Advances in CADASIL research

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UNIVERSITY OF
CAMBRIDGE

Clinical aspects

Identifying cognitive probelms in people with CADASIL

- The cognitive screening tests we have in clinic today are designed for Alzheimer's disease which is very different from CADASIL
- In CADASIL tests need to focus on planning , multi-tasking and information processing speed

Brief Memory and Executive Test

B-MET

Name _____

DOB _____ Date _____

Throughout the test, read the black italic text aloud to the patient.

Orientation

What is your full name?	☐	*Which date of the month is it?*	☐
What is your date of birth?	☐	*What year is it?*	☐
How old are you?	☐	*What is the season?*	☐
What day of the week is it?	☐	*What is the name of this place?*	☐
What month are we in now?	☐	*Which floor are we on?*	☐

Score 1 point per correct answer (max score 10) TOTAL 1 ☐☐

Five Item Repetition

Read out the words for all trials, 3 seconds per item.

Instructions: *Listen to the following words and try to remember them. When I have said them all please tell me the ones you remember.*

	Lion	*Toe*	*Book*	*Light*	*Three*	Trial Total
Trial 1	☐	☐	☐	☐	☐	☐
Trial 2	☐	☐	☐	☐	☐	☐
Trial 3	☐	☐	☐	☐	☐	☐

Score 1 point per correctly recalled word (max score 15) TOTAL 2 ☐☐

Letter-Number Matching

The patient must fill in the boxes in order (left-right) without skipping any boxes. Give sample item (appendix 1a)-explain any errors; Main test (appendix 1b) stopping after 45 seconds.

Instructions: *You see these letters each letter has its own number underneath. Look at the boxes (point); these have the numbers missing. Fill in the correct numbers as quickly as you can, <u>one after the other and do not leave any out.</u>*

Number completed in 45 seconds ☐☐ Errors ☐☐

Score 1 point per correctly filled space(max score 40). TOTAL 3 ☐☐

Motor Sequencing: Sample test (appendix 2a); Main test (appendix 2b).

Present the sample item (explain any errors); followed by the main test .If errors are made, say *'that is not correct'*, draw a cross at that point and redirect to the previous point (continue timing throughout). Discontinue after 180 seconds.

Instructions: *Start here [point] and draw along the line; keep going until you reach the end [point]. It is okay to cross through the boxes. Don't worry about neatness. Have a go at this sample one. Begin.*

Brief Memory and Executive Test

Letter Sequencing: Sample test (appendix 3a); Main test (appendix 3b).

The instructions are as for motor sequencing. Discontinue if the patient has not completed after 180 seconds.

Instructions: *Start here [point] and connect these letters in alphabetical order. Keep going until you reach the end [point].*

Main Test: *This time connect the letters as quickly as you can in alphabetical order, start here* [point] *and finish here* [point]. If you make a mistake, I will correct you as you go along. Begin.

Score = Time taken to complete the main test (seconds). TOTAL 5 ☐☐

Letter–Number Sequencing: Sample test (appendix 4a); Main test (appendix 4b).

The instructions as for motor sequencing. Discontinue if the patient has not completed after 300 seconds.

Instructions: [Demonstrating by pointing at the sample] *In this task there are some numbers and letters. You start with number one and draw a line to the first letter in the alphabet* [mimic drawing]. *Now you draw a line from the A to the next number, which is two* [make movement to the box with 2]. *You keep going alternating between numbers and letters in order. Remember you have a number, then the first letter, then the next number and then the next letter and so on. Have a go with this practice one*

Main Test: *This time connect the numbers and letters as quickly as you can. Remember you have a number, then the first letter, then the next number and then the next letter. Start here* [point] *and finish here* [point]. If you make a mistake, I will correct you as you go along. Begin.

Score = Time taken to complete the task (seconds). TOTAL 6 ☐☐

Five Item Memory (Delayed Recall)

Check the boxes for the words remembered and record any additional words as intrusions.

Instructions: *Earlier, I asked you to remember some words. Can you tell me what they were?*

Lion ☐ Toe ☐ Book ☐ Light ☐ Three ☐ Total correct ☐☐

Additional words: Total Intrusions ☐☐

Score = Total correct minus total intrusions. TOTAL 7 ☐☐

Five Item Memory (Delayed Recognition): Word list (appendix 5).

Give the patient the word list (appendix 5) and record correct recognition and false positives

Instructions: *Please circle the words that I asked you to repeat earlier.*

Correctly recognised ☐☐

False Positives ☐☐

Score = Total correct minus false positives. TOTAL 8 ☐☐

OPEN

Brief Screening of Vascular Cognitive Impairment in Patients With Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy Without Dementia

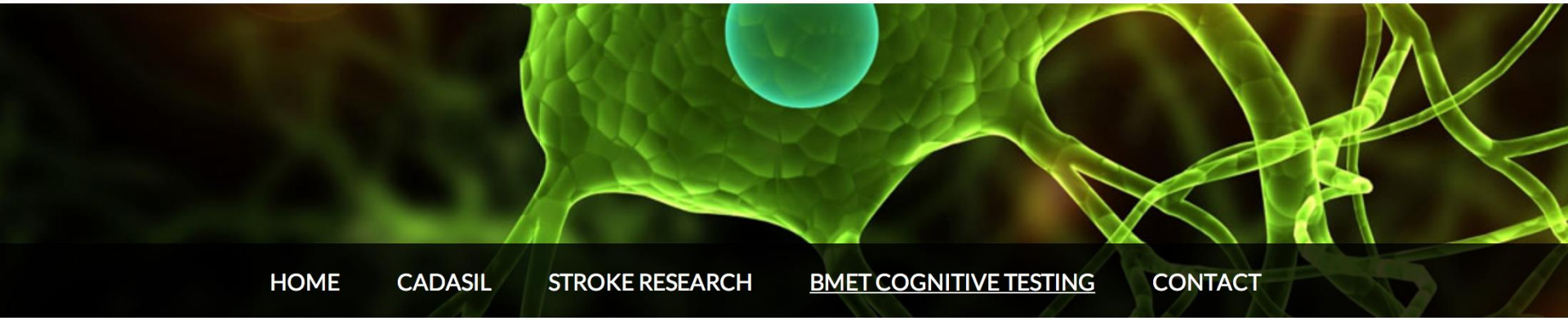
Rebecca L. Brookes, PhD; Matthew J. Hollocks, PhD; Rhea Y.Y. Tan, BSc; Robin G. Morris, PhD; Hugh S. Markus, DM, FRCP

BMET Validation
Brief memory and executive test

www.bmet.info

https://ra.cuh.org.uk/+CSCOE+/logon.html

CAMBRIDGE STROKE



HOME CADASIL STROKE RESEARCH BMET COGNITIVE TESTING CONTACT

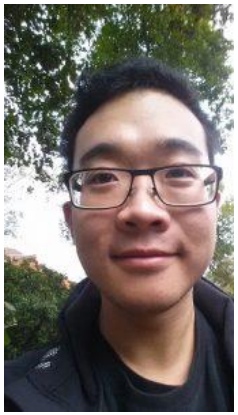
- HISTORY OF THE BMET
- BMET SUMMARY
- DOWNLOAD BMET
- SCORING & NORMATIVE DATA
- VALIDATION STUDY

