Cerebral small vessel disease (SVD) and its major clinical consequences, stroke and vascular dementia, represent an increasing health problem in aging societies. The role of genetic factors in SVD etiology is well established and a number of Mendelian forms, including CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) and CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy), have been described. However, only limited progress has been made in the last decades in identifying the underlying gene defects. The advent of deep DNA sequencing technologies has tremendously facilitated the search for disease-causing variants, a recent example being the identification of heterozygous HTRA1 mutations in several families with a previously unknown dominant form of SVD. In a study by Bugiani et al. published in this issue of Neurology, a whole-exome sequencing approach was used to detect the genetic cause of an adult-onset, dominantly inherited leukoencephalopathy of unknown origin in 2 families.

To characterize this condition, autopsy brain samples from 3 affected persons were examined, and a “whole-body” autopsy was performed on one of them. Detailed immunohistochemical, morphometric, and even ultrastructural examination was performed on the brain specimens. These analyses revealed white matter atrophy and scattered small infarcts widely distributed within white matter, deep gray matter, brainstem, and cerebellum. Small arterioles within the brain showed severe arteriosclerosis with mural fibrosis and loss of medial smooth muscle cells but no evidence (in vessel walls) of β-amyloid or the granular osmiophilic material characteristically found in CADASIL. In contradistinction to observations by others in persons with cerebroretinal vasculopathies, including HERNS (hereditary endotheliopathy), one whole-body autopsy failed to show systemic microvasculopathy—with the important caveat that the “n” is small, highlighting the importance of careful autopsy observations in this and other hereditary (and sporadic) microvasculopathies affecting the brain. Smooth muscle cell loss and cerebral vessel wall scarring appeared to be key to disease pathogenesis, as has been noted in other “angiomyopathies.”

To identify the genetic cause of this novel disease, whole-exome sequencing was performed in 2 patients and a healthy control from one family. Analysis of the data by a multistep filtering procedure resulted in the identification of 2 candidate variants, one of which, a heterozygous missense mutation in the CTS4 gene encoding cathepsin A, was detected in all patients, including a case from a second, independent family. Further evidence for CTS4 as causative gene came from its location within the chromosome 20q13 region, a locus previously associated with a vasculopathy showing a highly similar pathology. Both conditions likely represent the same disease, now termed cathepsin A–related arteriopathy with strokes and leukoencephalopathy (CARASAL).

Cathepsin A, also known as protective protein/cathepsin A, is a carboxypeptidase that associates with the lysosomal enzymes β-galactosidase and neuraminidase, promoting their stabilization. Homozygous CTS4 mutations cause galactosialidosis, a rare systemic lysosomal storage disorder that is fatal in the infantile form. While this disease mainly develops due to the absence of β-galactosidase and neuraminidase expression caused by the loss of the protective cathepsin A function, the pathomechanisms underlying the CARASAL mutation (R325C) are unclear. A dominant-negative effect, as recently reported for heterozygous HTRA1 mutations, seems unlikely in view of the considerable differences in CARASAL and galactosialidosis disease phenotypes. Instead, the R325C mutation might alter an alternative cathepsin A function or, as a consequence of the gain of an additional cysteine, could interfere with cathepsin A folding, provoking a neomorphic effect. In line with this hypothesis, Bugiani et al. observed an overexpression of cathepsin A in a patient’s white matter astrocytes. In this context, it is noteworthy that...
CADASIL, the most common monogenic SVD, is primarily caused by cysteine-affecting NOTCH3 mutations, promoting the formation of the characteristic granular osmiophilic material deposits. In addition to stabilizing β-galactosidase and neuraminidase, cathepsin A proteolytically inactivates endothelin-1, a vasoactive peptide mainly known for its role in blood pressure regulation. A recent report showed that endothelin-1 mediates the inhibition of oligodendrocyte maturation and remyelination by reactive astrocytes. Bugiani et al. observed a higher abundance of astrocytic endothelin-1 in the brains of patients with CARASAL than in controls, possibly a consequence of a reduced cathepsin A activity. The authors speculate that increased endothelin-1 levels might result in a general impairment of myelination, leading to a widespread leukoencephalopathy independently of vascular lesions. Although further studies on more families and additional mutants are needed to confirm the reported observations, the identification of a novel SVD gene with links to blood pressure regulation and myelination is likely to advance our understanding of the mechanisms underlying sporadic SVD.

Currently, CARASAL has to be classified as a very rare disease with limited effect on the daily diagnostic work of neurologists. Future investigations on the frequency of CTSA mutations are required to assess the prevalence of this condition. Nevertheless, for SVD patients with a positive family history, an unusual extensive leukoencephalopathy, and an absence of NOTCH3, HTRA1, and COL4A1/A2 mutations, a molecular analysis of the CTSA gene might be considered.

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**DISCLOSURE**

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**REFERENCES**