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Diagnosis of pseudoxanthoma elasticum following genomic re-analysis in a patient with chronic kidney disease: a case report

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Case Report

Keywords: Pseudoxanthoma elasticum, ABCC6, chronic kidney disease, phenotyping, whole genome sequencing, case report

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Diagnosis of pseudoxanthoma elasticum following genomic re-analysis in a patient with chronic kidney disease: a case report

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Abstract

Purpose

To describe a diagnosis of pseudoxanthoma elasticum following genomic re-analysis and to illustrate the challenge of determining whether chronic kidney disease represents an atypical manifestation of ABCC6-associated disease.

Methods

Following re-analysis of whole-genome sequencing data, historical renal, vascular, ophthalmic, laboratory and imaging records were reviewed. Reverse phenotyping was undertaken to assess the extent to which the patient's multisystem features were consistent with pseudoxanthoma elasticum and to examine possible explanations for his chronic kidney disease.

Results

An older man with progressive chronic kidney disease, low-grade proteinuria, severe visual impairment and extensive large-vessel peripheral arterial disease was found to have compound heterozygous pathogenic *ABCC6* variants, NM_001171.6 c.1741C>T; p.(Gln581Ter) and c.2787+1G>T. The diagnosis of pseudoxanthoma elasticum had not been recognized during life. His ocular and vascular disease were compatible with the phenotype of pseudoxanthoma elasticum; however, the renal phenotype was atypical. Renal ultrasonography and computed tomography showed chronic kidney disease without nephrolithiasis, nephrocalcinosis or renal calcification. Long-standing hypertension, severe vascular disease and a possible renovascular

component remained plausible alternative explanations for renal impairment. Renal biopsy was not performed, and the diagnosis was made after the patient's death, preventing targeted clinical reassessment.

Conclusions

Genomic re-analysis can identify previously unrecognized rare diseases and should prompt careful reverse phenotyping. In this case, the diagnosis of pseudoxanthoma elasticum explained important ocular and vascular features, but a direct causal relationship between *ABCC6* deficiency and chronic kidney disease could not be established. This case supports further characterization of kidney phenotypes in individuals with biallelic *ABCC6* variants.

Keywords

Pseudoxanthoma elasticum; ABCC6; chronic kidney disease; phenotyping; whole genome sequencing; case report

Introduction

Pseudoxanthoma elasticum (PXE) is an autosomal recessive inherited ectopic mineralization disorder caused by biallelic pathogenic variants in *ABCC6* (NM_001171.6), classically affecting the skin, retina and vasculature (Le Saux, Beck et al. 2001, Favre, Laurain et al. 2017, Moitra, Garcia et al. 2017). *ABCC6* encodes an ATP-dependent transmembrane transporter that contributes to extracellular pyrophosphate homeostasis (Moochhala, Sayer et al. 2008, Jansen, Duijst et al. 2014). It is expressed primarily in the liver and, to a lesser extent, in the kidney, although more recent evidence suggests a broader tissue distribution (Arányi, Bacquet et al. 2013). ABCC6 promotes extracellular ATP release, which is subsequently converted by ENPP1 to pyrophosphate, an important inhibitor of pathological mineralization (Shimada, Pomozi et al. 2021). A member of the ATP-binding cassette transporter superfamily, ABCC6 localizes predominantly to the basal and basolateral plasma membrane (Pomozi, Le Saux et al. 2013) and contains transmembrane and ATP-binding domains that facilitate ATP-dependent transport across cell membranes. Heterozygous carriers may exhibit a limited 'forme fruste' phenotype with subtle retinal or vascular changes and increased calcification risk, although most do not develop full PXE (Sherer, Bercovitch et al. 2001, Nollet, Campens et al. 2022). Although the established clinical manifestations of PXE have traditionally been defined by dermatological, ocular and cardiovascular manifestations, renal involvement has also been reported, particularly nephrolithiasis, Randall plaque formation, nephrocalcinosis and renal calcification (Letavernier, Kauffenstein et al. 2018, Ralph, Allawh et al. 2020, Farrell, Uribarri et al. 2026) (Table 1). Re-analysis of genomic data can identify diagnoses that were not recognized clinically at the time of original assessment, but such findings require careful reverse phenotyping to determine which

