Background and Purpose Premanifest mutation carriers with spinocerebellar ataxia (SCA) can exhibit subtle abnormalities before developing ataxia. We summarized the preataxic manifestations of SCA1, -2, -3, and -6, and their associations with ataxia onset.

Methods We included studies of the premanifest carriers of SCA published between January 1998 and December 2019 identified in Scopus and PubMed by searching for terms including 'spinocerebellar ataxia' and several synonyms of 'preataxic manifestation'. We systematically reviewed the results obtained in studies categorized based on clinical, imaging, and laboratory markers.

Results We finally performed a qualitative analysis of 48 papers. Common preataxic manifestations appearing in multiple SCA subtypes were muscle cramps, abnormal muscle reflexes, instability in gait and posture, lower Composite Cerebellar Functional Severity scores, abnormalities in video-oculography and transcranial magnetic stimulation, and gray-matter loss and volume reduction in the brainstem and cerebellar structures. Also, decreased sensory amplitudes in nerve conduction studies were observed in SCA2. Eotaxin and neurofilament light-chain levels were revealed as sensitive blood biomarkers in SCA3. Concerning potential predictive markers, hyporeflexia and abnormalities of somatosensory evoked potentials showed correlations with the time to ataxia onset in SCA2 carriers. However, no longitudinal data were found for the other SCA gene carriers.

Conclusions Our results suggest that preataxic manifestations vary among SCA1, -2, -3, and -6, with some subtypes sharing specific features. Combining various markers into a standardized index for premanifest carriers may be useful for early screening and assessing the risk of disease progression in SCA carriers.

Key Words spinocerebellar ataxia, premanifest, presymptomatic, marker, systematic review.

INTRODUCTION

Spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative disorders inherited in an autosomal dominant pattern, consisting of more than 40 subtypes. A systematic review of epidemiological studies found that the most common subtypes both worldwide and within Korea are SCA2 and -3, followed by SCA1, -6, and -7, which are known as polyglutamine SCAs. The main symptoms of polyglutamine SCAs include impairment of balance and coordination with slurred speech. The polyglutamine SCAs mainly affect the cerebellum and brainstem, and several pathophysiological mechanisms have been identified recently; for example, CAG repeats cause protein aggregation that leads to altered protein interactions and intranuclear inclusions. Moreover, DNA damage and transcriptional dysregulation can affect neurons in SCA patients. Ion-channel and mitochondrial dysfunctions are also known to be associated with the mechanism.

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Ataxia onset in polyglutamine SCAs most commonly occurs in the third or fourth decade of life. The premanifest stage of SCAs refers to an individual carrying a genetic mutation but not yet exhibiting overt cerebellar ataxia (Fig. 1), which has been recently defined by a SARA (Scale for the Assessment and Rating of Ataxia) score of <3. Reports on the premanifest stage have used various terms such as ‘presymptomatic’, ‘preclinical’, and ‘prodromal’. In this article we opted to use ‘premanifest’ to represent the conditions described by these terminologies, and described all clinical signs, laboratory, and image findings in this stage as ‘presymptomatic manifestations’.

Premanifest mutation carriers have been reported to exhibit certain abnormal clinical signs such as frequent muscle spasms, subtle gait, speech, and oculomotor signs, as well as abnormalities in brain imaging, blood-derived markers, and neurophysiological tests compared with healthy controls. Clinical scales for evaluating ataxia and neurological deficit in manifest SCA patients have been validated to show disease progression, which include the SARA and INAS (Inventory of Non-Ataxia Signs). However, no scales reflecting the disease severity in the premanifest stage have been established. This demonstrates the need to developing clinical assessment scales using presymptomatic manifestations in order to detect SCA patients in their premanifest stage.

Since polyglutamine SCAs show genetic anticipation, individuals with more CAG repeats will have earlier ataxia onset. The number of CAG repeats can be used for predicting ataxia onset in SCA patients, but it explains only a subset of the features of symptom development in SCA. Markers of premanifest SCA correlating with ataxia development and clinical progression would be particularly useful for prognostication and the future development of neuroprotective therapeutics applicable at the premanifest stage of SCA. More research is investigating the clinical, laboratory, and neuroimaging markers of the prodromal condition in other neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease. However, only a few studies have investigated polyglutamine SCAs.

