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Cerebellum

Motor performances of spontaneous and genetically modified mutants with cerebellar atrophy

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**Abstract** Chance discovery of spontaneous mutants with atrophy of the cerebellar cortex has unearthed genes involved in optimizing motor coordination. Rotorod, stationary beam, and suspended wire tests are useful in delineating behavioral phenotypes of spontaneous mutants with cerebellar atrophy such as *Grid2<sup>Lc</sup>*, *Grid2<sup>ho</sup>*, *Rora<sup>sg</sup>*, *Agtpbp1<sup>pcd</sup>*, *Reln<sup>rl</sup>*, and *Dab1<sup>scm</sup>*. Likewise, transgenic or null mutants serving as experimental models of spinocerebellar ataxia (SCA) are phenotyped with the same tests. Among experimental models of autosomal dominant SCA, rotorod deficits were reported in SCA1 to 3, SCA5 to 8, SCA14, SCA17, and SCA27 and stationary beam deficits in SCA1 to 3, SCA5, SCA6, SCA13, SCA17, and SCA27. Beam tests are sensitive to experimental therapies of various kinds including molecules affecting glutamate signaling, mesenchymal stem cells, anti-oligomer antibodies, lentiviral vectors carrying genes, interfering RNAs, or neurotrophic factors, and interbreeding with other mutants.

**Key words:** Cerebellum; Purkinje cells; Rotorod; Stationary Beam; Wire Suspension; Spinocerebellar ataxia.

**Conflict of interest:** The authors declare that they are no conflict of interest in their work.

## 1. Introduction

Naturally mutated mice with cerebellar atrophy have been known for over half a century.<sup>1,2</sup> Over the course of the last quarter century, technological advances in transgenic and targeted null mutations have yielded genetically modified mutants with cerebellar atrophy, notably to model autosomal dominant spinocerebellar ataxias (SCAs) numbered at the present time from SCA1 to SCA37 according to individually discovered genes. We review naturally mutated mice with cerebellar atrophy together with induced SCA mutations. Known for a longer time, the spontaneous mutants have been more thoroughly evaluated than the induced mutants and therefore serve as contrast with what remains to be determined in the newer models. Among the older models, we selected the most behaviorally characterized ones and those with more selective damage to the cerebellar cortex.

The main tests of motor coordination used to test natural mutations are stationary beam, suspended wire, and rotarod tests, all sensitive to cerebellar lesions.<sup>2,3</sup> Mice are placed on a stationary beam (Fig 1A) and either walk along it or remain still. In the suspended wire test, mice are placed upside-down on a horizontal wire and stay upside-down with two paws or four. If able to maintain their position with four paws, they can lift themselves upright on a sidebar of a coat-hanger (Fig 1B). On the rotarod (Fig 1C), mice are placed on a beam that rotates and must move in synchrony with it. In all three tasks, latencies before falling and number of falls are measured. In stationary beam and coat-hanger tasks, movement time (MT) can be estimated as defined by the time taken to walk or slide across the beam or bar. Different types of MT have been used in the coat-hanger version to delineate more precisely difficulties encountered while moving along the horizontal bar and climbing atop the diagonal bar. Since animals support their body weight in an upside-down position, the suspended wire test requires muscle strength all the more, relevant in this context because one of the main features of cerebellar symptoms is hypotonia. In some

lesioned animals, the loss in balance on the stationary beam can be compensated by remaining still, so that an additional measure can be used to disclose the deficit, namely the distance travelled along the beam or the time taken to reach the end of the beam. In contrast, the rotorod cannot be compensated by immobility unless the animal wraps its legs around the beam. After two successive rotations of this passive type, for example, the animal should be removed and the trial ended as if it fell.

## 2. Natural mouse mutations with cerebellar atrophy

Table 1 illustrates neurobehavioral characteristics of mice with natural mutations causing relatively selective degeneration of the cerebellar cortex and deficits in motor coordination tests.<sup>2,3</sup>

### 2.1 *Grid2*

The semi-dominant *Lurcher* mutation causes a gain-in-malfunction of *Grid2* located on chromosome 6 and encoding the GluR $\delta$ 2 ionotropic glutamate receptor associated with the amino-methyl-isoxazolepropionate (AMPA) receptor.<sup>4</sup> *Grid2* mRNA is predominantly expressed in cerebellar Purkinje cells.<sup>5</sup> The depolarized membrane potential of the *Grid2*<sup>Lc</sup> encoded receptor is probably responsible for the nearly total loss of Purkinje cells from postnatal week 2 to 4.<sup>6</sup>

Two autosomal recessive *hot-foot* alleles (*4J* and *nancy*) cause different deletions in the coding sequences of *Grid2*.<sup>7,8</sup> For the *ho-4J* allele, the truncated GluR $\delta$ 2 protein is expressed in Purkinje cell soma without being transported to the cell surface.<sup>9</sup> The main neuropathological marker in *Grid2*<sup>ho-nancy</sup> mutants is defective parallel fiber–Purkinje cell innervation and mild depletion of cerebellar granule cells, resulting in cerebellar ataxia and a hopping gait reminiscent of mice walking on a hot plate.<sup>10</sup> In contrast to the gain-in-malfunction subtending the *Lc* allele, *ho* alleles are non-functional, as indicated by the similar phenotype seen in the *Grid2* targeted null mutation marked by reduced synaptic contacts on Purkinje cells, ataxia, and motor

coordination deficits.<sup>11</sup> Thus, in *Grid2<sup>Lc</sup>* mutants<sup>12-16</sup> and *Grid2<sup>ho-nancy</sup>* mutants,<sup>10-12,17</sup> there is cerebellar ataxia as defined as a wide-spread gait and defective performances on stationary beam, coat-hanger, and rotorod tests relative to non-ataxic controls.

## 2.2 *Rora*

The autosomal recessive *staggerer* mutation deletes *Rora* located on chromosome 9, which encodes a retinoid-like nuclear receptor involved in neuronal differentiation and maturation highly expressed in Purkinje cells.<sup>18,19</sup> As in *hot-foot*, the lost function of the *Rora<sup>sg</sup>* mutation was confirmed by observing nearly identical neuropathological and behavioral phenotypes in targeted *Rora* null mutants.<sup>20,21</sup> In *Rora<sup>sg</sup>* homozygotes, Purkinje cells decline in number before postnatal day 5, and, at the end of the first postnatal month, 75% of them disappear.<sup>22</sup> Thus, the Purkinje cell loss begins at an earlier stage than *Grid2<sup>Lc</sup>* (postnatal day 8) but is less complete.<sup>6</sup> Even when present, metabotropic glutamate receptor type 1 (mGluR1)-mediated signaling at cerebellar parallel fiber-Purkinje cell synapses was disrupted in *Rora<sup>sg</sup>* mutants.<sup>23</sup> As with *Grid2* mutants, performances on stationary beam, coat-hanger, and rotorod tests were deficient in *Rora<sup>sg</sup>* mutants relative to non-ataxic controls.<sup>11,12,24,25</sup>

## 2.3 *Agtbp1*

The autosomal recessive *Purkinje cell degeneration (pcd)* mutation affects *Agtbp1* located on chromosome 13 and encoding ATP/GTP binding protein 1.<sup>26</sup> In normal mouse brain, *Agtbp1* mRNA is prominent in Purkinje cells, mitral cells of olfactory bulb, thalamic neurons, and retinal photoreceptors, all of them prone to degeneration in the mutant. Several alleles of the affected gene have been discovered, including *1J* on C57BR/cdJ, *2J* on SM/J, and *3J* on BALB/cByJ backgrounds, respectively. The *1J* allele was subsequently transferred to B6C3-a/a and C57BL/6J backgrounds and the *2J* allele to C57BL/6J. The predominant pathology in

*Agtbbp1<sup>pcd-1J</sup>* mutants concerns almost total Purkinje cell loss from the third to the fourth postnatal week.<sup>27,28</sup>

*Agtbbp1<sup>pcd/1J</sup>* mutant mice were deficient relative to non-ataxic controls on coat-hanger and rotarod tests.<sup>29</sup> When three adult mutant models were placed on the same rectangular stationary beam, only *Rora<sup>sg</sup>* mutants<sup>24</sup> fell sooner than their non-ataxic controls, not *Grid2<sup>Lc</sup>* mutants<sup>13</sup> or *Agtbbp1<sup>pcd/1J</sup>* mutants.<sup>29</sup> This result may be explained by the almost total loss of Purkinje cells in *Grid2<sup>Lc</sup>* and *Agtbbp1<sup>pcd/1J</sup>* mutants but a 75% loss in *Rora<sup>sg</sup>*, so that the existence of dysfunctional Purkinje cells and their abnormal dendritic arborization appears to cause a worse phenotype than their absence. A second possibility is the earlier onset of Purkinje cell degeneration in *Rora<sup>sg</sup>* relative to the other two worsens the behavioral phenotype in the adult.

