Abstract

Subarachnoid haemorrhage (SAH) results from leakage of blood into the subarachnoid space and carries high morbidity and mortality. However, there is limited understanding to date, of the risk factors, cellular, intermediate biochemical and genetic traits predisposing to SAH. Nevertheless, in conjunction with improved methods of diagnostic imaging and less invasive approaches to preventing aneurysmal rupture, there may be utility in gaining a better understanding of the pathogenesis and in identifying pre-disease markers. Additionally, it is not impossible that drugs of value (e.g. matrix or endothelial modifiers) could become available. Several different clinical subtypes can be recognised, distinguished by arterial or venous involvement, presence of unruptured arterial aneurysms, and apparently ‘sporadic’ and ‘familial’ occurrences. Epidemiological risk factors include alcohol consumption and smoking: hypertension is a risk factor for rupture. About 10% seem to reflect strong family history and this subset may be particularly illuminating with respect to the molecular pathogenesis. Haemodynamic stress and poor vascular structure may be the main mechanisms of pathogenesis. The epidemiological and statistical evidence for familial megaphenic genes and modifier genes is reviewed. This review focuses on the pathogenesis, as opposed to inflammatory response to SAH. It sets in context the roles of specific genes and their protein products, such as polycystin (PKD1), fibrillin (FBN1), collagen III (COL3A1), elastin (ELN), protease inhibitor or α1-antitrypsin (PI) and proteases. These considerations illustrate the shortfalls in current knowledge, the needs of future biochemical and cellular research and their potential implications for future prevention of this often fatal condition.

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Index terms: Subarachnoid haemorrhage; Stroke; Collagen; Elastin; Aneurysm; Intracranial aneurysm

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1. Clinical overview

Subarachnoid haemorrhage (SAH) is a condition caused by the escape of blood from a cerebral artery into the subarachnoid space along the surface of the brain. Spontaneous SAH usually presents with a sudden onset explosive headache followed by various degrees of deterioration of conscious level and of neurological status. There are often warning symptoms caused by small leaks of blood (warning leak, sentinel bleed), but unfortunately these are most often recognised retrospectively. SAH has a multitude of aetiologies but it is generally accepted that a ruptured intracranial aneurysm is the source of spontaneous SAH in about 80% of cases (Kalimo, Kaste, & Haltia, 2002). The other causes and general and molecular pathology are considered in more detail in the next sections. SAH is diagnosed by a detailed history, supported by a CT scan of the head. Small CT-negative bleeds are diagnosed by lumbar puncture and CSF spectroscopy to identify blood breakdown products, which can be detected between 12 h and 2 weeks after the bleed (Vermeulen & van Gijn, 1990). The mortality of diagnosed cases is about 40% within the first 30 days despite the best current therapy. This does not take the patients who die from undiagnosed SAH into account. Less than 25% have a good functional outcome and the disease has dramatic impact on the lives of carers and relatives (Pritchard, Foulkes, Lang, & Neil-Dwyer, 2001). Prevention of SAH is therefore of paramount importance. The two main aims of current treatment are to prevent rebleed and to counteract the effect of the initial bleed. Where an aneurysm is identified, rebleed is prevented by exclusion of the aneurysm from the circulation. The results of a recent multicentre study show that the best outcome is achieved by occluding the aneurysm with coils via the endovascular route. The alternative method is open microsurgery where a clip is placed across the aneurysm neck. Patients almost invariably require neurointensive care treatment to counteract the effects of the subarachnoid blood (for example cerebral artery spasm, hydrocephalus and brain swelling) and maintain adequate blood supply to the brain.

Counselling is essential and based on the current understanding of the pathogenesis of SAH. On account of the severity of SAH, patients and/or relatives usually seek information regarding risk factors and heritability. With the poor understanding of the pathogenesis the neurosurgical advice has been based on the known risk factors and known genetically determined risk conditions (Fig. 1). The aim has been to identify high-risk relatives in order to undertake effective screening with the use of MRI or conventional angiography. The current practice in most centres is to offer screening to first degree relatives in families with more than one member with intracranial aneurysms, and in addition to other relatives with risk conditions or a heavy risk factor load. The decision is often difficult and screening is sometimes performed on a psychological rather than rational indication. The decision to offer screening has had to be balanced with the significant mortality/morbidity of treatment of unruptured aneurysms (The International Study of Unruptured Intracranial Aneurysms Investigators, 1998). As a result of the International Subarachnoid
Fig. 1. Schematic overview of contributory factors to subarachnoid haemorrhage.

Aneurysm Trial (ISAT) study (ISAT, 2002), the less invasive intravascular treatment with coiling has been found to be safer than open surgery and has thereby potentially moved the balance towards screening more relatives, although there are really no new methods to identify relatives at risk. Identification of genes or biochemical, cellular or other markers involved in the molecular pathogenesis of SAH would be of fundamental importance, not only to identify relatives at high risk, but also with a potential for screening of individuals in the general population, who carry a heavy load of external risk factors (Fig. 1).

1.1. General risk factors, causes and outcomes

Subarachnoid haemorrhage (SAH) accounts for 10% of cerebrovascular disease and has an annual incidence of 10–15 per 100,000, with peak incidence of non-traumatic SAH from 40 to 60 years of age and an overall female/male ratio of 3/2 particularly after the age of 50 years. The prevalence of unruptured intracranial aneurysms detected at autopsy ranges from 0.2 to 8.9% (Tomasello, D’Avella, Salpietro, & Longo, 1998). This suggests that most intracranial aneurysms do not rupture. The commonest sites for intracranial aneurysms are shown on Fig. 2. Risk factors include hypertension, cigarette smoking, low body mass index, infection, excess consumption of alcohol or coffee, cocaine and amphetamine abuse, family history of intracranial aneurysms and some

![Commonest sites for Saccular Aneurysms](image-url)
hereditary conditions (see further) (Isaksen, Egge, Waterloo, Romner, & Ingebrigtsen, 2002; Kissela et al., 2002).

