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Genetically Engineered Mouse Models of the Trinucleotide-Repeat Spinocerebellar Ataxias

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Abstract

The spinocerebellar ataxias (SCA) are dominantly inherited disorders that primarily affect coordination of motor function but also frequently involve other brain functions. The models described in this review address mechanisms of trinucleotide-repeat expansions, particularly those relating to polyglutamine expression in the mutant proteins. Modeling chronic late-onset human ataxias in mice is difficult because of their short life-span. While this potential hindrance has been partially overcome by using over-expression of the mutant gene, and/or worsening of the mutation by increasing the length of the trinucleotide repeat expansion, interpretation of results from such models and extrapolation to the human condition should be cautious. Nevertheless, genetically engineered murine models of these diseases have enhanced our understanding of the pathogenesis of many of these conditions. A common theme in many of the polyglutamine-repeat diseases is nuclear localization of mutant protein, with resultant effects on gene regulation. Conditional mutant models and transgenic knock-down therapy have demonstrated the potential for reversibility of disease when production of mutant protein is halted. Several other genetically engineered murine models of SCA also have begun to show utility in the identification and assessment of more classical drug-based therapeutic modalities.

Keywords

spinocerebellar ataxia; Purkinje cell; transgenic mice; trinucleotide repeat disease

1. Introduction

The spinocerebellar ataxias (SCA) are a group of inherited neurodegenerative conditions that have ataxia as a major component of the clinical presentation. These patients usually have loss of coordination of the limbs and trunk, unstable gait, dysarthric speech, and nystagmus but may have other symptoms, including extrapyramidal dysfunction, dysautonomia, cognitive impairment, and motor and sensory impairments. The pathological process primarily involves the cerebellum, brainstem and spinal cord. The forebrain,

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especially the basal ganglia, as well as the peripheral and autonomic nervous systems also may be affected in some forms. Genetically, these diseases are inherited in an autosomal dominant pattern and there are approximately 30 different types identified to date with only about half having defined mutations. A number of these diseases, including SCA types 1, 2, 3, 6, 7, and 17 have an abnormal expansion of a CAG-repeat sequence, which codes for an expanded tract of glutamine (Q) residues within the mutated protein [28,48,64,66,71,75,83,99]. One form, SCA8, although also a trinucleotide repeat expansion, appears to have an RNA-related mechanism[54]. In most of these diseases the function of the mutated protein is unknown. Therefore, an *in vivo* approach to modeling the effects of the mutation is an attractive strategy for unraveling the pathogenetic mechanisms of these disorders.

Because SCA are neurodegenerative diseases that in most cases have an onset several decades into life, modeling them in mice may not allow enough time for disease to develop during their relatively short life span. As will be shown below, this concern has been realized in a number of models, thus requiring over-expression of the transgene or a worsening of the genetic mutation (e.g., increasing the length of the CAG-repeat expansion) in order to create a clinical phenotype. These manipulations create a potential for misinterpretation of results and require careful controls, such as lines with matched over-expression of normal allelic transgenes. Another tactical issue is whether to express the mutant transgene in all neurons or cells of the CNS, or to target critical populations such as the Purkinje cell (PC). The advantage of the former approach is that it more closely models the human disease, but in turn it makes interpretation of mechanisms more complex. The advantage of the latter approach is that PC are critical cells for cerebellar function, they are affected in nearly all forms of SCA, and damage to them usually creates a behavioral phenotype. In addition, PC have an elaborate dendritic structure which can be readily studied for morphological and even physiological alterations. A disadvantage is that most types of SCA, which have been modeled in this fashion, have more complex pathology in the human disease.

Although there are models of several forms of SCA that are not trinucleotide-repeat diseases, those conditions will not be reviewed here. References for those models are as follows: SCA5 [22,70], SCA13 [44,92], SCA14 [1,50,98] and SCA27 [56,80,87].

2. SCA1

Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant disorder caused by a CAG repeat expansion encoding a polyglutamine tract. It is characterized pathologically by loss of Purkinje cells in the cerebellar cortex and neuronal loss in brain stem nuclei and cerebellar dentate nuclei [100]. The *SCA1* gene encodes ataxin-1, a protein of 792 to 826 amino acids depending on the number of CAG trinucleotides [78]. Disease-related expansions range from approximately 40–80 polyglutamine residues. Several mouse models have been generated in an effort to understand the molecular mechanisms underlying SCA1 disease and ataxin-1 function.

The first mouse model was generated in 1995 to test the CAG expansion, gain-of-function hypothesis. Burright *et al.* [13] expressed the human SCA1 gene in mouse PC using a Purkinje cell-specific Pcp2/L7 promoter [65,82]. Two lines were created with various repeat lengths; a control line with over-expression of the normal interrupted allele containing 30 repeats, $(CAG)_{12}$ CATCAGCAT$(CAG)_{15}$, while the expansion construct contained 82 uninterrupted CAG repeats. The control SCA1[30Q] line, and the expansion SCA1[82Q] line progeny both inherited the transgene either paternally or maternally and in all animals the repeat was stable and showed no change in repeat size.

After one year of age, the 30Q line had a normal phenotype, suggesting intact PC function. In contrast, the mutant 82Q lines developed reduced cage activity and general uncoordinated movements, which become more pronounced with age until they had clearly ataxic cage behavior at 12 weeks. Footprint patterns indicated gait abnormalities and motor performance measured using a rotating-rod apparatus was abnormal as early as 5 weeks [21]. Pathologic changes were observed in the SCA1[82Q] cerebellum as early as P25 when clear cytoplasmic vacuoles were found in some of the somata of PC [21] The degeneration progressed with age and by 27 weeks the majority of PC had stunted, atrophic dendritic morphology. At 1 year, the cerebellar cortex was dramatically decreased in size secondary to both atrophy and loss of PC, frequent heterotopic localization of PC in the molecular layer, and diminished calbindin immunoreactivity in surviving PC. Purkinje cell loss was not extensive and was preceded by the ataxic phenotype. In addition, SCA1[82Q] PC accumulated ataxin-1- and ubiquitin-postiive aggregates, or neuronal intranuclear inclusions (NII), that co-localized with the proteasome and the molecular chaperone, HDJ-2/HSDJ, demonstrating that there is ataxin-1 misfolding in SCA1 disease [24].

