



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

CUBN is a gene locus for albuminuria

Citation for published version:

CKDGen Consortium, Böger, CA, Chen, M-H, Tin, A, Olden, M, Köttgen, A, de Boer, IH, Fuchsberger, C, O'Seaghda, CM, Pattaro, C, Teumer, A, Liu, C-T, Glazer, NL, Li, M, O'Connell, JR, Tanaka, T, Peralta, CA, Kutalik, Z, Luan, J, Zhao, JH, Hwang, S-J, Akyzbekova, E, Kramer, H, van der Harst, P, Smith, AV, Lohman, K, de Andrade, M, Hayward, C, Kollerits, B, Tönjes, A, Aspelund, T, Ingelsson, E, Eiriksdottir, G, Launer, LJ, Harris, TB, Shuldiner, AR, Mitchell, BD, Arking, DE, Franceschini, N, Boerwinkle, E, Egan, J, Hernandez, D, Reilly, M, Townsend, RR, Lumley, T, Siscovick, DS, Psaty, BM, Campbell, H, Vitart, V, Hastie, ND & Rudan, I 2011, 'CUBN is a gene locus for albuminuria', *Journal of the American Society of Nephrology*, vol. 22, no. 3, pp. 555-70. <https://doi.org/10.1681/ASN.2010060598>

Digital Object Identifier (DOI):

[10.1681/ASN.2010060598](https://doi.org/10.1681/ASN.2010060598)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Journal of the American Society of Nephrology

Publisher Rights Statement:

Copyright © 2011 by the American Society of Nephrology. Europe PMC open access link

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



CUBN Is a Gene Locus for Albuminuria

Carsten A. Böger,¹ Ming-Huei Chen,² Adrienne Tin,³ Matthias Olden,^{1,4} Anna Köttgen,^{3,5} Jan H. de Boer,⁶ Christian Fuchsberger,⁷ Conall M. O'Seaghdha,⁸ Cristian Pattaro,⁷ Alexander Teumer,⁹ Ching-Ti Liu,¹⁰ Nicole L. Glazer,¹¹ Man Li,³ Jeffrey R. O'Connell,¹² Toshiko Tanaka,^{13,14} Carmen A. Peralta,¹⁵ Zoltán Kutalik,^{16,17} Jian'an Luan,¹⁸ Jing Hua Zhao,¹⁸ Shih-Jen Hwang,¹⁹ Erneg Akylbekova,²⁰ Holly Kramer,²¹ Pim van der Harst,²² Albert V. Smith,^{23,24} Kurt Lohman,²⁵ Mariza de Andrade,²⁶ Caroline Hayward,²⁷ Barbara Kollerits,²⁸ Anke Tönjes,²⁹ Thor Aspelund,^{23,24} Erik Ingelsson,³⁰ Gudny Eiriksdottir,²⁴ Lenore J. Launer,³¹ Tamara B. Harris,³¹ Alan R. Shuldiner,³² Braxton D. Mitchell,³³ Dan E. Arking,³⁴ Nora Franceschini,³⁵ Eric Boerwinkle,³⁶ Josephine Egan,³⁷ Dena Hernandez,³⁸ Muredach Reilly,³⁹ Raymond R. Townsend,⁴⁰ Thomas Lumley,¹¹ David S. Siscovick,⁴¹ Bruce M. Psaty,⁴² Bryan Kestenbaum,⁶ Talin Haritunians,⁴³ Sven Bergmann,^{16,17} Peter Vollenweider,⁴⁴ Gerard Waeber,⁴⁴ Vincent Mooser,⁴⁵ Dawn Waterworth,⁴⁵ Andrew D. Johnson,¹⁹ Jose C. Florez,⁴⁶ James B. Meigs,⁴⁷ Xiaoning Lu,¹⁰ Stephen T. Turner,⁴⁸ Elizabeth J. Atkinson,²⁶ Tennille S. Leak,⁴⁹ Knut Aasarød,^{50,51} Frank Skorpen,⁵¹ Ann-Christine Syvänen,⁵² Thomas Illig,⁵³ Jens Baumert,⁵³ Wolfgang Koenig,⁵⁴ Bernhard K. Krämer,⁵⁵ Olivier Devuyst,⁵⁶ Josyf C. Mychaleckyj,⁵⁷ Cosetta Minelli,⁷ Stephan J.L. Bakker,⁵⁸ Lyudmyla Kedenko,⁵⁹ Bernhard Paulweber,⁵⁹ Stefan Coassin,²⁸ Karlhans Endlich,⁶⁰ Heyo K. Kroemer,⁶¹ Reiner Biffar,⁶² Sylvia Stracke,⁶³ Henry Völzke,⁶⁴ Michael Stumvoll,²⁹ Reedik Mägi,⁶⁵ Harry Campbell,⁶⁶ Veronique Vitart,²⁷ Nicholas D. Hastie,²⁷ Vilundur Gudnason,^{23,24} Sharon L.R. Kardia,⁶⁷ Yongmei Liu,²⁵ Ozren Polasek,⁶⁸ Gary Curhan,⁶⁹ Florian Kronenberg,²⁸ Inga Prokopenko,⁶⁵ Igor Rudan,⁷⁰ Johan Ärnlöv,⁷¹ Stein Hallan,^{50,51} Gerjan Navis,⁵⁸ the CKDGen Consortium, Afshin Parsa,⁷² Luigi Ferrucci,¹⁴ Josef Coresh,⁷³ Michael G. Shlipak,⁷⁴ Shelley B. Bull,⁷⁵ Andrew D. Paterson,⁷⁶ on behalf of DCCT/EDIC, H.-Erich Wichmann,^{53,77,78} Nicholas J. Wareham,¹⁸ Ruth J.F. Loos,¹⁸ Jerome I. Rotter,⁴³ Peter P. Pramstaller,⁷ L. Adrienne Cupples,¹⁰ Jacques S. Beckmann,⁷⁹ Qiong Yang,⁸⁰ Iris M. Heid,^{4,53} Rainer Rettig,⁸¹ Albert W. Dreisbach,⁸² Murielle Bochud,⁸³ Caroline S. Fox,^{19,84} and W.H.L. Kao¹³

¹Department of Internal Medicine II, University Medical Center Regensburg, Regensburg, Germany;

²Department of Neurology, Boston University School of Medicine, Boston, Massachusetts;

³Department of Epidemiology and the Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland;

⁴Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center, Regensburg, Germany;

⁵Renal Division, University Hospital of Freiburg, Freiburg, Germany;

⁶Division of Nephrology, University of Washington, Seattle, Washington;

⁷Institute of Genetic Medicine, European Academy of Bolzano/Bozen (EURAC), Italy and Affiliated Institute of the University of Lübeck, Lübeck, Germany;

⁸Division of Nephrology, Brigham and Women's Hospital and Harvard Medical School, Boston Massachusetts;

⁹Interfaculty Institute for Genetics and Functional Genomics, University of Greifswald, Greifswald, Germany;

¹⁰Department of Biostatistics, Boston University School of Public Health and NHLBI's Framingham Heart Study, Boston Massachusetts;

¹¹Cardiovascular Health Research Unit and Department of Biostatistics, University of Washington, Seattle, Washington;

¹²University of Maryland School of Medicine, Baltimore, Maryland;

¹³Medstar Research Institute, Baltimore, Maryland;

¹⁴Clinical Research Branch, National Institute on Aging, Baltimore, Maryland;

¹⁵Division of Nephrology, University of California, San Francisco Medical School and San Francisco VA Medical Center, San Francisco, California;

¹⁶Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland;

¹⁷Swiss Institute of Bioinformatics, Lausanne, Switzerland;

- 18 MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, United Kingdom;
- 19 NHLBI's Framingham Heart Study and the Center for Population Studies, Framingham, Massachusetts;
- 20 Jackson State University, Jackson, Mississippi;
- 21 Loyola University, Maywood, Illinois;
- 22 Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;
- 23 University of Iceland, Reykjavik, Iceland;
- 24 Icelandic Heart Association, Hjartavernd, Holtasmara, Kopavogur, Iceland;
- 25 Department of Biostatistical Sciences, Wake Forest University, Division of Public Health Sciences, Winston-Salem, North Carolina;
- 26 Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota;
- 27 MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Western General Hospital, Crewe Road, Edinburgh, Scotland;
- 28 Innsbruck Medical University, Division of Genetic Epidemiology, Innsbruck, Austria;
- 29 Department of Medicine, University of Leipzig, Leipzig, Germany;
- 30 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden;
- 31 Laboratory of Epidemiology, Demography, and Biometry, NIA, Bethesda, Maryland;
- 32 University of Maryland School of Medicine, Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, Maryland;
- 33 University of Maryland School of Medicine, Baltimore, Maryland;
- 34 McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland;
- 35 University of North Carolina at Chapel Hill, Chapel Hill, North Carolina;
- 36 Human Genetics Center, University of Texas Health Science Center, Houston, Texas;
- 37 Laboratory of Clinical Investigation, National Institute on Aging, Baltimore, Maryland;
- 38 Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland;
- 39 University of Pennsylvania Division of Cardiology, Perelman Center for Advanced Medicine, Philadelphia, Pennsylvania;
- 40 University of Pennsylvania Renal Electrolyte and Hypertension Division, Philadelphia, Pennsylvania;
- 41 Departments of Epidemiology and Medicine, University of Washington, Seattle, Washington;
- 42 Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services and Group Health Research Institute, Group Health Cooperative, Seattle, Washington;
- 43 Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California;
- 44 Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;
- 45 Genetics Division, GlaxoSmithKline, King of Prussia, Pennsylvania;
- 46 Center for Human Genetic Research and Diabetes Research Center (Diabetes Unit), Massachusetts General Hospital, Boston, Massachusetts, Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, and Department of Medicine, Harvard Medical School, Boston, Massachusetts;
- 47 Department of General Internal Medicine, Massachusetts General Hospital, Boston, Massachusetts;
- 48 Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota;
- 49 Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania;
- 50 St Olav University Hospital, Trondheim, Norway;
- 51 Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway;
- 52 Molecular Medicine, Department of Medical Sciences, Science for Life Laboratory, Uppsala University, Uppsala, Sweden;
- 53 Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany;
- 54 Zentrum für Innere Medizin, Klinik für Innere Medizin II - Kardiologie, Universitätsklinikum Ulm, Ulm, Germany;
- 55 University Medical Centre Mannheim, 5th Department of Medicine, Mannheim, Germany;
- 56 NEFR Unit Université Catholique de Louvain Medical School, Brussels, Belgium;
- 57 Center for Public Health Genomics, Charlottesville, Virginia;
- 58 Department of Internal Medicine, University Medical Center, Groningen, University of Groningen, Groningen, The Netherlands;
- 59 First Department of Internal Medicine, Paracelsus Medical University, Salzburg, Austria;
- 60 Institute of Anatomy and Cell Biology, University of Greifswald, Greifswald, Germany;
- 61 Institute of Pharmacology, University of Greifswald, Greifswald, Germany;
- 62 Clinic for Prosthodontic Dentistry, Gerostomatology and Material Science, University of Greifswald, Greifswald, Germany;
- 63 Nephrology Clinic for Internal Medicine A, University of Greifswald, Greifswald, Germany;
- 64 Institute for Community Medicine, University of Greifswald, Greifswald, Germany;
- 65 Wellcome Trust Centre for Human Genetics, and Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, United Kingdom;
- 66 Centre for Population Health Sciences, University of Edinburgh, Edinburgh, Scotland;
- 67

University of Michigan School of Public Health, Department of Epidemiology, University of Michigan, Ann Arbor, Michigan;

⁶⁸Gen-Info Ltd., Zagreb, Croatia;

⁶⁹Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts;

⁷⁰Center for Population Health Sciences, University of Edinburgh Medical School, Edinburgh, Scotland;

⁷¹Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden;

⁷²University of Maryland School of Medicine, Baltimore, Maryland;

⁷³Welch Center for Prevention, Epidemiology & Clinical Research, Johns Hopkins University, Baltimore, Maryland;

⁷⁴General Internal Medicine, University of California, San Francisco, San Francisco, California;

⁷⁵Samuel Lunenfeld Research Institute of Mount Sinai Hospital, Prosserman Centre for Health Research, Toronto, Ontario, Canada;

⁷⁶The Hospital for Sick Children, Toronto, Ontario, Canada;

⁷⁷Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany;

⁷⁸Klinikum Grosshadern, Munich, Germany;

⁷⁹Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland;

⁸⁰Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts;

⁸¹Institute of Physiology, University of Greifswald, Greifswald, Germany;

⁸²University of Mississippi Division of Nephrology, University of Mississippi, Jackson, Mississippi;

⁸³University Institute of Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, IUMSP, Lausanne, Switzerland; and

⁸⁴Division of Endocrinology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

✉ Corresponding author.