Although it may be possible to determine the cause of a subarachnoid haemorrhage at post mortem, a truer picture of the causes of subarachnoid haemorrhage is obtained by cerebral angiography. Defining the major causes of subarachnoid haemorrhage by cerebral angiography reveals three categories of vascular pathologies (Kalimo et al., 2002):

1. **Ruptured saccular aneurysm of a cerebral artery** in ~80% of cases.
2. **Bleeding from an arteriovenous malformation** in 5–10% of patients. Arteriovenous malformations are usually present from birth and arise in a variety of different forms. Neural crest cells are major contributors to mesenchymal structures in the head and neck including arteries (Etchevers, Vincent, Le Douarin, & Couly, 2001) and disorders of neural crest development may be a major factor in the formation of arteriovenous malformations (Bhattacharya et al., 2001).
3. **No cause** is identified in 10–15% (Fogelholm, Hernesniemi, & Vapalahti, 1993) and in 2/3 of these cases the bleed fulfils the criteria of a perimesencephalic SAH, which has a very low risk of rebleed and a better outcome than aneurysmal SAH (Marquardt, Niebauer, Schick, & Lorenz, 2000).

Other causes of subarachnoid haemorrhage include rupture of a mycotic aneurysm in which the vessel wall is weakened by bacterial (Frazee, Cahan, & Winter, 1980) or fungal (Horton, Abbott, & Porro, 1976) infection and the artery ruptures, and trauma in which a blood vessel in the subarachnoid space is injured and bursts. SAH is also associated with aortic coarctation and hypertension and with tumours, vasculitis and bleeding diatheses. Trauma is probably the most frequent cause of SAH, but the significance of this type of SAH is difficult to assess as it usually overshadowed by the effect of other simultaneous traumatic brain lesions.

Of the above causes of SAH, the familial causes may be the most illuminating to pathogenetic pathways because they may represent the paradigm of single isolated gene lesions representing one protein product in one pathway or structure important to the maintenance of normal structure and function of the cerebral vasculature.

### 1.2. Evidence for familiality in subarachnoid haemorrhage and intracranial aneurysm

Some early (1950s–1970s) case reports suggested familial occurrences of SAH and occurrences in identical twins. The advent of computer tomography scanning, then magnetic resonance imaging, led to the pre-symptomatic recognition of intracranial aneurysms and as a consequence, enhanced recognition of an apparently familial subset of intracranial aneurysm (IA) and subarachnoid haemorrhage (SAH).

Approaching 300 families have been described in the literature (e.g. De Brueckere, Perusse, Cantin, Bouchard, & Mathieu, 1996; Schievink, Schaid, Rogers, Piepgras, & Michels, 1994).

Familial occurrence is important to our understanding of the disease because if specific gene lesions occur, their identification and characterisation of the cognate protein product will define a pathway of aetiology. Different molecular genetic approaches may be suitable, dependent on whether heritability is monogenic, oligogenic or polygenic. It is therefore important to be certain both that there is heritability and to establish what types of heritability occur. Several different types of study have attempted to clarify this important question. These have included prevalence studies, cohort studies including incidence studies of subarachnoid aneurysm or haemorrhage in relatives, prognostic studies of familial versus non-familial SAH, case-control and descriptive case series analyses. Specific genetic studies have examined SAH occurrence in first and second degree relatives. Characteristics of sporadic and familial disease have also been compared. The principal conclusions which have been drawn from these studies are as follows. The case series have shown that frequency of subarachnoid haemorrhage varies amongst racial groups (Ronkainen et al., 1998). Prevalence of intracranial aneurysms range from 4% (Raaymakers, 1999) to 10% (Kojima et al., 1998) in the familial groups. The Finnish and Japanese studies both calculated population prevalence that was lower than in the familial groups (Kojima et al., 1998; Ronkainen et al., 1998). However, in the Japanese study the population was highly selected, representing individuals...
presenting for evaluation for brain diseases, which may account for the population prevalence observed to be higher than in the familial groups of some of the other studies. Clearly some of the frequency variation has depended on the mechanisms of ascertainment, and on the sensitivity and specificity of screening methods used. For intracranial aneurysm, magnetic resonance angiography shows 98% agreement with conventional angiography (Ronkainen et al., 1995).

In two studies of incidence of SAH in relatives (Gaist et al., 2000; Wang, Longstreth, & Koepsell, 1995) all SAH patients of interest were ascertained from a nationwide or specified geographical area and SAH was confirmed using specific diagnostic criteria. The nationwide study of SAH in relatives constructed prospectively in Denmark (Gaist et al., 2000) showed a three-five-fold increased incidence of SAH in first degree relatives compared with the general population. The retrospective study by Schievink et al. (1995) showed a four-fold increase in risk for first degree relatives, indicating that familial aggregation of ruptured aneurysms is not fortuitous but represents a distinctive epidemiological pattern. By contrast, the only case-control study of patients and relatives with SAH yielded an odds ratio of 1.8 for first degree relatives. However, this study used self-reported history rather than specific diagnostic criteria (Wang et al., 1995). Few studies have attempted to determine pattern of inheritance. However, Schievink et al. (1994) undertook a segregation analysis of published pedigrees. This segregation analysis was unable to distinguish between the various transmission models but concluded that risk of subarachnoid haemorrhage is genetically heterogeneous with some families being consistent with an autosomal dominant model of transmission, some autosomal recessive and perhaps some X-linked families. However, the authors also recognised a number of possible biases which could account for the failure of a single segregation model to explain the heritable risk of subarachnoid haemorrhage, so the failure of fit to a single segregation model cannot per se be taken as proof of more than one mode of inheritance. A large population based genealogy study from the Saguenay Lac-Saint-Jean region permitting recognition of consanguinity found no evidence suggesting autosomal recessive inheritance, which consanguinity predisposes (De Braekeleer et al., 1996). The observed coefficient of inbreeding was not higher in intracranial families than in a control population, but there was a diminishing frequency of aneurysms between first, second and third degree relatives supporting an autosomal dominant model.

It has also been recognised in these studies that there are characteristic clinical and pathological features of familial cases which seem to distinguish them from sporadic cases. Specifically, familial aneurysms rupture at a younger age, on an average 5 years earlier (Bromberg, Rinkel, Algra, Limburg, & van Gijn, 1995; Kasuya, Onda, Takeshita, Hori, & Takakura, 2000; Leblanc, Melanson, Tampieri, & Guttmann, 1995; Lozano & Leblanc, 1987; Ronkainen, Hernesniemi, & Tromp, 1995; Schievink et al., 1995). Additionally, the aneurysms in clearly familial cases rupture at a smaller size (Lozano & Leblanc, 1987; Ronkainen, Hernesniemi, et al., 1995; Lozano and Leblanc (1987) showed using multivariate methods that 70% of familial intracranial aneurysms had ruptured by age 50 years compared with 43% of non-familial aneurysms. Also, consistently, aneurysms of the anterior communicating artery complex are underrepresented and those of the middle cerebral artery are overrepresented among familial cases (Bromberg et al., 1995; Kasuya et al., 2000; Leblanc et al., 1995; Lozano & Leblanc, 1987; Ronkainen, Hernesniemi, et al., 1995; Schievink et al., 1995). However, the studies disagree about the evidence for female preponderance and aneurysm multiplicity in familial intracranial aneurysms, although aneurysm multiplicity does seem to be a frequent observation in familial cases.

