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Genetic Influence on Variation in Serum Uric Acid in American Indians: The Strong Heart Family Study

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Abstract

Hyperuricemia is associated with the metabolic syndrome, gout, renal and cardiovascular disease (CVD). American Indians have high rates of CVD and 25 % of individuals in the Strong Heart Family Study (SHFS) have high serum uric acid levels. The aim of this study was to investigate the genetic determinants of serum uric acid variation in American Indian participants of the SHFS. A variance component decomposition approach (implemented in SOLAR) was used to conduct univariate genetic analyses in each of three study centers and the combined sample. Serum uric acid was adjusted for age, sex, age*sex, BMI, estimated glomerular filtration rate, alcohol intake, diabetic status and medications. Overall mean ± SD serum uric acid for all individuals was 5.14 ± 1.5 mg/dl. Serum uric acid was found to be significantly heritable (0.46 ± 0.03 in all centers, and 0.39 ± 0.07, 0.51 ± 0.05, 0.44 ± 0.06 in Arizona, Dakotas and Oklahoma, respectively). Multipoint linkage analysis showed significant evidence of linkage for serum uric acid on chromosome 11 in the Dakotas center (logarithm of odds score (LOD) = 3.02) and in the combined sample (LOD = 3.56) and on chromosome 1 (LOD = 3.51) in the combined sample. A strong positional candidate gene in the chromosome 11 region is solute carrier family22, member 12 (*SLC22A12*) that encodes a major uric acid transporter URAT1. These results show a significant genetic influence and a possible role for one or more genes on chromosomes 1 and 11 on the variation in serum uric acid in American Indian populations.

Keywords

SLC22A12 gene; URAT1; variance component decomposition approach; chromosome

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Introduction

Increased serum uric acid or hyperuricemia is associated with gout, renal and cardiovascular disease (CVD) and the metabolic syndrome (Nakagawa *et al.* 2006). Although serum uric acid has been more closely associated with gout, its association with CVD has recently been recognized (Alderman 2002; Johnson *et al.* 2005; Chen *et al.*, 2009). Serum uric acid has been independently associated with insulin resistance, hypertension, dyslipidemia and obesity (Hayden and Tyagi 2004; Forman *et al.*, 2009), all disorders that are elements of the metabolic syndrome (Conen *et al.* 2004; Onat *et al.* 2006; Nan *et al.* 2008). Even in individuals with serum uric acid levels in the normal range, it was found that increasing serum uric acid was associated with an increased risk of metabolic syndrome (Yoo *et al.* 2005; Hikita *et al.* 2007). Higher serum uric acid levels have also been linked to increased risk of developing type 2 diabetes (Dehghan *et al.* 2008a). Endothelial dysfunction, another common finding in renal and CVD patients, may be induced by increased serum uric acid (Khosla *et al.* 2005). The possible mechanisms by which serum uric acid may have pathogenic role in CVD are i) promoting lipid peroxidation by oxygenation of low density lipoprotein cholesterol, ii) increasing production of free oxygen radicals and thus increasing the risk for atherosclerosis, iii) increasing platelet aggregation, and iv) inducing renal hypertension by intrarenal crystal deposition (Alderman 2002). However, it is not clear whether serum uric acid is an independent risk factor of CVD or is merely associated with other CVD risk factors or metabolic syndrome components. Irrespective of its importance as an independent risk factor, elevated serum uric acid is a matter of concern in individuals at risk for CVD (Hayden and Tyagi 2004).

Serum uric acid concentrations are highly variable in humans. Age, ethnicity, sex, high purine nutrient intake, alcohol consumption, defects in purine metabolism and genetic factors influence serum uric acid levels (Johnson *et al.* 2003). In addition, medications including losartan, allopurinol, diuretics and other hypertension medications impact uric acid metabolism (Sica and Schoolwerth 2002). Serum urate levels have been found to be significantly heritable in family-based studies (Rao *et al.* 1982; Rice *et al.* 1990; Tang *et al.* 2003; Yang *et al.* 2005; Nath *et al.* 2007; Voruganti *et al.* 2009). A few genome-wide studies of serum uric acid have been conducted in Caucasian, African American and Mexican American population with relatively little replication of chromosomal locations (Tang *et al.* 2003; Yang *et al.* 2005; Nath *et al.* 2007; Voruganti *et al.* 2009).

