# *SLC2A9* gene polymorphism in Korean patients with gouty arthritis

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Directed by Professor Yong-Beom Park

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This certifies that the Doctoral Dissertation of Soo-Jin Chung is approved.

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ABSTRACT

## *SLC2A9* gene polymorphism in Korean patients with gouty arthritis

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Gout is an inflammatory disease with accumulation of monosodium urate (MSU) crystals in joints. The prevalence of gout is continuously increasing due to Westernized diet and life style in Korea.

The predisposing factors of gout are male gender, old age, alcohol consumption, renal insufficiency, and use of diuretics. There were studies on the association of genetic predisposition such as single nucleotide polymorphism (SNP) of *SLC2A9* gene, which is involved in reabsorption of uric acid in renal tubule and gout. However, most of these studies on genetic association were performed on Caucasian populations, although genetic variations exist among different ethnic groups. Thus, an independent study is required to identify inter-racial genetic variations and gene polymorphisms unique to Korean gout patients. We set out to elucidate genetic polymorphisms of *SLC2A9* gene related to gout pathogenesis, and identify those findings to various clinical indices

related to gout.

Three hundred thirty three gout patients and 459 healthy controls were included in this study. Minor allele frequency exceeding over 5 percent was selected as tagging SNP through sequencing of exon, promoter, and intron near exon in *SLC2A9* gene in 12 gout patients and in 12 controls. Two SNPs within *SLC2A9* (*rs6820230*, *rs3775950*), which showed high correlation to gout in pilot study including 96 gout patients and 48 controls, were selected and genotyped using TaqMan SNP genotyping assays. Additionally, *rs16890979,* which had demonstrated significant correlation to gout and serum uric acid level among Caucasians in previous studies, and *rs1014290*, which had been reported to be associated to gout in Koreans, Japanese, and other Han Chinese, were selected to be analyzed. An association analysis was carried out using the Chi-squared test or Fisher's exact test. Genotype-phenotype analyses were conducted using Chi-squared test, Fisher's exact test or Kruskal-wallis analysis.

The major allele of *rs6820230* is C, minor allele is T, the major allele of *rs3775950* is A, minor allele is G, the major allele of *rs1014290* is T, minor allele is C, and the major allele of *rs16890979* is C, minor allele is T. The T allele of *rs6820230* was associated with increased risk of gout ($P$ = 0.0003, OR 1.977, 95% CI 1.363, 2.867), and the risk of gout was elevated 1.9 fold in subject with genotype TT than in subject with genotype CT, and in subject with CT than in subject with genotype CC, respectively. The G allele of *rs3775950* increased the risk of gout ($P$ < 0.0001, OR 2.133, 95% CI 1.457, 3.122), and the

risk of gout was 2.2 fold elevated in subject with genotype GG than in subject with genotype AG, and in subject with genotype AG than in subject with genotype AA, respectively. In *rs1014290*, T allele was found to be associated with the development of gout ($P < 0.0001$, OR 1.564, 95% CI 1.269, 1.928), and the risk of gout was 1.58 fold elevated in subject with genotype TT than in subject with genotype CT, and in subject with CT than in subject with CC, respectively. There was no significant association between blood pressure, body mass index, the level of cholesterol, triglyceride, urea nitrogen, creatinine, fasting glucose, and each SNPs. Stratification of the phenotypes by genotypes did not demonstrate any different results. The association between *rs16890979* and serum uric acid concentration was statistically significant only in male gout patients. Serum concentrations of uric acid were 9.39 ± 1.60 mg/dl, 7.5 mg/dl, and 11.80 ± 0.85 mg/dl in subjects with genotype CC, CT, and TT, respectively. The association between *rs3775950* and age of diagnosis was statistically significant only in female gout patients. There were no significant genotype-related differences among severe gout patients with tophi or X-ray abnormality, and gout patients who had experienced allopurinol hypersensitivity.

Our results suggest that genetic variants within *SLC2A9*, such as *rs6820230* (C/T), *rs3775950* (A/G), and *rs1014290* (T/C) polymorphisms have significant effects on the development of gout in Korean population. And these results demonstrate that there is an inter-racial genetic difference affecting the

pathogenesis of gout.

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Key words : gout, *SLC2A9* gene polymorphism, single nucleotide polymorphism

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## I. INTRODUCTION

Gout is an inflammatory disease which causes severe joint pain due to the deposition of monosodium urate (MSU) crystals. Without proper treatment, MSU crystals can form tophi, which can destroy joints and lead to chronic arthritis[1]. The prevalence of gout is reported as 0.16% to 11.7%, and the incidence and prevalence of gout have risen rapidly due to obesity, hypertension, and longer life spans[2]. In the past, gout was more common in the Western world than in Asian countries. However, the prevalence of gout in Korea has risen due to an increasingly Westernized diet and lifestyle change. The National Health Insurance Corporation of Korea reported that the number of documented gout patients has risen by 12.9 percent annually, from 80,583 in 2001 to 186,705 in 2008; in addition, the financial burden of gout has risen sharply over 7 years, from 12.5 billion won in 2001 to 31.7 billion won in 2008[3]. Therefore, more research is necessary to understand the pathogenesis of gout in Korean patients

with gouty arthritis.

Many risk factors for gout have been discovered, including hyperuricemia, male gender, old age, alcohol consumption, chronic renal disease, diuretic use, and family history[4]. Hyperuricemia is the most important risk factor for gout, as gout primarily manifests as an increase in serum uric acid concentrations. Although most patients with gout show hyperuricemia, not all patients with hyperuricemia suffer from gout. Only 20% of hyperuricemic patients experience gout, which suggests that many complex factors influence gout susceptibility[5].

Researchers have suspected that gout runs in families, but studies associating specific genes with gout have been limited to several rare mutations for decades[6, 7]. However, after the advent of genome-wide association studies (GWAS), research on several genes associated with serum uric acid concentration and gout susceptibility have advanced[8-11]. In particular, *SCL2A9/GLUT9* (solute carrier family 2, member 9/facilitated glucose transporter 9) gene, is located on chromosome 4, codes for the protein responsible for uric acid reabsorption in the renal proximal tubule, and is one of the most influential genes controlling uric acid concentration and gout development[10, 12-14]. A single nucleotide polymorphism (SNP) is a DNA sequence variation occurring when a single nucleotide (A, T, C or G) in the genome differs between paired chromosomes. SNPs may cause functional abnormalities in coding proteins. Several studies have associated uric acid levels or gout susceptibility with SNPs in *SLC2A9* gene. Vitart V et al. reported that *rs1014290*, *rs6449213* and *rs737267* polymorphisms of *SLC2A9* gene were associated with gout in a Croatian population, and they reproduced this result in

a UK population sample from the Island of Orkney[15]. Charles BA et al. reported that *rs3775948*, *rs7663032*, *rs6856396*, and *rs6449213* polymorphisms of *SLC2A9* gene were associated with serum uric acid concentrations from GWAS on an African American population[16]. Many studies have revealed genetic associations of *SLC2A9* gene with gout or uric acid concentrations[10, 17-23]. However, some results are inconsistent among different ethnic populations. While *SLC2A9* variants *rs3733591*, *rs3733589* and *rs1014290* were found to be related to the development of gout in Han Chinese subjects, this association was not present in Solomon Islanders[24]. Although *rs3733591* was associated with gout in Japanese, it was not consistently associated with gout risk in Polynesian or Caucasian subjects[25]. Likewise, *rs16890979* is reported to have a powerful influence on gout susceptibility and hyperuricemia, but no association was found between *rs16890979*, gout development, and uric acid concentrations in a Japanese population[26].

