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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
Author(s)	Shirai, Shinichi; Mizushima, Keiichi; Shibata, Yuka et al.
Citation	Movement disorders, 39(9), 1657-1658 https://doi.org/10.1002/mds.29975
Issue Date	2024-09-17
Doc URL	https://hdl.handle.net/2115/96114
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Type	journal article
File Information	Manuscripts_rev2.pdf

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Letter: Published Article

[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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Manuscript word count: 468 words

Tables: 0,

Figure: 0,

[Conflict of Interest]

None declared.

Funding: This work was supported by the Research Committee on the Medical Basis of Motor Ataxias, Health and Labor Sciences Research Grants, The Ministry of Health, Labor and Welfare, Japan (grant no 23FC1010 [to I. Yabe]).

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.

In June 2023, Tan and colleagues reported that a CAG repeat expansion in exon 1 of the gene encoding THAP domain containing 11 (*THAP11*) is a novel cause of spinocerebellar ataxia (SCA)[1]. It exhibits considerable phenotypical heterogeneity, encompassing asymptomatic carriers, mild ataxia, and cerebellar ataxia accompanied with epilepsy. The CAG repeats ranged in size from 20 to 38 in healthy individuals and from 45 to 100 in SCA patients. Its pathogenesis may be linked to polyglutamine toxicity, which is the most common mechanism underlying SCA[1]. However, Hsiao and colleagues reported that SCA patients with a *THAP11* CAG expansion are very rare or do not exist in Taiwan[2].

Since 1982, we have been conducting genetic analysis of autosomal dominant spinocerebellar degeneration in Hokkaido[3-5], the northernmost island of Japan, with a population of over 5 million people. Hokkaido is comparable to regions such as Taiwan. Many of its inhabitants are descendants of settlers from various parts of Japan who arrived after the country's political reformation in 1868 (the Meiji Restoration). This has resulted in a unique genetic composition that differs from the other regions of Japan, making Hokkaido a microcosm of the country. The population of Hokkaido is very similar to that of Taiwan, but their genetic backgrounds are different, so we believe that there is value in examining whether the *THAP11* CAG expansion is present within our large-scale cohort of patients with SCA in Hokkaido.

From April 1982 to December 2020[3-5], 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 *THAP11* analysis from 194 cases, and the CAG repeat in *THAP11* ranged in size from 23 to 37, with a median of 28/29 repeats; however, there were no patients with a CAG expansion in *THAP11*.

Furthermore, from January 2021 to June 2024, among 32 genetically undiagnosed cases with available DNA samples, the CAG repeat in *THAP11* ranged in size from 28 to 35, with a median of 28/29 repeats; similarly, there were no patients with a CAG expansion in *THAP11*.

In a previous study of this cohort [3-5], patients presenting with symptoms such as mild ataxia or cerebellar ataxia accompanied with epilepsy, which are phenotypes associated with a CAG expansion in *THAP11*, 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 *THAP11* based on clinical presentation alone, among those without a confirmed genetic diagnosis.

In conclusion, these findings suggest that CAG expansions in *THAP11* are not present

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

Acknowledgements

We thank all patients for their cooperation. We thank Rie Nomachi for data processing. We thank the neurologists at the Department of Neurology, Hokkaido University for their attentive care of patients during the study period.

This work was supported by the Research Committee on the Medical Basis of Motor Ataxias, Health and Labor Sciences Research Grants, The Ministry of Health, Labor, and Welfare, Japan (grant no: 23FC1010 [to I. Yabe]).

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