J Korean Med Sci 2001; 16: 809-13
ISSN 1011-8934

Copyright © The Korean Academy of Medical Sciences

Spinocerebellar Ataxia Type 6 and Episodic Ataxia Type 2 in a Korean Family

Spinocerebellar ataxia type 6 (SCA6), episodic ataxia type 2 (EA2) and familial hemiplegic migraine (FHM) have been known as allelic disorders, which are caused by the alteration of the α_{1A} voltage-dependent calcium channel subunit. Expansions of the CAG repeat in the *CACNA1A* gene on the short arm of the chromosome 19 induce SCA6, and point mutations in the same gene are responsible for EA2 and FHM. In recent studies, both SCA6 and EA2 have been concurrently found in families with 26 CAG repeats without previously reported point mutations either in coding sequences or in intron-exon junctions. We describe a Korean family with CAG26 repeats in the *CACNA1A* gene. Some of the affected family members had progressive ataxia typical of SCA6 whereas others had episodic vertigo responsive to acetazolamide typical of EA2. Our family support that SCA6 and EA2 are allelic disorders with a high phenotypic variability.

Key Words : *Ataxia; Calcium Channels; Spinocerebellar Ataxias*

Seong-Ho Koh, Hee-Tae Kim, Seung-Hyun Kim, Gyu-Yong Lee, Juhan Kim, Myoung-Ho Kim

Department of Neurology, Institute of Clinical Medicine, University of Hanyang, Seoul, Korea

Received : 9 October 2000
Accepted : 7 February 2001

Address for correspondence
Hee-Tae Kim, M.D.
Department of Neurology, Institute of Clinical Medicine, University of Hanyang,17 Haengdang-dong, Seongdong-gu, Seoul 133-792, Korea
Tel : +82.2-2290-8699, Fax : +82.2-2290-8377
E-mail : kimht@email.hanyang.ac.kr

INTRODUCTION

Spinocerebellar ataxia type 6 (SCA6), episodic ataxia type 2 (EA2) and familial hemiplegic migraine (FHM) have been considered to be diverse disorders phenotypically as well as genetically (1).

SCA6, named by Zhuchenko et al. (1) is an autosomal dominant disorder characterized by cerebellar functional deficit and atrophy, which are slowly progressive and permanent. SCA6 is caused by CAG repeat expansions in the *CACNA1A* gene on the short arm of the chromosome 19 (chromosome 19p) coding the α_{1A} voltage-dependent calcium channel subunit. The range of CAG repeats contained at the 3′ end of the *CACNA1A* gene in SCA6 is from 21 to 27 (2-5).

EA2 is inherited through an autosomal dominant pattern, and manifests as intermittent cerebellar dysfunction, such as attacks of vertigo, visual disturbance, dysarthria, and ataxia lasting minutes to days. Nystagmus and other cerebellar signs of variable severity are present during the interictal period (6-8). Because EA2 responds to the acetazolamide, it is also known as an acetazolamide-responsive/hereditary paroxysmal cerebellar ataxia (APCA/HPCA) (9). It has been reported that EA2 is caused by point mutations of the *CACNA1A* gene on chromosome 19p. Point mutations produce truncated proteins due to the disruption of the reading frame, and these proteins cause abnormal α_{1A} voltage-dependent calcium channel subunits.

In recent studies (10-12), both SCA6 and EA2 were concurrently found in families with 26 CAG repeats without any evidences for additional point mutations in either coding sequences or in intron-exon junctions or with one point mutation without any abnormality of the CAG repeat number suggesting that SCA6 and EA2 are allelic disorders with a high phenotypic variability.

Here we report Korean family with SCA6 and EA2 and with 26 CAG repeat allele without previously reported point mutations.

CASE REPORT

The proband presented himself to us at the age of 49 yr with a history of showing cerebellar ataxia and dysarthria since the age of 41 yr.

He had experienced several attacks of vertigo and ataxia lasting from minutes to hours in his early 40's. His episodic symptoms were induced by stress or fatigue. He was treated with dimenhydrinate (Dramamine^{R}) for the attacks. Over the subsequent years, the episodic symptoms slowly progressed in the frequency, severity, and duration. When he visited our hospital, he had permanent cerebellar ataxia and dysarthria.