#### 2.4 *Reln* and *Dabl*

The autosomal recessive *reeler* mutation disrupts *Reln* located on chromosome 5 and encoding reelin.<sup>30,31</sup> Two *Reln<sup>rl</sup>* alleles have been discovered: *Jackson* (J) and *Orleans* (Orl). The *Jackson* allele on the C57BL/6 or the hybrid B6C3 background has a deletion of the entire gene and *Orleans* on the Balb/c background a 220 bp deletion in the open reading frame, causing a frame shift.<sup>32</sup> Reelin is an extracellular matrix protein involved in neural adhesion and migration at critical stages of development.<sup>30-33</sup> *Reln<sup>rl-J</sup>* and *Rel<sup>orl</sup>* mutants display cell ectopias in cerebellum, hippocampus, and neocortex.<sup>34-36</sup> In line with elevated expression of *Reln* mRNA in granule but not Purkinje cells,<sup>37</sup> the former constitutes the main depleted cell type in the cerebellum of the mutant.<sup>38</sup> Among mutations upstream of the reelin signaling pathway, disruption of *Dabl* located on chromosome 4 and encoding disabled homolog 1 characterizes the autosomal recessive *Dabl<sup>scm</sup>* (*scrambler*) mutation with a similar phenotype to *Reln<sup>rl</sup>* ones.<sup>39</sup> Relative to non-ataxic controls, the performances on stationary beam, coat-hanger, and rotarod

tests were deficient in *Relrl<sup>orl</sup>* mutants<sup>40</sup> and *Dabl<sup>scm</sup>* mutants<sup>41</sup>, the latter being also deficient in climbing a vertical grid, a test better adapted to their motor capacity.<sup>42</sup>

### 3. Genetically modified mouse mutations with cerebellar atrophy

To provide features of SCA subtypes (Tables 2 and 3), genetically modified mice have been generated with human or animal versions of the mutated genes (transgenic) or with targeted deletion of the affected genes (null mutants).

#### 3.1 SCA1

SCA1 is an autosomal dominant disorder caused by over 39 cytosine–adenine–guanine (CAG) trinucleotide repeats of the *ATXN1* gene located on chromosome 6 and encoding ataxin-1,<sup>43</sup> found in Purkinje and other cells.<sup>44</sup> The CAG or CAA triplet is specific for the amino acid glutamine, excessively repeated in several diseases designated as polyglutamine and including cerebellar or basal ganglia anomalies such as Huntington’s disease. SCA1 causes adult-onset degeneration of cerebellar cortex and brainstem, leading to ataxia, dysarthria, and bulbar symptoms. Other SCA genes have been numbered and designated as “ataxins” (e.g. ataxin-2, ataxin-3, etc) when no previous function had yet been discovered.

To mimic human SCA1 disease, transgenic mice containing 82 CAG repeats in *ATXN1* driven by the Purkinje-cell specific *Pcp2* promoter were generated.<sup>45</sup> The cerebellar molecular layer of conditional *ATXN1/Q82* transgenic mice is thinner and Purkinje cells are ectopic and shrunken,<sup>46</sup> probably due to a gain-in-malfunction mutation, because *Atxn1* null mutants display neither Purkinje cell pathology nor ataxia.<sup>47</sup> Unlike natural mutations described above whose ataxia is noticeable during the first three weeks of life, the ataxia seen in *ATXN1/Q82* mice is only evident at 3 months.<sup>46</sup> Nevertheless, the mutants were already impaired on rotorod and stationary beam tests as early as 5 weeks of age, when cytoplasmic vacuoles in Purkinje cells are their main histopathologic feature. At one year of age, *ATXN1/Q82* transgenic mice became

impaired in foot-print analyses. Compared to mutants with 82 CAG repeats, *ATXNI/Q30* transgenic mice with 30 CAG repeats developed overt ataxia at a later onset and a milder form of Purkinje cell degeneration.<sup>48</sup> As seen in *Rora*<sup>sg</sup> mutants,<sup>23</sup> mGluR1-mediated signaling at cerebellar parallel fiber-Purkinje cell synapses was disrupted in *ATXNI/Q82* transgenic mice.<sup>49</sup> Facilitated MGLuR1 signaling after intracerebellar injection of the GABA<sub>B</sub> receptor agonist, baclofen, improved their rotorod performance. Contrariwise, intravermal injection of lentiviral vectors containing *ATXNI/Q76* or *ATXNI/Q30* with green fluorescent protein impaired rotorod performance in wild-type mice. The efficacy of intrathecally injected mesenchymal stem cells was also tested in *ATXNI/Q82* mice.<sup>50</sup> The cells mitigated Purkinje cell ectopias, dendritic thinning, and rotorod deficits, prompting the possible use of this technique in other neurodegenerative conditions.<sup>51</sup> Likewise, the injection of neural precursor cells derived from the subventricular zone into the cerebellar white matter of *ATXNI/Q82* mice recovered Purkinje cell loss and ectopias as well as increasing grip strength and rotorod performance.<sup>52</sup>

Another strategy used to modify the *ATXNI/Q82* phenotype comprises interbreeding with other mutants. Relative to the single transgenic, *ATXNI/Q82* mice crossbred with *Trp53* null mutant mice lacking the p53 protein involved in cell death counteracted Purkinje cell heterotopias and dendritic thinning as well as molecular layer shrinkage, though without affecting rotorod performance or formation of ataxin-1 nuclear inclusions.<sup>53</sup> When *ATXNI/Q82* transgenic mice were crossbred with mice overexpressing the inducible form of rat *Hsp70* encoding a molecular chaperone involved in protein folding, Purkinje cells had thicker and more arborized dendritic branches than the single transgenic but this time rotorod performance improved despite the absence of any change on ataxin-1 aggregates.<sup>54</sup> In contrast, *ATXNI/Q82* transgenic mice bred with *Ube3a* null mutants lacking E6-AP ubiquitin ligase had fewer ataxin-1 aggregates, but the Purkinje cell pathology was worse than the single transgenic, so that aggregates seem to have a

protective role in this case.<sup>55</sup> *ATXNI/Q82* mice were also evaluated on whether RNA interference inhibits polyglutamine-induced neurodegeneration.<sup>56</sup> This time, midline cerebellar injection of recombinant adeno-associated virus vectors expressing short hairpin RNAs resolved ataxin-1 inclusions in Purkinje cells, restored cerebellar molecular thickness, and improved rotarod performance. From two of the models described above,<sup>54,56</sup> different conclusions may be reached in regard to the role of ataxin-1 aggregates on sensorimotor coordination. In one model,<sup>56</sup> resolved ataxin-1 inclusions improved rotarod performance, leading to the conclusion that experimental therapies should aim at reducing the aggregates. But in another model,<sup>54</sup> rotarod performance improved despite the absence of any change in ataxin-1 aggregates, leading to the conclusion that the aggregates are irrelevant in regard to function. These results underline the sensitivity of the rotarod test over a neuropathological marker as a target in evaluating experimental therapies.

An inducible tetracycline-regulated *ATXNI/Q82* mouse model has also been generated with a transgene controlled by the *Pcp2* promoter with similar characteristics, including heterotopic Purkinje cells with cytoplasmic vacuoles and nuclear inclusions as well as reduced Purkinje cell dendritic arborization and lower cerebellar mGluR1 levels combined with rotarod deficits.<sup>57</sup> Halting inducible *ATXNI/Q82* expression with doxycycline in the drinking water reduced cytoplasmic vacuoles and nuclear inclusions and restored Purkinje cell dendritic arborization, cerebellar mGluR1 levels, and rotarod deficits, implicating the Purkinje cell–parallel fiber synapse on motor performance.

