福島県立医科大学学術成果リポジトリ
FUKUSHIMA MEDICAL UNIVERSITY

Linkage disequilibrium analyses of natriuretic peptide precursor B locus reveal risk haplotype conferring high plasma BNP levels

メタデータ	言語: English 出版者: Elsevier Inc. 公開日: 2010-06-08 キーワード (Ja): キーワード (En): BNP, NPPB, SNP, Aged, Analysis of Variance, Asian Continental Ancestry Group, Female, Gene Frequency, Genotype, Haplotypes, Humans, Japan, Linkage Disequilibrium, Male, Middle Aged, Natriuretic Peptide, Brain, Polymorphism, Single Nucleotide, Risk Factors 作成者: Takeishi, Yasuchika, Toriyama, Sayumi, Takabatake, Noriaki, Shibata, Yoko, Konta, Tsuneo, Emi, Mitsuru, Kato, Takeo, Kawata, Sumio, Kubota, Isao メールアドレス: 所属:
URL	https://fmu.repo.nii.ac.jp/records/2000009

Linkage disequilibrium analyses of natriuretic peptide precursor B locus reveal risk haplotype conferring high plasma BNP levels.

Yasuchika Takeishi, MD[1], Sayumi Toriyama, MS[4], Noriaki Takabatake, MD[1], Yoko Shibata, MD[1], Tsuneo Konta, MD[1], Mitsuru Emi, MD[4], Takeo Kato, MD[2], Sumio Kawata, MD[3], and Isao Kubota, MD[1].

[1]Department of Cardiology, Pulmonology, and Nephrology, [2]Department of Neurology, Hematology, Metabolism, Endocrinology and Diabetology, [3]Department of Gastroenterology, Yamagata University School of Medicine, Yamagata, and [4] HuBit genomix Inc. Research Institute, Tokyo, Japan.

A short title: NPPB SNP and plasma BNP

4 Tables and 3 Figures

Address for correspondence: Yasuchika Takeishi, M.D.
Department of Cardiology, Pulmonology, and Nephrology
Yamagata University School of Medicine
2-2-2 Iida-Nishi, Yamagata, Japan 990-9585
E-mail: takeishi@med.id.yamagata-u.ac.jp
Phone: +81-23-628-5302 Fax: +81-23-628-5305

ABSTRACT

Background: Brain natriuretic peptide (BNP) has been widely used for the diagnosis and prognostic evaluation of chronic heart failure (CHF). In the present study, we performed association study of single nucleotide polymorphisms (SNPs) surrounding the natriuretic peptide precursor B (NPPB) gene with plasma BNP levels in 2970 adult Japanese. **Methods and Results:** Association analysis between SNPs of the NPPB gene and plasma BNP revealed significant associations of the 8 SNPs surrounding the entire NPPB gene with plasma BNP levels. For instance, as to SNP rs198389 (T-381C), plasma BNP levels among the three genotypic categories, i.e., 2189 homozygous T-allele carriers (BNP 26.4 $\pm$ 0.6 pg/ml), 697 heterozygous carriers (35.0 $\pm$ 1.1 pg/ml) and 52 homozygous C-allele carriers (46.0 $\pm$ 4.1 pg/ml) indicated a co-dominant effect of the minor C-allele on elevating plasma BNP levels ($P < 0.0001$). Linkage disequilibrium (LD) analysis among the 8 SNPs revealed that the region consisted of two, 5' major and 3' minor, LD blocks. Haplotype-based association analysis demonstrated that plasma BNP levels were associated closely with the haplotypes-1 and -2 of the major LD block. **Conclusion:** These results suggest that genetic variation at the primary locus NPPB gene, represented by definition of risk haplotypes, may be an important determinant of plasma BNP levels.

Key words: BNP; NPPB; SNP

INTRODUCTION

Despite the significant reduction in mortality achieved in clinical trials, chronic heart failure (CHF) patients still have a poor prognosis (1). The role of cardiac biomarkers in the evaluation and risk stratification of patients presenting to the hospital with possible heart failure continues to increase in importance (2). Biomarkers can serve to confirm the diagnosis in symptomatic patients, help in the assessment of patients who present with nonspecific symptoms, and evaluate prognosis of patients. Brain natriuretic peptide (BNP) is a 32-amino acid protein secreted from cardiac ventricles in response to mechanical overload (3). BNP plays an important role in regulating blood pressure and body fluid volume. In addition, the diagnostic and prognostic value of plasma BNP levels in CHF is supported in many studies (4-6). Plasma BNP level monitoring has been proposed for the treatment optimization in patients with CHF (7). However, the actual mechanisms that control this cardiac hormone have not yet been clarified.