The neurological examination showed mild truncal ataxia, well-sustained jerky bilateral gaze-evoked and vertical nystagmus during lateral gaze, dysarthric and mildly scanning speech, bilateral dysmetria, mild bilateral decomposition, dysdiadochokinesia, falling tendency to either side on the tandem gait, and swing both in eye-open and closure on the Romberg test. For the initial treatment, 250 mg of acetazolamide was given twice a day. Acetazolamide seemed to

be effective in the beginning, but the episodic symptoms had slowly progressed. The 750 mg/day of acetazolamide was ineffective for controlling central gaze-evoked and vertical nystagmus and ataxia.

The results of complete blood cell count, electrolyte analysis, simple chest radiograph, tumor markers (αFP, CEA, CA19-9, βHCG, PSA, NSE), screening of intoxication of several kinds of the heavy metals, and test for the connective tissue disease were all in normal ranges. He had no history of drug or alcohol abuse.

The family history of the proband revealed 28 members including 78-yr-old mother (II-1) and 76-yr-old maternal aunt (II-2) who had been suffered from gait imbalance since their late 40's, and 46-yr-old sister (III-3) and 50-yr-old cousin (III-6) who had been suffered from gait imbalance, limb ataxia and dysarthria since their early 40's (Fig. 1, Table 1).

In addition, his mother (II-1) often complained of intermittent mild vertiginous sensation as well as interictal gait imbalance mentioned above. She was maintained with 150 mg of dimenhydrinate for symptomatic relief. His 43-yr-old brother (III-4) had experienced several attacks of vertigo, dysarthria, and ataxia lasting minutes to hours and showed mild interictal vertical nystagmus confirmed on neurological examinations. These symptoms had come out at the age of 39 yr. He has been taking daily 500 mg of acetazolamide, which was effective.

Other family members in the next generation of the proband's had no history of symptoms (Table 1). We performed special radiological studies on the proband. The brain MRI showed severe cerebellar atrophy, especially in vermis (Fig. 2A), and brain SPECT decreased perfusion to the cerebellum (Fig. 2B).

The molecular genetic studies for spinocerebellar ataxia type 1 (SCA1), type 3 (SCA3)/Machado-Joseph disease, and SCA6 were done on the proband and his five family members (III-1, III-3, III-4, III-5, IV-1, and IV-3). The results of the test were negative for SCA1 and SCA3/Machado-Joseph disease and positive for SCA6 in all subjects except one (III-4). The molecular genetic study on the chromosome 19p revealed that the number of the CAG repeat was 26. The molecular genetic study for the diagnosis of SCA6 using the

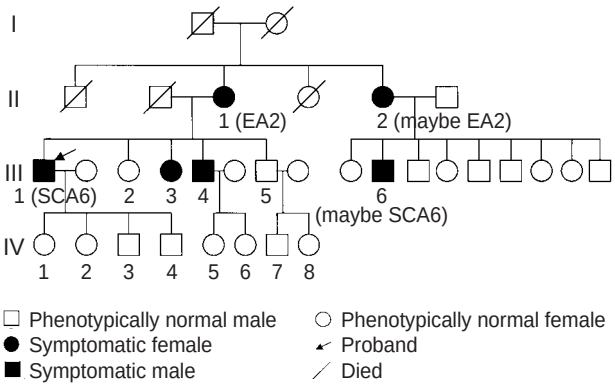

Fig. 1. Pedigree of a Korean family with spinocerebellar ataxia type 6. Roman numerals represent for the generation in chronological order and Arabic numerals for the respective individual within the generation, e.g., III-1 for proband. The parenthesis means phenotype. This designation for the family members is also used in Table 1 and 2, and Fig. 3.

