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Original Article

ORIGINAL ARTICLE

Novel somatic *PBX1* mosaicism likely masking syndromic CAKUT in an adult with bilateral kidney hypoplasia

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ABSTRACT

Background. Congenital abnormalities of the kidney and urinary tract (CAKUT) are characterized by vast phenotypic heterogeneity and incomplete penetrance. Although CAKUT represent the main cause of pediatric chronic kidney disease, only ∼20% can be explained by single-gene disorders to date. While pathogenic alterations of *PBX1* were recently associated with a severe form of syndromic CAKUT, most CAKUT patients survive childhood and adolescence to reach end-stage kidney disease later in life. Although somatic mosaicism is known to attenuate severity in other kidney diseases, it has rarely been described or systematically been assessed in CAKUT.

Methods. We conducted an in-depth phenotypic characterization of the index patient and his family using targeted next-generation sequencing, segregation analysis and workup of mosaicism with DNA isolated from peripheral blood cells, oral mucosa and cultured urinary renal epithelial cells (URECs).

Results. Somatic mosaicism was identified in a 20-year-old male with sporadic but mild syndromic renal hypoplasia. He was found to carry a novel *de novo* truncating variant in *PBX1* [c.992C>A, p.(Ser331*)]. This variant was detected in 26% of sequencing reads from blood cells, 50% from oral mucosa and 20% from cultured URECs.

Conclusions. *PBX1*-associated CAKUT is characterized by a wealth of *de novo* mutations. As in *de novo* cases, mutations can occur intra- or post-zygotically and genetic mosaicism might represent a more common phenomenon in *PBX1* disease, accounting for variable expressivity on a general basis. Consequently we suggest ruling out somatic mosaicism in sporadic CAKUT, notably in attenuated and atypical clinical courses.

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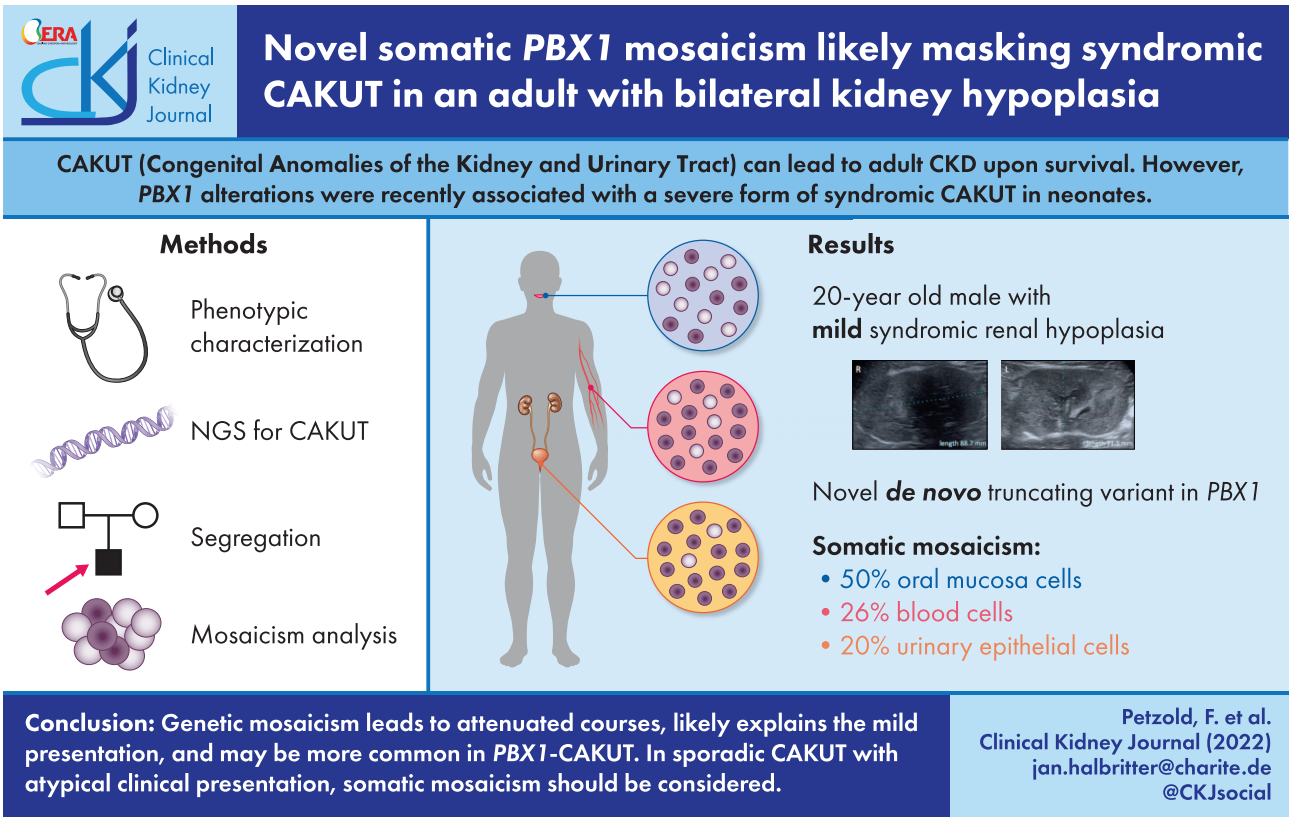
GRAPHICAL ABSTRACT



