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Short communication

Rethinking genotype-phenotype correlations in papillorenal syndrome: a case report on an unusual congenital camptodactyly and skeletal deformity with a heterogeneous *PAX2* mutation of hexanucleotide duplication

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ABSTRACT

Papillorenal syndrome (PRS), an autosomal dominant inherited condition, is clinically featured by renal hypoplasia and optic nerve dysplasia. Based on current knowledge of genotype-phenotype correlations in PRS, mutations in the *Paired box 2* (*PAX2*) gene have been recognized as a critical pathogenesis of typical renal and optic disease manifestations. However, little information is currently available on the skeletal abnormalities of PRS and the potential contribution of *PAX2* mutations. Here, we present a case of a 10-year-old female PRS patient with the typical features of chronic renal failure and severe myopia, but was unexpectedly discovered camptodactyly of her left middle finger which affects the proximal interphalangeal joint. Pathologically, the camptodactyly was further indicated by radiology as a skeletal deformity, demonstrating a decline of bone mineral density and disappearance of joint space. Molecular diagnostics revealed a heterozygous mutation, 220_225dup, in the exon 3 of her *PAX2* gene, which is *de novo* considering the lack of this mutation in her non-consanguineous parents. This mutation leads to duplication of glutamic acid at position 74 and tyrosine at position 75 in PAX2 protein, which may influence the DNA-binding function. Besides, the absence of *Spalt like transcription factor 4* (*SALL4*) mutation excluded the diagnosis of acro-renal-ocular syndrome (AROS), of which clinical characteristics are similar to our patient's. This case unravels a previously unrecognized phenotype of camptodactyly due to a significant skeletal deformity of PRS with a heterogeneous *PAX2* mutation of hexanucleotide duplication. This report challenges against the current belief of genotype-phenotype correlations in PRS.

1. Introduction

Papillorenal syndrome (PRS, OMIM 120330), also called renal coloboma syndrome (RCS), is an autosomal dominant condition characterized by both renal and ocular anomalies (Schimmenti, 2011). Additionally, a wide range of other lesions have been reported in PRS patients, such as hearing loss, central nervous system anomalies, elevated pancreatic amylase and hyperuricemia (Schimmenti et al., 1999). As to the molecular basis, *Paired box 2* (*PAX2*) mutation is recognized as the critical pathogenesis of PRS, which affects the function of PAX2 protein, a member of the PAX family of transcriptional regulators. Other than its pivotal roles in kidney and eye development, PAX2 regulation is known to be important for homeostasis of the midbrain/hindbrain boundary, the cerebellum, the hypothalamus, the spinal cord, the otic vesicle and the pancreas, establishing the current belief of genotype-phenotype correlations in PRS (Bower et al., 2012). However, function of PAX2 in the skeleton and the associated contribution of its mutation to PRS have not yet been uncovered. In the present study, we report an unexpected case of PRS with congenital camptodactyly, which is further attributed to an unusual skeletal deformity with a heterozygous *de novo PAX2* mutation of hexanucleotide duplication.

2. Patient and methods

2.1. Patient

A 10-year-old girl was admitted to Department of Pediatrics, Fuzhou Dongfang Hospital, China, for renal failure, which is confirmed by her

Abbreviations: AROS, acro-renal-ocular syndrome; BMPs, bone morphogenetic proteins; CT, Computed Tomography; Krd, kidney and renal defects; MRI, magnetic resonance imaging; OD, oculus dexter; OMIM, Online Mendelian Inheritance Man; OS, oculus sinister; PAX2, paired box 2; PIP, proximal interphalangeal; PRS, papillorenal syndrome; PTH, parathyroid hormone; RCS, renal coloboma syndrome; SALL4, spalt like transcription factor 4; TGF-β, transforming growth factor-β

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Table 1
Laboratory data at presentation.

Variable	Result	Reference range
Blood routine tests		
Erythrocytes (10^{12}/L)	**2.66**	3.8–5.1
Leucocyte (10^9/L)	5.84	3.5–9.5
Platelet count (10^9/L)	156.0	125–350
Hemoglobin (g/L)	**69**	115–150
Hematocrit (%)	**20.3**	35–45
Mean corpuscular volume (fL)	**76.3**	82–100
Mean corpuscular hemoglobin (pg)	**20.3**	27–34
Serum chemistry		
Urea nitrogen (mmol/L)	**54.5**	2.9–8.2
Creatinine (μmol/L)	**1423**	53–115
Uric acid (μmol/L)	**496.6**	155–428
Glucose (mmol/L)	**6.7**	3.9–6.1
Total protein (g/L)	80.3	65–85
Albumin (g/L)	44.6	40–55
Cholesterol (mmol/L)	**7.78**	< 5.2
Triglyceride (mmol/L)	**1.9**	< 1.7
High-density lipoprotein (mmol/L)	1.69	> 1.04
Low-density lipoprotein (mmol/L)	**5.6**	< 3.12
Apolipoprotein AI (g/L)	**2.51**	1.0–1.6
Apolipoprotein B (g/L)	**1.52**	0.6–1.2
Serum potassium (mmol/L)	4.23	3.5–5.3
Serum sodium (mmol/L)	140.2	137–147
Serum chlorine (mmol/L)	**97.4**	99–110
Serum calcium (mmol/L)	**1.4**	2.08–2.6
Serum magnesium (mmol/L)	1.1	0.7–1.1
Serum phosphorus (mmol/L)	**3.77**	0.9–1.34
Parathyroid hormone (pg/mL)	**536**	12–65
Urine test		
Specific gravity	1.010	1.003–1.030
Urinary protein	+ + +	−
Urine glucose	−	−
Urine ketone bodies	−	−
Urine bilirubin	−	−
Urinary occult blood	+	−
Cystatin C (mg/L)	**7.73**	0.55–1.55
Urinary α1-microglobulin (mg/L)	**113**	< 12
Urinary β2-microglobulin (mg/L)	**30.2**	0–0.2
Immunology		
Antistreptolysin O test (IU/mL)	**3070**	0–250
C-reactive protein (mg/L)	< 7.2	0–8
Complement C3 (g/L)	**0.478**	0.9–1.8
Complement C4 (g/L)	0.199	0.1–0.4
Immunoglobulin G (g/L)	13.00	6.94–16.2
Immunoglobulin M (g/L)	0.79	0.4–23
Immunoglobulin A (g/L)	1.84	0.68–3.78
Blood coagulation test		
D-dimer (mg/L)	**0.64**	< 0.5
Activated partial thromboplastin time (s)	32.0	21.1–36.5
Prothrombin time (s)	**13.9**	9.8–12.1
Prothrombin time-international normalized ratio	**1.2**	0.82–1.15
Thrombin time (s)	18.6	14–21

