What is CADASIL?

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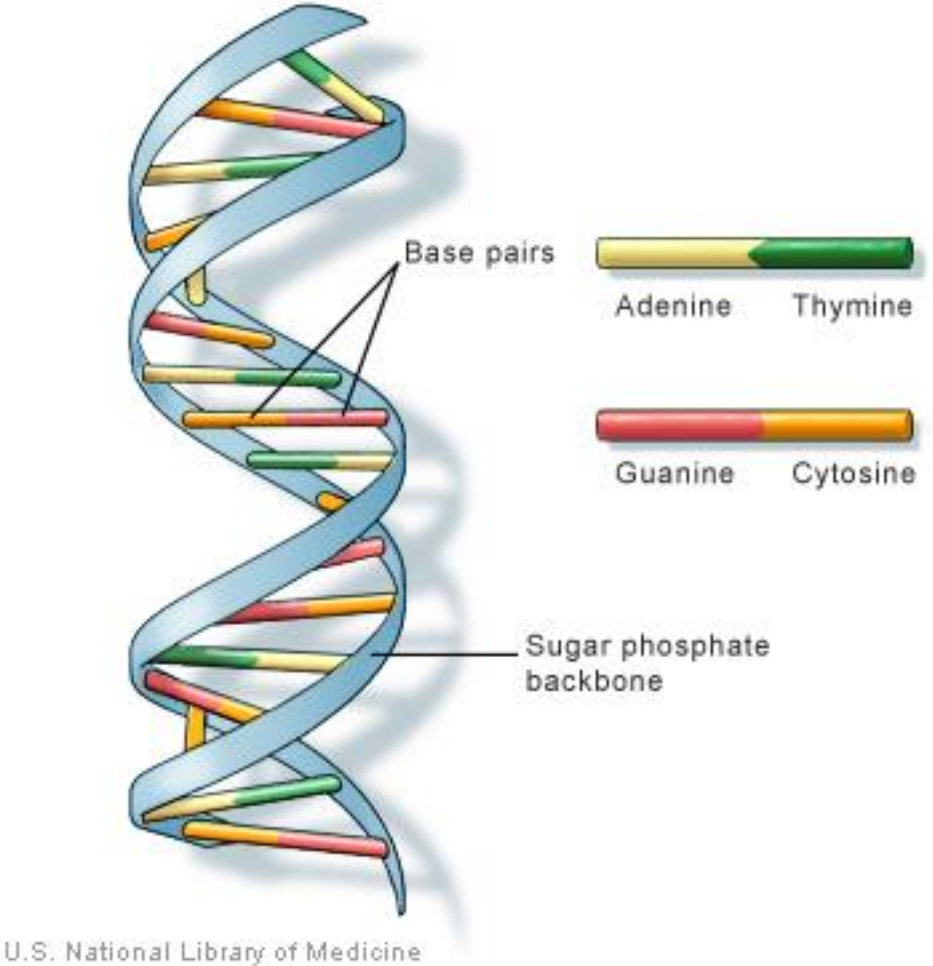
Familial types of stroke

MONOGENIC	POLYGENIC
A disease caused by a single gene having a major effect	A disease caused by a many gene small having a small effect
e.g. CADASIL	e.g. common stroke

CADASIL is the most common monogenic form of stroke

What is CADASIL?

- Most common familial from of stroke
- Autosomal dominant inheritance
- Notch 3 gene mutation
- Results in abnormal function of the small blood vessels in the brain
- Results in characteristic constellation of symptoms



U.S. National Library of Medicine

Types of inheritance for monogenic disease

DOMINANT

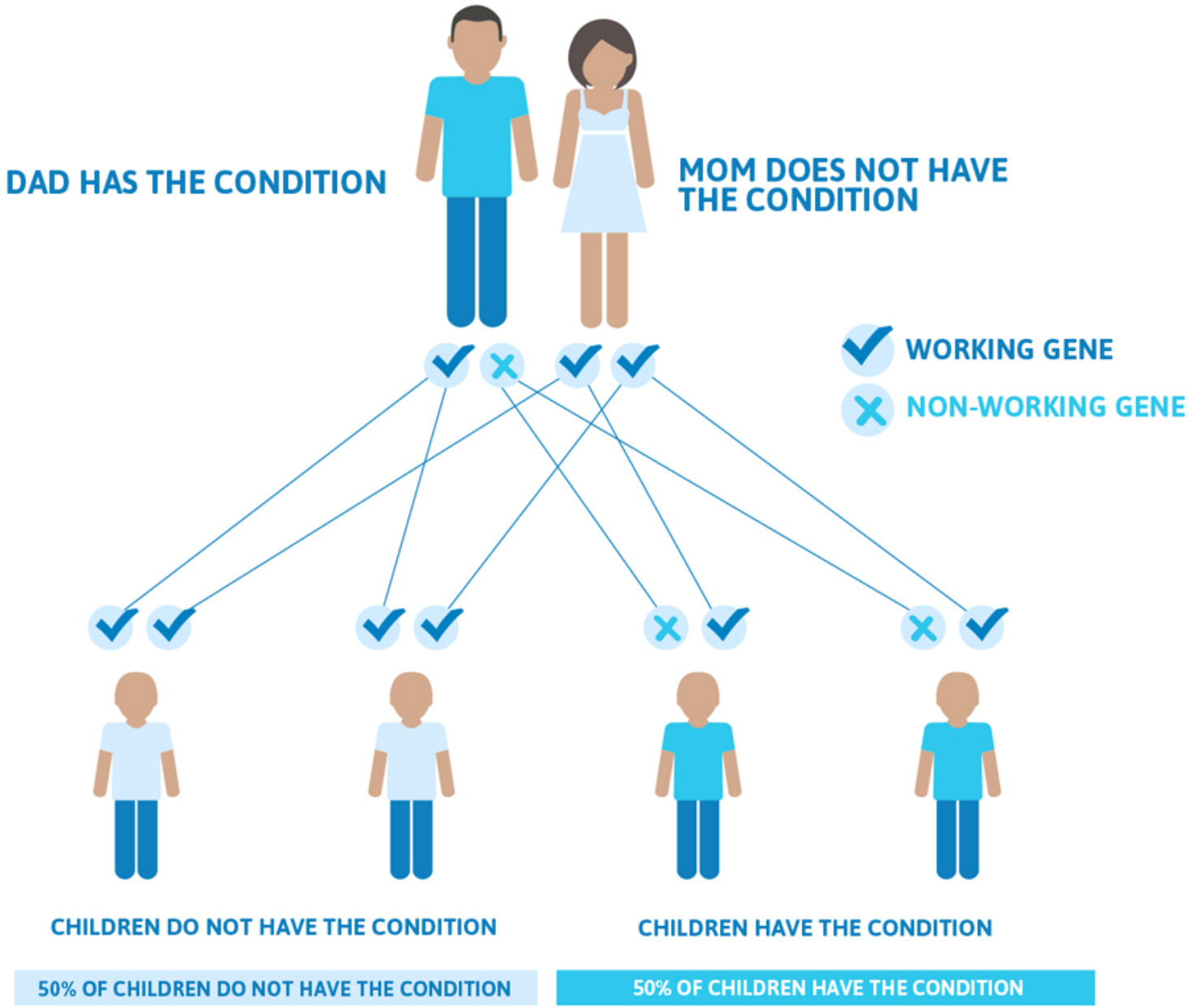
One allele from one parent can cause the disease

