

**Patient
Information**

Hereditary Fibrinogen A α -Chain Amyloidosis



Introduction

AFib amyloidosis (fibrinogen A α -chain amyloidosis) is a rare inherited genetic condition. People with this condition develop kidney disease caused by build-up of abnormal protein deposits called amyloid in their kidneys. Abnormal kidney function is usually first diagnosed in this condition in middle age. Kidney function then tends to become progressively worse over several years until the kidneys stop functioning altogether. 'Renal replacement' treatment (either dialysis or kidney transplantation) is then required. AFib amyloidosis is equally common in men and in women. In the UK it is most common in people of British Caucasian ancestry but it may occur in people of any ethnic origin.

What is amyloidosis?

Amyloidosis is a rare disease caused by abnormal deposition and accumulation of proteins in the tissues of the body. Amyloid deposits are primarily made up of protein fibres known as amyloid fibrils. These amyloid fibrils are formed when normally soluble body proteins aggregate (clump together) and then remain in the tissues instead of being safely cleared away. About 30 different proteins are known to form amyloid deposits in humans. These amyloid forming proteins are known as 'precursor proteins'. Amyloid deposits cause disease by gradually accumulating within organs and thereby disrupting the structure and damaging the function of the affected tissues.

Different types of amyloidosis



Different types of amyloidosis are named according to the precursor proteins which form the amyloid fibrils. All have the initial 'A' denoting amyloidosis followed by letter(s) identifying the particular precursor protein which forms amyloid fibrils. Each type of amyloidosis has different causes, different symptoms and different treatments.

In **AFib** amyloidosis, **Fibrinogen** is the amyloid precursor protein that forms the amyloid deposits. The types of amyloidosis listed below are all more common than AFib amyloidosis:

- **AL** amyloidosis: **L**ight chains (fragments of monoclonal immunoglobulins, antibodies) are the amyloid precursor protein. This is the most common form of amyloidosis and was formerly known as primary amyloidosis.
- **AA** amyloidosis: Serum amyloid **A** protein (SAA), a blood protein whose concentration rises when there is prolonged inflammation, is the amyloid precursor protein. This was formerly known as secondary amyloidosis.
- **ATTR** amyloidosis: Transthyretin (**TTR**), a normal blood protein, present in everybody, is the amyloid precursor protein.

It is important for the type of amyloidosis to be accurately diagnosed, so that patients can be treated appropriately.

What causes AFib amyloidosis?

In **AFib** amyloidosis, **Fibrinogen** is the amyloid precursor protein that forms the amyloid deposits. Fibrinogen is a normal blood protein, made only in the liver, present in everybody and essential for blood clotting.

AFib amyloidosis is always a hereditary disease, affecting people with alterations (mutations) in the gene for fibrinogen. The full name for the condition is 'hereditary fibrinogen A α -chain amyloidosis' because the mutations affect a part of the fibrinogen molecule that is called the 'A α -chain'. People with these mutations have structurally abnormal, amyloid-forming (amyloidogenic) fibrinogen in their blood, which clumps together and forms amyloid deposits in their tissues, mainly in the kidneys. The amyloid deposits in the kidneys disrupt kidney structure and cause abnormal kidney function which tends to become progressively more severe with time as amyloid deposits accumulate.

Who gets AFib amyloidosis?

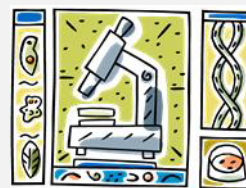
AFib amyloidosis is hereditary and 'autosomal dominant'. This means that the presence of just one copy of a mutated fibrinogen gene can cause the disease. Everybody receives two copies of the fibrinogen gene, one from each parent. People with AFib amyloidosis have just one affected parent. Each child of a person with AFib amyloidosis has a 50% (one in two) chance of inheriting a mutated copy of the fibrinogen gene.

Nearly half of all patients with AFib amyloidosis seen at the National Amyloidosis Centre have no known family history of the disease at the time of diagnosis. This may be because some people carrying the mutation never actually develop disease. This is known as 'variable penetrance'. No-one knows why some people with a mutation in the fibrinogen gene develop AFib amyloidosis and other family members with the same mutation do not.

Alternatively, the mutation may have arisen in the patient themselves for the first time, or a parent may have suffered from the disease but not been diagnosed. AFib amyloidosis was first described in 1993 in the medical literature. On receiving a diagnosis of AFib amyloidosis, patients and their families may recall that a parent suffered from kidney disease of unknown cause, sometimes in the era before the existence of AFib amyloidosis was known.

