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CASE REPORT

Hepatocyte nuclear factor 1B mutation in a Chinese family with renal cysts and diabetes syndrome: A case report

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Abstract

BACKGROUND

Renal cysts and diabetes (RCAD) syndrome is an autosomal dominant diabetic renal disease. Precise molecular diagnosis of RCAD syndrome has proven valuable for understanding its mechanism and personalized therapy.

CASE SUMMARY

A RCAD patient and her family were studied to investigate potential responsible genes by the whole exome sequencing (WES). Candidate pathogenic variants were validated by Sanger sequencing. The clinical characteristics of RCAD patient were collected from medical records. Unlike those typical RCAD patients, we observed renal manifestation and prediabetes phenotype, but not reproductive organ phenotype and hypomagnesaemia. A novel 7-bp deletion mutation in exon 4 of the hepatocyte nuclear factor 1B, NM_000458: c.882_888del (p.V294fs), was identified by WES and confirmed by Sanger sequencing.

CONCLUSION

This novel mutation identified in a Chinese family with RCAD syndrome might be the molecular pathogenic basis of this disorder.

Key Words: Renal cysts and diabetes; Hepatocyte nuclear factor 1B; Exome sequencing; Novel mutation; Autosomal dominant disorder; Case report

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Core Tip: Renal cysts and diabetes (RCAD) syndrome is an autosomal dominant diabetic renal disease. Precise molecular diagnosis of RCAD syndrome has proven valuable for understanding its mechanism and selecting optimal therapy. A novel deletion mutation of hepatocyte nuclear factor 1B gene (NM_000458: c.882_888del, p.V294fs) was identified in a Chinese family with RCAD syndrome by whole exome sequencing and Sanger sequencing. Considering the gene function and the genotype-phenotype correlation, mutation location, and its conservativeness, this mutation is considered to play a pathogenic role in the development of RCAD syndrome.

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INTRODUCTION

Renal cysts and diabetes (RCAD) syndrome (OMIM: 137920) is an autosomal dominant diabetic renal disease resulting from abnormal renal development. Highly variable phonotypes of the renal disease include renal cysts, glomerular tufts, aberrant nephrogenesis, primitive tubules, irregular collecting systems, oligomeganephronia, enlarged renal pelvises, abnormal calyces, small kidney, single kidney, horseshoe kidney, and hyperuricemic nephropathy[1]. The diabetic phonotypes of this disorder usually occur earlier than age 25 years and patients are thus diagnosed as having maturity-onset diabetes of the young type 5 (MODY5)[2]. Nevertheless, typical diabetic phonotypes may not occur in some cases.

At the molecular level, the RCAD syndrome is related to mutations of hepatocyte nuclear factor 1B (*HNF1B*). To date, more than 400 mutations of *HNF1B* gene have been identified in RCAD patients, and *de novo* mutations are encountered in up to 30%-50% of cases[3]. These mutations include missenses, nonsenses, frame shifts, splice site mutations, small indels, and large deletions. In fact, *HNF1B*-associated syndrome is much complicated, as this gene encodes a transcription factor of the homeodomain-containing superfamily that is expressed in multiple organs[4]. Most RCAD patients often present with renal cysts and renal function decline that precede the diabetes. Besides the phonotypes of diabetes and renal presentation, RCAD patients may also have anomalies of the organs such as the genital tract, including vaginal aplasia, rudimentary uterus, bicornuate uterus, epididymal cysts, and atresia of the vas deferens[5]. Thus, heterogeneous presentation of the multisystem phenotype is often found in *HNF1B*-associated syndrome. For example, a case study suggests that lack of *HNF1B* expression is related to chromophobe renal cell carcinoma, a rare renal cancer[6]. Notably, diabetes and renal cysts are not always present in *HNF1B*-mutated patients. Moreover, the phenotype of *HNF1B* mutant carriers is highly variable within and between families[7]. Recently, the clinical characteristics of *HNF1B*-related disorders in 33 patients were reported in a Japanese population[8]. Analysis of genotype-phenotype correlation showed that some clinical characteristics were significantly different between patients with heterozygous variant of *HNF1B* and those harboring a deletion of *HNF1B*. However, RCAD patients in the Chinese population are rarely reported. Here we report a frame shift mutation of *HNF1B* gene in a Chinese family with RCAD syndrome that has never been described previously.

