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Genetic and Molecular Aspects of Ischemic Stroke

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ABSTRACT: Stroke remains a leading cause of disability and death worldwide, with significant public health implications. Ischemic stroke is classified into various subtypes based on etiology, including large-artery atherosclerosis, small-vessel occlusion, and cardioembolism. The middle cerebral artery is often the most affected. The concept of the ischemic core and penumbra is crucial in understanding stroke pathology, where the core suffers irreversible damage, and the penumbra is at high risk if reperfusion is not timely. Genetic predispositions play a significant role in ischemic stroke, with heritability estimates around 37.9%. Monogenic causes account for 1-5% of cases, while polygenic factors are more prevalent. Genome-wide association studies (GWAS) have identified numerous genetic loci associated with ischemic stroke, revealing the complex genetic architecture of the disease. Molecular pathways such as neuroinflammation, excitotoxicity, oxidative stress, apoptosis, and autophagy are involved in the pathophysiology of ischemic stroke. Understanding these pathways offers potential therapeutic targets. This review aims to synthesise recent genetic studies and provide insights into future directions for research and clinical practice in ischemic stroke, emphasising the importance of personalised medicine and targeted therapies.

KEYWORDS: Genome-wide association studies (GWAS), Ischemic stroke, Stroke.

INTRODUCTION

Stroke is a major cause of disability and death worldwide, with a high incidence rate. It affects 16.0–23.0% of the global population and is a critical public health issue. In Thailand, stroke is the primary and secondary cause of death for Thai women and men, respectively. The mortality rate is high, with 10% of patients dying, and 50% of patients experiencing impairments. There are two main types of stroke: hemorrhagic strokes, which are caused by the rupture of a blood vessel inside the brain, and ischemic strokes, which are caused by the blockage of an artery in the brain. Both conditions cause local hypoxia that damages brain tissue. Ischemic stroke is primarily caused by an interruption in cerebral blood flow, which induces severe neural injuries and is one of the leading causes of death and disability worldwide. Several risk factors have been implicated in the pathogenesis of ischemic stroke, including diabetes, cigarette smoking, hyperlipidemia, and hypertension.Based on the etiology, the cause of ischemic stroke can be traced to embolism from the heart, artery-to-artery embolism, and in situ small vessel disease. Typically, stroke symptoms include sudden unilateral weakness, numbness, diplopia, slurred speech, ataxia, and non-orthostatic vertigo.

IS subtypes are categorized based on cause: large-artery atherosclerosis, small-vessel occlusion, cardioembolism, stroke of other determined etiology (e.g., vasculitis), and stroke of undetermined etiology. Middle cerebral artery has been found to be the main affected territory. Oxygen and glucose deprivation (OGD), one of the damaging mechanisms of IS, differentially affects brain regions. Within the first hours from IS onset, the affected brain tissue is mainly divided into two major areas . The first area, named the ischemic core, refers to a cerebral area with a strong decrease in blood flow and oxygen and glucose levels, which results in irreversible damage from a rapid depletion of neuronal energy stores. The second area, the ischemic penumbra, surrounds the ischemic core and represents a high-risk region for further damage. This latter area supports the concept of “time is brain”: in fact, in this zone, the blood flow is partially preserved, thus enabling the maintenance of structural integrity and metabolic activity of neuronal cells. However, the ischemic penumbra can become part of the ischemic if reperfusion is not rapidly restored.

Genetics are known to impact various aspects of ischemic stroke, including the alteration of individual stroke occurrence risk, modulation of treatment response, and the effectiveness of post-stroke functional recovery. Previous studies have found that the heritability of ischemic stroke is approximately 37.9%, with levels varying considerably in terms of the specific stroke subtype: 40.3% for large-vessel disease, 32.6% for cardioembolic, and 16.1% for small-vessel disease. The current literature has identified numerous genes associated with ischemic stroke through monogenic and polygenic underpinnings. Monogenic etiologies account

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for 1–5% of all ischemic strokes, while polygenic etiologies are more common, with various risk factors of an ischemic stroke itself having been found to have polygenic associations in large-scale genomic studies.

Ischemic stroke involves a variety of alterations in both the affected ischemic core and the surrounding penumbra. These alterations, which occur on both macroscopic and microscopic levels, are typically grouped into five main categories: Neuroinflammation, Excitotoxicity, Oxidative stress, Apoptosis, and Autophagy. The process of cell death in ischemic stroke is the result of complex interactions between these independent but mutually reinforcing series of pathological events. .This article aims to review the most recent findings from genetic studies related to various clinical and molecular aspects of ischemic stroke.

STROKE GENETICS

1. Cerebral Small Vessel Disease

Cerebral small vessel disease (CSVD) represents a cluster of pathologies with a heterogeneous etiology and a pathomechanism affecting elements of the brain vascular system such as small arteries, capillaries, arterioles and venules. Histopathologic studies demonstrate reduced lumens in affected vessels and also demonstrate the thickening of walls, which impedes perfusion and transmural gas transfer. The disease accounts for 20–30% of cases of ischemic stroke and cerebral hemorrhage. Moreover, CSVD has been shown to worsen functional outcomes after supra and infratentorial ischemic stroke because it disrupts the reorganization of brain networks that is essential for post-stroke recovery [1]. Cerebral SVD is not a single disease but can be caused by diverse pathological processes. The two most common pathologies underlying SVD are arteriolosclerosis caused by aging, hypertension, and other conventional vascular risk factors, and cerebral amyloid angiopathy (CAA) caused by vascular deposition of β-amyloid. Other rarer causes include monogenic conditions, such as cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL), venous col- lagenosis, and postradiation angiopathy [2].

Genetic studies, including those on rare familial syndromes and complex sporadic diseases, are crucial for understanding SVD. Stroke has a high heritability, with family history tripling the risk. Two main SVD manifestations, SVD stroke and white matter lesions, have heritability rates of 16% and 50%, respectively. Monogenic disorders like CADASIL, associated with the NOTCH3 gene, account for about 5% of all strokes. CADASIL is the most common hereditary stroke disorder, and it was also suggested as the most common inherited form of vascular dementia. Other genes linked to SVD include HTRA1, α-GAL (associated with Fabry disease), COL4A1, COL4A2, FOXC1, and FOXF2. CADASIL, the most common monogenic SVD, is caused by NOTCH3 mutations and presents with migraines, psychiatric disorders, cerebrovascular events, and progressive dementia. MRI changes, such as white matter hyperintensities, are diagnostic markers. HTRA1 mutations cause an autosomal recessive arteriopathy similar to CADASIL but with additional symptoms like gait disturbance and alopecia [3].

