Genetic Association Study for Cardiovascular Disease in Yonsei Cardiovascular Center

Dong-Jik Shin, Ph.D
Yonsei University College of Medicine
Cardiovascular Center
Cardiovascular Research Institute

Changes in Rankings for 15 Leading Causes of Death, 2002 and 2030

Category	Disease or Injury	2002 Rank	2030 Ranks	Change in Rank
Within top 15	Ischaemic heart disease	1	1	0
	Cerebrovascular disease	2	2	0
	Lower respiratory infections	3	5	−2
	HIV/AIDS	4	3	+1
	COPD	5	4	+1
	Perinatal conditions	6	9	−3
	Diarrhoeal diseases	7	16	−9
	Tuberculosis	8	23	−15
	Trachea, bronchus, lung cancers	9	6	+3
	Road traffic accidents	10	8	+2
	Diabetes mellitus	11	7	+4
	Malaria	12	22	−10
	Hypertensive heart disease	13	11	+2
	Self-inflicted injuries	14	12	+2
	Stomach cancer	15	10	+5
Outside top 15	Nephritis and nephrosis	17	13	+4
	Colon and rectum cancers	18	15	+3
	Liver cancers	19	14	+5

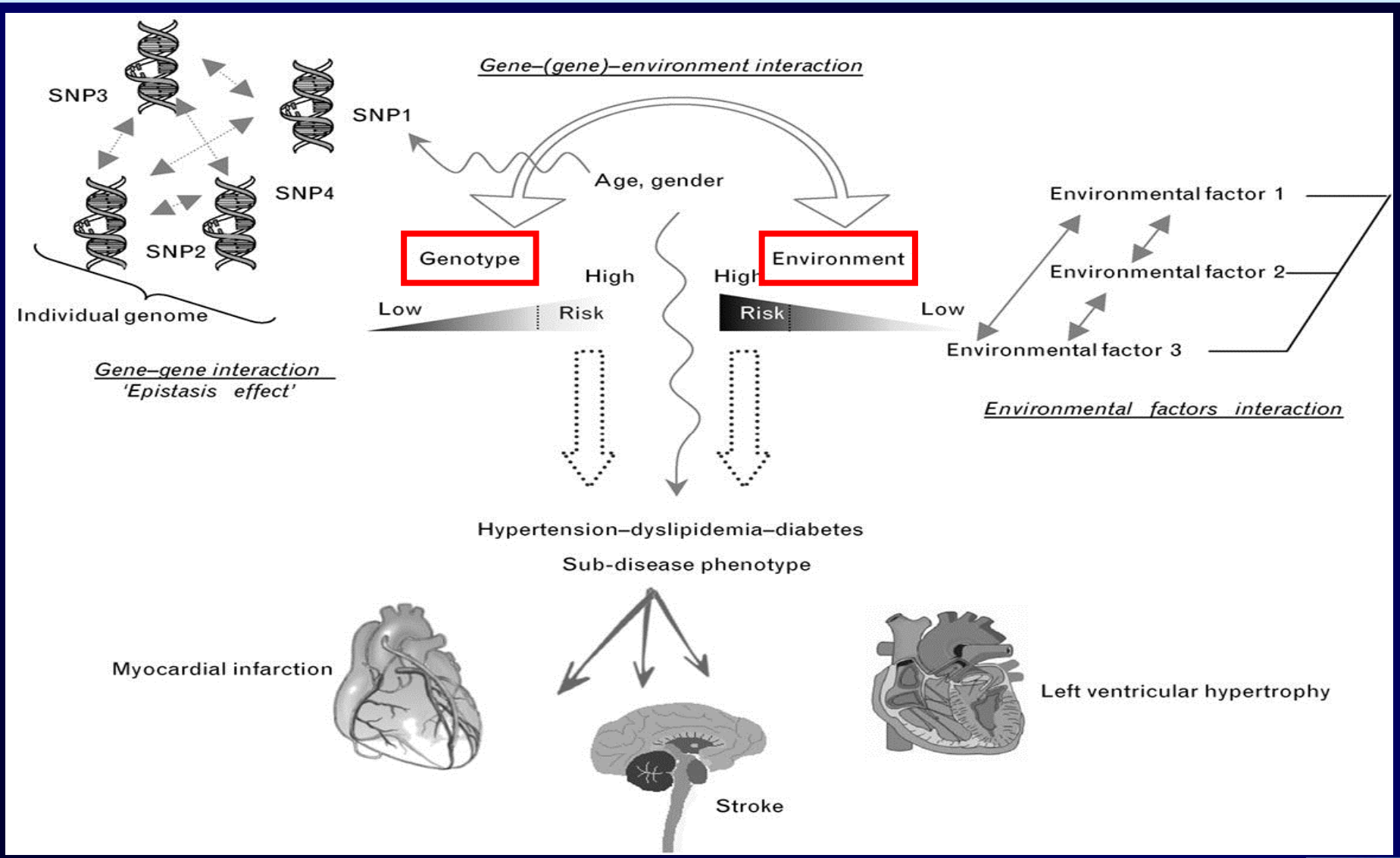
PLoS Med. 2006, 3(11);e442:2011-2030

한국인 10대 사망원인 (2009년)

순위	사 망 원 인	10만 명 당 사망률
1	악성신생물(암)	140.5
2	뇌혈관 질환	52.0
3	심장 질환	45.0
4	자살	31.0
5	당뇨병	19.6
6	운수사고	14.4
7	만성하기도 질환	13.9
8	간 질환	13.8
9	폐렴	12.7
10	고혈압성 질환	9.6

자료 : 통계청(www.kostat.go.kr)

Multiple interaction : Cardiovascular disease occurs when an individual has a high genetic risk or a high environment risk



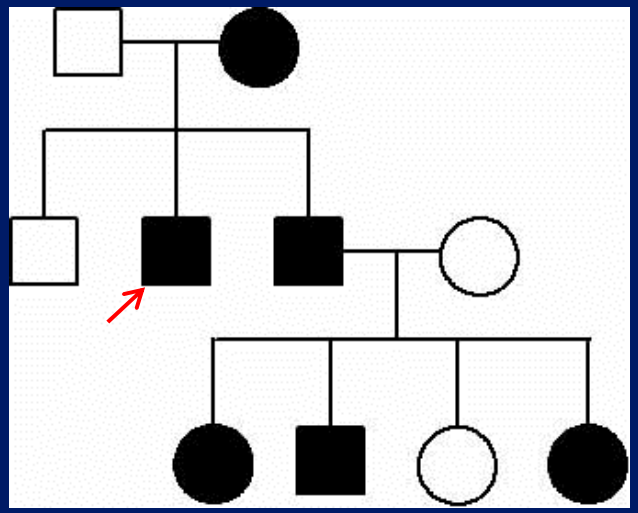
Curr Opin Lipidol. 2006 ;17(2):139-151

Genetic basis of CVD

- **Twin studies indicate that heritability of CVD is 30-60% (*N Engl J Med 1994;330:1041*)**
- **Heritability** as high as 63% for premature **MI** ***(Circulation 1980;61:503***)
- **History of premature death of a biological parent(<50 years) was associated with 4.5 fold increase in mortality for adopted offsprings → Risk not increased in adopted children with history of premature CAD in foster parents (*N Engl J Med 1988;318:727*)**

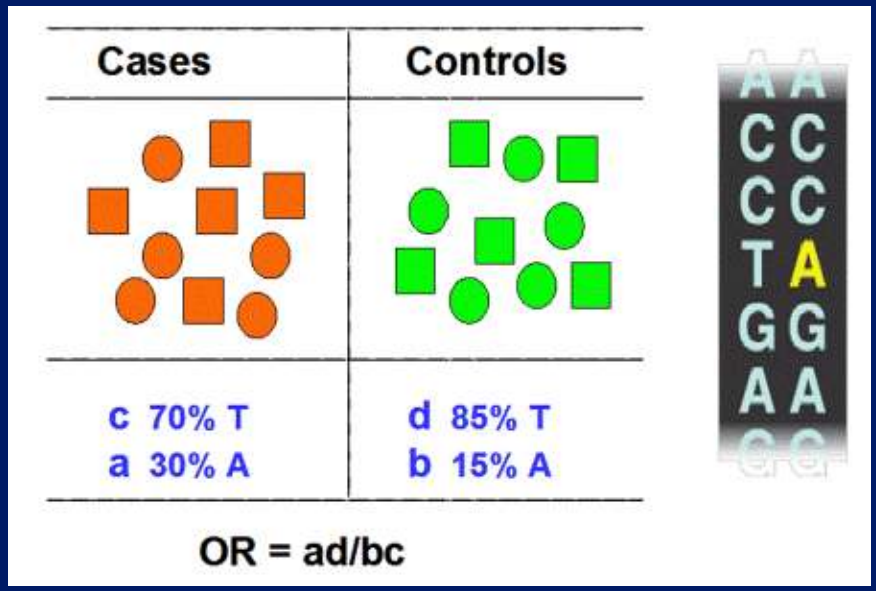
Strategies for Disease Gene Identification

Linkage Analysis (Family)



- Single gene
- Mendelian inheritance
- Rare, but high penetrance
- ~300-400 STR markers

Association Study (Population)

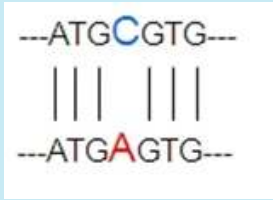


- Polygenic (also G X E)
- Complex inheritance
- Common
- Multiple polymorphic SNP markers

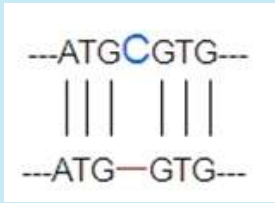
Human Genome Variations

Genome Variation

- Base Variation
  - Single Nucleotide Polymorphism (SNP)

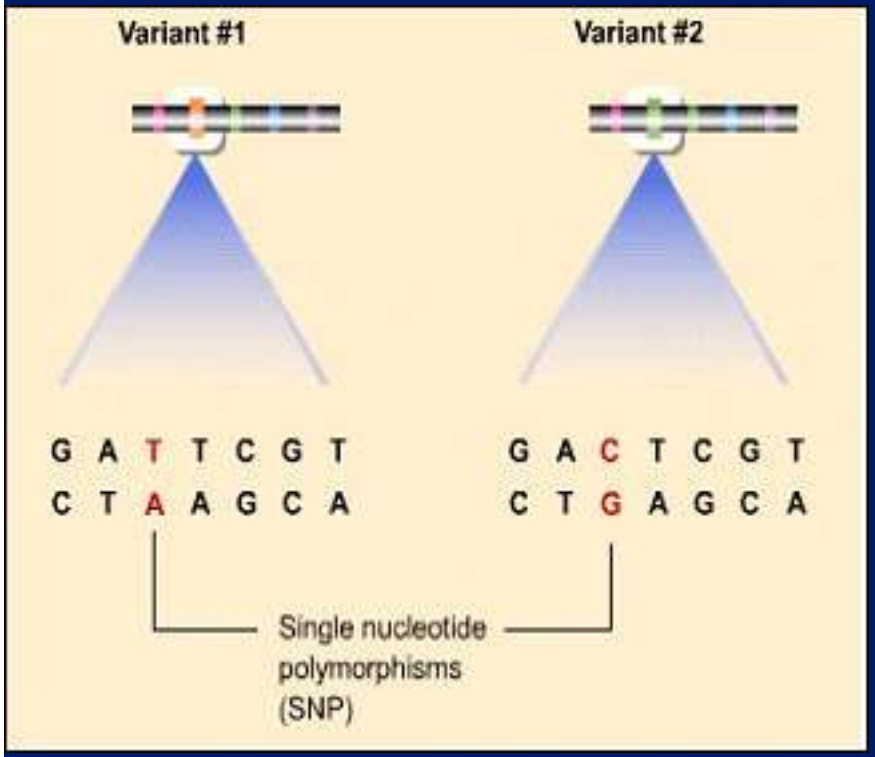


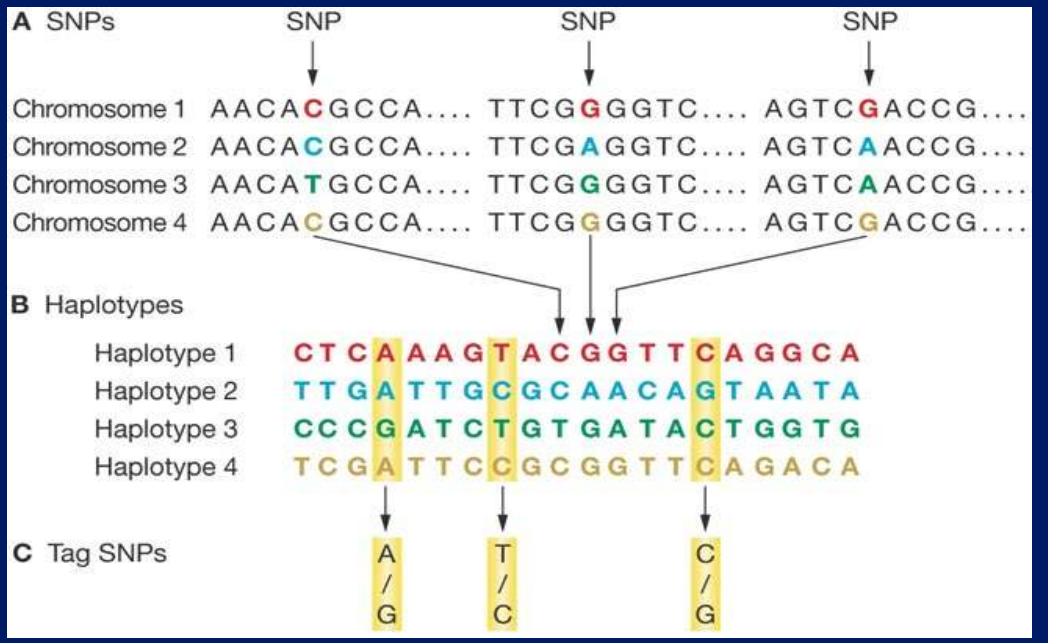
  - Insertion & Deletion(InDel)

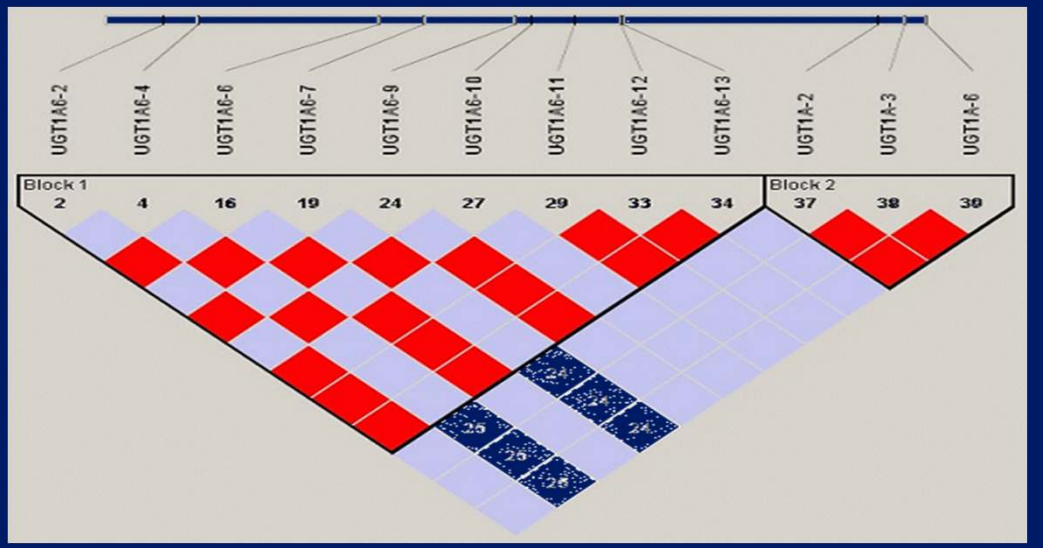


- Structural Variation
  - Copy Number Variation (CNV)
    - Copy Number Gain
    - Copy Number Loss
  - Normal CNV, Structural Variation
    - Inversion
    - Translocation

