Clinical Features of Familial Amyloidotic Polyneuropathy With Transthyretin p.Ala117Ser Mutation in Mainland China

Yeli Zhu

Southern Medical University Nanfang Hospital

Xiying Zhu

Central South University Third Xiangya Hospital

Wei Li

Southern Medical University Nanfang Hospital

Zhaoyong Zhang

Southern Medical University Nanfang Hospital

Hui Zheng

Southern Medical University Nanfang Hospital

Lingchao Meng

Peking University First Hospital

Ruxu Zhang

Central South University Third Xiangya Hospital

Haishan Jiang (✉ jianghs@smu.edu.cn)

Southern Medical University Nanfang Hospital <https://orcid.org/0000-0002-7388-8659>

Research

Keywords: Transthyretin amyloidosis (ATTR), familial amyloid polyneuropathy (FAP), clinical feature

Posted Date: October 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-966814/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Objective: Our study aimed to report the clinical features of ATTR-PN with TTR p.Ala117Ser mutation in mainland China.

Methods: Thirteen patients from 13 different families diagnosed with p.Ala117Ser ATTR-PN were identified from three centres. Clinical and laboratory data were retrospectively retrieved for analysis.

Results: The male/female ratio was 11:2. All patients showed late onset, with the age of onset at 57.8 ± 5.8 years. The initial symptom was numbness of the lower or upper extremities in 9 patients (69.2%). Paraesthesia was present in all patients. Eleven patients (84.6%) had autonomic dysfunction. Cardiac, renal, hepatic, and ocular dysfunctions were noted in 8 (61.5%), 1 (7.7%), 2 (15.4%), and 3 (23.1%) patients, respectively. Nerve conduction studies have shown axonal-type sensorimotor polyneuropathy. The decline in sensory nerve action potentials was more noticeable than in compound muscle action potentials. The nerve damage present in the lower limbs was more severe than that in the upper limbs. Nerve biopsy revealed positive Congo red staining in 7/10 patients (70%).

Conclusion: Our study is the largest population report on this rare p.Ala117Ser mutation in mainland China.

Introduction

Hereditary transthyretin amyloidosis with polyneuropathy (ATTR-PN) is an autosomal dominant genetic disorder, caused by point mutations of the *TTR* gene and is characterised by amyloid deposition in the peripheral nervous system and autonomic nervous system [1]. It is a systemic disease that involves various organs (such as the heart, eyes, kidney), and usually presents as progressive peripheral neuropathy with adult-onset. In 1952, Andrade first described familial amyloid polyneuropathy (FAP) in northern Portugal [2]. It was subsequently reported in Japan (1968) [3] and Sweden (1976) [4]. ATTR-PN has been reported in 29 countries, including Korea [5], the United states of America [6], China [7], and many European countries [8].

The *TTR* gene is located on chromosome 18 and comprises four exons [9]. Currently, more than 130 mutations have been identified associated with this gene [1]. The p.Val30Met variant of TTR is most commonly identified among patients living in small clusters and scattered families worldwide and was first described as the cause of FAP in 1984[10]. Moreover, certain specific mutations are associated with small clusters of families in particular areas. For example, the TTR p.Ala97Ser (now p.Ala117Ser) mutation is common among Chinese kindreds from Taiwan [11–14]. Subsequently, the first FAP family with a proven missense mutation c.349G>T (p.Ala117Ser) in mainland China was reported in 2018[15]. This study aimed to determine the clinical features of FAP with TTR p.Ala117Ser by studying 13 Chinese families from mainland China. To date, our study is the largest population report on this rare p.Ala117Ser mutation in mainland China.

Subjects And Methods

Patients

Thirteen patients from 13 different families diagnosed with p.Ala117Ser ATTR-PN were identified from the Department of Neurology of three centers: Southern Medical University Nanfang Hospital, Peking University First Hospital, Central South University Third Xiangya Hospital, from September 2013 to September 2020. All patients conformed to the clinical and electrophysiologic criteria of idiopathic adult-onset axonal polyneuropathy: 1) length-dependent neuropathy with clinical evidence of limb weakness and sensory symptoms and 2) electrophysiologic evidence of axonal polyneuropathy on nerve conduction studies (NCS). All patients were confirmed of the mutation of p.Ala117Ser. Furthermore, the clinical and laboratory data were retrieved for analysis. Procedures of the tests (NCS, UCG, CSF examination, routine blood and urine examinations, genetic analysis, and nerve biopsies, etc) followed established protocols.

