**Genome-wide significant variants for rapid kidney function decline from a meta-analysis of up to 35,000 cases and >100,000 controls**

**SUPPLEMENTARY MATERIAL**

**Supplementary Tables**

Supplementary Table 1A&B Description of participating studies.

Supplementary Table 2 Number of cases, controls and excluded individuals in the UK Biobank study and the KORA studies.

Supplementary Table 3 Genotyping and imputation information of participating studies.

Supplementary Table 4A Identified loci for rapid kidney function decline in individuals of European ancestry.

Supplementary Table 4B Identified loci for rapid kidney function decline and two APOL1 variants reported to be associated with Kidney Disease in individuals of African ancestry

Supplementary Table 5 Conditional analysis results in *UMOD-PDILT*, *WDR72*, *PRKAG2*, *LARP4B* and *GATM* loci for Rapid3 and CKDi25 in the All and European meta-analysis.

Supplementary Table 6A Credible set variants and their predicted genetic function.

Supplementary Table 6B The 99% credible set variants with significant eQTL results.

Supplementary Table 7A Genes in locus regions with a kidney-relevant phenotype in mouse.

Supplementary Table 7B Genes in the six locus regions with a kidney-relevant phenotype in human.

Supplementary Table 8 Gene PrioritiSation.

**Supplementary Figures**

Supplementary Figure 1A Study-specific information on proportion of cases versus Follow-  
up time for Rapid3 and CKDi25.

Supplementary Figure 1B Study-specific information on proportion of cases versus age for   
Rapid3 and CDKi25.

Supplementary Figure 2 Genetic effects for rapid eGFRcrea decline traits versus effects   
for cross-sectional eGFRcrea.

Supplementary Figure 3 Study-specific association and leave-one-out-analysis results for the *OR2S2* lead variant.

Supplementary Figure 4 Regional association for the six identified loci.

Supplementary Figure 5 Multi-tissue expression quantitative trait loci (eQTL) comparison of the *OR2S2* lead variant.

**Supplementary Methods**

**Supplementary Notes**

Supplementary Note 1 Meta-analysis of Rapid3 and CKDi25 in individuals of African American ancestry.

Supplementary Note 2 Two additional loci for rapid eGFRcrea decline from a candidate-based search.

Supplementary Note 3 Testing effect direction consistency of identified lead variants with annual change in eGFRcys and BUN in the UK Biobank.

**Supplementary References**

**Extended acknowledgements and study funding information**

**Supplementary Table 1A | Description of participating studies.** Shown are the study design and population characteristics from all studies from the Rapid3 and CKDi25 GWAS**.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Full name of the study** | **Study Design**  (population-based, selection or enrichment strategy) | **Serum creatinine assay and year of measurement, baseline** | **Study references** (PMID) |
| ADVANCE | Action in Diabetes and Vascular disease: preterAx and diamicroN mr Controlled Evaluation | factorial, multicentre, randomised controlled trial, with a 5- to 6-year follow-up. | 2001-2003 | 11848259 |
|
|
| AFTER EU | AFTER (EURAGEDIC) European Rational Approach for the Genetics of Diabetic Complications | Adult onset Type 1 Diabetes | Modified Jaffe | 18496510, 20357380 |
| ARIC | Atherosclerosis Risk in Communities study | Population-based | Modified kinetic Jaffé reaction, 1989 | 2646917 |
|
| ASPS | Austrian Stroke Prevention Study | Population-based | Modified kinetic Jaffe reaction, 1991 - 2005 | 10408549, 7800110 |
| BioMe | BioMe™ BioBank Program | Population-based | Jaffe, 2008 | 25349204 |
| CHS | Cardiovascular Health Study | Population-based | Colorimetric method on a Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY), 1989-90 and 1992-93 | 1669507 |
|
| DECODE | deCODE genetics/Amgen | Population-based | Enzymatic and modified kinetic Jaffe reaction assay since 1997 | 20686651, 25082825 |
| DIACORE | DIAbetes COhoRtE | Prospective cohort study of patients with diabetes mellitus type 2 | Serum Creatinine was measured 2010-2013 using an enzymatic assay traceable to NIST. | 23409726 |
| ESTHER | Epidemiological investigation of the chances of preventing, recognizing early and optimally treating chronic diseases in an elderly population | Population-based | Kinetic Jaffe-method, 2000 - 2002 | 23446902, 15578318 |

… to be continued

**Supplementary Table 1A: continued**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study  short name** | **Full name of the study** | **Study Design**  (population-based, selection or enrichment strategy) | **Serum creatinine assay and year of measurement, baseline** | **Study references** (PMID) |
| FHS | The Framingham Heart Study | Community- and family-based | Modified Jaffe method | 5921755, 1208363, 17372189 |
| FINCAVAS | The Finnish Cardiovascular Study | FINCAVAS follow-up cohort of consecutive patients undergoing exercise stress test | Enzymatic photometric, 1992-2015 | 16515696 |
| GCKD | German Chronic Kidney Disease study | Chronic kidney disease patients of European ancestry aged 18-74 years with an eGFR between 30–60 mL/min/1.73 m2 or an eGFR >60 mL/ min/1.73 m2 and a urinary albumin-to-creatinine ratio (UACR) >300 mg/g, albuminuria >300 mg/day, a urinary protein-to-creatinine ratio >500 mg/g, or proteinuria >500 mg/day | Serum creatinine was measured using the Creatinine plus enzymatic assay (Roche) on a Modular (P) analyzer in 2012 | 21862458, 25271006 |
| Jackson Heart Study (JHS) | Jackson Heart Study | Community and family-based | IDMS calibrated serum creatinine was used from visit 1 and visit 3. Creatinine measurements were made from 2000 on but calibration to the same standard was done in 2015. | 16320381  25806862 |
| KORA | Cooperative Health Research in the Augsburg Region | Population-based | Modified kinetic Jaffe reaction, 1994 | 16032514 |
| Lifelines | Lifelines Cohort Study | Population-based | Enzymatic, IDMS traceable, Roche (Modular); 2006-2013 | 18075776, 25502107, 26333164 |
| MDC-CC | Malmö Diet and Cancer Study- Cardiovascular Cohort | Population-based | Jaffé method and the IDMS-traceable standard was used | 11916347 |

… to be continued

**Supplementary Table 1A: continued**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study  short name** | **Full name of the study** | **Study Design**  (population-based, selection or enrichment strategy) | **Serum creatinine assay and year of measurement, baseline** | **Study references** (PMID) |
| MESA | Multi-Ethnic Study of Atherosclerosis | Population-based without CVD | Baseline year: 2002, exam 2: 2004, exam 3: 2005 and exam 4: 2007. All assays rate relectance spectrophotometry using thin film adaptation of creatine aminohydrolase method on the Vitros analyzer (Johnson and Johnson Clinical Diagnostics) | 12397006 |
|
|
| MyCode | MyCode Community Health Initiative (Geisinger Research) | Population-based | Enzymatic method done by Roche Cobas instruments, 1996+ | 26866580 |
| NESDA | Netherlands Study of Depression and Anxiety | Population-based, predominantly cases with major depression | Partly Jaffe, partly enzymatic; 2004-2007 | 18763692 |
| POPGEN | POPGEN control sample | Population-based | Serum creatinine was measured 2005-2008 using an enzymatic assay | 16490960 |
| PREVEND | Prevention of Renal and Vascular End-stage Disease study | Population-based | An isotope dilution mass spectrometry (IDMS) traceable enzymatic method on a Roche Modular analyzer using reagents and calibrators from Roche (Roche Diagnostics, Mannheim, Germany) ‘97-’98 | 12356629 |
| RS III | Rotterdam Study | Population-based | Enzymatic assay, 2006 |  |
| SHIP 1 | Study of Health in Pomerania | Population-based | Jaffe, 2002 |  |
| SiMES | Singapore Malay Eye Study | Population-based | Jaffe, 2004-2007 | 17365815, 21490949 |
| SINDI | Singapore Indian Eye Study | Population-based | Jaffe, 2007-2009 | 19995197, 24244560 |
| SOLID-TIMI 52 | SOLID-TIMI 52 | Clinical trial | Jaffe, 2010 | 21982651 |
| STABILITY | STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY | Clinical trial | Jaffe, 2009 | 24678955, 20934559 |
| UKBB | UK Biobank | Population-based | enzymatic analysis on a Beckman Coulter AU5800 | 25826379 |

… to be continued

**Supplementary Table 1A: continued**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study  short name** | **Full name of the study** | **Study Design**  (population-based, selection or enrichment strategy) | **Serum creatinine assay and year of measurement, baseline** | **Study references** (PMID) |
| Vanderbilt | Vanderbilt BioVU | Population-based with enrichment for a variety of disease studies | Extracted from clinical records | 18500243 |
| YFS | The Young Finns Study | Population-based | Serum creatinine was determined spectrophotometrically by the Jaffé method (picric acid; Olympus Diagnostica GmbH) from frozen plasma samples. Year 2001. | 18263651, 23069987 |

**Supplementary Table 1B | Description of participating studies.** Shown are details from the phenotype distribution across all studies from the Rapid3 and CKDi25 GWAs.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study short name** | **Sub**  **group** | **Ancestry** | **Male (%)** | **Diabetes (%)** | **Age median [years]** | **Baseline eGFR mean [ml/min/ 1.73m2]** | **Follow-up time [years]** | **N**  **cases Rapid3** | **N controls Rapid3** | **% of cases Rapid3** | **N**  **cases CKDi25** | **N controls CKDi25** | **% of cases CKDi25** |
| ADVANCE | 5 | EUR | 70% | 100% | 68 | 72.1 | 4.35 | 218 | 560 | 0.28 | -- | -- | -- |
| 6 | EUR | 62% | 100% | 68 | 72.1 | 4.35 | 598 | 1,630 | 0.27 | 267 | 1,349 | 0.17 |
| UKB | EUR | 59% | 100% | 68 | 72.1 | 4.35 | 337 | 755 | 0.31 | 160 | 513 | 0.24 |
| AFTER EU |  | EUR | 57% | 100% | 43 | 84.0 | 6 | -- | -- | -- | 174 | 487 | 0.26 |
| ARIC |  | AA | 37% | 20% | 53 | 111.5 | 8.38 | 611 | 348 | 0.64 | 107 | 1,767 | 0.06 |
|  | EUR | 47% | 9% | 55 | 99.6 | 8.69 | 970 | 1,693 | 0.36 | 351 | 6,831 | 0.05 |
| ASPS |  | EUR | 43% | 0% | 65 | 75.2 | 1 | 124 | 142 | 0.47 | -- | -- | -- |
| BioMe |  | AA | 35% | 5% | 47 | 96.4 | 5.34 | 744 | 411 | 0.64 | -- | -- | -- |
|  | EUR | 52% | 3% | 63 | 75.0 | 2.77 | 232 | 231 | 0.50 | -- | -- | -- |
|  | HIS | 37% | 6% | 48 | 90.7 | 4.97 | 820 | 598 | 0.58 | 115 | 1,967 | 0.06 |
| CHS |  | AA | 39% | 24% | 72 | 72.6 | 4 | 124 | 142 | 0.47 | -- | -- | -- |
|  | EUR | 44% | 12% | 71 | 65.7 | 6 | 134 | 1,111 | 0.11 | -- | -- | -- |
| DECODE |  | EUR | 47% | 5% | 44 | 93.0 | 14 | 9,980 | 59,017 | 0.14 | 8,235 | 96,496 | 0.08 |
| DIACORE |  | EUR | 60% | 100% | 67 | 79.0 | 2.96 | 705 | 532 | 0.57 | 124 | 1,584 | 0.07 |
| ESTHER |  | EUR | 42% | 17% | 62 | 89.4 | 5 | -- | -- | -- | 582 | 533 | 0.52 |
| FHS |  | EUR | 47% | 6% | 54 | 78.3 | 15 | -- | -- | -- | 198 | 1,342 | 0.13 |
| FINCAVAS |  | EUR | 61% | 13% | 58 | 84.9 | 8.9 | 126 | 327 | 0.28 | -- | -- | -- |
| GCKD |  | EUR | 60% | 35% | 63 | 49.4 | 2 | 1,652 | 641 | 0.72 | 121 | 523 | 0.19 |
| Jackson Heart Study (JHS) |  | AA | 38% | 22% | 56 | 94.1 | 6.6 | 345 | 844 | 0.29 | 158 | 1,847 | 0.08 |
| KORA | S3/F3 | EUR | 49% | 2% | 47 | 102.7 | 10 | 321 | 851 | 0.27 | 168 | 2,651 | 0.06 |
| S4/F4 | EUR | 49% | 2% | 49 | 93.0 | 7 | 241 | 1,368 | 0.15 | -- | -- | -- |
| Lifelines |  | EUR | 42% | 3% | 47 | 93.2 | 5.5 | 821 | 4,743 | 0.15 | -- | -- | -- |
| MDC-CC |  | EUR | 41% | 4% | 58 | 80.3 | 15.14 | -- | -- | -- | 296 | 2,279 | 0.11 |

… to be continued

**Supplementary Table 1B: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study short name** | **Sub-group\*** | **Ancestry\*\*** | **Male (%)** | **Diabetes (%)** | **Age median [years]** | **Baseline eGFR mean [ml/min/ 1.73m2]** | **Follow-up time [years]** | **N**  **cases Rapid3** | **N controls Rapid3** | **% of cases Rapid3** | **N**  **cases CKDi25** | **N controls CKDi25** | **% of cases CKDi25** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| MESA |  | AA | 46% | 17% | 63 | 82.3 | 4 | 312 | 458 | 0.41 | -- | -- | -- |
|  | EUR | 48% | 5% | 63 | 75.5 | 4 | 339 | 956 | 0.26 | 103 | 1,600 | 0.06 |
|  | HIS | 48% | 17% | 61 | 81.9 | 4 | 218 | 486 | 0.31 | -- | -- | -- |
| MyCode |  | EUR | 42% | 13% | 50 | 93.3 | 13 | 5,993 | 12,957 | 0.32 | 6,645 | 26,487 | 0.20 |
| NESDA |  | EUR | 34% | 4% | 43 | 103.7 | 6 | 253 | 607 | 0.29 | -- | -- | -- |
| POPGEN |  | EUR | 53% | 3% | 57 | 90.7 | 6 | 108 | 334 | 0.24 | -- | -- | -- |
| PREVEND |  | EUR | 52% | 4% | 49 | 83.9 | 4 | 361 | 1,144 | 0.24 | -- | -- | -- |
| RS III |  | EUR | 44% | 9% | 57 | 85.4 | 5.34 | 285 | 955 | 0.23 | -- | -- | -- |
| SHIP 1 |  | EUR | 48% | 9% | 55 | 88.8 | 3 | 217 | 832 | 0.21 | -- | -- | -- |
| SiMES |  | SA | 49% | 31% | 59 | 77.6 | 3.67 | 163 | 541 | 0.23 | -- | -- | -- |
| SINDI |  | SA | 51% | 40% | 57 | 90.2 | 4.68 | 215 | 605 | 0.26 | -- | -- | -- |
| SOLID-TIMI 52 |  | EUR | 75% | 26% | 64 | 77.1 | 2 | 2,006 | 1,280 | 0.61 | 294 | 4,244 | 0.06 |
| STABILITY |  | EUR | 82% | 37% | 65 | 72.8 | 3 | 1,201 | 2,561 | 0.32 | 291 | 5,312 | 0.05 |
| UKBB |  | EUR | 49% | 4% | 58 | 90.6 | 4.27 | 2,416 | 5,828 | 0.29 | 518 | 14,518 | 0.03 |
| Vanderbilt | 660 | EUR | 45% | 4% | 55 | 85.3 | 8.81 | 430 | 324 | 0.57 | 303 | 933 | 0.25 |
| AA1M | AA | 34% | 6% | 48 | 99.0 | 9.76 | 220 | 172 | 0.56 | 109 | 569 | 0.16 |
| Omni1 | EUR | 53% | 3% | 55 | 86.0 | 8.97 | 643 | 403 | 0.61 | 475 | 1,091 | 0.30 |
| Omni5 | EUR | 55% | 8% | 56 | 86.4 | 4.32 | 190 | 91 | 0.68 | 105 | 323 | 0.25 |
| YFS |  | EUR | 46% | 0% | 33 | 107.8 | 6 | 192 | 593 | 0.24 | -- | -- | -- |

\*Subgroup: subgrouping of study participants by homogeneous characteristics (SNP array; ancestry);

\*\*Ancestry: European (EUR), African American (AA), Hispanic (HIS), South Asian (SA)

**Supplementary Table 2 | Number of cases, controls and excluded individuals in the UK Biobank study and the KORA studies.** Shown are the cross-tables of cases, controls and exclusions for Rapid3 and CKDi25 in the three studies UKBB (n=15,462), KORAS3F3 (n=2,878) and KORAS4F4 (n=2,919) of unrelated, European individuals with all phenotypic information available. Due to the differing exclusion criteria for the two phenotypes, there were some individuals excluded for one or the other analysis.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| UK Biobank (a) median follow-up time = 4 years | |  | **CKDi25** | | | | | | |
|  | **Controls** |  | **Cases** |  | **Excluded (c)** |  | **SUM** |
| **Rapid3** | **Control** |  | 5,743 |  | 0 |  | 85 (0.5%) |  | 5,828 |
| **Case** |  | 1,830 |  | 516 |  | 70 (0.4%) |  | 2,416 |
| **Excluded** |  | 6,945 (d) |  | 2 (b) |  | 271 (1.8%) |  | 7,218 |
| **SUM** |  | 14,518 |  | 518 |  | 426 (2.8%) |  | 15,462 |
|  |  |  |  |  |  |  |  |  |  |
| KORAS3F3 (a) median follow-up time = 10 years | |  | **CKDi25** | | | | | | |
|  | **Controls** |  | **Cases** |  | **Excluded (c)** |  | **SUM** |
| **Rapid3** | **Control** |  | 834 |  | 0 |  | 17 (0.6%) |  | 851 |
| **Case** |  | 189 |  | 131 |  | 1 (0.0%) |  | 321 |
| **Excluded** |  | 1,628 (d) |  | 37 (b) |  | 41 (1.4%) |  | 1,706 |
| **SUM** |  | 2,651 |  | 168 |  | 59 (2.0%) |  | 2,878 |
|  |  |  |  |  |  |  |  |  |  |
| KORAS4F4 (a) median follow-up time = 7 years | |  | **CKDi25** | | | | | | |
|  | **Controls** |  | **Cases** |  | **Excluded (c)** |  | **SUM** |
| **Rapid3** | **Control** |  | 1,338 |  | 0 |  | 30 (1.0%) |  | 1,368 |
| **Case** |  | 170 |  | 66 |  | 5 (0.2%) |  | 241 |
| **Excluded** |  | 1,211 (d) |  | 19 (b) |  | 80 (2.7%) |  | 1,310 |
| **SUM** |  | 2,719 |  | 85 |  | 115 (3.9%) |  | 2,919 |

(a) The number of related or non-European individuals or individuals with missing age, sex or serum creatinine at baseline or follow-up was 471,947 in UKBB, 386 in KORAS3F3 and 869 in KORAS4F4. (b) Individuals were excluded in Rapid3 analysis due to annual eGFRcrea decline of 2.7 to 2.8 mL/min/1.73m2 /year in UK Biobank and 1.8 to 2.9 in the KORA studies; none was excluded due to an annual decline <-1 mL/min/1.73m2 /year. (c) Individuals were excluded for the CKDi25 analysis, when they had eGFRcrea <60 mL/min/1.73m2 at baseline (in parentheses, stating the proportion of excluded compared to total number of individuals in the study). (d) CKDi25 controls were excluded from Rapid3 analysis due to annual decline between 1 and 3 mL/min/1.73m2 /year.

