Variable Clinical Presentation of an *MUC1* Mutation Causing Medullary Cystic Kidney Disease Type 1

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Abstract

Background and objectives The genetic cause of medullary cystic kidney disease type 1 was recently identified as a cytosine insertion in the variable number of tandem repeat region of *MUC1* encoding mucoprotein-1 (MUC1), a protein that is present in skin, breast, and lung tissue, the gastrointestinal tract, and the distal tubules of the kidney. The purpose of this investigation was to analyze the clinical characteristics of families and individuals with this mutation.

Design, setting, participants, & measurements Families with autosomal dominant interstitial kidney disease were referred for genetic analysis over a 14-year period. Families without *UMOD* or *REN* mutations prospectively underwent genotyping for the presence of the *MUC1* mutation. Clinical characteristics were retrospectively evaluated in individuals with the *MUC1* mutation and historically affected individuals (persons who were both related to genetically affected individuals in such a way that ensured that they could be genetically affected and had a history of CKD stage IV or kidney failure resulting in death, dialysis, or transplantation).

Results Twenty-four families were identified with the *MUC1* mutation. Of 186 family members undergoing *MUC1* mutational analysis, the mutation was identified in 95 individuals, 91 individuals did not have the mutation, and111 individuals were identified as historically affected. Individuals with the *MUC1* mutation suffered from chronic kidney failure with a widely variable age of onset of end stage kidney disease ranging from 16 to >80 years. Urinalyses revealed minimal protein and no blood. Ultrasounds of 35 individuals showed no medullary cysts. There were no clinical manifestations of the *MUC1* mutation detected in the breasts, skin, respiratory system, or gastrointestinal tract.

Conclusion *MUC1* mutation results in progressive chronic kidney failure with a bland urinary sediment. The age of onset of end stage kidney disease is highly variable, suggesting that gene–gene or gene–environment interactions contribute to phenotypic variability.

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Introduction

There are three types of autosomal dominant interstitial kidney disease (ADIKD). Medullary cystic kidney disease (MCKD) type 2 (Online Mendelian Inheritance in Man [OMIM] 162000) is caused by mutations in the *UMOD* gene and results in juvenile hyperuricemia, frequent gout, and progressive CKD (1). Mutations in the *REN* gene (OMIM 613092) encoding renin cause childhood anemia, hyperuricemia, mild hyperkalemia, and slowly progressive CKD (2). MCKD1 (OMIM 174000) is characterized by a bland urinary sediment and no other associated features other than progressive CKD (3). Linkage of MCKD1–1q21 was first shown in the work by Christodoulou *et al.* (4) in 1998, with refinement of the genetic locus shown in the works by Fuchshuber *et al.* (5), Wolf *et al.* (6), and Wolf *et al.* (7). Kirby *et al.* (8) identified a mutation in *MUC1* (OMIM 158340) encoding mucoprotein-1 (MUC1) as the cause of MCKD1. MUC1 is a membrane-anchored mucoprotein expressed in the skin, breast, lung, gastrointestinal tract, salivary glands, and renal distal tubular cells (9). The mucoprotein provides a protective layer to cell surfaces and may be involved in signaling (10).

Before identification of the genetic cause of MCKD1, it was difficult to clinically characterize this disorder. Identification of the *MUC1* etiology for MCKD1 permits us, for the first time, to provide a clinical characterization of individuals with known MCKD1, including individuals who have mild disease and in whom diagnosis could not be ascertained in the past. The only prior detailed clinical characterizations of

this condition were in six families from Cyprus (11) and one Native American family (12) linked to chromosome 1. In this manuscript, we describe 24 families with an *MUC1* mutation. Our results show a diverse clinical presentation within and between families with regards to the progression of CKD.

The identification of a mutation in *MUC1* as the cause of MCKD1 was surprising, because MUC1 is widely expressed. With identification of a mutation in *MUC1* as a cause of this condition, we were able to more closely examine if occult clinical expression in other organ systems was present.

Materials and Methods

A registry of families with inherited interstitial kidney disease had been constructed by A.J.B. and V.R. over 14 years, with the referral of approximately 400 families by physicians and/or family members. Families were screened by A.J.B., and medical records were obtained from these families. Information collected included demographics, family pedigree, age of ESRD, laboratory values, and ultrasound results. If appropriate, DNA was obtained and analyzed for *UMOD* and *REN* gene mutations by S.K. and P.S.H. If mutations were not found in these genes, linkage analysis was performed. In this manner, six large families with linkage to chromosome 1 were identified (Table 1, families L1–L6), including a family (L3) linked to chromosome 1 in the work by Kiser *et al.* (12), another family (L5) linked to chromosome 1 in the work by Kimmel *et al.* (13), and four kindreds (L1, L2, L4, and L6) linked by P.S.H. Samples were sent to the Broad Institute in Boston, Massachusetts for genetic analysis (8). Southern blots were used to identify mutations in the variable number of tandem repeat (VNTR)–coding region of *MUC1* in the initial six families linked to chromosome 1. All families were found to have an additional cytosine insertion to a string of seven cytosines. A probe extension assay capable of distinguishing reference and mutant *MUC1* VNTR repeat units was then used to specifically identify this same mutation (a cytosine insertion after a string of seven cytosines) in other families (8). Because of the extreme technical difficulties in the mutational analysis of this gene (8), we did not test for other mutations in *MUC1*, and we were not able to identify the particular VNTR subunit in which the cytosine insertion occurred.

