Diseases of the cerebral vasculature contribute to diverse forms of brain dysfunction, injury, and cell death. Small vessel disease (SVD) of the brain accounts for ≈25% to 30% of strokes and is a leading cause of age-related and hypertension-related cognitive decline and disability. Despite its impact on the brain, there are currently no specific treatments for SVD, and therapeutic options for secondary prevention are particularly limited compared with those for other common causes of stroke.

Cerebral SVD refers to pathological processes that affect the structure or function of small vessels on the surface and within the brain, including arteries, arterioles, capillaries, venules, and veins. Clinically, the consequences of pathological changes of small vessels of the brain can be detected with neuroimaging. These consequences include white matter hyperintensities, small infarctions or hemorrhages in white or deep gray matter, and brain atrophy. SVD can progress silently for many years before becoming clinically evident. Hence, medical scientists must not only address the clinical impact of SVD but also identify targets for prevention and early treatment. Both these tasks require a better understanding of the pathogenesis of SVD.

The majority of SVD is sporadic and seems driven by a complex mix of genetic and cardiovascular risk factors, among which age and hypertension are deemed the most important. Rare monogenic forms of SVD have been identified and offer excellent opportunities for mechanistic studies among which age and hypertension are deemed the most important. The primary determinants of resting cerebral blood flow (CBF) include perfusion pressure, autoregulatory mechanisms, and local perfusion are prominent. For example, subcortical white matter is supplied by terminal arterioles with limited potential for collateral flow and a lower microvascular density compared with the gray matter. Collectively, such differences are thought to make this region particularly vulnerable to reductions in local microvascular pressure (local perfusion pressure), hypoperfusion, or ischemia.

Small vessels of the brain exhibit distinct characteristics. First, the brain has little means of energy storage. Mechanisms that regulate these vessels help to ensure that the brain normally receives an adequate supply of blood under a variety of conditions. The primary determinants of resting cerebral blood flow (CBF) include perfusion pressure, autoregulatory...
mechanisms, and vascular reactivity to the partial pressure of arterial CO\textsubscript{2}.\textsuperscript{7,10} Local changes in cellular activity (mostly neurons and glia) modulate CBF above or below this baseline level. Increases in cellular activity normally increase CBF, which serves to support enhanced glucose and oxygen demand.\textsuperscript{11} Our understanding of this phenomenon, known as functional hyperemia or neurovascular coupling, remains an active area of research. Local increases in CBF are induced by dilation of vascular muscle in nearby arteries and arterioles, supported by flow-mediated dilation of upstream vessels, and possibly by effects of pericytes on the diameter of capillaries. Both neurons and astrocytes interact closely with vascular cells and thus participate in the regulation of local CBF in response to the metabolic needs of surrounding tissue.\textsuperscript{6,12,13} Second, the brain is subjected to wide variations in arterial pressure during daily activity. Another important feature of the cerebral vasculature is its ability to autoregulate and maintain CBF relatively constant over a substantial range of arterial pressures.\textsuperscript{10} In relation to mechanisms, autoregulation results from the ability of arteries and arterioles to constrict or dilate when intravascular pressure increases or decreases, respectively. Although myogenic reactivity is thought to play a major role in these responses, other mechanisms likely contribute as well in vivo.\textsuperscript{10,14} Third, a fundamental feature of the central nervous system vasculature is reflected by the presence of the blood–brain barrier (BBB), which is largely impermeable to the passive movement of cells, proteins, and most bioactive compounds present in the blood. The BBB consists of endothelial cells anchored to each other by tight junction proteins supported by a continuous basement membrane.\textsuperscript{15} At the level of capillaries, the integrity of the BBB is also determined by pericytes, which are tightly apposed to endothelial cells and fully enwrapped by the same basement membrane and perivascular astrocytic endfeet, which cover large domains of these microvessels.\textsuperscript{15,16}

Therefore, precise control of CBF to support normal brain homeostasis and function relies on an elaborate and sophisticated ensemble of vascular cells working in concert with neurons and astrocytes. In the most distal segment of the circulation, this complex is often called the neurovascular unit.\textsuperscript{8} When other portions of the cerebral vasculature are taken into account, terms such as the vascular neural network are sometimes used.\textsuperscript{17} Considering the complexity of this network, it is not surprising that either structural or functional perturbations of small vessels in the brain can have dramatic consequences regarding function and integrity of white matter.

