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SCA8 SHOULD NOT BE TESTED IN ISOLATION FOR ATAXIA

OPEN

Spinocerebellar ataxia types 1 (SCA1, OMIM# 164400) and 8 (SCA8, OMIM# 608768) are autosomal dominant, inherited ataxias. SCA1 is caused by abnormal expansion of a CAG triplet repeat in the *ATXN1* gene, while SCA8 results from CAG and complementary CUG expansions from a bidirectionally transcribed locus comprising the *ATXN8OS* and *ATXN8* genes.[1] In both cases, the expansions are thought to act as toxic gain-of-function mutations, although loss of normal protein function could also play a role. Although expansions in SCA1 have been clearly determined as pathogenic, those in SCA8 have been more difficult to study. Some investigators have suggested that very large expansions of repeats in SCA8 may not be pathogenic at all, since these might be unstable and in fact have been reported both in clinically affected and unaffected persons.[2–6] To further complicate matters, pathogenic expansions in SCA1 along with SCA8 have been reported to coexist, just as for SCA1 and SCA6.[7]

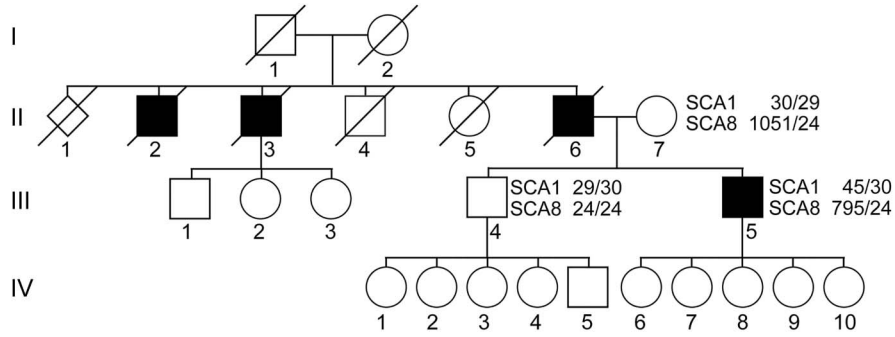
At presentation, the proband was 56 years old, with a history of progressive difficulty walking and slurred speech over the prior 3 years (figure, III.5). He provided informed consent to participate in a clinical research protocol (00-N-0043) approved by the NIH Combined NeuroScience Institutional Review Board. On examination, cognition and language were normal. Speech was dysarthric. Extraocular movements were normal. Muscle bulk and power were normal throughout, and there were no tremors or dystonia. Reflexes were also normal, but there was dysmetria on finger-to-nose testing as well as truncal instability. The proband could ambulate independently, but he had difficulty with tandem gait. Brain MRI revealed mild generalized cerebral volume loss and prominent atrophy of the cerebellar hemispheres, particularly the vermis. Nerve conductions studies were consistent with a demyelinating sensorimotor polyneuropathy. Detailed family history revealed that his father suffered from a similar syndrome and died at 74 years of age (figure, II.6). We were able to review his medical records, and on evaluation at 53 years of age, he was found to have dysarthria, truncal ataxia, leg dysmetria, and an ataxic and spastic gait—a syndrome similar to that of the proband.

Testing of the proband for pathogenic mutations in SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA17, and DRPLA loci revealed potentially pathogenic abnormalities at 2 loci (figure). There were 45 and 30 CAG repeats, respectively, in the 2 alleles at the SCA1 locus (normal ≤35, borderline 36–46, full mutation ≥47), while at the SCA8 locus, there were 795 and 24 CTA/CTG repeats (normal ≤50, borderline 51–70, full mutation ≥71). He was thus deemed to have potentially pathogenic mutations in both SCA1 and SCA8 loci. His unaffected brother had a normal neurologic examination as well as normal numbers of triplet repeats in both SCA1 and SCA8 (figure, III.4).

Since the possibility remained that both expanded alleles could have been inherited from his affected father, but DNA from the father was unfortunately not available for testing, we pursued genetic testing of his mother, who did not have any history or complaints suggestive of ataxia. Although she was unavailable to us for detailed examination, we were able to obtain a blood specimen for DNA testing. She had 30 and 29 CAG repeats at SCA1, both within the normal range, and 1,051 and 24 CTA/CTG repeats at SCA8. This indicated that the proband likely inherited the massive SCA8 expansion from his clinically unaffected mother and the borderline SCA1 expansion from his affected father. Thus, the SCA1 repeat was, unexpectedly, most likely responsible for his symptoms, although the long SCA8 expansion could conceivably influence the expression of the SCA1 phenotype.

This case illustrates the difficulty in determining pathogenic loci in cases where multiple ataxia–causing genes test positive. Reduced penetrance of SCA8 further complicates the issue. In this case, determination of the gene most likely pathogenic required testing of additional family members. This type of comprehensive genetic testing is especially important for providing accurate genetic counseling to the affected families. Furthermore, this case strongly suggests that SCA8 should not be evaluated

Figure **Four generations of the family afflicted with inherited ataxia**



The number of triplet nucleotide repeats at the spinocerebellar ataxia type 1 (SCA1) and SCA8 loci, where available, is shown to the right. Filled symbols represent afflicted individuals. Patient III.5 is the proband, while III.4 is the unaffected brother. Patients III.4 and III.5 were examined, but only DNA was available for II.7.

in isolation as a candidate gene and that its pathogenicity should be weighed based on the presence or absence of variants at other loci.

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