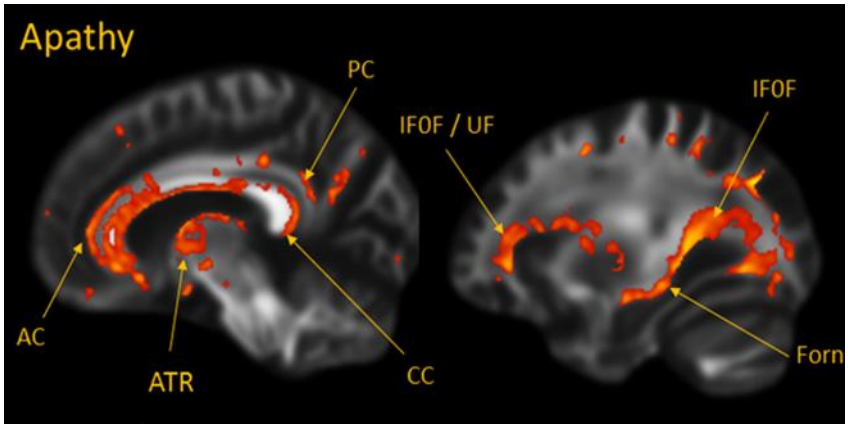
BMET Cognitive Testing

The Brief Memory and Executive Test (BMET) is a short cognitive screen to detect the cognitive deficit seen in patients with vascular cognitive impairment (VCI) due to cerebral small vessel disease. Its been designed to be suitable for use by clinicians and researchers. We have shown it is sensitive to VCI in this patient group, and has a high sensitivity and specificity in separating this from normal elderly and patients with Alzheimer's disease.

Apathy in CADASIL:

- A common problem in CADASIL
- Describes a loss of motivation
- Can be distressing for the patient and often even more their family
- We have funding from the Stroke Association to look at why people with disease of the small blood vessels in the brain including CADASIL get apathy
- This includes trying to develop better treatment approaches





Migraine in CADASIL

- First comprehensive description of migraine in CADASIL
- Triptans help some people with migraine and no major side effects were noted

PLOS ONE

RESEARCH ARTICLE

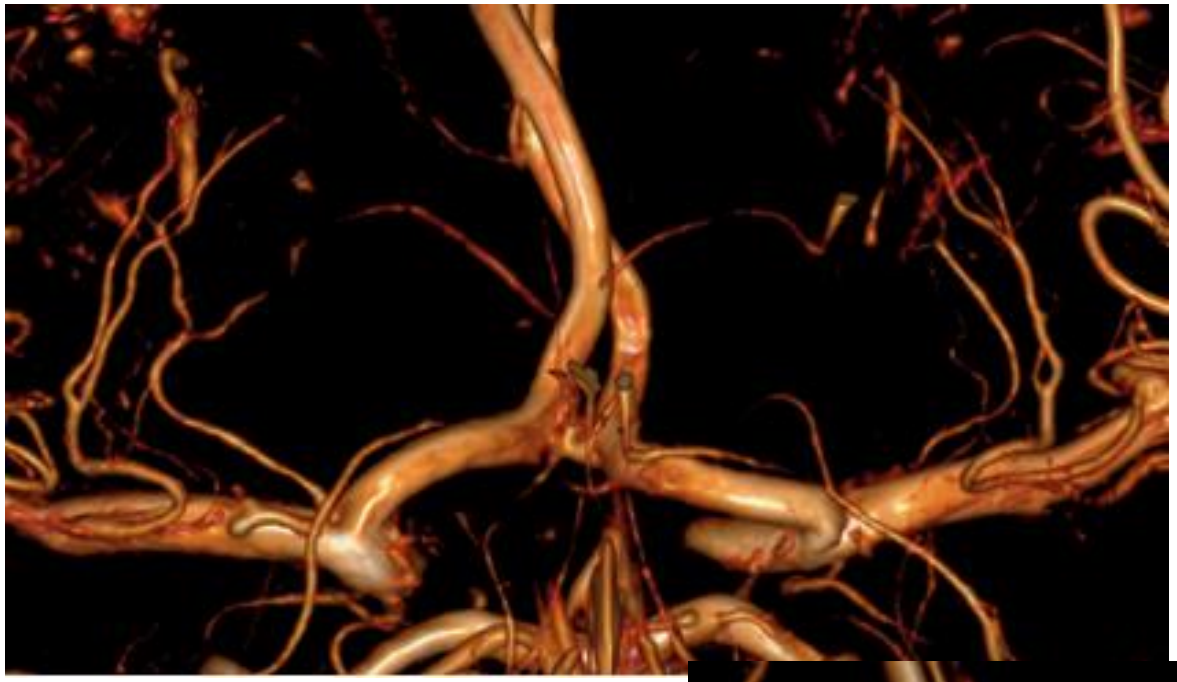
CADASIL: Migraine, Encephalopathy, Stroke and Their Inter-Relationships

Rhea Yan Ying Tan*, Hugh Stephen Markus

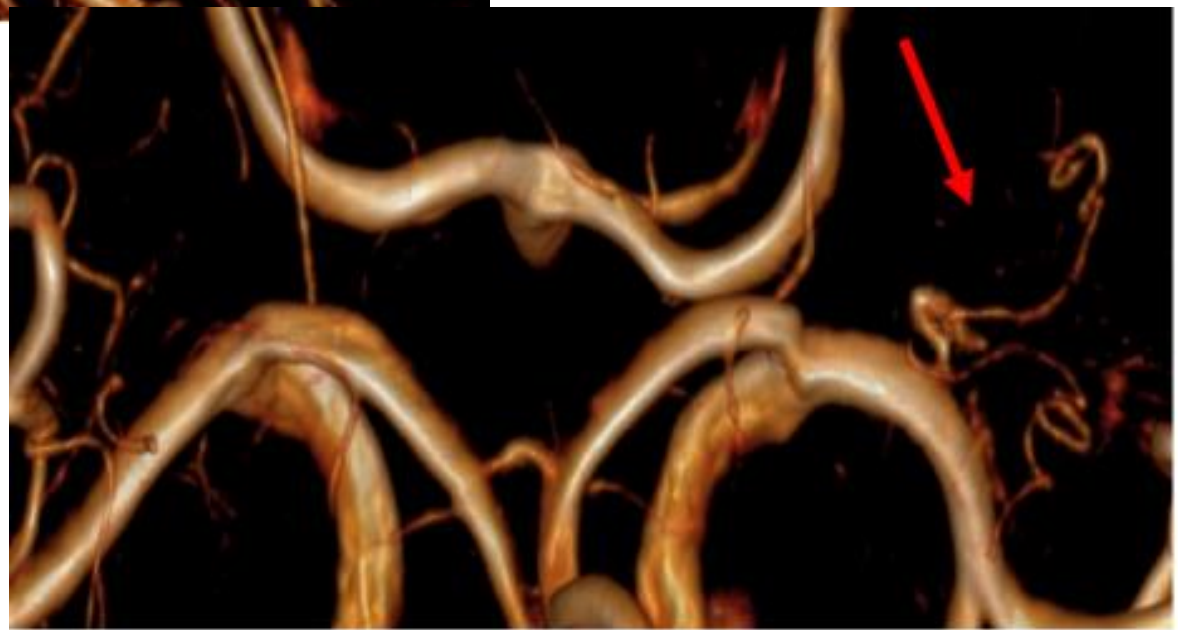
Stroke Research Group, Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom

How do the blood vessel abnormalities damage the brain?