**SVD of the Brain: Why Study Rare Mendelian Forms?**

**Vascular Risk Factor Approach**

Because the greatest risk factors for development of SVD are cardiovascular, previous efforts to elucidate its pathogenesis have relied mainly on vascular risk factor approaches. Studies of rodents and other models have documented many effects (mostly deleterious) of hypertension on the cerebral vasculature.\textsuperscript{18,19} For example, hypertension produces vascular structural and functional changes that are thought to contribute to reductions in resting CBF, impaired vasodilation and vasodilator reserve, and shifts in the autoregulatory curve (to the right) that increase vulnerability of the brain to hypotension.\textsuperscript{18,19} Multiple mechanisms likely underlie these changes, but angiotensin II, a major therapeutic target in hypertension and other forms of cardiovascular disease, seems to play a central role.\textsuperscript{18} Studies of human and animal models suggest that interrelated oxidant-dependent and immune-dependent mechanisms mediate many of the vascular effects of angiotensin II, with some effects being independent of changes in blood pressure.\textsuperscript{18–20} However, the direct causal link between
these vascular changes and brain lesions, particularly white matter disease and lacunar infarcts, is lacking.

Features of SVD have been described in the microvasculature in mouse models of hypertension, including impairment of vasodilator responses (endothelium-dependent and neurovascular coupling), narrowing of the arteriolar lumen (inward remodeling), and increased permeability of the BBB. In many of these models, the duration of hypertension has been relatively short. As a consequence, although studies using mouse models of hypertension have provided novel insight into mechanisms responsible for cerebrovascular changes, they have not yet established whether these models can fully recapitulate key elements of SVD, including parenchymal injury.

More work in this area has been performed using rat models, particularly genetic models of hypertension. Studies of the spontaneously hypertensive stroke-prone rats, which develop cerebral edema and hemorrhage, suggest that disruption of the BBB may be a key mechanism by which hypertension causes white matter lesions. However, although often cited as a model of sporadic SVD, the spontaneously hypertensive stroke-prone rat is a model of malignant severe hypertension, with blood pressures that are often well beyond the range of autoregulation and with variable phenotypic outcome depending on the dietary regimen. Genetic models with more modest sustained hypertension also develop features of SVD, including reduction in microvascular diameter and activation of perivascular microglia, but the specific impact of these changes on brain parenchyma is also unclear.

Despite being a risk factor for SVD, the relationship between elevated blood pressure and SVD is complex. Like most risk factors for SVD, only a fraction of patients with hypertension experiences development of the disease (and often only with age), and many patients with SVD are normotensive. Furthermore, in addition to the magnitude and the duration of blood pressure elevation, excessive blood pressure variability may contribute to the pathogenesis of SVD. Particularly in animal models, the lack of attention to vascular effects of aging, both alone and in the presence of hypertension, may partly explain the difficulty in developing better models of SVD. Hence, studying the pathogenesis of SVD through a vascular risk factor lens remains important but is an approach with challenges requiring further improvement.

### One-Mutated-Gene-at-a-Time Approach

Familial SVD, largely indistinguishable from sporadic SVD, has been characterized in recent years. Highly penetrant mutations have been identified in 5 distinct genes, including NOTCH3, COL4A1, COL4A2, TREX1, and HTRA1 (Table I in the online-only Data Supplement). Continued identification of related mutations is expected considering recent advances in next-generation sequencing technologies. Although there are no precise figures, it is increasingly appreciated that NOTCH3 and COL4A1/2 mutations account for a large proportion of familial SVD, whereas TREX1 and HTRA1 mutations are likely very rare.

