Genetic loci and prioritization of genes for kidney function decline derived from a meta-analysis of 62 longitudinal genome-wide association studies

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Estimated glomerular filtration rate (eGFR) reflects kidney function. Progressive eGFR-decline can lead to kidney failure, necessitating dialysis or transplantation. Hundreds of loci from genome-wide association studies (GWAS) for eGFR help explain population cross section variability. Since the contribution of these or other loci to eGFR-decline remains largely unknown, we derived GWAS for annual eGFR-decline and meta-analyzed 62 longitudinal studies with eGFR assessed twice over time in all 343,339 individuals and in high-risk groups. We also explored different covariate adjustment. Twelve genome-wide significant independent variants for eGFR-decline unadjusted or adjusted for eGFR-baseline (11 novel, one known for this phenotype), including nine variants robustly associated across models were identified. All loci for eGFR-decline were known for cross-sectional eGFR and thus distinguished a subgroup of eGFR loci. Seven of the nine variants showed variant-by-age interaction on eGFR cross section (further about 350,000 individuals), which linked genetic associations for eGFR-decline with age-dependency of genetic cross-section associations. Clinically important were two to four-fold greater genetic effects on eGFR-decline in high-risk subgroups. Five variants associated also with chronic kidney disease progression mapped to genes with functional *in-silico* evidence (*UMOD, SPATA7, GALNTL5, TPPP*). An unfavorable versus favorable nine-variant genetic profile showed increased risk odds ratios of 1.35 for kidney failure (95% confidence intervals 1.03-1.77) and 1.27 for acute kidney injury (95% confidence intervals 1.08-1.50) in over 2000 cases each, with matched controls). Thus, we provide a large data resource, genetic loci, and prioritized genes for kidney function decline, which help inform drug development pipelines revealing important insights into the age-dependency of kidney function genetics.

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Glomerular filtration rate (GFR) is accepted as best overall index of kidney function.[1] A GFR <60 ml/min per 1.73 m^2 defines chronic kidney disease (CKD),[2] which affects about 10% of adults.[3] A decline in GFR over time is characteristic for CKD progression, which can lead to kidney failure,[4] requiring dialysis or kidney transplantation, with a high risk of premature mortality.[5] In population studies on kidney function, estimated GFR (eGFR) is usually derived from serum creatinine,[6] and annual eGFR decline is the difference between 2 such assessments divided by the years between these assessments. Decline in eGFR is age related, with a physiological loss of ≈1 ml/min per 1.73 m^2 per year[2] generally and 3 ml/min per 1.73 m^2 per year in the presence of diabetes mellitus (DM), a major risk factor for CKD progression.[7,8] Therapeutic options to decelerate kidney function decline are limited. In addition to pharmacologic inhibitors of the renin-angiotensin-aldosterone system,[9] the recent introduction of sodium-glucose cotransporter-2 (SGLT2) inhibitors shows promising renoprotective effects.[10,11] An understanding of the mechanisms of kidney function decline and the development of new therapeutic options is thus of high clinical and public health relevance.[7,12]

Genes underneath genome-wide association study (GWAS) loci for diseases and biomarkers help identify new therapies.[13] Open access GWAS summary statistics from large sample sizes are a highly queried resource, also for causal inference studies.[14] Hundreds of loci and genes are identified by cross-sectional GWAS for eGFR (i.e., GWAS for eGFR based on a single serum creatinine measurement),[15–18] which

help explain population variability. However, the mechanisms underlying a genetic variant association with lower but stable eGFR over time might not always be disease relevant. GWASs on parameters more directly linked to disease progression are thought to better inform drug development.[19]

Current evidence from GWASs on annual eGFR decline is limited, owed to substantial logistics in conducting longitudinal studies and thus small sample sizes. Only one variant, in the *UMOD-PDILT* locus, has been identified at genome-wide significance[20] ($n \approx 60{,}000$). With an estimated heritability of 38% for annual eGFR decline,[20] comparable to 33% to 39% estimated for cross-sectional eGFR in general populations,[15,21] much more can be expected in larger sample sizes. Further 3 loci were genome-wide significant in an extreme phenotype approach, comparing individuals with large eGFR decline or steep decrease into CKD with respective controls.[22] Although these are important binary clinical end points, methodological literature supports the use of regression methods on undichotomized variables.[23]

The limited availability of longitudinal GWASs is not only an issue for kidney function decline, but also generally (e.g., change in lung function [$n = 27{,}249$[24]], glucose [$n = 13{,}807$[25]], or blood pressure [$n = 33{,}720$[26]]); consequently, locus findings on biomarker change are few and often unstable.[14] A challenge beyond power is limited experience in longitudinal GWASs with regard to covariate adjustment: clinical trials for disease-related biomarker change require control for differences in baseline levels between therapy groups.[27] However, covariate adjustment in GWASs requires a careful choice[28]: it can reveal important mediator effects (e.g., DM adjusted for body mass index[29]), alter the phenotype (e.g., waist-to-hip ratio "unexpected" by body mass index[28,30]), and yield artefacts from heritable covariates (collider bias[28]) or nonsense association (e.g., sex adjusted for height[31]). The impact of covariate adjustment on longitudinal GWASs on eGFR decline, and biomarker change generally, is not well explored.

We thus aimed to identify genetic loci associated with annual eGFR decline and CKD progression (defined as eGFR decline among individuals with CKD at baseline) and to prioritize genes that may inform drug development for slowing down eGFR decline and CKD progression. We also aimed to fill the gap of large-data genome-wide single-nucleotide polymorphism (SNP) summary statistics for annual eGFR decline and CKD progression, to help future meta-analyses and Mendelian randomization studies. Finally, we wanted to understand the impact of different covariate adjustment and whether an SNP associated with eGFR decline showed an age-dependent association on eGFR cross-sectionally (i.e., SNP-by-age interaction on eGFR cross-sectionally). By this, we aimed to contribute to a better understanding of the interpretation of genetic findings for eGFR decline and other progression traits.

To achieve these aims, we (i) increased sample size for GWASs on annual eGFR decline to >340,000 individuals based on the CKD Genetics (CKDGen) consortium[32] and UK Biobank,[33] (ii) applied a suite of covariate adjustment models, (iii) analyzed SNP-by-age interaction on eGFR cross-sectionally in >350,000 individuals independent of the GWAS on decline, and (v) conducted genetic risk score (GRS) analyses for acute kidney injury (AKI) and end-stage kidney disease (ESKD).

METHODS

We conducted GWAS meta-analysis based on study-specific summary statistics. Each study utilized data on 2 measurements of serum creatinine over time and genome-wide SNP information imputed to 1000 Genomes[34] phase 1 or phase 3, the Haplotype Reference Consortium[35] v1.1, or similar group (Supplementary Tables S1 and S2). Serum creatinine, measured at baseline and follow-up, was used to estimate eGFR at baseline and follow-up, respectively, according to the CKD Epidemiology Collaboration equation.[6] Annual eGFR decline was defined as "–(eGFR at follow-up – eGFR at baseline) / number of years of follow-up." GWAS analyses were conducted separately by ancestry (if applicable), where ancestry was defined by genetic principal components or participants' self-report. GWASs were based on linear regression with different covariate adjustment conducted overall and focused on individuals with DM or CKD at baseline.

Study-specific genome-wide summary statistics and detailed phenotype information were transferred to the meta-analysis center. For each SNP, summary statistics were pooled and genomic control was corrected. Significant genetic variants were identified, and respective locus regions were selected.

In addition, we investigated identified SNPs for SNP-by-age interaction on cross-sectional eGFR (based on creatinine or cystatin C [eGFRcrea or eGFRcys, respectively]) using UK Biobank data that were independent of the SNP identification step (excluding the individuals in the decline GWAS). We computed the GRS and its association on eGFR decline in The Trøndelag Health Study (The HUNT study) via linear regression and provided odds ratios (ORs) for GRS association in case-control studies on AKI and ESKD via logistic regression.

Detailed methods are provided in the Supplementary Methods.

RESULTS

Overview across studies and models for GWASs

This GWAS meta-analysis included 343,339 individuals from 62 studies (Supplementary Tables S1 and S3, Supplementary Figure S1, and Methods) and 12,403,901 analyzable SNPs. Most studies were population based (76%) and of European ancestry (74%). Study-specific median annual eGFR decline was independent of sample size and follow-up length (Supplementary Figure S2A and B), and the median across studies was 1.32 ml/min per 1.73 m^2 per year; follow-up length was 1 to 21 years (median [25th–75th percentile], 5 [4–7] years); and median age ranged from 33 to 77 years (Supplementary Figure S2C).

All analyses were adjusted for age-, sex-, and study-specific covariates, which is not mentioned further from here on (stable across different modes of age adjustment; Supplementary Figure S3). We had 5 GWAS results for eGFR decline (Methods): (i) "unadjusted," (ii) "DM adjusted," (iii) "adjusted for eGFR baseline," (iv) restricted to individuals with DM at baseline (unadjusted), and (v) restricted to individuals with CKD at baseline (unadjusted).

