Brain Arteriovenous Malformation and Its Genetic and Epigenetic Influences on Neurovascular Disorders: A Survey

www.surveyx.cn

Abstract

Brain arteriovenous malformations (bAVMs) represent a critical area of study within neurovascular disorders due to their potential to cause severe clinical outcomes, including hemorrhagic strokes and seizures. This survey paper explores the intricate interplay between genetic and epigenetic factors in the pathogenesis of bAVMs, highlighting the significance of hereditary patterns and specific genetic mutations. Recent advancements in genomic research have uncovered a complex genetic landscape, offering insights into potential therapeutic targets. Epigenetic modifications, influenced by environmental factors, further complicate the genetic framework, emphasizing the need for integrated diagnostic approaches. The paper also examines the role of the neurovascular unit (NVU) in neurodegenerative diseases, suggesting novel therapeutic strategies targeting NVU components. Technological advancements in imaging, such as Magnetic Particle Imaging (MPI) and MRI-based oxygen extraction fraction (OEF), provide enhanced diagnostic capabilities, crucial for understanding cerebral blood flow dynamics. Additionally, the potential of machine learning and computational models in refining diagnostic and therapeutic strategies is discussed. Despite significant progress, challenges remain in accurately diagnosing and treating bAVMs, necessitating continued research into genetic and epigenetic influences. This survey underscores the importance of a comprehensive approach that integrates genetic, epigenetic, and environmental factors to improve diagnostic precision and therapeutic outcomes for neurovascular disorders.

1 Introduction

1.1 Significance of Brain Arteriovenous Malformations

Brain arteriovenous malformations (bAVMs) are critical in neurovascular disorders due to their potential to cause severe clinical outcomes, including hemorrhagic strokes, seizures, and chronic headaches. Stroke remains a significant global health issue, impacting millions and contributing to substantial morbidity and mortality [1]. As life expectancy increases, the prevalence and consequences of stroke are likely to rise [2]. bAVMs not only heighten stroke risk but also serve as a vital model for investigating the intricate interactions between vascular anomalies and neurovascular health.

From a research perspective, bAVMs provide a unique opportunity to examine structural and functional changes in cerebral vasculature that affect cerebral blood flow and may lead to neurodegenerative disorders. The neurovascular unit (NVU), comprising endothelial cells, pericytes, astrocytes, and neurons, is crucial in the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's. Aging exacerbates NVU dysfunction, resulting in cognitive decline and increased vulnerability to these conditions. Consequently, bAVMs are central to research aimed at elucidating these complex interactions, ultimately enhancing diagnostic precision and therapeutic outcomes [3].

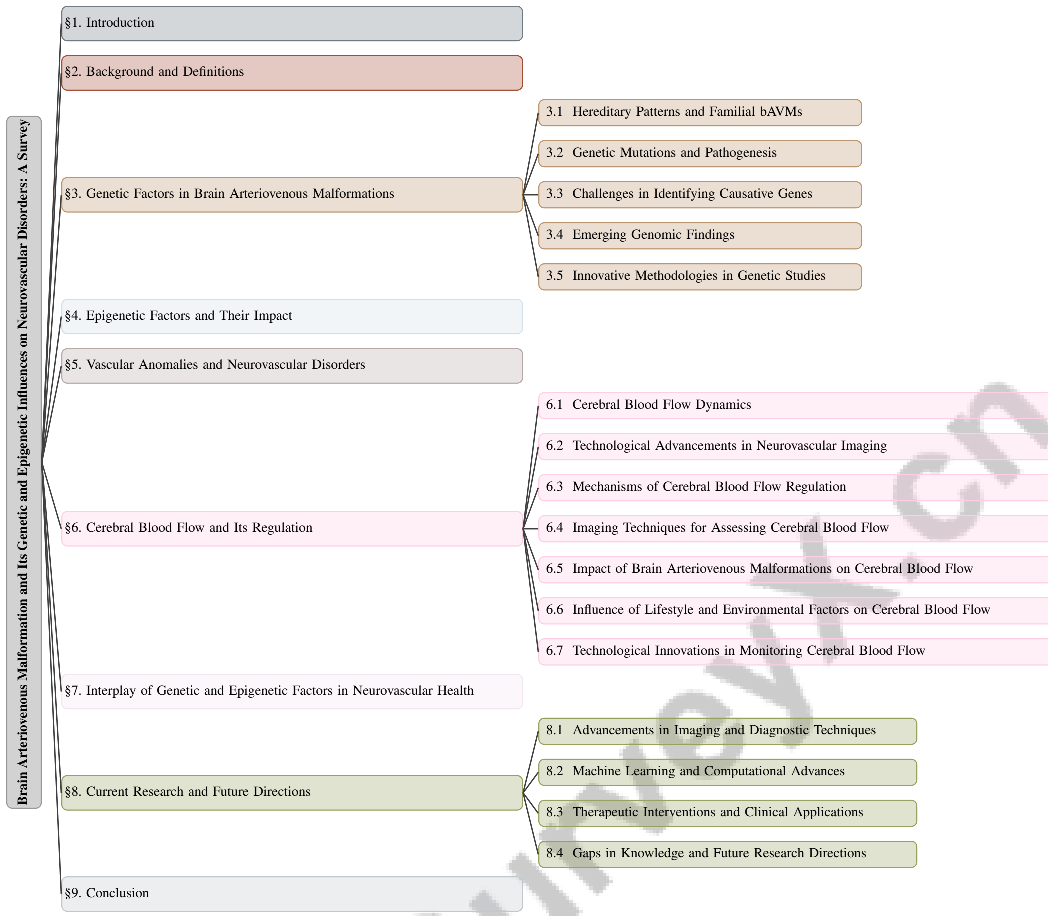


Figure 1: chapter structure

Managing bAVMs is complex, necessitating a comprehensive expert consensus on treatment modalities [4]. Despite advancements in imaging technologies like magnetic particle imaging (MPI), which offers real-time, high-resolution imaging with high sensitivity [5], many vascular anomalies remain resistant to conventional therapies. This highlights the need for innovative treatment approaches [6]. Moreover, effectively handling large-scale data in neurovascular studies is critical, as it significantly impacts clinical and research outcomes [7]. Thus, bAVMs are not only clinically relevant but also represent fertile ground for developing novel diagnostic and therapeutic strategies, with broader implications for managing neurovascular and neurodegenerative disorders.

1.2 Genetic and Epigenetic Influences

The pathogenesis of bAVMs is closely associated with genetic and epigenetic factors that shape the development and progression of these complex neurovascular anomalies. Genetic predispositions, including specific mutations and hereditary patterns, are pivotal in bAVM manifestation. Recent genomic advancements have revealed a multifaceted genetic landscape, identifying mutations that contribute to the aberrant vascular architecture characteristic of bAVMs [8]. These genetic insights are essential for understanding bAVM pathogenesis and offer potential therapeutic targets.

Epigenetic modifications, such as DNA methylation, histone modification, and non-coding RNA expression, also significantly influence bAVM phenotypes. These changes can be modulated by environmental factors and lifestyle choices, adding complexity to the genetic framework [9]. The interplay between genetic mutations and epigenetic alterations is crucial for understanding gene expression regulation in bAVMs, holding promise for identifying novel therapeutic targets [10].

Advanced methodologies, including human-induced pluripotent stem cells (iPSCs), offer promising avenues for modeling neurovascular disorders and evaluating therapeutic strategies [11]. These models can replicate the genetic and epigenetic context of bAVMs, thereby enhancing our understanding of disease mechanisms and facilitating drug efficacy assessments.

Despite significant progress, challenges remain in the accurate diagnosis and treatment of bAVMs, partly due to limitations in current imaging techniques and the lack of comprehensive non-invasive diagnostic methods [5]. Continued exploration of genetic and epigenetic influences is vital for overcoming these challenges and developing integrated diagnostic and therapeutic strategies that effectively address the multifaceted nature of bAVMs. The application of real-time data streaming with batch processing, as highlighted in recent methodological advancements, could further enhance our understanding through large-scale data analysis [7]. Additionally, investigating cerebral blood flow (CBF) reduction mechanisms emphasizes the importance of understanding how these genetic and epigenetic factors intersect with broader neurovascular health, impacting neuronal health and cognitive function in conditions like Alzheimer's disease [12].

1.3 Overview of Paper Structure

This paper provides a comprehensive survey of bAVMs and their genetic and epigenetic influences on neurovascular disorders. The introduction establishes the significance of bAVMs and the role of genetic and epigenetic factors in these conditions. The subsequent section, Background and Definitions, elaborates on key concepts such as vascular anomalies and neurovascular disorders, setting the stage for an in-depth exploration of bAVMs.

The third section, Genetic Factors in Brain Arteriovenous Malformations, delves into hereditary patterns, genetic mutations, and challenges in identifying causative genes, highlighting recent genomic findings and innovative methodologies. This is followed by an examination of Epigenetic Factors and Their Impact, analyzing the influence of environmental factors and lifestyle on epigenetic modifications and their therapeutic implications.

The paper then addresses the relationship between Vascular Anomalies and Neurovascular Disorders, discussing diagnostic challenges, hemodynamic pathologies, and the role of collateral blood supply. The section on Cerebral Blood Flow and Its Regulation explores the dynamics and mechanisms of cerebral blood flow, focusing on the impact of bAVMs and advancements in imaging techniques [3].

