Clinical and genetic profiles of hereditary transthyretin amyloidosis in Taiwan

Hua-Chuan Chao1,2, Yi-Chu Liu3,4, Yo-Tsen Liu3,4,5,6, Yuh-Cherng Guo7,8, Fu-Pang Chang2,9, Yi-Chung Lee3,4,5 & Kon-Ping Lin3,4

1Division of Neurology, Department of Medicine, Taipei Veterans General Hospital, Taoyuan branch, Taoyuan, Taiwan
2Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan
3Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan
4Department of Neurology, National Yang-Ming University School of Medicine, Taipei, Taiwan
5Brain Research Center, National Yang-Ming University, Taipei, Taiwan
6Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan
7Neuroscience Laboratory, Department of Neurology, China Medical University Hospital, Taichung, Taiwan
8School of Medicine, Medical College, China Medical University, Taichung, Taiwan
9Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

Correspondence
Kon-Ping Lin and Yi-Chung Lee, No. 201, Sec.2, Shihpai Road, Peitou District, Taipei, 112, Taiwan, R.O.C. Tel: +886-2-28757585; Fax: +886-2-28757584; E-mails: ycliu@vghtpe.gov.tw and kplin@vghtpe.gov.tw

Abstract

Objective: The clinical and genetic profiles of hereditary transthyretin amyloidosis (ATTR) in Chinese populations remain elusive. We aim to characterize the features of ATTR in a Taiwanese cohort of Han Chinese descent. Methods: Seventy-nine patients with molecularly confirmed ATTR from 57 Taiwanese families were identified by sequencing the transthyretin gene (TTR). The clinical and electrophysiological data were scrutinized. Cardiac involvement of ATTR was evaluated by echocardiography and cardiac scintigraphy. Four microsatellite and seven single-nucleotide polymorphism markers flanking TTR were genotyped to investigate the founder effect of the TTR Ala97Ser mutation. Results: Most of the patients had a peripheral neuropathy with variable autonomic symptoms. The average age at disease onset (AO) was 58.2 ± 7.2 years, and the male patients had an earlier AO than female patients (56.6 ± 5.7 years vs. 61.8 ± 8.9 years, P = 0.013). Electrophysiological studies revealed a generalized axonal sensorimotor polyneuropathy and isolated median neuropathy in 84.5% and 15.5% of the patients, respectively. Up to 80% of the patients with ATTR had symptomatic or subclinical cardiac involvement. Six TTR mutations were identified in the participants including one novel mutation Glu89Asp. Among them, Ala97Ser was the most common mutation, accounting for 91.2% of the ATTR pedigrees. Detailed haplotype analyses demonstrated a shared haplotype in the 47 patients with the Ala97Ser mutation, suggesting a founder effect. Interpretation: The present study delineates the distinct features of ATTR in Taiwan and provides useful information for the diagnosis and management of ATTR, especially in patients of Chinese descent.

Introduction

Hereditary transthyretin amyloidosis (ATTR) is an autosomal-dominantly inherited disorder caused by a mutation in the transthyretin gene (TTR), which alters the biochemical property of transthyretin to increase its propensity to be misfolded and lead to formation of pathologic amyloid aggregates. ATTR preferentially manifests with peripheral and autonomic neuropathy, also known as familial amyloidotic polyneuropathy (FAP); however, it may also involve other vital organs.1,2 Cardiac transthyretin amyloidosis, another important phenotype of ATTR, is a devastating cardiomyopathy characterized by concentric ventricular thickening, low cardiac output, atrial dilatation, and disturbed conduction system.3 Usually, ATTR patients may develop both cardiac and neuropathic phenotypes during their disease courses.4
More than 120 TTR mutations have been reported worldwide, and there are considerable genotype-phenotype variations among different ethnic groups.\textsuperscript{3} TTR Val30Met is the most common variant in the Portuguese, Swedish, and Japanese populations,\textsuperscript{1} while Val122Ile mutation is endemic in African-Americans.\textsuperscript{5,6} Patients harboring TTR Val30Met mutation usually present with peripheral neuropathy, but those carrying the Val122Ile mutation commonly manifest with late-onset cardiomyopathy.\textsuperscript{3} TTR Thr60Ala, the most common TTR mutation in the United Kingdom population, is associated with early cardiac involvement, autonomic dysfunction and peripheral neuropathy of variable severity.\textsuperscript{7,8} To be noticed, certain TTR mutations, such as Leu58His, Ile84Ser, and Tyr114His, are associated with neuropathy starting in the upper limbs as carpal tunnel syndrome (CTS).\textsuperscript{1} These findings suggest a broad genetic and phenotypic spectrum in ATTR and stress on the importance of clarifying the ethnic-specific spectrum of TTR mutations and the corresponding phenotype-genotype correlations.