The Strong Heart Family Study (SHFS) is an extension of an ongoing, longitudinal study of CVD in American Indians, the Strong Heart Study (SHS). American Indians have high rates of CVD and CVD-related mortality (Howard *et al.* 1999; North *et al.* 2003). Serum uric acid values can vary substantially based on ethnicity and geography (Alderman 2002). Serum uric acid levels > 7 mg/dl in men and 6mg/dl in women are considered high (Rathmann *et al.*, 1998; Krishnan *et al.*, 2007). However, serum uric acid levels > 4mg/dl have been associated with complications of atherogenesis and stroke in individuals who are diabetic or at risk for CVD (Lehto *et al.*, 1998; Hayden and Tyagi, 2004). Serum uric acid in this cohort also run high with more than 25 % and 76 % of individuals having serum uric acid levels more than 6 and 4mg/dl, respectively. These findings are a public health concern in a cohort that is at a higher risk for CVD. Given the high rates of CVD and serum uric acid levels, investigation of genetic factors that influence the variation in serum uric acid in this population is of utmost importance. Therefore the primary aim of this study was to identify quantitative trait loci (QTLs) influencing the variation in serum uric acid levels in American Indians.

Methods

Study population

The SHFS is family-based genetic study in the American-Indian community. It is an extension of the Strong Heart Study which is a population-based observational study of CVD and its risk factors in this population. More than 3600 members of multigenerational families were enrolled from all three centers located in Arizona, North and South Dakota and Oklahoma. The North and South Dakota centers have been grouped together as one center as the SHFS participants in the Dakotas are members of Sioux tribes whose reservations exist in both North and South Dakota. The Indian Health Service Institutional Review Board and the institutional review boards from the participating centers approved the SHFS protocol. All subjects gave informed consent. Study design and methods of the SHFS have been described before (North *et al.* 2003).

Phenotyping

During a clinical visit, information related to anthropometry, alcohol intake, medical history and medication use was obtained using a questionnaire. Weight was measured to the nearest 0.1 kilogram, using an ISO-9001 certified Scale-Tronix electronic scale with a capacity of 880 pounds (400 kilograms) (White Plains, NY). Standing height was measured twice, to the nearest centimeter, using a SECA wall-mounted stadiometer (Seca Corp., Hanover, MD). Body mass index (BMI) was computed as the ratio between weight in kilograms and height (in meters) squared. Blood was collected after an overnight fast and plasma and serum samples were stored at −80°C until analyzed. Fasting serum uric acid was oxidized in the presence of uricase to form hydrogen peroxide, which was measured photometrically (Domagk *et al.* 1968). Serum creatinine was estimated by modified kinetic Jaffe reaction (Beckman Synchron LX System, Beckman Coulter, Fullerton, CA). Estimated glomerular filtration rate (eGFR) was computed using the simplified modified diet and renal disease (MDRD) equation:

$$[\text{eGFR (ml/min/1.73m}^2) = 186 \times \text{sCr (mg/dl)}^{-1.154} \times \text{age (years)}^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})]$$ (Levey *et al.* 1999; Myers *et al.* 2006).

Genotyping

Genotyping was conducted with DNA isolated from fasting blood samples using organic solvents. All study participants were genotyped for about 400 microsatellite markers, using the ABI PRISM Linkage Mapping Set-MD10 Version 2.5 (Applied Biosystems, Foster City, CA) with markers spaced at an average interval of 10cM across the autosomal chromosomes. Genotyping procedures have been described previously (North *et al.* 2006). Pedigree and Mendelian errors were detected and corrected utilizing the software PREST (pedigree relationship statistical tests) (Sun *et al.* 2002) and SIMWALK2 (Sobel *et al.* 1996), respectively. Multipoint identity-by-descent (IBD) matrices for genome-wide linkage analyses were calculated using the linkage analysis package (LOKI) (Heath 1997). The chromosomal map used in these computations was based on marker locations reported by DeCode genetics (Kong *et al.* 2002).

Quantitative genetic analysis

To detect genetic influence on the variation in serum uric acid and localize quantitative trait loci (QTL) that affect serum uric acid, we employed a multipoint linkage analysis based on the variance components decomposition approach, implemented in the software program SOLAR and described in detail elsewhere (Blangero and Almasy 1997; Almasy and Blangero 1998). In short, it is an extension of the variance components approach in which variance due to a specific QTL is added to the basic model. It is based on estimating the effect of a specific QTL on the variation in phenotype, and can be modeled as a function of the IBD relationship at the

marker locus between family members. Traditionally, a logarithm of the odds (LOD) score, which is computed directly from the likelihood ratio tests, is reported in linkage analyses (Almasy and Blangero 1998).

An inverse normalization was performed for all traits after removing outliers greater than four standard deviation from the mean. To conduct multipoint linkage analysis in the combined sample, we combined samples from individual centers and used the cumulative data for analysis, incorporating center as a covariate in the final model in addition to other covariates. The serum uric acid was adjusted for the effects of factors that are known to influence its variation using regression methods. The covariates age, sex, age*sex, BMI, eGFR, type 2 diabetes status, alcohol intake and medications were included in the final model. Relative pairs that were major contributors to this study were parent-offspring, siblings, grandparent-grandchild, avuncular, half siblings, first, second and third cousins. Details of these pairs are shown in Table 1.

