HHS Public Access

Author manuscript

Obesity (Silver Spring). Author manuscript; available in PMC 2014 March 01.

Published in final edited form as:

Obesity (Silver Spring). 2013 September ; 21(9): E490–E494. doi:10.1002/oby.20303.

A genome wide association study of plasma uric acid levels in obese cases and never-overweight controls

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Abstract

Objective—To identify plasma uric acid related genes in extremely obese and normal weight individuals using genome wide association studies (GWAS).

Design and Methods—Using genotypes from a GWAS focusing on obesity and thinness, we performed quantitative trait association analyses (PLINK) for plasma uric acid levels in 1,060 extremely obese individuals [body mass index (BMI) >35 kg/m^2] and normal-weight controls (BMI<25kg/m^2). In 961 samples with uric acid data, 924 were females.

Results—Significant associations were found in *SLC2A9* gene SNPs and plasma uric acid levels (rs6449213, P=3.15×10^{-12}). DIP2C gene SNP rs877282 also reached genome wide significance(P=4,56×10^{-8}). Weaker associations (P<1×10^{-5}) were found in *F5, PXDNL, FRAS1, LCORL,* and *MICAL2*genes. Besides *SLC2A9*, 3 previously identified uric acid related genes *ABCG2* (rs2622605, P=0.0026), *SLC17A1* (rs3799344, P=0.0017), and *RREB1* (rs1615495, P =0.00055) received marginal support in our study.

Conclusions—Two genes/chromosome regions reached genome wide association significance (P< 1× 10^{-7}, 550K SNPs) in our GWAS : *SLC2A9*, the chromosome 2 60.1 Mb region

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Conflicts of Interest Statement

The authors declare that there is no duality of interest associated with this manuscript.

Author contributions: Wei-Dong Li: study design, oversee and conduct experiments, analyze data, write the manuscript; Hongxiao Jiao: analyze data, comment on the manuscript; Kai Wang: analyze data, comment on the manuscript;
Clarence Zhang: analyze data; Joseph T Glessner: oversee and conduct experiments; Struan F.A. Grant: oversee and conduct experiments; Hongyu Zhao: oversee and conduct data analyses; Hakon Hakonarson: oversee and conduct experiment, study design; R. Arlen Price: study design, oversee experiments and analyze data, write and comment on the manuscript.

(rs6723995), and the *DIP2C* gene region. Five other genes (*F5*, *PXDNL*, *FRAS1*, *LCORL*, and *MICAL2*) yielded $P<1\times 10^{-5}$. Four previous reported associations were replicated in our study, including *SLC2A9*, *ABCG2*, *RREB*, and *SLC17A1*.

Keywords

uric acid; genome wide association study; obesity

Introduction

Uric acid is the end product of purine metabolism. The prevalence of hyperuricemia (uric acid ≥ 420μmol/L in males, ≥ 360μmol/L in females) has increased rapidly over the past two decades (1, 2). The connection between hyperuricemia and gout has long been known; however, hyperuricemia is much more common than gout. Increasing evidence shows that hyperuricemia is a risk factor for metabolic syndrome(3) and cardiovascular diseases(4).

Although obesity and hyperuricemia are correlated, the genetic background of this association is not well understood. Several candidate genes, including *SLC2A9* and *ABCG2* (5, 6), have been identified in genome-wide association studies (GWASs) and follow-up replications. To investigate the possible role of these genes in obese individuals, we performed a genome wide association study (GWAS) for plasma uric acid in 1,060 obesity cases/controls using our previous genotyping data for body weight traits(7).

Methods and Procedures

Subjects

All subjects gave informed consent, and the protocol was approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania. Five hundred twenty (520) European-American obesity cases (BMI>35 kg/m^2) and 540 normal-weight controls (BMI<25 kg/m^2) were selected for analysis from ongoing studies (8). Clinical characteristics have been described previously (9). In 961 samples with uric acid data, 924 were females.

