Childhood-onset cerebellar ataxia in Japan: A questionnaire-based survey

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Abstract

Objective: The diagnosis of childhood-onset cerebellar ataxia (CA) is often challenging due to variations in symptoms and etiologies. Despite the known regional differences in the prevalence of etiologies underlying CA, the frequency and characteristics of CA in Japan remain unclear. We conducted a questionnaire-based survey to identify the clinical characteristics of childhood-onset CA in the Japanese population.

Materials and Methods: Questionnaires were sent to 1,103 board-certified pediatric neurologists in Japan from 2016 to 2017. The primary survey requested the number of patients with CA under care, and the follow-up secondary questionnaire requested additional clinical characteristics of the patients.

Results: The primary survey obtained 578 responses (response rate, 52.4%) on 385 patients with CA, including 171 diagnosed and 214 undiagnosed cases (diagnostic rate, 44.4%). The most frequent etiology was dentatorubropallidoluysian atrophy (DRPLA), followed by mitochondrial disorders and encephalitis. The secondary survey obtained the clinical characteristics of 252 cases (119 diagnosed and 133 undiagnosed cases). Multiple logistic regression analysis revealed that a younger age at onset, hearing issues, and short stature were associated with a higher risk of remaining undiagnosed with CA in Japan.

Conclusions: The diagnostic rate of childhood-onset CA in the current study was comparable to those reported in other countries. The high prevalence of autosomal dominant ataxia, especially DRPLA, was a signature of CA in Japan. These data offer insights into the characteristics of childhood-onset CA in the Japanese population.

Keywords
autosomal dominant ataxia, childhood-onset, dentatorubropallidoluysian atrophy, questionnaire-based survey
1 | INTRODUCTION

The prevalence rates and etiologies of childhood-onset cerebellar ataxia (CA), which defines a heterogeneous group of disorders, vary across regions (Musselman et al., 2014). For example, studies have shown that dentatorubropallidoluysian atrophy (DRPLA) is more frequent in Asia and Portugal compared to the rest of Europe and the Mediterranean (Coutinho et al., 2013; van de Warrenburg et al., 2014).

The information of childhood-onset CA in Japan is limited. A study including both adult- and childhood-onset SCAs in Japan reported that sporadic cases accounted for approximately double the number of hereditary cases and that, among hereditary SCAs, the autosomal dominant (AD) type was more common than the autosomal recessive (AR) type; this finding is contrast to that observed in the Caucasian population, in which Machado–Joseph disease/SCA3, SCA6, and DRPLA are the most common types (Tsuji, Onodera, Goto, & Nishizawa, 2008). Furthermore, Friedreich ataxia with GAA repeat expansion, the most common form of hereditary SCAs among Caucasians, has never been reported in the Japanese population (Maruyama et al., 2002). However, no studies thus far addressed childhood-onset CA in Japan.

Due to the diverse symptoms and pathogenesis along with variations in etiologies across regions, the diagnosis of childhood-onset CA is often challenging and might be facilitated by a better understanding of the prevalence of underlying etiologies. Thus, surveillance is necessary to update the epidemiology of childhood-onset CA.

In the current study, we conducted a survey to collect information on childhood-onset CA in Japan by sending questionnaires to pediatric neurologists. We also compared the clinical features between patients with and without CA diagnosis to further delineate the clinical presentation of childhood-onset CA.

2 | MATERIALS AND METHODS

This cross-sectional questionnaire-based survey was approved by the ethics committee of the National Center of Neurology and Psychiatry in Tokyo, Japan (approval number A2016-070). The primary objective was to determine the number of patients with childhood-onset CA in Japan and the prevalence rates of underlying etiologies. The secondary objective was to elucidate the clinical characteristics of childhood-onset CA.

Questionnaires were sent via postal mail to 1,103 pediatric neurologists who were certified by The Japanese Society of Child Neurology as the majority of the patients with childhood-onset CA in Japan were presumed to be under the care of these specialists. Furthermore, assessment of the neurological findings including ataxia by the pediatric neurologists was considered to be reliable.

