Cerebellar Ataxia Research update

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Head of Research

27th & 28th September 2024

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ATAXIA

Overview

Ataxia UK activities

Developments in diagnosis of ataxia

Developments in finding treatments

Clinical trials and taking part in research

Ataxia UK research activities

Funding Research

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

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Research events

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

Meeting for UK researchers
Sep 2023

Ataxia UK research activities

Ataxia UK links researchers and ataxia community

- Recruitment to studies
- Engagement in research
- Patient voice

Working with pharma and biotech companies

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

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UNDERSTANDING THE SPECTRUM OF SCA1, SCA2, SCA3, AND SCA6 THROUGH THE EYES OF PATIENTS: BURDEN OF ILLNESS AND QUALITY OF LIFE

Lauren C Seeberger, MD[1]; Melissa Wolfe Beiner, MD[2]; Michele Potashman, PhD[3]; Anne Neumann, RN, BSN[4]; Skyler Jackson, BA[5]; Austin R Letcher, MS[5]; Patti A Engel, BSN[6]; Lauren Moore, PhD[7]; Julie Greenfield, PhD[8]; Giovanni Ristori, MD[9,10]; Laura Heller, PharmD[11]

Developments in diagnosis of ataxia

New genes that cause ataxia identified

Developments in diagnosing non-inherited ataxias

Whole genome sequencing now available on the NHS

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Inherited ataxias

- Discovery of a genetic cause of CANVAS in 2019
  - Mutation in RFC1 gene
- Discovery of new genetic ataxia SCA49 in 2022
  - Mutation in SAMD9L gene
- Discovery of genetic ataxia SCA27B in 2022
  - Mutation in FGF14 gene
  - Late-onset ataxia which can start with episodes of ataxia symptoms
  - A small study shows promise with 4-AP treatment

If you do not have a specific ataxia diagnosis speak to your neurologist or visit a Specialist Ataxia Centre.
RFC1 mutations and **SCA27B** may be common causes of late onset ataxias.

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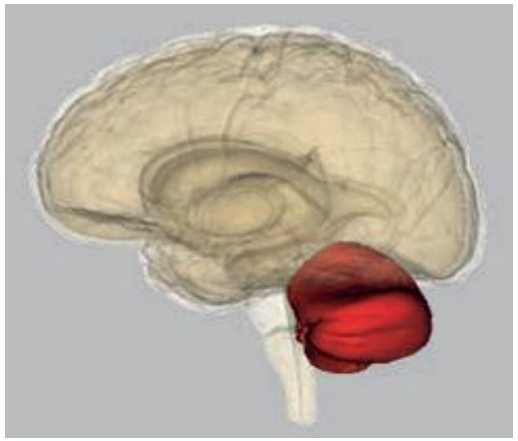
Developments in non-inherited ataxias

- **Gluten ataxia – treatable with diet**
- **Primary Autoimmune Cerebellar Ataxia (PACA)**
  - Caused by the body launching an unnecessary immune reaction against the cerebellum.
  - Sometimes the trigger of this immune response is known (e.g. gluten). If the trigger is unknown, the condition is PACA.

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

Primary autoimmune cerebellar ataxia (PACA)

How can neurologists diagnose PACA?

- No definitive test for PACA
- Prof Hadjivassiliou at Sheffield Ataxia Centre is an expert. He 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)

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.

Clinical research and developments in treatments for ataxias

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Process of clinical trials

Preclinical several years

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

Phase 1 Several months

- Safety of drug
- How the body processes drug and its effect on body
- Information on dosing

Phase II Several months to 2 years

- Potential risks and benefits
- Does drug work in people who have the condition?
- Continues to study safety

Phase III 1 to 4 years

- Potential risk and benefits compared to no treatment or existing treatment
- Typically, people are given the drug or placebo
- Continues to study safety and whether drug works in more people

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

Next step after a successful clinical trial

Step 1: a treatment needs to get a **licence** from a **regulatory agency** before it can be made available

Step 2: In the UK, **different bodies** decide whether the **NHS will provide** the treatment

UK: MHRA
Europe: EMA
US: FDA

England, Wales, NI: NICE
Scotland: SMC

Ataxia Global Initiative

Network of Ataxia Specialists worldwide – goal to facilitate clinical development of therapies for ataxia

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
- Creating database of global trial sites

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ATAXIA GLOBAL INITIATIVE

worldwide platform for clinical research in ataxias

Understanding the symptoms and progression of ataxias is important for trials and developing treatments

Natural history studies in ataxias:

- ESMI – European SCA3
- READISCA – US and some European SCA1, SCA3
- CRC- SCA – US SCA1, 2, 3, 6, 7, 8, 10
- PROSPAX – Europe and Canada SPG7 and ARSACS
- DRPLA – Worldwide

