ARTICLE

Genome-wide association study of the risk of chronic kidney disease and kidney-related traits in the Japanese population: J-Kidney-Biobank

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Chronic kidney disease (CKD) is a syndrome characterized by a gradual loss of kidney function with decreased estimated glomerular filtration rate (eGFR), which may be accompanied by an increase in the urine albumin-to-creatinine ratio (UACR). Although trans-ethnic genome-wide association studies (GWASs) have been conducted for kidney-related traits, there have been few analyses in the Japanese population, especially for the UACR trait. In this study, we conducted a GWAS to identify loci related to multiple kidney-related traits in Japanese individuals. First, to detect loci associated with CKD, eGFR, and UACR, we performed separate GWASs with the following two datasets: 475 cases of CKD diagnosed at seven university hospitals and 3471 healthy subjects (dataset 1) and 3664 cases of CKD-suspected individuals with eGFR <60 ml/min/1.73 m^2 or urinary protein ≥ 1+ and 5952 healthy subjects (dataset 2). Second, we performed a meta-analysis between these two datasets and detected the following associated loci: 10 loci for CKD, 9 loci for eGFR, and 22 loci for UACR. Among the loci detected, 22 have never been reported previously. Half of the significant loci for CKD were shared with those for eGFR, whereas most of the loci associated with UACR were different from those associated with CKD or eGFR. The GWAS of the Japanese population identified novel genetic components that were not previously detected. The results also suggest that the group primarily characterized by increased UACR possessed genetically different features from the group characterized by decreased eGFR.

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INTRODUCTION

Chronic kidney disease (CKD) is a global burden that affects 10–15% of the world population [1]. It is not only a risk factor for end-stage kidney disease, but also for other diseases, such as cardiovascular diseases, infection, and some types of cancer [1–4]. The multifaceted nature of CKD, in which many factors are intricately intertwined, makes it difficult to elucidate its pathogenesis. Furthermore, CKD has a variety of clinical courses, including one mainly showing decreased eGFR and one mainly showing increased albuminuria or an increased urine albumin-to-creatinine ratio (UACR). The difficulty in predicting CKD progression is also a crucial problem in clinical settings.

In this era of progress toward personalized medicine [5, 6], it is necessary to accurately estimate disease status using clinical information and elucidate the relationship between disease progression and genetic background. Genome-wide association studies (GWASs), methods of analyzing genome-wide genetic variations to determine which variations are associated with focused traits, have identified many loci associated with a variety of diseases and phenotypes [7–9]. However, the results of GWASs may vary depending on the population in which the studies are conducted because the frequency of each variant, called "minor allele frequency," or linkage disequilibrium (LD) varies by ethnicity [10]. Conducting a GWAS in a genetically homogeneous population is expected to extract certain genetic characteristics specific to that population, which would be difficult to detect by trans-ethnic analysis.

Several genetic factors associated with CKD risk and kidney function have already been reported in some previous studies with large numbers of participants [11–13]. However, to the best of our knowledge, few studies have investigated the genetic factors associated with multiple kidney-related traits in the Japanese population [14, 15], with none investigating the traits associated with urinary findings.

This study aimed to identify novel genetic susceptibility loci for the following three kidney function-related traits in Japanese

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patients with CKD: risk of CKD, estimated glomerular filtration rate (eGFR) level, and UACR.

MATERIALS AND METHODS

Ethics statement

All human studies were approved by the relevant institutional review boards and conducted in accordance with the Declaration of Helsinki (approval numbers: Kanazawa University, 521-4; Kawasaki Medical School, 3453; Kyoto University, G1157; Kyushu University, 815-01; Niigata University, G2018-0024; Okayama University, 2002-005; University of Tokyo, 2018026 G; and Tohoku Medical Megabank Organization (ToMMo), 2018-4-110). All participants provided written informed consent.

J-Kidney-Biobank

The J-Kidney-Biobank (JKB) is a biobank established in 2020 for the purpose of deep and comprehensive investigation into the genetic and environmental factors that affect the progression of kidney diseases (https://www.j-kidney-biobank.jp/en/sitemap.html). All JKB participants are patients with CKD. JKB collects and stores biological samples of patients with CKD, such as plasma, urine, and DNA solutions extracted from peripheral blood cells, and links them to detailed information about each patient, such as laboratory values and prescriptions extracted from electronic medical records. Recruitment of participants is still underway.

Tohoku Medical Megabank Organization

The ToMMo is conducting a prospective cohort study named "the Tohoku Medical Megabank Project Community-Based Cohort Study" [16, 17]. The project was launched for the purpose of reconstruction after the Great East Japan Earthquake on March 11, 2011, and the establishment of personalized healthcare and medicine. It contains more than 80,000 participants, mainly healthy individuals, and the data are collected mainly during health checkups. In addition, samples collected from JKB participants are stored in ToMMo's biobanking storage.

Participants

Between October 2018 and August 2020, 477 patients with CKD (cases in dataset 1 (DS1)) were recruited into the JKB cohort from one of seven university hospitals in Japan.

For some participants whose blood samples were already submitted for use in other clinical studies, the residual samples were utilized for this study, based on the approval of local ethics committees. Patients undergoing dialysis therapy and those who had already undergone kidney transplantation were excluded because the JKB collects not only genomic information, but also plasma and urine samples. Of the participants in ToMMo, 3471 healthy individuals who had eGFR >60 ml/min/1.73 m^2 and were negative for urine protein were included in DS1 as a control group (Fig. 1).

A ToMMo cohort also included 3664 participants with suspected CKD (sCKD), whose eGFR was <60 mL/min/1.73 m^2 and/or whose UACR was ≥30 mg/gCre at the time of recruitment. These 3664 patients suspected of having CKD and 5952 healthy controls were included in the analysis of dataset 2 (DS2) (Fig. 1). There were no duplicate cases between the control group in DS1 and that in DS2.

Although the ToMMo cohort study recruited residents in Miyagi and Iwate Prefectures, only participants living in Miyagi Prefecture, which is less genetically structured, were used in this study. Demographic and clinical information was obtained from questionnaires at the time of recruitment.

Clinical and laboratory data

Patients who fulfilled one or more of the following conditions were counted as cases with hypertension: systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg, taking antihypertensive medication. Patients who indicated in the questionnaire that they had diabetes mellitus were counted as cases with diabetes mellitus. Hemoglobin A1c (HbA1c) data were presented as National Glycohemoglobin Standardization Program values according to the recommendations of the Japanese Diabetes Society and the International Federation of Clinical Chemistry [18].

