Pseudoxanthoma elasticum (PXE) is an inherited systemic disease of connective tissue primarily affecting the skin, retina, and cardiovascular system. It is characterised pathologically by elastic fibre mineralisation and fragmentation (so called “elastorrhexia”), and clinically by high heterogeneity in age of onset and the extent and severity of organ system involvement. PXE was recently associated with mutations in the ABCC6 (ATP binding cassette subtype C number 6) gene. At least one ABCC6 mutation is found in about 80% of patients. These mutations are identifiable in most of the 31 ABCC6 exons and consist of missense, nonsense, frameshift mutations, or large deletions. No correlation between the nature or location of the mutations and phenotype severity has yet been established. Recent findings support exclusive recessive inheritance. The proposed prevalence of PXE is 1/25 000, but this is probably an underestimate. ABCC6 encodes the protein ABCC6 (also known as MRP6), a member of the large ATP dependent transmembrane transporter family that is expressed predominantly in the liver and kidneys, and only to a lesser extent in tissues affected by PXE. The physiological substrates of ABCC6 remain to be determined, but the current hypothesis is that PXE should be considered to be a metabolic disease with undetermined circulating molecules interacting with the synthesis, turnover, or maintenance of elastic fibres.

Pseudoxanthoma elasticum (PXE; MIM 264800) is an inherited systemic disease of connective tissue primarily affecting the skin, retina, and cardiovascular system. PXE is characterised by elastic fibre mineralisation and fragmentation, resulting in a diagnostic pathology picture called “elastorrhexia”. To a lesser extent, milder ultrastructural alterations of other extracellular matrix (ECM) components (collagen fibrils and glycosaminoglycans) have been demonstrated. Cutaneous PXE was first delineated in 1896 by Darier, who coined the term “pseudoxanthoma elasticum”, stating that the yellowish papules of PXE differed from authentic xanthomas and were related to elastic tissue fragmentation. Angioid streaks—the cardinal ophthalmological sign of PXE—were also described in the 19th century. They were independently related to PXE skin changes by Grönlund and Strandberg in 1929. Precocious atheromatosis was the last sign to be related to the condition. Carlborg reported cardiovascular elastic calcification in 29 Swedish patients with PXE in 1944.

PXE was thought for a long time to be a primary disorder of the elastic fibre system, with candidate genes encoding structural components of the fibres (elastin, fibrillins, or other microfibril associated (glyco)proteins) or related enzymes. Surprisingly, it was eventually linked to mutations in the ABCC6 (ATP binding cassette subtype C number 6) gene. ABCC6 encodes ABCC6, a member of the large ATP dependent transmembrane transporter family. ABCC6 is abundantly expressed in liver and kidney cell membranes, and to a lesser extent in other tissues affected or not by PXE (skin, vessel walls, and retina). Even though the substrates transported by ABCC6 remain to be determined, the association of PXE with ABCC6 efflux transport alterations raises new and exciting pathophysiological hypotheses. Among these, a current theory is that PXE is a systemic metabolic disease resulting from a lack or accumulation in the blood stream over time of molecules interacting with ECM synthesis, turnover, or maintenance.

METHODS
We searched Medline in November 2004 using the key words “pseudoxanthoma elasticum”, “PXE”, “ABCC6”, and “MRP6” and considered original papers and progress reports published after 1988. Characteristic clinical events and pathological findings in PXE have been described and reviewed in previous large series and these will be referred to as appropriate. Papers updating recent progress will be commented on in more detail.

Clinical features and management
PXE is found in all populations studied so far. Its prevalence seems higher in Afrikaners from South Africa, mainly because of a founder effect. A ubiquitous female to male ratio of around 2:1 is usually reported, but there is no satisfactory explanation for this. PXE is characterised by marked clinical heterogeneity, even

Abbreviations: ABCC6, ATP binding cassette, subfamily C, member 6; ECM, extracellular matrix; MRP6, multidrug resistance associated protein 6; NBF, nucleotide binding fold; PXE, pseudoxanthoma elasticum
between siblings, in relation to age of onset and the extent and severity of organ system involvement. Most patients have a normal life span.

