Genetics of ischemic stroke

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ABSTRACT

تعتبر السكتة الدماغية ثالث مسبب للوفاة وسبب رئيسي للإعاقة حول العالم. معظم حالات السكتة الدماغية الناتجة عن نقص التروية الدموية تُعزى إلى ارتفاع ضغط الدم ومسببات أخرى، ولكن في أكثر من 20% من الحالات يبقى السبب مجهولاً. أظهرت الأبحاث الحديثة بعض الجينات كمسبب للسكتة الدماغية الناتجة عن نقص التروية، مثل جينيّ الإنزيم، sHE، PDE4D، FLAP. كما إن الحالات المصاحبة مع زيادة في قابلية التجلط مثل: (Prothrombin G20210A mutation) و(factor V Leiden mutation) هي معروفة الآن كمسببات للسكتة الدماغية الناتجة عن نقص التروية بالشرايين، بالإضافة لكونها مسببة للجلطات الوريدية. في الوقت ذاته، توفر العلاج التعويضي بالإنزيمات لمرض فابري حديثاً، والفوائد المثبتة لنقل الدم المنتظم لبعض المرضى المصابين بفقر الدم المنجلي قد غير بشكل كبير النتيجة المتوقعة لهذه الأمراض الوراثية. لذلك فإن فهمنا لدور الجينات كمسبب للسكتة الدماغية يفتح آفاقاً جديدة للتحديد الدقيق لاحتمال إصابة الأفراد بالسكتة، وبالتالي اتخاذ الإجراءات اللازمة لمنع حدوث ذلك والتي قد تكون سبباً لإنقاذ حياتهم. المزيد من الأبحاث في مجال الجينات المسببة للسكتة الدماغية سيساعد بشكل واضح الجهود المحلية والعالمية للتقليل من حالات السكتة الدماغية.

Stroke is the third leading cause of death and a major cause of disability worldwide. Most cases of ischemic stroke are attributable to hypertension and other risk factors, but in over 20% of cases, the cause is unknown. Recent research has implicated some novel genes in the etiology of ischemic stroke, including genes for soluble epoxide hydrolase (sHE), 5-lipoxygenase activating protein (FLAP) and phosphodiesterase 4D (PDE4D). Moreover, thrombophilic states such as prothrombin G20210A mutation and factor V Leiden are now known to cause arterial stroke as well as venous thrombosis. Meanwhile, the recent availability of enzyme replacement therapy for Fabry disease and the proven benefits of regular blood transfusion in certain patients with sickle cell disease have greatly altered the outlook of these devastating inherited disorders. Thus, our understanding of the role of genetic factors in stroke raises the prospects for accurate assessment of future stroke risk among susceptible individuals, in whom early preventive measures may be life-saving. Further research into the genetics of stroke will clearly compliment ongoing national and international efforts to reduce the global burden of stroke.

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Stroke is the third leading cause of death worldwide and a major cause of disability in all countries.[1] In 2005, an estimated 5.7 million people died of stroke globally and 16 million suffered first-ever strokes.[2] The 1998 stroke incidence of 126/100,000 individuals in Saudi Arabia[3,4] was lower than the rate of 650/100,000 observed in Sweden in the same year,[5] however, the Saudi rate is expected to have risen over the past decade due to rapid ageing of the population and rising prevalence of stroke risk factors such as diabetes mellitus (DM) and obesity.[6,7] Worldwide, ischemic stroke (IS) constitutes 85-90% of all strokes, of which 60% is attributable to hypertension, DM, heart disease, elevated serum cholesterol, obesity, and cigarette smoking.[1] Of the remaining 40% of IS, approximately half is due to other acquired conditions and the other half is caused by unknown factors.[1]

The genetic basis of ischemic stroke. Inherited disorders may manifest with a stroke phenotype. However, disorders that exhibit classic Mendelian patterns of inheritance such as sickle cell disease (SCD) or homocysteinuria are believed to contribute to less than 1% of adult strokes in unselected populations.[8] Yet, many studies have shown the importance of genetic factors in the etiology of IS, including multifactorial stroke associated with hypertension, smoking, and so forth. Prospective population-based studies have shown a clear association between a family history of stroke

and an increased risk of future stroke.[9,10] For instance, in the Framingham Heart Study[10] a positive history of stroke or transient ischemic attack in the father or mother was associated with a 2.4 and 1.4-fold increase in risk of stroke in the offspring. However, a positive family history does not necessarily imply genetic linkage since family members are commonly exposed to the same environment, some of which may influence future stroke risk from early life. Indeed, there is a clear correlation between low birth weight and increased risks of hypertension, diabetes, and stroke in later life,[11] while lower social class and education in childhood may be related to higher levels of inflammatory markers in adulthood.[12] Further evidence of the role of genetic factors has come from twin studies showing a 2-4 fold increase in stroke risk in monozygotic twins compared to dizygotic twins.[13,14]

The past decade has witnessed intense research into the genetic basis of IS, and the molecular pathogenesis of inherited disorders associated with stroke. In this review, we present a summary of recent findings with emphasis on novel genes that influence common multifactorial stroke.

