CADASIL

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Overview

CADASIL is the most common monogenic cause of cerebral small vessel disease (CSVD) and of hereditary stroke in adults. It is caused by heterozygous, cysteine-altering variants in *NOTCH3* and is characterised by recurrent subcortical ischaemic events, migraine with aura, mood disturbance, apathy and progressive cognitive decline leading to subcortical dementia. The arteriopathy is systemic, but clinical manifestations are almost exclusively cerebral.

- **Inheritance:** autosomal dominant; near-complete but age-dependent penetrance in familial cases. De novo variants are rare.
- **Clinical prevalence:** estimated 2–5 per 100,000 (e.g. ~4/100,000 in the West of Scotland). Under-diagnosis is likely.
- **Population frequency:** cysteine-altering *NOTCH3* variants occur in roughly 1 in 300–450 people in large population databases (gnomAD, UK Biobank), most with a much milder phenotype — CADASIL is a spectrum rather than a uniformly severe disease.
- **Historical milestones:** first family described by van Bogaert (1955); acronym coined by Tournier-Lasserve et al. (1993) after linkage to chromosome 19q12; *NOTCH3* identified as the causal gene by Joutel et al. (1996).

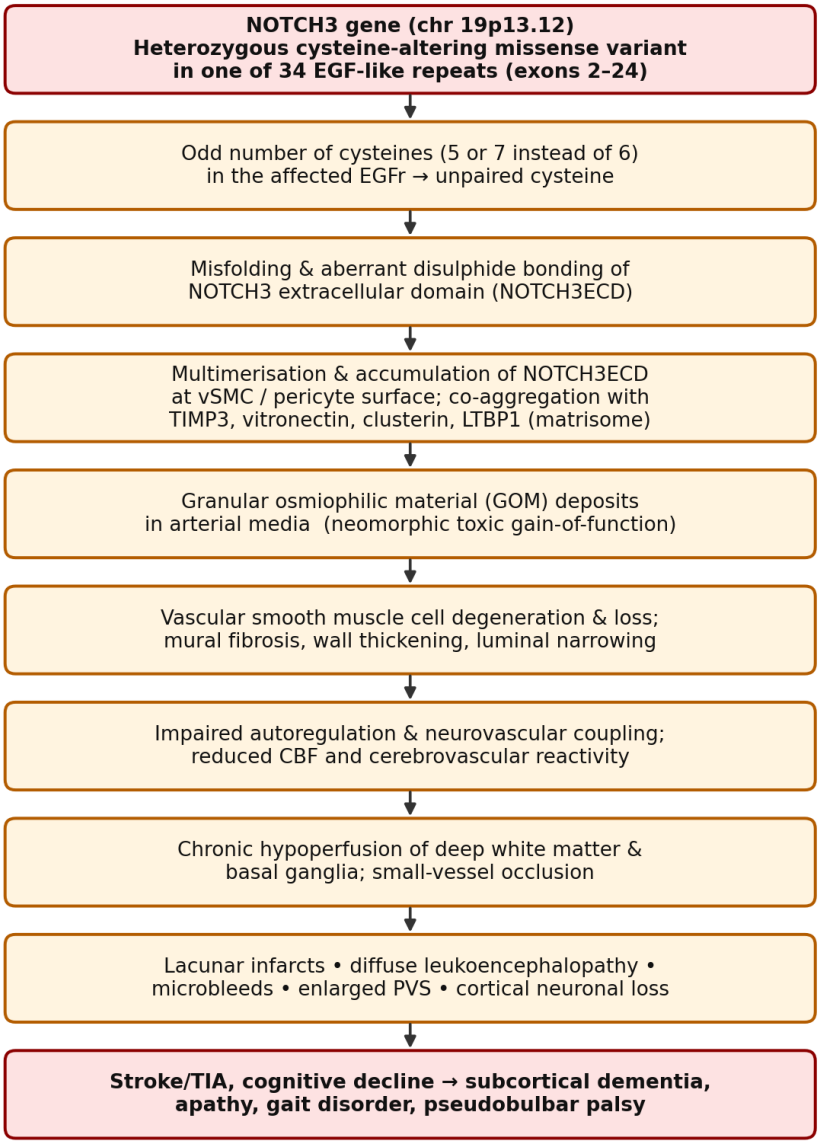
Genetics

- *NOTCH3* on **chromosome 19p13.12**; 33 exons; encodes a 2321-amino-acid single-pass transmembrane receptor expressed predominantly in **vascular smooth muscle cells (vSMCs) and pericytes**.
- The extracellular domain (NOTCH3ECD) contains **34 epidermal growth factor-like repeats (EGFr)**, encoded by **exons 2–24**, each with **six cysteine residues** forming three disulphide bonds.
- **Pathogenic hallmark:** a missense variant (or small in-frame deletion/duplication, or splice-site variant) that **creates or removes a cysteine** within an EGFr, leaving an **odd number of cysteines (5 or 7)**.