Results

3604 individuals (men = 1443, women = 2161) participated in this study. Of these, 1215 were from Arizona, 1186 from Dakotas and 1203 from Oklahoma. The distribution of age, BMI and serum uric acid by sex and center is given in Table 2. The overall mean ± SD serum uric acid for all individuals was 5.14 ± 1.5 mg/dl. According to the criteria for increased serum uric acid levels (men > 7 mg/dl and women > 6mg/dl) 12 %, 21 % and 17 % of individuals from Arizona, Dakotas and Oklahoma, respectively had hyperuricemia. As has been observed in previous studies (Mikkelsen *et al.* 1965;Freedman *et al.* 1995;Conen *et al.* 2004), men had higher levels of serum uric acid than women in all centers, despite being younger and having lower BMI. Approximately 20 % and 23 % of individuals had hypertension and type 2 diabetes, respectively. With respect to medication usage, 13 % of the individuals were taking aspirin and 15 % were taking angiotensin-converting enzyme (ACE) inhibitors. Approximately 7 % were taking diuretics. Diabetic drugs, insulin, metformin and sulfonyureas were taken by 6 %, 8 %, and 10 % of the participants, respectively. Each medication group was tested separately for significant effects on serum uric acid levels. The medication groups included aspirin, statins, fibrates, insulin, sulfonylureas, metformins, thiazolidinediones, ACE inhibitors, ARBs, beta blockers, calcium channel blockers, hydrocholrophiazides (diuretics), hypotensive agents, alpha blocking agents and vasodilating agents. Of these, aspirin, sulfonylureas, metformin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers and hydrochlorothiazide (diuretics) were found to be significantly associated with serum uric acid. The main effects of all covariates included in the final model are given in Table 3. Individuals who were taking diabetic medications, metformin or sulfonylureas had lower serum uric acid levels as compared to those who did not. However, individuals on aspirin or other blood pressure lowering medications had higher serum uric acid levels than others (Table 4).

Univariate genetic analysis showed serum uric acid to be significantly heritable, with the heritability being 0.46 ± 0.03 ($p = 6.5 \times 10^{-63}$) in all centers and 0.39 ± 0.07 ($p = 4.6 \times 10^{-12}$), 0.51 ± 0.05 ($p = 2.2 \times 10^{-32}$), and 0.44 ± 0.06 ($p = 1.5 \times 10^{-18}$) in Arizona, Dakotas and Oklahoma, respectively. Multipoint linkage analysis for serum uric acid conducted with age, sex and their higher order terms and interactions as covariates showed evidence of linkage on chromosome 11 with LOD scores of 3.0 and 2.1 in the combined data from all centers and in the Dakota data, respectively (data not shown). Inclusion of additional, significant covariates, BMI, eGFR, type 2 diabetes, alcohol intake and medications in the final model improved the signal both in the Dakotas and in data from all centers, combined (Figure 1). Linkage signals for Dakotas (LOD score = 3.02) and all centers (LOD score = 3.56) on chromosome 11 at 71cM are shown in Figure 2. Both these QTLs had one LOD support intervals of 22cM (Table 5). An additional QTL for serum uric acid was obtained for all centers

on chromosome 1, with a significant LOD score of 3.51 (Figure 3). For Arizona, the highest LOD score of 1.5 was obtained on chromosome 6 and for Oklahoma, a QTL on chromosome 8 was identified with a LOD score of 1.7.

Discussion

This is the first genome-wide study of variation in serum uric acid performed in American Indians. We found significant genetic influence on the variation in serum uric acid levels and identified two novel QTLs on chromosomes 1 and 11. Increased serum uric acid is a risk factor for gout, renal disease and CVD and is known to aggregate in families (Stecher *et al.* 1949; Dixon 1960; Friedlander *et al.* 1988; Cameron and Simmonds 2005; Nakagawa *et al.* 2006). We found significant heritability for serum uric acid in all centers confirming a genetic influence on its variation. Furthermore, heritabilities obtained in this study are in the same range as those reported by previous family-based genetic studies of individuals of different ancestry (Rao *et al.* 1982; Tang *et al.* 2003; Yang *et al.* 2005; Nath *et al.* 2007; Voruganti *et al.* 2009).

It is likely that multiple genes, and not a single gene influence the variation in serum uric acid (Wilk *et al.* 2000). Multiple QTLs have been reported in genome-wide scans of serum uric acid with little overlap in populations. This may be due to confounding by population stratification, or possibly due to genetic heterogeneity of this common, complex trait. Yang *et al.* (2005) reported a QTL on chromosome 15q (LOD = 3.3) for serum uric acid in a Caucasian population from the Framingham Heart Study. In another study, using serum uric acid as a part of the metabolic syndrome, a QTL was localized on chromosome 2q (Tang *et al.* 2003). Among Mexican Americans, a strong QTL for serum uric acid levels was found on chromosome 6 and a suggestive linkage on chromosome 3 (Nath *et al.* 2007). In a subsequent follow up study with a larger sample of individuals, the linkage on chromosome 3 reached genome-wide significance with a LOD score of 4.7 (Voruganti *et al.* 2009). Our study identified new QTLs for serum uric acid relevant to our population of American Indians.