Keywords: CAKUT, CAKUTHED, homeobox domain, kidney hypoplasia, mosaicism, PBX1

INTRODUCTION

Congenital abnormalities of the kidney and urinary tract (CAKUT) represent the main cause of pediatric chronic kidney disease (CKD), with vast phenotypic and genotypic heterogeneity [1]. Although the majority of patients suffering from CAKUT do not require kidney replacement therapy (KRT) prior to adulthood [2], its overall contribution to adult CKD is still poorly characterized. Recently, molecularly confirmed CAKUT was found in as much as 12% of an adult CKD population (syndromic 7%, isolated 5%) [3]. While CKD progression may critically depend on congenital nephron endowment [4], one factor contributing to attenuated disease severity is somatic mosaicism.

Pathogenic *PBX1* alterations were recently associated with a severe syndromic form of CAKUT mainly in pediatric patients [5, 6]. In contrast, we herein report on an adult who underwent genetic testing for previously unrecognized CAKUT who was found to carry a mosaic *PBX1* truncating variant, constituting the first symptomatic *PBX1* mosaicism in an adult with mild syndromic renal hypoplasia.

MATERIALS AND METHODS

We conducted a phenotypic characterization of a patient with a clinical presentation of kidney hypoplasia, including renal ultrasound of the patient and available family members. Additional bilateral audiometry tests, echocardiography and chest X-ray were performed to evaluate extrarenal features.

For genetic analysis, written informed consent was obtained from all available family members (Institutional Review Board, University of Leipzig IRB00001750; #402/16-ek). DNA isolated from peripheral blood cells was analyzed for CAKUT-associated genes (*BICC1*, *BMP4*, *EYA1*, *GATA3*, *HNF1B*, *ITGA8*, *PAX2*, *PBX1*, *RET*, *ROBO2*, *SALL1*, *TBX18*). The target regions were amplified and sequenced simultaneously by next-generation sequencing (NGS) using an Illumina HiSeq 1500 system (Illumina, San Diego, CA, USA) with an average coverage of 714-fold. For >99.5% of the regions of interest a 15-fold coverage was obtained. The detection limit for variants in mosaic status was ≥10%.

Next, oral mucosa–derived DNA and DNA from cultivated urinary renal epithelial cells (URECs) were employed for further characterization of the index patient's mosaicism by Sanger sequencing. For segregation analysis, Sanger sequencing of identified variants was performed in both parents.

The putative splice site variant of the *RET* gene was validated on the cDNA level after RNA extraction from patient and control blood samples (PAXgene Blood RNA Kit 762174, Qiagen, Hilden, Germany) and consecutive reverse transcription polymerase chain reaction (SuperScript IV VILO Master Mix with ezDNase Enzyme 11766050, Themo Fisher, Waltham, MA, USA)) (Supplementary Figure).

