

## CADASIL DEFINITION SHEET

**CADASIL is caused by a *Mutation* in the *Notch3* gene located on the chromosome 19**

**What genes are related to CADASIL?** Mutations in the NOTCH3 gene cause CADASIL. The NOTCH3 gene makes a protein called the Notch3 receptor protein, which plays a role in the development, function and maintenance of vascular smooth muscle cells. Mutations in the NOTCH3 gene lead to an abnormal version of the Notch3 protein that builds up in vascular smooth muscle cells. Accumulation of the abnormal Notch3 protein is thought to cause the degeneration of these muscle cells, leading to the loss of function of blood vessels in the brain and heart.

**What mutations are effected with CADASIL?** Almost all CADASIL mutations alter the number of cysteine residues in the epidermal growth factor (EGF)-like repeats in the extra cellular domain of the protein. More than 100 mutations that cause CADASIL have been reported. Almost all of these mutations change a single amino acid (a building block of proteins) in the Notch3 receptor. Evidence suggests that these mutations play a role in the degeneration of vascular smooth muscle cells. Loss of the muscle cells leads to reduction of blood flow to the brain and heart.

**Animal model** Animal model refers to a non-human animal with a disease or injury that is similar to a human condition. These test conditions are often termed as animal models of disease. The use of animal models allows researchers to investigate disease states in ways which would be inaccessible in a human patient, performing procedures on the non-human animal that imply a level of harm that would not be considered ethical to inflict on a human.

**Arginine** is an amino acid that plays a role in cell division, healing of wounds, removing ammonia from the body, improving immunity to illness, and hormone secretion. Arginine is used by the body to make nitric oxide, a substance that relaxes blood vessels.

**Arteries** any of the tubular branching muscular and elastic-walled vessels that carry blood from the heart through the body

**Asymptomatic** means there are no symptoms.

**Arteriopathy** disease of the arteries -

**Autosomal** inheritance means that the gene is located on one of the autosomes (chromosome pairs 1 through 22). This means that males and females are equally affected.

**Basil Gangalia** A group of brain areas that collectively are involved with control of normal movement and walking. The caudate nucleus and putamen (straitum), globus pallidus and substantia nigra are important basal ganglia structures.

**Blood Thinners** a drug used to prevent the formation of blood clots by hindering coagulation of the blood which should be avoided with patients who have been diagnosed with CADASIL.

**Cell** the smallest units of living structure capable of independent existence, composed of a membrane-enclosed mass of protoplasm and containing a nucleus or nucleoid. Cells are highly variable and specialized in both structure and function, though all must at some stage replicate proteins and nucleic acids, utilize energy, and reproduce themselves.

**Cholesterol** a waxy, fat-like substance made in the liver, and found in the blood and in all cells of the body, Cholesterol is important for good health and is needed for making cell walls, tissues, hormones, vitamin D, and bile acid. Cholesterol also comes from eating foods taken from animals such as egg yolks, meat, and whole-milk dairy products. Too much cholesterol in the blood may build up in blood vessel walls, block blood flow to tissues and organs, and increase the risk of developing heart disease and stroke.

<b>Cerebral</b>	is relating to the brain or cerebrum
<b>Chromosome</b>	chromosome is a very long DNA molecule and associated proteins, that carry portions of the hereditary information of an organism
<b>Condom Position</b>	a specific sequence of three consecutive nucleotides that is part of the genetic code and that specifies a particular amino acid in a protein or starts or stops protein synthesis
<b>DNA</b>	Deoxyribonucleic acid (DNA) is a nucleic acid that contains the genetic instructions for the development and functioning of living organisms. All living things contain DNA genomes
<b>Dementia</b>	loss of intellectual functions such as memory, learning, reasoning, problem solving, and abstract thinking while vegetative functions remain intact.
<b>Demyelination</b>	describes damage to the myelin sheaths which surround the nerve fibres in the central or peripheral nervous system. This prevents the nerve fibres from conducting impulses properly, which leads to symptoms and signs of problems in the nervous system.
<b>Dominant</b>	means that only one gene is necessary to have the trait. When a parent has a dominant trait, there is a 50 percent chance that any child they have will also inherit the trait.
<b>Epileptic Seizures</b>	the physical manifestations (as convulsions, sensory disturbances, or loss of consciousness) resulting from abnormal electrical discharges in the brain (as in epilepsy)
<b>Electron microscope</b>	an electron-optical instrument in which a beam of electrons is used to produce an enlarged image of a minute object
<b>Familial</b>	condition that tends to occur more often in family members than expected by chance alone. A familial disease may be genetic.
<b>Gait</b>	a manner of walking or moving on foot
<b>Gene</b>	the functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.
<b>Genetic Counselor</b>	genetic consultation is a health service that provides information and support to people who have, or may be at risk for, genetic disorders. During a consultation, a genetics professional meets with an individual or family to discuss genetic risks or to diagnose, confirm, or rule out a genetic condition
<b>Genetic Testing</b>	genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. Most of the time, testing is used to find changes that are associated with inherited disorders.
<b>Gene Therapy</b>	the insertion of usually genetically altered genes into cells especially to replace defective genes in the treatment of genetic disorders or to provide a specialized disease-fighting function (as the destruction of tumor cells)
<b>Grey Matter</b>	Those regions of the nervous system especially containing predominantly unmyelinated tissue and includes such regions as the cerebral cortex and areas such as cranial nerve nuclei and
<b>GOM</b>	Granular Osmiophilic Material which is thought to be made of clumps of excess protein in the skin of patients with CADASIL.
<b>Hetrozygous</b>	possessing two different forms of a particular gene, one inherited from each parent.

