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Structural renal abnormalities in the *DICER1* syndrome: a family-based cohort study

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Abstract

Background.—The *DICER1* syndrome is a tumor-predisposition disorder caused by germline pathogenic variation in *DICER1*, and is associated with cystic nephroma and other renal neoplasms. *Dicer1* mouse and rare human *DICER1* syndrome case reports describe structural kidney and collecting system anomalies. We investigated renal function and the frequency of structural abnormalities of the kidney and collecting system in individuals with germline loss-of-function variants in *DICER1*.

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Compliance with ethical standards. All participants provided written, informed consent, and the study was approved by the National Cancer Institute's Institutional Review Board (IRB). In addition, clinical, radiographic and genetic data on participants enrolled in the International PPB Registry and the International Ovarian and Testicular Stromal Tumor Registry were abstracted and reviewed. Both registries are overseen by the IRB at Children's Minnesota (protocols 98107, 0909–082, 1111–112). Participants in both registries provided informed, written consent for use of their registry data in the current analysis. The study adhered to the precepts in the Declaration of Helsinki.

Methods.—In this family-based cohort study, prospectively-ascertained germline *DICER1*-mutation carriers (“*DICER1*-carriers”) and unaffected family controls were evaluated at the National Institutes of Health Clinical Center with renal ultrasound and comprehensive laboratory testing. Two radiologists reviewed the imaging studies from all participants for structural abnormalities, cysts and tumors.

Results.—Eighty-nine *DICER1*-carriers and 61 family controls were studied. Renal cysts were detected in 1/33 children without history of cystic nephroma. Similar proportions of adult *DICER1*-carriers (8/48; 17%) and controls (11/50; 22%) had ultrasound-detected renal cysts ($P=0.504$). 8/89 (9%) *DICER1*-carriers harbored ultrasound-detected structural abnormalities of varying severity within the collecting system or kidney, nephrolithiasis or nephrocalcinosis. None of the family controls (0/61) had similar findings on ultrasound ($P = 0.02$). No meaningful differences in renal laboratory values between *DICER1*-carriers and unaffected family controls were observed.

Conclusions.—Our report is the first to systematically characterize renal function and anatomy in a large prospective cohort of *DICER1*-carriers and *DICER1*-negative family controls. *DICER1*-carriers may be at increased risk of structural anomalies of the kidney or collecting system. The role for *DICER1* in renal morphogenesis merits additional investigation.

Keywords

DICER1; kidney; structural abnormality; collecting system; renal cyst

Introduction

The *DICER1* syndrome is a pleiotropic tumor-predisposition disorder secondary to pathogenic germline variants in *DICER1*, an endoribonuclease integral to the processing of microRNAs [1, 2]. Pleuropulmonary blastoma (PPB) is the hallmark tumor of the *DICER1* syndrome. It is a rare, primitive, multipatterned lung sarcoma described in 1988 [3], and associated with high morbidity and mortality [4]. Subsequent to the recognition of PPB, it became apparent that other extra-pulmonary benign and malignant neoplasms occurred as manifestations of the *DICER1* syndrome, including ovarian Sertoli-Leydig cell tumor [5], thyroid carcinoma, [6], nasal chondromesenchymal hamartoma [7] and ciliary body medulloepithelioma [8]. The familial co-occurrence of PPB with urinary system tumors was initially reported in a 2006 study, which included 15 patients with cystic nephroma (CN), one family member with Wilms tumor (WT), intralobar nephrogenic rests and cysts either in probands with PPB or family members [9]. In a later study, germline pathogenic *DICER1* variants were detected in 15/20 (75%) CN, 0/6 cystic partially differentiated nephroblastomas, and 1/3 CN-associated renal sarcomas [10]. Although the *DICER1* syndrome is considered to be a rare disorder, the prevalence of germline pathogenic *DICER1* variants in the general population is more common than expected (1/10,600) [11]

Humans with mosaic missense mutations in the RNase IIIb domain of *DICER1*, a typically severe form of the *DICER1* syndrome [12], are reported to harbor unusual renal phenotypes. One patient (“Case 1”) [13] with mosaic *DICER1* p.D1713V at nine months had a Wilms tumor and abnormal kidney histology, which was similar to that of Beckwith-Wiedeman

syndrome, although there was no molecular genetic evidence of that disorder [13]. Another child (“Patient 3”) [14] with mosaic *DICER1* p.E1813D had a right renal medullary malformation with disorganized collecting system. *Dicer1* knockout mice develop a spectrum of anomalies including hydronephrosis due to ureteropelvic junction obstruction [15], renal parenchymal cysts and branching deficits [16, 17].

