

Identification of transport processes which influence the intracellular localization of ataxin-3

**Principal researcher: Dr Thorsten Schmidt, Medical Genetics,
University of Tuebingen, Germany**

Scientific summary

Ataxin-3, the affected protein in spinocerebellar ataxia type 3 (SCA3), is mainly localized in the cytoplasm. However, in SCA3 patients, protein aggregates can be found in the nucleus of neurones. Our data from transgenic mice revealed the importance of the intracellular localization of ataxin-3: ataxin-3, even with expanded polyglutamine repeat, is harmless as long as the protein is kept in the cytoplasm (Bichelmeier *et al.*, 2007). In addition, we recently identified two nuclear export signals and one nuclear localization signal within ataxin-3. In this application, we intend to identify the factors which are responsible for the transport of ataxin-3 from the cytoplasm to the nucleus. We will first generate an assay to quantify the intracellular localization of ataxin-3. We will then use this assay to assess the impact of transport proteins on the localization of ataxin-3. We also plan to measure *in vivo* the impact of these transport proteins on the fitness of ataxin-3-transfected cells. Positive transport proteins will then be analyzed for the interaction with ataxin-3 and their localization in affected tissue. We are convinced that understanding the mechanism which controls the intracellular localization of ataxin-3 will lead to the identification of novel therapeutic targets.

Bichelmeier U, Schmidt T, Hübener J, Boy J, Rüttiger L, Häbig K, Poths S, Bonin M, Knipper M, Schmidt WJ, Wilbertz J, Wolburg H, Laccone F, Riess O (2007) Nuclear localization of ataxin-3 is required for the manifestation of symptoms in SCA3: *in vivo* evidence. *J Neurosci* 27(28):7418-28.

Lay summary

In this project, we aim to identify transport proteins which could answer an important question in SCA3, an inherited neurodegenerative disease. While the affected protein, ataxin-3, is normally localized in the cytoplasm of a cell, in SCA3 patients protein aggregates can be observed in the nucleus. Why does a cytoplasmic protein form aggregates in the nucleus? Why is this protein transported into the nucleus? We recently identified two so called nuclear export signals within ataxin-3 and propose that these signals keep ataxin-3 in the cytoplasm and one nuclear localization signal, which may initiate the transport of ataxin-3 to the nucleus. We also found out that ataxin-3 is harmless as long as the protein remains in the cytoplasm and is not transported to the nucleus. But how is this protein transported into the nucleus? In



this project, we aim to identify proteins which are able to transport ataxin-3 to the nucleus. Understanding the nuclear transport may enable us to specifically target these proteins with certain compounds and may, therefore, lead to a novel therapy not only for SCA3 but also for other related diseases.

**For more support or information please contact: Ataxia UK, Lincoln House,
Kennington Park, 1 – 3 Brixton Road. London SW9 6DE**

Website: www.ataxia.org.uk.

Helpline: 0845 644 0606 Tel: +44 (0)20 7582 1444 Fax: +44 (0)20 7582 9444

Email: helpline@ataxia.org.uk.