Importantly, a single point mutation in these genes is sufficient to produce a highly penetrant disease, meaning that individuals carrying a pathogenic variant are at 100% risk for development of the disease, nearly independent of the environment. Although rare, these monogenic forms of SVD have immediate relevance to sporadic SVD. For example, the overall clinical and neuroimaging features of CADASIL resemble those of the most common sporadic SVD, except for an earlier age at onset of stroke events and an increased frequency of migraine with aura. Moreover, studies of these hereditary forms of SVD have provided insight into proteins that play critical roles in the cerebral vasculature. For example, type IV collagen is a major component of the basement membrane. Collagen IV is dispensable for deposition and initial assembly of components of the basement membrane during early development, but it is also required for the maintenance of membrane integrity. In addition to its structural role, collagen IV participates in cell–cell and cell–matrix interactions through integrin and nonintegrin receptors that are critically important for cell adhesion, migration, proliferation, and differentiation.

As another example, NOTCH3 is a receptor predominantly expressed in vascular smooth muscle and pericytes, which play a critical role in the maturation and function of small vessels of the brain. Finally, technical advances have permitted the generation of predictive relevant mouse models based on familial disease mutations. These approaches include the ability to express the mutated protein product in both temporal and cell-specific fashions.

In summary, the approach of mutating one gene at a time has provided significant opportunities to address some of the key scientific questions in the quest to identify SVD mechanisms, including identification of biological pathways that promote vascular changes, development of predictive mouse models of SVD, and deciphering the causal link(s) between vascular changes and resulting brain lesions.

### Modeling Mendelian SVD in the Mouse: A Mixed Picture

Because of the many technical possibilities that can be used to manipulate its genome, the mouse has become an extremely popular animal model. Despite these advantages, mice also have potential limitations, including relatively small brain and body size, short lifespan, and a lower ratio of white versus gray matter.

### COL4A1/2-Related SVD: A Mouse Model With Successful Translation

In the past, large collections of mutant mice have been produced by genome-wide random chemical mutagenesis using N-ethyl N-nitrosourea. After treatment with N-ethyl N-nitrosourea, mice are mated in forward phenotypic and genetic screens designed to uncover abnormal phenotypes and mutations responsible for these phenotypes. With this approach, a variety of mouse lines carrying substitutions of glycine residues in the collagenous domain of Col4a1 or Col4a2 genes, which play a crucial role in the formation and stabilization of the triple-helical molecule, has been obtained. Among these, Col4a1Δex41 mice (formerly called Col4a1Δex41), which express a mutant collagen α1(IV) chain with a 17 aa inframe deletion because of a mutation in the splice acceptor site of exon 41 (formerly called exon 40), have been the most extensively characterized.
At birth, all heterozygous Col4a1<sup>−/+</sup>41 mutant pups have cerebral hemorrhage, and approximately half of them die within 1 day.29 A small proportion of young adult mice has porencephalic cavities.29 Notably, adult mice also have development of spontaneous multifocal recurrent intracerebral hemorrhages, predominantly in the basal ganglia, that can be symptomatic or clinically silent.30 Unfortunately, we are not aware of any pathological data on cerebral white matter. Interestingly, mutant mice also exhibit eye (retinal arterial tortuosity, ocular anterior segment dysgenesis, optic nerve hypoplasia), kidney (microalbuminuria, hematuria), and skeletal muscle abnormalities.28,30 Electron microscopy has demonstrated basement membrane defects in cerebral vessels as well as in other tissues of the Col4a1 mutant mice, including uneven edges, variable density and thickness, focal disruption, splitting, and herniations.30 Of major importance, all of these clinical and pathological manifestations were subsequently recognized in families with SVD, and missense mutations resulting in the substitution for 1 of the invariant glycine residues within the Gly-Xaa-Yaa repeats in the collagenous domain have been identified in affected patients.30,31 COL4A2 assemblies with COL4A1 to form the heterotrimERIC triple helix of collagen IV. Recent studies indicate that COL4A2 mutations in humans and mice phenocopy COL4A1 mutations, although with a lesser severity.28