Fabry disease, due to α-GAL deficiency, leads to glycosphingolipid accumulation in tissues, resulting in neuropathy, gastrointestinal issues, and increased stroke risk. COL4A1 and COL4A2 mutations affect basement membrane stability, causing cerebral SVD and other organ involvement. Mutations in FOXC1 and FOXF2 genes also result in SVD with ocular abnormalities. TREX1 mutations lead to retinal vasculopathy with cerebral leukodystrophy-like syndromes, characterized by thickened vascular basement membranes and neuroimaging abnormalities. SVD is also linked to amyloid-related pathology, particularly cerebral amyloid angiopathy (CAA), with mutations in the APP gene leading to amyloid deposition in cerebral arterioles and lobar ICH. Genetic association studies have identified additional loci related to SVD, although further research is needed to pinpoint specific genes and mechanisms.

The latest and largest GWAS of stroke, from the MEGASTROKE collaboration, which included 67,162 stroke cases and 454,450 controls, identified several specific loci associated with SVD ischemic stroke. Notably, loci at 16q24 and 2q33 were linked to SVD stroke. The 16q24 locus, previously associated with SVD stroke and white matter hyperintensities (WMH), impacts the expression of the ZCCHC14 gene involved in DNA transcription regulation. The 2q33 region, known for its pleiotropic nature, involves the WDR12 gene, related to ribosome complex formation, and ICA1L, which mediates gene expression in the frontal cortex. Additionally, rare variants at the 14q22 locus, associated with large artery and SVD stroke, implicate the GCH1 gene in nitric oxide signaling. The 12q24 locus, initially linked to all ischemic stroke, shows a stronger association with SVD strokes, potentially driven by the SH2B3 gene, which is involved in signaling activities for growth factor and cytokine receptors.

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WMH, considered a reliable biomarker of cerebral SVD, has been studied through GWAS in both stroke and stroke-free populations. Key loci associated with WMH include 17q25, which involves genes like ACOX1, crucial for fatty acid beta-oxidation, and TRIM65, TRIM47, and WBP2, linked to apoptosis and transcription regulation. The 6q25 locus includes the PLEKHG1 gene, which affects endothelial cell response to mechanical stress, leading to WMH formation. The 2p16 region, containing the EFEMP1 gene, supports the matrisome's role in SVD pathogenesis, while the 5q14 locus implicates the VCAN gene in white matter structural integrity.

Intracerebral hemorrhage (ICH), divided into lobar and nonlobar categories, is associated with the 1q22 locus. This region includes the PMF1 and SLC25A44 genes, with a polygenic risk score for hypertension severity predicting nonlobar ICH risk, highlighting the link between hypertension and ICH [5]. For vascular dementia, a GWAS identified a locus on the X chromosome near the AR gene, with shared genetic contributions between SVD stroke and cognitive abilities, as well as associations with Alzheimer's disease (AD), indicating overlapping genetic risk factors. Finally, the APOE ε (19q13) locus, with ε2 and ε4 alleles, represents significant risk factors for CAA-related ICH and AD. These variants are also linked to increased WMH load, suggesting a role in arteriolosclerosis. Overall, further research is needed to characterize these genetic variants and understand their mechanisms, requiring dedicated post-GWAS studies and multidisciplinary approaches to unravel the genetic architecture of SVD.

Genetic mutations affecting collagen conformation can lead to impaired collagen deposition in vessel walls, resulting in weakened basement membranes, compromised vessel integrity, and increased blood-brain barrier (BBB) permeability. Common variants in COL4A1/2 are associated with sporadic SVD manifestations, supporting this pathway. Impairments in BBB development and integrity, as suggested by studies on FOXC1, are crucial for SVD pathogenesis. FOXC1 mutations affect BBB stability and endothelial cell proliferation, leading to SVD stroke and white matter hyperintensities (WMH). The matrisome, particularly through NOTCH3 genetic characterization, plays a significant role in SVD. Defective NOTCH3 ectodomain agglomerations disrupt TIMP 3 and vitronectin activity, leading to protein accumulation in vessel walls and dysfunctional cerebral blood flow. LTBP-1 also aggregates with NOTCH3, and HTRA1 mutations impair TGF-β1 signaling, affecting pericyte proliferation and BBB permeability. GWAS evidence for NOTCH3's role in SVD is limited, with few studies establishing a strong association [4].

2. Large vessel disease

Large vessel disease (LVD) constitutes 15–20% of ischemic strokes. It can be divided into two main types: large artery atherosclerosis (LAA) and nonatherosclerotic vasculopathy [7]. LAA, a prevalent subtype of ischemic stroke, is a major cause of cerebrovascular disorders. In terms of risk factors and pathogenesis, Research indicates positive correlation between LAA strokes and cerebral SVD [6]. Large artery atherosclerosis has traditionally been closely associated with established cardiovascular risk factors, such as diabetes mellitus, hypertension, and dyslipidemia. Therefore, genetic factors linked to cardiovascular risk, particularly those affecting lipid metabolism, can increase susceptibility to atherosclerosis. Moreover, genes related to endothelial or systemic inflammation can modulate the risk of ischemic stroke by altering the progression of atherosclerosis.

Genes linked to ischemic stroke are diverse, primarily involving familial hypercholesterolemia with Low-Density Lipoprotein Receptor gene (LDLR), Apolipoprotein B gene (APOB), LDLRAP1, and PCSK9. Additional genes in lipid metabolism pathways implicated include Apolipoprotein E gene (APOE), ATP Binding Cassette Transporter 1 gene (ABCA1), and SCARB1 gene. Non-lipid metabolism-related genes associated with ischemic stroke include Transforming Growth Factor Beta 1 Gene (TGFB1), Toll-Like Receptors (TLR) and Scavenger Receptor (SR) genes, Secreted Phosphoprotein Gene (SPP1), Tumor Necrosis Factor Receptor Superfamily Member 11b Gene (TNFRSF11B), and genes of the Matrix Metalloproteinase (MMP) family.

Nonatherosclerotic vasculopathy involves genetic factors associated with collagen disorders and connective tissue abnormalities, which can lead to structural abnormalities in large blood vessels affecting both the extracellular matrix and smooth muscle contractile components. This condition increases the risk of ischemic stroke, particularly due to vascular dissection and hemorrhage. Nonatherosclerotic vasculopathy encompasses disorders like Marfan syndrome, fibromuscular dysplasia, and Moyamoya disease. Monogenic disorders associated with large vessel disease (LVD) include conditions such as those listed. Additionally, numerous candidate genes, including PCMTD1, HDAC9, MTHFR, TCN2, CCER2, MRV1, PHACTR1, CYP11B2, PDE4D, ADIPOQ, LPL, and MMP9, have been identified as carrying polygenic risks for LVD [7].