Other SCA1 models overexpress mouse not human gene mutations. In particular, *Atxn1/Q154* knockin mice bear 154 CAG repeats of the mouse *Atxn1* locus and express full-length mutant ataxin-1 in its endogenous expression pattern and context, causing a loss in Purkinje cell number and dendritic branching, ataxia, paw-clasping, and rotarod deficits before

the onset of ataxia.<sup>58</sup> In contrast, *Atn1/Q78* knockins had no obvious sign of cerebellar atrophy or ataxia but were still deficient on the rotorod.<sup>59</sup> To establish the role of the mutation, a cerebellar extract was injected from *Atn1/Q154* knockin or wild-type mice into deep cerebellar nuclei of *Atn1/Q78-Q2* knockins.<sup>60</sup> The cerebellar extract from *Atn1/Q154* knockins increased oligomer formation in cerebellum and brainstem of *Atn1/Q78* knockins. As a form of experimental therapy, intraperitoneal injection of *Atn1/Q154* knockin mice with the anti-oligomer antibody, F11G3, reduced oligomers in Purkinje cells and improved rotorod acquisition. In addition, *Atn1/Q154* crossed with a *VEGFA* transgenic line expressing human vascular endothelial growth factor-A increased calbindin staining intensity of Purkinje cells and molecular layer thickness as well as speeding up rotorod acquisition.<sup>61</sup> Moreover, *Atn1/Q154* knockins acquired the rotorod task more quickly after a lithium diet,<sup>62</sup> a manipulation affecting the neurochemistry of the cerebellum at the level of energy metabolism, purines, and unsaturated free fatty acids as well as aromatic- and sulphur-containing amino acids.<sup>63</sup> Mitochondria-targeted antioxidant MitoQ also ameliorated motor coordination in *Atn1/Q154* knockins.<sup>64</sup>

Proteins interacting with ataxin-1 can promote SCA1-related neurodegeneration. In particular, pumilio1 regulates ataxin-1 levels in cells.<sup>65</sup> *Pum1* null mutant mice lacking pumilio1 had higher ataxin-1 levels in cerebellum and cerebrum than wild-type, leading to loss of Purkinje cell number and dendritic arborization. This form of neuropathology likely contributes to delayed acquisition of the rotorod task, the presence of hind-paw claspings, more horizontal but less vertical activity in the open-field, and foot-print anomalies such as a wider stance, shorter stride length, and greater stride frequencies. *Pum1* null mutants crossed with *Atn1/Q154* knockins increased the severity of the loss in Purkinje cell number and dendritic arborization and caused earlier onset of hind-paw claspings and mortality than the single transgenic. Contrariwise,

Purkinje cell loss and dendritic arborization as well as rotorod deficits and paw-clasping in *Pum1* null mutants were mitigated when intercrossed with *ATXN1* null mutants.

We notice from these series of experiments that the rotorod test is the standard most often used to phenotype SCA1 models and assess the possible improvement in motor functions following various forms of experimental therapy, the stationary beam test being used only once.<sup>46</sup> It remains to be determined to what extent the wire suspension test may contribute to phenotype more precisely SCA1 models.

### 3.2 SCA2

Like SCA1, SCA2 is an autosomal dominant disorder with CAG repeat expansions causing a gain-in-malfunction and leading to Purkinje cell degeneration, limb incoordination, and dysarthria.<sup>66,67</sup> Disease occurs whenever CAG repeats rise above 31 in *ATXN2* located on chromosome 12 and encoding ataxin-2. As with the *Atn1* knockout (KO), the *Atn2* mouse KO shows no sign of ataxia, prompting the conclusion that the disease leads to a gain-in-malfunction.<sup>68</sup>

*ATXN2/Q58* mice contain 58 CAG repeats of the transgene driven by the *Pcp2* promoter, leading to Purkinje cell loss, paw-clasping, reduced stride length, and rotorod deficits.<sup>69</sup> The mutants also had longer MTs and more foot-slips than wild-type on the stationary beam.<sup>70</sup> In experimental therapies, *ATXN2/Q58* transgenic mice fed dantrolene, a stabilizer of intracellular calcium signaling, exhibited a lesser degree of Purkinje cell loss as well as faster MTs and fewer foot-slips on the stationary beam. Moreover, adenovirus-mediated expression of inositol 1,4,5-phosphatase into deep cerebellar nuclei alleviated electrophysiological anomalies in Purkinje cells as well as accelerating MTs and reducing foot-slips on the stationary beam and increasing latencies before falling from the rotorod.<sup>71</sup> These results indicate that inhibiting enzyme-mediated calcium signals may provide therapeutic benefits in patients. Purkinje cell loss and rotorod

impairment were also alleviated after intraventricular transplantation of human mesenchymal stem cells.<sup>72</sup>

A second SCA2 transgenic murine model expresses the full-length human *ATXN2* gene with 75 CAG repeats controlled by the self *Atnx2* promoter.<sup>73</sup> *ATXN2/Q75* transgenic mouse brains contain Purkinje cell body shrinkage and loss of dendritic arborization and the mice have rotorod deficits. A third transgenic model with a longer expansion, *ATXN2/Q127*, was generated under control of the *Pcp2* promoter.<sup>74</sup> *ATXN2/Q127* mutants have cytoplasmic ataxin-2-containing insoluble aggregates in Purkinje cells, Purkinje cell loss, thinning of the cerebellar molecular layer, and rotorod deficits.

A fourth model, the *ATXN2/Q72-BAC* transgenic mouse, was generated with 72 CAG repeats of the human *ATXN2* gene controlled by the endogenous promoter on bacterial artificial chromosomes (BAC).<sup>75</sup> *ATXN2/Q72-BAC* transgenic mice had smaller dendritic arborization and rotorod deficits. A knockin model of SCA2 disease was generated by homologous recombination of embryonic stem cells to replace the endogenous *Atnx2* gene with a mutagenized mouse version containing 42 CAG repeats driven by the *Atnx2* promoter.<sup>76</sup> *Atnx2/Q42* knockins had cytoplasmic ataxin-2-containing aggregates and rotorod deficits, though without displaying overt ataxia or any change in foot-print analyses, grip strength, or open-field activity. Thus, the rotorod deficit seen in *Atnx2/Q42* knockins precedes overt ataxia, as reported in *ATXN1/Q82* mice<sup>46</sup> described above. And so the rotorod and perhaps other motor tests may be used in experimental therapies of SCA2 mutants before dysfunction appears under the naked eye.

### 3.3 SCA3

Like SCA1 and SCA2, SCA3, also called Machado-Joseph disease, is due to a polyglutamine expansion, this time an expansion of over 45 CAG repeats in *ATXN3* located on chromosome 14 and encoding ataxin-3.<sup>77-79</sup> SCA3 causes prominent cerebellar signs such as gait

ataxia, dysmetria, and dysarthria, along with parkinsonian signs<sup>80</sup> resulting from lesions in cerebellum, pontine nuclei, and substantia nigra pars compacta.<sup>81</sup> Ataxin-3 binds to the type 1 inositol 1,4,5-trisphosphate receptor, the intracellular calcium release channel.<sup>82</sup>

Several SCA3 mouse models are available,<sup>83</sup> one of which featuring *ATXN3/Q69* transgenic mice expressing the mutant gene driven by the *Pcp2* promoter.<sup>84</sup> *ATXN3/Q69* mice showed Purkinje cell ectopias and thinner dendrite branching along with overt ataxia and delayed rotorod acquisition, probably due to a gain-in-malfunction mutation, because *Atxn3* null mutants display neither Purkinje cell pathology nor ataxia.<sup>85</sup> Purkinje cell ectopias and rotorod performance ameliorated in *ATXN3/Q69* mice after midline cerebellar injection of lentiviral vectors expressing wild-type *CRMP1* (collapsin response mediator protein, CRAG), which degrades polyglutamine proteins via the ubiquitin–proteasome pathway.<sup>84</sup> In addition, integrase-defective lentiviral vectors injected into the cerebellum decreased ataxin-3 aggregates and improved rotorod performance.<sup>86</sup> Moreover, *ATXN3/Q69* mice had fewer nuclear inclusions and higher cerebellar calbindin immunoreactivity along with thicker molecular and granular layers as well as higher latencies before falling off the rotorod, larger stride length in foot-print analyses, and higher horizontal activity in the open-field after intracerebellar injection of lentiviral vectors of short-hairpin RNAs encoding allele-specific silencing sequences.<sup>87</sup>

A second SCA3 model employs the *ATXN3/Q71* transgene driven by the murine *Prp* promoter, exhibiting ataxin-3 nuclear inclusions and substantia nigra pars compacta cell loss combined with ataxia, tremors, seizures, foot-print anomalies, grip strength weakness, open-field hypoactivity, and rotorod deficits.<sup>88</sup> A third SCA3 transgenic model, *ATXN3/Q79-Pcp2*, expresses truncated ataxin-3 with an expanded polyglutamine stretch driven by the *Pcp2* promoter.<sup>89</sup> *ATXN3/Q79-Pcp2* mice have Purkinje cell loss and overt ataxia. A fourth model with the same number of repeats, *ATXN3/Q79-Prp*, was generated with a transgene driven by the

murine *Prp* promoter.<sup>90</sup> *ATXN3/Q79-Prp* transgenic mice display mutated ataxin-3 nuclear inclusions in dentate, pontine, and nigral nuclei, an ataxic gait, forelimb claspings, open-field hypoactivity, and rotorod deficits. The fact that mutated ataxin-3 directly causes cell death is shown by findings in cultured cerebellar and nigral neurons.<sup>91</sup> In these *ATXN3/Q79-Prp* transgenic mice, intraperitoneal injection of H1152, an inhibitor of rho-kinase (ROCK), decreased ataxin-3 protein concentrations at cerebellar, pontine, and neocortical sites as well as pontine cell death while counteracting open-field hypoactivity and rotorod deficits.<sup>92</sup> Likewise, foot-print analyses of gait, open-field hypoactivity, and rotorod deficits improved after intraperitoneal injection of sodium butyrate, an inhibitor of histone deacetylase, an effect that reverses transcriptional downregulation.<sup>93</sup> Moreover, pontine nuclei degeneration and rotorod deficits were mitigated after oral administration of an adenosine A2A receptor agonist, T1-11 [N6-(4-Hydroxybenzyl) adenosine], extracted from *Gastordia elata*, a Chinese medicinal herb, or its synthetic analog, JMF1907 [N6-(3-Indolylethyl) adenosine].<sup>94</sup>

An *ATXN3* transgene with a longer Q94 expansion driven by the *CMV* promoter exhibited mutant ataxin-3 inclusions and shrunken cells in cerebellum, pons, and substantia nigra combined with open-field hypoactivity and deficits on rotorod but not vertical pole or foot-print assays.<sup>95</sup> Thus, the *ATXN3/Q94* transgenic resembles the *Atn2/Q42* knockin<sup>76</sup> and *ATXN1/Q82* transgenic<sup>46</sup> which display rotorod deficits with no overt ataxia or anomalies in foot-print analyses.

