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Redefining the Pathogenic CAG Repeat Units Threshold in *CACNA1A* for Spinocerebellar Ataxia Type 6

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Abstract

Background and Objectives

Spinocerebellar ataxia type 6 (SCA6) is caused by expansion of CAG repeat units (RUs) in *CACNA1A*. While the pathologic threshold has been considered to be 20 or 21 RUs, the lower limit remains controversial. This study aimed to clarify the pathologic significance of RUs in SCA6, including the role of opposite alleles (OAs).

Methods

This was an observational study of patients with suspected spinocerebellar ataxia who underwent SCA6 genetic testing. We analyzed the relationship between *CACNA1A* RUs and age at onset (AAO). Family history positivity rates were examined for different RUs of the expanded allele (EA). Regression analyses were performed for AAO estimation based on the EA RUs. The influence of OAs on AAO was investigated, particularly in cases with 21–22 EA RUs.

Results

In total, 2,768 participants were enrolled. Family history positivity rates increased progressively above 19 RUs and plateaued at ≥23 RUs. Regression analysis of cases with ≥23 RUs showed that 96.20% of cases with ≥23 RUs, 90.67% of cases with 22 RUs, 91.15% of cases with 21 RUs, 61.54% of cases with 20 RUs, and 33.33% of cases with 19 RUs fell within the 95% prediction interval for AAO. However, no patients with ≤18 RUs were included. In the 21–22 RU group, OAs significantly influenced AAO, and ≥17 RUs had a significant effect. For ≥23 RUs, no significant OA effect was observed. Cases with 19–20 RUs showed a higher prevalence of OA with ≥19 RUs compared with cases with ≥23 RUs.

Discussion

Our findings suggest that clinical manifestation within a typical lifespan likely requires at least 19 RUs. The 19–20 RU range represents an intermediate zone where OA may influence disease likelihood. For 21-22 RUs, OA significantly affects AAO, indicating a complex interplay between EA and OA. ≥23 RUs seem sufficient to cause disease onset within a typical lifespan, regardless of OA. These results provide a new paradigm for SCA6 diagnosis and genetic counseling, emphasizing the need for cautious interpretation of the intermediate RU range and consideration of OA.

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Glossary

AAO = age at onset; **DRPLA** = dentatorubral-pallidoluysian atrophy; **EA** = expanded allele; **HD** = Huntington disease; **OA** = opposite allele; **RU** = repeat unit; **SCA6** = spinocerebellar ataxia type 6.

Introduction

Spinocerebellar ataxia type 6 (SCA6) is an autosomal dominant, slowly progressive cerebellar ataxia caused by abnormal expansion of CAG repeat units (RUs) in exon 47 of the α1A calcium channel gene (*CACNA1A*).[1] The age at onset (AAO) is inversely correlated with the number of RUs in the expanded allele (EA).[2-6] Traditionally, 21 or more RUs are considered pathologic, whereas 18 or fewer have been deemed normal.[3,4,7,8] However, the clinical significance of the 19–20 RU range remains controversial and has emerged as a critical issue in SCA6 diagnosis.[2-4,7-12]

Notably, there are few reports of patients with SCA6 with 19 or 20 RUs who have been homozygous or compound heterozygous.[2,11,13] These cases suggest that, within this intermediate RU range, both alleles may influence AAO. Indeed, some studies have indicated that the number of CAG RUs in the opposite allele (OA) affects AAO,[2,6,14,15] thus underscoring the need to stratify clinical studies of SCA6 by considering both EA and OA.

Previous studies have examined the influence of OA in groups with ≥20 or ≥21 RUs.[2,14,15] However, this approach has limitations. AAO occurred later in the groups with relatively shorter EAs (20 or 21 RUs). Consequently, some individuals may not manifest the disease during their lifespan. If OA affects AAO, the length of the OA may be biased toward longer alleles in the onset group because individuals who died before onset were excluded. This possibility should be considered when evaluating OA effects.

Our study was performed to address these gaps in understanding. First, we estimated the number of RUs that consistently led to SCA6 development within a typical lifespan by comparing familial accumulation rates. Then, based on the results, we used a cohort estimated to include all cases with a specific CAG RU and derived AAO predictions for each RU value. Subsequently, we examined the minimum number of RUs potentially associated with SCA6 manifestation within the normal human lifespan and then investigated the effect of CAG RUs in the OA on AAO for each RU value in the EA. In addition, we assessed the pathologic significance of 19–20 RUs.