The interplay of Genetic and Epigenetic Factors in Neurovascular Health is analyzed in the subsequent section, examining interaction frameworks, environmental influences, and regulatory mechanisms. The paper concludes with Current Research and Future Directions, summarizing recent advancements, identifying knowledge gaps, and proposing future research directions to enhance our understanding and treatment of bAVMs. The necessity for a holistic and individualized treatment approach, emphasized in the Spetzler-Martin Grading system, is integral to discussions on therapeutic interventions [4]. Additionally, applying statistical physics principles to analyze stroke onset provides a novel perspective on interactions within the cerebral vasculature [2].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Vascular Anomalies and Their Classification

Vascular anomalies comprise a diverse set of disorders characterized by atypical blood vessel development and function. Accurate classification is essential to mitigate misdiagnosis risks, given the phenotypic variability and historical inconsistencies in nomenclature [13, 14]. The International Society for the Study of Vascular Anomalies (ISSVA) provides a widely accepted framework, categorizing these anomalies into tumors and malformations. It differentiates proliferative vascular tumors, such as infantile hemangiomas, from vascular malformations, which are further classified by vessel type, including capillary, venous, lymphatic, and arteriovenous malformations (bAVMs).

bAVMs are a distinct type of vascular malformation, consisting of a tangled network of abnormal vessels that connect arteries and veins directly, bypassing the capillary bed. This condition disrupts normal hemodynamics and heightens hemorrhage risk, presenting significant clinical challenges. Recent research has identified specific genetic mutations associated with bAVM development, enhancing our understanding of their etiology [15].

Despite the clarity provided by the ISSVA classification, diagnosing vascular anomalies remains challenging, especially in pediatric cases. These anomalies, often referred to as birthmarks, affect about 1 in 10 infants, yet subtle visual differences and similarities to other dermatological conditions frequently lead to misdiagnosis or delayed referrals by pediatricians [16]. A thorough understanding of the ISSVA classification and specialized training in identifying and managing these conditions are crucial. Incorporating genetic insights into the classification framework promises to enhance diagnostic precision and guide targeted therapeutic interventions.

2.2 Neurovascular Disorders and Related Concepts

The complex relationship between vascular anomalies, particularly bAVMs, and neurovascular disorders is pivotal in understanding various cerebrovascular conditions. bAVMs, with their abnormal vessel connections, can lead to severe complications like intracranial hemorrhage. Recent studies highlight the role of genetic mutations and cellular changes in bAVM pathogenesis, indicating contributions from both hereditary and sporadic factors. This understanding enriches our knowledge of cerebrovascular pathophysiology and informs potential therapeutic strategies [11, 13, 4, 17, 18]. Neurovascular disorders encompass a spectrum of conditions affecting cerebral blood vessels, often exacerbated by underlying vascular anomalies that disrupt normal cerebral blood flow and contribute to pathological hemodynamic states.

bAVMs create high-flow, low-resistance shunts, resulting in increased intracranial pressure and hemorrhagic events. The phenotypic variability of vascular anomalies, compounded by inconsistent naming conventions, complicates classification and clinician communication [13]. This variability underscores the need for standardized terminology and diagnostic approaches, particularly regarding their role in neurovascular disorders.

The hemodynamic disturbances from bAVMs can initiate a cascade of neurovascular dysfunction, leading to conditions such as stroke, transient ischemic attacks, and chronic ischemic changes. These disturbances affect the neurovascular unit (NVU)—a complex of endothelial cells, pericytes, glial cells, and neurons crucial for maintaining cerebral homeostasis, blood-brain barrier integrity, and regulating cerebral blood flow (CBF). NVU dysfunction is linked to early pathophysiological changes in neurodegenerative disorders, including Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, highlighting its importance in brain health and disease progression [11, 19, 20].

Understanding the interplay between vascular anomalies and neurovascular disorders is essential for developing targeted therapeutic interventions. Advances in imaging techniques and genetic research are poised to enhance diagnostic accuracy and treatment outcomes. Enhanced classification systems that integrate genetic and phenotypic data can significantly improve communication and management strategies for complex conditions, facilitating the identification of heterogeneous predictors influencing disease outcomes and revealing gene-gene interactions contributing to disease etiology [21, 22, 14].

3 Genetic Factors in Brain Arteriovenous Malformations

Category	Feature	Method
Hereditary Patterns and Familial bAVMs	Genetic Factors	Mix-HP[14]
Genetic Mutations and Pathogenesis	Genetic and Physiological Modeling	NSE[23]
Challenges in Identifying Causative Genes	Sparsity and Feature Selection	EstHer[24], MTDFS[25]
Innovative Methodologies in Genetic Studies	Likelihood and Effect Assessment Gene Interaction and Dependence Computational and Resource Efficiency Covariate and Confounder Management Diagnostic and Classification Techniques	LIME[26] CIS[27], 3G-SPA[22] HDLA[7] GEE2[8], ICM[28] CNN[16]

Table 1: This table provides a comprehensive summary of various methodologies applied to genetic studies of brain arteriovenous malformations (bAVMs). It categorizes the methods based on hereditary patterns, genetic mutations, challenges in gene identification, and innovative approaches, highlighting their respective features and references. The table serves as a valuable resource for understanding the genetic complexities and methodological advancements in bAVM research.

Research underscores the pivotal role of genetic factors in brain arteriovenous malformations (bAVMs), with hereditary patterns particularly evident in familial cases. Understanding these patterns is essential for elucidating the genetic mechanisms underlying bAVM pathogenesis and the implications of genetic mutations in these vascular anomalies. Table 1 presents a detailed summary of the methodologies utilized in the study of genetic factors associated with brain arteriovenous malformations, highlighting the key features and methods employed in this research domain. Figure 2 illustrates the hierarchical structure of these genetic factors, encompassing hereditary patterns, genetic mutations, challenges in gene identification, emerging genomic findings, and innovative methodologies. Each category delves into specific genetic aspects, emphasizing the complexity and interrelatedness of genetic contributions to bAVM pathogenesis and potential therapeutic strategies. This comprehensive overview not only highlights the intricate genetic landscape but also sets the stage for future research aimed at unraveling the multifaceted nature of bAVMs.

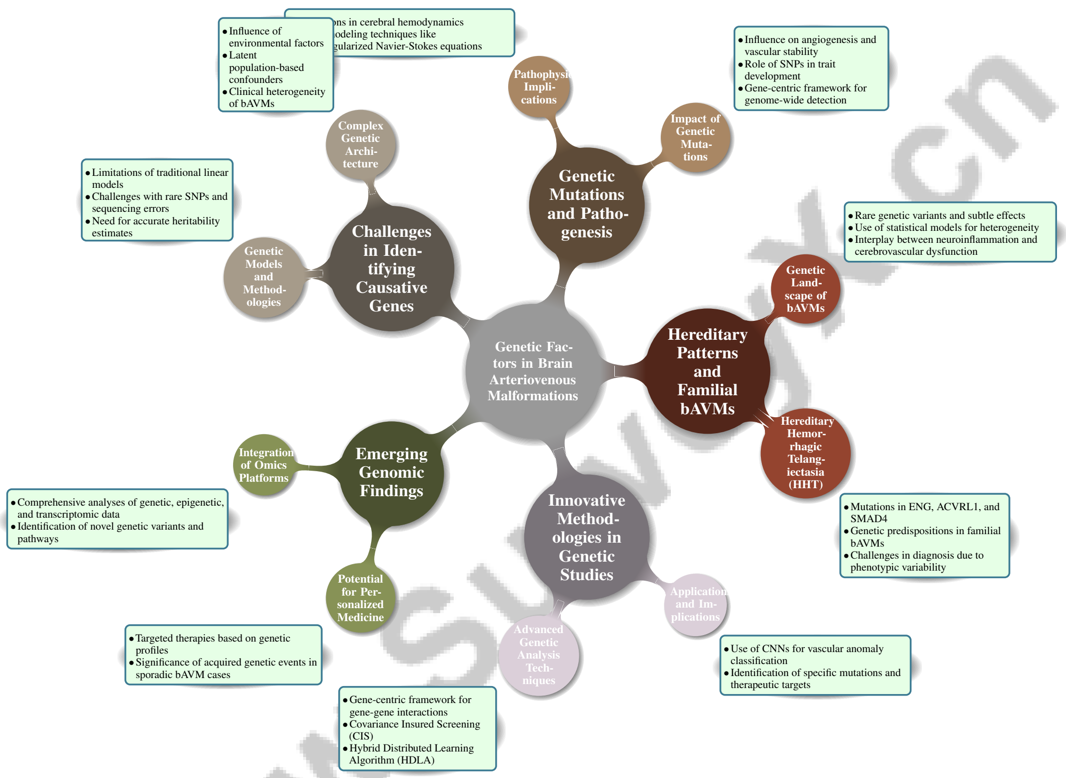


Figure 2: This figure illustrates the hierarchical structure of genetic factors influencing brain arteriovenous malformations (bAVMs), encompassing hereditary patterns, genetic mutations, challenges in gene identification, emerging genomic findings, and innovative methodologies. Each category delves into specific genetic aspects, emphasizing the complexity and interrelatedness of genetic contributions to bAVM pathogenesis and potential therapeutic strategies.

3.1 Hereditary Patterns and Familial bAVMs

Hereditary Hemorrhagic Telangiectasia (HHT), often linked to bAVMs, involves mutations in genes such as ENG, ACVRL1, and SMAD4, crucial for angiogenesis and vascular integrity [18]. These mutations highlight specific genetic predispositions in familial bAVMs. Diagnosing these cases is challenging due to phenotypic variability and overlapping features with other vascular anomalies, leading to potential misdiagnoses, especially in pediatric populations [16].

To illustrate these complexities, Figure 3 presents a figure that depicts the hierarchical structure of hereditary patterns and familial bAVMs, emphasizing the interplay of genetic factors, diagnostic challenges, and therapeutic approaches. Understanding the genetic landscape of bAVMs is vital, as rare genetic variants may exert subtle effects. Statistical models like the regularized finite mixture effects regression model are instrumental in identifying heterogeneity and performing feature selection [14]. Quantifying the heritability of neuroanatomical features associated with bAVMs involves estimating the proportion of phenotypic variance explained by genetic factors, which is critical for unraveling their genetic underpinnings. The interplay between neuroinflammation and cerebrovascular dysfunction further complicates therapeutic strategies, necessitating comprehensive approaches that consider both hereditary and acquired factors [29].

