A Genome-Wide Association Study to Identify Single Nucleotide Polymorphisms for Acute Kidney Injury

Bixiao Zhao, Qiongshi Lu, Yuwei Cheng, Justin M. Belcher, Edward D. Siew, David E. Leaf, Simon C. Body, Amanda A. Fox, Sushrut W. Waikar, Charles D. Collard, Heather Thiessen-Philbrook, T. Alp Ikizler, Lorraine B. Ware, Charles L. Edelstein, Amit X. Garg, Murim Choi, Jennifer A. Schaub, Hongyu Zhao, Richard P. Lifton, Chirag R. Parikh for the TRIBE-AKI Consortium

ONLINE DATA SUPPLEMENT

Supplementary Methods

AKI discovery case-control populations

The TRIBE population included adult patients undergoing cardiac surgery who were recruited from six North American medical centers (S1). AKI cases consisted of patients with a > 0.3 mg/dL or ≥ 50% increase in serum creatinine for at least 2 consecutive days after surgery compared to their pre-operative levels. Using these criteria results in fewer false positive cases compared to currently accepted standards (S2). The elevation for at least 2 days was included to minimize enrollment of patients whose rise in serum creatinine was due to a pre-renal etiology (e.g. hemodynamic derangement). Non-AKI controls consisted of patients with ≤ 25% increase in serum creatinine post-operatively in the first week after surgery. The threshold of ≤ 25% was selected to ensure that these patients had minimal alterations in kidney function despite an insult (e.g. renal ischemia with cardiopulmonary bypass) of equivalent severity as those with AKI. Based on the above criteria, the TRIBE study contained 244 possible cases, 457 possible controls, and 323 individuals with intermediate phenotype that could not be categorized as either case or control (serum creatinine increase > 25% but < 50%). All selected TRIBE patients were of reported Caucasian ethnicity.

The VALID population is an ongoing prospective study of critically ill adults recruiting from intensive care (medical, surgical, cardiac) and trauma units at Vanderbilt University Medical Center since 2006. AKI cases for this GWAS study were selected based on a ≥ 50% increase in baseline serum creatinine for at least 2 consecutive days to minimize enrollment of patients whose rise in serum creatinine was due to pre-renal etiology (S2,S3). Baseline creatinine was designated as the most recent outpatient level prior to hospital admission if available, or else the nadir measurement during index hospitalization admission. Since pre-admission outpatient serum creatinine data was not always available, we implemented our AKI case definition to at least 50% rise in serum creatinine and did not include patients with only a 0.3 mg/dL rise (as in TRIBE) in order to limit false positive AKI cases, particularly among

patients with chronic kidney disease (CKD). Patients with documented urinary tract obstruction and advanced liver disease were excluded. Non-AKI controls were defined by ≤ 25% increase in serum creatinine during inpatient hospital stay compared to baseline levels. Using these criteria, the VALID study consisted of 516 possible cases, 212 possible controls, and 245 patients that were neither cases nor controls due to intermediate phenotype. All selected VALID patients were ≥ 18 years of age and were of Caucasian ethnicity as per medical records.

In both the VALID and TRIBE populations, data on critical clinical variables were prospectively collected, including comorbidities (CKD, defined as baseline eGFR < 60 mL/min/1.73 m^2, hypertension, and diabetes), length of hospital stay, type of surgical procedure, cardiac bypass time, and requirements for dialysis. All patients provided informed consent and the study was approved by each site's institutional review board or ethics committee.

AKI replication case-control populations

The CABG Genomics population consisted of 1,672 prospectively enrolled patients that received coronary artery bypass graft and/or valve surgery at either Brigham and Women's Hospital (Boston, MA) or the Texas Heart Institute (Houston, TX) between August 2001 and November 2014 (S4). Subjects with a preoperative hematocrit < 25% or those who received transfusion of leukocyte-rich blood products within 30 days before surgery were not enrolled. Patients who were receiving preoperative dialysis were excluded. The BWH CSS population consisted of 210 prospectively enrolled patients that underwent cardiac surgery at BWH between August 2007 and March 2012 (S5). Inclusion and exclusion criteria for the BWH CSS study were chosen to capture patients at high risk of AKI following cardiac surgery. Inclusion criteria were baseline eGFR ≤ 30 ml/min/1.73m^2 or any two of the following: baseline eGFR 31-60 ml/min/1.73m^2, diabetes mellitus, left ventricular ejection fraction ≤ 40%, previous cardiac surgery, combined coronary artery bypass/valve procedure, urgent procedure, and preoperative intra-aortic balloon pump. Exclusion criteria were preoperative AKI (defined as a > 0.3 mg/dL

rise in serum creatinine over 24 hours or a > 0.5 mg/dL rise over 48 hours), recent aminoglycoside use, serum creatinine > 4.5 mg/dL, end stage kidney disease receiving dialysis, renal transplantation, and pregnancy. For both replication populations, case and control definitions were similar to the discovery phase. Study protocols for replication patient populations were approved by respective institutional review boards and participants were enrolled following written informed consent.

Genotyping, quality control, and association analysis in the AKI discovery population

DNA extractions from blood samples were performed using standard techniques. The initial discovery population consisted of 760 AKI cases and 669 non-AKI controls. Genotyping was performed at the W.M. Keck facility at Yale University in 3 different batches as follows: 632 VALID patients were genotyped using the Illumina HumanOmni1 Quad v1.0 BeadChip; 96 VALID and 296 TRIBE patients were genotyped using the Illumina HumanOmniExpress v1.0 BeadChip; 405 TRIBE patients were genotyped using the Illumina HumanOmniExpress v1.1 BeadChip. The Genotyping v1.9.4 module clustering algorithm from Illumina Genome Studio software was used for SNP calling. Samples with call rate < 97% or unexplained chromosomal variations in associated logR ratio and B-allele frequency plots were excluded from further analysis. Patients whose reported gender did not match X chromosome zygosity were removed. Pairwise identity-by-descent analysis was performed using Plink v1.07 to evaluate cryptic relatedness within the population and samples with kinship coefficient (π-hat) > 0.1 were omitted. We detected subtle ethnicity substructure in remaining patients and individuals of known ancestry (HapMap) (S6) through principal components analysis (PCA) using the EIGENSTRAT software (S7) (**Figure E2**). Samples that clustered apart from the European background were excluded for further analysis. The final discovery population contained 709 AKI cases and 619 non-AKI controls representing 93% of the enrolled patients in both settings.

Data for a total of 992,895 individual SNPs were generated during genotyping. Of these, 383,387 SNPs were excluded during quality control for having genotype call rate < 95%, minor allele frequency < 1%, or Hardy-Weinberg equilibrium deviation *P* value < 10^{-4}. The remaining 609,508 SNPs were checked for alignment against the 1000 Genomes Phase I integrated reference panel (release June 16, 2014) (S8) and used for haplotype phasing with SHAPEIT2 software (S9). Genome-wide SNP imputation using inferred haplotypes was performed using IMPUTE2 (S10), generating data for 9,237,809 SNPs. After removal of 161,689 imputed SNPs that had poor imputation quality (info score < 0.5), association testing was performed on 9,076,120 SNPs using the additive model in SNPTEST v2.4.1 (S11) with conditioning upon the following covariates: patient age, gender, recruitment site (TRIBE versus ICU), genotype chip, and the first three principle components for ethnicity. OR was calculated as the natural exponential function of β, the regression coefficient determined by SNPTEST. The distribution of GWAS *P* values was visualized by Manhattan plot and evaluated using quantile-quantile plot (**Figure E1**), which was used to calculate the genome-wide inflation factor (λ). Locus plots were generated using LocusZoom software (S12).