The questionnaires were sent in two phases. The primary survey requested the number and diagnosis of patients with CA as a symptom who were under the care of the pediatric neurologist. Information on patients with CA who did not receive a definitive diagnosis was also requested. The secondary survey requested further clinical information of the patients, including disease onset, sex, family history, and clinical course (progressive or nonprogressive), but did not include personal information that could specify the individual.

The primary survey took place from November 2016 to February 2017. The secondary survey was sent to those physicians who agreed to participate in the secondary survey among those who initially responded to have at least one patient with CA under care. All data were anonymized by the responding physicians, and the answers to the questionnaires were sent back by postal mail.

The inclusion criteria were as follows: disease onset between birth and 18 years of age, presence of cerebellar atrophy or hypoplasia confirmed by magnetic resonance imaging, and presence of ataxia.

The data extracted from the questionnaires were transcribed into an excel chart and categorized into two groups: one group comprising patients without a definitive diagnosis (undiagnosed group) and one group comprising patients with a diagnosis of a specific disorder (diagnosed group). The number of patients with specific diagnoses was determined in the diagnosed group.

In addition, multiple logistic regression analysis was performed to assess the ability of independent variables among symptoms, signs, and disease course to predict the definitive diagnosis of CA in the standard medical setting of Japan. A stepwise approach was adopted for variable selection with inclusion and exclusion of criteria with a p value of .15. The C-statistic and the Hosmer–Lemeshow test were used to measure the goodness of fit for the logistic regression model. A p value of <.05 was considered as statistically significant in all analyses. Statistical analysis was performed with SAS ver. 9.4 (SAS Institute).

3 | RESULTS

Figure 1 describes the flowchart for data collection via the primary and secondary surveys. A total of 578 replies were obtained from 1,103 requests sent during the primary survey (response rate 52.4%). Of the 578 physicians who replied, 150 stated that they had patients with childhood-onset CA under care, which yielded information on a total of 385 cases. Therefore, it was speculated that between 150/1,103 (13.6%) and 150/578 (26.0%) of the pediatric neurologists in Japan were engaged in the treatment of childhood-onset CA. The cases collected via the primary survey included 171 and 214 patients with and without diagnosis, respectively, indicating a diagnostic rate of 44.4% for childhood-onset CA.

The collected responses covered all of the 47 prefectures in Japan, with at least one patient reported in 39 prefectures and zero patients reported in eight prefectures (Fukushima, Fukui, Hiroshima, Tokushima, Wakayama, Kochi, Ehime, and Oita; Figure 2). The responses were obtained from university hospitals, general hospitals, special functioning hospitals (neurology, pediatrics, or rehabilitation),
regional medical care support hospitals, clinics, healthcare centers, and others (included research institutes and unanswered). The majority of the reported patients were under care of one of the following: university hospital, general hospital, or special functioning hospital (Figure 3).

In the secondary survey sent to the 150 pediatric neurologists, detailed clinical information on 263 patients, including 125 diagnosed and 138 undiagnosed patients, was obtained from 113 physicians responding to the survey (response rate, 75.3%). After examination by the authors, 11 patients, including six diagnosed and five undiagnosed patients, were excluded because they did not fulfill the inclusion criteria of the current study. Therefore, information on 252 patients, including 119 diagnosed and 133 undiagnosed patients, was included in the final analysis. The patients’ current age ranged from 1 to 55, and there were 201 individuals who were under age 20.

Table 1 summarizes the diagnoses of the patients with childhood-onset CA identified via the primary survey. Of the 171 diagnosed cases obtained by the primary survey, the most frequent diagnosis was DRPLA ($n = 30$), followed by mitochondrial disorders ($n = 20$), encephalitis ($n = 16$), Joubert syndrome and related disorders ($n = 14$), and ataxia telangiectasia (AT) and related disorders ($n = 14$).

There were 61 patients with spinocerebellar ataxias (SCAs). Among these, the AD SCAs ($n = 37$) were more predominant than the AR SCAs ($n = 21$). The most frequent AD SCA was DRPLA ($n = 30$), followed by SCA29 ($n = 4$). Among the AR SCAs, AT and related disorder ($n = 14$) were the most common, followed by ataxia with oculomotor apraxia type 1 (AOA1; $n = 5$). Other AR SCAs such as Marinesco–Sjögren syndrome and infantile-onset spinocerebellar degeneration, albeit observed, were less common.