**Skin involvement**

The primary skin lesion is a yellowish papule of 1 to 5 mm in diameter. Such papular lesions tend gradually to coalesce to form plaques with a cobblestone appearance (fig 1). Typical skin lesions of PXE are located on the neck and in flexural areas. Cervical lesions often develop first, appearing on the lateral aspects and commonly sparing, at least initially, the medial part of the nape. They often rise between the ages of 8 and 12 years, but may be more precocious. Flexural involvement tends to start in the teenage years. The most commonly affected sites are the axillae, but involvement of the antecubital and popliteal fossae and groins is also generally noted. Involvement of anterior aspects of the wrists, umbilicus, or lumbar skin area is less common. At the point of maximum papular coalescence, skin loses its elasticity (rather than becoming hyperelastic) and typical redundant skin folds develop (fig 2). Most patients have limited skin surface involvement, but generalised “cutis laxa-like” PXE can occur and is of considerable aesthetic concern.27 Recently, Lebwohl et al emphasised the clinical value of face involvement.28 These investigators showed that horizontal and oblique mental creases are a valuable sign of PXE (fig 3). These creases have a high specificity for the diagnosis of PXE before the age of 30. Less common cutaneous manifestations have been described occasionally: acne-like lesions on the neck or the trunk, featuring comedones or inflammatory papules;29 elastosis perforans serpiginosa, and reticulate pigmented rash.30 In very rare instances, spontaneous resolution of PXE skin changes has been reported.1 Calcinosis cutis is rarely associated with PXE, and when it occurs it is usually in association with disorders of calcium and phosphate metabolism.31–35 These conditions could be particular subgroups of PXE. Mucosal lesions identical to their cutaneous counterparts may be found on the inner aspect of the lower lip (fig 4), on the cheeks or the palate, or on the genitalia, but also all along the digestive tract mucous membrane.36

A skin biopsy specimen is mandatory for the diagnosis of PXE, in order to show the cardinal histological features. Aberrant clumped and fragmented elastic fibres are demonstrated in the mid-dermis by haematoxylin-eosin-safran staining, or by the use of more specific elastic stains (orcein or Verhoeff’s) which colour the fibres black (fig 5). Deposition of calcium and phosphorus may be shown by the von Kossa stain.17 Characteristic pathological features can be observed in clinically involved skin, but also in apparently normal skin. Lebwohl et al demonstrated occult axillary PXE in four patients who presented with premature cardiovascular disease and angioid streaks but no skin changes.38 The same group previously found pathological skin findings indicative of PXE in scar biopsies from six of 10 patients with angioid streaks but without clinically characteristic skin lesions.39 As an important consequence, the
diagnosis of PXE may be suspected and made in patients without any visible skin involvement.

Ultrastructural elastic tissue alterations are seen in both lesional and non-lesional skin, in contrast to other ECM changes which are only seen in involved skin in the vicinity of altered elastic fibres. Prominent abnormalities affect the elastic fibres, featuring small or large electron-dense bodies (calcifications) and holes in the core of the fibres (fig 6). Calcifications result in “fractures” of the fibres, which occur during biopsy severing. Collagen bundles display fibrils of irregular diameter and occasional flower-like features. Aggregates of filamentous material composed of elastin and proteoglycans are found close to the surface of elastic fibres. Electron microscopic observations are misleading unless elastorrhexia has been demonstrated by optic microscopy. Indeed, the ultrastructural changes described above are not specific for PXE, and may be encountered in other inherited diseases of the ECM, but also in skin aging.

Surgical reduction of excessive and redundant skin may be envisaged in some instances for cosmetic improvement. The long term outcome has been poorly evaluated as patient series are scarce. Viljoen et al reported favourable post-surgical outcome in eight female patients with a mean follow up of six years. Delayed healing and scarring occurred in two of these because of extrusion of transepidermal calcium particles. The efficacy of collagen or autologous fat injections in the mental creases remain to be evaluated.

