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The content of this piece has been developed with the invaluable collaboration of Prof Philip Hawkins, UK and Dr Isabel Conceição, Portugal

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Transthyretin familial amyloid polyneuropathy (TTR-FAP)

...Is a very rare disease that is passed on through families as a genetic disorder. TTR-FAP is inherited, but not necessarily by all the children of an affected person – on average, only half of the children of an affected parent will inherit the gene for the disease. Even when the problem genes are passed on, those family members who inherit them may never develop the TTR-FAP disease, and stay free from it for their entire lifetime. Those family members who do develop the disease may experience the symptoms at almost any time, from being a young adult to sometimes quite late in life.

More than 100 different types of genetic mutations have been identified from all over the world in people with TTR-FAP, and large clusters of the disease occur in particular places. For example, there are hundreds of people with one particular genetic cause of TTR-FAP (called V30M) in Portugal, Sweden and Japan. This is in contrast to what we see in the UK where the current number of people who have been diagnosed with this type of inherited TTR-FAP is less than 100.

The typical symptoms that occur in TTR-FAP develop due to the abnormal gene causing the deposition of a substance called amyloid. When this happens, amyloid is deposited in tissues and organs throughout the body. TTR-FAP mainly affects the nervous system, causing abnormal and reduced sensation to touch and temperature in the early stages. The symptoms of TTR-FAP will usually escalate over time and this will lead to muscle weakness in the limbs and problems with other nerves that control body functions such as blood pressure and the bladder, as well as digestive functions. Most of the genetic mutations involved in amyloidosis are linked to amyloid being deposited in heart muscle (although less so with the V30M type mentioned above). TTR-FAP can also affect the jelly of the eye and sometimes other vital organs.
Diagnosis of TTR-FAP usually requires a range of tests; particularly taking small samples of tissue for examination (known as a biopsy) and genetic tests which can identify the mutated genes known to cause the disease. As TTR-FAP usually gets worse over time, an early diagnosis of the disease (as soon as the symptoms start to appear) is very important in order for people to receive the best medical care as soon as possible.

Once TTR-FAP has been diagnosed there are many ways in which symptoms can be eased, for example by medicines that reduce nerve pain and digestive symptoms. The disease usually progresses and typically leads to death within 5–15 years.

One of the effective treatments for TTR-FAP is liver transplantation. This is because the liver produces the abnormal protein that directly leads to the formation of amyloid deposits. If a person with TTR-FAP is able to have a liver transplant, the source of the disease is removed. Transplantation has been most successful in younger people with the V30M type of mutation – particularly when performed soon after the first symptoms have developed.

There is also optimism that new and effective treatments will become available in the UK during the next few years. There are at least five medicines currently in development. Encouragingly, the first of these new drugs is expected to become available in the near future.

**Professor Philip N. Hawkins**
National Amyloidosis Centre
Division of Medicine,
UCL Medical School, Royal Free Hospital
Rowland Hill Street, London
Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP) - the genetic origins

> Sixty years after the first case was reported in Portugal, TTR-FAP is now identified in many more people around the world. As medical care has improved, doctors in specialist centres are becoming more experienced in the diagnosis and management of TTR-FAP.

Origins in Portugal

Transthyretin familial amyloid polyneuropathy (TTR-FAP) was originally described by doctors in the 1950s in Portugal. This was quickly followed by more identification in Japan and Sweden. Although TTR-FAP is a very rare disease (less than 1 in 100,000 people worldwide), it occurs more often in some countries because of the presence in families and communities of a specific type of genetic mutation. In particular, the V30M genetic mutation has been identified in as many as 1 in 1,000 people around Póvoa do Varzim in the northern part of Portugal. This mutation has also been found in many other countries, especially in the North of Sweden, and in Aro and Ogawa in Japan.