Genotyping

DNA was extracted from whole blood or lymphoblastoid cell lines using a high-salt method. All samples were genotyped on Illumina HumanHap550 SNP arrays (Illumina, San Diego, CA) with ~550,000 SNP markers, at the Center for Applied Genomics, Children's Hospital of Philadelphia.

Data analyses

Uric acid outliers (> 3SD) were deleted from the data set. Quantitative association studies were performed using PLINK 1.07 that based on the Wald test(10). To investigate the plausible influence of obesity status on uric acid levels, we also performed GWAS separately in obesity cases (BMI>35kg/m^2) and normal weight controls (BMI<27kg/m^2). Female-only analyses were also carried out after quantitative associations were conducted in all samples.

Results

Of the 1,060 obese cases and normal controls, 961 had plasma uric acid data. Thirty-seven (37) of those 961 individuals were male; 924 were female. Average age of the 961 subjects was 41.9±9.1 years (range, 16–65 years). Distributions of uric acid levels in all samples, cases, and controls are shown separately in Table 1. Q-Q plots showed normal distributions of uric acid levels in those 3 groups (Figure 1).

Significant associations were found between *SLC2A9* gene SNPs and plasma uric acid. The most significant result was for the SNP rs6449213 (all samples, $P=3.15\times10^{-12}$; female-only samples, $P=2.29\times10^{-12}$)(Table 2).

DIP2C gene SNP rs877282 also reached genome wide significance ($P=4{,}56\times10^{-8}$). Many SNPs in the DIP2C gene also showed associations ($P<1\times10^{-5}$) (Table 3).

Weaker associations ($P<1\times10^{-5}$) were found in *F5, PXDNL, FRAS1, LCORL, and MICAL2*gene SNPs. All 5 genes had multiple SNPs that associated with uric acid levels ($3.05\times10^{-6}< P <1\times 10^{-4}$)(Table 3).Three coding region non-synonymous SNPs in the coagulation factor V (*F5*) gene, rs6030(Met 1764 Val), rs4525 (His 865 Arg), and rs4524 (Lys 858 Arg), were associated with plasma uric acid, P values of those 3 SNPs for BMI adjusted uric acid were 3.05×10^{-6}, 0.00018, and 0.00017, respectively.

Besides *SLC2A9*, 3 previous found uric acid related genes *ABCG2*(rs2622605, P=0.0026), *SLC17A1*(rs3799344, P=0.0017), and *RREB1* (rs1615495, P =0.00055) received marginal support in our study (Table 4).

Discussion

Hyperuricemia has been considered as an independent risk factor of cardiovascular diseases and type 2 diabetes. Single gene mutations, including deficiency of hypoxanthine guanine phosphoribosyltransferase, lead to hyperuricemia; however, the risk attributable to these genes in the general population is minor(11).

Large (>10,000 individuals) GWASs and meta-analyses have shown that many genes are associated with plasma uric acid levels, including eight genes/regions (*SLC2A9*(5, 12, 13), *ABCG2*(6), *SLC22A11*, *SLC17A1*, *GCKR*, *R3HDM2-INHBC* gene region, *RREB1*, and *PDZK1*) that exceeded the genome-wide association level ($P<10^{-7}$)(14). *SLC2A9* has the most significant association with uric acid so far, which could explain 3.5% of uric acid variation in the general population (5).

SLC2A9 (GLUT-9) is a major transporter of uric acid. It controls uric acid influx in the basolateral and apical surface of the kidney proximal convoluted tubule (PCT).*SLC2A9* is highly expressed in kidney and liver. Interestingly, *ABCG2* is an efflux uric acid transporter that is expressed in the apical surface of the PCT. The *SLC2A9* and *ABCG2* associations are among the strongest of all uric acid associations so far (14).

Uric acid and glucose transport are often coupled, but *SLC2A9* is not a major glucose/fructose transporter. In our study, uric acid levels correlated with fasting glucose. It is

possible that *SLC2A9* polymorphisms account for the uric acid–glucose connection. However, the *SLC2A9* gene alone likely does not explain the 20% rate for hyperuricemia and almost the same rate for insulin resistance in general populations. Other genes with relatively minor genetic relative risk and/or gene–gene interactions may account for the rest of the genetic background for hyperuricemia.

