Does autosomal dominant pseudoxanthoma elasticum exist?

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ABSTRACT

Pseudoxanthoma elasticum (PXE) is a progressive disorder of elastic fibres in skin, eyes, and arterial walls. It is caused by mutations in the ABCC6 gene. Most patients are sporadic cases. The majority of familial cases show autosomal recessive (AR) inheritance, but autosomal dominant (AD) inheritance has also been reported. We reviewed the literature on AD PXE and we studied in detail, both clinically and by DNA studies, a selection of potentially AD pedigrees from our patient population consisting of 59 probands and their family members. Individuals were considered to have definite PXE if they had two of the following three criteria: characteristic ophthalmologic signs, characteristic dermatologic signs, and a positive skin biopsy. In the literature we found only three families with definite PXE in two successive generations and no families with definite PXE in three or more generations. Our own data set comprised three putative AD families. Extensive DNA studies revealed a mutation in only one ABCC6 allele in the patients of these families. Only one of our families showed definite PXE in two generations. Linkage studies revealed that pseudodominance was unlikely in this family. In the other two families AD PXE could not be confirmed after extensive clinical examinations and application of our criteria, since definite PXE was not present in two or more generations.

Conclusion: the inheritance pattern in PXE usually is AR. Part of the phenotype in family members of PXE patients might be due to expression in heterozygous carriers of an AR disease. AD inheritance in PXE may exist, but is both after careful literature study and in our patient material much rarer than previously thought.

Key words: autosomal dominant, pseudoxanthoma elasticum, ABCC6
INTRODUCTION

Pseudoxanthoma elasticum (PXE) is a heritable disease of elastic tissue, especially affecting the skin, the retina, and the cardiovascular system. Its prevalence is estimated to be about 1 in 100,000 subjects. The skin shows yellowish papules and plaques, mainly on the lateral side of the neck and on flexural areas of the body, sometimes accompanied by redundant skin folds. Common ocular signs are peau d’orange of the retina, followed by angioid streaks, which are ruptures in Bruch’s membrane in the retina. Neovascular membranes from the choriocapillaris can develop through these ruptures and cause disciform macular degeneration, eventually leading to severe visual loss. Patients have an increased risk of cardiovascular disease and of (mainly gastrointestinal) hemorrhages. Histopathologically, elastic fibers in the affected tissues show rather characteristic fragmentation, clumping, and calcification [1].

At a consensus conference in 1992, diagnostic criteria for PXE have been defined [2]. Major criteria were “characteristic skin involvement”, “characteristic histopathologic features of lesional skin” and “characteristic ocular disease in adults older than 20 years of age”. Minor criteria were “characteristic histopathologic features of nonlesional skin” and “family history of PXE in first-degree relatives”. Based on these criteria five different PXE categories were distinguished. Unfortunately, minimal diagnostic criteria for the diagnosis “PXE” have not yet been established. There are no pathognomonic clinical signs, apart from comet-like lesions in the retina [3].

Establishing the inheritance pattern in PXE pedigrees solely on the basis of clinical data is difficult and complicated by the variable expression of the disease, the presence of mild symptoms in heterozygous individuals, mimicking dermatoses, as well as potential pseudodominance due to consanguinity or high carrier frequency. The majority of PXE cases is sporadic [1]. In families, autosomal recessive (AR) inheritance was mostly observed, but a small subset of families was reported to have autosomal dominant (AD) inheritance. However, even when PXE symptoms are present in two subsequent generations, AD inheritance remains uncertain [1, 4].

Recently, the gene for PXE, ABCC6, was identified [5-7]. Mutations in ABCC6 have been found in sporadic patients, in families with AR as well as in families with reported AD PXE. There were no indications for genetic heterogeneity of the disease [8, 9]. Obviously, if both ABCC6 alleles of a patient carry a mutation, AR inheritance is most plausible in that family. However, if only one mutation is found, the presence of a second, as yet unknown, mutation can not be excluded. The current mutation detection rate for ABCC6 mutations implicated in PXE was at least 0.55 (mutations per allele). In 22 (37%) of 59 patients a mutation was found in both alleles [10]. For genetic counseling it is important to know if AD inheritance really exists in PXE and, if so, what its frequency and penetrance are. The aim of this paper was to scrutinize the existing literature on evidence for AD PXE according to present standards and to study our data set of 59 PXE patients and families, both clinically and by DNA studies, for evidence of AD inheritance.
MATERIAL AND METHODS

