Genetic approaches to human renal agenesis/hypoplasia and dysplasia

Simone Sanna-Cherchi · Gianluca Caridi · Patricia L. Weng · Francesco Scolari · Francesco Perfumo · Ali G. Gharavi · Gian Marco Ghiggeri

Received: 24 November 2006 /Revised: 26 January 2007 /Accepted: 26 January 2007 /Published online: 17 April 2007
© IPNA 2007

Abstract Congenital abnormalities of the kidney and urinary tract are frequently observed in children and represent a significant cause of morbidity and mortality. These conditions are phenotypically variable, often affecting several segments of the urinary tract simultaneously, making clinical classification and diagnosis difficult. Renal agenesis/hypoplasia and dysplasia account for a significant portion of these anomalies, and a genetic contribution to its cause is being increasingly recognized. Nevertheless, overlap between diseases and challenges in clinical diagnosis complicate studies attempting to discover new genes underlying this anomaly. Most of the insights in kidney development derive from studies in mouse models or from rare, syndromic forms of human developmental disorders of the kidney and urinary tract. The genes implicated have been shown to regulate the reciprocal induction between the ureteric bud and the metanephric mesenchyme. Strategies to find genes causing renal agenesis/hypoplasia and dysplasia vary depending on the characteristics of the study population available. The approaches range from candidate gene association or resequencing studies to traditional linkage studies, using outbred pedigrees or genetic isolates, to search for structural variation in the genome. Each of these strategies has advantages and pitfalls and some have led to significant discoveries in human disease. However, renal agenesis/hypoplasia and dysplasia still represents a challenge, both for the clinicians who attempt a precise diagnosis and for the geneticist who tries to unravel the genetic basis, and a better classification requires molecular definition to be retrospectively improved. The goal appears to be feasible with the large multicentric collaborative groups that share the same objectives and resources.

Keywords Renal agenesis/hypoplasia and dysplasia · Gene mapping · Linkage analysis · Association studies · Structural variants

Introduction and definition

Congenital abnormalities of the kidney and urinary tract are frequently observed in the first year of life, when they collectively represent a significant cause of morbidity [1] and mortality. Data from birth defects registries [Metropol-
Primary renal hypoplasia and dysplasia

Strictly speaking, renal hypoplasia is defined as a small kidney, which contains intact nephrons that are reduced in number, whereas a dysplastic kidney contains disorganized elements and maldifferentiated tissue. Noninvasive imaging studies such as ultrasounds and dimercaptosuccinic acid (DMSA) scan offer limited information to help distinguish a hypoplastic kidney from a dysplastic one. Unequivocal distinction between these two entities therefore depends on histological examination of renal tissue obtained from kidney biopsy or surgical nephrectomy, which are rarely performed. A further confounding factor is the reduction of kidney size due to chronic injury and scarring from VUR.

Most of the time, a DMSA scan helps differentiate primary hypoplasia or dysplasia from small kidneys secondary to VUR. However, a DMSA scan has a low negative predictive value in distinguishing primary hypoplasia or dysplasia from a secondary reduction in kidney size from VUR when scars or areas of negative isotope uptake are present. In practice, the diagnosis of primary renal hypoplasia is favored when the following criteria are satisfied: (a) a reduction of renal size by 2 standard deviations (SDS) from the mean size for the age, (b) exclusion of renal scarring by DMSA scan, and (c) a presence of compensatory hypertrophy of the contralateral kidney. In all cases, the exclusion of renal cysts by ultrasonography is mandatory to avoid confusion with primary renal hypoplasia associated with fibrosis and cysts, nephronophthisis being the most pertinent example. The presence of VUR and/or ureteropelvic junction obstruction (UPJO) does not automatically exclude the diagnosis of hypoplasia, as both conditions are frequently associated with primary renal-size defects. It is clear that this problem is difficult to resolve if the ureteral defect presents ipsilateral to renal hypoplasia. For example, severe antenatal hydronephrosis due to UPJO can determine the involvment of the renal parenchyma and lead to an erroneous diagnosis of primary renal agenesis after birth. In bilateral cases, syndromic traits as well as inherited disorders such as medullary cystic kidney disease/nephronophthisis have to be excluded. Unequivocal exclusion of renal dysplasia is usually not feasible except in rare cases for which histology is available. It is possible that in the near future, molecular genetic advances could modify our present understanding and allow for a more direct separation of the two pathological entities based on laboratory tests.