SNP, Haplotype and TagSNPs





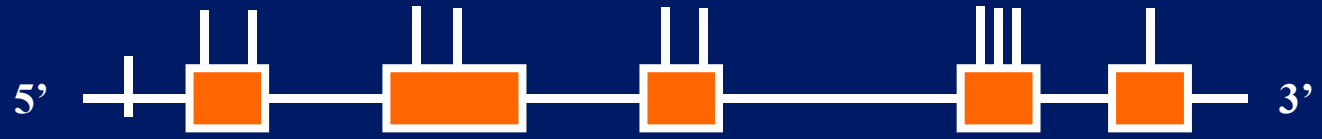


Approaches to determine susceptibility genes

- Candidate gene approach
- GWAS
- NGS

Analytic Tools of Association Study

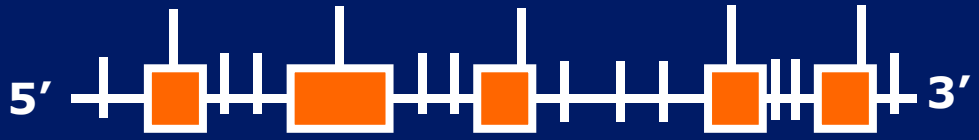
▪ Candidate genes approach



Catalog and test all coding SNPs for function

→ DNA Sequencing / SNapShot or TaqMan assay

▪ Genome-Wide Association approach

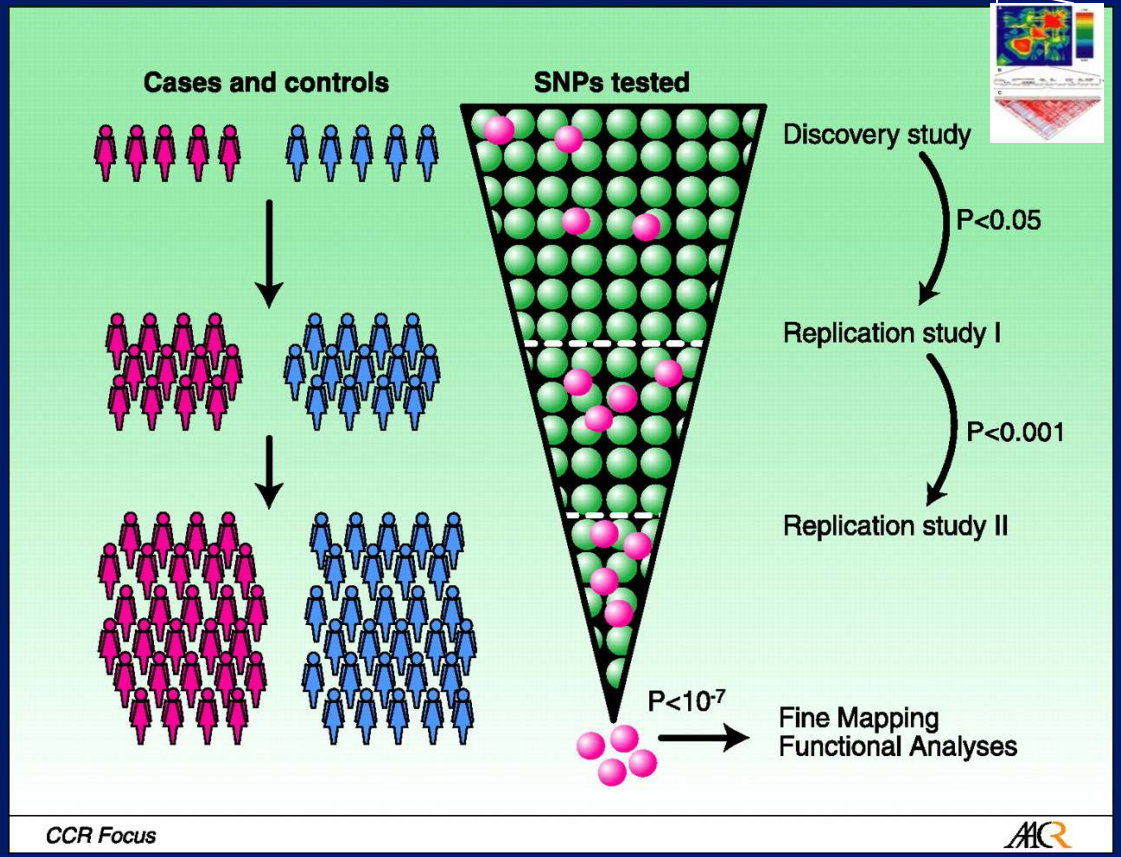


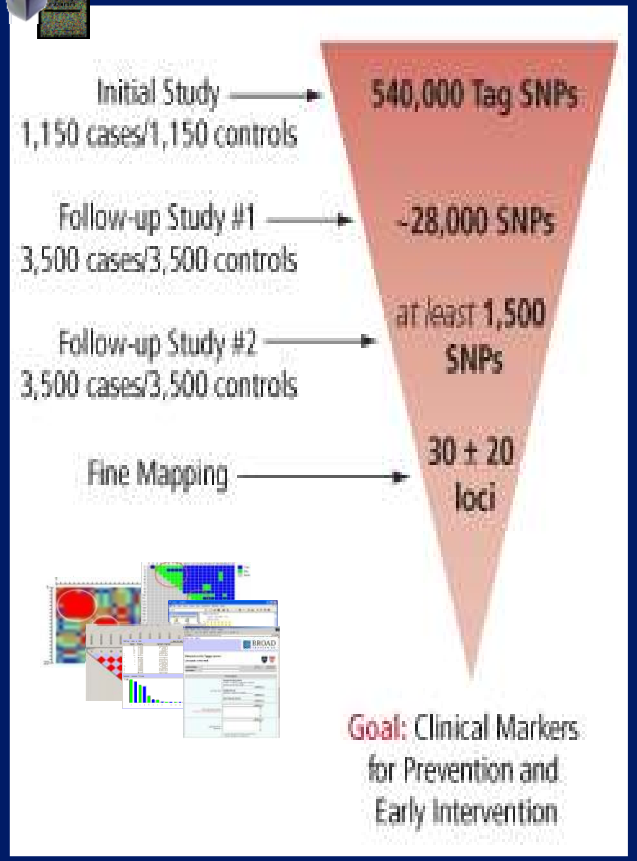
Use dense map of SNPs and test for LD (use association to find sites in entire sequence with function)

→ Affymetrix GeneChip / Illumina GeneChip

Genome-Wide Association Study (GWAS)

- **GWAS are used to identify common genetic factors (SNP, Ins/del) that influence health and disease.**

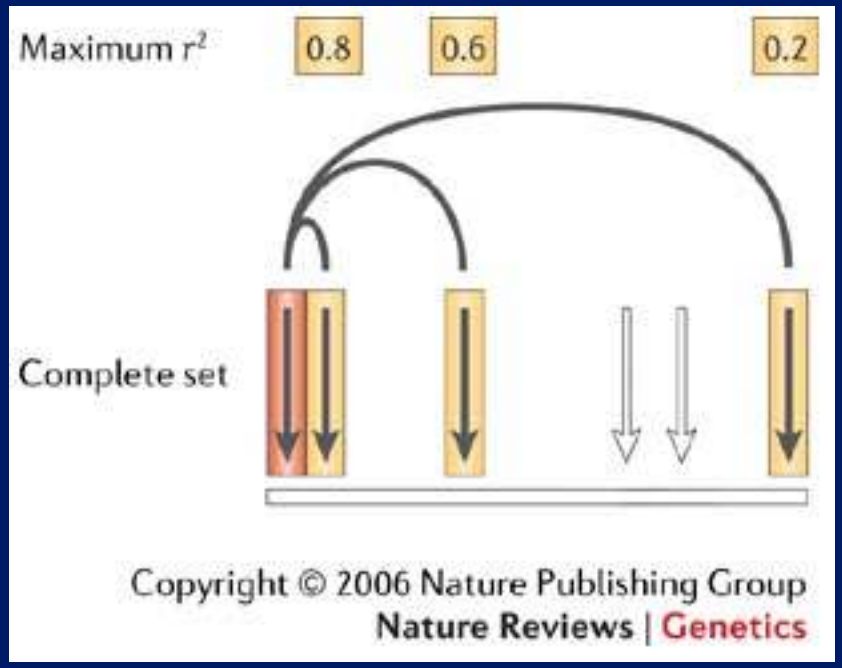




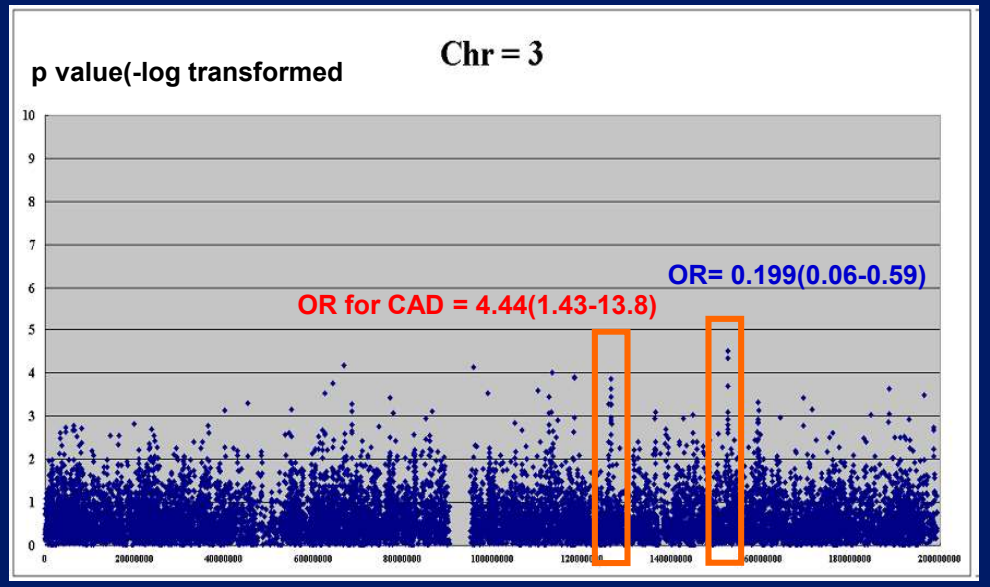
General GWAS strategy for common complex disease

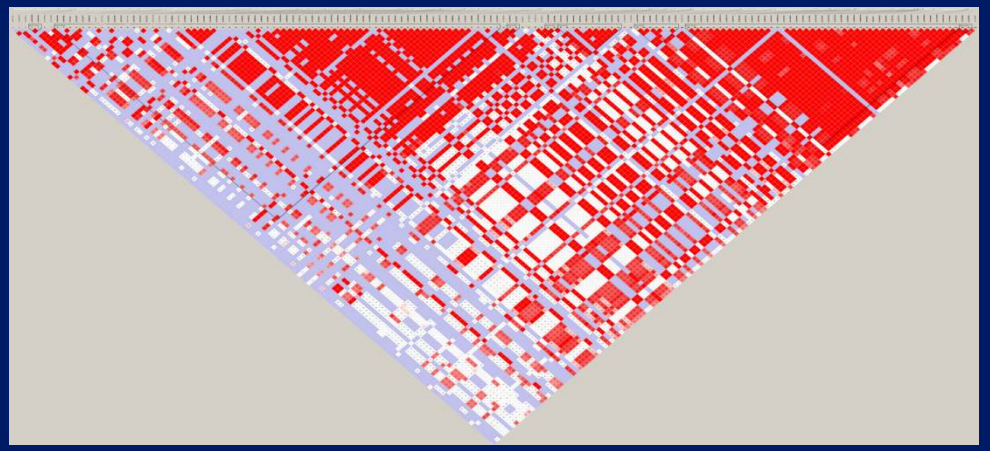
Linkage disequilibrium (LD) block & Association analysis

(A)

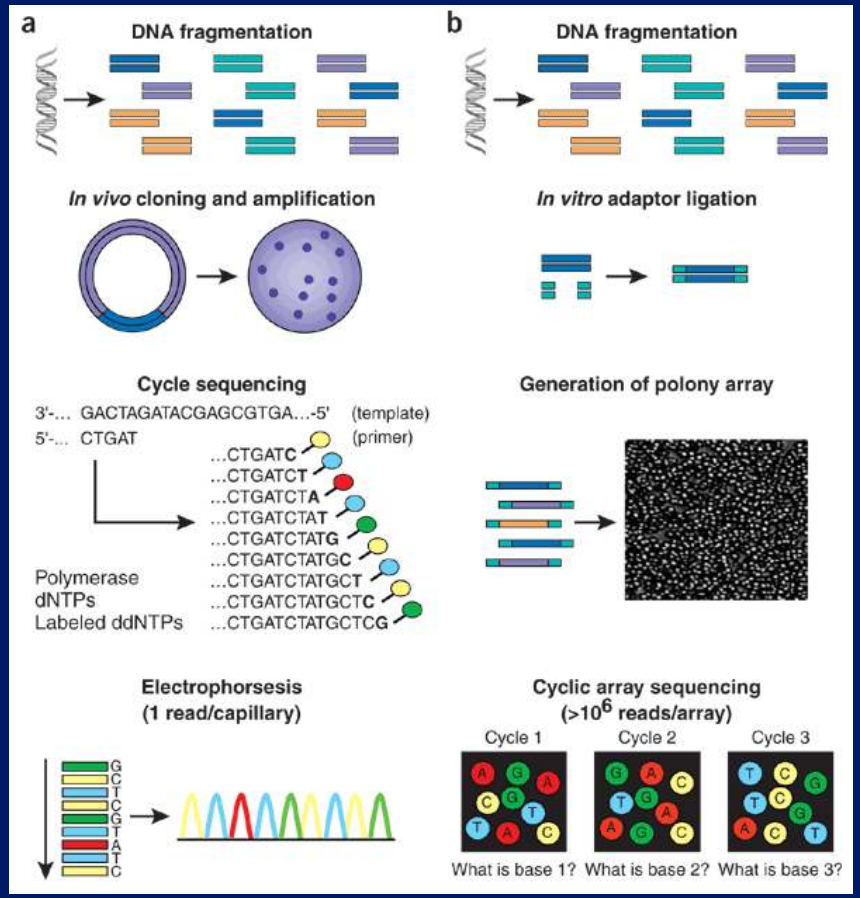


(B)

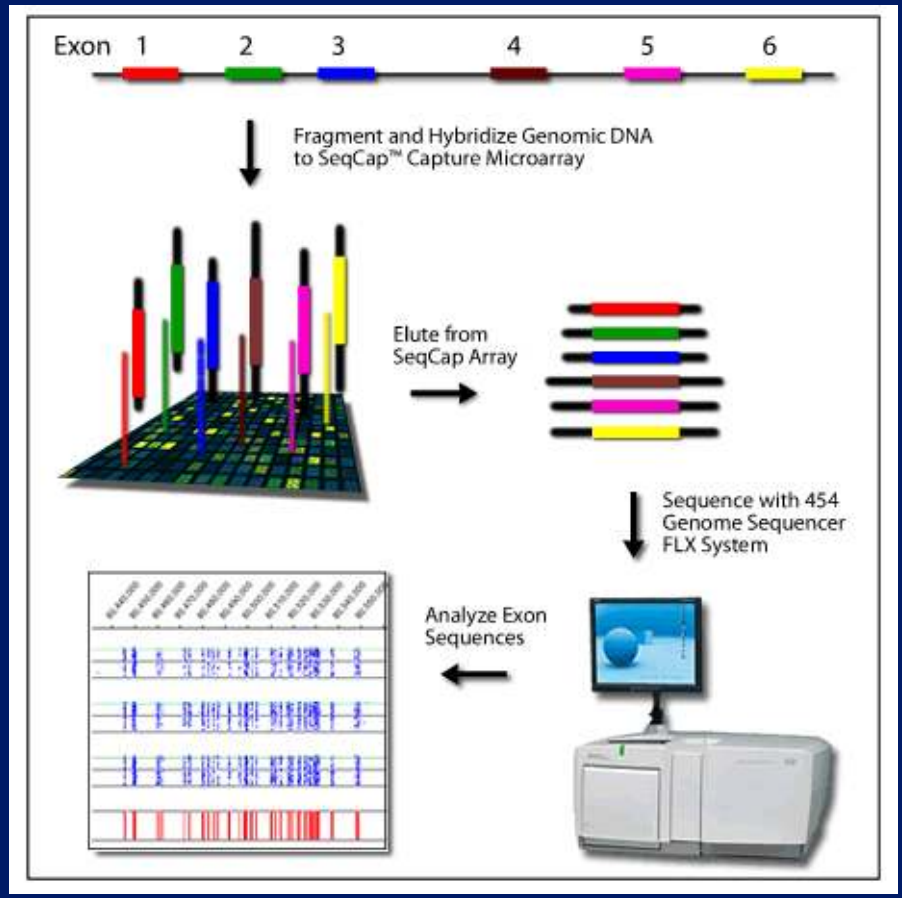




Next Generation Sequencing (NGS)

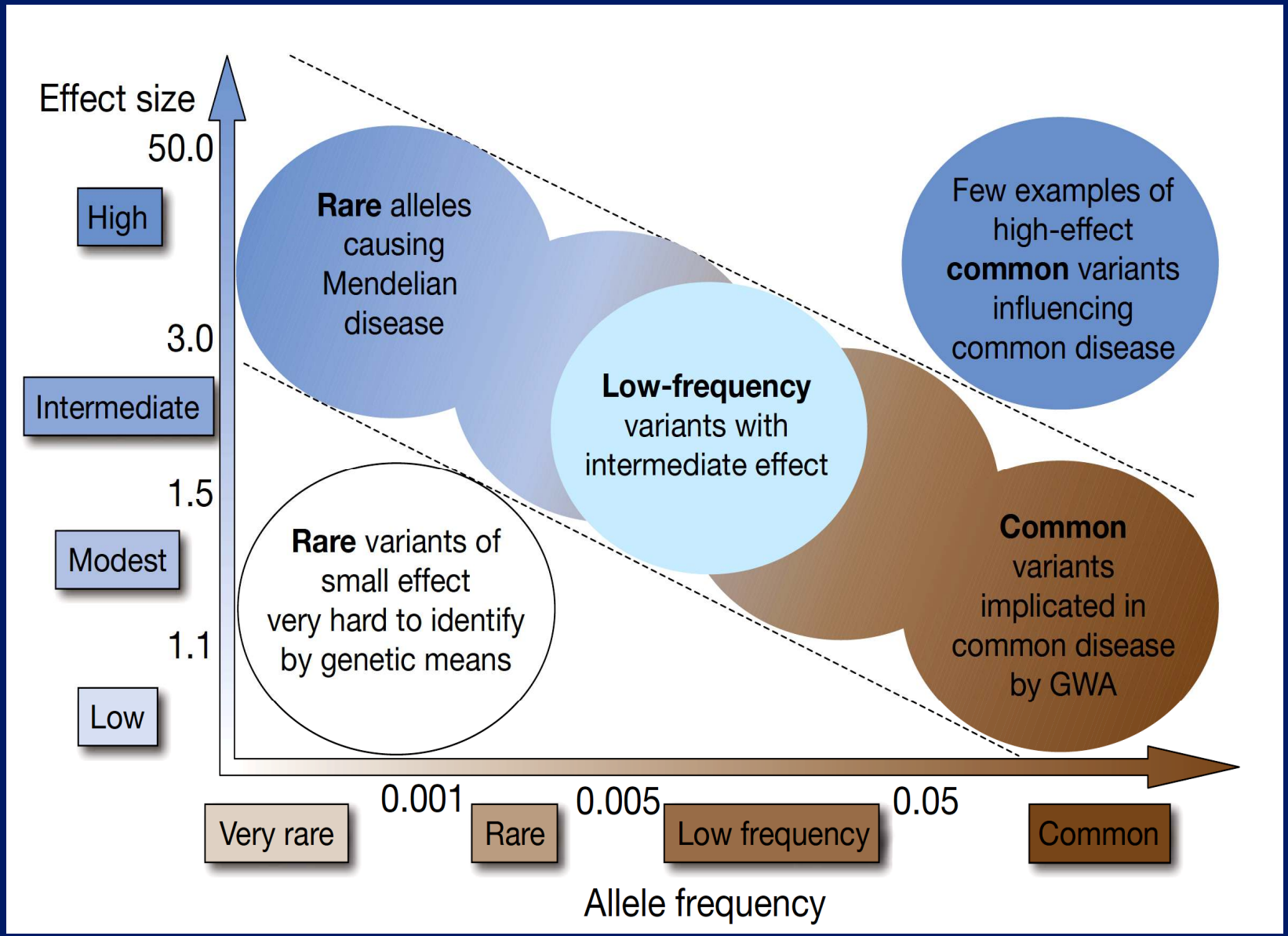


a) Sanger method (old), b) NGS (new)