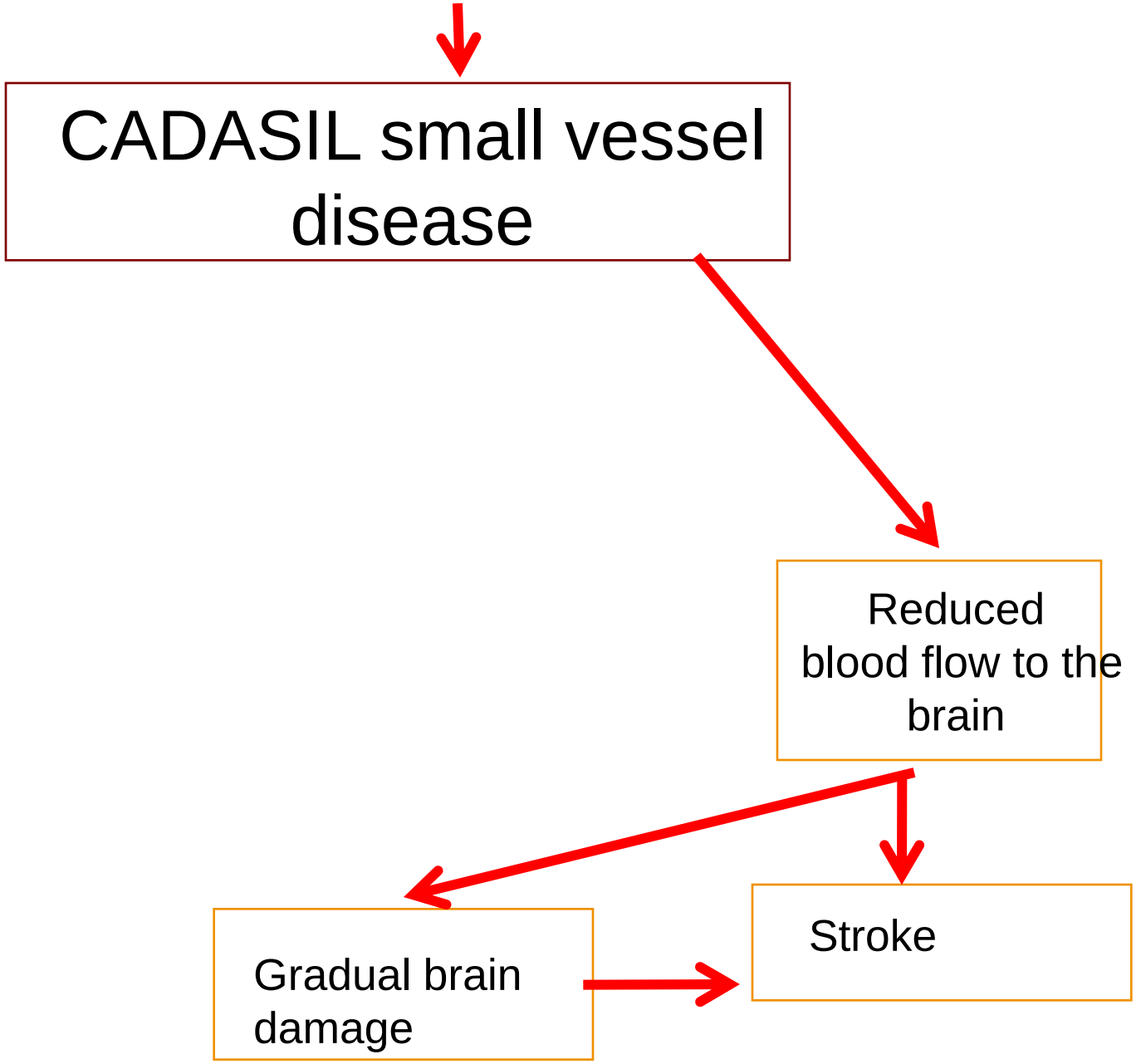
Ultra-high field (7T) MRI -Imaging perforating arteries

