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Smaller caliber renal arteries are a novel feature of uromodulin-associated kidney disease

Aleksander Prejbisz[1,12], Lorenz Sellin[2,12], Elżbieta Szwench-Pietrasz[1], Magdalena Woznowski[2], Ilona Michałowska[3], Dirk Blondin[4], Dariusz Sajnaga[5], Jorg T. Epplen[6], Mieczysław Litwin[7], Gabriele Dekomien[6], Magdalena Januszewicz[8], Udo Helmchen[9], Joanna Matuszkiewicz-Rowińska[10], Marcin Adamczak[11], Andrzej Więcek[11], Andrzej Januszewicz[1,13] and Lars C. Rump[2,13]

[1]Department of Hypertension, Institute of Cardiology, Warsaw, Poland; [2]Department of Nephrology, Medical School, Heinrich Heine University, University Hospital Duesseldorf, Duesseldorf, Germany; [3]Department of Radiology, Institute of Cardiology, Warsaw, Poland; [4]Department of Radiology, Medical School, Heinrich Heine University, Duesseldorf, Germany; [5]Department of Cardiology, Railway Hospital, Pruszków, Poland; [6]Department of Human Genetics, Ruhr University Bochum, Bochum, Germany; [7]Department of Nephrology and Arterial Hypertension, Department of Research, Children's Memorial Health Institute, Warsaw, Poland; [8]1st Department of Radiology, Medical University of Warsaw, Warsaw, Poland; [9]Nierenregister Hamburg, Department of Pathology, University Hospital Eppendorf, Hamburg, Germany; [10]Department of Nephrology, Dialysis and Internal Medicine, Medical University of Warsaw, Warsaw, Poland and [11]Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice, Poland

Hyperuricemia is very common in industrialized countries and known to promote vascular smooth muscle cell proliferation. Juvenile hyperuricemia is a hallmark of uromodulin-associated kidney disease characterized by progressive interstitial renal fibrosis leading to end-stage renal disease within decades. Here we describe a member of a Polish-German family with a history of familial background of chronic kidney disease, hyperuricemia, and gout. This patient had hypertension because of bilateral small renal arteries, hyperuricemia, and chronic kidney disease. Clinical and molecular studies were subsequently performed in 39 family members, which included a physical examination, Duplex ultrasound of the kidneys, laboratory tests for renal function, and urine analysis. In eight family members contrast-enhanced renal artery imaging by computed tomography–angiography or magnetic resonance imaging was conducted and showed that bilateral non-arteriosclerotic small caliber renal arteries were associated with hyperuricemia and chronic kidney disease. Of the 26 family members who underwent genotyping, 11 possessed the P236R mutation (c.707C>G) of the uromodulin gene. All family members with a small caliber renal artery carried the uromodulin P236R mutation. Statistical analysis showed a strong correlation between reduced renal artery lumen and decreased estimated glomerular filtration rate. Thus, bilateral small caliber renal arteries are a new clinical phenotype associated with an uromodulin mutation.

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Correspondence: *Aleksander Prejbisz, Department of Hypertension, Institute of Cardiology, Alpejska 42, Warsaw 04-628, Poland. E-mail: aprejbisz@ikard.pl or Lorenz Sellin, Department of Nephrology, Medical School, Heinrich Heine University, University Hospital Duesseldorf, Moorenstr. 5, Duesseldorf 40225, Germany. E-mail: Lorenz.sellin@med.uni-duesseldorf.de*

[12]These authors contributed equally to this work.

[13]Senior authors contributed equally.

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INTRODUCTION

Hyperuricemia is a widespread entity within the population of industrialized countries. Recent studies suggest that hyperuricemia is associated with increased mortality, cardiovascular morbidity, and renal impairment.[1,2] On the other hand, elevated uric acid levels seem to be essential for higher cognitive development in humans when compared with other mammals.[3,4] Thus, the definite role of elevated uric acid levels in the clinical setting except from gout seems to be an open question.

For many years the genes involved in a renal disease characterized by autosomal dominant inheritance, hyperuricemia, renal cysts, and renal dysfunction due to tubulointerstitial nephritis remained unknown. Several distinct phenotypes had been identified and labeled as familial juvenile hyperuricemic nephropathy or medullary cystic kidney disease (MCKD). Subsequently, two different loci for MCKD have been mapped—MCKD1 on chromosome 1q21 and MCKD2 on chromosome 16p11.2. Recent studies confirmed that familial juvenile hyperuricemic nephropathy and MCKD2 are disorders representing two facets of a single disease and resulting from mutations in the uromodulin (UMOD) gene encoding for uromodulin. Thus, the conditions caused by mutations in UMOD gene are nowadays preferentially termed uromodulin-associated kidney disease (UAKD). The phenotypic expression of the disease is inconsistent, overlapping, and indicates broader genetic and allelic heterogeneity.[5–8]

Detailed descriptions of the phenotype indicate that hyperuricemia represents the hallmark of the renal disease caused by UMOD mutations. It has also been reported that renal survival is characterized by high intrafamilial variability with only small effects of the UMOD genotype. This may suggest that other important factors, environmental and/or modifier genes, modulate the phenotype.[6]

Here we report a family carrying a particular UMOD mutation previously mentioned only once.[9] This mutation is linked to a novel phenotype: small caliber, non-arteriosclerotic renal arteries found in all adult carriers of this mutation. The small caliber renal artery points toward a link between hyperuricemia and changes of arterial vessel morphology. Its significance and relationship to the UAKD remains unresolved, but this finding may yield important insight into the underlying pathomechanism of the renal dysfunction.