There are several SNPs in culprit genes which may have an important role in gout pathogenesis, but these are population-specific properties. Thus, it is inappropriate to apply previously confirmed genetic data directly to a Korean population. No reports currently show associations between *SLC2A9* genotypes and gout susceptibility in Korean patients. Therefore, we hope to show genetic associations with gout in a Korean population. We conducted this study to examine the influence of SNP polymorphisms in *SLC2A9* gene on gout development in Korean patients.

## II. MATERIALS AND METHODS

### 1. Study population

Gout patients were recruited from the Department of Rheumatology at Yonsei University Severance Hospital, Seoul, Korea from January, 2011 to June, 2012. Sex, age, comorbidities, family history of gout, date of diagnosis with gout, palpable tophi, and experience of allopurinol hypersensitivity were investigated by questionnaire, and blood pressure, height, and weight were measured. The level of uric acid, glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), blood urea nitrogen (BUN), creatinine in the plasma, and uric acid in a 24hr urine collection were measured for all patients. A foot X-ray was reviewed to check for subchondral cysts or erosion due to tophi. This study protocol was approved by the institute of review board of Yonsei University, Seoul, Korea, and all subjects agreed to a written informed consent.

The diagnosis of gout was based on the American College of Rheumatology (ACR) criteria of gout[27]. The patient was diagnosed with gout if he or she satisfies at least 6 out of 12 clinical criteria, or identification of MSU crystal in synovial fluid or soft tissue, or presence of tophi.

(1) More than one attack of acute arthritis

(2) Maximum inflammation developed within 1 day

(3) Oligoarthritis attack

(4) Redness observed over joints

(5) First MTP joint painful or swollen

(6) Unilateral first MTP joint attack

(7) Unilateral tarsal joint attack

(8) Tophus (suspected or proven)

(9) Hyperuricemia

(10) Asymmetric swelling within a joint on X-ray

(11) Subcortical cysts without erosions on X-ray

(12) Joint fluid culture negative for organisms during attack

Healthy control subjects were recruited from the Cardiovascular Genome Center of Yonsei University, Seoul, Korea and the National Genome Research Institute of Korea National Institute of Health. The inclusion criteria were no prior history of gout and uncontrolled comorbidities, and no evidence of hyperuricemia. Normal value of serum uric acid was below 7.0 mg/dl in males and 6.0 mg/dl in females[28].

**2. Determination of Tagging SNP**

Genomic DNA was extracted from 6-8 ml of peripheral blood using a commercially available DNeasy Blood kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Extract genomic DNAs in 12 gout patients and in 12 controls were sequenced targeting *SLC2A9* gene (Chromosome 4, 9.44-9.65Mb) through Liquid Handler (Biomek® FX, Beckman Coulter) and High-throughput automated sequencing machine (ABI 3730xl). The promoter, exon, and intron near exon were contained and divided by 17 fragments according the length (500-700 bp). The primers using in sequencing were listed in Table 1.

**Table 1. Primers using in sequencing**

| Frag-ment | Forward Primer Sequence | Reverse Primer Sequence | Fragment length (bp) |
|---|---|---|---|
| 1 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 570 |
| 2 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 565 |
| 3 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 564 |
| 4 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 642 |
| 5 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 587 |
| 6 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 452 |
| 7 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 506 |
| 8 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 461 |
| 9 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 508 |
| 10 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 511 |
| 11 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 559 |
| 12 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 546 |
| 13 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 501 |
| 14 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 550 |
| 15 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 515 |
| 16 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 535 |
| 17 | CAGGAAACAGCTATGACC | TGTAAAACGACGGCCAGT | 626 |

The results were aligned using Phred and Phrap, or Polyphred software package, then confirmed SNPs, insertion/deletion, and repeat polymorphism. Linkage Disequilibrium (LD) was calculated by Haploview software version 4.0 (Broad Institute of MIT and Harvard, Cambridge, MA, USA) in SNPs more than 5% in minor allele frequency.

**3. Determination of genotypes**

Genotyping was performed by allelic discrimination using specific TaqMan SNP Genotyping Assays and following the manufacturer's instructions. The primers using PCR were as bellows:

5'-AAAGGACTGACCAATTTCTTTTTCG-3',

5'-TGAATCACTTTCTTCATCTTCTCCT-3' for *rs6820230*,

5'-GGGATGAAAGGTTTTGCCCAAAGCA-3',

5'-AGTTTCTTCCTTCCTTAGGAAAATA-3' for *rs3775950*,

5'-CTCAGTGCACAAGATACTGATCTAC-3',

5'-TCATCCACTGACTCATTCAACAAAC-3' for *rs1014290*,

5'-AGGACCTCCTCTACCTCTTGGGAAA-3',

5'-GTCTGCTTTACCCAAGAACGTTTGG-3' for *rs16890979*.

After PCR, end point discrimination of alleles was performed on the 7500 Real-Time PCR System (Applied Biosystems, Grand Island, NY).

**4. Statistical analysis**

Statistical analyses were performed using SAS statistical software package version 9.1 (SAS Institute, Cary, NC, USA), and *P*-values < 0.05 were considered statistically significant. $\chi^2$ test or Fisher's exact test were used to compare the genotype distribution and allele frequencies between controls and gout patients. Odds ratios (ORs) and 95% confidence intervals (CIs) were used as a measure of the power of relationships in the genotype distribution and allele frequencies between the controls and gout patients. $\chi^2$ test, Fisher's exact test or Kruskal-wallis analysis were used for genotype-phenotype analyses of the gout patients.

## III. RESULTS

### 1. Characteristics of controls and gout patients

In total, 333 gout patients and 459 controls were included. General characteristics of study participants are shown in Table 2. The mean age of gout patients was 56.32 ± 14.72 years, and the mean age of controls was 50.98 ± 10.29 years. Ninety four percent of patients were male gender, and 89% of controls were male gender. Blood pressure, the level of cholesterol, triglyceride, glucose, and creatinine were elevated in gout patients, and serum concentrations of uric acid were 9.49 ± 1.64 mg/dl in gout patients, and 5.25 ± 1.02 mg/dl in control group.