For sensitivity analysis of our AKI definitions, association testing was repeated using the same parameters except that AKI cases were newly defined as patients with a peak serum creatinine that represented at least an increase of 25%, 50%, or 100% relative to the baseline measurement or to the hospital trough value (if baseline is not available). To determine the influence of additional clinical covariates, including diabetes, hypertension, and CKD, association testing was performed as before but with additional conditioning upon any or all new covariates. To evaluate previously identified SNPs of interest in the discovery patient population more accurately, association testing was performed using the percentage of rise of serum creatinine from baseline as a continuous outcome in order to match the previously reported methodology (S13).

Genomic functional annotation and selection of SNPs for validation

GenoWAP uses a mixture model of multiple layers and empirical Bayes techniques to assign a posterior score to each SNP in the dataset. It has been shown that top signals with high posterior scores have substantially higher replication rates than signals based on *P* values (S14). Moreover, since GenoWAP integrates GWAS summary statistics with functional annotations associated with non-coding regions in the human genome (S15), it can prioritize non-coding SNPs in GWAS. Among the SNPs with highest potential for AKI association (*P* value $< 5 \times 10^{-6}$) in the discovery population that are found in protein-coding genes, up to three reasonably distant SNPs were selected for replication study from each gene in order to optimize coverage despite potential genotyping failure. Of the SNPs that reside in intergenic regions and the SNPs with marginal *P* values in the coding regions, GenoWAP was used to select candidates for validation. Additional loci of potential interest were identified from the 50 SNPs with highest posterior scores in GenoWAP. Similarly, up to three reasonably distant SNPs from each locus were selected. Finally, the genome-wide significant SNP rs148018420 was kept in the validation SNP set although it did not have a high posterior score in GenoWAP. In total, 38 SNPs from 18 loci were identified for replication analysis (**Table E2**).

Genotyping and association analysis in the AKI replication population

Genotyping was performed on a MassARRAY system using MALDI-TOF mass spectrometry with the iPLEX Gold chemistry (Agena Bioscience, San Diego, CA, USA). Assays were designed using the Assay Design Suite v2.0 with high multiplexing iPLEX parameters. Of the 38 SNPs that were selected for replication study, 19 directly passed the primer design stage and 3 were substituted with proximate SNPs from the same locus that were in strong linkage disequilibrium with the initially selected SNP. In total, 22 SNPs representing 13 loci were analyzed. Primer sequences are listed in **Table E7**. Automated genotype calling was done with Typer Analyzer 4.0.22.67. Genotype clustering was visually checked by an experienced

evaluator. For quality control, a gender marker was added to the 22 target SNPs and samples with gender discordances were excluded. In addition, DNA samples with call rates < 90% were removed.

AKI association testing for 22 SNPs of interest was performed in each of the replication populations using the additive model in SNPTEST v2.4.1 (S11) with the following covariates: patient age and gender. Conditioning on clinical covariates was not performed due to missing data on covariates and differences in covariate distribution in cases and controls between the individual replication studies. Meta-analysis of effect sizes and standard errors from the discovery and replication populations was performed by combining ORs for each of the 22 SNPs using random-effects models. The heterogeneity in effect size across patient populations was assessed by estimating between-population heterogeneity variance (τ^2) using a maximum likelihood procedure (S16). As heterogeneity was low, summary meta-analysis ORs and *P* values were determined using fixed-effects models (S17). Heterogeneity statistic I^2 was calculated according to Higgins *et al.* (S18). We also calculated Cochran's Q-statistic and associated *P* value using the estimated τ^2. SNPs with MAF < 1% in either replication population were not considered for further characterization. For the replication phase, we considered SNPs with nominal $P < 0.05$ as statistically significant. Successful replication was designated as having meta-analysis *P* value improved over discovery phase *P* value with similar directional effect.

Supplementary Figure Legends

Figure E1. **Quantile-quantile plot of the observed genome-wide *P* values from GWAS of AKI discovery case-control population compared to those of the uniform distribution.** The red line indicates expected values under the null hypothesis of no association.

Figure E2. Principal component analysis of AKI cases and controls in the discovery population and HapMap samples. Genome-wide genotyping signal was used for stratification by ethnicity (see **Methods**). Samples within the black-bordered box were considered to represent patients with European ancestries and were selected for further analysis.

Table E1. Patient demographics of the AKI replication case-control population

	CABG Genomics population		BWH CSS population	
	Cases (n = 162)	Controls (n = 1267)	Cases (n = 44)	Controls (n = 139)
Males (%)	122 (75%)	1027 (81%)	25 (57%)	85 (61%)
Age (years), mean (SD)	67.69 (11.18)	64.39 (9.86)	76.73 (9.64)	77.78 (8.9)
[p25, median, p75]	[61, 69, 76]	[57, 64, 72]	[67, 79, 84]	[74, 79, 84]
Diabetes	77 (48%)	393 (31%)	13 (30%)	51 (37%)
Hypertension	142 (88%)	933 (74%)	36 (82%)	115 (83%)
CKD*	78 (48%)	328 (26%)	33 (75%)	98 (71%)
Baseline Cr (mg/dL), mean (SD)	1.24 (0.43)	1.09 (0.29)	1.31 (0.40)	1.27 (0.38)
Surgery Details				
CPB time, Mean (SD)	105.16 (45.44)	96.82 (44.02)	183.16 (109.96)	143.96 (67.9)
Outcomes				
Acute dialysis	7 (4%)	0 (0%)	7 (4%)	0 (0%)
Length of ICU stay (days), mean (SD)	5.27 (8.98)	2.18 (2.89)	-	-
Length of Hospital stay (days), mean (SD)	14.75 (13.22)	8.81 (5.57)	19.07 (18.15)	14.79 (8.78)
In-Hospital mortality	14 (9%)	0 (0%)	8 (18%)	0 (0%)

*CKD (chronic kidney disease) was defined as pre-operative eGFR < 60 mL/min/1.73 m^2
Abbreviations: AKI (acute kidney injury), BWH CSS (Brigham and Women's Hospital Cardiac Surgery Study), CABG Genomics (Coronary Artery Bypass Graft Genomics study), CPB (cardiopulmonary bypass), ICU (intensive care unit), p25 (25^{th} percentile), p75 (75^{th} percentile)

Table E2. GWAS and GenoWAP functional annotation identify 38 SNPs of interest representing 18 genetic loci