In this article we systematically review the clinical, laboratory, and imaging markers investigated in premanifest mutation carriers of SCA1, -2, -3, and -6. We also review features associated with ataxia onset in premanifest SCAs.

**METHODS**

**Information sources and search procedure**
We used two search databases for this study: Scopus and PubMed. The searches were conducted on January 2020 and the results were limited to publication dates from January 1998 to December 2019. We applied the following search to the two databases: (‘spinocerebellar ataxia’ OR ‘SCA’) AND (‘premanifest’ OR ‘presymptomatic’ OR ‘asymptomatic’ OR ‘preclinical’ OR ‘subclinical’ OR ‘prodromal’ OR ‘preataxic’).

**Eligibility criteria**
We comprehensively reviewed published works by applying the following criteria. Eligible subjects were restricted to individuals who were genetically confirmed to have abnormal CAG repeats in SCA1, -2, -3, or -6 genes, and were matched...
for the premanifest stage as defined below. Although many previous studies have used SARA scores to define premanifest carriers, they have used different cutoffs. We adopted a SARA score cutoff of 3 (or 4 in some studies) to identify the premanifest stage. Nonataxic phenotypes of SCA that present with parkinsonism or dementia were not considered in this review. In addition, we only included studies that compared a specific symptom or test result between premanifest carriers and normal controls. Regarding study designs, we only included original researches, and excluded case series and case reports. The results of original researches reported in systematic reviews and review articles were also included.

### Study selection
After removing duplicates, we screened papers to filter out irrelevant studies; studies involving animal models, ethical issues, and subtypes other than SCA1, -2, -3, and -6 were excluded by examining each Abstract. Efforts to exclude duplicated reports on the same cohorts were also made by comparing the author names, study size, and main evaluation method of each study. After performing this screening, the full texts for the remaining studies were assessed by applying eligibility criteria as explained above. The results from the finally included studies were then systematically reviewed.

### RESULTS
There were 269 and 209 studies identified in Scopus and PubMed, respectively. Removing duplicates resulted in 273 studies remaining, of which 146 passed the screening process. Applying the eligibility criteria yielded 48 studies that were
finally included in the present analysis (Fig. 2).

**Presymptomatic manifestations of SCA mutation carriers**

Most of the studies involved SCA2 and -3, with few investigating presymptomatic manifestations of SCA1 and -6. Furthermore, some studies included fewer than five patients, and so the sample sizes were presented for those studies.

**Electrophysiological assessments**

**Video-oculography**

Oculomotor deficits can be evaluated using several parameters that are measured in video-oculography (VOG), and some of them exhibited significant changes in presymptomatic carriers. Increased error and latency in antisaccadic tasks and decreased maximum velocities of horizontal saccadic movements were the main features that presented in presymptomatic SCA2 carriers. Wu et al. showed that presymptomatic SCA3 carriers also shared these VOG features, although saccadic slowing occurred in vertical rather than horizontal movements. Also, these carriers showed additional VOG features such as impaired smooth pursuit and increased frequency and average amplitude of square-wave jerks during gaze fixation. In SCA6, gaze-evoked nystagmus, impaired smooth pursuit, and saccadic slowing as assessed by VOG separated the premanifest group (n=4) from controls.

**Transcranial magnetic stimulation**

The following parameters from transcranial magnetic stimulation (TMS) of the motor cortex were increased in presymptomatic SCA2 carriers: resting motor thresholds, active motor thresholds (measured during weak contraction), central motor conduction time (CMCT) using the F-wave method, and cortical silent periods. Farrar et al. found that CMCT was increased in two premanifest SCA3 carriers, who exhibited reduced cortical responses to stimuli, showing reduced threshold increases in motor evoked potentials immediately after (interval <7 ms) a conditioning stimulus compared with normal controls.

