The rs13129697 polymorphism of the SLC2A9 gene, but not rs7442295 is associated with impaired glucose tolerance/impaired fasting glucose complicated with hyperuricaemia in Han Chinese males

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Research article

Keywords: SLC2A9, SNPs, type 2 diabetes mellitus, Hyperuricemia

Posted Date: September 12th, 2019

DOI: <https://doi.org/10.21203/rs.2.14331/v1>

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Abstract

Aims SLC2A9 is also known as glucose transporter9 (GLUT9) or urate efflux transporter (URAT)v1, which should be involved in the transport of glucose and uric acid. To further verify it, the correlation of the SLC2A9 polymorphisms(rs13129697,rs7442295) with T2DM, Hyperuricemia (HUA) and T2DM compared with HUA will be investigated in male Han Chinese.

Methods Two SNPs of the SLC2A9, rs13129697, rs7442295, were genotyped in 285 T2DM patients, 300 HUA patients and 198 T2DM compared with HUA patients respectively through TaqMan-MGB Duplex real-time PCR, and 550 healthy subjects were selected as control group. The total 1333 subjects were all recruited from the Affiliated Hospital of Qingdao University Medical School.

Results Compared with control group, the variant SNP of rs13129697 was both significantly associated with HUA group($P<0.001$) and T2DM complicated HUA group($P<0.05$), but not with pure T2DM group. After adjustment for age, triglyceride and cholesterol, logistic regression analysis showed that people with GT/GG genotype had lower risks of HUA($OR=0.615$, 95%CI: 0.432-0.877, $P=0.007$; $OR=0.447$, 95%CI: 0.271-0.736, $P=0.002$) and T2DM complicated HUA($OR=0.578$, 95%CI: 0.360-0.923, $P=0.022$; $OR=0.393$, 95%CI: 0.208-0.740, $P=0.004$) than people with TT genotype. However, there were no statistical significance between control group and T2DM group, HUA group, or T2DM complicated with HUA group in rs7442295 genotypes($P>0.05$).

Conclusion The rs13129697 polymorphism of the SLC2A9 gene, but not rs7442295 is associated with impaired glucose tolerance/impaired fasting glucose complicated with hyperuricaemia. And G allele may protect against the risk to develop HUA.

Introduction

Hyperuricemia(HUA) as a result of the deposition of monosodium urate monohydrate crystals at the joints and adjacent tissues, caused by an overproduction of or by disturbances in the elimination of uric acid, is a metabolic disorder [1]. A causal association of elevated SUA levels with HUA has been considered not only the risk factor for cardiovascular diseases (CVDs) but also the cause of development of metabolic diseases, which has attracted increasing attention[2]. Hypertension, chronic kidney disease, and type 2 diabetes mellitus (T2DM) have been linked with high uric acid levels despite uric acid possessing strong antioxidative properties[3]. Furthermore, serum uric acid (SUA) levels was usually associated with serum glucose. People with higher uric acid levels have a higher risk of developing type 2 diabetes. Meta-analysis showed that an SUA increase of 1 mg/dl may result in 6% increase for incident type 2 diabetes[4]. More importantly, numerous studies have demonstrated that SUA was an independent risk factor for the development of T2DM[5–7]. The mechanisms underlying the association of SUA with T2DM are still unclear, but several studies have been explained[8, 9]. T2DM was characterized by insulinresistance and relative insulin deficiency and SUA was also found associated with insulin resistance. Animals and cell experiments revealed that elevated SUA could induce endothelial

dysfunction and inhibited glucose uptake through reducing bioavailability of nitric oxide, which may worsen insulin resistance and induce the development of T2DM[10, 11].

