What is CADASIL?

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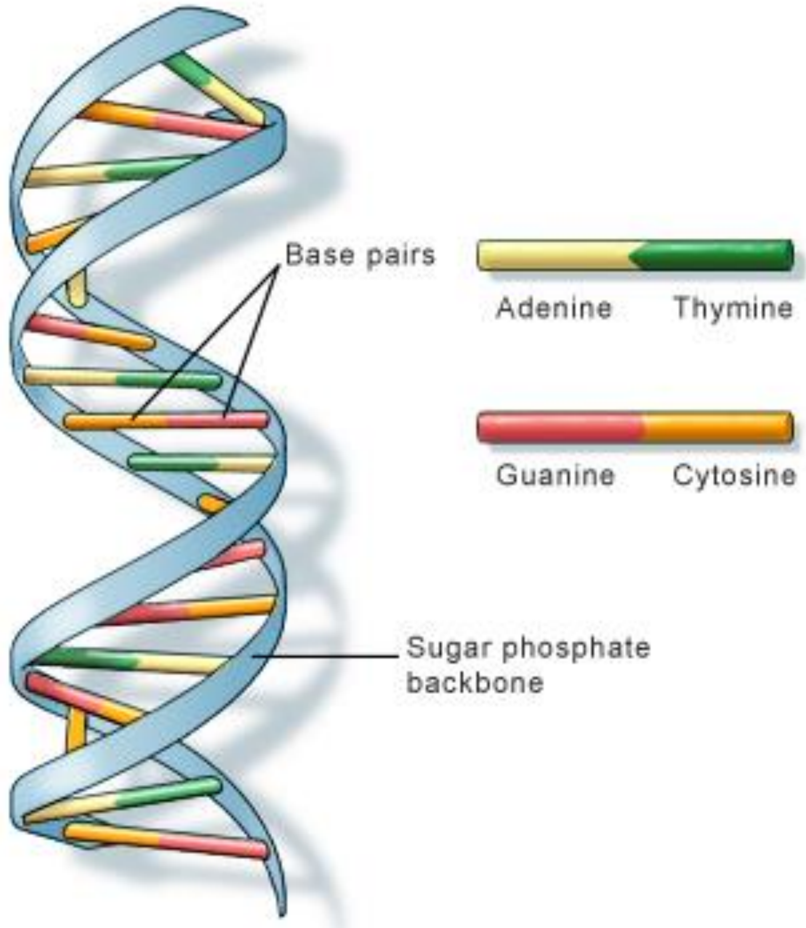
Familial types of stroke

MONOGENIC	POLYGENIC
A disease caused by a single gene having a major effevt	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 from 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

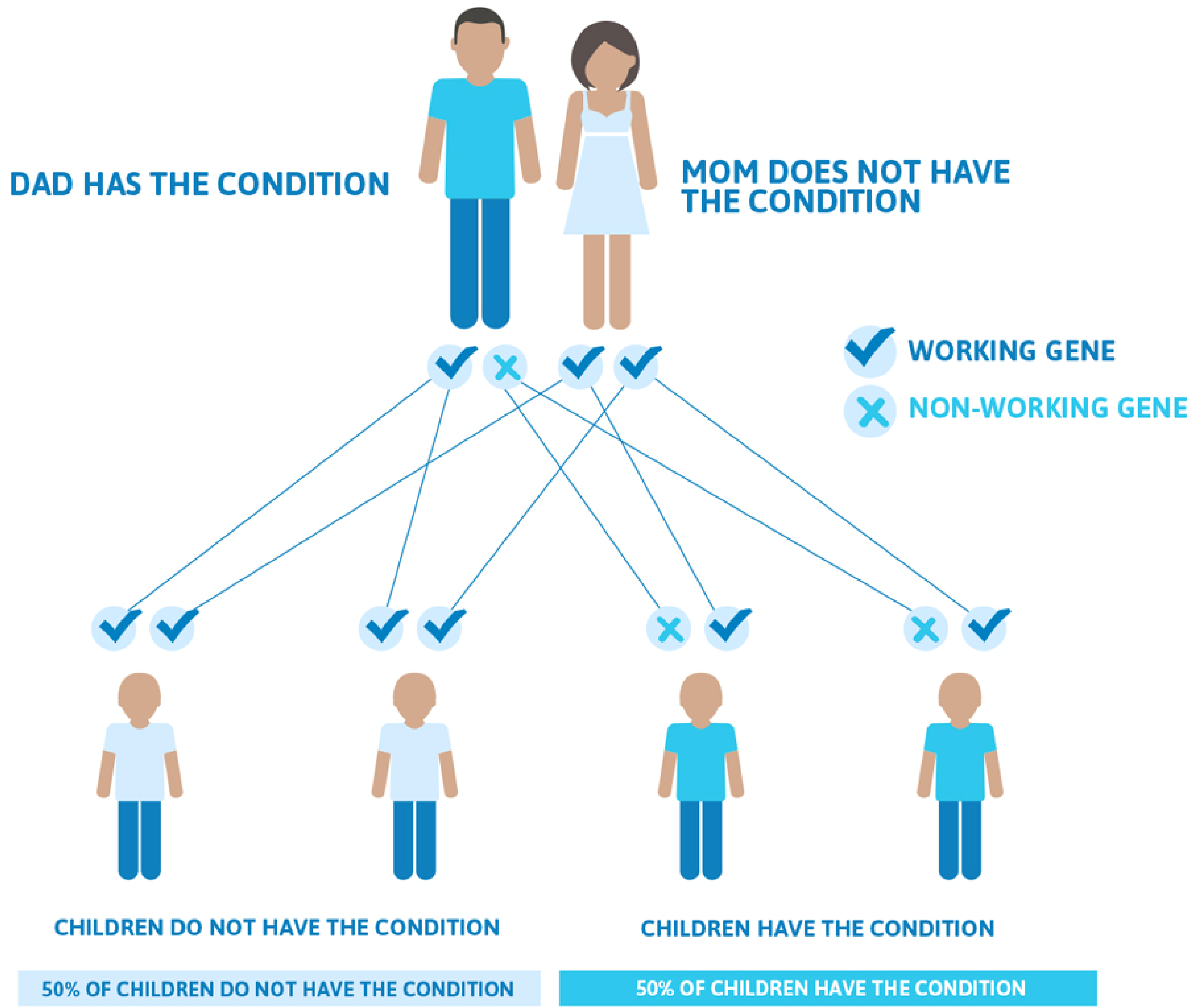


U.S. National Library of Medicine

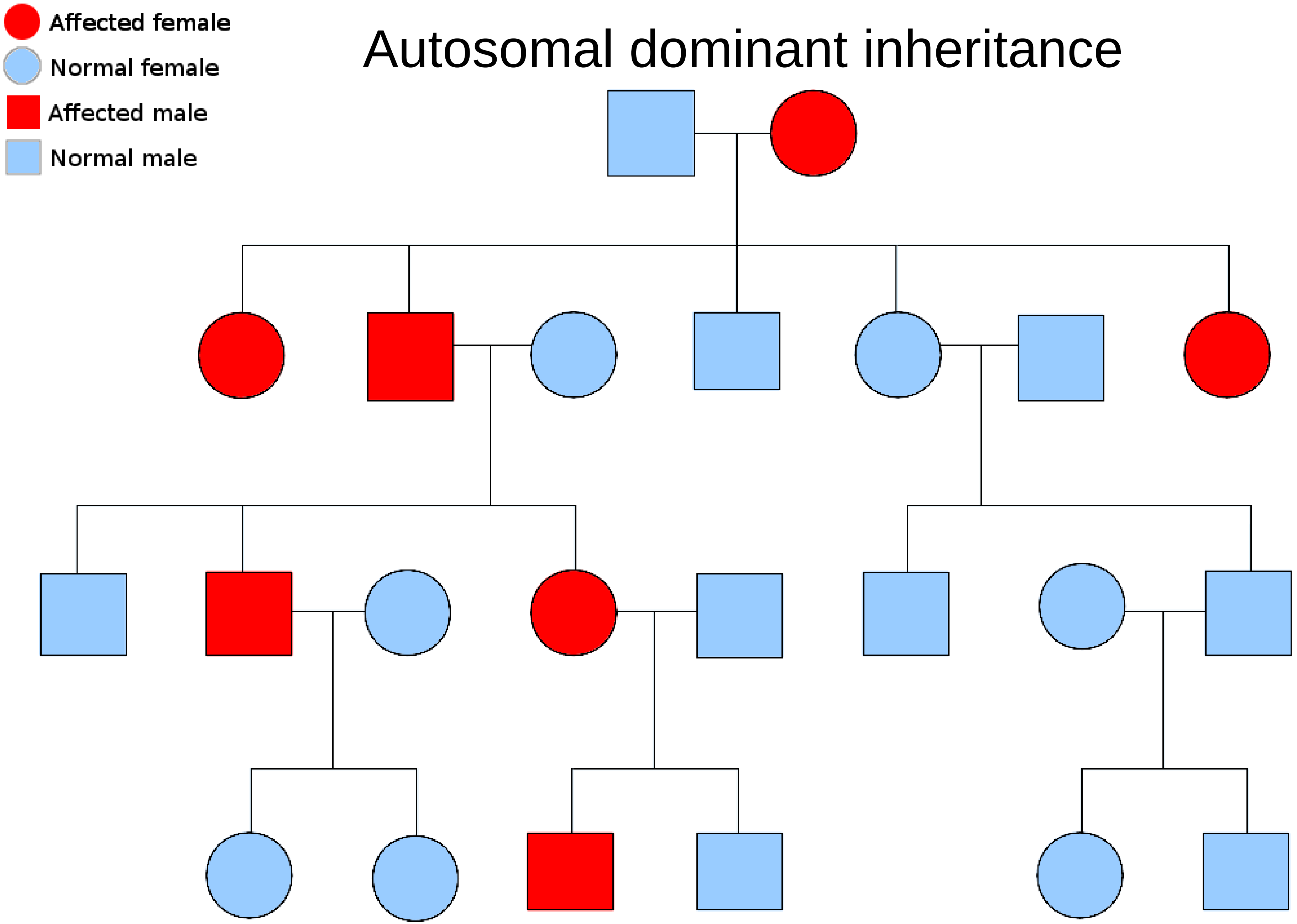
Types of inheritance for monogenic disease