Correspondence: Caroline S. Fox, NHLBI's Framingham Heart Study, 73 Mount Wayte Avenue Suite #2, Framingham, MA 01702., Phone: 508-933-3477; Fax: 508-872-2678, E-mail: foxca@nhlbi.nih.gov; or W.H. Linda Kao, Departments of Epidemiology and Medicine, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, MD 21205., Phone: 410-614-0945; Fax: 410-955-0863, E-mail: wkao@jhsph.edu.

C.A.B., M.-H.C., A.T., M.O., A.K., and I.H.B. jointly contributed to this work.

I.M.H., R.R., A.W.D., M.B., C.S.F., and W.H.L.K. jointly oversaw this work.

C.A.B., M.-H.C., A.K., I.H.B., C.M.O., J.S.B., I.M.H., R.R., A.W.D., M.B., C.S.F., and W.H.L.K. comprise the writing group.

A full list of members of the CKDGen Consortium is given in the Acknowledgments section.

Received June 7, 2010; Accepted October 19, 2010.

Copyright © 2011 by the American Society of Nephrology

Abstract

Identification of genetic risk factors for albuminuria may alter strategies for early prevention of CKD progression, particularly among patients with diabetes. Little is known about the influence of common genetic variants on albuminuria in both general and diabetic populations. We performed a meta-analysis of data from 63,153 individuals of European ancestry with genotype information from genome-wide association studies (CKDGen Consortium) and from a large candidate gene study (CARE Consortium) to identify susceptibility loci for the quantitative trait urinary albumin-to-creatinine ratio (UACR) and the clinical diagnosis microalbuminuria. We identified an association between a missense variant (I2984V) in the *CUBN* gene, which encodes cubilin, and both UACR ($P = 1.1 \times 10^{-11}$) and microalbuminuria ($P = 0.001$). We observed similar associations among 6981 African Americans in the CARE Consortium. The associations between this variant and both UACR and microalbuminuria were significant in individuals of European ancestry regardless of diabetes status. Finally, this variant associated with a 41% increased risk for the development of persistent microalbuminuria during 20 years of follow-up among 1304 participants with type 1 diabetes in the prospective DCCT/EDIC Study. In summary, we identified a missense *CUBN* variant that associates with levels of albuminuria in both the general population and in individuals with diabetes.

Elevated levels of urinary albumin (albuminuria) are a cardinal manifestation of chronic kidney disease (CKD) and affect as many as 8% of adults from the United States¹ and 6% of adults from Germany.²

Higher levels of albuminuria, even within the low normal range, are associated with not only increased risks of ESRD but also cardiovascular disease and mortality.^{3–6} Moreover, the presence of albuminuria offers key prognostic information at each stage of decline in GFR.⁷ However, the pathophysiologic basis of albuminuria remains incompletely understood, and as a result, interventions for the prevention and treatment of albuminuria are limited.

Diabetes mellitus and hypertension are key risk factors for albuminuria, but neither of these factors fully account for the high prevalence of albuminuria nor its association with adverse health outcomes.⁸ Heritability of albuminuria ranges from 0.16 to 0.49 in families enriched with hypertension or diabetes.^{9,10} Rare genetic variants are known to cause monogenic diseases featuring severe, nephrotic range proteinuria.¹¹ However, linkage or candidate gene studies have not reproducibly identified common genetic variants in association with lower levels of albuminuria.^{9,10} Given recent successes in the use of genome-wide association studies (GWAS) of quantitative traits that can lead to the identification of relevant variants for a disease phenotype,^{12,13} we conducted a genome-wide association (GWA) analysis of albuminuria in 31,580 participants of European ancestry from the CKDGen Consortium, with follow-up in 27,746 additional participants. Albuminuria was analyzed as the quantitative trait urinary albumin-to-creatinine ratio (UACR) and as the dichotomous trait microalbuminuria (MA). Concurrently, we performed an analysis of albuminuria in the CARE Consortium using the ITMAT/Broad/CARE Vascular Disease 50k (IBC) single-nucleotide polymorphism (SNP) chip array¹⁴ in 19,499 Europeans and 6981 African Americans. Here, we report the results of our combined findings.

RESULTS

Study Samples

Basic characteristics of the participants from the studies in CKDGen and CARE are shown in [Table 1](#). Studies in these consortia are primarily population-based, with mean age ranging from 42 to 74 years. Details regarding study-specific genotyping information can be found in Supplemental Table 1, A and B, and in the Supplemental Text (Methods).

CKDGen Stage 1

[Figure 1A](#) and Supplemental Figure 1A show the Manhattan plots of the meta-analysis *P* values for UACR and microalbuminuria (UACR >25 mg/g [women], >17 mg/g [men]), respectively. Meta-analysis of GWAs from CKDGen stage 1 showed that no locus achieved genome-wide significance ($P < 5.0 \times 10^{-8}$) for either UACR or microalbuminuria in both the overall and the nondiabetic analyses. Supplemental Figure 2, A and B, shows the quantile-quantile plot of the UACR and microalbuminuria meta-analysis results.

CKDGen Stage 2 Follow-up

In CKDGen, the 16 top independent SNPs (*P* value range 1.1×10^{-7} to 5.7×10^{-6}) were moved into stage 2 follow-up in 15 additional studies ($n = 27,746$ individuals of European descent). These SNPs and their study-specific imputation scores are displayed in Supplemental Tables 2 and 3, respectively. Supplemental Table 4 shows the results of these 16 SNPs for all analyzed traits.

Overall, rs1801239, a missense SNP (T→C) located in *CUBN* on chromosome 10 (minor allele frequency = 0.10), demonstrated direction-consistent association in stage 2 ($P = 0.02$, [Table 2](#)), with a genome-wide significant *P* value of 4.0×10^{-8} for UACR in the combined stage 1 and stage 2 analysis

(Supplemental Tables 2 and 4). The regional association plot for *CUBN* is shown in Figure 2A. The minor C allele of rs1801239 in *CUBN* leads to an isoleucine-to-valine substitution (I2984V) in the encoded protein cubilin, which is predicted to be “probably benign” (SIFT,¹⁵ FastSNP,¹⁶ and PolyPhen¹⁷). No additional nonsynonymous coding variants in high LD to rs1801239 ($r^2 > 0.2$) were observed in dbSNP. Because albuminuria is a risk factor for progressive CKD, we assessed whether rs1801239 is associated with estimated GFR (eGFR) and CKD in the CKDGen eGFR data set. Among 67,093 individuals with available data, we observed no association with eGFR ($P = 0.53$) or CKD ($P = 0.33$).¹⁸

The second highest ranking SNP for UACR in the combined stage 1 and stage 2 analysis was rs17319721, an intronic SNP in *SHROOM3* (Supplemental Table 4). The minor allele (A) of rs17319721 is associated with lower albuminuria levels, and we have previously identified this same allele in association with lower eGFR.¹⁹

CARe IBC SNP Array Stage 1

Concurrently, the CARe Consortium carried out a large densely tagged candidate gene screen using the IBC SNP array¹⁴ and identified the same SNP (rs1801239) in *CUBN* in association with UACR ($P = 2.9 \times 10^{-10}$; Table 2 and Figure 1B) and microalbuminuria (2100 cases and $P = 2.4 \times 10^{-7}$; Table 2) in 19,499 European Americans. The regional association plot for the *CUBN* tagging SNPs on the IBC array in the CARe European Americans is shown in Figure 2B. The only other significant SNP (significance threshold defined as $P < 2.2 \times 10^{-6}$ for the IBC array) in the CARe IBC analysis for UACR was rs13177732 ($P = 4.7 \times 10^{-7}$), but this SNP did not replicate in CKDGen stage 1 (discovery) studies after excluding overlapping studies ($n = 16,667$, $P = 0.71$ for UACR).

Joint CKDGen/CARe Analyses in Samples of European Ancestry

Because three of the studies from CARe (ARIC, CHS, and FHS) were also part of CKDGen, we removed them from CKDGen to avoid duplication. The overall P value for CKDGen stage 1 (after removing ARIC, CHS, and FHS), CKDGen stage 2 follow-up (after removing the ARIC in silico replication samples), and the CARe stage 1 analysis in participants of European ancestry for the association between rs1801239 and UACR was 1.1×10^{-11} ($n = 63,153$; Table 2), with 0.15% of the UACR variance explained by rs1801239. The study-specific association results are shown in Supplemental Figure 3A; there was no significant heterogeneity across studies ($I^2 = 19.6\%$, P value for heterogeneity = 0.18). The odds ratio for microalbuminuria per copy of the minor C allele at rs1801239 was 1.06 ($P = 0.001$; Table 2).

CARe African-American IBC SNP Array Results

Because albuminuria is an important manifestation of CKD across ethnicities, we examined rs1801239 in 6981 African-American CARe participants (1159 microalbuminuria cases) and found that the minor C allele (frequency = 0.03) was consistently associated with higher UACR ($P = 0.005$, explaining 0.06% of the UACR variance) and the presence of microalbuminuria. Each copy of the C allele at rs1801239 was associated with an odds ratio of 1.42 for microalbuminuria ($P = 0.008$; Table 2). The study-specific association results for UACR are shown in Supplemental Figure 3B. Given the potential for allelic heterogeneity across ethnic groups and the availability of densely genotyped IBC chip data, we further investigated the *CUBN* region (Figure 2C) to determine if there were any other SNPs that showed stronger association with UACR and microalbuminuria in African Americans. We uncovered rs1996316 in the *CUBN* gene region (minor allele frequency = 0.33, P value = 0.0009). The SNP rs1996316 was not correlated with rs1801239 ($r^2 = 0.01$); however, this SNP did not meet statistical significance after

correcting for multiple testing of 158 SNPs in the region ($0.05/158 = 0.0003$), nor was it associated with UACR in individuals of European descent from CKDGen ($P = 0.65$) or CARE ($P = 0.36$).

Stratified Analysis

Because hypertension and diabetes are key risk factors for albuminuria, we performed stratified analyses for rs1801239 in the joint CKDGen/CARE analysis of populations of European descent. For UACR, we observed significant association among individuals with ($n = 4915$; $P = 0.006$) and without ($P = 3.2 \times 10^{-8}$) diabetes as well as among individuals with ($n = 13,097$, $P = 7.5 \times 10^{-8}$) and without ($P = 1.3 \times 10^{-6}$) hypertension. Similar findings across these groups were also observed for microalbuminuria (Table 2). In particular, among individuals with diabetes, each copy of the C allele at rs1801239 was associated with an odds ratio of 1.27 for microalbuminuria (95% CI: 1.11 to 1.45).

To investigate if CKD modifies the association between rs1801239 and UACR, we performed an analysis of rs1801239 and UACR in 6 of the largest cohorts in CKDGen stratified by CKD status. We found that the association of the *CUBN* C allele and UACR was of similar magnitude among participants with CKD ($n = 1808$, $\beta = 0.09$, $P = 0.26$) as compared with those without CKD ($n = 21299$, $\beta = 0.10$, $P = 9.6 \times 10^{-11}$), although the power was low in the CKD stratum because of its smaller sample size.

Independent Replication in the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)

To understand the potential impact of rs1801239 on microalbuminuria in a high-risk population, we tested the association of rs1801239 with time to persistent microalbuminuria over 20 years of follow-up among 1304 participants of European ancestry with type 1 diabetes from the DCCT/EDIC Study (mean baseline age 26.7 years). With use of survival analysis, the minor C allele was associated with an increased risk of incident persistent microalbuminuria. Individuals with diabetes with one copy of the C allele had a 42% greater risk of developing persistent microalbuminuria than their counterparts with zero copies of the C allele (hazard ratio 1.42 per copy of the C allele, $P = 0.02$; Table 2). This association was essentially unchanged with further multivariable adjustment (Table 2).

DISCUSSION

We have identified and validated a missense SNP in the *CUBN* gene that is associated with albuminuria. This association is robust across subgroups defined by diabetes and hypertension, two major risk factors for albuminuria, and among populations of both European and African ancestry. Finally, we have validated this finding in association with persistent microalbuminuria among patients with type 1 diabetes from the DCCT/EDIC Study.

Cubilin was first identified as the intrinsic factor/vitamin B12 complex receptor in the ileal mucosa.²⁰ In the kidney, cubilin is expressed predominantly in the apical brush border of proximal tubular cells.²¹ We queried publicly available expression databases^{22–24} but did not find evidence for altered gene expression associated with the conservative amino acid substitution in cubilin encoded by rs1801239 (I2984V). On the basis of UniProt, the amino acid position 2984 is part of the 22nd, out of a total of 27, CUB domains. *In vitro*, CUB domains 22 through 27 demonstrated Ca^{2+} -dependent binding to megalin.²⁵ Together with megalin (*LRP2*) and amnionless (*AMN*), cubilin plays a key role in the receptor-mediated endocytotic reabsorption of albumin and other low-molecular-weight proteins.²⁶ Interrogation of these respective genomic regions in our data did not reveal any significant findings. The process of endocytotic reabsorption of albumin is of importance because an estimated 3 g of albumin per day are not retained by the glomerular filter and enter the primary urine.²⁶ Yet urine in its

final composition is nearly devoid of proteins in healthy humans, highlighting the effectiveness of the tubular reabsorptive process to prevent significant protein loss.

