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A male patient with pseudoxanthoma elasticum caused by isodisomy of chromosome 16 containing a nonsense variant of the *ABCC6* gene: A quarter-century treatment experience

Minoru Wakasa [a], Chihiro Nakagawa [a], Taka-aki Takamura [a], Kosuke Fujibayashi [a], Hironobu Akao [a], Michihiko Kitayama [a], Akira Shimizu [b], Yo Niida [c], Kouji Kajinami [a,*]

[a] Department of Cardiology, Kanazawa Medical University, Japan
[b] Department of Dermatology, Kanazawa Medical University, Japan
[c] Center for Clinical Genomics, Kanazawa Medical University Hospital, Japan

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ABSTRACT

Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive disorder characterized by fragmentation and calcification of the elastic fibers of the skin, eyes, and various arteries with highly variable clinical expression. PXE is predominantly caused by pathogenic variants of the *ABCC6* gene, which encodes the ABCC6 efflux transporter; however, the precise mechanism responsible for clinical manifestation remains unclear. We herein report the case of a male patient with PXE with premature coronary stenosis as his first presentation requiring catheter intervention, in association with typical ocular and skin lesions; the latter was confirmed histologically. A molecular analysis revealed an isodisomy of 6.8 Mb in the 16p13.11 region containing the nonsense mutation p.(Gln199Ter) in the *ABCC6* gene. We also describe the 25-year clinical course of this case, while focusing on cardiovascular lesions.

1. Introduction

Pseudoxanthoma elasticum (PXE; OMIM 264800) is a rare autosomal recessive disorder characterized by fragmentation and calcification of the elastic fibers of the skin, peripheral arteries, and eyes with highly variable clinical expression [1,2]. Nonetheless, vascular lesions, especially in the cerebral or coronary arteries, should be appropriately managed based on the pathophysiology of the vessel wall. PXE is caused predominantly by pathogenic variants of the *ABCC6* gene, which encodes the ATP-binding cassette sub-family C member 6 (ABCC6) efflux transporter located on chromosome 16p13.11 [3]. However, the precise function of ABCC6 and its substrate is not yet fully understood and not all cases have been genetically confirmed.

There are two possibilities for detecting a homozygous pathogenic variant of an autosomal recessive disease. One is when both parents carry the same variant. However, if the variant originates from a common ancestor, even if chromosomal homologous recombination occurs over generations, the area around the responsible gene will be isodisomy because the chromosome origin is the same [4]. Another possibility is uniparental disomy. In this case, only one parent is a carrier. The chromosome with the pathogenic variant is duplicated and passed on to the child, resulting in disease onset, while the other parent does not pass the chromosome to the child. Depending on the timing of chromosomal recombination during gametogenesis, the entire chromosome may be duplicated or only the area around the causative gene may be segmentally duplicated; however, the area around the causative gene will still show isodisomy [5].

In light of the above, we report a case of PXE in which detailed genetic analysis was performed. The patient was homozygous for an exon 5 nonsense variant NM_001171.6:c.595C > T p.(Gln199Ter) in the *ABCC6* gene accompanied by an isodisomy region encompassing 6.8 Mb on 16p13.11. We also describe the 25-year clinical course of systemic lesions in this case.

2. Methods

2.1. Subject

In 1998, a 28-year-old Japanese male was admitted for the evaluation of effort angina with ischemic electrocardiographic changes. He had been diagnosed with high blood pressure since his teenage years, but

* Corresponding author. 1-1 Daigaku, Uchinada, 920-0293, Japan.
E-mail address: kajinami@kanazawa-med.ac.jp (K. Kajinami).

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Abbreviations

ABCC6	adenosine triphosphate-binding cassette transporter C6
PCI	percutaneous coronary intervention
PXE	pseudoxanthoma elasticum
UPIT	uniparental isodisomy

had not undergone a detailed examination. Coronary angiography revealed high-grade stenosis of the middle circumflex artery, which was successfully treated with percutaneous catheter intervention (PCI) using a plain old balloon (Fig. 1). Two days after PCI, the patient presented with hematemesis and was diagnosed endoscopically with acute gastric hemorrhage resulting from an exposed stomach vessel requiring emergent clipping. An extensive survey of the condition causing non-atherosclerotic arterial lesions revealed angioid streaks in the skin and fundus of the eye (Figs. 2 and 3). The degeneration and calcification of the elastic fibers were histologically confirmed by skin biopsy (Fig. 2), leading to the clinical diagnosis of PXE. Vascular lesions other than coronary arteries and possibly stomach wall arteries, such as the renal, intracranial, or lower extremities, were not detected through noninvasive evaluations.

