Supplementary Information

An intermediate effect size variant in *UMOD* confers risk for chronic kidney disease

This file includes:

Supplementary Material & Methods

Web Resources

Allele frequency App: http://cardiodb.org/allelefrequencyapp/
cBioPortal MutationMapper: https://www.cbioportal.org/mutation_mapper
ClinVar: https://www.ncbi.nlm.nih.gov/clinvar
Clustal omega: https://www.ebi.ac.uk/Tools/msa/clustalo/
Ensembl: https://www.ensembl.org/index.html
Ensembl VEP: https://www.ensembl.org/info/docs/tools/vep/index.html
FASMA (Formatting and Analysing the Sequences in the Multiple Alignments): http://bioinformatica.isa.cnr.it/FASMA
GnomAD v2.1.1: https://gnomad.broadinstitute.org/
HGMD®: http://www.hgmd.cf.ac.uk/ac/index.php
Image J - Fiji: https://imagej.net/Fiji (1)
Mafft: https://mafft.cbrc.jp/alignment/server/
Missense3D: http://missense3d.bc.ic.ac.uk/missense3d/
Phyre^2: http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index
Pfam: https://pfam.xfam.org/
Progeny pedigree builder: https://pedigree.progenygenetics.com/
Prosite: https://prosite.expasy.org
ProteinPaint: https://pecan.stjude.cloud/proteinpaint (2)
PubMed: https://pubmed.ncbi.nlm.nih.gov/
PyMOL: https://pymol.org/2/
SDM: http://marid.bioc.cam.ac.uk/sdm2/
Varsome®: https://varsome.com/
Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) (3). World Wide Web URL: https://omim.org/

International ADTKD Cohort

The International ADTKD Cohort consists of patients from the Belgo-Swiss ADTKD registry and the US ADTKD registry and has been previously published (4). The inclusion criteria were those defined by the Kidney Disease: Improving Global Outcomes (KDIGO) consensus (5) including: a family history compatible with autosomal dominant inheritance of CKD with progressive loss of kidney function, bland urinary sediment, absent-to-mild albuminuria and/or proteinuria, normal-sized or small-sized kidneys on ultrasound; and/or (in absence of a positive family history of CKD) a history of early-onset hyperuricemia and/or gout and/or the presence of interstitial fibrosis and/or tubular atrophy on kidney biopsy. Exclusion criteria as previously described (4). Only patients screened for variants in *UMOD* (and *MUC1*) were included in the cohort. Anonymized demographics, clinical and genetic information were recorded in a database.

The ADTKD Cohort study was approved by the institutional review board of the Wake Forest School of Medicine, North Carolina, USA (Wake Forest University Health Sciences IRB00000352 “Characteristics of Individuals with Inherited Kidney Disease”), the Institutional review board of the Université Catholique de Louvain (UCL) Medical School and Saint Luc University Hospital, Belgium (2011/04MAI/184) and the European Community's Seventh Framework Program “European Consortium for High-Throughput Research in Rare Kidney Diseases (EURenOmics) Ethics Advisory Board (Table S12).

This registry has been supported by the European Reference Network for Rare Kidney Diseases (ERKNet), which is partly co-funded by the European Union within the framework of the

Third Health Programme 'ERN-2016-Framework Partnership Agreement 2017-2021'. In addition, a cohort of Irish families recruited as part of the Irish Kidney Gene Project (IKGP) and who were subjected to next generation sequencing to identify genetic variants underlying kidney disease, were screened for *UMOD* missense variants.

Genetic testing

Informed written consent was obtained from all patients. Genomic DNA was isolated from peripheral blood leukocytes using standard procedures. Direct sequencing of *UMOD* exons was initially performed by Sanger sequencing, as previously described (6). At least exons 3 and 4 were sequenced in all patients enrolled into the International ADTKD Cohort and all 10 coding exons were sequenced in a sizeable subset of patients from the Cohort. For genetic testing in the Genomics England 100,000 Genomes Project and the UK Biobank, see relevant sections below. *MUC1* genotyping was performed using probe extension assays as previously described (7–9). The tubulopathy gene panel utilizes massively parallel sequencing of 37 genes implicated in renal tubulopathies (including *UMOD*, *HNF1B* and *REN*) and has been previously described (10). The Brest panel v2 comprises 10 genes (*PKD1, PKD2, GANAB, DNAJB11, HNF1B, PKHD1, UMOD, SEC63, PRKCSH, LRP5*) and the Brest panel v4 comprises 24 genes (*ALG8, ALG9, AQP11, COL4A1, DNAJB11, DZIP1L, GANAB, HNF1B, LRP5, MOGS, OFD1, PKD1, PKD2, PKHD1, PMM2, PRKCSH, REN, SEC61A1, SEC61B, SEC63, TSC1, TSC2, UMOD, VHL*). The Irish customized gene panel includes 227 genes (including ADTKD genes) as previously reported (11). Direct Sanger sequencing of *REN* exons was performed in some families as previously described (12). In addition, screening for exon deletions or large rearrangements in *HNF1B* was performed using multiplex ligation-dependent probe amplification (MLPA) as previously described (13). For those individuals where massively parallel sequencing data were available, resulting variants have been filtered for following criteria: MAF ≤ 1% (in any gnomAD subpopulation), nonsynonymous or canonical splice-affecting, 301 nephrogenes (green or amber) from Genomics England Renal Superpanel (version 2.426, https://panelapp.genomicsengland.co.uk/panels/903/).

Control population and strategy to identify intermediate-effect *UMOD* variants

The Genome Aggregation Database (GnomAD) v2.1.1 (https://gnomad.broadinstitute.org/) comprises 125,748 exomes and 15,708 genomes sequenced as part of various population genetic studies, totaling 141,456 unrelated individuals from eight major populations (14). Genetic variants are aligned against the GRCh37 genome build and the dataset was released in March 2019. Genetic variants in *UMOD* were filtered for missenses and only those annotated for *UMOD* transcript ENST00000302509.8 were retained. A list of *UMOD* missense variants in gnomAD ("controls") with their allelic frequencies was intersected with *UMOD* variants reported in the International ADTKD Cohort (see above) or in HGMD® ("cases"). Our working hypothesis is based on following assumptions: (i) *UMOD* missense variants in ADTKD cases, in the absence of functional studies or additional genetic arguments (eg. segregation studies), are reported as variant of unknown significance (VUS) and potentially include intermediate-effect variants, (ii) high-effect size variants are in principle too rare for gnomAD (lowest AF in gnomAD: 3.6×10^{-6} vs. maximum credible population allele frequency for fully penetrant *UMOD* mutations: 1×10^{-7} (see below for details) (15), but enriched in ADTKD cases and (iii), low effect variants are not reported as (likely) pathogenic or VUS in ADTKD cases, because of their typical higher allele frequency. In theory, this would lead to a spectrum of very low to high-effect *UMOD* variants enriched at both extremes in control and case groups, respectively. Thus, variants that are shared between controls and cases are candidates for intermediate-effect variants as determined by their obligate intermediate phenotypical effect (non-fully penetrant or milder disease) (Figure 1B).

Maximum credible population allele frequency

The maximum credible population allele frequency and allelic count for pathogenic *UMOD* variants in gnomAD was estimated using the frequency calculator established by Whiffin et al. (15) under the following assumptions: a disease prevalence of 1/50,000; allelic heterogeneity of 1%; genetic heterogeneity of 100%; a penetrance of 100%; a reference population size of 282,000 alleles, and statistical confidence of 0.999.

Genomics England 100,000 Genomes project and default variant filtering

All participants in the 100,000 Genomes Project have provided written consent and the 100,000 Genomes research and clinical project model and its informed consent process has been approved by the United Kingdom National Research Ethics Service Research Ethics Committee for East of England – Cambridge South Research Ethics Committee (https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/) (Ref 14/EE/1112) (Table S12).

The 100,000 Genomes Project is managed by Genomics England Limited (a wholly owned company of the Department of Health and Social Care). The 100,000 Genomes Project is funded by the National Institute for Health Research and NHS England. The Wellcome Trust, Cancer Research UK and the Medical Research Council have also funded research infrastructure. The 100,000 Genomes Project uses data provided by patients and collected by the National Health Service as part of their care and support.

Whole genome sequencing (WGS) was performed using the Illumina TruSeq DNA PCR-Free sample preparation kit (Illumina, Inc.) and an Illumina HiSeq 2500 sequencer and reads were aligned to GRCh37 using Isaac Genome Alignment Software (version 01.14; Illumina, Inc.). Variant filtering and annotation was performed as previously described (16). In brief, variants (SNVs, indels) were shortlisted if (i) their MAF in control populations was < 1/1,000 for putative novel causal variants and < 25/1,000 for variants listed as disease-causing in HGMD®, (ii) their predicted impact according to the Variant Effect Predictor (VEP) was “HIGH” or “MODERATE” or if the consequences with respect to the designated transcript included one of “splice_region_variant” or non_coding_transcript_exon_variant” if the variant was in a non-coding gene, and (iii) the variant affected a gene with a known etiological role in the patient’s disease. For each case with prioritized variants, the variant calls, HPO-coded phenotype, and the relevant metadata were transferred to Congenica for visualization in the Sapientia™ web application during multidisciplinary team (MDT) meetings, where each variant was annotated with its likely level of pathogenicity, its contribution to the disease phenotype, and to generate research reports.

Statistical phasing: We performed haplotype phasing on 64,057 Genomics England short read-sequenced individuals. The ~60kb region chr16:20,313,393-20,372,369 (GRCh38) centered on *UMOD* was extracted and merged from genomic vcf files using bcftools version 1.12. The resulting multi-allelic vcf file was split into biallelic records using bcftools norm and the resulting file phased using SHAPEIT4 version 4.2 (Segmented HAPlotype Estimation and Imputation Tools version 4 (17)) using the recommended settings for sequencing data.

The resulting phased files had 13,679 variant sites with 149 common variants (minor allele frequency > 0.1). 8 *UMOD* SNPs covering the *UMOD* promoter and coding region were used to summarize the *UMOD* locus haplotypes (18). The distribution of phased haplotypes was then extracted for those haplotypes varying the *UMOD* p.Thr62Pro, p.Leu180Val and p.Thr469Met variants.

UK Biobank

UK Biobank is a large prospective study with over 500,000 participants aged 40–69 years when recruited in 2006–2010 and globally accessible to approved researchers who are undertaking health-related research that's in the public interest (19). Ethics approval for the UK Biobank study was obtained from the North West Centre for Research Ethics Committee (11/NW/0382) (Table S12). UK Biobank is supported by its founding funders the Wellcome Trust and UK Medical Research Council, as well as the Department of Health, Scottish Government, the Northwest Regional Development Agency, British Heart Foundation and Cancer Research UK. The organization has over 150 dedicated staff members based in multiple locations across the UK.

Genome-wide genotyping was performed on all UK Biobank participants using the Applied Biosystems UK Biobank Axiom Array. Approximately 850,000 variants, included *UMOD* p.Thr62Pro were directly measured. Furthermore, exome data on ~200,000 individuals have been made available (20). Individuals included in this study (project ID 43879) were those that were determined to have genetic ancestry of "Caucasian" (field ID 22006), were not excluded by genetic relatedness as determined by the ukb_gen_samples_to_remove function in the ukbtools library (21), and had not withdrawn by 20/1/2021.

German Chronic Kidney Disease Cohort

The German Chronic Kidney Disease (GCKD) study is an ongoing prospective multicenter observational cohort and has been previously described (22, 23). In brief, it includes 5,217 patients under regular nephrology care with following inclusion criteria: moderately reduced kidney function defined as eGFR of 30–60 ml/min per 1.73 m^2 (stage G3, A1–A3) or an eGFR >60 ml/min per 1.73 m^2 in the presence of overt proteinuria (stage G1–G2, A3). Exclusion criteria were non-Caucasian ethnicity, solid organ or bone marrow transplantation, active malignancy within 24 months prior to screening, New York Heart Association Stage IV heart failure, and legal attendance or inability to provide consent. 5,123 participants were genotyped for 2,612,357 markers at the Helmholtz Center Munich using the Illumina Infinium Omni 2.5 Exome-8 microarray (Illumina, GenomeStudio, Genotyping Module Version 1.9.4) and genotype imputation using the 1000 Genomes Phase 3 ALL reference panel was conducted, as previously described (24).

All participants provided written informed consent, and the GCKD Cohort was approved by the ethics commission of the Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany (Nr 3831) and by the ethics committees of all participating institutions and registered in the national registry for clinical studies (Deutsches Register Klinischer Studien 00003971) (https://www.gckd.de/) (Table S12).

The GCKD study was funded by the German Ministry of Research and Education (Bundesminsterium für Bildung und Forschung, BMBF, grant number 01ER0804, K.U.E.); by the Foundation KfH Stiftung Präventivmedizin and by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Projektnummer 246781735 – SFB 1140; and by grants provided by Bayer, Fresenius Medical Care and Amgen. Genotyping was supported by Bayer Pharma AG. Urinary UMOD measurements in GCKD were supported by the Swiss National Centre of Competence in Research Kidney Control of Homeostasis program and the Swiss National Science Foundation grant 310030_189044.

Analyses of UMOD processing

Western blot: HEK293 cells were lysed in octylglucoside lysis buffer (50 mM Tris-HCl, pH 7.4; 150 mM NaCl; 60 mM octyl β-D-glucopyranoside and protease inhibitors cocktail (Merck, Germany)) and analyzed by Western blot as described in Schaeffer et al (25), using mouse

monoclonal antibody against HA (1:2,000 dilution; Biolegend, San Diego, CA). Quantification was performed using the gel analysis option of ImageJ software (1).

Pulse-chase experiment: Pulse chase experiments on HEK293 cells stably expressing UMOD were performed as described in Schaeffer et al (25). UMOD was immunoprecipitated using a sheep anti-UMOD antibody (T0850B, United States Biological, Salem, MA).

Immunofluorescence on cells: Immunofluorescence experiments were performed essentially as described in Schaeffer et al (25). UMOD polymers on the surface of MDCK cells stably expressing the indicated UMOD isoform were revealed using an anti-HA antibody (1:500, Biolegend) followed by 1h staining with Alexa-Fluor 594 anti-mouse secondary antibody (1:500; Thermo Fisher Scientific). Images were acquired on an Applied Precision DeltavisionUltra system, using an Olympus 100x 1.4NA oil immersion objective, Z step size of 0.2 µm. Images were deconvolved with Applied Precision's softWorx software (GE Healthcare, Issaquah, WA). To quantify the amount of UMOD on the plasma membrane, immunofluorescence analysis was performed in HEK293 cells 10 hours after transfection of the indicated UMOD isoform. Before staining, cells were incubated 20 min at 4°C with 0.5 mg/mL EZ-Link® Sulfo-NHS-LC-Biotin (Thermo Fisher Scientific). UMOD was revealed with an anti-HA antibody (1:500, Biolegend, San Diego, CA) followed by 1h staining with Alexa-Fluor 594 anti-mouse secondary antibody (1:500; Thermo Fisher Scientific) and the biotinylated membrane with a FITC conjugated streptavidin (1:200, Sigma). All pictures were taken with an UltraVIEW ERS spinning disk confocal microscope (UltraVIEW ERS-Imaging Suite Software, Zeiss 63X/1.4; PerkinElmer Life and Analytical Sciences Boston, MA) and were deconvoluted with Huygens Professional version 19.04 (Scientific Volume Imaging, The Netherlands). Co-occurrence of UMOD (HA) signal with the one of the membrane (streptavidin) was quantified using the Coloc2 Plugins from ImageJ software (1). For each UMOD isoform between 30 and 50 cells from 3 independent experiments were analyzed. We set HA signal as channel 1 and streptavidin signal as channel 2 and the threshold was automatically assigned using the Costes method. Co-occurrence of the two signals was determined using tM1 and tM2 (Manders coefficient above threshold). tM2 can be considered as a readout of UMOD reaching the membrane.

Immunofluorescence on patient tissue: Immunodetection of UMOD and GRP78 was performed on 7-µm-thick kidney sections obtained from various normal human kidney samples, p.Thr62Pro biopsies and kidney samples from ADTKD-*UMOD* patients (Table S9). Slides were deparaffinized in xylene and rehydrated in a graded ethanol series. Antigen retrieval was carried out for 10 minutes with citrate buffer (pH 6.0) at 98 °C. After 1h in blocking solution, slides were incubated 1h in room temperature with sheep anti-UMOD primary antibody (1:800; K90071C; Meridian Life Science Inc., Memphis, TN), followed by 1h AlexaFluor488-conjugated donkey anti-sheep (1:400; Thermo Fisher Scientific). The slides were then probed 1h at room temperature with rabbit anti-GRP78 primary antibody (1:400; ab21685; Abcam, Cambridge, UK), followed by 1h incubation with AlexaFluor647-conjugated donkey anti-rabbit antibody (1:400; Thermo Fisher Scientific). Coverslips were mounted with Prolong gold antifade reagent with 4′,6-diamidino-2-phenylindole (Thermo Fisher Scientific) and analyzed under a Leica STELLARIS 5 Confocal Microscope (Leica Camera, Wetzlar, Germany) with a x63/1.4 Plan- Apochromat oil-immersion objective. The mean fluorescence intensity of GRP78 was measured in both UMOD-positive and UMOD-negative tubules using the ImageJ software. Briefly, the selection brush tool was used to manually trace the contour of each tubule, and the mean fluorescence intensity of the GRP78 signal was measured in each tubule. The tubular lumen was excluded from the quantification. The use of these samples has been approved by the local Ethical Review Boards.