The strength of the associations of *SLC2A9* gene SNPs and uric acid was well beyond the threshold for genome-wide significance. This is particularly notable given the moderate sample size (961 individuals). The *SLC2A9* associations have been replicated in several GWASs and follow-up association studies (5, 6, 13, 14), including European, African-American (15), and Japanese populations. Although this is not the first study to examine a European American population, we are interested in the *SLC2A9* association in extremely obese individuals. In our study, the BMI-adjusted uric acid yielded more significant association with *SLC2A9* polymorphisms than the unadjusted plasma uric acid. It is said that *SLC2A9* is not the major glucose transporter, although it is the main uric acid transporter in proximal convoluted tubule(16). In our subjects, uric acid was correlated with almost all body weight, lipid (except LDL), and insulin resistance phenotypes ($P<0.001$, data not shown). However, no direct association was found between *SLC2A9*gene-region SNPs and these other phenotypes(7). These results suggest that the phenotypic associations between uric acid levels and metabolic syndrome phenotypes are through pathways independent of SLC2A9..

All uric acid associated genes found in our GWAS, including *SLC2A9, DIP2C* (Homo sapiens DIP2 disco-interacting protein 2 homolog C (Drosophila)), F5 (coagulation factor V), *FRAS1*(Fraser syndrome 1), *PXDNL* (Homo sapiens peroxidasin homolog (Drosophila)-like), *LCORL* (ligand dependent nuclear receptor corepressor-like), and *MICAL2* (microtubule associated monoxygenase, calponin and LIM domain containing 2), , are expressed in kidney and/or liver. It is hard to predict functional connections among those genes and plasma uric acid levels, although we have already known that some genes have functions in transcription regulations (*DIP2C*and *LCORL*) and mesenchymal/epithelial transition (*FRAS1*).

Venous thromboembolism, insulin resistance, and hyperuricemia are correlated in general populations. Many studies have shown that Factor V (*F5*) mutations are associated with factor V Leiden thrombophilia characterizedby deep vein thrombosis (17), however, no established connection between factor V and uric acid has been reported.

The SLC2A9 associations remained significant in both obese cases and controls. Several associations, including MICAL2, FRAS1, and LCORL, were more significant in obese individuals, while F5 was more significant in normal weight controls. (Table 4). Although some of these associations varied in obese cases and controls, however, none of these genes were among the top BMI associations that found in our GWAS (7).

We have failed to replicated associations on *SLC22A11, GCKR*, and *PDZK1* genes that reported by previous large sample sized GWASs(18, 19).We could not explain if those lack

of association were due to a smaller sample size, but no marginal significant association (P<0.05) was found in either original or BMI adjusted uric acid levels.

In summary, two genes/chromosome regions reached genome wide association significance (P< 1×10^{-7}, 550K SNPs) in our GWAS : *SLC2A9*, the chromosome 2 60.1 Mb region (rs6723995), and the *DIP2C* gene region. Five other genes (*F5*, *PXDNL*, *FRAS1*, *LCORL*, and *MICAL2*) yielded P<1×10^{-5}. Four previous reported associations were replicated in our study, including *SLC2A9*, *ABCG2*, *RREB*, and the *SLC17A1*.

Acknowledgments

We thank all subjects who donated blood samples for genetic research purposes. This work was supported in part by NIH grants R01DK44073, R01DK56210, and R01DK076023 to R.A.P., a Scientist Development Grant (0630188N) from the American Heart Association, a grant (81070576) from the National Natural Science Foundation of China (NSFC), and a grant (12JCZDJC24700) from Tianjin Municipal Science and Technology Commission to W.D.L. Genome-wide genotyping was funded in part by an Institutional Development Award to the Center for Applied Genomics (H.H.) from the Children's Hospital of Philadelphia.

