



*The Genetic Aspects of A-T
&
Pre-natal Diagnosis*

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THE GENETIC ASPECTS OF A-T

Introduction

Ataxia-Telangiectasia (“A-T”) is a rare, genetic condition. It is inherited by a child who gets one “faulty” A-T gene from each parent. Thus the affected child has two copies of the faulty (changed) gene. The parents have one normal gene and one faulty gene and are called carriers. The parents do not have the condition since one normal gene is sufficient for good health. Implications for carriers will be discussed later.

It is estimated that around 1 in 100 people in the UK population may be carriers of the faulty A-T gene. This is worked out from the incidence of the condition in the population.

No one is responsible for these faulty genes. We all have faults (also known as mutations or changes) on several genes which could, in a double dose, lead to a genetic disorder. As long as we have a normal copy on the other chromosome (chromosomes are paired) there is no disease.

Many advances have been made in A-T research in the past few years. With the discovery of the gene, the focus now is on understanding how gene changes lead to cell damage. Ultimately this will reveal how to intervene to improve the outlook for people with A-T.

This paper is only a brief summary for reference and to help parents think through the questions which still puzzle them. The details may require updating in the light of new information. Every family in which A-T has been diagnosed should have access to specialists, in particular paediatric and adult neurologists, immunologists and clinical geneticists, to answer questions and advise on the management. Such specialists should preferably have experience of the condition.

The following areas are considered:

- **The inheritance pattern in A-T**
- **Some information about the A-T gene and ongoing research**
- **The possibility of identifying carriers among other interested relatives and the implications for them.**

(Pre-natal diagnosis is considered in the following paper.)

What are genes?

A lot of media attention now focuses on genes, genetic disorders and possible gene therapy. There is a world-wide initiative to identify all of our genes (approximately 30,000 in total) and their function. This initiative is called “The Human Genome Project.”

The reason that children resemble their parents in so many different ways, and may also inherit susceptibility to specific diseases, can now be better explained:

- Our inherited material is found on chromosomes which are present in the nuclei of our cells.
- Segments of a chemical called DNA, which makes up the chromosomes, are called genes.

- There are 23 pairs of chromosomes in each human cell, and on each chromosome there are several thousand individual genes, most of which are paired.
- Each gene makes a specific protein, which has a function in the cells of different parts of the body.
- If a gene is faulty, the correct protein is not produced and this may affect particular organs.
- In A-T, the nerve cells in the cerebellum (the part of the brain concerned with balance and co-ordination) and the lymphocytes (white blood cells which fight infection), are principally affected.

Inheritance

For some years it has been known that the gene fault which causes A-T is on chromosome 11. When the gene was specifically identified in 1995, the pattern of inheritance previously assumed was also confirmed.

Each of us has two copies of chromosome 11 in every cell in our body. If there is a fault on the A-T gene on one of these paired chromosomes, the other compensates (so that person is a healthy carrier). However, when we have children we only pass on one of each pair of chromosomes into the egg or sperm (each of which only has a single set of 23 chromosomes). Thus when two carriers have a family, their children could inherit a double dose of the faulty A-T gene. From the diagram on the next page you can see that it is a 1 in 4 chance for a child to receive two faulty copies. Carrier parents, of course, could not have known their carrier status beforehand. This is called **recessive inheritance**.

The chance of an affected child from carrier parents (1 in 4) would be the same in each pregnancy and is not related to whether or not existing children are affected.

In the majority of families who already have a child with A-T, pre-natal diagnosis (testing in pregnancy) is now an option. The following paper explains this in more detail. Also, because we all have pairs of chromosome 11, boys or girls have an equal chance of being affected.

