Genetic Susceptibility to Primary Intracerebral Haemorrhage

Efthimios Dardiotis,[1,2] Maria Dardioti,[1,2] Georgia Xiromerisiou,[1,2] Konstantinos Paterakis,[3] Kostas Fountas[3] and Georgios M Hadjigeorgiou[1,2]

1. Laboratory of Neurogenetics, Department of Neurology, University of Thessaly, University Hospital of Larissa; 2. Institute of Biomedical Research and Technology, CERETETH, Larissa; 3. Department of Neurosurgery, University of Thessaly, University Hospital of Larissa

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Abstract

Primary intracerebral haemorrhage (PICH) originates from the spontaneous rupture of cerebral arteries as a result of chronic degenerative alterations. Although the aetiology of PICH has not been fully elucidated, it may be the result of an interaction between genetic and environmental risk factors. Several genetic association studies have been conducted in patients with PICH with both positive and negative results. Most of them investigated the role of mutations in genes affecting the lipid metabolism, the coagulation processes, the inflammation and the regulation of blood pressure. In this article we briefly discuss the majority of these studies reporting the susceptibility genes that have been implicated in PICH.

Keywords

Primary intracranial haemorrhage (PICH), genetics, association studies, polymorphism

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Correspondence: Georgios M Hadjigeorgiou, Laboratory of Neurogenetics, Department of Neurology, School of Medicine, University of Thessaly, Greece. E: gmhadji@med.uth.gr

Primary intracerebral haemorrhage (PICH) originates from the spontaneous rupture of small arteries as a result of chronic degenerative changes due to chronic hypertension or amyloid angiopathy.[1] Although environmental factors are important, there is accumulating evidence that genetic elements also contribute to the pathogenesis of PICH.[2,3] In an epidemiological study, familial clustering of PICH was noticed, especially when involving deep brain structures, indicating genetic predisposition to cerebral haemorrhage.[4] Increased incidence of intracerebral haemorrhage in specific animal models also provided additional evidence for the existence of susceptibility genes.[5] The importance of genetic factors was unequivocally demonstrated with the identification of causative mutations in monogenic cases of familial intracerebral haemorrhage. Furthermore, several association studies have suggested the presence of susceptibility genes that predispose to PICH (see *Table 1*). In this article we briefly discuss the current state of knowledge regarding the known major and susceptibility genes that have been implicated in PICH.

Familial Cases

Familial Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is caused by the deposition of amyloid in the small and medium-sized cortical and leptomeningeal arteries leading to intracerebral haemorrhage, ischaemic infarction or dementia. Amyloid is caused by the aggregation of β-amyloid peptide (Aβ) and other proteins, promoting vasculopathic changes such as fibrinoid necrosis and microaneurysms. Aβ peptide is formed by the proteolytic fragmentation of amyloid precursor protein. Amyloid formation has also been reported in familial cases of CAA caused by mutations in the cystatin C gene,[6,7] the transthyretin gene[8–12] or the BRI gene.[13,14] The clinical presentation of these familial cases includes dementia, vascular cognitive decline and PICH. PICH has also been reported in a member of a Volga-German family with Alzheimer's disease and a mutation in the presenilin-2 gene.[15] Recently, a novel mutation in presenilin-1 gene was also associated with early-onset dementia of Alzheimer type and lobar PICH.[16] However, most familial cases of CAA and PICH are caused by mutations in the amyloid precursor protein. Of note, these mutations are located in the Aβ segment of the amyloid precursor protein, whereas mutations in the flanking regions cause Alzheimer's disease or ischaemic stroke. PICH has been documented in Flemish,[17] Dutch,[18] Arctic,[19] Iowan[20] and Italian[21] CAA families. Recently, duplication of the amyloid precursor protein gene was reported to be the cause of familial CAA presenting with dementia and PICH.[22,23]

