Supplemental table 1 General clinical and biologic features of patients who identified hereditary nephrolithiasis (NL) and (or) nephrocalcinosis (NC) in our center

Patient number	Gender	Onset-age	Family history	Height [a]	Weight [a]	NL/NC	Renal function	LMWP	Hypercalciuria [b]	Serum electrolyte	CAKUT/Extra-renal phenotype	Stone analysis
1	M	2y2m	no	10th	25th	NC	N	Y	Y	N	N/PMR	NA
2	M	3y3m	no	<3rd	<3rd	NC	N	Y	Y	N	N/N	NA
3	M	4y11m	no	<3rd	<3rd	NL + NC	N	Y	Y	N	N/N	NA
4	M	14y	no	75th	75th	NC	N	Y	N	N	N/N	NA
5	M	12.5y	no	<3rd	3rd-10th	NC	CKD2	Y	N	hypokalemia	N/knock knees	NA
6	F	9m	no	<3rd	<3rd	NC	N	Y	N	hypokalemia	N/N	NA
7	M	6y	no	<3rd	<3rd	NL	N	Y	Y	hypokalemia	N/knock knees	NA
8	F	1y8m	no	3rd-10th	<3rd	NC	N	Y	N	hypokalemia	N/N	NA
9	F	3m	no	<3rd	<3rd	NC	N	N	N	hypokalemia	N/ASD	NA
10	M	3y11m	no	<3rd	<3rd	NL + NC	N	Y	Y	hypokalemia	N/N	NA
11	F	3y9m	Maternal NL	<3rd	3rd-10th	NC	N	N	N	hypophosphatemia	N/bow legs, PMR	NA
12	F	2y11m	Maternal NL	50th	25th	NC	N	N	N	hypomagnesemia	N/N	NA
13	F	11m	no	10th-25th	<3rd	NC	CKD2	N	Y	hypercalcemia	N/muscle weakness, PMR	NA
14	M	10m	no	3rd	25th	NL	N	N	N	N	N/ASD	L-cystine stone
15	M	6y7m	no	25th	75th	NL	N	N	N	N	N/N	L-cystine stone
16	M	4m	no	90th	25th	NL + NC	N	N	N	N	N/renal rickets	NA
17	M	11m	no	3rd-10th	50th	NL	N	N	N	N	N/N	CaOx
18	M	13m	no	<3rd	25th	NL	N	Y	Y	N	N/N	CaOx
19	M	6m	Maternal NL	90th	90th	NL	N	N	N	N	N/PMR, ASD	NA
20	M	9m	no	3rd-10th	3rd-10th	NL	N	N	N	N	N/facial dysmorphism, PMR, ASD	NA
21	M	1y8m	no	<3rd	<3rd	NL	N	Y	NA	N	N/facial dysmorphism, PMR , ASD+VSD+PH	NA

22	M	8y	no	<3rd	10th	NC	N	Y	Y	N	N/facial dysmorphism, PMR, VSD	NA
23	M	3m	no	<3rd	<3rd	NL signal	N	Y	N	N	VUR + NB/facial dysmorphism, PMR	NA
24	M	8y	no	50th	25th-50th	NL + NC	N	N	N	N	renal cyst, ASD	NA
25	M	3m	no	<3rd	<3rd	NL + NC	CKD2	NA	N	N	N/facial dysmorphism, PMR, ASD	NA

a: The height and weight value is according to the percentage value table of body height and body mass of Chinese children and adolescents. b: Normal urinary values in spot urine samples and normal urinary values in 24-Hour urine collection: urine calcium-to-creatinine ratio: <7 mo <0.86, 7-18 mo <0.60, 19 mo-6 y <0.42, >6 y <0.20 (mg/mg) or 24-hour urinary calcium <4 mg/kg/24h; N: normal; Y:yes; NA: Not available; F: famale; M: male; LMWP: low-molecular weight protein (the elevated levels of urinary β2-microglobulin and α1-microglobulin); CAKUT: congenital anomalies of the kidney and urinary tract; PH: pulmonary hypertension; ASD: atrial septal defect; VSD: Ventricular septal defect; CKD: chronic kidney disease; VUR: vesicoureteric reflux; NB: neurogenic bladder; PMR: psychomotor retardation;

Supplemental table 2 General clinical and biologic features of patients who identified nephrolithiasis (NL) and (or) nephrocalcinosis (NC) but with negative genetic analysis in our center