Single nucleotide polymorphism (SNP) represents the most frequent type of human population DNA variation (8, 9). The world wide Human Genome Project and HapMap project have revealed the existence of numerous numbers of SNPs and ethnic differences of frequencies of SNPs among races in human population (10, 11). One of the main goals of

SNP research is to understand the genetics of the human phenotype variation (12).

In this study, we found significant association of 8 polymorphisms surrounding the natriuretic peptide precursor B (NPPB) gene including T-381C polymorphism in the promoter region with plasma BNP levels in a large general population of Japanese adults. We also evaluated linkage disequilibrium (LD) and haplotype structure within this gene.

METHODS

Subjects

This study is a part of the ongoing molecular epidemiological study utilizing the regional characteristics of the 21st Century Centers of Excellence (COE) program in Japan. The survey population in the present study is the general population over 40 years old in Takahata Town, Yamagata, Japan as described previously (13). Briefly, from 2004 to 2005, 2970 subjects (1343 males and 1626 females, mean age 63.0 $\pm$ 10.2 years) participated in the program and agreed to join the study (Table 1). The study protocol was approved by the Institutional Ethical Committee. All subjects gave written informed consent.

SNP typing

Analysis of genetic polymorphisms SNP genotyping was performed by Invader assay (Third Wave Technologies, Madison, WI, USA) (14, 15) and TaqMan Allelic discrimination assay (16). Reagents were purchased from Applied Biosystems (Foster City, CA, USA). TaqMan probes were designed and synthesized by Applied Biosystems, and distinguish the SNPs at the end of a polymerase chain reaction. One allelic probe was labeled with the fluorescent FAM dye and the other with the fluorescent VIC dye. Polymerase chain reaction was performed by TaqMan Universal Master Mix with polymerase chain reaction primers at

concentrations of 225 nM and TaqMan MGB probes at concentrations of 50 nM. Reactions were performed in 382-well formats in a total reaction volume of 3 μL using 3.0 ng of genomic DNA. The plates were then placed in a GeneAmp PCR system 9700 (Applied Biosystem) and heated at 95 °C for 10 min, followed by 40 cycles at 92 °C for 15 sec and at 60 °C for 1 min, with a final soak at 25 °C. The plates were read by the Prism 7900HT instrument (Applied Biosystems) where the fluorescence intensity in each well of the plate was read. Fluorescence data file from each plate were analyzed by the SDS 2.0 allele calling software (Applied Biosystems). Several data (signal intensity) were eliminated to preserve the reliability of the assay system (missing data were less than 1.1%).

Assay of plasma BNP levels

Blood samples were obtained for measurements of plasma concentrations of BNP. These samples were transferred to chilled tubes containing 4.5 mg of ethylenediaminetetra-acetic acid disodium salt (Na-EDTA) and aprotinin (500 U/ml), and centrifuged at 1,000 *g* for 15 min at 4 °C. The clarified plasma samples were frozen, stored at −70 °C and thawed just before assays (17). BNP concentrations were measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit, Shionogi Co. Ltd, Tokyo, Japan). The analytical range of assay was 4-2000 pg/ml.

Statistical analysis

The Hardy-Weinberg's equilibrium of alleles at the individual loci was evaluated using a chi-square test ($P > 0.05$) as implemented in R 2.5 package "genetics" (http://www.r-project.org/). The association between the genotypes and plasma BNP levels was tested by regression analysis and analysis of variance (ANOVA) using SPSS version 15.0.1J (SPSS, Inc., Chicago IL, USA). Linkage disequilibrium (LD) for all possible two-way combinations of the SNPs was tested with D' and r^2 by using Haploview Ver. 3.32 (18). Haplotypes were inferred, and haplotype frequencies were estimated using the modified expectation-maximization (EM) method of haplotype inference included in haplo.stats program (19). Haplotype-based association with clinical traits was performed using the haplo.stats program, output global score statistics and haplotype-specific scores derived from generalized linear models. In covariance, we estimated the relation genotype or haplotype and plasma BNP levels adjusted for age. The statistical significance was assigned at P value of less than 0.05.