e.g. CADASIL

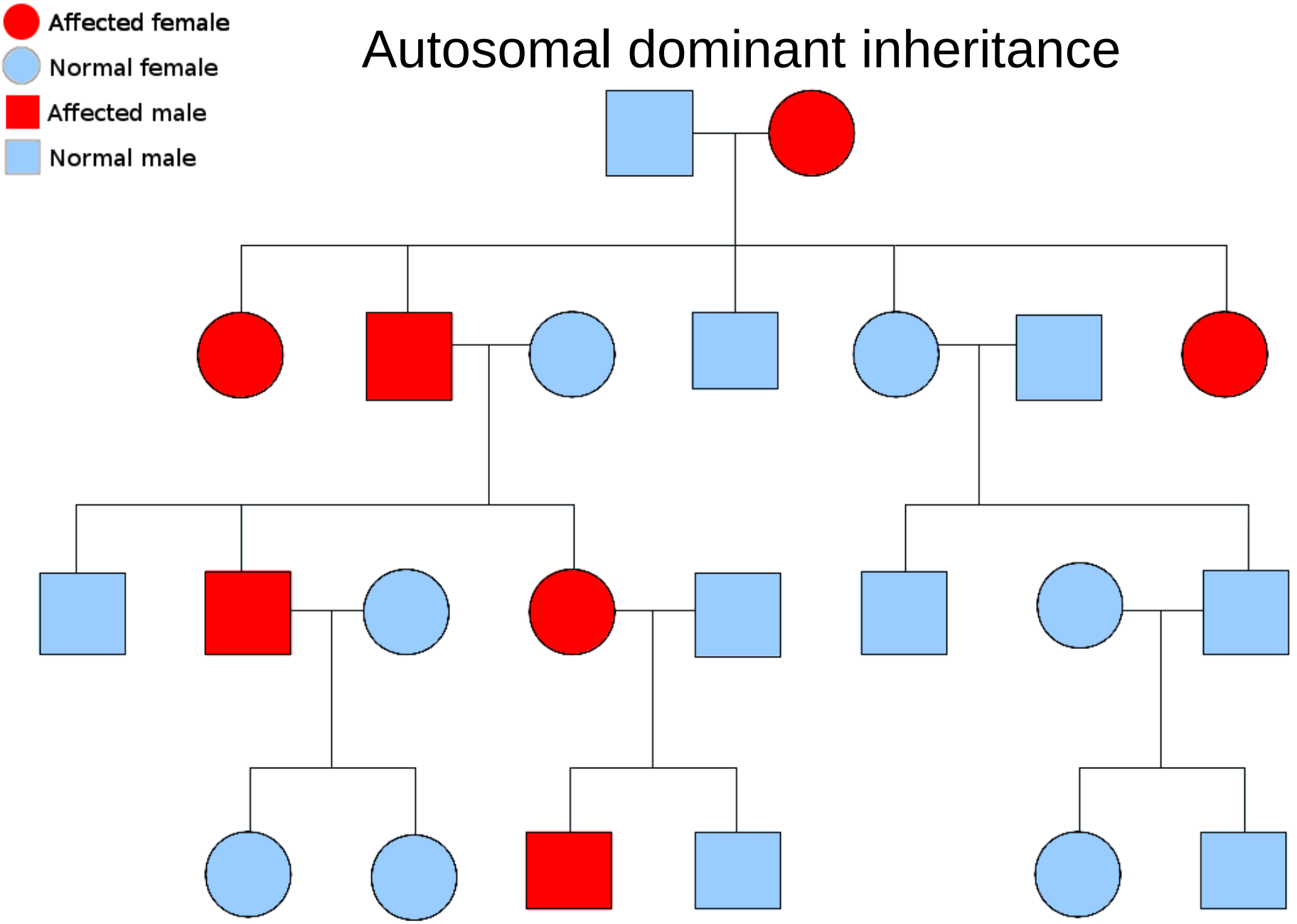
RECESSIVE

One allele from each parent required to develop the disease

Autosomal Dominant Inheritance Pattern



Autosomal dominant inheritance



Notch 3

membrane

Extra-cellular portion of notch3 protein

34 EGF repeats

Normal EGF repeat with
6 cysteine residues

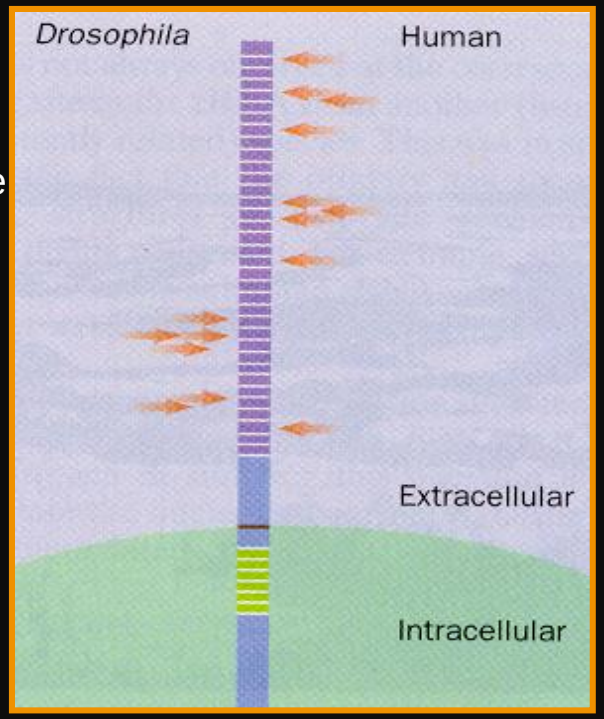
Unpaired
new cysteine
residue

Deleted
cysteine
residue

