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Review article

GENETIC ASPECTS OF ISCHEMIC STROKE

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Summary: Stroke is one of the most common causes of death and long term disability throughout the world. It is not only induced by classic vascular risk factors like hypertension, cigarette smoking and diabetes mellitus, but also by genetic factors. The genetic etiology of ischemic stroke is polygenic. The candidate »stroke risk« genes may be conveniently divided into five groups, affecting (i) lipid metabolism, (ii) the renin-angiotensin system, (iii) haemostasis, (iv) nitric oxide production, and (v) homocysteine metabolism. Since stroke is a complex disease comprising a heterogeneous group of disorders with multiple risk factors, research into genetics of stroke presents some unique challenges. Numerous studies have investigated the role of genetics in the pathogenesis of stroke, with varied and often contradictory results. Additional knowledge of the role of genes in ischemic stroke may improve our understanding of the cause of stroke, provide new insights into prevention and the factors that influence the outcome of stroke, and new therapeutic targets when preventive strategies have failed.

Key words: ischemic stroke, genetics, candidate genes

Introduction

As one of the leading causes of death within both the developed and the developing world, stroke is a worldwide problem. It primarily affects elderly people, but about 20% of strokes occur before the age of 65. Stroke describes a syndrome of different pathophysiological processes all resulting in the common end point of focal cerebral ischemia. Eighty five per cent have ischemic aetiology and 15% hemorrhagic (intracerebral and subarachnoid). Different pathophysiological processes are responsible for ischemic stroke, including cardioembolism, large vessel atherosclerosis with thromboembolism, and small vessel disease. Pathophysiological mechanisms and underlying genetic influences may differ for the different subtypes.

Besides well-documented conventional risk factors like hypertension, cigarette smoking and diabetes mellitus, genetic factors influence the risk of stroke. Twin and family-based studies, together with observations in animal models, have provided evidence that genetic factors are very important in the pathogenesis of stroke. The genetic etiology of ischemic stroke is polygenic and reflects the influence of many different loci modulating different pathophysiological processes. Genetic factors may act either by predisposing to conventional risk factors (hyperlipidemia, diabetes, hypertension), by modulating the effects of such conventional risk factors on the end organs, or by direct independent effect on stroke risk.

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Genetic factors in stroke risk

Human single-gene disorders associated with stroke

A large number of single-gene disorders can cause stroke by several pathophysiological mechanisms. These include cardioembolism, large artery disease, hematological disorders, small vessel disease, mitochondrial disorders, ion channel disorders, and connective tissue disorders leading to arterial dissection. One of the best examples is the *NOTCH3* gene, mutations of which cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a condition that leads to lacunar infarcts and vascular dementia.

Mutations of the *APP, CST3,* and *BRI* genes can cause autosomal dominant amyloid angiopathies, which lead to cerebral hemorrhage, vascular dementia, or both. *KRIT1* has been identified as one of the genes causing cavernous angiomas. Identification of these genes by reverse genetics has provided new and fascinating insights into the pathophysiology of stroke. This work is also the basis for clinically useful molecular diagnostic tests. Despite their low prevalence, monogenic conditions should always be considered in a young patient who presents with stroke or in a patient of any age with no evident vascular risk factor, especially when there is a family history. Indeed, the risk of stroke in persons carrying the mutated gene and in their relatives is very high. For example, in the case of an autosomal dominant disorder with complete penetrance, all persons who carry the mutated gene will have a stroke, as will half of their first-degree relatives.

Evidence for the genetic background of stroke

Both epidemiological and animal-based studies provide strong evidence that genetic factors are important in the pathogenesis of stroke. Epidemiological studies have used twin, affected sibling pair and family-based approaches. Twin studies provide the most robust evidence for genetic influences on stroke. The principle is the comparison of concordance rates between monozygotic and dizygotic twins for a disorder. It is assumed that, apart from genetic factors, monozygotic and dizygotic twins will be similar in other respects, such as environmental exposures. From the degree of concordance it is then possible to determine the heritability of a disorder, defined as the proportion of the phenotype that can be attributed to genetic factors. Twin and sibling studies have also shown that the intermediate phenotypes for stroke are under strong genetic control. Family-based studies have examined the relationship between a family history of stroke amongst first-degree relatives and risk of stroke in proband. However, most studies suggest that a family history of stroke is an independent risk factor for stroke, and this is consistent with a genetic component operating outside the usual risk factors. Recent observations in animal models have provided strong evidence for the existence of stroke susceptibility genes. A well-established experimental tool in the study of hypertension has been the spontaneously hypertensive rat (SHR).

Identifying genetic factors in ischemic stroke

Quantitative trait locus mapping in stroke-prone animals and candidate gene studies in man are the most frequently used methods in the identification of genetic factors in ischemic stroke. In polygenic stroke, the situation is difficult because of numerous factors: (i) late onset: the late onset of stroke makes genetic comparisons between living relatives difficult; (ii) phenotypic heterogeneity: the variety of stroke subtypes or phenotypes is likely to reflect different aetiologies; (iii) genetic heterogeneity: mutations in any one of several genes might result in an identical phenotype; (iv) phenocopy: some individuals who do not inherit a predisposing allele will still manifest stroke because of random or environmental causes; (v) variable penetrance: some individuals who inherit a predisposing allele may not manifest the disease; causes of variable penetrance include gene dose, gene–environment interaction and epistatic phenomena; (vi) confounders: the presence of coexistent risk factors, such as hypertension and diabetes, may make the effects of a single gene difficult to assess in affected individuals.

Human studies: the candidate gene approach

Candidate gene studies in stroke can be considered as belonging to two broad categories: (i) those investigating the role of genes which may influence stroke risk, and (ii) those investigating genes which determine infarct size after vessel occlusion by influencing vascular reactivity and collateral supply, and neuronal responses to injury. The candidate »stroke risk« genes may be conveniently divided in a few groups, affecting (i) haemostasis (genetic variants in components of the coagulation cascade: factor V, VII, XIII, prothrombin, fibrinogen; PAI-1, platelet glycoprotein receptor polymorphism), (ii) nitric oxide production (polymorphisms of genes encoding both the neuronal and the inducible form of nitric oxide synthase) (iii) lipid metabolism (polymorphic variants of genes encoding the apolipoproteins, lipoprotein receptors and the key enzyme of plasma lipoprotein metabolism), and (iv) homocysteine metabolism (genetic polymorphism of MTHFR, cystatione beta-synthase), (v) the renin-angiotensin system (ACE gene insertion/deletion polymorphism),. From the literature data a lot of association studies in ischemic stroke: hemostatic system, endothelial nitric oxide, lipid metabolism, homocysteine, and renin angiotensin pathway, are presented in *Table I* (1–125).