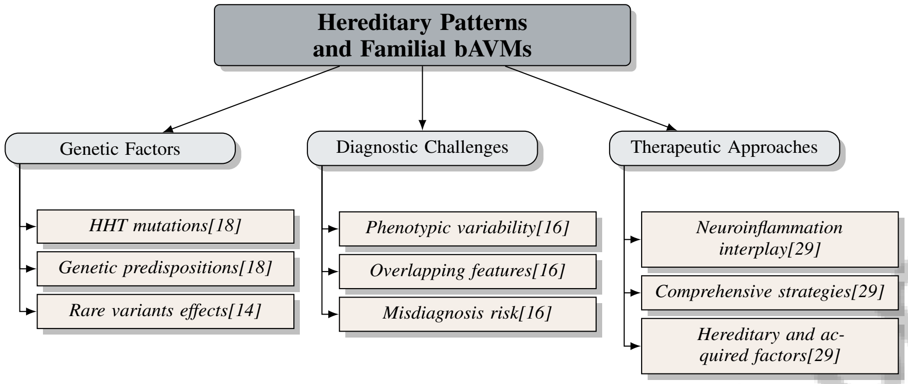


Figure 3: This figure illustrates the hierarchical structure of hereditary patterns and familial bAVMs, emphasizing genetic factors, diagnostic challenges, and therapeutic approaches.

3.2 Genetic Mutations and Pathogenesis

Genetic mutations significantly impact bAVM pathogenesis by influencing angiogenesis and vascular stability, leading to characteristic anomalous vascular architecture. These mutations often occur in genes critical for vascular development, necessitating advanced methods to decode the genetic architecture. Implicit causal models have been proposed to identify the role of single nucleotide polymorphisms (SNPs) in trait development, addressing challenges posed by complex interactions and confounding variables [28]. Recent advancements, such as a gene-centric framework for genome-wide detection of gene-gene interactions, have improved our understanding of bAVM genetics by modeling genetic variations at the gene level [22]. This framework, complemented by innovations in diagnostic tools like convolutional neural networks (CNNs), enhances diagnostic accuracy for vascular anomalies [16]. The pathophysiological implications of genetic mutations extend to cerebral hemodynamics, where disruptions in blood flow dynamics are evident. Modeling techniques, such as Leray-regularized Navier-Stokes equations, elucidate the hemodynamic consequences of genetic mutations in bAVMs [23].

3.3 Challenges in Identifying Causative Genes

Method Name	Genetic Complexity	Model Limitations	Data Challenges
MTDFS[25]	Complex Nonlinear Relationships	Inability TO Handle	Large Sample Sizes
ICM[28]	Complex Interactions	Strong Assumptions	Latent Confounders
GEE2[8]	Complex Trait Distributions	Biased Heritability Estimates	Non-normal Data Distributions
CIS[27]	-	Nonlinear Relationships	Latent Confounders
EstHer[24]	Unknown Genetic Architecture	Traditional Methods Inaccuracies	Clinical Heterogeneity, Sequencing

Table 2: Comparison of genetic analysis methods highlighting their genetic complexity, model limitations, and data challenges. This table provides insights into the strengths and weaknesses of various methodologies employed in the identification of causative genes for bAVMs.

Identifying specific genes responsible for bAVMs is challenging due to intricate genetic architecture and environmental influences. Traditional linear models often fail to select relevant genetic factors while modeling nonlinear relationships inherent in genetic data [25]. Latent population-based confounders obscure causal relationships between SNPs and phenotypic traits, leading to spurious correlations [28]. Clinical heterogeneity of bAVMs complicates the identification of causative genes, necessitating a deep understanding of the genetic landscape where rare genetic variants exert subtle effects [13]. Existing genetic models often rely on strong assumptions, leading to overparametrization and inaccuracies in estimating heritability [8]. Identifying causal variants among rare SNPs is complicated by sequencing errors and the need for large sample sizes, with existing methods potentially selecting irrelevant variables while missing relevant ones [27]. Advances in genetic methodologies that yield more accurate heritability estimates in sparse contexts are crucial for enhancing our understanding of genetic contributions to bAVMs [24]. Table 2 presents a comparative analysis of different genetic methodologies, elucidating their complexities, limitations, and data challenges in the context of identifying causative genes for bAVMs.

3.4 Emerging Genomic Findings

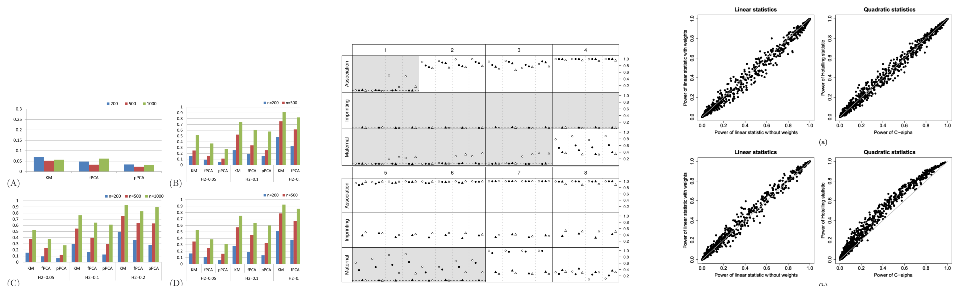
Recent genomic studies have significantly advanced our understanding of bAVM pathogenesis, emphasizing inherited and acquired genetic events. Integrating multiple omics platforms has been pivotal in unraveling the complex genetic landscape of bAVMs, facilitating comprehensive analyses of genetic, epigenetic, and transcriptomic data [17]. This holistic approach has identified novel genetic variants and pathways implicated in bAVM development, suggesting new therapeutic targets. Innovative methodologies like the 3G-SPA method have proven effective in detecting gene-gene interactions, providing a robust framework for analyzing complex traits associated with bAVMs [22]. Identifying specific genes associated with various vascular anomalies has opened avenues for targeted therapies tailored to individual patients' genetic profiles [15]. The potential for personalized medicine in treating bAVMs is underscored by these findings, highlighting the importance of integrating genetic data into clinical decision-making processes. Emerging evidence also points to the significance of acquired genetic events in sporadic bAVM cases, necessitating comprehensive genomic analyses considering both germline and somatic mutations [17]. Robust statistical models like LIME have enhanced the reliability of genetic analyses by mitigating overparametrization risks [26].

3.5 Innovative Methodologies in Genetic Studies

Innovative methodologies in genetic research on bAVMs have significantly advanced our understanding of their complex genetic architecture. The gene-centric framework enables genome-wide detection of gene-gene interactions through a two-step procedure that exhaustively searches for genetic effects and assesses the significance of interactions between identified gene pairs [22]. Covariance Insured Screening (CIS) exploits inter-feature dependence to identify predictors that are marginally associated with outcomes but jointly informative, crucial for detecting subtle genetic effects [27]. The Hybrid Distributed Learning Algorithm (HDLA) utilizes local and distributed computing resources to facilitate large-scale genetic analyses [7]. The GEE2 method introduces a robust framework for estimating genetic effects, providing robust standard errors and accommodating covariate effects that traditional methods often overlook [8]. Convolutional neural networks (CNNs) trained on clinical image datasets offer a novel approach for classifying various vascular anomalies, enhancing diagnostic accuracy [16]. Implicit causal models have shown significant improvements over traditional genetic methods in identifying causal factors [28]. These methodologies, encompassing advanced genomic and transcriptomic analyses, provide a comprehensive understanding of the genetic and cellular mechanisms contributing to bAVM formation and progression. By revealing specific mutations, such as those in the RAS-MAPK signaling pathway, and identifying changes in the neurovascular unit's cellular composition, these approaches facilitate targeted therapeutic interventions. This progress enhances our knowledge of bAVMs and supports personalized medicine in neurovascular health management, ultimately aiming to improve patient outcomes and treatment efficacy [20, 4, 17, 30, 18].

As shown in Figure 4, innovative methodologies have greatly enhanced the study of genetic factors in bAVMs. The first figure illustrates a comparative analysis of four principal component analysis (PCA) methods—KM, fPCA, pPCA, and another pPCA variant—under different heritability settings, highlighting the variance explained by each method. The second figure explores complex interactions of association, imprinting, and maternal effects on gene expression across different genotypes, offering insights into these factors' contributions to phenotypic variability in AVMs. The third figure contrasts the power of linear and quadratic statistical models, with and without weights, in detecting genetic associations, providing a nuanced view of statistical methodologies in genetic research. Collectively, these figures underscore the importance of employing sophisticated analytical techniques to unravel the genetic complexities of bAVMs, paving the way for more targeted therapeutic strategies [22, 26, 31].

AI-generated, for reference only.