clinical features are likely to be related to the molecular diagnosis. This case is presented as an example of that challenge after re-analysis of whole-genome sequencing data identified disease-causing variants in *ABCC6*, and previously unrecognized PXE in a patient with chronic kidney disease, vascular disease and retinal disease.

Case presentation

An 82-year-old English man (proband, II:6) was admitted to hospital with pulmonary oedema and was treated with loop diuretics. He had evidence of progressive chronic kidney disease (CKD) with a current eGFR of 25 mL/min/1.73 m^2 (Figure 1). Urinalysis showed low-grade proteinuria, with a urine protein–creatinine ratio of 45 mg/mmol.

Past medical history and clinical notes also described extensive large-vessel disease and severe ocular pathology. A general surgery letter from seven years earlier (aged 75 years) reported claudication, limb-length discrepancy and a reduced ankle–brachial pressure index. Combined with duplex imaging suggestive of right superficial femoral artery occlusion with proximal disease and superficial femoral artery stenosis on the left, this was consistent with significant large-vessel peripheral arterial disease (Figure 1). Ophthalmology correspondence over more than a decade described progressive and severe visual impairment, with earlier documentation recording visual acuity of counting fingers in the left eye and hand movements in the right eye, fundus examination showing chorioretinal atrophy involving the disc and macula in both eyes, and later letters noting that he was registered blind with bilateral macular degeneration or macular dystrophy and visual acuity reduced to hand movements in both eyes. Intraocular

pressures were recorded as 16 and 20 mm Hg on an earlier review and 14 and 13 mm Hg on a later review. Visual acuity was described as stable on subsequent follow-up despite profound visual loss. Based on longstanding hypertension and the documented peripheral arterial disease and systemic vascular comorbidity, the CKD was considered most likely to be hypertensive or renovascular in origin. Familial renal disease was considered possible, and blood was therefore stored for potential DNA testing. There was a sibling (II:4) who was also registered blind from age 45 years but no other relevant family history (Figure 1).

Renal ultrasonography demonstrated kidneys measuring 10.5 cm on the right and 9.8 cm on the left, with appearances consistent with CKD and no evidence of hydronephrosis, renal masses, nephrocalcinosis or calculi. A contrast-enhanced CT of the abdomen and pelvis showed normal appearances of the kidneys and adrenal glands, with no focal renal lesions, retroperitoneal lymphadenopathy, nephrolithiasis or renal calcification. The abdominal CT showed mild aneurysmal dilatation of the suprarenal part of the abdominal aorta, measuring 4cm at the level of the aortic hiatus, however, extensive vascular calcification was not noted on this scan. Immunological testing apart from the ribonucleoprotein A antibody was negative, indicating isolated connective tissue disease-type serology. Glycated hemoglobin was 34 mmol/mol without antidiabetic treatment, and blood pressure at review was 132/68 mmHg without antihypertensive therapy. Renal biopsy was not performed. Unfortunately, he died aged 82 years, following an episode of small bowel obstruction complicated by sepsis and multiorgan failure.

Subsequent re-analysis of whole-genome sequencing data identified biallelic *ABCC6* sequence variants. These were compound heterozygous pathogenic *ABCC6* variants, NM_001171.6

c.1741C>T; p.(Gln581Ter) and c.2787+1G>T leading to a posthumous diagnosis of pseudoxanthoma elasticum. This prompted a reconsideration of whether his progressive CKD formed part of the ABCC6-associated phenotype or was unrelated. Several of the proband's phenotypes were compatible with this diagnosis but the phenotype was incomplete, especially with a lack of cutaneous manifestations (Table 1). Following genetic counselling and informed consent, testing of the probands son (III:1), found him to be heterozygous for a single *ABCC6* variant (c.1741C>T p.(Gln581Ter)), confirming the variants were in trans in the proband. The son was phenotypically normal, with normal appearances of skin and a normal eye examination. A abdominal CT was performed which showed no evidence of urinary tract calcification or vascular calcification.