TTR gene analysis

Peripheral venous blood samples were obtained for DNA analysis from the patients. Genomic DNA was isolated from the blood samples following a standard protocol. Briefly, the 4 exons of the entire human *TTR* gene (NCBI Reference Sequence: NG_009490.1, NM_000371.3) were amplified by polymerase chain reaction (PCR). The PCR products were purified and sequenced directly by Sanger sequencing.

Electrophysiologic assessment

Neuroelectrophysiological assessment was done in all patients following standard procedures with surface stimulating and recording electrodes, including nerve conduction studies (orthodromic recording) of motor and sensory nerves at the lower and upper limbs in combination with the test of F wave. Motor conduction was investigated in the median, ulnar, tibial, and common peroneal nerve. Sensory conduction was investigated in the median, ulnar, superficial fibular, and sural nerves.

Nerve biopsy and pathological assessment

Sural nerve (or sensory branch of the superficial peroneal nerve) biopsy was performed under local skin and tissue anaesthesia, excluding the nerve. Nerve specimens were processed for routine stains (haematoxylin-eosin for overview and nerve morphology; Congo red for amyloid) on frozen sections and semi-thin sections (azure-methylene blue). Serial consecutive sections were assessed. Electron microscopy samples were fixed in a 2.5% glutaraldehyde buffer for 2h, then with osmium acid, dehydrated in acetone, and embedded with epoxy resin. The sections were observed under an electron microscope and photographed.

Statistical analyses

We used IBM SPSS Version 26 and Microsoft Office Excel. Descriptive statistics are mainly used in this study. Numeric variables are here described as means $\pm$ SD, numbers (n) with percentages (%) or median values, etc. Results were considered significant at $p < 0.05$.

Results

Clinical features

The basic information of the probands (11 males and 2 females) in the 13 families with p.Ala117Ser ATTR-PN is summarised in Table 1. All probands were from South China (see Figure 1). The age of onset was 57.8 ± 5.8 years (range 47–66). The time-period from the onset to the final diagnosis was 5.1 ± 3.8 years (range 1–13), and neurological assessments were performed at the time of diagnosis. Initial symptoms were numbness of the lower or upper extremities (9 patients), weakness of the lower limbs (1 patient), diarrhoea and constipation (1 patient), erectile dysfunction (1 patient), and chest tightness (1 patient). No cranial nerve defects, such as dysphagia, dysarthria, or atrophy of the tongue, were observed in any of the patients.

Table 1 The basic information of the probands with p.Ala117Ser ATTR-PN

Patient No.	Gender	Nationality	Age (years)		Interval (years)	Initial complaints	Muscle power upper/lower limbs		Tissue proof
			Diagnosis	Onset			Distal	Proximal	
1	M	Han	66	59	7	Numbness of upper extremities	3- / 2	4- / 4	None
2	M	Han	61	58	3	Numbness of limbs	5 / 4+	4+ / 3	None
3	M	Han	50	47	3	Diarrhea and constipation	5 / 5	5 / 5	Sural N/C+
4	M	Han	66	64	2	Chest tightness	5 / 5	5 / 5	None
5	M	Han	62	58	4	Numbness of upper extremities	1 / 2	3+ / 3+	Sural N/C+
6	M	Han	62	56	6	Weakness of lower extremities	1 / 2	4 / 4	Sural N/C+
7	M	Han	61	54	7	Erectile dysfunction	4- / 4-	4 / 5	Sural N/C+
8	M	Han	67	64	3	Numbness of lower extremities	NK / 0	4 / 4	Sural N/C+
9	M	Han	60	52	12	Numbness of upper extremities	5 / 5	5 / 5	Sural N/C+
10	M	Han	65	52	13	Numbness of upper extremities	4 / 3	4- / 4-	Sural N/C+
11	M	Han	59	57	2	Numbness of lower extremities	2 / 0	4- / 4-	SP N/C+
12	F	Han	68	65	3	Numbness of upper extremities	2 / 2	4- / 4-	SP N/C+
13	F	Han	67	66	1	Numbness of lower extremities	5 / 5	5 / 5	SP N/C+
Average			62.6 $\pm$ 4.8	57.8 $\pm$ 5.8	5.1 $\pm$ 3.8				

