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Genome-wide search for genes affecting serum uric acid levels: the Framingham Heart Study☆

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Abstract

Serum uric acid levels are associated with hypertension, cardiovascular disease, and renal disease. Uric acid has been shown to be heritable; however, genome-wide linkage analyses have not been reported.Genome-wide multipoint variance components linkage analyses with 401 markers spaced at approximately 10 centimorgan (cM) were conducted on 1258 subjects of the Framingham Heart Study, using the average of two serum uric acid measurements obtained in examinations 1 and 2 around 1971 and 1979. Covariates in fully adjusted model included sex, age, body mass index (BMI), serum creatinine, alcohol consumption, diabetes, diuretic treatment, and triglycerides. To investigate possible pleiotropic effects between uric acid and covariates that may have a genetic component, bivariate linkage analyses of uric acid with BMI, triglycerides, and glucose were conducted at the uric acid linkage regions.The heritability of uric acid was 0.63. The highest multipoint log-of-the-odds (LOD) score was 3.3 at 50 cM on chromosome 15 for age-sex–adjusted uric acid, but decreased to 1.5 after multivariable adjustment. Additional evidence of linkage was seen on chromosomes 2 (LOD score 1.1 at 4 cM) and 8 (LOD score 1.7 at 6 cM) for multivariable-adjusted uric acid. Pleiotropic effects were only found between uric acid and glucose and BMI at chromosomes 8 and 15 linkage locations, respectively.We have identified several novel loci linked to uric acid. We found possible pleiotropic effects between uric acid and BMI and glucose. Further research is necessary to identify the genes involved in uric acid metabolism and their roles in hypertension, cardiovascular disease, and renal disease.

1. Introduction

Serum uric acid levels are associated with hypertension, cardiovascular disease, and renal disease [1-6]. However, it is debatable whether uric acid has a direct role in the pathogenesis of these diseases or acts through other risk factors [7,8].

Serum uric acid levels are heritable, with estimates ranging from 0.25 to 0.73 [9-14]. Results from segregation analyses are inconsistent, and it is uncertain if there is a major gene that determines levels of serum uric acid. Early studies suggested a major gene effect [15,16], but more recent data support a multifactorial inheritance from multiple major genes and environmental factors [9,11,13,14]. Suggestive linkage to serum uric acid levels has been demonstrated on chromosome 2, near a locus for the metabolic syndrome [17]. However, genome-wide linkage analyses have not been reported for uric acid. A further understanding of the genes involved in uric acid metabolism in the general population may improve the understanding of the relationship between uric acid and hypertension, cardiovascular disease, and renal disease and, subsequently, better elucidate some of the mechanisms involved in these diseases. Thus, we conducted heritability and genome-wide linkage analyses for uric acid in the Framingham Heart Study (FHS), a population-based sample.

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2. Research design and methods

2.1. Subjects

The study subjects are members of the offspring cohort in the FHS. The selection criteria and study design of the FHS have been described in detail previously [18,19]. The study began in 1948 with the enrollment of 5209 participants, collectively referred to as the original cohort, from Framingham, Mass. Starting in 1971, 5124 individuals, adult children of the original cohort, and spouses of these adult children, referred to as the offspring cohort, were recruited. The members of the offspring cohort were examined every 4 years (except for an 8-year gap between the first and the second examinations). In the mid-1990s, 1702 original and offspring cohort subjects from 330 of the largest extended pedigrees were genotyped with a set of 401 microsatellite markers. Serum uric acid levels were measured on offspring participants at examination cycles 1 (1971-1974) and 2 (1979-1982). The linkage analysis reported here was based on 1258 persons of the offspring cohort who were members of the 330 largest extended pedigrees and whose serum uric acid levels were measured at both examination cycles.

All subjects provided informed consent before each clinic visit and the examination protocol was approved by the Institutional Review Board at Boston Medical Center (Boston, Mass).