- **Hotspot:** exon 4 harbours up to ~40–70% of variants in European series; exons 2–6 together account for the majority. Screening restricted to hotspot exons is no longer adequate.
- **Genotype–phenotype:** variants in **EGFr 1–6** are associated with earlier stroke onset, greater WMH burden and shorter survival than those in **EGFr 7–34** (Rutten et al., 2019). EGFr 7–34 variants dominate among asymptomatic population carriers.
- **Founder / regional variants:** p.Arg544Cys (EGFr 14, exon 11) is common in Taiwan (Chinese Han) and associated with late onset and less temporal pole involvement; p.Arg75Pro (a cysteine-sparing variant) is reported from Korea and Japan.
- **Cysteine-sparing variants:** a small number have been reported with GOM; their pathogenicity must be interpreted cautiously and ideally supported by skin biopsy and segregation.
- **Loss-of-function / truncating variants** do not cause classical CADASIL (NOTCH3 haploinsufficiency is not the mechanism); biallelic loss-of-function causes a distinct recessive leukoencephalopathy/arteriopathy.

Pathogenesis

The disease is caused by a **neomorphic (toxic gain-of-function)** effect of the mutant ectodomain rather than loss of canonical NOTCH3 signalling. The unpaired cysteine promotes aberrant intermolecular disulphide bonding, multimerisation and accumulation of NOTCH3ECD at the plasma membrane of vSMCs and pericytes, where it forms aggregates and recruits extracellular matrix proteins (TIMP3, vitronectin, clusterin, LTBP1,

HTRA1 sequestration). This perturbs matrisome homeostasis and TGF-β/Kv channel signalling, culminating in vSMC degeneration, wall fibrosis and luminal narrowing of small penetrating and leptomeningeal arteries.



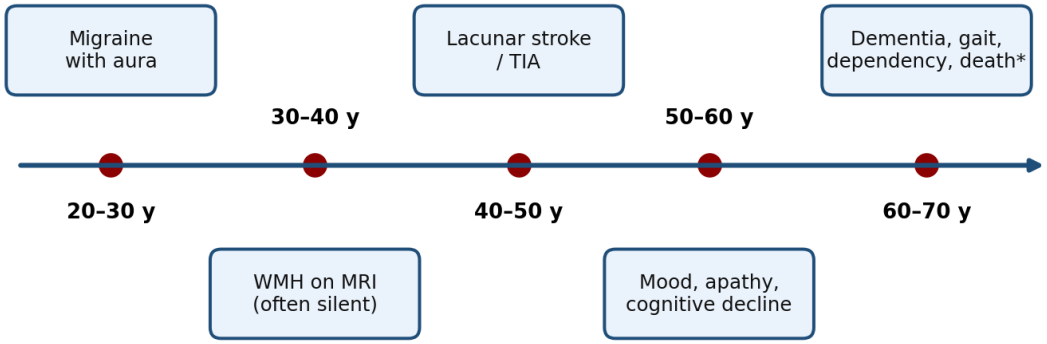
Flowchart 1. Pathogenic cascade from NOTCH3 variant to clinical phenotype.