**Eye involvement**

Elastic tissue is also present in the eye, in a thin layer between the retinal pigment epithelium and the choriocapillaris known as Bruch’s membrane. The elastic fibre content of Bruch’s membrane has a unique maze-like structure interwoven with collagen fibres at the side and differing from elastin structures in the skin and blood vessels. In PXE, Bruch’s membrane becomes calcified and brittle. Cracks in the membrane usually occur on the eye muscle/optic nerve head track forcing lines, so they are not caused by calcification of Bruch’s fibres alone. Elastic fibre alterations are responsible for acquired dehiscences and subsequent cracks in the membrane, ophthalmoscopically resulting in “angioid streaks” (fig 7). Angioid streaks are greyish irregular lines radiating outward from the optic papilla and grossly resembling vessels, hence the name. They are optimally visualised using fluorescein or indocyanine green angiograms. Angioid streaks are not in most cases responsible for visual symptoms but may be complicated by proliferation of aberrant choroidal neovessels into the subretinal space (fig 8). Neovessels have brittle walls, and this may result in recurrent, spontaneous, or trauma induced retinal haemorrhages. Neovessels and retinal haemorrhages result in macular symptoms (metamorphopsia, scotoma), peripapillary atrophy, disciform macular/foveal scarring, and definitive central visual loss. Eventual blindness is not uncommon in patients with PXE. Additional ocular features of PXE, such as the “peau d’orange” appearance (diffuse...
pectoris or silent coronary insufficiency may be present. Intermittent claudication in the lower limbs and tiredness suggest the diagnosis of PXE in young individuals. Absence of peripheral pulses is frequent, and should correlate with the development of arterial collaterality. Consequently, the slow course of vessel narrowing is associated with elastin fragmentation and proteoglycan accumulation in patients with pseudoxanthoma elasticum.

Cardiovascular involvement

Elastic fibre-rich arterial walls are also involved in the pathology of PXE, resulting in precocious and slowly evolving segmental arterial narrowing. This atheromatosis is histologically indistinguishable from other causes of atheroma such as tobacco use or chronic hypertension. The internal elastic laminae of small and middle sized arteries are mainly involved. The slow course of vessel narrowing is associated with the development of arterial collateralarity. Consequently, severe vascular symptoms are infrequent in PXE. Kornet et al found that a thicker and more elastic carotid artery was associated with elastin fragmentation and proteoglycan accumulation in patients with pseudoxanthoma elasticum. Two types of clinical manifestations may result from arterial involvement:

Oclusive arterial disease may be responsible for limb arteritis, coronary artery disease, digestive angina, and cerebrovascular disease. Absence of peripheral pulses is frequent, and should suggest the diagnosis of PXE in young individuals. Intermittent claudication in the lower limbs and tiredness in the upper limbs are the most common symptoms. Angina pectoris or silent coronary insufficiency may be present. Myocardial infarction is rare, but has been reported in teenagers or young individuals. Thus PXE should be considered in young patients with precocious coronary artery disease and no cardiovascular risk factors. Apart from rare reports to the contrary, surgical coronary revascularisation seems valuable. However, the left internal mammary artery may be involved in PXE and is not suitable for bypass grafting.

Ischaemic brain infarction in patients with PXE is caused by small vessel disease. This is uncommon but more prevalent than in the general population. In the same recent large series, an association between intracranial aneurysms and PXE was ruled out. Renovascular hypertension is probably also rare: we have only seen one case in our series of more than 60 individuals with PXE (unpublished data).

Mucosal bleeding may also occur as the consequence of arterial involvement, although its precise mechanism remains to be determined. Some investigators have proposed that bleeding may be related to defective submucosal vasoconstriction. The gastrointestinal tract is by far the most common location, but case reports appear to have overestimated this severe complication. The precise source of bleeding may be difficult to identify, and some haemorrhages require radical surgery. Three patients in our series have had a gastrectomy for haemostasis. Uterine or bladder bleeding has also occasionally been observed. However, it is worth noting that there is no vascular brittleness in PXE. Spontaneous rupture of vessel walls, as seen in the vascular type of Ehlers–Danlos syndrome, has not been reported in PXE. Thus vascular surgery or radiological procedures can be carried out if indicated.

Heart involvement is uncommon in PXE. Whether valvar diseases, such as aortic or mitral stenoses or mitral valve prolapse, are significantly associated with PXE remains to be determined using stringent diagnostic criteria. Restrictive cardiomyopathy in relation to diffuse endocardial fibroelastosis seems to be specific for PXE but is very rare.