Samples from 21 additional families with *UMOD*- and *REN*-negative ADIKD were analyzed for this specific *MUC1* mutation. Two of these families (Table 1, families 1 and 2) had previously been linked to chromosome 1 (14) (Scheinman SJ *et al.*, unpublished data). Also, more samples from family members from the first six families were analyzed. Individuals were considered affected (genetically affected) if they had an *MUC1* mutation. Individuals were considered to be unaffected (genetically unaffected) if they were negative for an *MUC1* mutation. Individuals were considered historically affected if genetic analysis could not be done and the individuals fulfilled two requirements: (*1*) they were related to genetically affected individuals in such a way that ensured that they could be genetically affected, and (*2*) they had an estimated GFR (eGFR; calculated throughout this work according to the Chronic Kidney Disease Epidemiology Collaboration equation) (15) that placed them in CKD stage IV or they had a history of kidney failure resulting in death, dialysis, or transplantation. The age of ESRD was calculated as the age of dialysis, kidney transplantation, or death from kidney failure.

Statistical analysis was performed with SAS, version 9.3 (Cary, NC). To determine change in eGFR over time for patients with eGFR≥50 or <50 ml/min per 1.73 m^2, the difference in eGFR between the two measurements with the greatest time interval between them was used, with an interval of at least 1 year between measurements; 50 ml/min per 1.73 m^2 was chosen arbitrarily as a cutoff point after visual inspection of the data showed a steep decline in eGFR in these individuals.

To determine if sex was associated with age of onset of ESRD, a univariate model was created with age of ESRD as the dependent variable and sex as the independent variable.

To compare the age of starting dialysis between affected parents and their children, mixed models (using PROC MIXED) were used to fit a regression between parent and child age of onset of ESRD (controlling for within-family clustering).

This study was approved by the Wake Forest School of Medicine Institutional Review Board, and it adhered to the Declaration of Helsinki. Informed consent was obtained from all individuals.

Results

Eight of eight families linked to chromosome 1 (L1–L6, 1, and 2) were found to have an *MUC1* mutation resulting in a cytosine insertion after a string of seven cytosines; 16 of 19 families with *UMOD*- and *REN*-negative ADIKD who had not been linked to chromosome 1 were found to have this same type of *MUC1* mutation.

Of 186 individuals undergoing *MUC1* genetic analysis, the *MUC1* mutation was identified in 95 individuals, and 91 individuals did not have the *MUC1* mutation. There were 111 individuals who were historically affected. There was one genetically unaffected individual with ESRD: this African American patient had a long history of nephrotic proteinuria and was considered *a priori* not to have MCKD1. Table 1 lists characteristics of the individual families.

Of 147 individuals who developed ESRD, ESRD developed in 1 individual (0.68%) at age<20 years, 24 (16.3%) individuals between 20 and 30 years, 72 (49.0%) individuals between 30 and 50 years, 37 (25.2%) individuals between 50 and 70 years, and 13 (8.8%) individuals at ≥70 years.

Figure 1 shows the age of onset of ESRD according to family. There seemed to be two groups of families: one group with a younger median age of ESRD and all family members on dialysis before age 50 years, and one group with a highly variable age of ESRD for individual family members and a higher median age of ESRD. In three families (5, 9, and 11), clinical information strongly suggested a *de novo* mutation (Figure 2, A–C).

We then analyzed eGFR values for affected and unaffected family members. Figure 3 shows the highest available