Similarities and differences across different model adjustments

There is, to date, no standard conduct for GWASs on eGFR decline with regard to covariate adjustment. We explored the impact of 2 potentially important covariates additional to age and sex: (i) DM, as an important risk factors for eGFR decline and potential mediator; and (ii) eGFR at baseline, as adjustment for baseline levels in analyses of change over time, has noted pros (larger effects and better detectability) and cons (biased effects).[36,37]

With regard to DM adjustment, this model was computed in all studies (n = 343,339; 62 studies) and compared with unadjusted results for a subset of studies of varying scope (n = 103,970). DM-adjusted SNP associations on eGFR decline were precisely the same as unadjusted, in terms of β estimates and SEs (Supplementary Figure S4A and Supplementary Note S1). We therefore did not distinguish these 2 models further.

In contrast, adjustment for eGFR baseline altered SNP associations on eGFR decline (Supplementary Figure S4B). Therefore, results from both eGFR decline unadjusted and adjusted for eGFR baseline were evaluated in the following. GWAS summary statistics for eGFR decline adjusted for eGFR baseline were formula derived from GWAS summary statistics for unadjusted eGFR decline and for eGFR baseline together with study-specific phenotypic information (Supplementary Note S2). In a subset of studies (n = 103,970), we validated that the formula approach worked well in our setting (Supplementary Note S3 and Supplementary Figure S4C and D). Meta-analysis yielded GWAS results for eGFR decline adjusted for eGFR baseline for 320,737 individuals (50 studies; Supplementary Figure S1).

Twelve variants identified for eGFR decline unadjusted or adjusted for eGFR baseline

First, our genome-wide screen for eGFR decline unadjusted for eGFR baseline (n = 343,339) identified 2 genome-wide significant independent variants near *UMOD-PDILT* ($P_{DECLINE} < 5 \times 10^{-8}$; Figure 1a and Table 1): *rs34882080*, highly correlated with *rs12917707* identified previously for this phenotype ($r^2 = 1.00$)[20]; and *rs77924615*, known for altering *UMOD* expression and urine uromodulin[15] and genome-wide significant for eGFR decline for the first time.

Second, we evaluated the 263 additional lead variants known for cross-sectional eGFR GWASs[15] for association with baseline-unadjusted eGFR decline (candidate approach); we had a prior hypothesis that cross-sectionally known variants might also show association with eGFR decline. We identified 2 additional variants for eGFR decline near *PRKAG2* and *SPATA7*, both new loci for this phenotype, at Bonferroni-corrected significance ($P_{DECLINE} < 0.05/263 = 1.90 \times 10^{-4}$; Table 1).

Third, our genome-wide screen for eGFR decline adjusted for eGFR baseline (n = 320,737) identified 12 independent variants across 11 loci ($P_{DECLINE}$ or $P_{DECLINE adj_{BL}} < 5 \times 10^{-8}$; Figure 1b), including the 4 variants already identified by the baseline-unadjusted analyses (directly or via high correlation; $r^2 \geq 0.9$). The 8 variants additionally identified pointed to novel loci for this phenotype. Of these, 5 variants also showed directionally consistent, significant association for eGFR decline unadjusted for eGFR baseline (Bonferroni-corrected, $P_{DECLINE} < 0.05/12 = 4.17 \times 10^{-3}$; near *FGF5*, *OVOL1*, *TPPP*, *C15ORF54*, and *ACVR2B*; Table 1), but 3 variants did not ($P_{DECLINE}$ from 0.156 to 0.710; near *GATM*, *CPS1*, *SHROOM3*; Table 1).

Overall, we found 12 variants across 11 loci with genome-wide significant association for eGFR decline unadjusted and/or adjusted for eGFR baseline ($P_{DECLINE}$ or $P_{DECLINE adj_{BL}} < 5 \times 10^{-8}$). All but one variant/locus were novel for this phenotype. All resided in loci known for eGFR cross-sectional GWAS,[15] but none was associated with DM status (Supplementary Table S4).

The 12 variants' associations showed no between-ancestry heterogeneity, stable statistics in various sensitivity analyses, and no impact by DM adjustment (Supplementary Table S5 and S6). Meta-analysis restricted to African American (n = 9038) did not identify associations for published *APOL1* risk variants,[38] but 2 other suggestive variants (Supplementary Table S7).

The 12 variants included 9 variants with nonzero effects on eGFR decline unadjusted for eGFR baseline (i.e., Bonferroni-corrected significant; $P_{DECLINE} < 4.17 \times 10^{-3}$).

SNP effects for eGFR decline were larger when baseline-adjusted than baseline-unadjusted

Several interesting aspects emerged when comparing genetic effect sizes of the 12 identified variants across models. First, we observed consistently larger effects for eGFR decline baseline-adjusted than baseline-unadjusted (Figure 2a), also when restricting to studies where the baseline-adjusted model was directly computed (inserted small panel; Figure 2a). This, together with the smaller SEs (Supplementary Figure S4B), explained the larger yield of genome-wide significant loci in the baseline-adjusted GWAS.

Second, we contrasted effect sizes for eGFR decline unadjusted for eGFR baseline with those for cross-sectional eGFR[15] (Figure 2b). Three variants showed relatively extreme cross-sectional effects and no effect on decline (near *GATM*, *SHROOM3*, and *CPS1*). For the other 9 variants, the faster-decline allele was always the cross-sectional eGFR-lowering allele (Spearman correlation coefficient = –0.32). A similar more schematic presentation (Figure 2c) illustrates the mathematical relationship between baseline-adjusted and baseline-unadjusted effect sizes (Supplementary Note S4). This yields a corollary on the directionality of baseline-adjusted effect sizes: when the faster-decline allele (i.e., $\widehat{\beta}_{DECLINE} > 0$) coincides with the baseline eGFR-lowering allele (i.e., $\widehat{\beta}_{BL} < 0$), then the baseline-adjusted eGFR-decline effect size is larger than baseline-unadjusted effect size (i.e., $\widehat{\beta}_{DECLINE_{adj_{BL}}} > \widehat{\beta}_{DECLINE}$), in theory. Our data confirmed this empirically (Figure 2a). The larger genetic effect sizes for eGFR decline adjusted for eGFR baseline are thus a direct consequence of the phenotypic and genetic correlation

