Abstracts

Papers appearing in the August 2018 issue

Noncoding repeat expansions for ALS in Japan are associated with the *ATXN8OS* gene

Objective To assess the contribution of noncoding repeat expansions in Japanese patients with amyotrophic lateral sclerosis (ALS).

Methods Sporadic ALS in Western countries is frequently associated with noncoding repeat expansions in the *C9ORF72* gene. Spinocerebellar ataxia type 8 (SCA8) is another noncoding repeat disease caused by expanded CTA/CTG repeats in the *ATXN8OS* gene. Although the involvement of upper and lower motor neurons in SCA8 has been reported, a positive association between SCA8 and ALS remains unestablished. Spinocerebellar ataxia type 36 is a recently identified disease caused by noncoding repeat expansions in the *NOP56* gene and is characterized by motor neuron involvement. We collected blood samples from 102 Japanese patients with sporadic ALS and analyzed the *ATXN8OS* gene by the PCR–Sanger sequencing method and the *C9ORF72* and *NOP56* genes by repeat-primed PCR assay.

Results Three patients with ALS (3%) had mutations in the *ATXN8OS* gene, whereas no patient had a mutation in the *C9ORF72* or *NOP56* gene. The mutation-positive patients were clinically characterized by neck weakness or bulbar-predominant symptoms. None of our patients had apparent cerebellar atrophy on MRI, but 2 had nonsymptomatic abnormalities in the white matter or putamen.

Conclusions Our finding reveals the importance of noncoding repeat expansions in Japanese patients with ALS and extends the clinical phenotype of SCA8. Three percentage seems small but is still relatively large for Japan, considering that the most commonly mutated genes, including the *SOD1* and *SQSTM1* genes, only account for 2%–3% of sporadic patients each.

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ASPMR1 splice variant: A predictor of fragile X-associated tremor/ataxia

Objective To explore the association of a splice variant of the *antisense fragile X mental retardation 1* (*ASPMR1*) gene, loss of *fragile X mental retardation 1* (*FMR1*) AGG interspersions and *FMR1* CGG repeat size with manifestation, and severity of clinical symptoms of fragile X-associated tremor/ataxia syndrome (FXTAS).

Methods A neurologic evaluation was carried out for premutation carriers (PMCs) with FXTAS, without FXTAS, and normal controls (NCs), whose skin and blood samples were collected. Expression of *ASPMR1* transcript/splice variant 2 (*ASPMR1-TV2*), nonspliced *ASPMR1*, total *ASPMR1*, and *FMR1* messenger RNA were quantified and compared using analysis of variance. Least absolute shrinkage and selection operator logistic regression and receiver operating characteristic analyses were performed.

Results Premutation men and women both with and without FXTAS had higher *ASPMR1-TV2* levels compared with NC men and women ($n = 135, 135, p < 0.0001$), and *ASPMR1-TV2* had good discriminating power for FXTAS compared with NCs but not for FXTAS from PMC. After adjusting for age, loss of AGG, larger CGG repeat size (in men), and elevated *ASPMR1-TV2* level (in women) were strongly associated with FXTAS compared with NC and PMC (combined).

Conclusions This study found elevated levels of *ASPMR1-TV2* and loss of AGG interruptions in both men and women with FXTAS. Future studies will be needed to determine whether these variables can provide useful diagnostic or predictive information.

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