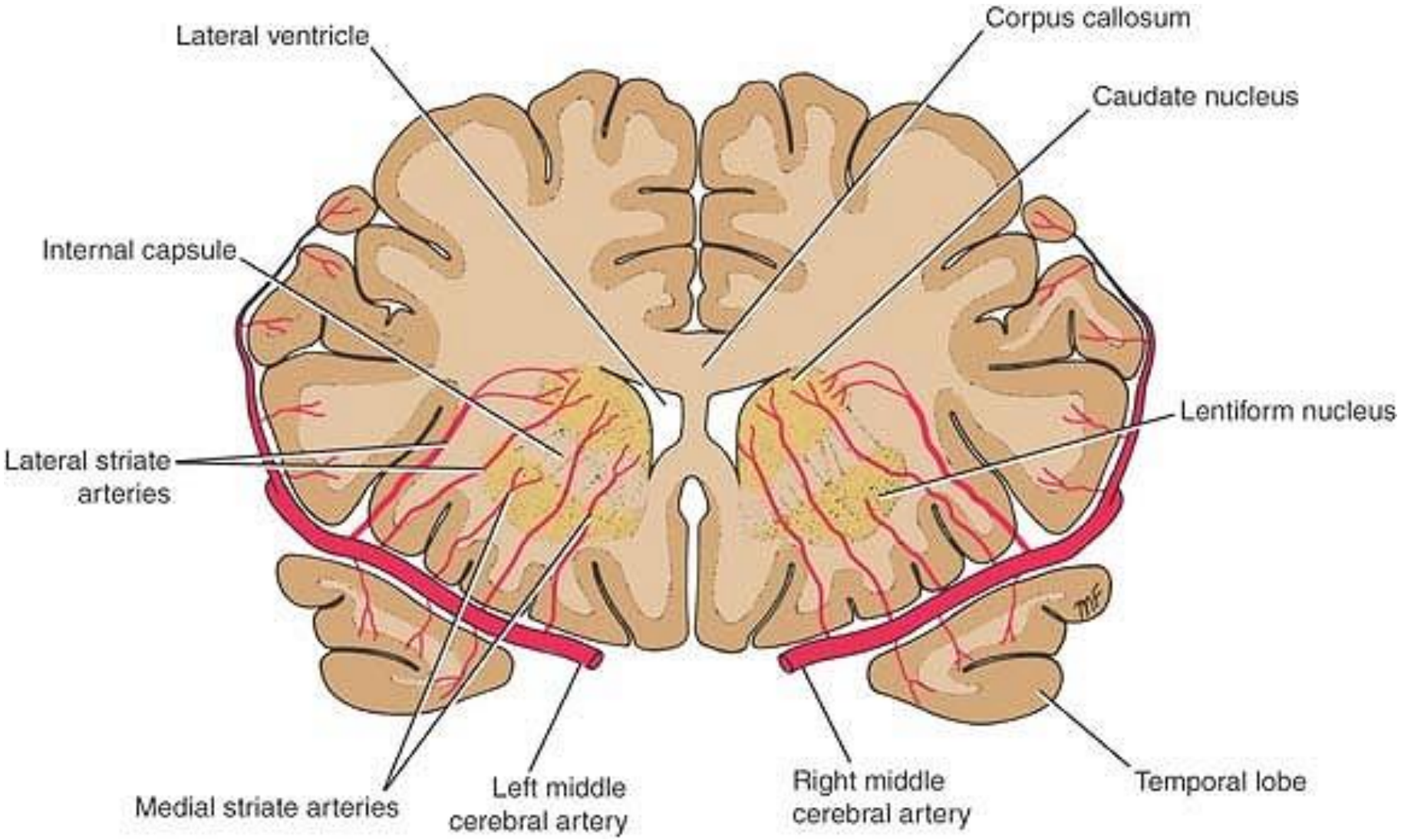
Unpaired cysteine
residue

or **Gain of a cysteine**

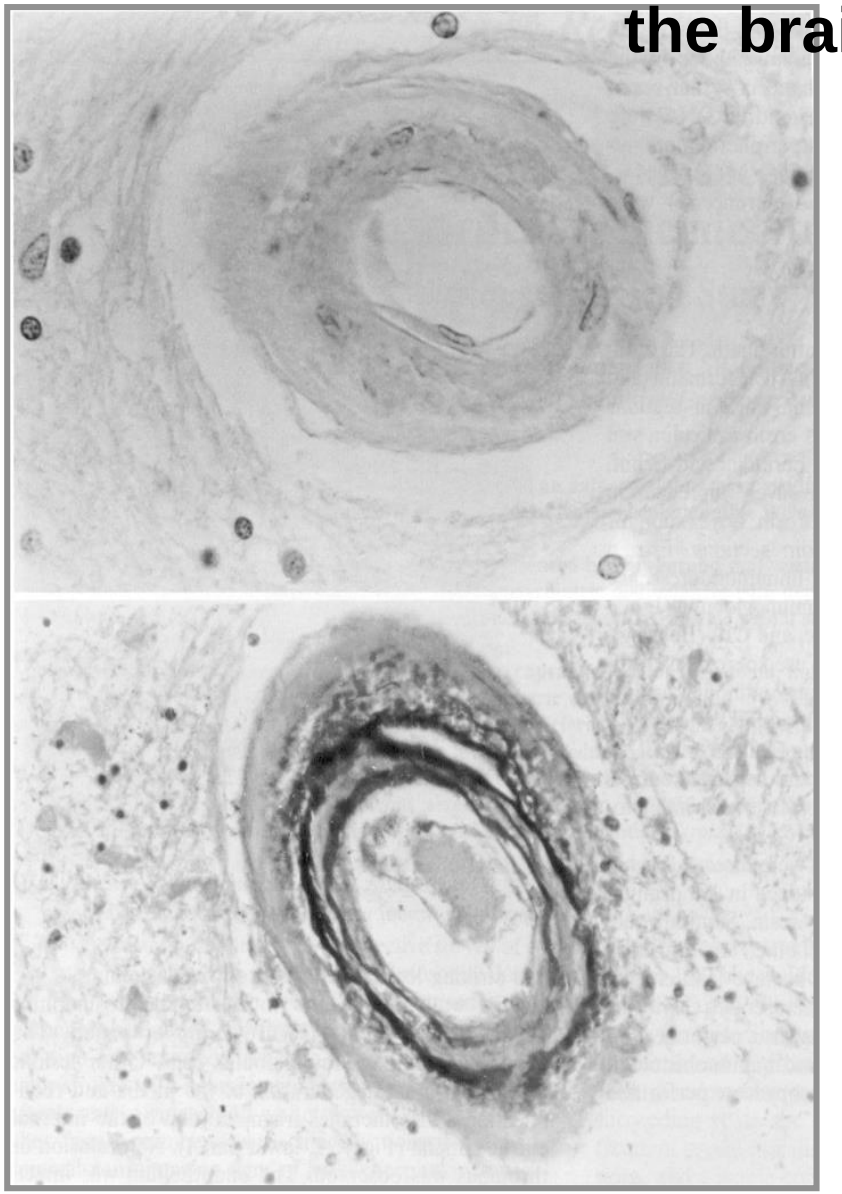
Loss of a cysteine

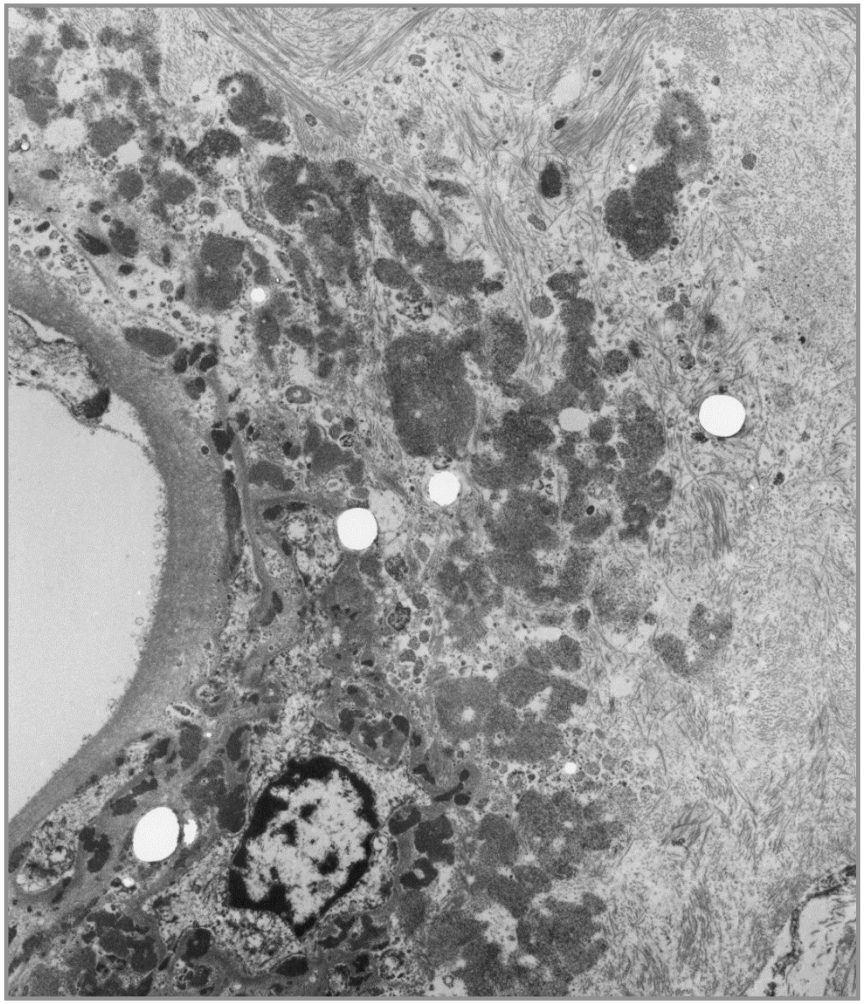


A disease of the small perforating arteries

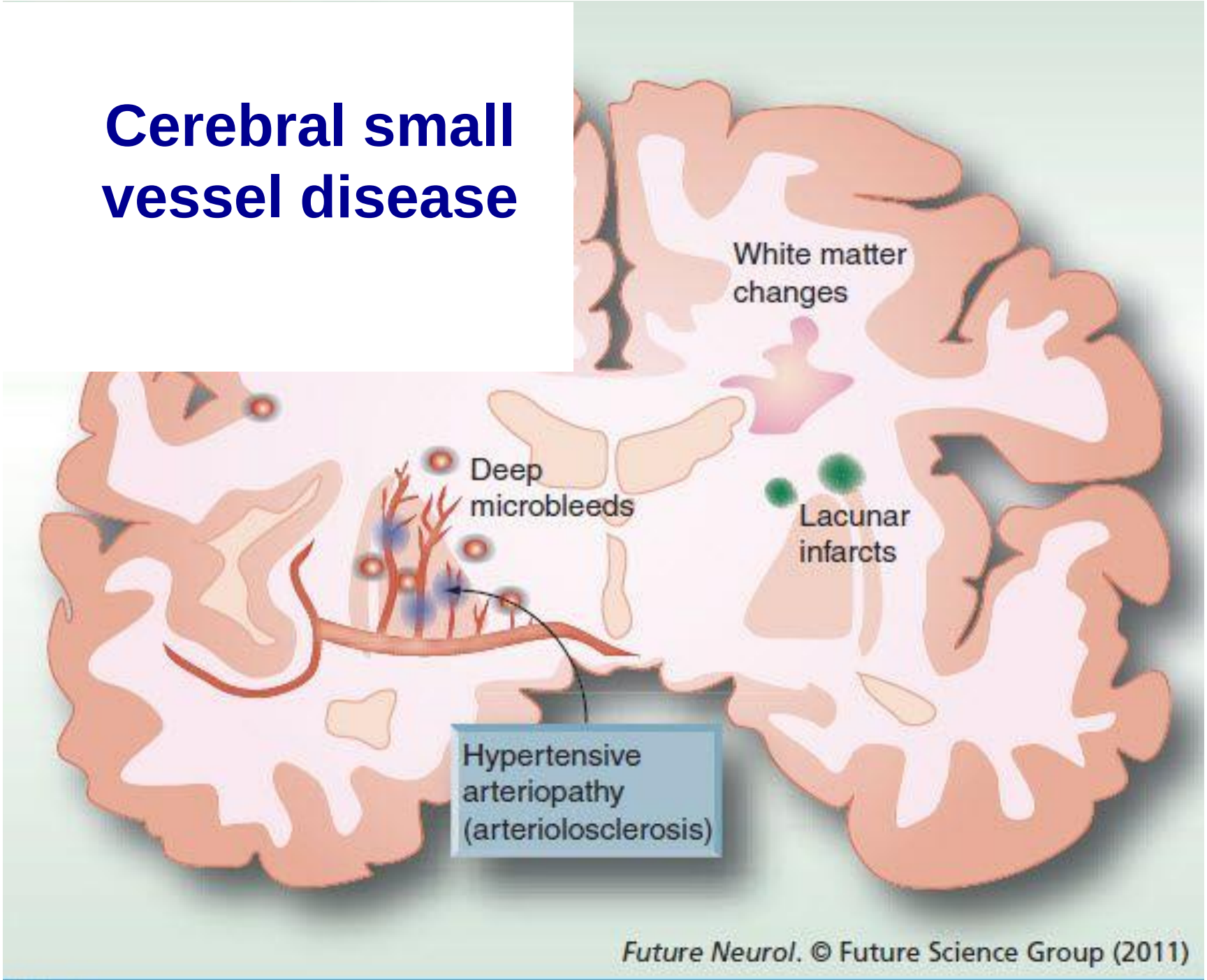


Abnormalities of the small vessel blood vessel (arteries) throughout the body but with more severe involvement of the brain arteries

