Charcot-Marie-Tooth families in Japan with MPZ Thr124Met mutation

S Kurihara, Y Adachi, C Imai, H Araki, N Hattori, C Numakura, Y Lin, K Hayasaka, G Sobue, K Nakashima

Background: The MPZ Thr124Met mutation is characterised by a late onset, pupillary abnormality, deafness, normal or moderate decreased motor nerve conduction velocity, and axonal damage in sural nerve biopsy.

Objective: To investigate the clinical manifestations of the axonal or demyelinating forms of the Japanese MPZ Thr124Met mutation originating in four different areas: Tottori, Nara, Aichi, and Ibaragi.

Results: Genotyping with DNA microsatellite markers linked to the MPZ gene on chromosome 1q22-q23 showed shared allelic characteristics between 12.65 cm and revealed a common haplotype in all Tottori families. Aichi and Ibaragi families shared parts of the haplotype around the MPZ gene. However, there was no consistency with a Nara family.

Conclusions: The high frequency of this peculiar genotype in the Tottori CMT population is presumably due to a founder effect, but in Thr124 it might constitute a mutation hotspot in the MPZ gene.

Methods

Sixteen patients from Tottori, Nara, Aichi, and Ibaragi prefectures were examined by direct sequence analysis, which revealed a C→T mutation at position 371 in the MPZ gene. We investigated the clinical features of these Japanese CMT families with four isolated ancestries.

Results

The clinical features of 16 patients are shown in table 1. They usually shared characteristic features of CMT, but from this study we found that pes planus was also present in MPZ Thr124Met patients. Neuropathic symptoms occurred later than usual for CMT1, and the patients were able to manage most aspects of their lives. Electrophysiologically, median motor nerve conduction velocities (MNCV) of MPZ Thr124Met were normal (42.3 (15.6) m/s) and median nerve compound muscle action potentials (CMAP) were decreased (3.9 (3.9) mV). Sural nerve biopsies showed a marked decrease of large myelinated fibres and the presence of regenerating fibres with small onion bulb formation. Teased nerves mainly showed axonal degeneration.

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Discussion

Japanese CMT families with four isolated ancestries were studied. There are at least two founders and Thr124 was the hotspot in the MPZ gene. The disease usually manifested in the fifth decade and showed slowly progressive symptoms. The mutation is associated with a clinically distinct phenotype characterised by late onset, marked sensory abnormalities, and in some families deafness and pupillary abnormalities.

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neuropathic symptoms. Pupillary abnormalities and deafness are sometimes present in other inherited neuropathies, but they were a constant feature in this mutation. The NCVs varied widely from less than 38 m/s to normal in early stage patients, and the values tended to fall within the range of CMT1 in severely affected patients. Clusters of remyelinating axons in the sural nerve biopsy showed axonal involvement with axonal regeneration. Phenotype-genotype correlations in 16 patients indicated that these were difficult to classify as CMT1B or CMT2. This tendency might derive from the character of the MPZ Thr124Met mutation. Haplotype analysis showed that the Nara CMT family was completely unrelated. However, other Japanese families shared a common founder. Thus more than two distinct ancestral Thr124 MPZ alleles exist in Japan. Our study strongly supports the hypothesis that the high frequency of the ACG to ATG transition in codon124 is not only due to a founder effect, but that Thr124 is a mutation hotspot.

In conclusion, CMT patients with slightly reduced or nearly normal NCVs should be screened for MPZ mutations, particularly when additional clinical features such as pupillary abnormalities or deafness are also present.

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Competing interests: none declared

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Received 3 June 2003

In revised form 25 December 2003

Accepted 13 January 2004

**REFERENCES**


**Table 1** Clinical, electrophysiological, and pathological data from Japanese MPZ Thr124Met patients

Table showing patient details with clinical and electrophysiological data.

**Figure 1** Disease associated haplotypes in Japanese Charcot-Marie-Tooth disease (CMT) families. In 13 cases from the six Tottori originating CMT families, there was a shared haplotype (‘‘11-30-17-21-13’’). For all five markers investigated, Aichi and Ibaragi families shared parts of repeats between 2.57 cm and 8.66 cm. The Nara originated family did not share contiguity markers (D1S2771, D1S2705).