For more information on genetics, see the appendix at the end of this information leaflet.

Genetic testing in family members



Genetic testing for mutations in the fibrinogen gene is available at the National Amyloidosis Centre. The test is performed on blood samples taken from the vein. Family members of patients with AFib amyloidosis are invited to contact Professor Julian Gillmore by email at julian.gillmore@nhs.net to discuss this possibility. Genetic testing in a healthy family member without symptoms can provide information on whether a mutation is present, but cannot predict whether the person will go on to develop amyloidosis. If the relevant fibrinogen mutation is not detected, however, that individual will not develop AFib amyloidosis and nor will their offspring.

When a mutation that may cause AFib amyloidosis is detected, careful monitoring of kidney function and blood pressure is always recommended.

It is very important not to have genetic testing for this condition undertaken without prior expert, professional genetic counselling.

Different mutations that can cause AFib amyloidosis

There are ten known amyloidogenic mutations in the gene for the fibrinogen A- α chain. The mutation that most commonly causes AFib amyloidosis results in production of abnormal (variant) fibrinogen, known as the E526V variant. A mutation is a permanent change in the sequence of DNA which makes up the genes in all cells in the body. The DNA acts like a blueprint or recipe for building the proteins that make up the body. The proteins are made up of strings of amino acids, assembled in a precise order. The DNA determines the order in which amino acids are assembled. In people with the E526V variant, an amino acid called glutamic acid is replaced by an amino acid called valine at position number 526 in the fibrinogen molecule. Several other, less common mutations have been described, often just in members of a single family.

When an amyloidogenic mutation is present, every fibrinogen molecule produced in the body is slightly different from normal, 'wild type' fibrinogen. This different, 'variant' fibrinogen is amyloidogenic, meaning that it tends to form amyloid fibrils in the body, whereas normal wild type fibrinogen does not.

Fibrinogen amyloid always involves the kidneys but there are often also amyloid deposits in the spleen and sometimes in the adrenal glands, though these do not usually cause any symptoms.

Symptoms of AFib amyloidosis

Patients with AFib amyloidosis usually come to medical attention because of abnormalities in kidney function, usually first appearing around age 50 to 60, although onset as early as age 33 and as old as age 83 have been described. End stage kidney disease, when the kidneys stop functioning altogether, usually develops within about 5 years after the first symptoms.

Protein in the urine (proteinuria) is always present at first. This may be detected on urine testing, and may cause no symptoms, unless there is a very large amount of protein (one of the signs of nephrotic syndrome) in which case, urine may appear frothy. Other signs of nephrotic syndrome are swollen ankles and weight gain due to fluid retention and low blood albumin (detected in blood tests).



Most patients with AFib amyloidosis also have hypertension (high blood pressure), either diagnosed before the kidney disease appeared or at the time of its appearance.

Many also have abnormal kidney filtration which is detected on blood tests (urea, creatinine and glomerular filtration rate (GFR)).

Diagnosis of amyloidosis is often delayed after disease is first detected, sometimes for many years. This delay occurs because kidney disease is very common, but only rarely caused by amyloidosis. Doctors have to think of the possibility of amyloidosis in order to make the diagnosis.

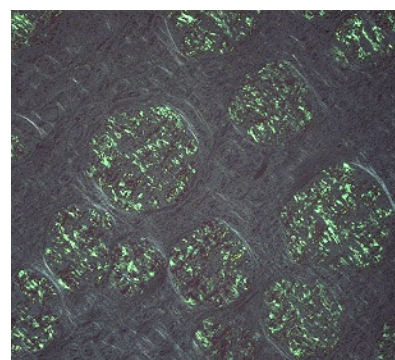
How is AFib amyloidosis diagnosed?

Tests used for diagnosing AFib amyloidosis include:

- kidney biopsy
- SAP scanning (only available at the NAC) – amyloid deposits are always seen in the kidneys, often in the spleen and sometimes in the adrenal glands
- genetic testing – mutations in the fibrinogen gene may be detected.