Discussion

The principal value of this case lies in illustrating the challenge of interpreting an unexpected genomic diagnosis in a patient with multisystem features and no unifying diagnosis. Whole-genome sequencing, and subsequent re-analysis of existing data, may yield clinically important diagnoses that may have been overlooked. The identification of pathogenic variants should prompt careful reassessment of the clinical phenotype to establish which features are consistent with the molecular diagnosis, rather than assuming that all findings can be attributed to the genotype. Unfortunately, the patient had died before the genetic findings became available, precluding further clinical assessment and targeted reverse phenotyping. Nevertheless, establishing a molecular diagnosis remains clinically important for surviving family

members, as it enables appropriate genetic counselling, cascade testing of at-risk relatives and, where relevant, targeted surveillance for manifestations of *ABCC6*-associated disease. Indeed, some carriers of heterozygous variants in *ABCC6* may display mild skin or eye involvement (Sherer, Bercovitch et al. 2001). A more recent study found that *ABCC6* heterozygosity may be associated with distinct 'comet-like' retinal alterations, a high prevalence of hypercholesterolaemia and diastolic dysfunction, accelerated lower limb atherosclerosis and medial vascular disease, abdominal organ calcification and testicular microlithiasis (Nollet, Campens et al. 2022). Heterozygous carriers were proposed to be at risk of coronary artery disease (Trip, Smulders et al. 2002) but in a larger and more recent study there was not an associated risk of IHD, myocardial infarction, ICVD, or ischemic stroke (Hornstrup, Tybjærg-Hansen et al. 2011). The *ABCC6* variants identified in our patient were both well-established loss-of-function variants. The c.1741C>T; p.(Gln581Ter) is a nonsense variant introducing a premature stop codon, expected to result in truncation or nonsense-mediated decay of the transcript (Plomp, Florijn et al. 2008). The c.2787+1G>T is a canonical splice-donor variant predicted to abolish normal splicing, also regarded as pathogenic and has been reported in patients with ABCC6-related disease (Grover and Kochhar 2025). Together, these variants provide strong molecular evidence for ABCC6 deficiency. By genetically testing the unaffected son, we have evidence that the variants were in trans, consistent with autosomal recessive PXE. The history of a sibling with severe visual impairment leading to blindness is suggestive that they may also have been affected with ocular features of *ABCC6*-related disease. There were no features in the pedigree to suggest heterozygote carriers or presumed heterozygous carriers had any overt clinical disease phenotypes.

The proband had several features that could fit within the phenotypic spectrum of pseudoxanthoma elasticum (Table1 and Table 2). *ABCC6*-associated disease is rare, estimated to affect between 1 in 25,000 and 1 in 100,000 people (Moitra, Garcia et al. 2017), classically involves the eye and vasculature, and published literature supports a broader multisystem calcification phenotype. In this context, the presence of severe ocular disease and extensive vascular disease makes the molecular genetic diagnosis clinically plausible. The diagnosis of PXE has previously been made in patients without characteristic skin lesions (Lebwohl, Phelps et al. 1987) as was the case here. Therefore, the absence of documented cutaneous findings does not exclude PXE. Phenotypic expressivity in ABCC6 deficiency is highly variable, and patients with predominantly ocular or vascular disease and minimal dermatological manifestations have been described. Furthermore, subtle cutaneous abnormalities may remain unrecognized without targeted dermatological assessment or skin biopsy.

