ORIGINAL RESEARCH

Annals of Internal Medicine

Whole-Exome Sequencing in Adults With Chronic Kidney Disease

A Pilot Study

Sneh Lata, PhD; Maddalena Marasa, MD; Yifu Li, MD; David A. Fasel, BS; Emily Groopman, BA; Vaidehi Jobanputra, PhD; Hila Rasouly, PhD; Adele Mitrotti, MD; Rik Westland, MD, PhD; Miguel Verbitsky, PhD; Jordan Nestor, MD; Lindsey M. Slater, MD; Vivette D'Agati, MD; Marcin Zaniew, MD; Anna Materna-Kiryluk, MD; Francesca Lugani, MD; Gianluca Caridi, PhD; Luca Rampoldi, PhD; Aditya Mattoo, MD; Chad A. Newton, MD; Maya K. Rao, MD; Jai Radhakrishnan, MD; Wooin Ahn, MD; Pietro A. Canetta, MD; Andrew S. Bomback, MD; Gerald B. Appel, MD; Corinne Antignac, MD; Glen S. Markowitz, MD; Christine K. Garcia, MD; Krzysztof Kiryluk, MD; Simone Sanna-Cherchi, MD; and Ali G. Gharavi, MD

Background: The utility of whole-exome sequencing (WES) for the diagnosis and management of adult-onset constitutional disorders has not been adequately studied. Genetic diagnostics may be advantageous in adults with chronic kidney disease (CKD), in whom the cause of kidney failure often remains unknown.

Objective: To study the diagnostic utility of WES in a selected referral population of adults with CKD.

Design: Observational cohort.

Setting: A major academic medical center.

Patients: 92 adults with CKD of unknown cause or familial nephropathy or hypertension.

Measurements: The diagnostic yield of WES and its potential effect on clinical management.

Results: Whole-exome sequencing provided a diagnosis in 22 of 92 patients (24%), including 9 probands with CKD of unknown cause and encompassing 13 distinct genetic disorders. Among these, loss-of-function mutations were identified in *PARN* in 2 probands diagnosed respectively with tubulointerstitial fibrosis and CKD of unknown cause. *PARN* mutations have been implicated in a short telomere syndrome characterized by lung, bone marrow, and liver fibrosis; these findings extend the phenotype of *PARN* mutations to renal fibrosis. In addition, review of the American College of Medical Genetics actionable genes identified a pathogenic *BRCA2* mutation in a proband who was diagnosed with breast cancer on follow-up. The results affected clinical management in most identified cases, including initiation of targeted surveillance, familial screening to guide donor selection for transplantation, and changes in therapy.

Limitation: The small sample size and recruitment at a tertiary care academic center limit generalizability of findings among the broader CKD population.

Conclusion: Whole-exome sequencing identified diagnostic mutations in a substantial number of adults with CKD of many causes. Further study of the utility of WES in the evaluation and care of patients with CKD in additional settings is warranted.

Primary Funding Source: New York State Empire Clinical Research Investigator Program, Renal Research Institute, and National Human Genome Research Institute of the National Institutes of Health.

Ann Intern Med. 2018;168:100-109. doi:10.7326/M17-1319 **Annals.org**

For author affiliations, see end of text.

This article was published at Annals.org on 5 December 2017.

Chronic kidney disease (CKD) affects an estimated 14% of Americans (1, 2). These persons have 10- to 15-fold higher morbidity and mortality rates than the general population (1, 3). In most patients with CKD, the diagnosis is based on standard office work-up and sometimes kidney biopsy findings. However, early-stage CKD is often clinically silent, and subtypes can be difficult to distinguish on the basis of clinical data alone. Thus, in many persons, the precise cause of kidney failure remains unknown. Approximately 10% to 25% of patients with CKD note a family history of nephropathy (4–6), suggesting that in many cases the disease has a hereditary component.

Recent advances in genomic technologies, such as chromosomal microarray and massively parallel ("next-generation") sequencing, enable genome-wide analysis at a modest cost and precise definition of the molecular cause of many complex diseases (7–13). Application of these methods has suggested opportunities for individualized diagnosis and risk stratification, including targeted work-up and surveillance for associated disease complications (11–13) and sometimes precision therapy (12–15). However, studies to date have focused mainly on a limited range of disorders in pediatric cohorts or on cancer in adults (7–17); thus, the clinical utility of these approaches for a broader spectrum of diseases, particularly among adults, remains unclear.

Applying chromosomal microarray analysis, we recently showed that 7.4% of 419 children with various forms of CKD had a major known pathogenic genomic imbalance that was not suspected after clinical assessment (18). These disorders were evenly distributed among patients clinically diagnosed with congenital and noncongenital forms of CKD, indicating that genetic analysis has utility across broad clinical categories. In most of these cases, the genetic findings either reclassified the disease or provided information that could guide subsequent clinical care, such as evaluation for metabolic or neuropsychiatric disease. Similarly, next-generation sequencing has been shown to

See also:

Web-Only
Supplement

have great utility for diagnosing genetic forms of nephrotic syndrome or congenital kidney defects in pediatric populations, albeit mainly in the context of targeted panels (19–21).

Whole-exome sequencing (WES) is a genome-wide testing approach that allows selective sequencing of the protein-coding regions of the genome, which are enriched for disease-associated variants (12–15). Because of its genome-wide coverage, WES enables screening of most genes associated with kidney disease and can therefore be applied across diverse categories of renal disorders. Moreover, it can potentially identify novel etiologic genes for nephropathy or detect actionable incidental mutations unrelated to the primary indications for testing. For these reasons, WES is emerging as a preferred diagnostic tool for hereditary disorders (12–15, 22, 23). In pediatric cohorts, WES recently identified diagnostic mutations in up to 11.5% of patients with congenital kidney anomalies and 26% of patients with steroid-resistant nephrotic syndrome, supporting its diagnostic utility for early-onset CKD (24, 25). However, the value of this sequencing method for the diagnosis and management of CKD in adults has not been adequately studied. We did a pilot study to test the utility of WES in adults referred for evaluation of CKD or hypertension.

METHODS

Study Design

The results of WES in a convenience sample of patients referred for evaluation of CKD were reviewed for their potential to inform clinical practice. To facilitate diagnostic interpretation of WES data, we compiled a list of genes encompassing most common Mendelian forms of kidney and hypertensive disorders. We next annotated the exomes for diagnostic variants in nephropathy genes and then analyzed other genes, including those recommended by the American College of Medical Genetics (ACMG), for return of medically actionable incidental findings (26).

Patient Population and Setting

The study sample was selected from a group of 344 patients seen at outpatient nephrology clinics between October 2013 and May 2014 at Columbia University Medical Center, a tertiary care medical center with a nephrology division offering highly specialized care for glomerular disorders. These 344 patients were referred for evaluation and management of kidney disease and consented to a general genetic research and biobanking protocol. **Supplement Table 1** (available at Annals.org) presents the characteristics of these 344 patients. From this group, we selected 81 adult patients (aged >18 years) (**Supplement Table 2**, available at Annals.org) for WES who fulfilled 1 of the following inclusion criteria: a family history of kidney disease (defined as any family member with urinary abnormalities or impaired kidney function, as reported by the patient), undiagnosed kidney disease, or clinical suspicion of a genetic kidney disease (for example, in a proband with young age of onset and no family history of nephropathy). The *PKD1* gene is not well-captured by WES because of gene duplication (27), so patients fulfilling clinical diagnostic criteria for autosomal dominant polycystic kidney disease were not included in the WES study.

