Importance of Low-Range CAG Expansion and CAA Interruption in SCA2 Parkinsonism

Jong-Min Kim, MD, PhD; Susie Hong, MS; Gyoun Pyoung Kim, MS; Yoon Jae Choi, MD; Yu Kyeong Kim, MD, PhD; Sung Sup Park, MD, PhD; Sang Eun Kim, MD, PhD; Beom S. Jeon, MD, PhD

Objectives: To examine the presence of an ATXN2 mutation in patients with parkinsonism in the Korean population and to find the difference in the ATXN2 mutation between ataxic and parkinsonian phenotypes.

Design: Survey.

Setting: Seoul National University Hospital (a referral center).

Patients: Patients with Parkinson disease (PD) (n=468) and the Parkinson variant of multiple system atrophy (MSA-P) (n=135) who were seen at our Department of Neurology during the past 3 years.

Main Outcome Measures: CAG expansion in spinocerebellar ataxia type 2 (SCA2) alleles was assessed by polymerase chain reaction amplification and fragment analysis, and its size and interruption were verified by cloning and sequencing. SCA2 was tested also in the family members of the probands. Striatal dopamine transporter (DAT) and D2 receptor status were evaluated in family members of the probands and their SCA2-positive family members using iodine I 123 [123I]–radiolabeled fluoropropyl (FP) 2-carbomethoxy-3-(4-iodophenyl) tropane (CIT) with single-photon emission computed tomography (SPECT) and carbon C 11 [11C]–radiolabeled raclopride positron emission tomography (PET).

Results: We found 3 patients with apparently sporadic disease with expanded CAG repeats in the ATXN2 locus of the patients were 35/22, 34/22, and 32/22, respectively (range in normal population, 19-27). The size of repeats was lower than the CAG repeats (38-51) in ataxic SCA2 in our population. The sequence of expanded CAG repeats was interrupted by CAA as (CAG)n(CAA)(CAG)n in all the patients. DNA analyses in 2 families showed 2 asymptomatic carriers in each family. In the patient with the PD phenotype, striatal DAT loss was more severe in the putamen than the caudate, and [11C]raclopride PET showed an increased relative putaman-caudate binding ratio. The patient with the MSA-P phenotype had severe DAT loss throughout the striatum. Two of 3 asymptomatic carriers had striatal DAT loss.

Conclusions: This study demonstrates that SCA2 is one of the genetic causes of PD and MSA-P. All 3 patients had apparently sporadic disease, emphasizing the need to screen even in patients with nonfamilial disease. CAG repeats were in the low expansion range and interrupted by CAA in all patients in the low-range expansion. Therefore, accurate determination of CAG expansion and ATXN2 sequencing are warranted. [123I]FP-CIT SPECT and [11C]raclopride PET provide a useful way to evaluate the degree of nigrostriatal dopaminergic damage in SCA2-related parkinsonism and gene carriers.

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Mutations in several genes have been identified in patients with familial parkinsonism.1 Among these, CAG trinucleotide repeat expansion within the spinocerebellar ataxia type 2 (SCA2) gene was recognized as a cause of parkinsonism in some families, especially those of Chinese origin.2,3 The ATXN2 mutation was also reported in white families with parkinsonism.4-9 SCA2 is the second most common form of autosomal dominant cerebellar ataxia, accounting for approximately 15% of patients in Europe, the United States, China, and Korea.10-14 SCA2 is characterized by progressive gait and limb ataxia, dysarthria, slow saccades, supranuclear ophthalmpoplegia, decreased or absent tendon reflexes, and dementia. Typical neuropathological changes occur in the cerebellar cortex, pontine nuclei, and inferior olivary nucleus; there is also marked degeneration in the substantia nigra.15-18 Despite the marked involvement of the substantia nigra, SCA2 is typically not associated with parkinsonism.19 However, patients with the ATXN2 mutation were reported in familial levodopa (L-dopa)-responsive parkinsonism and even in sporadic parkinsonism, suggesting that this mutation may be responsible for a subset
of parkinsonism.\textsuperscript{2,9,19,20} These studies, along with previous neuropathological studies, have highlighted the existence of dopaminergic dysfunction associated with \textit{SCA2}.