**CADASIL: Incomplete but Relevant Mouse Models**

CADASIL is caused by stereotyped missense mutations that alter the number of cysteine residues in the extracellular domain of NOTCH3 (Notch3<sup>ECD</sup>), leading to pathological accumulation and deposition of Notch3<sup>ECD</sup> at the plasma membrane of vascular muscle and in extracellular deposits called granular osmiophilic material (GOM).24 Recent studies suggest that CADASIL mutations produce novel gain of function(s) of mutated protein arising from unique protein–protein interactions rather than a loss of its canonical function.32 Knock-in and transgenic approaches, using smooth muscle–specific promoters or a P1-derived artificial chromosome (PAC) containing the entire Notch3 locus, have been used in the modeling of CADASIL in mice. These mice develop 2 pathological hallmarks of the disease, that is, Notch3<sup>ECD</sup> aggregates and GOM deposits in the brain and peripheral vessels.33 Yet, only increased mutant Notch3 levels by a factor of ≥4, under the control of the Notch3 promoter (TgPAC-Notch3<sup>30106C</sup>), result in fully penetrant brain lesions. Specifically, PAC-Notch3<sup>30106C</sup> transgenic mice exhibit Notch3<sup>ECD</sup> accumulation and GOM deposits by 1 and 5 months of age, respectively, and white matter alterations starting at 12 months of age.34 However, these mice have normal lifespans and do not exhibit lacunar infarction. Studies of CADASIL mouse models suggest that Notch3<sup>ECD</sup> and GOM deposits are the earliest vascular changes, both occurring before white matter lesions, which are likewise the earliest brain parenchyma changes, a finding which is clinically relevant.33 In humans, Notch3<sup>ECD</sup> aggregates and GOM deposits can be detected in skin vessels of mutation carriers more than a decade before the disease becomes clinically apparent.24 White matter hyperintensities are the earliest detected brain MRI change, preceding the onset of symptoms by 10 to 15 years, and have consistently been found in mutation carriers >35 years of age.24

Why has modeling CADASIL in the mouse been less successful than modeling collagen IV–related SVD? Compared with the latter, CADASIL has a later age of onset and may be driven by a toxic gain-of-function mechanism.32 As anticipated with such a mechanism, prolonged exposure to the mutant protein is assumed to be necessary to trigger cell dysfunction or degeneration. It is thus conceivable that the relatively short lifespan of mice is limiting. Alternatively, divergent results may reflect fundamentally different mechanisms underlying these 2 diseases.

**Retinal Vasculopathy With Cerebral Leukodystrophy and CARASIL**

No currently published mouse models stably express retinal vasculopathy with cerebral leukodystrophy–linked mutations in TREX1. At least 2 different lines of mice with constitutive inactivation of the HtrA1 gene, which mimics the loss-of-function nature of Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL)-associated mutations, have been generated. Reduced capillary density in the retina has been documented in 1 line and increased trabecular bone mass has been documented in the second.36 However, there is no mention of brain lesions, although the extent to which the brain parenchyma and the cerebral vasculature has been analyzed is unclear.

**Lessons and Opportunities From Col4A1-Related SVD and CADASIL Mouse Models**

**COL4A1/2-Related SVD Mouse Models**

In addition to playing a crucial role in the discovery of COL4A1/2 mutations in patients with SVD, Col4a1 mouse models have proven valuable in elucidating some important aspects of the disease.

Head trauma and intensive sport exercises have been reported as risk factors of intracerebral hemorrhages.31 Mouse studies have shown that surgical delivery of pups carrying the Col4a1 mutation strongly reduces the occurrence of severe perinatal cerebral hemorrhages, indicating that head trauma, particularly during delivery, is a predisposing factor for cerebral hemorrhages in COL4A1 mutation carriers.30 On the basis of this experimental observation, the follow-up of pregnant women who carry a pathogenic COL4A1 mutation includes repeated ultrasound evaluation and recommendation for a cesarean delivery. In addition, the patients and their physicians are informed about the risk of head trauma.31

