Associations of a *SHROOM3* variant with mild renal impairment and depressive symptoms in a Chinese Han population

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Research article

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Abstract

Background: To explore the associations of several genetic variants identified in the genome-wide association studies (GWAS) of European ancestry with mild renal impairment glomerular filtration rate (GFR) in Chinese Han population.

Methods: Data of 1788 community-dwelling elders from the baseline survey of the ageing arm of the Rugao Longevity and Ageing Study was used. Plasma creatinine based GFR was estimated using the eGFR-EPI equations.

Results: Of the 10 common polymorphisms identified in GWAS of the European ancestry, rs17319721 located in the first intron of the *SHROOM3*, was associated with GFR. A allele was associated with both decreased GFR level and greater odds of mild renal impairment (OR 1.12, 95% CI 1.01-1.23, p=0.029) defined by GFR<90 mL/min/1.73 m^2 after adjusting for multiple confounds of chronic kidney disease. In addition, compared with rs17319721-GG genotype, AA was associated with both higher depressive score and greater risk of depression prevalence, showing a pleiotropic effects of rs17319721. However, we did not found significant association of GFR levels with another 42 common polymorphisms that was previously reported to be associated with the traditional risk factors of kidney diseases.

Conclusions: *SHROOM3*-rs17319721 is associated with GFR levels, kidney impairment, and depressive symptoms in a Chinese population.

Background

Glomerular filtration rate (GFR)-defined chronic kidney disease (CKD) is a complex disease with a heritability of 30-70% [1, 2]. Understanding genetic predisposition to CKD is one approach to uncover underlying pathophysiological mechanisms for improved classification and targeted therapies. Over the past decade, genome-wide association studies (GWAS), a main population-based strategy to screen genetic risk factors, have identified a batch of CKD loci mainly in individuals of European ancestry [3, 4].

Recently, in GWAS conducted in the European populations, Köttgen et al [5, 6] and Chambers et al [5, 6, 7] identified 15 new loci affecting GFR and/ or CKD (Supplement Table1). According to the 1000genomes database [8], 10 of these single nucleotide polymorphisms (SNPs) had a minor allele frequency (MAF) greater than 5% in Chinese Han population. They are *GCKR*-rs1260326, *TFDP2*- rs347685, *SHROOM3*-rs17319721, DAB2-rs11959928, SLC34A1-rs6420094, VEGFA-rs881858, PIP5K1B-rs4744712, DACH1-rs626277, UBE2Q2-rs1394125, and SLC7A9-rs12460876. Some of these SNP-GFR associations were replicated in African Americans, highlighting similarity of the genetic variants across ethnicities [9]. Therefore, here we aimed to test whether these CKD associated variants observed in Europeans are still associated with CKD in Chinese Han population. In addition, hypertension, diabetes, dyslipidemia, and obesity are traditional environmental risk factors of CKD [10, 11]. In this study, we also observed the effects of some polymorphisms (some is which are functional variants) which was related to hypertension, diabetes, dyslipidemia, or obesity in previous studies [12, 13, 14, 15, 16] on renal impairment in Chinese population.

Methods

Study population

Baseline survey data of the ageing arm of Rugao longevity Ageing Study (RuLAS) was used in this study. As described elsewhere [17,18], 1,788 older adults aged 70-84 were recruited at baseline in Nov.-Dec. of 2014 from 31 communities of Jiang'an Township, Rugao city, according to 5-year age and gender strata. Follow-up survey was conducted 1.5 year later (Apri.-Jun. 2016, wave2) and 3 year later (Nov.–Dec. 2017, wave3) for repeated measurements of baseline variables and for morbidity and mortality data collections. The Human Ethics Committee of Fudan University School of Life Sciences approved the research. Written consent was obtained from all participants prior to participation.

Genotyping

Genomic DNA was extracted from EDTA anticogulated peripheral blood using a standard method. The aforementioned polymorphisms were genotyped. Primei online 3 (Version 0.040) and Oligo (Version 6.31) software were used to design specific primers. For each sample, genomic DNA (10 ng) was amplified and purified by three-round multiplex PCR following the recommendations of the manufacturer [19] and then purified PCR products mix was processed on a OneTouch 2 instrument and enriched on a OneTouch 2 ES station. Then the oligonucleotide mix was sequenced on a 318 chip using the Ion Torrent PGM and the Ion PGMTM Sequencing 200 Kit v2 according to the manufacturer's instructions. Original sequencing reads were exported to FASTQ files, the index and adapter sequence were trimed out by using cutadapt software, and BWA v0.7.12 was then used to align the targeted sequence to the SNP reference sequences (NCBI, dbSNP build 142) to generate SAM file. By using samtools, the sam file was transferred to mpileup file, and SNP locus were identified according to ligase detection reaction (LDR). All the genotyping success rates of these loci were >95%. To assess reproducibility, 5% of samples were analyzed in duplicate and the genotypes were 100% concordant for these samples.

