



SHORT COMMUNICATION

A preliminary identification of *PIN1* SNP linkage in patients with coronary heart disease from Handan, China



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Nitric oxide

Abstract Our aim was to perform an initial assessment of the polymorphic patterns of the *PIN1* gene in patients with coronary heart disease (CHD). The *PIN1*-encoded protein (Pin1) suppresses eNOS-NO signaling and may impair cardiovascular function. Blood collection, DNA extraction, PCR amplification and gene sequencing were performed for thirty CHD participants living in central China, focusing on nine single nucleotide polymorphisms (SNPs). Their genetic linkages were revealed and their allele frequencies were compared with SNP data from the NCBI. Three major linkage patterns were identified: [1.rs2287839-5.rs2233682], [3.rs2233679-4.rs1077220-8.rs2287838] and [6.rs889162-7.rs2010457], suggesting correlated involvement in CHD and possible simultaneous genetic origin in ancient times. The frequencies of six SNPs are consistent with the NCBI data, while the frequencies of three SNPs (2.rs2233678, 4.rs1077220 and 9.rs4804461) are not consistent with the NCBI. Especially, the 3.rs2233679-4.rs1077220 linkage is different from other populations worldwide and may be an interesting genetic characteristic of Chinese CHD patients. Predictably, 1.rs2287839, 2.rs2233678, 3.rs2233679 and 5.rs2233682 may be strongly associated with CHD risk, although this requires future verification. The *PIN1* SNP linkages lay a new genetic foundation for discovering novel molecular mechanisms of CHD and for exploring *PIN1*-based targeted treatment of CHD with nitric oxide regulatory therapies in clinical practice.

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PALAVRAS-CHAVE

Doença coronária;
PIN1;
SNP;
Linkage genético;
eNOS;
Óxido nítrico

Uma identificação preliminar de PIN1-SNP-Linkage em doentes com doença coronária em Handa, China

Resumo O objetivo deste estudo é avaliar os polimorfismos do gene PIN1 em doentes com doença arterial coronária (DAC). A proteína codificada pelo gene PIN1 (Pin1) suprime a sinalização eNOS-NO e pode afetar a função cardiovascular. Foram incluídos 30 indivíduos com DAC, residentes na China central, a quem foi recolhido sangue, extraído e amplificado o DNA por PCR. Foram estudados nove polimorfismos de nucleótidos únicos (SNPs) do gene PIN1. As suas associações genéticas foram estudadas e as frequências de alelo foram comparadas com os dados de SNPs do NCBI. Foram identificados três grandes padrões de linkage: [1.rs2287839-5.rs2233682], [3.rs2233679-4.rs1077220-8.rs2287838] e [6.rs889162-7.rs2010457], sugerindo o seu envolvimento na DAC e possível origem genética simultânea histórica. As frequências de seis dos SNPs foram consistentes com os dados do NCBI, enquanto as frequências de três dos SNPs (2.rs2233678, 4.rs1077220 e 9.rs4804461) não foram consistentes com o NCBI. Especificamente, a ligação 3.rs2233679-4.rs1077220 é diferente de outras populações mundiais e poderá constituir uma característica genética específica dos doentes chineses com DAC. Previsivelmente, 1.rs2287839, 2.rs2233678, 3.rs2233679 e 5.rs2233682 podem estar particularmente associados ao risco de DAC, requerendo validação ulterior. As ligações PIN1-SNP estabelecem uma nova base genética para a descoberta de novos mecanismos moleculares da DAC e para explorar o tratamento de precisão da DAC com medicamentos reguladores do óxido nítrico, baseado nos polimorfismos do gene PIN1.

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Introduction

Morbidity from coronary heart disease (CHD) is increasing worldwide, posing a major threat to health. CHD correlates with obesity, a high-fat diet, smoking, drinking, and other risk factors. However, many people without these unhealthy lifestyles and dietary habits still suffer from CHD, so researchers are paying more attention to genetic differences in CHD patients.¹⁻⁵

Pin1, encoded by the *PIN1* gene, regulates phosphorylation of proteins and is implicated in human diseases.⁶⁻¹¹ Our recent research predicted that (i) Pin1 may promote cardiovascular disease by suppressing endothelial nitric oxide synthase (eNOS) and production of nitric oxide (NO) in blood vessels,⁷ (ii) a potential glucose-Pin1-eNOS-NO pathway may lead to coronary atherosclerosis in diabetic patients,¹² and (iii) serum Pin1 may be associated with CHD and hypertension.¹¹ NO is a key vasoactive molecule that promotes vasodilation, reduces vascular sediments, and prevents atherosclerosis, but Pin1 inhibits eNOS and blocks NO bioactivity in animal and cellular experiments, and probably increases CHD risk in humans.^{8,9,12,13} However, no clinical research on the relationship between the *PIN1* gene and CHD has been published.

