New Frameshift Variant-associated Familial Hereditary Fibrinogen A-chainAmyloidosis.

Jie Liang1, Zi Run Zheng2*, Ke Ma2*, Shuai Lin He1, Yu Meng1,2,3

1 Central Laboratory, The Fifth Affiliated Hospital of Jinan University, Heyuan, China.

2 Department of Nephrology, The First Affiliated Hospital of Jinan University, Guangzhou, China.

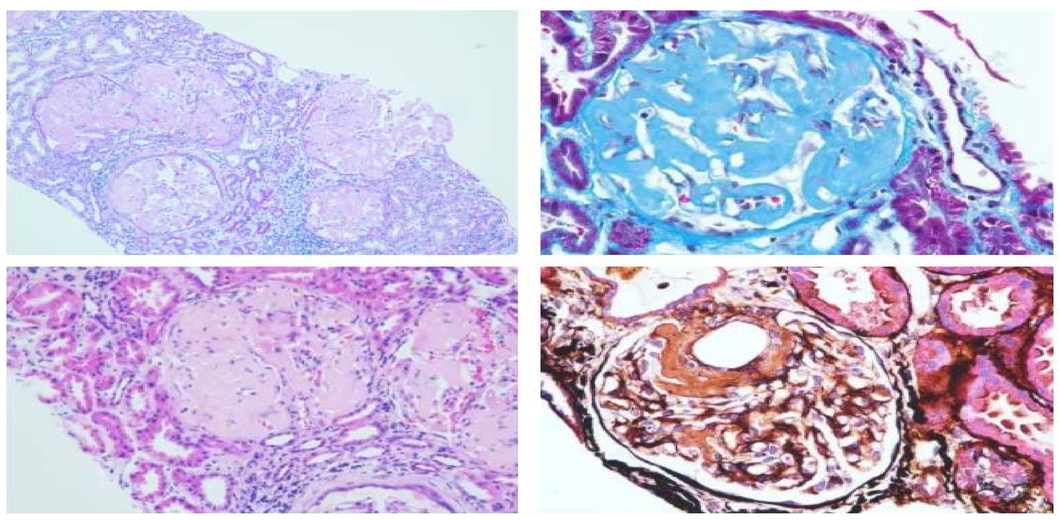
3 Jinan University Institute of Nephrology, Guangzhou, China.

* These authors shared the second authorship of the work, and each made an equal contribution.

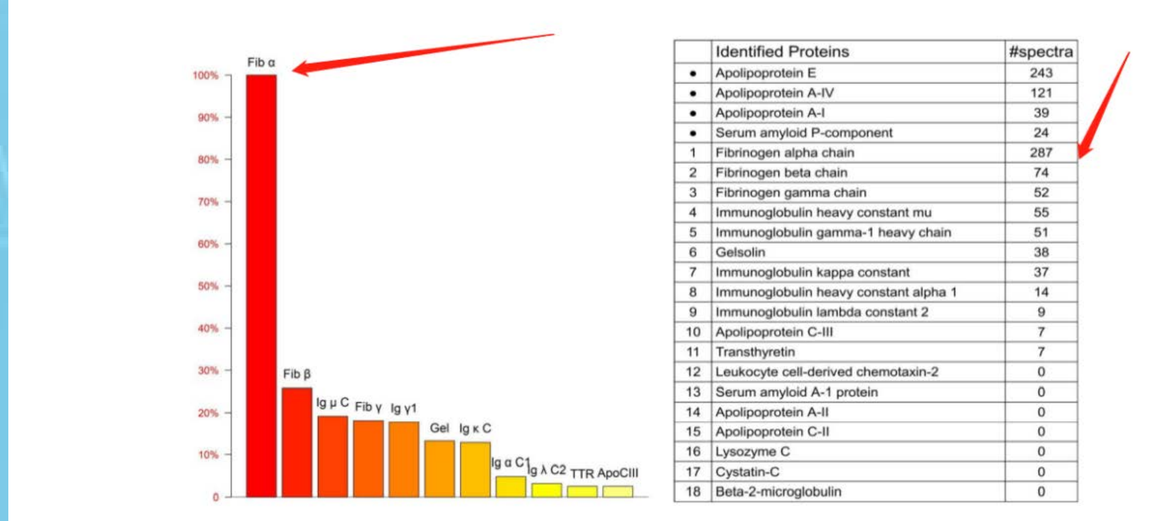
Corresponding Author: Yu Meng. Address: The Fifth Affiliated Hospital of Jinan University, Heyuan, China; Email: mengy@jnu.edu.cn

