Published in final edited form as:

Am J Med Genet A. 2019 March ; 179(3): 381–385. doi:10.1002/ajmg.a.61020.

Anomalies of the Genitourinary Tract in Children with 22q11.2 Deletion Syndrome

Jason P. Van Batavia¹, T. Blaine Crowley², Evanette Burrows², Elaine H. Zackai², Simone Sanna-Cherchi³, Donna M. McDonald-McGinn², and Thomas F. Kolon¹

¹Division of Urology, Children's Hospital of Philadelphia, Philadelphia, PA

²Division of Human Genetics, Children's Hospital of Philadelphia, PA

³Division of Nephrology, New York-Presbyterian Hospital Columbia University Medical Center, New York, NY

Abstract

The 22q11.2 deletion syndrome (22q11.2DS) involves multiple organ systems with variable phenotypic expression. Genitourinary tract abnormalities have been noted to be present in up to 30–40% of patients. At our institution, an internationally recognized, comprehensive and multidisciplinary 22q11.2DS care center has been providing care to these children. We sought to report on the incidence of genitourinary tract anomalies in this large cohort and therefore, retrospectively reviewed all patients who underwent a complete evaluation from 1992 to March 2017. We identified all children with any genital or urinary tract anomaly. For all children with a diagnosis of hydronephrosis, the underlying etiology was determined, when possible. Overall, 1,073 of 1,267 children with 22q11.2DS underwent renal evaluations at our institution. 162 (15.1%) children had structural abnormalities of their kidneys/urinary tracts. The majority of children with hydronephrosis (63%) had isolated upper tract dilation without any additional diagnoses. Boys were significantly more likely to be diagnosed with a genital abnormality than girls (7.7% vs. 0.5%, $p < 0.001$). Of the 649 boys in the entire cohort, 24 (3.7%) had cryptorchidism and 24 (3.7%) had hypospadias, which was noted to be mild in all except 1 boy. Overall, findings of hydronephrosis, unilateral renal agenesis, and multicystic dysplastic kidney occur at higher rates than expected in the general population. Given these findings, in addition to routine physical examination, we believe that all patients with 22q11.2DS warrant screening RBUS at time of diagnosis.

Keywords

22q11.2 deletion syndrome; DiGeorge syndrome; genitourinary; renal; pediatrics; urology

Introduction

Microdeletions of chromosome 22q11.2 are the most common cause of DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome. They are also identified in a subset of patients with Opitz G/BBB syndrome and Cayler Cardiofacial syndrome. The 22q11.2 deletion syndrome (22q11.2DS) involves multiple organ systems with variable phenotypic expression (McDonald-McGinn et al. 2015). The most common features include conotruncal cardiac anomalies, hypocalcemia often in association with hypoparathyroidism, immunodeficiency, gastrointestinal, palatal and skeletal abnormalities, developmental delay, learning differences, and psychiatric illness. In addition, genitourinary tract abnormalities, especially renal anomalies, have been noted to be present in up to 30–40% of patients with 22q.11.2 deletions (Kobrynski and Sullivan 2007, McDonald-McGinn et al. 2015, Kujat et al. 2006, Ryan et al. 1997, Lopez-Rivera et al. 2017, Stewart et al. 1999, Wu et al. 2002). Importantly, by conduction of a large-scale screen for copy number variations in children and young adults with congenital anomalies of the urinary tract (CAKUT), we recently identified the LCR22C-LCR22D region of the 22q11.2 deletion as a critical susceptibility locus (Lopez-Rivera et al. 2017). By means of a combination of targeted and whole exome sequencing, together with functional modeling in zebrafish and mouse, we identified *CRKL* as a main genetic driver of the kidney defects seen in this syndrome, as well as in the general population. In fact, chromosome 22q11.2 deletions were identified in 1.1% of 1,093 patients followed in kidney clinics for small or absent kidneys, as well as in 0.01% of 22,094 population controls (Lopez-Rivera et al. 2017). Although these patients were unaware that they had the 22q11.2 deletion, some later reported having symptoms commonly associated with the 22q11.2 deletion. A subsequent study analyzing the same mouse models confirmed haploinsufficiency of *CRKL* as a main driver for genitourinary malformations (Haller et al. 2017). These studies represent first steps in the understanding of how gene dosage at the chromosome 22q11.2 predispose to kidney and urinary tract malformations both in the context of DiGeorge/Velocardiofacial syndrome, and at the population level.