Kidney biopsy is the 'gold standard' (best available) test for diagnosis of amyloidosis. Most patients with AFib amyloidosis are diagnosed on the basis of a kidney biopsy. This is a procedure where a small sample of kidney tissue is obtained, processed and examined under the microscope. In order to detect amyloidosis in a biopsy, special techniques are necessary at both the processing and the examination stages. If these techniques are not used, or are used incorrectly by inexperienced laboratory staff, the diagnosis of amyloidosis may be missed. It is important that the doctor who sends the biopsy to the laboratory requests testing for amyloid. If the particular techniques needed to detect amyloid are not used, then amyloid deposits may be missed.

AFib amyloid deposits have a very characteristic appearance under the microscope. Nevertheless, if amyloid is detected on kidney biopsy, further laboratory techniques must be used to definitively identify the type of amyloid, as several other types of amyloid apart from AFib amyloidosis can affect the kidneys. See the appendix at the end of this information leaflet for more details on kidney biopsy.



AFib amyloid deposits in kidney tissue, viewed using specialist laboratory techniques. Reproduced with permission from *Int J Biochem Cell Biol*, 35(12):1608-1613, 2003.

If all of the following are present, then occasionally AFib amyloidosis may be diagnosed without the need for a kidney biopsy:

- kidney function abnormalities
- a known family history of AFib amyloidosis
- mutation in the AFib gene detected on genetic testing
- SAP scan showing characteristic AFib appearance of amyloid deposits in the kidneys (and sometimes in the spleen and adrenal glands).

Treatment

Supportive treatment

All patients with kidney disease due to AFib amyloidosis should be seen regularly by a nephrologist. Important principles of supportive treatment include:

- tight control of blood pressure
- careful monitoring and maintenance of fluid balance
- regular testing of kidney function with blood and urine tests
- use of diuretics when required.

Abnormal kidney function due to AFib amyloidosis may affect the ability of the kidneys to produce urine. This means that the body is unable to cope well with excess fluids. Patients with fluid overload may develop swelling in the legs (oedema) or difficulty breathing due to a build-up of fluid in the lungs. Fluid excess can be avoided by careful attention to the 3 **Ds**:

1. **D**iet
2. **D**iuretics
3. **D**aily weights

1. Diet:

Fluid intake should be steady and should usually not exceed 1.5 litres per day.

Salt intake should be limited. This includes attention not just to salt added to the food from the salt shaker, but also to food with high salt content such as crisps, bacon,



canned meats, sausages, canned soups and smoked fish. These dietary recommendations are general guidelines. Each patient should follow the personalised

advice given by the medical professionals treating them. It can be very helpful to meet with a dietician for precise and personalised dietary advice.

2. Diuretics:

Doctors will often prescribe diuretics (water tablets) which help the body to lose excess salt and water. Taking these drugs is not a substitute for avoidance of excessive dietary salt and water. Removal of excess body fluid reduces ankle swelling and breathlessness. Furosemide is usually prescribed first. Other diuretics such as spironolactone may be added later. Since diuretics increase the amount of urine produced, they should usually be taken in the morning sometimes with another dose at lunchtime.

3. Daily weights:

Some patients benefit from recording their weight regularly, usually daily or weekly. It is important that weight should be measured consistently using the same scales, at the same time of day. This is usually best done first thing in the morning after passing urine, just wearing underclothes. Several litres of fluid can accumulate in the body without it being very noticeable. An increase in weight can be an early sign of fluid excess. The doctor or nurse can then recommend appropriate measures such as increased diuretic dose, before the patient even feels unwell because of the fluid overload.



Surgery and anaesthesia

It is generally advisable for patients with amyloidosis to avoid undergoing surgery, anaesthesia and other invasive procedures.

If such procedures are necessary, patients should request that the surgeons, anaesthetists and other doctors involved contact the NAC doctors beforehand, to discuss any special considerations involved. For example, it is very important that great care is taken to monitor and maintain blood pressure and fluid balance throughout such procedures. Care should also be taken because of the tendency of tissues with amyloid in them to bleed and to heal poorly.

Renal replacement therapy

In most patients with AFib amyloidosis, kidney function worsens gradually with time and end stage kidney disease, when the kidneys stop functioning altogether, often develops after around 5 years. Renal replacement therapy is then necessary. This means either dialysis or kidney transplantation.

Dialysis

Healthy kidneys clean the blood by removing waste products (filtering), maintain a stable balance of fluid, salts and minerals in the blood and control blood pressure. When the kidneys stop filtering, waste products and fluid build up in the blood. Dialysis is a treatment that takes over some of these functions that failing kidneys can no longer perform. There are two types of dialysis:

1. **Haemodialysis:** The patient's blood is passed through an artificial kidney machine that removes waste from the blood.
2. **Peritoneal dialysis:** The blood is cleaned inside the patient's body. The abdominal area is slowly filled with dialysis fluid through a tube called a catheter. Extra fluid and wastes are drawn out of the body through the same catheter.

