의학 석사 학위 논문

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SCA17의 경계값에 대한 연구

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서울대학교 대학원

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신 정 환

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이 논문을 의학석사 학위논문으로 제출함

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신 정 환의 석사학위논문을 인준함

2014년 12월

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Abstract

Background: SCA17 is an autosomal dominant cerebellar ataxia with expansion of CAG/CAA trinucleotide repeats in TATA-binding protein (TBP) gene. SCA17 can present with various clinical presentation including parkinsonism, ataxia, chorea and dystonia. SCA17 is diagnosed with detection of expanded CAG repeats in TBP, but reported pathologic repeat numbers as low as 41 overlap with reported normal repeat numbers.

Methods: Subjects included those with involuntary movement disorders including cerebellar ataxia, parkinsonism, chorea and dystonia who visited Seoul National University Hospital between Jan, 2006 and Apr 2014 and who were screened for SCA17. Those who were diagnosed with other genetic diseases or nondegenerative diseases were excluded. DNA from the healthy subjects who did not have a family history of parkinsonism, ataxia, psychiatric symptoms, chorea or dystonia served as a control. Total 5242 chromosomes from 2099 patients and 522 normal controls were analyzed.

Results: Total number of patients included in the analysis was 2099 (parkinsonism, 1706; ataxia, 345; chorea, 37; and dystonia, 11) In normal control, up to 44 repeats were found. In 44 repeats, there were 7 (0.33%) patients and 1 (0.19%) normal control. In 43 repeats, there were 8 (0.38%) patients and 2 (0.38%) normal controls. In 42 repeats, there were 16 (0.76%) patients and 3 (0.57%) normal controls. In 41 repeats, there were 48 (2.29%) patients and 8 (1.53%) normal controls. Considering overlaps and non-significant differences of allelic frequencies between patients with normal controls in low-expansions, we couldn't locate the definite cut off value of SCA17.

Conclusions: As statistical analysis between normal control and patients in low expansions has failed to show difference so far, we must consider that clinical cases with low expansions could be idiopathic movement disorders showing coincidential CAG/CAA expansions. Thus we need to reconsider pathologic role of low-expansions(41-42). Long term follow up observation and comprehensive investigations using autopsy and imaging studies in patients and controls with low expansion are necessary to resolve the blurred cut off value of SCA17.

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Distribution of CAG/CAA repeats in the TATA-binding protein gene in normal controls and patients. Patients are shown as light colored bar, normal control as dark colored bar.

Table 1.

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Table 2.

Comparison of allelic frequencies of normal controls and patients in each allele.
No.: Number of patients or controls.

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Comparison of allelic frequencies of normal controls and patients with disease subtypes in each allele. Allelic frequency of chorea with 42 repeats were significantly higher than normal controls.($p=0.033$, analyzed with Fisher's exact test)
No. : Number of patients or controls.

Supplementary table 1

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Supplementary table 2.

Clinical characteristics of patients with 41 or more repeats of SCA 17.

C : Cerebellar symptom, P : Parkinsonism, Psy : Psychiatric symptom, Cog : Cognitive impairment, Cho : Chorea, N.I : no information, ND : Not done, WNL : within normal limit, SVD : small vessel disease

Introduction

Spinocerebllar ataxia type 17 is an autosomal dominant cerebellar ataxia characterized by ataxia, psychiatric symptoms, parkinsonism and involuntary movement such as chorea and dystonia.[1] It is caused by abnormal expansion of CAG/CAA trinucleotide repeats in the TATA binding protein(TBP) gene located in chromosome 6.[2, 3]

Typical SCA17 presents with ataxia and cognitive decline.[3] However some patients present with atypical symptoms such as Huntington disease like phenotype[4] and Parkinsonism.[5, 6] Even non ataxic features have been reported as well.[5, 7] Especially there were suggestions that lower-range expansions of the SCA17 are more likely to cause parkinsonism compared to ataxia.[8]

There have been an uncertainty about cut off points in SCA17.[9] Early reports proposing SCA17 as a new disease entity, cut off value was set as 47 or more.[3] Cut off value was then gradually lowered and currently accepted abnormal repeat number is 43 repeats or more.[9] However following studies suggested 42 repeats could be pathologic.[6, 10] Furthermore there were case reports of patients even with 41 repeats: one presenting with late onset progressive cerebellar ataxia[11]; one with late onset chorea and psychiatric symptoms[12]; and one with rapidly progressing cognitive phenotype.[13] On the other hand, healthy control with more than 42 repeats were reported including 44 repeats[6] and 45 repeats[7].

