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Review

Prospects and Challenges in Identifying Genetic Determinants of Age-Related Cerebral Small Vessel Disease

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ABSTRACT: Cerebral small vessel disease (CSVD), which is linked to age and vascular risk factors, is a prominent cause of vascular cognitive impairment and an important contributor to stroke incidence. The therapeutic management of vascular risk factors has failed to reduce the incidence of CSVD, and a trend toward an increasing prevalence of CSVD forms accompanied by neurodegeneration has been observed. These changes, driven primarily by aging and other poorly understood risk factors, coupled with the lack of pathogenetic therapy and specific biomarkers for disease progression, underscore the need for further molecular genetic research into CSVD. Advances in MRI-based CSVD diagnosis have enhanced the translational potential of such studies. The use of high-throughput technologies, such as next-generation sequencing (NGS) and tandem mass spectrometry (MS/MS), combined with meta-analytical approaches that integrate data from large, multi-ethnic cohorts, has enabled the identification of the first reproducible genetic determinants underlying various CSVD MRI markers, as well as their cell-type-specific expression patterns and roles in molecular processes. However, the identification of candidate therapeutic targets remains challenging, largely due to a lack of standardized experimental design for population-based studies. This review highlights key findings from large-scale population-based and multi-omics genetic research that hold promise for significant advancements in CSVD treatment.

Keywords: Cerebral Small Vessel Disease, Magnetic Resonance Imaging, Diffusion Tensor Imaging, Genome-Wide Association Study, Multiomics

Introduction

Cerebral small vessel disease (CSVD) is strongly associated with aging and vascular risk factors and is recognized as one of the most socially significant chronic diseases of the 21st century due to its high prevalence and substantial contribution to disability [1,2]. CSVD is implicated in more than 25% of ischemic strokes, most spontaneous intracerebral hemorrhages, up to 45% of dementia cases, as well as gait disturbances and emotional disorders in the elderly [2-6].

CSVD arises from pathology of the brain's small vessels—penetrating arterioles, venules, and capillaries—that constitute the neurovascular unit (NVU) and the blood-brain barrier (BBB). The classical paradigm of CSVD pathogenesis centers on arterial hypertension, leading to arteriolosclerosis and, consequently, cerebral ischemia and hypoxia [7-12]. For decades, the primary therapeutic strategy for CSVD has focused on blood pressure control. However, this approach is ineffective at preventing dementia and offers questionable protection against delayed brain injury; while it reduces white matter

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hyperintensity burden, it is associated with increasing global cerebral atrophy [13].

Simultaneously, risk factor modification has altered the clinical and pathological signs of CSVD. This shift is characterized by a decrease in manifestations related to severe arterial hypertension, an increase in cases without arterial hypertension, and a rise in mixed forms with co-existing neurodegeneration [14–17].

In 2013, the diagnostic STRIVE criteria (STandards for ReportIng Vascular changes on nEuroimaging) were established to diagnose CSVD based on MRI markers that reflect key histopathological features of cerebral small vessel injury, including white matter hyperintensities, lacunes, recent small subcortical infarcts, enlarged perivascular spaces, microbleeds, and brain atrophy) [4]. The STRIVE criteria enabled the study of CSVD in general populations, even at preclinical and early stages of the disease. However, they have not demonstrated a strong association with the severity and spectrum of clinical manifestations [18].

Recent histopathological, neuroimaging, and experimental studies have provided evidence for the significant role of non-ischemic mechanisms in the development of modern CSVD, including endothelial dysfunction, increased BBB permeability, neuroinflammation, glymphatic dysfunction, neurodegeneration, and alterations in the molecular composition and architecture of the extracellular matrix (ECM) [19,20]. Emerging evidence implicates NVU dysfunction as a key driver of cognitive decline [6], a potential target for Alzheimer's disease pathogenesis [21], and a contributor to mixed cognitive disorders [22]. However, the insights gained into these mechanisms, along with the possibilities of in vivo MRI diagnostics for detecting slowly progressing pathology within a "therapeutic window," have not yet translated into the development of disease-modifying treatments for CSVD [23].

All the aforementioned trends underscore the critical importance of molecular genetics research in CSVD, which originated with the study of its hereditary forms. To date, at least 15 genes associated with monogenic forms of CSVD have been identified, accounting for up to 5% of diagnosed cases [24]. The growing availability of high-throughput sequencing is accelerating the discovery of novel genes and pathogenic mutations for these hereditary forms. Detailed studies of monogenic CSVD have highlighted the critical role of Notch signaling in vascular smooth muscle cell dysfunction, the TGF-β pathway in regulating the ECM composition of cerebral vessels, and type IV collagen in maintaining the stability of the vascular basement membrane. Furthermore, population-based genetic studies are refining our understanding of the frequency and phenotypic spectrum of pathogenic variants associated with hereditary CSVD [25]. Notably, several independent studies have demonstrated that pathogenic *NOTCH3* variants—which cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the most common monogenic CSVD form—are approximately 100 times more prevalent in the general population than the clinical prevalence of CADASIL itself [26]. These findings suggest that modifying factors, potentially including epigenetic regulation, play a crucial role in determining clinical penetrance and shaping CSVD pathogenesis.

However, insights from monogenic forms of CSVD have limited translational potential for developing effective therapies for the much more prevalent sporadic cases. Research efforts have now established the necessary foundation for large-scale population-based and multi-omics studies of sporadic CSVD, creating unprecedented opportunities to elucidate its complex etiology. This review provides a concise overview of the reproducible genetic findings related to key diagnostic MRI features of CSVD, as defined by the STRIVE criteria, and to MRI markers of microstructural white matter damage, which hold promise for a potential breakthrough in the treatment of age-related CSVD.

Materials and methods

A comprehensive literature search was conducted using the PubMed electronic database to identify relevant publications for this review. The search covered articles published from January 1, 2012, to July 31, 2025, to capture the most recent and relevant research. To maintain a focus on age-related CSVD, studies on other neurological conditions were excluded, including vasculitides, migraine, neurodegenerative diseases, monogenic CSVD forms, atherosclerotic small vessel disease, vascular malformations, demyelinating diseases, and leukodystrophies. Although large genetic studies of all-cause ischemic stroke or vascular dementia were identified, only those containing specific data on CSVD were included to avoid overlap with more specialized reviews.

The search strategy was implemented in phases. The initial phase aimed to identify existing systematic reviews to establish the current understanding of the field. The query *[("GWAS" OR "genomics" OR "genetics") AND "small vessel disease"]* was used with the "Review/Systematic Review" filter, yielding 9 relevant reviews after applying exclusion criteria. The second phase focused on identifying original genome-wide association studies (GWAS), transcriptome-wide (TWAS), proteome-wide (PWAS), and epigenome-wide (EWAS) association studies for individual CSVD MRI markers as defined by the STRIVE criteria. The search for

white matter hyperintensities (WMH) utilized the terms *[("GWAS" OR "EWAS" OR "TWAS" OR "PWAS" OR "genetic risk factor" OR "genome-wide" OR "proteome") AND ("white matter hyperintensity" OR "white matter hyperintensities" OR "WMH" OR "leukoaraiosis")]*, which identified 20 relevant articles. For lacunes and lacunar strokes, the query [("GWAS" OR "EWAS" OR "TWAS" OR "PWAS" OR "genetic risk factor" OR "genome-wide" OR "proteome") AND ("lacunar stroke" OR "lacunes") AND "small vessel disease"] was used, retrieving 8 studies. A subsequent search for other STRIVE features employed the string [("GWAS" OR "EWAS" OR "TWAS" OR "PWAS" OR "genetic risk factor" OR "genome-wide" OR "proteome") AND ("perivascular space" OR "cortical atrophy" OR "cerebral microbleeds" OR "lobar hematoma" OR "deep intracerebral hemorrhage")], identifying 7 additional articles. The final phase aimed to capture integrative multi-omics research on CSVD using the search string *[("multiomics" OR "proteomic" OR "proteome" OR "transcriptome" OR "transcriptomic" OR "epigenetic" OR "epigenome" OR "methylome" OR "methylation" OR "chromatin") AND ("small vessel disease")]*, which led to the inclusion of 11 articles. In total, this multi-tiered search strategy identified 55 publications for in-depth analysis.