Chip-based capturing exome sequencing

Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect



Manolio et al, Nature 2009

In 2007: Discovery of 9p21 and the watershed moment for cardiovascular genetics

Science
AAAS

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction
Anna Helgadottir, *et al.*
Science **316**, 1491 (2007);
DOI: 10.1126/science.1142842

Science
AAAS

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease
Ruth McPherson, *et al.*
Science **316**, 1488 (2007);
DOI: 10.1126/science.1142447

The NEW ENGLAND JOURNAL of MEDICINE

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

Genomewide Association Analysis of Coronary Artery Disease

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Genomewide Association Analysis of Coronary Artery Disease

Nilesh J. Samani, F.Med.Sci., Jeanette Erdmann, Ph.D., Alistair S. Hall, F.R.C.P., Christian Hengstenberg, M.D., Massimo Mangino, Ph.D., Bjoern Mayer, M.D., Richard J. Dixon, Ph.D., Thomas Meitinger, M.D., Peter Braund, M.Sc., H.-Erich Wichmann, M.D., Jennifer H. Barrett, Ph.D., Inke R. König, Ph.D., Suzanne E. Stevens, M.Sc., Silke Szymczak, M.Sc., David-Alexandre Tregouet, Ph.D., Mark M. Iles, Ph.D., Friedrich Pahlke, M.Sc., Helen Pollard, M.Sc., Wolfgang Lieb, M.D., Francois Cambien, M.D., Marcus Fischer, M.D., Willem Ouwehand, F.R.C.Path., Stefan Blankenberg, M.D., Anthony J. Balmforth, Ph.D., Andrea Baessler, M.D., Stephen G. Ball, F.R.C.P., Tim M. Strom, M.D., Ingrid Brænne, M.Sc., Christian Gieger, Ph.D., Panos Deloukas, Ph.D., Martin D. Tobin, M.F.P.H.M., Andreas Ziegler, Ph.D., John R. Thompson, Ph.D., and Heribert Schunkert, M.D., for the WTCCC and the Cardiogenics Consortium*

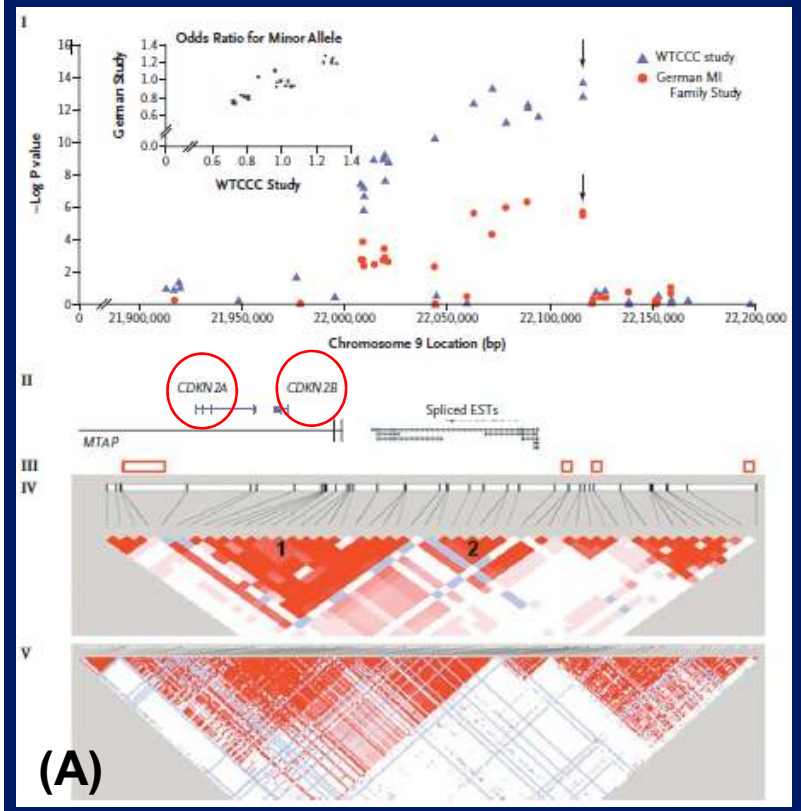


Table 2. Loci from the WTCCC Study with Significant Associations with Coronary Artery Disease That Were Replicated in the German MI Family Study.*

Chromosome	Lead SNP	Minor Allele in Controls	Risk Allele	Data	Frequency of Minor Allele		Odds Ratio for Risk Allele (95% CI)	Population Attributable Fraction	P Value
					Case Subjects	Controls			
2	rs2943634	A	C	WTCCC	0.30	0.34	1.22 (1.11–1.33)		1.19×10^{-5}
				German	0.32	0.37	1.20 (1.06–1.35)		0.004
				Adjusted German			1.08 (0.90–1.31)	0.10	0.03
6	rs6922269	A	A	WTCCC	0.29	0.25	1.23 (1.13–1.35)		6.33×10^{-6}
				German	0.30	0.26	1.24 (1.09–1.41)		0.001
				Adjusted German			1.23 (1.01–1.50)	0.11	0.009
9	rs1333049	C	C	WTCCC	0.55	0.47	1.37 (1.26–1.48)		1.80×10^{-14}
				German	0.54	0.48	1.33 (1.18–1.51)		6.80×10^{-6}
				Adjusted German			1.28 (1.07–1.53)	0.22	6.12×10^{-5}

(B)

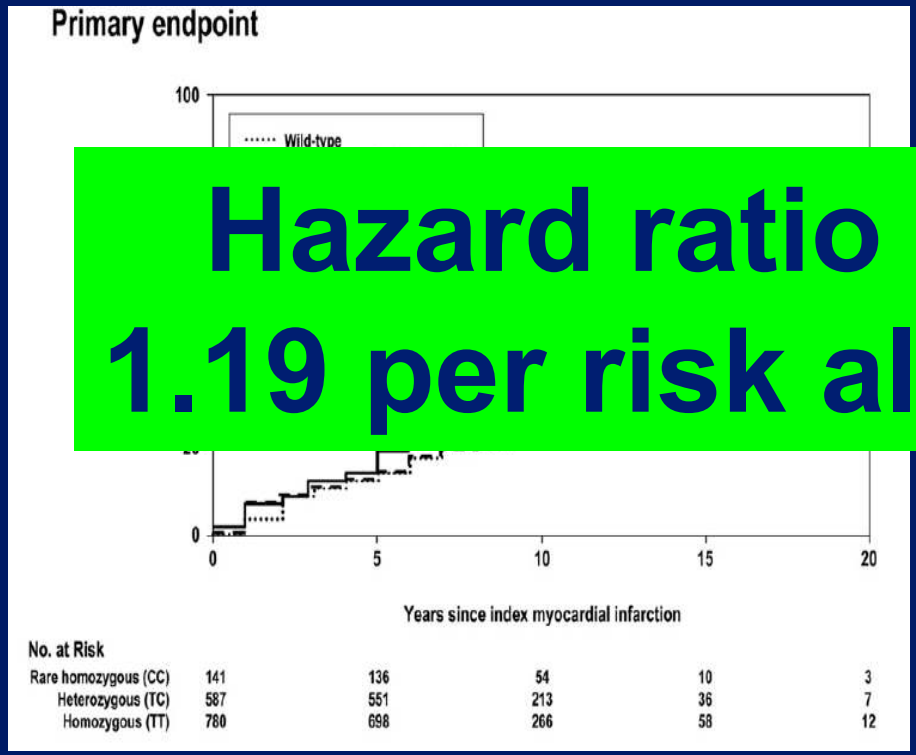
Human chromosome 9p21.3 (rs1333049) had the strongest association with CAD in WTCCC and Germans

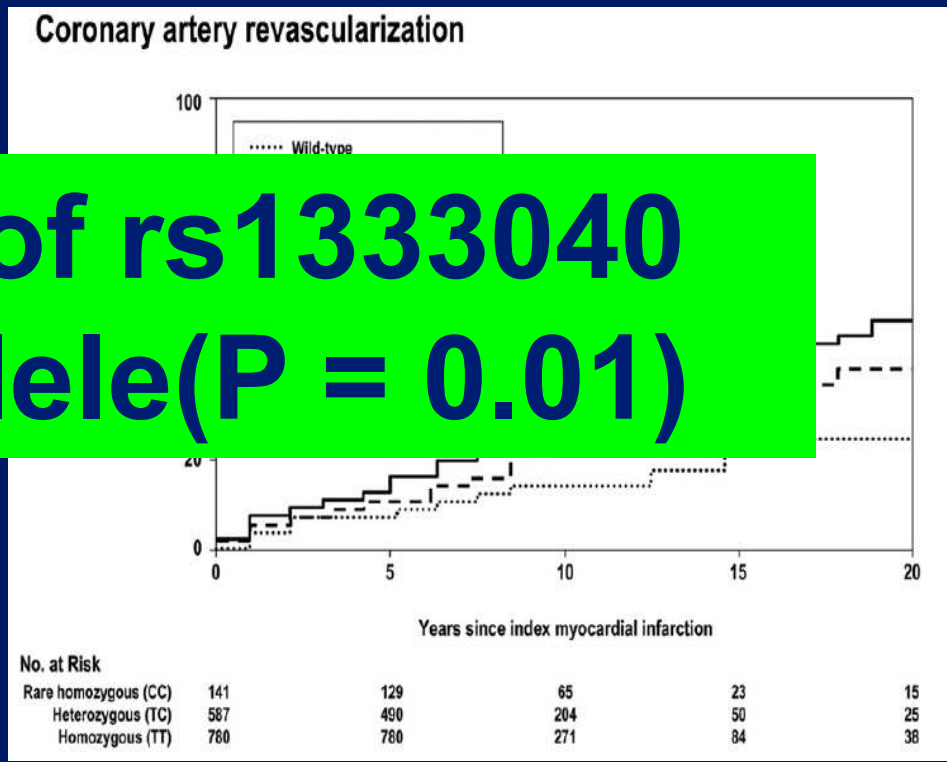
Samani NJ *et al*. NEJM 2007;357:443-453

Influence of 9p21.3 Genetic Variants on Clinical and Angiographic Outcomes in Early-Onset Myocardial Infarction

Ardissino D *et al*. J Am Coll Cardiol 2011;58:426-434

Hazard ratio of rs1333040
1.19 per risk allele(P = 0.01)





nature genetics

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

Fan Wang[1,12], Cheng-Qi Xu[1,12], Qing He[2,12], Jian-Ping Cai[2,12], Xiu-Chun Li[1,12], Dan Wang[1,12], Xin Xiong[1,12], Yu-Hua Liao[3,12], Qiu-Tang Zeng[3,12], Yan-Zong Yang[4,12], Xiang Cheng[3,12], Cong Li[1], Rong Yang[1], Chu-Chu Wang[1], Gang Wu[5], Qiu-Lun Lu[1], Ying Bai[1], Yu-Feng Huang[1], Dan Yin[1], Qing Yang[1], Xiao-Jing Wang[1], Da-Peng Dai[2], Rong-Feng Zhang[4], Jing Wan[6], Jiang-Hua Ren[6], Si-Si Li[1], Yuan-Yuan Zhao[1], Fen-Fen Fu[1], Yuan Huang[1], Qing-Xian Li[7], Sheng-Wei Shi[7], Nan Lin[7], Zhen-Wei Pan[8], Yue Li[9], Bo Yu[10], Yan-Xia Wu[11], Yu-He Ke[11], Jian Lei[11], Nan Wang[1], Chun-Yan Luo[1], Li-Ying Ji[1], Lian-Jun Gao[4], Lei Li[1], Hui Liu[1], Er-Wen Huang[1], Jin Cui[1], Na Jia[2], Xiang Ren[1], Hui Li[1], Tie Ke[1], Xian-Qin Zhang[1], Jing-Yu Liu[1], Mu-Gen Liu[1], Hao Xia[5], Bo Yang[5], Li-Song Shi[1], Yun-Long Xia[4], Xin Tu[1] & Qing K Wang[1]

Identification of significant association between 2 SNPs and CAD in Chinese

Chr.	SNP	Gene (nearby)	Risk allele	OR	P	*vs.* KOR/EUR
6p24.1	rs6903956	*C6orf105*	A	1.71	$5.0X10^{-3}$	N
9p21.3	rs1333048	*CDKN2A/2B*	G	1.29	$4.0X10^{-3}$	Y

The function of *C6orf105* gene is unknown, but Wang et al. suggested that decreased expression of *C6orf105* gene may be a possible pathogenic cause of CAD.

Clin Chem Lab Med 2009;47(8):917–922 © 2009 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2009.215

Chromosome 9p21 polymorphism is associated with myocardial infarction but not with clinical outcome in Han Chinese

Table 4 Association of rs1333049 with clinical outcome after MI.

	GG (n=99)	*GC* (n=265)	*CC* (n=156)	p-Value
Treatment				
Primary PCI, %	78.8	80.0	85.3	0.314
Aspirin, %	90.9	94.3	91.7	0.410
ACEI or ARB, %	67.7	64.9	62.8	0.730
β-Blocker, %	45.5	49.1	48.7	0.822
Statins, %	54.5	56.2	51.6	0.657
Duration, months	28±18	30±17	29±17	0.685
Adverse events				
Rehospitalization, n	1±1	1±1	1±1	0.263
Death, %	2.0	1.1	2.6	0.537
Non-fatal MI, %	5.1	1.9	3.2	0.265
Combined MACE, %	48.8	49.7	51.2	0.940

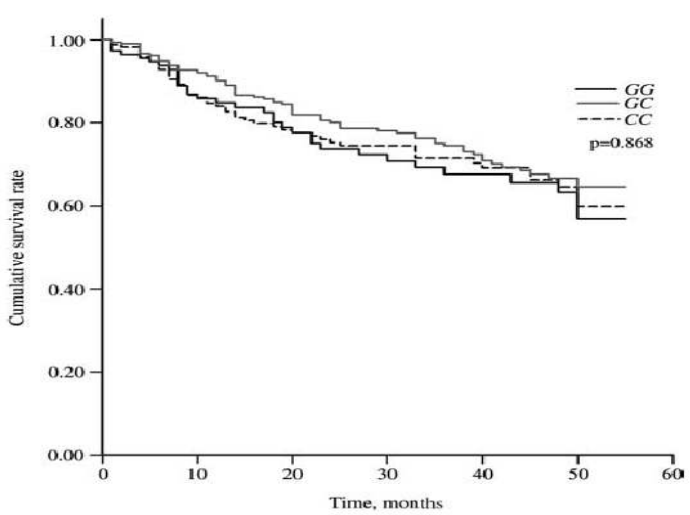
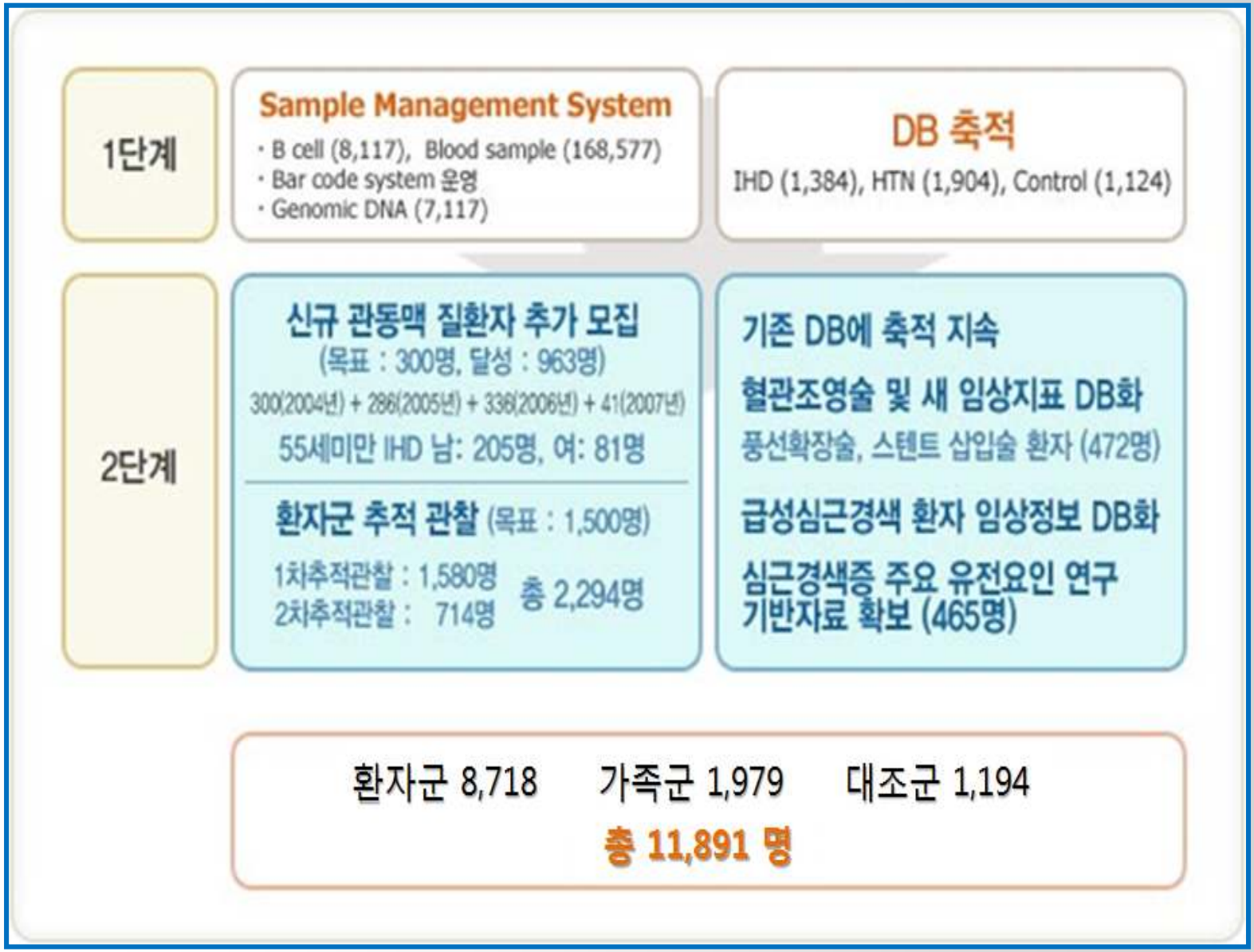