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3. Embolic Stroke of Undetermined Source

In 2014, Hart et al. introduced a new clinical framework proposing that non-lacunar ischemic strokes, which remained unexplained after standard diagnostic tests, should be classified as embolic strokes of undetermined source (ESUS) [8].The terms ESUS and cryptogenic stroke are not synonyms. While ESUS specifies a clearer subset with specific criteria, cryptogenic stroke may encompass patients with multiple potential causes or incomplete diagnostic assessments. The introduction of the term ESUS enabled randomized controlled trials in this population by establishing specific criteria for patient identification, which was not achievable with the original definition of cryptogenic stroke. ESUS represents an etiologically heterogeneous group and may arise from multiple different sources of thromboembolism, with the most common being the left atrium, left ventricle, and atherosclerotic plaques in the arterial tree supplying the territory of the infarct. ESUS comprises a significant proportion of ischemic stroke patients, around 17%, who are typically younger and experience mild strokes. Additionally, these patients have a notable annual stroke recurrence rate of 4% to 5% [9].

The precise determination of the underlying etiology of ESUS remains complex. Generalized anticoagulation strategies have not demonstrated superiority over antiplatelet agents in preventing secondary strokes in ESUS patients, largely due to difficulties in identifying the specific causes of ESUS. Genomic research aims to address this diagnostic and therapeutic challenge. Several genomic studies focusing on ESUS cohorts have yielded promising advancements in understanding the exact causal mechanisms involved. In a comprehensive GWAS, Marios Georgakis et al. investigated the genetic makeup of ESUS by analyzing 16,851 cases of ischemic stroke and 32,473 controls. They identified 19 genetic loci associated with ESUS that are shared with LAA, 2 loci with CES, and 5 loci with CSVD. In a separate study, Lu-Chen Weng et al. explored the relationship between AF and stroke risk in 26,145 individuals of European ancestry, leveraging genomic sequencing data. They developed a polygenic risk score (PRS) for AF and integrated this score with clinical risk factors to distinguish between cardioembolic and non-cardioembolic strokes. The combined use of AF PRS and clinical risk factors was found to modestly enhance the ability to differentiate cardioembolic strokes from non-cardioembolic strokes and improve the classification of stroke subtypes [7].

4. Cardioembolic Stroke (CES)

Cerebral ischemia occurs when blood flow to the brain is obstructed by a clot and constitutes 87% of all stroke cases. Around 25% of ischemic strokes are believed to originate from cardioembolic sources. Despite representing a smaller proportion of all ischemic strokes, CES are significant due to their tendency to be more severe compared to atherothrombotic strokes. They also exhibit higher rates of both early and late recurrence. Most of the strokes with ischemic origin are caused by atherosclerosis affecting the large artery and by embolism with cardiac genesis. Approximately 45% of ischemic strokes are provoked by a thrombus in a small or large artery whereas cardioembolic stroke accounts for 14–30% of all cerebral infarctions. Another important subtype is the lacunar one (15–25% of all ischemic strokes). Therefore, cardiac embolism, atherosclerosis of the cerebral circulation and occlusion of small vessels can be the cause of ischemic stroke.

The majority of ischemic strokes are caused by atherosclerosis affecting large arteries or embolism originating from the heart. Thrombi in small or large arteries account for about 45% of ischemic strokes, while cardioembolic strokes make up 14–30% of all cerebral infarctions. Another notable subtype is lacunar stroke, contributing to 15–25% of all ischemic strokes. Thus, cardiac embolism, atherosclerosis of the cerebral circulation and occlusion of small vessels can be the cause of ischemic stroke [10]. CES can stem from numerous cardiac conditions, including atrial fibrillation, left ventricular thrombi, cardiac tumors, valvular vegetations, and paradoxical emboli. Prevention strategies are largely effective for most causes of cardioembolic strokes [11]. Atrial fibrillation (AF) stands out as the leading cause, with the left atrial appendage being the primary source of thromboembolism. Patients with AF face a five-fold higher risk of stroke compared to the general population.

Genome-wide association studies (GWAS) have pinpointed various genetic loci linked to AF. These loci have been linked to genes, the functions of which can be divided into ion channels and non-ion channels. Ion channel genes include potassium channels (KCNQ1, KCNE2, KCNE5, KCNJ2, KCNA5) and sodium channels (SCN5A, SCN1B, SCN2B). Non-ion channel genes include NUP155, GJA5, NPPA gene, PITX2, ZFHX3, ZNF566, and PDZK1IP1. However, not all of the genes mentioned above have been related with ischemic stroke. Only four genes (PITX2, ZFHX3, ZNF566, and PDZK1IP1) have been linked to both AF and cardioembolic stroke [7].

The standard treatment for cardioembolic strokes typically involves the administration of anticoagulant medications. Drugs like warfarin, heparin, and direct oral anticoagulants (DOACs) are commonly used to prevent the formation of blood clots by thinning

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the blood. Additionally, several devices have been approved for stroke prevention, such as the Watchman device designed for closing the left atrial appendage. These devices are particularly beneficial for patients with atrial fibrillation who cannot tolerate anticoagulation therapy. By sealing off the left atrial appendage, these devices reduce the risk of atrial thrombi formed due to atrial fibrillation from embolizing into the systemic circulation [11].

Based on demographic projections and ongoing trends in vascular risk factors, cardiac embolism is expected to become a more prevalent cause of stroke in the future. Therefore, effective reduction of the stroke burden will necessitate improved efforts in preventing, detecting, and treating cardiac risk factors. Critical areas requiring further investigation include: (1) understanding the complete relationship between atrial fibrillation (AF), thrombogenic conditions in the atria, and stroke; (2) identifying optimal strategies for screening and managing subclinical AF at a population level; and (3) determining the best antithrombotic approaches for preventing cardiac embolism in patients with heart failure and acute myocardial infarction. Advancements in these areas are essential to sustain the declining trend in stroke incidence observed in high-income countries over recent decades and to initiate a broader reduction in stroke rates [12].

