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Genetic loci influencing kidney function and chronic kidney disease

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Using genome-wide association, we identify common variants at 2p12-p13, 6q26, 17q23 and 19q13 associated with serum creatinine, a marker of kidney function ($P = 10^{-10}$ to 10^{-15}). Of these, rs10206899 (near *NAT8*, 2p12-p13) and rs4805834 (near *SLC7A9*, 19q13) were also associated with chronic kidney disease ($P = 5.0 \times 10^{-5}$ and $P = 3.6 \times 10^{-4}$, respectively). Our findings provide insight into metabolic, solute and drug-transport pathways underlying susceptibility to chronic kidney disease.

In North America and Europe, chronic kidney disease (CKD) affects ~11% of adults. CKD is associated with high morbidity and, in the advanced

stage, requires life-support treatment by renal dialysis or transplantation¹. CKD is also a major risk factor for myocardial infarction and stroke.

CKD is a multifactorial disorder with an important genetic component². A number of monogenic disorders underlying CKD have been identified, though these account for only a small proportion of the total burden of kidney disease. Recent studies have identified common variants at the *UMOD*, *SHROOM3*, *GATM* and *MYH9* loci that are associated with kidney function in European and African-American populations^{2,3}. We carried out both a genome-wide association study and a replication study to identify loci associated with serum creatinine levels. Although creatinine levels may be partially influenced by non-renal factors, including diet and generation from muscle metabolism, serum creatinine is a validated measure of glomerular filtration rate⁴.

Genome-wide association was done in 23,812 participants of European descent from nine studies; characteristics of participants and genotyping arrays used are summarized in the **Supplementary Methods** and in **Supplementary Table 1**. Creatinine levels were transformed by \log_{10} to achieve approximate normality, and SNP associations were tested by linear regression using an additive genetic model adjusted for age and sex. Principal component scores were included as ancestry covariates in regression analyses, and test statistics were corrected for the genomic control inflation factor to adjust for population substructure (**Supplementary Methods**)⁵. Analyses were performed separately in each cohort and were followed by meta-analysis using z scores weighted by the square root of the sample size. Quantile-quantile plots showed good adherence to null expectations ($\lambda = 1.024$; **Supplementary Fig. 1**). Our genome-wide association study had 80% power to detect SNPs associated with 0.14% of population variation in creatinine levels at $P < 5 \times 10^{-7}$.

There were 109 SNPs associated with creatinine at $P < 5 \times 10^{-7}$, which were distributed over five loci (2p12-p13, 4q21, 6q26, 17q23 and 19q13; **Fig. 1** and **Supplementary Fig. 2**). At four of these loci (2p12-p13, 6q26, 17q23 and 19q13), common variants have not previously been reported to be associated with kidney function or CKD; at each locus, we selected the most strongly associated SNP for replication testing with creatinine in a further sample of 16,626 Europeans (**Supplementary Methods** and **Supplementary Table 2**). All four SNPs showed strong replication with creatinine ($P = 2.4 \times 10^{-3}$ to 7.0×10^{-9} ; **Table 1** and **Supplementary Table 3**). At 4q21, the most strongly associated SNP was rs9992101 ($P = 5.9 \times 10^{-9}$), which is located in *SHROOM3* and is in high linkage disequilibrium (LD) with rs17319721 ($r^2 = 0.78$, HapMap CEU population), a SNP previously reported to be associated with glomerular filtration rate².

Next we tested the four top-ranking SNPs for association with estimated glomerular filtration rate (eGFR) and cystatin c (two additional measures of kidney function⁴) and with CKD among the participants from the replication sample (**Supplementary Methods**). rs10206899 (2p12-p13) and rs4805834 (19q13) were associated with eGFR, cystatin c

