Supplementary Materials

Multiple Novel Loci are Associated with Indices of Renal Function and Chronic Kidney Disease

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Supplementary Methods

Discovery study samples, phenotypes, and genotyping

Atherosclerosis Risk in Communities Study (ARIC)

From 1987-89, 15,792 mostly Caucasian and African American study participants aged 45-64 years were recruited by probability sampling and underwent the baseline examination (visit 1) and three subsequent examinations scheduled approximately every three years.[1] Participants were excluded from genotyping for non-consent (n=53) or self-reported race other than "black" or "white" (n=47). For this project, genotype data was available for 8,861 white participants. Of these, 734 samples were removed in data cleaning steps for sex mismatch, discordance with previously-genotyped markers, first-degree relative of an included individual, and genetic outlier based on allele sharing[2] and principal components analyses.[3] Finally, individuals were excluded for missing outcome or covariates (n=58).

The ARIC Study used a cumulative CKD case definition to maximize power and reduce misclassification. CKD cases were defined based on eGFRcrea <60 ml/min/1.73m^2 at study visits 1, 2 or 4, when creatinine was measured. Individuals with CKD at an earlier study visit who reverted to being non-cases at a later visit were not counted as cases, unless they also had an ICD code for kidney disease listed on a hospital discharge record or death certificate which were collected from study inception in 1987 to January 1, 2005.[4] Incident CKD was defined as eGFRcrea <60 ml/in/1.73m^2 at study visits 2 or 4 in individuals with eGFRcrea ≥60 ml/in/1.73m^2 at study visit 1, or a kidney-disease specific ICD code on a hospital discharge record or death certificate as detailed previously.[4] The final study sample consisted of 8,069 individuals for the analyses of CKD, and 6,525 and 6,430 for the analyses of eGFR based on serum creatinine (eGFRcrea), and serum cystatin C (eGFRcys). Cross-sectional eGFRcrea and

eGFRcys were analyzed at study visit 4, on average 9 years after baseline, when cystatin C measurements were available, to allow for a direct comparison of eGFRcys and eGFRcrea measures. The difference in the sample size between the analyses for CKD and eGFRcrea therefore result from the different sample sizes at the baseline visit and visit 4. The association of CKD, eGFRcrea, and eGFRcys with the first 10 principle components was tested and not significant. Therefore, only genomic control adjustment was performed to account for population stratification.

In 2007-2008, genomic DNA was hybridized in accordance with the manufacturer's standard recommendations, and genotypes were determined using the Birdseed clustering algorithm. Individual samples were filtered to ensure high genotyping quality as outlined above. More information about selection criteria of SNPs for imputation and the imputation process is provided for all studies in Supplementary Table 1.

Cardiovascular Health Study (CHS)

The original predominantly white CHS cohort of 5,201 persons was recruited in 1989-1990 from random samples of Medicare eligibility lists and an additional 687 African-Americans were enrolled in 1992-93 for a total sample of 5,888. CHS participants completed standardized clinical examinations and questionnaires at study baseline and at nine annual follow-up visits. Details of the study design are summarized elsewhere.[5] A total of 1,908 persons were not genotyped because of prevalent coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack, or lack of available DNA. African American participants were excluded from this analysis of individuals of European ancestry. Individuals were also excluded if they had a call rate ≤95%, sex mismatch or discordance with prior genotyping. Further, individuals were excluded for

missing phenotypes at the baseline examination for a final study sample of 3,278 individuals in analyses of CKD and eGFRcrea, and 2,844 in analyses of eGFRcys. A principle components analysis was performed using the singular value decomposition to determine the first 10 principal components in the CHS population,[6] which were then tested for association with the phenotypes of interest. None of the first ten principal components were associated with CKD or eGFRcrea; therefore, only genomic control adjustment was performed to account for population stratification.

Blood samples were drawn on all participants at their baseline examination. DNA was extracted from blood, and genotyping was attempted in 2007-2008 in 3,397 white participants and was successful in 3,291 persons. More information about selection criteria of SNPs for imputation and the imputation process is provided for all studies in Supplementary Table 1.

The Framingham Heart Study (FHS)

The Framingham Heart Study began in 1948 with the enrollment of the Original Cohort.[7] In 1971, 5,124 participants (the Offspring Cohort) were enrolled into the Framingham Offspring Study; the design and methodology have been previously described.[8, 9] Study subjects consisted of original cohort participants attending examination cycle 15 (1977 to 1979) or cycle 24 (1995 to 1998) [n=2,338] and offspring cohort participants who attended the second examination cycle (1979 - 1983) or cycle 7 (1998-2001) [n=4,182]. Among these 6520 participants, 4140 had complete genotype data available. A variable indicating the cumulative prevalence of CKD was defined for participants with glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 at both the earlier examination cycle (15^{th} for original and 2^{nd} for offspring cohort) and later examination cycle (24^{th} for original and 7^{th} for offspring cohort) or diagnosed at the later examination cycles. The association of CKD with the first 10 principle components estimated from the genotype data

using the Eigenstrat program[3] was tested and not significant. Therefore, only genomic control adjustment was performed to account for population stratification.

Of the total 9,274 individuals that were genotyped in 2007, the following exclusions were made: sample call rate <97% (n=666), genotype heterozygosity greater than 5 standard deviations from the mean or ambiguous family data (n=127), resulting in 8,481 genotyped individuals. More information about selection criteria of SNPs for imputation and the imputation process is provided for all studies in Supplementary Table 1.

The Rotterdam Study (RS)

Participants

10,275 inhabitants of Ommoord, a district of Rotterdam in the Netherlands, who were 55 years or over, were invited to participate in this study of chronic diseases related to aging and 7,983 agreed to participate (78%).[10, 11] The baseline examination (1990-1993) was composed of a home interview and a visit to the research center for blood sampling and examination. Genotyping was conducted in 2007, and genotype data was available for 5,974 participants, subjects were excluded for excess autosomal heterozygosity, mismatch between called and phenotypic gender, or outliers identified by the identity by descent clustering analysis. The final sample for analysis in this study comprised 4,390 subjects with available phenotype and genotype data for the analyses of CKD and eGFRcrea.

Plated DNA was available for 6,680 (93.7%) of 7,129 participants who visited the research center at baseline, clean genotype data was available for 5,974 individuals. More information about selection criteria of SNPs for imputation and the imputation process is provided for all studies in Supplementary Table 1.