Similarly there is no agreement in prognostic studies concerning the outcome in familial versus non-familial subarachnoid haemorrhage using graded outcomes at discharge from hospital or at 12 months after the bleed. Nevertheless, these pathological and anatomical patterns point to distinct and specific cellular and molecular pathology in families showing evidence of a single megaphenic gene effect.

2. Tissue and cellular pathophysiology

2.1. Pathology

The majority of subarachnoid haemorrhages are due to the rupture of arteries and especially rupture of sacular aneurysms. In humans, the subarachnoid space
contains cerebrospinal fluid and forms a water-jacket around the brain. Large and medium sized arteries and veins reside in the subarachnoid space before they penetrate the surface of the brain to supply the cerebral cortex and deep white and grey matter. When subarachnoid haemorrhage occurs, therefore, blood is released into the subarachnoid space at arterial pressure and spreads diffusely over the surface of the brain bathing arteries in the subarachnoid space with fresh blood (Kalimo et al., 2002). Under these circumstances arterial spasm occurs and this results in cerebral ischaemia and infarction (Vermeulen & van Gijn, 1990). Mortality rates for rupture of saccular aneurysms are high either due to cerebral infarction or aneurysms bursting into the brain causing intracerebral haemorrhage. Re-bleeding from saccular aneurysms 1–7 days after the initial haemorrhage is common thus increasing the mortality rate (Rosenorn, Eskesen, Schmidt, & Ronde, 1987).

2.2. Pathology of saccular aneurysms

By definition, a saccular aneurysm is a berry-shaped or multi-lobed outpouching on a major cerebral artery usually associated with the circle of Willis at the base of the brain. Such aneurysms may be discovered incidentally at post mortem or may be revealed as a result of subarachnoid haemorrhage. They are distinguished by their shape and pathogenesis from fusiform aneurysms (due to dilatation of an atherosclerotic artery especially the basilar artery); mycotic aneurysms (due to focal necrosis of an artery wall following bacterial or fungal infection; dissecting aneurysms in which the blood ruptures into the wall of an artery and separates its layers often resulting in occlusion of the vessel. Dissecting aneurysmas of the carotid, middle cerebral and vertebral arteries are usually caused by trauma (Kalimo et al., 2002).

Some 60% of saccular aneurysms are diagnosed or found incidentally at post mortem in patients between 40 and 60 years of age. Less than 5% occur under the age of 20 years (Kalimo et al., 2002). About 12–15% of saccular aneurysms are familial and occur at a younger age than the sporadic aneurysms. Saccular aneurysms show a restricted location with 85–90% arising on the terminal part of the internal carotid artery or on the major branches of the anterior portion of the circle of Willis (Fig. 2). The internal carotid artery is the most frequent site (40%), followed by the anterior communicating artery (30%) and the proximal portion of the middle cerebral artery (20%). In adults, 5–10% of aneurysms are associated with the posterior cerebral or vertebral arteries whereas in children 40–45% of aneurysms occur in the posterior cerebral circulation (Kalimo et al., 2002). Multiple saccular aneurysms occur in 10–31% of patients, most frequently associated with the middle cerebral artery. Saccular aneurysms occur on the feeding arteries of arteriovenous malformations in 10% of cases (Batjer, Suss, & Samson, 1986), adding support to the hypothesis that haemodynamic stress plays a significant role in the pathogenesis of aneurysms.

The majority of saccular aneurysms occur at or near branches of major cerebral arteries around the circumference of Willis. They vary in size from 3 to 4 mm to the giant aneurysms ranging from 25 mm in diameter to 4–5 cm in exceptional cases. Although many are shaped like berries there is considerable variation in shape and they are often multi-lobed. Some aneurysms are almost completely destroyed during rupture and subarachnoid haemorrhage, others have thin translucent walls and a point of rupture at the apex. Many aneurysms are thick walled and opaque. Variation in shape not only applies to the fundus of the aneurysm but also to the neck by which which the aneurysm arises from the parent artery. Some aneurysms have very narrow necks whereas others have a broad neck comparable with the diameter of the aneurysm itself.

Saccular aneurysms are distinguished from fusiform aneurysms by their neck and not being in line with the artery. Multiple aneurysms are notable in familial cases, with different epidemiological and clinical characteristics (see Section 1.2); they can also occur in some sporadic cases. In the case of specific gene defects, the aneurysmal characteristics may differ. In Ehlers-Danlos syndrome (EDS) type IV (see Section 3.2), fusiform rather than saccular aneurysms are observed (Mirza, Smith, & Lim, 1979).

Although saccular aneurysms may extend inferiorly from the circle of Willis, some protrude superiorly into the brain substance and may thus be associated more with massive intracerebral or intraventricular haemorrhage rather than with subarachnoid haemorrhage.

All arteries and veins on the surface of the brain are located in the subarachnoid space between the thin outer layer of arachnoid mater and the delicate...
of the cerebral ventricles ensues (brospinal fluid and thus hydrocephalus with dilatation of the subarachnoid space, impedes the drainage of cerebrospinal fluid from the periventricular spaces). Arteries within the subarachnoid space may undergo spasm when surrounded by fresh blood and this results in poor cerebral perfusion and the ischaemia may be so severe that infarction occurs in the areas supplied by those arteries. Disruption of cerebrospinal fluid flow within the subarachnoid space may occur both acutely and some years after subarachnoid haemorrhage as the blood becomes organised into a saccular aneurysm. The wall of the aneurysm itself is composed of dense fibrous tissue of varying thickness. At the apex of an aneurysm the fibrous tissue may be very thin and the smooth muscle layer of the artery wall becomes attenuated and 70% and this has highlighted the probability that most sporadic aneurysms are due to ageing effects on the arteries.

