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Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
Cerebral Autosomal Dominant
CADASIL
TOGETHER WE HAVE HOPE
www.cadasilfoundation.org

# CADASIL Together We Have Hope Non-Profit Organization

## OUR SCIENTIFIC ADVISORY COMMITTEE MEMEMBERS

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## QUESTIONS ANSWERED BY THE SCIENTIFIC ADVISORY COMMITTEE

**1. PLEASE CLARIFY THIS STATEMENT:**
CADASIL is passed from parent to child through a mutation in a gene. Each offspring of a CA-DASIL parent has a 50% chance of inheriting the disease. If a person does not inherit the CADASIL gene, he or she will not develop the disease and cannot pass it to subsequent generations. A person who inherits the mutation gene will sooner or later develop the disease

The above statement is true: CADASIL is passed as a dominant mutation and offspring have a 50% chance of developing the disease. All mutation carriers develop some form of the illness (complete penetrance) though the timing and severity and symptoms may vary in family members with the same mutation. Women with CADASIL live longer than men on average. So there are other genetic and environmental factors, yet to be identified, that modulate gene expression. A de novo mutations (A de novo mutation is a new mutation) can rarely occur in exceptional isolated cases without a prior family mutation.

**2. SHOULD A CADASIL PATIENT TAKE ASPIRIN?** Yes, There is no scientific evidence that aspirin plays a preventive role in CADASIL, however, based on what is currently known in stroke patients, we usually recommend this treatment if there is non contra-indication and the occurrence of a first ischemic event. The tough decision is deciding what to do when patients have TIA's and strokes despite treatment with aspirin. Because of the risk of hemorrhage and lack of evidence, blood thinners such as warfarin and clot busters like TPA are not recommended.

**3. HOW MUCH ASPIRIN SHOULD BE TAKEN?** The dose of aspirin most currently evaluated in therapeutic trials is between 75 mg to 325mg. Asymptomatic CADASIL patient should have a low dosage of aspirin and a patient with a history of TIA's or stroke could be given a higher dose of aspirin per day. It is recommended to take coated aspirin.

## INSIDE THIS ISSUE:

## WHAT IS CADASIL?

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, usually called CADASIL, is an inherited form of stroke and other impairments. This condition affects small blood vessels, mainly in the brain. An abnormality in the muscle cells surrounding these blood vessels (vascular smooth muscle cells) gradually destroys the blood vessel cells. The resulting blood vessel damage can lead to migraines, emotional and mental disorders, stroke-like episodes, dementia, and other impairments of normal brain function. Patients with CADASIL are also at increased risk of heart attack (myocardial infarction) because of damaged blood vessels in the heart. Most patients with CADASIL do not have the common risk factors for stroke and heart attack, such as high blood pressure and high cholesterol, although in some cases these features may also be present.

**PRESENTATION ON BIOCHEMISTRY OF CADASIL BY SWATI SATHE, M.D.**
(FROM THE UNITED LEUKODYSTROPHY FOUNDATION JULY 2006)

Dr. Swati Sathe, of the Department of Neurology NYU School of Medicine, gave a presentation at the ULF conference held July 22, 2006. The talk is summarized here in the following sections.

1. **CADASIL Symptoms and their age of onset**
2. **Brain MRI and CADASIL Progression**
3. **Molecular Defect: details of the Notch3 gene defect**
4. **CADASIL Pathology & Treatment**

**1. CADASIL SYMTOMS** and their age of onset In a study of 18 patients [1] divided into age ranges: <20, 20 – 29, 30 – 39, 40 – 49 and 50 – 59 years, the following symptoms were demonstrated most strongly within the decades as shown.

| Symptom | Initial Symptoms Stratified by Age of Onset |
|---|---|
| **Migraine** | <20 |
| **Stroke/TIA** | 40 – 49 |
| **Other (includes cognitive decline)** | 40 – 49 |
| **Depression** | 50 – 59 |

Overall characteristics of a 76 member CADASIL group were as shown below. [2]

| | Percent of Group |
|---|---|
| **CADASIL-related symptoms** | |
| TIA/stroke | 76 |
| Cognitive impairment | 42 |
| Migraine with aura | 36 |
| Major depression | 11 |
| Epileptic seizures | 5 |
| **Vascular Risk Factors** | |
| Smokers | 36 |
| Hypertension | 24 |
| Hypercholesterolemia | 20 |
| Diabetes mellitus | 3 |

## 2. BRAIN MRI AND CADASIL PROGRESSION

Brain MRI images per Chabriat [3] demonstrate a pattern of increasing damage to the white matter at the center of the brain. This damage is consistent with the belief that capillaries collapse due to lack of support and there is loss of blood supply to the deep white matter, which is supplied by long penetrating blood vessels that do not form network. As a result their function cannot be taken over. The Brain MRI FLAIR image, per Gladstone JP et al. 2, demonstrates hyper intensities in the anterior temporal poles characteristic of CADASIL. The Van den Boom [5] at al slide presents the correlation of specific MRI detectable damage by age. For 100% of all ages, areas of hyper intensity are visible.