Among the mitochondrial diseases, there were Leigh encephalopathy ($n = 5$); myoclonus epilepsy associated with ragged-red fibers ($n = 3$); pyruvate dehydrogenase complex deficiency ($n = 3$); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes ($n = 2$); chronic progressive external ophthalmoplegia ($n = 1$); neuropathy, ataxia, and retinitis pigmentosa ($n = 1$); and other nonspecified mitochondrial disorders ($n = 5$); respectively.

The secondary survey provided more detailed information, and 119 diagnosed patients (Table A1 in Appendix 1) identified via the secondary survey were analyzed to elucidate age of onset.
for childhood-onset CA in Japan (Table 2). Briefly, among the 119 patients, the ages of disease onset were <1 year (infantile-onset), 1-5 years (early childhood-onset), and >6 years (middle childhood to adolescence onset) in 56 (48.3%), 34 (29.3%), and 26 (22.4%) patients, respectively, whereas information on age at onset was missing in three patients. In the infantile-onset group, the most common underlying disease was Joubert syndrome and related disorders (n = 11), followed by SCA29 (n = 4), mitochondrial diseases (n = 4), and CASK-related disorders (n = 4). In the early childhood-onset group, the most common etiology was DRPLA (n = 8), followed by AT (n = 7), and mitochondrial diseases (n = 7). In the middle childhood to adolescent-onset group, the most common diagnosis was DRPLA as well (n = 8), followed by encephalitis (n = 5). Of note, among the patients with the frequently observed hereditary diseases, the mean ages at onset were 6.4 (±5.0), 0.2 (±0.20), 2.5 (±1.6), and 3.9 (±4.0) years for DRPLA, SCA29, AT and related disorder, and AOA1, respectively.

Assessment of the 119 cases with a focus on family history revealed that 35 patients (30.2%) had a positive family history, whereas the remaining 81 patients (69.8%) had a negative family history in the diagnosed group. No information on family history was available for three patients. Among those with a positive family history, DRPLA (n = 15) was the most common, whereas mitochondrial diseases (n = 11), AT (n = 9), and Joubert syndrome (n = 7) were the most common among the patients with a negative family history (Table 2).

Among the diagnosed patients in the secondary survey (n = 119), 54 patients (45.4%) exhibited a progressive clinical course, 64 patients (53.8%) exhibited a nonprogressive course; there was one patient with missing information on their clinical course. Of the cases with the progressive course, the most frequent etiologies were DRPLA (n = 18), AT and related disorder (n = 9), and mitochondrial diseases (n = 7). In contrast, among the patients with a nonprogressive course, the most common cause was Joubert syndrome and related disorders (n = 12), followed by mitochondrial diseases (n = 7) and encephalitis (n = 5; Table 2).

The common symptoms and signs associated with CA in 252 patients for whom data were obtained via the secondary survey were intellectual disability (76.2%), followed by motor developmental delay (52.8%), seizures (31.3%), hypotonia (28.6%), increased deep tendon reflexes (26.2%), ophthalmologic problems (19.8%), muscle weakness (19.0%), and involuntary movements (18.7%).

Multiple logistic regression analysis of the 252 patients in the secondary survey, performed to identify predictive variables for definitive diagnosis, demonstrated that age onset (odds ratio [OR] 1.09, 95% confidence interval [CI] 1.01–1.18, p = .03), hearing issues (OR 0.07, 95%CI 0.01–0.88, p = .04), short stature (OR 0.32, 95%CI 0.12–0.82, p = .02), and decreased deep tendon reflexes (OR 6.38, 95%CI 2.03–20.1, p < .01) were significantly associated with definitive diagnosis for childhood-onset CA in Japan (Table 3). Albeit not statistically significant, negative family history and lack of motor developmental delays tended to be associated with failure of a definitive diagnosis (Table 3). The C-statistics was 0.70, and the p value of Hosmer-Lemeshow test was .76, indicating a good model fitting.