Öz *et.al.* demonstrated that biochemical changes in cerebellar neurochemical levels measured by proton magnetic resonance spectroscopy (^{1}H MRS) can distinguish patients with SCA1 from controls [67]. Specifically, patients exhibit decreased levels of N-acetylaspartate and glutamate, and increased levels of *myo*-inositol, which correlated with ataxia rating scores. These MRS biomarkers were similarly altered in SCA1[82Q] mice indicating parallel neurochemical changes in the SCA1[82Q] model and patients [68]

To study the function of wild-type ataxin-1 and to determine if SCA1 ataxia is caused by loss of function of ataxin-1, *Sca1* null mice were generated [60] *Sca1* exon 8 was targeted and deleted as the majority of the coding sequence resides in this exon. *Sca1*$^{(-/-)}$ mice were viable, and displayed both normal development and a normal life span. In addition, they displayed no ataxic symptoms or neurodegeneration even at 30 months of age. Further behavioral studies, including the open field test, elevated plus maze, and Morris water maze suggested *Sca1*$^{(-/-)}$ mice may have spatial learning deficits.

To study the effect of mutant ataxin-1 expression under control of its endogenous promoter, a knock-in model was generated by inserting an expanded CAG trinucleotide repeat into the mouse *Sca1* locus [59]. The original model, *Sca*$^{78Q/2Q}$, expressed endogenous levels of expanded ataxin-1 in the expected temporal and spatial patterns. However, the mice lacked any ataxic phenotype or neuropathological abnormalities. A second model was then generated with 154 CAGs [91]. The *Sca*$^{154Q/2Q}$ phenotype included muscle wasting, ataxia, abnormal gait, severe kyphosis and premature death between 35 and 45 weeks. *Sca*$^{154Q/2Q}$ animals displayed significant motor deficits by rotating-rod analysis at 5 and 7 weeks as well as impaired spatial learning deficits. In addition, the *Sca*$^{154Q/2Q}$ mice exhibited a decrease in long-term potentiation at 24 weeks. The *Sca*$^{154Q/2Q}$ animals were distinct from the SCA1[82Q] model in that they exhibited repeat instability similar to human patients [90]. Brains from *Sca*$^{154Q/2Q}$ animals were smaller than controls, though brain sections showed uniform atrophy rather than specific atrophy of the cerebellum more characteristic of SCA1 disease. While slight PC loss was observed, the molecular layer thickness was relatively intact even in 24-week-old animals.

Neuronal aggregates containing the mutant protein occur in many of the inherited polyglutamine disorders and have been suggested to be a common mechanism for neuropathology [73]To determine how cellular localization impacts disease and to examine the role aggregates play in SCA1, two additional transgenic models were developed. Using the SCA1[82Q] transgene, a lysine- to-threonine substitution at amino acid residue 772 disrupted the nuclear localization signal (NLS) function. A second model, Ataxin-1[77]Δ,

was developed by deleting the self-association region of ataxin-1 [52]. SCA1^{K772T} transgenics expressed ataxin-1 primarily in the cytoplasm of Purkinje cells in contrast to control SCA1[82Q] mice that expressed significant levels in both the cytoplasm and nucleus. More importantly, SCA1^{K772T} mice did not develop ataxia, as measured by rotating-rod deficits or ataxic cage behavior and they had no cerebellar pathology. SCA1[77]Δ transgenic mice expressed ataxin-1 in the PC cytoplasm and nucleus, similar to SCA1[82Q] animals. However, SCA1[77]Δ mice did not develop NII. The absence of NII, however, did not protect transgenics from developing PC pathology or ataxia. Indeed, SCA1[77]Δhad the same PC atrophy seen in SCA1[82Q] animals and performed similarly to SCA1[82Q] animals in behavioral examinations.

The amino acid sequence of ataxin-1 revealed several possible phosphorylation sites [4] and further analysis by mass spectrometry identified a serine at amino acid 776 as a major site. A phosphomimetic aspartic acid mutation at this site was shown to increase the interaction with RNA-binding motif protein 17 (RBM17) to levels comparable to ataxin-1[82Q]-S776 [57]. To examine whether phosphorylation regulates the function and pathogenicity of ataxin-1, mouse models either blocking phosphorylation by substituting alanine for serine (A776) [30], or mimicking phosphorylation by substituting aspartic acid for serine (D776) [29] were generated from the original 82Q and 30Q transgenes. At 5 weeks, ataxin-1[82Q]-A776 was localized to the nuclei of PC similarly to ataxin-1[82Q]. However, SCA1[82Q]-A776 mice formed substantially fewer NII compared to SCA1[82Q] transgenics at 32 weeks. In addition, SCA1[82Q]-A776 transgenics did not develop ataxic cage behavior, did not show deficits by rotating-rod testing, and had only mild PC pathology. SCA1[30Q]-D776 transgenics had impaired motor coordination on the Rotarod compared to wild-type and SCA1[30Q] control animals. The level of impairment was similar to that of SCA1[82Q] animals and progressed as animals aged until they could no longer perform the task. Similarly, SCA1[30Q]-D776 animals had a significantly widened gait typical of SCA1[82Q] animals. Both SCA1[30Q]-D776 and SCA1[82Q]-D776 mice at 12 weeks had PC atrophy but SCA1[30Q]-D776 did not progress to significant neuronal loss.

