International Journal of Pharmaceutical research and Applications
Volume 11, Issue 1, Jan-Feb 2026, pp:1431-1438 www.ijprajournal.com ISSN: 2456-4494

Genetics Basis of cerebrovascular Disease

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Date of Submission: 15-02-2026 Date of Acceptance: 28-02-2026

ABSTRACT
Cerebrovascular diseases (CVDs) comprise a spectrum of disorders affecting the blood vessels of the brain, with stroke being the most common and severe outcome. They represent one of the leading causes of death and long-term disability worldwide. While conventional risk factors such as hypertension, diabetes mellitus, hyperlipidaemia, smoking, and aging are well established, increasing evidence highlights the critical role of genetic determinants in disease susceptibility, onset, and progression. Advances in molecular genetics, including genome-wide association studies, have identified several genes and loci implicated in cerebrovascular pathophysiology. Mutations in genes such as *NOTCH3*, *COL4A1/2*, and *HTRA1* are associated with monogenic disorders like CADASIL and CARASIL, while polygenic influences contribute to common multifactorial stroke subtypes. Genetic variants also modulate vascular integrity, lipid metabolism, coagulation pathways, and inflammatory mechanisms that underlie cerebrovascular injury. Furthermore, pharmacogenomic studies demonstrate that genetic polymorphisms influence individual responses to antithrombotic and lipid-lowering therapies, emphasising the importance of personalised medicine in stroke prevention and management. Understanding genetic contributions enables early diagnosis, risk stratification, and the development of targeted interventions. Family history and genetic counselling provide additional value in identifying individuals at high risk. Ongoing integration of genomics with proteomic and epigenetic research continues to expand insights into cerebrovascular biology, offering opportunities for precision prevention and therapy. Ultimately, combining genetic knowledge with modification of environmental and lifestyle factors provides the most effective strategy to reduce the burden of cerebrovascular disease globally.

KEYWORDS
Cerebrovascular disease,Strokegenetics,Monogenic disorders (e.g., NOTCH3,COL4A1/COL4A2),Polygenicrisk factors,Genome-wide association studies (GWAS),Epigenetics,Gene–environment interaction

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I. INTRODUCTION

Cerebrovascular diseases (CVDs), which include ischaemic stroke, hemorrhagic stroke, and other vascular disorders of the brain, are a leading cause of morbidity and mortality globally. While environmental variables such as hypertension, smoking, and diabetes are well recognised contributors, growing evidence suggests that genetic factors play a substantial role in the propensity, pathogenesis, and course of these conditions.

Numerous loci and genes linked to cerebrovascular risk have been identified by genetic studies such as family-based analysis, twin studies, and genome-wide association studies (GWAS).Mutations in the NOTCH3 gene cause CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), a monogenic kind of stroke. Similarly, polymorphisms in genes such as PDE4D, HDAC9, and ZFHX3 have been associated to an increased risk of ischaemic stroke and atrial fibrillation, all of which contribute to cardiovascular disease