PIN1 has multiple polymorphic sites that may be related to many diseases, but previous studies analyzed these polymorphic sites in isolation without paying attention to their possible genetic linkages, which inevitably complicates research work and increases the cost of analysis.^{10,14-19} Hence, we aim to perform an initial exploration of the genetic linkages of the nine common single nucleotide polymorphisms (SNPs) of the *PIN1* gene and thus to lay a

foundation for simplifying relevant research in the future. To improve analytic efficiency, we initially analyzed the *PIN1* SNP linkages in CHD patients living in the city of Handan, China, and identified three typical genetically-linked SNP groups, which will facilitate future research and foster studies on the association of *PIN1* and CHD (as well as potentially other relevant genetic diseases).

Methods**Patient enrollment**

All participants belong to the Han nationality and live in the city of Handan (Hebei province, China). All participants provided written information including name, gender, age, height, weight, personal information, living and dietary habits, and other details. Thirty CHD patients were randomly enrolled in the cardiology department of the Affiliated Hospital of Hebei University of Engineering. The selection criterion for CHD was at least one coronary artery with >50% stenosis. The research was approved by the Ethics Committee of the Medical College of Hebei University of Engineering, and every participant signed an informed consent form.

Blood sample preparation

For each participant, 5 ml peripheral blood was collected in the morning using anticoagulant vacuum tubes. Blood plasma and blood cells were separated by centrifugation at 3000 rpm for 10 min and were then stored at -80°C.

Polymerase chain reaction amplification of *PIN1* gene fragments

All of the reagents used for DNA analysis were provided by Sangon Biotech, Shanghai. DNA was extracted using the Ezup column blood genomic DNA extraction kit (product number: B518253), and polymerase chain reaction (PCR) amplification was performed using Taq DNA polymerase (product number: B600090), 10× PCR Buffer (product number: B600017), and dNTP (product number: B500056). The PCR primers for analyzing the nine SNPs are shown in [Table 1](#).

Genotype sequencing of *PIN1* single nucleotide polymorphisms

PCR products were recycled using the SanPrep Column PCR Product Purification Kit (B518141), and the DNA sequences were determined using an ABI 3730xl DNA Analyzer (Applied Biosystems).

SNP frequencies of the *PIN1* gene were then compared with the US National Center for Biotechnology Information (NCBI) database (<https://www.ncbi.nlm.nih.gov/snp/>) as a public control.

Results

Characteristics of study participants with coronary heart disease

The clinical characteristics of the study participants are shown in [Table 2](#). Their age distribution ranged from about 50 to 70 years, and some individuals were slightly overweight but rarely reached the level of obesity. Mean values of blood components such as triglycerides, cholesterol, bile acids, and apolipoproteins were approximately within normal ranges, indicating that these traditional risk factors had less impact on CHD development in these participants, which strengthens our belief that genetic differences may substantially influence the incidence of CHD.

The distribution of *PIN1* single nucleotide polymorphisms in the study population

As shown in [Table 1](#), rs2233678 and rs2233679 are close to each other on chromosome 19 and were analyzed using the same pair of primers, and similarly rs2287838 and rs4804461 were analyzed together using another pair of primers. Examples of gene sequencing are shown in [Figure 1A](#). For six of these SNP loci, three types of genotypes were identified: wild type (WT), heterozygous type (HT), and mutant type (MT). However, only WT and HT were determined for 1.rs2287839, 5.rs2233682 and 9.rs4804461, and only the WT allele (G) was determined for 2.rs2233678.

Linkage patterns of *PIN1* single nucleotide polymorphisms in the study population

[Figure 1B](#) provides clues to the genetic linkage information of *PIN1* SNPs. Three typical genetic linkages

were revealed: Group I, 1.rs2287839-5.rs2233682; Group II, 3.rs2233679-4.rs1077220-8.rs2287838; Group III, 6.rs889162-7.rs2010457. No significant linkage between other SNP loci was found.

Based on these genetic linkages, the impact of *PIN1* on CHD can more easily be explored. In theory, examining several key SNPs, particularly 1.rs2287839, 2.rs2233678 and 3.rs2233679 in the gene promoter, will simultaneously present pathogenic information about their genetically-linked SNP loci in other exons and introns.