As a part of systemic screening of gene mutations in Korean patients with parkinsonism, we screened the \textit{ATXN2} mutation. Because it is not clear why \textit{SCA2} manifests ataxia in some patients and parkinsonism in others, we examined the difference in the \textit{ATXN2} mutation between ataxic and parkinsonian phenotypes. We investigated the presence and severity of nigrostriatal dopaminergic dysfunction in \textit{SCA2} patients with parkinsonism and gene carriers by iodine $^{123}$\textsuperscript{[123I]}--radiolabeled fluoropropyl (FP) 2-carbomethoxy-3-(4-iodophenyl) tropamine (CIT) with single-photon emission computed tomography (SPECT) and carbon $^{11}$\textsuperscript{[11C]}--radiolabeled raclopride positron emission tomography (PET) and compared it with that of Parkinson disease (PD).

### METHODS

#### PATIENTS

Genetic analysis for expanded CAG repeats in the \textit{ATXN2} gene was carried out in 603 patients with parkinsonism recruited over a 3-year period. All patients were personally seen by the senior neurologist (B.S.J.) at the Department of Neurology, Seoul National University Hospital. The clinical diagnoses of the patients were PD in 648 patients and the Parkinson variant of multiple system atrophy (MSA-P) in 135. We used UK Parkinson’s Disease Society Brain Bank criteria\textsuperscript{14} and the consensus criteria of MSA.\textsuperscript{22} Informed consent was obtained from all the participants after explaining the genetic implications of the study. The institutional review board of the hospital approved the study. \textit{SCA2} allele carriers by iodine $^{123}$\textsuperscript{[123I]}--radiolabeled fluoropropyl (FP) 2-carbomethoxy-3-(4-iodophenyl) tropamine (CIT) with single-photon emission computed tomography (SPECT) and carbon $^{11}$\textsuperscript{[11C]}--radiolabeled raclopride positron emission tomography (PET) and compared it with that of Parkinson disease (PD).

#### GENETIC ANALYSIS

Genomic DNA extraction was performed using a DNA isolation kit (Gentra PureGene; Gentra Systems Inc, Minneapolis, Minnesota). \textit{SCA2} allele sizes were determined by polymerase chain reaction (PCR) amplification and fragment analysis using the ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, Foster City, California) and GeneMapper version 3.5 software.\textsuperscript{13,14} We also studied \textit{SCA2} alleles in hair follicles, buccal cells, and urinary epithelial cells in the family of patient 1. Sequencing was done to verify repeat numbers and internal sequences of the CAG repeat structure of the \textit{ATXN2} gene. Briefly, the amplified fragment containing CAG repeats was subcloned into pCR2.1-TOPO vector (Invitrogen, Carlsbad, California) according to the manufacturer’s instructions. The PCR product of genomic DNAs and more than 3 cloned fragments were sequenced bidirectionally on an ABI PRISM 3100 Genetic Analyzer using a BigDye Terminator Cycle Sequencing Ready Reaction Kit (version 3.1; Applied Biosystems) to verify the CAG expansion and the interrupted sequences.

#### \textit{[123I]}FP-CIT SPECT AND \textit{[11C]}RACLOPRIDE PET

\textit{[123I]}FP-CIT SPECT was performed using a dual-headed gamma camera (ADAC Forte; Philips Medical Systems, Andover, Massachusetts) equipped with parallel-hole, low-energy, high-resolution collimators. The SPECT data acquisition was started 4 hours after intravenous injection of $1.85 \times 10^8$ Bq (to convert to curies, multiply by $2.7 \times 10^{-11}$) of \textit{[123I]}FP-CIT (DaTSCAN; Amersham GE Healthcare, Buckinghamshire, England). A total of 120 projections were acquired and a $128 \times 128$ matrix was used. Image reconstruction was performed using back projection filtered with a Butterworth filter (cutoff frequency, 0.3 cycle/cm, 10th order). Attenuation was corrected using the Chang method (attenuation coefficient, 0.12 cm$^{-1}$).\textsuperscript{3,3} The regions of interest (ROIs) for the caudate, putamen, and striatum as a whole were determined. The specific radiotracer binding to dopamine transporters (DATs) was calculated as the ratio of radioactivity in the ROIs and occipital cortex (specific binding potential = ROIs/occipital cortex – 1). Calculated values were the average caudate, putamen, and striatum uptake; the caudate-putamen ratio (C-P ratio); and the striatal asymmetry index (AI) (AI expressed as a percentage = [ipsilateral - contralateral]/[ipsilateral + contralateral] \times 100). In the \textit{SCA2} patients with bilateral disease, right and left striata were arbitrarily assigned as ipsilateral and contralateral. The SPECT data from healthy volunteers ($n=20$) and age- and sex-matched patients with PD ($n=100$) from our database were collected and analyzed with the same method for comparison. \textit{[11C]}Raclopride PET was performed using an ECAT EXACT PET scanner (Siemens, New York, New York), which provides 47 contiguous slices over a 16.2-cm axial field of view with a thickness of 3.4 mm. A 7-minute transmission scan was performed before radioisotope injection using a $68$Ge--$68$Ga (germanium 68--gallium 68) rotating rod source. Emission scan was started immediately after intravenous injection of about $5.5 \times 10^8$ Bq of \textit{[11C]}raclopride (specific activity, $>3700 \times 10^{10}$ Bq/mmol) and administered for 60 minutes in the 3-dimensional dynamic acquisition mode.