Although SUA was thought to be the result of a combination of genetic and environmental factors, but heritability influences estimates ranging from 25 to 70%[12]. Recently, genome-wide association studies (GWAS) showed that SUA levels was strong association with genetic variants within SLC2A9. Meanwhile, the influence of SLC2A9 SNP on SUA levels are different in gender, which accounted for 5–6% variables in the female and 1–2% in the male[13–15]. SLC2A9 gen, located in the chromosomal region 4p16.1, codes glucose transporter 9 (GLUT9) that is a protein of the GLUT9 facilitative glucose transporter family. In addition to be a glucose transporter, GLUT9 was also considered as a uric acid transporter as well as involving in the glucose-stimulated insulin secretion. Its SNPs have been identified as susceptibility factors and play critical roles in maintaining glucose and uric acid homeostasis[16]. Recently, several researches had demonstrated evidence that SLC2A9 polymorphisms (rs16890979, rs11942223, rs11942223, rs5028843 and so on) play a significant role in modulating the risk of gout and was strongly associated with SUA levels[17–20]. Some researches have also found common genetic variants of SLC2A9 that is strongly associated with serum urate level and gout in Caucasian cohorts from Italy, UK, Croatia, the United States, Germany, and Austria. But the results of these studies are inconsistent, which is likely due to relatively small sample sizes, ethnic variations, or epigenetic changes. The mechanism of uric acid excretion regulated by SLC2A9 is through the two variants, SLC2A9v1 and SLC2A9v2. In tandem with URAT1, the two variants are responsible for renal reabsorption of UA. Therefore, additional studies of SLC2A9 SNPs in different populations are imperative to explain the mechanism of SLC2A9.

Since GLUT9 was a dual transporter for fructose and uric acid, there may be a same transcription protein coded by SLC2A9 SNPs that is responsible for the development of HUA and T2DM. Although Many studies have enriched the assemblages of evidence for SUA level and T2DM interrelationship. SLC2A9 was found to be upregulated in T2DM animals and influenced insulin secretion in pancreatic β cells[21]. However, there has been few study involving the association between SLC2A9 SNPs and T2DM compared with HUA. Studying the association between SLC2A9 variations and T2DM or T2DM compared with HUA may offer more clues on the molecular mechanisms underlying the prevalent T2DM and HUA.

In our study, we examined the genotype and allele frequencies of SLC2A9 SNPs (rs13129697 and rs7442295) in the male Han Chinese and their association with T2DM, HUA and T2DM compared with HUA. Our results showed that SLC2A9 polymorphisms rs13129697 but not rs7442295 was susceptibility association with HUA and T2DM complicated HUA. More interestingly, we found **G allele** may protect against the risk to develop HUA, which suggested a plausible targeted therapies for HUA.

Subjects And Methods

2.1 Experimental subjects

A total of 1333 participants were recruited from Affiliated Hospital of Qingdao University Medical School between December 2011 and February 2014, including 550 a general population sample (control group), 285 subjects diagnosed with T2DM (T2DM group) 300 subjects diagnosed with HUA (HUA group) and 198 subjects diagnosed with T2DM complicated with HUA (T2DM complicated with HUA group). All the subjects were male with age between 28 –69 years old. Our study was approved by the the Ethics Committee of Medical School Hospital of Qingdao University in accordance with the second revision of the Declaration of Helsinki. All participants signed informed consent.

Subjects with T2DM were diagnosed based on the 1999 criteria of the World Health Organization (fasting plasma glucose ≥ 7.0 mmol/L, and/or 2-h oral glucose tolerance tests(OGTT) ≥ 11.1 mmol/L). Type1 diabetes and mitochondrial diabetes were excluded using clinical, immunological and genetic criteria. HUA Subjects were diagnosed by serum uric acid levels above 420 μ mol/L in men according to the American College of Rheumatology. The subjects that met both T2DM and HUA criteria were diagnosed by T2DM complicated with HUA. Subjects with malignant tumor, severe liver and kidney diseases, thyroid diseases, gastrointestinal diseases, blood systemic diseases, autoimmune diseases and drug history that affect the blood uric acid or blood sugar levels were excluded from this survey.