CASE PRESENTATION

Chief complaints

A 24-year-old Chinese Han woman was admitted to our department of nephrology for sudden back pain and frequent micturition.

History of present illness

The patient also suffered from a temporary fever with the highest temperature of 41

°C.

History of past illness

The patient was hospitalized in the department of urology at our hospital 2 years ago, and diagnosed with bilateral multiple renal cysts. She was the sole child of her parents and denied the genetic history of kidney diseases.

Personal and family history

The patient denied a family history of kidney diseases.

Physical examination

The patient's temperature was 41 °C, heart rate was 98 bpm, respiratory rate was 20 breaths per minute, and blood pressure was 110/76 mmHg.

Laboratory examinations

Laboratory test showed elevated levels of serum creatinine and uric acid (Table 1). Routine blood test showed normal white blood cell, neutrophil, and lymphocyte counts. Routine urine tests showed elevated levels of uric leucocytes and red cells, but without urine protein. The liver enzyme and magnesium levels were normal. Notably, the patient's plasma glucose level was 6.88 mmol/L.

Imaging examinations

In order to confirm the previous diagnosis, abdominal ultrasound examination and computed tomography were performed. Result showed bilateral slight renal atrophy with hyperechogenicity and multiple renal cysts (Figure 1A and B). The diameter of the largest cysts in the left and right kidneys was 2.4 cm and 2.0 cm, respectively. No obvious structural anomalies were observed in other abdominal organs including the liver, spleen, pancreas, and gallbladder.

MULTIDISCIPLINARY EXPERT CONSULTATION

To further analyze the renal disease, histopathology study of renal biopsy was performed. A total of six glomeruli were observed, with one glomerulus having ischemic sclerosis. The volume of the ischemic glomerulus was increased, while the mesangial cells and matrix showed slight hyperplasia. The morphology of podocytes and the basements was normal. There was no obvious positive signal of Congo red staining and Masson staining. Granular degeneration of renal tubular epithelial cells with focal tubular atrophy was observed. The cystic structure with serous substances was visible in three tubular lumens (Figure 1C and D). Mild to moderate intimal and medial thickening was observed in arcuate and interlobular arteries. All the immunological staining including IgA, IgG, IgM, complement C3, C4, C1q, κ, and λ was negative. Electron microscopy showed renal interstitial fibrosis, tubular basement membrane shrinkage, matrix collagen fibrosis, and lymphatic and monocyte infiltration.

As her serum glucose level was higher than normal, we wondered whether islet function was impaired. Thus, the release of insulin and C-peptide was measured by oral glucose tolerance test. As shown in Figure 2, the concentration of serum glucose constantly increased until 2 h after oral administration of glucose, which indicated a deficiency of insulin. However, autoantibody against diabetes was negative.

Blood samples were collected from this patient and her parents for genomic DNA extraction using the CWBIO Blood Genomic DNA Mini Kit (CWBIO, Beijing, China). Whole exome sequencing (WES) was performed by Chigene (Beijing) Translational Medical Research Center Co. Ltd (Beijing, China).

The sequence analysis revealed a novel heterozygous small deletion mutation, NM_000458: c.882_888del (p.V294fs), in exon 4 of the *HNF1B* gene. Sanger sequencing was performed to validate the identified variation (Figure 3A). The mutation was excluded from the Single Nucleotide Polymorphism database and the Human Genetic Variation Database. This *de novo* mutation was not found in her parents. The mutation was located in the DNA-binding domain of HNF1B, which contained about 60 amino acid residues and was highly conserved among species (Figure 3B). This variant can be classified as "pathogenic" (PS2+, PM2+, PM4) according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines[9]. After identifying the mutation in *HNF1B* gene, we also calculated the *HNF1B* score based on