**Supplementary Table 3 | Genotyping and imputation information of participating studies.** Shown are the information of the genotyping and imputation for all studies from the Rapid3 and CKDi25 GWAs.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Exclusions of individuals | Genotyping Array | Geno-type calling | Variant QC before imputation | # SNPs used for imputation | Software phasing and imputation  (imputation quality) | Imputation reference panel | Variant QC after imputation | Handling of population stratification |
| ADVANCE | Ethnic outliers, sex mismatches, CR < 95% | Affymetrix 5.0,  Affymetrix 6.0,  Affymetrix UKB | Affymetrix power tools 1.17.0 | avg\_het <23% or >30%; CR <97%; MAF <1%; snp CR <95%; HWE <0.001; | Affym.5.0: 363062;  Affym.6.0: 702628;  Affym.UKB:759238 | SHAPEIT2; IMPUTE2 (IMPUTE2 Info Score) | 1000G Phase 3 Version 5 | MAF<0.005; info <0.3 | PC 1 and 2 |
| AFTER EU | sample CR <98%, extreme heterozygosity, sex mismatches, non-European ancestry, cryptic relatedness, duplicates | Illumina HumanCore Exome v1.0/v1.1 | Illumina Genome Studio | CR≤95%, HWE<10e-6, INDELs, non 1KG variants, 40% MAF difference with 1000G, duplicate SNPs | 318207 | Shapeit v2 r837; Minimac3/Minimac3 version 2.0.1 (r2) | 1000G Phase 3 Version 5 (October 2015) | none | First 5 PCs |
| ARIC EA | 658 individuals: discrepancies with previous genotypes, sex mismatch, relatives, outliers (measures of average DST or >8 SD away on any of the first 10 PCs) | Affymetrix 6.0 | Birdseed | CR <95%, MAF<0.5%, pHWE<10e-5 | 682749 | SHAPEIT; IMPUTE2 (IMPUTE2 Info) | 1000G Phase 1 Version 3 ALL (March 2012) | none | first 10 PCs |
| ARIC AA | 336 individuals: discrepancies with previous genotypes, sex mismatch, relatives, outliers (measures of average DST or >6 SD away on any of the first 10 PCs) | Affymetrix 6.0 | Birdseed | CR <95%, MAF<1%, pHWE<10e-5 | 773,317 | SHAPEIT; IMPUTE2 (IMPUTE2 Info) | 1000G Phase 1 Version 3 ALL (March 2012) | none | first 10 PC |
| ASPS | Ethnic outliers; duplicates; gender mismatch; cryptic relatedness; sample CR < 98%; excess heterozygosity | Illumina Human610-Quad BeadChip | Illumina | CR< 98 %; MAF<1%; pHWE < 5×10-6 | 566930 | ShapeIt; IMPUTE2 (IMPUTE2 info) | 1000G Phase 1 Version 3 ALL (March 2012) | none | First 4 PCs |
| BioMe | none | Illumina HumanOmniExpressExome-8 v1.0 | BeadStudio | CR: < 98%; Heterozygosity < -0.1 or > 0.3 for common variants (MAF>1%); inbreeding coefficient < 0.4 or > 0.9 for rare variants (MAF<1%); MAF = 0; HWE < 1x10-5 | AA/HA: 828,109  EA: 688,734 | AA/HA: SHAPEIT2; IMPUTE2 (IMPUTE2 Info Score) EA: minimac; Michigan Imputation Server (minimac RSQ) | AA/HA: 1000G Phase 1 Version 3  EA: HRC 1.1 |  | PC1-PC8 |

… to be continued

**Supplementary Table 3: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Exclusions of individuals | Genotyping Array | Geno-type calling | Variant QC before imputation | # SNPs used for imputation | Software phasing and imputation  (imputation quality) | Imputation reference panel | | Variant QC after imputation | | | Handling of population stratification |
| CHS AA | CR<=95%; discordant genotype with known sex or prior genotyping | Illumina HumanOmni1-Quad\_v1 BeadChip | Illumina GenomeStudio | CR<97%, HWE<10-5,  > 1 duplicate error or Mendelian inconsistency (reference: CEPH trios), heterozygote frequency = 0 | 963248 SNPs (940567 autosomal, 22681 X) | none (no pre-phasing performed); IMPUTE version 2.2.2 (r2) | | 1000G Phase 3 | | Effective MAC < 5 | First 5 PCs | | |
| CHS EA | CHD, congestive heart failure, PVD, valvular heart disease, stroke or TIA at baseline or lack of available DNA; CR<=95% or if discordant genotype with known sex or prior genotyping | Illumina 370CNV BeadChip | Illumina BeadStudio | CR <97%, HWE P <10-5, > 2 duplicate errors or Mendelian inconsistencies (reference: CEPH trios), heterozygote frequency=0, SNP not in HapMap | 359592 | MaCH; minimac (r2) | | 1000G Phase 3 | | Effective MAC<10 | First 5 PCs | | |
| DECODE | CR < 97% | Illumina HumanHap300, HumanCNV370, HumanHap610, HumanHap1M, HumanHap660, Omni-1, Omni 2.5 or Omni Express bead chips | Graph-typer | Yield < 95%, MAF>0.01, HW < 0.001 |  | Inhouse software; Inhouse software, similar to IMPUTE (Info) | | Icelandic reference panel - variants matched with HRC or 1000G Phase 3 | | none |  | | |
| DIACORE | all patients included | Axiom UK Biobank Array | Axiom GT1 in Geno-typing Console 4.0 | Missing phenotype; Ancestry not European; Relatedness ≤2nd degree; sex mismatch; Gonosomal aberration; Excess of Hetero-cygosity; Low CR | 799756 | ShapeIT v2.r727; minimac-2013-7-17 (minimac RSQ) | | 1000G Phase 3 Version 5 | | none | first 10 PCs | | |
| ESTHER | sex mismatch, sample CR < 97%, duplicated or related samples, ethnic outliers (Germans only remained), | Illumina Infinium OncoArray-500K BeadChip | GenomeStudio | MAF 0.01, GENO 0.05, HWE 0.00001 (Anderson et al., Nat. Protoc. 2010) | 368205 | SHAPEIT; IMPUTE2 (IMPUTE2 Info) | | 1000G Phase 3 Version 5 | | none | not required | | |

… to be continued

**Supplementary Table 3: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Exclusions of individuals | Genotyping Array | Geno-type calling | Variant QC before imputation | # SNPs used for imputation | Software phasing and imputation  (imputation quality) | Imputation reference panel | | Variant QC after imputation | | | Handling of population stratification |
| FHS | CR <97%, sample failure, genotyped sex different from recorded sex, extreme heterozygosity or high Mendelian error rate | Affymetrix GeneChip Human Mapping 500K Array Set® and 50K Human Gene Focused Panel® | Affymetrix BRLMM | CR <97%, pHWE<1E-6, Mishap p<1e-9, >100 Mendel errors, MAF<1% | 412053 | SHAPEIT; MACH version 1.0.16 (MACH R2) | | 1000G Phase 1 Version 3 (March 2012) | | none | PCs associated with trait with p<0.05 | | |
| FINCAVAS | CRs < 95%, sex mismatch, MDS outliers, excess heterozygosity | Illumina HumanCoreExome and Metabochip | Genome Studio | CR<95%, pHWE<1e-6, monomorphic removed | HCE: 306474 MC: 155499 | Eagle2; Minimac3 (R2) | | HRC 1.1 | | none | PCs 1-5 | | |
| GCKD | CR < 97%, failed sex check, outside 2 SD of mean heterozygosity, cryptic relatedness; genetic ancestry outlier | Illumina Omni2.5Exome BeadChip | Illumina GenomeStudio | CR < 96%, HWE p < 1E-5, or MAF < 1% | 2337794 | Eagle; minimac3 (r2) | | HRC 1.1 | | none | no associated PCs | | |
| JHS | sex mismatches, sample duplications or swaps, sample CR <95% | Affymetrix 6.0 | Birdseed | CR <95% | 868969 | MACH 1.0; minimac (r2 from MACH) | | 1000G Phase 1 Version 3 (March 2012), ALL | | none | First 10 PCs, and kinship matrix for continuous traits | | |
| KORA\_S3F3 | Non-European ancestry, population outlier, sex mismatch, 5SD from mean heterozygosity rate, mismatch to previous genotyping | Illumina Omni 2.5/Illumina Omni Express | Genome Studio | CR <97% | 587981 (chr 1-22) | SHAPEIT; Michigan Imputation Server (r2) | | 1000G Phase 3 Version 5 | | none | PC1-PC10 | | |
| KORA\_S4F4 | Non-European ancestry, population outlier, sex mismatch, 5SD from mean heterozygosity rate, mismatch to previous genotyping | Affymetrix Axiom | Affymetrix Software | CR <97% | 508532 (chr 1-22) | SHAPEIT; Michigan Imputation Server (r2) | | 1000G Phase 3 Version 5 | | none | PC1-PC10 | | |
| Lifelines | Sample CR <80%; sex mismatch; heterozygosity > 4SD from mean; non-Caucasian ethnicity (by PCA), high relatedness (pi-hat > 0.4) | Illumina Cyto SNP12 v2 | Genome Studio | SNPs with MAF < 1%, HWE p-value ≤10-3, CR < 95% | 257581 | NA; Minimac (2012.10.3) (r2) | | 1000G Phase 1 Version 3 (March 2012) | | none | Top 10 PCs | | |

… to be continued

**Supplementary Table 3: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Exclusions of individuals | Genotyping Array | Geno-type calling | Variant QC before imputation | # SNPs used for imputation | Software phasing and imputation  (imputation quality) | Imputation reference panel | | Variant QC after imputation | | | Handling of population stratification |
| MDC-CC | bad CR, excess homozygosity, failed gender check, relatives, duplicates, Population outliers | Illumina HumanOmniExpressExome BeadChip v. 1.0 | Genome Studio v2011.1 | monomorphic, CR <95%, HWE p<10^-6 | ~ 800000 | SHAPEIT2; IMPUTE2 (Info score from snptest) | | 1000G Phase 1 Version 3 ALL (March 2012) | | none | 10 PC added | | |
| MESA-AA | Sex discrepancy, duplicates, CR <95%, heterozygosity, and outliers | Affymetrix Genome-Wide Human SNP Array 6.0 | Birdseed v2 | CR<95%, MAF<=1%, pHW <1E-6 | 897979 | SHAPEIT2; Michigan Imputation Server (r2) | | 1000G Phase 3 Version 5 ALL | | none | First 3 PCs | | |
| MESA-EA | Sex discrepancy, duplicates, CR <95%, heterozygosity, and outliers | Affymetrix Genome-Wide Human SNP Array 6.0 | Birdseed v2 | CR<95%, MAF<=1%, pHW <1E-6 | 897979 | SHAPEIT2; Michigan Imputation Server (r2) | | HRC | | none | First 3 PCs | | |
| MESA-HIS | Sex discrepancy, duplicates, CR <95%, heterozygosity, and outliers | Affymetrix Genome-Wide Human SNP Array 6.0 | Birdseed v2 | CR<95%, MAF<=1%, pHW <1E-6 | 897979 | SHAPEIT2; Michigan Imputation Server (r2) | | 1000G Phase 3 Version 5 ALL | | none | First 3 PCs | | |
| MyCode (Geisinger Research) | Sample CR < 90% | Illumina Human Omni express Exome | Illumina’s Genotype studio | IMPUTE2 info score <0.7, Marker CR < 99%, MAF < 0.01, pHWE < 1e-07, insertions and deletions | 589485 | SHAPEIT2; IMPUTE2 (IMPUTE2 Info Score) | | 1000G Phase 1 Version 3 ALL (March 2012) | | info <0.7 | not required | | |
| NESDA | Non-Caucasians, XO and XXY samples, CR <90%, high genome-wide homo-/ hetero-zygosity, excess IBS | Perlegen-Affymetrix 5.0; Affymetrix 6.0 907K | Birdseed | CR<95%; MAF<=0.01; pHWE<1E-5; ambiguous location/allele with reference; >20% AF from reference; ambiguous SNPs with MAF>35% | 378163 | MACH1; Minimac (r2) | | 1000G Phase 1 Version 3 ALL (March 2012) | | none | PC1-3 | | |
| POPGEN | CR < 90 %, sex mismatches, duplicates (IBD 0.185), heterozygosity outside mean +-3SD, not mapping to CEU (Hapmap), i.e. outside median +- 3\*IQR, samples with batch problems, i.e. outside median +-3\*IQR | Affymetrix Axiom, Affymetrix 6.0, Illumina Immunochip (Beadchip), Illumina Metabochip, Illumina 550k | Illumina Genome Studio or Illumina Opticall | CR < 5%, HWE < 1x10^-5, no MAF for QC but MAF pre-imputation | 1049248 | SHAPEIT2; IMPUTE2 (IMPUTE2 info) | | 1000G Phase 1 Version 3 ALL (March 2012) | | info <= 0.3 | not required | | |

… to be continued

**Supplementary Table 3: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Exclusions of individuals | Genotyping Array | Geno-type calling | Variant QC before imputation | # SNPs used for imputation | Software phasing and imputation  (imputation quality) | Imputation reference panel | | Variant QC after imputation | | | Handling of population stratification |
| PREVEND | CR <95%; sex mismatch; non-Caucasians; duplicates | Illumina Cyto SNP12 v2 | Illumina Genome Studio | CR < 95%; MAF <1%; pHWE< 1E-4 | 232571 | SHAPEIT; Michigan Imputation Server (Info Score) | | HRC | | none | exclusion of PC outliers, adjusting for PC1-5 | | |
| RS-III | MAF <0.05, CR <0.95 and/or HWE <1x10-7, excess heterozygosity, gender swaps, genetic ancestry, relatives | Illumina 610K and 660K | GeneCall | MAF < 0.05, SNP CR < 0.95 and/or HWE p-value < 1x10-9 | 517658 | MaCH and Minimac; Minimac 5 (r2) | | HRC 1.0 | | none | PC1-5 | | |
| SHIP | Duplicates (by IBS), reported/genotyped gender mismatch, CR <= 92% | Affymetrix SNP 6.0 | Birdseed2 | pHWE <= 0.0001 or CR <= 0.95 or monomorphic SNPs, duplicate IDs, inconsistent reference alleles, mapping problem to build 37 | 823635 | Eagle2; Minimac3 (minimac RSQ) | | HRC 1.1 | | none | not required | | |
| SiMES | monomorphic, CR <95%, heterozygosity, relatives/duplicates, discordant ethnicity, gender discrepancy. | Illumina Human610-Quad Beadchips | Genome Studio GenTrain and GenCall | pHW <1E-6, no match/ not present in 1000 Genomes phase 3 panel, AF difference >20% to reference in 1000Gp3, duplicates (T2D DIAMANTE protocol) | 549947 | SHAPEIT; Michigan Imputation Server (r2) | | 1000G Phase 3 Version 5 ALL | | none | PC1, PC2 | | |
| SINDI | monomorphic, CR <95%, heterozygosity, relatives/duplicates, discordant ethnicity, gender discrepancy. | Illumina Human610-Quad Beadchips | Genome Studio GenTrain and GenCall | pHW <1E-6, no match/ not present in 1000 Genomes phase 3 panel, AF difference >20% to reference in 1000Gp3, duplicates (T2D DIAMANTE protocol) | 552278 | SHAPEIT; Michigan Imputation Server (r2) | | 1000G Phase 3 Version 5 ALL | | none | PC1, PC2, PC3 | | |
| SOLID-TIMI 52 | CR <97%, >3rd degree relative (kindship coefficient, KING), sex mismatch | Axiom® Biobank Plus Genotyping Array |  | CRs <95%, monomorphic, Hardy-Weinberg <E-6, | ~547000 | NA; HAPI-UR (NA) | | 1000G Phase 1 Version 3 ALL (March 2012) | |  |  | | |
| STABILITY | CR <97%, >3rd degree relative (kindship coefficient, KING), sex mismatch | Illumina HumanOmniExpressExome-8 v1 array |  | CRs <95%, monomorphic, Hardy-Weinberg <E-7, | 881788 | SHAPEIT v2.644; University of Michigan - minimac (NA) | | 1000G Phase 1 Version 3 ALL (March 2012) | |  |  | | |

… to be continued

**Supplementary Table 3: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Exclusions of individuals | Genotyping Array | Geno-type calling | Variant QC before imputation | # SNPs used for imputation | Software phasing and imputation  (imputation quality) | Imputation reference panel | | | Variant QC after imputation | | Handling of population stratification |
| UKBB | sex effects, discordance across control replicates;  ancestry outliers, outliers for heterozygosity/missingness (https://www.biorxiv.org/content/early/2017/07/20/166298) | UK BiLEVE Axiom array, UK Biobank Axiom array | Axiom GT1 algorithm (Affymetrix Power Tools software) | Variants with batch/plate/array effects, departures from HWE,  Failed QC in > 1 batch, CR < 95%, MAF < 0.0001 (https://www.biorxiv.org/content/early/2017/07/20/166298) | 670739 | SHAPEIT3; IMPUTE4 (IMPUTE info score) | | HRC | None | | accounting for relatives in Linear Mixed Model (BOLT-LMM) | | |
| ULSAM | CR <95%; sex mismatch; extreme heterozygosity; relatives; ancestry outliers | Illumina 2.5M and Metabochip | Genome Studio | CR <95%, HWE p<10-6, MAF<1% | 1621481 | ShapeITv2; IMPUTE4 (Info Score) | | HRC | info<0.4 | | 2PCs | | |
| Vanderbilt-660 | sex mismatch, duplicates, CR <98%, HapMap concordance check | Illumina 660W | Genome Studio | CR <98%, HWE<0.001, MAF <0.001, HapMap concordance | 527715 | SHAPEIT; Minimac3 (R2) | | HRC 1.1 | none | | PCs 1-3 | | |
| Vanderbilt-AA1M | sex mismatch, duplicates, CR <98%, HapMap concordance check | Illumina 1M | Genome Studio | CR <98%, HWE<0.001, MAF <0.001, | 784048 | SHAPEIT; Minimac3 (R2) | | HRC 1.1 | none | | PCs 1-3 | | |
| Vanderbilt-Omni1 | sex mismatch, duplicates, CR <98%, HapMap concordance check | Illumina OMNI-Quad | Genome Studio | CR <98%, HWE<0.001, MAF <0.001 | 924162 | SHAPEIT; Minimac3 (R2) | | HRC 1.1 | none | | PCs 1-3 | | |
| Vanderbilt-Omni5 | sex mismatch, duplicates, CR <98%, HapMap concordance check | HumanOmni5-Quad | Genome Studio | CR <98%, HWE<0.001, MAF <0.001 | 3702007 | SHAPEIT; Minimac3 (R2) | | HRC 1.1 | none | | PCs 1-3 | | |
| YFS | CRs < 95%, sex mismatch, MDS outliers, excess heterozygosity | Illumina 670k Custom | Illuminus | CR<95%, pHWE<1e-6, monomorphic | 542086 | Eagle2; Minimac3 (R2) | | HRC 1.1 | None | | PCs 1-5 | | |

**Abbreviations:** CR, call rate; HRC, Haplotype Reference Consortium; AF = allele frequency, MAF, minor allele frequency; PC, principal component; MAC, minor allele count, Effective MAC = MAF\*sampleN\*2\*impQuality.

