Genetic profile of Chinese patients with Charcot-Marie-Tooth disease

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To the Editor: Charcot-Marie-Tooth disease (CMT) encompasses a genetically heterogeneous group of inherited neuropathies, characterized by progressive distal muscle weakness and atrophy, sensory deficits, impaired tendon reflexes, and foot deformities. To date, more than 80 causative genes have been identified in CMT patients, associated with either autosomal dominant or recessive inheritance, or X-linked transmission. The traditional classification of CMT was based on peripheral neuropathy type, as determined by nerve conduction velocity. As more causative genes were identified and the overlap of neuropathy phenotypes became apparent, the traditional classification system proved unwieldy and inadequate. Moreover, CMT needs to be distinguished from several entities including systemic disorders with neuropathy and other types of hereditary neuropathy. In clinical practice, overlap of phenotypes can present a major challenge in reaching the correct diagnosis. This study aimed to investigate the genetic profile in a cohort of Chinese CMT patients and evaluate the role of genetic testing in the diagnosis and subtyping of CMT.

A total of 66 unrelated Chinese probands with CMT were enrolled from March 2004 to April 2019. Neurological examinations were performed by two experienced neurologists. For 36 cases collected before May 2013, three microsatellite markers within the 1.4 Mb duplication region on chromosome 17p11.2-p12 were first used to detect PMP22 duplication. In probands with no PMP22 duplication, mutations analysis of PMP22, GJB1, and MPZ genes was further performed using denaturing high-performance liquid chromatography (DHPLC). For 30 cases collected after May 2013, multiplex ligation-dependent probe amplification was first performed to detect PMP22 duplication. In probands with negative results, next-generation sequencing, either whole-exome sequencing (n=1) or use of a targeted sequencing panel (n=5), was carried out to identify causative genes. Candidate mutations found by either DHPLC or next-generation sequencing were further confirmed by Sanger sequencing.

The most common cause of CMT in our cohort was PMP22 duplication (28/66, 42.4%). Four missense, c.22A>T (p.T8S), c.65G>T (p.R22L), c.223C>T (p.R75W), c.392T>C (p.L131P), and one nonsense mutations, c.64C>T (p.R22*), were identified in the second most common causative gene GJB1 (5/66, 7.6%). The novel variant c.22A>T (p.T8S) was not found in the population databases including 1000 Genomes Project and the Exome Aggregation Consortium. Co-segregation analysis was not performed because family members’ DNA samples were not available. Two known causative mutations, c.22A>C (p.T8P) and c.23C>T (p.T8I), have been found in codon 8, suggesting the critical biological function of this conserved residue. The other novel variant, c.65G>T (p.R22L) was also not found in the population databases mentioned above. This variant was detected in the proband and his affected mother. Four known causative mutations, c.64C>G (p.R22G), c.64C>T (p.R22*), c.65G>A (p.R22Q), and c.65G>C (p.R22P), have been found in codon 22, strongly indicating that this position was highly conserved through evolution. The American College of Medical Genetics and Genomics (ACMG) classification of both variants was “likely pathogenic.”

A novel homozygous FGD4 missense variant c.1303C>T (p.R435W) was identified in a 38-year-old woman born to...
Our study identified mutations in common causative genes (eg, PMP22 and GJB1) and rare ones (eg, FIG4 and FGD4), further expanding the mutational spectrum of CMT-related genes. CMT4H is a rare autosomal recessive hereditary neuropathy caused by FGD4 mutations and characterized by first-decade onset, slowly progressive distal muscle weakness, frequent scoliosis, and myelin outfoldings visible in nerve biopsy samples.[12] Cranial nerve involvement was only reported in one case, a 65-year-old man who had apparent external ophthalmoplegia, facial muscle palsies, and bilateral inner ear hearing loss.[13] Our case further supported cranial nerve involvement as a rare presentation in patients with CMT4H.

Biallelic FIG4 mutations are the cause of CMT4J while heterozygous mutations are associated with amyotrophic lateral sclerosis 11 (ALS11). FIG4 is a peripheral neuropathy characterized by childhood onset with accelerated limb weakness and muscle atrophy during the teenage years or adulthood that involve both distal and proximal limb muscles, while ALS11 had a less severe phenotype with adult onset and prominent corticospinal tract findings. The clinical significance of the heterozygous mutation c.923C>T found in both the proband and her affected father with ulnar nerve deficits remains unclear. More case reports are needed to demonstrate whether this could present a new phenotype of FIG4-related disorders.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

None.

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