RESULTS

Association of polymorphisms at NPPB with plasma BNP levels

To examine the relationship between the NPPB locus and plasma BNP levels, we performed association analysis with 8 SNPs that display minor allele frequencies > 0.1 (Figure 1). Nature of each SNP is summarized in Table 2. No deviation of genotypic frequencies from Hardy-Weinberg's equilibrium was observed ($P < 0.05$). We observed extremely significant association ($P < 0.0001$) of all the 8 SNPs at the NPPB gene with plasma BNP levels when the individuals were categorized into three groups for each of the SNPs (Table 3). For instance, as to the promoter SNP rs198389 (T-381C), plasma BNP levels among the three genotypic categories, i.e., 2189 homozygous T-allele carriers (BNP 26.4 $\pm$ 0.6 pg/ml), 697 heterozygous carriers (35.0 $\pm$ 1.1 pg/ml) and 52 homozygous C-allele carriers (46.0 $\pm$ 4.1 pg/ml) indicated a co-dominant effect of the minor C-allele on elevating plasma BNP levels ($P < 0.0001$) as shown in Figure 2.

LD and haplotype structure at the NPPB locus

We investigated LD for all possible two-way comparisons among the 8 selected SNPs in NPPB. Analysis of D' revealed two highly structured LD blocks ($|D'|>0.8$), a major LD block (SNPs rs6676300, rs198389, rs198388, rs6668352, rs198375, and rs632793) and a

minor LD block (SNPs rs5063 and rs198358) as shown in Figure 3. Haplotypes were constructed for the major LD block on the basis of genotypes for all sequence variations spanning the region, and haplotype frequencies in each of the three genotypic populations were estimated using the EM algorithm with phase-unknown samples. Two common haplotypes (frequency more than 5%) were observed within the region (Table 4). A haplotype-1 consisting of TTGCAT from SNP1 to SNP6 showed significantly negative haplotype-specific score (-6.2576, $P < 0.0001$), suggesting that this haplotype was inversely correlated with plasma BNP levels. In contrast, haplotypes-2 carrying the identical genotypic combination CCATGC from SNP1 to SNP6 appears to be the haplotypes responsible for risk of elevating effect on plasma BNP levels positive (haplotype specific score 7.0991, $P < 0.0001$).

DISCUSSION

In the present study, both single SNP analysis and haplotype-based analysis revealed that the population having the NPPB SNPs is associated with plasma BNP levels. Mean BNP levels were 26.4 $\pm$ 0.6, 35.0 $\pm$ 1.1, and 46.0 $\pm$ 4.1 pg/ml in population having NPPB rs198389 T/T, T/C, and C/C ($P < 0.0001$), respectively. LD profiles among SNPs revealed that the region analyzed consisted of 2 LD blocks. Haplotype-based association analysis demonstrated that plasma BNP levels were associated closely with the haplotypes 'TTGCAT' and 'CCATGC' in the major LD block.

It has been reported that plasma BNP levels are increased with aging (20) and inversely correlated with body mass index (BMI) in individuals with (21) and without (22) CHF. Plasma BNP concentrations are higher in women than in men (23). In the present study, we showed that the NPPB gene is a key source of inter-individual variation in plasma BNP levels. The fact that the strongest relationship was seen with a 5' flanking variant suggests that this effect may be due to differences in transcriptional regulation. The regulatory regions of the NPPB gene have been previously reported (24). Although the T-381C variant (rs198389) does not fall into verified regulatory sequences, it is in close proximity to known transcriptional factor binding sites. Recently, it has been reported that -381C allele was associated with higher BNP promoter activity in reporter gene assays (25).

Meirhaeghe et al. have assessed T-381C polymorphism (rs198389) and risk of type 2 diabetes. They found that individuals bearing the -381CC genotype had lower fasting glucose levels than -381TC or -381TT individuals in European study population (25). Moreover, the -381CC genotype was less frequent in individuals with type 2 diabetes (13.6%) or with impaired fasting glucose (12.9%) compared to normoglycemic individuals (17.8%). On the other hand, it has been reported that plasma BNP levels are higher in individuals with essential hypertension than in normotensive individuals (26). Therefore, Kosuge et al. assessed the relationship between polymorphisms in the NPPB gene and essential hypertension (27). They found that the 16-repeat allele of the variable number of tandem repeat polymorphism in the 5'-flanking region of NPPB is associated with essential hypertension among Japanese female.

Our data have potential implications for diagnostic and prognostic values of plasma BNP levels. The fact that variants in NPPB gene are associated with alterations in plasma BNP levels suggests that these variants may change the predictive abilities of BNP for diagnosing heart failure, determining prognosis, and responses to optimal medical therapy. Genetic analyses may be able to explain the wide variability of plasma BNP levels in the study population and better define the clinical utility of this important biomarker. Further study is necessary to define the impact of genetic variation on the clinical interpretation of plasma BNP levels.