Genetic polymorphisms and multifactorial stroke. Several genes have been reported to influence the risk of IS, but in only a few cases were results confirmed in independent populations. These include:

ALOX5AP and leukotrienes. Leukotrienes (LT) are pro-inflammatory molecules expressed from macrophages, neutrophils, and mast cells.[15] The gene *ALOX5AP* encodes 5-lipooxygenase activating protein (FLAP), which cleaves arachidonic acid in the presence of the enzyme 5-lipoxygenase to initiate a cascade resulting in the production of several members of the LT family. *LTB4, LTC4*, and *LTD4* bind to receptors to induce neutrophil chemoattraction, adhesion of leukocytes to vascular endothelium and migration of smooth muscle cells.[16] These processes have been shown to promote the development of atherosclerosis in humans.[17] A common haplotype of ALOX5AP (HapA) is associated with a 1.7 fold increased risk of IS in Iceland,[18] a finding that was later replicated in Scotland,[19] and in the United Kingdom, and Germany.[20] In fact, the later study has found stronger associations between certain variants of LTC4 and LTB4 receptor genes with subtypes of IS.

Phosphodiesterase 4D. The enzyme phosphodiesterase 4D (PDE4D) degrades cyclic adenosine monophosphate (cAMP), a signal transduction molecule present in many tissues, including vascular endothelium and inflammatory cells.[21] It is coded by the PDE4D gene, also known as STRK1, located on chromosome 5q12. A study in Iceland reported a significant correlation between polymorphisms in this gene and increased incidence of IS in the Icelandic population.[22] This observation was later confirmed by subsequent studies in the United Kingdom,[23] United States,[24,25] and Sweden,[26] although not in Germany,[27] perhaps due to racial and genetic variation or differences in study design.

Soluble epoxide hydrolase. Soluble epoxide hydrolase catabolizes epoxyeicosatrienoic (EET) acids, a group of molecules derived from arachidonic acid and involved in vascular inflammation, vascular smooth muscle tone, control of blood pressure, and atherosclerosis.[28] A recent German study[29] confirmed the findings of an earlier United States study, which reported significant associations between specific haplotypes in the epoxide hydrolase (EPHX2) gene and increased risks of IS,[30] an effect possibly mediated through altered epoxide hydrolase activity on EETs.[31]

Atrial natriuretic peptide. A large prospective study reported an association between some allelic variants of the atrial natriuretic peptide (ANP) gene with a 1.6-2 fold increase in risk of stroke among male US physicians.[32] A subsequent Italian study reported an even stronger association among female and male Sardinians, in whom a recessive allele of ANP conferred a relative risk of 3.8 for IS, independent of other risk factors.[33] Atrial natriuretic peptide plays important roles in the regulation of electrolyte and water balance and also modulates cellular growth in cardiac and vascular tissues.[34,35]

Angiotensin converting enzyme. The angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II, a peptide involved in vascular hypertrophy, vasoconstriction, and atherosclerotic processes.[36] Individuals homozygous for the D allele of the ACE gene have a 56% increase in ACE activity compared with I allele homozygotes.[37] Not surprisingly, the ACE gene has been implicated as a susceptibility locus for IS. In one meta-analysis of 11 studies involving more than 14,000 Caucasians, the D/D allele of the ACE gene was found to be associated with an odds ratio of 1.21 for IS compared to D/I and I/I alleles.[38] A summary of genetic polymorphisms influencing the risk of IS is displayed in **Table 1**.

Hereditary multisystem disorders associated with stroke. Sickle cell disease. This disorder results from a point mutation in the globin β-chain gene in which the replacement of thymine by adenine leads to the substitution of valine for glutamic acid at position 6 of the hemoglobin β-chain molecule. The resulting hemoglobin SS undergoes polymerization at low oxygen tension, leading to red cell sickling and hemolysis. Stroke affects 11% of individuals with SCD <20 years of age, but it is less common among older adults.[39] Chronic anemia and hypoxemia in SCD leads to a marked increase in cerebral blood flow. When the cerebral circulation is compromised by events such as an acute chest syndrome, the cerebral vasculature fails

to undergo further dilatation, resulting in ischemia.[40] In line with this theory are the high prevalence of border-zone infarctions seen in patients with SCD and the 40% increased risk of stroke in those with intracranial mean flow velocities (MFV) of 200cm/s or more on transcranial Doppler ultrasound (TCD).[41] Regular TCD screening of the proximal middle cerebral artery is now recommended for all young patients with SCD. Those with abnormal MFVs should then receive monthly blood transfusion, which has been shown to reduce stroke risk by 92% in the Stroke Prevention in Sickle Cell Anemia (STOP) trial.[42]

