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Case Report

A Novel Mutation of UMOD in a Chinese Family with IgA Nephropathy: A Case Report

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Keywords
Immunoglobulin · A nephropathy · Tubular dilatation · *UMOD* · Whole-exome sequencing · Case report

Abstract
IgA nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide, with varying clinical presentations. The hereditary susceptibility to IgAN is rather complex. In this report, a Chinese case of IgAN was recruited. Renal biopsy showed the tubular atrophy and dilatation, but the glomerular lesions were rather weak except slight mesangial hyperplasia. Immunological staining of kidney tissue revealed the positive immunological staining of IgA and C3. By using whole-exome sequencing, a heterozygous variant in *UMOD* gene was found and was confirmed by Sanger sequencing. The variant in *UMOD* gene might contribute to the disease and this case helps understand the correlation of genotype and phenotypes of UMOD mutations.

Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is the most prevalent primary glomerulonephritis (PGN) worldwide. In China, IgAN is the leading PGN diagnoses and counts for 53.7% of PGN [1]. It is diagnosed by immunohistochemical analysis of renal biopsies, with predominant IgA deposition in the glomerular mesangium. Despite varying clinical presentations, the main clinical features of IgAN include macroscopic or microscopic hematuria,

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proteinuria, hypertension, and the co-occurrence of mucosal infections [2]. Due to the mesangial deposition of IgA, glomerular injuries including mesangial hyperplasia and glomerulosclerosis are common in patients. Most patients will deteriorate to progressive renal insufficiency and end-stage renal disease within 20–30 years of diagnosis. Of note, IgAN can be combined with other renal diseases disease or syndrome. Recently, Bhattacharyya et al. [3] reported a case diagnosed with both Alport Syndrome and IgAN, based on the findings of immunofluorescence and electron microscopy. In addition, patients with lupus nephritis are often found to be combined with IgA deposition in the kidneys, and those patients have different clinicopathological characteristics and outcomes [4].

Accumulating evidence suggests a strong heritable component to IgAN, with an estimated heritability ranging from 39% to 80% [5]. There are numerous reports of familial aggregation of IgAN. Moreover, recent genome-wide association studies have identified multiple genetic loci involved in the disease pathogenesis [6]. Based on recent findings, IgAN represents a complex disease that is associated with genetic and environmental factors. Therefore, its genetic etiology has not been fully understood.

With the progresses in next-generation sequencing technology, whole-exome sequencing (WES) has been clinically applied to analyse of suspected cases, and more pathogenic mutations of IgAN are being discovered. Here, we reported a novel mutation of *UMOD* in Chinese families with IgAN, which might contribute to the disease.

Case Report

Patients and Clinical Evaluation

The authors followed the CARE checklist guidelines, and the CARE Checklist has been completed and attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531891). A 32-year-old Chinese Han man was admitted to our Department because of abnormal renal function. One month before, he suffered from edema of both lower limbs. He had also suffered from gout for about 5 years, as well as elevated serum uric acid. He had a family history of renal disease, as his mother was a hemodialysis patient with an onset-age of 42. For further treatment, he was referred to our hospital.

Physical examination showed no obvious abnormality. His blood pressure was normal. Slight decreased hemoglobin (HGB 114 g/L) and red cell count (3.54×10^{12}/L) were detected by blood test. Serum chemistry showed elevated levels of uric acid (659 μmol/L). Urine test showed proteinuria (1+) and hematuria (1+). The patient's proteinuria was further quantified, with a value of 24-h UP 0.42 g/d. However, all the parameters of immunology test were normal. Besides, the estimated glomerular filtration rate and the serum albumin were also normal. Abdominal ultrasound examination showed normal size of kidney but with increased echogenicity consistent with chronic kidney disease. No abnormality was detected in the liver, pancreas, and spleen by ultrasound examination.

Biopsy of the kidney was performed. Light microscopy revealed 10 glomeruli, all of which were normal except slight mesangial hyperplasia (Fig. 1a). No obviously podocytic abnormality was found. Of note, slight tubular atrophy and dilatation were observed, with the thickening of base membrane (Fig. 1b). Moderate tubulointerstitial fibrosis was observed. Electron microscopy revealed mesangial expansion with electron-dense deposits consistent with IgAN (Fig. 1c). The immunological staining of IgG, IgM, C4, and C1q was negative, while IgA, C3, κ, and λ were positive (Fig. 1d, e).

Based on these findings, the patient was initially diagnosed as IgAN. Due to the findings of proteinuria and hematuria, the patient was administered a renin-angiotensin system inhibitor, and traditional Chinese drugs were administrated to protect kidney function.