Population-based genetic studies of CSVD: challenges and prospects

The search for genetic determinants of age-related CSVD began in the 2010s with genome-wide association studies (GWAS), which investigate associations between common genetic variants—primarily single-nucleotide polymorphisms (SNPs), small insertions and deletions (indels) —and MRI features of CSVD. The increasing availability of high-resolution MRI, along with the development of novel neuroimaging techniques, has influenced the design of recent GWAS. In particular, these studies now incorporate diffusion tensor imaging (DTI) metrics to assess microstructural damage in normal-appearing white matter (NAWM), such as fractional anisotropy (FA) and mean diffusivity (MD). To date, CSVD GWAS are being conducted on large, multi-ethnic population-based cohorts comprising up to 40,000 patients. These advances have been facilitated by several major international consortia, including:

- MarkVCID (Markers of Vascular Contributions to Cognitive Impairment and Dementia), established to investigate biomarkers associated with the effects of vascular pathology on cognitive function;
- MEGASTROKE, which focuses on identifying genetic risk factors for stroke subtypes, particularly lacunar stroke;
- CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) - a consortium established to identify genetic determinants of common chronic diseases associated with aging.

Furthermore, samples from major international biobanks, such as the UK Biobank (which contains biospecimens from over 500,000 participants), are now actively utilized for CSVD GWAS. The standardization of data collection, processing, and storage for clinical, neuroimaging, and biospecimen data is a cornerstone of biobanking that significantly enhances the reproducibility of findings from population-based genetic studies.

For all STRIVE criteria of age-related CSVD and standard DTI metrics of NAWM microstructural damage, several independent GWAS have been conducted (Fig.1) [27]. These studies have identified significant polymorphisms (p value $< 5 \times 10{-}8$) in dozens of genetic loci. Notably, some of these loci overlap with genes harboring mutations responsible for monogenic CSVD forms (Fig. 1). The majority of CSVD-associated GWAS-significant polymorphisms are located in non-coding genomic regions, where they exert regulatory effects through cis (local) and trans (distant) mechanisms on gene expression [28]. Consequently, GWAS are now increasingly integrated with transcriptome-wide (TWAS) and proteome-wide (PWAS) association studies [29] (Fig. 2). Mapping GWAS-significant polymorphisms to expression quantitative trait loci (eQTL) further enables the investigation of CSVD pathogenesis through cell-type-specific molecular pathways [30].

TWAS have demonstrated that CSVD-associated polymorphisms primarily influence gene expression in endothelial cells. These findings are particularly relevant for early MRI manifestations of CSVD, such as isolated white matter hyperintensities (WMH) and microstructural changes in NAWM. At later CSVD stages, characterized by the development of lacunes and cortical atrophy, CSVD-associated polymorphisms exert a greater influence on genes expressed in vascular smooth muscle cells, pericytes, oligodendrocytes, and astrocytes [27].

By integrating TWAS and PWAS data, researchers can now classify genes from CSVD-associated GWAS loci into specific functional categories, including the regulation of BBB permeability, cellular processes (differentiation, aging, and apoptosis), organization of the matrisome and its interaction with cells, transmembrane molecular transport, and myelination. Mendelian randomization approaches help evaluate causal relationships between the growing number of CSVD-associated polymorphisms and established vascular risk factors for CSVD, such as arterial hypertension, diabetes mellitus, and dyslipidemia, thereby identifying candidate genes with hidden pathogenic potential. For example, CSVD-associated polymorphisms located within genes

regulating extracellular matrix (ECM) composition have been shown to exhibit the weakest association with vascular risk factors [27].

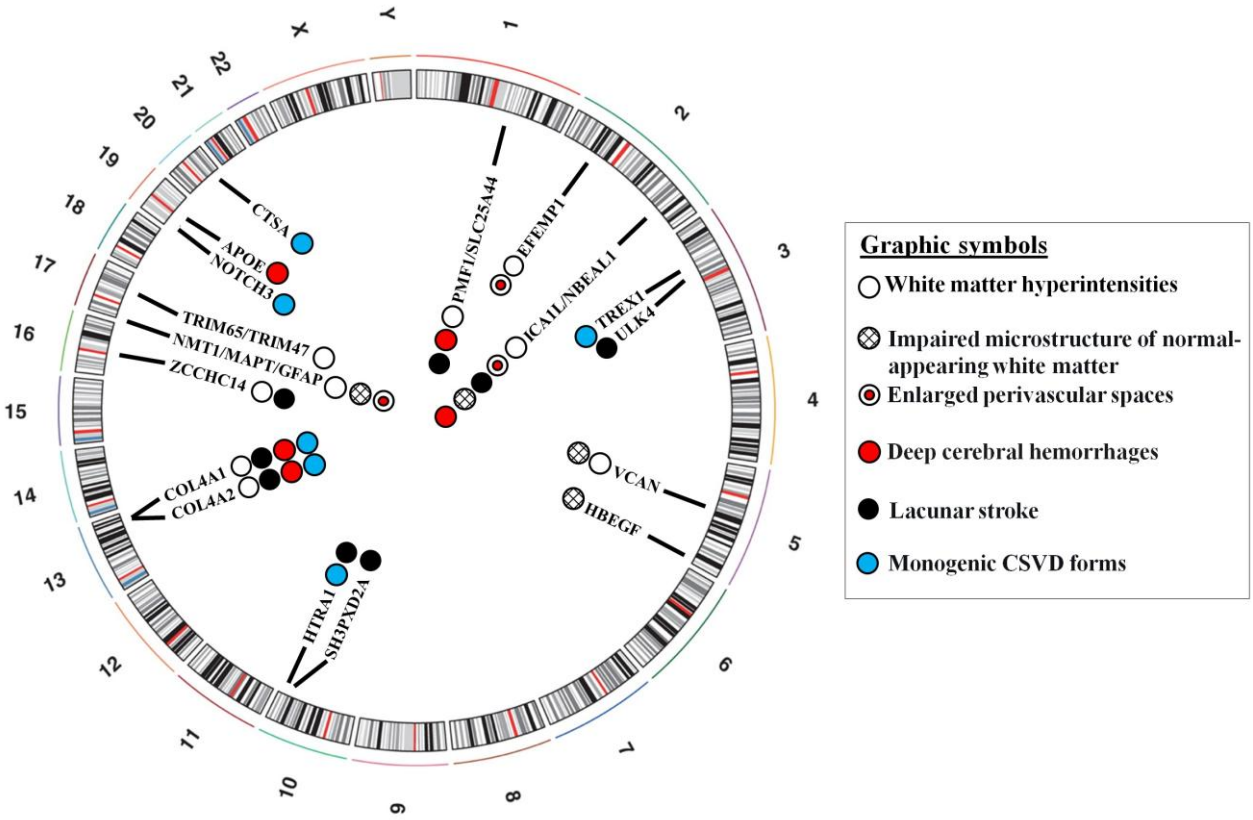

Figure 1. Genetic loci with the most reproducible GWAS-significant polymorphisms associated with key MRI features of CSVD.

