Journal of Human Genetics (2011) 56, 341–342

www.nature.com/jhg

COMMENTARY

A Commentary on Molecular diagnosis and clinical onset of Charcot–Marie–Tooth disease in Japan

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Journal of Human Genetics (2011) **56,** 341–342; doi:10.1038/jhg.2011.32; published online 24 March 2011

The article entitled 'Molecular diagnosis and clinical onset of Charcot-Marie-Tooth disease in Japan' offers new light on the remarkable ethnic diversity of Charcot–Marie–Tooth disease (CMT) in different populations.[1] CMT is indeed the most common inherited peripheral neuropathy. Whereas the prevalence is estimated at one patient per 2500 population in Europe and the United States, the precise prevalence in Japan still remains unexplored. CMT symptoms include an awkward gait, muscular atrophy of the distal extremities and foot deformities (Figure 1). Clinical observations indicate that CMT is highly heterogeneous and may range from patients who may be asymptomatic to those who are bedridden. Thus, CMT may have to be suspected in those patients with peripheral neuropathy and cavus foot, even if no other members of the family have been diagnosed with the disease. This clinical approach will therefore help in framing the precise prevalence and molecular epidemiology of CMT in Japan.

CMT constitutes a genetically heterogeneous group of diseases that affect the peripheral nervous system. Characterized by degeneration or abnormal development of the peripheral nerve and transmitted with different genetic patterns, CMT has been traditionally classified into demyelinating, axonal and intermediate forms based on nerve conduction studies. As for the disease causality, more than 40 genes have been identified (http://www.molgen.ua.ac.be/CMTMutations/Mutations). The proportions of different genotypes in patients with CMT have been reported often in the Caucasian population,[2,3] but rarely in the non-Caucasian population. The authors disclosed the proportions of different genotypes of CMT in the Japanese population, together with 14 novel disease-causing mutations of known CMT genes.[1] This study is a significant genetic survey involving 354 patients with CMT in the non-Caucasian population. They also showed the distinct age of onset in different CMT genes. Most of the patients carrying *PMP22*, *MPZ*, *NEFL*, *PRX* and *MFN2* mutations showed an early disease onset, while half of the patients with *PMP22* duplication and all patients with *GJB1* or *MPZ* mutations showing an axonal phenotype were late disease onset. They also highlighted two epidemiological features in the Japanese population that are distinct from those of the Caucasian population: lower prevalence of duplication of *PMP22* in the demyelinating CMT and more cases in which no causative genes were identified despite an extensive search on the representative CMT genes.[2,3] Arguably, the lower prevalence of *PMP22* duplication in the Japanese population is likely associated with the milder symptoms in this population owing to genetic and/or epigenetic modifying factors. Indeed, a genetic study is essential to identify the causative gene for CMT, to clarify the molecular mechanism of CMT and to pursue the development of novel treatment strategies.

Several questions still remain: How can we ultimately identify the causative genes in the patients with unknown cause? What are the genetic and epigenetic modifying factors that potentially affect the phenotypic expression of patients with *PMP22* duplica-

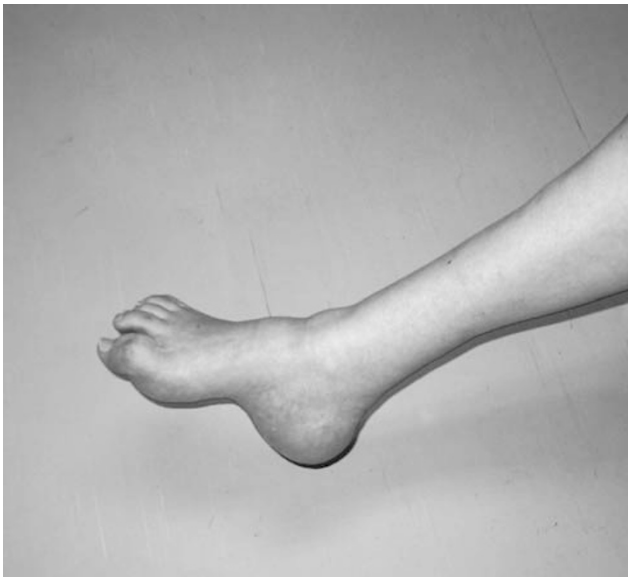

Figure 1 The cavus foot of a CMT patient.

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tion? It could be helpful to establish a high-throughput screening method using the next-generation sequencer for identification of the causative gene of patients with unidentified mutations and the genetic and epigenetic modifying factors of CMT. In addition, a molecular epidemiological study of CMT in Asian countries including Korea and China, where Japanese lineage may encroach, is needed, so as to provide more insight into the genetic background of the low prevalence of *PMP22* duplication in Japan.

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2 Mostacciuolo, M. L., Righetti, E., Zortea, M., Bosello, V., Schiavon, F., Vallo, L. *et al.* Charcot-Marie-Tooth disease type I and related demyelinating neuropathies: mutation analysis in a large cohort of Italian families. *Hum. Mutat.* **18,** 32–41 (2001).
3 Boerkoel, C. F., Takashima, H., Garcia, C. A., Olney, R. K., Johnson, J., Berry, K. *et al.* Charcot-Marie-Tooth disease and related neuropathies: mutation distribution and genotype-phenotype correlation. *Ann. Neurol.* **51,** 190–201 (2002).