The aim of the study was to clarify the influence of OAs on SCA6 onset and to explore the pathologic significance of CAG RUs in *CACNA1A* in detail. We sought to determine the minimum number of CAG RUs required to exert a pathologic effect, to assess the impact of the OA on AAO, and to clarify the clinical significance of the 19–20 CAG RU range. Our findings may have important implications for SCA6 diagnosis, prognosis, and genetic counseling.

Methods

Patients

We included patients in whom spinocerebellar degeneration was suspected and performed genetic testing for SCA6. A total of 2,768 patients were included: 1,498 patients for whom genetic testing was performed at the Department of Neurology, Niigata University Brain Research Institute, between January 1, 1992, and July 7, 2023, and 1,270 patients for whom genetic testing was performed at the Japan Consortium for Ataxias (J-CAT) between November 1, 2016, and August 23, 2023. In the Niigata University cases, we searched for pathogenic repeat expansion of SCA1, 2, 3, 6, 17, and 31; Huntington disease (HD); and dentatorubral-pallidoluysian atrophy (DRPLA) causative genes. Testing for SCA6 had been performed in all cases, but not all the other genes had been tested in every case. All cases with 19 or 20 EA RUs in *CACNA1A* were considered negative for SCA1, 2, 3, and 31 and DRPLA, which are the most frequent forms of spinocerebellar degeneration in Japan. In J-CAT cases, we searched for the causative genes of SCA1, 2, 3, 6, 8, 12, 17, and 31; HD; and DRPLA and excluded any patients who were positive for these diseases. We defined AAO as the age at which the patient first became aware of any neurologic symptoms related to spinocerebellar degeneration. Patients whose AAO was unknown were excluded. Clinical symptoms and the presence or absence of a family history were not included as study criteria.

Genetic analysis: Genomic DNA was extracted from leukocytes in the venous blood of patients. PCR was performed on the CAG RUs of *CACNA1A*, and the fragment size was analyzed by fluorescence capillary electrophoresis.

The primers used to amplify CAG RUs were as follows: For: (FAM) TCAACATCTGGGTACCAGCACTCC; Rev: TACCTCCGAGGGCCGCTGGTG (Niigata University)[16]; For: (FAM) CACGTGTCCTATTCCCCCCTGTGATCC; Rev: TGGGTACCTCCGAGGGCCGCTGGTG (J-CAT).

Statistical Analysis

A longer CAG RU in both alleles of *CACNA1A* was defined as the EA, and the shorter side was defined as the OA. If the number of RUs in both alleles was equal, that in the EA and OA groups was considered to be the same.

Family history was investigated using a questionnaire given at the time of the genetic test request or J-CAT registration. Through the interview process, patients with a first-degree relative with SCA were identified as having a family history. Statistical evaluation of the family history positivity rates was performed using the Fisher exact test.

The association between CAG RU number and AAO in SCA6 cases with ≥23 CAG RUs in the EA was assessed by regression analysis using linear, quadratic, and cubic equations, and the equation with the highest adjusted R-squared value was finally adopted. The prediction interval of the regression curve was determined and assessed to derive the proportion of cases that fell within the AAO prediction interval for each RU in cases with ≤22 CAG RUs.

To examine the influence of CAG RU number for the OA on AAO, multiple regression analysis was performed on diagnosed SCA6 cases using the number of CAG RUs for the EA and the OA as explanatory variables and AAO as the objective variable.

Statistical software R version 4.4.0 was used for the analysis. The Pearson correlation coefficient was calculated using the cor function. The lm and prediction functions were used to calculate the regression analysis predictions. Multiple testing corrections were performed using Bonferroni correction. The significance level was set at $p < 0.05$.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Ethics Committee for Genetic Analysis of Niigata University (approval numbers: G2018-0011 and G2021-0010) and the Ethics Committee of the National Center of Neurology and Psychiatry (approval numbers: A2015-050 and A2019-099). All the participants provided written informed consent.

Data Availability

The data set used for the analysis in this study is not publicly available. Further information is available from the corresponding author on reasonable request.

Results

Data Set Details

The number of EA RUs for patients in the data set used was 15.2 ± 4.2 (mean ± SD; Min 4, Max 30), and the number of OA RUs was 11.6 ± 2.3 (mean ± SD; Min 3, Max 22). The AAO was 49.7 ± 18.7 (mean ± SD) years (Min 0, Max 90 years). There were 1,420 men, 1,336 women, and 12 patients of unknown sex.