In addition to these 81 patients from Columbia University Medical Center, we also included 11 patients referred for suspected inherited kidney disease or hypertension from outside institutions. Three patients with familial tubulointerstitial nephropathy and 1 with early-onset hypertension were referred from 3 local practices in the United States (New York University and nephrology practices in suburban New York and Delaware). Four were referred for evaluation of Mendelian hypertension from the Polish Kidney Genetics Network (POLYGENES, www.polygenes.org), centered in the Department of Genetics at Poznań University of Medical Sciences and The Center of Medical Genetics GENESIS (Poznań, Poland). Three other patients were referred from Gaslini Institute (Genova, Italy) for evaluation of glomerulonephritis with nondiagnostic kidney biopsies.

All participants gave informed consent, and the study was approved by the Columbia University Institutional Review Board and local ethics committees.

WES and Sequence Interpretation

Staff extracted DNA from whole blood. Telomere length was measured using genomic DNA from whole blood, as previously described (28, 29). For WES, fragment libraries using 200 ng of genomic DNA were constructed from each sample, following the Agilent standard library preparation protocol for TruSeq (Illumina). Exome capture was done with the SureSelectXT Human All Exon V4 (51 Mb) kit (Agilent), and sequencing was done using the HiSeq 2000 or 2500 (Illumina) at the Columbia Genome Center. On average, 92.83 million independent paired-end reads (18.56-Gb bases) were generated per sample to provide an average coverage of 110-fold, with 99.17% of target regions being covered at least 10-fold. The paired-end reads (read size, 101 bp) were mapped to the human reference genome National Center for Biotechnology Information build 37 using Burrows–Wheeler Aligner, version 0.5.9. The Genome Analysis Toolkit, version 1.6-13, was used to call germline single nucleotide variants and insertions or deletions (indels).

Variants were annotated for predicted effect on protein function (using ANNOVAR and SnpEff); allele frequency in public databases (ExAC, dbSNP, and the 1000 Genomes Project); and predicted pathogenicity with in silico algorithms, including PolyPhen and Combined Annotation Dependent Depletion scores (30–36). Evidence for disease causality was assessed using ClinVar and the Human Genome Mutation Database (Qiagen), followed by manual review of the cited primary literature (33, 36). In addition, we developed a curated "priority" list of 287 Online Mendelian Inheritance in Man (OMIM; http://omim.org) genes implicated in Mendelian forms of kidney disorders and hy-

Table 1. Characteristics of Patients Having Exome Sequencing

Clinical Category	Patients, *n*	Men, *n*	Women, *n*	Positive Family History, *n (%)*	Mean Age at Presentation (SD), *y*
Glomerular disease	50	21	29	26 (52)	46 (16)
Tubulointerstitial disease	10	6	4	8 (80)	41 (15)
Developmental disorders	11	10	1	7 (64)	43 (16)
Hypertension	5	4	1	3 (60)	22 (7)
Undiagnosed disease/other	16	9	7	9 (56)	37 (11)
Total	92	50	42	53 (58)	42 (17)

pertension to facilitate clinical annotation (hereon, we refer to this gene list as nephropathy genes; see **Supplement Table 3**, available at Annals.org). A known limitation of exome sequencing is that some segments of the genome are not amenable to capture (23). Among the 287 nephropathy genes, 29 were identified with at least 1 exon that is not captured by the Agilent kit, representing potential blind spots in the analysis (**Supplement Table 3**).

Variant interpretation was done by a panel of nephrologists or molecular geneticists with domain expertise in inherited kidney diseases (K.K., S.S.C., C.A., L.R., E.G., and A.G.G.), bioinformaticians (S.L. and D.A.F.), and a clinical molecular geneticist (V.J.), using the ACMG guidelines for clinical sequence interpretation (37). Detailed classification criteria for pathogenic and likely pathogenic variants are in **Supplement Table 4** (available at Annals.org). We also reviewed potentially pathogenic mutations in OMIM genes associated with other heritable disorders and in the ACMG's 59 actionable genes (26). All diagnostic variants were confirmed by Sanger sequencing.

Finally, we verified the distribution of potentially functional variants in nephropathy genes in each exome. These potentially functional variants were defined as missense, nonsense, splice site, or indel variants with a minor allele frequency less than 1% in ExAC (a database of genetic variation in >60 000 persons) and a Combined Annotation Dependent Depletion score greater than 10 (indicating a variant score in the top 10% of deleteriousness in a large reference data set of variants). We also verified allele frequencies using an anonymized in-house control data set derived from 9012 persons who had undergone WES for indications other than nephropathy; these control data included healthy parents of children with a developmental disorder and participants from genetic studies of amyotrophic lateral sclerosis or seizure disorders.

Role of the Funding Source

The study was funded by the New York State Empire Clinical Research Investigator Program, the Renal Research Institute, and the National Human Genome Research Institute of the National Institutes of Health. The funding sources had no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

RESULTS

We performed WES in 92 adults with CKD with a clinical diagnosis compatible with a Mendelian genetic disease, a familial nephropathy of unclear cause, or unexplained kidney failure. The characteristics of the 92 participants are described in **Table 1** and **Supplement Table 2**. Nineteen participants (20%) were of self-declared non-Caucasian ancestry, 53 (58%) had a family history of nephropathy, and 50 (54%) had a clinical diagnosis of glomerulopathy (**Table 1**).

Diagnostic Variants in Known Nephropathy Genes

Using ACMG criteria, we identified 19 patients with a diagnostic mutation in 1 of the known nephropathy genes (**Table 2**): 9 had a pathogenic variant and 10 had a likely pathogenic variant. In 6 of these 19 cases, the genetic data confirmed the clinical diagnosis but were nonetheless valuable because they allowed discrimination of the mode of disease inheritance and enabled appropriate screening and counseling for family members. For example, in patients K009 and K024, WES helped to distinguish X-linked versus autosomal forms of Alport syndrome, thereby informing family counseling and selection of living related kidney donors. In the other 13 cases, including 7 patients presenting with CKD of unknown cause, WES clarified the clinical diagnosis or reclassified the patient's disease entirely, which significantly affected clinical decision making. For example, we found *COL4A3*, *COL4A4*, or *COL4A5* mutations in probands with a clinical diagnosis of familial focal segmental glomerulosclerosis (K078 and K058) or familial nephropathy of unknown cause (K014 and K028). These genetic diagnoses had direct consequences for medical management, including avoidance of immunosuppressive agents, usually considered first-line therapy for familial focal segmental glomerulosclerosis; auditory and ophthalmologic screening; screening for mutation carriers among family members; optimal selection of living related organ donors; and in some cases, referral to an ongoing clinical trial targeting patients with type IV collagen mutations (ClinicalTrials.gov: NCT02855268). In another case, WES identified a diagnostic mutation for Dent disease in a patient (KGY1) with undiagnosed familial CKD who had had 2 nondiagnostic kidney biopsies as a child; implications included treatment with citrate and thiazide diuretics, prioritization for transplantation, and molecular diagnosis in a brother with recently diagnosed CKD. We also