Pathology

- **Gross:** diffuse white matter rarefaction, multiple lacunes in the white matter, basal ganglia, thalamus and pons; enlarged perivascular spaces; relative sparing of cortex and U-fibres early.
- **Microscopic:** thickened arteriolar walls with loss of vSMCs, PAS-positive granular material in the media, fibrosis and luminal stenosis ("non-amyloid, non-atherosclerotic angiopathy").
- **Ultrastructure: granular osmiophilic material (GOM)** — electron-dense deposits (~10–15 nm granules) in indentations of the vSMC membrane; pathognomonic.
- **Immunohistochemistry:** NOTCH3ECD accumulation in vessel walls using anti-NOTCH3 antibody (1E4).
- **Systemic:** deposits are found in skin, muscle, peripheral nerve, retinal, renal and cardiac vessels — the basis for skin biopsy diagnosis.

Clinical Features

Onset, severity and sequence vary widely even within families. The typical natural history is summarised below.



**Median age at death ~65–70 y (earlier in men and with EGFr 1–6 variants)*

Flowchart 2. Typical natural history of CADASIL (approximate ages).

Feature	Frequency	Key points
Migraine with aura	20–40%	Usually first symptom (mean onset ~30 y). Atypical/prolonged auras (basilar, hemiplegic, confusional); aura without headache common. More frequent in Europeans than Asians.
Ischaemic stroke / TIA	60–85%	Most frequent manifestation; mean onset 45–50 y. Classic lacunar syndromes (pure motor, ataxic hemiparesis, pure sensory). Recurrent; often without conventional risk factors.
Cognitive impairment	Up to 60% (dementia ~75% of those >60 y)	Executive dysfunction and slowed processing speed first; memory relatively preserved early. Stepwise or insidious progression to subcortical dementia.
Mood disturbance	20–30%	Depression most frequent; bipolar disorder, anxiety, psychosis occasionally.
Apathy	~40%	Independent of depression; strongly associated with disability.
Acute (CADASIL) encephalopathy	~10%	Confusion, reduced consciousness, seizures, fever; frequently evolves from a migraine aura; reversible over days–weeks.
Seizures	5–10%	Usually secondary to stroke or encephalopathy.
Intracerebral haemorrhage	Uncommon	Risk increased with microbleeds, hypertension, antithrombotics; more frequent in East Asian cohorts.
Late features	—	Gait disturbance, pseudobulbar palsy, urinary incontinence, parkinsonism; bedbound state.

Modifiers of severity

- Male sex, **smoking** and **hypertension** are associated with earlier stroke and greater disability.
- Variant location (EGFr 1–6 > 7–34).
- MRI markers predicting decline: **lacune count, brain atrophy (brain parenchymal fraction), microbleeds and reduced white-matter microstructural integrity on DTI (e.g. PSMD)** — lacunes and atrophy predict cognition better than WMH volume.
- Pregnancy and the puerperium may precipitate migraine aura and stroke.

Neuroimaging

MRI is abnormal in virtually all symptomatic patients and in carriers from around 35 years; WMH may precede symptoms by 10–15 years.

MRI finding	Characteristic features
White matter hyperintensities	Symmetric, periventricular and deep, becoming confluent. Early sites: **anterior temporal poles** and **external capsules**, periventricular frontal regions and **superior frontal gyri**.
Anterior temporal pole involvement	Sensitivity ~90%, specificity ~100% vs sporadic SVD in European cohorts (O'Sullivan 2001); less frequent in East Asian patients (p.Arg544Cys).
External capsule / corpus callosum	External capsule sensitivity ~90% but lower specificity; corpus callosum involvement also typical.
Lacunes	Centrum semiovale, basal ganglia, thalamus, pons; strongest imaging correlate of disability and cognition.
Cerebral microbleeds (SWI)	25–70%; thalamus, subcortical and brainstem; increase with age, BP and ICH risk.
Enlarged perivascular spaces	Prominent in basal ganglia and temporal subcortical white matter ("temporal lacunes").
Others	Cortical microinfarcts, subcortical atrophy, secondary cortical thinning; recent small subcortical infarcts on DWI.
Advanced techniques	DTI (PSMD) as a sensitive progression marker; reduced cerebrovascular reactivity on perfusion imaging; normal large vessels on MRA/CTA.

