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# CADASIL

➤➤➤ A Guide for Patients and Families



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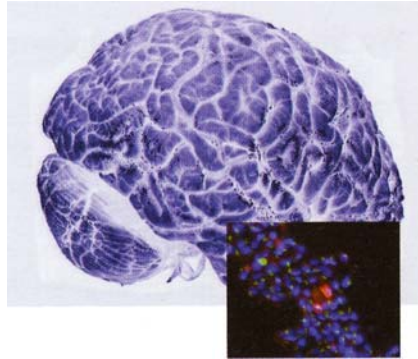


## How can I support research?

There are many ways to contribute to CADASIL research: by participating in clinical studies, through education (e.g., establishing a self-help group), by consenting to a brain donation, or through monetary contributions. Tax-deductible contributions to CADASIL research at Brown Medical School can be sent to:

Butler Hospital  
 Memory and Aging Program  
 Attn: CADASIL Research Fund  
 345 Blackstone Boulevard  
 Providence, RI 02906

For more information about supporting our CADASIL research program, please contact us at 401-455-6403.



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## Forward

Each year about 700,000 Americans suffer a stroke. A very small percentage of these patients have a rare hereditary condition called CADASIL. Many patients and even some physicians have never heard of CADASIL. The goal of this brochure is to help patients and their families to understand and cope with CADASIL. It is not a substitute for consulting with your physician. This brochure was developed by the Neurogenetic Study Group of the Neurological Clinic of the Grosshadern Clinics of Munich and the Butler Hospital Memory and Aging Program. The information in it is based on the clinical experience and scientific work of these and other research groups.

## What is CADASIL?

CADASIL is an inherited (or “genetic”) disease of the small blood vessels in the brain that causes strokes and other injuries, especially in the deep parts of the brain. The term “CADASIL” stands for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. Although this technical name is quite cumbersome, it accurately describes the key features of the disease: “Cerebral” means that the disease has to do with the brain. “Autosomal dominant” means that the disease is genetic and inherited in a particular way. “Subcortical” means that the disease affects internal parts of the brain. “Infarcts and leukoencephalopathy” means strokes and other injury to the brain, particularly within a deep part of the brain called “white matter.” The gene that causes CADASIL was



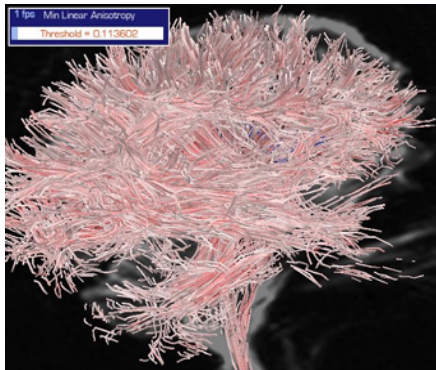
## Where Can I Find Additional Information On CADASIL?

This brochure should provide you with the essential information on CADASIL. Since this is a rare and relatively new disease, information for patients and family members is still quite sparse—to our knowledge there is no book of advice for lay people. Web sites on the Internet can be of inconsistent quality, but some of them are helpful for patients and families dealing with the disease. We recommend the following websites:

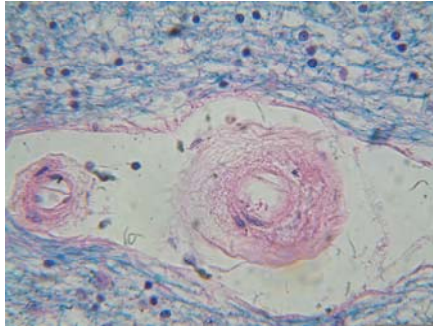
- ◆ <http://www.memorydisorder.org>  
Memory and Aging Program website
- ◆ <http://www.ulf.org/>  
United Leukodystrophy Foundation
- ◆ <http://www.cadasil.com>  
Comprehensive CADASIL site (in French)
- ◆ <http://ghr.nlm.nih.gov/condition=cadasil>  
U.S. National Library of Medicine website on CADASIL with many useful links
- ◆ <http://www.geneclinics.org/profiles/cadasil/>  
A detailed but technical description of CADASIL
- ◆ <http://www.cadasilfoundation.org/>  
A patient advocacy group based in the U.S.
- ◆ <http://www.cadasiltrust.org/>  
A patient advocacy group based in the U.K.



we have been studying the role of the *NOTCH3* gene in deterioration of small blood vessels in the brain. We are also using an advanced MRI technique called diffusion-tensor imaging (DTI) to evaluate the areas of the brain affected by CADASIL. Working closely with CADASIL researchers around the world we have played a leading role in developing and conducting the first medication trial for CADASIL.