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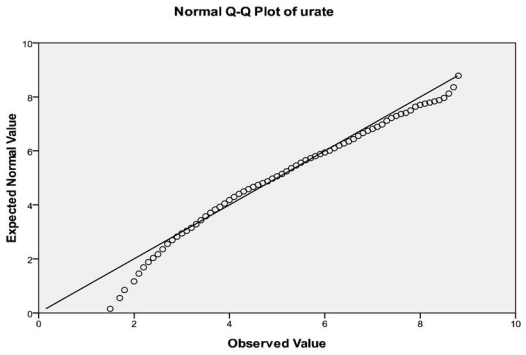
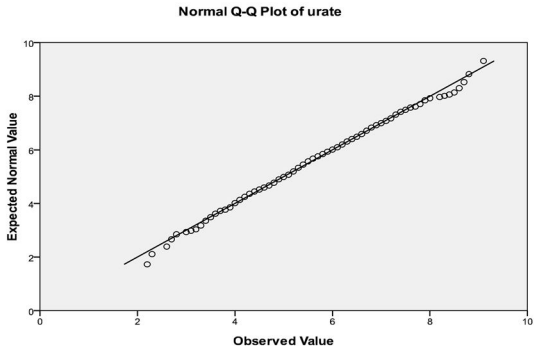
A. All samples



B. Obese cases (BMI>35kg/m^2)



C. Normal weight controls (BMI<25kg/m^2)

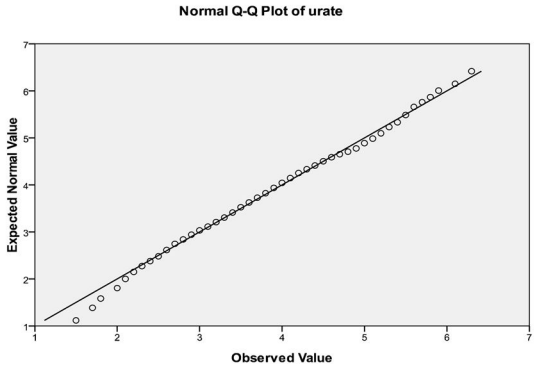


Figure 1.
Q-Q plots of plasma uric acid levels in all subjects, obesity cases, and controls

TABLE 1

Traits distributions of plasma uric acid in obese individuals (BMI>35kg/m^2), normal weight (BMI<25kg/m^2), and combined samples

	N	Minimum	Maximum	Mean	Std. Deviation	Skewness	Kurtosis
ALL							
Uric acid	962	1.500	8.800	4.667	1.4037	0.441	−0.219
FEMALE							
Uric acid	926	1.500	8.800	4.602	1.3628	0.441	−0.219
BMI>35							
Uric acid	487	2.200	9.100	5.523	1.258	0.127	−0.095
BMI<25							
Uric acid	472	1.500	6.300	3.768	0.881	0.147	−0.344