There may be a distinct spectrum of TTR mutations in Taiwan. Several small-scaled studies only identified the Ala97Ser mutations in Taiwanese patients with FAP,\textsuperscript{9–12} and this mutation has never been reported in Caucasian populations. Furthermore, 98% of Taiwanese populations are of Han Chinese descent and there is no large cohort study about ATTR in Chinese populations. Hence, it is intriguing and important to have a comprehensive knowledge of genotypic and phenotypic spectrum of TTR mutations in Taiwan, which may help diagnosis and management of ATTR, especially in patients of Chinese descent.

In this study, we characterized the clinical and genetic features of 79 Taiwanese patients with ATTR, including the cardiac manifestations. We also investigated the founder effect of the TTR Ala97Ser mutation.

**Materials and Methods**

**Subjects**

A consecutive series of 79 individuals with ATTR from 57 pedigrees of Han Chinese descent were recruited from the Neurological Service in Taipei Veterans General Hospital, which is a 2947-bed national medical center in Taiwan, serving both veterans and regular citizens and accepting difficult neuromuscular disease cases referrals. The diagnosis of ATTR was based on the consensus from the European Network for TTR-FAP (ATTReuNET).\textsuperscript{13} All the 79 participants had peripheral neuropathy with variable motor, sensory, and autonomic symptoms as well as a pathogenic TTR mutation. Another two asymptomatic gene carriers with a TTR Ala97Ser mutation were enrolled for the cardiac scintigraphic imaging study. The study was approved by the institutional review board of the Taipei Veterans General Hospital, and written informed consent was obtained from all participants.

**Clinical evaluation, disability assessment and electrophysiology**

The presence of relevant symptoms and neurological findings were recognized by detailed clinical evaluation, including history taking, medical record review, and physical examination. DN4 questionnaire, consisting of ten items with a total score of 10, was used to assess neuropathic pain with a cut-off value ≥ 4 points.\textsuperscript{14} In addition, the clinical functional status and the severity of disability were evaluated according to the clinical stages of Transthyretin Familial Amyloidotic Polyneuropathy (TTR-FAP) with a scale of 0 to III (stage 0, no symptoms; stage I, unimpaired ambulation, mostly with mild sensory, motor, and autonomic neuropathy in the lower limbs; stage II, assistance for ambulation required, mostly with a moderate motor, sensory, and autonomic impairment of the four limbs; stage III, wheelchair-bound or bedridden status with severe sensory, motor, and autonomic involvement of all limbs).\textsuperscript{15}

Electrophysiological studies were performed using a Medlec electromyograph. Our patients underwent motor nerve conduction studies in the upper and lower extremities, including median, ulnar, tibial, and peroneal nerves. Ring electrode recordings were carried out to assess sensory conduction of the median, ulnar, and sural nerves. The parameters, including distal latency, nerve conduction velocity, amplitude of compound muscle action potential, amplitude of sensory action potential, and minimal F response, were recorded.

