In children, stroke is as common as brain tumour and causes substantial mortality and long-term morbidity, with recurrence in up to 20%. There are three sets of international clinical guidelines relating to childhood stroke; however, acute and preventive treatment recommendations are based on interventions effective in adults, rather than data regarding efficacy in children. A wide spectrum of risk factors underlies childhood stroke, and these risk factors vary from those encountered in adults. Specific disease mechanisms implicated in childhood arterial ischaemic stroke have received little attention, but an increased understanding of disease pathogenesis could lead to novel targeted treatment approaches. Here, we consider insights into the pathogenesis of childhood arterial ischaemic stroke and cerebral arteriopathy, provided by current knowledge of Mendelian diseases that are associated with an increased risk of these conditions. We give particular attention to aspects of vascular development, homoeostasis, and response to environmental effects. Our analysis highlights a potential role for interventions already licensed for pharmaceutical use, as well as new therapeutic targets and avenues for further research.

Introduction
Stroke (focal cerebral injury with an underlying vascular basis) is increasingly recognised as an important childhood disorder, with an incidence of between 2 and 13 per 100 000 children per year (similar to that of childhood brain tumours). Stroke is one of the ten most common causes of death in children and three-quarters of survivors have residual neurological impairment. In the USA, the cost of acute paediatric stroke care in 2003 was $42 million, and 5-year health-care costs have been estimated as $135 000 per affected child. The personal and wider socioeconomic effects have not been studied in detail but are likely to be substantial.

Risk factors for stroke are different in children and adults. Although half of children who experience arterial ischaemic stroke (AIS) have a pre-existing medical condition (congenital heart disease and sickle-cell disease are the most common), the cause of AIS in previously healthy children is uncertain, probably involving an interplay of risk factors. Idiopathic childhood AIS is most often associated with non-atherosclerotic arteriopathies; the morphology and progression of such arteriopathy is the most important determinant of future recurrence risk, which is up to 20%. Current acute and preventive treatment recommendations are based on interventions that are effective in adults, rather than on data regarding efficacy in children. Whereas acute AIS treatments that limit ischaemic brain injury (thrombolysis or neuroprotection) might be applicable to all age groups, primary preventive measures aimed at avoiding cerebral arteriopathy and first stroke, and secondary measures aimed at preventing recurrence, should, ideally, be specifically targeted to the underlying disease mechanism. Because of the differences between adult and paediatric AIS—eg, the rarity of atheroma in children—effective primary and secondary preventive approaches might differ between the two groups. A better understanding and knowledge of the specific disease mechanisms underlying childhood AIS and arteriopathy could lead to development of targeted interventions.

Several association studies have assessed the relevance of genetic polymorphisms in prothrombotic, inflammatory, immune-mediated, or metabolic pathways contributing to paediatric AIS; however, these series were typically based on small numbers of patients and were seldom replicated, limiting the conclusions that can be drawn. By contrast, although somewhat uncommon, the association of childhood AIS with Mendelian genetic disorders can provide immediate insights into disease pathogenesis. Furthermore, rare-disease models can highlight potential candidate genes for apparently complex diseases. For these reasons, monogenic disorders associated with childhood AIS are the focus of this Review.

Arteries are formed of three layers, the tunica intima (endothelial cells layered on the internal elastic lamina), tunica media (vascular smooth muscle interspersed with connective tissue, and elastin fibres within the external elastic lamina), and tunica adventitia (connective tissue and vasa vasorum; figure 1). The development and growth of blood vessels is a complex process involving interaction between genetic factors and pathways mediating vasculogenesis (formation of blood vessels from embryonic precursors), angiogenesis (expansion of primitive vessels), and dynamic remodelling in response to genetic and local signals. The latter can be broadly subsumed under the heading of vascular homoeostasis. For this Review, we concentrate on monogenic disorders that show an association with paediatric cerebral (including cervical and intracranial) arteriopathy, where the underlying disease pathogenesis relates to a known or postulated role in vascular development, homoeostasis, or response to injury (table I). Familial moyamoya syndrome is also discussed. We do not consider inherited metabolic disorders, in which paediatric cerebral injury associated with stroke-like episodes is mediated by cellular energy failure (such as mitochondrial disorders...
or organic acidaemias), since, in these cases, brain injury does not have a primary vascular cause. We also do not discuss disorders associated with premature atheroma, prothrombotic disorders, or genetic polymorphisms predicting stroke risk in sickle-cell disease.

