A Genetic Perspective on Ischemic Stroke: Recent Advances and Future Directions

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Abstract

Objective. *This narrative review aimed to explore the multifaceted nature of ischemic stroke (IS) and its underlying genetic factors, emphasize the role of genetics in early detection and prevention, and acknowledge the complex influences on stroke prevalence across various countries.*

Methods. *An extensive overview of the causes, mechanisms, and genetics of IS was conducted by reviewing several studies and recent findings. The role of specific genes in monogenic stroke disorders, implications of polygenic influences, recent advances in genetic evaluation, and methods for early IS detection were synthesized and discussed.*

Results. *IS was influenced by genetics, underlying medical conditions, and lifestyle. Specific genes, including NOTCH3, HTRA1, COL3A1, and mtDNA, are involved in monogenic stroke syndromes and predominantly affect younger populations. Polygenic disorders, studied using genome-wide association study and sequencing techniques, play a prominent role in susceptibility to IS. Genetic evaluation has become instrumental in risk prediction, influencing clinical practices and potential therapeutic interventions. Early detection methods, such as enhanced imaging techniques and blood biomarkers, are crucial for managing IS outcomes.*

Conclusion. *Ischemic stroke is a complex disorder with a significant global impact. Understanding its genetic basis promises to improve early detection and effectively establish preventative measures. Although genetic evaluation and innovative detection techniques offer promise, focusing on lifestyle modifications and managing underlying health conditions remains paramount for reducing the incidence and severity of IS. Continuous research and technological advancements are essential for developing personalized medical approaches and improving global healthcare strategies.*

Keywords: *ischemic stroke; genetics; therapeutic; pathways; pathophysiology*

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Генетические аспекты ишемического инсульта: последние достижения и направления исследований

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Аннотация

Цель *данного нарративного обзора – описать многофакторность ишемического инсульта (ИИ) и генетические факторы его развития, подчеркнуть роль генетики в ранней диагностике и профилактике ИИ, а также осветить комплексное влияние на распространённость инсульта в разных странах.*

Проведён обзор исследований и последних данных для всестороннего освещения причин, механизмов и генетических аспектов развития ИИ. В статье обобщаются и обсуждаются роль специфических генов в развитии моногенных заболеваний, связанных с ИИ, последствия полигенных заболеваний, последние достижения генетических исследований и методы ранней диагностики ИИ.

На развитие ИИ влияют генетические факторы, сопутствующие заболевания и образ жизни. Специфические гены (NOTCH3, HTRA1, COL3A1) и гены митохондриальной ДНК задействованы в моногенных заболеваниях, связанных с ИИ и поражающих преимущественно молодых людей. Полигенные заболевания, изученные посредством полногеномного поиска ассоциаций и секвенирования, играют важную роль в предрасположенности к развитию ИИ. Генетические исследования становятся эффективными инструментами прогнозирования рисков, влияя на клиническую практику и потенциальные терапевтические вмешательства. Такие методы ранней диагностики, как специализированные модальности нейровизуализации и исследование биомаркеров крови, играют ключевую роль в улучшении исходов ИИ.

Заключение. *ИИ – комплексное заболевание, несущее значительное глобальное бремя. Понимание генетических факторов, влияющих на его развитие, поможет улучшить раннюю диагностику и эффективно внедрить профилактические меры. Несмотря на то что генетические исследования и инновационные методы диагностики вселяют надежду, коррекция образа жизни и лечение основных заболеваний сохраняют своё первостепенное значение в снижении частоты и тяжести ИИ. Непрерывная исследовательская деятельность и технологические достижения – ключ к разработке индивидуальных подходов к лечению и улучшению глобальных стратегий здравоохранения.*

Ключевые слова: *ишемический инсульт; генетика; лечение; сигнальные пути; патофизиология*

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Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы заявили об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Stroke is a multifaceted disorder with a range of contributing factors, including lifestyle choices such as smoking, underlying conditions such as dyslipidemia, hypertension, and diabetes; and a genetic component [1]. The most prevalent form of stroke is ischemic stroke (IS), which occurs when the blood supply to the brain is obstructed, often due to blood clots. It is the second leading cause of death and disability, with a substantial global impact [2]. Particularly in economically disadvantaged nations such as India, IS exerts a heavy toll [3]. Worldwide, stroke remains a significant cause of mortality and morbidity, with staggering statistics indicating that 1.5 million lives are claimed by stroke annually, while 2.5 million new cases are documented in China alone [4]. Among these, IS was predominant, accounting for 62.4% of all stroke cases.

One notable characteristic of IS is the development of arterial plaques, which may result in severe complications, including heart attack and stroke. However, genetic factors have often been overlooked. However, they are crucial for human development, particularly when discussing early-onset stroke [5]. Specific genetic abnormalities follow Mendelian inheritance patterns, leading to monogenic diseases often associated with distinct and uncommon stroke subtypes [6]. IS comprises various subtypes, including small-vessel disease, cardioembolism, and large-vessel atherosclerotic IS [7]. Among these subtypes, large artery stroke exhibits the highest hereditary factor, accounting for nearly 40% of cases, with cardioembolic IS closely trailing in 33% of the ISs.

In contrast, only 16% of strokes originating from small vessel disease are hereditary [8, 9]. Genetic factors are more likely to play a role in the development of diseases affecting both small and large blood vessels rather than being significant contributors to the causes of cardioembolic IS. However, the prevalence of single-gene disorders related to stroke is estimated at approximately 1%. These disorders predominantly affect younger individuals. However, the accuracy of these data cannot be guaranteed. Several monogenic disorders involve specific genes, including *NOTCH3*, *HTRA1*, *COL3A1*, *mtDNA*, and *TREX1*, as well as interleukins (IL), such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-6, all of which can contribute to the occurrence of IS. As research advances, polygenic disorders are emerging as a significant area of interest in IS genetics, accounting for approximately 38% of all ISs [10]. Studies conducted in previous years has provided valuable insights, but current research focuses on identifying modern risk factors and genetic markers that can facilitate early stroke risk detection and implementing preventive strategies.