5. Mitochondrial dysfunction

Mitochondria are essential organelles crucial for cellular homeostasis and determining cell fate. Besides their role as cellular powerhouses, mitochondria are pivotal in regulating fundamental cellular processes such as Ca^{2+} signaling, reactive oxygen species (ROS) production, inflammation, and cell death [13]. During acute ischemic stroke (IS), the cessation of cerebral blood flow disrupts the delivery of oxygen and glucose, leading to impaired mitochondrial oxidative phosphorylation and cellular bioenergetic stress. This dysfunction results in changes to mitochondrial function, which significantly contribute to the devastating outcomes associated with IS [14]. Mitochondrial dysfunction plays a significant role in both childhood and adult neurometabolic disorders that affect multiple organs, with an estimated global prevalence of 1 in 5000. Patients with mitochondrial disease exhibit diverse clinical manifestations, varying ages of onset, and varying degrees of severity. Research has identified over 1500 nuclear genome encoded proteins that participate in various mitochondrial functions. Because mitochondrial function is influenced by both nuclear and mitochondrial genomes, mutations in either or both can lead to mitochondrial dysfunction. Mitochondrial diseases are categorized according to mutations that affect gene expression and function within the organelle, arising from either the mitochondrial or the nuclear genome [15].

Mitochondrial dysfunction resulting from mutations in either mitochondrial DNA (mtDNA) or nuclear DNA can lead to a range of diseases [16]. These disorders manifest with diverse clinical features affecting multiple organs, varying age groups, and differing levels of severity. Among these conditions, one of the most common is mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS). Central to its diagnosis and pathogenesis are the triad of lactic acidosis, seizures, and stroke-like episodes. However, patients with MELAS can also exhibit additional symptoms such as migraine, cardiomyopathy, depression, cardiac conduction abnormalities, and diabetes, underscoring the systemic nature of this disease [17]. There are approximately 1500 mitochondrial genes that, if mutated, can lead to mitochondrial dysfunction, with at least 30 different mutations identified in MELAS syndrome. Among these mutations, the A3243G mutation in mtDNA, while extensively studied, still lacks clear understanding of the mechanisms underlying its clinical variations. The discovery of this adenine to guanine transition at position 3243 (A3243G) in mtDNA marked the beginning of investigating the molecular basis of MELAS syndrome. This missense mutation occurs in a conserved residue within the MT-TL1 gene, responsible for encoding tRNA-leu(UUR), which is presumably crucial for mitochondrial protein synthesis impairment.

In addition to MELAS syndrome, the clinical manifestations associated with the mtDNA A3243G mutation vary widely among patients, encompassing both neurological and non-neurological symptoms that range from asymptomatic carriers to severe phenotypes. This mutation accounts for approximately 80% of causative mutations related to mitochondrial disorders. Other mitochondrial syndromes, such as Myoclonic Epilepsy with Ragged Red Fibers syndrome and Leigh syndrome, have also been linked to this mutation. Furthermore, several other mtDNA mutations, including T3271C, A3252G, T3291C, G3959A, A10134C, T10191C, G10197A, G13513A, and T10158C, as well as mutations in nuclear genes such as polymerase gamma 1 (POLG1) and pyruvate dehydrogenase complex (PDHC) deficiency, can cause MELAS syndrome [18].

6. Haematological Disorders

Hematological diseases are rarely implicated as causes of stroke, particularly ischemic stroke. However, patients with hematological disorders frequently encounter cerebrovascular complications, including ischemic stroke, intracerebral and

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subarachnoid hemorrhage, microbleeds, posterior reversible encephalopathy syndrome (PRES), and thrombosis of dural sinuses and cerebral veins (CVT) [19].

Sickle cell disease (SCD) is an autosomal recessive condition caused by a point mutation in the HBB gene, leading to a single amino acid substitution in the β-globin chain. This genetic mutation causes red blood cells (RBCs) to adopt a sickle shape instead of their normal flat, round shape. Sickled RBCs disrupt blood flow and damage the inner lining of the blood cells. Interruption of blood flow to the brain can result in a stroke, where certain areas of the brain cease to function properly. Strokes associated with SCD can be fatal or lead to permanent difficulties in speech, movement, or learning. Additionally, SCD can cause silent infarctions, often referred to as silent strokes, which do not present with immediate symptoms but can cause issues such as learning difficulties [20].

Essential thrombocythemia (ET) is a rare, chronic myeloproliferative neoplasm characterized by excessive platelet production. Diagnosis of ET follows World Health Organization (WHO) criteria, which include elevated platelet counts, bone marrow biopsy results, and the presence of mutations in JAK2, CALR, or MPL genes. The JAK2 V617F mutation, found in about 50–60% of ET cases, plays a central role in driving the disease by continuously activating the Janus kinase-signal transducer and activator of transcription pathway. This leads to uncontrolled platelet production, resulting in a hypercoagulable state that heightens the risk of thrombotic complications, such as ischemic strokes. ET presents with varied clinical manifestations, ranging from asymptomatic to severe complications. In addition to thrombotic events, patients with ET may also experience significant hemorrhages and cardiovascular abnormalities [21].

Polycythemia vera (PV) is a myeloproliferative disorder characterized by the clonal expansion of hematopoietic stem cells, leading to abnormal increases in red blood cells, white blood cells, and platelets. This condition results in elevated blood viscosity and reduced blood flow velocity, which are hemorheological abnormalities contributing to thrombosis, including cerebral infarction. In some cases, PV can also lead to cerebral hemorrhage due to platelet aggregation dysfunction and prolonged activated partial prothrombin time. Stroke may present as the initial symptom in over 15% of individuals affected by PV [22]. PV arises primarily from a malignant genetic alteration occurring within a single bone marrow cell, leading to a clonal disorder. Nevertheless, the exact trigger for this acquired malignancy remains unclear. In 98% of PV cases, a driver mutation affecting the JAK2 gene has been identified. The remaining cases typically involve mutations in the pseudokinase domain of the JAK2 gene spanning exons 12 to 15. A small subset of PV patients may also exhibit "non-phenotypic driver mutations" in genes such as TET2, DNMT3a, or ASXL1. Recent research has implicated other genetic abnormalities, including modifications in the NF-E2 and LNK (SH2B3) genes, as potential contributors to the development of PV [23].

Genes Related to Ischemic Stroke Occurrence

1.Monogenic ischemic stroke, caused by mutations in single genes, is characterized by a specific pathogenic variant. These genetic mutations typically follow a Mendelian pattern of inheritance across generations [24]. They can predispose individuals to stroke or directly contribute to its development [25]. Some stroke-related conditions are hereditary and may affect multiple organs, while others are specific to the nervous system. Monogenic factors are implicated in approximately 1% of stroke cases, particularly among younger patients, although this figure is likely underestimated. The full genetic impact on stroke etiology remains unclear [24].