Type IV Collagen a1 Chain

Type IV collagen a1 chain (COL4A1) is an integral component of the basement membrane in the brain vasculature and other tissues. A few families and a sporadic case with PICH and mutations in COL4A1 have been reported so far.[24–27] Mutations in COL4A1 seem to compromise vascular wall integrity and blood supply, leading to small-vessel diseases including PICH, microbleeds, lacunar strokes or leukoaraiosis.[24–26,28] Electron microscopy of the vascular wall in patients with COL4A1 mutations reveals structural defects of the basement membrane such as interruptions, variable thickening and inconsistent density.[28]

Cerebral Autosomal-dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a monogenic disorder caused by a variety of mutations in the Notch3 gene, which is responsible for cell signalling and vascular development.[29] The clinical manifestations of this disorder include migraines, transient

Table 1: Genetic Association Studies in Primary Intracerebral Haemorrhage

Reference	Gene	Polymorphism	Methodology	Phenotype	Results	Comments
Nicoll et al., 1997[32]	ApoE	Apo ε2/ε3/ε4	36 CAA patients	CAA-related PICH	Positive	ε2 allele (p=0.003)
Greenberg et al., 1998[33]	ApoE	Apo ε2/ε3/ε4	97 patients 87 controls	CAA-related PICH	Positive	ε2 allele (p=0.03) ε4 allele (p=0.015)
McCarron et al., 1998[34]	ApoE	Apo ε2/ε3/ε4	111 patients 406 controls	CAA-related PICH	Positive	ε2 allele (p<0.01)
Alberts et al., 1995[40]	ApoE	Apo ε2/ε3/ε4	44 patients	PICH outcome	Positive	ε4 allele (p=0.0014)
McCarron et al., 1999[44]	ApoE	Apo ε2/ε3/ε4	74 patients	PICH outcome	Negative	–
Garcia et al., 1999[41]	ApoE	Apo ε2/ε3/ε4	48 patients 24 controls	PICH	Negative	–
O'Donnell et al., 2000[39]	ApoE	Apo ε2/ε3/ε4	71 patients	Recurrent PICH	Positive	ε2 allele: OR 4.7, 95% CI 1.4–15.9 ε4 allele: OR 3.7, 95% CI 1.1–11.7
Kokubo et al., 2000[75]	ApoE	Apo ε2/ε3/ε4	84 patients 1,126 controls	PICH	Positive	ε2/ε2 allele: OR 4.4, 95% CI 1.0–19.7 ε3/ε4 allele: OR 1.8, 95% CI 1.0–3.3
Catto et al., 2000[45]	ApoE	Apo ε2/ε3/ε4	60 patients 289 controls	PICH	Negative	–
Rosand et al., 2000[38]	ApoE	Apo ε2/ε3/ε4	41 patients 66 controls	Warfarin-related PICH	Positive	ε2 allele: OR 3.8, 95% CI 1.0–14.6
Chowdhury et al., 2001[43]	ApoE	Apo ε2/ε3/ε4	80 patients 190 controls	PICH	Positive	eε2 allele: in ages >60 years, OR 19.2, 95% CI 1.3–295.2; p<0,05
Woo et al., 2002[2]	ApoE	Apo ε2/ε3/ε4	188 patients 366 controls	PICH	Positive	Lobar PICH, ε2 or ε4 allele: OR 2.3, 95% CI 1.2–4.4
Sudlow et al., 2006[46]	ApoE	Apo ε2/ε3/ε4	571 patients 2,401 controls	PICH (meta-analysis)	Positive	ε2 allele: OR 1.32, 95% CI 1.01–1.74
Martinez-Gonzalez et al., 2006[76]	ApoE	Apo ε2/ε3/ε4	199 patients	PICH outcome (meta-analysis)	Negative	ε4+ genotypes: OR 1.38, 95% CI 0.99–1.92
Vernooij et al., 2008[77]	ApoE	Apo ε2/ε3/ε4	1,062 persons	Cerebral microbleeds	Positive	ε4 allele and lobar microbleeds: OR 1.87, 95% CI 1.25–2.81
Xia et al., 2004[58]	ApoH	G341A G817T G1025C C1080T	140 patients 100 controls	PICH	Positive Negative Negative Negative	A allele: p<0.05 – – –
Sun et al., 2003[57]	Lp(a)	PNTR	499 patients 1,817 controls	PICH	Positive	OR 1.62, 95% CI 1.09–2.37; p<0.001
Yamada et al., 2006[48]	152 genes	202 polymorphisms	282 patients 2,010 controls	PICH	Positive	-572G/C polymorphism of IL-6: OR 1.57, 95% CI 1.21–2.07; p<0.001
Wang et al.,2006[47]	VKORC1	+2255 T/C	499 patients 1,811 controls	PICH	Positive	OR 1.53, 95% CI 1.09–2.16
Alberts et al., 1997[50]	Endoglin	6 bp insertion	103 patients 202 controls	PICH	Positive	OR 4.8, 95% CI 1.28–21.6; p=0.012
Catto et al., 1996[52]	ACE	I/D in intron 16	49 patients 231 controls	PICH	Negative	–
Slowik et al., 2004[51]	ACE	I/D in intron 16	58 patients 116 controls	PICH in deep brain structures	Positive	OR 2.13, 95% CI 1.10–4.14; p=0.02
Vila et al., 2000[78]	ACT	-15A/T	38 patients 70 controls	PICH	Positive	OR 1.8, 95% CI 0.85–9.65
Obach et al., 2001[53]	ACT	-15A/T	99 patients 80 controls	PICH	Positive	OR 2.80, 95% CI 1.19–6.58
Fu et al., 2002[54]	ACT	-15A/T	220 patients 276 controls	PICH	Positive	OR 2.17; p<0.05
Pera et al., 2006[55]	ACT	-15A/T	95 patients 190 controls	PICH	Negative	–
Dardiotis et al., 2008[56]	ACT	-15A/T	147 patients 206 controls	PICH	Negative	–
Navarro-Nunez et al., 2007[68]	b-1-tubulin	Q43P	259 patients 449 controls	PICH	Positive	OR 2.36, 95% CI 1.25–4.45; p=0.008
Yoshida et al., 1998[60]	PAF-H	Val279Phe	99 patients 270 controls	PICH	Positive	p<0.05
Iniesta et al., 2003[59]	GP Ia GP IbA GP IIIa	807 C/T, HPA-5 VNTR HPA-1	141 patients 141 controls	PICH	Negative Negative Negative	– – –
Catto et al., 1998[61]	XIII	Val34Leu	62 patients 436 controls	PICH	Positive	OR=1.7; p=0.05