We further examined diagnostic tests that contributed to definitive diagnosis and found that genetic analysis, brain imaging, and testing of body fluids (blood and cerebrospinal fluid) were required in 73.1%, 49.6%, and 17.6% of the patients with a definitive diagnosis of childhood-onset CA, respectively. Of note, multiple test modalities were necessary to confirm the diagnosis in some patients.
| Diagnosis                                      | Number of patients | Disease category                                                                 |
|-----------------------------------------------|--------------------|----------------------------------------------------------------------------------|
| Dentatorubropallidoluysian atrophy            | 30                 | SCAs                                                                            |
| Mitochondrial disorder                        | 20                 | Inborn error of metabolism                                                       |
| Encephalitis                                  | 16                 | Encephalitis                                                                     |
| Joubert syndrome and related disorder         | 14                 | Joubert syndrome and related disorder                                            |
| Ataxia telangiectasia and related disorders   | 14                 | SCAs                                                                            |
| Dandy–Walker variants                         | 5                  | Brain malformation                                                               |
| Ataxia with oculomotor apraxia type 1         | 5                  | SCAs                                                                            |
| SCA29                                         | 4                  | SCAs                                                                            |
| CASK mutation                                 | 4                  | Other genetic disorders                                                           |
| KIF1A mutation                                | 4                  | Other genetic disorders                                                           |
| Opsoclonus myoclonus syndrome                 | 4                  | Paraneoplastic cerebellar degeneration                                            |
| Spinocerebellar degeneration                  | 3                  | SCAs                                                                            |
| Congenital disorder of glycosylation          | 3                  | Inborn error of metabolism                                                        |
| CACNA1A mutation                              | 3                  | Other genetic disorders                                                           |
| H-ABC                                         | 3                  | Degenerative disorders                                                           |
| Cerebellar hypoplasia                         | 2                  | Brain malformation                                                               |
| SCA5                                          | 2                  | SCAs                                                                            |
| Peroxisomal biogenesis disorders              | 2                  | Inborn error of metabolism                                                        |
| Glut1 deficiency                              | 2                  | Inborn error of metabolism                                                        |
| SEPSECS mutation                              | 2                  | Pontocerebellar hypoplasia                                                        |
| Phenytoin side effect                         | 2                  | Others                                                                          |
| Cerbellar vermis deficiency                   | 1                  | Brain malformation                                                               |
| Chiari malformation                           | 1                  | Brain malformation                                                               |
| Holoprosencecephaly                           | 1                  | Brain malformation                                                               |
| 18 trisomy                                    | 1                  | Chromosomal and congenital abnormality                                            |
| 21 trisomy                                    | 1                  | Chromosomal and congenital abnormality                                            |
| 5p syndrome                                   | 1                  | Chromosomal and congenital abnormality                                            |
| Chromosomal abnormality                       | 1                  | Chromosomal and congenital abnormality                                            |
| Partial monosomy 13                           | 1                  | Chromosomal and congenital abnormality                                            |
| Phelan–McDermid syndrome                      | 1                  | Chromosomal and congenital abnormality                                            |
| Cockayne syndrome                             | 1                  | Chromosomal and congenital abnormality                                            |
| Pontocerebellar hypoplasia type 7             | 1                  | Pontocerebellar hypoplasia                                                        |
| Marinesco–Sjögren syndrome                    | 1                  | SCAs                                                                            |
| SCA2                                          | 1                  | SCAs                                                                            |
| Infantile-onset spinocerebellar degeneration  | 1                  | SCAs                                                                            |
| L-2-hydroxyglutaric aciduria                  | 1                  | Inborn error of metabolism                                                        |
| Congenital GPI deficiency                     | 1                  | Inborn error of metabolism                                                        |
| KMT2B mutation                                | 1                  | Other genetic disorders                                                           |
| STXB1 mutation                                | 1                  | Other genetic disorders                                                           |
| PLA2G6-associated neurodegeneration           | 1                  | Other genetic disorders                                                           |
| MECP2 duplication                             | 1                  | Other genetic disorders                                                           |
| Ceroid lipofuscinosis neuronal 6              | 1                  | Other genetic disorders                                                           |
| MTHFR deficiency                              | 1                  | Other genetic disorders                                                           |
| 4H syndrome                                   | 1                  | Degenerative disorders                                                           |
| Infantine neuroaxonal dystrophy               | 1                  | Degenerative disorders                                                           |
| Chédiak-Higashi syndrome                      | 1                  | Abnormal immune system                                                            |
| Post-head trauma                              | 1                  | Others                                                                          |
| Cerebral palsy                                | 1                  | Others                                                                          |