Furthermore, the growing number of CSVD-associated polymorphisms identified by GWAS has enabled the construction polygenic risk scores (PRS), which are used to calculate the risk of developing CSVD manifestations in independent population-based cohorts. For instance, a PRS based on polymorphisms associated with CSVD-related cortical atrophy was shown to predict an increased risk of vascular dementia, but not Alzheimer's disease, in a large-scale study involving over 500,000 individuals [32]. Similarly, a PRS for WMH was associated with more pronounced alterations in fractional anisotropy (FA) and mean diffusivity (MD) in the NAWM of a cohort comprising 1,700 young volunteers [33].

Despite the identification of dozens of GWAS-significant polymorphisms for all STRIVE-defined features of CSVD, translating these large-scale genetic findings into specific therapeutic targets remains challenging. A key limitation of existing GWAS is their focus on individual STRIVE-defined features — predominantly isolated WMH—which confines discoveries primarily to the early stages of the disease. Furthermore, the effectiveness and reproducibility of these studies are hampered by the lack of standardized methods for quantifying and characterizing the spatial distribution of MRI features, particularly when they co-occur in advanced CSVD. Since the 2020s, a trend has emerged toward spatial stratification of MRI signs in GWAS design, for example, by separately analyzing deep and periventricular WMH [34], or enlarged perivascular spaces in distinct regions such as the temporal lobes and basal ganglia [31]. Notably, this refined approach significantly increases the yield of GWAS-significant polymorphisms.

In recent years, a trend has emerged toward implementing integrated statistical pipelines designed to translate findings from population-based genetic studies into actionable targets for disease-modifying therapy. A prominent example is the framework established by the GIGASTROKE consortium, which proposed a methodology for identifying candidate drug targets for various ischemic stroke subtypes, including lacunar stroke [35]. This translational pipeline typically involves several key steps. First, disease-associated gene and

protein expression profiles (from TWAS and PWAS) are analyzed for enrichment against known pharmacological targets using international databases such as GREP, DrugBank, or ChEMBL. Subsequently, a correlation analysis assesses the effect of relevant pharmacological compounds on candidate target expression, comparing it to the expression changes induced by the disease itself using tools like the Trans-Phar software. To evaluate the risk of potential side effects, the analysis is expanded to test for associations between candidate target expression and a broad spectrum of disease-related clinical phenotypes, thereby identifying potential disease complications or adverse effects of systemic therapy through phenome-wide association studies (PheWAS). This comprehensive statistical approach generates a shortlist of robust candidate molecular targets for subsequent validation of their pathogenic role and therapeutic potential in animal and cellular models. This strategy is now being actively incorporated into recent CSVD GWAS. For instance, one study suggested that the antidepressant mirtazapine and the microtubule-stabilizing peptide davunetide could modulate the expression of TWAS-significant genes associated with enlarged perivascular spaces in the deep cerebral hemispheres [31].

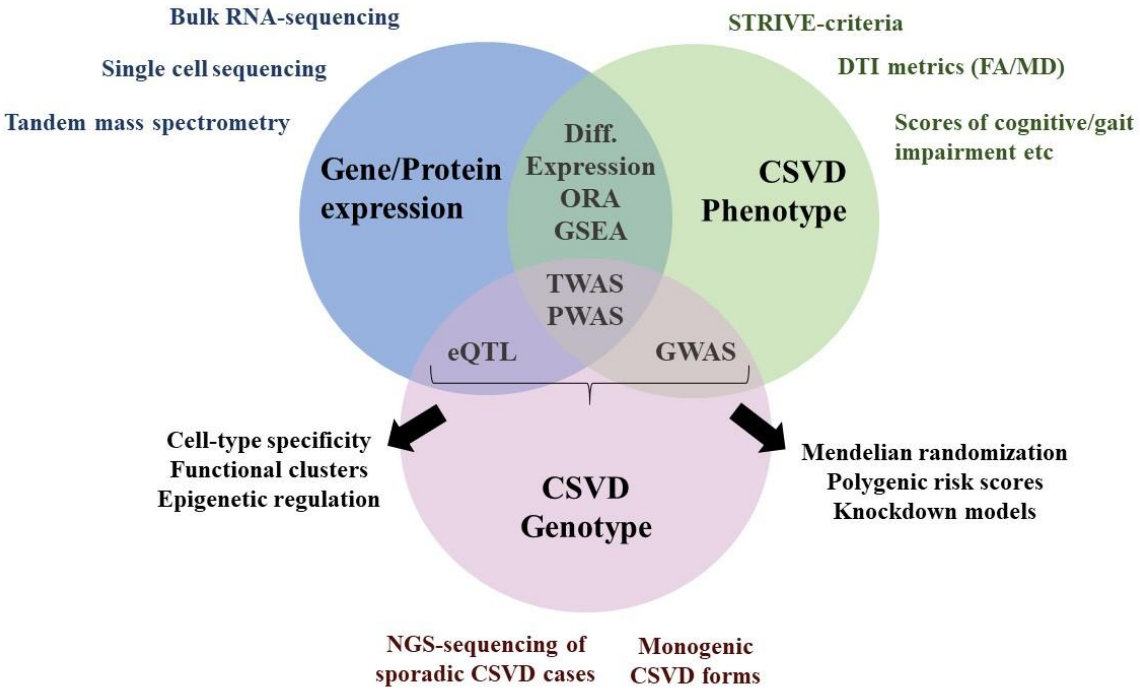

Figure 2. Population-based genetic studies as a promising approach for discovering new biomarkers of age-related CSVD. Abbreviations: STRIVE - STandards for ReportIng Vascular changes on nEuroimaging; DTI - diffusion tensor imaging; FA/MD – fractional anisotropy/mean diffusivity of normal-appearing white matter; ORA - over-representation analysis; GSEA - gene set enrichment analysis; TWAS - transcriptome-wide association studies; PWAS - proteome-wide association studies; GWAS - genome-wide association studies; eQTL - expression quantitative trait loci; NGS – next generation sequencing.