Phenotype definition

The diagnosis of CKD was based on the Kidney Disease: Improving Global Outcome (KDIGO) criteria: kidney damage that has continued for more than three months, as defined by structural or functional abnormalities of the kidney [19, 20].

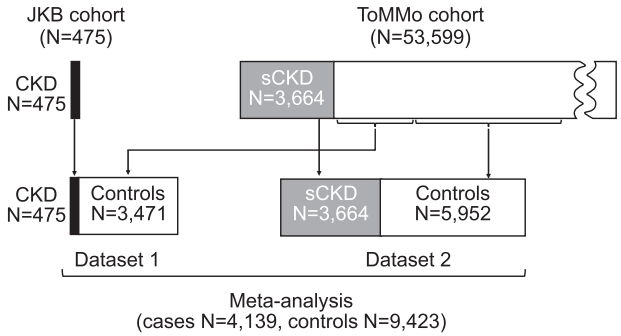

Fig. 1 Relationship between the two cohorts and datasets. Cases in dataset 1 comprised patients with CKD from the JKB cohort clinically diagnosed with CKD. Conversely, cases in dataset 2 were suspected CKD cases with eGFR <60 ml/min/1.73 m^2 and/or urinary protein ≥(1 +) at time of recruitment to the ToMMo cohort, which is a health check-up cohort. Controls of both datasets were participants in the ToMMo cohort with eGFR >60 ml/min/1.73 m^2 and negative urinary protein. CKD chronic kidney disease, eGFR estimated glomerular filtration rate, JKB J-Kidney-Biobank, ToMMo Tohoku Medical Megabank Organization, sCKD suspected chronic kidney disease

The kidney function-related traits assessed in this study included eGFR estimated using the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation [21] and UACR in milligrams per gram of creatinine. If the UACR record was missing and that of the urinary protein-to-creatinine ratio (UPCR) was present, estimated UACR was calculated from the UPCR using the following equation [22], and this estimated value was substituted for UACR ($N = 357$):

$$\begin{aligned}\mathrm{UACR} = \exp(&5.3920 + 0.3072 \times \log(\min(\mathrm{UPCR}/50,\ 1)) \\ &+ 1.5793 \times \log(\max(\min(\mathrm{UPCR}/500,\ 1),\ 0.1)) \\ &+ 1.1266 \times \log(\max(\mathrm{UPCR}/500,\ 1))\end{aligned}$$

Genotyping and imputation

The samples were genotyped using Japonica Array v2 [23]. Upon quality control of the samples based on the genotyping data, some samples were excluded owing to genotype defects (low call rate: call rate <0.95, $N = 2$). For quality control of the genotyped markers, single nucleotide polymorphisms (SNPs) with low call rates (<0.99), low p values in the Hardy–Weinberg equilibrium test (p value $< 1.0 \times 10^{-5}$), and low minor allele frequencies (<0.01) were filtered out. As a result, 535,684 SNPs were retained for the downstream analysis. The genotype data were further imputed with 1KG phase 3 genotype data [24] and Japanese whole-genome sequencing data, 3.5kJPNv2 [25], using IMPUTE4 (impute4.1.2_r300.3) software packages [26]. Approximately 6,500,000 loci were used for the downstream analysis.

Genome-wide association analysis

For all three traits handled in this study, i.e., presence/absence of CKD as a binary variable and eGFR and UACR as continuous variables, we performed a GWAS of each dataset using a linear mixed regression model under the assumption of additive allelic effects of the SNP dosage using BOLT-LMM [27], which was adjusted for sex, age, and the first 10 principal components of the genotypes. For the binary trait CKD, the obtained β values were multiplied by $(n1 + n2)^2/(n1*n2)$ to obtain the approximate β values for the logistic regression model, and further exponential transformation was performed to obtain the odds ratios [28]. In addition, we performed a GWAS of each dataset using REGENIE [29], a generalized linear mixed model-based software for unbalanced case–control phenotypes, for the CKD trait with the same adjustments. We set a genome-wide significance threshold at a level of $p = 5.0 \times 10^{-8}$ by applying the Bonferroni correction. We constructed a Manhattan plot and quantile-quantile plot (Q-Q plot) to visually evaluate the analysis results. We defined independent associated loci on the basis of genomic positions at least 1 Mbp apart from each other. Previously unreported associations were identified based on a

review of the published literature and by an individual look-up of each association in the NHGRI-EBI Catalog of human GWASs (GWAS Catalog, https://www.ebi.ac.uk/gwas/,CKD:EFO_0003884,eGFR:EFO_0005208,UACR:EFO_0007778,2022/5/20accessed).

Meta-analysis

Association summary statistics were combined via fixed-effects meta-analysis (inverse-variance weighting) implemented in METAL software [30]. Genomic control corrections [31, 32] were applied to the results of the meta-analysis. The genome-wide significance level was set at 5×10^{-8}. Heterogeneity in allelic effects between the datasets for each variant was assessed by calculating Cochran's Q statistics.

Fine mapping

We performed fine mapping of the region where many loci were significantly detected in a row, using FINEMAP (version 1.4) [33]. For each region, we constructed pairwise LD matrices with LDstore (version 2.0) [33] using a merged dataset of DS1 and DS2. We then applied FINEMAP using these matrices to conduct a shotgun stochastic search and Bayesian fine mapping using the following options: "-sss --n-causal-snps N --prob-cred-set 0.95 --prior-std 0.05" (where N is the number of SNPs in the focused region). We defined the "index" SNP as the variant with the lowest *p* value.

RESULTS

In the present study, we conducted a two-stage GWAS of CKD. First, we performed a GWAS with 475 CKD cases from JKB, which consisted of patients clinically diagnosed with CKD in nephrology units at university hospitals, and 3471 healthy controls from ToMMo (DS1). Simultaneously, we performed a GWAS with 3664 sCKD cases from ToMMo, who had low eGFR values and/or proteinuria at the time of their health checkups, and 5952 healthy controls from ToMMo (DS2). Subsequently, we conducted a meta-analysis of these two datasets, which accordingly included over 13,000 individuals. We also performed a GWAS on other kidney-related traits, such as eGFR and albuminuria, to investigate the genetic correlation between the clinical patterns primarily characterized by decreased eGFR and increased UACR.