**Supplementary Table 4A | Identified loci for rapid kidney function decline in individuals of European ancestry.** Shown are the significant lead variants from the GWAS for Rapid3 and CKDi25 (judged at genome-wide significance, P<5.00x10-8) and the significant variants from the candidate-based approach inquiring the 265 variants reported from the cross-sectional eGFRcrea GWAMA17; judged at Bonferroni-corrected significance, P‑value<0.05/265≈1.89x10-4).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | **Rapid3** | | | | | | |  | **CKDi25** | | | | | | |  | |  | |
| **RSID** | **Ident. analysis** | **Locus name** |  | | **OR** | **SE** | **P** | **N cases** | **N ctrls** | **N stud** |  | **OR** | **SE** | **P** | **N cases** | **N ctrls** | **N stud** |  | | **locus/ signal no.** | | **EUR GWAS lead variant in locus/ signal (R², a)** |
| rs13329952 rs12922822 | Rapid3 CKDi25 | [UMOD-PDILT] |  | | 1.099 1.102 | 0.0118 0.0121 | 1.39x10-15 1.27x10-15 | 31,072 31,100 | 102,422 102,481 | 28 28 |  | 1.21 1.23 | 0.017 0.017 | 4.36x10-30 1.67x10-33 | 19,374 19,409 | 168,943 169,085 | 19 19 |  | | 1.1 | | rs36060036 (0.86) same |
| rs77924615 | CKDi25 2nd (c) | [UMOD-PDILT] |  | | 1.022 | 0.0132 | 9.22x10-2 | 25,100 | 89,509 | 27 |  | 1.11 | 0.0194 | 2.50x10-8 | 12,767 | 142,607 | 18 |  | | 1.2 | | same |
| rs77593734 | CKDi25 | [WDR72] |  | | 1.036 | 0.0104 | 5.69x10-4 | 31,088 | 102,455 | 28 |  | 1.10 | 0.0144 | 2.06x10-11 | 19,396 | 169,030 | 19 |  | | 2 | | same |
| rs56012466 | CKDi25 | [PRKAG2] |  | | 1.041 | 0.0107 | 1.76x10-4 | 30,239 | 97,653 | 27 |  | 1.09 | 0.0145 | 3.97x10-9 | 19,366 | 168,911 | 19 |  | | 3 | | rs73158188 (0.84) |
| rs141809766 | Rapid3 | [OR2S2] |  | | 1.229 | 0.0349 | 4.32x10-9 | 24,592 | 88,498 | 24 |  | 1.06 | 0.0550 | 0.2276 | 12,767 | 142,607 | 18 |  | | 4 | | same |
| rs34882080  (b) | CKDi25; Rapid3 | [UMOD-PDILT] |  | | 1.102 | 0.0121 | 1.04x10-15 | 31,083 | 102,445 | 28 |  | 1.22 | 0.0170 | 2.02x10-32 | 19,392 | 169,015 | 19 |  | | 1.1 | | rs36060036 (0.95) rs12922822 (0.99) |
| rs77924615 | CKDi25;Rapid3 | [UMOD-PDILT] |  | | 1.083 | 0.0128 | 6.59x10-10 | 25,100 | 89,509 | 27 |  | 1.26 | 0.0207 | 6.68x10-29 | 12,767 | 142,607 | 18 |  | | 1.2 | | rs36060036 (0.39) rs12922822 (0.36) |
| rs690428 | CKDi25 | [WDR72] |  | | 1.031 | 0.0113 | 6.47x10-3 | 25,100 | 89,509 | 27 |  | 1.09 | 0.0179 | 4.16x10-6 | 12,767 | 142,607 | 18 |  | | 2 | | rs77593734 (0.42) |
| rs10254101 | CKDi25 | [PRKAG2] |  | | 1.037 | 0.0106 | 6.70x10-4 | 30,240 | 97,654 | 27 |  | 1.09 | 0.0144 | 4.52x10-9 | 19,363 | 168,899 | 19 |  | | 3 | | rs73158188 (0.84) |
| rs80282103 | CKDi25 | [LARP4B] |  | | 1.038 | 0.0174 | 3.33x10-2 | 31,080 | 102,438 | 28 |  | 1.11 | 0.0240 | 2.42x10-5 | 19,386 | 168,990 | 19 |  | | 5 | | same |
| rs1145077 | Rapid3 | [GATM] |  | | 1.039 | 0.0096 | 8.03x10-5 | 31,102 | 102,484 | 28 |  | 1.04 | 0.0133 | 1.09x10-3 | 19,411 | 169,093 | 19 |  | | 6 | | rs2486288 (1.00) |

**Ident. analysis**=Analysis where variant was significantly associated, **SE**/**P**=2nd GC corrected standard error/ P-value, **N cases/ N ctrls**=Number of cases and controls, **N stud**=Number of studies in analysis, **Locus/signal no.**=locus and signal number, **EUR GWAS lead variant in this locus/ signal (R²)**=Variant with lowest P-value in the European analysis (correlation R²). (a) Pairwise R² from LD LinkS1 in all European reference individuals (n=503), (b) Lead variant of the 2nd signal in [UMOD-PDILT] in the European analysis17, (c) Stated are OR and P-value adjusted for rs13329952 or rs12922822 for Rapid3 or CKDi25 using the 503 1000G PIIIv5 European individuals (OR and P-value unadjusted for rapid3 or CKDi25 respectively: OR= 1.08; 6.59x10-10; for CKDi25: OR=1.26; P-value=6.68x10-29), (d) 264 reported lead variants plus the 2nd signal index variant in [UMOD-PDILT] from eGFRcrea GWAMA and from UCR-association analyses, eGFRcrea=cross-sectional eGFRcrea17 (n=765,348 transethnic; n=567,460 EUR only for conditional analyses).

**Supplementary Table 4B | Identified loci for rapid kidney function decline and two APOL1 variants reported to be associated with Kidney Disease in individuals of African ancestry.** Shown are the significant lead variants from the GWAS for Rapid3 and CKDi25 and the significant variants from the candidate-based approach from the cross-sectional eGFRcrea GWAMA17 (same as **Supplementary Table 4A**) and two variants reported for Kidney Disease in the *APOL1* geneS2 in individuals of African Ancestry.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | **Rapid3** | | | | | | |  | **CKDi25** | | | | | | | |  | |
| **RSID** | **Ident. analysis** | **Locus name** |  | | **OR** | **SE** | **P** | **N cases** | **N ctrls** | **N stud** |  | | **OR** | **SE** | **P** | **N cases** | **N ctrls** | **N stud** |  | | **locus/ signal no.** | |
| rs13329952 rs12922822 | Rapid3 CKDi25 | [UMOD-PDILT] |  | | 1.091  1.031 | 0.0509  0.1052 | 0.09  0.77 | 2,356  2,356 | 2,375  2,375 | 6  6 |  | | 1.165  1.178 | 0.0941  0.1979 | 0.10  0.41 | 374  374 | 4,183  4,183 | 3  3 |  | | 1.1 | |
| rs77924615 | CKDi25 2nd (c) | [UMOD-PDILT] |  | | 0.922 | 0.1027 | 0.43 | 2,356 | 2,375 | 6 |  | | 1.144 | 0.1898 | 0.48 | 374 | 4,183 | 3 |  | | 1.2 | |
| rs77593734 | CKDi25 | [WDR72] |  | | 1.156 | 0.0582 | 0.01 | 2,356 | 2,375 | 6 |  | | 1.049 | 0.1055 | 0.65 | 374 | 4,183 | 3 |  | | 2 | |
| rs56012466 | CKDi25 | [PRKAG2] |  | | 1.029 | 0.0500 | 0.57 | 2,356 | 2,375 | 6 |  | | 1.199 | 0.0882 | 0.04 | 374 | 4,183 | 3 |  | | 3 | |
| rs141809766 | Rapid3 | [OR2S2] |  | | 1.462 | 0.5352 | 0.48 | 923 | 806 | 2 |  | | 0.698 | 0.9044 | 0.69 | 216 | 2,336 | 2 |  | | 4 | |
| rs34882080  (b) | CKDi25; Rapid3 | [UMOD-PDILT] |  | | 0.925 | 0.0779 | 0.31 | 2,356 | 2,375 | 6 |  | | 0.906 | 0.1402 | 0.48 | 374 | 4,183 | 3 |  | | 1.1 | |
| rs77924615 | CKDi25;Rapid3 | [UMOD-PDILT] |  | | 0.922 | 0.1027 | 0.43 | 2,356 | 2,375 | 6 |  | | 1.144 | 0.1898 | 0.48 | 374 | 4,183 | 3 |  | | 1.2 | |
| rs690428 | CKDi25 | [WDR72] |  | | 0.999 | 0.0464 | 0.99 | 2,356 | 2,375 | 6 |  | | 0.922 | 0.0843 | 0.34 | 374 | 4,183 | 3 |  | | 2 | |
| rs10254101 | CKDi25 | [PRKAG2] |  | | 1.007 | 0.0714 | 0.92 | 2,232 | 2,233 | 5 |  | | 1.047 | 0.1223 | 0.71 | 374 | 4,183 | 3 |  | | 3 | |
| rs80282103 | CKDi25 | [LARP4B] |  | | 0.937 | 0.0622 | 0.30 | 2,356 | 2,375 | 6 |  | | 1.086 | 0.1112 | 0.46 | 374 | 4,183 | 3 |  | | 5 | |
| rs1145077 | Rapid3 | [GATM] |  | | 1.076 | 0.0653 | 0.26 | 2,356 | 2,375 | 6 |  | | 1.002 | 0.1178 | 0.99 | 374 | 4,183 | 3 |  | | 6 | |
| rs73885319 | NA | [APOL1] |  | | 0.980 | 0.0621 | 0.45 | 2,356 | 2,375 | 6 |  | | 1.068 | 0.1156 | 0.19 | 374 | 4,183 | 3 |  | | NA | |
| rs60910145 | NA | [APOL1] |  | | 0.980 | 0.0622 | 0.45 | 2,356 | 2,375 | 6 |  | | 1.067 | 0.1156 | 0.20 | 374 | 4,183 | 3 |  | | NA | |

Column names are identical to those in **Supplementary Table 4A**. Variants rs73885319 and rs60910145 are the reported variants in *APOL1* associated with Kidney Disease in individuals of African ancestryS2. The coded alleles of rs73885319 and rs60910145 are the cross-sectional eGFRcrea lowering allele ‘G’ for both SNPs.

**Supplementary Table 5 | Conditional analysis results in *UMOD-PDILT*, *WDR72*, *PRKAG2*, *LARP4B* and *GATM* loci for Rapid3 and CKDi25 in the All and European meta-analysis.** Shown are the six variants from the candidate approach (**Table 1B**), except the *OR2S2* variant, the OR and P-values when adjusted for the lead variant from the cross-sectional GWAS (using the lead variant from the EUR cross-sectional GWAS).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **GWAS identified**  **lead variant** | **R² with GWAS identified lead variant (a)** |  | **Rapid3** | | | | |  | **CKDi25** | | | | |  |  |
|  |  |  |  | **All** | |  | **EUR** | |  |  | **All** |  | **EUR** | |  |  |
|  | **Ident. analysis** |  |  | **Adjusted for GWAS identified lead variant (b)** | | | | |  | **Adjusted for GWAS identified lead variant (b)** | | | | |  | **Locus/ signal no.** |
| **RSID** | **Locus name** |  | **OR** | **P** |  | **OR** | **P** |  | **OR** | **P** |  | **OR** | **P** |  |
| rs34882080 (c) | Rapid3 CKDi25 | [UMOD-PDILT] | rs12922822 rs13329952 | 0.99 0.91 |  | NA (d) NA (d) | NA (d) NA (d) |  | NA (d) NA (d) | NA (d) NA (d) |  | NA (d) NA (d) | NA (d) NA (d) |  | NA (d) NA (d) | NA (d) NA (d) |  | 1.1 |
| rs77924615 | CKDi25 | [UMOD-PDILT] | same | na |  | na | na |  | na | na |  | na | na |  | na | na |  | 1.2 |
| rs690428 | CKDi25 | [WDR72] | rs77593734 | 0.42 |  | 1.00 | 0.99 |  | 1.01 | 0.62 |  | 1.01 | 0.65 |  | 1.01 | 0.40 |  | 2 |
| rs10254101 | CKDi25 | [PRKAG2] | rs56012466 | 0.84 |  | 1.00 | 0.98 |  | 1.00 | 0.98 |  | 1.01 | 0.66 |  | 1.01 | 0.59 |  | 3 |
| rs80282103 | CKDi25 | [LARP4B] | same | na |  | na | na |  | na | na |  | na | na |  | na | na |  | 5 |
| rs1145077 | Rapid3 | [GATM] | rs1145089 | 1.00 |  | NA (d) | NA (d) |  | NA (d) | NA (d) |  | NA (d) | NA (d) |  | NA (d) | NA (d) |  | 6 |

**Ident. analysis**=Analysis where variant was significantly associated, **GWAS identified lead variant**=Lead variant from Rapid3 or CKDi25, respectively, **R2 with GWAS identified lead variant**=Correlation R2 with the lead variant from Rapid3 or CKDi25, respectively, **Locus/signal no.**=Locus number and signal number. (a) Pairwise R² from LD LinkS1 in all European reference individuals (n=503), (b) The GCTA-analyses use the 503 1000G Phase 3 version 5 European individuals, (c) Reported lead variant of the 2nd signal in UMOD-PDILT18, (d) too highly correlated, missing in GCTA.

**Supplementary Table 6A | Credible set variants and their predicted genetic function.** Shown are all 99% credible set variants, the respective Posterior Probability of driving the association signal, in which gene the variant resides, the predicted function per variant derived with VEP49 per variant. The credible sets were derived from the respective identifying traits from the genome-wide approach, i.e. (i) for the CDKi25-association for the loci [WDR72] and [PRKAG2] and (ii) for the Rapid3-association for the locus [OR2S2] (iii) for both Rapid3 and CKDi25 for [UMOD-PDILT]. Marked in blue are functional variants within a gene as in **Supplementary Table 8**.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus/ signal No.** | **Locus name** | **RSID** | **Chr** | **Position** | **Post. Prob. Rapid3** | **Post. Prob**  **CKDi25** | **Identifying analysis** | **In credible set cross-sectional** | **In gene: no/ gene name** | **Function (VEP)** |
| 1.1 | [UMOD-PDILT] | rs36060036 | 16 | 20,361,950 | 0.70 | 0.39 | CKDi25, Rapid3 | no | *UMOD* | intron\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs28362063 | 16 | 20,365,012 | 0.05 | 0.08 | CKDi25, Rapid3 | yes | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs13334589 | 16 | 20,366,459 | 0.04 | 0.09 | CKDi25, Rapid3 | yes | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs12922822 | 16 | 20,367,645 | 0.04 | 0.23 | CKDi25, Rapid3 | yes | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs9933330 | 16 | 20,366,810 | 0.04 | 0.11 | CKDi25, Rapid3 | yes | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs13329952 | 16 | 20,366,507 | 0.03 | NA | Rapid3 | yes | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs12917707 | 16 | 20,367,690 | 0.03 | 0.03 | CKDi25, Rapid3 | no | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs13333226 | 16 | 20,365,654 | 0.02 | NA | Rapid3 | no | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs34882080 | 16 | 20,361,441 | NA | 0.02 | CKDi25 | yes | *UMOD* | intron\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs35650857 | 16 | 20,361,491 | NA | 0.02 | CKDi25 | yes | *UMOD* | intron\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs4997081 | 16 | 20,365,234 | 0.01 | NA | Rapid3 | yes | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs4293393 | 16 | 20,364,588 | 0.01 | NA | Rapid3 | no | no | upstream\_gene\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs28544423 | 16 | 20,359,633 | 0.01 | 0.01 | CKDi25, Rapid3 | yes | *UMOD* | synonymous\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs35650857 | 16 | 20,361,491 | 0.01 | NA | Rapid3 | yes | *UMOD* | intron\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs34882080 | 16 | 20,361,441 | <0.01 | NA | Rapid3 | yes | *UMOD* | intron\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs9928003 | 16 | 20,358,248 | <0.01 | 0.01 | CKDi25, Rapid3 | yes | *UMOD* | intron\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs12934320 | 16 | 20,357,255 | NA | <0.01 | CKDi25 | yes | *UMOD* | intron\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs34356953 | 16 | 20,356,326 | NA | <0.01 | CKDi25 | yes | *UMOD* | intron\_variant, UMOD |
| 1.1 | [UMOD-PDILT] | rs60136849 | 16 | 20,353,815 | NA | <0.01 | CKDi25 | yes | *UMOD* | intron\_variant, non\_coding\_ transcript\_exon\_variant, UMOD |
| 1.2 | [UMOD-PDILT] | rs77924615 | 16 | 20,392,332 | NA | 0.9979 | CKDi25 | yes | *PDILT* | intron\_variant, PDILT |
| 2 | [WDR72] | rs77593734 | 15 | 54,002,606 | NA | 0.50 | CKDi25 | no | *WDR72* | intron\_variant, WDR72 |
| 2 | [WDR72] | rs11853157 | 15 | 54,006,275 | NA | 0.13 | CKDi25 | no | *WDR72* | intron\_variant, WDR72 |
| 2 | [WDR72] | rs1105903 | 15 | 53,919,558 | NA | 0.02 | CKDi25 | no | *WDR72* | intron\_variant, WDR72 |
| 2 | [WDR72] | rs75183529 | 15 | 53,921,457 | NA | 0.02 | CKDi25 | no | *WDR72* | intron\_variant, WDR72 |