Genome-wide association studies (GWAS) for gene discovery have been conducted mostly in individuals of European ancestry. These studies are biased towards common variants and the gene coverage varies depending on the platform used for genotyping. However, findings from GWAS have been more consistent. They identified common variants in solute carrier family2, member 9 (*SLC2A9*) that were associated with serum uric acid (Li *et al.* 2007; Vitart *et al.* 2008; Doring *et al.* 2008; Brandstattter *et al.* 2008; Stark *et al.* 2008; Wallace *et al.* 2008; Dehghan *et al.* 2008b; Matsuo *et al.*, 2008). Interestingly, *SLC2A9* encodes a transporter for urate as well as fructose, and is known to influence serum uric acid levels (Vitart *et al.* 2008). Within the confidence interval of our QTL for serum uric acid on chromosome 11 lies the gene for URAT1, solute carrier family22, member 12 (*SLC22A12*). URAT1 is an urate-anion exchanger and the main transporter responsible for reabsorption of uric acid from the glomerular filtrate in the apical membrane of the renal tubules (Enomoto *et al.* 2002). Mutations in *SLC22A12* have been associated with hypouricemia in Japanese patients (Enomoto *et al.* 2002; Komoda *et al.* 2004; Takahashi *et al.*, 2005; Wakida *et al.*, 2005; Ichida *et al.* 2008; Lee *et al.*, 2008) and Korean men (Jang *et al.* 2008). http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=220150.

A strong linkage signal for serum uric acid was localized to chromosome 1p36. Prominent candidate genes in this region are the kidney chloride channel A and B (*CLCNKA* and *CLCNKB*) genes. The CLCNKA and CLCNKB channels are part of a family of mammalian chloride channels (Saito-Ohara *et al.* 1996). Mutations in these genes cause Bartter's syndrome type 3 which is characterized by impaired salt reabsorption, salt wasting, hypokalemic metabolic alkalosis and hypercalciuria (Simon *et al.* 1997). Metabolic alkalosis can decrease

the excretion of uric acid thus contributing to hyperuricemia in patients with this type of Bartter's syndrome (Meyer *et al.* 1975). Thus these genes are strong positional candidate genes that may influence variation in serum uric acid in American Indians.

The rate of urate excretion and its renal handling play a major part in the variation of serum uric acid levels (Sica and Schoolwerth 2002). Therefore, medications that affect renal urate excretion have a significant influence on serum uric acid levels. Drugs such as losartan, have been shown to reduce serum uric acid levels by reducing its reabsorption from kidneys (Sica and Schoolwerth 2002). In the current study, among the medications that were associated with and adjusted against serum uric acid [aspirin, sulfonylureas, metformin, ACE inhibitors, beta blockers, calcium channel blockers and diuretics], diuretics was the most significant group. Diuretics, usually prescribed as the primary treatment for hypertension, are known to increase serum uric acid by increasing its reabsorption. They had the maximum effect on serum uric acid levels in all centers, except Arizona, when compared to other medications. Similarly beta blockers and ARBs, with the exception of losartan, are believed to increase serum levels of uric acid (Reyes 2003). Earlier genetic analyses explored diuretics and aspirin for effects on variation in serum uric acid (Wilk *et al.* 2000; Yang *et al.* 2005). However, the current study is the first one to investigate not only the effects of cardiovascular drugs such as ARBs, ACE inhibitors, beta blockers, calcium channel blockers and diuretics but also diabetic drugs such as sulfonylureas, metformin and insulin on the variation in serum uric acid levels. We observed that individuals taking metformin or sulfonyureas have comparatively lower levels of serum uric acid than those who don't take these medications. Serum uric acid has been linked to insulin resistance (Clausen *et al.*, 1998; Yoo *et al.*, 2005) and has often been advocated to be a part of the metabolic syndrome (Nakagawa *et al.*, 2005; Cirillo *et al.*, 2006). It has been reported that drugs such as metformin that improve insulin sensitivity are also known to decrease serum uric acid levels (Tsouli *et al.*, 2006). On the other hand, we observed that blood pressure lowering medications have an adverse effect on serum uric acid levels. Diuretics increase serum uric acid levels by either affecting its secretion or increased distal reabsorption (Langford *et al.*, 1987). ACE inhibitors are known to have a mild reducing effect on serum uric acid levels helping blunt the effect of diuretics (Reyes, 2003) however this was not observed in individuals in our study. Even though drugs that lower serum uric acid have not shown substantial improvements in vascular mortality, increased serum uric acid values provide useful prognostic information in individuals at risk for CVD (Wannamethee 2005).