Measurements of urinary levels of UMOD: A validated ELISA method was used to measure urinary uromodulin (uUMOD) levels (second morning urine sample) from patients with ADTKD-*UMOD* and individuals heterozygous for *UMOD* p.Thr62Pro (26). Urinary creatinine was measured

using a Synchron DXC800 analyzer (Beckman Coulter, Fullerton, CA). The control samples were obtained from the Cohorte Lausannoise (CoLaus), a population-based study including 6,000 people 35 to 75 years of age from the city of Lausanne, Switzerland (27). Urinary creatinine was used to normalize uUMOD levels as previously described (4). Informed consent was obtained from all participating individuals.

Measurements of ER stress markers expression: Expression levels of the indicated genes were measured in HEK293 cells transiently expressing the indicated UMOD isoforms. RNA was extracted with TriFast II (Euroclone, Pero, Italy) following the manufacturer's instructions 72h after transfection. When indicated, cells were treated with tunicamycin (20 ng/ml) for 12 hours before RNA extraction. RNA was retro-transcribed with the iScript gDNA Clear cDNA Synthesis Kit (Bio-Rad, Hercules, CA). Real-time qPCR was performed on the CFX96 Touch instrument (Bio-Rad) using the qPCR Core kit for SYBR® Green I No ROX (Eurogentec, Liège, Belgium) with specific primers for the indicated genes.

Target gene	**Primer Forward (5'>3')**	**Primer Reverse (5'>3')**
HSPA5 (Human)	CGCTGAGGCTTATTTGGGAAAG	TGCCGTAGGCTCGTTGATG
XBP1S (Human)	GAGTCCGCAGCAGGTG	ATACCGCCAGAATCCATGG
HPRT1 (Human)	AGCCCTGGCGTCGTGATTAGTG	TGTGATGGCCTCCCATCTCCTTCA

In silico modelling

Structural data: the structure of the first EGF of UMOD was obtained by using the software Phyre2 (28) (submitted sequence aa 25-65, Uniprot P07911-1). We obtained a homology-based model for residues 30-65. The different substitutions were introduced in the obtained PDB formatted model using the mutagenesis wizard in PyMOL, and in Missense 3D and SDM programs. The predicted effect of p.Leu180Val and p.Thr469Met variants was assessed, along with p.Thr62Pro, by using the full-length cryo-EM structure of native human UMOD (PDB 7PFP) (29) and PyMOL mutagenesis wizard.

EGF-like domain 1 sequence alignment in vertebrates: The EGF-like domain 1 of human UMOD was analyzed in Pfam, which identified a match with Pfam *EGF_3* (PF12947) family. All vertebrate sequences within PF12947 family were then retrieved (n = 8,622) and aligned with Mafft program. Aligned sequences were manually curated to identify sequences lacking the sixth cysteine (C_6). These sequences (n = 222) were scanned in Prosite to verify the presence or absence of the C_5-C_6 disulphide bond in the EGF-like domain. If this bond was present (n = 111), the missing part of the EGF-like domain sequence was added and realigned. If this bond was reported as absent (n = 111), the sequence was discarded from alignment. We finally retrieved 8,511 aligned sequences that were analyzed with FASMA to obtain the frequency of each of amino acid at the position preceding Cysteine 6 (X_{C6-1}), corresponding to Thr62 in human UMOD sequence.

Statistics

Categorical variables were compared using the Fisher's exact test. Continuous variables were compared using an unpaired two-tailed *t* test with Welch's correction when assuming unequal standard deviations, one way analysis of variance (ANOVA), followed by Bonferroni's or Tukey's multiple comparison post hoc testing for normally distributed variables or Kruskal-Wallis test with Dunn's multiple comparisons test for non-parametric values. Kaplan-Meier curves were generated

to display kidney failure-free survival. Patients who had not reached kidney failure at the end of the study (outcome of interest not occurred during follow-up time) were considered censored individuals. Censoring time was defined as age at last follow-up. A log-rank test was used for comparison of survival curves. Statistical analysis was performed within GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com). $P<0.05$ was considered statistically significant.

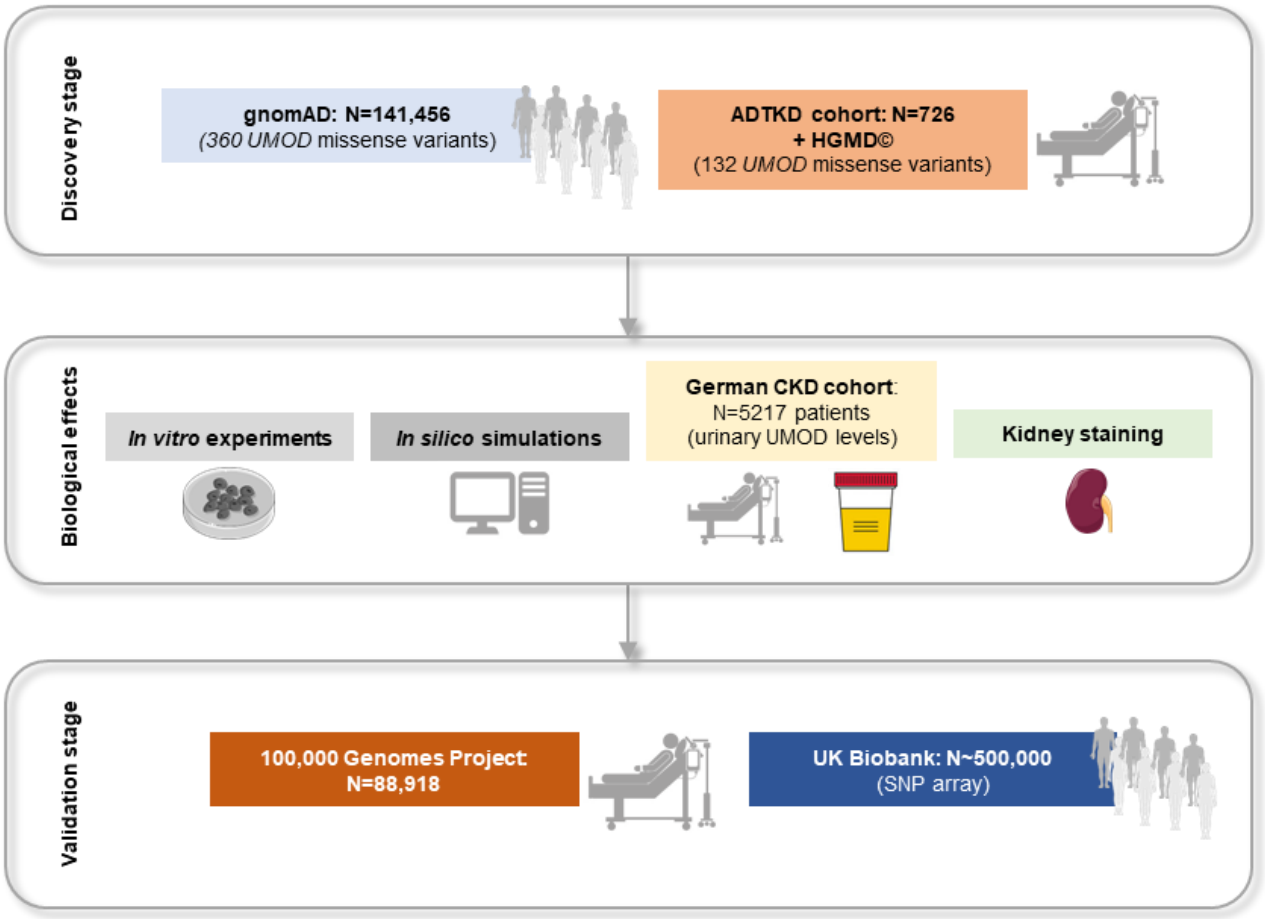
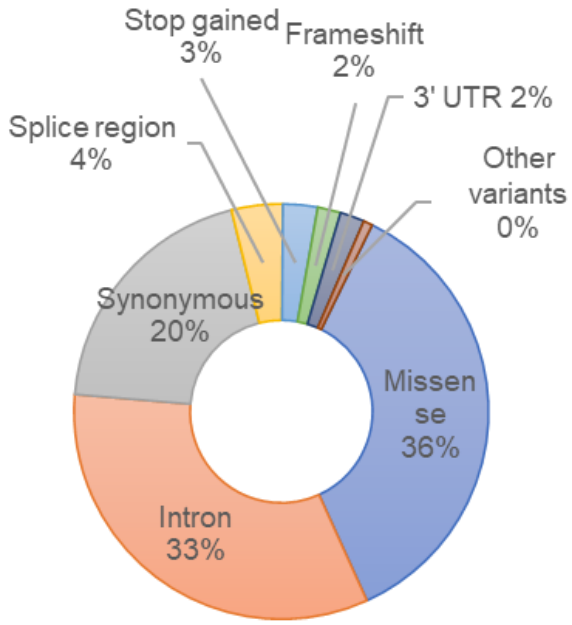


Fig. S1. Workflow for the identification and validation of intermediate-effect genetic variants in *UMOD*.

A



B

Type of variant	Variant counts
Missense	360
- Cysteine residue affected	1.4% (5 of 360)
- Nonpolar AA affected	46.1% (166 of 360)
- Polar AA affected	27.8% (100 of 360)
- Positively charged AA affected	13.9% (50 of 360)
- Negatively charged AA affected	12.2% (44 of 360)
Intron	331
Synonymous	198
Splice region	40
Stop gained	27
Frameshift	18
3' UTR	19
Splice donor	3
Splice acceptor	3
Inframe deletion	1
Total	1000

Fig. S2. **Landscape of *UMOD* genetic variation in the gnomAD population.** (A) Relative contribution of different classes of genetic alterations in the *UMOD* gene in exome and genome sequencing data from the Genome Aggregation Database (gnomAD v2.1.1) population (141,456 individuals). A total of 1000 variants are reported after removing data related to non-canonical transcripts (81 variants). (B) Quantitative details for *UMOD* variants reported in the gnomAD dataset. Variants denoting non-canonical transcripts have been removed (n=81) and consequences have been checked for consistency with *UMOD* transcript ENST00000302509.8.

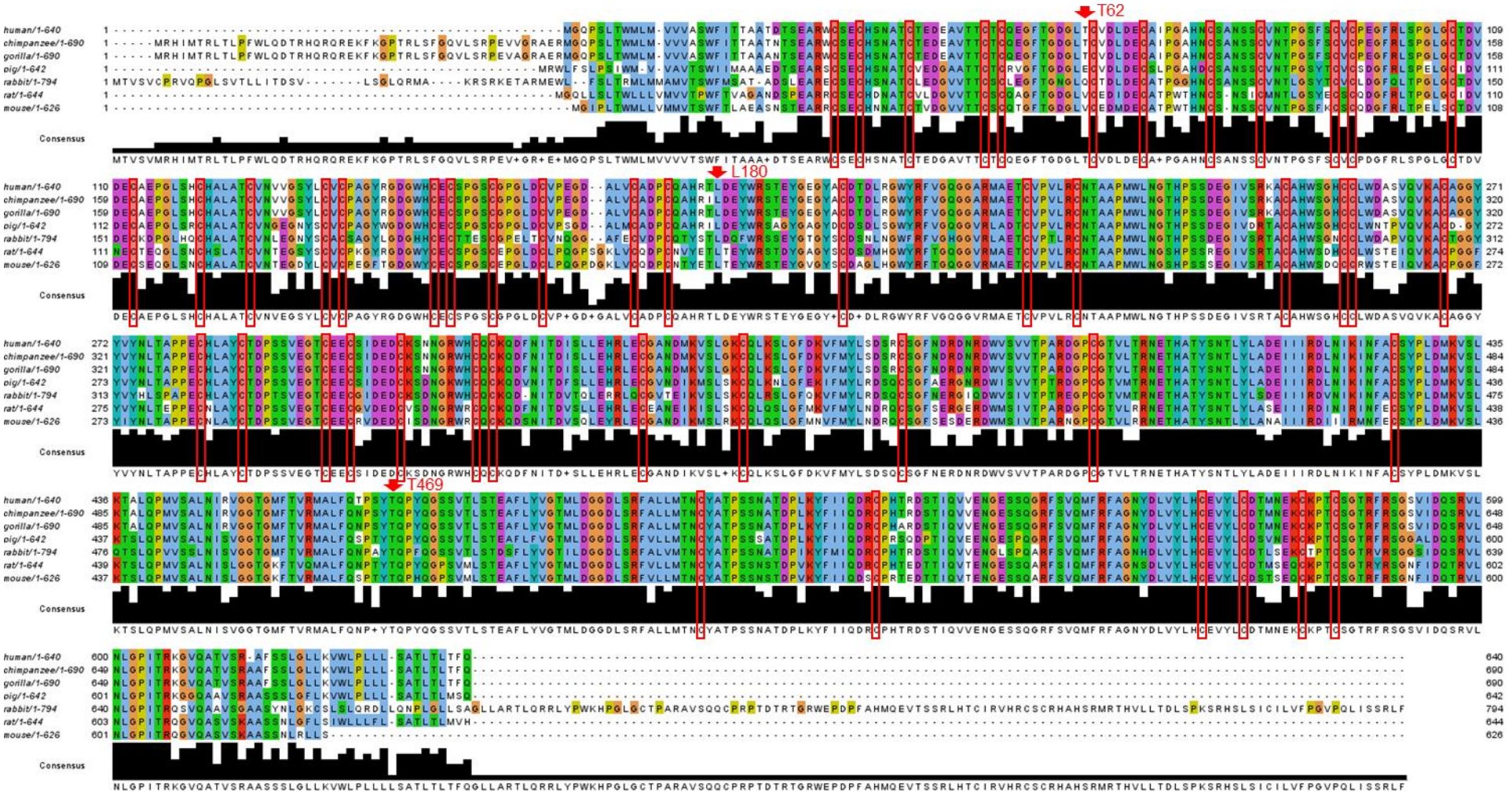


Fig. S3. UMOD amino acid conservation across mammalian species. Conservation of UMOD amino acids across indicated mammalian species using Clustal omega. Positions Thr62, Leu180 and Thr469 are indicated by red arrows. Note the 48 cysteine positions (boxed in red), all fully conserved.

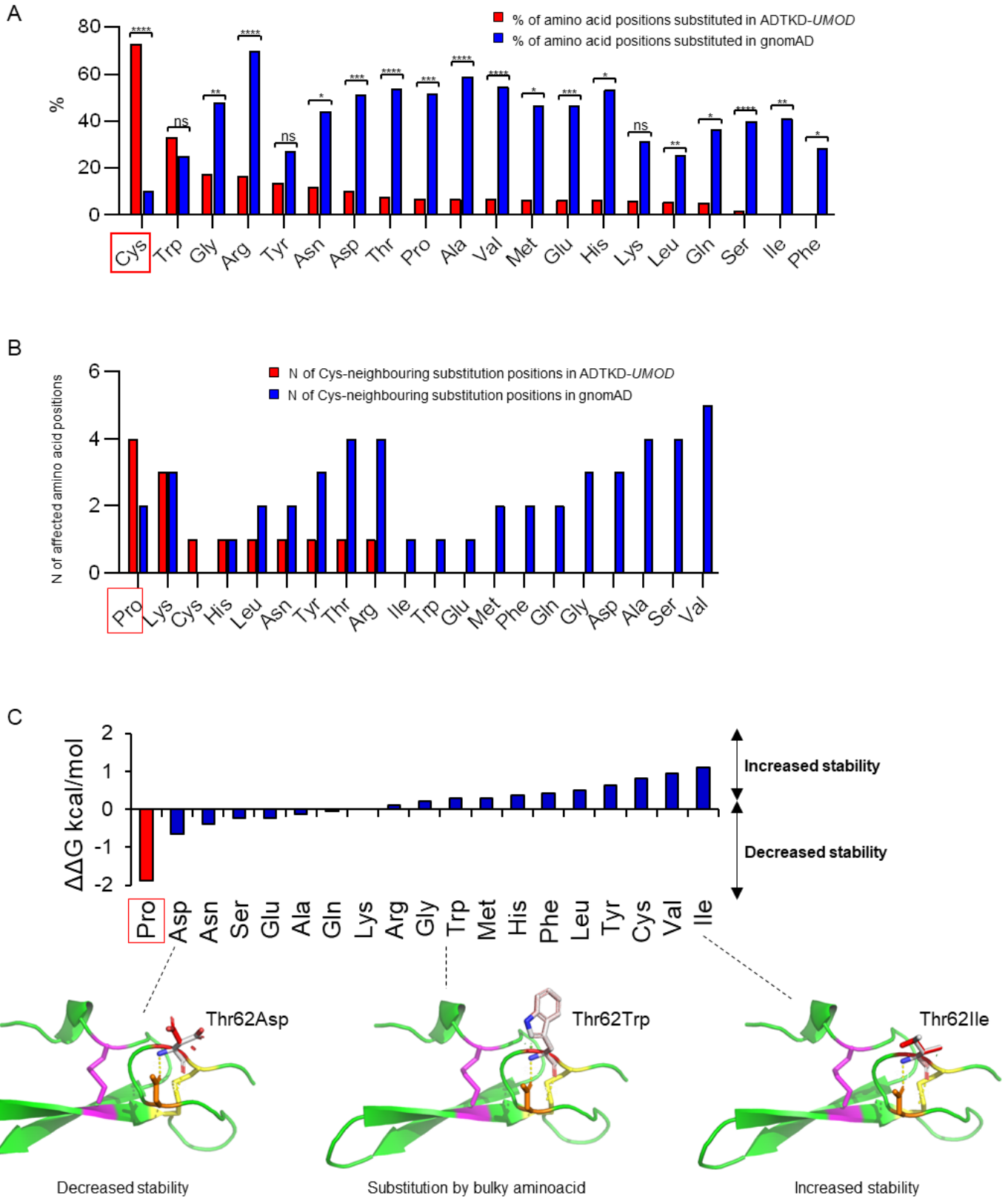

A
% of amino acid positions substituted in ADTKD-UMOD
% of amino acid positions substituted in gnomAD
%
80
60
40
20
0
Cys Trp Gly Arg Tyr Asn Asp Thr Pro Ala Val Met Glu His Lys Leu Gln Ser Ile Phe
B
N of Cys-neighbouring substitution positions in ADTKD-UMOD
N of Cys-neighbouring substitution positions in gnomAD
N of affected amino acid positions
6
4
2
0
Pro Lys Cys His Leu Asn Tyr Thr Arg Ile Trp Glu Met Phe Gln Gly Asp Ala Ser Val
C
ΔΔG kcal/mol
2
1
0
-1
-2
Increased stability
Decreased stability
Pro Asp Asn Ser Glu Ala Gln Lys Arg Gly Trp Met His Phe Leu Tyr Cys Val Ile
Thr62Asp
Thr62Trp
Thr62Ile
Decreased stability
Substitution by bulky aminoacid
Increased stability