… to be continued

**Supplementary Table 6A: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus/ signal No.** | **Locus name** | | | **RSID** | | **Chr** | | **Position** | | **Post. Prob. Rapid3** | | **Post. Prob**  **CKDi25** | | **Identifying analysis** | | **In credible set cross-sectional** | | **In gene: no/ gene name** | | **Function (VEP)** | |
| 2 | | [WDR72] | rs58901710 | | 15 | | 53,918,873 | | NA | | 0.02 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs11070995 | | 15 | | 53,923,458 | | NA | | 0.02 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs4536407 | | 15 | | 53,920,957 | | NA | | 0.02 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs1906411 | | 15 | | 53,927,803 | | NA | | 0.02 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs12442975 | | 15 | | 53,926,520 | | NA | | 0.02 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs10518731 | | 15 | | 53,936,418 | | NA | | 0.02 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs3911729 | | 15 | | 53,958,400 | | NA | | 0.02 | | CKDi25 | | no | | *WDR72* | | intron\_variant, regulatory\_region\_variant, WDR72 | |
| 2 | | [WDR72] | rs12442962 | | 15 | | 53,923,225 | | NA | | 0.02 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs4776164 | | 15 | | 53,926,368 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs17730323 | | 15 | | 53,927,089 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs10518732 | | 15 | | 53,939,042 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs3848137 | | 15 | | 53,959,375 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs17730281 | | 15 | | 53,907,948 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | WDR72, missense L819F | |
| 2 | | [WDR72] | rs62007961 | | 15 | | 53,965,346 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs732975 | | 15 | | 53,950,390 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs11070994 | | 15 | | 53,923,382 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs7166545 | | 15 | | 53,925,239 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs62005941 | | 15 | | 53,915,766 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs17730436 | | 15 | | 53,942,928 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs1031755 | | 15 | | 53,951,435 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, regulatory\_region\_variant, WDR72 | |
| 2 | | [WDR72] | rs1031756 | | 15 | | 53,951,548 | | NA | | 0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, regulatory\_region\_variant, WDR72 | |
| 2 | | [WDR72] | rs12593967 | | 15 | | 53,936,948 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, regulatory\_region\_variant, WDR72 | |
| 2 | | [WDR72] | rs4776168 | | 15 | | 53,936,907 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, regulatory\_region\_variant, WDR72 | |
| 2 | | [WDR72] | rs1906412 | | 15 | | 53,931,103 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs4776169 | | 15 | | 53,939,427 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs62005954 | | 15 | | 53,937,942 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs62005955 | | 15 | | 53,938,118 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs1906413 | | 15 | | 53,941,106 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |
| 2 | | [WDR72] | rs80025274 | | 15 | | 53,947,167 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | intron\_variant, WDR72 | |

… to be continued

**Supplementary Table 6A: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Locus/ signal No.** | **Locus name** | | | **RSID** | | **Chr** | | **Position** | | **Post. Prob. Rapid3** | | **Post. Prob**  **CKDi25** | | **Identifying analysis** | | **In credible set cross-sectional** | | **In gene: no/ gene name** | **Function (VEP)** | | |
| 2 | | [WDR72] | | rs7171932 | 15 | | 53,925,521 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | | intron\_variant, WDR72 |
| 2 | | [WDR72] | rs2675328 | | 15 | | 53,936,627 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | | intron\_variant, WDR72 |
| 2 | | [WDR72] | rs542780 | | 15 | | 53,939,214 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | | intron\_variant, WDR72 |
| 2 | | [WDR72] | rs10518733 | | 15 | | 53,940,307 | | NA | | <0.01 | | CKDi25 | | no | | *WDR72* | | | intron\_variant, WDR72 |
| 3 | | [PRKAG2] | rs56012466 | | 7 | | 151,406,788 | | NA | | 0.18 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs6464165 | | 7 | | 151,413,124 | | NA | | 0.11 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs73158188 | | 7 | | 151,415,233 | | NA | | 0.10 | | CKDi25 | | yes | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs10253736 | | 7 | | 151,415,256 | | NA | | 0.09 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs10224210 | | 7 | | 151,413,194 | | NA | | 0.08 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant, regulatory\_region\_variant |
| 3 | | [PRKAG2] | rs10254101 | | 7 | | 151,415,536 | | NA | | 0.08 | | CKDi25 | | yes | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs55779150 | | 7 | | 151,406,449 | | NA | | 0.07 | | CKDi25 | | yes | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs55791829 | | 7 | | 151,407,429 | | NA | | 0.07 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs10480300 | | 7 | | 151,406,005 | | NA | | 0.06 | | CKDi25 | | yes | | PRKAG2 | | | intron\_variant, regulatory\_region\_variant |
| 3 | | [PRKAG2] | rs10224002 | | 7 | | 151,415,041 | | NA | | 0.06 | | CKDi25 | | yes | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs10480299 | | 7 | | 151,405,818 | | NA | | 0.03 | | CKDi25 | | yes | | PRKAG2 | | | intron\_variant, regulatory\_region\_variant |
| 3 | | [PRKAG2] | rs73728279 | | 7 | | 151,411,494 | | NA | | 0.03 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs10265221 | | 7 | | 151,414,329 | | NA | | 0.03 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs7805747 | | 7 | | 151,407,801 | | NA | | 0.01 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs10263707 | | 7 | | 151,403,505 | | NA | | 0.01 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 3 | | [PRKAG2] | rs57807319 | | 7 | | 151,403,260 | | NA | | 0.01 | | CKDi25 | | no | | PRKAG2 | | | intron\_variant,NMD\_transcript\_variant, PRKAG2 |
| 4 | | [OR2S2] | rs141809766 | | 9 | | 35,937,931 | | 0.77 | | NA | | Rapid3 | | NA | | no | | | downstream\_gene\_variant, RP11-327L3.3 |
| 4 | | [OR2S2] | rs56289282 | | 9 | | 35,926,028 | | 0.23 | | NA | | Rapid3 | | NA | | no | | | upstream\_gene\_variant, RP11-327L3.3 |

**Locus/ signal No.**=Locus number and signal number, **Post. Prob. Rapid3/ CKDi25**=Posterior probability of a variant in the credible set from the identifying analysis Rapid3 or CKDi25. NA if the variant was not in the credible variant set or if it was not the identifying analysis, **In gene: no/ gene name**=Variant position is between start and end of gene (see **Supplementary Table 8**), **Function (VEP)**=The predicted function was obtained from the Ensembl Variant Effect Predictor49.

**Supplementary Table 6B | The 99% credible set variants with significant eQTL results.** Shown are the 99% credible set variants across the five genome-wide significant signals with significant eQTL results (FDR<0.05) in NephQTL50 (glomerulus or tubulointerstitium) or GTEx51 (kidney or any other tissue) for gene expression in the locus region. Marked in orange are significant eQTLs of genes in a locus region as in **Supplementary Table 8**.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | **NephQTL** | |  | **GTEx** | | | |
| **Locus**  **No.** | **Locus name** | **RSID** | **Gene** | **Post. Prob. Rapid3** | **Post. Prob. CKDi25** | **Significant eQTL (FDR<0.05)** | **Tissue with significant eQTL** |  | **Significant eQTL in kidney tissue (FDR<0.05)** | **Significant eQTL in other tissue (FDR<0.05)** | **Tissue with signficant eQTL** | |
| 1 | [UMOD-PDILT] | rs77924615 | *PDILT* | NA | 0.9979 | no | - | no | | yes | | Prostate & testis |
| 2 | [WDR72] | rs77593734 | *WDR72* | NA | 0.50 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs11853157 | *WDR72* | NA | 0.13 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs1105903 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs75183529 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs58901710 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs11070995 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs4536407 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs1906411 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs12442975 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs10518731 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs12442962 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs4776164 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs17730323 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs10518732 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs17730281 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs732975 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs11070994 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs7166545 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs62005941 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs17730436 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs1031755 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs1031756 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs12593967 | *WDR72* | NA | 0.00 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs3911729 | *WDR72* | NA | 0.02 | no | - | no | | yes | | multiple |

… to be continued

**Supplementary Table 6B: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | **NephQTL** | |  | **GTEx** | | | |
| **Locus**  **No.** | **Locus name** | **RSID** | **Gene** | **Post. Prob. Rapid3** | **Post. Prob. CKDi25** | **Significant eQTL (FDR<0.05)** | **Tissue with significant eQTL** |  | **Significant eQTL in kidney tissue (FDR<0.05)** | **Significant eQTL in other tissue (FDR<0.05)** | **Tissue with signficant eQTL** | |
| 2 | [WDR72] | rs3848137 | *WDR72* | NA | 0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs4776168 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs1906412 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs4776169 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs62005954 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs62005955 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs1906413 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs80025274 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs7171932 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs2675328 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs542780 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 2 | [WDR72] | rs10518733 | *WDR72* | NA | <0.01 | no | - | no | | yes | | multiple |
| 3 | [PRKAG2] | rs73728279 | *GALNTL5* | NA | 0.03 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs10224210 | *GALNTL5* | NA | 0.08 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs56012466 | *GALNTL5* | NA | 0.18 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs6464165 | *GALNTL5* | NA | 0.11 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs73158188 | *GALNTL5* | NA | 0.10 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs10253736 | *GALNTL5* | NA | 0.09 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs55779150 | *GALNTL5* | NA | 0.07 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs10480299 | *GALNTL5* | NA | 0.03 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs10224002 | *GALNTL5* | NA | 0.06 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs55791829 | *GALNTL5* | NA | 0.07 | yes | Tubulointerstitium | no | | no | | NA |
| 3 | [PRKAG2] | rs7805747 | *GALNTL5* | NA | 0.01 | yes | Tubulointerstitium | no | | no | | NA |
| 4 | [OR2S2] | rs141809766 | *OR2S1P* | 0.77 | NA | NA | NA | no | | yes | | Lung |
| 4 | [OR2S2] | rs56289282 | *OR2S1P* | 0.23 | NA | NA | NA | no | | yes | | Lung |

**Locus No.**=Locus number, **NA**=The variants in [OR2S2] are not in the NephQTL database, **Post. Prob. Rapid3/ CKDi25**=Posterior probability of a variant in the credible set from the identifying analysis Rapid3 or CKDi25. NA if the variant was not in the credible variant set or if it was not the identifying analysis.

**Supplementary Table 7A | Genes in locus regions with a kidney-relevant phenotype in mouse.** Shown are all genes that overlap any of the four locus regions with a phenotype relevant for kidney in the Mouse Genomics Informatics database (MGI52). Each reported phenotype is marked in green as in **Supplementary** **Table 8**.

|  |  |  |  |
| --- | --- | --- | --- |
| **Locus name** | **Locus no.** | **Gene** | **Mouse Phenotype** |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal kidney morphology |
| [UMOD-PDILT] | 1 | *UMOD* | isosthenuria |
| [UMOD-PDILT] | 1 | *UMOD* | renal interstitial fibrosis |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal proximal convoluted tubule morphology |
| [UMOD-PDILT] | 1 | *UMOD* | isosthenuria |
| [UMOD-PDILT] | 1 | *UMOD* | hydronephrosis |
| [UMOD-PDILT] | 1 | *UMOD* | renal fibrosis |
| [UMOD-PDILT] | 1 | *UMOD* | dilated renal glomerular capsule |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal papillary duct morphology |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal kidney papilla morphology |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal renal tubule morphology |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal juxtaglomerular apparatus morphology |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal papillary duct morphology |
| [UMOD-PDILT] | 1 | *UMOD* | nephrocalcinosis |
| [UMOD-PDILT] | 1 | *UMOD* | kidney failure |
| [UMOD-PDILT] | 1 | *UMOD* | renal interstitial fibrosis |
| [UMOD-PDILT] | 1 | *UMOD* | nephrocalcinosis |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal proximal convoluted tubule morphology |
| [UMOD-PDILT] | 1 | *UMOD* | increased renal glomerular filtration rate |
| [UMOD-PDILT] | 1 | *UMOD* | decreased kidney weight |
| [UMOD-PDILT] | 1 | *UMOD* | dilated kidney collecting duct |
| [UMOD-PDILT] | 1 | *UMOD* | decreased renal glomerular filtration rate |
| [UMOD-PDILT] | 1 | *UMOD* | glomerulosclerosis |
| [UMOD-PDILT] | 1 | *UMOD* | renal glomerulus cysts |
| [UMOD-PDILT] | 1 | *UMOD* | hydronephrosis |
| [UMOD-PDILT] | 1 | *UMOD* | kidney failure |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal renal tubule morphology |
| [UMOD-PDILT] | 1 | *UMOD* | renal fibrosis |
| [UMOD-PDILT] | 1 | *UMOD* | dilated renal glomerular capsule |
| [UMOD-PDILT] | 1 | *UMOD* | decreased renal glomerular filtration rate |
| [UMOD-PDILT] | 1 | *UMOD* | increased renal glomerular filtration rate |
| [UMOD-PDILT] | 1 | *UMOD* | renal tubular necrosis |
| [UMOD-PDILT] | 1 | *UMOD* | decreased creatinine clearance |
| [UMOD-PDILT] | 1 | *UMOD* | renal glomerulus cysts |
| [UMOD-PDILT] | 1 | *UMOD* | increased creatinine clearance |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal loop of Henle ascending limb thick segment morphology |
| [UMOD-PDILT] | 1 | *UMOD* | kidney inflammation |
| [UMOD-PDILT] | 1 | *UMOD* | kidney inflammation |
| [UMOD-PDILT] | 1 | *UMOD* | increased kidney apoptosis |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal loop of Henle ascending limb thick segment morphology |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal kidney morphology |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal kidney papilla morphology |
| [UMOD-PDILT] | 1 | *UMOD* | abnormal juxtaglomerular apparatus morphology |
| [UMOD-PDILT] | 1 | *UMOD* | renal tubular necrosis |
| [UMOD-PDILT] | 1 | *UMOD* | glomerulosclerosis |

… to be continued

**Supplementary Table 7A: continued**

|  |  |  |  |
| --- | --- | --- | --- |
| **Locus name** | **Locus no.** | **Gene** | **Mouse Phenotype** |
| [UMOD-PDILT] | 1 | *UMOD* | decreased creatinine clearance |
| [UMOD-PDILT] | 1 | *UMOD* | dilated kidney collecting duct |
| [UMOD-PDILT] | 1 | *UMOD* | increased kidney apoptosis |
| [UMOD-PDILT] | 1 | *UMOD* | decreased kidney weight |
| [UMOD-PDILT] | 1 | *UMOD* | increased creatinine clearance |
| [OR2S2] | 4 | *GNE* | expanded mesangial matrix |
| [OR2S2] | 4 | *GNE* | fused podocyte foot processes |
| [OR2S2] | 4 | *GNE* | kidney inflammation |
| [OR2S2] | 4 | *GNE* | dilated renal tubules |
| [OR2S2] | 4 | *GNE* | decreased nephron number |
| [OR2S2] | 4 | *GNE* | abnormal renal glomerulus basement membrane morphology |
| [OR2S2] | 4 | *GNE* | abnormal podocyte slit junction morphology |
| [OR2S2] | 4 | *GNE* | hydronephrosis |
| [OR2S2] | 4 | *GNE* | abnormal renal tubule morphology |
| [OR2S2] | 4 | *GNE* | kidney hemorrhage |
| [OR2S2] | 4 | *GNE* | abnormal renal glomerular capsule morphology |
| [OR2S2] | 4 | *GNE* | glomerulosclerosis |
| [OR2S2] | 4 | *GNE* | cortical renal glomerulopathies |
| [OR2S2] | 4 | *GNE* | podocyte foot process effacement |
| [OR2S2] | 4 | *GNE* | abnormal kidney morphology |
| [OR2S2] | 4 | *GNE* | increased glomerular capsule space |
| [OR2S2] | 4 | *GNE* | abnormal podocyte morphology |
| [OR2S2] | 4 | *GNE* | kidney failure |
| [OR2S2] | 4 | *GNE* | pale kidney |
| [OR2S2] | 4 | *GNE* | renal glomerulus hypertrophy |
| [OR2S2] | 4 | *CD72* | renal glomerular immunoglobulin deposits |
| [OR2S2] | 4 | *CD72* | renal glomerular protein deposits |
| [OR2S2] | 4 | *CD72* | glomerulonephritis |
| [OR2S2] | 4 | *CD72* | abnormal renal glomerulus morphology |
| [OR2S2] | 4 | *CD72* | cortical renal glomerulopathies |

**Supplementary Table 7B | Genes in the six locus regions with a kidney-relevant phenotype in human.** Shown are all genes that overlap any of the four locus regions with a phenotype relevant for kidney in The Online Mendelian Inheritance in Man database (OMIM53). Each reported human phenotype is marked in green as in **Supplementary** **Table 8**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Locus name** | **Locus no.** | **Gene** | **Disease** | **Kidney relevant phenotypes** |
| [UMOD-PDILT] | 1 | *UMOD* | HYPERURICEMIC NEPHROPATHY, FAMILIAL JUVENILE, 1 | Hyperuricemia,Renal biopsy shows chronic interstitial nephritis,Small medullary cysts,Nephropathy,Renal failure,Tubular atrophy,Thickening of the basement membrane |
| [PRKAG2] | 3 | *PRKAG2* | GLYCOGEN STORAGE DISEASE OF HEART, LETHAL CONGENITAL | Renomegaly |