Majority of trinucleotide repeat disorders including Huntington disease[14] or other SCAs[15-17] have intermediate zone with repeat number below cut off values. It is also called allele with reduced penetrance. There are cut off value issues in several SCAs including SCA17.[14-16] In the case of Huntington's disease, pathologic CAG repeat is known as 40 or more, 36-39 repeats are considered as allele with reduced penetrance. Although expansions below 30 was considered normal[18], autopsy proven Huntington's disease with 29 repeat was reported[19] As gap between normal and abnormal repeat numbers are very narrow in SCA17,[6] further investigation of repeats below cutoff is necessary.

In the present study, we reviewed the SCA17 repeat numbers in our patients with movement disorders and compared allele distribution with normal healthy controls to

investigate cutoff value of SCA17.

Method.

Retrospective analysis of patients with cerebellar ataxia, parkinsonism, chorea and dystonia 1) who visited Seoul National University Hospital Movement Disorder Clinic from Jan, 2006 to Apr 2014 and 2) who were tested with SCA17 was done. Not all patients who visited our clinic were tested with SCA17. Parkinson disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and dementia with Lewy body (DLB) were clinically diagnosed.[20-24] Those who had parkinsonian feature, but didn't meet the diagnostic criterias of the above parkinsonian syndromes were classified as other parkinsonism.

All patients were native Koreans. Blood samples were collected after written informed consent was obtained from each participant. The Institutional Review Board of Seoul National University Hospital approved this study. DNA from the healthy subjects who did not have a family history of parkinsonism, ataxia, chorea, dystonia or psychiatric features served as a control. Total 5242 chromosomes from 2099 patients and 522 normal controls were analyzed.

Molecular studies

Genomic DNA was extracted from peripheral blood leukocytes using a standard protocol. SCA17 allele size was determined as previously described.[6, 25, 26] In brief, genomic DNA was extracted using a DNA isolation kit (Gentra PureGene; Gentra Systems Inc, Minneapolis, Minnesota). SCA17 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 soft- ware.13,14

PCR was performed using the following primers:

forward, 5′-ATGCCTTATGGCACTGGACTG-3′ (6-FAM labeled);

and reverse, 5′-CTGCTGGGACGTTGACTGCTG-3′.

In order to examine the interrupted sequences, the amplified fragment containing CAG repeats was sub cloned 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 Ge- netic Analyzer using a BigDye Terminator Cycle Sequencing Ready Reaction Kit (version 3.1; Applied Biosystems).