Participant characteristics

The baseline characteristics of the study participants are presented in Table 1. A total of 13,562 participants were included in the meta-analysis of DS1 and DS2. The average age was 63.2 years, and 57.4% of the participants were female. The CKD cases in DS1 exhibited a very high complication proportion of hypertension of 94.9%, whereas the value for sCKD cases in DS2 was only 55.3%. Similarly, the complication proportion of diabetes mellitus was high at 81.9% in CKD cases in DS1, but only 7.1% in sCKD cases in DS2. In DS1, the average eGFR and UACR levels of CKD cases were 35.8 ml/min/1.73 m^2 and 385.0 mg/gCre, respectively. In DS2, the average eGFR and UACR levels of sCKD cases were 55.7 ml/min/1.73 m^2 and 65.5 mg/gCre, respectively. The principal component analysis plot did not show any apparent population stratification between the cases and controls in each dataset (Supplementary Fig. 1).

Identification of loci associated with CKD risk

Using BOLT-LMM [27] software, we identified 16 loci in DS1 and one locus in DS2 attaining genome-wide significant evidence of an association with the CKD risk ($p < 5.0 \times 10^{-8}$, Supplementary Table 1). There was no overlap in the loci that were significant between DS1 and DS2. In the meta-analysis of the two datasets, we identified 10 loci containing at least one CKD-associated SNP with genome-wide significance (Fig. 2A, Table 2). The Q-Q plot showed good adherence to null expectations ($\lambda GC = 1.059$, Supplementary Figure 2A). Of these, three loci (*GALNT15*, *DLGAP2*, and *BRAP*) were located within 1 Mbp of the previously reported SNPs associated with CKD [34–36], whereas the other seven loci had no previously reported loci in proximity.

Table 1. Baseline characteristics of participants

	Dataset 1			Dataset 2			Total		
	CKD cases ($N = 475$)	Controls ($N = 3471$)	ALL ($N = 3946$)	sCKD cases ($N = 3664$)	Controls ($N = 5952$)	ALL ($N = 9616$)	Cases ($N = 4139$)	Controls ($N = 9423$)	ALL ($N = 13,562$)
Age, mean (SD)	68.5 (12.0)	61.8 (8.5)	62.6 (9.3)	66.1 (6.8)	61.8 (8.4)	63.4 (8.1)	66.4 (7.6)	61.8 (8.4)	63.2 (8.5)
Female, *n* (%)	171 (36.0)	2113 (60.9)	2284 (57.9)	1827 (49.9)	3680 (61.8)	5507 (57.3)	1998 (48.3)	5793 (61.5)	7791 (57.4)
Hypertension, *n* (%)	451 (94.9)	1301 (37.5)	1752 (44.4)	2026 (55.3)	2353 (39.5)	4379 (45.5)	2477 (59.8)	3654 (38.8)	6131 (45.2)
Diabetes mellitus, *n* (%)	389 (81.9)	167 (4.8)	556 (14.1)	260 (7.1)	259 (4.4)	519 (5.4)	649 (15.7)	426 (4.5)	1 075 (7.9)
HbA1c, mean (SD)	6.9 (1.3)	5.6 (0.6)	5.8 (0.8)	5.7 (0.6)	5.6 (0.6)	5.7 (0.6)	5.9 (0.8)	5.6 (0.6)	5.7 (0.7)
Participants with eGFR data, *n*	474	3 470	3 944	3 664	5 952	9 616	4 138	9 422	13 560
eGFR, mean (SD), ml/min/1.73 m^2	35.8 (21.6)	78.7 (12.1)	73.5 (19.5)	55.7 (10.4)	78.7 (12.4)	69.9 (16.2)	53.4 (13.7)	78.7 (12.3)	71.0 (17.3)
Participants with UACR data, *n*	357	3 457	3 814	3 627	5 932	9 559	3 984	9 389	13 373
UACR, mean (SD), mg/gCre	385.0 (271.9)	15.0 (50.3)	49.7 (144.3)	65.5 (219.5)	14.7 (33.1)	34.0 (139.9)	94.2 (242.5)	14.8 (40.3)	38.5 (141.3)

Four CKD cases in DS1 had missing HbA1c values
CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c, *sCKD* suspected CKD, *SD* standard deviation, *UACR* urine albumin-to-creatinine ratio