**Table 2. Clinical characteristics of study participants**

| Variable | Gout (n = 333) | Control (n = 459) |
|---|---|---|
| Age (year) | 56.32 ± 14.72 | 50.98 ± 10.29 |
| Gender, n (%) | | |
| Male | 311 (93.39) | 409 (89.11) |
| Female | 22 (6.61) | 50 (10.89) |
| Body Mass Index ($kg/m^2$) | 24.79 ± 3.05 | 24.08 ± 2.85 |
| Blood pressure (BP) | | |
| Systolic BP (mmHg) | 129.35 ± 15.24 | 119.80 ± 13.65 |
| Diastolic BP (mmHg) | 77.82 ± 10.58 | 77.88 ± 9.81 |
| Cholesterol (mg/dl) | | |
| Total-C | 189.39 ± 42.13 | 196.33 ± 36.65 |
| HDL-C | 43.28 ± 11.82 | 49.15 ± 11.49 |
| LDL-C | 105.70 ± 36.15 | 119.57 ± 34.01 |
| Triglyceride (mg/dl) | 185.51 ± 128.21 | 139.96 ± 75.67 |
| Glucose (mg/dl) | 99.09 ± 16.51 | 92.83 ± 18.92 |
| BUN (mg/dl) | 20.62 ± 14.97 | |
| Cr (mg/dl) | 1.43 ±1.19 | 0.90 ± 0.19 |
| Uric acid (mg/dl) | 9.49 ± 1.64 | 5.25 ± 1.02 |
| 24hr urine urate (mg) | 561.18 ± 650.15 | |
| Age at diagnosis | 49.12 ± 15.12 | |
| CCr (ml/min) | 66.49 ± 24 | |
| Tophi, n | 49 | |
| X-ray abnormality, n | 68 | |
| Allopurinol hypersensitivity, n | 20 | |
| Metabolic SD, n | 151 | |

**2. Selection of tagging SNPs in this study**

In 12 gout patients and 12 controls, we found 68 SNPs in the promoter, exon and exon/intron boundary regions of *SLC2A9* gene (Table 3). Among those genes, the minor allele frequency of 36 SNPs was more than 5%. After using a haploid program, we selected 15 independent tagging SNPs (Figure 1, Table 4).

After comparing 15 tagging SNPs with genotype and allele frequencies in 96 gout patients and 48 controls, we found that *rs6820230* (C/T) *and rs3775950* (A/G) variants were significantly associated with the development of gout. Therefore, genotyping was performed on these two SNPs for all gout patients and controls. As previous reports have associated the development of gout in Japanese and Han Chinese populations with the SNP *rs1014290*, we investigated this SNP even though it was not included in our original sequencing because the allele was located in an intron. Because several studies have shown *rs16890979* to be the SNP that is most significantly associated with hyperuricemia in Caucasian, we investigated the associations of *rs16890979* with Korean gout patients even though sequencing of *rs16890979* showed monomorphic features[11, 18, 23].

**Table 3. Identification of *SLC2A9* SNPs using direct sequencing in this study**

| region | rs number | SNP Name | variation |
|---|---|---|---|
| promoter | *rs13124007* | -16341C/G | C/G |
| promoter | *rs56083430* | -16327G/T | G/T |
| promoter | *rs62293415* | -16296G/T | G/T |
| promoter | NEW | -16200G/A | G/A |
| promoter | *rs77678083* | -16134A/G | A/G |
| promoter | *rs6850166* | -16098A/G | A/G |
| promoter | *rs36036984* | -16042A/G | A/G |
| promoter | *rs78201117* | -15575G/T | G/T |
| promoter | *rs13137343* | -15438G/T | G/T |
| promoter | *rs79763149* | -15384A/G | A/G |
| promoter | *rs16892534* | -15348A/G | A/G |
| promoter | *rs13101785* | -15325A/T | A/T |
| promoter | *rs7685958* | -15260C/G | C/G |
| promoter | *rs13137074* | -15252A/G | A/G |
| promoter | *rs75245044* | -15096C/T | C/T |
| promoter | *rs61476037* | -15083A/G | A/G |
| promoter | *rs7349721* | -14972A/T | A/T |
| promoter | *rs74491687* | -14860C/T | C/T |
| promoter | *rs61446121* | -14652A/G | A/G |
| promoter | *rs7679916* | -14570A/G | A/G |
| promoter | *rs10516197* | -14510A/G | A/G |
| promoter | *rs16892493* | -14057A/G | A/G |
| promoter | *rs6449238* | -154C/T | C/T |
| promoter | *rs35305635* | -99-/C | -/- |
| promoter | *rs74794351* | -74C/T | C/T |

| | | | continued |
|---|---|---|---|
| promoter | *rs77817713* | -57C/T | C/T |
| promoter | *rs6449237* | -53C/T | C/T |
| promoter | *rs75673132* | -51C/T | C/T |
| exon | *rs6820230* | T17A | C/T |
| intron | *rs2240722* | IVS2-60C/T | C/T |
| exon | *rs76987454* | P52P | C/G |
| intron | *rs2240721* | IVS3+35C/T | C/T |
| intron | *rs2240720* | IVS3+119A/G | A/G |
| intron | *rs28592748* | IVS3-40A/G | A/G |
| exon | *rs77573696* | P74A | C/G |
| exon | *rs76019222* | D75D | C/T |
| exon | *rs13113918* | L79L | C/T |
| exon | *rs10939650* | T96T | A/G |
| exon | *rs71816262* | 108 | -/- |
| intron | *rs16891971* | IVS4+29G/T | G/T |
| exon | *rs3733589* | I139I | C/T |
| intron | *rs3733590* | IVS5+67A/G | A/G |
| exon | *rs13125646* | L160L | C/T |
| intron | *rs13115193* | IVS6+25A/G | A/G |
| intron | *rs74642325* | IVS6+38C/T | C/T |
| intron | *rs4292327* | IVS6-31C/T | C/T |
| exon | *rs77777425* | N236S | A/G |
| intron | *rs2276964* | IVS7+38A/T | A/T |
| intron | *rs2276965* | IVS7+62C/T | C/T |
| exon | *rs73225891* | H252D | C/G |
| exon | *rs16890979* | I253V | G/A |
| exon | *rs3733591* | H265R | A/G |
| exon | *rs75088806* | M266V | A/G |

| | | | continued |
|---|---|---|---|
| exon | *rs74651202* | R271C | C/T |
| exon | *rs35928671* | 275 | -/- |
| intron | *rs6823877* | IVS8+78A/G | A/G |
| exon | *rs2280205* | P321L | C/T |
| intron | *rs2280204* | IVS9+9A/C | A/C |
| exon | NEW | E347E | G/A |
| exon | NEW | T372T | G/A |
| intron | *rs28571073* | IVS10+95C/T | C/T |
| intron | *rs56343987* | IVS10+96C/T | C/T |
| intron | *rs10939602* | IVS10+132A/G | A/G |
| intron | *rs28489733* | IVS10+173G/T | G/T |
| intron | *rs6818572* | IVS10-182C/T | C/T |
| intron | *rs6836878* | IVS11+122A/G | A/G |
| intron | *rs4697905* | IVS11+149A/G | A/G |
| intron | *rs3775950* | IVS12+139A/G | A/G |
| intron | *rs1014290* | 250-3296C/T | T/C |