Dialysis can be done in a hospital, or at home. Patients can often decide, together with their doctors, which type of dialysis is best for them and where it should take place.

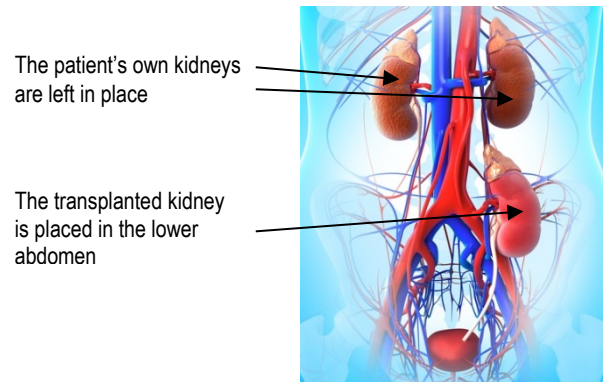
Kidney transplantation

Kidney transplantation is an operation, performed under general anaesthetic, where a healthy, functioning kidney is placed into the body of a person whose kidneys are no longer functioning properly due to end stage kidney disease.

The major advantage of kidney transplantation is that it allows the patient to lead a nearly normal lifestyle, without the inconvenience of spending hours every week on dialysis. After a transplant, patients often feel stronger and have more energy than they did before. There is no need to restrict fluid and salt intake.

Patients with kidney failure who decide that they would like to receive a transplant must be assessed to see if this is the best option for them. Sometimes doctors decide that transplantation is not suitable. Transplantation is a major operation, so very elderly people or those with heart or lung disease may not be fit enough to undergo the general anaesthetic and the operation itself. Kidney transplantation may not be recommended to people who have had cancer or serious infections because of the risk of a weakened immune system after the transplant. All candidates for kidney transplantation must undergo assessment by a nephrologist to determine whether this is suitable treatment for them.

During the transplant operation, the surgeon places the new kidney into the lower abdomen and connects the artery and vein of the new kidney to the patient's own arteries and veins. The patient's blood then flows through the new kidney which starts making urine and takes over all the functions that the patient's own kidneys no longer perform. The patient's own kidneys are left in place.



One healthy kidney is sufficient for a person to live a completely healthy life. So kidney donations can come from living donors, who donate one of their own kidneys. The donor then continues to live a completely healthy life with just the one remaining kidney. When the donor is a close relative there is less risk that the patient's body will reject the kidney. The donor must first undergo genetic testing and can only donate a kidney if the mutation causing AFib amyloidosis is not present.

Sometimes a patient who requires kidney transplantation has a relative who is willing to donate a kidney, but who is unable to do so because tissue typing shows that the donor kidney would be incompatible. This means that the recipient's body would reject the donor kidney because it has a different tissue type. Paired donation may be possible under these circumstances. An incompatible donor/recipient can be matched to another pair in the same situation, so the donor of the first pair gives to the recipient of the second and vice versa.

If a suitable living donor is not available, patients awaiting kidney transplantation are placed on the transplant waiting list to await availability of a kidney from a deceased donor. Sometimes patients undergo transplantation after they have been treated with dialysis while awaiting a suitable donor. Waiting periods vary depending on a number of factors including how common their tissue type is. Suitable donors are usually found more quickly for patients with more common tissue types. Sometimes kidney transplantation may be

planned while kidney function is deteriorating but before end stage kidney failure develops. Then it may be possible to perform a pre-emptive transplant without the need for a period of time on dialysis.

Short term risks of kidney transplantation include rejection, infection and blood clots. Patients need to take medication long term to prevent rejection, and long term risks are usually related to suppression of the immune system due to this medication. In patients with AFib amyloidosis, amyloid deposits slowly build up in the transplanted kidney, as discussed below.

Results of kidney transplantation in patients with AFib amyloidosis

Overall, the results of kidney transplantation in patients with AFib amyloidosis have been good, with patients enjoying many years of nearly normal quality of life after undergoing transplantation. Kidney transplants in patients with AFib amyloidosis have continued to function for a similar duration to kidneys transplanted for end stage kidney failure caused by more common, non-amyloid related diseases.