**Supplementary Table 8: Gene PrioritiSation.** For each gene in each of the four identified loci with genome-wide significance (locus region as lead variant ±500kB), these follow-up analysis results are shown: distance to the first and second signal lead variant; number of variants in the 99% credible set in each gene (details in **Supplementary Table 6A)**;predicted function as missense, nonsense-mediated decay (NMD) or altered splicing for each variant in the 99% credible set overlapping the gene’s region (**Supplementary Table 6A**); evidence of eQTL-modulated gene expression in NephQTL or GTEx data (**Supplementary Table 6B**); reported kidney-relevant mouse phenotype (**Supplementary Table 7A**) or human kidney phenotype from monogenic disease (**Supplementary Table 7B**). **Table 4** is a condensed version of this table focusing on genes with relevant findings; a sortable and searchable version of this table where the weights can be customized is provided online (www.genepi-regensburg.de/rapiddecline).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  | **Any credible set variants in gene** | | | **eQTL-modulated expression by any credible set variant** | | | | **Evidenced kidney phenotype** | |
| **Weight (Change weights here to change Gene Priority Score)** | | | | | | | | | | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | |
| **Locus name** | **Locus no.** | **Gene** | **Chromosome** | **Start of gene** | **End of gene** | **Distance of gene to first signal variant (a)** | **Distance of gene to second signal variant (b)** | **#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 | 20,344,372 | 20,364,200 | 0 | -28,132 | 10 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| [UMOD-PDILT] | 1 | *PDILT* | 16 | 20,370,491 | 20,416,033 | 2,846 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| [UMOD-PDILT] | 1 | *GPRC5B* | 16 | 19,870,292 | 19,896,956 | -470,689 | -495,376 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *ACSM5* | 16 | 20,420,855 | 20,452,655 | 53,210 | 28,523 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *ACSM2B* | 16 | 20,548,079 | 20,587,695 | 180,434 | 155,747 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *THUMPD1* | 16 | 20,744,985 | 20,753,286 | 377,340 | 352,653 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *LOC81691=*  *REXO5* | 16 | 20,817,766 | 20,860,990 | 450,121 | 425,434 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *GPR139* | 16 | 20,042,806 | 20,085,100 | -282,545 | -307,232 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *GP2* | 16 | 20,320,895 | 20,338,942 | -28,703 | -53,390 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *ACSM2A* | 16 | 20,462,782 | 20,498,991 | 95,137 | 70,450 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *ACSM1* | 16 | 20,634,558 | 20,709,110 | 266,913 | 242,226 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

…to be continued

**Supplementary Table 8: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  | **Any credible set variants in gene** | | | **eQTL-modulated expression by any credible set variant** | | | | **Evidenced kidney phenotype** | |
| **Weight (Change weights here to change Gene Priority Score)** | | | | | | | | | | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | |
| **Locus name** | **Locus no.** | **Gene** | **Chromosome** | **Start of gene** | **End of gene** | **Distance of gene to first signal variant (a)** | **Distance of gene to second signal variant (b)** | **#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 | *ACSM3* | 16 | 20,775,311 | 20,808,479 | 407,666 | 382,979 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [UMOD-PDILT] | 1 | *ERI2* | 16 | 20,791,514 | 20,817,795 | 423,869 | 399,182 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [WDR72] | 2 | *WDR72* | 15 | 53,805,937 | 54,055,075 | 0 |  | 37 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| [PRKAG2] | 3 | *PRKAG2* | 7 | 151,253,199 | 151,574,316 | 0 |  | 16 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| [PRKAG2] | 3 | *GALNTL5* | 7 | 151,653,463 | 151,717,019 | 246,675 |  | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *ABCF2* | 7 | 150,908,569 | 150,924,460 | -482,328 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *CHPF2* | 7 | 150,929,574 | 150,935,913 | -470,875 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *MIR671* | 7 | 150,935,506 | 150,935,624 | -471,164 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *SMARCD3* | 7 | 150,936,058 | 150,974,231 | -432,557 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *NUB1* | 7 | 151,038,846 | 151,075,547 | -331,241 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *WDR86* | 7 | 151,078,206 | 151,107,791 | -298,997 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *WDR86-AS1* | 7 | 151,106,246 | 151,110,440 | -296,348 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *CRYGN* | 7 | 151,125,917 | 151,137,899 | -268,889 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *MIR3907* | 7 | 151,130,574 | 151,130,725 | -276,063 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *RHEB* | 7 | 151,163,097 | 151,217,010 | -189,778 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *PRKAG2-AS1* | 7 | 151,574,126 | 151,576,308 | 167,338 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [PRKAG2] | 3 | *GALNT11* | 7 | 151,722,758 | 151,819,432 | 315,970 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *FAM166B* | 9 | 35,561,826 | 35,563,896 | -374,035 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *CD72* | 9 | 35,609,975 | 35,618,424 | -319,507 |  | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

…to be continued

**Supplementary Table 8: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  | **Any credible set variants in gene** | | | **eQTL-modulated expression by any credible set variant** | | | | **Evidenced kidney phenotype** | |
| **Weight (Change weights here to change Gene Priority Score)** | | | | | | | | | | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | |
| **Locus name** | **Locus no.** | **Gene** | **Chromosome** | **Start of gene** | **End of gene** | **Distance of gene to first signal variant (a)** | **Distance of gene to second signal variant (b)** | **#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)** |
| [OR2S2] | 4 | *OR2S1P* | 9 | 36,013,182 | 36,014,128 | 75,251 |  | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| [OR2S2] | 4 | *GNE* | 9 | 36,214,437 | 36,277,053 | 276,506 |  | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| [OR2S2] | 4 | *RUSC2* | 9 | 35,489,829 | 35,561,895 | -376,036 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *TESK1* | 9 | 35,605,280 | 35,610,038 | -327,893 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *MIR4667* | 9 | 35,608,090 | 35,608,156 | -329,775 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *LOC101926948* | 9 | 35,646,266 | 35,647,473 | -290,458 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *SIT1* | 9 | 35,649,294 | 35,650,947 | -286,984 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *RMRP* | 9 | 35,657,747 | 35,658,015 | -279,916 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *CCDC107* | 9 | 35,658,286 | 35,661,500 | -276,431 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *ARHGEF39* | 9 | 35,659,340 | 35,665,278 | -272,653 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *CA9* | 9 | 35,673,914 | 35,681,156 | -256,775 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *TPM2* | 9 | 35,681,989 | 35,690,053 | -247,878 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *TLN1* | 9 | 35,697,333 | 35,732,392 | -205,539 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *MIR6852* | 9 | 35,710,672 | 35,710,738 | -227,193 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *CREB3* | 9 | 35,732,316 | 35,737,005 | -200,926 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *MIR6853* | 9 | 35,732,918 | 35,732,992 | -204,939 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *GBA2* | 9 | 35,736,858 | 35,749,225 | -188,706 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *RGP1* | 9 | 35,749,276 | 35,753,264 | -184,667 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

…to be continued

**Supplementary Table 8: continued**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  | **Any credible set variants in gene** | | | **eQTL-modulated expression by any credible set variant** | | | | **Evidenced kidney phenotype** | |
| **Weight (Change weights here to change Gene Priority Score)** | | | | | | | | | | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | |
| **Locus name** | **Locus no.** | **Gene** | **Chromosome** | **Start of gene** | **End of gene** | **Distance of gene to first signal variant (a)** | **Distance of gene to second signal variant (b)** | **#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)** |
| [OR2S2] | 4 | *MSMP* | 9 | 35,752,986 | 35,754,274 | -183,657 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *NPR2* | 9 | 35,792,405 | 35,809,728 | -128,203 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *SPAG8* | 9 | 35,807,781 | 35,812,259 | -125,672 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *HINT2* | 9 | 35,812,956 | 35,815,042 | -122,889 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *FAM221B* | 9 | 35,817,013 | 35,828,744 | -109,187 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *TMEM8B* | 9 | 35,829,221 | 35,854,844 | -83,087 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *LINC00950* | 9 | 35,860,270 | 35,865,515 | -72,416 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *OR13J1* | 9 | 35,869,459 | 35,870,398 | -67,533 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *HRCT1* | 9 | 35,906,188 | 35,907,138 | -30,793 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *LINC00961*  *=SPAAR* | 9 | 35,909,479 | 35,911,617 | -26,314 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *OR2S2* | 9 | 35,957,104 | 35,958,151 | 19,173 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *RECK* | 9 | 36,036,909 | 36,124,452 | 98,978 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *GLIPR2* | 9 | 36,136,532 | 36,163,910 | 198,601 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *CCIN* | 9 | 36,169,388 | 36,171,331 | 231,457 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *CLTA* | 9 | 36,190,852 | 36,212,059 | 252,921 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| [OR2S2] | 4 | *RNF38* | 9 | 36,336,396 | 36,401,195 | 398,465 |  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

(a) Distance to the variant with lowest P in the region of the 1st signal from Rapid3 ([OR2S2]), CKDi25 ([UMOD-PDILT], [WDR72] and [PRKAG2]).

(b) Distance to the variant with lowest P in the region of the 2nd signal from CKDi25 in locus [UMOD-PDILT]

**Supplementary Table 9: Kidney function related biology in the OR2S2 locus**. For each of the 36 genes, the alternative gene names are stated and the findings from the literature search are summarized.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gene Name(s)a,b** | **Approved Gene Symbolc [HGNC]** | **GeneID [NCBI]** | **Approved gene name (HGNC) (WAS: DESCRIPTION)** | **Current knowledge about this gene [mouse models, monogenic renal disease, etc.] (PMID)** |
| *RUSC2, Iporin, MRT61* | *RUSC2* | 9853 | RUN and SH3 domain containing 2 | None**d** |
| *FAM166B* | *FAM166B* | 730112 | family with sequence similarity 166 member B | None |
| *TESK1* | *TESK1* | 7016 | testis associated actin remodelling kinase 1 | None |
| *MIR4667, mir-4667* | *MIR4667* | 100616214 | microRNA 4667 | None |
| *CD72, CD72b, LYB2* | *CD72* | 971 | CD72 molecule | A 13 nucleotides repeat in intron 8 was associated with nephritis in Japanese in 160 SLE cases and 277 controls (15459183). Vadasz et al (26883681) report that CD72 is elevated in SLE patients with renal involvement and might act as a potential biomarker for renal involvement in SLE in n=159 SLE cases, 40 rheumatoid arthritis patients and 100 healthy controls. |
| *LOC101926948* | *LOC101926948* | 101926948 | uncharacterized LOC101926948 | None |
| *SIT1, SIT, SIT-R* | *SIT1* | 27240 | signaling threshold regulating transmembrane adaptor 1 | None |
| *RMRP, CHH, NME1, RMRPR, RRP2* | *RMRP* | 6023 | RNA component of mitochondrial RNA processing endoribonuclease | None |
| *CCDC107, PSEC0222* | *CCDC107* | 203260 | coiled-coil domain containing 107 | None |
| *ARHGEF39, C9orf100* | *ARHGEF39* | 84904 | Rho guanine nucleotide exchange factor 39 | None |
| *CA9, CAIX, MN* | *CA9* | 768 | carbonic anhydrase 9 | Widely reported involvement in renal carcinoma. CA9 is not expressed in healthy kidney but activated in clear cell renal cell carcinomas and has 100% diagnostic specificity in solid renal tumors (20709527). |
| *TPM2, AMCD1, DA1, DA2B, DA2B4, HEL-S-273, NEM4, TMSB* | *TPM2* | 7169 | tropomyosin 2 | None |
| *TLN1, ILWEQ, TLN, talin-1* | *TLN1* | 7094 | talin 1 | None |
| *MIR6852, hsa-mir-6852* | *MIR6852* | 102465513 | microRNA 6852 | None |
| *CREB3, LUMAN, LZIP, sLZIP* | *CREB3* | 10488 | cAMP responsive element binding protein 3 | None |

… to be continued

**Supplementary Table 9: continued**

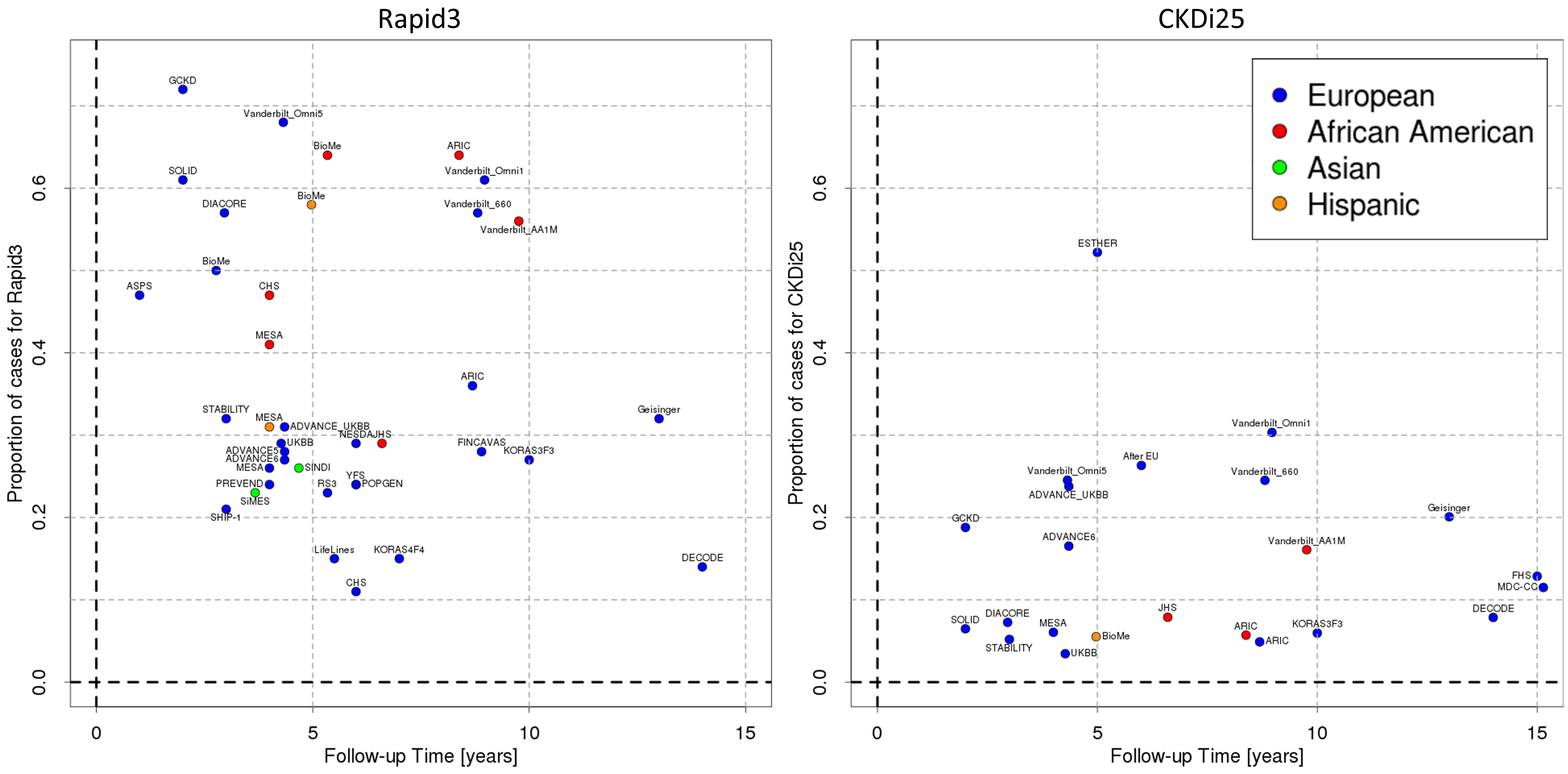
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gene Name(s)1,2** | **Approved Gene Symbol3 [HGNC]** | **GeneID [NCBI]** | **Approved gene name (HGNC) (WAS: DESCRIPTION)** | **Current knowledge about this gene [mouse models, monogenic renal disease, etc.] (PMID)** |
| *MIR6853, hsa-mir-6853* | *MIR6853* | 102466201 | microRNA 6853 | None |
| *GBA2, AD035, NLGase, SPG46* | *GBA2* | 57704 | glucosylceramidase beta 2 | None |
| *RGP1, KIAA0258* | *RGP1* | 9827 | RGP1 homolog, RAB6A GEF complex partner 1 | None |
| *MSMP, PSMP* | *MSMP* | 692094 | microseminoprotein, prostate associated | None |
| *NPR2, AMDM, ANPRB, ANPb, ECDM, GC-B, GCB, GUC2B, GUCY2B, NPRB, NPRBi, SNSK* | *NPR2* | 4882 | natriuretic peptide receptor 2 | None |
| *SPAG8, BS-84, CILD28, CT142, HSD-1, SMP1, SPAG3, hSMP-1* | *SPAG8* | 26206 | sperm associated antigen 8 | None |
| *HINT2, HIT-17* | *HINT2* | 84681 | histidine triad nucleotide binding protein 2 | None |
| *FAM221B, C9orf128* | *FAM221B* | 392307 | family with sequence similarity 221 member B | None |
| *TMEM8B, C9orf127, FP588, LINC00950, NAG-5, NAG5, NGX6, NGX6a* | *TMEM8B* | 51754 | transmembrane protein 8B | None |
| *TMEM8B, LINC00950, NAG5; NGX6; FP588; NAG-5; NGX6a; C9orf127; LINC00950* | *TMEM8B* | 51754 | transmembrane protein 8B | None |
| *OR13J1, OR9-2* | *OR13J1* | 392309 | olfactory receptor family 13 subfamily J member 1 | None |
| *HRCT1, LGLL338, PRO537, UNQ338* | *HRCT1* | 646962 | histidine rich carboxyl terminus 1 | None |
| *LINC00961, SPAAR, SPAR* | *SPAAR* | 158376 | small regulatory polypeptide of amino acid response | None |
| *PGAM1P2* | *PGAM1P2* | 392310 | phosphoglycerate mutase 1 pseudogene 2 | None |
| *OR2S2, OR37A, OST715* | *OR2S2* | 56656 | olfactory receptor family 2 subfamily S member 2 (gene/pseudogene) | None |