A critical next step in developing disease-modifying therapies is the validation of candidate molecular targets in cellular and animal models. This is typically achieved using gene knockdown or RNA interference to confirm their role in CSVD pathogenesis and to evaluate targeted pharmacological interventions. However, a significant challenge arises from the limitations of existing experimental models. Leading researchers emphasize that while current animal models replicate certain features and mechanisms of CSVD, they fail to recapitulate the full pathological and clinical spectrum of the human disease. Furthermore, these models often lack systematic characterization using neuroimaging markers that align with the STRIVE criteria [36, 37]. Commonly used models in CSVD research include spontaneously hypertensive stroke-prone rats (SHRSP) and models of chronic cerebral hypoperfusion, such as bilateral common carotid artery stenosis (BCCAS) or occlusion (BCCAO). The severe hypertension and diffuse hypoxia induced in these models do not fully mirror the features of modern CSVD, which often presents in the context of managed vascular risk factors. Consequently, models that focus on endothelial dysfunction may hold greater translational promise for replicating contemporary CSVD. For

instance, mice with a heterozygous deficiency in endothelial nitric oxide synthase ($eNOS^{+/-}$) develop lacunar infarcts, increased BBB permeability, and cerebral hypoperfusion under conditions of mild hypertension, mirroring key aspects of the human condition [38, 39]. The ongoing development of more relevant CSVD models necessitates the adoption of a standardized research protocol. Such a protocol should integrate in vivo or ex vivo MRI to verify STRIVE-defined features and diffusion metrics, complemented by comprehensive assessments of endothelial dysfunction, BBB integrity, neuroinflammation, hypoxia/ischemia, and cognitive and motor function [36, 40].

The following section provides a detailed examination of population-based genetic studies for specific CSVD MRI markers.

Population-based genetic studies of WMH and NAWM microstructural damage

White matter hyperintensities (WMH) remain the most extensively studied MRI marker in CSVD, with the the strongest associations reported in GWAS [31,34,41], largely due to their high prevalence in population-based cohorts [42–44]. The heritability of WMH is estimated to be as high as 80%, a figure largely driven by the involvement of deep occipital white matter [45].

The most significant and reproducible polymorphisms map to the 17q25.1 locus, which encompasses genes such as *TRIM47* and *TRIM65*[31,34,41]. These genes encode E3 ubiquitin ligases involved in regulating endothelial inflammatory responses. WMH-associated polymorphisms correlate with reduced *TRIM47* and increased *TRIM65* expression [31]. Experimentally, *TRIM47* knockdown increases endothelial permeability [46,47], while *TRIM47*-deficient mice exhibit reduced brain and lung tolerance to oxidative stress and viral infection [48,49]. The 17q25.1 locus also contains other genes implicated in proliferation, differentiation, apoptosis, and cellular aging. Among these is *H3F3B* gene encoding histone H3.3, which encodes histone H3.3—a protein thataccumulates with age and regulates chromatin organization [50]. These findings highlight the importance of investigating the epigenetic regulation of GWAS-identified loci. It is noteworthy that epigenetic research in age-related CSVD remains considerably less developed compared to Alzheimer's disease and other neurodegenerative disorders. While 17q25.1 locus is the primary GWAS-significant region for deep WMH [34], periventricular WMH demonstrate additional associations that overlap with those for other CSVD MRI markers [31, 33, 51, 52] (Fig. 3).

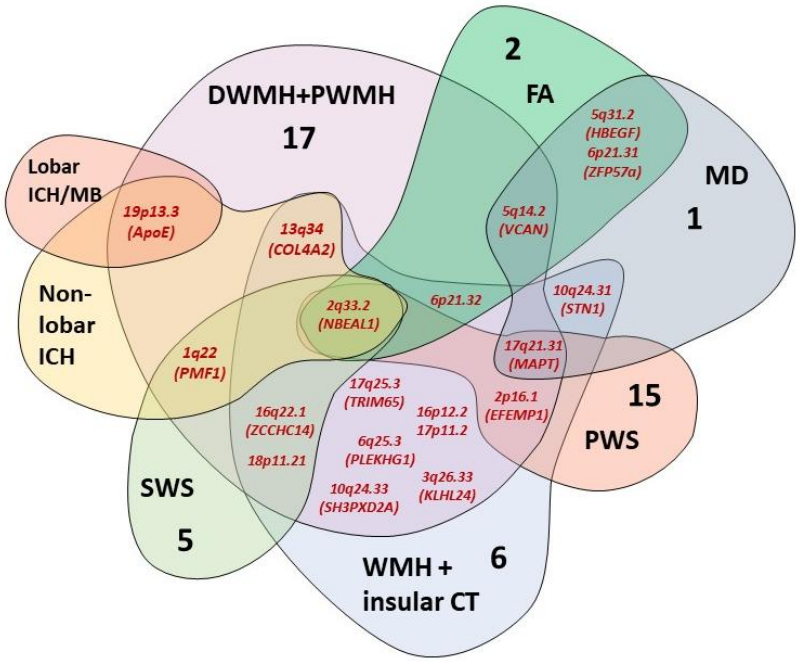

Figure 3. Overlap of GWAS-significant loci across CSVD MRI markers. Abbreviations: DWMH/PWMH – deep/periventricular white matter hyperintensities; ICH – intracerebral hemorrhages; MB – microbleeds; SWS – small vessel strokes (lacunar infarcts); PWS - perivascular spaces; FA/MD – fractional anisotropy/mean diffusivity of normal-appearing white matter; CT - cortical thickness. Numbers on the figure indicate unique significant loci for each of the MRI criteria.

For WMH that co-occur with other MRI signs of age-related CSVD, the 2q33.2 locus (*ICA1L-NBEAL1*) emerges as a key shared genetic risk region. Polymorphisms within this locus have been associated with autoimmune diseases, coronary artery disease, and vascular risk factors. CSVD-associated polymorphisms at this locus correlate with increased expression of *ICA1L* and *NBEAL1* in brain and vascular tissues, where they are hypothesized to exert protective effects by suppressing excitotoxicity and inflammation [33]. Both proteins are involved in vesicular transport and the synthesis of complex biomolecules, including ECM components. This underscores the importance of investigating post-translational modifications in the pathogenesis of age-related CSVD.

The growing availability of diffusion tensor imaging for clinical research has facilitated the first GWAS on microstructural changes in NAWM. The most significant polymorphisms associated with DTI metrics are located at the 5q14 (*VCAN*) and 5q31 (*HBEGF*) loci. The protein products of these genes, versican and heparin-binding EGF-like growth factor, are ECM components and play critical roles in angiogenesis and vascular wall repair [53,54].

Mean diffusivity (MD), one of the most sensitive MRI markers of CSVD-related cognitive impairment [55], is associated with significant polymorphisms at the 17q21.31 locus near the *MAPT* gene, which encodes the tau protein and is linked to tauopathies. These polymorphisms are associated with a generalized upregulation of genes across the 17q21 locus within the walls of cerebral arteries of various calibers [33]. The 17q21.31 locus also harbors polymorphisms identified as significant in GWAS for neurodegenerative diseases [56]. In mouse models of Alzheimer's disease, phosphorylated tau deposition has been observed along perivascular spaces of small vessels [57]. Excess tau is internalized by endothelial cells, leading to cellular senescence, BBB disruption, reduced luminal diameter of small vessels, and intermittent blood flow [58]. Thus, the 17q21.31 locus may represent a key genetic link in the development of mixed cognitive disorders.

Population-based genetic studies of other CSVD MRI signs

In contrast to WMH, other CSVD MRI features demonstrate substantially lower heritability and rarely occur in isolation. These factors have limited the number of reproducible genetic determinants identified in GWAS for these markers [31,59].

For lacunar infarcts, GWAS-significant polymorphisms are predominantly implicated in the differentiation, maturation, and apoptosis of pericytes and oligodendrocyte precursor cells, which are critical for myelination [60]. The most significant and reproducible associations map to the 16q24.2 locus. This association remains significant after adjustment for vascular risk factors and influences the expression of the transcriptional regulator *ZCCHC14* in small vessels [50,61]. Disruption of this locus has been linked to neurodevelopmental delay, autism spectrum disorder, and capillary dysplasia [62]. The region also contains polymorphisms associated with migraine and general ischemic stroke risk.