Visual complications are very difficult to treat and have the greatest impact on disability and quality of life in patients suffering from PXE. Laser therapy is used when there are submacular neovessels. This may be effective at stopping vessel proliferation or bleeding, but it causes retinal burns and subsequent scotomata. Because the anatomical lesions are reminiscent of age related macular degeneration, laser phototherapy coupled with verteporfin infusions has been attempted. To date, the functional results of such treatment remain unclear in PXE and comprehensive analysis of the results obtained in series of treated individuals is required. Finally, surgical procedures such as macular translocation for subfoveal choroidal neovascularisation have occasionally been undertaken. The use of antiangiogenic drugs in the prevention of choroidal neovascularisation and bleeding is in the domain of preclinical research.

Table 1: Clinical differential diagnosis of the skin lesions of pseudoxanthoma elasticum

<table>
<thead>
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<th>Feature</th>
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<td>Papules</td>
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<td></td>
<td>Skin aging [chronological and/or actinic]</td>
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<td></td>
<td>Elastoma, Buschke–Ollendorff syndrome</td>
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<tr>
<td></td>
<td>Pseudo-PXE related to saltpeter or D-penicillamine</td>
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<td>Papular elastorrhexia</td>
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<td></td>
<td>Elastosis perforans serpiginosa</td>
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<td></td>
<td>Perforating periluminal PXE</td>
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<tr>
<td>Plaques or</td>
<td>Elastoderma</td>
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<tr>
<td>redundant skin</td>
<td></td>
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<tr>
<td></td>
<td>Anetoderma</td>
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<td></td>
<td>Cutis laxa</td>
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<tr>
<td></td>
<td>Ehlers–Danlos syndrome (rare)</td>
</tr>
</tbody>
</table>

PXE, pseudoxanthoma elasticum.
Other manifestations
Gheduzzi et al recently showed that ultrastructural alterations in the elastic fibres were present in virtually all organs and tissues obtained postmortem from two PXE patients. However, clinical manifestations only occur in tissues that are rich in elastic fibres. The lung is a remarkable exception, for which there is no explanation. Interestingly, calcification may also be present on mammograms. This might be of diagnostic value in women, and breast tumour microcalcifications are usually easily ruled out.

Most women with PXE have normal pregnancies and deliveries. Case reports have overemphasised the risk of gastric bleeding during pregnancy, and it is certainly uncommon. Ophthalmological monitoring is, however, important in order to prevent retinal haemorrhages during labour. A recent review states that there is no basis for advising women with PXE to avoid becoming pregnant, and that most pregnancies in PXE are uncomplicated.

Positive and differential diagnosis
Positive diagnosis
A classification of PXE into clinical subtypes has been proposed previously. Its relevance should be re-evaluated in the light of the identification of ABCC6 as the causative gene. Up to now, the minimum criteria for the diagnosis of PXE have been the association of dermal elastorrhexia (with or without clinically visible changes) with angioid streaks. While this is most always true, we have shown in rare patients with two identified ABCC6 mutations that one or other criterion could be absent. This observation was confirmed by recent investigations in two Italian families in which one patient with two identified mutations showed only ocular symptoms, while another had only skin involvement. Neither a positive family history nor symptomatic atheromatosis is a constant feature of PXE, so the absence of either does not exclude the diagnosis. ABCC6 genotyping is at present only available in specialised centres and its value for diagnosis remains to be determined (see below).

Dermatological differential diagnosis
Clinical and pathological recognition of skin changes suggestive of PXE is often easy. Conditions that mimic PXE clinically are summarised in table 1. In most instances, pathological findings rule out the diagnosis by demonstrating increased or decreased elastic tissue without elastic fibre fragmentation or calcification. Cutaneous and articular hyperlaxity may occur in PXE but are less severe than in the Ehlers–Danlos syndromes.

Ophthalmological differential diagnosis
Angioid streaks are not specific for PXE and have also been encountered in inherited haemoglobinopathies, Marfan’s syndrome, Ehlers–Danlos syndromes, or Paget’s disease of bone. An additional and not yet well classified dominant autosomal condition has recently been described in a three generation Italian pedigree. In this family, affected individuals had mottled fundi, angioid streaks, and drusen in various combinations, but no skin involvement suggestive of PXE, and linkage to ABCC6 was excluded.

Recommendations for the care of patients with PXE
At present there is no specific treatment for PXE. Management focuses on prevention, screening, and monitoring of complications. However, standards of follow up (type and rhythm) do not exist in PXE, and the identification of individuals who will develop serious complications related to PXE is difficult.

