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Genetics of Adult Onset Stroke Subtypes: A Review of Current Knowldege and Future Prospects

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Abstract

The genetic contribution in stroke onset depends on the stroke subtypes. Understanding the genetic mechanism may influence the future direction in stroke management. There is complex interplay of genetic and environmental factors for any stroke event. Very small proportion of stroke is attributable to mendelian disorders. Stroke may also manifest as part of a syndromic disease in the form of single gene multisystem disorder. But there is no direct contribution of genetic polymorphism in conventional stroke subtypes. Specific genetic loci increase the suspectibility to development of hypertension, diabetes, dyslipideamia or influence the coagulation pathway or chance of atheroma formation and embolism. While chr9p21 locus or PITX2 and ZFHX3 are related to cardioemetabolic, HDAC9, TSPAN2 and 9p21 locus are responsible for the large vessel occlusion. On the otherhand, genome-wide significant locus on chromosome 1q22 the APOE locus are found to have significant association with intracerebral hemorrhage. But the direct pathophysiologic relationship of genetic plymorphirsm may be linked to onset of sub arachnoid hemorrhage. MMP-3, endothelial nitric oxide synthase (eNOS), tumor necrosis factor (TNF)-α, VCAM-1 etc have been found to be responsible for intracranial aneurysm formation, growth and risk of rupture. *[Journal of National Institute of Neurosciences Bangladesh, January 2021;7(1): 79-86]*

Keywords: : Extradural haematoma; traumatic head injury; road traffic accident; assault

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Introduction

Stroke is defined as a focal (or at times global) neurological impairment of sudden onset, lasting more than 24 h (or leading to death) and of presumed vascular origin[1]. An estimated 16.3 million people around the world suffer from stroke each year of which 11.2 million events occur in developing countries. Annually 5.8 million people die of stroke, the two third of which occurs in developing countries[2]. Another 64.5 million stroke patients survives an acute stroke event and live with varying degree of disability, which have made the disease the leading cause of morbidity[2]. The World Bank also reported that non-communicable diseases (NCDs) were responsible for almost two-thirds (63%) of Disability-adjusted life years (DALYs) in Bangladesh in 2016, while the contribution of communicable, maternal, neonatal and nutritional diseases accounted for 27% and injuries for 11% of DALYs[3]. According to the report, Ischemic heart disease (IHD), stroke and type 2 diabetes were the main contributors to the NCD burden. The Household Income and Expenditure Survey (HIES) done in the same year also reported that HTN, chronic heart disease and diabetes were among the most prevalent illnesses[3].

The geographic variations observed in stroke prevalence and mortality data can be attributed to difference of risk factor prevalence, genetic susceptibility and level of healthcare facilities. The INTERSTROKE case control study has provided the most reliable data on stroke risk factors in developing countries. Hypertension, current smoking, abdominal obesity, low physical activity and unhealthy cardiovascular diet accounted for the 80% of the risk of all type of stroke[4]. Meta-analysis of risk factors among the population in Bangladesh reported a prevalence of 14% for hypertension and 6% for diabetes[3]. Bangladesh is ranked among the top 10 countries with the highest number of people living with diabetes[3]. The lifetime risk of stroke has been estimated at one in five for middle-aged women and one in six for middle-aged men in the Framingham Heart Study[5].

Beside the known common risk factors a substantial proportion of stroke risk remains unexplained. Henceforth, a contribution of genetic factors are acknowledged by recent reports of common genetic variation associated with stroke risk through the genome-wide association studies (GWAS)[6]. Over the last decade we have observed a significant progress in unravelling the basis of single gene stroke disorders. But it has always been difficult to identify the underlying genes for common or multifactorial stroke, for which there is no obvious Mendelian pattern of inheritance is proven. In stroke genetics there are several focuses of clinical interest, for example, molecular genetic variations affecting risk of monogenic stroke syndromes and common stroke syndrome, epigenetic impact on protein expression during acute brain injury, the association of genetics with the stroke risk factor, genetic influence on stroke recovery, hereditary causes of familial aggregation, and pharmacogenetics[7]. In this review we have tried to accumulate the genetic basis of both single gene disorders causing rare type of stroke and the common conventional multifactorial stroke subtypes.