Imputation in the discovery samples

Using the Phase II CEU HapMap individuals as a reference panel, genotypes were imputed to a common set of ~2.5 million high-quality HapMap SNPs. Study-specific details on genotyping and imputation are provided in **Supplementary Table 1**. Software used for imputation were BimBam10 v0.95[12] (CHS) and MACH v1.0.15/16 (all others, http://www.sph.umich.edu/csg/abecasis/MACH/); FHS accounted for relatedness of participants. Imputed genotypes were expressed as an allelic dosage, a fractional value between 0-2.

Statistical analyses in the discovery samples

Regression analyses were conducted as described in the Methods section. More specifically, eGFR in FHS was analyzed using linear mixed effects regression modeling to account for within pedigree correlation by using the kinship package in R. Association with CKD in FHS was evaluated using the gee package in R for generalized estimating equations; pedigree correlations were adjusted for using the robust variance option. Analyses in AGES were conducted using the most likely genotype for the imputed SNPs and the software package PLINK.[2] In WGHS, logistic regression analyses of CKD were conducted using R, and linear regression association testing was performed using PLINK. All studies used an additive genetic model.

Power calculations indicate that at a type I error level of $4*10^{-7}$ as used in discovery samples, we had >80% power to detect variants with an odds ratio for CKD of 1.3 and risk allele frequency >34%, or an odds ratio of 1.4 and risk allele frequency >14%.

The proportion of variance explained by the combined genetic loci was calculated in the ARIC Study, the largest individual study contributing data. The contribution of the top SNPs at all loci showing genome-wide significant association with eGFRcrea after replication (*UMOD*, *SHROOM3*, *SPATA5L1/GATM*) to the eGFRcrea variance was evaluated by adding these SNPs

to a regression model adjusting for age, sex, and study center. Similarly, the contribution of SNPs at the *CST*, *STC1*, and *UMOD* loci was evaluated for their contribution to the variance in eGFRcys.

Meta-analysis was conducted using a fixed effects model and inverse-variance weighting as implemented in METAL (http://www.sph.umich.edu/csg/abecasis/Metal/index.html). Regression coefficients were combined across samples; phenotypic harmonization was addressed by calibrating serum creatinine and applying uniform covariate adjustment across the study samples. The genomic control parameter[13] was calculated within each study for each trait to assess potential inflation of the test statistics. If the parameter was larger than 1, an adjustment was performed by scaling the test statistics to the inflation factor. Only SNPs with minor allele frequency (MAF) ≥2% were analyzed based on CKD case numbers, corresponding to approximately 50 carriers of the minor allele with CKD. Statistical heterogeneity was evaluated using Cochrane's chi-square test (Q-test).

External replication study samples, phenotypes, and genotyping

Women's Genome Health Study (WGHS)

The study population derived from the Women's Genome Health Study (WGHS).[14] Briefly, participants in the WGHS include American women from the Women's Health Study (WHS) with no prior history of cardiovascular disease, cancer, or other major chronic illness who also provided a baseline blood sample at the time of study enrollment from which genomic DNA was extracted. The original Women's Health Study was initiated in 1992 to evaluate risks and benefits of aspirin and vitamin E in cardiovascular disease and cancer prevention.[15] Individuals were excluded from analyses for genotyping call rates <98%, discrepancies from comparisons to previously obtained genotypes, and outliers identified by

clustering analyses, resulting in 18,333 individuals with available genotypes. Of these, 18,247 had information on both phenotype and genotype available.

Genotyping was conducted in 2007-2008 using HumanHap300 Duo-Plus chip or the combination of the HumanHap300 Duo and I-Select chips, resulting in a total of 363,808 SNPs. SNP exclusion criteria included SNP call rates <90%, deviation from Hardy-Weinberg equilibrium ($p<10^{-5}$), and SNPs with minor allele frequency <1% in Caucasians, resulting in 340,923 SNPs for analysis.

AGES Reykjavik Study

The Reykjavik Study cohort originally comprised a random sample of men and women born in 1907–1935 and living in Reykjavik in 1967.[16] The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow-up and was examined in all stages. One group was designated a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. A total of 19,381 individuals still alive at the receipt of the study invitation responded, resulting in 71% recruitment rate over the period of 30 years. Between 2002 and 2006, the AGES-Reykjavik Study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study. The AGES Reykjavik Study GWAS was approved by the National Bioethics Committee (00-063-V8+1) and the Data Protection Authority and MedStar IRB for the Intramural Program of the National Institute on Aging.

Samples were genotyped in 2008 using the Illumina 370CNV BeadChip array on 3,664 participants. Samples were excluded from the dataset based on sample failure, genotype mismatch with reference panel, and sex mismatch, resulting in clean genotype data on 3,219 individuals. Standard protocols for working with Illumina data were followed, with clustering

score greater than 0.4. Prior to genotype imputation, SNPs were excluded using filters based on call rate (<97%), Hardy-Weinberg Equilibrium ($p<10^{*-6}$), mishap ($p<10^{*-9}$), and mismatched positions between Illumina, dbSNP and/or HapMap resulting in 325,094 SNPs passing all QC (of 353,202 prior to cleaning steps). Imputation was done using MACH against all the HapMap CEPH haplotypes (release 22/NCBI build 36) resulting in 2,533,153 total SNPs for analysis.

Meta-analysis across discovery and replication samples

Meta-analyses incorporating results from the external replication samples were also conducted using a fixed effects model and inverse-variance weighting.

Additional analyses

The expression of the gene products in human kidney was evaluated using the UCSC Genome Browser (http://genome.ucsc.edu/cgi-bin/hgGateway) and the Gene Expression Atlas (http://expression.gnf.org/cgi-bin/index.cgi). Public databases were searched to evaluate the association between top SNPs and gene expression.[17, 18]

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Supplementary Tables

Supplementary Table 1: Study-specific genotyping and imputation information				
Study	**ARIC**	**CHS**	**FHS**	**Rotterdam**
Array type(s)	Affymetrix 6.0	Illumina 370CNV	Affymetrix 500K, Affymetrix 50K supplemental	Illumina 550K
Genotype calling	Birdseed	Illumina BeadStudio	BRLMM	Illumina Beadstudio
QC filters for genotyped SNPs used for imputation	call rate <95%, MAF<1%, pHWE<10E-5	call rate <97%, heterozygotes=0, pHWE<10E-5, SNP not in HapMap	call rate <95%, pHWE<10E-6	call rate <90%, MAF<1%, pHWE<10E-5
No of SNPs used for imputation	602,642	306,655	503,526	530,683
Imputation	MACH version 1.0.16	BimBam	MACH version 1.0.15	MACH version 1.0.15
Imputation Backbone (NCBI build)	phased CEU haplotypes, HapMap release 21 (build 35)	HapMap CEU release 21A, build 36	phased CEU haplotypes, HapMap release 22 (build 36)	phased CEU haplotypes, HapMap release 22 (build 36)
Filtering of imputed genotypes	none	dosage variance < 0.01	none	none
Data management and statistical analysis	ProbABEL, PLINK, R	R	R, lmekin function in Kinship package for continuous traits and gee function in GEE package for dichotomous traits	ProbABEL, R
Further details on association testing in FHS and in the replication samples are provided in the Supplementary Materials.				