Prevention
The role of diet is not clear. A single study stated that early calcium restriction could have a positive influence on the evolution of PXE by reducing the extent of mineralisation. However, this work was based on a questionable (and unvalidated) system of severity grading and retrospective evaluation of calcium intake, which considerably reduced the validity of the author’s conclusions.

Sports using balls and combat sports are contraindicated, to reduce the occurrence of facial trauma and the subsequent development of angioid streaks or retinal haemorrhages. Reduction of atheromatosis risk factors has been proposed: avoidance of smoking; control of diabetes, lipid disorders, and hypertension. Aspirin, non-steroidal anti-inflammatory drugs, or other hypocoagulant drugs should be avoided because of the risk of mucosal bleeding. The benefit to risk ratio of these drugs in the presence of cardiovascular complications is unknown in PXE, and caution is advised.

MOLECULAR GENETICS
Identification of the PXE gene
PXE has previously been considered as a heritable connective tissue disease with primary involvement of elastic fibres. Genes encoding elastin and elastin associated proteins were therefore functional candidate genes. Subsequently, genes encoding elastin (located on chromosome 7) and fibrillin 1 and 2 (respectively located on chromosomes 15 and 5) were excluded by linkage analysis. Furthermore, other genes encoding members of the microfibrillar protein family and
lysyl oxidase, an enzyme participating in crosslinking of the elastic fibres, were also excluded. More recently, the PXE gene was mapped to chromosome 16p13.1 using positional cloning approaches. Further studies refined this locus to a region of about 500 kb containing five genes with no obvious relation to the extracellular matrix of connective tissue (ABCC1, ABCC6, MDR5, and two copies of an unknown gene subsequently identified as gene encoding the Nuclear Pore Interacting Protein (NPIP)). Direct sequencing of these genes identified pathogenic mutations in the ABCC6 gene. The PXE gene: ABCC6

ABCC6 belongs to the subfamily C of ATP binding cassette (ABC) genes which includes 13 members (ABCC1 to ABCC13). ABC proteins are active pumps that can transport various substrates—including ions, phospholipids, steroids, polysaccharides, amino acids, and peptides—against the substrate’s concentration gradient across membranes. They are implicated in drug and antibiotic resistance, signal transduction, protein secretion, and antigen presentation.

ABCC6 consists of 31 exons spanning ~73 kb. The ABCC6 mRNA, ~6 kb in size, has an open reading frame of 4.5 kb encoding ABCC6 (multidrug resistance associated protein 6), a 1503 amino acid protein. ABCC6 is predominantly expressed in human liver and kidneys. Low expression levels of ABCC6 were detected in tissues involved by PXE (skin, vessel walls, and retina), and in other tissues not affected by PXE. Two ABCC6 pseudogenes homologous to the 5’ part of ABCC6 (exon 1 through intron 9, and exon 1 through intron 4) were recently identified and are closely mapped to ABCC6.

The PXE protein: ABC6

ABC6 is composed of three hydrophobic membrane segments comprising five, six, and six transmembrane spanning domains, respectively, and two evolutionarily conserved intracellular nucleotide binding folds (NBF) (fig 9). NBFs contain conserved Walker A and B domains, and conserved C motif critical for ATP binding and transmembrane transporter functions.

ABCC6 was classified as a multidrug resistance-associated protein because of its homology with MRP1. Indeed, ABCC6 and MRP1 are the most closely related members of the MRP family, with 45% identity. MRP1 is a well characterized transmembrane efflux pump transporting amphipathic anionic conjugates and glucuronidated and sulphated compounds. ABC6 was associated, under in vitro conditions, with the MgATP dependent transport of the glutathione S-conjugate leukotriene C(4) and S-(2,4-dinitrophenyl)glutathione, and the cyclopentapeptide BQ123.