Table 1. Characteristics of families with *MUC1* mutation

Family Number[a]	Ethnicity	*MUC1* Mutation (*n*)	Historically Affected (*n*)	No *MUC1* Mutation (*n*)	Median Age of ESRD (yr)	Kidney Biopsy (*n*)	Kidney Ultrasound Available for Review (*n*)	Prior Linkage to Chromosome 1
L1	Middle Eastern	11	11	16	42	1	0	Yes
L2	African American	11	12	20	57	0	6	Yes
L3	Native American	22	5	36	45.5	8	7	Yes
L4	European American	7	9	6	60	3	2	Yes
L5	European American	9	6	0	34	2	0	Yes
L6	European American	4	5	6	41	0	2	Yes
1	European American	3	0	1	28.5	1	2	Yes
2	European American	3	2	0	67.5	2	3	Yes
3	European American	1	4	1	42	2	1	No
4	European American	1	5	0	31.5	2	1	No
5	African American	2	6	1	29	0	2	No
6	Finnish	1	19	0	52.5	1	1	No
7	European American	1	9	1	33.5	0	1	No
8	European American	1	1	0	31.5	0	0	No
9	European American	1	1	0	39	1	1	No
10	European American	2	0	0	No members yet with ESRD	1	0	No
11	Australian	2	1	0	31	2	0	No
12	Eastern European	1	0	0	29	1	0	No
13	Eastern European	1	0	0	44	1	0	No
14	European American	6	6	3	43.5	2	1	No
15	Australian	1	2	0	25	2	2	No
16	Russian	2	1	0	55	1	1	No
17	Australian	1	1	0	38	0	0	No
18	Israeli	1	5	0	39	1	2	No

[a]Family number: families L1–L6 refer to the first six families that were linked to chromosome 1 and had mutational analysis performed. Family numbering corresponds to numbering in ref. 8.

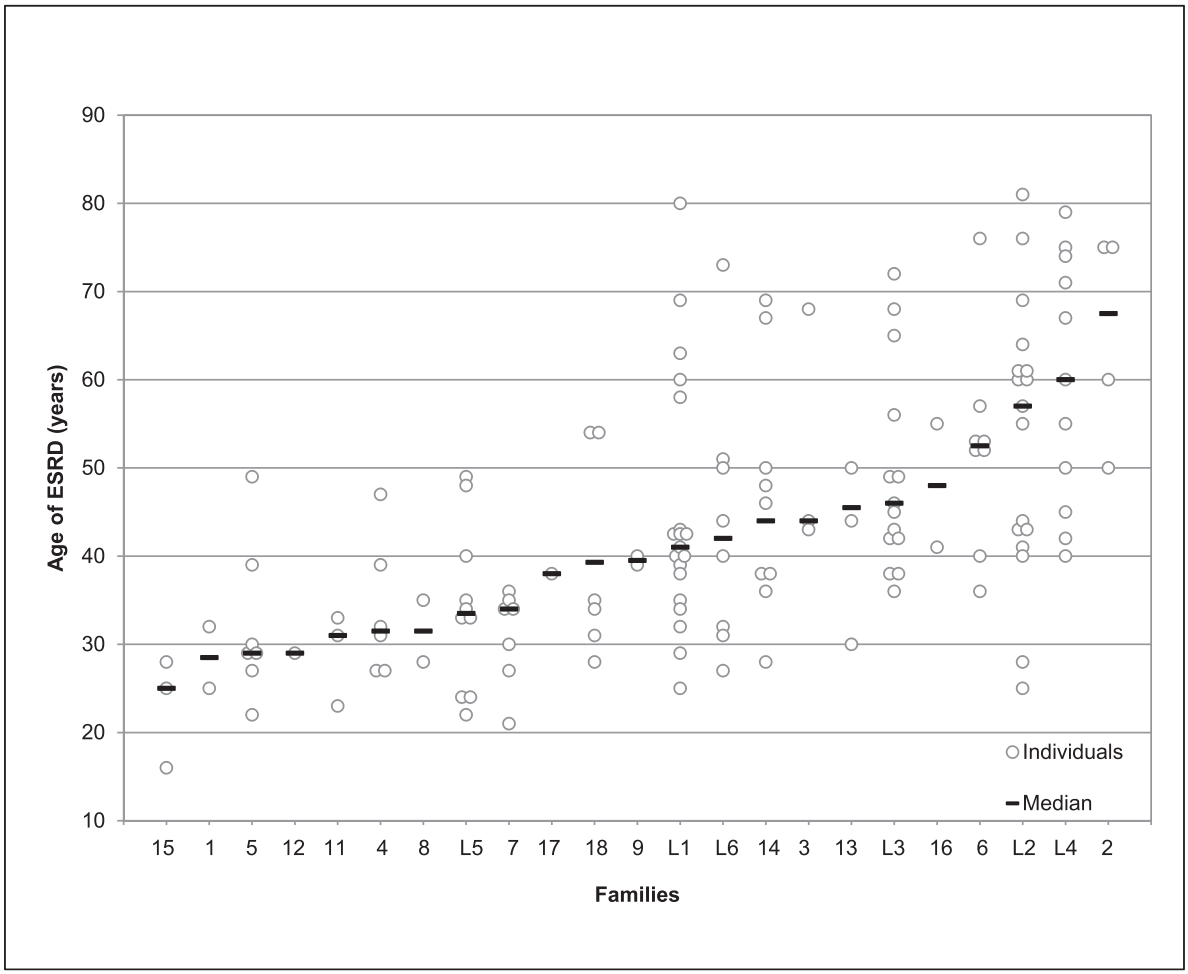

Figure 1. | **Age of onset of ESRD for individuals from families with the *MUC1* mutation.** (This figure does not include family members who have not developed ESRD. One family has no members with ESRD and, thus, is not represented here.)