Fig. S4. UMOD amino acid substitutions and *in silico* modelling of UMOD p.Thr62 isoforms. (A) Percentage of amino acid positions that are substituted in UMOD missense variants reported in gnomAD (blue) vs. in ADTKD-*UMOD* patients from the International ADTKD Cohort and HGMD® (red). Of note, 35/48 (73%) of cysteine positions have been substituted in patients with ADTKD-*UMOD* vs. only 5/48 (10%) positions in gnomAD. Statistical analysis using Fisher's exact test on number of substitutions in relation to total number of available positions for each amino acid; ns not significant; *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. (B) Number of amino acid substitution positions directly adjacent to cysteines in the gnomAD dataset (blue) vs. in ADTKD-*UMOD* patients from the international ADTKD cohort and HGMD® (red). Out of the total available cysteine-adjacent positions (n=94), 4 are substituted with a proline in ADTKD-*UMOD* patients, while only 2 positions are substituted with a proline in gnomAD (including p.Thr62Pro), indicating relatively poor tolerance for proline substitutions adjacent to cysteines. (C) The graph represents the double change in Gibbs free energy (ΔΔG; measure of the change in free energy between the folded and unfolded states in wild type protein and after insertion of the point mutation) as a read out of how the replacement of Thr62 with the indicated residue affects protein stability. Representative examples of modelling of UMOD EGF-like domain 1 variants at position 62. Here shown are substitutions of Thr62 with aspartic acid (as the most destabilizing mutation after proline), tryptophan (as an example of substitution with a bulky aminoacid) and isoleucine (as the most stabilizing substitution). Of note, tryptophan is the least frequent residue present in vertebrate EGF-like domains at the position corresponding to UMOD Thr62 (see Figure 3A). None of these substitutions has a strong impact on protein structure, except for p.Thr62Pro (see Figure 3B). Polar contacts are indicated by yellow dashed lines. Small green and red disks indicate the presence of atoms almost in contact and van der Waals overlap, respectively. The figure was made with PyMOL (Schrödinger LLC).

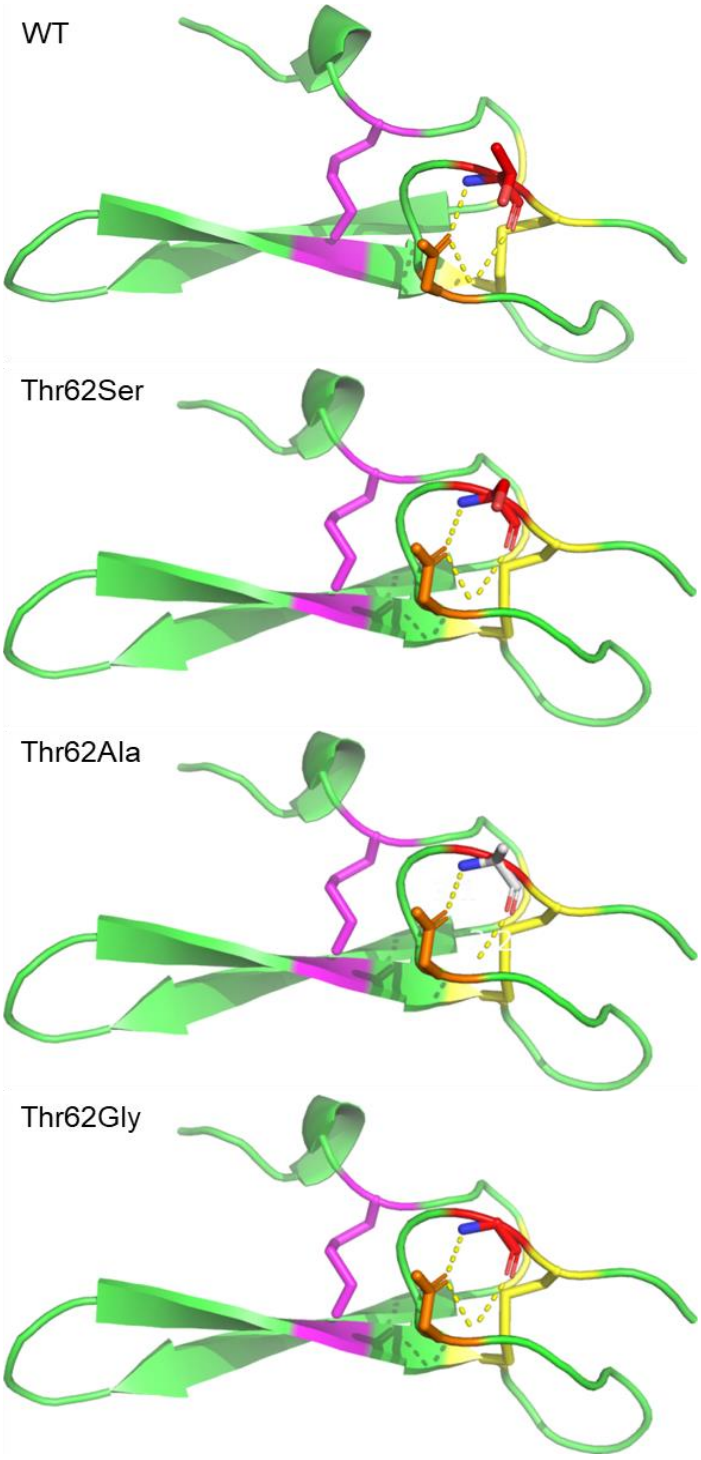


Fig. S5. *In silico* modelling of UMOD pThr62Ser, p.Thr62Ala and p.Thr62Gly. Shown here are substitutions with serine, a nucleophilic amino acid similar to proline, and two small amino acids, alanine and glycine. Polar contacts are indicated by yellow dashed line. Potential clashes in the structure are represented by red dots (not seen in any of these predictions). The figure was made with PyMOL (Schrödinger LLC).

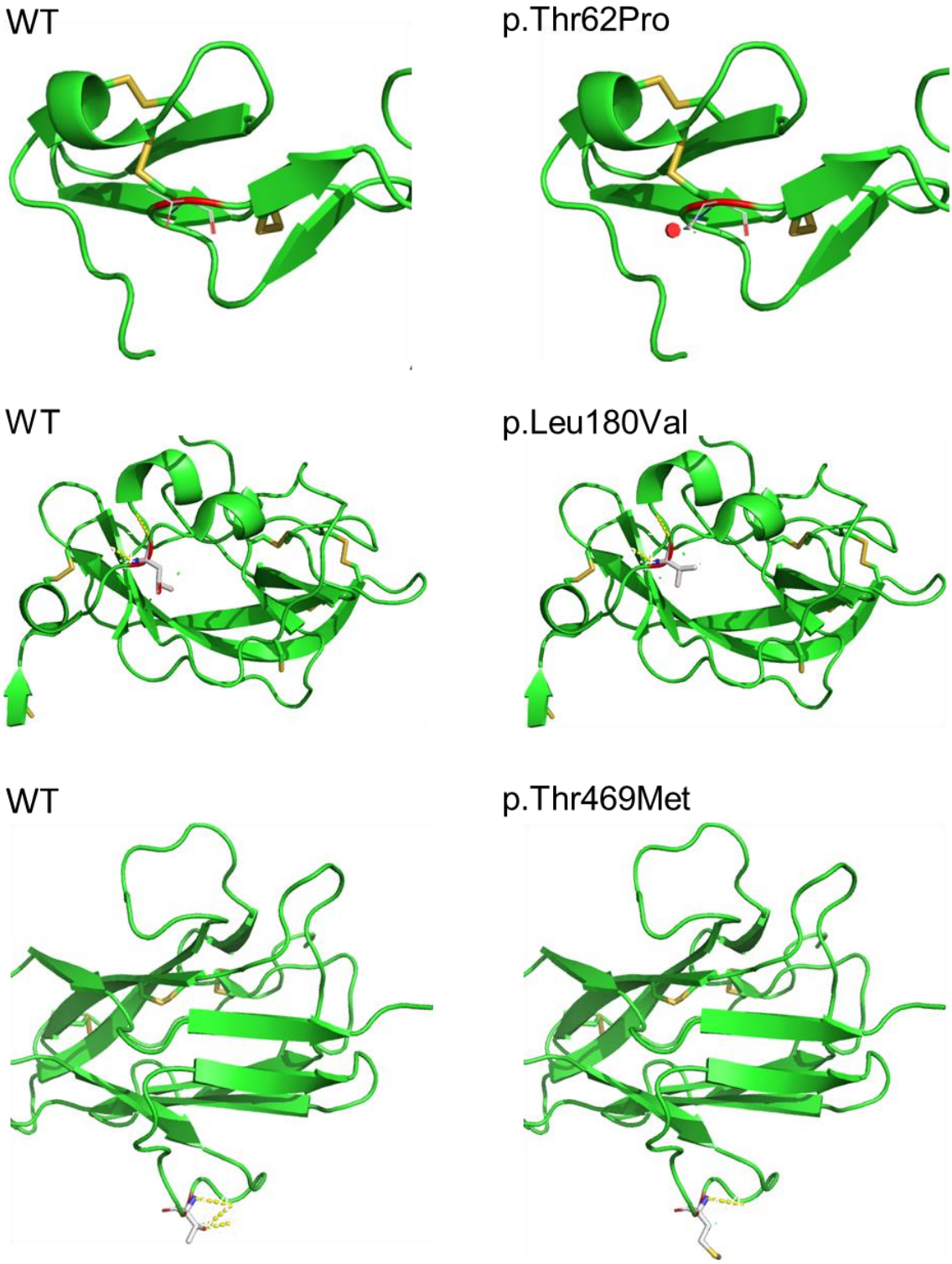


Fig. S6. *In silico* modelling of UMOD p.Thr62Pro, p.Leu180Val and p.Thr469Met. Polar contacts are indicated by yellow dashed line. Potential clashes in the structure, represented by red dots, are seen for p.Thr62Pro only. The figure was made with PyMOL (Schrödinger LLC).

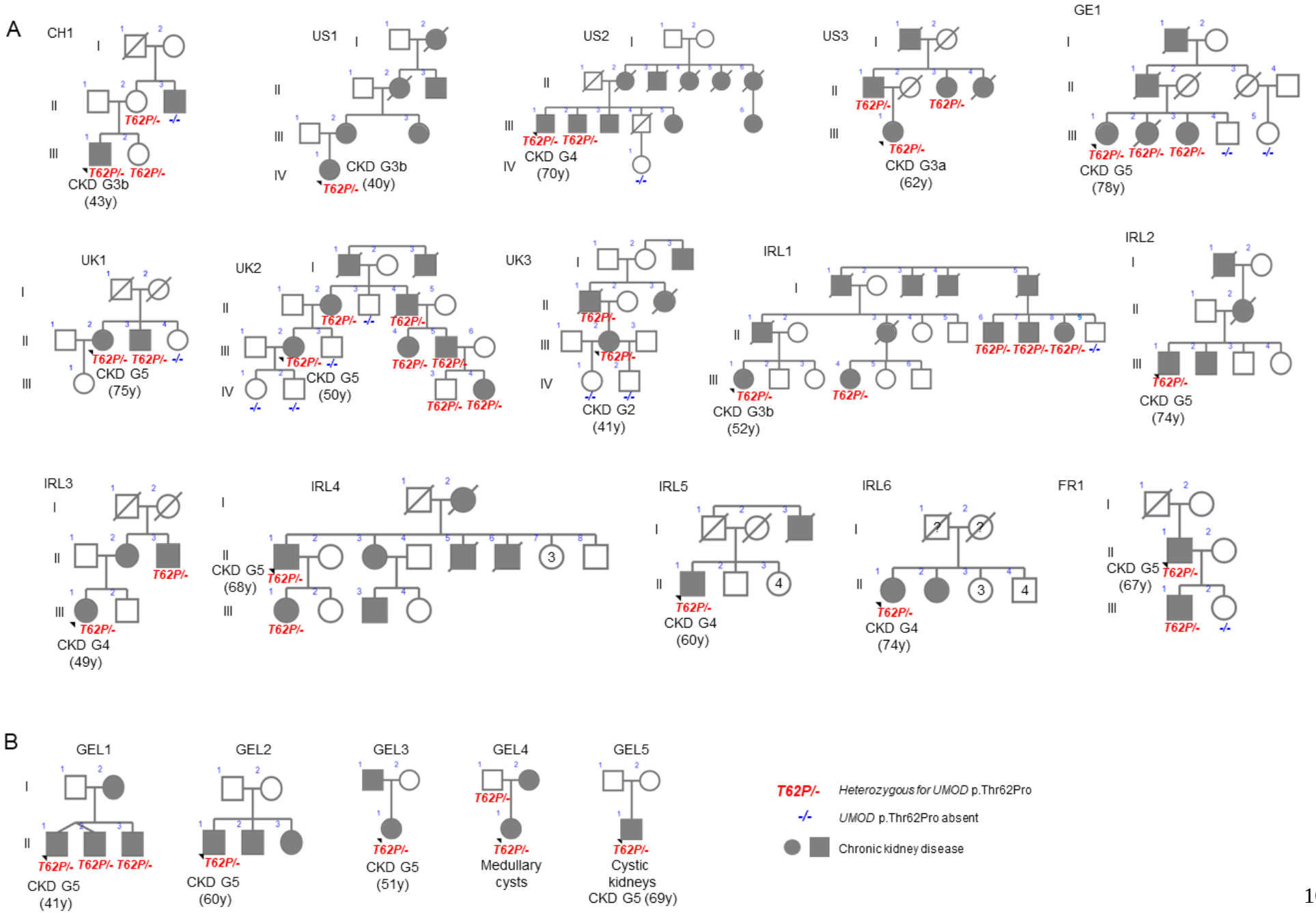

A
CH1
T62P/-
-/-
T62P/- T62P/-
CKD G3b
(43y)
US1
CKD G3b
T62P/- (40y)
US2
T62P/- T62P/-
CKD G4
(70y)
US3
T62P/-
T62P/-
T62P/-
CKD G3a
(62y)
GE1
T62P/- T62P/- T62P/-
-/-
-/-
CKD G5
(78y)
UK1
T62P/- T62P/-
-/-
CKD G5
(75y)
UK2
T62P/-
-/-
T62P/-
T62P/-
T62P/-
CKD G5
(50y)
-/-
-/-
T62P/- T62P/-
UK3
T62P/-
T62P/-
-/-
-/-
CKD G2
(41y)
IRL1
T62P/- T62P/- T62P/-
-/-
T62P/-
T62P/-
CKD G3b
(52y)
IRL2
T62P/-
CKD G5
(74y)
IRL3
T62P/-
T62P/-
CKD G4
(49y)
IRL4
CKD G5
(68y)
T62P/-
T62P/-
3
IRL5
4
T62P/-
CKD G4
(60y)
IRL6
?
?
3
4
T62P/-
CKD G4
(74y)
FR1
CKD G5
(67y)
T62P/-
T62P/-
-/-
B
GEL1
T62P/- T62P/- T62P/-
CKD G5
(41y)
GEL2
T62P/-
CKD G5
(60y)
GEL3
T62P/-
CKD G5
(51y)
GEL4
T62P/-
T62P/-
Medullary
cysts
GEL5
T62P/-
Cystic
kidneys
CKD G5 (69y)
T62P/- Heterozygous for UMOD p.Thr62Pro
-/- UMOD p.Thr62Pro absent
Chronic kidney disease

Fig. S7. *UMOD* p.Thr62Pro genetic load in familial CKD clusters. (A) *UMOD* p.Thr62Pro carriers in families with unexplained CKD and features compatible with autosomal dominant tubulointerstitial kidney disease identified in tertiary clinical centers in Switzerland (CH), US, the UK, the Republic of Ireland (IRL), Germany (GE), France (FR) and (B) identified through Genomics England 100,000 Genomes Project (GEL). Patients with chronic kidney disease (CKD) are marked in grey, unaffected family members in white. The index patient is marked with an arrowhead and is labelled with CKD stadium or kidney phenotype at last evaluation and age. For individuals with available genotype, the heterozygote status of p.Thr62Pro is marked in red, absence of *UMOD* p.Thr62Pro in blue. For full phenotype and genotype information see Table S4.

