Ischemic Stroke Genetics

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The etiology of ischemic stroke is multifactorial. Although receiving less emphasis, genetic causes make a significant contribution to ischemic stroke genesis, especially in early-onset stroke. Several stroke classification systems based on genetic information corresponding to various stroke phenotypes were proposed. Twin and family history studies, as well as candidate gene approach, are common methods to discover genetic causes of stroke, however, both have their own limitations. Genome-wide association studies and next generation sequencing are more efficient, promising and increasingly used for daily diagnostics. Some monogenic disorders, despite covering only about 7% of stroke etiology, may cause well-known clinical manifestations that include stroke. Polygenic disorders are more frequent, causing about 38% of all ischemic strokes, and their identification is a rapidly developing field of modern stroke genetics. Current advances in human genetics provide opportunity for personalized prevention of stroke and novel treatment possibilities. Genetic risk scores (GRS) and extended polygenic risk scores (PRS) estimate cumulative contribution of known genetic factors to a specific outcome of stroke. Combining those scores with clinical information and risk factor profiles might result in better primary stroke prevention. Some authors encourage the use of stroke gene panels for stroke risk evaluation and further stroke research. Moreover, new biomarkers for stroke genetic causes and novel targets for gene therapy are on the horizon.

stroke genetics | polygenic stroke risk | genetic stroke causes | monogenic stroke causes | single nucleotide polymorphism

1. Introduction

Stroke is a frequent medical emergency, the burden of which is rising annually [1]. In 2019, there were 12.2 million incident cases of stroke, making it the second-leading death cause in the world and third-leading cause of death and disability combined. Ischemic stroke was the most frequent among incident cases and constituted 62.4% of all strokes [2].

The etiology of ischemic stroke is multifactorial. Traditional modifiable risk factors, such as hypertension, smoking, diabetes and hyperlipidemia, are highlighted frequently [3][4], whereas the role of genetics is usually less accented, though no less substantial. As modern medicine tends to be individualized, personalized prevention and treatment strategies based on a patient's genetic information have gradually become routine practice [5][6]. It is well known that a genetic component plays an important role in early-onset strokes. Younger onset cases have a stronger genetic burden from common disease-associated single-nucleotide polymorphisms (SNP) [7], thus being the

extreme phenotypic expression of the genetic disorder. Less severe or older-onset stroke cases might remain genetically untested due to this bias. In such cases, stroke etiology might be attributed only to traditional modifiable risk factors without further risk stratification according to individual genetic profiles.

To create an appropriate strategy using genetically personalized approach, it is necessary to classify stroke according to genetic risk subtypes. The widely used TOAST classification is based on stroke phenotypical criteria, the main limitation of which is its post factum use; that is, the events are classified after their occurrence. While focusing on using genetic risk for stroke prevention, genetic stroke risk classification is needed. To address this need, several classification systems were proposed [8][9]. Differently from TOAST classification, it is based on genetic information corresponding to various stroke phenotypes, used in TOAST classification (i.e., large-vessel, small-vessel, cardioembolic etc.), which are further categorized into subphenotypes, e.g., extra- and intracranial.

To describe main genetic stroke risk factors, we modified the classification used by Ilinca et al. [9], omitting hemorrhagic stroke risk factors, as our review focuses primarily on the ischemic stroke topic (**Table 1**). Some factors increase stroke risk directly, while others are linked to stroke risk conditions: hypertension, hyperlipidemia, structural heart abnormalities and hypercoagulative states.

Table 1. Ischemic stroke subtypes classification by genetic risk, modified from Ilinca et al.

Large Artery Atherosclerosis	**Unspecified Hypercholesterolemia Hypertension**
Large artery structural abnormalities	Tortuosity/dolichoectasia Dissection Occlusion: Moyamoya-like/ fibromuscular dysplasia
Small-vessel disease	Isolated lacunar infarct Multiple lacunar infarcts White matter hyperintensities Hypertension
Cardioembolic	Arrhythmia: atrial fibrillation/flutter Morphological defect, such as patent foramen ovale Myopathy
Coagulopathy	Venous thrombosis Arterial thrombosis Hyperviscosity
Metabolic	Mitochondrial Defect of intermediary metabolism

The largest heredity of approximately 40% is seen in large artery stroke (LAS), followed by cardioembolic stroke (CES)—33%. So far only 16% of strokes caused by small-vessel disease (SVD) have been reported to have an etiological genetic component [10][11].

