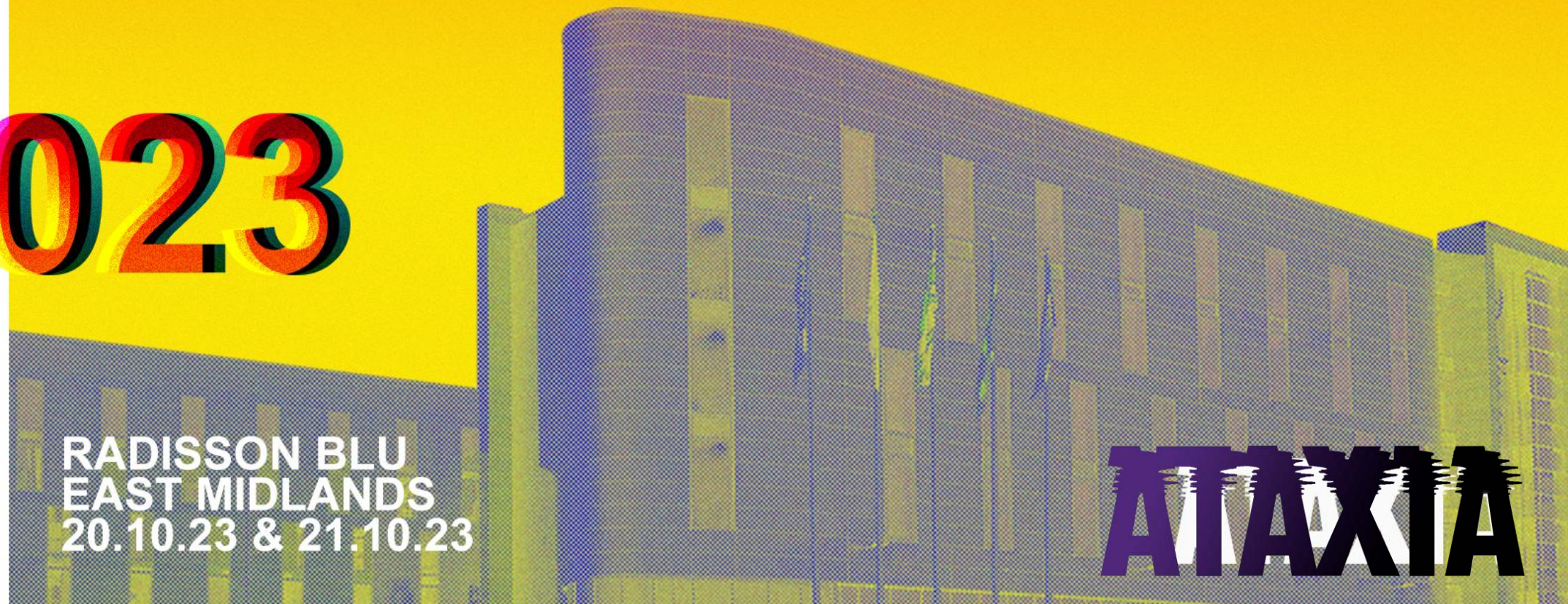
ANNUAL CONFERENCE

2023

Cerebellar Ataxia Research Update

Dr Ruby Wallis



RADISSON BLU
EAST MIDLANDS
20.10.23 & 21.10.23

ATAXIA

Overview

Ataxia UK activities and the process of research

Developments in diagnosis and treatment of ataxia

European and global ataxia research initiatives

Clinical trials and taking part in research

ANNUAL CONFERENCE 2023

Ataxia UK activities and the process of research

Ataxia UK research activities

Fund research projects mostly small grants to get initial results

2023 Impact Report
Every £1 Ataxia UK spent on research projects raised £5 in further funding for ataxia research

First event for UK-based researchers – Sep 2023

Organise research conferences

International Congress for Ataxia Research

ICAR

ATAXIA · ATAXIA GLOBAL INITIATIVE · FARA · NAF National Ataxia Foundation

SAVE THE DATE: ICAR 2024
November 12-15, 2024 • London, UK

Ataxia UK research activities

Ataxia UK links researchers and ataxia community:

- Recruitment to studies
- Patient engagement in research

Work with pharma and biotech companies:

- Encourage involvement in ataxia research
- Assist with programmes
- Collect useful information

Engagement at all stages of research

The process of research

Preclinical

several years

- Test drug in cells and/or animals
- Dosing and safety before giving to humans

*for rare conditions such as ataxia, the numbers of people in trials are much smaller and the different phases of trial might be combined

Developments in diagnosis of ataxia

Inherited ataxias

Advances in knowledge of genes that cause ataxia mean more inherited ataxias can be identified

- Whole genome sequencing (WGS) now available on the NHS
- We now know WGS can also detect repeat-expansion disorders, such as the SCAs
- WGS can aid in the discovery of new conditions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Genetics

Simple DNA test could detect common neurological disorders, study says

Exclusive: whole genome sequencing could end 'diagnostic odyssey' of multiple tests that still do not give precise diagnosis

Linda Geddes

Wed 16 Feb 2022 23.30 GMT

Newly identified inherited ataxias

Discovery of a genetic cause of CANVAS

- Genetic mutation in RFC1 gene was discovered by UK-based researchers

Discovery of genetic ataxia SCA27B

- Genetic mutation in FGF14 gene was discovered in 2023
- SCA27B is a late-onset ataxia which can start with episodes of ataxia symptoms (lasting from minutes to days)
- A small study shows promise with 4-AP treatment

If you have no specific ataxia diagnosis and are interested to find out if you have CANVAS, speak to your neurologist. Tests for RFC1 mutations and SCA27B can be organised via the researchers that identified the mutation (contact Ataxia UK).

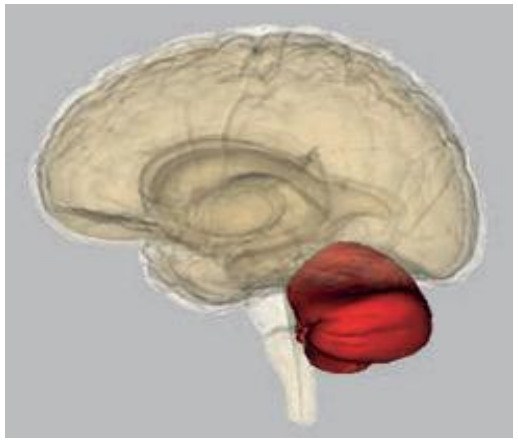
RFC1 mutations and SCA27B may be common causes of late onset ataxias

Non-inherited ataxias

Prof Marios Hadjivassiliou from the Ataxia UK-accredited Sheffield Ataxia Centre is a leading expert in:

- **Gluten ataxia**

- **Primary Autoimmune Cerebellar Ataxia (PACA)**

Trigger → **Immune response begins** →  → **Ataxia**

Primary autoimmune cerebellar ataxia (PACA)

Prof Marios Hadjivassiliou and Dr Priya D Shanmugarajah (Sheffield Ataxia Centre) have published two papers on PACA

PACA is a type of immune-mediated cerebellar ataxia

- These ataxias are caused by the body launching an unnecessary immune reaction against the cerebellum (the balance centre) causing damage.
- Sometimes the trigger of this immune response is known (e.g. gluten). If the trigger is unknown, the condition is PACA.

How neurologists can diagnose PACA

- There is no definitive test for PACA
- Prof Hadjivassiliou describes a comprehensive list of clues that neurologists should look for when considering the possibility that someone has PACA.

A diagnosis of PACA can be made if certain criteria are fulfilled, and if an experienced neurologist or ataxia specialist has ruled out other causes (such as genetic ataxia).

Primary autoimmune cerebellar ataxia (PACA)

A potentially treatable form of ataxia

- The team from the Sheffield Ataxia Centre treated 22 PACA patients with an immunosuppressive drug called Mycophenolate, which reduces the immune response that causes the ataxia.
- Their results using brain scans and ataxia rating scales showed that those receiving treatment improved or stabilised and those who did not got progressively worse.