… to be continued

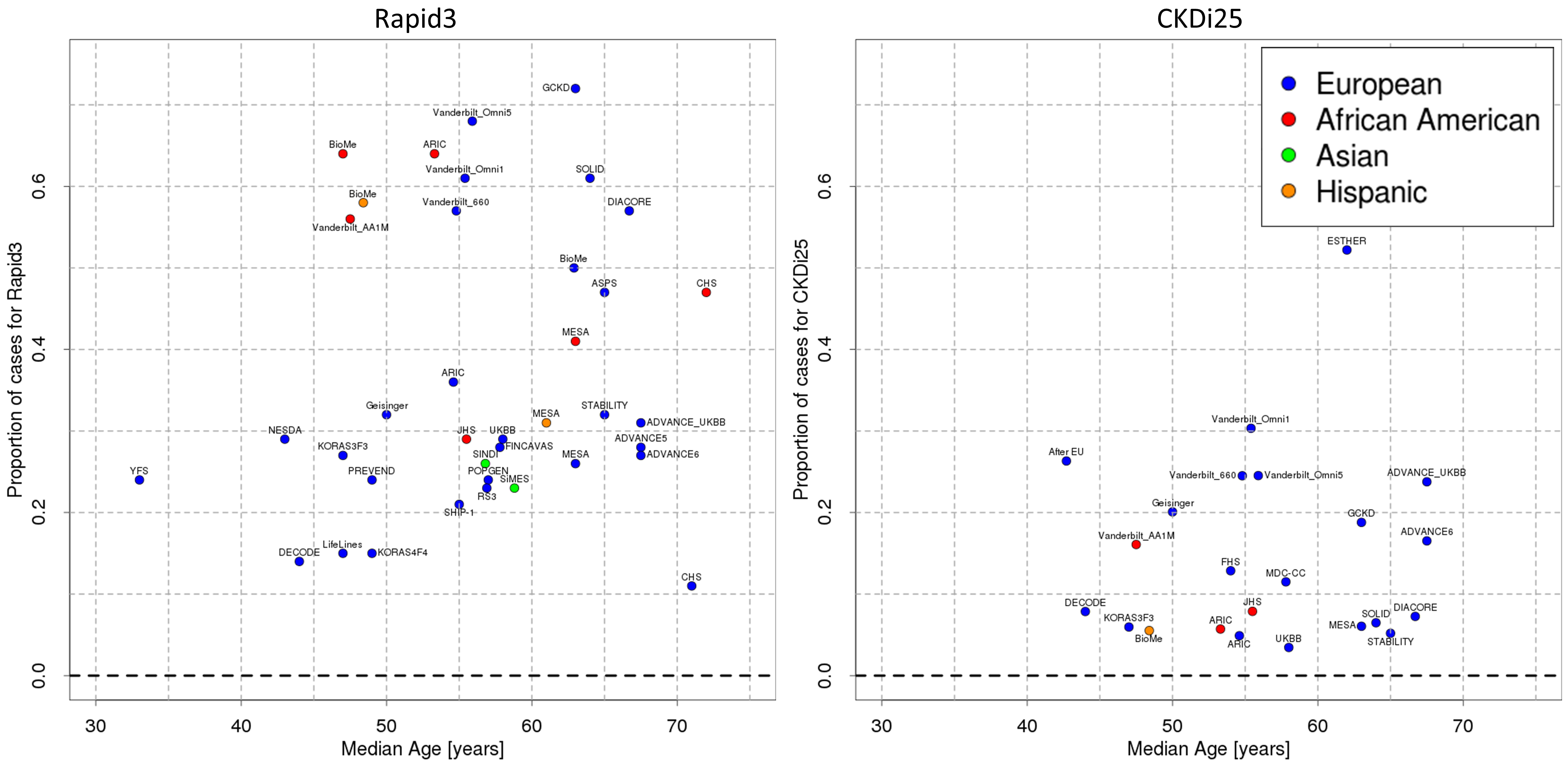
**Supplementary Table 9: continued**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gene Name(s)1,2** | **Approved Gene Symbol3 [HGNC]** | **GeneID [NCBI]** | **Approved gene name (HGNC) (WAS: DESCRIPTION)** | **Current knowledge about this gene [mouse models, monogenic renal disease, etc.] (PMID)** |
| *OR2S1P* | *OR2S1P* | 392313 | olfactory receptor family 2 subfamily S member 1 pseudogene | None |
| *RECK, ST15* | *RECK* | 8434 | reversion inducing cysteine rich protein with kazal motifs | None |
| *GLIPR2, C9orf19, GAPR-1, GAPR1* | *GLIPR2* | 152007 | GLI pathogenesis related 2 | Basal expression in kidney, but expression is strongly increased in fibrotic kidney. It has been proposed to induce epithelial to mesenchymal transition (EMT) in a renal epithelial cells (17055234). Overexpression promotes epithelial-to-mesenchymal transition (EMT) of tubular epithelial cells via the ERK1/2 signaling pathway. This is a critical event in development of renal interstitial fibrosis (23516513). |
| *CCIN, BTBD20, KBTBD14* | *CCIN* | 881 | calicin | None |
| *CLTA, LCA* | *CLTA* | 1211 | clathrin light chain A | None |
| *GNE, DMRV, GLCNE, IBM2, NM, Uae1* | *GNE* | 10020 | glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase | Mice carrying the M712T mutation have been proposed as a model for human glomerulopathy (22322304). Homozygous mice die by postnatal day 3 due to glomerular hematuria, proteinuria, and podocytopathy, with segmental splitting of the glomerular basement membrane, effacement of podocyte foot processes, and reduced sialylation of podocalyxin (17549255). In humans GNE mutations have been linked both to Nonaka Distal Myopathy (MIM 605820, autosomal recessive) and Sialuria (MIM 269921, autosomal dominant). |
| *HMGB3P24* | *HMGB3P24* | 646993 | high mobility group box 3 pseudogene 24 | None |
| *RNF38* | *RNF38* | 152006 | ring finger protein 38 | None |
| a Genes were obtained from https://hgdownload.soe.ucsc.edu/goldenPath/hg19/database/ncbiRefSeqCurated.txt.gz | | | | |
| b Gene Names were obtained from https://www.ncbi.nlm.nih.gov/gene; PGAM1P2 is from UCSC Genome browser | | | | |
| c Approved HGNC gene symbols obtained from https://biomart.genenames.org/ based on the GeneID | | | | |
| d None means throughout the table that no data are available about the gene, respectively no involvement in renal disease identified. | | | | |

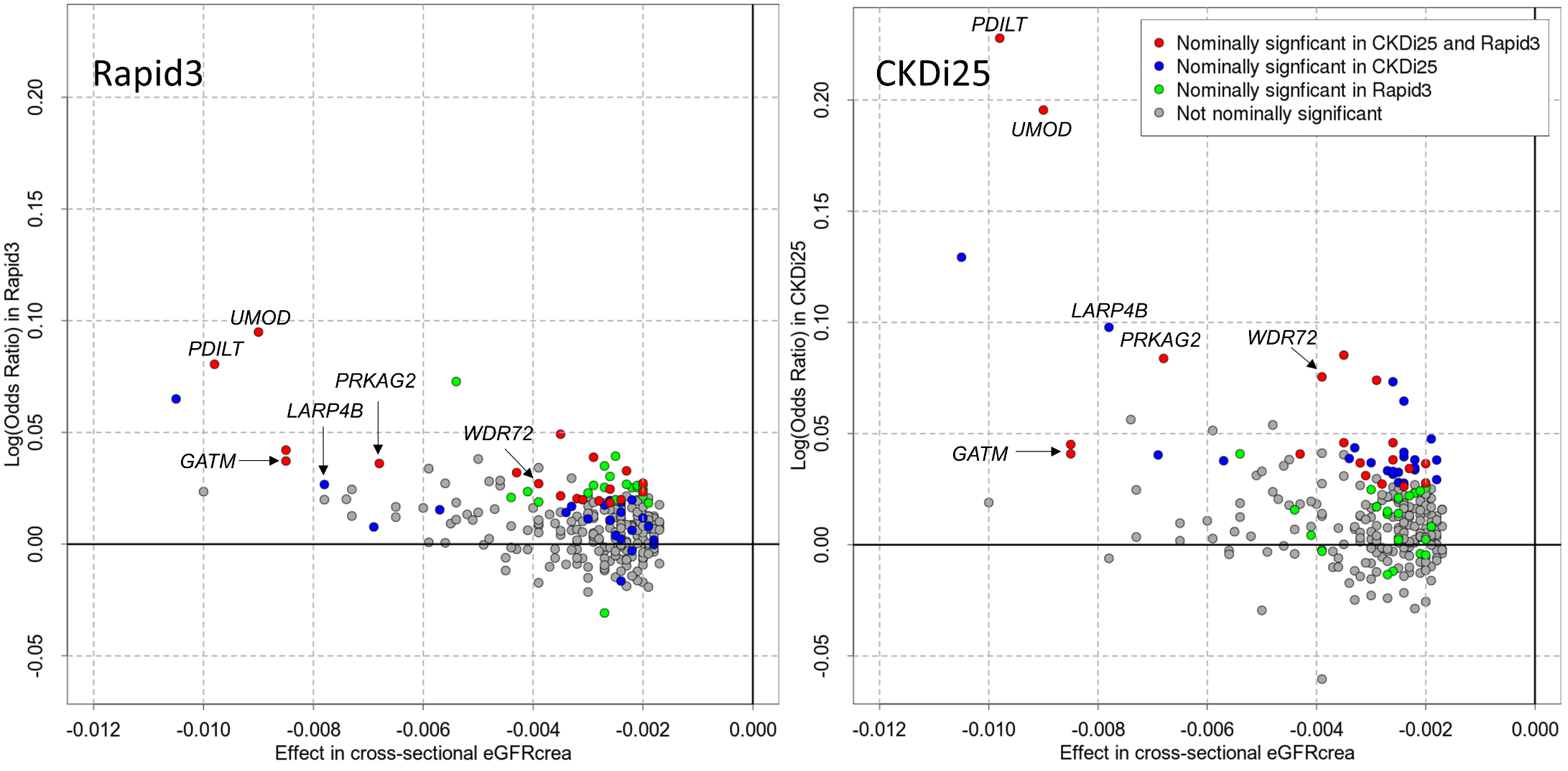
**Supplementary Figure 1A | Study-specific information on proportion of cases versus follow-up time for Rapid3 and CKDi25.** Shown are the study-specific proportions of cases versus median follow-up time for the case-control definitions of Rapid3 (34,874 cases; 107,090 controls) and CKDi25 (19,901 cases; 175,244 controls). Studies are color-coded by the pre-dominant ancestry of study participants. There was no association between proportion of cases and follow-up time (linear regression association P-value=0.31 and 0.88 for Rapid3 and CKDi25, respectively).



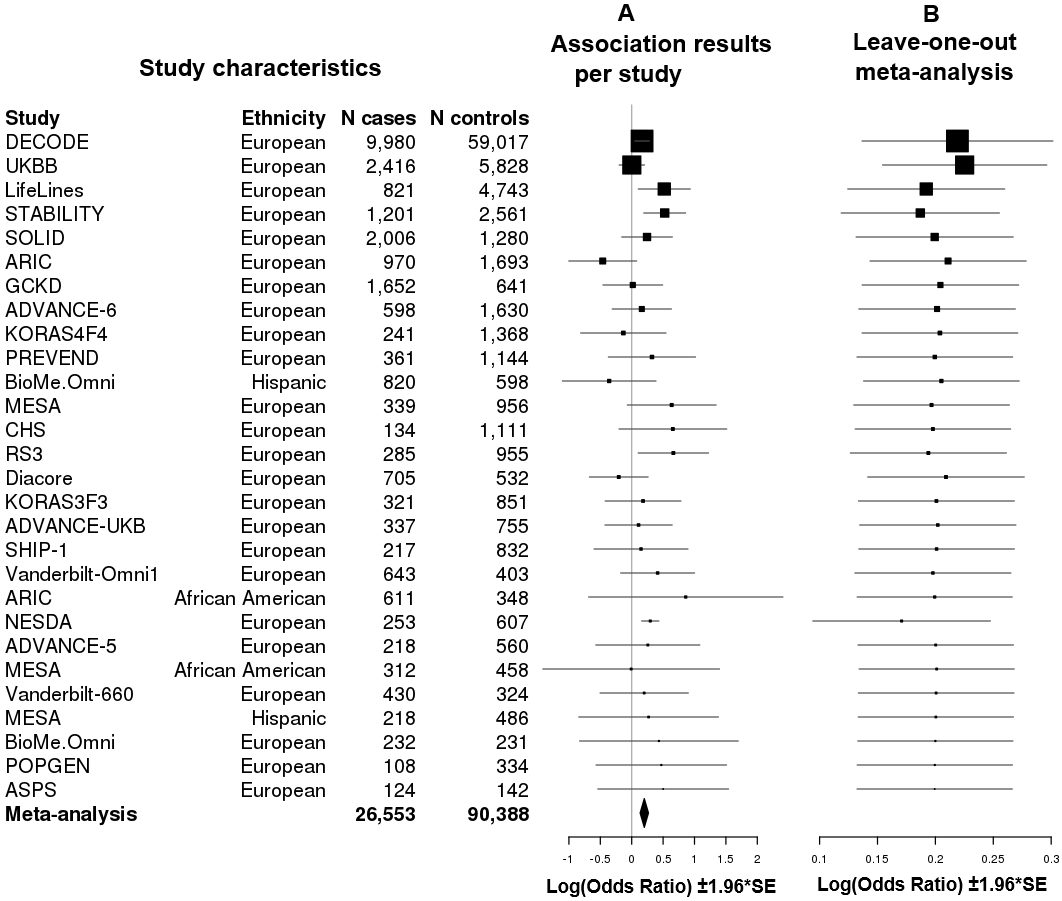
**Supplementary Figure 1B | Study-specific information on proportion of cases versus age for Rapid3 and CDKi25.** Shown are study-specific proportions of cases versus median age of study participants for the case-control definition of Rapid3 (34,874 cases; 107,090 controls) and CKDi25 (19,901 cases; 175,244 controls). Studies are color coded by their pre-dominant ancestry. There was no association between proportion of cases and age (linear regression association P-value=0.47 and 0.79 for Rapid3 and CKDi25, respectively).



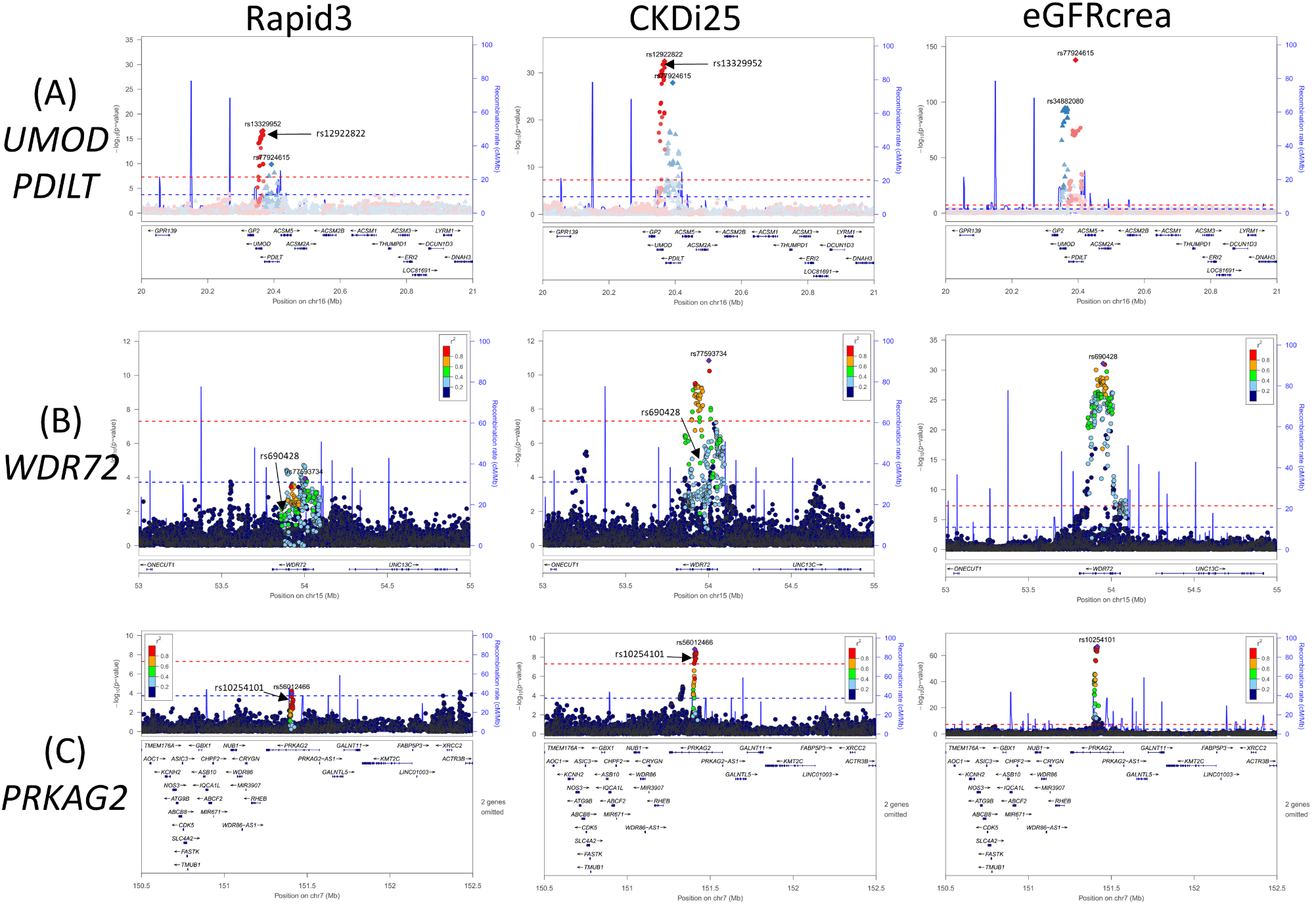
**Supplementary Figure 2 | Genetic effects for rapid eGFRcrea decline traits versus effects for cross-sectional eGFRcrea.** Shown are the 265 variants reported for cross-sectional eGFRcrea17 with their effects for Rapid3 (34,874 cases and 107,090 controls) and CKDi25 (19,901 cases and 175,244 controls) from this meta-analysis versus the previously reported effects for cross-sectional eGFRcrea17 (n up to 765,248). Genetic variants are colored when the association was nominally significant in any of the two rapid decline traits (P-value<0.05). Gene names are indicated for the six variants identified in our candidate-based approach.

