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Original Article

ORIGINAL ARTICLE

MUC1-associated autosomal dominant tubulointerstitial kidney disease: prevalence in kidney failure of undetermined aetiology and clinical insights from Danish families

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ABSTRACT

Background. Frameshift variants in the variable number tandem repeat region of *mucin-1* (*MUC1*) cause autosomal dominant tubulointerstitial kidney disease (ADTKD-*MUC1*) but are challenging to detect. We investigated the prevalence in patients with kidney failure of undetermined aetiology and compared Danish families with ADTKD-*MUC1*.
Methods. We recruited patients with suspected kidney failure of undetermined aetiology at ≤50 years and excluded those with a clear-cut clinical or histopathological kidney diagnoses or established genetic kidney diseases identified thorough medical record review. *MUC1* genotyping was performed by SNaPshot analysis, detecting the most common pathogenic cytosine duplication, followed by bioinformatics pipeline VNtyper analysis of short-read sequencing data.
Results. Of 172 recruited patients, 123 underwent SNaPshot analyses, which were abnormal in 5/123 patients (4%). Next, VNtyper genotyping was performed in all patients, including the five with abnormal SNaPshot analysis. VNtyper re-identified the common cytosine duplication in all five patients and revealed novel frameshift variants in two additional patients, while the analyses were normal in the remaining 116 patients. All patients carrying frameshift variants in *MUC1* fulfilled ADTKD criteria and had a family history of kidney failure. A considerable inter- and intrafamilial variability of chronic kidney disease stage relative to age was observed in families with ADTKD-*MUC1*.
Conclusions. ADTKD-*MUC1* was identified in 7/123 patients (6%) in a selected cohort of kidney failure of undetermined aetiology ≤50 years, and VNtyper effectively identified all pathogenic *MUC1* variants.

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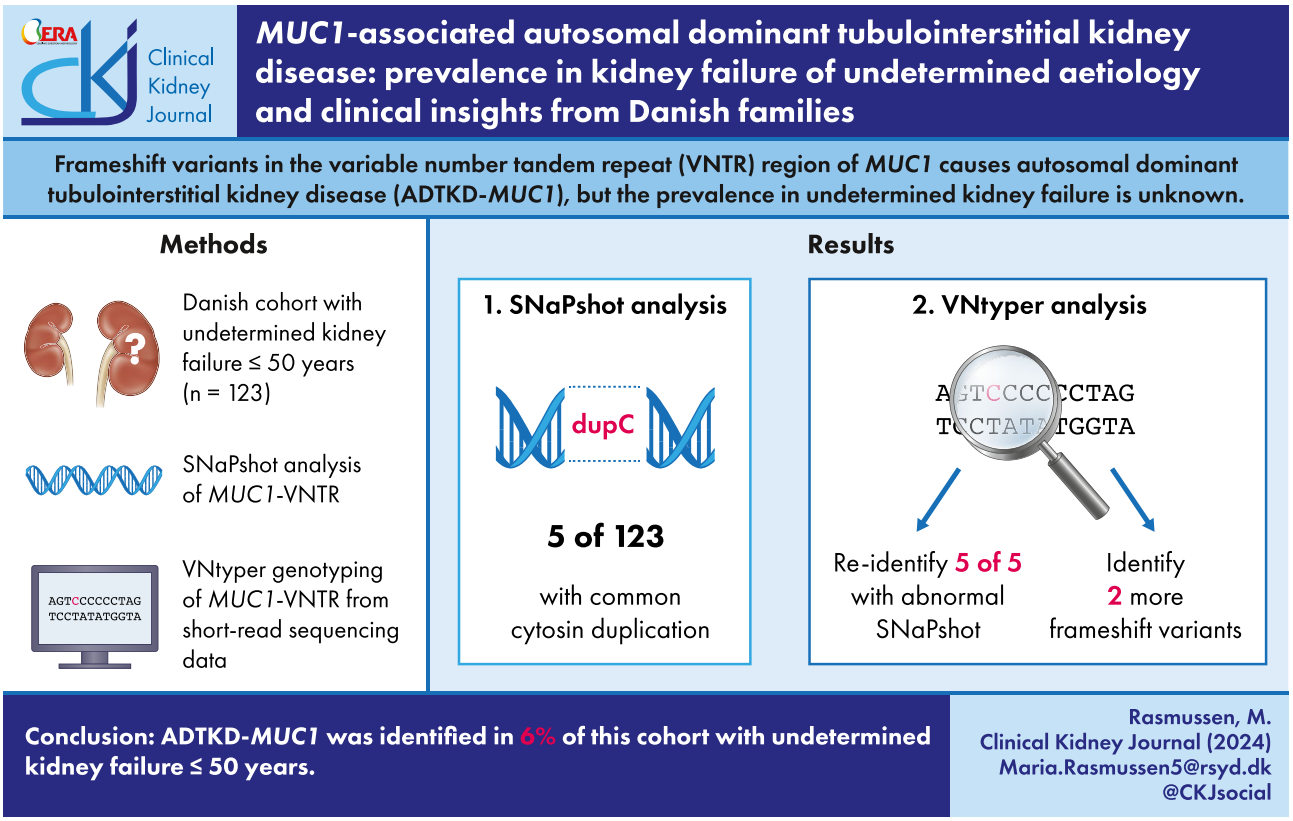
GRAPHICAL ABSTRACT



Keywords: ADTKD, *MUC1*, SNaPshot, undetermined kidney failure, VNtyper

KEY LEARNING POINTS

What was known:

- *Mucin-1* (*MUC1*)-associated autosomal dominant tubulointerstitial kidney disease (ADTKD-*MUC1*) is caused by frameshift variants undetectable by conventional sequencing methods, and the prevalence in patients with chronic kidney failure of undetermined aetiology (uKF) is unknown.

This study adds:

- Frameshift variants in *MUC1* were identified in 7 out of 123 patients with uKF ≤50 years using SNaPshot analysis and VNtyper genotyping.
- All seven patients had a family history of kidney failure and full-filled ADTKD criteria, and all *MUC1* variants were detectable with VNtyper using short-read sequencing data.

Potential impact:

- *MUC1* frameshift variants are not uncommon in patients with uKF ≤50 years and a positive family history, and *MUC1* analysis should be considered in such patients.

INTRODUCTION

The aetiology of chronic kidney disease (CKD) is often uncertain in adults, and uncovering the genetic basis of CKD is pivotal for advancing precision nephrology [1–3]. Massive parallel sequencing reveals monogenic causes in 12%–47% of adults with unexplained CKD [4–10] and provides a cost-saving diagnostic approach [11]. However, platforms sequencing short DNA fragments (i.e. short-read sequencing) miss certain genetic variants, resulting in diagnostic blind spots and a systematic underestimation of the genetic contribution to CKD.

