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A novel disease-causing mutation in the Renin gene in a Tunisian family with autosomal dominant tubulointerstitial kidney disease

Mayssa Abdelwahed[a,*], Yosr Chaabouni[b], Laurence Michel-Calemard[c], Khansa Chaabouni[d], Yves Morel[c], Jamil Hachicha[b], Fatma Ayedi Makni[d], Hassen Kamoun[e], Leila Ammar-Keskes[a], Neila Belghith[a,e]

[a] Laboratory of Human Molecular Genetics, Faculty of Medicine, Magida Boulila Street, 3029 Sfax, University of Sfax, Tunisia
[b] Renal Pathology Unity, UR12ES14, Nephrology Department Hedi Chaker Hospital, Sfax, Tunisia
[c] Department of Molecular Endocrinology and Rare Diseases, Center for Biology and Pathology, East Lyon, France
[d] Laboratory of Biochemistry, Habib. Bourguiba Hospital, Sfax, Tunisia
[e] Medical Genetics Department of Hedi Chaker Hospital, Route El Ain, Sfax 3089, Tunisia

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ABSTRACT

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a rare group of disease that affect the tubules of the kidney. There are 4 known subtypes of ADTKD classified based on causative genes and clinical features. In our study, we aimed to identify the causative subtypes of ADTKD in a Tunisian ADTKD family (3 affected members), in whom standard nephrological diagnosis did not provide clear subtype of ADTKD, until genetic testing was performed. Sanger sequencing was performed for UMOD, HNF1β and REN genes. Mutational analysis allowed us to detect a heterozygous mutation in the REN gene: c.1172C > G, (p.T391R) in exon 10. In silico analyses predicted that the novel likely pathogenic mutation affect protein stability and 3D structure. Our study highlights the importance of establishing a genetic diagnosis to identify the subtype of ADTKD for better patient care. To the best of our knowledge, we report here a first Tunisian ADTKD-REN family.

1. Introduction

Autosomal Dominant Tubulointerstitial Disease (ADTKD) is also known as Cystic Medullary Renal Disease, or Familial Hyperuricemic Juvenile Nephropathy (FJHN). It is a group of chronic tubulointerstitial nephropathy with distinct clinical features (Bleyer et al., 2017).

ADTKD is a rare group of disease characterized by a progressive tubulointerstitial fibrosis, a development of end-stage renal failure (ESRD) (Eckardt et al., 2015), a positive family history and a poor urinary sediment with no proteinuria and no hematuria. In addition, a normal or small kidneys, characterize it (Bollee et al., 2011; Faguer et al., 2011; Bleyer et al., 2014). Cysts and hyperuricemia with early gout are inconsistently found (Bleyer et al., 2014).

Causative genes including UMOD, REN, MUC1 and HNF1β have distinguished four clinical forms of ADTKD: ADTKD-UMOD, ADTKD-REN, ADTKD-MUC1 and ADTKD-HNF1β, respectively (Table 1).

The UMOD gene (OMIM, 191845, NM_003361) is located on the locus 16p12.3 and contains 12 exons. This gene encodes a protein called "Uromodulin", or "Tamm-Horsfall protein" (Middleton-Price et al., 1987; Hart et al., 2002; Dahan et al., 2003; Kudo et al., 2004) (Table 1).

The HNF1β gene or also called the TCF2 gene (OMIM, 189907; NM_000458) is located on chromosome 17q22 (Gudmundsson et al., 2007), it contains 9 exons and encodes a transcription factor 2 (TCF2) or also called hepatocyte nuclear factor 1 beta (Hepatocyte Nuclear Factor-1 B, HNF1β) (Horikawa et al., 1997; Levitin et al., 2005). Hepatocyte nuclear factor (HNF1β) mutations were initially described in patients with Renal Cysts and Diabetes syndrome (RCAD) (Bingham et al., 2001; Kolatsi-Joannou et al., 2001) (Table 1).

The MUC1 gene (OMIM, 158340; NM_001018016) is located on chromosome 1q22 (Scolari et al., 2004). It contains 7 exons and encodes a protein called "Mucin-1" (Gendler et al., 1990; Bach et al., 1991). The MUC1 mutation was found to be a single cytosine insertion in a single copy of the GC-rich variable number of tandem repeats (VNTRs) leading to an altered protein (MUC1-fs) (Eckardt et al., 2015) (Table 1).

The REN or "Renin" gene (OMIM, 179820, NM_000537) is located on chromosome 1 (1q32.1) (Kang and Johnson, 2015). It contains 10 exons and encodes a protein called "Renin". Mutations in the REN gene have been identified as a cause of several renal diseases e.g. Familial

* Corresponding author.
E-mail address: abdelwahed.mayssa@yahoo.fr (M. Abdelwahed).

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Table 1
Genetic classification of the major causes of autosomal dominant tubulo-interstitial kidney diseases and their related disorders.