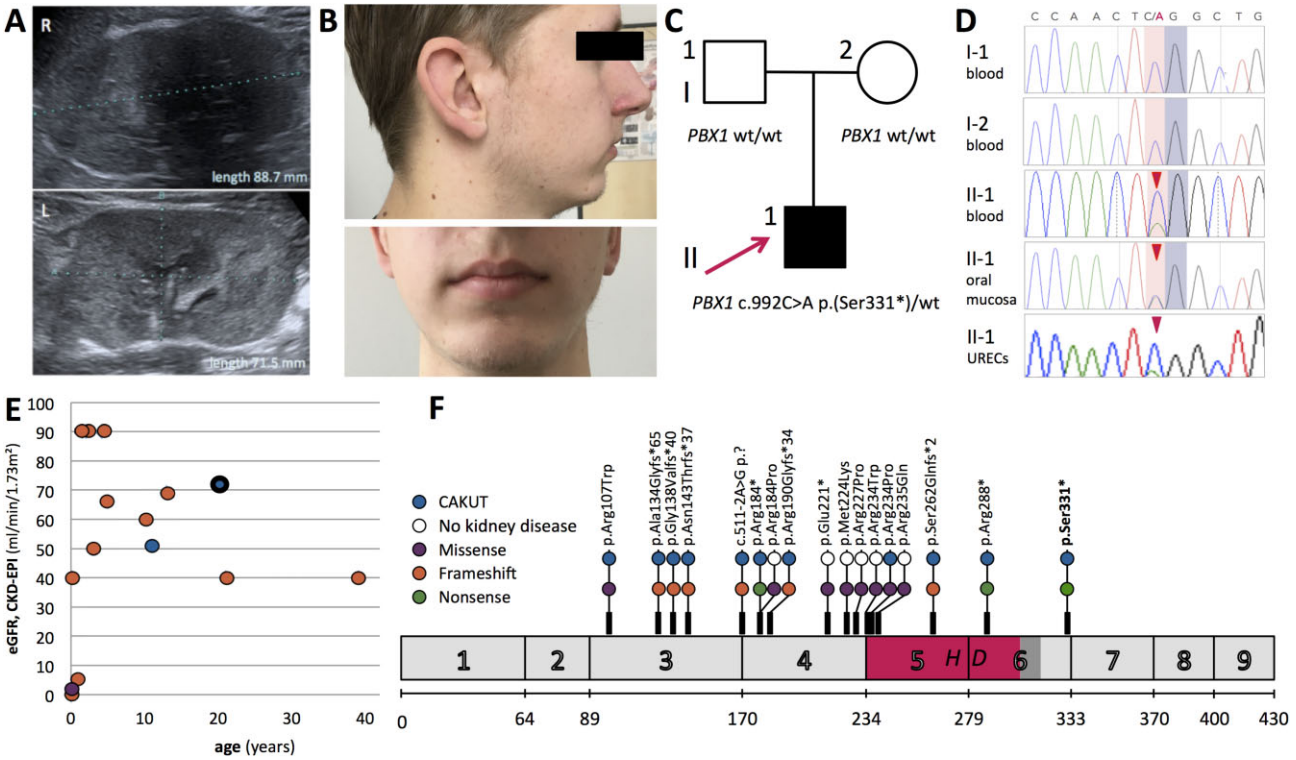


FIGURE 1: (A) Renal ultrasound with bilateral hypoplastic kidneys of the index patient. **(B)** Extrarenal features of low-set ears and slight micrognathia. **(C)** Pedigree with *de novo PBX1* variant of the index patient II-1 (marked by an arrow). **(D)** Chromatograms from the index patient (II-1) and his parents (I-1 father, I-2 mother) showing either *PBX1* wild-type (first and second panel) or different levels of the mosaic c.992C>A alteration generated from blood-derived DNA (third panel: 26% mosaic), oral mucosa≠ derived DNA (fourth panel: 50% mosaic) and URECs-derived DNA (fifth panel: 20% mosaic). **(E)** Kidney function (eGFR at age) and mutation type of the index patient (bold circle) in relation to previously published cases of *PBX1*-associated CAKUTHED. **(F)** Localization of the novel c.992C>A, p.(Ser331*) truncating variant (in bold) at the end of exon 6 in relation to the homeobox domain structure (HD: in pink) of *PBX1* (NM_002585.3).