One important example is *mucin-1* (*MUC1*)-associated autosomal dominant tubulointerstitial kidney disease (ADTKD-*MUC1*, OMIM #174 000), which is mainly caused by frameshift variants within a 60-base pair variable tandem repeat (VNTR) region of

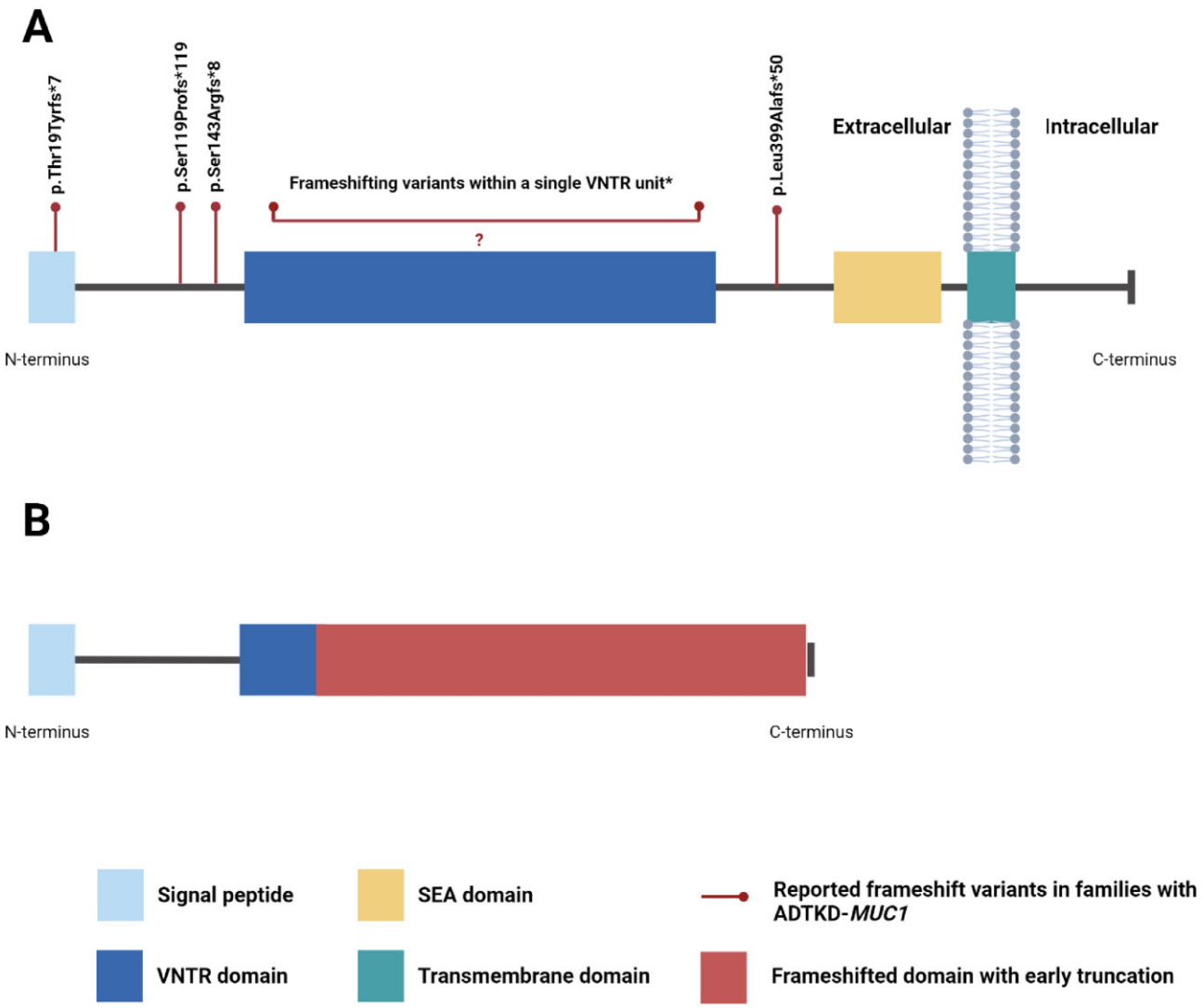


Figure 1: MUC1 protein structure. Schematic representations of the normal (**A**) and frameshifted (**B**) MUC1 protein based on description by Kirby *et al.* [12]. Previously reported frameshift variants identified in families with ADTKD-*MUC1* are shown with red markers according to the *MUC1* transcript NM_001204286.1 (Overview is provided in Supplementary data, Table S1.) Created with BioRender.com. SEA, sea urchin sperm protein.

MUC1 encoding the protein mucin-1 (Fig. 1, Supplementary data, Table S1). Specialized genetic analyses are required to detect these variants due to the complex and repetitive VNTR structure [12, 13]. ADTKD-*MUC1* is a subtype of the ADTKD disease group characterized by progressive CKD leading to kidney failure (KF), autosomal dominant inheritance, bland urinary sediment with minimal proteinuria, and unspecific kidney histopathology with interstitial fibrosis and tubular atrophy [14]. ADTKD-*MUC1* is primarily caused by a cytosine duplication within a single VNTR unit, forming an eight cytosine nucleotide (8C) sequence instead of the wild-type seven cytosine nucleotide (7C) sequence [12, 13, 15]. The frameshifted neoprotein product, MUC1-fs, truncates after the VNTR and accumulates in the kidneys leading to tubulointerstitial kidney disease [12, 16]. Additional frameshift variants within [15] and before [17, 18] the VNTR region have recently been identified in ADTKD-*MUC1* families (Supplementary data, Table S1).

Previous studies conducting systematic screening for ADTKD-*MUC1* have reported highly variable prevalences, ranging from 0% to 60% [12, 13, 15, 19–31] (Supplementary data, Table S2). These discrepancies can primarily be attributed to differences in study sizes, *MUC1* screening methods and patient selection. In particular, most studies screened only patients with suspected ADTKD, making it challenging to extrapolate the diagnostic utility of *MUC1* screening in a broader population of patients with KF.

We investigated the prevalence of ADKTD-*MUC1* in 123 families with KF of undetermined aetiology (uKF) ≤50 years. Furthermore, we analysed clinical characteristics of identified Danish ADTKD-*MUC1* families, which were identified either from the uKF cohort or through clinical genetic screening.