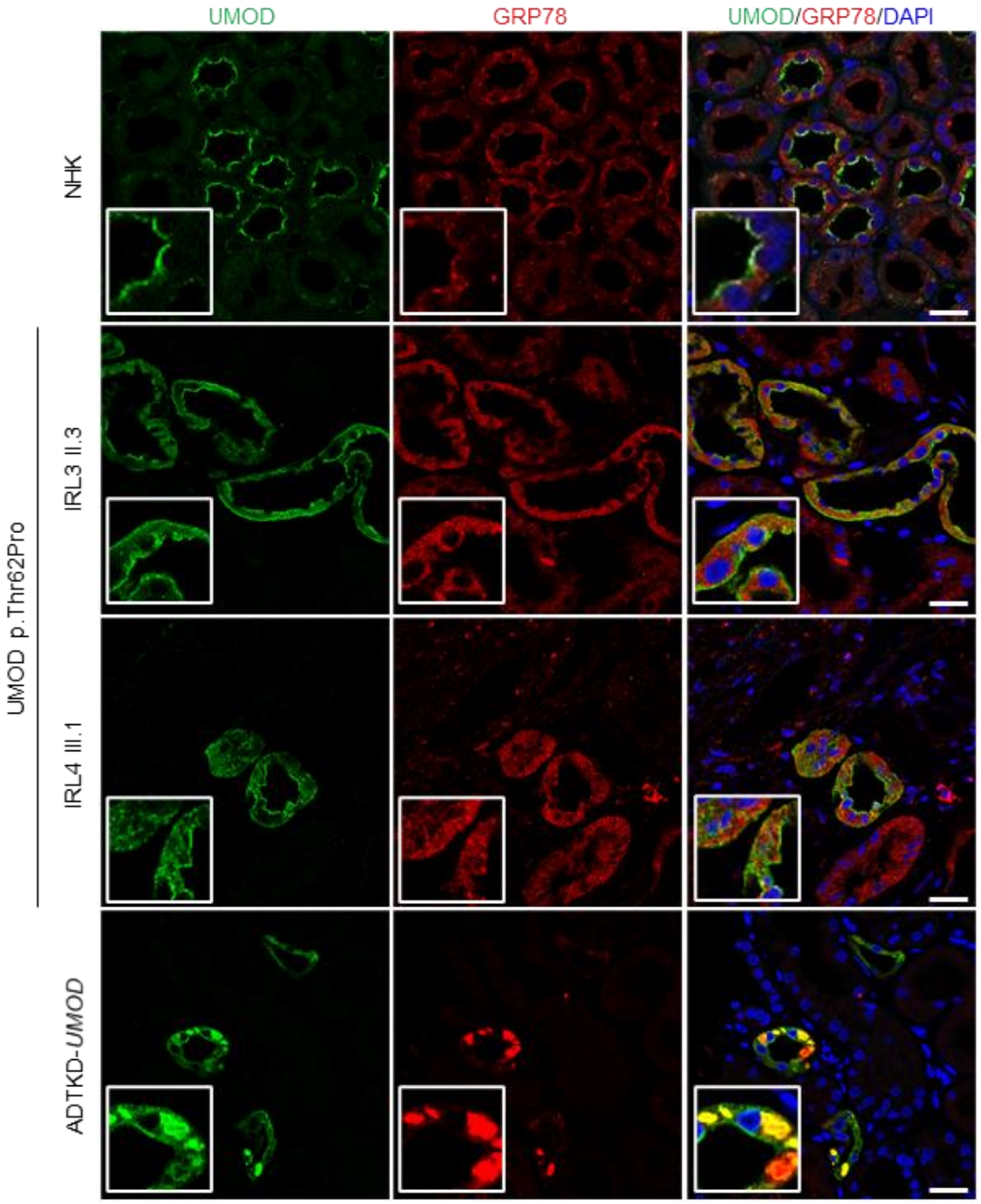


Fig. S8. Intracellular UMOD staining and upregulation of GRP78 in kidney tissue from *UMOD* p.Thr62Pro carriers. Immunofluorescence staining for UMOD (green) and glucose-regulated protein 78 (GRP78; red) in normal human kidney (NHK, tumor nephrectomy), *UMOD* p.Thr62Pro kidney biopsies from 2 different individuals and kidney tissue from an ADTKD-*UMOD* patient with a canonical *UMOD* mutation (p.Tyr274Cys). For more details see Table S9. Bars=25 µm. DAPI, 4′,6-diamidino-2-phenylindole.

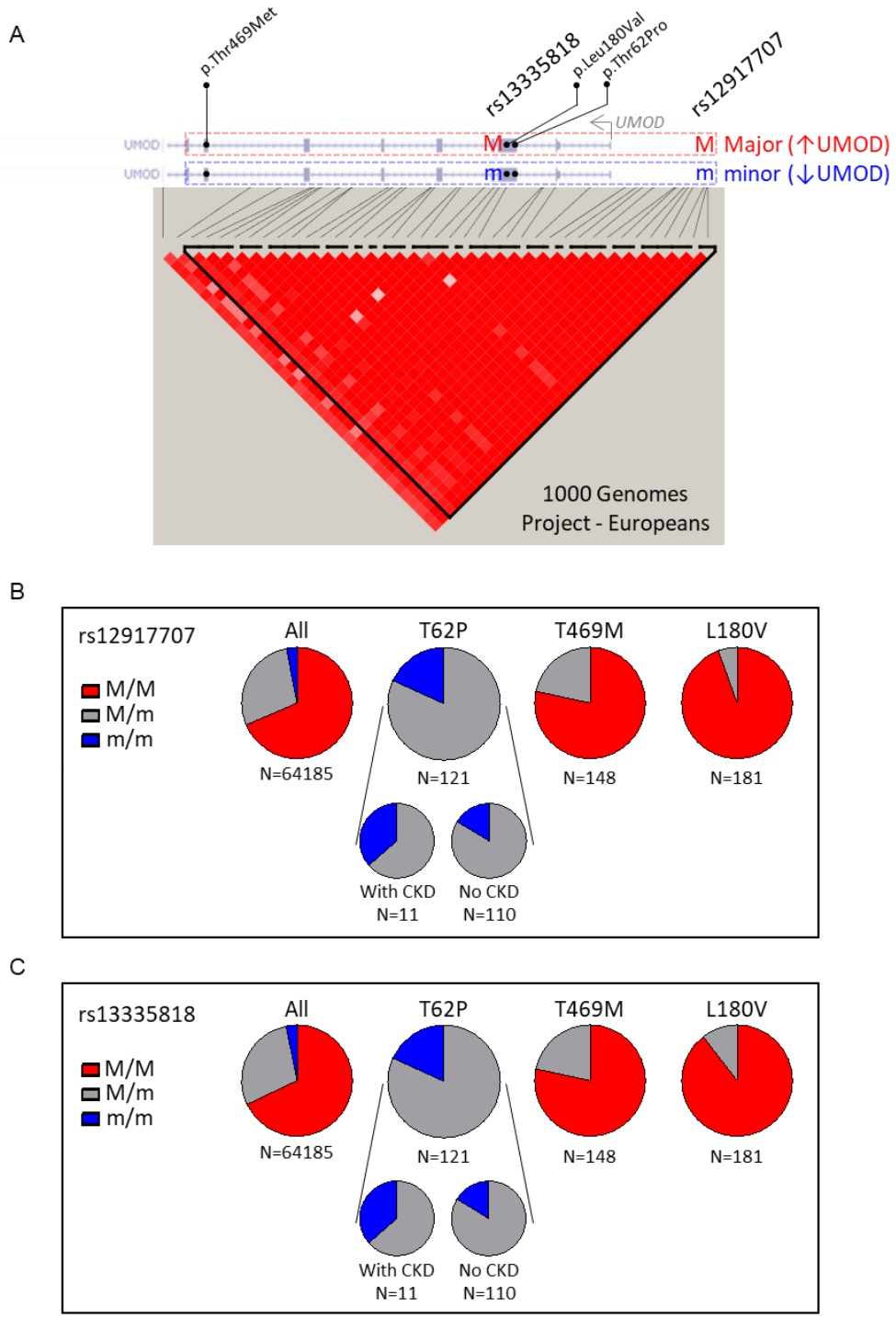


Figure S9: Distribution of common *UMOD* haplotype tagging SNPs rs12917707 and rs13335818 among carriers of *UMOD* p.Thr62Pro, p.Leu180Val and p.Thr469Met. (A) LD map of the *UMOD* locus based on 1000 Genomes Project summary data for European populations. D' values are shown in color-code with darker red being D'=1, and the two common SNPs and 3 rare SNVs of interest highlighted on the graph. Figure generated using Haploview 4.2. The major SNPs (M) are associated with higher *UMOD* expression levels compared with the minor SNPs (m) (18). (B) Distribution of rs12917707 and (C) rs13335818 alleles among the global 100,000 Genomes dataset and carriers of the three indicated SNV in *UMOD*. Individuals with *UMOD* p.Thr62Pro have been separated in those with CKD and without CKD.

Common SNP								*UMOD* missenses			
rs12917707	rs12922822	rs13329952	rs13333226	rs4293393	rs13335818	rs9928936	rs9928757	Total	p.T62P	p.L180V	p.T469M
M	M	M	M	M	M	M	M	93492	5	1	**122**
M	M	M	m	m	M	M	M	168	-	**148**	-
M	M	M	M	M	M	m	m	329	1	-	-
M	M	M	m	m	M	m	m	4	-	2	-
m	m	m	m	m	m	m	m	20731	**95**	-	-

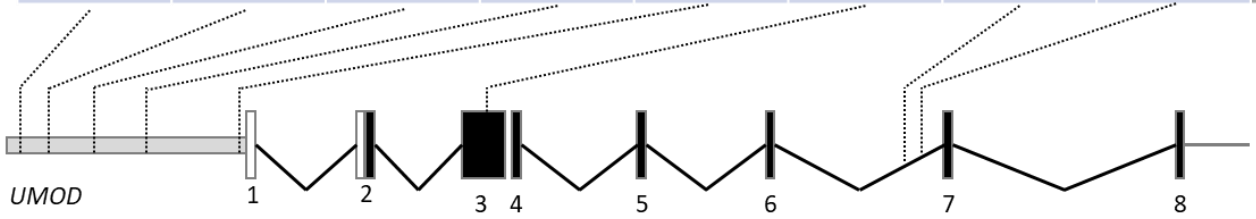


Figure S10: Estimated *UMOD* locus haplotypes carrying *UMOD* p.Thr62Pro, p.Leu180Val and p.Thr469Met. Haplotype phasing was performed using SHAPEIT4 version 4.2 on a ~60kb region centered on *UMOD* in Genomics England short read-sequencing data (GRCh38). 8 SNPs covering the *UMOD* promoter and coding regions and modulating *UMOD* expression (18) have been utilized to define over 120,000 statistically phased haplotypes. Haplotypes carrying *UMOD* p.Thr62Pro, p.Leu180Val and p.Thr469Met have been extracted and are represented here. M and m denote the major (reference) or minor (alternative) alleles respectively.

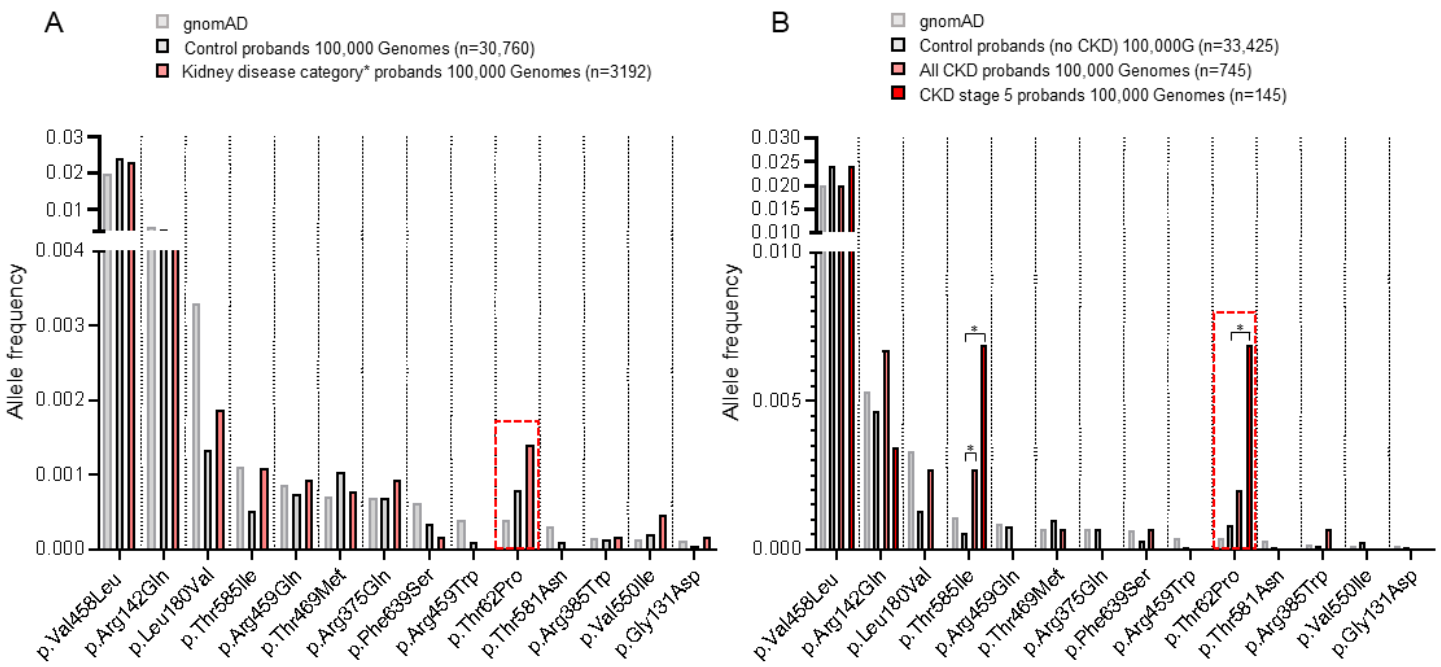
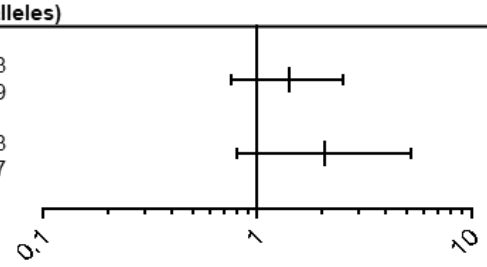


Fig. S11. Genetic load of rare and low-frequency *UMOD* missense variants in 100,000 Genomes Project kidney disease probands. Distribution of allelic frequencies for rare (gnomAD 10^{-3}>AF>10^{-4}) or low frequency (gnomAD AF>10^{-3}) *UMOD* missense variants in the general population (gnomAD) and in probands enrolled in Genomics England 100,000 Genomes project. (A) 100,000 Genomes probands enrolled under any of following kidney disease categories (*): 'congenital anomalies of the kidney and the urinary tract', 'cystic kidney disease', 'familial hematuria', 'proteinuric renal disease', 'renal tract calcification', 'unexplained kidney failure in young people' versus probands enrolled under any of the remaining disease categories. (B) 100,000 Genomes probands enrolled under Human Phenotype Ontology (HPO) terms 'chronic kidney disease' or 'chronic kidney disease stage 5' versus probands without chronic kidney disease. Significant enrichment using Fisher's exact test is indicated with *P<0.05.

A

100,000 Genomes	Allele counts (L180V/WT alleles)	AF (L180V/all alleles)	OR (95% CI)	P-value
Kidney disease categories*				
Control probands	82/61438	0.0013		
Case probands	12/6372	0.0019	1.41 (0.76-2.52)	0.29
HPO Chronic kidney disease				
Control probands	87/66763	0.0013		
All CKD cases	4/1486	0.0027	2.07 (0.80-5.21)	0.14
CKD stage 5 cases	0/290	0.00	-	-



B

100,000 Genomes	Allele counts (T469M/WT alleles)	AF (T469M/all alleles)	OR (95% CI)	P-value
Kidney disease categories*				
Control probands	64/61456	0.00104		
Case probands	5/6379	0.00078	0.75 (0.33-1.81)	0.68
HPO Chronic kidney disease				
Control probands	70/66780	0.00104		
All CKD cases	1/1489	0.00067	0.64 (0.063-3.65)	0.99
CKD stage 5 cases	0/290	0.00	-	-

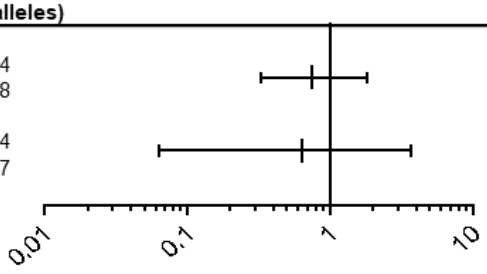


Fig. S12. *UMOD* p.Leu180Val and p.Thr469Met in 100,000 Genomes Project kidney diseases probands and controls. (A&B) Prevalence of p.Leu180Val and p.Thr469Met heterozygous alleles in probands from the Genomics England 100,000 Genomes project with indicated renal phenotypes and in control probands where the indicated phenotype is absent. *Kidney disease categories comprise: ‘congenital anomalies of the kidney and the urinary tract’, ‘cystic kidney disease’, ‘familial hematuria’, ‘proteinuric renal disease’, ‘renal tract calcification’, ‘unexplained kidney failure in young people’. P value computed using Fisher’s exact test.