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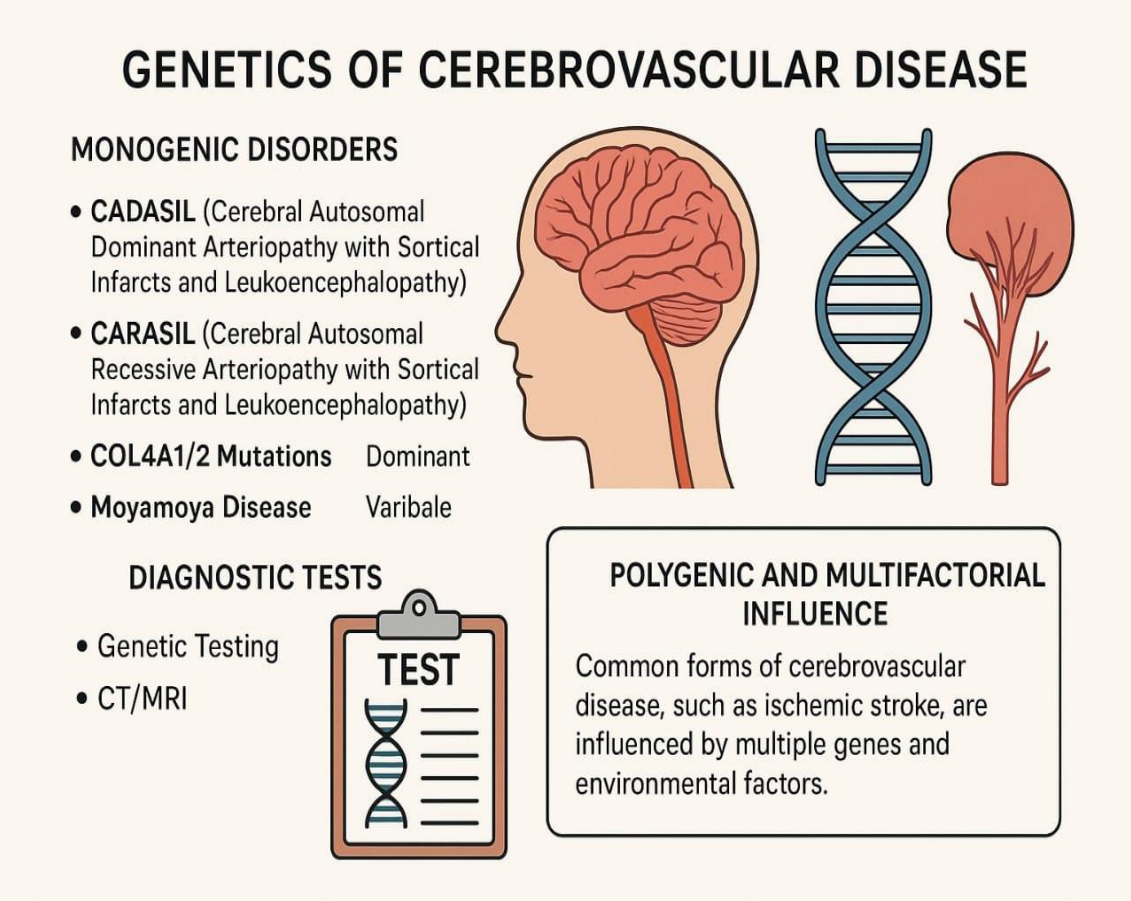

Fig1: Genetics of CVD

About 10% of deaths are caused by cerebrovascular illness

Cerebrovascular diseases are a heterogeneous group of disorders affecting the blood vessels of the brain, with stroke being the most prevalent and life-threatening manifestation. While environmental and modifiable risk factors such as hypertension, diabetes mellitus, hyperlipidaemia, and smoking are well established, genetic predisposition has emerged as a crucial determinant in disease susceptibility and progression (Meschia & Brott, 2018).[1]

Genetic influences range from rare monogenic disorders, such as **Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)** caused by *NOTCH3* mutations, to more common polygenic contributions identified through genome-wide association studies (GWAS). These studies have uncovered several risk loci associated with ischemic and haemorrhagic stroke, implicating genes involvE d in vascular remodelling, endothelial function, lipid metabolism, and coagulation pathways (Falcone et al., 2014; Malik et al., 2018).[2]

The identification of these genetic factors not only enhances the understanding of disease mechanisms but also opens avenues for precision medicine, where genetic testing and risk profiling can help in early detection, prevention, and individualised treatment strategies (Hankey, 2017). Thus, exploring the genetics of cerebrovascular disease is vital for bridging the gap between clinical neurology and molecular genomics.[3]

