

The Medical Genetics department at St George's performs NOTCH3 mutation analysis for CADASIL. Samples can be sent via your local genetics department to Dr Rohan Taylor, Department of Molecular Genetics, Jenner Wing, St George's University of London, Cranmer Terrace, London, SW17 0RE, UK. Tel: 020 8725 5964

How can I find out more information about CADASIL?

Because CADASIL is a rare disease, and because much of the information on it is very new, it is quite difficult to find out information about CADASIL. As far as I know there are no books for the general public about CADASIL. There are some patient and carer CADASIL websites;

- In the USA, (<http://home.earthlink.net/~cadasil>) set up by the wife of a CADASIL sufferer
- In the UK set up by a CADASIL sufferer (<http://www.cadasiltrust.org/>) .

These give information on the disease and are a way to get in touch with other CADASIL families.

A further site which gives details about medical aspects of CADASIL is:
<http://www.geneclinics.org/profiles/cadasil>.

Further copies of this leaflet and information about CADASIL at St George's can be downloaded from the St George's University of London website
<http://www.sgul.ac.uk/index.cfm?845A3352-9461-645C-4BED-DF78800E9072>

It will also be available on our new St George's stroke care website
<http://stroke.sgul.ac.uk/>

We are always happy to see any patients and members of families with CADASIL at the St George's CADASIL clinic- see above

Professor Hugh Markus
Clinical Neuroscience
St George's University of London
Cranmer Terrace
London
SW17 0RE
United Kingdom

(please note different address for clinic referrals in section on previous page)

Cover picture: This shows the characteristic involvement of the anterior temporal lobes (white areas) seen in CADASIL patients.

CADASIL

A Guide for Patients



Clinical Neuroscience
St. George's University of London



Version 3

What is CADASIL?

CADASIL is an abbreviation for a long name describing a rare hereditary form of stroke (**Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy**). The disease usually presents with multiple small strokes but migraine is also a prominent feature. It is caused by a small abnormality (mutation) in a gene called NOTCH3.

What does genetic mean?

In many diseases genetic factors are important. This means that part, or all of the risk, is passed down from one's parents. Certain diseases are caused by an abnormality in one single gene and CADASIL is one of these diseases. Genes produce proteins which are necessary for normal functioning of the body. Everybody has two copies of each gene, one passed down from their mother, and one from their father. In CADASIL, an abnormality in only one of these two copies results in the disease. We refer to this as autosomal dominant inheritance. A consequence of this is that if you have CADASIL, you have one normal copy and one abnormal copy of the gene. If you have a child, he or she will receive one copy of the gene from you, and one from your partner. Therefore there is a 50/50 chance that any child of yours will have the CADASIL gene and will be at risk of developing CADASIL.

What causes CADASIL?

We now know that CADASIL results from an abnormality in one very small part of a gene known as NOTCH3. We think that the protein produced by the NOTCH3 gene is responsible for communication between cells within the body. As yet, we don't know why the abnormalities in the NOTCH3 gene in individuals with CADASIL, result in the disease. It is likely that it will take a number of years to fully understand the process.

Although we don't fully understand the process, we do know that patients with CADASIL suffer from progressive damage within small blood vessels. This results in reduced blood flow and an inability of the blood vessels to regulate blood flow normally. A consequence of this is reduced blood flow in parts of the brain. Although abnormalities in blood vessels can be found throughout the body, they are most severe in the brain, and only produce problems (symptoms), noticed by the person with CADASIL, within the brain.

St. George's and CADASIL

At St George's we have a particular interest in CADASIL. We have a CADASIL research programme and run a clinical service for patients with CADASIL.

a) Research

We have an active research programme in CADASIL. We may ask you whether you would be prepared to take part in these, and other studies. If you are interested, we will explain the specific details of any individual study and it is always entirely up to you as to whether you take part. Any study is always approved by the local hospital ethics committee

Funded by a National Health Service Research & Development grant we carried out a British CADASIL prevalence study to find out how common CADASIL is in Great Britain. This showed it had been underdiagnosed. We have identified brain imaging (MRI) features which are now widely used to diagnose the disease. We have worked out the best way to screen from the disease using genetic tests in the UK population and have set up testing which is available to all through the NHS (South West Thames Genetics unit based at St George's).

More recently we have been involved in studies looking at why the disease is so variable between different CADASIL sufferers and have shown that smoking is associated with earlier onset of stroke. We have also been involved in a trial of CADASIL looking at whether the drug Donepezil helps patients with memory impairment. This was the first worldwide treatment study in CADASIL (an important milestone). The results will be available in early 2008.