Table 1. Clinical features of the proband and his family members

Number	Sex/Age (yr)	Age of onset (yr)	Symptoms and signs
II-1	F/78	45-50	Gait imbalance, intermittent vertiginous sensation
II-2	F/76	45-50	Gait imbalance, intermittent vertiginous sensation
III-1 (proband)	M/49	40	Marked truncal and limb ataxia, nystagmus (gaze-evoked and downbeat nystagmus), dysarthria and scanning speech
III-2	F/48	-	Asymptomatic
III-3	F/46	41	Gait imbalance, limb ataxia and dysarthria
III-4	M/43	39	Several episodes of transient ataxia
III-5	M/40	-	Asymptomatic
III-6	M/50	40	Limb ataxia, dysarthria and bilateral falling tendency
IV-1	F/24	-	Asymptomatic
IV-2	F/22	-	Asymptomatic
IV-3	M/20	-	Asymptomatic
IV-4	M/18	-	Asymptomatic
IV-5	F/16	-	Asymptomatic
IV-6	F/14	-	Asymptomatic
IV-7	M/13	-	Asymptomatic
IV-8	F/11	-	Asymptomatic

Table 2. Relation between clincal features and number of CAG repeat

Number	Clinical features	Number of CAG repeat
II-1	Gait imbalance, intermittent vertiginous sensation	26
III-1 (proband)	Marked truncal and limb ataxia, nystagmus (gaze-evoked and downbeat nystagmus), dysarthria and scanning speech	26
III-3	Gait imbalance, limb ataxia and dysarthria	26
III-4	Several episodes of transient ataxia	26
III-5	Asymptomatic	12
IV-1	Asymptomatic	26
IV-2	Asymptomatic	26
IV-3	Asymptomatic	26
IV-4	Asymptomatic	13
IV-5	Asymptomatic	26
IV-6	Asymptomatic	26
IV-7	Asymptomatic	26
IV-8	Asymptomatic	26