The essential role of the cubilin-megalin complex in the reuptake of albumin by the proximal tubule has been demonstrated in both animal and human studies.^{26, 27} For example, dogs with a functional defect in cubilin and mice lacking cubilin and/or megalin excrete large amounts of urinary albumin.^{27, 28} Similarly, humans with Imerslund-Gräsbeck disease (OMIM #261100), a rare autosomal-recessive condition caused by a variety of mutations in the *CUBN* gene or the cubilin-associated *AMN* gene, typically have anemia with varying degrees of proteinuria²⁹ as a result of a molecular defect leading to inefficient proximal tubular protein reabsorption.

Dysfunction of the megalin-cubilin system has also been implicated in the pathogenesis of diabetic kidney disease. In rat models, renal tubular expression of cubilin is decreased³⁰ and reabsorption of filtered albumin by the proximal tubule has been shown to be altered.^{31, 32} In humans, shedding of megalin and cubilin in urine is increased in individuals with type 1 diabetes and microalbuminuria compared with nonalbuminuric controls.³³ These studies suggest that reduced expression or loss of the cubilin-megalin complex may contribute to the albuminuria of early diabetic kidney disease via reduced tubular reuptake of filtered albumin, which is supported by our observed association of rs1801239 with incident persistent microalbuminuria in the DCCT/EDIC Study.

Our results suggest that levels of albuminuria in the general population are determined in part by tubular reabsorption, and not only by glomerular filtration. Although the prognostic implications of tubular as compared with glomerular albuminuria remain to be determined, a pathogenic role for tubular albuminuria, in addition to glomerular, has been demonstrated in experimental data.³⁴⁻³⁶ The identification of a SNP that is associated with albuminuria among individuals irrespective of diabetes or hypertension status suggests some common pathophysiology that is independent of these known albuminuria risk factors. The *CUBN* SNP we identified is specifically associated with albuminuria, and not with eGFR. Finally, results from the DCCT/EDIC Study underscore the relative strength of the *CUBN* SNP in association with persistent microalbuminuria that is comparable in magnitude to other albuminuria risk factors in patients with diabetes, including diabetes duration, BP, hemoglobin A1c, and obesity.³⁷⁻³⁹

Important strengths of this study include consistency of association across populations of European and African descent and across groups defined by diabetes and hypertension, as well as the known role of cubilin in tubular albumin reabsorption. The exploration of genetic determinants for albuminuria in predominantly population-based cohorts reduces confounding by disease progression, which may be related to important nongenetic factors. Nonetheless, some limitations warrant mention. First, the causal nature of the missense SNP in *CUBN* is unclear. Second, urine albumin and creatinine were assessed with different assays and at one point in time in most studies, which may lead to misclassification of the outcome and bias our results toward the null hypothesis. However, this is unlikely to yield a true positive finding.

In summary, through a series of genetic association analyses, we have identified a missense SNP in the *CUBN* gene that is associated with higher levels of albuminuria among individuals of European and African descent with and without diabetes or hypertension. These findings highlight a novel genetic susceptibility for albuminuria that is consistent across multiple study populations and shared across diverse clinical settings.

CONCISE METHODS

Overall Study Design

Genetic association testing for urinary albumin-to-creatinine ratio (UACR) and MA was performed in the CKDGen and CARE cohorts of European ancestry, with further follow-up genetic analysis of significant SNPs in CARE cohorts of African-American ancestry and in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study.

A graphical overview is given in Supplemental Figure 4.

CKDGen Stage 1 Discovery Meta-analysis

In the stage 1 (discovery) meta-analysis we searched for SNPs associated with UACR or MA in 12 CKDGen population-based cohorts totaling $n = 31,580$ patients of European descent. Individual GWA analyses encompassing approximately 2.5 million imputed SNPs were performed within each of the 12 stage 1 (discovery) CKDGen population-based cohorts. In each cohort, these analyses were performed in the overall group and separately in patients without diabetes. Next, we conducted four meta-analyses combining the study-specific UACR or MA GWA analysis results (i) including all patients and (ii) separately in patients without diabetes. From these four sets of meta-analysis results, we selected a list of independent SNPs (pairwise $r^2 < 0.2$) with a P value $< 1 \times 10^{-6}$ and minor allele frequencies (MAF) $> 5\%$. The 16 highest ranking SNPs from this list were then selected for CKDGen stage 2 follow-up to replicate our findings.

CKDGen Stage 2 Follow-up Meta-analysis

Association testing for each of the 16 SNPs for UACR and MA was performed in each of the 15 independent CKDGen stage 2 cohorts totaling $n = 27,746$ individuals of European descent, again, including all patients and separately in patients without diabetes. Study-specific association results of the 16 SNPs were then meta-analyzed across stage 2 studies.

SNPs showing evidence of replication in CKDGen stage 2 were further evaluated for their effects both in the presence and absence of diabetes and hypertension as major risk factors of albuminuria.

CARE Discovery Association Analysis

The CARE Consortium consists of nine studies. For the present analysis, we included five studies in European Americans (19,499 patients in total) and five studies in African Americans (6981 patients in total) with the IBC SNP chip.¹⁴ Study-specific genetic association analysis of UACR and MA were performed in the same manner as in CKDGen. CARE study-specific results were then meta-analyzed within each ethnic group for both UACR and MA.

Joint CKDGen and CARE Meta-analysis

For SNPs that reached genome-wide significance in the combined CKDGen stage 1 and stage 2 meta-analysis and were also significant in the CARE meta-analysis, we conducted meta-analyses for UACR and MA across a total of 28 nonoverlapping cohorts: in 9 CKDGen stage 1 studies with 16,667 patients (excluding ARIC, CHS, and FHS since they were also members of the CARE Consortium), 14 CKDGen stage 2 follow-up studies with 26,987 patients (excluding ARIC in silico results), and 5 CARE European American cohorts with 19,499 patients, involving a total of 63,153 patients of European descent.

Follow-up Analysis in DCCT/EDIC

Significant SNPs from the joint CKGen and CARE meta-analysis were replicated in the DCCT/EDIC Study, which currently consists of 1304 Caucasian participants who underwent genotyping on the

Illumina 1M SNP chip. This is a longitudinal study using Cox proportional hazards models to analyze time to renal events (see definition of the outcome below).

Study-Specific Information and Statistical Analysis

In all studies, all participants gave informed consent. All studies were approved by their appropriate Research Ethics Committees.

A list of all contributing studies is given in [Table 1](#) and more study-specific information including genotyping and imputation methods are given in Supplemental Table 1, A and B, as well as in the Study-Specific Methods Section of the Supplemental material. Details on statistical analyses on the study-specific level as well as for meta-analyses are given in the Supplemental material.

Outcomes and Covariates

In each of the CKDGen and CARE studies, the continuous outcome urinary albumin-to-creatinine ratio (mg/g, measured as described in the Study-Specific Methods section in the Supplemental material) as well as the dichotomous outcome microalbuminuria (MA, defined as urinary albumin-to-creatinine ratio >17 mg/g for men and >25 mg/g for women^{40, 41}) were analyzed. For creating the continuous trait UACR used in the analysis, urinary albumin-to-creatinine ratio was log-transformed, and sex-specific residuals were computed by regression on age and, in multicenter studies, on study center.

Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or treatment; and diabetes was defined as fasting plasma glucose of at least 126 mg/dl or treatment if not stated otherwise in the study-specific methods. We estimated GFR (eGFR) using the four-variable MDRD formula as described previously¹⁸ to determine the prevalence of chronic kidney disease (defined as eGFR < 60 ml/min per 1.73 m²) in each cohort.

In DCCT/EDIC, renal outcomes were (1) time from DCCT baseline until persistent microalbuminuria, defined as time to two consecutive albumin excretion rates (AERs) > 30 mg/24 h (> 20.8 μ g/min), and (2) severe nephropathy, defined as the time to AER > 300 mg/24 h (> 208 μ g/min) with prior persistent microalbuminuria or end-stage renal disease).

Genotypes

All the studies in CKDGen stage 1 had genotype data from genome-wide SNP arrays available, whereas the studies in the CARE Discovery studies genotyped the IBC SNP array,¹⁴ a gene-centric array containing 50,000 SNPs tagging genes across a range of cardiovascular, metabolic, and inflammatory syndromes. In CKDGen, the genotyped SNPs were imputed to approximately 2.5 million HapMap SNPs based on HAPMAP CEU samples. Imputation provides a common SNP panel across all studies to facilitate a meta-analysis across all contributing SNPs. Information on study-specific genotyping platforms and imputation procedures are presented in Supplemental Table 1, A and B. Information on genotyping in CKDGen stage 2 cohorts are given in the Study-Specific Methods section of the Supplemental material.

DISCLOSURES

Dawn Waterworth and Vincent Mooser are employees of GlaxoSmithKline.

Supplementary Material

Supplemental Data:

Acknowledgments

Author contributions:

Study design: E.I., J.A., S.K., R.R., K.E., S.S., H.V., N.J.W., P.P.P., B.P., F.K., Y.L., T.B.H., C.H., O.D., O.P., H.C., I.R., V.V., P.V., G.W., V.M., D.W., E.B., J.C., W.H.L.K., A.K., A.P., I.H.D., N.L.G., M.G.S., L.F., C.A.B., M.O., T.I., H.E.W., I.M.H., M.S., A.T., P.K., C.S.F., L.L., T.B.H., V.G., E.I., J.A., A.D.P., S.B.B., DCCT/EDIC.

Study management: E.I., J.A., S.K., S.T., R.R., K.E., R.B., H.V., R.F.J.L., N.J.W., C.P., C.F., P.P.P., B.K., L.K., B.P., F.K., S.C., Y.L., T.B.H., O.P., H.C., I.R., P.V., G.W., V.M., D.W., E.B., J.C., W.H.L.K., A.P., B.D.M., A.R.S., T.T., C.A.B., M.O., T.I., J.B., H.E.W., W.K., B.K.K., I.M.H., A.Tö., C.S.F., G.E., L.L., T.B.H., V.G., E.I., J.A., K.A., A.D.P., DCCT/EDIC, G.N., P.V.D.H., S.J.L.B.

Patient recruitment: J.A., S.T., R.R., R.B., S.S., H.V., N.J.W., P.P.P., B.P., T.B.H., O.P., I.R., P.V., G.W., J.C., B.D.M., A.R.S., T.I., H.E.W., A.T., C.S.F., G.E., V.G., G.C., J.A., S.H., K.A., DCCT/EDIC, N.H., S.J.L.B., G.N., E.I., J.A., A.S.

Interpretation of results: E.I., J.A., S.K., M.A., S.T., E.A., R.R., K.E., A.T., H.K.K., R.B., S.S., H.V., C.P., C.F., C.M., P.P.P., B.K., B.P., F.K., S.C., Y.L., T.S.L., T.B.H., C.H., O.D., V.V., J.B., M.B., J.C., W.H.L.K., A.K., A.P., I.H.D., N.L.G., M.G.S., J.E., C.A.B., M.O., W.K., B.K.K., P.V.D.H., S.J.L.B., G.N., I.M.H., C.S.F., L.A.C., C.-T.L., A.D., E.I., J.A., A.D.P., S.B.B., DCCT/EDIC, A.D.J.

Manuscript writing: S.K., R.R., C.P., J.B., M.B., W.H.L.K., A.K., A.P., I.H.D., C.A.B., M.O., I.M.H., C.S.F., C.O.S., J.B.M., L.A.C., C.-T.L., A.D., A.T., M.H.C.

Critical review of manuscript: E.I., J.A., A.C.S., S.T., R.R., K.E., A.T., H.K.K., R.B., S.S., H.V., J.L., J.Z., R.F.J.L., N.J.W., C.P., C.F., C.M., P.P.P., B.K., L.K., B.P., F.K., S.C., Y.L., K.L., T.S.L., T.B.H., C.H., O.D., O.P., H.C., I.R., V.V., Z.K., S.B., P.V., G.W., V.M., D.W., J.B., M.B., D.E.K., E.B., J.C., W.H.L.K., A.K., A.P., B.D.M., A.R.S., I.H.D., N.L.G., T.L., D.S.S., B.M.P., B.K., T.H., M.G.S., C.A.B., M.O., T.I., J.B., H.E.W., W.K., B.K.K., I.M.H., M.S., A.T., P.K., I.P., C.S.F., S.J.H., Q.Y., C.O.S., J.B.M., A.V.S., T.A., G.E., L.L., T.B.H., V.G., L.A.C., C.-T.L., E.A., G.C., E.I., J.A., A.C.S., A.D.J., H.K., J.I.R., J.G.M., C.P., R.M., M.R., R.T., M.H.C., N.H., S.J.L.B., G.N., P.V.D.H., A.D.J., J.C.F., N.F., A.Te., A.Ti., A.Tö.