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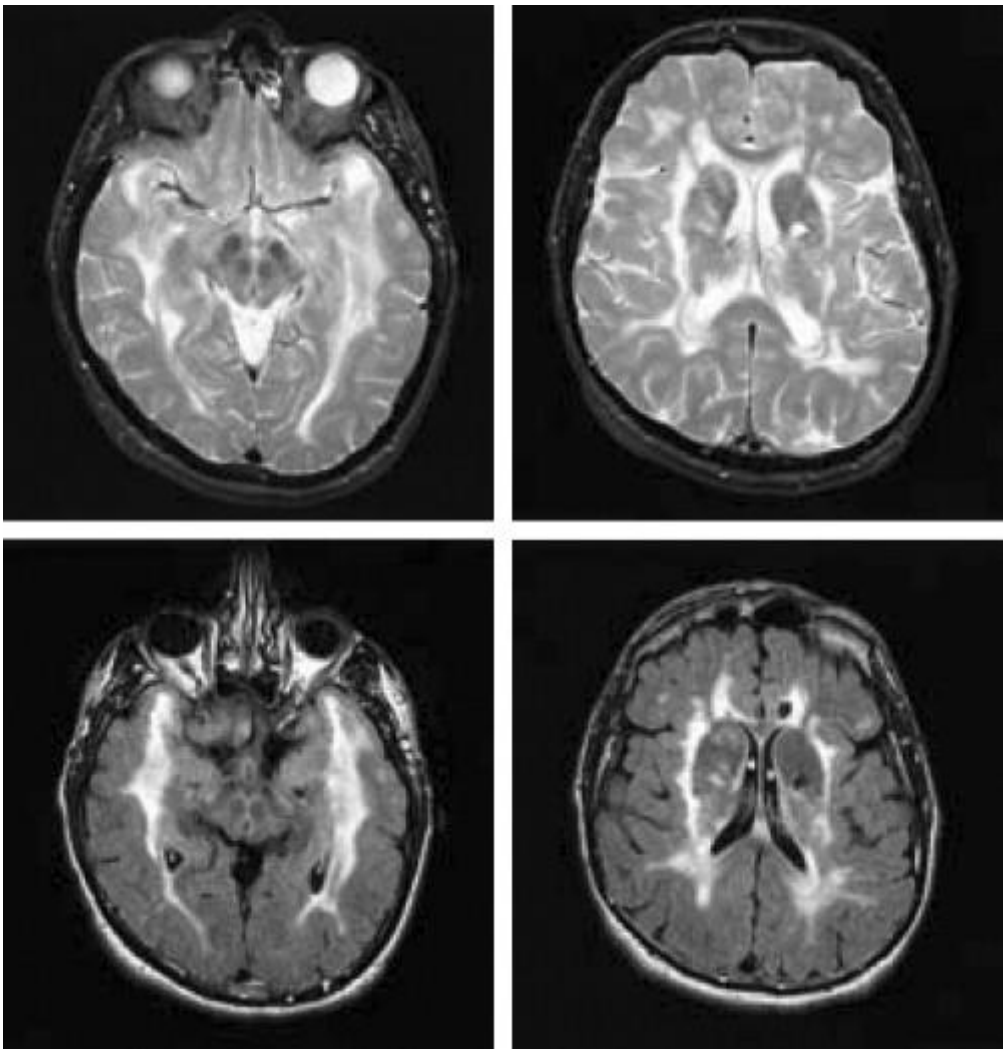

Figure 2:"MRI Brain Showing Small Vessel Ischemic Disease (SVID)"

The future of genetic application in cerebrovascular disease

Genetic technologies are likely to play an important role in improving the prevention and treatment of cerebrovascular disorders such as stroke, cerebral aneurysms, and vascular abnormalities. Advances in genomic research have helped identify several genes associated with blood vessel function, inflammation, blood clot formation, and lipid metabolism, all of which contribute to the development of these diseases

In the coming years, genetic risk assessment may allow early identification of individuals who are more susceptible to cerebrovascular diseases, enabling effective preventive measures. Pharmacogenomics will support personalized medication selection by tailoring antiplatelet and anticoagulant therapy according to a patient's genetic makeup, thereby enhancing therapeutic outcomes and reducing side effects.

New approaches including gene therapy, RNA-based treatments, and CRISPR gene-editing techniques show promise in targeting underlying disease mechanisms and aiding vascular repair. In addition, genetically modified stem cell therapies may help in restoring damaged brain tissue and improving neurovascular recovery after stroke.

The combination of genetic information with precision medicine and artificial intelligence is expected to improve early diagnosis, optimize individualized treatment plans, and ultimately

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enhance clinical outcomes in patients with cerebrovascular diseases.[4]

Discovery of Genes Involved in Cerebrovascular Diseases

Identification of genes related to cerebrovascular diseases has greatly improved with advances in genetic research techniques. Initially, researchers used family and linkage studies to detect inherited forms of stroke, which led to the discovery of genes responsible for rare genetic conditions such as CADASIL and CARASIL.[5]

Later, the introduction of genome-wide association studies (GWAS) made it possible to identify genetic variations associated with common cerebrovascular disorders, including ischemic and hemorrhagic stroke as well as cerebral aneurysms. These studies analyze large populations to find genetic markers linked to disease risk. Many of the identified genes are involved in maintaining blood vessel structure, regulating inflammation, blood clotting, lipid metabolism, and blood pressure.[6]

More recently, whole-exome and whole-genome sequencing techniques have helped uncover rare and previously unknown genetic mutations contributing to cerebrovascular diseases. In addition, epigenetic research has shown that changes in gene regulation, such as DNA methylation and microRNA activity, also play an important role in vascular dysfunction.