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<td>Intron 17</td>
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<td>IVS18-2delAG</td>
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<td>Intron 17</td>
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<td>63</td>
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<tr>
<td>IVS21-1G→-T</td>
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<td>Intron 21</td>
<td></td>
<td>86, 90</td>
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<td>IVS25-3C→-A</td>
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<td>Intron 25</td>
<td></td>
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<tr>
<td>IVS26-1G→-A</td>
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<td>Intron 26</td>
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<tr>
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<td>Exon 8</td>
<td>90</td>
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<tr>
<td>3544dupC</td>
<td>4220insAGAA</td>
<td>Frameshift</td>
<td>Exon 25</td>
<td>87</td>
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<tr>
<td>Small deletion</td>
<td>179_187del</td>
<td>Frameshift</td>
<td>Exon 2</td>
<td>78</td>
</tr>
<tr>
<td>179_195del</td>
<td></td>
<td>Frameshift</td>
<td>Exon 2</td>
<td>90</td>
</tr>
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NBF1 and NBF2, respectively), four are located in transmembrane domains, and only two mutations have been identified in extracellular domains. Distribution of the missense mutations through ABCC6 is indicated in fig 9. This distribution of mutations is consistent with the role of NBFs in ATP driven transport. Functional studies have already shown that ABCC6 transport is abolished by missense mutations located in the NBF2. This distribution suggests that intracellular domains different from NBFs are also functionally important, possibly through recognition of the substrate.

Although most of the 90 pathogenic mutations have been identified in one or a limited number of families, two variants (Ex23_29del and R1141X) are recurrent mutations. The frequency of these two recurrent mutations differs according to the population studied: mutation Ex23_29del represents 28% of the detected mutations in the US population and 28% in the European population. Mutation R1141X represents 4% in the European population, whereas mutation R1141X is found in 26% in Italian patients and 13% in the French population. A common founder effect was identified for mutation R1141X in French and Italian populations. We found that arginine codon 518 was a recurrently mutated amino acid in a cohort of 19 French families with PXE (11.5% of the detected mutations for each variant R518Q and R518X). These two mutations represent 19% of the mutations detected in the Italian population. In Japanese patients, neither R1141X nor Ex23_29del mutations were identified, whereas mutations 2542delG and Q378X account for 53% and 25%, respectively. In South African families of Afrikaansers, mutation R1339C represents more than half of the mutations detected, with a common haplotype indicating a founder effect. These mutations are rarely identified in American or European populations.

The detection rate in different studies varies from 0.55 to 0.83. Lack of mutation detection in some patients could reflect exonic deletions (for example, deletion of exon 15), splice site mutations distant from the coding sequence, mutations in the gene regulatory sequences, or investigation of patients with acquired PXE-like syndrome not related to ABCC6 mutations, such as seen in β thalassaemia and sickling syndromes (see below). Locus heterogeneity of PXE is unlikely, but cannot currently be ruled out.

### Table 2

<table>
<thead>
<tr>
<th>Nucleotide variation</th>
<th>Protein alteration</th>
<th>Location (gene)</th>
<th>Location (protein)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>220, 222del</td>
<td>V74del</td>
<td>Exon 3</td>
<td>88</td>
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<td>86delC</td>
<td>Frameshift</td>
<td>Exon 8</td>
<td>84</td>
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<td>10, 1120del</td>
<td>Q363, R373del</td>
<td>Exon 9</td>
<td>88</td>
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<td>1944, 1966del</td>
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<td>Exon 16</td>
<td>15, 87</td>
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<td>1995delG</td>
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<td>Exon 16</td>
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<td>254delG</td>
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<td>Exon 19</td>
<td>90</td>
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<td>3343, 3345del</td>
<td>Frameshift</td>
<td>Exon 23</td>
<td>This study</td>
<td></td>
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<td>3775delF</td>
<td>Frameshift</td>
<td>Exon 27</td>
<td>15, 87, 90</td>
<td></td>
</tr>
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<td>4104delC</td>
<td>Frameshift</td>
<td>Exon 29</td>
<td>90</td>
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<td>4318delA</td>
<td>Frameshift</td>
<td>Exon 29</td>
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<td>4318delA</td>
<td>Frameshift</td>
<td>Exon 30</td>
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<tr>
<td>Large deletion</td>
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<td>Exons 23–29</td>
<td>84, 85, 88, 90</td>
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<tr>
<td></td>
<td></td>
<td>ABCC6</td>
<td>15, 84</td>
<td></td>
</tr>
</tbody>
</table>

Nucleotide numbers are derived from cDNA ABCC6 sequences (GenBank accession no. NM_001712.2). CL X, cytoplasmic loop number X; COOH, C terminal portion; ECL X, extracellular loop number X; NBF X, nucleotide binding fold number X; T3 X, transmembrane segment number X.