At our institution, the 22q and You Center provides internationally recognized, comprehensive and multidisciplinary care to children with 22q11.2DS (McDonald-McGinn et al. 1999). An initial report from our center from 2002 described the urinary tract findings in 73 children who underwent renal and bladder ultrasound and the genital findings in 149 boys who underwent evaluation (Wu et al. 2002). While that study noted a 31% incidence of structural urinary tract anomaly and 14% incidence of cryptorchidism or hypospadias in boys, >900 additional children have subsequently undergone a urologic/renal assessment in the 15 years since that study was published. We therefore sought to update this prior study and report the incidence of genitourinary tract anomalies in a much larger cohort of children with 22q11.2DS at a single institution.

Material and Methods

We retrospectively reviewed the charts of all patients who underwent a complete evaluation at our institution's 22q and You Center from 1992 to March, 2017. A total of 1,267 patients were evaluated during this time and all patients underwent cytogenetic testing to confirm

diagnosis. Of this total cohort, 1,073 patients underwent renal evaluation with at least one renal and bladder ultrasound. Among these 1,073 patients, 362 patients underwent FISH testing only, but the vast majority of patients underwent either SNP microarray or MLPA to determine the exact size and location of their deletion. Using our electronic medical record (EMR) system, Epic (Epic Systems Corp., Madison, Wisconsin) and diagnosis specific codes (Table 1), we sought to identify children with any genital or urinary tract anomaly. For all children with a diagnosis of hydronephrosis (either diagnosed antenatally or post-natally), the underlying etiology for the hydronephrosis was determined based on additional diagnosis codes for that child. For all boys with a diagnosis of undescended testicle, chart reviews were performed to identify unilateral vs. bilateral, side of unilateral, and need for surgical intervention. Likewise, for all boys with a diagnosis of hypospadias, charts were reviewed to determine location and severity of hypospadias, and need for surgical correction.

Results

Overall, of the 1,267 patients seen in our institution's 22q clinic, 649 are boys and 618 are girls. 1,073 children (556 males, 517 females) with 22q11.2DS underwent renal, ureteral, and bladder evaluations with imaging at a mean age of 3.9 years (SD 5.5 years). Of these 1,073 children, 162 (15.1%) were found to have structural abnormalities of their kidneys/urinary tracts. Three hundred and sixty two of these children were diagnosed by FISH studies only and 16% were noted to have genitourinary malformations on imaging. In the remaining 711 children, CRKL analysis and deletion status was known and the breakdown of urinary abnormalities based on CRKL status is shown in table 2.

The most common upper tract finding was hydronephrosis which was detected in 63 patients (5.9% overall; 38.9% of all renal/urinary tract anomalies). Forty-one of patients with hydronephrosis had at least one follow-up visit at our institution and of these, the majority (26 patients; 63%) had isolated upper tract dilation without any additional diagnoses. The upper tract dilation remained stable or resolved spontaneously in all 26 patients. Additional renal abnormalities include unilateral renal agenesis in 34 patients (21.0% of all urinary tract anomalies; 3.2% of all 22q11.2 patients), multicystic dysplastic kidney in 13 (8.0% of urinary tract findings; 1.2% of all patients), hypoplastic kidney in 6, duplicated collecting system in 6, simple renal cyst in 3, and horseshoe kidney in 1. Twenty children (1.9% of all children with renal evaluations) were noted to have hyperechoic renal parenchyma on ultrasound. Ureteral anomalies included ureteropelvic junction (UPJ) obstruction in 1, ureterocele in 4, and primary megaureter in 1.