DOMINANT	RECESSIVE
One allele from one parent can cause the disease	One allele from each parent required to develop the disease
e.g. CADASIL	

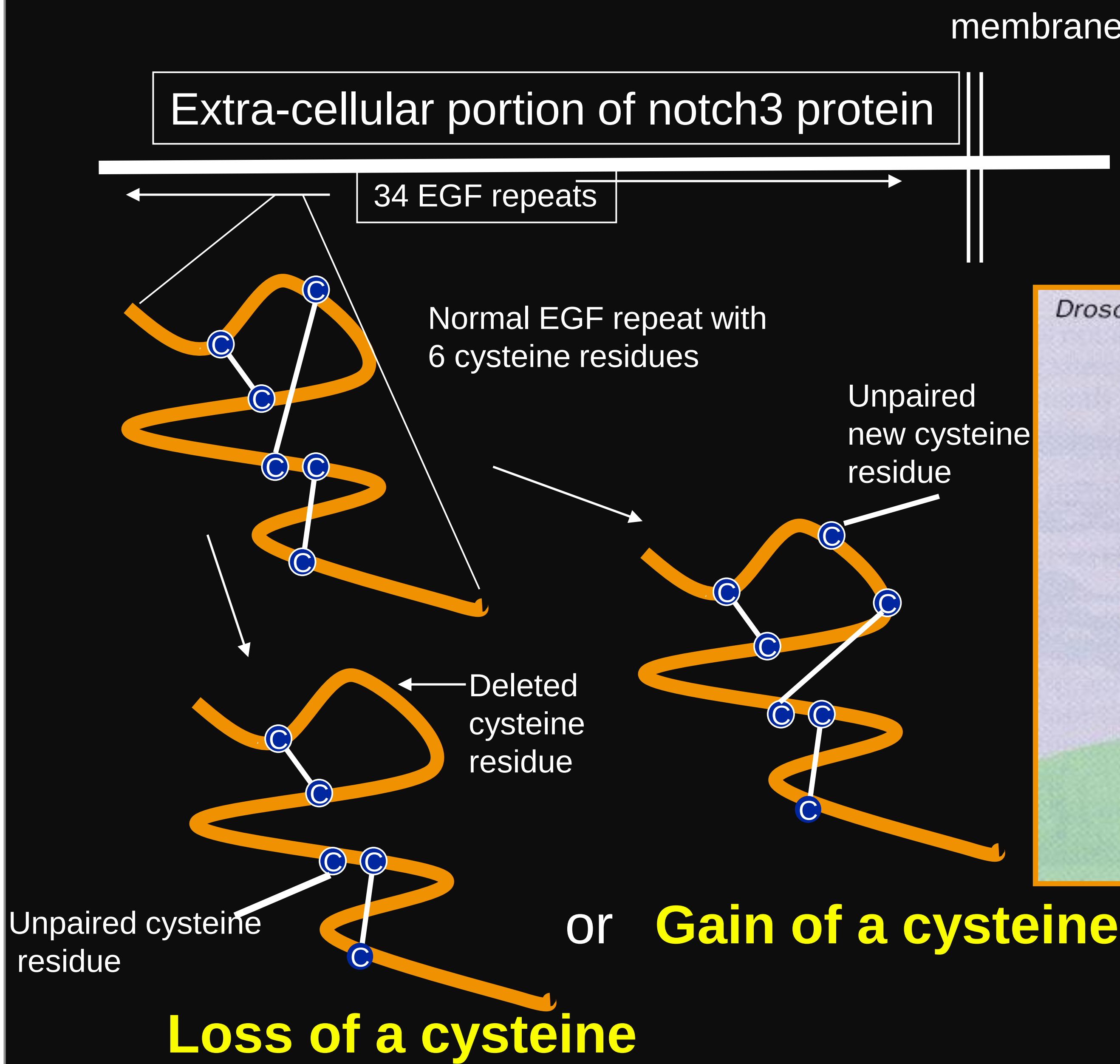
Autosomal Dominant Inheritance Pattern

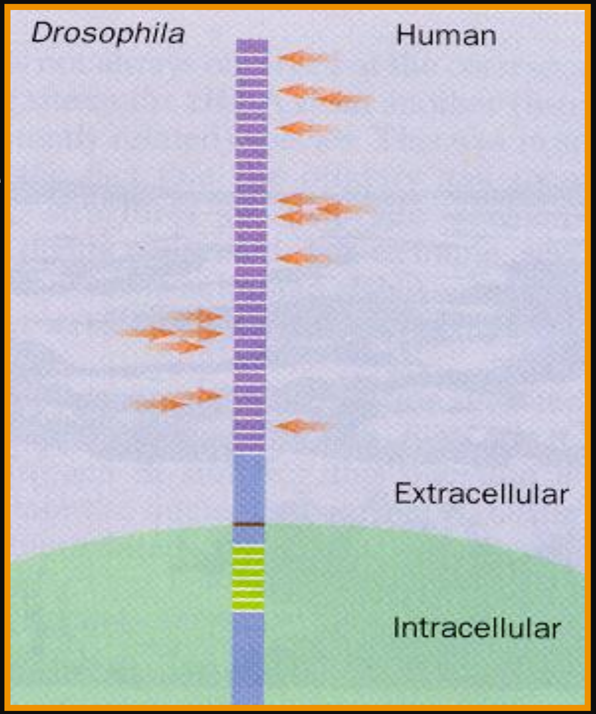


Autosomal dominant inheritance

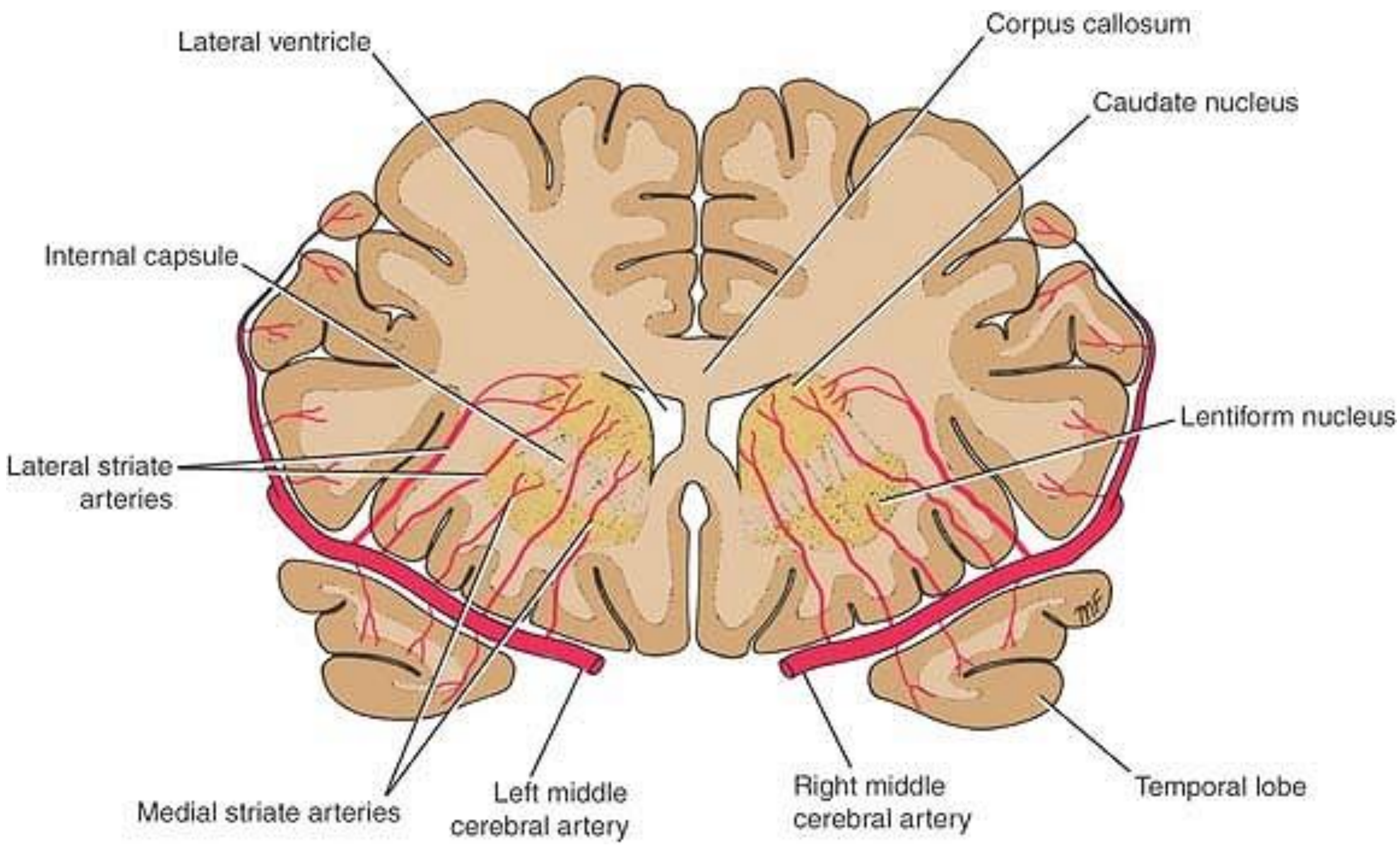


Notch 3

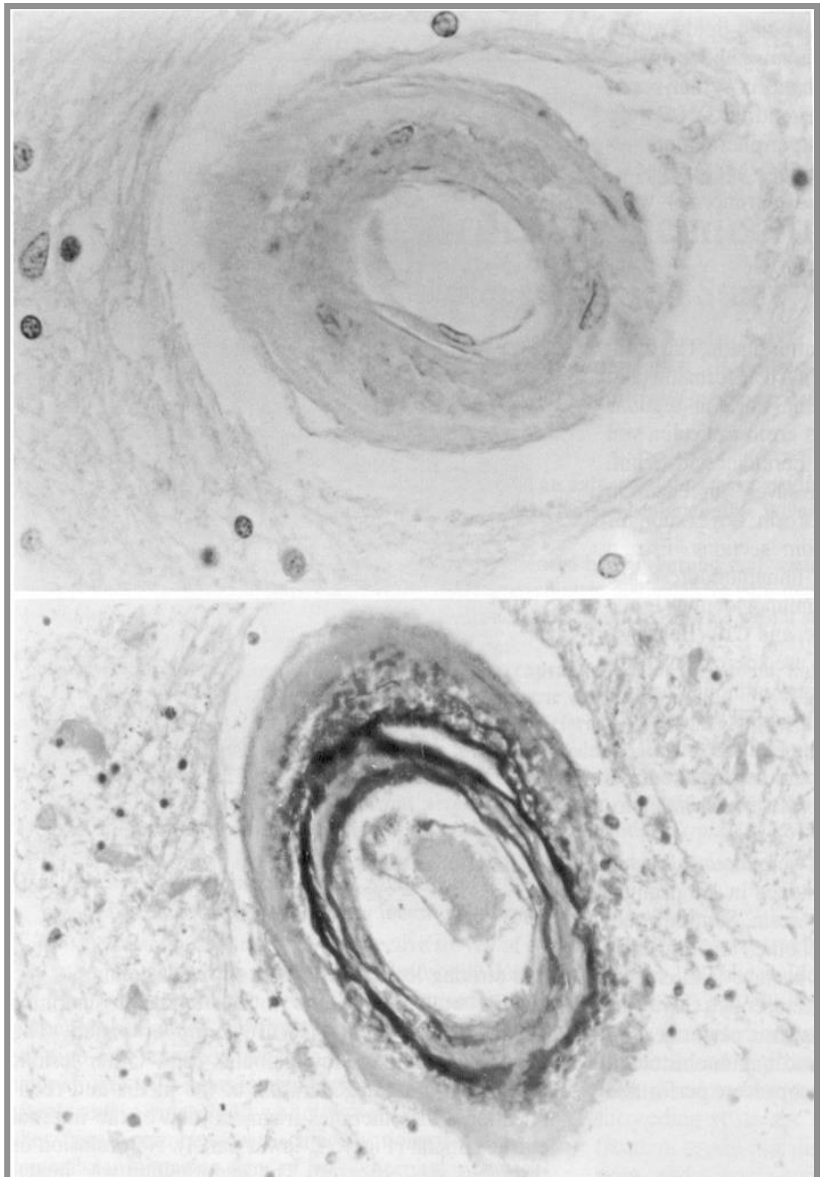

membrane
Extra-cellular portion of notch3 protein
34 EGF repeats