Outcome measurements

Plasma creatinine based GFR was estimated using the following equations: eGFR-EPI =144 × (serum creatinine [mg/dl]/0.7)$^{-0.329}$ × (0.993) ^{age} if female and serum creatinine ≤0.7) or eGFR-EPI =144 × (serum creatinine [mg/dl]/0.7)$^{-1.209}$ × (0.993)^{age} if female and serum creatinine>0.7) or eGFR-EPI =141 × (serum creatinine [mg/dl]/0.9)$^{-0.411}$ × (0.993) ^{age} if male and serum creatinine≤0.9) or eGFR-EPI =141 × (serum creatinine [mg/dl]/0.9)$^{-1.209}$ × (0.993) ^{age} if male and serum creatinine>0.9) [20]. Since the GFR of most participants is greater than 60 mL/min/1.73 m^2, we categorized them into mild renal impairment group (GFR<90 mL/min/1.73 m^2 group, category G1), or normal group (GFR≥90 mL/min/1.73 m^2 group) [21].

Depressive symptoms were assessed using the 15-item version of the Geriatric Depression Scale (GDS-15) with a score of 0-15. A score of ≥ 5 was considered depression symptoms. The cut-off score of ≥5 has a sensitivity of 0.97 and a specificity of 0.95 [22, 23].

Covariates

Covariates in this study include age, gender (male, female), educated (yes or no), marriage status (current married, other [never married, divorced, separated, or widowed]), cigarette smoking (current smoking, former smoking, or no smoking), alcohol drinking (current drinking, former drinking, or no drinking), life satisfaction (satisfied [very satisfied, satisfied, or fair] and unsatisfied [unsatisfied or very unsatisfied]), levels of body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglyceride (TG).

Statistical analysis

Characteristics were presented as the mean ± standard deviation (SD) or the percentage. The deviation from Hardy–Weinberg expectation for the genetic variants was tested by a chi-square statistic.

Comparisons of continuous variables were tested using a Student's t test. The effects of genetic variants on GFR level were examined using ACNOVA, adjusting for multiple covariates. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence interval (95% CI) for renal impairment and depressive symptoms, adjusting for multiple confounding factors. A p-value of less than 0.05 (two-tailed) was considered to be statistically significant. All data analysis was done by SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

Results

Table 1 summarizes the characteristics of the 1788 individuals included in this study. The mean age of the study participants was 75.36±3.91 years, and 53.6% was female. The GFR levels of the renal impairment group and normal group were 80.93±9.84 and 95.10±4.01, respectively. GFR decrease group was older, had less females, less coupled individuals and more smokers, with a higher TG level and a lower HDL-C level (Table 1). The genotype distributions of the studied polymorphisms ranged from 5.1% to 47.8% (Table 2 and Supplemental Table 2).

The association analysis results of the 10 selected SNPs identified in the GWAS of the European ancestry was presented in Table 2. Significant difference of GFR levels was observed across three DAB2-rs11959928 genotypes and a boardline significant difference of GFR levels was observed across three *SHROOM3*-rs17319721 genotypes. However, since the GFR level of the heterozygote of 11959928 is the highest among three genotypes, therefore, we did not further analyze this variant.

SHROOM3-rs17319721 was associated with both GFR levels and odds of renal impairment defined by GFR<90 mL/min/1.73 m^2, after adjusting for multiple confounds of CKD including adjusted for age, sex, education, marriage, smoking, alcohol drinking, life satisfaction, BMI, SBP, SBP, glucose, TG, HDL, and LDL levels (Table 3). A allele was associated with both decreased GFR level (85.95±11.45 mL/min/1.73 m^2 vs. 87.54±10.25 mL/min/1.73 m^2 for GA+AA and GG carriers, respectively) and greater odds of GFR decrease (OR 1.12, 95% CI 1.01-1.23, p=0.029) defined by GFR<90 mL/min/1.73 m^2, compared with GG genotype. In addition, compared with rs17319721-GG genotype, AA was associated with both higher depressive score (4.06±3.49 vs. 2.52±2.37) and greater risk of depression prevalence (OR 3.304, 95% CI 1.02-10.74), showing a pleiotropic effects of rs17319721 (Table 4).