measurement of eGFR at any time point for affected individuals and the lowest available eGFR measurement for unaffected individuals from families with *MUC1* mutation to determine how well eGFR differentiated between the groups. For individuals in whom only the ESRD age and no serum creatinine values were available, the eGFR at the start of dialysis was approximated as 5 ml/min per 1.73 m^2. Like in Figure 1, Figure 3 shows a wide variation in eGFR over time for affected individuals; some individuals had relatively preserved kidney function into their eighth decade, and other individuals required dialysis in their 20s. There is clear overlap between affected individuals and unaffected individuals caused by the presence of stages II and III kidney failure in a number of affected and unaffected individuals.

We analyzed the rate of decline in eGFR in affected individuals. In examination of the data, we noted that there were many measurements obtained by the patients' nephrologists when the eGFR was below 50 ml/min per 1.73 m^2, and the decline seemed quite rapid. We decided to arbitrarily analyze values ≥50 and <50 ml/min per 1.73 m^2. Figure 4 displays progression of kidney disease in all 11 affected individuals in whom we had at least 10 measurements of eGFR<50 ml/min per 1.73 m^2. In available data, 22 affected individuals with an eGFR≥50 ml/min per 1.73 m^2 had a mean eGFR change of 0.99±6 ml/min per 1.73 m^2 per year versus a mean eGFR change of −6.7±4.2 ml/min per 1.73 m^2 per year for 29 affected individuals with an eGFR≤50 ml/min per 1.73 m^2 ($P<0.001$).

We next evaluated whether ESRD developed at younger ages for successive generations. Figure 2D depicts a family in which this development seems to have occurred. To further evaluate the possibility, a graph was created (Figure 5), with parental age of ESRD on the *y* axis and the age of ESRD for the child on the *x* axis. There were 63 of 111 family pairs (57%) in which the parents were older at the start of ESRD, and there were 45 of 111 family pairs (41%) in which the child started at an older age than the parent. Using mixed models that accounted for clustering within families, the mean difference between parent and child age of starting ESRD was estimated at 4.9 years (SEM=2.0 years; parents being older when ESRD developed: 48.0±2.1 versus 43.1±2.1 years, $P=0.02$).

We then determined whether sex was associated with variation in the age of ESRD. In a univariate model with