Family History Positivity Rate for Each Number of CAG RUs

To estimate how the EA penetrance varied according to the RU number, we examined the family history positivity rate for each number of CAG RUs. The family history positivity rate was relatively constant at ≤18 RUs (average, 29.3%). Above 19 RUs, the positivity rate increased progressively, and at ≥23 RUs, it remained almost constant (average 84.2%) (Figure 1A, eTable 1).

There was no significant difference in the family history positivity rates between cases with ≤18 RUs and those with 19 or 20 RUs. Cases with 21 and 22 RUs had significantly higher family history positivity rates than those with ≤18 RUs (p = 2.04e-7 and p < 2.2e-16, respectively) but lower rates than those with ≥23 RUs (p = 3.13e-8 and p = 6.68e-6, respectively). Thus, it was possible to categorize the family history positivity rates into 3 groups: ≤20 RUs, ≥23 RUs, and an intermediate group.

Correlation Between AAO and the Number of EA CAG RUs

We generated a scatterplot illustrating the relationship between AAO and the number of EA CAG RUs (Figure 1B). Previous analyses of this relationship have defined the EA as having ≥20 or ≥21 RUs.[2-4,6,7] However, we observed a decrease in the family history positivity rate for patients with 22 or fewer EA RUs, suggesting that, in these groups, there may have been individuals who, despite carrying this allele, did not develop symptoms within their lifespan. Therefore, it is possible that the estimated AAO could be biased toward a younger age.

Therefore, we performed regression analyses (linear, quadratic, and cubic) using only patients with ≥23 RUs, where the family history positivity rate was high, and all carriers were assumed to be included. The number of EA CAG RUs was used as the explanatory variable and AAO as the objective variable. A quadratic equation provided the best fit (adjusted R-squared: 0.420).

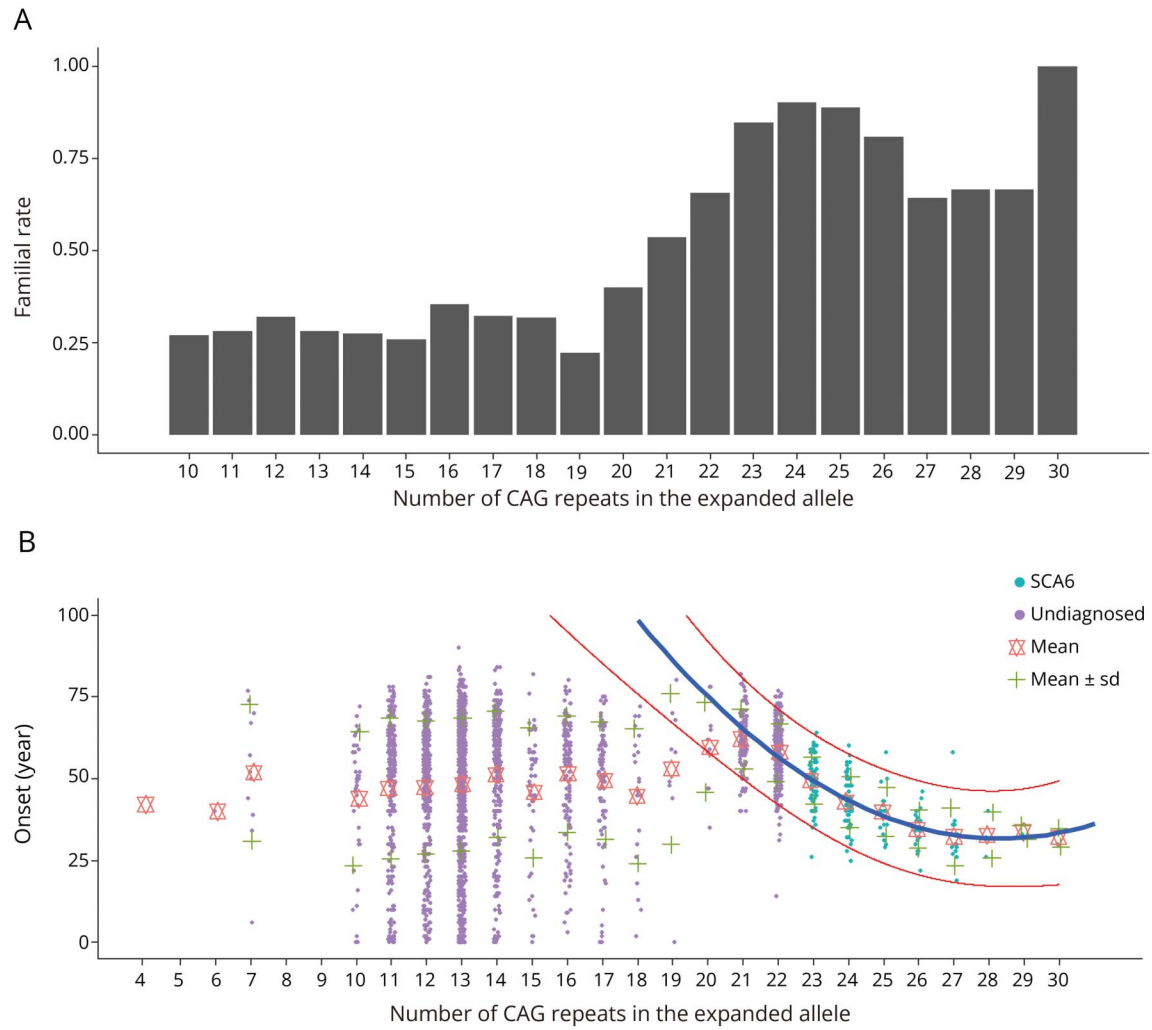
The regression curves estimated within the 95% prediction interval for AAO included 96.20% of the patients with ≥23 RUs, 90.67% of those with 22 RUs, and 91.15% of those with 21 RUs. For patients with 20 and 19 EA RUs, 61.54% and 33.33%, respectively, fell within the 95% prediction interval. None of the patients with ≤18 RUs fell within the 95% prediction interval (Figure 1B; Table 1). The estimated AAO at 18 RUs was 98.44 years, with a lower limit of 75.86 years for the 95% prediction interval.