Table 1 continued

Reference	Gene	Polymorphism	Methodology	Phenotype	Results	Comments
Corral et al., 2000[65]	XIII	Val34Leu	116 patients 465 controls	PICH	Negative	–
Gemmati et al., 2001[62]	XIII	Val34Leu	130 patients 200 controls	PICH	Positive	OR 1.7, 95% CI 1.16–2.51; p=0.009
Reiner et al., 2001[66]	XIII XIII XIII PAI	Val34Leu Tyr204Phe Pro564Leu -675 4G/5G	42 patients 345 controls	Women aged <45 years with PICH	Negative Positive Positive Negative	– OR 2.09, 95% CI 1.1–7.5 OR 4.3, 95% CI 1.4–1.7 –
Cho et al., 2002[79]	XIII	Val34Leu	58 patients 48 controls	PICH	Negative	–
Endler et al., 2003[64]	XIII	Val34Leu	94 patients 369 controls	PICH	Negative	–
Corral et al., 2001[63]	F-V leiden F-II F-VII XIII	Leiden 20210A -323 D/I Val34Leu	201 patients 201 controls	PICH	Positive Negative Positive Negative	OR 0.19, 95% CI 0.03–0.95 – OR 1.54, 95% CI 1.03–2.72 –
Greisenegger et al., 2007[73]	F-VII	-401G/T, -402 G/A	85 patients 85 controls	PICH	Negative	–
Obach et al., 2006[70]	Protein Z	c.573-79G/A	156 patients 147 controls	PICH	Negative	–
Munoz et al., 2007[74]	GAS6	8 variants	199 patients 150 controls	PICH	Negative	–
Li et al., 2003[72]	MTHFR	C677T	503 patients 1,832 controls	PICH	Negative	–
McCarron et al., 2003[71]	IL-1a	(-899) C/T	42 patients 167 controls	CAA-related PICH	Negative	–
Strand et al., 2007[49]	OPG IL-6	-1181G/C, -950T/C -174G/C	61 patients 773 controls	PICH	Positive Negative	-1181C/C genotype: OR 6.04, 95% CI 1.71–21.29; p=0.005 –
Strand et al., 2007[67]	ESR1	c.454-397T/C c.454-351A/G	61 patients 773 controls	PICH	Positive Negative	c.454-397T/T genotype: OR 3.94, 95% CI 1.54–10.03 –
Xu et al., 2008[69]	PON2	C311S, G148A	150 patients 120 controls	PICH	Negative	–