The same genetic abnormality can be associated with different types of symptoms in different countries

In Portugal, most people with the V30M mutation have developed symptoms in their thirties, whereas in Sweden, only 5–10% of the persons who carry the same mutation will develop TTR-FAP and symptoms will typically appear in their fifties. Other mutations of TTR are linked with different symptoms. The commonest mutation which is linked to TTR heart disease is thought to be present in as many as 5% of people with African ancestry. It is important to note that this type of genetic mutation has not been seen to lead to significant disease of the nervous system (as seen in TTR-FAP) but leads to deposition of amyloid directly into the muscle of the heart.

How is the diagnosis of TTR-FAP made?

If amyloidosis is suspected, this is often confirmed by tissue biopsy. Aspiration (removal by suction of tissue) of fatty tissue from beneath the skin after the skin has been made numb with local anaesthetic often provides sufficient tissues to diagnose amyloidosis. Other specific heart investigations (tests) may be included as additional tests. A genetic test is also a key part of diagnosis and is often used to confirm the suspicion of TTR-FAP following a biopsy or other tests.

Focus

- As an alternative to biopsy, a full body scan can be performed in some specialist centres.\(^5\)
This can show the distribution and amount of amyloid throughout the body. Serum amyloid P component (SAP) scans are painless and are performed 6 to 24 hours after an intravenous injection of a very small dose of radioactive tracer.\(^5\) The procedure is safe and can be repeated every 6 to 12 months to monitor the course of the amyloid deposits.

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Genetic testing – the key to uncovering an hereditary disease

Why might genetic testing be important?\(^1\)
In the families of those people affected, it is possible to identify relatives who carry the abnormal gene and who will therefore be at risk of developing the disease.

This testing (a blood test) is only offered to adults (over 18 years of age) once they have received important genetic counselling to understand what is involved and make the decision to take a test or not. Genetic counsellors have an important role in helping families understand more about this complex disease, the risks of transmission and the possible benefits and disadvantages of undergoing genetic testing.

Importantly, not all individuals who have inherited a genetic mutation linked to TTR-FAP will develop the disease.\(^2\)
Every family is different, so it is very important for doctors and family members to discuss the medical history of a particular family in order to evaluate the likelihood that anyone in the family with a TTR mutation will eventually develop the disease. The family medical history also provides important clues as to the likely age when symptoms of TTR-FAP may be expected to appear – this may be very different between families and different ethnic groups, even with the same type of gene mutation.

In some families, the start of symptoms often occurs a little earlier with each generation.\(^3\)

Even within the same family, it may be that each person with TTR-FAP will experience different symptoms than other family members with the same mutation.

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What’s important about genetic testing?

Genes are made from a long molecule called DNA, which is copied and inherited across generations. Genetic testing is done in a laboratory to look at the ‘instructions’ your DNA inherits from your mother and father. These tests can be used to identify the risk of developing diseases such as TTR-FAP and are one of the best ways to diagnose problems at an early stage, when treatments may be most effective.

What can a genetic test tell you?
There are many reasons you might consider taking a genetic test. Some examples include:

- Have symptoms that suggest an inherited disease
- Have family members who have an inherited disease and you would like to understand if you are also at risk
- Are worried that because a disease is present in your family that you may pass it on to your children, even if you did not have the symptoms
- If you are pregnant and want to establish if your baby has a genetic disease

How will I know if a genetic test is right for me?
Having a genetic test is a very individual and personal decision. Expert genetic counselling is important for...
anyone considering a test and will help you come to the right choice for you. Some of the questions which will be useful for you to discuss with a genetic counsellor may include:

- What does my family’s medical history mean in terms of my own risk of developing TTR-FAP?
- What are my chances of developing the disease if a test does show I have the genes which put me at risk (not all people who carry the mutations will develop TTR-FAP)?
- What treatments are available for TTR-FAP and how effective are they?
- What are the advantages of knowing I have the genes that put me at risk of developing TTR-FAP?
- Are there any disadvantages of taking a test?
- What are the disadvantages of knowing I have the genes that put me at risk of developing TTR-FAP?
Perspectives

- If my test shows I have the genes which put me at risk of TTR-FAP, what should I tell my family, should they all be tested as well?
- Will my results be confidential and kept from insurers and employers?