2.2 Clinical measurements and Genotyping

Genomic DNA samples were extracted from the peripheral venous blood using QIAamp DNA blood mini kit (QIAGEN) according to the manufacturer's instructions. Two SNPs of SLC2A9(rs13129697 and rs7442295) were selected, and genotyping was performed by the TaqMan SNP allelic discrimination assay with an ABI 7500 Sequence Detection System(Applied Biosystems Co. Ltd., Foster City, CA, USA). Serum triglyceride (TG), total cholesterol(TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), Serum uric acid(SUA) and creatinine (CR) levels were measured using a type 7600–020 Automated Analyser (Hitachi, Tokyo, Japan).

2.3 Statistical Analysis

All statistical analyses were carried out using SPSS 17.0. The count data were expressed as mean $\pm$ standard deviation and analyzed by multivariate analysis of variance. Student's t-test (LSD-t) and F variance test were used to compare the differences between each groups. Hardy–Weinberg equilibrium of the genotype distribution was tested using the homogeneity chi-square test(χ^2) to insure the reliability of their application to evaluate larger groups. χ^2 test was used to compare the differences of allele and genotype distributions between the case groups and the control group. After adjusted for ages, serum lipid, TG and other confounding factors, multivariate logistic regression analysis and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to examine the association of allele and genotype with T2DM, HUA and T2DM complicated with HUA. For statistical inference, two-tailed $p < 0.05$ were considered to be statistically significant.

Results

3.1 The clinical characteristics of the subjects analysis

The clinical characteristics of the subjects are shown in [Table 1](#). Compared with control group, T2DM, HUA and T2DM complicated with HUA group showed significantly difference in age, plasma glucose, TC, SUA and SCR ($P \leq 0.05$). Furthermore, between the T2DM and HUA group, a gradual and significant decreasing trend was observed in age, TC and plasma glucose ($P \leq 0.05$) but a increasing trend in TG, SUA and SCR. There was no significant difference between control group, T2DM, HUA and T2DM complicated with HUA group in LDL-c and HDL-c,

3.2 Genotyping analysis

All of the SNPs satisfied Hardy-Weinberg equilibrium (table 2). The genotype frequencies of the investigated SNPs rs13129697 (GG/GT/TT) were 21.6% 56.4% 22.0% in control group, 22.4% 51.6% 26.0% in T2DM group, 14.3% 54.0% 31.7% in HUA group and 15.7% 54.5% 29.8% in T2DM complicated with HUA group. There was statistical significance in the genotype frequency between control group and HUA ($P < 0.01$) or T2DM ($P < 0.05$) complicated with HUA group, but no difference with T2DM group ($P > 0.05$). The frequencies of the G allele were 49.8%, 48.0%, 41.3%, 42.9% in the control, T2DM, HUA and T2DM complicated with HUA group [respectively](#) and the T allele were 50.2%, 52.0%, 58.7% and 57.1%. There was significant difference between control group and HUA ($P < 0.01$) or T2DM complicated with HUA group ($P < 0.01$), as shown in table 2. No significant differences of the variants of rs7442295 were found among the groups (table 3).

After adjusted for ages, serum lipid, TG and other confounding factors, multivariate logistic regression analysis demonstrate the association of SNPs rs13129697 with the risk of T2DM, HUA and T2DM complicated with HUA. Our result showed that GT/TT were associated with lower risk of HUA (OR = 0.615, 95%CI: 0.432–0.877, $P = 0.007$; OR = 0.447, 95%CI: 0.271–0.736, $P = 0.002$) and T2DM complicated with HUA group (OR = 0.578, 95%CI: 0.360–0.923, $P = 0.022$; OR = 0.393, 95%CI: 0.208–0.740, $P = 0.004$) than TT genotype (table 4). The result that each copy of SNP 13129697 minor C allele was contributed to the low risk of HUA suggested a potential [therapy](#) target.