Relationship Between AAO and the Number of CAG RUs for the OA

We examined whether the OA affected the AAO of SCA6. A significant Pearson correlation was found between the number of CAG RUs for the OA and AAO in patients with 21 or 22 EA RUs (21 RUs: n = 110, p = 0.0375, R = −0.199, Figure 2A; 22 RUs: n = 315, p = 1.21e-5, R = −0.244, Figure 2B). There was no significant correlation in patients with ≥23 RUs.

We conducted multiple regression analysis using the number of CAG RUs for both the EA and OA groups as independent

Figure 1 Relationship Between the EA CAG RU Number and AAO or Rate of Familial Disease Occurrence



(A) Bar chart showing family history positivity rate plotted against EA CAG RU number. (B) Scatterplot of the relationship between AAO (y-axis) and EA RU number (x-axis) created by shifting the points horizontally using Geom jitter (height = 0, width = 0.1). Green dots represent cases with ≥23 RUs as a group with a high rate of family history positivity, and purple dots represent cases with ≤20 RUs. The mean is represented by a red star and the mean ± SD by an ochre cross. In addition, a regression line was created using the EA as the explanatory variable and AAO as the objective variable in patients with ≥23 RUs. AAO = age at onset; RU = repeat unit.

variables and AAO as the dependent variable. When only cases with 21 or 22 RUs for the EA were analyzed, the number of CAG RUs for the OA affected AAO significantly (n = 425, p = 2.46e-6). However, for cases with ≥23 EA RUs, the OA had no significant effect (n = 184, p = 0.321).

For the 425 cases with 21 or 22 EA RUs, we performed multiple regression analyses with 12 patterns, including all cases and excluding cases with any number of OA RUs from 12 to 22 or higher. After multiple testing corrections, cases in which 17 or fewer OA RUs influenced AAO were included (Table 2). We concluded that in this group, OA with 17 or more RUs affected AAO.

Pathologic Significance of Intermediate Alleles

Finally, we examined the EAs with 19 and 20 RUs. Based on previous reports and our examination of OAs, we hypothesized that both alleles affected disease onset in cases where the EA had 19 or 20 RUs. We then divided the cases into 2 groups in which the OAs had <19 and ≥19 RUs and calculated the percentages of cases in each group showing various numbers of EA RUs (Table 3). Cases with ≥19 OA RUs were significantly more prevalent among those with 19 or 20 EA RUs than among those with ≥23 EA RUs (Fisher exact test: 19 RUs, p = 0.0466; 20 RUs, p = 0.00240). One of 9 cases whose EA had 19 RUs had an OA with 19 RUs, and her age at onset was 70 years.