Polyglutamate repeats were further expanded with the *ATXN3/Q135* transgene also regulated by the *CMV* promoter.<sup>96</sup> *ATXN3/Q135* mutants have ataxin-3 nuclear inclusions, lower dentate nucleus volume and pontine nucleus number, as well as substantia nigra gliosis, causing ataxia, hindlimb claspings, tremor, shorter stride length, weaker grip strength, higher latencies before traversing the stationary beam, and lower latencies before falling off the hanging wire or

rotorod. Pontine cell number and ataxin-3 nuclear inclusions as well as stationary beam and rotorod performance improved after intraperitoneal injections of 17-DMAG, inhibitor of Hsp90, a heat shock protein.

Unlike wild-type mice where ataxin-3 is present in the cytoplasm, *ATXN3/Q70* and *ATXN3/Q148-Prp* transgenes controlled by the murine *Prp* promoter result in brain tissue containing ubiquitin- and ataxin-3-positive nuclear inclusions.<sup>97,98</sup> The *ATXN3/Q70* model showed shrunken Purkinje cell bodies and limb-clasping; both models displayed overt ataxia and tremor.<sup>97</sup> A similar *ATXN3/Q148-Hd* transgene driven by the rat *Hd* promoter was generated, exhibiting ataxin-3-positive nuclear inclusions in Purkinje and pontine cells along with rotorod deficits.<sup>99</sup> They also showed home-cage hyperactivity at a young age but yet home-cage hypoactivity at an older age.

*Atxn3/Q82* knockin mice were generated by introducing the murine gene with 82 polyglutamine repeats at the mouse locus, accumulating mutant ataxin-3 nuclear inclusions in Purkinje cells, pons, and substantia nigra.<sup>100</sup> However, 1-year old knockin mice did not differ from wild-type on stationary beam, rotorod, or open-field tests. In contrast, *ATXN3/Q91* knockin mice generated by introducing the human gene with 91 polyglutamine repeats at the mouse locus exhibited astrogliosis in cerebellum and substantia nigra, Purkinje cell loss, and rotorod deficits.<sup>101</sup>

Inducible double *ATXN3/Q77* transgenic mice were generated by applying the tetracycline-off system under control of the hamster *Prp* promoter, causing nuclear inclusions, a thinner molecular layer and smaller Purkinje cells, home-cage hyperactivity, limb-clasping, smaller steps in foot-print analyses, and rotorod deficits.<sup>102</sup> The prion protein promoter drives the expression of a fusion protein tTA (tetracycline transactivator) consisting of the tetracycline repressor (TetR) and a transcription activation domain (AD) in the promoter construct. In the

absence of tetracycline, the tTA protein can bind to the tetracycline responsive element (TRE) of a *CMV* minimal promoter in the responder construct, which activates *ATXN3* transcription. When tetracycline (Tc) or one of its derivatives such as doxycycline binds to tTA and abolishes the binding of tTA to the responder construct, *ATXN3* transcription is blocked. Crossbreeding the *PrP* promoter line with *ATXN3* responder mouse lines yielded double transgenic mice. In responder line 2904 with 77 CAG repeats, nuclear aggregates staining positive for ataxin-3 formed along with a thinner molecular layer and smaller Purkinje cells. The rotorod deficits were reversed by doxycycline. To improve behavior with a n-methyl-d-aspartate (NMDA) glutamate receptor antagonist in *ATXN3/Q77* mice, riluzole was dissolved in drinking water, which reduced soluble ataxin-3 levels but also calbindin expression in Purkinje cells and increased ataxin-3 positive accumulations without affecting home-cage hyperactivity and even worsened rotorod performance.<sup>103</sup>

Three more SCA3-related models exist, this time with yeast artificial chromosomes (YACs), namely *ATXN3/YAC-Q84*, *ATXN3/YAC-Q67* and *ATXN3/YAC-Q15* transgenes under control of endogenous elements.<sup>104</sup> Unlike the expanded (CAG)84 allele, the expanded (CAG)76 allele contracted to 64, 67, and 72 repeats in the original 76 repeats. *ATXN3/YAC-Q84* and *ATXN3/YAC-Q67*, but not *ATXN3/YAC-Q15* transgenic mice, exhibited cell loss in pons and dentate nuclei with a wide-spread gait, fore- and hind-limb clasping, and tremor. A second report in *ATXN3/YAC-Q84* transgenics revealed fewer than normal neuronal counts in pontine and substantia nigra, higher MTs and foot-slips on the stationary beam and shorter stride length on foot-print patterns.<sup>82</sup> *ATXN3/YAC-Q84* transgenic mice fed dantrolene had faster MTs and fewer foot-slips on the stationary beam and elevated stride length on foot-print patterns. Moreover, *ATXN3/YAC-Q84* mice had restored Purkinje cell firing and faster MTs on the stationary beam after intraperitoneal injection of an activator of potassium channels, SKA-31.<sup>105</sup> Likewise, ataxin-

3 nuclear accumulation was mitigated in *ATXN3*/YAC-Q84 mice by artificial microRNA mimics targeting the 3'-untranslated region of *ATXN3*.<sup>106</sup>

That mutant *ATXN3* can directly affect normal mice is indicated by findings that injected lentiviral vectors encoding full-length human mutant *ATXN3* into the mouse cerebellum of C57/BL6 mice causes intranuclear inclusions, neuropathological abnormalities, and neuronal death along with motor coordination deficits, a wide-based gait, and hyperactivity.<sup>107</sup> As in a SCA1 model described above,<sup>46</sup> decreased ataxin-3 aggregates or concentrations occurred in conjunction with improved rotorod performance in four experimental therapies of three SCA3 models.<sup>86,87,92,96</sup> The reverse pattern was found in another model, when more ataxin-3 aggregates led to poorer rotorod performance.<sup>103</sup> Thus, ataxin-3 aggregates appear relevant in the context of improving motor functions in SCA3 models.

### 3.4 SCA5

SCA5 consists in autosomal dominant in-frame deletions and missense mutations in *SPTBN2* located on chromosome 11 and encoding beta-III spectrin, involved in membrane protein adhesion in cytoplasm, a gene highly expressed in Purkinje cells.<sup>108-110</sup> The mutation-linked cerebellar cortical atrophy causes ataxia and dysarthria. SCA5 appears to result from a loss-of-function mutation in view of the ataxia of targeted null mutations of *Sptbn2*. One *Sptbn2* KO murine model exhibited Purkinje cell loss accompanied by wider hindlimb gait, tremor, increased foot-slips on the stationary beam, and decreased latencies before falling off the rotorod, though not off the suspended wire, the latter test being more dependent on muscle strength.<sup>111</sup> A second *Sptbn2* KO model exhibited a thinner than normal cerebellar molecular layer, shrunken Purkinje cells, ataxia, and myoclonic seizures as well as wire-suspension and rotorod deficits.<sup>112</sup>

Tet-response element (TRE) and *CMV* promoter were cloned with *SPTBN2* cDNA and the resulting mutants bred to tetracycline transactivator (tTA)/*Pcp2* transgenic mice to generate

conditional bigenics expressing recombinant transgenes specifically in Purkinje cells.<sup>113</sup> Conditional and inducible *SPTBN2*/double transgenics with a deletion mutation are characterized by a thinner molecular layer of the cerebellar cortex, overt ataxia, and rotorod deficits. The mutants also exhibited reduced mGluR1-alpha localization at Purkinje cell dendritic spines and decreased mGluR1-mediated responses, an indication that beta-III spectrin stabilizes mGluR1 at the cell membrane.

