*The UK Familial Stroke Study*

# Understanding why CADASIL is so variable between individuals

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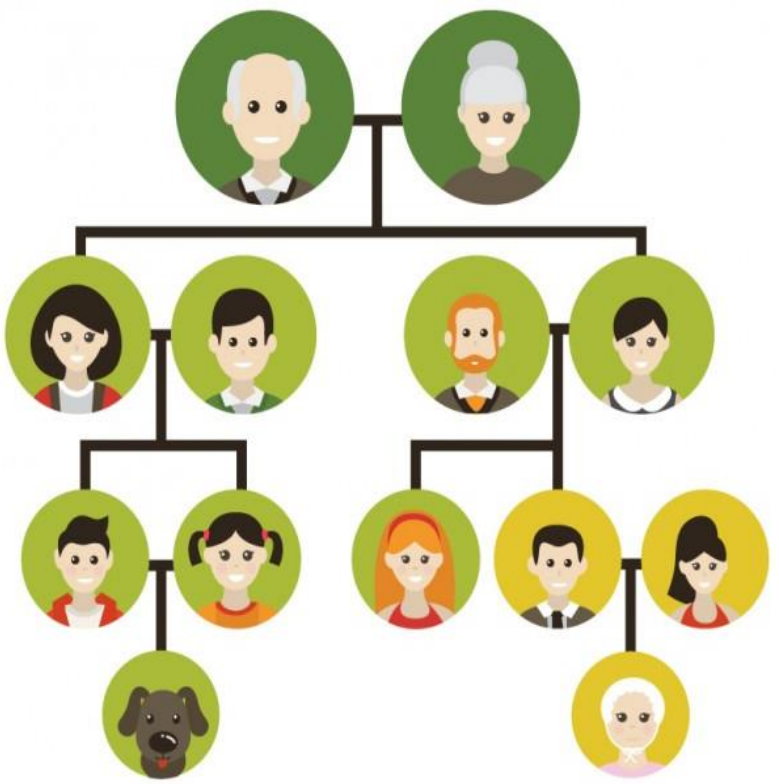
# Understanding the genetics behind CADASIL

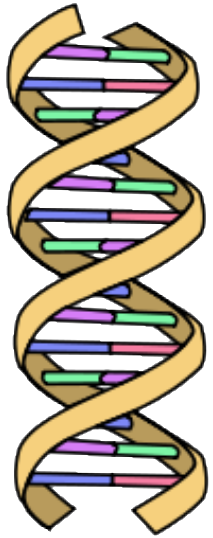
- CADASIL is a genetic disease that runs in families
- How CADASIL presents itself varies both between individuals, between families and even within families
- Symptoms that individuals experience can vary both in the type of symptoms and their onset
- Symptoms of CADASIL (**phenotype**) are caused by an abnormality in the NOTCH3 gene (**genotype**)
- We don’t understand why the disease varies so much between individuals even within families



# What do we mean by genotype and phenotype?

**Genotype**

Is the genetic makeup of an individual e.g.



**DNA**

**Phenotype**

Is how the gene is expressed as an observable trait in an individual e.g.