**Cardiac evaluation**

Echocardiography was performed with two-dimensional and M mode settings. Left ventricular (LV) wall thickening, systolic function, diastolic function, and left atrial (LA) diameter were measured. To evaluate cardiac amyloidosis, the cardiac single photon emission computed tomography with computed tomography (SPECT/CT) and \textsuperscript{99m}Technetium-pyrophosphate (\textsuperscript{99m}Tc-PYP) scintigraphy were performed after intravenous injection of 15 mCi \textsuperscript{99m}Tc-PYP for 1 h and 3 h, respectively. Myocardial PYP uptake was rated by semi-quantitative visual grading with the isotope intensity of rib as reference:\textsuperscript{16,17} Grade 0: no uptake and normal bone uptake; Grade 1: uptake less than rib uptake; Grade 2: uptake equal to rib uptake; Grade 3: uptake greater than rib uptake with mild or absent rib uptake.
Pathological diagnosis of amyloidosis was achieved in nine patients, including five with sural nerve biopsies, three with rectal biopsies, and one with bronchoalveolar lavage and bronchoscopic biopsy. Sections from paraffin-embedded biopsied tissues were stained with hematoxylin-eosin (H-E) and Congo red. Optical microscopy with polarized light was used to detect amyloid deposition. The presence of a pathogenic mutation in TTR, a family history, and either a typical clinical manifestation or pathological confirmation in another family member was sufficient for diagnosis of ATTR.

### Genetic analysis

Genomic DNA was isolated from white blood cells. Mutation analyses were performed by polymerase chain reactions (PCR) amplification using intronic primers and Sanger sequencing. The intronic primers used to amplify all the exons of TTR were described previously. All amplicons were sequenced for both sense and antisense strands using the Big Dye 3.1 dideoxy terminator method (Applied Biosystems, Foster City, CA) on an ABI Prism 3700 Genetic Analyzer (Applied Biosystems). Mutations were identified by aligning the amplicon sequences with the published human TTR coding sequence (RefSeq NM_000371.3).

### Haplotype analysis

To investigate whether there is a founder effect for the TTR Ala97Ser mutation, the haplotype analysis was performed in fifteen families carrying the mutation. Four polymorphic microsatellite and seven single nucleotide polymorphism (SNP) markers flanking TTR and covering a region of 1.5 Mb were genotyped. These markers are D18S49, rs12709651, rs7232282, rs7231553, D18S1242, rs1080093, rs1080094, rs8098191, D18S2021, rs614342, and D18S457. The first seven makers are centromeric and the following four markers are telomeric to TTR. All the information regarding these markers were obtained from the Genome Data Viewer (http://www.ncbi.nlm.nih.gov/genome/gdv/browser/).

### Statistical analysis

The demographic data of the participants were included for descriptive statistics. For inferential statistics, continuous variables were compared between two defined groups using Student’s t-test, while categorical variables were compared using Chi-square test or Fisher’s exact test where appropriate. A P-value less than 0.05 in a two-tailed test was considered to be statistically significant.

### Results

#### Clinical manifestations and electrophysiological findings

The demographic data and clinical features of the 79 ATTR patients are shown in Table 1. The mean age at onset (AO) was 58.2 ± 7.2 years (range: 40–75 years). The mean disease duration from symptom onset to first neurological evaluation was 4.1 ± 3.6 years (range: 0–13 years). The male participants had a significantly earlier AO than the female patients did (56.6 ± 5.7 vs. 61.8 ± 8.9, P = 0.013). The first symptoms usually were sensory abnormalities over bilateral upper limbs as carpal tunnel syndrome (CTS) (43%), asymmetric sensory symptoms presenting as radiculopathy pattern (13.9%), and symmetric sensory-motor complaints (13.9%). At evaluation, 81% of the patients had sensory-motor symptoms, and up to 70% had autonomic symptoms. Electrophysiological studies revealed generalized axonal sensorimotor polyneuropathy and isolated neuropathy in 84.5% and 15.5% of the patients, respectively. Approximately half of the Taiwanese ATTR patients had severe functional disability at the time of diagnosis, including 36.7% having impaired ambulation (FAP stage II) and another 13.9% being wheel-chair bound (FAP stage III). Furthermore, 22.8% of them had bulbar dysfunction and 44.3% had more than 5% of body weight loss within 6 months before diagnosis.