Molecular diagnosis was attempted by direct sequencing of all 31 exons with exon-intron boundaries with the *ABCC6* gene. A nonsense variant in exon 5, NM_001171.6:c.595C > T p.(Gln199Ter), was found

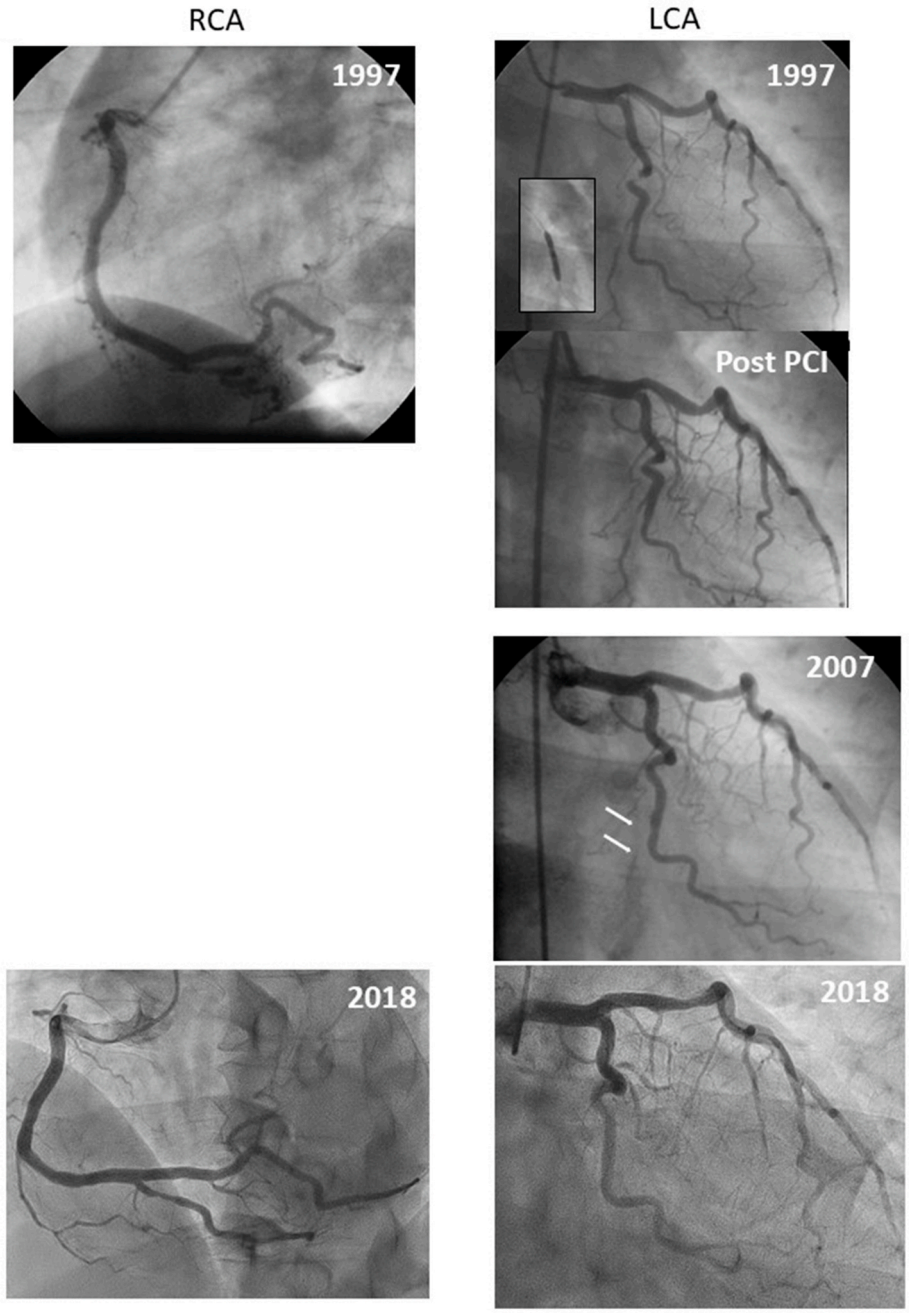

Fig. 1. Coronary angiographic findings of the case.
In 1997, high-grade stenosis of the middle circumflex artery was treated with a plain balloon (insert) without complications. In 2007, neither restenosis nor new lesions were observed, except for the occlusion of the small distal circumflex branch (white arrows). No new lesions were observed in the 2018 study.

