Although being female conveys a protective effect on the progression of chronic renal disease, the basis for this sex difference is not well understood. Little is known about the effects of sex on the development of the kidney. The numbers of glomeruli are the same for men and women, and the greater glomerular volume in males is related to the larger size of their kidneys and body surface area. In the absence of structural differences to account for the accelerated progression of renal injury in males, hormonal differences have been implicated. Animal models support the protective effect of estrogen on glomerulonephritis and the nephrotoxic effects of testosterone, yet a great deal of evidence implicates events occurring during embryonic development. The effect of poor nutrition and other maternal factors leading to low birth weight can reduce the numbers of nephrons in the developing kidney, but the effect is the same for males and females. What is generally ignored in any discussion of sex differences in renal disease are the relevant genes on the X chromosome, which when mutated interfere with normal kidney function. This review addresses the genetic and epigenetic programs that contribute to the sex differences in renal diseases.

Without doubt, the clinical manifestations of renal diseases are influenced by X inactivation, the developmental program that equalizes the transcriptional output of X-linked genes in males and females. X inactivation is an obligatory program, driven by the sex difference in the numbers of X chromosomes that arose during mammalian evolution. The human Y chromosome was created by destroying one member of the chromosome pair that evolved into our sex chromosomes. As a result, XX females have two X chromosomes, whereas XY males have only one. The DNA sequence of the human X chromosome reveals about 1100 genes, an eclectic group, encoding proteins needed for almost all of our body functions, some having to do with sex but most involving nonsexual activities. In contrast, the genes on the Y chromosome are far less diverse. Although a few share functions with their X-linked counterpart, most are unique to the Y; expressed only in the testes, they have to do with testicular function and fertility. With one X chromosome, males have only a single copy of their X-linked genes.

On the other hand, even though females have two copies of these genes, both are not expressed in the same cell. Only one X is programmed to work in each diploid somatic cell. All of the other X chromosomes in the cell become inactive during fetal development. Briefly, compensation for X dosage in our species is accomplished by a process that ensures only a single X is active in both sexes. In cells with more than two X chromosomes, all X chromosomes but one are silenced.

In human females, the choice of the active X chromosome is random so that the X inherited from the father has the same possibility of being active as the X inherited from the mother. Silencing of the other X or Xs is mediated by the synthesis of a special type of noncoding RNA molecule emanating from the X inactive transcript (XIST) locus on the X chromosome. Spreading along the chromosome, these molecules modify the underlying chromosome and induce transcriptional silence. Once silenced, most genes on the
inactive X usually remain mute in all daughter cells, so that the inactivation pattern is clonally inherited.\footnote{7}

As a consequence of clonal inheritance of the inactive X, human females are mosaics, a composite of two populations of cells that differ as to which X chromosome is expressed. This mosaicism would be meaningless if the alleles on maternal and paternal X chromosomes were identical as they are in inbred laboratory mice; however, we, as a species, are so heterozygous that females are indeed mosaic for a good number of their X-linked alleles. The size of the mosaic patch differs from tissue to tissue.\footnote{8} It is very large in the placenta where all of the cells within a chorionic villus have the same active X, and very small in the brain with a great deal of comingling of the two types of cells. The phenotype of any cell is determined not only by the allele it expresses, but also by the interactions with those neighbors, expressing the other allele. Such interactions are best seen in those neighbors, expressing the other allele, but also by the interactions with paternal X chromosomes were identical as shown in Table 1. It is this cellular mosaicism that provides biologic advantage to females carrying mutations responsible for kidney disease in males.