Clinical manifestations of COL4A1/2 mutations are extremely variable between and even within affected families, and the age of onset can range from the fetal period to adulthood.28 Mouse studies have pinpointed genetic modifiers as likely contributors to variable expressivity of the disease. Gould et al have shown that the phenotype resulting from Col4a1 mutation varied greatly among mice depending on the genetic background. For example, retinal arteriolar tortuosity and ocular anterior segment dysgenesis were highly penetrant in mice with the C57BL/6J background and almost absent in mice with the mixed CAST-BL/6 background.30 Further genetic analyses identified a locus on mouse chromosome 1, which likely contains the modifier gene(s).37 Allelic
heterogeneity may be another source of variability. Notably, mutations clustered within the N-terminus of the collagenous domain of COLA41 in humans are associated with a preferential phenotypic association, which includes the presence of arterial aneurysms; a high prevalence of eye, kidney, and skeletal manifestations; and Raynaud phenomenon, for which the term HANAC (Hereditary Angiopathy with Nephropathy, Aneurysms, and Cramps) syndrome has been coined. The analysis of new mouse models with HANAC syndrome–associated COLA41 mutations, under controlled genetic background, may be of interest to test this possibility.

In addition, the existing Col4a1 mouse models offer a unique opportunity to address many unresolved issues in collagen IV–related SVD, namely the exact mechanisms of white matter disease, cerebral hemorrhages, and porencephalic cavitites. Although disruption of the vascular basement membrane is likely to compromise vascular integrity, this possibility remains to be tested. Furthermore, based on initial studies of aorta, it is likely that these mutations also affect function in small cerebral vessels.

CADASIL Mouse Models

The analysis of CADASIL mouse models, particularly the PAC-Notch3R169C transgenic mouse model that recapitulates the presymptomatic stage of the human disease, has dramatically changed our view of the starting point for this disease.

A key initial finding relates to the potential mechanisms of white matter disease in CADASIL. In patients, imaging studies have revealed a decrease in CBF and cerebrovascular reactivity to CO2 or acetazolamide. However, reduced CBF was observed in patients with tissue lesions and, thus, might occur secondary to tissue loss. On the basis of autopsy studies of patients with CADASIL, it has been argued that vasoreactivity might be compromised as a consequence of arterial stiffening or stenosis of small penetrating arteries, particularly in white matter. Importantly, in old TgPAC-Notch3R169C mutant mice with diffuse white matter disease, there is neither stenosis nor fibrosis of the arterial wall; additionally, there is no evidence of degeneration of vascular muscle, and integrity of the BBB is preserved. Instead, in vivo and ex vivo functional analyses revealed, before the appearance of white matter lesions, cerebrovascular dysfunction, which includes decreased myogenic responses, impaired autoregulation during hypotension, and attenuated functional hyperemia. Moreover, a mild (10% to 20%), diffuse baseline hypoperfusion has been detected both in the unaffected gray and white matter in mutant mice. Another unexpected finding was the discovery of an age-dependent reduction in brain capillary density in these mice. These findings suggest that a key initiating event for the development of white matter disease is cerebrovascular dysfunction acting in concert with microcirculatory rarefaction to reduce resting CBF and disrupt diverse vasodilator mechanisms. Accordingly, there is evidence that white matter is highly vulnerable to moderate chronic hypoperfusion and may be more vulnerable to cerebrovascular dysfunction.

Another interesting finding pertains to migraine. In patients with CADASIL, the frequency of migraine with aura is 5-times higher than in the general population and is usually the first clinical manifestation (average age at onset, 30 years), which may occur in the absence of any neuroimaging abnormalities. Cortical spreading depression (CSD), the electrophysiological substrate of migraine aura, has been investigated in a transgenic mouse model (TgSM22α-hNotch3R169C), which develops age-dependent Notch3 cascade and GOM deposits but no brain tissue lesions. Notably, TgSM22α-hNotch3R169C mice overexpress a low amount of mutant human NOTCH3 under a smooth muscle–specific promoter. These mutant mice have a much lower threshold for CSD induction, as well as a higher CSD propagation speed. In addition to providing an explanation for the higher frequency of migraine with aura in patients with CADASIL, especially at the very beginning of the disease, these results suggest, for the first time to our knowledge, a causal link between primary brain vascular changes and a CSD phenotype. Such a relationship may be specific to CADASIL because the prevalence of migraine with aura is not increased in sporadic SVD. The observation that CSD susceptibility is unchanged in a mouse model of chronic forebrain hypoperfusion, induced by bilateral common carotid artery stenosis, argues against the involvement of hypoperfusion per se in this phenotype. Additional studies are required to determine the precise molecular basis of increased CSD susceptibility.