(a) Comparison of PCA Methods in Different Settings[22]

(b) Association, Imprinting, and Maternal Effects on Gene Expression in Different Genotypes[26]

(c) Scatter plots comparing the power of linear and quadratic statistics with and without weights[31]

Figure 4: Examples of Innovative Methodologies in Genetic Studies

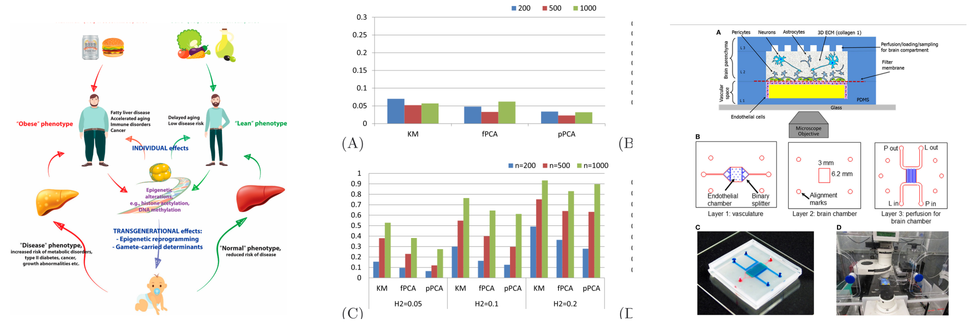
4 Epigenetic Factors and Their Impact

4.1 Environmental Influences on Epigenetic Modifications

Environmental factors significantly influence epigenetic modifications, impacting the development and progression of diseases like brain arteriovenous malformations (bAVMs). Nutritional and chemical exposures can alter the epigenome, increasing disease risk, notably cancer [32]. These factors interact with the epigenome through DNA methylation, histone modifications, and non-coding RNA expression, collectively regulating gene expression. Aging exacerbates these modifications, affecting DNA damage and the neurovascular unit, suggesting that environmental factors may intensify age-related epigenetic changes and neurovascular health [19]. Chronic inflammatory states, induced by repetitive head acceleration events and elevated miRNA levels, exemplify environmental stressors influencing brain perfusion and epigenetic regulation [33]. Despite advances in understanding vascular anomalies' genetic basis, the roles of identified genes and environmental influences on their expression remain under investigation [15]. Integrating epigenetic mechanisms into gene-environment interaction studies emphasizes their roles in inheritance and adaptation to environmental changes. Moreover, environmental factors can indirectly affect epigenetic marks through imaging techniques, such as generating synthetic cerebral 3D OCTA images [34]. Understanding cerebrovascular blood flow and oxygen transport is crucial, as these processes are intricately linked to epigenetic and metabolic pathways [35].

4.2 DNA Damage and Repair Mechanisms

DNA damage and repair mechanisms are crucial for genomic stability and epigenetic regulation, particularly in the aging neurovascular unit, where dysregulation can lead to neurodegenerative diseases [19]. The balance between DNA damage and repair is vital for preserving neurovascular integrity, increasingly challenged by age-related factors and environmental stressors. The complexity of epigenetic reprogramming in mammals, marked by extensive modifications during fertilization and early development, complicates understanding the transmission of epigenetic information [36]. Distinguishing genetic influences from environmental factors in human studies can lead to misinterpretations of epigenetic effects as transgenerational inheritance [37], highlighting the need for precise methodologies in studying DNA damage and repair mechanisms and their impact on epigenetic regulation. Advanced imaging techniques, such as transcranial 3D ultrasound localization, have improved our ability to map the brain's microvasculature, providing insights into the microenvironment where DNA damage and repair processes occur [38]. These techniques are crucial for understanding how hemodynamic changes, such as those during atrial fibrillation, can influence neurovascular health and exacerbate DNA damage [10]. Additionally, modeling dynamic conductivity in electrophysiological modalities captures the complex interactions between blood flow and DNA repair mechanisms [23]. This is particularly relevant in impaired cerebral blood flow contexts, where simulations of gas bubble dynamics provide insights into potential impacts on vascular integrity and DNA stability [39].



(a) Healthy Eating and Liver Health: The Role of Individual and Transgenerational Effects[32]

(b) Comparison of PCA and fPCA with different numbers of components and different values of H2[22]

(c) 3D Brain Tissue Culture Platform[30]

Figure 5: Examples of DNA Damage and Repair Mechanisms

As illustrated in Figure 5, the example on "Epigenetic Factors and Their Impact; DNA Damage and Repair Mechanisms" encompasses various biological and analytical processes. The first image presents a flowchart exploring the intricate relationship between diet and liver health, emphasizing the epigenetic influence on phenotypic outcomes like 'lean' and 'obese' phenotypes, which correlate with liver conditions and systemic health issues. The second image offers a comparative analysis of principal component analysis (PCA) methods, showcasing variance explained by different numbers of components, thus highlighting the role of statistical methods in understanding genetic interactions and their epigenetic implications. Lastly, the third image introduces a 3D brain tissue culture platform, serving as a model to study complex interactions within brain tissue and potentially offering insights into the epigenetic regulation of neural environments [32, 22, 30].

4.3 Epigenetic Inheritance and Transgenerational Effects

Epigenetic inheritance involves the transmission of epigenetic information across generations, significantly impacting how environmental and genetic factors influence phenotypic outcomes in descendants. The reliability of epigenetic information transmission through the germline in humans remains debated, particularly due to the confounding influences of genetic and environmental factors [37]. This complexity is exacerbated by the challenge of distinguishing true epigenetic inheritance from other genetic transmission forms. Epigenetic inheritance involves passing epigenetic marks, such as DNA methylation and histone modifications, through meiotic products, influencing future generations' phenotypic traits [36]. Investigating the extent of faithful inheritance of these epigenetic traits and their impact on subsequent generations is crucial. Understanding these mechanisms is essential for elucidating how environmental exposures, such as nutrition and chemical pollutants, can have lasting effects beyond the immediate generation, potentially affecting offspring's health and development [32]. Research categorizes epigenetic modification processes influenced by nutrition and environmental factors into prenatal, postnatal, and transgenerational impacts, highlighting critical windows during which environmental exposures exert their effects, potentially leading to persistent changes in gene expression patterns passed down through generations [32]. Such insights underscore the need to consider both genetic and epigenetic factors in inheritance and disease risk studies.

4.4 Epigenetic Modulators and Therapeutic Potential

Exploring epigenetic modulators as therapeutic agents presents promising avenues for treating complex diseases, including brain arteriovenous malformations (bAVMs). Epigenetic modulators, such as curcumin, have shown potential in cancer prevention and treatment through multifaceted biological activities, including regulating gene expression via epigenetic pathways [9]. Curcumin's ability to modulate epigenetic marks, such as DNA methylation and histone modifications, highlights its therapeutic promise in targeting underlying disease mechanisms. The development of advanced models, such as induced pluripotent stem cell (iPSC)-derived blood-brain barrier (BBB) models, underscores the potential of epigenetic modulators in understanding disease mechanisms and therapeutic strategies. These models provide insights into genetic influences on BBB function and facilitate drug screening, enhancing our understanding of how epigenetic modulators can be leveraged for therapeutic purposes [30]. Innovative methodologies, like the ST-Net, integrating spatial and temporal data with a specially designed physical loss function, demonstrate significant advancements in model performance compared to existing deconvolution methods. These advancements are crucial for improving the accuracy and efficacy of therapeutic interventions targeting epigenetic pathways [40]. Enhancing the precision of therapeutic targeting contributes to developing more effective treatments for bAVMs and other neurovascular disorders. The therapeutic potential of epigenetic modulators, such as curcumin, extends beyond cancer treatment, encompassing various diseases influenced by epigenetic dysregulation, including neurological disorders, inflammation, and metabolic conditions like diabetes. Curcumin's mechanisms of action involve inhibiting DNA methyltransferases, modulating histone modifications, and regulating microRNAs, collectively reversing harmful epigenetic changes. Moreover, environmental factors and dietary components significantly impact epigenetic marks, emphasizing the importance of nutrition and lifestyle in disease prevention and management through epigenetic pathways [9, 32]. Continued research into these modulators' mechanisms of action and their integration into therapeutic strategies promises to advance personalized medicine and improve outcomes for patients with complex neurovascular conditions.

5 Vascular Anomalies and Neurovascular Disorders

5.1 Diagnosis and Classification Challenges

The diagnosis and classification of vascular anomalies, such as brain arteriovenous malformations (bAVMs), are hindered by their heterogeneous nature. The ISSVA classification system provides a foundational framework but often struggles with phenotypic variability and overlapping features with other conditions, leading to potential misdiagnosis, particularly in pediatric cases where vascular anomalies can resemble dermatologic disorders [15, 16]. The interplay between genetic and environmental factors adds complexity to classification. While genomic research has pinpointed specific mutations associated with bAVMs, traditional genetic models inadequately capture the nonlinear relationships and latent confounders in genetic data [8, 28]. The lack of comprehensive non-invasive diagnostic methods remains a significant obstacle. Although advancements in imaging technologies, including CNNs trained on clinical datasets, have been made, accurate classification still demands specialized expertise [16]. Incorporating genetic insights into diagnostics could enhance accuracy, but computational challenges necessitate further methodological innovations [7].

5.2 Hemodynamic Pathologies and Surgical Interventions

bAVMs cause significant hemodynamic changes due to their direct arteriovenous shunts, which bypass the capillary network, resulting in high-flow, low-resistance circuits. This can increase intracranial pressure and lead to hemorrhagic events, making surgical intervention crucial to prevent severe neurological outcomes [39]. Recent advancements in imaging and computational modeling have enhanced our understanding of these hemodynamic alterations. The Local-AIF method, for example, provides a more accurate depiction of collateral blood supply compared to the Global-AIF, highlighting the importance of collateral circulation in infarct growth [41]. Surgical options for bAVMs include microsurgical resection, endovascular embolization, and stereotactic radiosurgery, with the Spetzler-Martin grading system guiding intervention choices based on bAVM characteristics. Machine learning advancements, such as a linear oscillatory model of blood velocity and pressure derived from clinical data, have the potential to enhance surgical planning and outcomes through precise hemodynamic assessments [42]. Hemodynamic changes associated with bAVMs may also impact cognitive function, as studies link reduced cerebral blood flow to cognitive decline in conditions like Alzheimer's disease [43], underscoring the need for timely surgical interventions to preserve cognitive health.