Acknowledgements

This study was supported in part by a grant-in-aid from the 21st Century Center of Excellence (COE) program of the Japan Society for the Promotion of Science.

REFERENCES

1. Cowburn PJ, Cleland JG, Coats AJ, Komajda M. Risk stratification in chronic heart failure. Eur Heart J. 1998; 19: 696-710.
2. Bettencourt P, Ferreira A, Dias P. Predictors of prognosis in patients with stable mild to moderate heart failure. J Card Fail. 2000; 6: 306-313.
3. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998; 339: 321-328.
4. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation. 1997; 96: 509-516.
5. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J. 1998; 135: 825-832.
6. Maeda K, Tsutamoto T, Wada A, Mabuchi N, Hayashi M, Tsutsui T, et al. High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. J Am Coll Cardiol. 2000; 36: 1587-1593.

7. Jourdain P, Jondeau G, Funck F, Gueffet P, Helloco AL, Donal E, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure. J Am Coll Cardiol 2007; 49: 1733-1739.

8. Gray IC, Campbell DA, Spurr NK. Single nucleotide polymorphisms as tools in human genetics. Hum Mol Genet 2000; 9:2403-2408.

9. McCarthy JJ, Hilfiker R. The use of single-nucleotide polymorphism maps in pharmacogenomics. Nat Biotechnol 2000; 18: 505-508.

10. Bentley DR. The human genome project—an overview. Med Res Rev 2000; 20: 189-196.

11. Cardon LR, Abecasis GR. Using haplotype blocks to map human complex trait loci. Trends Genet 2003; 19: 135-140.

12. Altshuler D, Brooks LD, Chakravarti A, Collins FS, Daly MJ, Donnelly P. International HapMap Consortium. A haplotype map of the human genome. Nature 2005; 437: 1299-1320.

13. Konta T, Hao Z, Abiko H, Ishikawa M, Takahashi T, Ikeda A, et al. Prevalence and risk factor analysis of microalbuminuria in Japanese general population: The Takahata study. Kidney Int 2006; 70: 751-756.

14. Lyamichev V, Mast AL, Hall JG, Prudent JR, Kaiser MW, Takova T, Kwiatkowski RW, Sander TJ, de Arruda M, Arco DA, Neri BP, Brow MA. Polymorphism identification

and quantitative detection of genomic DNA by invasive cleavage of oligonucleotide probes. Nat Biotechnol 1999; 17: 292-296.

15. Mein CA, Barratt BJ, Dunn MG, Siegmund T, Smith AN, Esposito L, Nutland S, Stevens HE, Wilson AJ, Phillips MS, Jarvis N, Law S, de Arruda M, Todd JA. Evaluation of single nucleotide polymorphism typing with invader on PCR amplicons and its automation. Genome Res 2000; 10: 330-343.
16. Livak KJ. Allelic discrimination using fluorogenic probes and the 5' nuclease assay. Genet Anal 1999; 14: 143-149.
17. Niizeki T, Takeishi Y, Arimoto T, Takahashi T, Okuyama H, Takabatake N, et al. A combination of heart-type fatty acid binding protein and brain natriuretic peptide can reliably risk stratify patients hospitalized for chronic heart failure. Circ J 2005; 69: 922-927.
18. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005; 21: 263-265.
19. Schaid DJ, Rowland CM, Tines DE, Jacobson RM, Poland GA. Score tests for association between traits and haplotypes when linkage phase is ambiguous. Am J Hum Genet 2002; 70: 425-434.
20. Hogenhuis J, Voors AA, Jaarsma T, Hillege HL, Boomsma F, van Veldhuisen DJ. Influence of age on natriuretic peptides in patients with chronic heart failure: a

comparison between ANP/NT-ANP and BNP/NT-proBNP. Eur J Heart Fail 2005; 7: 81-86.

21. Mehra MR, Uber PA, Park MH, Scott RL. Ventura HO, Harris BC, et al: Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004; 43: 1590-1595.
22. Wang TJ, Larson MG, Levy D, Benjamin EJ Leip EP, Wilson PW, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004; 109: 594-600.
23. Mir TS, Flato M, Falkenberg J, Haddad M, Budden R, Weil J, et al. Plasma concentrations of N-terminal brain natriuretic peptide in healthy children, adolescents, and young adults: effect of age and gender. Pediatr Cardiol 2006; 27: 73-77.
24. LaPointe MC. Molecular regulation of the brain natriuretic peptide gene. Peptides 2005; 9: 44-56.
25. Meirhaeghe A, Sandhu MS, McCarthy MI, Groote PD, Cottel D, Arveiler D, et al. Association between the T-381C polymorphism of the brain natriuretic peptide gene and risk of type 2 diabetes in human populations. Hum Mol Genet 2007; 16: 1343-1350.
26. Mukoyama M, Nakao K, Saito Y, Ogawa Y, Hosoda K, Suga S, et al. Human brain natriuretic peptide, a novel cardiac hormone. Lancet 1990; 335: 801-802.
27. Kosuge K, Soma M, Nakayama T, Aoi N, Sato M, Izumi Y, et al. A novel variable number of tandem repeat of the natriuretic peptide precursor B gene's 5'-flanking region

is associated with essential hypertension among Japanese females. Int J Med Sci 2007; 4: 146-152.

