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.
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, Thermo Fisher, Waltham, MA, USA) (Supplementary Figure).
Novel somatic PBX1 mosaicism in an adult with bilateral kidney hypoplasia

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 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.

Additionally, we identified a novel noncanonical splice site variant in the Hirschsprung and CAKUT-associated proto-oncoprotein 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 paternal 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 mosaicism 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 mosaicism 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 CAKUT-HED 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)

| Nucleotide | Protein  | Transmission | Mosaicism | Age | eGFR (mL/min/1.73 m²) | Kidney phenotype | Extrarenal phenotype | Ref. |
|------------|----------|--------------|-----------|-----|-----------------------|------------------|---------------------|-----|
| c.319G>T   | p.Arg107Trp | n/a | Yes | Adult | Normal | UL pelvis dilatation | No | Hypoplastic lungs, Small abdomen and chest, Brachydactyly | [10] |
| c.319G>T   | p.Arg107Trp | Paternal | No | n/a | n/a | BL pelvis dilatation, HSK | Yes | Brachydactyly | [10] |
| c.400dupG  | p.Ala134Glyfs*65 | de novo | No | 5 mo | n/a | Rectopic hypoplasia, Oligohydramnios | Yes | Diaphragmatic hernia, 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 | Slender thorax, short clavicles, clinodactyly, Scoliosis | [16] |
| c.428delA  | p.Asn143Thrfs*37 | de novo | No | 21 y | 40 | BL hypoplasia, oligonephronia, Oligohydramnios | Yes | Deafness | [5] |
| c.550C>T   | p.Arg184* | de novo | No | 11 y | 51 | BL cystic hydropsplasia, BL hyperechogenicity, atrophy, pyelectasia | Yes | External ear anomalies, frontal lobe atrophy, Choanal atresia | [17] |
| c.567delC  | p.Arg190Glyfs*34 | de novo | No | 2 y | CKD 3 | BL hyperechogenicity, atrophy, pyelectasia | Yes | PDA, tetralogy of Fallot, UL lung hypoplasia, PDA, pulmonic stenosis, Botal, Truncus arteriosus, Choanal atresia, Hypoplastic lungs, Pleuropericardial cyst, Obstructive sleep apnea, Congenital heart disease, Short nape | [6] |
| c.661G>T   | p.Glu221* | de novo | No | 1 y | n/a | Ragenesis, Hypoplasia | Yes | Wide neck/ nuchal fold | [15] |
| c.704G>A   | p.Arg234Pro | de novo | No | n/a | n/a | BL ureter dilatation | Yes | Brachydactyly | [6] |
| c.704G>A   | p.Arg234Pro | de novo | n/a | n/a | n/a | BL ureter dilatation | Yes | Wide neck/ nuchal fold | [6] |
| c.704G>A   | p.Arg234Pro | de novo | UL pyelocelextasis, | Hyperechogenicity | Hypoplasia | Yes | Wide neck/ nuchal fold | [6] |
| c.783dupC  | p.Ser262Glyfs*2 | de novo | No | n/a | n/a | UL pyelocelextasis, | Hyperechogenicity | Wide neck/ nuchal fold | [6] |
Table 1. Continued.