2.2. Measurement of uric acid levels

Fasting serum uric acid was measured using an auto-analyzer with a phosphotungstic acid reagent [20].

2.3. Genotyping

DNA was extracted from buffy coat of whole blood specimens using a Qiagen Blood and Cell Culture DNA Maxi Kit (Qiagen, Valencia, Calif) from offspring cohort participants attending the sixth examination cycle (1995-1998). The subjects from 330 largest extended pedigrees were genotyped with a set of 401 microsatellite markers, an average of 1 marker every 10 centimorgan (cM), over the 22 chromosomes. The genotyping was conducted by the Mammalian Genotyping Service in Marshfield, Wis.

Table 1
Characteristics of the 1258 subjects in the 330 extended pedigrees with serum uric acid measured at examinations 1 and 2

Characteristics	Examination 1	Examination 2
Female	50%	50%
Age (y)	33 ± 10	41 ± 10
BMI (kg/m^2)	25.0 ± 4.2	25.4 ± 4.3
Serum uric acid (mg/dL)	5.6 ± 1.4	5.1 ± 1.5
Diuretic use	3%	8%
Serum creatinine (mg/dL)	NA	1.38 ± 0.37
Alcohol consumption (oz/wk)	3.6 ± 4.9	3.9 ± 5.5
Triglycerides (mg/dL)	92.7 ± 70.9	101.3 ± 89.5
Diabetes	2%	3%

Values are expressed as percentage or mean ± SD.

Table 2
Unadjusted, age-sex–adjusted, and fully adjusted heritabilities of uric acid[a]

	No. of subjects	Heritability	SE
Unadjusted	1285	0.37	0.07
Age-sex adjusted	1285	0.59	0.07
Fully adjusted[b]	1263	0.63	0.07

[a] The average of examinations 1 and 2 serum uric acid levels was used in heritability analyses.

[b] Fully adjusted models adjusted for age, sex, BMI, serum creatinine, alcohol consumption, diabetes, diuretic treatment, and triglycerides.

The screening set 9 [21] and genotyping protocols are available at the Web site of the Center for Medical Genetics, Marshfield Medical Research Foundation (http://www.marshfieldclinic.org/research/genetics/).

In summary, the genotyping process was as follows: fluorescent-labeled primers and genomic template DNA were put in polymerase chain reaction to amplify selected microsatellite loci; amplified DNA fragments were then separated by electrophoresis in short, wide polyacrylamide gels; excitation lasers were then introduced in detection of dyes and allele calling was conducted using specialized computer software program. There were two major limitations in the genotyping method: first, some alleles may not be fully amplified, which may result in miscalling of allele size. Second, homoplasy may occur in which alleles are identical by state (identical in size) but not identical by descendant because of convergent mutations during the evolution [22]. The first limitation can be detected and corrected by repeated genotyping. The second limitation is generally not a significant problem because microsatellite markers are highly heterozygous.

2.4. Clinical definitions and covariate measurements

Body mass index (BMI) was calculated as the ratio of weight (kilograms) to the square of height (meter). Alcohol consumption was recorded as the usual number of drinks (of comparable ethanol content) per week. Diabetes (yes or no) was defined by fasting blood glucose of 126 mg/dL or greater or on diabetes treatment. Diuretic treatment (yes or no) was defined by if a person is using any type of diuretic drugs. Serum creatinine was measured using the modified Jaffe's method at examination cycle 2 [23]. Fasting triglyceride concentrations were measured as previously described [24].

