

The Genetics of Stroke

Stroke is not a single disease, but rather describes a syndrome of different processes all resulting in focal cerebral damage due to disruption of cerebral blood flow. Although the different processes share some obvious risk factors, they have different conventional and genetic risk factor profiles. Most strokes appear to be sporadic, with no obvious patterns of Mendelian inheritance. A minority can be ascribed to a monogenic cause, but genetic factors do also appear to be important in the remainder. There is considerable evidence from twin studies^{1,2}, family history studies^{3,4} and animal models^{5,6} that sporadic stroke is due in part to genetic influences. Rather than being due to a highly penetrant single gene disorder however, common sporadic strokes are thought to arise as a consequence of polygenic or multifactorial influences whereby multiple genes each exert a small influence or risk on phenotype, with individuals showing different combinations of genetic and environmental influences. This presents novel challenges in gene identification, not only due to the small effect size of each genetic influence, but also due to the incomplete penetrance and population stratification that these genetic factors may display. However, recent research suggests that these challenges may not be insurmountable.

Single gene disorders in stroke

When referring to stroke, a distinction must be made between isolated stroke in which there are no additional physical characteristics, and conditions in which stroke is just one feature of a multi-system disorder. CADASIL, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, is the only form of isolated stroke to display familial patterns of inheritance in which the responsible gene has been identified⁷. There are also several single gene disorders in which stroke is a secondary presenting feature in which genes have been identified and areas of linkage mapped, as detailed in table 1.

CADASIL usually presents with at least one of four manifestations, namely lacunar stroke and TIA, cognitive deficits, migraine with aura, and psychiatric disturbance, usually depression, which may precede the onset of stroke (30%). The disease most commonly presents in the 40s but can present from the 20s to 70s. MRI scans show characteristic changes with a combination of lacunar infarcts and white matter high signal or leukoaraiosis (figure 1). The latter often involves the anterior temporal pole and

external capsule. Diagnosis can be made by gene screening or skin biopsy for the characteristic granular osmiophilic material⁸.

CADASIL has been shown to be due to highly stereotyped mutations in the Notch3 gene⁹, a large transmembrane receptor involved in cell fate decisions during embryogenesis and promotion of vascular smooth muscle cell survival¹⁰. Mutations in Notch3 leading to CADASIL all disrupt highly conserved cysteine residues. As a consequence the usual number of six residues is converted to an odd number, resulting in abnormal multimerisation of Notch3 and possibly aberrant cell signalling. The phenotype is variable even within families and to date, despite more than 50 different mutations having been reported, no clear genotype-phenotype correlations have emerged.

Genetics of common stroke

The two stalwarts of genetic analysis for multifactorial stroke remain candidate gene studies and family based linkage studies. Many candidate gene studies have been performed in stroke¹¹, although most have proved inconclusive as a consequence of low power, insufficient sample size, population stratification, poor phenotyping of cases, and failure to appreciate the heterogeneity of stroke¹². More recently these limitations have been increasingly recognised, resulting in improved experimental design and appropriately powered study design and with collaborative ventures to strengthen future research.

Despite the lack of families available to aid stroke research, the most recent and exciting discovery in the field has come from such an approach – the identification of a gene that appears to confer an increased risk of ischaemic stroke, and specifically of cardioembolic and large vessel stroke subtypes¹³. The gene identified, phosphodiesterase 4D (PDE4D) is a regulator of cyclic AMP levels¹⁴, and is proposed to control the level of smooth muscle proliferation and immune function in vessels thereby leading to increased or decreased atherosclerosis and hence ischaemic stroke risk. Although causative mutations within PDE4D have yet to be identified, evidence of altered expression has been shown, with ischaemic stroke patients showing significantly reduced mRNA levels of PDE4D isoforms D1, D2 and D5¹⁵. The mechanism by which this change exerts its effects and predisposes to stroke is currently unclear, due in part to the very recent identification of this gene, and in part to



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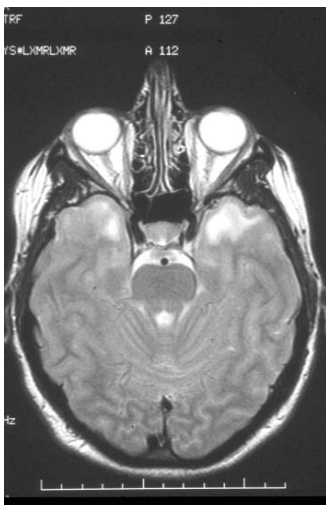


Figure 1. Characteristic MRI finding in a patient with CADASIL. On this FLAIR sequence high signal (leukoaraiosis) can be seen in the white matter and characteristic involvement of the anterior temporal pole is present (arrowed). (copyright with author-HM).