Literature search on AD PXE families
A PubMed search spanning the period 1966 to January 2003 was performed using search terms “pseudoxanthoma elasticum” and “dominant”. More articles were derived from the reference lists of these articles. For each published pedigree, the size and structure of the family, age of the family members, and the reported skin and eye abnormalities for each family member were reviewed. Individuals were considered to have definite PXE if they had at least two of the three following criteria: ophthalmologic or dermatologic signs or a positive skin biopsy, as mentioned below, even if not reported in detail (like ‘classical’ or ‘typical’ skin abnormalities). When only two criteria were mentioned and we were uncertain about one of these criteria, the diagnosis was considered probable.

Clinical examination of our patients
All 23 patients and family members from the three families, which participated in this study, were examined by an ophthalmologist and dermatologist. Ophthalmologic examination included assessment of visual acuity, slit-lamp examination, fundoscopy and, in case of doubt, fluorescein angiography. The majority of the participants (15/23) had a skin biopsy. The ophthalmologist, dermatologist, and pathologist were masked as to the genotype of the patients. Blood was taken for DNA studies. Permission for this was given by the medical ethical committee of the Academic Medical Center in Amsterdam and informed consent was obtained. We considered the diagnosis PXE definite if two of the following three criteria were present: 1. yellowish papules and/or plaques on the lateral side of the neck and/or flexural areas of the body (especially the axillae, antecubital fossae, groins and popliteal spaces); 2. typical histopathological changes in a skin biopsy after Von Kossa staining (fragmentation, clumping, and calcification of elastic fibers); and 3. one or more of the following retinal abnormalities (seen at any time during the patients life): peau d’orange, angioid streaks or comet-like streaks (pinpoint white lesions of the choroid with a hypopigmented tail in the retinal pigment epithelium, also called “comets”[3]).

Molecular analysis
Isolation of DNA from peripheral blood samples and haplotype analysis with microsatellite DNA markers was performed in families according to standard protocols essentially described elsewhere [11]. PCR primers were selected from the published sequence of human chromosome 16 BAC clone A-962B4 (GenBank Accession No. U91318), TIGR database (http://www.tigr.org), or the primers were a gift of collaborators (C. Boyd). To distinguish between the ABCC6 gene and pseudogene sequences, novel primers for exon 1-9 were developed [12]. To amplify and screen both exon and adjacent intron sequences, PCR products were derived from intronic sequences 20-50 bp out from the end of each ABCC6 exon. PCR was performed on DNA in each PXE patient. PCR products were pre-screened using SSCP. Fragments with a mobility shift were characterized by direct sequencing [5]. All putative disease causing mutations were also
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Screened in at least 100 control chromosomes from healthy (ophthalmologically examined) individuals from a hospital based Dutch population, to distinguish the disease causing mutations from polymorphic variants. The potential presence of intragenic large deletions of genomic DNA was confirmed by consistent lack of amplification of the relevant exons in patients who were heterozygous or homozygous for the deletion. Intragenic deletions were detected by FISH or Southern blots using PCR-amplified ABCC6 exons as a probe.

RESULTS

Literature on AD PXE families

Pope (1974) previously observed a frequency of AD PXE of 53% [13]. He reported to have clinicogenetical data on 142 patients. There were 121 index patients and families of which 64 were classified as AD, and the remainder as AR. The patients from families with multiple affected generations and with all possible combinations of parent-child transmission were placed in the AD group. The families with affected sibs but no affected parents or children were placed in the AR group. Based on clinical differences alone he distinguished two AR and two AD types [14]. It was not clear to us how this classification was brought about. Sporadic cases were allocated to one of these types based on clinical findings. On the other hand, Neldner (1988) found potential AD inheritance in only three (3%) out of a population of 100 PXE patients. Two of these three families comprised a mother-daughter pair, the third patient was said to have a father with PXE. No further details were given [1].

We selected 18 putative dominant PXE families from the literature, which were described in 16 publications. A summary of the data is presented in Table 1. In most reported ‘dominant’ families no definite diagnosis PXE could be made in two (or more) generations, on the basis of our criteria [15-27]. Only in a minority of patients a skin biopsy was reported.

