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Association between 9p21.3 genomic markers and coronary artery disease in East Asians: a meta-analysis involving 9,813 cases and 10,710 controls

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Abstract Recently, genome-wide association studies on coronary artery disease (CAD) identified a series of associated single-nucleotide polymorphisms (SNPs) in an intergenic region of chromosome 9p21.3, near the CDKN2A and CDKN2B genes. We investigated the association of this locus with CAD in 12 case–control studies of East Asians and undertook a meta-analysis for effect size, heterogeneity, publication bias, and strength of evidence. English and Chinese language articles were tested for 9p21.3 SNPs with coronary heart/artery disease or myocardial infarction as primary outcomes. Included articles also provided race, numbers of participants, and data to compute an odds ratio (OR). Articles were excluded if reporting other outcomes (e.g., stroke). Thirty-five articles were initially identified and 12 were included. Independent extraction was performed by two reviewers and consensus was reached. SNP rs1333049, rs2383206 and rs10757278 representing the 9p21.3 locus, were genotyped in 12 case–control studies involving a total of 9,813 patients and 10,710 controls. For rs1333049 (8 data sets), using a fixed-effects model, the summary OR was 1.29 (95 % CI, 1.23–1.36, $P = 0.001$). For rs2383206 (6 data sets), using a fixed-effects model, the summary OR was 1.24 (95 % CI, 1.18–1.31, $P = 0.001$). For rs10757278 (6 data sets), using a random-effects model, the summary OR was 1.34 (95 % CI, 1.21–1.50, $P = 0.001$). In addition, we defined the haploblock structure of SNPs within the region of 9p21.3 in China population in one study. This broad replication provides unprecedented evidence for association between genetic variants at chromosome 9p21.3 and risk of CAD in East Asians.

Keywords Coronary artery disease · Genetics · Meta-analysis · East Asian · China

Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability-adjusted life-years world wide, with increasing incidence and prevalence in low- and middle-income countries [1]. By 2020, more than 80 % of global CVD will be in these countries, with the largest burden occurring in the two largest countries, China and India, as they rapidly urbanise [1]. Nonmodifiable risk factors include increasing age, male sex, and heredity. Modifiable risk factors include smoking, hypertension, dyslipidemia, obesity, physical inactivity, and diabetes [2–4]. Biomarkers (e.g., C-reactive protein) have been combined with traditional risk factors to predict CVD events, and molecular markers hold further promise [5]. In 2007, genome-wide association studies on CVD identified a series of associated single-nucleotide polymorphisms (SNPs) in an intergenic region of chromosome 9p21, near the CDKN2A and CDKN2B genes [6, 7]. Recent success in identifying genes involved in complex diseases such as coronary artery disease (CAD) and myocardial infarction (MI) has been largely brought about by two major developments. First, modern array technology now enables simultaneous measurement of hundreds of thousands of single nucleotide

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polymorphisms (SNPs) across the human genome. Second, collaborations have been formed, bringing together large collections of well-phenotyped individuals.

However, only a small proportion of population of CAD has been explained in East Asia. In fact, for a typical association study with hundreds of cases and controls, the power to detect any effects at stringent significance levels is low. To increase the power, we formed a consortium to pool data across all published and multiple unpublished articles of East Asia population for CAD and MI. Here, we aim to provide a detailed description of the structure and functioning of our consortium.

Methods

Study populations

We systematically searched PubMed, Blackwell, Biosis Previews, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedical (CBM) and Wan Fang (Chinese) databases for relevant articles published in different languages up to February 2012. We used search term "9p21 AND (cardiovascular disease OR coronary artery disease OR acute myocardial infarction OR myocardial infarction OR structural heart disease OR coronary atherosclerosis) AND (China OR Chinese OR Japanese OR Korean OR Mongol OR Asian population)" in this study. Other eligible studies were identified by a search of references cited in published articles.

The inclusion criteria of this meta-analysis were showed as follows: (a) including patients with a diagnosis of contained primary outcomes of coronary heart disease (CHD), myocardial infarction (MI), or coronary artery disease (CAD) and without other relate diseases; (b) describing the association of SNPs in 9p21 polymorphisms with CAD risk; (c) reported race and numbers of affected and unaffected participants, and race was East Asia population; (d) describing the genotyping method; (e) provided frequency genotype and the odds ratio (OR) with confidence intervals (CIs) or data sufficient to compute it. If more than 1 outcome was reported, the best-described phenotype was chosen. Several included articles reported consortium results with multiple independent populations. These populations were listed as separate data sets; all data were extracted independently by two reviewers according to the inclusion criteria. Discrepancies were documented and resolved by discussion with a third reviewer. The following information was extracted from all the eligible studies: patients with a diagnosis of disease not related with CAD, other race, SNPs not in the 9p21.