M: male. F: female. NK: unknown. None: without biopsy. Sural N: sural nerve. SP N: superficial peroneal nerve. C-: Congo red staining negative. C+: Congo red staining positive

The clinical manifestations are shown in Table 2. Nine patients suffered from muscular weakness and amyotrophy in the upper and lower limbs to varying degrees, in a distally accentuated manner. Paraesthesia was noted in all patients. Almost half of the patients experienced pain in the upper or lower limbs, although sensory dissociation was not conspicuous. Decreased tendon reflexes and carpal tunnel syndrome were prominent in most patients. Eleven patients complained of autonomic dysfunction during the duration of the disease. However, specific symptoms varied from patient to patient. Constipation was observed in 10 patients. Six of the 10 patients complained about alternating occurrences of diarrhea and constipation. Eleven patients experienced weight loss. Orthostatic hypotension was seen in four patients. Erectile dysfunction was observed in 8 /11 male patients. Only three patients had hyperhidrosis. One patient complained of disturbances in urination (urine retention). Additionally, involvement of other organs was seen in eight patients. Cardiac dysfunction was the most common (8 patients), specifically arrhythmia, cardiac hypertrophy, and symptomatic heart failure. Only 1 – 2 patients had hepatic and/or renal dysfunction (manifested by elevated liver enzymes and abnormal 24-hour urine protein quantification). Three patients experienced ocular dysfunction: decreased vision (3 patients), vitreous opacity (1 patient), and cataract (1 patient). However, none of the patients had glaucoma. Other symptoms included oedema (7 patients), dry cough (5 patients), and haemorrhagic rash (2 patients). The various system dysfunction scores of the probands are shown in Figure 2.

Table 2
The clinical manifestations of the probands with p.Ala117Ser ATTR-PN

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13	
<i>Case history</i>														<i>Total</i>
Hypertension	0	0	0	0 ^a	0	0	0	0	0	1	1	1	0	3
Diabetes mellitus	0	0	0	1 ^b	0	0	0	0	0	0	0	0	0	1
<i>Dysfunction of peripheral nerves</i>														<i>Total</i>
Paresthesia	1	1	1	1	1	1	1	1	1	1	1	1	1	13
Sensory dissociation	1	0	0	1	0	0	0	0	1	0	1	0	0	4
Allodynia	0	0	1	1	1	1	0	0	0	0	1	1	0	6
Distal weakness	1	1	0	0	1	1	1	1	0	1	1	1	0	9
Proximal weakness	1	1	0	0	1	1	1	1	0	1	1	1	0	9
Amyotrophy	1	1	0	0	1	1	1	1	0	1	1	1	0	9
Decreased reflexs	1	1	1	1	1	1	0	1	1	1	1	1	0	11
Carpal tunnel syndrome	1	1	1	1	1	1	1	1	1	1	1	1	1	13
<i>Autonomic dysfunction</i>														<i>Total</i>
Diarrhea	0	1	1	1	0	0	1	0	1	0	1	0	0	6
Constipation	0	1	1	1	1	1	1	0	1	0	1	1	1	10
Weight reduction	0	1	1	1	1	1	1	1	1	1	1	1	0	11
Orthostatic hypotension	0	0	0	0	1	0	1	0	1	1	0	0	0	4
Hyperhidrosis	0	0	0	1	0	0	1	0	0	0	1	0	0	3
Erectile dysfunction	NK	1	1	NK	1	1	1	0	1	1	1	NA	NA	8 (11)
Urine retention	1	0	0	0	0	0	0	0	0	0	0	0	0	1
<i>Involvement of other organs</i>														<i>Total</i>
Cardiac dysfunction														
Arrhythmia	1	1	0	0	0	1	1	1	1	1	0	1	0	8
Cardiac hypertrophy	0	1	1	1	0	1	1	1	0	1	0	1	0	8
Symptomatic heart failure	1	1	0	1	0	0	0	0	0	1	0	1	0	5
Hepatic dysfunction	0	0	0	0	0	0	0	0	0	1	0	1	0	2
Renal dysfunction	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Ocular dysfunction														
Vision loss	0	0	0	0	0	1	0	0	NK	1	NK	1	0	3
Vitreous opacity	0	0	0	0	0	1	0	0	NK	NK	NK	0	0	1
Cataract	0	0	0	0	0	0	0	0	NK	NK	NK	1	0	1
Glaucoma	0	0	0	0	0	0	0	0	NK	NK	NK	0	0	0
<i>Others</i>														<i>Total</i>
Edema	1	1	0	1	0	0	0	0	1	1	0	1	1	7
Dry cough	0	1	0	1	1	0	0	0	0	0	1	1	0	5