These challenges in clinical diagnosis of renal hypoplasia complicate studies attempting to discover new genes underlying this anomaly. For research purposes, we utilize a tentative classification scheme for categorizing our subjects for genetic studies: (1) isolated bilateral hypoplasia/dysplasia, (2) isolated unilateral hypoplasia/dysplasia, and (3)
hypoplasia/dysplasia associated with lower tract abnormalities such as VUR or UPJO. Once the genetic basis of different subsets of urinary tract malformations is identified, the classification will likely be retrospectively changed and improved.

**Kidney development and mouse models**

The development of mammalian kidney derives from reciprocally inductive events between two tissue compartments of the embryonic metanephros: the ureteric bud (UB), an outgrowth of the nephric duct, and the MM. The ureteric bud invades the metanephric blastema at embryonic day 10.5–11 in the mouse and 35–37 in humans. The MM induces the ureteric bud to grow and branch while the ureteric bud induces the MM to transdifferentiate and form the nephrons’ epithelia (see recent reviews in kidney development in human and mice [7, 8]).

In recent years, many factors, specific for either the UB or the MM, have been demonstrated to induce and regulate the epithelial conversion in the mesenchymal cells and the UB branching, leading to the development of the final structure and function of the kidney. Most data constituting the basis of our current knowledge on the topic are based on gene targeting studies in mice (Table 1). A partial list of genes includes protooncogenes RET and Wingless-related 11 (WNT11) that are well recognized UB-specific molecules, whereas glial cell-line-derived neurotrophic factor (GDNF), Wilms tumor 1 (WT1), and Eyes absent 1 (EYA1) represent important examples of MM-specific factors. The paired-box gene 2 (PAX2) appears to be expressed in both structures during kidney development [7, 9]. It is noteworthy that almost half of the genes on the list are transcriptional factors or encode for proteins that are involved in the mesenchymal to epithelial conversion. GDNF signaling through the RET receptor is one of the best studied pathways, representing a critical step in the normal growth and branching of the UB during kidney development [10]. Perturbation of Gdnf/Ret signaling has been shown to be the downstream mechanism underlying impaired nephrogenesis in many other mutant models (e.g., in Gdf11 and Six1 null mice). Numerous factors other than the Gdnf/Ret pathway also participate in kidney and urologic development (e.g. Wnt signaling), as evidenced by the long list of mutant mice with malformations in the kidney and urologic tract (Table 1).

The interdependence between developmental pathways explains why defects in different genes result in similar phenotypes and why morphologic classification of abnormal-

---

**Table 1** Principal genes targeted in mice leading to renal agenesis, hypoplasia, dysplasia

| Gene      | Human homolog | Kidney phenotype                        | Reference          |
|-----------|---------------|-----------------------------------------|--------------------|
| Foxd1     | FOXD1         | Small, fused, undifferentiated kidneys   | Hatini et al. [59] |
| Eya1      | EYA1          | Absent kidneys                          | Johnson et al. [60]|
| Eya1      | EYA1          | Absent kidneys                          | Xu et al. [61]     |
| Eya1      | EYA1          | Absent kidneys                          | Miyamato et al. [62]|
| Hoxa11     | HOXA11/HOXD11 | Small or absent kidneys                  | Davis et al. [63]  |
| Lhx1      | LHX1          | Absent kidneys                          | Shawlot and Behringer [64] |
| Pax2      | PAX2          | Small or absent kidneys                  | Torres et al. [65] |
| Wt1       | WT1           | Absent kidneys                          | Kreidberg et al. [66] |
| Agrt2     | AGTR2         | Multiple urinary tract malformations     | Nishimura et al. [67] |
| Bmp4      | BMP4          | Altered ureteric bud (UB) branching      | Miyazaki et al. [68] |
| Bmp7      | BMP7          | Disrupted nephrogenesis                  | Dudley et al. [69] |
| Wnt4      | WNT4          | Undifferentiated kidneys                 | Stark et al. [70]  |
| Ret       | RET           | Absent kidneys, severe dysgenesis        | Schuchardt et al. [71] |
| Gdnf      | GDNF          | Absent kidneys, severe dysgenesis        | Sanchez et al. [72] |
|           |               |                                         | Moore et al. [73]  |
|           |               |                                         | Pichel et al. [74] |
| Six1      | SIX1          | Absent kidneys                          | Xu et al. [75]     |
| Six2      | SIX2          | Small kidneys                           | Self et al. [76]   |
| Sall1     | SALL1         | Absent kidneys                          | Nishinakamura et al. [77] |
| Fgfr1/Fgfr2| FGFR1/FGFR2  | Absent kidneys                          | Poladia et al. [78] |
| Slt3      | SLIT3         | Small or absent kidneys                  | Liu et al. [79]    |
| Pbx1      | PBX1          | Small or absent kidneys                  | Schnabel et al. [80] |
| Fgf8      | FGF8          | Small kidneys                           | Perantoni et al. [81] |
| Rara/Rarb2| RARA/RARB2   | Small kidneys                           | Mendelsohn et al. [82] |
| Lim1      | LIM1          | Absent kidneys                          | Kobayashi et al. [83] |