2. Polygenic ischemic stroke is influenced by variants in multiple genes, each with varying effects, and does not conform to a straightforward Mendelian inheritance pattern. Approximately 38% of ischemic stroke cases are associated with polygenic factors, although this percentage may be higher [26]. Each genetic variant related to ischemic stroke contributes incrementally to overall risk, but individually, they do not exert a significant impact [27].

Major genetic studies

Linkage analysis is used in genomic analysis to identify regions of the genome that are co-inherited in twins or families with multiple affected members. Genetic variants that co-occur with ischemic stroke serve as genetic markers to characterize the inheritance of genetic material across generations within affected individuals within a family [7]. By comparing the pattern of inheritance of these genetic markers with the pattern of disease transmission within families, researchers calculate linkage scores to

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estimate the connection between a genetic variant and ischemic stroke. Subsequently, the region or locus of interest can be subjected to further sequencing to identify specific genetic causes of the disease [7, 28].

Genome-wide association studies (GWAS) have emerged as a powerful tool in uncovering the genetic underpinnings of complex diseases, including ischemic stroke [29]. By scanning the genomes of large groups of individuals, GWAS aims to identify genetic variants that are more frequently associated with stroke incidence, offering insights into the biological pathways that could be targeted for prevention and treatment [30].

Ischemic stroke is influenced by both environmental factors and genetic predispositions. GWAS have identified numerous single nucleotide polymorphisms (SNPs) that are associated with an increased risk of stroke [31]. These genetic variants often lie in or near genes involved in vascular function, inflammation, and thrombosis—key processes implicated in stroke pathophysiology [32]. For instance, variants in the gene encoding Factor V, a protein involved in blood clotting, have been linked to an increased risk of stroke due to their role in promoting thrombosis [33].

Beyond identifying individual risk alleles, GWAS facilitate pathway analyses that help elucidate the broader biological mechanisms contributing to stroke [34]. By aggregating the effects of multiple genetic variants, researchers can pinpoint biological pathways that are statistically enriched for stroke-associated variants. Such analyses have highlighted the importance of pathways related to lipid metabolism, blood pressure regulation, and endothelial function in stroke risk [35].

One of the strengths of GWAS is their ability to detect genetic risk factors across different populations. This is crucial for stroke, which exhibits variations in incidence and risk factors across ethnic groups [36]. For example, GWAS conducted in Asian populations have identified risk loci that differ from those discovered in European cohorts, reflecting genetic diversity and pointing to the need for tailored prevention strategies [37, 38].

Modern GWAS in stroke research increasingly employ integrative approaches, combining genetic data with other 'omics' data such as transcriptomics and proteomics [39]. This integration allows for a more comprehensive understanding of how identified genetic variants influence gene expression and protein function, thereby affecting stroke risk [40]. For example, a variant that increases stroke risk might do so by altering the expression of a gene involved in arterial wall integrity [41].

Despite the successes of GWAS in identifying genetic factors associated with ischemic stroke, there are significant challenges [42]. Many variants identified have small individual effects, requiring very large sample sizes to detect reliably [43]. Furthermore, the functional relevance of many identified SNPs remains unclear, necessitating further functional studies to understand their role in disease mechanisms [44].

The future of GWAS in stroke research lies in larger, more diverse cohorts and in the application of newer technologies such as next-generation sequencing . These advances will enable the identification of rare variants with potentially larger effects on stroke risk. Additionally, deeper integration with clinical data will enhance the translation of GWAS findings into therapeutic and preventive strategies, ultimately aiming to reduce the burden of ischemic stroke globally [42].

By continuing to expand and refine GWAS methodologies, researchers are progressively unraveling the complex genetic landscape of ischemic stroke, paving the way for more personalized and effective approaches to combat this debilitating disease [44].

Molecular Pathways in Stroke Pathophysiology

Ischemic stroke triggers a complex cascade of molecular events that lead to brain tissue damage and functional deficits. Understanding these molecular mechanisms is critical for developing targeted therapeutic strategies to mitigate the damage and improve outcomes for stroke patients [45]. The primary pathways involved in stroke pathophysiology include cell death mechanisms, inflammatory responses, and oxidative stress, each playing a pivotal role in the progression of the disease [46].

Cell death in ischemic stroke occurs predominantly through apoptosis and necrosis. Apoptosis, or programmed cell death, is mediated by a series of tightly regulated biochemical events that lead to cell shrinkage, chromatin condensation, and DNA fragmentation without causing an inflammatory response. In the context of stroke, apoptosis is often triggered by the activation of caspases, which are enzymes that cleave specific intracellular proteins to initiate cell death [46, 47]. The intrinsic and extrinsic apoptotic pathways can be activated by various stress signals and cytokines released during ischemic injury.

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Necrosis, on the other hand, is a form of uncontrolled cell death that results from severe cellular damage and energy depletion, typical of the acute phase of stroke. Necrosis leads to cell swelling, membrane rupture, and the release of intracellular contents, which can provoke a strong inflammatory response in the surrounding tissue [48]. This inflammatory reaction can further exacerbate tissue damage and contribute to the expansion of the infarct area [49].

Inflammation plays a dual role in stroke pathophysiology. Initially, it is beneficial, aiming to clear debris and facilitate tissue repair. However, prolonged or excessive inflammation can be detrimental, leading to increased tissue damage and impaired recovery. Following ischemic stroke, damaged brain cells release danger-associated molecular patterns (DAMPs) that activate microglia and recruit peripheral immune cells to the site of injury. These activated cells release various cytokines, chemokines, and other inflammatory mediators that perpetuate the inflammatory cycle, contributing to secondary brain damage [50].

Oxidative stress is another critical factor in the pathophysiology of ischemic stroke. It results from an imbalance between the production of reactive oxygen species (ROS) and the brain's ability to detoxify these reactive intermediates or repair the resulting damage [50]. During ischemia, the reduced blood flow and subsequent reperfusion lead to excessive production of ROS, which can damage cellular lipids, proteins, and DNA. Oxidative stress is closely linked to inflammation, as ROS can activate transcription factors like NF-kB, which in turn upregulate the expression of pro-inflammatory genes [51, 52].
Moreover, oxidative stress can exacerbate cell death through the activation of additional cell death pathways, including autophagy and ferroptosis. Autophagy is a cellular process that degrades damaged organelles and proteins to maintain cellular homeostasis, but excessive autophagy can lead to cell death. Ferroptosis, a recently characterized form of cell death, is driven by iron-dependent lipid peroxidation, playing a notable role in the context of ischemic stroke [53].