Supplementary Table 2: Characteristics of CKD cases among the discovery cohorts				
	ARIC	**CHS**	**FHS**	**RS**
Number of cases	731	612	445	600
Age, years	63.4 (6.5)	74.3 (6.1)	69.9 (10.4)	77.6 (8.5)
Diabetes	19.3 (141)	13.1 (80)	15.0 (67)	20.0 (120)
Hypertension	68.8 (503)	64.2 (389)	75.3 (335)	46.2 (277)
eGFRcrea, ml/min/1.73m^2, median (IQR)	55.1 (50.2, 57.3)	53.4 (47.7, 58.3)	50.9 (44.6, 55.8)	53.8 (47.8, 57.4)

Information on demographics, hypertension, and diabetes are ascertained at the same visit as CKD. Abbreviations: eGFR: estimated glomerular filtration rate, IQR: interquartile range. Continuous variables are presented as mean (standard deviation), and categorical variables as % (n), unless indicated otherwise.

Supplementary Table 3: Summary of study-specific results from discovery and validation of top GWAS signals at each locus ($p<4*10^{-7}$) for CKD, eGFRcrea, and eGFRcys							
traits	**meta-analysis 6 cohorts**	**ARIC**	**CHS**	**FHS**	**RS**	**AGES**	**WGHS**
rs12917707 in the UMOD region, chr16: 20275191							
CKD							
p-value	2.27*10-12	3.4*10-5	3.9*10-5	0.74	1.4*10-4	1.6*10-6	0.20
OR (95% CI)	0.80 (0.75-0.85)	0.72 (0.61-0.84)	0.68 (0.56-0.82)	0.97 (0.82-1.15)	0.71 (0.59-0.85)	0.68 (0.58-0.79)	0.93 (0.83-1.04)
eGFRcrea							
p-value	5.2*10-16	1.2*10-5	5.3*10-7	0.37	3.1*10-6	4.0*10-10	0.004
beta (se)	0.018 (0.002)	0.022 (0.005)	0.044 (0.009)	-0.007 (0.007)	0.028 (0.006)	0.055 (0.009)	0.009 (0.003)
eGFRcys*							
p-value	2.0*10-7	3.8*10-4	9.2*10-6	0.21	NA	NA	NA
beta (se)	0.021 (0.004)	0.022 (0.006)	0.034 (0.008)	0.008 (0.007)	NA	NA	NA
rs6040055 in JAG1, chr20:10581313							
CKD							
p-value	0.006	1.4-*10-5	0.02	0.83	0.012	0.38	0.54
OR (95% CI)	1.07 (1.02-1.13)	1.37 (1.19-1.57)	1.17 (1.03-1.33)	1.02 (0.84-1.25)	1.20 (1.04-1.37)	0.95 (0.84-1.07)	0.97 (0.89-1.06)
eGFRcrea							
p-value	0.006	1.1*10-5	6.4*10-3	0.25	5.8*10-3	0.24	0.40
beta (se)	-0.005 (0.002)	-0.021 (0.005)	-0.019 (0.007)	-0.009 (0.008)	-0.013 (0.005)	0.009 (0.007)	0.002 (0.003)
eGFRcys*							
p-value	4.0*10-6	8.0*10-4	2.0*10-3	0.20	NA	NA	NA
beta (se)	-0.017 (0.004)	-0.020 (0.006)	-0.020 (0.006)	-0.010 (0.008)	NA	NA	NA
rs17319721 in SHROOM3, chr4:77587871							
CKD							
p-value	0.057	0.12	0.58	0.16	0.14	0.99	0.44
OR (95% CI)	1.05 (1.00-1.10)	1.09 (0.98-1.22)	0.96 (0.82-1.11)	1.11 (0.96-1.29)	1.10 (0.97-1.26)	1.0 (0.89-1.12)	1.04 (0.95-1.13)

eGFRcrea							
p-value	1.2*10-12	2.7*10-4	0.25	0.11	3.2*10-4	0.13	8.9*10-6
beta (se)	-0.012 (0.002)	-0.014 (0.004)	-0.009 (0.008)	-0.009 (0.006)	-0.017 (0.005)	-0.011 (0.007)	-0.011 (0.002)
eGFRcys*							
p-value	4.2*10-5	7.6*10-3	0.022	0.027	NA	NA	NA
beta (se)	-0.013 (0.003)	-0.012 (0.005)	-0.016 (0.007)	-0.012 (0.005)	NA	NA	NA
rs1731274 upstream of STC1, chr8:23822264							
CKD							
p-value	6.0*10-2	0.95	0.45	0.02	0.37	0.59	0.45
OR (95% CI)	1.05 (1.00-1.10)	1.00 (0.89-1.12)	1.05 (0.92-1.21)	1.22 (1.03-1.44)	1.06 (0.93-1.22)	1.03 (0.92-1.16)	1.03 (0.95-1.13)
eGFRcrea							
p-value	2.21*10-7	0.072	0.047	8.8*10-5	0.57	0.088	0.002
beta (se)	-0.009 (0.002)	-0.007 (0.004)	-0.014 (0.007)	-0.023 (0.006)	-0.003 (0.005)	-0.012 (0.007)	-0.008 (0.002)
eGFRcys*							
p-value	4.6*10-8	4.2*10-3	8.9*10-5	2.0*10-3	NA	NA	NA
beta (se)	-0.017 (0.003)	-0.013 (0.005)	-0.026 (0.007)	-0.017 (0.005)	NA	NA	NA
rs2467853 in SPATA5L1, chr15:43486085							
CKD							
p-value	7.6*10-8	0.14	0.003	0.07	0.25	0.0004	0.017
OR (95% CI)	1.14 (1.09-1.20)	1.09 (0.97-1.22)	1.23 (1.07-1.41)	1.15 (0.99-1.34)	1.08 (0.95-1.24)	1.24 (1.10-1.40)	1.11 (1.02-1.21)
eGFRcrea							
p-value	6.2*10-14	3.0*10-5	3.3*10-1	9.3*10-2	9.3*10-3	2.1*10-3	2.4*10-6
beta (se)	-0.013 (0.002)	-0.016 (0.004)	-0.007 (0.008)	-0.010 (0.006)	-0.012 (0.005)	-0.022 (0.007)	-0.012 (0.003)
eGFRcys*							
p-value	0.95	0.69	0.71	0.36	NA	NA	NA
beta (se)	0.000 (0.003)	-0.002 (0.005)	-0.003 (0.007)	0.005 (0.006)	NA	NA	NA
rs13038305 close to CST3, chr20:23558262							
CKD							
p-value	0.18	0.11	0.29	0.49	0.60	NA	NA
OR (95% CI)	0.94 (0.87-1.03)	0.89 (0.77-1.03)	0.91 (0.76-1.09)	1.07 (0.89-1.29)	0.96 (0.82-1.13)	NA	NA