5.3 Role of Collateral Blood Supply

Collateral blood supply plays a critical role in vascular anomalies such as bAVMs by providing alternative routes for cerebral perfusion when primary pathways are compromised. This supplementary circulation is essential for maintaining adequate cerebral blood flow amidst the high-flow, low-resistance shunts characteristic of bAVMs, which can disrupt normal hemodynamics and increase ischemic risks [41]. Robust collateral networks are associated with reduced infarct size and improved recovery following cerebrovascular incidents. Advances in imaging techniques have enhanced the evaluation of collateral blood supply, revealing its compensatory role in impaired cerebral perfusion. The Local-Arterial Input Function (Local-AIF) method offers a more precise assessment of collateral circulation than traditional Global-AIF approaches, aiding in diagnosis and therapeutic decision-making to enhance collateral flow [41]. The development of collateral networks is influenced by genetic and environmental factors, with certain genetic predispositions affecting the robustness of these pathways [8]. Understanding these influences is crucial for developing targeted therapies to enhance collateral blood flow, thereby improving outcomes for patients with bAVMs and other vascular anomalies. Additionally, integrating computational models and machine learning techniques may refine our understanding of collateral dynamics, paving the way for personalized treatment strategies [42].

6 Cerebral Blood Flow and Its Regulation

6.1 Cerebral Blood Flow Dynamics

Cerebral blood flow (CBF) dynamics are crucial for brain homeostasis, facilitating nutrient and oxygen delivery while removing metabolic waste. The regulation of CBF involves intricate interactions among neural, metabolic, and hemodynamic factors. Advanced imaging techniques, such as pseudo-continuous arterial spin labeling (pcASL), offer non-invasive assessments of cerebral perfusion through magnetic resonance signals, crucial for evaluating CBF distribution [44]. Theoretical models, including attractor reconstruction and nonlinear dynamics, enhance our understanding of CBF regulation, particularly the linear relationship between CBF and physiological parameters like PaCO2. Feedback control models further elucidate the impact of mean arterial blood pressure (MABP) on CBF [45].

Computational models, utilizing Navier-Stokes equations, simulate cerebral hemodynamics by modeling blood flow and conductivity within a multi-compartment head model. These models link CBF variations to neurotransmitter systems and metabolic demands, as demonstrated by studies employing advanced imaging and machine learning [40, 46, 47, 48]. Photon diffusion correlation spectroscopy (PDCS) enhances signal-to-noise ratio (SNR) by averaging measurements, enabling accurate detection of blood flow dynamics and correlating changes with neurotransmitter receptor densities. Integrating spatial information from parameter maps reduces noise, improving CBF assessment reliability [44].

6.2 Technological Advancements in Neurovascular Imaging

Recent advancements in neurovascular imaging have significantly improved the precision of CBF assessments, offering crucial insights into neurovascular disorders. Transcranial Ultrasound Localization Microscopy (tULM) uses ultrafast ultrasound for high-resolution cerebral vasculature mapping, providing detailed visualization of cerebral microcirculation [49]. Enhancements in arterial spin labeling (ASL) perfusion MRI, through denoising techniques, improve SNR, allowing more accurate CBF measurements without contrast agents [50, 51].

Programmable Scanning Diffuse Speckle Contrast Imaging (PS-DSCI) advances spatiotemporal resolution for CBF imaging, employing a digital micromirror device for fast line scanning, surpassing traditional methods [52]. Interferometric Speckle Visibility Spectroscopy (ISVS) enhances signal detection in CBF measurements, enabling accurate assessments with low photon counts [53]. Super-resolution ASL techniques, evaluated using peak signal-to-noise ratio (PSNR) and structural similarity index (SSIM), demonstrate improved image quality, refining diagnostic accuracy [54].

6.3 Mechanisms of Cerebral Blood Flow Regulation

CBF regulation is governed by physiological mechanisms ensuring perfusion meets brain tissue metabolic demands. Smooth muscle tone in cerebral vasculature, influenced by intracellular hydrogen ion concentration, affects vasoconstriction and vasodilation, impacting CBF [55]. Feedback mechanisms maintain CBF proportionality to MABP below a threshold, with a feedback system modulating flow regulation above it [56].

Advanced methods like ISVS provide non-invasive means to monitor CBF dynamics [53]. Deep learning architectures enhance CBF and arterial transit time (ATT) estimation from perfusion-weighted images (PWIs), even with limited post-labeling delays (PLDs) [57]. Smooth muscle cell relaxation, facilitated by decreased intracellular calcium, promotes vasodilation, highlighting the balance between cellular signaling and vascular dynamics [58]. The binary beat-by-beat classification algorithm (BBCA) uses spectral and morphological features to improve cerebral blood flow velocity (CBFV) signal analysis reliability [59]. Applying a least squares approach to noisy data allows robust parameter estimation for gamma variate curves, enriching understanding of blood flow modulation in response to stimuli [60].

6.4 Imaging Techniques for Assessing Cerebral Blood Flow

Assessing CBF is crucial for understanding neurovascular disorders. Advanced imaging techniques measure CBF, each providing unique insights into cerebral perfusion dynamics. Non-invasive MRI-based approaches assess cerebral oxygen extraction fraction (OEF) and utilize blood's signal properties, while machine learning algorithms estimate regional perfusion from resting-state functional MRI (rsfMRI) data. Mathematical modeling techniques, like convolution and deconvolution, analyze arterial and microvascular signals, facilitating CBF quantification [61, 46, 62].

Arterial spin labeling (ASL) perfusion MRI provides quantitative CBF measurements without exogenous contrast agents, using arterial blood water's magnetic properties as an endogenous tracer [55]. Transcranial Doppler (TCD) ultrasonography measures blood flow velocity in major cerebral arteries, assessing dynamic CBF changes in response to stimuli like blood pressure and CO2 level alterations. Mathematical modeling of baroreflex and cerebral autoregulation interaction simulates TCD data, providing insights into CBF regulatory mechanisms [63]. The feedback model of CBF regulation elucidates the relationship between MABP and cerebral perfusion, validated using experimental data from various species, facilitating practical research applications [64].

Advanced techniques like ISVS and tULM capture high-resolution images of cerebral microcirculation. ISVS enhances signal detection through interferometric methods, allowing detailed assessments of blood flow dynamics [64]. tULM uses ultrafast ultrasound to map cerebral vasculature, providing insights into microvascular changes associated with vascular anomalies.

6.5 Impact of Brain Arteriovenous Malformations on Cerebral Blood Flow

Brain arteriovenous malformations (bAVMs) significantly disrupt CBF due to their unique vascular structure, forming direct arteriovenous shunts that bypass the capillary network. This leads to high-flow, low-resistance circuits that disturb normal hemodynamics, increasing intracranial pressure and hemorrhagic event risk. Hemodynamic disturbances necessitate thorough evaluation and management to prevent severe complications, including ischemic deficits, hemorrhagic strokes, and chronic headaches. Advances in understanding bAVMs' genetic and cellular mechanisms emphasize personalized treatment approaches [17, 4, 18].

Recent imaging advancements enhance bAVMs' CBF impact assessment. Techniques like tULM provide detailed cerebral vasculature visualization, offering insights into cerebrovascular dynamics. Time-Resolved Laser Speckle Contrast Imaging (TR-LSCI) maps CBF variations at different depths with high spatial resolution, facilitating understanding of blood flow alterations in bAVMs [65]. The Electrocardiography Brain Perfusion index (EBPi) offers a novel approach to understanding bAVMs' cerebral perfusion impact [66].

Mathematical models elucidate bAVMs' hemodynamic changes. Coupled diffusion approximations capture complex interactions between blood flow, oxygen transport, and neural activity, offering detailed representations [35]. The PaCO2 and CBF relationship aids in predicting cerebral blood flow dynamics, facilitating animal data use in human studies [64]. These models highlight hemodynamic regulation complexity and potential CBF impacts. Clinical implications include phase synchronization alterations between arterial blood pressure (ABP) and intracranial pressure (ICP) in severe neurological injuries, assessing cerebrovascular reactivity and autoregulation integrity [64]. Integrating new spectral measures of Granger isolation (GI) and Granger autonomy (GA) complements traditional Granger causality (GC) analyses, providing insights into oscillatory processes affected by bAVMs [45].

6.6 Influence of Lifestyle and Environmental Factors on Cerebral Blood Flow

Lifestyle and environmental factors significantly influence CBF, affecting brain health and cognitive function. Regular physical activity enhances CBF, with long-term exercise interventions improving cerebral perfusion and cognitive outcomes [67]. Exercise induces neurovascular adaptations, promoting angiogenesis and enhancing endothelial function, improving cerebral hemodynamics. However, exercise effects on CBF vary among individuals, highlighting the need for personalized approaches to optimize cerebral perfusion benefits. Factors like age, baseline fitness, and genetic predispositions influence CBF improvements, necessitating individualized exercise programs for optimal outcomes.

Environmental factors, including pollutant and toxin exposure, adversely affect CBF by inducing oxidative stress and inflammation, impairing endothelial function and reducing vasodilation. A healthy lifestyle, characterized by a balanced diet and regular activity, enhances CBF, mitigating negative effects. Dietary components like nitrates and polyphenols improve CBF, while interventions like trans-resveratrol supplementation benefit those at cognitive decline risk. Excessive caffeine consumption reduces cerebral perfusion, while moderate alcohol intake may enhance CBF dose-dependently. Sustained exercise regimens improve CBF, maintaining cognitive function as populations age [67, 68]. Lifestyle choices, such as diet, smoking, and alcohol consumption, further influence CBF, with unhealthy habits exacerbating cerebrovascular dysfunction risk.

6.7 Technological Innovations in Monitoring Cerebral Blood Flow

Recent technological advancements have significantly enhanced CBF monitoring precision and accuracy. Non-invasive imaging techniques, leveraging ultrafast ultrasound and optical modalities, provide high-resolution cerebral hemodynamics insights. Transcranial Ultrasound Localization Microscopy (tULM) exemplifies such advancements, using ultrafast ultrasound to map cerebral vasculature in detail [49]. This technique visualizes cerebral microcirculation, crucial for understanding hemodynamic changes in neurovascular disorders.