The benefits of early diagnosis of TTR-FAP
As highlighted, taking a genetic test is a personal decision. One of the key aspects of TTR-FAP is that it is a progressive disease, where symptoms will get worse, usually over only a few years if the condition is not diagnosed and treated appropriately. Knowing that you carry the gene that puts you at risk of developing TTR-FAP in the future may be a major factor in getting a very early diagnosis and appropriate care from your doctor. People carrying a gene, which increases the risk of becoming symptomatic with TTR-FAP, can be carefully monitored (usually once a year) and as soon as minor signs or symptoms develop, appropriate early action can be taken by the healthcare team.

What is the best path for a person who may be concerned about TTR-FAP to consider genetic testing?
There is a well-established approach to genetic testing in order to ensure people are properly prepared and have adequate information. Expert genetic counselling (discussing the important facts and information) is the first step and usually takes place over several weeks. The conversations with the expert counsellor before and after the blood samples required for the genetic test offer space and time to discuss the disease. The main aim is to help people explain their own feelings and reasons for their request, their worries and their expectations. Asking for a test is not a matter to be taken lightly; on the contrary, it involves a commitment at both the individual and the family level, as with any genetic disease. Sometimes the request comes from a couple wishing to have a child. They want to know their status and be informed about the risks of passing on the disease and the possibility of medically-assisted conception (prenatal or pre-implantation genetic diagnosis).

The right to know... or not to know
A person can decide to stop the diagnostic process or delay the communication of test results at any time on personal grounds (examinations, family event, holidays, etc.). It is not possible to request a genetic test under the age of 18 years. This age limit has been set by medical authorities because no medical benefit is gained from knowing one's status earlier, as the disease does not appear until adulthood. Asking for a genetic test is a decision that may have a significant impact on the future and can only be taken by a person over the age of 18. When an 18-year old asks for a genetic test, medical staff will be particularly careful.

The typical diagnostic procedure for TTR-FAP usually includes 5 stages:
- Meeting with the neurologist (or a specialist in TTR-FAP) or a geneticist, who compiles a family tree
- Start of genetic counselling
- Blood samples are taken for the genetic test
- Communication of the test results by the neurologist (or a specialist in TTR-FAP)
- Psychological support: one consultation (or more than one if the patient wishes)
Carrying a genetic mutation does not mean being ill: between the moment a person learns that he/she has a mutation and the moment the disease develops, there is a whole period of life when he/she will still be healthy, the length of which can depend on the mutation. It is also important to know that many people who carry a genetic mutation never go on to develop TTR-FAP. The advantage which comes from the knowledge of carrying the mutation is that regular check-ups can then be done in order to pick up any early signs of TTR-FAP and effective treatment started as early as possible in order to slow the progression of symptoms.

What if the results show the presence of the mutation?
The point of diagnosis is a very emotionally intense moment. If the test shows that a mutation linked to TTR-FAP is present, the diagnosed person can be overwhelmed by a flood of feelings, including rebellion (“Why me, why my family, what have I done?”), fate (“I am going to be like my father”), etc. A team of experts is available to answer questions the person may have about the disease. Psychological support may be extremely valuable in helping the diagnosed person not to feel abandoned in this stage of their life and can enable them to overcome the emotional shock and regain control.

The psychologist needs to evaluate the reasons behind the request and be able to identify any potential family pressures that might reflect the anxiety of the parents, who perhaps carry a sense of guilt associated with the risks of transmission and are worried for the future of their children.
What is the typical pattern of symptoms on TTR-FAP?

> TTR-FAP is a progressive disease, in which the symptoms often change over time.