**Other methods**

Other electrophysiological assessments that were found to be effective were nerve conduction studies, evoked potentials, and coherence analysis by combining electroencephalography (EEG) and electromyography (EMG) data, although these investigations only involved premanifest SCA2. Sensory amplitudes in nerve conduction studies were decreased in the median and sural nerves. Abnormal morphology in somatosensory evoked potentials (SSEPs) and brainstem auditory evoked potentials were found in premanifest SCA2. Data on P40 latency alterations of SSEPs were inconsistent, with some studies showing increased P40 latency in premanifest SCA2 carriers and others showing no change. Additionally, statistical corticomuscular coherence (between EEG and EMG) and intermuscular coherence (between upper and lower limb EMG) were decreased in premanifest SCA2, showing reduced excitability and axonal integrity along the corticospinal tract.

**Neuroimaging assessments**

Magnetic resonance imaging (MRI) volumetry and diffusion-tensor imaging (DTI) are currently the most effective imaging modalities for distinguishing presymptomatic carriers of SCA1, -2, -3, and -6. In structural MRI, the volumes of brainstem structures (especially the pons) were reduced in premanifest SCA2 and -3, whilst volume reduction of the cerebellum was observed in SCA2 but not in SCA3 carriers. Gray-matter loss in the cerebellum was also observed in both premanifest SCA1 and -2, and gray-matter losses in the pons and medulla were additionally found in premanifest SCA1. Other structures found to have MRI volumetry abnormalities was the cervical spinal cord in SCA3 carriers. DTI microstructural alterations in the cerebellar peduncles can be useful for detecting premanifest SCA3. Fractional anisotropy (FA) was decreased and diffusivity measures (axial, radial, and mean) were increased in premanifest SCA3. For structures outside the cerebellum, axial diffusivity in the midbrain and mean diffusivity in the cerebral peduncles were increased. It was particularly interesting that one study showed a tendency for the alteration of these measures to be reversed in SCA6, with increased FA and decreased radial diffusivity observed in superior and middle cerebellar peduncles, suggesting compensatory changes against degeneration. However, the insufficient sample size (n=2) of that study indicates that further large-sample studies are necessary.

Other imaging modalities have also revealed certain changes in premanifest carriers. Magnetic resonance (MR) spectroscopy showed decreases in the N-acetylaspartate/creatine and choline/creatine ratios in the basilar part of the pons in two premanifest SCA1 carriers. Falcon et al. suggested a concept of cortical connectivity alteration in premanifest SCA6. Connectivity in the cerebral cortex in functional magnetic resonance imaging (fMRI) was decreased between parietal regions and increased between occipital lobe and frontal eye fields in two premanifest carriers.

**Molecular biomarkers**

Several serum biomarkers related to oxidative stress and mitochondrial dysfunction were found in premanifest SCA3,
with higher levels of serum eotaxin reflecting resistance to oxidative stress, and higher levels of serum neurofilament light chains, reflecting the progression of neurodegeneration. Raposo et al. found that premanifest SCA3 carriers had increased frequencies of a common deletion (del4977) in mitochondrial DNA and a decreased BCL2/BAX mRNA ratio, implying mitochondrial dysfunction. One study suggested serum reactive oxygen species and glutathione peroxidase as candidates of oxidative stress biomarkers in premanifest SCA, but the results were not statistically significant.

**Clinical evaluations and other ancillary tests**

**Gait and posture**
Alterations in gait and posture are the cardinal symptoms of SCA, and studies have shown that they were detectable in premanifest subjects, although they are subtle compared with the symptomatic stage. Several studies showed instabilities in gait and posture in premanifest SCA1, -2, and -6 carriers, although they used different quantification methods: body oscillation frequencies, body sway distance, and variabilities of step width and step time. Ilg et al. showed that a concept of ‘spatiotemporal variability,’ a method quantifying gait instabilities using both time and spatial movements, can be effective in distinguishing premanifest carriers of SCA1, -2, -3, and -6 from normal controls, although the subtypes were not separated in that study.