Micro bleeds are visible in about 20% of the 41 – 50 group. For ages 51 – 60, micro bleeds are visible in about 50% of the population studied. For ages 20 – 30, no lacunar infarcts [6] are seen, but for ages 31 – 60, lacunar infarcts 4 are seen in 80% - 90% of the population studied. Sub-cortical lacunar lesions are visible with increasing age ranging from 20% for the age 20 – 30 group and increasing to 70% for the age 51 – 60 group.

## 3. MOLECULAR DEFECT: DETAILS OF THE NOTCH 3 GENE DEFECT

The defective gene for CADASIL is located on chromosome 19p 13.1, the Notch3 gene. An alteration in the sequence (mutation) of this gene causes CADASIL; more than 75 such alterations have been described. Notch3 encodes a glycosylated transmembrane receptor which is a protein involved in cell-fate specification during development. Specifically, the alteration in the sequence affects the body's ability to manufacture correctly the 2321 amino acid protein. Sixty-six percent of the mutations are in exon 4. Ninety-five percent of the mutations are missense mutations, that is, one amino acid in the sequence is replaced by another. Often this change involves a cysteine (which is an amino acid) residue i.e. either a cysteine is added or deleted.

## 4. CADASIL PATHOLOGY AND TREATMENT—The following slides from the presentation are presented verbatim.

### 4.1 *Pathology*

- Smooth muscle cells of the media replaced with deposits of basophilic granular material which is also electron-dense
- Reduplication of the internal elastic lamina
- Multiple small infarcts (lacunar, cystic), in the subcortical white matter, basal ganglia, thalamus
- Stains for amyloid negative
- Stains for myosin, collagen IV positive [5]

### *4.2 Sites of Extra Neural Involvement*

- Retina
- Liver
- Sural nerves
- Retina
- Skin
- Muscle

### *4.3 Early Diagnosis*

- Complicated migraine
- Family History of strokes at a young age
- Stroke at a young age in an individual with no risk factors

### *4.4 Treatment Possibilities*

- Aspirin, Ticlopidine, Clopidegril to prevent stroke and coronary artery disease but there may not be an effective treatment for Micro bleeds
- Acetazolamide for cerebral vasodilatation (empiric therapy)
- Drugs to improve vascular reactivity
- HELP (Heparin-induced Extracorporeal LDL/fibrinogen Precipitation)
- Removal of the accumulated Notch3 extodomain
- Gene therapy with normal Notch3 gene
- Restore "Enhance of Split" function by gene therapy (a Notch3 signaling target)

### *4. 5 Treatment for Agitation and Disruptive Behavior*

- Respiridone (generic: Risperdal) and Olanzapine (generic: Zyprexa)

### *4.6 Contraindicated In CADASIL*

- Tricyclic antidepressants due to hypotensive effects [8] and Fibrinolytic therapy due to the danger of bleeding
- Angiography due to complications in 69% of patients (vs. the general population risk of 0.5 – 5%) and permanent neurological deficit in 13% [9, 10]

### *4. 7 Medication Usage Among 80 CADASIL Subjects* [11]

| | # | % |
|---|---|---|
| Antiplatelet [12] medication (e.g. Plavix) | 60 | 75 |
| Anticoagulants (e.g. Coumadin) | 1 | 1 |
| Antihypertensives | 17 | 21 |
| Statins | 16 | 20 |

### *4.8 Drug Treatment for Vascular Dementia* [13]

| | | |
|---|---|---|
| | • Piracetam | • Propentiofylline |
| | • Oxiracetam | • Aspirin |
| | • Nicergoline | • Triflusal |
| | • Citroline | • *Ginko biloba* |
| | • Pentoxifylline | • Nimodipine |
| | | • Memantine [14] |

References


Desmond: Stroke, Volume 30(6). June 1999. 1230 - 1233

[2] Peters N. et al., Stroke. 2004; 35:1603

[3] Chabriat, H et al.: Neurology, 51(2). 1998: 452 - 457

[4] Gladstone JP & Dodick, DW. The Neurologist 2005; 11: 19 - 29

[5] Van den Boom et al., Radiology 2003; 229: 683-690


[6] Lacunar infarct – An area of tissue in an organ or part that undergoes necrosis following cessation of blood supply. This small infarct is usually located in the deep noncortical cerebrum or brain stem resulting from occlusion of the penetrating branches of the cerebral arteries.

[7] Presentation delivered by Swati Sathe, M.D.

[8] Amytryptaline and Pamelor cause hypertension and dry mouth. Where once it was thought that the lower the blood pressure, the better; the current thinking is that blood pressure should be around 120/80; not too high and not too low.

[9] Dichgans & Peteresen, Lancet 1997; 49: 776-777

[10] In CADASIL strokes are small so there's nothing to open up via angiography

[11] Peters, et al., Stroke, 2004; 35: 1603-1608

[12] Dr Swati Sathe recommends that all CADASIL patients take an antiplatelet medication.