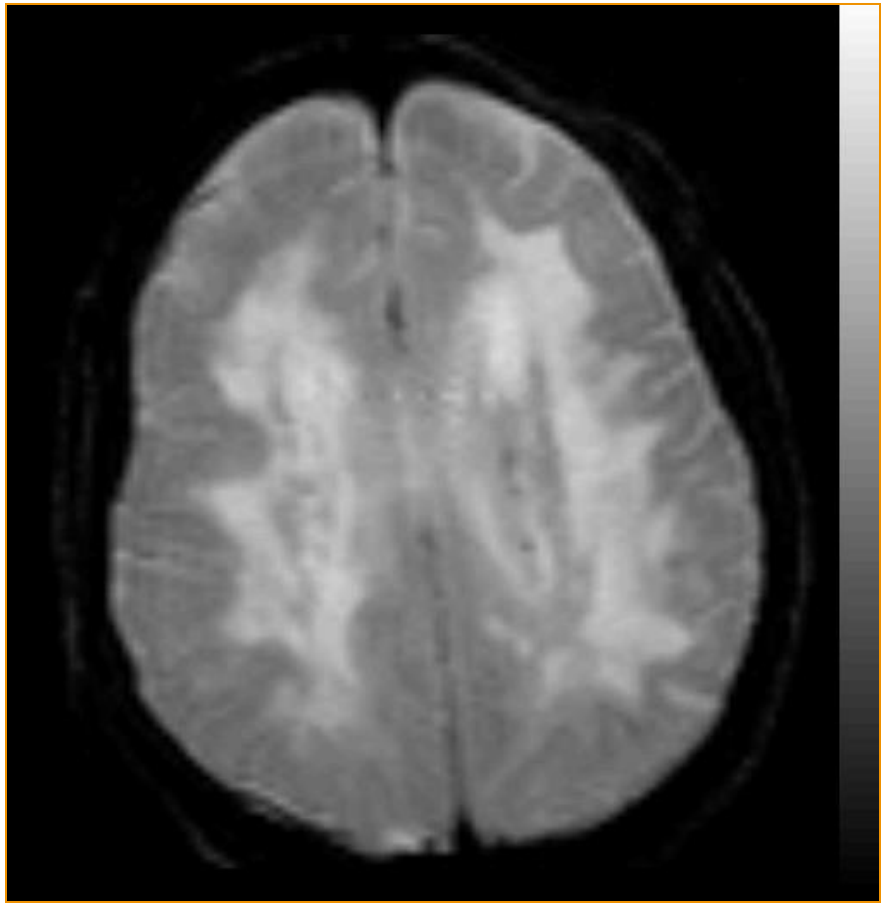


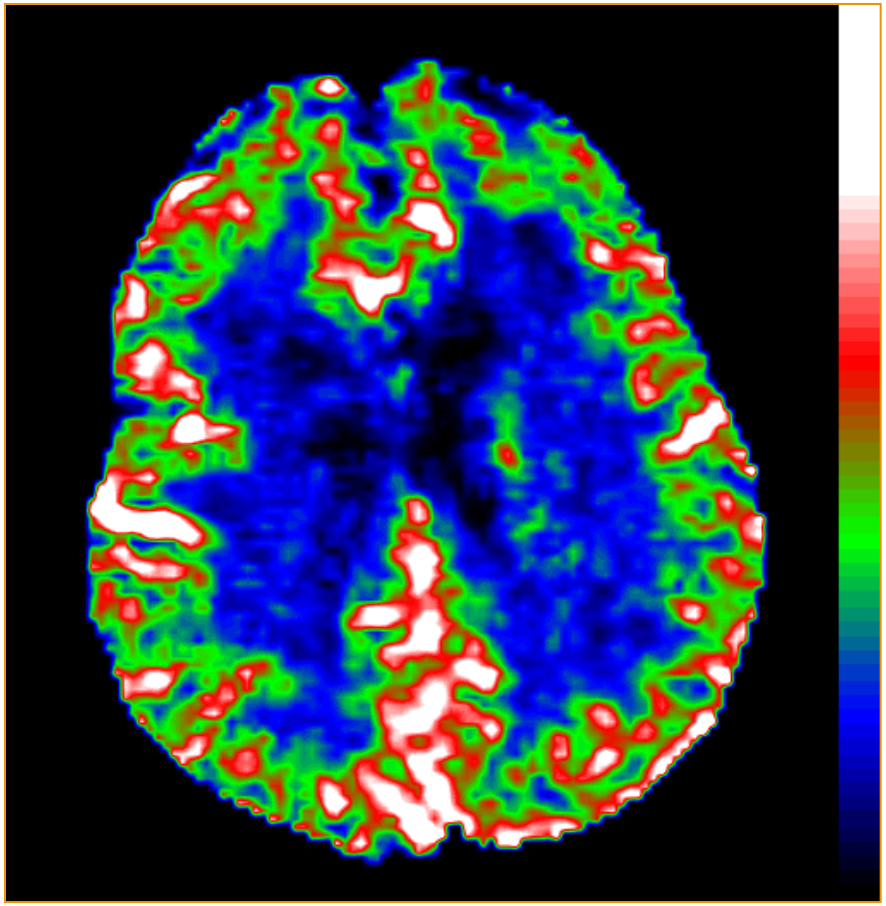
Healthy volunteer



Patient with SVD

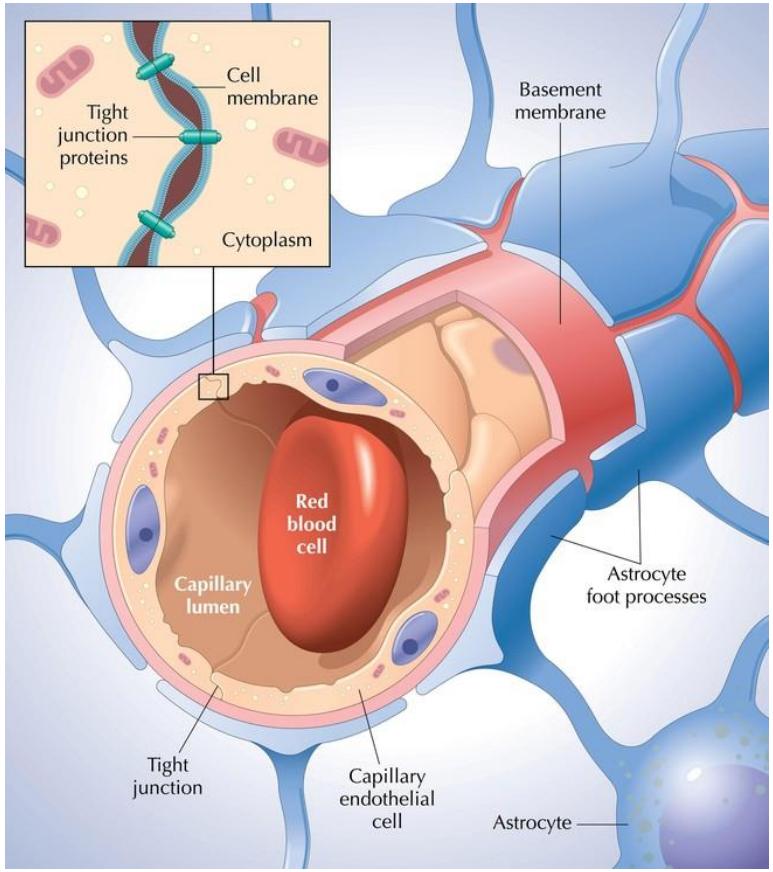

CADASIL small vessel disease
Reduced blood flow to the brain
Gradual brain damage
Stroke