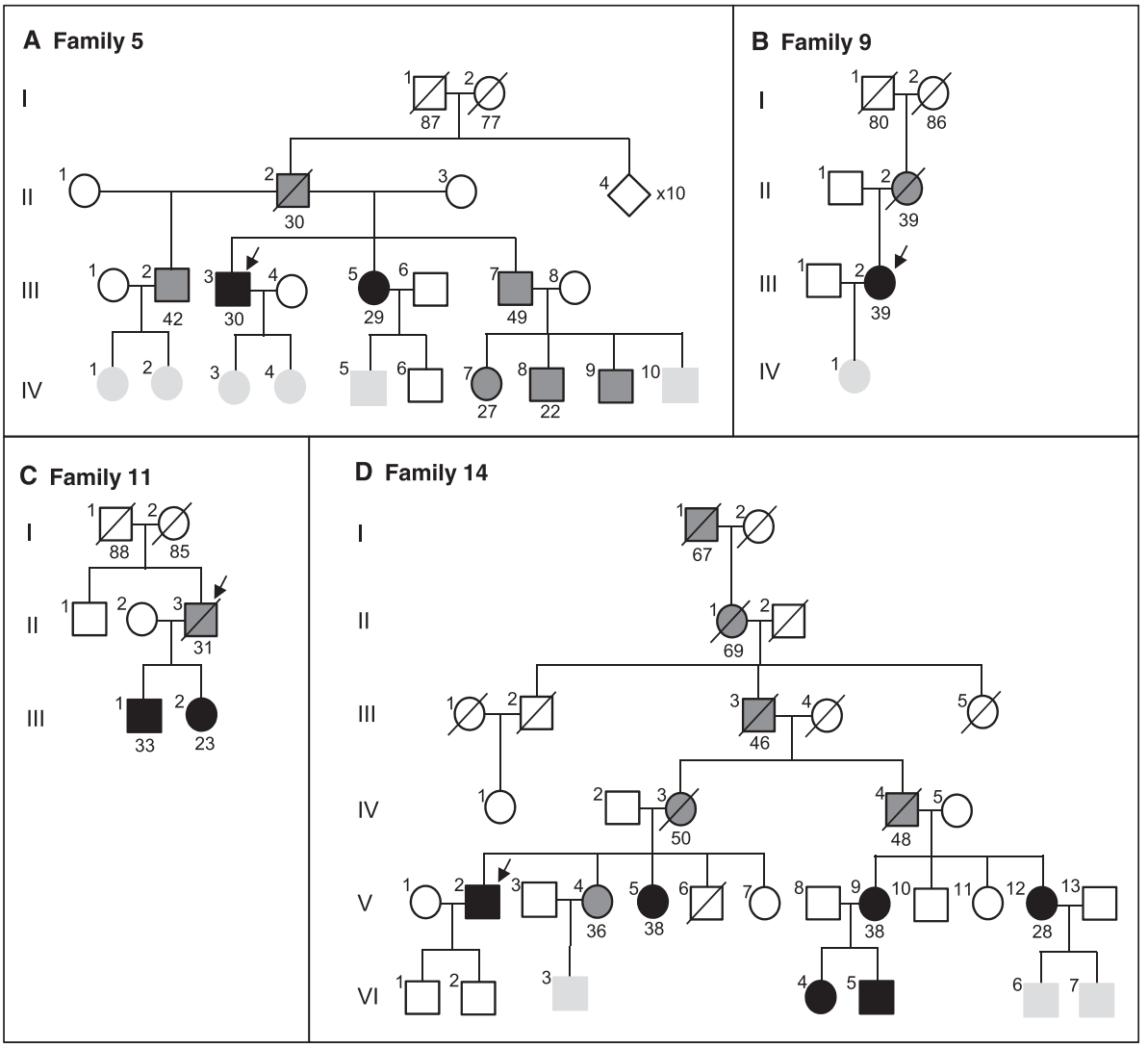

Figure 2. | **Representative pedigrees from families with the *MUC1* mutation.** Individuals with the *MUC1* mutation are represented with black symbols. Historically affected individuals are denoted with dark gray symbols. Individuals with unknown status are shown with light gray symbols. Age of ESRD (years) is given below affected individuals. The proband for each family is indicated with an arrow. A–C show families with new mutations. The age (years) of death of individuals in generation I is given below the symbol. D shows a family with earlier onset of ESRD in succeeding generations.

age of ESRD as the outcome variable, sex was not associated with the age of onset of ESRD (P=0.62). Only two affected individuals also suffered from diabetes mellitus. Their rate of progression seemed consistent with other affected individuals, with ESRD at 43 and 45 years.

Table 2 shows clinical characteristics of individuals with MCKD1. Gout was identified in 30 of 127 individuals (24%) in whom sufficient clinical information was available to ascertain the presence of gout. Of 27 patients who eventually required dialysis and had gout, 3 (11%) patients had gout more than 10 years before kidney failure, 7 (26%) patients had gout 6–9 years before kidney failure, and 17 (63%) patients had gout occurring within 5 years of dialysis or after starting dialysis. The eGFR was less than 50 ml/min per 1.73 m^2 in seven of eight (88%) patients in whom eGFR data were available at the time of gout.

In urinalyses from 29 individuals with *MUC1* mutation, urine protein was negative in 23 (79%) individuals, trace in 2 individuals, 1+ in 3 individuals, and 2+ in 1 individual. The urine dipstick was negative for blood in 22 individuals and trace positive in 7 individuals. In ultrasounds from 35 individuals, kidneys ranged from normal size to small as CKD progressed. Twenty-one patients (60%) had no cysts. Of the total 70 kidneys, 49 (70%) kidneys had no cysts, 9 (13%) kidneys had 1 cyst, and 12 (17%) kidneys had 2 or more cysts. There were no medullary cysts identified in any ultrasounds. MCKD was not suspected in any ultrasounds. There were 34 renal biopsies performed that all showed tubulointerstitial kidney disease. In four (12%) individuals, microcystic dilation of the tubules was noted; in two of these cases, MCKD was suggested as a cause; in one case, polycystic kidney disease was suggested as a cause, and in one case, a toxic injury to the tubules was