**COL4A1**
The COL4A1 gene encodes the alpha-1 chain of type IV collagen, the main constituent of basement membranes, which is widely expressed in all tissues, including vascular beds. Mutations in COL4A1 predispose to reduced stability of vascular basement membranes, apparent on electron microscopy. A wide range of phenotypes has been described in association with COL4A1 mutations, including idiopathic cerebral small-vessel disease in children. Occlusive and aneurysmal cerebral arteriopathies, resulting in ischaemic and haemorrhagic stroke phenotypes (figure 2), can occur in the same family. This heterogeneity of clinical and radiological phenotypes is a feature common to several Mendelian cerebral arteriopathies.

With COL4A1-related disease, susceptibility to cerebral haemorrhage might be associated with trauma, suggesting an interplay between environmental factors and genetic susceptibility. Ganesan and colleagues noted that trauma to the head or neck in the preceding 2 weeks was an important risk factor for AIS in previously healthy children, and such an association might involve genetically mediated vulnerability.

**ABCC6**
Pseudoxanthoma elasticum (PXE) is a disorder caused by mutations in the ABCC6 gene. How these mutations affect the assembly and deposition of elastic fibres and subsequent development of the phenotype remains unclear. Disruption of the transport function of ABCC6 in the kidney, liver, or both could precipitate secondary changes in the dermis and arterial wall, leading to calcification of elastic fibres and development of PXE. Therefore, some investigators suggest that PXE should be considered an inherited metabolic disorder rather than a primary connective-tissue disease. Although often diagnosed in the second or third decade of life, symptoms and signs might be present in childhood in the form of cutaneous manifestations. AIS and peripheral vascular disease are other prominent features. A range of cerebrovascular manifestations has been described, including ischaemic stroke, cerebral small-vessel disease, and aneurysms; reported a 2-year-old girl with moyamoya, PXE, and an ABCC6 mutation.

**ACTA2**
Actins are highly conserved proteins involved in maintaining cell structure and integrity. Actin alpha 2 (ACTA2), one of six known actin isoforms, is a main contractile protein of vascular smooth-muscle cells (SMCs). Polymerisation of ACTA2 forms the backbone of the thin filament of the sarcomere. Mutations in the ACTA2 gene disrupt polymerisation of alpha actin into thin filaments, which leads to increased vascular SMC proliferation. ACTA2 mutations result in a gain of proliferative function of SMCs, leading to occlusive disease in smaller arteries that are deficient in elastin, an important inhibitor of SMC proliferation. By contrast, larger arteries seem to be vulnerable to...
phenotypes associated with mutations in ACTA2 involved cerebral circulation in only a small proportion of cases; however, a novel phenotype associated with an R179H ACTA2 mutation specifically includes a severe childhood cerebral arteriopathy (figure 3). Mutations in ACTA2 were not common in Japanese patients with familial moyamoya disease.

**NF1**

Neurofibromatosis type 1 (NF1) results from mutations in the NF1 tumour-suppressor gene encoding neurofibromin, a regulatory protein that inhibits activity of the Ras signalling pathway. Lack of inhibitory regulation of the Ras pathway leads to excessive SMC proliferation and vascular occlusion.

Diffuse cerebral arteriopathy, showing occlusive and aneurysmal features, is seen in around 6% of children with NF1 (figure 4). Histological findings include intimal proliferation, nodules in smooth muscle, and fibrosis of the vascular media and adventitia. Continuing the theme of gene–environment interaction, the studies of Lasater and colleagues provide genetic and cellular evidence of vascular inflammation in mice that are heterozygous for NF1 and in patients with NF1. However, heterozygous inactivation of NF1 in endothelial cells or vascular SMCs alone was insufficient to produce neointimal formation; bone-marrow derived cells from mice heterozygous for NF1 were necessary for neointimal formation and vaso-occlusive disease. Increased concentrations of activated monocytes and proinflammatory cytokines have been shown in the peripheral blood of patients with NF1 with no overt evidence of vascular disease. These findings suggest that chronic inflammation is an important contributor to NF1 arteriopathy. The trigger for converting from a state of asymptomatic vascular dysfunction and inflammation to development of an arteriopathy remains unclear.