Figure 1 Kaplan-Meier survival plot by rs1333049. Cumulative survival rate was similar among the *GG* (n=99), *GC* (n=265), and *CC* (n=156) genotypes.

rs1333049 is associated with risk for MI, but not with post-MI prognosis in Han Chinese

Peng WH *et al*. CCLM 2009;47:917-22

심혈관질환 유전체은행 구성



심혈관질환 유전체 코호트 구축

- 55세 이하 남성, 60세 이하 여성 2VD 이상의 CHD 환자군
- 나이와 성별을 matching한 대조군

	Case (n=503)	Control (n=503)
DM	159 (31.6%)	7 (1.4%)
Hypertension	286 (56.9%)	15 (3.0%)
Smoke	353 (70.2%)	332 (66.0%)
BMI	25.4± 2.9	24.2± 2.8
Total-cholesterol	190.3± 47.3	197.2± 34.7
TG	165.6± 122.3	139.3± 76.2
HDL	41.4± 10.4	50.6± 14.1
Creatinine	1.0± 0.4	0.90± 0.2

GWAS of CAD in CGC study

Genome-wide association study (CAD: control=230:290)
CAD – multivesseles dx age<55

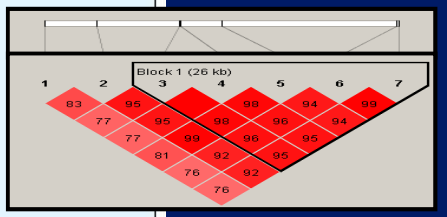
Affymetrix GeneChip Mapping 500K Array Set analysis

Significance SNP p<0.001 #2187
Including surrounding SNP, cSNP

2nd Validation Study (CAD:control = 1172:1087)
CAD – singlevessele dx age<65

Affymetrix Targeted GeneChip 3K array analysis

Significance SNP p<0.001 **#38**
Including significance SNP in Japanese



3rd Validation study [CGC Cohort]
(CAD : control = 502:648)

Confirmation of Korean specific SNPs

Cumulative association analysis

4th Validation study (CAD progress)

Identify significant SNPs

Clinical follow up study

Results of CAD-GWAS in CGC

			GWAS	Repl. 1	Repl. 2	Repl. 3
		Case / Control	230/290	1392/1355	502/648	2123/2690
		Mean age(case)	48.3±4.72	54.5 ±7.79	49.3 ±5.36	51.6±7.52
		Age criteria	≤55	≤65	≤55(m), 60(f)	< 55(m), 60(f)
Chr.	Gene	rs #	Stage1 (500K)	Stage2 (3K)	Stage3 (32)	Stage4 (15)
9p		rs133****	5.643E-05	3.080E-07	0.0109	3.30E-08
2p	SPTBN1	rs127****	3.009E-06	1.060E-05	0.0048	0.0034
5q		rs15****	3.125E-03	1.770E-05	0.0049	0.0455
12p	ARNTL2	rs1104****	8.994E-04	6.920E-06	0.0047	0.5961
19p	CACNA1A	rs150****	4.839E-05	4.320E-05	0.0890	-
1p	Vav3	rs1275****	6.192E-03	1.906E-03	0.3889	-
1p		rs599***	0.0272	-	0.8887	-
1q	MIA3	rs1746****	0.0860	-	0.0227	0.0934
10q		rs501***	0.9211	-	0.0100	-

Original research

Genome-wide association analysis and replication of coronary artery disease in South Korea suggests a causal variant common to diverse populations

Eun Young Cho,[2] Yangsoo Jang,[3] Eun Soon Shin,[2] Hye Yoon Jang,[2] Yeon-Kyeong Yoo,[2] Sook Kim,[2] Ji Hyun Jang,[2] Ji Yeon Lee,[2] Min Hye Yun,[2] Min Young Park,[2] Jey Sook Chae,[3] Jin Woo Lim,[4] Dong Jik Shin,[4] Sungha Park,[4] Jong Ho Lee,[3] Bok Ghee Han,[5] Kim Hyung Rae,[5] Lon R Cardon,[6] Andrew P Morris,[1] Jong Eun Lee,[2] Geraldine M Clarke[1]

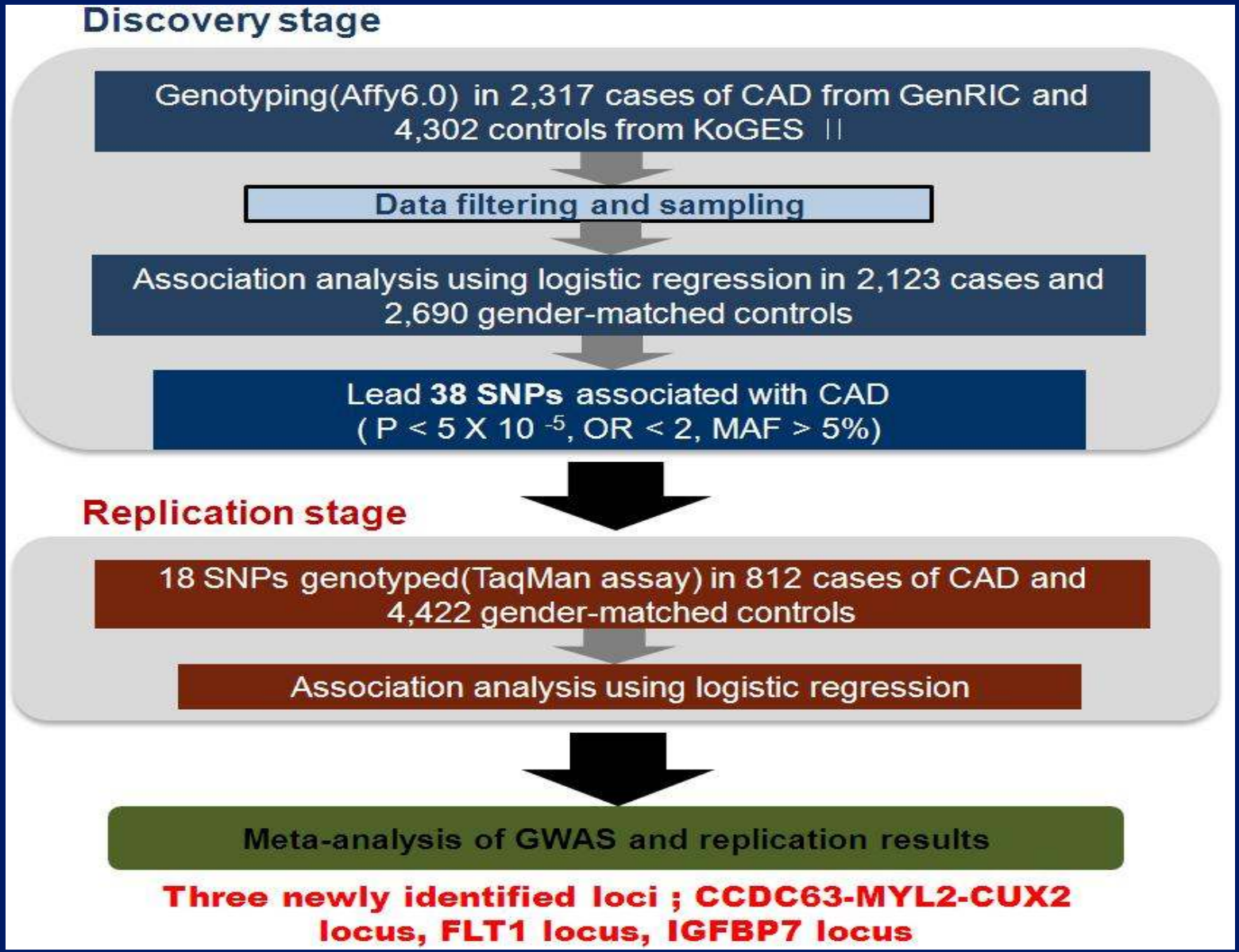
Table 2 Stage 1, Stage 2 and combined Stage 1 and Stage 2 samples association results for risk of coronary artery disease at single nucleotide polymorphisms in 9p21 with p<1e−04 in the combined sample

Single nucleotide polymorphism	Allele		Stage	Genotypes minor homozygous/heterozygous/major homozygous		Minor allele frequency		OR for risk allele (95% CI)	p Value
	Minor	Risk		Control	Case	Control	Case		
rs6475606	C	T	S1	24/124/120	13/80/132	0.32	0.24	1.55 (1.16 to 2.07)	3.24e−03
			S2	123/450/474	98/458/580	0.33	0.29	1.22 (1.08 to 1.39)	2.00e−03
			S1&S2	147/574/594	111/538/712	0.33	0.28	1.27 (1.13 to 1.43)	5.75e−05
rs4977574	G	G	S1	44/133/91	63/117/45	0.41	0.54	1.71 (1.31 to 2.22)	6.74e−05
			S2	199/522/345	274/569/315	0.43	0.48	1.22 (1.08 to 1.37)	1.27e−03
			S1&S2	243/655/436	337/686/360	0.43	0.49	1.29 (1.16 to 1.44)	4.61e−06
rs2891168	G	G	S1	43/134/91	63/116/45	0.41	0.54	1.73 (1.32 to 2.25)	5.16e−05
			S2	199/524/351	274/569/316	0.43	0.48	1.23 (1.09 to 1.38)	7.59e−04
			S1&S2	242/658/442	337/685/361	0.43	0.49	1.3 (1.17 to 1.45)	2.27e−06
rs1333042	A	G	S1	27/130/106	14/90/119	0.35	0.26	1.53 (1.15 to 2.04)	3.82e−03
			S2	156/473/455	122/490/555	0.36	0.31	1.23 (1.09 to 1.39)	1.04e−03
			S1&S2	183/603/561	136/580/674	0.36	0.31	1.27 (1.13 to 1.42)	3.71e−05
rs1333048	C	C	S1	55/134/76	71/119/35	0.46	0.58	1.68 (1.29 to 2.19)	1.38e−04
			S2	232/515/326	310/574/273	0.46	0.52	1.26 (1.12 to 1.42)	1.28e−04
			S1&S2	287/649/402	381/693/308	0.46	0.53	1.32 (1.18 to 1.47)	4.95e−07
rs1333049	C	C	S1	54/137/76	72/118/33	0.46	0.59	1.75 (1.34 to 2.29)	4.51e−05
			S2	232/519/334	309/574/282	0.45	0.51	1.25 (1.12 to 1.41)	1.50e−04
			S1&S2	286/656/410	381/692/315	0.45	0.52	1.32 (1.19 to 1.47)	3.08e−07

The most notable association with CAD was observed on chromosome 9p21.3.
The strongest signal was at rs1333049.
These results replicate signals first observed in Caucasians and subsequently observed in a variety of Asians including Japanese, Korean and Chinese Han.

Cho E *et al*. Heart Asia 2010;104-108

Schematic Overview of Identification of CAD Causative SNPs by GWAS [GenRIC Study]



Results of a meta-analysis for SNPs identified from both the GWAS and the replication cohorts

				GWAS - Korea				Replication - Japan				Combined analysis		
SNP	Chromosome	Gene	Func	Allele	N	OR	P	Allele	N	OR	P	OR	p	het.(*P*)
Previous publications														
rs4537545	**1q21.3e**	***IL6R***	**i**	**T**	**4735**	**0.8356**	**2.39E-05**	**T**	**5234**	**0.8936**	**0.04297**	**0.8659**	**4.74E-05**	**0.3376**
rs7588415	**2p24.1c**	***APOB***		**A**	**4778**	**0.7578**	**2.74E-05**	**A**	**5233**	**0.8232**	**0.02587**	**0.7914**	**2.47E-05**	**0.4498**
rs1333049	**9p21.3c**			**C**	**4770**	**1.263**	**3.30E-08**	**C**	**5000**	**1.47**	**1.8E-14**			
New identified loci														
rs1111782	9p21.2a	*TEK*	i	A	4716	0.8101	7.32E-07	T	5234	0.952	0.3684	0.8816	3.46E-04	0.0198
rs12114277	8q22.3b	*UBR5*	i	A	4674	0.8082	8.43E-07	A	5233	1.016	0.764	0.912	8.70E-03	9.00E-04
rs219822	7q22.1a	*TRRAP*	i	A	4783	1.229	9.64E-07	A	5232	1.068	0.2277	1.1422	1.35E-04	4.12E-02
rs12705702	7q31.1b			T	4781	0.8263	4.17E-06	G	5232	1.039	0.4792	0.9314	4.06E-02	8.00E-04
rs1163072	10q24.33			T	4780	1.203	1.04E-05	G	5231	1.051	0.3571	1.1208	9.86E-04	0.0487
rs41391154	3p26.1a	*GRM7*	i	T	4775	0.7166	1.24E-05	T	5233	0.9898	0.9076	0.8487	5.05E-03	0.0055
rs886126	12q24.11d	*CUX2*	i	C	4756	0.8244	1.31E-05	C	5232	0.9654	5.45E-01	0.8958	2.92E-03	0.0309
rs10012505	4q34.1b	*GALNT17*	i	G	4662	0.7661	1.67E-05	C	5233	0.9422	0.4594	0.8547	2.35E-03	0.0416
rs2122149	4q13.1a			A	4674	1.277	1.87E-05	A	5231	1.03	0.6516	1.14	2.96E-03	0.0138
rs9944810	18q21.31	*ALPK2*	cn	C	4783	0.8326	2.08E-05	C	5234	0.9488	0.3364	0.8914	1.09E-03	0.0603
SNP1	**12**	***MYL2***	**i**	**C**	**4762**	**1.255**	**2.13E-05**	**G**	**5232**	**1.262**	**9.85E-05**	**1.2586**	**1.13E-08**	**0.9446**
SNP2	**13**	***FLT1***	**i**	**C**	**4789**	**1.192**	**2.34E-05**	**G**	**5231**	**1.148**	**1.09E-02**	**1.1688**	**6.35E-06**	**0.5817**
SNP3	**4**	***IGFBP7***	**i**	**G**	**4781**	**1.187**	**3.27E-05**	**C**	**5233**	**1.116**	**0.04156**	**1.1491**	**4.91E-05**	**0.3625**

Hum Mol Genet [IF 8.058] Submitted

European Heart Journal
doi:10.1093/eurheartj/ehr267

Common variants in *RYR1* are associated with left ventricular hypertrophy assessed by electrocardiogram

Kyung-Won Hong[1†], Dong-Jik Shin[2,3†], Sang-Hak Lee[2,4], Nak-Hoon Son[2], Min-Ji-Eun Lim[1], Chol Shin[6], Yangsoo Jang[2,4*], and Bermseok Oh[1*]

[1]Department of Biomedical Engineering, School of Medicine, Kyung Hee University, #1 Hoeki-dong, Dongdaemun-gu, Seoul 130-702, Republic of Korea; [2]Cardiov Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei University Research Institute of Science for Aging, Yonsei University, Seoul, R [4]Severance Medical Research Institute, Yonsei University Health System, #250 Seongsanno, Seodaemun-gu, Seoul 120-752, Republic of Korea; [5]Center for Gen National Institute of Health, Seoul, Republic of Korea; and [6]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Korea University Ansan, Republic of Korea

Received 29 November 2010; revised 2 June 2011; accepted 7 July 2011

Aims To identify the genetic risk factors that influence the development of electrocardiographic (ECG) le hypertrophy (LVH), a major risk factor for cardiovascular (CV) morbidity and mortality.

Methods and results We performed a genomewide association study (GWAS) of ECG-LVH, in which the community-based K ation REsource (KARE) study (8432 controls and 398 cases) was analysed by Affymetrix SNP array 5.0 results were validated in hospital-based samples (597 controls and 207 cases). Fourteen single-nucleotid isms (SNPs) in eight genetic loci (5q35.1, 6p22.3-22.1, 8q24.2, 11p15, 11q21-22.1, 14q12, 17q11.2, and 1 associated with ECG-LVH in the original GWAS study ($P < 1 \times 10^{-5}$). Of these SNPs, 12 were genc hospital sample. There was consistent association with the 19q13.1 region which contains *RYR1* gene. nificant SNP in the region was rs10500279, which had genomewide significance in the combined GWA sample [odds ratio = 1.58 (confidence interval: 1.35–1.85), $P = 1.0 \times 10^{-8}$]. Mutations in *RYR1*, whi major Ca^{2+} channel in the skeletal muscle, have been reported to correlate with CV diseases.

Conclusion We performed the first GWAS for ECG-LVH, implicating the skeletal muscle Ca^{2+} channel protein RYR risk factor. These results might increase our understanding of the development of ECG-LVH.

REPORT

Adiponectin Concentrations: A Genome-wide Association Study

Sun Ha Jee,[1,2,11,*] Jae Woong Sull,[3,11] Jong-Eun Lee,[4] Chol Shin,[5] Jongkeun Park,[6,7] Heejin Kimm,[1] Eun-Young Cho,[4] Eun-Soon Shin,[4] Ji Eun Yun,[1] Ji Wan Park,[8] Sang Yeun Kim,[1] Sun Ju Lee,[1] Eun Jung Jee,[1] Inkyung Baik,[9] Linda Kao,[2] Sungjoo Kim Yoon,[6,7] Yangsoo Jang,[10,*] and Terri H. Beaty[2]

Adiponectin is associated with obesity and insulin resistance. To date, there has been no genome-wide association study (GWAS) of adiponectin levels in Asians. Here we present a GWAS of a cohort of Korean volunteers. A total of 4,001 subjects were genotyped by using a genome-wide marker panel in a two-stage design (979 subjects initially and 3,022 in a second stage). Another 2,304 subjects were used for follow-up replication studies with selected markers. In the discovery phase, the top SNP associated with mean log adiponectin was rs3865188 in *CDH13* on chromosome 16 ($p = 1.69 \times 10^{-15}$ in the initial sample, $p = 6.58 \times 10^{-39}$ in the second genome-wide sample, and $p = 2.12 \times 10^{-32}$ in the replication sample). The meta-analysis p value for rs3865188 in all 6,305 individuals was 2.82×10^{-83}. The association of rs3865188 with high-molecular-weight adiponectin ($p = 7.36 \times 10^{-58}$) was even stronger in the third sample. A reporter assay that evaluated the effects of a *CDH13* promoter SNP in complete linkage disequilibrium with rs3865188 revealed that the major allele increased expression 2.2-fold. This study clearly shows that genetic variants in *CDH13* influence adiponectin levels in Korean adults.