Treating inherited ataxias with genetic-based therapies

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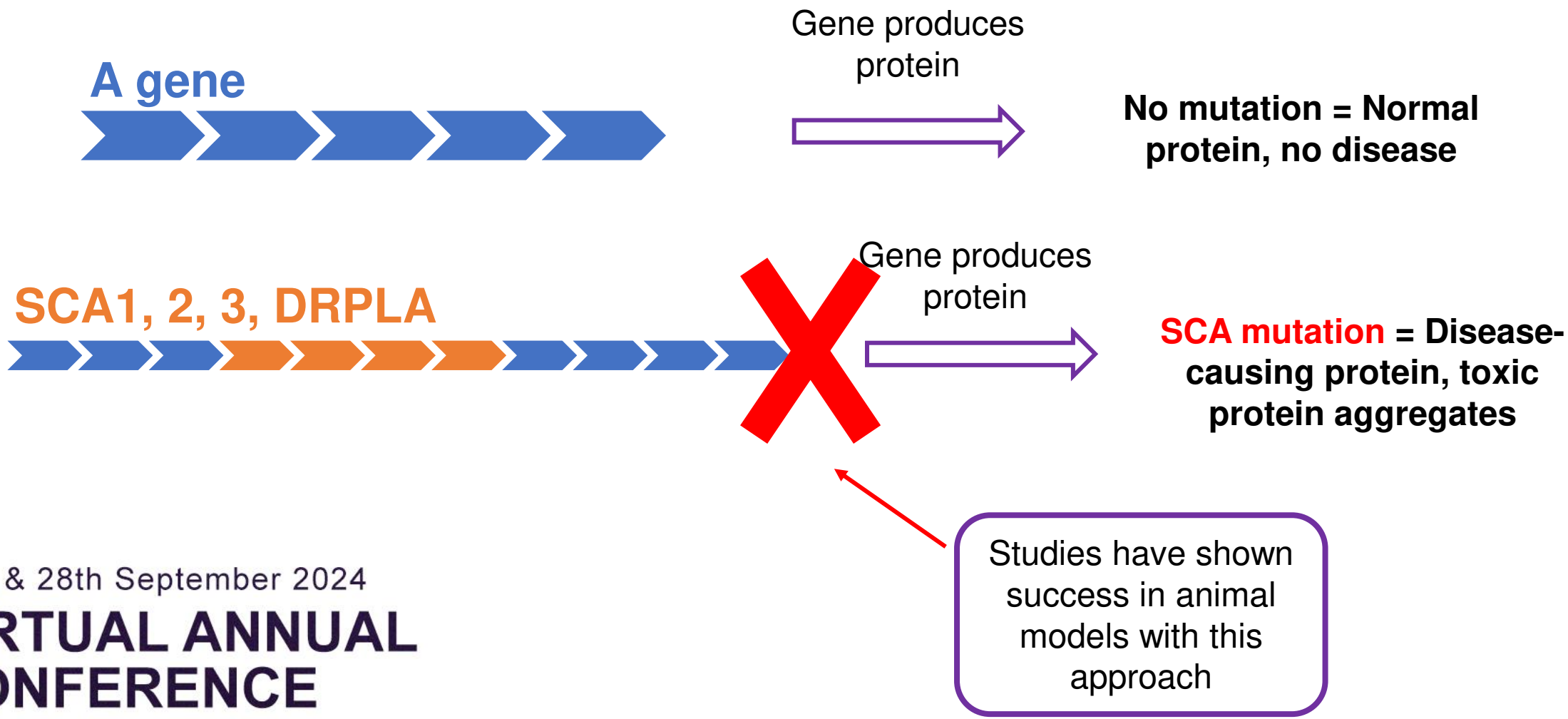
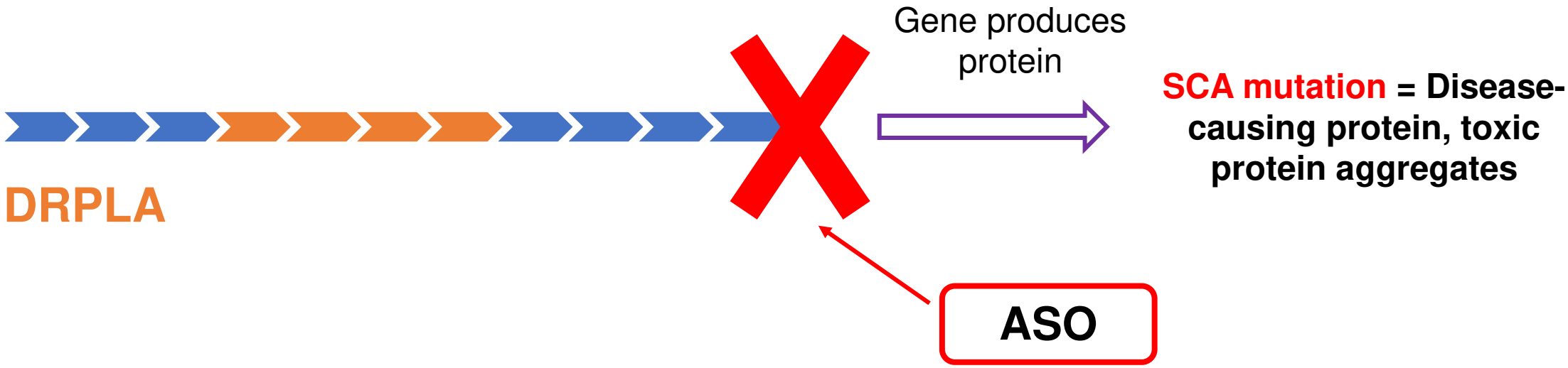
Genetic approaches in SCAs



