Electronic letter

Twenty CAG repeats are sufficient to cause the SCA6 phenotype

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EDITOR—Spinocerebellar ataxia type 6 (SCA6) is a dominantly inherited form of spinocerebellar ataxia, which usually manifests as a syndrome of progressive pure cerebellar ataxia with a late onset, and is caused by a small expansion of CAG repeats in the coding region of the α_{IA} subunit of the P/Q type voltage dependent calcium channel gene (*CACNA1A*).¹ In the original study, normal alleles were shown to have four to 16 CAG repeats, while expanded alleles with 21–27 CAG repeats were specifically associated with the clinical disorder. Subsequent studies have shown that pathogenic expansion ranges from 21–33 CAG repeats and that its size is inversely correlated with the age of onset,^{2–9} whereas the majority of normal alleles have 4–18 repeats and a few carriers possess 19–20 repeats.² The frequency of relatively larger alleles in the normal population correlates with the prevalence of various forms of dominant SCA caused by tandem repeat expansion¹⁰ and the intermediate allele of SCA6 itself can potentially harbour de novo mutations.¹¹ In all of these studies, an allele with 21 CAG repeats was considered to be the smallest expansion generating the clinical disorder.^{1–3 6–9} However, it is still uncertain whether 20 repeats can also cause clinical manifestations. We describe here two sibs with SCA6, who were both homozygous for 20 repeat alleles and presented with late onset pure cerebellar ataxia (fig 1).

Case reports

A 56 year old man (patient 1) first noticed mild loss of balance on standing at the age of 50. At the age of 53, he noted transient dizziness when looking upwards or turning his head, as well as some difficulty when looking downwards or during driving. His gait became progressively unsteadier thereafter and he was first admitted to our neurology clinic at the age of 56. Neurological examination showed limb and truncal ataxia, ataxic gait, slurred speech, disturbance of smooth pursuit eye movements, and conjugate downbeat nystagmus that was elicited when his neck was flexed or extended. This positional nystagmus corresponded with his positional vertigo. Otherwise, limb reflexes, sensory perception, and autonomic function were normal. Routine laboratory tests of the blood and urine, ECG, and chest x ray were all

normal. Brain MRI showed atrophy of the cerebellum, with no abnormalities of the cerebrum or brain stem. ¹²³I-IMP single photon emission computed tomography (SPECT) showed selective reduction of blood flow in the brain stem and cerebellum.

A 51 year old woman (patient 2) was a sister of patient 1 and first noticed positional vertigo at the age of 40. This occurred repeatedly when she adopted a recumbent position with her neck extended or when she lay supine on a bed. At the age of 45, unsteady gait and speech disturbance developed and became progressively worse thereafter. At the age of 51, she was first admitted to our clinic. Neurological examination showed slurred speech, disturbance of smooth pursuit eye movements, gaze evoked nystagmus, positional downbeat nystagmus (as observed in patient 1), limb ataxia, and ataxic gait. There were no other abnormalities. Brain MRI showed atrophy of the cerebellum, with no alterations of other CNS structures.

We also examined their parents. Neurological examination of their mother (80 years old) showed no signs or symptoms of ataxia. Brain MRI showed multiple lacunar infarcts, but no atrophy of the cerebellum. Also, cerebellar blood flow was not reduced on ¹²³I-IMP

Figure 1 The age at examination is shown for each subject. The number of CAG repeats in each SCA6 allele is shown in parentheses. Solid symbols show affected subjects.

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SPECT. Their father (86 years old) was bed ridden, but had no history of ataxia or episodic vertigo. CT scanning showed periventricular low density areas suggesting cerebral ischaemia, with no atrophy of the cerebellum. After obtaining informed consent, CAG repeats of the SCA6 gene were analysed in each subject. Their mother had 13 and 20 CAG repeats, while their father had 11 and 20 CAG repeats of the SCA6 alleles. Patients 1 and 2 were both homozygous for 20 CAG repeats of this allele. Their parents were unrelated. GAA repeat of the frataxin gene was not expanded in any of them.

Discussion

Our two homozygous patients showed the typical phenotype of SCA6. However, their parents with one normal SCA6 allele and one 20 CAG repeat allele had not developed ataxia even late in life. These observations clearly indicate that the 20 CAG repeat allele is pathogenic for SCA6. It has been controversial whether intermediate sized alleles with 19–20 repeats can produce the clinical disorder of SCA6.

Four subjects with 19 repeats were reported to be neurologically normal aged 70–75.² Recently, a patient with 7/19 CAG repeats was reported to show progressive ataxia at the age of 48.¹² However, this patient also had pyramidal signs as well as lacunar infarcts in the basal ganglia and the pons. In addition, the age of onset seems to be too early because previous reports have indicated that the age of onset for subjects with 19 repeats is expected to be at around 70 years. Therefore, investigation of similar cases is necessary to establish whether 19 repeats can cause the disorder. At present, six subjects with a normal allele and a 20 CAG repeat allele have been reported to show ataxia.^{2,13–15} Among them, the case described by Ishikawa *et al.*² did not show any signs of ataxia at the age of 30, so the clinical outcome is not clear. The three patients reported by Jodice *et al.*¹³ showed clinical features of episodic ataxia type 2, rather than progressive ataxia as observed in SCA6. In other reports, progressive ataxia was seen in a woman with onset at age 65¹⁴ and also developed in another woman at the age of 60.¹⁵ The latter patient died of sepsis aged 72 and necropsy showed that changes were confined to the cerebellum, including obvious loss of Purkinje cells and mild loss of granule cells. When compared with these two patients, the age of onset was 50 in our patient 1 and 40 in patient 2, implying that the age of onset is younger in homozygotes than in heterozygotes with 20 CAG repeats. A gene dosage effect has been detected in some previous studies,^{3,6,8,15} but not in others.^{2,7,17} The findings in our family seem to support the existence of such an effect since our two homozygotes with 20 CAG repeats showed obvious ataxia, whereas neither of their parents with only one 20 CAG repeat allele developed ataxia.

Based on our experience and previously published reports, it seems reasonable to conclude that 20 CAG repeats is the critical

size of the expansion that generates the phenotype of SCA6, and this needs to be taken into consideration during DNA testing and genetic counselling for late onset ataxia.

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