We studied subjects collected in eight different studies across China, Japan and Korea. All subjects were of East Asian origin. The large majority of cases had CAD as defined by China study ($n = 3{,}413$). The remaining cases had evidence of CAD based on either a revascularization procedure or anginal symptoms with a positive stress test. Details of each study are given in Table 1 and the online-only Data Supplement.

Not all researchers use the same 9p21 SNPs, and most articles reported results for multiple SNPs (uniquely identified by their rs number). As a proof-of-principle analysis, a number of SNPs in the 9p21 region with known association to CAD and MI were analyzed upfront. Specifically, 3 SNPs were reported as lead SNPs in the first publications by McPherson et al. (rs2383206), Helgadottir et al. (rs10757278), and Samani et al. (rs1333049). In addition, the SNP rs10757274 and rs2383207 in the same chromosomal region were also associated with CAD. We report here in three common SNPs (rs1333049, rs10757278, and rs2383206) that were included in more than six articles [8–19]. These SNPs are in high linkage disequilibrium ($D' > 0.9$; $r^2 > 0.85$) [19]. The remaining four articles used two additional SNPs, rs2383207 and rs10757278 [8–19]. These were also in high linkage disequilibrium. Information about age at diagnosis and race/ethnicity was also collected.

Genotyping

Different genotyping platforms have been used across the studies. An analysis restricted only to SNPs genotyped on all platforms would have been severely limited. For instance, the estimated overlap between the Affymetrix Genome Wide Human SNP Array 6.0 and the Illumina Human-1 mol/L chip is only about 250,000 SNPs. To allow for combined analyses across different platforms, missing SNPs were imputed by each study.

Haplotype analysis

Haplotype association analysis was performed with the Haploview software and SAS software (version 9.1.3, SAS Institute Inc) implementing the Stochastic-EM algorithm. Using this approach, we were able to simultaneously estimate haplotype frequencies for each haplotype pair consistent with the observed data. When ambiguous haplotypes were encountered, multiple, probability-weighted haplotypes were created.

Statistical analysis methods

For each data set, the observed genotype frequencies in controls were compared with expected frequencies based on Hardy–Weinberg equilibrium (χ^2 test with 2 degrees of freedom). All P values are 2-sided at the $P = 0.05$ level. After upload of the summary data and centralized quality

