Meta-analysis uncovers genome-wide significant variants for rapid kidney function decline

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Rapid decline of glomerular filtration rate estimated from creatinine (eGFRcrea) is associated with severe clinical endpoints. In contrast to cross-sectionally assessed eGFRcrea, the genetic basis for rapid eGFRcrea decline is largely unknown. To help define this, we meta-analyzed 42 genome-wide association studies from the Chronic Kidney Diseases Genetics Consortium and United Kingdom Biobank to identify genetic loci for rapid eGFRcrea decline. Two definitions of eGFRcrea decline were used: 3 mL/min/1.73m^2/year or more ("Rapid3"; encompassing 34,874 cases, 107,090 controls) and eGFRcrea decline 25% or more and eGFRcrea under 60 mL/min/1.73m^2 at follow-up among those with eGFRcrea 60 mL/min/1.73m^2 or more at baseline ("CKDi25"; encompassing 19,901 cases, 175,244 controls). Seven independent variants were identified across six loci for Rapid3 and/or CKDi25: consisting of five variants at four loci with genome-wide significance (near *UMOD-PDILT* (2), *PRKAG2*, *WDR72*, *OR2S2*) and two variants among 265 known eGFRcrea variants (near *GATM*, *LARP4B*). All these loci were novel for Rapid3 and/or CKDi25 and our bioinformatic follow-up prioritized variants and genes underneath these loci. The *OR2S2* locus is novel for any eGFRcrea trait including interesting candidates. For the five genome-wide significant lead variants, we found supporting effects for annual change in blood urea nitrogen or cystatin-based eGFR, but not for *GATM* or *LARP4B*. Individuals at high compared to those at low genetic risk (8-14 vs. 0-5 adverse alleles) had a 1.20-fold increased risk of acute kidney injury (95% confidence interval 1.08-1.33). Thus, our identified loci for rapid kidney function decline may help prioritize therapeutic targets and identify mechanisms and individuals at risk for sustained deterioration of kidney function.

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Rapid kidney function decline is an important risk factor for end-stage kidney disease (ESKD), cardiovascular events, and early mortality.[1,2] ESKD is a life-threatening condition with substantial individual and public health burden[3–5] and a major endpoint in clinical nephrology trials. However, identifying and monitoring individuals at risk for ESKD is challenging. Two definitions of rapid decline in creatinine-based eGFR (eGFRcrea) are reported to increase ESKD risk 5- and 12-fold,[6,7] respectively, and thus recommended for clinical use: (i) rapid eGFRcrea decline of >5 ml/min per 1.73 m^2 per year and (ii) a ≥25% decline of eGFRcrea along with movement into a lower category of chronic kidney disease.[7] Other surrogate endpoints of ESKD were implemented by interventional trials with a follow-up duration of <5 years,[8,9] such as a doubling of creatinine levels (equivalent to a 57% eGFRcrea decline[10]) or an eGFRcrea decline of 30% or 40%.

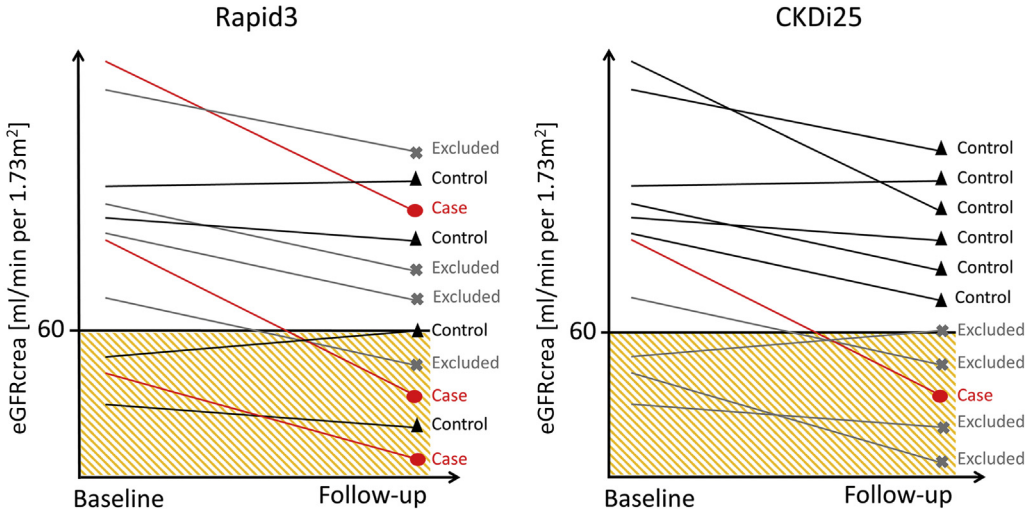

Figure 1 | Illustration of the case-control definitions of Rapid3 and CKDi25. Rapid3 defines cases as individuals with an glomerular filtration rate estimated from creatinine (eGFRcrea) decline >3 ml/min per 1.73 m^2 per year and controls with an eGFRcrea decline between −1 and +1 ml/min per 1.73 m^2 per year. CKDi25 defines cases as a ≥25% drop from baseline eGFRcrea ≥60 ml/min per 1.73 m^2 into eGFRcrea <60 ml/min per 1.73 m^2 at follow-up and controls as an eGFRcrea ≥60 ml/min per 1.73 m^2 at baseline and follow-up. Shown are cases (red), controls (black), and excluded individuals (gray) according to the eGFRcrea values observed at baseline and follow-up.

Besides specific therapies in autoimmune-driven glomerulopathies such as immunosuppressive agents[11] or tolvaptan in polycystic kidney disease,[12] therapeutic options to slow down kidney function decline are largely limited to glycemic and blood pressure control as well as lipid-lowering drugs. Before the recent advent of SGLT2 inhibitors in large clinical trials,[13] these therapies had shown only a moderate, if any, effect on clinically relevant renal endpoints.[14] Selecting genetically supported drug targets was estimated to double success rate in drug discovery,[15] in particular when the causal gene was suggested by Mendelian diseases or from genome-wide associations driven by coding variants.[16] This motivates genome-wide association studies (GWAS) for the identification and characterization of genetic variants associated with rapid kidney function decline.

A recent GWAS combining data from >1,000,000 individuals identified 264 loci associated with eGFRcrea based on 1 creatinine measurement ("cross-sectional eGFRcrea").[17] However, little is known about whether these or additional genetic factors are associated with rapid kidney function decline ("longitudinal kidney function traits"). Given the substantial organizational and temporal requirements of longitudinal studies, sample sizes for these studies are still limited compared with cross-sectional studies. Our previous longitudinal GWAS based on 61,078 individuals and approximately 3 million genetic variants did not identify any locus for rapid eGFRcrea decline.[18] New studies with longitudinal eGFRcrea measurements and new genomic reference panels enabling a denser and more precise genetic variant imputation now allow for a more powerful investigation.

We thus performed a GWAS meta-analysis across 42 longitudinal studies, consisting of 41 studies from the Chronic Kidney Disease Genetics (CKDGen) Consortium and UK Biobank, totaling >270,000 individuals with 2 eGFRcrea measurements across a time period of 1–15 years of follow-up. We implemented 2 definitions of rapid eGFRcrea decline that were feasible in population-based studies while preserving similarity to recommended surrogate clinical endpoints: (i) "Rapid3" cases defined as eGFRcrea decline of >3 ml/min per 1.73 m^2 per year compared with "no decline" ("Rapid3" controls, 1 to +1 ml/min per 1.73 m^2 per year); and (ii) "CKDi25" cases defined as ≥25% eGFRcrea decline during follow-up together with a movement from eGFRcrea ≥60 ml/min per 1.73 m^2 at baseline to eGFRcrea <60 ml/min per 1.73 m^2 at follow-up compared with "CKDi25" controls defined as eGFRcrea ≥60 ml/min per 1.73 m^2 at baseline and follow-up (Figure 1).