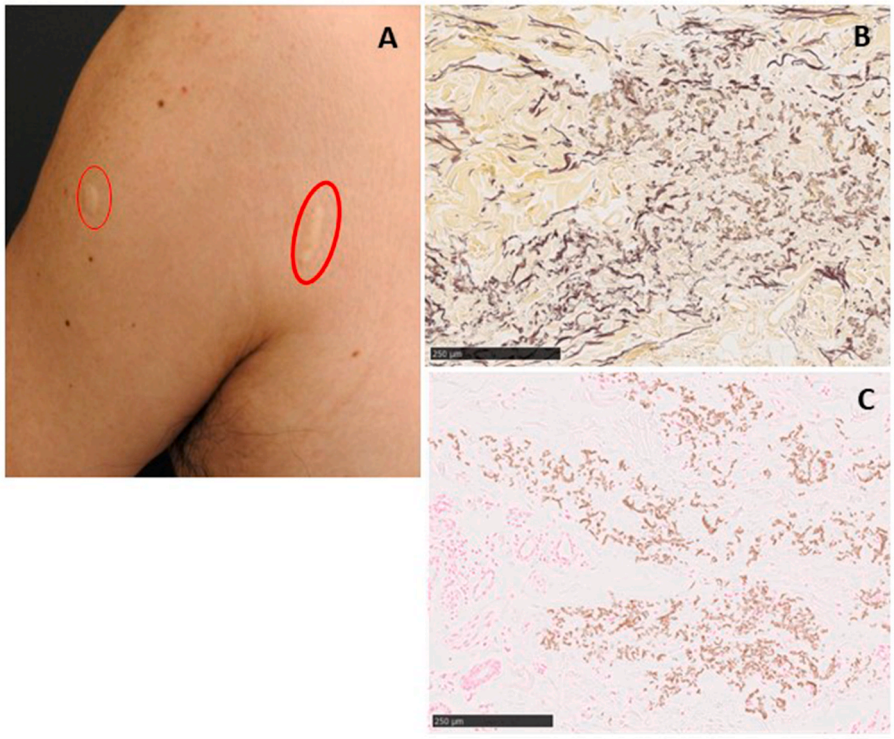

Fig. 2. Skin manifestation of the case.
Yellowish plaques (encircled in red) were observed in the left shoulder and arm (A). Microscopically, degeneration of elastic fibers was observed by Elastica van Gieson staining (B) in association with microcalcification confirmed by von Kossa staining (C).

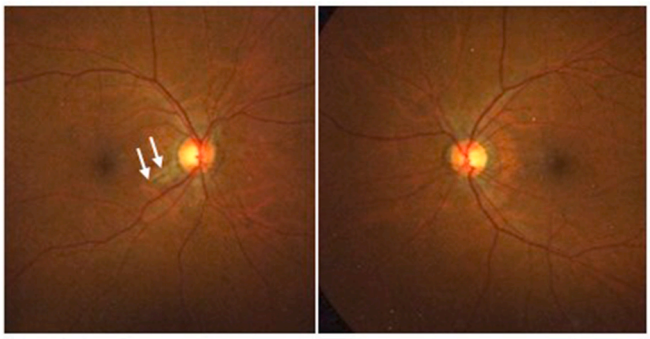

Fig. 3. Retinal lesion of this case.
The angioid streak is indicated by white arrows.

to be a common mutations in Japanese patients with PXE [6]. As no heterozygous polymorphisms were detected in the entire *ABCC6* gene analysis, it was not possible to determine whether PXE was caused by homozygosity for a nonsense variant or by compound heterozygosity due to the large deletion of another allele. Therefore, we investigated the large deletion and isodisomy in the ABCC6 region simultaneously using SNP microarrays (Affymetrics cytoscan 750K Array®, Affymetrics Japan, Tokyo, Japan) and identified a segmental isodisomy region of 6.8 Mb including the *ABCC6* gene (Fig. 4). We conclude that the patient had a homozygous nonsense variant of the same chromosomal origin. Unfortunately, the patient's parents had already died, and genetic testing of the parents was not possible.