### 3.5 SCA6

SCA6 is another CAG expansion disease, this time caused by mutations of *CACNA1A* located on chromosome 19 and encoding the P/Q-type voltage-gated alpha-1A subunit of a calcium channel,<sup>114-115</sup> causing a cerebellar syndrome marked by postural ataxia as well as limb and ocular dysmetria.<sup>115</sup> Exon 47 undergoes alternative splicing, leading to C-terminal isoforms containing either exon 47 alone or with polyglutamate repeats.<sup>116</sup> Human C-terminal fragments ending at exon 46 (CT-short) or exon 47 (CT-long) ending with 27 polyglutamine residues were expressed in transgenic mice with *CMV* and *ACTB* promoters.<sup>117</sup> Both models had Purkinje cell loss but onset was more precocious in *CACNA1A/Q27* mice than *CACNA1A/CT-short* mice. *CACNA1A/Q27* mice were deficient on stationary beam, inclined screen, and rotorod tests, whereas *CACNA1A/CT-short* mice were deficient only on the rotorod. Thus, the use of multiple tests helps delineate a more precise phenotype for two mutants of the same gene.

The C terminus of the alpha-1A subunit (alpha-1ACT) is a transcription factor that enhances expression of several Purkinje cell-expressed genes and partially rescued the phenotype of *Cacna1a* null mutants, whose electrophysiological properties resembled *leaner* and *tottering* spontaneous *Cacna1a* mutants.<sup>118</sup> The alpha1-ACT fragment was expressed via the *Pcp2* promoter and Tet-off system yielding *Pcp2-tTA/TRE-alpha1-ACT* mutants bred with

*CACNA1A/Q33* mice expressing 33 CAG repeats to generate double transgenic mice. *CACNA1A/Q33* mutants have molecular layer thinning in cerebellum and gait disturbances.

*Cacna1a/Q84* knockin mice were generated by introducing the mouse gene with 84 polyglutamine repeats at the mouse locus, causing cytoplasmic inclusions in Purkinje cells and rotorod deficits.<sup>119</sup> *Cacna1a/Q84* knockins also displayed Purkinje cell axon anomalies in the form of torpedoes as found in SCA6 patients.<sup>120</sup> *Cacna1a/Q84* knockin mice exhibited late-onset loss of Purkinje cell number but early-onset increase in foot-slips on the stationary beam and decreased latencies before falling off the rotorod despite the absence of any change in stride length or stance width.<sup>121</sup> As described in some SCA1, SCA2, and SCA3 mutants, *Cacna1a/Q84* knockins displayed rotorod deficits prior to changes in foot-prints. Moreover, the same pattern was found for the first time with the stationary beam. Anomalies in Purkinje cell firing rate were discernable as early as the second postnatal week.<sup>122</sup> A model with longer repeats, *Cacna1a/Q118* knockin mice, exhibited cytoplasmic inclusions in Purkinje cells, reduced Purkinje cell number and dendritic branching, short-stepped walking, and rotorod deficits, all of which being absent in a knockin with fewer repeats: *Cacna1a/Q11*.<sup>123</sup>

### 3.6 SCA7

Like SCA types 1, 2, and 3, SCA7 is an autosomal dominant disorder caused by CAG trinucleotide repeats, this time concerning *ATXN7* located on chromosome 3 and encoding ataxin-7.<sup>124-127</sup> Despite widespread distribution of ataxin-7, neurodegeneration mainly occurs in cerebellum, inferior olive, pons, and retinal photoreceptors. In one large cohort of patients, glutamine repeats ranged between 37 and 130, causing ataxia, dysmetria, dysarthria, blindness, and ophthalmoplegia as the principal clinical signs.<sup>125</sup> CAG repeat size was inversely correlated with disease onset, determining 71% of its variability. In patients with equivalent disease durations, CAG repeats were longer in those with blindness, ophthalmoplegia, and extensor

plantar reflexes. Ataxin-7 neurodegeneration appears to involve the two main protein degradation pathways in mammalian cells: the ubiquitin–proteasome system and autophagy.<sup>128</sup>

The *ATXN7/Q52* transgene driven by the *PDGFB* (platelet-derived growth factor beta-chain) promoter was generated in mice.<sup>129</sup> *ATXN7/Q52* mice displayed shrunken Purkinje cells with ataxin-7 nuclear inclusions and reduced dendritic arborization combined with overt ataxia, hindpaw clasping, open-field hypoactivity, and rotorod deficits.

Two longer CAG expansions have been generated, *ATXN7/Q92* transgenes expressed under control of either hamster *Pcp2* or human *RHO* (rhodopsin) promoters to affect either Purkinje cells or photoreceptors but accumulating ataxin-7 immunoreactive aggregates in each respective cell type.<sup>130</sup> *ATXN7/Q92-Pcp2* transgenic mice exhibited reduced Purkinje dendrite arborization without ectopias and rotorod deficits without overt ataxia. Another transgenic line expresses the same number of repeats but only in Bergmann glia of the cerebellum via the *Gfa2* promoter.<sup>131</sup> *ATXN7/Q92-Gfa2* mice developed Purkinje cell misalignment and dendrite thinning, ataxia, paw-clasping, and rotorod deficits, implicating glial dysfunction in polyglutamine-mediated ataxia. Another murine model with 92 CAG repeats, this time driven by the *Prp* promoter was generated, *ATXN7/Q92-Prp*, expressing polyglutamine-expanded ataxin-7 throughout the CNS except in Purkinje cells.<sup>132</sup> Nevertheless, *ATXN7/Q92-Prp* developed shrunken Purkinje cells with diminished dendritic branches and rotorod deficits, indicating non-cell autonomous cell degeneration in SCA7 pathogenesis. The accumulation of ataxin-7 immunoreactive neurons was observed in two other lines expressing 10 or 128 CAG repeats (*ATXN7/Q10* or *ATXN7/Q128*) generated with the *PDGFB* promoter, the latter line exhibiting ataxia.<sup>133</sup>

There also exists an *ATXN7/BAC-Q92* murine model spatially and temporally regulated with cDNA flanked by loxP sites at the start site of translation in murine *PrP* of a bacterial

artificial chromosome.<sup>134-136</sup> *ATXN7/BAC-Q92* mice displayed Purkinje cell loss, molecular layer thinning, paw-clasping, and rotorod deficits<sup>134,135</sup> The rotorod deficits were reversed by polyglutamine ataxin-7 excision when the single transgenic was transformed into a triple transgenic carrying additional *Pcp2-Cre* and *Gfa2-Cre* transgenes.<sup>134</sup> Polyglutamine ataxin-7 excision and reversal of rotorod deficits also occurred after interbreeding *ATXN7/BAC-Q92* mice with those expressing tamoxifen-inducible Cre recombinase and administered per os tamoxifen after the onset of motor abnormalities and neuropathology.<sup>136</sup> In addition, cerebellar nuclei injection of recombinant adeno-associated virus vectors expressing interfering RNAs reduced nuclear inclusions in the cerebellum, thickened the cerebellar molecular layer, improved rotorod performance, and mitigated paw-clasping responses in *ATXN7/BAC-Q92* mutants.<sup>135</sup>

*Atxn7/Q266* knockin mice contain 266 CAG repeats into the murine *Atxn7* locus with homologous recombination of embryonic stem cells. The resulting mice showed Purkinje cell shrinkage and ataxin-7 aggregates and photoreceptor degeneration combined with ataxia, tremors, myoclonic seizures, and rotorod deficits.<sup>137</sup> Purkinje cell shrinkage, low expression of cerebellar glutamate transporters, and rotorod deficits in *Atxn7/Q266* knockin mice were attenuated after intercrossing with mice expressing *HGF*, that encodes hepatocyte growth factor driven by the *NSE* (neuron-specific enolase) promoter, the growth factor being normally expressed in Purkinje and granule cells.<sup>138</sup> Moreover, *Atxn7/Q266* knockin mice improved after intraperitoneal injection of interferon-beta regarding ataxin-7 nuclear inclusions as well as stationary beam and horizontal ladder tests.<sup>139</sup> Thus, two sensorimotor tests were sensitive to a treatment in conjunction with mitigation of nuclear inclusions in a SCA7 model, as shown for the rotorod in SCA1 and SCA3 models.

In a viral-mediated model, lentiviral vectors express *ATXN7* fragments in the mouse vermis.<sup>140</sup> Two months after injection, mutant *ATXN7/Q100* but not wild-type *ATXN7* driven by

the *PGKI* (phosphoglycerate kinase-1) promoter caused nuclear ataxin-7 aggregates in cerebellum, shrinkage of granule and molecular layers near the injection site, open-field hypoactivity, missteps on the horizontal ladder, and rotorod deficits reminiscent of the transgene approach.

