

Genetics of Kidney Disease

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● Perhaps nothing in the fields of medicine and nephrology is moving more rapidly than genetics. From this movement are opportunities for discovery, new therapy, and better counseling for patients. At a level of basic science, renal medicine has been a consistent contributor to this emerging discipline, but our current approach to training in the methods and uses of human genetics probably will not keep up with the technology, nor the needs of the modern bedside practitioner. The facile use of genetics in the next century will require the construction and exploration of new disease models, rededication to human informatics, and teaching the language of molecular and population genomics.

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DURING THE PAST two decades, breakthroughs in molecular biology and genetics have set the stage for a revolution in medicine. Advances in gene cloning, gene mapping, and mutation analysis have contributed to an explosion of new information regarding the fundamental biological and pathophysiological basis for hundreds of human diseases. Accompanying this tidal wave of new information comes the recognition that most human diseases are substantially impacted by genetic factors.

In nephrology, a wide range of clinical phenotypes can now be explained at a molecular level. The greatest strides have been made in defining genes that are responsible for a variety of inherited syndromes, including polycystic kidney disease, cystinuria, Alport's syndrome, Bartter's syndrome, various renal neoplasms, and many others. Discoveries made in these and other mendelian (ie, single-gene) disorders have brought great excitement and optimism. During the next 50-year existence of the National Kidney Foundation, there will be countless new opportunities to unleash the power of genetics to improve the lives of patients with kidney disease. This review will summarize our current understanding of the genetic basis of kidney disease, emphasize the need to expand our understanding of genetically complex disorders affecting kidney function, and

focus attention on the need to develop improved methods for detection, prediction, and therapy of inherited risk factors for kidney disease.

MENDELIAN DISORDERS OF THE KIDNEY

A wide variety of renal disease entities are caused by defects in single genes. Table 1 lists inherited disorders with primary renal involvement collated from the extensive Online Mendelian Inheritance in Man (OMIM) database. Nearly all are transmitted in families as autosomal dominant, autosomal recessive, or X-linked traits, indicating that they are due to single-gene defects. Among the more than 50 disorders listed, there is a broad range of clinical expression, ranging from relatively benign metabolic disorders, diseases of moderate morbidity such as hypertension and nephrolithiasis, to life-threatening diseases associated with end-stage renal disease (ESRD) and cancer. Although many of these inherited diseases are manifest in childhood, a significant portion occur later in life. Polycystic kidney disease, renal neoplasms, glomerular disease, and milder metabolic defects generally emerge in adulthood. The importance of recognizing these and other late-onset disorders is that there is a window of opportunity to make pre-symptomatic diagnoses or to predict an individual's likelihood of developing the disease and to intervene therapeutically.

IDENTIFYING NEW INHERITED DISORDERS OF THE KIDNEY

Although the list in Table 1 is extensive, there are many other genetic disorders for which there has not been a concerted effort to collect and ascertain affected families and to initiate genetic linkage studies. There may also be, as yet, unrecognized clinical entities for which a genetic

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approach may one day reveal a molecular basis. Similarly, there are likely to be subtle or subclinical disease manifestations that could be tracked as a single-gene trait. Recognition of such entities will require greater emphasis on obtaining a thorough family history in extended pedigrees, as well as the careful consideration of the effects of reduced penetrance and variable expressivity in some disorders, characteristics that often mask the inheritance pattern of simple traits. The existence of phenocopies (nongenetic syndromes that closely resemble an inherited disease) also presents obstacles to the recognition and careful delineation of new inherited syndromes. In some cases, the high phenocopy rate in the population makes it difficult to dissect familial entities. Such is the case in defining familial IgA nephropathy and renal cell carcinoma.

MOLECULAR DIAGNOSTICS

Knowing the precise molecular genetic basis for a disease in an individual patient has great potential clinical utility. This information can be useful for diagnostic and prognostic evaluations and may soon be important for directing specific therapy. At present, clinically applicable molecular genetic tests are available for only a small fraction of the diseases listed in Table 1. Therefore, the development of highly sensitive and specific assays for identifying molecular markers of disease should receive greater emphasis in the future.