	ADTKD-UMOD	ADTKD-REN	ADTKD-MUC1	ADTKD-HNF1β/TCF2
Urinary Sediment	Bland (Bollee et al., 2011).	Bland	Bland	Bland
Gout	Occur frequently in childhood	Occur frequently in childhood	Occurs in advanced CKD	May occur in childhood
Clinical Manifestations	*Hypouricosuric (Bollee et al., 2011). *Hyperuricemia (Bollee et al., 2011). *Hypertension (Eckardt et al., 2015). *Normally or smaller kidney size (Bollée et al., 2009). *Occasionally observed cysts (Bollée et al., 2009).	*Hyperuricemia (Kmoch et al., 2015); *Normally or smaller kidney size (Kmoch et al., 2015).	*Hypertension (Stavrou et al., 2002).	*Hyperuricemia (Bingham et al., 2003); *Normally or smaller kidney size.
Other Symptoms	None	*Anemia; *Mild hyperkalemia; *Mild hypotension; *Acute kidney injury.	*Anemia (Stavrou et al., 2002).	*Renal malformations: familial glomerulocystic, cystic renal dysplasia, solitary kidney, oligomega-nephronia (Lindner et al., 1999, Bingham et al., 2000; Bingham et al., 2002). *Genital malformations: epididymal cyst, asthenospermia, bicornate uterus, rudimentary uterus (Bingham et al., 2002). *Diabetes type MODY 5 (Bollée et al., 2009). *Liver dysfunction (Bollée et al., 2009).
Age of ESRD	47 (19 to > 75)	50 (30 to > 60)	43 (17 to > 75)	Unknown
Gene	UMOD	REN	MUC1	HNF1β/TCF2
Protein	Uromodulin	Renin	Mucin-1	TCF2: a transcription factor 2 HNF1β : hepatocyte nuclear factor 1 beta
Physiopathology	*Decreased normal uromodulin production (Dahan et al., 2003); *Intracellular accumulation of mutant uromodulin in the endoplasmic reticulum of TAL cells (Dahan et al., 2003); *Intracellular trafficking defect of the co-transporter Na/K/2Cl at the apical surface of the ascending limb of Henle; *Reduced sodium reabsorption; *Increased acid uric reabsorption in the proximal tubule leads to hyperuricemia (Bleyer et al., 2017).	*Production of low levels of a normal renin in juxtaglomerular cells (Zivná et al., 2009); *Intracellular deposition of mutated renin (Zivná et al., 2009).	*Intracellular accumulation of mutated mucin-1 leads for tubulointerstitial fibrosis (Eckardt et al., 2015)	Unknown (Bingham et al., 2003).

hyperproreninemia (Villard et al., 1994) and Renal Tubular Dysgenesis (RTD) (Gribouval et al., 2005) (Table 1).

According to ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/), dbSNP database (https://www.ncbi.nlm.nih.gov/snp/) and HGMD (human gene mutation database) (http://archive.uwcm.ac.uk/uwcm/mg/docs/hohoho.html), about 26 mutations have been reported in UMOD, HNF1β, REN and MUC1 genes in ADTKD patients, including missense, non-sens, deletions and insertions mutations. These mutations were only detected in 50–60% of cases. However, the detection of non-pathogenic mutations in ˜ 40% of the ADTKD patients can be explained by the involvement of other genes such as Translocon Alpha 1 Subunit (SEC61A1) (Bolar et al., 2016).

The aim of this paper is to present a Tunisian ADTKD family with three affected members, in which initial nephrological diagnosis did not provide clear evidence to identify the causative subtype of ADTKD, until genetic testing was performed. Mutational analysis of UMOD, HNF1β and REN genes allows us to identify a heterozygous mutation in the REN gene (c.1172C > G, p.T391R). In addition, in silico approaches predicted that the novel likely pathogenic mutation have a negative effect on protein stability and 3D structure. Moreover, plasma Renin assay revealed that this novel mutation result in the production of a low level of a normal renin.

2. Patients and methods

2.1. The subject case

A family with three affected members of the south of Tunisia were collected from the nephrology department of Hedi Chaker Hospital of Sfax.

2.1.1. Patient 1 (P1)

The proband was 61 years old man. His was the fourth child of a non-consanguineous family (Fig. 1A). A family history revealed that his died father had renal failure, hyperuricemia and gout. This patient was diagnosed with ADTKD at the age of 44 years old when he had a severe gout attack. The serum uric acid and creatinine levels were elevated at 595 µmol/L and at 23,187 µmol/L, respectively. The hemoglobin concentration was normal at 123 g/100 ml. The biochemical finding was normal, with no proteinuria and no hematuria. Renal ultrasound showed a small size kidneys (RD: 9 cm; RG: 7,5 cm) without any cysts.

