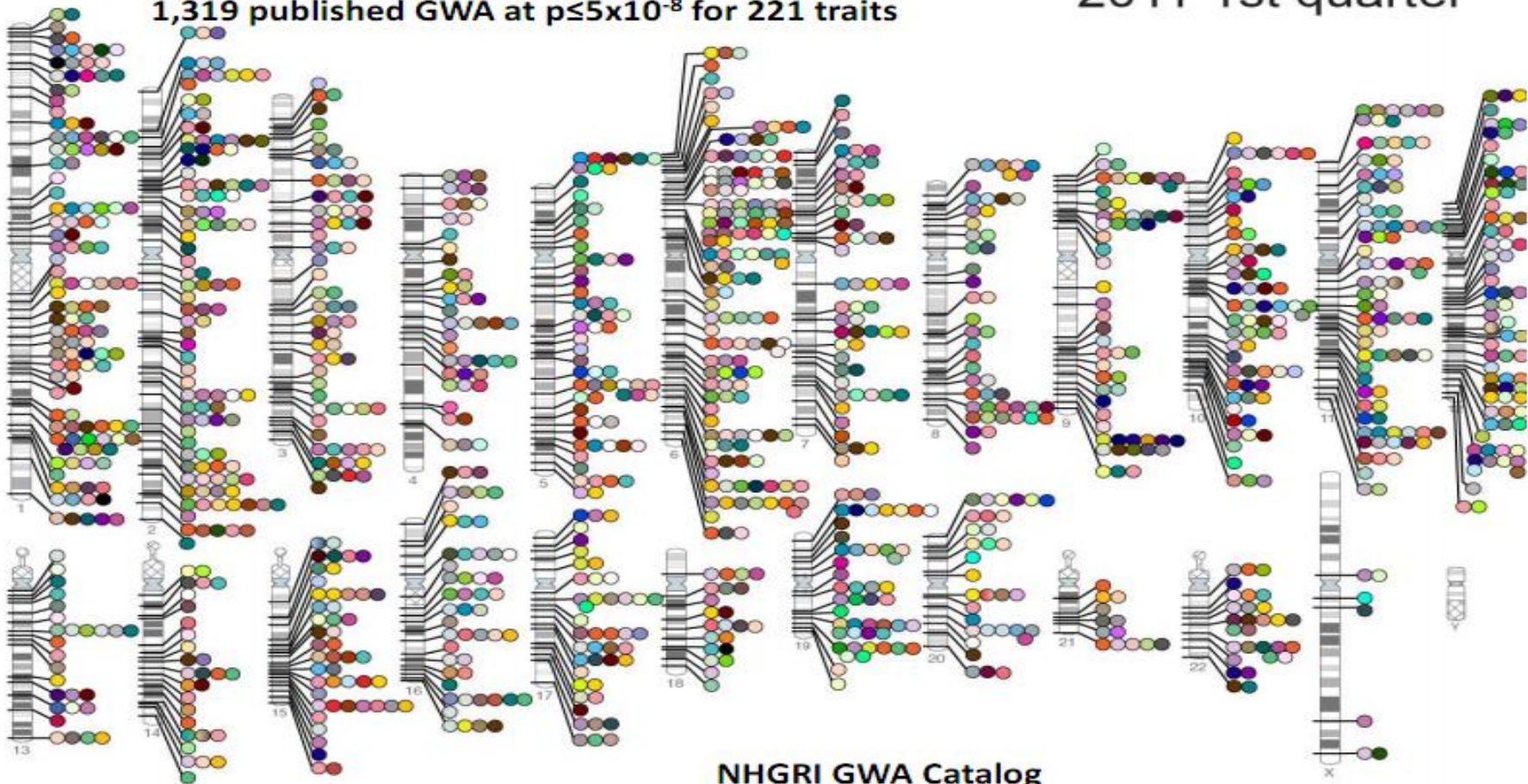
GWAS



- ❑ 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

Published Genome-Wide Associations through 03/2011,
1,319 published GWA at $p \leq 5 \times 10^{-8}$ for 221 traits

2011 1st quarter



NHGRI GWA Catalog
www.genome.gov/GWASudies

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

Anna Helgadóttir,^{1*} Gudmar Thorleifsson,^{1*} Andrei Manolescu,^{1*} Solveig Gretarsdóttir,¹ Thorarinn Blondal,¹ Aslaug Jonasdóttir,¹ Adalbjorg Jonasdóttir,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. Levev,³ Valgerdur

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Science Cente
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†To whom co

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

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 Cons

9p21.3

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®



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**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?

