Stroke

AHA SCIENTIFIC STATEMENT

Management of Inherited CNS Small Vessel Diseases: The CADASIL Example: A Scientific Statement From the American Heart Association

James F. Meschia, MD, FAHA, Chair; Bradford B. Worrall, MD, MSc, FAHA, Vice Chair; Fanny M. Elahi, MD, PhD; Owen A. Ross, PhD; Michael M. Wang, MD, PhD; Eric D. Goldstein, MD; Natalia S. Rost, MD, FAHA; Jennifer J. Majersik, MD, MS, FAHA; José Gutierrez, MD, MPH; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Hypertension

ABSTRACT: Lacunar infarcts and vascular dementia are important phenotypic characteristics of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, the most common inherited cerebral small vessel disease. Individuals with the disease show variability in the nature and onset of symptoms and rates of progression, which are only partially explained by differences in pathogenic mutations in the *NOTCH3* gene. Recognizing the disease early in its course and securing a molecular diagnosis are important clinical goals, despite the lack of proven disease-modifying treatments. The purposes of this scientific statement are to review the clinical, genetic, and imaging aspects of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, contrasting it with other inherited small vessel diseases, and to provide key prevention, management, and therapeutic considerations with the intent of reducing practice variability and encouraging production of high-quality evidence to support future treatment recommendations.

Key Words: AHA Scientific Statements ■ cerebral infarction ■ cerebral small vessel diseases ■ dementia, vascular ■ ischemic stroke ■ leukoencephalopathies ■ migraine

Lacunar infarctions are a core feature of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), the most common inherited cerebral small vessel disease (CSVD). CADASIL is caused by mutations in the *NOTCH3* gene expressed in endothelial smooth muscle cells. The NOTCH3 protein is a single-pass transmembrane receptor with extracellular epidermal growth factor (EGF) repeat domains. Low disease prevalence challenges recognition of CADASIL. About 12% of all strokes are attributable to small artery occlusion, but even among those with younger-onset lacunar strokes, <2% have genetically confirmed CADASIL.[1] Although CADASIL lacks a cure, expression of disease may be modifiable, thereby justifying a molecular diagnosis. Interpreting the results of a molecular diagnosis and providing consistent recommendations to patients and their at-risk family members are vital. Testing for *NOTCH3* mutations, the cause of CADASIL, is widely available, but interpreting the results can be challenging because of genetic heterogeneity, ranging from typical cysteine-changing mutations to cysteine-sparing mutations.[2]

The purposes of this scientific statement are to help clinicians recognize, diagnose, prognose, and manage CADASIL; to distinguish it from other heritable CSVDs; to provide insights into the genetics and pathophysiology of disease; and to suggest pathways for discovery of disease-modifying therapies.

OVERLAP AND DISTINCTION IN PHENOTYPES

The classic CADASIL phenotype consists of migraines, subcortical strokes, and ultimately vascular dementia.[3] Migraine with aura is associated with CADASIL.[4] For the ≈30% who will have migraines, mean age at onset is 30 years. Ischemic strokes occur at a mean age of 49 years (range, 20–70 years), often without vascular risk factors.

Stroke is available at www.ahajournals.org/journal/str

By stroke presentation, patients have at least moderate concomitant small vessel disease. Strikingly, the CADASIL phenotype is confined to the central nervous system despite immunohistochemical evidence of characteristic osmiophilic, PAS-positive granular material within blood vessel walls in most of visceral organs.[5] This helps to differentiate CADASIL from hypercoagulable states or systemic vasculitides. Family history of early-onset stroke or migraine with characteristic magnetic resonance findings should raise suspicion for the diagnosis.

Clinicians need to recognize the similarities and differences among CADASIL and other inherited CSVDs (Table 1). Fabry disease is an X-linked disorder caused by deficiency in α-galactosidase A that can manifest with albuminuria, angiokeratomas, renal disease, cardiomyopathy, and autonomic and painful peripheral neuropathies.[6] Fabry disease is particularly important to diagnose because of the availability of enzyme replacement therapies. *HTRA1* gene mutations can cause CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy), which has characteristic neurological and nonneurological features ("backache, baldness, and brain attack"),[7] and more recently have been recognized as causing an autosomal dominant CSVD (referred to as *HTRA1* [high-temperature requirement factor a serine peptidase 1]-related disease) that typically appears to have a milder clinical presentation than CARASIL (older age at onset, less consistent systemic features, milder magnetic resonance imaging [MRI] changes).[8,9] CARASAL (cathepsin-A–related arteriopathy with strokes and leukoencephalopathy) has prominent brainstem symptoms (tinnitus, hearing loss, and dysphagia).[10] *TREX1* gene mutations can cause RVCL-S (retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations), including liver and kidney disease.[11] Some *COL4A1/2* gene mutations cause HANAC (hereditary angiopathy with nephropathy, aneurysms, and muscle cramps) syndrome.[12] Others cause PADMAL (pontine autosomal dominant microangiopathy with leukoencephalopathy).[13] Hereditary cerebral amyloid angiopathies tend to have recurrent spontaneous cerebral hemorrhages as the predominant feature but can mimic CADASIL.[14]

MOLECULAR GENETICS OF CADASIL AND OTHER CSVDS

Classically, disease-associated *NOTCH3* gene mutations result in gain or loss of a cysteine residue within the 34 EGF repeat motifs of the protein.[15] However, traditional cysteine-affecting mutations are not all equally detrimental, with evidence suggesting that the location of the mutation within the gene can affect clinical presentation.[16,17] Indeed, it appears that variants in the first 6 repeats, and perhaps in repeats 18 through 34, are associated with earlier age at stroke onset and increased likelihood of encephalopathy and dementia.[16,17] The phenomenon of reduced penetrance has also been postulated,[18] with exon skipping returning the number of cysteine residues to an even number as a proposed contributor.[19] The naturally occurring phenomenon of exon skipping could prove a potential strategy for therapeutic intervention for CADASIL,[20] other *NOTCH3*-associated CSVDs,[21] and potentially other inherited CSVDs that may result in aberrant disulfide bonding (eg, cathepsin-A gene product in CARASAL),[22] as has been successfully implemented in other neurological diseases.[23] Both CARASIL and *HTRA1*-related CSVD result from nonsense/frameshift or missense mutations in the *HTRA1* gene.[9] Some evidence supports haploinsufficiency as the mechanism of disease in *HTRA1*-related CSVD whereby the production of protein by the normal wild-type allele is insufficient to meet the cellular needs. However, according to distinct mutation patterns, the molecular mechanisms that influence the development of CSVD in patients with CARASIL and *HTRA1*-related CSVD may differ.[9]

For CADASIL, the reduced penetrance or spectrum of effect sizes for the same variant is likely due to other genetic determinants,[24] as well as comorbidities and environmental factors[25] that either increase the pathogenic effect or protect against it. This has led to questions of determining the pathogenicity of rare variants, those affecting not only cysteine residues but also noncysteine substitutions.[26] Conferring a designation of pathogenicity to rare variants in genes like *NOTCH3* is a challenge faced by clinical genomics and will likely require functional evaluation and biological readouts. The creation of *NOTCH3* model systems that recapitulate the CADASIL phenotype will be critical.[27] The relationship between the genes implicated in these monogenic CSVD and sporadic small vessel disease remains unclear. For example, genome-wide association studies of sporadic small vessel stroke have detected risk variants in or near both *HTRA1*[28] and *COL4A1/2*[29] but not *NOTCH3*.

BRAIN IMAGING FOR DETECTING AND CHARACTERIZING DISEASE

Brain imaging is often key to a diagnosis of inherited CSVD, including CADASIL. The radiographic spectrum of CSVD involvement includes (1) diffuse, symmetrical, and often progressive white matter hyperintensities (WMHs) that are detected on T2-weighted/fluid-attenuated inversion recovery MRI or noncontrast head computed tomography as leukoaraiosis; (2) multiple subcortical (lacunar) infarcts that are either acute/recent (as seen on diffusion-weighted imaging MRI) or chronic (as seen on T2-weight/fluid-attenuated inversion recovery MRI and computed tomography); (3) dilated perivascular spaces (T2-weighted MRI); (4) cerebral microbleeds on T2* gradient recall echo or susceptibility-weighted imaging; and