However, the renal phenotype in our presented case is less typical of the kidney involvement reported in pseudoxanthoma elasticum. Published literature has predominantly described *ABCC6*-related kidney involvement in association with Randall plaque-like papillary calcification, nephrolithiasis, pyrophosphate-deficiency nephrocalcinosis, and renal vascular calcification. More recently, recurrent nephrolithiasis has also been reported in individuals with heterozygous *ABCC6* variants in the absence of classical PXE (Farrell, Uribarri et al. 2026), suggesting that partial loss of ABCC6 function may confer susceptibility to renal stone formation (Table 3).

In contrast, the available clinical information in this case describes progressive CKD with low-grade proteinuria and no evidence of nephrolithiasis, nephrocalcinosis or renal calcification on imaging. This distinction is important, because it limits the strength of any claim that the renal disease was directly caused by *ABCC6*-related disease. To our knowledge, this is among the first reports describing a patient with genetically confirmed biallelic ABCC6 deficiency in whom advanced CKD was a major clinical feature despite the absence of nephrolithiasis, nephrocalcinosis or overt renal calcification.

Different explanations for CKD in our patient are plausible. The patient was aged 82 years and had long-standing hypertension and significant vascular disease, both of which may have contributed to progressive CKD. He may have had renovascular disease mediated by PXE but we have no imaging proof of this. The presence of advanced CKD with relatively low-grade proteinuria and no evidence of nephrolithiasis, nephrocalcinosis or renal calcification raises the possibility that his renal impairment may represent a less well-characterized manifestation of *ABCC6*-associated disease. The available evidence is insufficient to distinguish between these possibilities.

Potential mechanisms of CKD in ABCC6-associated disease might include progressive vascular injury.

The association between peripheral arterial disease and CKD may reflect shared vasculopathic mechanisms (O'Hare, Glidden et al. 2004, Chen, Knicely et al. 2019). Progressive atherosclerosis, vascular calcification, and endothelial dysfunction can impair renal perfusion and promote chronic ischaemic nephropathy, while CKD itself accelerates systemic vascular disease through inflammation, oxidative stress, and disordered mineral metabolism (Mizobuchi, Towler et al. 2009). The bidirectional relationship between these conditions suggests that vascular injury may represent a common pathway contributing to both renal function decline and peripheral arterial disease.

Further characterization of renal phenotypes in individuals with biallelic *ABCC6* variants will be required to determine whether CKD can occur independently of the more established nephrolithiasis and renal calcification phenotype. While a direct causal relationship between *ABCC6* deficiency and the patient's CKD cannot be established, the atypical renal phenotype raises the possibility of a broader spectrum of kidney involvement that warrants further investigation.

A limitation of this case is the absence of retinal imaging and the lack of documented angioid streaks, choroidal neovascularisation or peau d'orange seen with PXE. Consequently, although the severe retinal degeneration was considered compatible with ABCC6-associated disease, retrospective confirmation of classic PXE ocular pathology was not possible in the proband or his deceased sibling. Other limitations include the posthumous diagnosis, the lack of skin examination or biopsy after diagnosis, no renal biopsy, no autopsy findings and no segregation of genetic variants.

It is noteworthy that recently the REACT-PXE (Research, Education and Advanced Care Teams for PXE) Consortium has been established to allow up to date diagnostic criteria and improved management of PXE (Martin, Spiering et al. 2026) This consortium propose revised diagnostic criteria, “red flags” for considering PXE, and a patient-centered approach to identifying meaningful outcomes. They also provide a useful molecular diagnostic workflow for a suspected PXE patient. Our proband would be classified as having one major criteria in the form of biallelic pathogenic variants (Genetic) but no other major or minor criteria based on lack of detailed eye phenotyping and absence of intraabdominal calcifications.

This case therefore highlights the need for reverse phenotyping after an unexpected genetic diagnosis. The identification of a molecular diagnosis should prompt targeted re-examination of the phenotype but should not lead to over-attribution of every clinical abnormality to the underlying genetic disorder. A review of the family tree, segregation of variants and testing of at-risk family members are also important, ideally in collaboration with clinical genetics or genomic counsellors.