2.1.2. Patient 2 (P2)

The proband's sister was 63 years old women. She was the third child of a nonconsanguineous family (Fig. 1A). She was diagnosed with ADTKD at the age of 46 years old when she had a severe gout attack. The serum uric acid level was elevated at 500 µmol/L. The serum creatinine was elevated at 274 µmol/L. Hemoglobin concentration was less than 11 g/100 ml of blood. Therefore, she was considered as anemic. Biochemical finding was normal, with no proteinuria and no hematuria. Renal ultrasonography revealed a small size kidneys (RD: 9 cm; RG: 7,5 cm) without any cysts. She reaches ESRD at the age of 58 years old.

2.1.3. Patient 3 (P3)

The proband's son was 31 years old man. His was the second child of a non-consanguineous family (Fig. 1A). ADTKD was diagnosed based on family history of ADTKD. Elevated serum uric acid (541 µmol/L) and creatinine levels (127 µmol/L) were seen. The hemoglobin concentration was normal at 12,3 g/100 ml. Biochemical finding was normal, with no proteinuria and no hematuria. Renal ultrasonography revealed a normal size kidneys (RD: 8.7 cm, RG: 10.2 cm) with regular contours and without any cysts. Blood samples from the three patients were obtained for chemical and genetic analysis. The genetic study was performed after informed consent of patients.

2.2. Controls

Fifty Tunisian healthy individuals from the same ethno cultural group were included in this study as controls. Twenty-four female and 26 male composed the control group and with a mean age of 40.5 ± 17 years.

This group include individuals with normal weight, BMI of 18.5–24.9 kg m − 2, with a normal kidney function tests ((Normal serum Uric acid level (less than360 µmol/l), normal serum creatinine level (less than 100 µmol/l), normal serum potassium level (5 mmol/L) and with no proteinuria and no hematuria)). We included individuals with normal blood pressure at 140/90 mmHg) and with normal hemoglobin concentration level at 123 g/100 ml.

In all individuals, ultrasonography measurements showed normal size kidneys with regular contours and without any cysts. We excluded all individuals who had a personal or family history of ADTKD and a history of genital malformation, liver dysfunction, diabetes, or other serious health complications. All controls signed informed consent.

2.3. Mutational analysis

DNA was extracted from whole blood samples on family members and from 50 healthy individuals, using phenol chloroform standard procedures (Lewin, Stewart-Haynes, 1992).

2.3.1. UMOD, HNF1β and REN genes sequencing

The UMOD, HNF1β and REN genes were PCR amplified from genomic DNA of patient P1 using designed primers. The presence of a novel REN gene mutation was checked in P2, P3 and in controls. All Gene specific primers were designed using current genomic information available from the national Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/) and using primers 3 Program (http://frodo.wi.mit.edu/) (Suppl.1).

2.4. In silico analyses

A blast homology search was performed using the "BLAST" program available at the National Center for Biotechnology Information Website to compare individual nucleotide sequences with wild-type sequences (http://blast.ncbi.nlm.nih.gov/Blast). The novelty of the variant was checked using the dbSNP databases (https://www.ncbi.nlm.nih.gov/snp).

2.4.1. The pathogenicity prediction of variation

A novel variant were analyzed by web-based software programs such as: SIFT (http://blocks.fhcrc.org/sift/SIFT.html), Mutation Taster (http://www.mutationtaster.org/), Align GVGD (http://agvgd.iarc.fr/) and I-Mutant Disease (http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi).

2.4.2. In silico analysis of the effect of missense variants on Protein stability

To evaluate the eventual effect of single point mutation on protein stability, the I-Mutant suite server (http://folding.biofold.org/cgi-bin/i-mutant2.0.cgi) was used.

2.4.3. Conservation analysis of amino acids

Sequence conservation between species was examined using the MAFFT server (http://mafft.cbrc.jp/alignment/server/index.html). Sequences from different species were obtained from NCBI (http://www.ncbi.nlm.nih.gov/).

2.4.4. Prediction of the pathogenic effect of variants on 3D protein structure

To investigate the eventual effect of the missense variation on 3D renin protein structure. We used D-JIGSAW (version 2.0) (http://bmm.cancerre&searchuk.org/˜3djigsaw/). This server builds three-dimensional models for proteins based on homologue of known structure.