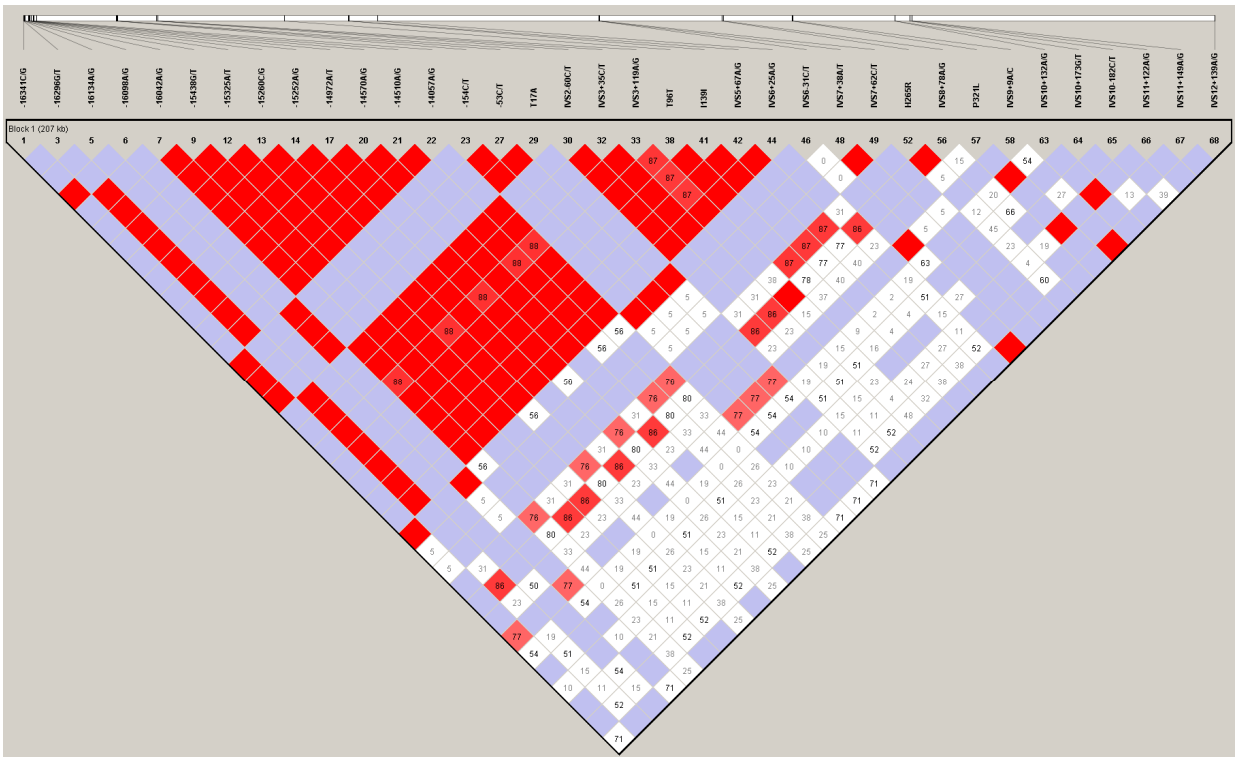


**Figure 1. Linkage disequilibrium (LD) by haploid program.** Linkage disequilibrium plot in exon, promoter region of *SLC2A9* gene with all minor allele frequency > 0.05 of SNPs. This plot was generated with the program Haploview, and SNPs with high LD were excluded.

**Table 4. Tagging SNPs**

| tagSNP | rs number |
|---|---|
| *rs13115193* | *rs2240720, rs62293415, rs13101785, rs13137343, rs13115193, rs2240721, rs2240722, rs7679916, rs13137074* |
| *rs10939650* | *rs10516197, rs7349721, rs36036984, rs10939650, rs3733590, rs3733589, rs16892493, rs7685958* |
| *rs6820230* | *rs6449237, rs6820230, rs6449238, rs13124007, rs6850166* |
| *rs2276965* | *rs2276965, rs2276964* |
| *rs3775950* | *rs3775950* |
| *rs6836878* | *rs6836878* |
| *rs6823877* | *rs6823877* |
| *rs4697905* | *rs4697905* |
| *rs2280205* | *rs2280205* |
| *rs6818572* | *rs6818572* |
| *rs10939602* | *rs10939602* |
| *rs3733591* | *rs3733591* |
| *rs28489733* | *rs28489733* |
| *rs77678083* | *rs77678083* |
| *rs2280204* | *rs2280204, rs4292327* |

### 3. Genotype and allele frequency

In total, 333 patients with gout and 450 controls were genotyped for *rs6820230* polymorphism, and 333 patients with gout and 453 controls were genotyped for *rs3775950* polymorphism. Three hundred thirty one patients with gout and 446 controls were genotyped for *rs1014290* polymorphism, and 332 gout patients and 451 controls were genotyped for *rs16890979* polymorphism. The genotype distribution and allele frequencies of each SNP for controls and patients are listed in Table 5. The major allele of *rs6820230* is C, and the minor allele is T. The genotypes of *rs6820230* were CC (n=266), CT (n=62), and TT (n=5) in gout patients, and CC (n=402), CT (n=44), and TT (n=4) in controls. The major allele of *rs3775950* is A, and the minor allele is G. The genotype distribution of *rs3775950* was AA (n=263), AG (n=69), and GG (n=1) in gout patients, and AA (n=407), AG (n=44), and GG (n=2) in controls. The major allele of *rs1014290* is T, and the minor allele is C. The genotype distribution of *rs1014290* was TT (n=143), TC (n=157), and CC (n=31) in gout patients, and TT (n=143), TC (n=217), and CC (n=86) in controls. The major allele of *rs16890979* is G, and the minor allele is A. The genotype distribution of *rs16890979* was GG (n=328), GA (n=2), and AA (n=2) in gout patients, and GG (n=446), GA (n=1), and AA (n=4) in controls.