A considerable body of evidence suggests that circulating hemostatic factors are risk factors for stroke. In the past, studies have proposed excess coagulation factors, increased levels of fibrinolytic inhibitors, or both. Circulating levels are subject to considerable biological influence, and the acute-phase response that accompanies an acute stroke event may hinder the interpretation of levels in a case-control study. Prospective studies are not subject to the confounding influence of acute phase reaction, but large numbers would be required

Table I Association studies in ischemic stroke

Gene	Reference	Polymorphism	Methodology	Phenotype	Result
Factor V	Catto et al. (1995, 1996a)	Q506 Leiden	Case-control: 348 cases, 247 controls	Ischemic stroke/stroke mortality	Negative
	Forsyth and Dolan (1995)	Q506 Leiden	Case-control: 45 patients, population controls	Ischemic stroke <45 years	Negative
	Kontula et al. (1995)	Q506 Leiden	Case-control: 236 cases, 137 controls	Ischemic stroke	Negative
	Lalouschek et al. (1995)	Q506 Leiden	Cross-sectional: 58 patients	TIA or minor ischemic stroke	Negative
	Ridker et al. (1995)	Q506 Leiden	Nested case-control: 209 cases, 209 controls	Ischemic stroke/PICH	Negative
	Albucher et al. (1996)	Q506 Leiiden	Case-control: 30 cases, 75 controls	Ischemic stroke	Positive
	Chimowitz et al. (1996)	Q506 Leiden	Case-control: 53 cases, 397 controls	Ischemic stroke 18–50 years	Positive
	Fisher et al. (1996)	Q506 Leiden	Case-control: 63 cases, 31 controls	Ischemic stroke	Negative
	Press et al. (1996)	Q506 Leiden	Case-control: 116 cases, 54/161/287 controls	Ischemic stroke in elderly/elderly controls with and without risk factors/young controls	
	van der Bom et al. (1996)	Q506 Leiden	Case-control: 112 cases, 222 controls	Ischemic stroke	
	Markus et al. (1996)	Q506 Leiden	Case-control: 180 cases, 80 controls	Ischemic stroke	
	Martinelli et al. (1997)	Q506 Leiden	Case-control: 155 cases, 155 controls	Ischemic stroke	Negative
	Sanchez et al. (1997)	Q506 Leiden	Case-control: 66 cases, 66 controls	Ischemic stroke	Negative
	Halbmayer et al. (1997)	Q506 Leiden	Case-control: 229 cases, 71 controls	Ischemic stroke	Negative
	De Lucia et al. (1997)	Q506 Leiden	Case-control: 14 cases, 75 controls	Young ischemic strokes from 3 families	Negative
	Longstreth et al. (1998)	Q506 Leiden	Case-control 106 cases, 391 controls	Ischemic stroke young women aged 18–44 years	Negative
	Lalouschek et al. (1999)	Q506 Leiden	Case-control: 81 cases, 81 controls	TIA or minor ischemic stroke	Positive trend
Prothrombin	Poort et al. (1996)	G20210A	Case-control: 104 cases, 104 controls	Ischemic stroke	
	Martinelli et al. (1997)	G20210A	Case-control: 155 cases, 155 controls	Ischemic stroke	
	Longstreth et al. (1998)	G20210A	Case-control: 106 cases, 391 controls	Ischemic stroke young women aged 18–44 years	Negative
	De Stefano et al. (1998)	G20210A	Case-control: 72 cases, 198 controls	Ischemic stroke <50 years	Positive
	Halbmayer et al. (1998)	G20210A	Case-control: 20 cases, 20 controls	Ischemic stroke young individuals	Negative
	Ridker et al. (1999)	G20210A	Nested case-control: 259 cases, 1744 controls	Ischemic stroke/PICH	Negative
Factor VII	Nishiuma et al. (1997)	R353Q	Case-control: 137 cases, 83/97 controls	Symptomatic stroke or MRI silent lacuneae in hypertensives. Hypertensive or normotensive controls	Negative
	Heywood et al. (1997)	R353Q	Case-control: 286 cases, 198 controls	Ischemic stroke/OCSP subtype/stroke mortality	Negative
	Corral et al. (1998)	R353Q/323A2	Case-control: 104 cases, 104 controls	Ischemic stroke	Negative
Fibrinogen	Kessler et al. (1997)	G455A	Case-control: 227 cases, 225 controls	Ischemic stroke/TOAST subtype	
	Carter et al. (1997)	β448(1/2)	Case-control: 305 cases, 197 controls	Ischemic stroke/OCSP subtype	Positive
	Nishiuma et al. (1998)	G455A	Case-control: 85 cases, 85/84 controls	Hypertensive strokes. Hypertensive/ normotensive controls	Positive
	Schmidt et al. (1998a)	β148(C/T)	Cross-sectional: 399 cases	Carotid atherosclerosis	Positive