#### Conventional cardiac evaluation and cardiac scintigraphic imaging

Only 5.1% of the ATTR patients reported cardiac symptoms as their first manifestations. However, up to 30% of all patients had heart failure or cardiac arrhythmia at the time of diagnosis (Table 1). Thirty-eight participants underwent echocardiography, and cardiac involvement was found in 73.7% of them with the findings of concentric left ventricular hypertrophy (CLVH), asymmetric septal hypertrophy, granular sparkling appearance of myocardium or systolic dysfunction.

Sixteen patients with ATTR and two asymptomatic gene carriers with a TTR Ala97Ser mutation received 99mTc-PYP scintigraphy. We categorized these participants into three groups according to the presence of neuropathy and cardiac symptoms. Group 1 included three patients with neuropathy and class 2 or more severe heart failure defined by New York Heart Association Functional Classification (NYHA Fc) (ATTR with HF). Group 2 contained...
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Table 1. Demographic data and clinical characterization of ATTR patients in Taiwan

| Demographics                  | Mean (SD) or patient number (%) | ATTR patients (n = 79) |
|-------------------------------|---------------------------------|------------------------|
| Demographics                  |                                 |                        |
| Male                          | 55 (69.6%)                      |                        |
| Family History                | 63 (79.7%)                      |                        |
| Age at onset (y)              | 58.2 (7.2)                      |                        |
| Age at evaluation (y)         | 62.3 (7.2)                      |                        |
| First symptoms1               |                                 |                        |
| Sensory symptoms of ULs       | 34 (43%)                        |                        |
| Sensory, asymmetry            | 11 (13.9%)                      |                        |
| Sensory-motor                 | 11 (13.9%)                      |                        |
| Sensory, symmetry             | 9 (11.4%)                       |                        |
| Motor                         | 5 (6.3%)                        |                        |
| Heart                         | 4 (5.1%)                        |                        |
| Autonomic symptoms            | 4 (5.1%)                        |                        |
| Generalized                   | 1 (1.3%)                        |                        |
| Presentation at evaluation    |                                 |                        |
| Sensory-motor                 | 64 (81.0%)                      |                        |
| Autonomic dysfunction         | 55 (69.6%)                      |                        |
| Neuropathic paral (DN4)       | 48 (60.8%)                      |                        |
| Body weight loss              | 35 (44.3%)                      |                        |
| Heart                         | 24 (30.4%)                      |                        |
| Heart failure                 | 15 (19.0%)                      |                        |
| Cardiac arrhythmia            | 11 (13.9%)                      |                        |
| Bulbar symptoms               | 18 (22.8%)                      |                        |
| Sensory                       | 13 (16.5%)                      |                        |
| Motor                         | 2 (2.5%)                        |                        |
| Clinical severity             |                                 |                        |
| (FAP stage)                   |                                 |                        |
| Stage I                       | 39 (49.4%)                      |                        |
| Stage II                      | 29 (36.7%)                      |                        |
| Stage III                     | 11 (13.9%)                      |                        |
| Electrophysiology             |                                 |                        |
| Isolated median neuropathy    | 11 (15.5%)                      |                        |
| Axonal sensorimotoropathy     | 60 (84.5%)                      |                        |
| Abnormal Echocardiography     | 28 (73.7%)                      |                        |

1 Sensory symptoms of ULs: symmetrically distal sensory symptoms of upper limbs as carpal tunnel syndrome; Sensory, asymmetry: asymmetric sensory symptoms of upper or lower limbs, referred as a radiculopathy pattern; Sensory-motor: symmetrically distal sensory-motor symptoms of four limbs; Motor: exclusive weakness or clumsiness involving upper or lower limbs; Autonomic symptoms: one of related symptoms including orthostatic intolerance, gastrointestinal symptoms (diarrhea, constipation, or alternative symptoms), urinary bladder dysfunction (dysuria and catheterization), impotence, hypohidrosis or anhidrosis; Generalized: symmetric sensory-motor complaints and autonomic symptoms.