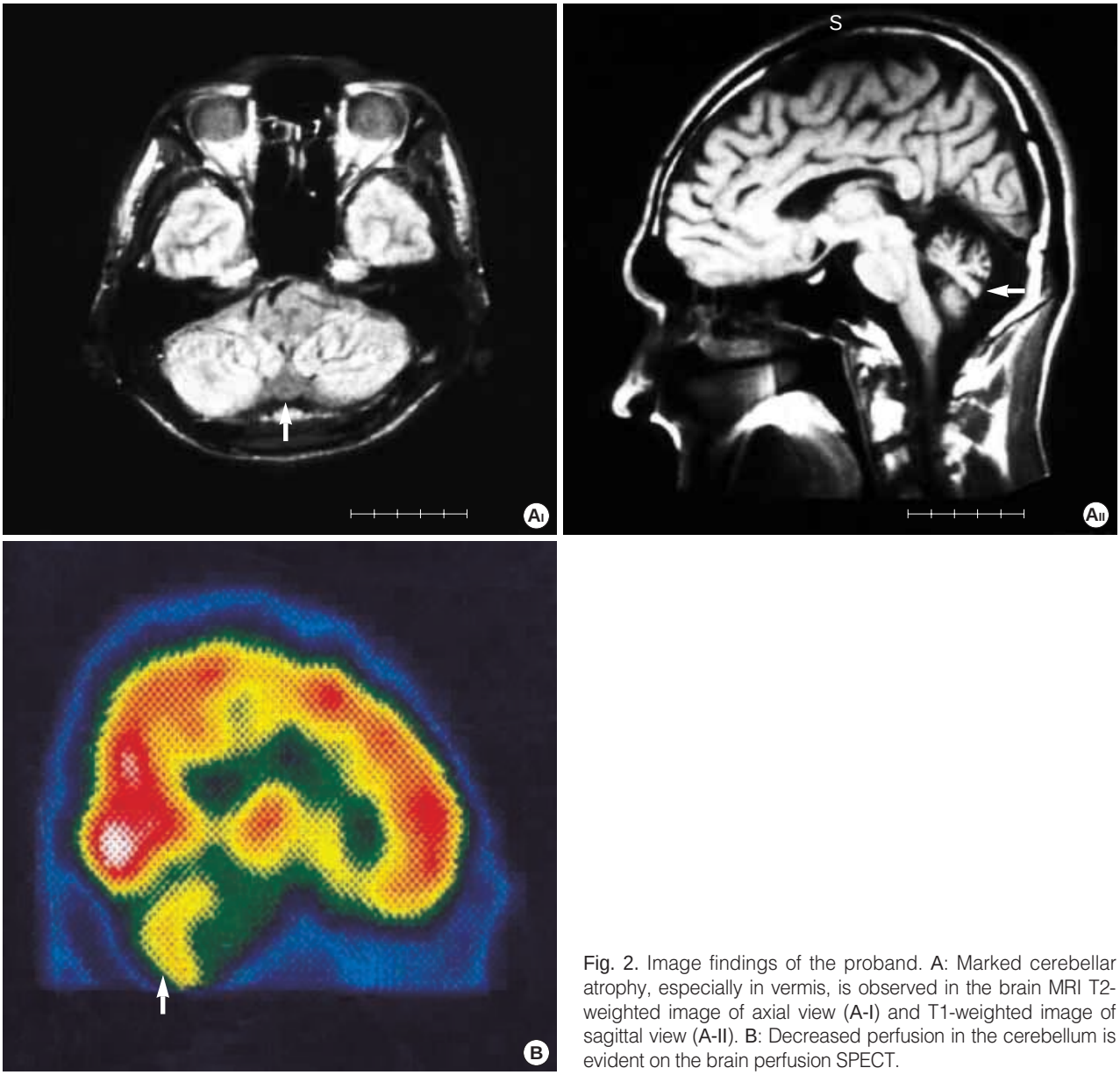

Fig. 2. Image findings of the proband. A: Marked cerebellar atrophy, especially in vermis, is observed in the brain MRI T2-weighted image of axial view (A-I) and T1-weighted image of sagittal view (A-II). B: Decreased perfusion in the cerebellum is evident on the brain perfusion SPECT.

method of Zhuchenko et al. (1) was done on the six subjects screen-ed and seven other family members (II-1, III-1, III-3, III-4, III-5, IV-1, IV-2, IV-3, IV-4, IV-5, IV-6, IV-7, and IV-8) and the result revealed that the number of the CAG repeat was 26.

Additional studies to confirm other possible point mutations, which were already well known, were done and there were no evidences for additional point mutations in these subjects.

DISCUSSION

EA2 is characterized by episodes of ataxia lasting hours with interictal nystagmus. SCA6 is classified autosomal dominant cerebellar ataxia with CAG repeat expansion.

Traditionally, the familial episodic ataxia has been classified separately from the hereditary spinocerebellar ataxia syndrome (13). Although the SCA6 and EA2 are the same allelic disorders, the symptom of the SCA6 is a progressive ataxia, rather than episodic ataxia as in EA2. However, progressive symptoms are seen in EA2 patients linked to the chromosome 19p (8). In other words, EA2 patients are phenotypically diverse. There are at least four different clinical profiles in EA2, i.e., basilar migraine-like attacks with minimal or no interictal signs, episodes of ataxia with interictal nystagmus and mild progressive truncal ataxia, ill-defined episodes of dizziness with progressive SCA, and hemiplegic migraine.

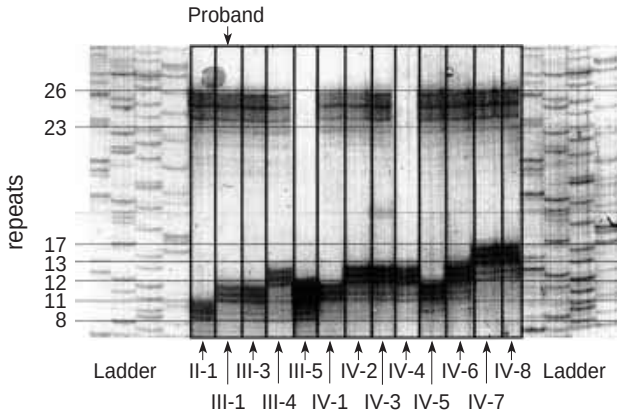

Fig. 3. The distributions of CAG repeats in *CACNA1A* gene obtained from the proband and his 12 family members. The number of CAG repeat was 26 in this family.

