The cerebellum is the part of the brain responsible for coordinating movement. It controls the timing, duration and amplitude of muscle activity. The structure of the cerebellum can be divided into two parts – the cerebellar cortex and the cerebellar nuclei. The Purkinje cells form a single layer in the cortex receiving input from a range of sources throughout the central nervous system. In turn they are the sole output of the cerebellar cortex, targeting the cerebellar nuclei.

The term ataxia is used clinically to describe a lack of motor co-ordination or posture that is not due to motor weakness or sensation deficits. It can be a consequence of immune diseases, cancer, hypothyroidism, drug abuse, a cerebellar abscess, other infectious diseases, or an inherited neurodegenerative disorder. Spinocerebellar ataxias (SCAs) are a heterogenous group of such inherited disorders. They are autosomal dominant diseases (only one gene needs to be defective) and onset of symptoms is typically later in life, normally within the third or fourth decade. Symptoms include abnormal eye movements, difficulties with speech, progressive deficits of limb movements and abnormalities of gait and posture. Patients with SCA are shown to have severe shrinkage of the cerebellum by magnetic resonance imaging (MRI) scans and autopsy examination shows a drastic loss of Purkinje cells.

Although people are generally unaware of these diseases, the prevalence of some SCAs can be as high as Huntington’s and motor neuron diseases. On average one individual in 17,000 will be afflicted with progressive ataxia. The exact cellular events that underlie progressive ataxia and cerebellar degeneration are still not clearly understood.

![Cerebellar Purkinje cell filled with Alexa 568](image)

**Figure 1: Cerebellar Purkinje cell filled with Alexa 568**
understood. This is despite knowing the genetic defects of the most common SCA subtypes for more than fifteen years. Some clinical trials have led to certain ataxic symptoms being ameliorated but to date there has been no success in preventing or even modifying disease. An improved understanding of the physiological mechanisms underlying disease progression is therefore essential if successful therapies are to be developed. The study of additional models of SCA represents an important route to identifying disease mechanisms.

**SCA5 AND β-III SPECTRIN**

In 2006 researchers in Minnesota identified, using a large kindred descended from the grandparents of President Abraham Lincoln, mutations in the gene encoding β-III spectrin as the genetic cause of spinocerebellar ataxia type 5. We are investigating the mechanisms through which the in-frame deletions and missense mutations cause disease using a combination of in vivo models and cell culture studies. We have created an in vivo β-III spectrin deficient model and found it develops characteristic features of cerebellar ataxia, including a splayed gait, progressive motor incoordination, tremor, and cerebellar degeneration. These features closely mirror symptoms seen in SCA5 patients making this model an excellent tool for studying disease mechanisms. To date we have identified sodium channel dysfunction and glutamate transporter loss, both neuronal (EAAT4) and astroglial (GLAST), as factors in disease pathogenesis. Our current research directions focus on 1) elucidating what changes to sodium channel expression, activity, or localization occur in the absence of wild type β-III spectrin or in the presence of β-III spectrin with mutations associated with SCA5; 2) identifying whether astrocytes play a role in Purkinje cell degeneration; 3) determining whether the disease phenotype can be rescued; 4) understanding the role of β-III spectrin in normal Purkinje cell development; and 5) identifying other proteins that interact with β-III spectrin, thus highlighting other potential cellular pathways that could underlie neurodegeneration. A variety of techniques including genetic crosses, electrophysiology, cellular imaging, cell culture studies and yeast two-hybrid screens are being employed in the lab to achieve the research aims.

**SELECTED REFERENCES**