Furthermore, when considering age-standardized mortality rates due to IS for the mentioned countries between 2020 and 2030, it is evident that some countries, such as South Africa (2.64%), Cyprus (4.16%), China (2.19%), Portugal (7.18%), Ethiopia (1.83%), Mongolia (2.38%), Ecuador (5.43%), Cabo Verde (8.17%), and Mauritius (10.90%) have experienced an increase in mortality rates, while Comoros (9%) has seen a decrease [11]. These trends highlight the intricate interplay of factors, such as evolving lifestyles, disparities in socioeconomic status, healthcare accessibility, and demographic shifts in shaping the prevalence of IS in different regions.

This narrative review **aimed** to explore the multifaceted nature of IS and its underlying genetic factors, emphasize the role of genetics in early detection and prevention, and acknowledge the complex influences on stroke prevalence across various countries.

Causes and mechanisms of ischemic stroke

Thrombotic IS is a common subtype of stroke that arises when a clot forms within an artery inside the brain. This blockage can be triggered by a thrombus or an embolus [12]. A significant contributor to thrombotic IS is atherosclerosis, which is characterized by plaque buildup along blood vessel walls. The rupture of this plaque can lead to the formation of a blood clot at the rupture site, culminating in thrombotic IS [13].

On the other hand, embolic ISs arise when a blood clot or other debris (embolus) forms elsewhere in the body, typically in the heart or major arteries. These emboli can travel through the bloodstream and eventually reach the brain, where they may become lodged in a small blood vessel, impeding blood flow and causing embolic IS. Familiar sources of emboli include blood clots originating in the heart, often associated with conditions such as atrial fibrillation or detachment of plaque particles from larger arteries [14].

In IS, reactive oxygen species (ROS) are responsible for the cerebral damage because they can deplete adenosine triphosphate and interfere with the ability to produce energy [15]. It involves a series of biochemical reactions that lead to neuronal death, disintegration of cell membranes, and ionic imbalance, which causes cell depolarization and glutamate release. These reactions are caused by disrupted levels of Ca^{2+}, K^{+}, and Na^{+} [16]. Excess levels of glutamate trigger the activation of N-methyl-D-aspartate receptors. This activation can be detrimental to cell health and cause damage to the central nervous system.

Furthermore, it can also lead to the release of more glutamate, which leads to excitotoxicity and activates the death signalling pathway through oxidative and nitrosative stress, mitochondrial dysfunction, and blood–brain barrier dysfunction. A subsequent cascade of injuries occurs as a result of ischemia-induced injury [17]. Figure 1 illustrates the IS mechanism.

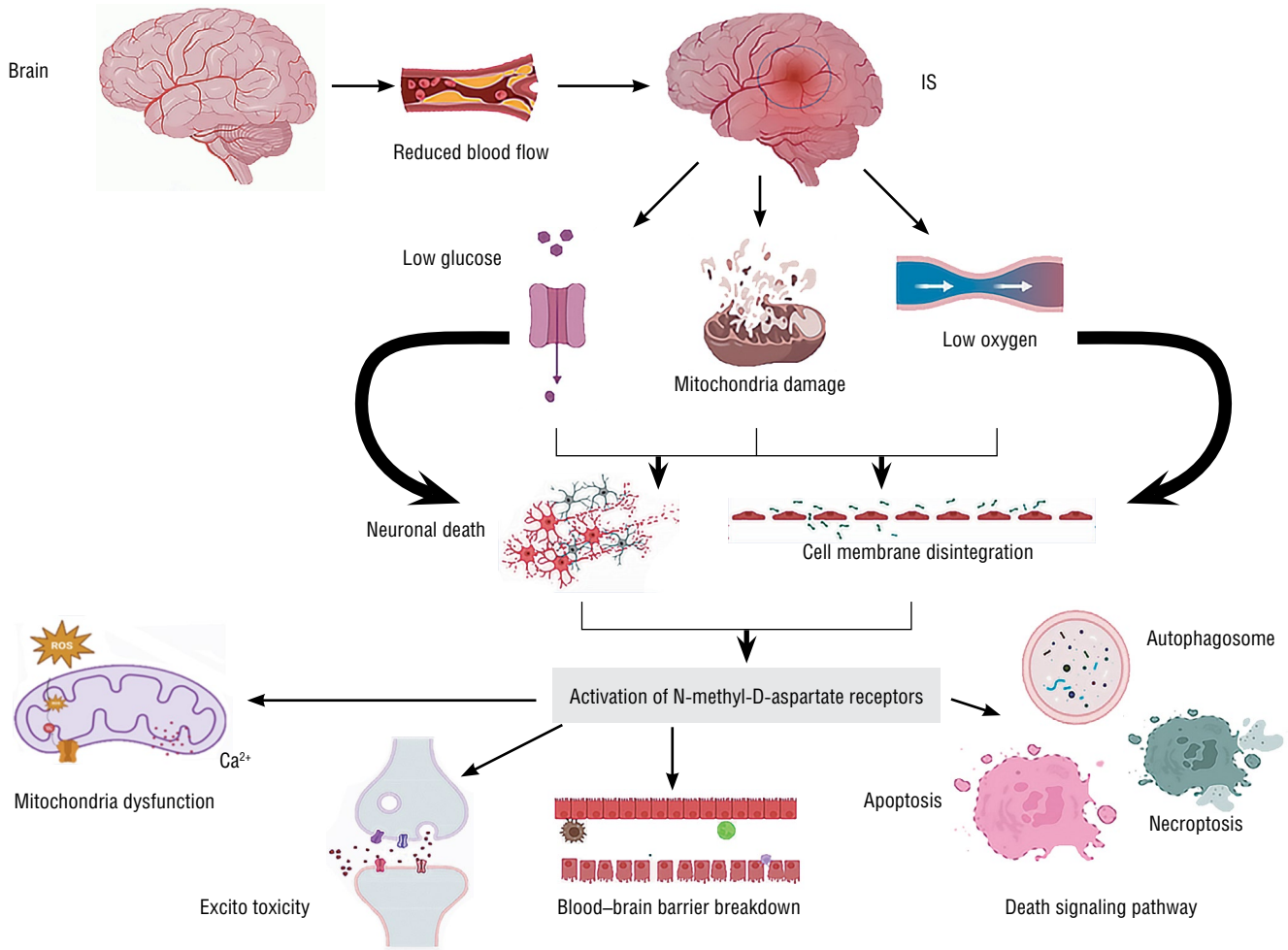

Fig. 1. Mechanism of IS.