Table 2. Diagnostic Variants Identified in Exome Sequencing

Patient Identification	Sex	Age, *y*	Race/ Ethnicity	Clinical Presentation	Genetic Diagnosis	Gene Symbol	Sequence Variant, RSID, and ExAC Frequency	Clinical Implications of Genetic Information
Genetic diagnoses that confirmed the clinical diagnosis and their potential implications for clinical care								
K008	Female	28	White	ESRD of unknown cause, has undergone kidney transplantation, son has Alport syndrome	X-linked Alport syndrome (OMIM 301050)	*COL4A5*	NM_000495:c.G3310T: p.G1104C† RSID: NA ExAC frequency: 0	Clarification of mode of inheritance; screening family members
K009	Male	26	White	Biopsy-proven Alport syndrome, negative FHx	X-linked Alport syndrome (OMIM 301050)	*COL4A5*	NM_000495:c.G2731A: p.G911R RSID: rs281874704 ExAC frequency: 0	Clarification of mode of inheritance; screening family members
K024	Female	31	White	Biopsy-proven Alport syndrome, negative FHx	X-linked Alport syndrome (OMIM 301050)	*COL4A5*	NM_000495:c.G5042A: p.C1681Y† RSID: NA ExAC frequency: 0	Clarification of mode of inheritance; screening family members
K079	Male	22	White	Biopsy-proven Alport syndrome, positive FHx	X-linked Alport syndrome (OMIM 301050)	*COL4A5*	NM_000495:c.G2474A: p.G825E† RSID: NA ExAC frequency: 0	Clarification of mode of inheritance; screening family members
K054	Female	31	White	Nail–patella syndrome with biopsy-proven FSGS	Nail–patella syndrome (OMIM 161200)	*LMX1B*	NM_001174146: c.775_776del: p.S259Cfs*38 RSID: NA ExAC frequency: 0	Do not consider immunosuppression; refer for transplantation
K015	Male	37	Asian	Fabry disease by biopsy and enzyme activity, ESRD	Fabry disease (OMIM 301500)	*GLA*	NM_000169:c.A886G: p.M296V RSID: rs104894830 ExAC frequency: 4×10^{-6}	Screening family members; continue enzyme therapy
Genetic diagnoses that provided new information and their potential implications for clinical care								
K030	Male	19	African American	CKD of unknown cause with bilateral renal hypoplasia, hypogonadism; history of repaired atrial septal defect; offspring of healthy parents	CHARGE syndrome (OMIM 214800)	*CHD7*	NM_017780:c.G8554A: p.D2852N† RSID: NA ExAC frequency: 0	Screening for hearing and vision loss, cranial nerve dysfunction, and learning disability; caution during anesthesia because of upper airway maldevelopment
KGY1	Male	35	White	Familial proteinuric CKD of unknown cause, inconclusive results on biopsies at age 6 and 12 y, brother with proteinuria (never had biopsy)	Dent disease 1 (OMIM 300009)	*CLCN5*	NM_000084:c.2057delG: p.S686Tfs*5 RSID: NA ExAC frequency: 0	Therapy with thiazide diuretics and citrates; no posttransplantation recurrence expected; brother screened and diagnosed with Dent disease 1
K014	Female	22	White	ESRD of unknown cause, has undergone kidney transplantation, positive FHx of microhematuria on father's side	Autosomal recessive Alport syndrome (OMIM 203780)	*COL4A3*	NM_000091:c.G1558C: p.G520R RSID: NA ExAC frequency: 0 NM_000091:c.T4421C: p.L1474P RSID: rs200302125 ExAC frequency: 0.003	Posttransplantation recurrence unlikely; compound heterozygosity confirmed by testing allele transmission in offspring; immunosuppressive therapy not indicated; family counseling
K078	Female	28	White	FSGS by biopsy, has undergone kidney transplantation, sibling died at age 17 y with anasarca, FHx of hematuria	Autosomal recessive Alport syndrome (OMIM 203780)	*COL4A4*	NM_000092:c.G4288A: p.G1430R RSID: NA ExAC frequency: 2.3×10^{-3} NM_000092:c.213_239del: p.P72_G80delPQGPIGPLG RSID: NA ExAC frequency: 0	Compound heterozygosity confirmed by testing allele transmission in offspring; immunosuppressive therapy not indicated; family counseling; patient opted to pursue pregnancy after genetic diagnosis clarified recessive inheritance
K058	Male	28	White	FSGS by biopsy, undergoing kidney transplantation evaluation, positive FHx for nephropathy	Autosomal dominant Alport syndrome (OMIM 104200)	*COL4A4*	NM_000092:c.G1145C: p.G382A† RSID: rs751952236 ExAC frequency: 4×10^{-5}	Immunosuppressive therapy not indicated; family screening for donor evaluation; referred for gene therapy trial
K028	Female	57	White	Mild CKD of unknown cause with hematuria, TBMD diagnosed as a child (self-reported)	X-linked Alport syndrome (OMIM 301050)	*COL4A5*	NM_000495:c.G5030A: p.R1677Q RSID: rs104886308 ExAC frequency: 2.3×10^{-5}	Auditory and ophthalmology screening; referred for clinical trial (NCT02855268)

Continued on following page

Table 2–Continued

Patient Identification	Sex	Age, y	Race/ Ethnicity	Clinical Presentation	Genetic Diagnosis	Gene Symbol	Sequence Variant, RSID, and ExAC Frequency	Clinical Implications of Genetic Information
K064	Male	48	White	CKD of unknown cause with congenital small left kidney, diabetes, no prior kidney biopsy	*HNF1B*-associated disease‡ (OMIM 137920)	*HNF1B*	NM_000458:c.C742T: p.Q248X RSID: NA ExAC frequency: 0	Insulin therapy; screening for hyperuricemia, hypomagnesemia, and hypoparathyroidism; family screening and counseling
K065	Male	20	White	Presented at age 13 y with hypertension and hypokalemia	Liddle syndrome (OMIM 177200)	*SCNN1G*	NM_001039:c.C1874G: p.P625R† RSID: NA ExAC frequency: 0	Treat with amiloride
K027	Female	44	White	Gitelman syndrome, type 2 diabetes	Gitelman syndrome (OMIM 263800)	*SLC12A3*	NM_000339:c.A2899G: p.R967G RSID: NA ExAC frequency: 0 NM_000339: c.2986_2987insGCTC: p.Y999Afs*50 RSID: NA ExAC frequency: 0	–
K006	Female	42	White	Biopsy-proven FSGS, mother with ESRD has undergone kidney transplantation	FSGS type 2 (OMIM 603965)	*TRPC6*	TRPC6:NM_004621: A434G:p.H145R† RSID: NA ExAC frequency: 0	Affected mother tested positive for mutation; immunosuppression is not indicated
K007	Male	55	White	CKD with chronic tubulointerstitial nephropathy on biopsy, undergoing kidney transplantation evaluation, strong FHx for dominant transmission of CKD/ESRD	Autosomal dominant medullary cystic kidney disease type 2 (OMIM 603860)	*UMOD*	NM_001008389:c.G317A: p.C106F† RSID: rs398123697 ExAC frequency: 3.7×10^{-5}	Family screening and counseling; monitor uric acid levels
K016	Male	21	White/ Hispanic	Gout and CKD of unknown cause, no biopsy; positive FHx for dominant transmission of ESRD/gout	Autosomal dominant medullary cystic kidney disease type 2 (OMIM 603860)	*UMOD*	NM_001008389:c.G774C: p.W258C† RSID: NA ExAC frequency: 0	Family screening and counseling; monitor uric acid levels
K043	Female	45	Asian	CKD with chronic tubulointerstitial nephropathy by biopsy, positive FHx for dominant transmission of CKD and gout	Autosomal dominant medullary cystic kidney disease type 2 (OMIM 603860)	*UMOD*	NM_001008389:c.T638A: p.M213K† RSID: NA ExAC frequency: 0	Family screening and counseling; monitor uric acid levels