Locus #	SNP	Chr	Position	Major allele	Minor allele	MAF cases	MAF ctrls	Gene	Source	Imputation info score	Before adjustment for clinical covariates*			After adjustment for clinical covariates*		
											P value	OR†	95% CI	*P* value	OR†	95% CI
1	rs12070215	1	84692710	G	A	0.10	0.06	PRKACB	Imputed	0.98	3.59×10^{-6}	2.06	1.52-2.80	4.08×10^{-6}	2.06	1.52-2.80
	rs12126586	1	84693144	G	T	0.10	0.06	PRKACB	Imputed	0.99	4.27×10^{-6}	2.02	1.50-2.73	4.65×10^{-6}	2.03	1.50-2.74
	rs12134263	1	84693204	C	T	0.10	0.06	PRKACB	Imputed	0.99	3.47×10^{-6}	2.06	1.52-2.79	3.91×10^{-6}	2.06	1.51-2.79
2	rs1416526‡	1	217236895	T	G	0.19	0.13	ESRRG	Imputed	0.94	2.47×10^{-6}	1.75	1.38-2.20	6.11×10^{-6}	1.71	1.36-2.16
3	rs10166390	2	43342608	T	C	0.11	0.07	Intergenic	Imputed	0.72	3.35×10^{-5}	1.98	1.43-2.73	5.76×10^{-5}	1.96	1.41-2.71
4	rs200933697	4	113270705	CTG	C	0.03	0.010	ALPK1	Imputed	0.65	2.81×10^{-6}	4.74	2.47-9.08	3.85×10^{-6}	4.79	2.46-9.31
5	rs66533303	4	160001395	G	A	0.04	0.02	Intergenic	Imputed	0.76	2.98×10^{-5}	3.13	1.83-5.34	3.55×10^{-5}	3.18	1.84-5.51
6	rs62341639	4	185159434	C	T	0.18	0.24	Intergenic	Imputed	0.90	4.01×10^{-6}	0.61	0.50-0.75	3.16×10^{-6}	0.60	0.49-0.75
	rs62341657	4	185159538	G	A	0.18	0.24	Intergenic	Imputed	0.90	3.98×10^{-6}	0.61	0.49-0.75	3.09×10^{-6}	0.60	0.49-0.75
7	rs10815380	9	6226086	C	T	0.19	0.26	IL33	Imputed	1.00	7.06×10^{-7}	0.61	0.50-0.74	6.93×10^{-7}	0.60	0.49-0.74
	rs10815381	9	6226289	A	G	0.19	0.26	IL33	Imputed	1.00	7.11×10^{-7}	0.61	0.50-0.74	6.96×10^{-7}	0.60	0.49-0.74
	rs10975499	9	6230072	G	A	0.19	0.26	IL33	Imputed	0.99	1.21×10^{-6}	0.61	0.50-0.75	1.13×10^{-6}	0.61	0.50-0.74
8	rs10810119	9	14226139	A	C	0.16	0.21	NFIB	Measured	1.00	3.49×10^{-5}	0.63	0.51-0.79	4.45×10^{-5}	0.63	0.51-0.79
	rs10961440	9	14234315	T	C	0.15	0.21	NFIB	Measured	1.00	1.53×10^{-5}	0.62	0.50-0.77	1.63×10^{-5}	0.62	0.50-0.77
	rs78959125	9	14235063	A	G	0.12	0.17	NFIB	Imputed	0.99	1.30×10^{-5}	0.59	0.46-0.75	2.54×10^{-5}	0.59	0.46-0.76
9	rs148955421	9	15463899	ATTACC	A	0.07	0.04	SNAPC3	Imputed	1.00	2.55×10^{-6}	2.36	1.65-3.38	3.07×10^{-6}	2.38	1.66-3.44
	rs2665515	9	15464743	G	A	0.07	0.04	PSIP1	Imputed	1.00	2.53×10^{-6}	2.37	1.65-3.39	3.07×10^{-6}	2.39	1.66-3.44
	rs7021840	9	15504000	C	G	0.07	0.04	PSIP1	Imputed	1.00	3.32×10^{-6}	2.32	1.63-3.30	4.54×10^{-6}	2.32	1.62-3.33
	rs2821525	9	15507286	G	C	0.07	0.04	PSIP1	Imputed	0.99	3.10×10^{-6}	2.31	1.62-3.27	3.86×10^{-6}	2.32	1.62-3.32
	rs28610358‡	9	15513026	G	A	0.07	0.04	Intergenic	Imputed	0.99	4.34×10^{-6}	2.27	1.60-3.22	5.55×10^{-6}	2.28	1.60-3.25
	rs114950412‡	9	15520416	C	T	0.07	0.04	Intergenic	Imputed	0.99	4.80×10^{-6}	2.25	1.59-3.19	6.32×10^{-6}	2.26	1.59-3.22
	rs7852936‡	9	15520616	G	A	0.07	0.04	Intergenic	Imputed	0.99	4.74×10^{-6}	2.25	1.59-3.19	6.24×10^{-6}	2.26	1.59-3.22
10	rs148018420	12	16438896	A	G	0.002	0.013	Intergenic	Imputed	0.58	1.43×10^{-8}	0.017	0.0042-0.070	1.02×10^{-8}	0.017	0.0042-0.068
11	rs56194898	13	111012570	G	A	0.06	0.03	COL4A2	Imputed	0.83	1.76×10^{-5}	2.64	1.70-4.12	2.15×10^{-5}	2.64	1.69-4.14
12	rs373721	13	111189265	T	A	0.17	0.23	RAB20	Imputed	0.93	2.05×10^{-5}	0.64	0.52-0.78	2.37×10^{-5}	0.63	0.51-0.78
	rs408184	13	111189273	C	T	0.17	0.23	RAB20	Imputed	0.93	2.01×10^{-5}	0.64	0.52-0.78	2.32×10^{-5}	0.63	0.51-0.78
13	rs11570785	14	50862057	T	A	0.02	0.05	CDKL1	Imputed	0.99	4.00×10^{-6}	0.35	0.22-0.55	2.35×10^{-6}	0.34	0.22-0.53
	rs11570784	14	50862100	G	A	0.02	0.05	CDKL1	Imputed	0.99	4.00×10^{-6}	0.35	0.22-0.55	2.35×10^{-6}	0.34	0.22-0.53
	rs72681624	14	51135609	G	A	0.03	0.06	Intergenic	Imputed	0.95	5.41×10^{-7}	0.34	0.22-0.52	4.41×10^{-7}	0.34	0.22-0.52
14	rs2294450	16	847597	T	C	0.29	0.22	CHTF18	Imputed	0.98	4.10×10^{-6}	1.56	1.29-1.89	2.23×10^{-6}	1.59	1.31-1.92
15	rs13054962	22	19608657	A	G	0.19	0.26	Intergenic	Imputed	0.99	1.19×10^{-5}	0.64	0.53-0.78	4.28×10^{-5}	0.66	0.54-0.80
	rs9618630	22	19609935	C	T	0.19	0.26	Intergenic	Imputed	1.00	9.84×10^{-6}	0.64	0.53-0.78	3.31×10^{-5}	0.66	0.54-0.80
	rs10854554	22	19610682	A	G	0.19	0.26	Intergenic	Measured	1.00	1.44×10^{-5}	0.65	0.53-0.79	4.46×10^{-5}	0.66	0.54-0.81
16	rs9623661	22	43093376	C	T	0.08	0.12	A4GALT	Imputed	0.92	2.22×10^{-5}	0.54	0.40-0.71	3.01×10^{-5}	0.54	0.40-0.72
17	rs35560890	22	43573382	AT	A	0.44	0.52	TTLL12	Imputed	0.96	1.81×10^{-6}	0.67	0.56-0.79	2.41×10^{-6}	0.67	0.56-0.79
	rs200992521	22	43573386	A	AT	0.44	0.52	TTLL12	Imputed	0.96	1.82×10^{-6}	0.67	0.57-0.79	2.42×10^{-6}	0.67	0.56-0.79
18	rs111732708	22	43787850	C	T	0.02	0.006	Intergenic	Imputed	0.92	2.51×10^{-5}	4.37	2.20-8.67	2.68×10^{-5}	4.48	2.22-9.01
	rs202139590	22	43791402	T	TG	0.02	0.004	Intergenic	Imputed	0.97	1.45×10^{-5}	4.94	2.40-10.18	1.52×10^{-5}	5.05	2.42-10.52

