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# Exploring outcome measures in adult patients with POLG-related mitochondrial disease

**Submission date**
15/08/2024

**Recruitment status**
No longer recruiting

**Registration date**
17/12/2024

**Overall study status**
Ongoing

**Last Edited**
17/12/2024

**Condition category**
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

## Plain English summary of protocol

Background and study aims
Mitochondria are crucial components found in most cells that generate energy from food to enable cells to function normally.
“Spelling mistakes” (mutations) in the POLG gene, cause mitochondrial dysfunction and subsequently disease, in organs with high energy demands.
The cerebellum, the part of the brain that regulates our balance and movement coordination, and peripheral nerves, are frequently affected in people with POLG-related mitochondrial disease. They develop ataxia, which is a medical term describing symptoms related to balance impairment and muscle incoordination, such as unsteadiness, walking difficulties and slurred speech.
The symptoms of ataxia in people with POLG-related mitochondrial disease are under-researched. Clinical rating scales and questionnaires are tools clinicians commonly use to determine the ataxia’s severity. However, these subjective methods have limitations. They are not sensitive enough to detect small changes in disease progression over a short time.
Given that there are many developments of new therapies for mitochondrial disease, it is vital to identify sensitive and clinically meaningful measures (trial endpoints) relevant to people with POLG-related mitochondrial disease.
Balance and walking (gait) assessments may be particularly useful as clinical trial endpoints for people with POLG-related mitochondrial disease as they have been shown to be sensitive measures in other medical conditions. Several blood tests (referred to as blood biomarkers) can potentially detect mitochondrial dysfunction and the health of nerve cells. However, they have not been specifically investigated in people with POLG-related mitochondrial disease.

Who can participate?
Patients with POLG-related mitochondrial disease (aged 16-75 years)

What does the study involve?
Three study visits will be scheduled over 12 months at the Newcastle upon Tyne Hospitals NHS Foundation Trust. Gait assessments will be performed in a specialised Gait Laboratory and home environment alongside clinical assessment tools and health questionnaires. Blood samples will be collected at each visit.

What are the possible benefits and risks of participating?
Participants will be asked to attend the study site in Newcastle on three occasions over a 12-month period. The visit requirements will be made clear to participants during the recruitment process. In order to minimise the financial burden of attending visits, travel, accommodation (if applicable) and parking costs will be met. Participants will also be provided with refreshments during their visits. The study assessments will be carried out at carefully chosen sites with facilities available to support participants with mobility issues (e.g. accessible facilities). The study visits will consist of a number of assessments and questionnaires some of which may be tiring for participants. The study team are highly experienced in working with this patient group and in managing tiredness in this cohort. Completion of study assessments will be paced accordingly, and participants will be provided with the opportunity to take breaks as needed. Medical and gait assessments will be supervised by research team members who are highly trained in the delivery of these and are able to manage any issues that occur. In order to minimise the visit burden further, participants will be able to complete the participant-reported outcomes remotely i.e. before or post-visit. At all stages participants will be provided with clear instructions and a contact point within the research team should they have any queries or require any support.
At each visit, participants will have a small blood sample taken (approx. 4-5 teaspoons of blood). If required atopical anaesthetic will be used if required to minimise discomfort. Samples will be obtained by appropriately qualified staff who are experienced in collecting blood samples from this patient group and in managing any issues that occur.
It is not anticipated that any findings of potential clinical significance will occur. However, should this happen this will be discussed with the Participant and the Principal Investigator. Appropriate further follow-up will then be arranged with the participant's clinical care team.
There will be no direct benefits to participants from taking part in this study. However, it is hoped that the information gained will help to inform the design of future clinical trials of treatments. Information obtained on the utility of study assessments may also be of use when making recommendations for clinical monitoring of patients with POLG-related mitochondrial disease

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
May 2024 to April 2027

Who is funding the study?
The POLG Foundation (UK)

Who is the main contact?
Dr Yi Shiau Ng, yi.ng@ncl.ac.uk

# Contact information

### Type(s)
Scientific

### Contact name
Dr Yi Shiau Ng

### ORCID ID

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# Additional identifiers

**Integrated Research Application System (IRAS)**
330454

**Central Portfolio Management System (CPMS)**
61953

# Study information

**Scientific Title**
Clinical trial readiness for POLG-related mitochondrial disease and ataxia: a prospective, longitudinal study identifying sensitive and ecologically valid biomarkers (C4TR-POLG)

**Acronym**
C4TR-POLG

**Study objectives**
To investigate emerging outcome measures alongside current clinician and patient-reported outcomes and potential barriers to their adoption in clinical trials.