PAI 1	Catto et al. (1997)	4G/5G	Case-control: 421 cases, 172 controls	Ischemic stroke/OCSP subtype and mortality	Negative
Factor XIII	Catto et al. (1998)	Val34Leu	Case-control: 529 cases, 437 controls	Ischemic stroke/OCSP subtype	Negative
GpIIb/IIIa	Ridker et al. (1997)	P1A2	Nested case-control: 209 cases, 209 controls	Ischemic stroke/PICH	Negative
	Carlsson et al. (1997)	HPA1/HPA3	Case-control: 218 cases, 165/321 controls	Ischemic stroke	Negative
	Carter et al. (1998)	P1A2	Case-control: 505 cases, 402 controls	Ischemic stroke/OCSP subtype and mortality	Positve
	Wagner et al. (1998)	P1A2	Case-control: 63 cases, 122 controls	Ischemic stroke young women aged 15–44 years	Negative
GpIb/IX	Gonzalez-Conejero et al. (1998)	HPA2/VNTR	Case-control: 104 cases, 104 controls	Ischemic stroke	Positive
GpIa/Iia	Carlsson et al. (1997)	C807T	Case-control: 227 cases, 170 controls	Ischemic stroke	Positive
	Carlsson et al. (1999)	HPA5	Case-control: 218 cases, 165/321 controls	Ischemic stroke	Negative
eNOS	Yahashi et al. (1998)	ecNOS 4a/b	Case-control: 127 cases, 91 controls	Atherothrombotic/lacunar/silent stroke	Negative
	Markus et al. (1998)	Glu298Asp	Case-control: 361 cases, 236 controls	Ischemic stroke/TOAST subtype	Negative
	Macleod et al. (1999)	Glu298Asp	Case-control: 265 cases, 293 controls	Ischemic stroke	Negative
MTHFR	Markus et al. (1997)	C677T	Case-control: 345 cases, 161 controls	Ischemic stroke/TOAST subtype	Negative
	Nakata et al. (1998)	C677T	Case-control: 48 cases, 105 controls	Ischemic stroke	Negative
	De Stefano et al. (1998)	C677T	Case-control: 72 cases, 198 controls	Ischemic stroke <50 years	Negative
	Reuner et al. (1998)	C677T	Case-control: 91cases, 182 controls	Ischemic stroke	Negative
	Kostulas et al. (1998)	C677T	Case-control: 126 cases, 126 controls	Ischemic stroke	Negative
	Morita et al. (1998)	C677T	Case-control: 256 cases, 325 controls	Ischemic stroke	Positive
	Salooja et al. (1998)	C677T	Case-control: 242 cases, 173 controls	Ischemic stroke	Negative
	Harmon et al. (1998)	C677T	Case-control: 174 cases, 183 controls	Ischemic stroke CT proven >60 years	Inconclusive
	Kristensen et al. (1999)	C677T	Case-control: 80 cases, 41 controls	Ischemic stroke	Negative
	Lalouschek et al. (1999)	C677T	Case-control: 81 cases, 81 controls	TIA or minor ischemic stroke	Negative
	Margaglione et al. (1999)	C677T	Case-control: 202 cases, 1036 controls	Ischemic stroke	Positive
	Notsu et al. (1999)	C677T	Case-control:147 (74) cases, 214(209) controls	Ischemic stroke	Positive
	Press et al. (1999)	C677T	Case-control: 136 case, 52 controls	Ischemic stroke	Negative
	Eikelboom et al. (2000)	C677T	Case-control: 219 cases, 205 controls	Ischemic stroke	Negative
	Voetsch et al. (2000)	C677T	Cross sectional: 153 cases, 225 controls	Ischemic stroke	Negative
	Yoo et al. (2000)	C677T	Case-control: 122 cases, 217 controls	Ischemic stroke	Negative
	Zheng et al. (2000)	C677T	Case-control: 115 cases, 122 controls	Ischemic stroke	Negative
	Lopaciuk et al. (2001)	C677T	Case-control: 100 cases, 238 controls	Ischemic stroke	Negative
	Topic et al. (2001)	C677T	Case-control: 56 cases, 124 controls	Ischemic stroke	Positive
	Wu et al. (2001)	C677T	Case-control: 77 cases, 229 controls	Ischemic stroke	Positive (women)
	Zhang et al. (2001)	C677T	Case-control: 102 case, 100 controls	Ischemic stroke	Negative
	Grossman et al (2002)	C677T	Case-control: 93 cases, 186 controls	Ischemic stroke	Negative
	McIlroy et al. (2002)	C677T	Case-control: 64 case, 71 controls	Ischemic stroke	Negative
	Pezzini et al. (2002)	C677T	Case-control: 31 cases, 36 controls	Ischemic stroke	Negative
	Yindong et al. (2002)	C677T	Case-control: 43 cases, 42 controls	Ischemic stroke	Negative
	Choi et al. (2003)	C677T	Case-control: 195 case, 198 controls	Ischemic stroke	Positive
	Pezzini et al. (2003)	C677T	Case-control: 125 case, 149 controls	Ischemic stroke	Negative
	Szolnoki et al. (2003)	C677T	Case-control: 867 cases, 743 controls	Ischemic stroke	Negative