Combining genetic data with bioinformatics and artificial intelligence is enhancing gene discovery and supporting improved risk prediction and targeted treatment approaches for cerebrovascular diseases.[7]

Functional Studies

Although rapid technological progress has generated extensive knowledge regarding genetic causes of disease, accurately predicting the pathogenicity and interpreting the clinical impact of a genetic variant (GV) remains complex. Functional studies represent the most reliable and validated method to clarify how a potential variant contributes to disease mechanisms. Among these, *in vivo* models provide the most convincing evidence, as animal models allow characterisation of the phenotype and mechanistic pathways through which candidate GVs lead to disease.[8] Knock-in and knock-out models have been widely used for decades, though they often fail to fully replicate the human condition.

Application of Stem Cells and Reprogrammed Cells in Cerebrovascular Disease Research

Cerebrovascular diseases, including ischemic stroke, hemorrhagic stroke, and cerebral vascular malformations, are major causes of disability and death worldwide. Conventional treatments are limited in their ability to repair damaged brain tissue. In recent years, stem cells and reprogrammed cells have gained attention for their potential to improve understanding of disease mechanisms and promote neural and vascular regeneration.

1.Role of Stem Cells in Cerebrovascular Disease Research

Stem cells are unique in their ability to continuously renew themselves and transform into various specialized cell types. In the field of cerebrovascular disease research, several types of stem cells—including mesenchymal stem cells (MSCs), neural stem cells, and endothelial progenitor cells—are employed to investigate brain damage and recovery mechanisms after stroke. These cells contribute to healing by suppressing inflammation, stimulating the growth of new blood vessels (angiogenesis), and safeguarding neurons through the release of growth factors and neuroprotective molecules.

2. Stem Cell Therapy for Stroke Recovery

Experimental studies have shown that transplanted stem cells can migrate to the site of brain injury and support tissue repair. They may replace damaged neurons and vascular cells or stimulate the brain's natural repair processes. Stem cell therapy has demonstrated potential in improving neurological function and reducing infarct size in preclinical models of ischemic and hemorrhagic stroke.

3. Reprogrammed Cells and Induced Pluripotent Stem Cells (iPSCs)

Reprogrammed cells, particularly **induced pluripotent stem cells (iPSCs)**, are generated by converting adult cells into pluripotent cells. iPSCs derived from patients with cerebrovascular diseases provide disease-specific models to study genetic abnormalities, vascular dysfunction, and stroke pathology. These models are valuable for understanding disease progression and testing new therapeutic agents.

4. Disease Modeling and Drug Screening

Stem cells and iPSC-derived cells enable the creation of in vitro models that closely mimic human cerebrovascular conditions. These models are useful for drug screening, toxicity testing, and

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evaluating therapeutic responses. Patient-specific iPSC models also support personalized medicine by predicting individual drug responses.

5. Neurovascular Regeneration and Repair

Stem cells contribute to neurovascular regeneration by promoting the repair of both neural and vascular components of the brain. They enhance endothelial repair, strengthen the blood–brain barrier, and support neuronal connectivity. Reprogrammed cells may also be genetically modified to improve their survival and therapeutic effectiveness(9)

Recommendations for inheritable testing and inheritable consultation

Recommendations for Inheritable (Genetic) Testing

1. **Early-onset cerebrovascular disease**

Genetic testing should be considered in patients who experience ischemic or hemorrhagic stroke before the age of 50 years, especially when traditional vascular risk factors such as hypertension, diabetes, or dyslipidemia are absent**.**

2. **Family history of cerebrovascular disorders**

Individuals with a first-degree relative affected by stroke, cerebral aneurysm, or vascular malformations should undergo genetic evaluation to identify potential inherited risk factors.

3. **Recurrent or cryptogenic cerebrovascular events**

Patients presenting with recurrent ischemic or hemorrhagic strokes of unknown etiology may benefit from genetic testing to detect inherited thrombophilic conditions or monogenic vascular diseases.