**ELN**

Williams-Beuren syndrome is a multisystem disorder resulting from deletions of the Williams-Beuren syndrome region on chromosome 7, which includes the ELN gene encoding elastin. Arteriopathy in Williams-Beuren syndrome most often manifests as supravalvular aortic stenosis (in 70% of patients); however, other vascular beds can be involved, including aorta, pulmonary, coronary, renal, and mesenteric vessels. This diverse arteriopathy highlights the role of elastin in the arterial wall, and results from overgrowth of SMCs. When stroke and cerebrovascular disease occur in children, the primary phenotype seems to be occlusive disease (figure 5), with intimal thickening and marked thinning of the media of large intracranial arteries (compatible with SMC proliferation), including moyamoya syndrome. Aneurysmal disease has not been described in Williams-Beuren syndrome.
**NOTCH3**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) results from mutations in the *NOTCH3* gene, which encodes a transmembrane receptor involved in the Notch signalling pathway that is mainly expressed in arterial SMCs. Although the main cerebrovascular manifestations are in small-vessel distribution, large-artery disease has also been observed. Histological studies show thickening of the arterial wall with consequent stenosis and widespread evidence of extracellular accumulation of granular osmophilic material in arterial media extending into the adventitia, even in clinically unaffected organs. There are also abnormalities of vascular SMCs and vascular reactivity. In animal models, complete absence of Notch3 does not result in CADASIL pathology, and evidence suggests that the pathological consequences of *NOTCH3* mutations relate to a gain of function.

Cerebral infarction was thought to occur only in adults with CADASIL; however, Granild-Jensen and colleagues reported a child with a family history of CADASIL who had migraine and an acute hemiparesis secondary to infarction in the basal ganglia and white matter. The patient had calibre variation in the anterior and middle cerebral arteries before developing asymptomatic progression of ischaemic changes in the white matter. Other paediatric cases have been reported, and with an estimated prevalence of around four per 100 000, the disease might be under-recognised in childhood.

**JAG1**

Almost 90% of individuals with Alagille syndrome harbour mutations in *JAG1*. The jagged-1 surface protein encoded by *JAG1* is a ligand for transmembrane receptors in the Notch signalling pathway, essential for determining cell fate during vascular development. In addition to vascular smooth-muscle differentiation, Notch receptors are involved in determining the response to vascular injury through interactions with various transcription factors. Studies have highlighted occlusive and aneurysmal arterial disease associated with ischaemic and haemorrhagic stroke, in adults and children with Alagille syndrome, affecting the cerebral circulation and other vascular beds (figure 6).

Figure 4: Axial T2-weighted MRI scan and time-of-flight magnetic resonance angiogram from a 2-year-old boy with neurofibromatosis type 1

(A) Axial T2-weighted MRI scan. (B) Time-of-flight magnetic resonance angiogram of the circle of Willis (frontal projection). The patient presented with right focal motor seizures with residual right hemiparesis and global developmental delay. The left internal carotid artery is occluded distal to the cavernous segment, and there is turbulence of flow in the proximal right middle cerebral artery. Lenticulostriate collaterals are apparent on the right, especially in (A). There is generalised atrophy of the left hemisphere.

Figure 5: Time-of-flight magnetic resonance angiogram of the circle of Willis (frontal projection) from a 15-year-old boy with Williams-Beuren syndrome

The patient presented with recurrent episodes of right arm weakness. There is severe stenosis of both proximal middle cerebral arteries with marked reduction in distal filling and profuse lenticulostriate collaterals, characteristic of bilateral moyamoya.