**Table 5. Genotype and allele distribution of detected polymorphisms in patients and controls**

| SNP | Genotype/ Allele | All subjects (n=783) | | *P* |
|---|---|---|---|---|
| | | Case (n=333) | Control (n=450) | |
| *rs6820230* | CC | 266 (79.88) | 402 (89.33) | |
| | CT | 62 (18.62) | 44 (9.78) | 0.0011 |
| | TT | 5 (1.50) | 4 (0.89) | |
| | C : T (%) | 89.19:10.81 | 94.22:5.78 | 0.0003 |
| | Genotype/ Allele | All subjects (n=786) | | *P* |
| | | Case (n=333) | Control (n=453) | |
| *rs3775950* | AA | 263 (78.98) | 407 (89.85) | |
| | AG | 69 (20.72) | 44 (9.71) | <0.0001 |
| | GG | 1 (0.30) | 2 (0.44) | |
| | A : G (%) | 89.34:10.66 | 94.70:5.30 | <0.0001 |
| | Genotype/ Allele | All subjects (n=777) | | *P* |
| | | Case (n=331) | Control (n=446) | |
| *rs1014290* | TT | 143 (43.20) | 143 (32.06) | |
| | TC | 157 (47.43) | 217 (48.65) | <0.0001 |
| | CC | 31 (9.37) | 86 (19.28) | |
| | T : C (%) | 66.92:33.08 | 56.39:43.61 | <0.0001 |
| | Genotype/ Allele | All subjects (n=783) | | *P* |
| | | Case (n=332) | Control (n=451) | |
| *rs16890979* | GG | 328 (98.80) | 446 (98.89) | |
| | GA | 2 (0.60) | 1 (0.22) | 0.7506 |
| | AA | 2 (0.60) | 4 (0.89) | |
| | G : A (%) | 99.10:0.90 | 99.00:1.00 | 0.8500 |

Analyzed with $\chi^2$ test or Fisher's exact test.

TT or CT genotypes for *rs6820230* showed a higher risk of gout compared to CC genotype ($P$ = 0.0002, OR 2.109, 95% CI 1.412, 3.152). The codominant model showed an OR of 1.901 (95% CI 1.320, 2.738, $P$ = 0.0004), and T allele was significantly associated with the development of gout ($P$ = 0.0003, OR 1.977, 95% CI 1.363, 2.867). In the case of *rs3775950*, GG and AG genotypes expressed a higher risk of gout development than AA genotype ($P$ < 0.0001, OR 2.355, 95% CI 1.574, 3.524). The OR was 2.192 in the additive model (95% CI 1.484, 3.237, $P$ < 0.0001), which, along with G allele showed a strong association with the gout development ($P$ < 0.0001, OR 2.133, 95% CI 1.457, 3.122). In *rs1014290*, TT or CT genotypes showed a higher risk of gout than CC genotype ($P$ = 0.0002, OR 20312, 95% CI 1.492, 3.583), and TT genotype demonstrated a higher risk of gout than CT or CC genotypes ($P$ = 0.0015, OR 1.612, 95% CI 1.200, 2.164). The T allele was found to increase the development of gout ($P$ < 0.0001, OR 1.564, 95% CI 1.269, 1.928). *rs16890979* showed no significant association to gout development in dominant, recessive, or codominant models, and there was no comparable difference in allele frequencies between gout and control groups (Table 6). Adjustment for age, sex, BMI, and creatinine did not affect the outcome. An analysis of gout patients with X-ray abnormalities showed that *rs6820230, rs3775950,* and *rs1014290* demonstrated the same tendency to increase the OR, as previously described in non-erosive gout.

**Table 6. Association of four SNPs with gout**

| SNP | Model | Gout vs. Control | | | | | | Erosive gout vs. Control | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OR | (95% CI) | *P* | OR* | (95% CI)* | *P* * | OR | (95% CI) | *P* |
| rs6820230 | Allele (T/C) | 1.977 | 1.363-2.867 | 0.0003 | | | | 2.488 | 1.408-4.397 | 0.0017 |
| | Dominant (TT+CT/CC) | 2.109 | 1.412-3.152 | 0.0002 | 2.645 | 1.540-4.544 | 0.0004 | 2.792 | 1.494-5.217 | 0.0013 |
| | Recessive (TT/CT+CC) | 1.700 | 0.453-6.739 | 0.4266 | 1.637 | 0.334-8.024 | 0.5437 | 1.664 | 0.183-15.114 | 0.6509 |
| | Codominant (TT/CT/CC) | 1.901 | 1.320-2.738 | 0.0004 | 2.199 | 1.364-3.544 | 0.0012 | 2.32 | 1.334-4.033 | 0.0029 |
| rs3775950 | Allele (G/A) | 2.133 | 1.457-3.122 | <0.0001 | | | | 2.727 | 1.535-4.845 | 0.0006 |
| | Dominant (GG+AG/AA) | 2.355 | 1.574-3.524 | <0.0001 | 2.93 | 1.704-5.038 | 0.0001 | 3.186 | 1.715-5.916 | 0.0002 |
| | Recessive (GG/AG+AA) | 0.679 | 0.061-7.522 | 0.748 | 0.783 | 0.039-15.848 | 0.8733 | 0 | 0-∞ | 0.9882 |
| | Codominant (GG/AG/AA) | 2.192 | 1.484-3.237 | <0.0001 | 2.626 | 1.571-4.387 | 0.0002 | 2.778 | 1.538-5.104 | 0.0007 |
| rs1014290 | Allele (T/C) | 1.564 | 1.269-1.928 | <0.0001 | | | | 1.731 | 1.175-2.549 | 0.0055 |
| | Dominant (TT+CT/CC) | 2.312 | 1.492-3.583 | 0.0002 | 2.408 | 1.367-4.239 | 0.0023 | 3.822 | 1.355-10.783 | 0.0113 |
| | Recessive (TT/CT+CC) | 1.612 | 1.200-2.164 | 0.0015 | 1.763 | 1.210-2.568 | 0.0032 | 1.673 | 0.996-2.809 | 0.0517 |
| | Codominant (TT/CT/CC) | 1.580 | 1.276-1.957 | <0.0001 | 1.666 | 1.266-2.193 | 0.0003 | 1.741 | 1.176-2.575 | 0.0056 |
| rs16890979 | Allele (A/G) | 0.906 | 0.321-2.556 | 0.8496 | | | | 1.482 | 0.317-6.932 | 0.6169 |
| | Dominant (AA+GA/GG) | 1.088 | 0.290-4.084 | 0.9002 | 0.197 | 0.021-1.813 | 0.1513 | 1.332 | 0.153-11.572 | 0.7951 |
| | Recessive (AA/GA+GG) | 0.677 | 0.123-3.720 | 0.6478 | 0.217 | 0.022-2.173 | 0.1935 | 1.668 | 0.184-15.148 | 0.6495 |
| | Codominant (AA/GA/GG) | 0.946 | 0.436-2.053 | 0.8876 | 0.44 | 0.139-1.394 | 0.1629 | 1.229 | 0.4.3-3.742 | 0.7172 |

*Data adjusted for age, sex, BMI, Cr.

