Serum Uric Acid Levels Are Associated with Polymorphism in the SAA1 Gene in Chinese Subjects

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Abstract

Objective: Serum uric acid (SUA) is a cardiovascular risk marker associated with inflammation. The serum amyloid A protein (SAA) is an inflammatory factor and is associated with cardiovascular disease (CVD). However, the relationship between genetic polymorphisms of SAA and SUA levels has not been studied. The objective of this study was to investigate the association between SUA levels and SAA genetic polymorphisms.

Methods: All participants were selected from subjects participating in the Cardiovascular Risk Survey (CRS) study. The single nucleotide polymorphism (SNP) rs12218 of the SAA1 gene was genotyped by using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. The association of SUA levels with genotypes was assessed by using the general liner model.

Results: The SNP rs12218 was associated with SUA levels by analyses of a dominate model (P = 0.002) and additive model (P = 0.005), and the difference remained significant after adjustment of sex, age, obesity, ethnicity, HDL-C, alcohol intake, smoking, and creatinine (P = 0.006 and P = 0.023, respectively). The TT genotype was associated with an increased SUA concentration of 39.34 mmol/L (95% confidence interval [CI], 3.61–75.06; P = 0.031) compared with the CC genotype, and the TT genotype was associated with an increased SUA concentration of 2.48 mmol/L (95% CI, 6.86–38.10; P = 0.005) compared with the CT genotype.

Conclusions: The rs12218 SNP in the SAA1 gene was associated with SUA levels in Chinese subjects, indicating that carriers of the T allele of rs12218 have a high risk of hyperuricemia.

Introduction

Serum uric acid (SUA) is the final product of purine metabolism in humans and higher primates. It has a well-established role in gout and is associated with other forms of inflammation and immune regulation as well [1]. The results of recent studies suggest that hyperuricemia is associated with inflammation and immune regulation [2,3]. A high level of SUA is associated with hypertension [4,5], insulin resistance [6,7], obesity [6,8] and cardiovascular events [5,9]. A potential mechanism by which uric acid could be associated with cardiovascular morbidity is via inflammation [10]. Experimental results show that SUA can stimulate the release of C-reactive protein (CRP) when entering vascular smooth muscle cells [11–12].

Serum amyloid A (SAA), one of the acute phase proteins, is an important inflammatory factor. The results of a previous study [13] show that in vivo concentrations of SAA can be dramatically increased (up to 1000-fold) in plasma during acute inflammatory conditions [14]. However, the relationship between SUA and SAA is unknown. In previous studies, we observed that the single nucleotide polymorphism (SNP) rs12218 in the SAA1 gene was associated with increased carotid artery intima–media thickness (IMT) values [15] and decreased HDL-C levels [16] and Ankle-to-Brachial Index [17], which are considered to be risk factors for cardiovascular disease (CVD). SUA levels were also associated with the risk of CVD via inflammation [10]. And SAA has been reported to be a more sensitive marker of inflammation and CVD than C-reactive protein (CRP) [13,14]. Therefore, we hypothesized that rs12218 of SAA1 is associated with SUA levels.

Methods

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University and was conducted according to the standards of the Declaration of Helsinki. Written, informed consent was obtained from the participants.
Subjects
All the participants were selected from the Cardiovascular Risk Survey (CRS) study, which was described previously [15,17]. Briefly, the CRS included 14,618 participants (5,757 Hans, 4,767 Uygurs, and 4,094 Kazakhs). Of these 14,618 subjects, 1,078 participants who were free from CVD were initially screened for the present study. The exclusion criteria were as follows: systolic and diastolic blood pressure (BP) $\geq$140/90 mmHg; fasting plasma glucose $\geq$ 7.0 mmol/L; total cholesterol $\geq$ 7.8 mmol/L; triglycerides $\geq$ 2.0 mmol/L; or electrocardiography (ECG) abnormalities and carotid artery plaques. Of the 1,078 screened, 107 were excluded, leaving us with 971 subjects for the present study. Among these 971 subjects, only 568 consented to providing blood samples for DNA analysis. The analysis presented in the present study was based on these 568 participants who met the eligibility criteria and for whom complete SAA1 genotype data were available.