Table 1 Description of Probands (Cases/Controls) in Participating Studies

First Author	Country	Study Type	Case/ controls	Male sex (Case/ controls), %	Age (Case/ controls), y	BMI (Case/ controls), kg/m^2	Primary outcome	Case definition	Control definition
Fang Xie	China	Case–control study	2335/1078	66.9/50.8	65.4/60.4	24.5/25.6	Coronary atherosclerosis	Atherosclerosis include: coronary artery disease (CAD) and its main complication myocardial infarction (MI).	No history of clinical CAD
Wei Wang	China	Case–control study	545/564	81.2/50.2	62.2/60.0	24.0/24.2	Coronary artery disease	≥50 % luminal diameter narrowing in at least one coronary artery	No history of clinical CAD
Hu Ding	China	Case–control study	510/554	77.1/62.1	61.7/62.3	24.3/23.7	Coronary artery disease	Patients who survived an acute myocardial infarction or were documented by coronary angiography to have at least a 70 % stenosis in a major epicardial artery were eligible.	No history of clinical CAD
Wen-Hui Peng	China	Case–control study	520/560	78.7/75.4	64.0/63.0	24.3/24.6	Coronary Artery Disease	angiographically documented diseased coronary arteries (luminal diameter stenosis ≥50 %)	No history of clinical CAD
Qi Zhang	China	case–control study	432/430	73.4/69.8	61.0/63.4	25.2/24.6	Coronary artery disease	Cases represented 80 % of hospitalized first, non-fatal MI patients	Subjects without an inquired history of CAD
Li Zhou	China	Case–control study	1360/1360	68.5/68.5	60.9/60.4	24.4/24.1	Coronary heart disease	The presence of a stenosis ≥50 % in at least 1 of the major segments of coronary arteries (the right coronary artery, left circumflex, or left anterior descending arteries) on coronary angiography	No history of clinical CAD
Yumiko Hiura	Japan	Case–control study	589/2475	86.6/40.9	65.1/61.322.8/ 23.7	22.8/23.7	Myocardial infarction	NA	Free from CAD
Zhong Chen	China	Case–control study	212/232	52.2/58.0	47.1/47.9	NA	Coronary artery disease	Early-onset CAD was defined as clinical CAD occurring by age <55 in male or <60 in female patients verified by angiography with ≥50 % luminal narrowing in at least one coronary artery or a definite diagnosis of acute MI defined by WHO criteria	No detectable coronary artery stenosis
Hinohara	Japan	Case–control study	604/1151	NA	NA	NA	Coronary artery disease	angiographic luminal stenosis >50 %	No history of clinical CAD
Hinohara	Korean	Case–control study	676/709	NA	NA	NA	Coronary artery disease	Angiographic luminal stenosis >50 %	No history of clinical CAD
Gong-Qing Shen	Korean	Case–control study	611/294	70.9/58.2	63.7/60.1	24.4/24.3	Coronary artery disease	Include >70 % luminal narrowing in at least one vessel by coronary angiography, percutaneous coronary angioplasty, coronary artery bypass graft, and MI	controls were in general good health and determined to have no CAD
Zhao-Hui Qiu	China	Case–control study	271/118	69.4/59.3	68.0/66.5	NA	Coronary heart disease	The presence of a stenosis ≥50 % in at least 1 of the major segments of coronary arteries (the right coronary artery, left circumflex, or left anterior descending arteries) on coronary angiography	No history of clinical CAD
Jin Guo	China	Case–control study	1148/1185	72.1/71.3	59.4/60.4	25.0/24.4	Acute myocardial infarction	First incident AMI were enrolled within 24 h of onset of symptoms	No history of clinical CAD

control, a meta-analysis across all studies is performed for every SNP separately. Here, depending on the heterogeneity between studies, fixed or random effects models are calculated, and outlying studies excluded. Summary ORs and corresponding 95 % CIs were derived (by reanalysis when possible) and summarized using random-effects modeling weighted by each data set's total variance (STATA) [20]. Subgroup differences were compared using the Q test for heterogeneity for each covariate separately. Publication bias was examined by performing a cumulative effects analysis [20, 21]. Wider ranges of these summary ORs indicate potential for publication bias.

Results

Literature search and meta-analysis databases

A total of 35 articles were identified in the initial search with the medical subject heading terms. After screening the abstracts or full contents, 23 articles were excluded (twelve were not related to CAD, five were not about polymorphism of SNPs in 9p21, four reported other races, two were republished studies). Finally, twelve studies (9,813 cases and 10,710 controls) were included in this meta-analysis. Eight studies of them were performed in China [8–13, 15, 18, 19], two in Japan [14, 16], and two in Korea (Table 1; Fig. 1). [15, 17] All genotype frequencies of studies were conformed to the HWE in control group.

Quantitative synthesis

The results of all the East Asia population for our proof-of-principle analysis are shown in Figs. 2, 3, 4 for rs1333049 (8 data sets), using a fixed-effects model, the summary OR was 1.29 (95 % CI, 1.23–1.36, $P = 0.001$). Heterogeneity was checked separately using Q statistic ($Q = 10.14$; $I^2 = 31$ %; $P = 0.181$). For rs2383206 (6 data sets), using a fixed-effects model, the summary OR was 1.24 (95 % CI, 1.18–1.31, $P = 0.001$). Heterogeneity was low ($Q = 8.24$; $I^2 = 39.3$ %; $P = 0.144$). For rs10757278 (6 data sets), using a random-effects model, the summary OR was 1.34 (95 % CI, 1.21–1.50, $P = 0.001$). Heterogeneity was checked separately using Q statistic ($Q = 13.20$; $I^2 = 62.1$ %; $P = 0.022$).