**4. Genotype-phenotype analysis**

We investigated various clinical indicators to confirm associations between *rs6820230*, *rs3775950*, *rs1014290*, and *rs16890979* variants of *SLC2A9* gene and specific clinical characteristics or comorbidities in gout patients. Patients with systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 90 mmHg, or who took prescribed antihypertensive drugs showed no significant association between gout and specific alleles. There was no significant association between gout and specific alleles in diabetic patients with antiglycemic drugs or fasting serum glucose more than 125 mg/dl. Patients with chronic kidney disease, which was defined as creatinine clearance (CCr) less than 60 ml/min, also showed no significant associations. No significant associations were found for metabolic syndrome, defined as three of the following four criteria: hypertriglyceridemia, low HDL, impaired fasting serum glucose ($\geqq$ 100 mg/dl), or pre-hypertensive state (systolic blood pressure $\geqq$ 130 mmHg or diastolic blood pressure $\geqq$ 85 mmHg).

There were no significant differences in systolic blood pressure, diastolic blood pressure, body mass index, cholesterol levels, triglyceride levels, BUN, creatinine, CCr, and fasting glucose among different genotypes in gout patients. The SNPs were not associated with serum concentration of uric acid in all gout patients as a group, but there was a significant difference among male gout patients. Male patients with CC, CT, and TT genotypes in *rs16890979* had uric acid concentrations of 9.39 ± 1.60 mg/dl, 7.5 mg/dl, and 11.80 ± 0.85 mg/dl, respectively (Table 7). *rs3775950* was associated with age of diagnosis in female gout patients, but not in males (Table 8). Some studies reported that SNP

variants which were not associated with the development of gout nonetheless, affected the development of gout with tophus crystals[25]. A tophus is a deposit of monosodium urate crystals in severe or chronic gout patients. Tophi can form in joints, cartilage, bones, and other places throughout the body. In our study, there were no significant associations between SNP variants and gout patients with tophus formation. Patients with severe gout who had erosive bony abnormalities on X-ray or patients with allopurinol hypersensitivity showed no significant association of gout to different genotype of SNPs.

**Table 7. Association of detected polymorphisms with concentrations of uric acid in gout patients**

| | | Total | | Male | | Female | |
|---|---|---|---|---|---|---|---|
| | | Uric acid (mg/dl) | *P* | Uric acid (mg/dl) | *P* | Uric acid (mg/dl) | *P* |
| | CC | 9.49 ± 1.67 | | 9.40 ± 1.64 | | 10.62 ± 1.70 | |
| *rs6820230* | CT | 9.48 ± 1.52 | 0.94 | 9.44 ± 1.51 | 0.93 | 10.70 ± 1.70 | 0.64 |
| | TT | 9.74 ± 1.58 | | 9.15 ± 1.00 | | 12.1 | |
| | AA | 9.51 ± 1.67 | | 9.42 ± 1.64 | | 10.54 ± 1.71 | |
| *rs3775950* | AG | 9.48 ± 1.53 | 0.43 | 9.35 ± 1.47 | 0.43 | 11.40 ± 1.27 | 0.35 |
| | GG | 7.8 | | 7.8 | | | |
| | CC | 10.14 ± 2.42 | | 10.24 ± 2.50 | | 9.33 ± 1.61 | |
| *rs1014290* | CT | 9.41 ± 1.56 | 0.27 | 9.33 ± 1.51 | 0.14 | 10.49 ± 1.97 | 0.13 |
| | TT | 9.46 ± 1.52 | | 9.32 ± 1.46 | | 11.38 ± 0.94 | |
| | GG | 9.49 ± 1.63 | | 9.39 ± 1.60 | | 10.76 ± 1.67 | |
| *rs16890979* | GA | 8.45 ± 1.34 | 0.07 | 7.5 | 0.04 | 9.4 | 0.31 |
| | AA | 11.80 ± 0.85 | | 11.80 ± 0.85 | | | |

**Table 8. Association of detected polymorphisms with age at diagnosis in gout patients**

| | | Total | | Male | | Female | |
|---|---|---|---|---|---|---|---|
| | | Age | *P* | Age | *P* | Age | *P* |
| | CC | 49.29 ± 15.15 | | 48.40 ± 14.96 | | 60.47 ± 13.20 | |
| *rs6820230* | CT | 48.40 ± 15.35 | 0.88 | 48.97 ± 15.19 | 0.97 | 32.00 ± 14.14 | 0.06 |
| | TT | 49.00 ± 13.64 | | 49.25 ± 15.74 | | 48.00 | |
| | AA | 49.55 ± 15.02 | | 48.59 ± 14.86 | | 62.22 ± 11.09 | |
| *rs3775950* | AG | 47.27 ± 15.45 | 0.22 | 48.02 ± 15.41 | 0.43 | 35.25 ± 11.87 | <0.01 |
| | GG | 66.00 | | 66.00 | | | |
| | CC | 49.23 ± 15.50 | | 48.00 ± 15.13 | | 60.67 ± 17.21 | |
| *rs1014290* | CT | 50.19 ± 15.61 | 0.42 | 49.67 ± 15.73 | 0.45 | 57.50 ± 12.20 | 0.90 |
| | TT | 47.79 ± 14.56 | | 47.22 ± 14.12 | | 56.00 ± 19.08 | |
| | GG | 49.08 ± 15.18 | | 48.51 ± 15.01 | | 57.19 ± 15.63 | |
| *rs16890979* | GA | 52.00 ± 11.31 | 0.55 | 44.00 | 0.52 | 60.00 | 0.90 |
| | AA | 59.00 ± 8.49 | | 59.00 ± 8.49 | | | |

## IV. DISCUSSION

In the present study, we analyzed the relationship of SNPs in *SLC2A9* gene to gout susceptibility in Korean patients. There were no previously reported polymorphisms of *SLC2A9* gene in Korean patients. We found that the genetic distributions of *rs6820230* (C/T), *rs3775950* (A/G), and *rs1014290* (T/C) were associated with gout susceptibility.

Gout is an inflammatory arthritis, characterized by elevated serum uric acid and deposition of MSU crystal. And the prevalence of gout is rising up sharply in Korea. Gout is related with other metabolic diseases such as hypertension and obesity, and it can cause a lot of loss of social and economic loss. Thus, to minimize this loss, it is needed to investigate in cause, treatment and prevention method of gout.