Programmable Scanning Diffuse Speckle Contrast Imaging (PS-DSCI) advances spatiotemporal resolution for CBF imaging, employing a programmable digital micromirror device for fast line scanning, surpassing traditional methods [52]. This method captures rapid blood flow changes, allowing cerebral hemodynamics assessments in response to stimuli. Interferometric Speckle Visibility Spectroscopy (ISVS) enhances weak signal measurements in CBF assessments, improving signal detection through interferometric methods, enabling accurate measurements with low photon counts [53]. This technique provides insights into microvascular changes during CBF regulation.

Machine learning integration with advanced imaging techniques improves CBF assessment accuracy and reliability. Deep learning architectures enhance CBF and arterial transit time (ATT) estimation from perfusion-weighted images (PWIs), even with limited post-labeling delays (PLDs) [57]. These algorithms leverage machine learning's power for accurate cerebral perfusion assessments, paving new avenues for personalized treatment strategies.

7 Interplay of Genetic and Epigenetic Factors in Neurovascular Health

7.1 Genetic and Epigenetic Interaction Frameworks

The intricate dynamics between genetic and epigenetic factors are pivotal for understanding neurovascular health, where gene expression is modulated by epigenetic mechanisms such as DNA methylation, histone modifications, and miRNA regulation [9]. This interaction forms a comprehensive framework that influences phenotypic outcomes, distinguishing genetic inheritance from transgenerational epigenetic inheritance, which is shaped by environmental and lifestyle factors. Such distinctions are crucial for interpreting heritability and understanding disease risk, emphasizing the need for therapies targeting both genetic and epigenetic dimensions of neurovascular disorders [37]. Epigenetic modulators like curcumin illustrate these complexities, highlighting their therapeutic potential in conditions marked by epigenetic dysregulation [9].

7.2 Environmental and Lifestyle Influences

Environmental and lifestyle factors significantly influence the genetic and epigenetic interactions affecting neurovascular health and disease susceptibility. Factors like diet, pollution, and stress induce epigenetic changes that alter gene expression, impacting vascular function and neurovascular disorders [9]. Beneficial lifestyle choices, such as regular exercise, enhance vascular health by promoting gene demethylation involved in angiogenesis and repair, crucial for maintaining cerebral blood flow [67]. Conversely, sedentary lifestyles and poor diets exacerbate epigenetic dysregulation, leading to adverse vascular outcomes. Genetic predispositions further complicate these interactions, necessitating personalized approaches for managing neurovascular health [37].

7.3 Signaling Pathways and Therapeutic Implications

Genetic and epigenetic factors critically impact signaling pathways involved in neurovascular disorders like brain arteriovenous malformations (bAVMs). These pathways, essential for angiogenesis, vascular stability, and neuronal function, are disrupted by genetic mutations and epigenetic modifications [9]. The TGF- signaling pathway, affected by mutations in genes such as ENG, ACVRL1, and SMAD4, is linked to hereditary hemorrhagic telangiectasia and bAVMs, with epigenetic modifications further influencing pathway activity [18]. The Notch signaling pathway, crucial for vascular morphogenesis, is similarly affected by genetic and epigenetic factors. Epigenetic modulators like curcumin offer therapeutic potential by restoring normal signaling dynamics [9]. Targeting these pathways with epigenetic drugs enables personalized treatment strategies, addressing genetic and epigenetic profiles to enhance therapeutic outcomes across various conditions [9, 22, 32, 37].

7.4 Regulatory Mechanisms and Cerebrovascular Health

Cerebrovascular health is deeply influenced by genetic and epigenetic mechanisms that regulate gene expression critical for vascular integrity. Genetic predispositions, marked by mutations in regulatory genes, impact pathways involved in angiogenesis, remodeling, and endothelial function, interacting with epigenetic modifications to maintain cerebrovascular homeostasis [9]. Epigenetic changes mediate environmental factors' effects on gene expression, with lifestyle choices like diet and exercise promoting vascular health by enhancing endothelial function and reducing inflammation [67]. Adverse exposures, such as pollution, lead to harmful epigenetic alterations, emphasizing the role of epigenetic regulation in adapting to environmental challenges [32]. Non-coding RNAs, including miRNAs, further modulate gene expression, playing critical roles in vascular function and serving as potential therapeutic targets for cerebrovascular disorders [33].

8 Current Research and Future Directions

Advancements in imaging and diagnostic techniques have significantly enhanced our understanding of brain arteriovenous malformations (bAVMs) and cerebral blood flow (CBF) dynamics, facilitating early diagnosis and informing targeted therapeutic strategies. This section explores the recent progress in imaging modalities and their implications for neurovascular health.

8.1 Advancements in Imaging and Diagnostic Techniques

Recent imaging advancements have markedly improved CBF assessments and bAVM diagnoses. Magnetic Particle Imaging (MPI) offers superior spatial and temporal resolution, sensitivity, and minimal background interference compared to traditional modalities like MRI, CT, PET, and SPECT, positioning it as a promising tool for real-time vascular imaging [5]. MRI enhancements, such as motion-corrected high-resolution anatomically-assisted reconstruction methods like MOCHA, have improved the quality of CBF maps derived from low-resolution arterial spin labeling (ASL) data by integrating motion correction with anatomical priors [69]. Time-Resolved Laser Speckle Contrast Imaging (TR-LSCI) effectively assesses CBF variations, demonstrating high spatial resolution and depth sensitivity in both phantom evaluations and in-vivo rodent studies, making it suitable for dynamic cerebral perfusion analysis [65]. Optical Coherence Tomography Angiography (OCTA) advancements, including the open-sourcing of synthetic datasets and annotated images, provide valuable benchmarks for future neurovascular imaging research [34]. Advanced computational techniques, including nonlinear fitting and joint spatial regularization in Python with GPU acceleration, have optimized imaging modalities, enhancing CBF assessment accuracy and efficiency [44]. Collectively, these innovations deepen the understanding of CBF dynamics and bAVM pathophysiology, facilitating early diagnoses and targeted therapies. Future research aims to explore innovative imaging techniques, such as advanced MRI-to-PET translation and multi-task deep learning frameworks, to further enhance cerebrovascular disease diagnostics and patient outcomes by leveraging the intricate relationship between CBF and neurovascular health [11, 70].

8.2 Machine Learning and Computational Advances

Machine learning and computational methods have significantly advanced bAVM research, offering new insights into pathophysiology and improving diagnostic and therapeutic strategies. Machine learning models utilizing spectral information from resting-state functional MRI (rsfMRI) predict regional CBF as a surrogate for ASL when traditional imaging is unavailable, enhancing CBF assessment accuracy [46]. Deep learning architectures, such as ASLDN-LFN, achieve improved denoising performance by training models using only noisy image pairs, refining image quality for more accurate diagnostics of vascular anomalies [71]. Machine learning applications extend to classifying blood flow anomalies, achieving 73

8.3 Therapeutic Interventions and Clinical Applications

Therapeutic interventions for bAVMs aim to address hemodynamic disruptions and reduce hemorrhagic event risks. Conventional treatments include surgical resection, endovascular embolization, and stereotactic radiosurgery, often guided by the Spetzler-Martin grading system, which evaluates bAVM size, location, and venous drainage patterns. Recent imaging advancements have enhanced these interventions' precision and efficacy. Super-resolution ASL imaging improves CBF measurement, informing surgical planning and postoperative assessments [54]. TR-LSCI provides a noncontact, high-resolution method for real-time CBF imaging, crucial for monitoring cerebral hemodynamics during and after interventions [65]. The Electrocardiography Brain Perfusion index (EBPi) shows promise as a complementary tool for EEG in monitoring cerebral perfusion and seizure activity. Machine learning and computational models have refined bAVM management, with a CNN classifier demonstrating high accuracy in diagnosing vascular anomalies, significantly enhancing diagnostic performance, particularly in resource-limited settings [16]. Advanced computational models leveraging graph neural networks (GNNs) show potential in predicting CBF and pressure, thereby enhancing therapeutic planning precision [72]. Future research should prioritize obtaining comprehensive human data to validate existing models and explore their implications for therapeutic interventions [64]. Targeted epigenetic modifications using CRISPR technologies present a novel therapeutic avenue, particularly in addressing meiotic epigenetic inheritance complexities related to bAVM pathogenesis [36].

8.4 Gaps in Knowledge and Future Research Directions

Despite significant advancements in understanding bAVMs and their neurovascular implications, critical knowledge gaps remain. A primary area of uncertainty is the intricate interplay of genetic mutations and environmental factors in bAVM development. Future research should integrate genetic findings into classification systems to enable personalized treatment approaches. Robust methodologies to isolate epigenetic effects from genetic and environmental factors are needed, necessitating exploration into the molecular mechanisms underlying meiotic epigenetic inheritance in mammals [36]. In imaging, there is a pressing need for standardized calibration models applicable across diverse patient populations, particularly for cerebral oxygen extraction fraction (OEF) assessments [61]. Enhancing compact, cost-effective devices for assessing cerebrovascular reactivity and health by measuring dynamic changes in CBF is crucial [73]. Optimizing computational methods for real-time imaging, especially expanding Transcranial Ultrasound Localization Microscopy (tULM) applications to various cerebrovascular conditions, remains a priority [38]. Future research should focus on refining computational models by incorporating detailed metabolic models of oxygen consumption and investigating viscosity effects on hemodynamic responses [35]. The exploration of implicit causal models should be improved to manage high-dimensional data better and extend their applicability beyond genetics [28]. Extending existing frameworks to multivariate datasets is necessary to analyze the impact of unobserved confounders and incorporate instantaneous effects

[45]. Developing innovative methodologies for real-time CBF monitoring, such as the EBPi, requires improved device design for comfort and larger trials to validate clinical utility [66]. Research into the long-term neurological sequelae of conditions like COVID-19 is essential to understand the mechanisms behind observed brain changes [74]. To bridge existing knowledge gaps surrounding bAVMs, focused research initiatives exploring the complex genetic and molecular mechanisms involved in their formation and progression are crucial. Such efforts will enhance our understanding of these neurovascular disorders and pave the way for improved clinical outcomes by identifying novel therapeutic targets and optimizing treatment strategies based on insights into bAVM pathogenesis and the neurovascular unit's role in maintaining cerebral health [20, 4, 17, 30, 18].