Patient number	Gender	Onset-age	Family history	Height a	Weight a	NL/NC	Renal function	LMWP	Hypercalciuria b	Serum electrolyte	CAKUT/ Extra-renal phenotype	Stone analysis
1	F	36m	no	<3rd	10th	NL	N	N	N	N	N/PMR	NA
2	F	35m	yes	75th	75th	NC	N	N	N	N	N/N	NA
3	M	22m	no	50th	10th	NL single	N	N	N	N	N/ASD	NA
4	M	12m	yes	10th	10th	NC	N	N	N	N	N/N	NA
5	F	7y	yes	50th	10th	NL	CKD2	Y	N	N	N/N	NA
6	M	38m	yes	50th	50th	NL single	N	N	N	N	N/N	NA
7	F	4.5y	yes	10th-25th	25th-50th	NL + NC	N	N	N	N	hydronephrosis	NA

Supplemental table 3 Outcome of genetic testing in 25 out of 32 NL and (or) NC patients with positive genetic variants

Patient	Gene	Nucleotide change	Amino acid change	Segregation	Mode	NL / NC	ACMG criteria	ACMG Evidence	PMID Ref.	Genetic diagnosis OMIM	OMIM
Genes of failed urinary acidification and hypercalciuria											
1	*OCRL1*	c.556 A > T (NM_000276)	p.K186X , 716	Maternal	XLR	NC	Pathogenic	PVS1+PM1+PM2+PP3	Novel	DD2	300535

										300555	
2	OCRL1	c.218 T > A (NM_000276)	p.L73X , 829	Maternal	XLR	NC	Pathogenic	PVS1+PM1+PM2+PP3	Novel	DD2 300555	300535
3	*CLCN5*	c.478 T > C (NM_001127899)	p.C160R	Maternal	XLR	NL + NC	Uncertain (VUS)	PM2+PP3+PP1	Novel	DD1 300009	300008
4	*CLCN5*	c.2131 T > C (NM_000084)	p.C711R	Maternal	XLR	NC	Likely pathogenic	PM1+PM2+PM5+PP3	Novel	DD1 300009	300008
5	*SLC4A1*	c.2102 G > A (NM_000342)	p .G701D	Hom	AR	NC	Pathogenic	PS+PS1+PS4+PM1+PM2+PM	9854053 Ref. 1	dRTA 611590	109270
6	*SLC4A1*	c.1765 C > T (NM_000342)	p.R589C	de novo	AD	NC	Pathogenic	PS2+PS1+PM1+PM2+PP3	9312167 Ref. 2	dRTA 179800	109270
7	*SLC4A1*	c.1766 G > A (NM_000342)	p.R589H	de novo	AD	NL	Pathogenic	PS2+PS1+PM1+PM2+PP3	9312167 Ref. 2	dRTA 179800	109270
8	*ATP6V1B1*	c.1153 C > A (NM_001692)	p.P385T	Paternal	AR	NC	Uncertain (VUS)	PM1+PM2+PP3	Novel	dRTA 267300	192132
		c.806 C > T (NM_001692)	p .P269L	Maternal			Uncertain (VUS)	PM1+PM2+PP3	Novel		
9	*ATP6V0A4*	c.1899 C ＞ A (NM_020632)	p.Y633X , 208	Hom	AR	NC	Pathogenic	PVS1+PM2+PP3	Novel	dRTA 602722	605239
10	*SLC4A1*	c.1765 C > T (NM_000342)	p.R589C	de novo	AD	NL + NC	Pathogenic	PS2+PS1+PM1+PM2+PP3	9312167 Ref. 2	dRTA 179800	109270
11	*PHEX*	c.1735 G > A (NM_000444)	p.G579R	Maternal	XLD	NC	Pathogenic	PS2+PS1+PM1+PM2+PP3	9097956 Ref. 3	XLH 307800	300550
12	*CLDN16*	loss1 (exon: 3) (NM_006580.3)	166 bp	Paternal	AR	NC	Likely Pathogenic	PVS1+PM2	Novel	FHHNC 248250	603959
		c.427 + 5 (IVS2) G > A (NM_006580)	–	Maternal			Likely Pathogenic	PM2+PP5+PP3	25852890 Ref. 4		
13	*CYP24A1*	c.1310 C > A (NM_000782)	p.P437H	Hom	AR	NC	Likely pathogenic	PM1+PM2+PP3	30633617 Ref. 5	IH 143880	126065

