KI REPORTS
KIReports.org



# Kidney-Predominant Thrombotic Microangiopathy Associated With *TREX1* Frameshift Mutation



Zhuo-ran Song[1,2,3,4,5], Lei Jiang[1,2,3,4,5], Yang Li[1,2,3,4,5], Chen-gang Xiang[1,2,3,4,5], Zhi-ying Liu[1,2,3,4,5], Meng-shi Li[1,2,3,4,5], Hong Zhang[1,2,3,4,5] and Xu-jie Zhou[1,2,3,4,5]

[1]Renal Division, Peking University First Hospital, Beijing, People's Republic of China; [2]Kidney Genetics Center, Peking University Institute of Nephrology, Beijing, People's Republic of China; [3]Key Laboratory of Renal Disease, Ministry of Health of China, Beijing, People's Republic of China; [4]Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, People's Republic of China; and [5]State Key Laboratory of Vascular Homeostasis and Remodeling, Peking University, Beijing, People's Republic of China

**Correspondence**: Xu-jie Zhou, Renal Division, Peking University First Hospital, Kidney Genetic Center, Peking University Institute of Nephrology, No.8 Xi Shi Ku Street, Xi Cheng District, Beijing 100034, China. E-mail: zhouxujie@bjmu.edu.cn

**Received 26 May 2023; revised 20 July 2023; accepted 24 July 2023; published online 4 August 2023**

*Kidney Int Rep* (2023) **8,** 2172–2176; https://doi.org/10.1016/j.ekir.2023.07.024


## INTRODUCTION

Thrombotic microangiopathy (TMA) is a pathological lesion associated with a broad range of underlying disorders. Although the kidney is the most frequently involved organ, kidney-limited or kidney-predominant TMA is not infrequently encountered.[1] In addition to the common complement-associated and coagulation-associated gene mutations, there are other unidentified genes involved in the TMA process. Here, we describe a family with kidney-predominant TMA, identifying a C-terminal heterozygous frameshift mutation in *TREX1* by whole exome sequencing.

## CASE PRESENTATION

A 34-year-old Chinese man with a history of proteinuria for 10 years was admitted to our center. In the past 10 years, he received supportive treatments without corticosteroids or immunosuppressants. His urine protein fluctuated between 3 and 4 g/d, and his serum creatinine slowly increased in the last 2 years, from 1.63 to 4.77 mg/dl, corresponding to an estimated glomerular filtration rate of 14 ml/min per 1.73 $m^2$. He had no previous medical history other than hypertension and osteonecrosis of the femoral head. On physical examination, including neurological and ophthalmologic examinations, no remarkable abnormality was observed except for bilateral lower extremities edema and positive Patrick's test, a sign of hip pathology (Supplementary Material). Laboratory tests showed that he had 10 to 12 dysmorphic red blood cells per high power field in urinalysis, his protein excretion was 3.53 g/d and serum albumin was 26.6 g/l. His liver function, electrolytes and cardiac enzymes were normal. Complement levels (C3, C4 and factor H), ADAMTS13 activity, antinuclear antibody and other autoantibodies were normal.

The patient's younger brother (III-2; Figure 1a), now 32 years old, also had a history of proteinuria for almost 10 years, with current protein excretion of 5.93 g/d, serum albumin of 37.3 g/l and serum creatinine of 3.14 mg/dl. He was hypertensive and diagnosed with osteonecrosis of the femoral head and had no remarkable systemic symptoms (including visual, neurologic, and psychiatric symptoms). No exception was indicated in ophthalmologic examination. T2 FLAIR hypertense white matter lesions were identified in brain magnetic resonance imaging, indicating lacunar infarction. Urinalysis showed protein (3+), 2 to 3 dysmorphic red blood cells per high power field. Like his elder brother, no microangiopathic hemolytic anemia, thrombocytopenia, and other ischemic organ injury were noted. No secondary causes including infection, autoimmunity or monoclonal protein were identified.

The proband's grandmother (I-1), mother (II-1), and 2 uncles (II-3 and II-5) all progressed to end-stage kidney disease in their late 30s. Details of their kidney disease and other conditions are unavailable. The proband's cousin (III-6), 28 years old now, has proteinuria and edema in chronic kidney disease stage 2.