Beyond the 2q33 and 16q24 loci shared with WMH, lacunar infarcts show significant associations with polymorphisms at the 3p22 locus, which are associated with reduced expression of the nearby gene *ULK4* in brain tissue and vessels [50]. Experimentally, *ULK4* knockdown has been shown to reduce neuronal myelination by nearly half [63]. Further validation is required for other recently identified polymorphisms near genes additionally associated with hereditary connective tissue disorders (*SLC39A13*, involved in zinc transport), monogenic CSVD forms (*HTRA1*, encoding a serine protease, and *COL4A2*, encoding a collagen subunit), and ischemic stroke (*SLC25A44*, a mitochondrial branched-chain amino acid transporter; *FOXF2*, a regulator of pericyte differentiation and proliferation; *SH3PXD2A*, involved in ECM degradation).

Current genetic studies of cerebral microbleeds (CMBs) are underpowered for GWAS due to limited cohort sizes. However, the association between *APOE* polymorphisms—well-known for their role in Alzheimer's disease risk—and an increased risk of lobar hemorrhage has been consistently replicated [64,65]. GWAS investigating mixed CSVD phenotypes that combine hemorrhagic features with other MRI markers are currently ongoing [51]. For deep hemorrhages that co-occur with lacunar infarcts, significant polymorphisms have been identified at the 1q22 (*SLC25A44-PMF1*), 2q33.2 (*ICA1L-NBEAL1*), and 13q34 (*COL4A2*) loci. These variants are associated with reduced expression of the nearby genes in neurons and large artery walls. These loci are predominantly expressed in endothelial cells, pericytes, and vascular smooth muscle cells [51].

The most recent GWAS in CSVD have begun to explore enlarged perivascular spaces (PVS) and cortical atrophy, although though these findings await confirmation through meta-analysis. The heritability of PVS is notably high in white matter (up to 80%), moderate in the basal ganglia (~40%), but remains low (<5%) in the hippocampus and brainstem [66]. GWAS profiles for enlarged PVS implicate genes associated with hereditary leukodystrophies (*GFAP, SLC13A3, PNPT1*), ECM organization, and endothelial differentiation [31]. Significant polymorphisms correlate with reduced expression of *LPAR1* (encoding a lysophosphatidic acid

receptor) in vascular tissues and decreased *ITGB5* (encoding integrin subunit beta 5) levelsin blood [31]. Reduced blood levels of *ITGB5* have also been associated with accelerated cognitive decline and cortical atrophy in patients with dementia [67,68].

For insular cortical atrophy associated with WMH, over 20 GWAS-significant loci have been identified [32]. More than half of these loci show overlapping genetic associations with both isolated WMH and established vascular risk factors. These loci are highly expressed in cells of the neurovascular unit, particularly astrocytes. Furthermore, fifteen of the 20 loci influence gene expression in cortical neurons, affecting processes such as cytoskeleton organization, axonal transport, and neuronal polarization.

Prospects of multi-omics in age-related CSVD research

Findings from population-based association studies are now being augmented by investigations into tissue-specific protein and gene expression profiles, alongside analyses of epigenetic factors such as DNA methylation, chromatin accessibility, non-coding RNA expression, and post-translational modifications. The application of multi-omics technologies in age-related CSVD is still in its early stages, lagging behind their established use in identifying therapeutic targets for neurodegenerative and major cardiovascular diseases.

Despite existing challenges, including high data variability and limited reproducibility, initial milti-omics studies on cohorts ranging from dozens to hundreds of patients with age-related CSVD have been published. A prominent trend is the integration of multi-omics data with high-resolution MRI, including standard DTI metrics.

Single-cell RNA sequencing has enabled cell-type-specific profiling of the NVU in white matter samples from healthy volunteers and patients with vascular dementia. A distinct population of endothelial cells exhibiting a senescent phenotype was identified exclusively in vascular dementia patients, present in both lesioned and normal-appearing white matter. This finding suggests that endothelial dysfunction may precede white matter damage detectable by neuroimaging and histopathology [69].

Integrative analyses of large-scale biobank data, powered by modern machine learning, are beginning to elucidate the relationship between CSVD progression and the plasma proteome. A landmark study profiling approximately 3,000 plasma proteins in 53,000 individuals from the UK Biobank (mean age 57 years, with ~15 years of follow-up) identified significant associations with 720 diseases, including the ICD-10 category “other specified cerebrovascular diseases,” which encompasses CSVD (affecting approximately 1,000 individuals) [70]. The resulting proteome-phenome atlas revealed that this disease category is associated with proteins involved in inflammatory responses, protein transport (notably IGF transport) and protein metabolism, ECM organization, with over 1,000 proteins demonstrating altered expression levels ($p < 0.05$). According to the atlas, epidermal growth factor receptor (EGFR) demonstrated the strongest protective association (Odds Ratio, OR = 0.34), although this effect was non-specific, as it was observed for 90 other conditions. A similar protective effect was associated with tetranectin (CLEC3B, OR = 0.40) and integrin alpha-V (ITGAV, OR = 0.41). Tetranectin, which is involved in plasmin-mediated ECM remodeling, shows reduced plasma levels in various cancers, cardiovascular diseases, and neurological disorders, including multiple sclerosis and Parkinson's disease [71]. Integrin alpha-V, a key regulator of cell migration and ECM structure, is similarly depleted in plasma of individuals with cognitive impairment and dementia [68]. Conversely, the strongest positive associations for "other specified cerebrovascular diseases" were observed for non-specific stress and inflammatory proteins, notably the urokinase plasminogen activator surface receptor (PLAUR, OR = 2.95) and adrenomedullin (ADM, OR = 2.94) [70].

Additional causal insights have been provided by mendelian randomization analysis of large European proteomic biobanks, such as the Iceland 36K study (n=35,892) and the UK Biobank Proteomics(n=34,557). These studies investigated associations between nearly a thousand proteins related to endothelial dysfunction and inflammation and core CSVD MRI features, includinglacunes, white matter hyperintensities, enlarged perivascular spaces, DTI metrics of NAWM, and cerebral microbleeds) [72]. Among the 13 proteins identified—which were primarily implicated in pro-inflammatory platelet and complement activation—five (EPHA2, METAP1D, FLT4, COL2A1, TIMD4) were also linked to cognitive impairment. Two of these, the tyrosine kinase receptor EPHA2 and phosphatidylserine receptor TIMD4, showed positive but non-specific associations with the "other specified cerebrovascular diseases" category [70]. Both EPHA2 and TIMD4 are established prognostic markers for atherosclerosis progression, sepsis, myocardial infarction, and ischemic stroke [73, 74]. Collectively, these findings underscore that despite significant advances in cohort size, proteomic breadth, and analytical power, defining specific biomarkers for CSVD progression remains contingent upon functional validation in dedicated experimental models.

Only a limited number of studies have investigated differential protein expression in the peripheral blood of

CSVD patients. One analysis of approximately 800 plasma proteins compared to 58 patients with pronounced CSVD MRI features to 38 healthy controls, identifying 52 differentially expressed proteins. These proteins were functionally enriched in peptidase regulation, localization to the collagen-containing ECM and circulating microparticles, and involvement in hemostasis, IGF transport, and platelet degranulation [75].