ORIGINAL ARTICLE

Interaction between *GNB3* C825T and *ACE* I/D polymorphisms in essential hypertension in Koreans

Y Bae[1], C Park[1], J Han[1], Y-J Hong[2], H-H Song[2], E-S Shin[3], J-E Lee[3], B-G Han[4], Y Jang[1], D-J Shin[1,7] and SK Yoon[5,6,7]

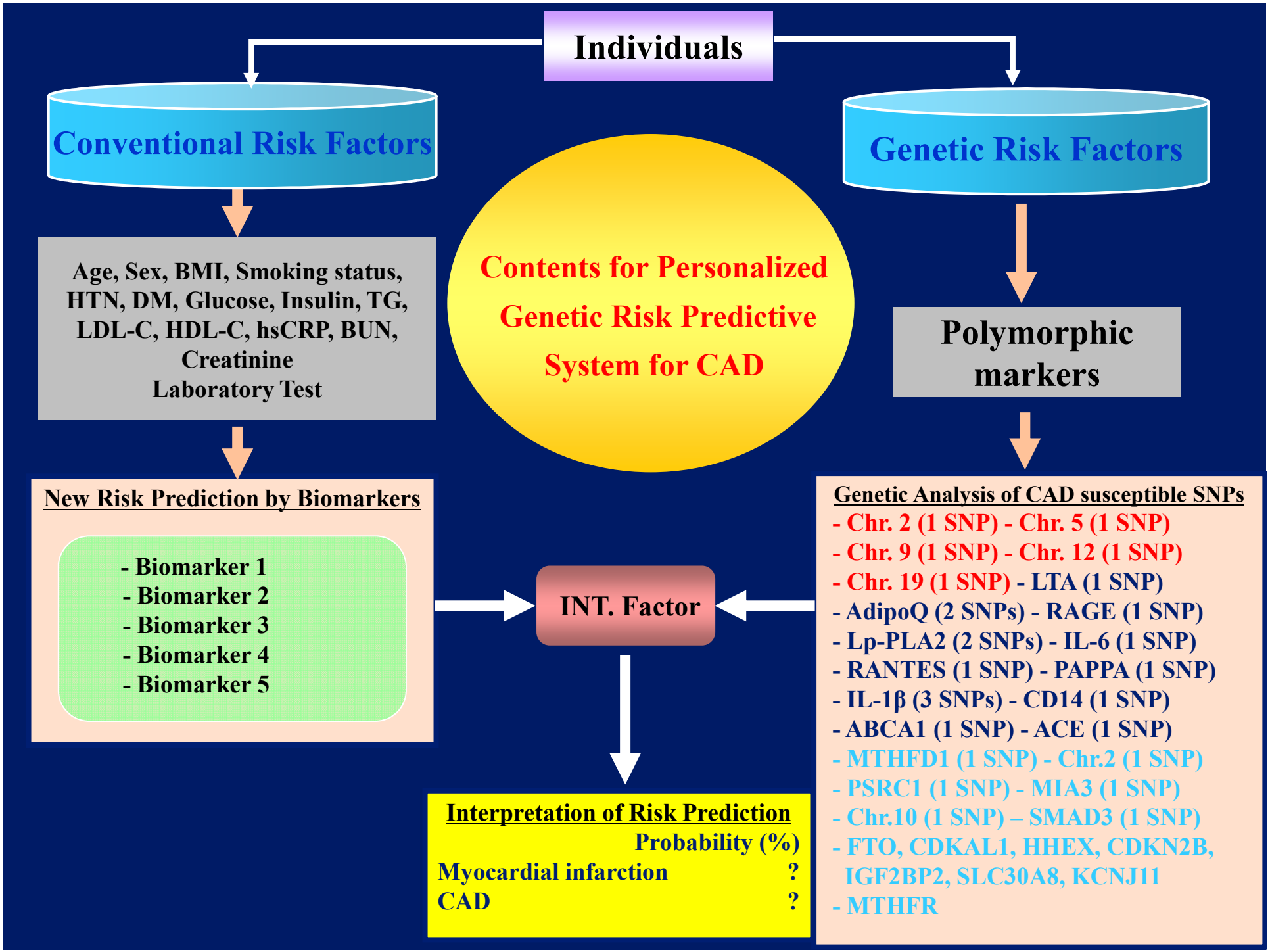
[1]*Cardiovascular Genome Center, Yonsei University College of Medicine, Seoul, Republic of Korea;* [2]*Department of Biostatistics, The Catholic University of Korea, Seoul, Republic of Korea;* [3]*DNA Link Inc, Seoul, Republic of Korea;* [4]*Division of Genome Resources, NGRI, NIH, Seoul, Republic of Korea;* [5]*Research Institute of Molecular Genetics, The Catholic University of Korea, Seoul, Republic of Korea and* [6]*Department of Biomedical Sciences, The Catholic University of Korea, Seoul, Republic of Korea*

Essential hypertension (EH) is considered a typical polygenic disease, so the evaluation of gene–gene interactions rather than the determination of single gene effects is crucial to understanding any genetic influences. The G-protein β3-subunit (*GNB3*) 825T allele, associated with enhanced G-protein signalling, is a strong candidate for interactions with polymorphisms, such as insertion/deletion (I/D) polymorphism of angio- genotypes for the *GNB3* C825T and *ACE* I/D polymorphisms were not found to be significantly associated with hypertensive status in either males or females. Logistic regression analysis indicated that the *GNB3* 825T allele carriers were positively associated with EH in males (odds ratio (OR) for TT/CT, 1.459; 95% confidence interval (CI), 1.048–2.033, $P = 0.0255$). In analysis of gene–gene interaction, we found that there was a

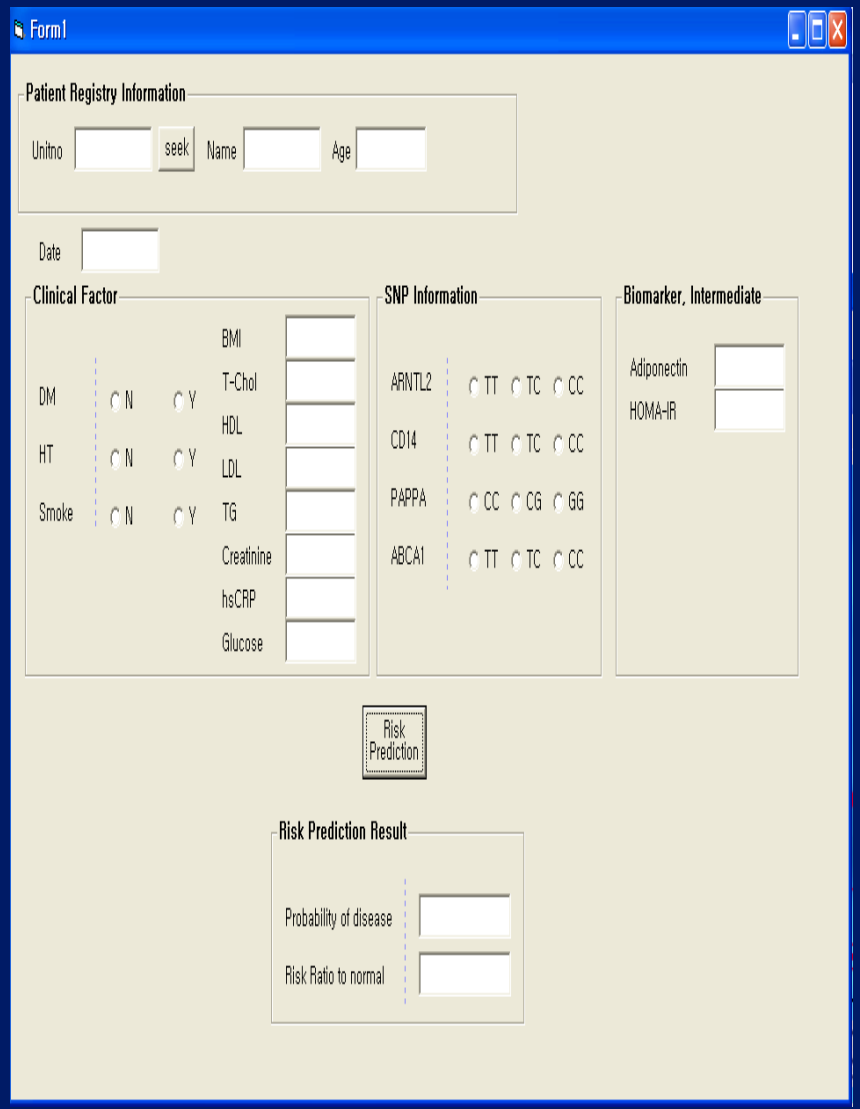
Relation of Genetic Polymorphisms in the Cytochrome P450 Gene With *Clopidogrel* Resistance After Drug-Eluting Stent Implantation in Koreans

Jung Myung Lee, MD[a], Sungha Park, MD, PhD[a], Dong-Jik Shin, PhD[a,b], Donghoon Choi, MD, PhD[a], Chi Young Shim, MD[a], Young-Guk Ko, MD, PhD[a], Jung-Sun Kim, MD, PhD[a], Eun-Soon Shin, PhD[c], Chong Won Chang, MS[d], Jong-Eun Lee, PhD[c], and Yangsoo Jang, MD, PhD[a,*]

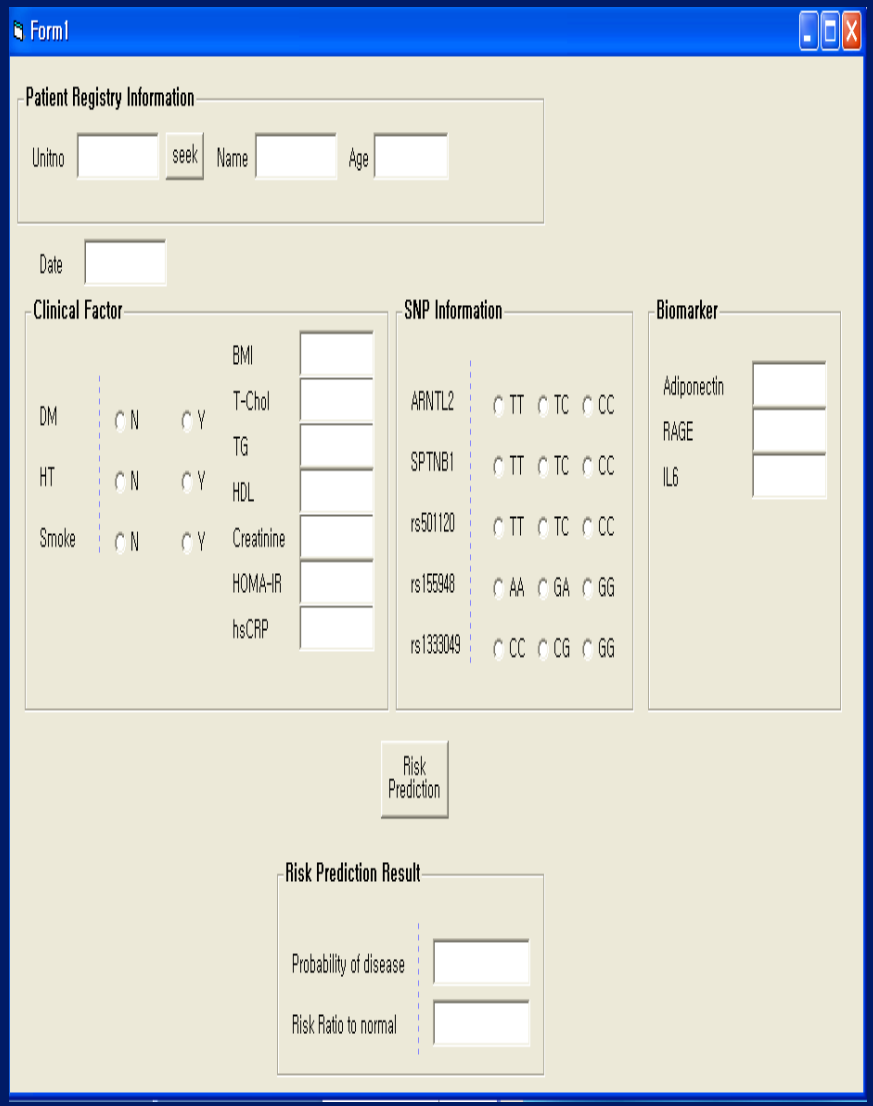
Clopidogrel is a prodrug that has to be converted to an active metabolite by hepatic cytochrome P450 (CYP) isoenzymes to inhibit platelet aggregation. Individual variability of platelet inhibition by clopidogrel suggests a possibility for genetic factors having a significant influence on clopidogrel responsiveness. In this study, we sought to determine the relation of genetic polymorphisms of *CYP* genes to clopidogrel resistance in Koreans. Four hundred fifty patients who underwent successful percutaneous coronary intervention with drug-eluting stents were randomly assigned to treatment with dual antiplatelet regimen (aspirin plus clopidogrel) or triple antiplatelet regimen (aspirin plus clopidogrel plus cilostazol). Clopidogrel resistance using VerifyNow P2Y12 assay and genetic analysis were performed in 387 patients. Clopidogrel resistance was found in 112 patients (28.9%). In the clopidogrel-responsive group, there was a significantly higher proportion of cilostazol use. Because cilostazol showed a significant influence on clopidogrel resistance, we examined the association of single-nucleotide polymorphisms and clopidogrel resistance in the dual and triple antiplatelet therapy groups, respectively. In all subjects, the *CYP2C19*3A* allele was significantly more prevalent in the clopidogrel-resistant group compared with the clopidogrel-responsive group. Multiple logistic regression analysis demonstrated that *CYP2C19*3* is an independent predictor of clopidogrel resistance. In conclusion, *CYP2C19*3* single-nucleotide polymorphisms is an independent risk factor of clopidogrel resistance in Korean subjects with coronary artery disease. (Am J Cardiol 2009;104:46–51)


Individuals
Conventional Risk Factors
Genetic Risk Factors
Age, Sex, BMI, Smoking status,
HTN, DM, Glucose, Insulin, TG,
LDL-C, HDL-C, hsCRP, BUN,
Creatinine
Laboratory Test
Contents for Personalized
Genetic Risk Predictive
System for CAD
Polymorphic
markers
New Risk Prediction by Biomarkers
- Biomarker 1
- Biomarker 2
- Biomarker 3
- Biomarker 4
- Biomarker 5
INT. Factor
Genetic Analysis of CAD susceptible SNPs
- Chr. 2 (1 SNP) - Chr. 5 (1 SNP)
- Chr. 9 (1 SNP) - Chr. 12 (1 SNP)
- Chr. 19 (1 SNP) - LTA (1 SNP)
- AdipoQ (2 SNPs) - RAGE (1 SNP)
- Lp-PLA2 (2 SNPs) - IL-6 (1 SNP)
- RANTES (1 SNP) - PAPPA (1 SNP)
- IL-1β (3 SNPs) - CD14 (1 SNP)
- ABCA1 (1 SNP) - ACE (1 SNP)
- MTHFD1 (1 SNP) - Chr.2 (1 SNP)
- PSRC1 (1 SNP) - MIA3 (1 SNP)
- Chr.10 (1 SNP) – SMAD3 (1 SNP)
- FTO, CDKAL1, HHEX, CDKN2B,
IGF2BP2, SLC30A8, KCNJ11
- MTHFR
Interpretation of Risk Prediction
Probability (%)
Myocardial infarction ?
CAD ?