Abstract

Hereditary fibrinogen Aα-chain amyloidosis is a type of autosomal dominant systemic amyloidosis caused by mutations in the fibrinogen Aα-chain（AFib) gene and is typically accompanied by renal disease. Here, we describe a case of familial hereditary fibrinogen Aα-chain amyloidosis associated with a novel frameshift mutation in the fibrinogen Aa-chain gene. The patient is a 36-year-old Chinese woman presenting with proteinuria and edema in both lower limbs. Her edema of both lower limbs and foam urine persisted for 15 days, accompanied by a family history of early deaths from uremia in his uncle and second uncle. She was identified as having urinary protein cause (serum albumin, 31g/L, urinary protein 9.9g/day). Renal biopsy revealed that amyloid deposits in most of the glomeruli without interstitial or vascular involvement, and the amyloid depositions were selectively stained with fibrinogen-specific antibodies (Figure 1). As determined by mass spectrometry study, the relative abundance of Fibα is the highest among known typing proteins in renal tissue, raising the likelihood of hereditary fibrinogen amyloidosis (Figure 2). And in the FGA gene testing, this patient possessed a frameshift mutation (c.1673del) in FGA gene testing, which was a deletion-mutation to be reported in patients with Aα-chain amyloidosis (Figure 3). Therefore, to lessen urine protein leakage, we have mostly provided treatment including symptom assistance, dietary advice, and valsartan. With blood albumin levels of 36.5 g/L and urine protein intake of 6.01 g/day, the patient's symptoms considerably improved after six months of treatment. Up to now, this is the ninth case of "familial hereditary fibrinogen Aα-chain amyloidosis" reported in an Asian individual. The distinctive renal histology, mass spectrometry analysis and gene testing all provided significant clues to the diagnosis.



ure 1. Findings of renal biopsy in a Chinese Aα-chain amyloidosis patient at the age of 36 years. Renal biopsy shows: 1) Heavy amyloid deposits mainly in glomerulus; 2) The positive staining is observed in immunohistochemistry. 3) PASM-MASSON shows homogeneous amyloid deposits mainly in the mesangial area and capillary loops. 4) The results of immunofluorescence show that IgG (-), IgA (+/-), IgM (+), C1q (-), PLA2R (+), C3 (+), Alb (-), Fib (-). 5) The results of special staining: Congo red (+), Congo red oxide (+).



	Identified Proteins	#spectra
•	Apolipoprotein E	243
•	Apolipoprotein A-IV	121
•	Apolipoprotein A-I	39
•	Serum amyloid P-component	24
1	Fibrinogen alpha chain	287
2	Fibrinogen beta chain	74
3	Fibrinogen gamma chain	52
4	Immunoglobulin heavy constant mu	55
5	Immunoglobulin gamma-1 heavy chain	51
6	Gelsolin	38
7	Immunoglobulin kappa constant	37
8	Immunoglobulin heavy constant alpha 1	14
9	Immunoglobulin lambda constant 2	9
10	Apolipoprotein C-III	7
11	Transthyretin	7
12	Leukocyte cell-derived chemotaxin-2	0
13	Serum amyloid A-1 protein	0
14	Apolipoprotein A-II	0
15	Apolipoprotein C-II	0
16	Lysozyme C	0
17	Cystatin-C	0
18	Beta-2-microglobulin	0

Figure 2. Findings of mass spectrometric typing of renal amyloidosis in a Chinese Aα-chain amyloidosis patient at the age of 36 years. Among the currently known typing proteins, the relative abundance of Fibα is the highest, suggesting AFib type which is hereditary amyloidosis.