Stroke. 2023;54:e00–e00. DOI: 10.1161/STR.0000000000000444

Table 1. Clinical and Radiographic Features of Inherited CSVDs

Name	Full condition name	Gene	Inheritance	Prevalence	Clinical features	Other organ system involvement	Brain imaging
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical strokes and leukoencephalopathy (OMIM 125310)	*NOTCH3*	AD	2–5/100 000 have classic presentation; 2–3/1000 have cysteine-changing mutations	Migraine with aura, small vessel infarctions, depression, vascular dementia	Little to none	Confluent white matter changes in anterior temporal lobes, external capsule, high-convexity white matter, enlarged perivascular spaces, lacunar infarctions, cerebral microbleeds, cerebral atrophy
CARASIL	Cerebral autosomal recessive arteriopathy with subcortical strokes and leukoencephalopathy (OMIM 600142)	*HTRA1*	AR or compound heterozygous	≈5000 cases of CARASIL reported	Migraine with aura, small vessel infarctions, depression, vascular dementia	Alopecia, skeletal deformities	Confluent white matter changes in pons/middle cerebral peduncle, frontal white matter, anterior temporal lobe, external capsules, and thalami; lacunar infarctions; cerebral microbleeds; cerebral atrophy
HTRA1-related CSVD	HTRA1-related CSVD (previously referred to as CADASIL2; OMIM 616779)	*HTRA1*	Most AD	5% of hereditary CSVD	Similar to CARASIL but later onset	Similar to CARASIL but milder and with later onset	Similar to CARASIL, typically milder, but may include corpus callosum
CARASAL	Cathepsin-A–related arteriopathy with strokes and leukoencephalopathy (OMIM none; ORPHA 575553)	*Cathepsin-A*	AD	<20 cases reported	Migraine and gait disturbance with prominent brainstem symptoms, including tinnitus, hearing loss, and dysphagia; also cognitive dysfunction, behavioral disinhibition, REM sleep behavioral disorder, depression	None	Confluent white matter changes in basal ganglia, thalamus, internal and external capsules, pons, and frontoparietal deep and periventricular white matter
RVCL-S	Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (OMIM 192315)	*TREX1*	AD	≈100 families described	Visual symptoms presenting at ≈40 y of age, cognitive decline, and psychiatric disturbances	Eye, thyroid, liver, and kidney manifestations typical	Transient pseudo-glioblastoma with heterogeneous signal, prominent edema, contrast enhancement
PADMAL	Pontine autosomal dominant microangiopathy with leukoencephalopathy (OMIM 618564)	*COL4A1/2*	AD	Rare	Lacunar infarcts and gait disturbance	None	Pontine lacunes and subcortical and periventricular lesions; temporal lobar lesions rare
HANAC	Hereditary angiopathy with nephropathy, aneurysm, and muscle cramps syndrome (OMIM 611773)	*COL4A1/2*	AD	Rate	Can cause lacunar stroke and is associated by migraine, but retinal tortuosity and muscle cramps usually more prominent	Retinal arteriolar tortuosity, muscle cramps with elevation of creatine phosphokinase, kidney involvement (renal cysts, hematuria, and renal insufficiency), Raynaud phenomenon, and supraventricular arrhythmia	White matter changes in prominently in centrum semiovale and to a lesser extent the external capsule and the posterior limb of the internal capsule; subtentorial involvement of the pons
Fabry disease	Fabry disease (OMIM 301500)	*α-Galactosidase*	X-linked	1/3100–1/11 700	Small vessel, large vessel, and cardioembolic infarctions	Albuminuria, angiokeratomas, and autonomic and painful peripheral neuropathies	WMHs and dilated vertebrobasilar arteriopathy
hCAA, HCHWA	Hereditary cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis (OMIM 105150, 604312, and 605714)	*APP*, *CST3*, *ITM2B*, *TTR*, *GSN*	AD	Variable but all rare	Recurrent lobar hemorrhages, amyloid spells	Varies by subtype	Lobar predominant microhemorrhages, high-convexity white matter changes, enlarged perivascular spaces

AD indicates autosomal dominant; AR, autosomal recessive; CSVD, cerebral small vessel disease; *HTRA1*, high-temperature requirement factor A serine peptidase 1; OMIM, Online Mendelian Inheritance in Man (www.omim.org); ORPHA, Orphan disease code (www.orpha.net); and WMH, white matter hyperintensity.

(5) brain atrophy on T1-weighted MRI.[30] In CSVD disorders with predominantly hemorrhagic manifestations such as familial cerebral amyloid angiopathy, superficial siderosis is frequently seen in addition to the intraparenchymal microhemorrhages and macrohemorrhages. Neuroimaging standards for detection of CSVD are continually evolving. Neuropathological correlates of CSVD seen on imaging include microangiopathies that affect intrinsic parenchymal and leptomeningeal perforating arteries, arterioles, and capillaries (eg, arteriolosclerosis or cerebral amyloid angiopathy), as well as small veins and venules (eg, venous collagenosis).[31] Radiographic manifestations of CSVD such as chronic lacunes and tissue cavitation have consistent neuropathological correlates with evidence of cell loss and gliosis, whereas WMH has heterogeneous neuropathological correlates, which include white matter rarefaction, ischemia, inflammation, blood-brain barrier leakage, myelin breakdown, axonal injury, loss of oligodendrocytes, and dilation of perivascular spaces.[32] The presence of MRI WMHs involving the anterior temporal poles, the frontal lobes (subinsular areas and superior frontal gyri), and the periventricular white matter has high discriminatory accuracy for CADASIL compared with sporadic subcortical arteriosclerotic encephalopathy[33] whereas subcortical, punctate fluid-attenuated inversion recovery lesions in the temporal lobes are highly specific for CADASIL but only moderately sensitive[34] (Figure 1). However, other inherited microangiopathies, including CARASIL, PADMAL, and *COL4A1/A2* syndromes, and even sporadic CSVD can have similar patterns.[35] There is evidence of polygenic risk for WMHs even among patients with CADASIL and other monogenic CSVDs.[36] Active investigation holds promise to optimize the use of MRI methods in diagnosis, prognosis, and management.[35]

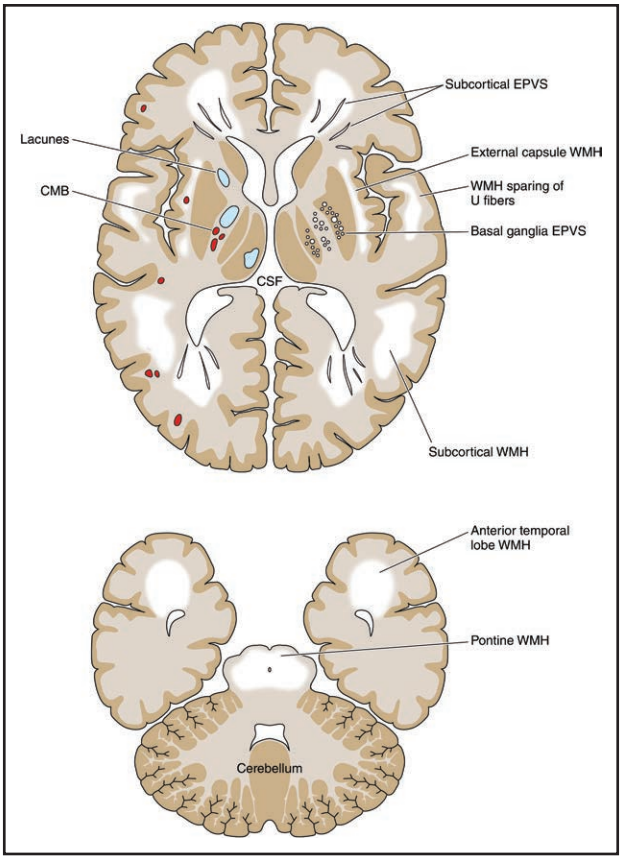

Figure 1. A schematic composite of common pathologies encountered in the central nervous system of patients with CADASIL.
CMB indicates cerebral microbleed; CSF, cerebrospinal fluid; EPVS, enlarged perivascular space; and WMH, white matter hyperintensity.

DIAGNOSTIC APPROACH TO CADASIL AND OTHER GENETIC CSVDS

Clinicians should tailor their approach to diagnosing patients with CADASIL and other monogenic CSVDs to the clinical scenario, symptom status, age, and family history. Currently, Fabry disease is the only monogenic CSVD with disease-specific therapy.[37] However, addressing vascular risk factors for sporadic vascular disease may delay onset, modify severity, or prolong the course for individuals with CADASIL and other inherited CSVDs.[25] Thus, securing a diagnosis may prove important for clinical practice and research.