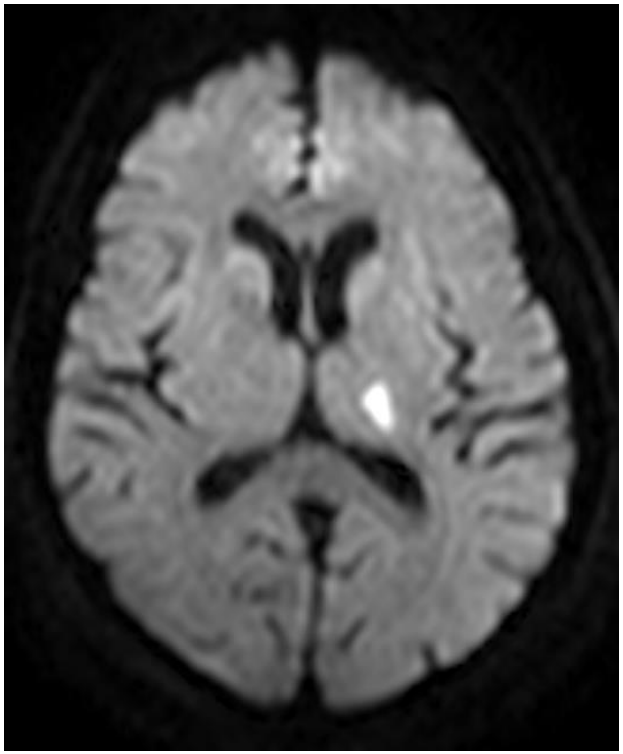




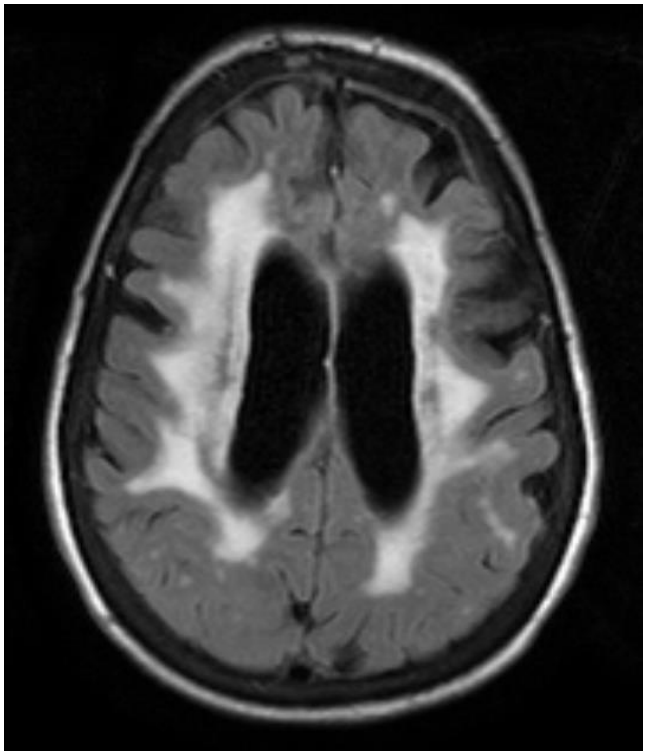
Cerebral small vessel disease



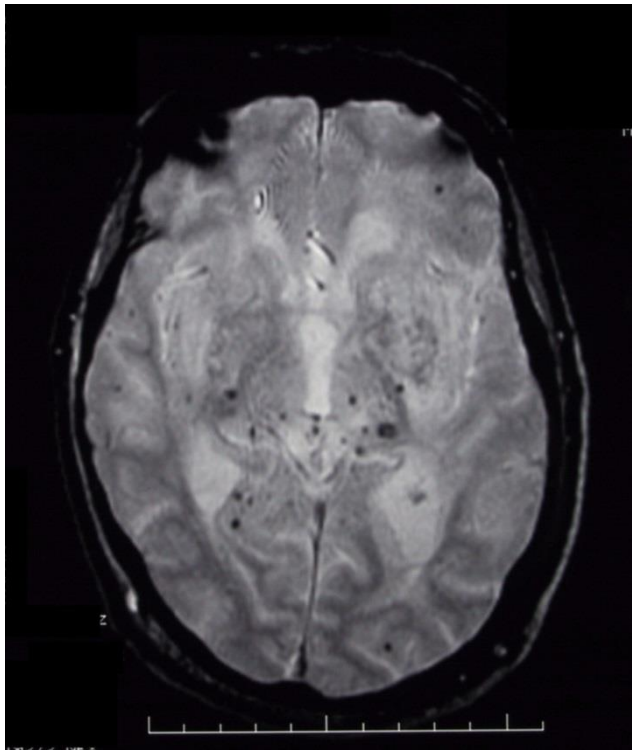
Small vessel disease



Lacunar infarct



White matter hyperintensities



Cerebral microbleeds

CADASIL

- Reported worldwide in all ethnics groups
- (Europe, Africa, South East Asia, China, South America, USA, Australia)
- >400 patients seen in our clinic from throughout GB
- SE Thames : 3.2 million population

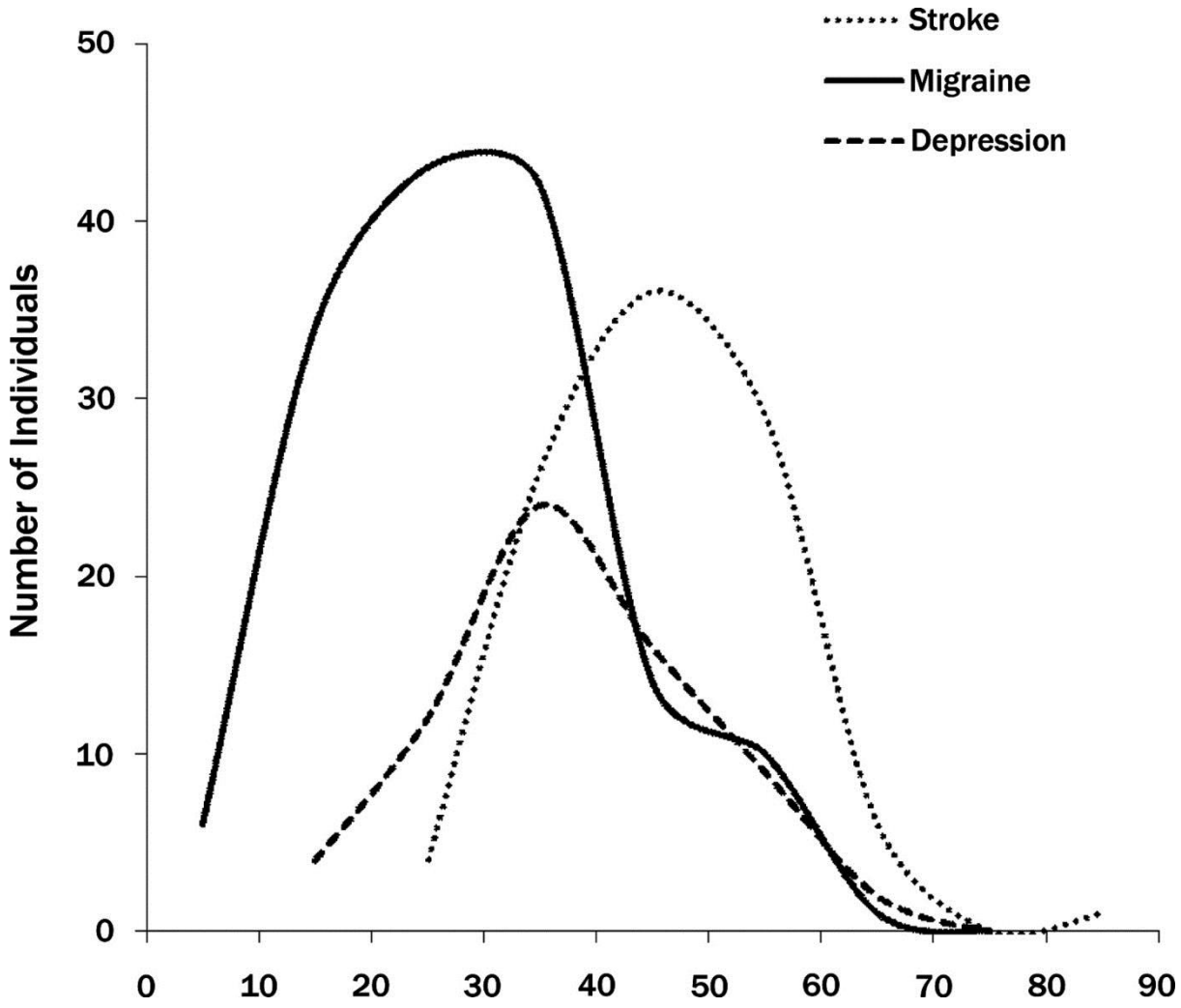
  8 families (2000)

  approx 32 cases ie 1 per 100000 UK
- Prevalence : very approx 1 per 50,000-100000

Clinical Spectrum of CADASIL in Britain

	1st symptom	1st major symptom
Stroke/TIA	23 (19%)	61 (58%)
Migraine	80 (67%)	
Dementia	3 (3%)	6 (7%)
Psychiatric	9 (8%)	
Encephalopathy	1 (1%)	12 (14%)
Epilepsy	2 (2%)	3 (4%)
Parkinsonian syndrome	1 (1%)	1(1%)