Statistical methods and analysis: E.I., M.A., E.A., A.Te., J.L., J.Z., C.P., C.F., B.K., F.K., S.C., Y.L., K.L., C.H., V.V., Z.K., S.B., D.E.K., M.L., A.K., J.O., N.L.G., T.L., T.T., J.E., C.A.B., M.O., I.M.H., I.P., C.S.F., J.H., A.V.S., T.A., V.G., L.A.C., C.-T.L., X.L., E.A., A.Ti., E.I., J.A., R.M., A.D.P., S.B.B., P.V.D.H., G.N., S.J.L.B., DCCT/EDIC, M.H.C.

Genotyping: A.C.S., M.A., A.Ti., H.K.K., R.F.J.L., N.J.W., F.K., S.D., Y.L., C.H., V.V., E.B., T.H., D.H., C.A.B., T.I., H.E.W., P.K., G.C., A.C.S., J.I.R., S.H., F.S., A.D.P., S.C., E.I., J.A., A.S., P.V.D.H., A.Te., A.Ti.

Bio-informatics: E.I., A.D.J., H.K.K., J.L., J.Z., C.F., K.L., C.H., V.V., Z.K., S.B., E.B., J.O., N.L.G., C.A.B., M.O., I.M.H., I.P., S.J.H., Q.Y., A.V.S., T.A., E.I., J.G.M., M.H.C., P.V.D.H., A.Te., A.Ti.

AMISH: The Amish studies are supported by grants and contracts from the NIH including R01 AG18728 (Amish Longevity Study), R01 HL088119 (Amish Calcification Study), U01 GM074518-04 (PAPI Study), U01 HL072515-06 (HAPI Study), U01 HL084756 and NIH K12RR023250 (University of Maryland MCRDP), NIH P30 DK072488 (Clinical Nutrition Research Unit of Maryland), and NIH P60 DK079637 (Baltimore Diabetes Research and Training Center). The University of Maryland General Clinical Research Center, grant M01 RR 16500, the Baltimore Veterans Administration Medical Center

Geriatrics Research and Education Clinical Center, and the Paul Beeson Physician Faculty Scholars in Aging Program. We thank our Amish research volunteers for their long-standing partnership in research, and the research staff at the Amish Research Clinic for their hard work and dedication.

ARIC: The Atherosclerosis Risk in Communities study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, R01HL087641, R01HL59367, and 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 numbers UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

BLSA: This study was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. A portion of that support was through a R&D contract with MedStar Research Institute.

CHARGE Consortium: We acknowledge the individual participating studies and investigators of the CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) consortium (AGES, ARIC, CHS, Framingham Heart Study, Rotterdam Study).

CHS: The Cardiovascular Health Study (CHS) research reported in this article was supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133, grants U01 HL080295 and R01 HL087652, and R01 AG027002 from the National Heart, Lung and Blood Institute, with additional contribution from the National Institute of Neurologic Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/pi.htm>. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

CKDGen Consortium: We thank all members of the CKDGen Consortium who contributed toward the eGFR and CKD data; all names are listed at the end of the acknowledgments.

CoLaus: The CoLaus authors thank Yolande Barreau, Mathieu Firmann, Vladimir Mayor, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sagnet, Jeanne Ecoffey, and Sylvie Mermoud for data collection. The CoLaus study received financial contributions from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (33CSCO-122661, 3200BO-111361/2, 3100AO-116323/1, and 310000-112552), the Swiss School of Public Health Plus, the Giorgi-Cavaglieri Foundation, and the European Framework Project 6 (EuroDia, AnEuploidy, and Hypergenes projects).

EPIC: The EPIC Norfolk Study is funded by program grants from the Medical Research Council UK and Cancer Research UK, and by additional support from the European Union, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, and the Wellcome Trust.

FENLAND: We are grateful to all of the volunteers for their time and help, and to the general practitioners and practice staff for help with recruitment. We thank the Fenland Study Co-ordination team, the Field Epidemiology team, and the Fenland Study Investigators. The albuminuria measurement was performed by the Department of Clinical Biochemistry and Immunology. The Fenland Study is funded by the Wellcome Trust and the Medical Research Council, as well as by the

Support for Science Funding program and CamStrad.

Framingham Heart Study: This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (contract no. N01-HC-25195) and its contract with Affymetrix, Inc. for genotyping services (contract no. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. The albuminuria measurement was supported by an American Diabetes Association Research Grant and by donation of microalbuminuria assay reagents from Roche Diagnostics Inc.

KORA: The genetic epidemiologic work was funded by the NIH subcontract from Children's Hospital, Boston, (H.E.W. and I.M.H, prime grant 1 R01 DK075787-01A1), the German National Genome Research Net NGFN2 and NGFNplus (H.E.W. 01GS0823; WK project A3, number 01GS0834), the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ, and by the Else Kröner-Fresenius-Stiftung (P48/08//A11/08; C.A.B. and B.K.K.). The kidney parameter measurements in F3 were funded by the Else Kröner-Fresenius-Stiftung (C.A.B. and B.K.K.) and the Regensburg University Medical Center, Germany; in F4 by the University of Ulm, Germany (W.K.). Genome-wide genotyping costs in F3 and F4 were in part funded by the Else Kröner-Fresenius-Stiftung (C.A.B. and B.K.K.). *De novo* genotyping in F3 and F4 were funded by the Else Kröner-Fresenius-Stiftung (C.A.B. and B.K.K.). The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, by the German Federal Ministry of Education and Research and by the State of Bavaria. Genotyping was performed in the Genome Analysis Center (GAC) of the Helmholtz Zentrum München. The LINUX platform for computation was funded by the University of Regensburg for the Department of Epidemiology and Preventive Medicine at the Regensburg University Medical Center.

MICROS: We owe a debt of gratitude to all participants. We thank the primary care practitioners Raffaella Stocker, Stefan Waldner, Toni Pizzocco, Josef Plangger, Ugo Marcadent, and the personnel of the Hospital of Silandro (Department of Laboratory Medicine) for their participation and collaboration in the research project. In South Tyrol, the study was supported by the Ministry of Health and Department of Educational Assistance, University and Research of the Autonomous Province of Bolzano, and the South Tyrolean Sparkasse Foundation.

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 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs, and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Genome-wide data have been supported by the Federal Ministry of Education and Research (grant 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany, and the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the "Center of Knowledge Interchange" program of the Siemens AG.

CARe Consortium: The authors wish to acknowledge the support of the National Heart, Lung and Blood Institute and the contributions of the research institutions, study investigators, field staff, and study participants in creating this resource for biomedical research. The following nine parent studies have contributed parent study data, ancillary study data, and DNA samples through the Massachusetts

Institute of Technology-Broad Institute (N01-HC-65226) to create this genotype/phenotype database for wide dissemination to the biomedical research community:

Atherosclerotic Risk in Communities (ARIC): University of North Carolina at Chapel Hill (N01-HC-55015), Baylor Medical College (N01-HC-55016), University of Mississippi Medical Center (N01-HC-55021), University of Minnesota (N01-HC-55019), Johns Hopkins University (N01-HC-55020), University of Texas, Houston (N01-HC-55022), University of North Carolina, Forsyth County (N01-HC-55018). *Cardiovascular Health Study (CHS)*: University of Washington (N01-HC-85079), Wake Forest University (N01-HC-85080), Johns Hopkins University (N01-HC-85081), University of Pittsburgh (N01-HC-85082), University of California, Davis (N01-HC-85083), University of California, Irvine (N01-HC-85084), New England Medical Center (N01-HC-85085), University of Vermont (N01-HC-85086), Georgetown University (N01-HC-35129), Johns Hopkins University (N01-HC-15103), University of Wisconsin (N01-HC-75150), Geisinger Clinic (N01-HC-45133), University of Washington (N01-HC-55222, U01 HL080295). *Cleveland Family Study (CFS)*: Case Western Reserve University (NIH HL 46380, M01RR00080). *Cooperative Study of Sickle Cell Disease (CSSCD)*: University of Illinois (N01-HB-72982, N01-HB-97062), Howard University (N01-HB-72991, N01-HB-97061), University of Miami (N01-HB-72992, N01-HB-97064), Duke University (N01-HB-72993), George Washington University (N01-HB-72994), University of Tennessee (N01-HB-72995, N01-HB-97070), Yale University (N01-HB-72996, N01-HB-97072), Children's Hospital-Philadelphia (N01-HB-72997, N01-HB-97056), University of Chicago (N01-HB-72998, N01-HB-97053), Medical College of Georgia (N01-HB-73000, N01-HB-97060), WA University (N01-HB-73001, N01-HB-97071), Jewish Hospital and Medical Center of Brooklyn (N01-HB-73002), Trustees of Health and Hospitals of the City of Boston, Inc. (N01-HB-73003), Children's Hospital-Oakland (N01-HB-73004, N01-HB-97054), University of Mississippi (N01-HB-73005), St. Luke's Hospital-New York (N01-HB-73006), Alta Bates-Herrick Hospital (N01-HB-97051), Columbia University (N01-HB-97058), St. Jude's Children's Research Hospital (N01-HB-97066), Research Foundation, State University of New York-Albany (N01-HB-97068, N01-HB-97069), New England Research Institute (N01-HB-97073), Interfaith Medical Center-Brooklyn (N01-HB-97085). *Coronary Artery Risk in Young Adults (CARDIA)*: University of Alabama at Birmingham (N01-HC-48047), University of Minnesota (N01-HC-48048), Northwestern University (N01-HC-48049), Kaiser Foundation Research Institute (N01-HC-48050), University of Alabama at Birmingham (N01-HC-95095), Tufts-New England Medical Center (N01-HC-45204), Wake Forest University (N01-HC-45205), Harbor-UCLA Research and Education Institute (N01-HC-05187), University of California, Irvine (N01-HC-45134, N01-HC-95100). *Framingham Heart Study (FHS)*: Boston University (N01-HC-25195, R01 HL092577-01A1, R01 HL076784, R01 AG028321). *Jackson Heart Study (JHS)*: Jackson State University (N01-HC-95170), University of Mississippi (N01-HC-95171), Tougaloo College (N01-HC-95172). *Multi-Ethnic Study of Atherosclerosis (MESA)*: University of Washington (N01-HC-95159), Regents of the University of California (N01-HC-95160), Columbia University (N01-HC-95161), Johns Hopkins University (N01-HC-95162, N01-HC-95168), University of Minnesota (N01-HC-95163), Northwestern University (N01-HC-95164), Wake Forest University (N01-HC-95165), University of Vermont (N01-HC-95166), New England Medical Center (N01-HC-95167), Harbor-UCLA Research and Education Institute (N01-HC-95169), Cedars-Sinai Medical Center (R01-HL-071205), University of Virginia (subcontract to R01-HL-071205). *Sleep Heart Health Study (SHHS)*: Johns Hopkins University (U01 HL064360), Case Western University (U01 HL063463), University of California, Davis (U01 HL053916), University of Arizona (U01 HL053938), University of Minnesota (relocating in 2006 to Univ Arizona) (U01 HL053934), University of Pittsburgh (U01 HL077813), Boston University (U01 HL053941), MedStar Research Institute (U01 HL063429), Johns Hopkins University (U01 HL053937).

Stage 2 Cohorts: AGES: The Age, Gene/Environment Susceptibility—Reykjavik Study has been funded by NIH contract N01-AG-12100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The researchers are indebted to the participants for their willingness to participate in the study.

AMISH: see above details for the Amish study; Replication genotyping was funded by the Else Kröner-Fresenius-Stiftung (P48/08//A11/08; to C.A. Böger, B.K. Krämer).

DCCT/EDIC: The DCCT/EDIC Research Group is sponsored through research contracts from the National Institute of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institutes of Health. The authors are grateful to the patients in the DCCT/EDIC cohort for their long-term participation. A.D.P. holds a Canada Research Chair in the Genetics of Complex Diseases. This work has received support from National Institute of Diabetes and Digestive and Kidney Diseases Contract N01-DK-6-2204, National Institute of Diabetes and Digestive and Kidney Diseases Grant R01-DK-077510 and support from the Canadian Network of Centres of Excellence in Mathematics and Genome Canada through the Ontario Genomics Institute. Clinical data and DNA from the DCCT/EDIC study will be made available through the National Institute of Diabetes and Digestive and Kidney Diseases repository at <https://www.niddkrepository.org/niddk/home.do>. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health.

GENOA: The GENOA Study genome-wide association study was funded by NHLBI R01-HL087660

Health ABC: This research was supported by NIA contracts N01AG62101, N01AG62103, and N01AG62106. The genome-wide association study was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

HUNT: The HUNT Study is a collaboration between the HUNT Research Center, Faculty of Medicine, Norwegian University of Science and Technology; The Norwegian Institute of Public Health; Nord-Trøndelag County Council; and Central Norway Regional Health Authority. The authors thank the health service and people of Nord-Trøndelag for their endurance and participation.