Many proteins bind to ataxin-1 via its AXH domain, including the RORα-Tip60 complex [77]. Mouse models expressing mutant forms of ataxin-1 expressed decreased levels of RORα and therefore decreased levels of RORα-mediated genes. To evaluate the role of RORα in SCA1 pathogenesis, SCA1[82Q] animals were crossed to staggerer heterozygous mice which lack one functional copy of *Rora* (sg/+). SCA1[82Q]:sg/+ mice had more severe Purkinje cell pathology suggesting that depletion of *Rora* enhances SCA1 disease. Crossing SCA1[82Q] animals to *Tip60*$^{+/-}$ animals transiently delayed the SCA1[82Q] cerebellar degeneration by increasing RORα and RORα-mediated gene expression [36]

Since SCA1 and SCA7 share a cerebellar degenerative phenotype, shared transcriptional changes were studied between the two knock-in models. Both *Sca*$^{154Q/2Q}$ and Sca7$^{266Q/2Q}$ mice significantly down-regulated insulin-like growth factor protein 5 (*Igfbp5*) in the granule neurons [35]. This down-regulation in granule cells also was observed in the SCA1[82Q] transgenic line, suggesting that it occurred by a non-cell-autonomous mechanism, as the change was a result of a pathogenic process initiated in Purkinje cells which solely expressed the mutant protein.

To determine if SCA1 disease is reversible, a conditional model of SCA1 was developed using the tetracycline-regulated system [101]. In this case, the *Pcp2/L7* promoter drives the tetracycline-transactivator specifically in Purkinje cells, which can then bind a universally expressed tetracycline response element to induce expression of SCA1[82Q] solely in PC. Administration of doxycycine (dox) abolishes this interaction and turns off expression of transgenic ataxin-1. Effects of reversal of transgene expression were assessed at early, mid,

and late stages of disease. At the early stage, 6-week-old mice demonstrated a rotating-rod deficit that could be reversed after 6 weeks of dox treatment. In addition, PC pathology improved by assessment of molecular layer thickness and dendritic arborization, although heterotopic PC still were present. At mid stage disease, 12 week on – 4 week off animals continued to have rotating-rod deficits similar to 12 and 16 week-on animals. After 8 weeks and 12 weeks of dox treatment, however, rotating-rod performance improved, but only partially. Interestingly, this 8-week timepoint coincided with the return of mGluR1α glutamate receptors at the Purkinje cell-parallel fiber synapses, albeit at a lower expression level. There was recovery of molecular layer thickness and improved arborization of PC dendrites demonstrating that halting *SCA1*[82Q] expression at the time of typical onset of ataxia prevents the progression of and partially reverses degenerative changes in PC. When the dox was given to animals at 32 weeks of age, there was no significant improvement of ataxia, but there was some improvement of PC pathology. At all disease stages, the presence of ataxin-1[82Q]-containing NII was rapidly reversible with dox treatment.

A second tetracycline-responsive conditional model was generated using the PrP promoter to drive expression of ataxin throughout brain tissues [37]. This tetracycline-on model showed embryonic lethality without administration of doxycycline to mating females. Behavioral ataxias similar to previous models were identified with the addition of reactive astrocytosis associated with $EAAT_1$ glutamtate transporter clustering in the cerebellum. The PC findings, however, were unusual in that ataxin-1 appeared to be widely expressed throughout the cytoplasm and dendritic tree while granular cell expression was nuclear. Dendritic changes in PC were milder than seen in Pcp2/L7-drivien lines.

Studies crossing two transgenic lines have been used to influence the pathology on the SCA1-transgenic lines. One of these studies crossed the Pcp2/L7[82Q] line with a transgenic mouse overexpressing HSP70 chaperone protein [25]. These animals had improvement in ataxic phenotype and Purkinje cell morphology supporting the hypothesis that protein misfolding and impaired clearance of proteins might be contribute to pathogenesis in polyglutamine diseases. Another study used a transgenic line with a duplication of the murine ataxin-1-like protein crossed to the 154Q-knock-in line [7]. They found that increased levels of ataxin-1-like diminished disease severity in the knock-in line by displacing mutant ataxin-1 from its native complex with Capicua (CIC). These findings support the concept that the selective neuropathology of SCA1 arises from modulation of a core functional activity of Ataxin-1. The authors suggested that finding and studying paralogs to the mutated proteins might be of help in understanding pathogenesis in these diseases. A third study cross-bred mice with a haploinsufficiency of 14-3-3-episilon to Sca1[154Q/+] mice and found improvement of the cerebellar pathology and motor phenotypes but no improvement of weight loss, respiratory function or premature death [49]. Wild-type and mutant ataxin-1 are known to interact with 14-3-3 proteins, and overexpression of 14-3-3 stabilizes ataxin-1 levels in cells and increases neurotoxicity of mutant ataxin-1 in *Drosophila* [15]. Although both wild-type and mutant ataxin-1 were reduced in the cerebellum, they were not reduced in the brainstem an area also affected in the Sca1[154Q] mice, which suggested that different pathogenic mechanisms may operate in different regions of the brain affected by the disease.

Models testing therapeutic intervention in SCA1 mice include the use of recombinant adeno-associated virus vectors that expressed short hairpin RNAs directed against human SCA1 [94]. SCA1[82Q/+] mice were injected at 7 weeks and evaluated at 16 weeks. Despite a relatively low overall transfection level of PC, there was improvement of motor coordination, correction of dendritic morphology and resolution of ataxin-1-containing NII. Another study [17] investigated the efficacy of transplantation of neural precursor cells derived from the subventricular zone of adult GFP-transgenic mice in the treatment of

SCA1[82Q] mice. Stereotactic injection of precursor cells into the cerebellar white matter was performed either at 5 weeks, 13 weeks and 24 weeks of age. Transplanted cells migrated into the cerebellar cortex only in mice with more significant PC pathology (24 weeks). Although no grafted cells assumed the morphology of PC, there was improvement of PC survival and thickness of the molecular layer. There also were improvements in PC electrophysiology and motor function of the animals. Based on microscopic observation and because there was no significant increase in levels of several neurotrophic factors in the transplanted mice, the authors suggested that the neuroprotection was mediated by direct contact of the engrafted cells with the PC of the recipient mice.