In summary, we identified two new loci on chromosomes 11q and 1q for variation in serum uric acid among American Indians, where strong positional candidate genes are located. Given the importance of serum uric acid as a likely biomarker and a potential independent risk factor for CVD, and the recent increase in CVD mortality in American Indians, these results assume considerable significance.

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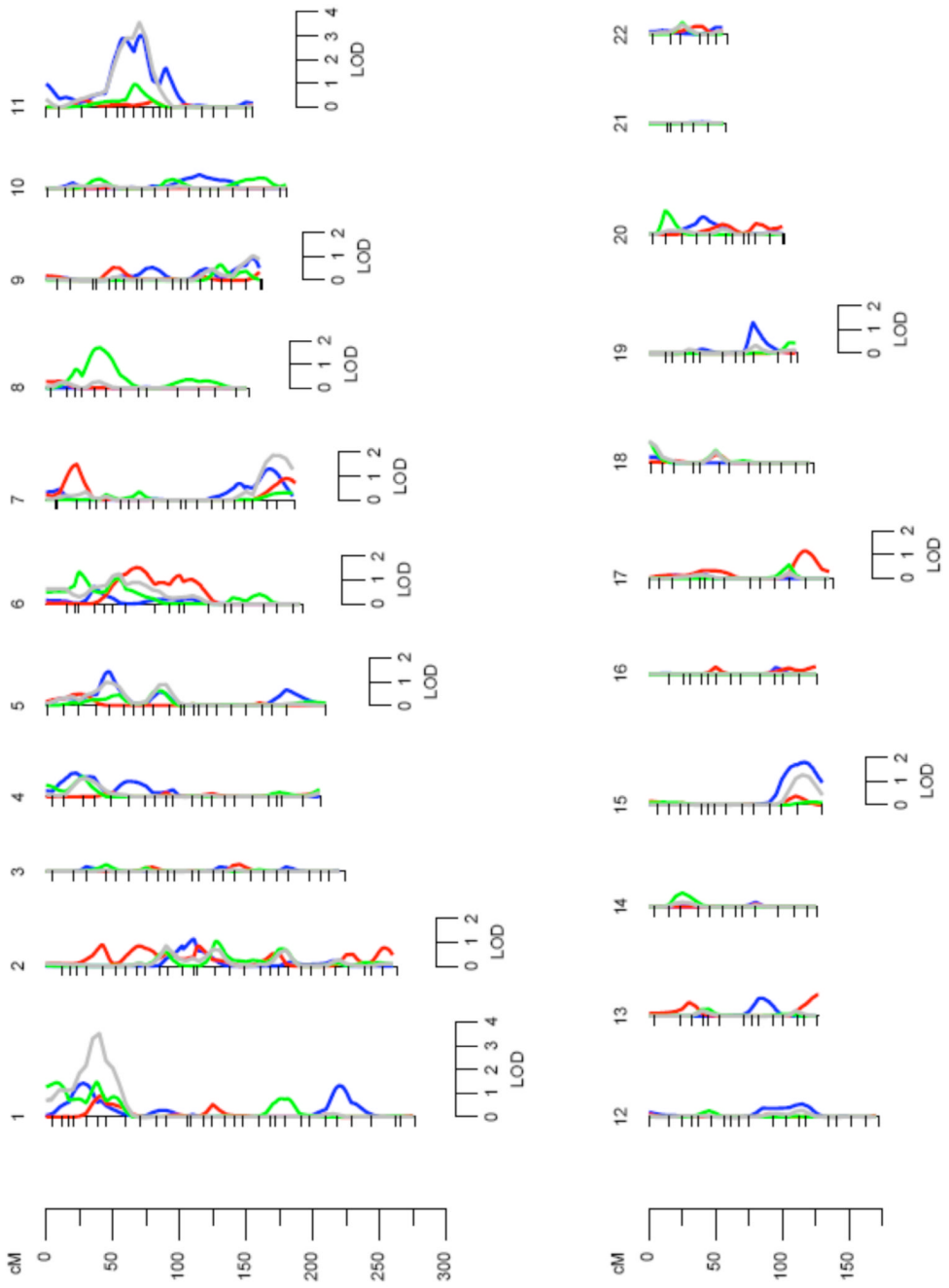

Figure 1.
Univariate linkage analysis by each chromosome (all centers and individual centers). Chromosomal location (cM) is represented on the x-axis and the LOD score shown on the y-axis. All – grey; Dakotas – blue; Oklahoma – green; Arizona - red