KORCULA: This study was supported through the grants from the Medical Research Council UK; and Ministry of Science, Education and Sport of the Republic of Croatia (no. 108-1080315-0302) and the European Union framework program 6 EUROSPAN project (contract LSHG-CT-2006-018947). We would like to acknowledge the invaluable contributions of the recruitment team in Korcula, the administrative teams in Croatia and Edinburgh, and the people of Korcula. The albuminuria measurements were supported by grants from the Belgian agencies FNRS and FRSM (3.4.592.06F), the “Fondation Alphonse & Jean Forton”, the Programme d'excellence “Marshall” DIANE convention from the Region Wallonne, the Interuniversity Attraction Pole (IUAP P6/05), and the Genecure (FP6) and EUNEFRON (FP7, GA#201590) programs of the European Community. We would also like to thank S. Druart and N. Amraoui for excellent technical assistance.

Nurses Health Study: This study is supported by the National Institutes of Health grants DK007791, DK066574, CA087969, and CA050385. Replication genotyping was funded by the NHLBI Intramural research program and the Center for Population Studies.

PREVEND: PREVEND study is supported by the Dutch Kidney Foundation (Grant E033), The Netherlands Heart Foundation (Grant 2006B140, 2006T003), and the EU project grant GENECURE (FP-6 LSHM CT 2006 037697). P. van der Harst is supported by NWO VENI grant 916.76.170 and the ICIN.

SAPHIR: The SAPHIR study was partially supported by a grant from the Kamillo Eisner Stiftung from the Medizinische Forschungsgesellschaft Salzburg, from the Paracelsus Medical University Salzburg (08/07/039) to B. Paulweber, and by grants from the “Genomics of Lipid-associated Disorders – GOLD” of the “Austrian Genome Research Programme GEN-AU” and the Austrian Heart Fund to F. Kronenberg. Replication genotyping was funded by the Else Kröner-Fresenius-Stiftung (P48/08//A11/08; to C.A. Böger and B.K. Krämer).

SORBS: This work was supported by grants from the Interdisciplinary Centre for Clinical Research at the University of Leipzig (B27 to M.S., P.K., and A.T.; N06 to P.K.) and from the German Diabetes Association (to A.T. and P.K.). M.S. is supported by a grant from the DFG (KFO 152). R.M. is funded by European Commission under the Marie Curie Intra-European Fellowship. We would like to thank Knut Krohn from the Microarray Core Facility of the Interdisciplinary Centre for Clinical Research (IZKF), University of Leipzig, Germany, Joachim Thiery, Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University of Leipzig, Germany, Nigel William Rayner from the Wellcome Trust Centre for Human Genetics, University of Oxford, U.K., and John Broxholm from the Bioinformatics Core Unit of the Wellcome Trust Centre for Human Genetics, Oxford, U.K., for their excellent support.

SPLIT: This study was supported through the grants from the Medical Research Council UK and Ministry of Science, Education and Sport of the Republic of Croatia (no. 108-1080315-0302). We would like to acknowledge the invaluable contributions of the recruitment team from the Croatian Centre for Global Health, University of Split, the administrative teams in Croatia and Edinburgh (Rosa Bisset), and the people of Split. The albuminuria measurements were supported by grants from the Belgian agencies FNRS and FRSM (3.4.592.06F), the “Fondation Alphonse & Jean Forton”, the Programme d'excellence “Marshall” DIANE convention from the Region Wallonne, the Interuniversity Attraction Pole (IUAP P6/05), and the Genecure (FP6) and EUNEFRON (FP7, GA#201590) programs of the European Community. We would also like to thank S. Druart and N. Amraoui for excellent technical assistance.

ULSAM: Genotyping was performed by the SNP Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman, and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University and the Knut and Alice Wallenberg Foundation. E.I. is supported by grants from the Swedish Research Council, the Swedish Heart-Lung Foundation, the Swedish Society of Medicine, the Swedish Foundation for Strategic Research, and the Royal Swedish Academy of Science. J.Ä. is supported by The Swedish Research Council (2006-6555), Swedish Heart-Lung foundation, Loo och Hans Ostermans foundation, Dalarna University, and Uppsala University.

Members of the CKDGen Consortium: Anna Köttgen, Cristian Pattaro, Carsten A. Böger, Christian Fuchsberger, Matthias Olden, Nicole L. Glazer, Afshin Parsa, Xiaoyi Gao, Qiong Yang, Albert V. Smith, Jeffrey R. O'Connell, Man Li, Helena Schmidt, Toshiko Tanaka, Aaron Isaacs, Shamika Ketkar, Shih-Jen Hwang, Andrew D. Johnson, Abbas Dehghan, Alexander Teumer, Guillaume Paré, Thor Aspelund, Gudny Eiriksdottir, Lenore J. Launer, Tamara B. Harris, Evadnie Rimpersaud, Braxton D. Mitchell, Eric Boerwinkle, Maksim Struchalin, Margherita Cavalieri, Andrew Singleton, Francesco Giallauria,

Jeffery Metter, Ian de Boer, Talin Haritunians, Thomas Lumley, David Siscovick, Bruce M. Psaty, M. Carola Zillikens, Ben A. Oostra, Mary Feitosa, Michael Province, Thomas Illig, Norman Klopp, Christa Meisinger, H.-Erich Wichmann, Wolfgang Koenig, Lina Zgaga, Tatijana Zemunik, Ivana Kolcic, Cosetta Minelli, sa Johansson, Wilmar Igl, Ghazal Zaboli, Sarah H. Wild, Alan F. Wright, Harry Campbell, David Ellinghaus, Stefan Schreiber, Yurii S. Aulchenko, Janine F. Felix, Fernando Rivadeneira, Andre G. Uitterlinden, Albert Hofman, Medea Imboden, Mladen Boban, Susan Campbell, Karlhans Endlich, Henry Völzke, Heyo K. Kroemer, Matthias Nauck, Uwe Völker, Ozren Polasek, Veronique Vitart, Sunita Badola, Alexander N. Parker, Paul M. Ridker, Stefan Blankenberg, Vilmundur Gudnason, Alan R. Shuldiner, Josef Coresh, Reinhold Schmidt, Luigi Ferrucci, Michael G. Shlipak, Cornelia M. van Duijn, Ingrid Borecki, Bernhard K. Krämer, Igor Rudan, Ulf Gyllenstein, James F. Wilson, Jacqueline C. Witteman, Peter P. Pramstaller, Rainer Rettig, Nick D. Hastie, Daniel I. Chasman, W. H. Kao, Iris M. Heid, and Caroline S. Fox.

Footnotes

Published online ahead of print. Publication date available at www.jasn.org.

See related editorial, "Are Cubilin (*CUBN*) Variants at the Heart of Urinary Albumin Excretion?" on pages [404–405](#).

Supplemental information for this article is available online at <http://www.jasn.org/>.

REFERENCES

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS.: Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038–2047, 2007. [PubMed: 17986697]
2. Lieb W, Mayer B, Stritzke J, Doering A, Hense HW, Loewel H, Erdmann J, Schunkert H.: Association of low-grade urinary albumin excretion with left ventricular hypertrophy in the general population: The MONICA/KORA Augsburg Echocardiographic Substudy. *Nephrol Dial Transplant* 21: 2780–2787, 2006. [PubMed: 16880179]
3. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE.: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 106: 1777–1782, 2002. [PubMed: 12356629]
4. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR.: Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 20: 1069–1077, 2009. [PMCID: PMC2678033] [PubMed: 19357254]
5. Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS.: Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The Framingham Heart Study. *Circulation* 112: 969–975, 2005. [PubMed: 16087792]
6. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS.: Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 110: 32–35, 2004. [PubMed: 15210602]
7. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M.: Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 303: 423–429, 2010. [PubMed: 20124537]

8. Ritz E, Viberti GC, Ruilope LM, Rabelink AJ, Izzo JL, Jr., Katayama S, Ito S, Mimran A, Menne J, Rump LC, Januszewicz A, Haller H.: Determinants of urinary albumin excretion within the normal range in patients with type 2 diabetes: The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study. *Diabetologia* 53: 49–57, 2010. [PMCID: PMC2789932] [PubMed: 19876613]
9. Fox CS, Yang Q, Guo CY, Cupples LA, Wilson PW, Levy D, Meigs JB.: Genome-wide linkage analysis to urinary microalbuminuria in a community-based sample: The Framingham Heart Study. *Kidney Int* 67: 70–74, 2005. [PubMed: 15610229]
10. Mottl AK, Vupputuri S, Cole SA, Almasy L, Goring HH, Diego VP, Laston S, Shara N, Lee ET, Best LG, Fabsitz RR, MacCluer JW, Umans JG, North KE.: Linkage analysis of albuminuria. *J Am Soc Nephrol* 20: 1597–1606, 2009. [PMCID: PMC2709673] [PubMed: 19369405]
11. Tryggvason K, Patrakka J, Wartiovaara J.: Hereditary proteinuria syndromes and mechanisms of proteinuria. *N Engl J Med* 354: 1387–1401, 2006. [PubMed: 16571882]
12. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Magi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparso T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proenca C, Kumari M, Qi L, Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, McCarroll SA, Payne F, Roccascella RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B, Barter P, Beilby JP, Ben-Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M, Boerwinkle E, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Bottcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M, Crawford G, Crisponi L, Day IN, de Geus EJ, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Fox CS, Frants R, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Groves CJ, Grundy S, Gwilliam R, Gyllenstein U, Hadjadj S, Hallmans G, Hammond N, Han X, Hartikainen AL, Hassanali N, Hayward C, Heath SC, Hercberg S, Herder C, Hicks AA, Hillman DR, Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jorgensen T, Jula A, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, Lecoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martinez-Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orru M, Pakyz R, Palmer CN, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Perola M, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W, Rayner NW, Rice K, Ripatti S, Rivadeneira F, Roden M, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurethsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvanen AC, Tanaka T, Thorand B, Tichet J, Tonjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van Hoek M, Varma D, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL, Watkins H, Weedon MN, Wild SH, Willemsen G, Witteman JC, Yarnell JW, Zeggini E, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, Borecki IB, Loos RJ, Meneton P, Magnusson PK, Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Rios M, Morris AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WH, Pankow JS, Sampson MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP, Wichmann HE, Illig T, Rudan I, Wright AF, Stumvoll M, Campbell H, Wilson JF, Bergman RN, Buchanan TA, Collins FS, Mohlke KL, Tuomilehto J,

Valle TT, Altshuler D, Rotter JI, Siscovick DS, Penninx BW, Boomsma DI, Deloukas P, Spector TD, Frayling TM, Ferrucci L, Kong A, Thorsteinsdottir U, Stefansson K, van Duijn CM, Aulchenko YS, Cao A, Scuteri A, Schlessinger D, Uda M, Ruukonen A, Jarvelin MR, Waterworth DM, Vollenweider P, Peltonen L, Mooser V, Abecasis GR, Wareham NJ, Sladek R, Froguel P, Watanabe RM, Meigs JB, Groop L, Boehnke M, McCarthy MI, Florez JC, Barroso I.: New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 42: 105–116, 2010. [PMCID: PMC3018764] [PubMed: 20081858]

13. Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, Loos RJ, Manning AK, Jackson AU, Aulchenko Y, Potter SC, Erdos MR, Sanna S, Hottenga JJ, Wheeler E, Kaakinen M, Lyssenko V, Chen WM, Ahmadi K, Beckmann JS, Bergman RN, Bochud M, Bonnycastle LL, Buchanan TA, Cao A, Cervino A, Coin L, Collins FS, Crisponi L, de Geus EJ, Dehghan A, Deloukas P, Doney AS, Elliott P, Freimer N, Gateva V, Herder C, Hofman A, Hughes TE, Hunt S, Illig T, Inouye M, Isomaa B, Johnson T, Kong A, Krestyaninova M, Kuusisto J, Laakso M, Lim N, Lindblad U, Lindgren CM, McCann OT, Mohlke KL, Morris AD, Naitza S, Orru M, Palmer CN, Pouta A, Randall J, Rathmann W, Saramies J, Scheet P, Scott LJ, Scuteri A, Sharp S, Sijbrands E, Smit JH, Song K, Steinthorsdottir V, Stringham HM, Tuomi T, Tuomilehto J, Uitterlinden AG, Voight BF, Waterworth D, Wichmann HE, Willemsen G, Witteman JC, Yuan X, Zhao JH, Zeggini E, Schlessinger D, Sandhu M, Boomsma DI, Uda M, Spector TD, Penninx BW, Altshuler D, Vollenweider P, Jarvelin MR, Lakatta E, Waeber G, Fox CS, Peltonen L, Groop LC, Mooser V, Cupples LA, Thorsteinsdottir U, Boehnke M, Barroso I, Van Duijn C, Dupuis J, Watanabe RM, Stefansson K, McCarthy MI, Wareham NJ, Meigs JB, Abecasis GR.: Variants in MTNR1B influence fasting glucose levels. *Nat Genet* 41: 77–81, 2009. [PMCID: PMC2682768] [PubMed: 19060907]

