

FACT SHEET: CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)

Before we go into detail about CADASIL, let's break down its complex name so that we understand what it means.

Cerebral: relating to the brain.

Autosomal dominant: a method of genetic inheritance, whereby a single abnormal copy of a gene causes disease, even though a good copy of the gene is also present.

Arteriopathy: disease of the arteries.

Subcortical: relating to the portion of the brain immediately below the cerebral cortex, which is the part of the brain responsible for most higher functions (sensation, voluntary muscle movement, thought, reasoning, memory, etc.)

Infarcts: areas of tissue that have undergone a type of cell death called necrosis, as a result of restricted blood supply.

Leukoencephalopathy: a type of change associated with the white matter, which includes localized areas of cell death.

What is the cause of CADASIL?

CADASIL is caused by mutations in a gene called Notch3, which is a protein that is involved in determining cell fate; for example, it might determine that a particular cell will be the type of cell that is present in the wall of a blood vessel, or that it will be a liver cell. Mutation in Notch3 causes the Notch3 protein to accumulate abnormally in brain vessels and peripheral tissue arteries. This also leads to diffuse loss of myelin throughout the brain, as well as deep infarcts in the white matter.

CADASIL is an autosomal dominant disease, which means that a single mutated copy of the Notch3 gene overrides the one "good" copy, producing disease (see our *Genetic Inheritance* fact sheet for more information). This means that if a parent is affected, any children of that parent have a 50% chance of having the disorder as well. If the child receives the mutated

gene, the child has a 100% chance of getting CADASIL.

What are the symptoms of CADASIL?

A person with CADASIL generally does not show symptoms until mid-life (40s-50s), though some cases have been identified where symptoms appear in the 20s. Though symptoms and course of disease can vary dramatically, the initial symptoms are generally migraine and MRI abnormalities. Over the next decades as the disease advances, strokes and dementia are common symptoms. Death generally occurs 10-20 years within the onset of symptoms.

The most common symptoms of CADASIL include:

- **Migraine with aura:** a migraine is a vascular headache resulting from changes in the sizes of the arteries in the brain. An aura refers to an abnormal sensation that the migraine is going to occur.
- **Psychiatric disturbance:** any number of mood disorders can occur as a result of CADASIL, including depression
- **Ischemic episodes:** Loss of blood flow to the brain, causing symptoms similar to those of a stroke. They result from low oxygen in the blood or tissues, generally as a result of an obstruction of the arterial blood flow.
- **Cognitive deficits:** these might include deficits in episodic memory and attention; the cognitive abilities generally decline as the disease worsens..
- Epileptic seizures
- Dementia
- Multiple strokes
- Visual impairment
- Hemiparesis: paralysis of one side of the body
- Progressive memory loss

How can CADASIL be diagnosed?

There are several different methods of diagnosing CADASIL. One of the most common methods is to take a skin biopsy, and examine it with a technique called electron microscopy, to look for the characteristic accumulations of granular material (called granular osmiophilic material, or GOM) commonly seen in CADASIL. This can positively diagnose CADASIL, though a negative result on this test does not necessarily mean that the disease is not present. Additionally, a skin biopsy can be tested for the accumulation of Notch3, using a molecule that specifically detects this protein. This accumulation occurs well before any manifestation of the disease, and can be used to diagnose the presymptomatic as well.

Magnetic Resonance Imaging (MRI) may be used to look for characteristic alterations of the brain that are present in CADASIL, but the alterations do not appear to be specific only to CADASIL, and therefore should not be considered useful as a single diagnostic tool.

Because most cases of CADASIL have been found to have mutations in the Notch3 gene, another method of diagnosing CADASIL is to sequence the Notch 3 gene. This method is highly reliable and can diagnose >95% of cases of CADASIL.

How is CADASIL treated?

Migraine can be treated with any number of drugs, including acetazolamide. Treatment of remaining symptoms of CADASIL is supportive.

Other Clinical Names for CADASIL

- Hereditary multi-infarct dementia
- Chronic familial vascular encephalopathy
- Familial disorder with subcortical ischemic strokes
- Agnogenic medial arteriopathy
- Familial Binswanger's disease