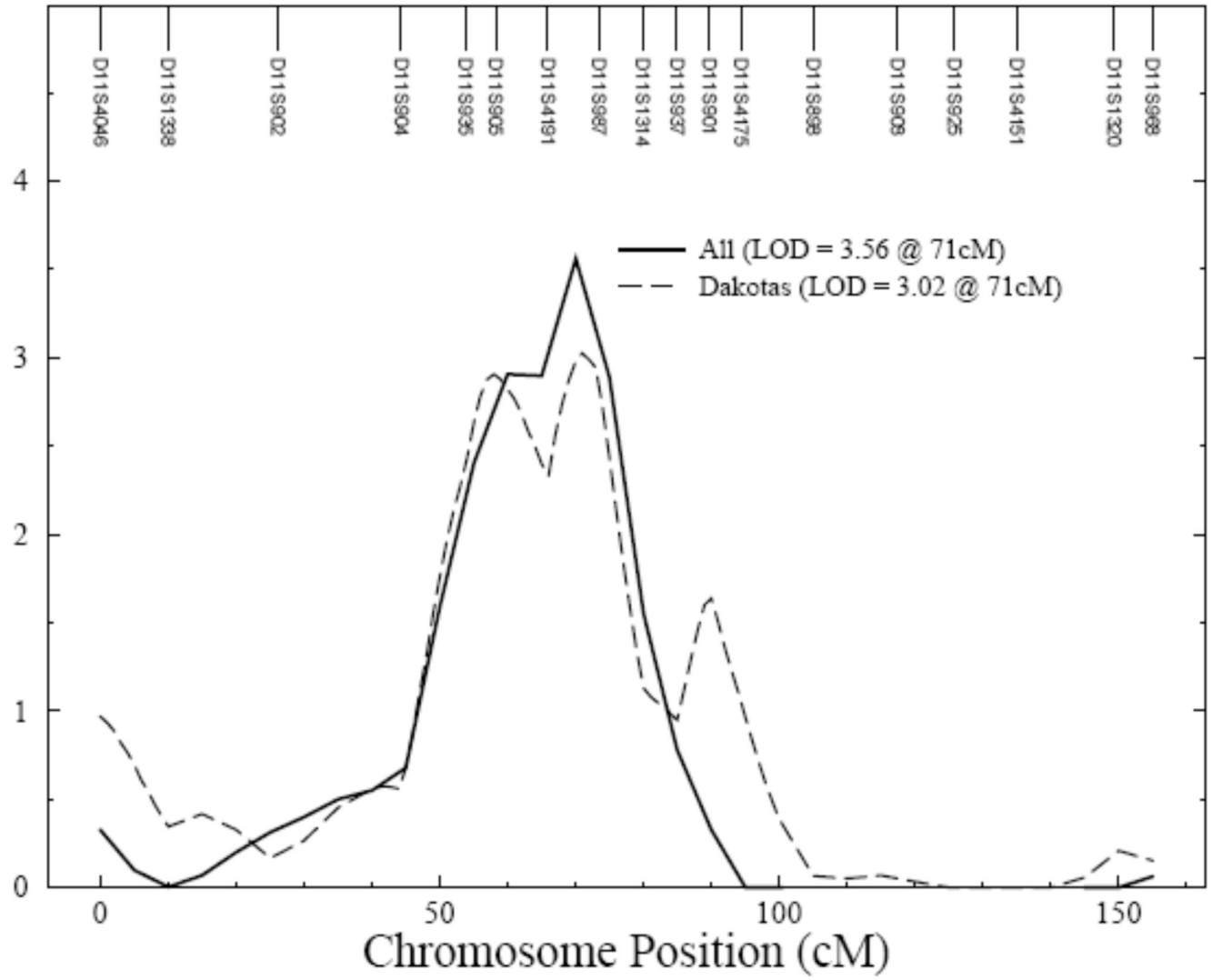

Figure 2.
Evidence of significant linkage for serum uric acid on chromosome 11 in Dakotas and all centers. Chromosomal location (cM) is represented on the x-axis and LOD score is shown on the y-axis. All – Solid line; Dakotas – dashed line