2.5. Statistical analysis

The average of the two serum uric acid measurements was used as the phenotype in the linkage analysis; the mean of uric acid was selected to reduce measurement error. To reduce the variability due to clinical variables and to account for any differences between men and women, studentized residuals from age-adjusted and fully adjusted sex-specific multiple linear regression models were also used as phenotypes in the linkage analyses. Covariates in fully adjusted model included age, BMI, serum creatinine, alcohol consumption, diabetes, diuretic treatment, and triglycerides. For all the continuous

Table 3
Maximum multipoint LOD scores of 1.5 or greater for age-sex–adjusted and fully adjusted uric acid

Chromosome	Location (cM)	Nearest marker	LOD score
Age-sex–adjusted			
2	7	GATA165C07	1.9
8	3	143xd8	2.2
15	50	GATA63A03	3.3
Fully adjusted[a]			
2	4	GATA165C07	1.1
8	6	198wd2	1.7
15	50	GATA63A03	1.5

[a] Fully adjusted models adjusted for age, sex, BMI, serum creatinine, alcohol consumption, diabetes, diuretic treatment, and triglycerides.

covariates, the average values from examinations 1 and 2 were used. For the dichotomous covariates, the proportions of yes in the two examinations were used.

Variance components models, implemented in SOLAR (Sequential Oligogenic Linkage Analysis Routines) [25] using multipoint identity-by-descendent (IBD) calculated by Loki [26], were used to estimate heritability and test for linkage. To estimate heritability, a polygenic model is assumed where the total variance of a trait is partitioned into 2 components: additive polygenic and random environment effects. Maximum likelihood methods are used to estimate the variance components. Heritability is then estimated as the ratio of the additive polygenic variance to the total variance. To test for linkage at a marker, the total variance of a trait is partitioned into 3 components: quantitative trait locus (QTL), residual additive polygenic, and random environmental effects. The log-of-the-odds (LOD) score, a measure for linkage, was used. The LOD score represents $\log_{10}$ of the maximum likelihood ratio of the linkage model to that of the polygenic model, distributed as an equal mixture of χ^2 with 1 degree of freedom and a point mass at zero. Multipoint IBD at each chromosome location was calculated using Loki [26] and then used by SOLAR to perform the linkage analyses. Multipoint IBD at each location incorporates inheritance information at all other markers on the same chromosome and thus is more powerful than 2-point IBD that only uses inheritance information at a single marker.

Similar to univariate analyses, in the bivariate heritability and linkage analyses, each trait is modeled with its own polygenic, QTL, and environmental effects, except that correlations are assumed between the polygenic effects of the two traits for heritability analysis and between the QTL effects and between the residual polygenic effects for linkage analysis [27]. Correlation coefficient take values between −1 and 1. For the QTL correlation coefficient, 0 means that there are no shared QTL effects in the region or co-linkage; 1 or −1 means the traits share the same QTL in the region (ie, complete pleiotropy). The LOD score from the bivariate linkage analysis contains 2 degrees of freedom. To make it comparable with the LOD score from the univariate analysis, the P value of the 2 degrees of freedom LOD score was transformed back to a 1 degree of freedom LOD score that was then reported as the LOD score in our bivariate analyses. The LOD score from the bivariate analyses evaluates whether at least one of the traits has a QTL variance greater than zero. To test against co-linkage (and thus for pleiotropy), an unconstrained linkage model is compared with a linkage model with the QTL correlation coefficient constrained to