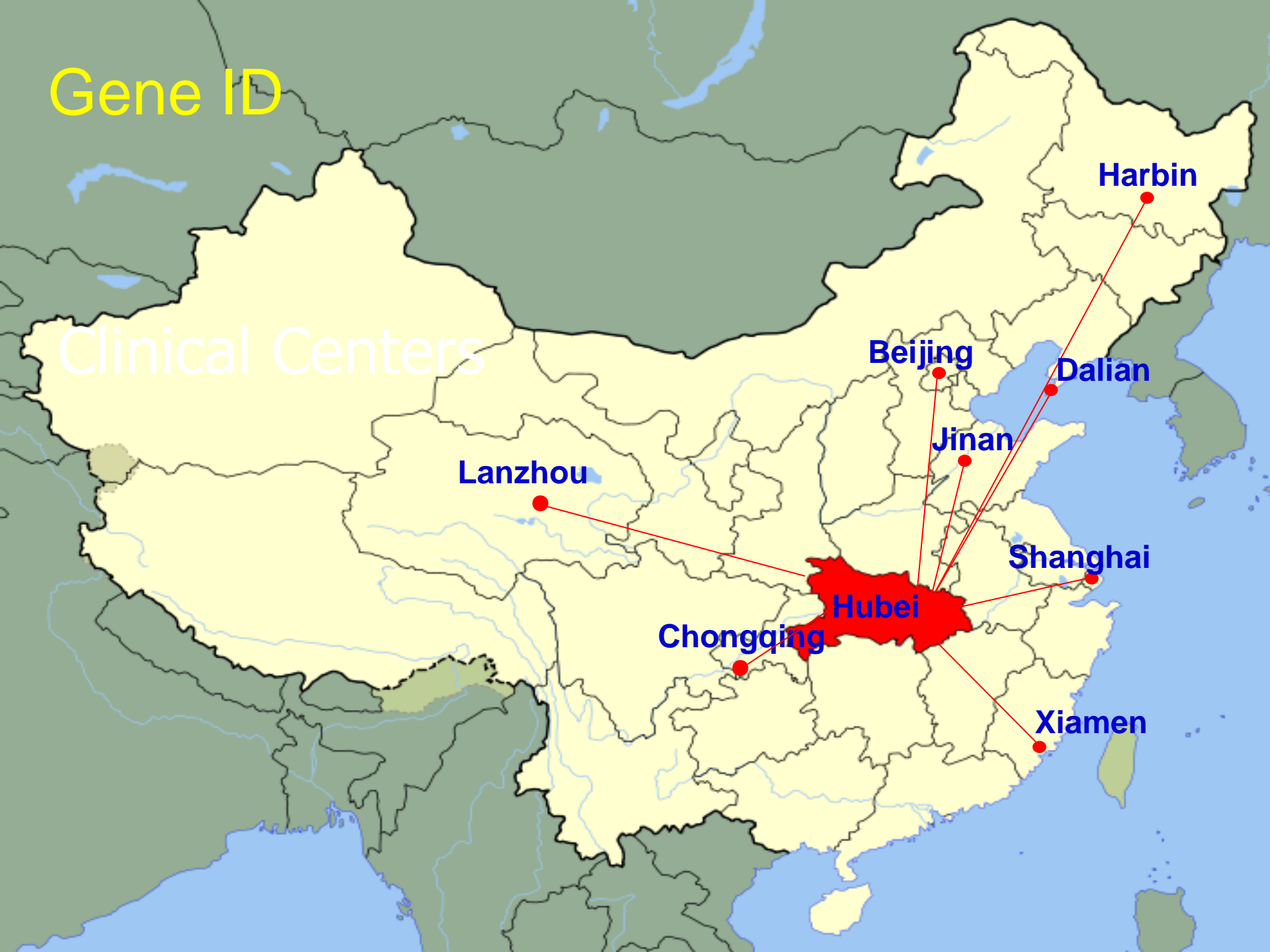
Gene ID

Bio-bank of Chinese

Cardiovascular Disease

Gene ID

Clinical Centers



Hubei Province



Tertiary referral centers

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

Gene ID Database

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

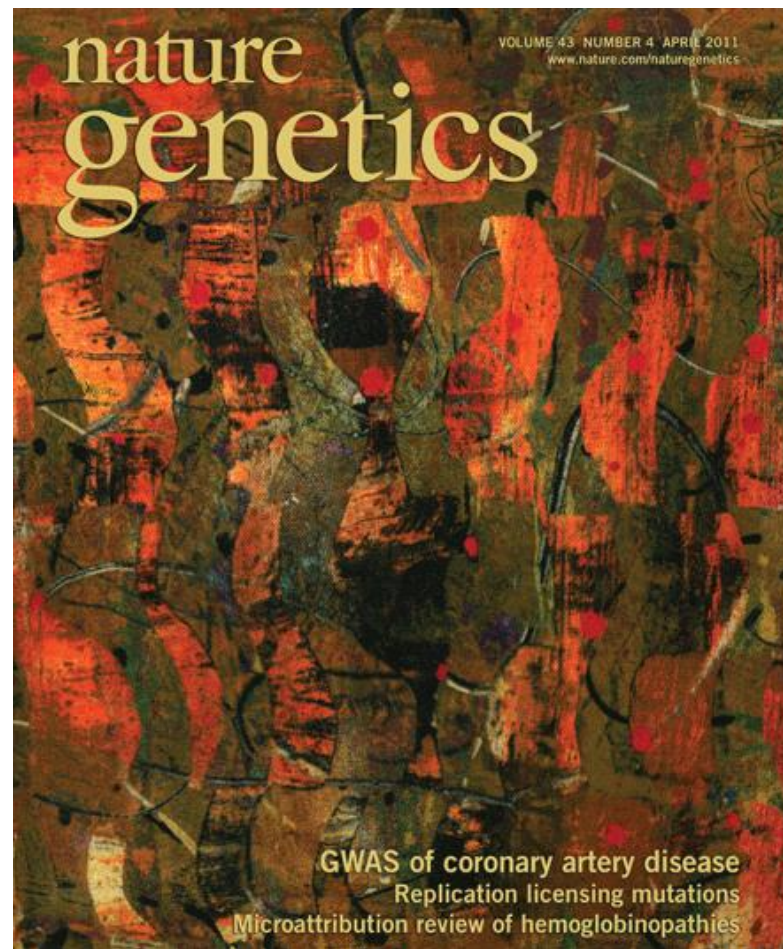
- **>9,000 CAD**
- **>1,450 AF (lone AF=230 cases)**
- **>800 VT/VF**
- **>2,000 stroke**
- **>12,000 Others (heart failure, congenital heart disease, hypertension, etc)**
- **>14,550 controls**