CHARGE = coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities; CKD = chronic kidney disease; ESRD = end-stage renal disease; ExAC = Exome Aggregation Consortium; FHx = family history; FSGS = focal segmental glomerulosclerosis; NA = not applicable; OMIM = Online Mendelian Inheritance in Man; RSID = Reference Single Nucleotide Polymorphism identification number; TBMD = thin basement membrane disease.
† A likely pathogenic mutation.
‡ Also known as renal cysts and diabetes syndrome or maturity-onset diabetes of the young type 5.

genetically diagnosed several rare diseases, including CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) syndrome (K030) and renal cysts and diabetes syndrome (K064), prompting targeted work-up for associated extrarenal comorbid conditions and providing a unifying explanation for some organ defects.

The genetic diagnostic rate was similar between glomerular and nonglomerular disorders (19% and 23%, respectively) and between persons of European and non-European ancestry (20% for both). The diagnostic rate in Columbia University Medical Center patients recruited during routine outpatient visits was 22%, compared with 9% among those referred for evaluation of genetic kidney disease from outside institutions. During the annotation process, we detected an average of 5 potentially functional variants in nephropathy genes per person, which is consistent with the known distribution of putatively functional variants in the general population (34). In many cases, these variants were in nephropathy genes that were not consistent with the clinical presentation and could therefore be eliminated from consideration; however, others were partially compatible with the clinical diagnosis and were classified as variants of unknown significance, pending additional corroborating clinical data. As an example, we list 5 cases where we detected rare, predicted, deleterious variants that potentially explained some aspects of the clinical presentation but were classified as variants of unknown significance because phenotypic evidence was insufficient to establish causality (Supplement Table 5, available at Annals.org).

Mutations in *PARN* in Patients With Tubulointerstitial Nephropathy

We next reviewed all genetically unresolved cases for mutations in OMIM genes. We identified the following 2 independent loss-of-function (LoF) mutations in

PARN: a nonsense variant, p.Q215*, in a proband with early-onset nonproteinuric nephropathy of unclear cause, and a splice site variant, c.554+1G>A, in a parent–child pair with tubulointerstitial nephropathy (Table 3). *PARN* encodes a poly(A)-specific ribonuclease that participates in telomere maintenance (38). Heterozygous LoF mutations in *PARN* have recently been implicated in late-onset idiopathic pulmonary fibrosis; myelodysplastic syndrome; and, rarely, liver fibrosis. However, to our knowledge they have yet to be associated with kidney disease (28, 39, 40). The *PARN* mutations detected in the patients with CKD were absent in all public databases. In comparison, we detected 2 LoF mutations in *PARN* in WES data from 9012 control participants (0.02%) from our institution; these 2 represented a substantial portion of the 43 nonglomerular CKD cases (4.7%). Kidney biopsy specimens were available in the parent–child pair and were histologically concordant, revealing chronic tubulointerstitial nephropathy with glomeruli exhibiting minimal and nonspecific changes. The predominant pathologic abnormalities were seen in the medulla, including interstitial fibrosis with a disorganized architecture, resembling changes seen in renal dysplasia (Figure).

We reviewed health records of mutation carriers for evidence of other organ dysfunction. At enrollment, none of the patients had evidence of extrarenal disease, but follow-up uncovered a new diagnosis of interstitial lung disease in 1 of the probands 3 years after enrollment (Table 3). The other proband had new evidence of macrocytic anemia, which in the presence of a *PARN* mutation prompted further investigation for possible incipient myelofibrosis. We also examined telomere length in *PARN* mutation carriers and, consistent with recent studies (29), did not detect differences compared with age-matched controls (Supplement Table 6, available at Annals.org).

ACMG Actionable Mutations

We searched for mutations in ACMG actionable genes and identified a *BRCA2* nonsense mutation (c.T2151A:p.C717*) in a 68-year-old woman with fibrillary glomerulonephritis but no diagnostic mutation in kidney disease genes. Review of the medical records revealed that the patient had been diagnosed with breast cancer shortly after enrollment into our study. The *BRCA2* variant was confirmed by Sanger sequencing in a clinical laboratory, and the patient and family were referred for additional cancer screening, genetic counseling, and cascade testing. Despite the lack of genetic explanation for the patient's nephropathy, the WES detection of a germline *BRCA2* mutation informed the selection and intensity of immunosuppressive therapy for her renal disease. Moreover, the subsequent cascade testing of family members resulted in identification of 2 mutation carriers, who opted for prophylactic mastectomy.

DISCUSSION

In this pilot study, we tested the utility of WES for diagnosis in adults with CKD. We identified many known and undiagnosed genetic disorders in 23% of a cohort of patients with familial or undiagnosed CKD. Diagnostic variants were detected across major clinical categories and among patients of both European and non-European ancestry. For most diagnosed cases, WES provided genetic information that subsequently affected clinical management and enabled family counseling (Table 2). Consistent with recent studies, we identified autosomal and X-linked forms of Alport syndrome among patients with a clinical diagnosis of focal segmental glomerulosclerosis, supporting the variable phenotypic expression of mutations in type IV collagen genes (41–43). These findings had immediate implications for surveillance for extrarenal complications, avoidance of immunosuppressive therapy in cases misdiagnosed as familial focal segmental glomerulosclerosis, and referral to a new clinical trial for Alport syndrome. Furthermore, we were able to obtain a genetic diagnosis in 9 probands with CKD of unknown cause, showing that WES has significant utility for diagnostic work-up in nephrology.