2 EF, left ventricular ejection fraction; IVS/PW, interventricular septal thickness/posterior wall thickness.

13 ATTR patients with neuropathy but no clinically evident heart failure. Group 3 consisted of two asymptomatic carriers. Their clinical information, neuropathy pattern and scintigraphic grading were demonstrated (Table 2). The clinical severity between the ATTR patients with or without heart failure was similar in their FAP staging. Significant amyloid deposition was identified in all the patients with heart failure and in 76.9% of patients without clinically evident heart failure. The two asymptomatic gene carriers both had an intermediate degree of cardiac amyloid deposition on 99mTc-PYP scan. Furthermore, there was no significant association between the pattern of peripheral nerve involvement and severity of cardiac amyloid deposition.

Mutational analysis of Taiwanese ATTR patients

Mutation analysis of the 57 Taiwanese ATTR pedigrees revealed six missense TTR mutations, including Ala45Thr (c.193G>A), Thr60Ala (c.238A>G), Ile73Val (c.277A>G), Ser77Try (c.290C>A), Glu89Asp (c.327G>T), and Ala97Ser (c.349G>T) (Fig. 1A). All the six mutations were present with a heterozygous form. The Glu89Asp mutation was novel, and the other five mutations had been reported as pathogenic mutations before. The Ala97Ser was the most common mutation in this ATTR cohort, accounting for 52 of the 57 ATTR pedigrees (91.2%). The pedigrees harboring the other five TTR mutations were demonstrated in Fig. 1B. The clinical characteristics of patients with different TTR mutations were shown in Table 3.

Several lines of evidence support the pathogenicity of the TTR Glu89Asp mutation. First, the mutation is not present in the 157,436 exome, and 15,708 whole-genome sequences from unrelated individuals in the Genome Aggregation Database (gnomAD) as well as the genome data of 1517 Taiwanese. Second, two different mutations at the same Glu89 amino acid residue, including Glu89Gln and Glu89Lys, had been identified as pathogenic mutations for ATTR. Third, two of the three popular bioinformatics tools for predicting the pathogenicity of nucleotide variants support the pathogenic role of TTR Glu89Asp. MutationTaster (http://www.mutationtaster.org) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2) predicted TTR Glu89Asp as a disease-causing variant, whereas SIFT (https://sift.bii.a-star.edu.sg) predicted it as a tolerated one. Fourth, the patient with the Glu89Asp mutation has a typical phenotype and pathological finding of ATTR, which is highly specific for TTR mutations. Therefore, TTR Glu89Asp is classified as a likely pathogenic variant according to the American College of Medical Genetics and Genomics (ACMG) guideline.26
Clinical information of the patient carrying the TTR Glu89Asp mutation

The patient with the TTR Glu89Asp mutation presented with distal paresthesia since age 59 years and intermittent chest tightness, diarrhea, and erectile dysfunction since age 64. Progressively ascending numbness, tingling pain and weakness of four limbs accompanying with loss of body weight up to 12 kg developed in the following 2 years. He was wheelchair-bound by age 68. The neurological examination at age 66 revealed severe hypophonia, generalized areflexia, weakness and muscle wasting and impaired sensation of all modalities in the distal four limbs. The nerve conduction study showed severe axonal polyneuropathy (Table S1). The sympathetic skin responses (SSR) were absent over lower limbs and diminished with prolonged latencies over upper limbs. The heart rate variability test revealed decreased variability on

Table 2. Clinical information of the individuals receiving scintigraphic analysis of cardiac involvement.

|                  | ATTR with HF | ATTR without HF | Asymptomatic carriers |
|------------------|--------------|-----------------|-----------------------|
|                  | n = 3        | n = 13          | n = 2                 |
| Male (%)         | 2 (66.7%)    | 9 (69.2%)       | 0                     |
| FAP stage        |              |                 |                       |
| Stage 1          | 2 (66.7%)    | 9 (69.2%)       | 0                     |
| Stage 2 & 3      | 1 (33.3%)    | 4 (30.8%)       | 0                     |
| PYP scan         |              |                 |                       |
| Intermediate (1) | 0 (0%)       | 3 (23.1%)       | 2 (100%)              |
| Significant (2 & 3) | 3 (100%)   | 10 (76.9%)      | 0                     |
| Peripheral neuropathy |        |                 |                       |
| Isolated median neuropathy | 1 (33.3%) | 5 (38.5%)       | 0                     |
| Sensorimotor polyneuropathy | 2 (66.7%) | 8 (61.5%)       | 0                     |

HF, Heart failure defined by New York Heart Association Functional Classification (NYHA Fc) class 2 or more; ATTR, transthyretin amyloidosis; FAP, familial amyloidotic polyneuropathy; PYP scan, 99mTc-technetium-pyrophosphate (99mTc-PYP) scintigraphy.