Two-stage model을 이용한 CAD 발생 위험 확률 계산 화면



One-stage model을 이용한 CAD 발생 위험 확률 계산 화면



CAD 발생 위험 예측모형 개발 결과

CAD 예측 실용 모형

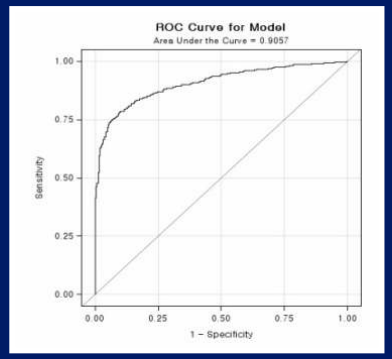
- SNPs

rs11***(ARNTL2), rs12***(SPTNB1),
rs15***(Ch5), rs13***(Ch9)

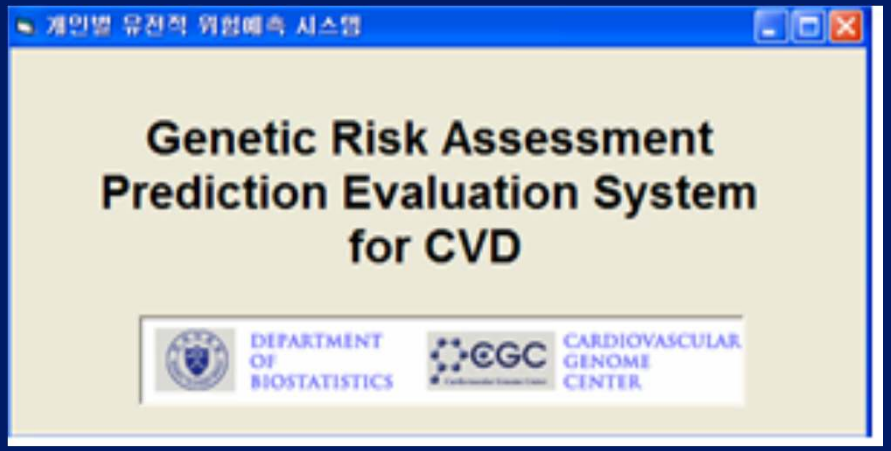
- Conventional risk factor

DM, hypertension, smoke, BMI, Total-cholesterol, Tg, HDL, Creatinine

- 민감도 80.4%, 특이도 84.5%,
  정확도 81.5%, AUC 0.906

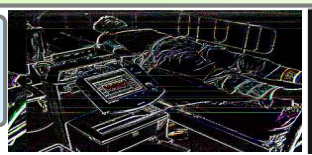


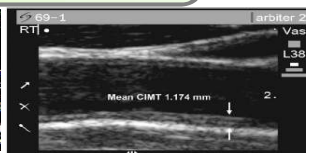
타당성 평가
(GenRIC + KCDC 자료)
민감도 100%,
특이도 73.5%,
정확도 86.5%



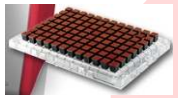
Genome-Wide Association Study for Arterial stiffness

Sample set selection (280 case/325 controls)





AFFYMETRIX



Affymetrix Axiom™ Asian-optimized panel assay

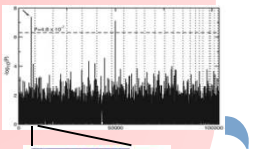
Selection criteria: P<0.001 SNPs

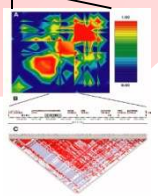
No. of assay SNPs : 579,759
Call rate : 98%

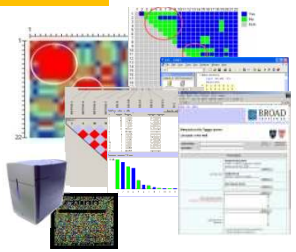
Association analysis & Gene/SNP selection

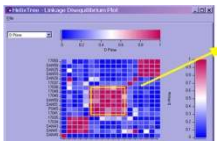
No. of P<0.001 SNPs : 1,035
No. of candidate genes : 6

*S***** gene re-sequencing &
Customized Targeted SNP Genotyping









No. of *S***** TagSNPs : 18

Replication study: Independent sample set

P<0.001 SNPs

Development for Early diagnostic kit contents

Genome-Wide Association Study for Kawasaki disease

1차 GWAS 및 유의 유전자 re-sequencing

Sample set 선정 (환자군 103 / 대조군 434)

AFFYMETRIX

Affymetrix Gene Chip® 500K Array

빈도 차이 $P < 10^{-4}$ SNP 선발

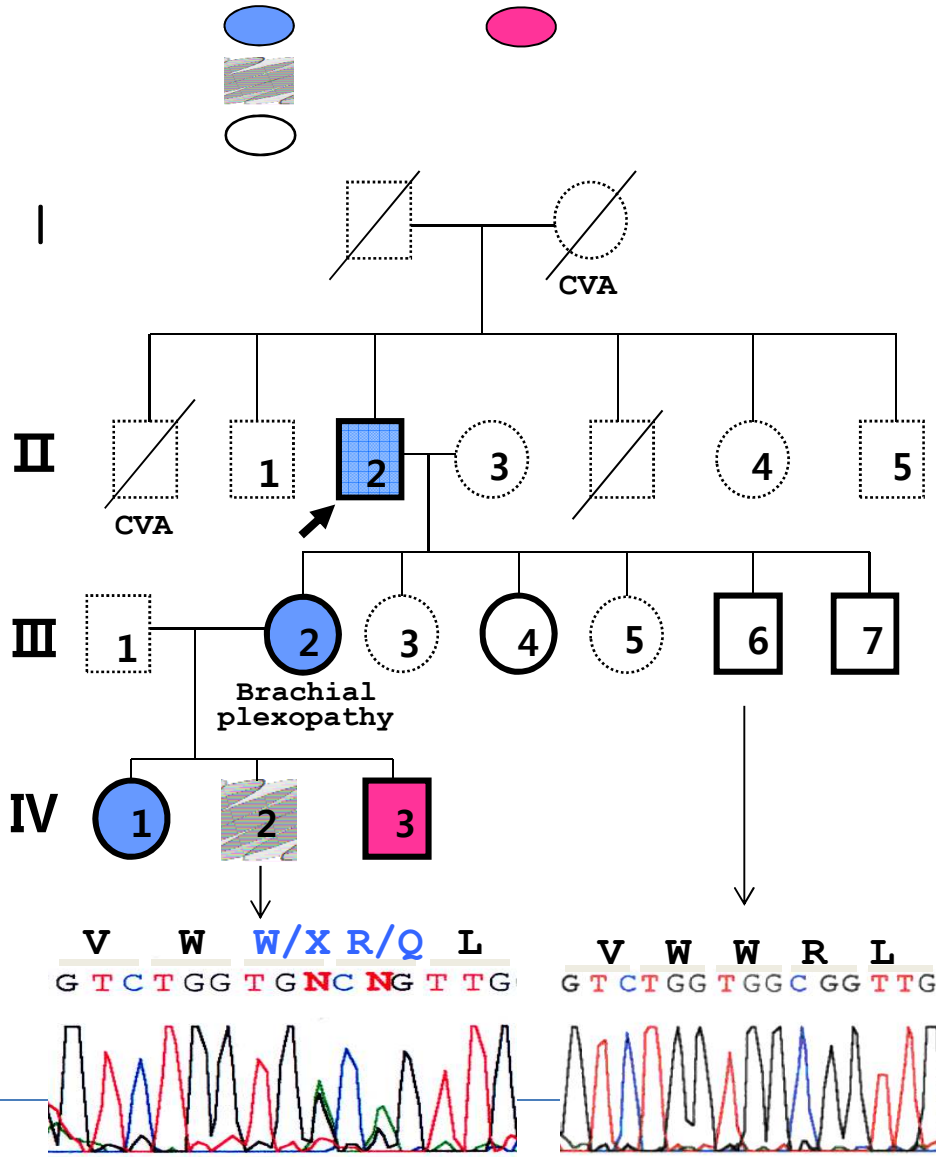
Association analysis

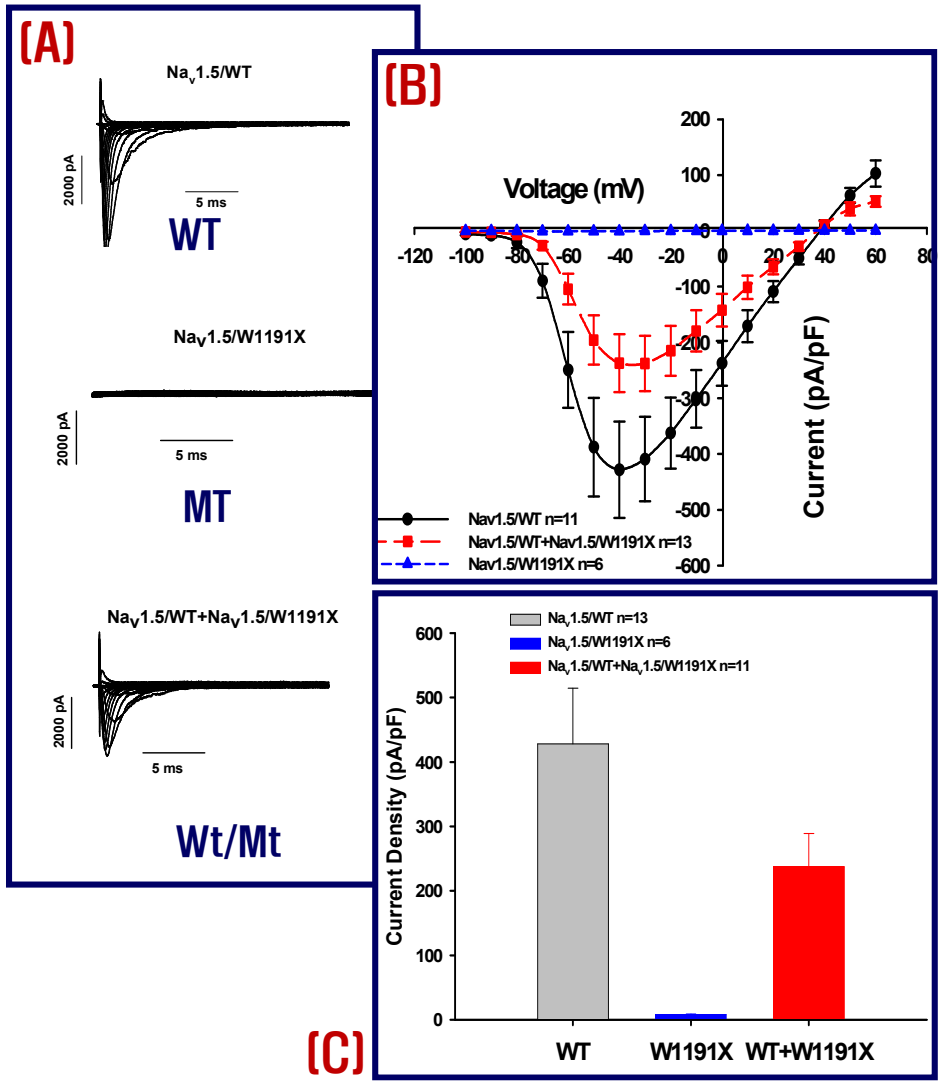
168 유전자 377 SNP 발굴

Validation SNP set 구축 / 1종 re-sequencing

Position	# of SNPs ($p < 10^{-4}$)
Exon	1
Intron	105
Promoter	5
5'-UTR	20
3'-UTR	2
Downstream	6
Intergenic	198
	337

Characterization of *SCN5A* (W1191X) in Brugada Syndrome

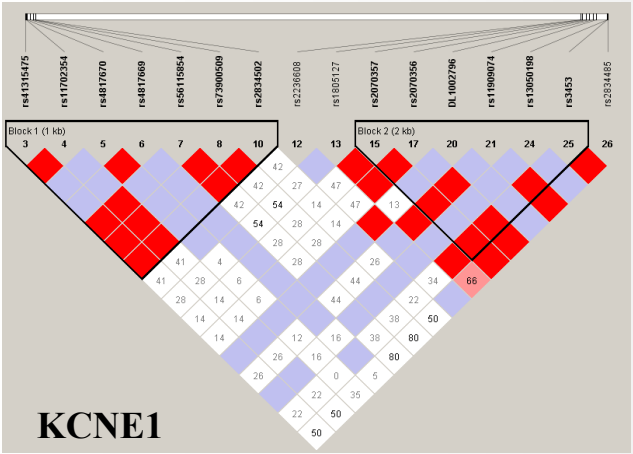


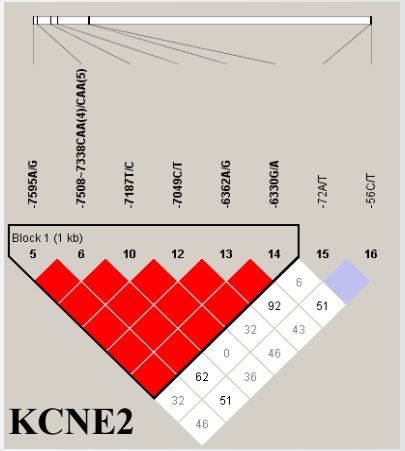


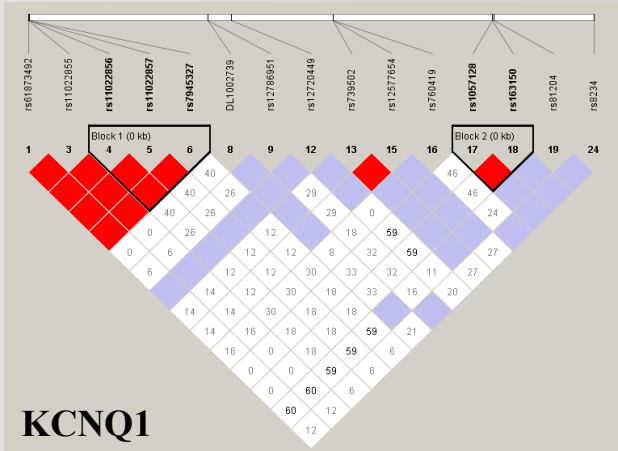
W1191X is a functional mutant

DJ Shin et al., Life Sci, 2007, 80:716 -724

Association of Atrial Fibrillation & *K* channel gene variants







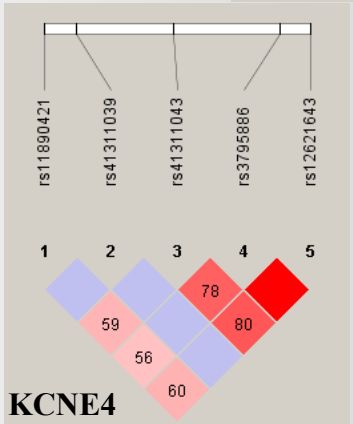
Sample set [AF: 354, control: 400]

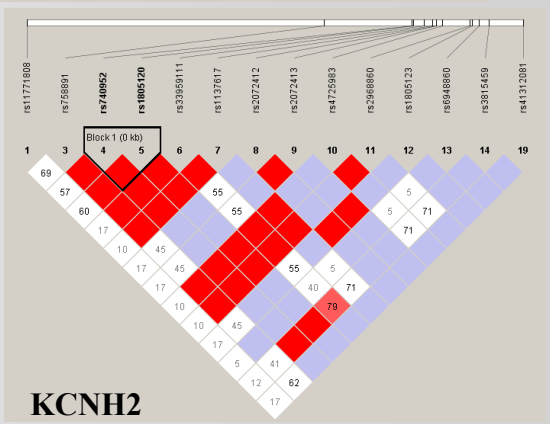
Direct sequencing for SNP discovery

34 Tag SNPs genotyping : TaqMan assay

SNP/haplotype : Association study

Significant SNPs: functional study

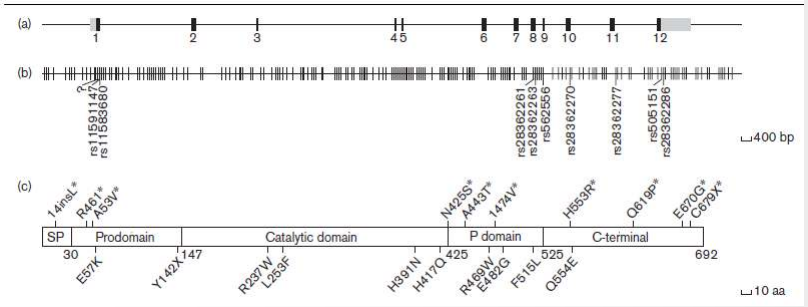


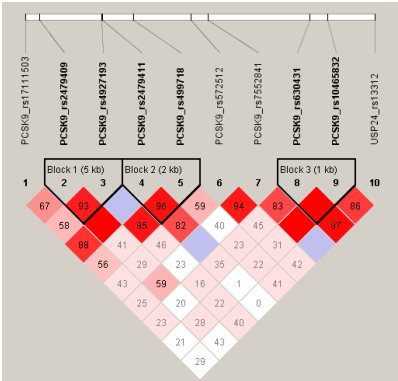


	Male	
Gene haplotype	OR (95% CI)	P
KCNE1 AAG*	2.238 (1.11–4.48)	0.021
KCNQ1 AGGCCAGCG**	2.103 (1.15–3.86)	0.015

Manuscript in preparation

PCSK9 & Hypercholesterolemia





Case 340, control 355

↓

Direct sequencing (24)

↓

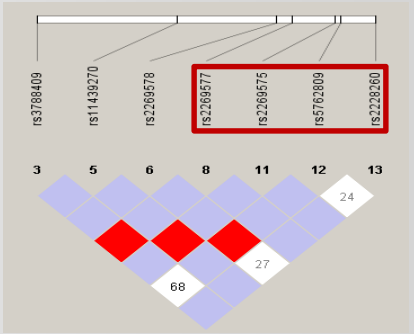
10 TagSNPs/Association

haplotype	OR (95% CI)	P
GATCCTCAG*	1.864 (1.10–3.15)	0.019
GGTCCTCAG*	1.560 (1.06–2.31)	0.024

*Adjusted for age, sex

- 2종의 haplotype을 보유한 사람은 정상인에 비해 hypercholesterolemia에 대한 감수성이 유의하게 높음

XBP1 & Hypercholesterolemia



Male

Locus/haplotype	OR (95% CI)	P
Rs57*****	1.78 (1.05–3.01)	0.028
haplotype CACG*	2.02 (1.18–3.45)	0.010

*Adjusted for age, sex

All

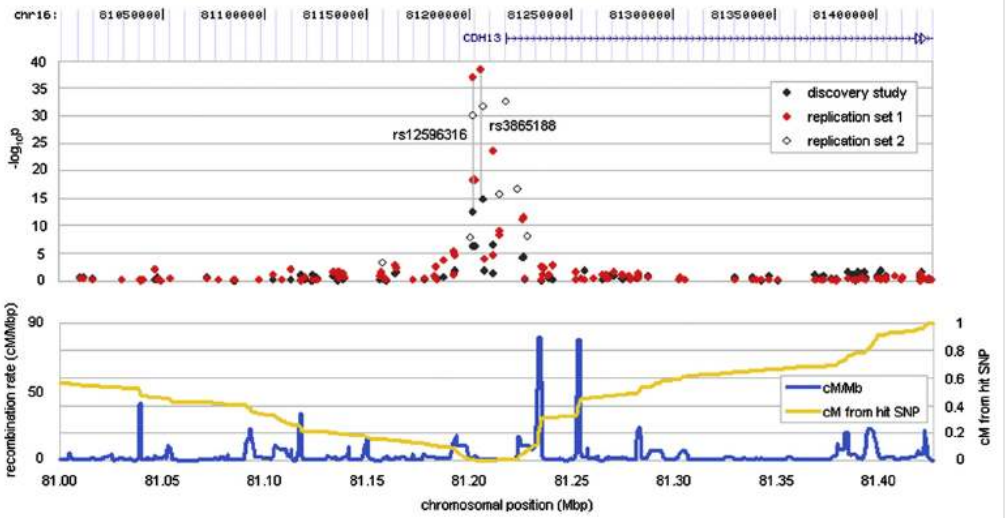
Locus/haplotype	P	Mean Tg
Rs22*****	0.015	증가
haplotype CGTG*	0.016	증가