RESULTS

Rapid eGFRcrea decline in 42 longitudinal studies

We collected phenotype summary statistics for Rapid3 and CKDi25 from 42 studies with genetic data and at least 2 measurements of creatinine (study-specific mean age of participants 33–68 years, study-specific median follow-up time 1–15 years; Methods, Supplementary Table S1). Most studies were from European ancestry and population (32 European ancestry–based, 34 population-based).

Several interesting aspects emerged: (i) as expected for studies covering general populations as well as elderly and patient populations, study-specific median baseline eGFRcrea ranged from 46.4 to 115.0 ml/min per 1.73 m^2 (overall median = 87.3 ml/min per 1.73 m^2); (ii) case proportions ranged from 11% to 72% for Rapid3 and from 3% to 52% for CKDi25 (median = 30% or 11%, respectively); (iii) there was no association of study-specific median age of participants or median follow-up time with Rapid3 or CKDi25

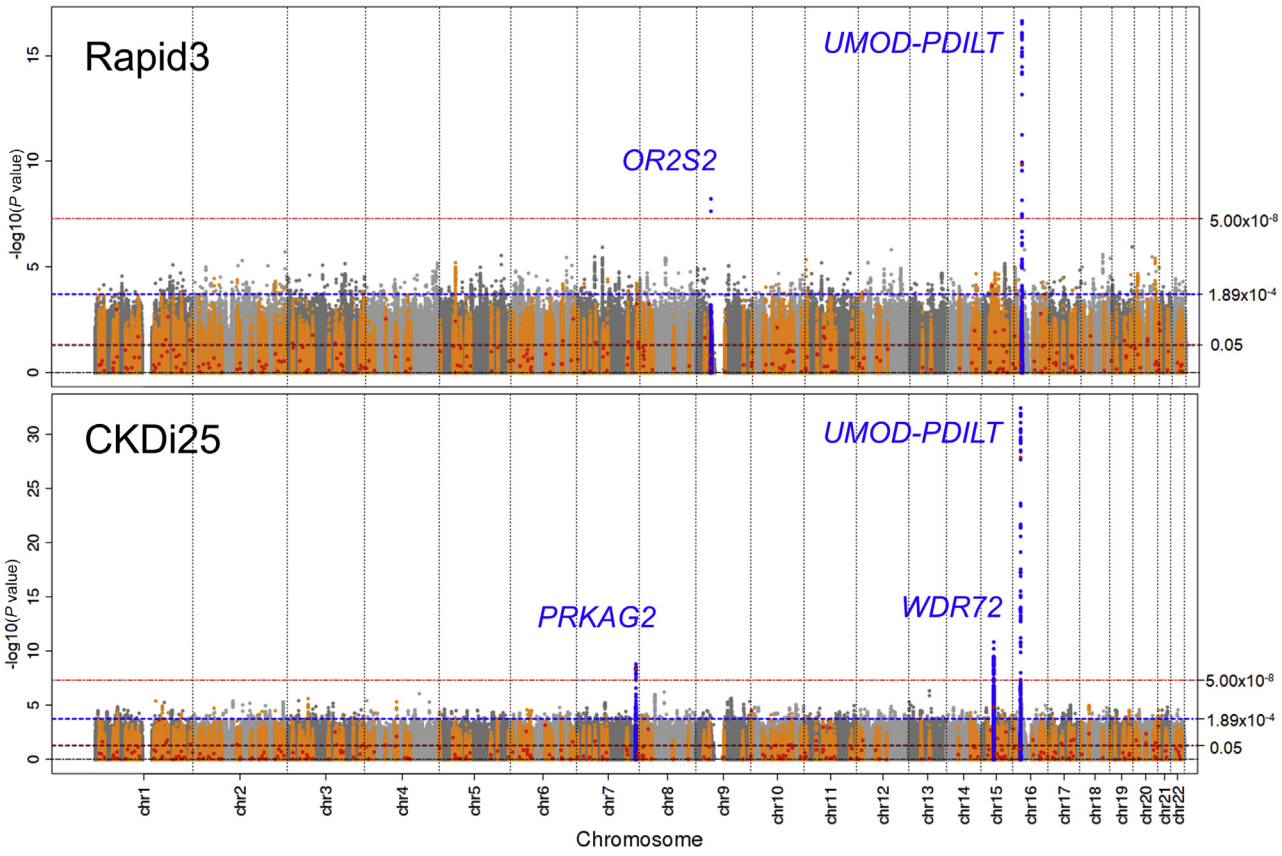

Figure 2 | Four loci identified with genome-wide significance for Rapid3 or CKDi25. Shown are association *P* values versus genomic position for Rapid3 (34,874 cases; 107,090 controls) and CKDi25 (19,901 cases; 175,244 controls). Horizontal dashed lines indicate genome-wide (5.00×10^{-8}), Bonferroni-corrected ($0.05/265 \approx 1.89 \times 10^{-4}$), and nominal (0.05) significance thresholds. The 4 identified genome-wide significant loci are annotated by the nearest genes (blue). The 264 loci reported previously for cross-sectional eGFRcrea[17] are marked in orange and respective lead variants as red dots. eGFRcrea, glomerular filtration rate estimated from creatinine.

(Supplementary Figure S1); (iv) most CKDi25 cases were a subgroup of Rapid3 cases in 3 example studies with different lengths of follow-up (Supplementary Table S2).

Four new genome-wide significant loci for rapid eGFRcrea decline

In each of the 42 studies, the >8 million genetic variants imputed via 1000 Genomes[19] or Haplotype Reference Consortium[20] reference panels were tested for association with Rapid3 and CKDi25 using logistic regression adjusting for age, sex, and baseline eGFRcrea (Supplementary Table S3, Methods). We meta-analyzed study-specific summary statistics by outcome (34,874 cases, 107,090 controls for Rapid3; 19,901 cases, 175,244 controls for CKDi25; Methods).

In our genome-wide approach, we selected genome-wide significant loci (i.e., ≥1 variant with a *P* value of $<5 \times 10^{-8}$ within ±500 kB; "lead variant" as the variant with the smallest *P* value); within each locus, we searched for independently associated signals by conditional analyses (Methods). By this, we identified 5 lead variants across 4 loci (*P* values = 5.94×10^{-9} to 3.51×10^{-33}, Figure 2, Table 1): (i) the *UMOD-PDILT* locus was associated with Rapid3 and CKDi25 and showed a second independent signal for CKDi25 (rs77924615; *P*-adjusted = 2.98×10^{-10}). For CKDi25, the independent odds ratios (ORs) for the 2 *UMOD-PDILT* lead variants (rs12922822, rs77924615) were 1.06 per adverse allele per variant in a model containing both variants. (ii) One variant in each of the *WDR72* and *PRKAG2* loci was identified for CKDi25. (iii) A variant near *OR2S2* was associated with Rapid3.

For all variants and both outcomes, we observed no to moderate heterogeneity across studies (I^2 = 0%–43%). A sensitivity analysis restricted to European ancestry (31,101 cases, 102,485 controls for Rapid3; 19,419 cases, 169,087 controls for CKDi25) identified the same loci with the same or highly correlated lead variants ($r^2 > 0.84$, Supplementary Table S4A). We also conducted a meta-analysis restricting to individuals of African ancestry (2356 cases and 2375 controls for Rapid3; 374 cases and 4183 controls for CKDi25), but limited sample sizes prohibited an informative comparison with EUR results (Supplementary Table S4B, Supplementary Note S1).

Overall, we identified 4 loci associated at genome-wide significance for these binary rapid eGFRcrea decline traits.