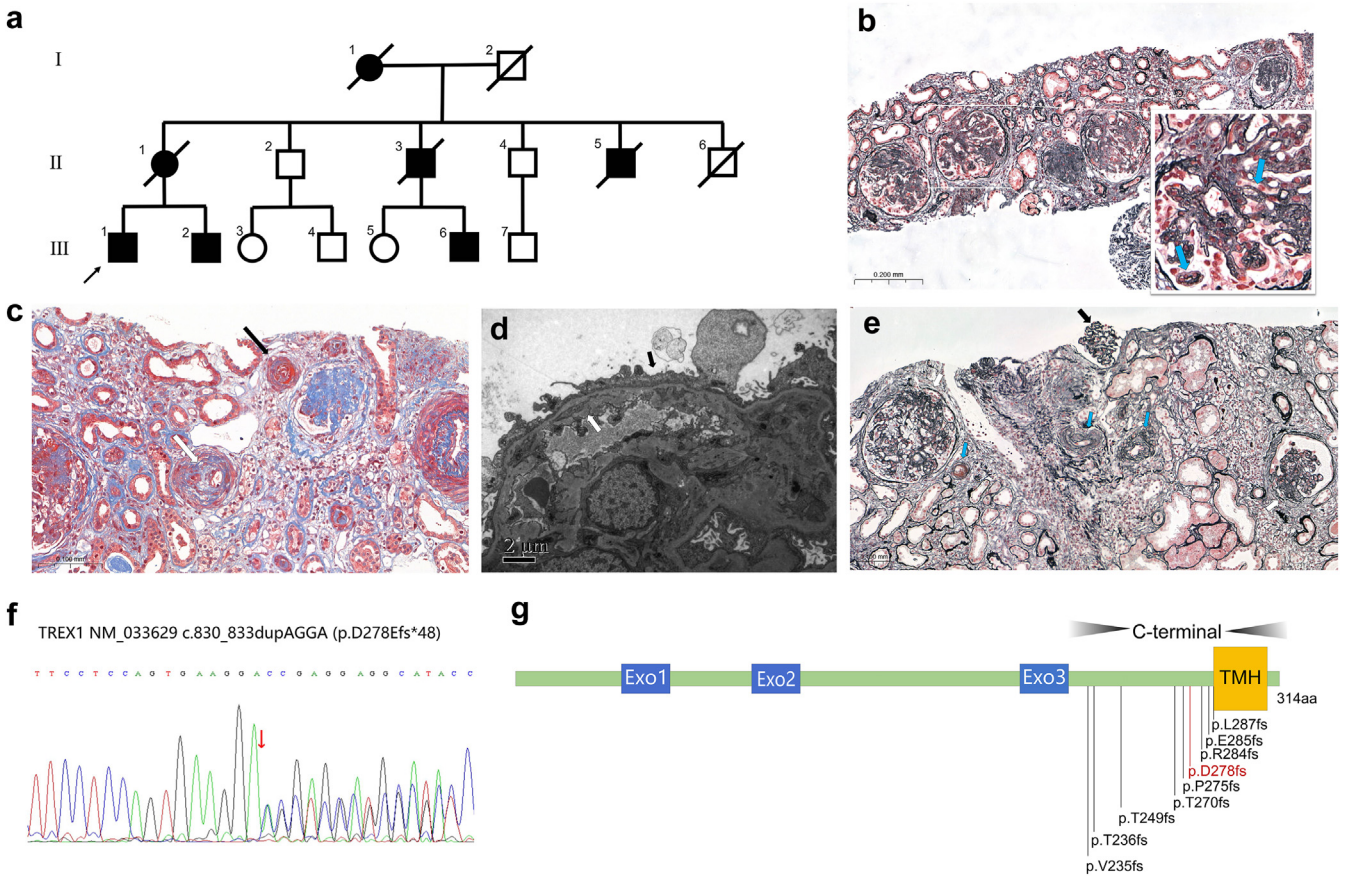


**Figure 1.** (a) Family pedigree. Kidney biopsy findings in the proband (b–d) and his brother (e). (b) Light microscopy showed segmental sclerosis, global sclerosis, and ischemic sclerosis. Double contours (blue arrows) can be seen in the non-sclerotic portion (PASM, 200×). (c) The interlobular arterioles showed intimal mucoid edema (white arrow) and fibrin thrombosis (black arrow) (Masson, 400×). (d) Electron microscopy showed duplication of glomerular basement membrane (white arrow) and diffuse effacement podocyte foot process (black arrow). (e) Light microscopy findings were similar with the proband, showing segmental sclerosis (white arrow), ischemic shrinkage (black arrow), and hyalinosis of arterioles (blue arrow) (PASM, 200×). (f) Sanger sequencing chromatograms of *TREX1*, confirming the c.830_833dupAGGA variant in the proband (III-1), his younger brother (III-2) and his cousin (III-6). (g) Schematic of the location of documented *TREX1* C-terminal frameshift variants. aa, amino acid; C-terminal, carboxy-terminal; Exo, exonuclease domain; PASM, periodic acid-silver methenamine; TMH, transmembrane helix.

## RESULTS

### Kidney Biopsy

Kidney biopsies were performed on the patient and the patient's younger brother. Light microscopy showed prominent segmental sclerosis, global sclerosis, and several ischemic sclerosis (Figure 1b). In the non-sclerotic portion, segmental endothelial swelling, moderate to severe mesangial cell proliferation with increased mesangial matrix can be seen. The glomerular basement membrane was segmentally thickened with double contours formation (Figure 1b). The lumens of interlobular arterioles were significantly narrowed due to intimal fibrosis, intimal mucoid edema or hyalinosis, with occasionally fibrin thrombosis found (Figure 1c). Tubular atrophy, interstitial inflammation, and fibrosis accounted for about 75% of the renal cortex area. On electron microscopy, duplication of the glomerular basement membrane and diffuse effacement podocyte foot process were observed (Figure 1d). The pathological diagnosis of TMA was made. The kidney pathology of the patient's brother was found to be almost identical (Figure 1e).

