論 文 要 旨

DNA analysis of benign adult familial myoclonic epilepsy reveals associations between the pathogenic TTTCA repeat insertion in *SAMD12* and the non-pathogenic TTTTA repeat expansion in *TNRC6A*

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Benign adult familial myoclonic epilepsy (BAFME) is an autosomal dominant disease characterized by adult-onset tremulous hand movement, myoclonus, and infrequent epileptic seizures. Recently, intronic expansion of unstable TTTCA/TTTTA pentanucleotide repeats in *SAMD12*, *TNRC6A,* or *RAPGEF2* were identified as pathological mutations in Japanese BAFME pedigrees. To confirm these mutations, we performed a genetic analysis on 12 Japanese BAFME pedigrees. A total of 143 participants, including 43 familial patients, five suspected patients, three sporadic non-familial patients, 22 unaffected familial members, and 70 unrelated controls, were screened for expanded abnormal pentanucleotide repeats in *SAMD12, TNRC6A, RAPGEF2, YEAT2, MARCH6,* and *STARD7*. DNA samples were analyzed using Southern blotting, long-range polymerase chain reaction (PCR), repeat-primed PCR and long-range PCR followed by Southern blotting. Of the 51 individuals with clinically diagnosed or suspected BAFME, 49 carried a *SAMD12* allele with an expanded TTTCA/TTTTA pentanucleotide repeat. Genetic and clinical anticipation was observed. As in previous reports, the one patient with homozygous mutant alleles showed more severe symptoms than the heterozygous carriers. In addition, screening for expanded pentanucleotide repeats in *TNRC6A* revealed that the frequency of expanded TTTTA repeat alleles in the BAFME group was significantly higher than in the control group. All patients who were clinically diagnosed with BAFME, including those in the original family reported by Yasuda, carried abnormally expanded TTTCA/TTTTA repeat alleles of *SAMD12*. Patients with BAFME also frequently carried a TTTTA repeat expansion in *TNRC6A*, suggesting that there may be unknown factors in the ancestry of patients with BAFME that make pentanucleotide repeats unstable.