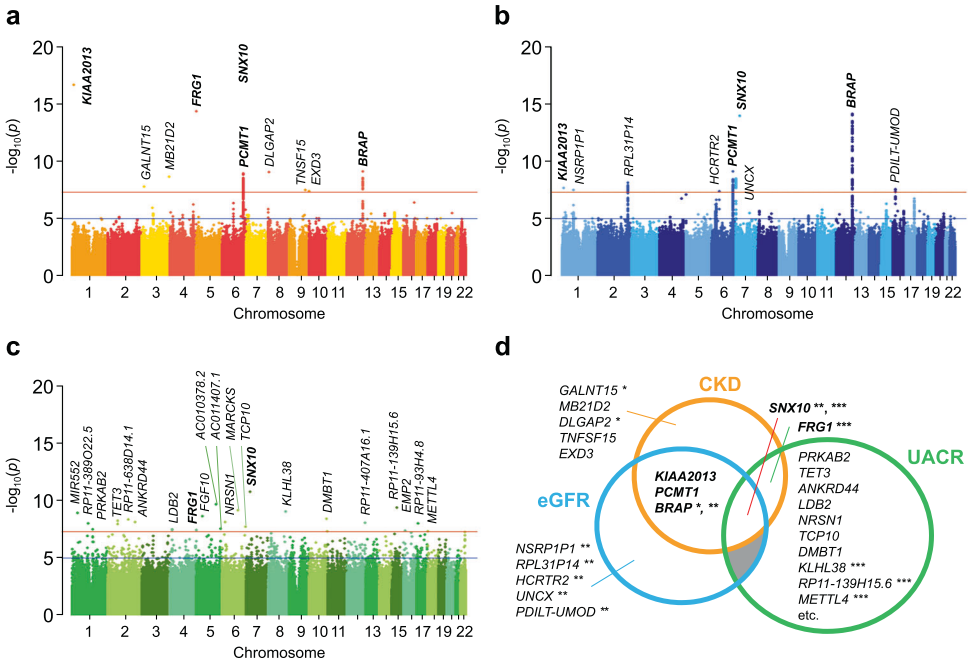

Fig. 2 GWAS meta-analysis for multiple kidney function-related traits. **A** Manhattan plot of CKD risk loci. As the upper limit of the Y-axis (−log10(*p* values)) is set to 20, the name of the locus (*SNX10*, $p = 4.37 \times 10^{-25}$) is indicated at the top. **B** Manhattan plot of eGFR-associated loci. **C** Manhattan plot of UACR-associated loci. **A**–**C**: The −log10(*p* values) of the SNPs are shown. Red lines indicate the level of genome-wide significance ($p = 5.0 \times 10^{-8}$). Loci that attained genome-wide significance for more than two traits (*BRAP*, *FRG1*, *KIAA2013*, *PCMT1*, and *SNX10*) are shown in bold. **D** Venn diagram of the loci significantly associated with CKD, eGFR, and UACR. Loci that were significant for each of the CKD, eGFR, and UACR traits in this study are summarized in the figure. Loci previously reported to be associated with each of the three traits are identified with asterisks (CKD*, eGFR**, UACR***). The one locus on intergenic regions, whose nearest gene is *SNX10*, was significantly associated with all three traits. There were no common loci between eGFR and UACR (shown as gray areas in the figure). GWAS genome-wide association study, CKD chronic kidney disease, eGFR estimated glomerular filtration rate, UACR urine albumin-to-creatinine ratio, SNPs single nucleotide polymorphisms

Table 2. Loci associated with risk of CKD

rsID	Chr.	Position (Hg19)	Gene	Ref/Alt	Frequency		GWAS meta-analysis	
					8.3kJPN	gnomAD	OR (95% CI)	*p* value
rs116802592	1	11979466	*KIAA2013*	C/T	0.0429	0.0142	0.699 (0.657–0.744)	2.18×10^{-17}
rs1048619	3	16269117	*GALNT15*[a]	G/T	0.0559	0.1214	0.789 (0.745–0.835)	1.77×10^{-8}
rs73200720	3	192665070	*MB21D2*[b]	C/T	0.0107	0.0191	0.635 (0.566–0.711)	2.39×10^{-9}
rs10031236	4	190298297	*FRG1*[b]	C/T	0.0251	0.1628	1.539 (1.417–1.672)	4.93×10^{-15}
rs9689694	6	150091773	*PCMT1*	C/T	0.7210	0.5028	1.215 (1.18–1.252)	1.15×10^{-9}
rs76762104	7	26431321	*SNX10*[†]	G/T	0.9927	0.9734	0.729 (0.708–0.751)	4.37×10^{-25}
rs757889	8	1504024	*DLGAP2*[a]	C/T	0.0642	0.1393	1.25 (1.186–1.317)	8.76×10^{-10}
rs7048659	9	117533289	*TNSF15*	C/T	0.9796	0.5913	0.76 (0.698–0.827)	3.20×10^{-8}
rs28488438	9	140268976	*EXD3*	C/T	0.0252	0.0450	0.747 (0.689–0.809)	4.40×10^{-8}
rs3782886	12	112110489	*BRAP* [a]	C/T	0.7870	0.9813	0.818 (0.793–0.845)	7.54×10^{-10}

8.3kJPN 8.3KJPN whole-genome variation panel, *Chr.* chromosome, *CI* confidence interval, *gnomAD* gnomAD v2.1.1, *CKD* chronic kidney disease, *OR* odds ratio, *SNP* single nucleotide polymorphism, *GWAS* genome-wide association study

Genomic control correction was applied to each *p* value. Odds ratios indicate the effect of the Alt allele on the Ref allele. The locus on chromosome 7 was filtered out in DS2 and detected as significant in the results for DS1 only. We identified 429 significant SNPs on chromosome 6, 149–150 Mb. Among these, rs9689694, with the smallest *p* value, is listed in the table. Similarly, 16 significant SNPs were identified on 112 Mb of chromosome 12, of which rs3782886 had the smallest *p* value, as listed in the table

[a]One or multiple SNPs associated with CKD have been previously reported within 1 Mbp of the locus

[b]The nearest gene name is shown if the SNP with the smallest *p* value is located in the intergenic region

One significant locus on chromosome 6 (149–150 Mbp) includes as many as 429 SNPs (smallest $p = 1.15 \times 10^{-9}$ at *PCMT1*), which is attributed to LD. As fine mapping revealed that the posterior probability for $k = 1$ was 0.953, where k is the number of causal SNPs, and the other significant SNPs were strongly correlated with the index SNP, as shown in Fig. 3A, only the index SNP with the smallest *p* value, located on chromosome 6 (150,091,773 bp, *PCMT*), was considered to be causal in this region.

Another locus on chromosome 12 (112 Mbp) was significant for the genes *BRAP, ACAD10, ALDH2, MAPKAPK5, NAA25, TRAFD1,*