### RESULTS

Among the total of 603 patients, 3 patients with parkinsonism were identified to have an expanded \textit{ATXN2} allele. None had any family history of parkinsonism, ataxia, or other neurodegenerative disorders. Patients 1 and 2 were clinically diagnosed as having idiopathic PD and they showed obvious L-dopa responsiveness. Patient 3 was clinically diagnosed as having MSA-P. He showed minimal response to L-dopa treatment. We performed a gene study in the families of patients 1 and 3. \textit{[123I]}FP-CIT SPECT and \textit{[11C]}Raclopride PET scans were done in \textit{ATXN2}-positive family members.

### CLINICAL INFORMATION

**Patient 1**

Patient 1 was a 74-year-old woman. She noted rest tremor in the left leg and felt slowness in the left arm and leg at age 70 years. These symptoms worsened. She had gait disturbance and trouble getting in and out of a chair. At age 71 years, she was diagnosed with PD at another hospital. Levodopa was given, with virtual disappearance of subjective motor difficulties. In the follow-up period with L-dopa treatment, she developed bilateral upgoing toes worse on the left side. Reportedly, dystonic toe movements were not clearly related to the dosing times of medication. Medication was irregularly taken. When she came to us at age 73 years, she showed masked face, hypophonia, mild bradykinesia, mild rigidity, and intermittent rest tremor worse on the left side. Her pull test score was 1+ on the Unified Parkinson’s Disease Rating Scale (UPDRS) Part III motor subscale section 27. She did not show cerebellar ataxia. Her saccadic eye movements were
normal. Her UPDRS motor score was 23, and her Hoehn and Yahr stage was 2.5. She did not complain of cognitive dysfunction. Her Mini-Mental State Examination score was 29 of 30. Findings of magnetic resonance imaging of the brain done at age 72 years were normal (Figure 1 A and B). She was treated with 5 mg of selegiline hydrochloride per day and 0.5 tablet of Sinemet CR (controlled release) 200/50 (200 mg of levodopa/50 mg of carbidopa) (Merck, Whitehouse Station, New Jersey) 3 times a day for 1 year. Her parkinsonism markedly improved, with a UPDRS motor score of 12. She was free of dyskinesia. DNA analysis for ATXN2 showed a CAG repeat of 35/22. Her parents and siblings had no neurologic symptoms. Patient 1 (II-3) had 2 sons and 2 daughters (Figure 2A); all were healthy in their late 30s to late 40s and had no neurologic symptoms. On examination, her 47-year-old daughter (III-2) was suspected to have subtle bradykinesia. DNA analysis for ATXN2 showed that III-2 and the patient’s 45-year-old son (III-3) had the same CAG expansion of 35. [123I]FP-CIT SPECT was done in the proband, III-2, and III-3.

Patient 2

Patient 2 was a 56-year-old woman who visited our hospital because of left-side tremor for 1 year. On neurologic

Figure 1. Representative magnetic resonance images. A and B, Patient 1. C and D, Patient 3. The magnetic resonance images of patient 1 were normal. In patient 3, mild cerebellar atrophy was observed.
examination, she showed hypomimia, left-hand rest tremor, mild rigidity, and bradykinesia. Postural tremor, ataxia, saccadic movement dysfunction, and hyporeflexia were not observed. She was diagnosed as having PD. Her tremor and hypomimia improved with L-dopa treatment. DNA analyses for ATXN2 showed CAG expansion of 34/22. She had no family history of Parkinsonism, ataxia, or other neurologic diseases. She had 3 sons in their 20s, and they were reportedly all healthy. The proband and other family members refused further study.

