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Novel mutation in the SALL1 gene in a four-generation Chinese family with uraemia: A case report

Novel SALL1 mutation cause uraemia

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Abstract

BACKGROUND

Approximately 10% of adults and nearly all children who receive renal replacement therapy have inherited or are related to genetic factors. In the past, due to the limitations of detection technology and the nonspecific manifestations of uraemia, the etiological diagnosis is unclear. In addition to common monogenic diseases and complex disorders, advanced testing techniques have led to the recognition of more hereditary renal diseases. Here, we report a four-generation Chinese family in which four individuals had a novel *SALL1* mutation and presented with uraemia or abnormal urine tests.

CASE SUMMARY

A 32-year-old man presented with end-stage renal disease with a 4-year history of dialysis. His father and paternal aunt both had a history of unexplained renal failure with haemodialysis, and his 10-year-old daughter presented with proteinuria.

The patient had multiple congenital abnormalities, including bilateral overlapping toes, unilateral dysplastic external ears and sensorineural hearing loss. His family members also presented with similar defects. Genetic testing revealed that the proband carried a novel heterozygous shift mutation in *SALL1*_exon 2 (c.3437delG), and Sanger sequencing confirmed the same mutation in all affected family members.

CONCLUSION

We report a novel *SALL1* exon 2 (c.3437delG) mutation and clinical syndrome with kidney disease, bilateral overlapping toes, unilateral dysplastic external ears and sensorineural hearing loss in a four-generation Chinese family.

Key Words: SALL1; Gene mutation; Uraemia; Hereditary renal diseases; End stage renal disease; Case report

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Core Tip: We report a novel SALL1 exon 2 (c.3437delG) mutation and clinical syndrome with kidney disease, bilateral overlapping toes, unilateral dysplastic external ears and sensorineural hearing loss in a four-generation Chinese family. As patients with kidney diseases do not have specific clinical presentations, symptoms other than kidney disease were relatively hidden or easily ignored resulted in missed diagnosis. Gene sequencing is recommended in patients with family history and with extrarenal phenotypes to avoid blind use of immunosuppressive drugs, which may cause adverse effects.

INTRODUCTION

Hereditary kidney disease is one of the important causes of end-stage renal disease (ESRD) in patients requiring renal replacement therapy. Rapid advances in detection techniques have allowed more unexplained kidney diseases to be accurately diagnosed, including polycystic kidney disease, Alport syndrome, Fabry disease, Bartter syndromes, Gitelman syndromes and other multifactorial disorders[1]. New genetic mutations causing kidney disease are constantly identified, along with other extrarenal phenotypes.

Townes-Brocks syndrome (TBS), first described by Philip L. Townes and Eric Brocks in 1972, is a rare autosomal dominant disease resulting from mutations in the developmental gene *SALL1*[2]. Its main features are the triad of anorectal, hand, and external ear malformations. Another key characteristic of TBS is kidney involvement, which results in progression to ESRD early in life. A report of 154 patients with TBS identified renal anomalies in 43% of affected individuals[3]. Previous reports have shown that syndrome-related kidney and genitourinary defects include renal hypoplasia, unilateral renal agenesis, dysplastic kidneys, vesicoureteric reflux, meatal stenosis, and glandular hypoplasia[4]. Here, we report a four-generation family

including four affected individuals suffering from kidney disease who carry a novel *SALL1* mutation. Among them, three patients progressed to ESRD.

CASE PRESENTATION

Chief complaints

A 32-year-old male was admitted to our hospital because of ESRD characterized by severe hypertension and elevated serum creatinine (SCr) for nine years and received renal dialysis for four years.

History of present illness

Nine years ago, the patient was admitted to the hospital because of syncope and was diagnosed with uraemia. After diagnosis, he was treated with traditional Chinese medicine. He started renal dialysis four years ago because of gradually deteriorating kidney function with an SCr level of 900 μmol/L. A kidney biopsy was not performed during the course of the kidney disease.