Abbreviations: 4H syndrome, hypomyelination with hypogonadotropic, hypogonadism and hypodontia syndrome; GPI, glucose phosphate isomerase; H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum; MTHFR, methylenetetrahydrofolate reductase; SCA, spinocerebellar ataxia.
Among the undiagnosed cases, 45 patients underwent genetic analyses including whole-exome sequencing (WES; n = 10) and disease-specific genetic analysis (n = 14). No precise information regarding genetic analyses was available for the remaining 21 patients.

The most common brain imaging finding that contributed to the diagnosis was molar tooth sign (vermian hypoplasia) in Joubert syndrome and related disorders. Other brain imaging findings which contributed to the diagnosis in the diagnosed group were diffuse brain atrophy in DRPLA, basal ganglia abnormalities in mitochondrial...
diseases, calcification of the basal ganglia in Cockayne syndrome, and vermian atrophy with enlarged posterior fossa in Dandy-Walker variant. Among the tests for body fluids, elevated lactate and pyruvic acid in mitochondrial diseases, elevated alpha-fetoprotein, and decreased immunoglobulin A in AT were described as contributory to the diagnosis. Other findings such as giant granules in white blood cells in Chédiak-Higashi syndrome and low blood glucose level in cerebrospinal fluid in GLUT1 deficiency were also reported as contributors to the diagnosis. Abnormal findings in transferrin electrophoresis were contributory to the diagnosis of carbohydrate-deficient glycoprotein syndrome type 1a.

4 | DISCUSSION

The current study demonstrated that definitive diagnosis was achieved in 44.4% of the patients with childhood-onset CA in Japan, with the 55.6% of the patients remaining undiagnosed; this finding is in agreement with previously published diagnostic rate of 47% in 2012 from Canada (Al-Maawali et al., 2012). Among the patients with a definitive diagnosis, DRPLA, mitochondrial diseases, encephalitis, AT and related disorders, and Joubert syndrome and related disorders were the most common etiologies of childhood-onset CA in Japan.

Given that the population of Japanese children younger than 20 years is 21,580,000 (e-Stat, 2019, January 20) and that 201 patients younger than 20 years were included in the current study, the estimated overall prevalence of children with CA in Japan is at least 0.93 per 100,000. Systematic reviews and meta-analyses to assess the frequency of childhood-onset CA reported the overall prevalence of ataxia in Europe was no more than 26 per 100,000 children (Musselman et al., 2014), which is higher than our findings, which might be attributable to differences in prevalence rates across countries or differences in methods used across studies.

Studies suggest the significance of age at onset, clinical progression (progressive or nonprogressive), and family history for the definitive diagnosis of childhood-onset CA (Fogel & Perlman, 2007; Singer, Mink, Gilbert, & Jankovic, 2015). The average age at onset for AT in the current study (2.5 ± 1.6 years) is lower than the previously reported onset age of above 5 years (Singer et al., 2015). Furthermore, the onset age for AOA1, which follows a similar clinical course as AT, was reported as approximately 7 years (Fogel & Perlman, 2007), which was 3.9 ± 4.0 years in the current study, indicating that the onset of AT and AOA1 might be earlier in the Japanese population. DRPLA is a well-known AD SCA with an early childhood onset (Fogel, 2012; Singer et al., 2015). Studies assessing adult-onset as well as childhood-onset DRPLA reported the age of onset for DRPLA as 36.9 ± 18.0 years in Japan (Al-Maawali et al., 2012; Maruyama et al., 2002); however, the current study indicated that the onset age for childhood-onset DRPLA was 6.4 ± 5.0 years.