A drug study using lithium, a treatment known to have neuroprotective effects, was conducted on the knock-in Sca1(154Q/2Q) line [89]. Dietary lithium carbonate was found to improve motor coordination, learning, and memory treated knock-in mice. Both presymptomatic and postsymptomatic treatment resulted in motor improvement. Neuropathologically, lithium treatment was shown to improve dendritic arborization in mutant hippocampal pyramidal neurons. Lithium therapy also restored the levels of isoprenylcysteine carboxyl methyltransferase, a protein that is down-regulated in the early stages of toxicity of mutant ataxin-1.

3. SCA2

SCA2 is characterized genetically by an expansion of a polyglutamine tract in the gene for ataxin-2 [48,71,75]. The range of disease-causing expansions is 33–77 glutamine residues but there are rare cases of massive expansions, resulting in infantile onset which can have a different phenotype than the olivopontocerebellar degeneration that is seen in most cases. Disease onset is more typically seen in early to mid-adult life. Patients usually have ataxia, tremor, slow saccadic eye movements, myoclonus, hyporeflexia and sensory neuropathy. There usually is involvement outside the cerebellar system with pathology seen in the substantia nigra, striatum, spinal cord and peripheral nerve. Both nuclear and cytoplasmic inclusions, immunoreactive for ubiquitin and expanded ataxin-2 have been described, but are not always demonstrable.

The first transgenic model of SCA2 utilized the expression of mutant (58Q) human ataxin-2 in Purkinje cells using the Pcp-2/L7 promoter [45]. The mutant mice had progressively decreased motor performance which correlated with dendritic atrophy and subsequent death in PC. Although NII were not seen, there were cytoplasmic inclusions in PC that were immunoreactive with antibodies to ataxin-2 and the 1C2 antibody, which recognizes expanded polyglutamine tracts. Subsequent studies using these same 58Q mice demonstrated that mutant ataxin-2 facilitated inositol-triphosphate-induced Ca++ release in cultured PC, and mGluR1/5 agonists sensitized PC to glutamate-induced apoptosis [58]. Dantorolene, a ryanodine-receptor inhibitor, blocked that response *in vitro* and when given to mutant transgenic mice from 2–11 months of age substantially reduced expression of disease.

Another model using human mutant (75Q) ataxin-2 under the direction of the native ataxin-2 promoter resulted in a severe and early-onset deficit in rotating-rod performance despite relatively low levels of transgene-expression [3]. The pathology was not well characterized. An ataxin-2 knock-out model had no motor phenotype although there was a tendency toward obesity [51] and decreased fear conditioning [46].

4. SCA3/Machado-Joseph disease

SCA3, also is a polyglutamine disease and has wide phenotypic variability, largely based on the length of the repeat expansion in the mutated gene (ataxin-3) [83]. The disease range is

from 51 to approximately 200 glutamine residues. This disease involves primarily cerebellar afferent and efferent pathways, the extrapyramidal system, and lower motor neurons. Targets include Clarke's nuclei, vestibular nuclei, basal pontine nuclei, dentate and red nuclei and dorsal root ganglia with concordant degeneration of their axonal pathways. The cerebellar cortex and olivary nuclei are largely spared. Extrapyramidal involvement includes the substantia nigra, subthalamic nuclei and to a lesser extent, the pallidum. Neuronal intranuclear inclusions containing ubiquitin and mutant ataxin-3 are characteristic of SCA3.

Although the disease does not principally target PC in affected patients, the first attempted transgenic model of SCA3 used the Pcp-2/L7 promoter to drive either a full-length ataxin-3 with a 79Q expansion or a truncated form of the same gene which primarily expressed the polyglutamine region. [47]. The animals with the full-length transgene did not develop a phenotype, while those expressing the truncated version had early-onset of severe cerebellar hypoplasia/degeneration including significant granular neuronal loss, possibly implicating a maldevelopmental process although a time course was not published. The authors suggested that a truncated rather than full-length form of the protein is actually the disease effecter in SCA3. A more recent model using the Pcp-2/L7 promoter [85] demonstrated early-onset ataxia with cerebellar hypoplasia obvious at P21, suggesting a maldevelopmental component. There were marked dendritic abnormalities and somatic heterotopia in targeted PC as well as prominent intranuclear ataxin-3 inclusions. They treated these animals at P21–25 with lentivector-mediated expression of CRAG, (collapsin response mediator protein (CRMP)-associated molecule (CRAM[CRMP-5])-associated GTPase), which has been shown to lead to the degradation of polyQ through the ubiquitin-proteasome pathway[72]. They found that Purkinje cells in treated mice cleared polyQ aggregates and re-activated dendritic differentiation with improved performance on behavioral measures of ataxia.

A yeast artificial chromosome (YAC) model was developed by Cemal, *et al* [14]with several lines of mutant ataxin-3 containing different repeat lengths. One line (67Q) had higher expression of the transgene and had more accelerated disease than another line (84Q) with lower expression. The phenotype consisted of gait abnormalities, tremor and limb clasping. Pathologically there was diffuse nuclear immunoreactivity for ataxin-3 with formation of NII. Neuronal loss was present in the pons and substantia nigra with some degree of PC atrophy and loss. Crossing the 67Q and 84Q lines worsened the phenotype. Nuclear magnetic resonance spectroscopy of tissues from the 84Q line found increased glutamate and glutamine and decreased GABA, choline, phosphocholine and lactate in cerebrum and cerebellum [39]. Treatment of the 84Q line with dantrolene, a ryanodine-receptor blocker, from 2–12 months of age reduced the severity of clinical and pathologic changes [16].