**Patient 3**

Patient 3 was a 60-year-old man. He had progressive slowness, and gait disturbance started 1 year prior to hospital admission. He later developed dysarthria, dysphagia, and falling tendency. He also complained of memory decline. He did not have orthostatic dizziness or urinary symptoms. However, he had erectile dysfunction for 2 years. On neurologic examination, he showed hypomimia, dysarthria, dysphagia, axial rigidity, bilateral bradykinesia, and gait disturbance with decreased arm swing. His saccadic eye movement was normal. Deep tendon reflexes were increased to a score of 3+ in the knee. There was no ataxia. He was a high school graduate and his Mini-Mental State Examination score was 29 of 30. Neuropsychological tests revealed mild depression and apathy. His UPDRS motor score was 24, and his Hoehn and Yahr stage was 2.5. Administration of Sinemet 250/25 (250 mg of levodopa/20 mg of carbidopa) twice a day provided only minimal improvement of Parkinsonian symptoms (UPDRS motor score of 23). His condition was progressive with worsening of dysphagia and falling. Magnetic resonance imaging of the brain showed mild cerebellar atrophy (Figure 1C and D). He was diagnosed as having MSA-P. DNA analysis for SCA2 showed CAG expansion of 32/22. He had no family history of neurologic disease, and his parents died in their 80s without neurologic abnormalities. He (II-5) had 1 son (III-11) (aged 32 years) and 2 daughters (III-12 and III-13) (aged 29 years and 26 years, respectively) (Figure 2B). DNA analysis for ATXN2 in the carriers showed that III-11 and III-13 had the same expansion of 32/22. Both of them were neurologically normal. \[^{[23]}\]FP-CIT SPECT was done for the proband and III-13.

**MOLECULAR GENETIC STUDY**

The range of CAG repeats in the normal Korean population is 19 to 27, which was obtained from 1215 persons.\[^{13,14}\] In our 30 patients with ataxia who had an ATXN2 mutation, the range of the CAG expansion was 38 to 51. Our patients with parkinsonism with ATXN2 expansion had 32, 34, and 35 CAG repeats. Repeat lengths examined by PCR amplification and fragment analysis were the same as in cloning and sequencing (Figure 3). All the sequences were interrupted with CAA. In patient 1 (II-3), the CAG repeats in the ATXN2 locus were 35/22. The sequence of expanded CAG repeats was (CAG)\(^{35}\) (CAA)\(^{22}\). The 22 repeat allele was (CAG)\(^{13}\) (CAA) (CAG)\(^{8}\). DNA analyses for III-2 and III-3, who were asymptomatic, showed the same repeats and sequence as the proband. We studied somatic mosaicism for the gene-positive members of patient 1’s (II-3) family, but there were no differences in CAG repeats among hair follicle cells, buccal cells, and urinary epithelial cells. The CAG repeats in patient 2 were 34/22 for ATXN2 alleles. The result of sequencing was (CAG)\(^{25}\) (CAA) (CAG)\(^{8}\). The 22 repeat allele was (CAG)\(^{17}\) (CAA) (CAG)\(^{8}\) (CAG)\(^{8}\). In patient 3 (II-5), the CAG repeats were 32/22. The sequence was (CAG)\(^{23}\) (CAA) (CAG)\(^{8}\). The 22 repeat allele was (CAG)\(^{15}\) (CAA) (CAG)\(^{8}\). III-11 and III-13 had the same number of expansion copies. The sequence of expansion was the same as the proband.

**NEUROIMAGING**

\[^{[23]}\]FP-CIT SPECT was done for the probands and SCA2-positive family members. In patient 1 (II-3), III-2, and III-3 (Figure 4D, E, and F), DAT density was reduced to a PD range (II-3, 1.98; III-2, 2.33; III-3, 2.28; mean±SD, PD, 1.78±0.79 and normal, 3.90±0.57) with a rostrocaudal gradient typical of PD (C-P ratio: II-3, 1.49; III-2, 1.45; III-3, 1.72; mean±SD, PD, 1.59±0.48 and normal, 1.29±0.11).\[^{23}\] The striatal AI in patient 1 was similar to PD (II-3, 11.7%; mean±SD, PD, 17.6%±6.3% and normal, 4.57%±3.49%). The AIs of III-2 and III-3 were in the range of healthy controls (4.85% and 4.74%, respectively). Results of \[^{11}\]C]raclopride PET done in II-3 and III-2 were normal and showed increased relative putamen/caudate raclopride binding (Figure 4I and J). In II-3, raclopride binding was more prominent in the right, where more severe reduction in DAT density was seen (Figure 4D and I). In patient 3 (II-5), striatal \[^{11}\]C]FP-CIT uptake was uniformly reduced in the whole field of the striatum, sug-
gestive of Parkinson plus syndrome such as MSA-P (Figure 4G). The severity of [123I]FP-CIT uptake reduction was similar between the caudate and the putamen. This resulted in a C-P ratio similar to those in healthy controls (II-5, 1.23). One of the 2 daughters and the son of patient 3 had expanded CAG repeats in the ATXN2 locus. Only the daughter (III-13) underwent [123I]FP-CIT SPECT imaging, and the results were normal (Figure 4H).