Clinical information of the patient carrying the TTR Glu89Asp mutation

The patient with the TTR Glu89Asp mutation presented with distal paresthesia since age 59 years and intermittent chest tightness, diarrhea, and erectile dysfunction since age 64. Progressively ascending numbness, tingling pain and weakness of four limbs accompanying with loss of body weight up to 12 kg developed in the following 2 years. He was wheelchair-bound by age 68. The neurological examination at age 66 revealed severe hypophonia, generalized areflexia, weakness and muscle wasting and impaired sensation of all modalities in the distal four limbs. The nerve conduction study showed severe axonal polyneuropathy (Table S1). The sympathetic skin responses (SSR) were absent over lower limbs and diminished with prolonged latencies over upper limbs. The heart rate variability test revealed decreased variability on

Figure 1. Pedigrees and electropherograms of the TTR mutations in this study. (A) The six TTR mutations identified in this study, with the sense strand electropherogram shown on the top and a limited reading frame depicting the corresponding amino acid substitutions shown below. (B) The pedigrees of the patients carrying the TTR mutations, including the Ala45Thr, Thr60Ala, Ile73Val, Ser77Tyr, and Glu89Asp mutations. The arrows indicate the probands. The squares and circles denote males and females, respectively. The filled and open symbols represent affected and unaffected members. Dotted symbols represent asymptomatic carriers. Slashed indicate deceased individuals.
R-R intervals. Severe postural hypotension (54/27 mmHg at 3rd minutes on standing) was demonstrated by head-up tilt test. Rectal biopsy of the patient revealed characteristic apple-green birefringence of amyloid deposits in the Congo red stain (Fig. 2A and B). The serum and urine protein electrophoresis with immunofixation did not find monoclonal band and the serum free light chain ratio analysis revealed normal values. The echocardiography showed preserved ejection fraction with mild CLVH at age 66 and mild systolic dysfunction at age 69. 99mTc-PYP scintigraphy and SPECT/CT imaging showed prominent amyloid deposition with visual score of grade 3, mainly locating in the left ventricle, at age 69 (Fig 2C and D).

**Founder Effect of TTR Ala97Ser in Taiwan**

Haplotype analysis was performed in 91 individuals from 15 pedigrees harboring the p.Ala97Ser mutation, including 47 patients, ten asymptomatic carriers and 34 unaffected subjects. The families were denoted as A to P (Fig. 3). These families shared a common haplotype covering a region of 0.48 Mb containing loci rs12709651, rs7232282, rs7231553, D18S1242, rs1080093, rs1080094, rs8098191, D18S2021, and rs614342 linked to TTR Ala97-Ser (C-C-A-1-C-A-mutation-G-1-C), suggesting the presence of a founder effect for the Ala97Ser mutation.