MATERIALS AND METHODS

Recruitment of uKF cohort

The recruitment of patients with uKF has been described previously [32], and genetic analyses with single nucleotide

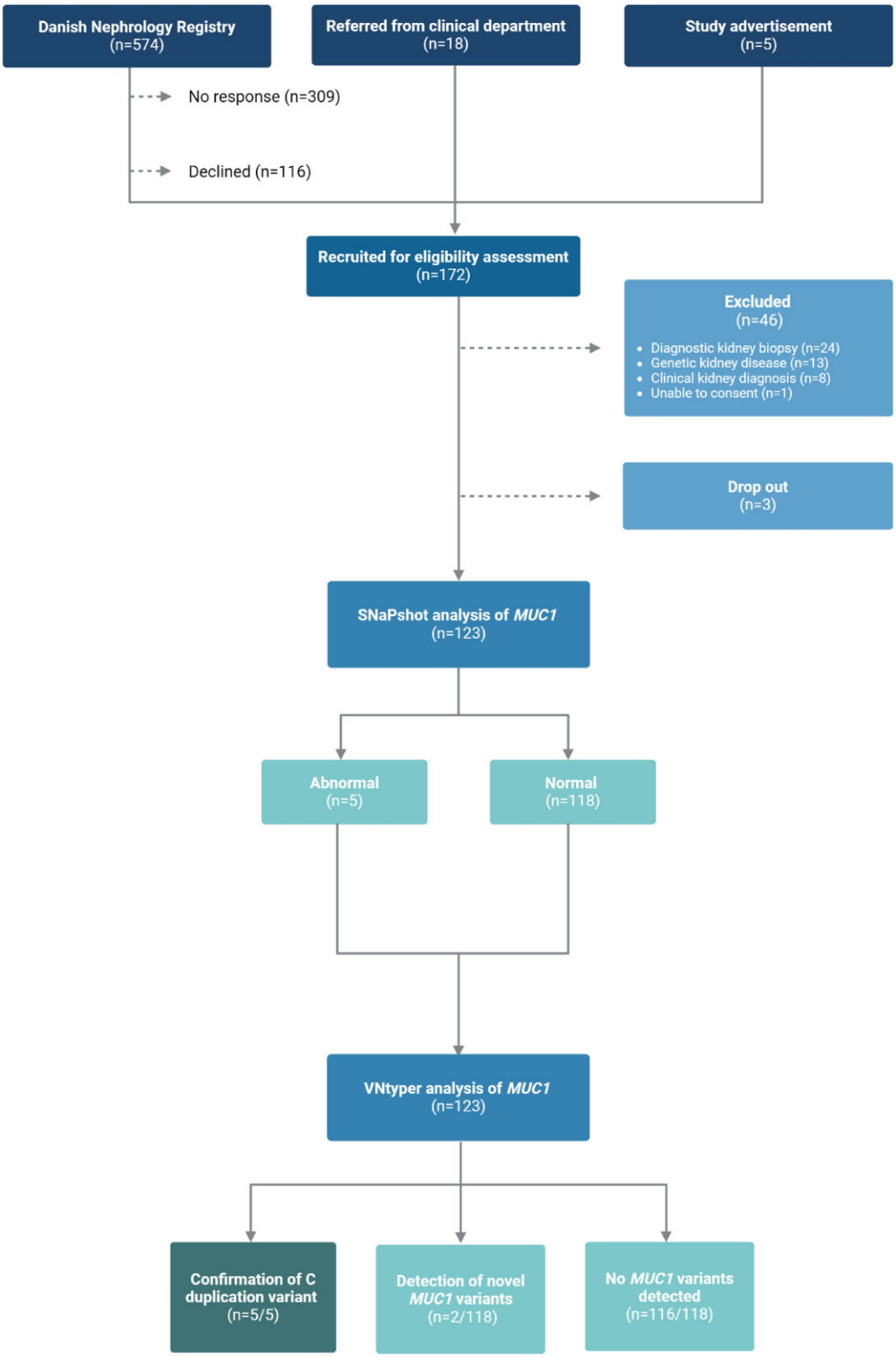


Figure 2: Flowchart of patient recruitment and *MUC1* screening. Patients were invited to participate via the Danish Nephrology Registry, study advertisement in the Danish Kidney Association or by referral from clinical departments. Recruited patients first underwent eligibility assessment by medical record review to exclude patients with determined kidney disease aetiologies. *MUC1*-VNTR genotyping was first performed by SNaPshot analysis and followed by VNtyper analysis. Created with BioRender.com.

Table 1: Cohort baseline characteristics.

Cohort characteristics ($n = 123$)	
Sex	
Male	67 of 123 (54%)
Female	56 of 123 (46%)
Age of KF[a]	
Mean (SD)	35 (11)
Median (IQR)	37 (28–45)
<18 years	10 of 121 (8%)
≥18 years	111 of 121 (92%)
PRD codes[b,c]	
CKD of unknown/unspecified aetiology	46 of 108 (43%)
Hypertensive kidney disease	12 of 108 (11%)
Glomerular kidney disease	35 of 108 (32%)
Congenital dysplasia/hypoplasia	5 of 108 (5%)
Tubulointerstitial kidney disease	6 of 108 (6%)
Familial nephropathy	4 of 108 (4%)
Hypertension at time of kidney disease diagnosis	56 of 123 (46%)
Native kidney biopsy performed	50 of 123 (41%)
Family history of CKD	40 of 123 (33%)
Family history of KF	25 of 123 (20%)
Fulfills ADTKD criteria[d]	19 of 123 (15%)

[a]N = 121 had KF at inclusion, as two patients with uCKD without KF were included based on a family history of KF before the age of 50 years.
[b]PRD codes were only available from 108 patients recruited from the Danish Nephrology Registry.
[c]Similar PRD codes are pooled into phenotype groups: CKD of unknown/unspecified aetiology (3555, 3564, 3691, 3708), hypertensive kidney disease (2359), glomerular kidney disease (1061, 1267, 1377, 3749), tubulointerstitial kidney disease (1884, 1897, 2005), congenital dysplasia/hypoplasia (1625) and familial nephropathy (2804, 3295, 3379).
[d]Criteria for suspected ADTKD were (i) a family history compatible with autosomal dominant inheritance, and (ii) a slowly progressive CKD with bland urinary sediment and absent-to-mild proteinuria, and (iii) normal or small-sized kidneys on renal ultrasound, and (iv) no obvious explanation of kidney disease [14].
SD, standard deviation; IQR, interquartile range; PRD, primary renal diagnosis.

polymorphism array and *MUC1* genotyping were subsequently performed in parallel. Briefly, patients with suspected uKF were recruited and underwent thorough medical record review to exclude any specific kidney disease aetiologies. Inclusion criteria for genetic screening were (i) onset uKF ≤50 years, or (ii) CKD of unknown aetiology and a family history of onset KF ≤50 years, and (iii) age >18 years at inclusion. We defined uKF similar to previous studies [7, 10] as the absence of any specific clinical, histopathological or structural kidney disease diagnosis. Cases with unspecific abnormal kidney morphology (e.g. hypodysplasia) or histology (e.g. focal segmental glomerulosclerosis), or hypertensive kidney disease were also categorized as uKF. We excluded patients with known genetic kidney diseases already identified by molecular genetic testing in a clinical setting.