---
ities alone cannot predict the location or nature of primary defects. Available data thus suggest a large list of candidate genes for human renal and urologic malformations, highlighting the potential for genetic heterogeneity of the trait.

**Genetic contribution to human renal agenesis/hypoplasia and dysplasia**

A genetic contribution to the development of renal hypoplasia/dysplasia has been recognized for many years. For the isolated, nonsyndromic renal agenesis/hypoplasia and dysplasia, only segregation studies have been performed, and no loci and/or genes have been mapped so far. Much more is known about rare syndromic forms, for which several genes have been already implicated.

**Syndromic forms**

Syndromic forms of renal hypoplasia/dysplasia include rare disorders affecting extrarenal organs such as the eye, the central nervous system, the skin, the limbs, and others. The list of syndromes that include the renal agenesis/hypoplasia/dysplasia phenotype consists of at least 73 clinical conditions (for more details, see Limwongse and Cassidy [11]). Several genes underlying these defects have been identified (Table 2). Renal-coloboma syndrome, orofaciocutaneous syndrome, branchiooto-renal syndrome, renal cysts and diabetes syndrome, and Fraser syndrome are the most frequent syndromes associated with renal parenchymal defects. It seems clinically relevant that the renal abnormalities may represent the first manifestation of the disease, thus requiring a detailed evaluation of other organs. A list of extrarenal signs and symptoms that clinicians should look for to define these syndromes include retinal coloboma [4], deafness, external ear abnormalities including cysts and fistulas [12, 13], anus imperforates and limb and ear anomalies [14], diabetes and renal cystic dysplasia [15], and others. Finally, renal agenesis/hypoplasia is frequently part of chromosomal disorders (Table 3) that must be recognized for genetic counseling. Most common syndromes that should be considered in the initial differential diagnosis are listed in Tables 2 and 3, and we suggest referring to popular Web sites for further details (links provided at the end).