Fabry disease. This is an X-linked recessive lysosomal storage disorder that is caused by a deficiency of α-galactosidase A, coded by the GAL A gene, leading to accumulation of globotriaosylceramide in vascular endothelium and other tissues.[43] Clinical characteristics include cutaneous, ocular, renal, and neurologic abnormalities, with strokes occurring in up to 24% of patients. In one German study, unrecognized Fabry disease was found in 4.9% of males and 2.4% of females presenting with cryptogenic stroke.[44] Diagnosis depends on measurement of enzyme levels in leukocytes or cultured skin fibroblasts, confirmed by DNA sequence analysis. The recent introduction of recombinant human α-Gal A (agalsidase beta) has altered the outlook for patients with Fabry disease, with treated patients showing significant improvements in renal function, cerebral hemodynamics and quality of life.[45]

Homocysteinuria and hyperhomocysteinemia. Homocysteine is a sulphur-containing amino acid derived from dietary methionine. It plays a vital role in cellular homeostasis, but elevated plasma levels may lead to thrombosis by its effects on the vascular wall structure and the blood coagulation system.[46] The metabolism of homocysteine is dependent on folic acid, pyridoxine, cyanocobalamin and the activities of the enzymes cystathione beta-synthase (CBS) and methylene tetrahydrofolate reductase (MTHFR).[47] Homozygous mutations of the CBS gene result in homocysteinuria, a pediatric syndrome characterized by a Marfanoid habitus, downward dislocation of optic lens, mental retardation, premature atherosclerosis, and early death.[48] In contrast, mild to moderate hyperhomocysteinemia in adults results from mutations in the MTHFR gene, located on chromosome 1p36. Among Caucasians, C677T mutations affect up to 44%, and A1298C mutations affect up to 13.8% of the population,[49,50] whereas in Saudi Arabia, this pattern is reversed as C677T and A1298C mutations account for 28% and 60% of MTHFR polymorphisms.[51] The more severe C677T homozygous state is prevalent in 2.1% of the native Saudi population.[52] Many studies have confirmed an association between hyperhomocysteinemia and IS,[53-55] as well as the MTHFR C677T phenotype[38] and ischemic stroke.

CADASIL. The syndrome of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is characterized by a small vessel vasculopathy within brain parenchyma that manifests with migraine, recurrent strokes, dementia, psychiatric disturbance, and seizures.[56] The disease results from

Table 1 - Studies implicating some novel genes in multifactorial ischemic stroke.

Study	Year	Location	Locus	Gene	Gene product	Remarks
Rubattu et al[33]	2004	Italy	1p	*ANP*	Atrial natriuretic peptide	A recessive allele confers a RR of 3.8 for IS
Rubattu et al[32]	1999	United States	1p	*ANP*	Atrial natriuretic peptide	Allele variants increase risk of stroke 1.5-fold
Gschwendtner et al[29]	2008	Germany	8p	*EPHX2*	Soluble epoxide hydrolase	3 SNPs associated with IS
Bevan et al[20]	2008	United Kingdom & Germany	13q	*ALOX5AP*	FLAP	RR 1.3 - 3.0 for IS & subtypes
				LTC4S	LTC4	RR 1.8 for IS, 2.2 for LAS
				LTB4R1/2	LTB4 receptors 1&2	RR 1.6 for IS, 2.3 for CES
Lohmussaar et al[27]	2005	Germany	13q	*ALOX5AP*	FLAP	One SNP associated with IS
			5q	*PDE4D*	Phosphodiesterase 4D	No association with IS
Helgadottir et al[18]	2004	Iceland	13q	*ALOX5AP*	FLAP	Haplotype A associated with IS & myocardial infarction
Gretarsdottir et al[22]	2003	Iceland	5q	*PDE4D*	Phosphodiesterase 4D	Certain SNPs associated with LAS & CES subtypes of IS
Woo et al[25]	2006	United States	5q	*PDE4D*	Phosphodiesterase 4D	Haplotypes associated with IS
Casas et al[38]	2004	Multi-national	17q	*ACE*	Angiotensin converting enzyme	D/D allele associated with OR of 1.2 for stroke