On the basis of our criteria, only three families, in three different reports, presented with PXE in two successive generations [13, 28, 29]. In Fig. 1 a review of these pedigrees is presented, adapted to our criteria. Interestingly, we did not find a single pedigree with definite PXE in three or more generations.

In addition to the families presented above, our search yielded the following reports on AD PXE, that we excluded for various reasons: A male proband with characteristic skin lesions, a positive biopsy, angioid streaks, and retinal hemorrhages had a maternal aunt, who also complained of poor vision and had a cutaneous condition similar to his. No more details were given [30]. A mother and her three children did have typical skin abnormalities, but no ophthalmologic signs. The mother had married her cousin, so that AR inheritance is most likely [31]. A father with PXE had a son with probable PXE, but no further details were given [32]. In yet three other patients, who were said to have AD PXE type I, the microscopic and biomechanic features of skin were studied, but the families of these patients were not described [33]. In four recently described families, in which the children were diagnosed with PXE, one of the parents appeared to have limited phenotypic expression [34]. Molecular studies had not been performed yet. The
<table>
<thead>
<tr>
<th>Authors</th>
<th>Ref.</th>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Other abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weve (1934)</td>
<td>[27]</td>
<td>male</td>
<td>54</td>
<td>AS</td>
<td>'very mildly affected'</td>
</tr>
<tr>
<td>Dentii (1938)</td>
<td>[19]</td>
<td>female proband</td>
<td>37</td>
<td>AS, bleeding</td>
<td>skin abn. on neck and elbows</td>
</tr>
<tr>
<td>Kat and Prick (1940)</td>
<td>[24]</td>
<td>female proband</td>
<td>24</td>
<td>AS</td>
<td>'indication of PXE on neck and elbows'</td>
</tr>
<tr>
<td>Osbourn and Olivo (1951)</td>
<td>[26]</td>
<td>female proband</td>
<td>29</td>
<td>AS</td>
<td>'biopsy typical of PXE'</td>
</tr>
<tr>
<td>Coffman and Sommers (1959)</td>
<td>[17]</td>
<td>female proband</td>
<td>68</td>
<td>normal</td>
<td>variable cardiac abn.</td>
</tr>
<tr>
<td>Capusan et al. (1960)</td>
<td>[16]</td>
<td>female proband</td>
<td>24</td>
<td>AS</td>
<td>'similar skin abn.'</td>
</tr>
<tr>
<td>Gills and Paton (1965)</td>
<td>[21]</td>
<td>male proband</td>
<td>24</td>
<td>AS</td>
<td>'biopsy typical of PXE'</td>
</tr>
<tr>
<td>Hull and Aaberg (1974)</td>
<td>[23]</td>
<td>female</td>
<td>60</td>
<td>AS</td>
<td>'compatible with PXE'</td>
</tr>
<tr>
<td>Hull and Aaberg (1974)</td>
<td>[23]</td>
<td>brother</td>
<td>55</td>
<td>AS</td>
<td>'PXE-biopsy proven'</td>
</tr>
<tr>
<td>Hull and Aaberg (1974)</td>
<td>[23]</td>
<td>-his daughter</td>
<td>16</td>
<td>AS</td>
<td>normal</td>
</tr>
<tr>
<td>Hull and Aaberg (1974)</td>
<td>[23]</td>
<td>-her son</td>
<td>14</td>
<td>AS</td>
<td>'coarse furrows in neck'</td>
</tr>
<tr>
<td>Cunningham et al. (1980)</td>
<td>[18]</td>
<td>female proband</td>
<td>10</td>
<td>AS, MD</td>
<td>'peau d'orange'</td>
</tr>
</tbody>
</table>