**Your shoe size**

**Your eye colour**

# The genotype and phenotype in CADASIL

## Genotype in CADASIL

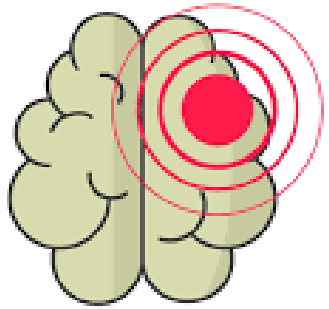
Abnormality on the NOTCH3 gene

## Phenotype in CADASIL

Mood changes

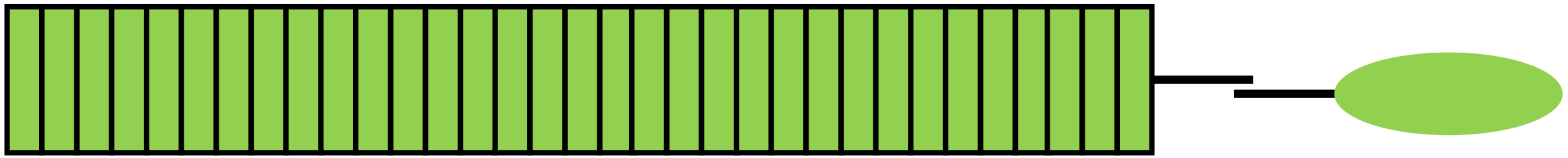
Memory troubles

Migraines



Strokes

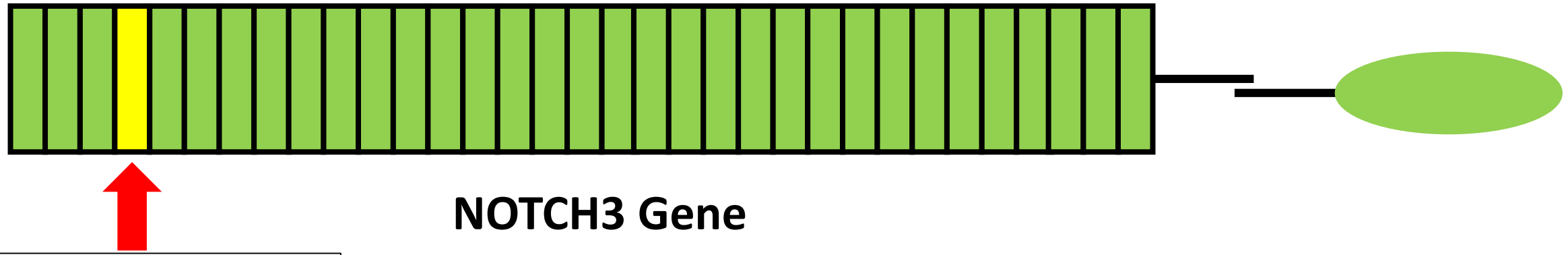
# Where do abnormalities occur on the NOTCH3 gene?