[13] Adapted from: Roman et al., The Lancet Neurology 2002; 1: 426-436

[14] Memantine is used with Aricept for moderate to severe dementia

## CADASIL WITH MINIMAL SYMPTOMS AFTER 60 YEARS OLD


Rev Neurol (Paris). 2006 Sep ;162(8-9):827-31 17028543


[My paper] A Mourad , M Levasseur , M G Bousser , H Chabriat


INTRODUCTION: CADASIL is a hereditary cerebral arteriopathy leading to progressive disability and dementia usually observed at 60 years. OBSERVATION: We report four patients aged>60 years with typical Notch3 mutations leading to CADASIL who did not have dementia or disability. Three of them presented with only transient neurological manifestations. MRI results showed extensive hyper intense signals in the white-matter on T2-weighted images contrasting with very few lacunar infarcts. CONCLUSION: These observations suggest that silent or symptomatic infarcts, which were rare in the present cases may be responsible for the clinical severity in this disorder.



Mesh-terms: Aged; CADASIL, physiopathology; CADASIL, psychology; Cognition Disorders, etiology; Disease Progres-

## THE ROLE OF NOTCH3 IN STROKE

**Investigators:** N. Carolyn Schanen, MD, PhD
**Background:** CADASIL is an inherited vascular dementia characterized by migraine with aura, severe mood disturbances, recurrent ischemic strokes, and dementia. In 1996, CADASIL was shown to be caused by mutations in the *NOTCH3* gene. *NOTCH3*, located on chromosome 19, is part of a gene family that encodes a large transmembrane receptor that is crucial for cell fate determination during embryonic development. Notch3 receptors consist of an extracellular domain involved in ligand binding and an intracellular domain involved in signal transduction, with all known CADASIL mutations residing in the extracellular domain of the Notch3 receptor.
**What We're Doing:**
Our research has primarily centered on studying the effects of these mutations on Notch3 function and the onset of CADASIL.
**Some of What We've Found:**
Utilizing five independent mutations analogous to those found in CADASIL patients, we studied the effects of these mutations on protein processing and cell surface expression. Both the unprocessed full-length form and the processed heterodimeric form were observed on the cell surface, suggesting that the Notch3 CADASIL mutations do not affect protein expression, processing, or cell surface localization. Given that the mutations all occur within the extracellular, ligand-binding domain of Notch3, we also evaluated whether ligand binding to a soluble form of the Delta1 ligand would be compromised with our CADASIL mutants. Delta1-Notch3 binding was detected for all five Notch3 CADASIL mutant proteins. Thus, these mutations do not inhibit receptor-ligand interactions. For more information, go to www.americanheart.org, N. Carolyn Schanen, MD, PhD, *Head, Human Genetics Research Lab, Adjunct Assistant Professor in Human Genetics, UCLA School of Medicine*

## SIX THINGS TO DO TO PREPARE FOR YOUR DOCTOR'S VISIT
## THE WAITING ROOM CHECKLIST

Here are six suggestions to make your delay a little less irritating and a lot more productive while seeing a doctor. * excerpts from Neurology Now September 2006 Dr. Orly Avitizur Neurologist

**1. *PRIORITIZE YOUR SYMPTOMS** – If you're a returning patient, what's happened since your last appointment. It's a good idea to select your top three problems and be ready to discuss them; you may have more, but start with the most severe. Neurologists want to know how often your symptoms occur, what makes them worse, and what makes them better. If you are a new patient, doctors want to know the main reason for your visit.
**2. WRITE DOWN YOUR TOP FEW QUESTIONS** – It's easy to get off track. Test results might need to be scheduled, new medications may need to be discussed and, before you know it, your appointment is over. When you start to wrap up, take a quick glance at your questions and make sure they've all been covered. This may remind you of something that you had forgotten to mention and could save you time playing phone tag later. A good idea to make sure you hear everything your doctor has said is to bring in a relative or friend to get the information and take responsibility for reviewing your questions.

**3. *LIST YOUR CURRENT MEDICATIONS** – it may be several months since your last visit. If you are like most neurology patients, you're probably seeing other doctor's as well. Since your last visit, your medications may have been changed or their dosages may have been adjusted. The new prescriptions from your other doctors may interact with one of the neurologist's prescriptions. If you haven't already made a list to keep in your wallet, now is the time to get started and make sure you keep your list up-to-date.

**4. ASK OFFICE STAFF TO CHECK TEST RESULTS** – If you've had tests (such as blood work, X-rays, scans) done since your last visit, ask a receptionist or nurse to check if they're in your chart. If not, there may be time to get the reports faxed to the office before your appointment starts. It will help your neurologist evaluate your condition and give you answers during your appointment. The longer the lag time between the visit and report, the less likely we are to remember the details of the results. Ask for copies of your test results and keep your own medical file at home. Remember that you are the center of your health care team.

**5. UPDATE OFFICE STAFF ON INSURANCE CHANGES** – The front-office staff needs to have your most current insurance information in order to get pre-authorizations and referrals, and the back-office staff needs it to make sure billing is handled smoothly. Incorrect information can cause inappropriate denials and delay requests for service or hold up your claims.

**6. READ UP ON YOUR CONDITON** – Learning about CADASIL will help you educate your Neurologist and help you both decide how to treat your symptoms. Please remember you must be your own case manager when it comes to CADASIL.