Challenges and New Areas of Investigation

In addition to the identification of additional molecular players in familial SVD, elucidation of the network of genes/gene products by which NOTCH3, COLA41/2, TRA1, and TREX1 mutations drive small vessel pathology is clearly an area that requires further investigations. The finding of impaired transforming growth factor-β family signaling in the brain vessels of patients with CARASIL needs to be further substantiated, and a causal link with the vascular defects observed in CARASIL remains to be established. The molecular mechanisms of COLA41/2 pathogenesis are still controversial, specifically regarding whether vessel changes are because of collagen IV haploinsufficiency at the basement membrane or intracellular accumulation of misfolded proteins into the endoplasmic reticulum. It is unknown whether cellular mislocalization of the mutant TREX1 protein interferes with its function. Finally, it is still debated whether a reduction in NOTCH3 activity might contribute to the CADASIL disease process. However, recent studies lend support to a Notch3 cascade hypothesis in CADASIL disease pathology, which proposes that aggregation/accumulation of Notch3 cascade is a central event, promoting the abnormal recruitment of functionally important extracellular matrix proteins that ultimately cause multifactorial toxicity. Given that collagen type IV is a core component of the extracellular matrix of brain vessels and HTRA1, a serine protease secreted into the extracellular matrix of brain vessels (A. Joutel, unpublished), this raises the possibility that alterations in the matrisome (defined as the ensemble of extracellular matrix proteins and associated factors) of the cerebral microvasculature might be a converging pathogenic mechanism underlying several forms of familial SVD.

Genetically engineered mouse models of hereditary SVD are still in their infancy. Mouse models of CARASIL and retinal vasculopathy with cerebral leukodystrophy need to be
developed, and better CADASIL models that recapitulate the full spectrum of the disease are also needed. In addition, there are at least 2 aspects in the characterization of existing SVD models that have been neglected to this point, namely neuroimaging and cognitive studies, which are instrumental to the definition of markers and consequences of SVD in humans. These are clearly areas that require further efforts.

Studies point to a possible loss of normal vascular integrity in the pathogenic effects of collagen type IV mutations and to early cerebrovascular dysfunction in the pathogenic effects of CADASIL-associated NOTCH3 mutations. The identification of cellular and molecular mechanisms involved offers great promise to develop genetic or pharmacological strategies that could reverse the vascular defects in existing COLA41 and CADASIL mouse models and establish the causal link between these vascular alterations and occurrence of brain tissue lesions. Another question is whether the diversity of tissue lesions (white matter hyperintensities, small infarctions or hemorrhages in the white or deep gray matter, visible perivascular spaces, and brain atrophy) in SVD reflects a diversity of underlying mechanisms. Interestingly, a recent study demonstrating that the majority of incident lacunes in patients with CADASIL develop at the edge of a white matter hyperintensity raises the possibility that the mechanisms of lacunes and white matter hyperintensities are intimately connected in CADASIL, and perhaps other pathologies.

The need for treatment for SVD, coupled with the availability of mouse models, is fueling interest in developing targeted therapeutic approaches. At this point, therapeutic opportunities are emerging for CADASIL, with the clearance of Notch3 aggregates or the reduction of mutant NOTCH3 expression, using, for example, antisense oligonucleotides.

Finally, several lines of evidence indicate that genetic susceptibility factors contribute to the occurrence of sporadic SVD as part of a multifactorial predisposition. There is a growing appreciation that variants in genes that underlie Mendelian diseases may also modulate the risk for complex forms of the same disease. A recent study suggests that common variants of the NOTCH3 gene increase the risk of age-related white matter lesions in hypertensive patients. Additionally, rare coding variants in the COL4A1 and COL4A2 genes, which may affect COL4A1 and COL4A2 secretion, have been identified in a small cohort of patients with sporadic intracerebral hemorrhages. These finding thus support the idea that monogenic and common non-Mendelian forms of SVD may have similar molecular underpinnings. Specifically, molecular changes and resulting small vessel pathology that arise in Mendelian SVD as a consequence of a single point mutation may be produced in sporadic SVD by a combination of vascular risk factors and altered expression/function of specific variants of Mendelian SVD-contributing genes.