**Sleep and autonomic measures**
Sleep abnormalities have been found in patients with premanifest SCA using polysomnography. Premanifest SCA2 patients had a lower density of sleep spindles in non-REM (rapid eye movement) sleep, and the proportion of time spent in REM sleep was also reduced. However, assessing sleep disturbances using subjective assessment tools such as the Pittsburgh Sleep Quality Index and simple interviews have produced results that were inconsistent among several studies.

**Cognitive and behavioral symptoms**
The scores for Composite Cerebellar Functional Severity (CCFS), a system consisting of tests evaluating cerebellar function such as nine-hole pegboard test, were lower in premanifest carriers of SCA1, -2, and -3 than in normal controls. The SCA Functional Index, consisting of an 8-min walking test, nine-hole pegboard test, and verbal repeat test, was also lower in premanifest SCA2 than in normal controls. Abnormalities in neuropsychological tests of executive function were also found, with premanifest SCA2 carriers showing increased times in Stroop interference tests.

**Other neurological signs**
Consistent with VOG results, premanifest SCA2 patients showed oculomotor disturbances such as horizontal saccadic slowing and gaze-evoked nystagmus in neurological examinations. In premanifest SCA3, horizontal gaze-evoked nystagmus was frequent but diplopia was inconsistent among studies. Painful, disturbing muscle cramps were more frequent in premanifest SCA1, -2, and -3 than in normal controls. Sensory neuropathic signs such as abnormal vibratory and algesic sensation were more frequent in premanifest SCA2 and -3. Deep tendon reflexes in lower limbs showed that both hyperreflexia and hyporeflexia were frequent in premanifest SCA2 and -3. Extrapyramidal signs were also found more frequently in premanifest SCA3. van Gaalen et al. showed that patients with premanifest SCA3 acquired less-conditioned eyelink responses after auditory stimuli in classical conditioning, implying that motor learning is impaired in premanifest SCA. Motor performance such as when throwing objects at a target was also slightly impaired in premanifest SCA2. Findings of handwriting problems in SCA2, positive Babinski reflex in SCA3, and episodic vertigo in SCA6 were inconsistent in patients in the premanifest stage. Dysarthria was also inconsistent in both premanifest SCA2 and -6.

**Markers associated with the time to ataxia onset**
Several longitudinal studies have investigated the relationship of ataxia onset with clinical and laboratory markers. In premanifest SCA2, hyporeflexia, lower sensory amplitudes in median and sural nerves, and prolonged P40 latencies in tibial nerve SSEPs were associated with a shorter time to ataxia onset. Cross-sectional studies have shown several presymptomatic manifestations to be associated with the predicted time to ataxia onset, which can be calculated using the patient’s age and number of CAG repeats. Applying several methods
evaluating postural and gait abnormalities revealed that displacement in body sway during stance (SCA1), body oscillation frequency during stance (SCA2), and spatiotemporal variability during tandem gait (SCA1, -2, -3, and -6; subtypes not separated) were correlated with the predicted time to ataxia onset.63,65 The rate of errors during throwing motions was also correlated in premanifest SCA2.76 Among electrophysiological assessments in premanifest SCA2, latency of antisaccadic movements during antisaccadic tasks in VOG,43,47 CMCT of tibialis anterior muscles in TMS studies,44 coherence between EEG signals at the CP3 electrode and EMG signals of the first dorsal interosseous muscle, and coherence between EMG signals of the first dorsal interosseous and flexor digitorum superficialis muscles were correlated with the predicted time to ataxia onset.53 Other ancillary tests in premanifest SCA2 showed that scores on CCFS,42 SCOPA-AUT,70 neuropsychological tests such as INECO frontal screening tests, extradimensional/extradimensional set shift tests, and delayed-matching-to-sample tests were associated with the predicted time to ataxia onset.43 In premanifest SCA1, the SCA Functional Index was related to the predicted time to ataxia onset.42

DISCUSSION

We have presented a systematic review of the presymptomatic manifestations in SCA1, -2, -3, and -6 by investigating previous investigations involving premanifest carriers. The presymptomatic manifestations can be divided into the following categories: clinical symptoms, electrophysiological findings, neuroimaging results, molecular biomarkers, and ancillary tests. As expected, most of the presymptomatic manifestations were shared among different SCA subtypes. Painful muscle cramps, abnormal muscle reflexes, instabilities in gait and posture, VOG abnormalities, TMS measures, volume reduction and gray-matter loss in structural MRI, microstructural changes in DTI measures, and abnormal CCFS scores were the presymptomatic manifestations evident in multiple SCA subtypes (Figs. 3 and 4). These results indicate that although different genetic etiologies and pathologies distinguish the SCA subtypes,3,5 there exist common features in the symptomatic development of polyglutamine SCAs in the premanifest stage.