**Sensory symptoms** usually occur first. Loss of temperature (cold/hot) sensation, as well as sensations such as tingling, prickling or numbness or feelings of intense pain (like burning) are typical early signs of TTR-FAP. These symptoms start in the lower legs and spread to the upper legs and hands. A few years after the start of symptoms, other nerve fibres are usually affected and cause muscle weakness, starting in the feet, which can make walking difficult. The loss of ability to extend the foot and toes can lead to a “slapping gait” or “foot drop” (the foot strikes the floor with a slap). Very early on, people may experience unintentional weight loss, constipation alternating with diarrhoea or sexual dysfunction due to nervous system problems. These symptoms progress with the disease alongside dizziness or a sensation of faintness on standing-up quickly due to low blood pressure. Muscle weakness and wasting also accompany progression of the disease.

**Heart involvement** may cause fainting or palpitations in the early years, and later on thickening of the heart muscle (cardiomyopathy) may lead to heart failure. A pacemaker is often necessary. Some particular genetic mutations are strongly associated with heart disease.

**Kidney involvement** is uncommon and, when it does happen, usually occurs late in the course of the disease. It may lead to kidney failure and the need for dialysis.

**Impaired vision** can occur in later stages of the disease, or earlier in association with certain rare mutations. If left untreated, the disease will lead to a worsening of symptoms, and eventually to death, which occurs on average within 10 years of the onset of symptoms. So early treatment, overseen by an expert doctor with experience in TTR-FAP is important and can make a real difference to people with the disease. There are many things that can be done to help slow the progression of symptoms and also preserve a person’s quality of life.

**What are the treatments?**

People with TTR-FAP are best cared for by a multidisciplinary team, involving a neurologist,

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a cardiologist and possibly a gastroenterologist or other specialists.\textsuperscript{3} When the disease has developed, a review every 6 to 12 months to assess the disease is typical. Depending on the types of symptoms, the person may need to see a range of different specialist doctors.

**Liver transplantation**
Until recently liver transplant used to be the only treatment option\textsuperscript{4} and by December 2009, nearly 1,800 transplants had been performed worldwide.\textsuperscript{5} Liver transplantation can help people with TTR-FAP live longer and improve quality of life if performed early in the course of the disease.\textsuperscript{6} Indeed, this procedure may delay progression of symptoms, although it cannot be expected to reverse damage to nerves and the nervous system.\textsuperscript{1}

This is why transplant is usually mainly considered for people early on in the course of the TTR-FAP disease.
Outcomes are better in people with the V30M mutation\textsuperscript{2} and in younger people, as well as in those with less advanced symptoms and good general fitness.\textsuperscript{7} It might not be possible, however, to perform transplants in some people due to disease severity and overall fitness of the person. Liver transplantation is a significant surgical procedure, which needs to be performed with the coordination of a specialised centre, which is expert in managing people with familial amyloid polyneuropathy. Long-term adverse effects may be associated with the use of anti-rejection drugs after the transplant.

In the event of a liver transplant, the team performing the operation maintains close follow-up. Psychological support, social assistance, physiotherapy and everyday living advice can also be offered.

**New medicines designed to treat TTR-FAP**
A medicine specifically for the treatment of TTR-FAP polyneuropathy in adults has been approved by the European Medicines Agency for patients with the disease in Europe.\textsuperscript{8} Research into new developments and ways to treat TTR-FAP is ongoing.

**Supportive Care**
The signs and symptoms of familial amyloid polyneuropathy are varied, and people may require several treatments to maintain their daily life activities. As the disease progresses, people will need increasing amounts of supportive care to help them manage their symptoms and maintain their independence and quality of life for as long as possible.