Recruitment of additional ADTKD-*MUC1* families

To further characterize the clinical profiles in patients with ADTKD-*MUC1*, we included three additional families already identified with this condition in a clinical setting. These were recruited via referring departments and/or the national NephroGENE network [33].

Phenotype data sources and definitions

Primary renal diagnosis codes and age at KF were obtained from the Danish Nephrology Registry where available. Clinical kidney diagnosis, any kidney imaging or biopsy results, and hypertension status at the time of initial kidney disease diagnosis were extracted from medical records after enrollment. Additionally, pedigrees were drawn for all patients.

We defined KF as eGFR <15 mL/min or kidney replacement therapy for ≥3 months [34] and family history as either CKD or KF present in one or more first- or second-degree relative. Consistent with the KDIGO criteria for suspected ADKTD [14], we considered ADTKD probable when: (i) there was a family history consistent with autosomal dominant inheritance, and (ii) patients exhibited slowly progressive CKD with bland urinary sediment, absent or mild proteinuria, and (iii) normal or small-sized kidneys on renal ultrasound, and (iv) there was no other obvious explanation of kidney disease.

Genetic analyses of *MUC1*

All analyses were performed at Department of Clinical Genetics, Lillebaelt Hospital, and detailed descriptions of the genetic analyses are provided in Supplementary Methods. We first genotyped *MUC1*-VNTR using SNaPshot minisequencing modified from Ekici *et al.* [13] to detect the most common pathogenic cytosine duplication (termed "8C duplication," see Supplementary data, Table S1 for nomenclature overview). Next, patients underwent additional VNtyper-Kestrel genotyping of *MUC1*-VNTR [30] using short-read sequencing data generated by customized probe capture (Integrated DNA Technologies, Coralville, IA, USA) targeting all exons and introns of the *MUC1* gene. These data were also analysed for the occurrence frameshift and truncating variants in VarSeq v.2.3.0 (Golden Helix, Bozeman, MT, USA) within or outside the VNTR region, without identifying any such variants.

Ethics

The study was approved by the Danish National Committee on Health Research Ethics (1 906 020) and conducted in accordance with the Helsinki Declaration. All patients received genetic counselling and provided written informed consent before participation. Patients from the previously identified ADTKD-*MUC1* families gave written consent for publication.

Statistics

Statistical analyses were performed using STATA 17 (Statacorp LLC, College Station, TX, USA). Categorical variables were expressed as frequencies and percentages. Numeric variables were expressed as medians with interquartile range. Fisher's exact test was used for all comparisons of categorical variables, while Wilcoxon rank-sum test was used to compare median age of KF between patients with and without ADTKD-*MUC1*. A two-tailed *P*-value <.05 was considered statistically significant.

RESULTS

Characteristics of uKF cohort

We initially included 172 unrelated patients into the study for eligibility assessment, excluding 46 after medical records review (Fig. 2A). Blood samples for genetic screening were successfully obtained from 123 patients, who comprised the uKF cohort. The baseline characteristics of the cohort is shown in Table 1. The median age of KF was 37 with 92% of the cohort having adult onset KF at age 18 years or older. A family history of CKD or KF