* Table 1. Literature on PXE in two or more generations.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Findings</th>
<th>Mother</th>
<th>Father</th>
<th>Sibling</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bao et al. (1991)</td>
<td>1991</td>
<td>Female proband</td>
<td>25</td>
<td>AS, peau d'orange</td>
<td>yellow papules and plaques</td>
<td>25</td>
<td>54</td>
<td>peau d'orange</td>
<td></td>
</tr>
<tr>
<td>Hausser and Anton-Lamprecht (1991)</td>
<td>1991</td>
<td>Female proband</td>
<td>47</td>
<td>visual impairment</td>
<td>typical lesions, pos. biopsy</td>
<td>18</td>
<td>54</td>
<td>peau d'orange</td>
<td></td>
</tr>
<tr>
<td>Katagiri et al. (1991)</td>
<td>1991</td>
<td>Female proband</td>
<td>21</td>
<td>AS, peau d'orange</td>
<td>peau d'orange, cutis laxa</td>
<td>21</td>
<td>47</td>
<td>visual impairment</td>
<td></td>
</tr>
<tr>
<td>Appelmans and Lebas (1953)*</td>
<td>1953</td>
<td>Female proband</td>
<td>50</td>
<td>AS, bleeding, MD</td>
<td>characteristic of PXE</td>
<td>28</td>
<td>50</td>
<td>AS, yellowish retina</td>
<td></td>
</tr>
<tr>
<td>Cahill (1957)*</td>
<td>1957</td>
<td>Female proband</td>
<td>39</td>
<td>AS, MD</td>
<td>characteristic of PXE</td>
<td>18</td>
<td>72</td>
<td>choroidoretinitis, blind, AS</td>
<td></td>
</tr>
<tr>
<td>Pope (1974)</td>
<td>1974</td>
<td>Female proband</td>
<td>42</td>
<td>AS</td>
<td>faint rash on neck, flexures</td>
<td>69</td>
<td>69</td>
<td>mild ‘salmon spotting’</td>
<td></td>
</tr>
</tbody>
</table>
| abn., abnormalities; AP, angina pectoris; AS, angioid streaks; GI, gastrointestinal; interm., intermittent; L, left; M, mother; MD, macular degeneration; MM, mother of M; MMM, mother of MM; pos., positive; ref., reference.

*Only relevant family members have been included.

Definite PXE in two or more generations.
authors concluded that the inheritance pattern in these families was not clear. In a short report a female proband with PXE was described [35]. The authors only mentioned briefly that several other family members were affected, in accordance with AD inheritance.

**Clinical and molecular results in our putative AD families**

We investigated and collected data from 59 apparently unrelated PXE probands from the Netherlands and their family members. In 41.9% of the families PXE segregated in a clear-cut AR fashion. Up to 53% of the patients were sporadic cases or the familial segregation pattern was not clear. The only three families (5%), in which there was a putative AD inheritance pattern, were investigated thoroughly and are described in detail here.

**Family 1.** The pedigree with clinical and DNA data is presented in Fig. 2. The female proband (III-1) was first seen by an ophthalmologist at age 27, because of perceived loss of visual acuity. Upon examination visual acuity was normal, but fundoscopy of both eyes did reveal angioid streaks and peau d’orange. Skin abnormalities on the neck had been noticed since age 4 years. Recent examination by a dermatologist revealed yellowish papules and plaques on the neck, the axillae and antecubital fossae. Histopathologic analysis of a skin biopsy revealed changes typical for PXE. The cardiologist did not find signs of cardiovascular disease. DNA studies showed a 4 bp insertion in exon 30 (4220insAGAA) in a single \( ABCC6 \) allele. The paternal grandfather (I-1) was said to have had a thickened skin of the neck. He died suddenly at age 79 due to a...
cerebrovascular accident. The paternal grandmother (I-2) had a cerebrovascular accident at age 81. The mother (II-1) had a normal fundus on ophthalmologic examination and no skin abnormalities. No ABCC6 mutation was found in her DNA. The father (II-2), aged 51, had normal visual acuity, peau d’orange, angioid streaks, some yellowish papules in the neck (too few to be typical for PXE), and a negative skin biopsy. The cardiologist did not find any abnormalities. The father did have the same mutation as his daughter in one allele. An uncle and two aunts (II-3, II-4, II-5) did not have any ophthalmologic or dermatologic abnormalities on clinical examination. Only one of them (II-4, aged 49) underwent a skin biopsy, that was normal. She had the ABCC6 mutation in one allele, her brother (II-3) and sister (II-5) did not. Fundoscopy of the 24-year-old brother (III-2) of the proband revealed peau d’orange and angioid streaks. Three years later he experienced loss of vision, caused by retinal hemorrhage due to a slap on his eye. He did not have evident skin abnormalities, had a normal skin biopsy and no signs of cardiovascular disease. DNA studies showed the same mutation in one allele and, for both alleles, the same haplotypes as in his sister. In summary, the proband had definite PXE, while her brother and father only had ophthalmologic signs. All three, and a healthy aunt, were heterozygous for the same ABCC6 mutation.