14. Keating BJ, Tischfield S, Murray SS, Bhangale T, Price TS, Glessner JT, Galver L, Barrett JC, Grant SF, Farlow DN, Chandrupatla HR, Hansen M, Ajmal S, Papanicolaou GJ, Guo Y, Li M, Derohannessian S, de Bakker PI, Bailey SD, Montpetit A, Edmondson AC, Taylor K, Gai X, Wang SS, Fornage M, Shaikh T, Groop L, Boehnke M, Hall AS, Hattersley AT, Frackelton E, Patterson N, Chiang CW, Kim CE, Fabsitz RR, Ouwehand W, Price AL, Munroe P, Caulfield M, Drake T, Boerwinkle E, Reich D, Whitehead AS, Cappola TP, Samani NJ, Lusk AJ, Schadt E, Wilson JG, Koenig W, McCarthy MI, Kathiresan S, Gabriel SB, Hakonarson H, Anand SS, Reilly M, Engert JC, Nickerson DA, Rader DJ, Hirschhorn JN, Fitzgerald GA.: Concept, design and implementation of a cardiovascular gene-centric 50 k SNP array for large-scale genomic association studies. *PLoS One* 3: e3583, 2008. [PMCID: PMC2571995] [PubMed: 18974833]

15. Kumar P, Henikoff S, Ng PC.: Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc* 4: 1073–1081, 2009. [PubMed: 19561590]

16. Yuan HY, Chiou JJ, Tseng WH, Liu CH, Liu CK, Lin YJ, Wang HH, Yao A, Chen YT, Hsu CN.: FASTSNP: An always up-to-date and extendable service for SNP function analysis and prioritization. *Nucleic Acids Res* 34: W635–W641, 2006. [PMCID: PMC1538865] [PubMed: 16845089]

17. Sunyaev S, Ramensky V, Koch I, Lathe W, 3rd, Kondrashov AS, Bork P.: Prediction of deleterious human alleles. *Hum Mol Genet* 10: 591–597, 2001. [PubMed: 11230178]

18. Köttgen A, Pattaro C, Böger CA, Fuchsberger C, Olden M, Glazer NL, Parsa A, Gao X, Yang Q, Smith AV, O'Connell JR, Li M, Schmidt H, Tanaka T, Isaacs A, Ketkar S, Hwang SJ, Johnson AD, Dehghan A, Teumer A, Pare G, Atkinson EJ, Zeller T, Lohman K, Cornelis MC, Probst-Hensch NM, Kronenberg F, Tonjes A, Hayward C, Aspelund T, Eiriksdottir G, Launer LJ, Harris TB, Rampersaud E, Mitchell BD, Arking DE, Boerwinkle E, Struchalin M, Cavalieri M, Singleton A, Giallauria F, Metter J, de Boer IH,

Haritunians T, Lumley T, Siscovick D, Psaty BM, Zillikens MC, Oostra BA, Feitosa M, Province M, de Andrade M, Turner ST, Schillert A, Ziegler A, Wild PS, Schnabel RB, Wilde S, Munzel TF, Leak TS, Illig T, Klopp N, Meisinger C, Wichmann HE, Koenig W, Zgaga L, Zemunik T, Kolcic I, Minelli C, Hu FB, Johansson A, Igl W, Zaboli G, Wild SH, Wright AF, Campbell H, Ellinghaus D, Schreiber S, Aulchenko YS, Felix JF, Rivadeneira F, Uitterlinden AG, Hofman A, Imboden M, Nitsch D, Brandstatter A, Kollerits B, Kedenko L, Magi R, Stumvoll M, Kovacs P, Boban M, Campbell S, Endlich K, Volzke H, Kroemer HK, Nauck M, Volker U, Polasek O, Vitart V, Badola S, Parker AN, Ridker PM, Kardina SL, Blankenberg S, Liu Y, Curhan GC, Franke A, Roach T, Paulweber B, Prokopenko I, Wang W, Gudnason V, Shuldiner AR, Coresh J, Schmidt R, Ferrucci L, Shlipak MG, van Duijn CM, Borecki I, Krämer BK, Rudan I, Gyllenstein U, Wilson JF, Witteman JC, Pramstaller PP, Rettig R, Hastie N, Chasman DI, Kao WH, Heid IM, Fox CS.: New loci associated with kidney function and chronic kidney disease. *Nat Genet* 42: 376–384, 2010. [PMCID: PMC2997674] [PubMed: 20383146]

19. Köttgen A, Glazer NL, Dehghan A, Hwang SJ, Katz R, Li M, Yang Q, Gudnason V, Launer LJ, Harris TB, Smith AV, Arking DE, Astor BC, Boerwinkle E, Ehret GB, Ruczinski I, Scharpf RB, Ida Chen YD, de Boer IH, Haritunians T, Lumley T, Sarnak M, Siscovick D, Benjamin EJ, Levy D, Upadhyay A, Aulchenko YS, Hofman A, Rivadeneira F, Uitterlinden AG, van Duijn CM, Chasman DI, Pare G, Ridker PM, Kao WH, Witteman JC, Coresh J, Shlipak MG, Fox CS.: Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet* 41: 712–717, 2009. [PMCID: PMC3039280] [PubMed: 19430482]

20. Moestrup SK, Kozyraki R, Kristiansen M, Kaysen JH, Rasmussen HH, Brault D, Pontillon F, Goda FO, Christensen EI, Hammond TG, Verroust PJ.: The intrinsic factor-vitamin B12 receptor and target of teratogenic antibodies is a megalin-binding peripheral membrane protein with homology to developmental proteins. *J Biol Chem* 273: 5235–5242, 1998. [PubMed: 9478979]

21. Birn H, Verroust PJ, Nexo E, Hager H, Jacobsen C, Christensen EI, Moestrup SK.: Characterization of an epithelial approximately 460-kDa protein that facilitates endocytosis of intrinsic factor-vitamin B12 and binds receptor-associated protein. *J Biol Chem* 272: 26497–26504, 1997. [PubMed: 9334227]

22. Schadt EE, Molony C, Chudin E, Hao K, Yang X, Lum PY, Kasarskis A, Zhang B, Wang S, Suver C, Zhu J, Millstein J, Sieberts S, Lamb J, GuhaThakurta D, Derry J, Storey JD, Avila-Campillo I, Kruger MJ, Johnson JM, Rohl CA, van Nas A, Mehrabian M, Drake TA, Lusk AJ, Smith RC, Guengerich FP, Strom SC, Schuetz E, Rushmore TH, Ulrich R.: Mapping the genetic architecture of gene expression in human liver. *PLoS Biol* 6: e107, 2008. [PMCID: PMC2365981] [PubMed: 18462017]

23. Dixon AL, Liang L, Moffatt MF, Chen W, Heath S, Wong KC, Taylor J, Burnett E, Gut I, Farrall M, Lathrop GM, Abecasis GR, Cookson WO.: A genome-wide association study of global gene expression. *Nat Genet* 39: 1202–1207, 2007. [PubMed: 17873877]

24. Göring HH, Curran JE, Johnson MP, Dyer TD, Charlesworth J, Cole SA, Jowett JB, Abraham LJ, Rainwater DL, Comuzzie AG, Mahaney MC, Almasy L, MacCluer JW, Kissebah AH, Collier GR, Moses EK, Blangero J.: Discovery of expression QTLs using large-scale transcriptional profiling in human lymphocytes. *Nat Genet* 39: 1208–1216, 2007. [PubMed: 17873875]

25. Ahuja R, Yammani R, Bauer JA, Kalra S, Seetharam S, Seetharam B.: Interactions of cubilin with megalin and the product of the amnionless gene (AMN): Effect on its stability. *Biochem J* 410: 301–308, 2008. [PubMed: 17990981]

26. Christensen EI, Verroust PJ, Nielsen R.: Receptor-mediated endocytosis in renal proximal tubule. *Pflugers Arch* 458: 1039–1048, 2009. [PubMed: 19499243]

27. Amsellem S, Gburek J, Hamard G, Nielsen R, Willnow TE, Devuyst O, Nexo E, Verroust PJ, Christensen EI, Kozyraki R.: Cubilin is essential for albumin reabsorption in the renal proximal tubule. *J Am Soc Nephrol* 21: 1859–1867, 2010. [PMCID: PMC3014001] [PubMed: 20798259]
28. Birn H, Fyfe JC, Jacobsen C, Mounier F, Verroust PJ, Orskov H, Willnow TE, Moestrup SK, Christensen EI.: Cubilin is an albumin binding protein important for renal tubular albumin reabsorption. *J Clin Invest* 105: 1353–1361, 2000. [PMCID: PMC315466] [PubMed: 10811843]
29. Birn H, Christensen EI.: Renal albumin absorption in physiology and pathology. *Kidney Int* 69: 440–449, 2006. [PubMed: 16514429]
30. Feng M, Zhang Z, Fu P, Huang SM, Yang YB, Su KL, Chen ZJ, Tang WX.: [Expression level of cubilin in the rat model of diabetic nephropathy]. *Sichuan Da Xue Xue Bao Yi Xue Ban* 37: 738–741, 2006. [PubMed: 17037740]
31. Russo LM, Sandoval RM, Campos SB, Molitoris BA, Comper WD, Brown D.: Impaired tubular uptake explains albuminuria in early diabetic nephropathy. *J Am Soc Nephrol* 20: 489–494, 2009. [PMCID: PMC2653682] [PubMed: 19118149]
32. Tojo A, Onozato ML, Ha H, Kurihara H, Sakai T, Goto A, Fujita T, Endou H.: Reduced albumin reabsorption in the proximal tubule of early-stage diabetic rats. *Histochem Cell Biol* 116: 269–276, 2001. [PubMed: 11685557]
33. Thrailkill KM, Nimmo T, Bunn RC, Cockrell GE, Moreau CS, Mackintosh S, Edmondson RD, Fowlkes JL.: Microalbuminuria in type 1 diabetes is associated with enhanced excretion of the endocytic multiligand receptors megalin and cubilin. *Diabetes Care* 32: 1266–1268, 2009. [PMCID: PMC2699744] [PubMed: 19366958]
34. Erkan E, Devarajan P, Schwartz GJ.: Apoptotic response to albumin overload: Proximal vs. distal/collecting tubule cells. *Am J Nephrol* 25: 121–131, 2005. [PubMed: 15812145]
35. Liu HC, Liao TN, Lee TC, Chuang LY, Guh JY, Liu SF, Hu MS, Yang YL, Lin SH, Hung MY, Huang JS, Hung TJ, Chen CD, Chiang TA, Chan JY, Chen SY.: Albumin induces cellular fibrosis by upregulating transforming growth factor-beta ligand and its receptors in renal distal tubule cells. *J Cell Biochem* 97: 956–968, 2006. [PubMed: 16267840]
36. Diwakar R, Pearson AL, Colville-Nash P, Brunskill NJ, Dockrell ME.: The role played by endocytosis in albumin-induced secretion of TGF-beta1 by proximal tubular epithelial cells. *Am J Physiol Renal Physiol* 292: F1464–F1470, 2007. [PubMed: 17213467]
37. Tapp RJ, Shaw JE, Zimmet PZ, Balkau B, Chadban SJ, Tonkin AM, Welborn TA, Atkins RC.: Albuminuria is evident in the early stages of diabetes onset: Results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Am J Kidney Dis* 44: 792–798, 2004. [PubMed: 15492944]
38. Vergouwe Y, Soedamah-Muthu SS, Zgibor J, Chaturvedi N, Forsblom C, Snell-Bergeon JK, Maahs DM, Groop PH, Rewers M, Orchard TJ, Fuller JH, Moons KG.: Progression to microalbuminuria in type 1 diabetes: Development and validation of a prediction rule. *Diabetologia* 53: 254–262, 2010. [PMCID: PMC2797626] [PubMed: 19908023]
39. Predictors of the development of microalbuminuria in patients with Type 1 diabetes mellitus: A seven-year prospective study. The Microalbuminuria Collaborative Study Group. *Diabet Med* 16: 918–925, 1999. [PubMed: 10588521]