## STEM CELL RESEARCH ENHANCEMENT ACT OF 2005 [H.R. 810, S. 471]

**Please note: CADASIL TOGETHER WE HAVE HOPE recognizes that stem cell research is an individual personal choice. By providing this information we are not endorsing stem cell research; we would simply like to inform you on the status of the debate.**

**What is the Stem Cell Research Enhancement Act of 2005?**

This proposed legislation would significantly alter current federal policy by requiring that the federal government conduct and support embryonic stem cell research, regardless of the date on which the stem cell lines were derived and provided that the embryos used were: originally created for in vitro fertilization; would otherwise be discarded; and were donated by fully informed, consenting individuals.

**What is the debate?**

Current policy limits federal funding of stem cell research to stem cell lines created without harming or destroying an embryo or those embryonic stem cell lines that were created before August 9, 2001. As a result, stem cell research in the United States has been considerably limited in scope.

Supporters of the Stem Cell Research Enhancement Act assert that the lack of federal funding for embryonic stem cell research unnecessarily burdens the scientific community, slowing the progress of research that they believe will lead to significant improvements in the treatment of injury and disease.

Opponents of the proposed legislation, on the other hand, argue that the American public should not be forced to fund research that they find morally problematic. Instead, these individuals urge the federal government to invest in research that explores other sources of stem cells. Meanwhile, in the absence of federal funding, states have begun to address the issue on their own, at times providing state funds for the same research that the federal government is unwilling to finance. As the research landscape changes, concerns about both the ethics of embryonic stem cell research and equal access to research technologies and treatment continue to arise.

**What is the status of the bill?**

On July 19, 2006, the President vetoed the bill. Congress was unable to override the veto. On July 18, 2006, the Senate passed the bill by a vote of 63–37. On May 24, 2005, the US House of Representatives passed H.R. 810 by a vote of 238–194. On February 28, 2005, the Senate version, S. 471, was introduced in the Senate and referred to the Committee on Health, Education, Labor, and Pensions.

On February 15, 2005, the House version, H.R. 810, was introduced and referred to the Committee on Energy and Commerce. The House will take up the same bill (probably with a different bill number) the week of January 8. It will be one of the first three bills they consider. The Senate will follow not long after.

For additional details on what specifically was passed by the House, you can reference the Library of Congress web site at http://thomas.loc.gov/cgi-bin/query/D?c110:2:./temp/

## ANNOUCEMENTS

## GUESTBOOK HAS CHANGED IT'S NAME TO THE CADASIL REGISTRY

We do not require membership to join our foundation. Our non-profit organization is the only one which holds the most comprehensive registry of affected individuals and families with CADASIL. Every number counts..... If you or someone in your family has CADASIL and has not yet signed the registry, please go to www.cadasilfoundation.org *and click on the bar registry.*

Once you have registered with us, you will be kept informed with the up-to-date information about CADASIL by receiving e-mail alerts and newsletters. If you provide us with your mailing address we will be glad to mail you a welcome information packet. The registry tracks the number of confirmed cases all over the world. All information provided to us is kept strictly confidential! We will print new data in the newsletters. As of January 1, 2007 we have 35 unconfirmed cases and have 568 confirmed cases as reported to the foundation.

**Confirmed Cases All Over the World—Maps are located on the website**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Australia | 6% | France | 1% | New Zealand | 0.50% | Spain | 0.25% |
| Austria | 0.25% | Germany | 1% | Norway | 0.50% | Sweden | 0.25% |
| Belgium | 0.25% | Holland | 0.25% | Puerto Rico | 0.50% | Switzerland | 0.25% |
| Brazil | 2% | Ireland | 1% | Portugal | 0.25% | Turkey | 0.25% |
| Canada | 8% | Korea | 0.25% | Scotland | 2% | USA | 68% |
| England | 7% | Netherlands | 0.25% | South Africa | 0.25% | | |

Maps are located on the website

## THE FOUNDATION HAS SET UP A NEW TOOL TO FACILITATE ONLINE DISCUSSION AND MAKE GENERAL ANNOUNCEMENTS—SIGN UP NOW

The Foundation makes extensive use of email as a means of communication. Email is quick and cost effective - which is of particular benefit for a non-profit organization that does not charge membership fees. Everyone is welcome to sign up for the Forum. You are invited to join over a hundred other families on the online CADASIL Family Discussion List. You will find caregivers, spouses, patients and even a few doctors and other medical staff here; all bound together by the common experience of CADASIL. in addition, the CADASIL Foundation periodically will send out announcements about key information or activities to an extended list of friends, supporters, professionals, educators, press, etc. via the Discussion Group List. Do note that if there were breaking news regarding CADASIL, it would be sent both via the Discussion Group List as well as our existing newsletter distribution list. E-mail Discussion Group Lists allow people to communicate on their own time lines, or to simply "hang back" and observe. This is different than an on-line chat as the readers may not receive your message for hours and will respond when they have a moment (or are awake - we have members from literally across the world!). This way we all can communicate on our own schedules. Unlike discussion boards, these messages have a sense of timeliness to them as they pop into your in-box.