Cerebral arteries in infants are vessels with a relatively thin smooth muscle coat (media) and a lumen lined by endothelium abutting on to an internal elastic lamina. There is little connective tissue separating internal elastic lamina from the endothelium and the internal elastic lamina itself is convoluted when examined at post mortem, as reflects the elasticity of the artery wall. There is probably minimal turbulence at the bifurcation (Fig. 3a). With ageing, and probably due to haemodynamic stress upon the endothelium, layers of fibrous tissue develop between the endothelium and the internal elastic lamina (Mordant & Weller 2002, unpublished observation). This decreases the elasticity of the vessel wall and furthermore raises mounds or pads of fibrous tissue under the endothelium. Such pads are particularly prominent at vessel bifurcations thus gradually the sharp V-shaped bifurcation becomes rounded (Fig. 3b). This change in shape of the bifurcation may alter the direction of haemodynamic stress on the bifurcation resulting in pressure to form an outpouching at the bifurcation (Fig. 3c). It has long been observed that the smooth muscle coat of arteries and even the internal elastic lamina may be defective at the bifurcations of cerebral arteries and this may be one feature that predisposes these regions of an artery to the formation of aneurysms (Fig. 4) (Fujimoto, 1996).

On microscopic examination of saccular aneurysms, the smooth muscle wall (media) and the internal elastic lamina of the artery end abruptly at the neck of the aneurysm. The wall of the aneurysm itself is composed of dense fibrous tissue of varying thickness. At the apex of an aneurysm the fibrous tissue may be very

2.3. Pathogenesis and the stages involved in the formation of saccular aneurysms

About 12–15% cases of saccular aneurysm are familial, often with an autosomal dominant pattern of inheritance (Kalimo et al., 2002). There is an increased incidence of saccular aneurysms in families with polycystic kidney disease, fibromuscular dysplasia, and moyamoya disease and other connective tissue disorders including Marfan syndrome and EDS type IV. Although originally hypertension was thought to be a major factor in the formation of aneurysms, it appears to play a minor role in the formation of aneurysms although it may be associated with their rupture. Other factors such as cigarette smoking increase the risk of subarachnoid haemorrhage although the mechanisms are unclear (Fogelholm & Murros, 1987).

Some 85–90% of saccular aneurysms are sporadic with no obvious predisposing systemic factors. In these cases, it appears that haemodynamic stress at branches of the circle of Willis is a major factor in the pathogenesis of saccular aneurysms (Sheffield & Weller, 1980; Weller, 1995). Branching patterns of the circle of Willis show wide individual variation. In many cases, the branches are asymmetrical. The majority of aneurysms occur between the ages of 40 and 70 and this has highlighted the probability that most sporadic aneurysms are due to ageing effects on the arteries.

Thus, the major complications of ruptured saccular aneurysms are either due to intracerebral or intraventricular haemorrhage or due to the effects of blood within the subarachnoid space.
Fig. 3. Pathogenesis of saccular aneurysms: (a) in an infant artery there would be little turbulence of blood flow past the V-shaped carina of the artery bifurcation; (b) haemodynamic stress damages the endothelium, pads of fibrous scar tissue form and change the conformation of the vessel carina; (c) with the change in the direction of the haemodynamic stress, there is out-pouching of an aneurysm at the carina.

thin and this is the preferential site of rupture. In larger aneurysms, layered thrombus may be formed on the inner aspect of the aneurysm wall and there may be little residual lumen. Although much is known about the structure and fate of saccular aneurysms and the evolution of their structure can be presumed, the role of individual components such as endothelium, fibrous tissue, internal elastic lamina and smooth muscle cells in the formation of aneurysms is unclear. As pads of fibrous tissue and aneurysms in cerebral vessels develop very slowly it is rare to glimpse any of the intermediate

Fig. 4. Variations in the structure of cerebral artery bifurcations. In a proportion of arteries, there are gaps in the smooth muscle media and internal elastic lamina.
Fig. 5 sets out the predicted stages in the formation of a saccular aneurysm drawing information from the homologous tissue reactions that occur during the formation of atherosclerotic plaques in arteries in many regions of the body. Fig. 5a shows damage to the endothelium from haemodynamic stress which results in the deposition of platelets and fibrin on the surface of the vessel wall (Fig. 5b). Monocyte–macrophages from the blood or vessel wall remove the thrombus on the wall of the artery (Fig. 5c) and as (Fig. 5d) fibroblasts form collagenous scar tissue of the small intimal pad, the endothelium grows over the surface to reconstitute the vessel wall lining. Repeated episodes of damage and scarring ensure the enlargement of intimal pads and the changes of shape of the vessel wall leading to the haemodynamic forces extruding the aneurysmal sac at the vessel bifurcation. Genes encoding the proteins and enzymes involved in the cellular pathogenesis of saccular aneurysms offer themselves as possible candidates for the molecular pathogenesis of subarachnoid haemorrhage. Although hypertension appears to be a significant risk factor for the rupture of saccular aneurysms, no clear association with structural components of the artery is apparent other than the increased stress on the vessel wall itself (Coutard, 1999; Peters et al., 2001).

2.4. Cellular and molecular architecture of the vessel wall

The cerebral arteries lack an external elastic lamina but are otherwise similar to other arteries. Arteries comprise sequentially from the lumen: a monolayer of lining endothelial cells; an intima bounded by the internal elastic lamina; a medial layer; an external elastic lamina; and adventitia. A cellular and molecular overview is schematised in Fig. 6.

The elastic laminae mainly have a longitudinal arrangement of fibres. These structures are responsible for dilatation and recoil. The fibres contain an elastin core formed from the polymerisation of tropoelastin molecules which have a random coil structure but which are cross-linked by lysyl oxidase. Lysyl oxidase, a Cu(II)-dependent enzyme, cross-links four lysine sidechains to form the unique desmosine moiety. These sidechains may belong to up to four different polypeptide chains, including those of other arterial wall proteins such as fibrillins and collagens. Within the elastic lamina, the elastin core is modelled onto a microfibrillar lattice, itself made from fibrillin-1 and -2. These are structurally very similar, but display different temporal and spatial expression patterns (Zhang et al., 1994; Zhang, Hu, & Ramirez, 1995). The main content of fibrillins is tandem repeats of calcium-binding epidermal growth factor-like...
domains interspersed by cysteine-rich sequences homologous to a TGF-β binding protein motif. Fibrin monomers polymerise head-to-tail to form microfibrils. Both linear, lateral and three-dimensional interactions are stabilised by calcium (Kielty & Shuttleworth, 1995). The magnitude and direction of stresses on the vessel determines the shaping of the elastic fibres. Microfibrils are distributed throughout the arterial wall as an architecture of flexible links, whereas the elastic fibres are longitudinal in the internal elastic lamina of the cerebral artery but radial and concentric in the tunica media.