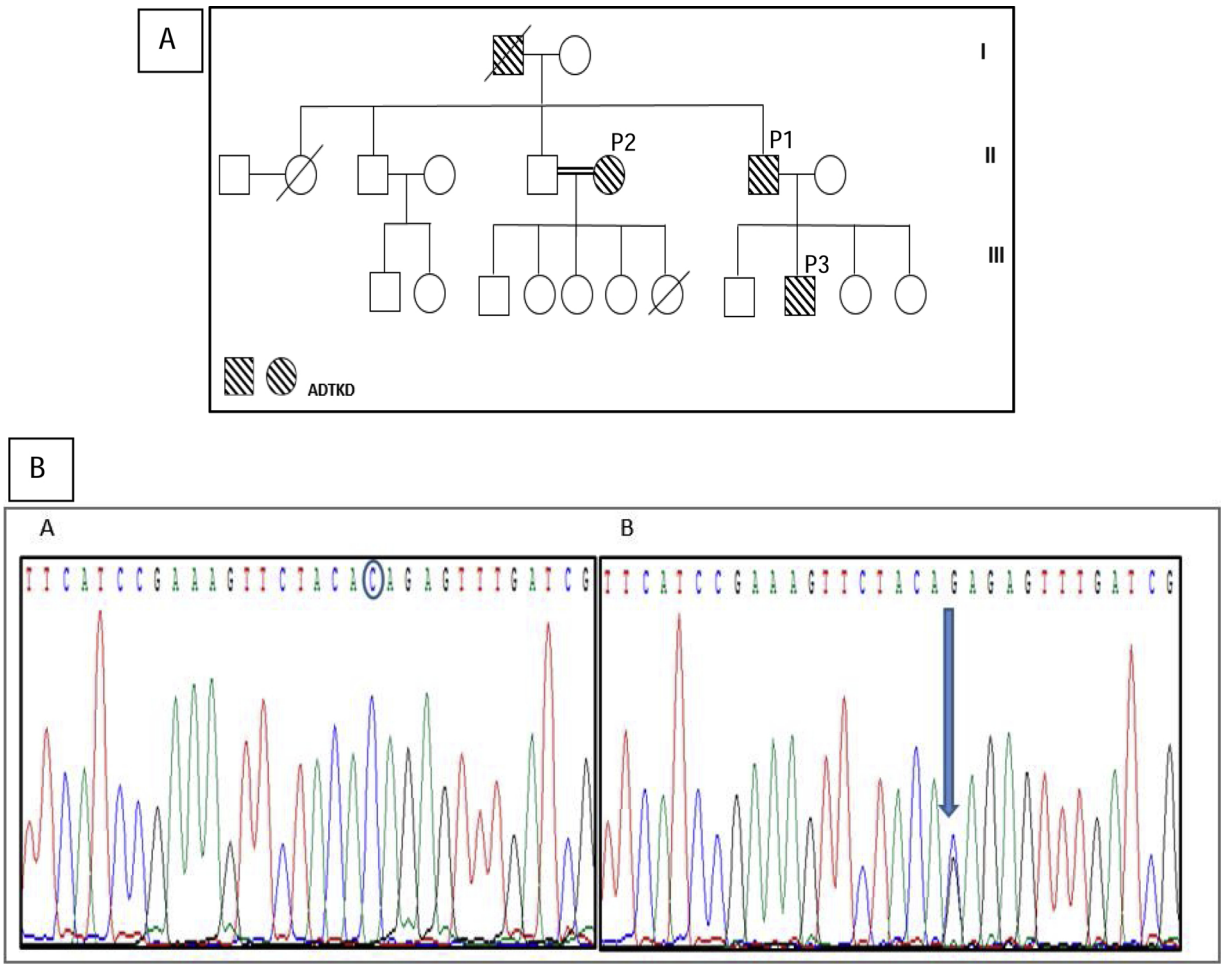

Fig. 1. A. Family tree is shown. Black symbols cross hatching denote clinically affected individuals (P1, P2, and P3). White symbols denote clinically unaffected individuals. B. Sequencing results of *REN* gene from the ADTKD patients revealed a heterozygous state. C.1172C > G (NM_000537.3) mutation in patients. A. the wild type sequence. B. The mutated type sequence.

The PyMol (V2.1) software was used to compare normal and mutated models.

2.5. Plasma renin assay

Plasma renin activity was measured by a sensitive solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principal. In this method, a monoclonal mouse antibody directed towards a unique antigenic site of the human active Renin molecule must be immobilized on a solid surface and then a patient sample that contains a human active Renin molecule will be added. Quantification was carried out by the addition of a monoclonal antiRenin antibody conjugated with horseradish peroxidase, which produce a colorimetric reaction. The intensity of color is proportional to the concentration of active Renin in the patient sample.

3. Results

3.1. Mutational analysis

Based on the literature and on clinical diagnosis of ADTKD, hyperuricemia and history of gout, PCR following by sequencing were performed in patient P1 to search for pathogenic variants in UMOD and HNF1β genes. However, no variants have been detected in both genes.

Based on this findings and to literature, a serum potassium assay was recommended in the three patients. The results showed a mild elevated potassium level in P1, P2 and P3 at 5,8 mmol/L, 5,24 mmol/L and 5,1 mmol/L, respectively. So, we searched for a pathogenic variant in the third candidate gene of ADTKD "REN gene". The results revealed a heterozygous variant c.1172C > G encoding p.T391R in exon 10 (Fig. 1B). This variant was also identified in P2 and P3 suggesting an autosomal dominant inheritance pattern. This variant has not been previously reported, neither in the published literature, nor in dbSNP, ClinVar or HGMD databases. In addition, it was not found in controls. Hence, the c.1172C > G variant was considered as a novel variation.