Guideline-directed medical therapy consisting of losartan and diltiazem for blood pressure reduction, atorvastatin for low-density lipoprotein cholesterol reduction, and aspirin for coronary lesions after PCI in combination with gastric acid suppression medication was introduced. Coronary lesions did not show any changes, including restenosis at the PCI site, in 2007; however, in early 2018 (at 48 years of age), the patient gradually complained of exertional dyspnea with exercise-induced ST depression. Coronary angiography showed mild-to-moderate stenosis of the left anterior descending branch (unchanged since 2007) and occlusion of the small distal branch of the circumflex artery with good collateral flow (Rentrop grade 3) from the right coronary artery (Fig. 1). The left ventriculogram confirmed normal contraction with a significant elevation of the endo-diastolic pressure (23 mm Hg). The carotid arteries showed small plaques and irregular walls with scattered calcifications. In the lower extremity arteries, there was no flow-limiting narrowing, and the ankle-brachial index remained 0.9–1.0 throughout his clinical course. A brain magnetic resonance angiogram showed wall irregularity of both internal carotid arteries and moderate stenosis of the left middle cerebral artery, neither of which changed from 2008 to 2024 (data not shown). Neither the skin nor ocular lesions changed significantly during the clinical course. The patient experienced a left ureteral stone with spontaneous excretion in 2010; however, recurrence was noticed in 2022.

3. Discussion

Premature coronary artery disease can occur because of non-atherosclerotic vascular lesions, with PXE as a potential cause. However, considerable variability exists in its clinical manifestations, some of which are attributable to genetic heterogeneity, leading to the difficulties in its early diagnosis. In our case, the skin and ocular manifestations were remarkable for clinical diagnosis, and being a true homozygote for the nonsense mutation might be responsible for his typical manifestations, as described in recent reports demonstrating genotype-phenotype correlation or potential manifestation of obligate heterozygotes in PXE [7].

Disease-specific treatment strategies have never been established for PXE, although the potential of calcification-modifying approaches such as etidronate use seems to have some promise [8]. Similar to the present