If you have been diagnosed with idiopathic ataxia and would like to explore the possibility that you might have PACA, we recommend that you speak to your neurologist about these publications.

Developments in treatments for ataxia

Genetic approaches in SCAs

A gene

Gene produces protein

No mutation = Normal protein, no disease

Some SCAs

Gene produces protein

SCA mutation = Disease-causing protein

Studies have shown success in animal models with this approach

Genetic approaches in SCAs

- **Two Ataxia UK-funded projects on genetic treatment for SCA1**

  - One project testing a type of gene therapy called SMaRT, which if successful could be tested on other ataxias in the future
  - Another project targeting small changes to the gene to prevent the mutated SCA1 gene from producing the toxic ataxin-1 protein

Genetic approaches in SCAs

- Vico therapeutics
- VO659 – Antisense oligonucleotide therapy (ASO)
- Targets expanded 'CAG' repeats, stopping production of toxic proteins
- Started Phase 1/2a trial in SCA1 and SCA3 in 2023 in European sites
- UK trial site due to open at London Ataxia Centre

Examples of Ataxia UK-funded projects

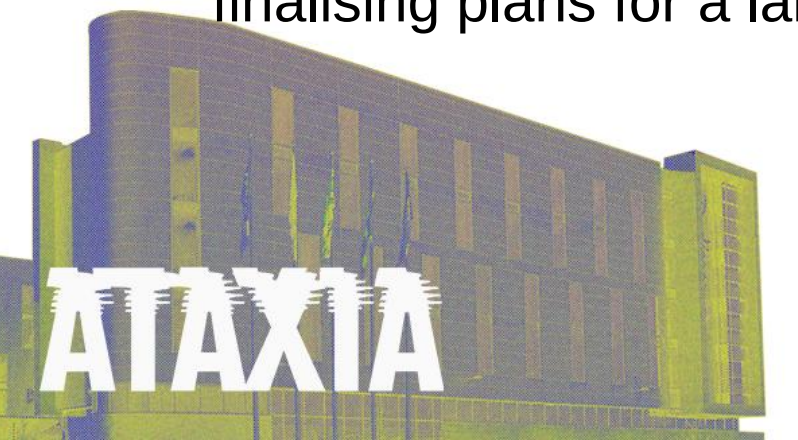
- Two research groups in Portugal looking at nanobodies as a treatment for SCA3, and using anti-depressants to treat SCA3.

- Funded two projects on spastic ataxia type 8, aiming to conduct a natural history study and develop gene therapy. These grants were made possible by a generous donation from the DVS Foundation.

- Ataxia UK and US Foundation CureDRPLA have a research programme working on DRPLA.

Speech therapy projects

- Ataxia UK have funded projects on speech therapy for people with ataxia
- Speech therapy focusing on good voice production and clear articulation can help some people with ataxia to improve their speech and their confidence in communicating
- ClearSpeechTogether – peer support model tested in collaboration with Ataxia UK – published as a successful method of providing speech therapy
- Prof Lowit is currently testing one more therapy to decide on the best approach, before finalising plans for a larger trial



European and global ataxia research initiatives

European research initiatives

Cerebellum and emotional networks (CEN) project

- Investigating neuronal basis of emotions
- Focuses on the role of the cerebellum
- 8 academic and 7 industry/charity partners, including Euro-ataxia

TREAT-ARCA

- Group of researchers studying autosomal recessive cerebellar ataxias
- Focus is on testing treatments in animal models of ARSACS and CoQ8A-ataxia
- Euro-ataxia representing people with ataxia, with support from Ataxia UK

European research initiatives

PROgression chart of SPAstic ataXias (PROSPAX)