eGFRcrea							
p-value	0.22	0.53	0.42	0.38	0.71	NA	NA
beta (se)	0.004 (0.003)	0.003 (0.005)	0.007 (0.009)	0.006 (0.007)	0.002 (0.006)	NA	NA
eGFRcys*							
p-value	2.2*10-88	1.7*10-48	1.6*10-18	9.6*10-26	NA	NA	NA
beta (se)	0.076 (0.004)	0.082 (0.006)	0.074 (0.008)	0.068 (0.007)	NA	NA	NA

In each study, results were adjusted for age, sex, and cohort/study center if applicable. For eGFR, betas indicate the change in eGFR per minor allele for the natural logarithmic transformation of eGFR. eGFRcys*: no external validation was available for eGFRcys as AGES and WGHS had no cystatin C measurements available. SNPs with proxies in the WGHS (proxy/r2 to CHARGE SNP): rs12917707 (rs4293393/1), rs17319721 (rs4859682/0.87), rs1731274 (rs1705699/0.97), rs2467853 (rs1153860/1). Genomic position based on Build 36.2, hg18.

Supplementary Table 4: SNPs associated with CKD at p<4*10E-7 in 19,877 CHARGE participants (2,388 cases)

SNP	chr	position	gene	genes within 60 kb	modeled allele	beta	s.e.	p value	n
rs12917707	16	20275191		FLJ20581;UMOD;GP2;PDILT	t	-0.270	0.045	2.85E-09	19,877
rs12922822	16	20275146		FLJ20581;UMOD;GP2;PDILT	t	-0.268	0.045	3.12E-09	19,877
rs13333226	16	20273155		FLJ20581;UMOD;GP2;PDILT	a	0.261	0.045	5.02E-09	19,877
rs4293393	16	20272089		FLJ20581;UMOD;GP2;PDILT	a	0.259	0.045	5.49E-09	19,877
rs13329952	16	20274008		FLJ20581;UMOD;GP2;PDILT	t	0.259	0.045	7.22E-09	19,877
rs9928936	16	20260550	UMOD	UMOD;GP2;PDILT	a	-0.255	0.045	1.19E-08	19,877
rs13335818	16	20267332	UMOD	UMOD;GP2;PDILT	t	-0.254	0.045	1.37E-08	19,877
rs9928757	16	20260364	UMOD	UMOD;GP2;PDILT	c	-0.229	0.044	2.06E-07	19,877

Summary statistics for the minor allele frequencies are removed to ensure anonymity of participants. Genomic position based on Build 36.2, hg18; gene annotations based on RefSeq Genes from the UCSC Genome (Build 36.2) hg18 tracks.

Supplementary Table 5: SNPs associated with eGFRcrea at p<4*10E^{-7} in 18,127 CHARGE participants

SNP	chr	position	gene	genes within 60 kb	modeled allele	beta	s.e.	p value	n
rs12917707	16	20275191		FLJ20581;UMOD;GP2;PDILT	t	0.022	0.003	2.99E-11	18127
rs12922822	16	20275146		FLJ20581;UMOD;GP2;PDILT	t	0.021	0.003	3.28E-11	18127
rs4293393	16	20272089		FLJ20581;UMOD;GP2;PDILT	a	-0.021	0.003	4.88E-11	18127
rs13329952	16	20274008		FLJ20581;UMOD;GP2;PDILT	t	-0.021	0.003	5.02E-11	18127
rs13333226	16	20273155		FLJ20581;UMOD;GP2;PDILT	a	-0.021	0.003	5.49E-11	18127
rs13335818	16	20267332	UMOD	UMOD;GP2;PDILT	t	0.020	0.003	1.63E-10	18127
rs9928936	16	20260550	UMOD	UMOD;GP2;PDILT	a	0.020	0.003	1.98E-10	18127
rs9928757	16	20260364	UMOD	UMOD;GP2;PDILT	c	0.019	0.003	1.39E-09	18127
rs6040055	20	10581313	JAG1	JAG1;C20orf94	t	-0.017	0.003	1.01E-08	18127
rs17319721	4	77587871	SHROOM3	FLJ25770;SHROOM3	a	-0.014	0.003	9.68E-08	18127
rs1398018	4	77591947	SHROOM3	FLJ25770;SHROOM3	t	0.013	0.003	1.03E-07	18127
rs1398016	4	77586712	SHROOM3	FLJ25770;SHROOM3	a	-0.013	0.003	1.26E-07	18127
rs17253722	4	77586311	SHROOM3	FLJ25770;SHROOM3	a	-0.013	0.003	1.30E-07	18127
rs4859682	4	77629342	SHROOM3	SHROOM3	a	-0.013	0.003	3.01E-07	18127
rs2467853	15	43486085	SPATA5L1	C15orf48;SPATA5L1;GATM	t	0.013	0.003	3.40E-07	18127
rs2453533	15	43428517		SPATA5L1;GATM	a	-0.013	0.003	3.58E-07	18127
rs2467862	15	43431135		SPATA5L1;GATM	t	0.013	0.003	3.67E-07	18127
rs1153849	15	43482987	SPATA5L1	C15orf48;SPATA5L1;GATM	a	-0.014	0.003	3.67E-07	18127
rs12440038	15	43494031	SPATA5L1	SPATA5L1;C15orf48;GATM	a	0.014	0.003	3.69E-07	18127
rs1365610	15	43481902	SPATA5L1	C15orf48;SPATA5L1;GATM	t	-0.014	0.003	3.71E-07	18127
rs1346267	15	43478281		C15orf48;SPATA5L1;GATM	t	0.013	0.003	3.79E-07	18127
rs3809472	15	43481610		C15orf48;SPATA5L1;GATM	t	-0.014	0.003	3.86E-07	18127
rs2461700	15	43427919		SPATA5L1;GATM	t	0.013	0.003	3.92E-07	18127
rs1426932	15	43474548		SPATA5L1;C15orf48;GATM	t	0.013	0.003	3.93E-07	18127

Summary statistics for the minor allele frequencies are removed to ensure anonymity of participants. Genomic position based on Build 36.2, hg18; gene annotations based on RefSeq Genes from the UCSC Genome (Build 36.2) hg18 tracks.