CAA = cerebral amyloid angiopathy; CI = confidence interval; OR = odds ratio; PICH = primary intracranial haemorrhage; IL = interleukin.

ischaemic attacks, lacunar strokes and subcortical dementia. Magnetic resonance imaging reveals extensive peri-ventricular white matter leucoencephalopathy and the presence of microbleeds, predominantly in subcortical areas and the thalamus, detected on T2-weighted gradient echo imaging. Microbleeds can be present in 31–69% of patients with CADASIL.[30] It was found that PICH can occur in 25% of symptomatic patients with CADASIL, and this is closely related to the number of cerebral microbleeds.[31]

It was found that primary intracerebral haemorrhage can occur in 25% of symptomatic patients with CADASIL, and this is closely related to the number of cerebral microbleeds.

Genetic Association Studies

Apolipoprotein E

Apolipoprotein E (ApoE) is a glycoprotein involved in cholesterol transport and has three isoforms: ε2, ε3 and ε4. Accumulating evidence implicates ApoE ε2/ε3/ε4 polymorphism with CAA-related PICH.[32–34] The e4 allele increases Aβ deposition in the cerebral vasculature in a dose-dependent manner.[35,36] The ε2 allele is associated with vasculopathic changes in amyloid-laden vessels and rupture.[33] It has also been documented that ε2 and ε4 alleles of the ApoE gene are risk factors for the occurrence of lobar PICH, probably due to the presence of cerebral amyloid angiopathy in the carriers of these alleles.[2] In addition, the e4 allele was associated with earlier age at onset of CAA-related PICH[37] and with warfarin-related PICH.[38] ε2 and ε4 allele carriers are also at increased risk of recurrent haemorrhage compared with ε3 carriers.[39] Moreover, the presence of the e4 allele was linked to poor outcome of PICH patients.[40] However, other studies did not find any association between ApoE polymorphism and PICH.[41–45] In a recent meta-analysis, the ε2 allele was found to be an independent risk factor for PICH (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.01–1.74), whereas ε4 genotypes were not (OR 1.16, 95% CI 0.93–1.44).[46]

VKORC1 Gene

An interesting association between a haplotype in the vitamin K epoxidase reductase complex subunit 1 (VKORC1) gene and arterial vascular diseases including PICH (OR 1.53, 95% CI 1.09–2.16; p<0.05) has been reported.[47] VKORC1 is implicated in haemostatic processes through γ-carboxylation of vitamin-K-dependent proteins. Common polymorphisms of VKORC1 gene have also been found to affect interindividual differences in warfarin sensitivity.

Interleukin-6 Gene

In a large-scale association study, 282 Japanese patients with PICH and 2,010 controls were genotyped for 202 polymorphisms of 152 genes that were implicated in vascular biology, platelet function, leukocyte biology, coagulation processes, regulation of the circulation, blood pressure or endocrine function and various metabolic factors, as well as lipid, glucose and homocystein metabolism. It was found that the C allele of the interleukin-6 (IL-6) gene -572G/C polymorphism increased the risk of PICH (OR 1.57, 95% CI 1.21–2.07; p<0.001). It was suggested that IL-6 may damage the vascular wall through induction of matrix metalloproteinases, which degrade the extracellular matrix around blood vessels and thus weaken the vascular wall.[48] However, recently, in a small group of patients IL-6 -174G/C gene polymorphism was not found to be an independent risk factor for PICH.[49]

Primary intracerebral haemorrhage is a complex multifactorial disorder that probably results from an interaction between various environmental factors and the genetic background of the patient.

