Renal malformations associated with mutations of developmental genes: messages from the clinic

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Abstract Renal tract malformations (RTMs) account for about 40% of children with end-stage renal failure. RTMs can be caused by mutations of genes normally active in the developing kidney and lower renal tract. Moreover, some RTMs occur in the context of multi-organ malformation syndromes. For these reasons, and because genetic testing is becoming more widely available, pediatric nephrologists should work closely with clinical geneticists to make genetic diagnoses in children with RTMs, followed by appropriate family counseling. Here we highlight families with renal cysts and diabetes, renal coloboma and Fraser syndromes, and a child with microdeletion of chromosome 19q who had a rare combination of malformations. Such diagnoses provide families with often long-sought answers to the question “why was our child born with kidney disease”. Precise genetic diagnoses will also help to define cohorts of children with RTMs for long-term clinical outcome studies.

Keywords Deletion · Gene · Mutation · Malformation · Renal tract

Introduction

Children with renal tract malformations (RTMs) constitute a large part of the clinical practice of pediatric nephrologists and RTMs also account for about 40% of children with end-stage renal failure (ESRF) [1–3]. RTMs also contribute to adult ESRF populations where they may be under- or mis-diagnosed, for example appearing in categories such as “tubulo-interstitial disease” and “unknown” [4]. As recently reviewed [5], the term “RTM” covers three main types of kidney malformation: (1) agenesis, where the embryonic kidney fails to initiate; (2) dysplasia, where the kidney contains immature and metaplastic components, and may be cystic; and (3) hypoplasia, where the kidney contains fewer glomeruli/nephrons than normal, with oligomegane-uphoria being a hypoplasia subtype with grossly enlarged nephrons [6]. Dysplastic kidneys sometimes spontaneously involute, either antenatally or in the first few years after birth [7]. This process, which is associated with marked apoptotic death of dysplastic cells [8], can result in a tiny “aplastic” kidney which has no excretory function and which is below the limit of detection on ultrasound scanning. Thus, because during routine clinical practice one cannot directly examine a kidney, agenesis and aplasia cannot be distinguished in an individual unless the results of previous imaging are available that show the involution of a (previously visible) dysplastic kidney.

Kidney malformations are often accompanied by lower tract anomalies, an association readily understood when it is appreciated that the kidney and ureter both arise from a single embryonic structure, the metanephric kidney rudiment.
Furthermore, impairment of fetal urine flow from functional or anatomical lower tract obstruction distorts the shape of the fetal kidney and perturbs its differentiation [10, 11]. Neither of these insights, however, explain why the primary anomaly in the kidney or lower tract occurred in the first place. Perhaps environmental factors outside the renal tract can perturb its development. Indeed, animal studies show that embryonic exposure to altered (low protein) maternal diet, or high concentrations of vitamin A metabolites or corticosteroids can variously cause renal agenesis [12], cystic dysplasia [13], and hypoplasia [14]. However, the relevance of these observations to human RTMs is unclear.

A second category of primary insult might be genetic. Approximately 20 years ago, investigators provided proof-of-principle that aberrant human kidney differentiation could be caused by mutation of a gene normally active in the maturing kidney. This was the discovery of the cause of the WAGR (Wilms' tumor, aniridia, genitourinary anomalies and mental retardation) syndrome where both the Wilms tumor 1 (WT1) gene and its next-door-neighbor on chromosome 11p13-p12, Paired box 6 (PAX6), are deleted. Both genes code for transcription factor proteins, which themselves control the expression of yet other genes. WT1 is expressed in metanephrine cells which will form glomeruli [15, 16], and also in the gonad, while PAX6 is expressed in the developing eye. With hindsight, the biology of WT1 has proved to be more relevant in understanding the biology of human kidney tumors and normal differentiation podocyte and testis differentiation (e.g. in the context of Denys-Drash syndrome) [17] rather than RTMs. Indeed, WT1 mutations have yet to be reported in individuals with renal agenesis, dysplasia, or hypoplasia.