Supplementary Table 6: SNPs associated with eGFRcys at p<4*10E-7 in 12,266 CHARGE participants

SNP	chr	position	gene	genes within 60 kb	modeled allele	beta	s.e.	p value	n
rs13038305	20	23558262		CST3;CST4;CST9	t	0.076	0.004	2.17E-88	12,266
rs6048956	20	23557301		CST3;CST9L;CST4;CST9	t	0.076	0.004	2.51E-88	12,266
rs911119	20	23560737		CST3;CST4;CST9	t	-0.076	0.004	2.76E-88	12,266
rs6036478	20	23559359		CST3;CST4;CST9	a	0.076	0.004	2.91E-88	12,266
rs1010117	20	23556421		CST3;CST9L;CST4;CST9	c	0.076	0.004	3.17E-88	12,266
rs3827143	20	23567617		CST3;CST4;CST9	a	-0.077	0.004	5.89E-88	12,266
rs2424582	20	23570550		CST3;CST4;CST9	a	-0.077	0.004	5.78E-87	12,266
rs6036465	20	23536003		CST3;CST9L;CST9	t	0.072	0.004	6.00E-87	12,266
rs8116859	20	23538703		CST3;CST9L;CST9	a	-0.073	0.004	6.26E-87	12,266
rs6048929	20	23536855		CST3;CST9L;CST9	t	-0.072	0.004	6.92E-87	12,266
rs6048930	20	23540492		CST3;CST9L;CST9	t	-0.073	0.004	7.67E-87	12,266
rs17751897	20	23540714		CST3;CST9L;CST9	t	-0.073	0.004	8.76E-87	12,266
rs6048952	20	23555257		CST3;CST9L;CST4;CST9	a	-0.074	0.004	8.79E-87	12,266
rs6114201	20	23555231		CST3;CST9L;CST4;CST9	a	0.073	0.004	9.66E-87	12,266
rs12625716	20	23554845		CST3;CST9L;CST4;CST9	a	0.073	0.004	1.01E-86	12,266
rs7265178	20	23551382		CST3;CST9L;CST9	c	-0.073	0.004	1.08E-86	12,266
rs13043266	20	23536127		CST3;CST9L;CST9	t	0.073	0.004	1.11E-86	12,266
rs6036474	20	23552414		CST3;CST9L;CST9	a	0.073	0.004	1.11E-86	12,266
rs8121283	20	23553002		CST3;CST9L;CST9	c	0.073	0.004	1.13E-86	12,266
rs1011226	20	23553833		CST3;CST9L;CST9	a	-0.073	0.004	1.18E-86	12,266
rs6048928	20	23533988	CST9	CST3;CST9L;CST9	t	-0.073	0.004	1.27E-86	12,266
rs13038337	20	23547918		CST3;CST9L;CST9	t	-0.073	0.004	1.29E-86	12,266
rs6048945	20	23550228		CST3;CST9L;CST9	t	0.074	0.004	1.66E-86	12,266
rs8114619	20	23549813		CST3;CST9L;CST9	t	0.074	0.004	1.66E-86	12,266
rs6048946	20	23550307		CST3;CST9L;CST9	t	0.074	0.004	1.66E-86	12,266
rs8121147	20	23549708		CST3;CST9L;CST9	t	-0.074	0.004	1.69E-86	12,266

rs4815224	20	23542112		CST3;CST9L;CST9	c	0.074	0.004	1.70E-86	12,266
rs6048933	20	23543637		CST3;CST9L;CST9	t	-0.074	0.004	1.72E-86	12,266
rs13043610	20	23534941		CST3;CST9L;CST9	a	0.073	0.004	3.15E-86	12,266
rs6114208	20	23569734		CST3;CST4;CST9	c	-0.077	0.004	4.22E-86	12,266
rs13037490	20	23531725	CST9	CST3;CST9L;CST9	t	-0.073	0.004	5.13E-86	12,266
rs3004145	20	23530876		CST3;CST9L;CST9	c	0.071	0.004	1.81E-85	12,266
rs6515375	20	23558841		CST3;CST4;CST9	a	0.078	0.004	8.24E-85	12,266
rs6048926	20	23528987		CST3;CST9L;CST9	a	0.071	0.004	8.66E-85	12,266
rs2208289	20	23527526		CST3;CST9L;CST9	a	0.071	0.004	1.34E-84	12,266
rs6048924	20	23526996		CST3;CST9L;CST9	a	0.071	0.004	3.00E-84	12,266
rs6036463	20	23526940		CST3;CST9L;CST9	a	0.071	0.004	4.87E-84	12,266
rs3004139	20	23526674		CST9;CST3;CST9L	t	-0.071	0.004	5.36E-84	12,266
rs4815223	20	23525112		CST3;CST9L;CST9	a	0.071	0.004	6.39E-84	12,266
rs6036461	20	23524754		CST3;CST9L;CST9	c	0.071	0.004	6.94E-84	12,266
rs4815222	20	23524964		CST3;CST9L;CST9	a	0.071	0.004	7.07E-84	12,266
rs12710327	20	23517689		CST3;CST9L;CST9	t	0.071	0.004	7.09E-84	12,266
rs6048920	20	23524844		CST3;CST9L;CST9	t	-0.071	0.004	7.52E-84	12,266
rs1158167	20	23526189		CST3;CST9L;CST9	a	-0.070	0.004	9.08E-84	12,266
rs4346460	20	23517400		CST3;CST9L;CST9	t	0.071	0.004	1.07E-83	12,266
rs2405392	20	23517186		CST3;CST9L;CST9	t	0.071	0.004	1.13E-83	12,266
rs6048923	20	23526206		CST3;CST9L;CST9	t	0.072	0.004	2.01E-83	12,266
rs6036476	20	23558308		CST3;CST4;CST9	c	-0.074	0.004	1.98E-77	12,266
rs6114214	20	23575924		CST3;CST4;CST9	a	-0.073	0.004	6.62E-66	12,266
rs13037020	20	23577222		CST3;CST4;CST9	t	-0.070	0.004	7.43E-66	12,266
rs13039144	20	23581755		CST3;CST4;CST9	a	-0.072	0.004	7.54E-66	12,266
rs2145231	20	23573547		CST3;CST4;CST9	a	0.070	0.004	3.55E-65	12,266
rs2424591	20	23585093		CST3;CST4;CST9	t	-0.061	0.004	1.98E-46	12,266
rs2424590	20	23584980		CST3;CST4;CST9	t	-0.061	0.004	3.01E-46	12,266
rs3810575	20	23531392	CST9	CST3;CST9L;CST9	a	0.066	0.005	1.55E-41	5,836