Engoglin Gene

Endoglin is a glycoprotein in the surface of endothelial cells that interacts with transforming growth factor-β. Endoglin is important for vascular development and structural integrity. Variable mutations in the endoglin gene were found to cause hereditary haemorrhagic telangiectasia. A homozygous 6bp insertion in the endoglin gene was found in 8.7% of PICH patients compared with 2% of controls (OR 4.76, 95% CI 1.28–21.6; p=0.012).[50] The same polymorphism was also associated with increased frequency of intracranial aneurysms.

Angiotensin-converting Enzyme Gene

Angiotensin-converting enzyme (ACE) plays an important role in regulating both the production of angiotensin II and the degradation of bradykinin at the endothelial surface. Angiotensin II, which is the main active product of the renin–angiotensin system, has been linked to vascular remodelling, inflammation and endothelial dysfunction. It was reported that the DD genotype of ACE insertion/deletion (I/D) polymorphism in intron 16 was over-represented in Polish patients with non-lobar PICH (OR 2.13, 95% CI 1.10–4.14; p=0.02). However, after excluding the individuals who were receiving ACE inhibitors and adjusting for other variables, the association was no longer statistically significant.[51] In a previous study, the distribution of ACE genotypes and alleles was the same among the controls and patients.[52] It was shown that ACE I/D polymorphism only partially determines the variation in plasma ACE levels, and it is uncertain whether it represents a functional polymorphism; this may explain the inconsistency between the two studies.

Alpha-1 Antichymotrypsin Gene

Alpha-1 antichymotrypsin (ACT) is an acute-phase protein member of the serine proteinase inhibitors that has been implicated in vascular pathology. ACT has anti-inflammatory properties as it strongly inhibits neutrophil cathepsin G, but it is also known to interact with Aβ peptide, promoting amyloid plaque formation. The TT genotype of ACT A/T signal peptide polymorphism was associated with PICH in Spanish patients (OR 2.80), especially those with normal blood pressure (OR 3.40).[53] By contrast, a study from China reported a more robust association in hypertensive patients.[54] However, these associations were not replicated in a study from Poland[55] and in a group of 147 Greek patients from our department.[56] In our group we observed only a marginal association in the non-hypertensive group (p=0.05). It is possible that in non-hypertensive patients the absence of hypertension unmasks the relatively minor effects of ACT A/T signal peptide polymorphism on the cerebral vasculature, making it more susceptible to haemorrhage.

Lipoprotein a Gene

Elevated lipoprotein a (Lp(a)) levels have been associated with increased risk of cardiovascular diseases, possibly by being implicated in atherosclerotic arterial damage. In a large multicentre study in a Chinese population, low numbers of TTTTA repeats (PNTR polymorphisms) of the Lp(a) gene were found in patients with PICH.[57]

Apolipoprotein H Gene

Apolipoprotein H (ApoH) has been implicated in several physiological pathways including lipid metabolism, coagulation and increased blood pressure. In a study in a Chinese population it was found that the Ser88Asn (G341A) polymorphism was associated with increased risk of PICH.[58]

Platelet Glycoproteins

Glycoproteins Ia, IbA and IIIa are platelet surface receptors for fibrinogen, von Willebrand factor and collagen, playing an important role in platelet adhesion and aggregation. However, genetic polymorphisms of these factors were not found to increase the risk of PICH.[59]

Implementation of genome-wide scans may provide substantial benefits, including the development of genetic markers for determination of specific molecular profiles in individuals and assessment of disease risk.