**Sex Differences in Renal Development**

The development of the kidney is intricate because of its architectural complexity. The entire urinary collecting system starts as an outgrowth of the Wolffian duct and forms by a complex process of branching and remodeling.\footnote{10} According to Costantini,\footnote{10} branching may be initiated in localized regions of the ureteric bud by small groups of cells that communicate with adjacent groups of cells, all of this under the control of a variety of transcription and other signaling factors. And the development of glomeruli requires interactions between epithelial cells and infiltrating endothelial cells. What is not known is the nature of the sex differences in this process. There are bound to be sex differences because of the cellular mosaicism resulting from X inactivation. Also not known is the mosaic composition of the kidney. Do the different cells that communicate to induce the kidney express the same or different parental X chromosomes? The onset of X inactivation is timed with the differentiation events that give rise to the various tissues;\footnote{11,12} therefore, in the kidney, it might coincide with the earliest events in renal differentiation. Clearly, the time when X inactivation occurs precedes the time when the kidney is completely formed in humans. From what is known about development of the mouse kidney, most nephro-

<table>
<thead>
<tr>
<th>Disease</th>
<th>OMIM#</th>
<th>X Map*</th>
<th>Mutated Gene</th>
<th>Male Renal Phenotype\textsuperscript{a}</th>
<th>Female Renal Phenotype\textsuperscript{b}</th>
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<tr>
<td>Alport syndrome</td>
<td>301050</td>
<td>Xq22.3</td>
<td>COL4A5</td>
<td>Nephritis; glomerulitis; hematuria; ESRD</td>
<td>Some hematuria; rarely ESRD</td>
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<td>Xq22.3</td>
<td>COL4A5 &amp;</td>
<td>Nephritis; glomerulitis; hematuria; ESRD</td>
<td>Some hematuria; rarely ESRD</td>
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<td>nephropathology\textsuperscript{c}</td>
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<td>COL4A6</td>
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<td>300009</td>
<td>Xp11.22</td>
<td>CLCN5</td>
<td>Progressive proximal tubular disease; ESRD; hypercalciuria;</td>
<td>Usually asymptomatic; occasionally proteinuria and hypercalciuria</td>
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<td>Low molecular weight</td>
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<td>proteinuria</td>
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<td>OCRL</td>
<td>Proteinuria; aminoaciduria; phosphaturia</td>
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<td>OCRL</td>
<td>Cytoplasmic inclusions, proteinuria, ESRD</td>
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<td>Xq22</td>
<td>GLA</td>
<td>Hypophosphatemia; nephrocalcinosis</td>
<td>More variable and less severe</td>
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<td>Xp22.1–2</td>
<td>PHEX</td>
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<tr>
<td>resistant)</td>
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<td>300322</td>
<td>Xq26–27.2</td>
<td>HPRT</td>
<td>Uric acid stones, nephropathy, and renal obstruction</td>
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<td>304800</td>
<td>Xq28</td>
<td>AVPR2\textsuperscript{−}</td>
<td>Excessive diuresis</td>
<td>Milder symptoms if any</td>
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<td>insipidus</td>
<td></td>
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<tr>
<td>Syndrome of inappropriate</td>
<td>300539</td>
<td>Xq28</td>
<td>AVPR2\textsuperscript{+}</td>
<td>Gain of function: hyponatremia, systolic hypertension</td>
<td>Variable, but usually less severe</td>
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<td>Xp22.2</td>
<td>OFD1</td>
<td>Fetal death</td>
<td>Polycystic disease, ESRD</td>
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<tr>
<td>syndrome 1</td>
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</table>

\textsuperscript{a}ESRD, End-stage renal disease.

\textsuperscript{b}Location of the gene on the X chromosome.

\textsuperscript{c}Hemizygous male and heterozygous female.

\textsuperscript{c}Contiguous gene syndrome with large deletions.
BRIEF REVIEW

Sex Differences in Renal Disease

Table 1 shows the sex differences in expression of some diseases that affect the kidney; most affect predominantly males and have variable penetrance in carriers. The list is not exhaustive, and it consists mainly of syndromes associated with severe deficiencies of the gene products. The reference numbers for the On-line Mendelian Inheritance of Man (OMIM) are included as a source of further information. There are more OMIM numbers than the number of mutant genes because the syndromes were described before the genes were known. The identification of mutations has led to a broader appreciation of the spectrum of disorders attributable to mutations in a single gene. Some of the phenotypic variations are the result of different effects of multiple mutations within the same gene.