| Gene       | Human syndrome                          | Kidney phenotype                                      | OMIM      |
|------------|-----------------------------------------|-------------------------------------------------------|-----------|
| JAG1, NOTCH2 | Alagille syndrome                      | MCDK, kidney dysplasia, kidney mesangioliopidosis      | #118450   |
| BBS1-BBS11 | Bardet-Biedl syndrome                   | Renal dysplasia and calyceal malformations            | #209900   |
| EYA1, SIX1, SIX2 | Branchiooto-renal syndrome          | Renal agenesis/dysplasia                              | #113650   |
| SOX9       | Campomelic dysplasia                   | Diverse renal malformations                           | #114290   |
| CHD7       | CHARGE syndrome                        | Diverse urinary tract malformations                   | #214800   |
| Del. 22q11 | Di George syndrome                     | Renal agenesis, dysplasia, VUR                        | #188400   |
| GATA3      | Hypothyroidism, sensorial deafness, renal anomalies (HDR) | Renal agenesis, dysplasia, VUR                      | #146255   |
| DNA repair | Fanconi anemia                          | Renal agenesis                                        | #227650   |
| FRAS1, FREM2 | Fraser syndrome                        | Renal agenesis, dysplasia                              | #219000   |
| KALL1, FGFR1 | Kallman’s syndrome                     | Renal agenesis, dysplasia                              | #308700, #147950 |
| PAX2       | Renal coloboma syndrome                | Renal hypoplasia, MCDK, VUR                            | #120330   |
| TCF2       | Renal cysts and diabetes syndrome      | Renal dysplasia, cysts                                | #137920   |
| GPC3       | Simpson-Golabi-Behmel syndrome         | Renal dysplasia, cysts                                | #300209   |
| DHCR7      | Smith-Lemli-Opitz syndrome             | Renal dysplasia, cysts                                | #270400   |
| SALL1      | Townes-Brocks syndrome                 | Renal dysplasia, lower urinary tract malformations     | #107480   |
| LMX1B      | Nail-patella syndrome                  | Glomerulus malformation, renal agenesis              | #161200   |
| NIPBL      | Cornelia de Lange syndrome             | Renal dysplasia                                        | #122470   |
| CREBBP     | Rubinstein-Taybi syndrome              | Renal agenesis                                        | #180849   |
| WNT4       | Rokitansky syndrome                    | Renal agenesis                                        | #277000   |
| PEX-family | Zellweger syndrome                     | Renal dysplasia, cysts                                | #214100   |
| GLI3       | Pallister-Hall syndrome                | Renal agenesis, dysplasia                              | #146510   |
| p57(KIP2)  | Beckwith-Wiedemann syndrome            | Renal dysplasia                                        | #130650   |
| SALL4      | Okhitro syndrome                      | Renal ectopia with or without fusion, lower urinary tract malformations | #607323   |
| TBX3       | Ulnar-Mammary syndrome                 | Renal agenesis                                        | #181450   |

MCDK multicystic dysplastic kidney, VUR vesicoureteral reflux
Nonsyndromic forms

It is well known that nonsyndromic renal malformations may occur as hereditary traits and can present with familial aggregation. Evidence in favor of a genetic determination of the disease is raised by an increased recurrence risk among first-degree relatives and by several reports of familial occurrence of multiple malformations, including renal agenesis/hypoplasia and dysplasia. The relative recurrence risk of bilateral and unilateral agenesis has been estimated at 4–9% [6, 16, 17]. For familial cases, in most of the pedigrees, the suggested mode of inheritance was autosomal dominant with reduced penetrance, estimated to range between 50% and 90% [16]. For example, a large pedigree with an autosomal dominant mode form of nonsyndromic renal hypoplasia and dysplasia has recently been described [18]. However, a Somali kindred in which the trait was segregating in an autosomal recessive fashion has been reported [19]. Nevertheless, until recently, no linkage studies in familial renal agenesis/hypoplasia and dysplasia have been reported. Incomplete penetrance, variable expression and the fact that anatomical defects in many family members can be clinically silent, complicate recruitment of large pedigrees that would be suitable for linkage analysis.

Strategies for gene discovery

Strategies to find genes causing renal agenesis/hypoplasia and dysplasia vary significantly depending on the characteristics of the study population available. Different data sets of patients have potential advantages and possible pitfalls.

Candidate gene studies

So far, candidate gene studies have been the only alternative to linkage analysis to find genes underlying both Mendelian and complex traits. Such studies have identified many genes causing rare genetic diseases [20] (The Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/ac/index.php) and most of the genes that are known contribute to susceptibility to common diseases [21, 22]. Large cohorts of sporadic cases or small pedigrees can be utilized in case-control association studies to find common disease associated alleles. Such cohorts can also be screened by resequencing of candidate genes to detect rare variants with large effects that account for disease in a small proportion of the patients. Selection of one approach over the other depends on the expected degree of genetic and allelic heterogeneity of the trait under investigation. Genetic heterogeneity refers to the situation where mutations in different genes account for disease in different affected individuals. Allelic heterogeneity refers to the presence of many independent mutations in a given gene. For a trait with high locus and allelic heterogeneity, the search for common disease-contributing alleles is problematic, and resources would be better directed toward comprehensive resequencing of candidate genes to discovery the rare disease-causing variants. In practice, the heterogeneity parameters are difficult to predict a priori. The resequencing approach has been successfully applied to find several genes causing kidney developmental disorders. As an example, mutations in the uroplakin III gene, which produce VUR in mice [23], explain a small fraction of human renal hypodysplasia [24–28]. Similarly, results from the ESCAPE study recently provided the first comprehensive analysis of renal developmental genes in children affected by nonsyndromic renal hypodysplasia, showing a fairly high prevalence of PAX2 and TCF2 mutations [5, 29]. Another success of the candidate gene approach is the latest discovery of mutations in genes of the renin-angiotensin system (RAS) in severe forms of renal tubular dysgenesis [30]. The search for common variants predisposing to nonsyndromic renal hypodysplasia has not been frequently applied. However, these common predisposing alleles may not be recognized until a comprehensive search is undertaken. As an example, a common noncoding variant in a RET

