

# Clinical and genetic features of transthyretin-related familial amyloid polyneuropathy in China

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Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is an autosomal dominant, life-threatening, and treatable disorder caused by *TTR* mutation. It is characterized by amyloid deposition in the peripheral nerves and major organs, including the heart, kidneys, and eyes. So far, more than 130 *TTR* mutations have been identified, in which p.Val30Met is the most common in endemic countries. TTR-FAP has been reported in 29 countries, including many countries in Europe, USA, Japan, China, and India. Clinical and genetic features of TTR-FAP are relatively clear in Europe and Japan, however, it still need to be carried out in China. Here, we reported the clinical and genetic features of 8 Chinese TTR-FAP families.

There were 396 unrelated inherited peripheral neuropathy (IPN) families recruited from the Neurology Department of The Third Xiangya Hospital and Xiangya Hospital from 2006 to 2019. All patients were comprehensively checked by two experienced neurologists and met with the IPN diagnosis criteria. Genomic DNA was extracted from peripheral blood using phenol-chloroform procedures, mutation screening of *TTR* were performed by Sanger sequencing. Amino acid changes in *TTR* were numbered according to the beginning of the mature protein, as described historically, rather than including the 20 amino acid signal sequence. The severity of the TTR-FAP patients was measured by the neuropathy impairment score (NIS). All individuals signed informed written consent before enrollment. This study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University.

We detected 5 *TTR* mutations (c.112G>A, c.161G>C, c.165G>C, c.200G>A, c.349G>T; p.Asp18Asn, p.Arg34Thr, p.Lys35Asn, p.Gly47Glu, p.Ala97Ser) in eight unrelated IPN families including 15 symptomatic patients and seven presymptomatic individuals [Figure 1]. The c.112G>A related to peripheral neuropathy and cardiomyopathy and the c.161G>C associated with pure peripheral neuropathy were first reported in Chinese population. We discovered the coexistence of homozygous and heterozygous c.349G>T in Family 1. The proband (III-1) harboring homozygous c.349G>T experienced alternate constipation and diarrhea at age 47. He developed progressively distal numbness and weakness in limbs at age 50 and presented in our clinic. Examination showed distal weakness in upper and lower limbs (score 4/5), hypalgesia in the regions below the wrists and ankles and generalized areflexion. No postural hypotension and muscle atrophy were found. Electromyogram (EMG) studies showed axonal polyneuropathy with upper limb predominance. His NIS score was 77. The other three family members (II-1, II-3, and IV-1) with age at onset ranging from 23 to 80 years had similar symptoms, and II-3 died of malnourishment caused by severe diarrhea at age 70. Individuals II-1, IV-1, and IV-2 carried the heterozygous c.349G>T; however, IV-2 had no symptoms at age 20. The NIS scores of II-1 and IV-1 were both 75.

In these eight TTR-FAP families, the mean age at onset was  $46.0 \pm 15.3$  years (range: 23–80 years). The most common initial symptoms were diarrhea or constipation affecting six of 15 symptomatic patients, and the most common manifestations were weakness in limbs affecting 13 of the 15 symptomatic patients. Eleven patients complaint of paresthesia in limbs and eleven patients manifested with postural hypotension. Cardiac involvement was suspected in seven patients with c.112G>A, c.200G>A, and

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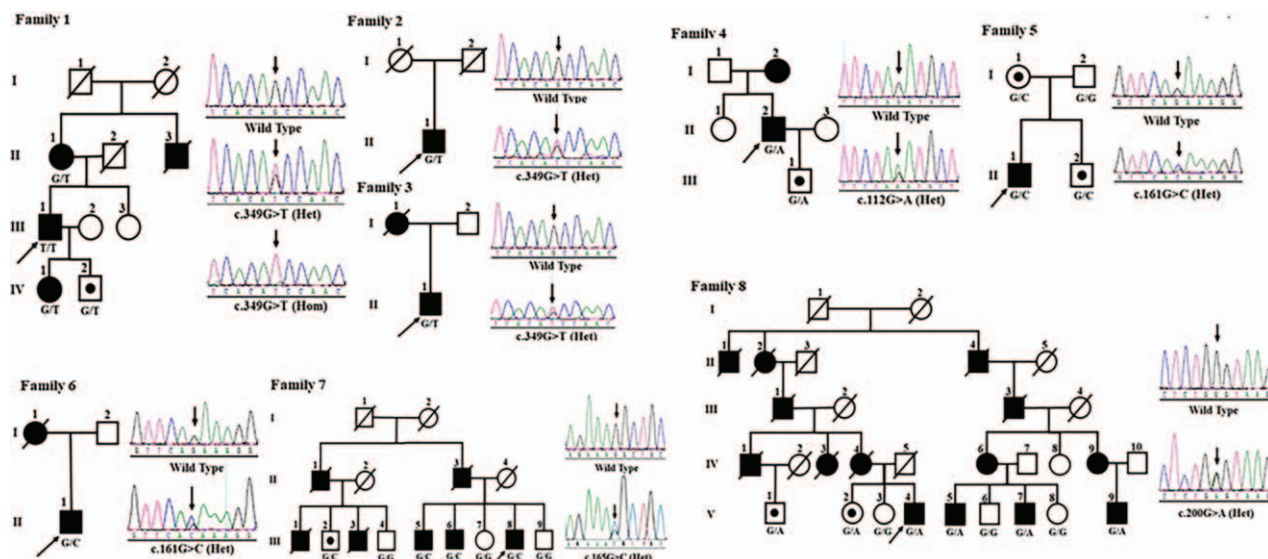
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**Figure 1:** Pedigrees and sequencing results of eight transthyretin-related familial amyloid polyneuropathy families in our cohort.