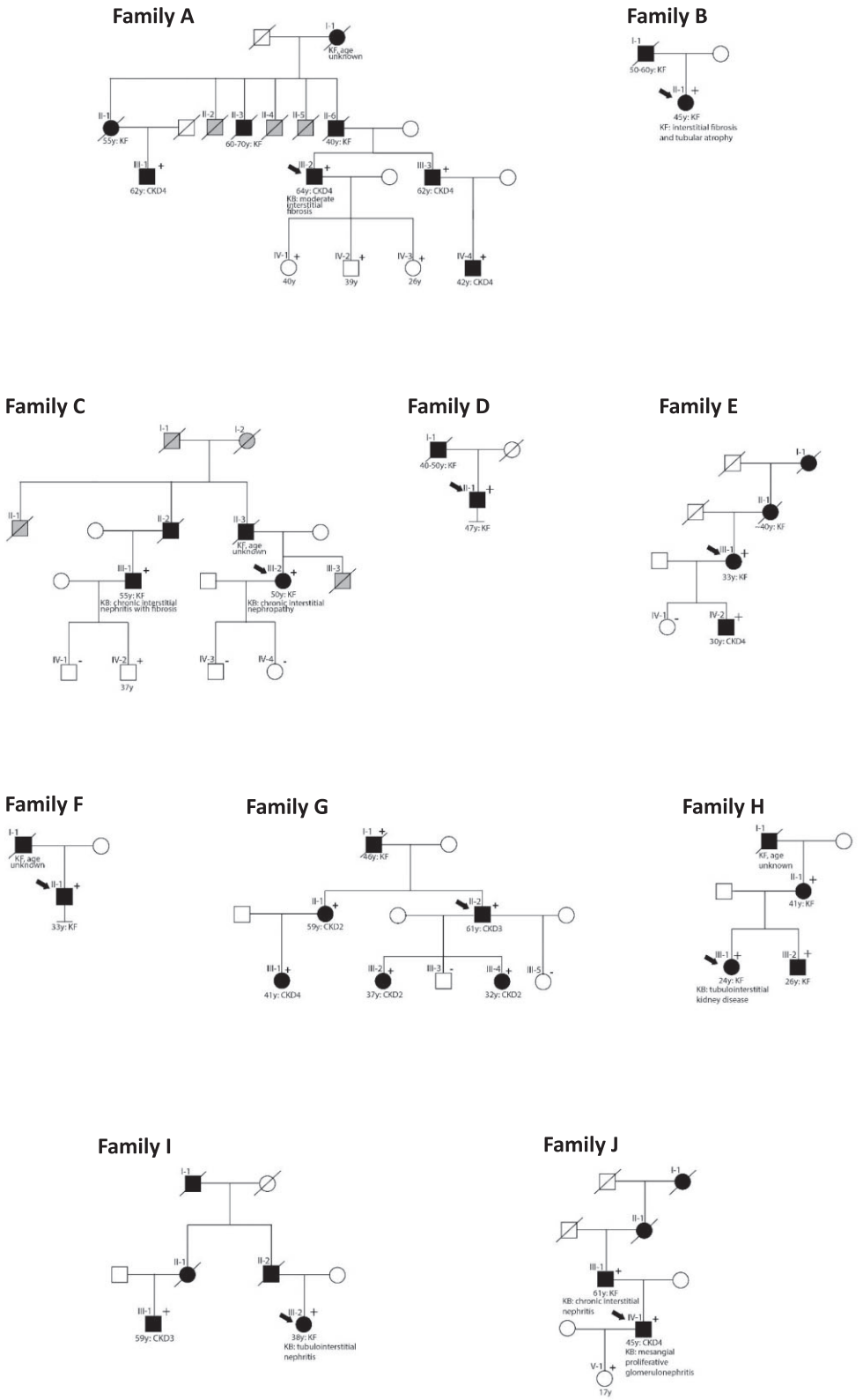


Figure 3: Pedigrees of Danish ADTKD-*MUC1* families. Families A–G were identified from the uKF cohort, while families H–J were identified by clinical genetic screening. Black fill: individual with kidney disease. The genetic analysis of I-1 in Family G was performed on FFPE tissue. White fill: individual without kidney disease. Grey fill: unknown status. Arrow denotes proband. '+' denotes genetic screening with detection of patogenic *MUC1* variant. '–' denotes genetic screening without detection of pathogenic *MUC1* variant. KB, kidney biopsy; y, years.

Table 2: Clinical characteristics of probands diagnosed with ADTKD-*MUC1*.

Family	Sex	Age of KF (years)	Clinical history	Family history[b]	Kidney biopsy	*MUC1* variant
A[a]	M	n.a.	Diagnosed with CKD at age 57 from suspected DM2 or hypertension	uCKD over three generations	IF and unspecific hypertensive changes	8C[c]
B	F	45	Diagnosed with CKD at age 37 from suspected hypertension	uCKD over two generations. Father had KF in his fifties	IF, TA and arteriosclerosis	8C[c]
C	F	50	Diagnosed with CKD, hypertension and hematuria with proteinuria at age 40	uCKD over two generations	IF and diagnosed with chronic interstitial nephritis at age 49	8C[c]
D	M	47	Diagnosed with CKD and hypertension at age 43	uCKD over two generations. Father with KF in his forties	Not performed	8C[c]
E	F	33	Diagnosed with CKD, hypertension, and proteinuria during third pregnancy at age 33	uCKD over four generations. Mother with KF in her forties	Not performed	8C[c]
F	M	33	Diagnosed with uCKD and bilateral nephropathic kidneys at age 31	Father with KF, age unknown	Not performed	16ins[d]
G	M		Diagnosed with CKD and hypertension at age 54. CKD3 at age 61. Hearing impairment	uCKD over three generations	Not performed	41C[d]
H	F	24	Diagnosed with uCKD and anaemia at age 18	uCKD over three generations	Tubulointerstitial kidney disease	8C[c]
I	F	38	uCKD with slight proteinuria discovered during pregnancy at age 28	uCKD over three generations	Chronic interstitial fibrosis at age 29	8C[c]
J	M		Diagnosed with CKD at age 38 with suspected lupus nephritis. CKD4 at age 49. Arthritis urica	uCKD over four generations	Mesangial proliferative glomerulonephritis	8C[c]

[a]A detailed description of Family A was previously published in Granhøj *et al.* [39].
[b]Pedigrees are provided in Figure 3.
[c]Identified by SNaPshot minisequencing.
[d]Identified by VNtyper genotyping.
DM2; diabetes mellitus type 2; F, female; FH, family history; IF, interstitial fibrosis; KB, kidney biopsy; M, male; na, not applicable; TA, tubular atrophy; uCKD, chronic kidney disease of undetermined aetiology.

was reported in 33% and 20%, respectively, with 15% of the patients meeting KDIGO ADTKD criteria.

Prevalence of ADTKD-*MUC1* in uKF cohort

The SNaPshot analyses were abnormal in 5 out of 123 patients (4%) (Fig. 2B). All patients with abnormal SNaPshot analyses had a family history of CKD consistent with autosomal dominant inheritance. Notably, the 8C duplication was only identified in patients who met KDIGO ADTKD criteria, reaching a diagnostic yield of 26% (5/19) in this subgroup.

We hypothesized that some patients may carry other frameshifting variants in *MUC1*-VNTR undetectable by the SNaPshot analysis, as this only identifies the common pathogenic cytosine duplication. Therefore, we screened the remaining 118 patients using VNtyper genotyping of *MUC1*-VNTR, along with the five patients with abnormal SNaPshot analyses for validation. VNtyper genotyping effectively re-identified all five patients with ADTKD-*MUC1* determined by SNaPshot analysis. Moreover, we identified a novel C-insertion at position 41 and a 16-base pair insertion in two additional families that also met KDIGO ADTKD criteria (Supplementary data, File 2). The remaining 116 analyses were normal.

The novel C-insertion was shown to segregate in blood samples from additional affected families members and in a 30-year-old formalin-fixed, paraffin embedded (FFPE) tissue sample from the deceased father with KF, thus supporting the pathogenicity of the variant (Fig. 3, Family G). Of note, the C-insertion at position 41 is simultaneously called in both the M and the J motif of I-1, and only in the M motifs of the remaining family members, suggesting the called motifs can be ambiguous. The 16-base pair insertion in Family F was also called in two motifs, but no additional family members were available for segregation analysis. However, the same 16-base pair sequence has previously been reported as a pathogenic duplication in *MUC1*-VNTR [22]. It is possible that these are the same variants, as the