Normal EGF repeat with 6 cysteine residues
Unpaired new cysteine residue
Deleted cysteine residue
Unpaired cysteine residue
or Gain of a cysteine
Loss of a cysteine

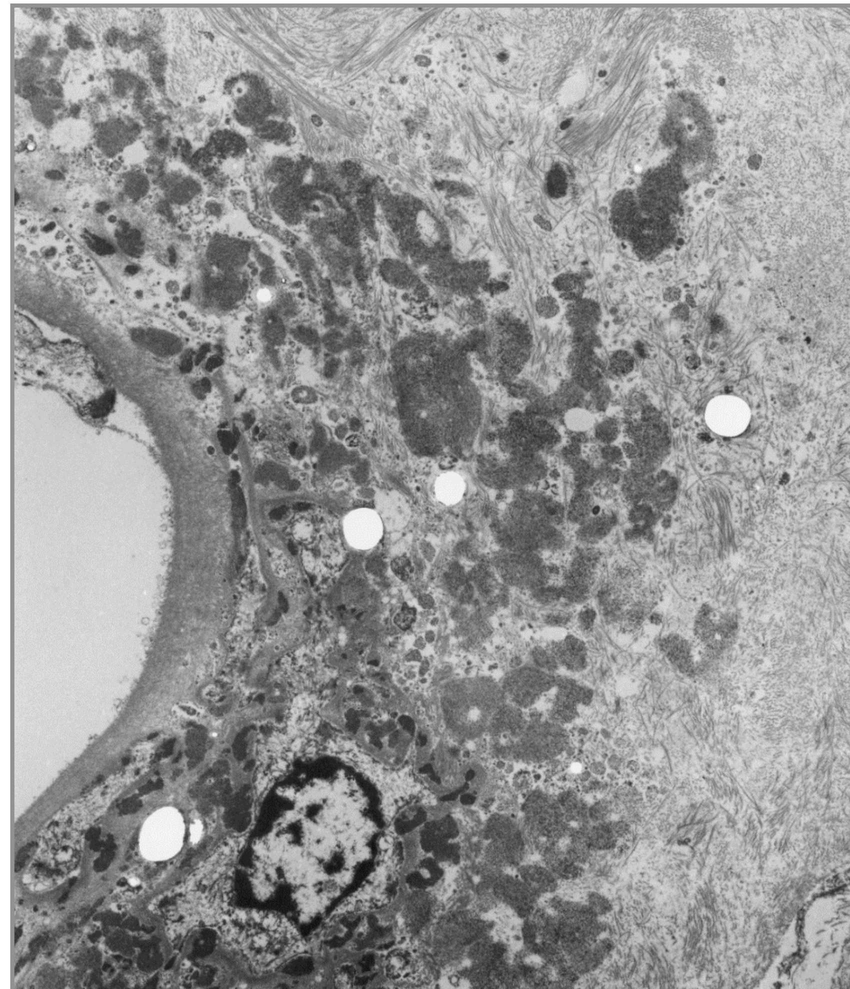

Drosophila
Human
Extracellular
Intracellular

A disease of the small perforating arteries

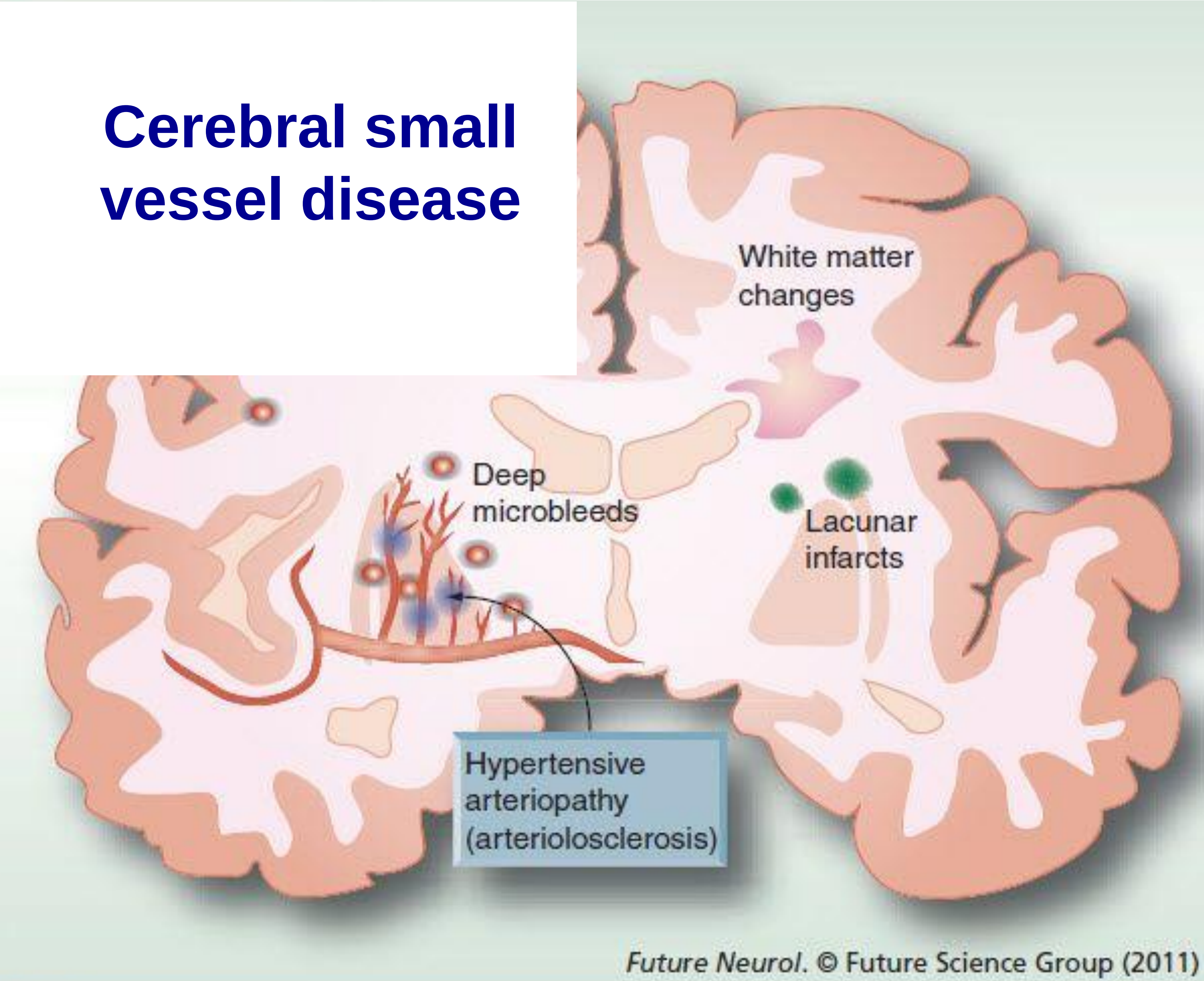


Abnormalities of the small vessel blood vessel (arteries) throughout the body but with more severe involvement of the brain arteries