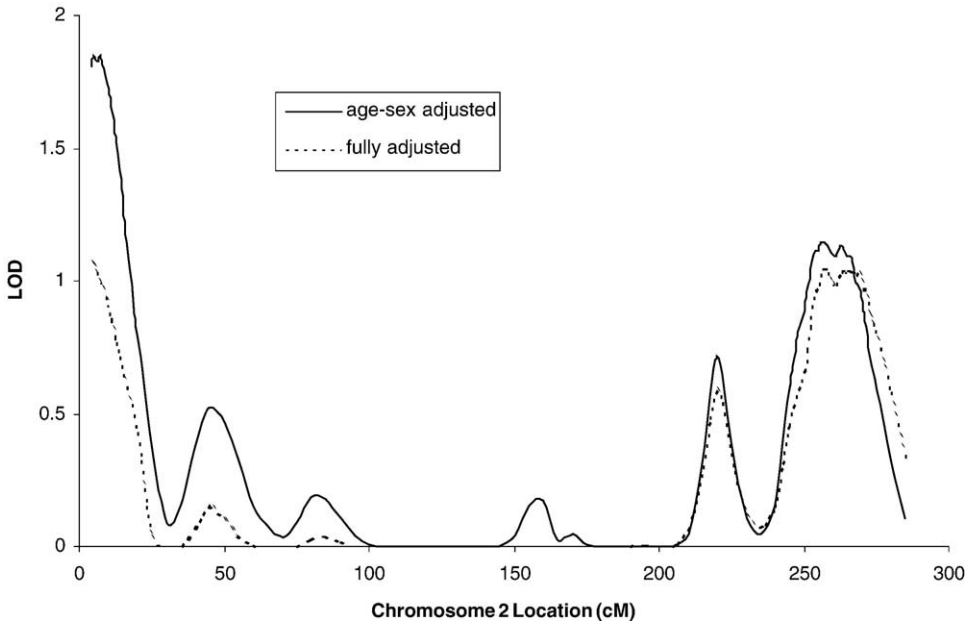

Fig. 1. Multipoint LOD scores of linkage to uric acid on chromosome 2.

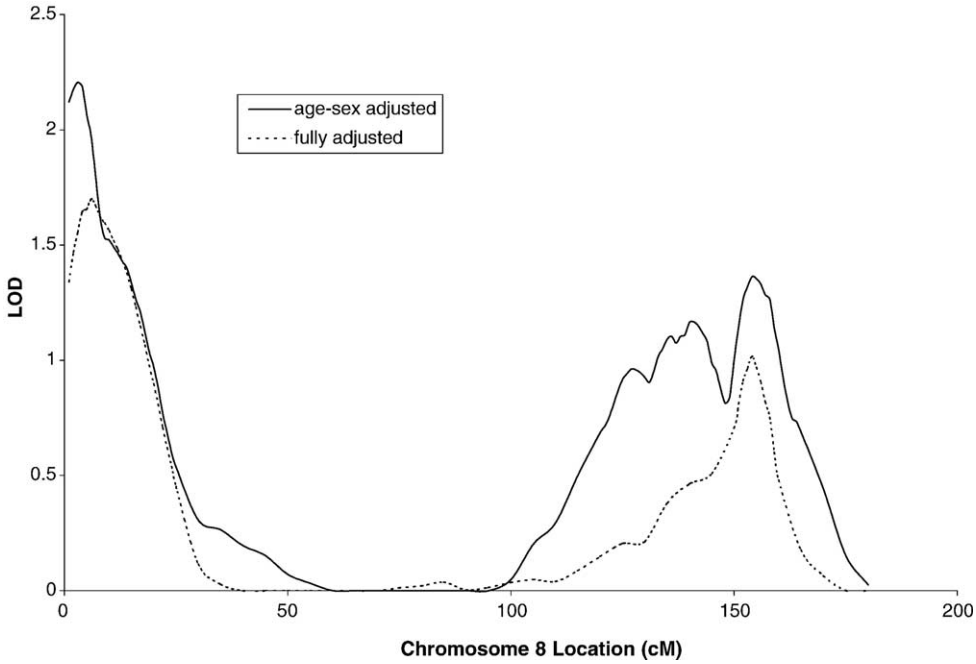

Fig. 2. Multipoint LOD scores of linkage to uric acid on chromosome 8.

zero, and the likelihood ratio statistic is distributed as χ^2 with 1 degree of freedom.

