

Molecular function of human senataxin protein, mutated in ataxia oculomotor apraxia type 2 (AOA2) and amyotrophic lateral sclerosis type 4 (ALS4), in the pathology of these conditions

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Scientific summary

Ataxia oculomotor apraxia type 2 (AOA2) and amyotrophic lateral sclerosis type 4 (ALS4) are neurodegenerative inherited disorders characterised by degeneration in the brain and spinal cord, causing progressive muscle weakness and finally atrophy. The gene mutated in these highly disabling conditions encodes a senataxin (SETX) protein, a putative DNA/RNA helicase. This PhD project will investigate the function of human senataxin protein, uncovering the molecular mechanism underlying the pathology of AOA2 and ALS4. In particular, this project will characterise the transcriptional and RNA processing defects associated with the disorders and investigate the behaviour and function of the mutant forms of senataxin protein detected in people with the conditions. It will also examine the correlation between disruption of the senataxin function in human gene expression, and severity of the conditions. Furthermore, the novel senataxin-interacting partners will be identified, and their function in human cells and role in AOA2 and ALS4 pathology will be established.

Understanding the molecular basis of AOA2 and ALS4 has to be ranked as one of the current major challenges in development of therapies for the conditions. This project will advance our understanding of gene regulation in AOA2 and ALS4 and provide a solid foundation for the development of novel molecular therapies, improving the health and quality of patients' lives.

Lay summary

This research project will investigate the mechanism underlying the pathology of ataxia oculomotor apraxia type 2 (AOA2) and amyotrophic lateral sclerosis type 4 (ALS4); highly disabling neurodegenerative inherited disorders, which are characterized by degeneration in the brain and spinal cord, causing progressive muscle weakness and finally atrophy. The same gene is mutated in these conditions; it encodes a protein called senataxin (SETX). Since the discovery of mutations causing AOA2 in 2004, little progress has been made in terms of understanding the function of senataxin protein.

To study the function of senataxin protein in human cells, we will use our extensive expertise in protein/RNA field in combination with innovative technologies

in this field. This approach will allow us to explore the intricacies of gene regulation in patients with defects in senataxin protein. In particular, we will perform experiments in human cells in which production of senataxin protein has been shut off. We will investigate the behaviour and function of the mutant forms of senataxin protein, detected in AOA2 and ALS4 patients. In particular, we will examine the correlation between disruption of the senataxin function in human gene expression and severity of the condition. We will also test if the lack of senataxin protein causes any secondary effects to occur in human cells. We are proposing that the AOA2/ALS4 pathologies are due to defects in senataxin's function as a helicase enzyme which unwinds hybrids between RNA and DNA, appearing during the process of transcription in the cells (an important part of gene regulation). If RNA/DNA hybrids are not resolved properly, their accumulation can be detrimental to the cells. We will determine if RNA/DNA hybrid profile is perturbed in AOA2/ALS4 patients, and how it contributes to neurodegeneration. In addition, we will identify new senataxin-interacting partners and study their role in AOA2/ALS4 pathology.

This research project will make a significant impact on our understanding of cause of AOA2 and ALS4 and attract further funding for this research project. In the long term, the development of novel pharmacological and RNA-based therapies for AOA2 and ALS4 is a likely prospect from this research; this would improve the health and quality of life for people with these conditions.

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