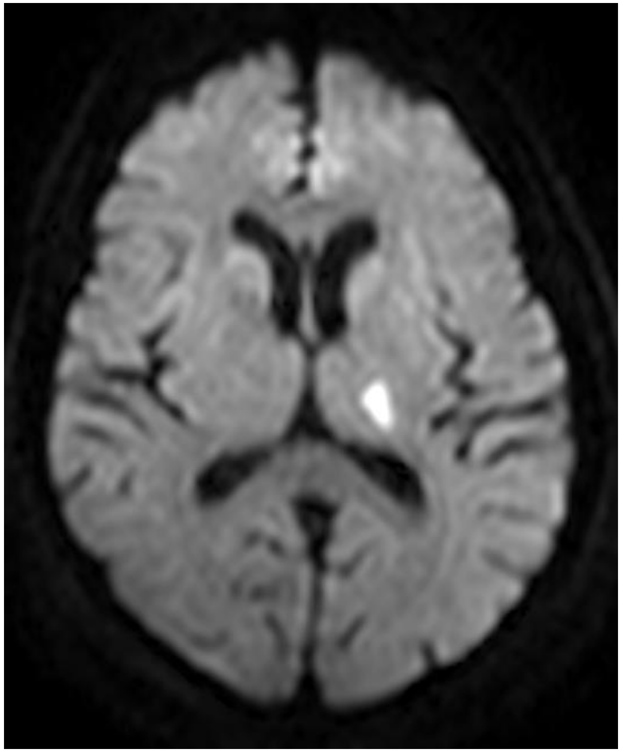




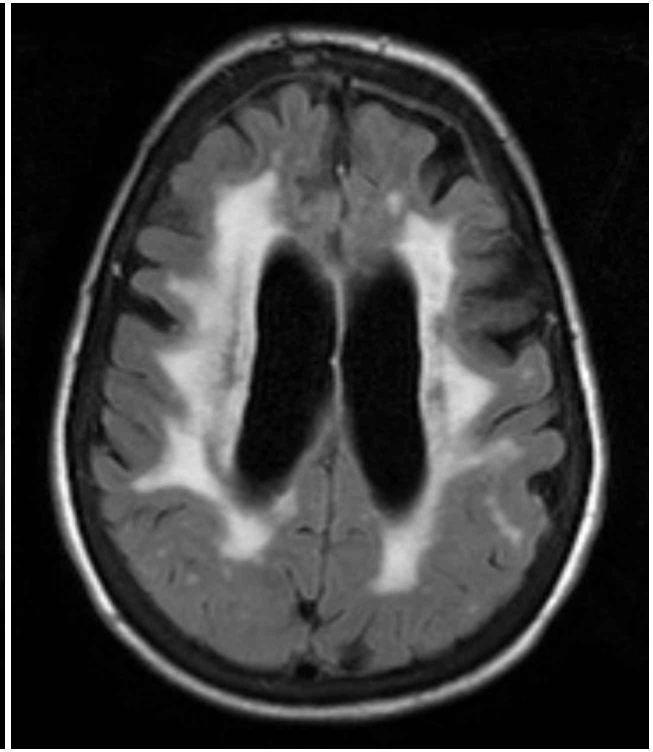
Cerebral small vessel disease



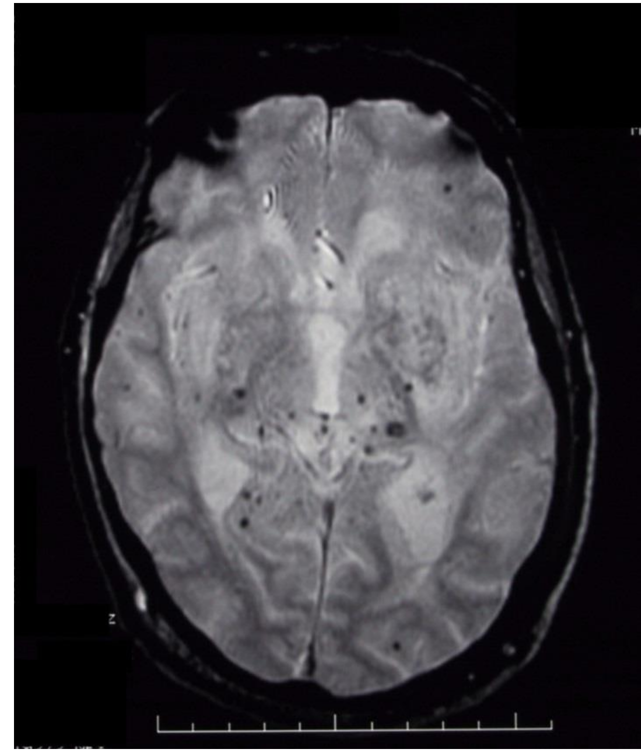
Small vessel disease



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

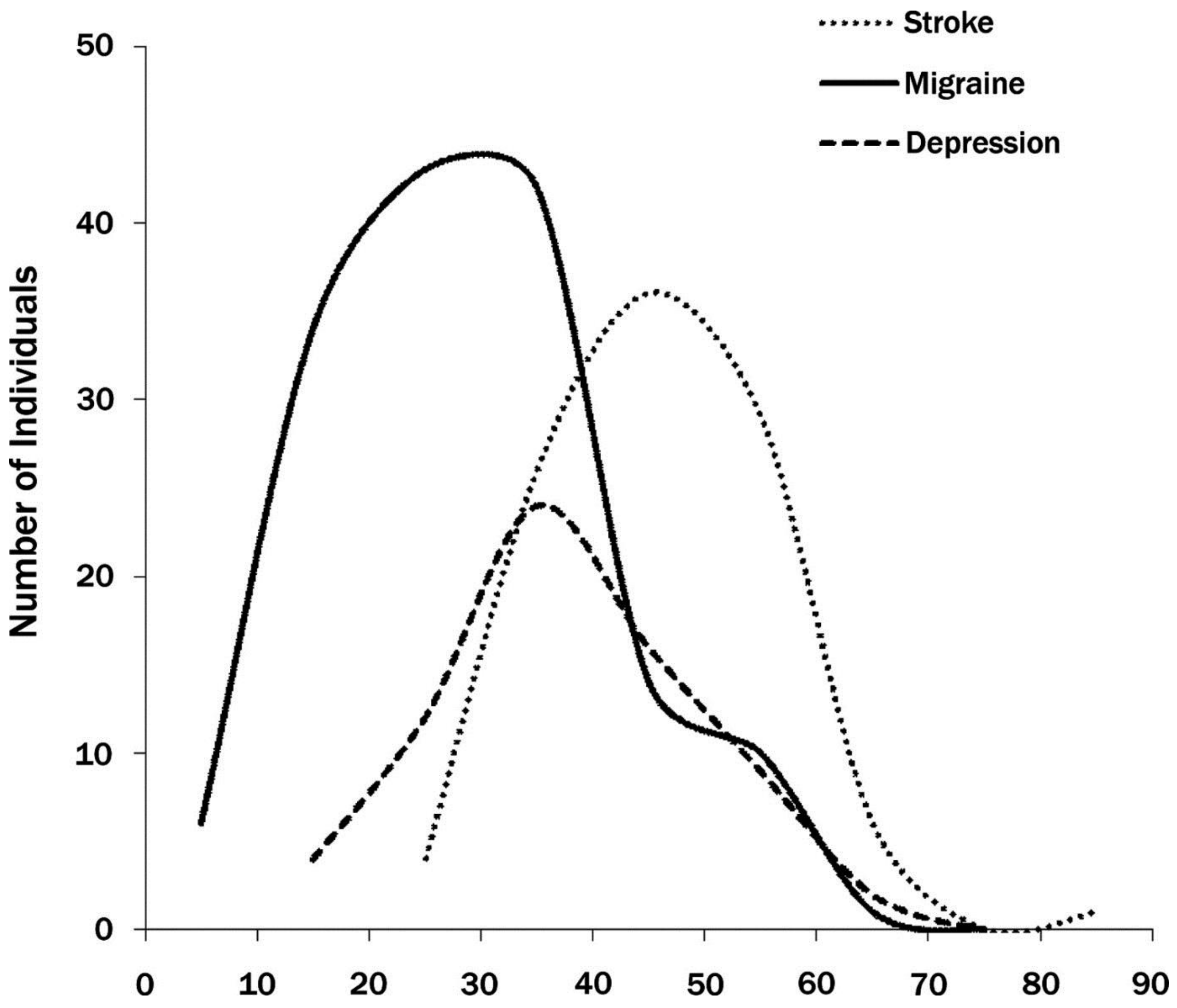
  8 families (2000)