The molecular pathways involved in ischemic stroke are interconnected, with each pathway influencing and exacerbating the others [34]. This complex interplay underscores the challenges in developing effective therapeutic interventions. Targeting these pathways individually or in combination, through the modulation of apoptosis, inhibition of necrosis, control of inflammation, and reduction of oxidative stress, holds promise for improving clinical outcomes in stroke patients [50]. Continued research into these molecular mechanisms is essential for advancing our understanding and treatment of ischemic stroke [43, 53].

Future Directions in Genetic and Molecular Studies

In recent years, significant advancements have been achieved in unraveling the genetic variability associated with stroke risk. However, substantial further endeavors are imperative to comprehensively elucidate the genetic underpinnings of stroke and to leverage these insights for a deeper understanding of the molecular pathways involved [54]. The future of genetics in ischemic stroke holds great promise, with ongoing research poised to revolutionize our comprehension of this complex neurological condition. As scientific knowledge expands and technological capabilities evolve, the landscape of genetics in ischemic stroke is rapidly progressing towards promising and innovative directions that have the potential to transform approaches to diagnosis, treatment, and prevention [7]. These future directions cover several crucial areas:

1. Next-generation sequencing on a large scale

To maximize genomic discoveries, extensive efforts are underway to conduct larger-scale genome-wide association studies (GWAS) and expand whole genome sequencing (WGS) studies. These initiatives aim to capture the impact of rare genetic variants and enable precise mapping of GWAS loci. Advanced algorithms now facilitate the detection of copy number variants, short tandem repeats, and mobile genetic elements using WGS data, which are not effectively identified by standard single nucleotide polymorphism-based approaches [54]. Genetic investigations, including GWAS, are expected to uncover additional variants associated with the risk of ischemic stroke. These findings hold potential to reveal new biological pathways and mechanisms underlying disease development, setting the stage for further validation and exploration of therapeutic strategies. International collaborations, such as those involving biobanks in the UK, Estonia, Finland, and Japan, are poised to significantly advance our understanding of genetics in common diseases.

2. Integration of multi-omics data to understand stroke pathophysiology

Ischemic stroke incidence and recovery are intricate and diverse pathophysiological processes influenced by a multitude of genetic, epigenetic, transcriptomic, proteomic, metabolomic, and pharmacogenomic factors. Integrating multi-omics approaches, which combine data from various biological layers, will provide a comprehensive understanding of the complex interactions among

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biological pathways and regulatory networks that contribute to the onset, progression, and recovery of ischemic stroke. Future research efforts are needed to fully elucidate the comprehensive picture of stroke multi-omics.

3. Gene therapy

While gene therapy for ischemic stroke is not currently available in clinical practice, promising preclinical studies have demonstrated its potential effectiveness. Emerging technologies such as CRISPR-Cas9 and base editing show promise in correcting genetic mutations associated with ischemic stroke, which could potentially prevent the disease in individuals at risk [7]. CRISPR-mediated interference and activation technologies are particularly relevant in stroke research, as many stroke-associated genetic variants are located in non-coding regions that can affect neighboring gene expression (e.g., rs2107595 SNP in the HDAC9 gene) and are involved in the long-range regulation of gene expression in a tissue-specific way. Moreover, CRISPR-based screening methods can analyze open chromatin regions, transcription factors, histone marks, and even the entire genome. Nevertheless, ethical considerations continue to pose challenges in advancing gene therapy approaches [55].

4. Precision medicine

As genetic information becomes more accessible, healthcare providers can analyze an individual's genetic predisposition to ischemic stroke and its risk factors, predict their response to treatment, and anticipate outcomes. This enables clinicians to tailor personalized prevention strategies, implement targeted interventions, minimize medication side effects, and optimize treatment outcomes.

5. New drug development

Genetic research has led to the discovery of new therapeutic biomarkers and targets for treating ischemic stroke. Targeted therapies that address the underlying molecular mechanisms represent promising avenues for developing neuroprotective agents and interventions aimed at mitigating the burden of stroke.

6. Broadening genetic studies to underrepresented populations

The majority of genetic research investigating the mechanisms behind ischemic stroke has predominantly focused on populations of European ancestry, resulting in an underrepresentation of diverse ancestral backgrounds compared to real-world diversity. It is crucial to increase the participation of non-European ancestry populations in genome-wide association studies (GWAS) and next-generation sequencing studies to ensure the generalizability of association findings and to maximize the potential for fine-mapping and risk prediction [7]. Recent initiatives have emerged to explore stroke genetics in African and Asian cohorts, presenting unique opportunities for discovery, particularly within African genomic studies. Initiatives such as the SIREN project in Nigeria are pivotal in advancing this field [54]. These efforts, alongside future cohorts, have the potential to significantly advance our understanding of stroke genetics, narrowing the gap in understanding the underlying mechanisms, identifying biomarkers, and developing therapeutic approaches [7].

7.Enhancement of global collaboration

International collaborations and initiatives for sharing data will enhance our comprehension of the genetic basis of ischemic stroke, especially across diverse populations, thereby enhancing the applicability of research findings. Leading international consortia in stroke genetics, such as the International Stroke Genetics Consortium (ISGC), MEGA STROKE Consortium, and GISCOME consortium, are pivotal in advancing this collaborative effort [7].

CONCLUSION

The literature review provides a comprehensive synthesis of the key findings in the field of genetic and molecular discoveries related to ischemic stroke. It highlights several critical insights regarding genetic factors, molecular mechanisms, biomarkers, therapeutic implications, and the potential for personalised medicine.

Numerous genetic variants have been identified that contribute to the susceptibility and severity of ischemic stroke, including polymorphisms in genes involved in coagulation, inflammation, and vascular integrity. Advances in molecular biology have elucidated several pathways implicated in the pathogenesis of ischemic stroke, such as oxidative stress, excitotoxicity, and apoptosis. Understanding these mechanisms has paved the way for the development of targeted therapies.

The identification of specific biomarkers has the potential to improve the early diagnosis and prognosis of ischemic stroke. Biomarkers such as microRNAs and circulating endothelial cells offer promise for non-invasive testing and risk stratification. Novel

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therapeutic approaches targeting genetic and molecular pathways are under investigation, including gene therapy, RNA interference, and the use of neuroprotective agents that mitigate the effects of ischemic injury at the cellular level.