*Adjusted for age, sex

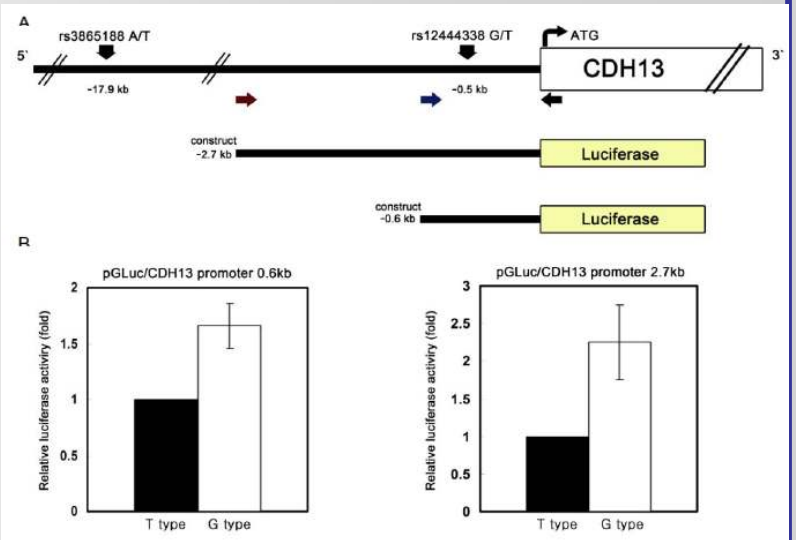
rs57**** A carriers에서 질환 위험이 78% 증가, rs22**** T형을 보유한 사람은 혈중 Tg의 농도가 유의하게 높아져 HC 위험 증가

Association of Adiponectin Concentration & *CDH13* SNPs

A)



C)



B)

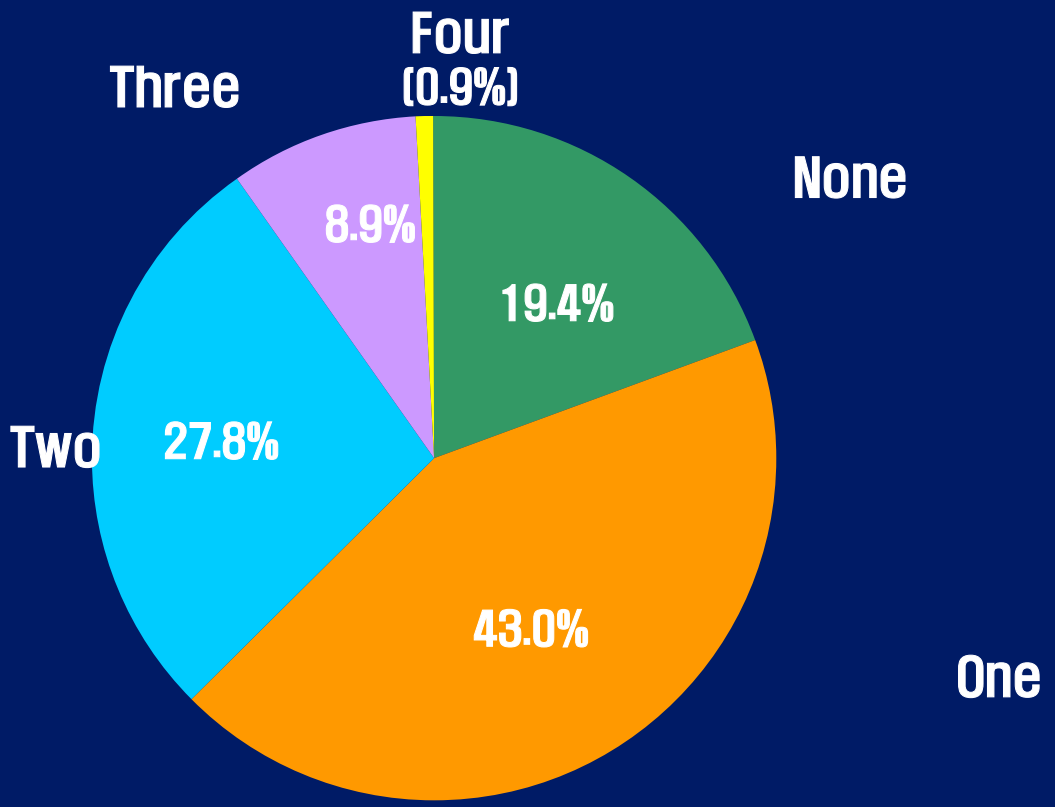
Table 3. Two Most Strongly Associated SNPs from the Seoul Project for Log_{10}(Total Adiponectin) Based on Linear Regression Model and Meta-analysis Results in 6,305 Samples

	Seoul	Ansan	Bundang-gu			
SNP	Effect Size (SE) (μg/ml)	Effect Size (SE) (μg/ml)	Effect Size (SE) (μg/ml)	Meta-analysis Effect Size (μg/ml)	Meta-analysis p Value	Meta-analysis Heterogeneity Q (p)
rs3865188	−0.095 (0.0118)	−0.096 (0.0073)	−0.079 (0.0066)	−0.09	2.82×10^{-83}	3.58 (0.167)
rs12596316	−0.088 (0.012)	−0.096 (0.0074)	−0.076 (0.0065)	−0.09	3.09×10^{-77}	4.13 (0.1268)

p values were calculated under a linear regression under an additive model incorporating age, sex, smoking status, and body mass index as covariates. Effect sizes are given with standard error (SE).

Am J Hum Genet 87(4): 545–552 (2010), IF 11.680

허혈성 심장질환 환자들에서의 주요 위험요인 동반개수



Total patients=87 869
CHD=coronary heart disease
†smoking, hypertension, hypercholesterolaemia and diabetes mellitus

1/3 to 1/2 of CHD disease occurs in patients classified as low risk by conventional Risk factors

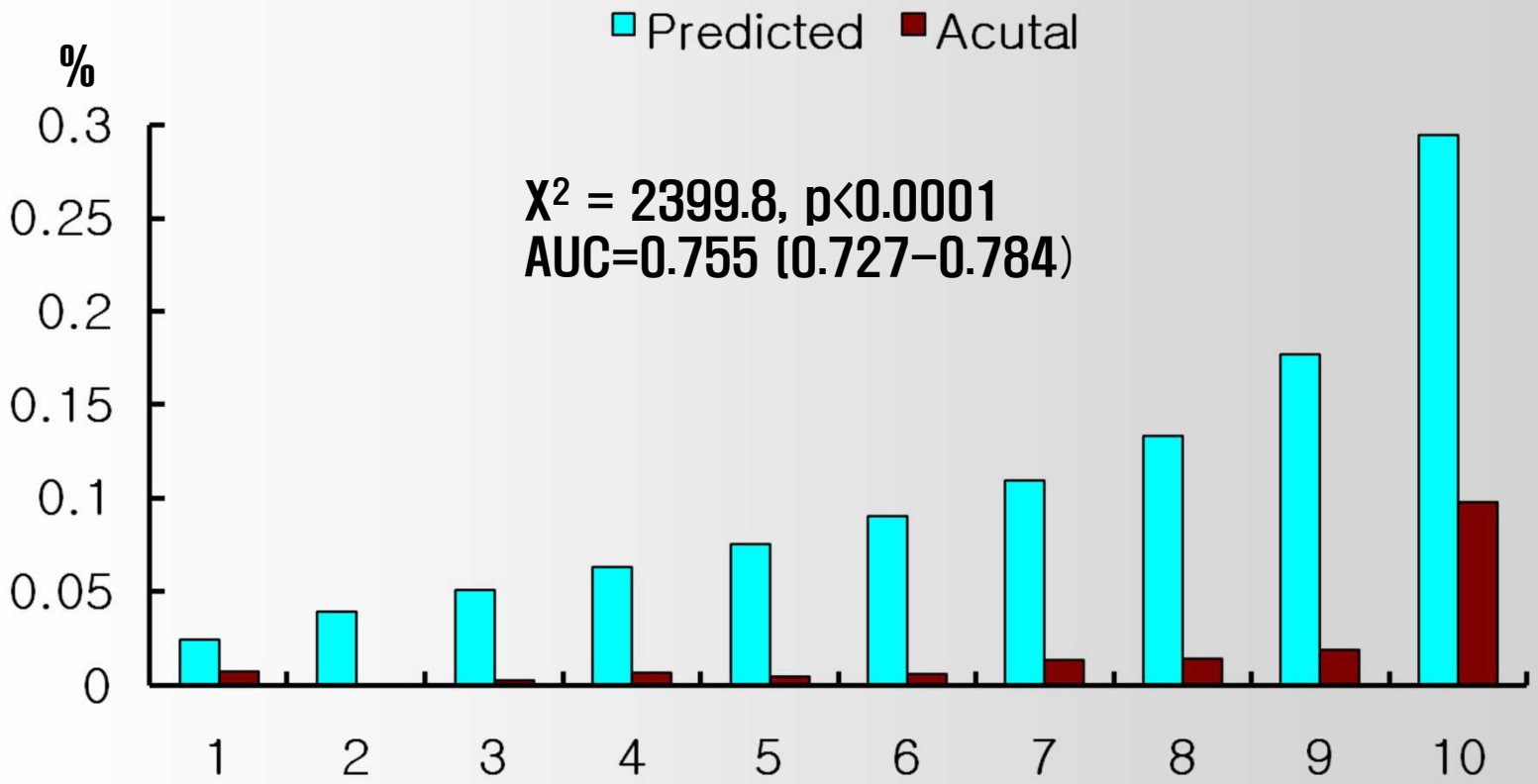
Khot UN *et al. JAMA* 2003; 290: 898–904

국가별 CVD 발생률 요약

- 미국인의 발생률은 남자 1000, 여자 300 수준
- 한국인의 발생률은 50-100 수준
- 중국인의 발생률은 60-150 수준

➡ 미국인의 발생률은 한국인의 8-10배

10 year CVD risk in Korean men using FHS functions, 30–74

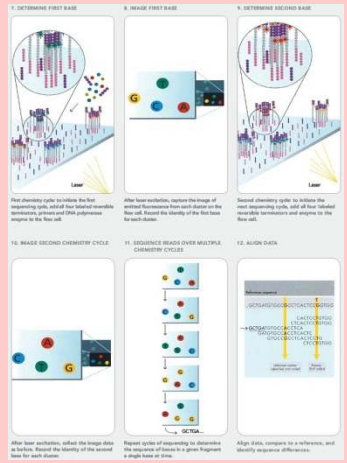


Korean Heart Study, 2010

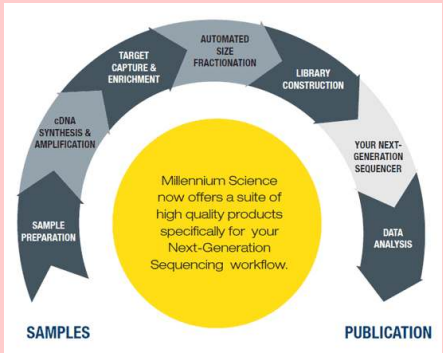
새로운 심혈관질환 예측모형 콘텐츠 발굴 전략

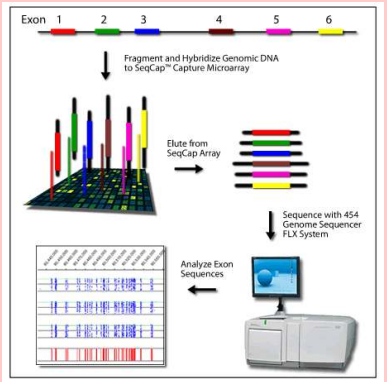
CAD case-control study (CGC)

Candidate gene approach를 통해 유의한 연관성을 나타난
유전자 가운데 GWAS SNP chip에 포함되지 않은 유전자



GenRIC study에서 발굴된
유전자 선발



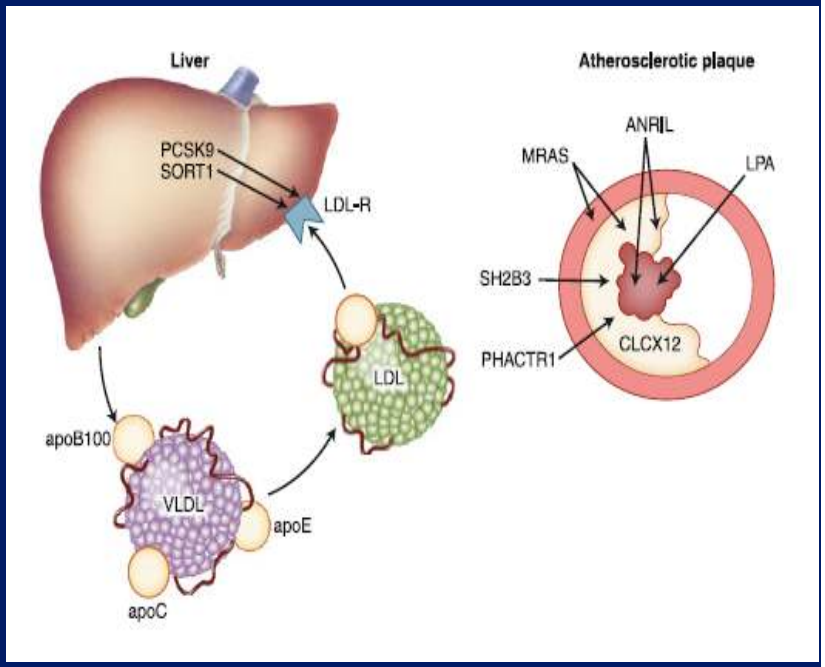


Target capture NGS analysis

SNP contents validation

17 Genetic Loci associated with CAD

Loci	Chromosomal location	SNP	RAF, %	Odds ratio per risk allele (95% CI)	Candidate genes	Putative mechanism
1	1p13	rs599839	77	1.13 (1.08–1.19)	*CELSR2, PSCR1, SORT1*	LDL mediated
	1p13	rs646776	81	1.19 (1.13–1.26)	*CELSR2, PSCR1, SORT1*	
2	2p32	rs11206510	81	1.15 (1.10–1.210	*PCSK9*	LDL mediated
3	1q41	rs3008621	72	1.10 (1.04–1.17)	*MIA3*	Unknown
	1q41	rs17465637	72	1.14 (1.10–1.19)	*MIA3*	
4	2q33	rs6725887	14	1.17 (1.11–1.19)	*WDR12*	Unknown
5	2q36	rs2972416	37	0.46	*IRS1*	Defective insulin signaling and NO production
6	3q22	rs9818870	15	1.15 (1.11–1.19)	*MRAS*	Adhesion signaling
7	6p21.31	rs2814982	16	0.49	*C6orf106*	Unknown
8	6p24	rs12526453	65	1.12 (1.08–1.17)	*PHACTR1*	Coronary calcification
9	6q26–6q27	rs2048327	18	1.20 (1.13–1.28)	*LPA,LPAL2, SLC22A3*	Promotes atherothrombosis
	6q26–6q27	rs3127599	18	1.20 (1.13–1.28)	*LPA,LPAL2, SLC22A3*	
	6q26–6q27	rs7767084	18	1.20 (1.13–1.28)	*LPA,LPAL2, SLC22A3*	
	6q26–6q27	rs10755578	18	1.20 (1.13–1.28)	*LPA,LPAL2, SLC22A3*	
	6q26–6q27	rs3798220	2	1.47 (1.35–1.60)	*LPA,LPAL2, SLC22A3*	
	6q26–6q27	rs10455872	7	1.68 (1.43–1.98)	*LPA,LPAL2, SLC22A3*	
10	7q32	rs4731702	48	0.59	*KLF14*	Unknown
11	8p22	rs1495741	22	2.85	*NAT2*	Unknown
12	9p21	rs1333049	52	1.20 (1.16–1.25)	*ANRIL, CDKN2A, CDKN2B, MTAP*	Increased proliferation of smooth muscle cells
	9p21	rs4977574	56	1.29 (1.25–1.34)	*ANRIL, CDKN2A, CDKN2B, MTAP*	
	9p21	rs10757274	48		*ANRIL, CDKN2A, CDKN2B, MTAP*	
	9p21	rs28383206	51		*ANRIL, CDKN2A, CDKN2B, MTAP*	
	9p21	rs2383207	51	1.22 (1.13–1.33)	*ANRIL, CDKN2A, CDKN2B, MTAP*	
	9p21	rs107572378	47	1.25 (1.15–1.36)	*ANRIL, CDKN2A, CDKN2B, MTAP*	
	9p21	rs10116277	48		*ANRIL, CDKN2A, CDKN2B, MTAP*	
13	10q11	rs501120	84	1.11 (1.05–1.18)	*CXCL12*	Neointima formation after arterial injury,
	10q11	rs1746048	84	1.17 (1.11–1.24)	*CXCL12*	platelet activation in atherosclerotic lesions
14	12q24	rs2259816	37	1.08 (1.05–1.11)	*HNF1A*	apoM-mediated HDL modification
15	12q24	rs3184504	40	1.13 (1.11–1.19)	*SH2B3*	Reduced anti-inflammatory activity contributes
	12q24	rs11065987	34	1.14 (1.10–1.19)	*SH2B3*	to the progression of plaques
16	16p13	rs1122608	75	1.15 (1.10–1.21)	*LDLR*	LDL-mediated
17	21q22	rs9882601	13	1.20 (1.14–1.27)	*KCNHE2, MRPS6, SLC5A3*	Unknown



Sivapalaratnam S *et al*. Curr Atheroscler Rep 2011;13:225-232

Thirty-five common variants for coronary artery disease: the fruits of much collaborative labour

John F. Peden and Martin Farrall*

Department of Cardiovascular Medicine, The Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK

