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16q-linked autosomal dominant cerebellar ataxia: A clinical and genetic study

Y. Ouyang [a], K. Sakoe [a], H. Shimazaki [a], M. Namekawa [a], T. Ogawa [a], Y. Ando [a], T. Kawakami [a], J. Kaneko [b], Y. Hasegawa [c], K. Yoshizawa [d], T. Amino [e], K. Ishikawa [e], H. Mizusawa [e], I. Nakano [a], Y. Takiyama [a,*]

[a] *Department of Neurology, Jichi Medical School, Tochigi 329-0498, Japan*
[b] *Kaneko Clinic, Gunma 373-0841, Japan*
[c] *Department of Neurology, Showa University School of Medicine, Tokyo 142-8555, Japan*
[d] *Department of Neurology, National Mito General Hospital, Ibaraki 311-3193, Japan*
[e] *Department of Neurology and Neurological Science, Graduate School, Tokyo Medical and Dental University, Tokyo 113-8519, Japan*

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Abstract

The autosomal dominant cerebellar ataxias (ADCAs) comprise a genetically and clinically heterogenous group of neurodegenerative disorders. Very recently, a C-to-T single nucleotide substitution in the *puratrophin-1* gene was found to be strongly associated with a form of ADCA linked to chromosome 16q22.1 (16q-linked ADCA; OMIM 600223). We found the C-to-T substitution in the *puratrophin-1* gene in 20 patients with ataxia (16 heterozygotes and four homozygotes) and four asymptomatic carriers in 9 of 24 families with an unknown type of ADCA. We also found two cases with 16q-linked ADCA among 43 sporadic patients with late-onset cortical cerebellar atrophy (LCCA). The mean age at onset in the 22 patients was 61.8 years, and that of homozygous patients was lower than that of heterozygous ones in one family. Neurological examination revealed that the majority of our patients showed exaggerated deep tendon reflexes in addition to the cardinal symptom of cerebellar ataxia (100%), and 37.5% of them had sensorineural hearing impairment, whereas sensory axonal neuropathy was absent. The frequency of 16q-linked ADCA was about 1/10 of our series of 110 ADCA families, making it the third most frequent ADCA in Japan.

Keywords: 16q-linked ADCA; *Puratrophin-1* gene; Heterozygote; Homozygote; Haplotype analysis

1. Introduction

Autosomal dominant cerebellar ataxias (ADCAs) comprise a genetically and clinically heterogeneous group of neurodegenerative disorders characterized by progressive cerebellar ataxia that can be variably associated with other neurological features [1]. ADCAs are now classified on the basis of the causative genes or gene loci. To date, at least 26 subtypes of ADCA have been identified including spinocerebellar ataxia (SCA) type 1, 2, Machado-Joseph disease (MJD/SCA3), 4–8, 10–19/22, 21, 23, 25–28, and dentatorubral and pallidoluysian atrophy (DRPLA) [2,3].

Among these subtypes, SCA4 was mapped to chromosome 16q22.1 in a Scandinavian family residing in Utah and Wyoming in 1996 [4]. This family showed prominent sensory axonal neuropathy and pyramidal tract signs in addition to cerebellar ataxia. In 2003, a German family characterized by cerebellar ataxia and sensory axonal neuropathy was assigned to the same locus as SCA4 [5].

Meanwhile, the gene locus responsible for six Japanese families with ADCA was mapped to the same region as SCA4 in 2000 [6]. Although SCA4 and this form of ADCA might be allelic, the clinical features of the Japanese families

* Corresponding author. Tel.: +81 285 58 7352; fax: +81 285 44 5118.
E-mail address: ytakiya@jichi.ac.jp (Y. Takiyama).