Four different models of SCA3 have been generated using the mouse prion protein (PrP) gene promoter. The first used a 71Q form of mutant human ataxin-3 [38]. The neurological phenotype largely was limited to homozygous mice and consisted of postural instability, gait ataxia and weight loss. Immunoreactive ataxin-3 was expressed in neuronal nuclei and there were NII present. Neuronal loss was not seen in the deep cerebellar nuclei at 7 months but there was neuronal loss in the substantia nigra. A “toxic” 37 kDa poly-Q-containing fragment of ataxin-3 was found in the nuclear fraction of brain homogenates only in diseased mice. A modification of this 71Q line in which an amino-acid segment (residues 190–220) was truncated from the full length protein had similar pathology and a shorter “toxic” fragment [23]. When the 71Q line was crossed with a partial or complete knock-out of CHIP (C-terminus of heat-shock protein 70-interacting protein) there was a worsening of the phenotype [93]. Another 71Q transgenic line, which had lower ataxin-3 expression, when expressed alone did not produce a disease phenotype, but became affected after crossing with CHIP-null mice.

A second model using a mouse PrP-promoter was developed in which lines containing 70Q and 148Q versions of mutant ataxin-3 developed a severe neurological phenotype with tremor, ataxia and decreased activity [5]. Pathologically there were NII and some changes in PC although some of the Prp promoters apparently do not express transgenes in that cell population [6,10,31]. The 148Q mice had a more rapid, severe course. Other lines in which the 148Q transgene was modified by addition of either a nuclear export sequence (NES) or a nuclear localization sequence (NLS), resulted in a reduction and an exacerbation of the disease, respectively. These results suggested that nuclear localization of mutant ataxin-3 is important for pathogenesis. A later study [43] in which the 70Q line was crossed with the 148Q containing the NES showed exacerbation of pathology suggesting that the mutant 70Q could help sequester the 148Q protein in the nucleus. Menzies, *et al.*[61] using the 70Q line found that temsirolimus, an mTOR-inhibitor known to increase autophagic protein degradation, resulted in decreased formation of ataxin-3 aggregates and decreased the levels of soluble cytosolic mutant protein. The drug treatment also normalized a number of gene transcripts that typically were reduced in these mice.

A third mouse PrP-based model was made by Chou, et al.[20] using a 79Q mutation of ataxin-3. These mice had a deficit on the rotating-rod apparatus at 7–8 months of age. NII were present in the deep cerebellar nuclei and substantia nigra and there were mild changes in PC dendrites. Microarray analysis revealed altered expression of genes related to synaptic transmission, signal transduction, intracellular calcium mobilization and regulation of neuronal survival. They proposed using histone deacetylase inhibitors as therapy. A recent study using such an agent, sodium butyrate [19] in this line has shown improvement of the pathology.

Boy, et al.[10] developed a conditional model of SCA3 using a tetracycline-off strategy, employing a PrP promoter and a 77Q mutation. The untreated animals developed a phenotype similar to other PrP models which was largely abrogated by prolonged treatment with doxycycline. There was no immunohistochemical expression of mutant ataxin-3 in the cerebellar cortex before therapy except in Bergmann glia. The same laboratory generated a 148Q line using the huntingtin promoter [9]. These mice had onset of motor coordination deficits at about one year of age and NII which did not occur until much later.

Other SCA3 models include two ataxin-3-knock-out lines, neither of which expresses a neurological phenotype [76,84]. In one of these knock-out lines [76], there were increased levels of ubiquitinated proteins in brain and testis, supporting a deubiquitinating function for ATXN3. Two CMV-driven lines with 83Q- and 94Q-expansions developed a mild phenotype detectable on the rotating-rod apparatus. There were no NII and no fragments of ataxin-3 that were associated with disease [81].

5. SCA6

SCA6 is a polyglutamine disease caused by a mild expansion, 20–31 residues, of a polyglutamine-containing region in the C-terminal region of the CACNA1A subunit of a voltage-gated calcium channel, Ca(v)2.1[99]. It often has onset in mid-to-late adult life with ataxia as the principal finding. Pathologically, it is characterized by Purkinje cell loss with little involvement elsewhere. Saegusa, *et al.* [74] using a knock-in strategy generated mice with a 28Q mutation. Homozygotes died at age three weeks, while heterozygotes had no neurological phenotype or electrophysiological abnormalities of the Ca(v)2.1 channel.. Watase, *et al.* [88] made knock-in mice with 30Q and 84Q mutations, the latter far beyond the range of expansions seen in SCA6. The 30Q mice had no neurological phenotype at 20 months. Homozygous 84Q mice had deficits on the rotating rod at 7 months while heterozygotes had deficits at 19 months. There was no cerebellar pathology except for

polyglutamine inclusions, mostly cytoplasmic, in PC at 22 months in homozygous mice. Isolated PC did not have electrophysiological abnormalities. These studies suggest that SCA6 is not likely to be a loss-of-function channelopathy.

