Ataxin-2 gene: a powerful modulator of neurological disorders

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Purpose of review
To provide an update on the role of Ataxin-2 gene (ATXN2) in health and neurological diseases.

Recent findings
There is a growing complexity emerging on the role of ATXN2 and its variants in association with SCA2 and several other neurological diseases. Polymorphisms and intermediate alleles in ATXN2 establish this gene as a powerful modulator of neurological diseases including lethal neurodegenerative conditions such as motor neuron disease, spinocerebellar ataxia 3 (SCA3), and peripheral nerve disease such as familial amyloidosis polyneuropathy. This role is in fact far wider than the previously described for polymorphism in the prion protein (PRNP) gene. Positive data from antisense oligo therapy in a murine model of SCA2 suggest that similar approaches may be feasible in humans SCA2 patients.

Summary
ATXN2 is one of the few genes where a single gene causes several diseases and/or modifies several and disparate neurological disorders. Hence, understanding mutagenesis, genetic variants, and biological functions will help managing SCA2, and several human diseases connected with dysfunctional pathways in the brain, innate immunity, autophagy, cellular, lipid, and RNA metabolism.

Keywords
Ataxin-2 gene, C9orf72, cytosine adenine guanine-repeats, spinocerebellar ataxia 2, TDP43

INTRODUCTION
Spinocerebellar ataxia 2 (SCA2) is an autosomal dominant lethal disease caused by ≥32 cytosine adenine guanine (CAG) repeats in Ataxin-2 gene (ATXN2) [1–3]. In SCA2, the main affected tissues are the cerebellum, pons, olive, brainstem, frontal lobe, medulla oblongata, cranial and peripheral nerves. The pattern of neurodegeneration extends into the substantia nigra, and affects motoneurons as well [4]. The clinical manifestations of SCA2 include progressive gait ataxia, dysarthria, dysphagia, cognitive decline, slow eye movements, ophthalmoplegia, Parkinsonism, pyramidal features, and/or neuropathy.

The pathological CAG expansion is unstable in both germlinal and somatic tissues, hence offspring may inherit a shorter or larger version of the pathogenic repeats. ATXN2 CAG somatic mosaicism, i.e., the presence of different CAG, cytosine uracil guanine (CUG), and/or polyQ length stretches, exists in different body tissues. Intermediate CAG expansions in ATXN2 (≥29CAG/CAA repeats) increase the risk for many other neurological diseases. The genetic alteration locates in the first exon of ATXN2 with locus at 12:111,452,214–111,599,676 (GRCh38) harboring 25 exons and encoding a very ubiquitous RNA binding protein. In the same ATXN2 locus a novel gene, called ATXN2-A5 encoding a natural antisense transcript (NATs) with a CUG tract, has been described. For this review, we cover relevant articles on ATXN2 published during the last 18 months.

Spinocerebellar ataxia 2 MUTAGENESIS AND FOUNDER EFFECTS
Mutagenesis in SCA2 is thought to occur in predisposed haplotypes, particularly in those alleles with loss of 5′ CAA located within the CAG sequence [5,6]. This haplotype is universal for SCA2 families...
and is shared with a lower range of CAG repeats (22–31CAG), suggesting a common mutagenic mechanism [7] (Fig. 1A,B).

The second most frequent CAG/CAA sequence pattern is (CAG)13CAA(CAG)8 and had an opposite distribution in a Chinese SCA2 cohort compared to a control population [8]. This is interesting since the allele 13CAG-CAA-8CAG shares the SCA2 risk haplotype in other populations [5] where the loss of allele 13CAG-CAA(CAG)8 shares the SCA2 risk haplotype [5]. This is interesting since the distribution in a Chinese SCA2 cohort compared to a control population [8]. This is interesting since the allele 13CAG-CAA-8CAG shares the SCA2 risk haplotype in other populations [5] where the loss of allele 13CAG-CAA(CAG)8 shares the SCA2 risk haplotype [5].