Genetic Risk of Stroke

People often wonder, is stroke heritable? The answer comes mostly from twin studies. The risk of stroke is 1.65 times higher in monozygotic twins[7]. Though insignificant in small vessel disease, genome-wide SNP data suggests similar heritability for cardioembolic and large vessel occlusions[8]. Several other factors like age, sex and stroke subtypes may also modify the relationship. Yonger patients and women are more likely to have a first degree relative suffering such event[9,10]. The contribution of hereditary factor as a risk of stroke remains complex. Influnce of conventional risk factors, variations in vulnerability of stroke among population along with heterogenicity of stroke subtypes have made the situation worse. Genetic risk of stroke may be explained by several proposed mechanisms. Firstly, single gene disorders, though rare, contributes to familial stroke syndromes like cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL). Secondly, there are some single gene disorder that casue multisystem disease like sickle cell anemia which sometimes may present with stroke in course of time. Thirdly, conventional stroke risk factors may also have underlying genetic basis. Moreover, genetic polymorphisms had been linked to risk of stroke[11].

Single Gene Disorder Presenting Primarily as Stroke

The most common example of this entity is CADASIL which is a small vessel vasculopathy affecting central nervous system and skin. The disease is linked mostly to missense mutation in the Notch3 gene on chromosome 19q12 which leads to alteration in cysteine residue expressed on extracellular receptors[12,13]. Although granular eosinophilic material on skin biopsy may be pathonomognic, patients may have negative result for common mutations[14,15]. There are several other rare single gene mutations implicated in stroke aetiology. For example, HTRA serine peptidase-1 gene for cerebral autosomal recessive arteriopathy with subcortical infarct and leukoencephalopathy (CARASIL), SLC2A10 gene for arterial tortiousity syndrome and cystatin C mutation causing familial cerebral amayloid angiopathy[16-19]. Monogenic disorders associated with stroke and their pattern of inheritance are summarized in table 1.

Single gene multisystem disorder associated with stroke

There are several single gene disorders where cerebrovascular events may occure as an important manifestation of disease. Around 25% of the patients with sickle cell anemia may experience ischemic stroke by the age of 45 years19. Polymerization of red blood cells in low oxygen tension may lead to recurrent event, some of which may be clinically silent[20,21]. The X-linked Fabry disease, the second most common lysosomal storage disorder is caused by a missense or nonsense mutation in GLA gene. This typically involves young patients affecting both small and large vessel in posterior circulation[22]. Mutation in mitochondrial gene may also lead to stroke like episodes. The syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke like episode (MELAS) caused mostly by an A3243G

Table 1: Monogenic disorder associated with stroke[12-19]