A DTI image showing the white matter in the brain



A blood vessel showing the effects of CADASIL

### Visiting Us

If you wish to make an appointment for a clinical assessment of CADASIL and to participate in our research, you or your doctor should call Diane at 401-455-6403 or visit us on the web at [www.memorydisorder.org](http://www.memorydisorder.org)



discovered in 1996. Since then, the disease has been gaining greater scientific and popular attention.

### What is a “genetic” disease?

A genetic disease is one that is caused by a gene. Genes are chemical codes that our bodies use to build proteins, which are the basic building blocks of life. Genes are formed from groups of smaller molecules called nucleic acids. Humans have about 25,000 genes. The genes themselves are grouped together into larger molecules called DNA, which, in turn, are grouped into even larger molecules called chromosomes. Humans have 46 chromosomes grouped into 23 pairs, so each gene is paired – one member of each pair comes from the father, the other comes from the mother. Each cell in our body has all 23 pairs of chromo-

somes. Genes are responsible for many properties such as the color of our eyes and our height. However, in many cases genes also play a role in the development of diseases. Genes can cause diseases when they become “mutated.” That is, there is a mistake in the order of nucleic acids that make up the gene, like a misprint in a book. Since genes are the codes for making proteins, mutated genes can produce abnormal proteins, which, in turn, can cause disease.





## What does “autosomal dominant” mean?

Some of our 23 chromosome pairs are important for sex characteristics and some are important for other functions. These non-sex chromosomes are called autosomes. So, the word “autosomal” means the gene that causes CADASIL is not located on a sex chromosome.

As we said above, genes come in pairs located on chromosomes. Genes can be either “dominant” or “recessive”. A gene is dominant when the trait it controls is always expressed; a gene is recessive when the trait it controls is expressed only when paired with a recessive partner. For example, the gene for brown eyes is dominant and the gene for blue eyes is recessive. This means that you will have brown eyes whether you inherit two brown-eyed genes (one from each parent) or one

brown-eyed and one blue-eyed gene. To have blue eyes, you must inherit the gene for blue eyes from both parents.

The gene involved in CADASIL is dominant. Patients with CADASIL have one mutated copy of the gene and one normal copy. This means that if one parent has CADASIL then each child has a 50% chance of inheriting the disease. Occasionally, a new mutation in the gene can occur and cause the disease even though both parents are healthy.

People who have the defective gene are called “mutation carriers.” Almost all mutation carriers will develop the symptoms of CADASIL at some point in their lives. Exactly when this will occur in any one person is not yet understood. However, within one family there may be considerable differences in the disease among those affected.



## Memory and Aging Program

Patients and families are evaluated at the Memory & Aging Program, located at Butler Hospital, a major teaching hospital at Brown Medical School in Providence, RI. Our caring staff, which includes neurologists,



Butler Hospital

neuropsychologists, research and clinical nurses, interns and post-doctoral fellows, and research assistants, combines compassionate care with the latest diagnostic and treatment tools to address the impact of CADASIL on patients and families. We are currently receiving referrals for 2-4 new CADASIL

families each month from around the U.S. Treatment recommendations are coordinated with the patient’s primary care physician and local neurologist.

## Research

New treatments for CADASIL can only come about through a more thorough knowledge of the disease process. Our research program is dedicated to using the latest scientific techniques to understand the pathway leading from the genetic mutation to the symptoms of the disease.

Our research team includes faculty from the Brown Departments of Neurology, Psychiatry, Pathology, Molecular Biology, Diagnostic Imaging, and Computer Science. Using tissue from our CADASIL brain bank,





## CADASIL Care & Research at Butler Hospital and Brown Medical School

### Memory & Aging Program at Butler Hospital, Providence, RI & Brown Medical School

Our clinic, under the leadership of Dr. Stephen Salloway, Chief of Neurology at Butler Hospital, has become a leading center for CADASIL clinical care and research in the United States. Over the past 10 years, Dr. Salloway and his colleagues at Brown Medical School have developed a comprehensive CADASIL research program. Currently, we are a national referral center for this disease and are

following a large number of CADASIL families in the United States.