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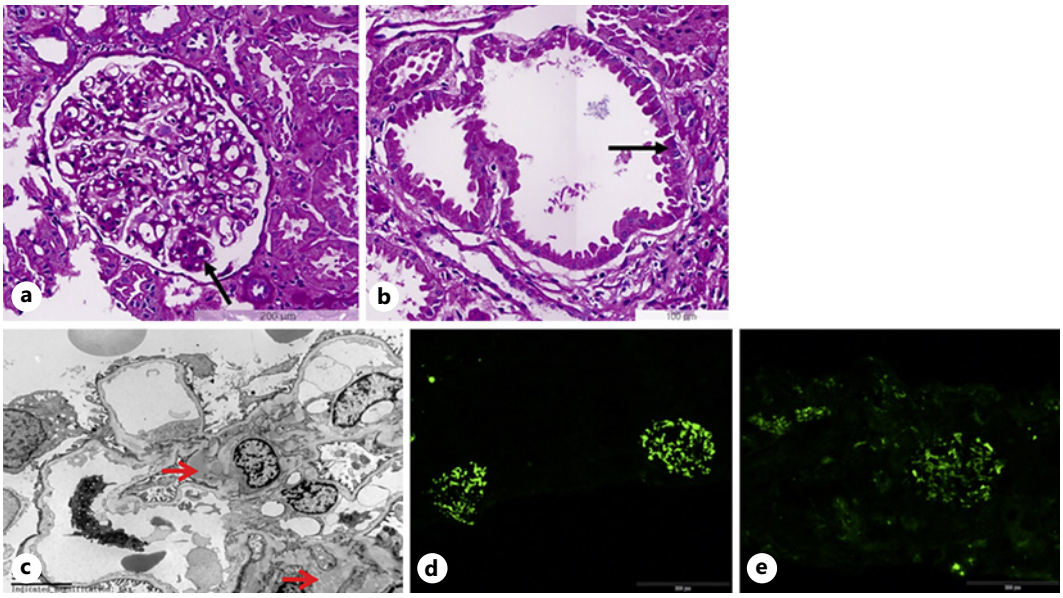

Fig. 1. Histopathology study of renal biopsy from the proband. **a** PAS staining showed the normal glomerulus with slight mesangial hyperplasia (black arrow), Bar: 200 μm. **b** PAS staining showed the tubular dilatation and epithelial hyperplasia (black arrow), Bar: 100 μm. **c** Electron microscopy revealed mesangial deposition of electron-dense consistent (red arrow), Bar: 5 μm. **d** Immunological staining of IgA was positive. **e** Immunological staining of C3 was positive.

Genetic Analysis

As positive family history of kidney disease was observed, he was recommended to have genetic test. Thus, DNA samples obtained from the proband and his parents were analyzed by Chigene (Beijing) Translational Medical Research Center (Beijing, China), as previously described [7]. Sequence analysis showed a heterozygous variant of *UMOD*, NM_003361 c.199G>C. Both the proband and his mother were heterogeneous. This variant led to a missense substitution, and it was excluded from the Single Nucleotide Polymorphism database and the Human ClinVar Database. In addition, the variant was further confirmed by Sanger sequencing (Fig. 2). The 5-year-old son of the patient had the heterozygous variant without any clinical presentations. According to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines, the variants were categorized as "Likely pathogenic" (PM1+PM2+PP2+PP3). Based on the genetic analysis, this patient was finally diagnosed as autosomal dominant tubulointerstitial kidney disease (ADTKD) combined with IgAN.

Discussion

The diagnosis of IgAN is based on the finding of the mesangial deposition of IgA by immunofluorescence of kidney biopsies. As renal biopsy is invasive, a fraction of the patients whose renal biopsy is unavailable will be challenging. Therefore, establishment of diagnosis based on genetic testing is very useful. IgAN is currently thought to be a genetic heterogeneous disorder of either monogenic or multifactorial, depending on its familial aggregation in a given kindred.