3. Results

3.1. Baseline characteristics

Characteristics of the 1258 offspring cohort subjects used in the analysis are presented in Table 1. The mean ages at the two examinations were 33 years (range, 10-64 years) and 41 years (range, 17-72 years), respectively. The mean serum uric acid levels at the two examinations were 5.6 mg/dL (range, 2.2-12.4 mg/dL) and 5.1 mg/dL (range, 1.2-11.8 mg/dL), respectively. The mean of the average of the two serum uric acid level measurements was 5.4 mg/dL (range, 2.1-10.3 mg/dL); this variable was used for the ensuing genetic analyses. The Pearson correlation coefficient between the two serum uric acid measurements was 0.71 (P = .001). Together, the baseline characteristics including age, BMI, serum creatinine, alcohol consumption,

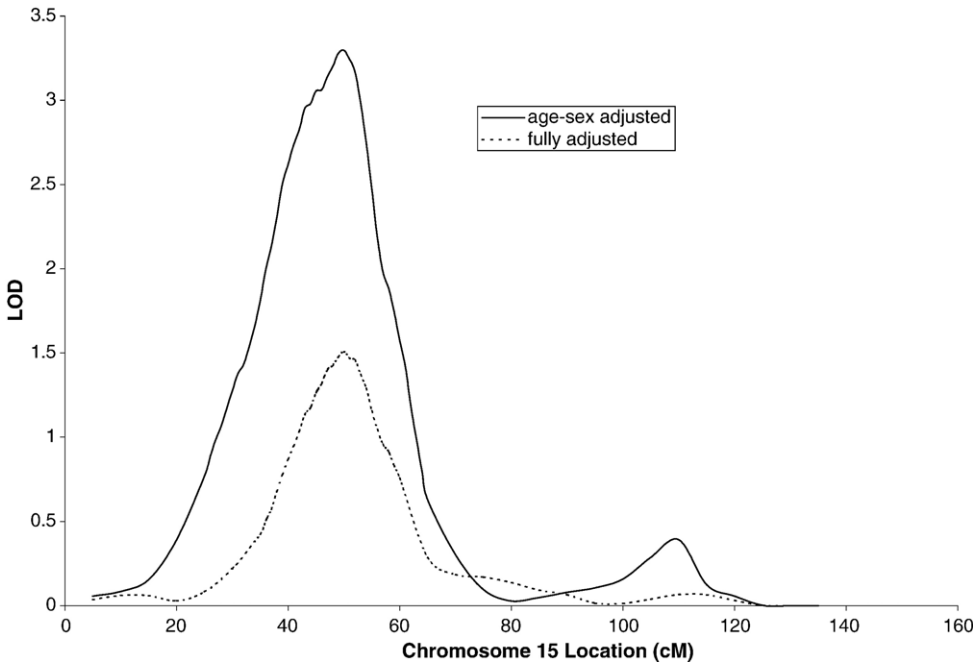

Fig. 3. Multipoint LOD scores of linkage to uric acid on chromosome 15.

diabetes, diuretic treatment, and triglycerides explained 56% of the variance of serum uric acid levels.

3.2. Heritability estimates

Unadjusted, age-sex–adjusted, and fully adjusted heritabilities of serum uric acid levels are presented in Table 2. The heritability estimates were 0.37, 0.59, and 0.63 for unadjusted, age-sex–adjusted, and fully adjusted uric acid levels.

3.3. Linkage analysis

All multipoint LOD scores of 1.5 or greater are presented in Table 3. The highest multipoint LOD score was 3.3 at 50 cM on chromosome 15, nearest to marker GATA63A03, in the age-sex–adjusted model; this decreased to 1.5 in the fully adjusted model. An age-sex–adjusted multipoint LOD score of 1.9 was found at 7 cM on chromosome 2, and a LOD score of 2.2 was found at 3 cM on chromosome 8; both were attenuated to 1.1 and 1.7 in the fully adjusted model. Multipoint LOD scores on chromosomes 2, 8, and 15 are plotted in Figs. 1-3.

3.4. Bivariate heritability and linkage analyses

Because the linkage evidence was weakened after adjusting for all the covariates, we used bivariate analyses to determine whether that was partly due to pleiotropy between some of the covariates and uric acid. Body mass index, diabetes, and triglycerides were covariates in the fully adjusted model and had genetic components as previously demonstrated in other studies; thus, we examined whether the loci involved in uric acid metabolism may be partly mediated through these variables. To do this, we used bivariate linkage analysis between uric acid and each of BMI, triglycerides, and fasting glucose (as a surrogate for diabetic subjects) while adjusting for all other covariates.