rs2983608	20	23590839		CST3;CST4;CST9	t	-0.051	0.004	1.12E-39	12,266
rs3004153	20	23590458		CST3;CST4;CST9	a	0.050	0.004	1.23E-39	12,266
rs8184852	20	23591460		CST3;CST4;CST9	a	0.050	0.004	1.35E-39	12,266
rs3004154	20	23591605		CST3;CST4;CST9	a	0.050	0.004	2.03E-39	12,266
rs2424598	20	23596032		CST3;CST4	a	-0.050	0.004	8.61E-39	12,266
rs1884861	20	23595482		CST3;CST4	c	-0.050	0.004	8.71E-39	12,266
rs2226058	20	23620147		CST1;CST3;CST4	a	0.069	0.005	2.42E-38	12,266
rs726217	20	23532116	CST9	CST3;CST9L;CST9	a	-0.036	0.003	4.58E-31	12,266
rs2983640	20	23534360	CST9	CST3;CST9L;CST9	a	-0.036	0.003	5.65E-31	12,266
rs2983636	20	23530023		CST3;CST9L;CST9	a	-0.036	0.003	1.53E-30	12,266
rs2093145	20	23527283		CST3;CST9L;CST9	t	0.036	0.003	2.71E-30	12,266
rs2983644	20	23540966		CST3;CST9L;CST9	a	-0.036	0.003	6.07E-30	12,266
rs2424577	20	23561750		CST3;CST4;CST9	a	-0.037	0.003	6.07E-30	12,266
rs2424576	20	23558881		CST3;CST4;CST9	t	-0.037	0.003	6.44E-30	12,266
rs2424574	20	23556980		CST3;CST9L;CST4;CST9	t	-0.037	0.003	7.03E-30	12,266
rs2104006	20	23555874		CST3;CST9L;CST4;CST9	t	0.036	0.003	8.42E-30	12,266
rs911122	20	23573746		CST3;CST4;CST9	a	-0.032	0.003	3.19E-25	12,266
rs4611705	20	23688147		CST1	a	-0.062	0.006	3.81E-25	12,266
rs8123349	20	23584830		CST3;CST4;CST9	a	0.051	0.005	8.73E-25	12,266
rs2180663	20	23581617		CST3;CST4;CST9	c	-0.033	0.003	9.60E-25	12,266
rs16985615	20	23590427		CST3;CST4;CST9	t	0.050	0.005	2.97E-24	12,266
rs8117359	20	23593826		CST3;CST4;CST9	c	0.050	0.005	3.89E-24	12,266
rs4815205	20	23465989		CST9L;CST8	a	-0.050	0.006	4.58E-20	12,266
rs3761285	20	23618480		CST1;CST3;CST4	t	0.042	0.005	1.17E-19	12,266
rs11907623	20	23436080		CST9L;CST8;CST11	t	0.048	0.005	5.62E-19	12,266
rs11907129	20	23435731		CST9L;CST8;CST11	a	-0.048	0.005	5.69E-19	12,266
rs6048998	20	23621915		CST1;CST3;CST4	a	0.033	0.004	5.52E-18	12,266
rs6049003	20	23625829		CST1;CST3;CST4	t	-0.031	0.004	1.31E-17	12,266
rs2224219	20	23422808	CST8	CSTL1;CST8;CST11	t	0.043	0.005	9.63E-16	12,266

