Rare co-occurrence of osteogenesis imperfecta type I and autosomal dominant polycystic kidney disease

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Background: **There are several clinical reports about the co-occurrence of autosomal dominant polycystic kidney disease (ADPKD) and connective tissue disorders. A simultaneous occurrence of osteogenesis imperfecta (OI) type I and ADPKD has not been observed so far.**

Methods: **This report presents the first patient with OI type I and ADPKD.**

Results: **Mutational analysis of *PKD1* and *COL1A1* in the index patient revealed a heterozygous mutation in each of the two genes. Mutational analysis of the parents indicated the mother as a carrier of the *PKD1* mutation and the father as a carrier of the *COL1A1* mutation. The simultaneous occurrence of both disorders has an estimated frequency of 3.5:100 000 000.**

Conclusion: **In singular cases, ADPKD can occur in combination with other rare disorders, e.g. connective tissue disorders.**

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Introduction

Osteogenesis imperfecta (OI) is a rare connective tissue disorder associated with fragility, deformity, and growth deficiency.[1] OI is a genetically heterogeneous disease comprising 15 types with either autosomal dominant or autosomal recessive patterns of inheritance.[2]

OI type I is characterized by the triad of fractures, blue sclerae, and hearing loss.[1] Patients present with near normal stature, minimal bone deformation, and fractures that typically lessen in frequency after puberty.[1] OI type I has an estimated frequency of 3.5:100 000 and is caused by mutations in one *COL1A1* allele (chromosome 17) leading to mRNA instability and haploinsufficiency.[1-3] To date, 756 mutations are described in *COL1A1*, 292 of them are associated with OI type I (Human Gene Mutation Database, HGMD® professional release, Cardiff, https://portal.biobase-international.com, release 2015.3).

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder with an incidence of 1:1000 individuals.[4] It is characterized by abnormal proliferation of renal tubular epithelial cells, which manifests as renal cysts leading to massive kidney enlargement and end-stage renal disease (ESRD).[5] ADPKD is a genetically heterogeneous disorder with mutations in *PKD1* (chromosome 16) accounting for 85% of cases and mutations in *PKD2* (chromosome 4) accounting for 15% of all cases.[5] To date, 2322 mutations are described in *PKD1* and 278 in *PKD2* (ADPKD Mutation Database, http://pkdb.mayo.edu/).

Up to now, a simultaneous occurrence of OI type I and ADPKD disease has not been reported. There are only a few reports in the literature describing patients with ADPKD and overlap connective tissue disorders.[6] Additionally, patients with Ehlers-Danlos syndrome and OI type IV in combination with cystic kidneys and ultrasonographic features similar to PKD have been reported.[7] Here we report the first case of a patient with both OI type I and ADPKD, both proven by molecular analysis of the patient and his family.

Case report

A boy of Turkish origin presented to our department for the first time in 2012 at the age of 13 years because of a familial history of bilateral polycystic kidneys

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and ESRD. His own medical history was unremarkable with a blood pressure of 100/50 mmHg, body weight of 51.3 kg (49th percentile), and height of 156 cm (18th percentile). Physical examination showed only blue sclerae. Laboratory investigations disclosed blood urea nitrogen 18 mg/dL, serum creatinine 0.34 mg/dL (IDMS-traceable Roche enzymatic method), cystatin C 1.14 mg/L, urine albumin 25 mg/L, urine creatinine 81.6 mg/dL (albumin-to-creatinine-ratio 30.6 mg/g), hemoglobin 12.5 g/dL, platelet count of 242.0/mm^3, and white blood cell count of 5.0/mm^3. The glomerular filtration rate (GFR) determined by the multi-variable Schwartz formula was 120 mL/min per 1.73 m^2.[8] Urine analysis revealed no abnormalities. Abdominal ultrasonography in this patient showed multiple cysts in both kidneys with a maximum size of 1.74 cm. Renal volume measured by ultrasonography was 128 mL (152%) for the left kidney and 82.7 mL (98%) for the right kidney. In 2013, the patient developed a shaft fracture of the left ulna and a fracture of the left olecranon within two weeks, both caused by minimal traumas.

The family history of the patient revealed that his mother also had renal cysts. His maternal grandmother once underwent a kidney transplantation after developing ESRD because of PKD. His father had to stop playing soccer because of recurrent fractures of the lower extremities after minimal traumas. The patient has two healthy sisters.

Genomic DNA was extracted from blood using the Chemagic STAR DNA Blood400 Kit (PerkinElmer, Aachen, Germany). As a first step, direct sequencing was performed in the index patient for the *PKD1* gene (NM_00296.3) and for the *COL1A1* gene (NM_000088.3) using the dideoxy chain termination method on an ABI capillary sequencer 3730 (Applied Biosystems, Foster City, USA). Primers were designed by Primer3 program (http://frodo.wi.mit.edu/primer3/input.htm). DNA alignment and sequence variant analysis were carried out using the Sequence Pilot^{CE} software (JSI Medical Systems GmbH, Kippenheim, Germany). DNA samples of the remaining family members were afterwards sequenced by target diagnostics.