Single nucleotide polymorphism analysis compared with the NCBI data

In order to better understand the racial distributions of *PIN1* SNPs, we compared the SNP frequencies with the information from the NCBI's SNP database, shown in [Table 3](#). Briefly, the frequencies of most mutant alleles are very close to the NCBI ranges, except 2.rs2233678, 4.rs1077220 and 9.rs4804461.

Firstly, for 2.rs2233678, the NCBI frequency of the mutant allele C is about 7.7-15.1%, but unexpectedly we did not observe this (C: 0%, [Figure 1](#) and [Table 3](#)) in the study participants, which implies that the homozygous WT genotype (GG, enhanced *PIN1* transcription¹⁰) may elicit a higher CHD risk. In other words, people carrying the mutant allele C may face such a lower CHD risk that they were not included in our CHD participants this time, so further clinical case-control investigation will be particularly necessary for this SNP.

Secondly but also very interestingly, 3.rs2233679 and 4.rs1077220 are completely linked in the study participants, and the frequencies of their mutant alleles (T of 3.rs2233679, and G of 4.rs1077220) are both 40% ([Table 3](#)). However, although the frequency of 3.rs2233679-T (40%) is nearly the same as the NCBI data (39.9-41.4%), the frequency of 4.rs1077220-A (60%) is significantly different from the NCBI (21.8-35.7%). This inconsistency argues against complete linkage between 3.rs2233679 and 4.rs1077220 ([Figure 1B](#)). Hypothetically, this seems to indicate that the 3.rs2233679-4.rs1077220 linkage may be a specific chromosomal characteristic that distinguishes Chinese CHD patients from other racial groups, which also requires further clinical verification.

Discussion

The first issue needing explanation is why only female patients were analyzed here. Several recent studies suggested that smoking and alcohol may interact with the *PIN1* gene and have synergistic pathogenic effects in human lung cancer and in mouse cardiac cells, respectively.^{10,13} Therefore, only women who did not smoke or drink were enrolled, to avoid the potential influence of tobacco and alcohol on *PIN1* expression. Secondly, although [Figure 1B](#) clearly indicates the potential genetic linkages, the authors do not wish to exaggerate these associations. After all, the sample size is still limited in this study, so we suggest that these preliminary conclusions should be confirmed in large-scale studies by us or by researchers in other regions of China and other countries in the future.

Table 1 Polymerase chain reaction primers for amplifying *PIN1* single nucleotide polymorphisms.

No.	SNP sites	Primer sequences
1	rs2287839	F: 5'-GTCAGAGTCAGGATTCCTTAACAC-3' R: 5'-ATCTACTGTCATTAGCCGGAGG-3'
2	rs2233678	F: 5'-AGGTCGCATAGCAAGTGCAGT-3' R: 5'-GGAGATGAGCACCTAAGTACCC-3'
3	rs2233679	Same as for rs2233678
4	rs1077220	F: 5'-AGTGAGGGGTATGAAGGAGTGAA-3' R: 5'-AAACTGAAGGAACCTCGTCCAAGA-3'
5	rs2233682	F: 5'-CTCTGTTCCATCACTCTGGGTTAT-3' R: 5'-AAGGCTCACCTGGGAGAAGAC-3'
6	rs889162	F: 5'-ATCCTTCTTGCTTCTACTGGC-3' R: 5'-AGAATAATAAGACCCACTTCACAGG-3'
7	rs2010457	F: 5'-GATGATGCCAGGAAGAAAGTGAT-3' R: 5'-GTGCTCATGCTCGTGAAGG-3'
8	rs2287838	F: 5'-CAGGCTACATCCAGAAGATCAAGT-3' R: 5'-AGTGCGGAGGATGATGTGGAT-3'
9	rs4804461	Same as for rs2287838

Table 2 Characteristics of the study population with coronary heart disease (n=30).

Variables	Values	Remarks
<i>Gender</i>		
Female ^a	30 (100%)	
Male	0 (0%)	
<i>Age, years</i>		
<60	2 (6.7%)	
50-60	16 (53.3%)	Major population
60-70	6 (20.0%)	
>70	5 (16.7%)	
<i>BMI, kg/m²</i>		
<18.4	1 (3.3%)	Underweight
18.5-24.9	10 (33.3%)	Normal weight (major)
25.0-29.9	14 (46.7%)	Overweight (major)
>30.0	1 (3.3%)	Obese
<i>Blood components</i>		
Triglycerides, mmol/l	1.65±0.70	0.48-1.88
Total cholesterol, mmol/l	5.04±1.23	3.35-6.45
HDL cholesterol, mmol/l	1.22±0.27	1.00-1.94
LDL cholesterol, mmol/l	2.77±0.93	<3.12
Total bile acid, μmol/l	7.69±7.44	5.1-19
Apolipoprotein A1, g/l	1.27±0.28	1.0-1.6
Apolipoprotein B, g/l	1.01±0.36	0.6-1.1
Lipoprotein(a), mg/l	238±228	0-300

Data are presented as n (%) or mean ± standard deviation.

