FEATURED ARTICLES

Non-coding? Nonsense!

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The gene associated with spinal cerebellar ataxia 8 is transcribed in both directions to produce transcripts with CUG and CAG expansions.

Have you ever looked for your glasses only to find that you are already wearing them? Genes can also hide in obvious places. Many dominant spinal cerebellar ataxias are caused by expansion of CAG repeat regions, resulting in proteins with long polyglutamine tracts. In contrast, spinal cerebellar ataxia 8 (SCA8) is controversially associated with CTG expansion of the *SCA8* gene. Moseley *et al.* find a polyglutamine expansion protein encoded antisense to *SCA8* in a recent article in *Nature Genetics*.

Mice with high copy numbers of the BAC-Exp transgene show curvature of the spine and abnormal posturing.

To examine the mechanism of SCA8, the authors created transgenic mice with bacterial artificial chromosomes (BACs) containing the cDNA for human *SCA8* with either 11 (BAC-Ctl) or 118 (BAC-Exp) CTG repeats. CTG expansion caused neurological impairment that was most severe in mice with high copy numbers of the BAC-Exp transgene. BAC-Exp mice with 9–13 copies of BAC-Exp survived 4–18 months and showed motor deficits that included stiffness, abnormal posturing and muscular rigidity by 4 months. Mouse lines with 1–5 copies of the BAC-Exp transgene had milder neurological impairment, including abnormal gait and limb dragging, that developed between 6–18 months.

Despite the neurological phenotype in BAC-Exp mice, the authors found no evidence of neuronal death, gliosis or demyelination. They then looked for disease-associated protein inclusion bodies using the 1C2 antibody, which recognizes proteins with polyleucine and polyglutamine tracts. Cerebellar and brainstem neurons from BAC-Exp mice and people with SCA8 showed 1C2-positive nuclear inclusion bodies, whereas neurons from BAC-Ctl mice and normal humans did not.

The 1C2 antibody recognized a 40 kDa protein in cells transfected with *SCA8* cDNA. However, 1C2 did not recognize the polyleucine ((CTG)_n) protein translated from an expression vector containing only the terminal exon of *SCA8*. Shifts in the *SCA8* open reading frame would result in proteins with either polyalanine ((GCT)_n) or polycysteine ((TGC)_n) tracts, but neither was recognized by 1C2 *in vitro*. 1C2 did recognize polyglutamine ((CAG)_n) protein, which could only be produced by the antisense strand in the *SCA8* allele. The authors referred to this new antisense transcript as *ATXN8* and the traditional *SCA8* gene as *ATXN8OS*.

ATXN8 is almost entirely composed of CAG repeats, with a methionine start codon immediately upstream and a poly A tail 1.5 kb downstream of the CAG repeat region. The authors detected *ATXN8* transcripts in BAC-Exp and BAC-Ctl mice and humans with and without SCA8 by RT-PCR. They used a reverse transcription

primer that was modified with a linker sequence and PCR primers specific for the linker sequence to prevent detection of *ATXN8OS*. BAC-Exp mice expressed *ATXN8* in the cerebellum, basal ganglia and cortex. BAC-Exp and BAC-Ctl mice expressed similar amounts of *ATXN8* transcripts, suggesting *ATXN8* differs only by the number of CAG repeats in healthy and diseased subjects.

This is the first report of a disease-associated gene transcribed in both directions to produce two types of neurotoxic trinucleotide expansion protein. The authors believe that similar antisense transcripts might be important in other CTG expansion diseases, including myotonic dystrophy and Huntington disease-like 2.

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1. Moseley , M. L. *et al.* Bidirectional expresssion of CUG and CAG expansion transcripts and intranuclear polyglutamine inclusions in spinocerebellar ataxia type 8. *Nature Genetics*. **7**, 758–769 (2006) | [Article](#) |