Statistical analysis

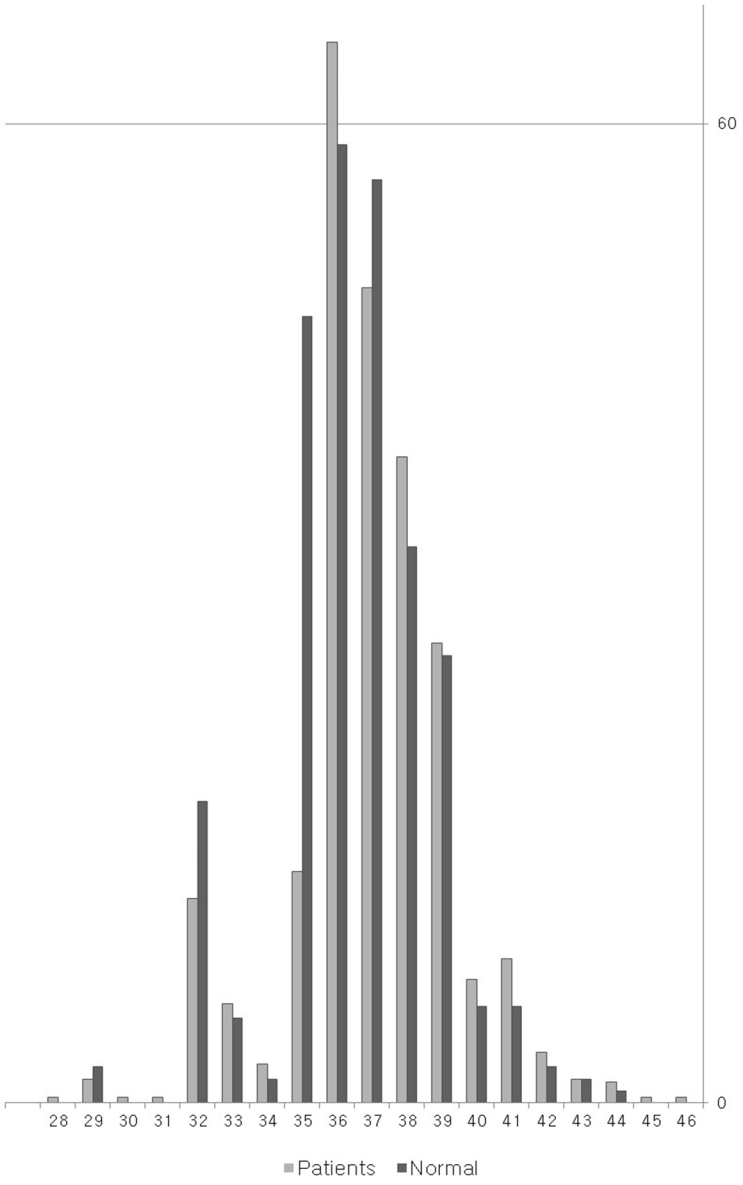
Independent t-test and Mann-Whitney test was used to compare variables between groups. Pearson Chi-square test and Fisher's exact test were used to compare categorical variables. The level of statistical significance was set at $p < 0.05$. The statistical package for the social sciences (SPSS 21.0) was used for all analysis.

Results.

Total number of patients included in the analysis was 2099 (Classified by dominant clinical phenotype: parkinsonism, 1706; ataxia, 345; chorea, 37; and dystonia, 11). Parkinsonism consisted of PD (n=1069, 50.9%), MSA-parkinsonian type (n=153, 7.3%), PSP (n=23, 1.1%), CBS (n=6, 0.3%) and DLB(n=65, 0.3%) and other Parkinsonism (n=449, 21.4%). Ataxia was consisted of MSA with cerebellar type(n=125, 6.0%) and adult-onset cerebellar ataxia (n=220, 10.5 %). Mean age of normal controls(63.9 ± 9.1-year-old [standard deviation], range 38-87 years) were higher than patients(61.3 ± 10.2-year-old [standard deviation], range 3-91 years) with statistical significance ($p<0.0001$). The number of repeats of SCA17 in the alleles ranged from 29 to 44 in normal controls and 23 to 46 in the patients.(Figure 1) Mode was 36 in both patient and control group. As we compare allelic distributions between patients and normal controls by each repeat numbers, allelic percentage was quite similar although slightly larger in patient group above repeat number

41 without statistical significance.(Table 1) Patients with low expansions showed variable clinical features including parkinsonian syndromes, cerebellar ataxia and chorea.

Figure 1.



Distribution and clinical diagnosis are summarized in Table 1. Comparison of allelic frequencies between normal controls with patients are in Table 2 and 3. Clinical presentations of patients are described in Supplementary table 2.

Table 1

No. of repeats	**Patient**		**Control**	
	Phenotypes	%	phenotypes	%
46	2 (1 MSA, 1 Pism)	**0.09**	0	**0.00**
45	2 (PD)	**0.09**	0	**0.00**
44	7 (2 PD, 1 MSA, 2 Pism, 2 CA)	**0.33**	1	**0.19**
43	8 (4 PD, 3 Pism, 1 MSA,)	**0.38**	2	**0.38**
42	16 (7 PD, 3 MSA, 1 HDL, 1 PSP ,2 Pism, 1 CA)	**0.76**	3	**0.57**
41	48 (27 PD, 8 Pism, 7 MSA, 4CA, 1 HDL, 1 CBS)	**2.29**	8	**1.53**
Cumulation /Total	83/2099		14/522	

Table 2.

Allele	Patients numbers	Patients (%)	Normal control numbers	Normal (%)	P value
46	2	0.048	0	0.000	1.000
45	2	0.048	0	0.000	1.000
44	7	0.167	1	0.096	0.611
43	8	0.191	2	0.192	0.684
42	17	0.405	3	0.287	0.759
41	48	1.143	8	0.766	0.721
40	41	0.977	8	0.766	0.560
Total	4198	100	1044	100	

Table 3.