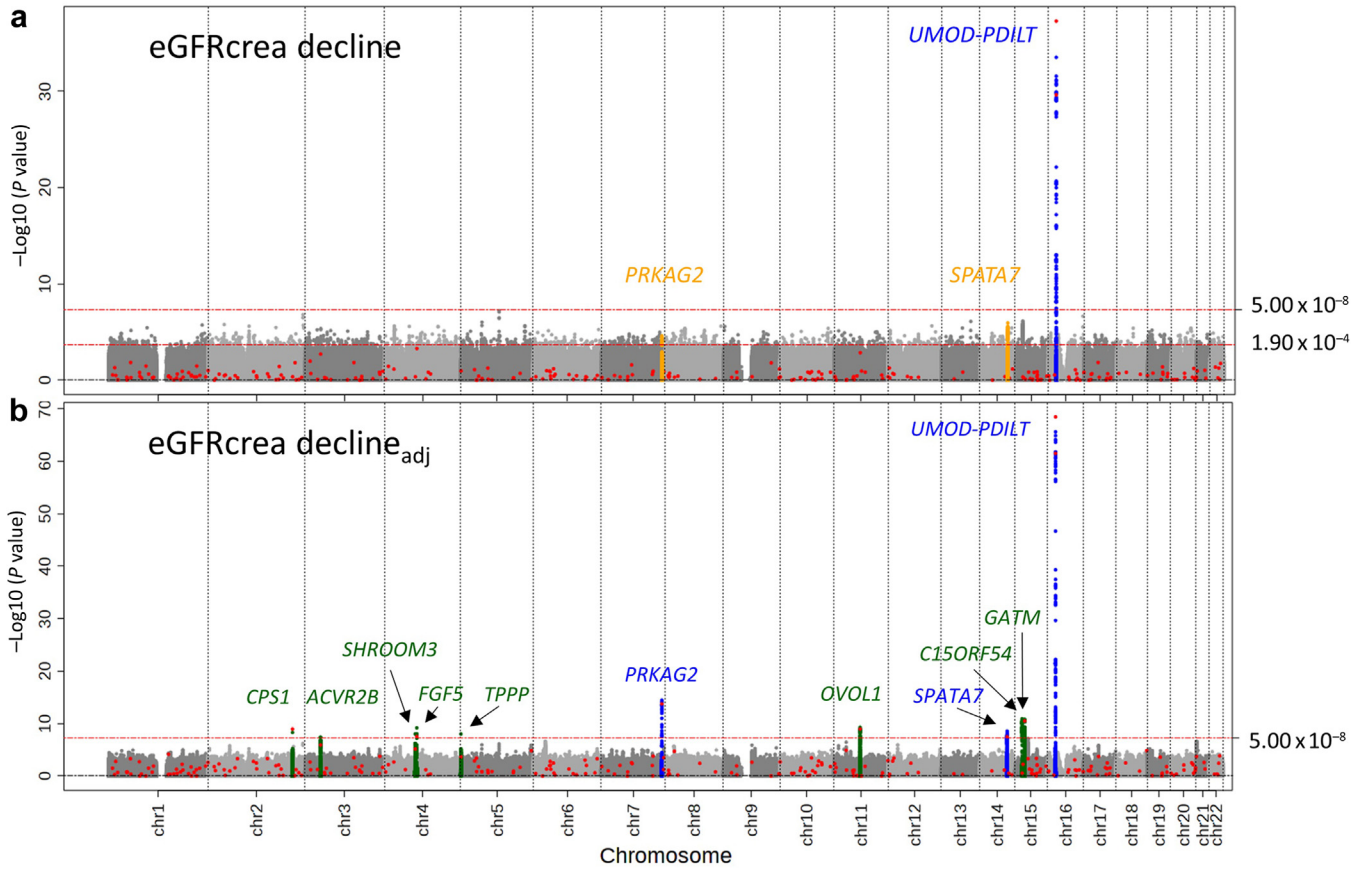

Figure 1 | Eleven loci identified by genome-wide association study (GWAS) for estimated glomerular filtration rate (eGFR) decline unadjusted and/or adjusted for eGFR baseline. We conducted GWASs for eGFR decline baseline-unadjusted and baseline-adjusted (n up to 343,339 or 320,737, respectively). Shown are association *P* values versus genomic position, identified loci annotated by nearest gene. (**a**) Association for eGFR decline baseline-*unadjusted* identified 1 genome-wide significant locus for decline ($P < 5 \times 10^{-8}$) and 2 Bonferroni-corrected significant loci among the 263 lead variants for cross-sectional eGFR[15] outside of *UMOD-PDILT* (red dots, $P < 0.05/263 = 1.90 \times 10^{-4}$; known locus for decline marked in blue; novel loci for this phenotype in orange). (**b**) Association for eGFR decline baseline-*adjusted* identified 8 additional loci (novel loci marked in green; known loci or loci already identified in [**a**] marked in blue). Altogether, 11 loci were identified with genome-wide significance for eGFR decline unadjusted and/or adjusted for eGFR baseline. eGFRcrea, eGFR based on creatinine.

between eGFR decline and eGFR baseline. The genetic effect for eGFR decline unadjusted for eGFR baseline provides the relevant effect size for further use and allows us to distinguish between a "genuine association with eGFR decline" (9 variants) and a pure "collider bias" effect (3 variants).

Four genes with compelling biological *in silico* evidence mapped to novel eGFR-decline loci

All 11 identified loci for eGFR decline coincided with loci detected for cross-sectional eGFR: among the 12 identified variants, 11 were genome-wide significant for cross-sectional eGFR,[15] and the variant near *TPPP* showed $P = 7.63 \times 10^{-6}$ cross-sectionally with genome-wide significant variants nearby (Supplementary Figure S5A–C and Supplementary Note S5).

The 8 loci with genuine association for eGFR decline included the well-known *UMOD-PDILT* locus. Biological evidence at the other 7 loci was summarized using the Gene PrioritiSation tool,[18] generated from GWAS data on cross-sectional eGFR, including evidence for SNP-modulated gene expression (expression quantitative trait locus; false-discovery rate, <0.05): 4 lead variants or highly correlated proxies were expression quantitative trait loci in tubule-interstitial kidney tissue with upregulating effects for *SPATA7* and *GALNTL5* (in *PRKAG2* locus, kidney-tissue specific), a downregulating effect for *FGF5* (kidney-tissue specific), and an upregulating effect for *TPPP* using the Nephrotic Syndrome Study Network (NEPTUNE[39]). This supported these 4 genes in novel loci for eGFR decline as kidney tissue relevant and potentially causal genes for the association signals.

SNPs for eGFR decline showed SNP-by-age interaction on cross-sectional eGFR

In the absence of birth cohort effects, we hypothesized that an SNP associated with eGFR decline might also show an age-dependent association on cross-sectional eGFR, which is SNP-by-age interaction on cross-sectional eGFR. Of note, the age effect on eGFR should reflect the age effect on filtration rate, not on creatinine metabolism, within limits of uncertainty of the CKD Epidemiology Collaboration formula.[6] To empirically assess this hypothesis, we tested the identified 12

Table 1 | Twelve independent variants in 11 loci identified for association with eGFR decline unadjusted and adjusted for eGFR baseline

						Decline		$Decline_{adj}$		Cross-sectional	
SNPID	Locus name	Chr	Pos	EA/OA	EAF	β	*P*	β	*P*	β	*P*
From GWAS/candidate search for decline (baseline-unadjusted)[a]											
rs34882080	*UMOD-PDILT*	16	20, 361, 441	a/g	0.815	0.065	**2.45×10^{-30}**	0.092	**3.31×10^{-62}**	–0.009	**2.86×10^{-95}**
rs77924615	*UMOD-PDILT*	16	20, 392, 332	g/a	0.798	0.074	**5.30×10^{-38}**	0.099	**3.75×10^{-69}**	–0.010	**1.45×10^{-138}**
rs10254101	*PRKAG2*[d]	7	151, 415, 536	t/c	0.276	0.020	**4.10×10^{-5}**	0.037	**1.78×10^{-14}**	–0.007	**1.85×10^{-67}**
rs1028455	*SPATA7*[d]	14	88, 829, 975	t/a	0.657	0.021	**5.90×10^{-6}**	0.024	**3.43×10^{-8}**	–0.002	**4.78×10^{-10}**
From GWAS for $decline_{adj}$, with association for decline (baseline-unadjusted)[b]											
rs1458038	*FGF5*	4	81, 164, 723	c/t	0.690	0.019	**3.87×10^{-5}**	0.028	**6.85×10^{-10}**	–0.003	**7.49×10^{-24}**
rs4930319	*OVOL1*	11	65, 555, 458	c/g	0.333	0.015	**9.93×10^{-4}**	0.028	**5.27×10^{-10}**	–0.003	**2.21×10^{-24}**
rs434215	*TPPP*[e]	5	699, 046	a/g	0.277	0.020	**3.70×10^{-4}**	0.032	**7.19×10^{-9}**	–0.003	7.63×10^{-6}
rs28857283	*C15ORF54*[f]	15	39, 224, 711	g/a	0.656	0.021	**1.47×10^{-6}**	0.030	**1.31×10^{-11}**	–0.002	**6.20×10^{-9}**
rs13095391	*ACVR2B*	3	38, 447, 232	a/c	0.502	0.017	**1.77×10^{-4}**	0.025	**4.03×10^{-8}**	–0.003	**6.57×10^{-15}**
From GWAS for $decline_{adj}$, without association for decline (baseline-unadjusted)[c]											
rs9998485	*SHROOM3*	4	77, 362, 445	a/g	0.466	0.007	0.156	0.027	**9.84×10^{-9}**	–0.005	**1.22×10^{-41}**
rs1047891	*CPS1*	2	211, 540, 507	a/c	0.293	0.004	0.441	0.029	**1.15×10^{-9}**	–0.007	**1.18×10^{-75}**
rs2453533	*GATM*	15	45, 641, 225	a/c	0.422	0.002	0.710	0.029	**1.72×10^{-11}**	–0.009	**4.57×10^{-141}**

β, genetic effect coefficient of association; Chr, chromosome on GRCh37; $Decline_{adj}$, adjusted decline; EAF, effect allele frequency; EA/OA, effect allele/other allele; eGFR, estimated glomerular filtration rate; GWAS, genome-wide association study; Locus name, nearest gene; Pos, position on GRCh37; *P*, association *P* value; SNPID, variant identifier on GRCh37.

We conducted GWASs for eGFR decline baseline-unadjusted and baseline-adjusted ("decline", n up to 343,339; $decline_{adj}$, n up to 320,737).

[a]Two variants were identified with genome-wide significance for eGFR decline baseline-unadjusted (*UMOD-PDILT*; $P_{decline} < 5 \times 10^{-8}$) and 2 further variants in a candidate search of the 263 variants known for cross-sectional eGFR[15] outside *UMOD-PDILT*, judged at Bonferroni-corrected significance ($P_{decline} < 0.05/263 = 1.90 \times 10^{-4}$; *PRKAG2* and *SPATA7*).

[b]Five variants were identified with genome-wide significance for eGFR decline baseline-adjusted AND Bonferroni-corrected significant baseline-unadjusted ($P_{decline\text{-}adj\text{-}BL} < 5 \times 10^{-8}$, and $P_{decline} < 0.05/12 = 4.17 \times 10^{-3}$).

[c]Three variants were identified with genome-wide significance for eGFR decline baseline-adjusted but not significantly associated baseline-unadjusted ($P_{decline\text{-}adj\text{-}BL} < 5 \times 10^{-8}$, and $P_{decline} \geq 4.17 \times 10^{-3}$). For each identified variant, we show results for decline (baseline-unadjusted), for decline baseline-adjusted, and for cross-sectional eGFR.[15] The β estimates are in ml/min per 1.73 m^2 per year and per faster-decline allele; significant *P* values are stated in bold.

[d]In *PRKAG2* and *SPATA7* loci, variants with smallest $P_{decline}$ (*rs73158188* and *rs7160717*, respectively) were highly correlated with these candidate-based variants ($r^2 = 1.00$ and 0.93, respectively).

[e]Because the *TPPP* locus lead variant had imputation quality <0.6 in 45% of the studies (median, 0.64), we analyzed this locus omitting the imputation quality filter (with filter: $decline_{adj}$ $\beta = 0.033$, $P = 1.00 \times 10^{-8}$; decline $\beta = 0.015$, $P = 0.039$; median imputation quality = 0.74).