Supportive care can minimise symptoms associated with polyneuropathy. Analgesics or drugs acting on nerve fibres (anti-epileptic, antidepressant drugs) can alleviate the pain associated with damaged nerves in TTR-FAP (“neuropathic pain”); their doses will be adapted to ensure the best efficacy and tolerance. Precautions should be taken to protect insensitive feet and legs. Some nerve

\begin{quote}


\end{quote}
Special feature

(yellow): paresthesia (loss of touch), muscle weakness, pain

(orange): And at least one of the following: dizziness on standing, sexual dysfunction, alternating constipation and diarrhoea, and weight loss
It is important to remember that you are not alone and the multidisciplinary team of healthcare experts is one of the best sources of support and help for you and your family.

Symptoms can be reduced by certain measures, such as drinking enough water, wearing support stockings, and using some medicines to prevent low blood pressure. Taking numerous small meals and using specific medicines may help control gastrointestinal symptoms. Other medicines given as tablets or injections can help prevent diarrhoea or reduce sexual dysfunction. In addition, rehabilitation and physiotherapy are important in order to limit muscle and movement disorders. If necessary, symptomatic treatments can address symptoms associated with a build-up of amyloid deposits in the heart, kidney and eye. For some people for instance, a pacemaker will be an effective method to protect their heart.
How did you learn about your diagnosis?
I found out I had the gene for this disease when my mother died of TTR amyloidosis in 1991. At first I was not too worried as I was only in my early thirties and the amyloid gene did not affect my family until their fifties. Since then, however, I have tried to live my life as ‘life is too short’! Also, I have made sure that I have all my insurances and my will up to date. I was worried that when the time came my family would have to experience what I went through with my mother. I developed the first symptoms in summer 2008 (slight gastrointestinal disturbance and constipation), and during a check-up, I was found to have early asymptomatic (no symptoms experienced) cardiac amyloidosis. The first manifestations of peripheral neuropathy appeared one year later. In February 2010, I had the chance to benefit from a liver transplant and since then I feel that I have a brighter and hopefully longer future, even though I am still recovering from the surgery.

How does TTR-FAP affect your everyday life?
My quality of life has been inevitably impacted by both TTR-FAP and the liver transplant. My nervous system has been damaged by the amyloid, which means I have constant pins and needles in my fingers, making it harder for me to turn pages in books. I also have reduced sensation in my penis. My lower legs and feet are tender, and I have to be careful with what I choose to eat and drink as it affects my bowel movements. I also have an irritating cough that my wife finds annoying! Regarding the liver transplant, the anti-rejection drugs have side effects that impact on my daily life: hand tremors, lack of concentration, and mood swings. Due to the operation I have been lacking in stamina and suffer from low blood pressure. This has caused me to rethink the way I tackle my daily tasks, such as resting occasionally while doing energetic things such as cutting the lawn. I also have a defibrillator which was fitted before the transplant. Although this does not impact my quality of life, I find that I do not pick up my daughters as much, as I am worried that they will knock it. Finally, I am currently working only 4 days a week as I need the fifth day to rest. Having gone through this it has made me seriously look at my “life/work” balance.

Did TTR-FAP change your relationships with your relatives?
It was only when I started to get symptoms and be on the transplant waiting list that I found myself becoming very inward-focussed and started to shut everyone out – even my wife. I became very worried that I had little time to complete all the things I wanted to do. It was then that I had counselling, which was very helpful to me and which has been a significant source of support.
The patient's journey to diagnosis

> For people with amyloidosis, the pathway to an accurate diagnosis is often a long one as the symptoms can be confused with those of more common diseases: it will depend on a number of factors, such as family history and the type and severity of symptoms.