A second breakthrough is more pertinent to our current topic. This was the 1995 report [18] that mutations of another transcription factor gene, called PAX2, itself normally expressed both in developing ureters and nephrons [16], were associated with renal hypoplasia and vesico-ureteric reflux (VUR). Since the link between PAX2 mutations and RTMs was made, numerous other genes have been reported to be mutated in individuals with RTMs, often occurring in the context of multi-organ malformation syndromes. For details of these syndromes, the interested reader is directed to the constantly updated Web resource called Online Mendelian Inheritance in Man [19]. Several RTM syndromes are summarized in tables found in previous reviews [20, 21] and in the current paper (Table 1). It has become apparent that Hepatocyte nuclear factor 1B (HNF1B; also known as TCF2) is an important human RTM gene, and accordingly it is discussed in detail, below.

### A genetic RTM clinic

In 2006, two of the authors (A.S.W., a nephrologist, and R.C.H., a clinical geneticist) initiated a joint clinic at Great Ormond Street Hospital NHS Trust, London, UK, aiming to provide genetic diagnoses and counseling for children in the following categories: (1) a child with a RTM accompanied by syndromic features such as neuro-developmental delay, external dysmorphology, and malformations of non-renew tract internal organs; and/or (2) a child with RTM with one or more siblings and/or a parent with a RTM. The clinic was established as a clinical service rather than a research clinic. Therefore, the physicians generally only had access to mutation testing services at their own hospital (specifically, comparative genomic hybridization by microarray which became available in 2008) [22] or tests available through the UK Genetic Testing Network [23].

Between 2006 and 2009, 91 new referrals (mostly from pediatric nephrologists and urologists) were assessed, from

| Gene (syndrome) | Genetic mechanism | Type of RTM | Manifestations other than RTMs |
|-----------------|-------------------|-------------|--------------------------------|
| **PAX2 (renal coloboma syndrome)** | Autosomal dominant | Renal hypoplasia (also renal dysplasia and VUR) | Visual acuity defects with optic disc coloboma (also sensorineural hearing loss, Arnold Chiari malformation, seizures and joint laxity) |
| **HNF1B (Renal cysts and diabetes syndrome)** | Autosomal dominant | Renal dysplasia, usually with cysts (also glomerulocystic disease, renal hypoplasia and hydonephrosis) | Diabetes mellitus, hyperuricemia and gout, hypomagnesemia and uterus malformations (and possibly chromophobe renal tumor) |
| **KAL1 (X-linked Kallmann syndrome)** | X-linked recessive | Renal agenesis (also renal dysplasia) | Anosmia and hypogonadotrophic gondadism (also high arched palate, pes cavus, and synkinesia) |
| **EYA4/SIX1 (branchio-oto-renal syndrome)** | Autosomal dominant | No typical manifestation but can include: renal agenesis, renal dysplasia, and calyceal cysts/diverticula | Pre-auricular pits, branchial fistulae, and deafness |
| **FRAS/FREM2 (Fraser syndrome)** | Autosomal recessive | Renal agenesis | Cryptophthalmos, syndactyly, abnormal genitalia, laryngeal malformations, and anal stenosis |
68 families. These numbers exclude observations of parents, undertaken when clinically appropriate. Twenty-seven children could be assigned to a recognized genetic syndrome and/or were found to have a mutation considered to be the cause of the RTM. The clinical stories behind several of these families are given below. Of these 27, the most common diagnosis was RTM associated with \textit{HNF1B} mutation (nine cases, excluding three parents also found to carry a mutation).

In the remaining 64 referrals, no specific genetic or syndromic diagnosis could be made and these included three families with two brothers affected by posterior urethral valves, several families with inherited non-syndromic primary VUR and several other index cases with “unique” combinations of malformations of several organ systems in which microarray analyses were normal.