c.349G>T mutations. Renal involvement was detected in two patients carrying c.165G>C and c.200G>A mutations. Vitreous opacity was suspected in one patient with c.165G>C mutation. The clinical and genetic features of 8 families were shown in detail in Supplemental Table 1, <http://links.lww.com/CM9/A317>. And the available EMG data were presented in Supplemental Table 2, <http://links.lww.com/CM9/A317>.

TTR-FAP accounted for 2.0% in our IPN cohort and it was a life-threatening and treatable disorder, which indicated that routine *TTR* screening is needed in IPN patients. The c.112G>A related to peripheral neuropathy and cardiomyopathy was firstly detected in Chinese population, while the American family harbored the same mutation presented with pure heart involvement. The c.161G>C was first detected in China and related to pure peripheral neuropathies, which is different from the first case reported in an Italy family featured by peripheral neuropathies with restrictive cardiomyopathy. Besides the reported phenotype of late-onset axonal polyneuropathy with prominent pain and autonomic dysfunction, our patients bearing c.165G>C also exhibited renal failure and vitreous opacity. In accordance to the reported Macau families, the c.200G>A also exhibited length-dependent peripheral polyneuropathy with cardiomyopathy. The c.349G>T was related to late-onset sensory dominant polyneuropathy and minor heart involvements, and in accordance with the phenotype in reported Taiwan patients.

We first described the coexistence of homozygous and heterozygous p.Ala97Ser with no phenotypic difference in one family. It is reported that homozygous p.Val30Met did not result in a more severe phenotype than the heterozygous one in Swedish, Japanese, and Turkish patients, however, it was associated with vitreous amyloidosis and relatively less autonomic involvements. Another African American family coexistent with homozygous and heterozygous p.V122I exhibited that the homozygous locus was

associated with earlier onset of amyloid cardiomyopathy when compared to the heterozygous one. The phenotypic variation between homozygous and heterozygous *TTR* mutations and the underlying mechanism need to be observed and studied further when more cases are available.

We retrieved 32 literatures reporting 86 Chinese *TTR*-FAP families with 32 mutations from 1994 to 2019. With the eight *TTR*-FAP families we reported, there were 94 Chinese families and 34 different mutations in total. The most frequent mutation was p.Ala97Ser (31.9%) followed by p.Val30Met (6.4%) and p.Val30Ala (6.4%), which indicated that p.Ala97Ser might be the hotspot mutation in China. The hotspot feature is different from that of other endemic areas, such as p.Val30Met in Cyprus, Portugal, Japan, and Brazil, p.Val122Ile and p.Thr60Ala in North America.<sup>[1-5]</sup> The age at onset in Chinese population ( $44.62 \pm 13.63$  years) was earlier when compared to American ( $59.6$  years), Swedish ( $56.7 \pm 13.2$  years), and Cypriote ( $48.6 \pm 15.0$  years), but was later than those in Portuguese ( $42.8 \pm 15.0$  years), Turkish ( $40.4 \pm 13.9$  years), and Brazilian ( $32.5$  years) population.<sup>[1,2,4-7]</sup> Early-onset type accounted for the majority of Chinese *TTR*-FAP patients (60.4%) which is similar in Portugal (71.3%) population, while late-onset is predominant in American (79.2%) population.<sup>[2,8]</sup> The main clinical features of Chinese *TTR*-FAP were axonal peripheral polyneuropathy with predominant autonomic dysfunction (84.6%) and with organ involvements including cardiomyopathy (35.2%), vitreous opacity (25.3%), renal failure (5.6%), and meningeal involvement (2.5%).

In conclusion, routine *TTR* screening is needed in IPN patients. This study first reported c.112G>A and c.161G>C in Chinese population and the coexistence of homozygous and heterozygous c.349G>T mutation with no phenotypic difference. The p.Ala97Ser might be the hotspot mutation. The clinical features were relative early-onset axonal peripheral neuropathies with autonomic dysfunctions predominance.

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### Conflicts of interest

None.

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