40. Mattix HJ, Hsu CY, Shaykevich S, Curhan G.: Use of the albumin/creatinine ratio to detect microalbuminuria: Implications of sex and race. *J Am Soc Nephrol* 13: 1034–1039, 2002. [PubMed: 11912263]
41. Warram JH, Gearin G, Laffel L, Krolewski AS.: Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 7: 930–937, 1996. [PubMed: 8793803]
42. Whitlock MC.: Combining probability from independent tests: The weighted Z-method is superior to Fisher's approach. *J Evol Biol* 18: 1368–1373, 2005. [PubMed: 16135132]
43. Bacanu SA, Devlin B, Roeder K.: The power of genomic control. *Am J Hum Genet* 66: 1933–1944, 2000. [PMCID: PMC1378064] [PubMed: 10801388]
44. Aulchenko YS, Ripke S, Isaacs A, van Duijn CM.: GenABEL: An R library for genome-wide association analysis. *Bioinformatics* 23: 1294–1296, 2007. [PubMed: 17384015]
45. Abecasis GR, Cherny SS, Cookson WO, Cardon LR.: Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. *Nat Genet* 30: 97–101, 2002. [PubMed: 11731797]
46. Chen MH, Yang Q.: GWAF: An R package for genome-wide association analyses with family data. *Bioinformatics* 26: 580–581, 2010. [PMCID: PMC2852219] [PubMed: 20040588]
47. Mitchell BD, McArdle PF, Shen H, Rampersaud E, Pollin TI, Bielak LF, Jaquish C, Douglas JA, Roy-Gagnon MH, Sack P, Naglieri R, Hines S, Horenstein RB, Chang YP, Post W, Ryan KA, Brereton NH, Pakyz RE, Sorkin J, Damcott CM, O'Connell JR, Mangano C, Corretti M, Vogel R, Herzog W, Weir MR, Peyser PA, Shuldiner AR.: The genetic response to short-term interventions affecting cardiovascular function: Rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study. *Am Heart J* 155: 823–828, 2008. [PMCID: PMC2443415] [PubMed: 18440328]
48. Rampersaud E, Bielak LF, Parsa A, Shen H, Post W, Ryan KA, Donnelly P, Rumberger JA, Sheedy PF, 2nd, Peyser PA, Shuldiner AR, Mitchell BD.: The association of coronary artery calcification and carotid artery intima-media thickness with distinct, traditional coronary artery disease risk factors in asymptomatic adults. *Am J Epidemiol* 168: 1016–1023, 2008. [PMCID: PMC2720772] [PubMed: 18805900]
49. The Atherosclerosis Risk in Communities (ARIC) Study: Design and objectives. The ARIC investigators. *Am J Epidemiol* 129: 687–702, 1989. [PubMed: 2646917]
50. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D.: Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 38: 904–909, 2006. [PubMed: 16862161]
51. Hsu CC, Brancati FL, Astor BC, Kao WH, Steffes MW, Folsom AR, Coresh J.: Blood pressure, atherosclerosis, and albuminuria in 10,113 participants in the atherosclerosis risk in communities study. *J Hypertens* 27: 397–409, 2009. [PMCID: PMC2792744] [PubMed: 19226709]
52. Shock NW, Greulich RC, Andres R, Arenberg D, Costa PT, Jr., Lakatta EG, Tobin JD.: Normal Human Aging: The Baltimore Longitudinal Study of Aging [technical report]. NIH Publication 84, Washington D.C., U.S. Government Printing Office, 1984.
53. Tanaka T, Scheet P, Giusti B, Bandinelli S, Piras MG, Usala G, Lai S, Mulas A, Corsi AM, Vestri A, Sofi F, Gori AM, Abbate R, Guralnik J, Singleton A, Abecasis GR, Schlessinger D, Uda M, Ferrucci L.:

- Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. *Am J Hum Genet* 84: 477–482, 2009. [PMCID: PMC2667971] [PubMed: 19303062]
54. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, et al. : The Cardiovascular Health Study: Design and rationale. *Ann Epidemiol* 1: 263–276, 1991. [PubMed: 1669507]
55. Firmann M, Mayor V, Vidal PM, Bochud M, Pecoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, Danoff TM, Stirnadel HA, Waterworth D, Mooser V, Waeber G, Vollenweider P.: The CoLaus study: A population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 8: 6, 2008. [PMCID: PMC2311269] [PubMed: 18366642]
56. Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N.: EPIC-Norfolk: study design and characteristics of the cohort. *European Prospective Investigation of Cancer. Br J Cancer* 80 [Suppl 1]: 95–103, 1999. [PubMed: 10466767]
57. Lee CT, Adler AI, Forouhi NG, Luben R, Welch A, Khaw KT, Bingham S, Wareham NJ.: Cross-sectional association between fish consumption and albuminuria: The European Prospective Investigation of Cancer-Norfolk Study. *Am J Kidney Dis* 52: 876–886, 2008. [PubMed: 18534731]
58. Dawber TR, Kannel WB, Lyell LP.: An approach to longitudinal studies in a community: The Framingham Study. *Ann N Y Acad Sci* 107: 539–556, 1963. [PubMed: 14025561]
59. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP.: The Framingham Offspring Study. Design and preliminary data. *Prev Med* 4: 518–525, 1975. [PubMed: 1208363]
60. Garrison RJ, Castelli WP, Feinleib M, Kannel WB, Havlik RJ, Padgett SJ, McNamara PM.: The association of total cholesterol, triglycerides and plasma lipoprotein cholesterol levels in first degree relatives and spouse pairs. *Am J Epidemiol* 110: 313–321, 1979. [PubMed: 224699]
61. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB, Sr., Fox CS, Larson MG, Murabito JM, O'Donnell CJ, Vasan RS, Wolf PA, Levy D.: The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: Design, recruitment, and initial examination. *Am J Epidemiol* 165: 1328–1335, 2007. [PubMed: 17372189]
62. Wichmann HE, Gieger C, Illig T.: KORA-gen—resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* 67 [Suppl 1]: S26–S30, 2005. [PubMed: 16032514]
63. Baumeister SE, Böger CA, Krämer BK, Döring A, Eheberg D, Fischer B, John J, Koenig W, Meisinger C.: Effect of chronic kidney disease and comorbid conditions on health care costs: A 10-year observational study in a general population. *Am J Nephrol* 31: 222–229, 2009. [PubMed: 20068286]
64. Pattaro C, Marroni F, Riegler A, Mascalzoni D, Pichler I, Volpato CB, Dal Cero U, De Grandi A, Egger C, Eisendle A, Fuchsberger C, Gogele M, Pedrotti S, Pinggera GK, Stefanov SA, Vogl FD, Wiedermann CJ, Meitinger T, Pramstaller PP.: The genetic study of three population microisolates in South Tyrol (MICROS): Study design and epidemiological perspectives. *BMC Med Genet* 8: 29, 2007. [PMCID: PMC1913911] [PubMed: 17550581]
65. John U, Greiner B, Hensel E, Ludemann J, Piek M, Sauer S, Adam C, Born G, Alte D, Greiser E, Haertel U, Hense HW, Haerting J, Willich S, Kessler C.: Study of Health In Pomerania (SHIP): A health examination survey in an east German region: Objectives and design. *Soz Präventivmed* 46: 186–194, 2001. [PubMed: 11565448]

66. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR, Jr., Liu K, Savage PJ.: CARDIA: Study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 41: 1105–1116, 1988. [PubMed: 3204420]
67. Taylor HA, Jr., Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, Nelson C, Wyatt SB.: Toward resolution of cardiovascular health disparities in African Americans: Design and methods of the Jackson Heart Study. *Ethn Dis* 15[4 Suppl 6]: S6–4-17, 2005.
68. Fuqua SR, Wyatt SB, Andrew ME, Sarpong DF, Henderson FR, Cunningham MF, Taylor HA., Jr.: Recruiting African-American research participation in the Jackson Heart Study: Methods, response rates, and sample description. *Ethn Dis* 15: S6–18-29, 2005. [PubMed: 16317982]
69. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR, Jr., Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP.: Multi-ethnic study of atherosclerosis: Objectives and design. *Am J Epidemiol* 156: 871–881, 2002. [PubMed: 12397006]
70. Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, Thorgeirsson G, Aspelund T, Garcia ME, Cotch MF, Hoffman HJ, Gudnason V.: Age, Gene/Environment Susceptibility-Reykjavik Study: Multidisciplinary applied phenomics. *Am J Epidemiol* 165: 1076–1087, 2007. [PMCID: PMC2723948] [PubMed: 17351290]
71. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. *Kidney Int* 47: 1703–1720, 1995. [PubMed: 7643540]
72. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: The Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290: 2159–2167, 2003. [PMCID: PMC2622725] [PubMed: 14570951]
73. Daniels PR, Kardia SL, Hanis CL, Brown CA, Hutchinson R, Boerwinkle E, Turner ST.: Familial aggregation of hypertension treatment and control in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Am J Med* 116: 676–681, 2004. [PubMed: 15121494]
74. Zemunik T, Boban M, Lauc G, Jankovic S, Rotim K, Vataavuk Z, Bencic G, Dogas Z, Boraska V, Torlak V, Susac J, Zobic I, Rudan D, Pulanic D, Modun D, Mudnic I, Gunjaca G, Budimir D, Hayward C, Vitart V, Wright AF, Campbell H, Rudan I.: Genome-wide association study of biochemical traits in Korcula Island, Croatia. *Croat Med J* 50: 23–33, 2009. [PMCID: PMC2657564] [PubMed: 19260141]
75. Tönjes A, Zeggini E, Kovacs P, Bottcher Y, Schleinitz D, Dietrich K, Morris AP, Enigk B, Rayner NW, Koriath M, Eszlinger M, Kempainen A, Prokopenko I, Hoffmann K, Teupser D, Thiery J, Krohn K, McCarthy MI, Stumvoll M.: Association of FTO variants with BMI and fat mass in the self-contained population of Sorbs in Germany. *Eur J Hum Genet* 18: 104–110, 2010. [PMCID: PMC2987177] [PubMed: 19584900]
76. Holmen JMK, Kruger O.: The Nord-Trøndelag health study 1995–97 (HUNT 2): Objectives, methods and participation. *Norsk Epidemiologi* 13: 19–32, 2003.
77. Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ.: Lifetime nonnarcotic analgesic use and decline in renal function in women. *Arch Intern Med* 164: 1519–1524, 2004. [PubMed: 15277282]
78. Forman JP, Fisher ND, Schopick EL, Curhan GC.: Higher levels of albuminuria within the normal range predict incident hypertension. *J Am Soc Nephrol* 19: 1983–1988, 2008. [PMCID: PMC2551568] [PubMed: 18579639]

79. Heid IM, Wagner SA, Gohlke H, Iglseider B, Mueller JC, Cip P, Ladurner G, Reiter R, Stadlmayr A, Mackevics V, Illig T, Kronenberg F, Paulweber B.: Genetic architecture of the APM1 gene and its influence on adiponectin plasma levels and parameters of the metabolic syndrome in 1,727 healthy Caucasians. *Diabetes* 55: 375–384, 2006. [PubMed: 16443770]

80. Byberg L, Zethelius B, McKeigue PM, Lithell HO.: Changes in physical activity are associated with changes in metabolic cardiovascular risk factors. *Diabetologia* 44: 2134–2139, 2001. [PubMed: 11793014]

81. Ingelsson E, Sundstrom J, Lind L, Riserus U, Larsson A, Basu S, Arnlov J.: Low-grade albuminuria and the incidence of heart failure in a community-based cohort of elderly men. *Eur Heart J* 28: 1739–1745, 2007. [PubMed: 17495987]

Figures and Tables

Table 1.