We did not found significant association of GFR levels with 42 common polymorphisms that was previously reported associated with hypertension, diabetes, dyslipidemia, or obesity, which is the established risk factors of CKD (Supplement Table2).

Discussion

Previously, *SHROOM3*-rs17319721 was found associated with GFR in the European ancestry. In the present study, we found that *SHROOM3*-rs17319721 is associated with GFR levels and kidney impairment in another race-Chinese Han population. In addition, for the first time, we found that rs17319721 was associated with depressive symptoms. However, we did not found significant association of GFR levels with another 42 common polymorphisms that was previously associated with the traditional risk factors of kidney diseases.

Population studies of the *SHROOM3*-rs17319721

Encoded by *SHROOM3*, shroom3 is an actin binding protein which regulate cell morphology by coordinating the assembly of cytoskeleton [24]. In 2009, Kottgen et al conducted the first GWAS of GFR in Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium found that the minor A allele of the *SHROOM3*-rs17319721 was associated with an decreased $eGFR_{cre}$ level and increased risk of CKD [6]. The association of rs17319721 with $eGFR_{cre}$ was also found in another larger GWAS conducted in European ancestry populations [5] and replicated in the clinical epidemiology follow-up studies conducted in European populations [25, 26, 4]. In the present study, we replicated this association in Chinese population.

However, rs17319721-GFR association was not detected among participants of African ancestry [9], suggesting that allelic heterogeneity exists across ethnicities. For *SHROOM3*-rs17319721, the MAF is indeed quite different across different ethnic groups, ranging from 43.9% in Europeans, to 21.7% in Africans, and 10.4% in Chinese Han population [8].

Although *SHROOM3* rs17319721-A allele decreases GFR and increases the risk of kidney impairment, it was associated with lower albuminuria [27]. The pleiotropic and contradiction association of this gene with GFR and albuminuria may be due to different etiology between them (albuminuria was associated with more smoking, diabetes and elevated triglycerides [28]), different genetic correlations between them [29], and the less coexist of them in early kidney disease [27, 30].

At personalized treatment researches, *SHROOM3*-rs17319721 was found to influence allograft injury. The presence of the *SHROOM3* risk A allele in the donor correlated with increased allograft fibrosis and with reduced GFR at 12 months after transplant [31]. In 189 Chinese patients, Yan et al found that rs17319721-A allele carriers had a significantly higher GFR levels than GG genotype from month 1 to month 6 after transplantation [32]. In allografts of US patients, rs17319721 AA was associated with reduced albuminuria by 2 years after transplant [33].

Possible mechanisms link *SHROOM3*-rs17319721 to CKD

SHROOM3 interacts with FYN via SH3-binding domain to regulate FYN activation and downstream signaling, and maintenances podocyte actin cytoskeleton and phenotype [33]. Rs17319721 is located in the first intron of the high conserved region of the *SHROOM3* gene. Rs17319721 A allele is associated with an increased expression of the *SHROOM3* than GG genotype. The sequence containing rs17319721-A allele is a TCF7L2 (transcription factor 7-like 2) dependent enhancer that increases *SHROOM3* transcription, and then promotes profibrotic gene expression by facilitating TGF-β1/SMAD3 signaling pathway [31]. In podocypes, AA preserves interaction with FYN, activates FYN kinase (Y418 phosphorylation), and stabilizes actin cytoskeleton [33]. In addition, rs17319721-A allele results in an elevated expression of a shorter isoform lacking the PDZ domain [34].

SHROOM3-rs17319721 variant and psychological traits

Since multiple lines of evidence are consistent with widespread pleiotropy for complex traits that many segregating variants affect multiple traits [35], we further explore whether pleiotropy effects exist for SHROOM3-rs17319721 in our cohort population. For 17319721, it was not only associated with eGFR/CKD in the general populations [5, 6, 36], but also associated with GFR in the diabetes patients [37] and associated with allograft fibrosis in renal transplant patients [31, 38]. In this study, we not only found the association of *SHROOM3*-rs17319721with GFR, but also with depressive symptoms and risk of depression.

Genetic variant of the *SHROOM3* was indeed previously related to psychological traits. In a GWAS conducted in Europeans, rs12513013 and rs12509930 of the *SHROOM3* were associated with neuroticism [39]. In the participants of the New England Centenarian Study, Bae et al replicated the association of rs12509930 with neuroticism [40]. In the present study, we found that *SHROOM3*-rs17319721 was associated with depressive symptoms. The mechanisms that rs17319721 is simultaneously associated with kidney disease and psychological traits are unknown at this stage, but previous studies showed that kidney impairment was linked to psychological traits including lower Quality of Well-Being [41], mental health impairment [42], depression and suicidal ideation [43, 44].