To join the announcements and discussion group you simply send us an e-mail with a brief introduction of yourself to: discuss-on@CADASILfoundation.org The list host reviews all requests to join our list to assure that we maintain a healthy community. The list host will normally honor your request within 24-48 hours. After you receive an acknowledgment from the list server you can simply send messages to the list address and watch for the response. To sign off from the announcement and discussion group you need to also write the list host so that he can process your request: discuss-off@CADASILfoundation.org To change your address please send both your old and new email address to discuss-off@CADASILfoundation.org

## CURRENT STATUS OF GENETIC NONDISCRIMINATION ACT

**The status of this bill** History - Legislation on genetic nondiscrimination was first introduced in the House of Representatives in 1995 by Rep. Louise Slaughter (D-NY). In 1996, Sen. Olympia Snowe (R-ME) introduced similar legislation in the Senate. Both bills specifically addressed discrimination in health insurance. Neither bill passed in that, the 104th Congress. Similar legislation was introduced in both chambers of Congress in the 105th and 106th Congresses. None of these bills made it to the President's desk.

The Genetic Information Nondiscrimination Act (GINA) was first introduced in 2002 during the 107th Congress by Sen. Olympia Snowe (R-ME). The bill addressed discrimination in both health insurance and employment decisions. The bill did not pass. Similar legislation was introduced in the 108th Congress. In the House of Representatives, the bill (H.R.1910) was introduced by Rep. Louise Slaughter (D-NY) and gained 242 co-sponsors. In the Senate, the bill (S.1053) was introduced by Sen. Olympia Snowe (R-ME) and gained 23 co-sponsors. The Senate bill passed 95-0. The House bill did not. In the 109th Congress, the bill (H.R.1227) was introduced in the House of Representatives by Rep. Judy Biggert (R-IL). It gained 244 co-sponsors, but again it did not pass. In the Senate, Sen. Olympia Snowe (R-ME) introduced the bill (S.306) and it passed 98-0. Please note the bill number has been changed to HR. 493 and was presented on January 16 of this year in the house.

**What are you asking me (your representative) to do?** Please write to your Senator(s) and House Representative and ask them to support the Genetic Information Nondiscrimination Act (GINA). Both the Senate and the House of Representatives have web sites where you can get contact information and in most cases send an e-mail. You can contact your State Representative at http://www.house.gov/writerep/ . You can contact your Senator(s) at http://www.senate.gov/ and in the upper right is a prompt 'find your senator'. Senator Judy Biggert co-sponsored the legislation. You can also sign on as a co-sponsor to the Genetic Information Nondiscrimination Act . For more information, contact Brian Petersen in Representative Judy Biggert's office at 202.225.3515. Also, urge your colleagues to sign on as a co-sponsor.F or more information on the legislation, please go to http://www.geneticfairness.org/act.html

## RAISING AWARENESS – LETTER WRITING CAMPAIGN

Below is a list of places to write to inform others about CADASIL. Please share how you coped or learned about CADASIL. As promised in the next coming newsletters we will print additional addresses for everyone to write to raise awareness for CADASIL.

Neurology Now
222 Seventh Ave, 19th Floor
New York, NY 10001

The View Producer
320 West 66th St.
New York, NY 10023

Primetime
147 Columbus Ave.
New York, NY 10023

The Montel Williams Show
433 West 53rd Street
New York, NY 10019

60 Minutes Producer
524 West 57th St.
New York, NY 10019

ABC's World News This Morning
47 West 66th St.
New York, NY 10023

## STORIES AND OTHER ITEMS

### SHOULD I GET TESTED OR NOT

Noelle is our 18 year old daughter. For the past 8 years, she has wanted to get tested for CADASIL. She has recently started to have migraines. She felt it was the time to know. It had always bothered her if she had CADASIL or not. She saw a Medical Geneticist who took the history of both sides of the family tree at the end of November of 2006. The doctor asked her how she felt about knowing if she had CADASIL. She said she has seen her father, Steve, for the past 9 years live with CADASIL and since he has a very positive outlook she said, she could also live like her father even if she had CADASIL. She also mentioned that her mother was the president of CADASIL Together We Have Hope and grew up knowing more about CADASIL than others her age do. The papers were signed by the Geneticist to draw the blood for Noelle for the test and her father from his primary care physician signed the lab work slip. They were scheduled to go on Monday, December 18th, 2006 to the lab to draw the blood and send it off. Sunday night Noelle talked with us as the next day was her 19th birthday. She explained to us in detail about her doubts of being tested and how she would live knowing she might have CADASIL. She decided that night she would not get tested unless she showed further symptoms. Noelle knew she did not want to hinder her life by getting an early positive result from the test. She said she would carry on with her preventive measures, over the counter and prescription medicines. We were relieved that she decided not to get tested at this point. As a positive early result and the uncertainty news that it brings may affect the decisions she makes about her future. Noelle's father would feel a lot of guilt knowing he could pass the genetic illness to his daughter. We know that Noelle might not have CADASIL but our daughter is so young that Noelle needs to live her life now and worry about CADASIL later on in life.