[f]In the *C15ORF54* locus, the identified lead variant for decline was highly correlated with a second signal lead variant for cross-sectional eGFR (*rs28833881*; $r^2 = 0.90$), but not with the first signal lead variant (*rs12913015*; $r^2 = 0.04$).

SNPs for SNP-by-age interaction on cross-sectional eGFRcrea or eGFRcys in UK Biobank data, which was independent from and similarly sized as the decline GWAS (n = 351,462 or 351,601 for eGFRcrea or eGFRcys, respectively; Methods). For 8 of the 12 SNPs, we found SNP-by-age interaction for eGFRcrea and/or eGFRcys at Bonferroni-corrected significance ($P_{SNPxage} < 0.05/12 = 4.17 \times 10^{-3}$; Table 2). Interaction effect sizes were similar between eGFRcrea and eGFRcys (Figure 3a), except for the SNP near *GATM*.

The age dependency of all SNP effects and main age effects was approximately linear (Supplementary Figure S6 and Supplementary Note S6). The SNP-by-age interaction effect size can also be interpreted as the genetically modified age effect on eGFR. This effect was large (e.g., 5 unfavorable alleles decreased eGFRcys by –0.136 ml/min per 1.73 m^2 per year, which was ≈10% of the overall age effect on eGFRcys [–1.024 ml/min per 1.73 m^2 per year; Supplementary Note S6]). SNP-by-age interaction effects on eGFRcys were highly correlated with SNP effects on eGFR decline (both in units of ml/min per 1.73am^2 per allele and year: "per year of age difference between individuals" and "per year of person's aging," respectively; Figure 3b).

There was a noteworthy pattern with regard to presence and direction of SNP-by-age interaction. (i) Among the 9 variants with genuine association for eGFR decline, 7 showed significant SNP-by-age interaction on cross-sectional eGFRcys (Table 2). All interaction effects were negative (i.e., the cross-sectional SNP effect became larger [in absolute value] with older age). (ii) Among the 3 SNPs without genuine association for eGFR decline, 2 showed no SNP-by-age interaction; the third (near *GATM*) showed SNP-by-age interaction, but only for eGFRcrea and with positive direction ($\widehat{\beta}_{SNPxage} = 0.138$; $P_{SNPxage} = 9.71 \times 10^{-5}$). Thus, the *GATM* SNP effect on cross-sectional eGFRcrea gets smaller (in absolute value) by higher age. This might be explained by *GATM* being the rate-limiting enzyme in creatine synthesis in muscle, age-related loss of muscle mass, and thus decreased creatinine production with increasing age, in line with the lack of interaction with eGFRcys, which is unrelated to muscle mass.

A concept of 3 classes of SNPs for cross-sectional eGFR distinguished by their eGFR-decline association

Our results suggested that SNPs for eGFR decline were found among SNPs associated with eGFR cross-sectionally. This

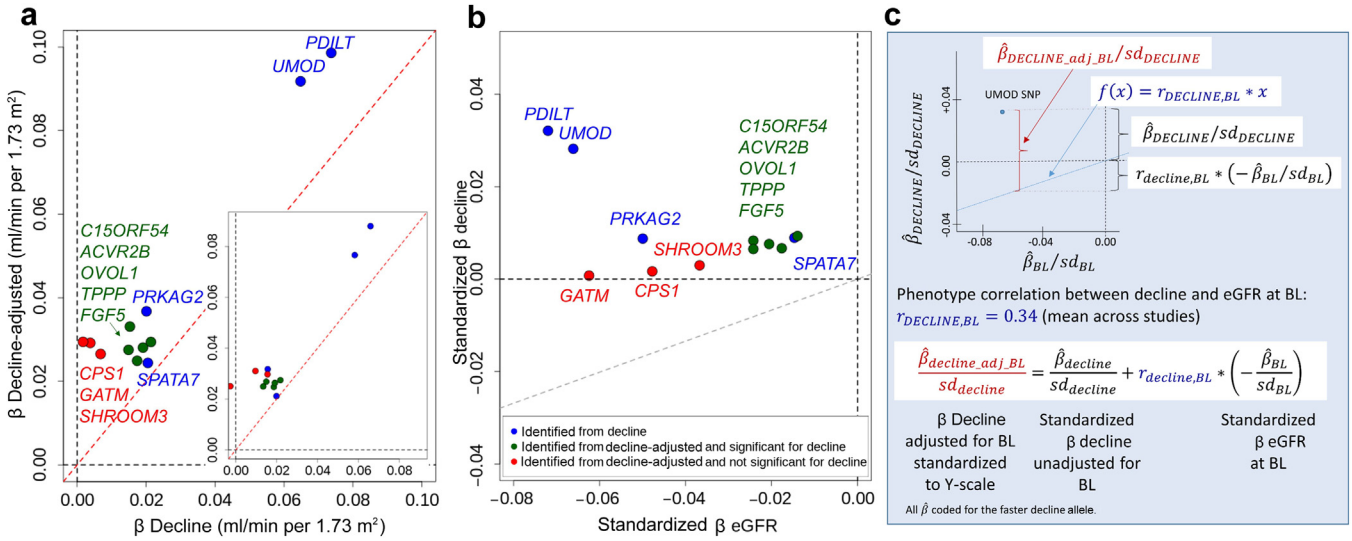

Figure 2 | Relationship of single-nucleotide polymorphism (SNP) effects on estimated glomerular filtration rate (eGFR)–decline baseline (BL)–unadjusted with baseline-adjusted effects for the 12 identified variants. (**a**) SNP effects per year and allele for eGFR decline baseline-*unadjusted* ("decline") versus eGFR decline baseline-*adjusted* in all studies ($n_{decline}$ = 343,339; $n_{decline\text{-}adj}$ = 320,737) and restricted to studies where baseline-adjusted results were computed rather than formula derived (inserted panel; n = 103,970; red line indicates identify line). (**b**) Standardized SNP effects per year and allele for eGFR decline baseline-*unadjusted* ($\hat{\beta}_{DECLINE}/sd_{DECLINE}$, n = 343,339) and per allele for cross-sectional eGFR on ln scale ($\hat{\beta}_{BL}/sd_{BL}$, n = 765,348[15]); gray line indicates phenotype correlation line $y = 0.34 * x$ (0.34 = mean phenotype correlation across studies). (**a,b**) Coding allele is the faster-decline allele (=cross-sectional eGFR-lowering allele). Color codes whether SNP was identified for decline baseline-unadjusted and/or baseline-adjusted. (**c**) Illustration of the SNP effect for eGFR decline baseline-adjusted (standardized to Y-scale) as a sum of the SNP effect baseline-unadjusted (standardized) and the correlation-weighted SNP effect on eGFR at baseline (standardized).

motivated the idea of, in theory, 3 classes of SNP associations on cross-sectional eGFR (intercept) distinguished their eGFR-decline association unadjusted for eGFR baseline (slope; Figure 4): no association with slope (*class I*), association of the eGFR-baseline lowering allele with flatter slope (*class II*), or association of the eGFR-baseline lowering allele with steeper slope (*class III*).

Table 2 | SNP-by-age interaction for cross-sectional eGFR for the 12 identified variants

			SNP × age interaction eGFRcrea		SNP × age interaction eGFRcys	
SNPID	Locus name	EA/OA	β	*P*	β	*P*
From GWAS/candidate search for decline (baseline-unadjusted)						
rs34882080	*UMOD-PDILT*	a/g	−0.043	**5.53×10^{-22}**	−0.045	**2.37×10^{-17}**
rs77924615	*UMOD-PDILT*	g/a	−0.050	**2.55×10^{-29}**	−0.054	**6.59×10^{-25}**
rs10254101	*PRKAG2*	t/c	−0.009	0.0263	−0.015	**9.84×10^{-4}**
rs1028455	*SPATA7*	t/a	−0.014	**2.19×10^{-4}**	−0.014	**1.06×10^{-3}**
From GWAS for $decline_{adj}$, with association for decline (baseline-unadjusted)						
rs1458038	*FGF5*	c/t	−0.013	**7.11×10^{-4}**	−0.013	**3.12×10^{-3}**
rs4930319	*OVOL1*	c/g	−0.015	**2.55×10^{-5}**	−0.016	**1.84×10^{-4}**
rs434215	*TPPP*	a/g	−0.028	**1.02×10^{-10}**	−0.033	**5.02×10^{-11}**
rs28857283	*C15ORF54*	g/a	−0.010	5.09×10^{-3}	−0.006	0.148
rs13095391	*ACVR2B*	a/c	0.004	0.227	0.002	0.695
From GWAS for $decline_{adj}$, without association for decline (baseline-unadjusted)						
rs9998485	*SHROOM3*	a/g	−0.004	0.206	−0.009	0.022
rs1047891	*CPS1*	a/c	0.004	0.228	0.005	0.244
rs2453533	*GATM*	a/c	0.014	**9.71×10^{-5}**	0.002	0.722

β, genetic effect coefficient of association; $decline_{adj}$, adjusted decline; EA/OA, effect allele/other allele; eGFR, estimated glomerular filtration rate; eGFRcrea, estimated glomerular filtration rate based on creatinine; eGFRcys, estimated glomerular filtration rate based on cystatin C; GWAS, genome-wide association study; Locus name, nearest gene; *P*, association *P* value; SNP, single-nucleotide polymorphism; SNPID, variant identifier on GRCh37.
For the 12 identified variants, we conducted SNP-by-age interaction analysis for cross-sectional eGFRcrea and eGFRcys in UK Biobank (excluding individuals from decline GWAS; n = 351,462 for eGFRcrea, and n = 351,601 for eGFRcys; main age effect modeled nonlinearly, main SNP effect linearly, age centered at 50 years). The interaction term (age effect and SNP effect modeled linearly) was judged at Bonferroni-corrected significance level ($P < 0.05/12 = 4.17 \times 10^{-3}$). The β estimates are in ml/min per 1.73 m^2 per year and per cross-sectional eGFR-lowering allele (which was equivalent to faster-decline allele for each SNP); significant *P* values are stated in bold. The *TPPP* variant *rs434215* is well imputed in the UK Biobank (imputation quality = 0.82).