In 2013, sixteen kidney transplants had been performed in patients with AFib amyloidosis followed at the NAC. After transplantation, AFib amyloid deposits usually start to build up in the transplanted kidney, and in many cases this eventually leads to failure of the transplanted kidney. However, the build-up of amyloid is slow, and unpredictable, and most kidney transplants continue to function for between six and thirteen years. During this time patients usually enjoy a near normal quality of life. In two patients, the transplanted kidneys are still functioning well after thirteen years.

Combined liver and kidney transplantation

All the fibrinogen in the body is produced by the liver. Transplantation of the liver therefore removes the source of the amyloidogenic 'variant' fibrinogen and prevents the build-up of new amyloid deposits in a transplanted kidney. In theory, combined liver and kidney transplantation seems to be a promising treatment for patients with AFib amyloidosis. However, in practice, this procedure involves major surgery and carries significant risks.

In 2013, ten UK patients had undergone combined liver and kidney transplantation for AFib amyloidosis. Three of these patients died soon after due to complications related to the operation. One kidney failed after around five years due to chronic rejection, unrelated to amyloid. In the seven surviving patients, all liver and six kidney transplants were functioning well in 2013. There are no data on the long term survival.

Kidney transplantation versus combined kidney and liver transplantation

Combined kidney and liver transplantation offers the theoretical advantage of removing the source of the amyloidogenic protein. However, kidney transplantation is probably more suitable for most patients with AFib amyloidosis.

The long term outcomes of kidney transplantation are generally very good, and the procedure is less dangerous than the more complicated combined liver and kidney transplantation. To date no patients have died as a result of kidney transplantation for AFib amyloidosis. In contrast, three out of the ten patients who underwent combined liver and kidney transplantation died due to complications of the procedure.

For occasional patients, such as those who are unusually young when diagnosed or those with significant amyloid deposits in the liver, the option of combined liver and kidney transplantation may be considered. The NAC consultants will recommend the most appropriate treatment for individual patients after considering all aspects of their condition.

Outlook for patients with AFib amyloidosis

Around 60% of patients with AFib amyloidosis followed at the NAC over the last 20 years reached end stage kidney failure. On average, they started renal replacement therapy at about 60 years of age, about five years after the appearance of proteinuria and two years after diagnosis of amyloidosis.

The rate of progression of kidney disease varied widely. The longest follow up without development of end stage

kidney disease was over twelve years. Doctors cannot predict the rate of progression for an individual patient when they are first diagnosed.

Patients with AFib amyloidosis treated with long term dialysis tend to do well, with most surviving for about ten years, and some for longer. Their survival is better than

that of patients of the same age receiving dialysis for other, non-amyloid related causes of kidney failure.

Average survival from the time of diagnosis of AFib amyloidosis is 15 years, and many patients have survived for longer than this.

Appendix 1

Diagnostic techniques

Kidney biopsy

Tissue biopsy is the 'gold standard' for diagnosis of amyloid. This means that it is the best test and all other tests are measured against it. Kidney biopsy is a relatively simple procedure, involving removal of a small tissue sample from the kidney. The patient lies on his/her front on a bed and local anaesthetic is injected into the skin of the back, just under the ribcage, over the area where the kidney is situated. A needle is then inserted into the numbed area of skin, and pushed through until it reaches the kidney, where a small tissue sample is taken. Ultrasound is often used to help the doctor to insert the needle at exactly the right spot. There is a small risk of bleeding after the procedure, so the patient is monitored for several hours before going home.

In the laboratory, slides are prepared from the tissue sample and stained with a dye called Congo red. Then the stained slides are examined under very strong illumination using polarised light. When this is done correctly, and the plane of polarised light is changed by rotation of a filter in the microscope beam, amyloid deposits stained with Congo red dye uniquely show up as red changing to a very characteristic apple green colour, and back again. This phenomenon, known as birefringence or dichroism, is the gold standard for diagnosis of amyloid. It is crucial that all stages in the procedure are performed carefully and correctly by experienced laboratory staff. Any errors in the preparation, staining or viewing of the slides may lead to a missed or incorrect diagnosis.