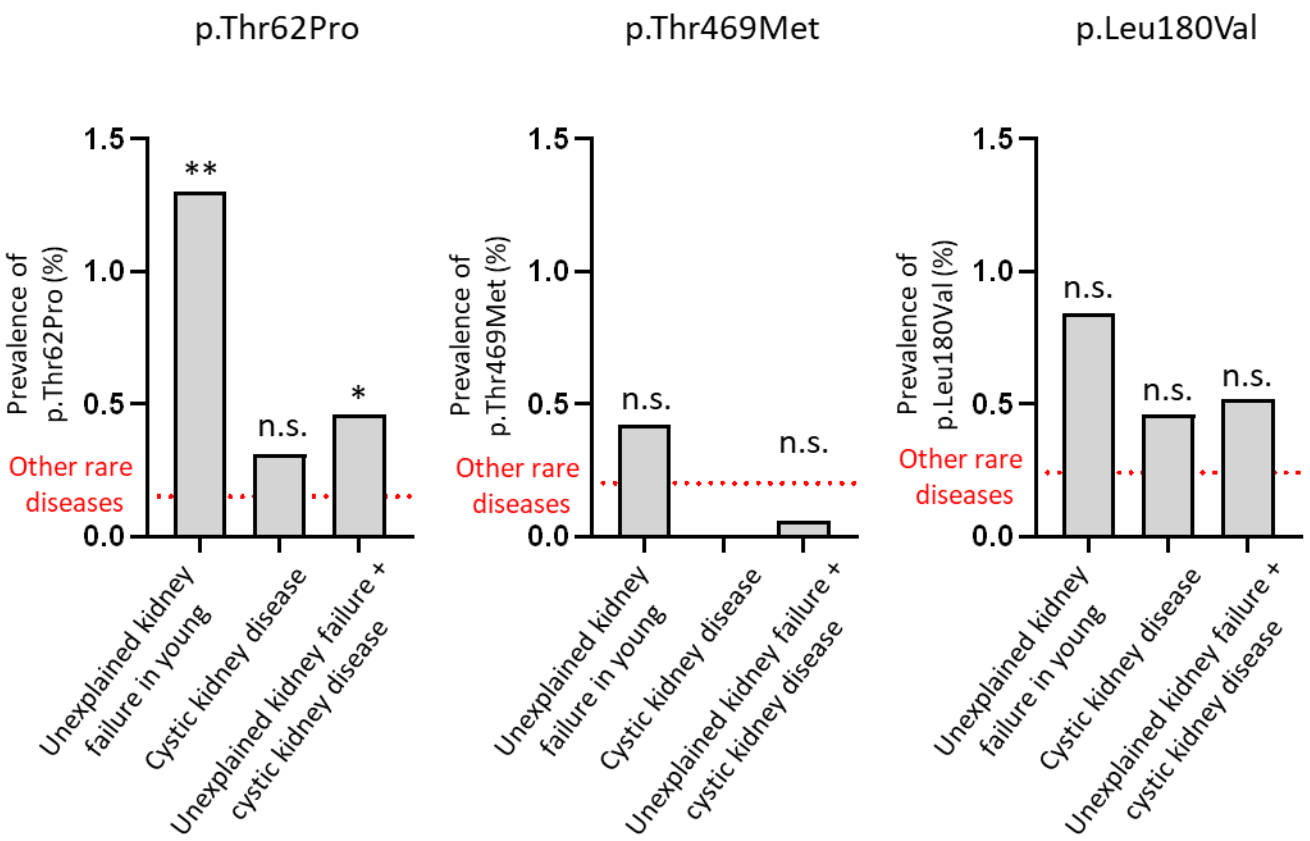


Fig. S13. Prevalence of *UMOD* p.Thr62Pro, p.Thr469Met and p.Leu180Val in probands from 100,000 Genomes Project specific disease groups. *UMOD* p.Thr62Pro is detected in 3/238, 4/1302 and 7/1540 probands recruited under 'Unexplained kidney failure in young people', 'Cystic kidney disease' and both groups combined, respectively. This compares with 50/33832 for probands recruited under every other rare disease group. The corresponding numbers for *UMOD* p.Thr469Met are 1/238, 0/1302, 1/1540 and 66/33832 and for *UMOD* p.Leu180Val are 2/238, 6/1302, 8/1540 and 81/33832. P values are computed using Fisher's exact test; **P≤0.01; * P≤0.05; n.s. non significant.

A

	Allele counts (T62P/WT alleles)	AF (T62P/all alleles)	OR (95% CI)	P-value
N183 CKD stage 3				
Controls	243/306301	0.00079		
Cases	2/2670	0.00075	0.94 (0.24-3.80)	>0.99
N184 CKD stage 4				
Controls	245/308581	0.00079		
Cases	0/390	0.00000	-	-
N185 CKD stage 5				
Controls	143/308623	0.00046		
Cases	2/328	0.00606	12.40 (3.06-50.27)	0.012
Transplantation of kidney				
Controls	243/308763	0.00079		
Cases	2/208	0.00952	12.22 (3.02-49.46)	0.012

B

	Allele counts (L180V/WT alleles)	AF (L180V/all alleles)	OR (95% CI)	P-value
N183 CKD stage 3				
Controls	1/306543	3.26E-06		
Cases	0/2672	0.00000	-	-
N184 CKD stage 4				
Controls	1/308825	3.24E-06		
Cases	0/390	0.00000	-	-
N185 CKD stage 5				
Controls	1/308865	3.24E-06		
Cases	0/350	0.00000	-	-
Transplantation of kidney				
Controls	1/309005	3.24E-06		
Cases	0/205	0.00000	-	-

C

	Allele counts (T469M/WT alleles)	AF (T469M/all alleles)	OR (95% CI)	P-value
N183 CKD stage 3				
Controls	446/306090	0.00145		
Cases	4/2666	0.00150	1.03 (0.39-2.76)	0.8
N184 CKD stage 4				
Controls	450/308366	0.00146		
Cases	0/390	0.00000	-	-
N185 CKD stage 5				
Controls	450/308406	0.00146		
Cases	0/350	0.00000	-	-
Transplantation of kidney				
Controls	450/308546	0.00146		
Cases	0/205	0.00000	-	-

Fig. S14. *UMOD* p.Thr62Pro, p.Leu180Val and p.Thr469Met and kidney disease in UK Biobank exome data. Prevalence of p.Thr62Pro, p.Leu180Val, p.Thr469Met alleles in controls and in individuals with indicated kidney phenotypes in the UK biobank exome data (unrelated individuals with “Caucasian” genetic ancestry). P values computed using Fisher’s exact test.

Table S1. Top 25 most common *UMOD* missense variants in gnomAD.

Chr	Position	rsID	REF	ALT	AA change	Allele Count	Allele Number	AF
16	20352618	rs55772253	C	A	p.(Val458Leu)	5653	282538	0.02001
16	20360198	rs199835347	C	T	p.(Arg142Gln)	981	184668	0.00531
16	20360085	rs187555378	G	C	p.(Leu180Val)	578	174180	0.00332
16	20348036	rs111992415	G	A	p.(Thr585Ile)	323	282822	0.00114
16	20352614	rs201761378	C	T	p.(Arg459Gln)	247	282566	0.00087
16	20352584	rs143583842	G	A	p.(Thr469Met)	203	282716	0.00072
16	20357506	rs151061376	C	T	p.(Arg375Gln)	196	282574	0.00069
16	20344643	rs145165861	A	G	p.(Phe639Ser)	177	281046	0.00063
16	20352615	rs139607138	G	A	p.(Arg459Trp)	109	282528	0.00039
16	20360439	rs143248111	T	G	p.(Thr62Pro)	99	282046	0.00035
16	20348048	rs143641292	G	T	p.(Thr581Asn)	84	282786	0.00030
16	20357477	rs200414962	G	A	p.(Arg385Trp)	41	282438	0.00015
16	20348705	rs188709583	C	T	p.(Val550Ile)	36	282824	0.00013
16	20360231	rs368943553	C	T	p.(Gly131Asp)	23	202250	0.00011
16	20360193	rs769398465	C	T	p.(Asp144Asn)	17	183688	0.00009
16	20357449	rs532447307	G	A	p.(Thr394Met)	25	282444	0.00009
16	20352618	rs55772253	C	G	p.(Val458Leu)	25	282538	0.00009
16	20359938	rs756226236	T	A	p.(Met229Leu)	19	229628	0.00008
16	20348027	rs387907549	C	T	p.(Arg588Gln)	22	282850	0.00008
16	20357476	rs141355380	C	T	p.(Arg385Gln)	19	251092	0.00008
16	20359889	rs753492646	C	T	p.(Arg245His)	16	216168	0.00007
16	20359781	rs543775691	T	C	p.(Glu281Gly)	19	278806	0.00007
16	20352446	rs550521976	G	A	p.(Thr515Met)	19	282720	0.00007
16	20352542	rs779351986	G	A	p.(Ala483Val)	15	251422	0.00006
16	20359865	rs760253448	C	T	p.(Gly253Asp)	15	258220	0.00006

Variants denoting non-canonical transcripts have been removed and consequences have been checked for consistency with *UMOD* transcript ENST00000302509.8. *UMOD* p.Thr62Pro is the 10th most common *UMOD* variant reported in gnomAD (Status 08/2021).

Table S2. Top predicted pathogenic *UMOD* missense variants in gnomAD (REVEL score >0.75).

Location	Allele	HGVSc	HGVSp	SIFT	Condel	PolyPhen	REVEL	ClinVar	gnomAD AC
16:20359916	A	c.707C>T	p.Pro236Leu	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.973	P/LP	1
16:20359802	C	c.821A>G	p.Tyr274Cys	deleterious(0)	deleterious(0.935)	probably_damaging(0.999)	0.955	-	1
16:20360264	T	c.359G>A	p.Cys120Tyr	deleterious(0)	deleterious(0.935)	probably_damaging(0.999)	0.954	-	1
16:20348774	G	c.1579T>C	p.Cys527Arg	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.930	-	1
16:20359829	A	c.794A>T	p.Lys265Met	deleterious(0)	deleterious(0.919)	probably_damaging(0.998)	0.909	-	1
16:20360306	A	c.317G>T	p.Cys106Phe	deleterious(0)	deleterious(0.935)	probably_damaging(0.999)	0.906	Conflicting	2
16:20352482	C	c.1508T>G	p.Met503Arg	deleterious(0)	deleterious(0.867)	probably_damaging(0.979)	0.886	-	1
16:20357461	T	c.1169G>A	p.Gly390Glu	deleterious(0)	deleterious(0.919)	probably_damaging(0.998)	0.882	-	1
16:20348656	T	c.1697G>A	p.Cys566Tyr	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.874	-	1
16:20348659	C	c.1694A>G	p.His565Arg	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.862	-	1
16:20359902	T	c.721G>A	p.Gly241Ser	deleterious(0.02)	deleterious(0.883)	probably_damaging(1)	0.860	-	1
16:20357644	G	c.986T>C	p.Leu329Pro	deleterious(0)	deleterious(0.911)	probably_damaging(0.997)	0.843	-	1
16:20357626	T	c.1004G>A	p.Cys335Tyr	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.834	-	1
16:20360507	A	c.116C>T	p.Ala39Val	deleterious(0)	deleterious(0.919)	probably_damaging(0.998)	0.829	-	1
16:20360231	T	c.392G>A	p.Gly131Asp	deleterious(0)	deleterious(0.902)	probably_damaging(0.995)	0.822	B	23
16:20359943	A	c.680C>T	p.Ala227Val	deleterious(0.01)	deleterious(0.835)	probably_damaging(0.983)	0.819	-	1
16:20348662	T	c.1691T>A	p.Leu564Gln	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.813	-	1
16:20348684	T	c.1669G>A	p.Gly557Arg	deleterious(0.01)	deleterious(0.905)	probably_damaging(1)	0.802	-	1
16:20359873	T	c.750C>A	p.His250Gln	deleterious(0.02)	deleterious(0.561)	possibly_damaging(0.527)	0.801	-	1
16:20359826	A	c.797C>T	p.Ala266Val	deleterious(0)	deleterious(0.889)	probably_damaging(0.991)	0.798	VUS	3
16:20348759	A	c.1594G>T	p.Asp532Tyr	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.794	-	1
16:20357552	T	c.1078T>A	p.Tyr360Asn	tolerated(0.05)	deleterious(0.820)	probably_damaging(0.998)	0.794	-	1
16:20348638	C	c.1715A>G	p.Asp572Gly	deleterious(0)	deleterious(0.902)	probably_damaging(0.995)	0.788	-	2
16:20352569	A	c.1421G>T	p.Gly474Val	deleterious(0)	deleterious(0.935)	probably_damaging(0.999)	0.788	-	1
16:20359818	T	c.805G>A	p.Gly269Ser	deleterious(0.01)	deleterious(0.626)	possibly_damaging(0.63)	0.788	-	1
16:20352630	T	c.1360G>A	p.Gly454Ser	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.779	-	3
16:20352636	T	c.1354G>A	p.Gly452Arg	deleterious(0)	deleterious(0.935)	probably_damaging(0.999)	0.779	-	8

16:20352554	G	c.1436T>C	p.Leu479Pro	deleterious(0)	deleterious(0.945)	probably_damaging(1)	0.760	-	1
16:20360297	T	c.326T>A	p.Val109Glu	deleterious(0)	deleterious(0.871)	probably_damaging(0.982)	0.759	LP	3
16:20357554	C	c.1076T>G	p.Met359Arg	tolerated(0.14)	deleterious(0.484)	possibly_damaging(0.664)	0.758	-	2

UMOD transcript ENST00000302509.4. Variants detected in ADTKD patients are shaded in grey. SIFT, Sorting Intolerant From Tolerant; Condel, CONsensus DELeteriousness; REVEL, rare exome variant ensemble learner (27) (a score >0.75 corresponds to a sensitivity of ~0.5 and a specificity of ~0.95 for pathogenic variants in the training dataset). ClinVar last accessed 06.2021, B, benign; P, pathogenic; LP, likely pathogenic; VUS, variant of unknown significance. AC, allele count.

Table S3. Missense *UMOD* variants reported in ADTKD families.

Nr	Exon	Domain	Nucleotide Change	Effect on Coding Sequence	Families ADTKD Cohort	Phenotype HGMD®	Ref paper HGMD®	families HGMD®	Families total
1	3	I	c.95G>A	p.(Cys32Tyr)	1	FJHN/MCKD syndrome	(30)	1	**2**
2	3	I	c.96C>G	p.(Cys32Trp)	1	Hyperuricaemic nephropathy, juvenile	(31)	1	**2**
3	3	I	c.100G>A	p.(Glu34Lys)	1	Tubulointerstitial nephritis	(13)	1	**1***
4	3	I	c.115G>A	p.(Ala39Thr)	1			0	**1**
5	3	I	C.122G>A	p.(Cys41Tyr)	1			0	**1**
6	3	I	c.149G>C	p.(Cys50Ser)	0	Reduced kidney function, hyperuricaemia and impaired urine-concentrating ability	(32)	1	**1**
7	3	I	c.155G>A	p.(Cys52Tyr)	1	Chronic kidney disease, autosomal dominant	(8)	1	**2**
8	3	I	c.155G>C	p.(Cys52Ser)	1			0	**1**
9	3	I	c.156T>G	p.(Cys52Trp)	0	Hyperuricaemic nephropathy, juvenile	(33)	1	**1**
10	3	I	c.163G>A	p.(Gly55Ser)	1			0	**1**
11	3	I	c.172G>T	p.(Gly58Cys)	0	Uromodulin-associated kidney disease	(34)	1	**1**
12	3	I	c.176A>C	p.(Asp59Ala)	1	Hyperuricaemic nephropathy, juvenile	(6)	1	**1***
13	3	I	c.184A>C	p.(Thr62Pro)	1	Chronic kidney disease, autosomal dominant?	(8)	1	**2**
14	3	I	c.188G>C	p.(Cys63Ser)	1			0	**1**
15	3	I	c.187T>C	p.(Cys63Arg)	0	Hyperuricaemic nephropathy, juvenile	(35)	1	**1**
16	3	I	c.189C>G	p.(Cys63Trp)	0	Hyperuricaemic nephropathy, juvenile	(36)	1	**1**
17	3	II	c.202G>A	p.(Glu68Lys)	1			0	**1**
18	3	II	c.206G>A	p.(Cys69Tyr)	0	Uromodulin-associated kidney disease	(34)	1	**1**
19	3	II	c.205T>C	p.(Cys69Arg)	1	Tubulointerstitial nephritis	(13)	1	**1***
20	3	II	c.228C>G; c.229T>G	p.(Asn76Lys) p.(Cys77Gly)	1			0	**1**
21	3	II	c.229T>G	p.(Cys77Gly)	0	FJHN/MCKD syndrome	(37)	1	**1**