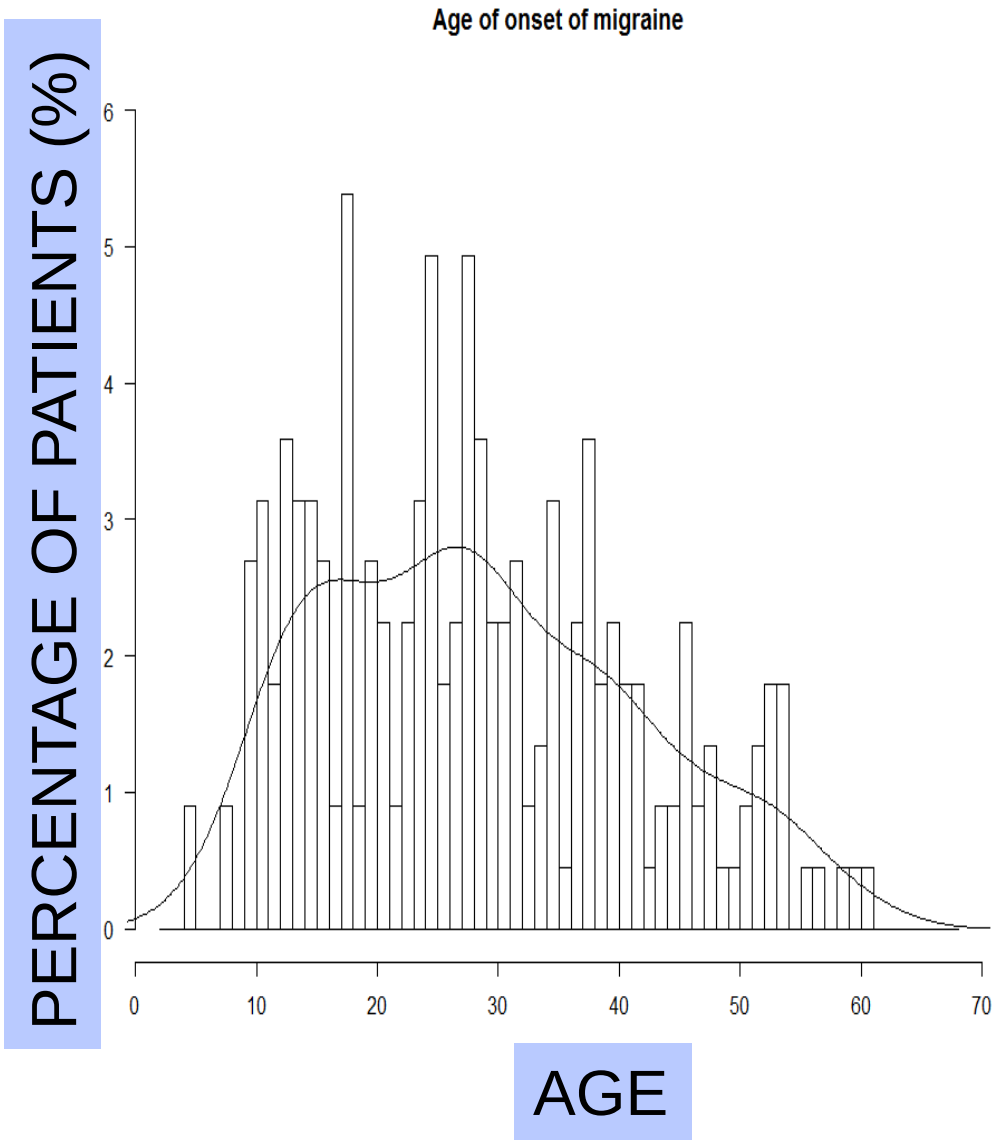
Distribution of age at onset of different symptoms of CADASIL



Adib-Samii, P. et al. Stroke 2010;41:630-634

PATTERN OF MIGRAINES IN CADASIL

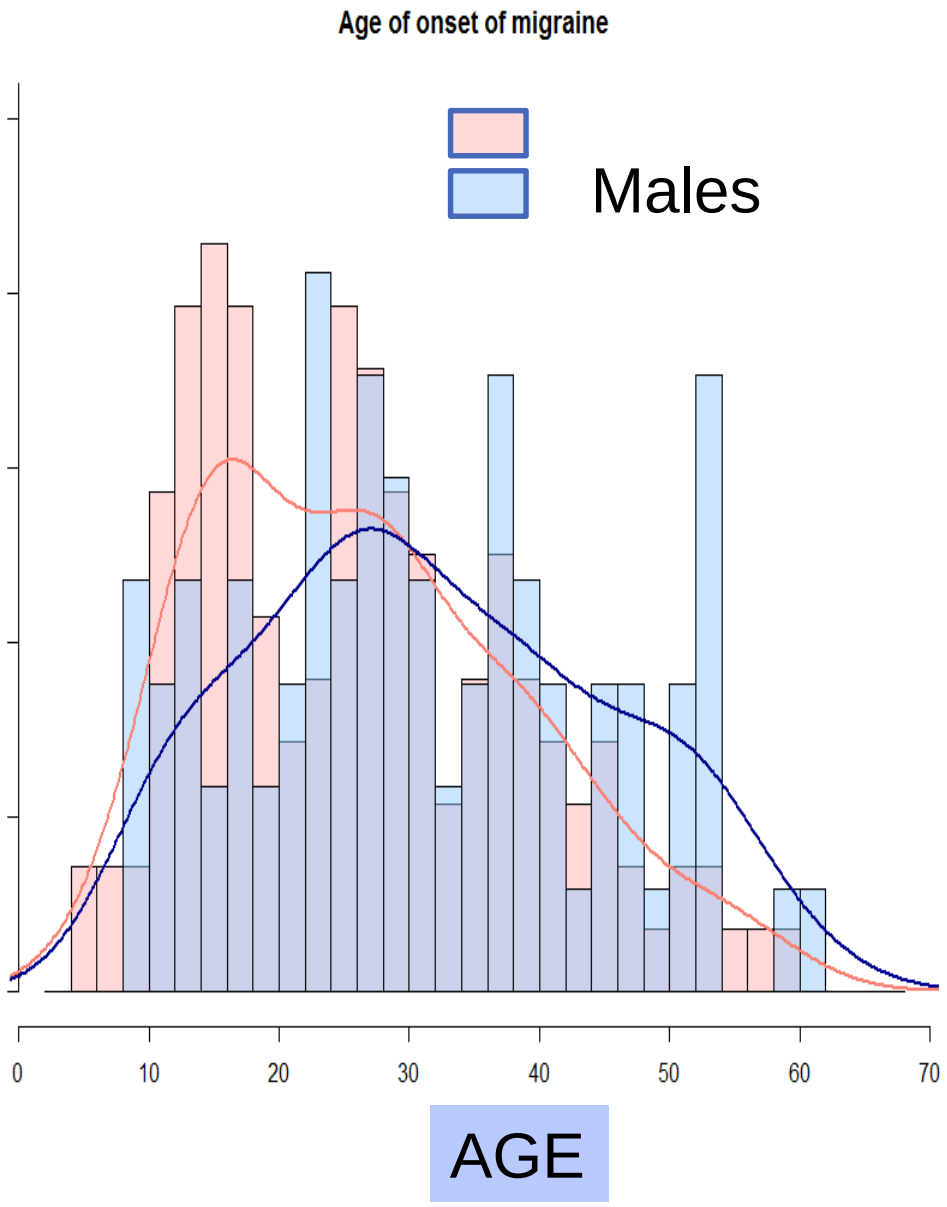
- 296 symptomatic patients
- 76.0% of had migraines (225 of 296)
- Migraine was first feature in 68.6% (203 of 296)
- Variable age of onset – mean 28.6 ± 13.0 years



MIGRAINES – DIFFERENCES BETWEEN THE SEXES

	MALES	FEMALES
Prevalence (% symptomatic patients)	66.9%	82.8%
Age of onset (mean ± SD)	31.6 ± 13.6	26.7 ± 12.4
	p=0.007	