Discussion

[Hyperuricemia](#) is the consequence of aberrant expression of uric acid, which has been associated with metabolic syndrome, HUA, cardiovascular disease and hypertension. With the increasing prevalence of T2DM and HUA, the [mechanism](#) of the diseases have attracted much attention. Since the increase of SUA concentration resulted in risk for developing T2DM, large numbers of studies have linked HUA with T2DM [7, 22]. Many researches had demonstrate that approximately 8.7% of all new cases of T2DM were statistically [ascribed](#) to HUA [23, 24]. Ogbera et al. reported a 25% prevalence of HUA in Nigerian patients with T2DM, while in Chinese T2DM patients, HUA prevalence was 36.1% in women and 28.4% in men [25,

26]. However, the underlying molecular mechanism remained obscure until SLC2A9 gene was identified in 2007[13]. Four independent genome-wide association studies proved that SLC2A9 SNPs were strongly associated with uric acid levels[13–15, 27]. Several researches have also found common genetic variants of SLC2A9 be strongly associated with serum urate level and gout in Caucasian cohorts from Italy, UK, Croatia, the United States, Germany, and Austria[28, 29]. Studying the sequence variations in SLC2A9 gene may [avail](#) to clarify the molecular mechanisms underlying the prevalent disease.

Our previous studies have evidenced that SLC2A9 SNP rs4529048/rs734553 and 137A/G were correlated with HUA complicated with T2DM[30]. The SNP rs13129697 variation is a nucleotide transversion from G to T, which is located in the intron 7 of SLC2A9 gene. In this studies, we showed that in male Han Chinese, the SLC2A9 SNP rs13129697 was associated with HUA and HUA complicated with T2DM. Meanwhile, the minor G-allele of SNP rs13129697 was found to associate with lower risk of HUA. Similar result was also found in recent study[31]. Karns R[14] found strongest association of SUA with SLC2A9 rs13129697 ($P < 0.001$) with significant gender-specific effects. However, we didn't examine the effect on female. People with GT/TT genotype have lower risk of HUA (OR = 0.615/OR = 0.447) than those with TT genotype (table 4), which suggested a potential loci for the therapy of HUA.

GLUT9 encoded by SLC2A9 is a dual transporter with the ability of fructose and uric acid transport. More and more studies have identified GLUT9 as high capacity urate transporter rather than glucose and/or fructose transporter[15]. In our study, we didn't show SNP rs13129697 variation is associated with T2DM. ANITA et al also did not find an association between the genetic variants within the SLC2A9 gene and type 2 diabetes[32]. The association of SLC2A9 SNPs with glucose, insulin, triglycerides, high density lipoprotein, systolic blood pressure were not found in Scottish in Vitart V study[27]. However, some studies also found GLUT9 was upregulated in liver and kidney tissue in diabetic mouse and affected the glucose-sensing insulin secretion in pancreatic β cell[16]. This can explain that the effects of SLC2A9 SNPs are different in ethnicity and [mutation site](#). Since the SLC2A9 was associated with SUA levels, we supposed that insulin resistance was the consequence of SUA. Some animal and cell experiments have evidenced that SUA could inhibit nitric oxide (NO) bioavailability, which may result in inhibited glucose uptake and then worsen insulin resistance[21, 33]. All these can contribute to the development of T2DM. However, this proof requires examination of several thousand individuals. Liu WC showed that SLC2A9 rs1014290 was associated with T2DM, but the DM subgroup has higher uric acid. They didn't show rs1014290 was associated with T2DM with normal uric acid level. Wei and Giri et al. also found that SLC2A9 gene variants were associated with SUA level in Chinese Han and Indians type 2 diabetes patients[14, 21]. No studies have found that the variants of SLC2A9 SNP were associated with pure T2DM. Although genetic is an important factor for the development of T2DM, but the direct association of SLC2A9 with serum glucose may be not so important as we thought. SLC2A9 SNPs may regulate serum glucose levels through uric acid concentration. Whether there was a common transcript protein encoded by SLC2A9 that was responsible for both T2DM and SUA still need further study.