In closing, the identification of major genetic causes of nonhypertensive adult onset SVD has provided an important advancement in the field of SVD, and it is increasingly appreciated that monogenic forms of adult-onset SVD are invaluable paradigms for understanding the pathogenesis of SVD. Furthermore, it is anticipated that one of the next chapters in this field may involve closing the loop between rare familial SVD and common sporadic SVD.

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Disclosures
None.

References


Cerebral Small Vessel Disease: Insights and Opportunities From Mouse Models of Collagen IV–Related Small Vessel Disease and Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

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SUPPLEMENTAL MATERIAL

Cerebral small vessel disease (SVD): Insights and opportunities from mouse models of collagen IV-related SVD and CADASIL

Authors
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### Supplementary Table I: Key features of Mendelian forms of non-amyloid-SVD

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Cerebral features</th>
<th>Extracerebral manifestations</th>
<th>Vascular changes</th>
<th>Mutations - Molecular pathogenesis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CADASIL (Dominant)</td>
<td>NOTCH3 (transmembrane receptor)</td>
<td>migraine with aura, recurrent ischemic strokes, mood disturbance, cognitive decline, disability &gt; death 65-70 years WMH, lacunar infarcts, dilated PVS, microbleeds, brain atrophy</td>
<td>None</td>
<td>GOM, notch3&lt;sup&gt;1&lt;/sup&gt; deposits (arteries, veins, capillaries), loss of SMC, thickening and fibrosis of small penetrating arteries</td>
<td>odd number of cysteine residues in the EGFR&lt;br&gt;Gain-of-novel function (titration of proteins of the extracellular matrix) Notch3 haploinsufficiency (?)</td>
<td>1</td>
</tr>
<tr>
<td>COL4A1/2-related SVD (Dominant)</td>
<td>COL4A1/COL4A2 (Collagen type IV, alpha chains)</td>
<td>infantile hemiparesis, intracerebral hemorrhage (perinatal, young or adult) porencephalic cysts, microbleeds, WMH, intracranial aneurysms (HANAC)</td>
<td>arterial retinal tortuosity cataracts hematuria, renal cysts, cramps (HANAC)</td>
<td>basement membrane defects</td>
<td>substitution of a glycine residue of the Gly-X-Y repeat&lt;br&gt;COL4A1/2 haploinsufficiency (?)&lt;br&gt;ER stress (?)</td>
<td>2</td>
</tr>
<tr>
<td>Retinal Vasculopathy with Cerebral Leukodystrophy (Dominant)</td>
<td>TREX1 (3' DNA exonuclease)</td>
<td>stroke-like episodes, migraine-like headache, cognitive decline, death 5-10 years after the onset WMH, brain pseudotumors</td>
<td>progressive visual impairment, abnormal fluorescein angiogram systemic vasculopathy (skin, liver, intestine) (subset of patients)</td>
<td>fibrinoid necrosis, thickened and fibrotic arterial wall, basement membrane defects of capillaries</td>
<td>frameshift mutations in the C-terminus&gt; C-ter Truncated protein&lt;br&gt;mislocalization of TREVX1</td>
<td>3</td>
</tr>
<tr>
<td>CARASIL (Recessive)</td>
<td>HTRA1 (Serine protease)</td>
<td>recurrent ischemic strokes, cognitive decline, disability &gt; death alopecia spondylosis deformans, disk degeneration</td>
<td>alopecia spondylosis deformans, disk degeneration</td>
<td>loss of SMC, intimal proliferation, double barreling</td>
<td>nonsense or missense mutations in the serine protease domain&lt;br&gt;loss of HTRA1 function &lt;br&gt;increased TGFβ signaling (?)</td>
<td>4</td>
</tr>
</tbody>
</table>

WMH: white matter hyperintensities  
PVS: perivascular spaces