Bladder abnormalities include vesicoureteral reflux (VUR) in 10 patients (6 girls, 4 boys; 0.9% of all evaluated 22q11.2 patients), only 3 of whom (30%) had a history of urinary tract infection. On follow-up, repeat imaging showed spontaneous VUR resolution in 5 patients (including 3 with grade 3 or higher VUR) and 3 additional patients without repeat imaging were asymptomatic and UTI-free (2 children are currently off antibiotic prophylaxis and 1 boy aged 6 months is currently on antibiotic prophylaxis and awaiting follow-up). Only two patients (20%) with VUR underwent surgery. One girl with a history of high grade bilateral VUR and neurogenic bladder secondary to spina bifida (also associated with 22q11.2DS) underwent vesicostomy creation as part of her bladder management and one boy with a

history of left grade 4 VUR and right paraureteral diverticulum had bilateral open ureteral reimplantation with excision of the diverticulum. Urethral anomalies were noted in only 2 of the 649 boys (0.3%) and both boys were diagnosed with posterior urethral valves (PUVs).

In terms of genital anomalies, boys were significantly more likely to be diagnosed with an abnormality than girls (7.7% vs. 0.5%, $p < 0.0001$, Fisher's exact test). Of the 649 boys, 24 (4%) had cryptorchidism. Excluding 7 boys for whom laterality could not be determined, 7 boys had bilateral undescended testes (UDTs), 7 had a left UDT, and 3 had a right UDT. Eighteen boys underwent orchiopexy and 6 boys are either scheduled for surgery or follow up. Hypospadias was diagnosed in 24 of the 649 boys (3.7%) and was noted to be mild (megameatus or glanular) in all except 1 boy. Twelve of the boys (50%) were diagnosed with megameatus intact prepuce (MIP) after neonatal circumcision and only 2 of these boys required surgical repair for associated ventral penile curvature. The only female genital anomalies noted were vaginal agenesis in 2 patients and absent uterus in 1 patient (Sundaram et al. 2007).

Incidence rates of spina bifida and anorectal malformation were also determined as both conditions often have genital and/or urinary tract manifestations. Overall, 12 of the 1,267 children (0.9%) were diagnosed with spina bifida and 10 children (0.8%) were diagnosed with congenital absence, atresia, or stenosis of the anus (6 males, 4 females). All of the patients with anal anomalies were noted to have imperforate anus, except for one boy who had feeding difficulties and was diagnosed with anal stenosis.

Discussion

Children with chromosome 22q11.2 deletion can have congenital anomalies of multiple organ systems including the genitourinary tract. Several previous studies have found a high association with structural abnormalities of the urinary tract, especially of the kidney. In one of the earliest studies to report on genitourinary anomalies in patients with DiGeorge syndrome, prior to identification of the association with the 22q11.2 deletion, Conley and colleagues in 1979 described autopsy findings in 25 patients (Conley et al. 1979). The authors noted the presence of hydronephrosis or hydroureter in 6 patients (24%) and renal cystic disease in 2 patients (8%). In addition, 1 patient was found to have an undescended testis at autopsy suggesting an association with genital anomalies as well as urinary tract ones (Conley et al. 1979). Of note, these children could have had DiGeorge syndrome due to other causes such as CHARGE syndrome due to a *CHD7* mutation, genomic imbalances at chromosome 10p14, or secondary to a teratogen, such as is seen in infants of a diabetic mother. Since that report, several other studies have described urinary tract findings in addition to hydroureteronephrosis including unilateral renal agenesis, renal hypoplasia, vesicoureteral reflux, megaureter, multicystic dysplastic kidney, and ureteropelvic junction obstruction (Devriendt et al. 1996, Driscoll, Budarf and Emanuel 1992, Kujat et al. 2006, Lipson et al. 1991, Wilson et al. 1993, Wu et al. 2002).

