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SHORT REPORT

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Small heat-shock protein 22 mutated in autosomal dominant Charcot-Marie-Tooth disease type 2L

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Abstract Charcot-Marie-Tooth (CMT) disease is the most common inherited motor and sensory neuropathy. We have previously described a large Chinese CMT family and assigned the locus underlying the disease (CMT2L; OMIM 608673) to chromosome 12q24. Here, we report a novel c.423G → T (Lys141Asn) missense mutation of small heat-shock protein 22-kDa protein 8 (encoded by *HSPB8*), which is also responsible for distal hereditary motor neuropathy type (dHMN) II. No disease-causing mutations have been identified in another 114 CMT families.

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Introduction

Charcot-Marie-Tooth (CMT) is the most common inherited peripheral neuropathy and is further subdivided into CMT1 or CMT2, the demyelinating and axonal forms respectively (De Jonghe et al. 1997). Eight loci and six genes have been reported to cause dominant inherited CMT2 (Inherited Peripheral Neuropathies Mutation Database, http://molgen-www.uia.ac.be/CMTMutations/). We have previously mapped CMT2L to a 6.8-cM candidate region at 12q24 in a Chinese family (Tang et al. 2004). In this study, we report a novel missense mutation (c.423G → T) in *HSPB8*, which is also the gene responsible for distal hereditary motor neuropathy type (dHMN) II (Irobi et al. 2004).

Patients and methods

Patients

A large Chinese CMT2L family was ascertained (Tang et al. 2004). Another 114 unrelated families, all diagnosed as exhibiting CMT by two or more neurologists according to generally accepted diagnosis criteria (De Jonghe et al. 1998), and 200 control individuals were included in this study.

Mutation analysis

Genomic DNA was extracted from peripheral blood leukocytes by standard extraction methods. All known exons and intron-exon boundaries of the selected 26 known candidate genes (*KSR2*, *RFC5*, *JIK*, *HSPB8*, *RAB35*, *RPLP0*, *PXN*, *SIRT4*, *PLA2G1B*, *MSI1*, *SFRS9*, *RNF10*, *CABP1*, *P2RX7*, *RNF34*, *ARHF*, *MGC33630*, *MONDOA*, *VPS33A RSN*, *HM74*, *DENR*, *ABCB*, *RNP24*, *EIF2B1*, and *GTF2H3*) were sequenced in the CMT2L family.

Results

Clinical information

The clinical information of the CMT2L family was as described previously (Tang et al. 2004). Motor nerve conduction velocities of the median nerves in the six patients subjected to electrophysiological examinations were normal, ranging from 56.7 to 69.2 m/s. Compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) were decreased or absent in all six patients. A superficial peroneal nerve biopsy of the proband (IV:13) confirmed the presence of axonal neuropathy with an important loss of large myelinating fibers and a large number of clusters with mostly thinly myelinated axons.

Genetic analysis

A novel c.423G → T transition (Lys141Asn; Fig. 1) was identified in small heat-shock 22-kDa protein 8 (encoded by *HSPB8*; also called *HSP22*) co-segregating perfectly with the CMT2 phenotype, but not in 200 normal control individuals. No disease-causing mutations were identified in another 114 unrelated patients diagnosed as having the CMT1 or CMT2 phenotype.

Discussion

We have shown here that the c.423G → T mutation of *HSPB8* is involved in CMT2L. Recently, two different mutations, viz., c.423G → C (Lys141Asn) and c.421A → G (Lys141Glu), of *HSPB8* were identified in four dHMN II families (Irobi et al. 2004). Our CMT2L family shares the Lys141Asn substitution but appears to have a distinct phenotype. The changes of CMAPs, SNAPs and pathology in the CMT2L family showed that the CMT2L family was different from the dHMN II family previously reported (Timmerman et al. 1992) according to the classification and diagnostic guidelines for CMT2 and dHMN (De Jonghe et al. 1998).

This is the third time that mutations in the same genes have been shown possibly to cause both CMT and dHMN, as dominant mutations in *GARS* are associated with CMT2D and dHMN V (Antonellis et al. 2003) and dominant mutations in *HSPB1* are associated with CMT2F and a form of dHMN (Evgrafov et al. 2004). The reason that the *HSPB8* gene mutations cause different diseases remains unclear. We suggest that the dysfunction of HSPB8 leads to the formation of aggregates that may block axonal transport. The different regions, such as the anterior horn cells or peripheral nerves, in which the aggregates are deposited may be associated with the different phenotypes, i.e., CMT and dHMN.

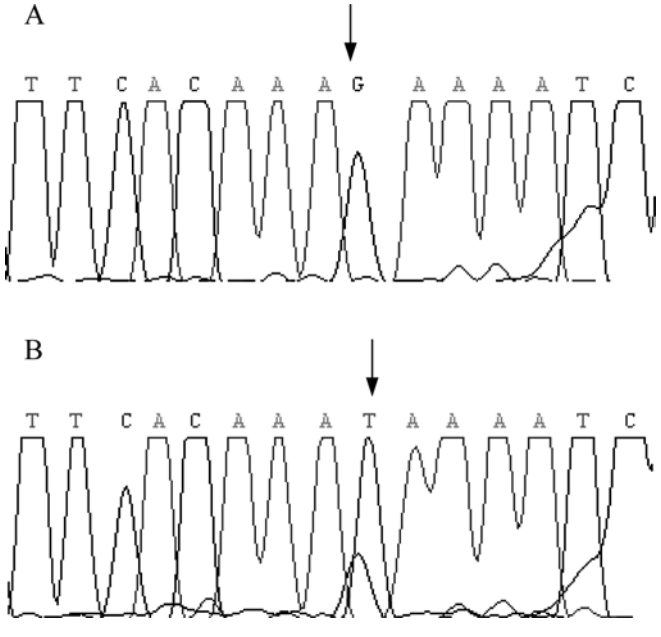

Fig. 1 Partial sequence of exon 2 in a control individual (**a**) and the proband (**b**) of the CMT2L family. The patient shows a G → T transition causing the Lys141Asn substitution

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