Women with ALAS2 mutations: information for patients

Why is this leaflet just for women?

Most information about ALAS2 is written as though only boys and men are affected, and as though women are simply "carriers" who pass the condition on without being unwell themselves. That is not the whole story, and if you have been told you are "just a carrier" while feeling tired and anaemic for years, this leaflet is for you.

Women with an ALAS2 mutation can be genuinely anaemic. Some are as severely affected as any man with the condition. For most conditions, being a "carrier" is a healthy situation with no symptoms. For ALAS2, being a "carrier" may not actually mean being well.

Who does this affect?

ALAS2 is a gene that gives the instructions for the first step in making haem – the part of haemoglobin that holds onto iron and carries oxygen in the blood.

When the gene has an error in it (doctors call this a mutation), that first step does not work properly. The gene sits on the X chromosome, which is why it affects men and women differently.

In men, the result is usually a condition called X-linked sideroblastic anaemia. Because haem cannot be made normally, iron arrives inside the developing red blood cell and has nowhere to go, building up in a ring around the centre of the cell. Under the microscope these are called ring sideroblasts, and they give the condition its name. Red blood cells in men with this condition are typically small and pale.

In women, things are more complicated – and more unpredictable.

Three ways this gene can affect women

Women have two X chromosomes; men have one. In every cell of a woman's body, one of the two is switched off early in development. Which one is usually a matter of chance, so most women end up with a mixture: roughly half their cells using one X, half the other. If one X carries an ALAS2 mutation and the other is normal, that mixture is often enough to keep her well. This is why women have traditionally been described as unaffected carriers.

But there are at three ways a woman can end up anaemic anyway.

(1) The first is when a woman inherits 2 abnormal copies of the ALAS2 gene. This is extremely rare as it requires the father to have sideroblastic anaemia due to ALAS2 mutation and the mother to also be a carrier of ALAS2 mutation.This is most likely to happen in families where marriages occur within a very close community (eg cousins). The condition is called **sideroblastic anaemia** exactly like in men.

(2) The second is when the switching off is uneven. In some women, by chance or because it runs in the family, most of the working cells end up using the X that carries the mutation, and the normal copy is largely switched off. Doctors call this skewed X-inactivation. When it happens in the bone marrow, a woman can become just as anaemic as a man with the same mutation, and her red blood cells often look similar – small and pale. This balance can also shift with age, which is why a woman who was well for decades can slowly become anaemic later in life. The condition is called **sideroblastic anaemia** exactly like in men.

(3) The third was only described more recently, and looks quite different. Some ALAS2 mutations are severe enough that the faulty copy disrupts red blood cell production in a way that does not depend on uneven switching off at all. In this situation the red blood cells are large rather than small, and the bone marrow shows cells developing abnormally – something doctors call dyserythropoiesis. This has been given its own name: **X-linked macrocytic dyserythropoietic anaemia**. Iron overload can be part of the picture.

You may see this second condition grouped with the CDAs (congenital dyserythropoietic anaemias). It is not one of them – those are caused by different genes entirely – but the word "dyserythropoietic" gives the right idea, and it describes what is happening in the bone marrow accurately.

These pictures are not always neatly separate. Some women have large red cells and uneven switching off. Some have a mixture of large and small cells on the same blood film. Your team may need genetic testing, and sometimes specialised tests, to work out which picture fits you. It is a reasonable thing to ask them.

X-linked macrocytic dyserythropoietic anaemia has been described in only a small number of families. That means there is a lot that is genuinely not yet known. If your doctors seem uncertain, it may not be because they have missed something – it may be because the answer does not exist yet.

Why is ALAS2 so often missed?

Several things conspire to hide this diagnosis in women.

Neither picture matches the textbook. Doctors are taught that ALAS2 causes small, pale red cells in men. A woman whose cells are large, or mixed, or normal-sized does not fit that description, so the thought does not get triggered.

The anaemia is easily mistaken for iron deficiency, which is extremely common in women. Heavy periods and pregnancy make it a reasonable first assumption. So iron tablets get prescribed, they do not work, and the cycle repeats – sometimes for many years.

Large red cells with an abnormal bone marrow can also look like other conditions entirely, including myelodysplastic syndrome. Some women have been given that label, or told they have an anaemia of unknown cause, before the right answer was found.

Family history does not always help either. The condition can appear in a woman with no affected male relatives at all.

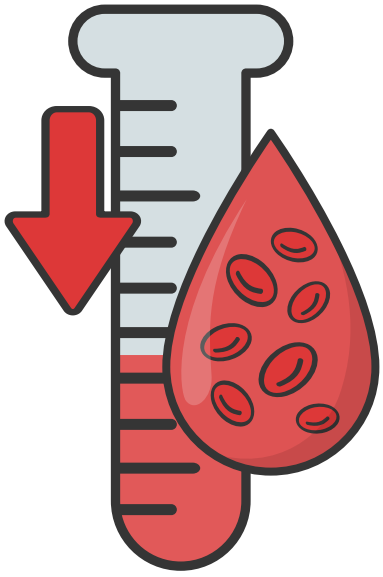
What are the symptoms?

The anaemia can be mild, or severe enough to need transfusions. Many women sit somewhere in between, and it is common to have adjusted to feeling tired over so many years that it stops registering as abnormal.

Anaemia can cause fatigue, weakness and a lack of energy, breathlessness on exertion, dizziness, headaches and difficulty concentrating. Skin may look pale, and for people with darker skin this is often seen best inside the mouth, on the lips or the tongue.

Iron overload can also develop – and, importantly, it can develop in someone who has never had a transfusion, and while they are still anaemic. This surprises people, understandably. It happens because the body senses the anaemia and absorbs more iron from food in response, but that iron cannot be used properly. Iron overload causes no symptoms for years, which is exactly why it is monitored with blood tests and scans rather than waited for. See our leaflet on 'iron overload without blood tranfusions'.