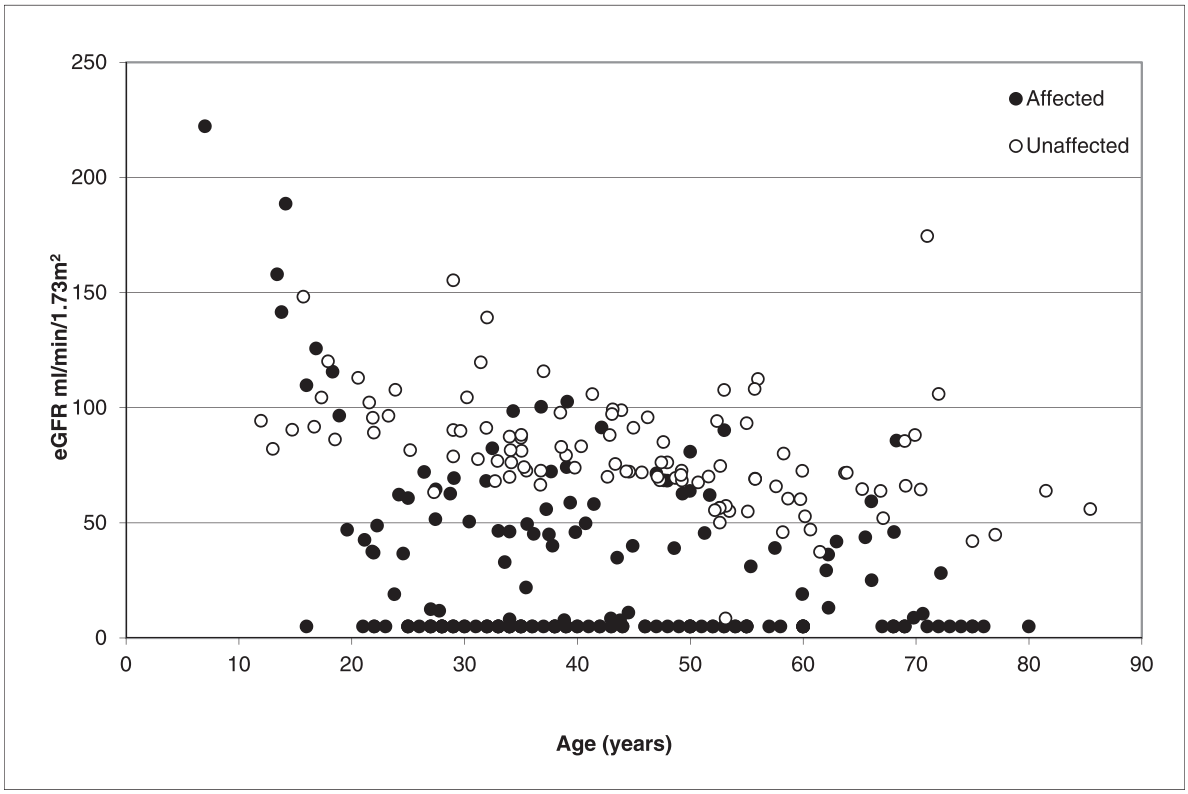

Figure 3. | **Estimated GFR (eGFR) versus age for individuals in families with the MUC1 mutation.** This graph shows the highest available eGFR measurement for affected individuals and the lowest available eGFR measurement for unaffected individuals to determine overlap. Patients in whom only the age of ESRD is available are depicted with an eGFR value of 5 ml/min per 1.73 m^2. There is considerable overlap between groups.

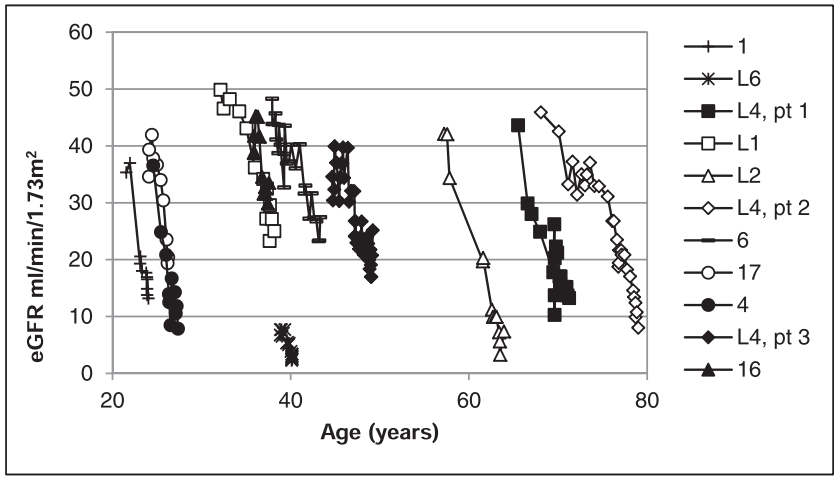

Figure 4. | **Decline in eGFR over time for individuals with more than 10 eGFR measurements.** Decline was rapid when eGFR was <50 ml/min per 1.73 m^2. The family to which each individual belongs is identified (family numbers correspond to Table 1).

suggested as a cause. There was no increased incidence of polyuria, renal calculi, or urinary tract infections in affected individuals.