The frequency of structural abnormalities of the kidney or collecting system in individuals with germline loss-of-function variants in *DICER1*, the most common genotype in the syndrome [12] is unknown. In this study, we investigated the prevalence of ultrasound-detected renal anomalies and renal-associated clinical laboratory data in a large cohort of prospectively-ascertained and systematically-phenotyped individuals with a pathogenic *DICER1* variant and family controls.

Patients and methods

Study participants, *DICER1* genetic testing, and phenotyping.

Individuals with a known or suspected *DICER1*-associated phenotype were recruited to participate in a natural history study of the *DICER1* syndrome from physician- and self-referral, as well as collaboration with the International Pleuropulmonary Blastoma Registry and Ovarian and Testicular Stromal Tumor Registry. Probands and their family members were offered germline *DICER1* genetic testing. All participants or their guardians completed Individual Information Questionnaires (IIQ) about past medical and surgical history, including kidney-associated pathology. Pathogenic *DICER1*-mutation carriers (“*DICER1*-carriers”) and family controls (no detected pathogenic germline *DICER1* variants by sequencing, or inferred negative by pedigree analysis) were invited to undergo detailed phenotyping at the National Institutes of Health (NIH) Clinical Center (CC), including kidney ultrasound and comprehensive laboratory testing. Curved phased-array multifrequency transducers were routinely used to obtain longitudinal and transverse views of each kidney, supplemented by linear phased-array transducers as needed. Studies were conducted by experienced sonographers. Six individuals with negative germline *DICER1* testing but with at least one known *DICER1*-associated tumor were also invited for Clinical Center evaluation (Supplemental Table S1); these patients are likely either mosaic or have sporadic (tumor-confined) disease (“mosaic/sporadics”). A single radiologist (AL) systematically reviewed all the imaging studies for structural abnormalities, cysts and tumors; for every lesion, length and width, number, location, laterality, and imaging characteristics (e.g., cystic, solid, partial solid/cystic, or indeterminate) were documented. A pediatric radiologist (MR) with experience in *DICER1*-associated CN and kidney disease then reviewed all studies deemed abnormal. Discrepancies were resolved by consensus.

Statistical analyses.

Participants with *DICER1*-associated tumors but in whom germline (blood) *DICER1* testing was negative (six mosaic/sporadic patients listed in Supplemental Table S1) were not included in statistical analyses and are reported separately. We used the chi square test for proportions or Fisher’s exact test when limited by infrequent cell counts ($n < 5$). We used the Wilcoxon rank-sum test for continuous variables, and calculated cumulative incidence using

the complement of the Kaplan-Meier product limit estimator. The cross-sectional area of renal cysts was estimated assuming lesions are approximately elliptical in shape. We compared the proportion of laboratory values that were abnormal (high or low) at examination, as well as the continuous distribution laboratory values. Serum, plasma or urinalysis laboratory values for which the normal range did not vary substantially by age or gender were analyzed without stratification. Select labs were stratified by gender, adulthood, or both gender and adulthood as appropriate. Qualitative and semi-quantitative urinalysis results were classified as either abnormal or normal/negative, per Supplemental Table S6, and other normal ranges were provided by the NIH Clinical Center Department of Laboratory Medicine. We considered P values ≤ 0.05 significant. All statistical tests were two-sided and conducted using Stata/SE 13.1 (Stata Corp., College Station, TX, USA).

Results

General demographics.