Several obstacles hinder the development of reliable, clinically useful molecular diagnostic assays for inherited renal diseases. Two such issues that conspire to make molecular diagnostic approaches highly challenging are genetic heterogeneity and allelic heterogeneity. Genetic heterogeneity, the ability of more than one gene to cause a particular phenotype, has been recognized in polycystic kidney disease, Alport's syndrome, Bartter's syndrome, cystinuria, and other entities. Allelic heterogeneity, the existence of two or more distinct mutations in a gene causing a given phenotype, is common in virtually all inherited disease. For example, in X-linked Alport's syndrome, more than 150 different mutations have been identified in the gene encoding the type IV collagen alpha 5 chain (*COL4A5*) (allelic heterogeneity) and numerous other mutations are found in either *COL4A3* or *COL4A5* in

the recessive form of the disease (genetic heterogeneity).^{1,2} The genomic organization of all three collagen genes is highly complex, with multiple exons spanning large genomic distances. In isolated cases of Alport's syndrome in males, it may be especially difficult to determine which gene is responsible. This, coupled with the enormous task of screening even one collagen gene for mutations, presents a formidable obstacle for performing molecular diagnostics in a sufficiently sensitive and routine manner. In some studies, mutations have been detected in only approximately 50% of screened probands,² suggesting that either the techniques are insensitive or mutations lie outside of the regions examined. The structural complexity of genes also presents obstacles for the mutational analysis of the *PKDI* and *PKD2* genes.³ Mutational analysis of *PKDI* is complicated by the existence of a nearly identical sequence on the same chromosomal segment.⁴ Although progress has been made in devising *PKDI*-specific mutational analysis methods,^{5,6} more work is necessary before such tests can be routinely deployed. Technological breakthroughs, such as the use of microarrays and high-throughput DNA sequencing technology, will soon make genetic testing more sensitive, approachable, and affordable. With an expanded range of available genetic tests, it becomes critical to institute procedures to guarantee patient confidentiality and obtain appropriate informed consent.

GENETICALLY COMPLEX DISORDERS OF THE KIDNEY

With the exception of polycystic kidney disease, cystinuria, Alport's syndrome, and a few others, single-gene disorders with primary renal involvement are rare. By contrast, a wide variety of common disorders affecting the kidney stem from complex interactions between genetic predisposition and environmental factors (Table 2). Such genetically complex traits, also known as polygenic disorders, must be viewed differently from diseases caused by defects in single genes. Rather than a one-to-one relationship between a definable genetic defect and the occurrence of a specific disease, common diseases such as essential hypertension, renal cancer, and nephrolithiasis occur in patients who have a unique genetic susceptibility that arises from subtle variations in multiple genes. Furthermore, genetic susceptibil-