Table 1 Laboratory data at presentation

Parameter	Proband	Mother	Father	Reference
Height (cm)	160	155	168	-
Weight (kg)	44	54	72	-
BMI (kg/m²)	17.19 ↓	22.5	25.5	18.5-24
WBC count, 10^9/L	4.03	4.2	5.22	3.5-9.5
NEUT%	0.60	0.63	0.65	40-75
LYM%	32.8	35	34.0	20-50
HGB, g/L	129.0	122	140.0	115-150
Platelet count,10^9/L	254.0	267	289.0	125-350
RBC count, 10^{12}/L	4.54	4.20	4.83	3.8-5.1
Urine routine tests				
Specific gravity	1.010 ↓	1.020	1.020	1.015-1.030
Urine protein	-	-	-	-
Urinary occult blood	3+	-	-	-
Urine glucose	-	-	-	-
Urine ketone bodies	-	-	-	-
24 h UPE, g/d	0.09	0.01	0.01	0-0.12
Immunoglobulin A, g/L	1.36	1.58	2.04	0.7-4.0
Immunoglobulin G, g/L	13	10	12	7-15
Immunoglobulin M, g/L	1.36	1.52	1.47	0.4-2.6
Complement C3, g/L	0.64 ↓	2.5	2.1	0.9-2.1
Complement C4, mg/dL	12.70 ↓	22.10	24.50	16-38
Lambda, mg/dL	475.00	528.00	601.00	313-723
Kappa, mg/dL	975.00	876.00	930.00	629-1350
Fasting plasma glucose	6.88↑	7.1↑	5.8	3.9-6.1
HBA1C, %	6.7↑	5.4	5	4.0-6.0
Albumin, g/L	48.40	45.30	48.00	40-55
Globulin, g/L	28.40	25.17	26.09	20-40
Serum creatinine, umol/L	112.3↑	56.9	69	45-105
eGFR (mL/min/1.73m²)	59↓	110	110	> 90
Serum uric acid, umol/L	535.7↑	362.5	378.6	140-420
Cystatin-C, mg/L	1.47↑	0.89	0.79	0-1.16
PTH, pg/mL	79.40↑	44	60	12-65
Insulin autoantibody				
IAA	-	-	-	-
GADA	-	-	-	-
ICA-40KD	-	-	-	-
ICA-64KD	-	-	-	-
ICA-120KD	-	-	-	-

Blood values in result column indicate the abnormal values out of the reference range. WBC: White blood cell; NEUT%: Neutrophil ratio; LYMP%: Lymphocyte ratio; HGB: Hemoglobin; RBC: Red blood cell; UPE: Urinary protein excretion; PTH: Parathyroid hormone; IAA: Insulin autoantibody; GADA: Glutamic acid decarboxylase antibody; ICA: Islet cell antibody.