PERCENTAGE OF MALES OR FEMALES



TYPES OF MIGRAINE AURA

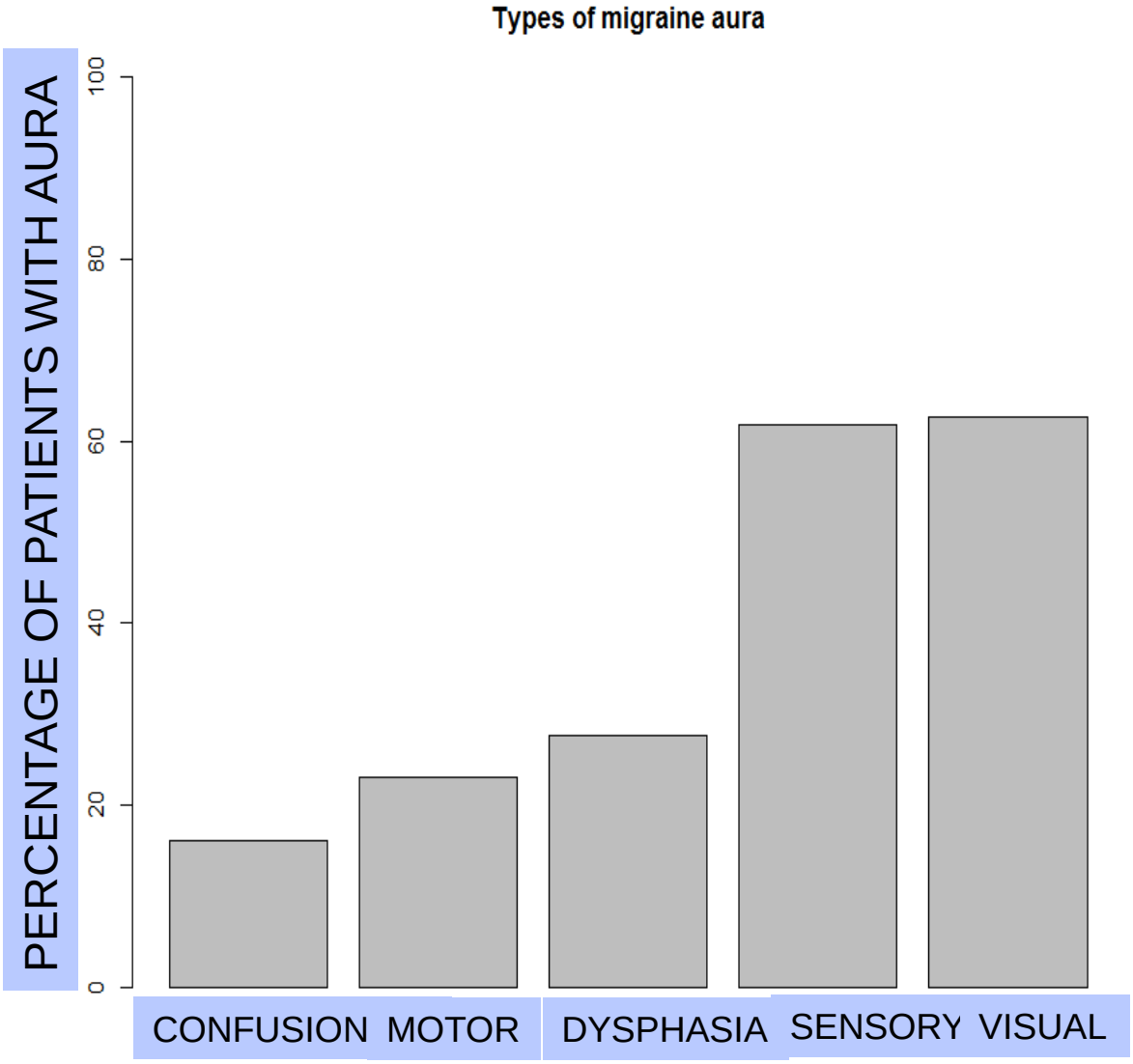
MIGRAINE TYPES

Of 225 patients with migraine,

89.8% experience aura

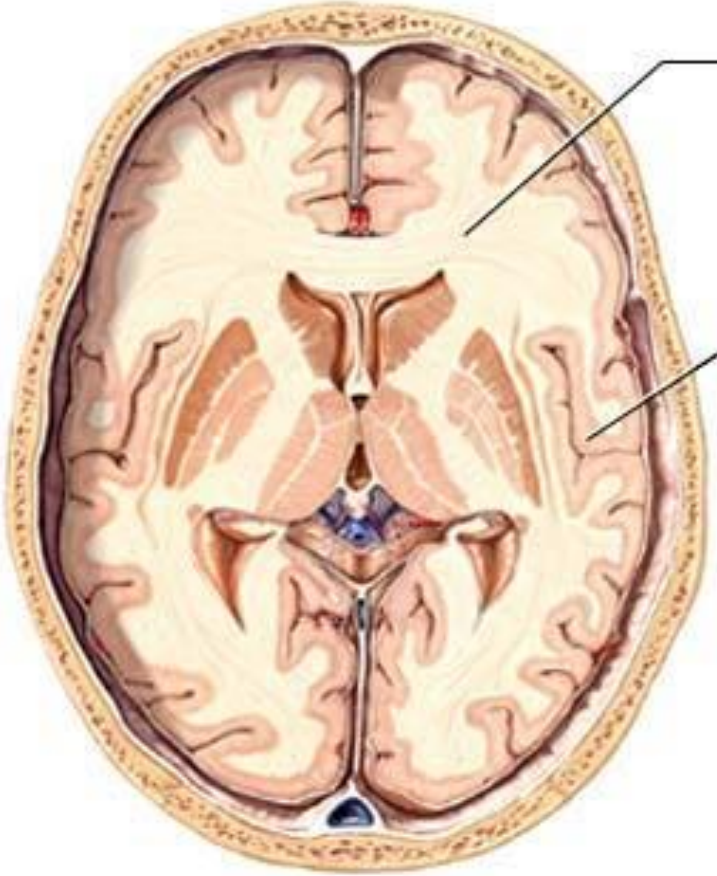
Of those with aura:

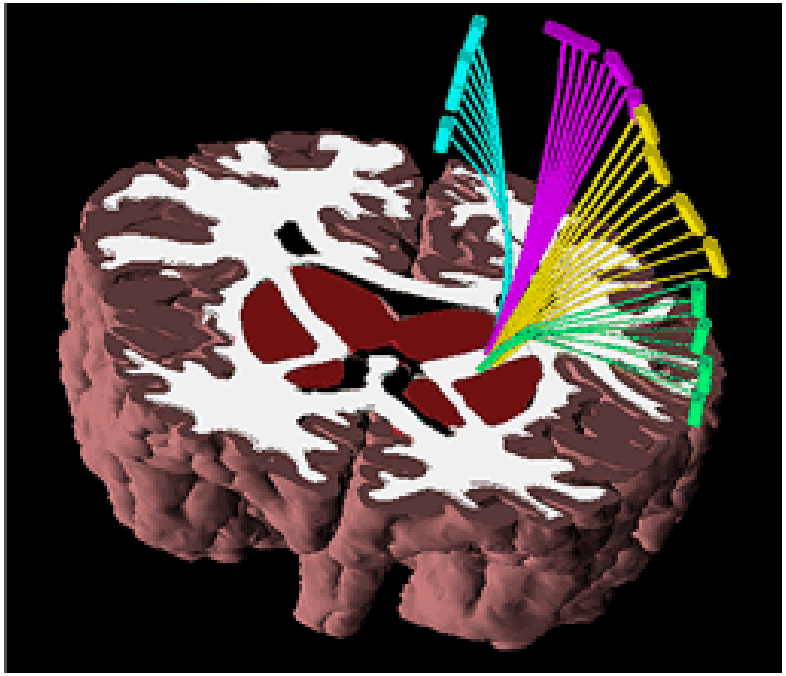
2 aura types	70
3 aura types	78
4 aura types	46
5 aura types	8

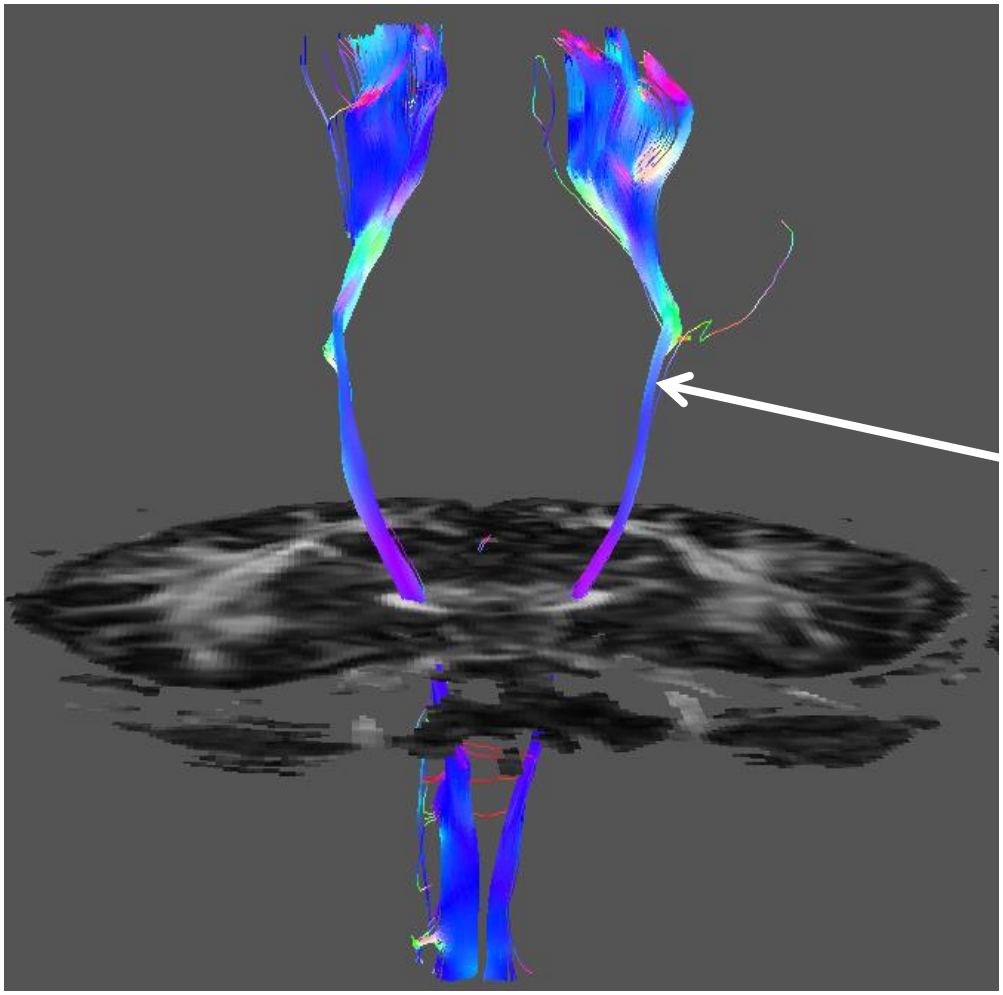


Stroke in CADASIL

- Lacunar infarcts
  - Disrupt descending and ascending pathways
  - Results in either
    - Symptoms – stroke
    - Asymptomatic infarct – contributes to “ disease burden”


