



Study Protocol

International A-T Registry

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1. Introduction

The purpose of this study is:

- To establish an international registry for A-T and closely related conditions
- To make data from the registry available to clinicians and researchers seeking to understand and develop new and improved treatments for A-T and related conditions

The hypothesis underpinning the design of the A-T International Registry is that gathering detailed clinical data, both cross-sectional and longitudinal, on people with A-T and related conditions will improve our understanding of the conditions and the phenotypes they produce and contribute to the production of natural histories of the conditions. This in turn could lead to improvements in patient care and aid the development of new therapies and drugs. It will also facilitate the identification and recruitment of participants in future clinical trials.

1.1 Ataxia telangiectasia

Ataxia-telangiectasia (A-T) is a complex multi-system autosomal recessive disorder caused by mutations in the ATM gene, affecting around 1 in 300,000 births. This gene codes for a protein kinase which is involved in many cellular processes triggered by stress such as DNA repair, anti-oxidation and autophagy. A-T is characterised by a range of clinical features including but not limited to:

- progressively worsening neurological manifestations (including ataxia, dystonia, tremor, oculomotor apraxia, dysarthria and dysphagia)
- oculo-cutaneous telangiectasias
- recurrent infections to the chest, ears and sinuses
- a wide range of immunological abnormalities, including deficiencies of immunoglobulin and reduced lymphocyte numbers
- An increased risk of developing malignancies (22% in the UK)
- Increased radiosensitivity to therapeutic doses of ionizing radiation,

Despite discovery of the gene in 1995 and much research aimed at understanding the role of the protein and how its lack leads to the symptoms of AT, much is still unknown or poorly understood. Treatment tends to focus on the management of symptoms, secondary infections and downstream effects such as lung disease and where these occur, malignancies.

The complex multisystem nature of the disease coupled with its life shortening effects calls for an expert multi-disciplinary approach to treatment. This has led to the development of specialist centres in a number of countries. Nevertheless the rarity of the condition means that in many countries this has not happened and many people are treated by clinicians with a very limited experience of the condition. This, along with the heterogeneity of the phenotype makes it difficult to bring together large enough cohorts to build up an evidence-based understanding of the condition. Hence the urgent need for this registry.

1.2 Other related conditions

There are a number of other conditions caused by the lack of proteins which operate in similar cellular pathways to the ATM protein which give rise to conditions which share different aspects of the A-T phenotype. These are all rarer than A-T, which is why they are included in this registry rather than having one of their own.

These conditions are:

- ATLD (A-T-like disorder), caused by mutations to the MRE11 gene. This produces symptoms very similar to those of A-T, especially neurological symptoms. Progression of symptoms seems to be somewhat slower than in classic A-T.
- AOA1 (ataxia-oculomotor apraxia type 1), caused by mutations to the APTX gene which produces a protein called Aprataxin. Like A-T, it usually develops in childhood, and causes a similar range of movement and visual problems. However there are usually no associated immunological problems and telangiectasias do not appear to develop.
- AOA2 (ataxia-oculomotor apraxia type 2) has a range of symptoms similar to those of AOA1, however it tends to develop later, typically in late adolescence or early teens. It is the result of mutations on yet another gene, the SETX gene. AOA2 seems to be a little more common than AOA1.
- Nijmegen breakage symptom (NBS) caused by mutations to the NBS protein. NBS produces microcephaly with distinctive facial features and mild to moderate intellectual disability. In common with A-T it also gives immunological deficits leading to recurrent respiratory tract infections, as well as an increased risk of cancer.
- Nijmegen breakage symptom-like disorder (NBSLD). Only a handful of patients have been diagnosed with this condition, which is due to mutations in the RAD50 gene, so there is little certainty about the phenotype. However it appears to produce mild microcephaly and altered facial features with mild ataxia and radio-sensitivity, but no evidence of immunodeficiency. Cancer risk is unknown.

2. The International A-T Registry

The database has been designed to gather and collate information about the different aspects of A-T from doctors and clinical centres across Europe and the rest of the world.

It is our intention that information on the UK CF Registry can also be compared with information collected by the A-T Families Global Platform and by other registries or database collecting relevant data, such as the registry of the European Society of Immunodeficiencies (ESID).

Local staff will enter data from their patients. They are able to see all the data from their own patients and are able to generate local reports.

Registry staff are able to see the merged data from all participating centres. As trends in the disease are tracked over time longitudinal data are held. However, this centrally held data is anonymised. Only staff at the participating centres can link the relevant data to particular patients.

Use of data in the national database is subject to approval from the International A-T Registry Steering Committee. Where appropriate, research projects will require the relevant approvals from a Research Ethics Committee.

2.1 Patient anonymity

Patient anonymity is paramount within the registry. This is achieved by the generating a unique number for each patient at the time of initial registration by their centre at registration. This PIN identifies the patient within the database but its link to identifying data is not stored centrally on the database and is known only to the centre entering the data. Should the patient transfer to another A-T clinic, staff at the original centre can change the clinic

associated with this PIN. They will continue to be able to see the data they entered, but not that entered at the new centre. This mechanism ensures that patient names are known only to their immediate carers and will not normally be known even by authorised members of the Registry team.

2.2 Compliance with the data protection act

The database is fully compliant with the principles of the Data Protection Act.

2.3 Gathering Clinical Information

Routine clinical data will be collected in accordance with local protocols and entered in the patients' hospital notes. Data will then be transferred to the database.

2.4 Emergence of significant findings for individual

Should any research using data from the registry identify anything which might affect the treatment and care of a patient, this will immediately be notified to the clinician or centre responsible for that patient's data./

2.5 Data accuracy

Data accuracy considered central to the database protocol. Monthly audits and sampling checks will be carried out. All queries or errors will be notified back to the A-T centres within two weeks of identification.

2.6 Access to data

Access to the entire database is regulated by the A-T International Registry Scientific Board which considers requests by email and conference call.

Authorised personnel at the A-T Society will have access to the database for administration and data verification purposes.

Authorised clinicians or personnel at a registered A-T centre will be able to review data entered on the centre's patients. This will enable local clinicians to review individual trends and facilitate the planning of the patients' clinical management. Personnel will be only able to review data from their own centre; they will not be able to view data from other centres.

3. Publication Policy

The publication policy will be discussed and agreed with the A-T International Registry Scientific Board.

Annual reports will be produced by the A-T society in conjunction with the Scientific Board.

4. Amendments

All amendments must be submitted to and approved by the Research Ethics Committee.