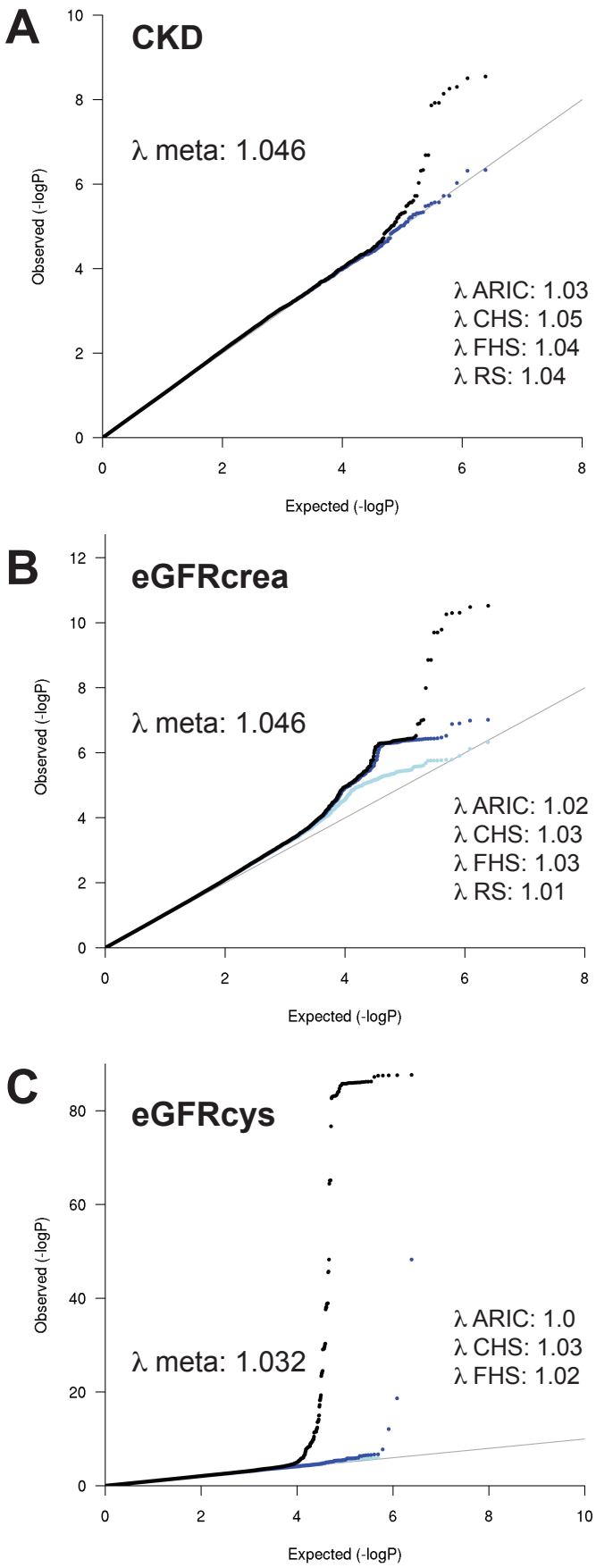
rs2273378	20	23424389	CST8	CSTL1;CST8;CST11	a	-0.043	0.005	9.97E-16	12,266
rs7264999	20	23621897		CST1;CST3;CST4	a	-0.039	0.005	7.16E-15	12,266
rs7271100	20	23624624		CST1;CST3;CST4	a	-0.038	0.005	1.34E-14	12,266
rs6515382	20	23628056		CST1;CST4	a	-0.038	0.005	1.97E-14	12,266
rs7270028	20	23629073		CST1;CST4	a	-0.038	0.005	1.98E-14	12,266
rs7263120	20	23638021		CST1;CST4	t	-0.038	0.005	2.52E-14	12,266
rs7263473	20	23638467		CST1;CST4	a	-0.039	0.005	2.63E-14	12,266
rs2424592	20	23586021		CST3;CST4;CST9	t	-0.025	0.003	3.62E-13	12,266
rs8123755	20	23630133		CST1;CST4	a	0.035	0.005	5.61E-13	12,266
rs2424596	20	23593518		CST3;CST4;CST9	a	-0.025	0.003	7.92E-13	12,266
rs13041159	20	23657627		CST1;CST4	a	0.038	0.005	1.06E-12	12,266
rs8121173	20	23674948		CST1;CST4	t	0.038	0.005	2.91E-12	12,266
rs8114437	20	23674888		CST1;CST4	t	-0.038	0.005	2.92E-12	12,266
rs238668	20	23438123		CST9L;CST8;CST11	a	0.021	0.003	2.93E-12	12,266
rs2983303	20	23437197		CST9L;CST8;CST11	t	0.021	0.003	2.96E-12	12,266
rs2983302	20	23436418		CST9L;CST8;CST11	t	0.021	0.003	3.05E-12	12,266
rs8115789	20	23675039		CST1;CST4	t	-0.038	0.005	3.16E-12	12,266
rs8115901	20	23675241		CST1;CST4	t	-0.038	0.006	3.41E-12	12,266
rs8115868	20	23675291		CST1;CST4	a	0.038	0.006	3.61E-12	12,266
rs4331584	20	23675735		CST1;CST4	a	-0.038	0.006	3.72E-12	12,266
rs3004118	20	23435503		CST9L;CST8;CST11	t	-0.021	0.003	3.75E-12	12,266
rs6138058	20	23694203		CST2;CST1	a	-0.025	0.004	4.92E-12	12,266
rs6036492	20	23650171		CST1;CST4	a	0.021	0.003	3.44E-11	12,266
rs3004119	20	23437678		CST9L;CST8;CST11	t	-0.020	0.003	5.89E-11	12,266
rs6106691	20	23543741		CST3;CST9L;CST9	a	-0.026	0.004	1.22E-10	12,266
rs6036464	20	23531023		CST3;CST9L;CST9	t	-0.026	0.004	1.44E-10	12,266
rs6106689	20	23539463		CST3;CST9L;CST9	a	-0.026	0.004	1.49E-10	12,266
rs10485646	20	23540543		CST3;CST9L;CST9	t	-0.026	0.004	1.51E-10	12,266
rs2983641	20	23534977		CST3;CST9L;CST9	t	-0.026	0.004	1.65E-10	12,266

rs6048927	20	23529234		CST3;CST9L;CST9	a	0.026	0.004	1.66E-10	12,266
rs2983639	20	23534184	CST9	CST3;CST9L;CST9	t	-0.026	0.004	2.38E-10	12,266
rs11907773	20	23642711		CST1;CST4	t	-0.028	0.005	4.06E-10	12,266
rs11907747	20	23642762		CST1;CST4	t	-0.028	0.005	4.17E-10	12,266
rs6114234	20	23640725		CST1;CST4	a	-0.021	0.003	4.19E-10	12,266
rs6114235	20	23640973		CST1;CST4	a	0.020	0.003	4.37E-10	12,266
rs13044242	20	23647253		CST1;CST4	c	-0.028	0.005	4.52E-10	12,266
rs7266357	20	23648824		CST1;CST4	t	0.028	0.005	4.99E-10	12,266
rs4378870	20	23647433		CST1;CST4	a	0.028	0.005	5.76E-10	12,266
rs2424599	20	23597463		CST3;CST4	t	0.025	0.004	6.29E-10	12,266
rs947010	20	23626890		CST1;CST4	a	0.019	0.003	8.51E-10	12,266
rs6049010	20	23640919		CST1;CST4	t	0.020	0.003	1.00E-09	12,266
rs6114230	20	23633804		CST1;CST4	a	0.019	0.003	1.00E-09	12,266
rs6076119	20	23643459		CST1;CST4	a	0.020	0.003	1.03E-09	12,266
rs6114237	20	23647223		CST1;CST4	a	0.020	0.003	1.07E-09	12,266
rs6049097	20	23701552		CST2;CST1	t	0.020	0.003	1.35E-09	12,266
rs6114275	20	23701925		CST2;CST1	a	0.023	0.004	3.30E-09	12,266
rs6048991	20	23614934	CST4	CST3;CST4	t	-0.026	0.004	3.71E-09	12,266
rs6106719	20	23725924		CST2;CST1	a	-0.022	0.004	3.77E-09	12,266
rs6132653	20	23652288		CST1;CST4	a	0.019	0.003	4.07E-09	12,266
rs4328700	20	23657545		CST1;CST4	a	-0.019	0.003	4.07E-09	12,266
rs3004126	20	23472229		CST9L;CST9;CST8	a	-0.026	0.004	4.13E-09	12,266
rs6114319	20	23753520	CST2	CST2;CST5	c	-0.023	0.004	4.42E-09	12,266
rs6138046	20	23652388		CST1;CST4	c	0.019	0.003	4.51E-09	12,266
rs6114303	20	23738008		CST2;CST1	t	-0.022	0.004	4.70E-09	12,266
rs6114308	20	23740498		CST2	c	-0.022	0.004	5.03E-09	12,266
rs6106724	20	23744154		CST2	t	0.022	0.004	5.14E-09	12,266
rs6114318	20	23751966		CST2;CST5	a	0.022	0.004	5.34E-09	12,266
rs6048993	20	23615657	CST4	CST3;CST4	a	0.026	0.004	5.49E-09	12,266