^a 1: with the symptom. ^b 0: without symptoms NA: not applicable. NK: unknown.

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13	
Hemorrhagic rash	0	0	0	0	0	0	0	0	1	1	0	0	0	2
a 1: with the symptom. b 0: without symptoms NA: not applicable. NK: unknown.														

Neurophysiological manifestations

NCS showed axonal-type sensorimotor polyneuropathy (detailed in Table 3). Most patients had long distal latency of the upper or lower extremities, but it was much smaller than the demyelinating lesion. All patients had reductions in the amplitudes of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) from mild to severe. It is worth noting that the decline in SNAP was more noticeable than that in CMAP. The nerve damage of the lower limbs was more severe than that of the upper limbs. The SNAP of most of the lower extremities was not observed. Additionally, a decrease in the F wave was observed in nearly all tested nerves.

Table 3
The NCS of the probands with p.Ala117Ser ATTR-PN

Patient No.	Age (years)	DL (mS) R/L		CMAP (mV) R/L				SNAP (μV) R/L				F wave(%) R/L	
		Median	Tibal	Median	Ulnar	Tibal	Peroneal	Median	Ulnar	Peroneal	Sural R/L	Median	Tibal
1	66	6.1 / NR	NR / NR	1.0 / 3.4	0.6 / 2.0	NE / NE	NE / NE	NE / NE	NE / NE	NR / NR	NE / NE	6 / 12	0 / 0
2	61	NR / 6.3	NE / 7.2	NR / 1.6	NR / 3.9	NE / 0.5	0.1 / 0.4	NR / NE	NR / NE	NE / NE	NR / NR	NR/ NR	NR / NR
3	50	4.5 / NR	4.6 / 5.2	4.4 / NR	4.6 / NR	2.5 / 1.5	2.0 / 1.4	0.3 / NR	7.3 / NR	NR / NR	2.2 / 2.4	NR / NR	NR / NR
4	66	4.9 / 4.8	5.4 / 4.6	5.9 / 5.1	5.1 / NR	1.2 / 2.3	1.0 / NR	NE / NE	NE / NE	NE / NE	0.6 / NR	↓ / ↓	↓ / ↓
5	62	2.4 / 1.9	5.4 / 5.7	2.4 / 2.7	4.9 / 3.2	2.2 / 4.2	1.8 / 2.5	0.4 / NE	0.7 / NE	NR / NR	NE / 0.4	100 / 0	NR / NR
6	62	NE / 5.5	NR / NR	NE / 1.1	2.6 / 0.9	NR / NR	NE / NE	NE / NE	NE / NE	NE / NE	NE / NE	NR / NR	NR / NR
7	61	3.9 / 3.4	5.7 / 3.1	5.4 / 7.3	5.1 / NR	2.6 / 11.1	1.2 / NR	NE / 2.6	NE / 2.6	NE / NR	NR / NR	NE / NR	NR / NR
8	67	3.0 / 2.8	8.2 / NE	1.7 / 1.5	4.1 / 1.1	0.3 / NE	NE / NE	NE / NE	NE / 1.3	NR / NR	NE / NE	0 / 100	NR / NR
9	60	6.5 / 4.5	4.5 / 3.8	4.2 / 7.3	1.8 / 3.7	1.4 / 4.8	0.4 / 0.1	NE / NR	NE / NR	NR / NR	NE / NR	NR / 56.3	NR / NR
10	65	NR / 4.1	NE / 4.3	NR / 3.3	NR / 6.9	NE / 0.1	0.3 / 0.2	NR / NE	NR / 9	NR / NR	NE / NE	NR / 43.8	NR / 0
11	59	6.5 / NR	NE / NE	0.9 / NR	2.5 / NR	NE / NE	NE / NE	NE / NE	NE / NE	NR / NR	NE / NE	55.0 / NR	0 / 0
12	68	5.8 / NE	4.2 / 3.3	1.3 / NE	1.6 / 3.1	0.5 / 2.0	0.1 / NE	NE / NE	NE / NE	NE / NE	NE / 1.2	95.0 / NR	NR / 55.0
13	67	NR / 4.2	4.4 / 5.1	NR / 10.5	NR / 12.7	3.4 / 4.2	NE / 2.6	NR / 10.7	NR / 11.1	NE / NE	NE / NE	NR / NR	NR / 94.4