Paraoxonase 1	Cao et al. (1998)	glu192arg	Cross-sectional: 197 cases	IMT in NIDDM	Negative
apoE	Mahieux et al. (1990)	E2/E3/E4	Case-control: 59 cases, 28 controls	Ischemic sroke	Negative
	Pedro-Botet et al. (1992)	E2/E3/E4	Case-control: 100 cases, 100 controls	Ischemic sroke	Positive
	Couderc et al. (1993)	E2/E3/E4	Case-control: 69 cases, 68 controls	Ischemic sroke or TIA	Positive
	Coria et al. (1995)	E2/E3/E4	Case-control: 104 cases, 94 controls	Ischemic sroke	Negative
	De Andrade et al. (1995)	E2/E3/E4	Case-control: 145 cases, 224 controls	Carotid atherosclerosis	Positive
	Kuusisto et al. (1995)	E2/E3/E4	Cohort study: stroke 64, no stroke 1067	Ischemic sroke	Negative
	Basun et al. (1996)	E2/E3/E4	Cohort study:1077 subjects	Ischemic sroke	Negative
	Hachinski et al. (1996)	E2/E3/E4	Case-control: 89 cases, 89 controls	Ischemic sroke	Negative
	Terry et al. (1996)	E2/E3/E4	Cross sectional: 130 cases, 130 controls	IMT in patients with and without CHD	Positive
	Ferrucci et al. (1997)	E2/E3/E4	Cohort study: stroke 150, no stroke 1664	Ischemic sroke	Positive
	Kessler et al. (1997)	E2/E3/E4	Case-control: 227 cases, 225 controls	Ischemic sroke	Positive
	Nakata et al. (1997)	E2/E3/E4	Case-control: 55 cases, 61 controls	Ischemic stroke	Negative
	Schmidt et al. (1997)	E2/E3/E4	Cross-sectional: 280 cases	Silent white matter disease	Positive
	Aalto-Setala et al. (1998)	E2/E3/E4	Cross sectional: 231 cases	Carotid atherosclerosis in patients with ischemic stroke	Negative
	Ji et al. (1998)	E2/E3/E4	Case-control: 123 cases, 117 controls	Ischemic stroke	Positive
	Margaglione et al. (1998)	E2/E3/E4	Case-control: stroke 100, no stroke 108, controls 398	Ischemic stroke	Positive
	McCarron et al. (1998)	E2/E3/E4	Cohort study: 640 cases	Ischemic stroke survival	Positive
	Peng et al. (1999)	E2/E3/E4	Case-control: 90 cases, 90 controls	Ischemic stroke	Positive
	McCarron et al. (1999)	E2/E3/E4	Case-control: 767 cases, 735 controls	Ischemic stroke	Positive
	Catto et al. (2000)	E2/E3/E4	Case-control: 592 cases, 289 controls		Negative
	Kokubo et al. (2000)	E2/E3/E4	Case-control: 322 cases, 1126 controls	Ischemic stroke	Positive
	McCarron et al. (2000)	E2/E3/E4	Case-control: cases 189		Negative
	Chowdhury et al. (2001)	E2/E3/E4	Case-control: cases 147, controls 190	Ischemic stroke	Positive
	FrikkeSchmidt et al. (2001)	E2/E3/E4	Case-control: cases 738, controls 8938	Ischemic stroke / carotid stenosis	Negative
	MacLeod et al. (2001)	E2/E3/E4	Case-control: cases 491, controls 400		Negative
	Serteser et al. (2001)	E2/E3/E4	Case-control: cases 79, controls 126	Ischemic stroke	Positive
	Slooter et al. (2001)	E2/E3/E4	Cases 5401	Carotid atherosclerosis	Negative
	Topić et al. (2001)	E2/E3/E4	Case-control: cases 92, controls 124	Ischemic stroke/ Carotid atherosclerosis	Negative
	Yang et al. (2002)	E2/E3/E4	Case-control: cases 36, controls 100	Ischemic stroke	Positive
	Luthra et al. (2002)	E2/E3/E4	Case-control: cases 36, controls 57	Ischemic stroke	Positive
	Szolnoki et al. (2002)	E2/E3/E4	Case-control: cases 689, controls 652	Ischemic stroke	Positive
	Souza et al. (2003)	E2/E3/E4	Case-control: cases 107, controls 100	Ischemic stroke (atherothrombotic)	Positive
	Jin et al. (2004)	E2/E3/E4	Case-control: cases 226, controls 201	cerebral infarction	Positive
	Pezzini et al. (2004)	E2/E3/E4	Case-control: cases 124, controls 147	Ischemic stroke	Positive
apo A1/CIII	Aolto-Setala et al. (1998)	SstI	Cross-sectional: 234 cases	Carotid atherosclerosis in patients with ischemic stroke <60 years	Negative
	Patsch et al. (1994)	XmnI	Cross-sectional: 268 cases	IMT in groups with different lipid profiles	Positive
apo B	Aolto-Setala et al. (1998)	XbaI	Cross-sectional: 234 cases	Carotid atherosclerosis in patients with ischemic stroke <60 years	Negative
Lipoprotein lipase	Huang et al. (1997)	A291G	Case-control: 125/56 cases, 95 controls	Ischemic stroke / carotid atherosclerosis	Negative
ACE	Sharma et al. (1994)	I/D	Case-control: 100 cases, 73 controls	Ischaemic stroke	Negative
	Markus et al. (1995)	I/D	Case-control: 100 cases, 137 controls	TOAST subtype	Positive
	Ueda et al. (1995)	I/D	Case-control: 488 cases, 188 controls	Ischaemic stroke and OCSP subtype	Negative
	Castellano et al. (1995)	I/D	Cross-sectional: 199 cases	IMT patients aged 50-64 years	Positive
	Dessi-Fulgheri et al. (1995)	I/D	Case-control: 193 cases, 147 controls		
	Catto et al. (1996b)	I/D	Case-control: 418 cases, 231 controls	Ischaemic stroke, OCSP subtype and mortality	Negative
	Pullicino et al. (1996)	I/D	Case-control: 60 cases, published controls	Lacunar stroke	Negative
	Margaglione et al. (1996)	I/D	Case-control: 101 cases, 109 controls	Ischaemic stroke	Positive
	Kario et al. (1996)	I/D	Case-control: 228 cases, 90/104 controls	Symptomatic stroke or MRI silent lacunae in hypertensives. Hypertensive/normotensive controls	Positive
	Hosoi et al. (1996)	I/D	Cross-sectional: 288 cases	IMT NIDDM patients	Positive
	Sertic et al. (1996)	I/D	Case-control: 50 cases, 25 controls	Cerebral atherosclerosis	
	Nakata et al. (1997)	I/D	Case-control: 55 cases, 61 controls	Ischaemic stroke	Positive
	Doi et al. (1997)	I/D	Case-control 181 cases, 271 controls	Ischaemic stroke (atheroembolic/lacunar)	Positive
	Watanabe et al. (1997)	I/D	Cross-sectional: 169 cases	Carotid atherosclerosis/asymptomatic lacunar stroke	Positive
	Agerholm-Larsen et al. (1997)	I/D	Case-referent: 184 cases, 5028 referent	Ischaemic stroke	Negative
	Agerholm-Larsen et al. (1997)	I/D	Case-referent: 268 cases, 4015 referent	Ischaemic stroke	Negative
	Elbaz et al. (1998)	CT 2/3	Case-control: 510 cases, 510 controls	Ischaemic stroke and subtype	Positive
	Sharma (1998)	I/D	Meta-analysis: 1918 cases, 722 controls	Ischaemic stroke	Positive
	Aalto Setala et al. (1998)	I/D	Cross-sectional: 234 cases	Carotid atherosclerosis in patients with ischaemic stroke aged <60 years	Negative
	Molyaka et al. (1998)	I/D	Case-control: 52 cases, 80 controls	Non hypertensive patients with ischemic stroke	
	Pfohl et al. (1998)	I/D	Case-control: 388 cases	Ischaemic stroke/extracranial artery stenosis	
	Seino et al. (1998)	I/D	Case-control: 26 cases, 28 controls	Cerebral infarction	
	Zee et al. (1999)	I/D	Nested case-control: 348 cases, 348 controls	Ischaemic stroke/PICH	Negative
	Kostulas et al. (1999)	I/D	Case-control: 100 cases, 100 controls	Ischaemic stroke/carotid stenosis	
	Lin et al. (2000)	I/D	Case-control: 306 cases, 300 controls	Stroke	
	Szolnoki et al. (2000)	I/D	Case-control: 406 cases	Stroke	
	Um et al. (2001)	I/D	Case-control: 106 cases, 498 controls	Cerebral infarction	
	Szolnoki et al. (2002)	I/D	Case-control: 689 cases, 652 controls	Cerebral infarction	
	Um et al. (2003)	I/D	Case-control: 365 cases, 319 controls	Cerebral infarction	
	Karagiannis et al. (2004)	I/D	Case-control: 100 cases, 100 controls	Ischaemic stroke	
Angiotensinogen	Barley et al. (1995)	M235T	Case-control: 100 cases, 45 spouse controls	Ischaemic stroke/IMT/carotid atheroma	Negative
	Nakata et al. (1997)	M235T	Case-control: 55 cases, 61 controls	Ischaemic stroke	Negative