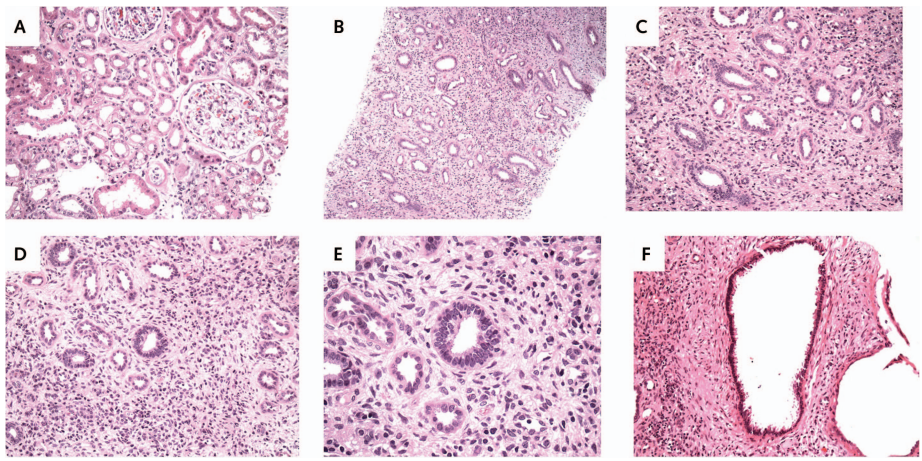
In addition to detecting diagnostic variants in known nephropathy genes, WES identified *PARN* haploinsufficiency as a new genetic cause of CKD. *PARN* is required for maturation of the telomerase RNA compo-

Table 3. Characteristics of Patients With *PARN* (NM_002582) Mutations

Characteristic	K017	K018	K060
Clinical diagnosis	CKD of unknown cause, tubulointerstitial nephropathy with dysplastic features on biopsy	CKD of unknown cause, tubulointerstitial nephropathy with dysplastic features on biopsy	CKD of unknown cause, no kidney biopsy available
Sex	Male (father)	Female (daughter)	Female
Age at presentation	44 y	23 y	48 y
Kidney outcome	ESRD, has undergone kidney transplantation	ESRD, has undergone kidney transplantation	ESRD, has undergone kidney transplantation
Follow-up clinical findings	Work-up for interstitial lung disease 3 y after study enrollment	None	Secondary hyperparathyroidism, normal findings on chest radiography at age 50 y, macrocytic anemia
Sequence variant†	c.554+1G>A	c.554+1G>A	c.C643T:p.Q215*

CKD = chronic kidney disease; ESRD = end-stage renal disease.
† Absent in the Short Genetic Variations (Single Nucleotide Polymorphism) and Exome Aggregation Consortium databases.

Figure. Kidney biopsy findings in a *PARN* mutation carrier (K018).



A. Low-power view of the renal cortex shows mild acute tubular injury and mild tubulointerstitial scarring. Glomeruli appear unremarkable (hematoxylin–eosin stain; original magnification, ×200). **B.** Low-magnification view of the renal medulla reveals more pronounced abnormalities. The tubular architecture is broadly disorganized, with a haphazard arrangement of tubules. The interstitium is notable for a diffuse increase in cellularity (hematoxylin–eosin stain; original magnification, ×100). **C.** Most tubules are lined by cuboidal to columnar epithelium. Flattened epithelium consistent with the thin limbs of the loop of Henle is difficult to discern (hematoxylin–eosin stain; original magnification, ×200). **D.** The interstitium is diffusely hypercellular, and most of the cellularity is composed of mesenchymal cells. Intermixed lymphocytes and plasma cells are also noted (hematoxylin–eosin stain; original magnification, ×200). **E.** High-magnification image shows columnar epithelium and apparent mesenchymal cuffing (hematoxylin–eosin stain; original magnification, ×600). **F.** A cyst within the medulla is lined by cuboidal to columnar epithelium (hematoxylin–eosin stain; original magnification, ×200).

nent (38). Recessive mutations in *PARN* cause dyskeratosis congenita (44), a rare multisystem disorder presenting as severe bone marrow failure and abnormal cancer, skin, and mucosal pathology; many other organs, including the kidney, can also be affected (45). *PARN* haploinsufficiency produces variably penetrant pulmonary, bone marrow, and liver fibrosis in older adults, but the reason for interindividual differences in affected organs is unknown (28, 40, 46). The finding of 2 independent LoF mutations in 3 patients with nephropathy extends the phenotypes associated with *PARN* mutations and identifies renal tubulointerstitial fibrosis as another potential consequence of *PARN* haploinsufficiency, suggesting new avenues for investigating mechanisms of kidney injury. Of interest, the kidney biopsy revealed dysplastic features in the medulla, reminiscent of renal phenotypes associated with mutations in DNA repair genes in Fanconi anemia (47) and dyskeratosis congenita (44, 45). These findings further indicate that disorders of DNA maintenance may present predominantly as kidney dysfunction and fibrosis and have important implications for clinical care among *PARN* mutation carriers, including potential monitoring of kidney function and heightened awareness when dosing potentially nephrotoxic drugs.

Epidemiologic data suggest that hereditary or congenital disorders account for 10% of adult CKD (4–6), but the precise cause is frequently unknown. Recent investigations indicate that many late-onset constitutional disorders, such as amyotrophic lateral sclerosis (48) and pulmonary fibrosis (28, 40), also have a strong genetic basis that can be identified using these technologies. Our study similarly suggests that WES can provide a specific, molecular-level diagnosis, supporting its utility as part of the clinical diagnostic work-up. In comparison with other WES studies indexed in PubMed in the past 5 years, the diagnostic yield in our population was similar to those reported for pediatric developmental disorders (7–13). These findings motivate further examination of the utility of genomic technologies for diagnosis and stratification in the adult CKD population.

Our study has some limitations. The high diagnostic yield likely results from studying a cohort enriched for familial or suspected genetic forms of kidney disease, and the modest sample size limits generalizability to the broader CKD population. Hence, systematic WES analysis of larger, unselected CKD cohorts will provide a better assessment of its overall diagnostic yield in nephrology practice. Whole-exome sequencing also does not provide uniform coverage of all coding segments of the genome and may fail to capture some diagnostically relevant genomic regions. For example, because of inadequate capture of duplicated or repetitive segments in *PKD1* and *MUC1,* WES has limited sensitivity for assessment of polycystic kidney disease and medullary cystic disease. Thus, the participants with autosomal dominant transmission of tubulointerstitial nephropathy and negative WES results in this study may have medullary cystic disease due to a *MUC1* mutation. In addition, WES currently has limited ability to detect genomic imbalances and does not assess mutations in noncoding regions of the genome, leaving additional blind spots. Physician knowledge of these technical limitations will be important as WES is increasingly incorporated into clinical practice.

Constitutional genetic testing in adults is generally more complicated because family members are fre-

quently not available to test inheritance of candidate variants (for example, to ascertain de novo status) and there is no pairwise comparison of diseased versus normal tissue to prioritize variants, unlike in cancer genomics. Other challenges include correct and consistent interpretation of genomic findings, integration of data into care in a clinically relevant time frame, development of test reports that are readily comprehensible to patients and providers to facilitate informed decisions, and demonstration that clinical sequencing is cost-effective and improves outcomes. Moreover, genome-wide tests like WES can discover actionable mutations unrelated to primary indications for testing, such as the *BRCA2* mutation discovered in our study. The possibility of incidental findings leading to additional testing and therapy is a well-established challenge in clinical diagnostics, and the same principles of determining overall costs and benefits will need to be applied to genetic testing.