**COMMENT**

Our results show that SCA2 is a rare genetic cause of parkinsonism in our population (0.5%). All 3 patients had apparently sporadic disease, emphasizing the need to screen even in patients with nonfamilial disease. The prevalence of SCA2 in parkinsonism varies. Shan and colleagues tested 19 families with familial parkinsonism and found that 2

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Figure 3. Representative results of ATXN2 analysis (patient 2). A, Fragment analysis of polymerase chain reaction amplified genomic DNA shows 34/22 CAG repeats. B, Sequencing of the cloned fragment verifies the sequence (CAG)_{22}(CAA)(CAG)_{8} and the presence of CAA interruption (arrow). The black area indicates the CAG repeat sequence.
Hardy and colleagues reported a Chinese patient with milial parkinsonism ranged from 1.5% to 10%.\(^2\) In patients with PD with a positive family history of parkinsonism. They identified 2 patients with apparently sporadic parkinsonism, Shan et al\(^19\) reported that 4 families with familial parkinsonism. Payami and colleagues\(^6\) tested 136 patients with PD (0.4%), which is similar to our result. Lim and colleagues\(^20\) identified a patient with sporadic PD with 36 CAG repeats among 91 patients with PD.

Clinical presentation was consistent with features seen in otherwise typical patients with PD or MSA-P and without cerebellar abnormalities. The ages at onset were in the usual range of those for PD or MSA-P. SCA2-related parkinsonism may present without ataxia,\(^2\)\(^-\)\(^9\),\(^19\),\(^20\),\(^25\) even though some patients in previous reports of SCA2-related parkinsonism have ataxia.\(^2\)\(^-\)\(^6\),\(^8\),\(^28\)\(^,\)\(^30\)

In our patients with parkinsonism, CAG repeat expansions were 35/22, 34/22, and 32/22, which were in an intermediate range between the normal population and individuals with ataxic SCA2. Other reports also show that most patients with SCA2-associated parkinsonism may present without ataxia,\(^2\)\(^-\)\(^6\),\(^8\),\(^9\),\(^19\),\(^20\),\(^25\) even though some patients in previous reports of SCA2-associated parkinsonism had ataxia.\(^2\)\(^-\)\(^8\),\(^26\),\(^28\)

Figure 4. Iodine I 123 \(^{[123I]}\)-radiolabeled fluoropropyl (FP) 2-carbomethoxy-3-(4-iodophenyl) tropate (CIT) with single-photon emission computed tomography (SPECT) (A-H) and carbon C 11 \(^{[11C]}\)-radiolabeled raclopride positron emission tomography (PET) (I-J). A, Healthy control, aged 68 years. B, Patient with Parkinson disease (control), aged 68 years. C, Patient with Parkinson variant of multiple system atrophy (control), aged 73 years. D, Patient 1 (II-3). E and F, III-2 and III-3 of patient 1. G, Patient 3 (II-5). H, III-13 of patient 3. I, Patient 1 (II-3). J, III-2 of patient 1. Patient 1 (D) shows severe reduction of FP-CIT binding bilaterally, more severe on the right and in the posterior putamen. The asymptomatic gene carriers III-2 (E) and III-3 (F) show reduction of FP-CIT binding in the posterior putamen. \(^{[11C]}\)raclopride PET (I) shows increased binding on the right and in the posterior putamen, where more severe reduction in dopamine transporter density was seen in part D.