Table 1. Inherited Disorders With Primary Renal Involvement

Disease/Category	Protein	Gene/Locus	OMIM*
Primary glomerular disease			
Alport's syndrome, X-linked†	Type IV collagen, α 5	<i>COL4A5</i> , Xq22	301050
Alport's syndrome, autosomal recessive	Type IV collagen, α 3	<i>COL4A3</i> , 2q26-q37	203780
	Type IV collagen, α 4	<i>COL4A4</i> , 2q26-q37	203780
Benign familial hematuria	Type IV collagen, α 4	<i>COL4A4</i> , 2q26-q37	141200
Glomerulopathy with fibro-nectin deposits	?	1q32	601894
Congenital nephrosis I (Finnish type)	Nephrin	<i>NPHN</i> , 19q13.	256300
Focal segmental glomerulosclerosis I	?	19q13	603278
Focal segmental glomerulosclerosis II	?	11q21-q22, ? other	603965
Nail patella syndrome	LIM-homeodomain protein	<i>LMX1B</i> , 9q34.1	161200
Familial nephrotic syndrome	?	1q25-q31	600995
Familial mesangial sclerosis	Wilms' tumor suppressor 1	<i>WT1</i> , 11p13	256370
Familial IgA nephropathy	?	?	161950
Cystic renal diseases			
Polycystic kidney disease 1†	Polycystin I	<i>PKD1</i> , 16p13.3	601313
Polycystic kidney disease 2†	Polycystin II	<i>PKD2</i> , 4q21-q23	173910
Infantile severe polycystic kidney disease with tuberous sclerosis	Polycystin I and tuberin	<i>PKD1</i> and <i>TSC2</i> , 16p13.3	600273
Autosomal recessive polycystic kidney disease†	?	6p21.1-p12	263200
Medullary cystic kidney disease 1	?	1q21	174000
Medullary cystic kidney disease 2	?	16p12	603860
Familial juvenile nephronophthisis 1†	MAL-like protein	<i>NPHP1</i> , 2q13	256100
Infantile nephronophthisis	?	9q22-q31	602088
Renal tubular diseases			
Distal renal tubular acidosis	Anion exchanger 1	<i>SLC4A1</i> , 17q21-q22	179800
Primary hypomagnesemia	Paracellin-1	<i>PCLN1</i> , 3q	248250
Renal tubular acidosis with neural deafness	β ₁ subunit, H ⁺ ATPase	<i>ATP6B1</i> , 2cen-q13	192132
Renal tubular acidosis with osteopetrosis	Carbonic anhydrase II	<i>CA2</i> , 8q22	259730
Renal glycosuria	?	16p11.2, 6p21.3	233100
Dent's disease	Cl channel, ClC-5	<i>CLCN5</i> , Xp11.22	300009
X-linked recessive nephrolithiasis with renal failure	Cl channel, ClC-5	<i>CLCN5</i> , Xp11.22	310468
X-linked recessive hypophosphatemic rickets†	Cl channel, ClC-5	<i>CLCN5</i> , Xp11.22	307800
Fanconi renotubular syndrome	?	?	134600
Proximal renal tubular acidosis	?	?	312400
Nephrogenic diabetes insipidus (X-linked)†	Vasopressin receptor type 2	<i>AVPR2</i> , Xq28	304800
Nephrogenic diabetes insipidus (autosomal)	Aquaporin 2 water channel	<i>AQP2</i> , 12q13	125800
Familial hypocalcemic hypercalcemia	Ca ²⁺ -sensing receptor	<i>CASR</i> , 3q13.3-q21	145980
X-linked hypophosphatemia†	Endopeptidase homolog	<i>PEX</i> , Xp22.1	307800

Table 1. Inherited Disorders With Primary Renal Involvement (Cont'd)

Disease/Category	Protein	Gene/Locus	OMIM*
Pseudovitamin D deficiency rickets	1 α -hydroxylase	<i>CYP27B1</i> , 12q14.1	264700
Autosomal dominant hypophosphatemic rickets	?	12p13.3	193100
Bartter's syndrome type 1	Na-K-2Cl cotransporter	<i>SLC12A1</i> , 15q15-q21	241200
Gitelman's syndrome	Na-Cl cotransporter	<i>SLC12A3</i> , 16q13	263800
Bartter's syndrome type 2	ROMK K channel	<i>KCNJ1</i> , 11q24	601678
Bartter's syndrome type 3	Cl channel, ClC-Kb	<i>CLCNKB</i> , 1p36	602023
Pseudoaldosteronism (Liddle syndrome)	Epithelial Na channel β , γ subunits	<i>SCNN1B</i> , <i>SCNN1G</i> , 16p13-p12	177200
Recessive pseudohypoaldosteronism type 1	Epithelial Na channel α , β , γ subunits	<i>SCNN1A</i> , 12p13; <i>SCNN1B</i> , <i>SCNN1G</i> , 16p13-p12	264350
Dominant pseudohypoaldosteronism type I	Mineralocorticoid receptor	<i>MLR</i> , 4q31.1	177735
Pseudohypoaldosteronism type 2 (Gordon syndrome)	?	1q31-q42, 17p11-q21	145260
Apparent mineralocorticoid excess	11 β -hydroxysteroid dehydrogenase	<i>HSD11B2</i> , 16q22	218030
Familial idiopathic hypercalciuria	?	4q33-qter	143870
Cystinuria, type I	Cystine transporter	<i>SLC3A1</i> , 2p16.3	220100
Cystinuria, non-type I	Cystine transporter	<i>SLC7A9</i> , 19q13.1	600918
Lysinuric protein intolerance	? amino acid transporter	<i>SLC7A7</i> , 4q11.2	222700
Hartnup disease	?	11q13	234500
Iminoglycinuria	?	?	242600
Inherited renal neoplasms			
Wilms' tumor 1, 2†	Transcription factor	<i>WT1</i> , 11p13; 11p15.5	194070
Wilms' tumor 3†	?	16q	194090
Wilms' tumor 4†	?	17q12-q21	601363
Renal cell carcinoma	Translocation-related gene	<i>TRC8</i> , 8q24.1	144700
Papillary renal cell carcinoma (translocation-related)†	Gene fusion	<i>PRCC</i> , 1q21; <i>TFE3</i> , Xp11.2	179755/312390
Hereditary papillary renal carcinoma†	MET proto-oncogene	<i>MET</i> , 7q31	164860
Von Hippel-Lindau syndrome†	Tumor suppressor	<i>VHL</i> , 3p26-p25	193300