History of past illness

The patient was born with multiple congenital abnormalities, including limb malformation (bilateral overlapping toes) and unilateral dysplastic external ears (Figure 1). A unilateral moderate degree of sensorineural hearing loss was noted when he was 10 years old.

Personal and family history

The family pedigree for the patient (proband, III.3) is shown in Figure 2A. The patient's grandmother (I.2) died at an early age without a clear diagnosis due to the poor level of medical care. However, she presented with a sixth finger malformation, unilateral dysplastic external ears and hearing loss. The patient's father (II.5) had unilateral dysplastic external ears, hearing loss, and bilateral overlapping toes. At the age of 53 years, he began dialysis therapy. The patient's aunt (II.4) was born with unilateral

dysplastic external ears, hearing loss and limb malformation (unilateral preaxial polydactyly of one hand). At the age of 53 years, she also began haemodialysis due to unexplained ESRD. The patient's daughter (IV.1) was born with bilateral dysplastic external ears, without limb malformation, and was found to have unilateral hearing dysfunction misdiagnosed as otitis media.

Physical examination

Vital signs were in the normal ranges: body temperature, 36.7 ℃, respiratory rate, 18 breaths/min, pulse rate, 80 bpm and blood pressure (under antihypertensive treatment) of 134/85 mmHg. Limb malformation (bilateral overlapping toes) and unilateral dysplastic external ears existed. His ophthalmic examination results were normal, and no anorectal abnormalities were found.

Laboratory examinations

Laboratory analysis revealed an increased SCr level (941.9 μmol/L), high potassium level (6.87 mmol/L), high phosphate level (2.73 mmol/L), normal haemoglobin (145 g/L) and high parathyroid hormone level (663.6 pg/mL). The patient was anuria.

Imaging examinations

Ultrasound examination revealed bilaterally small kidneys (left kidney, 52x34 mm; right kidney, 50x25 mm) with multiple 5-7 mm medullary cysts. The urinary tract was normal, and no additional abnormalities of the liver, spleen, or pancreas were detected in the imaging studies.

FINAL DIAGNOSIS

After obtaining informed consent, we conducted high-throughput detection and analysis of approximately 20,000 genes of the proband, focusing on the genes related to uraemia and nephropathy. One pathogenic mutation, a heterozygous shift mutation in *SALL1*_ exon 2(c.3437delG), was found to be related to the patient's symptoms (Figure

2B). It was verified that the three relatives mentioned above carried the same mutation (Figure 2B). The genetic pattern of *SALL1* associated with TBS is autosomal dominant. It is speculated that this pathogenic mutation is the main cause of familial hereditary disease. Finally, based on clinical features and the presence of the *SALL1* pathogenic variant, the suspected diagnosis of TBS without imperforate anus was confirmed.

TREATMENT

The patient received maintenance haemodialysis three times a week, a sevelamer carbonate tablet of 1.6 g three times per day, calcitriol soft capsules of 0.5 μg per day, and nifedipine controlled-release tablets of 60 mg per day.

OUTCOME AND FOLLOW-UP

The patient and two relatives were on dialysis and received regular follow-up. His daughter currently presents with minimal proteinuria and normal SCr. She was treated with losartan potassium tablets of 25mg per day and was followed up every three months.

DISCUSSION

In this four-generation family diagnosed with TBS with renal manifestations, uraemia was the first symptom to prompt the affected members to go to the hospital. The diagnosis of TBS was confirmed by a genetic testing in four family members, three of whom had already progressed to ESRF. This indicates that symptoms other than kidney disease were relatively hidden or easily ignored and resulted in missed diagnosis.

The transcoding mutation resulted in a change in the amino acid at position 1158 from glycine to glutamate, which changed the subsequent reading frame and caused advanced termination at the downstream codon 45. This mutation site has not been previously included in the ClinVar database. The frequency of mutation at this locus in the normal East Asian population has not been reported.