Normal value	55 - 64	<4.1	<5.1	>7	>7	>4	>3	>12.7	>6.9	>0.6	>1.6	>73	>80
	65 - 74	<4.2	<5.1	>6	>7	>4	>3	>10.7	>6.8	>0.5	>1.2	>73	>80
NCS, nerve conduction studies DL: distal latency. CMAP: compound motor action potential. SNAP: sensory nerve action potential. NR: not recordable. NE: not elicited. ↓: decreased (specific value is unknown).													

Histopathological findings

Ten patients underwent a sural or peroneal nerve biopsy. The main pathological changes in peripheral nerves were moderately to severely decreased myelinated and unmyelinated nerve fibres, accompanied by degenerative or regenerative changes in the axons and myelin sheath

of myelinated nerve fibres, which is in accordance with the pathological characteristics of chronic active mixed peripheral neuropathy. Nerve biopsy revealed positive Congo red staining in 7/10 patients (70%). Congo red staining showed multiple red-stained amyloid deposits and bright apple green coloration under a polarising microscope. Axonal degeneration of green substances was found in some large myelinated fibres by MGT staining. The histopathologic findings of patient no. 10 are showed in Figure 3.

Discussion

The occurrence of ATTR-PN is relatively rare in China. In the 1990s, a family with ATTR-PN was first diagnosed at the Peking Union Medical College Hospital [16]. It is estimated that there are approximately 1997 cases in China (ranging from 435 to 10134) [17]. Over 40 case reports have been published in recent years, including reports of multiple ATTR-PN families. Studies describe a mutation in the *TTR* gene, which is different from that observed in Europe [18–21]. Shortly before, a unicentric retrospective study reported that TTR p.Val30Met remains the most common mutation type in mainland China[22]. However, TTR p.Ala117Ser mutations are relatively rare. Based on previous studies, the TTR p.Ala117Ser mutation was one of the most common variants in the Chinese population, especially in Chinese kindreds from Taiwan. This mutation has never been reported in Caucasian populations. Detailed haplotype analyses demonstrated a shared haplotype in most patients with the p.Ala117Ser mutation in Taiwan, suggesting a founder effect[23]. Except for the first report of the FAP family with a proven *TTR* p.Ala117Ser mutation from mainland China[15], our study reported another 13 pedigrees with the same mutation. Furthermore, all probands came from Southern China, including Hunan and Guangdong Province. We speculate that the TTR p.Ala117Ser mutation first originated in mainland China despite the lack of genetic verification.

