

Pseudoxanthoma elasticum (PXE): A case report

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Summary

Pseudoxanthoma elasticum (PXE) is a heritable disorder that affects the connective tissue, resulting in destruction of elastic fibers in the skin, the arteries and the retina (OMIM 177850 and 264800). This process eventually leads to loss of elasticity in the affected dermal areas, arterial stiffness with a predisposition to early onset arteriosclerosis and retinal haemorrhages with subsequent retinal scarring and central visual field blindness [1]. Autosomal dominant and recessive forms of PXE have been described. Recently, the disease locus was mapped to chromosome 16 [2] and subsequently mutations in the ABC transporter gene, *ABCC6*, have been identified to cause PXE [3]. Here we describe the clinical findings and the identification of two mutations in *ABCC6* in a 60 year old man with PXE.

Figures

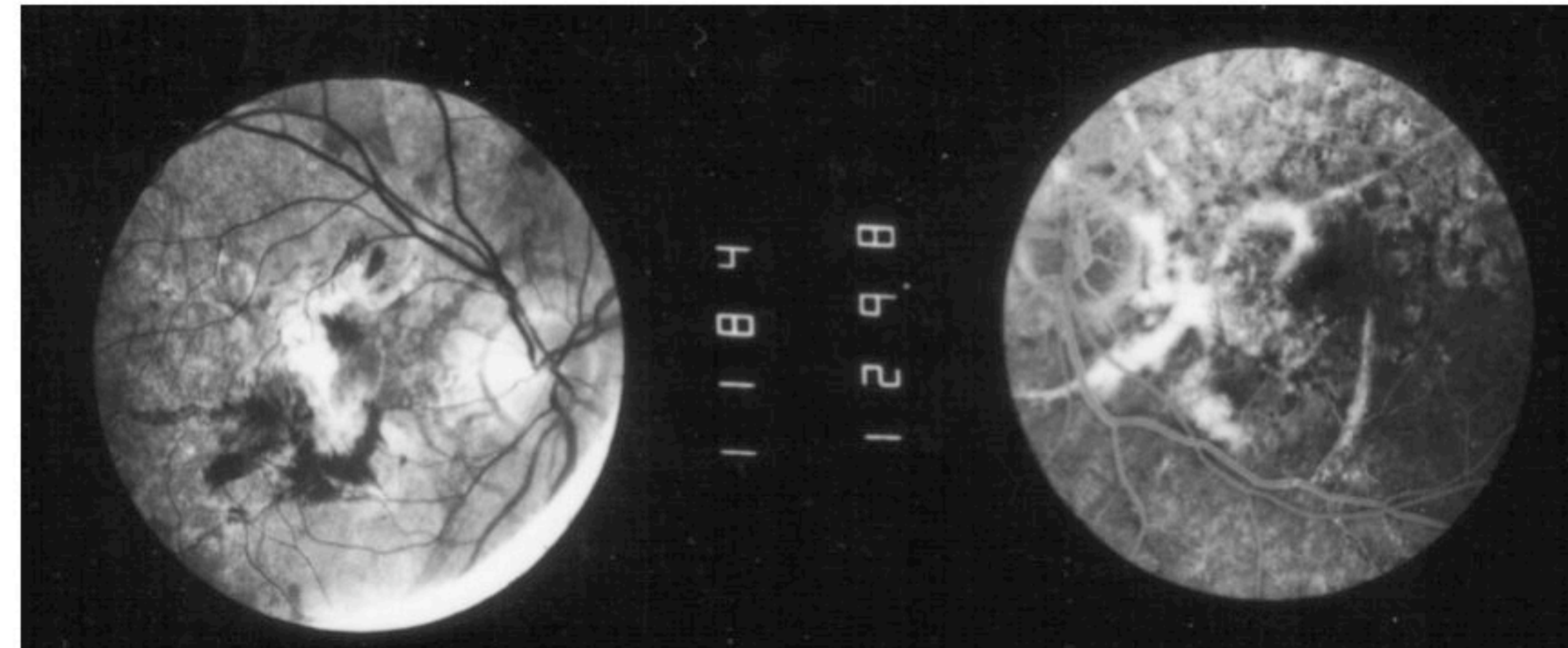
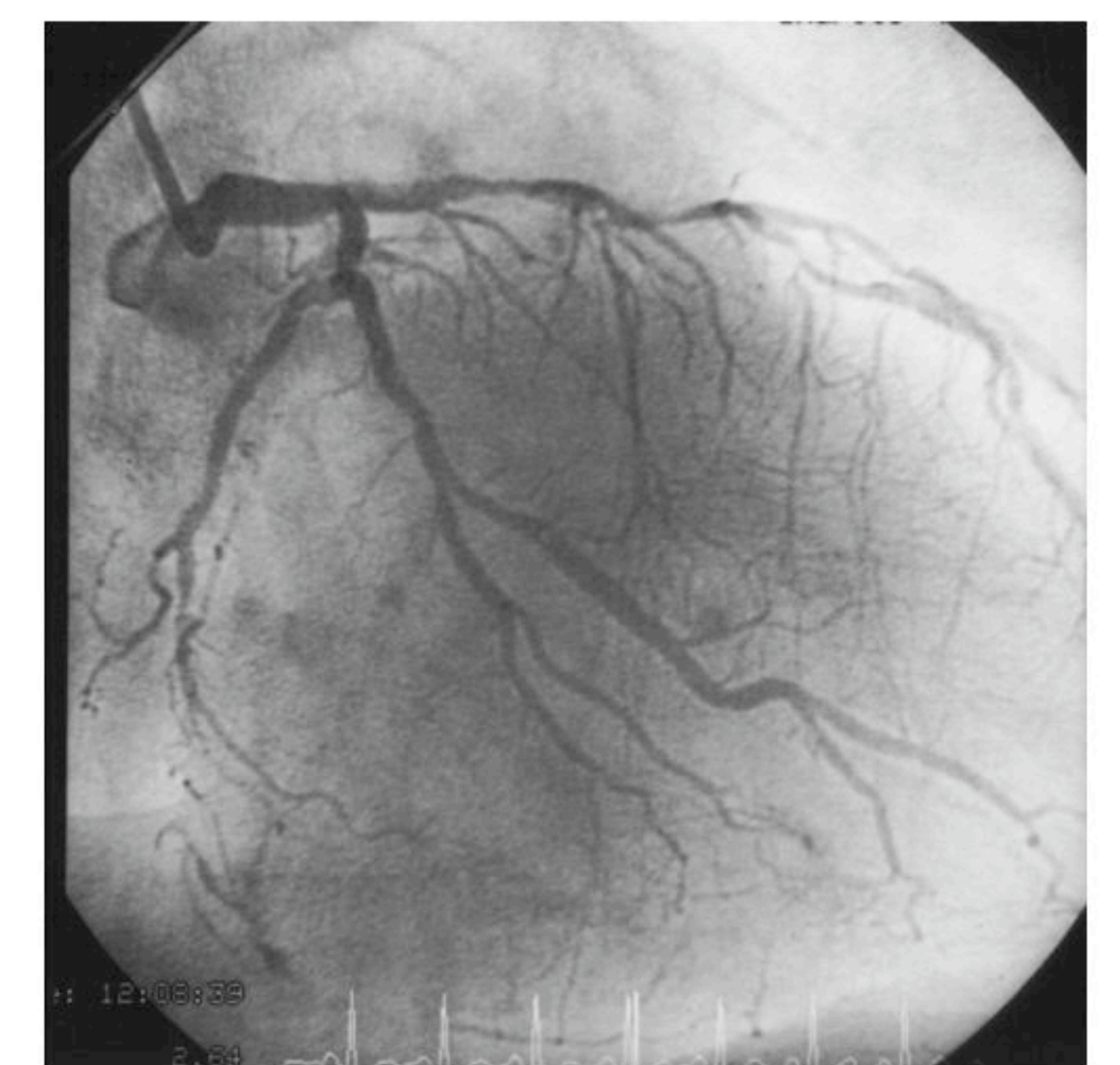


Figure 1: Fluorescin angiography of the retinal vessels showing angoid streaks.

Figure 2: Coronary angiography showing disseminated coronary sclerosis.