RESULTS

A 20-year-old male presented with bilateral hypoplastic kidneys (Fig. 1A) first manifested at the age of 10 years with persistent nocturnal enuresis. For CKD stage 2 (eGFR 72 mL/min/1.73 m², using the Chronic Kidney Disease Epidemiology Collaboration equation), hypertension and moderate albuminuria (300 mg/day), he was treated with the angiotensin-converting enzyme inhibitor ramipril. Additionally, marginal facial dysmorphism with low-set ears and micrognathia was apparent (Fig. 1B). Bilateral audiograms did not reveal any signs of hearing impairment and upon echocardiography, no cardiac or vascular malformations were reported. Sexual development presented as normal.

In terms of family history, the index patient's non-consanguineous parents as well as three maternal half siblings presented as clinically unremarkable.

Genetic analysis revealed a novel *PBX1* truncating variant: c.992C>A, p.(Ser331*) (NM_002585.3), absent from patient and population databases (Fig. 1C). As this variant was detected in only 26% of NGS reads (in a 649× covered region), we investigated the pattern of putative mosaicism by direct sequencing of amplified DNA extracted from patient tissues, such as oral mucosa and renal tubular epithelium, the latter obtained from cultivated URECs. While oral mucosa cells revealed the mutated allele in 50% of reads, renal epithelial cells showed a 20% mosaicism. In contrast, segregation analysis of both parents yielded *PBX1* wild-type (Fig. 1D), ruling out parental germline transmission.

Additionally, we identified a novel noncanonical splice site variant in the Hirschsprung and CAKUT-associated protooncogene *RET* (MIM# 142623): c.1760–5C>A, p.? (NM_020975.4) [7]; a variant that was found to be absent from both patient and population databases and parental segregation demonstrated paternal inheritance. This substitution was predicted to affect splicing at the acceptor site of *RET* exon 10. However, a *RET* splice site analysis from peripheral blood revealed wild-type sequences in both patient and control samples, disproving *in silico* prediction and classifying *RET* c.1760-5C>A as a benign variant without aberrant splicing effect (Supplementary Figure).

DISCUSSION

Genetic mosaicism is defined as the occurrence of two or more cell lineages with different genotypes in a single individual. This phenomenon is arising from new mutations after fertilization, representing a post-zygotic event. Due to increased sensitivity of NGS techniques, even low-grade mosaicisms have become readily detectable. The detection limit in our NGS panel approach was ≥10%. Targeted NGS panel sequencing is an efficient technique for the identification of mosaicisms because of high coverages (200–1000×) compared with other sequencing approaches like whole exome sequencing (WES) and whole genome sequencing (WGS) with mean coverages of 100–200× and 30–60×, respectively. With the latter techniques, the allele fraction of the *PBX1* mutation detected here would probably have been missed.

Table 1. Review of the literature (HGMD professional version 2021.4) summarizing 31 *PBX1*-associated CAKUTHED patients/families, respective genotypes (including transmission, mosaicism) and phenotypes (including renal ultrasound, eGFR, prenatal anomalies, craniofacial dysmorphism, developmental delay, lung/heart malformation, bone malformations, cryptorchidism, other extrarenal symptoms)

