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A family-based association study after genome-wide linkage analysis identified two genetic loci for renal function in a Mongolian population

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The estimated glomerular filtration rate is a well-known measure of renal function and is widely used to follow the course of disease. Although there have been several investigations establishing the genetic background contributing to renal function, Asian populations have rarely been used in these genome-wide studies. Here, we aimed to find candidate genetic determinants of renal function in 1007 individuals from 73 extended families of Mongolian origin. Linkage analysis found two suggestive regions near 9q21 (logarithm of odds (LOD) 2.82) and 15q15 (LOD 2.70). The subsequent family-based association study found 2 and 10 significant single-nucleotide polymorphisms (SNPs) in each region, respectively. The strongest SNPs on chromosome 9 and 15 were rs17400257 and rs1153831 with *P*-values of 7.21×10^{-9} and 2.47×10^{-11}, respectively. Genes located near these SNPs are considered candidates for determining renal function and include *FRMD3*, *GATM*, and *SPATA5L1*. Thus, we identified possible loci that determine renal function in an isolated Asian population. Consistent with previous reports, our study found genes linked and associated with renal function in other populations.

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The decline in glomerular filtration rate (GFR), which is an overall indicator of renal function, has been recognized as a global health problem, leading to an increased risk of cardiovascular events and mortality.[1,2] Previous studies have provided evidence for genetic factors affecting renal function, showing heritability ranging from 0.41 to 0.75 in populations with risk factors such as hypertension or diabetes[3,4] and from 0.21 to 0.33 in general populations.[5–7]

To date, there have been several linkage studies to identify genetic loci determining renal function in individuals with renal disease or in the normal population.[8–11] Puppala *et al.* suggested candidate regions including 2q36.3 and 9q21.31–q21.33 in the Mexican–American population, and Schelling *et al.* reported the 1q43, 7q36.1, 8q13.3, and 18q23.3 regions using multiethnic diabetic populations.[9,11] There are several additional regions that have been suggested from other linkage studies, including 7p15.3–p13, 12p12.2, and 16q12.2–16q23.1.[8,10] In recent years, researchers have tried to determine in more detail the genetic basis of the estimated GFR (eGFR) through genome-wide association studies (GWAS), and have begun suggesting some genes or variants as determinants of eGFR or chronic kidney disease.[12–14] These studies, based on a large number of samples, have identified several variants showing a high level of significance and reproducibility near or within genes including *UMOD*, *SHROOM3*, *GATM*, and *SPATA5L1*.[12–15]

Although a number of genetic loci have been implicated from the genome-wide linkage and association studies, few studies have been carried out in Asian populations. In addition, some studies were focused on samples from patients having a specific disease, and the results might not reflect the renal function of the general population.[9,11,16–18] This study was conducted as a part of the GENDISCAN project (GENe DIScovery for Complex traits in large isolated families of Asians of the Northeast), which was designed to

investigate genetic influences on complex traits in extended families in Mongolia.[19–22] This project has several unique features compared with other studies: (1) the study population is isolated in a rural area and has relatively little ethnic admixture; (2) the subjects mostly consist of large extended families; and (3) the sample selection was unbiased by health status, and thus the samples represent the community-based population. These points strengthen the power of the genetic studies, and enable the identification of causal genetic loci for each phenotype.[23]

Family studies have a long history in human genetics. In particular, linkage analysis using families was successful in mapping for human oligogenic traits. In the past few years, along with the advances in genotyping technology, a population-based GWAS has become a popular tool for gene mapping of common complex diseases. However, the inability of the common variants identified by GWAS to explain the heritability of diseases has again led to interest in family-based studies, such as association studies based on linkage information.[24]

In this study, we aimed to investigate the genetic background of eGFR in isolated Mongolian families. Subsequently, the candidate loci were compared with those identified in previous studies on different populations, and the reproducibility of the results determined.