Among the cases whose AAO fell within the 95% interval predicted by the previously created quadratic regression curve, one of 3 whose EA had 19 RUs and one of 6 whose EA had 20 RUs had an OA with ≥19 RUs. Among the 19-RU EA cases, the mean number of OA RUs was 14.33 for those within the 95% prediction interval and 13.17 for those outside it. For

Table 1 Relationship Between Regression Analysis Predictions and Mean ± SD for Specific Numbers of CAG Repeats in the Expanded Allele

Allele repeats	Number of cases	Mean (y)	Mean-SD (y)	Mean + SD (y)	Predicted value (y)	Prediction interval-lower limit (y)	Prediction interval-upper limit (y)
30	2	32.00	29.17	34.83	33.47	17.59	49.35
29	3	33.67	31.59	35.75	31.95	17.02	46.89
28	3	32.67	25.64	39.69	31.69	17.17	46.21
27	14	32.21	23.42	41.01	32.69	18.30	47.08
26	21	34.48	28.63	40.32	34.95	20.59	49.31
25	18	39.89	32.44	47.34	38.47	24.14	52.81
24	51	42.88	35.11	50.65	43.26	28.96	57.55
23	72	49.38	42.26	56.49	49.30	34.98	63.63
22	315	57.96	49.12	66.79	56.61	42.00	71.21
21	110	62.07	53.01	71.14	65.18	49.81	80.54
20	10	59.50	45.84	73.16	75.00	58.15	91.86
19	9	52.89	29.88	75.90	86.09	66.85	105.34
18	22	44.64	24.10	65.17	98.44	75.86	121.03
17	90	49.41	31.50	67.33	112.06	85.18	138.93
16	127	51.39	33.64	69.13	126.93	94.88	158.98
15	50	45.70	25.76	65.64	143.06	104.99	181.13
14	277	51.24	31.99	70.49	160.46	115.58	205.34
13	950	48.15	27.86	68.44	179.12	126.66	231.57
12	354	47.19	26.83	67.55	199.03	138.27	259.79
11	220	46.96	25.46	68.46	220.21	150.42	290.00
10	37	43.84	23.51	64.16	242.65	163.13	322.17
7	11	51.82	30.94	72.70	317.54	204.66	430.42
6	1	40.00	NA	NA	345.03	219.66	470.39
4	1	42.00	NA	NA	403.78	251.40	556.16

the 20-RU EA cases, the mean number of OA RUs was 14.00 both within and outside the 95% prediction interval.