Large control databases, such as ExAC (34), are of great value for interpretation of WES data, helping prioritize predicted deleterious variants on the basis of their frequency in the population. New variant annotation algorithms that consider genomic context to assess mutation intolerance may also facilitate variant classification in adult singletons, independent of prior clinical reports (49–51), and help standardize clinical interpretation of genomes. Hence, many initiatives are currently examining the clinical relevance of genes and variants for use in genomic medicine (such as ClinGen, www.clinicalgenome.org) and will provide more evidence about the utility of genetic testing in diverse clinical settings (52, 53). Emerging data suggest that the introduction of genetic testing in the primary care setting does not improve or adversely affect standards of care and that some of the resulting increased health care use is clinically appropriate (54).

Altogether, WES offers the advantage of screening most relevant nephropathy genes at once, providing genetic diagnoses across diverse clinical categories, and enabling the identification of novel phenotypic extensions, as shown by the findings of *PARN* mutations in tubulointerstitial nephropathy. Because of its genome-wide approach, WES also enables periodic re-evaluation of the sequence data for new genetic diagnoses as new disease genes are identified. In this study, WES had substantial diagnostic yield and affected clinical management in a referral population of adults with CKD, inviting more extensive investigation of the broader clinical utility of genetic testing for the CKD population.

From Columbia University, New York, New York; Columbia University, New York, New York, and VU University Medical Center, Amsterdam, the Netherlands; Nephrology Associates, Newark, Delaware; Krysiewicza Children's Hospital, Poznań, Poland; Poznań University of Medical Sciences and Center for Medical Genetics GENESIS, Poznań, Poland; IRCCS Giannina Gaslini Children's Hospital, Genova, Italy; IRCCS San Raffaele Scientific Institute, Milan, Italy; New York University School of Medicine, New York, New York; University of Texas Southwestern Medical Center, Dallas, Texas; and French Institute of Health and Medical Research (INSERM) U1163, Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, and Necker Hospital, Paris, France.

Acknowledgment: The authors thank all study participants for contributing to this effort, David Goldstein and the Columbia Institute for Genomic Medicine for providing annotation tools and data from in-house controls, and Adam Platt for helpful comments.

Grant Support: By a New York State Empire Clinical Research Investigator Program grant, a research grant from the Renal Research Institute, and grant U01HG008680 from the National Human Genome Research Institute of the National Institutes of Health. Dr. Sanna-Cherchi is supported by grant 1R01DK103184 from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

Disclosures: Dr. Newton reports grants from National Insti-tutes of Health during the conduct of the study. Dr. Bomback reports grants from the National Institute on Minority Health and Health Disparities of the National Institutes of Health during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-1319.

Reproducible Research Statement: *Study protocol and data set:* Available from Dr. Gharavi (e-mail, ag2239@columbia.edu). *Statistical code:* Not applicable.

Requests for Single Reprints: Ali Gharavi, MD, Department of Medicine, Division of Nephrology, Columbia University, 1150 Saint Nicholas Avenue, Russ Berrie Pavilion #413, New York, NY 10032; e-mail, ag2239@columbia.edu.

Current author addresses and author contributions are available at Annals.org.

References

1. **U.S. Renal Data System.** USRDS 2016 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda: National Institutes of Health; 2016.
2. **Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al.** Prevalence of chronic kidney disease in the United States. JAMA. 2007;298:2038-47. [PMID: 17986697]
3. **Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY.** Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296-305. [PMID: 15385656]
4. **Freedman BI, Wilson CH, Spray BJ, Tuttle AB, Olorenshaw IM, Kammer GM.** Familial clustering of end-stage renal disease in blacks with lupus nephritis. Am J Kidney Dis. 1997;29:729-32. [PMID: 9159307]
5. **Freedman BI, Soucie JM, Stone SM, Pegram S.** Familial clustering of end-stage renal disease in blacks with HIV-associated nephropathy. Am J Kidney Dis. 1999;34:254-8. [PMID: 10430971]
6. **Skrunes R, Svarstad E, Reisæter AV, Vikse BE.** Familial clustering of ESRD in the Norwegian population. Clin J Am Soc Nephrol. 2014;9:1692-700. [PMID: 25092600] doi:10.2215/CJN.01680214
7. **Kiezun A, Garimella K, Do R, Stitziel NO, Neale BM, McLaren PJ, et al.** Exome sequencing and the genetic basis of complex traits. Nat Genet. 2012;44:623-30. [PMID: 22641211] doi:10.1038/ng.2303