RESULTS

The family tree of UAKD with hyperuricemia, gout, and renal failure

Study participants originated from a large three-generation family in which the disorder was tracked back to one sibship (Figure 1). The family had a long history of hyperuricemia, gout, and renal failure inherited in an autosomal dominant manner with clinical findings consistent with UAKD. The index patient is subject II:1 (Figure 1).

Genotyping of the point mutation UMOD c.707C>G

Out of the 39 family members, 33 subjects were investigated (6 subjects refused any examination). In 26 family members, genetic screening was performed (6 subjects refused genetic screening; from one deceased subject DNA was not available). A missense mutation in UMOD exon 3 was found in 11 subjects. The UMOD mutation c.707C>G is a single base exchange causing an amino-acid exchange for p.P236R (Figure 2). All family members carrying this mutation had elevated uric acid levels with or without impaired renal function. In two patients, the initial symptom was gout, another two patients presented with renal impairment. In five family members, the disease was newly diagnosed during this study. In one patient, data regarding the first symptoms are not known (Table 1). Only one 11-year-old male family member (III:12) carries the UMOD mutation without any apparent pathological finding (Figure 1 and Table 1). In two affected patients who refused genetic screening, the first symptoms were hypertension and renal impairment. All other nonaffected family members had normal findings and did not carry the mutation (Figure 1). The renal ultrasound data is presented in Table 2. The detailed clinical description of the index patient and the other family members is given in the Supplementary Material.

Small caliber renal arteries in the angiography

On computed tomography (CT)/magnetic resonance imaging scan a small caliber renal artery was found in all adult cases of UAKD associated with the UMOD mutation with the mean renal artery diameter of 3.5 ± 0.9 mm (2.25–4.7 mm) measured at 5 mm distal of the aortic ostium (Table 3 and Figure 3). The literature indicates that renal arteries are usually 5–6 mm or more in diameter.[10] Recently, it was shown in a large cohort of patients undergoing CT- angiography that normal right and left renal arteries have a mean diameter

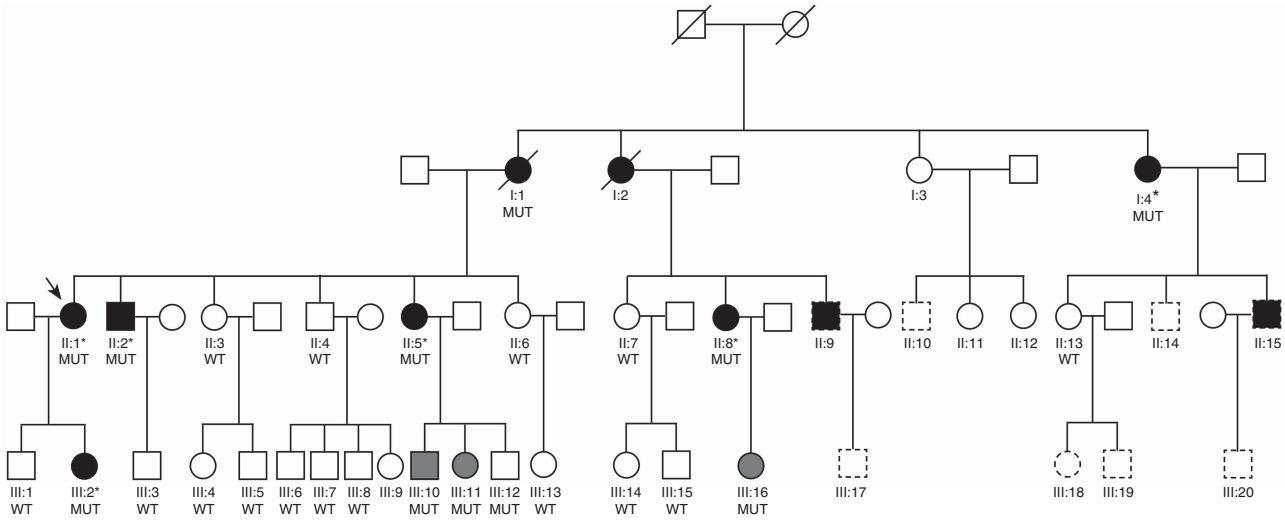

Figure 1 | Family tree. The three generations of the investigated family of Polish origin live in Poland and Germany. The index patient (arrow) II:1 was found to have small caliber renal arteries. Black symbols mark family members with renal insufficiency and hyperuricemia. Gray symbols mark family members with hyperuricemia. Dashed symbol outlines indicate anamnestic information. The genotype for UMOD P236R (if available) is shown below the symbols (WT—wild type, MUT—mutant). Family members with small renal arteries in the angio-CT are marked with an (*). In case of deceased family members the clinical symptoms could only be obtained historically and genomic DNA was available only from the mother of the index case (I:1). Information about the parents of the generation I was not available.