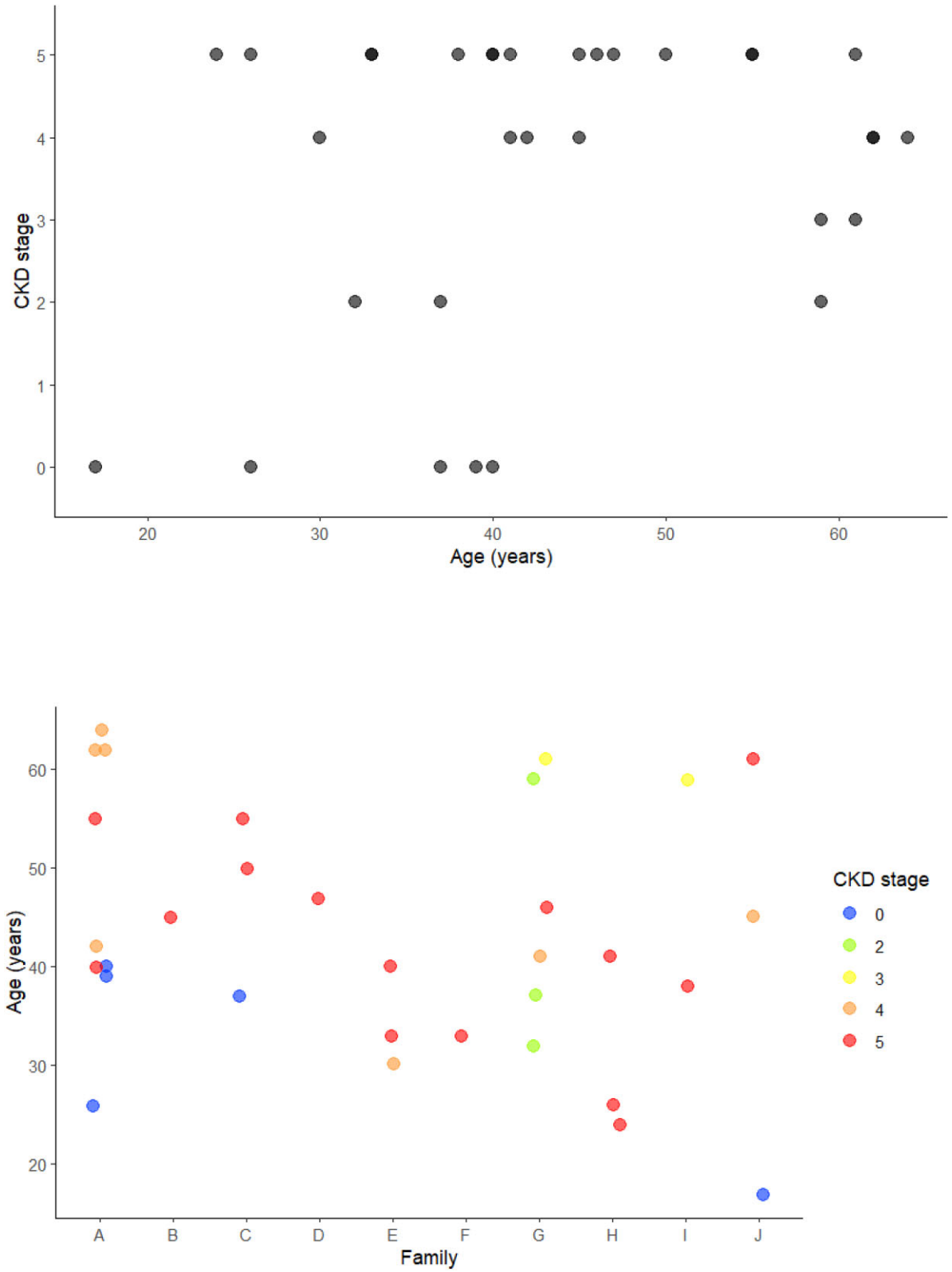


Figure 4: CKD stage versus age in Danish ADTKD-*MUC1* families. (**A**) Age versus CKD stage in carriers of pathogenic *MUC1* variants. (**B**) Distribution of age and CKD stages in Danish families with pathogenic *MUC1* variants. CKD stage based on eGFR. CKD0 denotes individuals without CKD. CKD5 comprises eGFR <15 mL/min or requirement of renal replacement therapy.

distinction between insertion versus duplication depends on the 5′-flanking sequence of the 16-base variant within the true motif. Overall, the prevalence of ADTKD-*MUC1* was 7/123 (6%) in this cohort with uKF with all identified patients meeting KDIGO ADTKD criteria. As expected, the proportion of patients with a family history of KF and the proportion of patients full filling the ADTKD criteria were significantly higher in patients with ADTKD-*MUC1* compared with patients with normal *MUC1* analysis (Supplementary data, Table S3).

Characterization of Danish families with ADTKD-*MUC1*

We collected clinical data from 10 families with ADTKD-*MUC1*; seven from the uKF cohort (A–G) and three families identified through clinical genetic screening (H–J). The pedigrees of the families are provided in Fig. 3, and the clinical characteristics of the probands are summarized in Table 2.

We observed considerable variability in both the age of diagnosis and the age of KF. While the kidney phenotypes of the probands were generally unremarkable, consistent features were signs of advanced chronic kidney disease, such as hypertension and chronic histopathological changes, along with a family history indicating autosomal dominant inheritance.

Although the ages at which *MUC1* carriers reached CKD4 and CKD5 varied widely, none of the 32 *MUC1* carriers was above the age of 40 years without CKD (Fig. 4A). The median age of KF was 41 years (interquartile range 35.5–48.5, $n = 15$). Grouping by families (Fig. 4B) revealed substantial variation in CKD stage distribution relative to age both across and within ADTKD-*MUC1* families. For example, in Family G, one individual reached KF at age 46 years, while others remained at CKD2 or 3 into their sixties.

DICUSSION

The overall prevalence of ADTKD-*MUC1* was 6% in our cohort comprising 123 patients with uKF ≤50 years, while the prevalence was 37% in patients meeting KIDGO ADTKD criteria (7/19). The prevalence of ADTKD-*MUC1* in larger cohorts with clinical ADTKD ranges between 10% and 60%, similar to our findings (Supplementary data, Table S2). However, studies that systematically investigated *MUC1* in unselective cohorts of patients with kidney disease reported much lower prevalences. No cases of ADTKD-*MUC1* were identified among 271 patients from the German CKD cohort with unspecific primary diagnoses screened with SNaPshot and code-adVNTR analyses [29]. Likewise, ADTKD-*MUC1* was identified in only 1% of the unselective 'Renome cohort' comprising 2910 patients with renal symptoms using VNtyper for *MUC1* genotyping [30], and in 0.6% of 818 Spanish patients with uKF using probe-capture based gene panel and optimized Sanger sequencing [31]. Recently, the prevalence of ADTKD-*MUC1* was 0.7% in a French cohort of 4337 patients with CKD of unknown cause utilizing SharkVNtyper pipeline on exome sequencing data [35]. Thus, the prevalence of 6% in our uKF cohort is remarkable and may be explained by either enrichment due to the selection based on KF rather than CKD or by a founder effect, recognizing that Denmark is a geographically small country. Additionally, patients from ADTKD families could also be more inclined to respond to study invitation due to the strong family history of CKD, causing a selection bias and overestimation of the ADTKD-*MUC1* prevalence.