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

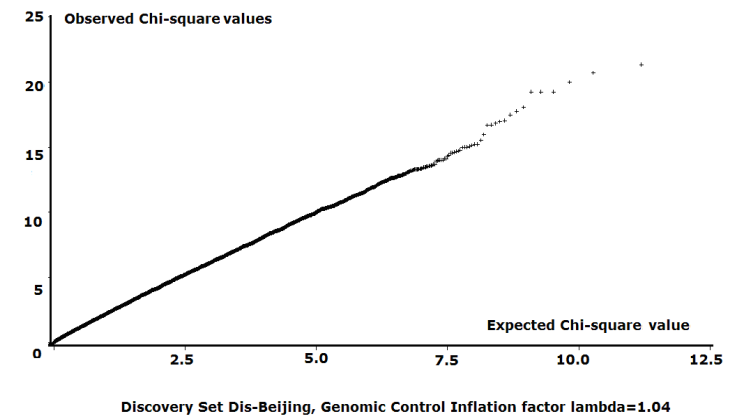
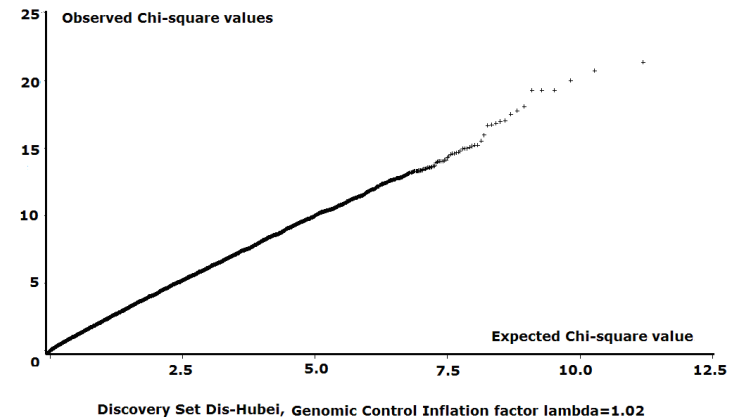
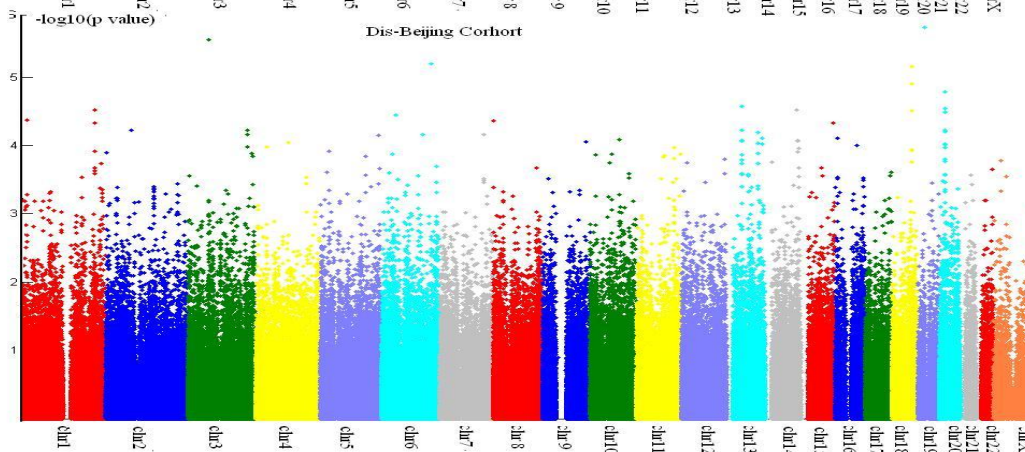
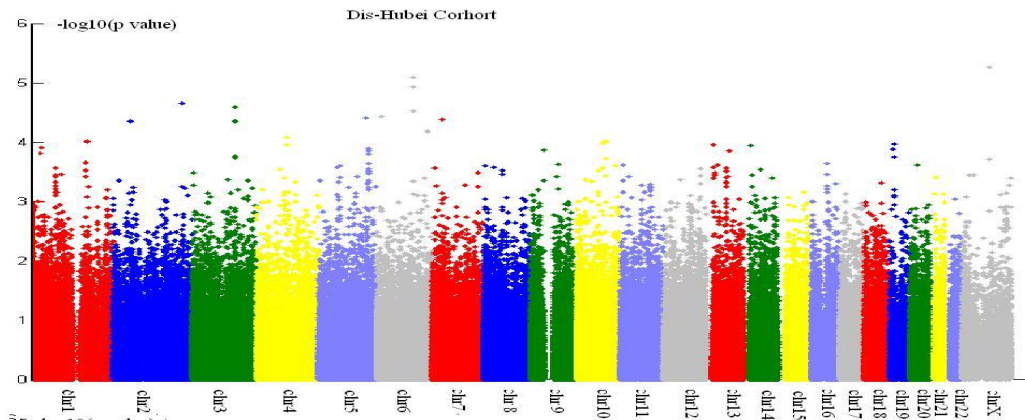
Stage 3 Rep-Hubei
1012 cases vs. 1732
controls