The other major extracellular constituent of the arterial wall is the collagenous network, which contains types I and III collagen. Type III collagen is specifically associated with vascular diseases (see further) whereas type I collagen is much more generally expressed. Type III fibres (reticular fibres) seem to form particularly in tissues subjected to periodic stress. Type III collagen is a homotrimer of α1 subunits. The three subunits nucleate self-assembly from their C-termini. Critical elements to stable folding and assembly include the occurrence of glycine at every third amino acid position and the hydroxylation of lysines and prolines occurring in the positions immediately preceding glycines in the sequence (van der & Garrone, 1991).

A range of proteases (e.g. matrix metalloproteinases, elastase) and their inhibitors (TIMPs, α1-antitrypsin, α2-macroglobulin), growth factors and cytokines determine the modelling and turnover of the vascular wall, secreted by or regulating the smooth muscle cells abundant in the tunica media, or introduced by monocytes, macrophages and polymorphs arriving at the endothelial surface and fibroblasts particularly in the adventitial layer responsible for tensile strength.

Both structure of individual components, their interactions and turnover are equally important to the overall integrity of the vessel wall and in this context both environmental factors and genetic factors can exert diverse effects. It is easy to imagine, for example, how a haploinsufficiency or defective protein (dominant negative effect) could lead to aneurysm, but less obvious how that could lead to stenosis. However, considering the interdependences of remodelling, a deficiency of one component can lead to an overexpression of another, as illustrated (see further) by elastin deficiency in supravalvular aortic stenosis.

3. Molecular pathology

Several genes and their cognate proteins have been specifically implicated in the molecular pathology of aneurysms (Table 1) and these are considered in detail in the following Sections 3.1–3.6.

3.1. PKD1 gene and polycystin

Adult polycystic kidney disease is an autosomal dominant disorder in which renal cysts form, leading to progressive loss of glomerular filtration and subsequently to renal failure and end-stage renal disease. As early as 1960, Ditlefsen and Tonjum (1960) described a family containing 15 cases with polycystic kidney disease including 6 who had suffered from cerebral haemorrhage including one case who had been proven to have a middle cerebral artery aneurysm. Subsequent surveys (e.g. Chapman et al., 1992) have contrasted the frequency of asymptomatic intracranial aneurysms in polycystic kidney disease (upper 95% confidence bound 9%), with that in the general population (1%), although the lower 95% confidence bound makes it possible that there is no difference from
Table 1
Proteins of potential importance in intracranial aneurysm

<table>
<thead>
<tr>
<th>Protein</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Polycystin</td>
<td>Mutated in polycystic kidney disease, in which IA seems to be increased</td>
</tr>
<tr>
<td>Collagen III</td>
<td>Obvious candidate on account of the structural role of type III collagen in the arterial wall; deficient in some cases of SAH; gene defects cause Ehlers-Danlos syndrome type IV which predisposes arterial ruptures; similar outcomes for mouse gene knockout</td>
</tr>
<tr>
<td>Elastin</td>
<td>Obvious candidate on account of role of elastic laminae in arterial integrity; hypothesis-free linkage tests of genome in sib pairs affected by IA, show linkage to genome region containing elastin gene—also strong association of IA with a specific elastin haplotype in sib pairs</td>
</tr>
<tr>
<td>α1-Antitrypsin (protease inhibitor)</td>
<td>Major inhibitor of elastase, therefore obvious candidate; suggestion in case studies of association of deficiency genotypes (of alleles Z and S) with IASAH</td>
</tr>
<tr>
<td>Collagen IV</td>
<td>Intimal basement membrane component; mutated in Alport’s syndrome; one case report of IA prior to traumatic SAH in 14-year-old boy in Alport’s syndrome</td>
</tr>
<tr>
<td>Fibrillin-1</td>
<td>Structural role in arterial wall microfibris, mutated in Marfan syndrome of which a major cause of mortality is abdominal aortic aneurysm and rupture; unproven role in IA</td>
</tr>
<tr>
<td>Collagen I</td>
<td>Structural role in cerebral artery, but wide tissue expression profile</td>
</tr>
<tr>
<td>Fibrillin-2</td>
<td>Close homology and co-function with fibrillin-1</td>
</tr>
<tr>
<td>Matrix metalloproteinases, elastase, inhibitors</td>
<td>Functional role in vessel wall turnover</td>
</tr>
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population risk. Nevertheless, there can be no doubt that in individual families with specific polycystic kidney disease mutations, intracranial aneurysms and haemorrhage can occur very frequently. The pleitropy of the disease is further marked by other extrarenal manifestations including cysts in the gastrointestinal system and diverse cardiac vavular defects. Hossack, Leddy, Johnson, Schrier, and Gabow (1988) concluded that the latter defects marked a fundamental biochemical defect in the extracellular matrix. The gene causing adult polycystic kidney disease, named PKD1, was mapped to an extremely CpG-rich region in human chromosome 16p13.3 (Germino et al., 1992) and its complete structure was reported by the International Polycystic Kidney Disease Consortium in 1995. The 14.5kb transcript comprises 46 exons encoding a 4304-amino acid protein named polycystin. The N-terminal half of the protein contains leucine-rich repeats flanked by cysteine-rich structures, LDL-A and C-type lectin domains and fourteen 80-amino acid units of an unknown type of domain. These domains suggest that polycystin participates in protein–protein and protein–carbohydrate interactions in the extracellular matrix. Immunostaining shows the presence of polycystin in arterial smooth muscle cells and myofibroblasts; and in intracranial aneurysms in ADPKD there is disruption of elastic laminae (Griffin, Torres, Grande, & Kumar, 1997). Polycystin 1, together with polycystin 2, is thought to function as a part of a multiprotein membrane-spanning complex involved in cell-cell and cell-matrix interactions. Polycystin 1 can initiate signal transduction, leading to the activation of various downstream effectors including heterotrimeric G-proteins, protein kinase C, mitogen-activated protein kinases, β-catenin and the AP-1 transcription factor. At least in the renal context, PKD cells respond to raised cyclic AMP by a paradoxical increase in the rate of cell proliferation (Calvet & Grantham, 2002). Reeder (1992) proposed a two-hit mutational model for PKD1, a model well recognised in the field of autosomal dominant cancers. Since most nephrons appear to be normal, it could be that only a somatic mutation of the second PKD1 allele in cells already affected by a germ line defect of one PKD1 allele, leads to cyst formation. Such a two-hit model should also be considered for the extrarenal manifestations. Indeed, for autosomal dominant forms of aneurysms in general (see further), a two-hit hypothesis represents one possible aetiological model. Mutations causing different defects in the same protein are another aspect of the genotype-phenotype relationship and of phenotypic heterogeneity. However, for the PKD1 locus, there does not seem to be any phenotypic difference of renal features between patients with major PKD1 gene deletions and those with single missense amino acid
changes. This suggests that haploinsufficiency rather than dominant negative effects occur. However, there must be other modifiers since the same mutation in different cases in the same family can manifest both severe childhood and typical adult onset, as evidenced in a family with a tyr3818stop mutation (Peral et al., 1996). Mutations specifically predisposing intracranial aneurysms have not been reported.