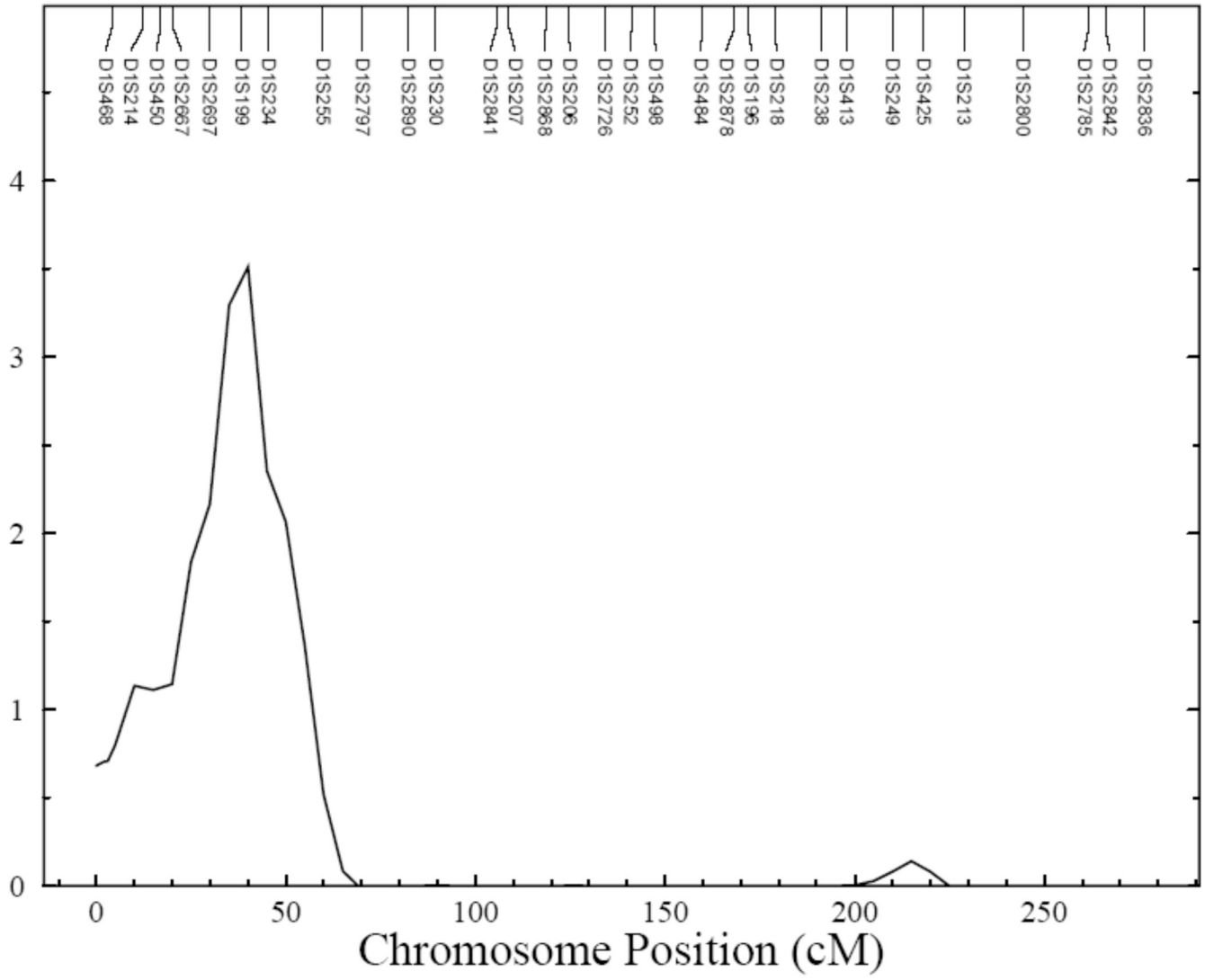

Figure 3.
Evidence of significant linkage for serum uric acid on chromosome 1 in all centers. Chromosomal location (cM) is represented on the x-axis and LOD score is shown on the y-axis

Table 1

Relative pairs utilized in this study

Relationship	ALL	AZ	DK	OK
Parent-offspring	2822	842	1026	954
Siblings	2657	846	941	870
Grandparent-grandchild	1068	361	375	332
Avuncular	6741	1961	2555	2225
Half siblings	943	304	323	316
Grand avuncular	3027	782	1236	1009
Half avuncular	1393	441	422	530
First cousins	9148	2801	3517	2830
First cousins, once removed	12562	3676	5027	3859
Half first cousins	1325	523	375	427
First cousins, twice removed	1485	354	389	742
Half first cousins, once removed	1607	799	266	542
Second cousins	7083	2184	3060	1839
Second cousins, once removed	2697	869	967	861
Half second cousins	801	421	133	247
Third cousins	915	180	562	173
Others	3075	689	1312	1074
Total	59349	18033	22486	18830

Table 2

Distribution of age, BMI and serum uric acid (mg/dl) in Strong Heart Study participants by center

	Age			BMI			Serum uric acid		
Center	**All**	**Women Mean (SD)**	**Men**	**All**	**Women Mean (SD)**	**Men**	**All**	**Women Mean (SD)**	**Men**
ALL	39.96 (17.0)	41.07 (17.2)	38.30 (16.6)	32.14 (7.6)	32.67 (7.7)	31.24 (7.5)	5.14 (1.5)	4.58 (1.9)	5.98 (1.4)
AZ	37.21 (16.0)	38.16 (16.5)	35.65 (15.0)	35.13 (8.2)	35.73 (8.2)	34.12 (8.1)	4.87 (1.5)	4.35 (1.2)	5.72 (1.4)
DK	39.04 (17.11)	40.37 (17.3)	37.12 (16.7)	30.17 (6.8)	30.83 (6.9)	29.22 (6.7)	5.34 (1.5)	4.81 (1.3)	6.12 (1.5)
OK	43.65 (17.3)	44.92 (17.2)	41.89 (17.3)	31.15 (6.9)	31.29 (6.9)	30.96 (6.8)	5.22 (1.5)	4.60 (1.3)	6.08 (1.4)