Several approaches have been developed to help clinicians prioritize gene testing. For at least 2 decades, it has been recognized that anterior temporal polar WMH on brain MRI is a marker of CADASIL with good sensitivity and specificity.[38] The Pescini scale ranges from 0 to 25 points (>14 points suspicious of CADASIL) and uses clinical features like stroke or transient ischemic attack onset before 50 years of age.[39] A version of this scale for use in Japanese populations required substantial modification,[40] suggesting a need for consideration of population characteristics for such tools to be valid. In the future, clinical decision support tools derived from electronic medical record data may help clinicians identify those warranting genetic testing.[41]

Strong consideration should be given to genetic counseling to allow discussion of the ramifications of obtaining genetic test results on the individual patient and their family. Even in the era of legal protections, counseling must address issues surrounding health, life, disability, and long-term care insurance, as well as employment discriminations, before testing. Genetic testing of one individual may reveal the status of others who may not have consented to or be prepared for genetic testing. One should distinguish diagnostic testing in individuals who have clinical manifestations of disease from predictive or presymptomatic testing. In general, children, unless emancipated minors, should not undergo predictive testing because this robs them of the choice of knowing or not knowing their status. The penetrance of *NOTCH3* variants is incomplete and highly variable. Testing and finding mutations in *NOTCH3* can lead to pessimistic

Stroke. 2023;54:e00–e00. DOI: 10.1161/STR.0000000000000444

prognostication and bias of detecting asymptomatic brain lesions with MRI. This can have life-changing, negative psychological consequences. Posttest counseling can help with interpretation, especially of variants of unclear significance, and navigating grief or guilt from positive, negative, and equivocal results.[42]

A known pathogenic *NOTCH3* mutation within a family simplifies testing because only a single mutation needs to be investigated. When the mutation is unknown or unavailable, the laboratory must undertake a more complex analysis; the general approach involves staged testing for the more common variants within the more commonly affected EGF domains, followed by a second stage of targeted testing, followed by sequencing of the whole exome/gene. When multiple CSVDs are under consideration, the use of increasingly available genetic panels can be considered. These bundled tests can be more cost-effective than ordering each test separately. Although used less frequently, there is still a role for skin biopsy to look for pathognomonic granular osmophilic material on electron microscopy that may clarify the clinical significance of a mutation of uncertain or unknown significance. The accuracy of skin biopsy is enhanced by the use of immunochemistry.[43]

Epidemiological data on the prevalence of CADASIL, or indeed other genetic CSVDs, in different racial and ethnic groups are incomplete or frankly lacking. Data on individuals of European and Asian ancestry abound, whereas identification of CADASIL or other CSVDs in people of African ancestry remains rare.[44,45] The differences in the literature may reflect true differences in prevalence or penetrance of *NOTCH3* mutations, but underreporting of disease as a result of resource limitations, underrecognition, and undertesting may account for these differences. To suggest that CADASIL or other CSVDs should be considered only in certain populations might compound health inequities.

ROLE OF ANTITHROMBOTIC AND THROMBOLYTIC THERAPIES

In CADASIL, the role of antiplatelet therapy in preventing recurrent ischemic stroke is unknown. Extrapolating from general guidelines, physicians have treated many patients with CADASIL with antiplatelet agents. In Japan, nearly 74% of patients received antiplatelet therapy.[46] Intracerebral hemorrhage can occur with or without exposure to antithrombotic therapy.[47] A 2020 European guideline notes that there is no evidence to support the use of antiplatelet agents in patients with CADASIL without prior ischemic stroke.[48] Although there are no high-quality data on the safety or efficacy of antiplatelet therapies in patients with CADASIL, low-dose aspirin likely carries low risk and is frequently given in patients with prior ischemic stroke. Recurrent lacunar strokes have been seen in PADMAL[49] and in CARASAL[10] despite antithrombotic therapy.

The indications for or against anticoagulation use are uncertain in CADASIL. Anticoagulant-associated intracerebral hemorrhage is uncommon. In a series of patients with CADASIL in Taiwan, 5.9% (15/255) had symptomatic intracerebral hemorrhage, and of those, 6.7% (1/15) were associated with anticoagulant use.[50] Investigators found that having cerebral microbleeds in the brainstem and >10 microbleeds was independently associated with intracerebral hemorrhage. European guidelines state that in patients with CHA_2DS_2-VASc scores >2 and atrial fibrillation or other indication for anticoagulation, oral anticoagulation is not contraindicated.[48] In patients with both CADASIL and atrial fibrillation, left atrial appendage device closure may be a reasonable alternative to long-term anticoagulation. This is particularly true for patients with high CHA_2DS_2-Vasc scores and high microbleed count.

Little is known about the safety or efficacy of thrombolysis or thrombectomy in patients with CADASIL presenting with acute stroke. There are examples of use of thrombolytics without bleeding complications.[51] Pending systematic study, decisions on reperfusion or recanalization therapy should be made on a case-by-case basis. It is not known to what extent the experiences with thrombolytic therapy in CADASIL are relevant to other genetic CSVD.

MIGRAINE AND ITS MANAGEMENT

The diagnostic criteria for migraine associated with CADASIL are well defined in the third edition of the International Classification of Headache Disorders. The migrainous aura may be severe and can vary in semiologies, including hemiplegia, hemi-anesthesia, and visual scotoma.[52] Although unclear if migrainous in pathogenesis, episodes of fever, confusion, and reduced arousal, called CADASIL coma, may occur in up to 8.5% (6/70) of patients with CADASIL.[53] These episodes last weeks and self-resolve to the patient's preexisting neurological baseline.

The physiological link between CADASIL and migraine is unclear; hypotheses include whether cortical-spreading depression from migraine is an innate protective strategy to aid cerebral vasoactivity.[54] Supporting a protective quality of migraine, those with migraine with aura tend to have a lower stroke risk, less disability, less cognitive insufficiency, and fewer radiographic cerebral microbleeds compared with those without migraine in CADASIL.[55]

In roughly a third of individuals, migraine may be severe and refractory and impair quality of life.[52] No randomized trial has sought to elucidate the optimal treatment for migraine in CADASIL. A meta-analysis reviewing prophylactic medications for migraine in CADASIL notes that most common prophylactic medication choices were equivocal, although propranolol seemed to have a

deleterious effect and both acetazolamide and sodium valproate may be physiologically beneficial.[56] Migraine triggers in patients with CADASIL are similar to those in patients without CADASIL, and although there are no robust data, avoiding triggers and maintaining good sleep and exercise should be considered. Abortive treatment reports are limited; however, triptans may be safe.[48] No robust data exist on the benefit of onabotulinum toxin-A, wearable devices, acupuncture or acupressure, or calcitonin gene-related peptide modulators.

CADASIL is not the only monogenic CSVD associated with migraine. RVCL-S and other conditions caused by *TREX1* mutations can have migraine as a prominent feature preceding cerebral complications, although migraine is not typically the presenting symptom.[57] The same ambiguity exists on the best migraine treatments for *TREX1* spectrum conditions as with CADASIL.

NEUROPSYCHIATRIC PHENOMENA

Neuropsychiatric complications may occur in up to 30% of those with CADASIL, with most occurring after the fourth decade.[58] Adjustment disorders, dysthymia, apathy, and pseudobulbar palsy are the most common and lead to worse quality of life.[59–61] Impaired cognition, from mild cognitive impairment to vascular dementia, may be the sole symptom in 10% of individuals.[59,62] Cognitive profiles early in the disease typically display executive dysfunction and inattention, progressing to a multidomain cognitive impairment and dementia after 60 years of age in ≈60% of individuals.[62] It is notable that for CADASIL, memory is relatively spared.[62]

Optimal therapies for neuropsychiatric symptoms are not well defined, relying on conventional pharmacotherapy such as selective serotonin reuptake inhibitors. Sodium valproate might have physiological benefits due to effects on the NOTCH3 receptor.[63] However, mood disturbances are often refractory.[64] A randomized trial of donepezil showed no benefit in overall cognition, as measured by the Vascular Dementia Assessment Scale cognitive subscale score, but did show benefit for several subscores of executive function.[65] Trials have shown benefit for memantine in vascular dementia not related to CADASIL[66]; thus, a trial testing the use of memantine in CADASIL might be reasonable. Similarly, goal-oriented cognitive rehabilitation therapy has demonstrated benefit in everyday functioning for individuals with vascular dementia[67] but not specifically CADASIL or other genetic CSVD.

MANAGING MODIFIABLE VASCULAR RISK FACTORS

The prevalence of modifiable vascular risk factors in patients with CADASIL varies by study type, including duration of follow-up, patient age at time of study, country, and number of vascular risk factors ascertained. Early studies reported a low prevalence of vascular risk factors (eg, hypertension as low as 8%),[58] but more recent work has found vascular risk factors to be more prevalent (Table 2). In one analysis, vascular risk factors did not differ by mutation location.[75]

Hypertension and glucose control are associated with cerebral microbleeds.[69,74,75] However, the association between hypertension and lacunar volumes has been inconsistent,[69,75] and an association between glucose control and volume of WMHs or lacunar infarcts has not been found, possibly because of a lack of power.[69]

In CADASIL, hypertension has been shown to be associated with incident dementia,[76] disability due to dementia,[72] and overall disability.[75] However, diabetes has not been shown to be associated with cognitive decline.[76] One prospective study[73] found tobacco smoking to be a predictor of dementia, but another prospective study[76] found no association between tobacco smoking and multiple measures of cognition.

In CADASIL, hypertension is associated with incident stroke[71] and intracerebral hemorrhage.[74] When adjusted for age and vascular risk factors, tobacco smoking is independently associated with incident ischemic stroke and earlier onset of stroke.[71,73]

We identified no randomized trials studying the effects of management of vascular risk factors on clinical outcomes in patients with CADASIL. From the aforementioned observational studies and the expected deleterious effects of vascular risk factors on arteriolosclerosis-related brain health, tight control of blood pressure seems prudent in CADASIL. At a minimum, this will help prevent cognitive decline and stroke attributed to vascular risk factors, which would only add to those inherent to CADASIL. Given reported associations between tobacco smoking and earlier onset of stroke in patients with CADASIL, smoking cessation should be strongly encouraged. A clear association of hyperlipidemia with clinical outcomes in CADASIL has yet to be established. Despite the failure of short-term use of atorvastatin to improve hemodynamic parameters in a small group of patients with CADASIL,[70] the value of treating comorbid dyslipidemia remains unknown.