### Genetic Testing

Because of the familial TMA, whole exome sequencing was performed, and a *TREX1* heterozygous variant, c.830-833dupAGGA (p.D278Efs*48) was identified, which indicated a frameshift mutation in the carboxy terminus, leading to an altered reading frame and generating a premature stop codon at amino acid 325. According to the American College of Medical Genetics Standards and Guidelines, this mutation was filtered as pathogenic (PVS1 + PS1). No other pathogenic or likely pathogenic mutations related to TMA were found, such as C3, complement factor B/H/I, complement factor H-related proteins 1 to 5, membrane cofactor protein,

**Table 1.** The main impaired organs and documented kidney impairment details of *TREX1* C-terminal heterozygous frameshift mutations

| Mutation | Main affected organs and references | Kidney impairment details | | | | |
|---|---|---|---|---|---|---|
| | | Patient/Origin/Published Yr | Gender | Kidney function | Proteinuria | Kidney biopsy |
| V235fs | CNS + Retina[4,S2–S4] | / | / | / | / | / |
| | CNS + Retina + Kidney + Liver et al[5,6,S5–S6] | III4[S5]/Caucasian/2008 | M | NA | NA | TMA |
| | | III1[5]/Chinese/2021 | F | Scr 3.58mg/dl at 46y | 2+ | NA |
| | (Only with nephropathy) | III2[5]/Chinese/2021 | M | ESKD at 41y | 1.47g/d | NA |
| | | III4[5]/Chinese/2021 | F | eGFR 41.49ml/min/1.73m$^2$ at 39y | NA | NA |
| | | III7[5]/Chinese/2021 | M | Scr 3.26mg/dl at 35y | 3.47g/d | NA |
| T236fs | CNS + Retina[4,S7] | / | / | / | / | / |
| T249fs | CNS + Retina + Kidney[4,6,S8] | III2[S8]/Chinese/1997 | F | Scr 2.5mg/dl at 31y | 300mg/dl | Arterial and arteriolar endothelial cells were multilayered |
| T270fs | CNS + Retina + Kidney + Liver + Osteonecrosis[S6] | Patient 1[S6]/Italian/2015 | M | ESKD at 25y | NA | Thickening of the arteriolar vessels with intimal fibrosis |
| P275fs | CNS + Retina + Kidney[9] | Index Patient[9]/Caucasian/2015 | M | NA | NA | Thickening of the GBM but no vasculitis |
| D278fs | CNS + Retina + Kidney[7] | Index Patient[7]/American/2016 | M | Scr 2.9mg/dl at 44y | 1.18g/d | TMA |
| | Kidney[8] | I-1[8]/American/2018 | M | ESKD in his sixth decade | NA | NA |
| | | II-1[8]/American/2018 | M | Scr 1.8mg/dl at 59y | 1.5g/d | TMA |
| | | II-ii[8]/American/2018 | M | CKD stage 3 in his early 50s | NA | TMA |
| | Kidney + Osteonecrosis[reported herein] | III1[reported herein]/Chinese/2023 | M | ESKD at 34y | 3.53g/d | TMA |
| | | III2[reported herein]/Chinese/2023 | M | Scr 3.14mg/dl at 32y | 5.93g/d | TMA |
| R284fs | CNS + Retina + Kidney[4,S9] | / | / | / | / | / |
| E285fs | CNS + Retina[S10] | / | / | / | / | / |
| L287fs | Not reported[4] | / | / | / | / | / |