CKD risk factor-related loci and kidney impairment

In the present study, we also explored the association of a batch of CKD risk factor-related loci with GFR in our cohort population. Among them, *GCKR* (Glucokinase regulatory protein) is another pleiotropic gene, the protein of which inhibits hepatic glucokinase. Common variants in *GCKR* was previously associated with a variety of risk factors of CKD, including serum triglycerides, fasting glucose, C-reactive protein, and diabetes [12]. This locus was associated with GFR in the GWAS of European ancestry [5]. However, in the present study, we did not found significant association between the variant of this locus with GFR level and kidney impairment. In addition, another pleiotropic locus, *NPPB* was associated with both blood pressure [16] and GFR [45] in previous large GWA studies. However, a functional variant of *NPPB*, rs198389 (-381T>C), was not associated with GFR or kidney impairment in our study (Supplement Table2). Insufficient statistical power resulting from the relative small sample size of the present study may account for the insignificant association.

Conclusions

SHROOM3-rs17319721-A allele was associated with decreased GFR level and greater odds of mild renal impairment in a Chinese population. AA genotypes was also associated with higher depressive score and greater risk of depression prevalence, suggesting a pleiotropic effects of rs17319721. Since the sample size of this study is relatively small, the associations need to be validated in other larger population studies.

Abbreviations

BMI:body mass index; CKD:chronic kidney disease; DBP:diastolic blood pressure; GCKR:Glucokinase regulatory protein; GDS-15:the Geriatric Depression Scale; GWAS:the genome-wide association studies; GFR:glomerular filtration rate; HDL:high density

lipoprotein; LDL:low density lipoprotein; ORs:odds ratios; RuLAS:Rugao Longevity and Ageing Study; SBP:systolic blood pressure; SD:standard deviation; SNPs:single nucleotide polymorphisms; TG:triglyceride; MAF:minor allele frequency;

Declarations

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XH Sun and XY Jiang were responsible for managing the participant database and retrieving follow-up information; they also contributed to article preparation, in the analyses of data and in drafting the article. J Chen, ZK Chen, and ZJ Bao supervised the ongoing research, taking part in the initiation of the study and contributing to article preparation. XH Sun, ZJ Bao and XY Jiang contributed to analyses of data and in article preparation. ZJ Bao, XY Jiang and XF Wang conceived the study, participated in its design and coordination, and helped draft the article. All authors read and approved the final article.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (This study was approved by the Human Ethics Committee of the School of Life Sciences of Fudan University, Shanghai, China.) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consents were obtained from all participants prior to participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table1 Descriptive characteristics of the study subjects and univariate analysis for eGFR

Characteristics	All participants (n=1788)	Mild renal impairment group (n=995)	Normal group (n=793)	p
Age (years)	75.36±3.907	76.75±3.88	73.62±3.17	<0.001
Female (%)	958 (53.6%)	509 (51.2%)	449(56.6%)	0.021
Educated (%)	818 (46.5%)	521 (53.5%)	419(53.4%)	0.984
Current married (%)	1167(65.7%)	616 (62.5%)	551 (69.8%)	0.001
Life satisfied (%)	1531 (86.5%)	851 (86.5%)	680 (86.5%)	0.985
Cigarette smoking				
Current smoking	255 (14.4%)	143 (14.6%)	122 (14.2%)	0.020
Former smoking	195 (11.1%)	126 (12.9%)	69 (8.8%)	
No smoking	1314 (74.5%)	709 (72.5%)	605 (77.0%)	
Alcohol drinking				
Current drinking	332 (18.8%)	818 (46.5%)	818 (46.5%)	0.459
Former drinking	184 (10.4%)	109 (11.1%)	75 (95%)	
No drinking	1251 (70.8%)	684 (69.7%)	567 (72.0%)	
BMI (kg/m^2)	24.10±3.54	24.23±3.58	23.94±3.49	0.094
SBP (mmHg)	155.72±22.25	156.37±22.87	154.91±21.43	0.172
DBP (mmHg)	81.91±11.52	82.31±11.97	81.41±10.94	0.101
TG (mM)	1.40±0.99	1.44±0.99	1.35±0.98	0.048
Total cholesterol (mM)	5.12±0.95	5.12±0.97	5.12±0.92	0.828
HDL-C (mM)	1.47±0.33	1.44±0.31	1.50±0.34	<0.001
LDL-C (mM)	2.79±0.72	2.79±0.73	2.80±0.70	0.792
Glucose (mmol/L)	5.86±1.67	5.82±1.68	5.90±1.67	0.354
GFR ($mL/min/1.73\ m^2$)	87.21±10.52	80.93±9.84	95.10±4.01	<0.001