Allele	PD No (%)	MSA No (%)	Chorea No (%)	Parkinsonism No (%)	Cerebellar ataxia No (%)	Normal No (%)
46	0 (0)	1 (0.18)	0 (0)	1 (0.11)	0 (0)	0 (0)
45	2 (0.09)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
44	2 (0.09)	1 (0.18)	0 (0)	2 (0.22)	2 (0.45)	1 (0.10)
43	4 (0.18)	1 (0.18)	0 (0)	3 (0.33)	0 (0)	2 (0.19)
42	7 (0.33)	3 (0.54)	2 (2.70)*	3 (0.33)	1 (0.23)	3 (0.29)
41	27 (1.26)	7 (1.26)	1 (1.35)	9 (1.00)	3 (0.68)	8 (0.77)
Total	2138	556	74	898	440	1044

44 repeats

In our normal population, largest expansion was a 44 repeat. Even though asymptomatic, this 51 year old normal control showed a severe reduction in DAT binding, as previously reported by our group[6] There were 7 (0.3%) patients, who showed parkinsonism as a dominant phenotype except for 2 cerebellar ataxic phenotype.(Table 1) Patient number 9(Table 4) with pure cerebellar ataxia showed decreased striatal uptake in FP-CIT PET, although she had no parkinsonism.

43 repeats

2 (0.4%) normal controls and 8 (0.4 %) patients showed 43 or more repeats, which is currently accepted as lower pathologic margin. Comparing the allelic frequency between these two groups, there was no statistical significance. One of two normal controls showed modest reduction in DAT binding also, as reported by our group.[6] Other normal control was not tested with DAT image.

42 repeats

3 (0.6%) normal controls and 16 (0.8 %) patients showed 42 repeats. Allele percentage of normal controls were 0.3% while 0.4% in patients. In each disease subgroups, allelic frequency of PD patients were 0.3%; 0.5% in MSA; 2.7% in chorea.(Table 3) Allelic frequency of chorea with 42 repeats were higher than normal population with statistical significance (p=0.033), Other correlation analysis showed no statistical difference between each groups.

One normal control showed mild reduction in DAT binding considering his age,[6] other two normal controls were not tested with DAT images. Patient number 23 showed marked cerebellar ataxia with cerebellar atrophy and familial history (3 of her 4 sisters were reported to show cerebellar ataxia). SCA 1, 2, 3, 6, 7, DRPLA and Friedreich's ataxia were excluded

in this patient. But unfortunately genetic tests were not done in her sisters.

41 repeats

8 (1.5%) of normal controls and 48 (2.3 %) patients had 41 repeats. Allele percentage harboring 41 repeats was 0.7% in normal controls and 1.14% in patients, which showed no statistical difference. Among patients with 41 repeats, Patient number 63 showed parkinsonism with generalized chorea which appeared before medication. Huntington disease and DRPLA were excluded by gene tests in this patient. There were no other identifiable secondary cause and abnormalities on brain MR. Patient 56 and 75 who also have 41 repeats, showed cerebellar ataxia with cerebellar and middle cerebellar peduncle atrophy in brain MRI. Father of Patient 75 was reported to have cerebellar ataxia. Unfortunately his father was not tested for SCA17 because he passed away before the patient first came to the clinic.

When we compared normal controls who were more than 55 years of age (N=434) with patients, allelic frequencies and distributions were not different between patients with normal controls, similar to the above results.

Sequence analysis of the CAA/CAG repeats was done in 36 patients (10 in Kim et al[6] and 8 in Yun et al[8], 18 additional patients with ataxia, parkinsonism or chorea (listed in supplementary table 1) , which all showed interrupted sequence except for 2 patients included in Yun et al[8].

Discussion.

The objective of this study was to investigate the cut off value in SCA17 and we compared distribution of CAG/CAA repeat of between patients and normal controls.

Normal controls were older than the patient group in our population.(63.9± 9.1 versus 61.3 ± 10.2) Age at onset of SCA17 is known to range from age 3 to 75 years in the previous

review[27], hence normal controls with young age can be presymptomatic patients. In terms of minimizing the chance of including presymptomatic patients in normal control group, age distribution seems to be acceptable. In addition, we did separate analysis in normal control aged over 55 to minimize the problem of presymptomatic cases, which gave the same results.