4. **Suspected monogenic cerebrovascular syndromes**

Genetic testing is recommended when clinical and radiological findings suggest inherited disorders such as CADASIL, CARASIL, Fabry disease, Ehlers–Danlos syndrome, or hereditary cerebral amyloid angiopathy.

5. **Cerebral aneurysms and vascular malformations**

Genetic assessment should be considered in patients with multiple intracranialaneurysms or a family history of aneurysmal subarachnoid hemorrhage to identify inherited connective tissue or vascular abnormalities.

6. **Pharmacogenomic applications**

Testing for genetic variants affecting drug metabolism, such as *CYP2C19*, may help optimize antiplatelet and anticoagulant therapy, improving efficacy while reducing adverse drug reactions.

Recommendations for Genetic (Inheritable) Consultation

1. **Pre-test counseling**

Explains the purpose, benefits, limitations, and possible outcomes of genetic testing.

2. **Post-test result interpretation**

Assists in understanding genetic findings and their clinical significance.

3. **Family risk assessment**

Identifies at-risk relatives and evaluates hereditary transmission patterns.

4. **Preventive guidance**

Supports personalized prevention strategies and surveillance planning.

5. **Reproductive counseling**

Provides guidance on inheritance risks and reproductive options.

6. **Long-term follow-up**

Ensures ongoing risk evaluation and updated management based on new genetic insights.

Caution in interpretation:

- A **negative result** in the proband means no disease-causing mutation was found in the tested genes — but the cause may still be genetic.
- New GVs must be treated cautiously until confirmed by **functional studies** and verified in **large family studies** or **independent populations**.

CLASSIFICATION

Category	Definition	Utility for proband	Utility for family
Pathogenic	Loss-of-function and pathogenic variants shown to cause the disease through co-segregation and linkage analysis or functional studies in large families	Establishes diagnosis, may inform management	Can be used for predictive genetic testing
Likely pathogenic	Evidence for the causal role based on statistical enrichment in small families and trios with the	Possibly suggests diagnosis, may inform management	Predictive genetic testing of unaffected relatives should be approached

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	disease. Robust linkage is hindered by the small size of families or the sporadic nature of the disease. To reduce the possibility of random co-segregation in small families, findings require testing for replication in independent populations	or lead to additional diagnostic tests	with great caution, may be combined with phenotypic evaluation and surveillance
Variant of unknown significance	Case-control studies will show an association between genetic variants and the phenotype.It is required to replicate in a separate study population. . Disease-associated variants may be in linkage disequilibrium with the actual pathogenic variants, requiring additional studies to confirm actual pathogenicity	Unknown	Should not be used for predictive genetic testing. Testing of affected relatives for segregation may provide evidence of causality
Likely benign	These variants may affect expression levels, structure and function of proteins, but have not been associated with disease	None	No option for predictive genetic testing, rely on longitudinal phenotypic evaluation
Benign	Comprises the vast majority of genetic variants in the genome, which have absolutely no impact on protein expression, structure and function, and no impact on phenotype	None	No option for predictive genetic testing, rely on longitudinal phenotypic evaluation

TABLE: 1. Classification of genetic variants

Methods Involved in Cerebrovascular Disease

Study Design

Research related to cerebrovascular disease commonly adopts observational study designs, including prospective and retrospective cohort studies, case–control studies, and cross-sectional analyses. These designs are effective for identifying associations between risk factors and stroke occurrence, as well as for evaluating disease progression and outcomes. In addition, population-based stroke registries and hospital-based surveillance systems are widely used to generate epidemiological data and assess real-world clinical practices.[10]

Study Population

The study population typically includes adult individuals aged 18 years and above who are diagnosed with ischemic stroke, intracerebralhemorrhage, subarachnoid hemorrhage, or transient ischemic attack (TIA). Patients with early-onset stroke, recurrent cerebrovascular events, or strong familial predisposition are often included to better understand genetic and non-traditional risk factors. Clear inclusion and exclusion criteria are applied to ensure homogeneity and reliability of study findings.