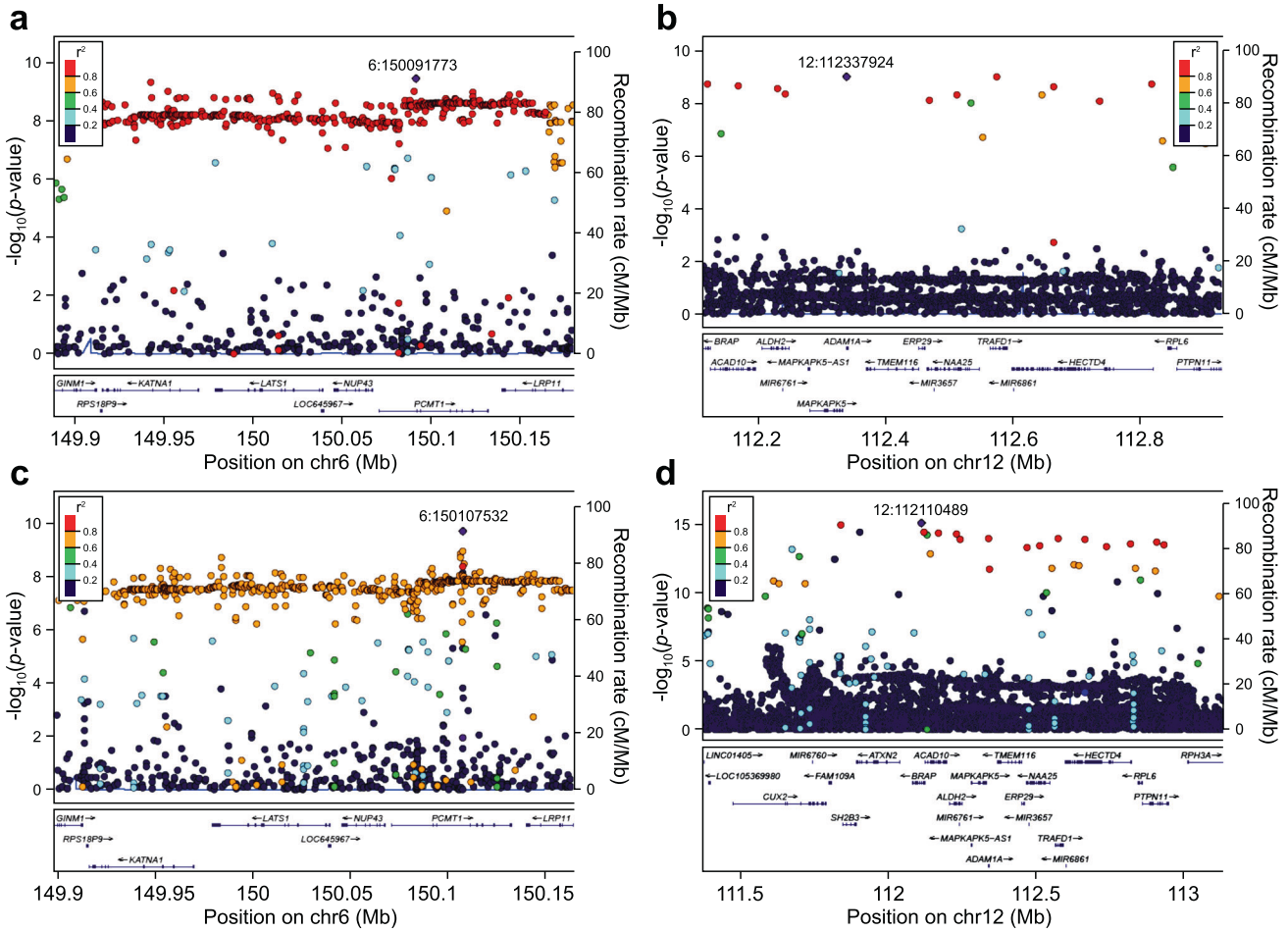

Fig. 3 Zoomed-in plots of regions where many loci were significantly detected in a row. −log10(*p* values) for CKD-associated signals at the loci on (**A**) chromosome 6 and (**B**) chromosome 12 and those for eGFR-associated signals at the loci on (**C**) chromosome 6 and (**D**) chromosome 12. Variants are colored according to linkage disequilibrium (r^2) with the index variant for each signal. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

HECTF4, RPL7AP60, and *PTPN11* (smallest $p = 7.54 \times 10^{-10}$ at *BRAP*), containing 16 SNPs. The two SNPs in this locus, rs671 and rs11066132, were found in *ALDH2* and *NAA25*, respectively, which were previously reported to be associated with kidney function [11, 13]. To examine whether only one index SNP on *BRAP* was truly significant and the others were detected because of LD, we also performed fine mapping for this region. The posterior probability for $k = 1$ was 0.757, and the r^2 values between the index SNP and the other significant SNPs were all above 0.8 (Fig. 3B). In this region, only the index SNP with the smallest *p* value, located on chromosome 12 (112 110 489 bp, *BRAP*), was considered causal.

In addition, we performed a GWAS on each dataset using REGENIE software [29] (Supplementary Figure 3), and its meta-analysis showed that only the three loci, one on chromosome 6 (149–150 Mbp, the smallest $p = 2.28 \times 10^{-8}$ at *GINM1*), one on chromosome 7, *SNX10* ($p = 7.87 \times 10^{-11}$), and one on chromosome 12, *BRAP* ($p = 2.95 \times 10^{-8}$), were significantly associated with CKD risk.

Identification of loci associated with eGFR

We identified 11 and five significant loci associated with eGFR in DS1 and DS2, respectively ($p < 5.0 \times 10^{-8}$, Supplementary Table 2). There was no overlap in the loci that were significant in each dataset. The meta-analysis of DS1 and DS2 for eGFR showed no evidence of an unmodeled population structure (λGC = 1.071, Supplementary Fig. 2B) and identified nine significant loci (Fig. 2B, Table 3). Seven loci (*NSRP1P1, RPL31P14, HCRTR2, UNCX, SNX10, BRAP*, and *PDILT-UMOD*) were located within 1 Mbp of the previously reported SNPs associated with eGFR [11, 36–40]. To the best of our knowledge, the other two loci (*KIAA2013* and *PCMT1*) have not been previously reported.

Similar to the CKD trait, one locus containing 158 SNPs on chromosome 6 (149–150 Mbp, smallest $p = 8.12 \times 10^{-10}$ at *PCMT1*) and another locus containing 51 SNPs on chromosome 12 (112 Mbp, smallest $p = 7.97 \times 10^{-15}$ at *BRAP*) were significantly detected for the eGFR trait.

Because fine mapping of chromosome 6 (149–150 Mbp) yielded the highest posterior probability of 0.898 for $k = 1$, only one SNP with the smallest *p* value was considered to be causal (Fig. 3C). It is worth noting that the index SNP associated with eGFR was 15 kbp apart from that associated with CKD, although they were in the same region (chromosome 6, 149–150 Mbp) and on the same gene, *PCMT1*. However, the fine mapping of chromosome 12 (112 Mbp) showed the highest posterior probability of 0.637 for $k = 4$. In this region, many SNPs have been detected as a result of LD, but more than one causal SNP may exist (Fig. 3D).

We also performed fine mapping of the following three loci, which included multiple SNPs: chromosome 2 (217 Mbp), chromosome 7 (1 Mbp), and chromosome 16 (20 Mbp) (Supplementary Fig. 4A–C). The loci on chromosome 7 (1 Mbp) showed the highest posterior probability of 1.000 for $k = 4$, suggesting multiple causal SNPs in this region, whereas the other two loci yielded the highest probability for $k = 1$, indicating only one causal SNP in each.