22	3	II	c.229T>C	p.(Cys77Arg)	1			0	**1**
23	3	II	c.230G>A	p.(Cys77Tyr)	2	Hyperuricaemic nephropathy, juvenile	(38)	1	**3**
24	3	II	c.247T>C	p.(Cys83Arg)	1			0	**1**
25	3	II	c.254A>G	p.(Asn85Ser)	1			0	**1**
26	3	II	c.255C>G	p.(Asn85Lys)	2			0	**2**
27	3	II	c.274T>C	p.(Cys92Arg)	1			0	**1**
28	3	II	c.274T>G	p.(Cys92Gly)	1			0	**1**
29	3	II	c.275G>A	p.(Cys92Tyr)	2			0	**2**
30	3	II	c.282C>G	p.(Cys94Trp)	1			0	**1**
31	3	II	c.307G>T	p.(Gly103Cys)	1	Medullary cystic kidney disease 2	(39)	1	**1***
32	3	II	c.317G>T	p.(Cys106Phe)	9			0	**9**
33	3	II	c.316T>G	p.(Cys106Gly)	2			0	**2**
34	3	II	c.317G>A	p.(Cys106Tyr)	1	Uromodulin-associated kidney disease	(34)	1	**2**
35	3	III	c.326T>A	p.(Val109Glu)	0	Hyperuricaemic nephropathy, juvenile	(40)	1	**1**
36	3	III	c.334T>C	p.(Cys112Arg)	1	Hyperuricaemic nephropathy, juvenile	(6)	1	**1***
37	3	III	c.358T>C	p.(Cys120Arg)	1			0	**1**
38	3	III	c.376T>C	p.(Cys126Arg)	1	Hyperuricaemic nephropathy, juvenile	(38)	1	**2**
39	3	III	c.383A>G	p.(Asn128Ser)	4	Hyperuricaemic nephropathy, juvenile	(38)	1	**5**
40	3	III	c.404G>A	p.(Cys135Tyr)	2			0	**2**
41	3	III	c.403T>A	p.(Cys135Ser)	1	Hyperuricaemic nephropathy, juvenile	(33)	1	**2**
42	3	III	c.404G>T	p.(Cys135Phe)	2			0	**2**
43	3	III	c.405C>G	p.(Cys135Trp)	1			0	**1**
44	3	III	c.403T>G	p.(Cys135Gly)	0	Uromodulin-associated kidney disease	(41)	1	**1**
45	3	III	c.410G>A	p.(Cys137Tyr)	0	Hyperuricaemic nephropathy, juvenile	(42)	1	**1**
46	3	III	c.442T>C	p.(Cys148Arg)	2	Tubulointerstitial nephritis	(13)	1	**2***
47	3	III	c.442T>A, c.443G>C	p.(Cys148Ser)	2			0	**2**
48	3	III	c.443G>A	p.(Cys148Tyr)	4	Hyperuricaemic nephropathy, juvenile	(39)	1	**4***
49	3	III	c.444T>G	p.(Cys148Trp)	0	Medullary cystic kidney disease 2	(43)	1	**1**

50	3		c.449G>C	p.(Cys150Ser)	1	Medullary cystic kidney disease 2	(43)	1	**2**
51	3		c.448T>A	p.(Cys150Ser)	0	Uromodulin-associated kidney disease	(34)	1	**1**
52	3		c.463T>C	p.(Cys155Arg)	0	Chronic kidney disease	(44)	1	**1**
53	3		c.478G>C	p.(Asp160His)	1			0	**1**
54	3		c.509G>A	p.(Cys170Tyr)	2	Hyperuricaemic nephropathy, juvenile	(6)	1	**2***
55	3		c.514G>C	p.(Asp172His)	2	Tubulointerstitial nephritis	(13)	1	**2***
56	3		c.518C>T	p.(Pro173Leu)	1			0	**1**
57	3		c.518C>G	p.(Pro173Arg)	0	Hyperuricaemic nephropathy, juvenile	(45)	1	**1**
58	3		c.520T>C	p.(Cys174Arg)	2	Uromodulin-associated kidney disease	(46)	1	**3**
59	3		c.533G>C	p.(Arg178Pro)	14			0	**14**
60	3		c.539T>C	p.(Leu180Pro)	2			0	**2**
61	3		c.538C>G	p.(Leu180Val)	1			0	**1**
62	3		c.552G>C	p.(Trp184Cys)	1	Tubulointerstitial nephritis	(13)	1	**1***
63	3		c.553C>A	p.(Arg185Ser)	1	Hyperuricaemic nephropathy, juvenile	(6)	1	**1***
64	3		c.554G>A	p.(Arg185His)	2	Tubulointerstitial nephritis	(13)	1	**2***
65	3		c.553C>T	p.(Arg185Cys)	4	Tubulointerstitial nephritis	(13)	1	**4***
66	3		c.553C>G	p.(Arg185Gly)	1	Hyperuricaemic nephropathy, juvenile	(47)	1	**1***
67	3		c.584G>A	p.(Cys195Tyr)	1	Hyperuricaemic nephropathy, juvenile	(48)	1	**2**
68	3		c.584G>T	p.(Cys195Phe)	0	Hyperuricaemic nephropathy, juvenile	(33)	1	**1**
69	3		c.585_586CG>TA	p.(Asp196Asn)	1			0	**1**
70	3		c.586G>T	p.(Asp196Tyr)	2	Hyperuricaemic nephropathy, juvenile	(49)	1	**3**
71	3		c.586G>A	p.(Asp196Asn)	0	Hyperuricaemic nephropathy, juvenile	(31)	1	**1**
72	3	D8C	c.602G>A	p.(Gly201Asp)	1			0	**1**
73	3	D8C	c.605G>C	p.(Trp202Ser)	1	Hyperuricaemic nephropathy, juvenile	(33)	1	**2**
74	3	D8C	c.606G>T	p.(Trp202Cys)	1			0	**1**
75	3	D8C	c.607T>G	p.(Tyr203Asp)	1			0	**1**
76	3	D8C	c.611G>C	p.(Arg204Pro)	1			0	**1**
77	3	D8C	c.610C>G	p.(Arg204Gly)	4	Hyperuricaemic nephropathy, juvenile	(6)	1	**4***
78	3	D8C	c.628G>A	p.(Gly210Ser)	2	Tubulointerstitial nephritis	(13)	2	**2***

79	3	D8C	c.634C>T	p.(Arg212Cys)	0	Uromodulin-associated kidney disease	(50)	1	**1**
80	3	D8C	c.649T>G	p.(Cys217Gly)	1	Hyperuricaemic nephropathy, juvenile	(6)	1	**1***
81	3	D8C	c.651C>G	p.(Cys217Trp)	0	Hyperuricaemic nephropathy, juvenile	(31)	1	**1**
82	3	D8C	c.649T>C	p.(Cys217Arg)	1	Hyperuricaemic nephropathy, juvenile	(39)	1	**1***
83	3	D8C	c.665G>C	p.(Arg222Pro)	1	Hyperuricaemic nephropathy, juvenile	(6)	1	**1***
84	3	D8C	c.668G>A	p.(Cys223Tyr)	2	Hyperuricaemic nephropathy, juvenile	(51)	1	**2***
85	3	D8C	c.667T>C	p.(Cys223Arg)	0	Hyperuricaemic nephropathy, juvenile	(31)	1	**1**
86	3	D8C	c.674C>T	p.(Thr225Met)	4	Hyperuricaemic nephropathy, juvenile	(6)	1	**4***
87	3	D8C	c.674C>A	p.(Thr225Lys)	1	Medullary cystic kidney disease 2	(52)	1	**2**
88	3	D8C	c.686T>G	p.(Met229Arg)	1	FJHN/MCKD syndrome	(30)	1	**2**
89	3	D8C	c.688T>C	p.(Trp230Arg)	1	Uromodulin-associated kidney disease	(34)	1	**2**
90	3	D8C	c.706C>T	p.(Pro236Ser)	2			0	**2**
91	3	D8C	c.707C>G	p.(Pro236Arg)	1	Hyperuricaemic nephropathy, juvenile	(53)	1	**2**
92	3	D8C	c.707C>T	p.(Pro236Leu)	6	Hyperuricaemic nephropathy, juvenile	(33)	1	**7**
93	3	D8C	c.707C>A	p.(Pro236Gln)	0	Hyperuricaemic nephropathy, juvenile	(40)	1	**1**
94	3	D8C	c.710C>G	p.(Ser237Cys)	1	Tubulointerstitial nephritis	(13)	1	**1***
95	3	D8C	c.744C>G	p.(Cys248Trp)	2	Medullary cystic kidney disease 2	(52)	1	**3**
96	3	D8C	c.743G>C	p.(Cys248Ser)	0	Uromodulin-associated kidney disease	(34)	1	**1**
97	3	D8C	c.749A>T	p.(His250Leu)	1	Tubulointerstitial nephritis	(13)	1	**1***
98	3	D8C	c.750C>A	p.(His250Gln)	0	Tubulointerstitial nephropathy and hyperuricaemia	(54)	1	**1**
99	3	D8C	c.757G>T	P.(Gly253Cys)	1			0	**1**
100	3	D8C	c.764G>A	p.(Cys255Tyr)	0	Hyperuricaemic nephropathy, juvenile	(38)	1	**1**
101	3	D8C	c.767G>A	p.(Cys256Tyr)	0	Uromodulin-associated kidney disease	(50)	1	**1**
102	3	D8C	c.770T>C	p.(Leu257Pro)	2			0	**2**
103	3	D8C	c.774G>C	p.(Trp258Cys)	1			0	**1**
104	3	D8C	c.800G>T	p.(Cys267Phe)	1			0	**1**
105	3	D8C	c.805G>T	p.(Gly269Cys)	1			0	**1**
106	3	D8C	c.808G>T	p.(Gly270Cys)	1	Uromodulin-associated kidney disease	(55)	1	**2**

107	3	D8C	c.817G>C	p.(Val273Leu)	1			0	**1**
108	3	D8C	c.817G>T	p.(Val273Phe)	0	FJHN/MCKD syndrome	(30)	1	**1**
109	3	D8C	c.820T>C	p.(Tyr274His)	1			0	**1**
110	3	D8C	c.821A>G	p.(Tyr274Cys)	0	Uromodulin-associated kidney disease	(34)	1	**1**
111	3	D8C	c.844T>C	p.(Cys282Arg)	1	Hyperuricaemic nephropathy, juvenile	(6)	1	**1***
112	3	D8C	c.844T>A	p.(Cys282Ser)	1			0	**1**
113	3	D8C	c.851T>C	p.(Leu284Pro)	2			0	**2**
114	3	D8C	c.854C>A	p.(Ala285Glu)	3			0	**3**
115	3	D8C	c.857A>G	p.(Tyr286Cys)	2			0	**2**
116	3	D8C	c.860G>A	p.(Cys287Tyr)	1			0	**1**
117	4	IV	c.890G>A	p.(Cys297Tyr)	1	Tubulointerstitial nephritis	(13)	1	**1***
118	4	IV	c.891T>G	p.(Cys297Trp)	1	Renal insufficiency	(56)	1	**2**
119	4	IV	c.898T>G	p.(Cys300Gly)	1	Hyperuricaemic nephropathy, juvenile	(38)	1	**2**
120	4	IV	c.899G>A	p.(Cys300Tyr)	0	Medullary cystic kidney disease 2	(57)	1	**1**
121	4	IV	c.898T>A	p.(Cys300Ser)	1			0	**1**
122	4	IV	c.920A>C	p.(Lys307Thr)	0	Hyperuricaemic nephropathy, juvenile	(58)	1	**1**
123	4	IV	c.943T>C	p.(Cys315Arg)	2	Glomerulocystic kidney disease	(43)	1	**3**
124	4	IV	c.944G>A	p.(Cys315Tyr)	2	Tubulointerstitial nephritis	(13)	3	**3***
125	4	IV	c.947A>C	p.(Gln316Pro)	1	Hyperuricaemic nephropathy, juvenile	(59)	2	**3**
126	4	IV	c.950G>A	p.(Cys317Tyr)	1	Medullary cystic kidney disease 2	(43)	1	**2**
127	5	ZP_N	c.1039T>G	p.(Cys347Gly)	0	Hyperuricaemic nephropathy, juvenile	(60)	1	**1**
128	5	ZP_N	c.1039T>C	p.(Cys347Arg)	0	Congenital anomalies of the kidney and urinary tract	(61)	1	**1**
129	7	IHP	c.1382C>A	p.(Ala461Glu)	1	Hyperuricaemic nephropathy, juvenile	(62)	1	**2**
130	7	ZP_C	c.1406C>T	p.(Thr469Met)	2	Tubulointerstitial nephritis	(13)	1	**2***
131	7	ZP_C	c.1462G>C	p.(Gly488Arg)	1	Hyperuricaemic nephropathy, juvenile	(31)	1	**2**
132	9	CTP	c.1813A>G	p.(Thr605Ala)	0	Hyperuricaemic nephropathy, juvenile	(63)	1	1

*HGMD® entries correspond to patients included in the International ADTKD Cohort
86 mutations from HGMD® database (Version 2019.1, updated in March 2019) and 101 mutations from the International ADTKD Cohort (Belgo-Swiss and Wake Forest). *UMOD* transcript: ENST00000302509. Abbreviations as follows: FJHN, familial juvenile hyperuricaemic nephropathy; MCKD, medullary cystic kidney disease.

Table S4. Families with *UMOD* p.Thr62Pro and unexplained CKD.

Fam	Patient	Genetic testing	Genotype *UMOD*	Genotype *MUC1*	Additional results	Phenotype
CH1	III.1 (index)	Tubulopathy gene panel	*UMOD* p.T62P (+)	-	-	CKD G3b (43y), minimal proteinuria, low FEUA with gout, small kidneys with cortical cysts
		Brest panel v2	-	-	no additional findings	-
		HNF1B MLPA	-	-	negative	-
		MUC1 probe extension	-	wild-type	-	-
	III.2	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	Unaffected
	II.2	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	Unaffected (71y): normal eGFR and serum electrolytes, no proteinuria, normal uric acid, normal sonography of kidneys
	II.3	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	CKD G5 (47y), proteinuria (2.9g/d), arterial hypertension
US1	IV.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G3b (40y)
		REN Sanger sequencing	-	-	negative	-
		MUC1 probe extension	-	wild-type	-	-
	III.2	/	/	-	-	CKD G5 (53y)
	III.3	/	/	-	-	CKD
	II.2	/	/	-	-	CKD G5 (early 50s)
	II.3	/	/	-	-	Kidney failure in 50s
	I.2	/	/	-	-	CKD
US2	III.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G4 (70y), gout (67y)
		MUC1 probe extension	-	wild-type	-	-
	III.2	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (58y)
		MUC1 probe extension	-	wild-type	-	-

	IV.1	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
	III.3	/	/	-	-	CKD G5
	III.5	/	/	-	-	CKD G5
	III.6	/	/	-	-	CKD G5
	II.2	/	/	-	-	CKD G5, diabetes mellitus
US3	III.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G3a (62y)
		MUC1 probe extension	-	wild-type	-	-
	II.1	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (79y)
		MUC1 probe extension	-	wild-type	-	-
	II.3	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (74y)
		MUC1 probe extension	-	wild-type	-	-
	II.4	/	/	-	-	CKD G4
UK1	II.2 (index)	Brest panel v2	*UMOD* p.T62P (+)	-	no additional findings	CKD G5 (75y), minimal proteinuria, family history of gout
		HNF1B MLPA	-	-	negative	-
		MUC1 probe extension	-	wild-type	-	-
	II.3	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G3b (78y)
	II.4	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
UK2	III.2 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (50y), minimal proteinuria
		MUC1 probe extension	-	wild-type	-	-
		REN Sanger sequencing	-	-	negative	-
	II.2	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (55y)
	II.4	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (36y), gout
	III.4	*UMOD* Sanger	*UMOD*	-	-	CKD G5 (38y), gout

		sequencing	p.T62P (+)			
	III.5	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (42y), gout (late 20s)
	IV.3	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	no CKD (16y)
	IV.4	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD (15y)
	IV.1	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
	IV.2	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
	III.3	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
	II.3	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
	I.1	/	/	-	-	CKD G5 (58y)
	I.3	/	/	-	-	CKD
UK3	III.2 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G2 (41y), minimal proteinuria
		Brest panel v2	-	-	see Table S5	-
	II.1	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (<40y), gout
		Brest panel v2	-	-	see Table S5	-
		MUC1 probe extension	-	wild-type	-	-
	II.3	/	/	-	-	CKD G5 (40s)
	I.3	/	/	-	-	CKD G5
	IV.1	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
	IV.2	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
IRL1	III.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G3b (52y), no proteinuria, no hematuria, normal size kidneys without cysts
		MUC1 probe extension	-	wild-type	-	-
		Brest panel v4	-	-	see Table S5	-

	III.4	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (31y)
		MUC1 probe extension	-	wild-type	-	-
	II.6	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (65y), HTN, non-enlarged multicystic kidneys (MRI)
		Brest panel v4	-	-	see Table S5	-
	II.7	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G3a (70y), bland urine, HTN
		Brest panel v4	-	-	see Table S5	-
	II.8	Whole exome sequencing	*UMOD* p.T62P (+)	-	see Table S5	CKD G5 (63y), kidney cysts
	II.9	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected (62y)
IRL2	III.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (74y), gout (30y), protein 2+, no hematuria
		MUC1 probe extension	-	wild-type	-	-
IRL3	III.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G4 (49y), no proteinuria, no hematuria, 1 simple kidney cyst, kidneys not enlarged
		MUC1 probe extension	-	wild-type	-	-
		Customized 227 gene panel	-	-	see Table S5	-
	II.3	Customized 227 gene panel	*UMOD* p.T62P (+)	-	see Table S5	CKD G5 (60y), gout, hypertension, kidney biopsy: arteriosclerosis and 2nd FSGS
IRL4	II.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (68y), kidney biopsy: extensive fibrosis
		MUC1 probe extension	-	wild-type	-	-
	III.1	Whole exome sequencing	*UMOD* p.T62P (+)	-	see Table S5	CKD G4 (35y)
IRL5	II.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G4 (60y), HTN, kidney biopsy: extensive interstitial fibrosis
		MUC1 probe extension	-	wild-type	-	-
IRL6	II.1 (index)	Whole exome sequencing	*UMOD* p.T62P (+)	-	see Table S5	CKD G4 (74y), T2DM, HTN, no proteinuria, hematuria, normal-sized kidneys with cortical thinning (US)
		MUC1 probe extension	-	wild-type	-	-