**RTMs with \textit{HNF1B} mutations**

\textit{Family 1} At fetal ultrasonography (US) screening a Caucasian female presented with a unilateral (left) multicystic dysplastic kidney (MCDK). In the first few postnatal years, this involuted, and isoencephalyography indicated that the contralateral kidney was functional and normal in shape. This kidney failed to “hypertrophy”, a normal response in healthy solitary functioning kidneys [21], with its length remaining in the normal age-matched range [24]; moreover, it was echobright on US. In the first decade, glomerular filtration rates (GFRs) were 60–70 ml/min/1.73 m² and transaminases were increased to twice the upper normal limit. Aged 11 years, she experienced weight loss and polyuria and was found to have blood glucose of 30 mM but without ketoacidosis. She was commenced in insulin and control of her diabetes mellitus was considered good. One year later she presented with gastroenteritis, severe volume depletion, and acute renal failure, requiring several weeks of peritoneal dialysis, with a subsequent return to her baseline GFR after this episode of acute tubular necrosis in the solitary kidney. She has not had more than 1+ of proteinuria on dipstick testing. At the age of 13 she complained of abdominal pain; this was caused by hematocolpos, itself considered to be secondary to an imperforate hymen with overtly normal uterine structure. She has a heterozygous mutation (c.810-2A>C/N) in intron 3 of \textit{HNF1B} predicted to result in aberrant splicing. Both her mother and father were found to have normal renal US. Her mother had a normal \textit{HNF1B} sequence but the father’s DNA has not been analyzed.

\textit{Family 2} A Caucasian sister and brother from separate pregnancies had strikingly similar presentations, each with an antenatal (middle trimester) US diagnosis of left MCDK with the contralateral kidney found postnatally to be of normal shape and size but echobright. Each child had a mildly impaired GFR. Neither had proteinuria or glycosuria on dipstick testing. When they were 8 and 5 years old, each was found to have mild bilateral sensorineural hearing deficits. At this time, the sister was noted to have a plasma magnesium of 0.61 mM (lower end of normal range being 0.66 mM) and the brother’s level was 0.55 mM. Both have a heterozygous \textit{HNF1B} mutation (c.544+3_c.544+6delAAGT/N) at the intron 2 splice donor site. The same mutation is carried by their father who, although he has an overtly normal renal US in his fourth decade, has a history of recurrent acute gout treated with allopurinol. None of these individuals (yet) have diabetes mellitus.

Families 1 and 2, both listed in the large cohort outlined by Adalat et al. [25], demonstrate several clinical features associated with \textit{HNF1B} mutations. The gene, located on chromosome 17q12, codes for a transcription factor expressed in kidney epithelia [26] where it controls the expression of numerous other genes which themselves encode proteins involved in cell growth, maturation, and physiology [27]. The developmental disease is dominant (i.e. RTMs are caused by mutations of just one of the two alleles) and mutations, especially whole gene deletions, can arise de novo or be inherited. In 21 children with \textit{HNF1B} mutations and RTMs, Adalat et al. [25] noted that all RTMs had been evident on antenatal US screening, usually presenting as enlarged kidneys. Postnatally, there was a dramatic spectrum of anatomical severity reflected in a wide range of GFRs (8–113 ml/min/1.73 m²). The cohort contained 12 cases with whole gene deletions and nine individuals with various other mutations (e.g. frame shift, splice-site, etc.) detected on direct sequencing. There was, however, no obvious correlation of type of mutation with severity of RTM. As evident from this and other series [28–32], the spectrum of RTMs associated with \textit{HNF1B} mutations include MCDK, cystic dysplastic kidneys, a polycystic phenotype associated with glomerular cysts, as well as lower tract anomalies such as hydrenephrosis.