FIGURE LEGENDS

Figure 1. The 8 polymorphisms in the NPPB gene with surrounding polymorphisms examined in the present study.

Figure 2. Comparisons of plasma BNP levels among genotypically determined groups according to one NPPB variation, rs198389.

Figure 3. Major haplotypes of the major LD block of the NPPB locus consisting of 6 SNPs.

Table 1. Baseline clinical characteristics of the study population.

	n=2970	Male (n=1343)	Female (n=1626)
Age (year)	63.0 ± 10.2	63.4 ± 10.4	62.7 ± 10.1
height (cm)	156.6 ± 9.0	163.4 ± 6.9	151 ± 6.2
weight (kg)	57.8 ± 10.2	62.8 ± 9.8	53.7 ± 8.6
BMI (kg/m^2)	23.5 ± 3.2	23.5 ± 2.9	23.5 ± 3.4
SBP (mm Hg)	134.2 ± 15.8	136.0 ± 15.5	132.7 ± 16.0
DBP (mm Hg)	79.3 ± 10.0	81.8 ± 9.8	77.3 ± 9.8
BNP (pg/ml)	28.8 ± 31.0	28.1 ± 34.2	29.3 ± 27.9

*The sex of one subject was unknown and was excluded from analysis.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic polypeptide.

Values are presented as mean ± SD.

Table 2. The 8 polymorphisms in the NPPB gene with surrounding polymorphisms examined in the study.

SNPID	Gene Symbol	NCBI SNP Reference	SNP Type	Chr	Public Location Position (B36.2)	Allele 1	Allele 2	Allele frequency		Genotype			Heterozygosity
								Allele 1	Allele 2	11	12	22	
SNP1	-	rs6676300	Intergenic	1	11798170	T	C	0.86	0.14	2158	722	66	0.248
SNP2	NPPB	rs198389	Promoter	1	11792217	T	C	0.86	0.14	2189	697	52	0.236
SNP3	NPPB	rs198388	3' near gene	1	11790644	G	A	0.86	0.14	2191	712	57	0.240
SNP4	-	rs6668352	Intergenic	1	11789021	C	T	0.87	0.13	2267	641	51	0.220
SNP5	-	rs198375	Intergenic	1	11786566	A	G	0.84	0.16	2081	808	76	0.271
SNP6	-	rs632793	3'-untranslated	1	11784631	T	C	0.86	0.14	2212	701	52	0.235
SNP7	NPPA	rs5063	Coding	1	11780518	C	T	0.91	0.09	2451	495	18	0.163
SNP8	-	rs198358	Intergenic	1	11777433	T	C	0.89	0.11	2356	582	29	0.192

NCBI, National Center for Biotechnology Information; NPPA, natriuretic peptide precursor A; NPPB, natriuretic peptide precursor B; Chr, chromosome; Allele 1, major allele; Allele 2, minor allele.

Table 3. The association analysis of each SNP examined in the study with the plasma BNP level using parametric measure.

SNP ID	NCBI reference ID	ANOVA	Post-hock (LSD) *p* value			mean ± SE			genotype		
		p value	11 vs. 12	11 vs. 22	12 vs. 22	11	12	22	11	12	22
SNP1	rs6676300	< 0.0001	< 0.0001	< 0.0001	0.019	26.4 ± 0.6	34.5 ± 1.1	43.4 ± 3.6	T/T	T/C	C/C
SNP2	rs198389	< 0.0001	< 0.0001	< 0.0001	0.010	26.4 ± 0.6	35.0 ± 1.1	46.0 ± 4.1	T/T	T/C	C/C
SNP3	rs198388	< 0.0001	< 0.0001	< 0.0001	0.004	26.5 ± 0.6	34.0 ± 1.1	45.6 ± 3.9	G/G	G/A	A/A
SNP4	rs6668352	< 0.0001	< 0.0001	< 0.0001	0.001	26.9 ± 0.6	33.9 ± 1.2	48.0 ± 4.1	C/C	C/T	T/T
SNP5	rs198375	< 0.0001	< 0.0001	< 0.0001	0.031	26.7 ± 0.6	33.0 ± 1.0	40.6 ± 3.3	A/A	A/G	G/G
SNP6	rs632793	< 0.0001	< 0.0001	< 0.0001	0.003	26.8 ± 0.6	33.8 ± 1.1	46.0 ± 4.0	T/T	T/C	C/C
SNP7	rs5063	< 0.0001	< 0.0001	NS	NS	27.4 ± 0.6	35.0 ± 1.3	37.6 ± 6.8	C/C	C/T	T/T
SNP8	rs198358	< 0.0001	< 0.0001	NS	NS	27.4 ± 0.6	33.7 ± 1.2	36.5 ± 5.4	T/T	T/C	C/C