Since Townes and Brocks first described TBS in 1972[2], hundreds of similar cases have been reported. It is characterized by ear anomalies, thumb anomalies (preaxial polydactyly, triphalangeal thumbs, hypoplastic thumbs), and anal anomalies. The prevalence of TBS is estimated to be 1/250 000[5]. The gene mutated in TBS is *SALL1*, which is located on chromosome 16q12.1 and encodes a zinc finger protein believed to act as a transcriptional repressor[6]. *SALL1* is expressed in the metanephric mesenchyme surrounding the ureteric bud. Homozygous deletion of *SALL1* produces incomplete ureteric bud outgrowth. Therefore, *SALL1* is important for metanephros development[7]. Most mutations occur within a hotspot prior to the first C2H2 zinc finger domain encoded within exon 2 and result in the truncation of the protein upstream of the DNA binding domain[8].

In a murine experiment, all of the *SALL1* knockout mice (*SALL1*-/-) died within 24 h after birth owing to renal agenesis or severe dysgenesis[7]. Mutant mice that produced a truncated *SALL1* protein exhibited more severe defects than *SALL1*-null mice, including renal agenesis, exencephaly, and limb and anal deformities[9]. This finging may be explained by the fact that truncated proteins arising from certain *SALL1* mutations can disrupt cilia formation and function. Therefore, TBS might be considered a ciliopathy-like disease, just as the proband presented with multiple renal cysts. A recent study showed that the Dishevelled Binding Antagonist Of Beta Catenin 1 (DACT1) c.1256G>A nonsense variant was causative of a specific genetic syndrome with features overlapping those of Townes-Brocks syndrome[10]. Therefore, genetic testing to identify the mutated gene is critical for the diagnosis.

Newman first drew attention to symptomatic renal failure in TBS[11]. A previous study of TBS showed that 43% of affected individuals exhibited renal abnormalities. To determine genotype-phenotype correlations in the renal manifestations of TBS, we reviewed 76 affected individuals from 51 families, including 44 men (57.9%), 29 women (38.1%), and three (3.9%) for whom sex was not reported, giving a female-to-male ratio of 0.5:1. The details of the *SALL1* gene variations and renal manifestations in these 76 patients with TBS are summarized in **Table I**. Overall, 43 different variants

were identified, including 29 frameshift mutations, 12 nonsense mutations, one intronic mutation, and one exonic deletion. The most common renal manifestations were renal hypodysplasia and unilateral renal agenesis (n = 25), followed by vesicoureteral reflux (n = 17). Almost half of the individuals had varying degrees of renal impairment, and 22% of the individuals progressed to renal failure. Some of the patients successfully underwent kidney transplantation, and two of them experienced graft rejection[4, 8, 11-13].

Because TBS is a polymorphic syndrome, it needs to be distinguished from the following syndromes: VATER/VACTERL association (vertebral, anal, cardiac, tracheal-esophageal, renal and limb anomalies)[14], Goldenhar syndrome (oculo-auriculo-vertebral) (impaired development of structures such as eyes, ears, lip, tongue, palate, mandible, maxilla and deformations of the tooth structures)[15], Okihiro syndrome (forearm malformations with Duane syndrome of eye retraction)[16] , branchio-oto-renal syndrome (hearing loss, auricular malformations, branchial arch remnants, and renal anomalies) [17]and STAR syndrome (syndactyly, telecanthus, anogenital, and renal malformations)[18].

As patients with kidney diseases do not have specific clinical presentations, it is possible to find rare diseases in any dialysis patients. Doctors are advised to concern about the following issues: ask patients for family history of kidney diseases, see whether the patient has ocular or hear pathologies, see whether there is poliglobulia or abdominal masses or a family history of cerebral aneurysms, and verify that if there is neuropathy or cardiopathy, they do not obey to uremia or hypertension alone. Gene sequencing is recommended in the following categories of patients with kidney disease: individuals with a family history of kidney disease; individuals with an unexplained renal phenotype associated with extrarenal phenotypes, especially in the eyes and ears; and individuals with polycystic kidney disease. Patients and their families can avoid the blind use of immunosuppressive drugs, which may cause adverse effects.

CONCLUSION

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