Genetics of ischemic stroke

Notably, in cases of early onset, genetic factors are important in the development of IS. Several genes have been linked to IS, including *NOTCH3*, *HTRA1*, *COL3A1*, and some genes of mitochondrial DNA (*mtDNA*). The hereditary form of IS known as CADASIL is associated with the *NOTCH3* gene. Additionally, IS has been linked to mutations in *HTRA1*. Moreover, TNF-α polymorphisms and a range of tandem repeats in the IL-1 receptor antagonist gene have been linked to an increased risk of IS. Moreover, there is evidence of a genetic predisposition to small-vessel IS. Multiple environmental and genetic factors contribute to the development of IS. However, the precise genetic mechanisms underlying IS and its subtypes remain to be elucidated.

Monogenic disorders

Monogenic disorders are a class of hereditary illnesses caused by mutations in a single gene. These disorders are often referred to as Mendelian. Inheritance of a mutant or faulty copy of a particular gene from one or both parents often defines these illnesses.

NOTCH 3

NOTCH3 (Notch Receptor 3) is a protein-coding gene located in Chr19 with a 33-exon count and codes for 2321 amino acids. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic disorder, is the most frequent monogenic trigger for IS. Autosomal dominant inheritance and *NOTCH3* gene mutations are the causes of CADASIL [18]. Consequently, the walls of the tiny blood vessels in the brain accumulate the protein NOTCH3. This can cause vessels to become narrow and stiff, leading to an increased risk of IS. It is diagnosed using molecular genetic testing or skin biopsy, with immunohistochemistry and electron microscopy revealing the typical features [19]. The NOTCH3 protein is a transmembrane protein with a single pass. Most vascular smooth muscle cells express this protein. The NOTCH3 protein comprises an extracellular domain (NOTCH3ECD) and an intracellular

domain. The protein undergoes three cleavage stages when a specific ligand (either Jagged or Delta) binds to NOTCH-3ECD. The intracellular domain eventually reaches the nucleus, which functions as a transcription factor. *NOTCH3* mutations in CADASIL, a genetic disorder affecting the brain and blood vessels, can lead to an unequal number of cysteine residues in the mutant EGFr proteins. This typically results in 5 or 7 cysteine residues that can significantly affect protein function and cause symptoms of illness. There may be an issue with the formation of disulfide bridges in EGFr, which could lead to protein misfolding. Additionally, this issue may be related to increased multimerization of NOTCH3 with cysteine. A.P. Pan et al. reported 914 patients (median age of 60 years) with CADASIL of whom 65.2% had documented cerebrovascular events (i.e., CADASIL-Stroke patients) between September 2018 and April 2020. It is essential to investigate these findings further to understand their underlying mechanisms and potential implications for human health [20].

HTRA1

HTRA1 (High-Temperature Requirement A Serine Peptidase 1), situated on chr10q26, comprises nine exons and encodes the p-serine protease HTRA1, which consists of 480 amino acids. Cerebral autosomal recessive artery disease with subcortical infarcts and leukoencephalopathy is a rare hereditary condition among the general population. It primarily affects the brain and the blood vessels. Patients with CARASIL typically experience difficulty in walking, early onset dementia, hair loss, and lower back pain. CARASIL: besides the symptoms above, patients with CARASIL may experience visual problems, muscle weakness, and urinary incontinence. CARASIL has been reported in three cases: a mutation in the *HTRA1* gene, p. Arg302end, and the p. Ala252Thr mutation in a sibling [21, 22]. It is a serine protease essential for several cellular functions, including transforming growth factor (TGF) signaling [23]. Abnormal TGF-β signalling is thought to play a role in the emergence of CARASIL. Studies have shown that when mutations occur in CARASIL, the function of *HTRA1* is often disturbed.

TGF-binding protein-1 (LTBP-1) is a matricellular factor that plays a significant role in TGF-bioactivation and acts as a physiological substrate for HTRA1. This discovery may have important implications for our understanding of this complex biological process [24]. Down-regulation of the TGF pathway is essential for CARASIL development. It has also been found that LTBP-1 is a significant substrate of HTRA1 in this process. Furthermore, it as been shown that LTBP-1 is a crucial protein in this pathway, and there is currently no cure for CARASIL. Treatment aims to reduce symptoms and enhance quality of life. Individuals with a family history of CARASIL must seek genetic counseling before planning to have children [25].

COL3A1

The *COL3A1 (Collagen Type III Alpha 1 Chain)* gene on Chr2q32.2 comprises 51 exons and codes for a protein pro-alpha1 chain of type III collagen consisting of 1466 amino acids. Vascular Ehlers–Danlos syndrome (EDS), also known as EDS type IV, is caused by *COL3A1* mutation. Individuals with EDS type IV often exhibit unique facial features and premature aging of the limb extremities (acrogeria), making them susceptible to vascular and digestive ruptures and uterine perforations during pregnancy. This condition is caused by a genetic mutation that affects collagen III production. Collagen III is a vital protein that helps regulate the behavior and function of cells by binding to integrated cell surface receptors. In addition, they provide structural support to tissues and play crucial roles in angiogenesis, cell differentiation, and wound healing. Collagen III is critical for maintaining healthy cellular function and promoting optimal physiological processes. Heterozygous mutations in *COL3A1* give rise to this condition, resulting in compromised connective tissues, particularly the skin, blood vessels, and organs, which may lead to potential weakness. The pro1(III) triple-helix domain is often altered by substituting glycine residues with conventional triplet repeats.