SAP scintigraphy

In 1987 Sir Mark Pepys invented a completely new test for amyloidosis called SAP scintigraphy or SAP scanning and Professor Philip Hawkins developed it for routine clinical use. This technique shows the distribution and amount of amyloid in the organs throughout the body without the need for biopsies, which can only sample a microscopic amount of tissue from a limited number of places. SAP scanning has revolutionised understanding of the natural course of amyloidosis and its response to treatment. Unfortunately the method is complex, requires sophisticated materials, technology and equipment and is very expensive. As a result it is only

available in the National Amyloidosis Centre, where its development was funded by the UK Medical Research Council for 11 years and its routine application is now funded by the UK Department of Health. The SAP scan is safe and painless. No adverse effects have been observed from more than 10,000 SAP scans that have been performed in the NAC over the last 25 years.

The basis for the test is injection of a small amount of radiolabelled SAP which homes in on amyloid deposits throughout the body. This method is:

- safe
- painless
- non-invasive
- capable of providing a whole body overview
- a very powerful technique for diagnosis and monitoring of amyloidosis.

How does the SAP scan work?

Serum amyloid P component (SAP) is a normal blood protein, present in everybody, which is always present in amyloid deposits, in all types of amyloidosis because it binds strongly to amyloid fibrils of all types. In healthy people there are very small quantities of SAP and it is only present inside the bloodstream, but not in the organs. In the bodies of patients with amyloidosis, in addition to the small quantities of SAP in the blood, there are large quantities of SAP coating the amyloid deposits in the organs. In the SAP scan, all of this coating shows up clearly, as if it has been highlighted, or labelled. This is achieved using radiolabelled SAP: human SAP molecules that have a radioactive 'label' attached to them.

The radiolabelled SAP:

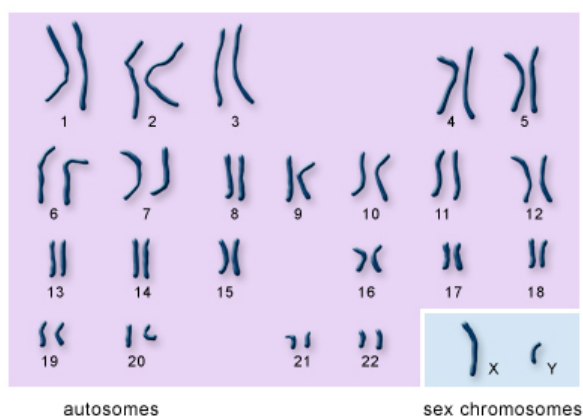
- is injected into the patient.
- homes in on the amyloid deposits and coats them, just like most of the SAP already in the body.
- transmits a small amount of radioactive signal.

This signal is picked up using a detector called a gamma camera. All body parts where radioactive signal is detected must contain amyloid deposits. So a very clear picture is obtained of the location and quantity of the amyloid deposits in organs throughout the body.

Appendix 2

Basic genetics - understanding inheritance

The human body is made up of millions of tiny cells, each of which contains identical copies of the genes which we inherit from our parents. These genes function like an instruction manual, or a recipe book for the cells to construct the proteins and other substances which make up the body. Human cells each contain about 25,000 different genes.



U.S. National Library of Medicine

Each cell contains two copies of each gene, one from each of our parents. Within each cell, the genes are arranged into forty six long strings, called chromosomes. Twenty three chromosomes come from the father and twenty three from the mother. Complicated interactions between the two copies of each gene determine how the body is composed, inside and out. External traits, like hair colour, eye colour and height and internal traits like blood group are all a consequence of which genes we inherit from our parents. The sex chromosomes determine whether a person is a man or a woman. Women have two X chromosomes and men have one X and one Y chromosome in every cell of their bodies. The illustration above shows the chromosomes from the cell of a man.

When a gene is located within one of the sex chromosomes, the way in which it is inherited is called 'sex-linked'. Diseases that result from a mutation (abnormality) in a gene within a sex chromosome may be passed from parent to child by 'sex-linked' inheritance.

All the other 44 chromosomes apart from the X and Y chromosomes are referred to as 'autosomes'. Diseases that result from mutations in genes within the

autosomes may be passed on from parent to child by 'autosomal dominant' inheritance or by 'autosomal recessive' inheritance.

AFib amyloidosis is inherited by autosomal dominant inheritance, discussed below.

How do mutations cause amyloidosis?

The genes act like an instruction manual or a recipe for protein production inside every cell of the body. Sometimes an alteration or error may arise within a gene. This is called a mutation.