							Extrarenal phenotype							
Nucleotide	Protein	Transmission	Mosaicism	Age	eGFR (mL/min/1.73 m^2)	Kidney phenotype	Prenatal anomalies	Craniofacial dysmorphism	Developmental delay	Lung/heart malformation	Bone malformations	Cryptorchidism	Others	Ref.
c.319C>T	p.Arg107Trp	n/a	Yes	Adult	Normal	UL pelvis dilatation	No							[10]
c.319C>T	p.Arg107Trp	Paternal	No	n/a	n/a	BL pelves dilatation, HSK				Hypoplastic lungs	Small abdomen and chest		Diaphragmatic hernia	[10]
c.400dupG	p.Ala134Glyfs*65	*de novo*	No	5 mo	n/a	R ectopic hypoplasia	Oligohydramnios	Yes	Yes	PDA	Brachydactyly		Glaucoma, corneal clouding, anterior segment dysgenesis, malformed pinnae, small auditory canals	[23]
c.413_419del	p.Gly138Valfs*40	*de novo*	No	4 y	59	BL hypoplasia, hyperechogenicity		Yes	Yes		Slender thorax, short clavicles, clinodactyly	Yes		[16]
c.428delA	p.Asn143Thrfs*37	*de novo*	No	21 y	40	BL hypoplasia					Scoliosis		Deafness	[5]
c.511–2A>G	p.?	*de novo*	No		n/a	BL hypoplasia, oligonephronia	Oligohydramnios							[5]
c.550C>T	p.Arg184*	*de novo*	No	11 y	51	BL cystic hypodysplasia		Yes	Yes					[5]
c.567delC	p.Arg190Glyfs*34	*de novo*	No	2 y	CKD 3	BL hyperechogenicity, atrophy, pyelectasia		Yes	Yes				External ear anomalies, BL frontal lobe atrophy	[17]
c.661G>T	p.Glu221*	*de novo*	No	1 y	n/a	R agenesis, L hypoplasia		Yes	Yes				Choanal atresia	[15]
c.704G>A	p.Arg234Pro	*de novo*	No	n/a	n/a	BL ureter dilatation		Yes		PDA, tetralogy of Fallot, UL lung hypoplasia	Brachydactyly	Yes	Wide neck/nuchal fold	[6]
c.701G>C	p.Arg235Gln	*de novo*	No	n/a	n/a	UL pyelocaliectasis, hyperechogenicity				PDA			Wide neck/nuchal fold	[6]
c.783dupC	p.Ser262Glnfs*2	*de novo*	No	n/a	n/a	Hypoplasia		Yes					Dysplastic ears, Microtia, EAC stenosis, UL hearing loss	[6]

Table 1. Continued.