3.2. Computational analysis

In silico programs based on different approaches revealed that this substitution was scored as pathogenic/likely pathogenic (Table 2). In addition, the novel mutation replaced an amino-acid "Threonine" with an "Arginine" residue at position 391 in C-terminal domain. The analysis of the multiple sequences from different species revealed that the Threonine residue at position 391 in Renin was located in a highly conserved domain. Therefore, it seems to be essential for the renin function (Fig. 2A).

Modeling and superimposition of the normal and mutated 3D model (T391 and R391) were performed to evaluate the structural effect of the p.T391R substitution. The comparison of normal and mutated 3D models showed the loss of the hydrogen bond between amino acids T391 and F389 in the wild type protein, and the establishment of a new hydrogen bond between amino acids R391 and L381 in the mutated protein (Fig. 2B). As a consequence, instability index is decreased with a DDG score of -0.99Kcal/mol which make the protein less stable.

Table 2
Results of bioinformatics prediction.

Variante	Mutation Taster	SIFT		I-mutant Disease	[a]Align-GVGD
	Prediction	Score	Prediction	Prediction	Prediction
c.1172C > G	Pathogene	0.000	Pathogene	Pathogene	Class C65

[a] Align-GVDG: GD > = 65+Tan(10)x(GV^2.5) = > Class C65 < = > most likely, GD > = 55+Tan(10)x(GV^2.0) = > Class C55, GD > = 45+Tan(15)x (GV^1.7) = > Class C45, GD > = 35+Tan(50)x(GV^1.1) = > Class C35, GD > = 25+Tan(55)x(GV^0.95) = > Class C25, GD > = 15+Tan(75)x (GV^0.6) = > Class C15, Else (GD < 15+Tan(75)x(GV^0.6)) = > Class C0 < = > less likely.

3.3. Biochemical findings

Low level of plasma renin activity was detected in patient P2 (The plasma renin activity was < 0, 81 ng/l). Unfortunately, plasma renin activity levels could not be evaluated in P1 or P3 because samples were not available

4. Discussion

ADTKD is a rare disease but the prevalence of this disease remains unknown. However, it is likely that many cases are not detected due to genetic and phenotypic variability, lack of standardized diagnostic criteria, and a variable terminology of this disease (Eckardt et al., 2015).

We present here a first Tunisian ADTKD pedigree with three affected members suffering from hyperuricemia, gout, mild hyperkalemia and with slow progression to end-stage renal failure (ESRD). Our patients present a number of similarities and clinical differences in comparison with other patients described with an ADTKD-REN subtype (Zivná et al., 2009; Bleyer et al., 2010b.). All patients with REN mutation were diagnosed with infantile anemia, hyperuricemia, mild hyperkalemia and chronic kidney disease. This difference highlights the phenotypic variability of ADTKD. This variation suggests that other genetic or environmental factors may affect the progression of the disease. The identification of these factors allows to early prevention and possibly slowing to end-stage renal failure (ESRD).

Mutational analysis revealed a novel heterozygous mutation c.1172C > G in the REN gene encoding p.T391R in exon 10.

Renin, the central regulator of the renin-angiotensin cascade, is an aspartic peptidase, it is synthesized as a pre-pro-polypeptide during its translation into the endoplasmic reticulum. The signal peptide sequence is cleaved upon translocation into the endoplasmic reticulum, to generate the inactive pro-renin. Pro-renin is glycosylated and activated during intracellular transport through the Golgi apparatus and stored in the secretory granules. Then, Renin is secreted by exocytosis through these granules (Hackenthal et al., 1990, Bader and Ganten, 2000).

Mutations in the REN gene result in the absence of renin production have been reported in patients with Renal Tubular Dysgenesis (RTD) (Gribouval et al., 2005). According to the literature, only a few heterozygous mutations in the REN gene have been identified in patients