A total of 89 pathogenic *DICER1*-carriers, 61 *DICER1*-negative family controls, and six mosaic/sporadic participants underwent evaluation at the NIH Clinical Center; all participants received kidney ultrasounds (US). Questionnaire data were available for all *DICER1*-carriers and 60/61 controls. Laboratory data drawn mainly from urinalysis were not available for a small minority of study participants (Table 1). Although the *DICER1*-carriers were younger than controls, the continuous distribution of age was not statistically different between *DICER1*-carriers and controls within the gender or child/adult strata (Table 1). There were 41 *DICER1*-carrier children and 48 *DICER1*-carrier adults. Clinical data on the six mosaic/sporadics are summarized in Supplemental Table S1 and are not considered further except where noted; none had a phenotype akin to those associated with mosaic *DICER1* RNase IIIb domain mutations [13, 14].

Prevalence of urinary tract tumors in *DICER1*-carriers.

Eight of the 41 *DICER1*-carrier children (6 males/2 females) had been diagnosed with CN (median age=1.6 years; range=0.4–4 years) (Supplemental Table S2); a ninth boy (a mosaic/sporadic) (76-01-001) had a CN at age 1.5 years (Supplemental Tables S1 and S2). Renal US at the Clinical Center on these nine children at a median of 2.4 years after nephrectomy or nephroureterectomy (range=0.46–9.8 years) identified a 3.2×1.7 cm circumscribed multicystic mass in the right kidney (mid-pole) of a 15-month-old boy with a history of bilateral CN at age 10 months (52-01-001). A right partial nephrectomy in this child at age 20 months showed a CN with atypical spindle cell features, with a resemblance in some respects to the type I or cystic PPB. One 7-year-old female mosaic/sporadic (40-01-001) had a 3.5×2.5 cm area of increased echogenicity in the left upper kidney radiographically consistent with pyelonephritis. Review of abdominal computed tomography (CT) scans approximately one year before and after the NIH renal US exam showed a stable contour abnormality affecting the left kidney, and bilateral extrarenal pelvises.

Among *DICER1*-carriers in our cohort, there were no cases of known *DICER1*-associated malignant renal neoplasms (*i.e.*, WT, renal sarcoma) or malignancies of the ureter or bladder. We found lesions radiographically suspicious for angiomyolipoma on renal US in one 43-

year-old female family control (one tumor) and on renal US and follow-up renal CT in one 65-year-old female *DICER1*-carrier (four tumors in left kidney: three mid-pole and one lower pole). One 54-year-old female control, a former smoker, had a 3×3×3.4 cm mass in the right upper kidney detected on our study US and confirmed by follow-up kidney CT scan. Urinalysis and constitutional symptoms were unremarkable. She was subsequently diagnosed with a renal cell carcinoma.

The prevalence of renal cysts in *DICER1*-carrier adults was comparable to family controls.

Prior to Clinical Center evaluation, none of the controls reported a history of renal cysts, compared with 4/81 (4.9%) *DICER1*-carriers. However, similar proportions of adult *DICER1*-carriers and controls had renal cysts detected at Clinical Center US (Table 2): 11/50 (22%) adult controls had at least one lesion detected on US, compared with 8/48 adult *DICER1*-carriers (17%) ($P=0.504$). The imaging characteristics of lesions in *DICER1*-carriers were similar to those in family controls.

Renal cysts were infrequent in *DICER1*-carrier children and controls.

At Clinical Center US, no lesions were detected in childhood family controls. Of 33 *DICER1*-carriers age 18 years without a history of CN, one (3%) girl (age 2.8 years; 28-01-002; Table 2) harbored an hypoechogenic 0.78 cm² complex cyst in her right kidney, mid-pole. It had neither calcification nor irregular margins. There were no statistically significant differences in the frequency of renal cysts in *DICER1*-carrier children and controls.

Structural renal abnormalities in *DICER1*-carriers vs. family controls.

Table 3 summarizes the results of the review of renal US and IIQ data from 89 *DICER1*-carriers. Excluding undefined masses, cysts and evidence of previous nephrectomy, there were five (6%) *DICER1*-carriers with structural abnormalities of varying severity of the collecting system or kidney, including one child and one adult with a duplicated collecting system (83-01-001 and 82-02-002), and one child with incomplete rotation of the left kidney and collecting system (28-01-002). None of the children with a history of CN harbored additional structural abnormalities. Of the five *DICER1*-carriers with a collecting system abnormality, one child (80-01-001) had a history of surgery for ureteropelvic junction obstruction and one adult male (39-04-003) had a history of an unspecified renal anomaly. None of the five had abnormal renal function by blood urea nitrogen/creatinine. Two women (89-01-001 and 11-02-002) had previously-undiagnosed nephrolithiasis. A third woman (39-02-002) had previously-undiagnosed bilateral medullary nephrocalcinosis; her father (39-04-003) had non-stone hydronephrosis, caliectasis and a low-lying left kidney.