8. **Ng SB, Buckingham KJ, Lee C, Bigham AW, Tabor HK, Dent KM, et al.** Exome sequencing identifies the cause of a mendelian disorder. Nat Genet. 2010;42:30-5. [PMID: 19915526] doi:10.1038/ng.499
9. **Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BW, Willemsen MH, et al.** Genome sequencing identifies major causes of severe intellectual disability. Nature. 2014;511:344-7. [PMID: 24896178] doi:10.1038/nature13394
10. **Sifrim A, Hitz MP, Wilsdon A, Breckpot J, Turki SH, Thienpont B, et al; INTERVAL Study.** Distinct genetic architectures for syndromic and nonsyndromic congenital heart defects identified by exome sequencing. Nat Genet. 2016;48:1060-5. [PMID: 27479907] doi:10.1038/ng.3627
11. **Do R, Stitziel NO, Won HH, Jørgensen AB, Duga S, Angelica Merlini P, et al; NHLBI Exome Sequencing Project.** Exome sequencing identifies rare *LDLR* and *APOA5* alleles conferring risk for myocardial infarction. Nature. 2015;518:102-6. [PMID: 25487149] doi:10.1038/nature13917
12. **Lee H, Deignan JL, Dorrani N, Strom SP, Kantarci S, Quintero-Rivera F, et al.** Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. 2014;312:1880-7. [PMID: 25326637] doi:10.1001/jama.2014.14604
13. **Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, et al.** Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. N Engl J Med. 2013;369:1502-11. [PMID: 24088041] doi:10.1056/NEJMoa1306555
14. **Dixon-Salazar TJ, Silhavy JL, Udpa N, Schroth J, Bielas S, Schaffer AE, et al.** Exome sequencing can improve diagnosis and alter patient management. Sci Transl Med. 2012;4:138ra78. [PMID: 22700954] doi:10.1126/scitranslmed.3003544
15. **Bamshad MJ, Ng SB, Bigham AW, Tabor HK, Emond MJ, Nickerson DA, et al.** Exome sequencing as a tool for Mendelian disease gene discovery. Nat Rev Genet. 2011;12:745-55. [PMID: 21946919] doi:10.1038/nrg3031
16. **Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al.** Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375:443-53. [PMID: 27433846] doi:10.1056/NEJMoa1603144
17. **Tarailo-Graovac M, Shyr C, Ross CJ, Horvath GA, Salvarinova R, Ye XC, et al.** Exome sequencing and the management of neurometabolic disorders. N Engl J Med. 2016;374:2246-55. [PMID: 27276562] doi:10.1056/NEJMoa1515792
18. **Verbitsky M, Sanna-Cherchi S, Fasel DA, Levy B, Kiryluk K, Wuttke M, et al.** Genomic imbalances in pediatric patients with chronic kidney disease. J Clin Invest. 2015;125:2171-8. [PMID: 25893603] doi:10.1172/JCI80877
19. **Sadowski CE, Lovric S, Ashraf S, Pabst WL, Gee HY, Kohl S, et al; SRNS Study Group.** A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2015;26:1279-89. [PMID: 25349199] doi:10.1681/ASN.2014050489
20. **Lovric S, Fang H, Vega-Warner V, Sadowski CE, Gee HY, Halbritter J, et al; Nephrotic Syndrome Study Group.** Rapid detection of monogenic causes of childhood-onset steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2014;9:1109-16. [PMID: 24742477] doi:10.2215/CJN.09010813
21. **Hwang DY, Dworschak GC, Kohl S, Saisawat P, Vivante A, Hilger AC, et al.** Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract. Kidney Int. 2014;85:1429-33. [PMID: 24429398] doi:10.1038/ki.2013.508
22. **Goldstein DB, Allen A, Keebler J, Margulies EH, Petrou S, Petrovski S, et al.** Sequencing studies in human genetics: design and interpretation. Nat Rev Genet. 2013;14:460-70. [PMID: 23752795] doi:10.1038/nrg3455
23. **Katsanis SH, Katsanis N.** Molecular genetic testing and the future of clinical genomics. Nat Rev Genet. 2013;14:415-26. [PMID: 23681062] doi:10.1038/nrg3493
24. **Bierzynska A, McCarthy HJ, Soderquest K, Sen ES, Colby E, Ding WY, et al.** Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management. Kidney Int. 2017;91:937-47. [PMID: 28117080] doi:10.1016/j.kint.2016.10.013
25. **Bekheirnia MR, Bekheirnia N, Bainbridge MN, Gu S, Coban Akdemir ZH, Gambin T, et al.** Whole-exome sequencing in the molecular diagnosis of individuals with congenital anomalies of the kidney and urinary tract and identification of a new causative gene. Genet Med. 2017;19:412-20. [PMID: 27657687] doi:10.1038/gim.2016.131
26. **Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, et al.** Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19:249-55. [PMID: 27854360] doi:10.1038/gim.2016.190
27. **Rossetti S, Hopp K, Sikkink RA, Sundsbak JL, Lee YK, Kubly V, et al.** Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. J Am Soc Nephrol. 2012;23:915-33. [PMID: 22383692] doi:10.1681/ASN.2011101032
28. **Stuart BD, Choi J, Zaidi S, Xing C, Holohan B, Chen R, et al.** Exome sequencing links mutations in *PARN* and *RTEL1* with familial pulmonary fibrosis and telomere shortening. Nat Genet. 2015;47:512-7. [PMID: 25848748] doi:10.1038/ng.3278
29. **Newton CA, Batra K, Torrealba J, Kozlitina J, Glazer CS, Aravena C, et al.** Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. Eur Respir J. 2016;48:1710-20. [PMID: 27540018] doi:10.1183/13993003.00308-2016
30. **Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al.** A method and server for predicting damaging missense mutations [Letter]. Nat Methods. 2010;7:248-9. [PMID: 20354512] doi:10.1038/nmeth0410-248
31. **Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J.** A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet. 2014;46:310-5. [PMID: 24487276] doi:10.1038/ng.2892
32. **Wang K, Li M, Hakonarson H.** ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res. 2010;38:e164. [PMID: 20601685] doi:10.1093/nar/gkq603
33. **Landrum MJ, Lee JM, Benson M, Brown G, Chao C, Chitipiralla S, et al.** ClinVar: public archive of interpretations of clinically relevant variants. Nucleic Acids Res. 2016;44:D862-8. [PMID: 26582918] doi:10.1093/nar/gkv1222
34. **Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al; Exome Aggregation Consortium.** Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536:285-91. [PMID: 27535533] doi:10.1038/nature19057
35. **Sherry ST, Ward MH, Kholodov M, Baker J, Phan L, Smigielski EM, et al.** dbSNP: the NCBI database of genetic variation. Nucleic Acids Res. 2001;29:308-11. [PMID: 11125122]
36. **Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, et al.** The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665-77. [PMID: 28349240] doi:10.1007/s00439-017-1779-6
37. **Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al; ACMG Laboratory Quality Assurance Committee.** Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. [PMID: 25741868] doi:10.1038/gim.2015.30
38. **Moon DH, Segal M, Boyraz B, Guinan E, Hofmann I, Cahan P, et al.** Poly(A)-specific ribonuclease (*PARN*) mediates 3′-end maturation of the telomerase RNA component. Nat Genet. 2015;47:1482-8. [PMID: 26482878] doi:10.1038/ng.3423
39. **Kropski JA, Reiss S, Markin C, Brown KK, Schwartz DA, Schwarz MI, et al.** Rare genetic variants in *PARN* are associated with pulmonary fibrosis in families. Am J Respir Crit Care Med. 2017. [PMID: 28414520] doi:10.1164/rccm.201703-0635LE

40. **Petrovski S, Todd JL, Durheim MT, Wang Q, Chien JW, Kelly FL, et al.** An exome sequencing study to assess the role of rare genetic variation in pulmonary fibrosis. Am J Respir Crit Care Med. 2017; 196:82-93. [PMID: 28099038] doi:10.1164/rccm.201610-2088OC
41. **Malone AF, Phelan PJ, Hall G, Cetincelik U, Homstad A, Alonso AS, et al.** Rare hereditary *COL4A3*/*COL4A4* variants may be mistaken for familial focal segmental glomerulosclerosis. Kidney Int. 2014;86:1253-9. [PMID: 25229338] doi:10.1038/ki.2014.305
42. **Deltas C, Savva I, Voskarides K, Papazachariou L, Pierides A.** Carriers of autosomal recessive Alport syndrome with thin basement membrane nephropathy presenting as focal segmental glomerulosclerosis in later life. Nephron. 2015;130:271-80. [PMID: 26201269] doi:10.1159/000435789
43. **Gast C, Pengelly RJ, Lyon M, Bunyan DJ, Seaby EG, Graham N, et al.** Collagen (*COL4A*) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2016;31:961-70. [PMID: 26346198] doi:10.1093/ndt/gfv325
44. **Tummala H, Walne A, Collopy L, Cardoso S, de la Fuente J, Lawson S, et al.** Poly(A)-specific ribonuclease deficiency impacts telomere biology and causes dyskeratosis congenita. J Clin Invest. 2015;125:2151-60. [PMID: 25893599] doi:10.1172/JCI78963
45. **Savage SA.** Dyskeratosis congenita. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mefford HC, et al, eds. GeneReviews. Seattle: Univ Washington; 1993. [PMID: 20301295]
46. **Dhanraj S, Gunja SM, Deveau AP, Nissbeck M, Boonyawat B, Coombs AJ, et al.** Bone marrow failure and developmental delay caused by mutations in poly(A)-specific ribonuclease (*PARN*). J Med Genet. 2015;52:738-48. [PMID: 26342108] doi:10.1136/jmedgenet-2015-103292
47. **Zhou W, Otto EA, Cluckey A, Airik R, Hurd TW, Chaki M, et al.** *FAN1* mutations cause karyomegalic interstitial nephritis, linking chronic kidney failure to defective DNA damage repair. Nat Genet. 2012;44:910-5. [PMID: 22772369] doi:10.1038/ng.2347
48. **Cirulli ET, Lasseigne BN, Petrovski S, Sapp PC, Dion PA, Leblond CS, et al; FALS Sequencing Consortium.** Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. Science. 2015;347:1436-41. [PMID: 25700176] doi:10.1126/science.aaa3650
49. **Petrovski S, Wang Q, Heinzen EL, Allen AS, Goldstein DB.** Genic intolerance to functional variation and the interpretation of personal genomes. PLoS Genet. 2013;9:e1003709. [PMID: 23990802] doi:10.1371/journal.pgen.1003709
50. **Gussow AB, Petrovski S, Wang Q, Allen AS, Goldstein DB.** The intolerance to functional genetic variation of protein domains predicts the localization of pathogenic mutations within genes. Genome Biol. 2016;17:9. [PMID: 26781712] doi:10.1186/s13059-016-0869-4
51. **Samocha KE, Robinson EB, Sanders SJ, Stevens C, Sabo A, McGrath LM, et al.** A framework for the interpretation of de novo mutation in human disease. Nat Genet. 2014;46:944-50. [PMID: 25086666] doi:10.1038/ng.3050
52. **Bowdin S, Gilbert A, Bedoukian E, Carew C, Adam MP, Belmont J, et al.** Recommendations for the integration of genomics into clinical practice. Genet Med. 2016;18:1075-84. [PMID: 27171546] doi:10.1038/gim.2016.17
53. **Green RC, Goddard KA, Jarvik GP, Amendola LM, Appelbaum PS, Berg JS, et al; CSER Consortium.** Clinical sequencing Exploratory Research Consortium: accelerating evidence-based practice of genomic medicine. Am J Hum Genet. 2016;99:246. [PMID: 27392080] doi:10.1016/j.ajhg.2016.06.002
54. **Vassy JL, Christensen KD, Schonman EF, Blout CL, Robinson JO, Krier JB, et al; MedSeq Project.** The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients: a pilot randomized trial. Ann Intern Med. 2017. [PMID: 28654958] doi:10.7326/M17-0188