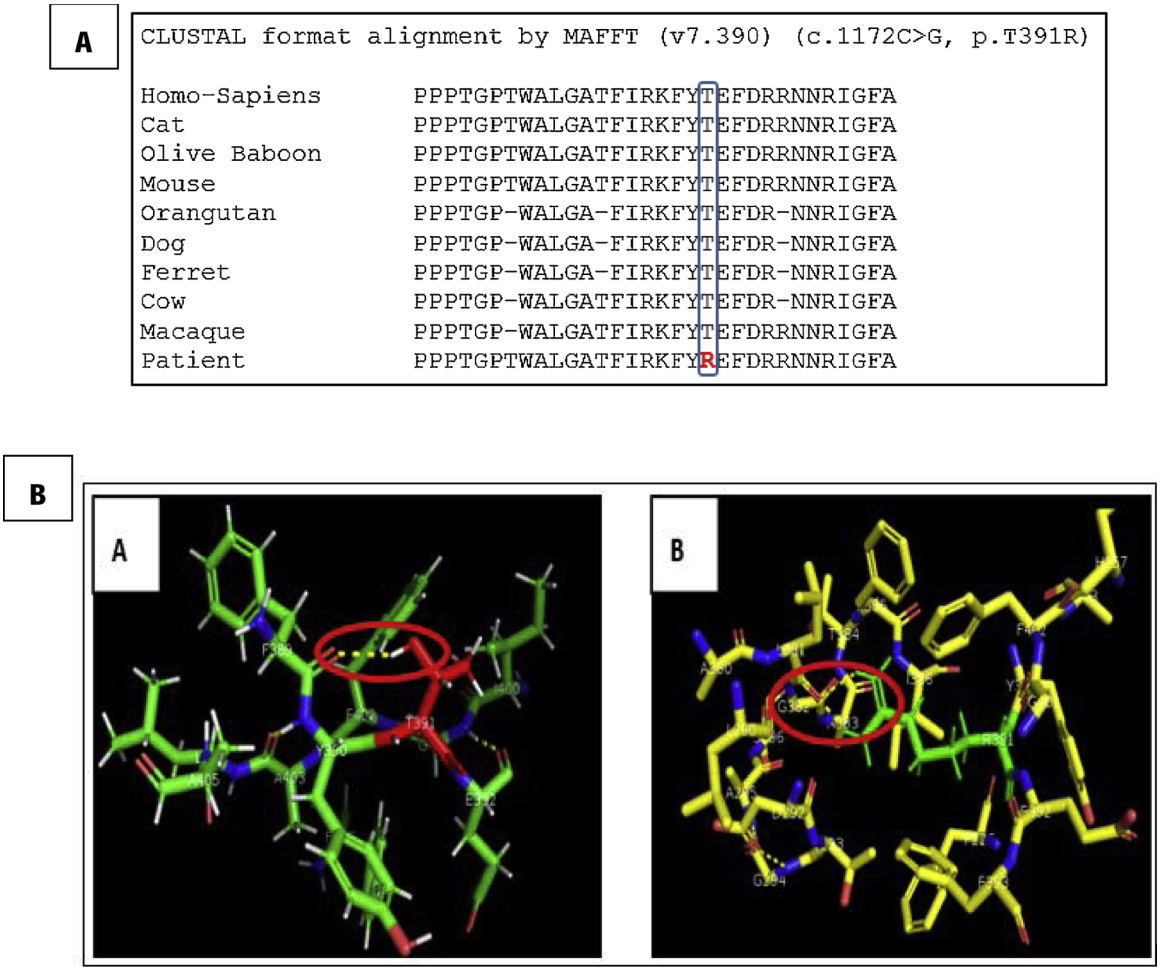

Fig. 2. (A). The phylogenetic results showed the conservation of «Threonine "T"» amino acid between species. (B). Modeling and superimposition of the normal and mutated 3D model (T391 and R391) using PyMol (V2.2) software. A. The wild type protein structure. B The mutated type protein structure.

with ADTKD (Gribouval et al., 2005; Zivná et al., 2009; Bleyer et al., 2010b). These mutations result: first, the production of low levels of a normal renin in juxtaglomerular cells. So, patients have a low renin level, low aldosterone level, and a mild hyperkaliemia (Zivná et al., 2009). Second, the signal peptide sequence of renin is not present in the mutated form which could have effects on the biosynthesis and trafficking of renin because the wild-type signal peptide is implicated in protein stability and plays an important role in the translocation. Third, the pre-pro-renin is produced but accumulated in the intracellular region, leading to accelerate apoptosis, which induce the loss of kidney function (Zivná et al., 2009).

Mutations in ADTKD patients have been mostly reported in the signal peptide of renin (Gribouval et al., 2005; Zivná et al., 2009; Bleyer et al., 2010b). While in our study, the novel mutation has been identified in the C-terminal region. In silico approaches showed that this mutation could affect the 3D structure and the stability of the renin. The C-terminal region is a part of a six-beta sheet, located in the junction between the two domains of renin, which could play a crucial role in renin structure (Villard et al., 1994). In fact, given the modification of the three-dimensional conformation of the protein, the unstable renin could either not be stored in the granules, or rapidly degraded during the secretion process (Villard et al., 1994). We suggest that the lack of renin secretion from the abnormal renin allele is responsible for the low level of renin in the proband's sister.

From a clinical point of view, our results highlight the importance of genetic testing in ADTKD pedigree with hyperuricemia, mild hyperkalemia, and with a slow progressive renal failure. We are also the first team to study the clinical features of ADTKD-REN and to identify a novel mutation in the REN gene in the Tunisian population. We report here the 15th ADTKD-REN pedigree in the world and the first one in Tunisia.

Declaration of Competing Interest

All the authors declared that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biocel.2019.105625.

References

Bach, I., Mattei, M.G., Cereghini, S., Yaniv, et M., 1991. Two members of an HNF1 homeoprotein family are expressed in human liver. Nucleic Acids Res. 19 (13), 3553–3559.