Biological and lifestyle measurements
Height and body weight were measured as described previously [18]. Sitting blood pressure was measured three times during 10 min, and the median value was used for statistical analysis. Smoking and drinking status was self-reported via the study questionnaire as described previously [19,20]. Body mass index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared. Obesity was defined as BMI $\geq$ 25 kg/m$^2$, which was based on the WHO Asia-Pacific Area criterion for obesity described previously [18]. We measured the serum concentration of uric acid, total cholesterol, triglyceride, blood urea nitrogen (BUN), creatinine (Cr), low density lipoprotein (LDL), high density lipoprotein (HDL), and fasting glucose using chemical analysis equipment (Dimension AR/AVL Clinical Chemistry System, Newark, NJ) in the Clinical Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University as described previously [15–17,19,20].

SAA1 SNP genotyping
As described in the previous study [17], there are 115 SNPs for the human SAA1 gene listed in the National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/SNP). Using the Haploview 4.2 software and the HapMap phrase II database, we obtained four tagging SNPs (rs12218, rs4638289, rs7131332 and rs1603089) for Chinese Hans by using minor allele frequency (MAF) $\geq$ 0.05 and linkage disequilibrium patterns, with $r^2$ $\geq$ 0.8 as a cutoff. Because we found that only rs12218 was associated with CVD risks in the previous studies [15–17], we selected rs12218 for the present study. We genotyped rs12218 according to the protocol described previously [17]. To ensure the results were verified, 10% of the genotyped samples were duplicated, and at least one positive and one negative control per 96-well DNA plate were used in our assays. The accuracy of the genotyping was determined by assessing the genotype concordance between duplicate samples. We obtained a 100% concordance between the genotyped duplicate samples for the SNP. The genotyping success rate was 100%.

Table 1. Demographic and Risk Profile of the Study Population.

| Risk factor | No. (%) or Mean (SD) | Total cohort (n = 658) | Men (n = 450) | Women (n = 118) |
|-------------|----------------------|-----------------------|--------------|----------------|
| Age (years) |                      | 57.24 (11.84)         | 57.18 (12.28) | 57.46 (10.01) |
| Obesity     |                      | 150 (26.40)           | 124 (27.56)  | 26 (22.03)     |
| Never drink |                      | 312 (54.9)            | 237 (52.7)   | 75 (63.6)      |
| Former drinker (%) |          | 154 (27.1)            | 114 (25.3)   | 40 (33.9)      |
| Current drinker (%) |        | 102 (18.0)            | 99 (22.0)    | 3 (2.5)        |
| Never smoking (%) |              | 213 (37.5)            | 136 (30.2)   | 77 (65.3)      |
| Former smoking (%) |             | 153 (26.9)            | 114 (25.3)   | 39 (33.1)      |
| Current smoking (%) |            | 202 (35.6)            | 200 (44.4)   | 2 (1.7)        |
| BUN (mmol/L) |                      | 5.16 (1.53)           | 5.27 (1.56)  | 4.76 (1.36)    |
| Cr (mmol/L) |                       | 75.29 (19.96)         | 78.91 (20.03)| 61.49 (12.21)  |
| Uric acid (µmol/L) |                | 321.32 (92.68)        | 336.18 (93.63)| 264.68 (62.46) |
| Glucose (mmol/L) |                     | 4.69 (0.82)           | 4.67 (0.85)  | 4.75 (0.68)    |
| Triglyceride (mmol/L) |         | 1.81 (1.39)           | 1.86 (1.43)  | 1.65 (1.23)    |
| Total cholesterol (mmol/L) |          | 4.58 (1.16)           | 4.58 (1.18)  | 4.61 (1.10)    |
| HDL-C (mmol/L) |                     | 1.40 (0.46)           | 1.39 (0.47)  | 1.45 (0.39)    |
| LDL-C (mmol/L) |                      | 3.06 (1.0)            | 3.06 (0.98)  | 3.09 (1.07)    |

Note: HDL, high-density lipoprotein; LDL, high-density lipoprotein; doi:10.1371/journal.pone.0040263.t001

Table 2. Distribution of rs12218 in Han, Uygur, and Kazak population.

| rs12218 | Ethnicity | P value |
|---------|-----------|---------|
|         | Han (n = 321) | Uygur (n = 115) | Kazak (n = 132) |
| CC, n (%) | 19 (5.92) | 1 (0.87) | 8 (6.06) | 0.012 |
| CT, n (%) | 124 (38.63) | 64 (55.65) | 57 (43.18) | 0.250 |
| TT, n (%) | 178 (55.45) | 50 (43.48) | 67 (50.76) | 0.300 |

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Statistical analysis

All analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). Hardy-Weinberg equilibrium was assessed by chi-square analysis. Serum UA levels were normally distributed; therefore, the original values were used for analysis. General linear model (GLM) analysis was performed to test for associations between SNP genotypes and serum UA after adjusting for confounding variables. Two-tailed $P$-values were considered to be significant at the 0.05 level.