Overall, the rate of renal and urinary tract anomalies ranges from 10–40% in most studies (Conley et al. 1979, Devriendt et al. 1996, Kobrynski and Sullivan 2007, Ryan et al. 1997, Stewart et al. 1999, Wu et al. 2002). Interestingly, the most recently published series

of 22q11.2 patients report a 31–37% rate of renal and urinary tract abnormalities which is higher than the rate of 15% noted in the current study (Kobrynski and Sullivan 2007, Wu et al. 2002). While all of these studies, including the current one, are retrospective reviews, all of the previously published series are limited by much smaller sample sizes (only one with >80 patients with renal evaluations) compared to 1267 patients in the present study (Conley et al. 1979, Ryan et al. 1997, Stewart et al. 1999, Wu et al. 2002). In the majority of the previous studies, less than 25% of all patients with 22q11.2DS had appropriate renal/urinary tract imaging to allow for evaluation of urinary tract anomalies (Ryan et al. 1997, Wu et al. 2002). The largest series to date on renal and urinary tract abnormalities is from a European study that involved questionnaires sent to 23 centers on proven cases of 22q11.2 deletion (Ryan et al. 1997). This series included 558 patients with 22q11.2DS but only 136 of these patients (24%) had complete renal and urinary tract information, which suggests the possibility of selection bias as questionnaire responders might be more likely to answer queries in the renal section if an abnormality was present versus in cases with normal renal findings (Ryan et al. 1997). Our current single institution study has a considerably higher yield of patients with complete renal/urinary tract evaluations (1,073 of 1,267 total patients, 85%) which may reduce selection bias and account for our lower overall prevalence of renal and urinary tract anomalies. Another explanation for the lower prevalence of kidney and urinary tract defects in our study, partially related to the retrospective nature of our data, is that subtle defects or defects that improve or resolve with age, such as vesicoureteral reflux and hydronephrosis, are less likely to be captured in electronic medical records or by simple ultrasound screening.

Hydronephrosis is the most common urinary tract diagnosis in our cohort (5.9%) and was found at a prevalence 8 times higher than the 0.7% rate expected in the general population (Lee and Borer 2016). In the majority of cases (63%), the hydronephrosis was self-limiting or stable over time with no underlying etiology discovered. While the rates of unilateral renal agenesis (3.2%) and multicystic dysplastic kidney (1.2%) are lower than those noted in the previously mentioned studies, both rates are considerably higher than the estimated incidence rates (<0.1%) in the general population (Cardona-Grau and Kogan 2015, Westland et al. 2013). Given these higher rates of renal and urinary tract abnormalities, we recommend as a clinical standard that all patients with 22q11.2DS undergo a screening renal and bladder ultrasound to provide appropriate care and counseling to patients and their families.

Recently, we identified *CRKL1*, located between LCR22C-LCR22D within the 22q11.2 deletion (Figure 1) as the driver of renal defects in these patients (Lopez-Rivera et al. 2017, McDonald-McGinn et al. 2015) as well as in patients who had not otherwise come to attention. Significantly, this serves to highlight the frequency of the deletion and the fact that there may be other patients followed in Urology/Nephrology who have not yet been diagnosed with 22q11.2 deletion syndrome due to the fact that they don't have congenital heart disease as a presenting symptom.

Vesicoureteral reflux (VUR) was only diagnosed in 10 patients or 0.9% of all evaluated children in our cohort. The majority of children with VUR had spontaneous resolution or remained asymptomatic without any treatment or antibiotic prophylaxis. Only two children

underwent surgical intervention and in both, the child had additional anatomic or neurologic anomalies. Therefore, when VUR is an isolated finding in children with 22q11.2 deletion, it likely can be managed nonoperatively. Notably, the prevalence of VUR in our cohort of 22q11.2DS patients is not higher than that of the general population, suggesting that VUR was coincidental in these patients (Sargent 2000). On the other hand, diagnosis of VUR requires the execution of voiding cystourethrogram (VCUG), usually conducted following recurrent urinary tract infections in children below age of 6 years, while screening ultrasound can easily miss it.