**NOTCH3 Gene**

Located on chromosome no. 19

# Where do abnormalities occur on the NOTCH3 gene?

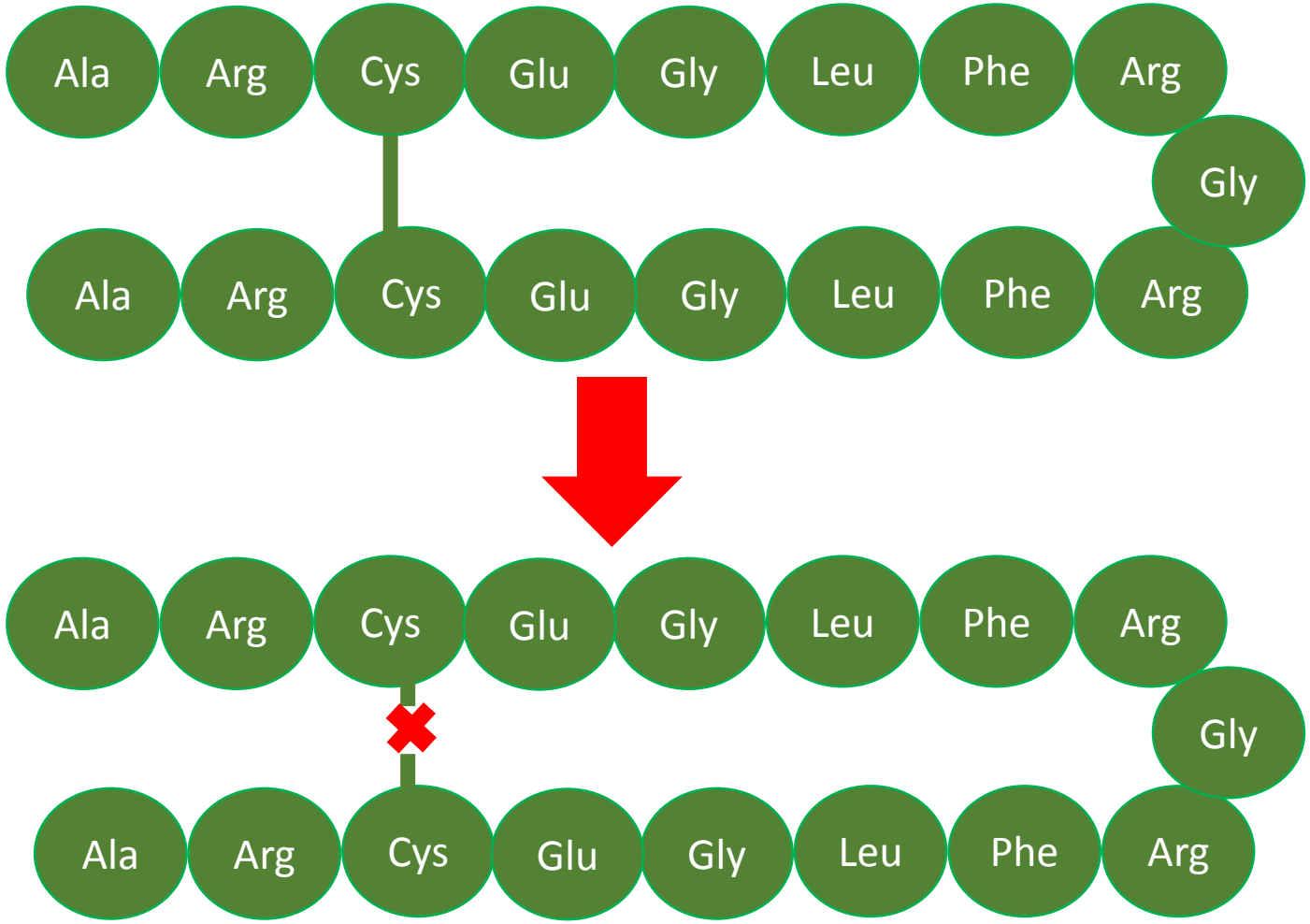


**NOTCH3 Gene**

Exon 4 = most common site for abnormality to occur on the gene within European populations *(Federico, Bianchi and Dotti, 2005)*

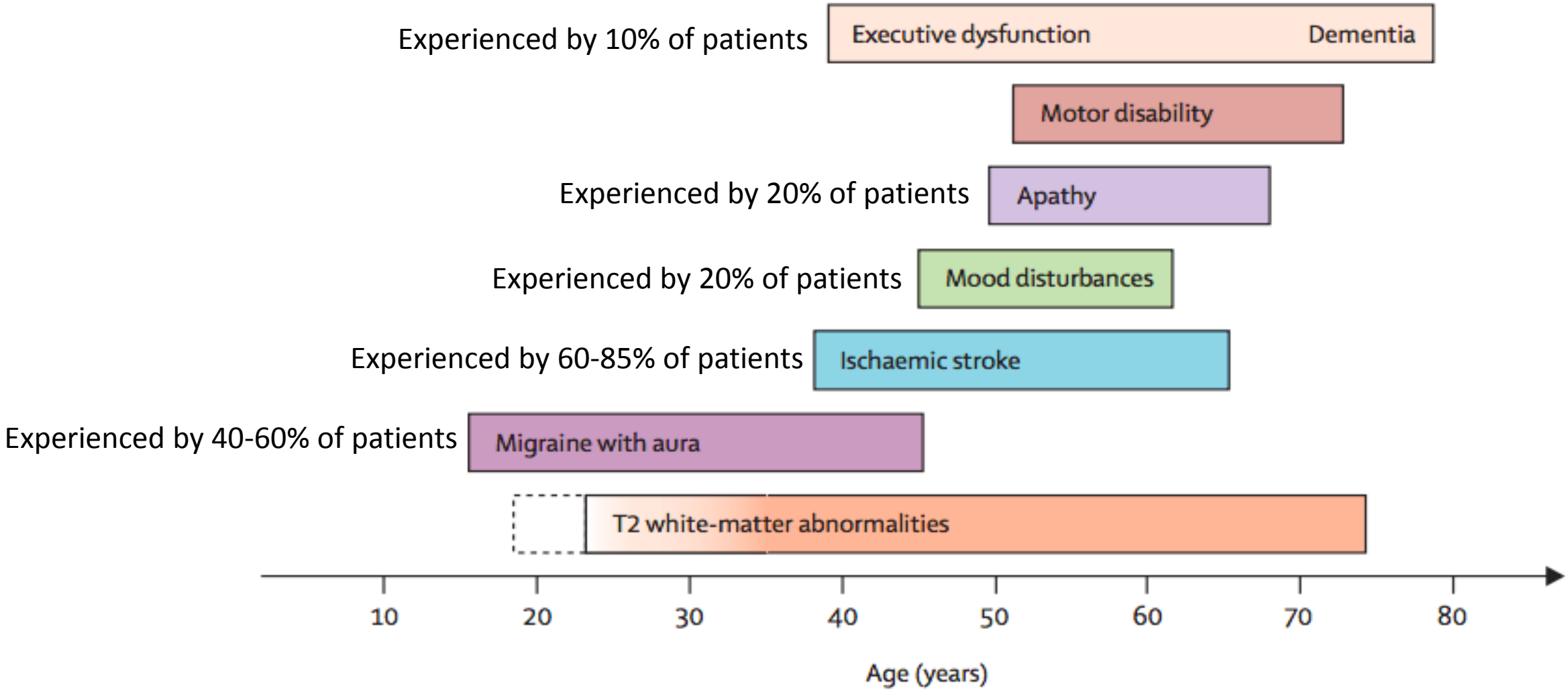
But abnormalities can occur at any sites from exon 2-24 in CADASIL