Generally, the sex differences in the manifestations of X-linked diseases fall into two categories: Either males have a disease, and females have no manifestations or attenuated manifestations, or females uniquely manifest the disease because the mutation is lethal in males. Carriers with the same mutation survive because enough of their cells express the normal allele to carry out the function of the gene, or the gene product can be transferred from normal to deficient cells. Sharing of gene products takes place in the usual ways that cells communicate with each other, namely, metabolic cooperation through gap junctions, endocytosis, and other intercellular channels. If gene products cannot be shared, then normal cells may outgrow the mutant ones and eventually eliminate them. Such strategies are carried out in a tissue-specific fashion; those tissues unable to metabolically cooperate may undergo cell selection instead. These interactions, occurring uniquely in females, ameliorate their phenotype so that they may have no clinical manifestations at all.

Cell-to-cell transfer of gene products masks the genotype, as the mutant cells are no longer deficient. Good examples are mutations affecting the metabolism of large intracellular proteins. The enzymes needed to digest such molecules can be transferred from one cell to another by mannose-6 phosphate-mediated endocytosis. Without sufficient enzyme, the undigested proteins can induce kidney disease, which is the case in Fabry disease.

Fabry Disease

The lysosomal enzyme alpha galactosidase A (GLA) is ubiquitously expressed, as it is needed to break down glycosphingolipids present in most cell membranes. In the absence of sufficient enzyme, the glycosphingolipids accumulate and plug the blood vessels in all tissues, producing severe episodic pain and premature death.

The severe kind of renal disease occurs most often in males, who usually require enzyme replacement therapy with human recombinant GLA and kidney transplants for end-stage renal disease (ESRD). In the kidney, the glycosphingolipids colocalize with the lysosomes and are deposited in the glomeruli, renal tubules, and blood vessels. Fabry nephropathy consists of glomerular sclerosis, tubular fibrosis, and hyalinization of the blood vessels. Clinically, the renal disease manifests as hypertension, moderate proteinuria, lipiduria, and microscopic hematuria.

Many heterozygous females manifest some signs of the disease, but in an attenuated form. These affected females usually have a later onset of symptoms, live significantly longer, and their symptoms can be more easily relieved by enzyme...
replacement than males. In any case, the symptoms and circulating levels of GLA are more variable in females, and the disease has a slower rate of progression. Clearly, the milder renal disease is the result of the effect of having cells that produce normal amounts of GLA. Also, the normal cells can export the enzyme by endocytosis to the mutant cells, thereby ameliorating their deficiency. Enzyme transfer is enough to preclude elimination of mutant cells but inadequate to correct the defect, which explains why heterozygotes may be symptomatic. The GLA enzyme is taken up poorly compared with other lysosomal enzymes, perhaps explaining why almost all carriers have the lens opacities characteristic of Fabry disease. Generally benign, their presence suggests that having 50% normal cells is not enough to prevent all manifestations of this disease.14

Approximately 10% of Fabry carriers eventually undergo dialysis or kidney transplants, usually because such “manifesting” heterozygotes have significantly more mutant than wild-type cells, reflecting skewed rather than random patterns of X inactivation. In this case, the skewing is not the result of a growth advantage of the mutant cells but reflects instead stochastic events, or skewing for reasons unrelated to the mutant gene, such as chromosome abnormalities and twinning.7 The effect of skewed X inactivation on phenotype is most evident in the occasional carrier (approximately 1 in 200) that fully manifests Fabry syndrome. In these cases, the affected female has only mutant cells, reflecting severe skewing (>95% mutant cells). The influence of X inactivation is striking in a pair of female MZ twins, who are uniquely prone to skewing. Only one twin had the classic form of Fabry disease, and her cells predominantly express the mutant allele.15