Heritabilities and polygenic correlations are presented in Table 4. Body mass index had the highest polygenic correlation of 0.22 (P value = .03) with uric acid.

Maximum multipoint LOD scores from bivariate analyses in the linkage regions of uric acid are presented in Table 5. The highest LOD score was 2.5 at 5 cM on chromosome 2 for uric acid and glucose levels. All 3 bivariate analyses resulted in LOD scores of 1.8 or greater on chromosome 15. Bivariate analyses of uric acid and glucose levels also resulted in LOD scores of 1.8 or greater on all 3 chromosomes.

Table 4
Heritabilities of BMI, triglycerides, and glucose and their polygenic correlations with uric acid

	Heritability[a]	Polygenic correlation (ρ_g)	SE of ρ_g	P ($\rho_g \neq 0$)	P ($\rho_g < 1$)
BMI	0.54	0.22	0.10	.03	<.0001
Triglycerides	0.48	0.16	0.10	.13	<.0001
Glucose	0.36	0.17	0.11	.14	<.0001

[a] Adjusted for age, sex, serum creatinine, alcohol consumption, and diuretic treatment.

Table 5
Maximum multipoint LOD scores from bivariate linkage analyses[a] in the linkage region of uric acid

Uric acid	BMI		Triglycerides		Glucose	
Chromosome	Location (cM)	LOD	Location (cM)	LOD	Location (cM)	LOD
2	4	1.1	5	1.0	5	2.5
8	9	1.5	12	1.4	6	1.8*
15	47	1.8*	47	2.0	52	1.8

[a] Adjusted for age, sex, serum creatinine, alcohol consumption, and diuretic treatment.

* $P < .05$ for pleiotropy.

For those bivariate analyses with LOD scores greater than 1.5, QTL correlation coefficient, ρ_q, was found significantly greater than zero only between uric acid and BMI at 47 cM on chromosome 15 ($\rho_q = 0.84$, $P = .02$ for $\rho_q \neq 0$) and between uric acid and glucose at 6 cM on chromosome 8 ($\rho_q = 0.65$, $P = .04$ for $\rho_q \neq 0$). The chromosome 15 locus accounted for 29% of the variation in uric acid and 13% of the variation in BMI. The maximum multipoint LOD score from the univariate analysis of BMI in this region was about 0.5. The chromosome 8 locus accounted for 28% of the variation in uric acid and 15% of the variation in glucose. The maximum multipoint LOD score from univariate analysis of glucose in this region was about 0.3.

4. Discussion

We have found evidence for linkage to uric acid, with significant evidence for linkage on chromosome 15 for age-sex–adjusted uric acid according to the guidelines for interpreting linkage results [28]. Suggestive evidence for linkage was also found on chromosomes 2 and 8 for the age-sex–adjusted model. For the multivariable-adjusted model, the linkage signals at these loci weakened but did not completely disappear. Our report also confirms prior studies and demonstrates that serum uric acid is heritable, with results comparable with previous reports [11,12,14].

Environmental factors account for over half of the variance in uric acid levels. Despite this, evidence for linkage was found on 3 chromosomes. Not surprisingly, the linkage signals weakened after multivariable adjustment, confirming a multifactorial inheritance for uric acid as suggested in previous studies [9,11,13,14].

Our bivariate linkage results indicate possible pleiotropy effects between uric acid and BMI and glucose. The LOD scores from the bivariate analyses are higher than from univariate analyses of BMI and glucose. This demonstrates that when there is a pleiotropic effect present, the power to detect weakly linked traits can be improved [27]. Our results also suggest co-linkage between uric acid and glucose at the

chromosomes 2 and 15 linkage regions and between uric acid and triglycerides at the chromosome 15 linkage regions. In aggregate, these results have improved our understanding of the genetic relationship between uric acid and BMI and glucose. Indeed, the chromosome 15 linkage region is near a locus previously linked to the metabolic syndrome that included BMI and glucose (LOD score 2.53 at 26 cM) [17]. A potentially interesting candidate gene in this region is *LIPC* (hepatic lipase), an important enzyme in high-density lipoprotein metabolism.