### 3.7 SCA8

Unlike the polyglutamine-related SCAs described above, SCA8 pathogenesis involves a poly-leucine CTG expansion in *ATXN8* located on chromosome 13 and encoding ataxin-8.<sup>141</sup> SCA8 results in ataxia, dysmetria, and nystagmus.<sup>142,143</sup>

Although several lines of evidence implicate a gain-in-malfunction,<sup>144</sup> *Atxn8* null mutants limited to Purkinje cells exhibited a thinner cerebellar molecular layer and rotorod deficits.<sup>145</sup> The authors hypothesize that the human disease leads to a gain-in-malfunction in some areas but a loss in function of *ATXN8* in Purkinje cells. Another SCA8 mouse model was generated in which full-length human *ATXN8* with 116 CAG repeats was transcribed via its endogenous promoter. *ATXN8/Q116* transgenic mice developed nuclear inclusions in Purkinje and basal pontine neurons, a loss in cerebellar molecular layer inhibition, and rotorod deficits.<sup>146</sup>

### 3.8 SCA10

SCA10 pathogenesis is caused by autosomal dominant transmission of an intronic ATTCT pentanucleide repeat in *ATNX10* located on chromosome 22 and encoding ataxin-10.<sup>147,148</sup> The gain-in-malfunction leads to ataxia, intention tremor, dysmetria, dysarthria, nystagmus, and seizures.<sup>149-151</sup>

McFarland and Ashizawa<sup>152</sup> reviewed the two existing mouse models of SCA10 (Table 3). A model containing the *ATNX10* transgene with 500 ATTCT repeats driven by the rat *Eno2* (neuronal enolase) promoter suffered from reproductive unfitness.<sup>153</sup> A second transgenic model containing the *ATNX10* transgene with 500 ATTCT repeats driven by the rat *Prp* promoter was

fit for reproduction and showed pontine (though no cerebellar) neuropathology, ataxia, hindlimb claspings, seizures, open-field hypoactivity, and shorter steps as well as greater variability in step width on foot-print analyses but normal rotorod testing.<sup>154</sup> This constitutes the reverse pattern of SCA1, SCA2, SC3, SCA6, and SCA7 models when anomalies of rotorod testing occurred in non-ataxic mice. It would be most useful to test this SCA10 model in other sensorimotor tests to gauge the sensitivity of these tests relative to the rotorod, often appearing as the standard in cerebellar models.

### 3.9 SCA13

SCA13 is caused by dominant-negative missense mutations in *KCNC3* located on chromosome 19 and encoding Kv3.3, a potassium voltage-gated channel of the Kv3 subfamily.<sup>155</sup> SCA13 may be of childhood- or adult-onset characterized by ataxia, dysarthria, and seizures.<sup>156</sup> The F363L mutation in *Kcnc3* of zebrafish, corresponding to human infant-onset F448L, caused axonal path-finding errors in primary motor neurons.<sup>157</sup> Lentiviral expression of *Kcnc3* harboring the R424H missense mutation slowed down dendritic development and caused death of murine cultured Purkinje cells.<sup>158</sup>

Null mutant mice lacking *Kcnc3* had increased lateral deviation and foot-slips on the stationary beam.<sup>159-161</sup> The motor deficits were mitigated after selective restoration of Kv3.3 channels in Purkinje cells.<sup>161</sup>

### 3.10 SCA14

SCA14 is caused by autosomal dominant-negative missense mutations in *PRKCG* located on chromosome 19 and encoding the gamma isoform of protein kinase C (PKC-gamma).<sup>162,163</sup> SCA14 is characterized by cerebellar ataxia, dysarthria, and nystagmus.<sup>164</sup>

The *PRKCG* transgene with the dominant-negative H101Y mutation driven by the *CMV* promoter yields mice with lower cerebellar PKC activity and Purkinje cell loss, a possible cause

of their paw-clasping responses.<sup>165</sup> In another model, viral vectors containing the *PRKCG*-Green fluorescent protein transgene with the dominant-negative S119P mutation were injected into developing cerebellum, forming mutant aggregates in Purkinje cells and climbing fiber poly-innervation of Purkinje cells.<sup>166</sup> The first vector expresses tetracycline (tet) transactivator (tTA) under control of the *Pcp2* promoter. The second set of vectors express respective genes driven by a tet-responsive promoter transactivated by tTA. Because mutant PKC-gamma colocalized with wild-type PKC-gamma, the mutation probably acts in a dominant-negative manner on wild-type PKC. Despite normal locomotion in their home-cage, one-week-old but not 1-month old *PRKCG/S119P* mutants had rotorod deficits.

### 3.11 SCA15

SCA15 is due to autosomal dominant deletions of *ITPR1* located on chromosome 3 and encoding inositol 1,4,5-triphosphate receptor 1, permitting calcium release from intracellular stores.<sup>167-169</sup> SCA15 causes a relatively pure cerebellar syndrome particularly affecting the vermis and marked by ataxia, intention tremor, and nystagmus.<sup>170,171</sup>

A targeted *Itpr1* null mutation led to ataxia and tonic or tonic-clonic seizures.<sup>172</sup> In addition, two spontaneous murine mutants with *Itpr1* deletions have been discovered. The *opisthotonos* (*opt*) mouse is characterized by low inositol 1,4,5-trisphosphate receptor 1 levels, abnormal calcium responses in Purkinje cells, ataxia, and convulsions.<sup>173</sup> A second spontaneous deletion of *Itpr1* also decreases inositol 1,4,5-triphosphate receptor 1 levels in Purkinje cells and causes ataxia.<sup>168</sup>

### 3.12 SCA17

SCA17 is an autosomal dominant disorder caused by over 43 CAG repeats in *TBP* located on chromosome 6 and encoding the TATA-binding protein, a transcription factor for many

genes.<sup>174,175</sup> SCA17 is characterized by ataxia, nystagmus, dystonia, and, unlike other SCA diseases, prominent neuropsychiatric signs and dementia.<sup>176</sup>

SCA17 murine models were reviewed.<sup>177</sup> Mice were generated with the *TBP/Q* transgene containing 109 or 69 CAG repeats driven by the *Pcp2* promoter.<sup>178</sup> *TBP/Q109* transgenic mice sustained losses in Purkinje cells and brainstem but also basal ganglia and neocortex, leading to gait anomalies on foot-print analyses, paw-clasping, open-field hyperactivity, and rotorod deficits. Mutated TBP aggregates were colocalized in Purkinje cells with ubiquitin and heat shock chaperone Hsc70. Purkinje cell loss, open-field hyperactivity, and rotorod deficits were mitigated by subcutaneous injection of granulocyte-colony stimulating factor to mobilize blood progenitor cells, its receptor being expressed on Purkinje cells.<sup>178,179</sup> Likewise, Purkinje cell misalignment and rotorod deficits were mitigated by intraperitoneal injection of an extract from the leaves of *Ginkgo biloba*, EGb 761.<sup>180</sup>

Inducible *TBP/Q105* knockin mice were generated by replacing exon 2 of the murine *Tbp* gene with exon 2 of human *TBP* carrying 105 CAGs.<sup>181</sup> The stop codon is flanked by two loxP sites as a targeting vector. The floxed mice were crossed with those carrying a rat *Nes* (nestin) promoter-driven Cre transgene and the stop codon removed via Cre-loxP recombination, resulting in knockin mice which express mutant and normal *TBP* under the influence of the endogenous promoter. *TBP/Q105* knockins exhibited nuclear aggregates in Purkinje cells, Purkinje cell loss, home-cage hypoactivity, and rotorod deficits. To induce the expression of mutated mice at different ages, floxed heterozygous *TBP/Q105* knockin mice were crossed with CreER transgenic mice expressing a fusion protein of Cre recombinase with an estrogen receptor ligand binding site driven by the chicken *Actb* ( $\beta$ -actin) promoter. The intraperitoneal injection of tamoxifen, an estrogen receptor ligand, binds the Cre recombinase fusion protein and makes it enter the nucleus to act on loxP sites, removing the stop codon.<sup>182</sup> Tamoxifen-inducible

*TBP/Q105* knockin mice exhibited Purkinje cell loss, reduced stride length on foot-print patterns, paw-clasping, slower MTs on the stationary beam, and rotorod deficits. The Purkinje cell loss was mitigated by intracerebellar injection of lentiviral vectors expressing mesencephalic astrocyte-derived neurotrophic factor (MANF) or after interbreeding with *MANF* transgenic mice, the latter method also improving stationary beam, paw-clasping, and foot-print anomalies.

In addition to murine models, a rat model of SCA17 is available with 64 CAA/CAG repeats driven by the murine *Prp* promoter.<sup>183</sup> *TBP/Q64* transgenic rats displayed nuclear aggregates in granule, Purkinje, and stellate cells, Purkinje cell loss, paw-clasping, and more foot-slips than wild-type on the stationary beam but no effect on rotorod acquisition. This result points again to the usefulness of the stationary beam as a test to be used in conjunction with the rotorod. Relative to wild-type, they also showed home-cage hyperactivity at a young age and hypoactivity at an older age, but with decreased rearing throughout.