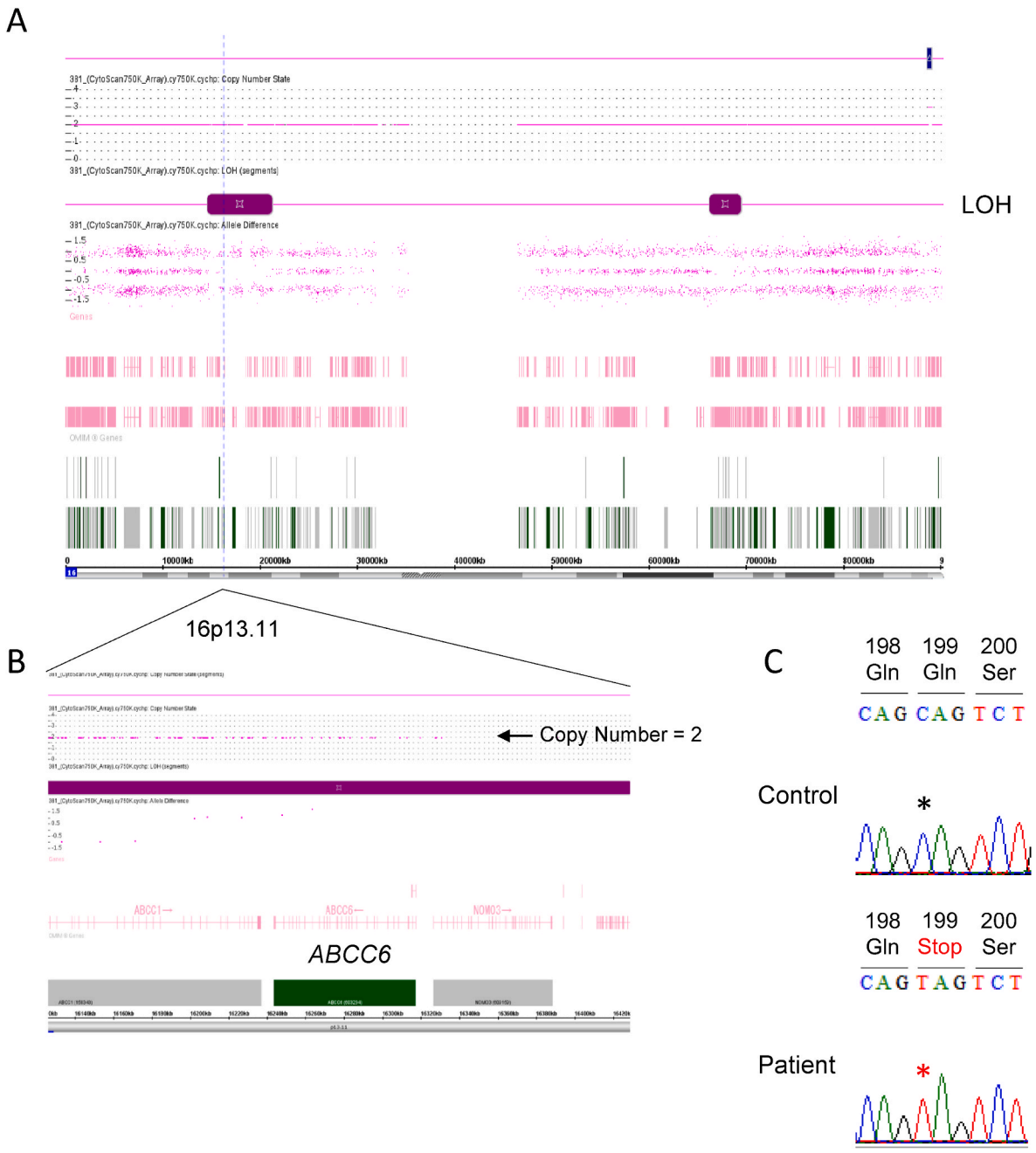

Fig. 4. Identification of the isodisomy region of 16p13.11 in this case.
The SNP array revealed isodisomy as segmental copy neutral loss of heterozygosity (LOH), as indicated by purple boxes. The 16p13.11 isodisomy region spans 6.8 Mb and includes ABCC6. The entire chromosome 16 (A) and the ABCC6 region (B). The nonsense variant was detected using Sanger sequencing of ABCC6 (C).

case, most patients with PXE and flow-limiting arterial lesions are treated with vascular intervention, and guideline-directed medical therapy for cardiovascular risk factors, including statins and antiplatelet agents. Recently, a novel hypothesis was reported, linking the role of ABCC6 to cholesterol metabolism [9–11] and thereby raising the possibility that statins could play a greater role in preventing lesion development in patients with PXE than in those non-PXE patients. In this regard, the lack of clinically detectable lesion development in the arteries (coronary and lower legs), skin, and eyes in our case might have been due to long-term statin administration, keeping his LDL cholesterol around 100 mg/dl throughout the clinical course. In contrast, left ventricular diastolic dysfunction developed during the 25-year treatment period. In previous reports, impaired distensibility of the left ventricle [12] and microvascular dysfunction [13] have been proposed as potential causes of this alteration. The discordant changes between vascular lesions and diastolic dysfunction in our case could provide a basis for future investigations of the pathophysiology and treatment strategy for PXE.

Genetic analysis revealed that both alleles of the nonsense variant found in the patient originated from the same chromosome. If both parents were carriers, the nonsense variant would have originated from a common ancestor, thus demonstrating a founder effect. The frequency of this variant in the general population is higher in Asians than in other ethnic groups, with a frequency of 0.000384 in the Japanese population (ToMMo 60KJPN, jMorp https://jmorp.megabank.tohoku.ac.jp/). It has also been reported in 7.2 % of Japanese patients with PXE, making it highly likely that there is a founding effect [6]. However, there are rare case reports of segmental uniparental isodisomy that results in

autosomal recessive disorders [5]. Although unlikely, this could not be ruled out in this case because it was not possible to test the parents. Despite its rarity, genotype-phenotype relationships, such as the reason for variabilities in clinical manifestation and treatment responses, as well as the possibility of disease-modifying genes [14–16], should be investigated by constructing a worldwide registration database that is fully filled with its molecular background.

Data availablitily

Data described in this manuscript could be available upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Aknowledgement

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