ALOX5AP - arachidonate 5-lipoxygenase activating protein gene, CES - cardioembolic stroke, FLAP - 5-lipoxygenase activating protein, IS - ischemic stroke, LAS - large artery stroke, OR - odds ratio, RR - relative risk, SNP - single nucleotide polymorphism, LTB4 - leukotriene B4, LTC4 - leukotriene C4

mutations in the Notch3 gene, which encodes the human Notch3 receptor, a large protein involved in cell signaling. Screening of 19 patients from 4 families from Kuwait, Sudan, and Saudi Arabia identified heterozygous and homozygous exon 3 Notch3 mutations in 3 families, while no mutation was detected in one family.[57] A tentative diagnosis of CADASIL can be made with a skin biopsy, which shows the presence of granular osmiophilic material and positive staining with monoclonal antibody against the extracellular domain of Notch3 receptor.[58] However, a definitive diagnosis can be made only with a DNA analysis of the Notch3 gene sequence.

HERNS and cerebroretinal vasculopathy. Hereditary endotheliopathy with retinopathy, nephropathy, and stroke was described in a Chinese American family over a decade ago.[59] Clinical features include retinal macular edema and telangiectasia, renal failure, and neurologic complications including migraine-like headaches and cerebral vasculopathy. A similar disorder named cerebroretinal vasculopathy was later described in several Dutch families, in whom subsequent genetic studies revealed linkage to chromosome 3p21.[60,61] Both conditions express autosomal dominant inheritance but their molecular pathogenesis remains to be determined.

Inherited disorders of coagulation and fibrinolysis. The procoagulant molecules prothrombin and factor V, and the natural anticoagulants protein C, protein S, and antithrombin III are plasma protein molecules that play important roles in limiting the size and extent of thrombi formed during normal hemostasis. These processes involve inhibition of factors XII, XI, IX and X by antithrombin III, degradation of factors V and VII by protein C acting in the presence of protein S, and the formation of the fibrinolytic enzyme plasmin through the actions of protein C and tissue plasminogen activator.[62] Thus, mutations involving the genes for these factors may result in altered protein activity, hypercoagulable states and vascular thrombosis.

Factor V Leiden and prothrombin G20210A mutation. Factor V Leiden (FVL) is a mutated factor V gene that causes an amino acid substitution in the factor V protein, resulting in its resistance to activated protein C, while prothrombin G20210A mutation results in increased activity of prothrombin.[62] Both conditions have been associated with increased risks of vascular thrombosis. In the Estrogen Replacement and Atherosclerosis (ERA) trial,[63] the risk of venous thromboembolism was significantly increased in women who were carriers of the FVL mutation and taking hormone therapy compared with non-FVL women taking placebo. Likewise, significant risks of venous thrombosis have been described in association with other thrombophilic states, including the prothrombin G20210A mutation.[64] It has been suggested that IS in these patients may be partly due to the presence of an unrecognized patent foramen ovale, allowing a paradoxical thrombus from the right side of the heart to reach the cerebral

Table 2 - Genetic syndromes associated with an increased susceptibility to ischemic stroke.

Disease	Inheritance	Locus	Genetic abnormality
Sickle cell disease	AR	11p	β-globin gene mutation causes an amino acid substitution in hemoglobin & sickling of RBCs
Homocysteinuria and hyperhomocysteinemia*	AR, AD	21q 1p	Mutation in cystathione β-synthase gene mutation in *MTHFR* gene
Fabry disease	X-linked	Xq	Mutation in *GLA*, the gene for α-galactosidase
CADASIL	AD	19p	Mutations in *Notch-3* gene which encodes Notch3 receptor, a protein involved in cell signaling
HERNS	AD	3p	-
Cerebroretinal vasculopathy	AD	3p	-
MELAS	AD	Mit-DNA	Mutations in tRNA gene of mitochondrial DNA
Protein C deficiency	AD	2q	Mutations in protein C gene
Protein S deficiency	AD	3p	Mutations in protein S gene
Factor V Leiden	AD	1q	Mutations in factor V gene leads to factor V resistance to activated protein C
AT-III deficiency	AD	1q	Mutations in Antithrombin III gene
PT-G20210A mutation	AD	11p-q	Guanine to adenine transition causes an amino acid substitution and increased prothrombotic activity