RESULTS

Descriptive characteristics of study subjects

The descriptive characteristics of the study subjects are shown in Table 1. This study consists of two steps of analysis: (1) genome-wide linkage analysis followed by (2) a family-based association study. The study population used for the linkage analysis includes 73 families comprising 1007 individuals. The number of individuals per family ranged from 4 to 54. Of these, 722 individuals from 54 families were genotyped with a single-nucleotide polymorphism (SNP) microarray and chosen for the subsequent association study. The minimum and maximum numbers of individuals per family were 6 and 54, respectively. As shown in Table 1, the distribution of each trait in samples for the association study shows no difference to that in samples for the linkage study. The eGFR, which represents the renal function of each subject, was calculated according to the MDRD-6 (Modification of Diet in Renal Disease) equation.[25]

Table 1 | Characteristics of study participants

Characteristics	Linkage study *N* (%) or mean (s.d.)	Association study *N* (%) or mean (s.d.)
Subject information		
No. of families	73	54
No. of participants	1007	722
Minimum no. of individuals per family	4	6
Median no. of individuals per family	18	20
Maximum no. of individuals per family	54	54
Risk factor of renal function		
Age (years)	33 (16.3)	32 (16.0)
Female (%)	537 (53.3)	392 (54.3)
BMI (kg/m^2)	23.4 (4.2)	23.3 (4.1)
Smoking (yes)	180 (17.9)	117 (16.2)
Under antihypertensive treatment (yes)	122 (12.1)	82 (11.4)
Fasting glucose (mg/dl)	95.4 (18.6)	95.3 (19.9)
SBP (mm Hg)	115 (16.1)	114.2 (15.7)
Renal function		
eGFR[a] (ml/min per 1.73 m^2)		
Male	99.8 (26.5)	101.2 (26.6)
Female	96.4 (22.9)	96.5 (22.6)
Total	98.0 (24.7)	98.6 (24.6)
No. of CKD	23 (2.3)	13 (1.8)

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
[a]eGFR was estimated by the MDRD-6 (Modification of Diet in Renal Disease).[25]

Genetic evidence of eGFR from familial correlation and heritability analyses

To identify the evidence of genetic factors for eGFR levels, we calculated familial correlation coefficients in familial pairs and estimated the heritability, which is a useful concept to evaluate the amount of genetic contribution to total phenotypic variation (Supplementary Table S1 online). Overall, there were 760 parent–offspring pairs, 623 sibling pairs, 725 avuncular pairs, 520 cousin pairs, and 94 spouse pairs. In the age- and sex-adjusted model (Model 1), sibling correlation was significant ($r = 0.20$, $P < 0.01$), and among all the subtype pairs the highest correlation was shown in brother–brother pairs ($r = 0.37$, $P < 0.01$). The narrow-sense heritability for eGFR was 0.27 ($P < 0.01$). In the multivariable-adjusted model (Model 2), parent–offspring and sibling correlations were estimated to be 0.10 ($P = 0.02$) and 0.18 ($P < 0.01$), respectively. Similar to the age- and sex-adjusted model, the highest correlation was shown in brother–brother pairs ($r = 0.35$, $P < 0.01$). Among subtypes of parent–offspring pairs, mother–daughter pairs had a significant familial correlation ($r = 0.14$, $P = 0.03$). As shown in Supplementary Table S1 online, the narrow-sense heritability in the multivariable-adjusted model was slightly higher than that of the age- and sex-adjusted model ($h^2 = 0.29$, $P < 0.01$). As a result, in both models of analyses, the overall familial correlations for genetically related pairs were significant. However, the correlations for spouse pairs, which indicate shared environmental or assortative mating effect, were not significant. This correlation pattern may suggest the importance of genetic components for eGFR, along with the significant heritability.

Genome-wide linkage scan for eGFR

Results for suggestive linkages with a logarithm of odds (LOD) score greater than 1.9 are reported in Figure 1 and Table 2.[26] The two suggestive linkage peaks in this study were detected on chromosomes 9 and 15 (Figure 1a). The linkage