| Nucleotide | Protein | Transmission | Mosaicism | Age | eGFR (mL/min/1.73 m²) | Kidney phenotype | Prenatal anomalies | Craniofacial dysmorphism | Developmental delay | Lung/heart malformation | Bone malformations | Cryptorchidism | Others | Ref. |
|------------|---------|--------------|-----------|-----|----------------------|----------------|----------------|-----------------------|------------------------|----------------------|------------------|---------------|--------|------|
| c.862C>T  | p.Arg288*| de novo      | No        | n/a | n/a                  | hypoplasia, urinary tract infections | Yes | Ebstein anomaly | VSD, lung hypoplasia | Brachydactyly | Dysplastic ears, EAC stenosis | [6] |
|           |         |              |           |     |                      | R hypoplasia | Yes           | Double aortic arch  | Brachy-/clindactyly | Arnold Chiari malformation | [18] |
|           |         |              |           |     |                      |                |               | Growth retardation | Yes                    |                        |                        |               |        |      |
|           |         |              |           |     |                      |                |               | Growth retardation | Yes                    |                        |                        |               |        |      |
|           |         |              |           |     |                      |                |               |                        |                        |                        |                        |               |        |      |
| 0.28 Mb incl ex. 1-8 | n/a | No | 4.2 y | 10 mo | 130 | CKD 5 (KTx) | R ectopic dysplasia, BL dys-/hypoplasia | Yes | Yes | Mitral regurgitation, LVH | [19] |
| 0.896 Mb incl entire gene + 1 other | n/a | No | 0.28 Mb incl ex. 1-8 | n/a | No | 1.518 Mb incl. entire gene | de novo | No | 2 y | 106 | BL hypoplasia, hyophrenchogenicity, BL hypoplasia | Yes | Yes | Skeletal anomalies | Polydactyly | [19] |
|           |         |              |           |     |                      |                |               |                        |                        |                        |                        |               |        |      |
| 1.871 Mb incl. entire gene & LMX1A | de novo | No | Interrupted pregnancy | 39 y | 40 | HS | Oligohydramnios, growth retardation | Yes | Yes |                        | [20] |
| 2.46 Mb incl. entire gene + 7 others | de novo | No | 2.8 Mb incl. entire gene + 10 others | de novo | No | 2.46 Mb incl. entire gene + 7 others | de novo | No | 2 y | 106 | BL hypoplasia, hyophrenchogenicity, BL hypoplasia | Yes | Yes |                        | [20] |
|           |         |              |           |     |                      |                |               |                        |                        |                        |                        |               |        |      |
| 3.6 Mb incl. entire gene + 15 others | de novo | No | 3.6 Mb incl. entire gene + 15 others | de novo | No | 3.6 Mb incl. entire gene + 15 others | de novo | No | 2.8 Mb incl. entire gene + 10 others | de novo | No | 2.46 Mb incl. entire gene + 7 others | de novo | No | 2 y | 106 | BL hypoplasia, hyophrenchogenicity, BL hypoplasia | Yes | Yes |                        | [20] |
|           |         |              |           |     |                      |                |               |                        |                        |                        |                        |               |        |      |
| 37 kb incl. ex. 3-6 | Maternal | No | n/a | n/a | n/a | BL hypoplasia | Yes | Tetralogy of Fallot | UL hip dysplasia | Yes | CC hypoplasia, sacral pit, anal malposition, hearing loss | [19] |
| 5.97 Mb incl. entire gene + 35 others | de novo | No | 37 kb incl. ex. 3-6 | Maternal | No | 37 kb incl. ex. 3-6 | Maternal | No | n/a | n/a | n/a | BL hypoplasia | Yes | Yes | Tetralogy of Fallot | UL hip dysplasia | [19] |
|           |         |              |           |     |                      |                |               |                        |                        |                        |                        |               |        |      |
| 57.1 kb incl. entire gene | de novo | No | 57.1 kb incl. entire gene | de novo | No | 57.1 kb incl. entire gene | de novo | No | 1.5 mo | 40 | BL hypoplasia, hyophrenchogenicity, BL hypoplasia | Yes | Yes | VSD, ASD, PDA |                        | [19] |
| 6.92 Mb incl. entire gene + 50 others | de novo | No | 57.1 kb incl. entire gene | de novo | No | 57.1 kb incl. entire gene | de novo | No | 1.5 mo | 40 | BL hypoplasia, hyophrenchogenicity, BL hypoplasia | Yes | Yes | VSD, ASD, PDA |                        | [19] |
| 9.1 Mb incl. entire gene + 130 others | de novo | No | 9.1 Mb incl. entire gene + 130 others | de novo | No | 9.1 Mb incl. entire gene + 130 others | de novo | No | 1.5 mo | 40 | BL hypoplasia, hyophrenchogenicity, BL hypoplasia | Yes | Yes | VSD, ASD, PDA |                        | [19] |
| 9.21 Mb incl. entire gene + 61 others | de novo | No | 9.21 Mb incl. entire gene + 61 others | de novo | No | 9.21 Mb incl. entire gene + 61 others | de novo | No | 1.5 mo | 40 | BL hypoplasia, hyophrenchogenicity, BL hypoplasia | Yes | Yes | VSD, ASD, PDA |                        | [19] |

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 duplicated 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 ectopic 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 eversion 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 cjonline online.

ACKNOWLEDGEMENTS

F.P. is funded by the German Research Foundation [Deutsche Forschungsgemeinschaft (DFG), grant PE 3135/1-1]. R.S. is funded by the Else Kröner-Fresenius-Stiftung. J.H. receives funding from the DFG (HA 6908/3-1).

CONFLICT OF INTEREST STATEMENT

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

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