						Extrarenal phenotype							
Nucleotide	Protein	Trans-mission	Mosai-cism	Age	eGFR (mL/min/ 1.73 m^2)	Kidney phenotype	Prenatal anomalies	Cranio-facial dysmorph-ism	Develop-mental delay	Lung/heart malformation	Bone malforma-tions	Cryptorchi-dism	Others	Ref.
c.862C>T	p.Arg288*	*de novo*	No	n/a	n/a	hypoplasia, urinary tract infections		Yes		Ebstein anomaly	Brachydactyly		Dysplastic ears, EAC stenosis	[6]
> = 13.28 Mb incl. entire gene		n/a	No	2 d	n/a	R hypoplasia		Yes		VSD, lung hypoplasia	Brachy-/clinodactyly			[18]
> = 14.1 Mb incl. entire gene		n/a	No	5 y	n/a	HSK	Growth retardation	Yes	Yes	Double aortic arch	Brachydactyly		Arnold Chiari malformation	[18]
> = 6.22 Mb incl. entire gene		n/a	No	10 y	n/a	Double ureter, nephrotic syndrome	Growth retardation	Yes	Yes		Craniosynostosis	Yes		[18]
> = 6.92 Mb incl. entire gene		n/a	No	5 y	n/a	HSK		Yes	Yes	PFO, PDA	Brachy-/clinodactyly		Sensorineural hearing loss	[18]
0.28 Mb incl. ex. 1–8		n/a	No	4.2 y	130	R ectopic dysplasia		Yes	Yes			R	Joint laxity	[19]
0.876 Mb incl. entire gene + 1 other		n/a	No	10 mo	CKD 5 (KTx)	BL dys-/hypoplasia			Yes	Mitral regurgitation, LVH		UL	Spina bifida occulta, UL inguinal hernia	[19]
1.518 Mb incl. entire gene		*de novo*	No	2 y	106	BL hypoplasia, hyperechogenicity		Yes	Yes		Skeletal anomalies	Yes		[19]
1.871 Mb incl. entire gene & LMX1A		*de novo*	No	Interrupted pregnancy		BL hypoplasia	Oligohydramnios, growth retardation				Polydactyly			[20]
2.46 Mb incl. entire gene + 7 others		*de novo*	No	39 y	40	HSK, corticomedullary dedifferentiation							Deafness	[5]
2.8 Mb incl. entire gene + 10 others		*de novo*	No	5 y	66	L dys-/hypoplasia, R ectopia, hyperechogenicity, corticomedullary dedifferentiation		Yes	Yes	VSD, PDA			Sacral pit	[19]
3.6 Mb incl. entire gene + 15 others		*de novo*	No	3 y	CKD 3	BL hypoplasia		Yes	Yes		Clinodactyly		CC hypoplasia, sacral pit, anal malposition, hearing loss	[19]
37 kb incl. ex. 3–6		Maternal	No	n/a	n/a	BL hypoplasia			Yes	Tetralogy of Fallot	UL hip dysplasia	Yes	Dysmorphic external ears	[9]
5.97 Mb incl. entire gene + 35 others		*de novo*	No	n/a	n/a	Bifid R ureter, BL pelvis dilatation, BL VUR		Yes	Yes				Sacral pit	[19]
571 kb incl. entire gene		n/a	No	n/a	n/a	Kidney anomaly	No							[21]
6.92 Mb incl. entire gene + 50 others		*de novo*	No	5 y	Normal	HSK		Yes	Yes	VSD, ASD, PDA	Cleft of the posterior arch of L5			[19]
9.1 Mb incl. entire gene + 130 others		*de novo*	No	18 mo	Normal	UL agenesis, hyperechogenicity		Yes	Yes					[5]
9.21 Mb incl. entire gene + 61 others		*de novo*	No	1.5 mo	40	BL hypoplasia, nephrocalcinosis	No							[19]
Translocation t(1;5)(q23;q22)		*de novo*	No	n/a	n/a	R ectopic hypoplasia, L malrotation	No							[22]

ASD, atrial septal defect; BL, bilateral; CC, corpus callosum; EAC, external auditory canal; HSK, horseshoe kidneys; incl.: including; L, left; LVH, left ventricular hypertrophy; n/a: not available; PDA, patent ductus arteriosus; PFO, patent foramen ovale; R, right; UL, unilateral; VSD, ventricular septal defect.

While somatic mosaicism was shown to account for almost 7% of *de novo* cases, this phenomenon is not systematically assessed in CAKUT and mosaicism as such has rarely been reported in CAKUT to date [8]. As mosaicism is associated with aberrant and often milder courses, mosaic patients may be overlooked or experience significant delay in obtaining their diagnosis.

Defects of the transcription factor PBX1 (PBX Homeobox 1) due to pathogenic *PBX1* alteration were recently associated with syndromic CAKUT [5]; a phenotype for which the acronym CAKUTHED (Congenital Anomalies of the Kidney and Urinary Tract syndrome with or without Hearing loss, abnormal Ears or Developmental delay) was coined (MIM# 617641) [5].

According to patient databases (HGMD Professional Version 2021.4), 31 different pathogenic *PBX1* variants have been published to date (5 nonsense including frameshift and splice sites, 4 missense, 22 indels) (Table 1). Kidney phenotypes comprise uni- and bilateral renal hypoplasia with or without hyperechogenicity, horseshoe kidneys, renal pelvis dilatation, dilated or duplex ureters, renal ectopia and, more rarely, renal agenesis. Most patients are <5 years of age at the time of first diagnosis and show variable decline of their kidney function (Fig. 1E). Remarkably, only two adult cases of CAKUTHED have been reported, both at CKD stage 3 (eGFR 40 mL/min/1.73 m²) with bilateral kidney hypoplasia and deafness (Fig. 1E, Table 1) [5].