There were no controls with collecting system anomalies, nephrolithiasis or nephrocalcinosis on Clinical Center renal US (vs. cases (8/89); Fisher exact $p=0.02$). There was no significant difference in cases vs. controls for structural abnormalities only (5/89 vs. 0/61; Fisher exact $p=0.08$). We reviewed questionnaire data from controls and identified two individuals with a self-reported (unverified) history of kidney abnormalities: one 42-year-old female with a history of “ureter surgery” as an infant in the 1970s reported no subsequent kidney problems, and one 18-month-old male was reported by his mother to have had

bilateral nephrocalcinosis at age 6 weeks. Review of the Clinical Center renal US for both controls showed no anomalies.

Laboratory measures of renal function were not significantly different between *DICER1*-carriers and family controls.

Most laboratory values did not differ between *DICER1*-carriers and family controls in either the proportions that were abnormal or their distributions (Supplemental Table S3 and Supplemental Table S4). Selective *post-hoc* review of medical records suggested those values that differed likely had non-*DICER1*-related explanations (Supplemental Table S3). The components of a standard urinalysis did not differ between *DICER1*-carriers and controls except for an increased prevalence of abnormal urobilinogen (9.88% vs. 0%; $P=0.021$; Supplemental Table S5).

Discussion

Our report is the first to systematically characterize renal function and anatomy in a large prospective cohort of *DICER1*-carriers and *DICER1*-negative family controls. In 89 *DICER1*-carrier adults and children, we identified eight (9%) individuals with US-detected collecting system anomalies, nephrolithiasis or nephrocalcinosis; no such anomalies were observed in 61 family controls, a significant difference. Laboratory measures of renal function were not significantly different between *DICER1*-carriers and family controls. To our knowledge, there are two reported patients with mosaic *DICER1* RNase IIIb-domain missense mutations, a particularly severe manifestation of the *DICER1* syndrome, with structural kidney and/or collecting system anomalies [13, 14], but none in individuals with germline loss-of-function *DICER1* variation. For comparison, the incidence of ureteropelvic junction obstruction on routine live birth antenatal US is estimated to be 1/500 (0.2%) [18, 19]. In another multi-center study of pre-natal US performed on 709,030 fetuses (including live-birth, stillbirths, abortions), 259 (0.03%) had US-detected dilation of the upper tract [20]. We acknowledge that there was no significant difference in the frequency of structural abnormalities only in our cases and controls, however, we believe that our findings are provocative. Collectively, the published *Dicer1* mouse [15–17], human mosaic *DICER1* RNase IIIb patients [13, 14] and our data suggest that *DICER1*-carriers may be at increased risk of structural anomalies of the kidney or collecting system. This observation needs validation in an independent cohort of *DICER1*-carriers. Conversely, the prevalence of *DICER1* germline pathogenic variants in cohorts with collecting system anomalies is unknown and merits investigation. Careful attention to abnormalities of the collecting system is warranted for *DICER1*-carrier children when undergoing renal US to screen for CN or malignant renal tumors, as per current surveillance guidelines [21].

US also revealed evidence of nephrolithiasis in two asymptomatic adult *DICER1*-carriers, neither of whom had an underlying renal structural anomaly or a known prior history of nephrolithiasis. No stones were available for analysis. No family controls had a history of nephrolithiasis. Given the high prevalence of nephrolithiasis in the general population, absence of this phenotype in the *Dicer1* mouse models, and the lack of clear pathophysiologic link between miRNA dysregulation and the biology of nephrolithiasis

formation, additional evidence is needed before drawing any conclusions on this association. We observed asymptomatic, undiagnosed medullary nephrocalcinosis in one adult *DICER1*-carrier; one pediatric-aged control had a history of medullary nephrocalcinosis but no evidence of this was apparent on US. Renal function as measured by a variety of standard clinical blood and urine laboratory studies in *DICER1*-carriers was normal (or likely explained by non-*DICER1* processes), which is consistent with *Dicer1* mouse modeling [22]. Importantly, there was no evidence of glomerular dysfunction in mouse or man.