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Table 1 | Six loci from the genome-wide and candidate-based search for association with Rapid3 or CKDi25

RSID	Chr:Position	Identifying analysis	Locus name	EA/OA	EAF	Rapid3		CKDi25		Locus/signal no.	Reference variant (R^2)
						OR	*P*	OR	*P*		
Genome-wide search (genome-wide significance, *P* value $<5.00 \times 10^{-8}$)[a]											
rs13329952	16:20,366,507	Rapid3	[UMOD-PDILT]	t/c	0.79	1.101	**2.35×10^{-17}**	1.203	6.22×10^{-30}	1.1	rs13329952 (0.91)
rs12922822	16:20,367,645	CKDi25		c/t	0.81	1.103	1.13×10^{-16}	1.224	**3.51×10^{-33}**		
rs77924615	16:20,392,332	CKDi25 2nd[b]	[UMOD-PDILT]	g/a	0.79	1.023	0.0384	1.112	**2.98×10^{-10}**	1.2	
rs77593734	15:54,002,606	CKDi25	[WDR72]	t/c	0.72	1.040	1.18×10^{-4}	1.102	**1.42×10^{-11}**	2	
rs56012466	7:151,406,788	CKDi25	[PRKAG2]	a/g	0.27	1.041	1.12×10^{-4}	1.090	**1.53×10^{-9}**	3	
rs141809766	9:35,937,931	Rapid3	[OR2S2]	g/a	0.02	1.222	**5.94×10^{-9}**	1.065	0.252	4	
Candidate approach based on 265[c] reported lead variants from cross-sectional eGFRcrea GWAS (significance *P* value $<0.05/265 \approx 1.89 \times 10^{-4}$)[d]											
rs34882080[e]	16:20,361,441	CKDi25; Rapid3	[UMOD-PDILT]	a/g	0.81	1.100	**1.11×10^{-15}**	1.216	**2.98×10^{-31}**	1.1	rs12922822 (0.99)
rs77924615	16:20,392,332	CKDi25; Rapid3	[UMOD-PDILT]	g/a	0.79	1.084	**1.40×10^{-10}**	1.256	**1.29×10^{-28}**	1.2	
rs690428	15:53,950,578	CKDi25	[WDR72]	a/c	0.71	1.027	0.0117	1.078	**1.46×10^{-5}**	2	rs77593734 (0.42)
rs10254101	7:151,415,536	CKDi25	[PRKAG2]	t/c	0.28	1.037	5.35×10^{-4}	1.087	**4.32×10^{-9}**	3	rs56012466 (0.84)
rs80282103	10:899,071	CKDi25	[LARP4B]	t/a	0.08	1.027	0.100	1.103	**2.97×10^{-5}**	5	
rs1145077	15:45,683,795	Rapid3	[GATM]	t/g	0.40	1.038	**7.94×10^{-5}**	1.042	1.93×10^{-3}	6	rs1145089 (0.99)

RSID, variant identifier on GRCh37; Chr:Position, chromosome and position on GRCh37; identifying analysis, trait and analysis for which the variant was identified with significant association ("2nd" indicating the second signal analysis); locus name, nearest gene, stated in brackets to distinguish from gene and protein names; EA, effect allele: cross-sectional eGFRcrea-lowering allele; EAF, effect allele frequency; locus/signal no., locus number and signal number highlighting that 4 of the 6 candidate-based identified variants capture the same locus/signal as the GWAS; OA, other allele; OR, odds ratio; P, genomic control corrected association *P* value; reference variant (R^2), variant to which the identified variant is compared with in terms of correlation (Spearman correlation coefficient squared).

[a]The significant lead variants from the GWAS (genome-wide significance, *P* value $< 5.0 \times 10^{-8}$)

[b]Stated are OR and *P* value for Rapid3 and CKDi25 adjusted for the lead variant of the respective primary GWAS (rs13329952 or rs12922822). Unadjusted OR = 1.08 and 1.26 (*P* value = 1.40×10^{-10} and 1.29×10^{-28}) for Rapid3 and CKDi25, respectively.

[c]A total of 264 reported lead variants plus the lead variant of the 2nd signal in [*UMOD-PDILT*] from cross-sectional eGFRcrea GWAS.[17]

[d]The significant variants from the candidate-based approach inquiring the 265 variants reported for cross-sectional eGFRcrea[17] (Bonferroni-corrected significance, *P* value $< 0.05/265 \approx 1.89 \times 10^{-4}$).

[e]Lead variant of the 2nd signal in [*UMOD-PDILT*] from cross-sectional eGFRcrea analysis in European ancestry.[17]

Bold values indicate genome-wide significant *P* values ($<5.00 \times 10^{-8}$) in the identifying trait in [a] and a Bonferroni corrected significant *P* value ($<1.89 \times 10^{-4}$) in [d].

Table 2| Validation of the 7 identified variants association with an alternative renal biomarker in UK Biobank

Locus/signal no. [name]	RSID	eGFRcys change[a] UKBB		BUN change[a] UKBB		eGFRcys[b] UKBB		BUN[b] UKBB (CKDGen)	
		Effect	*P*	Effect	*P*	Effect	*P*	Effect	*P*
1.1 [UMOD-PDILT]	rs13329952	0.0271	0.02	−0.0036	0.45	−0.0045	6.06×10^{-86}	0.0024(0.0040)	1.08×10^{-18} (1.62×10^{-22})
1.1[UMOD-PDILT]	rs12922822	0.0289	0.01	0.0018	0.53	−0.0046	2.17×10^{-85}	0.0025 (0.0044)	1.09×10^{-18} (8.79×10^{-21})
1.2 [UMOD-PDILT]	rs77924615	0.0289	0.01	−0.0519	0.03	−0.0051	1.74×10^{-108}	0.0029 (0.0053)	2.38×10^{-26} (2.57×10^{-42})
2 [WDR72]	rs77593734	0.0026	0.41	−0.0429	0.03	−0.0016	1.88×10^{-16}	0.0014 (0.0026)	1.59×10^{-9} (8.46×10^{-17})
3 [PRKAG2]	rs56012466	0.0238	0.02	−0.0652	2.75×10^{-3}	−0.0039	1.56×10^{-81}	0.0046 (0.0057)	8.73×10^{-80} (1.69×10^{-41})
4 [OR2S2]	rs141809766	0.0537	0.04	−0.1245	0.02	0.0005	0.80	−0.00345 (−0.0018)	0.70 (0.89)
5 [LARP4B]	rs80282103	0.0241	0.10	−0.0362	0.17	−0.0037	4.87×10^{-29}	0.0026 (0.0026)	2.49×10^{-11} (4.90×10^{-7})
6 [GATM]	rs1145077	−0.0096	0.82	0.0150	0.75	0.0001	0.74	−0.0004 (<0.0001)	0.95 (0.46)

BUN, blood urea nitrogen; effect, genetic effect; eGFRcys, estimated glomerular filtration rate based on cystatin C; locus/signal no. [name], locus number and signal number [locus name]; *P*, one-sided association *P* value; RSID, variant identifier; UKBB, UK Biobank.

[a]Annual change of eGFRcys and BUN was calculated as the baseline value minus the follow-up value divided by the years between baseline and follow-up. The age, sex, and baseline eGFRcys/BUN-adjusted residuals were regressed on allele dosage.

[b]The age- and sex-adjusted residuals of the log eGFRcrea, eGFRcys, and BUN were regressed on allele dosage.

Association results for annual change in eGFRcys and BUN in UK Biobank (n up to 15,746 or 15,277, respectively). One-sided *P* values are provided testing the allele that increased the risk of rapid eGFRcrea decline (usually the eGFRcrea-lowering allele, except for the *OR2S2* lead variant) into the direction of annual eGFRcys decline and annual BUN increase. For completeness, also shown are association results for cross-sectional eGFRcys and BUN from UK Biobank (n up to 364,819 and 358,791) as well as previously reported BUN results from CKDGen[17] (n = 416,076), where 1-sided *P* values test the eGFRcrea-lowering allele into the direction of decreased eGFRcys and increased BUN levels.

Two additional loci for rapid eGFRcrea decline from a candidate-based search

Genetic variants with established association for cross-sectional eGFRcrea are candidates for association with rapid eGFRcrea decline. For our candidate-based approach, we selected the 264 lead variants and the second signal lead variant in the *UMOD-PDILT* locus reported previously for eGFRcrea[17] and tested these for association with Rapid3 and CKDi25 (judged at Bonferroni-corrected significance; $0.05/265 = 1.89 \times 10^{-4}$). Among these, we found 6 variants in 5 loci significantly associated with Rapid3 and/or CKDi25 (Table 1), yielding 2 variants that were associated with Rapid3 and/or CKDi25 independently from the 5 GWAS-identified variants, 1 each in *LARP4B* and *GATM*, significantly associated with CKDi25 or Rapid3 (Supplementary Note S2, Supplementary Table S5, Supplementary Figure S2). Overall, our genome-wide and candidate-based approaches yielded 7 independent variants in 6 loci associated with at least 1 of the rapid eGFRcrea decline traits.