PREGNANCY IN CADASIL

Overall, there is a scarcity of studies on the effects of CADASIL in mothers on pregnancy course and in the postpartum period or risks to fetus. One case series from Italy included 93 pregnancies in 50 women with *NOTCH3* mutations.[77] CADASIL was not associated with higher rates of complications during pregnancy, peripartum, or postpartum. Of note, although antithrombotic treatments

Stroke. 2023;54:e00–e00. DOI: 10.1161/STR.0000000000000444

Table 2. Prevalence of Vascular Risk Factors in Patients With CADASIL as Reported in Prospective Studies

	Singhal et al[68]	Viswanathan et al[69]	Peters et al[70]*	Adib-Samii et al[71]	Ciolli et al[72]	Chabriat et al[73]	Lee et al[74]	Hack et al[75]†
Publication year	2004	2006	2007	2010	2014	2016	2017	2022
Patient age at assessment, mean±SD, y	46.9	51.8±11.2	49.2±9.8	47.7±11.4	50.3±13.8	50.6±11.4	62.6±12.5	EGFr 1–6: 48.9±12.3 EGFr 7–23: 55.6±11.3
Female, %	59.8	42.9	50.0	57.0	52.9	55.2	44.7	53.0
Country or region	United Kingdom	France, Germany	Germany	United Kingdom	Italy	France, Germany	Korea	The Netherlands
Patients/families, n	127/65	147/NR	25/20	200/NR	51/40	290/>100	94/76	200/NR
Hypertension, %	20.0	42.9	4.2	23.9	35.3	19.0	53.2	25.5
Hyperlipidemia, %	44.5	49.7	16.7	68.6	36.0	38.0	25.5	37.5
Diabetes, %	3.9	2.7	0.0	4.0	7.8	2.1	17.0	6.5
Ever-smoker, %	53.2	49.0	20.8	51.0	30.6		38.3	50.5
Current alcohol use, %	NR	53.1	NR	NR	NR	7.8% (>2 drinks/d)	NR	61.0
BMI, mean±SD	NR	NR	NR	NR	28.0±5.1	NR	NR	27.1
Hyperhomocysteinemia, %	17.6	NR	NR	16.8	NR	NR	NR	NR
Atrial fibrillation, %	NR	NR	NR	NR	NR	NR	3.2	NR

BMI indicates body mass index; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; EGFr, epidermal growth factor-like repeat; and NR, not reported.

*Results for age and sex taken from table rather than text.

†Vascular risk factors did not vary by EGFr.

are not common in CADASIL, nearly half of the pregnant patients with CADASIL were on antithrombotic therapy during pregnancy. A Finnish study retrospectively studied 25 female carriers of the R133C mutation for a total of 43 completed pregnancies.[78] Using structured questionnaires and medical records, the authors found that almost half experienced transient neurological symptoms, mainly in the puerperium. For most of the patients, these spells were the first manifestations of disease and were more common in those >30 years of age. The 2020 European guidelines assert a lack of need for antithrombotics during pregnancy.[48] There are no data showing that vaginal birth is unsafe. Similarly, there are scant data on preterm complications of fetuses that carry a mutation in *NOTCH3*.

PERIOPERATIVE MANAGEMENT

There has been no systematic study of perioperative management in CADASIL. However, neuraxial[79] and general anesthesia[80] have been used without postoperative stroke or delirium. There are pathophysiological reasons to think that patients could be at increased risk of perioperative stroke or delirium. Patients have reduced vasoreactivity to carbon dioxide.[81] Positron emission tomography studies have shown a significant decrease in cerebral blood flow in white matter, corresponding to WMHs on MRI.[82] It has been proposed that intraoperative mean arterial pressure should be >60 mm Hg (8 kPa), that end-tidal carbon dioxide should be ≈40 mm Hg (5.3 kPa), and that head-down positioning should be restricted or avoided to avoid obstructing venous return.[80]

AVOIDING CATHETER ANGIOGRAPHY

Most reports of cerebral angiography in patients with CADASIL indicated normal appearance of blood vessels, although subtle distal changes can occur.[83] The first reports of complications of cerebral catheter angiography emerged in the 1990s.[84] In a review of individuals with CADASIL undergoing cerebral catheter angiography, 69% (11/16) experienced neurological symptoms lasting hours to weeks.[84] Because cerebral catheter angiography is unnecessary for diagnosing CADASIL, a clinical or genetic diagnosis of CADASIL should be considered a relative contraindication to cerebral catheter angiography, the exception being a known symptomatic acute large vessel occlusion for which a catheter procedure would be done for therapeutic, not merely diagnostic, reasons.

PATHWAYS TO DISEASE-MODIFYING THERAPIES

The *NOTCH3* gene product is expressed in vascular smooth muscle cells and pericytes of the brain, and a single copy of mutant *NOTCH3* (but not *NOTCH3* functional knockouts) is sufficient to generate granular osmiophilic material (a pathognomonic feature of the disease) in vessels of experimental animals. Furthermore, mutations in *NOTCH3* frequently alter cysteine residues,

which are invariantly conserved with the 34 EGF repeats of the protein and scaffold protein shape. Therefore, many mechanistic models posit that mutant NOTCH3 protein triggers a pathological gain of function within the cerebral vasculature. In accordance, human biospecimen analysis and model systems have uncovered dysregulated signaling pathways with an emphasis on abnormal extracellular matrix proteins. Contributing proteins identified include mutated and modified NOTCH3 and other proteins such as collagens, small leucine-rich proteoglycans, VTN (vitronectin), and TIMP3 (tissue inhibitor of metalloproteinase 3).[85–87] The last 2 proteins in a mouse model affect cerebral autoregulation and activity-dependent neurovascular coupling through diminished EGF receptor signaling that lowers levels of phospholipids such as PIP2 (plasma membrane intrinsic protein), a key regulator of the inward rectifier potassium channel (Kir2.1).[88]

From a cellular perspective, CADASIL is characterized by disruption of the vessel wall architecture (Figure 2). Impaired perivascular clearance may result from dysfunctional autophagy-lysosomal degradation of vascular smooth muscle cells.[89] Impaired clearance may be a shared mechanism in CADASIL and cerebral amyloid angiopathy–Alzheimer disease, which feature a modest number of overlapping proteins.[24,90] An overlap between CADASIL vessel proteins and targets of the CARASIL factor HTRA1, a protease, implicates convergent pathways of impaired protein clearance in CADASIL and CARASIL.[91] In addition, decreased baseline relaxation of vascular smooth muscle cells due to abnormalities in sGC/cGMP signaling[92] and inadequate H_2O_2 production compound defects in vessel reactivity in animal models. A Rho kinase inhibitor, fasudil, attenuates CADASIL-related physiological abnormalities in vitro.

Although most investigations emphasize mechanisms relating to cell membrane, proteostasis, and extracellular molecular pathologies, other pathways need to be investigated such as the role of physiological nuclear NOTCH3 signaling, with potential effects on *NFKB* (nuclear factor of kappa light polypeptide b)–regulated inflammatory genes. The role of immune dysfunction is underappreciated in CADASIL despite symptomatic manifestations known to involve immune components such as stroke and migraine headaches. Collectively, the large number of divergent molecular pathways identified needs prioritization by application of omics technologies in human biospecimen and preclinical models to distinguish which abnormalities initiate disease versus result from disease progression.

Further exploration is required to elucidate how comorbidities and environmental risk factors modify outcomes. The mechanisms of how hypertension and smoking affect CADASIL progression may lead to insights relevant to disease modification.

Future development of biomarkers should be useful in clinical trials investigating whether treatment of comorbidities and modulation of environmental factors are effective. Blood biomarkers would help elucidate whether specific diets and exercise modify disease course.