9 Conclusion

The exploration of genetic and epigenetic factors in brain arteriovenous malformations (bAVMs) offers critical insights into their impact on cerebral blood flow and the broader spectrum of neurovascular disorders. This survey has highlighted the complex interactions between hereditary patterns, genetic mutations, and epigenetic modifications, which collectively influence the onset and progression of bAVMs. By integrating these genetic and epigenetic perspectives, we can better understand the underlying pathophysiology of these vascular anomalies.

Environmental influences, such as dietary components and exposure to toxins, play a pivotal role in shaping epigenetic landscapes, thereby affecting disease vulnerability across generations. This underscores the importance of adopting personalized approaches in the management of neurovascular health, which consider both genetic predispositions and environmental exposures. The dysfunction of the neurovascular unit (NVU) emerges as a significant factor in the pathogenesis of neurodegenerative diseases, suggesting that therapeutic strategies targeting NVU components could be particularly effective.

Advancements in imaging technologies, especially those enabling non-invasive evaluations of brain function and metabolism, hold substantial promise for clinical applications in various brain disorders. Early detection of vascular impairments is crucial, as they can detrimentally affect brain health, contributing to both neurodevelopmental and neurodegenerative conditions. Strategies to maintain blood-brain barrier integrity and modulate glial cell activity are essential for reducing neuroinflammation and preventing cognitive decline.

Moreover, the development of hybrid distributed learning algorithms (HDLA) offers a valuable approach for addressing the complexities inherent in large-scale genetic and epigenetic data analysis. Ongoing research in this area is imperative for devising targeted therapeutic interventions and improving clinical outcomes for individuals affected by these complex neurovascular disorders.

AI-generated, for reference only.

References

[1] Yu Xi Huang, Simon Mahler, Aidin Abedi, Julian Michael Tyszka, Yu Tung Lo, Patrick D. Lyden, Jonathan Russin, Charles Liu, and Changhuei Yang. Correlating stroke risk with non-invasive tracing of brain blood dynamic via a portable speckle contrast optical spectroscopy laser device, 2024.

[2] J. P. Hague and E. M. L. Chung. Statistical physics of cerebral embolization leading to stroke, 2009.

[3] Luoyu Wang, Yitian Tao, Qing Yang, Yan Liang, Siwei Liu, Hongcheng Shi, Dinggang Shen, and Han Zhang. Revolutionizing disease diagnosis with simultaneous functional pet/mr and deeply integrated brain metabolic, hemodynamic, and perfusion networks, 2024.

[4] Yoko Kato, Van Dong, Feres Chaddad, Katsumi Takizawa, Tsuyoshi Izumo, Hitoshi Fukuda, Takayuki Hara, Kenichiro Kikuta, Yasunobu Nakai, Toshiki Endo, et al. Expert consensus on the management of brain arteriovenous malformations. *Asian journal of neurosurgery*, 14(04):1074–1081, 2019.

[5] Lyndia C Wu, Yanrong Zhang, Gary Steinberg, H Qu, S Huang, M Cheng, T Bliss, F Du, J Rao, G Song, et al. A review of magnetic particle imaging and perspectives on neuroimaging. *American Journal of Neuroradiology*, 40(2):206–212, 2019.

[6] Paloma Triana, Mariela Dore, Vanesa Nuñez Cerezo, Manuel Cervantes, Alejandra Vilanova Sánchez, Miriam Miguel Ferrero, Mercedes Díaz González, and Juan Carlos Lopez-Gutierrez. Sirolimus in the treatment of vascular anomalies. *European Journal of Pediatric Surgery*, 27(01):086–090, 2017.

[7] Kevin P. O'Keeffe and Adam Mahdi. Bayesian approach to uncertainty quantification for cerebral autoregulation index, 2018.

[8] Jaron Arbet, Matt McGue, and Saonli Basu. A robust and unified framework for estimating heritability in twin studies using generalized estimating equations, 2018.

[9] Faiz-ul Hassan, Muhammad Saif-ur Rehman, Muhammad Sajjad Khan, Muhammad Amjad Ali, Aroosa Javed, Ayesha Nawaz, and Chengjian Yang. Curcumin as an alternative epigenetic modulator: mechanism of action and potential effects. *Frontiers in genetics*, 10:514, 2019.

[10] Matteo Anselmino, Stefania Scarsoglio, Andrea Saglietto, Fiorenzo Gaita, and Luca Ridolfi. Transient cerebral hypoperfusion and hypertensive events during atrial fibrillation: a plausible mechanism for cognitive impairment, 2016.

[11] Julie Ouellette and Baptiste Lacoste. From neurodevelopmental to neurodegenerative disorders: the vascular continuum. *Frontiers in aging neuroscience*, 13:749026, 2021.

[12] Nils Korte, Ross Nortley, and David Attwell. Cerebral blood flow decrease as an early pathological mechanism in alzheimer's disease. *Acta neuropathologica*, 140(6):793–810, 2020.

[13] Jack E Steiner and Beth A Drolet. Classification of vascular anomalies: an update. In *Seminars in interventional radiology*, volume 34, pages 225–232. Thieme Medical Publishers, 2017.

[14] Yan Li, Chun Yu, Yize Zhao, Robert H. Aseltine, Weixin Yao, and Kun Chen. Pursuing sources of heterogeneity in modeling clustered population, 2021.

[15] Kayo Kunimoto, Yuki Yamamoto, and Masatoshi Jinnin. Issva classification of vascular anomalies and molecular biology. *International Journal of Molecular Sciences*, 23(4):2358, 2022.

[16] Justin Chan, Sharat Raju, Randall Bly, Jonathan A. Perkins, and Shyamnath Gollakota. Identifying pediatric vascular anomalies with deep learning, 2019.

[17] Ethan A Winkler, Mark A Pacult, Joshua S Catapano, Lea Scherschinski, Visish M Srinivasan, Christopher S Graffeo, S Paul Oh, and Michael T Lawton. Emerging pathogenic mechanisms in human brain arteriovenous malformations: A contemporary review in the multiomics era. *Neurosurgical focus*, 53(1):E2, 2022.

[18] Leandro Barbosa Do Prado, Chul Han, S Paul Oh, and Hua Su. Recent advances in basic research for brain arteriovenous malformation. *International journal of molecular sciences*, 20(21):5324, 2019.

[19] Yan Li, Lv Xie, Tingting Huang, Yueman Zhang, Jie Zhou, Bo Qi, Xin Wang, Zengai Chen, and Peiying Li. Aging neurovascular unit and potential role of dna damage and repair in combating vascular and neurodegenerative disorders. *Frontiers in Neuroscience*, 13:778, 2019.

[20] Xing Yu, Caihong Ji, and Anwen Shao. Neurovascular unit dysfunction and neurodegenerative disorders. *Frontiers in neuroscience*, 14:334, 2020.

[21] Nguyen Xuan Vinh. Genetic testing for complex diseases: a simulation study perspective, 2011.

[22] Shaoyu Li and Yuehua Cui. Gene-centric gene-gene interaction: A model-based kernel machine method, 2012.

[23] Maryam Samavaki, Arash Zarrin Nia, Santtu Söderholm, and Sampsa Pursiainen. Navier-stokes modelling of non-newtonian blood flow in cerebral arterial circulation and its dynamic impact on electrical conductivity in a realistic multi-compartment head model, 2023.

[24] Anna Bonnet, Céline Lévy-Leduc, Elisabeth Gassiat, Roberto Toro, and Thomas Bourgeron. Improving heritability estimation by a variable selection approach in sparse high dimensional linear mixed models, 2016.

[25] Chenglin Yu, Dingnan Cui, Muheng Shang, Shu Zhang, Lei Guo, Junwei Han, Lei Du, and Alzheimer's Disease Neuroimaging Initiative. A multi-task deep feature selection method for brain imaging genetics, 2021.

[26] Jingyuan Yang and Shili Lin. Robust partial likelihood approach for detecting imprinting and maternal effects using case-control families, 2013.

[27] Kevin He, Jian Kang, Hyokyoung Grace Hong, Ji Zhu, Yanming Li, Huazhen Lin, Han Xu, and Yi Li. Covariance-insured screening, 2018.

[28] Dustin Tran and David M. Blei. Implicit causal models for genome-wide association studies, 2017.

[29] Weidong Cao, Christopher J Pirozzi, Jian Song, and Zenghui Teng. Neurovascular changes in neuroinflammatory diseases, 2022.

[30] Allison M Bosworth, Shannon L Faley, Leon M Bellan, and Ethan S Lippmann. Modeling neurovascular disorders and therapeutic outcomes with human-induced pluripotent stem cells. *Frontiers in Bioengineering and Biotechnology*, 5:87, 2018.

[31] Andriy Derkach, Jerry F. Lawless, and Lei Sun. Pooled association tests for rare genetic variants: A review and some new results, 2014.

[32] Céline Tiffon. The impact of nutrition and environmental epigenetics on human health and disease. *International journal of molecular sciences*, 19(11):3425, 2018.

