

# The complex structure of *ATXN2* genetic variation

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In this issue, Tojima et al.<sup>1</sup> describe the occurrence of a progressive cerebellar ataxia of 1-year duration in an 81-year-old Japanese woman that was associated with the presence of 31 DNA CAG repeats in the *ATXN2* gene. The pathologic threshold for disease causing spinocerebellar ataxia type 2 (SCA2) is usually considered to be 33 repeats and above, whereas 31 repeats would not be considered to be causative for cerebellar neurodegeneration. The twist in this case report is the fact that the patient carried 2 alleles with 31 repeats, suggesting that the 31-CAG repeat allele acted in a recessive fashion.

The gene causing SCA2 was independently identified by 3 groups using different ethnic groups in 1996.<sup>2–4</sup> The mutation is an expansion of a CAG DNA repeat in the coding region of the *ATXN2* gene, encoding a polyglutamine. Although the lower threshold for dominant pathologic alleles was originally thought to be  $\geq 35$  repeats, subsequent studies identified SCA2 patients with  $\geq 33$  repeats.<sup>5,6</sup> Consistent with dominant inheritance in human pedigrees, the CAG repeat expansion acts as a gain-of-function mutation. This is also supported by cerebellar neurodegeneration seen on transgenic overexpression of mutant *ATXN2*<sup>7–9</sup> and by absence of a neurodegenerative phenotype in mice lacking functional *Atxn2* alleles.<sup>10–12</sup> Gain-of-function of expanded *ATXN2* is also supported by therapeutic responses to antisense oligonucleotides that lower *ATXN2* expression in SCA2 mouse models.<sup>13</sup>

In most normal individuals, the repeat is once or twice interrupted by a CAA codon, which also codes for glutamine. In all populations, the 22-repeat allele is the most common, followed by the 23-repeat allele. The frequency of the 27-repeat allele can be highly variable.

The *ATXN2* gene is a good example for the complexities associated with genetic variation in a given gene and the associated risk for a number of diseases. At least 4 categories of variation can be distinguished: dominant deterministic alleles leading to SCA2, a multisystem neurologic disease affecting primarily or initially the cerebellum, repeat alleles that are unstable and although not disease-causing in the carrier can expand to give rise to disease in the offspring, risk alleles for other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) frontotemporal dementia (FTD) and ALS/FTD, dominant acting repeat alleles giving rise to noncerebellar phenotypes, and now also recessively acting alleles causing very late-onset cerebellar disease.

## Other phenotypes associated with deterministic dominant alleles

SCA2 patient phenotypes are dominated by cerebellar Purkinje cell and deep cerebellar nuclei pathology. Careful clinical and pathologic examination also revealed the involvement of other neurologic systems.<sup>14–17</sup> Several years were needed, however, to appreciate that some of these “noncerebellar” phenotypes could occur in patients without cerebellar ataxia and that they could even segregate in families. For example, parkinsonian signs and symptoms and L-dopa

## RELATED CLINICAL/ SCIENTIFIC NOTE

Homozygous 31 trinucleotide repeats in the SCA2 allele are pathogenic for cerebellar ataxia

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responsiveness are seen in many SCA2 patients in the presence of cerebellar signs. In some patients, however, L-dopa-responsive Parkinson disease without overt cerebellar findings has been described and this “restricted” phenotype can even segregate in families.<sup>18–20</sup>

The importance of motor neuron degeneration in SCA2 was highlighted initially by molecular studies that identified ATXN2 as a protein interacting with TDP-43, a protein mutated or aggregating in most patients with ALS and in some with FTD. These molecular insights prompted Elden et al.<sup>21</sup> to examine ATXN2 alleles in patients with ALS. They showed that alleles with  $\geq 27$  repeats were a risk factor for ALS. Subsequent meta-analyses in 2 nonoverlapping data sets led to more precise assessments of risk associated with long normal alleles indicating that alleles with 27–29 repeats do not increase ALS risk<sup>22</sup> and that the 27-repeat allele may actually be protective.<sup>23</sup> For alleles with 30–34 repeats, ALS risk increases in a length-dependent fashion. Pedigrees segregating an ataxia and an ALS phenotype in separate individuals also exist.<sup>24</sup> Of note, the sister of the patient described in the study by Tojima et al.<sup>1</sup> developed ALS, although her genotype is not known.

## Meiotic and mitotic stability

As in other DNA repeat diseases, the ATXN2 CAG repeat is meiotically and mitotically unstable. Meiotic instability leads to the phenotypic phenomenon of anticipation. In one study in Cuban SCA2 pedigrees, the repeat on average increased by  $\sim 5$  units, when inherited from the father, but only by  $\sim 1.5$  units when inherited from the mother.<sup>25</sup> One-fifth of large expansions occurred in relatively short mutant alleles with 36 repeats. The risk of expansion in normal alleles is unknown, although it seems likely that the risk increases with increasing length of the normal allele and with the lack of interruptions by CAA repeats. The presence of CAA interruptions may also influence phenotypic expression of ATXN2 repeat mutations in that interrupted repeats are more stable in a lineage-dependent fashion during neurogenesis or during DNA repair in postmitotic cells.

## ATXN2 variation in common disease

In addition to CAG repeat expansion, other genetic variation within or near the ATXN2 gene exists. This genetic variation has largely been explored through genome-wide association studies. Common variants in ATXN2 have been associated with a number of disease traits such as obesity, insulin resistance, or glaucoma (reviewed in references 26 and 27). The ATXN2 locus is also thought to influence human longevity.<sup>28</sup>

The recessive mode of alleles with 31 repeats is not totally surprising as an effect of normal alleles on age at onset of SCA2 had been reported. These results, however, were largely focused on the more common alleles of 23–27 repeats and

showed that CAG repeat length in the normal allele was inversely related to age at onset in SCA2.<sup>29</sup>

The results of the study by Tojima et al.<sup>1</sup> deserve confirmation. Despite the most diligent efforts, phenocopies and presence of other genetic variants or environmental effects can never be completely excluded. Although a true causal relationship between the 31/31 genotype and very late-onset ataxia is difficult to prove, the rarity of the CAG31 allele and especially the 31/31 genotype would strengthen a causal relationship. A fertile population to examine the presence of recessive alleles and the importance of repeat interruptions exists in the Holguin province, Cuba.<sup>25,30</sup>

In summary, genetic counseling for individuals with long normal ATXN2 repeat alleles will require a very nuanced approach, correct determination of repeat length, and knowledge of the precise repeat configuration. The instability of the repeat when transmitted to offspring needs to be discussed as well as the increased relative risk for ALS. Fortunately, long normal ATXN2 repeat alleles are rare in the general population.

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