Last, maturing technologies such as gene silencing, gene editing, and monoclonal antibody production could be applied to CADASIL. Harnessing the observed naturally occurring exon skipping may be a useful approach to gene therapy.[19–21] Disease mechanisms likely relate

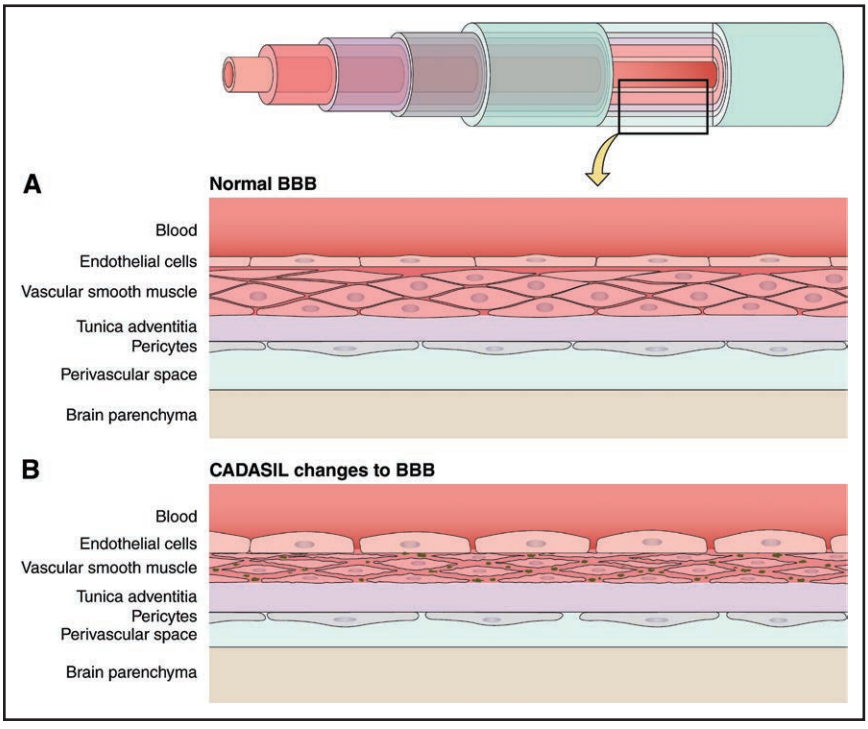

Figure 2. Cross-sectional schematics of a normal arteriole and of an arteriole with the pathological changes that occur in patients with CADASIL.
BBB indicates blood-brain barrier; and CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Stroke. 2023;54:e00–e00. DOI: 10.1161/STR.0000000000000444

Table 3. Considerations for Managing Patients With CADASIL

Management issue	Clinical considerations
When to test for *NOTCH3* mutations	Consider gene testing in patients with small vessel stroke before 55 y of age with a paucity of vascular risk factors (eg, normotensive, nondiabetic, nonsmoker) or positive family history of CADASIL.
Antithrombotic therapy	Avoid antiplatelet therapy for primary stroke prevention. Aspirin monotherapy may be safe for preventing recurrent ischemic stroke, but evidence for efficacy is lacking. Oral anticoagulants can be given to patients with high-risk atrial fibrillation, but atrial appendage occlusion device placement may be preferred to long-term anticoagulation, particularly if there is a high microbleed burden.
Thrombolytic therapy	Safety and efficacy are unknown for thrombolysis in patients with CADASIL presenting with small vessel stroke. For patients presenting with unrelated large vessel stroke, MT without thrombolysis may be preferred to MT with thrombolysis.
Migraine	Abortive therapy with triptans appears sufficiently safe. Consider avoiding β-blockers for migraine prophylaxis. Acetazolamide and sodium valproate may be preferred for prophylaxis.
Neuropsychiatric symptoms	Donepezil at a dose of 10 mg/d may be considered to improve impaired executive function.
Vascular risk factors	Intensive control of blood pressure and avoiding tobacco smoking are recommended.
Pregnancy	Antithrombotic prophylaxis is not required.
Perioperative management	Maintain an intraoperative mean arterial pressure at >60 mm Hg (8 kPa) and end-tidal carbon dioxide at ≈40 mm Hg (5.3 kPa), and head-down positioning should be restricted or avoided.
Catheter angiography	A clinical or genetic diagnosis of CADASIL should be considered a relative contraindication to cerebral angiography, the exception being a known symptomatic acute large vessel occlusion.

CADASIL indicates cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; and MT, mechanical thrombectomy.

to a toxic gain of function,[93] particularly in light of the requirement for a single copy of mutant *NOTCH3* for production of granular osmiophilic material. Thus, efforts to knock down or knock out mutant alleles offer potential avenues for treatment. The most severe disease-associated mutations are found in the N-terminus of *NOTCH3*,[94] suggesting that recombinant immunoglobulins against disease-related NOTCH3 epitopes could be developed as therapeutic tools.

FUTURE DIRECTIONS

Although infrequent or rare, inherited CSVDs can have profound effects on those harboring disease-causing mutations. With the notable exception of Fabry disease, inherited CSVDs lack disease-specific, targeted therapies. In this scientific statement, we focused on CADASIL, the most common CSVD, suggesting that therapeutic uncertainty should not translate to therapeutic nihilism (Table 3). Early manifestations of CADASIL such as migraine and later manifestations such as lacunar infarcts, when occurring in patients without a pathogenic *NOTCH3* mutation, have several evidence-based therapies. Whether these therapies are effective in patients with CADASIL is unknown. Challenges to generating reliable evidence for rare disorders include limited statistical power and, in some instances, disease heterogeneity, although dedicated international trial consortia and establishment and use of biomarkers may offer a pathway forward. While we await high-quality empirical evidence for symptomatic and disease-modifying treatments, standardizing medical recommendations to avoid confusing or contradictory recommendations remains valuable.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on May 15, 2023, and the American Heart Association Executive Committee on June 21, 2023. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

The American Heart Association requests that this document be cited as follows: Meschia JF, Worrall BB, Elahi FM, Ross OA, Wang MM, Goldstein ED, Rost NS, Majersik JJ, Gutierrez J; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Hypertension. Management of inherited CNS small vessel diseases: the CADASIL example: a scientific statement from the American Heart Association. *Stroke.* 2023;54:e•••–e•••. doi: 10.1161/STR.0000000000000444

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit https://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
James F. Meschia	Mayo Clinic	None	None	None	None	None	Woolsey Pharmaceuticals, Inc*	None
Bradford B. Worrall	University of Virginia	None	None	None	None	None	None	None
Fanny M. Elahi	Icahn School of Medicine at Mount Sinai	None	None	None	None	None	None	None
Eric D. Goldstein	Warren Alpert Medical School of Brown University	None	None	None	None	None	None	None
José Gutierrez	Columbia University Medical Center	NIA (local PI for NIH-funded CADASIL consortium)†	None	None	None	None	None	None
Jennifer J. Majersik	University of Utah School of Medicine	NIH-NINDS (UT StrokeNet)†	None	None	None	None	Woolsey Pharmaceuticals, Inc*	None
Owen A. Ross	Mayo Clinic	Florida State (He is funded to create a Florida Registry for Cerebrovascular disease.)*	None	None	None	None	None	None
Natalia S. Rost	Harvard Medical School	None	None	None	None	None	None	None
Michael M. Wang	University of Michigan	NIH (principal investigator on grant)†; Department of Veteran Affairs (principal investigator on grant)†	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Christopher D. Anderson	Massachusetts General Hospital	NIH†; AHA†	None	None	None	None	None	None
John W. Cole	Veterans Affairs Maryland Health Care System, University of Maryland School of Medicine	None	None	None	None	None	None	None
Mandip S. Dhamoon	Icahn School of Medicine at Mount Sinai	None	None	None	None	None	None	None
Steven J. Kittner	University of Maryland	NINDS (R01NS105150, Genetics of Early-Onset Ischemic Stroke Consortium)†; NINDS (R01NS100178, Genetics of Stroke in the SiGN Consortium)*	None	None	None	None	None	None

(*Continued*)

Reviewer Disclosures Continued

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Helmi L. Lutsep	Oregon Health & Science University	NINDS (site PI of CADASIL Consortium grant)*	None	None	None	None	None	None
Paul A. Nyquist	Johns Hopkins School of Medicine	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