Lesch-Nyhan Syndrome
The kidney disease in males with Lesch-Nyhan mutations is most often acute renal failure caused by crystal nephropathy. These boys have an almost complete deficiency of the enzyme hypoxanthine phosphoribosyl transferase (HPRT), which is needed, especially in the brain, for the reutilization of breakdown products of DNA, specifically the purine bases (hypoxanthine and guanine). In addition to mental retardation and spastic cerebral palsy, severe HPRT mutations result in uric acid deposits in joints and kidney. Less severe HPRT mutations in males usually produce only gout and kidney stones (the Kelley-Seegmiller syndrome, OMIM #300323). However, in some cases, they also result in ESRD, often unrecognized because of the lack of other symptoms. These boys and others who are treated with allopurinol for a long time may also develop xanthinuria and xanthine urolithiasis with staghorn calculi.16

On the other hand, women, heterozygous for severe Lesch-Nyhan mutations, even though they have deficient cells in many tissues, manifest none of these symptoms, not even gout. In many of their tissues, inosinic acid, the product of the HPRT metabolic reaction, is transferred from the normal to the mutant cells by means of gap junctions. Connecting the cytoplasmas of neighboring cells, these channels mediate the transfer of small molecules, such as inosinic acid, across the lipid bilayer of the cell membranes. However, in blood cells (both erythroid and leukocytic lineages), which lack gap junctions (and hence the ability to transfer inosinic acid), the mutant cells have a growth disadvantage and are completely eliminated after the first decade of life.7

At least seven females are reported to have the full biochemical and clinical manifestations of the syndrome.17 All are heterozygous for an HPRT mutation, but their normal allele is never transcribed because it is always on the inactive X. One girl, presenting with acute renal failure at the age of 2 months, had only mutant cells because of a balanced X-autosome translocation with a breakpoint within the HPRT gene creating the mutation. As happens in such cases, the translocation chromosome is always the active X, so the mutation is expressed in all her cells. Another affected female is an identical twin with mostly mutant skin cells; her normal co-twin had no skewing. The discordant phenotype observed in monozygotic twins suggests that twinning can trigger skewed X inactivation.18 The severe HPRT deficiency in manifesting females results from at least two events: mutation in one HPRT allele along with nonrandom inactivation of the X chromosome carrying the normal allele.

Alport Syndrome
Alport syndrome is a group of hereditary diseases affecting the kidney that may also cause hearing loss and ocular lesions. In the kidney, there is hematuria and proteinuria, often leading to ESRD. The molecular defects involve the basement membranes of both tubules and glomeruli, most often caused by deficiency of one of their type IV collagen components. Approximately 85% of Alport syndrome results from mutations in the X-linked COL4A5 collagen gene (XLAS). Males with a COL4A5 deficiency almost always end up with ESRD, whereas females have a wide range of phenotypes ranging from asymptomatic to disease as severe as that of males.19 According to Kashtan,19 as many as 25% of carriers may have severe renal disease, but their disease usually begins later than in males. Attempts to correlate the phenotype of carriers with their X inactivation patterns in blood cells have been generally unsuccessful. This is expected, as the blood cells are not affected by these mutations. Kashtan and colleagues studied the glomeruli of human females with COL4A5 mutations and female mice carrying a human Alport mutation.20 Figure 1B shows a glomerulus from a human Alport heterozygote immunolabeled with an antibody to COL4A5. Striking is the mosaic pattern in the kidney, with a block of labeled cells, most likely normal clone(s), and blocks that are not labeled, most likely mutant clone(s). In mice, the pattern varies, with some glomeruli more labeled than others,20 suggesting that each glomerulus is composed of progeny of several progenitor cells, and are often mosaic with respect to basement membrane function. In the case of COL4A5 mutations, the deficiency is cell autonomous. However, one could imagine that other gene products might be passed between glomerular cells. The
availability of female mice with the Alport mutation provides the means to determine how much of a glomerulus needs to be functional and how many normal glomeruli are needed for adequate renal function.