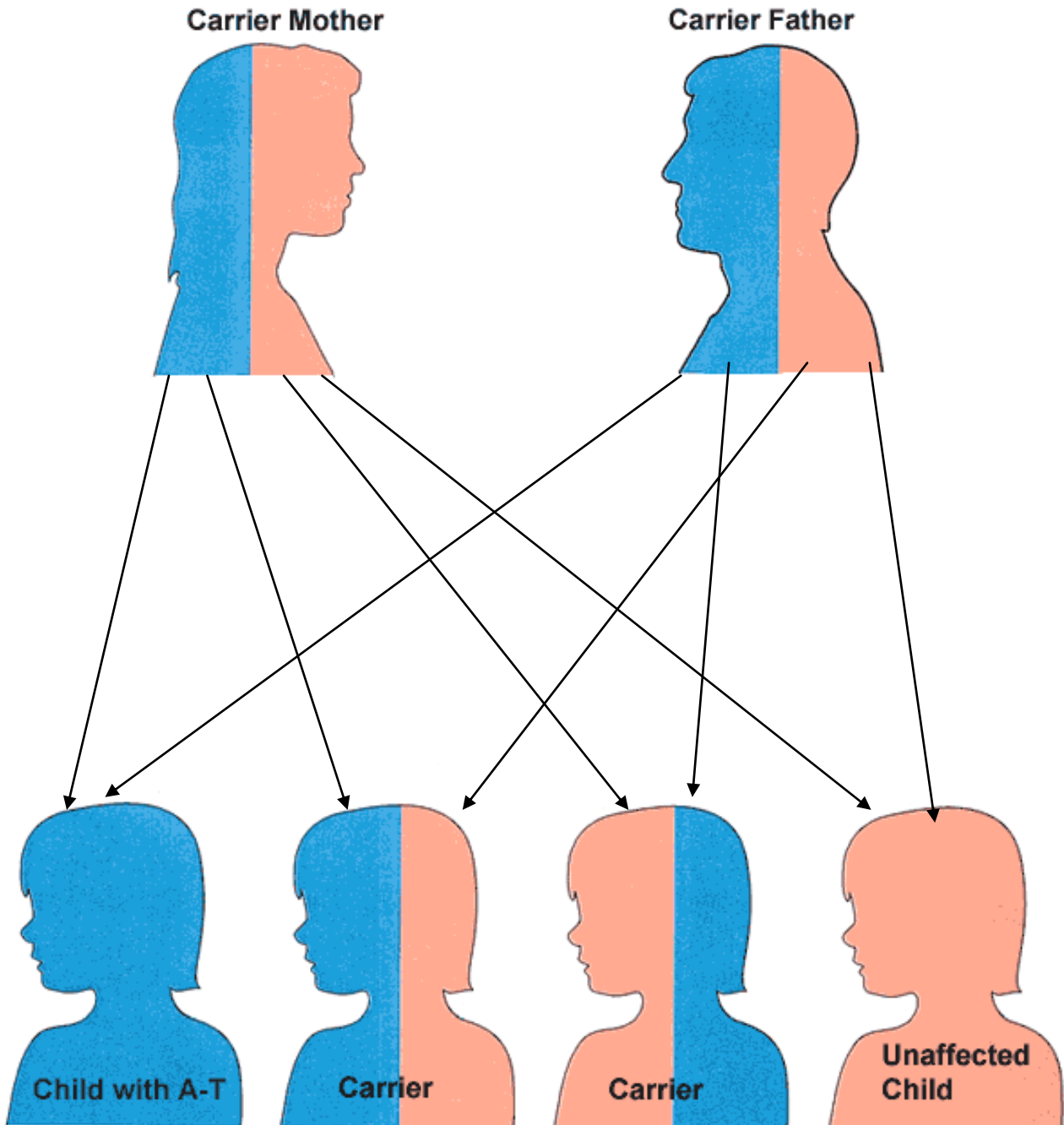
The A-T Gene

After many years of collaborative work by several laboratories around the world the A-T gene was identified in the summer of 1995. It is a large gene as it has a longer stretch of DNA compared to some other genes. Professor Malcolm Taylor and his team at the University of Birmingham were instrumental in the discovery of the gene and are continuing to research into its function. There may be different effects of the gene in different cells e.g. cerebellar cells and lymphocytes.

Different changes (mutations) in the gene may also result in different effects. From our experience at the A-T Clinic we know there is a lot of variation in how A-T affects individuals. Professor Taylor and his team are currently trying to identify, as far as possible, the mutations (changes) in all A-T patients in the UK.

If it can be shown that people with similar mutations (i.e. the same type of change in the same position in the A-T gene), have similar problems, e.g. impaired immunity or radiosensitivity, then, hopefully, in the future it will be possible to predict the likely problems and help to monitor (screen) appropriately. Ultimately the aim of all this research is to contribute to the development of a treatment for A-T.

RECESSIVE INHERITANCE



Carrier Testing

Within a family who already have a child with A-T: when a couple has a child with A-T both parents must be carriers of the A-T gene. It follows, therefore, that any unaffected children have a two out of three chance of being a carrier, as shown in the diagram earlier.

By testing blood samples from all the family and comparing the inherited patterns around the gene on chromosome 11 (and/or the actual mutation if it has been identified in the family) it is usually possible to tell fairly accurately whether or not the unaffected child is a carrier.

Siblings: even if the brother or sister of an affected child is a carrier, there is a much lower risk of them having affected children because it would depend on them also meeting another carrier – a **1 in 100** chance. **Thus the chance of having an affected child would be around 1 in 400.**

Carrier testing for partners of known carriers and the general population: at present we cannot offer carrier tests to partners of known carriers or, indeed, the general population since we have not identified all the changes in the gene which would need to be excluded. However this may change if the majority of mutations are detected.

Possible Health Risks to Carriers

Studies suggest that carriers of the A-T gene, although otherwise healthy, may have a moderately increased risk of some types of cancer, breast cancer in female carriers being the most significant.

At present the Department of Health is reviewing whether or not it should recommend that known carriers of A-T enter the current breast screening programme (every 3 years from age 50 years) earlier. **However, if anyone (including carriers of A-T) has a strong family history of breast cancer, this should be considered separately.** Carriers of A-T should certainly mention their status to their doctors.