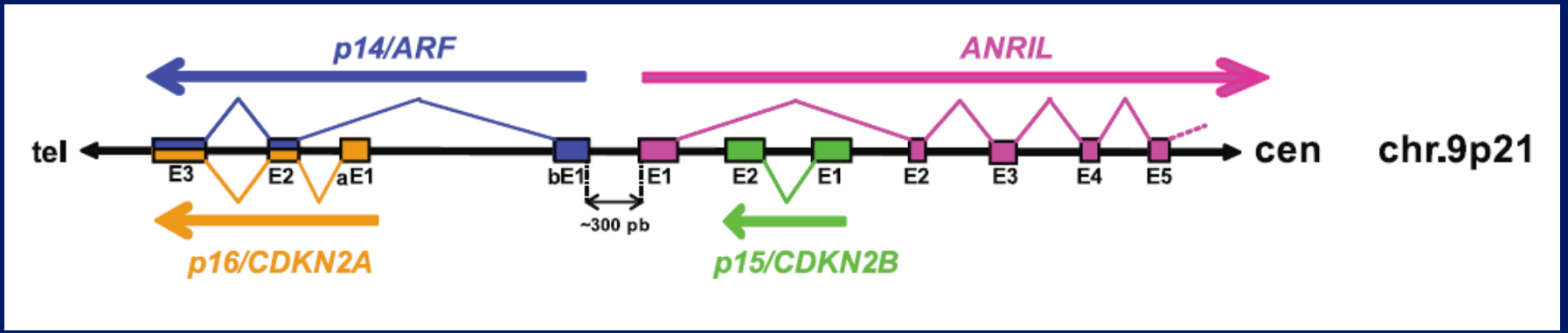
Hum Mol Genet 2011;20:R198

Chr	Position	Locus[a]	SNP	References	Reported effect EAF	OR	SNP-specific heritability (h^2_{SNP}), % K_p= 2%	K_p= 5%	K_p= 10%
1	55 496 039	PCSK9	rs11206510	MIGen (36)	0.82	1.08	0.03	0.04	0.05
1	56 962 821	PPAP2B	rs17114036	CARDIoGRAM (3)	0.91	1.17	0.07	0.09	0.11
1	109 822 166	SORT1	rs599839	Samani *et al.* (58), MIGen (36)	0.78	1.11	0.06	0.08	0.10
1	222 823 529	MIA3	rs17465637	Samani *et al.* (58), MIGen (36)	0.74	1.14	0.12	0.15	0.18
2	44 072 576	ABCG8	rs4299376	HumanCVD (8)	0.29	1.09	0.04	0.05	0.07
2	203 745 885	WDR12	rs6725887	MIGen (36)	0.15	1.14	0.07	0.09	0.11
3	138 119 952	MRAS	rs2306374	Erdmann *et al.* (59)	0.18	1.12	0.06	0.07	0.09
5	131 867 702	IL5	rs2706399	HumanCVD (8)	0.48	1.02	0.01	0.01	0.01
6	11 774 583	C6orf105	rs6903956[b]	Wang *et al.* (7)	0.07	1.51	0.35	0.45	0.56
6	12 927 544	PHACTR1	rs12526453	MIGen (36)	0.67	1.10	0.06	0.08	0.10
6	35 034 800	ANKS1A	rs17609940	CARDIoGRAM (3)	0.75	1.07	0.03	0.04	0.05
6	134 214 525	TCF21	rs12190287	CARDIoGRAM (3)	0.62	1.08	0.05	0.06	0.07
6	160 961 137	LPA	rs3798220	Clarke *et al.* (30)	0.02	1.92	0.25	0.32	0.40
6	161 010 118	LPA	rs10455872	Clarke *et al.* (30)	0.07	1.70	0.57	0.73	0.90
7	107 244 545	7q22	rs10953541	C4D 2011 (4)	0.80	1.08	0.05	0.06	0.08
7	129 663 496	ZC3HC1	rs11556924	CARDIoGRAM (3)	0.62	1.09	0.06	0.07	0.09
8	126 495 818	TRIB1	rs10808546	HumanCVD (8)	0.65	1.04	0.02	0.02	0.02
9	22 098 574	ANRIL/CDKN2BAS	rs4977574	WTCCC (60), McPherson *et al.* (61), Helgadottir *et al.* (62), Samani *et al.* (58), MIGen (36)	0.46	1.29	0.53	0.68	0.84
9	136 154 168	ABO	rs579459	CARDIoGRAM (3), Reilly *et al.* (6)	0.21	1.10	0.05	0.06	0.08
10	30 335 122	KIAA1462	rs2505083	C4D 2011 (4), Erdmann *et al.* (5)	0.38	1.07	0.05	0.06	0.08
10	44 775 824	CXCL12	rs1746048	Samani *et al.* (58), MIGen (36)	0.87	1.09	0.03	0.03	0.04
10	91 002 927	LIPA	rs1412444	C4D 2011 (4)	0.42	1.08	0.05	0.07	0.08
10	104 719 096	CYP17A1-NT5C2	rs12413409	CARDIoGRAM (3)	0.89	1.12	0.04	0.05	0.07
11	103 660 567	PDGFD	rs974819	C4D 2011 (4)	0.32	1.08	0.05	0.06	0.08
11	116 648 917	APOA1-C3-A4-A5	rs964184	CARDIoGRAM (3)	0.13	1.13	0.05	0.07	0.09
12	111 884 608	SH2B3	rs3184504	Soranzo *et al.* (63)	0.44	1.07	0.04	0.05	0.06
13	110 960 712	COL4A1-A2	rs4773144	CARDIoGRAM (3)	0.44	1.07	0.04	0.05	0.06
14	100 133 942	HHIPL1	rs2895811	CARDIoGRAM (3)	0.43	1.07	0.04	0.05	0.06
15	79 111 093	ADAMTS7	rs4380028	C4D 2011 (4), CARDIoGRAM (3), Reilly *et al.* (6)	0.60	1.07	0.05	0.06	0.08
17	2 126 504	SMG6-SRR	rs216172	CARDIoGRAM (3)	0.37	1.07	0.03	0.05	0.06
17	17 543 722	PEMT	rs12936587	CARDIoGRAM (3)	0.56	1.07	0.04	0.05	0.06
17	46 988 597	GIP-ATP	rs46522	CARDIoGRAM (3)	0.53	1.06	0.03	0.04	0.04
19	11 163 601	LDLR	rs1122608	MIGen (36)	0.77	1.14	0.10	0.12	0.15
19	45 395 619	APOE	rs2075650	HumanCVD (8)	0.14	1.14	0.07	0.09	0.11
21	35 599 128	MRPS6	rs9982601	MIGen (36)	0.15	1.18	0.11	0.14	0.18
h^2_{total}							**3.30**	**4.27**	**5.29**

ANRIL, a long, noncoding RNA, is an unexpected major hotspot in GWAS

Eric Pasmant,*,†,1 Audrey Sabbagh,*,† Michel Vidaud,*,† and Ivan Bièche*,†

*Unité Mixte de Recherche (UMR)745 Institut National de la Santé et de la Recherche Médicale (INSERM), Université Paris Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, Paris, France; and †Service de Biochimie et Génétique Moléculaire, Hôpital Beaujon, Clichy, France

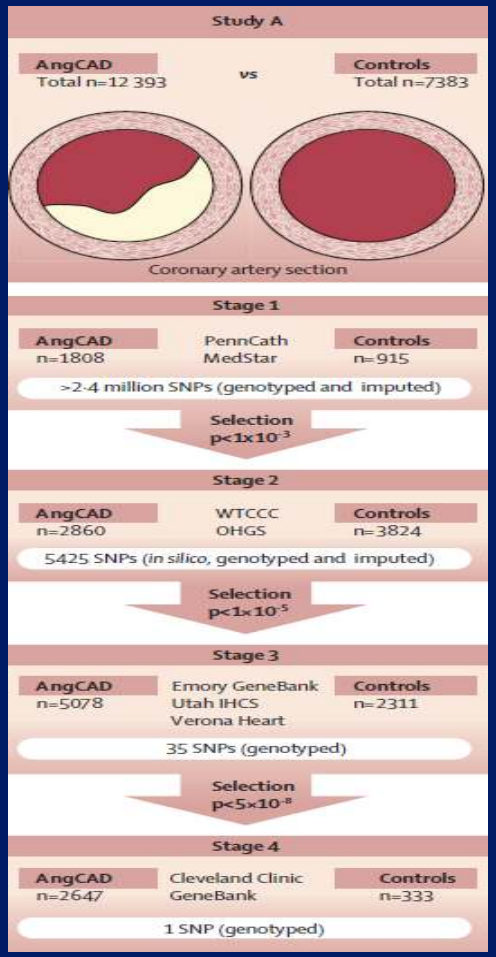


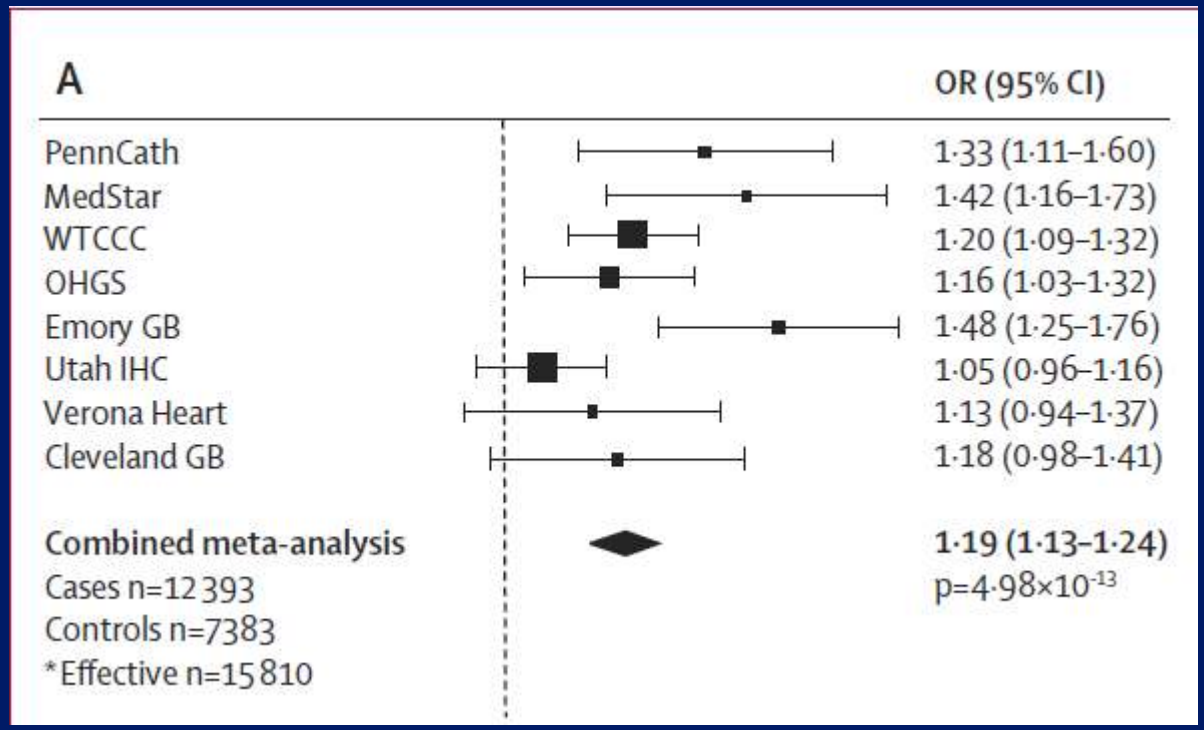
ANRIL important for expression of CDK activity and vascular proliferation

Pasmant E *et al*. FASEB J 2011;25:444-448

Identification of *ADAMTS7* as a novel locus for coronary atherosclerosis and association of *ABO* with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies

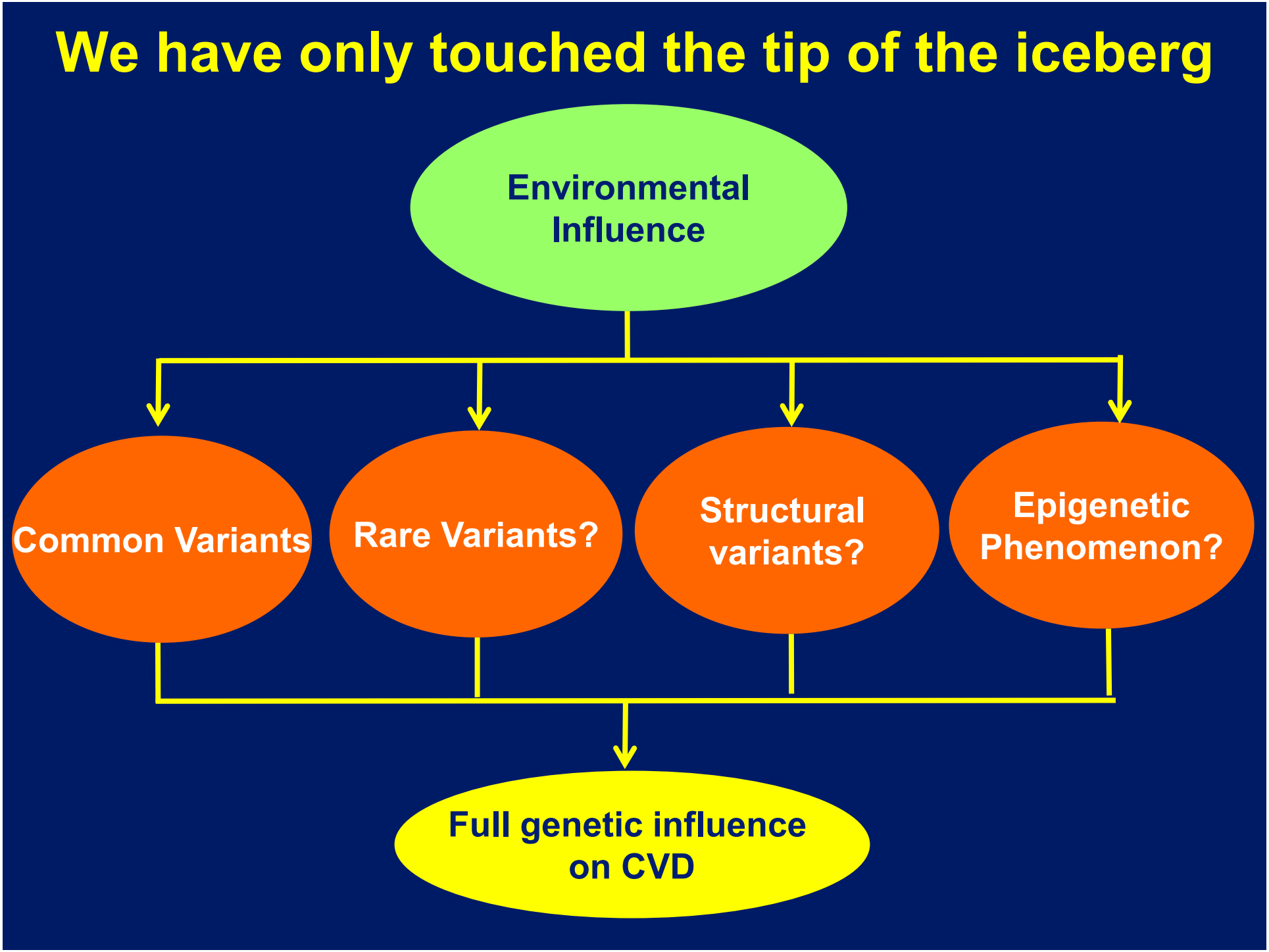
Reilly M *et al*. Lancet 2011;377:383-392

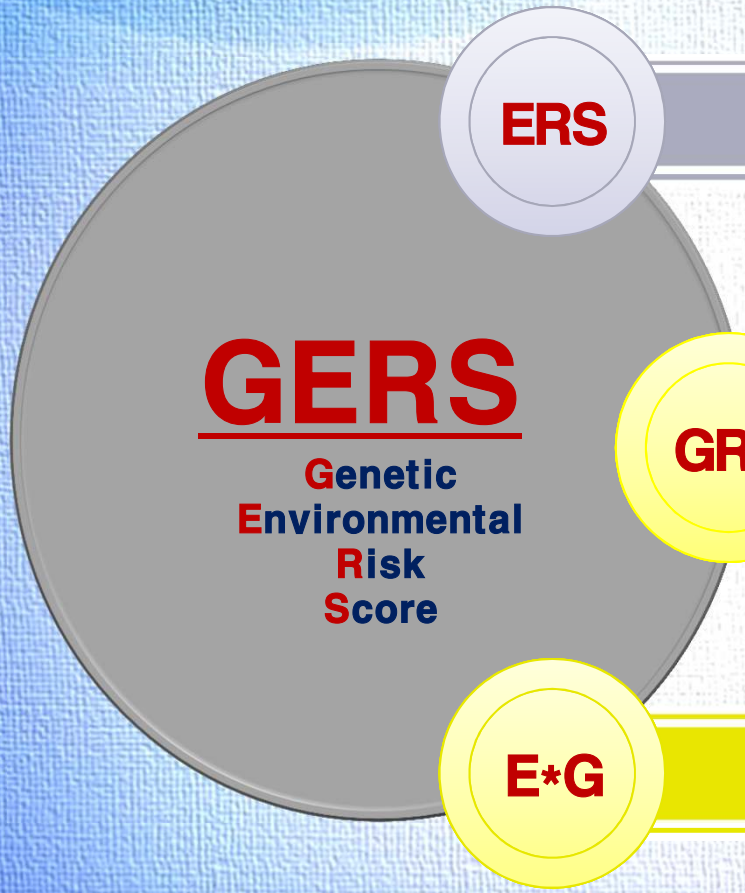




Odds Ratio of CAD According to Presence of ADAMTS7 variant

We have only touched the tip of the iceberg





ERS

Environmental Risk Score

- Healthy Lifestyle Score 활용- 한국인 위험점수 개발
- Risk factors (biomarkers 포함) 요소별 가중치 확인

GRS

Genetic Risk Score

- Imputation methods - candidate SNPs replication
  - 새로운 대상자를 통해 SNPs의 유용성 확인
  - 한국인 특이적인 SNP별 가중치 부여

E*G

Gene-environmental Interaction Effects

- ERS & GRS의 고위험군 선별
- 두 가지 상호작용의 효과 모형에 적용

비 전

질병유전체 중개·임상 연구를 통한 맞춤의료 구현, 미래 바이오 경제의 초석

목 표

국제적 수준의 유전체은행 확보

지속 가능한 맞춤의료 시스템 구축 및 국민 보건의 질적 향상

	2000-2011년	2011-16
심혈관질환 유전체 중앙은행 구축	거점은행 설립 및 외부분양	국제협력은행 개설
Variome 분석 및 시스템 정보화	질환별 유전체 분석	개인별 유전체정보화
예측시스템 적용 유전 표지자 개발	질환관련 기능적 마커 및 예측 표지자 발굴	질환 예측 표지자 확립 및 컨텐츠 적용
질병예측 모형 개발 및 임상적용	질병예측 모형식 개발	예측모형 확립 및 임상 적용 연구

4대 전략

1. 미래 고부가가치 진단/예측시스템 실용화
2. 유전체자원 통합 및 연계시스템 강화
3. 생명자원의 산업적 활용체계 강화
4. 질환 예방 및 관리 대국민 홍보

Yonsei Cardiovascular Hospital

Yonsei University College of Medicine