PAF-H Gene

Platelet-activating factor acetylhydrolase (PAF-H) is implicated in thrombosis. A Val2793Phe substitution in the PAF-H gene has been associated with ischaemic stroke, possibly through increased thrombotic processes. The same mutation was also found to be a risk factor for PICH.[60]

Factor XIII Gene

Blood coagulation factor XIII plays an important role in clot stabilisation by cross-linking fibrin chains. A point mutation in codon 34 (Val34Leu) of XIII gene was known to be protective against thrombotic diseases including myocardial infarction and ischaemic stroke. However, a potential association of Val34Leu and PICH was reported.[61] The authors suggested that the Leu34 allele might cause the formation of weaker fibrin structures that predispose to PICH. Subsequently, this polymorphism was extensively investigated in various populations but with contradictory results.[62–66]

Other Association Studies

Other genetic variants that have been associated with PICH are polymorphisms in the oestrogen receptor alpha gene,[67] the osteoprotegerin gene,[49] factor V-leiden,[63] factor VII[63] and b1-tubulin.[68] Genetic variants not associated with PICH are polymorphisms in the paraoxonase 2 gene,[69] the protein Z gene,[70] the interleukin-1a gene,[71] the methylenetetrahydrofolate reductase (MTHFR) gene,[72] prothrombin,[63] factor VII,[73] the growth-arrest-specific gene[74] and plasminogen activator inhibitor-1 (PAI-1).[66]

Conclusions

PICH is a complex multifactorial disorder that probably results from an interaction between various environmental factors and the genetic background of the patient. Linkage analyses in familial cases of PICH have identified chromosomal loci linked to PICH. In addition, several association studies of sporadic cases have revealed a number of genetic variants that possibly confer susceptibility to PICH. Whole-genome association studies are now feasible via current technology. Implementation of genome-wide scans may provide substantial benefits, including the development of genetic markers for determination of specific molecular profiles in individuals and assessment of disease risk. In the future, this may offer the prospect of early diagnosis, personalised risk assessment and novel genomic-based preventative therapies.[3] ■

Efthimios Dardiotis is a Post-doctoral Fellow at the Institute for Biomedical Research at Technology at CERETETH in Larissa, where he is responsible for the genetic databases of patients with various neurological diseases. He graduated from the Medical School of Aristotle University of Thessaloniki, Greece in 1997 and was a resident in neurology in the Department of Neurology at the University Hospital of Larissa, Greece. In 2007 he completed his doctoral thesis at the Laboratory of Neurogenetics, Faculty of Medicine, University of Thessaly on the genetics of primary intracerebral hemorrhage.

Georgios M Hadjigeorgiou is an Associate Professor of Neurology at the University Hospital of Larissa, Faculty of Medicine, University of Thessalia, and Head of the Laboratory of Neurogenetics at the Institute of Biomedical Research at Technology at CERETETH in Larissa, Greece. Dr Hadjigeorgiou received his MD and PhD from Kapodistrian University of Athens and was a resident in neurology at the Red Cross Hospital in Athens. He was then a post-doctoral research fellow at the University of Milan and Columbia University, New York, where he studied molecular genetics in metabolic myopathies and mitochondrial encephalomyopathies.