*Clinical covariates include the presence or absence of diabetes mellitus, hypertension, and chronic kidney disease in cases and controls

†Odds ratio (OR) was calculated as e^{β}, where β represents the regression coefficient of the additive model in SNPTEST (S11)

‡SNPs with *P* values above threshold ($P < 5 \times 10^{-6}$) after adjustment for clinical covariates were nonetheless considered for replication study due to proximity of the adjusted values to the threshold figure

Abbreviations: Chr (chromosome), CI (confidence interval), ctrls (controls), GenoWAP (Genome Wide Association Prioritizer program), GWAS (genome wide association study), info score (imputation quality score from SNPTEST program), MAF (minor allele frequency), SNP (single nucleotide polymorphism)

Table E3. Association analysis of 22 SNPs of interest in replication case-control populations

						Discovery population					Replication population					Meta-analysis					
Locus #	SNP	Chr	Position	Major allele	Minor allele	*P* value	Cases MAF	Ctrls MAF	OR*	95% CI	*P* value	Cases MAF	Ctrls MAF	OR*	95% CI	*P* value	OR*	95% CI	I^2	τ^2	Cochran's *P*
1	rs12134263	1	84693204	C	T	3.47×10^{-6}	0.10	0.06	2.06	1.52-2.79	0.81	0.080	0.084	0.95	0.65-1.40	5.01×10^{-4}	1.53	1.20-1.94	89.5	0.26	2.1×10^{-3}
2	rs1416526	1	217236895	T	G	2.47×10^{-6}	0.19	0.13	1.75	1.38-2.20	0.45	0.19	0.17	1.11	0.84-1.48	3.84×10^{-5}	1.46	1.22-1.74	82.8	0.08	0.016
3	rs10166390	2	43342608	T	C	3.35×10^{-5}	0.11	0.07	1.98	1.43-2.73	0.99	0.0874	0.0871	1.00	0.69-1.46	1.79×10^{-3}	1.47	1.16-1.88	86.6	0.20	6.3×10^{-3}
6	rs62341639	4	185159434	C	T	4.01×10^{-6}	0.18	0.24	0.61	0.50-0.75	0.014	0.14	0.19	0.71	0.54-0.93	2.48×10^{-7}	0.64	0.55-0.76	0	0	0.40
6	rs62341657	4	185159538	G	A	3.98×10^{-6}	0.18	0.24	0.61	0.49-0.75	0.018	0.14	0.19	0.72	0.54-0.94	3.26×10^{-7}	0.65	0.55-0.76	0	0	0.37
7	rs10815381	9	6226289	A	G	7.11×10^{-7}	0.19	0.26	0.61	0.50-0.74	0.35	0.21	0.23	0.89	0.69-1.14	7.85×10^{-6}	0.70	0.60-0.82	81.8	0.06	0.019
7	rs10975499	9	6230072	G	A	1.21×10^{-6}	0.19	0.26	0.61	0.50-0.75	0.54	0.22	0.23	0.92	0.72-1.19	2.85×10^{-5}	0.72	0.61-0.84	84.4	0.07	0.011
8	rs10810119	9	14226139	A	C	3.49×10^{-5}	0.16	0.21	0.63	0.51-0.79	0.82	0.20	0.19	1.03	0.79-1.34	2.28×10^{-3}	0.77	0.65-0.91	87.3	0.10	5.0×10^{-3}
8	rs10961436	9	14229179	G	A	4.40×10^{-5}	0.09	0.14	0.58	0.45-0.75	0.33	0.13	0.12	1.18	0.85-1.63	1.04×10^{-2}	0.77	0.63-0.94	91.0	0.23	8.7×10^{-4}
8	rs10961440	9	14234315	T	C	1.53×10^{-5}	0.15	0.21	0.62	0.50-0.77	0.87	0.192	0.191	1.01	0.78-1.31	5.69×10^{-4}	0.75	0.63-0.88	85.4	0.09	8.8×10^{-3}
9	rs148955421	9	15463899	ATTACC	A	2.55×10^{-6}	0.07	0.04	2.36	1.65-3.38	0.40	0.06	0.05	1.23	0.76-2.00	1.85×10^{-5}	1.88	1.41-2.50	77.8	0.17	0.034
9	rs2821525	9	15507286	G	C	3.10×10^{-6}	0.07	0.04	2.31	1.62-3.27	0.46	0.06	0.05	1.20	0.74-1.94	2.60×10^{-5}	1.84	1.38-2.44	78.4	0.17	0.032
9	rs28610358	9	15513026	G	A	4.34×10^{-6}	0.07	0.04	2.27	1.60-3.22	0.49	0.053	0.046	1.19	0.73-1.94	3.40×10^{-5}	1.82	1.37-2.42	77.3	0.16	0.036
9	rs114950412	9	15520416	C	T	4.80×10^{-6}	0.07	0.04	2.25	1.59-3.19	0.63	0.054	0.049	1.13	0.70-1.82	6.55×10^{-5}	1.78	1.34-2.35	80.8	0.19	0.022
10†	rs148018420	12	16438896	A	G	1.43×10^{-8}	0.002	0.013	0.017	0.0042-0.070	0.92	0.010	0.009	1.06	0.36-3.17	6.82×10^{-4}	0.22	0.09-0.53	95.1	8.11	5.6×10^{-6}
11	rs56194898	13	111012570	G	A	1.76×10^{-5}	0.06	0.03	2.64	1.70-4.12	0.95	0.053	0.054	0.99	0.63-1.57	1.77×10^{-3}	1.66	1.21-2.29	88.5	0.40	3.3×10^{-3}
13	rs11570785	14	50862057	T	A	4.00×10^{-6}	0.02	0.05	0.35	0.22-0.55	0.42	0.04	0.05	0.82	0.51-1.32	9.15×10^{-5}	0.52	0.38-0.72	84.9	0.31	0.010
15	rs9617814	22	19609943	A	G	2.04×10^{-5}	0.22	0.29	0.66	0.54-0.80	0.040	0.20	0.25	0.77	0.60-0.99	3.81×10^{-6}	0.70	0.60-0.81	0	0	0.32
15	rs10854554	22	19610682	A	G	1.44×10^{-5}	0.19	0.26	0.65	0.53-0.79	0.012	0.17	0.22	0.72	0.55-0.93	6.53×10^{-7}	0.67	0.57-0.79	0	0	0.54
17	rs35560890	22	43573382	AT	A	1.81×10^{-6}	0.44	0.52	0.67	0.56-0.79	0.12	0.53	0.49	1.19	0.96-1.47	5.01×10^{-3}	0.83	0.73-0.94	94.2	0.16	3.1×10^{-5}
18†	rs111732708	22	43787850	C	T	2.51×10^{-5}	0.02	0.006	4.37	2.20-8.67	0.11	0.005	0.02	0.47	0.19-1.18	1.58×10^{-2}	1.97	1.14-3.41	93.1	2.31	1.4×10^{-4}
18†	rs202139590	22	43791402	T	TG	1.45×10^{-5}	0.02	0.004	4.94	2.40-10.18	0.14	0.007	0.02	0.53	0.23-1.22	1.98×10^{-2}	1.92	1.11-3.33	93.6	2.35	7.8×10^{-5}