	II.2	/	/	-	-	CKD G5 (70y), HTN
GE1	III.1 (index)	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (78y), no gout, no proteinuria, small kidneys, kidney biopsy: IF/TA
		MUC1 SnaPshot Miniseq	-	wild-type	-	-
		HNF1B (including MLPA), *REN, SEC61A1*	-	-	negative	-
		COL4A3, COL4A4, COL4A5	-	-	negative	-
		Whole exome sequencing	-	-	see Table S5	-
	III.2	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G5 (74.5y), small kidneys
		Whole exome sequencing	-	-	see Table S5	-
	III.3	*UMOD* Sanger sequencing	*UMOD* p.T62P (+)	-	-	CKD G3a (73y)
		MUC1 SnaPshot Miniseq	-	wild-type	-	-
		HNF1B (including MLPA), *REN, SEC61A1*	-	-	negative	-
	III.4	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected (69y)
		Whole exome sequencing	-	-	see Table S5	-
	III.5	*UMOD* Sanger sequencing	*UMOD* p.T62P (-)	-	-	Unaffected (80y)
	II.1	/	/	-	-	CKD G5 (65y)
	I.1	/	/	-	-	CKD G5 (65y)
FR1	II.1 (index)	Whole exome sequencing	*UMOD* p.T62P (+)	-	see Table S5	CKD G5 (67y), no relevant proteinuria, non-enlarged kidneys with bilateral cysts, kidney biopsy: tubulointerstitial nephropathy with nephroangiosclerosis
		UMOD, REN, HNF1B Sanger sequencing	-	-	negative	-
	III.1	Whole exome sequencing	*UMOD* p.T62P (+)	-	-	bilateral kidney microcysts, normal eGFR, no proteinuria
	III.2	Whole exome sequencing	*UMOD* p.T62P (-)	-	-	Unaffected
GEL1	II.1 (index)	Whole genome sequencing	*UMOD* p.T62P (+)	-	see Table S5	CKD G5, dialysis (41y), arterial HTN

			(tier2), no tier1/2			
	II.2	Whole genome sequencing	*UMOD* p.T62P (+), no tier1/2	-	see Table S5	CKD G5 (57y)
	II.3	Whole genome sequencing	*UMOD* p.T62P (+), no tier1/2	-	see Table S5	CKD non-G5 (66y), gout, arterial HTN
GEL2	II.1 (index)	Whole genome sequencing	*UMOD* p.T62P (+) (tier2), no tier1/2	-	see Table S5	CKD G5, Peritoneal dialysis (60y), mild proteinuria, micro. hematuria, arterial HTN
GEL3	II.1 (index)	Whole genome sequencing	*UMOD* p.T62P (+) (tier2), no tier1/2	-	see Table S5	CKD G5 (51y), arterial HTN
GEL4	II.1 (index)	Whole genome sequencing	*UMOD* p.T62P (+) (tier2), no tier1/2	-	see Table S5	Multiple small medullary cysts, multiple glomerular cysts
	I.1	Whole genome sequencing	*UMOD* p.T62P (+)	-	-	Unaffected
GEL5	II.1 (index)	Whole genome sequencing	*UMOD* p.T62P (+) (tier2), no tier1/2	-	see Table S5	CKD G5 (69y), multiple kidney cysts, enlarged kidneys, HTN

(+) denotes presence and (-) absence of p.Thr62Pro heterozygous change. Tubulopathy gene panel comprising 37 genes, as previously described (10). The Brest panel v2 comprises 10 genes (*PKD1, PKD2, GANAB, DNAJB11, HNF1B, PKHD1, UMOD, SEC63, PRKCSH, LRP5*), the Brest panel v4 comprises 24 genes (*ALG8, ALG9, AQP11, COL4A1, DNAJB11, DZIP1L, GANAB, HNF1B, LRP5, MOGS, OFD1, PKD1, PKD2, PKHD1, PMM2, PRKCSH, REN, SEC61A1, SEC61B, SEC63, TSC1, TSC2, UMOD, VHL*). The Irish customized gene panel includes 227 genes (including ADTKD genes) as previously reported (11). *MUC1* probe extension with mass spectrometry and SnaPshot minisequencing as previously described (7–9). Family GE1 has been previously described as “family 3” (8). *MUC1, HNF1B, REN* and *SEC61A1* can also cause autosomal dominant tubulointerstitial kidney disease, *MUC1* and *UMOD* being by far the most prevalent etiologies (4, 64). Abbreviations as follows: CKD, chronic kidney disease; FEUA, fractional excretion of uric acid; HTN, hypertension; IF/TA, interstitial fibrosis/tubular atrophy; MLPA, multiplex ligation-dependent probe amplification; T2DM, type 2 diabetes mellitus.

Table S5. Filtered genetic variants detected in CKD families/cases with *UMOD* p.Thr62Pro.

Patient ID	Genetic testing	Gene	Variant	GT	Associated Disease (relevant for kidney)	gnomAD AF	REVEL Score	ACMG
IRL1 II.8	Whole exome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		PKHD1	(NM_138694.3) p.Asp3290Asn	0/1	Polycystic kidney disease 4, with or without hepatic disease [AR], MIM 263200	13/249,966/0	0.2	VUS (PM2, BP4)
		ATP6V0A4	(NM_020632.2) p.His710Arg	0/1	Distal renal tubular acidosis 3, with or without sensorineural hearing loss [AR], MIM 602722	15/251,402/0	0.21	VUS (PM2, BP4)
		HNF1B	(NM_000458.3) p.Asp82Asn	0/1	Renal cysts and diabetes syndrome [AD], MIM 137920	154/249,854/0	0.89	VUS (PM1, PP2, PP3, BS1)[8]
		COQ2	(NM_015697.7) p.Thr317Ala	0/1	Coenzyme Q10 deficiency, primary, 1 [AR], MIM 607426	5/152,196/0	0.88	LP (PM2, PM5, PP2, PP3, PP5)
		SLC4A4	(NM_003759.3) p.Pro727Ser	0/1	Renal tubular acidosis, proximal, with ocular abnormalities [AR], MIM 604278	374/250,948/0	0.32	VUS (PM2, BP4)
		CENPF	(NM_016343.3) p.Tyr1206Cys	0/1	Stromme syndrome [AR], MIM 243605	589/231,036/0	0.02	VUS (PM2, BP4)
		KMT2D	(NM_003482.3) p.Gly2279Glu	0/1	Kabuki syndrome 1 [AD], MIM 147920	35/248,452/0	0.41	B (BS1, BS2, BP4, BP6)
		ADAMTS13	(NM_139025.4) p.Ser1314Leu	0/1	Thrombotic thrombocytopenic purpura, hereditary [AR], MIM 274150	89/251,192/1	0.11	LB (PM2, PP2, BP4, BP6)
		INF2	(NM_022489.3) p.Cys484Tyr	0/1	Charcot-Marie-Tooth disease, dominant intermediate E [AD], MIM 614455	564/124,310/1	0.07	B (BS1, BS2, BP4, BP6)
		DYNC2H1	(NM_001377.2) p.Ala2961Thr	0/1	Short-rib thoracic dysplasia 3 with or without polydactyly [AR, DR], MIM 613091	475/152,144/1	0.31	VUS (PM2, PP3, BP6)
IRL1 III.1	Brest panel v4[10]	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
IRL1 II.7	Brest panel v4[10]	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]

		HNF1B	(NM_000458.3) p.Asp82Asn	0/1	Renal cysts and diabetes syndrome [AD], MIM 137920	154/249,854/0	0.89	VUS (PM1, PP2, PP3, BS1)[8]
IRL1 II.6	Brest panel v4[10]	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		PKHD1	(NM_138694.3) p.Asp3290Asn	0/1	Polycystic kidney disease 4, with or without hepatic disease [AR], MIM 263200	13/249,966/0	0.2	VUS (PM2, BP4)
UK3 III.2	Brest panel v2[9]	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		GANAB	(NM_198335.4) p.Ser271Cys	0/1	Polycystic kidney disease 3 [AD], MIM 600666	5/251,236/0	0.73	VUS (PP3, BS2)[7]
UK3 II.1	Brest panel v2[9]	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		GANAB	(NM_198335.4) p.Ser271Cys	0/1	Polycystic kidney disease 3 [AD], MIM 600666	5/251,236/0	0.73	VUS (PP3, BS2)[7]
IRL3 III.1	Customized 227 gene panel[5]	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		IFT122	(NM_052985.4) p.Asn488Ser	0/1	Cranioectodermal dysplasia 1 [AR], MIM 218330	53/251,452/0	0.37	VUS (PM2)
		PKD2	(NM_000297.4) p.Tyr487Cys	0/1	Polycystic kidney disease 2 [AD], MIM 613095	2/251,302/0	0.89	VUS (PM2, PP2, PP3)[6]
		NUP93	(NM_014669.5) p.Arg31Gln	0/1	Nephrotic syndrome, type 12 [AR], MIM 616892	4/115,368/0	0.49	VUS (PM2, PP3)
IRL3 II.3	Customized 227 gene panel[5]	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		PKD2	(NM_000297.4) p.Tyr487Cys	0/1	Polycystic kidney disease 2 [AD], MIM 613095	2/251,302/0	0.89	VUS (PM2, PP2, PP3)[6]
IRL4 III.1	Whole exome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		WDPCP	(NM_015910.7) p.Asn688Ser	0/1	?Bardet-Biedl syndrome 15 [AR], MIM 615992	2348/249,322/22	0.061	B (BP6, BS1, BS2, BP4)
		SLC26A1	(NM_022042.4) p.Asp636Tyr	0/1	?Nephrolithiasis, calcium oxalate [AR], MIM 167030	409/191,100/0	0.56	VUS (PM2, PP3, BP6)

		FAT1	(NM_005245.4) p.Val3147Gly	0/1	Glomerulotubular nephropathy [AR] (PMID: 26905694)	515/247,512/0	0.4	VUS (PM2)
		DAAM2	(NM_001201427.2) p.Ile856Thr	0/1	Nephrotic syndrome, type 24 [AR], MIM 619263	956/249,206/5	0.18	B (BS1, BS2, BP4)
		AHI1	(NM_001134831.2) p.Tyr933Cys	0/1	Joubert syndrome 3 [AR], MIM 608629	992/243,656/4	0.16	B (BS1, BS2, BP4, BP6)
		GLI3	(NM_000168.6) p.Val403Ile	0/1	Pallister-Hall syndrome [AD], MIM 146510	21/250,226/0	0.047	B (BP6, BS2, BP4)
		ANKS6	(NM_173551.5) p.Ala515Val	0/1	Nephronophthisis 16 [AR], MIM 615382	5/24,9456	0.044	VUS (PM2, BP4)
		DLG5	(NM_004747.4) p.Glu624Gln	0/1	Cystic kidneys, nephrotic syndrome, hydrocephalus, limb abnormalities, congenital heart disease and craniofacial malformations [AD, AR] (PMID: 32631816)	2243/251,388/22	0.23	B (BS1, BS2, BP1, BP6)
		SCNN1A	(NM_001159576.2) p.Pro37Leu	0/1	Pseudohypoaldosteronism, type I [AR], MIM 264350	266/250,544/1	0.13	VUS (PM2, PP2, BP4)
		CEP290	(NM_025114.4) p.Arg557His	0/1	Senior-Loken syndrome 6 [AR], MIM 610189	88/190,282/0	0.24	VUS (PM2, PP3)
		SLC5A2	(NM_003041.4) p.Ile433Val	0/1	Renal glucosuria [AD, AR], MIM 233100	416/245,048/1	0.33	VUS (PM2)
		LAMA5	(NM_005560.6) p.Val1735Met	0/1	Nephrotic syndrome [AR] (PMID: 29534211)	1325/250,530/5	0.42	B (PP3, BS1, BS2, BP6, BP1)
IRL6 II.1	Whole exome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		NOTCH2	(NM_024408.4) p.Pro2359Ala	0/1	Alagille syndrome 2 [AD], MIM 610205	1148/251,234/3	0.15	B (PP5, BP6, BS1, BS2, BP4)
		CENPF	(NM_016343.4) p.Leu2537Phe	0/1	Stromme syndrome [AR], MIM 243605	0	0.14	VUS (PM2, BP4)
		IFT172	(NM_015662.3) p.Ile1582Thr	0/1	Bardet-Biedl syndrome 20 [AR], MIM 619471	1931/251,446/20	0.06	B (BP6, BS1, BS2, BP4)
		XDH	(NM_000379.4) p.Glu1103Asp	0/1	Xanthinuria, type I [AR], MIM 278300	8/251,478/0	0.14	VUS (PM2, BP4)
		FRAS1	(NM_025074.7) p.Val3276Ala	0/1	Fraser syndrome 1 [AR], MIM 219000	103/248,214/0	0.22	VUS (PM2, PP3)
		PKD2	(NM_000297.4) p.Arg807Gln	0/1	Polycystic kidney disease 2 [AD], MIM 613095	754/251,136/3	0.44	B (PP2, PP5, BP6, BS1, BS2)

		ITGA8	(NM_003638.3) p.Ser512Pro	0/1	Renal hypodysplasia/aplasia 1 [AR], MIM 191830	156/251,044/1	0.12	VUS (PM2, BP4)
		HPSE2	(NM_021828.5) p.Arg494Cys	0/1	Urofacial syndrome 1 [AR], MIM 236730	32/251,376/0	0.3	VUS (PM2, PP3)
		KCNJ1	(NM_153766.3) p.Met338Thr	0/1	Bartter syndrome, type 2 [AR], MIM 241200	1830/251,362/17	0.39	B (PS3, PP2, BS1, BS2, BS3, BP4)
		TSC2	(NM_000548.5) p.Ala583Thr	0/1	Tuberous sclerosis-2 [AD], MIM 613254	507/250,872/1	0.68	B (PP3, BP6, BS1, BS2)
		PKD1	(NM_001009944.3) p.Arg2765Cys	0/1	Polycystic kidney disease 1 [AD], MIM 173900	1156/247,274/7	0.28	VUS (PM1, PP5, PP2, PP3, BP6, BS1)
		KANK2	(NM_001136191.3) p.Val4Ile	0/1	Nephrotic syndrome, type 16 [AR], MIM 617783	771/250,328/3	0.02	B (BP6, BS1, BS2, BP4)
		GNAS	(NM_001077490.2) p.Arg147Ser	0/1	Pseudohypoparathyroidism Ia, Ib, Ic, pseudopseudohypoparathyroidism [AD], MIM 103580, 603233, 612462, 612463	292/223,074/1	0.19	B (PP2, BP6, BS1, BS2, BP4)
		MYH9	(NM_002473.6) p.Arg1400Trp	0/1	Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss [AD], MIM 155100	251/251,412/1	0.67	B (PP3, BP6, BS1, BS2)
FR1 II.1	Whole exome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		DGKE	(NM_003647.2) p.Val493Ala	0/1	Nephrotic syndrome, type 7 [AR], MIM 615008	0	0.31	VUS (PM2, PP2)
		ADAMTS13	(NM_139025.4) p.Cys1125Ser	0/1	Thrombotic thrombocytopenic purpura, hereditary [AR], MIM 274150	0	0.86	LP (PM1, PM2, PP2, PP3)
		FN1	(NM_002026.2) p.Pro1270Ser	0/1	Glomerulopathy with fibronectin deposits 2 [AD], MIM 601894	2/251,204/0	0.85	VUS (PM2, PP3)
		CFH	(NM_000186.3) p.Lys834Gln	0/1	Complement factor H deficiency [AD, AR], MIM 609814	0	0.36	VUS (PM2, BP4)
		PKHD1	(NM_138694.3) p.Arg669Cys	0/1	Polycystic kidney disease 4, with or without hepatic disease [AR], MIM 263200	16/251,080/0	0.18	VUS (PM2, BP4)
		FREM2	(NM_207361.4) p.Arg710Cys	0/1	Fraser syndrome 2 [AR], MIM 617666	634/251,340/1	0.18	VUS (PM2)

		SLC34A1	(NM_003052.4) p.Val202Met	0/1	Hypercalcemia, infantile, 2 [AR], MIM 616963; Nephrolithiasis/osteoporosis, hypophosphatemic, 1 [AD], MIM 612286	23/251,144/0	0.86	VUS (PM2, PP3, BP6)
		WNK4	(NM_032387.4) p.Thr790Asn	0/1	Pseudohypoaldosteronism, type IIB [AD], MIM 614491	663/251,446/2	0.09	B (BS1, BS2, BP4, BP6)
		LAMA5	(NM_005560.4) p.Gly3685Arg	0/1	Nephrotic syndrome [AR] (PMID: 29534211)	1817/215,090/8	0.6	LB (BS1, BP1, BP6)
		ACE	(NM_000789.3) p.Thr916Met	0/1	Renal tubular dysgenesis [AR], MIM 267430	997/251,304/4	0.22	B (PP3, BS1, BS2, BP6)
		KIAA0753	(NM_014804.2) p.Arg886Gln	0/1	Short-rib thoracic dysplasia 21 without polydactyly [AR], MIM 619479	169/248,688/0	0.05	LB (PM2, BP4, BP6)
GEL1 II.1	Whole genome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		TSC1	(NM_000368.5) p.Ser403Leu	0/1	Tuberous sclerosis-1 [AD], MIM 191100	87/251,090/0	0.38	LB (BS2)
		XDH	(NM_000379.4) p.Pro177Gln	0/1	Xanthinuria, type I [AR], MIM 278300	8/251,462/0	0.09	VUS (PM2, BP4)
GEL1 II.2		*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		TSC1	(NM_000368.5) p.Ser403Leu	0/0	Tuberous sclerosis-1 [AD], MIM 191100	87/251,090/0	0.38	LB (BS2)
		XDH	(NM_000379.4) p.Pro177Gln	0/1	Xanthinuria, type I [AR], MIM 278300	8/251,462/0	0.09	VUS (PM2, BP4)
GEL1 II.3		*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		TSC1	(NM_000368.5) p.Ser403Leu	0/1	Tuberous sclerosis-1 [AD], MIM 191100	87/251,090/0	0.38	LB (BS2)
		XDH	(NM_000379.4) p.Pro177Gln	0/1	Xanthinuria, type I [AR], MIM 278300	8/251,462/0	0.09	VUS (PM2, BP4)
GEL2 II.1	Whole genome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]