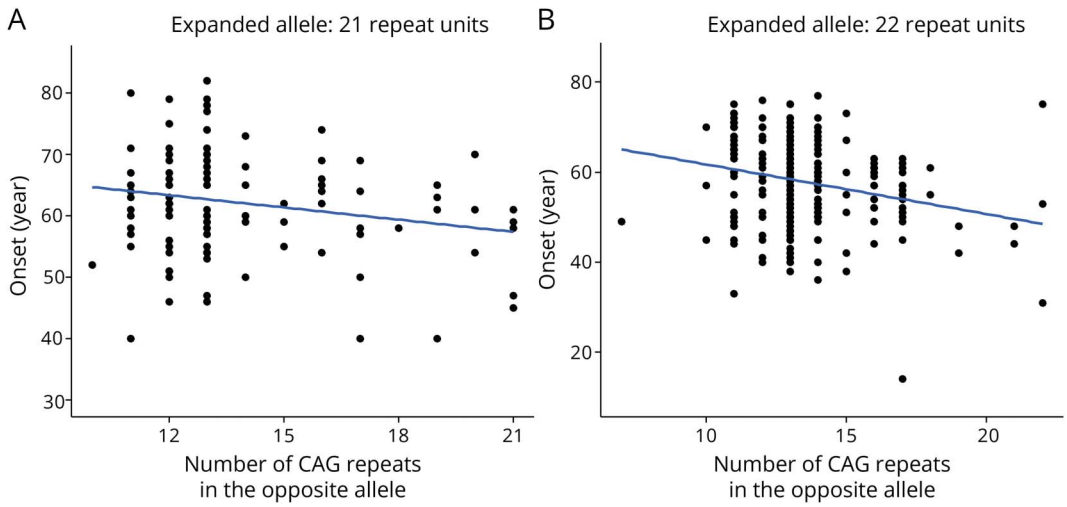
Discussion

This study of SCA6 has provided new insights into the pathologic significance of CAG RUs in *CACNA1A*. Traditionally, 20 or 21 RUs have been considered as pathologic thresholds.[2-4,7-10] However, our findings suggest that ≥21 RUs are pathologic alleles, that 19–20 RUs are intermediate alleles, and that ≤18 RUs are normal alleles. In addition, patients with 21–22 EA RUs revealed a significant correlation between the number of OA RUs and AAO.

The negative correlation between RU number and AAO suggests that a shorter expansion of RUs corresponds to a later AAO. Ataxia may be challenging to diagnose in older individuals owing to various age-related factors, and some individuals may not live long enough to manifest the disease. Our analysis showed that for 18 EA RUs, the estimated AAO was 98.44 years, and that the lower limit of the 95% prediction interval was 75.86 years. AAO for cases with ≤18 RUs did not fall within the 95% prediction interval of the regression curve. Therefore, we inferred that it is difficult to detect disease onset within a typical lifespan unless the EA has at least 19 RUs.

Our results revealed that cases with 19–20 RUs were more likely to deviate from the regression curve between the AAO and the number of RUs and had a lower family history positivity rate. In addition, more patients in this group had an OA with 19 or more RUs. These findings suggest that diagnosis of SCA6 within this range of RUs requires careful consideration of both the AAO and the number of OA RUs. However, the

Figure 2 Effects of the OA on AAO



(A) Among patients with 21 EA RUs, the relationship between the number of OA RUs and AAO was assessed using a scatterplot. (B) Among patients with 22 EA RUs, the relationship between OA RU number and AAO was assessed using a scatterplot. AAO = age at onset; RU = repeat unit.

number of cases with 19–20 RUs in our study cohort was limited, and more data on intermediate alleles will be needed before their pathologic significance can be defined more clearly.

Our results also showed that the group with 21 or 22 EA RUs had a lower family history positivity rate than the group with ≥23 EA RUs, and that the number of OA RUs was significantly correlated with AAO. This suggests that cases with 21–22 RUs may be influenced by the OA, and that in some cases, individuals may not manifest the disease within their lifetime. Conversely, in the group with ≥23 EA RUs, we observed no differences in family history positivity rates and no effect of the OA on AAO. Therefore, we conclude that alleles with ≥23 RUs alone exert a sufficient influence to cause disease onset within a typical lifespan.

21–22 EA RUs revealed a significant correlation between the number of OA RUs and AAO, particularly when OA had a minimum of 17 RUs. However, this does not imply that EAs above 17 RUs have a pathogenic threshold. It has been reported that *ATXN1* and *ATXN7* RUs affect the age at SCA6

Table 2 Regression Analysis Coefficients and Their *p* Values for CAG Repeats in the Opposite Allele

	Shorter allele		
No. of repeat units in the opposite allele	**Regression coefficient**	***p* Value**	**Adjusted *p* value**
−22	−0.93	2.46E-06	2.95E-05
−21	−0.97	2.49E-06	2.99E-05
−20	−0.89	1.33E-04	1.60E-03
−19	−0.97	7.65E-05	9.18E-04
−18	−0.89	7.87E-04	9.44E-03
−17	−0.93	7.46E-04	8.95E-03
−16	−0.58	8.38E-02	1.00E+00
−15	−0.64	1.38E-01	1.00E+00
−14	−0.48	2.96E-01	1.00E+00
−13	−0.11	8.49E-01	1.00E+00
−12	0.97	4.75E-01	1.00E+00
−11	3.59	1.20E-01	1.00E+00

Table 3 Numbers of Repeats in the Opposite Alleles for Each Expanded Allele

		Opposite allele		
		<19	≧19	Total
Expanded allele	19*	8 (88.9%)	1 (11.1%)	9
	20**	8 (80%)	2 (20%)	10
	21**	98 (89.1%)	12 (10.91%)	110
	22	308 (97.8%)	7 (2.22%)	315
	≥23	184 (100%)	0 (0%)	184

Opposite allele ≧19: Fisher exact test; *$p < 0.05$, **$p < 0.005$.

onset, but these do not cause SCA6.[15] Similarly, *CACNA1A* 17–18 RUs can be seen as a modifier of the AAO, and careful consideration is needed as to whether it is an onset factor.