Assessment of the clinical progression in the study cohort revealed that SCAs were the most common etiology among patients with a progressive course, whereas Joubert syndrome and related disorders was the most common cause among the nonprogressive cases. Previous studies implicated that ataxias with congenital or nonspecific causes, including cerebral palsy, tended to exhibit a static course; an acute progressive course might result from intoxications, infections, or inflammatory processes; and chronic progressive ataxia might result from genetic disorders (Fogel, 2012; Singer et al., 2015). These findings are in agreement with the current study findings, suggesting that genetic disorders should be considered in chronic progressive cases and that congenital malformations should be included in the differential diagnosis for nonprogressive cases in patients with childhood-onset CA in Japan. However, it should be noted that certain genetic disorders with extremely slow progression might be misdiagnosed as nonprogressive CA.

Among the SCAs with a positive family history, DRPLA was the most common cause; however, there were four patients with DRPLA who had no family history even though a positive family history is a common feature of AD SCAs. In the current study, SCA29 (n = 4) was the second most common cause of AD SCAs, with three patients exhibiting no family history.

In the current study, the mean onset age of 2.3 ± 3.5 years and positive family history rate of 18.8% within the undiagnosed group were similar to those reported in cohorts from Canada, demonstrating that the majority (82%) of undiagnosed cases presented at ages younger than 2 years and comprised a smaller population (19%) with a positive family history (Al-Maawali et al., 2012).

### TABLE 3  Multiple logistic regression analysis on clinical features of 252 diagnosed and undiagnosed cases collected via secondary survey

| Variables | Diagnosed | Undiagnosed | Odds ratio | Lower CL | Upper CL | p Value |
|-----------|-----------|-------------|------------|----------|----------|---------|
| Number of patients | 119 | 133 | | | | |
| Sex [female:male] | 60:59 | 67:66 | | | | |
| Age at onset [mean (SD)] | 3.4 (4.2) | 2.3 (3.5) | 1.09 | 1.01 | 1.18 | .03 |
| Positive family history [N (%)] | 35 (29.4) | 25 (18.8) | 1.92 | 1.00 | 3.69 | .05 |
| Motor developmental delay [N (%)] | 66 (55.5) | 67 (50.4) | 1.67 | 0.92 | 3.01 | .09 |
| Hearing issues [N (%)] | 2 (1.7) | 5 (3.8) | 0.07 | 0.01 | 0.88 | .04 |
| Short stature [N (%)] | 8 (6.7) | 22 (16.5) | 0.32 | 0.12 | 0.82 | .02 |
| Decreased deep tendon reflex [N (%)] | 21 (17.6) | 8 (6.0) | 6.38 | 2.03 | 20.10 | <.01 |

Note: Odds ratios for other than "age at onset" are described as "yes/no". Sex was not selected with the stepwise procedure in the logistic model. Abbreviations: CL, confidence limit; SD, standard deviation.
Multiple regression analysis using clinical features as variables indicated that younger age of onset, hearing issues, and short stature were risk factors for not receiving a definitive diagnosis for childhood-onset CA in Japan. Patients with C10ORF2 mutation, pontocerebellar hypoplasia type 7, Marinesco–Sjögren syndrome, DRPLA, MECP2 mutation, or mitochondrial disorders were included in the diagnosed individuals who had young age onset, with either hearing issue or short stature. Therefore, these disorders may be first considered as differential diagnosis if not have been assessed. Further, AR SCAs are generally associated with clinical findings outside the nervous system (Fogel & Perlman, 2007; Singer et al., 2015). Hearing issues and a short stature might be unrelated to the nervous system, and the undiagnosed cohort of the current study might have included patients with AR SCAs. Another speculation might be that individuals with childhood-onset CA harboring hearing issues or a short stature might be representing a new disease entity with these signs that is yet to be identified.