Abbreviations as in Table 2.

Table 4. Association of major haplotypes (frequency more than 5%) comprised from SNP1 to SNP6 with the plasma BNP levels.

Haplotypes							Frequencies	Haplotype-Specific Score Statistic	p-value
	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6			
	rs6676300	rs198389	rs198388	rs6668352	rs198375	rs632793			
Hap-1	T	T	G	C	A	T	0.8154	−6.2576	< 0.0001
Hap-2	C	C	A	T	G	C	0.1155	7.0991	< 0.0001

Global Score Statistics Global Statistics 52.03 df = 2 Global p-value < 0.0001

Chromosome 1

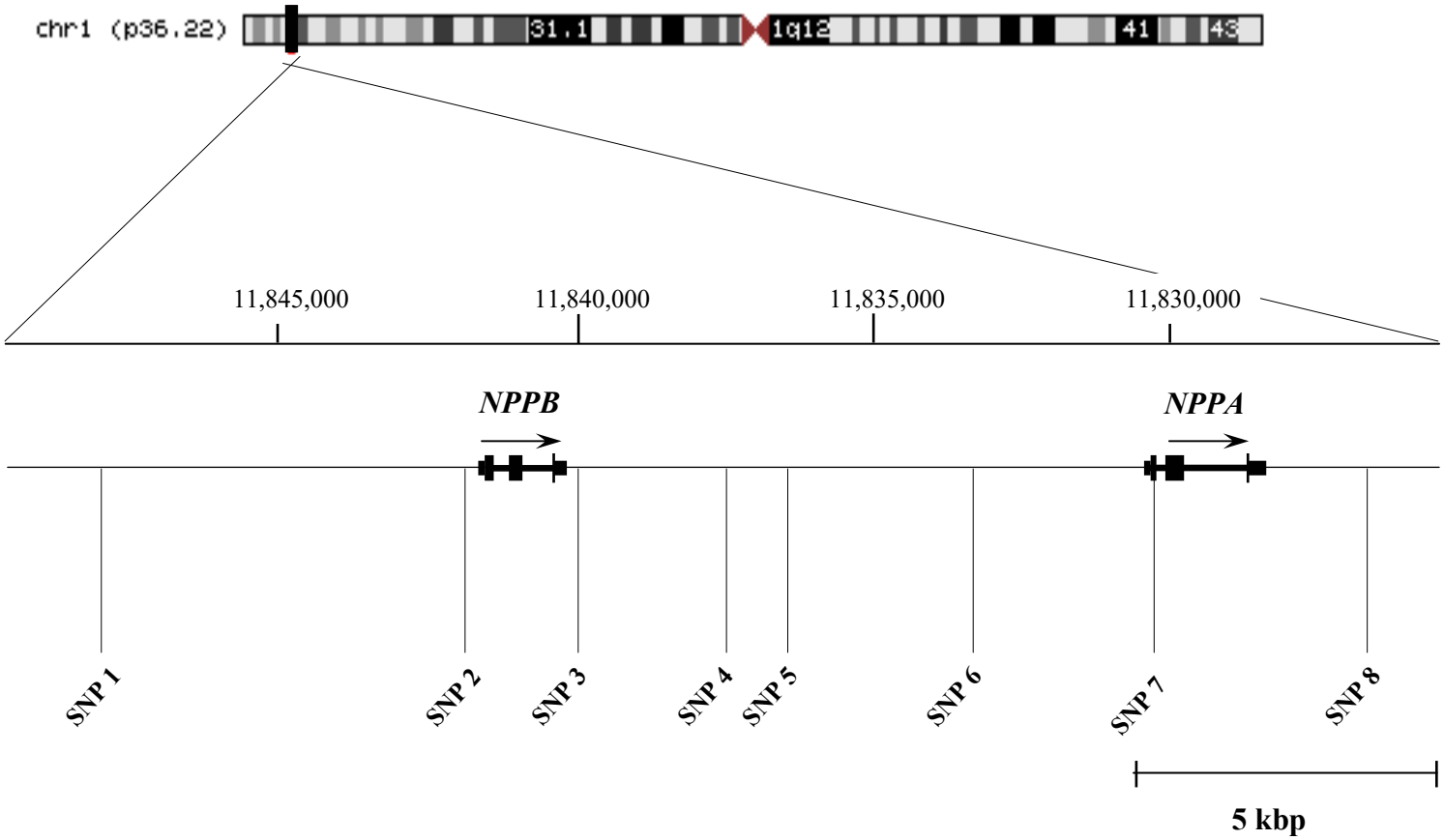

Figure 1

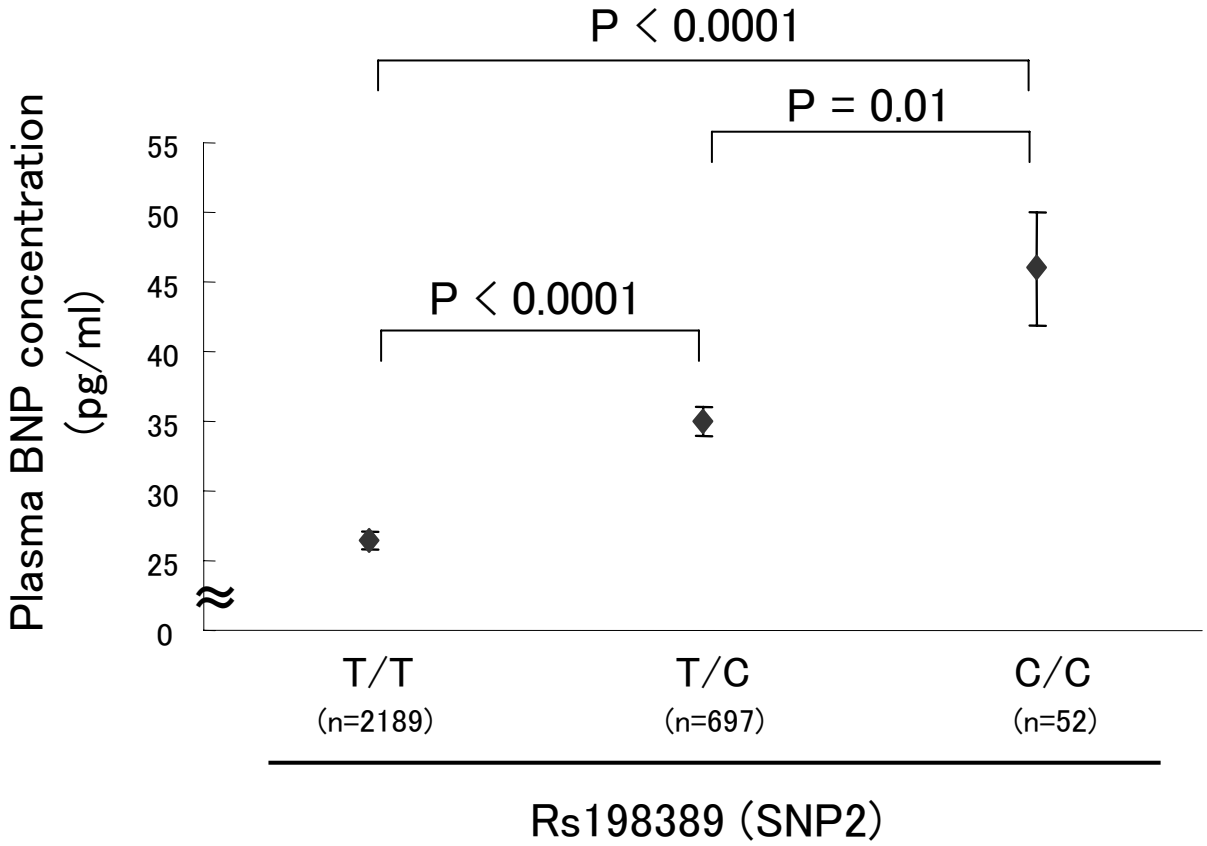
P < 0.0001
P = 0.01
P < 0.0001
Plasma BNP concentration (pg/ml)
55
50
45
40
35
30
25
0
T/T
(n=2189)
T/C
(n=697)
C/C
(n=52)
Rs198389 (SNP2)