*Online Mendelian Inheritance in Man database (<http://www.ncbi.nlm.nih.gov/Omim>).

†Indicates availability of clinical molecular genetic testing (see <http://www.genetests.org>).

Table 2. Complex Genetic Traits Involving the Kidney

Essential hypertension
Susceptibility to ESRD
Diabetic nephropathy
Hypertensive nephrosclerosis
Susceptibility to acute renal injury
Renal neoplasms
Nephrolithiasis
Acquired renal cystic disease
Primary glomerular diseases
Immune-mediated renal disease
Lupus nephritis
IgA nephropathy

ity should not be necessarily equated with a high likelihood of disease occurrence. A familiar illustration of this point is essential hypertension.^{7,8} It is well established that genetic factors account for a substantial degree of familial aggregation of blood pressure, but there are important and substantial contributions from the environment. In the absence of a triggering environmental stimulus, such as high salt intake for patients prone to essential hypertension, genetic preprogramming may never be manifest as overt disease.

Genetic susceptibility to common diseases requires the simultaneous inheritance of allelic

variants in two or more genes. Allelic variants responsible for genetic susceptibility may be common polymorphisms occurring anywhere in the gene and may have minimal impact by themselves on gene function. Polymorphisms in elements that control gene transcription may affect gene expression to an extent that by itself renders no phenotype, but in the presence of other genetic factors or environmental stimuli, a disease process may be manifest. The example of essential hypertension is again appropriate to illustrate this concept. Recent work has defined specific nucleotide sequence variations in the angiotensinogen gene (*AGT*) that are more common in patients with hypertension and pre-eclampsia.⁹⁻¹¹ A specific molecular variant of *AGT*, threonine-235, is associated with higher plasma angiotensinogen concentrations and greater likelihood of elevated blood pressure.⁹ Recently, a functionally significant nucleotide substitution in the promoter region of *AGT* was discovered that is in linkage disequilibrium with threonine-235, thus providing a potential explanation for the biological association of this allele with altered angiotensinogen levels.¹²

Greater effort is needed to uncover genetic factors that predispose individuals to common disorders involving the kidney. Such efforts will likely lead to improved understanding of the molecular basis of renal disease, help identify individuals at risk, and contribute to improving clinical outcomes. In particular, understanding susceptibility to the development of acute and chronic renal injury and the progression to ESRD could have a substantial impact on efforts to ameliorate the morbidity and mortality of this condition and to lessen its financial burden on society. There is strong evidence that the susceptibility to developing ESRD in association with hypertension, diabetes, and immune-mediated renal disease has a genetic basis.¹³ Nephrologists are familiar with the racial differences in the incidence of ESRD among patients with hypertension, diabetes mellitus, and human immunodeficiency virus (HIV) infection. There is also recent evidence that there is familial aggregation of renal disease associated with these and other systemic disorders.¹⁴⁻²⁰ Such studies have drawn attention to the observation that first-degree relatives of ESRD patients have a greater prevalence of renal disease than the general population.