Bader, M., Ganten, D., 2000. Regulation of renin: new evidence from cultured cells and genetically modified mice. J. Mol. Med. 78 (3), 130–139.

Bingham, C., Ellard, S., Allen, L., Bulman, M., Shepherd, M., Frayling, T., Hattersley, A.T., 2000. Abnormal nephron development associated with a frameshift mutation in the transcription factor hepatocyte nuclear factor-1 beta. Kidney Int. 57 (3), 898–907. https://doi.org/10.1046/j.1523-1755.2000.057003898.x.

Bingham, C., Bulman, M.P., Ellard, S., Allen, L.I., Lipkin, G.W., Hoff, W.G., Hattersley, A.T., 2001. Mutations in the hepatocyte nuclear factor-1beta gene are associated with familial hypoplastic glomerulocystic kidney disease. Am. J. Hum. Genet. 68 (1), 219–224. https://doi.org/10.1086/316945.

Bingham, C., Ellard, S., Cole, T.R.P., Jones, K.E., Allen, L.I.S., Goodship, J.A., Hattersley, A.T., 2002. Solitary functioning kidney and diverse genital tract malformations associated with hepatocyte nuclear factor-1beta mutations. Kidney Int. 61 (4), 1243–1251. https://doi.org/10.1046/j.1523-1755.2002.00272.x.

Bingham, C., Ellard, S., van't Hoff, W.G., Simmonds, H.A., Marinaki, A.M., Badman, M.K., Hattersley, A.T., 2003. Atypical familial juvenile hyperuricemic nephropathy associated with a hepatocyte nuclear factor-1beta gene mutation. Kidney Int. 63 (5), 1645–1651. https://doi.org/10.1046/j.1523-1755.2003.00903.x.

Bleyer, A.J., Kidd, K., Živná, M., Kmoch, S., 2017. Autosomal dominant tubulointerstitial kidney disease. Adv. Chronic Kidney Dis. 24 (2), 86–93. https://doi.org/10.1053/j.ackd.2016.11.012.

Bleyer, A.J., Kmoch, S., Antignac, C., Robins, V., Kidd, K., Kelsoe, J.R., Hart, P.S., 2014. Variable clinical presentation of an MUC1 mutation causing medullary cystic kidney disease type 1. Clin. J. Am. Soc. Nephrol.: CJASN 9 (3), 527–535. https://doi.org/10.2215/CJN.06380613.

Bleyer, A.J., Zivná, M., Hulková, H., Hodanová, K., Vyletal, P., Sikora, J., Hart, P.S., 2010b. Clinical and molecular characterization of a family with a dominant renin gene mutation and response to treatment with fludrocortisone. Clin. Nephrol. 74 (6), 411–422.

Bolar, C., et al., 2016. Heterozygous loss-of-function SEC61A1 mutations cause autosomal-dominant tubulo-interstitial and glomerulocystic kidney disease with anemia. Am. J. Hum. Genet. 99, 174–187.

Bollée, G., Antignac, C., Noël, L.H., Knebelmann, B., 2009. Néphropathies Tubulo-Interstitielles Héréditaires. Actualités Néphrologiques de Necker.

Bollee, G., Dahan, K., Flamant, M., Moriniere, V., Pawtowski, A., Heidet, L., Lacombe, D., et al., 2011. Phenotype and outcome in hereditary tubulointerstitial nephritis secondary to UMOD mutations. Clin. J. Am. Soc. Nephrol. 6 (10), 2429–2438. https://doi.org/10.2215/CJN.01220211.

Dahan, K., Devuyst, O., Smaers, M., Vertommen, D., Loute, G., Poux, J.-M., Viron, B., et al., 2003. a cluster of mutations in the UMOD gene causes familial juvenile hyperuricemic nephropathy with abnormal expression of uromodulin. J. Am. Soc. Nephrol.: JASN 14 (11), 2883–2893.

Eckardt, K.-U., Alper, S.L., Antignac, C., Bleyer, A.J., Chauveau, D., Dahan, K., Kidney Disease: Improving Global Outcomes, 2015. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management-a KDIGO consensus report. Kidney Int. 88 (4), 676–683. https://doi.org/10.1038/ki.2015.28.

Faguer, S., Decramer, S., Chassaing, N., Bellanné-Chantelot, C., Calvas, P., Beaufils, S., Chauveau, D., 2011. Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. Kidney Int. 80 (7), 768–776. https://doi.org/10.1038/ki.2011.225.

Gendler, S.J., Cohen, E.P., Craston, A., Duhig, T., Johnstone, G., Barnes, et D., 1990. The locus of the polymorphic epithelial mucin (PEM) tumour antigen on chromosome 1q21 shows a high frequency of alteration in primary human breast tumours. Int. J. Cancer 45 (3), 431–435.

