

**Regulation of voltage-gate calcium channels in ataxia**  
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**Scientific abstract**

Mutations in voltage-gated  $\text{Ca}^{2+}$  channels ( $\text{Ca}_v$ ) implicated in ataxia have been linked to G-Protein Coupled Receptor (GPCR) signalling but little is known about how the regulation of these channels is impaired leading to channel dysfunction in ataxic disease. Research of this nature will further our understanding of how alterations in the signalling pathways regulating P/Q channels ( $\text{Ca}_v2.1$ ) can cause ataxia. We will use a multidisciplinary approach to test the hypothesis that certain ataxic  $\text{Ca}_v2.1$  mutations disrupt interactions in the GPCR pathway in which Neuronal Calcium Sensor 1 (NCS-1) is involved. We will make mutations in  $\text{Ca}_v2.1$  and  $\text{Ca}_v$  subunit cDNAs corresponding to human mutations that cause ataxia focusing on those linked to Episodic Ataxia-type 2 and Spinocerebellar Ataxia-type 6. These mutant cDNAs will be expressed in both heterologous-systems and neuroendocrine cells. Molecular/cell biological and electrophysiological methods will be used to examine ataxic channel dysfunction. The therapeutic outcome of this work is that it can lead to the identification of novel protein targets in the pathway regulating P/Q channels for chemical screens that would lead to drugs used for the treatment of ataxia. New drugs that help re-establish normal channel regulation could restore efficient neuromuscular transmission in patients with ataxia.

**Lay summary**

This project involves studying a number of mutations in a calcium channel that cause different types of ataxias: SCA6, episodic ataxia type 2 and familial hemiplegic migraine. It studies the calcium channel dysfunction and how this causes ataxia. Although it is a basic science research project, it may identify targets for therapeutic intervention.

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