Some presymptomatic manifestations were detected using different methods specifically in a single SCA subtype, such as when using MR spectroscopy in SCA1, neuropsychological tests and certain electrophysiological assessments (horizontal saccadic slowing, evoked potentials, and coherence between EEG and EMG) in SCA2, oxidative stress biomarkers in SCA3, and cortical connectivity shifting as measured by fMRI in SCA6. These findings suggest the presence of...
SCA-subtype-specific pathophysiological mechanisms; however, further studies are required to confirm them.

Some changes in premanifest SCA showed opposite tendencies to those in manifest SCA. For example, DTI studies have shown increased radial diffusivity and decreased FA in both premanifest carriers and manifest patients with SCA3. In contrast, SCA6 patients showed decreased radial diffusivity and increased FA in the premanifest stage (asterisks in Fig. 3), whereas there was an increase in radial diffusivity and a decrease in FA in the manifest stage of SCA6. In SCA3, premanifest patients showed decreased resting motor thresholds and cortical silent periods in TMS, while these TMS measures were restored to the normal ranges in manifest patients. For serum biomarkers, premanifest SCA3 carriers showed more-pronounced mitochondrial DNA common deletions and serum eotaxin levels than patients with fully manifested SCA3. We suppose that such presymptomatic manifestations reflect adaptive changes for compensating neurodegeneration, which subsequently reverse during disease progression in the manifest stage of SCA.

The nature of this polyglutamine disorder means that the number of CAG repeats is the strongest predictor of disease progression. However, besides CAG repeats, some markers can be candidates for predicting the time to ataxia onset. Longitudinal studies have found that in premanifest SCA2, sensory amplitudes in nerve conduction studies, P40 latencies in tibial nerve SSEPs, CCFS scores, and abnormal muscle reflexes were correlated with the time to ataxia onset.

Limitations of current literature
There are notable limitations in the current knowledge of the premanifest stage of polyglutamine SCAs. First, there have been insufficient studies, with some presymptomatic manifestations only being evaluated in a single SCA subtype. Also, only a few premanifest patients were enrolled in most studies because they have instead focused on the manifest stage in the same project. It is difficult to find evidence of predictive markers for disease progression besides the number of CAG repeats in premanifest SCA, since only a few longitudinal studies have been conducted in the premanifest stage, and those studies were limited to SCA2.
Table 1. Summary of findings in premanifest carriers of SCA1, -3, and -6

| SCA1                          | Presymptomatic manifestations* | Sample size: carriers (vs. controls) | Reference |
|-------------------------------|--------------------------------|--------------------------------------|-----------|
| **Neuroimaging**              |                                |                                      |           |
| MRI volumetry                 | Gray-matter loss in pons, medulla oblongata, and cerebellum | 39 (vs. 33) | 42        |
| MR spectroscopy               | Reduced N-acetylaspartate/creatinine and choline/creatinine in basilar pons | 2 (vs. 10) | 58        |
| **Clinical symptoms and other ancillary tests** |                                |                                      |           |
| Muscle cramps                 | Painful muscle cramps (carriers: 40%, controls: 19%) | 50 (vs. 32) | 42        |
| Gait and posture              | Increased instability (body sway) in static posture | 9 (vs. 17†) | 62        |
| **Functional scoring system** | Lower CCFS score               | 50 (vs. 32) | 42        |