*Hyperhomocysteinemia may also result from environmental factors, AD - autosomal dominant, AR - autosomal recessive, AT-III - antithrombin 3, CADASIL - cerebral autosomal dominant arteriopathy with subcortical infarcts and leuko-encephalopathy, HERNS - hereditary endotheliopathy with retinopathy, nephropathy, and stroke, MELAS - mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Mit-DNA - mitochondrial DNA, MTHFR - 5,10-methylene tetrahydrofolate reductase, PT - prothrombin

circulation.[65] Yet, the role of inherited thrombophilias in the etiology of arterial stroke has been controversial, with some studies showing no, or marginal associations,[66-68] and other studies showing significant associations with stroke in the young,[69-71] and the middle-aged.[72] A meta-analysis of 120 studies investigating genetic susceptibility to ischemic stroke was conducted in 2003 in an effort to clarify these findings.[38] Polymorphisms involving 10 of the 32 genes studied were responsible for various thrombophilic states but only FVL and prothrombin G20210A mutation were unequivocally associated with ischemic stroke, with odds ratios of 1.33 and 1.44, respectively. Mutations involving 2 other genes (glycoprotein 1b-α and plasminogen activator inhibitor-1) showed significant associations with stroke but the dataset contained too few studies for firm conclusions. A summary of some inherited disorders predisposing to stroke is shown in **Table 2**.

Summary and conclusions. Recent advances in research have yielded much insight into genetic polymorphisms influencing ischemic stroke. This has helped clinicians understand the molecular pathogenesis of common multifactorial stroke as well as stroke associated with inherited disorders such as SCD and FVL. Since risk factor modification is the most effective means of stroke prevention, this knowledge may enhance prediction of disease risk and early institution of appropriate measures in susceptible individuals. Further research in this field will clearly compliment national and international efforts to reduce the global burden of stroke.

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References

1. Ezzati M, Vander Hoorn S, Lopez AD, Danaei G, Rodgers A, Mathers CD, et al. Comparative quantification of mortality and burden of disease attributable to selected risk factors. In: Lopez AD, Mathers CD, Ezzati M, Murray CJL, Jamison DT, editors. Global burden of disease and risk factors. New York (NY): Oxford University Press; 2006: p. 241-268.
2. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. ***Lancet Neurol*** 2007; 6: 182-187.
3. Alrajeh S, Larbi E, Bademosi O, Awada A, Yousef A, Al Freihi H, et al. Stroke register: Experience from the eastern province of Saudi Arabia. ***Cerebrovasc Dis*** 1998; 8: 86-89.
4. Alrajeh S, Awada A. Stroke in Saudi Arabia. ***Cerebrovasc Dis*** 2002; 13: 3-8.
5. Pessah-Rasmussen H, Engstrom G, Jerntorp I, Janzon L. Increasing stroke incidence and decreasing case fatality, 1989-1998. A study from the Stroke Register in Malmo, Sweden. ***Stroke*** 2003; 34: 913-918.
6. Al-Nuaim AR, al-Rubeaan K, al-Mazrou Y, al-Attas O, al-Daghari N, Khoja T. High prevalence of overweight and obesity in Saudi Arabia. ***Int J Obes Relat Metab Disord*** 1996; 20: 547-552.
7. Al-Shammari SA, Khoja TA, al-Maatouq MA, al-Nuaim LA. High prevalence of clinical obesity among Saudi females; a prospective, cross-sectional study in the Riyadh region. ***J Trop Med Hyg*** 1994; 97: 183-188.
8. Dichgans M. Monogenic causes of ischemic stroke. In: Markus HS, editor. Stroke Genetics. Oxford (UK): Blackwell Science; 2003: p. 127-163.
9. Jousilahti P, Rastenyte D, Tuomilehto J, Sarti C, Vartiainen E. Parental history of cardiovascular disease and risk of stroke: a prospective follow-up of 14371 middle-aged men and women in Finland. ***Stroke*** 1997; 28: 1361-1366.
10. Kiely DK, Wolf PA, Cupples LA, Beiser AS, Myers RH. Familial aggregation of stroke. The Framingham Study. ***Stroke*** 1993; 24: 1366-1371.
11. Barker DJ, Lackland DT. Prenatal influences on stroke mortality in England and Wales. ***Stroke*** 2003; 34: 1598-1602.
12. Pollitt RA, Kaufman JS, Rose KM, Diez-Roux AV, Zeng D, Heiss G. Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. ***Eur J Epidemiol*** 2007; 22: 55-66.
13. Brass LM, Isaacsohn JL, Merikangas KR, Robinette CD. A study of twins and stroke. ***Stroke*** 1992; 23: 221-223.
14. Bak S, Gaist D, Sindrup SH, Skytthe A, Christensen K. Genetic liability in stroke: a long-term follow-up study of Danish twins. ***Stroke*** 2002; 33: 769-774.
15. Henderson WR. The role of Leukotrienes in inflammation. ***Ann Intern Med*** 1994; 121: 684-697.
16. Goodarzi K, Goodarzi M, Tager AM, Luster AD, von Adrian UH. Leukotriene B4 and BLT1 control cytotoxic effector T cell recruitment to inflamed tissues. ***Nat Immunol*** 2003; 4: 965-973.
17. Spanbroek R, Grabner R, Lotzer K, Hildner K, Urbach A, Ruhling K, et al. Expanding expression of the 5-lipoxygenase pathway within the arterial wall during human atherogenesis. ***Proc Natl Acad Sci USA*** 2003; 100: 1238-1243.
18. Helgadottir A, Manolescu A, Thorleifsson G, Gretarsdottir S, Jonsdottir H, Thorsteinsdottir U, et al. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. ***Nat Genet*** 2004; 36: 233-239.
19. Helgadottir A, Gretarsdottir S, St Clair D, Manolescu A, Cheung J, Thorleifsson G, et al. Association between the gene encoding 5-lipoxygenase activating protein and stroke replicated in a Scottish population. ***Am J Hum Genet*** 2005; 76: 505-509.
20. Bevan S, Dichgans M, Wiechmann E, Gschwendtner A, Meitinger T, Markus HS. Genetic variation in members of the leukotriene biosynthesis pathway confers an increased risk of ischemic stroke. A replication study in two independent populations. ***Stroke*** 2008; 39: 1109-1114.
21. Dichgans M. Genetics of ischemic stroke. ***Lancet Neurol*** 2007; 6: 149-161.
22. Gretarsdottir S, Thorleifsson G, Reynisdottir ST, Manolescu A, Jonsdottir S, Jonsdottir T, et al. The gene encoding Phosphodiesterase 4D confers risk of ischemic stroke. ***Nat Genet*** 2003; 35: 131-138.
23. Bevan S, Porteous L, Sitzer M, Markus HS. Phosphodiesterase 4D gene, ischemic stroke, and asymptomatic carotid atherosclerosis. ***Stroke*** 2005; 36: 949-953.
24. Meschia JF, Brott TG, Brown RD Jr, Crook R, Worrall BB, Kissela B, et al. Phosphodiesterase 4D and 5-lipoxygenase activating protein in ischemic stroke. ***Ann Neurol*** 2005; 58: 351-361.
25. Woo D, Kaushal R, Kissela B, Sekar P, Wolujewicz M, Pal P, et al. Association of Phosphodiesterase 4D with ischemic stroke. A population-based case-control study. ***Stroke*** 2006; 37: 371-376.