^a The reason that only women were enrolled will be explained in the results.

BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

In theory, higher Pin1 activity in vivo could be largely attributed to highly-expressed *PIN1* genotypes. Hence, the major impact of *PIN1* SNPs on higher Pin1 expression as well as higher CHD risk can be predicted in the following respects:

1.rs2287839-5.rs2233682: Compared to the WT G allele of 1.rs2287839 (-5185 in the promoter), the mutant C allele may enhance *PIN1* transcription by rejecting a suppressor

of the *PIN1* promoter.¹⁸ 5.rs2233682 results in a same-sense mutation from CAG to CAA (encoding glutamine) in exon 2, but its influence on *PIN1* transcription and protein translation needs to be clarified in the future.

2.rs2233678: Compared to the variant C allele (-842 in the promoter), the WT G allele enhances *PIN1* transcription and is associated with several cancers.^{10,16,17,19,20} In this work, all of the study participants were of the GG genotype (100%,

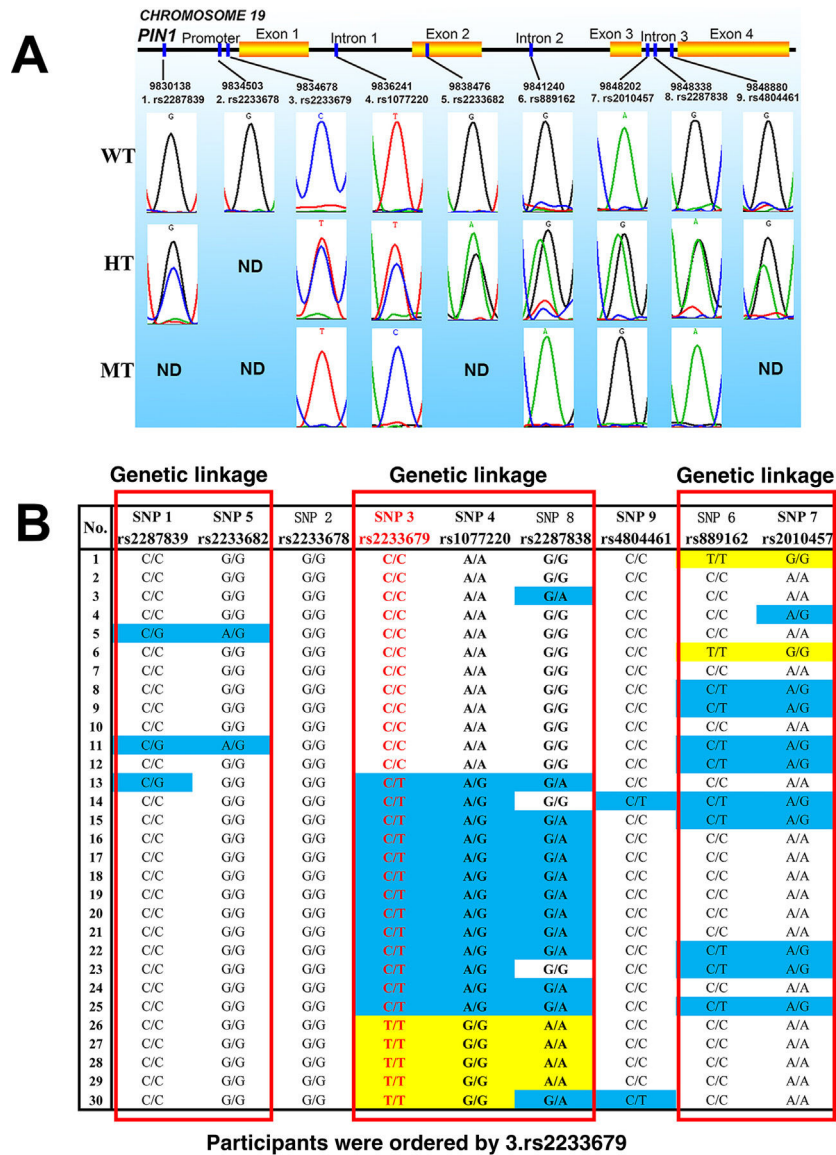


Figure 1 (A) Genotyping examples of *PIN1* single nucleotide polymorphisms (SNPs). WT: wild type; HT: heterozygous type; MT: mutant type; ND: not detected; (B) gene sequencing results and linkage patterns of *PIN1* SNPs. White: wild type; blue: heterozygous type; yellow: mutant type.

