

ES1-1

Pentanucleotide repeat expansions in benign adult familial myoclonic epilepsy (BAFME)

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Benign adult familial myoclonic epilepsy (BAFME) is an autosomal dominant disorder characterized by infrequent generalized epilepsy and myoclonic tremor. The causative genes for BAFME have not been identified.

Fifty one families including 91 patients were enrolled in the study. We found conserved haplotypes among the families, which enabled us to narrow the candidate region to 134 kb. An intensive search of the whole genome sequence data revealed TTTCA and TTTTA repeat expansions in intron 4 of *SAMD12*, which were found exclusively in the patients in the 49 families. In a homozygous patient, mild and diffuse loss of Purkinje cells and halo-like amorphous materials around the cytoplasm of several Purkinje cells were evident, whereas the feature was inconspicuous in patients with heterozygous mutations. RNA foci consisting of UUUCA repeats, but not of UUUUA repeats, were observed in neurons of the autopsied brains. No ubiquitinated inclusions were found in autopsied brains.

We hypothesized that the same repeat motifs in other genes might be involved in the remaining two families without repeat expansion mutations in *SAMD12*. We found accumulated short reads filled with TTTCA and TTTTA repeats, which led to identification of repeat expansion mutations of the same motifs in intronic sequences of *TNRC6A* in a family and of *RAPGEF2* in the other family.

The findings that the same expanded repeat motifs in the three independent genes lead to BAFME phenotypes emphasize the role of TTTCA repeat expansions in BAFME, presumably through RNA-mediated toxicity.

ES1-2

A modifier of the unconventional aggregate pathologies in C9orf72-FTLD/ALS

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An intronic GGGGCC (G4C2) repeat expansion in C9orf72 was identified as a leading genetic cause of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). The hexanucleotide DNA repeat is bidirectionally transcribed into repeat RNA accumulating within RNA foci. We and others revealed the repeat RNA is even translated into five distinct proteins with dipeptide-repeat motifs in the absence of the canonical translation initiation codon (AUG). We named these proteins as dipeptide-repeat protein (DPR). DPR forms characteristic inclusions in C9orf72 patient's brain. Since the identification of DPR, cytotoxic properties of DPR has been extensively shown in multiple models of the disease. Repeat-dependent toxicity in C9orf72 may affect nuclear import machinery. hnRNPA3 is a nucleo-cytoplasmic shuttling heterogeneous nuclear ribonucleoprotein (hnRNP) that we found specifically binds to the G4C2 repeat RNA. We revealed a reduction of hnRNPA3 leads to enhanced production and deposition of DPR proteins as well as RNA foci. Moreover, reduced nuclear hnRNPA3 correlates with increased DPR depositions in the hippocampus of patients with C9orf72 repeats. In summary, we identified major constituents of the unconventional protein aggregate pathology in C9orf72-FTLD/ALS patients. Moreover, we postulate hnRNPA3 as an endogenous modifier of the DPR and RNA aggregate pathologies. References 1. Mori K et al, EMBO Reports 17, 1314-1325, 2016 2. Mori K et al, Acta Neuropathologica 126, 881-893, 2013 3. Mori K et al, SCIENCE 339, 1335-1338, 2013 4. Mori K et al, Acta Neuropathologica 125, 413-423, 2013