CKD, chronic kidney disease; CNS, central nervous system; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; F, female; GBM, glomerular basement membrane; M, male; NA, not available; Scr, serum creatinine; TMA, thrombotic microangiopathy.

**Table 2.** Teaching points

| Teaching points |
|---|
| 1 In addition to the common complement-associated and coagulation-associated gene mutations, there are still other unidentified genes involved in the TMA process. |
| 2 Whole exome sequencing is an effective method in the diagnosis of familial TMA. |
| 3 Patients with *TREX1* C-terminal heterozygous frameshift mutation can present with renal-limited TMA. |
| 4 *TREX1* D247fs is a hotspot mutation within *TREX1* that is strongly associated with TMA of renal significance. |
| 5 Do not forget autosomal dominant inheritance with *TREX1* mutation in familial thrombotic microangiopathy. |

TMA, thrombotic microangiopathy.

plasminogen, and thrombomodulin. Sanger sequencing confirmed the frameshift mutation of *TREX1* in the patient, his affected brother and cousin (Figure 1f).

The patient had already progressed to chronic kidney disease stage 5 when he came to our center. He was thus given supportive therapy. Later, he received steroid with 1 mg/kg/d in another hospital but that did not show any benefits, thus receiving hemodialysis 5 months later; and he received a kidney transplant shortly after that. The transplanted kidney is currently in good condition. The patient's brother is currently in chronic kidney disease stage 4, receiving regular follow-up.

## DISCUSSION

TMA is a pathologic description that can manifest diverse presentations; however, kidney injury is a common prominent clinical manifestation because of the glomerular endothelial damage and occlusion.[2] A majority of TMA occurs as a consequence of complement dysregulation or ADAMTS13 deficiency, which can be treated by plasma exchange and anticomplement therapy.[3]

*TREX1* is a DNA-specific 3′ to 5′ exonuclease ubiquitously expressed in mammalian cells,[4] playing a vital role in DNA repair, protein glycosylation, and innate immune regulation.[5] The transmembrane helix domain which is located in the C-terminal represents the putative transmembrane helix that localizes *TREX1* to the endoplasmic reticulum.[6] Heterozygous C-terminal frameshift mutation in *TREX1* gene may cause retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S).[5]

RVCL-S is a microvascular disease presenting with predominant cerebroretinal vasculopathy,[5] characterized by neurological decline, visual impairment, and premature death. Impaired kidney function can also appear to be part of the clinical spectrums but is usually with an accompanying brain and/or retinal symptoms.[6] The main impaired organs and documented kidney impairment details of *TREX1* C-terminal heterozygous frameshift mutations are summarized in Table 1. As summarized in Table 1, kidney-predominant TMA is the key feature in different pedigrees with *TREX1* D247fs mutation,[7,8] suggesting the presentation of a hotspot mutation in *TREX1* that could contribute to a more severe and predominantly kidney-related phenotype. The precise pathophysiological mechanisms are unclear now; however, it seems not to be related to complement dysregulation.[9,S1]