Note: Bold values in result column indicate the abnormal detected values out of the reference range.

laboratory findings (Table 1). As shown by the urine dipstick analysis, her urine was + for occult blood and + + + for protein. Furthermore, her urinary α1-microglobulin was 113 mg/L and urinary β2-microglobulin was 30.20 mg/L, both over the normal ranges. Serological analysis additionally demonstrated abnormal levels of urea nitrogen, creatinine and cholesterol, respectively at 54.5 mmol/L, 1423.0 μmol/L and 7.78 mmol/L. Moreover, as revealed by Computed Tomography (CT), her left kidney size was 53 × 22 mm and her right kidney size was 61 × 27 mm, indicating bilateral renal atrophy, especially her left kidney (Fig. 1A, B). In addition, her history of medical examination did not show any obvious abnormality except nocturnal enuresis continuing from birth, while lifestyle guidance, water restriction and alarm treatment did not result in favorable responses. As for the treatments, the patient started continuous ambulatory peritoneal dialysis to relieve the deterioration of her renal function after admission. Because of the unfavorable urinemia, renal transplantation is now being considered.

She was also identified with a history of severe myopia. At 4 years old, she was found significant visual acuity of − 20.12DS/ − 1.62 DC × 12 (OD) and + 1.50DS/ − 3.12 DC × 8 (OS). As revealed by funduscopy, bilateral atypical optic nerve coloboma existed in which the right eye was much more diseased (Fig. 1C, D). In a further evaluation by magnetic resonance imaging (MRI), cystic malformation of the right eye was discovered, while the left eye was smaller but not microphthalmia, correlated with its milder myopia (Fig. 1E, F). The patient has healthy non-consanguineous parents, and the family history is negative for renal diseases.

The patient's left middle finger with camptodactyly which affects the proximal interphalangeal (PIP) joint was unexpectedly discovered, while physical examination revealed no other dysmorphic features (Fig. 1G, H). As shown, she has functional deformities due to the severity of 60° flexion contracture and about 30° extension lag at the PIP joint. Acral radiography confirmed mild flexion deformity of the patient's left middle finger and further suggested decline of bone mineral density and disappearance of joint space (Fig. 1I, J). However, passive range of motion exercise of the PIP joint did not result in a favorable response. According to clinical evaluation of the affected digit, surgery should be performed (Netscher et al., 2015). Besides, in order to investigate the possibility of skeletal deformity due to renal osteodystrophy, given the observed hypocalcemia and hyperphosphatemia, parathyroid hormone (PTH) was additionally tested with an over-ranged 536 pg/mL (Table 1). However, it is notable that her history of lab examination did not show any obvious abnormality before the present admission.

2.2. Methods

After obtaining informed consent, genomic DNA from the patient and her parents was extracted from peripheral blood according to standard procedures. The study was approved by the ethical committee of Fuzhou Dongfang Hospital.

The patient was analyzed for variants in all coding exons and exon-intron boundaries of 3409 disease-related genes associated with 4387 kinds of monogenic conditions using Roche NimbleGen V2 Target Enrichment (Roche NimbleGen, Madison, WI, USA), followed by next-generation sequencing HiSep 2500, Illumina (Illumina, San Diego, CA, USA). Data analysis was performed by BclToFastq2 Software 2.18.0 (Illumina, San Diego, CA, USA) and BWA 0.7.11-r1034 (Wellcome Trust Sanger Institute, Cambridge, UK). Variants detected from above experiments were further verified by bi-directional Sanger sequencing in the patient and her parents.

3. Results

A heterozygous mutation in *PAX2* exon 3, 220_225dup, was identified in the patient. This mutation leads to the duplication of glutamic acid at position 74 and tyrosine at position 75 in PAX2 protein. (Glu74Thr75dup). The identical *PAX2* mutation was not detected in her parents (Fig. 1K). Moreover, to further confirm the diagnosis of PRS, *Spalt like transcription factor 4* (*SALL4*) mutation was also examined in this patient, which is recognized as a molecular basis of acro-renal-ocular syndrome (AROS, OMIM 607323) with similar clinical characteristics to our patient's. However, the mutation in *SALL4* gene was absence in the patient.

4. Discussion

PRS, the severe autosomal dominant condition, was first described by Weaver et al. in 1988 (Weaver et al., 1988). Since then, emerging evidence has been raised regarding PRS and its urogenital and ocular manifestations, but PRS with congenital camptodactyly and skeletal