  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



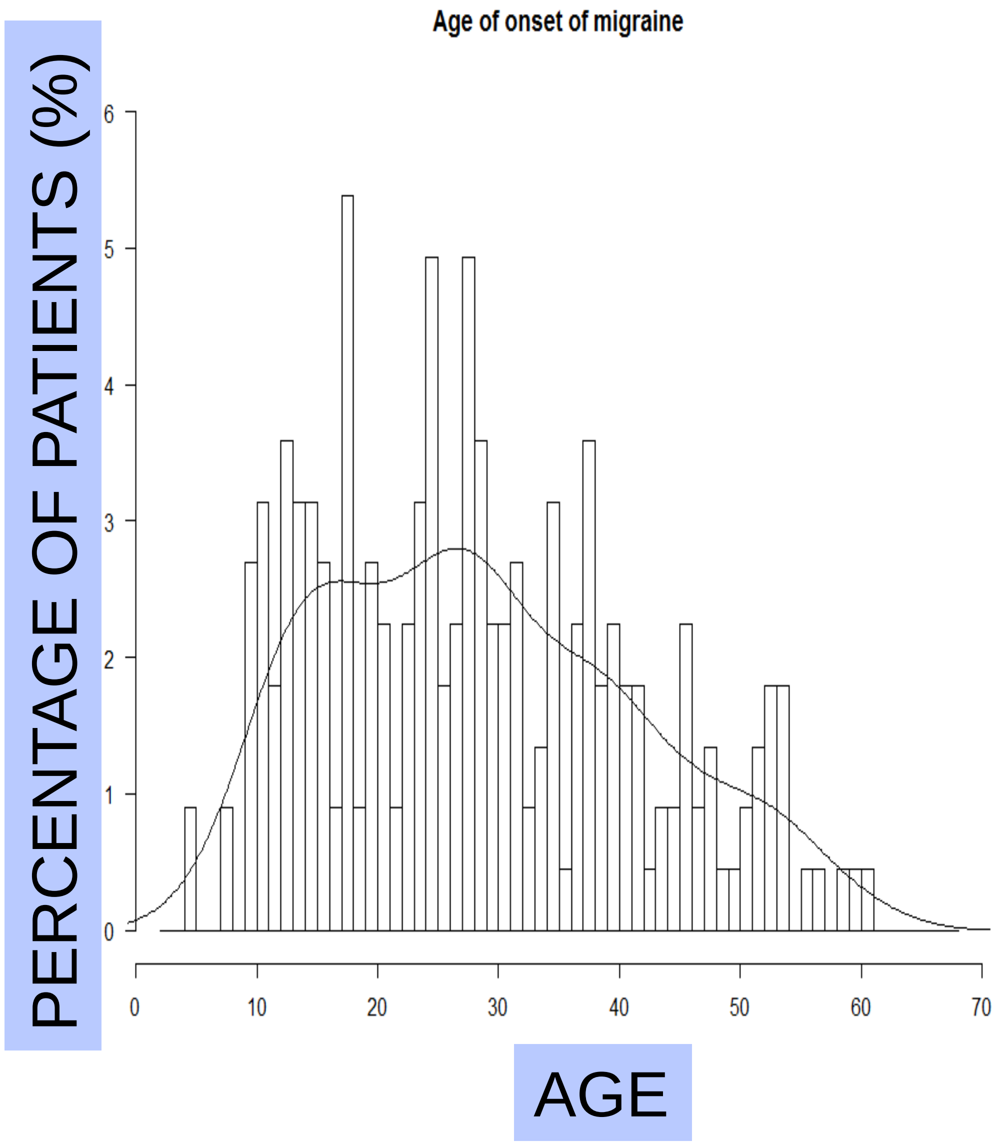
Adib-Samii, P. et al. Stroke 2010;41:630-634

But we do seem to see increased number of people with mildly symptoms in their 60s and 70s