*Odds ratio (OR) was calculated as e^{β}, where β represents the regression coefficient of the additive model in SNPTEST (S11)
†Removed from analysis due to having MAF that remained < 1% after replication testing
Heterogeneity variance (τ^2) and statistic (I^2) were calculated as described in **Methods**; Cochran's *P* value is reported for Cochran's Q test
Abbreviations: BWH CSS (Brigham and Women's Hospital Cardiac Surgery Study), CABG Genomics (Coronary Artery Bypass Graft Genomics study), Chr (chromosome), CI (confidence interval), Ctrls (controls), inf (infinity), MAF (minor allele frequency), SNP (single nucleotide polymorphism)

Table E4. Sensitivity analysis of association testing in the AKI discovery population

			Definition of AKI cases*							
			Currently in use (n = 709)		> 25% change in Cr (n = 707)		> 50% change in Cr (n = 626)		> 100% change in Cr (n = 419)	
SNP	Chr	Position	Association *P* value	β	Association *P* value	β	Association *P* value	β	Association *P* value	β
rs12070215	1	84692710	3.59×10^{-6}	0.72	2.98×10^{-6}	0.73	3.17×10^{-6}	0.81	4.08×10^{-3}	0.64
rs12126586	1	84693144	4.27×10^{-6}	0.71	3.55×10^{-6}	0.71	3.47×10^{-6}	0.79	4.66×10^{-3}	0.62
rs12134263	1	84693204	3.47×10^{-6}	0.72	2.88×10^{-6}	0.73	3.11×10^{-6}	0.81	4.05×10^{-3}	0.64
rs1416526	1	217236895	2.47×10^{-6}	0.56	1.93×10^{-6}	0.56	1.08×10^{-4}	0.50	6.75×10^{-5}	0.62
rs10166390	2	43342608	3.35×10^{-5}	0.68	2.81×10^{-5}	0.69	2.29×10^{-5}	0.75	1.57×10^{-5}	0.93
rs200933697	4	113270705	2.81×10^{-6}	1.56	2.82×10^{-6}	1.56	2.52×10^{-5}	1.57	9.47×10^{-4}	1.51
rs66533303	4	160001395	2.98×10^{-5}	1.14	2.68×10^{-5}	1.15	2.06×10^{-4}	1.13	2.08×10^{-5}	1.60
rs62341639	4	185159434	4.01×10^{-6}	-0.49	3.57×10^{-6}	-0.50	2.45×10^{-5}	-0.48	2.71×10^{-4}	-0.48
rs62341657	4	185159538	3.98×10^{-6}	-0.49	3.54×10^{-6}	-0.50	2.39×10^{-5}	-0.48	2.66×10^{-4}	-0.48
rs10815380	9	6226086	7.06×10^{-7}	-0.50	6.63×10^{-7}	-0.50	7.50×10^{-5}	-0.42	6.55×10^{-4}	-0.44
rs10815381	9	6226289	7.11×10^{-7}	-0.50	6.67×10^{-7}	-0.50	7.54×10^{-5}	-0.42	6.58×10^{-4}	-0.44
rs10975499	9	6230072	1.21×10^{-6}	-0.49	1.14×10^{-6}	-0.49	1.26×10^{-4}	-0.41	8.36×10^{-4}	-0.43
rs10810119	9	14226139	3.49×10^{-5}	-0.45	3.15×10^{-5}	-0.46	6.23×10^{-4}	-0.40	3.10×10^{-2}	-0.30
rs10961440	9	14234315	1.53×10^{-5}	-0.47	1.87×10^{-5}	-0.47	1.16×10^{-4}	-0.45	9.61×10^{-3}	-0.37
rs78959125	9	14235063	1.30×10^{-5}	-0.53	1.57×10^{-5}	-0.53	2.25×10^{-4}	-0.48	5.77×10^{-3}	-0.44
rs148955421	9	15463899	2.55×10^{-6}	0.86	2.21×10^{-6}	0.87	5.12×10^{-7}	1.00	5.60×10^{-5}	1.00
rs2665515	9	15464743	2.53×10^{-6}	0.86	2.20×10^{-6}	0.87	5.13×10^{-7}	1.00	5.56×10^{-5}	1.00
rs7021840	9	15504000	3.32×10^{-6}	0.84	2.89×10^{-6}	0.85	8.42×10^{-7}	0.97	8.11×10^{-5}	0.95
rs2821525	9	15507286	3.10×10^{-6}	0.84	2.69×10^{-6}	0.84	1.15×10^{-6}	0.95	9.81×10^{-5}	0.93
rs28610358	9	15513026	4.34×10^{-6}	0.82	3.79×10^{-6}	0.82	1.58×10^{-6}	0.93	1.11×10^{-4}	0.92
rs114950412	9	15520416	4.80×10^{-6}	0.81	4.21×10^{-6}	0.82	1.72×10^{-6}	0.92	1.00×10^{-4}	0.93
rs7852936	9	15520616	4.74×10^{-6}	0.81	4.15×10^{-6}	0.82	1.70×10^{-6}	0.92	9.92×10^{-5}	0.93
rs148018420	12	16438896	1.43×10^{-8}	-4.07	1.52×10^{-8}	-4.06	4.35×10^{-8}	-4.01	7.87×10^{-6}	-3.32
rs56194898	13	111012570	1.76×10^{-5}	0.97	1.58×10^{-5}	0.98	7.79×10^{-5}	0.99	9.23×10^{-3}	0.78
rs373721	13	111189265	2.05×10^{-5}	-0.45	2.59×10^{-5}	-0.45	2.72×10^{-4}	-0.42	3.67×10^{-3}	-0.40
rs408184	13	111189273	2.01×10^{-5}	-0.45	2.54×10^{-5}	-0.45	2.68×10^{-4}	-0.42	3.64×10^{-3}	-0.40
rs11570785	14	50862057	4.00×10^{-6}	-1.05	4.35×10^{-6}	-1.05	7.05×10^{-7}	-1.22	1.05×10^{-4}	-1.11
rs11570784	14	50862100	4.00×10^{-6}	-1.05	4.35×10^{-6}	-1.05	7.07×10^{-7}	-1.22	1.05×10^{-4}	-1.11
rs72681624	14	51135609	5.41×10^{-7}	-1.07	5.92×10^{-7}	-1.07	5.12×10^{-7}	-1.14	3.62×10^{-5}	-1.09
rs2294450	16	847597	4.10×10^{-6}	0.45	4.08×10^{-6}	0.45	1.13×10^{-6}	0.50	1.92×10^{-3}	0.39
rs13054962	22	19608657	1.19×10^{-5}	-0.44	1.15×10^{-5}	-0.45	1.29×10^{-4}	-0.41	2.25×10^{-5}	-0.56
rs9618630	22	19609935	9.84×10^{-6}	-0.44	9.51×10^{-6}	-0.44	1.29×10^{-4}	-0.41	2.10×10^{-5}	-0.56
rs10854554	22	19610682	1.44×10^{-5}	-0.44	1.39×10^{-5}	-0.44	1.72×10^{-4}	-0.40	2.31×10^{-5}	-0.56
rs9623661	22	43093376	2.22×10^{-5}	-0.62	2.60×10^{-5}	-0.62	1.93×10^{-4}	-0.58	3.76×10^{-4}	-0.68
rs35560890	22	43573382	1.81×10^{-6}	-0.40	2.20×10^{-6}	-0.40	3.17×10^{-6}	-0.42	3.84×10^{-4}	-0.39
rs200992521	22	43573386	1.82×10^{-6}	-0.40	2.22×10^{-6}	-0.40	3.20×10^{-6}	-0.42	3.92×10^{-4}	-0.39
rs111732708	22	43787850	2.51×10^{-5}	1.47	2.33×10^{-5}	1.48	2.19×10^{-4}	1.46	9.18×10^{-3}	1.29
rs202139590	22	43791402	1.45×10^{-5}	1.60	1.35×10^{-5}	1.60	1.75×10^{-4}	1.58	9.41×10^{-3}	1.37