### 3.13 SCA27

SCA27 is an autosomal dominant-negative disorder caused by mutations in *FGF14* located on chromosome 14 and encoding fibroblast growth factor 14, an accessory subunit of voltage-gated sodium channels.<sup>184-186</sup> SCA27 causes a combination of cerebellar and basal ganglia symptoms including ataxia, dysarthria, nystagmus, tremors, and dyskinesia.<sup>187</sup> In normal mice, *Fgf14* transcripts are expressed in cerebellar granule and dorsal striatal cells.<sup>188</sup>

In the cerebellar slice preparation of *Fgf14* null mutants, AMPA receptor-mediated excitatory postsynaptic currents evoked by parallel fiber stimulation were lower than those of wild-type.<sup>188</sup> *Fgf14* null mutant mice exhibited overt ataxia, dyskinesia, paw-clasping, reduced grip strength, open-field hyperactivity, and slowed MT before reaching the top of an inclined screen as well as shortened latencies before falling from an inverted screen or rotorod.<sup>189,190</sup> The

dyskinesia appears in the form of paroxysmal forelimb clonic spasms with hyperextended hindlimbs.

### 3.14 SCA28

SCA28 is an autosomal dominant-negative disorder caused by mutations in *AFG3L2* located on chromosome 18 and encoding part of the mitochondrial ATPase-associated protease superfamily.<sup>191,192</sup> The neuropathology comprises a loss in cerebellar and brainstem volumes along with extraocular muscle atrophy.<sup>193</sup> SCA28 is characterized by ataxia, dysarthria, nystagmus, and ophthalmoparesis.<sup>194</sup>

Homozygous *Afg3l2* null mutant mice die on the second postnatal week. In heterozygous *Afg3l2* null mutants, ATP synthesis in brain is defective due to insufficient assembly of respiratory complexes I and III.<sup>195</sup> *Afg3l2* haploinsufficiency led to granule and Purkinje cell loss, an impaired negative geotaxic response (turning upward on an inclined grid), limb-clasping, more foot-slips than normal on the stationary beam, and rotorod deficits.<sup>196</sup> Purkinje cell degeneration and foot-slips diminished after interbreeding *Afg3l2* haploinsufficient mice with *Grm1* haploinsufficient mice lacking mGluR1, which prevents high calcium influx into Purkinje cells.<sup>197</sup>

### 3.15 Concluding remarks

The present overview on SCA models illustrates the methodology used by researchers to determine behavioral phenotypes of cerebellar dysfunction. The cerebellum is intrinsically linked to ataxia and deficits in motor coordination since the 1917 paper by Holmes, who described the consequences of human gunshot wounds.<sup>198</sup> The main function of the cerebellum is to integrate sensory input with motor output, to modulate movements, not cause them, so that lesions of this area cause neither sensory deficit (hypoesthesia, blindness, or deafness) nor paralysis.

Spontaneous cerebellar mutants are featured prominently in the “Catalog of the neurological mutants of the mouse”, a 1965 monograph by Sidman et al,<sup>199</sup> because a new cerebellar mutation is all the easier to detect in a cage, even by uninformed laboratory personnel, as a result of the obvious lurching and swaying mice, in contrast to other neurologic signs that might go undetected or are even undetectable on casual viewing. Moreover, many mutations affecting the cerebellum are embryologically non-lethal and the mutant is not generally attacked by the non-mutant in their home cage. In a laboratory maximizing animal protection, the mutation permits a relatively long life span and the possibility of analyzing behavior from early development to old age. We pointed out the use of limb clasping<sup>200</sup> and myoclonic jumping<sup>201</sup> as additional features in phenotyping neurologic mutants, including those affecting the cerebellum. In addition to qualitative observations of mutants, the need arose to provide quantified measurements of motor coordination, among which the rotorod gained prominence after the original 1962 paper by Plotnikoff et al<sup>202</sup> and the 1968 paper by Jones and Roberts.<sup>203</sup>

As shown in the present review, the rotorod is the most common sensorimotor test used to evaluate SCA models. Indeed, rotorod deficits were reported in 10 SCA models, namely SCA1 to 3, SCA5 to 8, SCA14, SCA17, and SCA27. Stationary beam deficits were described in 8 SCA models, namely SCA1 to 3, SCA5, SCA6, SCA13, SCA17, and SCA27, but wire suspension deficits in only SCA3 and SCA5. SCA1, SCA2, SCA3, SCA6, SCA7, and SCA14 models showed rotorod defects without overt ataxia or anomalous foot-print patterns. The reverse pattern of abnormal foot-print patterns and normal rotorod performance was found only in a SCA10 model. Moreover, a SCA6 model without ataxia was deficient on the stationary beam and a SCA17 model was deficient on the stationary beam but not on the rotorod, which should promote the use of the stationary beam as a test to be used in conjunction with the rotorod.

The rotorod task may be less time-consuming than other tasks in that ataxic mice are more likely to fall early, whereas early falls sometimes occur only from the narrowest stationary beam, which may cause mutants to wrap their limbs around it to prevent a fall. In the latter case, MT and distance travelled may be used as additional measures. The limb-wrapping strategy also occurs on the suspended wire, so that MT can be added on the coat-hanger version of the test. Passive rotation on the rotorod can be counteracted by removing mice from the apparatus as soon as the behavior appears and considering it akin to a fall.<sup>42</sup> All three tests are complimented by foot-print analyses to document the existence of an ataxic gait.

The question arises as to what extent stationary beam, suspended wire, and rotorod tests are selective for a cerebellar lesion relative to lesions elsewhere in the brain. The answer is that rotorod deficits have been reported after selective lesions of cerebellar afferent or efferent regions such as the inferior olive<sup>204</sup> and ventrolateral thalamus,<sup>205</sup> respectively, but also parts of the basal ganglia such as the substantia nigra pars compacta<sup>206</sup> or lateral pallidum.<sup>207</sup> Likewise, cerebellar<sup>208,209</sup> or dorsostriatal<sup>210</sup> lesions impair stationary beam performance, though the suspended wire has been less extensively investigated.<sup>211</sup> Therefore, current sensorimotor tests dependent on postural control seem meant to detect a central nervous system deficit rather than a specifically cerebellar-related one.

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**Table 1** Neurobehavioral characteristics of natural mouse mutations with cerebellar atrophy

Mutant	Chromosome	Neuropathology	Motor test	Genetic reference
<i>Grid2<sup>lc</sup></i>	6	Purkinje cell loss	↓ stationary beam coat-hanger rotorod	Caddy and Biscoe <sup>6</sup>
<i>Grid2<sup>ho</sup></i>	6	granule cell loss	↓ stationary beam coat-hanger rotorod	Guastavino et al <sup>10</sup>
<i>Rora<sup>sg</sup></i>	9	Purkinje cell loss	↓ stationary beam coat-hanger rotorod	Herrup and Mullen <sup>22</sup>
<i>Agtpbp1<sup>pcd</sup></i>	13	Purkinje cell loss	↓ coat-hanger rotorod	Mullen et al <sup>28</sup>
<i>Reln<sup>rl</sup></i>	5	granule cell loss	↓	Mariani et al <sup>34</sup>

			stationary beam coat-hanger rotorod	
<i>Dab1<sup>scm</sup></i>	5	granule cell loss	↓ stationary beam coat-hanger rotorod vertical grid	Sweet et al <sup>39</sup>

↓ decreased performance

**Table 2** Neurobehavioral characteristics of SCA1 to SCA8 mouse mutations with cerebellar atrophy on sensorimotor tests