? why

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



TYPES OF MIGRAINE AURA

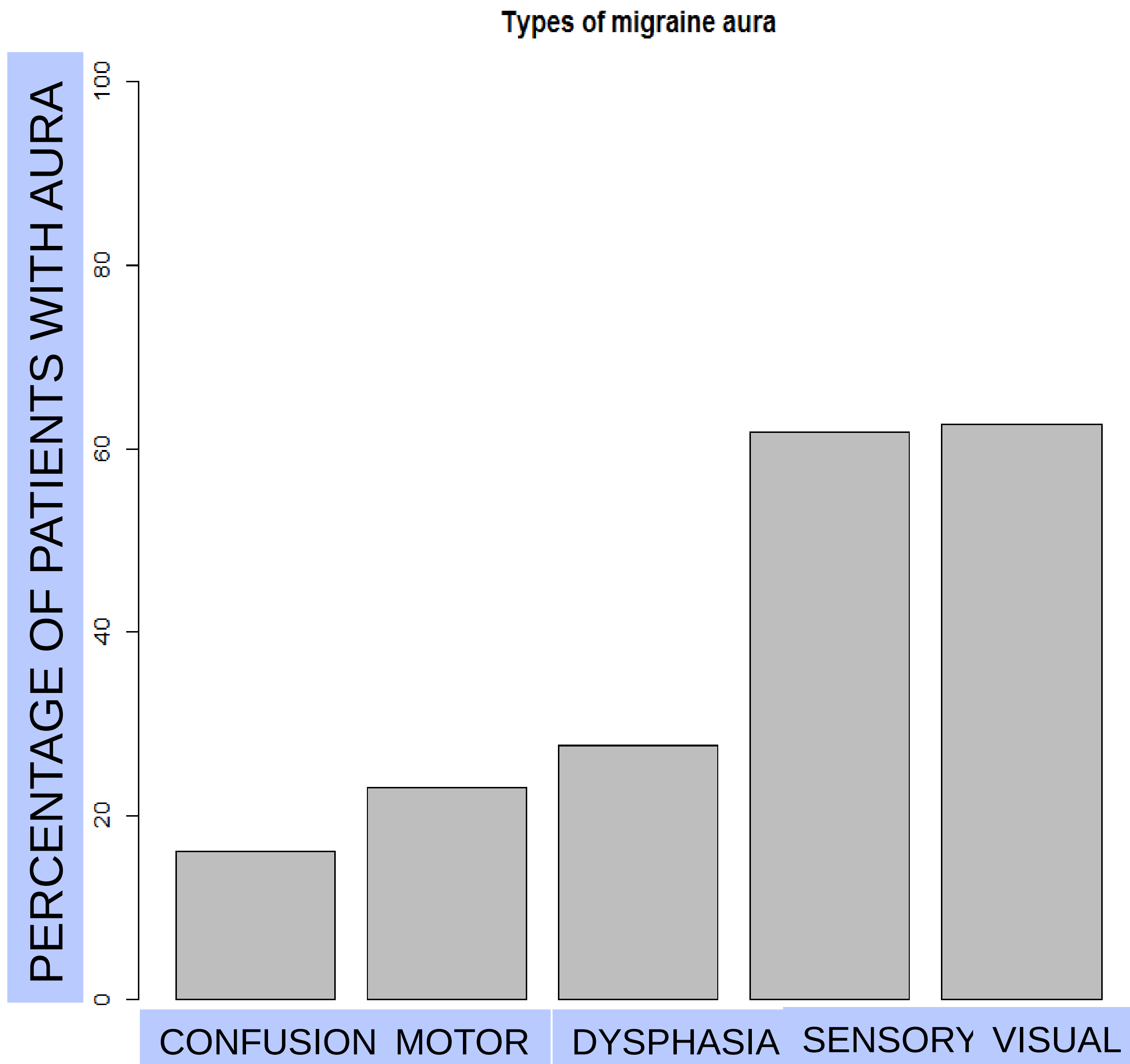
MIGRAINE TYPES

Of 225 patients with migraine,

89.8% experience aura

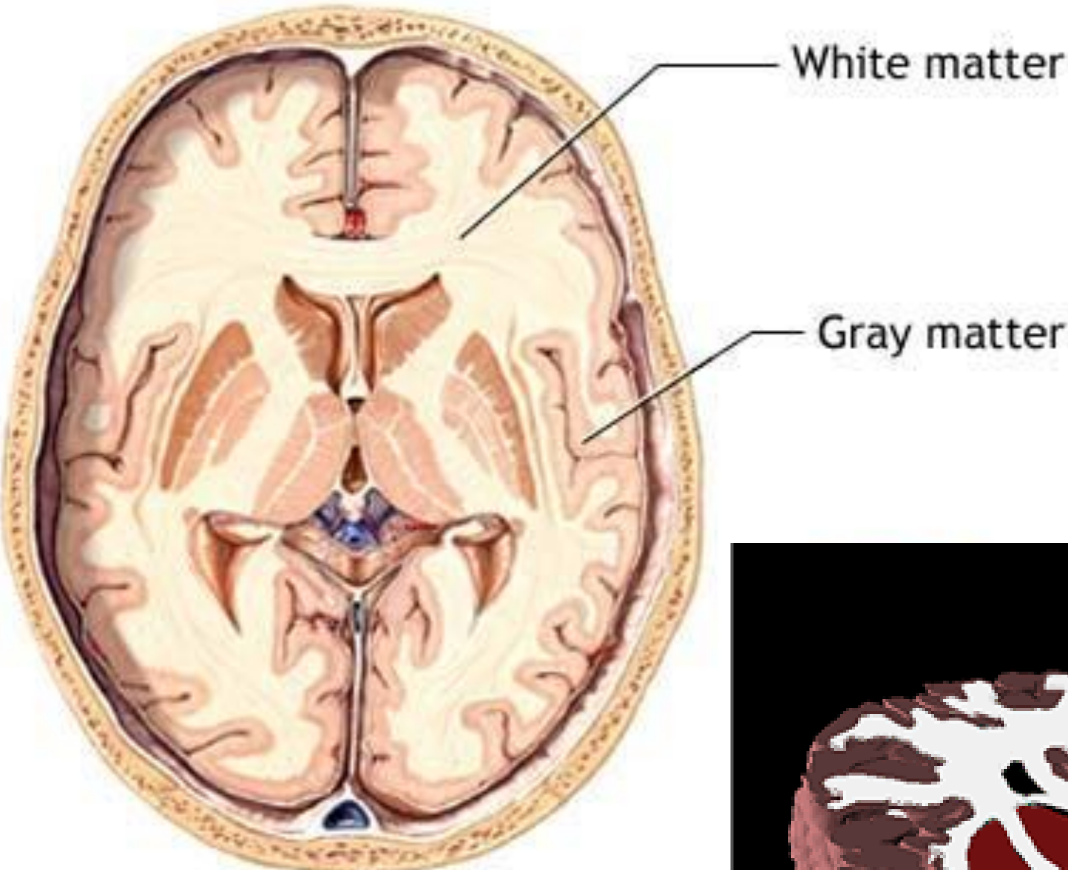
Of those with aura:

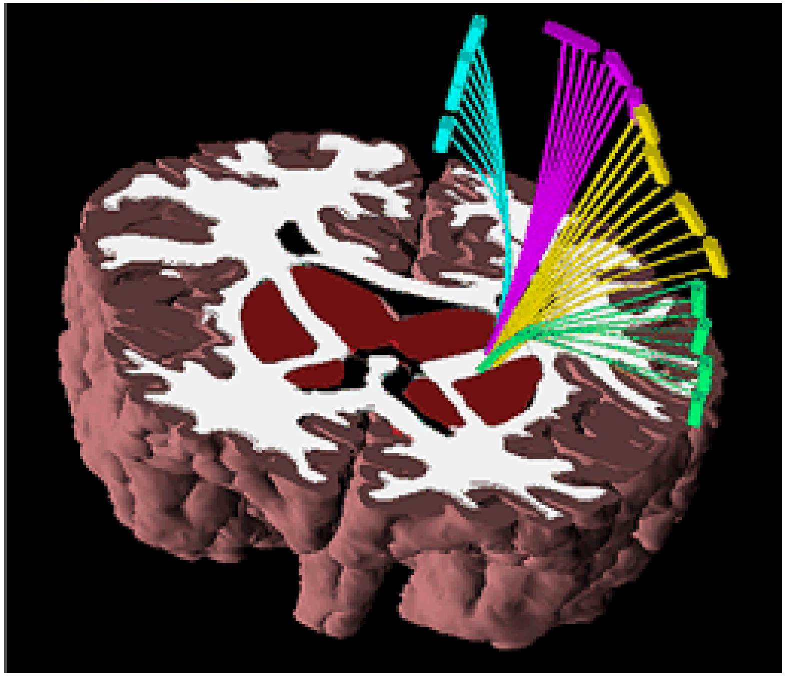
2 aura types	70
3 aura types	78
4 aura types	46
5 aura types	8