Clinical report

A 60-year old man reported about **yellowish skin papules** located around the neck, noted after birth. The further postnatal and childhood history was unremarkable.

At the age of 45 years he noted a rapid loss of vision. Visual acuity was 0.05 and 0.1 on the right and left eye, respectively. Funduscopic examination and Fluorescin angiography revealed angiod streaks of the retina with severe macula involvement (figure 1).

At age 50 years he noticed pain in his right leg after a walking distance of 500 meter. Angiography showed a stenosis of the right external iliacal artery. Subsequently he noticed dyspnoe and chest pain during exercise. Coronary angiography revealed **a severe disseminated sclerosis** of the coronary vessels and left ventricular hypertrophy, illustrated in figure 2.

Clinical examination at age 60 years revealed papulous skin lesions around the neck. The skin showed reduced elasticity and pain sensitivity was reduced in this area. A skin biopsy showed accumulation of morphologically altered, often fragmented appearing material primarily in the mid dermis, typical for PXE.

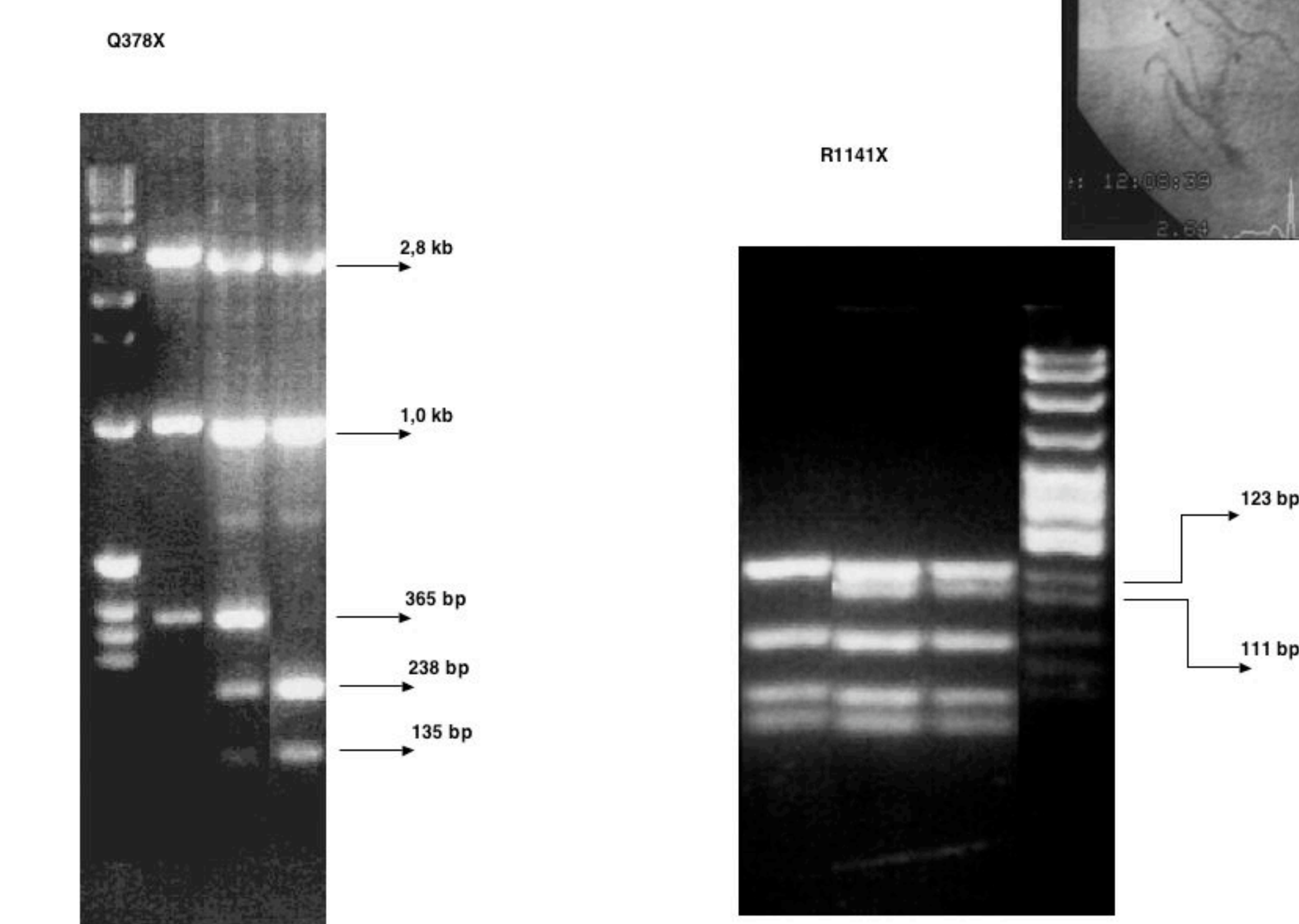


Figure 3 left panel: Analysis of Q378X-specific digestion of the long range PCR products with *XmnI* and *PstI*. M = marker; Lane 1, homozygous control for Q378X; Lane 2, patient; Lane 3, negative control. The 365 bp PCR fragment appears only in carriers of the Q378X mutation, due to a loss of the restriction site for *PstI*.

Figure 3 right panel: Analysis of the R1141X nonsense-specific digestion with *BsiI*. Lane 1, negative control; Lane 2, patient; Lane 3: heterozygous control for R1141X; M = Marker. The R1141X nonsense mutation leads to the loss of a restriction site for *BsiI* resulting in an additional band at 123 bp. The patient shows the same pattern as the positive control in lane 3.

Molecular genetic analysis

Mutation analysis in *ABCC6* was performed for exon 1 to 31 by direct sequencing of PCR products generated from genomic DNA using intronic primers derived from publicly accessible sequence data (Gene bank accession number U91318).