*Definitions in use for AKI cases include > 0.3 mg/dL or ≥ 50% increase in serum Cr for at least 2 consecutive days in TRIBE and ≥ 50% increase in serum Cr for at least 2 consecutive days in VALID; uniform definitions of AKI cases for sensitivity analysis are based on the indicated % change of the peak serum Cr value relative to the baseline measurement

Abbreviations: AKI (acute kidney injury), Chr (chromosome), Cr (creatinine)

Table E5. Evaluation of previously identified SNPs of interest in the AKI discovery population

	Study								
	PEGASUS*		CATHGEN*			Yale (dichotomous AKI)†		Yale (continuous Δ Cr)†	
SNP	β	Association *P* value	β	Association *P* value	Meta-analysis *P* value	β	Association *P* value	β	Association *P* value
rs2352039	10.07	9.78×10^{-6}	6.23	0.07	2.45×10^{-6}	-0.10	0.37	0.02	0.62
rs13317787	21.56	9.67×10^{-6}	22.04	0.022	5.35×10^{-7}	0.52	0.09	-0.02	0.89
rs10262995	14.33	1.83×10^{-6}	9.51	0.034	2.24×10^{-7}	-0.11	0.42	-0.08	0.15
rs2248098	-7.48	3.60×10^{-6}	-0.21	0.942	4.22×10^{-5}	-0.07	0.39	-0.01	0.77
rs1109836	37.57	5.67×10^{-7}	-11.32	0.36	0.0001	0.18	0.43	0.06	0.54
rs8086030	7.64	7.33×10^{-6}	-1.07	0.705	0.0002	0.09	0.30	0.03	0.45
rs8099036	8.47	9.01×10^{-7}	-0.44	0.88	2.74×10^{-5}	0.07	0.43	0.03	0.46
rs2831026	8.95	1.11×10^{-6}	-5.39	0.081	0.0009	-0.04	0.71	0.01	0.74
rs1551588	11.86	9.14×10^{-8}	-7.52	0.044	0.0003	-0.13	0.26	-0.05	0.31

*Previously described discovery (PEGASUS) and replication (CATHGEN) cohorts studying AKI (S13)
†Association testing with outcome as either dichotomous for AKI (case-control) or continuous for percentage change in serum Cr relative to baseline measurements
Abbreviations: AKI (acute kidney injury), Cr (creatinine), SNP (single nucleotide polymorphism)

Table E6. Expression quantitative train loci found among the 38 SNPs of interest

Locus*	SNPs	Affected genes†	*P* value†	Effect sizes†	Affected tissues†
9	rs2665515 rs7021840 rs2821525 rs28610358 rs114950412 rs7852936	CCDC171	$< 10^{-5}$	0.4 – 0.7	esophagus, artery, skin, thyroid, adipose tissue
12	rs373721 rs408184	RAB20	$< 10^{-11}$	0.5	thyroid
14	rs2294450	MSLN	$< 10^{-5}$	0.4 – 0.5	lung, thyroid
14	rs2294450	RPUSD1	$< 10^{-6}$	-0.2	stomach
14	rs2294450	MSLNL	$< 10^{-5}$	0.4	lung
17	rs35560890	TTLL12	$< 10^{-9}$	-0.3 – -0.5	esophagus, artery, skin, thyroid, muscle, adipose tissue

*Locus corresponding to **Supplementary Table 2**

†Data for expression quantitative train loci found in the GTEx project database (S19); *P* values effect sizes, and affected tissues pertain to all SNPs affecting the indicated gene

Abbreviations: SNP (single nucleotide polymorphism)

Table E7. Primer sequences for genotyping of SNPs of interest in replication case-control populations