| SCA3 (Machado-Joseph Disease) |                                |                                      |           |
|**Electrophysiological assessments** |                                |                                      |           |
| VOG                           | Impaired smooth pursuit (vertical), increased error of antisaccadic movements, saccadic slowing (vertical), more frequent and large gaze-evoked nystagmus and square-wave jerks during fixation | 12 (vs. 26†) | 48        |
| TMS                           | Increased CMCT and decreased resting motor threshold, cortical silent period, and cortical adaptation | 2 (vs. 62†) | 50        |
| MRI volumetry                 | Reduced volumes of midbrain, pons, and cervical spinal cord | 12 (vs. 91‡) | 54        |
| DTI                           | Increased diusivity and decreased FA in cerebellar peduncles | 12 (vs. 91‡) | 54        |
| 16 (vs. 16)                   |                                                                    |           | 56        |
| **Molecular biomarkers**       |                                |                                      |           |
| Nucleic acid                  | Decreased BCL2/BAX mRNA ratio | 16 (vs. 16²) | 60        |
|                                | Increased frequency of common deletion (del4977) in mitochondrial DNA | 16 (vs. 16²) | 60        |
| Other serum biomarkers        | Higher levels of serum eotaxin | 13 (vs. 43) | 20        |
|                                | Higher levels of serum neurofilament light chains | 26 (vs. 21†) | 59        |
| **Clinical symptoms and other ancillary tests** |                                |                                      |           |
| Muscle cramps                 | Painful muscle cramps (carriers: 81%, controls: 16%) | 13 (vs. 15†) | 74        |
| Motor signs                   | Hyperreflexia in lower limbs (carriers: 8.3%, controls: 0%) (carriers: 23.1%, controls: 0%) | 12 (vs. 26⁷) | 48        |
|                              | Hyporeflexia in lower limbs (carriers: 8.3%, controls: 0%) (carriers: 15.4%, controls: 0%) | 12 (vs. 15†) | 74        |
|                              | Extrapyramidal signs (carriers: 15.4%, controls: 0%) Positive Babinski reflex (inconsistency) | 13 (vs. 15†) | 48,74     |
| Oculomotor symptoms           | Gaze-evoked nystagmus (carriers: 39%, controls: 5%) (carriers: 17%, controls: 0%) | 26 (vs. 20) | 42        |
|                              | Diplopia (inconsistency) | 48 (vs. 42) | 28        |
| Sensory symptoms              | Sensory neuropathic signs (carriers: 15.4%, controls: 0%) | 13 (vs. 15†) | 74        |
| Classical conditioning test    | Impaired eyelblink conditioning after auditory stimuli | 18 (vs. 16†) | 75        |
| Functional scoring system     | Lower CCFS score | 26 (vs. 20) | 42        |

| SCA6                          |                                |                                      |           |
|**Electrophysiological assessments** |                                |                                      |           |
| VOG                           | Multivariate analysis including gaze-evoked nystagmus, smooth pursuit, and saccadic slowing as variables | 4 (vs. 7⁷) | 49        |
| DTI                           | Decreased diusivity and increased FA in cerebellar peduncles | 2 (vs. 20†) | 57        |
| fMRI                          | Alterations in cortical connectivity | 2 (vs. 20†) | 57        |
| **Clinical symptoms and other ancillary tests** |                                |                                      |           |
| Gait and posture              | Increased variabilities in step time and step width | 6 (vs. 24) | 64        |
| Dysarthria and others         | Speech abnormalities and episodic vertigo (inconsistency) | 24,42 | 24,42     |

*Inconsistency* indicates that different studies showed both significant (*p*<0.05) and not-significant (*p*>0.05) changes in carriers, *Age-matched controls, 'Age- and sex-matched controls.