The COL4A5 gene is located in the middle of the long arm of the X, not close to the pseudoautosomal region that is homologous on X and Y chromosomes—where the genes are expressed from all sex chromosomes. Some X-linked genes in other regions of the X are said to escape inactivation as they are expressed from the inactive X to some extent; their expression is limited because the chromatin of all but the pseudoautosomal region is quite repressed. The COL4A5 locus has not been studied directly; however, the unlabeled cells in glomeruli (Figure 1) suggest there is little expression of COL4A5 from the inactive X. Severe skewing that by chance favors the mutant allele has been observed in normal glomeruli (Figure 1) suggest there is little expression of COL4A5 from the inactive X. Severe skewing that by chance favors the mutant allele has been observed in kidney cells from a heterozygote, manifesting severe renal disease.

A subset of patients with Alport syndrome has disseminated smooth-muscle tumors of the esophagus, large airways, and female reproductive tract. In these cases, the mutation is a deletion encompassing not only COL4A5 but its neighbor COL4A6 as well (Table 1). Females with one copy of the deletion manifest the smooth-muscle tumors as often as males do, but their renal disease tends to be milder with only rare females affected with ESRD. Although not tested, presumably such females are the ones with greater numbers of mutant cells in their kidneys. As a result of a severe growth disadvantage during embryogenesis, most deleted X chromosomes are inactive in every cell, but these Alport deletions are apparently not large enough to influence the growth of the mutant cell. If they were, then the deleted X would always be inactive, and the mutation would not be expressed at all.

**Dent 1 Disease**

Dent disease is an X-linked disorder that usually affects males. Mutations are almost always associated with low-molecular weight proteinuria, aminoaciduria, and progressive renal failure. Most males also have hypercalciuria and nephrocalcinosis, resulting in renal stones, and some have hypophosphatemic rickets. The disease is the result of inactivating mutations of CLCN5, encoding a member of the CLC family of voltage-gated chloride channels and transporters. CLCN5 localizes to endosomes of the proximal tubule. In the absence of CLCN5, there are less of the scavenger protein receptors, megalin and cubilin, in the proximal tubules, where they are needed to take up low molecular weight proteins from the glomerular filtrate. Because random inactivation provides enough normal cells, females are usually asymptomatic, but some may have hypophosphatemia and decreased urine osmolality.

**Dent 2 Disease (Lowe Syndrome)**

Another cause of renal tubular dysfunction is Lowe oculocerebrorenal syndrome, which affects multiple tissues and organs. The culprit is OCRL1, an X-linked gene encoding inositol 5-phosphatase enzyme located in the Golgi complex, now called OCRL enzyme. The lack of this phosphatase causes cataracts and abnormal neurologic and renal function by interfering with Golgi vesicular transport. Lowe syndrome is also called Dent 2 disease because the mechanism of kidney disease is similar to that of Dent 1 disease. In both cases, the renal tubules lack the receptors that control the exchange of certain small molecules between the urine and the blood. OCRL attaches itself to an adaptor molecule, involved in the sorting and signaling of cell surface receptors in the brain and kidney. In the kidney, that receptor protein is megalin, just as in Dent 1 disease.

Historically, Lowe syndrome was defined as only affecting boys, in whom it causes more frequent cataracts, rickets, and tubular proteinuria than seen in Dent 1 disease. Female carriers are usually asymptomatic, but most of them, like carriers of Fabry disease, have lens opacities that do not cause visual problems. This suggests that the lens is particularly sensitive to mutations in the heterozygous state. In any case, lens opacities provide a rather sensitive assay for heterozygotes in both diseases. A few Lowe heterozygotes are fully affected as males, and in one case this was explained by severe skewing such that only mutant cells were present, with her normal allele mute on her inactive X.