The majority of gout patients have hyperuricemia due to decreased renal uric acid excretion. Thus, many studies have been conducted to identify the genes which encode the renal urate transporter. Renal urate transporters include *GLUT-9* (*SLC2A9*), urate anion transporter 1 (*URAT1*, *SLC22A12*), solute carrier family 22 members 6, 8, 11, and 13 (*SLC22A6*, *SLC22A8*, *SLC22A11*, *SLC22A13*), multidrug resistance-associated protein 4 (*MRP4*), sodium coupled monocarboxylate transporter 1 and 2 (*SLC5A8*, *SLC5A12*), and ATP-binding cassette subfamily G member 2 (*ABCG2*)[8]. *GLUT-9*, which is encoded by *SLC2A9* gene, was initially known as the glucose/fructose transporter. However, later studies identified that the major role of *GLUT-9* was uric acid reabsorption in the proximal tubule, and *GLUT-9* is considered to be one of the most

powerful urate transporters[12-15, 29]. Therefore, this study aimed to investigate the effects of *SLC2A9* gene on the pathogenesis and development of gout in a Korean population.

We determined tagging SNPs by sequencing of *SLC2A9* promoter, exon and exon/intron boundary region in 12 gout patients and 12 controls. Since our current technology and equipment is unable to study entire SNPs all at once, many previous studies only focused on the "suspected" target SNPs. Sometimes, target SNPs were randomly chosen from backward engineering, which identified the protein related to a specific disease and found its coding gene. Other methods included choosing SNPs which were proven to be associated with a certain disease and then extracting nearby base pairs in a somewhat arbitrary manner. For these reasons, many studies failed to demonstrate associations between certain SNPs and the disease in one population, despite showing strong associations in another ethnic population. Our study was expanded to identify target SNPs, and sequenced the exon and promoter regions of *SLC2A9* gene in the sampled patients. This allowed us to identify coding SNPs even with minor allele frequencies and select tagging SNPs with high scientific probability.

The human genome has one SNP for every 200 to 300 base pairs in a relatively even distribution, and scientists speculate that there are about one million SNPs in every individual. Approximately 50% of SNPs are thought to be in coding regions, and about half of that 50% are thought to effect actual changes in protein structure or function by modifying the amino acid sequence. These are known as non-synonymous SNPs[30]. Reported non-synonymous SNPs

in *SLC2A9* gene include *rs16890979* (V253I), *rs3733591* (R265H), *rs2280205* (P321L), and *rs6820230* (A17T)[18]. In our study, we found 9 non-synonymous SNPs (*rs6820230* (T17A), *rs77573696* (P74A), *rs77777425* (N236S), *rs73225891* (H252D), *rs16890979* (I253V), *rs3733591* (H265R), *rs75088806* (M266V), *rs74651202* (R271C), *rs2280205* (P321L)) in *SLC2A9* gene. Among those genes, only *rs3733591* (R265H), *rs2280205* (P321L), and *rs6820230* (A17T) showed minor allele frequency greater than 5%. *rs6820230* (A17T) was found to be associated with the development of gout in a Korean population. However, *rs3733591* (R265H) and *rs2280205* (P321L) did not demonstrate any significant associations in a preliminary analysis that included 96 gout patients and 48 controls, so these SNPs were dropped out of the final analysis. *rs16890979* (V253I) showed monomorphic features from sequencing results of 12 gout patients and 12 controls, and no further genotyping was conducted.

Genetic studies are greatly influenced by ethnicity or race of the subjects. Therefore, completely different results can be seen for the same SNP based on its target population. Our study elaborated racial differences by analyzing *rs16890979* on exonic regions of *SLC2A9* gene, which is mostly known to affect serum uric acid concentrations in Western population studies. Our results showed that there was no association between that SNP and uric acid concentration in a Korean population. Then, we determined the reproducibility of SNP associations between Korea and other Asian countries such as Japan and China, which are relatively closely related from a genomic point of view. To do this, we used *rs1014290*, which was not initially included in our sequencing study because it is located in intron, but is often reported in several Japanese

and Han Chinese papers. Although *rs1014290* was located in intron, the development of gout was encouraged by the T variant. The study of *rs1014290* of *SLC2A9* gene, conducted on a Han Chinese population, demonstrated that the C allele was associated with hypouricemia in female and non-hypertensive patients, whereas our study showed no significant association between this SNP and serum uric acid level in any gender[31]. We also studied the coding SNP *rs3733591*, which was reported to be associated with gout in a Japanese study[26]. This SNP was selected as a tagging SNP because it showed minor allele frequency in a preliminary study with 24 gout patients. However, we found no significant association when we compared 96 gout patients with 48 controls.

Many earlier studies on gout demonstrated an association between SNPs in *SLC2A9* gene, gout development, and serum uric acid concentration. We tried to replicate this through target SNPs in our study but have failed to make any associations using unstratified gout patients. Though there have been reports of more significant associations between hyperuricemia and *SLC2A9* gene in female patients, we analyzed this after sex adjustment but still found no significant associations[15, 18, 21, 22]. Strangely, in subgroup analysis on male gender with *rs16890797*, uric acid level showed significant difference in GG, GA, and AA alleles (9.39 ± 1.60 mg/dl, 7.5 mg/dl, and 11.80 ± 0.85 mg/dl, respectively).

There are several limitations to our study. Firstly, we selected and sequenced SNPs from the promoter, exon and exon/intron boundary regions of *SLC2A9* gene because they are most likely to be directly involved in amino acid coding.

However, since there are reports of non-coding SNPs located in introns that can affect the development of gout and uric acid concentration, we cannot

completely ignore the capability of intronic SNPs. Future studies may benefit from full sequencing of various SNPs in different genes through GWAS and investigation of their inter-genetic interactions. Secondly, the subjects of this study were recruited from a single tertiary medical center, and for this reason, we cannot fully compensate for loco-regional differences. However, our institution has been known to be generally visited evenly from patients in many regions of Korea. This bias can be overcome with nationwide multi-center studies that have a sufficient number of gout patients and controls, which we hope to perform in the future. Thirdly, the date of diagnosis of gout, allopurinol hypersensitivity, and gout family history were all based on the patient's testimony. Therefore, patients who were diagnosed a long time ago may underestimate the duration of their disease, and all patients may have an incomplete or inadequate recollection of the familial history of gout and allopurinol hypersensitivity. Lastly, the variant of *rs3775950* showed an association with age of diagnosis of gout in female gout patients, but there were only 22 female gout patients in our study; 12 of them were over 60 years old and had renal dysfunction. This is largely due to the huge male predominance of gout patients, which reaches up to 90% of all Korean gout patients. This bias can only be overcome by a large-scale study including female gout patients with normal renal function.

This is the first study to demonstrate significant associations between SNPs in *SLC2A9* gene and gout susceptibility in the Korean population. We found meaningful variants of *rs6820230*, *rs3775950*, and *rs1014290* that could influence gout development in Korean patients. Specifically, *rs6820230* and

*rs3775950* were first to be founded in our study to be associated with gout development through direct sequencing of the target SNP.