CCFS: Composite Cerebellar Functional Severity, CMCT: central motor conduction time, DTI: diffusion-tensor imaging, FA: fractional anisotropy, fMRI: functional magnetic resonance imaging, MR: magnetic resonance, MRI: magnetic resonance imaging, SCA: spinocerebellar ataxia, TMS: transcranial magnetic stimulation, VOG: video-oculography.
Table 2. Summary of findings in premanifest carriers of SCA2

| Predictive symptoms and tests | Presymptomatic manifestations* | Sample size: carrier (vs. controls) | Reference |
|------------------------------|--------------------------------|-------------------------------------|-----------|
| SCA2                         |                                |                                     |           |
| Electrophysiological assessments |                              |                                     |           |
| VOG                          | Increased error and latency of antisaccadic movements | 37 (vs. 37*) 43 |           |
|                              | Saccadic slowing (horizontal)  | 54 (vs. 56*) 47                    |           |
| Nerve conduction study       | Decreased sensory amplitudes (median and sural nerves) | 21 (vs. 19*) 26 |           |
| Evoked potentials            | Abnormal morphology in BAEP    | 62 (vs. 80) 52                     | 51        |
|                              | Abnormal morphology in SSEP    | 62 (vs. 80) 52                     | 52        |
|                              | Increased P40 latency in SSEP (inconsistency) | 26, 51, 52 |           |
| TMS                          | Increased CMCT, resting motor threshold, active motor threshold, and cortical silent period | 37 (vs. 37*) 43 |           |
| EEG and EMG coherence        | Decreased corticomuscular EEG–EMG coherence and intermuscular EMG–EMG coherence between upper and lower limbs | 15 (vs. 25*) 53 |           |
| Neuroimaging                 | Gray-matter loss in cerebellum | 12 (vs. 33) 42                     |           |
| MRI volumetry                | Reduced volume of brainstem (especially pons) and cerebellum | 16 (vs. 18*) 55 |           |
| Clinical symptoms and other ancillary tests |                              |                                     |           |
| Muscle cramps                | Painful muscle cramps (carriers: 81%, controls: 16%) | 21 (vs. 19*) 26 |           |
|                              | (carriers: 81%, controls: 27%) | 37 (vs. 37*) 43 |           |
|                              | (carriers: 35%, controls: 13%) | 31 (vs. 78) 42 |           |
| Motor signs                  | Hyperreflexia in lower limbs (carriers: 33%, controls: 0%) | 21 (vs. 19*) 26 |           |
|                              | Hyporeflexia in lower limbs (carriers: 43%, controls: 0%) | 37 (vs. 37*) 43 |           |
|                              | (carriers: 38%, controls: 5%) | 21 (vs. 19*) 26 |           |
| Oculomotor symptoms          | Oculomotor disturbance such as saccadic slowing and gaze-evoked nystagmus (carriers: 22%, controls: 0%) | 37 (vs. 37*) 43 |           |
| Dysarthria                   | Speech abnormalities (inconsistency) | 20 (vs. 30*) 63 |           |
| Gait and posture             | Increased instability (body oscillation frequency) in static posture | 20 (vs. 28*) 76 |           |
| Motor performance (upper limbs) | Increased errors when throwing objects at a target | 28 (vs. 28*) 76 |           |
| Sensory symptoms             | Sensory neuropathic signs (carriers: 81%, controls: 21%) | 21 (vs. 19*) 26 |           |
|                              | (carriers: 62%, controls: 19%) | 37 (vs. 37*) 43 |           |
| Sleep problems               | Lower density of sleep spindles in non-REM sleep | 20 (vs. 20*) 68 |           |
|                              | Reduced proportion of REM sleep | 20 (vs. 20*) 68 |           |
|                              | Subjective sleep disturbance (inconsistency) | 36 (vs. 36*) 67 |           |
| Autonomic dysfunction        | Higher SCOPA-AUT score | 37 (vs. 37*) 43 |           |
|                              | Heart-rate variability index abnormalities | 48 (vs. 48*) 71 |           |
| Neuropsychological test      | Impaired executive function and visual memory | 20 (vs. 20*) 68 |           |
| Functional scoring system    | Lower CCPS score and SCA Functional Index | 31 (vs. 78) 42 |           |

*Iinconsistency* indicates that different studies showed both significant (p<0.05) and not-significant (p>0.05) changes in carriers,*Age-matched controls,* Age- and sex-matched controls.