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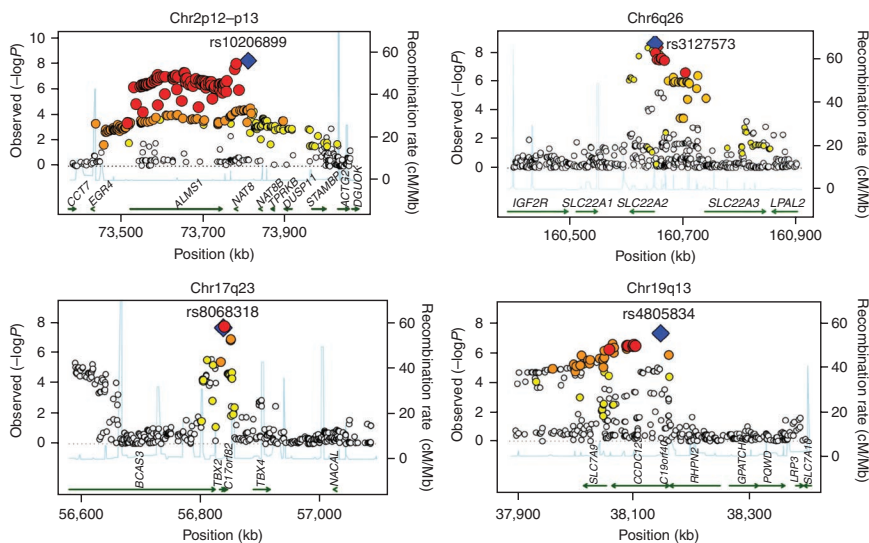


Figure 1 Architecture of the loci associated with creatinine in the genome-wide association study. The most significant SNP in each region is plotted in blue. LD is based on the HapMap CEU sample and is color-coded as red (r^2 to top SNP, 0.8–1.0), orange (0.5–0.8), yellow (0.2–0.5) and white (<0.2).

and CKD (Table 1 and Supplementary Table 4). In contrast, rs3127573 (6q26) and rs8068318 (17q23) were associated with eGFR but not with cystatin c or CKD. None of the four SNPs were associated with weight, hypertension, diabetes or other clinical parameters known to influence creatinine levels (Supplementary Table 5), and the relationships of these SNPs with creatinine were similar among people with and without diabetes or hypertension (Supplementary Table 6).

rs10206899 (2p12–p13), which is associated with creatinine, eGFR, cystatin c and CKD, is near several genes, including *NAT8*, *NAT8B*, *ALMS1*, *DUSP11* and *TPRKB* (Fig. 1). *NAT8* is a biologically compelling candidate for the observed association. *NAT8* is a member of the GCN5-related N-acetyltransferase (GNAT) superfamily, a group of enzymes that catalyze transfer of an acetyl group from acetyl-coenzyme A to a wide range of acceptor substrates⁶. *NAT8* is strongly and almost exclusively expressed in kidney (Supplementary Fig. 3), in particular by tubular cells of the renal cortex (Supplementary Figs. 4 and 5). Acetylation is a key metabolic pathway for the detoxification of nephrotoxic substances such as aminoglycosides, inhalational anesthetics and environmental toxins, including industrial solvents such as trichloroethylene^{7,8}. rs10206899 is in high LD ($r^2 = 1.0$) with the only common nonsynonymous SNP in *NAT8*, rs15358 (causing a A595G change). rs15358 produces a non-conservative amino acid change (F143S) within the acetyl-coenzyme

kinase-binding protein and is of unknown function. Neither is strongly or preferentially expressed in kidney.

rs4805834 (19q13) is near *SLC7A9*, a cationic amino acid transporter highly expressed in kidney tubular cells (Supplementary Fig. 3)¹⁰. *SLC7A9* is a strong candidate for the association of rs4805834 with creatinine, eGFR, cystatin c and CKD; mutations in *SLC7A9* cause cystinuria and nephrolithiasis and are associated with increased risk of CKD¹⁰. rs4805834 is also near *CCDC123* and *C19orf40*. The latter (also known as *FAAP24*) has been identified as a component of the Fanconi anemia core complex, which plays a crucial role in DNA damage response¹¹ but has no reported relationship to kidney function. The function of *CCDC123* is not known.

rs3127573 (6q26) and rs8068318 (17q23) were associated with creatinine and eGFR. rs3127573 is near *SLC22A2*, an organic cation transporter strongly and preferentially expressed in kidney (Supplementary Fig. 3) that contributes to secretion of creatinine and other substrates by renal tubular epithelial cells¹². Common variants at this locus are reported to influence kidney injury caused by nephrotoxic drugs such as cisplatin¹³. rs8068318 is located in *TBX2*, which encodes a member of the highly conserved T-box family of transcription factors¹⁴. Mouse *Tbx2*^{-/-} mutants have a range of morphological defects, including limb deformities and cardiac anomalies, but a renal phenotype has not previously been described for them¹⁴. *Tbx2* is widely expressed in many tissues, including developing and adult

A binding site, an effect predicted to influence acetylation by *NAT8* (Supplementary Fig. 6). rs15358 was also closely associated with creatinine levels in the genome-wide study ($P = 1.8 \times 10^{-8}$). Our findings raise the possibility that common genetic variation in *NAT8* may influence acetylation pathways, disturbances of which are known to be associated with drug- and toxin-induced kidney injury.