Table 3. Loci associated with eGFR

rsID	Chr.	Position (Hg19)	Gene	Ref/Alt	Frequency		GWAS meta-analysis	
					8.3kJPN	gnomAD	β	*p* value
rs116802592	1	11979466	*KIAA2013*	C/T	0.0429	0.0142	−2.6321	2.14×10^{-8}
rs140327554	1	78309785	*NSRP1P1*[a]	TAAAA/TAAA	0.3056	0.1165	1.2513	3.27×10^{-8}
–	2	217654793	*RPL31P14*[a]	C/CA	0.5337	–	−1.1482	7.61×10^{-9}
rs4715517	6	54973761	*HCRTR2*[a]	C/A	0.0650	0.0077	−2.1673	4.39×10^{-8}
rs374648186	6	150107532	*PCMT1*	C/T	0.4103	0.3054	−1.4632	8.12×10^{-10}
rs10277115	7	1285195	*UNCX*[a]	T/A	0.6827	0.4176	1.2478	3.51×10^{-9}
rs76762104	7	26431321	*SNX10*[a, b]	G/T	0.9927	0.9734	14.7294	1.22×10^{-14}
rs3782886	12	112110489	*BRAP*[a]	C/T	0.7870	0.9813	1.8793	7.97×10^{-15}
rs77924615	16	20392332	*PDILT-UMOD*[a]	G/A	0.2300	0.1640	1.3304	2.92×10^{-8}

8.3kJPN 8.3KJPN whole-genome variation panel, *Chr.* chromosome, *gnomAD* gnomAD v2.1.1, *eGFR* estimated glomerular filtration rate, *SNP* single nucleotide polymorphism, *GWAS* genome-wide association study

Genomic control correction was applied to each *p* value. *β* values indicate the effect of the Alt allele on the Ref allele. The locus on chromosome 7 was filtered out in DS2 and detected as significant in the results for DS1 only. A total of 30 SNPs on chromosome 2 (217 Mb), 158 SNPs on chromosome 6 (149–150 Mb), 17 SNPs on chromosome 7 (1 Mb), and 51 SNPs on chromosome 12 (111 Mb) were significantly associated with eGFR. The SNPs with the smallest *p* values for each region are listed in the table

[a]One or multiple SNPs associated with eGFR have been previously reported within 1 Mbp of the locus

[b]The nearest gene name is shown if the SNP with the smallest *p* value is located in the intergenic region

Identification of loci associated with UACR

We identified 33 loci in DS1 and 70 loci in DS2 that attained genome-wide significant evidence of an association with UACR ($p < 5.0 \times 10^{-8}$, Supplementary Table 3). There was no overlap in the loci that were significant in each dataset. We performed a meta-analysis of the two datasets and found no evidence of unaccounted stratification (λGC = 1.022, Supplementary Fig. 2C). We identified 22 UACR-associated loci with $p < 5.0 \times 10^{-8}$ (Fig. 2C, Table 4). The five loci (*FRG1*, *SNX10*, *KLHL38*, *RP11-139H15.6*, and *METTL4*) were located near known loci that were previously reported to be associated with UACR.

Relationship between CKD-associated loci and other kidney function-associated loci

As shown in Fig. 2D, some loci were commonly associated with both CKD and eGFR, including one locus on *KIAA2013*, another on *PCMT1*, and another on *BRAP*. Of the 22 loci significantly associated with UACR, most were not detected as being significantly associated with eGFR or CKD. The locus rs10031236 on chromosome 4, whose nearest gene is *FRG1*, was associated with UACR and common with the significant loci associated with CKD risk. Notably, rs76762104 on chromosome 7, whose nearest gene is *SNX10*, was significantly associated with CKD risk, eGFR level, and UACR.

Significant loci comparison with previous reports

Although replication could not be performed in this study, we performed a comparison with previous reports and databases for the Japanese population.

In total, four GWASs have been conducted on the CKD trait in the Japanese population, including the present study [14, 15, 41]. When compared, their results were not replicated; however, the GWAS Catalog (https://www.ebi.ac.uk/gwas/,CKD:EFO_0003884,2022/5/20accessed), an international database, included three of the 10 loci detected here (*GALNT15*, *DLGAP2*, and *BRAP*).

Next, we compared the results for the trait eGFR with those of previous reports and databases. Four out of the nine loci detected as significant in our study have been previously reported in the Japanese population (*KIAA2013*, *HCRTR2*, *UNCX*, and *PDILT-UMOD*) [13–15]. In addition, PheWeb [42], a database containing summary statistics of GWAS in the Japanese population conducted by the Biobank Japan Project, listed five out of the nine significant loci found herein (*RPL31P14*, *HCRTR2*, *UNCX*, *BRAP*, and *PDILT-UMOD*), whereas the GWAS Catalog (https://www.ebi.ac.uk/gwas/,eGFR:EFO_0005208,2022/5/20accessed), listed seven. One locus on *PCMT1* was newly identified in the present study.

As there is only one previous report on the UACR trait in the Japanese population [43] conducted using ToMMo data, which was also included in the current study, we made no comparisons because of participant overlap. The GWAS Catalog (https://www.ebi.ac.uk/gwas/,EFO_0007778,2022/5/20accessed) included 5 out of the 22 loci significant in this study (*FRG1*, *SNX10*, *KLHL38*, *RP11-139H15.6*, and *METTL4*).

Heterogeneity between the two datasets

In conducting a meta-analysis of the two datasets, we examined the heterogeneity between them using Cochran's Q test (Supplementary Fig. 5). No significant loci were found on loci significantly associated with CKD, eGFR, or UACR, although the power of this test is low when the number of datasets is relatively small [44].

DISCUSSION

In this study, we performed a GWAS for three kidney-related traits: CKD risk, eGFR level, and UACR. Few studies have analyzed multiple kidney-related traits in a Japanese population [14, 15] and did not include the results on albuminuria. Although some of the loci associated with each examined trait were already detected in previous studies, which helps validate our study, 22 unique loci were detected in the present analysis (CKD: *KIAA2013*, *MB21D2*, *FRG1*, *PCMT1*, *SNX10*, *TNSF15*, *EXD3*, eGFR: *KIAA2013*, *PCMT1*, UACR: *RP4-657M3.2/MIR52*, *RP11-389O22.5*, *PRKAB2*, *TET3*, *RP11-638D14.1*, *ANKRD44*, *LDB2*, *FGF10*, *AC010378.2*, *AC011407.1*, *RP11-31K13.1/NRSN1*, *MARCKS*, *TCP10/RP11-351J23.2*, *DMBT1/C10orf120*, *RP11-407A16.1*, *EMP2*, *RP11-963H4.8*). In addition to the loci detected in previous studies conducted in Japan, the 22 newly detected loci in this study could be genetic characteristics unique to the Japanese population.

As replication studies could not be performed, a comparison with previous reports and databases was performed as an alternative evaluation.