White matter
Gray matter





Motor pathways

Right sided face, arm and leg weakness

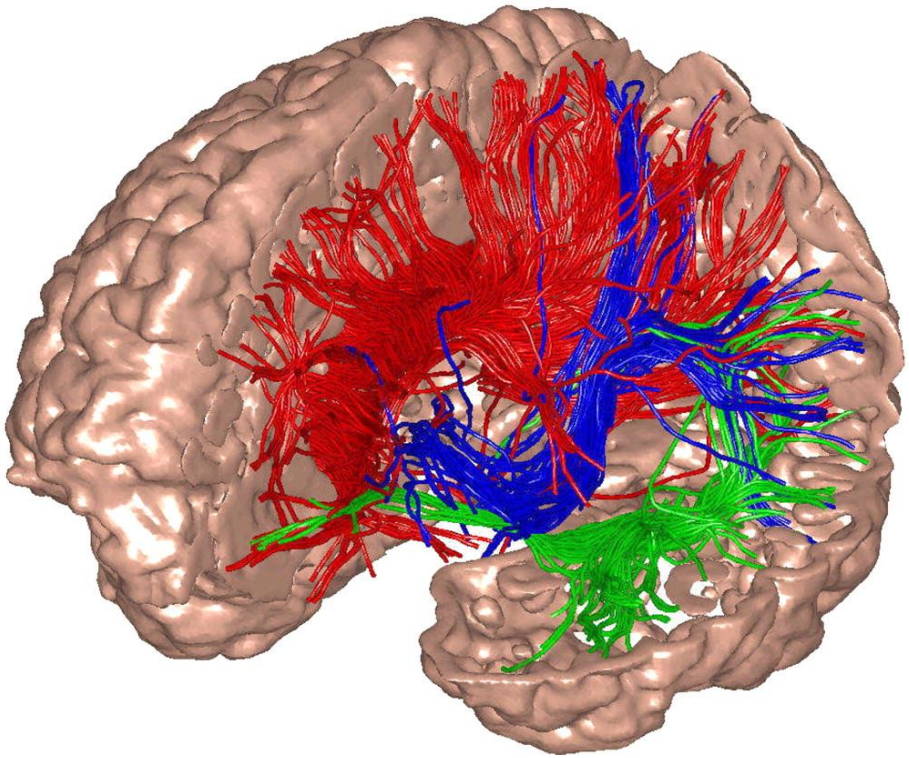
Stroke in CADASIL

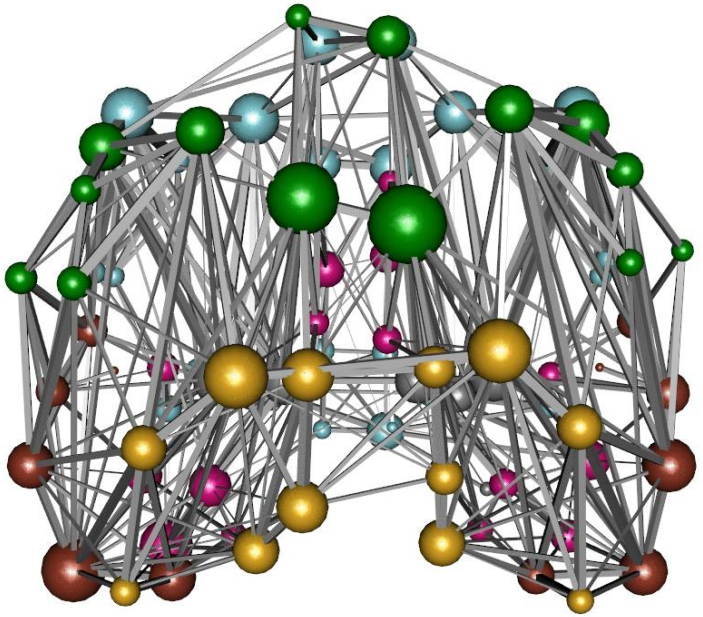
- Lacunar strokes
  - Pure motor stroke- weakness down one side
  - Pure sensory stroke- loss of sensation down one side
  - Sensorimotor stroke – weakness and sensory loss down one side
  - Higher cortical functions (eg speech production) rarely affected

Cognitive impairment

- Can occur from middle age on
- Very different from Alzheimer's like dementia which affects higher brain functions eg memory / speech
- Typically affects subcortical structures and disrupts connections within the brain
- Slowed processing
- "Executive dysfunction" – planning, organisation, multitasking

Brain network analysis





Small strokes, and more diffuse white matter damage disrupts white matter pathways leading to distribution of complex brain networks and therefore cognitive impairment

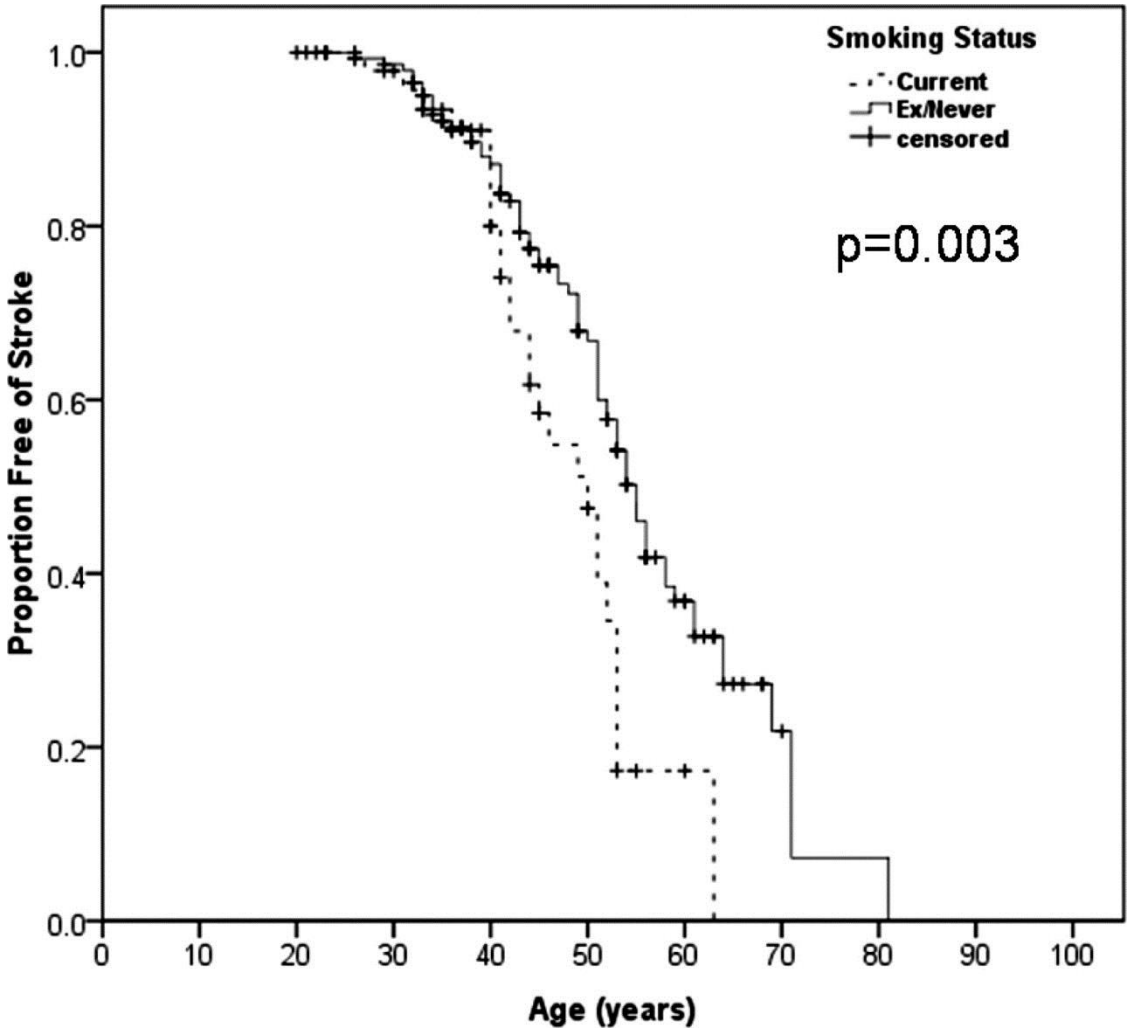
Other features

- Depression – often very treatable
- Encephalopathy – CADASIL coma
- Seizures
- Apathy

Does the severity of CADASIL stay the same within families?

- My mum had bad disease – does that mean I will?
- NO
- We don’t understand why the disease varies so much amongst different people but the follwpoing may be important:
  - Other stroke risk factors: smoking, high blood pressure
  - Other genes modulating the effect og the notch 3 mutation

Kaplan-Meier plot showing age at onset of stroke, stratified according to smoking status



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Stroke

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Table 3. Relations Between Cardiovascular Risk Factors and Clinical Features

	Stroke
Age, y	1.05 (1.03–1.08)*
Male sex	1.29 (0.74–2.27)
Hypertension	2.57 (1.29–5.14)*
Ever-smoker	1.13 (0.65–1.96)
Smoking, pack-years	1.07 (1.03–1.11)*
Hypercholesterolemia	1.06 (0.57–1.96)
Hyperhomocysteinemia	0.99 (0.40–2.43)
Body mass index >25 kg/m^2	1.39 (0.70–2.75)

Values shown are ORs with 95%
*$P<0.01$, †$P<0.02$.