**Oral Facial Digital Syndrome Type 1**

The syndrome, characterized by malformations of the face, oral cavity, and digits, affects primarily females because affected males die in utero. Polycystic kidneys are found in up to half the cases, especially when the OFDI mutation affects a splice site. The protein encoded by the gene (OFD1 protein) is located in the centromere of the basal body of primary cilia. Deficiency of the protein causes ciliary dysfunction, resulting in early developmental defects in the heart, neural tube, kidney, and affecting laterality because of absent cilia in the embryonic node.

The severity of the polycystic renal disease in heterozygous females varies widely, and undoubtedly their X inactivation status plays a role in determining how severe it will be. From studies of the OFDI gene in cultured fibroblasts, we know it is expressed to some extent from the inactive X, most likely because of its telomeric location (Xp22.3). It is likely that human heterozygous females are protected to some extent by the small amount of protein produced from the normal allele on their inactive X. In mice, the gene on the inactive X is completely silent, and all affected females have polycystic kidneys, surviving only a short time after birth. In any case, along with variation in the nature of the mutation, the variability either in expression from the inactive X or in the number of normal cells clearly explains the variability in renal disease among carriers. Some may have sufficient OFDI protein for cillum assembly. Because the homologous locus on the Y chromosome is a nonexpressed pseudogene, affected males cannot benefit from the allele on their Y chromosome. It is likely the leaky expression of the normal allele from the inactive X weakens the influence of X inactivation on the severity of the polycystic disease. Studies show that 7 of 23 patients had skewing, but in none was it extreme (>90%), and neither the normal nor mutant allele was favored.
Nephrogenic Diabetes Insipidus

Body water homeostasis requires a fine balance between thirst to bring water into the body and the release of antidiuretic hormone (vasopressin) to minimize water loss. Diabetes insipidus is a disease of water homeostasis resulting from failure to concentrate urine. Although some cases can be central in origin because of an insufficient production of vasopressin, most are caused by an impaired renal response to vasopressin. Approximately 90% of the patients with nephrogenic diabetes insipidus (NDI) are boys with mutations in the X-linked gene encoding the arginine vasopressin receptor 2 (AVPR2); the rest have an autosomal NDI, caused by mutations in the gene encoding the aquaporin-2 water channel. Most of the AVPR2 mutations result in V2 receptors that cannot reach the plasma membrane because they are trapped within the renal cell. Affected males have excessive thirst and produce large quantities of dilute urine, even when treated with exogenous vasopressin.

Because most patients are males, the few affected females are usually considered to have a mutation in the autosomal gene. However, van Lieburg et al., who described three NDI families in which females had classic features of the disease, considered the possibility that some could be the result of AVPR2 mutations. They suggested that the manifesting females had too many mutant cells because of skewed X inactivation. This hypothesis was tested by Nomura et al., who reported two related heterozygous females with clinical disease. Both manifesting females had skewed X inactivation in blood cells; the most severe had the greatest amount of skewing. The skewing responsible for the variable degrees of polyuria and polydipsia is not attributable to a growth advantage of either normal or mutant cell. Of interest, a heterozygous female developed transient AVPR2 for the first time at the age of 55 when undergoing the stress of a surgical procedure. Approximately 80% of her blood cells were of the mutant type.

A gain-of-function mutation (R137C) in the AVPR2 gene also produces the nephrogenic syndrome of inappropriate antidiuresis. Originally reported in male infants only, a few adults have been identified. Affected males have systolic hypertension and spontaneous episodes of hypertension, whereas the carriers are usually asymptomatic, but some have mild polydipsia and abnormal water-load tests.

Hypophosphatemic Rickets

X-linked hypophosphatemia, also known as vitamin D resistant rickets, is a disorder of phosphate homeostasis caused by mutations at the PHEX locus that produce defects in the renal reabsorption of filtered phosphate and in the metabolism of vitamin D. Clinically, X-linked hypophosphatemia manifests as defective mineralization of growth plates (rickets) and bone (osteomalacia). Many patients have ultrasonic evidence of nephrocalcinosis. The gene belongs to the family of endopeptidases that degrade or activate a variety of peptide hormones. PHEX is expressed in bone, rather than in the kidney, suggesting that the renal abnormalities are secondary to the skeletal defect.