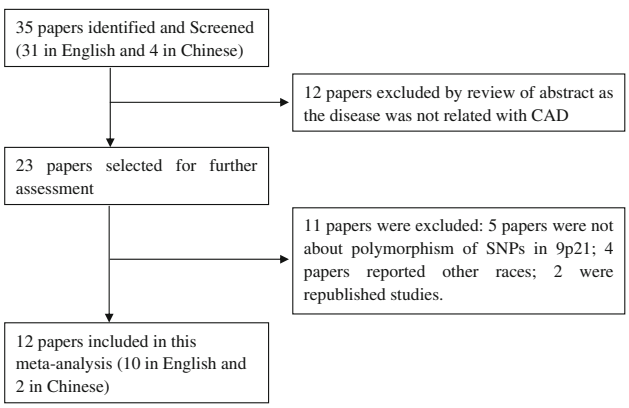

Fig. 1 Paper identification and exclusion

In subgroup analyses, the G allele was also significantly associated with CAD in every race (Table 2). But there were little differences in ORs found between China population (5 data sets) and other races (Japan 2 data sets, Korea 1 data sets) (ORs of rs1333049, 1.27, 1.38, and 1.19).

Sensitivity analysis

Sensitivity analyses were performed by excluding the studies that were not in HWE, and the pooled OR were not materially altered in recessive genetic model (data not shown), indicating that the model results were statistically robust. Sensitivity analyses could not be done because of the small sample size in the subgroup analyses.

Publication bias

Begg rank correlation method and Egger weighted regression method were performed to assess the publication bias in recessive genetic model. No publication bias evidence was found (Table 2).

Discussion

Based on previous studies, evidence for the association between heart disease and chromosome 9p21 SNP markers had strong credibility. The 9p21 SNP markers have been identified though genome wide association studies and appear independent of traditional risk factors or family history [20, 22, 23]. The associated SNPs were rs1333049 (18 researches, OR = 1.23), rs10757274 (17 researches, OR = 1.24), rs2383207 (6 researches, OR = 1.28), rs2891168 (4 researches, OR = 1.29), rs10757278 (2 researches, OR = 1.27) [2]. In Asian race, rs1333049 (Japan, China), rs10757274 (China), rs10757278 (China) showed an association with the MI [2].

Most data sets are limited to white populations, usually of European descent, so the results for other racial groups might differ. We aim to investigate the association of this locus with CAD in 12 case–control studies of East Asians and undertook a meta-analysis for effect size, heterogeneity, publication bias, and strength of evidence. The SNP rs1333049 was also part of the previous meta-analysis by Schunkert et al. [24, 25]. In that report, the overall OR was

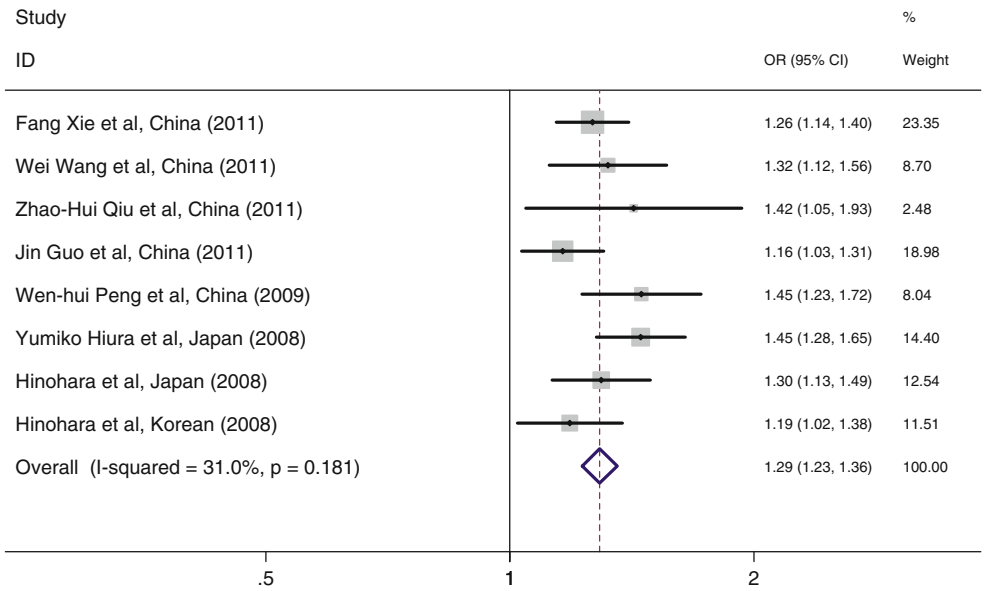

Fig. 2 Forest plots for SNP rs1333049 (risk allele = C); the fixed effects (FE) model was calculated. Heterogeneity between the studies is indicated by I^2