Our study demonstrated the characteristics of ATTR-PN with the TTR p.Ala117Ser mutation in mainland China. Similar to previous reports, there were significantly more men than women diagnosed with this mutation. It is unclear whether there are protective factors in women. The Ala117Ser patients showed late onset – almost all were over 50 years of age. It was different from Val30Met patients, which showed early or late onset [24]. The course from the onset to final diagnosis ranged from 1 to 13 years, while there was no significant correlation between this and the severity of clinical manifestations. Numbness of the lower or upper extremities was one of the most common initial symptoms.

Because of its insidious onset, the diagnosis of this disease is usually delayed, rendering treatment difficult. Apart from peripheral nerve dysfunction, autonomic dysfunction was also particularly prominent. Constipation was more common than orthostatic hypotension, and it (constipation) often manifested as alternating between diarrhoea and constipation. Remarkably, almost all males had erectile dysfunction at an early stage, which is an important feature that differentiates them from female patients. Cardiac dysfunction was the most common involvement of other organs. One of the 13 patients died of a cardiac incident shortly after the diagnosis. A unique phenotype of ATTR-PN has been reported in a case report describing a distinctive chronic dry cough [15]. In our study, five patients had similar symptoms. It occurred at different stages of the disease. Further research is needed to confirm this mechanism. Although nerve biopsy helped diagnose the disease, not all patients in our study underwent a nerve biopsy. Only 7/10 (70%) patients showed positive Congo red staining. Patients with ATTR-PN negative Congo red staining might get misdiagnosed. Neurophysiological examinations also helped with the diagnosis. The final diagnosis was based on genetic and pathological examinations.

In addition, many factors, such as the rarity of the disease in the general population, physicians' lack of understanding of various clinical features, and limited diagnostic tools (i.e. histopathology and gene screening) lead to a high misdiagnosis rate and poor prognosis. ATTR-PN is often misdiagnosed as chronic idiopathic axonal polyneuropathy, chronic inflammatory demyelinating polyneuropathy, and lumbar spinal stenosis. Diabetes or chronic alcoholism may cause polyneuropathies such as ATTR-PN. It may also be misdiagnosed as Charcot-Marie-Tooth or motor neuron disease. Delayed diagnosis is the main obstacle to the optimal management of ATTR-PN in China. There is usually an interval of several years from the initial clinical symptoms of the disease to the final diagnosis. Because of the significant unmet medical needs for this rare and fatal disease, there is an urgent need to raise disease awareness to facilitate early diagnosis and timely treatment.

Conclusion

In this study, we described the characteristics of ATTR-PN with TTR p.Ala117Ser mutation. To date, our study is the largest population report on this rare mutation in mainland China. However, a large-scale study is needed to explore a complete picture of the disease.

Declarations

Availability of data and materials

The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.. All data generated and analyzed during this study are included in this article.

Funding

Supported by grants from the Guangdong Provincial Natural Science Foundation (#2016A030313579) to H.J.

Acknowledgements

We thank the patients who participated in this study. We thank the professors of Peking University First Hospital, Third Xiangya Hospital of Central South University, for providing valuable cases. We thank the technicians in the Neuromuscular Pathologic Team, Electron Microscope Room, and Neurophysiology Room of Nanfang Hospital of Southern Medical University, Department of Neurology, for their assistance.

Author Information

Affiliations

Department of Neurology, Southern Medical University Nanfang Hospital, Southern Medical University, Guangzhou, China

Yeli Zhu, Wei Li, Zhaoyong Zhang, Hui Zheng, Haishan Jiang

Department of Neurology, Central South University Third Xiangya Hospital, Central South University, Hunan, China

Xiying Zhu, Ruxu Zhang

Department of Neurology, Peking University First Hospital, Peking University, Beijing, China

Lingchao Meng

Contributions

YZ and XZ wrote and edited the manuscript. WL contributed pathological assessment. ZZ and HZ designed the figures and tables. LM, RZ and HJ provided clinical samples and information.

Corresponding Author

Correspondence to Lingchao Meng, Ruxu Zhang & Haishan Jiang

Ethics declarations

Ethics approval and consent to participate

Approved by Medical Ethics Committee of Southern Medical University Southern Hospital.