In addition to EA2, the phenotypic variability has been reported on SCA6. According to the previous report, none of the SCA6 patients showed episodic ataxia (3). But, it was noted that SCA6 showed episodic exacerbations (4). According to a recent report (10, 11), SCA6 patients showed episodic ataxia responsive to acetazolamide, and genetic studies showed 22 CAG repeats. From a clinical standpoint the average age for the onset of SCA6 was about 40 yr and the progression of symptoms was slower in SCA6, whereas most of the patients with EA2 began having episodes before the age of 20 yr.

However, the onset of progressive interictal ataxia was much later in patients with EA2. It was suggested that the differences in the clinical phenotypes between SCA6 and EA2 probably reflect different genetic alterations, that is, CAG repeat expansions in SCA6 versus point mutations in EA2 (1-5, 14).

Zhuchenko et al. (1) reported that the age at disease onset in SCA6 patients were 28-31 yr for 27 CAG repeats and 40-50 yr for 22-23 CAG repeats, and that some patients with EA, had much milder symptoms and smaller CAG repeats than SCA6. Contrary to the report of Zhuchenko et al. (1), the proband in this report had a CAG_{26} repeat expanded allele and the age of onset was 41 yr.

Geschwind et al. (4) and Jen et al. (11) reported SCA6 patients with typical EA2. These patients had the onset at the age of 42 to 63 yr and the number of CAG repeat was 22. Although the number of SCA6 patients with EA2 was too small in these studies, these results seem to suggest that there is no correlation between the number of CAG repeat and the age of onset. The differences in genetic backgrounds or environmental factors might explain the relatively later onset of symptoms in our family compared to the findings by Zhuchenko et al. (1)

In our study, the proband showed a central type of vertical nystagmus induced by lateral gaze. The cerebellar lesion, especially involving the flocculus, can cause vertical nystagmus and the patients with SCA6 had Purkinje cell loss on autopsy (5, 14). In this report, the brain MRI showed severe cerebellar atrophy, especially in vermis. The brain SPECT revealed a deficit of cerebellar perfusion. Jodice et al. (10) reported that patients with EA2 as well as SCA6 also had the CAG expansion and cerebellar atrophy. The CAG expansion affects the function of the calcium channel to trigger the progressive neuronal loss by alteration of polyglutamine expansion causing abnormal level of intracellular Ca^{2+} leading to cell death (15). The CAG repeat expansion of SCA6 occurs in the coding region of a gene that is known to be important for the normal function and the survival of Purkinje cells (5).

Like ordinary EA2 patients, our patients reported episodes of vertigo and ataxia precipitated by fatigue and stress. Such episodes may result from transient impairments of the calcium channel triggered by environmental factors. According to the previous reports (1, 8), FHM and EA2 are allelic disorders that have been attributed to point mutations in the same gene of *CACNA1A* on chromosome 19p. The gene affected in SCA6 is similar with that in EA2 but the alteration is CAG repeat expansion rather than a point mutation. Jen et al. reported patients with SCA6 and with positional vertigo and acetazolamide-responsive episodic ataxia (11). In those patients, the causative genetic alteration was an 22 CAG repeats in *CACNA1A*, not a point mutation. It has been suggested that a CAG repeat leads to progressive features and a point mutation to purely episodic features. EA2 is clinically not benign, and progressive symptoms are often seen in affected members of a kindred with typical chromosome 19p-linked EA2 (4, 8).

In this report, we noted that EA2 with SCA6 could be caused by a smaller size of CAG repeats (26 repeats) in the *CACNA1A* calcium gene. EA2 and SCA6 are not only allelic but also can have overlapping phenotypes. The mechanism for this phenotypic variability or an overlapping syndrome in families with EA2 and SCA6 linked to chromosome 19p is unclear. But according to the present reports, the plausible mechanisms could be; 1) loss of function due to haploinsufficiency, 2) a dominant negative effect due to the expansion or 3) a novel gain of function (10, 11).

In the present time, the pathogenic effect of a CAG repeat expansion with regard to periodic neurological dysfunction versus progressive disease can not be determined.

In addition, the individuals in the fourth generation in our family who were asymptomatic but had abnormal CAG expansions are presumed to represent nonpenetrance due to their young age.