ASO treatment strategy in DRPLA



- Block the ability of a certain gene to make a protein.
- Prevent protein aggregation in DRPLA, and therefore reverse or slow down DRPLA progression.

ASO treatment strategy in DRPLA

- ASO preclinical studies in cells and animal models promising results
- Launched n=1 trial in one DRPLA patient in the US
- Partnership CureDRPLA, Columbia University and n-Lorem Foundation

ASO treatment strategy in SCAs

Vico therapeutics programme

- VO659 – ASO targets expanded 'CAG' repeats, stopping production of toxic proteins
- Started Phase 1/2a trial in SCA1 and SCA3 in 2023 in European sites
- Trial completion date – estimated 2025

London Ataxia Centre currently recruiting participants

Genetic approaches in SCAs

Two Ataxia UK-funded preclinical projects on genetic treatment for SCA

- 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

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Treating ataxias with new drugs or drug repurposing

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Ataxia UK-funded preclinical studies

Nanobodies as a treatment for SCA3 – researchers in Portugal

- Small antibodies made in the lab, destroy harmful matter
- Target toxic protein ataxin-3 aggregates
- Test in animal model
- Co-funded with Plataforma R+SCAs, AISA, ACAH, Swedish SCA-network

Using anti-depressants to treat SCA3 – researchers in Portugal

- Encouraging preliminary data
- Comparing effect of two drugs in mouse models

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Drug repurposing

SIMPATHIC Consortium

- SIMPATHIC - developing 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 EU
- Euro-ataxia one of the patient groups representing people with neurological conditions on this project, supported by Ataxia UK

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euro ataxia

Clinical trials and taking part in research

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Biohaven SCA trial

In September 2024, Biohaven announced positive topline results from their Troriluzole trial in people with SCA.

Phase 3 trial: 3 years, including people with different SCAs (SCA1,2,3,6,7,8,10).

- Compared those on the trial with natural history data, using the ataxia rating scale f-SARA.
- Those treated with Troriluzole showed a 50-70% slowing of disease progression, compared with untreated people in the natural history study.
- This highlights the importance of taking part in natural history studies, such as EuroSCA, as data can be used to show the benefit of treatments in clinical trials.

Biohaven drug seeking approval

- Troriluzole is being evaluated by EMA for the treatment of SCA3 only – based on previous clinical trial results (submitted Oct 2023)
- Euro-ataxia submitted a letter to EMA.
- Based on these very recent results, Biohaven also plans to submit an application to the FDA by the end of 2024, for the treatment of all SCA genotypes by Troriluzole.

Speech therapy projects

- Ataxia UK has 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 other therapies to decide on the best approach, before finalising plans for a larger trial

Drug approval by the FDA for Nieman Pick Type C

25th Sep 2024

IntraBio Inc. is pleased to announce that the U.S. Food and Drug Administration (FDA) has approved AQNEURSA™ (levacetylleucine) for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing ≥15 kg.
AQNEURSA is available now in the United States.

https://www.businesswire.com/news/home/20240925347296/en/IntraBio-Announces-U.S.-FDA-Approval-of-AQNEURSA-for-the-Treatment-of-Niemann-Pick-Disease-Type-C

- NPC – rare neurological disorder, can present with ataxia
- Drug showed improvements in ataxia rating scale
- Drug has potential in inherited ataxias (eg: AT trials)

Opportunities to take part in research

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Natural history and progression studies

DRPLA natural history and biomarker study - Study how DRPLA changes over time, and identify genetic factors and biomarkers. Recruiting people with DRPLA and without ataxia as a comparison.

SIMPATHIC - 60-90 minute online focus group with 3-6 participants to understand the problems faced by those with rare neurological conditions, including SCA3.

ESMI - Developing disease markers and understanding progression of SCA3.

