Spincerebellar degeneration (SCD) is a group of disorders characterized by progressive ataxia caused by dysfunction and atrophy of the cerebellum or its projections. Approximately one-third of SCD cases are familial SCD, the majority of which are attributed to CAG triplet repeat expansions including spinocerebellar ataxia (SCA1, SCA2, Machado-Joseph disease (MJD))/SCA3, SCA6, SCA8, SCA12, SCA17, and dentate-rubro-pallido-luysian atrophy (DRPLA). The triplet repeat number of the alleles representing complete penetrance varies among diseases. Generally, there is a gap between the normal alleles and the complete penetrance alleles. Rarely, intermediate alleles with the repeat numbers between the abnormal and normal ranges are observed, although the implications of these intermediate alleles remain ambiguous.

MJD is one of the most frequent triplet repeat diseases worldwide. The number of CAG expansion repeats for complete penetrance alleles ranges from 60 to 87, whereas that for normal alleles ranges from 12 to 44. Intermediate expansion alleles, with repeats ranging from 45 to 59, are reported to be rare, and their clinical implications have not been completely delineated. Herein, we describe a pedigree with compound heterozygous intermediate alleles in the MJD locus representing progressive cerebellar ataxia and sensory axonal neuropathy.

Methods. DNA samples were obtained from all the siblings except for individual II-1 with institutional review board–approved informed consent. PCR-based fragment analysis was performed to detect repeat expansions in SCA1, SCA2, MJD, SCA6, SCA8, SCA12, SCA17, and DRPLA loci. Direct nucleotide sequencing method confirmed CAG expansions in the MJD locus (e-Methods).

Results. The CAG repeat numbers in the MJD locus of individuals II-2, II-3, II-4, and II-5 were determined as 50/7, 55/49, 57/21, and 55/49, respectively (figure). The repeat numbers in other loci in the index patient were within the normal ranges.

Discussion. This study demonstrated that the compound heterozygous intermediate CAG expansions in the MJD locus were associated with cerebellar ataxia with sensory axonal neuropathy. The symptoms and signs identified in II-4 were probably due to alcohol intoxication, although the heterozygous intermediate allele might also contribute to the mild phenotype. The different length of intermediate alleles suggested repeat instability, PCR stuttering, or nonpaternity. A rare normal allele with 7 CAG repeat was observed. Clinical manifestations of the
patients with heterozygous MJD intermediate alleles in previous reports varied, including ataxia with autonomic dysfunction or restless leg syndrome with sensory axonal neuropathy without overt cerebellar ataxia. Thus, this study provides insight into the clinical implications of MJD intermediate alleles.

Of note, the intermediate alleles are assumed to have an additive effect considering that each intermediate allele by itself was unlikely to cause complete penetrance phenotypes in this pedigree. Homozygous complete penetrance alleles in MJD loci tended to cause more severe phenotypes with earlier onset than heterozygous complete penetrance alleles. The underlying mechanism was postulated as follows: homozygous expanded polyglutamine tracts in ataxin-3 proteins more likely aggregate than heterozygous expanded tracts. Likewise, this study raises the possibility that 2 intermediate alleles together might confer the polyglutamine-derived cytotoxicity above the threshold, triggering multiple mechanisms for the development of MJD.

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