**HTRA1**

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is associated with mutations in the HtrA serine peptidase-1 gene, *HTRA1*. Mutations result in a loss of protease activity and consequent dysregulation of TGFβ (transforming growth-factor beta) signalling. Histological studies have shown arteriosclerosis with intimal thickening and dense collagen fibres, loss of vascular SMCs, and hyaline degeneration of the media in cerebral small arteries. Small-vessel disease usually manifests in adulthood, although other features of CARASIL, particularly alopecia, can begin in adolescence. *HTRA1* dysfunction in CARASIL highlights the importance of TGFβ signalling in vascular homoeostasis. This theme is further emphasised by Loeys-Dietz syndrome, which is characterised by arterial tortuosity and large-vessel, non-cerebrovascular aneurysmal
disease, and is caused by \textit{TGFBR1} and \textit{TGFBR2} mutations. Another example, Marfan’s syndrome, results from mutations in the \textit{FBN1} gene that encodes fibrillin 1, a glycoprotein important in the microfibrillar system. Patients with Marfan’s syndrome are at risk of aortic aneurysmal dilatation.

\textbf{SAMHD1}

Aicardi-Goutières syndrome is an encephalopathy. The disorder is genetically heterogeneous and, to date, is associated with mutations in five genes. Ramesh and co-workers\textsuperscript{55} described five children with mutations in \textit{SAMHD1}, who had a cerebral arteriopathy with either occlusive or aneurysmal features (figure 7). All had severe peripheral vascular disease (chilblains) showing that, as with \textit{ACTA2}-related disease, the skin can indicate the presence of cerebrovascular disease. Two of five patients had leukocytoclastic vasculitis on skin biopsy, and in one patient, post-mortem neuropathology showed evidence of arterial inflammation. Thiele and colleagues\textsuperscript{56} also described cerebral arteriopathy in four patients with \textit{SAMHD1} mutations, two of whom had features of systemic inflammatory disease. Both of the above reports include individuals who were neurodevelopmentally preserved and who, in several cases, survived to adulthood. Although the functions of \textit{SAMHD1} are unknown, evidence suggests that the protein has a role in the innate immune response.\textsuperscript{57} Thiele and colleagues\textsuperscript{56} speculated that increased expression of interleukin 8, noted in their patients, might mediate the observed inflammatory arteriopathy. These descriptions of large-artery disease in individuals with \textit{SAMHD1} mutations raise questions about the wider role of SAMHD1 protein in the genesis of arteriopathy, and the screening for cerebrovascular disease in \textit{SAMHD1}-related phenotypes.

\textbf{PCNT}

Microcephalic osteodysplastic primordial dwarfs type II (MOPD II) is an autosomal recessive disorder caused by mutations in the pericentrin gene (\textit{PCNT}). The disorder is characterised by microcephaly, prenatal and postnatal growth failure, skeletal dysplasia, and dysmorphism.\textsuperscript{58} Childhood cerebrovascular disease is often associated with MOPD II; in a recent study, cerebrovascular abnormalities were identified in 13 of 25 patients,\textsuperscript{59} with substantial attendant morbidity and mortality. The most common vascular disorder is moyamoya syndrome; however, cerebrovascular aneurysmal disease has also been reported. Cerebrovascular disease can be progressive and patients should be screened every 12–18 months, even if asymptomatic.

Pericentrin is a centrosomal protein thought to be important for progression of the cell cycle. It has been proposed that cells deficient in pericentrin are susceptible to cell death, and that this accounts for the observed growth restriction. As with other disorders discussed here, vascular disease is not confined to the cerebral circulation and is seen in many vascular beds including the heart and major arteries. Recent studies of mouse models suggest a role for pericentrin in intracellular secretion and distribution of insulin,\textsuperscript{60} so that, in addition to its centrosomal role, the protein might have other, organ-specific functions. The emergent and progressive nature of cerebrovascular disease in patients with MOPD II suggests an acquired rather than developmental disturbance, supporting a role for pericentrin in vascular homeostasis.

\textbf{ATP7A}

Menkes disease is an X-linked recessive disorder that affects copper transport and is caused by mutations in the \textit{ATP7A} gene.\textsuperscript{61} Clinical phenotypes vary; the mildest
form of the disorder manifests as occipital horn syndrome (mainly connective-tissue abnormalities), and the most severe form is progressive neurodegenerative disorder resulting in death in infancy. Sparse and friable hair, which led to the term kinky-hair syndrome, is a prominent feature. Both ischaemic and haemorrhagic stroke have been reported. A structural abnormality of cerebral arteries (which appear tortuous), oxidative injury, and energy failure have all been implicated in the pathogenesis of the associated vascular phenotype.