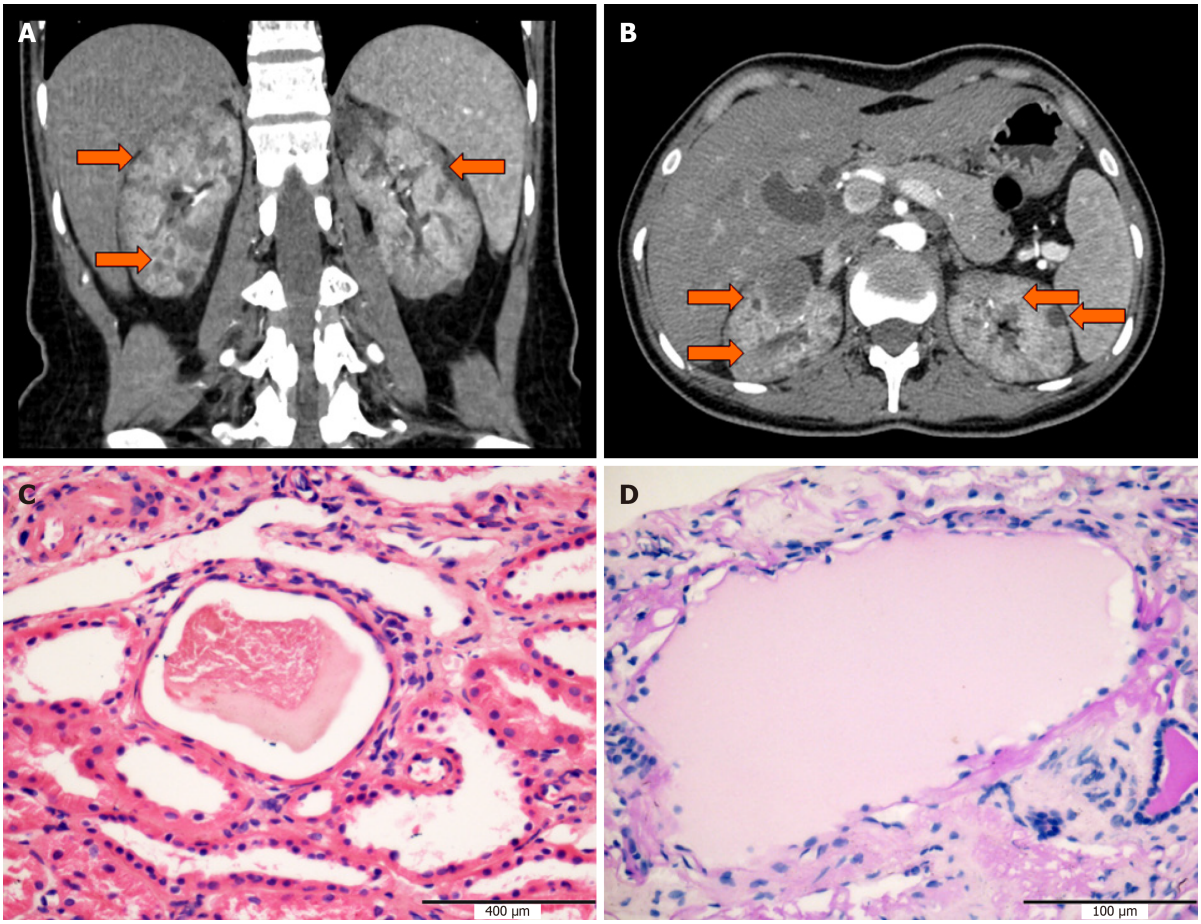

Figure 1 Computed tomography images and classic histological features of the kidney. A and B: Abdominal computed tomography revealed multiple renal cysts in the proband (orange arrow), and cystic structure with serous-like substances was visible in tubular lumens; C: Section stained with hematoxylin-eosin; D: Section stained with Periodic acid-Schiff.

those items including antenatal discovery, family history, and the involved organs including the kidney, pancreas, liver, and genital tract. This tool provides a more rational approach to select patients for *HNF1B* screening[10]. The *HNF1B* score of this patient was 8, just the same as the optimal cutoff threshold for the negative predictive value.

FINAL DIAGNOSIS

The final diagnosis of the presented case was RCAD syndrome.

TREATMENT

The patient received metformin to control blood sugar, and renin-angiotensin-aldosterone system blockade to delay the progression of kidney disease. She was recommended to have a high-quality protein, low-salt (< 6 g/d) diabetes diet.

OUTCOME AND FOLLOW-UP

After 2 year of follow-up, the patient's blood glucose and renal function were relatively stable.