Billie and Steve Duncan-Smith

### CATHY'S STORY...

Let me tell you about Cathy. She was a typical Jersey Girl, funny, kind and caring but with an attitude and mouth to back it up. She was married at 18 to the love of her life Marc, and had two sons with him. She lost her husband after fourteen short but happy years of marriage to a tragic homicide. She never re-married nor did she date. She continued to be a devoted mother and raised her children into loving good men. When her grandson was born in 2005, Cathy relocated to Nevada to live with her oldest son and his family. Her son had lived in Nevada for almost six years and noticed a change in his mom as soon as she arrived. The twinkle in her eyes had faded and she seemed constantly depressed. Family discussions of the past weren't so easy for her. Her memory seemed to be failing and she complained of headaches and weakness.

On March 8, 2006 Cathy suffered a stroke. Once we, her family, were in the hospital she told us that she had "white matter disease", which we had no idea what that was and why on earth we hadn't been told about it before. So the research began and come to find out there are a lot of illnesses with the related term "white matter". Upon further research of old medical records, we found out Cathy has CADASIL. We rush to the hospital with the records, showed them to the neurologist and he told us Cathy instead had MS. When Cathy failed all other MS tests, the doctor diagnosed Cathy with CADASIL. He told us that day that in his 30+ years of neurology he had never seen a brain scan that looked as bad as Cathy's. His actions that day left us with little hope.

Once we left the hospital Cathy told us that she knew she had CADASIL for about four years, and that her symptoms began when she was around 24 years of age. She failed to tell us because she didn't want us to worry. She has since had three additional strokes. Cathy now believes that there is very little that can be done for her. But we, her family, know that isn't true. We constantly remind her that things are being done everyday to research this disease. We try to keep her hopeful. Cathy went back to Jersey to be with her sister, also a CADASIL sufferer. Cathy's story is unique. Cathy is a daughter, a sister, a mother and a grandmother. She has been through more in her 54 years than most go through in a lifetime. My prayer for Cathy and everyone else who suffers from CADASIL is that there will be a cure in the near future.

### A POSTITIVE AND UPBEAT PERSON LIVING WITH CADASIL

My wife and I got married in 1993, I was 33 she was 29. We are both very active and fit. She is a busy body, if there is something to get done, she does it. She has always had these migraines but they would go away. They would slow her down for a couple of hours, but not for long. But after our third daughter was born in 1999, she had a very bad migraine with aura. She was curled up in the fetal position for a couple of days and we had a brand new baby at home and two other toddlers. I knew this was different then the others. I took her to the emergency room and she was admitted. After a couple of days they determined that she had MS. I went for a second opinion at one of the research hospitals in Chicago and he immediately dismissed the MS diagnosis and said it was something different. We were referred to a Neurologist and she had the test to confirm the CADASIL diagnosis.

My wife is 42 and doing great right now. I feel a little guilty in saying that as I know others are struggling. But her story is very similar to others I have read. She is the 3rd of four children. Her mother had migraines and a stroke and she fell once and hit her head, and

because she was on blood thinner, there was massive bleeding in her brain. She died at age 65. We always thought the fall was the cause of death. We know now that she had CADASIL. My wife's grandfather died of a stroke; we now know it must have been CADASIL. One of my wife's sisters has been tested and was positive for CADASIL. The other two siblings do not have symptoms and seem to have escaped the disease. We have three daughters, ages 11, 9, and 7. The most beautiful little girls you can imagine and the worst part of everything is knowing they may have this. We do not discuss it with them as it is a burden they don't need to carry at these young ages. My wife takes her medicine, works out almost every day, volunteers constantly at school, is on the church board, runs the children's ministry, cooks, cleans takes care of all of us and is constantly giving of herself. Her word recall is really the only way I can tell anything is going on with her. Most people don't even know she has the condition. She is the most positive and upbeat person I know. We are thankful and prayerful that so far things have gone well.

I am in the insurance business; I have my own agency here in the Chicago suburbs. We cannot get her anymore life insurance or Long Term Care. We had purchased as much as we could on the kids before we got the diagnosis. We are limited in our ability to change group health insurance because of the condition, but we have coverage and we are glad for that. We really don't have any claims right now. Insurance is definitely a problem with this condition. I try to stay informed and prepared for what may come in the future. We say prayers every night with our children and they don't know it, but all of you are in our prayers every night. John

## MY HUSBAND IN AUSTRALIA

My Husband had his first stroke in July 1998 at age 47. Six years later he had a second stroke and six months later, his third which was his worst one putting him is hospital because he could not swallow. He was tube fed until physiotherapy strengthened his gag reflex. He does not suffer with migraines at all and is on a disability pension at age 56 now. It's been 18 months since the last stroke. Our General Practitioner is not familiar with CADASIL; we have a neurologist who is. He is taking PLAVIX for the blood thinning, he takes antidepressants and tablets for high blood pressure. He does lose his balance sometimes and his memory plays havoc with him. He does get frustrated. I hope with more recognition of the disease that doctors will eventually find a cure or at least a treatment. My husband has 3 living cousins in one family and two have CADASIL.
October 15, 2006

## IS LAUGHTER THE BEST MEDICINE

**From Health watch CBC Online News Article dated April 7, 2006**

(WebMD) Feeling run down? Try laughing more. Some researchers think laughter just might be the best medicine, helping you feel better and putting that spring back in your step. "I believe that if people can get more laughter in their lives, they are a lot better off," says Steve Wilson, M.A., CSP, a psychologist and laugh therapist. "They might be healthier, too." Yet researchers aren't sure if it's actually the act of laughing that makes people feel better. A good sense of humor, a positive attitude, and the support of friends and family might play a role, too. "The definitive research into the potential health benefits of laughter just hasn't been done yet," says Robert R. Provine, professor of psychology and neuroscience at the University of Maryland, Baltimore County and author of Laughter: A Scientific Investigation. But while we don't know for sure that laughter helps people feel better, it certainly isn't hurting.