**Discussion**

The present study comprehensively investigates the clinical features and mutational spectrum of a cohort of 79 patients with ATTR from 57 pedigrees of Han Chinese descent in Taiwan. The studied cohort is the largest ATTR cohort in Han Chinese populations. There are several intriguing findings in this study. Firstly, TTR Ala97-Ser mutation is the most common cause of ATTR in Taiwan, accounting for 91.2% of the pedigrees. The patients with the Ala97Ser mutation usually present with a late-onset peripheral neuropathy and autonomic dysfunction at their late fifties, and approximately half of them have CTS as the initial presentation. Upon the time of diagnosis, majority of them had significant cardiac amyloid deposition and abnormal cardiac echocardiographic findings despite less than one-third of patients report heart symptoms. Secondly, TTR Glu89Asp is a novel pathogenic mutation for ATTR. Furthermore, there is a founder effect for the Ala97Ser mutation in Taiwan. Moreover, there was no correlation between the pattern or severity of neuropathy and the severity of cardiac amyloidosis in the ATTR cohort. Cardiac evaluation is mandatory in every patient with ATTR, even in those with very early-stage disease and trivial symptom.
Taiwanese ATTR population is particular because of the TTR Ala97Ser mutation, which contributes to the majority of ATTR in Taiwan but is absent in other populations. Several other population-specific TTR mutations have also been identified. For example, the Thr60Ala mutation, which is prevalent in British patients with ATTR, is associated with early cardiac and autonomic symptoms and variable severity of peripheral neuropathy in advanced disease stage.

In addition to the Ala97Ser mutation, five other TTR mutations were identified in the Taiwanese ATTR cohort, including the novel Glu89Asp mutation, manifesting as late-onset neuropathy with obvious autonomic and cardiac involvement. Our work also demonstrated a common haplotype consisting of nine neighboring loci of the microsatellite or SNP markers linked to the TTR Ala97Ser mutation in the 15 ATTR families. These findings suggest that the Taiwanese patients harboring the Ala97Ser mutation may be descendants from a common ancestor. A founder effect for the TTR Val30Met mutation has also been shown in the Japanese, Swedish and Portuguese populations.

Our study underlines the importance of cardiac evaluation in every patient with ATTR, even in those without heart symptoms. In the Taiwanese ATTR cohort, less than one-third of the patients had cardiac symptoms, but near three-fourths of the ATTR patients receiving echocardiography had abnormal findings. Furthermore, 99mTc-PYP scintigraphy revealed significant cardiac amyloid deposition in 76.9% of ATTR patients without an overt heart failure symptom. Even for the two asymptomatic TTR mutation carriers, an intermediate degree of cardiac involvement was detected.

Figure 2. Rectal biopsy and the 99mTc-PYP scintigraphy and SPECT/CT imaging of the patient with the novel TTR Glu89Asp mutation. (A) Pathological sections with the Congo red stain showed an amorphous, small focus of amyloid deposition in submucosa of rectum. (B) Under polarized light examination, the amyloid deposition showed apple-green birefringence. (C) 99mTechnetium-pyrophosphate (99mTc-PYP) scintigraphy reveals increased PYP uptake in the heart with visual score of grade 3. (D) The SPECT/CT image shows the amyloid deposition mainly located in the left ventricle. Bars = 100 µm.
Amyloidosis was detected by $^{99m}$Tc-PYP imaging in both of them. To be noticed, there was no correlation between the pattern or severity of neuropathy and the severity of cardiac amyloidosis in the Taiwanese ATTR cohort. Similar findings were also found in an ATTR cohort in US. Within this cohort, 10 of the 12 (84%) asymptomatic TTR mutation carriers had cardiac amyloidosis revealed by $^{99m}$Tc-PYP scintigraphy. Since newly emerging RNA interference and antisense oligonucleotide therapies have changed the therapeutic paradigm for ATTR, routinely genetic testing for TTR mutations in individuals at risk and aggressively monitoring cardiac amyloidosis in asymptomatic TTR mutation carriers may allow early intervention.

In conclusion, we demonstrated the distinct clinical and genetic profiles of ATTR in Taiwan, where TTR Ala97Ser accounts for approximately 90% of ATTR and is associated with a late-onset neuropathy with autonomic and cardiac involvement. There is a founder effect for the Ala97Ser mutation in Taiwan. One novel mutation for ATTR, Glu89Asp, was identified. Cardiac evaluation is important in ATTR patients, even in those without heart symptoms. These findings provide useful information for the diagnosis and management of ATTR, especially in patients of Chinese descent.

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**Conflict of Interest**

None declared.

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Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Serial clinical information of the patient with the TTR Glu89Asp mutation was demonstrated in the supplementary table, including nerve conduction study, echocardiography, and cardiac scintigraphy at the age of 66 and 69.