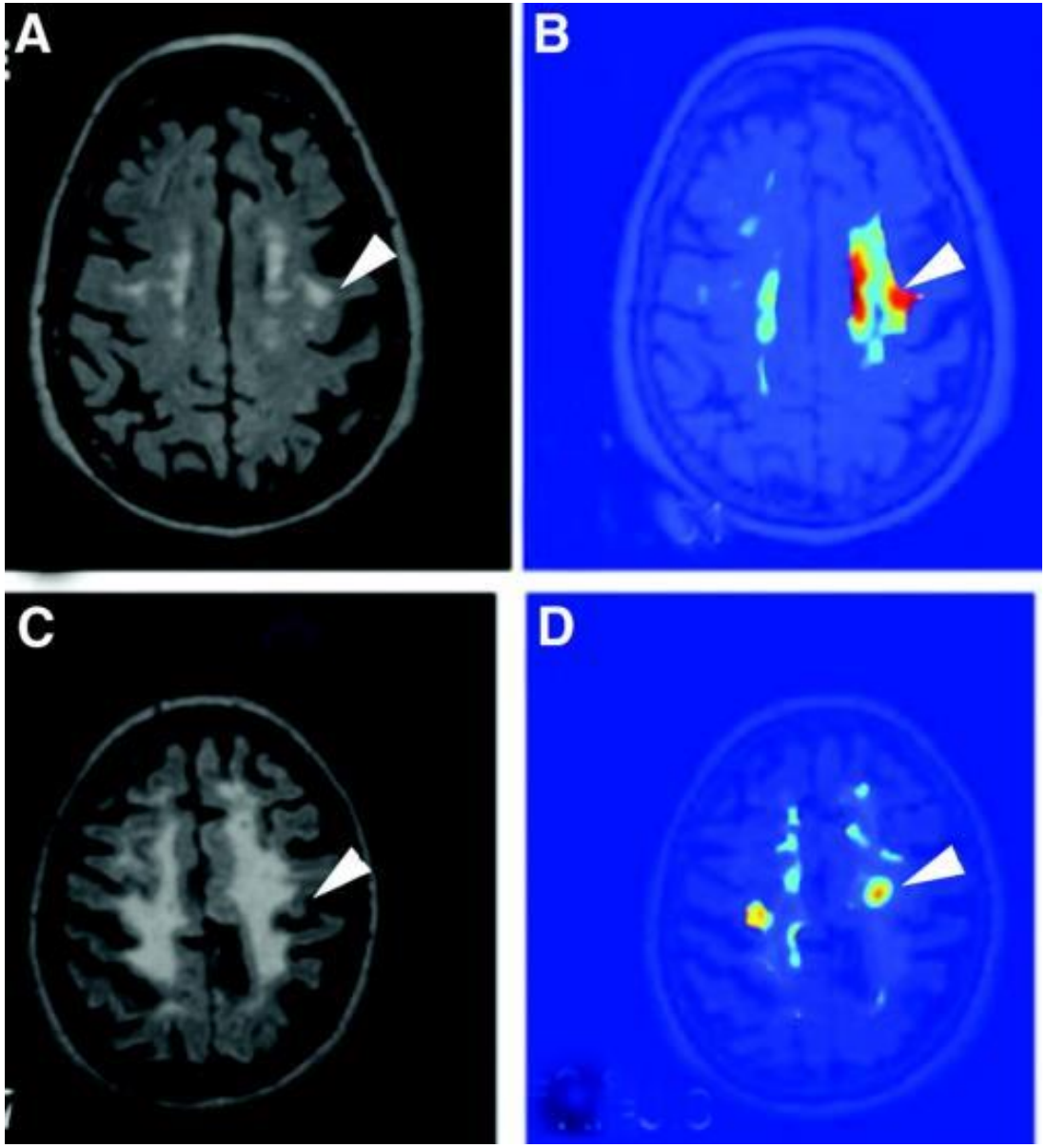




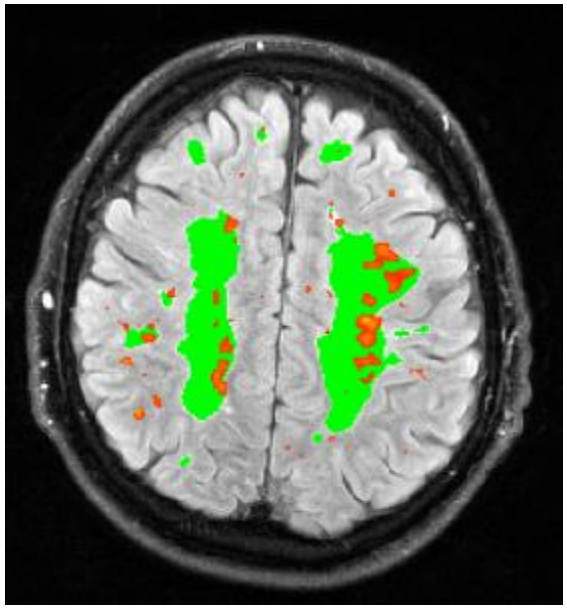
Reduced brain blood flow in CADASIL

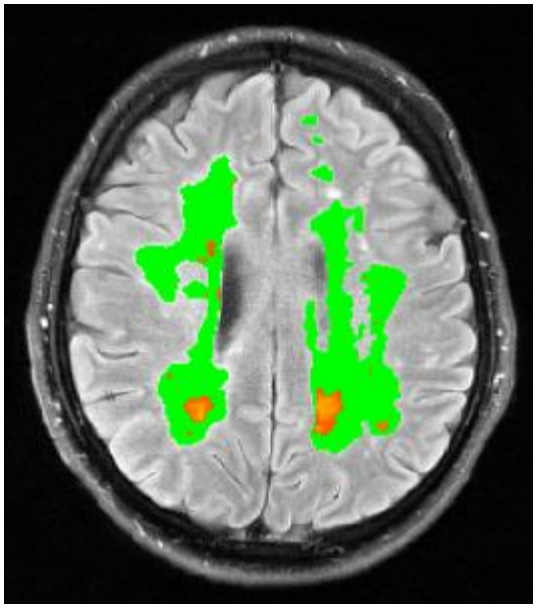
A role for blood brain barrier leakage

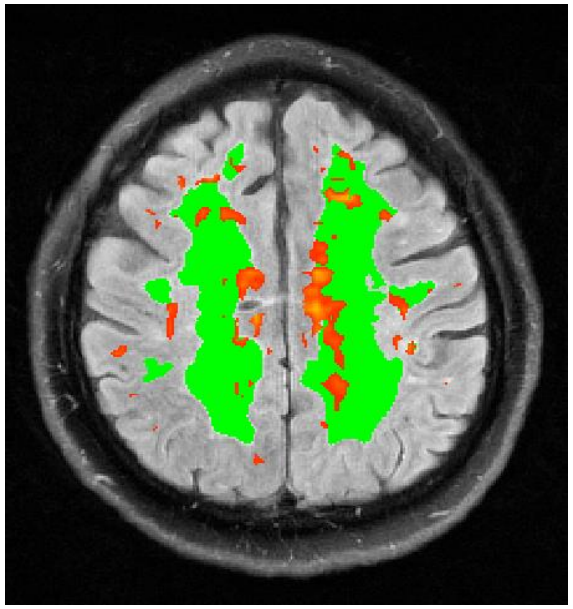


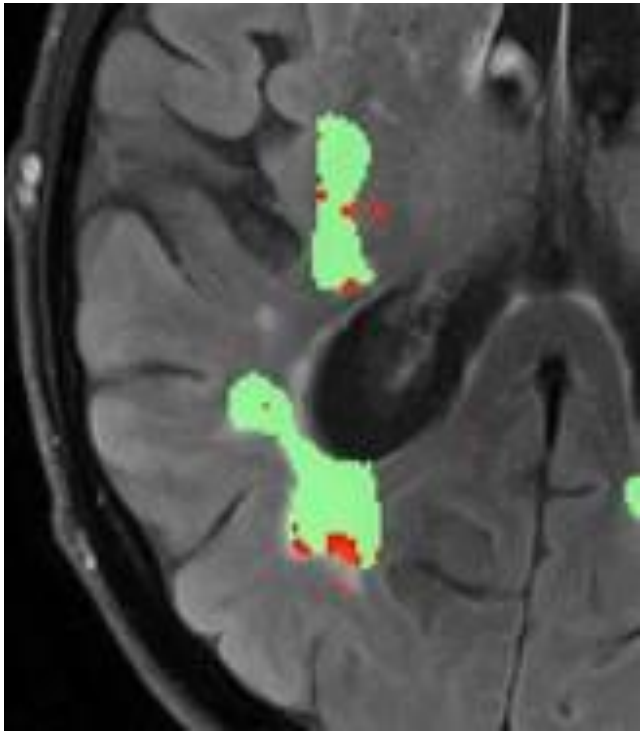


Taheri S et al. Stroke 2011;42:2158-2163









Can we switch off the disease process?