Another typical mutation is in-frame exon skipping, which occurs in approximately 25% of cases owing to splice site changes. Insertions or small in-frame deletions can occur in rare cases. Procollagen III is a homotrimeric protein synthesized from regular and mutant 1(III) chains. As a result, 1, 2, or 3 mutant chains were found in approximately 88% of homotrimers. Thirteen distinct subtypes of EDS and mutations in 20 genes have been identified. This highlights the genetic complexity of this condition and the need for further research to understand and treat each subtype [26]. Although there is no cure for EDS type IV, patients with this condition can benefit from regular medical monitoring and symptom management.

TREX1

The *TREX1 (Three Prime Repair Exonuclease 1)* gene on chr3.48 consists of three exons that encode a protein. Three-prime repair exonuclease 1 comprises 314 amino acids. Retinal vasculopathy with cerebral leukodystrophy (RVCL) is inherited in an autosomal dominant manner, affecting both the retina and the central nervous system [27]. It is a minor hereditary vascular disease affecting the cerebral cortex. Hereditary vascular retinopathy, Cerebroretinal vascular disease, and hereditary endotheliopathy, retinopathy, nephropathy, and stroke are the three significant illnesses covered by RVCL [28]. Heterozygous frameshift mutations affecting the C terminus of *TREX1*, which encodes a 3'-5' exonuclease, lead to renal failure, vascular retinopathy, and focal neurologic symptoms, including ischemia events and cognitive deterioration. *TREX1* mutations result in RVCL and systemic manifestations (RVCL-S) [29].

A malfunctioning gene leads to the production of a truncated form of TREX1. Typically located within cells in the endoplasmic reticulum (ER), a network of membranes crucial for protein synthesis and release, the normal TREX1 protein is affected in RVCL-S due to one mutant copy of the *TREX1* gene, with mutations occurring in the gene's final quarter. This region encodes a portion of the protein required to maintain it in the ER compartment. Mutations in this region allow the protein to escape the ER and become mislocalized throughout the cell. Mislocalized TREX1 protein specifically affects and eventually destroys the lining of blood vessels, disrupting brain and ocular function in an unknown way. According to the autosomal dominant inheritance pattern, most individuals inherit RVCL-S from an affected parent. Disease onset and severity can differ significantly even within the same family. A 50% chance exists for an individual with RVCL-S to pass on the *TREX1* pathogenic variant to their progeny [30].

Both males and females are equally susceptible to RVCL-S, typically in middle-aged individuals (35–50 years). Initial signs often involve eye issues such as increased 'floaters' or 'blind patches.' Cases of RVCL-S have been identified in various countries, including Spain, Turkey, the United Kingdom, the United States, Australia, Japan, the Netherlands, China, France, Germany, Italy, Mexico, Switzerland, and Taiwan [31].

mtDNA

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) Mitochondrial disorders, a diverse group of illnesses, result from gene mutations producing the proteins necessary for proper mitochondrial function. These disorders vary significantly in clinical presentation, biochemical features, and challenging diagnosis and management [32]. Among the mitochondrial diseases with the highest prevalence are those caused by mutations in the mtDNA, including MELAS. They may not necessarily represent genuine ISs but may arise from mitochondrial cytopathy, mitochondrial angiopathy, or a combination of both. Human mtDNA comprises two strands of DNA and contains 37 genes. These genes encode 13 structural peptide subunits of the oxidative phosphorylation system and numerous other molecules, making mtDNA an essential component of cellular respiration and energy production [33]. This medical condition is characterized by various symptoms, including episodic headaches, stroke-like episodes, short stature, lactic acidosis, vomiting, seizures, and skeletal myopathy. These symptoms typically occur before the age of 40 years and can be debilitating [34]. mtDNA has a single-base pair mutation rate that is much higher than that of the nuclear DNA. Therefore, mtDNA is more susceptible to changes in its genetic code over time, which has important implications in genetic and evolutionary research. Although this difference in mutation rates is not yet fully understood, scientists believe it may be due to the lack of efficient DNA repair mechanisms in the mitochondria compared to the nucleus.

ROS damage is widely accepted as the main factor leading to mtDNA mutagenesis. Continued mutations increase mitochondrial dysfunction and ROS generation, perpetuating a harmful cycle [35]. Additionally, mtDNA is vulnerable to chemical damage because histone proteins do not shield it. Furthermore, mutations in polymerase are the most common cause of inherited mitochondrial diseases [36]. MELAS disorders caused by mutations in oxidative phosphorylation components impair adenosine triphosphate synthesis and increase ROS generation. Mutations in mtDNA can have severe consequences for cellular health. Mutations in mitochondrial DNA can result in reductions in transfer RNA (tRNA) and proteins involved in oxidative phosphorylation. This may result in reduced adenosine triphosphate production, which may increase ROS production and cause oxidative stress. Oxidative stress can result in apoptosis, tissue damage, and mutations in mtDNA. Mitochondrial dysfunction can also disrupt calcium ion (Ca^{2+}) metabolism, leading to cell enlargement and death. Therefore, it is essential to understand the mechanisms underlying mtDNA mutations and their effects on cell health [37].