CAG repeats in the ATXN2 locus were interrupted with CAA in all of our patients with SCA2-positive parkinsonism. CAG repeats are interrupted by CAA in the majority of normal alleles, whereas the expanded alleles of high-range repeats consist of an uninterrupted stretch of CAG. Together with low-range CAG expansion, the interruption of CAG repeats might have a role in determining phenotypes.\(^2\)\(^-\)\(^6\),\(^8\),\(^9\),\(^20\),\(^25\),\(^28\)\(^,\)\(^30\)

The supporting evidence is circumstantial based on the limited number of case studies. The Table summarizes the literature. Of the 17 SCA2-parkinsonism cases who underwent a sequence-interruption study,\(^2\)\(^-\)\(^6\),\(^9\),\(^20\),\(^25\),\(^28\) only 1 did not have interruption.\(^8\) Fourteen were interrupted by CAA; 1, by CCG; and 1, by CGG. Therefore, we suspect that interruption of CAG repeats may have an influence on the phenotype. Because CAA encodes glutamine as CAG, an influence on the phenotype will not be explained at the protein level but at the genomic context.\(^25\) The interruption of a CAG stretch may confer stability in meiotic transmission.\(^25\),\(^31\) CAA interruption may have a moderating influence on the phenotype by preventing instability and high-range expansion. CGG encodes arginine, which is similar to glutamine. Interruption by CGG may be similar to CAA.\(^23\) CCG encodes proline instead of glutamine by CAG. This change will lead to a structural change in the protein, which may have an influence on the phenotype.\(^23\) However, some patients with interrupted CAG repeats presented with predominant ataxia and mild parkinsonism or parkinsonism accompanied by mild ataxia (Table).\(^2\) Therefore, the relationship between interruption and parkinsonian phenotype remains to be fur-
ther examined. In our patients, the expanded allele sizes remained constant across 2 generations. We studied somatic mosaicism, and there were no differences of CAG repeats among various tissues.

This study also highlights the need for testing asymptomatic carriers. In 2 SCA2-positive but asymptomatic carriers, DAT density on [123I]FP-CIT SPECT was reduced to the parkinsonian range. The presence of subclinical abnormalities will necessitate neuroprotective therapies.

Puls et al reported that CAG repeat variation in the CACNA1A calcium channel subunit gene might be an excellent candidate for a disease modifier in SCA2. We tested CAG repeats in the CACNA1A gene among our patients with SCA2-associated parkinsonism and their asymptomatic offspring. The CAG repeats were 11 to 14 (normal range, /H11349 18) and did not correlate with age at onset. However, the sample size was too small. Furthermore, the CACNA1A gene, as is expressed in Purkinje cells, may have no substantial roles as a disease modifier in parkinsonism.

In patient 1, the pattern of dopamine terminal loss determined by striatal [123I]FP-CIT uptake was similar to PD, with a rostrocaudal gradient and a significant asymmetry, and is consistent with other published data of DAT imaging in SCA2 patients with L-dopa–responsive parkinsonism (Table). [123I]FP-CIT SPECT in SCA2-positive but asymptomatic carriers, the daughter (III-2) and son (III-3) of patient 1, showed reduced DAT density, but the reduction of DAT density was symmetric. This DAT reduction suggests that they have a substantial degree of nigrostriatal dopaminergic dysfunction and may eventually develop clinical parkinsonism and therefore are good candidates for neuroprotective therapies.

Results of [11C]raclopride PET done in patient 1 and her daughter (III-2) were normal and showed increased relative putamen/caudate raclopride binding. In patient 1, (continued)
raclopride binding was more prominent in the side with more severely reduced DAT density. These [123I]FP-CIT SPECT and [11C]raclopride PET data support presynaptic abnormalities of parkinsonism in the affected and pre-symptomatic carriers.7,25 Patient 3 had more uniform nigrostriatal damage on [123I]FP-CIT SPECT, which is a pattern of MSA-P. Therefore, DAT imaging was quite consistent with the clinical phenotype. In the 26-year-old daughter of patient 3 (III-13), striatal DAT density was normal. This result may be because of her young age, and she will be followed up with DAT imaging.