Notch 3

membrane

Extra-cellular portion of notch3 protein

34 EGF repeats

Normal EGF repeat with 6 cysteine residues

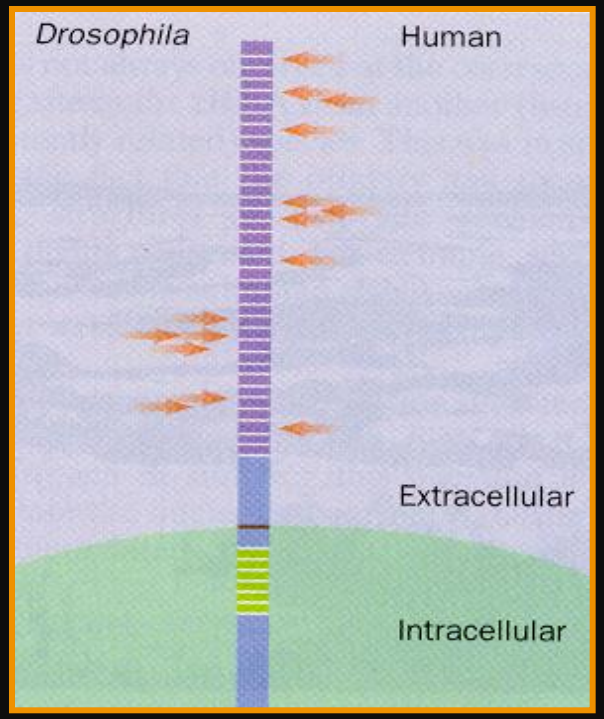
Unpaired new cysteine residue

Deleted cysteine residue

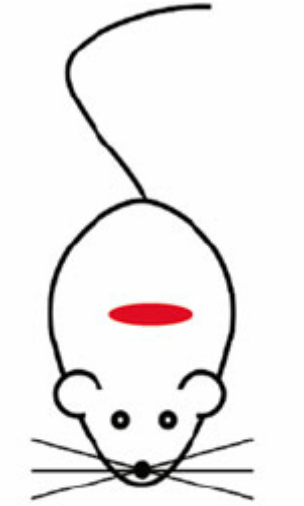
Unpaired cysteine residue

Loss of a cysteine

or **Gain of a cysteine**



An animal model of CADASIL

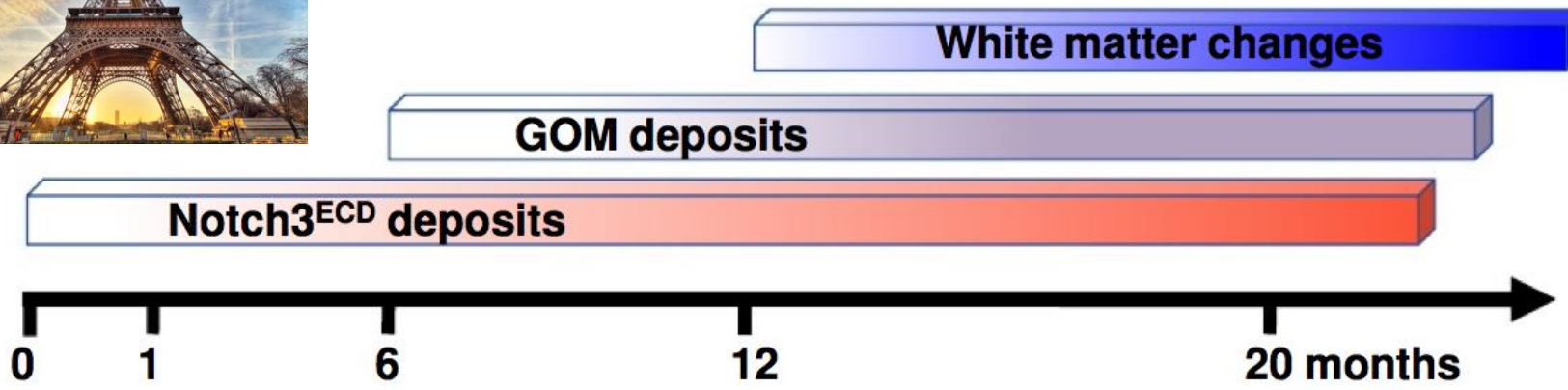


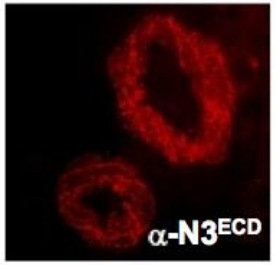
Genetic Engineered Mouse (GEM)

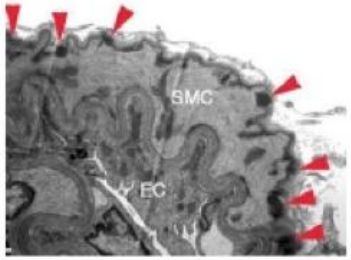
- Insert a CADASIL gene abnormality
- Use it to study disease processes and screen new treatments
- Now a number of models worldwide

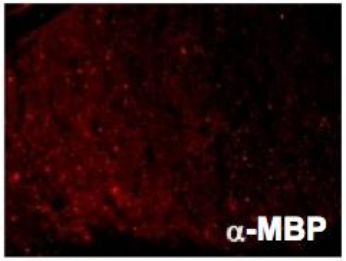
An animal model of CADASIL

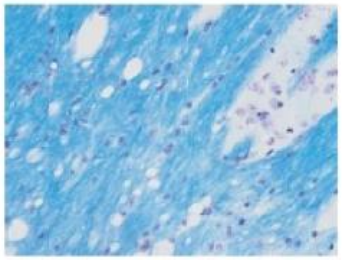
Copies many of the features of the human disease