- Large study taking place across Europe (including the UK) and Canada
- Aim to study spastic ataxias over time to learn about progression – starting with ARSACS and SPG7
- Will also learn about biomarkers and animal models
- In order to become ready for clinical trials
- Euro-ataxia representing people with ataxia, with support from Ataxia UK

euro ataxia

PROSPAX

European research initiatives

SIMPATHIC Consortium

- Traditionally, drugs are developed one disease at a time, which is costly and time-consuming
- The SIMPATHIC Consortium is developing a novel method for accelerating the use of existing drugs currently being used for other conditions
- SCA3 is one of the neurological conditions that will be studied
- The Consortium received an €8.8million grant from the European Commission
- Euro-ataxia one of the patient groups representing people with neurological conditions on this project, supported by Ataxia UK

euro ataxia

Ataxia Global Initiative

Network of Ataxia Specialists worldwide

- For rare and common ataxias
- Researchers, pharma, patient groups (Ataxia UK – Exec Committee)
- Get consensus on standardised data and sample collection to help with trials
- Coordination of joint research projects globally
- Education and training
- Young investigators initiative

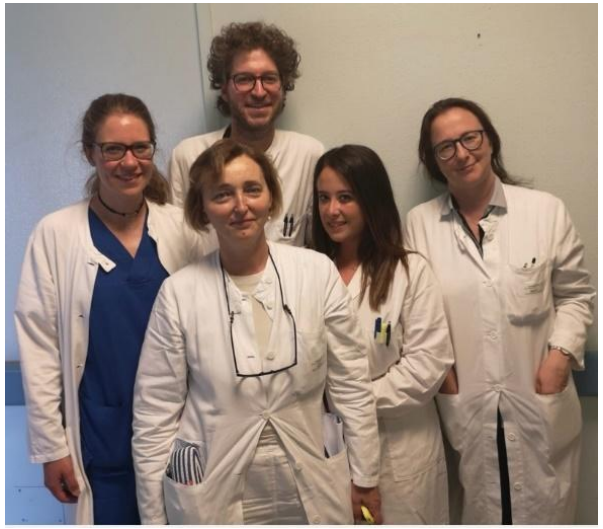
ATAXIA GLOBAL INITIATIVE

worldwide platform for clinical research in ataxias

Clinical trials and taking part in research

Symptom relief trial

- Applying a **low electrical current** to the scalp may alleviate symptoms of ataxia.
- Cerebellar transcranial Direct Current Stimulation (tDCS)
  - Ataxia UK funded a tDCS trial in Italy
  - Range of ataxias (FA, SCAs, MSA)
  - Results in 2021 showed improvements in ataxia rating scales
  - Results in other studies have shown mixed results
- Transcranial Alternating Current Stimulation (tACS)
  - Ataxia UK funded tACS trial by same group
  - Results in 2023 showed that tACS improved ataxia rating scales



Comparison of tDCS and tACS showed that tDCS was more effective at improving the symptoms of ataxia

Seelos Therapeutics trehalose trial - paused

- Phase 2/3 trial, testing trehalose in people with SCA3
- Planned a one year trial with 245 participants, from up to 30 sites
- Paused in March 2023, as a business decision due to financial considerations
- Not based on any data related to safety or therapeutic effects

Biogen SCA3 trial - stopped

Biogen planned a Phase I clinical trial for SCA3 treatment BIIB132.

- BIIB132 is antisense oligonucleotide (ASO) - it can block the ability of a gene to make a protein
- The decision to stop the trial was made after careful assessment of the nonclinical safety data, clinical pharmacodynamic data, and future development of BIIB132.

Biohaven SCA trial –see later talk

- Troriluzole is a symptom relief treatment

- Phase 3 trial: 1 year, focus on SCA1, SCA2, SCA3, SCA6, SCA7, SCA8 and SCA10, higher dose, 218 participants
  - Main measure used to see if treatment worked (f-SARA score) was not improved by troriluzole
  - However, when only looking at participants with SCA3, they did see an improvement in the f-SARA score in people taking troriluzole
  - In May 2023, Biohaven submitted a New Drug Application (NDA) to the regulators in America (the FDA) for the treatment of SCA3
  - **In July 2023, the FDA announced they would not be reviewing the NDA as the primary endpoint of the trial was not met. Biohaven stated that they will request a meeting with the FDA to discuss. Ataxia UK joined NAF campaign asking FDA to review NDA**