6. SCA7

SCA7 is another polyglutamine expansion-disease [28] but it affects both the retina and the olivopontocerebellar system. The range of repeat-expansion in the ataxin-7 gene is from 37 to greater than 200 residues. There is a wide range of age of onset from infancy to adult life, depending upon the size of the repeat expansion. The typical pathology is olivocerebellar degeneration with milder involvement of the basis pontis. Patients with earlier onset have more obvious visual problems at the time of presentation. The extrapyramidal system and lower motor neurons also are affected. Retinal pathology consists of severe loss of photoreceptors and ganglion cells with atrophy of the nuclear and plexiform layers. A number of transgenic models of SCA7 have been developed, many focusing primarily on the retina. Yvert *et al.* [97] using the Pcp-2/L7 promoter expressed a 90Q-repeat ataxin-7 transgene and found NII in PC, a severe deficit in rotating rod performance at 11 months and dendritic simplification of PC at 16 months. Retinal changes also were present in mice using the same transgene under the regulation of the rhodopsin promoter. The same laboratory generated mice with a 128Q-expansion driven by the PDGF chain B promoter [96]. Those mice developed ataxia at 5 months of age. Accumulation of ataxin-7 was seen in nuclei but not restricted to degenerating neuronal populations. A number of transcription factors and other nuclear proteins were sequestered in NII. The expanded repeat also appeared to stabilize the ataxin-7. Chou, et al. [18] used the same promoter to express a 52Q-repeat transgenic ataxin-7. They found both neuronal and glial expression and development of motor problems at 7 months with a deficit in rotating rod performance at 9 months. There was mild somatic and dendritic atrophy of PCs and NII in PCs by 11 months. Using microarray analysis, they found altered expression of many genes associated with a number of functions, including myelination, synaptic transmission, axonal transport, signal transduction, protein translation, glial function and regulation of neuronal differentiation and survival. There also was loss of neurons in the inferior olivary nuclei with increased expression of Puma and Bax, two p53-regulated pro-apoptotic factors, in those areas [86]. There were increases in phospho-p53 without increases in total p53 protein or mRNA, suggesting that mutant ataxin-7 may enhance p53 activation.

Another model using the mouse prion promoter and a 92Q-repeat expansion developed retinal degeneration with NII [55]. These same mice [34] did not show transgene expression in PC but had early-onset ataxia in two different lines. Pathologically, there was no loss of PC but there was somatic atrophy. NII were noted in cerebellar granular neurons. Another model [26] without PC expression utilized a 92Q-repeat SCA7 transgene driven by the Gfa2-promoter, a version of the glial fibrillary acid protein promoter used for restricted expression in Bergmann astrocytes [11].These mice had expression in Bergmann glia but not PCs. They developed a deficit in rotating- rod performance at 12 months although there were other motor problems that may not have been ataxia. There was a decrease in the activity of GLAST, a Bergmann-glial glutamate transporter, and broadening of Bergmann glial fibers. Changes in PC were seen ultrastructurally and attributed to glutamate toxicity. Calbindin immunostaining also was decreased in PC. These studies led to the suggestion that some of the effects of the mutant protein may not be entirely cell-autonomous.

Studies using retinally directed expression of the mutant ataxin-7 have shown that there was down-regulation of transcription factors controlling rod differentiation [2], and that this was mediated by ataxin-7, which is known to be a subunit of histone acetylase transferase complexes [42]. When mutationally expanded, ataxin-7 induced histone H3

hyperacetylation, and these hyperacetylated genes were transcriptionally down-regulated [41]. Expression-analysis revealed that nearly all rod-specific genes were affected, leading to visual impairment in SCA7 mice. When these mice were crossed with a knock-in line expressing JUNAA, an alanine-substituted form of jun which is inactive, the retinal phenotype was improved and there was restoration of Nrl, a factor active in transcription of rod-specific proteins [62].

Knock-in SCA7 mice were developed by Yoo, *et al.* [95] using a 266Q-repeat, mimicking one of the larger human SCA7 expansions reported. These animals developed a severe neurological phenotype beginning at 5 weeks. There was weight loss, visual impairment, ataxia, muscle wasting, kyphosis, and tremor. Homozygotes died by 2 months and heterozygotes by 4–5 months. There were NII but they were not present until after the onset of symptoms. Cerebellar pathology was relatively mild, with decreased PC somatic size but no loss of PC or major dendritic atrophy. There also was down-regulation of photoreceptor genes in the retina with cone-related genes more affected. When these mice were crossed with transgenic mice that express a green fluorescent protein -based reporter substrate of the ubiquitin proteasomal system, the levels of the reporter remained low during the initial phase of disease, but late in disease there were increased levels of the reporter in the most vulnerable neurons [8]. The latter increase was secondary to increased transcription in those cells rather than a reduction of proteasomal activity. There was an inverse relationship between the presence of NII and the increase in the reporter, suggesting that NII provide a protective role against neuronal dysfunction.

7. SCA8

SCA8 is a trinucleotide repeat disease arising from an untranslated CTG-repeat expansion [53] Onset of SCA8 ranges from congenital to over age 70, but most patients present in mid-adult life. Slowly progressive gait and limb ataxia and dysarthria are typical, but spasticity, oculomotor deficits, sensory loss and cognitive changes also can be present.

A bacterial artificial chromosome (BAC) transgenic line expressing a 116CTG-repeat under its own promoter was generated [63]. The mice had a neurological phenotype with a deficit on the rotating-rod test, although not a classical ataxia by cage behavior. There was no degenerative pathology of PC but there were 1C2-positive NII in PC and brainstem neurons in these animals as well as in patients with SCA8, suggesting that there is bi-directional expression (CTG/CAG) of the expanded gene. Optical imaging-based physiological studies found alterations in GABAergic inhibition in the cerebellar molecular layer. Other studies [27] in these same mice found CUG-positive ribonuclear inclusions that co-localized with the splicing factor, muscle-blind-like-1 (Mbnl1), in cerebellar interneurons and deep nuclei but not in PC. Crossing the SCA8 mice with Mbnl-knockout mice enhanced motor deficits. An Mbnl1-regulated target, the GAT4 GABA-A transporter, was up-regulated in the SCA8 mice which could account for the decreased GABAergic inhibition seen with optical imaging. A recent study in these mice [102] found that the CAG expansion constructs expressed homopolymeric polyalanine proteins without an ATG start codon which could be detected by immunohistochemistry in PC of the mice and human SCA8 patients. These homopolymeric proteins may be toxic and have a role in pathogenesis.