3.2. COL3A1 and type III collagen

Foetal and blood vessel collagen is also called collagen III and it has long been known that its synthesis is defective in EDS type IV. The COL3A1 gene on chromosome 2 (2q31) encodes the polypeptide known to be defective in this syndrome. The features of EDS type IV (aortic rupture risk, thin transparent skin, easy bruising, joint laxity, ligament weakness, bowel rupture and other soft tissue risks) and vascular expression of COL3A1 render this gene an obvious candidate in all types of arterial aneurysms. Inactivation of the gene in the mouse results in much shorter life span, with the main cause of death being rupture of major blood vessels (Liu, Wu, Byrne, Krane, & Jaenisch, 1997). Systematic study of many different mutations identified in EDS type IV has not revealed genotype-phenotype correlation. Nevertheless, vascular events without other features have been observed in conjunction with COL3A1 mutation, for example Gly619Arg heterozygosity was identified in a family prone to fatal rupture of aortic aneurysm. This particular mutation causes type III collagen to unfold at a decreased temperature. As early as 1981, study of type III collagen in 12 patients with cerebral aneurysms revealed deficiency in type III to type I collagen, although mutations could not be detected in COL3A1 (van den Berg et al., 1998).

3.3. Fibrillin-1 and other linkages in aortic and mixed vessel aneurysmal disease

The Marfan syndrome is an autosomal dominant heritable disorder of connective tissue with prominent manifestations affecting the skeletal, ocular and cardiovascular systems. The incidence is estimated to be up to 1/5000 (Pyeritz, 2000) with perhaps 25% of cases representing new mutations. Essentially all classical Marfan families and cases have turned out to display linkage to human chromosome 15q21.1 and/or mutations in the FBN1 gene encoding fibrillin-1. Mutations in this same gene also cause a series of other related disorders of connective tissue collectively known as type I fibrillinopathies (Robinson et al., 2002). Whilst the skeletal abnormalities of Marfan syndrome may be the most obvious, including long bone overgrowth, joint laxity, scoliosis and pectus abnormalities, it is the cardiovascular features which are often fatal. In particular, progressive dilatation of the aortic root and aortic dissection and rupture are frequent, and mitral and aortic valve insufficiency may also occur early. These features are the predominant causes of death in over 90% of patients (Nienaber & Von Kodolitsch, 1999). Genotype-phenotype correlations are recognised and neonatal onset Marfan syndrome associates particularly with mutations in exons 24–32. Such subjects show unusual features including crumpled ears, flexion contractures, pulmonary emphysema and loose skin, and often die before age 2 years from cardiac failure caused by valve defects (Booms et al., 1999). Whereas one-third of Marfan mutations are premature stop codons, splicing and exon deletions, no nonsense mutation has been described for the neonatal disease, in which mutations identified are either amino acid changes or exon skipping leading to shortened fibrillin.
monomers taking part in fibril formation. This suggests that there might be dominant negative effect in the neonatal subclass of Marfan syndrome, whereas haploinsufficiency is the more likely basis of effect where one allele is not expressed at all. Mutation R1170H, on the other hand, has been observed in two families with mild features and lacking aortic complications. A distinct set of missense mutations in exons 24–32 seem to predispose to early onset of cardiovascular complications (Putnam et al., 1996). Milder fibrillinopathies associated with isolated ectopia lentis (e.g. Lonnqvist et al., 1994), isolated skeletal defects and other combinations, show mutations clustering in exons 59–65. Missense mutations in the proline-rich exons 1–10 seem to lead to late-onset, mild cardiovascular complications. No study has been reported of the fibrillin-1 gene in other categories of vascular dilatation and aneurysm, but it is clear that such studies will be well worthwhile, although laborious, given the pleitropy and phenotypic heterogeneity already observed for fibrillin-1 gene variations.

While there is little family-based linkage data for SAH yet, more linkage information has begun to emerge for aortic aneurysms. In addition to recognition of the role of fibrillin-1 in aortic aneurysm, studies during 2001 have identified linkage of familial aortic aneurysm (FAA) to chromosome 11q23.2–q24 in one family and excluded linkage to fibrillin-1, to COL3A1, to 11q, to 3p24.2–p25, or fibrillin-2 in another family (Vaughan et al., 2001). A study of 15 families with dominant inheritance of thoracic aortic aneurysms (TAA) and dissections revealed a linkage in 9 families to chromosome 5q13–q14 (Guo et al., 2001). The loci on chromosomes 5 and 11 have not yet been identified but clearly represent protein products and pathways which may also be relevant to intracranial aneurysms. Within the Wessex region of the UK, we are undertaking studies of a family with some Marfan features including aortic pathology in several members, and several occurrences of intracranial aneurysm or bleed have occurred in the same kindred (Dennis, Simpson, Day, & Zhang, unpublished observation). The range of locus heterogeneity, gene pleitropy and phenotypic heterogeneity of specific mutations first requires the identification of each of the specific biochemical lesions, but it is evident that there will be some overlap of pathogenesis between some categories of arterial aneurysm.