26. Nilsson-Ardnor S, Wiklund PG, Lindgren P, Nilsson AK, Janunger T, Escher SA, et al. Linkage of ischemic stroke to the PDE4D region on 5q in a Swedish population. ***Stroke*** 2005; 36: 1666-1671.
27. Lõhmussaar E, Gschwendtner A, Mueller JC, Org T, Wichmann E, Hamann G, et al. ALOX5AP gene and the PDE4D gene in a central European population of stroke patients. ***Stroke*** 2005; 36: 731-736.
28. Wei Q, Doris PA, Pollizotto MV, Boerwinkle E, Jacobs DR Jr, Siscovick DS, et al. Sequence variation in the soluble epoxide hydrolase gene and subclinical coronary atherosclerosis: Interaction with cigarette smoking. ***Atherosclerosis*** 2007; 190: 26-34.
29. Gschwendtner A, Ripke S, Freilinger T, Lichtner P, Muller-Myshok B, Wichmann HE, et al. Genetic variation in soluble epoxide hydrolase (EPHX2) is associated with an increased risk of ischemic stroke in white Europeans. ***Stroke*** 2008; 39: 1593-1596.
30. Fornage M, Lee CR, Doris PA, Bray MS, Heiss G, Zeldin DC, et al. The soluble epoxide hydrolase gene harbors sequence variation associated with susceptibility to and protection from incident ischemic stroke. ***Hum Mol Genet*** 2005; 14: 2829-2837.
31. Chiamvimonvat N, Ho CM, Tsai HJ, Hammock BD. The soluble epoxide hydrolase as a pharmaceutical target for hypertension. ***J Cardiovasc Pharmacol*** 2007; 50: 225-237.
32. Rubattu S, Ridker P, Stampfer MJ, Volpe M, Hennekens CH, Lindpaintner K. The gene encoding atrial natriuretic peptide and the risk of human stroke. ***Circulation*** 1999; 100: 1722-1726.
33. Rubattu S, Stanzione R, Di Angelantonio E, Zanda B, Evangelista A, Tarasi D, et al. Atrial natriuretic peptide gene polymorphisms and risk of ischemic stroke in humans. ***Stroke*** 2004; 35: 814-818.
34. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. ***N Engl J Med*** 1998; 339: 321-328.
35. Itoh H, Pratt RE, Dzau VJ. Atrial natriuretic polypeptide inhibits hypertrophy of vascular smooth muscle cells. ***J Clin Invest*** 1990; 86: 1690-1697.
36. Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. ***Pharmacol Rev*** 2000; 52: 11-34.
37. Agerholm-Larsen B, Nordestgaard BG, Tybjaerg-Hansen A. ACE gene polymorphism in cardiovascular: meta-analysis of small and large studies in whites. ***Arterioscler Thromb Vasc Biol*** 2000; 20: 484-492.
38. Casas J, Hingorani AD, Bautista LE, Sharma P. Meta-analysis of genetic studies in ischemic stroke: thirty-two genes involving approximately 18,000 cases and 58,000 controls. ***Arch Neurol*** 2004; 61: 1652-1662.
39. Wang WC. The pathophysiology, prevention, and treatment of stroke in sickle cell disease. ***Curr Opin Hematol*** 2007; 14: 191-197.
40. Seidman C, Kirkham F, Pavlakis S. Pediatric stroke: current developments. ***Curr Opin Pediatr*** 2007; 19: 657-662.
41. Adams R, McKie V, Nichols F, Carl E, Zhang DL, McKie K, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. ***N Engl J Med*** 1992; 326: 605-610.
42. Adams RJ, McKie VC, Hsu L, Files B, Vischinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial ultrasonography. ***N Engl J Med*** 1998; 339: 5-11.
43. Desnick RJ, Ioannou YA, Eng CM. α-galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. 8th ed. New York (NY): McGraw-Hill; 2001. p. 3733-3774.