Hereditary hemorrhagic telangiectasia

People with Osler–Weber–Rendu disease, an autosomal dominant condition that does not occur very often, tend to bleed, and abnormal blood vessel growth and development can be seen all over the body. It can affect the arms, fingers, conjunctiva, trunk, and gastrointestinal tract. Symptoms may not appear until the late stages of life or later (approximately 90% of patients show signs by age 40) [38]. Patients with Osler–Weber–Rendu disease and their relatives can undergo genetic testing to determine whether the relevant genes, such as the chromosome 12 activin receptor-like kinase type I (*ALK-1*) gene and the endoglin gene (*ENG*) in chromosome 9, have mutations [39], both of which encode TGF-beta (TGF-β) superfamily receptors that are essential for the healthy formation of blood vessels. The *ALK-1* gene, associated with hereditary hemorrhagic telangiectasia (HHT) type 2, and the *ENG* gene, linked to HHT type 1, are commonly recognized as the most frequently implicated genes in HHT. Other genes are less regularly associated [40]. Both type III and type I TGF receptors, ALK-1 and endoglin, occur only in vascular endothelial cells. Endoglin enables the phosphorylation of type I TGF-β receptors, specifically ALK-5 and ALK-1, when TGF binds to type II TGF-β receptors on endothelial cells. Endoglin and ALK-1 directly bind to BMP-9 and BMP-10, and their interaction with the type II BMP receptor results in aberration [41]. Phosphorylation of ALK-5 and ALK-1 activates the downstream proteins Smad2/3 and Smad1/5, respectively. Subsequently, these activated Smad proteins detach from

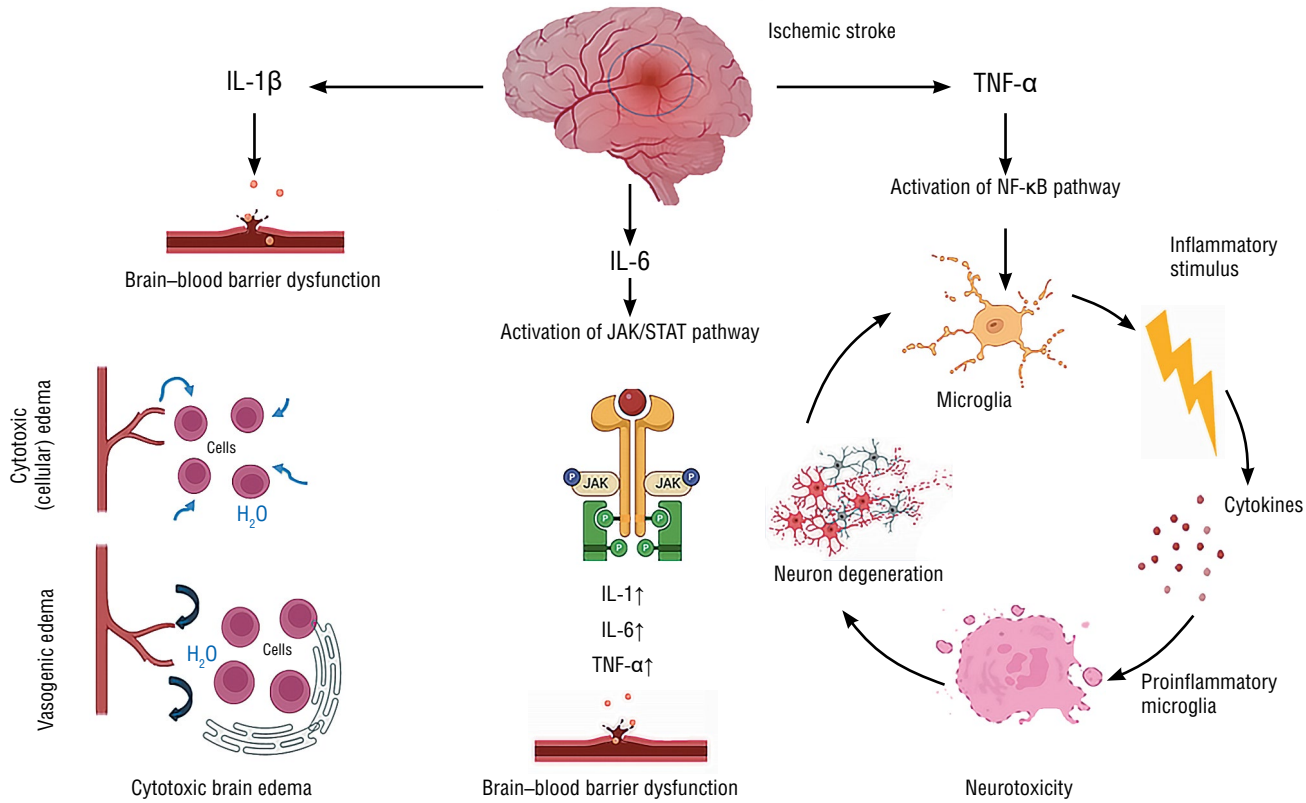

Fig. 2. Role of interleukin gene in IS.

the type I TGF receptor, combine with Smad4, and enter the nucleus to modulate the transcription of specific gene promoters associated with angiogenesis.

Genes involved in the mechanisms of IS

Interleukin genes

Research has indicated that proinflammatory cytokines play a vital role in the development of atherosclerosis. A lymphocyte medium termed an IL, mediates the connection between immunological cells and white blood cells. It belongs to the same class of cytokines as the blood cell growth factors. It is also essential for information transmission, immune cell activation and control, T and B cell activation, multiplication, differentiation, and inflammatory response [42]. Some major interleukins associated with IS are *IL-6*, *IL-1β*, and *TNF-α*. Figure 2 shows the involvement of the interleukin genes in IS.