Renal parenchymal cysts are an established feature of multiple *Dicer1* mouse models [16, 17]. A large study of US-detected renal cysts in children estimated a prevalence of 0.22% (35/16,102) [23]. We observed a non-significant excess of simple cysts in 2/41 (4.9%) *DICER1*-carrier children; the rate is 1/33 (3.0%) if excluding those with a history of CN. One *DICER1*-carrier child with an apparent calyceal diverticulum also had concomitant incomplete ventral-lateral rotation of the collecting system, a rare finding (Table 3). In adults, renal cysts are more common in men than women and their incidence increases with age; one study of 14,314 individuals reported a prevalence of renal cysts in about 10% of men and 5.7% of women, aged 40–49 years [24]. These proportions are lower than those observed in our cases and controls, whose median age was about 41 years. We did not observe a significant excess of renal cysts in our adult cohort compared with family controls. This may be explained by the natural history of renal cysts or by the cross-sectional nature of our data. Although rare, renal cysts in children are frequently observed in the context of a hereditary disorder or malformation syndrome [25]. Over time, renal cysts become more common, presumably due to a variety of etiologies, and the relative contribution of one etiology (like the *DICER1* syndrome) is increasingly diluted.

Limitations of this study include a modest sample size (a frequent challenge in rare disorders) and enrollment of families in the study due to ascertainment bias: families needed at least one member with a known *DICER1*-associated phenotype to come to clinical attention. In addition, our small sample size included a very limited number of pediatric-aged family controls and thus we had to compare the prevalence of renal cysts with previously published proportions. There are limits to the sensitivity of ultrasonography to detect renal and urinary tract malformations and structural abnormalities. Lastly, the cross-sectional nature of the study also limits our conclusions.

Conclusion

In our study of prospectively phenotyped *DICER1*-carriers and family controls, 6% of adults and children with a germline pathogenic *DICER1* variant harbored a structural abnormality of the renal collecting system. Our findings are of importance since *DICER1*-carriers are more common than expected [11] and renal anomalies as described in this report may aid in the identification of families at risk. These observations and their clinical significance need replication and study in a larger cohort. In young *DICER1*-carrier children undergoing serial renal US to screen for CN, attention should also be paid to the presence of a collecting system abnormality. The prevalence of germline pathogenic *DICER1* variants in individuals with collecting system anomalies remains to be determined.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographics of the NCI *DICER1* syndrome cohort. Table excludes six *DICER1* mosaic/sporadic patients, whose data are listed in Supplemental Table S1

	Total Sample		<18 Years Old		18 Years Old	
	Controls (n=61)	<i>DICER1</i> (n=89)	Controls (n=11)	<i>DICER1</i> (n=41)	Controls (n=50)	<i>DICER1</i> (n=48)
Female gender	25 (41%)	45 (51%)	5 (45%)	14 (34%)	20 (40%)	31 (65%)*
Age < 18 years	11 (18%)	41 (46%)*	-	-	-	-
Median age, years (range)	38 (0.9 – 74)	24 (0.8 – 73)**	3.7 (0.9 – 17.6)	5.5 (0.8 – 17)	41.9 (24 – 74)	40.8 (1873)
Missing at least one lab (typically urinalysis)	7 (11.5%)	8 (9.0%)	4 (36%)	8 (19.5%)	3 (6%)	0 (0%)

* P=0.015;

** P=0.0046;

*** P<0.001

Table 2.

Findings on renal ultrasound in *DICER1*-carriers and controls. Of the *DICER1*-carriers <18 years of age, there was one 2.8 year-old-girl (28-01-002) with a 0.78 cm² complex cyst and one 15-month-old boy (52-01-001) with a history of bilateral cystic nephroma with a 4.3 cm² mass later shown to be a cystic nephroma. Data on six children with negative germline *DICER1* testing but with a *DICER1*-associated tumor (mosaic/sporadic) are shown in Supplemental Table S1.