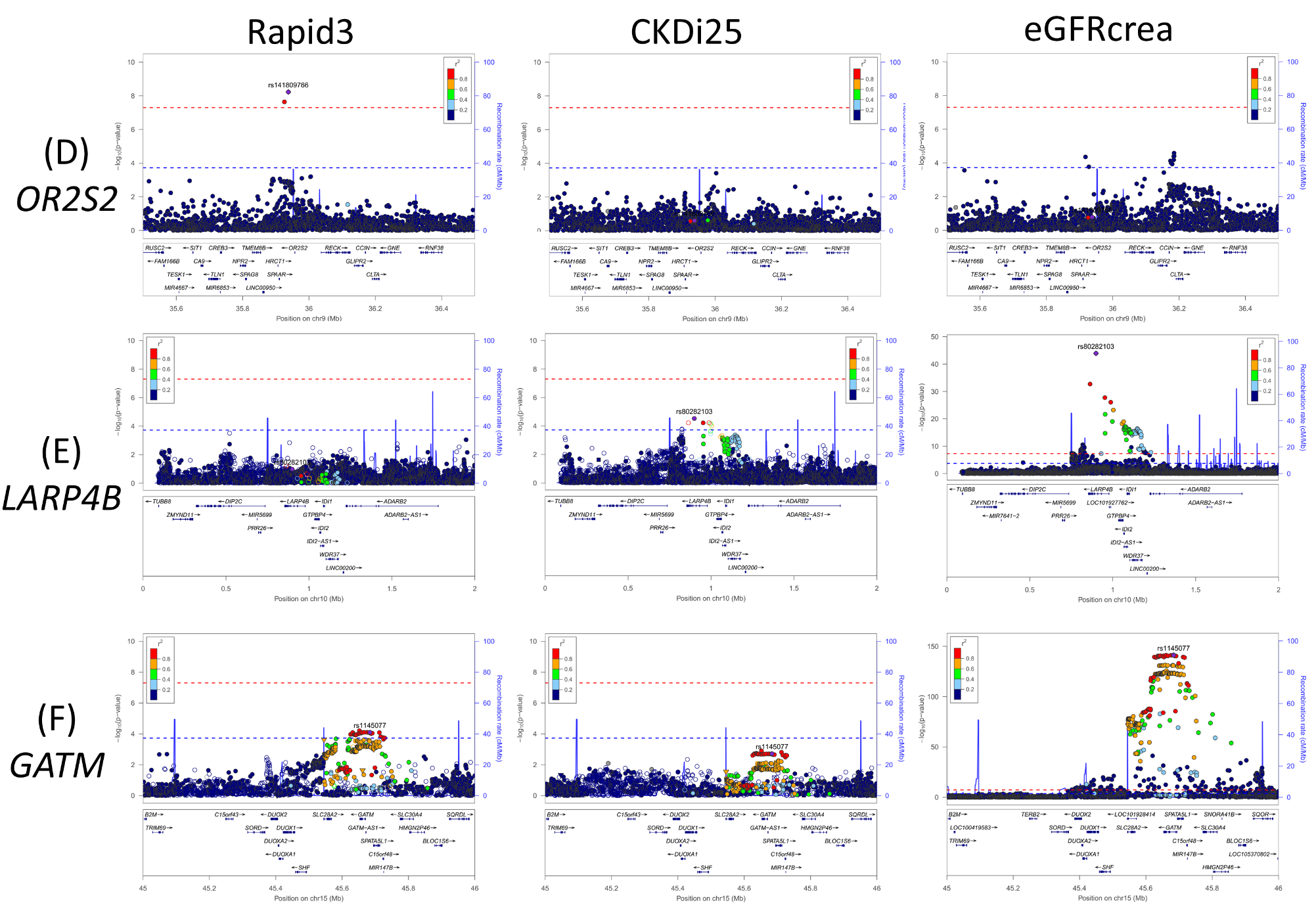


**Supplementary Figure 3 | Study-specific association and leave-one-out-analysis results for the *OR2S2* lead variant.** Shown are log odds ratios and 95% confidence intervals (CI) for the *OR2S2* locus lead variant (rs141809766, effect allele ‘G’, overall 26,553 Rapid3 cases and 90,388 controls) and its association for Rapid3: (**A**) association per study to evaluate consistency across the 28 studies and (**B**) leave-one-out meta-analysis results (i.e. excluding one study at a time) to rule-out that the signal was driven by a single study. Also shown are study-study characteristics like pre-dominant ethnicity and number of Rapid3 cases and controls for rs141809766 after quality control (imputation quality >0.6, MAC >10).

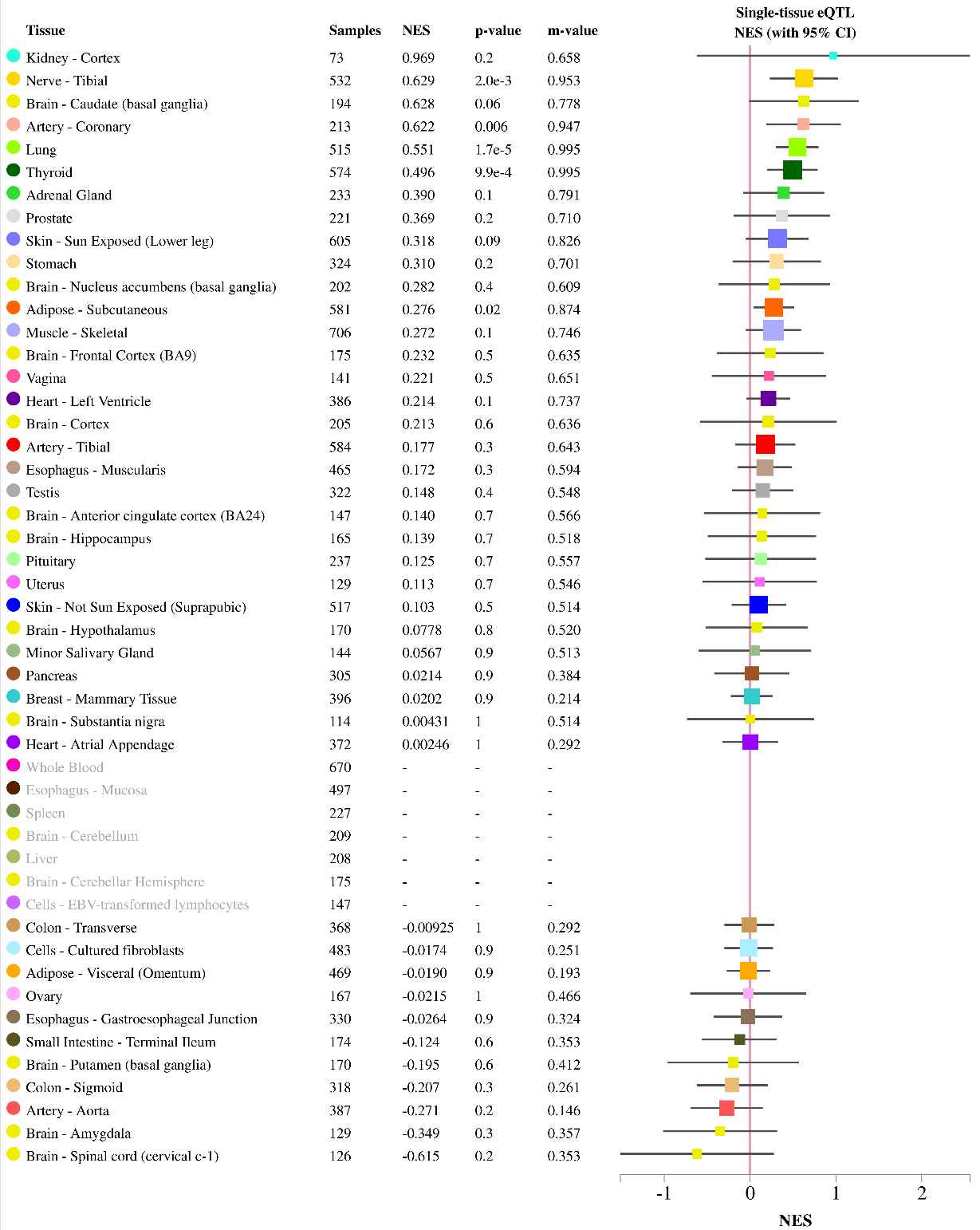


**Supplementary Figure 4 | Regional association for the six identified loci.** Shown are association P-values versus genomic position for **(left column)** Rapid3 (34,874 cases and 107,090 controls), **(middle column)** CKDi25 (19,901 cases and 175,244 controls) and **(right column)** cross-sectional eGFRcrea17, n up to 765,248) in the *UMOD-PDILT*, *WDR72*, *PRKAG2*, *OR2S2*, *LARP4B* and *GATM* loci. Red and blue horizontal lines represent the threshold for genome-wide significance (5.00x10-8) or for the Bonferroni-correct threshold in the candidate-based approach testing 265 reported variants (0.05/265=1.89x10-4). SNPs are color coded by their correlation R².

****

****

**Supplementary Figure 5 | Multi-tissue expression quantitative trait loci (eQTL) comparison of the *OR2S2* lead variant**. In the GTEx version 8 data51, we found the *OR2S2* lead variant rs141809766 to capture an eQTL for *OR2S1P* (40kb upstream of *OR2S2).* Shown is the tissue-specific association of this variant with normalized gene expression (stated as and sorted by normalized effect size, NES). Also given are number of samples per tissue, P-value for eQTL association and the posterior probability from METASOFT (m-value). We observe significant eQTLs (FDR<0.05) for Lung, Thyroid, Nerve – Tibial, Artery – Coronary, and Adipose – subcutaneous).



**Supplementary Methods**

## Overview

An analysis plan and standardized scripts for phenotype generation and GWAS analysis had been sent to all 42 participating studies (**Supplementary Table 1A&B**). Each study conducted the GWAS and had its own research protocol approved by its respective local ethics committee, and written informed consent was provided by participants in all studies.

## Phenotype description

In each study serum creatinine obtained by the Jaffé assay prior to 2009 (**Supplementary Table 1A)** were calibrated by multiplying by 0.953, and used to estimate eGFRcrea according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation11 in studies with adult participants (>18 years of age) with the R package ‘nephro’ version 1.1S3.

The variable “annual eGFRcrea decline” was defined as the difference between eGFRcrea at baseline and eGFRcrea at follow-up divided by the number of years of follow-up. By this definition, the variable is positive, if there was a deteriorating kidney function over time. Most studies were population-based with a baseline survey and one follow-up, with blood collection at these two time points and thus two measurements of serum creatinine over time. For the few studies with more than one follow-up and more than two creatinine measurements over time, eGFRcrea decline was estimated based on the baseline survey and the last follow-up.

From the “annual eGFRcrea decline”, each study analyst derived whether the participant had experienced a rapid decline yes/no using two case-control-definitions: (1) “Rapid3” cases defined as eGFRcrea decline of >3 mL/min/1.73m² per year compared to “no decline” (“Rapid3” controls, ‑1 to +1 mL/min/1.73m² per year), (2) ”CKDi25” cases defined as ≥25% eGFRcrea decline during follow-up together with a movement from eGFRcrea≥60 mL/min/1.73m² at baseline to eGFRcrea<60 mL/min/1.73m² at follow-up compared to “CKDi25” controls defined as eGFRcrea≥60 mL/min/1.73m² at baseline and follow-up (**Figure 1**).

## Genotyping, genotype imputation, and association analysis per study

Genotyping was based on different genotyping arrays and imputation used the 1000 Genomes phase 3 v5 ALL47 or Haplotype Reference Consortium v.1.148 reference panels. Imputation quality scores were provided (IMPUTE2S4 info score, R2 or minimacS5 RSQ) for each variant(**Supplementary Table 3).**

Each binary phenotype was regressed on variant dosage assuming an additive genetic model using logistic regression models adjusted for sex, age and baseline eGFRcrea in each of the studies. Other variables, such as genetic principal components, were used in a study-specific manner to control for specific design issues. A total of 38 studies contributed GWA summary statistics to the meta-analysis of Rapid3 and 23 studies to the meta-analysis of CKDi25 (42 studies for either Rapid3 or CKDi25, **Supplementary Table 1**).Summary statistics and study characteristics were collected centrally and quality-controlled with custom scripts and GWAtoolboxS6.

## Rapid eGFRcrea decline meta-analyses and locus identification

Before meta-analysis, all multi-allelic variants, variants with a Minor Allele Count (MAC) <10 and imputation quality score <0.6 were removed. A fixed-effects inverse-variance-weighted meta-analysis was conducted on GWA results including all studies that had at least 100 cases and 100 controls. We used METALS7 with genomic control (GC) correction if the study GC lambda was >1. Between-study heterogeneity was assessed using the I² statistic. Meta-analyses were conducted including studies from all ancestries (“All meta-analysis”) and restricting to studies of European descent (“EUR meta-analysis”). The “All meta-analysis” was conducted on 38 studies for Rapid3 (34,874 cases and 107,090 controls) and 23 studies for CKDi25 (19,901 cases and 175,244 controls). The “EUR meta-analysis” included 28 Rapid3 studies (31,101 cases, 102,485 controls) and 19 CKDi25 studies (19,419 cases, 169,087 controls).

To select genome-wide significant lead variants and locus regions, we selected the variant with the smallest genome-wide P-value as the primary lead variant and defined this locus’ region as this variant ±500 kB. Then, we omitted this region and selected the next variant with the smallest genome-wide P-value; we repeated this procedure until genome-wide no variant with P-value<5x10-8 was observed. The *MHC* region was considered a single locus. A locus overlapped with any of the 265 loci reported for cross-sectional eGFRcrea17, when our detected primary lead variant resided in the reported locus. In each of our identified loci, we searched for 2nd signals with a summary statistics based conditional analysis using GCTAS8 by conditioning the association of each variant in the respective locus on the primary lead variant (adjusted P-values). A 2nd signal was identified, when a variant with an adjusted P-value<5x10-8 was retained and the variants with the smallest adjusted P-value in the locus was defined as 2nd lead variant. We continued this until no further signal was found in the locus.

For the candidate-based search, we evaluated association with Rapid3 and CKDi25 for the 264 lead variants reported for cross-sectional eGFRcrea17. We also included the lead variant of the 2nd signal in the *UMOD-PDILT* locus, yielding 265 candidate variants in total. We judged significance of these variants at the Bonferroni-corrected level (0.05/265≈1.9x10-4). To clarify the overlap of our detected signals for Rapid3 or CKDi25 with cross-sectional eGFRcrea signals, we derived the correlation of our lead variant to the nearest eGFRcrea lead variant (LD LinkS1 in European (“EUR”, n=503) and conditioned our association result for the respective eGFRcrea lead variant to see whether the adjusted P-value of our lead variant was still <5x10-8.

## Validating identified effects by alternative renal markers

We assessed the association of identified variants for consistent association with annual change in eGFRcys11 or annual change in BUN as well as cross-sectional eGFRcys and BUN. For this, we used UKBiobank (n=15,746; 15,277; 364,819 and 358,791, respectively). The age, sex and baseline adjusted residuals of annual change in eGFRcys or BUN were regressed on allele dosage of each variant. We investigated directionally consistent nominal significance (one-sided P-value < 0.05) of the Rapid3- or CKDi25-increasing risk allele with annual change in eGFRcys and BUN and for cross-sectional eGFRcys and BUN.

## From lead variants to statistical signals and biology

We generated region plots using LocusZoom v1.4S9. We computed the Bayes Factor based Posterior Probability of association (PPA) of each variant within identified signal using z‑scoresS10. We ranked variants by their PPAs and added them to the set of variants with a cumulative PPA>99% per regionS11. By this, we obtained 99% credible sets of variants for each signal, We compared credible set variants for Rapid3, CKDi25 with those derived previously from the cross-sectional eGFRcrea17 in terms of size and overlap. For each gene in the identified locus regions (±500kB around lead variant), we conducted a range of statistical and functional follow-up analyses for prioritizing genes: We annotated the credible set variants across the five genome-wide significant signals for being protein altering via VEP49 or a significant eQTL-variant in glomerulus or tubulointerstitium from NephQTL50 or in any tissue from GTEx v851 (judged at a false-discovery rate<5%). We annotated the 64 genes in the five loci for containing a protein-altering credible set variant, for being a target of a significant eQTL-variant, or for having shown a kidney-related phenotype in MGI52 or OMIM53.

## The cumulative effect on rapid kidney function decline, ESKD, and AKI

To estimate the joint effect of variants increasing the risk for progression of kidney function, we calculated a genetic risk score (GRS) as the number of risk increasing alleles of the identified variants. For this, we compared individuals at high risk (GRS≥7.5 alleles) with those at low risk (GRS≤5.5 allele) via logistic regression in UK Biobank, DIACORE, KORA-F3, and KORA-F4 (unrelated European). We used the same GRS and the same high-risk versus low-risk comparisons as described above, to compute the relative risk on ESKD and AKI:

(i) unrelated Europeans from UK Biobank were defined as cases via health records (ICD10 code N18.0 or N18.5, n=528) and as controls when there was no record of N18 code and eGFRcrea>60 mL/min/1.73m² (frequency-matched by age-group and sex; n=1,584); (ii) 470 GENDIAN ESKD cases versus 1,545 KORA-F4 controls as done previously36 (eGFRcrea>60 mL/min/1.73m²; frequency-matched on age-groups and sex); (iii) 1100 4D ESKD cases versus 1601 KORA-F3 controls as done previously36 (eGFRcrea>60 mL/min/1.73m², frequency matched by age-groups and sex). We estimated the OR for ESKD per data source via logistic regression adjusting for matching variables age-groups and sex as well quantitative age and meta-analyzed risk estimates. For AKI, we used UK Biobank (cases: ICD10 code N17 “Acute Renal Failure”, n=4,123; controls: without ICD10 code N17 frequency matched on age-group and sex, n=12,369). We estimated the OR for AKI in the same fashion as for ESKD.

**Supplementary Note 1 | Meta-analysis of Rapid3 and CKDi25 in individuals of African American ancestry**

We conducted a meta-analysis restricting to individuals of African ancestry (2,356 cases and 2,375 controls from six studies for Rapid3; 374 cases and 4,183 controls from three studies for CKDi25), effect sizes had large standard errors due to the limited sample sizes, which prohibited an informative comparison with EUR effect sizes (**Supplementary Table 4B**). For the *APOL1* locus variants rs73885319 and rs60910145 reported for strong effects on kidney diseases in African ancestryS2, we found directionally consistent effects for CKDi25 (OR=1.068 and 1.067), but not for Rapid3 (both OR=0.980).