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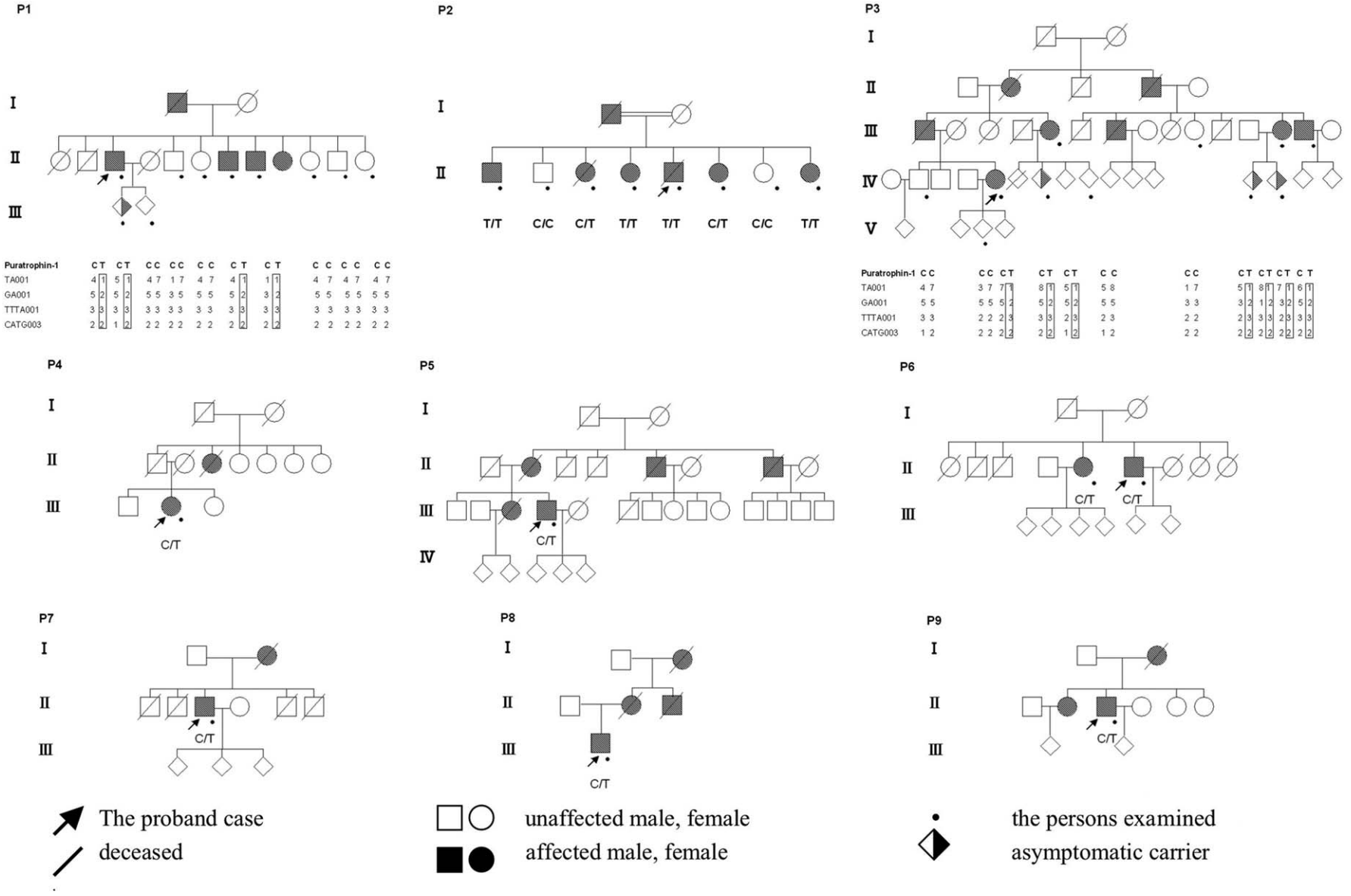

Fig. 1. The pedigrees of nine Japanese families with 16q-linked ADCA. In pedigrees 1 and 3, the gender is concealed in those individuals, including asymptomatic ones, denoted by diamonds to maintain the anonymity of the families.