It is intriguing why parkinsonism appears especially in SCA2 with low-range CAG expansion and interruption. Du¨rr and colleagues18 emphasized the striking discrepancy between the severe pathological changes observed in the substantia nigra and the lack of overt parkinsonian features. Interestingly, DAT imaging of SCA2 patients without evident parkinsonism shows a similar degree of nigrostriatal dopaminergic damage as that of patients with PD.33-35 Thus, additional factors may be required for parkinsonian signs to appear. In ataxic SCA2, parkinsonism could be masked by severe cerebellar dysfunction even in the presence of significant nigrostriatal impairment.36 Relatively short repeat expansions may lead to less severe cerebellar abnormalities.25 Alternatively, the involvement of other nuclei in the extrapyramidal system, such as the globus pallidus and the subthalamic nucleus,16,18 could account for the lack of parkinsonism in ataxic SCA2.34 The mechanism revealed by the SCA2-related parkinsonism may turn out to be very important.37 Comprehension of a parkinsonian phenotype in SCA2 may shed light on the pathogenesis of PD. The product of the ATXN2 gene, ataxin-2 protein, may be involved in RNA splicing and protein interaction.38 However, it remains unclear how mutated

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<td>Furtado et al²⁵  (<em>New Cases</em> section)</td>
<td>38, 34, 39, and 33</td>
<td>NC, NC, NC, and CAA</td>
<td>NA, NA, NA, and NA</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Lee et al²⁶</td>
<td>Mean ± SD, 37 ± 1</td>
<td>NC</td>
<td>NA</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Perier et al²⁷</td>
<td>34 and 34</td>
<td>NC</td>
<td>NA</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Costanzo-Porrini et al²⁸</td>
<td>CAA and CAA</td>
<td>NA and NA</td>
<td>Abnormal results</td>
<td>WNL</td>
<td></td>
</tr>
<tr>
<td>Fernandez et al²⁹</td>
<td>Mother, 33; and uncle, 36</td>
<td>Mother, negative results</td>
<td>+</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Current study</td>
<td>35, Asymptomatic daughters and sons: 35, 34, 32, 32</td>
<td>3 CAA, CAA, and 3 CAA</td>
<td>Negative results, and negative results</td>
<td>Abnormal results⁶</td>
<td>Abnormal results⁴</td>
</tr>
</tbody>
</table>

Abbreviations: CBGD, corticobasal ganglionic degeneration; MND, motor neuron disease; MSA-P, Parkinson variant of multiple system atrophy; NA, unavailable because of a lack of familial genetic study; NC, not mentioned in the article; NT, not tested; PCR, polymerase chain reaction; PD, Parkinson disease; PSP, progressive supranuclear palsy; WNL, results within normal limits; +, positive.

*Detailed description of patients is available in the original source.

Presumed diagnosis prior to SCA testing.

*Asymptomatic carrier study, footnote expressed after data only when done.

Interruption in the expanded allele.

Abnormal raclopride binding results, with binding potentials slightly higher in the putamen than the caudate.
ATXN2 causes neuronal death and why CAG expansion, especially in the low range and interrupted, is associated with parkinsonism. Further studies using transgenic mice with mutated ATXN2 may be helpful to solve these questions. Postmortem neuropathological analyses of SC2A patients with pure parkinsonism will aid in the solution of CAG expansion and parkinsonism.

In summary, to our knowledge, this study is the first to evaluate the status of SC2A and the nigrostriatal dopaminergic system in patients with apparently sporadic parkinsonism in the Korean population. We found that SC2A is one of the genetic causes of PD or MSA-P and needs to be screened in apparently sporadic parkinsonism. CAG repeats were in the low-range expansion and interrupted by CAA in all patients. Therefore, accurate determination of SC2A expansion and gene sequencing, especially in the low-range patients, is warranted. Dopamine transporter and D2 receptor imaging may provide means of nigrostriatal dopaminergic integrity, preclinical diagnosis, follow-up, and evaluating neuroprotective therapy in SC2A-related parkinsonism and asymptomatic carriers.

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Correspondence: Beom S. Jeon, MD, PhD, Department of Neurology, Seoul National University Hospital, Chongno-Ku Yunkeun-Dong 28, Seoul 110-744, South Korea (brain@snu.ac.kr).

Author Contributions: Dr J.-M. Kim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jeon. Acquisition of data: Hong, G. P. Kim, Y. K. Kim, Park, S. E. Kim, and Jeon. Analysis and interpretation of data: J.-M. Kim, Choi, and Jeon. Drafting of the manuscript: J.-M. Kim. Critical revision of the manuscript for important intellectual content: J.-M. Kim, Hong, G. P. Kim, Choi, Y. K. Kim, Park, S. E. Kim, and Jeon. Administrative, technical, and material support: J.-M. Kim, Hong, G. P. Kim, Choi, Y. K. Kim, Park, and S. E. Kim. Study supervision: Jeon.

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