Results

Characteristics of study participants

The study cohort consisted of 568 subjects (450 men, 118 women). The clinical and metabolic characteristics of the study population are shown in Table 1. Table 2 shows the distributions of rs12218 in the Han, Uygur, and Kazak populations. Genotype distributions between each ethnicity were significantly different ($P=0.012$). Table 3 shows the characteristics of study participants according to their rs12218 genotypes. Each genotype was significantly different in terms of SUA, HDL-C, and drinking behavior ($P<0.05$ for all comparisons).

Table 3. Demographic and Risk Profile of the Study Population According to rs12218 Genotypes.

| Risk factor          | rs12218 genotypes [No. (%) or Mean (SD)]  | $p$  |
|----------------------|------------------------------------------|------|
|                      | CC (n = 28)                              |      |
|                      | CT (n = 245)                             |      |
|                      | TT (n = 295)                             |      |
| Age (years)          | 56.43(12.07)                             |      |
| Obesity              | 8 (28.57)                                |      |
| Never drink (%)      | 12 (42.86)                               |      |
| Former drinker (%)   | 15 (53.57)                               |      |
| Current drinker (%)  | 1 (3.57)                                 |      |
| Never smoking (%)    | 10 (35.71)                               |      |
| Former smoking (%)   | 8 (28.57)                                |      |
| Current smoking (%)  | 10 (35.71)                               |      |
| BUN (mmol/L)         | 5.02(1.44)                               |      |
| Cr (mmol/L)          | 70.94(23.3)                              |      |
| Uric acid (mmol/L)   | 293.62(92.89)                            |      |
| Glucose (mmol/L)     | 4.69(0.64)                               |      |
| Triglyceride (mmol/L)| 1.63(0.85)                               |      |
| Total cholesterol (mmol/L) | 4.47(1.17) |      |
| HDL–C (mmol/L)       | 1.26(0.40)                               |      |
| LDL–C (mmol/L)       | 3.24(1.23)                               |      |

Note: HDL, high-density lipoprotein; LDL, high-density lipoprotein; doi:10.1371/journal.pone.0040263.t003

Table 4. SUA levels and SAA1 genotypes.

| SNP                  | Unadjusted model | Adjusted model |
|----------------------|------------------|----------------|
| rs12218 Genotypes    | SUA (mmol/L)     | $P$ value      | SUA (mmol/L)     | $P$ value      |
|                      | Mean (SD)        |                | Mean (SE)        |                |
| Additive model       |                  |                |
| CC (n = 28)          | 293.62 (92.89)   | 0.005          | 309.72 (15.25)   | 0.023          |
| CT (n = 245)         | 310.48 (89.80)   |                | 312.10 (5.15)    |                |
| TT (n = 295)         | 332.96 (93.68)   |                | 330.49 (4.68)    |                |
| Dominant model       |                  |                |
| CC+CT (n = 273)      | 308.75 (90.09)   | 0.002          | 311.86 (4.87)    | 0.006          |
| TT (n = 295)         | 332.96 (93.68)   |                | 330.49 (4.68)    |                |
| Recessive model      |                  |                |
| CC (n = 28)          | 293.62 (92.89)   | 0.105          | 309.88 (15.33)   | 0.436          |
| CT+TT (n = 540)      | 322.76 (92.53)   |                | 322.16 (3.47)    |                |

$^1$Analysis of covariance adjusted for sex, age, Cr, obesity, ethnicity, HDL-C, smoking and drinking. 