How is it diagnosed?



A full blood count will show anaemia, and the blood film may show small cells, large cells, or a mixture. Iron studies typically show that iron is plentiful rather than lacking – often the first real clue that this is not iron deficiency.

A bone marrow test may be done, looking for ring sideroblasts or for the abnormal red cell development described above. Genetic testing confirms the mutation in the ALAS2 gene and is what gives a definite answer. In some families the diagnosis was only reached when the whole family was tested together.

Testing for the pattern of X-inactivation is sometimes done in specialist centres, and can help explain why one woman in a family is unwell while her sister is not.

Why iron tablets are the wrong treatment

If your anaemia is caused by an ALAS2 mutation, iron tablets will not help – and taking them can do harm. The problem is not a shortage of iron. It is that your red blood cells cannot use the iron they already have. Adding more adds to a load your body cannot get rid of.

If you have been taking iron for a long time for an anaemia that never improved, this is worth raising with your doctor. Do not simply stop a prescribed medicine without discussing it, but do ask the question. It is a reasonable and important one, and the answer changes what should happen next.

What is the treatment?

Pyridoxine (vitamin B6). The ALAS2 enzyme needs a helper molecule made from vitamin B6 in order to work. Some mutations affect the enzyme's ability to hold onto that helper – and in those cases, flooding the system with extra B6 can partly overcome the fault. This is the approach that is used in men with sideroblastic anaemia and it can be tried in women with ALAS2 mutations.

Whether it works depends on the particular mutation, so a trial of pyridoxine is usually worth doing. If it works, response shows within a few weeks, and treatment then continues lifelong, because the anaemia returns if it is stopped. Your team will use the lowest dose that keeps you well: high doses over a long period can damage nerves, causing numbness and unsteadiness, so this is not a vitamin to self-prescribe or to take more of than advised. The dose needed to get a response is usually higher than the dose needed to maintain it.

Monitoring and treating iron overload. Iron levels are checked with blood tests, and sometimes with an MRI scan that measures iron in the liver and heart directly. If iron builds up, it is removed – either by venesection (removing blood, like a blood donation) if you are not too anaemic to tolerate it, or by iron chelation medicines. Which is appropriate depends on your haemoglobin. See our leaflet on 'iron overload without blood transfusions'.

Blood transfusions. Some women need these, either occasionally – through a pregnancy, or during an illness – or regularly if the anaemia is severe.

Folic acid. Usually recommended, as the bone marrow is working hard.

What does this mean for my children and my family?

This is the part where the honest answer is: it depends on your particular mutation and your particular family, and it needs a proper conversation rather than a leaflet.

In the more usual pattern, each son has a 1 in 2 chance of inheriting the mutation and would be affected if he does, because he has no second X chromosome to fall back on.

Each daughter has a 1 in 2 chance of inheriting it, but whether she would be anaemic is much harder to predict – she may be entirely well, mildly affected, or significantly anaemic, and she may be well for years and become anaemic later.

But some ALAS2 mutations behave differently, and in some families the pattern in the family tree does not look like the textbook at all. Where a mutation is severe, the effects on a pregnancy can be different, and this is one of the reasons a specialist opinion matters rather than a general rule.

If you are thinking about having children, or if you have had difficulties in pregnancy, please ask for a referral to a genetic counsellor who can look at your own family tree and your own mutation. Bring what you know about your relatives – who was anaemic, who was not, and any pregnancy losses. That information is genuinely useful and is often the thing that makes the picture clear.

Once a mutation is identified in one person, other family members can be tested. In a condition this often missed, that can end years of unexplained anaemia for a relative. Our leaflet on preimplantation genetic diagnosis (PGD) covers the options for people planning a pregnancy who want to discuss them.

What can I do to help myself?

Keeping generally well helps – staying hydrated, a balanced diet, regular exercise. Alcohol is worth being careful with, as it interferes with the same haem-making pathway and can make the anaemia worse.

Do not take iron supplements, or multivitamins containing iron, unless your haematologist has specifically told you to. Check the labels, as iron turns up in over-the-counter supplements that are not obviously iron tablets.

Ask whether your care involves a specialist centre for inherited anaemias. This condition is rare, the picture in women is atypical, and it is easy for it to be managed as though it were something else.

If you have carried an unexplained anaemia for a long time, it is worth saying plainly that finally having a name for it can bring up a lot – relief, but sometimes anger at the years it took, or at not being believed. That reaction is common, and it is one of the things other people in the same position understand best.

Having an ALAS2 mutation does not mean giving up on living a full and active life.

When to seek medical advice

Contact your team if you notice:

- Worsening tiredness or breathlessness
- Numbness, tingling or unsteadiness on your feet, if you are taking pyridoxine
- Joint pain, abdominal pain, or other possible signs of iron overload
- That you are pregnant or planning a pregnancy
- That you have been prescribed iron by another doctor who may not know your diagnosis

Can we help?

CAN (Congenital Anaemia Network) is a charity specifically for patients with inherited anaemias. It was started by a group of patients and doctors, working together to tackle some of the problems of having an inherited anaemia – the lack of information and the loneliness of not knowing anyone else with your condition. We run events for patients to meet each other, as well as provide some additional information, support and services for patients who need that extra bit of help.

If you want to know more visit www.togetherwecan.uk or email us: info@togetherwecan.uk

Do you know your care should involve a specialist centre for inherited anaemias? These conditions are rare enough that few doctors see many of them and all patients with rare inherited anaemias should be under the care of a haemoglobinopathy specialist. Please read our 'How red cell services are organised in England' information sheet. If you don't know who your specialist service should be, please get in touch with us so we can help you find out.