**SLC2A10**
Arterial tortuosity syndrome (ATS) is an autosomal recessive disorder caused by mutations in *SLC2A10* (GLUT10), a gene that encodes a facilitative glucose transporter. Cartwright and co-workers reported AIS in an adolescent with clinical features of ATS and no other risk factors. In addition to occlusive arteriopathy, the researchers argued that arterial tortuosity itself might be a risk factor for development of occlusion related to changes in neck position or dissection. On histological examination, arteries in affected patients show disruption of elastic fibres and fragmentation of the internal elastic membrane. *SLC2A10* localises to the mitochondria of SMCs and insulin-stimulated adipocytes, where it facilitates transport of L-dehydroascorbic acid (a cofactor for collagen and elastin hydroxylases) into secretory pathways. In ATS, loss of *SLC2A10* activity results in defective collagen, elastin, or both. TGFβ activation is a secondary response to a defective extracellular matrix.

**GLA**
Fabry's disease is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene encoding α-galactosidase. Deficiency of α-galactosidase results in accumulation of globotriaosylceramide within the vascular endothelium, causing endothelial injury and a progressive arteriopathy that affects large and small vessels and can present in childhood. The incidence of stroke with vessel ectasia is about 40% in hemizygous men with Fabry's disease. In a recent study of patients aged 18–55 years with a first-ever stroke, 2.4% had missense mutations in *GLA*, with equal occurrence in men and women. The likelihood of mutation was higher in those with cryptogenic stroke or posterior circulation infarcts; the characteristic clinical features of Fabry's disease were generally absent.

**Homocysteinuria**
Classic homocysteinuria is an autosomal recessive disorder caused by deficiency of cystathione-β synthase and is characterised by increased concentrations of homocysteine and methionine. Classic homocysteinuria is associated with stroke, and hyperhomocysteinaemia is a risk factor for thrombosis and vascular events. The deleterious effects of hyperhomocysteinaemia on cerebral circulation are thought to occur through dysfunction of the vascular endothelium and via a procoagulant effect. The arteriopathy in classic homocysteinuria is non-specific in morphology.

**Moyamoya**
Moyamoya is a rare cerebral arteriopathy comprising (usually) bilateral occlusive disease of the terminal internal carotid arteries with basal collaterals (figure 8). Clinically and morphologically, moyamoya can be considered the most severe of the childhood cerebral arteriopathies and, because of its association with disease in other organ systems, a marker for disease affecting vascular beds more widely. Histological and immunohistochemical studies of intracranial arteries from autopsied patients with moyamoya disease show that the arteriopathy is non-atheromatous, and that occlusive disease is the result of over-proliferation of SMCs, with colocalisation of inflammatory cells, such as macrophages and T cells in some cases. Several Japanese and Korean studies have reported an association between HLA alleles (HLA-B35, HLA-B51, HLADRB1*0405, DQB1*0502, and *0401) and idiopathic moyamoya disease, further supporting a role for the immune system and inflammation in the pathogenesis. Reid and colleagues showed histological evidence of abnormal SMC proliferation in intracranial arteries and systemic arteries, such as the ascending aorta and superior mesenteric arteries, at post mortem in a child with radiologically typical sporadic moyamoya who was negative for mutations in *ACTA2*. These observations provide additional data regarding the histological basis of...
moyamoya and support the hypothesis that patients with moyamoya might have a generalised arteriopathy, probably genetically mediated with a tendency for dysregulation of SMC proliferation.

In genetics literature, the term moyamoya has been used with different degrees of precision, so that not all cases described would meet strict radiological diagnostic criteria. Improved description and characterisation of complex vascular disease in this context could improve phenotypic classification and facilitate future genotype–phenotype correlations.

Although most cases of moyamoya, either idiopathic moyamoya disease or secondary moyamoya syndrome, seem to be sporadic, roughly 10–15% of cases are familial in Japan, and around 6% in the USA. Mineharu and colleagues described inheritance patterns in 15 families with 52 individuals affected by familial moyamoya, and their data supported an autosomal dominant pattern with incomplete penetrance. Linkage studies in familial Japanese cases have implicated several loci. A study in an Algerian family reported a phenotype characterised by moyamoya syndrome, short stature, hypogonadotropic hypogonadism, azoospermia, premature greying, and dysmorphic features with an X-linked pattern of inheritance. Since moyamoya often represents one aspect of a more diffuse arteriopathy, future identification of single-gene disorders associated with moyamoya could lead to a better understanding of childhood cerebral arteriopathy.