Regarding the CKD trait, besides the present study, three other reports have been conducted on the Japanese population [14, 15, 41]; however, the reported loci differed completely with

Table 4. Loci associated with UACR

rsID	Chr.	Position (Hg19)	Gene	Ref/Alt	Frequency		GWAS meta-analysis	
					8.3kJPN	gnomAD	β	*p* value
rs191954357	1	34847375	*RP4-657M3.2, MIR552*[a]	C/T	–	0.0023	117.946	1.17×10^{-9}
rs61732477	1	113741619	*RP11-389O22.5*	C/T	–	0.0281	57.4107	1.05×10^{-8}
rs77307668	1	146622739	*PRKAB2*	G/A	0.9840	0.9963	−39.8705	3.24×10^{-8}
–	2	74321359	*TET3*	G/A	–	–	−45.6043	5.95×10^{-9}
rs142587251	2	147482206	*RP11-638D14.1*	G/A	–	0.0016	65.7656	4.68×10^{-9}
rs763997494	2	197904396	*ANKRD44*[a]	TGTGTGTGC/T	0.0098	0.0065	136.023	7.59×10^{-9}
rs13115639	4	16569606	*LDB2*	G/A	0.0787	0.0479	18.4621	3.18×10^{-8}
rs10031236	4	190298297	*FRG1*[b,c]	C/T	0.0251	0.1628	29.5671	3.83×10^{-8}
rs1383220102	5	44451469	*FGF10*[a,c]	T/Del	0.0104	0.0021	133.934	2.30×10^{-9}
rs748100735	5	138886722	*AC010378.2*	C/T	0.0132	0.0002	58.0022	2.26×10^{-10}
rs149509413	5	171924465	*AC011407.1*	C/T	0.0111	-	43.1525	2.69×10^{-8}
rs183062876	6	24023427	*RP11-31K13.1, NRSN1*[d]	G/C	-	0.9988	−71.9094	7.61×10^{-9}
-	6	114096716	*MARCKS*[c,d]	CTTTTTTT/Del	-	-	96.0015	7.27×10^{-10}
rs145244410	6	167905133	*TCP10,RP11-351J23.2*[a]	G/C	-	0.9729	−120.117	1.87×10^{-8}
rs76762104	7	26431321	*SNX10*[b,c,a]	G/T	0.9927	0.9734	−100.5	1.70×10^{-11}
-	8	124611215	*KLHL38*[b,c]	AATA…(111 bp)/Del	-	-	58.351	9.75×10^{-10}
rs576217269	10	124430036	*DMBT1, C10orf120*	C/T	-	0.0048	62.9036	3.81×10^{-9}
rs184385689	12	127001150	*RP11-407A16.1*	G/A	-	0.9997	−42.6178	8.87×10^{-9}
-	15	55641464	*RP11-139H15.6*[b]	G/T	-	-	−69.2692	4.00×10^{-10}
rs527994431	16	10685260	*EMP2*[c]	C/T	0.0149	0.00003	39.8073	4.02×10^{-8}
rs73977230	17	10905596	*RP11-963H4.8*	C/T	-	0.0221	64.5706	9.34×10^{-9}
rs569245088	18	2510795	*METTL4*[b]	G/A	-	0.00003	57.0629	4.57×10^{-8}

8.3kJPN 8.3KJPN whole-genome variation panel, *Chr.* chromosome, *gnomAD* gnomAD v2.1.1, *UACR* urine albumin-to-creatinine ratio, *SNP* single nucleotide polymorphism, *GWAS* genome-wide association study

Genomic control correction was applied to each *p* value. *β* values indicate the effect of the Alt allele on the Ref allele. When multiple SNPs within 1 Mbp were significantly associated with UACR, the SNP with the smallest *p* value is listed in the table

[a]Loci were filtered out in DS2 and detected as significant in the results for DS1 only

[b]One or multiple SNPs associated with UACR have been previously reported within 1 Mbp of the locus

[c]The nearest gene name is shown if the SNP with the smallest p value is located in the intergenic region

[d]Loci were filtered out in DS1 and detected as significant in the results for DS2 only

no overlap. There are two possible reasons for this observation: the first is differences in the definition of CKD. In previous reports, CKD was determined based only on the data of eGFR <60 ml/min/1.73 m^2 at one point, whereas in the DS1 of our study, a stricter definition of CKD was used. In other words, CKD was defined as a case with an eGFR of < 60 ml/min/1.73m^2 and/or findings suggestive of renal impairment such as positive urine protein for more than three months. In addition, CKD cases in DS1 primarily included relatively advanced cases. The second is the difference in the data used for imputation. As we performed cross-imputation using international data (1KG phase 3) [24] and Japanese data (3.5 kJPNv2) [25], whereas previous reports imputed the data only using 1KG phase 3, it is possible that the results of the present study may differ. At the same time, the accuracy of imputation was higher in our study than in previous studies.

Of the loci detected herein, *PCMT1* was newly identified, whereas *PCMT1* (chromosome 6, 149–150 Mbp), *SNX10*, and *BRAP* were significantly associated with CKD even when analyzed using different software (REGENIE [29]), which may cause less *p* value inflation, suggesting a strong association. Further investigation of the CKD trait in larger GWASs on Japanese or East Asian populations is therefore warranted.

For the eGFR trait, unlike the CKD trait, approximately half of the loci overlapped with previous reports [13–15] or PheWeb [42], a catalog of summary statistics obtained from large GWAS performed on the Japanese population. This is presumably because the definition of eGFR is common among the studies. Meanwhile, the remaining loci did not overlap, possibly because our cohort (especially DS1) had cases with very low eGFR levels, an entity that is not included in other cohorts.

For the UACR trait, a comparison with previous findings is not meaningful as there has been only one study on this trait in the Japanese population, with significant overlap between its participants and those in this study [43].

Notably, for each of the three traits, some loci were replicated in the GWAS Catalog (https://www.ebi.ac.uk/gwas/,CKD:EFO_0003884,eGFR:EFO_0005208,UACR:EFO_0007778,2022/5/20accessed), which validates our results.

Among the newly detected loci, a locus on *PCMT1* (chromosome 6, 149–150 Mbp) was found to be significantly associated with CKD and eGFR. *PCMT1* encodes protein-L-isoaspartate (D-aspartate) *O*-methyltransferase (PIMT), which catalyzes the repair of abnormal L-isoaspartyl linkages in age-damaged proteins [45]. It is expressed in a variety of organs including the kidney [46].