### Table 3 Common chromosomal disorders associated with urinary tract anomalies

| Chromosomal disorders                  | Renal agenesis | Hypoplasia | Other associated anomalies                               |
|----------------------------------------|----------------|------------|---------------------------------------------------------|
| Patau syndrome (trisomy 13)            | +              |            | Holoprosencephaly, midline anomalies, cleft lip/palate  |
| Miller-Dieker syndrome (17p13 deletion)| +              |            | MR, lissencephaly, microgyria, agyria, typical facies, seizures |
| Edward syndrome (trisomy 18) 18q deletion | +              |            | IUGR, CHD, clenched hands, rocker bottom feet SS, MR, microcephaly, narrow external ear canals, long hands |
| Down syndrome (trisomy 21)            | +              |            | MR, hypotonia, CHD, typical face, clinodactyly         |
| Catseye syndrome (tetrasomy 22p)      | +              |            | MR, CHD, colobomas, anal/digital anomalies              |
| Velocardiofacial syndrome (22q11 deletion) | +              | +          | Conotruncal CHD, thymic face, cleft palate             |
| Turner syndrome (45,X or 46,X,i(Xq))  | +              |            | SS, amenorrhea, webbed neck, cubitus valgus, hypogonadism |

MR mental retardation, IUGR intrauterine growth retardation, CHD congenital heart disease, SS short stature
 enhancer has recently been shown to be a strong risk allele for Hirschsprung disease, explaining the paucity of coding mutations found in families showing linkage to the RET locus [31].

Traditional linkage studies and genetic isolates

The genome-wide linkage analysis/positional cloning approach is a time-tested method used to identify disease-causing mutations, and it has been extremely successful in the past few decades for mapping genes that underlie monogenic Mendelian diseases [32, 33]. This approach hinges on availability of single, uniquely large pedigrees that segregate genes with large effect or a large number of small-sized pedigrees. Mutations in genes underlying Mendelian forms of disease usually account for a fraction of sporadic forms (e.g. PAX2 and TCF2).

For renal agenesis/hypoplasia and dysplasia, large pedigrees amenable for linkage analysis are very difficult to ascertain because these traits have incomplete penetrance (due to genetic and environmental modifiers). Moreover, many malformations, such as unilateral agenesis can be clinically silent and will not be detected without systematic screening of family members. As for candidate gene studies, locus heterogeneity is another potentially complicating factor that may dilute the power of linkage studies. Our previous data demonstrated that in the setting of reduced penetrance, variable expressivity, and very high genetic heterogeneity, approaches based on a limited number of uniquely large pedigrees or a very large number of medium-sized kindreds, are more likely to be successful to map a disease gene [34]. As a result of these difficulties, no linkage studies of renal agenesis/hypoplasia have been published so far. These kinds of patient cohorts are very arduous to collect and require multicenter collaborative efforts. We have been able to collect seven multigenerational extended pedigrees segregating congenital anomalies of the kidney and urinary tract, including renal agenesis/hypoplasia, as an autosomal dominant trait with reduced penetrance trait. These families allowed us to localize a gene for this trait to a ~7 Mb interval to chromosome 1p32–33 in a setting of genetic heterogeneity [35]. This work represents the first step toward the discovery of a new gene and, possibly, a new pathway, in kidney development.