because stroke event rates are comparatively low (in comparison with MI), making this a resource-intensive task. In addition, circulating levels obtained from peripheral blood samples may bear no relationship to local intracerebral levels of hemostatic proteins. One way to overcome this problem is to study the genetic regulation of the circulating levels of the hemostatic proteins, and the remainder of this article considers a number of hemostatic proteins (excluding platelet glycoproteins) and their genetic variants in relation to CVD.

Coagulation and fibrinolytic system in stroke

Factor V Leiden (G1691A). A misense mutation in codon 506 (Arg^{506}-Gln) of the factor V Leiden gene (G1691A) is directly associated with resistance to activated protein C (APC) through prolongation of the action of factor Va. Two to seven percent of the general population carry this mutation, and the mutation is now considered to be the most common inherited form of venous thrombosis, occurring in 10–40% of cases with venous thromboembolism. Most larger case–control studies have failed to find an association between prothrombotic states, such as activated protein C resistance or the underlying Leiden factor V mutation, and ischemic stroke in older individuals. This gene defect may be responsible for stroke in some younger individuals, but these prothrombotic states are unlikely to be important causes of multifactorial stroke in middle-aged and elderly patients. Evidence suggests that factor V Leiden and another mutation in the 3'-UTR of the prothrombin gene (G20210A) are candidate genes for stroke resulting from cerebral venous thrombosis.

Fibrinogen. A number of prospective studies have shown a strong association between elevated fibrinogen levels and risk for MI and cerebral infarction. Interestingly, levels of fibrinogen are associated with peripheral vascular disease, which itself is associated with a poorer outcome of ischemic stroke (although whether this is mediated through fibrinogen is not known). In the Northwick Park Heart Study, it was noted that in middle-aged men an increase of only 0.6 g/dl in fibrinogen levels (equivalent to 1 SD) was associated with an 84% increased risk of MI over 5 years. Circulating fibrinogen levels are determined by a number of factors including smoking, age, and gender. In contrast to other hemostatic factors, there is evidence for a relatively strong genetic component to fibrinogen levels. As much as 57% of the variation in levels can be attributed to genetic factors. There are fewer studies of fibrinogen and genotype with risk for CVD compared to ischemic heart disease. However, the Austrian Stroke Prevention Study studied 399 subjects for an association between the [beta]-chain –148C/T fibrinogen polymorphism, fibrinogen levels, and carotid atherosclerosis. The T/T genotype had a greater degree of atherosclerosis than C allele carriers ($p = 0.003$). The T/T genotype was a significant (OR 6.17) predictor of disease in a multivariate model, although there were relatively small numbers of subjects with this genotype. However, no association was found between genotype and fibrinogen levels. A separate group has reported an association between b-chain 448 fibrinogen variant and CVD in 149 female patients compared with controls free from CVD. This is one of the few examples of a possible gender-specific association with fibrinogen levels and suggests a protective role for the lysine allele in females. There is also a relationship between the [beta]-promoter polymorphism G/A -455 with stroke in Japanese subjects and also the C/T 148 with carotid atheroma. Raised fibrinogen levels may predispose to stroke both by accelerated atherosclerosis and prothrombotic mechanisms.

Factor XIII. Relatively little is known about the molecular structure and function of the fibrin clot in vascular disease, and nothing is known about fibrin structure and function in ischemic stroke or PICH. A common G-to-T point mutation (Val34Leu) in exon 2 of the [alpha]-subunit of the factor XIII gene in relation to vascular disorders was investigated, demonstrating that possession of the Leu allele is protective against atherothrombotic disease and venous thrombosis, but appears to be involved in the pathogenesis of ICH. Data indicate that among 642 subjects with CVD (the pathologic type of which was defined by cranial CT scan and the Oxfordshire Community Stroke Project classification) and 750 healthy controls, in the 62 subjects with PICH there was a higher prevalence of the Leu allele. This supports the hypothesis that factor XIIIVal34Leu may play a role in the stability of the fibrin clot, and extends previous observations by indicating that possession of the Leu allele is protective against thrombotic disease but increases the risk of hemorrhage. The GENIC investigations found a protective association.

The Leu allele appears to alter fibrin structure/function, and the protective effect is mediated by increased rates of fibrinolysis compared to the Val allele in the presence of platelets and to an interaction between Val34Leu and elevated fibrinogen that alters the rate of activation of factor XIII. The clinical and laboratory findings implicate factor XIIIVal34Leu in both thrombotic and hemorrhagic disease and provide clear therapeutic targets for intervention. Decreased fibrin porosity, turbidity and fiber mass–length ratios for factor XIII Leu allele were also found. The few clinical investigations into ex-vivo fibrin clot structure have been in CAD, but they have produced contrasting findings: decreased permeability of fibrin clots from patients with MI due to tight and rigid fibrin with reduced fiber mass–length ratio, increased fiber mass–length ratio. Fibrin structures with reduced fiber mass–length ratio and reduced pore size are associated with slower rates of lysis by plasmin, while cross-linking of fibrin by factor XIII increases resis-

tance of the clot to lysis. Increased cross-linking by factor XIII has been found in acute MI, but whether the same property operates in ischemic stroke or PICH has not been reported. However, it is probable that genetic variants in the hemostatic system also play a role in the pathogenesis of intracranial hemorrhage. Polymorphism in the coding region of the a-chain (Thr312Ala) was also investigated. This is of interest because it lies close to the factor XIII cross-linking site at position 328. It is also in a region involved in factor XIII A- and B-subunit dissociation and factor XIII activation. We studied aThr312Ala in post-stroke mortality, and possession of the A allele was associated with a dose-related significant reduction in survival compared to those subjects homozygous for the T allele. These findings support the hypothesis that possession of the A allele influences clot stability, although further clinical and in vitro studies are now under way to clarify this issue.

Factor VII. Data on the association of FVII levels with IHD are contradictory: the prospective Northwick Park Study related elevated levels to fatal (but not non-fatal) MI, but the Edinburgh Artery Study found no association. The gene coding for factor VII is polymorphic and probably accounts for approximately 30% of variance in levels of factor VII. There is no clear relationship between the polymorphic variants and vascular disease. A factor VII gene polymorphism (R353Q) has been associated with higher levels of factor VII:C, but in a later study no association was found between levels of factor VII:C or between the R353Q variant and ischemic cerebrovascular disease. To our knowledge, there is only one study of factor VII levels and genotype in ischemic stroke. The results support prior findings of a relationship between genotype and levels of factor VII, but neither were associated with ischemic CVD. This is consistent with the results of a separate large study of arterial thrombotic events. Another study examining factor VII polymorphisms in hypertensive small vessel disease also gave negative results.