Statistical evidence for the *OR2S2* locus

For the *OR2S2* locus, the only 2 genome-wide significant variants identified for Rapid3 were highly correlated and showed the largest OR of all 7 identified variants (rs141809766, rs56289282, $r^2 = 0.95$; OR =1.22 and 1.21; *P* value $= 5.94 \times 10^{-9}$ and 2.11×10^{-8}, respectively). Because these variants were not associated with cross-sectional eGFRcrea[17] (*P* value = 0.16 or 0.18, n = 542,354) and of low frequency in the general population (minor allele frequency [MAF] = 0.02), we evaluated the statistical robustness of this association: (i) the majority of studies showed consistent risk for rs141809766 (Supplementary Figure S3A); (ii) a leave-one-out sensitivity analysis showed no influential single study driving the signal (Supplementary Figure S3B); (iii) when focusing on European ancestry, we found similar results (Supplementary Table S4); (iv) the lack of association with cross-sectional eGFRcrea was confirmed in independent data (UK Biobank, n = 364,686, e.g., rs141809766, *P* value = 0.65). In summary, these analyses supported this locus as a genuine finding.

Characterizing identified effects by alternative markers for kidney function

A challenge in using eGFRcrea to detect genetic variants for kidney function is the fact that it is influenced by both kidney function and creatinine production, the latter being linked to muscle mass.[21] Alternative biomarkers such as estimated GFR based on cystatin C[22] (eGFRcys) and blood urea nitrogen[17] (BUN) can be used to support eGFRcrea loci as kidney function loci. We thus evaluated the 7 lead variants for their direction-consistent association with annual change in eGFRcys and BUN in UK Biobank (n = 15,746 or 15,277, respectively; mean follow-up time = 4.3 years): annual decline of eGFRcys and/or annual increase of BUN for the Rapid3/CKDi25-risk increasing allele. For completeness, we also present the 7 variants' association with cross-sectional

Table 3 | Size of 99% credible sets of variants for the 7 identified signals for Rapid3 or CKDi25

Locus/ signal no.	Locus name[a]	Identifying trait[b]	Locus region[c]			No. of genes	No. of variants in 99% credible set (overlap with eGFRcrea sets)		No. of variants in 99% credible set (overlap with CKDi25 sets)
			Chr	Start	Stop		Rapid3[d]	CKDi25[d]	eGFRcrea[d]
1.1	[UMOD-PDILT]	Rapid3, CKDi25	16	19,866,507	20,867,645	13	**14 (10)**	**13 (11)**	16 (10)
1.2	[UMOD-PDILT]	CKDi25 2nd	16	19,866,507	20,867,645	s.a.	1059	**1 (1)**	1 (1)
2	[WDR72]	CKDi25	15	53,502,606	54,502,606	1	2931	**37 (0)**	41 (0)
3	[PRKAG2]	CKDi25	7	150,906,788	151,906,788	14	2671	**16 (6)**	6 (6)
4	[OR2S2]	Rapid3	9	35,437,931	36,437,931	36	**2**	2573	NA
5	[LARP4B]	CKDi25	10	399,071	1,399,071	10	2955	2806	**1**[e]
6	[GATM]	Rapid3	15	45,183,795	46,183,795	17	1438	2493	**1**[e]

Chr, chromosome of the locus region; s.a., see above; start/stop, start and stop of the locus region on GRCh37.
[a]Nearest gene(s), stated in brackets to distinguish from gene and protein names.
[b]Indicates the trait for which the variant was identified with significant association ("CKDi25 2nd" indicating that this is the second independent signal for the CKDi25 trait analysis).
[c]Locus region defined as the region of the 2 lead variants identified for Rapid3 and CKDi25 in [UMOD-PDILT] or for the single lead variant identified for Rapid3 or CKDi25 in the other loci ±500 kB. The CKDi25 2nd signal (signal no. 1.2) is mapped to the [UMOD-PDILT] locus region from signal no. 1.1.
[d]Bold values indicate the credible set of variants for the analysis that identified the locus/signal.
[e]For the candidate-based identified loci [LARP4B] and [GATM], the statistics for the credible sets were instable due to the lack of genome-wide significance and yielded extremely wide credible set intervals. Because the CKDi25 or Rapid3 signal was very similar to the signal for cross-sectional eGFRcrea (Supplementary Figure S4E and F), we conducted the bioinformatic follow-up for the credible set variant derived from eGFRcrea previously.
Number of genes overlapping each of the 6 locus regions (lead variant ±500 kB) and the number of variants in the 99% credible set for each of the 7 signals. The credible sets of variants were computed (i) for the 2 rapid eGFRcrea decline traits (Rapid3 and CKDi25) highlighting the set for the analysis that identified the locus/signal (signals 1.1–4 from the genome-wide approach, signals 5 and 6 from the candidate-based approach) and (ii) for cross-sectional eGFRcrea from CKDGen data as reported previously.[17]

eGFRcys and BUN (n = 364,819 and 358,791). These analyses with alternative renal biomarkers supported *UMOD-PDILT*, *WDR72*, *PRKAG2*, and *OR2S2*, but not *LARP4B* or *GATM* loci (Table 2, Supplementary Note S3).

From lead variants to the statistical signals

Each lead variant represents a signal consisting of correlated variants. Regional association plots (Supplementary Figure S4) illustrate that the 7 rapid eGFRcrea decline signals mostly coincided with the cross-sectional eGFRcrea signal, except for a weaker signal in the *WDR72* locus and no corresponding *OR2S2* signal for cross-sectional eGFRcrea. Between the 2 traits, Rapid3 and CKDi25, the signals were mostly comparable, except for *LARP4B* and *OR2S2*.

To prioritize variants at identified signals, we ranked each signal variant by its posterior probability of driving the observed association and added them to the "99% credible set of variants" until the cumulative posterior probability was >99% (Methods). Such a credible set is thus a parsimonious set of variants that most likely include the causal variant, assuming that there is exactly 1 causal variant per signal and that this variant was analyzed.[23] When deriving the 99% credible sets of variants for each of the 7 identified signals for Rapid3 and CKDi25 (Methods) and comparing them with cross-sectional eGFRcrea credible sets,[17] we found the following (Table 3): (i) for most GWAS-derived signals, the credible sets coincided with those for cross-sectional eGFRcrea, except for the *WDR72* locus; (ii) the credible set of the second *UMOD-PDILT* signal for CKDi25 consisted of precisely 1 variant, rs77924615, which was exactly the 1 credible set variant for eGFRcrea supporting this as the most likely causal variant for this association signal; (iii) the 2 correlated genome-wide significant variants in the *OR2S2* locus for Rapid3 formed the credible set (posterior probability 77% and 23%, respectively); (iv) the credible sets for the 2 candidate-approach–derived loci, *LARP4B* and *GATM*, included 1438–2955 variants for Rapid3 and CKDi25, which was due insufficiently strong associations resulting from the lack of genome-wide significance. We thus considered these credible sets unsuitable for *in silico* follow-up and focused on further evaluation on the 5 genome-wide significant signals.

From statistical evidence to biology

One of the key challenges in translating GWAS associations into an understanding of the underlying biology is the identification of variants and genes causing the statistical signal. It is unclear exactly what evidence to weigh in and how expansive the search for causal genes should be; ±500 kB around the lead variant is often used ("locus region"). A variant is often considered more likely causal when it is in a credible set and predicted to have a relevant function, such as protein-altering (e.g., changing the peptide sequence, truncating, affecting RNA splicing) or modulating a gene's expression[24] (expression quantitative trait locus [eQTL]). A gene is often considered more likely causal when it (i) contains a protein-altering credible set variant, (ii) is a target of an eQTL variant, or (iii) has a kidney-related phenotype reported from animal models or monogenic disease. We annotated the credible set variants and the 64 genes across the 5 genome-wide significant signals accordingly (Methods, Supplementary Tables S6A and B and S7A and B). We summarized the evidence per gene in a Gene PrioritiSation table and implemented a customizable score, where each category's weight can be modified according to personal interest or preference (Supplementary Table S8).