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Table 5. Interaction of rs12218 and other confounders on SUA.

| Source            | Squares | df | Mean Square | F     | P       |
|-------------------|---------|----|-------------|-------|---------|
| Corrected Model   | 1.801×10^{-6} | 19 | 94787.509   | 17.145 | <0.001  |
| Rs12218           | 14194.811 | 2  | 7097.406    | 3.155  | 0.043   |
| Age               | 27856.254 | 1  | 27856.254   | 5.039  | 0.025   |
| BUN               | 27943.440 | 1  | 27943.440   | 5.054  | 0.025   |
| Glucose           | 7013.364  | 1  | 7013.364    | 1.269  | 0.261   |
| Cr                | 403270.745 | 1  | 403270.745  | 72.944 | <0.001  |
| Triglyceride      | 201494.695 | 1  | 201494.695  | 36.446 | <0.001  |
| Total cholesterol | 1215.210  | 1  | 1215.210    | 0.220  | 0.639   |
| HDL-C             | 4810.028  | 1  | 4810.028    | 0.870  | 0.351   |
| LDL-C             | 6430.867  | 1  | 6430.867    | 11.631 | 0.001   |
| Sex               | 91370.100 | 1  | 91370.100   | 16.527 | <0.001  |
| Drinking          | 1869.215  | 1  | 1869.215    | 0.338  | 0.561   |
| Obesity           | 42965.305 | 1  | 42965.305   | 7.772  | 0.005   |
| Rs12218 * sex     | 11572.711 | 2  | 5786.355    | 1.047  | 0.352   |
| Rs12218 * drinking| 8397.275  | 2  | 4198.638    | 0.759  | 0.468   |
| Rs12218* HDL-C    | 693.427   | 2  | 346.713     | 0.063  | 0.939   |

R Squared = 0.374 (Adjusted R Squared = 0.352).

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SAA1 genotype and SUA

The genotype frequencies for the rs12218 were in Hardy-Weinberg equilibrium (P>0.05). Table 4 shows that rs12218 was associated with SUA by analyses of a dominate model (P = 0.002) and an additive model (P = 0.005), and the difference remained significant after adjustment for sex, age, ethnicity, HDL-C, obesity, alcohol intake, smoking, and creatinine levels (P = 0.006, P = 0.023, respectively). The TT genotype was associated with an increased SUA concentration of 39.54 mmol/L (95% confidence interval [CI], 3.61–75.06, P = 0.031) compared with the GG genotype, and the TG genotype was associated with an increased SUA concentration of 2.48 mmol/L (95% CI, 3.86–38.10; P = 0.005) compared with the CT genotype. Taking into account the possible interactions between rs12218 and other variables, we analyzed all these variables using a general linear model and found no interactions between rs12218 and sex, alcohol intake, or HDL-C level (Table 5).

Discussion

In the present study, we observed that variation in the SAA1 gene is associated with SUA in Chinese subjects. Individuals with the T allele of rs12218 had significantly higher SUA levels than did C allele carriers. To the best of our knowledge, this is the first study to investigate the common allelic variant in the SAA1 gene and its association with SUA levels.

Hyperuricemia has been implicated in multiple physiologic outcomes, including coronary artery disease, hypertension [4,5], and obesity [6,8]. Hyperuricemia is suspected to influence the development of CVD via its role in inflammation [10]. SAA is in a family of proteins that forms a major component of the acute-phase inflammatory response [21]. It is synthesized in the liver in response to inflammation and infection [22] and is considered to be a sensitive marker of an acute inflammatory state. Therefore, SUA and SAA may be associated. However, up to date, the relationship between SAA and SUA remains unclear.

Accumulated evidence generated from genome-wide association studies (GWAS) has linked uric acid to specific genomic loci, such as SLC2A9, PDZK1, GCKR, SLC16A9, SLC22A11, SLC22A12, and ABCG2, in individuals of European and Asian descent [23–26]. Although the foundation for human studies examining putative causative genes that may be involved in hyperuricemia is based on a GWAS method, the candidate-gene approach is an important way to explore the association of hyperuricemia with genetic polymorphisms. This approach involves selecting a functionally relevant gene to study and subsequently investigating its association with SUA levels. The gene for SAA1 is a candidate hyperuricemia gene because it encodes the important inflammation factor SAA. This factor was identified in the early 1970s as the plasma protein responsible for forming tissue deposits called amyloid (AA-type), which are seen clinically in diseases with underlying persistent acute inflammation [27,28].