\textit{HNF1B} mutations have been described in the “renal cysts and diabetes” (RCAD) syndrome [28], and the index case in Family 1 fits this description. However, it is important to note that only a minority of children with \textit{HNF1B} mutations and RTMs have diabetes mellitus and, furthermore, not all their RTMs contain cysts evident on US [25]. When diabetes occurs in mutation carriers, it can manifest as maturity onset diabetes of the young (MODY) type 5, characterized by C-peptide being persistently detectable and a lack of pancreas autoantibodies [33]. As in Family 1, the diabetes typically begins in adolescence [25, 33] and it can also appear after renal transplantation, presumably triggered by combinations of stress, and glucocorticoid and/or tacrolimus therapies [34, 35]. \textit{HNF1B} is normally expressed in the developing pancreas [26] and...
mutations can cause pancreas hypoplasia and exocrine, as well as endocrine, insufficiency [32, 36]. Offspring of mothers with diabetes mellitus have long been recognized to have an increased risk of various malformations, probably including RTMs [37]. This relationship has been interpreted as a teratogenic effect of glucose, a contention supported by experiments showing that hyperglycemia perturbs metanephric development [38]. However, given that HNF1B controls both kidney and pancreas maturation, inherited HNF1B mutations provide another explanation for the occurrence of maternal diabetes and RTM in offspring.

Other variable features associated with HNF1B mutations are hypomagnesemia [25, 32] (manifest in Family 2), hyperuricemia and/or gout [32, 39] (manifest in Family 2) and female genital tract structural anomalies [29, 40] (possibly manifest in Family 1). Both siblings with HNF1B mutations in Family 2 have mild sensorineural deafness and perhaps this is yet another new feature of the syndrome. Indeed, we note that the gene is implicated in the formation of the internal ear in zebrafish [41]. There also exist reports of chromophobe renal cancers arising in adult kidney of mice [42]. A broader spectrum of disease may occur in individuals with HNF1B mutations where a deletion extends [43] to putatively disrupt adjacent genes with other functions. Raile et al. [33] noted that such mutations could be associated with severe developmental delay, coloboma, and cataract.

Family 3 A boy of Pakistani descent had a third trimester diagnosis of an unspecified renal tract anomaly and presented in the first postnatal months with fever and vomiting when US showed small, echobright kidneys with cortical cysts, compatible with renal cystic dysplasia. Cystography showed bilateral VUR but there was no scarring.

A caveat is that not all HNF1B variants are necessarily implicated in the pathogenesis of RTMs. This is illustrated by Family 3 where structural renal anomalies in the index case and his father segregated with a mis-sense change. However, the variant allele was not present in the proband’s brother who also had an RTM. Indeed, the leucine substitution is predicted to have minimal or no effect on protein function, and the same heterozygous variant was found in 3/151 ethnically matched controls [25]. Thus one can view the variant as incidental or perhaps as a polymorphism which determines the severity or type of RTM.

RTMs and PAX2 mutations

Family 4 A Caucasian female neonate with respiratory distress was incidentally noted to have an elevated plasma creatinine concentration (178 μM) 3 days after birth. She was the product of a pregnancy complicated by gestational diabetes mellitus. Antenatal US was reported as normal but scanning soon after birth showed that both kidneys were echobright and small, compatible with a diagnosis of bilateral renal hypoplasia. By 3 months of age, she appeared to have abnormal vision on the basis of lack of eye contact and abnormal eye movements. This impression was confirmed by finding abnormal visual evoked responses, consistent with post-retinal dysfunction, and the discovery of bilateral optic disc colobomas. A provisional diagnosis of renal coloboma syndrome was made and subsequently a heterozygous mutation was identified in PAX2 comprising a duplication (c.221_226dupAGACCG) in exon 3 leading to an insertion of two amino acids (p.T75_G76insET). At 1 year of age, she had significant proteinuria with urine albumin/creatinine ratio of 77 mg/mmol (upper normal limit, 9 mg/mmol). She was treated with Enalapril, with albuminuria falling to 37 mg/mmol. At 16 months, her GFR was 61 ml/min/1.73 m². Her brother has normal renal US and normal fundoscopy. The father of the index case has a “slightly anomalous optic disc” in the left eye but has no visual impairment; his PAX2 gene and renal tract have yet to be investigated.