Disease	Responsible Gene/chromosomal location	Inheritance Mood
CADASIL	NOTCH3 19p13.2-p13.1	**autosomal dominant**
CARASIL	HTRA1 10q26.3	**autosomal recessive**
RVCL	TREX1 3p21.3	**autosomal dominant**
CRV and HERNS	3p21.1–21.3	**autosomal dominant**
Sickle cell disease	HBB, Haemoglobin S, and SC 11p15.5	**autosomal recessive**
Homocystinuria	CBS, MTHFR, and other 21q22.3, 1p36.3 and other	**autosomal recessive**
Fabry disease	alpha-galactosidase A gene X chromosome	**X-linked**
PXE	ABCC6 16p13.1	**autosomal recessive**
Dyslipidaemias	ABHD5 mutations and others	**autosomal dominant**
Moyamoya disease	3p24.2–26 and 17q25	**autosomal dominant**
Neurofibromatosis type I	NFI gene 17q11.2	**autosomal dominant**
Vascular EDS	COL3A1	**autosomal dominant**
Marfan syndrome	FBN1 15q21.1	**autosomal dominant**
MELAS	tRNA Leu Mitochondrial DNA	**maternal inheritance**
CAA	APP, CST3 21q21.3 and other	**autosomal dominant**
COL4A1 syndrome	COL4A1 13q34	**autosomal dominant**
Protein C, S	Protein S and C genes	**autosomal dominant**
Antithrombin III deficiency	Antithrombin III gene	**autosomal dominant**
Familial anticardiolipin syndrome	Unknown	**autosomal dominant**
Activated protein C resistance	Factor V Leiden mutation	**autosomal dominant**
Ehlers-Danlos syndrome type IV	collagen type III gene 2q31	**autosomal dominant**
Fibromuscular dysplasia	Unknown	**autosomal dominant**
von Hippel-Lindau syndrome	VHL 3p25.3	**autosomal dominant**

CADASIL= cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL= Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; RVCL= Retinal vasculopathy with cerebral leukodystrophy; CRV= Cerebroretinal vasculopathy; HERNS= Hereditary endotheliopathy, retinopathy, nephropathy, and stroke; PXE= Pseudoxanthoma elasticum; Vascular EDS= Vascular Ehlers-Danlos syndrome; MELAS= Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes; CAA= Cerebral amyloid angiopathy; COL4A1 = Collagen alpha-1(IV) chain

substitution within tRNA gene[23]. Stroke like episodes may be observed in MELAS but the pathogenesis is mainly metabolic rather than vasooclussive[23]. Genetic disorders of collegen tissue may also affect cerebral vasculature. Mutation in Type-III collagen involving COL3A1 or COL4A1 leads to vascular fragility causing

arterial dissection or aneurysm formation[24]. Marfan syndrome and ACTA2 associated vasculopathy also manifests with stroke in similar mechanism[25]. They also increase the risk of aretial dissection, moyamoya disease, aneurysm formation and also even in small vessel disease[26].

Genes Responsible for Common Conventional Multifactorial Stroke Subtypes

Genetic Contribution in Ischemic Stroke: Understanding the genetics behind the common pattern of stroke is more important in respect to clinical practice and practical point of view. Genetic predisposition to common stroke subtypes does not act directly. There are several mechanisms, for example; increasing the susceptibility to common risk factors like hypertension or diabetes, by influencing mechanism of stroke e.g. atheroma or atrial fibrillation, altering coagulation pathways and by influencing tolerance to ischemic injury[27]. The largest effort to identify the genetic mutation was MetaStroke that involved case control studies from 15 countries in Europe, North America and Australia. They found a gene variant that is related to blood group (rs505922), mostly associated with large vessel occlusion and cardio-embolic stroke[28]. The chr9p21 locus or the ABO locus on chromosome 9 was found to be responsible. Moreover, PITX2 and ZFHX3 were found to be related to cardioemetabolic and HDAC9, TSPAN2 and 9p21 locus to the large vessel occlusion[29]. Studies determining the genetic influence of small vessel occlusion had not been uniform in phenotypic definition of small artery occlusion. Genetic contribution in small vessel occlusion also varies across the ethnicity. The association of PRKCH gene with small vessel stroke was only found in the Japanese and Chinese population, but not in Europeans[30-33]. Genome-wide association studies (GWAS) also identified a locus on 6p25 (rs 12204590) that is associed with small vessel disease and manifests either as stroke event of white matter hyperintensity on imaging studies[34]. Forkhead transcription factor gene FOXF2 located nearby is also associed with extensive white matter disease in young if deleted[35]. Moreover, several gene locus and single neucleotide polymorphism (SNP) had been found associated with ischemic stroke irrespective of stroke subtypes. The chr12q24.12, SH2B3, ALDH2 HABP2 and AQP9 has been attributed[36-40]. Another risk loci was identified by CADISP consortium for carotid artery dissection in young stroke patients. They suggested that PHACTR1 expressed in certain tissue may play a majore role in vascular tube formation and actin polymerization[41].