## V. CONCLUSION

The present study was performed to confirm the association between SNP polymorphism in *SLC2A9* gene and gout susceptibility in Korean. In total, 333 gout patients and 459 controls were included, and four SNPs in *SLC2A9* gene (*rs6820230*, *rs3775950*, *rs1014290*, and *rs16890979*) were genotyped using TaqMan SNP genotyping method.

The genotype distribusions of *rs6820230* (C/T), *rs3775950* (A/G), *rs1014290* (T/C) were associated with gout susceptibility.Our results suggest that genetic variants within *SLC2A9* have significant effects on the development of gout in the Korean population.

There were no significant differences in systolic BP, diastolic BP, BMI, cholesterol, triglyceride, BUN, creatinine, CCr, and fasting glucose among different genotypes in gout patients. However, the association between genotype of *rs16890979* and serum uric acid concentration was statistically significant only in male gout patients. And the association between genotype of *rs3775950* and age of diagnosis was statistically significant only in female gout patients. There were no significant genotype-related differences among severe gout patients with tophi or X-ray abnormality, and gout patients who had experienced allopurinol hypersensitivity.

This study demonstrates the associations between SNPs in *SLC2A9* genes and gout susceptibility in Korean population. It is meaningful that we found variants of *rs6820230*, *rs3775950*, and *rs1014290* which could influence to the gout development in Korean.

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ABSTRACT (IN KOREAN)

# 한국인 통풍 환자에서 *SLC2A9* 유전자 다형성에 관한 연구

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**배경:** 통풍은 체내에 요산이 과다하게 축적되어 관절에 염증을 일으키는 질환으로, 식이, 생활습관이 서구화됨에 따라 국내 유병률이 지속적으로 증가추세에 있다. 통풍 발생의 요인으로는 남성, 고연령, 알코올 섭취, 신부전, 이뇨제 사용 등이 알려져 있고, 일부 유전적 요인이 관여할 것이라는 연구도 진행된 바 있어 *SLC2A9* 유전자와 같이 신세뇨관에서 요산의 재흡수, 분비에 관여하는 유전자들의 단일염기다형성(single nucleotide polymorphism, SNP)이 연구되고 있다. 하지만 기존의 연구들은 주로 백인들에 대해서 이루어졌고, 유전자 연구는 인종간 차이가 존재할 가능성이 크므로 한국인 고유의 통풍 유전자 연구가 필요하다. 본 연구에서는 한국인 통풍 환자를 대상으로 통풍 발생과 연관이 있는 *SLC2A9* 유전자의 다형성을 밝혀내고, 다양한 임상 지표와의 연관성을 확인하고자 하였다.

**방법:** 통풍 환자 12명과 대조군 12명을 대상으로 *SLC2A9* 유전자의 exon, promoter, exon-intron 경계 부위를 sequencing하여 minor allele frequency가 5%가 넘는 SNP를 tagging SNP로 정하고 통풍환자 96명과 대조군 48명을 대상으로 genotype, allele frequency를 분석한 결과

*rs6820230* (C/T)와 *rs3775950* (A/G)의 variant가 통풍의 발병과 유의한 연관성을 보였다. 이 두 SNP와 서양에서 통풍 혹은 혈중 요산 농도에 가장 큰 영향을 미치는 것으로 알려진 *rs16890979*, 그리고 intron에 위치하고는 있지만 일본, 한족을 비롯한 동양인에서 통풍과의 연관성이 보고된 바 있는 *rs1014290* 등 4개의 SNP variant를 통풍 환자 333명과 대조군 459명을 대상으로 분석하였다.

**결과:** 분석 결과 *rs6820230*의 major allele은 C, minor allele은 T, *rs3775950*의 major allele은 A, minor allele은 G, *rs1014290*의 major allele은 T, minor allele은 C, 그리고 *rs16890979*의 major allele은 C, minor allele은 T로 나타났다. *rs6820230*의 경우 T allele이 C allele보다 통풍의 위험성을 1.98배 증가시키는 것으로 나타났고 ($P$ = 0.0003, OR 1.977, 95% CI 1.363, 2.867), genotype이 TT인 사람이 CT인 사람보다, CT인 사람이 CC인 사람보다 각각 1.9배 통풍 발생 가능성이 높아졌다. *rs3775950*의 경우 G allele이 A allele보다 통풍의 위험성을 2.13배 증가시켰고 ($P$ < 0.0001, OR 2.133, 95% CI 1.457, 3.122) genotype에 따라 GG가 AG보다, AG가 AA보다 각각 2.2배 통풍의 위험도를 증가시켰다. *rs1014290*에서는 T allele이 C allele에 비해 통풍의 발생을 1.56배 증가시키는 것으로 나타났고 ($P$ = 0.0055, OR 1.564, 95% CI 1.269, 1.928) genotype에 따라 TT가 CT보다, CT가 CC보다 각각 1.6배 통풍의 위험도를 증가시켰다. *rs16890979*는 genotype이나 allele frequency가 모두 통풍의 발생에 유의한 연관성을 보이지 않았다.

*SLC2A9* 유전자의 *rs6820230*, *rs3775950*, *rs1014290*, *rs16890979* variant가 통풍 환자의 특정 임상양상과 연관이 있는지를 확인하기 위해 여러 가지 임상 지표와의 연관성을 확인하였으나 수축기 혈압, 이완

기 혈압, 체질량지수, 콜레스테롤, triglyceride, BUN, creatinine, CCr 및 공복혈당 모두 통계적인 유의성을 보이지 않았다. 다만, 남자 환자만을 대상으로 하여 분석하였을 때 *rs16890979*의 SNP variant에 따라 혈중 요산 농도에 차이를 보였고, 여자 환자만을 대상으로 하였을 때 *rs3775950*의 SNP variant에 따라 통풍을 처음 진단받은 나이가 차이를 보였다. 일부 연구에서 통풍의 발생에 영향을 주지 못하는 SNP variant가 통풍결절을 동반한 통풍의 발생에는 영향을 주는 것이 보고된 바 있어 본 연구에서도 통풍결절을 동반한 환자를 대상으로 분석을 시행하였으나 통계적으로 의미는 없었다. X-ray 상 미란이 관찰되었던 severe gout나 allopurinol hypersensitivity를 경험한 환자에 대해서도 genotype에 따른 유의한 차이는 발견할 수 없었다.

**결론:** 본 연구를 통해 한국인에서 통풍 발생에 연관된 *SLC2A9* 유전자의 SNP가 존재함을 확인할 수 있었다. 이 중에는 백인, 한족, 일본인 등 다른 인구를 대상으로 한 연구의 결과들과 일치하는 것도 있고 기존 연구 결과에 부합되지 않는 것도 있어 유전자 연구에 있어서 인종간의 특이성이 존재함을 다시 한 번 확인할 수 있었다.

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핵심되는 말 : 통풍, *SLC2A9* 유전자 다형성, 단일염기다형성