**Clinical features suggesting a genetic cause for childhood AIS**

Recognition of cases where childhood AIS or arteriopathy might have a genetic basis is key to contributing to knowledge about disease mechanisms and could aid appropriate clinical management, including primary and secondary prevention. Table 2 summarises clinical and radiological features that could suggest an underlying genetic disorder in a child presenting with AIS. A detailed family history is essential, as shown by Guo and colleagues in their characterisation of families with ACTA2 mutations, and the phenotypic information sought in association with disease affecting diverse vascular beds should be comprehensive. Thus, in addition to stroke, clinical history should enquire about migraine, porencephaly, learning difficulties, and static motor disorders. In terms of clinical examination, patients should be assessed for disease in other vascular beds, including the skin, eyes, heart and great vessels, kidneys, and other viscera. Consideration should be given to the observation of both occlusive and aneurysmal disease, causing ischaemia and haemorrhage, in an individual or within the wider family. Although the Mendelian disorders discussed here could possibly be expressed as isolated cerebrovascular involvement, we suggest that genetic investigations should be pursued only in patients with other suggestive features, as discussed in table 2.

**Directions for future research**

Although the proportion of AIS in children attributable to the single-gene disorders discussed above is probably small, these associations could provide key pathogenic insights that inform future research. Studies should focus on specific mechanisms of vascular injury and susceptibility pathways, and large-scale interrogation of candidate genes should be done using new sequencing technologies, by direct mutation analysis rather than searching for associations with single nucleotide polymorphisms of vague clinical significance. Such research could identify important therapeutic targets that are applicable to the specific conditions discussed, and possibly to childhood vascular disease more widely. Current treatment approaches in childhood AIS are derived from those in adults, in whom different risk factors contributing to AIS and cerebral arteriopathy apply. Current therapies for children, such as antiplatelet drugs, anti-inflammatory drugs, and anticoagulants are likely to continue to have a role in secondary prevention, because thrombosis and inflammation are also important themes in AIS pathogenesis in this age group. However, study of the Mendelian disorders discussed here could lead to a more detailed understanding of underlying disease mechanisms, which would provide a more robust and targeted framework for use of the drugs available and might also suggest novel preventive and treatment approaches.

Some of the associations described above are only rarely reported in literature. Our clinical experience in a specialist paediatric cerebrovascular service for more than 10 years suggests that these diseases are under-recognised. The role of genetic factors in paediatric AIS has not received wide attention, and current investigation protocols have not focused on this aspect of clinical assessment. Identification of an underlying genetic disorder could have important implications for the affected individual and their family. Treatments are available for some of the disorders mentioned (eg, Fabry’s disease and homocysteinuria), and lifestyle advice might be appropriate for others. Animal models have shown that surgical delivery of mouse pups carrying a mutated COL4A1 allele can prevent severe perinatal cerebral haemorrhage often seen with normal delivery. It remains to be assessed whether similar interventions modify the natural history in other vascular diseases and whether these might be applicable to affected humans.

Disruption of the vascular response to traumatic, inflammatory, or oxidative injury (aspects of vascular homeostasis) is an important theme. More detailed study of the role of these mechanisms in childhood AIS and arteriopathy might inform trials of anti-inflammatory and proangiogenic therapies. From a clinical perspective, the role of inflammation in childhood AIS and arteriopathy is debated. A key question is whether inflammatory disease is active at the time of clinical presentation, or whether arterial abnormalities are the
end result of a now-quiescent inflammatory process, an important distinction in relation to the efficacy of anti-inflammatory treatments. Current studies investigating biomarkers of ongoing vascular injury are likely to prove inflammatory treatments. Current studies investigating important distinction in relation to the efficacy of anti-

The role of SMC proliferation in NF1 and ACTA2-associated disorders (AD) might be effective in susceptible individuals. Studies support this premise; for example, mouse models with partial or complete loss of neurofibromin expression in SMCs were given imatinib, a potent inhibitor of the Ras-Erk signalling cascade, which prevented the proliferative smooth-muscle response to vascular injury. The association with thrombophilia and the role of thrombosis in several of the single-gene disorders discussed suggests that antiplatelet and anticoagulant drugs might help limit brain injury and prevent recurrence. Data from Bernard and colleagues show that hypercoagulability might be differentially important.