Consent for publication

Not applicable.

Competing interests

None declared.

Additional information

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. *Nat Rev Neurol*. 2019 Jul;15(7):387–404.
2. ANDRADE C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. *Brain*. 1952 Sep;75(3):408–27.

3. Araki S, Mawatari S, Ohta M, Nakajima A, Kuroiwa Y. Polyneuritic amyloidosis in a Japanese family. *Arch Neurol*. 1968 Jun;18(6):593–602.
4. Andersson R. Familial amyloidosis with polyneuropathy. A clinical study based on patients living in northern Sweden. *Acta Med Scand Suppl*. 1976;590:1–64.
5. Ryu JK, Baik HW, Bae JS, Hwang TJ, Paik SY, Yu HJ, Choi BO, Takei Y, Ikeda S. Familial amyloid polyneuropathy in Korea: the first case report with a proven ATTR Lys35Asn gene. *Amyloid*. 2005 Mar;12(1):62–4.
6. Zhen DB, Swiecicki PL, Zeldenrust SR, Dispenzieri A, Mauermann ML, Gertz MA. Frequencies and geographic distributions of genetic mutations in transthyretin- and non-transthyretin-related familial amyloidosis. *Clin Genet*. 2015 Oct;88(4):396–400.
7. Liu G, Ni W, Wang H, Li H, Zhang Y, Wang N, Wu Z. Clinical features of familial amyloid polyneuropathy carrying transthyretin mutations in four Chinese kindreds. *J Peripher Nerv Syst*. 2017 Mar;22(1):19–26.
8. Parman Y, Adams D, Obici L, Galán L, Guergueltcheva V, Suhr OB, Coelho T, European Network for TTR-FAP (ATTReuNET). Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. *Curr Opin Neurol*. 2016 Feb;29(Suppl 1(Suppl 1):3–13.
9. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve*. 2007 Oct;36(4):411–23.
10. Saraiva MJ, Birken S, Costa PP, Goodman DS. Family studies of the genetic abnormality in transthyretin (prealbumin) in Portuguese patients with familial amyloidotic polyneuropathy. *Ann N Y Acad Sci*. 1984;435:86–100.
11. Liu YT, Lee YC, Yang CC, Chen ML, Lin KP. Transthyretin Ala97Ser in Chinese-Taiwanese patients with familial amyloid polyneuropathy: genetic studies and phenotype expression. *J Neurol Sci*. 2008 Apr 15;267(1-2):91–9.
12. Yang NC, Lee MJ, Chao CC, Chuang YT, Lin WM, Chang MF, Hsieh PC, Kan HW, Lin YH, Yang CC, Chiu MJ, Liou HH, Hsieh ST. Clinical presentations and skin denervation in amyloid neuropathy due to transthyretin Ala97Ser. *Neurology*. 2010 Aug;10(6):532–8. 75(.
13. Chao CC, Huang CM, Chiang HH, Luo KR, Kan HW, Yang NC, Chiang H, Lin WM, Lai SM, Lee MJ, Shun CT, Hsieh ST. Sudomotor innervation in transthyretin amyloid neuropathy: Pathology and functional correlates. *Ann Neurol*. 2015 Aug;78(2):272–83.
14. Hsu HC, Liao MF, Hsu JL, Lo AL, Kuo HC, Lyu RK, Wu VC, Wang CW, Ro LS. Phenotypic expressions of hereditary Transthyretin Ala97Ser related Amyloidosis (ATTR) in Taiwanese. *BMC Neurol*. 2017 Sep;7(1):178. 17(.
15. Yuan Z, Guo L, Liu X, Xiao X, Jiao B, Wang J, Yan X, Tang B, Shen L. Familial amyloid polyneuropathy with chronic paroxysmal dry cough in Mainland China: A Chinese family with a proven heterozygous missense mutation c.349G>T in the transthyretin gene. *J Clin Neurosci*. 2019 Feb;60:164–6.
16. Guan HZ, Liu Q, Chen L, Qian M, Liu Z, Guan YZ, Ren HT, Zhao YH, Chen M, Tian Z, Zou X, Cui LY. The clinical, pathological and genetic studies of transthyretin familial amyloid polyneuropathy. *Chin J Neurol*. 2015;48(1):7–12.