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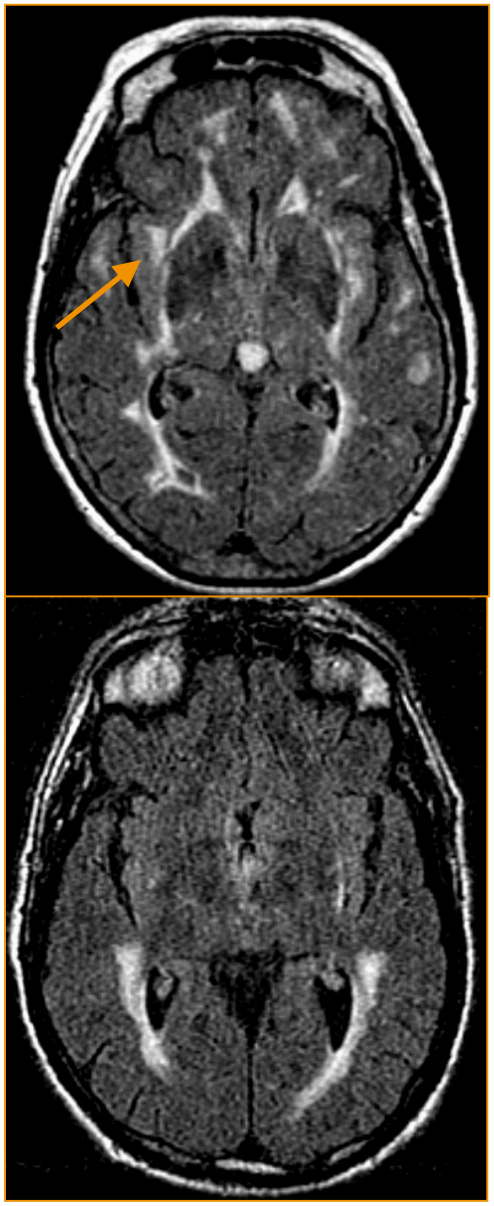
CADASIL

Sporadic SVD



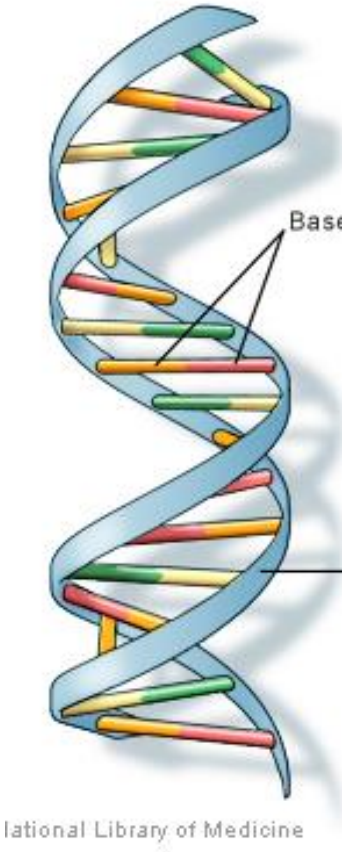
O'Sullivan et al Neurology 2001
Auer et al Radiology 2001
Markus et al Neurology 2002

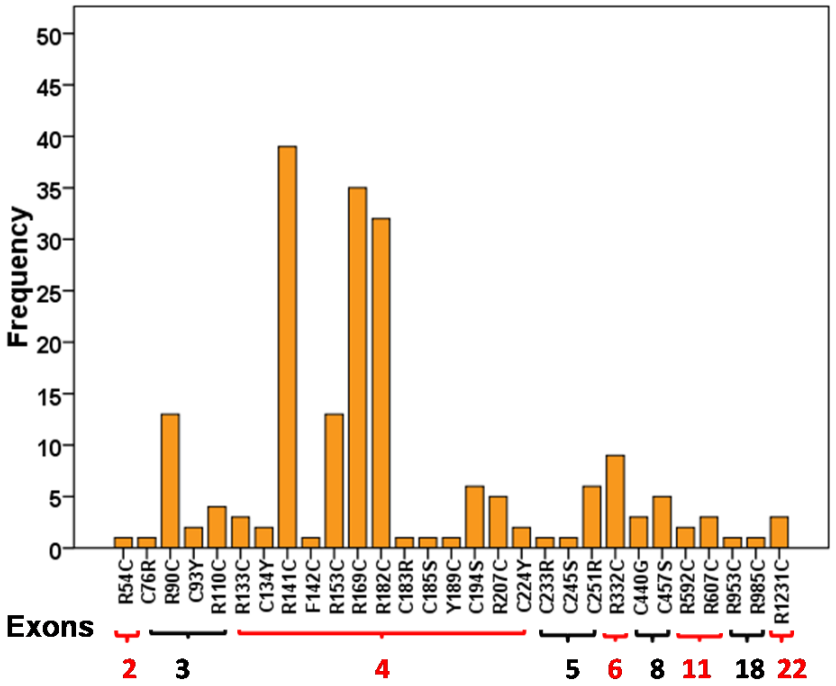
Sensitivity 91%
Specificity 86%

Sensitivity 93%
Specificity 45%

Genetic diagnosis

- Identification of underlying mutation
- Mutation site differs in different families
- Identification allows easy testing of other family members





CADASIL skin biopsy

Sensitivity 60% ; Specificity 100%

CADASIL management

- Treatment of risk factors
  - Good evidence for smoking and BP
  - Sensible to treat others- exercise/weight/ healthy diet/cholesterol

CADASIL management

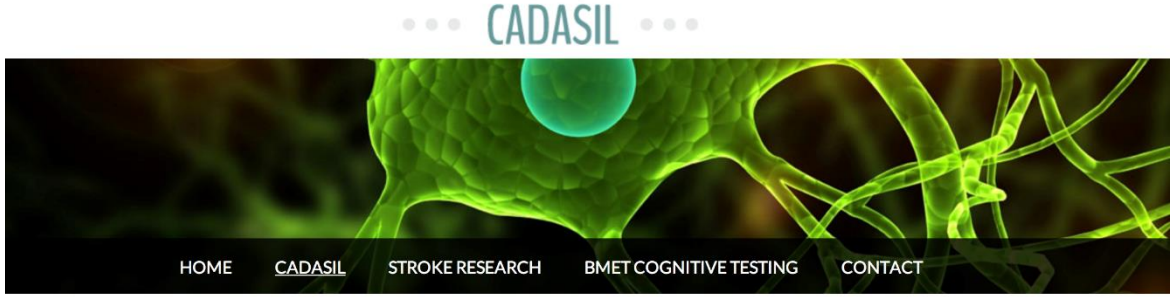
- Treatment of risk factors
  - Good evidence for smoking and BP
  - Sensible to treat others- exercise/weight/ healthy diet/cholesterol

- Antiplatelets
  - Clopidogrel or aspirin not both – after age 40
  - Avoid warfarin

CADASIL management

- Treatment of complications
  - Migraine
  - Depression
- Genetic counselling
- Pre-natal testing

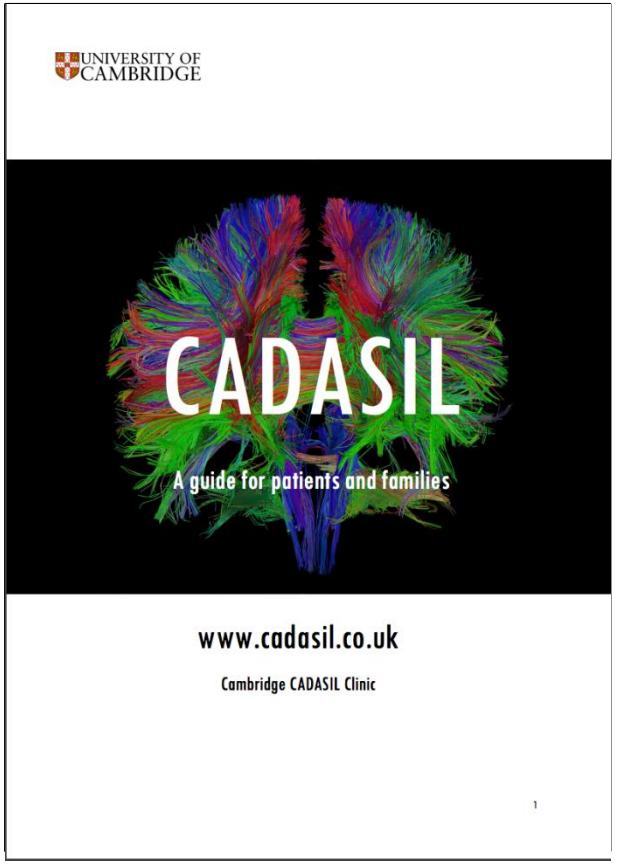
www.cadasil.co.uk



- WHAT IS CADASIL
- THE CADASIL CLINIC
- INVESTIGATIONS
- GENETIC TESTING
- PSYCHOLOGICAL DIFFICULTIES
- COGNITION
- RESEARCH ADVANCES
- FAQS
- USEFUL LINKS
- DONATIONS
- GLOSSARY

WELCOME TO THE CADASIL WEBSITE

Welcome to the CADASIL website, a new resource for those diagnosed with CADASIL, their relatives and carers. As CADASIL is a rare condition, little reliable information is available on the internet. On this website we hope to be able to provide up-to-date and accurate information. We hope that the website will expand over the coming months and years and would welcome input from patients and family members. In addition to providing useful information for CADASIL patients and relatives we also supply links to other websites where more information can be gained.

The information on this website has been primarily provided by Professor Hugh Markus, Professor of Stroke Medicine at the University of Cambridge and Consultant Neurologist at Addenbrooke's Hospital, Cambridge and by Glen Brice, Genetic Counsellor from the Clinical Genetics Department at St George's Hospital, London. Together, we have been involved in caring for CADASIL sufferers and their families for many years and have a wide range of experience in dealing with the problems associated with the condition.

As with any medical condition, we do rely on hearing the experiences of patients and family members in order to develop new services which better cater to the needs of those affected. If you have any suggestions for improvement to the website or new sections which you think we should add, please do contact us.