<b>Infarct</b>	a pathological process consisting of a sudden insufficient blood supply to an area, which results in necrosis of that area. An area of tissue death due to a local lack of oxygen.
<b>Infarction</b>	the formation of an infarct, an area of tissue death due to a local lack of oxygen
<b>Leukoencephalopathy</b>	the destruction of the myelin sheaths that cover nerve fibers. These sheaths, composed of lipoprotein layers, promote the transmission of a neural impulse along an axon.
<b>Mental Disorder</b>	broad class of abnormalities of thought, feeling, and behavior, resulting in distress or impairment.
<b>Migraines</b>	neural condition characterized by a severe recurrent vascular headache, usually on one side of the head, often accompanied by nausea, vomiting, and photophobia, sometimes preceded by sensory disturbances.
<b>Mutation</b>	mutation is a permanent change in the DNA sequence of a gene. Mutations in a gene's DNA sequence can alter the amino acid sequence of the protein encoded by the gene.
<b>Mutation Carriers</b>	people have the defective gene for CADASIL
<b>MRI</b>	magnetic resonance imaging (MRI) is a method for making detailed images of the brain. MRI uses magnetic fields and radio wave to make its images.
<b>MID</b>	Multi-infarct dementia (MID) is the most common form of vascular dementia, which is a deterioration in mental function caused by strokes. "Multi-infarct" means that multiple areas in the brain have been injured due to a lack of blood.
<b>Myelin</b>	sometimes referred to as "white matter" because of its white, fatty appearance, protects and insulates the axons. It consists of a protective sheath of many different molecules that include both lipids (fatty molecules) and proteins. This protective sheath acts in a manner very similar to that of the protective insulation that surrounds an electric wire; that is, it is necessary for the rapid transmission of electrical signals between neurons. It does this primarily by containing the electrical molecules (called ions) within the axon so that they are properly transmitted to the next neuron.
<b>Myocardial infarction</b>	term "myocardial infarction" focuses on the myocardium (the heart muscle) and the changes that occur in it due to the sudden deprivation of circulating blood. The main change is necrosis (death) of myocardial tissue.
<b>New Mutation</b>	an alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself.
<b>Nucleotide Position</b>	one of the structural components, or building blocks, of DNA and RNA. A nucleotide consists of a base (one of four chemicals: adenine, thymine, guanine, and cytosine) plus a molecule of sugar and one of phosphoric acid.
<b>PGD</b>	Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member.
<b>Prevalence</b>	the proportion of individuals in a population having a disease. Prevalence is a statistical concept referring to the number of cases of a disease that are present in a particular population at a given time.
<b>Protein</b>	molecule made up of amino acids that are needed for the body to function properly. Proteins are the basis of body structures such as skin and hair and of substances such as enzymes, cytokines, and antibodies.

<b>Psychological</b>	relating to, characteristic of, directed toward, influencing, arising in, or acting through the mind especially in its affective or cognitive functions
<b>Receptor</b>	molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell.
<b>Risk Factor</b>	something that may increase the chance of developing a disease. Some examples of risk factors for cancer include age, a family history of certain cancers, use of tobacco products, certain
<b>RNA</b>	Ribonucleic acid (RNA) is a nucleic acid polymer consisting of nucleotide monomers. RNA serves as the template for translation of genes into proteins, transferring amino acids to the ribosome to form proteins, and also translating the transcript into proteins.
<b>Skin Biopsy</b>	under local anesthesia, a small piece of skin is taken from upper arm or thigh and is closed with one or two sutures.
<b>Stroke</b>	is a term for brain hemorrhage and brain infarction. If a brain artery is blocked, for instance by a blood clot, the flow of oxygen-saturated blood to a large number of nerve cells is obstructed.
<b>Subcortical</b>	the portion of the brain immediately below the cerebral cortex.
<b>TIA</b>	Transient ischemic Attack is a reversible episode of oxygen depletion. The attacks are caused by blood clots that dissolve before oxygen deficiency has caused permanent brain damage.
<b>Vascular</b>	of, relating to, constituting, or affecting a tube or a system of tubes for the conveyance of a body fluid (as blood or lymph)
<b>Vessels</b>	tube or canal (as an artery, vein, or lymphatic) in which a body fluid (as blood or lymph) is contained and conveyed or circulated
<b>White Matter</b>	neural tissue especially of the brain that consists largely of myelinated nerve fibers bundled into tracts, has a whitish color, and typically underlies the gray matter

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

**Patients blood positive test might look like this:** Heterozygous for a C to T base change at nucleotide 505 of the Notch 3 gene that changes a codon for arginine (CGC) to one for cysteine (TGC) at amino acid position 169. This patient's mutation would be a R169C- mutation.

**This Education Sheet was created by:  
CADASIL TOGETHER WE HAVE HOPE  
[www.cadasilfoundation.org](http://www.cadasilfoundation.org)**

created 9-06 updated 01/09

*This resource is only a guide which should not be used as a substitute for professional medical care or advice. Users seeking information about a personal genetic disease, syndrome, or condition should consult with a qualified healthcare professional.*

Resources used: [www2.merriam-webster.com/cgi-bin/mwmednlm](http://www2.merriam-webster.com/cgi-bin/mwmednlm)

<http://ghr.nlm.nih.gov/condition=cadasil>