In our population, 79 (3.73%) among 2099 patients showed repeats from 41 to 45. Among 79 patients, 66 (3.14%) were 41 or 42 repeats which is considered controversial.

Although, we could find interesting cases harboring 41 or 42 repeats, allelic frequencies as high as 43 were similar between patients and controls. Also, normal controls showed expansions as large as 44. Thus we couldn't locate the definite cut off value of SCA17. Recent report[28] compared allelic distribution of normal control with autosomal dominant PD in polyglutamine disease including SCA17. They found significant different distribution in SCA 2, but not with other genes. It is consistent with our results with SCA17.

Current evidences suggesting pathologic role of SCA17 with low expansions are mostly based on case descriptions showing movement disorders or psychiatric symptoms accompanied by CAG expansions in TBP[10-13]. As statistical analysis between normal control and patients in low expansions has failed to show difference so far, we must consider that clinical cases with low expansions could be idiopathic movement disorders showing coincidential CAG/CAA expansions. Thus we need to reconsider pathologic role of low-expansions(41-42).

In order to set the definite cut off, following evidences can be considered. Repeat numbers which have never been reported in normal population or repeats with pathologic confirmation of cerebral tissue or repeats showing different allelic distribution compared with normal control might be considered as cut off. Largest expansion reported in the normal population is 45[7] and there being lack of pathological and statistical evidence suggesting cut off in low expansions so far, definite cut off can be set as 46 or more. 41 through 45 should be considered as intermediate range and needs cautious interpretation.

To make a further understanding of cut off in SCA17, autopsy results of patients and normal controls with low expansion should be investigated. Whether patients or

asymptomatic normal control with low-range expansion has intra-nuclear polyglutamine inclusions might be key finding of this issue. Also, functional image such as dopamine transporter image in low expansion including 41 in normal controls with serial follow up might reveal subclinical pathology and provide us with more evidence for clear cut off value in SCA17.

Our results demonstrated that cut off value in SCA 17 is blurred, and we should carefully examine the pathologic role of low-expansions in SCA17. Long term follow up observation and comprehensive investigations using autopsy and imaging studies in patients and controls with low expansion are necessary to resolve the blurred cut off value of SCA17.

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Supplementary table 1

Patient No.	Sex/Age	Diagnosis	TNR	
3	M/68	PD	45/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)25CAACAG
				(CAG)3(CAA)3(CAG)6CAACAGCAA(CAG)19CAACAG
8	M/58	Pism	44/37	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)24CAACAG
				(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)17CAACAG
9	F/64	CA	44/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)24CAACAG
				(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)16CAACAG
11	F/48	PD	44/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)24CAACAG
				(CAG)3(CAA)3(CAG)6CAACAGCAA(CAG)19CAACAG
17	F/68	MSA	43/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)23CAACAG
				(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)16CAACAG
18	F/58	PD	43/37	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)23CAACAG
				(CAG)3(CAA)3(CAG)8CAACAGCAA(CAG)18CAACAG
20	M/66	MSA	43/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)22CAACAG
				(CAG)3(CAA)3(CAG)8CAACAGCAA(CAG)18CAACAG
23	F/64	CA	42/37	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)22CAACAG
				(CAG)3(CAA)3(CAG)8CAACAGCAA(CAG)18CAACAG
31	M/66	PD	42/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)22CAACAG
				(CAG)3(CAA)3(CAG)8CAACAGCAA(CAG)17CAACAG
33	M/76	Chorea	42/37	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)22CAACAG
				(CAG)3(CAA)3(CAG)8CAACAGCAA(CAG)18CAACAG
34	F/59	MSA	42/37	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)22CAACAG

				(CAG)3(CAA)3(CAG)6CAACAGCAA(CAG)20CAACAG
36	F/68	chorea	41/37	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)21CAACAG
				(CAG)3(CAA)3(CAG)6CAACAGCAA(CAG)20CAACAG
37	M/51	MSA	41/38	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)21CAACAG
				(CAG)3(CAA)3(CAG)8CAACAGCAA(CAG)17CAACAG
38	M/72	Pism	41/38	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)3CAA(CAG)17CAACAG
				(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)18CAACAG
44	M/51	MSA	41/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)21CAACAG
				(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)16CAACAG
55	F/55	CA	41/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)21CAACAG
				(CAG)3(CAA)3(CAG)8CAACAGCAA(CAG)17CAACAG
75	M/59	CA	41/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)21CAACAG
				(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)16CAACAG
79	M/68	CA	41/36	(CAG)3(CAA)3(CAG)9CAACAGCAA(CAG)21CAACAG
				(CAG)3(CAA)3(CAG)8CAACAGCAA(CAG)17CAACAG