Genes of hyperuricosuria, cystinuria, hyperglycinuria

14	*SLC3A1*	c.541C > T (NM_000341)	p.R181W	Paternal	AR	NL	Likely Pathogenic	PM1+PM2+PM	Novel	Cystinuria 220100	104614
		c.850 G > C (NM_000341)	p.D284H	Maternal			Likely pathogenic	PM1+PM2+PM	Novel		
		c.1173 C > G (NM_000341)	p.D391E	Maternal			Uncertain (VUS)	PM1+PM2+PP3	Novel		
15	*SLC7A9*	c.376 G > A (NM_001243036)	p.A126T	Paternal	AR	NL	Likely pathogenic	PS1+PM2+PP3	1115779 Ref. 6	Cystinuria 220100	604144
		c.149 T > G (NM_001243036)	p.V50G	Maternal			Uncertain (VUS)	PM1+PM2+PP3	Novel		
16	*AGXT*	c.25 _ c.26 insC (NM_000030)	p.T9Tfs * 159	Paternal	AR	NL + NC	Pathogenic	PVS1+PM3+PP5	Novel	PH1 259900	604285
		c.121 G > A (NM_000030)	p.G41R	Maternal			Pathogenic	PS1+PM1+PM2+PP2+PP3	8101040 Ref. 7		
17	*HOGA1*	c.834 + 1 (IVS6) G > T (NM_138413)	–	Paternal	AR	NL	Pathogenic	PVS1+PS1+PM2+PP3	25972204 Ref. 8	PH3 613616	613597
		c.356 T > G (NM_138413)	p.V119G	Maternal			Likely pathogenic	PM3+PM1+PM2+PP3	Novel		
18	*HOGA1*	c.103 A > G (NM_138413)	p.I35V	Paternal	AR	NL	Uncertain (VUS)	PM1+PM2	Novel	PH3 613616	613597
		c.845 G > A (NM_138413)	p.R282H	Maternal			Likely pathogenic	PS4 +PM1+PM2+PP3	Novel		

19	*SLC6A19*	c.284 G > C(NM_001003841)	p.R95P	Paternal	AR	NL	Likely pathogenic	PM1+PM2+PP3+PP1	Novel	FG	608893
		c.461 C > T(NM_001003841)	p.P154L	Maternal			Likely pathogenic	PM1+PM2+PP3+PP1	Novel	167030	
		c.1018 C > T (NM_213613)	p.R340C	Maternal	AR/AD		SNP	-	-		610130
	SLC26A1										

Other genes

20	*KMT2D*	c.15113_c.15115 del AGG (NM_003482)	p.E5038_G5039delinsG	de novo	AD	NL	Likely pathogenic	PS2+PM2+PM4	Novel	KS 147920	602113
21	*KMT2D*	c.6595 delT (NM_003482)	p.Y2199fs	de novo	AD	NL	Pathogenic	PVS1+PS2+PS1+PM1+PM2+PP3	Novel	KS 147920	602113
22	*KMT2D*	C.15686 dupG (NM_003482)	P.C5230Lfs*5	de novo	AD	NC	Pathogenic	PVS1+PS2+PS1+PM1+PM2+PP3	Novel	Ks 147920	602113
23	*KAT6A*	c.3070 C > T (NM_006766)	p.R1024X , 981	de novo	AD	NL signal	Pathogenic	PVS1+PS2+PS1+PM2+PP3	Novel	ATS 616268	601408
24	*PKD1*	c.9806 G > A (NM_001009944)	p.R3269Q	Maternal	AD	NL + NC	Likely pathogenic	PM1+PM2+PP3	Novel	ADPKD 173900	601313
25	CNV	chr10: 130378377 - 135427935 q26.2 - q26.3	–	de novo	-	NL + NC	VUS	The parents are wild type and have no clinical phenotype. There is no report in DGV ordinary people database. Clinvar database has partial overlap of several possible pathogenic CNV fragments involved in renal dysplasia.	Novel	CNV	

ACMG: American College of Medical Genetics and Genomics; PMID: PubMed ID; Hom: homozygous mutation; AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; XLR: X-linked recessive inheritance; XLD: X-linked dominant inheritance; CNV: chromosome copy number variation; SNP: single nucleotide polymorphism; DD: Dent disease; XLH: X-1inked dominant hypophosphate; dRTA: distal renal tubular acidosis; IH: infantile hypercalcaemia; FHHNC: Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis; PH: primary hyperoxaluria; FG: familial glycosuria; KS: Kabuki syndrome; ADPKD: autosomal dominant polycystic kidney disease; ATS: Arboleda-Tham syndrome; VUS: variant of unknown significance.

Analysis of new missense mutations in pathogenicity analysis using multiple protein function prediction software PP2 (polyphen2 http://genetics.bwh.harvard.edu/pph2/) and SIFT (sorting intolerant from tolerant http://sift.jcvi.org/ MutationTaster: http://www.mutationtaster.org).

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