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TABLE 2

Significant associations between SLC2A9 gene SNPs and uric acid

CHR	SNP	bp	*P* all subjects	*P* cases	*P* controls	gene
4	rs6449213	9603313	3.15×10^{-12}	1.61×10^{-7}	1.01×10^{-12}	*SLC2A9*
4	rs1014290	9610959	1.13×10^{-9}	3.59×10^{-6}	4.26×10^{-12}	*SLC2A9*
4	rs7660895	9594543	1.47×10^{-9}	8.48×10^{-7}	1.91×10^{-9}	*SLC2A9*
4	rs6832439	9533417	5.64×10^{-11}	6.09×10^{-6}	3.19×10^{-12}	*SLC2A9*
4	rs13129697	9536065	1.12×10^{-10}	2.53×10^{-6}	3.48×10^{-10}	*SLC2A9*
4	rs13131257	9590987	9.17×10^{-11}	1.15×10^{-5}	1.44×10^{-11}	*SLC2A9*
4	rs737267	9543842	2.73×10^{-11}	7.34×10^{-6}	1.79×10^{-12}	*SLC2A9*
4	rs10805364	9884616	1.67×10^{-9}	0.00019	1.41×10^{-12}	*SLC2A9*
4	rs4698014	9895399	1.67×10^{-9}	0.00069	7.55×10^{-13}	*SLC2A9*
4	rs4698036	9940392	2.89×10^{-9}	0.0013	7.78×10^{-12}	*SLC2A9*
4	rs714436	9923765	2.48×10^{-8}	0.00072	6.46×10^{-11}	*SLC2A9*
4	rs10022911	9749649	3.29×10^{-6}	0.0057	5.42×10^{-13}	*SLC2A9*
4	rs17420080	9954646	3.53×10^{-8}	0.00051	1.55×10^{-10}	*SLC2A9*
4	rs4698050	10019846	2.05×10^{-8}	0.0022	1.22×10^{-10}	*SLC2A9*
4	rs4643800	10016670	1.08×10^{-7}	0.0030	8.53×10^{-11}	*SLC2A9*
4	rs12498956	9559803	3.14×10^{-7}	0.00026	8.71×10^{-7}	*SLC2A9*
4	rs4447863	9548067	5.06×10^{-6}	0.00074	2.26×10^{-6}	*SLC2A9*
4	rs3733585	9645437	2.36×10^{-5}	0.0015	7.19×10^{-7}	*SLC2A9*
4	rs6845554	9622271	1.30×10^{-5}	0.0019	3.18×10^{-7}	*SLC2A9*
4	rs6827754	9627251	1.22×10^{-5}	0.0020	3.05×10^{-7}	*SLC2A9*
4	rs1860910	9884568	1.35×10^{-7}	5.25×10^{-5}	3.28×10^{-5}	*SLC2A9*

TABLE 3

Quantitative association studies (PLINK) for uric acid levels in obese cases and controls ($P<1\times10^{-4}$)

CHR	SNP	Position(bp)	*P* (all subjects)	*P* (cases)	*P* (controls)	gene
1	rs6030	167765599	3.05×10^{-6}	0.0013	7×10^{-5}	*F5*
1	rs4656687	167771782	3.76×10^{-5}	0.0020	0.00040	*F5*
4	rs1506613	17558037	5.81×10^{-5}	0.0028	0.041	*LCORL*
4	rs2251890	17575646	3.38×10^{-5}	0.00096	0.044	*LCORL*
4	rs4423900	79240461	1.69×10^{-5}	0.0012	0.183	*FRAS1*
4	rs4583783	79243548	1.21×10^{-5}	0.00095	0.21	*FRAS1*
4	rs10033428	79259915	2.28×10^{-5}	0.0012	0.20	*FRAS1*
4	rs9995229	79261976	2.02×10^{-5}	0.0011	0.26	*FRAS1*
4	rs6845871	79267514	3.88×10^{-5}	0.00024	0.45	*FRAS1*
4	rs17002988	79298781	6.45×10^{-6}	0.00079	0.098	*FRAS1*
8	rs2979126	52590614	1.42×10^{-5}	0.0050	0.063	*PXDNL*
10	rs7092652	746109	8.72×10^{-7}	0.069	0.0075	*DIP2C*
10	rs11599917	752288	1.08×10^{-6}	0.028	0.011	*DIP2C*
10	rs877282	761532	**$4.56X10^{-8}$**	0.0073	0.011	*DIP2C*
10	rs1769242	777896	2.73×10^{-6}	0.019	0.018	*DIP2C*
10	rs2256711	792272	3.91×10^{-6}	0.019	0.0085	*DIP2C*
11	rs1385850	12191171	2.74×10^{-5}	3.22×10^{-5}	0.7647	*MICAL2*

TABLE 4

Previous uric acid associated genes were replicated in our GWAS

CHR	SNP	BP	All	cases	controls	gene
4	rs2622605	89298410	0.0026	0.037	0.00017	*ABCG2*
4	rs1481017	89316501	0.0044	0.11	0.0011	*ABCG2*
6	rs1615495	6979458	0.00055	0.011	0.011	*RREB*
6	rs473437	6982476	0.00052	0.0068	0.068	*RREB*
6	rs3799344	25894972	0.0017	0.37	0.011	*SLC17A1*
6	rs2070642	25939191	0.0084	0.35	0.10	*SLC17A1*