### CLINICAL GENETICS

#### Mode of inheritance

PXE was first described as a sporadic disorder, but both autosomal recessive and autosomal dominant inheritances have been reported. In fact, no molecular evidence for autosomal dominant inheritance has been established to date, and a body of evidence supports a common (probably exclusive) autosomal recessive inheritance of PXE. First, no family with PXE transmitted through three generations has been published. Second, both dominant and recessive forms of PXE have been linked to the same chromosomal region 16p13.1, and ABCC6 mutations were identified in families described with autosomal recessive or dominant inheritance. Moreover, no specific dominant mutation has been described, and the same mutations have been identified in recessive and dominant families. Third, identification of ABCC6 mutations established pseudodominant inheritance in two families. Finally, clinical delineation of the disease may be confusing because limited manifestations can be detected in some heterozygous carriers, and because cutaneous findings mimicking PXE, or cardiovascular manifestations, can be found in the general population, although at an older age.

A recent review questioning autosomal dominant PXE concluded that this mode of inheritance might exist, but it would then be marginal.

#### Genotype–phenotype correlation

To date, no correlation has been established between the phenotype and the nature or the position of the mutations. A high degree of allelic heterogeneity makes such an approach difficult. Nevertheless, homozygosity or compound heterozygosity for mutations leading to a premature stop codon is not significantly associated with a more severe phenotype. High intrafamilial phenotypic variation is suggestive of the contribution of factors other than ABCC6 genetic background to phenotype severity, such as nutrition, hormones, lifestyle, environmental factors, or medical history. ABCC6 independent modifying genetic factors may also contribute to the phenotype severity.

#### Epidemiology and allelic frequencies

The prevalence of PXE in the general population is still uncertain, but estimates have increased dramatically over recent decades. A few years ago an estimated prevalence of 1 in 10^5 births or less could be found in textbooks. This was undoubtedly an underestimate, probably reflecting in part a
lack of knowledge of PXE by physicians. In 2000, the American patients support group PXE International proposed a prevalence of PXE of ~1/25 000 in New England. According to this prevalence, the calculated frequency of heterozygosity using the Hardy–Weinberg law is 1.25% (1/80).*

In 2002, Trip et al reported that the prevalence of the sole R1414X mutation was significantly increased in young individuals with coronary artery disease (3.2%), but was also frequent in the general Dutch population. They identified eight heterozygous carriers for mutation R1414X among 1057 controls (0.76%). This mutation represents about one quarter of the mutant alleles in this population. Thus the frequency of heterozygous carriers in the population could be estimated to be approximately 3% (0.76%×4). This high rate of heterozygous carriers was unexpected. This result should be confirmed by other studies in other countries (even if PXE is a ubiquitous condition), but it suggests that the prevalence of PXE individuals (temporarily defined as individuals carrying two ABCC6 mutations) is around 1/4450, assuming this population is in Hardy–Weinberg equilibrium.†

One critical issue is to determine whether all individuals carrying two ABCC6 mutations have a PXE phenotype. In France (750 000 liveborn infants/year), with a disease prevalence of 1/4450, 169 individuals carrying two ABCC6 mutations should be born each year (or 30 with a prevalence of 1 in 25 000). However, far fewer than 1000 patients are recognised as having PXE in France. Do the remaining individuals have a mildly symptomatic form of PXE that does not prompt them to seek medical advice? Do they have a total absence of symptoms? The consequence of this observation is that the classical PXE phenotype may only represent a small proportion of the ABCC6 mutation carriers.

Heterozygous carriers
Sherer et al have reported on mild ophthalmological or cutaneous involvement in heterozygous carriers but they did not indicate the frequency of this phenomenon in their cohort of patients. A few reports have emphasised the carriage of a sole ABCC6 mutation as a cardiovascular risk factor. In the study by Trip et al, mutation R1414X in ABCC6 appeared to be an independent risk factor for coronary heart disease in young people. This observation, if confirmed in other similar cohorts, could be of course of considerable concern for public health.

Because some PXE patients sometimes have only moderate symptoms, it can be very difficult to distinguish patients with mild PXE from heterozygous carriers with mild expression. The course and prognosis are probably not the same for these two categories, and this should prompt clinicians to consider molecular diagnosis in members of pedigrees with a patient suffering from PXE.