The integration of genetic and molecular data into clinical practice supports the move towards personalised medicine. Tailoring prevention and treatment strategies based on an individual's genetic profile can enhance efficacy and reduce adverse effects.The potential impact of these discoveries on the prevention and treatment of ischemic stroke is profound. By identifying individuals at higher risk through genetic screening, it is possible to implement early preventive measures. Moreover, understanding the molecular underpinnings of ischemic stroke allows for the development of more effective, targeted therapies. As research continues to evolve, the integration of genetic and molecular insights into clinical protocols holds promise for significantly improving outcomes for patients with ischemic stroke.

REFERENCES

1. Litak J, Mazurek M, Kulesza B, Szmygin P, Litak J, Kamieniak P, et al. Cerebral Small Vessel Disease. International Journal of Molecular Sciences. 2020 Dec 20;21(24):9729.
2. Markus HS, de Leeuw FE. Cerebral small vessel disease: Recent advances and future directions. International Journal of Stroke. 2022 Dec 27;18(1):4–14.
3. Giau VV, Bagyinszky E, Youn YC, An SSA, Kim SY. Genetic Factors of Cerebral Small Vessel Disease and Their Potential Clinical Outcome. International Journal of Molecular Sciences. 2019 Sep 3;20(17):4298.
4. Marini S, Anderson CD, Rosand J. Genetics of Cerebral Small Vessel Disease. Journal of the American Heart Association. 2019 Jan 1;51(1):12-20.
5. Chung J, Marini S, Pera J, Norrving B, Jordi Jimenez-Conde, Jaume Roquer, et al. Genome-wide association study of cerebral small vessel disease reveals established and novel loci. Brain. 2019 Oct 1;142(10):3176–89.
6. Shi Y, Guo L, Chen Y, Xie Q, Yan Z, Liu Y et al. Risk factors for ischemic stroke: differences between cerebral small vessel and large artery atherosclerosis aetiologies. Folia Neuropathologica. 2021;59(4):378-385.
7. Zhang K, Loong S, Yuen L, Narayanaswamy Venketasubramanian, Chin HL, Lai P, et al. Genetics in Ischemic Stroke: Current Perspectives and Future Directions. Journal of Cardiovascular Development and Disease. 2023 Dec 13;10(12):495–5.
8. Navi BB, Kasner SE, Elkind MSV, Cushman M, Bang OY, DeAngelis LM. Cancer and Embolic Stroke of Undetermined Source.Journal of the American Heart Association. 2021 Jan 28;52(3):1121-1130.
9. Ntaios G. Embolic Stroke of Undetermined Source: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jan 28;75(3):333-340.
10. Maida CD, Norrito RL, Daidone M, Tuttolomondo A, Pinto A. Neuroinflammatory Mechanisms in Ischemic Stroke: Focus on Cardioembolic Stroke, Background, and Therapeutic Approaches. *International Journal of Molecular Sciences*. 2020 Sep 4; 21(18):6454.
11. Pillai AA, Tadi P, Kanmanthareddy A. Cardioembolic Stroke [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Jun 9]. Available from: https://pubmed.ncbi.nlm.nih.gov/30725675/
12. Kamel H, Healey JS. Cardioembolic Stroke. Journal of the American Heart Association. 2017 Feb 3;120(3):514-526.
13. Carinci M, Vezzani B, Patergnani S, et al. Different Roles of Mitochondria in Cell Death and Inflammation: Focusing on Mitochondrial Quality Control in Ischemic Stroke and Reperfusion. *Biomedicines*. 2021 Feb 9;9(2):169.
14. An H, Zhou B, Ji X. Mitochondrial quality control in acute ischemic stroke. *J Cereb Blood Flow Metab*. 2021 Sep 22;41(12):3157-3170.
15. Chakrabarty S, Govindaraj P, Sankaran BP, et al. Contribution of nuclear and mitochondrial gene mutations in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. *J Neurol*. 2021 Jan 23;268(6):2192-2207.
16. Ueda S, Yagi M, Tomoda E, et al. Mitochondrial haplotype mutation alleviates respiratory defect of MELAS by restoring taurine modification in tRNA with 3243A > G mutation. *Nucleic Acids Res*. 2023 Jul 13;51(14):7480-7495.
17. Barros CDS, Coutinho A, Tengan CH. Arginine Supplementation in MELAS Syndrome: What Do We Know about the Mechanisms? *International Journal of Molecular Sciences*. 2024 Mar 24; 25(7):3629.