2. Current Insights

Genetic studies on strokes provide us with new significant information that could potentially contribute to personalized stroke care. Although these findings might seem hardly applicable in clinical practice at the first glance, major breakthrough is evident as genetic risk scores and gene therapies are developing. Numerous genetic risk scores have been already proposed for various conditions, including stroke [12]. Genetic risk scores (GRS) that estimate a cumulative contribution of genetic factors to a specific outcome can be extended to polygenic risk scores (PRS) by taking into account all known genetic markers possibly correlated to the outcome, covering even the loci of the small effects that do not reach genome-wide significance. In 2014, Malik et al. created a multilocus GRS for stroke. They found that combining genetic risk score data with Framingham risk score was significantly associated with ischemic stroke risk. However, its power for predicting a stroke was still limited and did not differ substantially from the power of traditional scores based on clinical risk factors [13]. Similar findings were reported by Swedish authors, who conducted three studies related to hypertension genetic risk factors and ischemic stroke risk. GRS for hypertension was significantly associated with the stroke risk, although it did not perform better while predicting the stroke compared to the clinical risk factor of hypertension itself [14]. Another study conducted in an Asian population showed that the PRS created by the authors predicted a significant stroke risk independently of environmental risk factors [15]. What is the reason for relatively minor predictive value of GRS? It is worth noting that, so far, the studies were concentrated on the risk of overall stroke, while the risk of specific stroke subtypes was not analysed. A study conducted in 2021 evaluated the risk of stroke in subjects with cardiometabolic disease compared to CHA_2DS_2-VASc score. GRS containing 32 SNPs was a strong, independent predictor of ischemic stroke. In patients with atrial fibrillation but lower CHA_2DS_2-VASc scores, the GRS identified patients with risk comparable to those with higher CHA_2DS_2-VASc scores [16]. As can be seen, a more specific population was chosen in this study. It is also interesting that although there are lots of genes linked to increased AF risk, not all of them are associated with the ischemic stroke risk. This might be due to the fact that those gene variants are too rare to detect their impact for stroke risk so far. Nevertheless, if we found in future that some of those genes are linked to AF, but not to CES, it could be a major gamechanger in the field of cardioembolic stroke prevention. Moreover, as novel stroke risk loci are being detected and more information is gained on their individual impact and their interconnections, the precision of GRS and PRS increases.

Despite the fact that genetic risk scores might be less useful when patient already has clinical risk factors, they could provide us with useful insights for primary stroke prevention. In young people with genetic risk factors, earlier and more intensive prevention and treatment strategies could be applied before the clinical risk factors become evident and cause deleterious consequences.

Ilinca et al. have created stroke gene panels for research and clinical practice. The clinical panel includes 61 genes related to stroke directly and 27 more genes related to disorders causing stroke that might be relevant to consider their evaluation in clinical practice. The authors encourage the use of their panels for stroke risk evaluation and further stroke research [9].

Another benefit of detecting stroke risk genes is that they could be potential targets for gene therapy in future. HDAC inhibitors have been postulated as a treatment for stroke [17]. One study in knock-out mice suggests a new strategy for acute stroke treatment by suppressing HDAC2 in peri-infarct zone. The authors claim that application of HDAC inhibitors from five to seven days after stroke enhances cell survival and neuroplasticity as well as reduces inflammation, which could potentially provide a wider therapeutic window for stroke recovery [18]. Systemic administration of an agonist NOTCH3 antibody was studied in transgenic mice and showed protective effects against impaired cerebral blood flow [19]. Other genetic stroke risk studies implicated messengerRNA (mi-RNA) as a potential drug target. Zou et al. detected five miRNAs to be potential biomarkers or therapeutic targets for CES, particularly miR-27a-3p, miR27b-3p, and miR-494-3p [20]. Transcriptome-wide colocalization analyses showed association of WMH-volume with expression of 39 genes, of which four encode known drug targets [21].

3. Conclusions

Current advances in human genetics combined with relatively modest costs allow clinicians to prevent stroke earlier and classify different stroke subtypes according to their etiology prior to the occurrence of clinical risk factors. This is especially important for young patients who have a genetic predisposition for stroke without clinical manifestations. More precise strategies of constructing GRS for IS and combining GRS with risk factor profiles and clinical information might eventually result in better risk prediction. Detection of novel therapeutic targets and development of corresponding monoclonal antibodies might be a revolution in personalized stroke care.

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