#### What We Offer

- comprehensive neurological assessment
- genetic counseling and testing
- treatment trials
- molecular biology and genetics research
- assessment of memory and other thinking abilities
- development of new brain imaging techniques
- brain donation program
- education about CADASIL for patients, families, and physicians.



Brown University

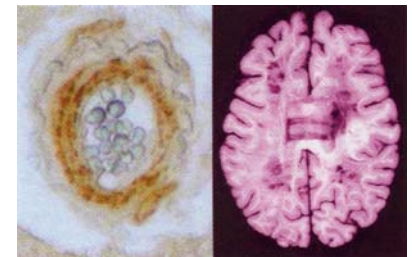


## What causes CADASIL?

CADASIL is caused by a mutation in the *NOTCH3* gene located on chromosome 19. The *NOTCH3* gene is responsible for making a protein called Notch3 which is important for the health of muscles in the walls of the small blood vessels in the brain. In CADASIL, the genetic mutation causes problems with the Notch3 protein and also causes deterioration of the muscles in the walls of the vessels. Current research is aimed at trying to understand exactly how this process causes the disease and is looking for ways to stop or prevent it.

However, today we already know a great deal about the indirect consequences of the genetic defect. High-powered microscopes show abnormal accumulations (clumps) of the Notch3 protein in the walls of the

small blood vessels of CADASIL patients. In addition, there are a number of other vessel wall changes that result in the brain being inadequately supplied with oxygen and nutrients. Although these vascular wall changes can be detected throughout the entire body, CADASIL seems to damage only the brain.



Left: a blood vessel showing damage from CADASIL. Right: a cross-section of a brain showing the effects of CADASIL.



## What are the symptoms of CADASIL?

The most common symptom of CADASIL is a stroke. Strokes are characterized by a number of neurological symptoms including paralysis, loss of sensation, problems walking, slurred speech or other speech problems, etc. These symptoms might improve rapidly (so-called transient ischemic attacks (TIAs)) or lead to more persistent losses (completed stroke).

Strokes caused by CADASIL usually occur for the first time between the ages of 30 and 50. However, as with all the other symptoms, there is a great range of variation and individual patients may remain free of symptoms for many years.

Approximately one-third of patients with CADASIL suffer from migraine-like headaches. The headache attacks often begin between the ages of 20 and 30,

but again there is a lot of variability from person to person. Migraines in CADASIL are usually accompanied by an "aura". Auras are transient neurological



symptoms that occur before or during the headache, such as changes in vision, numbness in the hands or feet, and speech problems.

CADASIL patients also frequently suffer from psychological symptoms such as anxiety or depression. It is not uncommon for a patient to respond psychologically to a stroke by becoming depressed, but in many cases

and psychological reasons why this is discouraged, the details of which can be discussed with your physician or a genetics counselor. If your child is an adult, you may wish to talk with him or her about your diagnosis and about the fact that CADASIL is inherited. Your child can then discuss this with his or her own treating physician and make a decision about whether or not to have a detailed neurological evaluation including MRI and genetic testing.

◆ **Should we talk to our children about the disease and the fact that it is hereditary? If so, when is the correct time to do this?**

Our view is that it is appropriate and important, at some point in

time, for your children to learn of your disease and the fact that it is hereditary. This information may be particularly important with respect to your adult children's family planning. There is no "best time" to talk with your children about CADASIL, and the decision will depend on many factors such as their age, maturity, and typical psychological reactions to stressful news. Par-



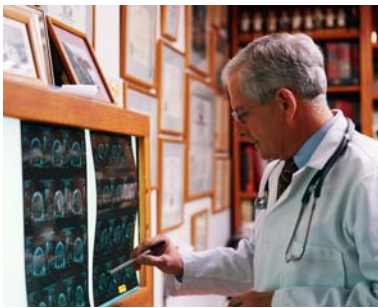
ents often have a better sense of this than do physicians. As a rule of thumb, we feel that the discussion should preferably occur before the start of family planning.





◆ **My physician has said that I have already had several strokes—but I haven't noticed anything!**

Your doctor's statement is probably based on MRI or CT images. In CADASIL patients, these tests frequently show small "scars" indicating minor



circulation disorders (strokes) that have already occurred. Small strokes, especially early in the disease, can occur without any symptoms.