Based on these results, we propose a refined clinical interpretation of *CACNA1A* EAs. In patients with ataxia, if the EA has ≤18 RUs, SCA6 can be ruled out, whereas for patients with 19–20 RUs, the number of OA RUs may influence the likelihood of developing SCA6. Our analysis suggests a higher probability of disease onset when the OA has ≥19 RUs. However, careful judgment is needed when considering the AAO and the possibility of other diseases. SCA6 can be diagnosed when patients with ataxia have ≥21 RUs. However, for asymptomatic individuals with 21–22 RUs, estimation of future onset requires cautious judgment that considers patient age and number of OA RUs. These findings have important implications for refining the diagnostic criteria for SCA6 and improving genetic counseling.

A number of reports have documented the influence of alleles on the AAO.[2,6,14,15] This study provides further clarification on the role of alleles in AAO, using a larger number of cases than previously reported. It suggests that OA only affect AAO when there are 21 or 22 EA RUs and not when there are 23 or more EA RUs. This is regarded as a condition in which EA is sufficiently toxic to exert a dominant effect, rendering OA nonfunctional when EA has 23 or more RUs. The pathogenic threshold of the allele, which has not been sufficiently investigated in previous reports, was also estimated from family history and regression analysis, indicating that its pathogenic significance should be carefully considered at 19 and 20 RUs.

The impact of homozygous intermediate alleles on age at onset is also a significant area of concern. In this regard, a case with *CACNA1A* homozygous EA of 19 RUs was reported, with a relatively young onset age of 33 years.[11] Conversely, the homozygous 19-RU case in this study had an onset age of 70 years. Because the heterozygous 19-RU cases in this study included non-SCA6, it is challenging to make a comparison of the age at onset differences with the homozygous cases. Currently, there are not yet a sufficient number of cases to study this issue in depth, and it is an area that requires further investigation in the future.

The influence of the OA on AAO provides a new perspective to understanding SCA6 pathophysiology. Both α1A calcium channel dysfunction and polyglutamine protein aggregation have been proposed as possible pathomechanisms.[17] Indeed, gene dosage effects have been demonstrated in many polyglutamine diseases, but not in Huntington disease, which is also a polyglutamine disease.[2,18] This suggests that the gene dosage effect in polyglutamine diseases may not be explained by aggregation alone. The gene dosage effect observed in our study suggests that dysfunction of α1A calcium channels in both alleles may cause further disruption of intracellular calcium homeostasis.[19] In addition, RNA transcripts from both alleles may adversely affect cellular function through formation of aberrant RNA-protein complexes.[20]

Our study had several limitations. Self-reported AAO may have affected the accuracy of the CAG RU and AAO correlations. Selection bias resulting from the inclusion of only genetically tested patients may have underestimated the proportions of carriers, especially in mild or presymptomatic cases. Our genealogical studies relied primarily on interviews without genetic testing. Furthermore, Tezenas du Montcel et al. discovered that the CAG RUs of *ATXN1* and *ATXN7* influence AAO of SCA6.[15] However, in this study, the impact of genes other than *CACNA1A* on AAO was not considered. The difference in family history positivity rates between the ≤22 and ≥23 RU groups suggests possible intergenerational changes in the RU number, although intergenerational alterations of the RU number are not well documented in SCA6.[4]

To address these limitations, we propose comprehensive investigations of asymptomatic individuals in SCA6 families, along with prospective cohort studies using objective neurologic rating scales. In addition, population-based large-scale screening studies would provide robust data to validate and extend our findings.

In conclusion, this study has refined our understanding of the pathologic significance of CAG RU number in patients with SCA6 and provides a new paradigm for diagnosis, management, and research. Ongoing investigations should focus on long-term follow-up of 18–22 RU carriers and clarification of SCA6 pathogenesis mechanisms. These efforts could lead to improved diagnostic and therapeutic strategies for SCA6 and related neurologic disorders.

Author Contributions

Y. Hatano: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. T. Ishihara: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. S. Hirokawa: major role in the acquisition of data. H. Date: major role in the acquisition of data. Y. Takahashi: major role in the acquisition of data. H. Mizusawa:

major role in the acquisition of data. O. Onodera: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

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