18. Fan HC, Lee HF, Yue CT, Chi CS. Clinical Characteristics of Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes. *Life (Basel)*. 2021 Oct 20;11(11):1111.
19. Ferro JM, Infante J. Cerebrovascular manifestations in hematological diseases: an update. *J Neurol*. 2021 Feb 13;268(9):3480-3492.
20. Light J, Boucher M, Baskin-Miller J, Winstead M. Managing the Cerebrovascular Complications of Sickle Cell Disease: Current Perspectives. *J Blood Med*. 2023 Apr 14;14:279-293.
21. Kim BK, Eah KY, Park JM. Essential Thrombocythemia and Ischemic Stroke: A Case Series of Five *JAK2*-Positive Patients. *Medicina (Kaunas)*. 2023 Jul 14;59(7):1300.
22. Balagopal K, Mathew A, Koshy AG, Jacob JP. Polycythemia Vera Presenting as Hemorrhagic Stroke. *J Neurosci Rural Pract*. 2021 May 5;12(3):601-602.
23. Regimbeau M, Mary R, Hermetet F, Girodon F. Genetic Background of Polycythemia Vera. *Genes (Basel)*. 2022 Apr 2;13(4):637.
24. Cho BP, Harshfield EL, Al-Thani M, Tozer DJ, Bell S, Markus HS. Association of vascular risk factors and genetic factors with penetrance of variants causing monogenic stroke. JAMA neurology. 2022 Dec 1;79(12):1303-11.
25. Chang LH, Chi NF, Chen CY, Lin YS, Hsu SL, Tsai JY, Huang HC, Lin CJ, Chung CP, Tung CY, Jeng CJ. Monogenic Causes in Familial Stroke Across Intracerebral Hemorrhage and Ischemic Stroke Subtypes Identified by Whole-Exome Sequencing. Cellular and Molecular Neurobiology. 2023 Aug;43(6):2769-83.
26. Huang S, Joshi A, Shi Z, Wei J, Tran H, Zheng SL, Duggan D, Ashworth A, Billings L, Helfand BT, Qamar A. Combined polygenic scores for ischemic stroke risk factors aid risk assessment of ischemic stroke. International Journal of Cardiology. 2024 Jun 1;404:131990.
27. Ekkert A, Šliachtenko A, Grigaitė J, Burnytė B, Utkus A, Jatužis D. Ischemic stroke genetics: what is new and how to apply it in clinical practice?. Genes. 2021 Dec 24;13(1):48.
28. Li J, Abedi V, Zand R. Dissecting Polygenic Etiology of Ischemic Stroke in the Era of Precision Medicine. Journal of Clinical Medicine. 2022 Oct 11;11(20):5980.
29. Liu X, Wang Q, Zhu R. Association of GWAS-susceptibility loci with ischemic stroke recurrence in a Han Chinese population. The Journal of Gene Medicine. 2021 Jan;23(1):e3264.
30. Lee JM, Fernandez-Cadenas I, Lindgren AG. Using human genetics to understand mechanisms in ischemic stroke outcome: from early brain injury to long-term recovery. Stroke. 2021 Sep;52(9):3013-24.
31. Knol MJ, Lu D, Traylor M, Adams HH, Romero JR, Smith AV, Fornage M, Hofer E, Liu J, Hostettler IC, Luciano M. Association of common genetic variants with brain microbleeds: a genome-wide association study. Neurology. 2020 Dec 15;95(24):e3331-43.
32. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. Nature Reviews Cardiology. 2021 Sep;18(9):666-82.
33. Kelly PJ, Lemmens R, Tsivgoulis G. Inflammation and stroke risk: a new target for prevention. Stroke. 2021 Aug;52(8):2697-706.
34. Zhang T, Cao Y, Zhao J, Yao J, Liu G. Assessing the causal effect of genetically predicted metabolites and metabolic pathways on stroke. Journal of Translational Medicine. 2023 Nov 17;21(1):822.
35. Debette S, Markus HS. Stroke genetics: discovery, insight into mechanisms, and clinical perspectives. Circulation Research. 2022 Apr 15;130(8):1095-111.
36. Sukumaran R, Nair AS, Banerjee M. Ethnic and region-specific genetic risk variants of stroke and its comorbid conditions can define the variations in the burden of stroke and its phenotypic traits. eLife. 2024 Apr 2;13.
37. Stefanou MI, Giannopapas V, Kitsos DK, Chondrogianni M, Theodorou A, Kosmidou M, Vlotinou P, Bakirtzis C, Andreadou E, Tzartos JS, Giannopoulos S. Prevalence and epidemiology of stroke in patients with multiple sclerosis: a systematic review and meta-analysis. Journal of Neurology. 2024 Apr 4:1-1.
38. Rajashekar D, Wilms M, MacDonald ME, Schimert S, Hill MD, Demchuk A, Goyal M, Dukelow SP, Forkert ND. Lesion-symptom mapping with NIHSS sub-scores in ischemic stroke patients. Stroke and Vascular Neurology. 2022 Apr 1;7(2).

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IJCSRR @ 2024
www.ijcsrr.org

39. Jung J, Lu Z, de Smith A, Mancuso N. Novel insight into the etiology of ischemic stroke gained by integrative multiome-wide association study. Human Molecular Genetics. 2024 Jan 15;33(2):170-81.
40. Jung J, Lu Z, de Smith A, Mancuso N. Novel insight into the etiology of ischemic stroke gained by integrative transcriptome-wide association study. medRxiv. 2023 Mar 31.
41. Wu BS, Chen SF, Huang SY, Ou YN, Deng YT, Chen SD, Dong Q, Yu JT. Identifying causal genes for stroke via integrating the proteome and transcriptome from brain and blood. Journal of translational medicine. 2022 Apr 21;20(1):181.
42. Ekkert A, Šliachtenko A, Grigaitė J, Burnytė B, Utkus A, Jatužis D. Ischemic stroke genetics: what is new and how to apply it in clinical practice?. Genes. 2021 Dec 24;13(1):48.
43. Debette S, Paré G. Stroke Genetics, Genomics, and Precision Medicine. Stroke. 2024 Mar 21.
44. Cullell N, González-Sánchez J, Fernández-Cadenas I, Krupinski J. Generation and Applicability of Genetic Risk Scores (GRS) in Stroke. Stroke Biomarkers. 2020:23-34.
45. Montaner J, Ramiro L, Simats A, Tiedt S, Makris K, Jickling GC, Debette S, Sanchez JC, Bustamante A. Multilevel omics for the discovery of biomarkers and therapeutic targets for stroke. Nature Reviews Neurology. 2020 May;16(5):247-64.
46. Chavda V, Chaurasia B, Garg K, Deora H, Umana GE, Palmisciano P, Scalia G, Lu B. Molecular mechanisms of oxidative stress in stroke and cancer. Brain Disorders. 2022 Mar 1;5:100029.
47. Qin C, Yang S, Chu YH, Zhang H, Pang XW, Chen L, Zhou LQ, Chen M, Tian DS, Wang W. Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions. Signal transduction and targeted therapy. 2022 Jul 6;7(1):215.
48. Mao R, Zong N, Hu Y, Chen Y, Xu Y. Neuronal death mechanisms and therapeutic strategy in ischemic stroke. Neuroscience bulletin. 2022 Oct;38(10):1229-47.
49. Tuo QZ, Zhang ST, Lei P. Mechanisms of neuronal cell death in ischemic stroke and their therapeutic implications. Medicinal research reviews. 2022 Jan;42(1):259-305.
50. Klegeris A. Regulation of neuroimmune processes by damage-and resolution-associated molecular patterns. Neural Regeneration Research. 2021 Mar 1;16(3):423-9.
51. Chavda V, Chaurasia B, Garg K, Deora H, Umana GE, Palmisciano P, Scalia G, Lu B. Molecular mechanisms of oxidative stress in stroke and cancer. Brain Disorders. 2022 Mar 1;5:100029.
52. Fang C, Xu H, Yuan L, Zhu Z, Wang X, Liu Y, Zhang A, Shao A, Lou M. Natural compounds for SIRT1-mediated oxidative stress and neuroinflammation in stroke: a potential therapeutic target in the future. Oxidative medicine and cellular longevity. 2022;2022(1):1949718.
53. Liu Y, Fang Y, Zhang Z, Luo Y, Zhang A, Lenahan C, Chen S. Ferroptosis: An emerging therapeutic target in stroke. Journal of neurochemistry. 2022 Jan;160(1):64-73.
54. Debette S, Markus HS. Stroke Genetics: Discovery, Insight Into Mechanisms, and Clinical Perspectives. Circulation Research. 2022 Apr 15;130(8):1095–111.
55. Granata A. Functional genomics in stroke: current and future applications of iPSCs and gene editing to dissect the function of risk variants. 2023 Apr 29;23(1).