Table2 GFR levels across genotypes of studied polymorphisms in Rugao cohort population

SNPs	Gene	MAF in this study	Percentages	GFR levels			P
			Maj/ Het/ Min	Major homo	Heterozygote	Minor homo	
rs1260326	*GCKR*	T/C=44.2	30.7/50.2/19.1	86.87±10.53	87.71±9.86	86.86±11.54	0.243
rs347685	*TFDP2*	A/C=29.3	49.9/41.6/8.5	86.87±10.66	87.68±10.36	87.92±9.80	0.240
rs17319721	*SHROOM3*	G/A=9.10	82.8/16.2/1.0	87.54±10.25	85.98±11.39	85.31±12.76	0.055
rs11959928	*DAB2*	T/A=12.5	76.5/22.0/1.5	86.99±10.70	88.31±9.44	83.60±13.54	0.020
rs6420094	*SLC34A1*	A/G=27.2	52.3/41.0/6.8	87.18±10.55	87.27±10.50	87.82±9.28	0.827
rs881858	*VEGFA*	A/G=17.5	68.7/27.7/3.6	87.16±10.39	87.85±10.53	85.73±11.33	0.232
rs4744712	*PIP5K1B*	C/A=47.8	27.0/50.4/22.6	87.33±11.18	87.32±10.00	87.10±10.46	0.937
rs626277	*DACH1*	C/A=10.2	80.8/18.0/1.2	87.26±10.45	87.31±10.17	87.22±13.08	0.996
rs1394125	*UBE2Q2*	G/A=10.2	80.7/18.1/1.1	87.29±10.40	87.55±10.54	84.83±11.82	0.540
rs12460876	*SLC7A9*	C/T=28.8	50.7/41.2/8.2	87.32±10.26	87.46±10.65	85.96±11.42	0.319

Table3 Associations of SHROOM3-rs17319721 with GFR levels and odds of renal impairment

	GFR levels	Renal impairment	
		No, GFR≥90 (n, /%)	Yes, GFR<90 (n, /%)
GG	87.54±10.25	657 (85.0)	780 (81.0)
GA+AA	85.95±11.45	116 (15.0)	183 (19.0)
GA+AA vs GG	p	OR (95% CI), p	
Crude model	0.017	1.10(1.01-1.20), 0.029	
Model1	0.029	1.11(1.01-1.22), 0.032	
Model2	0.038	1.11(1.01-1.22), 0.036	
Model3	0.019	1.12(1.01-1.23), 0.029	

Model1: adjusted for age and sex.

Model2: adjusted for age, sex, education, marriage, smoking, alcohol drinking, and life satisfaction.

Model3: adjusted for age, sex, education, marriage, smoking, alcohol drinking, life satisfaction, BMI, SBP, SBP, glucose, TG, HDL, and LDL levels.

Table4 Associations of SHROOM3-rs17319721 with depressive score and odds of levels and odds of depression

Genotype	Depressive score	Depression	
		GDS≥5 (n, /%)	GDS<5 (n, /%)
GG	2.52±2.37	196 (80.3%)	1240(83.2%)
GA	2.63±2.42	42(17.2%)	240(16.1%)
AA	4.06±3.49	6(2.5%)	11(0.7%)
GA vs. GG	p	OR (95% CI), p	
Crude model	0.580	1.107(0.77-1.59)	
Model1	0.623	1.095(0.76-1.58)	
Model2	0.916	1.095(0.76-1.58)	
Model3	0.803	0.948(0.62-1.44)	
AA vs. GG	p	OR (95% CI), p	
Crude model	0.016	3.689(1.33-10.24)	
Model1	0.012	3.689(1.33-10.24)	
Model2	0.033	3.500(1.11-11.06)	
Model3	0.047	3.304(1.02-10.74)	

Model1: adjusted for age and sex.

Model2: adjusted for age, sex, education, marriage, smoking, alcohol drinking, and life satisfaction.

Model3: adjusted for age, sex, education, marriage, smoking, alcohol drinking, life satisfaction, BMI, SBP, SBP, glucose, TG, HDL, and LDL levels.

Supplementary Files

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