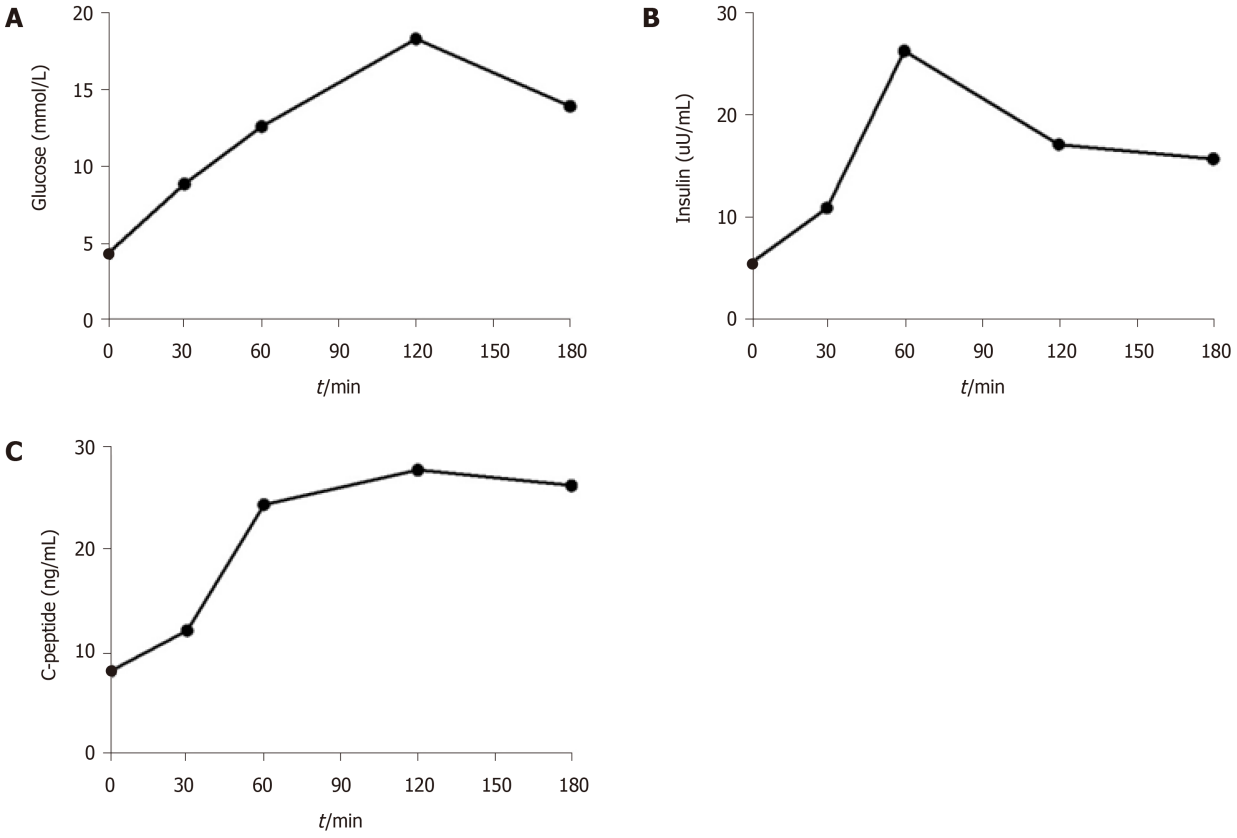

Figure 2 Oral glucose tolerance test. A: Glucose; B: Insulin; C: C-peptide concentration during oral glucose tolerance test.

DISCUSSION

We report a novel small deletion mutation in exon 4 of the *HNF1B* gene in a RCAD patient from a Chinese family. As RCAD syndrome is an autosomal dominant disorder, the *de novo* mutation might occur at the somatic level, as the genotypes of parents are normal.

HNF1B is a developmentally regulated transcription factor required for tissue-specific gene expression in mouse epithelial cells[11]. It activates or represses transcription of target genes through binding of its specific domain. A previous study showed that mice with renal-specific inactivation of *HNF1B* developed polycystic kidney disease, and renal cyst formation was accompanied by a drastic defect in the transcriptional activation of *UMOD*, *Pkhd1*, and *Pkd2* genes[12]. Recently, cell experiment also showed that ablation of *HNF1B* in proximal tubule cells led to a shift from oxidative phosphorylation to glycolysis[13]. Such evidence suggests that the *HNF1B* gene is vital for mouse renal development and function. In humans, mutations of the *HNF1B* gene are found in patients with inherited and sporadic malformations of the kidney and genitourinary tract. Recently, the mutant spectrum of *HNF1B* gene was analyzed in a Japanese population and their finding of genotype-phenotype correlation was interesting[8]. The clinical characteristics of *HNF1B*associated syndrome include renal phenotype, diabetes, pancreatic phenotype, and reproductive organ phenotype[8]. A study in 2018 found that kidney anomalies including bilateral cystic dysplasia and bilateral hyperechogenic kidneys were the most frequent[14]. In addition, more than one-third of the patients with *HNF1B* mutations developed moderate to severe chronic kidney disease. Our patient was diagnosed as having bilateral multiple renal cysts at the age of 22 years. Her renal manifestation included multiple renal cysts and hyperechogenicity. Histopathology study of renal biopsy confirmed the kidney anomalies in glomeruli and tubules. Analysis of *HNF1B* score suggested that her molecular basis of the disease might be associated with mutation of *HNF1B* gene.