The genetically confirmed ADTKD-*MUC1* families all had a family history of kidney failure and fulfilled KDIGO ADTKD criteria. The median age of KF was 41 years with highly variable age of onset and considerable inter- and intrafamilial variability with the youngest reaching KF at age 24 years. Despite the age-specific inclusion criteria in the uKF cohort, these findings align with previous results from US/Belgo-Swiss [15] and Spanish [21] cohorts of confirmed *MUC1*-ADTKD patients, highlighting that ADTKD-*MUC1* should also be considered in younger patients with CKD, despite being typically described as a slowly progressive form of CKD.

The difficulty of genotyping *MUC1*-VNTR is reflected by the variety of screening methods employed in this and previous studies. This also produces an inconsistent use of nomenclature, as similar variants are reported differently dependent on the methodology. Long-read sequencing allows total reconstruction of the *MUC1*-VNTR and precise localization of the identified variants [36]. However, the analysis is laborious and costly compared with bioinformatics approaches using NGS data like code-adVNTR [37], VNtyper [30], SharkVNtyper [35] or Mutation Counter [38]. In this study, VNtyper effectively identifies frameshift variants in *MUC1*-VNTR and provides an attractive option readily implemented into the pipelines of most genetic laboratories. Moreover, the VNtyper even allowed identification of the novel C-insertion in DNA extracted from a 30-year-old FFPE tissue sample, showing potential for segregation analysis in deceased relatives.

The strengths of this study includes the systematic screening for ADTKD-*MUC1* in a cohort with uKF ≤50 years not preselected using ADTKD criteria and the employment of two different approaches to genotype *MUC1*-VNTR. The main limitations of our study are a relative small sample size from a single population and the lack of long-read sequencing data, making it impossible to pinpoint the exact VNTR location of the identified variants.

To conclude, while whole-exome sequencing has emerged as an effective diagnostic approach in patients with CKD [6, 9, 11], it is noteworthy that frameshift variants in *MUC1*-VNTR are usually missed with this method and the contribution of ADTKD-*MUC1* may therefore be underestimated. Indeed, the prevalence of ADTKD-*MUC1* was 6% in this cohort with uKF ≤50 years, suggesting that *MUC1* genotyping should be pursued in patients with a strong family history of CKD, especially if initial genetic screening is negative. VNtyper effectively detected all identified frameshifting *MUC1*-VNTR variants, demonstrating promising potential for making *MUC1* screening more accessible in the clinical settings.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

J.G., H.B., D.L.L. and M.R. conceived and designed the study. J.G., K.V.P., B.G.T., T.K., M.D. and M.R. recruited patients and acquired data. J.G., M.S., A.H.P., M.M.A. and M.R. conducted genetic analyses and analysed genetic data. J.G. drafted the article with critical input from co-authors. All authors participated in analysis and interpretation of the data and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Connaughton DM, Hildebrandt F. Personalized medicine in chronic kidney disease by detection of monogenic mutations. *Nephrol Dial Transplant* 2020;**35**:390–7. https://doi.org/10.1093/ndt/gfz028
2. Carriazo S, Vanessa Perez-Gomez M, Ortiz A. Hypertensive nephropathy: a major roadblock hindering the advance of precision nephrology. *Clin Kidney J* 2020;**13**:504–9. https://doi.org/10.1093/ckj/sfaa162
3. Dahl NK, Bloom MS, Chebib FT *et al*. The clinical utility of genetic testing in the diagnosis and management of adults with chronic kidney disease. *J Am Soc Nephrol* 2023;**34**:2039–50. https://doi.org/10.1681/ASN.0000000000000249
4. Lata S, Marasa M, Li Y *et al*. Whole-exome sequencing in adults with chronic kidney disease: a pilot study. *Ann Intern Med* 2018;**168**:100–9. https://doi.org/10.7326/M17-1319
5. Connaughton DM, Kennedy C, Shril S *et al*. Monogenic causes of chronic kidney disease in adults. *Kidney Int* 2019;**95**:914–28. https://doi.org/10.1016/j.kint.2018.10.031
6. Groopman EE, Marasa M, Cameron-Christie S *et al*. Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med* 2019;**380**:142–51. https://doi.org/10.1056/NEJMoa1806891
7. Ottlewski I, Munch J, Wagner T *et al*. Value of renal gene panel diagnostics in adults waiting for kidney transplantation due to undetermined end-stage renal disease. *Kidney Int* 2019;**96**:222–30. https://doi.org/10.1016/j.kint.2019.01.038
8. Schrezenmeier E, Kremerskothen E, Halleck F *et al*. The underestimated burden of monogenic kidney disease in adults waitlisted for kidney transplantation. *Genet Med* 2021;**23**:1219–24. https://doi.org/10.1038/s41436-021-01127-8
9. Doreille A, Lombardi Y, Dancer M *et al*. Exome-first strategy in adult patients with CKD: a cohort study. *Kidney Int Rep* 2023;**8**:596–605. https://doi.org/10.1016/j.ekir.2022.12.007
10. Robert T, Raymond L, Dancer M *et al*. Beyond the kidney biopsy: genomic approach to undetermined kidney diseases. *Clin Kidney J* 2024;**17**:1–12.
11. Becherucci F, Landini S, Palazzo V *et al*. A clinical workflow for cost-saving high-rate diagnosis of genetic kidney diseases. *J Am Soc Nephrol* 2023;**34**:706–20. https://doi.org/10.1681/ASN.0000000000000076
12. Kirby A, Gnirke A, Jaffe DB *et al*. Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in MUC1 missed by massively parallel sequencing. *Nat Genet* 2013;**45**:299–303. https://doi.org/10.1038/ng.2543
13. Ekici AB, Hackenbeck T, Morinière V *et al*. Renal fibrosis is the common feature of autosomal dominant tubulointerstitial kidney diseases caused by mutations in mucin 1 or uromodulin. *Kidney Int* 2014;**86**:589–99. https://doi.org/10.1038/ki.2014.72
14. Eckardt KU, Alper SL, Antignac C *et al*. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—a KDIGO consensus report. *Kidney Int* 2015;**88**:676–83. https://doi.org/10.1038/ki.2015.28
15. Olinger E, Hofmann P, Kidd K *et al*. Clinical and genetic spectra of autosomal dominant tubulointerstitial kidney disease due to mutations in UMOD and MUC1. *Kidney Int* 2020;**98**:717–31. https://doi.org/10.1016/j.kint.2020.04.038
16. Dvela-Levitt M, Kost-Alimova M, Emani M *et al*. Small molecule targets TMED9 and promotes lysosomal degradation to reverse proteinopathy. *Cell* 2019;**178**:521–35.e23. https://doi.org/10.1016/j.cell.2019.07.002
17. Yamamoto S, Kaimori JY, Yoshimura T *et al*. Analysis of an ADTKD family with a novel frameshift mutation in MUC1 reveals characteristic features of mutant MUC1 protein. *Nephrol Dial Transplant* 2017;**32**:2010–7. https://doi.org/10.1093/ndt/gfx083
18. de Haan A, van Eerde AM, Eijgelsheim M *et al*. Novel MUC1 variant identified by massively parallel sequencing explains interstitial kidney disease in a large Dutch family. *Kidney Int* 2023;**103**:986–9. https://doi.org/10.1016/j.kint.2023.02.021
19. Bleyer AJ, Kmoch S, Antignac C *et al*. Variable clinical presentation of an MUC1 mutation causing medullary cystic kidney disease type 1. *Clin J Am Soc Nephrol* 2014;**9**:527–35. https://doi.org/10.2215/CJN.06380613
20. Musetti C, Babu D, Fusco I *et al*. Testing for the cytosine insertion in the VNTR of the MUC1 gene in a cohort of Italian patients with autosomal dominant tubulointerstitial kidney disease. *J Nephrol* 2016;**29**:451–5. https://doi.org/10.1007/s40620-016-0282-9
21. Ayasreh N, Bullich G, Miquel R *et al*. Autosomal dominant tubulointerstitial kidney disease: clinical presentation of patients with ADTKD-UMOD and ADTKD-MUC1. *Am J Kidney Dis* 2018;**72**:411–8. https://doi.org/10.1053/j.ajkd.2018.03.019
22. Živná M, Kidd K, Přistoupilová A *et al*. Noninvasive immunohistochemical diagnosis and novel MUC1 mutations causing autosomal dominant tubulointerstitial kidney disease.