Supplementary table 2

No	Sex/Age	TNR	Diagnosis	C	P	Psy	Cog	Cho	Brain MRI	DAT/SPECT	Family History
1	F/61	46/42	Pism	(+)	(+)	(-)	(-)	(-)	WNL	ND	(-)
2	F/57	46/36	MSA	(+)	(+)	(-)	(-)	(-)	MCP atrophy	ND	(-)
3	M/68	45/36	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	N.I
4	F/55	45/37	PD	(-)	(+)	(-)	(-)	(-)	WNL	ND	(-)
5	F/60	44/36	CA	(+)	(-)	(-)	N.I	(-)	MCP,cerebellar atrophy	Decreased Striatal uptake	(-)
6	M/66	44/36	Pism	(+)	(+)	(-)	(-)	(-)	SVD	ND	(-)
7	M/71	44/36	PD	(-)	(+)	(-)	(-)	(-)	WNL	ND	(-)
8	M/58	44/37	Pism	(-)	(+)	(-)	N.I	(-)	SVD	Decreased Striatal uptake	(-)
9	F/64	44/36	CA	(+)	(-)	(-)	(-)	(-)	Cerebellar atrophy	Decreased Striatal uptake	(-)
10	M/74	44/36	MSA	(+)	(-)	(-)	(-)	(-)	SVD	ND	(-)
11	F/48	44/36	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)
12	M/43	43/36	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)
13	F/68	43/36	PD	(-)	(+)	(+)	N.I	(-)	putaminal iron deposition	ND	(-)
14	M/80	43/36	Pism	(-)	(+)	(+)	(+)	(-)	SVD	ND	(-)
15	F/72	43/36	Pism	(+)	(+)	(-)	(-)	(-)	SVD	ND	(-)
16	F/55	43/35	PD	(-)	(+)	(-)	(-)	(-)	WNL	Decreased Striatal uptake	(-)
17	M/60	43/36	MSA	(-)	(+)	(-)	(+)	(-)	MCP,cerebellar atrophy	ND	(-)
18	F/58	43/37	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)

No	Sex/Age	TNR	Diagnosis	C	P	Psy	Cog	Cho	Brain MRI	DAT/SPECT	Family History
19	F/50	43/36	Pism	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)
20	M/66	42/37	MSA	(+)	(-)	(-)	(-)	(-)	MCP, cerebellar atrophy	ND	(-)
21	M/61	42/36	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)
22	M/84	42/37	Pism	(-)	(+)	(-)	(+)	(-)	putaminal iron deposition	ND	N.I
23	F/64	42/37	CA	(+)	(-)	(-)	N.I	(-)	Cerebellar atrophy	ND	(+)
24	M/77	42/36	Pism	(-)	(+)	(-)	N.I	(-)	SVD	ND	N.I
25	F/58	42/36	PD	(-)	(+)	(-)	(-)	(-)	WNL	ND	(-)
26	M/70	42/36	PSP	(+)	(-)	(-)	N.I	(-)	WNL	ND	(-)
27	M/72	42/38	PD	(-)	(+)	(-)	(-)	(-)	SVD	ND	(-)
28	M/85	42/36	chorea	(-)	(-)	(+)	(+)	(+)	WNL	ND	N.I
29	M/59	42/36	PD	(-)	(+)	(-)	(-)	(-)	SVD	Decreased Striatal uptake	(-)
30	M/66	42/36	MSA	(-)	(+)	(-)	(-)	(-)	Cerebellar atrophy	WNL	(-)
31	M/66	42/36	PD	(-)	(+)	(+)	(-)	(-)	SVD	Decreased Striatal uptake	(-)
32	F/53	42/40	PD	(-)	(+)	(+)	N.I	(-)	WNL	Decreased Striatal uptake	(+)
33	M/76	42/37	Chorea	(-)	(-)	(-)	(-)	(+)	SVD	ND	(+)
34	F/68	42/37	MSA	(-)	(+)	(-)	N.I	(-)	SVD	ND	(-)
35	F/56	42/38	PD	(-)	(+)	(-)	(-)	(-)	WNL	ND	N.I
36	F/69	41/37	chorea	(-)	(-)	(+)	(-)	(+)	Right frontal cerebromal acia	ND	N.I
37	M/52	41/38	MSA	(+)	(+)	(+)	(-)	(-)	WNL	ND	N.I
38	M/73	41/38	Pism	(-)	(+)	(-)	(-)	(-)	ND	Decreased Striatal uptake	N.I
39	F/77	41/37	PD	(-)	(+)	(-)	(-)	(-)	SVD	ND	N.I