The vast majority of patients ($n = 27/31$) presented with extrarenal manifestations, most frequently with craniofacial dysmorphism ($n = 18$), developmental delay ($n = 16$), bone malformations ($n = 15$), heart and lung defects ($n = 12$), ear anomalies with or without hearing impairment ($n = 9$) and cryptorchidism ($n = 7$) (Table 1). More rarely, in three patients, central nervous system malformation (frontal lobe atrophy, corpus callosum hypoplasia, Arnold Chiari malformation) was described. Recently, eye involvement in terms of glaucoma was first reported in a patient with *PBX1* disease [23].

Remarkably, genetic *PBX1* alterations are rarely found to be familial. In the literature, only two instances of parental transmission have been reported [9, 10], whereas all other cases are described as being *de novo* (29/31) (Table 1), although low-grade mosaicism in the parents cannot fully be excluded without more sensitive sequencing techniques, such as NGS.

PBX1 encodes a 430 amino acid protein with a DNA-binding homeobox domain (HD) at residues 233–305 (Fig. 1F), acting as a transcription factor. PBX1 plays an important role during dimerization with other three-amino acid-loop-extension homeodomain proteins from the myeloid ecotropic integration site and PBX regulating protein families to form nuclear complexes, thus enhancing the binding specificity of HOX proteins to DNA and regulating transcription during embryonic development [6]. While all pathogenic variants reported so far are located in the homeobox domain itself or further upstream (Fig. 1F), functional analyses indicate more C-terminal residues to be equally important for efficient cooperative DNA binding with HoxA5 in addition to the homeobox domain [11]. These data suggest that truncation of the PBX1 C-terminus downstream of p.Ser331 may also interfere with efficient DNA binding (Fig. 1F).

Although the *de novo PBX1* p.Ser331* variant presumably impacts DNA binding activity, the patient's phenotype appears remarkably mild compared with the severe syndromic affection in all previously published cases (Table 1). This is likely explained by the mosaic status of the *PBX1* variant, present in only 26% of NGS reads in blood cells, 50% in oral mucosa and 20% in urinary epithelial cells compared with germline mutations affecting all body cells equally. This is in line with a recently reported family where the father was found to carry a low-grade *PBX1* mosaicism in blood and sperm cells, displaying subclinical hydronephrosis in childhood without CKD progression in adulthood [10]. In contrast, his two children showed lethal congenital abnormalities, such as pulmonary hypoplasia, CAKUT, asplenia, diaphragmatic eventration and complete sex reversal associated with a heterozygous *PBX1* mutation [10]. Because mosaics are postzygotic events, it is reasonable that the parents of our index patient did not carry the *PBX1* variant, rendering all siblings at no risk of disease transmission.

Somatic mosaicism has been shown to modulate disease severity in other kidney diseases, such as autosomal dominant polycystic kidney disease and tuberous sclerosis complex [12, 13]. Since little is known about the prevalence of somatic mosaicism in CAKUT, its impact on modulating disease severity and expressivity cannot be fully appreciated. Apart from the recently published instance of an inherited *PBX1* mosaicism [10] and an inherited mosaic alteration in the newly identified CAKUT gene *ZMYM2* [14], it is unknown to what extent genetic mosaicism accounts for the vast phenotypic variability in CAKUT to date.

In summary, we suggest *PBX1* as a CAKUT gene that may be prone to mosaicism (2/31), conveying milder courses of disease. Mosaicism has to be suspected upon atypical presentation and requires systematic analysis of different cell lineages of a single individual. In CAKUT cases that present sporadically (*de novo*), somatic mosaicism has to be ruled out in both index patients and their parents to fully capture the contribution of congenital kidney anomalies to CKD in the general population.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no potential conflicts of interest.

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