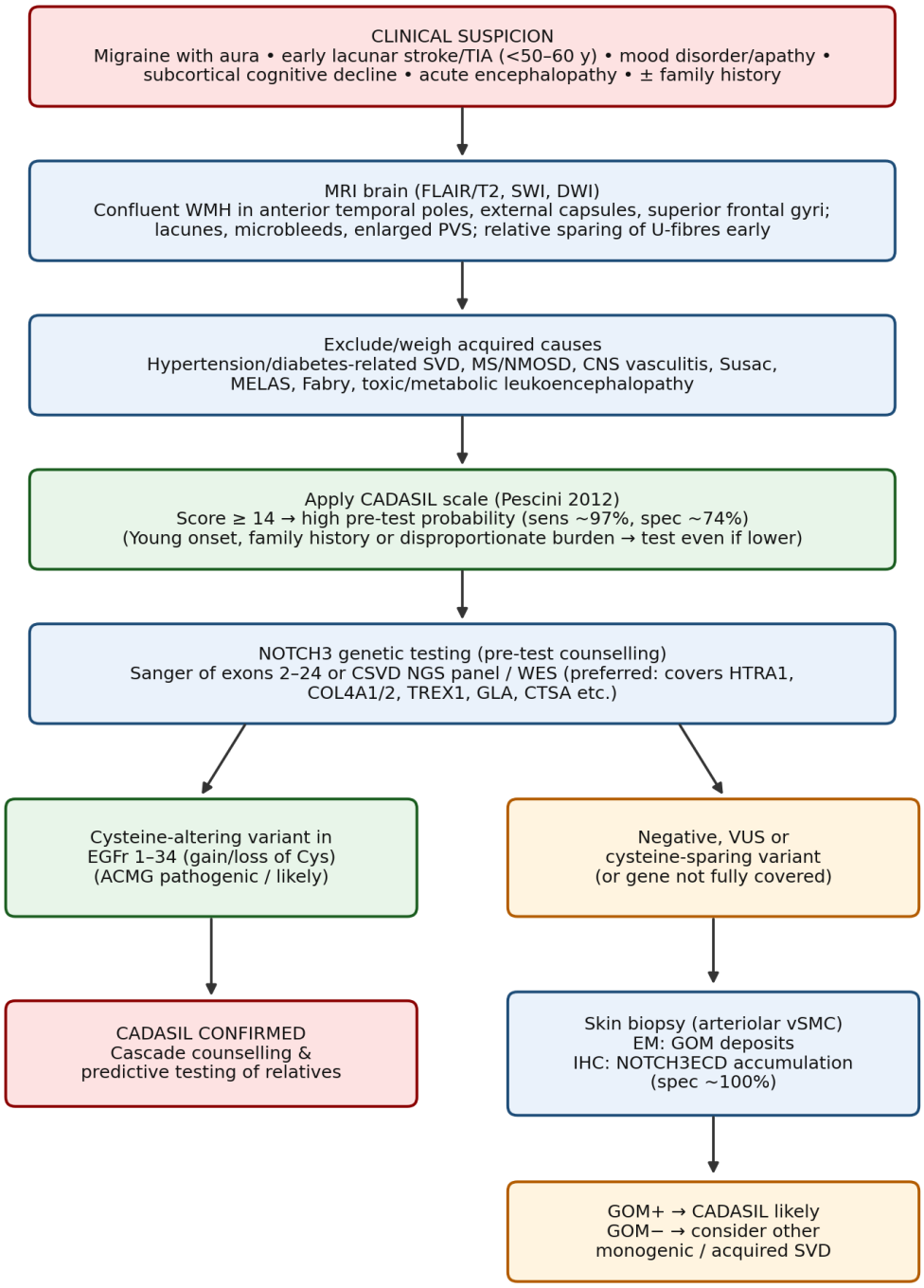
Diagnosis

CADASIL scale (Pescini et al., 2012)

A 12-item clinical–radiological screening scale (family history, migraine and its onset age, TIA/stroke and onset age, psychiatric disturbance, cognitive decline, leukoencephalopathy and its extension to the temporal poles and external capsule, subcortical infarcts, and absence of vascular risk factors). A score **≥14** identifies patients who should undergo genetic testing (sensitivity 96.7%, specificity 74.2%). A modified version has been proposed for Asian populations.