During the past decades, much effort has been made to elucidate the genetic factors associated with IgAN. However, no clear causative gene has been completely identified. With

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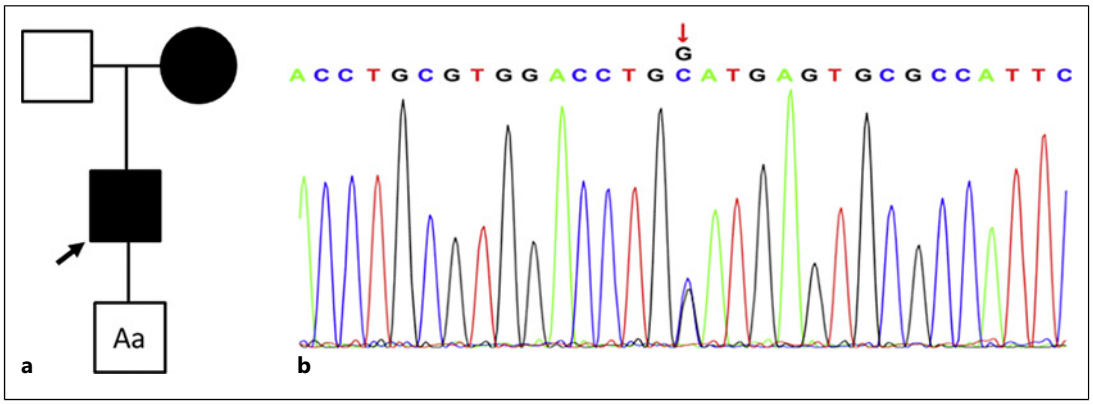

Fig. 2. Identification of the heterozygous variant in the family. **a** Pedigree of the Chinese family. Affected family members are denoted in black. Arrow indicates the proband. The 5-year-old son of the proband also had heterozygous variant (indicated as Aa). **b** Direct Sanger sequencing confirmed the heterozygous variant in *UMOD* gene.

the fast development of next-generation sequencing, several studies have been carried out WES to identify candidate genes for IgAN. One such study of Liu et al. [7] has discovered 6 deleterious variants in 4 genes associated with familial IgAN. These genes included *MYCT1*, *DEFA4*, *CARD8*, and *ZNF543*. Another study analyzed 16 kindreds of South Italian ancestry and found that 24 private or extremely rare linked variants segregating with IgAN status [8]. Similarly, Stapleton et al. [9] performed WES in 10 Irish families with multiple affected members, and they detected candidate variants in 3 of 10 families. These genes included *COL4A5*, *COL4A3*, and *LMX1B*. Besides, many cases revealed various rare variants associated with IgAN. For example, a likely pathogenic variant of *WT1* was found by WES to be co-segregated with proteinuria in a six-generation Chinese family with IgAN [10]. In this family, another WT1 variant was harbored by those patients whose phenotype was more severe. However, the relationship between IgAN and *UMOD* gene is unclear. In IgAN patients, the serum levels of UMOD were associated with renal function, and a lower level might be a risk factor for worsening renal function [11]. Dinic et al. [12] found that *UMOD* polymorphism rs12917707 was not associated with severe or stable IgA nephropathy (IgAN) in a large Caucasian cohort, and they concluded that UMOD was unlikely to play a role in neither IgAN pathogenesis nor progression to end-stage renal failure. Therefore, more studies are needed to clarify this issue. In our case, genetic analysis by WES revealed that the proband and his mother harbored a heterogeneous variant of *UMOD*. Although his son was also a heterozygote, he had no any renal phenotype. The age might be the reason why his son was normal.

UMOD encodes Tamm-Horsfall protein, the most abundant protein in mammalian urine under physiological conditions. It is the first identified gene that causes ADTKD. ADTKD is mainly characterized by tubular damage and interstitial fibrosis in the absence of glomerular lesions, according to the guidelines of KDIGO consensus [13]. In our case, the index patient was definitely diagnosed as IgAN, according to the findings of renal biopsy. Of note, his glomeruli were almost normal except slight mesangial hyperplasia, without any sclerosis. And the tubular atrophy and dilatation were evident. These findings are different to the most-often observed histopathological presentations of IgAN. Compared with the KDIGO consensus report, the histopathological phenotypes of renal biopsy in this case fit better with that of ADTKD, except the positive immunological staining. Therefore, the patient was finally

diagnosed as ADTKD combined with IgAN. Our case study is limited in that the kindred had few family members. As the samples of the proband's grandparents were unavailable, the origin of the likely pathogenic variant was not clear.

Acknowledgments

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Statement of Ethics

Written informed consent to participate in the study was obtained from the patient and his parents. The present study was ethically approved by the Ethics Committee of Xinqiao Hospital at Army Medical University (Chongqing, China) (2020-047-01). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration. Written informed consents for publication of identifying images and other personal and clinical details were obtained from the patient and his family. These materials include diagnostic images, treatment and prognostic information, genetic testing results, and other related data used in this report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.Z.: conception and design. F.L., H.Z., and T.X.: development of methodology and acquisition of data. L.L., F.L., B.Z., and J.Z.: analysis and interpretation of data. B.Z. and J.Z.: writing and reviewing the manuscript. All authors: contributed to the article and approved the submitted version.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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