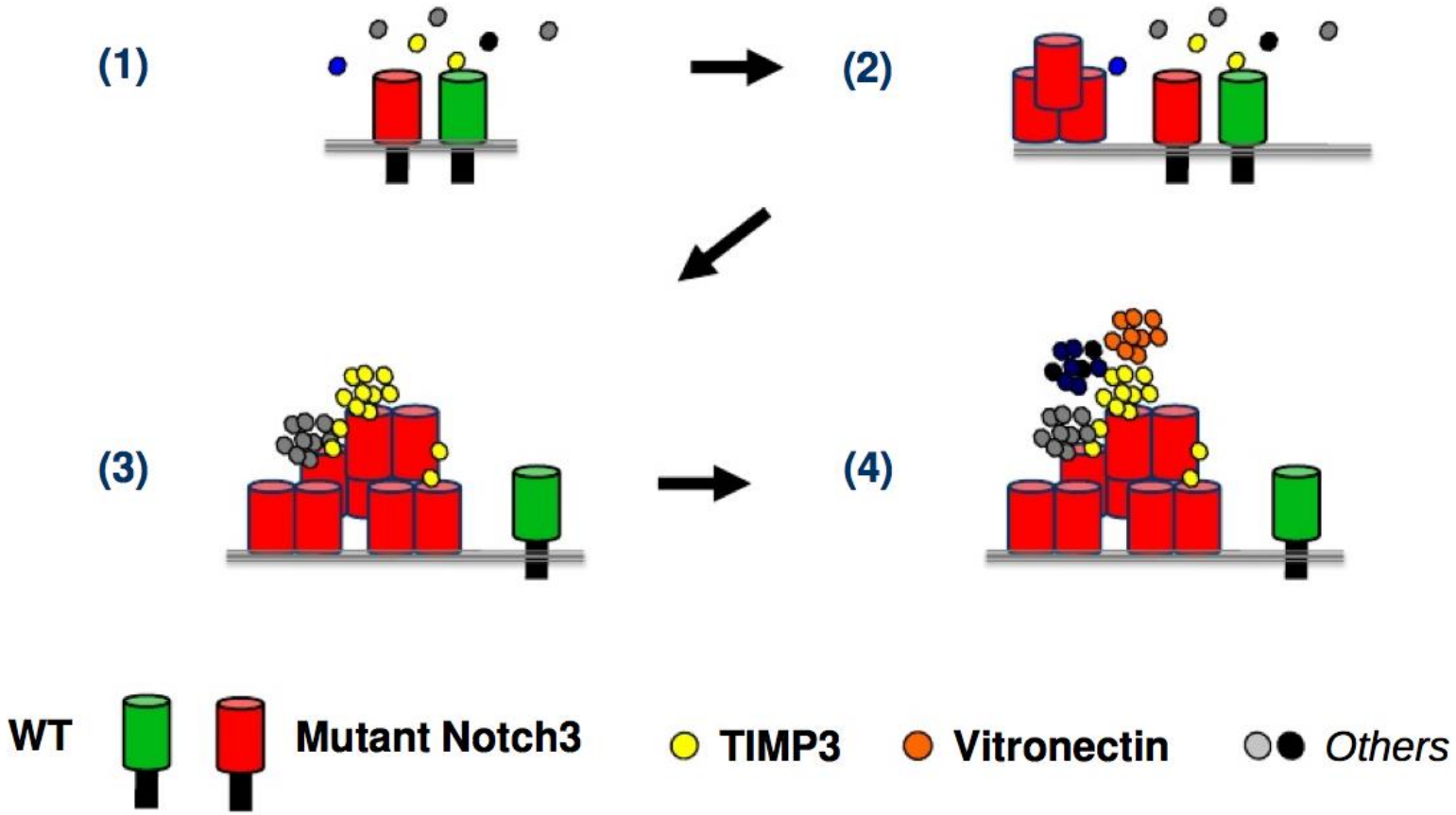


An animal model of CADASIL

So far told us:

- About how the small blood vessels don’t function normally
- Key insights into how the genetic abnormality causes blood vessel damage

The CADASIL notch 3 mutation initiates a cascade of events leading to vessel damage



EXCITING FINDINGS

It may be possible to slow down or stop this cascade of damage

Reducing Timp3 or Vitronectin Ameliorates Disease Manifestations in CADASIL Mice

Carmen Capone, PhD,[1,2] Emmanuel Cognat, MD,[1,2] Lamia Ghezali, PhD,[1,2]
Céline Baron-Menguy, PhD,[1,2] Déborah Aubin, MSc,[1,2]
Laurent Mesnard, MD, PhD,[3,4] Heidi Stöhr, PhD,[5] Valérie Domenga-Denier,[1,2]
Mark T. Nelson, PhD,[6,7] and Anne Joutel, MD, PhD[1,2]

ANN NEUROL 2016;79:387–403

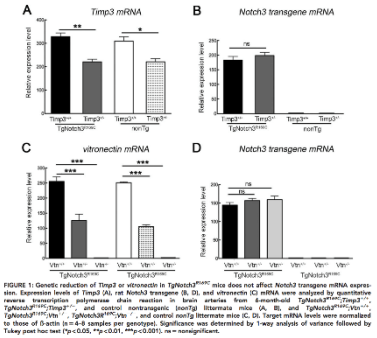
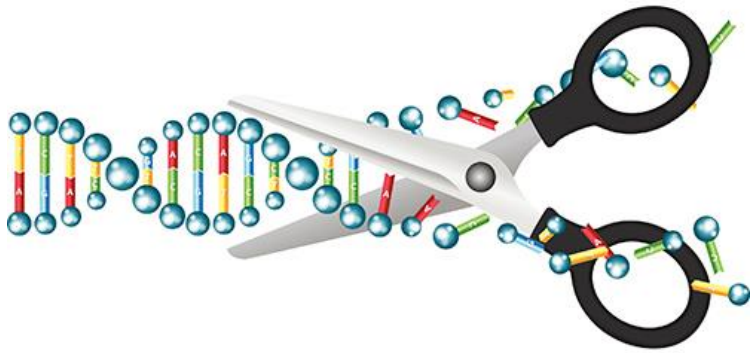


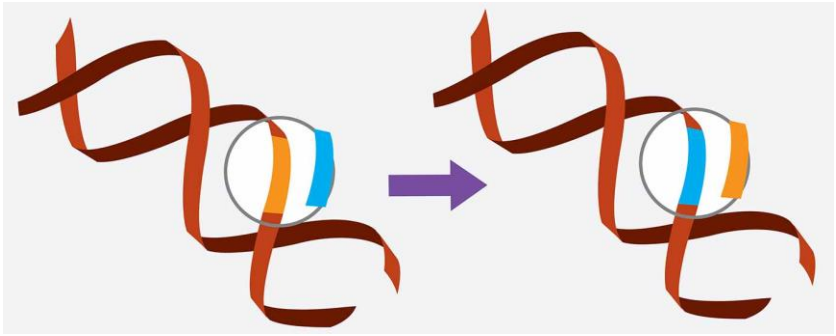
FIGURE 1: Genetic reduction of *Timp3* or *vitronectin* in TgNotch3^{R1031C} mice does not affect *Notch3* transgene mRNA expression. Expression levels of Timp3 (A), rat Notch3 transgene (B, D), and vitronectin (C) mRNA were analyzed by quantitative reverse transcription polymerase chain reaction in brain arteries from 6-month-old TgNotch3^{R1031C};Timp3$^{+/+}$, TgNotch3^{R1031C};Timp3$^{-/-}$, and control nontransgenic (nonTg) littermate mice (A, B), and TgNotch3^{R1031C};Vtn$^{+/+}$, TgNotch3^{R1031C};Vtn$^{-/-}$, TgNotch3^{R1031C};Vtn$^{+/-}$, and control nonTg littermate mice (C, D). Target mRNA levels were normalized to those of β-actin (n = 4–8 samples per genotype). Significance was determined by 1-way analysis of variance followed by Tukey post hoc test (*p < 0.05, **p < 0.01, ***p < 0.001). ns = nonsignificant.

Can we correct the genetic abnormality?

