博士論文　（要約）

Molecular genetic study of the *FMR1* CGG repeat configurations in the Japanese population and patients with Fragile X-Associated Tremor/Ataxia Syndrome

（日本人集団および脆弱 X 振戦/失調症候群発症者の *FMR1*

遺伝子 CGG 繰り返し配列構造の分子遺伝学的解析）

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Fragile X–Associated Tremor/Ataxia Syndrome (FXTAS) is an adult-onset neurodegenerative disorder, usually affecting individuals over 50 years of age, caused by an expansion of CGG triplet repeats between 55–200 CGG repeats (premutation) in the *FMR1* gene. *FMR1* Premutation may also cause another disease in women, which is Fragile X-Associated Primary Ovarian Insufficiency. An expansion into >200 CGG repeats (full mutation) leads to Fragile X Syndrome, an inherited intellectual disability disorder. Typically, individuals possess under 45 CGG repeats (normal), and those with the range of expansion between 45-54 CGG repeats (intermediate) have not been linked to any known phenotype.

We performed a wide population-based molecular genetic study for the *FMR1* gene in Japan. We recruited 1095 Japanese patients with movement disorders (348 patients with cerebellar ataxia, 702 patients with multiple system atrophy, and 45 patients with neuronal intranuclear inclusion disease) and 384 healthy controls. We identified three male patients with *FMR1* premutation. Two carriers were in a group of 76 male patients with sporadic-late cerebellar ataxia, giving an estimation of 2.7%, which is a high rate considering the low prevalence of the *FMR1* premutation in the Japanese general population. Their CGG repeat lengths in *FMR1* were 84 and 103 CGG repeats. And one carrier with 60 CGG repeats, among 106 male patients with multiple system atrophy-parkinsonism. Also, we identified two male patients and one female patient with multiple system atrophy as carriers for *FMR1* intermediate, in addition to two males and three females with *FMR1* intermediate in healthy controls.

In the present study, we characterized the CGG repeats motif and AGG interruption in a group of 346 Japanese patients with cerebellar ataxia and 103 healthy controls. We found that the modal length of CGG repeats in the Japanese population was 29, followed by 30, and 36 CGG repeats, which is compatible with values in other populations, except for the 36 CGG repeats which is unique for Asian people.

Furthermore, we studied the correlation between the genotype and the phenotype of FXTAS patients and compared them with 188 previously reported FXTAS cases in the literature. We found that tremor is the first recognizable symptom of FXTAS in the majority of patients (57.3%), and ataxia is the second most common presentation (25.2%), followed by parkinsonism and cognitive impairment (3.1%), separately. Age of onset of ataxia in males showed inverse linkage to the CGG repeat length in line with previous studies, while there is no correlation between age of onset of ataxia and CGG repeat length in females was elucidated.