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, family history studies, and animal models 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 cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, the only form of isolated stroke to display familial patterns of inheritance in which the responsible gene has been identified. 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. 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 material.

CADASIL has been shown to be due to highly stereotyped mutations in the Notch3 gene, a large transmembrane receptor involved in cell fate decisions during embryogenesis and promotion of vascular smooth muscle cell survival. 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 mislocalisation 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 stroke, 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 stroke.

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 subtypes. The gene identified, phosphodiesterase 4D (PDE4D) is a regulator of cyclic AMP levels, 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 D5. 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 external capsule. Diagnosis can be made by gene screening or skin biopsy for the characteristic granular osmiophilic material.

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 data suggest that confluent WMH progress and appear to represent small vessel cerebrovascular disease. (Copyright with author-HM).
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 stroke, and white matter hyperintensities on MRI as an intermediate phenotype for small vessel disease stroke (Figure 2). 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 design. 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

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

References

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