- Pre-implantation
- Correcting the deficit after birth

Gene editing



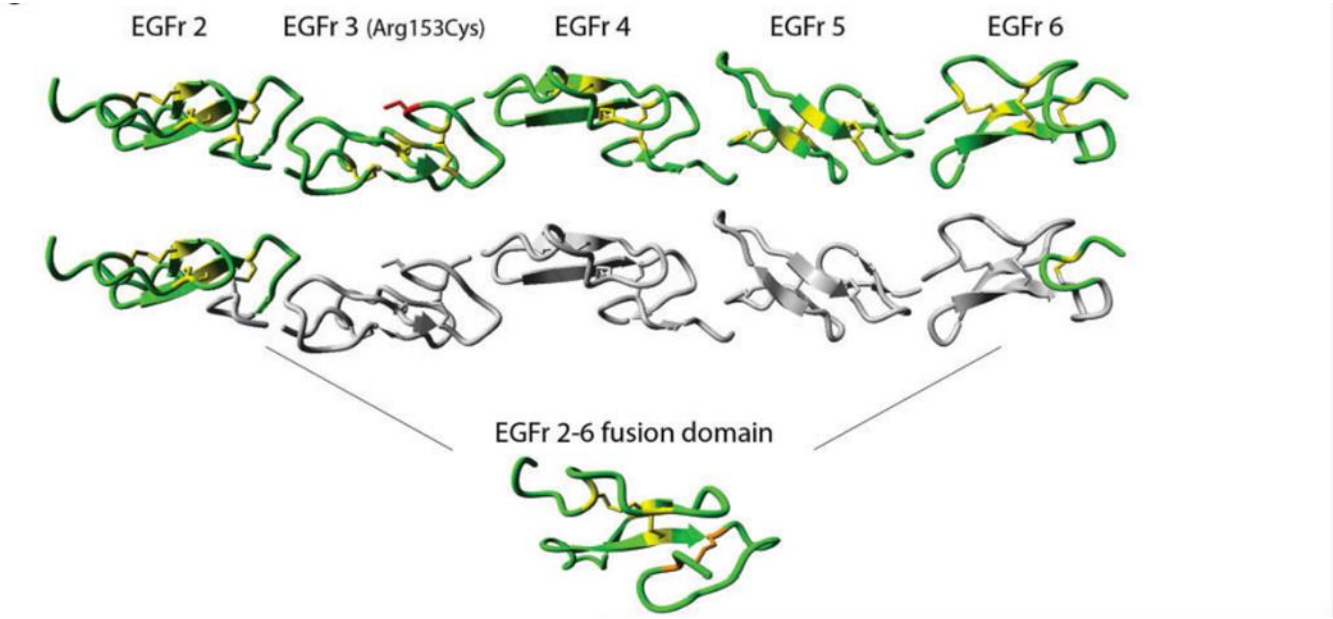


doi:10.1093/brain/aww011 BRAIN 2016: 139; 1123–1135 | 1123

BRAIN
A JOURNAL OF NEUROLOGY

Therapeutic NOTCH3 cysteine correction in CADASIL using exon skipping: *in vitro* proof of concept

Julie W. Rutten,[1,2] Hans G. Dauwerse,[1,2] Dorien J. M. Peters,[1] Andrew Goldfarb,[1] Hanka Venselaar,[3] Christof Haffner,[4] Gert-Jan B. van Ommen,[1] Annemieke M. Aartsma-Rus[1] and Saskia A. J. Lesnik Oberstein[2]



Proof of concept

Removed faulty exons and preserved notch 3 protein function

Importance of International Collaboration

We work with groups in
Munich, Germany
Paris, France
Florence, Italy
Leiden, Netherlands

If you'd like to be involved

We have a register of CADASIL patients

We can let you know about additional research projects
Each has a separate ethics and info sheet

Fort most projects you need to registered as a patient at Addenbrookes, or another hospital involved in the research

ACKNOWLEDGEMENTS

Stroke Group, Cambridge

Rebecca Brookes
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Dan Tozer
Matthew Traylor
Hasan Sari
Jessica Walsh
Anna Drazyk
Jonathan Tay
Alex Granata

NHS Secretaries
Kate Rose
Margaret Rawlings

Glen Brice

Cambridge ACT CADASIL fund

Make a donation

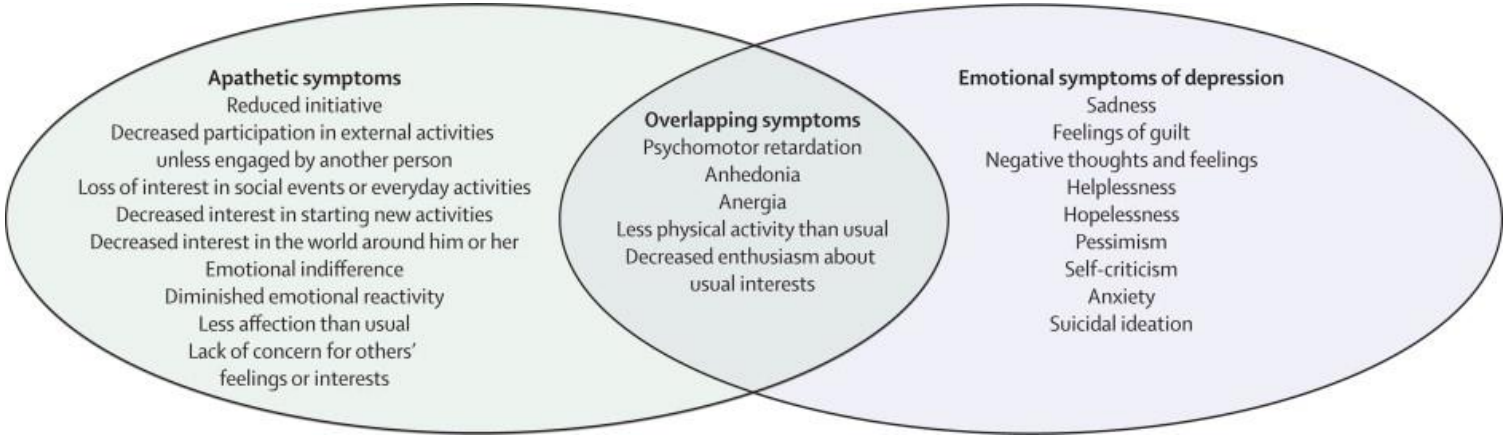
We have an active programme of research into CADASIL and other genetic froms of stroke. This has greatly benefited from donations in the past and we are grateful to all our supporters. Donations go into a CADASIL fund which is managed by the Cambridge Addenbrookes Hospital Charitable Trust. You can donate money direct via the link below or send cheques to the address below. On line donations can be gift aided which allows the fund to claim back tax and increases the value of your donation.

ONLINE DONATIONS

Click on the link below. You can make on off or regular donations.
On the donation page its important you mention that your wish your donation to go to the "CADASIL fund (ACT fund 9147)" in the "about your donation section" in the box (item 4).

DONATE HERE

See donations tab on www.cadasil.co.uk


Apathetic symptoms
Reduced initiative
Decreased participation in external activities unless engaged by another person
Loss of interest in social events or everyday activities
Decreased interest in starting new activities
Decreased interest in the world around him or her
Emotional indifference
Diminished emotional reactivity
Less affection than usual
Lack of concern for others' feelings or interests
Overlapping symptoms
Psychomotor retardation
Anhedonia
Anergia
Less physical activity than usual
Decreased enthusiasm about usual interests
Emotional symptoms of depression
Sadness
Feelings of guilt
Negative thoughts and feelings
Helplessness
Hopelessness
Pessimism
Self-criticism
Anxiety
Suicidal ideation