Family 2. The female proband of this family (III-1, Fig. 3) had progressive skin abnormalities in the neck since age 8 years. The dermatologist saw yellowish papules and plaques, mainly on the neck and less pronounced on the axillae and periumbilical area. Histopathologic study of

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Fig. 2. Pedigree of family 1. Bars represent haplotypes of microsatellite markers flanking the ABCC6 gene. The gene is located between the markers 118F2TAA and D16S764. See Fig. 1 for symbol definition; -, mutation absent; +, mutation present; N, unaffected. Definite PXE was only present in III-1.

Fig. 3. Pedigree of family 2. See legend of Fig. 1 and 2. Definite PXE was only present in III-1.
a skin biopsy showed abnormalities characteristic of PXE. Ophthalmologic examination at age 14 showed peau d’orange and one comet-like streak. Extensive screening of the ABCC6 gene revealed a R1141X mutation in only one allele. The maternal grandfather (I-1) was said to have no skin abnormalities. Ophthalmologic examination did not reveal any signs of PXE. However, he did have the R1141X mutation. The father (II-1) was normal. Examination of the mother (II-2) revealed some skin papules, mainly at the right cubital fossa. Histopathologic study of a skin biopsy showed abnormalities characteristic of PXE. She did not have ophthalmologic abnormalities. She also had the R1141X mutation in a single allele. An aunt (II-3) had some yellowish papules on the neck and the cubital fossae. Her skin biopsy showed mild abnormalities in accordance with PXE. At fundoscopy no signs of PXE were noticed. She also was heterozygous for the R1141X mutation. Two uncles and the youngest aunt (II-4, II-5, II-6) all had some yellowish papules at the cubital fossae, not characteristic of PXE. Their skin biopsies and ophthalmologic examinations did not show any abnormalities. One of the uncles had the R1141X mutation. In summary, only the proband had definite PXE. Her mother and aunt only had minimal skin abnormalities. All three, a healthy uncle and the grandfather had the same mutation in one allele.

**Family 3.** The mother (II-2 in Fig. 4) had noticed acute vision loss of the left eye at age 62. On fundoscopy a peripapillary hemorrhage was seen in addition to disciform macular degeneration and angioid streaks. Dermatologic examination showed skin lesions typical for PXE. Histopathology of a skin biopsy, taken in 1973, revealed thickening, fragmentation, and

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**Fig. 4.** Pedigree of family 3, with definite PXE in two generations. The haplotypes in generation II were reconstructed.
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clumping of elastic fibres. No DNA was taken from her before her death. However, the presence of an R1459C mutation in the \( ABCC6 \) gene of a nephew (III-9) suggested that she transmitted this mutation to her affected children (Fig. 4). She had eight children. Two daughters (III-1, III-6) and a son (III-8) had no signs of PXE on examination by both the ophthalmologist and dermatologist. They did not have the R1459C mutation. The eldest son (III-2) noticed visual deterioration at age 48. He had disciform macular degeneration and skin abnormalities characteristic of PXE. Extensive screening of the \( ABCC6 \) gene revealed an R1459C mutation in one allele only. Direct sequencing of the entire cDNA, derived from both alleles, showed one mutated (R1459C) and one wild type \( ABCC6 \) transcript (not shown). Son III-3 was examined at age 61. He had normal visual acuity and angioid streaks. The dermatologist saw some yellowish papules on the neck and axillae, not enough to be characteristic of PXE. Histopathology of a skin biopsy showed doubtful increase of elastic fibres, not conclusive for PXE. He did have the R1459C mutation. Daughter III-4 was examined at age 59. Visual acuity was normal and on fundoscopy, peripapillary atrophy was noted. Fluorescein angiography showed peau d’orange and angioid streaks in both eyes. Dermatologic examination, including a skin biopsy, did not reveal any signs of PXE. She had the R1459C mutation in one allele. Son III-5 had visual deterioration at age 55, caused by retinal detachment of the right eye. He had angioid streaks in both eyes and pigmentary changes in the left macula. One year later he had a hemorrhage in this eye. The dermatologist saw yellowish papules in the subclavicular/presternal area. Histopathologic study of a skin biopsy showed some clumping of elastic fibres. He also had the R1459C mutation in one allele. The youngest daughter (III-7) noticed visual deterioration at age 48. She had angioid streaks and choroidal neovascular membranes in both eyes, for which she had laser therapy. The dermatologist found yellowish papules on the neck, the axillae and antecubital fossae. Histopathologic study of a skin biopsy showed clumping and fragmentation of elastic fibres. DNA studies showed the R1459C mutation in one allele.