**Laughter Therapy: What Happens When We Laugh?**
We change physiologically when we laugh. We stretch muscles throughout our face and body, our pulse and blood pressure go up, and we breathe faster, sending more oxygen to our tissues. People who believe in the benefits of laughter say it can be like a mild workout — and may offer some of the same advantages as a workout. "The effects of laughter and exercise are very similar," says Wilson. "Combining laughter and movement, like waving your arms, is a great way to boost your heart rate." One pioneer in laughter research, William Fry, claimed it took 10 minutes on a rowing machine for his heart rate to reach the level it would after just one minute of hearty laughter. And laughter appears to burn calories, too. Maciej Buchowski, a researcher from Vanderbilt University,laughter burned 50 calories. While the results are intriguing, don't be too hasty in ditching that treadmill. One piece of chocolate has about 50 calories; at the rate of 50 calories per hour, losing one pound would require about 12 hours of concentrated laughter!

**Laughter's Effects on the Body**
In the last few decades, researchers have studied laughter's effects on the body and turned up some potentially interesting information on how it affects us:

- Blood flow. Researchers at the University of Maryland studied the effects on blood vessels when people were shown either comedies or dramas. After the screening, the blood vessels of the group who watched the comedy behaved normally — expanding and contracting easily. But the blood vessels in people who watched the drama tended to tense up, restricting blood flow.

- Immune response. Increased stress is associated with decreased immune system response, says Provine. Some studies have shown that the ability to use humor may raise the level of infection-fighting antibodies in the body and boost the levels of immune cells, as well. Blood sugar levels. One study of 19 people with diabetes looked at the effects of laughter on blood sugar levels. After

eating, the group attended a tedious lecture. On the next day, the group ate the same meal and then watched a comedy. After the comedy, the conducted a small study in which he measured the amount of calories expended in laughing. It turned out that 10-15 minutes of group had lower blood sugar levels than they did after the lecture. Relaxation and sleep. The focus on the benefits of laughter really began with Norman Cousins' memoir, Anatomy of an Illness. Cousins, who was diagnosed with ankylosing spondylitis, a painful spine condition, found that a diet of comedies, like Marx Brothers films and episodes of Candid Camera, helped him feel better. He said that 10 minutes of laughter allowed him two hours of pain-free sleep.

**The Evidence: Is Laughter the Best Medicine?**

But things get murky when researchers try to sort out the full effects of laughter on our minds and bodies. Is laughter really good for you? Can it actually boost your energy? Not everyone is convinced. "I don't mean to sound like a curmudgeon," says Provine, "but the evidence that laughter has health benefits is iffy at best." He says that most studies of laughter have been small and not well conducted. He also says too many researchers have an obvious bias: they go into the study wanting to prove that laughter has benefits. For instance, Provine says studies of laughing have often not looked at the effects of other, similar activities. "It's not really clear that the effects of laughing are distinct from screaming," Provine says. Provine says that the most convincing health benefit he's seen from laughter is its ability to dull pain. Numerous studies of people in pain or discomfort have found that when they laugh they report that their pain doesn't bother them as much. But Provine believes it's not clear that comedy is necessarily better than another distraction. "It could be that a compelling drama would have the same effect." One of the biggest problems with laughter research is that it's very difficult to determine cause and effect. For instance, a study might show that people who laugh more are less likely to be sick. But that might be because people who are healthy have more to laugh about. Or researchers might find that, among a group of people with the same disease, people who laugh more have more energy. But that could be because the people who laugh more have a personality that allows them to cope better. So it becomes very hard to say if laughter is actually an agent of change — or just a sign of a person's underlying condition.

**Laughing It Up for Quality of Life**

Laughter, Provine believes, is part of a larger picture. "Laughter is social, so any health benefits might really come from being close with friends and family, and not the laughter itself," he says/ In his own research, Provine has found that we're 30 times more likely to laugh when we're with other people than when we're alone. People who laugh a lot may just have a strong connection to the people around them. That in itself might have health benefits. Wilson agrees there are limits to what we know about laughter's benefits. "Laughing more could make you healthier, but we don't know," he tells WebMD. "I certainly wouldn't want people to start laughing more just to avoid dying — because sooner or later, they'll be disappointed." But we all know that laughing, being with friends and family, and being happy can make us feel better and give us a boost — even though studies may not show why. So Wilson and Provine agree that regardless of whether laughter actually improves your health or boosts your energy, it undeniably improves your quality of life. "Obviously, I'm not anti-laughter," says Provine. "I'm just saying that if we enjoy laughing, isn't that reason enough to laugh? Do you really need a prescription?"