Further work in this area to define the proportion of ESRD risk attributable to genetic factors should exploit twin studies or take advantage of larger patient populations available through ESRD networks. Large, carefully ascertained patient populations are essential for performing genome-wide genetic screens to identify susceptibility genes. Current trends in human genetics suggest that family-based association studies are most amenable and powerful to detect genetic factors in complex traits.^{21,22} Such tests require the ascertainment and DNA banking of affected sibling pairs or parent/child sets. The large sample populations needed for gene mapping in complex traits requires organized and consolidated multi-center efforts. Mapping susceptibility genes in kidney disease is clearly the next challenge in understanding the biological basis of many common kidney disorders.

In the future, an individual's susceptibility to developing renal or other disease may be predictable based on genotype analysis. Although we may be several years away from use of "genetic report cards" for defining an individual's disease risk profile, the accelerated pace of the Human Genome Project and several emerging technologies strongly suggest that this may become a reality sooner than expected. Newer molecular diagnostic tools will soon be available to screen patients for disease-associated alleles, leading to a new era of molecular and genetic epidemiology. In the future, genetic testing will be as common as measurement of serum cholesterol to assess cardiovascular disease risk. With this evolution in clinical diagnostics will come a greater emphasis on preventive medicine and strong motivation to develop new therapies designed to reduce genetically defined disease susceptibility. These advances will also require a greater level of patient and physician education regarding the significance and impact of genetic testing. Genetic counseling of patients for whom diagnostic tests indicate increased disease risks will need to be performed by the physician or ancillary staff. Proactive efforts by the medical community will also be imperative to obviate misuse of genetic information.

GENETIC THERAPY OF KIDNEY DISEASE

The nature of inherited disease syndromes makes them theoretically amenable to therapies

aimed at correcting or replacing the defective gene. Although the promise of gene therapy for inherited diseases may not be fulfilled for several more years, the prospects are very good. In addition to the treatment of classical inherited diseases, genetic therapies may one day be tailored to modify disease susceptibility in complex traits such as hypertension and the progression to ESRD, and modulate the immune response in acute transplant rejection, acute glomerulonephritis, or other immune-mediated renal disease processes.^{23,24} Finally, molecular genetic techniques are already showing promise for providing an alternative vehicle for administration of recombinant proteins such as erythropoietin (EPO).

The kidney presents unique opportunities and obstacles for the effective deployment of genetic therapy.^{25,26} The highly vascular nature and single arterial supply of the kidney are conceivable advantages for targeted delivery to this organ. Additional delivery routes available include retrograde infusion through the ureter to the renal pelvis, and direct intraparenchymal injection. On the other hand, the complex architecture of the kidney, coupled with its cellular heterogeneity, poses formidable problems to gene delivery. Different delivery strategies will almost certainly be required to effectively transduce cells of the glomerulus, tubular epithelium, and interstitium.

Gene delivery systems for the kidney have been developed primarily around the use of viral and certain nonviral methods. Retroviral vectors that provide an efficient method to deliver genes to dividing target cells are likely to be inadequate for gene transfer into nondividing, highly differentiated kidney cells.²⁶ The exception may be situations in which the targeted cell is part of an inflammatory infiltrate, such as in acute transplant rejection or other immune-mediated disease processes. Other viral vectors, including adenovirus, adeno-associated virus, and lentiviruses, have been shown to succeed in transducing nondividing cells and to have a broad predilection for different host cells. Newer adeno-associated viruses and re-engineered adenoviruses appear to incite less inflammatory reaction than their predecessors.²⁶ Integration of the viral DNA into the host genome is generally required for long-lived expression of the delivered gene. This integration poses certain problems of expression variability and the risk for unintended genetic

consequences secondary to gene disruption at the site of integration. Certain nonviral gene transfer methods have shown promise in delivery of genetic material to the kidney. Early success has been reported with the use of HVJ liposomes and cationic liposomes for transducing kidney cells.^{27,28} Much more work is needed in the future to perfect gene delivery systems for the kidney such that their clinical utility can be realized.