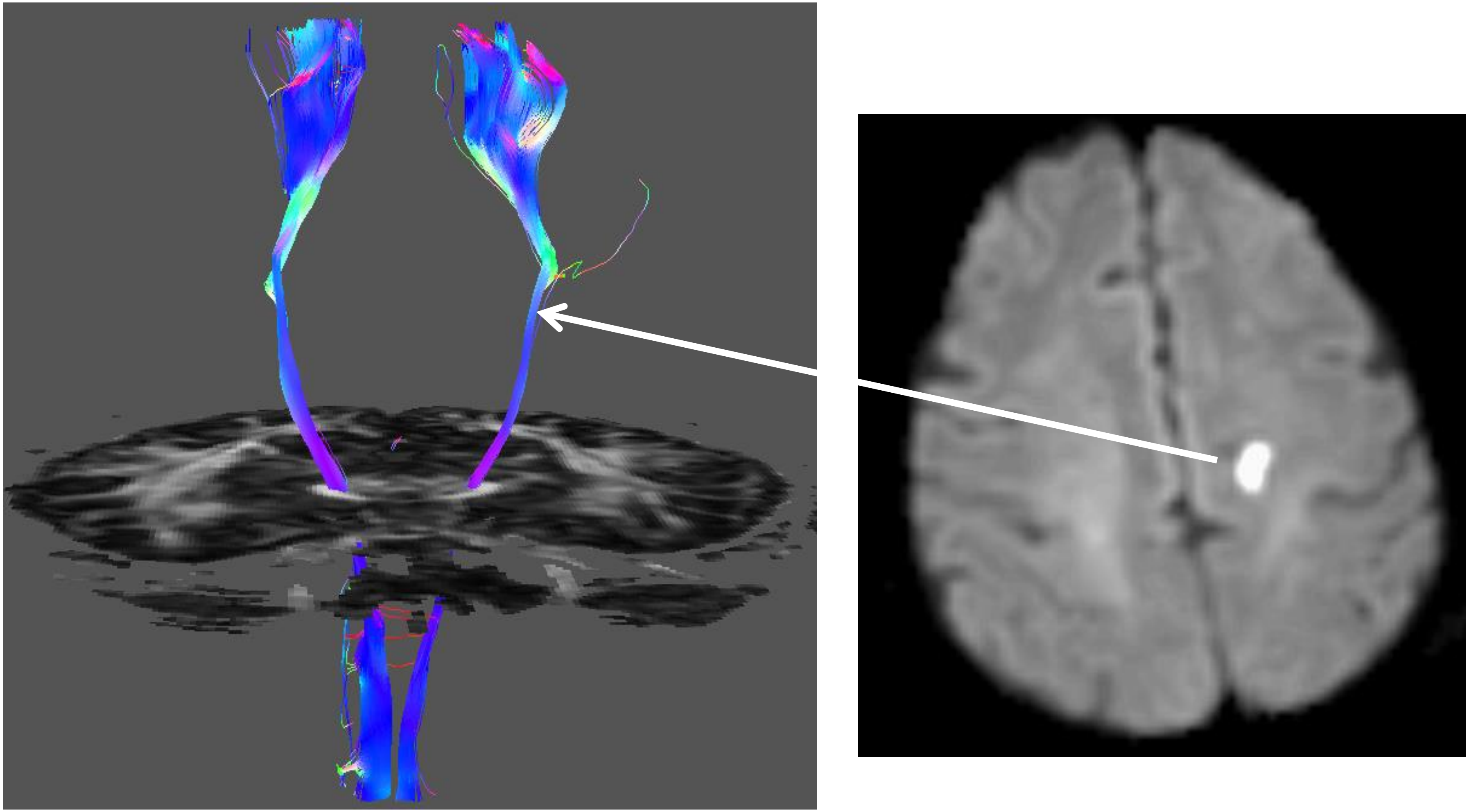


Stroke in CADASIL

- 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

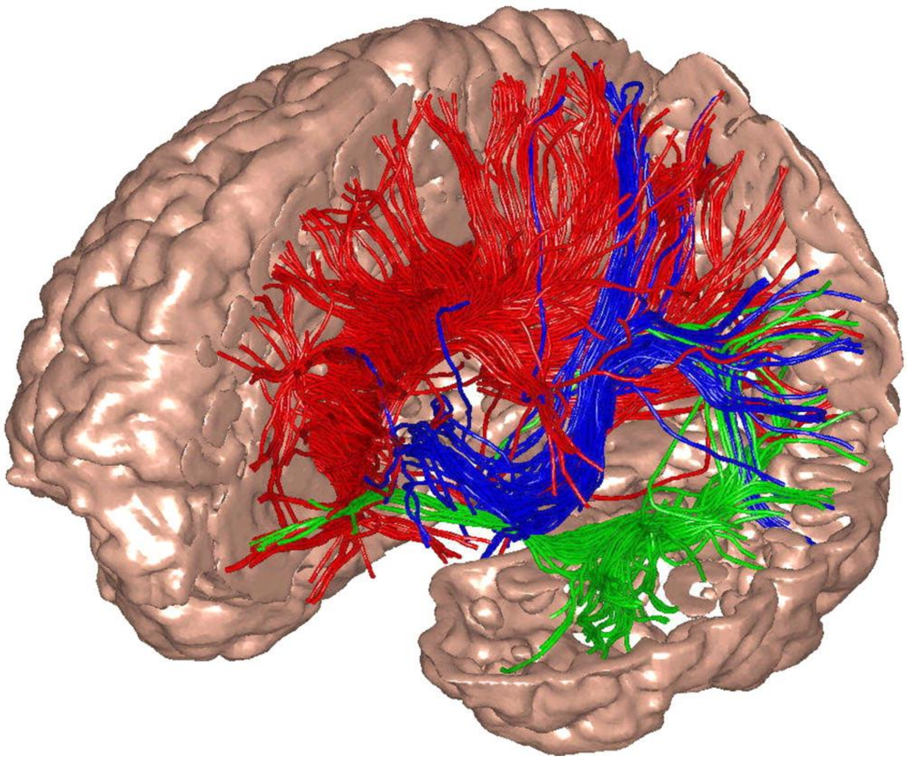
Stroke in CADASIL

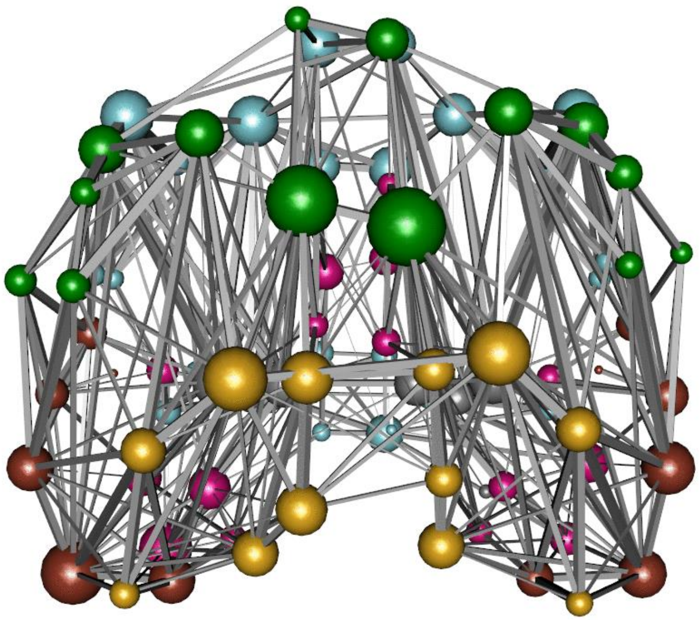
- Lacunar strokes
    - Pure motor stroke- weakness down one side
    - Pure sensory stroke- loss of sensation down one side
    - Sensorimotor stroke – weakness and sensory loss down one side
  - Higher cortical functions (eg speech production) rarely affected

Cognitive impairment

- Can occur from middle age on
- Very different from AD like dementia which affects the cortex
- Typically affects subcortical structures and disrupts connections within the brain
- Slowed processing
- “Executive dysfunction” – planning, organisation, multitasking

Brain network analysis





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

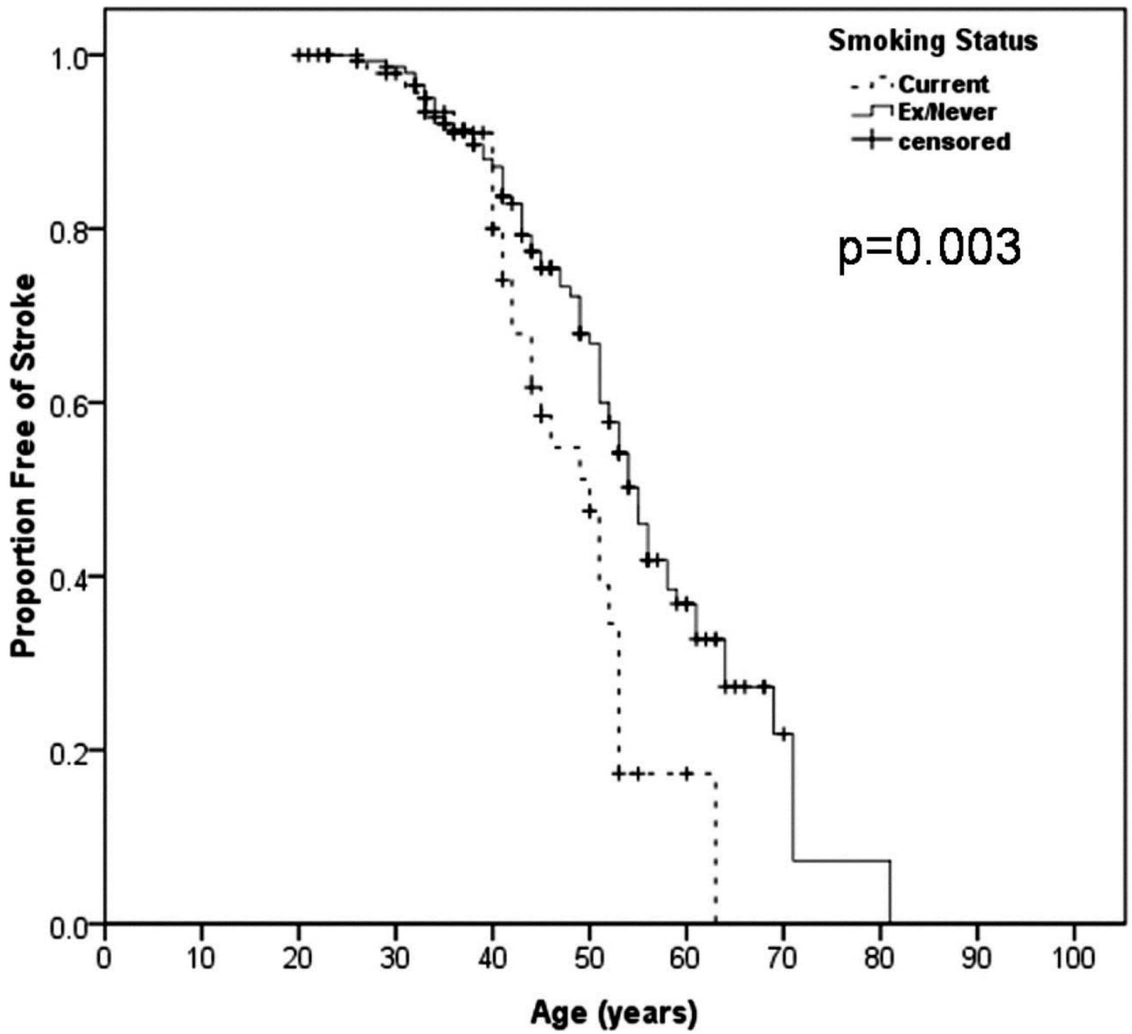
Other features

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

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 following may be important:
    - Other stroke risk factors: smoking, high blood pressure
    - Other genes modulating the effect of the notch 3 mutation

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



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Stroke

High blood pressure and smoking associated with worse disease

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%
*$P<0.01$, †$P<0.02$.

Adib-Sameii Stroke 2010

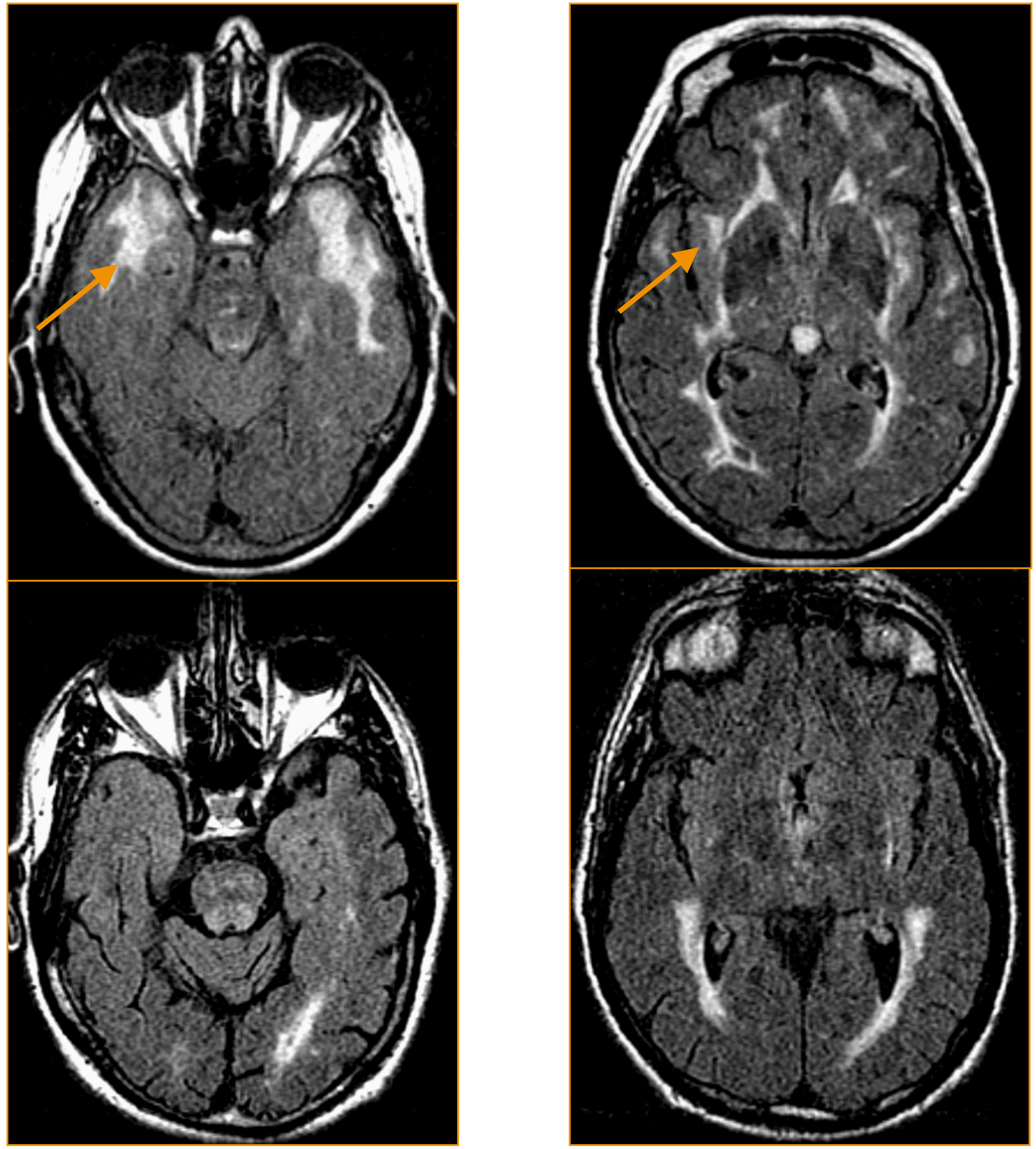
How do you make the diagnosis of CADASIL?