This case highlights the potential for a broader spectrum of kidney involvement in *ABCC6*-associated disease and the need for systematic renal phenotyping in genetically diagnosed individuals.

Conclusion

This case demonstrates the value of genomic re-analysis in identifying previously unrecognized rare diseases and highlights the importance of reverse phenotyping following unexpected molecular diagnoses. The patient's vascular and ocular manifestations support a diagnosis of ABCC6-associated pseudoxanthoma elasticum despite the absence of documented skin findings. Although CKD formed a major component of the clinical presentation, available evidence was insufficient to establish causality. Further study is required to define whether chronic kidney disease represents part of the phenotypic spectrum of ABCC6 deficiency.

Statement and declarations

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Authors’ contributions

JS contributed to the study conception and design. TB and HM were responsible for data collection and initial draft preparation. All authors participated in revising the drafts and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Informed and written consent was obtained from patient's relatives.

Consent for publication

Patient's relatives provided informed written consent for this report.

Competing interests

Professor John Sayer is a co-author of this case report and an editorial board member of the journal. He was not involved in the editorial handling or decision-making process for this manuscript. The rest of the authors declare that they have no competing interests.

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Figures

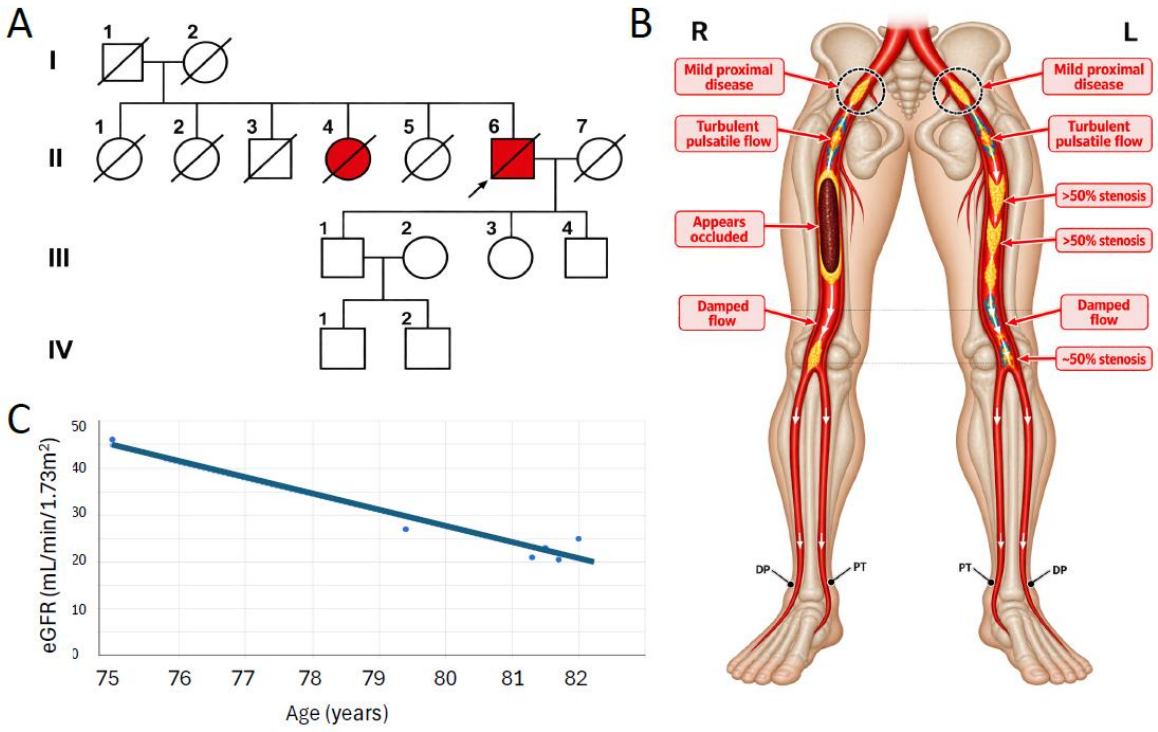


Figure 1. Family pedigree and clinical features of proband

A. Family pedigree diagram showing proband and sibling with severe visual loss leading to early onset blindness. B. Schematic showing lower limb doppler studies in proband, showing severe generalized calcification resulting in significant peripheral vascular disease. C. Plot of eGFR (CKD-EPI formula) showing progressive decline in kidney function over time.

Tables

Table 1 Relationship between the patient's clinical phenotype and recognized features of pseudoxanthoma elasticum

Clinical features in this patient	Potential relationship to Pseudoxanthoma Elasticum (PXE) / ABCC6-associated disease
Severe ocular disease with visual impairment	Potentially consistent with the PXE spectrum, although the documented ophthalmic phenotype does not demonstrate the characteristic angioid streak pattern.
Extensive peripheral vascular disease and claudication	Consistent with the recognized vascular phenotype of PXE.
Chronic kidney disease with low-grade proteinuria	Not typical of the classical renal phenotype of PXE; its relationship to *ABCC6*-associated disease remains uncertain