In addition to the variety of gene delivery systems, there are multiple strategies for effecting gene replacement and repair. The treatment of a recessive disorder can most easily be accomplished by introducing a functional copy of the normal gene. In some cases, this strategy may also work in a dominantly inherited disorder when the mechanism of the disease involves haploinsufficiency (50% reduction in functional gene dosage). This strategy may be appropriate for use in polycystic kidney disease and certain inherited renal neoplasms where somatic mutation and loss of heterozygosity of a growth-suppressor gene may initiate cystic or malignant transformation of renal cells.²⁹⁻³⁴ In addition to haploinsufficiency, certain dominant disorders arise because of the negative influence of the mutant gene product on the wild-type allele. In the setting of a dominant-negative disease mechanism, introduction of an additional copy of the normal gene may not have a therapeutic effect. Conceptionally, repair of the mutant gene or its corresponding messenger RNA may be more effective in certain dominant diseases.

Two distinct approaches for gene repair have been described recently. Various investigators have demonstrated the utility of using *trans*-splicing ribozymes to mediate repair of messenger RNA *in vitro*.^{35,36} Ribozymes are small RNA molecules that possess various catalytic activities in absence of proteins.³⁷ This strategy has recently been demonstrated to work in correcting mutations associated with sickle cell anemia and possibly in myotonic dystrophy.^{36,38} Targeting messenger RNA rather than genomic DNA has certain advantages. This approach provides for an added layer of specificity because it targets RNA expressed only in affected tissues. It also leaves the repaired gene under its normal transcriptional control mechanisms. Current prob-

lems with this method include low efficiency and imperfect target specificity at the molecular level.

Another approach for effecting repair of genomic DNA in a sequence-specific manner is the use of RNA/DNA hybrid oligonucleotides.³⁹⁻⁴¹ In this approach, a synthetic RNA/DNA hybrid molecule base pairs with complementary sequences in the target gene and creates a mismatch at the site of the disease-producing mutation. By creating this intentional mismatch, the host cell's DNA repair mechanisms remove the abnormal nucleotide and replace it with the normal sequence as dictated by the RNA/DNA chimera. This approach has recently been demonstrated to succeed in treatment of sickle cell hemoglobin mutations *in vitro*⁴² and in repairing the genetic defect in the Gunn rat model of Crigler-Najjar syndrome.⁴³ This strategy may have several advantages, including the lack of risks associated with viral DNA integration in the host genome and maintenance of normal transcriptional regulation of the repaired gene. Current problems include low efficiency and the need to design unique allele-specific RNA/DNA hybrids for every mutation. It is also not clear if this strategy will work for genetic defects other than single-base substitutions (ie, micro-deletions and insertions). Nonetheless, gene repair offers an exciting new opportunity for exploiting molecular biology in the treatment of genetic disease.

DELIVERING EPO BY GENE TRANSFER

Gene transfer strategies are already showing promise as an alternative vehicle for delivering certain therapeutic recombinant proteins such as EPO. Investigators have demonstrated the ability of a recombinant EPO gene to induce ectopic production of the hormone from skeletal muscle⁴⁴ or dermis.⁴⁵ This is accomplished by mere injection of plasmid DNA encoding EPO into skeletal muscle of experimental animals. Under the control of a constitutively active promoter (such as the cytomegalovirus immediate early promoter), animals have been shown to maintain an elevated hematocrit and plasma EPO level for several months. More recently, somatic cell delivery of EPO using a rapamycin inducible system has been shown to permit regulated expression of EPO in both rodent and primate experimental animals.⁴⁶ This inducible gene expression sys-

tem provides a mechanism for regulating the desired level of circulating EPO and avoiding the potentially harmful effects of uncontrolled EPO expression. Somatic cell delivery of EPO should conceivably provide a less expensive alternative to the direct use of the recombinant protein for treatment of the anemia of ESRD. This same approach could conceivably be used to deliver other recombinant proteins, such as growth factors, that might have clinical utility in treating renal disease.