Because SCA8 is caused by large CTG repeat expansions in the untranslated antisense RNA of the Kelch-like 1 gene (KLHL1) mouse models were made in which Klhl1 was deleted either completely or specifically in PC [40]. Mice either homozygous or heterozygous for the total body Klhl1 deletion had early onset gait abnormalities and developed significant loss of motor coordination by 24 weeks of age. Mice with Klhl1 deleted only in PC had a similar phenotype. There were PC dendritic changes, measured by molecular layer

thickness, in both lines, which were more severe in homozygotes. These results suggest that loss of KLHL1 activity also could play a role in the pathogenesis of SCA8.

8. SCA17

A CAG-repeat expansion in the TATA-binding protein (TBP) gene, a general transcription initiation factor, causes SCA17 [64]. SCA17 is clinically variable and can present with ataxia, dementia, Parkinsonism, Huntington-like involuntary movements, and hyperreflexia. There is a wide range of age at onset and the repeat expansions range from 43–66 polyglutamine residues. Neuropathological findings include neuronal loss in cerebral cortex, caudate nucleus and medial thalamic nuclei in addition to loss of Purkinje cells and inferior olivary neurons. Neuronal intranuclear inclusions which immonlabel for the expanded TBP also are characteristic[12].

Transgenic lines expressing 71Q and 105Q repeats using the mouse PrP promoter were found to have an abnormal phenotype by rotating-rod behavior [32]. At 31 weeks the 71Q mice had decreased calbindin immunostaining in PC with probable dendritic atrophy. Using a modification of that model, it was shown that the polyglutamine region affected binding of TBP to promoter DNA and that TBP with expanded polyglutamine tracts could induce neuronal toxicity even when the primary DNA-interacting region of TBP was deleted [33]. These mice had a severe phenotype with early death. The pathology was not characterized except that NII and diffusely immunoreactive nuclei could be detected with the 1C2 antibody with cerebellar localization primarily in granular neurons. They also found that small TBP fragments without the C-terminus were aggregated in nuclei. TrkA, the high-affinity nerve growth factor receptor, is down-regulated in PC of the 71Q mice, implicating mutant TBP in altered gene regulation [79].

9. Discussion

There are several problems inherent in modeling human neurodegenerative diseases in mice. The human forms of SCA often have an onset well into adult life and then progress over years to decades. Therefore, in order to produce disease in the short life-span of mice, genetic manipulations not present in the human disease often need to be employed. In SCA1 knock-in models, which are more likely to recapitulate the cell-specificities seen in the human diseases, no disease phenotype develops unless there is a massive expansion of the CAG-repeat beyond what is seen in human disease [59,91]. Even when massive expansions do occur in human polyglutamine diseases they can significantly alter the phenotype [69], a finding recapitulated in the Sca1[154Q/+] [91] and Sca7[266Q] [95] homozygous and heterozygous knock-in mice. The approach that has been most successful in creating a disease phenotype within the murine life-span is to over-express transgenic mutant protein. In most systems, lines with increased copy number and transgene expression have more severe phenotypes. In the trinucleotide-repeat diseases, this strategy usually has been coupled with using expansion-lengths in the upper range of what is seen in human counterparts. Animals that over-express transgenic non-mutant alleles are essential controls for this approach.

The cellular targeting of the transgene also is an important consideration in developing genetically engineered models. As discussed above, knock-in mice are more likely to have involvement of all of the neuronal populations affected in human disease, because they are under control of the native promoter, but they have been disappointing in robustly mimicking the human phenotype. They are, however, more suitable for biochemical studies because the gene expression is more widespread. Overexpression-transgenic approaches have employed targeting a specific cell type, usually the PC, or expression systems such as

the PrP-promoter or YAC or BAC constructs which have broader target-cell populations. An advantage of targeting the PC is that it has a distinctive morphology which is altered in disease and its dysfunction elicits a behaviorally measurable phenotype. If the PC is the only cell expressing the mutant transgene, changes can be interpreted as autonomous effects of the mutant gene and not secondary effects related to dysfunction of other associated glial or neuronal cells. Disadvantages of PC-targeting include greater difficulty using the transgenic tissues for biochemical studies because only a small population of cells express the mutant transgene and wild-type protein may dilute potential effects. Crossing these types of mice to knock-out backgrounds can mitigate this disadvantage. Because PC-only targeting does not truly recapitulate the distribution of pathology seen in most of the human ataxias, such models are less beneficial in evaluating therapeutic strategies, except as proof-of-principle or screening experiments. More generalized targeting of cell populations has been used in a number of disease models, often employing the PrP promoter. Depending upon the construct used, this promoter may not have high expression in PC [6,10,31]. However, alterations in PC morphology have been claimed in several PrP-driven lines modeling SCA1[37], SCA3[5,18], SCA7 [34] and SCA17 [32], but they generally are modest or equivocal. An interesting observation in a line expressing transgenic ataxin-7 in Bergmann glia was that there are apparent non-autonomous effects of the transgene in PC, although again those changes are not characteristic of either the human disease or PC-targeted models.

The role of the full-length protein in pathogenesis has been shown in many of the polyglutamine disease models. Interestingly, full-length ataxin-3 did not cause disease when expressed only in PC, but smaller fragments containing mostly the polyglutamine tract induced PC death [47]. This finding correlates with the preservation of PC in human SCA3 and indicates that the pathogenesis is more complex than the mere presence of the polyglutamine expansion. Although the full-length protein is the ideal genetic construct for faithfully reproducing the disease, manipulating the mutant gene to alter elements of its function also has been a useful strategy in understanding pathogenesis. Deletion of the self-aggregation region of ataxin-1 failed to alter pathogenesis in SCA1-transgenic mice despite the prevention of NII [52], and in SCA17-transgenic mice, deletion of the primary DNA-interacting region of TATA-binding protein did not prevent neurotoxicity [33]. Mutation of nuclear localization sequences (NLS) has been shown to protect against disease in SCA1 [52] and SCA3 [5] models and nuclear localization of the mutant protein is a common theme in nearly all of the polyglutamine diseases. An eye-catching feature of several of the polyglutamine-ataxias is the presence of NII, both in human disease and in their transgenic models. The importance of these inclusions in pathogenesis has been controversial. The presence of NII does reflect levels of mutant protein as they can be reversed in conditional models [101], but their presence does not appear to be correlated with pathogenesis in several models [52,95] and may even be protective [8].