Genetic isolates represent a population structure that can greatly facilitate gene identification efforts. The genetic isolates are populations that are originated from a limited group of founders with little subsequent immigration into the population. Without an inflow of genes, a long period of time would be required for spontaneous mutations to rebuild genetic diversity. Therefore, genetic isolates are likely to harbor few disease-contributing alleles that have been inherited identical by descent from common ancestors [36–38]. These ancestral mutations can be detected by searching for a shared haplotype signature in affected individuals, representing a powerful shortcut to narrow down a linkage interval to a handful of genes. This strategy, called linkage disequilibrium (LD) mapping, has allowed the identification of several genes for Mendelian disorders [39–41]. Hence, the advantages of studying a genetic isolate rely on: (a) a higher prevalence of certain diseases, allowing traits with reduced penetrance to express and show their hereditary component, (b) a more uniform genetic background, thus reducing the genetic heterogeneity, (c) usually good genealogical records, (d) a more uniform environment, and (e) the possibility of speeding up gene discovery through linkage disequilibrium mapping. We have recently characterized a genetic isolate in an Italian valley, in which different glomerular diseases occurred at a much higher prevalence compared with the general population, in apparently unrelated individuals. The genealogical reconstruction allowed us to reconnect most of the patients to a few founders up to the sixteenth century [42]. This study is an example of how an isolate can allow traits that display reduced penetrance and variable expressivity to express their genetic component and represent a first step to find genes causing or predisposing to such diseases. Further investigation of recognized population isolates for developmental disorders, especially renal agenesis/hypoplasia and dysplasia, might help to accelerate gene mapping.

Genome-wide association studies

The genome-wide association study is an approach aimed at exhaustively covering the genome to look for causative variants. Similar to genome-wide linkage studies, no assumptions are made about either the location of the causative variant or the biological role of the disease gene. Therefore, this approach represents an unbiased method to find disease-causing genes, with also a very high probability of discovering new genes, thus unraveling new pathophysiological pathways. Genome-wide association studies were not feasible until now because of the lack of information about the variability in the human genome and lack of low-cost, high-throughput genotyping technology. This situation has changed in the past 2 years: dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) now contains about 5 million SNPs, including most of the SNPs with a minor allele frequency higher than 1% estimated to exist in the human genome [43]. Moreover, the HapMap project [44] represents a fundamental advance to performing efficient and successful genome-wide studies through the determination of LD patterns and haplotype blocks across the genome. Another important step has been the tremendous improvement in genotyping technology, with the
development of platforms for fast, high-throughput, low-cost SNPs genotyping. Such platforms allow the simultaneous genotyping of 100–500,000 SNPs in a single assay, allowing a dense coverage of the human genome [45, 46]. Some examples of success of this approach have been recently published. For example, genome-wide association studies on patients affected by age-related macular degeneration allowed the individuation of a common variant in the complement factor H as a major risk-associated allele [47, 48]. Similarly, polymorphisms in the transcription factor TCF7L2 have been found to confer risk to type 2 diabetes in different populations [49, 50]. Whether genome-wide association studies will lead to significant discoveries in renal agenesis/hypoplasia and dysplasia is still unclear, but certainly, this approach represents a very promising strategy to identify common variants conferring susceptibility to more frequent, complex traits.

Search for structural variations in the genome

A number of urogenital malformations are associated with chromosomal abnormalities. For example, a deletion on chromosome 10q26 has been implicated in urogenital development [51]. Similarly, two distinct loci for renal malformations, including VUR, have been mapped to chromosome 13q by deletion mapping using microsatellites in a limited number of affected individuals [52, 53]. Advances in technology, mainly, genome-scanning array technologies and comparative DNA-sequence analyses, have identified a high prevalence of DNA variations that involve segments that are smaller than those recognized by standard cytogenetics techniques [54]. These structural variations are a common feature of our genomic landscape, encompassing deletions, duplications, inversions, and translocations, which range from a few bases up to hundreds of kilobases. These rearrangements comprise benign polymorphisms, as well as deleterious mutations that can disrupt gene structure or affect gene regulation. Newer techniques now allow for the identification of structural variation at the genome-wide level, enabling examination of single patients to rapidly define a chromosomal region (locus) of interest. Several studies have already reported structural variations associated to human disease, leading in some cases to a molecular definition of a disorder before a recognized clinical syndrome [55–57].

These technologies have also been already successfully applied to developmental disorders. A genome-wide search for structural variations using comparative genomic hybridization (CGH) array allowed the discovery of the gene CHD7 as a cause of CHARGE syndrome, a rare, complex disorder in which congenital anomalies affect in a nonrandom fashion several tissues, including the urinary tract [58]. Careful clinical selection of patients and application of genome-wide methods for searching structural variation in renal agenesis/hypoplasia and dysplasia can help find new loci linked to the disease, confirm and narrow loci obtained by linkage analysis, and speed up the discovery of causative genes.