17. Schmidt HH, Waddington-Cruz M, Botteman MF, Carter JA, Chopra AS, Hopps M, Stewart M, Fallet S. & Amass L. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. *Muscle Nerve*. 2018 May;57(5):829–37.
18. Liu JY, Guo YJ, Zhou CK, Ye YQ, Feng JQ, Yin F, Jiang XM. Clinical and histopathological features of familial amyloidotic polyneuropathy with transthyretin Val30Ala in a Chinese family. *J Neurol Sci*. 2011 May;15(1-2):83–6. 304(.
19. Meng LC, Lyu H, Zhang W, Liu J, Wang ZX, Yuan Y. Hereditary Transthyretin Amyloidosis in Eight Chinese Families. *Chin Med J (Engl)*. 2015 Nov;5(21):2902–5. 128(.
20. Chen H, Zhou X, Wang J, Wang X, Liu L, Wu S, Li T, Chen S, Yang J, Sham PC, Zhu G, Zhang X, Wang B. Exome Sequencing and Gene Prioritization Correct Misdiagnosis in a Chinese Kindred with Familial Amyloid Polyneuropathy. *Sci Rep*. 2016 May;23:6:26362.
21. Liu G, Ni W, Wang H, Li H, Zhang Y, Wang N, Wu Z. Clinical features of familial amyloid polyneuropathy carrying transthyretin mutations in four Chinese kindreds. *J Peripher Nerv Syst*. 2017 Mar;22(1):19–26.
22. Du K, Li F, Wang H, Miao Y, Lv H, Zhang W, Wang Z, Yuan Y, Meng L. Hereditary transthyretin amyloidosis in mainland China: a unicentric retrospective study. *Ann Clin Transl Neurol*. 2021 Apr;8(4):831–41.
23. Chao HC, Liao YC, Liu YT, Guo YC, Chang FP, Lee YC, Lin KP. Clinical and genetic profiles of hereditary transthyretin amyloidosis in Taiwan. *Ann Clin Transl Neurol*. 2019 Apr 9;6(5):913–922.
24. Misu Ki, Hattori N, Nagamatsu M, Ikeda Si, Ando Y, Nakazato M, Takei Yi, Hanyu N, Usui Y, Tanaka F, Harada T, Inukai A, Hashizume Y, Sobue G. Late-onset familial amyloid polyneuropathy type I (transthyretin Met30-associated familial amyloid polyneuropathy) unrelated to endemic focus in Japan. *Clinicopathological and genetic features*. *Brain*. 1999 Oct;122(Pt 10):1951–62.

Figures

Figure 1

Geographical distribution of the probands with p.Ala117Ser ATTR-PN. The dark blue above: Hunan province, China. The gray below: Guangdong province, China. The pink dots: the 13 probands based on Table 1.

Figure 2

Various systems dysfunction scores of the probands with p.Ala117Ser ATTR-PN. P1-13: No. 1-13 patient. Radar Map (a) and Line Chart (b) shows the various system dysfunction scores of all patient based on Table 2. One point for each of the following symptoms: Paresthesia, Sensory dissociation, allodynia, weakness, amyotrophy, decreased reflexes, carpal tunnel syndrome, diarrhea, constipation, weight reduction, orthostatic hypotension, hyperhidrosis, erectile dysfunction, urine retention, arrhythmia, cardiac hypertrophy, symptomatic heart failure, hepatic dysfunction, renal dysfunction, vision loss, vitreous opacity, cataract, glaucoma.

Figure 3

Histopathologic findings of No.10 Patient. Multiple red-stained amyloid deposits were observed by HE (a) and Congo red staining (c). Axonal degeneration of green substances was found in some large myelinated fibres by MGT staining (b). Moderately to severely decreased unmyelinated nerve fibres in each nerve bundle were showed by NF staining (d).