In summary, in this family definite PXE occurred in two generations. \( ABCC6 \) transcript analysis showed the presence of one mutated (R1459C) and one wild type allele in all affected family members.

**DISCUSSION**

**Literature on AD PXE families**

The unusually high frequency of AD inheritance (53%), found by Pope, can be explained by the fact that Pope questionably allocated sporadic patients to an AD type, only on grounds of their clinical pattern. Pope described two AD families more extensively. The pedigree of his family 1 is presented in Fig. 1, in which we only show the data that were available from the text. Persons with a question mark were said to be affected, but no further data were given, nor was mentioned whether they had been examined by dermatologist and/or ophthalmologist. In most patients the only ophthalmic sign mentioned was ‘(choroido)retinopathy’. If we assume that this consisted of retinal signs of PXE, AD PXE with reduced penetrance is most
likely. Signs of PXE were present in four generations and there was father-to-son inheritance. Pseudodominance is unlikely, because definite PXE was present in the offspring of three sibs, although it is not clear whether consanguinity could have played a role. In his family we cannot be sure about the diagnosis PXE, partly due to lack of detailed data. The hyperextensible skin and hypermobile joints in this family could also point to Ehlers-Danlos syndrome, that is also associated with angioid streaks.

From our literature search, we selected two more reports of probably AD PXE families (Fig. 1). In these families, described by Appelmans & Lebas (1953) and Cahill (1957), respectively, definite PXE was present in two generations, and, in the latter, only one diagnostic criterion in the third generation. Appelmans & Lebas did not mention the possibility of consanguinity. In the family reported by Cahill no history of consanguinity was said to be obtainable. Pseudodominance can not be excluded in these two small families. Pseudodominance has been reported before and becomes more likely if the carrier frequency of the disease is high. \textit{ABCC6} mutation analysis of a control population of 1,057 persons in our lab yielded 8 carriers of the R1141X mutation. This mutation appears to make up one-third of all \textit{ABCC6} mutations in our PXE population, so that PXE carrier frequency could be as high as 2.4%. This is much higher than expected on the basis of the earlier mentioned prevalence of 1 in 100,000, by which the carrier frequency would be 0.6%. This is also supported by the fact that we know an AR family in which an aunt and her niece had PXE, and an AR family, in which at least five cousins in three nuclear families (see Fig. 5 for the latter) were affected, without indications for consanguinity of the parents. Consequently, pseudodominance could be a common phenomenon in PXE.

**Our family studies**

In family 1 PXE seemed to be present in two generations (Fig. 2). While the index patient had definite PXE, her brother and father only had ophthalmologic signs of PXE, the brother more severe than the father. The mutation in this family was a 4 bp insertion in exon 30, which has not been found yet in other patients. One possibility is that this mutation can cause AD PXE.
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That case, penetrance would be reduced, because a healthy female (II-4, aged 49) in the second generation had the mutation. Similarly, one of the grandparents (first generation) probably had the mutation. However, the grandfather (I-1) only was known to have had thickened skin of the neck and a cerebrovascular accident at age 79, the grandmother a cerebrovascular accident at age 81. Obviously, this is too little to make a diagnosis of PXE. Another possibility is AR inheritance. The index patient and her brother (III-1 and III-2) could have had a (yet undetected) mutation in their second allele, which they shared. Their father could have had a milder expression due to the heterozygous state. Mild skin and ophthalmologic abnormalities in putative heterozygote carriers of PXE have been reported [38-40].

In our second family, a 14-year old girl (III-1) had definite PXE. Her mother and aunt only had mild skin abnormalities, that could be expression of a heterozygous state. The R1141X mutation was found in one allele of these three individuals and in a healthy uncle (II-5). This mutation has been found in 30% of alleles of PXE patients, heterozygous, combined with other mutations (compound heterozygous), as well as homozygous. We did not find additional possible AD families with this mutation. Expression studies in our lab suggested that the R1141X mutation leads to absence of protein by nonsense-mediated RNA decay [41]. In that case AR inheritance is most likely. The patients with definite PXE, in whom one R1141X mutation was found, could have a second, as yet unknown, mutation.