Diagnostic confirmation

- **Genetic testing (gold standard):** identification of a heterozygous cysteine-altering variant in one of the 34 EGFr of *NOTCH3*. Sanger sequencing of exons 2–24, or preferably a CSVD gene panel / exome (NGS), which simultaneously screens mimics. Sensitivity approaches 100%.
- **Skin biopsy:** electron microscopy for **GOM** (specificity ~100%; sensitivity 45–100% depending on sampling and expertise) and/or NOTCH3ECD immunostaining (sensitivity ~85–96%). Indicated for VUS, cysteine-sparing variants, or negative genetics with strong suspicion.
- **Genetic counselling** before and after testing; **predictive testing** of asymptomatic relatives follows Huntington disease–type protocols.



Flowchart 3. Diagnostic algorithm for suspected CADASIL.

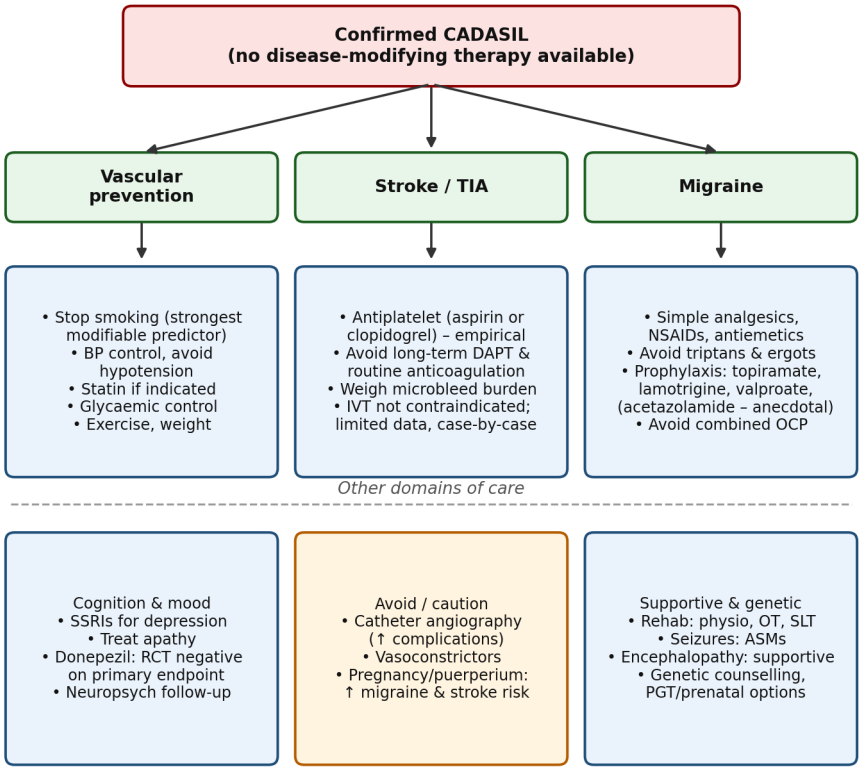
Differential Diagnosis

Condition	Gene / cause	Distinguishing features
CARASIL	*HTRA1* (biallelic)	Autosomal recessive; premature alopecia, spondylosis/lumbago, onset 20s–30s; arc sign in pons.
HTRA1 heterozygous CSVD	*HTRA1* (monoallelic)	AD, later onset; CADASIL-like MRI without temporal pole predominance; variable extra-neurological features.
COL4A1/COL4A2 disorders	*COL4A1/2*	Haemorrhagic strokes, porencephaly, infantile hemiparesis, retinal arteriolar tortuosity, cataract, HANAC (nephropathy, aneurysms, cramps).
RVCL-S	*TREX1* (C-terminal	Retinal vasculopathy, tumefactive contrast-enhancing