3.4. Genomewide-linkage and haplotype association at chromosome 7q11 in the elastin gene

Traditional genetic linkage studies rely on the identification and sampling of a large family in which a disease is segregating in a clearly bimodal fashion. Characterisation of several hundred highly polymorphic microsatellite loci distributed evenly throughout the genome, in all family members, enables the identification of which region of which chromosome is segregating with the disease. This usually narrows down the search for the relevant gene and its protein product, to a choice between tens or hundreds of ‘positional candidates’ within the linked region. The recent availability of a reasonably complete human genome sequence (Lander et al., 2001) has facilitated the identification of positional candidates, although frequently the investigator must still first improve the map or sequence quality in the region. Unfortunately, although kindreds with many occurrences of SAH are known, the frequent fatality of the condition at first presentation has hindered DNA sampling of sufficient family members (e.g. 10 affected members) to obtain statistical power in any single family. Furthermore, although more recently imaging techniques have enabled identification of a pre-symptomatic trait, routine screening or research screening are ethically complex given the uncertain benefit relative to the risks, of preventative interventions. An alternative approach to single kindred studies, is to pool resources from kindreds containing at least two affected members. In this non-parametric design (i.e. no assumptions about dominance or recessivity of inheritance), chromosome regions will, according to Mendelian segregation, display sharing of the same pair of parental alleles for 25% of first degree relatives; sharing of one parental allele for 50% of first degree relatives; and sharing of no parental allele for 25% of first degree relatives. However, if a genomic region is important to a disease, and relative pairs were ascertained on the basis of their dual affection status, then observed allele sharing for that region will be greater than that expected. This approach to analysis does not require that a region be causative, it could just be predisposing: neither does the approach require that the region contains a gene acting in all families. However, the combination of extent of effect and number of families in which the gene is acting, must be sufficient
to be statistically evident in the eventual analysis. The approach should therefore be successful in any disease for which there is a substantial genetic component caused by a relatively small number of loci (genes) overall in the population. This approach has recently been applied in Japan, in a study comprising 104 sib pairs affected by intracranial aneurysm, collected from systematic enquiry in 100 neurosurgical centres (Onda et al., 2001). Genomewide, the three most prominent linkage regions identified were 7q11, 14q22 and 5q22–q31, with maximum LOD scores of 3.22, 2.31 and 2.24, respectively. Notwithstanding issues of multiple statistical testing, expected number of positive regions and multipoint versus single point linkage, these values correspond with \(P\)-values less than 0.001, 0.01 and 0.01, respectively. Linkage on 7q11 was strongest at microsatellite locus D7S2472. Proximity to the elastin gene (ELN) was notable, and so further analysis of this gene was undertaken using a set of common single nucleotide polymorphisms to define common haplotypes. Association analysis identified a haplotype comprising markers in introns 20 and 23 which was more prevalent in aneurysm patients than in controls, at an odds ratio of 1.85. In a global test of all pairwise combinations from nine polymorphisms, this haplotype emerged with \(P = 3.81 \times 10^{-6}\) (Onda et al., 2001). Candidate genes in the chromosome 5 region include lysyl oxidase (LOX), fibrillin-2 (FBN2) and fibroblast growth factor 1 (FGF1), and latent transforming \(\beta\)-binding protein 2 (LTBP2) on chromosome 14. While external elastic lamina is absent in cerebral arteries, internal elastic lamina (Fig. 6) is the major structural support (Glynn, 1940). Pathological examinations of intracranial aneurysms have pointed to defects of the internal elastic lamina (Carmichael, 1945). Elastin fibril destruction by elastase (Miskolczi, Guterman, Flaherty, & Hopkins, 1998) or by \(\beta\)-aminopropionitrile which inhibits elastin cross-linking (Hashimoto, Handa, & Hazama, 1978) both cause intracranial aneurysm formation in animal models. The statistical approach used to illustrate the elastin locus (or plausibly not the elastin locus but a nearby locus in strong linkage disequilibrium) seems to have yielded significant evidence that variation in the elastin gene affecting either its molecular structure or expression level, may be important in intracranial aneurysm. However, a combination of replication and functional follow studies will now be needed to confirm and further clarify the possible aetiological chain.

Genotype-phenotype considerations may be important for the elastin gene. It was shown by Curran et al. (1993) that a breakpoint in the elastin gene in 7q11.23 causes supravalvular aortic stenosis. Other studies Ewart et al. (1993) showed that this same region is deleted in Williams syndrome in which supravalvular aortic stenosis is also a major feature. All mutations identified (deletions, splice and stop codons) are consistent with a haploinsufficiency effect, although the penetrance of the effect can vary between members of the same family. The basis of arterial thickening occurring as a result of elastin deficiency has been elucidated by mouse gene knockout experiments by Li et al. (1998). Deficiency of elastin led to subendothelial cell proliferation and reorganisation of smooth muscle. Some frameshift mutations of elastin have been observed as the basis of cutis laxa; a condition of loose skin, also with tendency to hernias, valvular and cardiac abnormalities (Zhang et al., 1999). These observations would suggest that if elastin is an aetiogenic gene in aneurysm formation, then either dominant negative (e.g. by a changed amino acid) rather than haploinsufficiency effect must be the cause, or alternately that tissue-specific expression, splicing, matrix structure or other feature enable the elastin gene to lead to vessel thickening in one context but aneurysm formation in another.

3.5. Collagen IV and other basement membrane constituents

While there have been few specific studies of other proteins in the wall of the cerebral artery, several protein families recognised in other arteries merit further investigation. The intimal layer (Fig. 6) contains a basement membrane which supports the endothelial cells. Other basement membranes contain other specialised collagens such as collagen IV and collagen XVIII. Collagen XVIII trimers via its carboxy-terminal domain which as a cleavage product becomes endostatin. Endostatin domain oligomerisation is essential for inhibition of endothelial capillary tube formation in vitro and the more diffusible endostatin localises to the elastic lamina. Two separate sites on endostatin respectively bind cell surface heparin sulphate glycosaminoglycan and laminin (Javaherian...
et al., 2002). Laminins, of which there are several distinct genes and polypeptide chains, are found in both the intima and medial layers of the artery. Another basement membrane constituent interacting with laminin, is nidogen. Both these proteins and fibronectin and collagen IV display remodelling in experimentally formed aneurysms in response to haemodynamic stresses (Kittelberger, Davis, & Stehbens, 1990). Collagen IV has been shown to be present in cerebral artery basement membranes. Molecular defects in collagen IV cause Alport’s syndrome, which is characterised by sensorineural hearing loss and haematuria. However, a recent case report of a traumatically induced subarachnoid haemorrhage in a 14-year-old male identified a pre-existing left carotid artery bifurcation aneurysm and a pre-existing history, proven by renal biopsy, of Alport’s syndrome (Vaicys, Hunt, & Heary, 2000). It is therefore a plausible new hypothesis that defects in the basement membrane as well as defects in the elastic and medial layers may predispose intracranial aneurysms. It is also an example which invites further investigation of the possibility that traumatic subarachnoid haemorrhage could be more frequent in individuals rendered susceptible by molecular structural variations leading to a more fragile arterial wall.