The prevalence rate of cryptorchidism in the current study (4%) is similar to rates seen in previous studies of boys with 22q11.2 deletion (4–8%) as well as to the estimated rate in the general population (1–4.6% in full term boys at birth)(Ryan et al. 1997, Sijstermans et al. 2008, Wu et al. 2002). Only three of these boys were also diagnosed with mild hypospadias. The lack of more severe hypospadias in these children with cryptorchidism suggests that the UDT was not the result of a more global disorder such as hypogonadotropic hypogonadism. Our prevalence rate of hypospadias (3.7%) is similar to that noted in other series of 22q11.2 deletion boys (1.5–8%) but still higher than that reported in the general population (0.2–0.4%) (Ryan et al. 1997, Fisch et al. 2009, Bergman et al. 2015, Wu et al. 2002). Interestingly, half of the boys in this study with a hypospadias were diagnosed with MIP variant after neonatal circumcision, reiterating the need for careful examination of the urethral meatus prior to circumcision.

Limitations of this study include its retrospective nature and selection biases that may occur when searching EMR for diagnosis codes. Additionally, not all renal and urinary tract imaging studies were performed at our institution and therefore criteria for some renal findings such as hydronephrosis and urinary tract dilation may have differed based on where the imaging was obtained and who read the studies. Lastly, not all children were evaluated by a pediatric urologist and thus minor genital anomalies such as megameatus or glanular hypospadias may be under-diagnosed in our cohort.

Conclusions

In this large single institution review of patients with 22q11.2DS, 15.1% have associated renal or structural urinary tract anomalies. Findings of hydronephrosis, unilateral renal agenesis, and multicystic dysplastic kidney occur at higher rates than expected in the general population, although in the majority no surgical intervention is necessary. Genital abnormalities occur more often in boys than girls. Despite, the higher than expected rate of hypospadias, most are mild distal hypospadias that may not require surgical correction. Given these genitourinary associations, in addition to routine physical examination, all patients with 22q11.2DS warrant screening renal/bladder ultrasound at time of diagnosis as part of their clinical standard of care.

Acknowledgments

Funding

Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number **KL2TR001879**. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References:

- Bergman JE, Loane M, Vrijheid M, Pierini A, Nijman RJ, Addor MC, Barisic I, Beres J, Braz P, Budd J, Delaney V, Gatt M, Khoshnood B, Klungsoyr K, Martos C, Mullaney C, Nelen V, Neville AJ, O'Mahony M, Queisser-Luft A, Randrianaivo H, Rissmann A, Rounding C, Tucker D, Wellesley D, Zymak-Zakutnia N, Bakker MK & de Walle HE (2015) Epidemiology of hypospadias in Europe: a registry-based study. *World J Urol*, 33, 2159–67. [PubMed: 25712311]
- Cardona-Grau D & Kogan BA (2015) Update on Multicystic Dysplastic Kidney. *Curr Urol Rep*, 16, 67. [PubMed: 26255066]
- Conley ME, Beckwith JB, Mancer JF & Tenckhoff L (1979) The spectrum of the DiGeorge syndrome. *J Pediatr*, 94, 883–90. [PubMed: 448529]
- Devriendt K, Swillen A, Fryns JP, Proesmans W & Gewillig M (1996) Renal and urological tract malformations caused by a 22q11 deletion. *J Med Genet*, 33, 349.
- Driscoll DA, Budarf ML & Emanuel BS (1992) A genetic etiology for DiGeorge syndrome: consistent deletions and microdeletions of 22q11. *Am J Hum Genet*, 50, 924–33. [PubMed: 1349199]
- Fisch H, Lambert SM, Hensle TW & Hyun G (2009) Hypospadias rates in new york state are not increasing. *J Urol*, 181, 2291–4. [PubMed: 19303092]
- Haller M, Mo Q, Imamoto A & Lamb DJ (2017) Murine model indicates 22q11.2 signaling adaptor CRKL is a dosage-sensitive regulator of genitourinary development. *Proc Natl Acad Sci U S A*, 114, 4981–4986. [PubMed: 28439006]
- Kobrynski LJ & Sullivan KE (2007) Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. *Lancet*, 370, 1443–52. [PubMed: 17950858]
- Kujat A, Schulz MD, Streng S & Froster UG (2006) Renal malformations in deletion 22q11.2 patients. *Am J Med Genet A*, 140, 1601–2. [PubMed: 16761295]
- Lee R & Borer J. 2016 Chapter 124: Perinatal Urology. In Campbell-Walsh Urology, eds. Wein A, Kavoussi L, Partin A & Peters C. Philadelphia, PA: Elsevier.
- Lipson AH, Yuille D, Angel M, Thompson PG, Vandervoord JG & Beckenham EJ (1991) Velocardiofacial (Shprintzen) syndrome: an important syndrome for the dysmorphologist to recognise. *J Med Genet*, 28, 596–604. [PubMed: 1956057]
- Lopez-Rivera E, Liu YP, Verbitsky M, Anderson BR, Capone VP, Otto EA, Yan Z, Mitrotti A, Martino J, Steers NJ, Fasel DA, Vukojevic K, Deng R, Racedo SE, Liu Q, Werth M, Westland R, Vivante A, Makar GS, Bodria M, Sampson MG, Gillies CE, Vega-Warner V, Maiorana M, Petrey DS, Honig B, Lozanovski VJ, Salomon R, Heidet L, Carpentier W, Gaillard D, Carrea A, Gesualdo L, Cusi D, Izzi C, Scolari F, van Wijk JA, Arapovic A, Saraga-Babic M, Saraga M, Kunac N, Samii A, McDonald-McGinn DM, Crowley TB, Zackai EH, Drozd D, Miklaszewska M, Tkaczyk M, Sikora P, Szczepanska M, Mizerska-Wasiak M, Krzemien G, Szmigielska A, Zaniew M, Darlow JM, Puri P, Barton D, Casolari E, Furth SL, Warady BA, Gucev Z, Hakonarson H, Flogelova H, Tasic V, Latos-Bielenska A, Materna-Kiryluk A, Allegri L, Wong CS, Drummond IA, D'Agati V, Imamoto A, Barasch JM, Hildebrandt F, Kiryluk K, Lifton RP, Morrow BE, Jeanpierre C, Papaioannou VE, Ghiggeri GM, Gharavi AG, Katsanis N & Sanna-Cherchi S (2017) Genetic Drivers of Kidney Defects in the DiGeorge Syndrome. *N Engl J Med*, 376, 742–754. [PubMed: 28121514]
- McDonald-McGinn DM, Kirschner R, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, Moss E, Solot C, Wang P, Jacobs I, Handler S, Knightly C, Heher K, Wilson M, Ming JE, Grace K, Driscoll D, Pasquariello P, Randall P, Larossa D, Emanuel BS & Zackai EH (1999) The Philadelphia story: the 22q11.2 deletion: report on 250 patients. *Genet Couns*, 10, 11–24. [PubMed: 10191425]
- McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JA, Zackai EH, Emanuel BS, Vermeesch JR, Morrow BE, Scambler PJ & Bassett AS (2015) 22q11.2 deletion syndrome. *Nat Rev Dis Primers*, 1, 15071. [PubMed: 27189754]
- Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, Schuffenhauer S, Oechsler H, Belohradsky B, Prieur M, Aurias A, Raymond FL, Clayton-Smith J, Hatchwell E, McKeown C,