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							Any credible set variants in gene			eQTL-modulated expression by any credible set variant				Evidenced kidney phenotype	
Weight							1	1	1	1	1	1	1	1	1
Locus name	**Locus no.**	**Gene**	**Chromosome**	**Distance to 1st signal variant**	**# Credible set variants in gene**	**Gene Priority Score**	**Missense**	**NMD**	**Altered splicing**	**NephQTL glomerulus**	**NephQTL tubulointerstitium**	**GTEx v8 kidney tissue**	**GTEx v8 any other tissue**	**In mice (MGI)**	**In human (OMIM)**
[UMOD-PDILT]	1	*UMOD*	16	0	10	2									
[UMOD-PDILT]	1	*PDILT*	16	2,846	1	1									
[WDR72]	2	*WDR72*	15	0	37	2									
[PRKAG2]	3	*PRKAG2*	7	0	16	2									
[PRKAG2]	3	*GALNTL5*	7	246,675	0	1									
[OR2S2]	4	*OR2S1P*	9	75,251	0	1									
[OR2S2]	4	*GNE*	9	276,506	0	1									
[OR2S2]	4	*CD72*	9	-319,507	0	1									

Figure 3 | Gene PrioritiSation (GPS) for the genes across the 4 loci identified with genome-wide significance. Shown are genes across the 4 loci, for which we found any relevant evidence: (i) blue: gene contains at least 1 credible set variant that was protein-altering (missense, nonmediated decay, NMD, or altered splicing; Supplementary Table S6A, information obtained from VEP[25]); (ii) orange: the gene's expression shows a modulation by any of the signal's credible set variant (expression quantitative trait loci, eQTL, in NephQTL[26] or GTEx v8;[27] Supplementary Table S6B), (iii) gene shows a kidney phenotype in mouse or human (MGI,[28] OMIM;[29] Supplementary Tables S7A and B). The full GPS shows all genes overlapping the 4 loci (Supplementary Table S8) and the online version is searchable and customizable (i.e., the weights per column can be altered) to re-sort the table reflecting other preferences (www.genepi-regensburg.de/rapiddecline). Locus name = nearest gene(s), stated in brackets to distinguish from gene or protein names; #credible set variants in gene region = no. of variants in the 99% credible set overlapping the gene's region; Gene Priority Score = cumulative score (here, weighing all categories equally; see Supplementary Table S8 for all genes in locus regions and online version for customization of weights). Blue section: gene contains ≥1 credible set variant overlapping the gene with relevant function (yes, blue; no, white); orange section: locus/signal contains ≥1 credible set variant that modulates gene expression (yes, orange; no, white) in NephQTL glomerulus, NephQTL tubulointerstitium, GTEx v8 kidney tissue, or GTEx v8 any tissue; green section: gene shows a kidney-related phenotype (yes, green; no, white) in MGI Mouse kidney phenotype or OMIM Human kidney phenotype.

By this, we identified 8 genes with functional evidence (score ≥1; Figure 3, customizable version of the Figure als.xls at www.genepi-regensburg.de/rapiddecline): 2 genes with protein-altering variant (*WDR72*, *PRKAG2*), 4 genes as a target of a significant eQTL variant (*PDILT*, *WDR72*, *GALNTL5*, and *OR2S1P*), and 4 genes with a phenotype in mice and/or human (*UMOD*, *PRKAG2*, *GNE*, and *CD72*). Particularly interesting were the 36 genes in the *OR2S2* locus (Supplementary Table S9) and the findings from *in silico* follow-up in 3 of these genes: *OR2S1P* as an eQTL target of the lead variant rs141809766 in lung tissue with a particularly high effect estimate also for kidney tissue (Supplementary Figure S5; no data available in NephQTL) and *GNE* as well as *CD72* with abnormal morphology of podocytes or renal glomerulus in mice providing candidates for a potential kidney function biology.

The cumulative genetic effect

A genetic risk score (GRS) is an approach to summarize the genetic profile of a person across the identified variants. We computed the GRS across the 7 variants in 4 studies for Rapid3 and CKDi25 (overall 3683 cases vs. 8579 controls for Rapid3; 895 cases vs. 21,472 controls for CKDi25) and defined genetic high-risk and low-risk groups (individuals with 8–14 adverse alleles, approximately 30% in UK Biobank; 0–5 alleles, approximately 20%, respectively; Methods). In the meta-analysis of study-specific ORs, we found a 1.11-fold increased risk for Rapid3 (95% confidence interval = 0.99–1.24, *P* value = 0.07) and a 1.29-fold increased risk for CKDi25 (1.06–1.57, *P* value = 0.01, Table 4). The lower risk for Rapid3 compared withCKDi25 can be explained by the less pronounced effect sizes for Rapid3 for most variants in the GRS and by the fact that the only variant with a high effect for Rapid3 (near *OR2S2*) was rare and thus with little impact on the distribution of the GRS.

Because rapid eGFRcrea decline is known to be associated with high ESKD risk, we were interested to see whether the genetic risk carried forward also to the severe renal endpoint further down the road. We gathered data on individuals with ESKD from 3 different sources (*International Classification of*

Table 4 | GRS analyses of Rapid3, CKDi25, ESKD, and AKI

			High- versus low-risk group: 8–14 adverse alleles versus 0–5							
							High-risk group		Low-risk group	
Study	Number of cases	Number of controls	OR	L95	U95	*P*	Number of cases	Number of controls	Number of cases	Number of controls
Rapid3										
UK Biobank	2416	5828	1.05	0.92	1.20	0.49	488	1205	721	1840
DIACORE	705	532	0.95	0.70	1.31	0.77	169	136	189	147
KORA-F3	321	851	1.85	1.26	2.72	0.00	85	184	69	250
KORA-F4	241	1368	1.34	0.88	2.03	0.17	52	314	61	388
Meta-analysis	3683	8579	1.11	0.99	1.24	0.07	794	1839	1040	2625
CKDi25										
UK Biobank	518	14,518	1.19	0.92	1.53	0.18	113	2972	142	4514
DIACORE	124	1584	1.22	0.72	2.05	0.46	34	359	32	449
KORA-F3	168	2651	1.68	1.03	2.74	0.04	49	592	32	735
KORA-F4	85	2719	1.50	0.79	2.83	0.21	25	598	21	773
Meta-analysis	895	21,472	1.29	1.06	1.57	0.01	221	4521	227	6471
ESKD[a]										
4D_KORA-F3	1100	1601	0.91	0.73	1.14	0.43	227	363	298	438
GENDIAN_KORA-F4	470	1545	1.11	0.82	1.50	0.50	103	345	124	455
UKBBCaCo	528	1584	1.09	0.82	1.45	0.56	108	329	153	504
Meta-analysis	2098	4730	1.01	0.87	1.18	0.91	438	1037	575	1397
AKI[b]										
UKBBCaCo	4123	12,369	1.20	1.08	1.33	4.45×10^{-4}	889	2398	1243	3956

GRS, Genetic Risk Score; L95/ U95, lower and upper 95% confidence intervals; OR, odds ratio; study, study name; UKBBCaCo, cases and controls from UK Biobank.
[a]ESKD, end-stage kidney disease, cases: ICD10 code N18.0 or N18.5; controls: no ICD10 code N18, eGFRcrea > 60 ml/min per 1.73 m^2, frequency-matched by age group and sex.
[b]AKI, acute kidney injury, cases: ICD 10 code N17; controls: no ICD10 code N17, frequency-matched by age group and sex.
The results of the unweighted GRS across the 7 variants identified for Rapid3 and/or CKDi25 counting Rapid3- or CKDi25-risk increasing alleles and its association with Rapid3, CKDi25, ESKD, and AKI. We show ORs for the comparison of genetic high-risk versus low-risk individuals (GRS ≥ 7.5 vs. GRS ≤ 5.5). Associations are adjusted for age, sex, and baseline eGFRcrea for Rapid3 and CKDi25 and adjusted for matching variables age group and sex as well as quantitative age for ESKD and AKI.