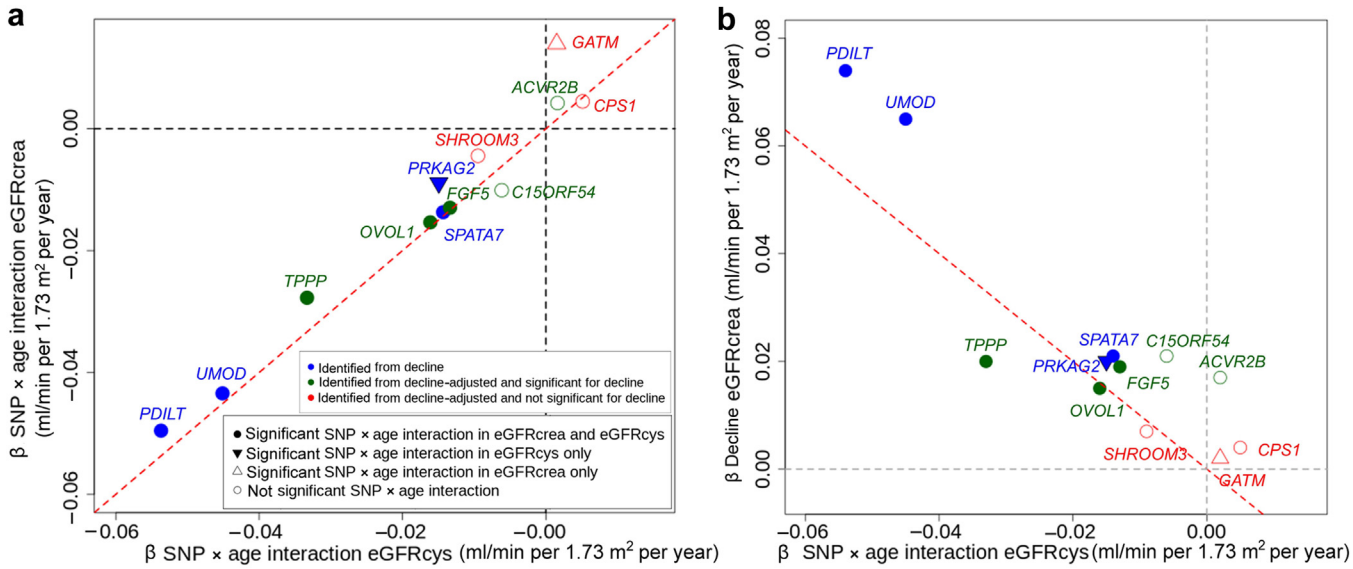

Figure 3 | Relationship of single-nucleotide polymorphism (SNP)–by–age interaction effects for estimated glomerular filtration rate based on cystatin C (eGFRcys) with those of estimated glomerular filtrate rate based on creatinine (eGFRcrea) and with SNP effects for estimated glomerular filtration rate (eGFR) decline for the 12 identified variants. Shown are SNP-by-age interaction effect sizes per year and allele for cross-sectional eGFRcys (UK Biobank individuals independent from genome-wide association study; $n_{SNPxage}$ = 351,601; main age effect modeled nonlinearly, main SNP effect linearly, age effect and SNP effect in interaction term linearly, age centered at 50 years) versus: (**a**) SNP-by-age interaction effects on cross-sectional eGFRcrea ($n_{SNPxage}$ = 351,462) and (**b**) SNP effects on eGFR decline baseline-unadjusted per year and allele ($n_{decline}$ = 343,339). Coding allele is the faster-decline allele (=cross-sectional eGFR-lowering allele); color code as in Figure 2; red line indicates identity line; symbol types code significance of interaction term ($P < 0.05/12$). Among the 9 SNPs with genuine eGFR-decline association, 7 SNPs showed interaction for eGFRcrea or eGFRcys (all negative), and all 3 SNPs without genuine eGFR-decline association showed no interaction for eGFRcys (1 with positive significant interaction for eGFRcrea).

In our data, we found the following. (i) Of the 12 SNPs as *class I*, 3 were in line with the lack of SNP-by-age interaction on eGFR cross-sectionally (judged for eGFRcys). (ii) No variant was *class II*, consistent with the lack of positive SNP-by-age interaction on eGFRcys. (iii) The 9 variants with genuine eGFR-decline association were *class III*, and 7 of these showed negative SNP-by-age interaction on eGFR. Thus, our data supported 2 classes of genetic effects on eGFR: no association with slope or steeper slope for the eGFR-lowering allele.

Larger SNP effects for eGFR decline were observed in high-risk subgroups

Individuals with DM and/or CKD (defined as eGFR <60 ml/min per 1.73 m^2) are at higher risk for CKD progression and kidney failure, prompting us to quantify SNP effects on eGFR decline in these high-risk subgroups (meta-analysis for eGFR decline unadjusted for eGFR baseline restricted to DM or CKD at baseline; n = 37,375 or 26,653, respectively; Methods). For the 9 variants with genuine eGFR-decline association, we found almost all effects to be 2- to 4-fold larger in DM or in CKD compared with the overall analysis (Table 3; average effect size [ml/min per 1.73 m^2 per year and allele]: 0.061 in DM, 0.079 in CKD, compared with 0.030 overall).

To get an idea of the magnitude, we scaled the effects to "per 5 unfavorable average alleles," resulting in a decline of 0.305 in DM, 0.395 in CKD, compared with 0.150 ml/min per 1.73 m^2 per year overall. This compared well with the 9-variant weighted GRS effect on eGFR decline per 5 unfavorable average alleles in the HUNT study (n = 2235 with DM, n = 502 with CKD, and n = 46,328 overall; Methods): 0.219 in DM, 0.262 in CKD, and 0.102 ml/min per 1.73 m^2 per year overall (1-sided $P = 1.57 \times 10^{-5}$, $P = 0.0193$, and $P = 1.06 \times 10^{-34}$, respectively).

The genetic effect sizes were also larger in the 2 subgroups when viewed relative to the phenotype variance (on the example of HUNT; Methods): *rs77924615* variant (*UMOD-PDILT* locus) explained 0.38% of the eGFR-decline variance in DM, 0.47% in CKD, and 0.22% overall; the 9 variants jointly explained 1.14%, 1.48%, and 0.51%, respectively. Of note, the explained variance of eGFR decline overall was comparable to the explained variance of cross-sectional eGFR (*rs77924615*: 0.21%; 9 variants: 0.62%), but narrow-sense heritability was smaller (Supplementary Note S7).

GALNTL5, *SPATA7*, and *TPPP* were identified as candidates for CKD progression

Variants associated with CKD progression and mapped genes might help identify drug targets against disease progression.[19] We queried the 9 SNPs with genuine association for eGFR decline for significant association with CKD progression (i.e., whether they still showed significant association with eGFR decline when focusing on individuals with CKD at baseline [judged at $P < 0.05/9 = 5.56 \times 10^{-3}$; n up to 26,547]). We found 5 such SNPs: (i) 2 in the *UMOD-PDILT* locus, which confirmed *UMOD* for a role in CKD progression; and (ii) 3 SNPs in novel loci for eGFR decline, which mapped to 3 genes

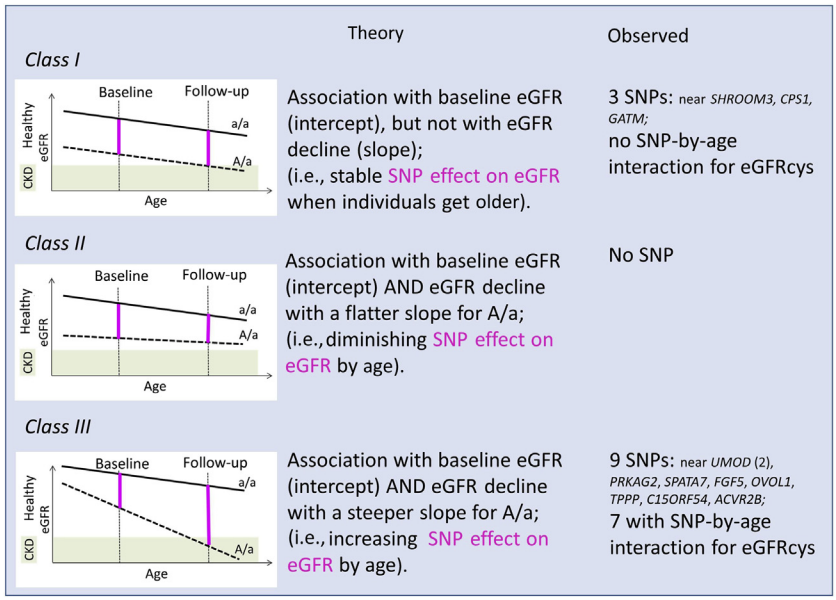

Figure 4 | A concept for 3 classes of single-nucleotide polymorphism (SNP) associations on cross-sectional estimated glomerular filtration rate (eGFR) distinguished by the presence and direction of the SNP association with eGFR decline. Let *A/a* be the genotype group of individuals with, on average, lower cross-sectional eGFR compared with *a/a* (*A* = effect allele). Let us further assume that eGFR declines monotonously by age (approximated as linear decline) and that there is no "crossover" between genotype groups. Shown are (left) a graphical scheme, (middle) the theoretical association, and (right) the observed SNPs in line with the respective class. In the 3 graphical schemes, black lines illustrate mean eGFR decline by genotype group; SNP effects on eGFR for these individuals captured cross-sectionally at different ages are magenta. When a cross-sectional study captures individuals of relevant ages, the SNP effects on eGFR should show an interaction by age for *class II* and *class III* SNPs (positive and negative, respectively). The 9 variants with genuine eGFR-decline association were *class III*, whereas the other 3 variants were *class I*. CKD, chronic kidney disease; eGFRcys, eGFR based on cystatin C.