J Am Soc Nephrol 2018;**29**:2418–31. https://doi.org/10.1681/ASN.2018020180
23. Cormican S, Connaughton DM, Kennedy C *et al*. Autosomal dominant tubulointerstitial kidney disease (ADTKD) in Ireland. *Ren Fail* 2019;**41**:832–41. https://doi.org/10.1080/0886022X.2019.1655452
24. Gong K, Xia M, Wang Y *et al*. Autosomal dominant tubulointerstitial kidney disease genotype and phenotype correlation in a Chinese cohort. *Sci Rep* 2021;**11**:3615. https://doi.org/10.1038/s41598-020-79331-w
25. Okada E, Morisada N, Horinouchi T *et al*. Detecting MUC1 variants in patients clinicopathologically diagnosed with having autosomal dominant tubulointerstitial kidney disease. *Kidney Int Rep* 2022;**7**:857–66. https://doi.org/10.1016/j.ekir.2021.12.037
26. Wopperer FJ, Knaup KX, Stanzick KJ *et al*. Diverse molecular causes of unsolved autosomal dominant tubulointerstitial kidney diseases. *Kidney Int* 2022;**102**:405–20. https://doi.org/10.1016/j.kint.2022.04.031
27. Leenen E, Erger F, Altmüller J *et al*. Alport syndrome and autosomal dominant tubulointerstitial kidney disease frequently underlie end-stage renal disease of unknown origin-a single-center analysis. *Nephrol Dial Transplant* 2022;**37**:1895–905. https://doi.org/10.1093/ndt/gfac163
28. Domingo-Gallego A, Pybus M, Bullich G *et al*. Clinical utility of genetic testing in early-onset kidney disease: seven genes are the main players. *Nephrol Dial Transplant* 2022;**37**:687–96. https://doi.org/10.1093/ndt/gfab019
29. Popp B, Ekici AB, Knaup KX *et al*. Prevalence of hereditary tubulointerstitial kidney diseases in the German Chronic Kidney Disease study. *Eur J Hum Genet* 2022;**30**:1413–22. https://doi.org/10.1038/s41431-022-01177-9
30. Saei H, Morinière V, Heidet L *et al*. VNtyper enables accurate alignment-free genotyping of MUC1 coding VNTR using short-read sequencing data in autosomal dominant tubulointerstitial kidney disease. *iScience* 2023;**26**:107171. https://doi.org/10.1016/j.isci.2023.107171
31. Blasco M, Quiroga B, Garcia-Aznar JM *et al*. Genetic characterization of kidney failure of unknown etiology in Spain: findings from the GENSEN study. *Am J Kidney Dis* 2024;**6**:719–30. https://doi.org/10.1053/j.ajkd.2024.04.021
32. Granhøj J, Pedersen KV, Aagaard MM *et al*. The role of genomic disorders in chronic kidney failure of undetermined aetiology ≤50 years. *Clin Kidney J* 2024;**17**:sfae166. https://doi.org/10.1093/ckj/sfae166
33. Lildballe DL, Frederiksen AL, Schonewolf-Greulich B *et al*. National clinical Genetic Networks—GENets—establishment of expert collaborations in Denmark. *Eur J Med Genet* 2023;**66**:104872. https://doi.org/10.1016/j.ejmg.2023.104872
34. Levey AS, Eckardt KU, Dorman NM *et al*. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int* 2020;**97**:1117–29. https://doi.org/10.1016/j.kint.2020.02.010
35. Bensouna I, Robert T, Vanhoye X *et al*. Systematic screening of ADTKD-MUC1 27dupC pathogenic variant through exome sequencing. *J Am Soc Nephrol* 2024. https://doi.org/10.1681/ASN.0000000503
36. Wenzel A, Altmueller J, Ekici AB *et al*. Single molecule real time sequencing in ADTKD-MUC1 allows complete assembly of the VNTR and exact positioning of causative mutations. *Sci Rep* 2018;**8**:4170. https://doi.org/10.1038/s41598-018-22428-0
37. Park J, Bakhtiari M, Popp B *et al*. Detecting tandem repeat variants in coding regions using code-adVNTR. *iScience* 2022;**25**:104785. https://doi.org/10.1016/j.isci.2022.104785
38. Fages V, Bourre F, Larrue R *et al*. Description of a new simple and cost-effective molecular testing that could simplify MUC1 variant detection. *Kidney Int Rep* 2024;**9**:1451–7. https://doi.org/10.1016/j.ekir.2024.01.058
39. Granhøj J, Tougaard B, Lildballe DL *et al*. Family history is important to identify patients with monogenic causes of adult-onset chronic kidney disease. *Nephron* 2022;**146**:49–57. https://doi.org/10.1159/000518175

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