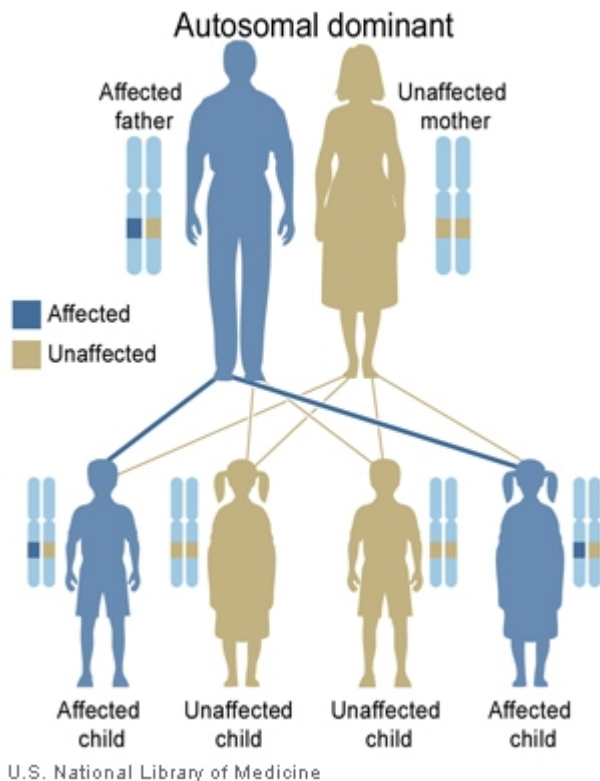
Anyone who has ever baked a cake knows that a single error in the recipe may have a number of different effects on the final product. It may lead to complete disaster, for example if you put in salt instead of sugar, or forgot the baking powder. Alternatively, there may be little effect on the final product, for example if you used margarine instead of butter.

Similarly, a mutation in a gene may have a number of different effects. Some mutations have minimal effects or no effects either on the proteins produced or on the person's health. Other mutations may lead to abnormal protein production, causing a wide variety of diseases.

The mutated genes that cause hereditary systemic amyloidosis have important effects on the abnormal so-called 'variant' proteins whose production they determine. The differences in structure between the normal and the amyloidogenic variant proteins are usually extremely small but nonetheless they have very important effects on the behaviour of the variant proteins. In all cases the variants have an increased tendency to clump together and form amyloid fibrils. Thus even a very small change in a gene can lead to serious disease.

Autosomal dominant inheritance

Complex rules control the inheritance of many characteristics, and of many diseases. AFib amyloidosis is inherited in a fashion known as autosomal dominant. This means that the presence of just one copy of a mutated fibrinogen gene can cause the disease.



Autosomal dominant inheritance is illustrated in the figure. The yellow box represents an unaffected gene and the blue box represents an affected gene, carrying a mutation. The two columns next to each person in the figure represent two identical chromosomes (strings of genes) each person inherits, one from each parent.

In the figure, the father has one copy of a mutated gene, and one copy of a normal gene. He therefore suffers from the disease, since, as mentioned above, in this type of disorder, just one copy of a mutated gene is enough to cause disease. The mother, like the vast majority of the population, has two normal genes and is healthy. Each child gets one copy of each gene from their mother, and one from their father.

When there is simple autosomal dominant inheritance of a condition:

- Each child has a 50% (1 in 2) chance of receiving a mutated copy of the gene from the affected parent.
- Each child has a 50% (1 in 2) chance of receiving a normal copy of the gene from the affected parent.
- Half of the children have a mutated gene and develop the disease. They can then pass the mutated gene and the disease on to half of their children.
- Half of the children have two copies of the normal gene. They are healthy and they cannot pass the disease on to their children.
- Brothers and sisters of people with the disease have a 50% (1 in 2) chance of having the mutated gene and developing disease.
- Men and women have equal chances of receiving the mutated gene and of developing disease.

Incomplete penetrance

For many of the diseases that are passed on by autosomal dominant inheritance, all people with a mutation in the gene develop disease. However, for AFib amyloidosis, this is not the case. An additional genetic principle called incomplete penetrance operates, making the situation more complicated.

Incomplete penetrance means that:

- Some people who inherit a mutated copy of the gene do not develop any amyloid at all.
- Some people who inherit a mutated copy of the gene develop only a small amount of amyloid and do not suffer from any clinical problems.
- Some patients diagnosed with AFib amyloidosis have no family history of the disease.

Information about a particular family is important for evaluation of the likelihood that a young healthy person with a mutation will develop disease.

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Laura Lock*

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