SOURCES: Steve Wilson, M.A., CSP, psychologist, Columbus Ohio; board member of the American Association for Therapeutic Humor, Columbus, Ohio. Robert R. Provine, professor of psychology and neuroscience, University of Maryland, Baltimore County; author, Laughter: A Scientific Investigation. Association for Applied and Therapeutic Humor Web site: "The Humor Connection." Gervais M. and Wilson D.S. Quarterly Review of Biology, December, 2005. Hayashi K et al, Diabetes Care, May 2003. Panksepp J. Psychological Science, December 2000. Rosner F. Cancer Investigation, 2002. University of Maryland School of Medicine, news release: "University Of Maryland School Of Medicine Study Shows Laughter Helps Blood Vessels Function Better."

## BRAIN POWER – THE HUMAN BRAIN

http://www.fi.edu/brain/exercise.htm

Your brain is a thinking organ that learns and grows by interacting with the world through perception and action. Mental stimulation improves brain function and actually protects against cognitive decline, as does physical exercise.

The human brain is able to continually adapt and rewire itself. Even in old age, it can grow new neurons.

Severe mental decline is usually caused by disease, whereas most age-related losses in memory or motor skills simply result from inactivity and a lack of mental exercise and stimulation. In other words, use it or lose it.

These are exercises that can strengthen neural connections and even create new ones.

Switch the hand you are using to control the computer mouse. Use the hand you normally do NOT use.

Try other neural building and strengthening exercises with everyday movements.

Use your opposite hand to brush your teeth, dial the phone or operate the TV remote.

Is it harder to be precise and accurate with your motions?

Listen to classical music
Drawer or paint (art)
Brainteasers
Crossword puzzles
Trivia board games
Riddles
Math Puzzles

If you are feeling uncomfortable and awkward don't worry, your brain is learning a new skill.

**DEFINITIONS**

A number of the articles sited are written by medical doctors and some of the terms may be unfamiliar to someone who does not work in the medical profession. For your convenience, we have provided you a link to the National Institute of Health Medical Dictionary which can be found at:
http://www.nlm.nih.gov/medlineplus/mplusdictionary.html .

- Amyloid - a waxy translucent substance consisting primarily of protein that is deposited in some tissue under abnormal condi tions (as in Alzheimer's disease)
- Angiopathy - a disease of the blood or lymph vessels
- Basal Ganglion - any of four deeply placed masses of gray matter within each cerebral hemisphere
- Lacunar infarct – an area of tissue in an organ or part that undergoes necrosis following cessation of blood supply
- Myosin - are a large family of motor proteins found in eukaryotic tissues. They are responsible for actin-based motility.
- Eeukaryote is an organism with a complex cell or cells, in which the genetic material is organized into a membrane-bound nucleus or nuclei
- Necrosis - death of living tissue; *specifically* **:** death of a portion of tissue differentially affected by local injury (as loss of supply, corrosion, burning, or the local lesion of a disease)
- Sural - of, relating to, or being a sural nerve or branches of the popliteal (of or relating to the back part of the leg behind the knee joint) artery or vein that ramify in the area of the calf of the leg

**In Loving Memory of Ronald Stringer .. .**

**The Global Dentist**

Dr. Ronald Stringer, a Mililani dentist who did volunteer work in the Dominican Republic, The Democratic Republic of Congo (formerly Zaire), and Nepal, died October 11, 2006 of CADASIL, a rare neurological disease in Honolulu. He was 56. Stringer was born in Berkeley, Calif., and moved to Hono-lulu in 1974 to complete his residency at St. Francis Medical Center. He met and married his wife, Linda Wong, started a family and began a private practice. In 1979, Stringer joined the Christian Medical Society on a missionary trip to the Dominican Republic where patients walked for hours to the schoolyard clinic where he did dental work. In the late 1980s, he and his wife signed on as mission co-workers with the Presbyterian Church (USA), and with their three children headed to Zaire where he was the only American-trained dentist within a radius of 500 miles. Stringer taught and trained local dentists. In July 1991, the family returned to Hawaii's and Stringer earned a Master's in Public Health from the University of Hawai'i-Manoa. He next worked with the Community Development Health Program under the United Mission to Nepal, and later served as chief of the dental department at Kathmandu Patan Hospital. He wrote oral healthcare guidelines and a training manual, and participated in the first joint conference of the World Dental Federation and Nepal Oral Health Society in 1997. The family returned to Hawai'i in 1999. Stringer is survived by his wife, Linda; son, Daniel; daughters, Cheryl and Amy; mother, Beverly Stone; brothers, Philip and Paul; and sister, Cheryl Vivers. Services were held at Kalihi Union Church on October 28, 2006. Excerpt from the Honolulu Advertiser— Our thoughts and prayers are with his family

## WE NEED YOUR SUPPORT!

**CADASIL Together We Have Hope is an all volunteer organization**. We do not have any paid employees. Your donation is tax deductible and will be used to further the goals of CADASIL Together We Have Hope. We are devoted to promoting awareness, support and research for this rare genetic disease working with patients, families, friends and healthcare providers. We have created a communication network among families and continue to identify sources of medical care and social services .

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Thank you for those who contributed to this newsletter.

CADASIL Together We Have Hope and please remember you are not alone!