Enomoto et al. identified the first kidney specific urate transporter URAT1 (SLC22A12) in 2002, and inactivating mutations in this gene have been subsequently found in individuals with idiopathic RHUC,

which [deciphered](#) the molecular defect for Hereditary renal hypouricemia (RHUC)[34]. However, some research found patients without URAT1 mutations also present RHUC, which suggested the presence of additional major urate regulators[35]. As the only member of GLUT proteins family whose substrate is urate, GLUT9 act in tandem with URAT1 in renal reabsorption of UA. According to the different amino in their N terminus, GLUT has two variants—long (GLUT9L) and short (GLUT9S), which are located in different subcellular. GLUT9L is expressed mainly in kidney, liver, placenta, and leukocytes, while GLUT9S was detected only in kidney and placenta. GLUT9L is the only major urate efflux transporter at the basolateral membrane, but the function is still unknown. GLUT9S, localized on the apical membrane, act with URAT1, which mediate urate uptake from the tubular lumen into the cell. Hence, the loss of GLUT9 function can almost inhibit the efflux of UA from the cell[28, 36]. Although the function of SLC2A9 have almost been identified, but the precise mechanism of SLC2A9 SNPs on SUA levels is still further examination.

The SNP rs7442295 variation is a nucleotide transversion from A to G located in the intron 6 of SLC2A9 gene. Its minor allele frequency in Asian is about 1%, which is lower than the 21% in [European](#) according to International HapMap Project. Brandstätter A showed highly significant associations of rs7442295 with uric acid levels in America. Besides, increasing age strengthened the association of SNPs in women and decreased the association in men[37]. [Tom M](#) demonstrate that the Variation at SLC2A9 (rs7442295) was associated with an increase of about 5% in the risk of hyperuricemia in Copenhagen General Population[31]. Other studies also found the correlation of rs7442295 with the risk for gout in German and Denmark[38]. [However](#), we didn't find the association of rs7442295 with SUA or T2DM in male Han Chinese, which appears plausible with the other studies. On one hand, the limited sample size or the significant heterogeneity across the studies maybe one factor. SLC2A9 polymorphisms predispose to SUA levels in both genders: lower in men and higher in women[15]. We only investigated the effect of rs7442295 in male, so, the small subjects may hide the [real](#) effects. Secondly, ethnicity should also be taken into consideration. Since, the environment, life style and [genotype frequency](#) are different in different areas, which may affect the function of SLC2A9 SNPs. Interestingly, the similar [phenomenon](#) was also found in SLC2A9 c.844G>A and c.881G>A variants. Some studies found that the c.844G>A variant was associated with elevated serum uric acid concentration (especially in women) in the Framingham and Rotterdam cohorts, and in the island population of the Adriatic coast of Croatia but not in African-Americans[14, 39]. Variant c.881G>A was significantly associated with elevated serum uric acid concentrations and gout in the Han Chinese, Solomon Island and Japanese cohorts, but not in the Eastern Polynesians, Western Polynesians and Europeans[40]. The accurate mechanism of SLC2A9 SNPs remains to be further study.

Conclusion

[In summary](#), We have demonstrated that rs13129697 was susceptibility association with HUA and T2DM complicated HUA, but not with the pure T2DM in male Han Chinese. And [G allele](#) may protect against the risk for the development of HUA. However, we didn't find the correlation between rs7442295 and HUA. To

be clearly understand the mechanism of SLC2A9 gene SNPs, larger number of participants and ethnically diverse populations are recommended to study.

Declarations

Funding

This study was funded by the National Natural Science Foundation of China (8167061120. 81100554), Young and Middle-Aged Scientists Research Awards Fund of Shandong Province (BS2012YY003), the Scientific and Technical Development Project of Department of health of Shandong Province(2011QZ007 and 2016WS0259), Shandong Province Natural Science Fund Project(ZR2014HM015), a Project of Shandong Province Higher Educational Science and Technology Program (J14LK11) and the Scientific and Technical Development Project of Qingdao (12-1-4-20-jc, 2012-1-3-2-(1)-nsh, 2013-13-008-YY, 2014-1-72 and 17-3-3-15-nsh).