Conclusions

Renal agenesis/hypoplasia and dysplasia still represents a challenge for both the clinicians who attempt a precise diagnosis and for the geneticists who try to unravel the genetic basis. Genetic and clinical approaches are now converging toward a common goal, which is the discovery of genetic markers, to make the diagnosis of this trait easier. The final objective is to improve classification, to make a reliable prognosis, and to attempt prevention. Based on advances from the last few years, the goal appears to be more feasible with large multicentric collaborative groups that share the same objectives and resources.

References

1. Woolf AS (2000) A molecular and genetic view of human renal and urinary tract malformations. Kidney Int 58:500–512
2. Schulman J, Edmonds LD, McClearn AB, Jensvold N, Shaw GM (1993) Surveillance for and comparison of birth defect prevalences in two geographic areas–United States, 1983–88. MMWR CDC Surveill Summ 42:1–7
3. Pope JC 4th, Brock JW 3rd, Adams MC, Stephens FD, Ichikawa I (1999) How they begin and how they end: classic and new theories for the development and deterioration of congenital anomalies of the kidney and urinary tract, CAKUT. J Am Soc Nephrol 10:2018–2028
4. Eccles MR, Schimmenti LA (1999) Renal-coloboma syndrome: a multi-system developmental disorder caused by PAX2 mutations. Clin Genet 56:1–9
5. Weber S, Moriniere V, Knuppel T, Charbit M, Dusek J, Gighieri GM, Jankauskiene A, Mir S, Montini G, Peco-Antic A, Wahli E, Zawrowska AM, Mebhs O, Antignac C, Schafer F, Salomon R (2006) Prevalence of mutations in renal developmental genes in children with renal hypodysplasia: results of the ESCAPE Study. J Am Soc Nephrol 17:2864–2870
6. Carter CO, Evans K, Pescia G (1979) A family study of renal agenesis. J Med Genet 16:176–188
7. Vainio S, Lin Y (2002) Coordinating early kidney development: lessons from gene targeting. Nat Rev Genet 3:533–543
8. Woolf AS (2004) Embryology. In: Pediatric nephrology, 5th edn. Lippincott Williams & Wilkins, Philadelphia, pp 3–24
9. Majumdar A, Vainio S, Kispert A, McMahon J, McMahon AP (2003) Wnt11 and Ret/Gdnf pathways cooperate in regulating ureteric branching during metanephric kidney development. Development 130:3175–3185
10. Costantini F, Shykay R (2006) GDNF/Ret signaling and the development of the kidney. Bioessays 28:117–127
11. Limwongse C, Clarke SK, Cassidy SB (2004) Syndromes and malformations of the urinary tract. In Barratt TM, Avner ED, Harmon WE (eds) Pediatric Nephrology. Philadelphia, USA, pp 93–121
12. Abdelhak S, Kalatzis V, Heilig R, Complain S, Samson D, Vincent C, Weil D, Cruaud C, Sahly I, Leibovici M, Bitter-Glindzicz M, Francis M, Lacombe D, Vigneron J, Charachon R, Boven K, Bedbeder P, Van Regemorter N, Weissenbach J, Petit C (1997) A human homologue of the Drosophila eye absent gene underlies branchio-oto-renal (BOR) syndrome and identifies a novel gene family. Nat Genet 15:157–164

13. Ruf RG, Xu PX, Silivus D, Otto EA, Beekmann F, Muerb UT, Kumar S, Neuhaus TJ, Kemper MJ, Raymond RM Jr, Brophy PD, Berkman J, Gattas M, Hyland V, Ruf EM, Schwartz C, Chang EH, Smith RJ, Stratakis CA, Weil D, Petit C, Hildebrandt F (2004) SIX1 mutations cause branchio-oto-renal syndrome by disruption of EYA1-SIX1-DNA complexes. Proc Natl Acad Sci U S A 101:8090–8095

14. Kohlbasse J, Wissermann A, Reichenbach H, Frister U, Engel W (1998) Mutations in the SALL1 putative transcription factor gene cause Townes-Brocks syndrome. Nat Genet 18:81–83