SNP	1st PCR Primer	2nd PCR Primer	Extension Primer
rs9617814	ACGTTGGATGCGCTGCTAAGTCAGGGTTG	ACGTTGGATGTCGGCCCGAAGATTCCCAT	CCATCCAGTTCACTGC
rs11570785	ACGTTGGATGTGACACAAATGGGATATCTG	ACGTTGGATGAAAGTGAATGCCACCTTACC	CTCACCTTACCTGGCAC
rs56194898	ACGTTGGATGGGCATGGATAGAATTGGTGG	ACGTTGGATGGACATGGAGAAGAATGCAG	CAGAGTCGCTCTAGACA
rs12134263	ACGTTGGATGCCTTCCTGTTCTATCCCCTT	ACGTTGGATGGAAATAAAATCTTCTGCCA	CTTCTGCCAAATAGCAGT
rs202139590	ACGTTGGATGGGGAAATTCTGGGCAGGAGA	ACGTTGGATGTACTATCCACGCTGAGCGG	TTGATCTCAGAGCCCCCCCC
rs111732708	ACGTTGGATGAGTGGAAACGTCACAGGGG	ACGTTGGATGGTGTTTCAAACAGTTTCTAA	ATGTTCATTTCCATTTCACT
rs28610358	ACGTTGGATGGGAAGTACCATACTTAGCTC	ACGTTGGATGTGTTTAAAGGGTATCTCCTG	CAAACTACCACAGGTTGAAG
rs10961436	ACGTTGGATGTTCACGTACAGGTAATCTCC	ACGTTGGATGGAATTCATTGAGTTCCGACC	GCCGATGAGCTTTTAGAGCA
rs10166390	ACGTTGGATGTTCAATTCTAGCTTTCACTG	ACGTTGGATGGGATGTGGAAATCAGTAG	GGTGGAAATCAGTAGACACAG
rs10961440	ACGTTGGATGCATTTAAGAGAGAAGCTACC	ACGTTGGATGATATACCTACATGCCTCCTC	TCATCTCATTCCTTCTTATCCT
rs10810119	ACGTTGGATGAGCTTGTTAAAAGGGAGATG	ACGTTGGATGCTAAATGATGACAATTTGGC	CCCCAATTTGGCTTTGTAACAC
rs148018420	ACGTTGGATGGTTTTCTGCTTGTTCAGTTGC	ACGTTGGATGATTCTCAAACTACGCATCTG	CGCATCTGACAAAGGTCTAGTA
rs1416526	ACGTTGGATGGAGTCTGTCTTTGAGCCTG	ACGTTGGATGAGTTAGGTTACCCAACCACG	GGACCATAAAAAAGGGCTGCTTA
rs62341639	ACGTTGGATGGCTCTTCAGAAAGGCGTTA	ACGTTGGATGTTCTCCTCCATCAGATTGGC	CCCCCAAGAAGTTCTGACATAGTG
rs114950412	ACGTTGGATGTTGCTTATTCTCCTTGAAC	ACGTTGGATGGGATTACAACAAAATTCTAC	CTAAAACAAAATTCTACAGGACAA
rs62341657	ACGTTGGATGGCCACACTTACTCCTGTATC	ACGTTGGATGATAAGTGTCAGAAGCAGACC	GGAAGGTGCTTCTCTAGGTAAGTG
rs10854554	ACGTTGGATGTTGGCTTCAGTGGTCTGTG	ACGTTGGATGATGACGTTGTCTCCTAACTC	TTTATCCTAACTCTTAGAGAAGAGG
rs10975499	ACGTTGGATGCATGGTGAATTGAGGAATGG	ACGTTGGATGACTACCTGCCCCATCAACTT	GTCCACTTTTCCAACCTTACTTACCC
rs2821525	ACGTTGGATGAGTACTGCTTTAGTCCTGAG	ACGTTGGATGAATCATCAGGTGCTGTCACG	TCACGTCTAATATATCCATAATACTT
rs35560890	ACGTTGGATGGGAAGATAGTGTCAAAGAG	ACGTTGGATGACTCTAGCCTGGACAAAAGC	TAAAGACCCTATCTTTTTTAAAAAAT
rs10815381	ACGTTGGATGTCAAGCAGATAGAAAGAAAGA	ACGTTGGATGCCTGGTCTCAAGAGATCATC	GCCTAAGCTTCCAAAAGTGCTGGGACT
rs148955421	ACGTTGGATGAAGGGAGGGTGAACAAAAGA	ACGTTGGATGGTCACAGAGGTTGTGCTGTT	AGTAAGCTCAAGATGATAAAAAATAAA

Abbreviations: PCR (polymerase chain reaction), SNP (single nucleotide polymorphism)

Supplementary References

S1. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX; TRIBE-AKI Consortium. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol. 2011 Sep;22(9):1748-57.

S2. Lin J, Fernandez H, Shashaty MG, Negoianu D, Testani JM, Berns JS, Parikh CR, Wilson FP. False-Positive Rate of AKI Using Consensus Creatinine-Based Criteria. Clin J Am Soc Nephrol. 2015 Oct 7;10(10):1723-31.

S3. Parr SK, Clark AJ, Bian A, Shintani AK, Wickersham NE, Ware LB, Ikizler TA, Siew ED. Urinary L-FABP predicts poor outcomes in critically ill patients with early acute kidney injury. Kidney Int. 2015 Mar;87(3):640-8.

S4. Fox AA, Muehlschlegel JD, Body SC, Shernan SK, Liu KY, Perry TE, Aranki SF, Cook EF, Marcantonio ER, Collard CD. Comparison of the utility of preoperative versus postoperative B-type natriuretic peptide for predicting hospital length of stay and mortality after primary coronary artery bypass grafting. Anesthesiology. 2010 Apr;112(4):842-51.

S5. Leaf DE, Rajapurkar M, Lele SS, Mukhopadhyay B, Rawn JD, Frendl G, Waikar SS. Increased plasma catalytic iron in patients may mediate acute kidney injury and death following cardiac surgery. Kidney Int. 2015 May;87(5):1046-54.

S6. International HapMap Consortium. The International HapMap Project. Nature. 2003;426(6968):789-96.

S7. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006 Aug;38(8):904-9.

S8. 1000 Genomes Project Consortium, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. An integrated map of genetic variation from 1,092 human genomes. Nature. 2012 Nov 1;491(7422):56-65.

S9. Delaneau O, Marchini J, 1000 Genomes Project Consortium. Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. Nat Commun. 2014;5:3934.

S10. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet. 2009;5(6):e1000529.

S11. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447(7145):661-78.

S12. Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, Gliedt TP, Boehnke M, Abecasis GR, Willer CJ. LocusZoom: regional visualization of genome-wide association scan results. Bioinformatics. 2010 Sep 15;26(18):2336-7.

S13. Stafford-Smith M, Li YJ, Mathew JP, Li YW, Ji Y, Phillips-Bute BG, Milano CA, Newman MF, Kraus WE, Kertai MD, Shah SH, Podgoreanu MV; Duke Perioperative Genetics and Safety Outcomes (PEGASUS) Investigative Team. Genome-wide association study of acute kidney injury after coronary bypass graft surgery identifies susceptibility loci. Kidney Int. 2015 Oct;88(4):823-32.

S14. Lu Q, Yao X, Hu Y, Zhao H. GenoWAP: GWAS signal prioritization through integrated analysis of genomic functional annotation. Bioinformatics. 2016 Feb 15;32(4):542-8.

S15. Lu Q, Hu Y, Sun J, Cheng Y, Cheung KH, Zhao H. A statistical framework to predict functional non-coding regions in the human genome through integrated analysis of annotation data. Sci Rep. 2015 May 27;5:10576.

S16. Viechtbauer, W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. J Educ Behav Stat. 2005;30(3):261-93,

S17. de Bakker PI, Ferreira MA, Jia X, Neale BM, Raychaudhuri S, Voight BF. Practical aspects of imputation-driven meta-analysis of genome-wide association studies. Hum Mol Genet. 2008 Oct 15;17(R2):R122-8.

S18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.

S19. GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science. 2015;348(6235):648-60.