Review of records did not reveal an increased frequency of any clinical pathophysiology of the lungs, breasts, or gastrointestinal tract—tissues in which *MUC1* is highly expressed. There were no instances of chronic obstructive pulmonary disease or other lung disease, lung cancer, gastric ulcers, or gastric cancer. Records were obtained on 17 women who had undergone mammograms. Of these women, 7 women had negative results, and 10 women were called back for additional evaluation. Of these 10

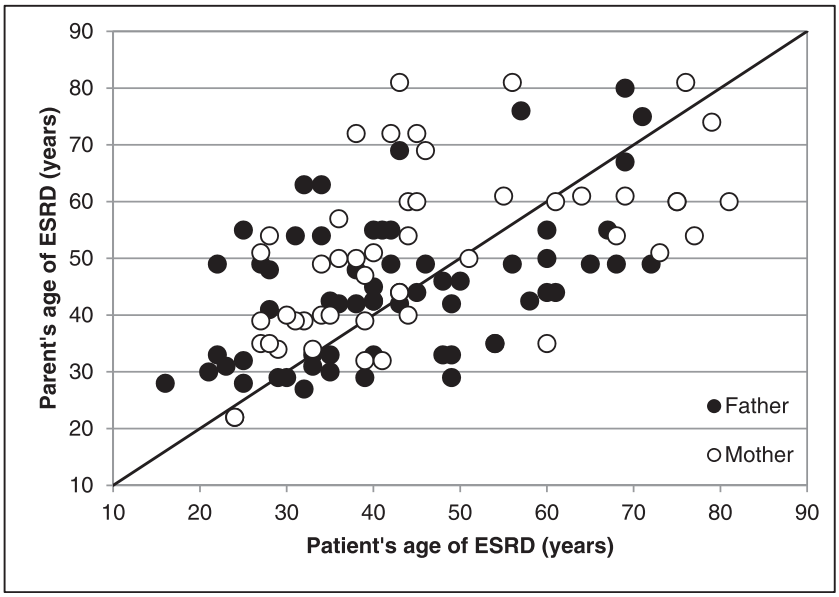

Figure 5. | **Age of onset of ESRD for affected parents versus children.** Parental age of ESRD is plotted versus the age of ESRD for the affected child. The line represents where parental age of ESRD would equal the child's age of ESRD. Points that are above the line represent parental ESRD age being older than the child ESRD age. Points below the line represent parental ESRD age being lower than the child ESRD age.

Table 2. Characteristics of affected individuals

Characteristic	Number of Individuals with the Characteristic Evaluated	Value
N	206	
Sex (% men)	206	100 (48.5%)
Age of ESRD (yr)[a]	147	44.9±15.4
Range of age of ESRD (yr)	147	16–81
Age of ESRD for women (yr)	79	44.4±16.1
Age of ESRD for men (yr)	68	45.6±14.8
Receiving antihypertensive therapy (%)	70	43 (61.4%)
Systolic BP (mmHg)	83	126±18.7
Diastolic BP (mmHg)	83	76.0±11.1
Gout (%)	127	30 (24%)
Serum uric acid level for individuals not on allopurinol	43	7.4±1.89
Renal cysts on imaging (%)	27	48.15
Medullary cysts on imaging (%)	27	0
Urinalysis dipstick for protein negative	29	23 (79%)

[a]Continuous variables are represented as mean±SD.

women, there were five biopsies; of these five biopsies, two individuals had cancer. Of 99 affected women for whom we have records, only 2 women were identified as having breast cancer.

Discussion

One cannot fully appreciate the clinical spectrum of a genetic disease until the mutation causing the disease has been identified. Identification of an *MUC1* mutation in MCKD1 enables us to considerably increase our knowledge about the clinical manifestations of MCKD1, particularly for mild manifestations.

The mutation causing MCKD1 is in *MUC1*. *MUC1* has a repetitive sequence of 60 nt that occurs 20–125 times (VNTR domain). This sequence encodes for a corresponding serine- and threonine-rich amino acid domain of MUC1. Glycosylation of the VNTR determines the mucinous properties of the protein. In all families identified in this work, the *MUC1* mutation originates from the insertion in 1 of 60 nucleotide repeat units of a single cytosine within a consecutive sequence of seven cytosines. The mutation encodes within the VNTR domain for a shift in *MUC1* transcript translation and results in proteosynthesis of an MUC1 neoprotein that contains a novel repeat and a C-terminal amino acid sequence lacking characteristic

Table 3. Clinical characteristics of autosomal dominant interstitial kidney disease

Characteristic	Medullary Cystic Kidney Disease Type 1 (Caused by Mutations in the *MUC1* Gene)	Medullary Cystic Kidney Disease Type 2 (Caused by Mutations in the *UMOD* Gene)	Mutations in the *REN* Gene Encoding Renin
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant
Urinary sediment	Bland	Bland	Bland
Urinary protein	Absent/minimal	Absent/minimal	Absent/minimal
Medullary cysts	Rare	Rare	Absent
Age of ESRD (yr)	Variable: late 20s to >70	Variable: 30–60	Variable: 40–70
Gout in many affected family members (often occurring early in life)	Absent	Present	Present
Hyperkalemia and low BP (symptoms of low renin state)	Absent	Absent	Present
Anemia in childhood	Absent	Absent	Present

protein post-translational processing, transmembrane anchoring, and intracellular signaling domains of the wild-type MUC1.