CADASIL

Sporadic SVD

CADASIL

Sporadic SVD

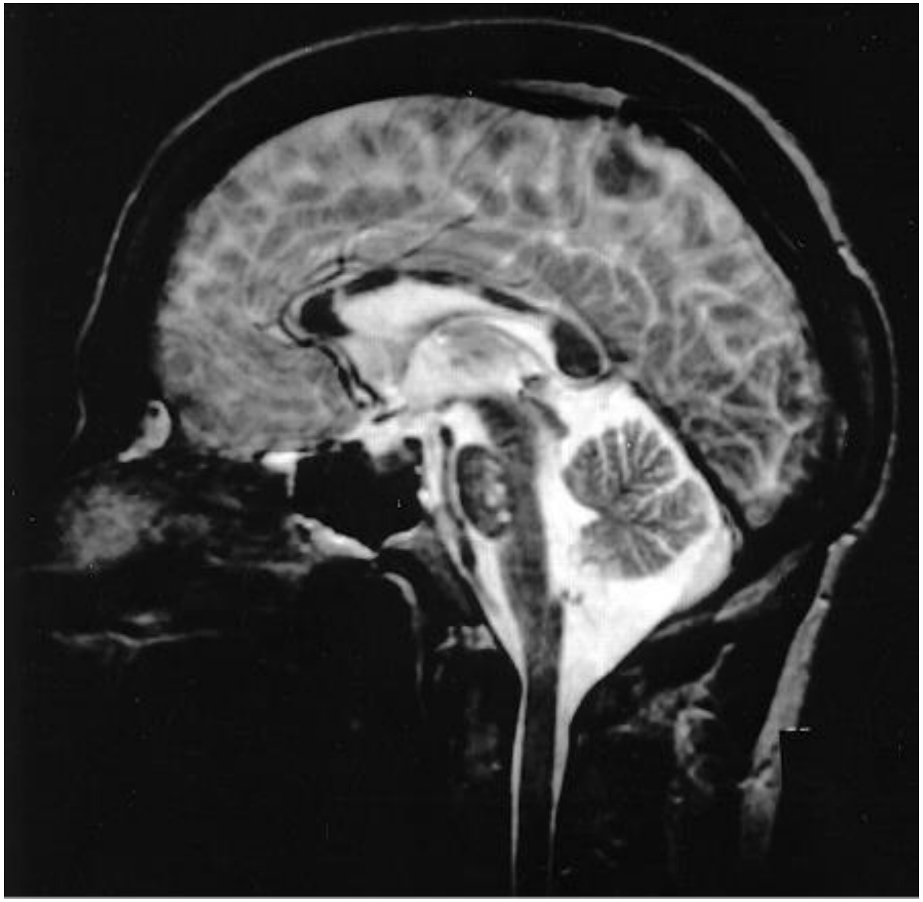


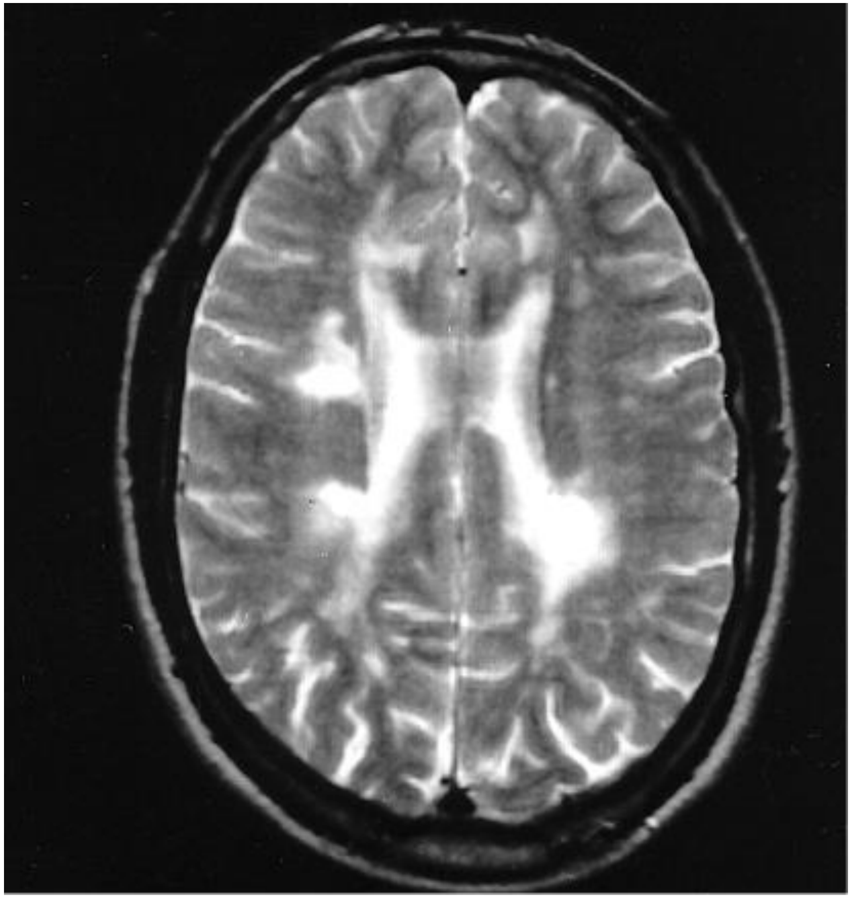
Sensitivity 91%
Specificity 86%

Sensitivity 93%
Specificity 45%

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

Corpus Callosum involvement

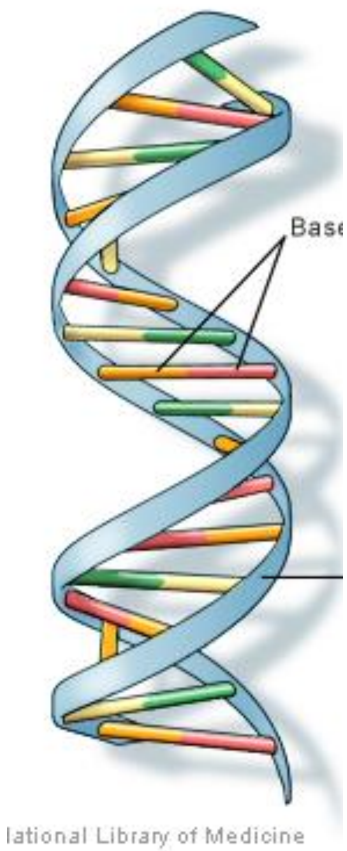


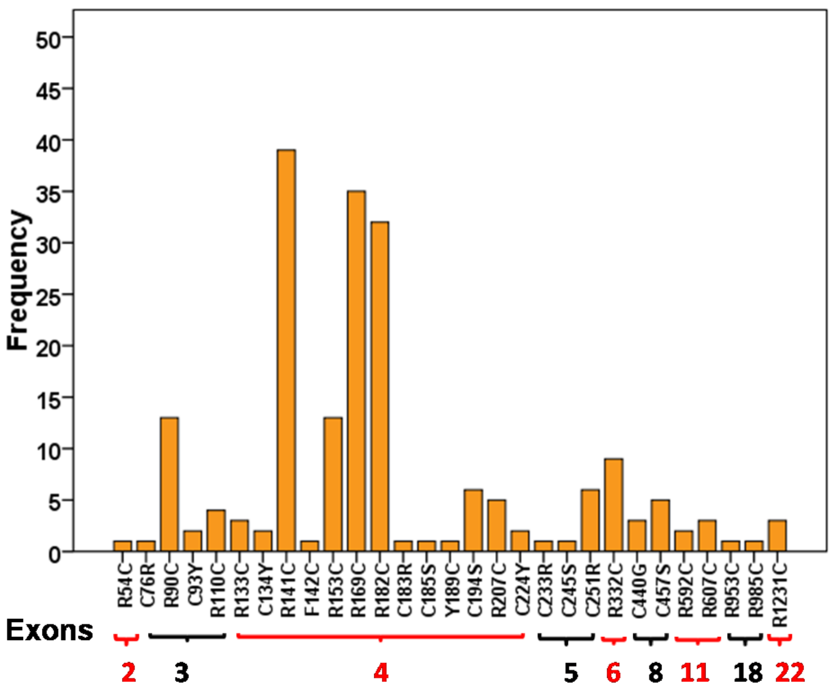


Leads to misdiagnosis of CADASIL as Multiple Sclerosis

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

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

CADASIL management

Treatment of complications

- **Migraine**
  - Avoid triggers
  - Acute episode
    - Painkillers and anti-emetics
    - Triptans eg Imigran
  - Prevention
    - Variety of agents

- **Depression**
  - CBT / counselling
  - Anti-depressants

CADASIL management

- Genetic counselling
- Pre-natal testing

www.cadasil.co.uk