IL-1β causes a variety of biological reactions that help the body respond to damage or infection, such as fever, sleepiness, appetite loss, acute phase protein synthesis, vasodilatation, adhesion, generation of chemokines, molecular upregulation, and the pro-coagulant condition, as well as the creation and release of growth factors, matrix metalloproteinases, and hematopoiesis. *IL-1*, *IL-1a*, and *IL-1b* contain 2 molecules. The *IL-1* gene complex, which contains three related genes: *IL1a*, *IL1b*, and *IL-b*, is found on chromosome 14. Five alleles exist within IL-1: IL-1RN1, IL-1RN2, IL-1RN3, IL-1RN4, and IL-1RN5. Among these, IL-1RN2 is considered a genetic risk factor for IS, a condition closely associated with coronary artery disease, and polymorphism is considered a genetic risk factor. Reduced blood flow in IS can cause nerve cell damage and inflammation. IL-1β, a potent proinflammatory cytokine, causes blood–brain barrier dysfunction by activating enzymes that break down arachidonic acid and release prostaglandins and leukotrienes. These compounds increase the blood–brain barrier permeability, causing vasogenic brain edema, potentially leading to pressure buildup and brain damage. They also cause cytotoxic brain edema through reduced oxygen and glucose after stroke, leading to cytotoxic brain edema [43]. The interaction between vasogenic and cytotoxic edema can increase cranial pressure, harm brain tissue, and cause cerebral herniation. *IL-1β* promotes the expression of adhesion molecules in endothelial cells. Ischemia triggers an inflammatory response by attracting immune cells to the affected area, causing them to migrate to this area [44].

IL-6-driven inflammation is a mechanism that drives various types [45]. *IL-6* mediates cellular communication via two different mechanisms: classic and trans-signalling [46].

The conventional *IL-6* signaling pathway involves binding of *IL-6* to its transmembrane receptor, IL-6R. The cleavage of transmembrane IL-6R gives rise to a naturally occurring soluble form known as sIL-6R. sIL-6R can bind to IL-6, enabling IL-6 responsiveness in cells lacking the transmembrane IL-6R. Upon binding to membrane-bound IL-6R or sIL-6R, *IL-6* induces the oligomerization of gp130, initiating the Janus kinase/signal transducer and activator of transcription pathway. Numerous cytokines and growth factors alter gene expression by sending signals via Janus kinase and signal transducer and activator of transcription pathways from the cell surface to the nucleus. A soluble antagonist of gp130 effectively inhibits IL-6/sIL-6R activity by binding to the IL-6/sIL-6R complex. This antagonist specifically discriminates between trans-signaling, where *IL-6* affects cells lacking IL-6R, and the conventional signaling pathway involving membrane-bound IL-6R, as it only interferes with trans-signaling and does not affect the traditional signaling pathway [47].

Macrophages in the immune system produce *TNF-α*, which plays a role in various physiological functions. *TNF-α* is located in the primary histocompatibility complex class III region of Chromosome 6. Depending on the situation and the specific pathways activated, TNF-α can exhibit both pro- and anti-inflammatory effects [48]. Studies have mainly concentrated on the G308A mutation in the etiology of IS concerning TNF-α gene polymorphisms. TNF-α mutations in the gene's promoter region may alter the transcriptional activity of the gene [49]. This genetic variation can increase the activity of the TNF-α gene, resulting in the excessive production of TNF-α within the body.

Increased concentrations of TNF-α in blood have significant implications. It disrupts the blood flow to the brain, leading to damage and inflammation. Microglia are the brain cells involved in this condition, and activated astrocytes release significant amounts of TNF-α. Excessive TNF-α is deemed harmful because it affects transmission and plasticity, contributing to the core symptoms observed in patients with IS. TNF-α plays an essential role in the brain; on one hand, when it binds to its receptors, it triggers a pathway called NF-κB activation. This activation can lead to neurotoxic and neuroprotective responses. G308A variation in the promoter region of TNF increased TNF production and promoted IS progression. Elevated TNF-α levels can affect transmission and plasticity, leading to cognitive impairment in IS patients. Furthermore, the interaction of TNF-α with its receptors can trigger NF-κB activation, which has complex and context-dependent effects on brain cells and influences neurotoxicity and neuroprotective responses. The diverse outcomes of TNF-α signaling in the brain depend on factors such as the stage of neuronal development, the type of brain cell involved, and the specific receptor subtypes engaged [50].

Table 1 illustrates the functions of all the genes related to the disorder.

Polygenic disorder

IS is significantly influenced by polygenic disorders that arise from the interaction of multiple genes. Various sequencing techniques, including Mendelian sequencing, genomewide association studies (GWAS), whole-exome sequencing (WES), and whole-genome sequencing (WGS), play a crucial role in studying IS. Mendelian sequencing is used to detect monogenic disorders that can result in recognizable clinical manifestations, including IS. Researchers are making rapid advancements in identifying polygenic variations associated with these conditions. One of the primary tools employed in this pursuit is GWAS [51]. Uncovering the connections between genetic variations and complex traits or disorders is invaluable. GWAS is essential for understanding the genetic underpinnings of IS in the context of polygenic diseases. A study found a correlation between hereditary imbalances detected through GWAS and unfavorable outcomes three months after a IS [52]. Although monogenic disorders contribute to only approximately 7% of IS cases, they can lead to recognizable clinical symptoms, including IS. GWAS can assist in identifying the genetic elements responsible for these disorders and their association with IS [53]. Thousands of genetic variations that affect human disease susceptibility and its characteristics have been revealed. Nonetheless, understanding how these genetic variations, particularly those in non-coding regions, influence the development of related diseases and traits continues to pose a substantial challenge [54].

A compelling discovery in IS genetics is the link between the 7q21 region near the histone deacetylase 9 (*HDAC9*) gene (polymorphism rs12524866) and the LAA subtype of IS. This finding marked a significant breakthrough as it was the first widely replicated genetic association with this particular IS subtype [55]. Subsequent studies and additional patient data from Europe, America, and Australia consistently confirmed this genetic relationship. Furthermore, ongoing GWAS investigations have uncovered additional genetic variations associated with LAA stroke. Notably, variations on chromosome 6p21.1 and genes *MMP12* (rs12122539) and *TSPAN2* (rs13107327) have been associated with this IS subtype [45]. Furthermore, a genetic variation located on chromosome 14q13.3 in proximity to *PTCSC3* has been documented to be associated with LAA stroke in the Chinese Han population [56]. Genetic variation near *ABCC1* (rs74475935) has also been linked to IS in European and African populations [57], as shown in Table 2. These findings collectively demonstrate the power of GWAS in unraveling the intricate genetic components that increase the risk of IS within the realm of polygenic disorders.