Genetic Risk for Conventional Intracerebral Hemorrhage (ICH): The genetic pattern differ for subtypes of ICH as well. The recent discovery of a genome-wide significant locus on chromosome 1q22 by the International Stroke Genetics Consortium has put a new light to pathogenesis of common non-lobar intra cerebral hemorrhages. The same locus was also reported to be associated with white matter hyperintensity burden[42]. Moreover in a larger candidate gene study the APOE locus was found to have significant association with ICH. The APOE2 and APOE4 had genome wide significant association with lobar hemorrhage[43].

Genetic Background of Aneurysmal Subarachnoid Hemorrhage (SAH): People having the first-degree relative with aneurysm are at higher risk to develop aneurysm[44,45]. Different studies showed that MMP-3 (matrix metalloproteinases-3) plays a crucial role in aneurysm formation by activating several other pro-MMPs[46]. Ehlers-Danlos syndrome (EDS) type II and IV, Marfan syndrome, neurofibromatosis type I (NF-1), multiple endocrine neoplasia type I, pseudoxanthoma elasticum, hereditary hemorrhagic telangiectasia, all these heritable connective-tissue disorders support a genetic contribution to cerebral aneurysms (CA)[46-49]. TIMP-1 and TIMP-2 (tissue inhibitor of matrix metalloproteinase) play a critical role in preventing the CA progression[50]. Genes that are responsible for maintaining the extracellular matrix are associated with intracranial aneurysm (IA)[51]. Single-nucleotide polymorphisms (SNPs) in the endothelial nitric oxide synthase (eNOS) gene contribute to the IA formation and progression. The elevated level of IL-6 in the plasma contributes to the pathogenesis of IA. They release adhesion molecules and chemokine, which eventually cause endothelial dysfunction[52]. Studies showed the association of apoptosis and inflammatory response with IA development. Researchers found the presence of various cytokines expression and macrophage infiltration in human IAs. Upregulation of tumor necrosis factor (TNF)-α, C-X-C chemokine receptor type 4 (CXCR4), interleukin (IL)-1β, molecule (VCAM)-1, vascular cell adhesion, and chemokine ligand (CCL) 5 have been seen in human IA walls[53]. In IA formation, nuclear factor (NF)-κB contributes as a transcription factor[54]. The chromosomal location associated with aneurysm formation and progression have been summarized in Table 2.

Table 2: List of Chromosomal Location Associated With Aneurysm Formation And Progression

Chromosome region	Outcome
1p34.3–p36.13[55]	Confirmed linkage
7q11[56-58]	Confirmed linkage
19q13.3[59]	Confirmed linkage
Xp2259,[60]	Confirmed linkage
5q22-31[57,58,60]	Evidence of linkage
19q13[60]	Confirmed linkage
14q22[57]	Evidence of linkage
5q31[61,62]	Association with FGF1
8p21[63]	Linkage to LOXL2 gene
14q23[64]	Evidence of association
19q12-13[65]	Evidence of predisposing genes
14q23-31[66]	Confirmed linkage
11q24-25[66]	Confirmed linkage
4q32[67]	Confirmed linkage
8q12.1[67,68]	Confirmed linkage to SOX17 gene
9p21[68-71]	Confirmed linkage to CDKN2A, CDKN2B, and CDKN2BAS genes
7p21-15[72]	Confirmed linkage to IL-6 gene
7q35-36[72]	Confirmed linkage to eNOS gene
10q24.32[73]	Confirmed linkage to CNNM2 gene
13q13.1[73]	Confirmed linkage to STARD13-KL gene
18q11.2[73]	Confirmed linkage to RBBP8 gene