Diseases, 10th Revision codes N18.5 and N18.6; UK Biobank, GENDIAN[30] and 4D,[31] together 2098 cases) and compared them with "healthy" individuals frequency-matched by age groups and sex per case source (eGFRcrea >60 ml/min per 1.73 m^2, no health record for chronic kidney impairment; UK Biobank, KORA-F3, KORA-F4, together 4730 controls). When comparing the same GRS high-risk versus low-risk group as defined above, we found no association with ESKD risk (OR = 1.01, 95% confidence interval = 0.87–1.18, *P* value = 0.91; Table 4).

When comparing the same GRS high-risk versus low-risk group for acute kidney injury (AKI) risk in UK Biobank (*International Classification of Diseases, 10th Revision* codes N17.0–N17.9, 4123 cases; 12,369 controls frequency-matched on age group and sex, eGFRcrea >60 ml/min per 1.73 m^2, no record of AKI), we found a 1.20-fold statistically significant increased risk (95% confidence interval = 1.08–1.33, *P* value = 4.45×10^{-4}; Table 4). Thus, the derived GRS across the 7 identified variants was associated with increased risk of AKI, but not ESKD.

DISCUSSION

Overall, we identified 7 independent genetic variants across 6 loci that were significantly associated with 2 binary traits of rapid eGFRcrea decline, Rapid3 and/or CKDi25. In this GWAS meta-analysis of >40 studies with the follow-up time of up to 15 years, we provide—to our knowledge—the first record of genome-wide significant variants for these traits. Although there are several genetic studies for cross-sectional eGFRcrea (e.g., papers by Wuttke *et al.*[17] and Hellwege *et al.*,[32] summarized in a review[33]) and some on annual eGFRcrea decline,[18,34,35] we adopted this extreme phenotype approach and focused on 2 binary traits for rapid eGFRcrea decline reported for increased ESKD risk.[6] Our work is unique in its large sample size for these 2 case-control definitions with approximately 35,000 Rapid3 cases and approximately 20,000 CKDi25 cases versus >100,000 controls. These trait definitions were based on precisely 2 creatinine measurements over time, which does not allow for a characterization of the slope, but for differentiating persons with rapid decline yes/no. Besides the fact that these traits require longitudinal data with all known challenges to maintain sample size, another challenge is the stringent case-control definitions as they exclude individuals with moderate decline or baseline eGFRcrea <60 ml/min per 1.73 m^2 (neither a case, nor a control). To derive these case-control sample sizes, we had >270,000 individuals with at least 2 assessments of kidney function from population-based studies, exceeding previous work[18] by >4-fold. Despite the relatively large sample size, we cannot exclude that the lack of association of an identified variant for one trait or the other as well as differences in effect sizes between traits might result

from chance. We expect that the analysis of even larger samples in the future might increase the overlap of findings between the 2 traits and allow for a more formal comparison of effect sizes.

It might be considered a limitation that these binary traits were only similar, but not identical to KDIGO-recommended surrogate endpoints for ESKD. However, those endpoints would have limited the GWAS sample size even more. Our sample size is still much smaller than GWAS sample sizes for cross-sectional eGFRcrea, which might explain the relatively few identified loci for rapid decline, even with the candidate approach allowing for a less stringent threshold of significance, compared with the vast number of loci identified for cross-sectional eGFRcrea.[17] For example, our sample size for Rapid3 enabled a power of >80% to detect a variant with MAF = 30% (2%) with 1.13-fold (1.28-fold) increased Rapid3 risk with genome-wide significance. There might be genetic variants with smaller MAF or smaller risk that have been missed. The sample size in non–European ancestry individuals was too small for separate evaluation. There are current efforts to substantially enhance longitudinal studies and their molecular content,[36–38] also with non–European ancestry, which will foster more GWAS on clinical endpoints in the future. Among the 6 identified loci for Rapid3 and/or CKDi25, 4 were identified with genome-wide significance (near *UMOD-PDILT* [2 signals], *PRKAG2*, *WDR72*, and *OR2S2*) and 2 among previously reported loci for cross-sectional eGFRcrea[17] (*LARP4B* and *GATM*). Our *in silico* follow-up highlighted the relevance of genome-wide significant associations for fine-mapping: credible sets identified via candidate-based approach contained >1000 variants, rendering the Gene PrioritiSation unfeasible. For the 4 loci with genome-wide significance, the credible sets contained 1–40 variants, providing a more practical number of targets to turn the statistical signals into potentially relevant biological findings. For the 4 loci with genome-wide significance, our Gene PrioritiSation helps prioritize genes for functional follow-up and provides the opportunity to customize the weighing of each piece of bioinformatic evidence. Although some of the findings overlap with previous reports[17] including functionally interesting variants' mapping to the *PRKAG2* and *GALNTL5* genes both residing in the *PRKAG2* locus, the *WDR72* gene is supported with a missense variant that was not among credible set variants for cross-sectional eGFRcrea. Our data also highlight the 2 independent variants in the *UMOD-PDILT* locus known for large effects on eGFRcrea[17] as the 2 strongest genetic risk factors for rapid eGFRcrea decline with each of the 4 adverse alleles increasing CKDi25 risk by 1.06-fold. One variant captures the signal in *UMOD* with unclear function and the other is the *PDILT*-residing variant rs77924615. The rs77924615 was reported as likely causal, modulating *UMOD* expression and urinary uromodulin concentrations.[17] The fact that this variant is the sole variant in the credible set for CKDi25 and for cross-sectional eGFRcrea[17] provides a proof-of-concept that overlapping single-variant credible sets between cross-sectional and longitudinal traits may be indicative of the causal variant.

Particularly interesting is the *OR2S2* locus, which was not identified by the previous GWAS of cross-sectional eGFRcrea[17] and showed no association with cross-sectional eGFRcys or BUN here. In this locus, the genes *OR2S1P*, *GNE*, and *CD72* were supported by our Gene PrioritiSation: *CD72* and *GNE* with evidence of abnormal morphology of podocytes or renal glomerulus, respectively, and by a link of CD72 molecules to patients with systemic lupus erythematosus with renal involvement[39] or *GNE* mutation in mice as a model for human glomerulopathy.[40] There is little published evidence on *OR2S1P*, but we find *OR2S1P* as a target of an eQTL variant that is a credible set variant and thus a likely variant to drive the association signal. We provide no independent replication for this locus association due to the lack of available comparable data for the low-frequency (MAF approximately 2%) driver variants, but our sensitivity analyses supported the signal as genuine.

The genuineness of the *OR2S2* locus for rapid kidney function decline was supported by consistent association with annual change in eGFRcys and BUN. These alternative biomarker results also supported 5 of the 7 identified variants to be associated with kidney function (*UMOD-PDILT* [2 variants], *WDR72*, *PRKAG2*, *OR2S2*), but not the loci near GATM and *LARP4B*.

A challenge in clinical practice is the identification of individuals at increased risk of ESKD and little evidence on genetic factors for ESKD. Some GWAS including 500–4000 ESKD cases reported genome-wide significant loci, but none of these overlap with the loci identified here.[34,41–49] Two genetic variants were identified in approximately 4000 ESKD cases and equal number of controls[41] testing 16 variants known for cross-sectional eGFRcrea. One variant, rs12918807, is highly correlated with our *UMOD-PDILT* lead variant rs12922822 (R^2 = 1.00), but the other variant rs1260326, near *GCKR*, was not associated with rapid eGFRcrea decline (OR = 1.01 and 1.00, *P* value = 0.396 and 0.757). Previous GWAS on ESKD may have been hampered by sample size: to detect a variant with MAF 30% (10%) and 1.1-fold increased disease risk at genome-wide significance with 80% power, the required sample size sizes is 13,500 (31,000) cases and a similar number of controls; to detect such a variant with nominal significance, 2700 (6100) cases are needed. Therefore, ESKD case-control data with thousands of cases might work for candidate-based approaches but will be underpowered for GWAS. Although the genetic variants identified for rapid kidney function decline might be effective candidates, we did not find increased ESKD risk comparing the high versus low genetic profile in >2100 patients with ESKD and health controls. This could be due to insufficient power or survival bias on the adverse alleles,[50] but the data would also be in line with a lack of effect.