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And finally, the CAG expansions have emerged in different populations independently of each other.

SCA2 is highly prevalent in Holguin, Eastern Cuba. The original founder haplotype was introduced in this region ~375 years ago according to predictions with Monte-Carlo simulation [9] using microsatellites markers in 13 families (Fig. 1C). This point in time corresponds to 1615, 70 years after the foundation of Holguin village. Thus, the Spanish conquista introduced either intermediate alleles and/or a founder SCA2 mutation. The genetic profiles of SCA2 Cuban families are very similar to Spanish ones (Laffita-Mesa et al. manuscript in preparation). African slaves are an unlikely source for SCA2 founder effect as they were brought into this part of Cuba several years later since sugar plantations were not so prominent. Most likely, a full penetrant mutation was not the original founder event as individuals carrying such mutations would be negatively selected. Instead, a premutation or low penetrance alleles (clinically irrelevant) within predisposing haplotype seems to have been a more reasonable event. Social conditions, cultural replicators, endogamous and closed-cycle marriages, religion, wars, syndemics resulted in a bottleneck effect increasing the number of premutation carriers among the Spanish settlers.

Key Points

- Advances in the understanding of ATXN2 CAG repeat expansions mutagenesis and the impact of founder effect help to understand not only SCA2 but also to explain the origin of intermediate alleles and its role in other neurodegenerative diseases (e.g., ALS, FTD, ALS/FTD, and Parkinson’s Disease).
- ATXN2 isoforms are prominently expressed in brain and its role in RNA, lipid, and amino acids metabolism influence human brain functioning.
- Novel ATXN2 variants may play a role as modifiers factor but their occurrence needs to be evaluated in diverse populations.
- Advances in deep phenotyping of prodromal SCA2 stage improve our understanding of the pathophysiology and may provide a therapeutic window.
- Progress in therapeutical targeting of ATXN2 in animal models seems promising not only for treating SCA2 but also for other more common neurological diseases.
- Future investigations may combine SCA2 haplotype information to address allele-specific targeting and its impact on wet biomarkers for both prodromal and manifest SCA2.

Ataxin-2 gene expression

Expression of ATXN2 is ubiquitous (https://gtexportal.org/home/gene/ENSG00000204842.14). At least 27 splice variants are predicted in Gtsex but only few have been experimentally confirmed [10] (Fig. 1D).

Ataxin-2 gene and brain functioning, health and neurodegeneration

ATXN2 is essential for neurodevelopment in Drosophila [11]. Both ATXN2 levels and its subcellular location determine the spacing of dendritic branches for the optimal dendritic receptive fields in sensory neurons in Drosophila [12]. This may also have implications for neuronal synaptic plasticity, where FMR1 and ATX2 function together in a microRNA-dependent process mediating long-term olfactory habituation [13].

Massive Atxn2-CAG expansion in mice cause early disruption of excitability and communication in cerebellar neuronal layers [14].

In humans, an antagonistic pleiotropic role in cognition is emerging. ATXN2 and its substitute ATXN2L positively influence several cognitive domains such as verbal–numerical reasoning, reaction-time, educational attainment, and cognitive resilience [15,16]. Nevertheless, ATXN2 CAG repeat length polymorphisms, are associated with smaller volume in both the putamen and thalamus, but also with atrophy in amygdala and globus pallidus conferring cognitive decline in old age [17].

On the other hand, many lines of evidence suggest that ATXN2 genetic alterations may lead to disruption of innate immunity, autophagy, Krebs cycle, amino acid homeostasis, lipid, and RNA metabolism [18,19]. This altogether with the intracellular dynamics [20**] explain the global effect in brain functioning caused by ATXN2 gain and/or loss of function.