In our third family, all available clinical, genealogical, genetic, molecular and allelic expression data pointed towards AD inheritance, although variable expression within the pedigree existed. It is remarkable that the three most seriously affected sibs (III-2, III-5 and III-7) had exactly the same haplotypes, including the disease-associated haplotype. In contrast, the two sibs with a milder phenotype (III-3 and III-4) shared another second allele. Theoretically, this could point to pseudodominance and AR inheritance with partial expression in heterozygotes. In that case, the father should have had one and the mother two mutations. Given the molecular data and segregation of markers in the pedigree this is very unlikely. First, we would have missed two different ABCC6 mutations, one in the DNA of the mother and one in the DNA of the father. Second, if both ABCC6 haplotypes of mother carry a mutation, all sibs would obviously have inherited at least one mutation. If one of the paternal haplotypes would also carry an ABCC6 mutation it is evident, given the segregation of markers in the pedigree this is very unlikely. First, we would have missed two different ABCC6 mutations, one in the DNA of the mother and one in the DNA of the father. Second, if both ABCC6 haplotypes of mother carry a mutation, all sibs would obviously have inherited at least one mutation. If one of the paternal haplotypes would also carry an ABCC6 mutation it is evident, given the segregation of markers in the pedigree, that either III-1, III-2, III-5, III-6, III-7, III-8 or, alternatively, III-3 and III-4, would have inherited a paternal ABCC6 mutation. Given the healthy, non-PXE, phenotype of III-1, III-6 and III-8, it is highly unlikely that they have two (one maternal, one paternal) ABCC6 mutations. Alternatively, III-3 and III-4 could have two ABCC6 mutations, and the other sibs from the second generation only one. This is also unlikely, since III-3 and III-4 presented with a milder phenotype (angioid streaks only, no skin lesions) than the other affected sons and daughter. Taken all data together, AR inheritance with pseudodominance in this pedigree can be virtually excluded.

Does AD PXE exist?

In the literature we found only three families in which AD PXE seemed likely. In two of these there could be pseudo-dominant inheritance, in the third one this was unlikely. In other
families, there was no definite PXE in two or more generations, but only part of the phenotype appeared to be present in a second generation. Partial expression could be due to the heterozygous state of an AR inherited disease, which is also possible in our families 1 and 2. Recently, heterozygosity for the R1141X mutation was found to be associated with increased risk of cardiovascular disease [37]. Expression in heterozygotes has also been described in other diseases caused by mutations in ATP-binding cassette (ABC) transporter genes. Mutations in both ABC1 alleles cause Tangier disease, while heterozygous mutations have been found in families with AD HDL-cholesterol deficiency, which is a much milder phenotype [42]. Subjects heterozygous for mutations in CFTR (ABCC7, the cystic fibrosis gene) may have an increased risk for disseminated bronchiectasis and sarcoidosis [43]. Heterozygous mutations in ABCLA4, the gene for AR Stargardt disease, may increase the risk for age-related macular degeneration [44]. Comparable with this, an ABCC6 mutation in heterozygote carriers usually does not result in pathology, depending on other genetic or environmental factors. Obviously, the clinical classification of the heterozygotes determines whether or not the mode of inheritance is AD or AR. Given the earlier mentioned uncertainties in clinical classification and pathogenesis of PXE it should be kept in mind that part of the problem in determining the inheritance mode in our families still may be created by misclassification. For accurate genetic counseling we will have to know in due time the expression of the specific alleles in homozygous, compound heterozygous and heterozygous states, as well as the possible influence of other loci. Our family 3 shows that R1459C might be a mutation that can cause PXE in the heterozygous state. In summary, we conclude that AD inheritance in PXE may exist, but that it is much rarer than previously assumed (1/59 (1.7%) of our population), and probably has low penetrance. More detailed clinical and molecular studies of families with (features of) PXE in two or more generations should shed further light on this issue. At this moment it seems that offspring of patients with PXE does have a slightly increased risk of symptoms of PXE, but full-blown PXE in two or more generations is very rare.
REFERENCES


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