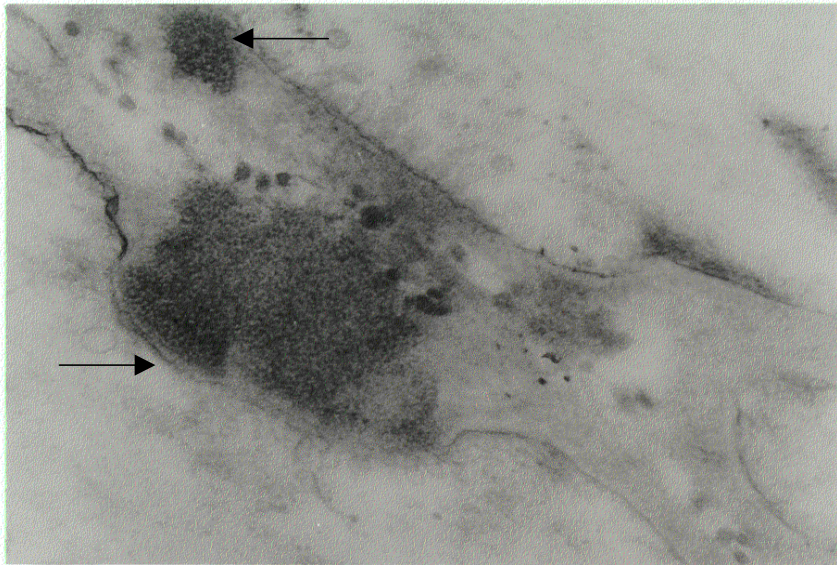
If you wish to support the work at St George's, donations can be made to "St Georges University of London (CADASIL fund)" and sent to Professor Markus at the address at the end of the leaflet

b) Clinical Service

At St George's Hospital we have a specialised CADASIL clinic at which we see patients suspected of having CADASIL or family members who wish to have genetic screening. We have facilities to perform skin biopsies in the clinic. We are always happy to see referrals there; if you wish to be seen please ask your GP or hospital consultant to refer you to Professor Markus, Department of Neurology, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT. Tel 020 8725 2470, Fax 020 8725 3291. It is very helpful to have copies of any previous hospital assessment and of original MRI scans if these have been performed

2. Skin biopsy

CADASIL results in characteristic changes in the blood vessels. For obvious reasons it is difficult to look at the blood vessels within the brain. However, even though CADASIL itself only produces symptoms within the brain, abnormalities within the blood vessels can be seen elsewhere in the body. The easiest way to look for these is in the skin. A very small skin biopsy is performed under local anaesthetic. We carry this out as an outpatient procedure in our CADASIL clinic. It is important this is processed in a special way allowing it to be looked at under



high magnification using an electron microscope. Under this magnification, in patients with CADASIL, one can frequently see abnormal collections of material called GOM (**G**ranular **O**smiophilic **M**aterial) as shown by the arrows in the figure. If these GOM are present we can be certain that the individual does have CADASIL. However, the skin biopsy can be normal. It appears that skin biopsy is positive in 60-80% of CADASIL patients, but in our experience a skin biopsy can be negative in patients with definite CADASIL.

3. Genetic testing

If we can detect an abnormality on genetic testing, we can be 100% sure that someone has CADASIL. In CADASIL the abnormalities that occur are all within one gene which is called the NOTCH3 gene. However, this gene is made up of many thousands of building blocks (base pairs). In CADASIL, there is an

abnormality (mutation) in only one of these. It can be a very time-consuming process, excluding an abnormality in the whole gene. For this reason routine genetic testing of the whole gene, is not offered in CADASIL. Luckily, most of the abnormalities tend to occur in certain parts of the gene so we can identify most of CADASIL cases by screening these "hot spots". The St Georges's laboratory now screens exons 3, 4, 5, 6, 8, 11, 18 & 22. By doing this we are able to detect around 90% of NOTCH3 gene changes in a UK population.

If one member of a family has CADASIL, any other member of the same family that also has CADASIL, will have exactly the same underlying genetic abnormality. Therefore, once we've found the underlying genetic abnormality within a particular family, it is relatively easy to determine whether other family members have the same abnormality and therefore are affected or may become affected in the future.

Is there any treatment for CADASIL?

There is no specific treatment for CADASIL available at the moment. In the long run, we hope that we will be able to discover exactly how this results in the blood vessel damage, and therefore design drugs to prevent this damage. However, this is likely to be a number of years away.

Aspirin has been shown to reduce the risk of recurrent stroke by about 20% for common stroke, although it has not been tested specifically in CADASIL. Therefore most doctors would recommend that patients with CADASIL take a small dose of aspirin per day (75-300mg/day). Occasionally we also use other drugs to reduce blood clotting, such as Dipyridamole (Persantin) and Clopidogrel (Plavix). We would avoid warfarin, or the combination of aspirin and clopidogrel, as this could increase the risk of bleeding within the brain.