Beyond CAG repeats, duplication in Ataxin-2 gene lowers age of onset in spinocerebellar ataxia 3 and C9-ALS

Recently, we identified a 9bp-duplication c.109_117 delinsCGGAGCGGG/GCCTCGCCC in the ATXN2-S/AS region as modifier in familial neurodegeneration.
Furthermore, a mosaic with a different CAG/CAA-repeat sequence pattern within the 22CAG allele associated with the 9-bp duplication was also found [21]. Other structural alterations in this region are a 17 bp deletion CCCGCCCGCTCCGCCG, a 9 bp insertion, CCCGCCCGCT dbSNP (rs1249427887), and 18 bases insertion CCCGCCCGCTCCGCCGCG all of them located at the same loci 12–11599394-C-CCCGCCC GCTCCGCCCGCT and at frequency, 6.6e-5, 3e-3, 6.6e-5 with CADD values of 12.2, 12.6 and 22.7 (gnomAD v3.1). The 17 bp deletion encodes a polypeptide 39.85% homologous to ATXN2, when aligned with exon-1 (Fig. 2A,B).

As shown in Fig. 2C,D, the controls had the predicted v1-v2 peaks at ~800 bp and ~440 bp [22] but mutants showed a shifted v2 profile, with no exon-2 variant and less 2+3 exon for v2 and v1 respectively suggestive for aberrant processing of the ATXN2-AS transcripts in patients with the 9bp-dup (Fig. 2C,D). Furthermore, this genetic change duplicates the phosphorylation and methylation sites on Serine and Arginine residues, Ser38-Gly-Arg40-Ser41-Gly-Arg43 located in the N-terminal intrinsically disordered region (IDRs). Indeed, this region is targeted by multiple kinases, such as PKC, GSK3, and Cdk5 [23].

**Ataxin-2 gene CAG length variation in neurological diseases**

The presence of at least one ATXN2 allele >22CAG decreased age at onset by 6 years in Portuguese patients with transthyretin familial amyloid polyneuropathy associated with the Val30Met variant.
ATXN2 intermediate alleles lowers AO in frontal-temporal dementia (FTD) [25], in addition, those patients had parkinsonism and psychotic symptoms at the time of disease onset [25]. Intermediate alleles are overrepresented also in Alzheimer’s disease and behavioral FTD suggesting a potential link between ATXN2 with tauopathies [26].

An autopsy performed in an individual with corticobasal syndrome recently confirmed ATXN2 genotype with 27/39CAG. The full expanded allele, which otherwise cause SCA2 at midlife, was interrupted by four CAA motifs (CAG8–CAA–CAG4–CAA–CAG4–CAA–CAG9–CAA–CAG10) and accompanied by a 27CAG intermediate allele (CAG8–CAA–CAG4–CAA–CAG4–CAA–CAG8) [27]. The patient had not cerebellar ataxia, neuroimaging abnormalities or neuropathological hallmarks for SCA2. This aggressive phenotype is in contrast with the late levodopa-responsive parkinsonism associated with interrupted expansions. It is claimed that CAA interruptions may influence variable phenotypes (Fig. 3A,B). Likewise, allelic interaction may determine a phenotype different than the expected for ATXN2 intermediate alleles in ALS and full CAG expansions in SCA2. This notion, of allelic interaction, is reinforced by appearance of late onset SCA2 resulting from homozygous 31/31CAG, and a case ALS with cognitive decline and 28/28CAG in homozygous state [28,29].

The phenotype compatible with ALS/SCA2 in a woman with ATXN2 32CAG repeats suggests that the length of the CAG determines the timing of ALS and ataxia phenotypes in a disease continuum [30]. This continuum may also include Parkinsonism, pure cerebellar SCA2, and infantile-onset SCA2, with genetic and neuropathological overlap with TDP43 pathology.