REFERENCES

1. Tan RYY, Traylor M, Megy K, Duarte D, Deevi SVV, Shamardina O, Mapeta RP, Ouwehand WH, Graf S; Downes K, et al; NIHR BioResource: Rare Diseases Consortium. How common are single gene mutations as a cause for lacunar stroke? A targeted gene panel study. *Neurology*. 2019;93:e2007–e2020. doi: 10.1212/WNL.0000000000008544
2. Muino E, Gallego-Fabrega C, Cullell N, Carrera C, Torres N, Krupinski J, Roquer J, Montaner J, Fernandez-Cadenas I. Systematic review of cysteine-sparing NOTCH3 missense mutations in patients with clinical suspicion of CADASIL. *Int J Mol Sci*. 2017;18:1964. doi: 10.3390/ijms18091964
3. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. CADASIL. *Lancet Neurol*. 2009;8:643–653. doi: 10.1016/S1474-4422(09)70127-9
4. Guey S, Mawet J, Herve D, Duering M, Godin O, Jouvent E, Opherk C, Alili N, Dichgans M, Chabriat H. Prevalence and characteristics of migraine in CADASIL. *Cephalalgia*. 2016;36:1038–1047. doi: 10.1177/0333102415620909
5. Sangle N, Baringer JR, Majersik J, DeWitt LD. CADASIL with multiorgan involvement: a complete autopsy examination report. *Can J Neurol Sci*. 2016;43:202–205. doi: 10.1017/cjn.2015.240
6. Germain DP, Altarescu G, Barriales-Villa R, Mignani R, Pawlaczyk K, Pieruzzi F, Terryn W, Vujkovac B, Ortiz A. An expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease. *Mol Genet Metab*. 2022;137:49–61. doi: 10.1016/j.ymgme.2022.07.010
7. Badachi S, John SK, Sekhar M, Mathew T. CARASIL: the backache, baldness, brain attack syndrome: the Indian scenario. *Ann Indian Acad Neurol*. 2020;23:559–561. doi: 10.4103/aian.AIAN_31_20
8. He Z, Wang L, Zhang Y, Yin C, Niu Y. Clinical features and pathogenicity assessment in patients with *HTRA1*-autosomal dominant disease. *Neurol Sci*. 2023;44:639–647. doi: 10.1007/s10072-022-06454-5
9. Uemura M, Nozaki H, Kato T, Koyama A, Sakai N, Ando S, Kanazawa M, Hishikawa N, Nishimoto Y, Polavarapu K, et al. *HTRA1*-related cerebral small vessel disease: a review of the literature. *Front Neurol*. 2020;11:545. doi: 10.3389/fneur.2020.00545
10. Budhdeo S, de Paiva ARB, Wade C, Lopes LCG, Della-Ripa B, Davagnanam I, Lucato L, Mummery CJ, Kok F, Houlden H, et al. A rare cause of monogenic cerebral small vessel disease and stroke: cathepsin a-related arteriopathy with strokes and leukoencephalopathy (CARASAL). *J Neurol*. 2022;269:6673–6677. doi: 10.1007/s00415-022-11302-9
11. Stam AH, Kothari PH, Shaikh A, Gschwendter A, Jen JC, Hodgkinson S, Hardy TA, Hayes M, Kempster PA, Kotschet KE, et al. Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. *Brain*. 2016;139:2909–2922. doi: 10.1093/brain/aww217
12. Alamowitch S, Plaisier E, Favrole P, Prost C, Chen Z, Van Agtmael T, Marro B, Ronco P. Cerebrovascular disease related to COL4A1 mutations in HANAC syndrome. *Neurology*. 2009;73:1873–1882. doi: 10.1212/WNL.0b013e3181c3fd12
13. Verdura E, Herve D, Bergametti F, Jacquet C, Morvan T, Prieto-Morin C, Mackowiak A, Manchon E, Hosseini H, Cordonnier C, et al. Disruption of a mir-29 binding site leading to COL4A1 upregulation causes pontine autosomal dominant microangiopathy with leukoencephalopathy. *Ann Neurol*. 2016;80:741–753. doi: 10.1002/ana.24782
14. Psychogios K, Xiromerisiou G, Kargiotis O, Safouris A, Fiolaki A, Bonakis A, Paraskevas GP, Giannopoulos S, Tsivgoulis G. Hereditary cerebral amyloid angiopathy mimicking CADASIL syndrome. *Eur J Neurol*. 2021;28:3866–3869. doi: 10.1111/ene.14981
15. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383:707–710. doi: 10.1038/383707a0
16. Cho BPH, Jolly AA, Nannoni S, Tozer D, Bell S, Markus HS. Association of NOTCH3 variant position with stroke onset and other clinical features among patients with CADASIL. *Neurology*. 2022;99:e430–e439. doi: 10.1212/WNL.0000000000200744
17. Dupe C, Guey S, Biard L, Dieng S, Lebenberg J, Grosset L, Alili N, Herve D, Tournier-Lasserve E, Jouvent E, et al. Phenotypic variability in 446 CADASIL patients: impact of NOTCH3 gene mutation location in addition to the effects of age, sex and vascular risk factors. *J Cereb Blood Flow Metab*. 2023;43:153–166. doi: 10.1177/0271678X221126280
18. Rutten JW, Hack RJ, Duering M, Gravesteijn G, Dauwerse JG, Overzier M, van den Akker EB, Slagboom E, Holstege H, Nho K, et al. Broad phenotype of cysteine-altering NOTCH3 variants in UK Biobank: CADASIL to nonpenetrance. *Neurology*. 2020;95:e1835–e1843. doi: 10.1212/WNL.0000000000010525
19. Gravesteijn G, Dauwerse JG, Overzier M, Brouwer G, Hegeman I, Mulder AA, Baas F, Kruit MC, Terwindt GM, van Duinen SG, et al. Naturally occurring NOTCH3 exon skipping attenuates NOTCH3 protein aggregation and disease severity in CADASIL patients. *Hum Mol Genet*. 2020;29:1853–1863. doi: 10.1093/hmg/ddz285
20. Rutten JW, Dauwerse HG, Peters DJ, Goldfarb A, Venselaar H, Haffner C, van Ommen GJ, Aartsma-Rus AM, Lesnik Oberstein SA. Therapeutic NOTCH3 cysteine correction in CADASIL using exon skipping: in vitro proof of concept. *Brain*. 2016;139:1123–1135. doi: 10.1093/brain/aww011
21. Schoemaker D, Arboleda-Velasquez JF. Notch3 signaling and aggregation as targets for the treatment of CADASIL and other NOTCH3-associated small-vessel diseases. *Am J Pathol*. 2021;191:1856–1870. doi: 10.1016/j.ajpath.2021.03.015
22. Bugiani M, Kevelam SH, Bakels HS, Waisfisz Q, Ceuterick-de Groote C, Niessen HW, Abbink TE, Lesnik Oberstein SA, van der Knaap MS. Cathepsin a-related arteriopathy with strokes and leukoencephalopathy (CARASAL). *Neurology*. 2016;87:1777–1786. doi: 10.1212/WNL.0000000000003251
23. Costamagna G, Govoni A, Wise A, Corti S. Bridging the gap: gene therapy in a patient with spinal muscular atrophy type 1. *Neurology*. 2022;99:952–956. doi: 10.1212/WNL.0000000000201294
24. Zellner A, Muller SA, Lindner B, Beaufort N, Rozemuller AJM, Arzberger T, Gassen NC, Lichtenthaler SF, Kuster B, Haffner C, et al. Proteomic profiling in cerebral amyloid angiopathy reveals an overlap with CADASIL highlighting accumulation of htra1 and its substrates. *Acta Neuropathol Commun*. 2022;10:6. doi: 10.1186/s40478-021-01303-6
25. Cho BPH, Harshfield EL, Al-Thani M, Tozer DJ, Bell S, Markus HS. Association of vascular risk factors and genetic factors with penetrance of variants causing monogenic stroke. *JAMA Neurol*. 2022;79:1303–1311. doi: 10.1001/jamaneurol.2022.3832
26. Wollenweber FA, Hanecker P, Bayer-Karpinska A, Malik R, Bazner H, Moreton F, Muir KW, Muller S, Giese A, Opherk C, et al. Cysteine-sparing CADASIL mutations in NOTCH3 show proaggregatory properties in vitro. *Stroke*. 2015;46:786–792. doi: 10.1161/STROKEAHA.114.007472