SCA3 natural history study - recruiting

- **ESMI**
- Aims to create a patient registry and carry out a natural history study to assess how SCA3 progresses over time
- Recently identified possible biomarkers for SCA3
- Multi-centre European SCA3 project coordinated at the German Centre for neurodegenerative diseases in Bonn, and involving 5 countries

London Ataxia Centre is recruiting: If you have been diagnosed with SCA3 and are interested in taking part, please contact the team at uclh.ataxia@nhs.net

SCA6 gait project - recruiting

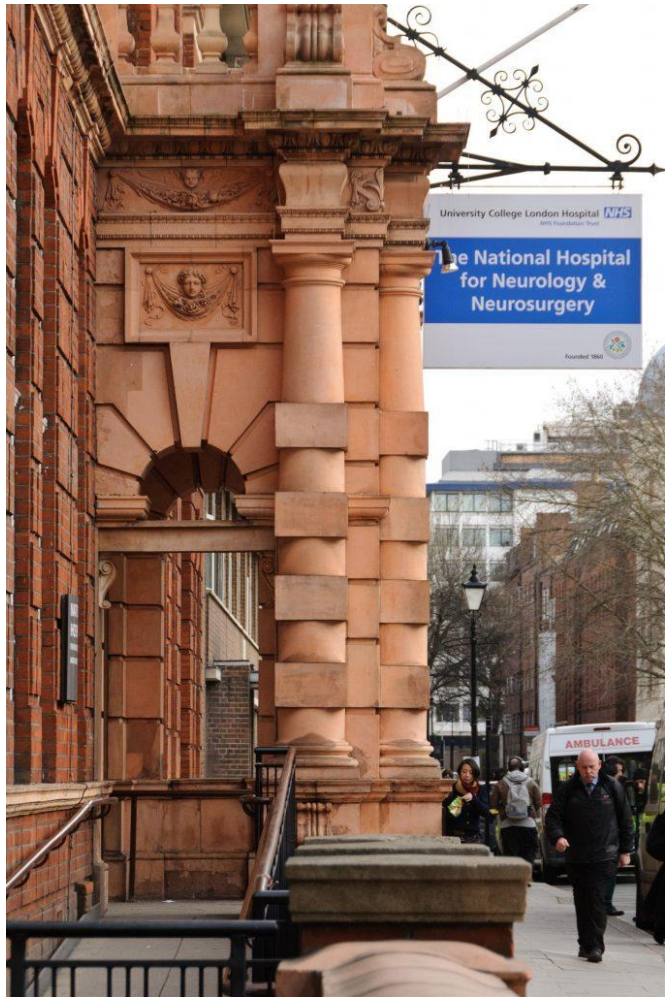
- Ataxia UK is funding a study looking at balance and gait in people with SCA6
- Taking part will involve one visit to the study site, and wearing a sensor at home for 7 days
- The researchers expect that this project will generate useful data in support of using gait measurements in future clinical trials

The site in Newcastle is recruiting: If you have been diagnosed with SCA6 and are interested in taking part, please contact the team at mito.ataxia.study@ncl.ac.uk.

ARSACS project - recruiting

Taking a measurement from the eye (called OCT) to find out whether this can be used to diagnose ARSACS, and to better understand the clinical features of ARSACS.

London Ataxia Centre is recruiting: If you have been diagnosed with ARSACS and are interested in taking part, please contact the team at uclh.ataxia@nhs.net