Table 3 *PIN1* allele counts (n=60) and frequencies in the study population compared to the allele information from the NCBI database.

No.	Gene location	Potential impact	SNPs	WT alleles	MT alleles	Frequencies in NCBI
1	Promoter	Gene transcription	rs2287839	C (57, 95.0%)	G (3, 5.0%)	G (5.6-17.0%)
2	Promoter	Gene transcription	rs2233678	G (60, 100.0%)	C (0, 0.0%) ^a	C (7.7-15.1%)
3	Promoter	Gene transcription	rs2233679	C (36, 60.0%)	T (24, 40.0%)	T (39.9-41.4%)
4	Intron 1	RNA splicing	rs1077220	A (36, 60.0%) ^a	G (24, 40.0%)	A (21.8-35.7%)
5	Exon 2	Protein translation	rs2233682	G (58, 96.7%)	A (2, 3.3%)	A (0.4-8.4%)
6	Intron 2	RNA splicing	rs889162	C (47, 78.3%)	T (13, 21.7%)	T (18.0-24.1%)
7	Intron 3	RNA splicing	rs2010457	A (46, 76.7%)	G (14, 23.3%)	G (29.1-39.8%)
8	Intron 3	RNA splicing	rs2287838	G (39, 65.0%)	A (21, 35.0%)	A (31.1-41.8%)
9	Intron 3	RNA splicing	rs4804461	C (58, 96.7%)	T (2, 3.3%) ^a	T (14.5-25.9%)

^a These allele frequencies are obviously different from the NCBI data.

MT: mutated type; NCBI: US National Center for Biotechnology Information database; SNPs: single nucleotide polymorphisms; WT: wild type.

significantly higher than NCBI data), possibly indicating that the G allele may elicit a higher CHD risk.

3.rs2233679-4.rs1077220-8.rs2287838: 3.rs2233679 is another key polymorphic locus in the *PIN1* promoter (-667), although its influence on Pin1 function has been somewhat controversial.^{16,17,21} For example, two studies recently showed that the -842C-667C haplotype has a protective effect against lung and esophageal cancer (higher Pin1 results in cancers),^{10,22} which hints that -667C may decrease Pin1 levels and lead to lower CHD risk. In addition, 4.rs1077220 and 8.rs2287838 may play less important roles compared to 3.rs2233679 because the two SNPs are located in the introns of the *PIN1* gene.

Taken together, the presented results provide a new genetic basis for early prevention and targeted treatment of CHD. In particular, 2.rs2233678 is considered an important SNP that affects *PIN1* transcription and Pin1 protein levels,^{10,17} whereas only the WT G allele was identified in our study population, implying that the GG genotype might be a risk factor for CHD, which necessitates further investigations in large-scale case-control studies in the future.

Typical CHD therapies such as nitrate esters, calcium channel blockers and estrogens show beneficial therapeutic efficacy by improving NO-stimulated vascular diastolic function, but recent evidence supports the hypothesis that higher Pin1 may reduce NO production and result in coronary atherosclerosis.^{7,8,12,13} Therefore, a possible association of the polymorphic patterns of the *PIN1* gene and CHD should be considered. For example, *PIN1* polymorphism may be a new genetic basis for screening high-risk CHD populations and for defining new CHD subtypes, and *PIN1*-based targeted prevention and treatment for CHD may be achieved via novel Pin1 inhibitors (such as juglone and small molecules that are currently being developed by structural biologists). According to the principles of pharmacogenomics,²³⁻²⁷ *PIN1* SNPs may be valuable biomarkers for optimizing the therapeutic dosages of NO-regulating drugs such as nitrates, calcium channel blockers and estrogen, in order to achieve greater efficacy as well as to minimize potential clinical side effects.

Conclusion

This work succinctly reveals the SNP profiles of *PIN1* in CHD patients. To our knowledge, this is the first research that focuses on the relationship between the *PIN1* gene and human CHD and is also the first explicit linkage determination of nine *PIN1* SNPs in humans. This linkage analysis predicts synergistic CHD risks and may exclude redundant SNPs for more convenient, efficient and economical CHD risk assessment.

The above findings also highlight a novel genetic basis for promoting molecular mechanism studies, early prevention and targeted treatment of CHD and other Pin1-related comorbidities. These predictions need to be verified in clinical studies on CHD patients and control individuals in the near future.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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