In conclusion, SCA6 and EA2 are allelic disorders with a phenotypic variability and we report on one Korean family with EA2 and SCA6 caused by a CAG_{26} repeat expansion, which is not reported yet in Korea.

REFERENCES

1. Zhuchenko O, Bailey J, Bonnen P, Ashizawa T, Stockton DW, Amos C, Dobyns WB, Subramony SH, Zoghbi HY, Lee CC. *Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the α_{1A}-voltage-dependent calcium channel. Nature Genet 1997; 15: 62-9.*
2. Zoghbi HY. *CAG repeats in SCA6: Anticipating new clues. Neurology 1997; 49: 1196-9.*
3. Matsumura R, Futamura N, Fujimoto Y, Yanagimoto S, Horikawa H, Suzumura A, Takayanagi T. *Spinocerebellar ataxia type 6. Molecular and clinical features of 35 Japanese patients including one homozygous for the CAG repeat expansion. Neurology 1997; 49: 1238-43.*
4. Geschwind DH, Perlman S, Figueroa KP, Karrim J, Baloh RW, Pulst SM. *Spinocerebellar ataxia type 6. Frequency of the mutation and genotype-phenotype correlations. Neurology 1997; 49: 1247-51.*
5. Gomez CM, Thompson RM, Gammack JT, Perlman SL, Dobyns WB, Truwit CL, Zee DS, Clark HB, Anderson JH. *Spinocerebellar ataxia type 6: gaze-evoked and vertical nystagmus, Purkinje cell degeneration, and variable age of onset. Ann Neurol 1997; 42: 933-50.*
6. Gancher ST, Nutt JG. *Autosomal dominant episodic ataxia: a heterogeneous syndrome. Mov Disord 1986; 1: 239-53.*
7. Bain PG, O'Brien, Keevil SF, Porter DA. *Familial periodic cerebellar ataxia: a problem of cerebellar intracellular pH homeostasis. Ann Neurol 1992; 31: 147-54.*
8. Baloh RW, Winder A. *Acetazolamide-responsive vestibulocerebellar syndrome: clinical and oculographic features. Neurology 1991; 41: 429-33.*
9. Kim HJ, Jeon BS. *Acetazolamide-responsive hereditary paroxysmal ataxia: report of a family. J Korean Med Sci 1998; 13: 196-200.*
10. Jodice C, Mantuano E, Veneziano L, Trettel F, Sabbadini G, Calandriello L, Francia A, Spadaro M, Pierelli F, Salvi F, Ophoff RA, Frants RR, Frontali M. *Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the CACNA1A gene on chromosome 19p. Hum Mol Genet 1997; 6: 1973-8.*
11. Jen JC, Yue Q, Karrim J, Nelson SF, Baloh RW. *Spinocerebellar ataxia type 6 with positional vertigo and acetazolamide responsive episodic ataxia. J Neurol Neurosurg Psychiatry 1998; 65: 565-8.*
12. Denier C, Ducros A, Vahedi K, Joutel A, Thierry P, Ritz A, Castelnovo G, Deonna T, Gerard P, Devoize JL, Gayou A, Perrouty B, Soisson T, Autret A, Warter JM, Vighetto A, Van Bogaert P, Alamowitch S, Roullet E, Tournier-Lasserve E. *High prevalence of CACNA1A truncations and broader clinical spectrum in episodic ataxia type 2. Neurology 1999; 52: 1816-21.*
13. Harding AE. *Clinical feature and classification of inherited ataxias. Adv Neurol 1993; 61: 1-14.*
14. Sasaki H, Kojima H, Yabe I, Tashiro K, Hamada T, Sawa H, Hiraga H, Naga-shima K. *Neuropathological and molecular studies of spinocerebellar ataxia type 6 (SCA6). Acta Neuropathol (Berl) 1998; 95: 199-204.*
15. Restituito S, Thompson RM, Eliet J, Raike RS, Riedl M, Charnet P, Gomez CM. *The polyglutamine expansion in spinocerebellar ataxia type 6 causes a beta subunit-specific enhanced activation of P/Q-type calcium channels in Xenopus oocytes. J Neurosci 2000; 20: 6394-403.*