27. Manini A, Pantoni L. CADASIL from bench to bedside: disease models and novel therapeutic approaches. *Mol Neurobiol*. 2021;58:2558–2573. doi: 10.1007/s12035-021-02282-4
28. Mishra A, Malik R, Hachiya T, Jurgenson T, Namba S, Posner DC, Kamanu FK, Koido M, Le Grand Q, Shi M, et al; COMPASS Consortium; INVENT Consortium; Dutch Parelsnoer Initiative (PSI) Cerebrovascular Disease Study Group; Estonian Biobank; PRECISE4Q Consortium; FinnGen Consortium; NINDS Stroke Genetics Network (SiGN); MEGASTROKE Consortium; SIREN Consortium; China Kadoorie Biobank Collaborative Group; VA Million Veteran Program; International Stroke Genetics Consortium (ISGC); Biobank Japan; CHARGE Consortium; GIGASTROKE Consortium. Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature*. 2022;611:115–123. doi: 10.1038/s41586-022-05165-3
29. Rannikmae K, Davies G, Thomson PA, Bevan S, Devan WJ, Falcone GJ, Traylor M, Anderson CD, Battey TW, Radmanesh F, et al; METASTROKE Consortium. Common variation in col4a1/col4a2 is associated with sporadic cerebral small vessel disease. *Neurology*. 2015;84:918–926. doi: 10.1212/WNL.0000000000001309
30. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, et al; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–838. doi: 10.1016/S1474-4422(13)70124-8
31. Pasi M, Cordonnier C. Clinical relevance of cerebral small vessel diseases. *Stroke*. 2020;51:47–53. doi: 10.1161/STROKEAHA.119.024148
32. Rost NS, Brodtmann A, Pase MP, van Veluw SJ, Biffi A, Duering M, Hinman JD, Dichgans M. Post-stroke cognitive impairment and dementia. *Circ Res*. 2022;130:1252–1271. doi: 10.1161/CIRCRESAHA.122.319951
33. Auer DP, Putz B, Gossl C, Elbel G, Gasser T, Dichgans M. Differential lesion patterns in CADASIL and sporadic subcortical arteriosclerotic encephalopathy: MR imaging study with statistical parametric group comparison. *Radiology*. 2001;218:443–451. doi: 10.1148/radiology.218.2.r01fe24443
34. van Den Boom R, Lesnik Oberstein SA, van Duinen SG, Bornebroek M, Ferrari MD, Haan J, van Buchem MA. Subcortical lacunar lesions: an MR imaging finding in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Radiology*. 2002;224:791–796. doi: 10.1148/radiol.2243011123
35. Jouvent E, Duering M, Chabriat H. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: lessons from neuroimaging. *Stroke*. 2020;51:21–28. doi: 10.1161/STROKEAHA.119.024152
36. Opherk C, Gonik M, Duering M, Malik R, Jouvent E, Herve D, Adib-Samii P, Bevan S, Pianese L, Silvestri S, et al. Genome-wide genotyping demonstrates a polygenic risk score associated with white matter hyperintensity volume in CADASIL. *Stroke*. 2014;45:968–972. doi: 10.1161/STROKEAHA.113.004461
37. Sheng S, Wu L, Nalleballe K, Sharma R, Brown A, Ranabothu S, Kapoor N, Onteddu S. Fabry's disease and stroke: effectiveness of enzyme replacement therapy (ERT) in stroke prevention: a review with meta-analysis. *J Clin Neurosci*. 2019;65:83–86. doi: 10.1016/j.jocn.2019.03.064
38. Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH, Powell JF. Diagnostic strategies in CADASIL. *Neurology*. 2002;59:1134–1138. doi: 10.1212/wnl.59.8.1134
39. Pescini F, Nannucci S, Bertaccini B, Salvadori E, Bianchi S, Ragno M, Sarti C, Valenti R, Zicari E, Moretti M, 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. doi: 10.1161/STROKEAHA.112.665927
40. Koizumi T, Mizuta I, Watanabe-Hosomi A, Mukai M, Hamano A, Matsuura J, Ohara T, Mizuno T. The CADASIL Scale-J, a modified scale to prioritize access to genetic testing for JAPANESE CADASIL-suspected patients. *J Stroke Cerebrovasc Dis*. 2019;28:1431–1439. doi: 10.1016/j.jstrokecerebrovasdis.2019.03.026
41. Morley TJ, Han L, Castro VM, Morra J, Perlis RH, Cox NJ, Bastarache L, Ruderfer DM. Phenotypic signatures in clinical data enable systematic identification of patients for genetic testing. *Nat Med*. 2021;27:1097–1104. doi: 10.1038/s41591-021-01356-z
42. Goldman JS. Genetic testing and counseling in the diagnosis and management of young-onset dementias. *Psychiatr Clin North Am*. 2015;38:295–308. doi: 10.1016/j.psc.2015.01.008
43. Joutel A, Favrole P, Labauge P, Chabriat H, Lescoat C, Andreux F, Domenga V, Cecillon M, Vahedi K, Ducros A, et al. Skin biopsy immunostaining with a NOTCH3 monoclonal antibody for CADASIL diagnosis. *Lancet*. 2001;358:2049–2051. doi: 10.1016/S0140-6736(01)07142-2
44. Lee SJ, Meng H, Elmadhoun O, Blaivas M, Wang MM. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy affecting an African American man: identification of a novel 15-base pair NOTCH3 duplication. *Arch Neurol*. 2011;68:1584–1586. doi: 10.1001/archneurol.2011.781
45. Akinyemi RO, Owolabi MO, Ihara M, Damasceno A, Ogunniyi A, Dotchin C, Paddick SM, Ogeng'o J, Walker R, Kalaria RN. Stroke, cerebrovascular diseases and vascular cognitive impairment in Africa. *Brain Res Bull*. 2019;145:97–108. doi: 10.1016/j.brainresbull.2018.05.018
46. Shindo A, Tabei KI, Taniguchi A, Nozaki H, Onodera O, Ueda A, Ando Y, Urabe T, Kimura K, Kitagawa K, et al. A nationwide survey and multicenter registry-based database of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in Japan. *Front Aging Neurosci*. 2020;12:216. doi: 10.3389/fnagi.2020.00216
47. Palazzo P, Le Guyader G, Neau JP. Intracerebral hemorrhage in CADASIL. *Rev Neurol (Paris)*. 2021;177:422–430. doi: 10.1016/j.neurol.2020.10.009
48. Mancuso M, Arnold M, Bersano A, Burlina A, Chabriat H, Debette S, Enzinger C, Federico A, Filla A, Finsterer J, 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. doi: 10.1111/ene.14183
49. Li Q, Wang C, Li W, Zhang Z, Wang S, Wupuer A, Hu X, Wumaier K, Zhu Y, Li H, et al. A novel mutation in COL4A1 gene in a Chinese family with pontine autosomal dominant microangiopathy and leukoencephalopathy. *Transl Stroke Res*. 2022;13:238–244. doi: 10.1007/s12975-021-00926-0
50. Liao YC, Hu YC, Chung CP, Wang YF, Guo YC, Tsai YS, Lee YC. Intracerebral hemorrhage in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: prevalence, clinical and neuroimaging features and risk factors. *Stroke*. 2021;52:985–993. doi: 10.1161/STROKEAHA.120.030664
51. Khan MT, Murray A, Smith M. Successful use of intravenous tissue plasminogen activator as treatment for a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a case report and review of literature. *J Stroke Cerebrovasc Dis*. 2016;25:e53–e57. doi: 10.1016/j.jstrokecerebrovasdis.2015.12.006
52. Goldstein ED, Badi MK, Klaas JP, Glover P, Rozen TD, Huang JF, Lin MP, Meschia JF. A cross-sectional analysis of migraine-related disability in CADASIL: a Mayo Clinic cohort. *Neurologist*. 2019;24:161–164. doi: 10.1097/NRL.0000000000000253
53. Schon F, Martin RJ, Prevett M, Clough C, Enevoldson TP, Markus HS. "CADASIL coma": an underdiagnosed acute encephalopathy. *J Neurol Neurosurg Psychiatry*. 2003;74:249–252. doi: 10.1136/jnnp.74.2.249
54. Eikermann-Haerter K, Yuzawa I, Dilekoz E, Joutel A, Moskowitz MA, Ayata C. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy syndrome mutations increase susceptibility to spreading depression. *Ann Neurol*. 2011;69:413–418. doi: 10.1002/ana.22281
55. Nannucci S, Rinnoci V, Pracucci G, MacKinnon AD, Pescini F, Adib-Samii P, Bianchi S, Dotti MT, Federico A, Inzitari D, et al. Location, number and factors associated with cerebral microbleeds in an Italian-British cohort of CADASIL patients. *PLoS One*. 2018;13:e0190878. doi: 10.1371/journal.pone.0190878
56. Glover PA, Goldstein ED, Badi MK, Brigham TJ, Lesser ER, Brott TG, Meschia JF. Treatment of migraine in patients with CADASIL: a systematic review and meta-analysis. *Neurol Clin Pract*. 2020;10:488–496. doi: 10.1212/CPJ.0000000000000769
57. Pelzer N, Hoogeveen ES, Haan J, Bunnik R, Poot CC, van Zwet EW, Inderson A, Fogteloo AJ, Reinders MEJ, Middelkoop HAM, et al. Systemic features of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations: a monogenic small vessel disease. *J Intern Med*. 2019;285:317–332. doi: 10.1111/joim.12848
58. Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP. The natural history of CADASIL: a pooled analysis of previously published cases. *Stroke*. 1999;30:1230–1233. doi: 10.1161/01.str.30.6.1230
59. Dichgans M, Mayer M, Uttner I, Bruning R, Muller-Hocker J, Rungger G, Ebke M, Klockgether T, Gasser T. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol*. 1998;44:731–739. doi: 10.1002/ana.410440506
60. Reyes S, Viswanathan A, Godin O, Dufouil C, Benisty S, Hernandez K, Kurtz A, Jouvent E, O'Sullivan M, Czernecki V, et al. Apathy: a major symptom in CADASIL. *Neurology*. 2009;72:905–910. doi: 10.1212/01.wnl.0000344166.03470.f8
61. Brookes RL, Willis TA, Patel B, Morris RG, Markus HS. Depressive symptoms as a predictor of quality of life in cerebral small vessel disease, acting independently of disability; a study in both sporadic small