Stage 3 Rep-North
845 cases vs. 1367
controls

■ Stage 1
● Stage 2
▲ Stage 3



Stage I –Discovery GWAS QQ plot



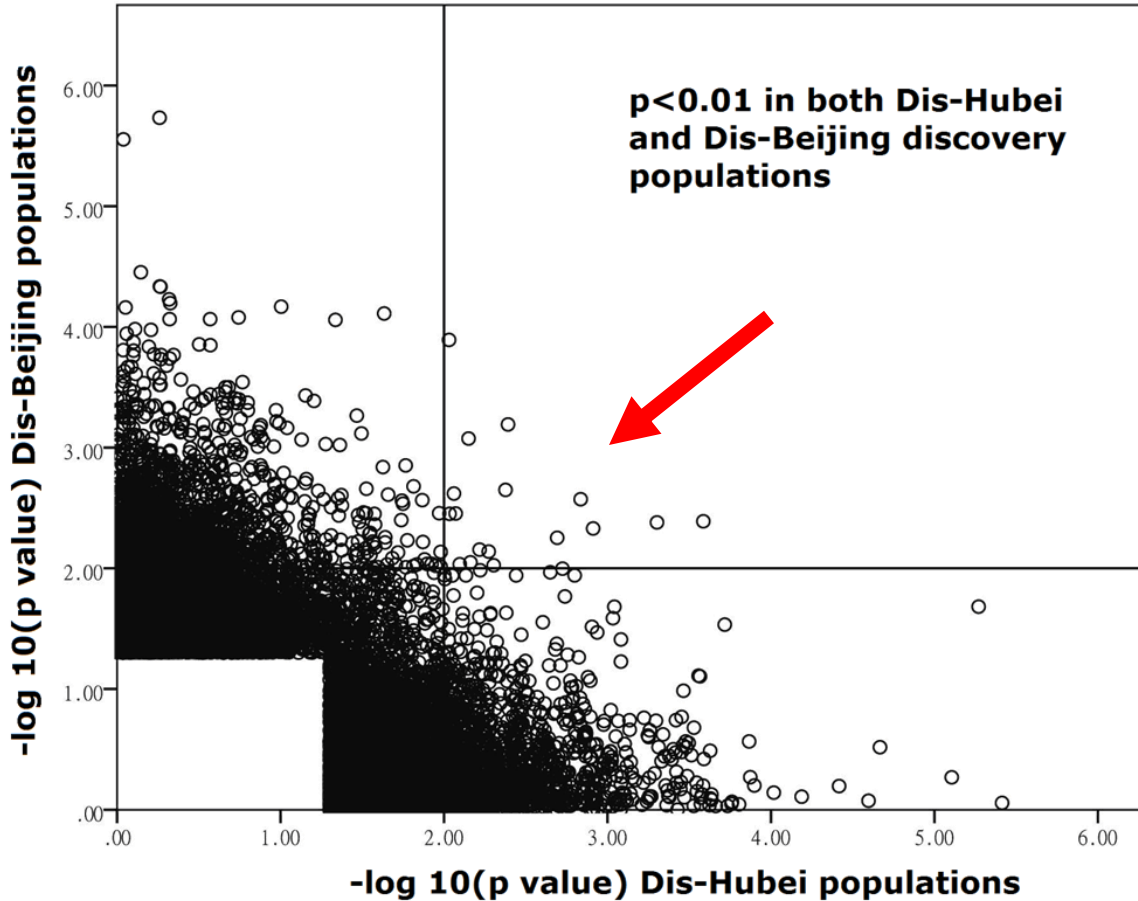
Wang, F., et al., *Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population.* Nature genetics, 2011. **43**(4): p. 345-349.