NAT8B is highly homologous to *NAT8* and also contains an acetyltransferase domain but is only expressed at low levels in kidney (Supplementary Fig. 3). Mutations in *ALMS1* are responsible for Alström Syndrome, a rare autosomal-recessive multi-system disorder characterized by progressive kidney and hepatic failure, obesity and insulin resistance, and blindness and hearing loss⁹. Although *DUSP11* and *TPRKB* are also near rs10206899, neither has been implicated in kidney function. *DUSP11* is a dual-specificity protein phosphatase; *TPRKB* encodes the p53-related protein-

Table 1 Association results for top-ranking SNPs in the genome-wide association and replication study

SNP	Locus	Alleles	MAF	n	Creatinine						Chronic kidney disease (replication sample)		
					GWA sample		Replication sample		Combined		Odds ratio (95% CI)	P	
					Effect size (95% CI)	P	n	Effect size (95% CI)	P	Effect size (95% CI)			P
rs10206899	2p12–p13	A/G	0.22	23,812	-0.9 (-1.2 to -0.6)	5.9×10^{-9}	16,167	-1.0 (-1.4 to -0.7)	7.0×10^{-9}	-1.0 (-1.2 to -0.7)	1.2×10^{-15}	0.85 (0.79 to 0.92)	5.0×10^{-5}
rs3127573	6q26	A/G	0.13	21,857	1.4 (1.0 to 1.8)	5.0×10^{-9}	16,427	0.7 (0.2 to 1.1)	2.4×10^{-3}	1.1 (0.8 to 1.4)	6.5×10^{-10}	1.07 (0.97 to 1.17)	0.17
rs8068318	17q23	A/G	0.27	23,812	0.9 (0.6 to 1.2)	2.2×10^{-8}	16,350	0.6 (0.2 to 0.9)	6.1×10^{-4}	0.8 (0.6 to 1.0)	3.4×10^{-10}	1.05 (0.98 to 1.13)	0.16
rs4805834	19q13	G/A	0.13	23,812	-1.1 (-1.5 to -0.7)	5.3×10^{-8}	16,241	-0.9 (-1.3 to -0.5)	4.7×10^{-5}	-1.0 (-1.3 to -0.7)	4.5×10^{-11}	0.84 (0.76 to 0.92)	3.6×10^{-4}

Alleles, reference allele/minor allele; MAF, minor allele frequency; GWA, genome-wide association; effect size, % change in serum creatinine (95% CI) or odds ratio for CKD (95% CI) per copy of minor allele under an additive genetic model and adjusted for (i) age, gender and principal component scores in the genome-wide association study and (ii) age and gender in the replication study. Effect sizes were estimated by meta-analysis of cohort-specific beta estimates using the inverse variance method and a fixed effects model.



kidneys¹⁵, but the function of Tbx2 in the kidney is not known. rs8068318 is also near *BCAS3* and hypothetical gene *C17orf82*. *BCAS3* may be involved in angiogenesis, but is not known to be involved in kidney function.

In addition to *SHROOM3*, we also replicated previously reported associations² of rs12917707 in *UMOD* ($P = 1.7 \times 10^{-5}$) and rs2467853 in *GATM* ($P = 6.0 \times 10^{-6}$) with creatinine in the genome-wide association study. Although we did not find a relationship of the *MYH9* locus with creatinine, this may simply reflect the low prevalence (~4%) of the *MYH9* risk haplotype in Europeans (**Supplementary Methods**)³.

Our findings of common genetic variants associated with creatinine, cystatin c and CKD provide insight into the metabolic, solute and drug-transport mechanisms underlying kidney function and CKD. Further evaluation of these pathways may enable biomarker discovery and the development of new strategies to protect kidney function and prevent CKD.

Note: Supplementary information is available on the Nature Genetics website.

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AUTHOR CONTRIBUTIONS

J.C.C., P.E., L.L., J.S., G.N. and J.S.K. designed the study. J.C.C., W.Z., D.A.L. and P.v.d.H. led the data analysis. J.C.C., P.E., L.L., J.S., G.N. and J.S.K. wrote the manuscript, with contributions from all the authors.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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