- Beemer FA, Dallapiccola B, Novelli G, Hurst JA, Ignatius J, Green AJ, Winter RM, Brueton L, Brondum-Nielsen K, Scambler PJ & et al. (1997) Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet*, 34, 798–804. [PubMed: 9350810]
- Sargent MA (2000) What is the normal prevalence of vesicoureteral reflux? *Pediatr Radiol*, 30, 587–93. [PubMed: 11009294]
- Sijstermans K, Hack WW, Meijer RW & van der Voort-Doedens LM (2008) The frequency of undescended testis from birth to adulthood: a review. *Int J Androl*, 31, 1–11.
- Stewart TL, Irons MB, Cowan JM & Bianchi DW (1999) Increased incidence of renal anomalies in patients with chromosome 22q11 microdeletion. *Teratology*, 59, 20–2. [PubMed: 9988879]
- Sundaram UT, McDonald-McGinn DM, Huff D, Emanuel BS, Zackai EH, Driscoll DA & Bodurtha J (2007) Primary amenorrhea and absent uterus in the 22q11.2 deletion syndrome. *Am J Med Genet A*, 143a, 2016–8. [PubMed: 17676598]
- Westland R, Schreuder MF, Ket JC & van Wijk JA (2013) Unilateral renal agenesis: a systematic review on associated anomalies and renal injury. *Nephrol Dial Transplant*, 28, 1844–55. [PubMed: 23449343]
- Wilson DI, Burn J, Scambler P & Goodship J (1993) DiGeorge syndrome: part of CATCH 22. *J Med Genet*, 30, 852–6. [PubMed: 8230162]
- Wu HY, Rusnack SL, Bellah RD, Plachter N, McDonald-McGinn DM, Zackai EH & Canning DA (2002) Genitourinary malformations in chromosome 22q11.2 deletion. *J Urol*, 168, 2564–5. [PubMed: 12441983]

Figure 1. Low copy repeats and genes within the 22q11.2 deletion. Schematic representation of the 3-Mb 22q11.2 region that is commonly deleted in 22q11.2 deletion syndrome, including the four low copy repeats (LCR22s) that span this region (LCR22A, LCR22B, LCR22C, and LCR22D). (from McDonald-McGinn DM, et al, 22q11.2 deletion syndrome. Nat Rev Dis Primers 2015; 19;1:15071)

Table 1.

List of ICD-10 diagnosis codes used to query electronic medical records of children with 22q11.2 deletions for genitourinary tract anomalies.

Diagnosis	ICD-9 Code	ICD-10-DM Code
Congenital absence, atresia and stenosis of anus with or without fistula	751.2	Q42.2–3
Congenital hydronephrosis	753.29	Q62.0–1
Congenital megaureter	753.22	Q62.2
Congenital occlusion of ureteropelvic junction	753.21, 753.29	Q62.11
Congenital occlusion of ureterovesical orifice	753.22	Q62.12
Congenital posterior urethral valves	753.6	Q64.2
Congenital ureterocele and other ureteral abnormalities	753.23, 753.4, 753.4D	Q62.3–6, Q62.8
Cystic kidney disease	753.1–9	Q61.0–9
Hematuria	599.7, 791.2	R31.0–9
Horseshoe kidney	753.3	Q63.1
Hydronephrosis	591	N13.0–3
Hydroureter	593.5	N13.4
Hypospadias	752.61	Q54.0–9
Other congenital malformations of female genitalia	752.49	Q52.1–9
Other congenital malformations of kidney	753.3	Q63.0–9
Other obstructive and reflux uropathy	753.29,	N13.8–9
Renal agenesis and other reduction defects of kidney	753.0	Q60.0–6
Spina bifida	741.90	Q05.0–9
Undescended and ectopic testicle	752.51	Q53.0–9
Urinary tract infection	599.0	N39.0
Vaginal agenesis	752.45	Q52.0
Vesicoureteral reflux	593.70–73	N13.70–73, Q62.7

Table 2.

Prevalence of urinary abnormalities as detected by renal/bladder imaging in the 711 22q11.2DS patients with known CRKL status. CRKL status and specific deletion breakpoint locations are shown with rates of abnormal urinary findings. Overall, urinary abnormalities were present in 15% of patients with CRKL deletions compared with 8% in patients without CRKL deletions. The difference between prevalences between these two groups was not statistically significant ($p = 0.11$).

CRKL deleted?	Breakpoints	Abnormal		Normal		Total	
		N	%	N	%	N	Prevalence
YES	A-D	93	15.5	504	84.5	597	15%
	B-D	0	0.0	30	100.0	30	
	C-D	2	20.0	8	80.0	10	
	Total CRKL	95	14.9	542	85.1	637	
NO	A-B	3	7.7	36	92.3	39	8%
	A-C	3	16.7	15	83.3	18	
	Misc. Atypical	0	0.0	17	100.0	17	
	Total Non-CRKL	6	8.1	68	91.9	74	