Plasminogen activator inhibitor-1. Plasminogen activator inhibitor-1 (PAI-1) is the fast-acting inhibitor of tissue plasminogen activator (t-PA). Evidence to support the role of the fibrinolytic system comes from studies demonstrating suppressed fibrinolysis or high PAI-1 levels to CAD presenting as either angina or MI. In prospective studies, diminished fibrinolysis predicts MI and high PAI-1 activity predicts recurrence of MI in young men but not in older patients. The evidence for a role of PAI-1 levels in stroke is less clear. In some studies, elevated levels of PAI-1 are seen in acute stroke, whereas in others, suppression or no difference in PAI-1 levels is seen. The conflicting results probably reflect differing analytical techniques for PAI-1 and the population of stroke subjects studied. The gene coding for PAI-1 has several polymorphic loci, and the 4G/5G polymorphism exhibits differential transcriptional responses to interleukin-1 in HepG2 cells, with higher rates of PAI-1 synthesis in cells with the homozygous 4G/4G genotype. In one large case-control study involving over 600 subjects with CVD, there was no difference in genotype frequency compared to a control group and no relationship between the 4G/5G genotype and PAI-1 levels, although Margaglione did suggest an association of the 5G/5G genotype with stroke. It is likely that the overall influence of the 4G/5G genotype on the pathogenesis of ischemic stroke is small. However, it has recently been suggested that the 4G allele is associated with a reduced risk for cerebrovascular mortality in females. The authors suggested that PAI-1 might be acting via pathways other than fibrinolysis. They hypothesize that PAI-1 might protect against destabilization of the atherosclerotic plaque, or inhibit the neurotoxic action of tissue plasminogen activator in the brain.

Platelet glycoprotein receptor. The role of platelet glycoprotein receptor polymorphisms has also been studied extensively in patients with ischemic stroke. These molecules are members of the integrin family and, when activated, bind fibrinogen, von Willebrand factor or collagen, and therefore promote platelet aggregation and thrombosis. The P1A2 variant of the platelet fibrinogen receptor Gp IIa/IIIb has been reported a risk factor for acute coronary syndromes specifically in young patients. Subgroup analysis in a case–control study has suggested that the P1A2 allele may also be an important risk factor in stroke patients aged less than 50 years. The other study failed to find an overall association between this polymorphism and cerebral infarction in young women. Conflicting genotype–phenotype correlations have also been found with the HPA2 (human platelet antigen 2) and VNTR (variable number of tandem repeats) variants of the platelet von Willebrand factor receptor, Gp Ia/IIa. It has been reported recently that a silent point mutation (GpIa C807T), correlating with increased expression of the collagen receptor *in vitro*, is an independent risk factor for stroke in young patients. However, association studies of different polymorphisms in this gene have revealed a lack of association.

Homocystein. In recent years, attention has focused on the role of plasma homocyst(e)ine (Hcy) as one such candidate risk factor. Following early observations of premature atherothrombotic complications in children with severe hyperhomocyst(e)inemia (hyper-Hcy; Hcy level, >100 μmol/L) due to inborn errors of metabolism, subsequent studies have supported a possible relationship between an elevated Hcy level and atherosclerotic vascular disease. Several studies have addressed the question of a potential association between hyper-Hcy and CVD defined as clinical stroke, carotid atherosclerosis, or intima–media thickening. Some of these have reported no evidence of an association, whereas others have reported a strong link between hyper-Hcy and

CVD. Interpretation of the results of these studies as a group is complicated by the variability in study design, sample size, entry criteria, and outcome measures employed. The prevalence of heterozygosity for the cystathione β-synthase gene is estimated at 0.5–0.15% of the population, heterozygous individuals possessing ~30% of the normal enzyme activity. Several studies determined whether allele heterozygosity is itself a significant risk factor for polygenic ischemic stroke. Two studies found an increased frequency of heterozygotes in patients with occlusive cerebrovascular disease compared with controls, and this has also been shown in patients with asymptomatic carotid artery atherosclerosis. In contrast, no association was found between heterozygosity for the cystathione β-synthase gene and either carotid intima media thickness or asymptomatic carotid atherosclerosis. These inconsistencies may reflect the different ages of the patients examined, mechanisms other than wall disease through which homocysteine acts, or the influence of multiple risk factors on homocysteine levels and carotid artery damage in carriers. Very rarely, patients with homocysteinuria have complete deficiency of methylene tetrahydrofolate reductase, a folate-dependent enzyme catalysing the rate-limiting step in the methylation of homocysteine to methionine. In 1988, a common thermolabile variant of methylene tetrahydrofolate reductase associated with decreased enzyme activity and mildly elevated plasma homocysteine levels was identified. A single base pair (677C→T) substitution in the human MTHFR gene predicts phenotypic expression of a heat-sensitive variant with reduced enzymatic activity. This variant has been considered an ideal candidate genetic polymorphism for predisposition to ischemic stroke, as it is common in many populations studied to date and the genotype correlates highly with the plasma Hcy level in a dose-dependent fashion. However, studies that have examined the risk for atherosclerotic vascular disease and stroke associated with the MTHFR 677C→T polymorphism have reported conflicting results, which has prevented a definitive conclusion to date. A small influence (pooled relative risk, 1.23) of the MTHFR 677TT genotype on stroke risk, which tended toward, but did not reach, the threshold for statistical significance was found. Despite these considerations, evidence from several sources supports the concept that moderate elevations in the plasma Hcy concentration may contribute to the pathogenesis of atherosclerosis and ischemic stroke. First, children with homocystinuria due to mutations in homocysteine-pathway enzymes develop complications of premature atherosclerosis and thrombosis, in the absence of other vascular risk factors. Second, prospective cohort studies have demonstrated a dose-dependent relationship between plasma Hcy concentration and other measures of vascular disease, such as carotid atherosclerosis and intima–media thickening. Third, several studies have described in vivo reversible impairment of endothelial-dependent vasodilatation associated with an elevated Hcy level, thus supporting the concept of Hcy-mediated endothelial injury. Finally, experimental and clinical data suggest that in vivo auto-oxidation of homocysteine sulfhydryl groups results in the formation of reactive oxygen species, promoting peroxidation of lipids bound to low-density lipoproteins. Both endothelial injury and low-density lipoprotein–lipid peroxidation are thought to be important early pathophysiologic processes in the development of atherosclerotic lesions. Most studies have demonstrated that the TT genotype is consistently associated with greater plasma Hcy concentrations, compared with those in normal CC or CT heterozygous subjects. Despite this observation, studies that have investigated the potential role of the 677C→T polymorphism in determining susceptibility to ischemic stroke have obtained widely differing results, some reporting no association, whereas others have reported a greater than threefold increased risk associated with the homozygous state. The explanation for these findings is unclear at this time. A meta-analysis found that the C677T variant was associated with mild homocysteinaemia but not increased vascular risk. There is an interaction with folate, and it is still possible that the methylene tetrahydrofolate reductase polymorphism may be a risk factor in younger individuals with low folate intake, but further studies are required in these populations.