Ataxin-2 gene as a genetic risk factor, spinocerebellar ataxia 2 mutations, variable phenotype and massive expansions in different populations and whole-genome sequencing projects

Increasingly, ATXN2 CAG repeat expansions have a prominent role in different populations either as...
genetic risk factor, SCA2 de novo cases or massive repetitions causing SCA2 in the childhood. Gardiner et al., 2019 analyzed 14,196 individuals with a wide age range (18–99 years) from The Netherlands, Scotland, and Ireland, and found that ~11% carried intermediate alleles in the major nine genes causing polyQ diseases [31*]. For ATXN2, they found both intermediate alleles and pathological expansions (30–36 units). Furthermore, Akcimen et al., 2020 used ExpansionHunter to estimate the trinucleotide repeats in whole-genome sequencing (WGS) data of unrelated healthy individuals from different geographic regions. The frequency of abnormal ATXN2 CAG repeats was 3.32% with a CAG number ranging between 27–36 units. Pathological SCA2 alleles were of low penetrance ≥34CAG repeats [32]. Likewise, Ibanez et al. identified patients with variable phenotypes, ALS (22/33CAG), levodopa-responsive early-onset Parkinson’s disease (31/41CAG), progressive cerebellar ataxia (22/40CAG), and SCA2 (22/42CAG) [33].

One girl with intellectual disability had 99CAG repeats with apparently healthy parents [33]. Two little sisters with more than 180 CAG repeats presented with systemic features including global developmental delay, infantile spasms, hypotonia, seizures, dysautonomia, hearing and visual impairment, dysphagia, sleep, and mood disorders. The germinal instability started in the grandfather with 22/37CAG who transmitted an unstable ATXN2 mutation (43CAG) to one of his dizygotic sons with further massive expansions of up to ≥180CAG [8]. Another child was reported in Mexico. The maternal SCA2 mutation, 49CAG, expanded to ~884 in her son whom at age 5yrs presented with ataxia, gaze-evoked nystagmus, and spasticity [34].

**Prodromal spinocerebellar ataxia 2 and phenotype insights**

Jacobi et al. described the prodromal features for European SCA1, 2, 3, and 6 cohorts and evaluated the sensibility of SARA and other clinical tools to detect changes in SCAs prodromal phase [35*]. The longitudinal observation was performed between 2008–2015, with assessments at baseline, 2, 4, and 6 years. Twenty-two (59%) of SCA2 mutation carriers phenoconverted into SCA2, with a median age of onset around ~36 years. They had an increase in the SARA from the time of inclusion, which was influenced by the age at first visit and the CAG expansion. There was a progressive cerebellar functioning deterioration determined by clinical scales and supported by volume loss in the cerebellum and pons. This was paralleled by annual decline in non-ataxia signs and sleep quality. On the other hand, Nigri et al. found isolated volume loss in the pons, and cortical thinning in specific frontal and parietal areas in preclinical SCA2 [36]. No other clinical or cognitive changes were evidenced in this one-year
longitudinal study. In the prodromal phase, mutation carriers had larger variability in both gait and postural sway control [37], suggesting deterioration of the vestibulocerebellar network. Furthermore, there is a gradual worsening of speech and swallowing [38]. These preclinical abnormalities seem to be dampened with physical rehabilitation [39]. All this knowledge provides insights that will help design future disease modifying therapies (Fig. 5B,C). One challenge will be to make a fair prediction of the ‘estimated years to symptom onset’ (EYO) based on the different expanded CAG alleles and to identify gene modifiers of this stage.

Antisense therapy proved to be efficient in ALS and spinocerebellar ataxia 2 preclinical models

ATXN2 and TDP43 interact through RNA molecules (Fig. 4) [40,41,42,43]. In spinal cord neurons of ALS...
patients, ataxin-2 and TDP43 are abnormally localized. Similarly, TDP-43 mislocalized in SCA2 and there is neuropathological and phenotype overlapping with Frontotemporal Lobar Degeneration (FTLD) cases manifest as pure FTLD-ALS without ataxia [44,45]. Pathological phosphorylation of TDP43 is seen in ALS, and its levels are increased in cases with ALS with C9ORF72 or ATXN2 expansions [46].