FGF1 = fibroblast growth factor 1; FBN2 = fibrillin 2; LOX = lysyl oxidase; LOXL = lysyl oxidase-like; IL-6 = interleukin 6; eNOS = endothelial nitric oxide synthase

Importance of Stroke Genetics

Stroke should be thought of as a clinical syndrome, not a single disease which can be caused by several different pathologies. There are pieces of evidence of genetic associations with various diseases that are associated with stroke (Table 1). Gene-environment interactions can play an important role in stroke pathogenesis[74]. In a study with 200 consecutively recruited CADASIL individuals showed the association of conventional cardiovascular risk factors, predominantly hypertension, and smoking with an earlier age of stroke onset, which gives significant insight in the importance of gene–environmental interactions as well as careful risk factor control in individuals with monogenic stroke disorders, for example, CADASIL[75]. A number of studies shown significant findings in identifying genes for multifactorial stroke. Future srudies with a large number of sample are required to detect the genetic risk factors of stroke. Genetic predisposition to stroke is supported by epidemiologic evidence. Stroke genetics will help to get a better insight into how some individuals with the same risk factor profiles remain stroke-free, whereas others develop stroke. These types of studies may help to find novel stroke mechanisms and suggest new treatment approaches. The majority of stroke is polygenic. Monogenic stroke is rare. In many rare monogenic diseases, exome sequencing has been successful[76]. To screen for multiple single-gene causes of stroke, exome sequencing may offer a cost-effective way in one assay. Detecting the responsible gene for monogenic stroke might be used to diagnose and intervene in some cases. The risk of drug-related adverse effects and drug efficacy is affected by genetic variations. An individual's genotype can be used for determining the optimal dose with maximum efficacy with minimal adverse effects[77]. Stroke genomics can help in understanding new mechanisms underlying drug action. This understanding will lead to the development of new therapeutic agents. Stroke genetics can provide insights into the educated prediction of risks. Educated prediction enables counseling of individual, and prenatal testing whenever requirement. The possibility and degree of the functional outcome as well as the responses to therapies after stroke can vary between patients due to underlying genetic variations.

Method of Identifying Genes Responsible for Stroke

To identify genes for stroke three main methods have been used like linkage analysis, the candidate gene approach, genome-wide association studies (GWAS). The linkage method is used to find the association of chromosomal markers with disease phenotype within families. Genes associated with high risk can be successfully detected by this method. This technique has been used to find many disease-causing genes, predominantly single-gene disorders. Linkage is less successful in more common polygenic diseases. The candidate gene method was used to look for genes predisposing to common stroke. In this method a candidate gene is selected, which is thought to be involved in stroke risk, followed by identification of genetic variants, usually single-nucleotide polymorphisms (SNPs) for that candidate gene. After that using a case-control approach frequency of the SNP is compared between controls and stroke patients. Novel genes cannot be identified by candidate-gene studies. Recently, GWAS is mostly used in the field of complex stroke genetics. This technique uses microarray technology to genotype more than one million SNPs, spanning the whole genome. The frequency of individual SNPs between controls and disease cases is compared by cohort or case-control

approach. Associations between novel chromosomal loci and disease can be identified by GWAS[76]. Application of next generataion sequencing (NGS) along with existing method is expected to facilitate the process of gene discovery in near future.

Conclusion

Researchers found common genetic variants associated with stroke, which helps us to get a better insight into the underlying pathophysiology. Identification and understanding of single-gene disorders associated with stroke have substantially broadened our knowledge, nevertheless we do not have a clear understanding of the genetic factors influencing polygenic and multifactorial stroke. Future studies should focus on identifying potential interactions among various genetic and environmental factors of polygenic stroke, which will lead to development of new drugs as part of precision medicine approach. As we know from various studies, different forms of stroke are affected by genetic factors in different ways. Therefore, studies of large sample size on individual stroke subtypes must be conducted get a better understanding about the genetic factors driving stroke outcome.

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