A cerebrospinal fluid (CSF) proteomic study of over 850 individuals, one-third of whom exhibited various CSVD MRI features (including WMH, lacunes, and CMBs), has further enriched this landscape [76]. The study identified a group of proteins with increased expression in CSVD, which were found to be most enriched in endothelial cells and smooth muscle cells of medium-caliber cerebral arteries. The most significant finding was elevated CSF levels of matrix metallo-proteinases (notably MMP12), elastin, and collagen proteins in the early stages of CSVD, primarily in cases with isolated WMH. MMP12 plays a key role in cleaving elastin and other ECM components, a process that, under pathological conditions, can compromise vessel wall integrity and elasticity. The co-occurrence of WMH with CMBs was associated with increased expression of proteins related to immune response and cellular adhesion, whereas the presence of lacunes was linked to the upregulation of non-specific stress-induced proteins. Furthermore, the expression of certain —specifically those expressed in oligodendrocyte precursor cells and involved in axonal guidance, synaptogenesis, and neuronal signaling—was higher in cases with lacunes and microbleeds compared to those with isolated WMH. Collectively, these proteomic data complement findings from population genetic studies, underscoring the pivotal role of ECM remodeling in early CSVD and highlighting compensatory, stress-induced processes, such as remyelination at more advanced stages characterized by lacunes and microbleeds.

Epigenetic alterations in cerebral small vessel disease —including changes in genome-wide DNA methylation, chromatin architecture, and histone modifications— represent the most understudied domain within multi-omics research on this pathology. Key challenges include the high cost of sample processing and sequencing under epigenetic protocols, which constrains the scale of population-based studies. Furthermore, epigenetic signs are highly susceptible to pre-analytical variables, such as temperature fluctuations, mechanical stress, and light exposure during sample storage and processing, all of which can introduce significant confounding effects. An additional layer of complexity stems from the heterogeneity of CSVD MRI phenotypes, which complicates the stratification of epigenetically homogeneous patient subgroups.

In patients with CSVD, increased WMH volume, after adjustment for modifiable risk factors, has been consistently associated with accelerated epigenetic aging, as calculated frommethylation profiles of CpG islands across the genome [77,78]. A comprehensive epigenome-wide association study (EWAS) investigated the relationship between CpG methylation patterns and isolated WMH volume in a multi-ethnic population cohort of approximately 10,000 participants [79]. Among the 450,000 CpG sites analyzed in peripheral blood, a significant association was found between WMH and and methylation at the cg24202936 locus near the *SEPTIN7P11* gene, alongside 11 other conditionally significant differentially methylated CpG loci, including one near the *TRIM67* gene; however, these results were not replicated in an independent population cohort. Pathway analysis revealed that the organization of intercellular interactions was the most enriched molecular process among the differentially methylated CpG loci. The heritability of methylation levels for target CpG loci was reliably estimated at approximately 40%. The analysis also identified 46 differentially methylated regions (DMRs) associated with CSVD. These included a region near *SH3PXD2A*—a gene previously established in GWAS for its role in all ischemic stroke subtypes—as well as regions overlapping known hypertension susceptibility genes (*ENPEP*, *SLC35F3*, *SLC45A4*). A subset of 13 DMRs was successfully replicated in an independent population cohort. Functional enrichment analysis indicated that these DMRs were primarily involved in immune response pathways.

Conclusions

Molecular genetic research into age-related CSVD significantly lags behind comparable efforts in neurodegenerative disorders, despite its substantial contribution to cognitive impairment and disability in the aging population. This disparity underscores a critical need to elevate awareness of CSVD within the scientific community and to systematically integrate high-throughput technologies, biobanking principles, and consortium-based collaborations into mainstream research of CSVD.

Initial findings reveal the dynamic nature of CSVD pathogenesis, which sequentially involves different components of the NVU. Endothelial dysfunction appears to dominate the early stages, characterized by isolated WMH, while dysfunction of pericytes, oligodendrocytes, and astrocytes becomes more prominent in advanced stages with lacunes and microbleeds. The most reproducible genetic polymorphisms identified through GWAS remain significant even after adjusting for established vascular risk factors. TWAS further

underscore the pivotal role of ECM remodeling in early CSVD and highlight protective mechanisms—such as the suppression of neuroinflammation, neuronal remyelination, and the regulation of cellular aging—in later disease stages.

There is an urgent need to develop more standardized methodologies for population-based association studies, particularly for complex, mixed CSVD MRI phenotypes and their relationship with epigenetic regulation. Current evidence emphasizes the importance of investigating the structure of the cerebral small vessel ECM and its interactions with posttranslational modifications and senescent cell phenotypes. Ultimately, a key factor for the success of future molecular genetic studies will be the development and validation of a robust animal model that faithfully recapitulates the spectrum of age-related CSVD.

Author Contributions

P.S. and L.D. conceptualized the review. P.S. conducted the literature review, designed the figures, and drafted the manuscript. L.D., E.G., and E.R. provided critical revision of the manuscript. All authors have read and approved the final version.

Competing interests

The authors declare that they have no competing interests.

References

[1] Rosenberg GA, Wallin A, Wardlaw JM, Markus HS, Montaner J, Wolfson L, et al. (2016). Consensus statement for diagnosis of subcortical small vessel disease. J Cereb Blood Flow Metab, 36:6–25.

[2] Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF (2019). CNS small vessel disease: A clinical review. Neurology, 92:1146–1156.

[3] Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke, 42:2672–2713.

[4] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol, 12:822–838.

[5] Azarpazhooh MR, Avan A, Cipriano LE, Munoz DG, Sposato LA, Hachinski V (2018). Concomitant vascular and neurodegenerative pathologies double the risk of dementia. Alzheimers Dement, 14:148–156.

[6] Santisteban MM, Iadecola C (2018). Hypertension, dietary salt and cognitive impairment. J Cereb Blood Flow Metab, 38:2112–2128.

[7] Fisher CM (1998). Lacunes: small, deep cerebral infarcts. 1965. Neurology, 50:841 and 11 pages following.

[8] Fisher CM (1982). Lacunar strokes and infarcts: a review. Neurology, 32:871–876.

[9] Pantoni L (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol, 9:689–701.

[10] Wardlaw JM, Benveniste H, Williams A (2022). Cerebral Vascular Dysfunctions Detected in Human Small Vessel Disease and Implications for Preclinical Studies. Annu Rev Physiol, 84:409–434.

[11] Markus HS, de Leeuw FE (2023). Cerebral small vessel disease: Recent advances and future directions. Int J Stroke, 18:4–14.

[12] Hainsworth AH, Markus HS, Schneider JA (2024). Cerebral Small Vessel Disease, Hypertension, and Vascular Contributions to Cognitive Impairment and Dementia. Hypertension, 81:75–86.

[13] SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, et al. (2019). Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. JAMA, 321:553–561.

[14] Sonnen JA, Santa Cruz K, Hemmy LS, Woltjer R, Leverenz JB, Montine KS, et al. (2011). Ecology of the aging human brain. Arch Neurol, 68:1049–1056.

[15] Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, et al. (2013). Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. Brain, 136:2697–2706.

[16] Kapasi A, Yu L, Petyuk V, Arfanakis K, Bennett DA, Schneider JA (2022). Association of small vessel disease with tau pathology. Acta Neuropathol, 143:349–362.