Clinical Evaluation

A comprehensive clinical evaluation is a fundamental component of cerebrovascular disease assessment. This includes detailed documentation of medical history, family history of stroke or vascular disorders, and a complete neurological examination to assess motor, sensory, cognitive, and speech functions. In addition, modifiable and non-modifiable vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol consumption, obesity, and physical inactivity are systematically evaluated.[11]

Neuroimaging Methods

Neuroimaging is essential for confirming the diagnosis, determining stroke type, and guiding management decisions. Non-contrast computed tomography (CT) is commonly used in the acute phase to rapidly differentiate ischemic stroke from

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intracranial hemorrhage. Magnetic resonance imaging (MRI), including diffusion-weighted imaging, provides detailed visualization of ischemic lesions, small vessel disease, and silent infarcts. Advanced vascular imaging techniques such as CT angiography (CTA) and MR angiography (MRA) are used to assess extracranial and intracranial vessels, while digital subtraction angiography (DSA) serves as the gold standard for evaluating complex vascular abnormalities and planning interventional procedures.[12]

Laboratory Investigations

Laboratory investigations are conducted to identify metabolic, hematological, and inflammatory contributors to cerebrovascular disease. Routine tests include lipid profile, fasting and postprandial blood glucose levels, renal and liver function tests, and coagulation parameters. In selected patients, additional investigations such as inflammatory markers, autoimmune profiles, and thrombophilia screening are performed to detect underlying conditions that may predispose individuals to stroke.[13]

Genetic and Molecular Methods

Genetic and molecular evaluation is increasingly incorporated into cerebrovascular research, particularly in cases of early-onset or unexplained stroke. Targeted genetic testing is used to identify known monogenic stroke disorders, while next-generation sequencing (NGS) panels allow simultaneous analysis of multiple genes associated with cerebrovascular disease. Pharmacogenomic testing helps predict individual responses to antiplatelet and anticoagulant therapies, supporting personalized treatment approaches.

Cardiac Evaluation

Cardiac assessment is an important part of cerebrovascular disease evaluation, as many ischemic strokes result from cardioembolic sources. Electrocardiography (ECG) is routinely performed to detect arrhythmias such as atrial fibrillation. Echocardiography, including transthoracic or transesophagealapproaches, is used to identify valvular abnormalities, intracardiac thrombi, or structural defects. Prolonged cardiac rhythm monitoring, such as Holter monitoring, improves detection of intermittent atrial fibrillation that may otherwise remain undiagnosed.[14]

Case Ascertainment and Stroke Classification

Cerebrovascular events are confirmed using standardized diagnostic criteria that integrate clinical symptoms, neuroimaging findings, and medical records. Stroke subtype classification is performed using established systems such as the TOAST classification, which categorizes ischemic stroke based on underlying etiology. Accurate classification aids in determining appropriate treatment strategies and predicting patient outcomes.[15]

Outcome Assessment

Outcome assessment focuses on both short-term and long-term consequences of cerebrovascular disease. Clinical outcomes such as stroke recurrence, mortality, and complications are recorded during follow-up. Functional outcomes and disability levels are evaluated using validated scales such as the modified Rankin Scale, enabling objective assessment of recovery and quality of life.[16]

Ethical Considerations

All studies involving human participants adhere to ethical principles and institutional guidelines. Written informed consent is obtained prior to participation, and confidentiality of patient data is strictly maintained. Study protocols are reviewed and approved by institutional ethics committees to ensure participant safety, ethical conduct, and compliance with regulatory standards.[17]

II. CONCLUSION

Cerebrovascular diseases represent a major global health burden, arising from a complex interaction between environmental influences and genetic susceptibility. While modifiable risk factors such as hypertension, diabetes, and lifestyle choices remain central to prevention, advances in molecular genetics have clearly demonstrated that inherited factors significantly contribute to disease risk, progression, and clinical variability. From rare monogenic disorders such as CADASIL to common polygenic influences identified through genome-wide association studies, genetic research has deepened our understanding of the biological pathways underlying vascular dysfunction, thrombosis, inflammation, and neurovascular injury.

Emerging technologies—including whole-genome sequencing, epigenetic analysis, functional modelling, and stem cell research—are further clarifying disease mechanisms and uncovering novel therapeutic targets. The integration of genetic profiling with precision medicine, pharmacogenomics, and artificial intelligence holds strong potential for earlier risk identification, individualized treatment strategies, and improved patient outcomes.

Although challenges remain in translating genetic discoveries into routine clinical practice, ongoing research continues to bridge the gap

between genomics and neurology. A comprehensive understanding of genetic contributions to cerebrovascular diseases will be essential for developing more effective preventive strategies, targeted therapies, and regenerative approaches, ultimately reducing the global impact of these debilitating conditions.

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