In AD SCAs, genetic panel testing screening is a mainstream diagnostic approach for SCA types 1, 2, 3, 6, 7, and 17, and DRPLA (van de Warrenburg et al., 2014). Several recent studies demonstrated the utility of WES for the diagnosis of childhood-onset CA, especially AR SCAs, a rapidly expanding group following the implementation of this technology (Fogel, 2012; Ohba et al., 2013; Sasaki et al., 2015; Sawyer et al., 2014; van de Warrenburg et al., 2014). Given the possibility that there might be patients with AR ataxias in the undiagnosed group, the diagnostic rate might improve with the implementation of WES for all patients with no definitive diagnosis.

One notable limitation of the current study was the administration of the survey to a limited number of physicians and facilities. Nonetheless, to best of our knowledge, this is the first study to investigate patients with childhood-onset CA in Japan, providing new insights on the prevalence and etiologies and the feasibility of potential predictors of diagnosis in these patients.

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### APPENDIX 1

**TABLE A1** Summary of the 119 diagnosed cases collected via secondary survey

| Diagnosis                                           | Number of patients | Disease category                      |
|-----------------------------------------------------|--------------------|---------------------------------------|
| Dentatorubropallidoluysian atrophy                 | 20                 | SCAs                                  |
| Mitochondrial disorder                             | 14                 | Inborn error of metabolism            |
| Joubert syndrome and related disorder              | 12                 | Joubert syndrome and related disorder |
| Ataxia telangiectasia and related disorders        | 11                 | SCAs                                  |
| Encephalitis                                       | 6                  | Encephalitis                          |
| Ataxia with oculomotor apraxia type 1              | 5                  | SCAs                                  |
| SCA29                                              | 4                  | SCAs                                  |
| CASK mutation                                      | 4                  | Other genetic disorders               |
| CACNA1A mutation                                   | 4                  | Other genetic disorders               |
| Glut1 deficiency                                   | 3                  | Inborn error of metabolism            |
| KIF1A mutation                                     | 3                  | Other genetic disorders               |
| Dandy–Walker variants                              | 2                  | Brain malformation                    |
| SEPSecs mutation                                   | 2                  | Pontocerebellar hypoplasia            |
| Congenital disorder of glycosylation               | 2                  | Inborn error of metabolism            |
| Marinesco–Sjögren syndrome                         | 2                  | SCAs                                  |
| Peroxisomal biogenesis disorders                   | 2                  | Inborn error of metabolism            |
| PLA2G6-associated neurodegeneration                | 2                  | Other genetic disorders               |
| TUBA1A mutation                                    | 1                  | Brain malformation                    |
| Cerebellar hypoplasia                              | 1                  | Brain malformation                    |
| Holoprosencephaly                                  | 1                  | Brain malformation                    |
| Pontocerebellar hypoplasia type 7                  | 1                  | Pontocerebellar hypoplasia            |
| Chromosome 22 partial duplication                   | 1                  | Chromosomal and congenital abnormality |
| Cockayne syndrome                                  | 1                  | Chromosomal and congenital abnormality |
| Phelan–McDermid syndrome                            | 1                  | Chromosomal and congenital abnormality |
| Phenytoin side effect                              | 1                  | Others                                |
| Opsoclonus myoclonus syndrome                      | 1                  | Paraneoplastic cerebellar degeneration |
| SCA5                                               | 1                  | SCAs                                  |
| SCA13                                              | 1                  | SCAs                                  |
| SCA2                                               | 1                  | SCAs                                  |
| Infantile-onset spinocerebellar degeneration        | 1                  | SCAs                                  |
| Friedreich ataxia<sup>a</sup>                      | 1                  | SCAs                                  |
| Spinocerebellar degeneration                       | 1                  | SCAs                                  |
| Multiple system atrophy                            | 1                  | SCAs                                  |
| KCNA2 mutation                                      | 1                  | Other genetic disorders               |
| LONP1 mutation                                      | 1                  | Other genetic disorders               |
| MECP2 duplication                                   | 1                  | Other genetic disorders               |
| STXBP1 mutation                                     | 1                  | Other genetic disorders               |
| Chédiak-Higashi syndrome                            | 1                  | Abnormal immune system                |

Abbreviation: SCA, spinocerebellar ataxia.

<sup>a</sup>Not confirmed by gene analysis.