# Understanding and correcting glucose metabolism defects in AT

**Research Project information**

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**Cost:** £125.820,50 over 36 months in partnership with the Action for A-T (UK), AEFAT (Spain) and BrAshA-T (Australia)
**Start Date:** 1st of April 2023

**What are the researchers proposing to do?**
Costanzo and team will test the hypothesis that ATM (the protein which is missing or not functioning completely in AT) controls chemical reactions required for the correct use of glucose. Glucose usage defects could lead to glycogen accumulation*, which might be toxic for brain cells. They will study the molecular reactions controlled by ATM that promote the correct usage of glucose and assess possible toxicity of glycogen accumulation to understand how these defects occur and how they could be corrected.

*Glycogen is the body's stored form of glucose.

**Why?**

AT is caused by the lack of functional ATM protein. ATM regulates the activation of chemical reactions that promote cell survival. The details of ATM function in the control of these reactions are poorly understood. Preliminary experiments indicate the presence of defects in glucose usage, leading to the discovery that AT patients' cells accumulate glycogen.

**How will the research be done?**

The team will study the mechanisms leading to inefficient glucose processing and glycogen accumulation in AT cells and the impact of glycogen accumulation on AT cell survival. They will monitor glucose metabolism in primary AT cells. They will directly measure the activity of enzymes controlling key regulatory reactions in glucose processing. To understand whether glucose usage defects are linked to mitochondrial impairments they will also measure mitochondrial function. To identify possible alterations in pathways controlling energy metabolism in AT cells they will explore the impact of known enzymes involved in glycogen accumulation and AT cell survival. Finally, to validate the impact of the alterations linked to impaired glucose metabolism they will use Purkinje neurons derived from both healthy and AT human reprogrammed cells in the lab.

The team will study the clinical symptoms, blood biomarkers and brain imaging findings in a subgroup of AT caused by the so called "UK mutation". Team members are experts in all aspects of this study including translational research, state-of-the-art imaging and eye assessment. They will involve AT patients and their family members in the research and also in the design of a future clinical trial. They will also actively engage with AT charities to enable a better distribution of information to patients.

**How could it make a difference to the lives of those affected by AT?**

This study will help us to understand the natural history of AT and aims to allow rapid progression to trial-readiness, vital to the delivery of clinical trials, such as a novel ASO therapy to a cohort of AT patients. They will ensure the most thorough methods to fairly assess therapy effectiveness, which will benefit any future clinical trial in AT. They will involve AT patients and their family members in the design of a future clinical trial.