9p21.3 CAD Locus in GeneID

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

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 decreased expression of putative gene *C6orf105* mRNA

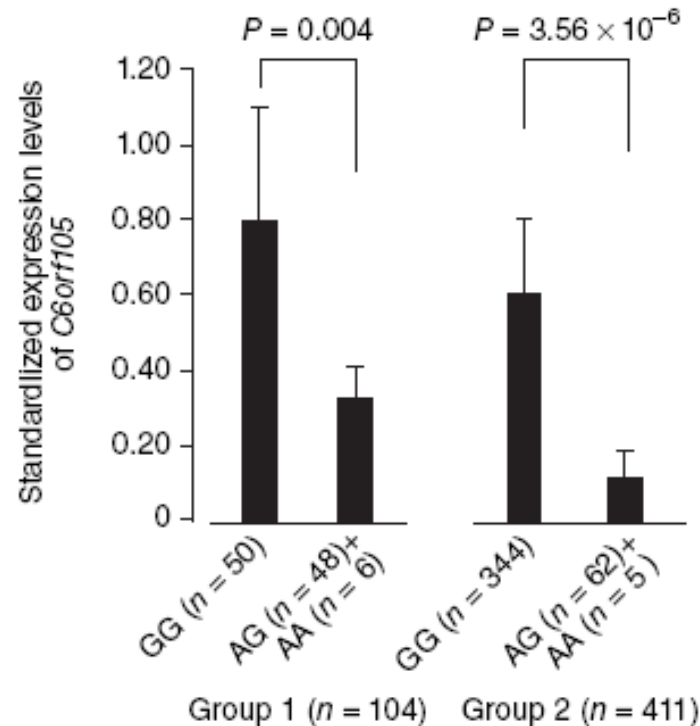


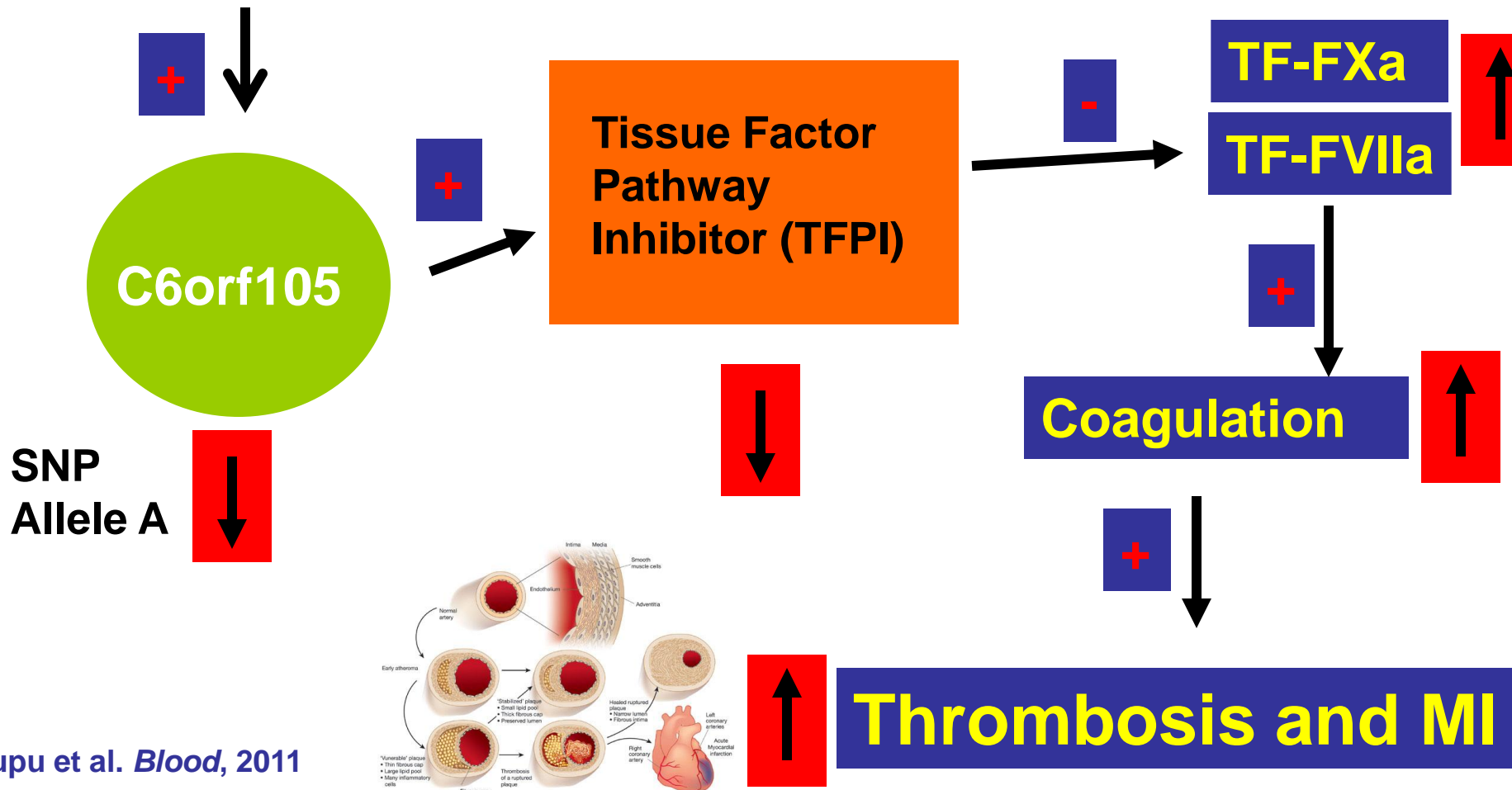
Figure 1 Association of the risk allele A of rs6903956 with decreased expression of *C6orf105* mRNA assuming a dominant model. Error bars, ± 2 s.e.