Frequencies	Age <18 years		Age 18+ years	
	Control (n=11)	<i>DICER1</i> -carrier (n=41)	Control (n=50)	<i>DICER1</i> -carrier (n=48)
# of CN/nephrectomy	-	8	-	-
At least 1 lesion	0%	3.0% [+1.9%]	22% (+2%)	17% (+2.1%)
# of lesions				
0	11	32 [+7]	38	39
1	0	1 [+1]	8 (+1 [*])	7
2	-	-	1	1
3	-	-	2	0
4	-	-	0	(+1 [*])
Lesion-level analysis	(n=0)	(n=2)	(n=16+1 [*])	(n=9+4 [*])
Right	-	2	7	3
Left	-	-	9 (+1 [*])	6(+4 [*])
Cystic	-	1	13	9
Partially cystic/solid	-	-	-	-
Solid	-	1	1 (+1 [*])	(+4 [*])
Indeterminate	-	-	2	-
Upper pole	-	-	6	4
Mid pole	-	2	5 (+1 [*])	4(+3 [*])
Lower pole	-	-	5	1 (+1 [*])
Hypoechogenic	-	1	9	5
Calcifications	-	-	1	-
Area (cm ²)	-	0.78, 4.3		
Mean (SD)	-	2.5 (1.8)	3.9 (9.8)	1.68 (3.3)
Median (range)	-	2.5 (0.78 – 4.3)	0.79 (0.01 – 40.8)	0.60 (0.05 – 12.4)

[Bracketed values include children with histories of cystic nephromas]

(^{*}) Likely angiomyolipoma(s) in one *DICER1*-carrier and one control

Table 3.

Structural renal and collecting system anomalies, nephrolithiasis and medullary calcosinosis in 89 *DICER1*-carriers evaluated at the NIH Clinical Center. Review of 61 control renal ultrasounds showed no evidence of structural anomalies, nephrolithiasis or medullary calcosinosis. One pediatric control had a diagnosis of medullary nephrocalcosinosis. *IIQ* Individual Information Questionnaire, *UPJ* ureteropelvic junction obstruction

ID	Gender	Age at Exam (years)	Abnormality	Cystic Structures	Kidney Disorders from IIQ (years)	BUN/Cr (mg/dL)	<i>DICER1</i> Germline Variant
Abnormalities of the collecting system							
28-01-002	F	2.8	Incomplete (ventral-lateral) rotation of left kidney and collecting system	1 (9 mm mid-right complex cyst); consider calyceal diverticulum	None	8/0.31	c.1408G>T; p.E470X
80-01-001	M	4.3	Residual dilation of right collecting system following UPJ repair; left kidney unremarkable	None	Right UPJ obstruction surgery (0.75)	14/0.24	c.735-1_741delGGTATACCTinsA
83-01-001	F	4.5	Duplex left collecting system with mild dilation of upper moiety of pelvis. Upper pole collecting system likely dysplastic.	None	None	15/0.37	c.4407_4410delTTCT
82-02-002	F	33	Right duplicated collecting system; simple 8 mm outer cortex	None	Renal cyst, unknown laterality (4)	12/0.79	c.2830C>T; p.R944X
39-04-003 (Father of 39-02-002)	M	57	Marked dilation, hydronephrosis and caliectasis on left; left kidney also low-lying; right kidney unremarkable	None	Unspecified kidney abnormality (55)	15/0.79	c.2650+1G>T
Nephrocalcosinosis and renal calculi							
39-02-002 (Daughter of 39-04-003)	F	31	Bilateral medullary nephrocalcosinosis	Cyst vs. caliceal diverticulum in right kidney	None	13/0.74	c.2650+1G>T
89-01-001	F	34	Bilateral ~5 mm calculi; not obstructive	None	None	10/0.59	c.2247C>A; p.Y749X
11-02-002	F	41	2 < 1cm calculi in right kidney but no obstruction; evidence of multiple superficial injuries	None	None	10/0.64	c.1870C>T; p.R624X