**Ethics approval required**
Old ethics approval format

**Ethics approval(s)**
Approved 01/05/2024, London-Bromley Research Ethics Committee (2 Redman Place, Stratford, E20 1JQ, UK; +44 (0)207 104 8118; bromley.rec@hra.nhs.uk), ref: 24/LO/0308

**Primary study design**
Observational

**Study design**
Observational cohort study

**Study type(s)**
Other

## Health condition(s) or problem(s) studied
POLG-related mitochondrial disease

## Interventions
At the Screening/Baseline visit, participants will be asked to provide written informed consent and eligibility will be confirmed in writing. The following study assessments will then be conducted:
1. Biometric assessments (including medical history, physical examination, demographics and anthropometrics and clinical review of medical records)
2. Participant-completed questionnaires (on ataxia, balance and quality of life)
3. Clinical rating scales
4. Functional assessments of upper limb, co-ordination and gait
5. Instrumented gait and balance assessments
6. Habitual physical activity monitoring via wearable sensor (for 3 days post-visit)
7. Blood sample

Participants will return to site for two further visits at Month 6 and Month 12, at which the above assessments will be repeated. At the final study visit (Month 12) participants will also be asked to provide feedback on their participation in the study.

Following the completion of physical activity monitoring for three days following the end of study visit, study participation for each participant will end.

Pseudo-anonymised data collected in this study will be combined with data collected via a twin study (operating under separate approvals and governance) undertaken in Tübingen Germany.

## Intervention Type
Other

## Phase
Not Specified

## Primary outcome(s)
1. The feasibility of monitoring real-world mobility (habitual activity and gait) in ambulatory patients with POLG-related mitochondrial disease via instrumented measures of balance and gait using wearable sensors in a controlled setting at baseline, month 6 and month 12
2. Attrition rate assessed using the number of participants who consent to participate who remain in the study until the end of follow-up at 12 months

## Key secondary outcome(s)
All measures will be performed at baseline, 6 months and 12 months depending on participants' abilities:
1. Disease severity will be measured using the Newcastle Mitochondrial Disease Adult Scale (NMDAS) Sections I, II and III
2. Severity of ataxia will be measured using the Scale for Assessment and Rating of Ataxia (SARA)
3. Balance and gait will be assessed using wearable sensors to evaluate postural sway, gait within the gait laboratory and habitual physical activity in the free-living environment. A clinical assessment of gait will be measured by the Functional Gait Assessment.
4. Upper limb coordination will be measured using the nine-hole pegboard test
5. Cognitive function will be measured using the Montreal Cognitive Assessment (MOCA) and

Cerebellar Cognitive Affective Scale (CCAS)
6. Patient-reported outcomes:
6.1. Falls and balance measured using the Falls Efficacy Scale-International (FES-I) and the Activities-specific Balance Confidence (ABC) scale.
6.2. Fatigue measured using the Fatigue Severity Scale (FSS)
6.3. Ataxia measured using the Patient-Reported Outcome Measure of Ataxia (PROMA)
6.4. Quality of life measured using EQ-5D-3L and the Newcastle Mitochondrial QoL Questionnaire (NMQ)
6.5. Disease severity measured using the Patient Global Impression (PGI) Scales for Severity (PGI-S) (Baseline) and Change (PGI-C) (6 months, 12 months)
7. Fluid biomarkers including creatinine kinase, serum lactate, serum neurofilament light chain, FGF21, GDF15 and circulating cell free mitochondrial DNA

### Completion date
01/04/2027

## Eligibility

### Key inclusion criteria
1. Be aged >=16 years and <=75 years at the start of study (Baseline)
2. Have the ability, in the opinion of the study team, to participate in study activities
3. Have the mental capacity to provide informed consent
4. Have sufficient basic understanding of written and spoken English in order to complete the study questionnaires/assessments
5. Have a genetically confirmed diagnosis of POLG-related mitochondrial disease
6. Be willing to wear three sensors (lower back and both feet) and keep an activity diary for three consecutive days
7. Have no other known neurological or musculoskeletal disorder significantly affecting balance and mobility

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
16 Years

### Upper age limit
75 Years

### Sex
All

### Key exclusion criteria

1. Are aged <16 or >75 years
2. Have a significant learning disability or cognitive impairment that limits the individual's ability to provide informed consent
3. Do not have a sufficient understanding of written or spoken English for completion of study questionnaires/assessments
4. Are enrolled in an interventional study or clinical trial at the time of recruitment, or have participated in an interventional study/trial within four weeks of baseline
5. Are pregnant at the time of enrolment
6. Have been hospitalised for refractory seizures in the preceding three months and/or have required frequent adjustment of anti-seizure medications

### Date of first enrolment
20/06/2024

### Date of final enrolment
01/04/2026

## Locations

### Countries of recruitment
United Kingdom

England

Scotland

Germany

### Study participating centre
**Freeman Road Hospital**
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

### Study participating centre
**Hertie Institute for Clinical Brain Research (Lead Centre)**
Otfried-Müller-Strasse 25
Tuebingen
Germany
D-72076

### Study participating centre

**Oxford University Hospitals NHS Foundation Trust**
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

**Study participating centre**
**Queen Elizabeth University Hospital**
1345 Govan Road
Glasgow
United Kingdom
G51 4TF

# Sponsor information

**Organisation**
Newcastle upon Tyne Hospitals NHS Foundation Trust

**ROR**
https://ror.org/05p40t847

# Funder(s)

**Funder type**
Charity

**Funder Name**
The POLG Foundation

# Results and Publications

**Individual participant data (IPD) sharing plan**
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

**IPD sharing plan summary**
Published as a supplement to the results publication

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Participant information sheet | version 1.0 | 21/03/2024 | 04/09/2024 | No | Yes |