WES and WGS are increasingly employed in daily diagnostics and are more efficient and promising techniques. WES has been applied to investigate young IS patients with familial clustering of stroke, whereas WGS has been applied to analyze families where a monogenic cause of stroke seems likely [58]. According

Table 1. IS-associated genes related to disorder and their function

Ген Gene	Gene name	Chromosome number	Number of exons	Amino acid	Role	Disorder	Mutation	Source
NOTCH3	Notch receptor 3	19	2321	33	Receptor for membrane-bound ligands	CADASIL	*De novo* mutation	[19]
HTRA1	HtrA serine peptidase 1	10	480	9	Stimulate synovial cells to increase the production of MMP1 and MMP3	CARASIL	Homozygous mutation	[24]
COL3A1	Collagen type III alpha 1 chain	2	1466	51	Participates in the control of cortical development	EDS	Autosomal dominant mutations	[26]
TREX1	Three prime repair exonuclease 1	3	314	3	Inhibits the autonomous triggering of autoimmunity within cells	Retinal vasculopathy with cerebral leukodystrophy	«Truncating mutation	[31]
IL-1β	Interleukin-1β	2	7	269	Potent proinflammatory cytokine	Cytotoxic brain edema	Chronic deletion	[43]
IL-6	Interleukin-6	7	5	212	Potent inducer of the acute phase response	Blood–brain barrier dysfunction	Gain-of-function mutations	[45]
TNF-α	Tumor necrosis factor-α	6	4	233	Stimulate cell proliferation and induce cell differentiation	Neurotoxicity	*G-A* mutation	[48]

to a recent article, the introduction of massive parallel sequencing methods, such as WES and WGS, has led to the detection of an increasing number of gene-disease associations. Regularly reassessing data, updating gene panels, and incorporating recent detailed information on the phenotype can improve the diagnostic yield of WES and WGS tests in stroke patients [59].

Genetic disorder related to stroke

A genetic syndrome is a collection of distinct genetic disorders or medical conditions that exhibit shared characteristics due to abnormalities or mutations in one or more genes. Typically, these syndromes affect various organ systems, leading to physical, developmental, and intellectual difficulties. These genetic syndromes may either be inherited from parents or arise from spontaneous genetic mutations.

Familial moyamoya

Moyamoya disease is an uncommon genetic disorder that affects the blood vessels of the brain, particularly the internal carotid arteries and their branches. This disorder can result in symptoms such as transient ischemic attacks (mini-strokes), strokes, and seizures. Occasionally, delicate blood vessels that form as a response to narrowed arteries can develop protrusions (aneurysms) or bursts, leading to brain bleeding [60]. Moyamoya's disease can affect individuals across various age groups, and the types of ischemic events experienced may vary by age. This condition predominantly results in brain ischemic events in children, whereas it can give rise to both ischemic and hemorrhagic events in adults [61].

Ehlers–Danlos syndrome

EDS encompasses a spectrum of inherited connective tissue disorders that can potentially affect various organ systems, including blood vessels. Among the different subtypes of EDS, the vascular subtype is notably associated with an elevated risk of cerebrovascular complications such as stroke and intracranial aneurysms. These neurological aspects of EDS, including IS and cerebrovascular disease, have garnered increased attention in recent years [62]. Although the primary molecular defect in EDS does not typically target the nervous system directly, there has been a growing focus on

Table 2. IS

Gene	Chromosome	Polymorphism	*p*	Odds ratio (95% CI)	Association	Source
HDAC9	7q21	rs12524866	1.47E-08	1.11 (1.08–1.14)	Associated with LAA	[55]
MMP12	6p21.1	rs12122539	1.54E-08	1.09 (1.06–1.12)	Associated with LAA	[45]
TSPAN2	6p21.1	rs13107327	8.75E-09	1.10 (1.07–1.12)	Associated with LAA	[45]
ABCC1	16p13.11	rs74475935	3.01E-05	1.373 (1.182–1.594)	Associated with CG-type IS stroke	[56]
PTCSC3	14q13.3	rs2415317	1.37E-05	1.394 (1.199–1.620)	Associated with LAA	[57]

its neurological symptoms, encompassing conditions such as IS and cerebrovascular disease. EDS is also associated with neurological issues such as musculoskeletal pain, fatigue, headaches, muscle weakness, and paresthesias [62].

Methylmalonic acidemia

Methylmalonic acidemia is a genetic disorder that follows an autosomal recessive pattern and affects amino acid metabolism. This genetic disorder is marked by a deficiency in the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. It has been associated with an increased risk of IS, particularly affecting the bilateral globus pallidi [63]. Methylmalonic acidemia is a hereditary disorder transmitted within families and falls into the "inborn errors of metabolism." Typically, this condition is identified during the initial years of a person's life[1].

Fabry disease

Fabry disease is associated with an increased risk of IS, particularly in younger individuals. The disease is an X-linked lysosomal storage disorder caused by a mutation in the α-galactosidase A enzyme, leading to a deficiency of this enzyme. Progressive accumulation of globotriaosylceramide within the endothelium of blood vessels is thought to play a primary role in vasculopathy and the risk of IS in patients with Fabry disease. It accounts for approximately 1–5% of all stroke cases, with stroke being a primary manifestation of some hereditary disorders [64]. Males affected by the classic phenotype experience acroparesthesia, hypohidrosis, and corneal opacities as children, and in their third or fifth decade of life, they may experience stroke, cardiac hypertrophy, or renal failure. Certain female heterozygotes exhibited no symptoms, whereas others experienced symptoms comparable to those of males. Regardless of sex, individuals with Fabry disease may experience transient cerebral ischemia and stroke as part of the natural progression of the illness, even at a young age [65].