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* expression
- *C6orf105*
 - 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)



Genetics 2011 Research Highlights

Medical genetics: Follow your heart

Felix Cheung

Published online: 04 May 2011 | [doi:10.1038/nchina.2011.35](https://doi.org/10.1038/nchina.2011.35)

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).

Sequencing technology: An alternative strategy for alternative polyadenylation **OPEN !**

Felix Cheung

Published online: 04 May 2011 | [doi:10.1038/nchina.2011.36](https://doi.org/10.1038/nchina.2011.36)

Original article citation:

Fu, Y. *et al.* Differential genome-wide profiling of tandem 39 UTRs among human breast cancer and normal cells by high-throughput sequencing. *Genome Res.* [doi:10.1101/gr.115295.110](https://doi.org/10.1101/gr.115295.110) (2011).

Gene therapy: Little RNA keeps cancer away

Felix Cheung

Published online: 06 April 2011 | [doi:10.1038/nchina.2011.19](https://doi.org/10.1038/nchina.2011.19)

Original article citation:

Jin, H. *et al.* Identification of miRNomes in human liver and hepatocellular carcinoma reveals miR-199a/b-3p as therapeutic target for hepatocellular carcinoma. *Cancer Cell* **19**, 232–243 (2011).

Plant genomics: Soy story

Felix Cheung

Published online: 02 March 2011 | [doi:10.1038/nchina.2011.15](https://doi.org/10.1038/nchina.2011.15)

Original article citation:

Lam, H. M. *et al.* Resequencing of 31 wild and cultivated soybean genomes identifies patterns of genetic diversity and selection. *Nature Genet.* **42**, 1053–1059 (2010).

Medical genetics: Markers for polycystic ovary syndrome

Felix Cheung

Published online: 02 February 2011 | [doi:10.1038/nchina.2011.7](https://doi.org/10.1038/nchina.2011.7)

Original article citation:

Chen, Z. J. *et al.* Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. *Nature Genet.* **43**, 55–59 (2011).

Research Highlights

➤ **Subject Categories:** [Genetics](#) [Clinical medicine](#)

Published online: 4 May 2011 | [doi:10.1038/nchina.2011.35](https://doi.org/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.

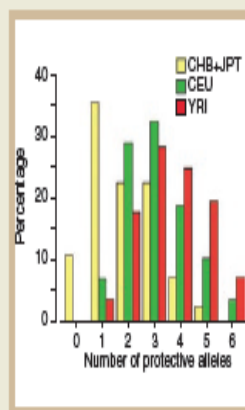
Kenneth Qing Wang and Xin Tu at Huazhong University of Science and Technology in Wuhan and co-workers¹ have now performed a genome-wide association study on a Chinese population and identified a new SNP associated with CAD.

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.

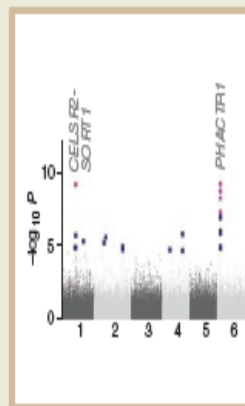


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GWAS of coronary artery disease
Replication licensing mutations
Microattribution review of hemoglobinopathies



Loci associated with susceptibility to IgA nephropathy (p 321)



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



333 Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease

H Schunkert, I R König, S Kathiresan, M P Reilly, T L Assimes, H Holm, M Preuss, A F R Stewart, M Barbalić, C Gieger, D Absher, Z Aherrahrou, H Allayee, D Altshuler, S S Anand, K Andersen, J L Anderson, D Ardicino, S G Ball, A J Balmforth, T A Barnes, D M Becker, L C Becker, K Berger, J C Bis, S M Boekholdt, E Boerwinkle, P S Braund, M J Brown, M S Burnett, I Buyschaert, Cardiogenics, J F Carlquist, L Chen, S Cichon, V Codd, R W Davies, G Dedoussis, A Dehghan, S Demissie, J M Devaney, P Diemert, R Do, A Doering, S Eifert, N E E Mokhtari, S G Ellis, R Elosua, J C Engert, S E Epstein, U de Faire, M Fischer, A R Folsom, J Freyer, B Gigante, D Girelli, S Gretarsdottir, V Gudnason, J R Gulcher, E Halperin, N Hammond, S L Hazen, A Hofman, B D Horne, T Illig, C Iribarren, G T Jones, J W Jukema, M A Kaiser, L M Kaplan, J J P Kastelein, K-T Khaw, J W Knowles, G Kolovou, A Kong, R Laaksonen, D Lambrechts, K Leander, G Lettre, M Li, W Lieb, C Loley, A J Lotery, P M Mannucci, S Maouche, N Martinelli, P P McKeown, C Meisinger, T Meitinger, O Melander, P A Merlini, V Mooser, T Morgan, T W Mühleisen, J B Muhlestein, T Münzel, K Musunuru, J Nahrstaedt, C P Nelson, M M Nöthen, O Olivieri, R S Patel, C C Patterson, A Peters, F Peyvandi, L Qu, A A Quyyumi, D J Rader, L S Rallidis, C Rice, F R Rosendaal, D Rubin, V Salomaa, M L Sampietro, M S Sandhu, E Schadt, A Schäfer, A Schillert, S Schreiber, J Schrezenmeir, S M Schwartz, D S Siscovick, M Sivanathan, S Sivapalaratnam, A Smith, T B Smith, J D Snoep, N Soranzo, J A Spertus, K Stark, K Stirrups, M Stoll, W H W Tang, S Tennstedt, G Thorgeirsson, G Thorleifsson, M Tomaszewski, A G Uitterlinden, A M van Rij, B F Voight, N J Wareham, G A Wells, H-E Wichmann, P S Wild, C Willenborg, J C M Witteman, B J Wright, S Ye, T Zeller, A Ziegler, F Cambien, A H Goodall, L A Cupples, T Quertermous, W März, C Hengstenberg, S Blankenberg, W H Ouwehand, A S Hall, P Deloukas, J R Thompson, K Stefansson, R Roberts, U Thorsteinsdottir, C J O'Donnell, R McPherson, J Erdmann & N J Samani for the CARDIoGRAM Consortium