Mutational analysis of the *PKD1* gene in the index patient revealed the heterozygous mutation c.5722C>T (p.Gln1908*) in exon 15 (Fig. 1). This mutation has already been described by Yu et al as causative for ADPKD.[9] Further mutational analysis of the *COL1A1* gene in the patient revealed the additional heterozygous mutation c.2450delC (p.Pro817Leufs*291) in exon 36 (Fig. 1). This mutation has not been described in the literature but leads to a premature termination of the protein. The identified mutation was classified by the prediction program MutationTaster (www.mutationtaster.org) as possibly damaging. Mutational

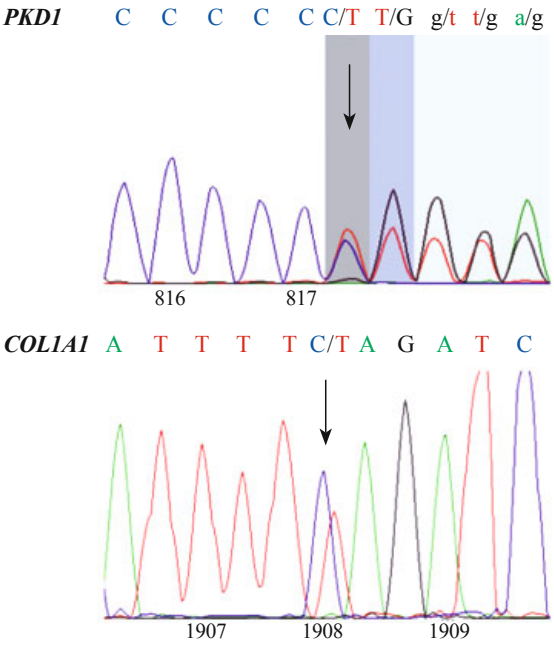

Fig. 1. Partial nucleotide sequence of exon 15 of the *PKD1* gene (c.5722C>T, p.Gln1908*) and exon 36 of the *COL1A1* gene (c.2450delC, p.Pro817Leufs*291) of the patient.

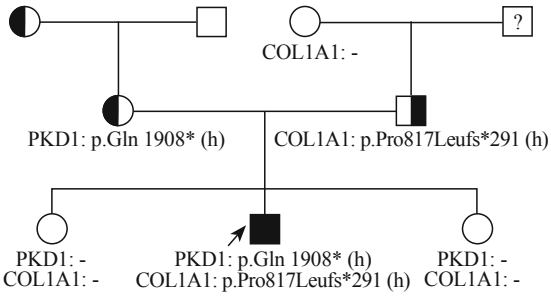

Fig. 2. Pedigree of the family and the results of the mutational analysis of *PKD1* and *COL1A1*. Circles denote females, squares denote males, arrow denotes the index patient, and h denotes heterozygous. "-": no mutation present.

analysis of the parents revealed the mother as a carrier of the *PKD1* mutation and the father as a carrier of the *COL1A1* mutation (Fig. 2). Both sisters of the patient had not inherited either of the mutations. With exception of the paternal grandmother, the grandparents were unfortunately not available for mutational analysis.

Discussion

As OI type I has an incidence of 3.5:100 000 (I_{OI}) and ADPKD of 1:1000 (I_{ADPKD}), the estimated probability of simultaneous occurrence of both diseases is therefore 3.5:100 000 000 ($I_{combined}=I_{OI}\times I_{ADPKD}$).[4,10] However, both diseases will be inherited with a 50% risk of recurrence.

Case reports of patients with simultaneous inheritance of ADPKD and other types of connective

tissue disorders have been published. Kaplan et al[7] described a male patient with OI type IV and multiple cysts within both kidneys compatible with PKD. Mutational analysis was not performed in this patient. Furthermore, patients with combined Ehlers-Danlos syndrome/ADPKD and Marfan syndrome/ADPKD have been reported.[6] As in all combinations of ADPKD and connective tissue disorders the two affected genes are located on different chromosomes, associations are likely to occur by chance. Therefore, no genetic evidence for dependent inheritance exists so far.[11] Accordingly, in this case of ADPKD and OI type I, the co-occurrence of both disorders could be determined as a coincidental event by mutational analysis and segregation analysis in the family. In singular cases ADPKD can occur in combination with other rare disorders, e.g. connective tissue disorders, and additional diagnoses besides ADPKD should then be genetically evaluated.

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Contributors: HJ, MK, MC, and KHG performed mutational analysis in this patient. MK treated the patient. HJ and AM drafted the manuscript. All authors approved the final version.

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