In our case, both the index patient and his younger brother presented with nephrotic-range proteinuria and progressive kidney function decline with a family history of chronic kidney disease. Kidney biopsy revealed TMA but no other systemic manifestations such as microangiopathic hemolytic anemia, thrombocytopenia, or ischemic end-organ injury were observed, suggesting a kidney-predominant TMA. C3, C4, complement factor H and complement-associated genes screening were all normal, indicating it was not complement-associated. Heterogenous C-terminal mutation of *TREX1* found by whole exome sequencing revealed the underlying etiology. The presence of osteonecrosis of the femoral head in the proband and his affected brother (III-2) may indicate a systemic small vascular lesion in RVCL-S. Because heterozygous C-terminal frameshift mutation in *TREX1* gene may cause retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations, neurological deficits were evaluated. Despite the absence of typical clinical manifestations of neurological and visual impairment, T2 FLAIR hypertense white matter lesions observed in the affected brother may be a reflection of RVCL-S. The kidney-predominant presentation in this family is a reminder to nephrologists that whereas some RVCL-S patients may initially present with predominant kidney manifestations, subtle extrarenal systemic manifestations may not be apparent at the time of presentation or may develop over time during long-term follow-up.

In conclusion, we report a case of familial kidney-limited TMA caused by *TREX1* heterozygous variant in the C-terminal and emphasize the phenotypic heterogeneity in *TREX1* C-terminal heterozygous frameshift mutation, highlighting the importance of whole exome sequencing in familial TMA, alerting nephrologists to recognize both renal and extrarenal manifestations caused by *TREX1* C-terminal heterozygous frameshift mutation (Table 2).

## DISCLOSURE

The authors declare that they have no other conflicting interests.

## PATIENT CONSENT

The authors declare that they have obtained consent from the patient for the clinical information to be published in the Case Report.

## ACKNOWLEDGMENTS

Support was provided by National Science Foundation of China (82022010, 81970613, 82000680), Beijing Natural Science Foundation (Z190023), Academy of Medical Sciences–Newton Advanced Fellowship (NAFR13\1033), Fok Ying Tung Education Foundation (171030), Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-046, 2020-JKCS-009), and the National High Level Hospital Clinical Research Funding (Interdisciplinary Clinical Research Project of Peking University First Hospital, 2022CR41). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Supplemental Article Text.**

**Supplemental References.**

## REFERENCES

1. Genest DS, Patriquin CJ, Licht C, John R, Reich HN. Renal thrombotic microangiopathy: a review. *Am J Kidney Dis*. 2022;81:591–605. https://doi.org/10.1053/j.ajkd.2022.10.014
2. Brocklebank V, Wood KM, Kavanagh D. Thrombotic microangiopathy and the kidney. *Clin J Am Soc Nephrol*. 2018;13:300–317. https://doi.org/10.2215/CJN.00620117
3. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014;371:654–666. https://doi.org/10.1056/NEJMra1312353
4. Richards A, van den Maagdenberg AMJM, Jen JC, et al. C-terminal truncations in human 3′-5′ DNA exonuclease TREX1 cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy. *Nat Genet*. 2007;39:1068–1070. https://doi.org/10.1038/ng2082
5. Xie N, Sun Q, Yang J, et al. High clinical heterogeneity in a Chinese pedigree of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S). *Orphanet J Rare Dis*. 2021;16:56. https://doi.org/10.1186/s13023-021-01712-9
6. Stam AH, Kothari PH, Shaikh A, et al. Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. *Brain*. 2016;139:2909–2922. https://doi.org/10.1093/brain/aww217
7. Vodopivec I, Oakley DH, Perugino CA, Venna N, Hedley-Whyte ET, Stone JH. A 44-year-old man with eye, kidney, and brain dysfunction. *Ann Neurol*. 2016;79:507–519. https://doi.org/10.1002/ana.24583
8. Gulati A, Bale AE, Dykas DJ, et al. TREX1 mutation causing autosomal dominant thrombotic microangiopathy and CKD-A novel presentation. *Am J Kidney Dis*. 2018;72:895–899. https://doi.org/10.1053/j.ajkd.2018.05.006
9. Schuh E, Ertl-Wagner B, Lohse P, et al. Multiple sclerosis-like lesions and type I interferon signature in a patient with RVCL. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e55. https://doi.org/10.1212/NXI.0000000000000055