Condition	Gene / cause	Distinguishing features
	frameshift)	lesions, Raynaud's, hepatic/renal disease.
Fabry disease	*GLA* (X-linked)	Neuropathic pain, angiokeratomas, cornea verticillata, renal and cardiac disease; pulvinar T1 hyperintensity; enzyme/Lyso-Gb3.
CARASAL	*CTSA*	AD; late-onset; treatment-resistant hypertension, brainstem involvement.
MELAS	mtDNA (m.3243A>G)	Stroke-like lesions not respecting vascular territories, lactate peak, diabetes, deafness, short stature.
Multiple sclerosis	Acquired	Ovoid juxtacortical/periventricular lesions, Dawson fingers, spinal cord lesions, OCBs; lacunes absent.
Primary CNS vasculitis / Susac	Acquired	Enhancing lesions, CSF pleocytosis, angiographic changes; Susac: callosal snowballs, BRAO, hearing loss.
Sporadic hypertensive SVD / CAA	Acquired	Older age, vascular risk factors, lobar microbleeds/cSS in CAA; temporal poles usually spared.

Management

There is currently **no disease-modifying therapy**. Care is directed at vascular risk reduction, secondary stroke prevention, symptomatic treatment and genetic counselling. Recommendations are largely based on observational data and expert consensus (EAN guideline, Mancuso et al., 2020).



Flowchart 4. Management framework in confirmed CADASIL.

Key practical points

- **Antiplatelets:** aspirin or clopidogrel are used empirically after ischaemic stroke/TIA; no RCT evidence. Avoid long-term dual antiplatelet therapy; consider microbleed load.

- **Anticoagulation:** only for a separate indication (e.g. atrial fibrillation), with careful haemorrhage-risk assessment.
- **Thrombolysis:** CADASIL is not a formal contraindication to IV thrombolysis; data are limited to case series, and decisions should be individualised (microbleed burden).
- **Migraine:** triptans and ergot derivatives are generally avoided because of vasoconstriction; use simple analgesics/NSAIDs. Preventives: non-vasoactive agents (e.g. topiramate, lamotrigine, valproate); acetazolamide has anecdotal benefit for prolonged auras. CGRP monoclonal antibodies lack safety data in CADASIL.
- **Cognition:** a phase 2 RCT of donepezil (Dichgans et al., 2008) showed **no effect on the primary endpoint** (V-ADAS-cog), with modest improvement in executive measures.
- **Avoid:** conventional catheter angiography (higher rate of neurological complications), smoking, and hormonal contraception with oestrogen in patients with migraine with aura.
- **Encephalopathy:** supportive care, treat seizures; exclude infection, venous thrombosis and non-convulsive status.
- **Reproductive counselling:** 50% transmission risk; prenatal diagnosis and pre-implantation genetic testing (PGT-M) are options.

Experimental and emerging therapies

- **Antisense oligonucleotide–mediated exon skipping** to remove the EGFr containing the mutant cysteine (Rutten et al., 2016).
- **Immunotherapy** with antibodies targeting NOTCH3ECD (e.g. 5E1) to prevent/clear deposits in mouse models (Machuca-Parra et al., 2017; Ghezali et al., 2018).
- Agonist antibodies to NOTCH3, and approaches targeting TIMP3/Kv-channel dysregulation, remain preclinical.

Prognosis

- Progressive disability; most patients become dependent in their 60s.
- Median age at death ~65–70 years (earlier in men); death often from aspiration pneumonia or complications of immobility.
- Wide variability: some carriers remain minimally symptomatic into the 70s, especially with EGFr 7–34 variants and without vascular risk factors.