Current Author Addresses: Dr. Lata: Claritas Genomics, 99 Erie Street, Cambridge, MA 02139.
Drs. Marasa, Rao, Radhakrishnan, Ahn, Canetta, Bomback, and Appel: Department of Medicine, Division of Nephrology, College of Physicians and Surgeons, Columbia University, 622 West 168th Street, New York, NY 10032.
Drs. Li, Rasouly, Mitrotti, Westland, Verbitsky, Nestor, Kiryluk, Sanna-Cherchi, and Gharavi; Mr. Fasel; and Ms. Groopman: Department of Medicine, Division of Nephrology, College of Physicians and Surgeons, Columbia University, 1150 Saint Nicholas Avenue, New York, NY 10032.
Dr. Jobanputra: New York Genome Center, 101 Avenue of the Americas, New York, NY 10013.
Dr. Slater: Nephrology Associates, 4923 Ogletown Stanton Road #200, Newark, DE 19713.
Drs. D'Agati and Markowitz: Department of Pathology, College of Physicians and Surgeons, Columbia University, Room VC14-224, 630 West 168th Street, New York, NY 10032.
Dr. Zaniew: Osiedle Zwyciestwa 5H/27, 61-644 Poznań, Poland.
Dr. Materna-Kiryluk: Department of Medical Genetics, Poznan University of Medical Science, 8 Rokietnicka Street, 60-806 Poznań, Poland.
Drs. Lugani and Caridi: Istituto Giannina Gaslini, Largo G. Gaslini 5, 16148 Genova, Italy.
Dr. Rampoldi: Division of Genetics and Cell Biology, San Raffaele Scientific Institute, Via Olgettina 58, 20132 Milan, Italy.
Dr. Mattoo: New York University Division of Nephrology, 560 1st Avenue #251, New York, NY 10016.
Drs. Newton and Hines: Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390.
Dr. Antignac: Imagine Institute, 24 Boulevard de Montparnasse, 75015 Paris, France.

Author Contributions: Conception and design: S. Lata, M. Marasa.
Analysis and interpretation of the data: S. Lata, M. Marasa, Y. Li, D.A. Fasel, E. Groopman, V. Jobanputra, H. Rasouly, A. Mitrotti, V. D'Agati, G. Caridi, C.A. Newton, C. Antignac, C.K. Garcia, S. Sanna-Cherchi, A.G. Gharavi.
Drafting of the article: S. Lata, M. Marasa, F. Lugani, G.S. Markowitz, A.G. Gharavi.
Critical revision of the article for important intellectual content: E. Groopman, R. Westland, F. Lugani, L. Rampoldi, M.K. Rao, A.S. Bomback, G.B. Appel, C. Antignac, G.S. Markowitz, K. Kiryluk, S. Sanna-Cherchi, A.G. Gharavi.
Final approval of the article: S. Lata, M. Marasa, Y. Li, D.A. Fasel, E. Groopman, V. Jobanputra, H. Rasouly, A. Mitrotti, R. Westland, M. Verbitsky, J. Nestor, L.M. Slater, V. D'Agati, M. Zaniew, A. Materna-Kiryluk, F. Lugani, G. Caridi, L. Rampoldi, A. Mattoo, C.A. Newton, M.K. Rao, J. Radhakrishnan, W. Ahn, P.A. Canetta, A.S. Bomback, G.B. Appel, C. Antignac, G.S. Markowitz, C.K. Garcia, K. Kiryluk, S. Sanna-Cherchi, A.G. Gharavi.
Provision of study materials or patients: M. Marasa, L.M. Slater, V. D'Agati, A. Materna-Kiryluk, F. Lugani, G. Caridi, A. Mattoo, M.K. Rao, J. Radhakrishnan, P.A. Canetta, A.S. Bomback, G.S. Markowitz, S. Sanna-Cherchi.
Statistical expertise: K. Kiryluk, A.G. Gharavi.
Obtaining of funding: S. Lata, A.G. Gharavi.
Administrative, technical, or logistic support: S. Lata, Y. Li, M. Verbitsky, C.A. Newton, M.K. Rao.
Collection and assembly of data: S. Lata, M. Marasa, Y. Li, A. Mitrotti, R. Westland, M. Verbitsky, J. Nestor, M. Zaniew, A. Materna-Kiryluk, F. Lugani, C.A. Newton, W. Ahn, P.A. Canetta, G.S. Markowitz, S. Sanna-Cherchi.

Correction: Whole-Exome Sequencing in Adults With Chronic Kidney Disease: A Pilot Study

The second sentence of the Results section of the abstract in a recent article (1) should read as follows: Among these, loss-of-function mutations were identified in PARN in 2 probands respectively diagnosed with tubulointerstitial fibrosis and chronic kidney disease of unknown cause.

This has been corrected.

Reference

1. Lata S, Marasa M, Li Y, Fasel DA, Groopman E, Jobanputra V, et al. Whole-exome sequencing in adults with chronic kidney disease: a pilot study. Ann Intern Med. 2018;168:100-9. [PMID: 29204651] doi: 10.7326/M17-1319