[17] Lammie GA, Brannan F, Slattery J, Warlow C (1997). Nonhypertensive cerebral small-vessel disease. Stroke, 28:2222–2229.

[18] Debette S, Schilling S, Duperron M-G, Larsson SC, Markus HS (2019). Clinical Significance of Magnetic Resonance Imaging Markers of Vascular Brain Injury: A Systematic Review and Meta-analysis. JAMA Neurol, 76:81–94.

[19] Joutel A, Haddad I, Ratelade J, Nelson MT (2016). Perturbations of the cerebrovascular matrisome: A convergent mechanism in small vessel disease of the brain? J Cereb Blood Flow Metab, 36:143–157.

[20] Mok VCT, Cai Y, Markus HS (2024). Vascular cognitive impairment and dementia: Mechanisms, treatment, and future directions. Int J Stroke, 19:838–856.

[21] Zlokovic BV (2011). Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci, 12:723–738.

[22] Beishon L, Panerai RB (2021). The Neurovascular Unit in Dementia: An Opinion on Current Research and Future Directions. Front Aging Neurosci, 13:721937.
[23] Dupré N, Drieu A, Joutel A (2024). Pathophysiology of cerebral small vessel disease: a journey through recent discoveries. J Clin Invest. doi: 10.1172/JCI172841.
[24] Manini A, Pantoni L (2023). Genetic Causes of Cerebral Small Vessel Diseases: A Practical Guide for Neurologists. Neurology, 100:766–783.
[25] Ferguson AC, Thrippleton S, Henshall D, Whittaker E, Conway B, MacLeod M, et al. (2022). Frequency and Phenotype Associations of Rare Variants in 5 Monogenic Cerebral Small Vessel Disease Genes in 200,000 UK Biobank Participants. Neurol Genet, 8:e200015.
[26] Yamamoto Y, Liao Y-C, Lee Y-C, Ihara M, Choi JC (2023). Update on the Epidemiology, Pathogenesis, and Biomarkers of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. J Clin Neurol, 19:12–27.
[27] Bhagat R, Marini S, Romero JR (2023). Genetic considerations in cerebral small vessel diseases. Front Neurol, 14:1080168.
[28] Schipper M, Posthuma D (2022). Demystifying non-coding GWAS variants: an overview of computational tools and methods. Hum Mol Genet, 31:R73–R83.
[29] Tak YG, Farnham PJ (2015). Making sense of GWAS: using epigenomics and genome engineering to understand the functional relevance of SNPs in non-coding regions of the human genome. Epigenetics Chromatin, 8:57.
[30] Mai J, Lu M, Gao Q, Zeng J, Xiao J (2023). Transcriptome-wide association studies: recent advances in methods, applications and available databases. Commun Biol, 6:899.
[31] Duperron M-G, Knol MJ, Le Grand Q, Evans TE, Mishra A, Tsuchida A, et al. (2023). Genomics of perivascular space burden unravels early mechanisms of cerebral small vessel disease. Nat Med, 29:950–962.
[32] Patel Y, Shin J, Sliz E, Tang A, Mishra A, Xia R, et al. (2024). Genetic risk factors underlying white matter hyperintensities and cortical atrophy. Nat Commun, 15:9517.
[33] Persyn E, Hanscombe KB, Howson JMM, Lewis CM, Traylor M, Markus HS (2020). Genome-wide association study of MRI markers of cerebral small vessel disease in 42,310 participants. Nat Commun, 11:2175.
[34] Armstrong NJ, Mather KA, Sargurupremraj M, Knol MJ, Malik R, Satizabal CL, et al. (2020). Common Genetic Variation Indicates Separate Causes for Periventricular and Deep White Matter Hyperintensities. Stroke, 51:2111–2121
[35] Mishra A, Malik R, Hachiya T, Jürgenson T, Namba S, Posner DC, et al. (2022). Stroke genetics informs drug discovery and risk prediction across ancestries. Nature, 611:115–123.
[36] Hainsworth AH, Allan SM, Boltze J, Cunningham C, Farris C, Head E, et al. (2017). Translational models for vascular cognitive impairment: a review including larger species. BMC Med, 15:16.
[37] Hainsworth AH, Markus HS (2008). Do in vivo experimental models reflect human cerebral small vessel disease? A systematic review. J Cereb Blood Flow Metab, 28:1877–1891.
[38] Liao F-F, Lin G, Chen X, Chen L, Zheng W, Raghow R, et al. (2021). Endothelial Nitric Oxide Synthase-Deficient Mice: A Model of Spontaneous Cerebral Small-Vessel Disease. Am J Pathol, 191:1932–1945.
[39] Tan X-L, Xue Y-Q, Ma T, Wang X, Li JJ, Lan L, et al. (2015). Partial eNOS deficiency causes spontaneous thrombotic cerebral infarction, amyloid angiopathy and cognitive impairment. Mol Neurodegener, 10:24.
[40] Mustapha M, Nassir CMNCM, Aminuddin N, Safri AA, Ghazali MM (2019). Cerebral Small Vessel Disease (CSVD) - Lessons From the Animal Models. Front Physiol, 10:1317.
[41] Sargurupremraj M, Suzuki H, Jian X, Sarnowski C, Evans TE, Bis JC, et al. (2020). Cerebral small vessel disease genomics and its implications across the lifespan. Nat Commun, 11:6285.
[42] Carmelli D, DeCarli C, Swan GE, Jack LM, Reed T, Wolf PA, et al. (1998). Evidence for genetic variance in white matter hyperintensity volume in normal elderly male twins. Stroke, 29:1177–1181.
[43] Atwood LD, Wolf PA, Heard-Costa NL, Massaro JM, Beiser A, D'Agostino RB, et al. (2004). Genetic variation in white matter hyperintensity volume in the Framingham Study. Stroke, 35:1609–1613.
[44] Turner ST, Jack CR, Fornage M, Mosley TH, Boerwinkle E, de Andrade M (2004). Heritability of leukoaraiosis in hypertensive sibships. Hypertension, 43:483–487.
[45] Sachdev PS, Thalamuthu A, Mather KA, Ames D, Wright MJ, Wen W, et al. (2016). White Matter Hyperintensities Are Under Strong Genetic Influence. Stroke, 47:1422–1428.
[46] Li Y, Huang X, Guo F, Lei T, Li S, Monaghan-Nichols P, et al. (2020). TRIM65 E3 ligase targets VCAM-1 degradation to limit LPS-induced lung inflammation. J Mol Cell Biol, 12:190–201.
[47] Mishra A, Duplaà C, Vojinovic D, Suzuki H, Sargurupremraj M, Zilhão NR, et al. (2022). Gene-mapping study of extremes of cerebral small vessel disease reveals TRIM47 as a strong candidate. Brain, 145:1992–2007.
[48] Qian Y, Wang Z, Lin H, Lei T, Zhou Z, Huang W, et al. (2022). TRIM47 is a novel endothelial activation factor that aggravates lipopolysaccharide-induced acute lung injury in mice via K63-linked ubiquitination of TRAF2. Signal Transduct Target Ther, 7:148.
[49] Duplàa C, Delobel V, Boulestreau R, Rubin S, Vaurs J, Jaspard-Vinassa B, et al. (2024). Cerebral Small Vessel Disease genetic determinant TRIM47 controls brain homeostasisviathe NRF2 antioxidant system. bioRxiv. doi: 10.1101/2024.10.08.616723.
[50] Tvardovskiy A, Schwämmle V, Kempf SJ, Rogowska-Wrzesinska A, Jensen ON (2017). Accumulation of histone variant H3.3 with age is associated with profound

changes in the histone methylation landscape. Nucleic Acids Res, 45:9272–9289.