		LRP4	(NM_002334.4) p.Ala666Ser	0/1	Cenani-Lenz syndactyly syndrome [AR], MIM 212780	0	0.72	VUS (PM2, PP4)
		NIPBL	(NM_133433.4) p.Gly290Val	0/1	Cornelia de Lange syndrome 1 [AD], MIM 122470	1/250,734/0	0.45	P (PVS1, PM2, PM5, PP2, PP3)[2]
		TTC8	(NM_144596.4) p.Leu44Met	0/1	Bardet-Biedl syndrome 8 [AR], MIM 615985	0	0.066	VUS (PM2, BP4)
GEL3 II.1	Whole genome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		BBS10	(NM_024685.4) p.Ser396Pro	0/1	Bardet-Biedl syndrome 10 [AR], MIM 615987	0	0.51	VUS (PM2, PP2, BP4)
		ALG8	(NM_024079.5) p.Met1Val	0/1	Polycystic liver disease 3 with or without kidney cysts [AD], MIM 617874	9/158,858/0	0.4	P (PVS1, PM2, PP3)[3]
GEL4 II.1	Whole genome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		TMEM260	(NM_017799.4) p.Thr260Ile	0/1	Structural heart defects and renal anomalies syndrome [AR], MIM 617478	0	0.56	VUS (PM2, PP3)
		ADAMTS13	(NM_139027.6) p.Met1019Thr	0/1	Thrombotic thrombocytopenic purpura, hereditary [AR], MIM 274150	1/250,402/0	0.043	VUS (PM1, PM2, PP2, BP4)
		LAMA5	(NM_005560.6) p.Ala3312Thr	0/1	Nephrotic syndrome [AR] (PMID: 29534211)	5/184,556/0	0.003	LB (BP1, BP4)
GEL5 II.1	Whole genome sequencing	*UMOD*	(NM_003361.3) p.Thr62Pro	0/1	Tubulointerstitial kidney disease, autosomal dominant, 1 [AD], MIM 162000	99/282,046/0	0.54	B (PM1, PP2, BS1, BS2, BP4)[1]
		CEP290	(NM_025114.4) p.Asp2426Asn	0/1	Senior-Loken syndrome 6 [AR], MIM 610189	20/232,108/0	0.43	VUS (PM2, PP3)
		KIAA0586	(NM_001329943.3) p.His1281Tyr	0/1	Short-rib thoracic dysplasia 14 with polydactyly [AR], MIM 616546	11/176,246/0	0.05	VUS (PM2, BP4)
		PLCE1	(NM_016341.4) p.Asn1704Ser	0/1	Nephrotic syndrome, type 3 [AR], MIM 610725	54/249,366/1	0.08	VUS (PM2, BP4)

		FN1	(NM_002026.2) p.Pro2016Leu	0/1	Glomerulopathy with fibronectin deposits 2 [AD], MIM 601894	83/251,386/0	0.45	VUS (PP3, BS2)
		SLC7A9	(NM_014270.5) p.Glu436Ter	0/1	Cystinuria [AD, AR], MIM 220100	1/251,490/0	NA	P (PVS1, PM2, PP5, PP3)[4]
GE1 III.1, III.2 & III.4	Whole exome sequencing (trio)	Except *UMOD* p.Thr62Pro, no variants passing filtering criteria and segregating with disease status in family to report						

Applied filtering: MAF≤1% (in any gnomAD subpopulation), nonsynonymous or canonical splice-affecting, 301 nephrogenes (green or amber) from Genomics England Renal Superpanel (version 2.426, https://panelapp.genomicsengland.co.uk/panels/903/).
For cases from Genomics England (GEL1-5), only tiered variants were considered (MAF≤1% for recessive and≤0.1% for dominant disorders and predicted high or moderate impact coding consequence and following the relevant mode of inheritance (but allowing also incomplete penetrance for dominant disorders). B, benign; LB, likely benign; LP, likely pathogenic; P, pathogenic; VUS, variant of unknown significance.
[1]This semi-automated "benign" ACMG classification is driven by the allele frequency of *UMOD* p.Thr62Pro in gnomAD.
[2]Predicted to affect splicing and lead to in-frame deletion of exon 9. Phenotype was not suggestive of Cornelia de Lange syndrome 1.
[3]Identical variant identified in 7 additional individuals from the Genomics England 100,000 Genomes Project. None of them showed a kidney phenotype.
[4]not consistent with phenotype of affected individual.
[5]customized gene panel including 227 genes (including ADTKD genes) as previously reported (11).
[6]Not consistent with phenotype: kidneys not enlarged, 1 simple cyst reported.
[7]Not consistent with phenotype: no liver cysts reported.
[8]Does not segregate with disease status and was detected in 136 individuals from the Genomics England 100,000 Genomes Project without indication of kidney failure.
[9]comprises 10 genes (*PKD1, PKD2, GANAB, DNAJB11, HNF1B, PKHD1, UMOD, SEC63, PRKCSH, LRP5*).
[10]comprises 24 genes (*ALG8, ALG9, AQP11, COL4A1, DNAJB11, DZIP1L, GANAB, HNF1B, LRP5, MOGS, OFD1, PKD1, PKD2, PKHD1, PMM2, PRKCSH, REN, SEC61A1, SEC61B, SEC63, TSC1, TSC2, UMOD, VHL*).

Table S6. Phenotypic categories of all *UMOD* p.Thr62Pro carriers in Genomics England 100,000 Genomes Project.

Characteristics of *UMOD* p.Thr62Pro carriers in 100,000 Genomes Project	
affected/unaffected	n=69/52 (total=121)
phenotypes	Unexplained kidney failure in young people (n=5/N=3) *
	Cystic kidney disease (n=5/N=5) **
	CAKUT (n=2/N=2) ***
	Brain channelopathy (n=2/N=1)
	Charcot-Marie-Tooth disease (n=3/N=2)
	Classical tuberous sclerosis (n=2/N=2)
	Complex parkinsonism (n=2/N=2)
	Congenital myopathy (n=1/N=1)
	Dilated Cardiomyopathy (n=1/N=1)
	Distal myopathies (n=2/N=2)
	Early onset and familial Parkinson's disease (n=1/N=1)
	Early onset dementia (n=2/N=2)
	Early onset dystonia (n=1/N=1)
	Epilepsia plus other features (n=2/N=2)
	Epileptic encephalopathy (n=1/N=1)
	Familial breast and/or ovarian cancer (n=1/N=1)
	Fetal structural CNS abnormalities (n=1/N=1)
	Hereditary ataxia (n=2/N=2)
	Spastic paraplegia (n=2/N=1)
	Macular dystrophy (n=3/N=2)
	Inherited optic neuropathies (n=1/N=1)
	Intellectual disability (n=13/N=13)
	Lipoedema disease (n=1/N=1)
	Multiple epiphyseal dysplasia (n=1/N=1)
	Multiple Tumors (n=1/N=1)
	Neurofibromatosis type 1 (n=1/N=1)
	Primary immunodeficiency (n=4/N=3)
	Rod cone dystrophy (n=1/N=1)
	Stickler syndrome (n=1/N=1)
	Ultrarare undescribed monogenic disorder (n=4/N=3)
	N/A (n=52/N=51)

* all 3 families appear in Fig S7 (GEL1, GEL2, GEL3)
** 2 families appear in Fig S7 (GEL4, GEL5), other 3 families have mutations in *PKD1/2*
*** Phenotype not consistent with UMOD pathophysiology

Table S7. Characteristics of global CKD case and control groups in the 100,000 Genomes project (Participant Explorer data).

	No CKD	CKD any stage	No kidney failure	Kidney failure	All T62P heterozygotes (with available data)	T62P heterozygotes with CKD	T62P heterozygotes without CKD
n (total)	84,465	4,453	87,567	1,351	120	11	109
n probands	31,094 (36.8%)	2,235 (50.2%)	32,371 (37.0%)	958 (70.9%)	57 (47.5%)	6 (54.6%)	51 (46.8%)
Age (years, mean±SD)	43.6±21.6	56.7±24.9	44.1±22.0	49.0±21.0	43.0±19.7	57.5±17.8	41.5±19.4
Females	53.6%	47.0%	53.4%	43.2%	58.3%	18.2%	62.4%
Ethnicity: Asian or Asian British	8.1%	6.6%	8.0%	9.0%	0.8%	9.1%	0%
Ethnicity: Black or Black British	2.2%	4.1%	2.2%	7.1%	0%	0%	0%
Ethnicity: Mixed	1.8%	1.6%	1.8%	1.6%	0.8%	0%	0.9%
Other ethnic groups	1.7%	1.4%	1.7%	1.8%	0.8%	0%	0.9%
Ethnicity: White	68.8%	68.6%	68.8%	66.3%	80.1%	54.5%	82.6%
Ethnicity not stated or not available	17.4%	17.7%	17.5%	14.2%	17.5%	36.4%	15.6%
Probands with affected parent(s)	15.1%	20.8%	15.2%	24.5%	22.8%	50.0%	9.2%
Probands with affected sib(s)	14.5%	18.6%	14.6%	20.8%	15.8%	33.3%	6.4%

Information on age, gender and ethnicity provided for all individuals recruited (probands + relatives). Gender information and ethnic categories as provided by the 100,000 Genomes Project. CKD, chronic kidney disease.

Table S8. Urinary UMOD levels in controls, *UMOD* p.Thr62Pro carriers and ADTKD patients with canonical *UMOD* mutations.

***UMOD* p.Thr62Pro family**	**Individual**	**CKD stage**	**uUMOD (mg/g creat)**
CH1	III.1	CKD G3b	3
CH1	III.2	Normal eGFR (90 mL/min/1.73m^2)	8
UK3	III.2	CKD G2	13
IRL1	III.1	CKD G3b	16
IRL1	II.6	CKD G5	7
IRL1	II.7	CKD G3a	15
IRL5	II.1	CKD G4	5
IRL6	II.1	CKD G4	11
IRL4	II.1	CKD G4	4
FR1	II.1	CKD G3a	6
GE1	III.3	CKD G3a	21
GE1	III.2	CKD G3b	2
GE1	III.1	CKD G4	4
GCKD	T62P-1	CKD G3b	4
GCKD	T62P-2	CKD G3b	7
GCKD	T62P-3	CKD G3b	8
GCKD	T62P-4	CKD G3a	16
GCKD	T62P-5	Normal eGFR (>90 mL/min/1.73m^2)	4
Cohort	**N**	**eGFR (mL/min/1.73m^2), mean±SD**	**uUMOD (mg/g creat), mean±SD**
Controls CoLaus (eGFR 30-60)	227	54.4±5.6	17±10
Canonical *UMOD* mutation (eGFR 30-60)	26	40.6±8.4	2±2

Abbreviations: CoLaus, Cohorte Lausannoise; GCKD, German Chronic Kidney Disease Cohort; uUMOD, urinary uromodulin. CKD stage at time of urine sampling.

Table S9. Details for kidney tissue data displayed in Figs. 4C, 4D, S8 as well as mean GRP78 intensities and numbers of tubules quantified.

ID	Type of sample	*UMOD* variant	Gender	Genetic background	Progression of kidney disease (age)*	Mean (±SD) GRP78 signal UMOD pos. tubules (N)	Mean (±SD) GRP78 signal UMOD neg. tubules (N)
NHK #1	Tumor nephrectomy	Wild-type	-	White - European	normal eGFR	46.8 ± 5.0 (26)	37.6 ± 4.1 (24)
NHK #2	Tumor nephrectomy	Wild-type	-	White - European	normal eGFR	21.1 ± 2.9 (14)	26.4 ± 6.7 (15)
NHK #3	Tumor nephrectomy	Wild-type	-	White - European	normal eGFR	24.1 ± 5.8 (32)	21.9 ± 3.0 (33)
GE1 III.1	Biopsy, CKD G3	p.Thr62Pro	Female	White - European	CKD G5 (78y)	56.1 ± 11.3 (20)	30.2 ± 5.8 (17)
IRL3 II.3	Biopsy, CKD G4	p.Thr62Pro	Male	White - European	CKD G5 (60y)	37.6 ± 8.4 (14)	26.2 ± 6.5 (16)
IRL4 III.1	Biopsy, CKD G3a	p.Thr62Pro	Female	White - European	CKD G4 (35y)	54.7 ± 7.9 (25)	31.5 ± 4.9 (18)
ADTKD-*UMOD* #1	Nephrectomy, CKD G5	p.Arg185Ser	Male	White - European	CKD G5 (42y)	109.4 ± 32.7 (27)	24.9 ± 6.4 (17)
ADTKD-*UMOD* #2	Biopsy, CKD G3b	p.Cys256Tyr	Male	White - European	CKD G5 (53y)	57.7 ± 10.5 (17)	29.6 ± 7.1 (11)
ADTKD-*UMOD* #3	Biopsy, CKD G2	p.Tyr274Cys	Female	White - European	CKD G4 (41y)	84.4 ± 29.5 (14)	24.8 ± 6.5 (17)

*last recorded information

Table S10. Odds ratio for kidney failure in Blacks according to *APOL1* risk alleles and in Whites with *UMOD* p.Thr62Pro in Genomics England.

100,000 Genomes	Kidney failure (N)	No kidney failure (N)	Proportion kidney failure / total	OR (95% CI)
Blacks: 1 *APOL1* risk allele	24	784	3.0%	1.1 (0.6-1.8)
Blacks: 0 *APOL1* risk alleles	37	1,301	2.8%	
Blacks: 2 *APOL1* risk alleles	32	264	10.8%	4.3 (2.6-7.1)
Blacks: 0 *APOL1* risk alleles	37	1,301	2.8%	
Blacks: 2 *APOL1* risk alleles	32	264	10.8%	4.0 (2.3-6.8)
Blacks: 1 *APOL1* risk allele	24	784	3.0%	
Whites: *UMOD* p.Thr62Pro heterozygote	7	104	6.3%	4.2 (1.9-8.6)
Whites: *UMOD* p.Thr62Pro wild-type	863	53,319	1.6%	

Ethnic categories as provided by the 100,000 Genomes Project. Blacks: “Black or Black British: African”, “Black or Black British: Any other Black background”, “Black or Black British: Caribbean”, “Mixed: White and Black African”, “Mixed: White and Black Caribbean”. Whites: “White: British”, “White: Irish”, “White: any other White background”. Kidney failure as defined by: N18.5 Chronic kidney disease stage 5, Z94.0 Kidney transplant status, Z49.1 Extracorporeal dialysis, Y84.1 Kidney dialysis, HP:0003774 Stage 5 chronic kidney disease, including mapped and descendant concepts. Cochran Armitage trend test for 0, 1 and 2 *APOL1* risk alleles: $P=1.4 \times 10^{-7}$. Fisher’s exact test for 0 vs. 1 p.Thr62Pro allele: P=0.002.

Table S11. Summary of *UMOD* p.Thr62Pro individuals detected in screened disease cohorts.

Genomics England 100,000 Genomes Project		
p.Thr62Pro carriers/all individuals with CKD (N18 & HP0012622)	11/4,453	0.25%
UK Biobank		
p.Thr62Pro carriers/all individuals with CKD stage 3, 4, 5 or kidney transplantation (N18.3, N18.4, N18.5 & M01)	10/4,324	0.23%
p.Thr62Pro carriers/all individuals with CKD (N18)	14/6,703	0.21%
Eurofins Biomnis Exomes		
p.Thr62Pro carriers/all indications for exome (non-related probands)	2/3,122	0.06%
p.Thr62Pro carriers/all nephrological indications	2/1,340	0.15%
p.Thr62Pro carriers/cystic & tubulointerstitial kidney disease & unknown etiology CKD	2/508	0.39%
p.Thr62Pro carriers/glomerular or vascular kidney disease	0/492	0%

Table S12. Overview of participating cohorts/centers and ethics committees/institutional review boards.

Cohort name	Ethics Committee / Institutional Review Board (IRB)	approved / waived
UK Biobank	North West Multi-centre Research Ethics Committee which covers the UK (approval number: 11/NW/0382)	Approved
100,000 Genomes Project	East of England - Cambridge South Research Ethics Committee, UK (REC Ref 14/EE/1112)	Approved
German Chronic Kidney Disease Cohort	Deutsches Register Klinischer Studien DRKS00003971, Ethik-Kommission der Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany, Nr 3831	Approved
ADTKD cohort (Belgium/Switzerland/USA)	Institutional review board of Wake Forest School of Medicine, North Carolina, USA (Wake Forest University Health Sciences IRB00000352 “Characteristics of Individuals with Inherited Kidney Disease”)	Approved
	Institutional review board of the Université Catholique de Louvain (UCL) Medical School and Saint Luc University Hospital, Belgium (2011/04MAI/184)	Approved
	European Community's Seventh Framework Programme “European Consortium for High-Throughput Research in Rare Kidney Diseases (EURenOmics) Ethics Advisory Board. Participating centres (amongst others): University of Zurich (Switzerland), Newcastle University (UK)	Approved
Local IRB: UK	The North East - Newcastle & North Tyneside 1 Research Ethics Committee, UK (18/NE/350)	Approved
Local IRB: Ireland	Ethics Review Board of Beaumont Hospital, Dublin, Ireland (REC 19/28)	Approved
Local IRB: Germany	Ethics committee of the Friedrich-Alexander University Erlangen-Nürnberg, Germany (approval number: 251_18 B)	Approved

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Appendix: The Genomics England Research Consortium

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