Healthcare research

Google’s AI for Social Good programme

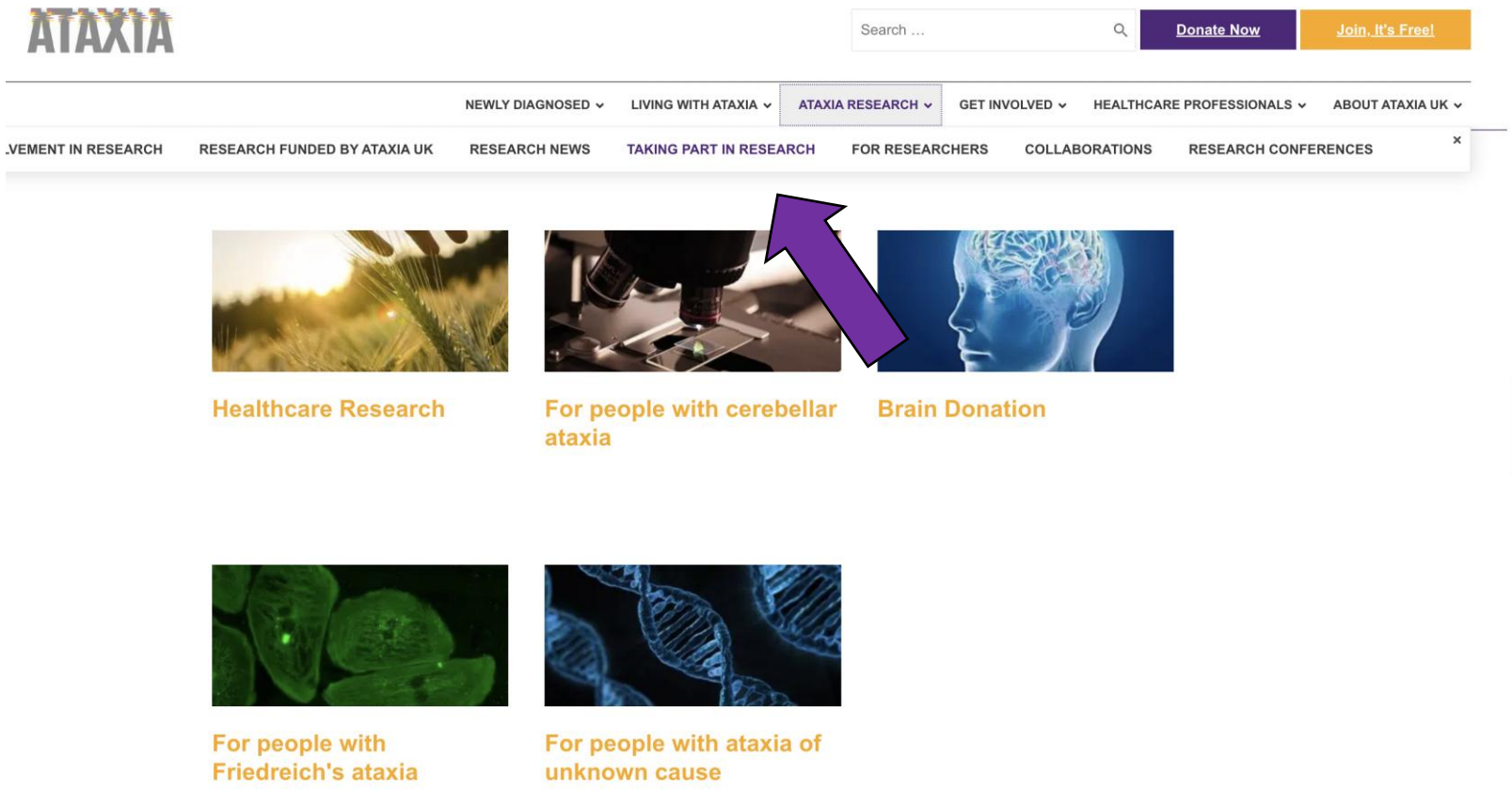
Project Euphonia

Collecting speech samples from people with speech difficulties in order to improve voice recognition technology – for example to improve Google Assistant.

SCA-Remote study

This study aims to better understand how different symptoms in spinocerebellar ataxias (SCAs) change over time. Two-year study involving 30 minutes of computer activities every month. Recruiting people with SCA1, 2, 3, or 6. This study is also recruiting people without ataxia to take part as a comparison group.

All studies can be found on our website ataxia.org.uk



Thank you for listening!

www.ataxia.org.uk

Please contact research@ataxia.org.uk if you have any further questions!