A case of familial amyloidotic polyneuropathy with a rare Phe33Leu mutation in the TTR gene

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Familial amyloidotic polyneuropathy (FAP) is a hereditary polyneuropathy caused by transthyretin (TTR) mutation, and characterized by length-dependent sensorimotor polyneuropathy, autonomic dysfunction, and visceral organ involvement. TTR is a tetrameric protein with binding sites for thyroxine and retinol-binding protein (RBP)/vitamin A complex. About 100 different disease-causing mutations of the TTR gene have been reported. The most common mutation worldwide is Val30Met, which is endemic in Portugal, Sweden and Japan. Here, we report a Taiwanese FAP family with a rare TTR mutation, Phe33Leu.

A 50-year-old man presented with intractable diarrhea since the age of 47. Orthostatic dizziness, erectile dysfunction, anhidrosis and hyperalgesia in the distal parts, and limb weakness developed in the following 3 years. There were no similar symptoms among his parents and siblings. Neurological examination revealed muscle wasting with weakness of the limbs, generalized areflexia, hyperalgesia in a glove-stocking distribution, and unsteadiness with a positive Romberg’s test. Prominent orthostatic hypotension was documented (blood pressure = 116/75 mmHg in the supine position and 67/50 mmHg upon standing). Routine blood tests and spinal fluid studies were unremarkable. The nerve conduction study showed an axonal type sensorimotor polyneuropathy and autonomic dysfunction. A transthoracic echocardiogram showed a restrictive cardiomyopathy with sparkling myocardium. The endoscopic biopsy of gastric and intestine mucosa confirmed the presence of amyloid fibrils.

A TTR-associated FAP was highly suspected in the index case according to the clinical features. Sequencing of the human TTR gene identified a heterozygous transversion of ‘T’ to ‘C’ at nucleotide 183 (Fig. 1A), predicted to a Phe33Leu change. No similar change was observed in 200 Taiwanese controls. Furthermore, Phe33 is highly conserved in vertebrate species (Fig. 1A). Molecular mimicry demonstrated that the mutated TTR had a reduced size of the cleft in the surface receptor for RBP/vitamin A complex binding (Fig. 1B). The patient’s two asymptomatic daughters also harbored the same mutation.

The Phe33 is a highly conserved amino acid of the TTR protein during evolution. The replacement of the aromatic ring associated with phenylalanine for leucine could cause a conformational change in the TTR protein, which may lead to destabilization of the tetrameric molecule, further resulting in the formation of amyloid fibrils. Whether an alteration in the distance across the surface receptor for RBP/vitamin A plays a role in amyloidogenic TTR formation needs further investigation.

To date, the TTR Phe33Leu mutation has only been reported in four families, originating from the Baltic states and Scandinavia: two un-related Polish-American families, one Polish-Lithuanian family, and one Swedish family.
Thus, this is the first case with a TTR Phe33Leu mutation from the Asian populations. The clinical features of the disease in our patient (i.e., mid-aged onset, axonal type sensorimotor polyneuropathy, cardiomyopathy and autonomic dysfunction) were consistent with the reported cases. In conclusion, genetic screening for TTR-related FAP is valuable, since pre-symptomatic genetic counseling and novel therapeutic approaches are both important for the affected patients and their relatives.

References