The renal coloboma (also called papillorenal) syndrome is characterized by hypoplastic kidneys and optic nerve anomalies (OMIM). As first reported by Sanyanusin et al. [18], it is caused by dominant mutations of PAX2, a gene located on chromosome 10q24.3-q25.1 which is expressed in the developing eye, ear, midbrain/hindbrain, and kidney [16, 43]. In the metanephros, PAX2 acts as a survival factor, protecting epithelia from premature apoptotic death [44]. Eye disease associated with PAX2 mutation can be severe, leading to significantly compromised vision [45], as found in the index case in Family 4. However, eye symptoms and signs may be subtle, with essentially normal visual acuity and minimal changes in the optic disc when assessed by fundoscopy [6, 45–47]. Thus, it is possible that the father of the index case in Family 4 may carry a PAX2 mutation.

The characteristic RTM in the renal coloboma syndrome is bilateral renal hypoplasia [6, 48, 49]. Although this is technically a histological diagnosis (i.e. finding too few nephrons/per kidney), it is compatible with US visualization of two normally shaped kidneys which are significantly
shorter than the age-matched lower limit [24]. Furthermore, a hypoplastic kidney (unlike, for example, a MCDK) retains some function when assessed by renal isotope scanning. On the other hand, not all cases of bilateral hypoplasia have PAX2 mutations [6]. As with the case in Family 4, the RTM can be accompanied by proteinuria [48] and progressive renal failure and ESRD can occur [49]. Notably, Quinlan et al. [50] reported that a common polymorphism of PAX2 is inversely associated with kidney size in otherwise healthy neonates, suggesting that minor changes in activity of this gene are one of the (probably many) factors that determine kidney size and perhaps even nephron number/kidney which itself shows considerable variation in normal populations [51]. PAX2 mutations have also been found in individuals with cystic dysplastic kidneys [48, 52]. While VUR featured prominently in the first family found to have a PAX2 mutation [18], VUR has subsequently been noted in only a small proportion of individuals with PAX2 mutations [48, 49]. While PAX2 seemed a good candidate gene to explain familial, non-syndromic VUR, neither PAX2 mutations [53] nor association with polymorphisms within the gene [54] have been found in such families.

Other syndromes associated with human RTMs

Family 5 A Caucasian female child was born to a mother whose previous pregnancy was terminated at 4 months gestation, following US detection of oligohydramnios with an autopsy showing bilateral renal agenesis. In the pregnancy leading to the current birth, the fetus was noted to have a solitary, pelvic kidney, and this was confirmed by scans postnatally. The child also had a laryngeal web with subglottic stenosis, bilateral upper eyelid colobomas, increased distance between the medial canthi of the eyes (telecanthus) which were in part fused to the conjunctivae, an absence of eyelashes on lower lids, narrow face, narrow nasal bridge, thin lips, short philtrum, posteriorly rotated and protruding ears, aplasia cutis (absence of a portion of skin) in the occipital area with fine hair elsewhere on the head, thin lips, tongue-tie, crowded teeth, speech delay, a narrow thorax with extra nipple, small nails, clinodactyly of the fifth finger, bilateral pes cavus, and dry skin. In the first years of life he suffered recurrent chest infections and wheezing. Although prenatal US had not reported a RTM, postnatal imaging revealed bilateral short, echogenic kidneys with the left side contributing 87% function. Between 7 and 11 years of age, his plasma creatinine concentration increased from 106 to 336 µM, and urinary albumin/creatinine ratio increased from 46 to 149 mg/mmol. Microarray analysis demonstrated abnormal male karyotype with a cryptic deletion of chromosome 19 with breakpoints at 19q12 and 19q13.12. (i.e. 46 X,Y.ish del (19) (q12q13.12)). The boy’s mother was found to have a normal microarray result but the father has not yet been tested.

Several of the dysmorphic features of the index case in Family 6 resemble those in two previous reports [63, 64] of four individuals with deletions at a similar locus. Transient perinatal hydronephrosis was noted in the affected del(19) (q12q13.1) individual reported by Kulharya et al. [63] whereas renal features were not specifically mentioned in the three individuals described by Malan et al. [64]. Deletions of which genes in the critical regions are responsible for the renal, and other, manifestations remain to be elucidated.
Conclusions and future directions