The increase in cancer risk may be related to the fact that cells from some carriers show a slightly increased radiosensitivity (tested on a blood sample). This change is not as high as in people with A-T but is intermediate between A-T and normal. **Thus, treatment may be modified for any cancer in an A-T carrier whether its presence is related to the A-T gene or not, to avoid problems of radiation side effects.**

The issues raised above are now the focus of extensive continuing research. No definite guidelines about screening tests for carriers of the A-T gene have yet been suggested. However advice in individual cases can be obtained from your local Genetic Centre or from the A-T Clinic in Nottingham.

PRE-NATAL DIAGNOSIS IN A-T

Introduction

When a child develops Ataxia-Telangiectasia (“A-T”), we know that the healthy parents both carry a changed gene on a part of chromosome 11 and that the child has inherited a “double dose”. This is “recessive inheritance” and the chance of this occurring is 1 in 4 each time the couple has a pregnancy. If they wish to consider pre-natal diagnosis in a subsequent pregnancy, this has to be fully explored in advance. **This testing is only available to couples who already have a child diagnosed with A-T.**

Pre-natal Diagnosis

One accurate method for detecting if a foetus is affected by A-T, is by measuring the response of cells from the pregnancy to ionising radiation:- chromosomal radiosensitivity testing. This can be done by chorionic villus sampling (“CVS” see below). The reliability of this test would depend on having demonstrated radiosensitivity in the existing child(ren) with A-T and this should be done in advance of the pregnancy. This test is currently performed at Guy’s Hospital, London.

Alternatively, in families where we know the exact gene changes, the nearest Clinical Genetics Centre can arrange for pre-natal testing by CVS. Some of the sample is sent to Professor Malcolm Taylor at the University of Birmingham and some to another laboratory in Sheffield for testing. The result takes about 2 weeks. The CVS test is usually carried out at around 10 weeks into the pregnancy. Therefore the result should be available at around 12 weeks’ gestation.

The above tests will give an accurate answer as to whether or not the foetus is affected (although no test is ever 100% certain). If the foetus is affected, parents would then have the choice about whether or not to continue the pregnancy.

Pre-natal diagnosis is usually sought by parents who have decided in advance to terminate an affected pregnancy. This is not an acceptable option for everyone for differing reasons, but whatever you do, you would be supported by the professionals involved.

What is involved?

Prior to a further pregnancy, the specialist laboratories would wish to check the situation and make sure pre-natal diagnosis is feasible. This means blood samples from the whole family should have been analysed by the Birmingham laboratory and a blood sample from an existing affected child should have been checked for radiosensitivity at Guy’s Hospital. **It is absolutely essential to do this before conception.**

Tests in Pregnancy

Two are available: chorionic villus sampling (CVS) and amniocentesis.

Chorionic Villus Sampling (CVS)

This test is usually carried out at around 10 weeks into the pregnancy. The procedure takes around half an hour and involves visiting the hospital for no more than a couple of hours. A fine,

flexible, plastic tube is passed from below, through the cervix, under ultrasound control and a small sample is taken from the edge of the developing placenta, which contains the same chromosome pattern as the foetus. Women who have had this done say the sensation is similar to having a cervical smear test.

The sample can be taken fairly locally, although it should then be sent to the relevant specialist laboratories (arranged in advance). A result should be available in about two weeks. There is a small chance that the procedure may cause the pregnancy to miscarry (about 1%) and this should be borne in mind. If the foetus is affected and the couple decide to terminate the pregnancy, the procedure is like a D & C (Dilation and Curettage) and is carried out under a general anaesthetic if the pregnancy is still at an early stage.

Amniocentesis

This test is carried out later in the pregnancy, at about 16-18 weeks. A sample of the fluid surrounding the baby is taken, again under ultrasound scan control, via a needle through the abdominal wall. It has a slightly lower risk of causing miscarriage than the CVS but the results are not available until about 19 weeks into the pregnancy. A termination at that stage would involve a mini-labour.

Remember, always consult the relevant specialists, in advance of a pregnancy, before deciding for or against pre-natal diagnosis so that you receive the most upto date information. The obstetrician can then liaise with the geneticist and the relevant laboratories to check that all necessary preliminary investigations have been carried out.

If in doubt, please contact us at the A-T Clinic, City Hospital, Nottingham. Referral can be via your GP, your specialist or the A-T Society.

Conclusion

I hope these papers have answered many of your questions but, no doubt, they may have raised many more! These papers are no substitute for detailed individual family counselling and good local support from medical staff, physiotherapists, occupational therapists, speech therapists and other professionals as appropriate. The A-T Society is working with the professional teams to increase knowledge about all medical aspects of A-T. It can also advise about entitlement to benefits, grants, etc.

At the multi-disciplinary A-T Clinic in Nottingham we have seen more than 100 families already. We would be happy to see any family to discuss further the above issues, including management in a way complementary to local arrangements. Referral can be via your GP, your specialist, or the A-T Society.

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The Ataxia-Telangiectasia Society

Supporting the Family—Fighting the Disease

The Ataxia-Telangiectasia Society is a national charity. Our objective is to alleviate the suffering and distress that A-T causes. We do this by:-

- Supporting families
- Improving clinical management through two specialist clinics
- Providing information and raising awareness
- Funding research

We rely totally upon voluntary donations to continue our work.