Study sample characteristics in the CKDGen and CARE Consortia

Study	n ^a	Women %	Age, years	UACR ^b	MA %	CKD %	HTN %	DM %
Stage 1: GWAS								
Amish	744	45.0	42.8	3.8 (2.2, 6.1)	NA	1.2	11.6	0.7
ARIC	6525	53.1	63.1	3.9 (2.0, 7.7)	9.4	9.1	42.9	13.6
BLSA	354	46.9	69.8	7 (4.4, 11.0)	NA	15.5	53.7	14.4
CHS	1865	60.8	71.2	9.3 (5.3, 19.9)	23.0	16.0	61.2	13.7
Colaus	5311	53.2	53.4	5.1 (3.4, 9.1)	9.5	3.8	36.1	9.6
EPIC	2371	53.3	59.2	3.6 (1.5, 8.3)	8.1	NA	49.3	3.0
Fenland	1398	56.2	44.9	4.5 (3.2, 7.1)	5.5	0.9	18.9	1.4
Framingham Heart Study	6523	53.2	47.6	4.6 (2.6, 9.9)	9.6	3.4	27.4	5.3
KORA F3	1530	50.5	62.5	4.9 (2.1, 11.1)	11.7	10.8	41.1	10.3
KORA F4	1803	51.3	60.9	10.7 (7.0, 18.4)	20.9	7.0	20.9	9.2
Micros	503	56.3	46.0	NA	5.4	3.6	40.6	3.7
SHIP	2653	48.9	55.3	8.9 (5.0, 20.6)	25.3	8.5	54.2	12.4
Stage 2								
AGES	3196	57.9	76.4	2.66 (1.2, 7.0)	11.9	24.2	80.6	11.6
Amish	695	54.4	47.2	7 (4.3, 13.5)	NA	NA	21.0	11.5
ARIC	759	56.0	63.0	3.9 (2.1, 7.5)	7.6	7.7	39.3	13.1
GENOA	987	43.0	59.0	3.1 (1.7, 5.9)	6.4	10.7	73.5	15.8
Health ABC	211	27.0	73.9	13.9 (6.1, 49.6)	42.2	25.0	64.1	100.0
HUNT	2386	54.5	51.4	6.1 (4.4, 9.2)	8.6	4.7	43.4	4.0
KORA F3	1392	52.4	50.8	4.4 (1.9, 9.6)	10.9	5.5	28.6	4.5
KORA F4	1197	52.3	49.2	10.1 (6.6, 20.1)	23.7	5.9	13.4	4.0
KORCULA	863	63.9	56.3	4.6 (2.5, 10.4)	12.4	7.5	57.3	10.4
Nurses Health Study	4138	100.0	58.2	2.8 (1.7, 4.5)	3.6	10.4	36.1	4.4
PREVEND	7803	50.5	49.5	7.1 (4.8, 13.3)	16.7	6.4	33.5	3.7

SAPHIR Study	1707	37.3	51.4	3.8 (2.3, 8.2)	9.8	1.4	56.5	3.2
SORBS	877	58.7	48.0	6.8 (4.6, 13.5)	13.6	4.0	52.1	9.2
SPLIT	472	56.5	49.3	2.5 (1.3, 5.8)	7.8	3.6	39.4	5.1
ULSAM	1063	0.0	71.0	7.5 (4.9, 16.1)	15.9	15.2	74.0	11.0
CARE Consortium								
European Americans ^c								
CARDIA	1242	50.4	40.7	4.4 (3.3, 6.9)	4.5	0.53	9.3	5.0
MESA	2289	52.1	62.7	4.7 (3.1, 8.6)	9.6	9.7	38.7	6.3
African Americans								
ARIC	2256	64.5	61.7	2.7 (0.9, 9.6)	16.3	7.3	70.9	27.7
CARDIA	1089	56.3	39.5	4.3 (3.1, 7.4)	9.6	0.9	24.7	6.4
CHS	426	64.3	72.1	10.9 (5.0, 26.9)	31.9	18.4	68.2	24.4
Jackson Heart Study	1530	58.5	51.8	6 (4.0, 13.0)	17.8	5.9	58.8	16.1
MESA	1680	54.6	62.2	5.5 (3.1, 13.2)	16.6	8.5	59.8	17.8

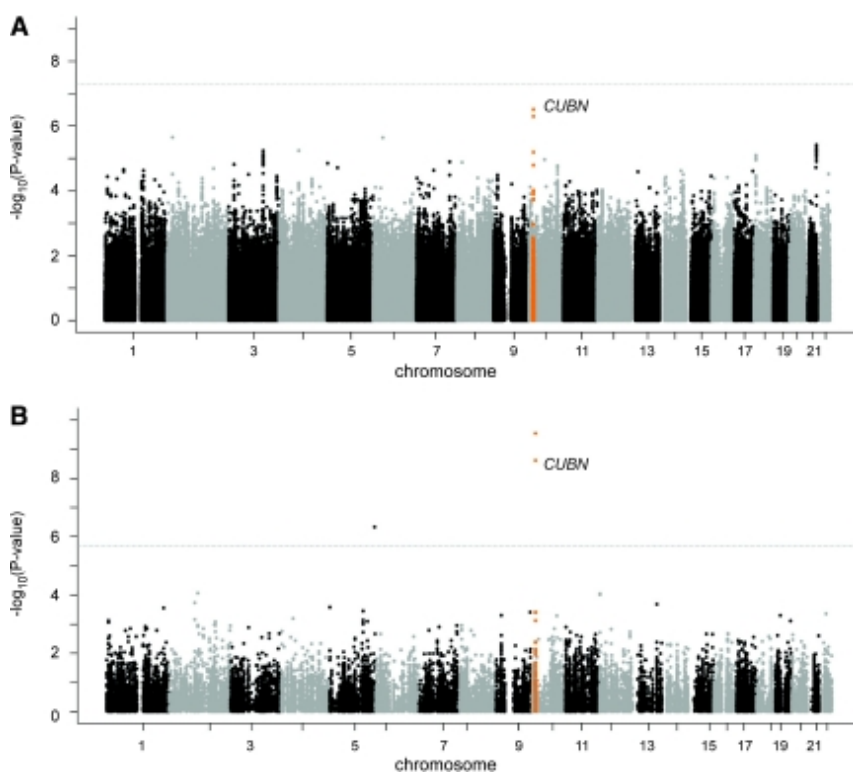
Data presented as means except where otherwise indicated. DM, diabetes; HTN, hypertension.

^aRefers to the successfully genotyped and analyzed sample with UACR or MA data, which may differ from the recruited sample described in Supplemental online Methods.

^bMedian (interquartile range: 25th percentile, 75th percentile).

^cRefers to studies that are nonoverlapping with CKDGen; the sample size of ARIC, CHS, and FHS in CARE was 7687, 2073, and 6208, respectively.

Figure 1.



Genome-wide \log_{10} P value plot from stage 1 analyses of UACR. Participants of European ancestry in the CKDGen Consortium (A) and the CARE Consortium [IBC chip analyses; (B)].

Table 2.

Results for CUBN SNP rs1801239 on chromosome 10 in the CKDGen and CARE Consortia^a and DCCT/EDIC

	UACR P Value ^b	Microalbuminuria P value ^c	Odds Ratio (95% CI) for Clinical Outcomes per Copy of Minor C Allele
Overall samples			Microalbuminuria (MA)
CKDGen Stage 1 discovery	3.0×10^{-7}	8.7×10^{-7}	1.25 (1.15 to 1.37)
CARE IBC discovery in European Americans	2.9×10^{-10}	2.4×10^{-7}	1.31 (1.18 to 1.45)
CKDGen Stage 2 follow-up	0.02	0.43	1.01 (0.98 to 1.05)
Combined populations of European ancestry ^d	1.1×10^{-11}	0.001	1.06 (1.02 to 1.09)
CARE African Americans	0.005	0.008	1.42 (1.10 to 1.84)
Diabetes stratified ^d			
no diabetes	3.2×10^{-8}	0.06	1.03 (1.00 to 1.07)
diabetes	0.006	4.7×10^{-4}	1.27 (1.11 to 1.45)
Hypertension stratified ^e			
no hypertension	1.3×10^{-6}	6.0×10^{-4}	1.23 (1.09 to 1.38)
hypertension	7.5×10^{-8}	1.4×10^{-7}	1.34 (1.20 to 1.49)
DCCT/EDIC ^f			
			Persistent MA
simple model		0.02	1.42 (1.08 to 1.88)
extended model		0.02	1.41 (1.06 to 1.87)
			Severe Nephropathy
simple model		0.53	1.14 (0.76 to 1.69)
extended model		0.67	1.10 (0.72 to 1.67)

^aSample sizes are as follows (microalbuminuria case numbers in parentheses): CKDGen Stage 1: 31580 (3698); CARE European Americans: 19,499 (2100); CKDGen Stage 2: 27,746 (3313); CARE African Americans: 6981 (1159).

^b P values from CKDGen and CARE European and African American Stage 1 analyses are from the inverse variance weighted fixed effects method, and P values from the CKDGen Stage 2 analyses, the combined analyses, and the hypertension- and diabetes-stratified analyses are from the sample size weighted Z score method. In all analyses, the minor allele C showed an increase in UACR, direction consistent with the odds ratio for MA.

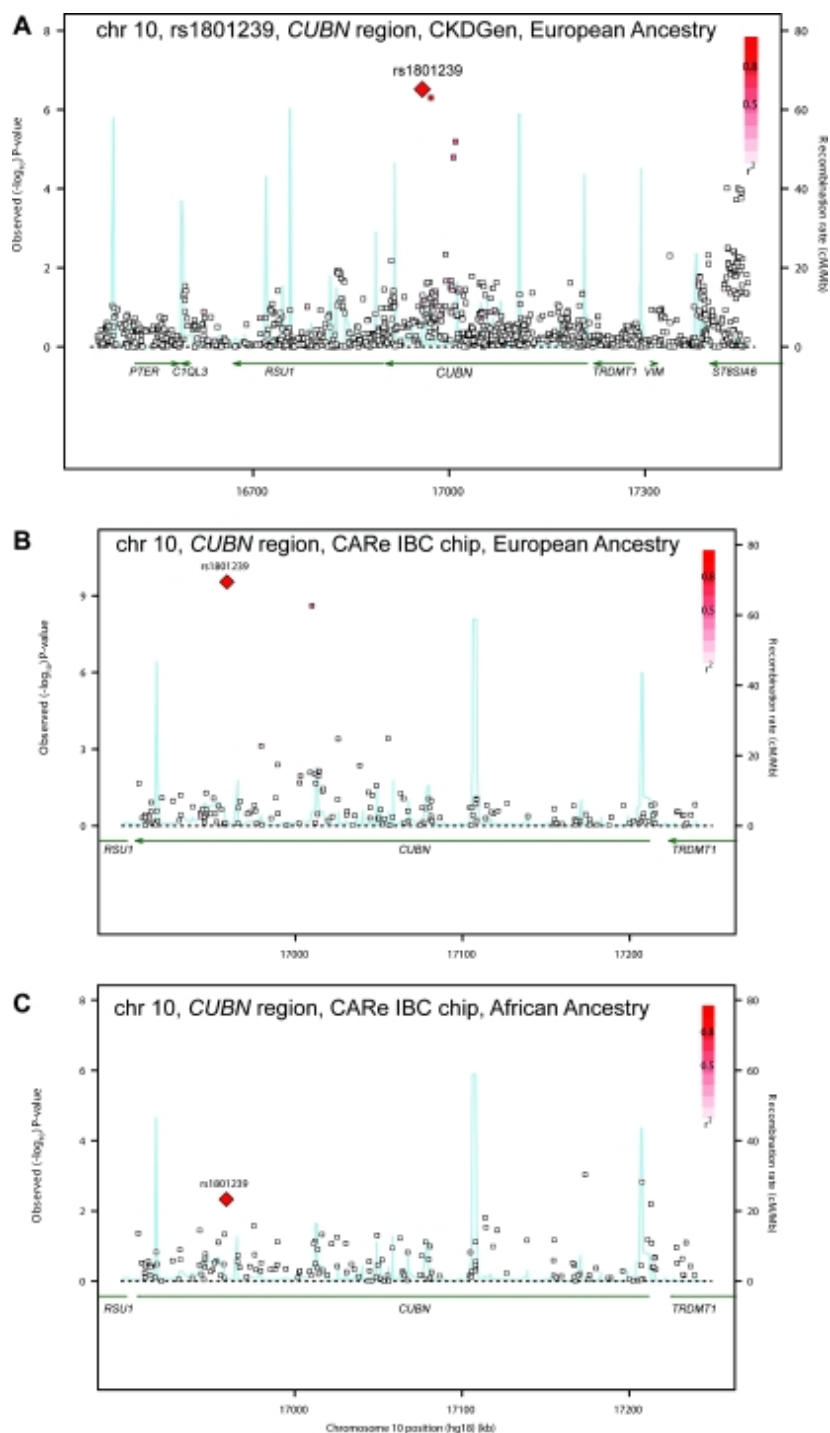
^c P values from inverse variance weighted fixed effects model.

^dCombined populations of European ancestry, includes CKDGen Stages 1 and 2 (after removal of ARIC, CHS, and FHS) and all five cohorts of CARE European Americans: 63,153 (7383 microalbuminuria cases).

^eCombined populations of European ancestry, includes CKDGen Stage 1 (after removal of ARIC, CHS, and FHS) and all five cohorts of CARE European Americans: 36,166 (4128 microalbuminuria cases).

^fModeled as hazard ratio; $n = 1304$ including 318 cases of persistent microalbuminuria and 116 cases of severe nephropathy.

Figure 2.



Regional Association Plot for the *CUBN* gene region. CKDGen Consortium stage 1 analyses (A), CARE IBC SNP chip results in participants of European Ancestry (B) and African ancestry (C). \log_{10} P values are plotted versus genomic position (build 36). The lead SNP in each region is labeled. Other SNPs in each region are color-coded based on their LD to the lead SNP (LD based on the HapMap CEU and YRI for the participants of African ancestry; see color legend). Gene

annotations are based on UCSC Genome Browser (RefSeq Genes, b36) and arrows indicate direction of transcription. Graphs were generated using the software SNAP (<http://www.broadinstitute.org/mpg/snap/index.php>). Regions vary between panels because there was no coverage beyond the *CUBN* gene on the IBC chip used to generate panels B and C.

Articles from Journal of the American Society of Nephrology : JASN are provided here courtesy of **American Society of Nephrology**