Lowering ATXN2 expression with antisense oligo in TDP-43 ALS mice prolongs their survival which is therapeutically relevant for both ALS and SCA2 [47]. However, recent studies have shown reduced ATXN2 expression suggesting either loss of function as part of the disease process or neuroprotective role in FTLD-TDP and other TDP-43 proteinopathies [20*]. The last notion is well supported as proper ataxin-2 amounts are needed for optimal dendritic arborization in Drosophila neurons. In contrast, upregulated ATXN2 levels affects the distribution of FMRP and other RNA binding proteins inducing aberrant dendritic morphology [12].

The same antisense oligo therapy reduced the levels of both wild-type and mutant ataxin-2 in SCA2 bacterial artificial chromosome mice (BAC-Q72). Moreover, ALS-related proteins Eaat2, Pcp4, TBK1 and p62/Sqstm1 were significantly dysregulated in spinal cord and cerebellum. This therapy corrected the expression levels of all but two ALS proteins and also improved motor coordination [19].

These promising preclinical results raise hope for future trials in humans. However, since ATXN2 function is pleiotropic and the long-term effect of reducing both the normal and mutated ataxin-2 alleles in humans remains unclear, an allele-specific therapy is the most desirable approach.

One future direction would be combining haplotype information with oligo antisense silencing. All SCA2 families share the universal SNPs haplotype C–C for rs695871 and rs695872 markers located in ATXN2 exon-1. Furthermore, about 45% of ALS cases with intermediate alleles have the same SCA2 haplotype [5,48]. Therefore, this information would be relevant for developing allele-specific therapies. In SCA3, another polyQ disease, Prudencio et al., 2020 demonstrated the effectiveness of this approach in silencing the pathological ATXN3 allele [49].

Of note, the novel compound naphthyridine-azaquinolone (NA) was found to specifically binds...
| Biomarker                       | Commentary                                                                                                                                                                                                 | SCA2 phases* | ATXN2 mutation specific? | Techniques                  | Sample type                     |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------------------|-----------------------------|---------------------------------|
| ATXN2 mRNA levels             | New alternative splicing variants were found lacking exon 12 and exon 24, and this could be relevant for disease progression [10]. Furthermore, genotyping of both DNA and RNA levels may shed evidence about mutant allele expression, as was recently shown in SCA3 and C9ORF72 ALS [21**]. | A++, B++, C+  | Y+++                     | QPCR, DDPCR                  | Blood-edta, blood pax, fibroblasts. |
| ATXN2 CAG somatic mosaicism   | Mosaicism of unstable CAG repeats was confirmed in SCA2 brain and lymphoblasts cell lines. The mosaicism varied within the brain and spinal cord and was smaller in the cerebellum than in other brain tissues [58]. Furthermore, CAG somatic mosaicism in DNA and mRNA are correlated in ATXN3 gene [59]. | A++, B++, C+  | Y+++                     | Fluorescent PCR, fragment analysis | Blood-edta, blood pax, fibroblasts. |
| ATXN2-AS profile              | ATXN2-AS transcripts with a CUG repeat expansion are toxic in an SCA2 cell model. This was associated with aberrant splicing of amyloid beta precursor protein and N-methyl-D-aspartate receptor 1 in SCA2 brains [22]. | ?             | Y+++                     | Fluorescent PCR, fragment analysis | Blood-edta, blood pax, fibroblasts. |
| ATXN2 AUUUA binding function  | Yokoshi et al. found that ATXN2 binds, stabilizes, and regulates the translation of more than 4,000 mRNA molecules [41].                                                                                                                                                  | ?             | Y                        | In vitro RNA binding          | Blood-edta, blood pax            |
| R-loop                        | Human ATXN2 deficiency leads to genome destabilizing Rloops accumulation [60]. TDP-43 is also crucial in maintaining genomic stability through a co-transcriptional process that prevents aberrant R-loop accumulation [61] and controlling replication stress. | ?             | Y                        | Qpcr, DDPCR                  | blood-edta, blood pax            |
| Cell free DNA                 | Cell-free circulating DNA in plasma is significantly increased in Friedreich’s ataxia, SCA2 and in SCA12 patients. It was possible to distinguish between ataxia patients and healthy controls using plasma DNA [62].                                                                                                                          | ?             | Y/N                      | WGS, QPCR, DDPCR, PicoGreen fluorescent assay | CSF, Plasma, serum               |
| NFL                           | Levels of serum NfL were elevated in SCA3 individuals and correlated with disease severity. The was also high concentrations starting from early disease stage and correlated with disease severity [63]. Likewise, blood NfL levels were increased with proximity to the predicted onset of ataxia in SCA3 individuals [64].                                   | A++, B++, C+  | N                        | Different platforms            | CSF, Plasma, serum               |
| Micro-RNA, and small RNAs     | Bañez- et al., 2012 provide evidence involving HTT CAG repeats interfering with cell viability at the RNA level. Pathological CAG repeats ≥40 units induced neuronal cell death and increased levels of small CAG-repeated RNAs (sCAGs) of ≥21 nucleotides in a Dicer-dependent manner [65]. Furthermore, the severity of the toxic effect of HTT mRNA and sCAG generation correlated with CAG expansion length. Likewise, Creus–Muncunill et al., 2021 demonstrated that sRNA produced in the putamen of HD patients are sufficient to recapitulate HD pathophysiology in vivo [66]. | ?             | Y/N                      | WGS, QPCR, DDPCR              | Blood-pax                        |
slipped-CAG DNA intermediates of Huntington’s disease (HD) mutations. The therapeutic potential is highlighted as NA reduces both somatic mosaicism for the HD expanded allele and mutant HTT protein aggregates in striatum [50].