◆ **How good are alternative treatment methods?**

So far there have not been any reliable studies of alternative treatments for CADASIL. It does

not appear that any such treatments influence the disease process itself. However, we do

not actively discourage some alternative treatments such as



acupuncture, natural homeopathic preparations, etc. for specific problems (e.g., stubborn headaches) and as appropriate in the individual case (for example, relaxation exercises for headaches). However, you should inform your doctor before starting such treatments.

◆ **We have two children. Should we have our children tested?**

It is generally not advisable for children who are minors to have genetic testing for CADASIL, particularly if they are not showing symptoms of the disease. There are a number of practical



this is reversible and—if necessary—treatable. In individual cases psychiatric symptoms such as hallucinations, delusions, anxieties, changes in perception or mood (manic or depressive) may be the first symptoms of this disease. In these patients a specialist should be consulted for therapy.

In a small percentage of patients, epileptic seizures occur but can be treated well with medication. In individual cases, episodes of confusion or disturbances in consciousness have been observed and last for a few hours to days and may be associated with fever or epileptic seizures.

In a majority of patients, problems in memory and other thinking skills occur. These symptoms are usually mild at first but may become worse in the later

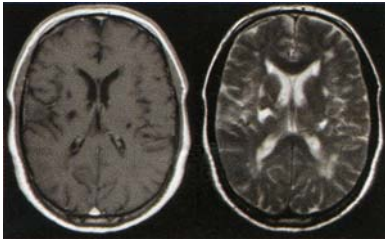
stages of the disease. These symptoms can also be treated (see below).





## Diagnosing CADASIL

### 1. Magnetic Resonance Imaging (MRI)



Magnetic resonance imaging (MRI) is a method for making detailed images of the brain. In CADASIL, the MRI shows changes in the deep regions of the brain, particularly in the white matter. The white matter lies below the outer layers of the brain (the cortex or grey matter) and forms the connections among brain areas so that they work in a unified way. The blood supply to the white matter is provided by small blood vessels which make it especially vulnerable to CADASIL. Other disorders, such as multiple sclerosis,

cause white matter changes that look similar on MRI, so CADASIL cannot be diagnosed from MRI alone. However, CADASIL might be suspected if the white matter changes are concentrated in certain brain areas (frontal lobes and/or temporal lobes). MRI uses magnetic fields and radio waves to make its images and involves no x-rays or other forms of radiation. It is a safe and reliable test method with few health risks. However, it is not safe for people with pacemakers or certain other implanted medical devices or for people who may have small metal fragments or dust in their eyes. It is often helpful to have MRI scans repeated every few years to look for progression of the disease.



## Frequently Asked Questions about CADASIL

◆ **My father/mother who has CADASIL has become severely ill—should I expect the same fate if I have CADASIL?**

No, not necessarily. The severity of the disease fluctuates greatly within a family.

◆ **I would like to play sports — is that allowed?**

Yes. The best sports for you are endurance sports (e.g., swimming, jogging, hiking). Extreme sports should be avoided. There are no medical objections to taking vacations (including airline flights).

◆ **If I have CADASIL, can I drive a car?**

The answer to this question depends on your symptoms. The deciding factor is whether by driving you would endanger

yourself and/or other people on the road. Symptoms that can impair driving ability include vi-



sion disorders, reduced coordination, paralysis, epileptic seizures, slow reaction times, etc. You should discuss this question with your doctor. You can also take a driving test with the proper authorities.

◆ **Is CADASIL contagious?**

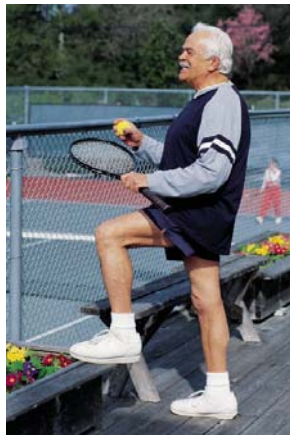
No, you cannot become “infected” with CADASIL. The only possible means of transmission is through genetic inheritance.



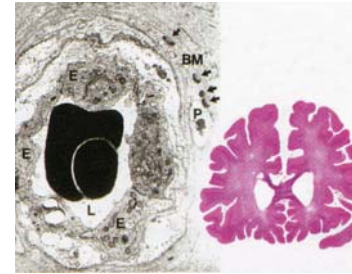
## What can you do to counteract the progression of the disease?