The second frequent clinical characteristic of *HNF1B*-associated syndrome is diabetes. More than half of the patients with *HNF1B* mutations presented diabetes or prediabetes. Although no obvious structural anomalies were observed in other abdominal organs including the liver, spleen, pancreas, and gallbladder, a functional

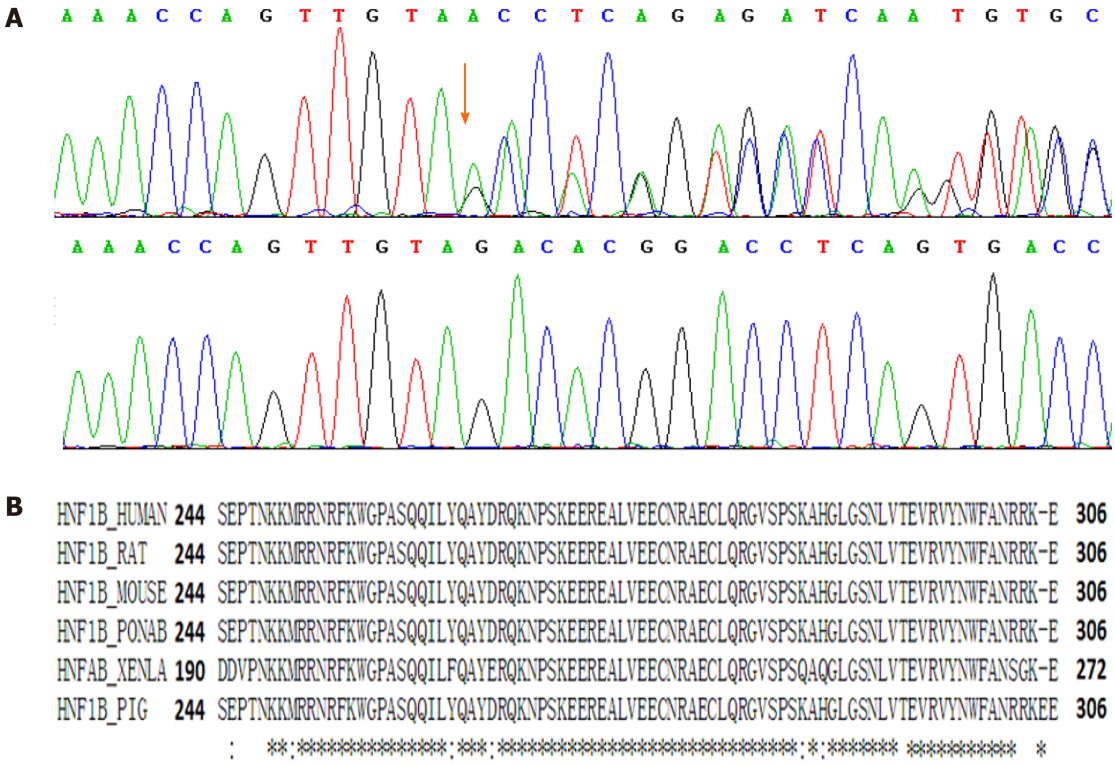

Figure 3 Mutation analysis of the renal cysts and diabetes patient. A: Sanger sequencing of the renal cysts and diabetes patient (upper panel) and her parents (lower panel). Black arrow indicates the mutation position; B: The amino acid sequence of the DNA-binding domain of NHF1B is highly conserved among species.

test showed that the patient's islet function was impaired, which suggested the existence of diabetes. This is also in line with the fact that RCAD patients often present with renal phenotype preceding the diabetes, as diabetes in these cases usually appears in the second and third decades of life[15]. Another characteristic of *HNF1B*-associated syndrome is hypomagnesaemia. However, this was absent in our patient. Comparing all the clinical characteristics of our patient with those in literature, we speculated that this patient was just at the early stage of RCAD syndrome.