Genome editing technologies, such as CRISPR-Cas9, may harbor great potential for future therapies in SCA2 and other polyQ disorders. These techniques include the use of guided RNAs to either alter, excise, or insert a specific DNA sequence in a precise or predetermined manner. In one patent the use of rare cutting endonucleases and transposases for altering ATXN2 expression is claimed [51]. Another genome editing application (WO/2018/154462) comprises ex and in vivo methods for correcting abnormal ATXN2 CAG repeats [52]. Significant improvement are expected of genome editing applied for correcting the pathological ATXN2 CAG repeats and other polyQ diseases -SCA1, SCA3 and HD- [53–55]. However, finding biomarkers that may be precede the prodromal clinical changes and predictors of phenoconversion remain as other unmet needs in the field [56,57] (Fig. 5A, see Table 1).

**CONCLUDING REMARKS**

Almost three decades ago, the goal in the field was to provide accurate SCA2 presymptomatic diagnostic, prenatal diagnosis, and symptomatic treatment [72]. At present, preimplantation genetic testing by karyomapping enabled the first birth of three healthy babies without pathogenic CAG expansions for HD, SCA2 or SCA12 [73]. Currently, drug screening, experimental disease modelling, and deep-phenotyping studies in patients with SCA2 prepare the ground for future trials. Many of the SCA2 features overlap with different diseases. Hence, if we accurately dissect all SCA2 phenotypes it may uncover features of other disorders, or human traits...
influenced whenever ATXN2 homeostasis and/or sequence is altered. The increasing knowledge of ATXN2 in several disparate neurological diseases resembles the major impact polymorphisms at different codons in the prion protein gene (PRNP) have over both sporadic and familial prion diseases. Research on ATXN2 is intense, productively, therapeutically driven and aimed to understand gain and loss of ATXN2 functions. Understanding the SCA2 mutagenesis and novel ATXN2 genetic alterations will help in to improve genetic counseling and to design future therapeutic trials for SCA2.

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Conflicts of interest

There are no conflicts of interest.

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