1. Qureshi AI, Tuhrim S, Broderick JP, et al., *N Engl J Med*, 2001;344:1450–60.
2. Woo D, Sauerbeck LR, Kissela BM, et al., *Stroke*, 2002;33:1190–95.
3. Rost NS, Greenberg SM, Rosand J, *Stroke*, 2008;39:2166–73.
4. Alberts MJ, McCarron MO, Hoffmann KL, et al., *Neuroepidemiology*, 2002;21:18–21.
5. Iida S, Baumbach GL, Lavoie JL, et al., *Stroke*, 2005;36:1253–8.
6. Palsdottir A, Abrahamson M, Thorsteinsson L, et al., *Lancet*, 1988;2:603–4.
7. Levy E, Lopez-Otin C, Ghiso J, et al., *J Exp Med*, 1989;169:1771–8.
8. Vidal R, Garzuly F, Budka H, et al., *Am J Pathol*, 1996;148:361–6.
9. Herrick MK, DeBruyne K, Horoupian DS, et al., *Neurology*, 1996;47:988–92.
10. Petersen RB, Goren H, Cohen M, et al., *Ann Neurol*, 1997;41:307–13.
11. Mascalchi M, Salvi F, Pirini MG, et al., *Neurology*, 1999;53:1498–1503.
12. Brett M, Persey MR, Reilly MM, et al., *Brain*, 1999;122:183–90.
13. Vidal R, Frangione B, Rostagno A, et al., *Nature*, 1999;399:776–81.
14. Mead S, James-Galton M, Revesz T, et al., *Brain*, 2000;123 (Pt 5):975–91.
15. Nochlin D, Bird TD, Nemens EJ, et al., *Ann Neurol*, 1998;43:131–5.
16. Sanchez-Valle R, Llado A, Ezquerra M, et al., *Eur J Neurol*, 2007;14:1409–12.
17. Hendriks L, van Duijn CM, Cras P, et al., *Nat Genet*, 1992;1:218–21.
18. Levy E, Carman MD, Fernandez-Madrid IJ, et al., *Science*, 1990;248:1124–6.
19. Nilsberth C, Forsell C, Axelman K, *Soc Neurosci Abstr*, 1999;25:297.
20. Grabowski TJ, Cho HS, Vonsattel JP, et al., *Ann Neurol*, 2001;49:697–705.
21. Tagliavini F, Rossi G, Padovani A, *Alzh Reports*, 1999;2:S28.
22. Rovelet-Lecrux A, Frebourg T, Tuominen H, et al., *J Neurol Neurosurg Psychiatry*, 2007;78:1158–9.
23. Cabrejo L, Guyant-Marechal L, Laquerriere A, et al., *Brain*, 2006;129:2966–76.
24. Gould DB, Phalan FC, Breedveld GJ, et al., *Science*, 2005;308:1167–71.
25. Gould DB, Phalan FC, van Mil SE, et al., *N Engl J Med*, 2006;354:1489–96.
26. Breedveld G, de Coo IF, Lequin MH, et al., *J Med Genet*, 2006;43:490–95.
27. Vahedi K, Kubis N, Boukobza M, et al., *Stroke*, 2007;38:1461–4.
28. van der Knaap MS, Smit LM, Barkhof F, et al., *Ann Neurol*, 2006;59:504–11.
29. Joutel A, Corpechot C, Ducros A, et al., *Nature*, 1996;383:707–10.
30. Lesnik Oberstein SA, van den Boom R, van Buchem MA, et al., *Neurology*, 2001;57:1066–70.
31. Choi JC, Kang SY, Kang J H, et al., *Neurology*, 2006;67:2042–4.
32. Nicoll J A, Burnett C, Love S, et al., *Ann Neurol*, 1997;41:716–21.
33. Greenberg SM, Vonsattel JP, Segal AZ, et al., *Neurology*, 1998;50:961–5.
34. McCarron MO, Nicoll JA, *Neurosci Lett*, 1998;247:45–8.
35. Greenberg SM, Rebeck GW, Vonsattel JP, et al., *Ann Neurol*, 1995;38:254–9.
36. Premkumar DR, Cohen DL, Hedera P, et al., *Am J Pathol*, 1996;148:2083–95.
37. Greenberg SM, Briggs ME, Hyman BT, et al., *Stroke*, 1996;27:1333–7.
38. Rosand J, Hylek EM, O'Donnell HC, et al., *Neurology*, 2000;55:947–51.
39. O'Donnell HC, Rosand J, Knudsen KA, et al., *N Engl J Med*, 2000;342:240–45.
40. Alberts MJ, Graffagnino C, McClenny C, et al., *Lancet*, 1995;346:575.