In previous studies, we found that the rs12218 SNP in the SAA1 gene was associated with IMT [15], HDL level [16], and ABI [17], which is involved in CVD. In the present study, we found that the rs12218 polymorphism is associated with SUA concentration, which is also related to CVD. Compared with C-allele carriers, individuals with the T allele of rs12218 had significantly higher SUA levels. This association remains significant after adjustment for age, sex, obesity, ethnicity, HDL-C, alcohol intake, smoking status, and creatinine levels.

The mechanisms which may link SAA1 genetic polymorphisms to SUA levels are largely unknown. The results of previous studies show a close association between elevated SUA and several inflammatory markers such as white blood cells, TNF-α, and CRP [29]. Also, uric acid directly stimulates the production of inflammatory mediators such as CRP in vascular cells [30]. However, the relationship between SAA and SUA remains unclear. In the present study, we observed that the SAA1 genetic polymorphism was associated with elevated SUA after adjusting for other confounders, indicating that the SAA1 gene polymorphism may be independently related to SUA level. However, the relationship between rs12218 and SUA may simply reflect their association with other inflammatory factors. Therefore, functional studies of rs12218 should be performed in the future.

In addition, rs12218 is a synonymous mutation and does not result in amino acid changes in the protein. However, rs12218 acting as a tagging SNP of SAA1 gene may be in total linkage disequilibrium with a nonsynonymous mutation, which we did not examine. Because both SAA and SUA are related to inflammation, the association of SAA1 polymorphism with SUA may be linked to SUA levels. In 1999, Yama et al. [31] reported that the SAA1 allele influences the plasma concentration of SAA. In the Japanese population, subjects with the SAA1.5 allele have a higher plasma concentration of SAA than those lacking this allele. In the present study, we did not examine the differences in SAA levels between each genotype, which was a limitation of our analysis. We think that this SNP may be associated with rs12218 although we could not identify the rs number of the SAA1.5 polymorphism described by Yama et al. [29]. Dietary intake of certain macronutrients and food items may also significantly affect SUA concentration. However, because both SAA and SUA are related to inflammation, we did not include these factors in our multivariable analysis, which is also a limitation of our study. We also did not perform experiments related to SAA1 gene function. In addition, in the present study, we found that there was significantly difference in distributions of genotypes in Han, Uygur, and Kazak population. However, due to the very small sample size in Uygur
and in Kazak population, we did not analyze the relationship between rs12218 and SUA in each ethnicity. Alternatively, we pooled these three ethnicities together to analyze the data and adjusted the effect of ethnicity by using multivariable analysis. This may be another limitation in our research.

In conclusion, a polymorphism of SAA1 gene was associated with the SUA level in Chinese subjects; our observation requires replication in a different population.