Table 2: Clinical features that might suggest a single-gene disorder in children with AIS and cerebral arteriopathy

<table>
<thead>
<tr>
<th>Neurological presentations in addition to stroke</th>
<th>Musculoskeletal features</th>
<th>Ocular features</th>
<th>Cutaneous features</th>
<th>Other organ involvement</th>
<th>Key neuroimaging features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COL4A1 (AD)</strong></td>
<td>Migraine, cerebral palsy</td>
<td>Muscle cramps</td>
<td>Cataracts, retinal tortuosity</td>
<td>Renal cysts, nephropathy, aneurysms</td>
<td>Occlusive or aneurysmal cerebral arteriopathy; intracranial haemorrhage, including microbleeds; cerebral infarction; porenchephaly</td>
</tr>
<tr>
<td><strong>Pseudoxanthoma elasticum (AR)</strong></td>
<td>Increased skin laxity, redundant skin folds</td>
<td>Peau d’orange, angioid streaks, neovascularisation, haemorrhage</td>
<td>Popular skin lesions</td>
<td>Peripheral artery disease, visceral calcification</td>
<td>Lacunar infarcts, small-vessel disease, haemorrhage, white-matter signal abnormalities</td>
</tr>
<tr>
<td><strong>ACTA2-associated disorders (AD)</strong></td>
<td>Hypotonic bladder</td>
<td>Congenital mydriasis</td>
<td>Livedo reticularis</td>
<td>PDA, thoracic aortic aneurysms and dissection, premature coronary artery disease</td>
<td>Occlusive disease including moyamoya, aneurysms in other arterial beds</td>
</tr>
<tr>
<td><strong>Neurofibromatosis type 1 (AD)</strong></td>
<td>Seizures, optic glioma, glioma</td>
<td>Sphenoid dysplasia, scoliosis</td>
<td>Lisch nodules, optic gliomas</td>
<td>Café-au-lait patches, axillary freckling</td>
<td>Neurofibromas</td>
</tr>
<tr>
<td><strong>Williams-Beuren syndrome (sporadic or AD)</strong></td>
<td>Developmental delay</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>Occlusive cerebral arteriopathy (including moyamoya)</td>
</tr>
<tr>
<td><strong>CADASIL (AD)</strong></td>
<td>Migraine with aura, cognitive impairment, psychiatric features</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>Usually subcortical white-matter infarction though large-artery infarcts described</td>
</tr>
<tr>
<td><strong>Alagille syndrome (AD)</strong></td>
<td>Developmental delay</td>
<td>Butterfly vertebrae</td>
<td>Posterior embryotoxon</td>
<td>..</td>
<td>Occlusive or aneurysmal cerebral arteriopathy (including moyamoya)</td>
</tr>
<tr>
<td><strong>CARASIL (AR)</strong></td>
<td>Dementia, psychiatric features</td>
<td>Spondyloysis deformans</td>
<td>..</td>
<td>Alopecia</td>
<td>White-matter signal abnormalities and lacunar lesions</td>
</tr>
<tr>
<td><strong>Acicardio-Goutières syndrome (AR)</strong></td>
<td>Severe encephalopathy, regression, developmental delay</td>
<td>Contracture, arthopathy</td>
<td>..</td>
<td>Chilblains or Raynaud’s phenomenon</td>
<td>Occlusive or aneurysmal cerebral arteriopathy (including moyamoya), basal ganglia calcification, leukenocephalopathy</td>
</tr>
<tr>
<td><strong>MOPD II (AR)</strong></td>
<td>Motor delay</td>
<td>Skeletal dysplasia, microcephaly, short stature, abnormal teeth</td>
<td>..</td>
<td>Café-au-lait patches</td>
<td>Dysmorphism, type 2 diabetes, precocious puberty</td>
</tr>
<tr>
<td><strong>Menkes disease (XLR)</strong></td>
<td>Hypotonia, developmental delay, seizures, regression</td>
<td>Joint laxity, osteoporosis</td>
<td>..</td>
<td>..</td>
<td>Pili torti (kinky hair)</td>
</tr>
<tr>
<td><strong>Arterial tortuosity syndrome (AD)</strong></td>
<td>..</td>
<td>Arachnodactyly, joint and skin laxity</td>
<td>..</td>
<td>..</td>
<td>Intracranial and extracranial dissections and aneurysms, craniosynostosis, Chian malformation</td>
</tr>
<tr>
<td><strong>Homocysteinuria (AR)</strong></td>
<td>..</td>
<td>Tall stature</td>
<td>Dislocated lens</td>
<td>Aortic dissection</td>
<td>Large vessel or lacunar strokes</td>
</tr>
<tr>
<td><strong>Fabry’s disease (XLR)</strong></td>
<td>Acroparesthesia hypohidrosis, exercise intolerance</td>
<td>Cataracts, corneal opacity</td>
<td>Angiokeratoderma</td>
<td>Proteinuria or renal tubular dysfunction, coronary artery disease, arthrythmia, gut dysfunction</td>
<td>Posterior circulation infarction more common, stroke phenotype includes haemorrhage and ischaemia</td>
</tr>
</tbody>
</table>