vessel disease and CADASIL. *Int J Stroke*. 2013;8:510–517. doi: 10.1111/j.1747-4949.2011.00763.x
62. Buffon F, Porcher R, Hernandez K, Kurtz A, Pointeau S, Vahedi K, Bousser MG, Chabriat H. Cognitive profile in CADASIL. *J Neurol Neurosurg Psychiatry*. 2006;77:175–180. doi: 10.1136/jnnp.2005.068726
63. Yuan P, Salvadore G, Li X, Zhang L, Du J, Chen G, Manji HK. Valproate activates the Notch3/c-Flip signaling cascade: a strategy to attenuate white matter hyperintensities in bipolar disorder in late life? *Bipolar Disord*. 2009;11:256–269. doi: 10.1111/j.1399-5618.2009.00675.x
64. Wang J, Li J, Kong F, Lv H, Guo Z. Bipolar II disorder as the initial presentation of CADASIL: an underdiagnosed manifestation. *Neuropsychiatr Dis Treat*. 2017;13:2175–2179. doi: 10.2147/NDT.S142321
65. Dichgans M, Markus HS, Salloway S, Verkkoniemi A, Moline M, Wang Q, Posner H, Chabriat HS. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol*. 2008;7:310–318. doi: 10.1016/S1474-4422(08)70046-2
66. Mobius HJ, Stoffler A. Memantine in vascular dementia. *Int Psychogeriatr*. 2003;15:207–213. doi: 10.1017/S1041610203009219
67. Clare L, Kudlicka A, Oyebode JR, Jones RW, Bayer A, Leroi I, Kopelman M, James IA, Culverwell A, Pool J, et al. Individual goal-oriented cognitive rehabilitation to improve everyday functioning for people with early-stage dementia: a multicentre randomised controlled trial (the GREAT trial). *Int J Geriatr Psychiatry*. 2019;34:709–721. doi: 10.1002/gps.5076
68. Singhal S, Bevan S, Barrick T, Rich P, Markus HS. The influence of genetic and cardiovascular risk factors on the CADASIL phenotype. *Brain*. 2004;127:2031–2038. doi: 10.1093/brain/awh223
69. Viswanathan A, Guichard JP, Gschwendtner A, Buffon F, Cumurcuic R, Boutron C, Vicaut E, Holtmannspotter M, Pachai C, Bousser MG, et al. Blood pressure and haemoglobin A1c are associated with microhaemorrhage in CADASIL: a two-centre cohort study. *Brain*. 2006;129:2375–2383. doi: 10.1093/brain/awl177
70. Peters N, Freilinger T, Opherk C, Pfefferkorn T, Dichgans M. Effects of short term atorvastatin treatment on cerebral hemodynamics in CADASIL. *J Neurol Sci*. 2007;260:100–105. doi: 10.1016/j.jns.2007.04.015
71. Adib-Samii P, Brice G, Martin RJ, Markus HS. Clinical spectrum of CADASIL and the effect of cardiovascular risk factors on phenotype: study in 200 consecutively recruited individuals. *Stroke*. 2010;41:630–634. doi: 10.1161/STROKEAHA.109.568402
72. Ciolli L, Pescini F, Salvadori E, Del Bene A, Pracucci G, Poggesi A, Nannucci S, Valenti R, Basile AM, Squarzanti F, et al. Influence of vascular risk factors and neuropsychological profile on functional performances in CADASIL: results from the Microvascular Leukoencephalopathy Study (MILES). *Eur J Neurol*. 2014;21:65–71. doi: 10.1111/ene.12241
73. Chabriat H, Herve D, Duering M, Godin O, Jouvent E, Opherk C, Alili N, Reyes S, Jabouley A, Zieren N, et al. Predictors of clinical worsening in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: prospective cohort study. *Stroke*. 2016;47:4–11. doi: 10.1161/STROKEAHA.115.010696
74. Lee JS, Ko K, Oh JH, Park JH, Lee HK, Floriolli D, Paganini-Hill A, Fisher M. Cerebral microbleeds, hypertension, and intracerebral hemorrhage in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Front Neurol*. 2017;8:203. doi: 10.3389/fneur.2017.00203
75. Hack RJ, Cerfontaine MN, Gravesteijn G, Tap S, Hafkemeijer A, van der Grond J, Witjes-Ane MN, Baas F, Rutten JW, Lesnik Oberstein SAJ. Effect of *NOTCH3* EGFr group, sex, and cardiovascular risk factors on CADASIL clinical and neuroimaging outcomes. *Stroke*. 2022;53:3133–3144. doi: 10.1161/STROKEAHA.122.039325
76. Brice S, Reyes S, Jabouley A, Machado C, Rogan C, Gastellier N, Alili N, Guey S, Jouvent E, Herve D, et al. Trajectory pattern of cognitive decline in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Neurology*. 2022;99:e1019–e1031. doi: 10.1212/WNL.0000000000200805
77. Donnini I, Rinnoci V, Nannucci S, Valenti R, Pescini F, Mariani G, Bianchi S, Dotti MT, Federico A, Inzitari D, et al. Pregnancy in CADASIL. *Acta Neurol Scand*. 2017;136:668–671. doi: 10.1111/ane.12784
78. Roine S, Poyhonen M, Timonen S, Tuisku S, Marttila R, Sulkava R, Kalimo H, Viitanen M. Neurologic symptoms are common during gestation and puerperium in CADASIL. *Neurology*. 2005;64:1441–1443. doi: 10.1212/01.WNL.0000158655.71323.8A
79. Lamberg JJ, Cherian VT. Neuraxial anesthesia in CADASIL syndrome. *J Neurosurg Anesthesiol*. 2013;25:216. doi: 10.1097/ANA.0b013e3182836086
80. Dieu JH, Veyckemans F. Perioperative management of a CADASIL type arteriopathy patient. *Br J Anaesth*. 2003;91:442–444. doi: 10.1093/bja/aeg182
81. Pfefferkorn T, von Stuckrad-Barre S, Herzog J, Gasser T, Hamann GF, Dichgans M. Reduced cerebrovascular co(2) reactivity in CADASIL: a transcranial Doppler sonography study. *Stroke*. 2001;32:17–21. doi: 10.1161/01.str.32.1.17
82. Tuominen S, Miao Q, Kurki T, Tuisku S, Poyhonen M, Kalimo H, Viitanen M, Sipila HT, Bergman J, Rinne JO. Positron emission tomography examination of cerebral blood flow and glucose metabolism in young CADASIL patients. *Stroke*. 2004;35:1063–1067. doi: 10.1161/01.STR.0000124124.69842.2d
83. Bousser MG, Tournier-Lasserve E. Summary of the proceedings of the first international workshop on CADASIL. Paris, May 19-21, 1993. *Stroke*. 1994;25:704–707. doi: 10.1161/01.str.25.3.704
84. Dichgans M, Petersen D. Angiographic complications in CADASIL. *Lancet*. 1997;349:776–777. doi: 10.1016/S0140-6736(05)60202-4
85. Dong H, Blaivas M, Wang MM. Bidirectional encroachment of collagen into the tunica media in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Brain Res*. 2012;1456:64–71. doi: 10.1016/j.brainres.2012.03.037
86. Zhang X, Lee SJ, Young MF, Wang MM. The small leucine-rich proteoglycan BGN accumulates in CADASIL and binds to NOTCH3. *Transl Stroke Res*. 2015;6:148–155. doi: 10.1007/s12975-014-0379-1
87. Monet-Lepretre M, Haddad I, Baron-Menguy C, Fouillot-Panchal M, Riani M, Domenga-Denier V, Dussaule C, Cognat E, Vinh J, Joutel A. Abnormal recruitment of extracellular matrix proteins by excess NOTCH3 ECD: a new pathomechanism in CADASIL. *Brain*. 2013;136:1830–1845. doi: 10.1093/brain/awt092
88. Dabertrand F, Harraz OF, Koide M, Longden TA, Rosehart AC, Hill-Eubanks DC, Joutel A, Nelson MT. Pip2 corrects cerebral blood flow deficits in small vessel disease by rescuing capillary kir2.1 activity. *Proc Natl Acad Sci USA*. 2021;118:e2025998118. doi: 10.1073/pnas.2025998118
89. Hanemaaijer ES, Panahi M, Swaddiwudhipong N, Tikka S, Winblad B, Viitanen M, Piras A, Behbahani H. Autophagy-lysosomal defect in human CADASIL vascular smooth muscle cells. *Eur J Cell Biol*. 2018;97:557–567. doi: 10.1016/j.ejcb.2018.10.001
90. Young KZ, Xu G, Keep SG, Borjigin J, Wang MM. Overlapping protein accumulation profiles of CADASIL and CAA: is there a common mechanism driving cerebral small-vessel disease? *Am J Pathol*. 2021;191:1871–1887. doi: 10.1016/j.ajpath.2020.11.015
91. Zellner A, Scharrer E, Arzberger T, Oka C, Domenga-Denier V, Joutel A, Lichtenthaler SF, Muller SA, Dichgans M, Haffner C. CADASIL brain vessels show a HTRA1 loss-of-function profile. *Acta Neuropathol*. 2018;136:111–125. doi: 10.1007/s00401-018-1853-8
92. Neves KB, Morris HE, Alves-Lopes R, Muir KW, Moreton F, Delles C, Montezano AC, Touyz RM. Peripheral arteriopathy caused by NOTCH3 gain-of-function mutation involves ER and oxidative stress and blunting of NO/SGC/CGMP pathway. *Clin Sci (Lond)*. 2021;135:753–773. doi: 10.1042/CS20201412
93. Donahue CP, Kosik KS. Distribution pattern of NOTCH3 mutations suggests a gain-of-function mechanism for CADASIL. *Genomics*. 2004;83:59–65. doi: 10.1016/s0888-7543(03)00206-4
94. Rutten JW, Van Eijsden BJ, Duering M, Jouvent E, Opherk C, Pantoni L, Federico A, Dichgans M, Markus HS, Chabriat H, 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. doi: 10.1038/s41436-018-0088-3