References

1. Shi Y, Evans JE, Rock KL (2003) Molecular identification of a danger signal that alerts the immune system to dying cells. Nature; 425:516–521.
2. Levy A, Anker SD, Godbold DF, Trerezira M, Helleswell PG, et al. (1998) Uric acid in chronic heart failure: A marker of chronic inflammation. European Heart Journal; 19: 1814–1822.
3. Shi Y (2010) Caught red-handed: uric acid is an agent of inflammation. J Clin Invest; 120:1809–1011.
4. Alger AR, Chen W, Lao Y, Srivivasan SR, Berenson GS, et al. (2005) Childhood uric acid predicts adult blood pressure: the Bogalusa Heart Study. Hypertension; 45: 34–38.
5. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, et al. (2003) Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension; 41: 1183–1190.
6. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, et al. (1996) Relationship of uric acid concentration to cardiovascular risk factors in young men. Role of obesity and central fat distribution. The Verona Young Men Atherosclerosis Risk Factors Study. Int J Obes Relat Metab Disord; 20: 975–980.
7. Ogura T, Matsuura K, Matsushita Y, Mimura Y, Kishida M, et al. (2002) Recent trends of hyperuricemia and obesity in Japanese male adolescents, 1991 through Metabolism; 2004; 53: 448–453.
8. Nakashima N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, et al. (2003) Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. Eur J Epidemiol; 18: 523–530.
9. Alderman MH, Cohen H, Madhavan S, Kivlighn S (1999) Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension; 34: 144–150.
10. Matsumoto E (2007) Uric acid: an old actor for a new role. Intern Emerg Med; 2: 1–2.
11. Montalcini T, Gorgone G, Gazzaroto C, Seiti G, Perricone F, et al. (2007) Relation between serum uric acid and carotid intima-media thickness in healthy postmenopausal women. Intern Emerg Med; 2: 19–23.
12. Martinou F, Petrelli V, Mayor A, Tzirivel A, Tschopp J (2006) Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature; 440: 237–241.
13. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, et al. (2003) Replication of the five novel loci for uric acid concentration and potential mediating mechanisms. Human Molecular Genetics, 19:387–395.
14. Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, et al. (2009) Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS Genet, 5(6): e1000504.
15. Wallace C, Newhouse SJ, Braund P, Zhang F, Tobi M, et al. (2008) Genome-wide association study identifies genes for biomarkers of cardiovascular disease: Serum urate and diastolic blood pressure as potential new targets for therapy. Eur J Hum Genet; 16: 1072–1080.
16. Xie X, Ma YT, Yang YN, Fu ZY, Li XM, et al. (2010) Association of genetic polymorphisms of serum amyloid protein A1 with plasma high density lipoproteins cholesterol. Zhonghua Yi Xue Za Zhi.; 90:1824–6.
17. Xie X, Ma YT, Yang YN, Fu ZY, Li XM, et al. (2011) Polymorphisms in the SAA1 gene are associated with ankle-to-brachial index in Han Chinese healthy subjects. Blood Pressure; 20(5):232–8.
18. Patel S, Flyvbjerg A, Kozáková M, Fryxell J, Ibrahim IM, et al. (2008) Variation in the APOPOQ gene promoter is associated with carotid intima media thickness independent of plasma adiponectin levels in healthy subjects. Eur Heart J; 29: 338–343.
19. Xie X, Ma YT, Fu ZY, Yang YN, Ma X, et al. (2009) Haplotype Analysis of the CYP1A1 gene associated with myocardial infarction. Clin Appl Thromb-Hem; 15: 574–580.
20. Xie X, Ma YT, Fu ZY, Yang YN, Ma X, et al. (2009) Association of polymorphisms of PTGS2 and CYP1A1 with myocardial infarction. Clin Chem Lab Med; 47: 347–352.
21. Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med.; 340: 448–454.
22. Uhlar CM, Whitehead AS (1999) Serum amyloid A, the major vertebrate acute-phase reactant. Eur J Biochem; 265:501–323.
23. van der Harst P, Bakker SJL, de Boer R, Wolfenbuttel BHR, Johnson T, et al. (2010) Replication of the five novel loci for uric acid concentrations and potential mediating mechanisms. Human Molecular Genetics, 19:387–395.
24. Zoller M, Johnson T, Sanna S, Teumer A, Vitart V, et al. (2009) Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS Genet, 5(6): e1000504.
25. Wallace C, Newhouse SJ, Braund P, Zhang F, Tobi M, et al. (2008) Genome-wide association study identifies genes for biomarkers of cardiovascular disease: Serum urate and diastolic blood pressure as potential new targets for therapy. Eur J Hum Genet; 16: 1072–1080.
26. Caulfield MJ, Munroe PB, O’Neill D, Witkowska K, Charach JF, et al. (2008) SLCA2A9 is a high-capacity urate transporter in humans. PLoS Med, 5(10): e197.
27. Bennett EP, Eriksen N, Hermodson MA, Ericsson LH (1971) The major proteins of human and monkey amyloid substance: Common properties including unusual N-terminal amino acid sequences. FEBS Lett; 19:169–173.
28. Levin M, Franklin EC, Frangione B, Pras M (1972) The amino acid sequence of an unusual N-terminal amino acid sequences. FEBS Lett; 19:169–173.
29. Leather LF, Whitehead AS (1999) Serum amyloid A, the major vertebrate acute-phase reactant. Eur J Biochem; 265:501–323.
30. van der Harst P, Bakker SJL, de Boer R, Wolfenbuttel BHR, Johnson T, et al. (2010) Replication of the five novel loci for uric acid concentrations and potential mediating mechanisms. Human Molecular Genetics, 19:387–395.
31. Kang DH, Park SK, Lee IK (2005) Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol; 16: 3553–3562

Author Contributions

Conceived and designed the experiments: XX YTM. Performed the experiments: XX YNY XML BDC YYZ. Analyzed the data: FL YH XM. Contributed reagents/materials/analysis tools: ZYF BDC ZXY YC. Wrote the paper: XX YTM.