[33] Yufen Chen, Amy A Herrold, Zoran Martinovich, Anne J Blood, Nicole Vike, Alexa E Walter, Jaroslaw Harezlak, Peter H Seidenberg, Manish Bhomia, Barbara Knollmann-Ritschel, James L Reilly, Eric A Nauman, Thomas M Talavage, Linda Papa, Semyon Slobounov, and Hans C Breiter. Brain perfusion mediates the relationship between mirna levels and postural control, 2019.

[34] Bastian Wittmann, Lukas Glandorf, Johannes C. Paetzold, Tamaz Amiranashvili, Thomas Wälchli, Daniel Razansky, and Bjoern Menze. Simulation-based segmentation of blood vessels in cerebral 3d octa images, 2024.

[35] Maryam Samavaki, Santtu Söderholm, Arash Zarrin Nia, and Sampsa Pursiainen. A coupled diffusion approximation for spatiotemporal hemodynamic response and deoxygenated blood volume fraction in microcirculation, 2024.

[36] Ksenia Skvortsova, Nicola Iovino, and Ozren Bogdanović. Functions and mechanisms of epigenetic inheritance in animals. *Nature reviews Molecular cell biology*, 19(12):774–790, 2018.

[37] Bernhard Horsthemke. A critical view on transgenerational epigenetic inheritance in humans. *Nature communications*, 9(1):2973, 2018.

[38] Paul Xing, Vincent Perrot, Adan Ulises Dominguez-Vargas, Stephan Quessy, Numa Dancause, and Jean Provost. Towards transcranial 3d ultrasound localization microscopy of the nonhuman primate brain, 2024.

[39] J. P. Hague, C. Banahan, and E. M. L. Chung. Modelling of impaired cerebral blood flow due to gaseous emboli, 2013.

[40] Anbo Cao, Pin-Yu Le, Zhonghui Qie, Haseeb Hassan, Yingwei Guo, Asim Zaman, Jiaxi Lu, Xueqiang Zeng, Huihui Yang, Xiaoqiang Miao, Taiyu Han, Guangtao Huang, Yan Kang, Yu Luo, and Jia Guo. Quantitative perfusion maps using a novelty spatiotemporal convolutional neural network, 2023.

[41] Mira M. Liu, Niloufar Saadat, Steven P. Roth, Marek A. Niekrasz, Mihai Giurcanu, Timothy J. Carroll, and Gregory A. Christoforidis. Quantification of collateral supply with local-aif dynamic susceptibility contrast mri predicts infarct growth, 2024.

[42] Irem Topal, Alexander Cherevko, Yuri Bugay, Maxim Shishlenin, Jean Barbier, Deniz Eroglu, Édgar Roldán, and Roman Belousov. Machine learning for cerebral blood vessels' malformations, 2025.

[43] Marije R Benedictus, Annebet E Leeuwis, Maja AA Binnewijzend, Joost PA Kuijer, Philip Scheltens, Frederik Barkhof, Wiesje M van der Flier, and Niels D Prins. Lower cerebral blood flow is associated with faster cognitive decline in alzheimer's disease. *European radiology*, 27:1169–1175, 2017.

[44] Oliver Maier, Stefan M Spann, Daniela Pinter, Thomas Gattringer, Nicole Hinteregger, Gerhard G. Thallinger, Christian Enzinger, Josef Pfeuffer, Kristian Bredies, and Rudolf Stollberger. Non-linear fitting with joint spatial regularization in arterial spin labeling, 2021.

[45] Laura Sparacino, Yuri Antonacci, Chiara Barà, Angela Valenti, Alberto Porta, and Luca Faes. A method to assess granger causality, isolation and autonomy in the time and frequency domains: theory and application to cerebrovascular variability, 2023.

[46] Ganesh B Chand, Mohamad Habes, Sudipto Dolui, John A Detre, David A Wolk, and Christos Davatzikos. Estimating regional cerebral blood flow using resting-state functional mri via machine learning, 2019.

[47] A. Gersten. Evaluation of the extension of the cerebral blood flow and its main parameters, 2005.

[48] Cerebral blood flow predicts dif.

[49] Charlie Demené, Justine Robin, Alexandre Dizeux, Baptiste Heiles, Mathieu Pernot, Mickael Tanter, and Fabienne Perren. Transcranial ultrafast ultrasound localization microscopy of brain vasculature in patients. *Nature biomedical engineering*, 5(3):219–228, 2021.

[50] Danfeng Xie, Li Bai, and Ze Wang. Denoising arterial spin labeling cerebral blood flow images using deep learning, 2018.

[51] Ramy Hussein, David Shin, Moss Zhao, Jia Guo, Guido Davidzon, Michael Moseley, and Greg Zaharchuk. Brain mri-to-pet synthesis using 3d convolutional attention networks, 2022.

[52] Faezeh Akbari, Xuhui Liu, Fatemeh Hamedi, Mehrana Mohtasebi, Lei Chen, and Guoqiang Yu. Programmable scanning diffuse speckle contrast imaging of cerebral blood flow, 2024.

[53] J. Xu, A. K. Jahromi, J. Brake, J. E. Robinson, and C. Yang. Interferometric speckle visibility spectroscopy (isvs) for human cerebral blood flow monitoring, 2020.

[54] Jianan Cui, Kuang Gong, Paul Han, Huafeng Liu, and Quanzheng Li. Super resolution of arterial spin labeling mr imaging using unsupervised multi-scale generative adversarial network, 2020.

[55] James Duffin, David J Mikulis, and Joseph A Fisher. Control of cerebral blood flow by blood gases. *Frontiers in Physiology*, 12:640075, 2021.

[56] Alexander Gersten. A simple model of cerebral blood flow dependence on arterial blood pressure, 2011.

[57] Acceleration of cerebral blood flow and arterial transit time maps estimation from multiple post-labeling delay arterial spin-labeled mri via deep learning.

[58] Ravi L Rungta, Bruno-Félix Osmanski, Davide Boido, Mickael Tanter, and Serge Charpak. Light controls cerebral blood flow in naive animals. *Nature communications*, 8(1):14191, 2017.

[59] Federico Wadehn, Andrea Fanelli, and Thomas Heldt. Segmentation of tcd cerebral blood flow velocity recordings, 2018.

[60] Ishmael N. Amartey, Andreas A. Linninger, and Thomas Ventimiglia. The derivation and reconstruction of the gamma variate function for tracer dilution curves, 2024.

[61] Dengrong Jiang and Hanzhang Lu. Cerebral oxygen extraction fraction mri: techniques and applications, 2022.

[62] Ishmael N. Amartey, Andreas A. Linninger, and Thomas Ventimiglia. Quantification of tracer dilution dynamics: An exploration into the mathematical modeling of medical imaging, 2024.

[63] Adam Mahdi, Mette S. Olufsen, and Stephen J. Payne. Mathematical model of the interaction between baroreflex and cerebral autoregulation, 2015.

[64] Alexander Gersten. Peculiarities of brain's blood flow : Role of carbon dioxide, 2011.

[65] Faraneh Fathi, Siavash Mazdeyasna, Dara Singh, Chong Huang, Mehrana Mohtasebi, Xuhui Liu, Samaneh Rabienia Haratbar, Mingjun Zhao, Li Chen, Arin Can Ulku, Paul Mos, Claudio Bruschini, Edoardo Charbon, Lei Chen, and Guoqiang Yu. Time-resolved laser speckle contrast imaging (tr-lsci) of cerebral blood flow, 2023.

[66] Samuel J van Bohemen, Jeffrey M Rogers, Aleksandra Alavanja, Andrew Evans, Noel Young, Philip C Boughton, Joaquin Valderrama, and Andre Z Kyme. Safety, feasibility, and acceptability of a novel device to monitor ischaemic stroke patients, 2024.

[67] Review.

[68] Peter J Joris, Ronald P Mensink, Tanja C Adam, and Thomas T Liu. Cerebral blood flow measurements in adults: a review on the effects of dietary factors and exercise. *Nutrients*, 10(5):530, 2018.

[69] Abolfazl Mehranian, Colm J. McGinnity, Radhouene Neji, Claudia Prieto, Alexander Hammers, Enrico De Vita, and Andrew J. Reader. Motion-corrected and high-resolution anatomically-assisted (mocha) reconstruction of arterial spin labelling mri, 2019.

[70] Ramy Hussein, Moss Zhao, David Shin, Jia Guo, Kevin T. Chen, Rui D. Armindo, Guido Davidzon, Michael Moseley, and Greg Zaharchuk. Multi-task deep learning for cerebrovascular disease classification and mri-to-pet translation, 2022.

[71] Danfeng Xie, Yiran Li, Hanlu Yang, Li Bai, Lei Zhang, and Ze Wang. A learning-from-noise dilated wide activation network for denoising arterial spin labeling (asl) perfusion images, 2020.

[72] Seungyeon Kim, Wheesung Lee, Sung-Ho Ahn, Do-Eun Lee, and Tae-Rin Lee. Graph neural network for cerebral blood flow prediction with clinical datasets, 2024.

[73] Yu Xi Huang, Simon Mahler, Maya Dickson, Aidin Abedi, Julian M. Tyszka, Jack Lo Yu Tung, Jonathan Russin, Charles Liu, and Changhuei Yang. A compact and cost-effective laser-powered speckle visibility spectroscopy (svs) device for measuring cerebral blood flow, 2024.

[74] Yuanyuan Qin, Jinfeng Wu, Tao Chen, Jia Li, Guiling Zhang, Di Wu, Yiran Zhou, Ning Zheng, Aoling Cai, Qin Ning, et al. Long-term microstructure and cerebral blood flow changes in patients recovered from covid-19 without neurological manifestations. *The Journal of clinical investigation*, 131(8), 2021.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.

AI-generated, for reference only.