Renin–angiotensin system. The ACE gene is probably the most extensively investigated candidate gene in ischemic stroke, after an initial study by Cambien and co-workers which suggested that an intron 16 insertion/deletion polymorphism was associated with myocardial infarction. A number of studies have reported an association with stroke, with a relative risk usually of the order of 1.5–2.5, but other studies have failed to find a significant association. A meta-analysis has evaluated the risk of stroke in 1918 subjects versus 722 controls from seven studies. It was concluded that the ACE genotype conferred a small but modest effect, with an odds ratio of 1.31 (95% confidence interval 1.06–1.62), according to a dominant model of inheritance. A weaker association was seen under a recessive model. A nested case–control study was performed on the US Physicians Health cohort and a negative result was reported. Although reducing the risk of false-positive results due to selection bias, such prospective cohort studies tend to suffer from poor stroke phenotyping; in this study the cases included both ischemic and haemorrhagic stroke, and no subtyping of ischemic stroke subtypes was performed. Such analyses will fail to detect a selective association with a particular stroke phenotype, and this may be of particular importance with the ACE gene. A number of studies have reported an association that was strongest or exclusively with lacunar stroke, and these findings are consistent with reported associations between the deletion allele and MRI-detected silent small vessel disease in hyper-

tensives. A weak association was found between the deletion polymorphism and all ischemic stroke cases in Han Chinese in Taiwan. When a further study was performed with more detailed investigations allowing recruitment of only lacunar stroke patients, a much stronger positive association was found. ACE deletion/insertion polymorphism is not a major risk factor in an unselected group of patients with ischemic stroke, but it may be a risk factor for small vessel disease. A variant of the angiotensinogen gene (M235T) has also been implicated in vascular disease, but its evaluation in stroke so far suggests that it does not behave as an important risk factor. However, it has recently been proposed that an epistatic interaction with the ACE gene may exist.

Lipid metabolism. Individuals with higher levels of plasma cholesterol, increased HDL (high-density lipoprotein) and decreased LDL (low-density lipoprotein) have a higher risk of premature atherosclerosis. The phenotype may arise not only from single gene disorders, as discussed above, but also from a number of genetic and environmental factors, including polymorphic variants of genes encoding the apolipoproteins, lipoprotein receptors and the key enzymes of plasma lipoprotein metabolism. The role of apolipoproteins and enzymes in relation to stroke and carotid artery disease is considered in *Table I*. The studies to date have produced conflicting results as to the importance of apoE alleles in predisposition to ischemic stroke. In small case–control or cross-sectional studies, both the 2/3 genotype and the E4 allele have been over-represented in patients with ischemic stroke. Other groups have examined the role of the apoE genotype in modulating the outcome of cerebral infarction as this lipoprotein appears to be an important regulator of lipid turnover within the brain and of neuronal membrane maintenance and repair. Studies in patients with head injury and intracerebral hemorrhage have indicated that the E4 allele is a predictor of poor outcome in terms of death and disability, and this is consistent with studies of cognitive decline in 4 carriers with cerebrovascular disease. McCarron and colleagues found a favorable effect of E4 on stroke outcome. Stanković and colleagues (126) gave detailed description of the conflicting results as to the importance of apoE alleles in predisposition to ischemic stroke.

Endothelial nitric oxide synthase. The activity of the L-arginine/nitric oxide synthase system is an important mediator of endothelial function. Nitric oxide (NO) plays a key role in the regulation of vascular tone, and reduces vascular smooth muscle cell proliferation and adhesion of platelets and leucocytes. A few studies on coronary disease suggest that NO deficiency may have a genetic basis, while others did not find any association of the Glu298Asp polymorphism and the 27-basepair repeat in intron 4 of the endothelial constitutive NO synthase gene with ischemic stroke. However, preliminary results of the GÉNIC study are in favour of an association of the GG genotype of the Glu298Asp polymorphism with ischemic stroke, and more particularly with lacunes. A higher frequency of the *nn* (GG) genotype was found in lacunes compared with other subtypes. Strong evidence from animal and human studies indicates that the activity of this system is under genetic control. Work in the stroke-prone SHR rat has suggested that impaired endothelial dysfunction is an important predisposing factor leading to stroke. In addition, knockout mice deficient in endothelial nitric oxide synthase are highly sensitive to focal cerebral ischaemia and have marked vessel wall abnormalities. An earlier study had demonstrated that a functional variant of nitric oxide synthase (ecNOS 4a) was associated with increased risk of significant coronary artery disease and myocardial infarction in smokers. However, neither this nor another variant with unknown functional significance (Glu298Asp) has been shown to be an important risk factor for ischemic cerebrovascular disease. The genes encoding both the neuronal and the inducible form of nitric oxide synthase are potential candidate genes for stroke. In animal models, their inhibition reduces infarct size, which is also smaller in knockout mice. Both genes have been cloned and common polymorphisms described.

Atrial natriuretic peptide. Evidence for the existence of genes directly contributing to stroke occurrence was first obtained in the animal model of stroke-prone spontaneously hypertensive rat through a linkage analysis approach in F2 segregating hybrid populations. Several quantitative trait loci were detected in different chromosomes of the rat. Candidate genes were identified (ANP, BNP, adrenomedullin) and subsequently analyzed to obtain information on the fine disease mechanisms possibly dependent on specific sequence mutations. Gene encoding ANP appeared to play a role in the disease. Characterization of both BNP and adrenomedullin failed to identify differences between the stroke-prone animal model and its related control. Furthermore, we were unable to demonstrate an involvement of these genes in the human disease, and no positive findings have so far been reported by other groups. In contrast, our experience with the gene encoding ANP has been so far quite promising. Among other genes, the atrial natriuretic peptide (*ANP*) gene has been involved in the pathogenesis of stroke. In fact, structural abnormalities of *ANP* are significantly associated with stroke in both an animal model, the stroke-prone spontaneously hypertensive rat, and the North American white population of male physicians recruited in the Physicians Health Study (PHS) and an Italian population from Sardinia. These two human studies identified a twofold risk of stroke independent of hypertension, obesity, and diabetes in subjects-carriers of an exon 1 mutation of the ANP gene carrying the exon 1 mutation (mutation responsible for a Val/Met trans-

position within the 1-30 proANP (long-acting natriuretic peptide) and 3.8-fold increased risk of ischemic stroke in carriers of a stop codon mutation (responsible for the synthesis of a 30 rather than 28 aa mature ANP peptide) (127).