Mutant	Promoter	Neuropathology	Motor test	Identifier reference
<i>ATXN1/Q82</i>	<i>Pcp2</i>	Purkinje cell loss	↓ stationary beam rotorod	SCA1 Burright et al <sup>45</sup>
<i>ATXN1/Q30</i>	<i>Pcp2</i>	Purkinje cell loss	?	SCA1 Fernandez- Funez et al <sup>48</sup>
Inducible <i>ATXN1/Q82</i>	<i>Pcp2</i>	ectopic Purkinje cells	↓ rotorod	SCA1 Zu et al <sup>57</sup>
<i>Atxn1/Q154</i>	endogenous	Purkinje cell loss	↓ rotorod	SCA1 Watase et al <sup>58</sup>
<i>Atxn1/Q78</i>	endogenous	no atrophy	↓ rotorod	SCA1 Lorenzetti et al <sup>59</sup>
<i>ATXN2/Q58</i>	<i>Pcp2</i>	Purkinje cell loss	↓ stationary beam rotorod	SCA2 Huynh et al <sup>69</sup>
<i>ATXN2/Q75</i>	<i>ATXN2</i>	Purkinje soma shrinkage	↓ rotorod	SCA2 Aguiar et al <sup>73</sup>
<i>ATXN2/Q127</i>	<i>Pcp2</i>	Purkinje cell loss	↓ rotorod	SCA2 Hansen et al <sup>74</sup>
<i>ATXN2/Q72-BAC</i>	<i>ATXN2</i>	reduced Purkinje cell dendrite branches	↓ rotorod	SCA2 Dansithong et al <sup>75</sup>
<i>Atxn2/Q42</i>	<i>Atxn2</i>	ataxin-2 aggregates	↓ rotorod	SCA2 Damrath et al <sup>76</sup>
<i>ATXN3/Q69</i>	<i>Pcp2</i>	Purkinje cell ectopias, thin dendrite branches	↓ rotorod	SCA3 Torashima et al <sup>84</sup>
<i>ATXN3/Q71</i>	<i>Prp</i>	nuclear inclusions	↓ rotorod	SCA3 Goti et al <sup>88</sup>
<i>ATXN3/Q79-Pcp2</i>	<i>Pcp2</i>	Purkinje cell loss	?	SCA3 Ikeda et al <sup>89</sup>
<i>ATXN3/Q79-Prp</i>	<i>Prp</i>	nuclear inclusions	↓ rotorod	SCA3 Chou et al <sup>90</sup>
<i>ATXN3/Q94</i>	<i>CMV</i>	shrunken cells	↓ rotorod	SCA3 Silva-Fernandes

				et al <sup>95</sup>
<i>ATXN3/Q135</i>	<i>CMV</i>	loss in dentate volume and pontine cell number	stationary beam wire suspension rotorod	SCA3 Silva-Fernandes et al <sup>96</sup>
<i>ATXN3/Q148-Prp</i>	<i>Prp</i>	nuclear inclusions	?	SCA3 Bichelmeier et al <sup>97</sup>
<i>ATXN3/Q148-Hd</i>	<i>Hd</i>	nuclear inclusions	rotorod	SCA3 Boy et al <sup>99</sup>
<i>Atxn3/Q82</i>	endogenous	nuclear inclusions	NE stationary beam rotorod	SCA3 Chou et al <sup>100</sup>
<i>ATXN3/Q91</i>	endogenous	Purkinje cell loss	rotorod	SCA3 Switonski et al <sup>101</sup>
Inducible <i>ATXN3/Q77</i>	<i>Prp</i>	shrunken Purkinje cells, thin molecular layer	rotorod	SCA3 Boy et al <sup>102</sup>
<i>ATXN3/YAC-Q84</i>	endogenous	cell loss in pons and dentate	stationary beam	SCA3 Cemal et al <sup>104</sup>
<i>ATXN3/YAC-Q67</i>	endogenous	cell loss in pons and dentate	?	SCA3 Cemal et al <sup>104</sup>
<i>Sptbn2</i> KO	not applicable	Purkinje cell loss	NE wire suspension rotorod	SCA5 Perkins et al <sup>111</sup>
<i>Sptbn2</i> KO	not applicable	thin molecular layer, shrunken Purkinje cells	wire suspension rotorod	SCA5 Stankewich et al <sup>112</sup>
Inducible <i>SPTBN2</i> deletion	<i>CMV</i>	thin molecular layer	rotorod	SCA5 Armbrust et al <sup>113</sup>
<i>CACNA1A/Q27</i>	<i>CMV</i> and <i>ACTB</i>	Purkinje cell loss	stationary beam inclined screen rotorod	SCA6 Mark et al <sup>117</sup>
<i>CACNA1A/CT-short</i>	<i>CMV</i> and <i>ACTB</i>	Purkinje cell loss	rotorod NE stationary	SCA6 Mark et al <sup>117</sup>

			beam	
<i>CACNA1A/Q33</i>	<i>Pcp2</i>	thin molecular layer	?	SCA6 Du et al <sup>118</sup>
<i>Cacna1a/Q84</i>	endogenous	Purkinje cell loss	↓ stationary beam rotorod	SCA6 Watase et al <sup>119</sup>
<i>Cacna1a/Q118</i>	endogenous	Purkinje cell loss	↓ rotorod	SCA6 Unno et al <sup>122</sup>
<i>CACNA1A/Q33</i>	<i>Pcp2</i>	thin molecular layer	?	SCA6 Du et al <sup>123</sup>
<i>ATXN7/Q52</i>	PDGF	shrunken Purkinje soma, smaller dendritic branches	↓ rotorod	SCA7 Chou et al <sup>129</sup>
<i>ATXN7/Q92-Pcp2</i>	<i>Pcp2</i>	reduced Purkinje cell dendrite branches	↓ rotorod	SCA7 Yvert et al <sup>130</sup>
<i>ATXN7/Q92- Gfa2</i>	<i>Gfa2</i>	Purkinje cell misalignment and dendrite thinning	↓ rotorod	SCA7 Custer et al <sup>131</sup>
<i>ATXN7/Q92-Prp</i>	<i>Prp</i>	Purkinje cell loss	↓ rotorod	SCA7 Garden et al <sup>132</sup>
<i>ATXN7/Q10</i> <i>ATXN7/Q128</i>	<i>PDGF</i>	ataxin-7 aggregates	?	SCA7 Yvert et al <sup>133</sup>
<i>ATXN7/BAC-Q92</i>	<i>Prp</i>	Purkinje cell loss	↓ rotorod	SCA7 Furrer et al <sup>134</sup>
<i>Atxn7/Q266</i>	endogenous	shrunken Purkinje soma	↓ rotorod	SCA7 Yoo et al <sup>137</sup>
<i>ATXN7/Q100</i> lentivirus	<i>PGK1</i>	ataxin-7 aggregates	↓ rotorod	SCA7 Alves et al <sup>140</sup>
<i>Atxn8 KO</i>	not applicable	thin molecular layer	↓ rotorod	SCA8 He et al <sup>145</sup>
<i>ATXN8/Q116</i>	endogenous	nuclear aggregates	↓ rotorod	SCA8 Moseley et al <sup>146</sup>

↓ decreased performance

NE= no effect

? no sensorimotor test was evaluated

**Table 3** Neurobehavioral characteristics of SCA10 to SCA28 mouse mutations with cerebellar atrophy on sensorimotor tests

Mutant	Promoter	Neuropathology	Motor test	Identifier reference
<i>ATNX10</i> KO	not applicable	pontine nuclei loss	?	SCA10 White et al <sup>154</sup>
<i>Kcnc3</i> KO	not applicable	?	↓ stationary beam	SCA13 McMahon et al <sup>159</sup>
<i>PRKCG/H101Y</i>	<i>CMV</i>	Purkinje cell loss	?	SCA14 Zhang et al <sup>165</sup>
Inducible <i>PRKCG/S119P</i>	<i>Pcp2</i>	climbing fiber poly-innervation of Purkinje cells	↓ rotorod	SCA14 Shuvaev et al <sup>166</sup>
<i>Itp1</i> KO	not applicable	?	?	SCA15 van de Leemput et al <sup>168</sup>
<i>Itp1</i> KO	not applicable	?	?	SCA15 Matsumoto et al <sup>172</sup>
<i>opt</i>	not applicable	abnormal calcium responses in Purkinje cells	?	SCA15 Street et al <sup>173</sup>
<i>TBP/Q109</i>	<i>Pcp2</i>	Purkinje cell loss	↓ rotorod	SCA17 Chang et al <sup>178</sup>
Inducible <i>TBP/Q105</i>	endogenous	Purkinje cell loss	↓ stationary beam rotorod	SCA17 Huang et al <sup>181</sup>
<i>TBP/Q64</i>	<i>Prp</i>	Purkinje cell loss	↓ stationary beam NE rotorod	SCA17 Kelp et al <sup>183</sup>
<i>Fgf14</i>	not applicable	parallel fiber anomalies	↓ inclined screen inverted screen rotorod	SCA27 Wang et al <sup>189</sup>
<i>Afg3l2</i>	not applicable	granule and Purkinje cell loss	↓ inclined grid stationary beam rotorod	SCA28 Maltecca et al <sup>196</sup>

↓ decreased performance

NE = no effect

? no sensorimotor test was evaluated

### Figure legend

Fig 1 a) Stationary beam test: mice are placed on top of the beam and left there until they fall. b) Coat-hanger test: mice are placed upside down above a padded surface and movement time (MTs) are measured until the mice reach the mid-point (MT1) or the end (MT2) of the horizontal bar (nose criterion), lift themselves on the diagonal bar with 2, 3, or 4 paws (MT3-MT5) and reach up to the mid-point (MT6) or top (MT7) of the diagonal bar. c) Rotorod test: mice are placed on top of the rotating beam and left there until they fall or turn passively.