Several interesting candidate genes at the site of the chromosome 2 linkage region may affect either glucose or uric acid levels. *ACP1* is involved in the modulation of signal transduction by insulin, platelet-derived growth factor receptors, and T-cell receptors. A previous candidate gene study of *ACP1* reported a significant association among subjects with type 2 diabetes [29]. Other candidate genes in this region include *RRM2* (ribonucleotide reductase m2 polypeptide), residing at approximately 10 MB and involved in providing the necessary precursors for DNA synthesis; *NT5C1B*, (5′-nucleotidase), another enzyme involved in purine metabolism, residing at approximately 19 MB and involved in nucleotide dephorphorylation, the process of converting purine nucleotides to nucleotides.

Although not significant, we did find small peaks with LOD scores of 1.1 for uric acid on chromosome 2 at approximately 240 cM, near to the loci linked to unadjusted serum uric acid (LOD score 1.88 at 288 cM) and the metabolic syndrome (LOD score 3.34 at 240 cM) reported by the Family Heart Study [17]. Our bivariate linkage analyses of uric acid and glucose produced a LOD score of 1.6 and suggested co-linkage at 260 cM. This region was also recently mapped to obesity [30], fasting glucose [31], and type 2 diabetes [32].

Strengths of our study include a study sample not ascertained for disorders known to be associated with abnormal levels of uric acid, increasing the generalizability of our results. We were also able to use the mean serum uric acid from two points in time rather than relying on a 1-time measure, reducing measurement error. We conducted bivariate analyses of uric acid and related components of metabolic syndrome.

Limitations of this study include a study sample that is primarily white, limiting the generalizability of our findings to other ethnic groups. Furthermore, many of our results are suggestive of linkage only and will require confirmation in other study samples. Our sample size and the marker spacing of approximately 10 cM in the genome-wide linkage analysis may limit our power to localize disease-influencing QTL in linkage to uric acid. Although there may be additional QTLs not detected in our study, simulation studies using finer marker maps have demonstrated that the location error of a detected QTL is similar in maps using marker spacing of 10 cM and of 2, 1, or 0.5 cM [33] for a QTL that explains a small proportion of the total variation, suggesting that marker spacing should not have a substantial effect on our results.

There have been reports of strong association between serum uric acid levels and insulin resistance, plasma insulin concentrations, and renal uric acid clearance [34-36]. Because insulin resistance, plasma insulin concentrations, and renal uric acid clearance were not measured on FHS subjects at the examinations 1 or 2 when the serum uric acid levels were measured, we were not able to evaluate the linkage after adjusting for these 3 variables. The generalizability of our linkage results is thus limited by the lack of adjustment for these important variables.

Our linkage results, although not conclusive, represent the first genome-wide search for genes influencing uric acid metabolism in the general population. With further confirmation in other populations and fine mapping in the linkage region, we may discover novel genes or better understand existing genes for their role in uric acid metabolism. Because uric acid levels are associated with diseases such as hypertension, cardiovascular disease, and renal disease, understanding genes involved in uric acid may elucidate pathophysiological mechanisms involved with these conditions.

In summary, we have found evidence for linkage on chromosomes 2, 8, and 15 to serum uric acid levels. With multivariable adjustment, the evidence at these loci weakened but did not completely disappear. Possible pleiotropic effects between uric acid and BMI and glucose have been found in the regions where we found linkage to uric acid. Further research is necessary to identify the genes involved in uric acid metabolism, which may also play a role in hypertension, cardiovascular disease, and renal disease.

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