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[Title]

CAG Repeat Expansion in *THAP11* is Not Detected in a Cohort with Spinocerebellar Ataxia from Hokkaido, the Northernmost Island of Japan.

[Short running title]

CAG Repeat Expansion in *THAP11* is Not Detected in Hokkaido

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Author contributions

SS, KM, YS, MM, II, HY, and IY contributed to study conception and design. SS, KM, YS, MM, II, HY, and IY contributed to data acquisition and analysis. SS, KM, YS, MM, II, HY, and IY drafted the manuscript.

1 In June 2023, Tan and colleagues reported that a CAG repeat expansion in exon 1 of the
2 gene encoding THAP domain containing 11 (*THAPII*) is a novel cause of spinocerebellar
3 ataxia (SCA)¹⁾. It exhibits considerable phenotypical heterogeneity, encompassing
4 asymptomatic carriers, mild ataxia, and cerebellar ataxia accompanied with epilepsy. The
5 CAG repeats ranged in size from 20 to 38 in healthy individuals and from 45 to 100 in
6 SCA patients. Its pathogenesis may be linked to polyglutamine toxicity, which is the most
7 common mechanism underlying SCA¹⁾. However, Hsiao and colleagues reported that
8 SCA patients with a *THAPII* CAG expansion are very rare or do not exist in Taiwan²⁾.

9 Since 1982, we have been conducting genetic analysis of autosomal dominant
10 spinocerebellar degeneration in Hokkaido³⁻⁵⁾, the northernmost island of Japan, with a
11 population of over 5 million people. Hokkaido is comparable to regions such as Taiwan.
12 Many of its inhabitants are descendants of settlers from various parts of Japan who arrived
13 after the country's political reformation in 1868 (the Meiji Restoration). This has resulted
14 in a unique genetic composition that differs from the other regions of Japan, making
15 Hokkaido a microcosm of the country. The population of Hokkaido is very similar to that
16 of Taiwan, but their genetic backgrounds are different, so we believe that there is value
17 in examining whether the *THAPII* CAG expansion is present within our large-scale
18 cohort of patients with SCA in Hokkaido.

From April 1982 to December 2020³⁻⁵⁾, we have performed genetic analyses on 847 cases with SCA in our Hokkaido cohort. Among these cases, 256 were not diagnosed with a known genetic cause of SCA such as Machado-Joseph disease/SCA3 or SCA6. Out of these 256 cases, DNA samples were available for *THAPII* analysis from 194 cases, and the CAG repeat in *THAPII* ranged in size from 23 to 37, with a median of 28/29 repeats; however, there were no patients with a CAG expansion in *THAPII*.

Furthermore, from January 2021 to June 2024, among 32 genetically undiagnosed cases with available DNA samples, the CAG repeat in *THAPII* ranged in size from 28 to 35, with a median of 28/29 repeats; similarly, there were no patients with a CAG expansion in *THAPII*.

In a previous study of this cohort³⁻⁵⁾, patients presenting with symptoms such as mild ataxia or cerebellar ataxia accompanied with epilepsy, which are phenotypes associated with a CAG expansion in *THAPII*, were genetically diagnosed with SCA6, SCA31, or dentatorubral-pallidoluysian atrophy. To the extent that clinical symptoms could be ascertained, there were no patients in this cohort who were strongly suspected of having a CAG expansion in *THAPII* based on clinical presentation alone, among those without a confirmed genetic diagnosis.

In conclusion, these findings suggest that CAG expansions in *THAPII* are not present

37 or are extremely rare in Hokkaido, the northernmost island of Japan.

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