Currently, more than 400 mutations of *HNF1B* gene have been recorded in the ClinVar database. Among the records in the ClinVar, 303 records of mutation are classified as "pathogenic" and "likely pathogenic". As this gene encodes a transcription factor highly conserved among species, small indels and point mutations of *HNF1B* gene are found to be pathogenic. Nevertheless, copy number variations (CNVs) including microdeletion and microduplication of *HNF1B* gene can also be pathogenic. Fu *et al*[16] found that CNVs of *HNF1B* region were revealed by chromosome microarray analysis testing in fetal multicystic dysplastic kidneys. The encoded protein has three domains. The N-terminal domain (8-173) contains a dimerization sequence and an acidic region that may mediate the formation of HNF-1B homodimers or heterodimers with the related protein HNF-1α[17]. The homeodomain (240-305) is the DNA-binding domain involved in the transcriptional regulation of key eukaryotic developmental processes, and its crystal structure has already been determined[18]. The C-terminal domain (314-550) is responsible for the activation of transcription. The homeodomain is the most conservative region (Figure 3). The 7-bp deletion mutation of *HNF1B* gene leads to a frame shift mutation and the mutated protein lacks the C-terminal domain. Based on the gene function and the genotype-phenotype correlation in this family, the mutation was classified as "pathogenic" according to the ACMG guidelines. Moreover, point mutations of this motif are also classified as "pathogenic" in the ClinVar database.

Here, we summarize the previously reported HNF1B mutations in the Chinese population (Table 2). Most studies of the mutations in *HNF1B* gene in the Chinese population are concerned with MODY5. For example, Wang *et al*[19] found a substitution of S36F in an MODY family. Amazingly, the phenotype of mutation carriers in this family was different: One had early onset diabetes, renal function impairment, and renal cyst, while the other had impaired glucose tolerance only. Similarly, a case report by Wang *et al*[20] showed that a missense mutation (c.1007A>G, p.H336R) in

Table 2 Review of previously reported hepatocyte nuclear factor 1B mutations in the Chinese population

S/N	Sex	Age at diagnosis	Amino acid change	Clinical symptoms	Ref.
1	Male	37	p.ES36F	Diabetes mellitus, mild renal dysfunction; one cyst in the left kidney; impaired concentration function of the renal tubules	Wang *et al*[19]
2	Female	30	p.H336R	Diabetes mellitus; albuminuria; diabetic nephropthy, peripheral neuropathy, and diabetic retinopathy; lipid metabolism disorder; kidney stones	Wang *et al*[20]
3	Male	39	p.D221V	Diabetes mellitus and mild renal dysfunction; microalbuminuria; epididymal cysts and bilateral hydrocele testis	Wang *et al*[21]
4	Female	11	p.R165H	Low birth weight, diabetes mellitus, and microalbuminuria; renal structural abnormalities; pancreatic hypoplasia (lack of pancreatic body and tail); liver cysts	Wang *et al*[21]
5	Female	65	p.E260D	Diabetes mellitus; microalbuminuria; renal structural abnormalities; pancreatic hypoplasia (lack of pancreatic body and tail); liver cysts	Wang *et al*[21]
6	Female	11	p.G239E	Low birth weight and diabetes mellitus; elevated levels of serum creatinine, urea, liver enzymes, and uric acid; hyperosmolality; atrophy of the pancreas; agenesis of the left kidney combined with hydronephrosis, and multiple cysts in the right kidney	Luo *et al* [22]

the *HNF1B* gene was found in a Chinese family of MODY with diabetic kidney disease. However, in these cases, the diabetes phenotype occurred earlier than renal phenotype. These findings suggest that the phenotype of *HNF1B*-related disorders might be relative to ethnic region.

CONCLUSION

A novel deletion mutation of *HNF1B* gene (NM_000458: c.882_888del, p.V294fs) was identified in a Chinese family with RCAD syndrome by using WES and Sanger sequencing. Considering the gene function and the genotype-phenotype correlation, mutation location, and its conservativeness, this mutation is considered to play a pathogenic role in the development of RCAD syndrome.

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