Our impressions were that families appreciated having specific genetic diagnoses made even if these have yet not led to specific treatments for the RTMs themselves. Such diagnoses provided families with often long-sought answers to the question “why was our child born with kidney disease”. After finding a mutation of HNF1B, one can inform carriers of the increased risk of diabetes and they can attempt to avoid exacerbating factors such as obesity. In addition, such patients can be screened for hypomagnesemia to detect, and treat, this deficiency before they become symptomatic. Precise genetic diagnoses will also help to define cohorts of children with RTMs for long-term clinical outcome studies. As examples: (1) do children with unilateral MCDKs and solitary functioning kidney associated with HNF1B mutations have a better, or worse, renal prognosis versus unilateral MCDK without such a mutation?; and (2) do children with renal hypoplasia and PAX2 mutations have a different risk of proteinuria and progression to ESRF versus those with renal hypoplasia but lacking PAX2 mutations? Parents also appreciated the opportunity to discuss in detail the possible pathogenesis of RTMs even if no definitive genetic diagnosis could yet be made in their own family. An example is the kindred described by Kerecuk et al. [65] with autosomal dominant inheritance of non-syndromic renal hypoplasia and dysplasia but no mutations found in HNF1B or PAX2.

A technical limitation of such a (non-research) clinic is that few genetic tests relevant to the diagnosing RTMs are as yet available on the UK Genetic Testing Network [23]. On the other hand, the network did provide access for testing for HNF1B mutations, and this proved to be an invaluable resource. In the longer term, one could envisage that all children with RTMs may be tested for mutations in a range of “nephrogenesis genes”. One research study that has begun to take this approach was described by Weber et al. [31] who found variants of both PAX2 and SIX1 in such individuals. Similar considerations apply to deciding whether to screen for RTMs (and then test for mutations) in siblings and/or parents of index cases. In Family 2, where the father of two children with MCDKs shared their HNF1B mutation yet had a normal renal US, his genetic disease manifested as gout. For these reasons, we suggest that such screening should be undertaken with nephrologists (ideally both pediatric and adult) and clinical geneticists working closely together.

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Multiple choice questions

(Answers appear following the reference list)

(one correct answer indicated for each question)

Question 1.

A. Renal tract malformations (RTMs) account for nearly all children with end-stage renal failure (ESRF).
B. RTMs are found in about 40% of children with ESRF.
C. There is only one histological type of kidney malformation.
D. Lower renal tract anomalies rarely occur in the same individual who has a kidney malformation.

Question 2.

A. Individuals with HNF1B mutations always have both renal cysts and diabetes mellitus.
B. Individuals with HNF1B mutations can present with diabetes mellitus after renal transplantation
C. HNF1B mutations never occur de novo.
D. HNF1B mutations always lead to renal failure in the first decade of life.

Question 3.

A. Eye disease associated with PAX2 mutations may be minimal despite the presence of a RTM.
B. The most common renal manifestation of PAX2 mutation is vesicoureteric reflux.  
C. PAX2 mutations are not associated with proteinuria.  
D. Most children with renal hypoplasia have PAX2 mutations.

Question 4.
A. Making a genetic diagnosis in a child with a RTM has no relevance to the wider family.  
B. Genetic diagnosis in children with RTMs ideally requires close liaison between the Nephrology and Clinical Genetics teams.  
C. The genetic basis for non-syndromic VUR is well-established.  
D. The mature human kidney arises from an embryonic structure called the mesonephros.

Question 5.
A. Solitary functioning kidneys never lead to renal impairment.  
B. The severity of RTM in members of the same family with inherited PAX2 or HNF1B mutations does not vary.  
C. Renal hypoplasia and renal dysplasia mean the same thing.  
D. Pediatric Nephrologists should examine children with RTMs for extra-renal manifestations.

Question 6.
A. In Fraser syndrome, the characteristic RTM is a multicystic dysplastic kidney.  
B. Fraser syndrome usually does not short life-span.  
C. Microarray analysis may find genetic lesions in children with RTMs accompanied by syndromal features such as developmental delay, dysmorphism and multi-organ involvement.  
D. Branchio-oto-renal syndrome is autosomal recessive.

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Answers:

1. B
2. B
3. A
4. B
5. D
6. C