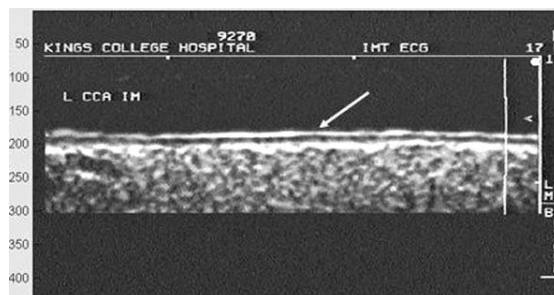
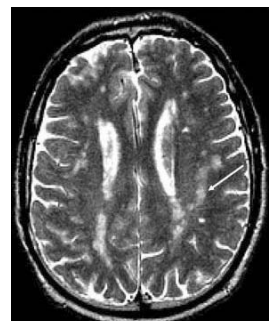


Figure 2. Intermediates phenotypes used in stroke genetic research. A. Common carotid artery intima-media thickness on the posterior wall of the artery. IMT (arrowed) includes the inner bright line and the dark line deep to this. B. White matter hyperintensities (one arrowed) on a T2 weighted MRI scan. Recent data¹⁶ suggest that confluent WMH progress and appear to represent small vessel cerebrovascular disease. (copyright with author-HM).



Disorder	Gene	Mechanism of Action	Type of Stroke
CADASIL – cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy	Notch3	Pure stroke syndrome affecting small cerebral vessels	Small vessel
CARASIL – cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy	Unknown	Pure stroke syndrome affecting small cerebral vessels	Small vessel
CRV & HERNS – cerebro-retinal vasculopathy and hereditary endotheliopathy with retinopathy, nephropathy and stroke	Linkage to 3p21.1-21.3	Microangiopathy of the brain in combination with vascular retinopathy	Small Vessel
MoyaMoya disease	Linkage to 3p24.2-26, and 17q	Spontaneous occlusion of basal intracerebral arteries	Large intracranial vessel disease
Ehlers-Danlos syndrome type IV	Collagen 3A1	Collagen disorder, 10% of patients show neurovascular complications	Large vessel disease
Marfan Syndrome	Fibrillin	Musculoskeletal disorder 4% show neurovascular complications	Large vessel disease
Pseudoxanthoma Elasticum	ABCC6	Connective tissue disorder with high prevalence of cardiovascular complications	Large vessel disease
Fabry disease	/ galactosidase A leading to damaged vascular endothelial cells	Lysosomal enzyme deficiency disease	Large and small vessel
Sickle Cell Disease	Haemoglobin S	Stroke, TIA or neurological complications present in up to 25% of cases	Large and small vessel disease
HHT – Hereditary hemorrhagic telangiectasia	Endoglin and ALK1	Vascular dysplasia with variable expressivity leading to venous malformations	Embolic stroke

Table 1. Rare single gene disorders with stroke as a primary or significant secondary clinical characteristic. Although multiple genes have been identified, the low frequency of these conditions in the general population means their clinical significance is limited.

the complexity of its downstream pathway and the multitude of effects cAMP exerts on a cell as a secondary messenger.

The PDE4D gene contributes to only a minority of strokes, and its association with stroke needs to be replicated in other independent populations. Nevertheless its identification is ‘proof of principal’ that taking the genetic approach to understanding and eventually treating stroke is sound.

Intermediate phenotypes

Stroke involves a series of pathophysiological processes often occurring over many years. Each may be influenced by a number of different genes. One way of studying a simplified system in which fewer genes may be involved is

the use of intermediate phenotypes, or stages, in the disease process. Two are being widely used in stroke genetics, namely carotid artery intima-media thickness (IMT) and plaque quantified by ultrasound as an intermediate phenotype for large vessel disease stroke¹⁴, and white matter hyperintensities on MRI as an intermediate phenotype for small vessel disease stroke (Figure 2)¹⁵. Both have been shown to have a significant genetic component in twin and family studies. Their use has emphasised the importance of gene-environment interactions, which should be taken into account in study design¹⁶. The study of intermediate phenotypes allows larger populations to be collected with relative ease, but suffers from the effects of phenocopy and heterogeneity in that the phenotype may be due to variable factors and not all of the cohort will go

on to display future stroke events. Despite this the use of intermediate phenotypes remains of importance, not least because it allows the use of a more statistically powerful continuous variable rather than a dichotomous presence or absence variable. It also overcomes the problems of covert disease whereby a control in a case-control study may have sub-clinical cerebrovascular disease.

Conclusions

The genetics of multifactorial disease remains a complex area. Yet recent advances in the identification of PDE4D and the confirmation that the genetic component of diseases such as stroke can be found give hope to the idea that, little by little, we may understand how our genetic makeup and our environment interact to cause stroke. Such advances will require large collaborative studies with rigorous design and phenotyping.

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