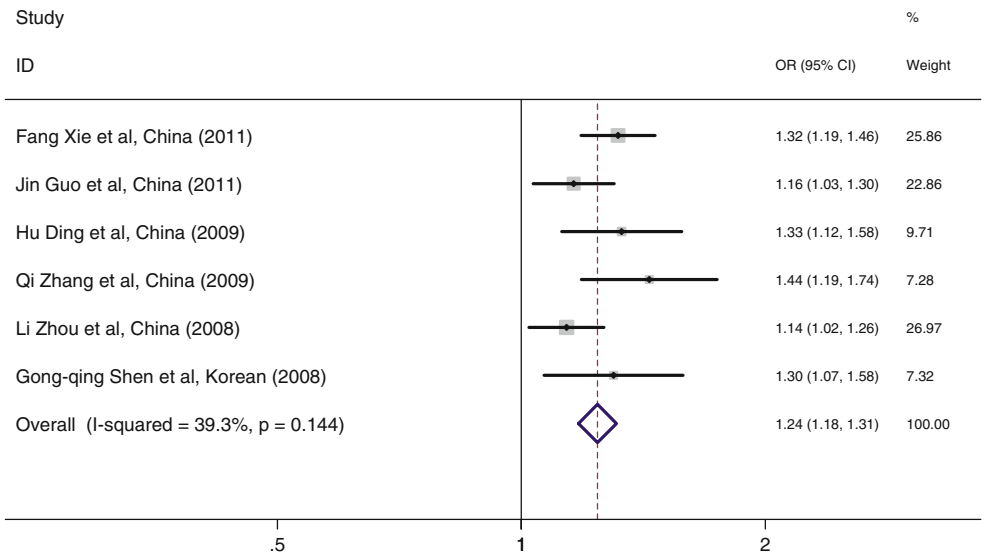

Fig. 3 Forest plots for SNP rs2383206 (risk allele = G); the fixed effects (FE) model was calculated. Heterogeneity between the studies is indicated by I^2

1.29 with a 95 % CI of 1.22–1.37, virtually identical to our current result. In our research, for rs1333049 (8 data sets), we received the similar result that the summary OR was 1.29 (95 % CI, 1.23–1.36, $P = 0.001$). The OR associated with rs2383206 was 1.24 (95 % CI, 1.18–1.31, $P = 0.001$). It was lower than rs2383206 analyzed in Europe population (OR = 1.28 (95 % CI, 1.22–1.35, $P = 1.64 \times 10^{-20}$), by Michael Preuss et al.). The OR associated with rs10757278 was 1.34 (95 % CI, 1.21–1.50, $P = 0.001$). It was higher than rs10757278 analyzed in Europe population (OR = 1.28 (95 % CI, 1.21–1.35, $P = 1.64 \times 10^{-20}$), by Michael Preuss et al.).

HapMap data suggests that rs10757274 and rs2383206 were located within 20 kb of each other on chromosome 9p21 and were in strong linkage disequilibrium ($r^2 = 0.89$) in North American population [5], and the five SNPs (rs2383206, rs2383207, rs10757274, rs10757278, and rs1333049) are in 1 block, and the D' between each of the 5 SNPs was 1.0 in Chinese Han origin [13]. In our study, we identified one haploblock in the 9p21 region (rs10757274,

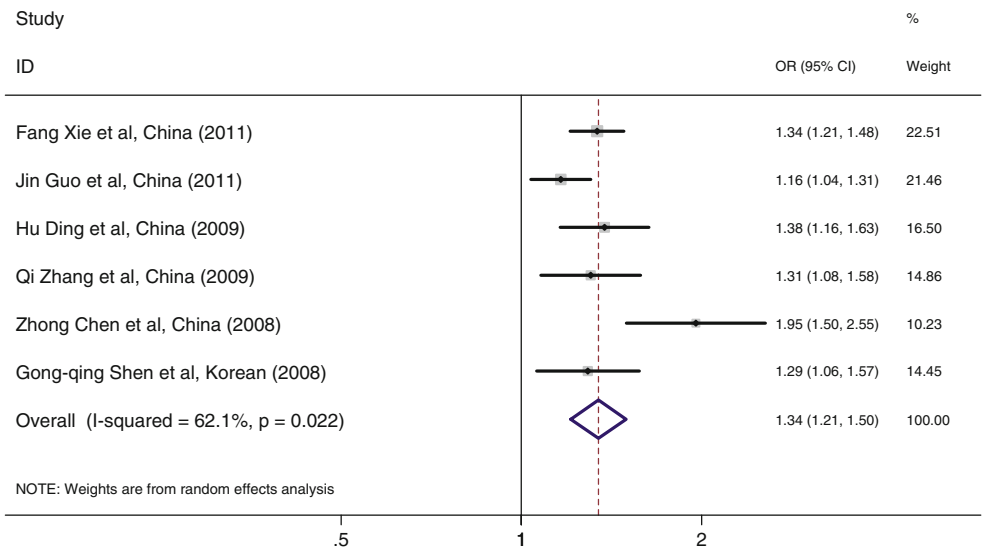

Fig. 4 Forest plots for SNP rs10757278 (risk allele = G). Random effects (RE) models were calculated. Heterogeneity between the studies is indicated by I^2