41. Garcia C, Pinho e Melo T, Rocha L, et al., *J Neurol*, 1999;246:830–34.
42. Yamada M, Itoh Y, Suematsu N, et al., *Ann Neurol*, 1996;39:683–4.
43. Chowdhury AH, Yokoyama T, Kokubo Y, et al., *J Epidemiol*, 2001;11:131–8.
44. McCarron M, Muir KW, Weir CJ, et al., *Stroke*, 1998;29:1882–7.
45. Catto AJ, McCormack LJ, Mansfield MW, et al., *Acta Neurol Scand*, 2000;101:399–404.
46. Sudlow C, Martinez Gonzalez NA, Kim J, et al., *Stroke*, 2006;37:364–70.
47. Wang Y, Zhang W, et al., *Circulation*, 2006;113:1615–21.
48. Yamada Y, Metoki N, Yoshida H, et al., *Arterioscler Thromb Vasc Biol*, 2006;26:1920–25.
49. Strand M, Soderstrom I, Wiklund PG, et al., *Cerebrovasc Dis*, 2007;24:418–25.
50. Alberts MJ, Davis JP, Graffagnino C, et al., *Ann Neurol*, 1997;41:683–6.
51. Slowik A, Turaj W, Dziedzic T, et al., *Neurology*, 2004;63:359–61.
52. Catto A, Carter AM, Barrett JH, et al., *Stroke*, 1996;27:435–40.
53. Obach V, Revilla M, Vila N, et al., *Stroke*, 2001;32:2588–91.
54. Fu Y, Xie R, Wang Y, et al., *Zhonghua Yi Xue Za Zhi*, 2002;82:915–17.
55. Pera J, Slowik A, Dziedzic T, et al., *Stroke*, 2006;37:906–7.
56. Dardiotis E, Hadjigeorgiou G M, Dardioti M, et al., *Eur Neurol*, 2008;59:307–14.
57. Sun L, Li Z, Zhang H, et al., *Stroke*, 2003;34:1617–22.
58. Xia J, Yang QD, Yang QM, et al., *Cerebrovasc Dis*, 2004;17:197–203.
59. Iniesta J A, Corral J, Gonzalez-Conejero R, et al., *Cerebrovasc Dis*, 2003;15:51–5.
60. Yoshida H, Imaizumi T, Fujimoto K, et al., *Thromb Haemost*, 1998;80:372–5.
61. Catto AJ, Kohler HP, Bannan S, et al., *Stroke*, 1998;29:813–16.
62. Gemmati D, Serino ML, Ongaro A, et al., *Am J Hematol*, 2001;67:183–8.
63. Corral J, Iniesta J A, Gonzalez-Conejero R, et al., *Blood*, 2001;97:2979–82.
64. Endler G, Funk M, et al., *Br J Haematol*, 2003;120:310–14.
65. Corral J, Iniesta J A, Gonzalez-Conejero R, et al., *Hematol J*, 2000;1:269–73.
66. Reiner AP, Schwartz SM, Frank MB, et al., *Stroke*, 2001;32:2580–86.
67. Strand M, Soderstrom I, Wiklund PG, et al., *Cerebrovasc Dis*, 2007;24:500–508.
68. Navarro-Nunez L, Lozano ML, Rivera J, et al., *Haematologica*, 2007;92:513–18.
69. Xu H W, Yuan N, Zhao Z, et al., *Cerebrovasc Dis*, 2008;25:87–94.
70. Obach V, Munoz X, et al., *Thromb Haemost*, 2006;95:1040–41.
71. McCarron MO, Stewart J, McCarron P, et al., *Stroke*, 2003;34:e193–5.
72. Li Z, Sun L, Zhang H, et al., *Stroke*, 2003;34:2085–90.
73. Greisenegger S, Weber M, Funk M, et al., *Eur J Neurol*, 2007;14:1098–1101.
74. Munoz X, Obach V, Hurtado B, et al., *Thromb Haemost*, 2007;98:406–12.
75. Kokubo Y, Chowdhury AH, Date C, et al., *Stroke*, 2000;31:1299–1306.
76. Martinez-Gonzalez NA, Sudlow CL, *J Neurol Neurosurg Psychiatry*, 2006;77:1329–35.
77. Vernooij MW, van der Lugt A, Ikram MA, et al., *Neurology*, 2008;70:1208–14.
78. Vila N, Obach V, Revilla M, et al., *Stroke*, 2000;31:2103–5.
79. Cho KH, Kim BC, Kim MK, et al., *J Korean Med Sci*, 2002;17:249–53.

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