Recent studies have shown that other risk factors for common stroke, such as smoking and high blood pressure, are associated with earlier onset of stroke or increased rate of worsening on MRI in CADASIL sufferers. Therefore we feel that it is important to prevent any other damage to the blood vessels. For this reason, it is important not to smoke, and to monitor blood pressure and cholesterol, and treated these if they become abnormal. It is also advisable not to take the combined oral contraceptive pill or HRT as these can increase the risk of blood clotting and could increase stroke risk.

If required during attacks of migraine, standard migraine painkillers can be taken. These include drugs such as Migralve. However, it is probably not advisable to take some of the newer anti-migraine drugs such as Imigran, which act by

reducing the blood flow to the brain. If migraine attacks are frequent then normal migraine prevention therapies seem effective.

It is important to look for, and treat when necessary, depression in patients with CADASIL. This can be treated with standard anti-depressant drugs and the response can be very good. Epilepsy can also be well treated with standard epilepsy drugs.

Should other members of the family be tested for the disease?

For the reasons explained above, if one member of a family has CADASIL there is a 50/50 chance that other family members will be at risk of the disease. It is possible to look for this in two ways. Firstly, if the underlying genetic abnormality is known, it is relatively simple to look for it in other family members. This will allow us to be 100% sure whether or not an individual carries the CADASIL gene, and is at risk from the disease. Secondly it is possible to carry out magnetic resonance scanning in other family members. This can frequently pick up the characteristic changes of the disease in the 20s, before symptoms occur.

Before testing family members for CADASIL, it is very important that a careful discussion of the pros and cons is carried out. This is usually performed by a genetic counsellor. The knowledge that a healthy person is likely to develop CADASIL can obviously be very distressing, and it is possible that it could influence a number of factors including things such as life insurance. Therefore we only test other family members if they were absolutely certain that this is what they wanted to be done. In individuals who have had no symptoms of disease our standard practice is to discuss the pro and cons with you, and ask you to think about it for a period of a month before going ahead with testing. It would be extremely unusual for us to test children.

A potential advantage of being tested for the disease is that it is possible to determine whether one's children are at risk of the disease. If you have the abnormal gene, any children you have, also have a 50/50 chance of having the abnormal gene. However, if the abnormal gene has not been passed to you, neither you nor your children are at risk. Furthermore, if tests do show that you have the abnormal gene, it is now possible to determine whether the baby has a genetic abnormality fairly early in the pregnancy. If you wished, if the abnormality was present, you could then have a termination. Clearly there are complex ethical issues, and individual people have different views on how they would like to address these. If you are keen on having such genetic testing during pregnancy, it is very important that you discuss this well before you plan to become pregnant.

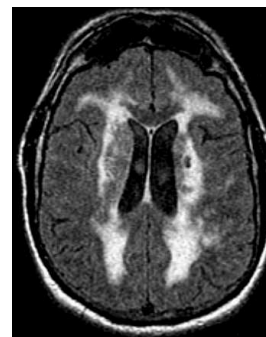
What are the features of the disease?

Most people with the disease will suffer from strokes. These most commonly first occur in the 30s to 50s although the disease can be very variable, and in some people no problems may occur until their 60s or even later. There are a few individuals identified with CADASIL who remain well in their 70s. The strokes are what we refer to as lacunar strokes (literally meaning a small lake or hole in the brain). Because they are small, they tend to be fairly mild and individuals often recover well. The most common type of stroke is weakness affecting one side of the body. If recurrent strokes occur, this can lead to persistent disability which is most usually arm or leg weakness, or slurring of the speech.

Migraine is a common feature of the disease. This most commonly starts in the 20s but the onset is variable. Usually this is what we call "complex" migraine (also known as migraine with aura). This means that in addition to the headache there are short-lived neurological symptoms; most commonly involving vision disturbance, numbness down one side of the body, or speech disturbance.

Individuals with CADASIL can suffer from anxiety or depression. Not surprisingly, depression is very frequent after any stroke. However, occasionally, depression may occur before any other symptoms of CADASIL. Rarely, seizures (epilepsy) occur as part of CADASIL. Over time, as the disease progresses, memory and other cognitive problems may occur and can lead to a dementia; this differs from dementias such as Alzheimer's in that problems in planning things and speed of thinking are prominent. An unusual feature is of the onset of confusion and reduced consciousness over a period of hours or days, sometimes with fever and seizures; this often follows a migraine attack. This is known as encephalopathy. It recovers completely over 1 to 2 weeks.

Investigations when CADASIL is suspected



1. Brain scans

A magnetic resonance brain scan (MRI) is usually performed and shows characteristic appearances with abnormalities in the deeper parts of the brain known as the white matter (they appear as white on this example). Involvement of certain brain areas including a region called the anterior temporal lobe appears to be a useful guide to the diagnosis. This is a safe scan that involves no radiation but some people find it claustrophobic and its noisy.