Figure E1

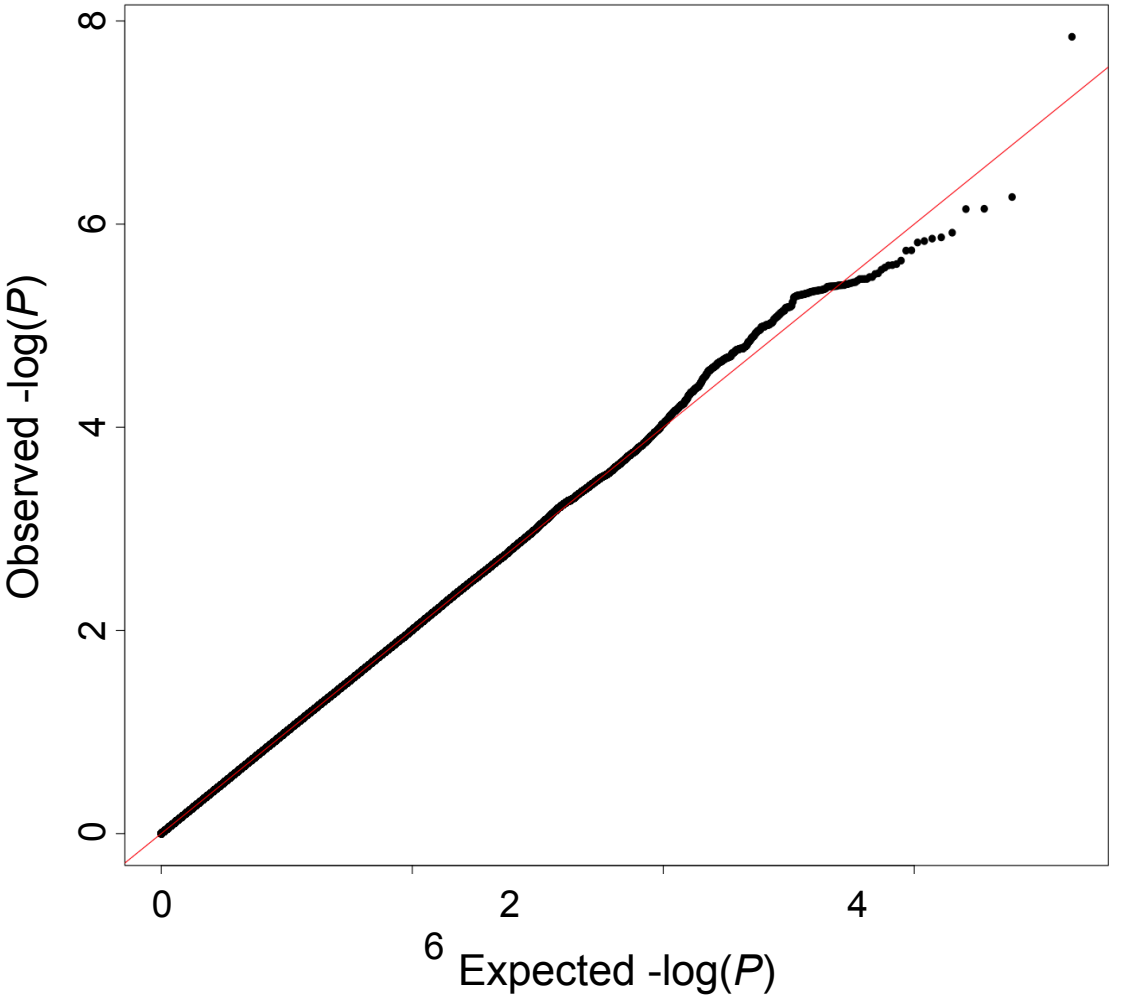
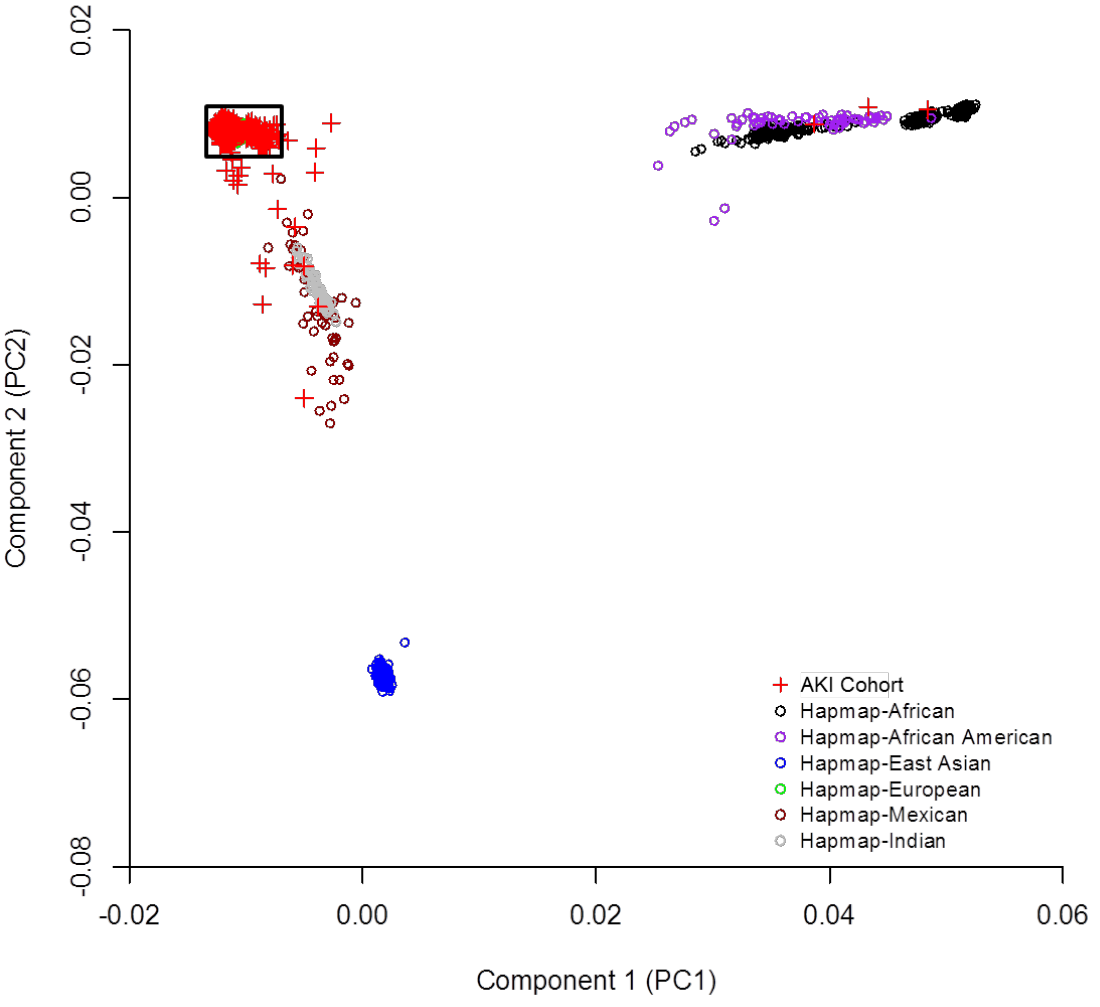


Figure E2


0.02
0.00
-0.02
-0.04
-0.06
-0.08
Component 2 (PC2)
-0.02
0.00
0.02
0.04
0.06
Component 1 (PC1)
AKI Cohort
Hapmap-African
Hapmap-African American
Hapmap-East Asian
Hapmap-European
Hapmap-Mexican
Hapmap-Indian