Direct sequencing revealed two nonsense mutations: *R1141X*, 3421C>T in exon 24 and *Q378X*, 1132C>T in exon 9 that is also present in *ABCC6-ψ1* in all controls tested.

Therefore, long range PCR for the detection of *Q378X* in *ABCC6* was performed using Long & Accurate Taq Polymerase (TAKARA).

Subsequently, both mutations were confirmed by RFLP analysis.

Sequence screening of all other exons of *ABCC6* did not detect any other mutations.

Patient support

PXE-Netzwerk: <http://www.pxe-netzwerk.de>

NAPE: <http://www.napxe.org>

Discussion

PXE was reported to be inherited in an autosomal recessive and dominant mode. Therefore the inheritance pattern in a sporadic case and recurrence risks for relatives of affected individuals can not be specified unequivocally.

In this patient two nonsense mutations were identified. The identification of the *Q378X* mutation has been hampered by a neighboring pseudogene (*ABCC6-ψ1*) with a 99.995% homology to exons 1-9 of *ABCC6*. Interestingly, the pseudogene carries the *Q378X* mutation in all individuals tested so far. Therefore, gene conversion is the most likely mechanism for the presence of *Q378X* in *ABCC6* in PXE patients found to carry this mutation by long range PCR [4].

In this patient mutation analysis confirms a recessive mode of inheritance and therefore allows the precise specification of recurrence risks for his relatives.

References:
1. Neldner KH and Struk B: Pseudoxanthoma Elasticum. In: Royce PM, Steinmann B, (eds). Connective Tissue und Its Heritable Disorders: Molecular, Genetic and Medical Aspects. 2nd ed NewYork: Wiley-Liss, 2002

2. B. Struk, K.H. Neldner, V.S. Rao, P. St Jean, K. Lindpaintner *Hum. Mol. Genet.* 1997; 6:1823-28

3. Struk B, Cai L, Zach S, Ji W, Chung J, Lumsden A, Stumm M, Huber M, Schaen L, Kim CA, Goldsmith LA, Viljoen D, Figuera LE, Fuchs W, Munier F, Ramesar R, Hohl D, Richards R, Neldner KH, Lindpaintner K *J Mol Med* 2000 78:282-86.

4. Cai L, Lumsden A, Guenther UP, Neldner SA, Zach S, Knoblauch H, Ramesar R, Hohl D, Callen DF, Neldner KH, Lindpaintner K, Richards RI, Struk B. *J Mol Med* 2001 79:536-46