[51] Traylor M, Persyn E, Tomppo L, Klasson S, Abedi V, Bakker MK, et al. (2021). Genetic basis of lacunar stroke: a pooled analysis of individual patient data and genome-wide association studies. Lancet Neurol, 20:351–361.

[52] Chung J, Marini S, Pera J, Norrving B, Jimenez-Conde J, Roquer J, et al. (2019). Genome-wide association study of cerebral small vessel disease reveals established and novel loci. Brain, 142:3176–3189.

[53] Mehta VB, Besner GE (2007). HB-EGF promotes angiogenesis in endothelial cells via PI3-kinase and MAPK signaling pathways. Growth Factors, 25:253–263.

[54] Yang W, Yee AJ (2013). Versican V2 isoform enhances angiogenesis by regulating endothelial cell activities and fibronectin expression. FEBS Lett, 587:185–192.

[55] Vernooij MW, Ikram MA, Vrooman HA, Wielopolski PA, Krestin GP, Hofman A, et al. (2009). White matter microstructural integrity and cognitive function in a general elderly population. Arch Gen Psychiatry, 66:545–553.

[56] Harerimana NV, Goate AM, Bowles KR (2022). The influence of 17q21.31 and genetic ancestry on neurodegenerative disease risk. Front Aging Neurosci, 14:1021918.

[57] Vilor-Tejedor N, Ciampa I, Operto G, Falcón C, Suárez-Calvet M, Crous-Bou M, et al. (2021). Perivascular spaces are associated with tau pathophysiology and synaptic dysfunction in early Alzheimer's continuum. Alzheimers Res Ther, 13:135.

[58] Hussong SA, Banh AQ, Van Skike CE, Dorigatti AO, Hernandez SF, Hart MJ, et al. (2023). Soluble pathogenic tau enters brain vascular endothelial cells and drives cellular senescence and brain microvascular dysfunction in a mouse model of tauopathy. Nat Commun, 14:2367.

[59] Traylor M, Bevan S, Baron J-C, Hassan A, Lewis CM, Markus HS (2015). Genetic Architecture of Lacunar Stroke. Stroke, 46:2407–2412.

[60] Markus H, Traylor M (2021). Twelve loci provide insights into the genetic basis of lacunar stroke and small vessel disease: a meta-analysis of genome-wide association studies. doi: 10.17863/CAM.73712.

[61] Traylor M, Malik R, Nalls MA, Cotlarciuc I, Radmanesh F, Thorleifsson G, et al. (2017). Genetic variation at 16q24.2 is associated with small vessel stroke. Ann Neurol, 81:383–394.

[62] Handrigan GR, Chitayat D, Lionel AC, Pinsk M, Vaags AK, Marshall CR, et al. (2013). Deletions in 16q24.2 are associated with autism spectrum disorder, intellectual disability and congenital renal malformation. J Med Genet, 50:163–173.

[63] Liu M, Xu P, Guan Z, Qian X, Dockery P, Fitzgerald U, et al. (2018). Ulk4 deficiency leads to hypomyelination in mice. Glia, 66:175–190.

[64] Knol MJ, Lu D, Traylor M, Adams HHH, Romero JRJ, Smith AV, et al. (2020). Association of common genetic variants with brain microbleeds: A genome-wide association study. Neurology, 95:e3331–e3343.

[65] Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, et al. (2011). APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. Lancet Neurol, 10:702–709.

[66] Duperron M-G, Tzourio C, Sargurupremraj M, Mazoyer B, Soumaré A, Schilling S, et al. (2018). Burden of Dilated Perivascular Spaces, an Emerging Marker of Cerebral Small Vessel Disease, Is Highly Heritable. Stroke, 49:282–287.

[67] Marini S, Chung J, Han X, Sun X, Parodi L, Farrer LA, et al. (2023). Pleiotropy analysis between lobar intracerebral hemorrhage and CSF β-amyloid highlights new and established associations. Int J Stroke, 18:804–811.

[68] Tanaka T, Lavery R, Varma V, Fantoni G, Colpo M, Thambisetty M, et al. (2020). Plasma proteomic signatures predict dementia and cognitive impairment. Alzheimers Dement (N Y), 6:e12018.

[69] Mitroi DN, Tian M, Kawaguchi R, Lowry WE, Carmichael ST (2022). Single-nucleus transcriptome analysis reveals disease- and regeneration-associated endothelial cells in white matter vascular dementia. J Cell Mol Med, 26:3183–3195.

[70] Deng Y-T, You J, He Y, Zhang Y, Li H-Y, Wu X-R, et al. (2025). Atlas of the plasma proteome in health and disease in 53,026 adults. Cell, 188:253–271.e7.

[71] Iram S, Rahman S, Choi I, Kim J (2024). Insight into the function of tetranectin in human diseases: A review and prospects for tetranectin-targeted disease treatment. Heliyon, 10:e23512.

[72] Sun Z, Harshfield EL, de Leeuw F-E, Burgess S, Butterworth AS, Riksen NP, et al. (2025). Proteins Involved in Endothelial Function and Inflammation Are Implicated in Cerebral Small Vessel Disease. Stroke, 56:692–704.

[73] Finney AC, Funk SD, Green JM, Yurdagul A Jr, Rana MA, Pistorius R, et al. (2017). EphA2 Expression Regulates Inflammation and Fibroproliferative Remodeling in Atherosclerosis. Circulation, 136:566–582.

[74] Wang Z, Chen C, Su Y, Ke N (2023). Function and characteristics of TIM-4 in immune regulation and disease (Review). Int J Mol Med. doi: 10.3892/ijmm.2022.5213.

[75] Wang Y-C, Zhu H-H, He L-C, Yao Y-T, Zhang L, Xue X-L, et al. (2025). Proteome Profiling of Serum Reveals Pathological Mechanisms and Biomarker Candidates for Cerebral Small Vessel Disease. Transl Stroke Res, 16:1606–1620.

[76] Hristovska I, Kumar A, Binette AP, van Westen D, Janelidze S, Stomrud E, et al. (2023). Identification of distinct and shared biomarkers in cerebral small vessel disease (SVD) through proteomic profiling of cerebrospinal fluid. Alzheimers Dement. doi: 10.1002/alz.082927.

[77] Jiménez-Balado J, Giralt-Steinhauer E, Fernández-Pérez I, Rey L, Cuadrado-Godia E, Ois Á, et al. (2022).

Epigenetic Clock Explains White Matter Hyperintensity Burden Irrespective of Chronological Age. Biology, 12:33.

[78] Raina A, Zhao X, Grove ML, Bressler J, Gottesman RF, Guan W, et al. (2017). Cerebral white matter hyperintensities on MRI and acceleration of epigenetic aging: the atherosclerosis risk in communities study. Clin Epigenetics, 9:21.

[79] Yang Y, Knol MJ, Wang R, Mishra A, Liu D, Luciano M, et al. (2023). Epigenetic and integrative cross-omics analyses of cerebral white matter hyperintensities on MRI. Brain, 146:492–506.