Currently, there are limited medical interventions for controlling the natural progression of CADASIL. However, patients with the disease should make healthy lifestyle choices that reduce the risk of additional injury to the blood vessels. Such risk factors include high blood pressure, diabetes, high cholesterol, obesity, smoking, lack of physical exercise, and other controllable conditions. This means that smokers should stop smoking. Blood pressure, blood sugar levels and cholesterol levels should be monitored at regular intervals and treated if necessary. Exercise is also important. The contraceptive pill is also a risk factor. Therefore, if possible, women should stop using the pill or, if necessary, switch to a

preparation having a lower estrogen content (estrogen content less than 50 µg). In addition, subjects should ensure an adequate intake of fluids (2 to 3 liters of fluid per day, not counting coffee, tea or alcoholic beverages). This is especially true in hot weather.



## 2. Skin Biopsy



CADASIL causes characteristic changes in the blood vessels in almost all regions of the body. These vascular changes may be crucial in making a diagnosis but can only be seen under a powerful electron microscope. Since the blood vessels of the brain cannot be analyzed directly, microscopic examination is performed on the more readily accessible blood vessels in the skin. Under local anesthesia, a small piece of skin is taken from the upper arm or thigh and the resulting wound is closed with one or two sutures. The tissue sample is then sent to a facility that has an electron microscope. Under magnification, the

changes typical of CADASIL can be seen in the vascular walls. One of these characteristics is called granular osmiophilic material, or GOM, which is thought to be made of clumps of excess protein. If such changes can be detected, the CADASIL diagnosis can be regarded as confirmed. The key limitation to skin biopsy is that there is a small chance that the disease could be missed if the skin specimen does not happen to contain any diseased blood vessels.

## 3. Genetic Testing

CADASIL is caused by a mutation (mistake) in the structure of



the *NOTCH3* gene. It turns out, however, that the mutation can take different forms, and that not



all people with CADASIL have the same precise mutation. Within a family, all those affected with the disease will have the same *NOTCH3* mutation. Detection of a mutation is considered 100% proof of the existence of the disease. Since the *NOTCH3* gene is very large, the search for mutations can be tedious, complex, and expensive. For this reason, many diagnostic laboratories test only the locations on the gene most likely to contain the CADASIL mutation. This makes the genetic test somewhat easier and less expensive, but some mutations may be missed. Therefore, in individual cases, it may be necessary to search the entire gene for a mutation.

Only a small amount of blood, which can be taken from a vein, is needed for genetic testing. In the United States, there is only one commercial laboratory that

offers genetic testing for CADASIL. You and/or your physician can find more detailed information about the lab on the Internet at [www.athenadiagnostics.com](http://www.athenadiagnostics.com)

A decision to test for a genetic disorder is an important and sometimes difficult one. Learning that you have a genetic disorder can be psychologically distressing and can have an impact on health insurance. Some people with symptoms may want to know – others may not. The decision to have the test can be even more difficult for healthy members of a CADASIL family. You should discuss your concerns with your doctor before having the test. Genetics counselors have special expertise in working with people with genetic disorders and may provide helpful advice and guidance in making your decisions.



## Is there a treatment for CADASIL?

So far there is no cure for CADASIL, and there are no medications that reliably slow or prevent progression of the disease. Cures or treatments might become available in the future as more is learned about the mechanisms of CADASIL, but it is impossible to predict when this will happen.

However, many symptoms of CADASIL can be treated effectively. For example, epileptic seizures and migraine attacks can be treated with conventional anti-seizure and migraine drugs. Other forms of therapy in addition to medication should also be considered. Physical therapy, counseling, speech therapy, and occupational therapy often have a positive influence on symptoms of the disease. Ask your neurologist about these programs.

Depression and memory loss can also be treated with medications. These medications should be prescribed by a trained neurologist or psychiatrist.

We still do not know whether CADASIL patients benefit from treatment with “blood thinning” medications that are often used to help prevent stroke. Your neurologist may recommend that you take a low-dose aspirin or a similar medication daily to try to prevent a stroke. Warfarin (coumadin) and TPA (to dissolve blood clots) should be avoided because they increase the risk of bleeding in the brain. Triptans to treat migraine should also be avoided because they increase the risk of stroke..