Gene	*FGA*	Chromosome	chr4:155506908	Mutation information	c.1673del (p.Lys558Argfs*10)
NP24F02633 Proband, Forward sequencing Heterozygosity					
NP24F02633 Proband, Reverse sequencing Heterozygosity					

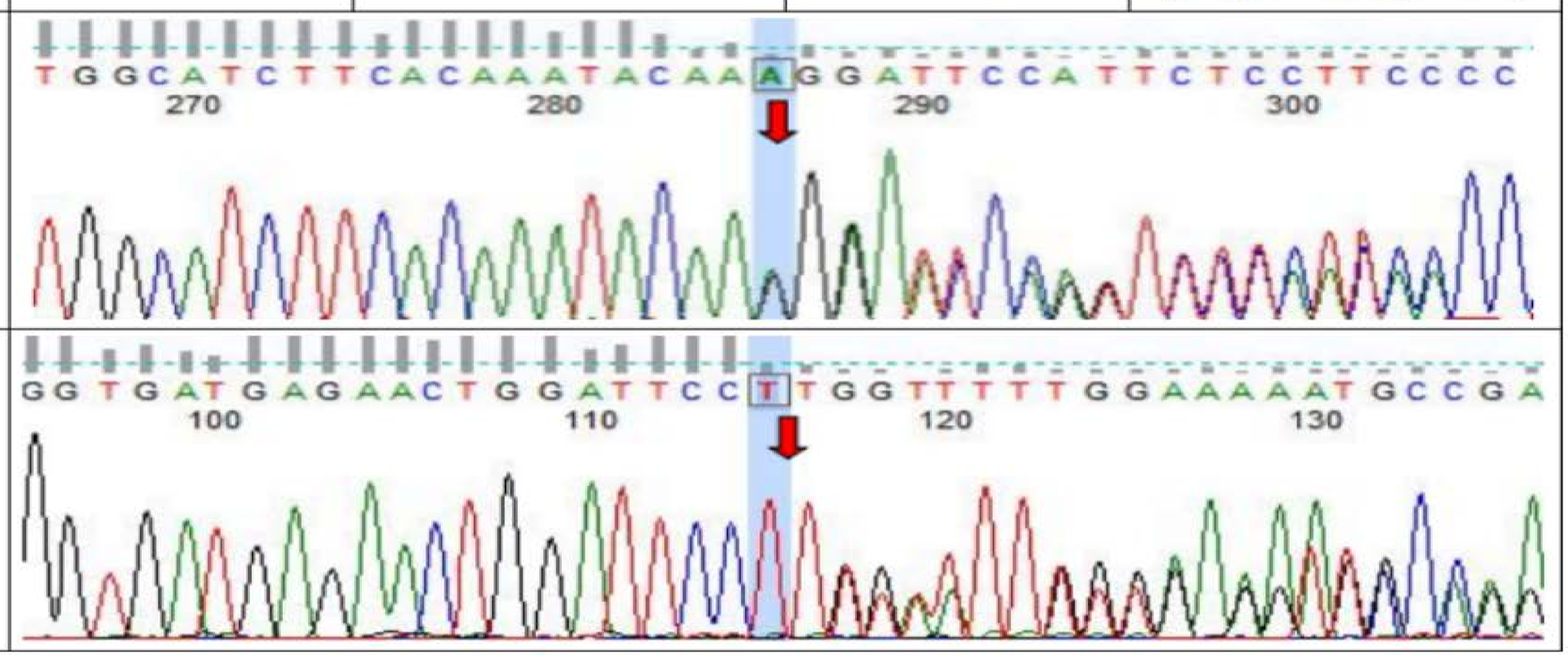


Figure 3. Findings of FGA gene sequence in a Chinese Aα-chain amyloidosis patient at the age of 36 years. In the coding region of FGA gene related to familial amyloidosis, c.1673del (p. Lys558Argfs × 10) carried by the patient was detected. This mutation is a frameshift mutation caused by base deletion in the coding region of FGA gene, which can lead to loss of protein function (through nonsense mediated mRNA degradation or early termination of coding amino acid sequence).