For the first six families investigated, full mutational analysis of *MUC1* was performed. Because of the intrinsic, laborious difficulties of screening the entire VNTR, the remaining families were only examined for mutations that would have included an extra cytosine residue (8). A high proportion (16 of 19; 84%) of families with ADIKD and no mutations in *UMOD* and *REN* was found to have a cytosine insertion in the VNTR of *MUC1*. Thus, it is important to screen for this mutation in families with *UMOD*- and *REN*-negative ADIKD. The three families that tested negative for the *MUC1* insertion were too small for linkage analysis. It is possible that their condition results from a different mutation in *MUC1* or mutation of another gene. However, the vast majority of individuals with this condition have the cytosine insertion in the VNTR of *MUC1*. These findings suggest that the neoprotein that is created because of the cytosine insertion is central to the pathogenesis of the disease. Moreover, the presence of clinical changes only in the kidney is suggestive that this neoprotein has a specific deleterious effect in renal tubular cells.

It was also not possible to determine in which particular VNTR subunit the mutation occurred. It is likely that the mutation occurs in different subunits for each family, although each family will have the mutation in the same VNTR subunit for all affected family members.

The most important findings of this study were the variable age of onset of ESRD within and between families, and the rapid progression to dialysis in the third decade of life in several families. Previously, families with early onset kidney failure had not been identified, because these families are smaller (because of limited time for childbearing as a result of ESRD) and could not provide definitive genetic linkage. The site of the mutation (in an earlier versus later portion of the VNTR) might be responsible for this difference, although, at this time, it has not yet been possible to determine the precise position of the mutation for the individual families.

In some genetic conditions, the phenotype can worsen with succeeding generations. It was difficult to determine if ESRD occurred at younger ages with succeeding generations. In general, children proceeded to dialysis earlier than their affected parent. However, this finding was not always the case. The work by Christodoulou *et al.* (4) was the first to suggest early age of ESRD in succeeding generations in a study of six large Cypriot families that had shown DNA linkage to the MCKD1 locus. There is no biologic mechanism that has been identified that would suggest that the mutation under study would lead to this phenomenon. The temporal trends of starting patients on dialysis earlier or receiving transplantation earlier could be potentially responsible for these findings.

We found that the rate of eGFR decline seemed to be accelerated when the eGFR declined below 50 ml/min per 1.73 m^2. This finding must be interpreted with caution. We arbitrarily chose to evaluate values $\geq$50 and $<$50 ml/min per 1.73 m^2 after visual inspection of the data, and we did not have a large number of patients in our sample. Additional analyses will be required with a larger number of patients and evaluation in a prospective manner. However, clinicians may consider following laboratory values more closely when patients reach this level of eGFR until more data are available.

Like other investigators (11), we found that MCKD1 has a very limited clinical presentation. Urinalyses showed a bland sediment and minimal protein. Although MUC1 is produced in many tissues, we could not find evidence of clinical alterations of organs or tissues besides the kidney. The recall rate for mammograms was 58%, which was similar to the lifetime recall rate of 61.3% in a large study of mammogram screening (16). Renal ultrasounds showed occasional cysts, and medullary cysts were not identified in any patients. As initially described in the work by Hildebrandt and Omram (17), MCKD is a poor name for this condition, because cysts are often absent, and the misnomer may impede diagnosis of this condition. Kidney biopsy specimens did show tubular microcystic dilation in a small proportion (4 of 34) of biopsies.

There was considerable overlap in eGFR values between unaffected and affected members of families with *MUC1* mutations. The high prevalence of stage III CKD in

unaffected individuals may have been caused by a significant number of African Americans with stage III CKD, the use of the lowest available eGFR for unaffected individuals, and interlaboratory variation in serum creatinine determinations. These results show that it is not yet possible to clinically differentiate individuals without genetic testing, and there is no clinical method to diagnose MCKD1 or determine if families or family members are affected or unaffected.

Given the different characteristics of MCKD1, MCKD2, and *REN* mutations (Table 3), we propose a stepwise approach to genetic testing. In individuals with ADIKD, genetic testing for *REN* mutations should be performed if patients also suffer from anemia, mild hyperkalemia, and low normal BPs. If gout is a significant component of disease, mutational analysis of the *UMOD* gene should be performed. If these tests are negative or if gout, anemia, and mild hyperkalemia are absent, *MUC1* testing should be done. In the future, tandem genetic analyses for all three conditions will likely become available. Currently, genetic testing is only available in a research setting, and we would be happy to discuss testing for families that may potentially be affected. Please contact A.J.B. with any questions in this regard.

In summary, MCKD1 is caused by a mutation in the *MUC1* gene. Onset of ESRD is very variable between and within families. Although MUC1 is produced in many tissues, we could only find clinical abnormalities in the kidney.

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Disclosures

None.

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