Figure 2

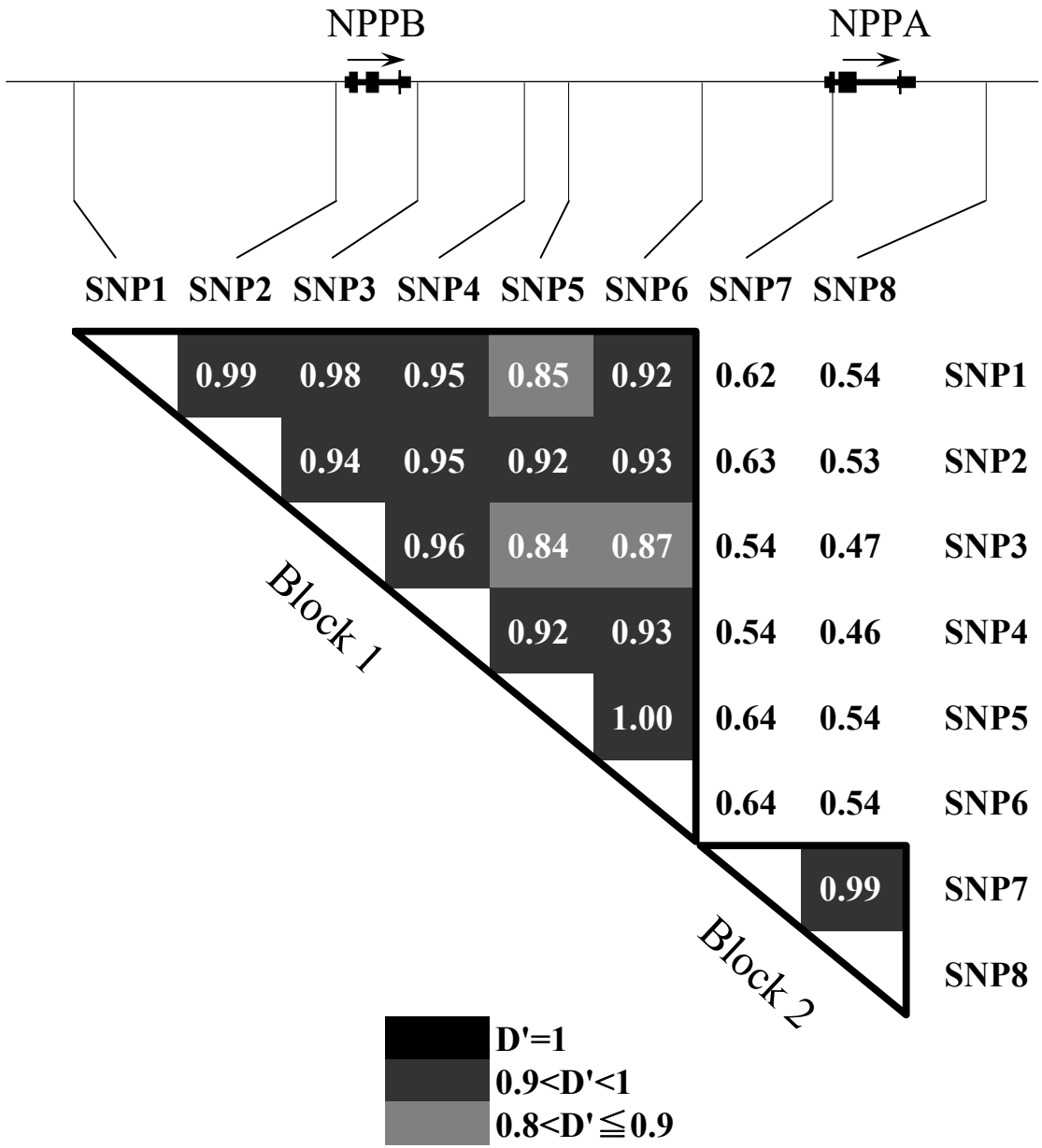
NPPB
NPPA
SNP1 SNP2 SNP3 SNP4 SNP5 SNP6 SNP7 SNP8
0.99 0.98 0.95 0.85 0.92 0.62 0.54 SNP1
0.94 0.95 0.92 0.93 0.63 0.53 SNP2
0.96 0.84 0.87 0.54 0.47 SNP3
0.92 0.93 0.54 0.46 SNP4
1.00 0.64 0.54 SNP5
0.64 0.54 SNP6
0.99 SNP7
SNP8
Block 1
Block 2
D'=1
0.9<D'<1
0.8<D'≦0.9

Figure 3