Genetic counselling
PXE mode of inheritance is probably exclusively autosomal recessive. Risk for parents of an affected child is therefore one in four for another pregnancy, without the possibility of evaluating the phenotype severity. For a PXE patient the risk of having affected children varies, in the absence of consanguinity, with the rate of heterozygous carriage in their population. In the light of the recent data, that risk could lie somewhere between 1/66 (for a rate of 1/33 heterozygous carriers (%)) to 1/160 (for a rate of 1/80 heterozygous carriers). This risk is significant and could explain pseudo-dominant inheritance in some families.

Novel issues in pathophysiology and perspectives
Pathophysiology
Both elastin synthesis and degradation are accelerated in the dermis of PXE patients compared with controls, and this seems to correlate with age and with the extent of the disease. The time dependent mineralisation of elastic fibres has been recurrently studied by several groups over the past 20 years. A critical step in the pathogenesis of PXE was achieved when Baccarani-Contri et al revealed the mechanisms whereby PXE elastic fibres become calcified and secondarily fragmented. Using immuno-electron microscopy these investigators showed that elastic fibres had enhanced expression of normal constitutive proteins (for example, vitronectin), but also accumulated aberrant matrix proteins known for their high affinity for calcium and normally involved in mineralisation processes (such as alkaline phosphatase, bone sialoprotein, and osteonectin). The investigators therefore stated that PXE was primarily a disorder of the fibroblast, in accordance with their previous results showing arguments for aberrant fibroblast behaviour. The study by Quaglino et al showed that PXE skin fibroblasts had altered cell–cell and cell–matrix interactions and enhanced proliferation, with synthesis capabilities in vitro.

Other biochemical reports are also in favour of a role of the fibroblast in PXE, as other matrix structural alterations have been demonstrated in addition to elastorrhexia. Aggregates of thread material containing glycosaminoglycans, as well as structural collagen fibril alterations, are seen in the vicinity of elastic fibres. Abnormalities in the metabolism of glycosaminoglycans have been found.

Most of these observations were made before the identification of ABCC6 as the PXE gene, and the outstanding question now is to find the link between the absence or the functional insufficiency of a membrane transporter in liver and kidney and the mineralisation of elastic fibres in distant organs. The hypothesis that PXE is a metabolic disorder with impaired and circulating factors responsible for elastic tissue changes has been proposed. The metabolic hypothesis does not exclude the possibility of local changes in clinically involved tissues and cells.

β Globin diseases: another pathway to the phenotype?
One of the most puzzling findings in the field of clinical and basic PXE research is that patients with inherited haemoglobinopathies, most often β thalassaemia, but also sickling syndromes, may have elastic tissue changes closely resembling PXE. Indeed, the so called “PXE-like” clinical syndrome consists in skin, eye, and cardiovascular symptoms indistinguishable from those of “classic PXE”. Notably, these manifestations occur later in life than in patients with PXE, and their prevalence increases with advancing age. Their frequency is significant in patients with major or intermediated β thalasaemia: in a cohort of 100 consecutive patients, 15 had skin changes, 20 had angiod streaks, and 26 at least one of both symptoms. The causative defect is believed to be acquired and related to the primary haemoglobinopathy. Baccarani-Contri et al showed, however, that structural elastic changes were strictly identical to those they had described in “classic” PXE. Hence, the “PXE-like” phenotype identified in a number of cases of thalassaemia is indistinguishable from “classic PXE”, but with no defect in

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* Hardy–Weinberg law: \( p^2+2pq+q^2=1 \), with \( p \) and \( q \) being the frequency of the wild type and the mutated alleles respectively, \( p^2 \) the frequency of homozygosity for the wild type allele, \( 2pq \) the frequency of heterozygosity, and \( q^2 \) the frequency of the disease. Here, \( q^2 = 1/25 000, q = 1-(1/25 000) = 0.99963; p = 1-q = 1-0.0063\) = 0.9937. Thus the frequency of one heterozygous carrier (2pq) can be calculated as \( 2-0.9937\times0.0063 \approx 0.0125 \) (1/80).

† Here the frequency of heterozygous carriers (2pq) = 0.03 (3%). Thus, considering \( p \approx 1, q = 0.03/2 = 0.015, \) and the frequency of the disease \( q^2 = 0.015^2 = 2.25\times10^{-4} \approx 1/4450 \).
We thank our colleagues Drs P Bonicel, F Maître, and B Arbeille for

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