Vascular diseases related to stroke

Cerebrovascular diseases encompass a spectrum of conditions that affect blood flow to the brain, with notable associations with atrial fibrillation, hypertension, and diabetes. Both hypertension and IS are strongly associated with an increased risk for cognitive impairment. Hypertensive individuals face a 3.9 times higher risk of cerebral hemorrhage than non-hypertensive individuals, with a 2.8 times higher relative risk in the case of aneurysmal subarachnoid hemorrhage [66]. Chronic hypertension exerts detrimental effects on cerebral vessels and tissues, leading to atrophy, silent infarctions, micro hemorrhages, and white matter lesions [67]. This physiological mechanism reinforces a correlation between hypertension and cognitive impairment. Diabetes, as an independent risk factor for atherothrombotic IS, mainly affects women and contributes significantly to the risk of IS, second only to hypertension. It is a primary risk factor for cerebral small vessel disease, demonstrating a substantial association with symptomatic recurrence after a first lacunar-type cerebral infarction [68, 69]. Atrial fibrillation and atrial flutter, often linked to cardioembolic IS, are crucial and controllable risk factors. Cardioembolic infarction is recognized as the most severe subtype of IS [70]. In individuals over 70 years of age, approximately 5% show atrial fibrillation, and in the absence of organic heart disease, there is a 3- to 4-times higher risk of IS [71].

[1]Noonan syndrome.
URL: https://medlineplus.gov/genetics/condition/noonan-syndrome (accessed: 20.11.2023).

Impact of genetic evaluation

Genetic evaluation influences multiple facets of IS, including drug discovery, risk prediction, and clinical practice. Across diverse ancestries, distinct genetic regions associated with stroke have been identified, providing pivotal insights for future biological investigations of IS etiology and proposing potential therapeutic targets for intervention. The primary role in vasculopathy and risk of IS in patients with Fabry disease is believed to be due to the progressive accumulation of globotriaosylceramide within the endothelium of blood vessels. Fabry disease accounts for approximately 1–5% of all stroke cases, and in some hereditary disorders, stroke is a primary manifestation [72].

Polygenic scores derived from genetic variations associated with vascular risk factors accurately predict outcomes across individuals with diverse ancestries. These scores are valuable in forecasting genetic susceptibility to IS and demonstrate predictive efficacy independent of clinical risk variables [73]. Genetic studies have successfully established connections between monogenic disorders and stroke, prompting some experts to advocate the incorporation of IS gene panels in risk assessment and broader stroke research. Identifying new biomarkers for the genetic basis of IS and distinctive targets for gene therapy may advance gene therapy and enhance tailored IS care [74].

Advances in stroke genetics

Exploration of the genetic underpinnings of stroke has undergone significant advancements in recent years, particularly in the domains of hemoglobinopathies, thrombophilia, and disorders affecting small vessels and cardioembolic pathways. Researchers have identified genetic variations associated with increased susceptibility to cardioembolic IS, shedding light on the fundamental processes underlying clot formation in the heart and subsequent embolism in the brain [75]. There is growing emphasis on understanding the impact of genetic variables on cerebral microvascular function and small vessel integrity in minor vessel disorders. This focus has yielded crucial insights into the genetic susceptibility of minor artery disorders and the intricate pathophysiology governing them [76]. Notable strides have been made in genetic research related to hemoglobinopathies to elucidate the connection between abnormal hemoglobin variations and the risk of stroke. For individuals with hemoglobinopathies predisposed to stroke, the identification of specific genetic markers has facilitated risk assessment and formulation of tailored treatment plans [77]. Similarly, substantial progress has been made in understanding the genetic components contributing to thrombophilia, a condition characterized by abnormal blood clotting that can lead to stroke. This knowledge directly informs therapeutic strategies and preventive measures, enabling healthcare professionals to better manage individuals at risk of stroke due to thrombophilia [78].

Early detection of IS

Several promising approaches have emerged for IS detection and diagnosis. A groundbreaking, nonlinear, modified Laplacian pyramid technique was introduced to improve the early identification of IS in computerized tomography scans. This approach plays a crucial role in facilitating accurate and prompt IS detection, thereby expediting the initiation of appropriate treatment [79]. Furthermore, there has been a significant exploration of blood biomarkers for their potential utility in the early detection of IS. One notable example is the stroke chip study, which rigorously assessed a panel of biomarkers. It aimed to differentiate between genuine strokes and conditions that mimic strokes and distinguish among various stroke subtypes [80]. Additionally, the application of computer-aided detection techniques, such as segmentation and texture feature analysis, has shown promise for the early identification of IS. When applied to magnetic resonance imaging, these methods aid in recognizing stroke lesions and determining the necessity for thrombolysis [12]. Together, these innovative approaches and studies contribute coherently to ongoing efforts to enhance IS's early detection and management of IS.

Conclusions and future prospects

In conclusion, IS remains a significant cause of mortality and morbidity worldwide, and distinct genetic and environmental factors underlie its development. Several polygenic and monogenic disorders have been associated with an increased risk of stroke, and current research continues to identify new genetic markers and risk factors. Genetic evaluation has emerged as a critical tool in facilitating early detection and prevention strategies for IS. As the understanding of the genetic underpinnings of IS progresses, the focus on genetic syndromes associated with stroke and the exploration of innovative techniques continue to offer possibilities for early detection and targeted treatments. These advances hold significant promise for globally reducing IS's incidence and adverse impact. However, while improvements in diagnosis and treatment have shown promising results, preventative measures such as lifestyle modifications, early risk factor identification, and timely intervention remain crucial in reducing the global burden of IS. Therefore, continued research efforts to uncover the multifaceted interactions and mechanisms underlying IS are essential for developing effective preventive and therapeutic strategies.

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