AIS=arterial ischaemic stroke. AD=autosomal dominant. AR=autosomal recessive. PDA=patent ductus arteriosus. UBO=undefined bright object. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukenocephalopathy. CARASIL=cerebral autosomal recessive arteriopathy with subcortical infarcts and leukenocephalopathy. CSF=cerebrospinal fluid. IFN-α=interferon alpha. MOPD=microcephalic osteodysplastic primordial dwarfism type II. XLR=X-linked recessive.
in specific stroke subtypes, suggesting that therapy should be modified accordingly. This is an early example of the concept that treatment should be targeted to the underlying disease mechanism, a potential outcome of the future lines of study suggested here.

Infection is emerging as an important risk factor for childhood AIS,9,10 but has not been specifically studied in the context of the single-gene disorders discussed above. Data from the International Paediatric Stroke Study11 suggest a role for antecedent infection in the genesis of non-atherosclerotic cerebral arteriopathies. Affected individuals could be vulnerable because of genetic factors, and infection might be an important link in terms of genetic susceptibility and environmental precipitants. For example, Charakida and colleagues12 found that flow-mediated dilatation was impaired after childhood infection and was predicted by mannose-binding lectin phenotype. Immunisation is likely to affect the incidence of post-varicella zoster cerebral infarction, and active varicella vasculitis can be treated with steroids and acyclovir.9,13 Additionally, a better understanding of arteriopathy, “genetics,” “moyamoya,” and “polymorphisms.” Articles were also identified through searches of the authors’ files. Only articles published in English were included. Articles describing associations between paediatric AIS or cerebral arteriopathy and genes implicated in vascular development, homoeostasis, or response to injury were selected for review.

Finally, the role of 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, or statins, in the prevention of AIS recurrence in children has not been explored, but could be important based on the mechanisms discussed above. Apart from their lipid-lowering properties, statins modulate pathways involved in SMC proliferation and migration, inflammation, endothelial-cell function, and platelet aggregation.14 The beneficial effect of statins on reducing vascular morbidity in adults has been attributed to these actions and to their effects on serum cholesterol. Elucidation of disease pathogenesis in childhood AIS could reinforce the rationale for a trial of statins already available and licensed for clinical use in secondary prevention of childhood AIS.

In summary, we have brought together current knowledge of single-gene disorders associated with childhood AIS in an attempt to focus debate and research relevant to underlying disease mechanisms. In view of the differences in pathogenesis, extrapolating from treatments shown to be effective in adult AIS to children is likely to have limited applicability; novel strategies are needed to move towards targeted treatments, through an understanding of the genesis of childhood cerebrovascular disease.

Contributors
All authors contributed to the determination of aims and structure of the Review. PM did the primary literature search, reviewed selected papers, and wrote the initial draft. VG and YJC supplemented the literature review and edited the text.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgments
YJC acknowledges the support of Manchester National Institute for Health Research (NIHR) and Biomedical Research Centre (BRC).

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