15. Bingham C, Bulman MP, Ellard S, Allen LI, Lipkin GW, Hoff WG, Woolf AS, Rizzoni G, Novelli G, Nicholls AJ, Hattersley AT (2001) Mutations in the hepatocyte nuclear factor-IIbeta gene are associated with familial hypoplastic glomerulocystic kidney disease. Am J Hum Genet 68:219–224

16. McPherson E, Carey J, Kramer A, Hall JG, Pauli RM, Schimke RW, Kachar B, Sun TT (2000) Ablation of uroplakin III gene haploinsufficiency reveals a role in renal and ductal morphogenesis. Proc Natl Acad Sci U S A 97:16471–16476

17. Kerecuk L, Sajoo A, McGregor L, Berg J, Haq MR, Sebire NJ, McPherson E, Carey J, Kramer A, Hall JG, Pauli RM, Schimke RW, Kachar B, Sun TT (2000) Ablation of uroplakin III gene causes renal hypodysplasia leading to severe kidney failure. J Am Soc Nephrol 16:2141–2149

18. Ostrer H, Shapiro E, Yu J, Sun TT (2004) Lack of major involvement of human uroplakins in vesicoureteral reflux: implications for disease heterogeneity. Kidney Int 66:10–19

20. Pasch A, Hoefele J, Grimminger H, Hacker HW, Hildebrandt F (2004) Multiple urinary tract malformations with likely recessive inheritance in a large Somali kindred. Nephrol Dial Transplant 19:3172–3175

21. Stenson PD, Ball EV, Mort M, Phillips AD, Shiel JA, Thomas NS, Abeyesinghe S, Krawczak M, Cooper DN, Green AJ, Puri P, Barton DE (2005) Uroplakin III is not a major candidate gene for primary vesicoureteral reflux. Eur J Hum Genet 13:500–502

22. Konka A, Murer L, Scolari F, Ravazzolo R, Ghiggeri GM, Hirschsprung disease risk. Nature 434:857–863

23. Hirschhorn NJ, Daly MJ (2005) Genome-wide association studies for common diseases and complex traits. Nat Rev Genet 6:95–108

24. Juan Neum J, Daly MJ (2005) Genome-wide association studies for common diseases and complex traits. Nat Rev Genet 6:95–108

25. Jimenez-Sanchez G, Childs B, Valle D (2001) Human disease genes. Nature 409:853–855
78. Poladia DP, Kish K, Kutay B, Hains D, Keeg H, Zhao H, Bates CM (2006) Role of fibroblast growth factor receptors 1 and 2 in the metanephric mesenchyme. Dev Biol 291:325–339
79. Liu J, Zhang L, Wang D, Shen H, Jiang M, Mei P, Hayden PS, Sedor JR, Hu H (2003) Congenital diaphragmatic hernia, kidney agenesis and cardiac defects associated with Slit3-deficiency in mice. Mech Dev 120:1059–1070
80. Schnabel CA, Godin RE, Cleary ML (2003) Pbx1 regulates nephrogenesis and ureteric branching in the developing kidney. Dev Biol 254:262–276
81. Perantoni AO, Timofeeva O, Naillat F, Richman C, Pajni-Underwood S, Wilson C, Vainio S, Dove LF, Lewandoski M (2005) Inactivation of FGF8 in early mesoderm reveals an essential role in kidney development. Development 132:3859–3871
82. Mendelsohn C, Lohnes D, Decimo D, Lufkin T, LeMeur M, Chambon P, Mark M (1994) Function of the retinoic acid receptors (RARs) during development (II). Multiple abnormalities at various stages of organogenesis in RAR double mutants. Development 120:2749–2771
83. Kobayashi A, Kwan KM, Carroll TJ, McMahon AP, Mendelsohn CL, Behringer RR (2005) Distinct and sequential tissue-specific activities of the LIM-class homeobox gene Lim1 for tubular morphogenesis during kidney development. Development 132:2809–2823

Web resources

National Center for Biology Information. Online Mendelian Inheritance in Man (OMIM). http://www.ncbi.nlm.nih.gov/Omim/
March of Dimes. http://www.marchofdimes.com
Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff (2006) http://www.hgmd.cf.ac.uk/ac/index.php
National Center for Biology Information. dbSNP database. http://www.ncbi.nlm.nih.gov/projects/SNP/
International HapMap Project. http://www.hapmap.org/