We did find a 1.20-fold increased risk for AKI comparing the genetic high-risk versus low-risk group in UK Biobank

including 4000 individuals recorded for AKI. Although AKI is defined as an acute event, AKI and particularly repeated episodes of AKI are known to deteriorate patients' kidney function also chronically, at least for a subgroup.[51] Because of the nature of population-based studies in contrast to hospital-based studies, it is conceivable that some of the individuals in the GWAS studies had AKI between baseline and follow-up and that those with chronically rather than transiently reduced kidney function could have become cases for rapid decline. We assume it unlikely that persons in the acute phase of AKI come to the study center for a follow-up visit. Although not each patient with an AKI episode will experience long-term and rapid deterioration of kidney function, individuals in the genetic high-risk group might include individuals at a higher risk of sustained deterioration of kidney function after AKI. Therefore, the genetic variants identified for rapid kidney function decline might capture mechanisms and individuals at increased risk for sustained kidney function deterioration after AKI.

METHODS

Overall, 42 studies contributed GWAS results estimated via logistic regression on Rapid3 and CKDi25 with 1000 Genomes phase 3 v5 ALL[52] or Haplotype Reference Consortium v.1.1[53] reference variants. After an inverse-variance weighted meta-analysis, genome-wide significantly associated loci including primary and secondary lead variants were identified. In addition, we identified loci among known loci for cross-sectional eGFRcrea.[17] We validated identified effects by alternative cross-sectional and longitudinal renal markers eGFRcys and BUN. We derived credible sets of variants for each identified signal and conducted a comprehensive *in silico* follow-up for all genes underneath identified loci. Finally, we estimated the cumulative genetic effect of the identified lead variants on rapid kidney function decline, ESKD, and AKI. A detailed description of the methods can be found in the Supplementary Methods.

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AUTHOR CONTRIBUTIONS

MG, BJ, PRM-G, CAB, AK, FK, CP, and IMH wrote the manuscript. MG, MWu, AT, CAB, AK, and CP designed the study. BJ, MS, BOT, TSA, SJLB, BB, EB, HB, RJC, JChal, CC, JCo, MHdB, KEc, RTG, CG, PH, KeH, BH, MAI, MKä, CK, WKo, HKr, BKK, TL, RJFL, MAL, OM, YM, GNN, MLO, MO, SAP, BWJHP, BMP, OTR, RRe, MR, PR, CSa, HSc, RS, BS, KStr, PvdH, UV, LWal, DMW, HDW, JGW, TWo, MW, QY, MY, YZ, HSn, CAB, AK, FK, and CP managed an individual contributing study. MG, BJ, YL, MWu, CHLT, TW, VW, JChai, AC, MC, MF, SG, AH, KH, ML, TN, MS, KBS, AT, ATi, JW, BOT, TSA, PA, MLBig, RJC, JChal, MLiC, SF, MGh, PH, EH, SH, NSJ, CK, HKr, BK, LAL, LLy, PPM, NM, MN, BN, IMN, SAP, MHP, LMR, MR, KMR, CSc, SSe, SSz, JTr, PvdH, PJvdM, NV, MW, QY, LMY, CW, CAB, AK, CP, and IMH performed statistical methods and analysis. MG, YL, MWu, ST, MK, TW, VW, AC, MC, SG, AH, KH, ML, TN, MS, KBS, JW, TSA, PA, RJC, FD, AF, PG, PH, EH, NSJ, CK, LLy, YM, PPM, SAP, MHP, CSc, SSe, CMS, SSz, JTr, PJvdM, LMY, CW, CAB, and IMH performed bioinformatics. MG, BJ, YL, MWu, ST, TW, VW, MF, SG, KH, ML, MS, KBS, AT, BOT, TSA, JChal, KEn, MGh, CG, PH, KeH, SH, WKo, SAP, MR, SSe, JTr, LC, PvdH, NV, LWal, HDW, MW, MY, LMY, CAB, AK, CP, and IMH interpreted results. MK, MF, AT, EB, CC, AF, RTG, PH, MKä, CK, WKo, LAL, TL, LLy, TM, OM, YM, NM, JcM, MO, BWJHP, MHP, OTR, JIR, KDT, JTr, PvdH, UV, MWa, JGW, CW, CAB, and FK performed genotyping. MG, BJ, YL, PRM-G, MWu, ST, TW, VW, AC, MF, SG, AH, ML, TN, MS, KBS, AT, ATi, BOT, TSA, PA, SJLB, NB, MLBig, EPB, HB, JChal, JCo, MHdB, KEc, KEn, AF, PG, MGh, CG, PH, KeH, BH, NH, SH, MKä, WKo, HKr, BKK, BK, LAL, TL, WL, RJFL, LLy, CM, TM, OM, GNN, MN, KN, BN, IMN, MLO, MO, SAP, BWJHP, MHP, BMP, LMR, OTR, RRe, MR, KMR, AR, PR, CSa, BS, CSc, SSe, KStr, JTr, LC, PvdH, NV, UV, MWa, LWal, DMW, HDW, JGW, MW, QY, YZ, HSn, CAB, AK, FK, CP, and IMH critically reviewed the manuscript. BJ, EPB, HB, JChal, MLingC, CC, JCo, KEc, RTG, PH, VHXF, NH, MKä, TL, WL, CM, KN, MLO, SAP, BWJHP, OTR, MR, AR, PR, RS, LWal, HDW, JGW, TWo, MW, CAB, AK, and CP recruited subjects.

APPENDIX

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All authors contributed to the management and coordination of all research activities, planning, and execution. All authors contributed to the review process for the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Description of participating studies.

Table S2. Number of cases, controls, and excluded individuals in the UK Biobank study and the KORA studies.

Table S3. Genotyping and imputation information of participating studies.

Table S4A. Identified loci for rapid kidney function decline in individuals of European ancestry.

Table S4B. Identified loci for rapid kidney function decline and 2 APOL1 variants reported to be associated with kidney disease in individuals of African ancestry.

Table S5. Conditional analysis results in *UMOD-PDILT*, *WDR72*, *PRKAG2*, *LARP4B*, and *GATM* loci for Rapid3 and CKDi25 in the all and European meta-analysis.

Table S6A. Credible set variants and their predicted genetic function.

Table S6B. The 99% credible set variants with significant eQTL results.

Table S7A. Genes in locus regions with a kidney-relevant phenotype in mouse.

Table S7B. Genes in the 6 locus regions with a kidney-relevant phenotype in human.

Table S8. Gene PrioritiSation.

Table S9. Kidney function–related biology in the OR2S2 locus.

Figure S1. (**A**) Study-specific information on proportion of cases versus follow-up time for Rapid3 and CKDi25. (**B**) Study-specific information on proportion of cases versus age for Rapid3 and CDKi25.

Figure S2. Genetic effects for rapid eGFRcrea decline traits versus effects for cross-sectional eGFRcrea.

Figure S3. Study-specific association and leave-one-out-analysis results for the *OR2S2* lead variant.

Figure S4. Regional association for the 6 identified loci.

Figure S5. Multi-tissue expression quantitative trait loci (eQTL) comparison of the *OR2S2* lead variant.

Supplementary Methods.

Note S1. Meta-analysis of Rapid3 and CKDi25 in individuals of African American ancestry.

Note S2. Two additional loci for rapid eGFRcrea decline from a candidate-based search.

Note S3. Testing effect direction consistency of identified lead variants with annual change in eGFRcys and BUN in the UK Biobank.