No	Sex/Age	TNR	Diagnosis	C	P	Psy	Cog	Cho	Brain MRI	DAT/SPECT	Family History
40	M/63	41/37	PD	(-)	(+)	(-)	(-)	(-)	SVD	ND	N.I
41	M/61	41/36	Pism	(-)	(+)	(+)	(-)	(-)	SVD	ND	N.I
42	F/75	41/40	PD	(-)	(+)	(+)	(-)	(-)	SVD, old infarction in PICA	ND	(-)
43	F/59	41/36	PD	(-)	(+)	(+)	(-)	(-)	SVD	ND	(-)
44	F/61	41/36	MSA	(+)	(-)	(-)	(-)	(-)	cerebellar atrophy	ND	(-)
45	F/60	41/38	PD	(-)	(+)	(-)	(-)	(-)	SVD	ND	(-)
46	F/69	41/36	PD	(-)	(+)	(+)	(-)	(-)	WNL	ND	(-)
47	M/71	41/36	PD	(-)	(+)	(+)	(-)	(-)	WNL	ND	(-)
48	M/61	41/36	MSA	(-)	(+)	(-)	(-)	(-)	WNL	ND	N.I
49	M/61	41/36	Pism	(-)	(+)	(-)	(-)	(-)	SVD	ND	(-)
50	F/67	41/36	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)
51	F/76	41/37	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)
52	M/53	41/37	Pism	(-)	(+)	(+)	(-)	(-)	WNL	ND	N.I
53	F/74	41/36	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)
54	F/64	41/39	CA	(+)	(+)	(-)	(-)	(-)	SVD	ND	(-)
55	F/57	41/36	CA	(+)	(-)	(-)	(-)	(-)	SVD	ND	N.I
56	F/54	41/36	CA	(+)	(-)	(-)	(-)	(-)	MCP,cerebellar atrophy	ND	N.I
57	F/76	41/36	PD	(-)	(+)	(+)	(+)	(-)	WNL	ND	(-)
58	M/54	41/35	Pism	(-)	(+)	(-)	(-)	(-)	SVD	ND	(-)
59	M/54	41/36	MSA	(+)	(-)	(-)	(-)	(-)	cerebellar atrophy	ND	(-)
60	F/56	41/36	PD	(-)	(+)	(-)	(-)	(-)	SVD	ND	(-)
61	M/65	41/36	MSA	(+)	(+)	(-)	(-)	(-)	WNL	ND	(-)