**Delay in getting the right diagnosis**

One of the reasons for the delay in diagnosis is the fact that the first symptoms may not necessarily prompt people to visit their physician immediately. Sensory symptoms, such as tingling or loss of sensitivity in the feet or lower legs, are the most common presenting features, occurring in approximately 50% of people who develop TTR-FAP. These patients are usually referred to a neurologist.
Autonomic symptoms, such as alternating bouts of constipation and diarrhoea or erectile dysfunction, are less frequently the first problems experienced, but when they are they may lead patients to consult a gastroenterologist (with suspected irritable bowel syndrome, for instance) or a urologist. Due to its rarity, TTR-FAP is not often considered by doctors as a possible diagnosis. As a consequence, people often undergo numerous assessments and sometimes painful testing for a range of possible and more common diagnoses, potentially leading to inappropriate treatment. Delay in diagnosis is typically shorter in regions where the disease is less rare (where families and communities have experience of the disease), where people and doctors are much more likely to be aware of familial amyloid polyneuropathy. Genetic testing of family relatives of people who are diagnosed with TTR-FAP can be a significant factor in identifying those who carry the TTR-FAP gene. These individuals can then be monitored on a regular basis by expert doctors and, should symptoms appear, an accurate diagnosis and care plan can be put in place early.
Lifestyle tips

Maintaining the best possible quality of life with TTR-FAP

Once TTR-FAP has developed, people have found that taking a new approach to everyday living will help reduce the impact of the disease and maintain a certain quality of life

- Adapting your work conditions (part-time working, home working, workplace adaptations, etc.) can help you to maintain a rewarding and active working life.
- Inform your close relatives about TTR-FAP in order to help them understand your situation. Do not hesitate to talk to your relatives. They can feel helpless and distressed, particularly as it is a genetic disease that can affect the whole family. Some members may suffer from it while others may not, but all are involved. It often helps to have a united approach despite the disease: your close relatives are on your side against the disease.
- Develop your social network as much as possible: ask your friends to join you in leisure time or everyday activities.

If they are to help you, it is best that they do things with you.
- Whenever you need it, healthcare professionals can offer support: psychologists, nutritionists, etc. Genetic counselling services play a key role in supporting not only people with TTR-FAP, but also the family and potential carriers.
- You can also make contact with other people affected by TTR-FAP through patient associations: exchanging life experiences can make you feel less alone.
### List of research centres and patient organisations

**> FOR AMYLOIDOSIS IN PARTICULAR:**

- **National Amyloidosis Centre** (Professor Hawkins)
  
  *Royal Free Hospital, Rowland Hill Street, London, NW3 2PF.*

  The National Amyloidosis Centre provides a diagnostic and management advice service for the UK’s patients with all types of amyloidosis (and related disorders).

  [http://www.ucl.ac.uk/medicine/amyloidosis/nac](http://www.ucl.ac.uk/medicine/amyloidosis/nac)

- **Orphanet** is the reference portal for information on rare diseases and orphan drugs for all audiences. It offers information on specialised clinics, medical laboratories, ongoing research projects, clinical trials, registries, networks, technological platforms and patient organisations, in 40 European countries. For information on amyloidosis, enter “TTR neuropathy” in the simple search tool of [www.orpha.net](http://www.orpha.net).

**> FOR RARE DISEASES IN GENERAL:**

- **Genetic Alliance UK** is the national charity of patient organisations with a membership of over 150 charities supporting all those affected by genetic disorders. It provides information on genetic diseases and campaigns to raise awareness of genetic conditions to improve the quality of services and information available to patients and families (such as access to insurance, etc.). [www.geneticalliance.org.uk](http://www.geneticalliance.org.uk)

- **Rare Disease UK** is an alliance of key stakeholders brought together to develop a national plan for Rare Diseases in the UK. Information on rare disease policy can be found on the website, as well as stories and experiences from patients and families: [www.raredisease.org.uk](http://www.raredisease.org.uk)

- **Eurordis**

  Promotes the implementation of services adapted to the situation and special needs of people living with rare diseases, such as respite and recreation centres for patients and their families or help lines: [http://www.eurordis.org/](http://www.eurordis.org/)
at the heart of health information

You can find us online at:
www.magpatients.org/brochure/eng-fap.html