# What happens to the NOTCH3 gene?




- An abnormality on the NOTCH3 gene changes the number of a type of protein called **cysteine** and therefore slightly changes the structure of the gene
- This change in structure is what is identified through genetic testing for CADASIL and allows the location of the abnormaility to be determined

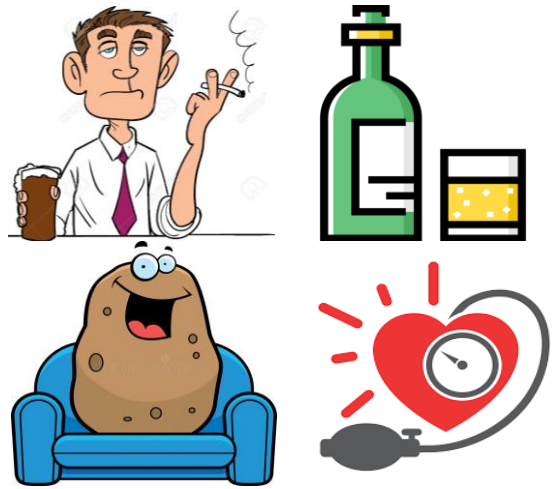
# The CADASIL phenotype varies between people with the gene




*(Chabriat et al; 2009)*

# What factors make CADASIL vary between individuals?

- Possibilities include:
  - **Genetic factors**, e.g. location of the abnormality on the NOTCH3 gene
  - **Cardiovascular and environmental risk factors**, e.g. smoking, alcohol consumption, blood pressure



# What have other studies shown?

- *Research into genetics:*
- The site of abnormality **may** affect disease severity - abnormalities in higher exons associated with less severe disease *(as discussed by Professor Lesnik-Oberstein)*
- Other genetic factors appear to be important as modifying factors:

**Heritability of MRI Lesion Volume in CADASIL**

**Evidence for Genetic Modifiers**

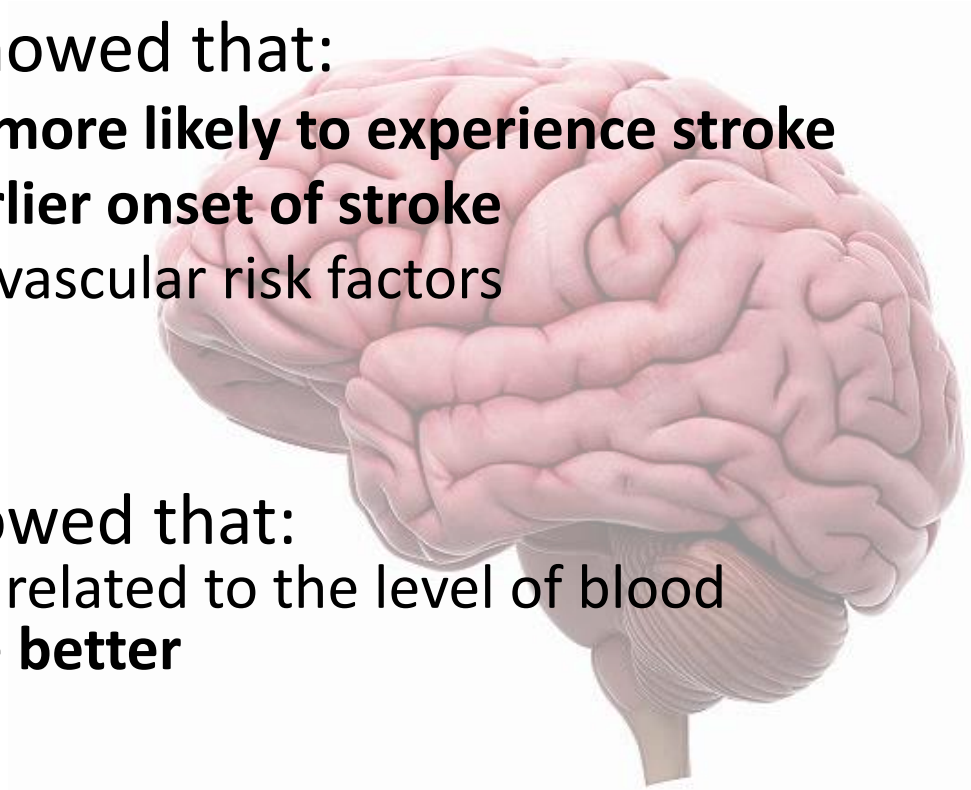
Christian Opherk, MD; Nils Peters, MD; Markus Holtmannspötter, MD; Andreas Gschwendtner, MD; Bertram Müller-Myhsok; Martin Dichgans, MD

# What have other studies shown?

*Research into risk factors:*

- A 2010 study of 200 CADASIL patients showed that:
  - Those with **high blood pressure were 2.5x more likely to experience stroke**
  - **Smoking status was associated with an earlier onset of stroke**
  - But no other associations with other cardiovascular risk factors
    *(Adib-Samii et al; 2010)*

- A 2005 study of 62 CADASIL patients showed that:
  The rate of progression of changes on MRI was related to the level of blood pressure- i.e. **the lower the blood pressure the better**
  *(Holtmannspotter et al; 2005)*



# The UK Familial Stroke Study

A study aiming to develop more information about hereditary stroke conditions, mainly CADASIL