BAEP: brainstem auditory evoked potential, EEG: electroencephalography, EMG: electromyography, REM: rapid eye movement, SCOPA-AUT: Scales for Outcomes in Parkinson’s Disease–Autonomic Dysfunction, SCA: spinocerebellar ataxia, SSEP: somatosensory evoked potential.
Markers of Premanifest SCA 1, 2, 3, and 6

Second, review papers (including the present work) cannot avoid bias caused by the dominant publication by one author in a specific subtype. For example, publications in the premanifest stage of SCA2 are dominated by one primary author and his colleagues.25-28,43,44,47,51-53,63,76-78 Bias caused by overlapping individual participants (e.g., one premanifest carrier being included in multiple studies) and data from a single hospital may also exist, and so global multicenter studies are required to resolve this limitation.

Third, different evaluation methods used in different studies need to be standardized for each presymptomatic manifestation. For example, various methods were used to evaluate instabilities in gait and posture, with some studies calculating the distance of body sway and others measuring the frequency of body oscillation.63,65

Fourth, there is no consensus on the criteria for ‘premanifest’ SCA. The subjects were assessed using the SARA score in some studies, while in others they were simply defined as not having overt cerebellar ataxia. The lack of standardized criteria for the definition of premanifest SCA limits the ability to interpret our findings.

Further implications
The present findings have several important implications. First, there is a need to establish a standardized measurement tool for premanifest carriers of SCA. VOG, MRI, measurement of serum biomarkers, and evaluations of muscle cramps, gait, and postural reflexes can be applied in clinical practice to sensitively detect early changes in premanifest SCA patients. The early diagnosis of SCA at the premanifest stage would lead to early intervention and provide patients with opportunities to participate in future clinical trials. Many attempts have been made to develop therapeutics for SCAs,82-91 but disease-modifying therapies are yet to be established.

Second, SCA-specific presymptomatic manifestations need to be defined. Some of the presymptomatic manifestations reviewed in this article may also develop in nonataxic SCA or in other neurodegenerative diseases involving the cerebellum. Clinical symptoms such as postural reflex changes and dysarthria may be nonspecific premanifest signs of SCA, whereas serum biomarkers and certain neuroimaging signs may act as specific markers of premanifest SCA. Future studies should investigate these SCA-specific presymptomatic manifestations distinguished from other neurodegenerative diseases involving the cerebellum. In addition, the progressively worsening of presymptomatic markers in manifest SCA is particularly important because these markers may reflect the pathophysiology of the progressive nature of SCA; many of the patients included in the cross-sectional studies reviewed in the present study showed progression in the manifest stage, such as volumetric reductions and DTI changes in premanifest SCAs being more severe in manifest patients. Longitudinal studies measuring the rate of change from the presymptomatic stage to the clinical manifestation of cerebellar ataxia could provide useful information for developing the markers needed for future disease-modifying trials in premanifest SCA.

Presymptomatic markers correlated with the time to ataxia onset could also be predictive markers for use in risk assessments and the monitoring of high-risk individuals. These markers also may shed light on the pathogenesis of SCA, because they are closely related to disease manifestation. The probabilities of developing SCA and the predicted time to ataxia onset are currently calculated only based on the number of CAG repeats and by performing survival analysis in population studies.24,32-35 However, further studies focused on accurate predictions of disease development may make it possible to redefine the premanifest stage based on laboratory-based biomarkers rather than ataxic symptoms, and also stratify the risk and progression during the early stage of SCAs.

Author Contributions
Conceptualization: Jee-Young Lee. Data curation: Dong-Hoi Kim. Formal analysis: Dong-Hoi Kim. Investigation: Dong-Hoi Kim, Ryul Kim. Visualization: Dong-Hoi Kim. Writing—original draft: Dong-Hoi Kim, Ryul Kim. Writing—review & editing: Jee-Young Lee, Kyoung-Min Lee.

ORCID iDs
Dong-Hoi Kim https://orcid.org/0000-0002-3004-4958
Ryul Kim https://orcid.org/0000-0002-8754-9180
Jee-Young Lee https://orcid.org/0000-0002-9120-2075
Kyoung-Min Lee https://orcid.org/0000-0002-3685-7642

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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