No	Sex/Age	TNR	Diagnosis	C	P	Psy	Cog	Cho	Brain MRI	DAT/SPECT	Family History
62	F/53	41/37	PD	(-)	(+)	(-)	(-)	(-)	WNL	ND	(-)
63	M/65	41/32	Pism	(-)	(+)	(-)	(-)	(+)	SVD	ND	(+)
64	M/59	41/36	Pism	(-)	(+)	(+)	(+)	(-)	putaminal iron deposition	ND	(-)
65	F/64	41/36	PD	(-)	(+)	(-)	(-)	(-)	WNL	ND	(-)
66	F/58	41/36	R/O CBS	(-)	(+)	(+)	(+)	(-)	WNL	ND	(-)
67	M/73	41/36	MSA	(-)	(+)	(+)	(-)	(-)	SVD	Decreased Striatal uptake	(+)
68	F/67	41/36	PD	(-)	(+)	(-)	(+)	(-)	ND	ND	(-)
69	M/74	41/37	PD	(-)	(+)	(+)	(-)	(-)	SVD	Decreased Striatal uptake	(-)
70	M/66	41/36	PD	(-)	(+)	(-)	(-)	(-)	SVD	ND	(-)
71	F/71	41/36	MSA	(+)	(+)	(-)	(-)	(-)	diffuse brain atrophy	ND	(-)
72	F/61	41/38	PD	(-)	(+)	(+)	(-)	(-)	WNL	ND	(-)
73	M/68	41/38	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(+)
74	M/47	41/38	PD	(-)	(+)	(-)	(-)	(-)	SVD	ND	(-)
75	M/60	41/36	CA	(+)	(-)	(-)	(-)	(-)	MCP,cerebellar atrophy	ND	(+)
76	M/51	41/37	PD	(-)	(+)	(-)	(-)	(-)	ND	Decreased Striatal uptake	(-)
77	M/45	41/36	PD	(-)	(+)	(-)	(-)	(-)	WNL	nd	(-)
78	M/73	41/37	PD	(-)	(+)	(-)	(-)	(-)	WNL	nd	(-)
79	M/69	41/36	CA	(+)	(+)	(-)	(-)	(+)	WNL	WNL	(-)
80	F/55	41/36	PD	(-)	(+)	(+)	(-)	(-)	ND	ND	(-)
81	M/69	41/36	PD	(-)	(+)	(+)	(-)	(-)	ND	ND	(-)
82	M/55	41/37	PD	(-)	(+)	(-)	(-)	(-)	ND	ND	(-)

No	Sex/Age	TNR	Diagnosis	C	P	Psy	Cog	Cho	Brain MRI	DAT/SPECT	Family History
83	M/49	41/37	PD	(-)	(+)	(-)	(-)	(-)	WNL	Decreased Striatal uptake	(-)

국문 초록

배경 : SCA17은 우성으로 유전되는 소뇌성 실조증으로, TATA 결합 단백질의 CAG/CAA 삼염기 서열의 확장으로 발병된다. SCA17은 파킨슨증, 실조증, 무도증과 근긴장이상증을 포함한 다양한 임상증상을 보일수 있다. SCA 17은 유전자 검사를 통한 CAG 확장으로 진단하는데, 반복수가 41까지 낮은 임상 증례가 보고된 바 있으며, 이는 정상군의 범위와 중복되는 문제점이 있다.

방법 : 2006년 1월부터 2014년 4월까지 서울대병원 신경과에 내원한 환자중, 실조증, 파킨슨증, 무도증과 근긴장이상증을 보였던 환자들이 포함되었다. 다른 유전적 질환 혹은 비퇴행성질환으로 진단된 환자들은 제외하였다. 건강한 대조군들은 파킨슨증, 실조증, 정신증상, 무도증 혹은 근긴장이상증의 가족력이 없는 사람들로 구성되었다. 2099명의 환자와 522명의 건강한 대조군으로 부터 얻은 5242개의 염색체를 분석하였다.

결과 : 분석에 참여한 환자수는 총 2099명이었다. (파킨슨증, 1706;실조증, 345; 무도증, 37; 그리고 근긴장이상증, 11). 정상 대조군에서 44 반복수까지 나타남을 확인하였다. 44 반복수에서는 7명 (0.33%)의 환자와 1명(0.19%)의 정상인이 있었다. 43 반복수에는 8명(0.38%)의 환자와 2명(0.38%)의 정상군이 있었다. 42 반복수에서는 16명(0.76%)의 환자와 3명 (0.57%)의 정상군이 있었다. 41 반복수에서는 48명(2.29%)의 환자와 8명(1.53%)의 정상군이 있었다. 각 반복수에 따른 대립유전자 빈도의 통계적 유의성이 없고, 정상인과 환자군의 분포가 겹쳐 있음을 확인하였고, 따라서 SCA17의 정확한 경계값을 정할수 없었다.

결론 : 낮은 반복수에서 환자군과 정상군의 대립유전자 빈도의 차이에 대한 통계적 유의성이 없었으므로, 낮은 반복수를 보이는 임상증례들이 CAG/CAA 반복이 우연히 동반되었을 가능성에 대한 고려가 필요하다. 따라서 41과 42의 낮은 반복수의 병리적 역할에 대해 재고하여야 한다. SCA17의 경계값을 명확히 하기 위해서는 추후 낮은 반복수를 보이는 환자군과 정상군을 대상으로 영상소견의 시간적 변화를 장기 추적관찰하고 부검을 통한 병리소견에 대해 확인하는 것이 필요하다.