44. Rolfs A, Bottcher T, Zschiesche M, Morris P, Winchester B, Bauer P, et al. Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study. ***Lancet*** 2005; 366: 1794-1796.
45. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, et al. Fabry disease, an under-recognized multisystemic disorder: Expert recommendations for diagnosis, management, and enzyme replacement therapy. ***Ann Intern Med*** 2003; 138: 338-346.
46. Durand P, Prost M, Loreau N, Lussier-Cacan S, Blache D. Impaired homocysteine metabolism and atherothrombotic disease. ***Lab Invest*** 2001; 81: 645-672.
47. Selhub J. Homocysteine metabolism. ***Ann Rev Nutrition*** 1999; 19: 217-246.
48. Ropper AH, Brown RH. The inherited metabolic diseases of the nervous system. In: Ropper AH, Brown RH, Brown RH, editors, Adams and Victors' Principles of Neurology. 8th ed. New York (NY): McGraw-Hill; 2005. p. 797-849.
49. Botto L, Yang Q. 5, 10-methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. ***Am J Epidemiol*** 2000; 151: 862-877.
50. Rothenbacher D, Fischer HG, Hoffmeister A, Hoffmann MM, März W, Bode G, et al. Homocysteine and methylene-tetrahydrofolate reductase genotype: association with risk of coronary heart disease and relation to inflammatory, hemostatic and lipid parameters. ***Atherosclerosis*** 2002; 162: 193-200.
51. Abu-Amero KK, Wyngaard CA, Dzimiri N. Prevalence and role of methylenetetrahydrofolate reductase 677 C→T and 1298 A → C polymorphisms in coronary artery disease in Arabs. ***Arch Pathol Lab Med*** 2003; 127: 1349-1352.
52. Saour J, Mammo L. Prevalence of FVL, Prothrombin G20210A and MTHFR C667T in Saudi Arabia: A preliminary report for the Saudi Thrombosis and Familial Thrombophilia (S-TAFT) Registry. ***J Thromb Haemostasis*** 2005; 3: 1863.
53. Perry IJ, Refsum H, Morris RW, Ebrahim SB, Ueland PM, Shaper AG. Prospective study of total homocysteine concentration and risk of stroke in middle-aged British men. ***Lancet*** 1995; 346: 1395-1398.
54. Yoo JH, Chung CS, Kang SS. Relation of plasma homocysteine to cerebral infarction and cerebral atherosclerosis. ***Stroke*** 1998; 29: 2478-2483.
55. Alkali NH, Watt H, Bwala SA, Gadzama A. Association of plasma homocysteine and ischemic stroke in a Nigerian population. ***Pak J Med Sci*** 2006; 22: 405-408.
56. LaPoint SF, Patel U, Rubio A. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). ***Adv Anat Pathol*** 2000; 7: 307-321.
57. Bohlega S, Al-Shubili A, Abu-Amero KK, Edris A, Khairallah T, Kambouns M. CADASIL in Arabs. ***Neurosciences*** 2003; 8: 41.
58. Rumbaugh JA, LaDuca JR, Shan Y, Miller CA. CADSIL: the dermatologic diagnosis of a neurologic disease. Cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy. ***J Am Acad Dermatol*** 2000; 43: 1128-1130.
59. Jen J, Cohen AH, Yue Q, Stout JT, Vinters HV, Nelson S, et al. Hereditary endotheliopathy with retinopathy, nephropathy and stroke (HERNS). ***Neurology*** 1997; 49: 1322-1330.
60. Terwindt GM, Haan J, Ophoff RA, Groenen SM, Storimans CW, Lanser JB, et al. Clinical and genetic analysis of a large Dutch family with autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon. ***Brain*** 1998; 121: 303-316.

