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Review

# Genetics of ischaemic stroke in young adults

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ABSTRACT

*Background:* Stroke may be a clinical expression of several inherited disorders in humans. Recognition of the underlined genetic disorders causing stroke is important for a correct diagnosis, for genetic counselling and, even if rarely, for a correct therapeutic management. Moreover, the genetics of complex diseases such the stroke, in which multiple genes interact with environmental risk factors to increase risk, has been revolutionized by the Genome-Wide Association Study (GWAS) approach.
*Scope of review:* Here we review the single-gene causes of ischemic stroke, bringing the reader from the candidate gene method toward the exciting new horizons of genetic technology.
*Major conclusions:* The aetiological diagnosis of ischemic stroke in young adults is more complex than in the elderly. The identification of a genetic cause is important to provide appropriate counseling and to start a correct therapy, when available. The advent of GWAS technology, such as for other complex pathological conditions, has contributed enormously to the understanding of many of these genetic bases. For success large, well phenotyped case cohorts are required, and international collaborations are essential.
*General significance:* This review focuses on the main causes of genetically-based ischemic stroke in young adults, often classified as indeterminate, investigating also the recent findings of the GWAS, in order to improve diagnostic and therapeutic management.


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## 1. Introduction

Despite substantial progress in prevention and treatment, stroke remains a very relevant condition representing the first cause of adult disability [1], the second cause of dementia [2,3] and the third cause of mortality in developed countries [4,5]. Therefore, increasing our understanding of the risks, causes and treatment of ischaemic stroke is of great importance.

Only in Italy, every year there are about 196,000 new cases of stroke: among these about a 20% dies in the following month and about 30% survives with disabling consequences [6,1,7]. The incidence of stroke rises exponentially with age, and is quite low in young adults [8]. However, ischemic stroke is a common cause of admission of young patients in stroke units [9,10]. In particular, the yearly incidence of stroke increased from 2.4 per 100,000 for people aged 20–24 years, to 4.5 per 100,000 for people aged 30–34 years, and to 32.9 per 100,000 for people aged 45–49 years. Stroke is slightly more frequent in women aged 20–30 years and in men older than 35 years [9].

Traditional risk factors for stroke such hypertension and diabetes and pathological conditions like large extracranial and intracranial atherosclerosis, small vessel disease and atrial fibrillation, which play an important role in older patients, are much less frequent in young adults; therefore, the main clinical challenge in management of a young adult with stroke is the identification of its cause, which often (35% to 42%) remains undetermined [11].

Stroke is believed to be a complex multifactorial and polygenic disease, arising from a wide number of gene-gene and gene-environment interactions. Genetic factors could act by predisposing to conventional risk factors, by modulating the effects of those risk factors on the target organs or, conversely, by a direct independent effect on stroke risk and on infarct evolution.

The proportion of strokes of undetermined or rare causes is much higher for young adults than for elders, and in many cases underlying causes are genetic-related. The clearest evidence that genetics may cause ischemic stroke comes from monogenic forms of the disease, although these account for only a relatively small percentage of overall ischaemic strokes. In most cases, it is likely that multiple genes are involved in stroke pathogenesis acting on a wide range of candidate pathways, such as the haemostatic and inflammatory system, homocysteine metabolism, rennin angiotensin aldosterone system, and so on [revised in 12,13]. Genetic investigation of individuals who have had a stroke is a promising approach for identification of novel biological mechanisms that underlie the development of cerebrovascular disease. Thanks to modern advances in the field of stroke genetics, many cases of cryptogenic stroke have been clarified; the discovery of new pathogenetic pathways might lead in the future to the development of preventive strategies and acute treatments [14,15]. The genetic component is more prevalent in large-vessel ischemic stroke than in small-vessel or cryptogenic ischemic stroke [16], and in patients younger than 70 years of age [17]. Multicentre studies concluded that siblings usually develop the same stroke subtype. These findings have been confirmed and extended by studies in which the heritability of ischemic stroke was calculated from genome-wide data, giving estimates of 40% for large-vessel ischemic stroke, 33% for cardioembolic stroke, 16% for small-vessel ischaemic stroke, and 38% for the combined endpoint of any ischemic stroke [18,19].

In this review, the most well-characterized monogenic disorders associated with stroke will be cover. Recent advances in both common polygenic conditions associated with stroke and GWA available reports will also be presented.

## 2. Monogenic diseases

Monogenic diseases are responsible of about 5% of stroke cases [20]. However, the percentage is likely to be underestimated because of the diagnostic complexity and the high phenotypic variability of these conditions. There are more than 50 monogenic diseases that can cause stroke [20] [see Table 1]. Recognition of individuals and families carrying mutations causing Mendelian or mitochondrial diseases with stroke as a phenotypic manifestation remains an important challenge for clinicians. Mendelian disorders can be recognised by their familial aggregation, relatively young age of onset, more severe clinical course, and higher recurrence rates, compared with sporadic diseases. Vice versa, mitochondrial-related strokes may be maternally inherited, frequently multi-systemic and life-threatening.

**Table 1**
Common mutations in monogenic diseases for details see the text.

| Monogenic diseases | Involved genes | Genes functions | References |
|---|---|---|---|
| MELAS | *tRNA (Leu) A3243G* | Mitochondrial tRNA | [21,22] |
| | *tRNA (Leu) T3271C* | Mitochondrial tRNA | [23] |
| | *tRNA (Lys) A8344G* | Mitochondrial tRNA | [24] |
| Familial hemiplegic migraine | *CACNA1A* | Encoding the alpha1A sub-unit of the voltage-gated calcium channels in neurons | [39] |
| CADASIL | *NOTCH3* | Unknown | [40] |
| CARASIL | *HTRA1* | Protease | [40] |
| FABRY | *α-GAL A* | Encoding α-galactosidase A enzyme | |
| Small vessel disease | *COL4A1* | Encoding the α1[IV]-chain of type IV collagen | [40] |
| HERNS | *TREX1* | Encoding three-prime repair exonuclease 1 | [40] |
| Stroke and vasculopathy with ADA2 mutations | *CECR1* | Encoding the ADA2 protein (important for endothelial and leukocyte development and differentiation) | [63] |
| Homocystinuria | *Multiple genes encoding different enzymes* | Deficiencies of this enzymes can cause very high plasma concentrations of homocysteine and homocystinuria | [12] |
| Sickle cell disease | *Haemoglobin beta chain gene* | Encoding for beta chain of normal haemoglobin (mutation of this gene causes polymerization or aggregation of abnormal hemoglobin -. HbS - within red blood cells) | [39] |
| Vascular Ehlers-Danlos syndrome | *COL3A1* | Encoding collagen type III | [12] |
| Marfan syndrome | *FBN1* | Encoding fibrillin 1 | [65] |
| Pseudoxanthoma elasticum | *ABCC6* | ATP-binding cassette C6 | [66] |