CONSOLIDATING RESOURCES AND PROVIDING TRAINING IN GENETICS

Resources to develop genetic information in nephrology are building, but are in their infancy. Most inherited renal syndromes are orphan diseases, and progress will be quicker if nephrology organizations in collaboration with interested governments and foundations are willing to establish consortia able to hold and distribute data sets. The need for links between accurate data sets is pressing, so that navigation from polymorphisms, to cells, and then on to discrete biochemical pathways creates a seamless interface for functional genomics.⁴⁷ It is likely that genomic profiling of index cases of renal diseases can be accomplished by analysis of pathology holdings of biopsy blocks, particularly if these are linked to good medical records. However, the chart descriptions of medical illness probably will not contain rigorous family histories satisfactory to geneticists until we improve history taking and develop standardized record templates. Microprocessing of genetic donations, data storage, and phenotype privacy are also emerging issues⁴⁸ with few safeguards currently in place for patients or investigators.^{49,50}

Monogenetic diseases of mendelian inheritance are likely to remain popular as first attempts to specify genes of interest to nephrology. Transporter mutations, channelopathies, and metabolic pathway disorders that have clear definition should come quickly as the density of the human physical map improves.⁵¹ Other renal diseases will be more difficult because they represent complex genetic traits. The search for a genetic component to these latter disorders likely will require nonparametric sibling pair or relative pair analyses,⁵² or other even more challenging epidemiologic approaches like segregation

analysis, or case-control or cohort studies.^{53,54} As the density of single-nucleotide polymorphisms increase, the prospects for whole-genome mapping of disease-related genes may become feasible.⁵⁵

These approaches to genetic susceptibility require a new generation of trainees experienced in molecular epidemiology and this needs to become part of nephrology's curriculum. For inflammatory renal diseases in particular, nephrology suffers in the difficulty of aligning gene action with a phenotype of illness that is often inadequately delineated at the bedside. As a product of empiricism, our definitions of disease are frequently based on the arbitrary feature and timing of a biopsy, and the relative penetrance of injury may be wholly inadequate to accurately subspeciate groups of individuals for purposes of gene identification. This concern speaks to the need for standard phenotype definitions. For rare disorders that are typical of nephrologic conditions, there is also the problem of not having large enough numbers of discrete genetic material to strengthen searches for genetic linkage. International consortiums and cooperative multi-center repositories will be absolutely essential for progress in renal disorders.

One area where progress has come quickly is the development of transgenic or gene substitution mice, and mutagenesis screens for models of human disease in mice. The catalog of interesting phenotypes is expanding rapidly, but more important is the new facility with which known genes can be altered to probe cell fate,⁵⁶ signaling, and biochemical pathways.⁵⁷ The return of microphysiology for the mouse is an important tool box for high-throughput genotyping of interesting phenotypes.⁵⁸

Finally, the lack of training of internists and nephrologists in the language of genetic science is a significant obstacle to discovery. Essential instruction in the molecular biology of gene action, genomics history taking, and genetic counseling⁵⁹ needs to be better taught at the bedside in traditional training environments. At a more advanced level is the need for trainees with competence in bioinformatics.⁶⁰ Realignment of the training curriculum of the Residency Review Committee for Internal Medicine and the American Board of Internal Medicine are important next steps for immersion in the field of genetics.

The discipline has few mentors for this effort, and special programs for gene mapping of complex human disease are urgently needed in internal medicine, much less nephrology.

SUMMARY

The downstream opportunities that emerge from the Human Genome Project, as well as the sequencing of other species, is in the illumination of basic biology and pathophysiology, genetic susceptibility, pharmacogenomics, gene therapy, and experimental therapeutics. The first informatics platform for many of these initiatives will come from comparative genetics, mutagenesis screens for experimental models, and human polymorphism biology. Additional riches of knowledge will be mined from informatic warehouses by investigators grounded in the proteomics of protein design, assembly, addressing, and cell biology. In spite of our progress, the future clinical investigator in nephrology will need special training in the use of international resources to fully take advantage of genetic medicine.

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