61. Ophoff RA, DeYoung J, Service SK, Joose M, Caffo NA, Sandkuijl LA, et al. Hereditary vascular retinopathy, cerebroretinal vasculopathy, and hereditary endotheliopathy with retinopathy, nephropathy, and stroke map to a single locus on chromosome 3p21.1-p21.3. ***Am J Hum Genet*** 2001; 69: 447-453.
62. Nestoridi E, Buonanno FS, Jones RM, Krishnamoorthy K, Grant PE, Van Cott EM, et al. Arterial ischemic stroke in childhood: the role of plasma-phase risk factors. ***Curr Opin Neurol*** 2002; 15: 139-144.
63. Herrington DM, Vittinghoff E, Howard TD, Major DA, Owen J, Reboussin DM, et al. Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease. ***Arterioscler Thromb Vasc Biol*** 2002; 22: 1012-1017.
64. Bouaziz-Borgi L, Almawi WY, Mtiraoui N, Nsiri B, Keleshian SH, Kreidy R, et al. Distinct association of factor V-Leiden and prothrombin G20210A mutations with deep venous thrombosis in Tunisia and Lebanon. ***Am J Hematol*** 2006; 81: 641-643.
65. Bushnell CD, Hurn P, Colton C, Miller VM, del Zoppo G, Elkind MSV, et al. Advancing the study of stroke in women. Summary and recommendations for future research from an NINDS-sponsored multidisciplinary working group. ***Stroke*** 2006; 37: 2387-2399.
66. Berge E, Haug KBS, Sandset C, Haugbro KK, Turkovic M, Sandset PM. The factor V Leiden, prothrombin gene 20210GA, methylenetetrahydrofolate reductase 677CT and platelet glycoprotein IIIa 1565TC mutations in patients with acute ischemic stroke and atrial fibrillation. ***Stroke*** 2007; 38: 1069-1079.
67. Hankley GJ, Eikelboom JW, van Bockxmeer FM, Lofthouse E, Staples N, Baker RI. Inherited thrombophilia in ischemic stroke and its pathologic subtypes. ***Stroke*** 2001; 32: 1793-1799.
68. Ridker PM, Hennekens CH, Miletich JP. G20210A mutation in prothrombin gene and risk of myocardial infarction, stroke, and venous thrombosis in a large cohort of US men. ***Circulation*** 1999; 99: 999-1004.
69. Margaglione M, D'Andrea G, Giuliani N, Brancaccio V, De LD, Grandone E, et al. Inherited Prothrombotic conditions and premature ischemic stroke: sex difference in the association with factor V Leiden. ***Arterioscler Thromb Vasc Biol*** 1999; 19: 1751-1756.
70. Pezzini A, Del Zotto E, Magoni M, Costa A, Archetti S, Grassi M, et al. Inherited thrombophilic disorders in young adults with ischemic stroke and patent foramen ovale. ***Stroke*** 2003; 34: 28-33.
71. Nabavi DG, Junker R, Wolff E, Ludemann P, Doherty C, Evers S, et al. Prevalence of factor V Leiden mutation in young adults with cerebral ischaemia: a case-control study on 225 patients. ***J Neurol*** 1998; 245: 653-658.
72. Lalouschek W, Schillinger M, Hsieh K, Endler G, Tentschert S, Lang W, et al. Matched case-control study on factor V Leiden and the prothrombin G20210A mutation in patients with ischemic stroke/transient ischemic attack up to the age of 60 years. ***Stroke*** 2005; 36: 1405-1409.

Related topics

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JAN, MM. Pediatric stroke: Genetic and metabolic causes. ***Neurosciences*** 2004; 9: 64-64.

Bohlega S, Al-Shubili A, Abu-Amero K, Edris A, Khairallah T, Kambouris M. CADASIL in Arabs. ***Neurosciences*** 2003; 8: 41-41.