Phosphodiesterase 4D. Linkage based approaches applied to Icelandic stroke patients identified a locus for a gene for common stroke on chromosome 5q12. Initial analyses suggested that it was a risk factor for ischemic stroke but not for other types of vascular disease such as myocardial infarction or peripheral arterial disease. By further analyses, the responsible gene-phosphodiesterase 4D (PDE4D) was identified and characterized. The PDE4D gene encodes a cyclic nucleotide phosphodiesterase which is involved in the selective degradation of second messenger cAMP, which has a central role in signal transduction and regulation of physiological responses. In vascular smooth muscle cells, low cAMP levels lead to cell proliferation and migration that is mediated in part by PDE4D, and increase immune functions which lead to the development and progression of atherosclerosis. The highest risk haplotype (present in 9% of controls) conferred a twofold relative risk. A protective haplotype (present in 21% of controls) was identified with a relative risk of 0.7. However, none of the associated variants were present in protein coding or gene splicing regions, suggesting that the identified or associated variants affect gene regulation (for example expression level) rather than having a direct functional effect on the protein. The association between PDE4D and stroke now needs replication in independent populations. This may represent a completely new pathophysiological process causing stroke and could open the way for new therapeutic opportunities for disease prevention (128).

5-lipoxygenase activating protein. The identification and characterisation of *ALOX5AP*, gene coding for 5-lipoxygenase activating protein, in which certain common haplotypes double the risk of both stroke and myocardial infarction, was reported. The initial finding was a suggestive linkage to a region of chromosome 13 in a series of 296 Icelandic families with multiple affected members. A case-control association study was carried out using a high density of markers across the implicated region (containing 40 known genes) which led to the identification of the *ALOX5AP* susceptibility gene. This was confirmed in a UK population, although the associated haplotype was different. The individual or combination of variants associated with disease risk remain to be identified. ALOX5AP and 5-lipoxygenase together convert unesterified arachidonic acid to the leukotriene LTA4, which is further converted to LTB4 or LTC4. These are important proinflammatory mediators which are active in macrophages and leukocytes invading atherosclerotic lesions (129).

Inflammatory molecules. In recent years, there has been increasing appreciation of the fact that inflammatory molecules, as well as single nucleotide polymorphisms of genes encoding inflammatory mediators, may contribute to the development and progression of a large number of pathological conditions (130). Single nucleotide polymorphism of proinflammatory and anti-inflammatory genes may strongly influence the plasma levels and biological activity of the corresponding proteins with potentially important clinical implications. It has been suggested that proinflammatory gene variations may act synergistically and determine genetic profiles associated with increased risk for diseases. The polymorphisms of C-reactive protein (1059G/C), interleukin-4 (582C/T), interleukin-6 (174G/C), macrophage migration inhibitory factor (173G/C), monocyte chemoattractant protein-1(2518A/G), intracellular adhesion molecule-1 (469E/K), E-selectin (Ser128Arg), P-selectin (Val640Leu), matrix metalloproteinase-3 genes (11715A/6A), were associated with ischemic stroke in different studies. Also, the relationship between single nucleotide polymorphism (SNP) in the gene that encodes the amiloride-sensitive epithelial sodium channels (ENaCs) and ischemic cerebrovascular event was identified in the newer studies.

Conclusion

The identification of novel and important genes that appear to be responsible for some cases of ischemic stroke will open new avenues of investigation for those interested in genetics and ischemic stroke. Additional knowledge of the role of genes in ischemic stroke may improve our understanding of the cause of stroke, provide new insights into prevention and the factors that influence the outcome of stroke, and new therapeutic targets when preventive strategies have failed. Stroke therapy will undergo a great revolution in the present decade. The knowledge of the human genome, gene interactions and proteomics will permit a new concept of drug development for stroke. Gene therapy by modification of gene expression will be useful in treating atherosclerosis and hypertensive microangiopathy, or in the acute phase, when we will manipulate the acute gene expression induced by ischemia or the apoptotic gene program. However, a single abnormal gene, as in monogenic diseases, is easier to replace than several genes in complex multigenic disorders. Gene therapy, stem cell therapy and neurological grafts for stroke are still in the experimental phase, and many hurdles will have to be jumped before the introduction of these therapies into human clinical stroke trials. A more immediate clinical application of genetics to stroke therapy is the development of pharmacogenetics that analyzes the influence of genetic variability of individuals on drug response. A new era of personalized therapy is dawning where specific DNA biochips will help stroke clinicians decide on the better use of thrombolytics, neuroprotectants, antithrombotics, statins or antihypertensives.

GENETSKI FAKTORI U ISHEMIJSKOJ BOLESTI MOZGA

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Kratak sadržaj: Ishemijska bolest mozga je jedan od vodećih uzroka smrtnosti i invaliditeta odraslih širom sveta. Ona nije indukovan samo klasičnim vaskularnim faktorima rizika kao što su hipertenzija, pušenje, dijabetes, već i genetskim faktorima. Genetička epidemiologija ishemijske bolesti mozga je poligenska. Geni kandidati koji se ispituju u moždanom udaru dele se u pet grupa: na one koji utiču na metabolizam lipida, rennin angiotenzin system, hemostazu, sintezu azotmonoksida i metabolizam homocisteina. Kako je ishemijska bolest mozga kompleksna bolest koju čini heterogena grupa poremećaja i za koju su evidentni brojni faktori rizika, istraživanja na polju genetike ove bolesti predstavljaju pravi izazov za istraživače. Brojne studije koje su se bavile ovim problemom dale su različite i često kontradiktorne rezultate. Dodatna saznanja o ulozi gena u moždanom udaru mogu da poboljšaju razumevanje uzroka ove bolesti, da otvore nove vidike u smislu prevencije i faktora koji utiču na ishod moždanog udara, kao i da pomognu u otkrivanju novih terapeutskih sredstava u slučajevima kada preventiva zataji.

Ključne reči: ishemijska bolest mozga, genetika, geni kandidati

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