## Supplementary Note 2 | Two additional loci for rapid eGFRcrea decline from a candidate-based search

For our candidate-based approach, we selected the 264 lead variants and the 2nd signal lead variant in the *UMOD-PDILT* locus reported previously for eGFRcrea17 and tested these for association with Rapid3 and CKDi25 (judged at Bonferroni-corrected significance; 0.05/265=1.89x10-4). Among these, we found six variants in five loci significantly associated with Rapid3 and/or CKDi25 (**Table 1B**): (i) the two variants in the *UMOD-PDILT* locus were significant for CKDi25 and/or Rapid3 and they were identical (rs77924615) or highly correlated (rs34882080) with our GWAS lead variants. (ii) Two reported variants, one each in the *PRKAG2* and *WDR72* loci, were significantly associated with CKDi25. They were correlated with the respective CKDi25-GWAS lead variants (R²=0.84 for *PRKAG2*, 0.42 for *WDR72*) and lost association when adjusted for the respective CKDi25-GWAS lead variantS8 (**Methods**; P-values from 0.40 to 0.99, **Supplementary Table 5**). The candidate-based signals thus coincided with the genome-wide detected signals. (iii) Two reported variants, one each in *LARP4B* and *GATM*, were significantly associated with CKDi25 or Rapid3. These variants had the smallest P-value in this locus for the respective trait.

Among the tested 265 variants, 64 were associated with Rapid3 or/and CKDi25 at nominal significance, and 55 of the 64 were direction-consistent (i.e. the eGFRcrea-lowering allele increased rapid decline risk; **Supplementary Figure 2**). Heterogeneity of the six variants’ association across studies was zero to moderate (I² from 0 to 41%). A sensitivity analysis restricted to European ancestry participants showed similar results (**Supplementary Table 5**).

**Supplementary Note 3 | Testing effect direction consistency of identified lead variants with annual change in eGFRcys and BUN in the UK Biobank**

We evaluated the seven 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 an annual increase of BUN for the Rapid3/CKDi25-risk increasing allele. For five of the seven variants, we found a direction-consistent, nominally significant association for annual change in eGFRcys and/or BUN (*UMOD*-*PDILT* (2), *WDR72*, *PRKAG2*, *OR2S2;* one-sided P-value=2.75x10-3 to 0.04, **Table 2**), but not for *LARP4B* or *GATM* (one-sided P-value=0.10 to 0.82). While the *LARP4B* associations with BUN change and eGFRcys change were into the expected directions, the *GATM* associations were directionally unexpected. For completeness, we also evaluated the seven variants’ association with cross-sectional eGFRcys and BUN (n=364,819 and 358,791; **Table 2**).

We also evaluated the seven variants’ association with cross-sectional eGFRcys and BUN (n=364,819 and 358,791; **Table 2**). Five variants showed highly significant, direction-consistent associations for BUN and eGFRcys (i.e. BUN increase and eGFRcys decrease for the eGFRcrea-lowering allele; *UMOD*-*PDILT* (2), *WDR72*, *PRKAG2*, *LARP4B*; one-sided P-value=1.74x10-108 to 1.59x10-9). This extended previous results for BUN in CKDGen17 (n=416,076) not only by replication in independent data, but also by confirmation with eGFRcys. Two variants did not show any association for cross-sectional eGFRcys or BUN (*OR2S2* and *GATM* loci, one-sided P-value=0.70 to 0.95).

**Supplementary References**

S1. Machiela MJ, Chanock SJ. LDlink: A web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics*. 2015. doi:10.1093/bioinformatics/btv402

S2. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science (80- )*. 2010. doi:10.1126/science.1193032

S3. Pattaro C, Riegler P, Stifter G, Modenese M, Minelli C, Pramstaller PP. Estimating the glomerular filtration rate in the general population using different equations: Effects on classification and association. *Nephron - Clin Pract*. 2013. doi:10.1159000351043

S4. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet*. 2009. doi:10.1371/journal.pgen.1000529

S5. Fuchsberger C, Abecasis GR, Hinds DA. Minimac2: Faster genotype imputation. *Bioinformatics*. 2015. doi:10.1093/bioinformatics/btu704

S6. Fuchsberger C, Taliun D, Pramstaller PP, Pattaro C. GWAtoolbox: An R package for fast quality control and handling of genome-wide association studies meta-analysis data. *Bioinformatics*. 2012. doi:10.1093/bioinformatics/btr679

S7. Willer CJ, Li Y, Abecasis GR. METAL: Fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010. doi:10.1093/bioinformatics/btq340

S8. Yang J, Ferreira T, Morris AP, et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat Genet*. 2012. doi:10.1038/ng.2213

S9. Pruim RJ, Welch RP, Sanna S, et al. LocusZoom: Regional visualization of genome-wide association scan results. In: *Bioinformatics*. ; 2011. doi:10.1093/bioinformatics/btq419

S10. Kichaev G, Yang WY, Lindstrom S, et al. Integrating Functional Data to Prioritize Causal Variants in Statistical Fine-Mapping Studies. *PLoS Genet*. 2014. doi:10.1371/journal.pgen.1004722

S11. Grassmann F, Heid IM, Weber BHF, et al. Recombinant haplotypes narrow the ARMS2/HTRA1 association signal for age-related macular degeneration. *Genetics*. 2017. doi:10.1534/genetics.116.195966

**Extended acknowledgements and study funding information**

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the US Department of Health and Human Services. The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) supported this work – Project-ID 387509280 – SFB1350 (Subproject C6 to I.M.H.).

**4D** The 4D study (Die Deutsche Diabetes Dialyse Studie) has received funding from the German Ministry of Education and Research (project 01GL0304: Comprehensive Heart Failure Center).

**ADVANCE** ADVANCE genomic sub-studies were supported by grants from the Ministry of Science and Innovation from the Quebec Government, from Genome Quebec, from the Consortium Québécois du Médicament, from the Canadian Institutes of Health Research and from Medpharmgene, OPTITHERA Inc and Les Laboratoires Servier.

**AFTER EU** The AFTER EU study is the Danish part of the EURAGEDIC study which was supported by the European Commission (contract QLG2-CT-2001– 01669). The genotyping for this study was part of the Genetics of Diabetic Nephropathy (GenDN) study, primarily funded by Juvenile Diabetes Research Foundation (JDRF) International Prime Award Number 17-2013- 8. Tarunveer S Ahluwalia was also funded by the GenDN study grant and Lundbeck foundation Travel Grant (Ref. Number 2013-14471).

**ARIC** The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I and HHSN268201700005I), R01HL087641, R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. The work of Anna Köttgen was supported by a Heisenberg Professorship (KO 3598/5-1) as well as CRC 992 of the German Research Foundation.

**ASPS** The authors thank the staff and the participants for their valuable contributions. We thank Birgit Reinhart for her long-term administrative commitment, Elfi Hofer for the technical assistance at creating the DNA bank, Ing. Johann Semmler and Anita Harb for DNA sequencing and DNA analyses by TaqMan assays and Irmgard Poelzl for supervising the quality management processes after ISO9001 at the biobanking and DNA analyses. The research reported in this article was funded by the Austrian Science Fond (FWF) grant number P20545-P05, P13180 and PI904 as well as by the Austrian National Bank (OeNB) Anniversary Fund grant number P15435 and the Austrian Federal Ministry of Science, Research and Economy under the aegis of the EU Joint Programme Neurodegenerative Disease Research (JPND)-www.jpnd.eu. The Medical University of Graz supports the databank of the ASPS.

**BioMe** The Mount Sinai IPM Biobank Program is supported by The Andrea and Charles Bronfman Philanthropies. Ruth Loos is funded by R01DK110113, U01HG007417, R01DK101855, and R01DK107786.

**CHS** Cardiovascular Health Study: This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and U01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**DECODE** The study was funded by deCODE Genetics/Amgen inc. We thank the study individuals for their valuable participation and our colleagues, who contributed to data collection, sample handling, and genotyping

**DIACORE** Cohort recruiting and management was funded by the KfH Stiftung Präventivmedizin e.V. (Carsten A. Böger). Genome-wide genotyping was funded the Else Kröner-Fresenius-Stiftung (2012\_A147), the KfH Stiftung Präventivmedizin and the University Hospital Regensburg. The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) supported this work – Project-ID 387509280 – SFB 1350 (Subproject C6 to I.M.H.) and Iris Heid and Carsten Böger received funding by DFG BO 3815/4-1.

**ESTHER** The ESTHER study was funded by the Saarland state Ministry for Social Affairs, Health, Women and Family Affairs (Saarbrücken, Germany), the Baden-Württemberg state Ministry of Science, Research and Arts (Stuttgart, Germany), the Federal Ministry of Education and Research (Berlin, Germany) and the Federal Ministry of Family Affairs, Senior Citizens, Women and Youth (Berlin, Germany).

**FHS** The Framingham Heart Study is supported by HHSN268201500001.

**FINCAVAS** The Finnish Cardiovascular Study (FINCAVAS) has been financially supported by the Competitive Research Funding of the Tampere University Hospital (Grant 9M048 and 9N035), the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Emil Aaltonen Foundation, Finland, the Tampere Tuberculosis Foundation, EU Horizon 2020 (grant 755320 for TAXINOMISIS; grant 848146 for To\_Aition), and the Academy of Finland grant 322098. The authors thank the staff of the Department of Clinical Physiology for collecting the exercise test data.

**GCKD** The GCKD study was funded by the German Ministry of Research and Education (Bundesministerium für Bildung und Forschung, BMBF), by the Foundation KfH Stiftung Präventivmedizin. Unregistered grants to support the study were provided by Bayer, Fresenius Medical Care and Amgen. Genotyping was supported by Bayer Pharma AG. The work of Matthias Wuttke was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Projektnummer 246781735 – SFB 1140 and the Else Kroener Fresenius Forschungskolleg NAKSYS. The work of Yong Li was supported by DFG KO 3598/4-2.

**JHS** The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I/HHSN26800001) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute for Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS. James G. Wilson is supported by U54GM115428 from the National Institute of General Medical Sciences. Laura M. Raffield is supported by T32 HL129982.

**KORA** The KORA research platform (KORA, Cooperative Health Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München - German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians Universität, as part of LMUinnovativ. Statistical KORA analyses were supported by DFG BO-3815/4-1 (to Carsten A. Böger), BMBF 01ER1206, 01ER1507 (to Iris M. Heid), by the University of Regensburg and by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project-ID 387509280 – SFB 1350 (Subproject C6 to I.M.H.) and DFG BO 3815/4-1.

**Lifelines** The LifeLines Cohort Study, and generation and management of GWAS genotype data for the LifeLines Cohort Study is supported by the UMCG Genetics Lifelines Initiative (UGLI), the Netherlands Organization of Scientific Research NWO (grant 175.010.2007.006), the Economic Structure Enhancing Fund (FES) of the Dutch government, the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation and Dutch Diabetes Research Foundation. The authors wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants.

**MDC-CC** This study was supported by the European Research Council (Consolidator grant nr 649021, Orho-Melander), the Swedish Research Council, the Swedish Heart and Lung Foundation, the Novo Nordic Foundation, the Swedish Diabetes Foundation, and the Påhlsson Foundation, and by equipment grants from the Knut and Alice Wallenberg Foundation, the Region Skåne, Skåne University Hospital, the Linneus Foundation for the Lund University Diabetes Center and Swedish Foundation for Strategic Research for IRC15-0067.

**MESA** MESA and the MESA SHARe projects are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420. Also supported by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

**MyCode**

**(Geisinger)**

We would like to acknowledge the participants, staff, and our colleagues associated with the Geisinger MyCode Community Health Initiative. We also thank the staff of the PACDC of Geisinger for assistance with the phenotypic data, and the staff of the Biomedical & Translational Informatics and Kidney Health Research Institute.

**NESDA**  Funding was obtained from the Netherlands Organization for Scientific Research (Geestkracht program grant 10-000-1002); the Center for Medical Systems Biology (CSMB, NWO Genomics), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL), VU University’s Institutes for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam, University Medical Center Groningen, Leiden University Medical Center, National Institutes of Health (NIH, R01D0042157-01A, MH081802, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH089995). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health.Computing was supported by BiG Grid, the Dutch e-Science Grid, which is financially supported by NWO.

**PREVEND** The Prevention of Renal and Vascular Endstage Disease Study (PREVEND) genetics is supported by the Dutch Kidney Foundation (Grant E033), the EU project grant GENECURE (FP-6 LSHM CT 2006 037697), the National Institutes of Health (grant LM010098), the Netherlands organization for health research and development (NWO VENI grant 916.761.70), and the Dutch Inter University Cardiology Institute Netherlands (ICIN). Niek Verweij was supported by NWO VENI grant 016.186.125.

**POPGEN** The PopGen 2.0 network was supported by a grant from the German Ministry for Education and Research (01EY1103). Sandra Freitag-Wolf was supported by German Research Foundation, Clusters of Excellence 306, Inflammation at Interfaces.

**RS** The Rotterdam Study (RS) has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The RS has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. The generation and management of GWAS genotype data for the RS (RS I, RS II, RS III) was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands. The GWAS datasets are supported by the Netherlands Organisation of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA), project nr. 050-060- 810. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters, and Carolina Medina-Gomez, for their help in creating the GWAS database, and Karol Estrada, Yurii Aulchenko, and Carolina Medina-Gomez, for the creation and analysis of imputed data. The RS is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff from the RS and the participating general practitioners and pharmacists.

**SHIP** SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network ‘Greifswald Approach to Individualized Medicine (GANI\_MED)’ funded by the Federal Ministry of Education and Research (grant 03IS2061A). Genome-wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthineers, Erlangen, Germany and the Federal State of Mecklenburg- West Pomerania. The University of Greifswald is a member of the Caché Campus program of the InterSystems GmbH.

**SiMES** The Singapore Malay Eye Study (SiMES) was funded by the National Medical Research Council (NMRC 0796/2003 and NMRC/STaR/0003/2008) and Biomedical Research Council (BMRC, 09/1/35/19/616). The Genome Institute of Singapore provided services for genotyping.

**SINDI** The Singapore Indian Eye Study (SINDI) was funded by grants from the Biomedical Research Council of Singapore (BMRC 09/1/35/19/616 and 08/1/35/19/550), and the National Medical Research Council of Singapore (NMRC/STaR/0003/2008). The Genome Institute of Singapore provided services for genotyping.

**SOLID-TIMI 52** The SOLID-TIMI 52 trial was supported and funded by grants from GlaxoSmithKline.

**STABILITY** The STABILITY trial was supported and funded by grants from GlaxoSmithKline.

**Vanderbilt** The data used for the analyses were obtained from Vanderbilt University Medical Center’s BioVU, which is supported by numerous sources: institutional funding, private agencies, and federal grants. These include the NIH funded Shared Instrumentation Grant S10RR025141; and CTSA grants UL1TR002243, UL1TR000445, and UL1RR024975. Genomic data are also supported by investigator-led projects that include U01HG004798, R01NS032830, RC2GM092618, P50GM115305, U01HG006378, U19HL065962, R01HD074711; and additional funding sources listed at https://victr.vanderbilt.edu/pub/biovu/. Jacklyn N. Hellwege is supported by the Vanderbilt Molecular and Genetic Epidemiology of Cancer training program, funded by T32CA160056.

**YFS** The Young Finns Study has been financially supported by the Academy of Finland: grants 322098, 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research ; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; EU Horizon 2020 (grant 755320 for TAXINOMISIS; grant 848146 for To\_Aition); European Research Council (grant 742927 for MULTIEPIGEN project); and Tampere University Hospital Supporting Foundation. We thank the teams that collected data at all measurement time points; the persons who participated as both children and adults in these longitudinal studies; and biostatisticians Irina Lisinen, Johanna Ikonen, Noora Kartiosuo, Ville Aalto, and Jarno Kankaanranta for data management and statistical advice.

**LifeLines group author genetics**

LifeLines Cohort Study

Behrooz Z Alizadeh1, H Marike Boezen1, Lude Franke2, Pim van der Harst3, Gerjan Navis4, Marianne Rots5, Harold Snieder1, Morris Swertz2, Bruce HR Wolffenbuttel6, Cisca Wijmenga2.

*1Department of Epidemiology, University of Groningen, University Medical Center Groningen, The Netherlands. 2Department of Genetics, University of Groningen, University Medical Center Groningen, The Netherlands, 3Department of Cardiology, University of Groningen, University Medical Center Groningen, The Netherlands, 4Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, The Netherlands, 5Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, The Netherlands, 6Department of Endocrinology, University of Groningen, University Medical Center Groningen, The Netherlands*

**Regeneron Genetics Center Banner Author List and Contribution Statements**

All authors/contributors are listed in alphabetical order.

RGC Management and Leadership Team

Goncalo Abecasis, Ph.D., Aris Baras, M.D., Michael Cantor, M.D., Giovanni Coppola, M.D., Aris Economides, Ph.D., Luca A. Lotta, M.D., Ph.D., John D. Overton, Ph.D., Jeffrey G. Reid, Ph.D., Alan Shuldiner, M.D. Contribution: All authors contributed to securing funding, study design and oversight. All authors reviewed the final version of the manuscript.

Sequencing and Lab Operations

Christina Beechert, Caitlin Forsythe, M.S., Erin D. Fuller, Zhenhua Gu, M.S., Michael Lattari, Alexander Lopez, M.S., John D. Overton, Ph.D., Thomas D. Schleicher, M.S., Maria Sotiropoulos Padilla, M.S., Karina Toledo, Louis Widom, Sarah E. Wolf, M.S., Manasi Pradhan, M.S., Kia Manoochehri, Ricardo H. Ulloa. Contribution: C.B., C.F., K.T., A.L., and J.D.O. performed and are responsible for sample genotyping. C.B, C.F., E.D.F., M.L., M.S.P., K.T., L.W., S.E.W., A.L., and J.D.O. performed and are responsible for exome sequencing. T.D.S., Z.G., A.L., and J.D.O. conceived and are responsible for laboratory automation. M.P., K.M., R.U., and J.D.O are responsible for sample tracking and the library information management system.

Genome Informatics

Xiaodong Bai, Ph.D., Suganthi Balasubramanian, Ph.D., Leland Barnard, Ph.D., Andrew Blumenfeld, Gisu Eom, Lukas Habegger, Ph.D., Alicia Hawes, B.S., Shareef Khalid, Jeffrey G. Reid, Ph.D., Evan K. Maxwell, Ph.D., William Salerno, Ph.D., Jeffrey C. Staples, Ph.D. Contribution: X.B., A.H., W.S. and J.G.R. performed and are responsible for analysis needed to produce exome and genotype data. G.E. and J.G.R. provided compute infrastructure development and operational support. S.K., S.B., and J.G.R. provide variant and gene annotations and their functional interpretation of variants. E.M., L.B., J.S., A.B., L.H., J.G.R. conceived and are responsible for creating, developing, and deploying analysis platforms and computational methods for analyzing genomic data.

Research Program Management

Marcus B. Jones, Ph.D., Lyndon J. Mitnaul, Ph.D.

Contribution: 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.