Gudmundsson, J., Sulem, P., Steinthorsdottir, V., Bergthorsson, J.T., Thorleifsson, G., Manolescu, A., Rafnar, T., et al., 2007. two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat. Genet. 39 (8), 977–983. https://doi.org/10.1038/ng2062.

Gribouval, O., Gonzales, M., Neuhaus, T., Aziza, J., Bieth, E., Laurent, N., Gubler, M.C., 2005. Mutations in genes in the renin-angiotensin system are associated with autosomal recessive renal tubular dysgenesis. Nat. Genet. 37 (9), 964–968. https://doi.org/10.1038/ng1623.

Hackenthal, E., Paul, M., Ganten, D., Taugner, R., 1990. Morphology, physiology, and molecular biology of renin secretion. Physiol. Rev. 70 (4), 1067–1116. https://doi.org/10.1152/physrev.1990.70.4.1067.

Hart, T.C., Gorry, M.C., Hart, P.S., Woodard, A.S., Shihabi, Z., Sandhu, J., Shirts, B., et al., 2002. Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. J. Med. Genet. 39 (12), 882–892.

Horikawa, Y., Iwasaki, N., Hara, M., Furuta, H., Hinokio, Y., Cockburn, B.N., Lindner, T., et al., 1997. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. Nat. Genet. 17 (4), 384–385. https://doi.org/10.1038/ng1297-384.

Kang, Johnson, 2015. Chapter 35 - Uric Acid Metabolism and the Kidney. https://doi.org/10.1016/B978-0-12-411602-3.00035-4.

Kmoch, S., Živná, M., Bleyer, A.J., 2015. Autosomal Dominant Tubulointerstitial Kidney Disease, REN-Related. Synonyms: ADTKD-REN; Early-Onset Hyperuricemia, Anemia, and Progressive Tubulointerstitial Nephropathy; Familial Juvenile Hyperuricemic Nephropathy Type 2; FJHN2. GeneReviews®.

Kolatsi-Joannou, M., Bingham, C., Ellard, S., Bulman, M.P., Allen, L.I., Hattersley, A.T., Woolf, A.S., 2001. Hepatocyte nuclear factor-1beta: a new kindred with renal cysts and diabetes and gene expression in normal human development. J. Am. Soc. Nephrol.: JASN 12 (10), 2175–2180.

Kudo, E., Kamatani, N., Tezuka, O., Taniguchi, A., Yamanaka, H., Yabe, S., Osabe, D., et al., 2004. Familial juvenile hyperuricemic nephropathy: detection of mutations in the Uromodulin Gene in five Japanese families. Kidney Int. 65 (5), 1589–1597. https://doi.org/10.1111/j.1523-1755.2004.00559.x.

Levitin, F., Baruch, A., Weiss, M., Stiegman, K., Hartmann, M.-L., Yoeli-Lerner, M., Ziv, R., et al., 2005. A novel protein derived from the MUC1 gene by alternative splicing and frameshifting. J. Biol. Chem. 280 (11), 10655–10663. https://doi.org/10.1074/jbc.M406943200.

Lewin, H.A., Stewart-Haynes, J.A., 1992. A simple method for DNA extraction from leukocytes for use in PCR. BioTechniques 13 (4), 522–524.

Lindner, T.H., Njolstad, P.R., Horikawa, Y., Bostad, L., Bell, G.I., Sovik, O., 1999. A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1beta. Hum. Mol. Genet. 8 (11), 2001–2008.

Middleton-Price, H., van den Berghe, J., Harding, A., Scott, J., Malcolm, S., 1987. Analysis of markers on chromosome 1. Abstract) Cytogenet. Cell Genet 46, 662.

Scolari, F., Caridi, G., Rampoldi, L., Tardanico, R., Izzi, C., Pirulli, D., Amoroso, A., Casari, G., Ghiggeri, et G.M., 2004. uromodulin storage diseases: clinical aspects and mechanisms. Am. J. Kidney Dis. 44 (6), 987–999.

Stavrou, C., Koptides, M., Tombazos, C., Psara, E., Patsias, C., Zouvani, I., Deltas, C.C., 2002. Autosomal-dominant medullary cystic kidney disease type 1: clinical and molecular findings in six large Cypriot families. Kidney Int. 62 (4), 1385–1394. https://doi.org/10.1111/j.1523-1755.2002.kid581.x.

Villard, E., Lalau, J.D., van Hooft, I.S., Derkx, F.H., Houot, A.M., Pinet, F., Soubrier, F., 1994. A mutant renin gene in familial elevation of prorenin. J. Biol. Chem. 269 (48), 30307–30312.

Zivná, M., Hůlková, H., Matignon, M., Hodanová, K., Vylet'al, P., Kalbácová, M., Kmoch, S., 2009. Dominant renin gene mutations associated with early-onset hyperuricemia, anemia, and chronic kidney failure. Am. J. Hum. Genet. 85 (2), 204–213. https://doi.org/10.1016/j.ajhg.2009.07.010.