with expression quantitative trait loci in kidney tissue (*GALNTL5* in *PRKAG2* locus, kidney-tissue specific; *SPATA7*, and *TPPP*), making these compelling candidates as CKD-progression genes.

Unfavorable GRS increased the risk for ESKD and AKI

Finally, we wanted to understand the cumulative impact of the 9 genuine eGFR-decline variants for severe clinical end points. We thus evaluated the 9-variant weighted GRS in cases-control studies for ESKD and AKI via logistic regression (n_{cases} = 2068 and 3878, and $n_{controls}$ = 4640 and 11,634, respectively; Methods). The GRS effect per 5 unfavorable average alleles showed a significant OR of 1.12 for ESKD (95% confidence interval [CI], 0.99–1.23; 1-sided $P = 0.033$) and OR of 1.18 for AKI (95% CI, 1.09–1.27; 1-sided $P < 0.0001$; Table 4). When comparing the individuals with GRS ≥90th versus ≤10th percentile (i.e., ≥14.6 unfavorable alleles vs. ≤8.3 in UK Biobank), we found a significant OR of 1.35 for ESKD (95% CI, 1.03–1.77; 1-sided $P = 0.0157$) and OR of 1.27 (95% CI, 1.08–1.50; 1-sided $P = 0.002$; Table 4).

DISCUSSION

Herein, we provide data and results on a large longitudinal GWAS on annual eGFR decline with >340,000 individuals from mostly population-based studies; to our knowledge, this is the largest GWAS on annual eGFR decline so far and probably one of the largest longitudinal GWASs of any trait. We identified 12 variants across 11 loci as genome-wide significant for annual eGFR decline unadjusted and/or adjusted for eGFR baseline (Figure 5). These included 9 variants across 8 loci with nonzero association unadjusted for eGFR baseline, which we termed "genuinely" associated with eGFR decline. Of these 9 variants, 7 also showed SNP-by-age interaction on cross-sectional eGFR in independent data of >350,000 individuals, whereas the 3 variants without genuine association did not. We generated and provide genome-wide summary statistics for eGFR decline, CKD progression, and eGFR decline in DM. This data resource is informative for future meta-analyses, causal inference studies via Mendelian randomization,[40] and drug development pipelines.

Clinically important is our finding of the 2- to 4-fold larger genetic effects of almost all identified variants when focusing on individuals with DM or CKD at baseline, because these individuals are already at higher risk of kidney failure. This observation is in line with a "horse-racing effect"[41] ("a faster horse is more likely observed up front"): individuals with an accumulation of faster eGFR-decline alleles are more likely observed with low eGFR at a given point in time, implying that these genetic effects might partly explain lower eGFR at baseline. A part of the larger eGFR-decline effect among CKD individuals might reflect collider bias. However, DM status does not fulfill the characteristics of a collider for the SNP

Table 3 | The 9 variants' effects on eGFR decline unadjusted for eGFR baseline in high-risk subgroups

		Decline among DM at baseline		Decline among CKD at baseline		Decline among all	
SNPID	Locus name	β	95% CI	β	95% CI	β	95% CI
From GWAS/candidate search for decline (baseline-unadjusted)							
rs34882080	*UMOD-PDILT*	0.159[a]	0.108, 0.211	0.138[a]	0.074, 0.203	0.065	0.054, 0.076
rs77924615	*UMOD-PDILT*	0.136[a]	0.084, 0.189	0.167[a]	0.099, 0.235	0.074	0.063, 0.085
rs10254101	*PRKAG2*	0.065	0.020, 0.110	0.095[a]	0.042, 0.148	0.020	0.010, 0.030
rs1028455	*SPATA7*	0.030	−0.011, 0.071	0.085[a]	0.034, 0.135	0.021	0.012, 0.029
From GWAS for decline$_{adj}$, with association for decline (baseline-unadjusted)							
rs1458038	*FGF5*	0.030	−0.013, 0.072	0.040	−0.013, 0.092	0.019	0.010, 0.028
rs4930319	*OVOL1*	0.021	−0.021, 0.062	0.031	−0.019, 0.080	0.015	0.006, 0.024
rs434215	*TPPP*[b]	0.031	−0.024, 0.086	0.112[a]	0.043, 0.180	0.020	0.006, 0.035
rs28857283	*C15ORF54*	0.046	0.005, 0.086	0.042	−0.007, 0.091	0.021	0.013, 0.030
rs13095391	*ACVR2B*	0.029	−0.021, 0.080	0.006	−0.054, 0.066	0.017	0.008, 0.026
Average		0.061		0.079		0.030	

95% CI, 95% confidence interval of β (β ± 1.96 * SE of the association); β, genetic effect of genetic association where the effect alleles are the same as in Table 1 and Table 2; CKD, chronic kidney disease; decline$_{adj}$, adjusted decline; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GWAS, genome-wide association study; Locus name, nearest gene; SNPID, variant identifier on GRCh37.

[a]Statistically significant different from 0 ($P < 0.05/9 = 5.56 \times 10^{-3}$).

[b]Because the lead variant had imputation quality <0.6 in 45% of the studies (median, 0.64), we analyzed this variant omitting the imputation quality filter (with filter: decline among DM at baseline β = −0.093, $P = 0.338$, n = 927; decline among eGFR <60 ml/min per 1.73 m^2 β = 0.022, $P = 0.618$, n = 2924; median imputation quality = 0.74). Shown are the 9 variants with genuine association for eGFR decline for their association with eGFR decline restricted to individuals with baseline DM (n up to 38,206) or baseline CKD (i.e., eGFR <60 ml/min per 1.73 m^2; n up to 26,653). The β estimates and 95% CIs are in ml/min per 1.73 m^2 per year and per faster-decline allele.

associations with eGFR decline (no impact by adjusting for DM status, and no SNP association with DM status), rendering the higher eGFR-decline effects in DM genuine.

The clinical relevance is further underscored by the 9-variant GRS being associated with increased risk of AKI and ESKD. This observation requires further analyses in future larger data. If substantiated, this may indicate a genetic risk of incomplete kidney function recovery after AKI and a genetic predisposition for ESKD.

The 9 identified variants across 8 loci included the *UMOD-PDILT* locus associated with eGFR decline and CKD progression, which is largely confirmatory but serves as proof of concept. A variant near *MIR378C*, previously identified for CKD progression,[42] (n ≈ 3000) was not confirmed herein. Our other 7 loci are novel for eGFR decline (near/in *PRKAG2-GALNTL5*, *SPATA7*, *FGF5*, *OVOL1*, *TPPP*, *C15ORF54*, and *ACVR2B*). These included at least 3 loci associated with CKD progression (defined as eGFR decline in individuals with CKD at baseline), mapping to the genes *GALNTL5*, *SPATA7*, and *TPPP* by SNP-modulated expression in tubulointerstitium.[15,18] These associations and genes for CKD progression are in strong demand as genetic

Table 4 | GRS analyses for ESKD and AKI

			Per 5 unfavorable average alleles			High vs. low GRS group					
						5% vs. 95%			10% vs. 90%		
Study	No. of cases	No. of controls	OR	95% CI	*P* (1 sided)	OR	95% CI	*P* (1 sided)	OR	95% CI	*P* (1 sided)
ESKD (cases: *ICD-10* code N18.0 or N18.5; controls: no *ICD-10* code N18, eGFR >60 ml/min per 1.73 m^2, frequency matched by age group and sex)											
4D_KORA-F3	1100	1601	1.122	0.925, 1.362	0.121	1.260	0.669, 2.377	0.237	1.526	0.978, 2.379	0.0313
GENDIAN_KORA-F4	470	1545	1.146	0.923, 1.423	0.108	0.954	0.468, 1.946	0.449	1.036	0.625, 1.719	0.445
UKBBCaco	498	1494	1.085	0.885, 1.330	0.216	1.220	0.639, 2.329	0.273	1.479	0.921, 2.373	0.0525
Meta-analysis	2068	4640	1.117	0.993, 1.256	0.0329	1.150	0.785, 1.686	0.236	1.349	1.027, 1.773	0.0157
AKI (cases: *ICD-10* code N17; controls: no *ICD-10* code N17, eGFR >60 ml/min per 1.73 m^2, frequency matched by age group and sex)											
UKBBCaCo	3878	11,634	1.179	1.095, 1.270	6.47×10^{-6}	1.524	1.204, 1.931	4.70×10^{-4}	1.272	1.080, 1.499	1.97×10^{-3}

95% CI, 95% confidence interval of the association; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease (individuals analyzed herein are distinct from the eGFR-decline genome-wide association study [GWAS], except for the KORA-F3 and KORA-F4 controls); GRS, genetic risk score; *ICD-10*, *International Classification of Diseases, Tenth Revision*; OR, odds ratio of the GRS association; *P* (1 sided), 1-sided association *P* value; Study, study name; UKBBCaCo, cases and controls from UK Biobank distinct from UK Biobank study participants used in the GWASs for eGFR decline.