Table 3

Covariate effects on serum uric acid*

Covariate		All centers		Arizona		Dakotas		Oklahoma	
		P value	Effect	P value	Effect	P value	Effect	P value	Effect
Age		0.002	0.004	2.3×10^{-6}	−0.013	NS	-	NS	-
Sex (female)		9.2×10^{-139}	−1.028	5.4×10^{-53}	−0.102	4.2×10^{-44}	−0.949	3.7×10^{-49}	−0.973
Age × sex		2.0×10^{-6}	0.008	0.012	0.008	0.029	0.005	5.2×10^{-7}	0.014
Center		0.0003	0.107	NA	-	NA	-	NA	-
BMI		6.7×10^{-17}	0.019	0.018	0.008	4.7×10^{-17}	0.036	6.3×10^{-13}	0.030
eGFR		9.8×10^{-38}	−0.008	5.1×10^{-11}	−0.006	1.1×10^{-10}	−0.007	1.9×10^{-18}	−0.010
Diabetes status		2.0×10^{-7}	−0.202	1.7×10^{-8}	−0.341	NS	-	NS	-
Alcohol intake		NS	-	0.014	−0.250	NS	-	NS	-
Medications									
	Aspirin	0.0002	0.171	NS	-	0.0116	−0.207	0.004	0.212
	Sulfonylureas	1.5×10^{-7}	−0.278	5.9×10^{-8}	−0.430	NS	-	NS	-
	Metformin	6.6×10^{-6}	−0.265	5.4×10^{-7}	−0.430	NS	-	NS	-
	ACE inhibitors	0.0018	0.140	NS	-	0.027	0.186	0.0039	0.220
	Beta blockers	0.00002	0.344	0.0017	0.483	0.0225	0.315	0.053	0.258
	Calcium channel blockers	0.00018	0.256	NS	-	0.0008	0.438	0.023	0.253
	Hydrochlorothiazide (diuretics)	1.6×10^{-13}	0.470	0.034	0.255	7.1×10^{-10}	0.717	3.0×10^{-10}	0.465

*All covariates were tested separately without having other covariates in the model

*Covariates which were significant in at least one center were included in the final model

Table 4

Distribution of serum uric acid (mg/dl) based on the usage of medication*

Medication	All centers		Arizona		Dakotas		Oklahoma	
	No	Yes	No	Yes	No	Yes	No	Yes
Aspirin	5.10 (1.5)	5.42 (1.7)	4.85 (1.4)	5.00 (1.6)	5.29 (1.5)	5.72 (1.7)	5.17 (1.5)	5.48 (1.7)
Sulfonylureas	5.19 (1.5)	4.72 (1.5)	4.95 (1.4)	4.37 (1.4)	5.36 (1.5)	5.09 (1.6)	5.24 (1.5)	5.02 (1.4)
Metformin	5.17 (1.5)	4.77 (1.5)	4.94 (1.5)	4.34 (1.2)	5.34 (1.5)	5.44 (1.7)	5.23 (1.5)	5.02 (1.4)
ACE inhibitors	5.11 (1.5)	5.32 (1.6)	4.85 (1.5)	4.96 (1.5)	5.30 (1.5)	5.69 (1.8)	5.18 (1.5)	5.43 (1.5)
Beta blockers	5.12 (1.5)	5.71 (1.9)	4.84 (1.4)	5.57 (1.7)	5.32 (1.5)	5.82 (1.8)	5.19 (1.5)	5.72 (2.0)
Calcium channel blockers	5.12 (1.5)	5.55 (1.7)	4.85 (1.4)	5.13 (1.6)	5.30 (1.5)	6.18 (1.7)	5.20 (1.5)	5.50 (1.6)
Hydrochlorothiazide (diuretics)	5.08 (1.5)	5.88 (1.9)	4.84 (1.8)	5.32 (2.0)	5.27 (1.5)	6.49 (1.9)	5.14 (1.5)	5.85 (1.9)

*Medications with significant effects on serum uric acid are shown in the table.

Table 5

Loci affecting serum uric acid levels

Center	Highest LOD score	Chromosome (location)	Flanking markers	One LOD support interval
ALL	3.51	1 (39cM)	D1S199 and D1S234	31–43cM
	3.56	11 (71cM)	D11S4191 and D11S987	55–77cM
AZ	1.5	6 (68cM)	D6S1610 and D6S257	60–81cM
DK	3.02	11 (71cM)	D11S4191 and D11S987	55–77cM
OK	1.7	8 (40cM)	D8S258 and D8S1771	35–44cM