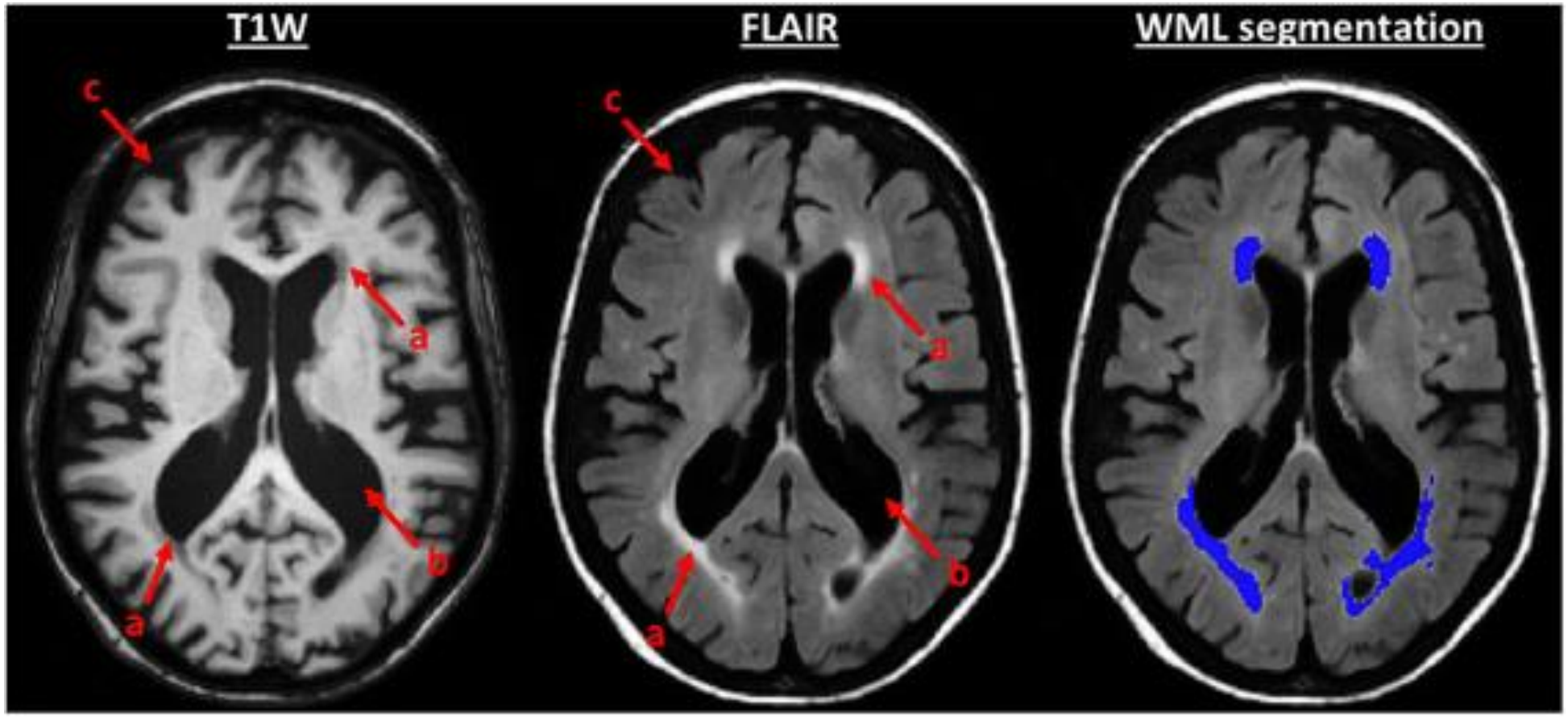
**Aims**

- To collect information from hundreds of patients with CADASIL
- To collect detailed information on risk factors including early life risk factors
- To correlate (a) these risk factors and (b) genetics:
  - Features of the disease
  - Severity of the disease measured on MRI scans

# The UK Familial Stroke Study

- Currently running in Cambridge, Leeds, Sheffield and 2 London sites
- We have ethics permission to collect data from people with the CADASIL gene abnormality from throughout the UK and can also collect it remotely via telephone and skype
- We collect a questionnaire information about your health, medical history, and a little insight to your family tree as well as a blood sample (which can be sent in the post)
- If you have had an MRI scan we need to get a copy of your scan
- For people we have not seen in clinic we need copies of your medical records / GP and clinic letters
- If we see you in person we also organise cognitive tests (taking about 30 minutes)

We use the MRI scans to semi-automatically segment and measure the extent of white matter changes as a marker of the severity of the disease



# The UK Familial Stroke Study

- If you are interested in taking part please do let us know
- Patients attending our clinic will be invited to take part
- If you are not under the Cambridge clinic then we can still include you if you would like to take part.

- Contact us on:

  E-mail: he267@medschl.cam.ac.uk

  Phone: 01223 596221

  …Or fill in the interested in research slip today

UK FAMILIAL SMALL VESSEL DISEASE STUDY