339 A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease

The Coronary Artery Disease (CAD) Genetics Consortium

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

F Wang, C-Q Xu, Q He, J-P Cai, X-C Li, D Wang, X Xiong, Y-H Liao, Q-T Zeng, Y-Z Yang, X Cheng, C Li, R Yang, C-C Wang, G Wu, Q-L Lu, Y Bai, Y-F Huang, D Yin, Q Yang, X-J Wang, D-P Dai, R-F Zhang, J Wan, J-H Ren, S-S Li, Y-Y Zhao, F-F Fu, Y Huang, Q-X Li, S-W Shi, N Lin, Z-W Pan, Y Li, B Yu, Y-X Wu, Y-H Ke, J Lei, N Wang, C-Y Luo, L-Y Ji, L-J Gao, L Li, H Liu, E-W Huang, J Cui, N Jia, X Ren, H Li, T Ke, X-Q Zhang, J-Y Liu, M-G Liu, H Xia, B Yang, L-S Shi, Y-L Xia, X Tu & Q K Wang

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 (CAD) Genetics Consortium analyzed 8,424 European patients and 6,996 South Asian patients and found 5 new variants/loci for CAD

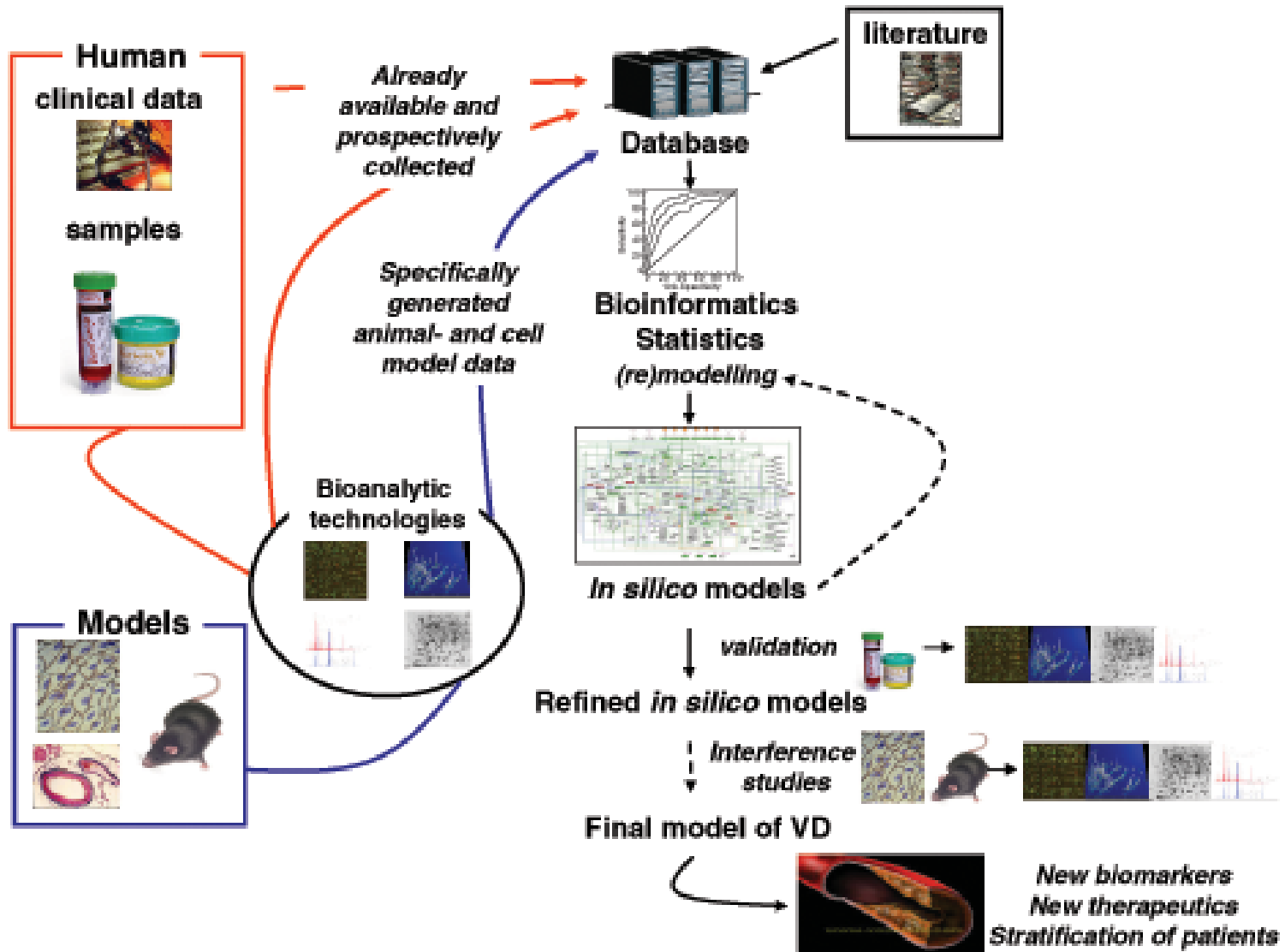
Summary: GWAS for CAD/MI

- 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)

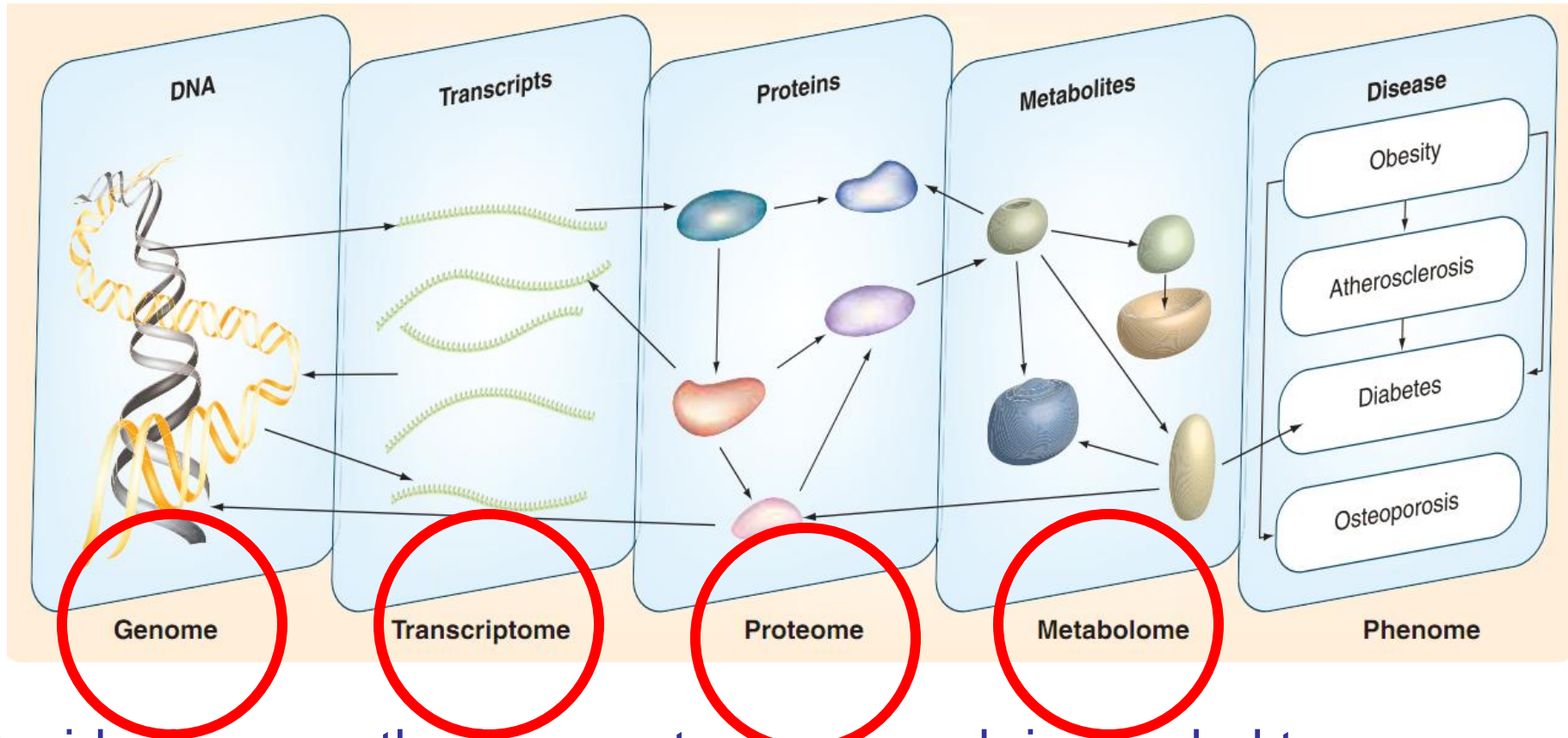
Future

- (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

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

Translational Steps from Bench to Bedside



**A First Step in a Long
Journey!**

Future: Systems Biology



谢谢!