High-Yield Points

- Most common monogenic CSVD; autosomal dominant; *NOTCH3* on chromosome 19p13.12.
- Hallmark variant: gain or loss of a cysteine in one of 34 EGFr (exons 2–24) → odd number of cysteines.
- Toxic gain-of-function via NOTCH3ECD aggregation, not haploinsufficiency.
- Classic tetrad: migraine with aura, subcortical ischaemic events, mood disturbance/apathy, cognitive decline.
- Anterior temporal pole and external capsule WMH are the imaging signatures (less so in East Asians).
- GOM on electron microscopy of skin biopsy is pathognomonic.
- CADASIL scale ≥14 → genetic testing.
- No disease-modifying therapy; stop smoking and control BP; avoid triptans and catheter angiography.
- EGFr 1–6 variants → more severe phenotype than EGFr 7–34.

References

1. Tournier-Lasserve E, Joutel A, Melki J, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. *Nat Genet*. 1993;3:256–259.
2. Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383:707–710.
3. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. CADASIL. *Lancet Neurol*. 2009;8:643–653.
4. Chabriat H, Joutel A, Tournier-Lasserve E, Bousser MG. CADASIL: yesterday, today, tomorrow. *Eur J Neurol*. 2020;27:1588–1595.
5. Di Donato I, Bianchi S, De Stefano N, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) as a model of small vessel disease: update on clinical, diagnostic, and management aspects. *BMC Med*. 2017;15:41.
6. Mancuso M, Arnold M, Bersano A, et al. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. *Eur J Neurol*. 2020;27:909–927.
7. Pescini F, Nannucci S, Bertaccini B, et al. The Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) Scale: a screening tool to select patients for NOTCH3 gene analysis. *Stroke*. 2012;43:2871–2876.
8. Rutten JW, Van Eijsden BJ, Duering M, et al. The effect of NOTCH3 pathogenic variant position on CADASIL disease severity: NOTCH3 EGFr 1–6 pathogenic variant are associated with a more severe phenotype and lower survival compared with EGFr 7–34 pathogenic variant. *Genet Med*. 2019;21:676–682.
9. Rutten JW, Dauwerse HG, Gravesteijn G, et al. Archetypal NOTCH3 mutations frequent in public exome: implications for CADASIL. *Ann Clin Transl Neurol*. 2016;3:844–853.
10. Cho BPH, Nannoni S, Harshfield EL, et al. NOTCH3 variants are more common than expected in the general population and associated with stroke and vascular dementia: an analysis of 200 000 participants. *J Neurol Neurosurg Psychiatry*. 2021;92:694–701.
11. O'Sullivan M, Jarosz JM, Martin RJ, et al. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. *Neurology*. 2001;56:628–634.
12. Tikka S, Mykkänen K, Ruchoux MM, et al. Congruence between NOTCH3 mutations and GOM in 131 CADASIL patients. *Brain*. 2009;132:933–939.
13. Dichgans M, Markus HS, Salloway S, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol*. 2008;7:310–318.
14. Tan RYY, Markus HS. CADASIL: migraine, encephalopathy, stroke and their inter-relationships. *PLoS One*. 2016;11:e0157613.
15. Razvi SSM, Davidson R, Bone I, Muir KW. The prevalence of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) in the west of Scotland. *J Neurol Neurosurg Psychiatry*. 2005;76:739–741.
16. Rutten JW, Dauwerse HG, Peters DJ, et al. Therapeutic NOTCH3 cysteine correction in CADASIL using exon skipping: in vitro proof of concept. *Brain*. 2016;139:1123–1135.
17. Machuca-Parra AI, Bigger-Allen AA, Sanchez AV, et al. Therapeutic antibody targeting of Notch3 signaling prevents mural cell loss in CADASIL. *J Exp Med*. 2017;214:2271–2282.
18. Ghezali L, Capone C, Baron-Menguy C, et al. Notch3ECD immunotherapy improves cerebrovascular responses in CADASIL mice. *Ann Neurol*. 2018;84:246–259.
19. Mizuta I, Watanabe-Hosomi A, Koizumi T, et al. New diagnostic criteria for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in Japan. *J Neurol Sci*. 2017;381:62–67.
20. Joutel A, Faraci FM. Cerebral small vessel disease: insights and opportunities from mouse models of collagen IV-related small vessel disease and CADASIL. *Stroke*. 2014;45:1215–1221.