Absence of renal calculi on ultrasound	Does not support the more commonly reported nephrolithiasis-associated renal phenotype of PXE.

Clinical features in this patient	Potential relationship to Pseudoxanthoma Elasticum (PXE) / ABCC6-associated disease
Absence of nephrocalcinosis or renal calcification	Does not support a typical calcification-associated renal phenotype and limits attribution of the chronic kidney disease directly to PXE.
Absence of cutaneous manifestations	Does not support the more commonly reported skin phenotype of PXE.

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Table 2 Key recognized phenotypic features of pseudoxanthoma elasticum

Phenotypic domain	Key manifestations reported in Pseudoxanthoma Elasticum (PXE) / ABCC6-associated disease
Cutaneous	Yellow papules in flexural areas, lax or redundant skin, and histological fragmentation/mineralization of elastic fibers.
Ocular	Angioid streaks, choroidal neovascularization, and progressive visual impairment.
Vascular/cardiovascular	Peripheral vascular disease, intermittent claudication, arterial calcification, and broader cardiovascular involvement.
Renal	Nephrolithiasis and nephrocalcinosis. Randall plaque formation.

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376 **Table 3 *ABCC6*-related kidney involvement in published reports**

Study type	Main kidney findings	Comment	Reference
PXE patients and *Abcc6−/−* (knockout) mice	Kidney stones in ~40% of PXE patients; papillary apatite calcifications (Randall plaque–like) in mice	Links ABCC6 deficiency to papillary calcification and kidney stones	(Letavernier, Kauffenstein et al. 2018)
Case series of 3 patients with heterozygous	Recurrent nephrolithiasis without classic PXE features	Suggests that single-allele *ABCC6* variants may increase kidney stone risk	(Farrell, Uribarri et al. 2026)

ABCC6 variants			
Review of PXE with *ABCC6* variants	Nephrolithiasis and nephrocalcinosis associated with low circulating pyrophosphate	Suggests systemic pyrophosphate deficiency as a mechanism for renal calcification in ABCC6 disease	(Letavernier, Bouderlique et al. 2019)
CKD cohort with ABCC6 variants	CKD progression, renovascular hypertension, cortical vessel calcification, some reaching kidney failure	Expands ABCC6 phenotype to include advanced kidney disease and renal vascular calcification	(Schott, Dilliott et al. 2024)

Mechanistic review of ABCC6	Highlights renal expression and role in systemic mineralization control	Provides biological basis for kidney involvement in ABCC6-related conditions	(Verschuere, Van Gils et al. 2020)

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378 PXE, pseudoxanthoma elasticum; CKD, chronic kidney disease

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