Supplementary References.

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REFERENCES

1. Matsushita K, Selvin E, Bash LD, et al. Change in estimated GFR associates with coronary heart disease and mortality. *J Am Soc Nephrol*. 2009;20:2617–2624.
2. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014;311:2518–2531.
3. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081.
4. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*. 2011;79:1331–1340.
5. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
6. Turin TC, Coresh J, Tonelli M, et al. Short-term change in kidney function and risk of end-stage renal disease. *Nephrol Dial Transplant*. 2012;27:3835–3843.

7. Andrassy KM. Comments on "KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.". *Kidney Int*. 2013;84:622–623.
8. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the national kidney foundation and the US food and drug administration. *Am J Kidney Dis*. 2014;64:821–835.
9. Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis*. 2020;75:84–104.
10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
11. Kidney Disease: Improving Global Outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2:139–274.
12. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367:2407–2418.
13. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31–39.
14. Taylor KS, McLellan J, Verbakel JY, et al. Effects of antihypertensives, lipid-modifying drugs, glycaemic control drugs and sodium bicarbonate on the progression of stages 3 and 4 chronic kidney disease in adults: a systematic review and meta-analysis. *BMJ Open*. 2019;9:e030596.
15. Nelson MR, Tipney H, Painter JL, et al. The support of human genetic evidence for approved drug indications. *Nat Genet*. 2015;47:856–860.
16. King EA, Wade Davis J, Degner JF. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. *PLoS Genet*. 2019;15:e1008489.
17. Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet*. 2019;51:957–972.
18. Gorski M, Tin A, Garnaas M, et al. Genome-wide association study of kidney function decline in individuals of European descent. *Kidney Int*. 2015;87:1017–1029.
19. Auton A, Abecasis GR, Altshuler DM, et al. A global reference for human genetic variation. *Nature*. 2015;526:68–74.
20. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet*. 2016;48:1279–1283.
21. Schutte JE, Longhurst JC, Gaffney FA, et al. Total plasma creatinine: an accurate measure of total striated muscle mass. *J Appl Physiol Respir Environ Exerc Physiol*. 1981;51:762–766.
22. Köttgen A. Genome-wide association studies in nephrology research. *Am J Kidney Dis*. 2010;56:743–758.
23. Maller JB, McVean G, Byrnes J, et al. Bayesian refinement of association signals for 14 loci in 3 common diseases. *Nat Genet*. 2012;44:1294–1301.
24. Schaid DJ, Chen W, Larson NB. From genome-wide associations to candidate causal variants by statistical fine-mapping. *Nat Rev Genet*. 2018;19:491–504.
25. McLaren W, Gil L, Hunt SE, et al. The Ensembl Variant Effect Predictor. *Genome Biol*. 2016;17:122.
26. Gillies CE, Putler R, Menon R, et al. An eQTL landscape of kidney tissue in human nephrotic syndrome. *Am J Hum Genet*. 2018;103:232–244.
27. Aguet F, Brown AA, Castel SE, et al. Genetic effects on gene expression across human tissues. *Nature*. 2017;550:204–213.
28. Bult CJ, Blake JA, Smith CL, et al. Mouse Genome Database (MGD) 2019. *Nucleic Acids Res*. 2019;47:D801–D806.
29. Amberger JS, Hamosh A. Searching Online Mendelian Inheritance in Man (OMIM): a knowledgebase of human genes and genetic phenotypes. *Curr Protoc Bioinforma*. 2017;58:1.2.1–1.2.12.
30. Böger CA, Haak T, Götz AK, et al. Effect of ACE and AT-2 inibitors on mortality and progression to microalbuminuria in a nested case-control study of diabetic nephropathy in diabetes mellitus type 2: results from the GENDIAN study. *Int J Clin Pharmacol Ther*. 2006;44:364–374.
31. Wanner C, Krane V, März W, et al. Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): demographic and baseline characteristics. *Kidney Blood Press Res*. 2004;27:259–266.
32. Hellwege JN, Velez Edwards DR, Giri A, et al. Mapping eGFR loci to the renal transcriptome and phenome in the VA Million Veteran Program. *Nat Commun*. 2019;10:3842.
33. Köttgen A, Pattaro C. The CKDGen Consortium: ten years of insights into the genetic basis of kidney function. *Kidney Int*. 2020;97:236–242.
34. Parsa A, Kanetsky PA, Xiao R, et al. Genome-wide association of CKD progression: the chronic renal insufficiency cohort study. *J Am Soc Nephrol*. 2017;28:923–934.
35. Kaewput W, Thongprayoon C, Chewcharat A, et al. Rate of kidney function decline and factors predicting progression of kidney disease in type 2 diabetes mellitus patients with reduced kidney function: a nationwide retrospective cohort study. *Ther Apher Dial*. 2020;24:677–687.
36. German National Cohort (GNC) Consortium. The German National Cohort: aims, study design and organization. *Eur J Epidemiol*. 2014;29:371–382.
37. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779.
38. Leitsalu L, Haller T, Esko T, et al. Cohort profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int J Epidemiol*. 2015;44:1137–1147.
39. Vadasz Z, Goldeberg Y, Halasz K, et al. Increased soluble CD72 in systemic lupus erythematosus is in association with disease activity and lupus nephritis. *Clin Immunol*. 2016;164:114–118.
40. Kakani S, Yardeni T, Poling J, et al. The Gne M712T mouse as a model for human glomerulopathy. *Am J Pathol*. 2012;180:1431–1440.
41. Böger CA, Gorski M, Li M, et al. Association of eGFR-related loci identified by GWAS with incident CKD and ESRD. *PLoS Genet*. 2011;7:e1002292.
42. Sambo F, Malovini A, Sandholm N, et al. Novel genetic susceptibility loci for diabetic end-stage renal disease identified through robust naive Bayes classification. *Diabetologia*. 2014;57:1611–1622.
43. Iyengar SK, Sedor JR, Freedman BI, et al. Genome-wide association and trans-ethnic meta-analysis for advanced diabetic kidney disease: Family Investigation of Nephropathy and Diabetes (FIND). *PLoS Genet*. 2015;11:e1005352.
44. Palmer ND, Ng MCY, Hicks PJ, et al. Evaluation of candidate nephropathy susceptibility genes in a genome-wide association study of African American diabetic kidney disease. *PLoS One*. 2014;9. e0088273.
45. Salem RM, Todd JN, Sandholm N, et al. Genome-wide association study of diabetic kidney disease highlights biology involved in glomerular basement membrane collagen. *J Am Soc Nephrol*. 2019;30:2000–2016.
46. Sandholm N, Van Zuydam N, Ahlqvist E, et al. The genetic landscape of renal complications in type 1 diabetes. *J Am Soc Nephrol*. 2017;28:557–574.
47. Guan M, Ma J, Keaton JM, et al. Association of kidney structure-related gene variants with type 2 diabetes-attributed end-stage kidney disease in African Americans. *Hum Genet*. 2016;135:1251–1262.
48. Guan M, Keaton JM, Dimitrov L, et al. An exome-wide association study for type 2 diabetes–attributed end-stage kidney disease in African Americans. *Kidney Int Reports*. 2018;3:867–878.
49. Sandholm N, Salem RM, McKnight AJ, et al. New susceptibility loci associated with kidney disease in type 1 diabetes. *PLoS Genet*. 2012;8:e1002921.
50. Reichel H, Zee J, Tu C, et al. Chronic kidney disease progression and mortality risk profiles in Germany: results from the Chronic Kidney Disease Outcomes and Practice Patterns Study. *Nephrol Dial Transplant*. 2020;35:803–810.
51. See EJ, Jayasinghe K, Glassford N, et al. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. *Kidney Int*. 2019;95:160–172.
52. The 1000 Genomes Project Consortium. An integrated map of genetic variation. *Nature*. 2012;135:1–113.
53. Marchini J, Abecasis G, Durbin R. Haplotype Reference Consortium. Available at: http://www.haplotype-reference-consortium.org/. Accessed February 13, 2020.