Table 2 Main results of rs1333049 in the total and subgroup analysis

Race	Total		Heterogeneity		Model	Bias in total	
	OR (95 % CI)	*P* value	Q_x (p)	I^2		*P* value for begg's test	*P* value for Egger's test
Total: G vs C	1.29 (1.23–1.36)	0.0001*	10.14 (0.181)	31.0	FE	0.266	0.370
China: G vs C	1.27 (1.19–1.36)	0.0001*	5.41 (0.248)	26.1	FE	0.221	0.242
Japan: G vs C	1.38 (1.26–1.51)	0.0001*	1.37 (0.242)	26.8	FE	.	.
Korea: G vs C	1.19 (1.02–1.38)	0.025*	.	.	.	.	.

* The pooled OR has a statistically significant

FE fixed effect model, *RE* random effect model

rs2383206, rs10757278, and rs1333049) in Chinese population, and it's similar to previous North American population study. On the basis of the stringent analysis of these SNPs and replication in our research, we are confident that 9p21 region is a strong candidate locus for CAD susceptibility in the Chinese population. Figure 5 shows the results of haplotype analysis for the SNPs examined. And then we calculated possible haplotype frequency of 8 loci in 9p21, using haploview and SAS software. Using the genotypes of 1,185 persons, we defined the haploblock structure of SNPs within the region of 9p21 in the Chinese population. By defining a solid spine of LD as $D' > 0.90$, we identified one haploblock in the 9p21 region.

The region of chromosome 9p21 contained the coding sequences of gene for 2 cyclin-dependent kinase inhibitors, *CDKN2A* and *CDKN2B*, which played an important role in the regulation of the cell cycle and would be implicated, through their role in transforming growth factor (TGF)-β-induced growth inhibition, in the pathogenesis of atherosclerosis [13, 26–28]. Given the strong implication of this genomic region in CHD, the exact molecular mechanism of

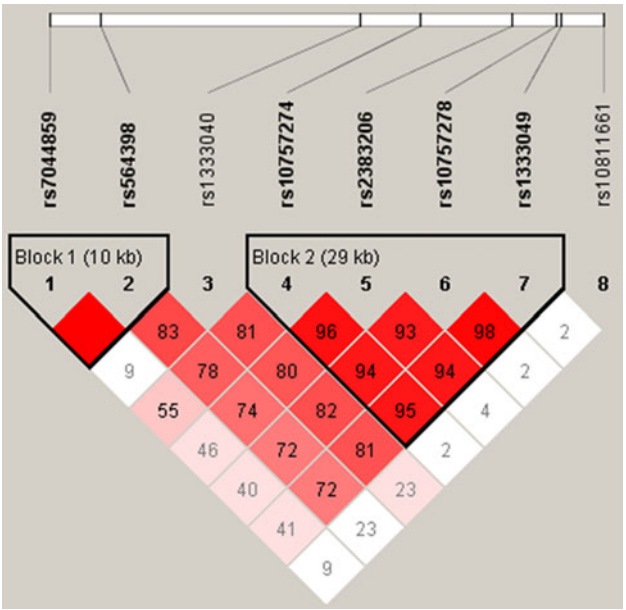

Fig. 5 Pair-wise LD among eight SNPs in 9p21 in the China population. The numbers inside the squares are $D' \times 100$

its involvement remains to be confirmed. McPherson et al. [7] resequenced the coding regions of the 2 genes most proximal to the risk locus and found no explanation of the CHD risk associated with this locus. However, the same region has recently been associated with increased susceptibility to type 2 diabetes [29, 30]. These results suggest that the region of 9p21 plays a role in multiple complex diseases. Further studies should focus on the identification of the underlying mechanism at this locus of CHD. In addition, the interactions between gender, smoking, and overweight with these SNPs need to be replicated in other populations.

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