3.6. α1-Antitrypsin (protease inhibitor)

Despite its name, α1-antitrypsin is the most abundant and potent natural inhibitor of elastase. Deficiency is a well known cause of pulmonary emphysema and liver disease, particularly associated with homozygosity for the ‘Z’ allele which leads to reduced serum levels and enzyme function and particularly exacerbated in smokers. α1-Antitrypsin activity has been claimed to be reduced in both intracranial (Tartara et al., 1996) and abdominal aortic (Cohen, Mandell, Margolis, Chang, & Wise, 1987) aneurysm. The epidemiological risk of SAH in smokers (see Section 3.7) is also of note. Some relatively small studies of α1-antitrypsin genotype in sporadic SAH case series, classifying wildtype allele (M), deficient allele (Z) and slightly deficient allele (S), have claimed positive association of S and Z heterozygosity with SAH, for example Schievink, Katsmann, Piepras, and Schaid (1996) finding 16% prevalence for 100 consecutive cases compared with 8% population prevalence. In another study, St. Jean et al. (1996) found an 8-fold overrepresentation of the Z allele in a subsample of 46 intracranial aneurysm patients, but in the overall study and after correction for multiple testing, this was not significant. Larger study sizes or eventual meta-analysis of literature will be necessary to determine whether the existing literature represents a positive reporting bias.

3.7. Association studies in sporadic intracranial aneurysm and subarachnoid haemorrhage

First degree relatives of patients with subarachnoid haemorrhage recruited prospectively on presentation, show an estimated 2–5% lifetime risk of also developing a subarachnoid haemorrhage (Bromberg, Rinkel, Algra, Greebe, et al., 1995). This suggests that there may be genetic modifiers in sporadic intracranial aneurysm and haemorrhage in addition to the clear-cut major gene effects in a small subset of families. Studies of common genetic diversity which might exert such effects, have followed similar hypotheses to those applied to abdominal aortic aneurysm. Studies are focussing on several categories of gene, mainly in the context of causation but occasionally in the context of outcome:

1. Genes encoding matrix proteins of the vessel wall, for example common variation of the COL3A1 gene (Brega et al., 1996).
2. Genes encoding matrix modifiers (e.g. enzymes) of the vessel wall (Peters, Kassam, St. Jean, Yonas, & Ferrell, 1999; Zhang et al., 2001), genes encoding cytokines and other factors which may modify cellular function.
3. Classic genetic epidemiological candidate genes, HLA, apolipoprotein E gene (APOE); and angiotensin converting enzyme gene (ACE) (Dunn, Stewart, Murray, Nicol, & Teasdale, 2001; Hirose et al., 1998; Keramatipour et al., 2000; Leung, Poon, Yu, Wong, & Ng, 2002; Niskakangas et al., 2001; Ryba et al., 1992; Takenaka et al., 1998).
4. Genes influencing atherothrombotic and oxidation pathways such as APOE, lipoprotein(a) (Roberts et al., 2001), and methylene tetrahydrofolate reductase (MTHFR).

Broadly, the same candidates have been considered in intracranial aneurysm events as in abdominal aortic aneurysm formation and rupture. However,
no claim has been consistently replicated with strong statistical significance. A specific difficulty facing research groups is that sporadic subarachnoid haemorrhage is rare and pre-symptomatic aneurysms cannot readily be ascertained. Thus most studies in regional centres based on sequential case admissions (and suitably selected controls) are based on study sizes of 50–200 subjects, which limits power to detect any genotypic effect of less than a two–three-fold relative risk (Risch & Merikangas, 1996). However, such magnitude of effect would represent a comparatively major modifier gene, not dissimilar from the effects of HLA genotype in type I diabetes (Undlien, Lie, & Thorpy, 2001), of APOE alleles in late onset Alzheimer’s disease occurrence (Saunders, 2000), and greater than the odds ratio of the specific haplotype identified in the elastin gene apparently conferring an odds ratio of 1.85 for intracranial aneurysm in patients selected on the basis of being a member of a family containing two affected sibs (Onda et al., 2001). Ultimately therefore, as studies accrue, literature meta-analysis or prior pooling of clinical collections will be necessary to fully explore gene effects in sporadic intracranial aneurysm.

4. Future lines of investigation

The target of molecular investigations in subarachnoid haemorrhage is to understand the common sporadic category, but there is some promise that the smaller subset of truly familial occurrence will provide the tools to gain a greater insight. Large affected relative pair studies and long term prospective sampling and follow up to achieve single kindred linkage studies will be essential. Animal models using gene knockouts, conditional knockouts or specific introduced mutations will help to determine sequences of pathogenesis. Comprehensive expression studies using microarray technology may help to define more fully, the expression changes taking place in cells of the vessel wall during cerebral artery aneurysm development. Genetic epidemiological studies may identify gene–environment interactions of significance. For example, smoking has an important role, and the elastin genomic region has been implicated by linkage, independent of any functional hypothesis in aneurysm formation. Hypothesis testing has also claimed association of α1-antitrypsin (elastase inhibitor) genotype with subarachnoid aneurysm. However, very large well designed epidemiological analyses will be needed to prove the latter and test interaction of the three factors. Parallel functional studies may be equally informative. Further systematic association analysis in sporadic SAH of haplotypes of genes encoding structural proteins of the arterial wall and regulatory factors and enzymes, and high throughput mutation scanning of these same genes in families prone to SAH, may be informative.

Gene tests to reassure at risk family members that they have not inherited a defective gene, and to identify others for frequent non-invasive imaging and safer minimally invasive management of ‘critical’ aneurysms, would be of clinical value. It is also possible that other avoidable environmental factors may be identified during cellular and molecular studies of pathogenesis. Drugs capable of modifying matrix turnover are an active area of pharmaceutical research and given identifiable, predictable subphenotypes of SAH, could also plausibly become part of a future arsenal of medical options.

Note added in proof

A second genomewide linkage scan, comparable with the Japanese study described in Section 3.4, has recently been published (Olson et al., BMC Med Genet, 2002, 3(1) 7). This study of 85 Finnish families identified several possible linkages, the most significant (maximal multipoint LOD score 2.6) being on chromosome 19q. The possible causal gene in this interval is not obvious although there are many plausible candidates to be investigated. The general lack of correlation of linkages with the Japanese study may reflect occurrence of different risk genotypes and different molecular causality of familial SAH in these very different populations.

Acknowledgements

BZ is a Hope (Wessex Medical Trust) Senior Research Fellow and thanks the British Heart Foundation for project grant support. INMD thanks Hope for their pilot support to develop the Southampton Familial Subarachnoid Haemorrhage project, research sister Lesley Foulkes for family tracing and the late
Professor Fausto Iannotti for collaboration in the early stages of the programme.

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