R-PROMS - Aims to assess remote self-reported measures of progression in mitochondrial disease and SCAs

SCA6 and SCA27B survey - a 30-minute online survey to understand the genetic and environmental factors that influence the onset, severity and progression of SCA6 and SCA27B.

Healthcare or service improvement studies

Improving the diagnosis and management of gluten ataxia
Collaboration of Sheffield Ataxia Centre with other UK sites

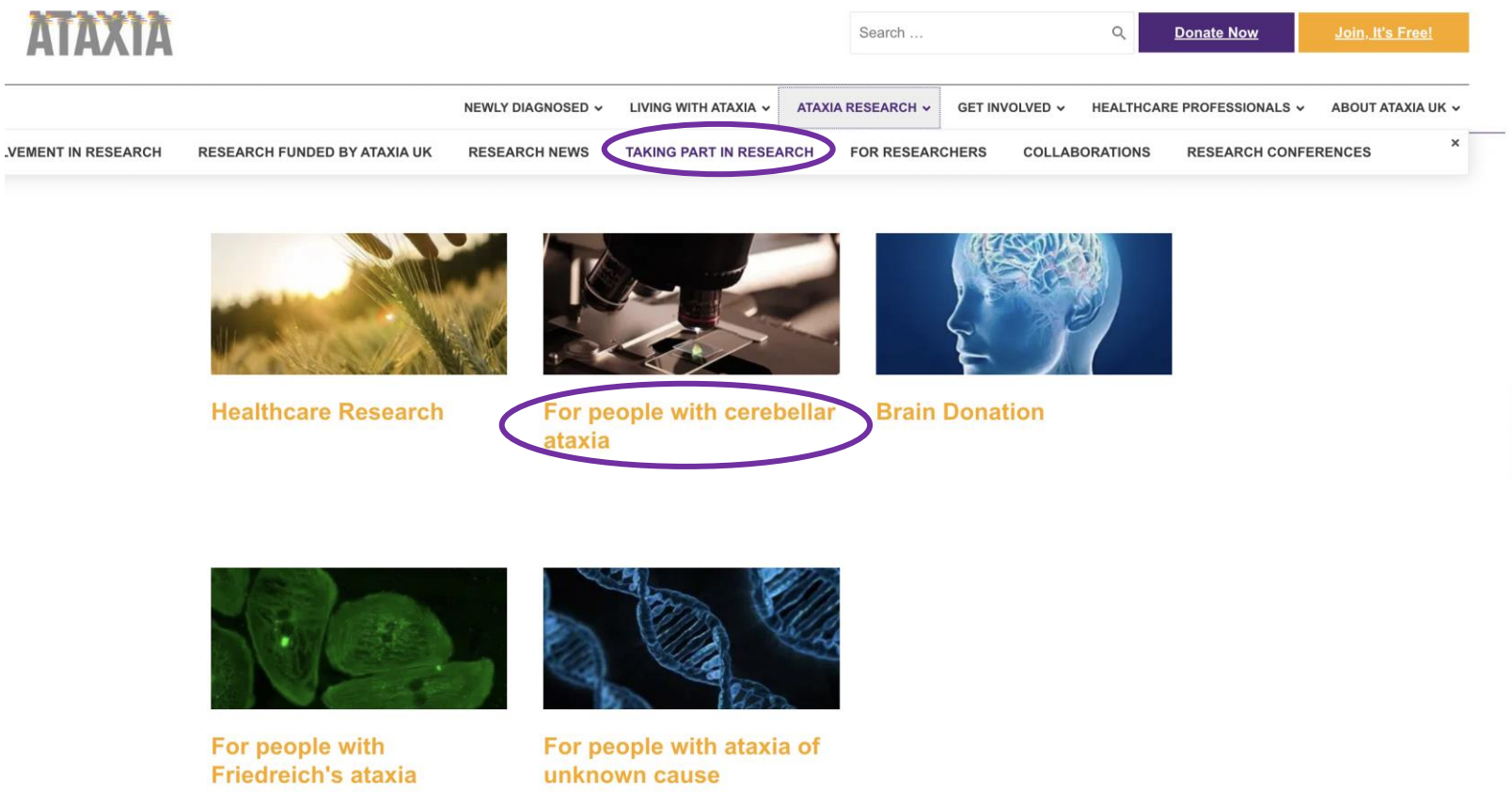
Project Euphonia
Aims to record speech samples to improve voice recognition software for people with dysarthria (speech that is difficult to understand).This is part of Google's AI for social good programme

Other studies

London Ataxia Centre VO659 trial
Aims to test the safety and tolerability of a ASO called VO659, developed by Vico Therapeutics, in those with SCA1 and SCA3

Speech features in ataxias
Aims to investigate speech features in a range of ataxias including SPG-7, CANVAS and Gluten ataxia

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



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Thank you for listening!

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www.ataxia.org.uk

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