Post-translational modification of the mutant proteins also is a key factor in some disease processes, such as SCA1, where phosphorylation of serine residue-776 has a critical effect on progression of pathology [30] and substitution of a phosphomimetic glutamate residue at that site can mimic the pathogenetic mechanism even when using a transgene with a non-expanded 30Q repeat [29]. The full-length protein and its post-translational modifications probably are important for the interactions of the mutant proteins with other cellular elements, many of which have been identified in the various models described here. A common theme, particularly in the polyglutamine diseases, is interaction of the mutant protein with regulators of gene expression with subsequent alterations their function [18,20,41,77]. Other proteins which may play an interactive role in pathogenesis are those related to proteasomal pathways [24,93].

Ultimately, genetic models become most valuable as tools to assess therapeutic strategies. As a proof of principle that these conditions might be reversible under the proper time frame, conditional transgenic models using tetracycline regulation have been developed for SCA1 [101] and SCA3 [10], and both have found that the disease can be reversed or slowed by the cessation of production of the mutant protein depending on the stage of disease at intervention. These results along with knock-down experiments [94] give encouragement for genetic manipulations as possible treatments. One caveat is that knock-down therapy may be more difficult to attain in models that mimic the neuronal distribution of their human disease counterparts. Grafting of neuronal precursor cells into the cerebellum also has been attempted in a PC-targeted SCA1 transgenic line [17]. Again this strategy becomes more difficult in many of the ataxias with involvement of non-cerebellar structures.. Based on data obtained from SCA2 and SCA3 transgenic lines that calcium regulation is altered, trials of dantrolene, a ryanodine-receptor blocker, have shown improvement in the disease phenotype when administered repeatedly from 2–12 months of age to transgenic mice expressing either mutant ataxin-2 [58] or ataxin-3 [16]. Based on data that expanded ataxin-3 causes cerebellar transcriptional downregulation by inducing histone hypoacetylation, a histone deacetylase inhibitor, sodium butyrate, recently has been used to successfully treat a model of SCA3 [19]. A drug that increases autophagy, temsirolimus, decreased ataxin-3 both in soluble and aggregate forms and reduced pathology in a SCA3-transgenic line. Other potential targets for therapeutic intervention include influencing post-translational modifications such as phosphorylation using more classical pharmacological agents.

Although none of the models described in this review perfectly reproduces the human diseases being studied, the variety of approaches with regard to targeting of transgenes, knock-in vs. over-expression models, and full-length vs. modified transgenic protein structures have shown advantages that can be complementary to one another in gaining understanding of pathogenesis and potential therapies of the spinocerebellar ataxias.

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Abbreviations

A	alanine
BAC	bacterial artificial chromosome
NII	neuronal intranuclear inclusion
PC	Purkinje cell
PrP	prion protein
Q	glutamine
RORalpha	retinoid-related orphan receptor-alpha
S	Serine
SCA	spinocerebellar ataxia
Tet	tetracycline
Tg	transgenic
YAC	yeast artificial chromosome

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Highlights

- We review murine transgenic models of spinocerebellar ataxia.
- Polyglutamine-associated ataxias have been modeled most frequently.
- These models provide insight to pathogenetic mechanisms such as gene regulation.
- The role of the entire mutant protein and post-translational modification is important.
- The efficacy of therapeutic intervention can be evaluated in these model systems.

Table 1

Disease	Genetics	Human Phenotype	Transgenic Models	Manipulations of Models
SCA1	poly-Q	ataxia +	Pcp2/L7-tg (13)	functional modification of mutant gene (29,30,52,57)
	Ataxin-1	motor neurons	Tet-Pcp2/L7-tg (101)	crossed with other tg mice (25,77)
		extrapyramidal	Knock-in (59,91)	gene therapy (94)
			Knock-out (60)	precursor cell transplantation (17)
			Tet-PrP-tg (37)	drug therapy (89)
SCA2	poly-Q	ataxia +	Pcp2/L7-tg (45)	drug therapy (58)
	Ataxin-2	extrapyramidal	ATX2 promoter-tg (3)	
		motor-sensory	Knock-out (51)	
SCA3	poly-Q	ataxia +	Pcp2/L7-tg (47,85)	functional modification of mutant gene (5,47)
	Ataxin-3	motor neurons	YAC-tg (14)	crossed with other tg mice (93)
		extrapyramidal	PrP-tg (5,20,38)	gene therapy (72)
		peripheral n.	Tet-PrP-tg (10)	drug therapy (16,19,61)
			Htt-tg (9)	
			CMV-tg (81)	
			Knock-out (76,84)	
SCA6	poly-Q CACNA1A	ataxia	Knock-in (74,78)	
SCA7	poly-Q	ataxia +	Pcp2/L7-tg (97)	crossed with other tg mice (62)
	Ataxin-7	blindness	PDGF-B-tg (18,96)	
		motor neurons	PrP-tg (55)	
		extrapyramidal	Gfa2-tg (26)	
			Rhodopsin-tg (2)	
			Knock-in (95)	
SCA8	CTG-expansion	ataxia +	BAC-tg (63)	
	Ataxin-8OS	spasticity	klhl-1-KO (40)	
SCA17	poly-Q	ataxia +	PrP-tg (32)	
	TATA-BP	dementia		
		extrapyramidal		