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval

The study has been approved by the ethical committee of the Affiliated Hospital of Qingdao University and has been performed in accordance with the ethical standards of the National Research Centre committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1 The clinical characteristics of the subjects

Group	Control group	T2DM group	HUA group	T2DM complicated HUA with group
Characteristics				
n	550	285	300	198
Ages(years)	45.07±9.67	53.08±9.24 ^a	43.03±9.06 ^{ab}	52.26±11.33 ^{abc}
Glucose(mmol/L)	4.99±0.44	8.48±2.65 ^a	5.17±0.46 ^{ab}	7.97±1.92 ^{abc}
Triglyceride(mmol/L)	1.44±0.97	1.82±1.42	2.41±1.87 ^{ab}	3.32±3.23 ^{abc}
Cholesterol(mmol/L)	4.98±0.75	5.48±0.96 ^a	5.22±1.06 ^{ab}	5.21±1.19 ^{ab}
Serum Uric Acid (μmol/L)	330.54±54.68	313.17±57.38 ^a	480.0±51.55 ^{ab}	479.32±56.31 ^{ab}
Creatinine(mmol/L)	92.97±8.76	96.74±19.34 ^a	101.0±12.17 ^{ab}	105.14±41.134 ^{abc}
HDL-c	1.27±0.41	1.26±0.53	1.25±0.43	1.31±0.29
LDL-c	2.89±0.58	3.06±0.77	3.00±0.82	3.05±0.79

compared with ctontrol group□P□0.05□b compared with T2DM group□P□0.05□c: T2DM compared with HUA group□P□0.05

Table 2 Table 2 Genotype and allele frequency of **rs13129697**in all groups. n(□)

Group	genotype and frequency(%)			allele and frequency(%)		OR(95%CI)	P
	GG	GT	TT	G	T		
Control group	119(21.6)	310(56.4)	121(22.0)	548 (49.8)	552 (50.2)		
T2DM group	64 (22.4)	147 (51.6)	74 (26.0)	275 (8.0)	295 (52.0)	0.929□0.742- 1.163□	0.520
HUA group	43 (14.3)	162 (54.0)	95 (31.7)	248 (41.3)	352 (58.7)	0.686□0.552- 0.852□	0.001
T2DM complicated with HUA group	31 (15.7)	108 (54.5)	59 (29.8)	170(42.9)	226 (57.1)	0.681□0.516- 0.900□	0.007

Table 3 Genotype and allele frequency in all groups of **rs7442295**. n(□)

Group	genotype and frequency(%)		allele and frequency(%)		OR(95%CI)	P
	AA	AG	A	G		
Control group	529(96.2)	21(3.8)	1079(98.1)	21(1.9)		
T2DM group	275(96.5)	10(3.5)	560(98.2)	10(1.8)	1.326(0.578-3.040)	0.509
HUA group	288(96.0)	12(4.0)	588(98.0)	12(2.0)	1.231(0.568-2.668)	0.599
HUA complicated with T2DM group	190(96.0)	8(4.0)	388(98.0)	8(2.0)	1.575(0.580-4.279)	0.373

Table 4 Binary logistic regression analysis for T2DM, HUA and HUA complicated with T2DM

	T2DM			HUA			T2DM complicated with HUA	
	OR(95%CI)	P		OR(95%CI)	P		OR(95%CI)	P
rs13129697								
TT	1			1			1	
GT	0.691(0.469-1.020)	0.063		0.615(0.432-0.877)	0.007		0.578(0.360-0.923)	0.022
GG	0.901(0.547-1.484)	0.680		0.447(0.271-0.736)	0.002		0.393(0.208-0.740)	0.004
RS7442295								
AA	1			1			1	
AG	1.326(0.578-3.040)	0.509		1.231(0.568-2.668)	0.599		1.575(0.580-4.279)	0.373