Variations in *PCMT1* have been reported to be associated with neurological diseases, some types of cancer, and type 1 diabetes mellitus [45, 47–50]. Although the association of *PCMT1* with renal function or CKD risk not been reported to date, given its role in repairing damaged proteins, it is possible that *PCMT1* is involved in the pathogenesis of CKD. Functional analysis of *PCMT1* or PIMT is a topic for future research.

Another locus on *BRAP* (chromosome 12, 112 Mbp) is significantly associated with both CKD and eGFR. Moreover, there were two SNPs in its proximity that were localized to the previously described genes *NAA25* and *ALDH2*. The loci on *NAA25* were previously associated with eGFR in a study of millions of individuals that mainly included Europeans [11]. rs671 on *ALDH2* was significantly associated with kidney function in the present study and a previous study in an East Asian population [13, 51], and several studies have already been conducted to elucidate the mechanism by which *ALDH2* affects kidney function [52]. In our study, although the SNPs on *NAA25* and *ALDH2* were also significant, with p values less than 5.0×10^{-8}, fine mapping showed that only the SNP on *BRAP* was causally associated with the CKD trait. When we performed fine mapping for eGFR, this region had the highest likelihood of having four causal SNPs. The SNP on *BRAP* may be associated with the onset of CKD or relatively large changes in eGFR levels that result in an eGFR <60 ml/min/1.73 m^2, whereas other SNPs in this region may be associated with relatively small changes in eGFR that do not result in an eGFR <60 ml/min/1.73 m^2. The presence of a previously reported SNP in the focused region does not necessarily mean that there are no other causal SNPs in the same region, and careful analysis using fine mapping or other methods may be necessary.

Another locus that shows similar results as previously reported is the locus on *UMOD* (chromosome 16, 20 Mbp). *UMOD* is one of the most outstanding loci associated with eGFR/CKD in the general population because it has a large effect on eGFR and CKD risk that is consistent across different ethnic groups [11, 13, 53–56]. In our study, one SNP (rs77924615) in the intronic region of *PDILT*, which is the neighboring gene of *UMOD*, was significantly associated with eGFR levels. Some SNPs around *PDILT* have been previously reported to be involved in the transcriptional regulation of *UMOD* [11], and it is possible that the present SNP may function in a similar manner. Furthermore, the same SNP (rs77924615) was significantly associated with the level of serum creatinine in another study of 150,266 Japanese individuals (https://pheweb.jp/variant/16:20392332-G-A), which supports the finding that the SNPs detected in this study are related to eGFR. *UMOD-PDILT* may be a genetic factor affecting renal function in various ethnicities, including the Japanese population.

Among the detected loci, rs76762104 on chromosome 7 (located near *SNX10*) was significantly associated with all three traits, CKD, eGFR, and albuminuria. The other three loci on *KIAA2013*, *PCMT1*, and *BRAP* were significantly associated with both CKD and eGFR traits. Another locus on *FRG1* was significantly associated with the CKD trait and the UACR trait. Although half of the loci associated with CKD were common to those associated with eGFR, there were not many shared loci between those associated with UACR and those associated with eGFR or CKD. Thus, UACR and eGFR/CKD may have different genetic backgrounds, in agreement with the results of large-scale trans-ethnic genome-wide meta-analyses. Specifically, 59 loci were significantly associated with the level of UACR in one large-scale genome-wide meta-analysis [12], of which only 18 loci (30.5%) were significantly associated with the level of eGFR in another analysis [11], according to the authors' assessment. Although there are few studies on urinary findings, such studies may be important because they may provide additional insights into kidney function.

For the UACR trait, more loci satisfied the suggestive level ($p < 1 \times 10^{-5}$) than for the CKD or eGFR traits (Fig. 2A–C), possibly because the distribution of UACR is right-skewed and deviates from the normal distribution, resulting in a slight inflation of p values [57]. Some studies used the natural logarithm of UACR in an attempt to normalize the distribution but were unsuccessful; hence, the UACR values were treated as is in this study.

This study has some limitations that warrant discussion. First, the number of participants was relatively small among the GWAS meta-analyses published in recent years because the subjects for the analysis were limited to the Japanese population. We are planning to conduct another such study with a larger number of participants living in East Asia to overcome this limitation. Second, the results were not consistent between DS1 and DS2, which makes interpretation difficult. This may be because the population defined as the case group differed between the two datasets, although Cochran's Q test for heterogeneity did not detect heterogeneity among the two datasets. Compared to the cases in DS2, the cases in DS1 consisted of patients who strictly met the definition of having decreased renal function or findings suggestive of renal dysfunction for more than three months, and who attended university hospitals and had high complication proportions of hypertension and diabetes mellitus. Although data are not available, they are expected to have high proportions of other diseases as well. Third, the effect of the identified loci on renal function was not clarified in this study; thus, it will be necessary to verify the results on a larger scale and elucidate the mechanism by functional analysis in the future.

In conclusion, a GWAS meta-analysis of two Japanese cohorts with 4139 CKD/sCKD cases and 9423 controls revealed 10 significant loci associated with CKD risk. At the same time, the meta-analysis revealed 9 and 22 significant loci associated with eGFR levels and UACR, respectively. Although some of these loci have already been reported, a total of 22 were newly detected in the present analysis (CKD: *KIAA2013*, *MB21D2*, *FRG1*, *PCMT1*, *SNX10*, *TNSF15*, *EXD3*, eGFR: *KIAA2013*, *PCMT1*, UACR: *RP4-657M3.2/MIR52*, *RP11-389O22.5*, *PRKAB2*, *TET3*, *RP11-638D14.1*, *ANKRD44*, *LDB2*, *FGF10*, *AC010378.2*, *AC011407.1*, *RP11-31K13.1/NRSN1*, *MARCKS*, *TCP10/RP11-351J23.2*, *DMBT1/C10orf120*, *RP11-407A16.1*, *EMP2*, *RP11-963H4.8*), suggesting a unique genetic background for CKD risk and the level of eGFR/UACR in the Japanese population. CKD in different ethnic groups may be influenced by different genetic backgrounds as well as common genetic mechanisms. Furthermore, it is possible that the group mainly showing decreased eGFR is genetically different from the group mainly showing increased UACR.

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YS, YH, HN, SK, MY, and NK conceptualized the study. YS, YH, HN, AK, JW, MS, TW, HK, TN, HK, MY, SG, IN, and MN conducted SNP array study in each institution. AN and GT conducted GWAS. MY and NK supervised the study. YS and AN wrote the manuscript and the other authors revised the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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