In 3 case-control studies for ESKD and 1 for AKI, we computed the weighted GRS across the 9 eGFR-decline variants (counting the faster-decline alleles, weighted by effect size for eGFR decline unadjusted for eGFR baseline; divided by sum of weights and multiplied by 9 [i.e., scaled as 0 to 18]). Shown are ORs, 95% CIs, and *P* values (1 sided) for the quantitative GRS association (per 5 "average" unfavorable alleles) and for a high versus low GRS association (≥95th versus ≤5th and ≥90th versus ≤10th GRS percentiles derived in UK Biobank) with (**A**) ESKD and (**B**) AKI. Associations are derived by logistic regression adjusted for matching variables age group and sex (AKI additionally for principal components).

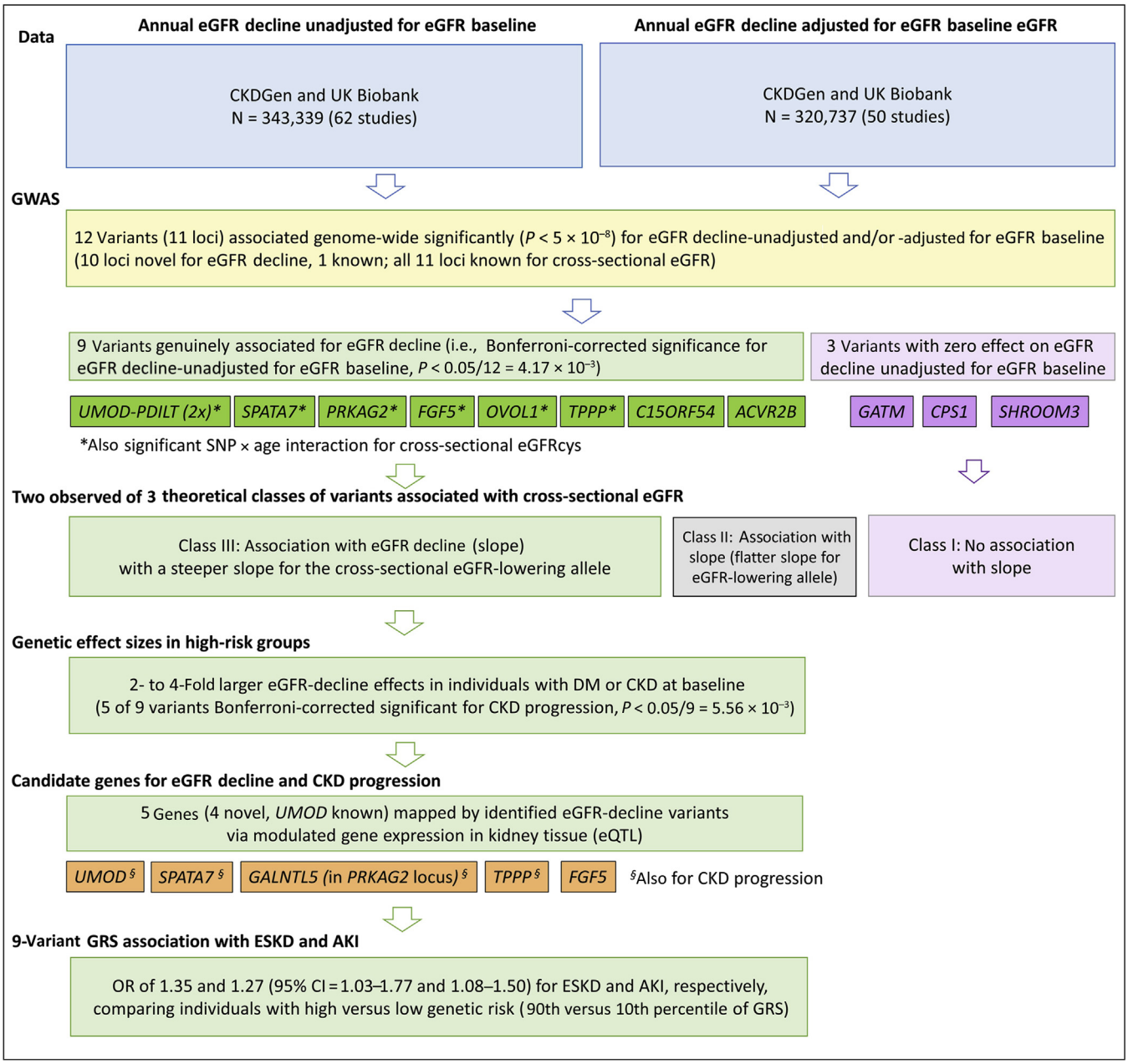

Figure 5| Data, analyses, and results in a nutshell. Chronic kidney disease (CKD) progression indicates estimated glomerular filtration rate (eGFR) decline in CKD individuals. AKI, acute kidney injury; CI, confidence interval; CKDGen, CKD Genetics consortium; DM, diabetes mellitus; eQTL, expression quantitative trait loci; ESKD, end-stage kidney disease; GWAS, genome-wide association study; GRS, genetic risk score; SNP, single-nucleotide polymorphism.

information on a disease progression phenotype, to help identify treatment.[19] Our data particularly flag *TPPP* by its locus' large effect on eGFR decline and CKD progression, making it second only after *UMOD*. This also documents the value of longitudinal GWASs in revealing relevance of genes like *TPPP*: the *TPPP* locus was one of hundreds of small-effect loci cross-sectionally, but among the few loci longitudinally.

Our results highlight some overlap of quantitative eGFR-decline genetics with binary extreme decline genetics,[22] but also distinction. All loci identified herein were directionally consistent, nominally significant with "rapid3" and/or "CKDi25" (1-sided $P < 0.05$), and 2 were genome-wide significant for rapid3 or CKDi25 (*UMOD-PDILT* and *PRKAG2-GALNTL5*). Particularly, the loci identified herein for CKD progression, which is among individuals with CKD at baseline, complement the previously reported associations with CKDi25, which is among individuals without CKD at baseline. Methodologically, regression applied to a quantitative rather than dichotomized outcome has larger power and statistical advantages.

Although all variants identified for eGFR-decline captured loci known from cross-sectional eGFR,[15] these associations are important on various accounts. First, the mere fact that eGFR-decline genetics is a subgroup of cross-sectional eGFR genetics is informative for future searches. Second, the finding that the full genetic signals were the same enabled the use of fine-mapping results from cross-sectional GWASs in >1 million individuals[18] to prioritize genes also for longitudinal eGFR decline. Third, all faster-decline alleles were the cross-sectional eGFR-lowering alleles. Together, this supported 2 classes of genetic variants for cross-sectional eGFR, distinguished by lack or presence of a slope effect, with steeper slope for the cross-sectional eGFR-lowering allele. The data rendered the third theoretical option (i.e., presence of a slope effect, with flatter slope for the cross-sectional eGFR-lowering allele) void.

Some limitations warrant mentioning. Although this GWAS is currently the largest GWAS on eGFR decline so far, more loci for eGFR decline and CKD progression might be detectable on further increased sample size. The yield of eGFR-decline loci in >340,000 individuals was comparably low, considering older GWASs for cross-sectional eGFR having already detected >50 loci in 170,000 individuals.[43] We used the CKD Epidemiology Collaboration formula containing an ancestry term,[6] accounted for by ancestry-specific GWASs; future work should utilize the new ancestry term–free CKD Epidemiology Collaboration formula 2021.[44] Evaluating the potential existence of sex-specific genetic effects on eGFR decline is of interest but was not addressed in this project. The target population is primarily population based, including kidney diseases proportional to respective prevalence, and primarily European ancestry. Larger all-ancestry meta-analyses on eGFR decline will open up opportunities to also utilize differential linkage disequilibrium between ancestries to help narrow down causal variants and genes. The interpretability of the SNP-by-age interaction on cross-sectional eGFR is limited to the age spectrum in the data (40–70 years) and by the power given the sample size; still, the sample size used was large and the age range typical also for most eGFR-decline GWAS studies. Two aspects need mentioning regarding the phenotype definition: uncertainty in eGFR decline may be larger for studies with shorter follow-up, which decreases power; but measurement error in the outcome does not induce bias in linear regression.[45] By defining annual eGFR decline from 2 eGFR assessments over time, our SNP associations capture only the linear component of decline. Serial eGFR assessments are better to characterize eGFR trajectories, but at the cost of limiting sample size, because such studies are few and typically small. Furthermore, generalized additive mixed models for nonlinear eGFR trajectories are complex and require particularly large sample sizes. The linear modeling of eGFR decline is a reasonable approximation of monotonous decline, maintaining large sample sizes and limiting model complexity to be applicable for GWASs. Overall, the choices of the adjustment, target population, and phenotype definition are important to consider when interpreting results. Although some modeling aspects are addressed herein, other covariate adjustment or relative decline as phenotype might reveal further or other genetic loci. Future work is warranted to quantify effects in different target populations and the genetically determined shape of the decline, which requires more—and larger—longitudinal studies, ideally with >2 eGFR assessments over time.