rs8119679	20	23670593		CST1;CST4	a	0.027	0.005	5.98E-09	12,266
rs8124057	20	23667928		CST1;CST4	c	0.027	0.005	6.71E-09	12,266
rs6114273	20	23699715		CST2;CST1	a	0.022	0.004	7.66E-09	12,266
rs10854252	20	23617305	CST4	CST1;CST3;CST4	c	0.026	0.004	7.85E-09	12,266
rs12329441	20	23698897		CST2;CST1	a	0.022	0.004	7.98E-09	12,266
rs3004148	20	23541829		CST3;CST9L;CST9	t	0.023	0.004	8.15E-09	12,266
rs6138047	20	23655717		CST1;CST4	t	0.018	0.003	9.66E-09	12,266
rs6138054	20	23670020		CST1;CST4	a	0.018	0.003	9.81E-09	12,266
rs6049048	20	23670319		CST1;CST4	t	-0.018	0.003	9.87E-09	12,266
rs6049064	20	23675145		CST1;CST4	t	0.019	0.003	1.04E-08	12,266
rs4375938	20	23697636		CST2;CST1	a	0.022	0.004	1.09E-08	12,266
rs6049065	20	23675254		CST1;CST4	t	0.019	0.003	1.15E-08	12,266
rs6049062	20	23674957		CST1;CST4	t	0.018	0.003	1.29E-08	12,266
rs3761286	20	23619740		CST1;CST3;CST4	a	-0.025	0.005	1.44E-08	12,266
rs4303784	20	23662820		CST1;CST4	t	-0.018	0.003	1.62E-08	12,266
rs7273134	20	23678479	CST1	CST1	c	0.019	0.003	1.64E-08	12,266
rs6114315	20	23750073		CST2;CST5	t	0.022	0.004	3.64E-08	12,266
rs1731274	8	23822264		STC1	a	0.017	0.003	4.64E-08	12,266
rs2983544	20	23849446		CST5	a	-0.062	0.011	4.77E-08	12,266
rs819196	8	23798666		STC1	a	0.017	0.003	7.18E-08	12,266
rs1705699	8	23837398			t	0.017	0.003	9.73E-08	12,266
rs6083269	20	23733807		CST2;CST1	a	-0.017	0.003	1.43E-07	12,266
rs12917707	16	20275191		FLJ20581;UMOD;GP2;PDILT	t	0.021	0.004	2.00E-07	12,266
rs12922822	16	20275146		FLJ20581;UMOD;GP2;PDILT	t	0.021	0.004	2.09E-07	12,266
rs13333226	16	20273155		FLJ20581;UMOD;GP2;PDILT	a	-0.020	0.004	2.60E-07	12,266
rs4871907	8	23842729			a	0.017	0.003	2.71E-07	12,266
rs4293393	16	20272089		FLJ20581;UMOD;GP2;PDILT	a	-0.020	0.004	2.85E-07	12,266
rs13329952	16	20274008		FLJ20581;UMOD;GP2;PDILT	t	-0.020	0.004	3.04E-07	12,266
rs13036932	20	23586306		CST3;CST4;CST9	t	0.036	0.007	3.49E-07	12,266

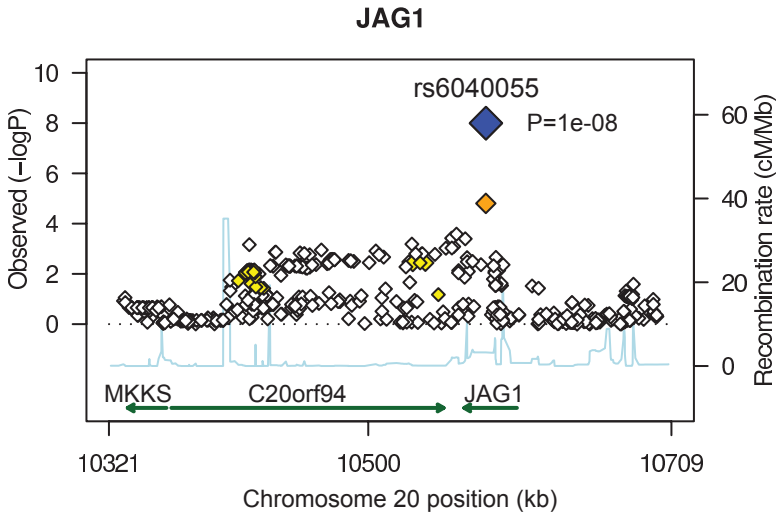
rs13040731	20	23590389		CST3;CST4;CST9	t	-0.036	0.007	3.57E-07	12,266
rs13335818	16	20267332	UMOD	UMOD;GP2;PDILT	t	0.020	0.004	3.64E-07	12,266
Summary statistics for the minor allele frequencies are removed to ensure anonymity of participants. Genomic position based on Build 36.2, hg18; gene annotations based on RefSeq Genes from the UCSC Genome (Build 36.2) hg18 tracks.									

Supplementary Figure 1: Quantile-Quantile Plots of expected vs. observed -log10(P-value) for CKD (A), eGFRcrea (B), and eGFRcys (C) in the discovery samples.



Genomic control factors (λ) were calculated within study and after meta-analysis. Color coding: black: all SNPs, dark blue: after removal of associations with p<5*10-8, light blue: after removal of associations with p<4*10-7.

Supplementary Figure 2: Genetic architecture of the genome-wide significant susceptibility locus for eGFRcrea in the *JAG1* region in the discovery samples.



(–$\log_{10}$ P-values) are plotted versus genomic position (Build 36).
The most significant SNP in the region is plotted in blue. LD based on the HapMap CEU sample is color-coded: red (r2 to top SNP 0.8-1.0), orange (0.5-0.8), yellow (0.2-0.5), and white (<0.2). Gene annotations are based on Build 36 and arrows present direction of transcription.