Methodologically unique is our contrasting of GWAS SNP associations on eGFR decline for different covariate adjustment, which fills an important gap and helps design future studies. This is highly relevant, because covariate adjustment can alter GWAS findings and interpretation.[28–31,46] Adjusting for baseline DM status had no impact, but genetic effects for eGFR decline were larger when restricting to DM individuals; this suggests DM status as modulator for the SNP association with eGFR decline rather than mediator (i.e., in the causal pathway from SNP to eGFR decline) or collider (i.e., generating biased association). Adjustment for eGFR baseline yielded larger eGFR-decline effects and more genome-wide significant variants. Glymour *et al.* highlight that adjustment for baseline levels in analyses of change may help detect effects, but can induce spurious associations when the rate of change observed after baseline reflects a rate of change experienced in the past.[36] This might reflect the situation herein rendering the larger genetic effects adjusted for eGFR baseline—and the larger genetic effects when restricting to individuals with CKD at baseline—reflective of collider bias. Glymour *et al.* recommend the documentation of change effects without baseline adjustment.[36] In line with this, we considered a variant's association with eGFR decline genuine, when the variant reached genome-wide significance baseline-unadjusted or baseline-adjusted and Bonferroni-corrected significance baseline-unadjusted. The baseline-unadjusted model provides the relevant genetic effect sizes for eGFR decline.

Interestingly, 2 of the 3 associations without genuine eGFR-decline association may relate to biomarker generation rather than kidney function: *GATM* and *CPS1*, known for a role in creatine biosynthesis[41] and urea cycle,[42] respectively, reside in loci without supporting association with cross-sectional cystatin-based eGFR.[18] Conversely, the *SHROOM3* locus was associated with cystatin-based eGFR,[15,18] and experimental studies support a role of *SHROOM3* in kidney pathology[47–49]; thus, *SHROOM3* appears to have an effect on cross-sectional kidney function, but not on kidney function decline within the limits of detectability by sample size.

A further unique aspect of our work is the empirical evidence for a link between SNP effects on eGFR decline with SNP-by-age interaction effects on cross-sectional eGFR. By this, we provide important insights into the age dependency of kidney function genetics as well as into the genetic dependency of aging eGFR in adult general populations, in whom "aging" includes onset of age-related diseases as they develop in populations. Considering the much broader availability of cross-sectional than longitudinal data, the

further parallel exploitation of SNP-by-age interaction might be a promising route to help improve our understanding of the mechanisms of kidney function decline over time.

In summary, we provided GWAS summary statistics, identified genetic loci, and prioritized genes for kidney function decline and CKD progression. Although *UMOD* has drawn attention already, *GALNTL5*, *SPATA7*, and *TPPP* may now receive more focus as therapeutic targets for disease progression. Our exploration of different covariate adjustment and the comparison to age dependency of SNP effect on eGFR cross-sectional provides important insights into the interpretation of these effects. With the emerging large biobank data linking medical records, longitudinal GWASs will become important in the future. Our methodological framework is informative and applicable generally for longitudinal phenotypes.

DISCLOSURE

JÄ reports personal fees from AstraZeneca, Boehringer Ingelheim, and Novartis, outside the submitted work. Sanofi Genzyme currently employs Kevin Ho. WK reports modest consultation fees for advisory board meetings from Amgen, DalCor, Kowa, Novartis, Pfizer, and Sanofi; and modest personal fees for lectures from Amgen, AstraZeneca, Novartis, Pfizer, and Sanofi, outside the scope of this work. CML received grants/research support from Bayer Ag/Novo Nordisk, and their husband works for Vertex. KBS, LMY-A, DMW, and MAL are full-time employees of GlaxoSmithKline. MLO received grant support from GlaxoSmithKline, MSD, Eisai, AstraZeneca, MedCo, and Janssen. BMP serves on the steering committee of the Yale Open Data Access Project, funded by Johnson & Johnson. PR received fees to his institution for research support from AstraZeneca and Novo Nordisk; for steering group participation from AstraZeneca, Gilead, Novo Nordisk, and Bayer; for lectures from Bayer, Eli Lilly, and Novo Nordisk; and for advisory boards from Sanofi and Boehringer Ingelheim, outside of this work. LW received institutional grants from GlaxoSmithKline, AstraZeneca, BMS, Boehringer-Ingelheim, Pfizer, MSD, and Roche Diagnostics. HDW received grants and nonfinancial support from GlaxoSmithKline, during the conduct of the study; received grants from Sanofi-Aventis, Eli Lilly, the National Institutes of Health, Omthera Pharmaceuticals, Pfizer New Zealand, Elsai Inc., and Dalcor Pharma UK; received honoraria and nonfinancial support from AstraZeneca; and is on advisory boards for Sirtex/Acetilion and received personal fees from CSL Behring and American Regent, outside the scope of this work. GS, DFG, HH, IO, KSte, PS, and UT are employees of deCODE/Amgen Inc. All the other authors declared no competing interests.

DATA STATEMENT

To support future work, we provide genome-wide summary statistics on estimated glomerular filtration rate (eGFR) decline unadjusted for eGFR baseline (adjusted for age, sex, and diabetes mellitus [DM] status) overall and restricted to individuals with DM or chronic kidney disease (CKD) at baseline (all adjusted for age and sex; https://www.genepi-regensburg.de/decline and http://ckdgen.imbi.uni-freiburg.de). The summary statistics on eGFR decline in individuals with CKD at baseline can be considered genetic effects on CKD progression. We also provide genome-wide summary statistics on eGFR decline adjusted for eGFR baseline (additionally to adjustment for age and sex), but these summary statistics should be used with great care and with an understanding that β estimates are subject to collider bias. For quantification of the genetic effect on eGFR decline, the results unadjusted for eGFR baseline should be utilized.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Note S1. Equivalence of diabetes mellitus (DM)–adjusted versus not DM-adjusted genome-wide association study (GWAS) on estimated glomerular filtration rate (eGFR) decline in the validation meta-analysis.

Note S2. Formula-based covariate adjustment using genome-wide association study (GWAS) summary statistics.

Note S3. Validation of the formula-derived association for estimated glomerular filtration rate (eGFR) decline adjusted for eGFR baseline.

Note S4. Graphical illustration of the relationship between single-nucleotide polymorphism (SNP) effects on estimated glomerular filtration rate (eGFR) decline unadjusted and adjusted for eGFR baseline.

Note S5. Comparison of the signals for estimated glomerular filtration rate (eGFR) decline unadjusted and adjusted for eGFR baseline and cross-sectional eGFR for the 11 identified loci.

Note S6. Age dependency of single-nucleotide polymorphism (SNP) effects and main age effect on estimated glomerular filtration rate (eGFR).

Note S7. Narrow-sense heritability.

Figure S1. Meta-analysis workflow.

Figure S2. Study-specific median annual estimated glomerular filtration rate (eGFR) decline versus sample size, follow-up time, and median age.

Figure S3. Influence of alternative adjustments for age on estimated glomerular filtration rate (eGFR) decline in UK Biobank.

Figure S4. (**A**) No influence from adjusting single-nucleotide polymorphism (SNP) associations for estimated glomerular filtration rate (eGFR) decline for diabetes mellitus (DM). (**B**) Differences between SNP association for eGFR decline unadjusted versus adjusted for eGFR baseline. (**C**) Validation of formula-derived adjustment for eGFR baseline in eGFR-decline associations (part 1). (**D**) Validation of formula-derived adjustment for eGFR baseline in eGFR-decline associations (part 2).

Figure S5. Region plots of loci identified for estimated glomerular filtration rate (eGFR) decline unadjusted and adjusted for eGFR baseline.

Figure S6. Age dependency of estimated glomerular filtration rate (eGFR) and age dependency of the variant effects on eGFR in UK Biobank.

Table S1. Description of participating studies: study design.

Table S2. Description of participating studies: genotyping and imputation.

Table S3. Description of participating studies: phenotype distribution.

Table S4. The 12 identified variants for estimated glomerular filtration rate (eGFR) decline were associated with other kidney phenotypes, but not with diabetes mellitus (DM) status.

Table S5. The 12 identified variants for estimated glomerular filtration rate (eGFR) decline do not show heterogeneity between ancestries, and FHS is not an influential study.

Table S6. No influence by diabetes mellitus (DM) adjustment versus no DM adjustment or by model- versus formula-based adjusting for baseline estimated glomerular filtration rate (eGFR; BL) on the 12 variants' association with eGFR decline.

Table S7. Association of *APOL1* risk variants in African American and European CKDGen studies.
Supplementary References.
Supplementary Extended Acknowledgements, Study Funding Information, and Author Contributions.

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