Males usually have overt bone manifestations, whereas females tend to have a wider range of bone disease, from severe to none at all. Also, affected females have a higher rate of tubular phosphate reabsorption than affected males. However, serum phosphate levels are similar in both sexes and do not differ in homozygous mutants, hemizygous males, or heterozygotes. No one has yet compared the levels of mRNA encoding PHEX in bone cells where PHEX is predominantly expressed, a more direct assay for gene dosage effects. The locus maps to the tip of the human X chromosome where genes may escape inactivation. Studies of hybrid cells suggest that there may be some leaky expression from the inactive X in some individuals, but the level of expression is not known. X inactivation studies of blood samples from 12 carriers did not show any skewing. The inactivation status of the mouse PHEX gene is also unknown, but the availability of heterozygous mice carrying a conditional deletion of the PHEX gene in osteoblasts and osteocytes should shed light on such issues.

Other X-Linked Diseases With a Role in Kidney Development

In the case of the mutations in X-linked genes known to be involved in the differentiation and function of the kidney, most affect renal function directly through deficiency of receptors and other structural elements, or indirectly through nephrolithiasis or renal obstruction. Males usually bear the brunt of the problem. Most females have far less severe abnormalities than males with the same mutation. The only female-specific disorder is X-linked polycystic disease because males do not survive gestation. The lack of other X-linked development disorders of the kidneys no doubt reflects the fact that mutations in X-linked genes expressed in the kidney interfere with the development of other organs as well. For example, the Simpson-Golabi-Behmel syndrome (OMIM 312870), producing large dysplastic kidneys along with congenital heart defects, splenomegaly, cryptorchidism, and hypospadias, is caused by a mutation in the Glypcan-3 gene at Xq26. Almost all of the reported individuals are male, but some female relatives have minor malformations. The rare manifesting females have disruptions in the gene from X-autosome translocations that also caused skewed X inactivation.

Because the development of the kidney is a multifactorial process, many gene products contribute to the end result. Therefore, it is not surprising that mutations in more than one gene may be needed to produce developmental problems of the urinary tract, especially if the mutations produce partial deficiencies. None may be detrimental alone but, in collaboration, are sufficient. Mutations in the gene encoding the angiotensin II receptor, type 2 (AGTR2) (OMIM 300034) are implicated in the development of uropelvic junctionstenosis or atresia. Mice carrying a null allele for X-linked AGTR2 have phenotypes that resemble congenital anomalies of the human kidney and urinary tract. These mice lack other somatic anomalies, and inheritance does not follow a typical mendelian pattern. AGTR2 has a role in apoptosis, which is essential for elimin-
ing mesenchymal cells surrounding the Wolffian duct and ureter. Nishimura et al. speculate that delayed apoptosis may cause the diverse anatomic abnormalities."43 Males with AGTR2 mutations also have X-linked mental retardation. No females have been ascertained, but then, only males are usually studied. On the other hand, many abnormalities of the renal-gonadal system may be sex-limited.

Other Diseases With a Gender Preference

Clearly, not all sex differences in renal disease originate from the X chromosome. Certainly, the sex hormones have an effect on the progression of renal disease and perhaps specifically the renal diseases associated with hypertension, namely, the protective effect of estrogen or the nephrotic effect of testosterone. Perhaps hormones are a factor in systemic lupus erythematosus (SLE), as this could explain the preponderance of females among affected individuals. The cause of SLE is not known, but genes in the major histocompatibility complex have been identified as susceptibility genes. Some of them exert effect on recognition of self. It seems that SLE is not like thyroiditis and scleroderma, autoimmune disorders, in which a good proportion of affected females have severely skewed X inactivation.44–46 The current belief is that skewing is a cause of these autoimmune disorders, as it results in minor population of cells that may be missed by sampling at the time when immune tolerance forms. Yet, although it has been looked for, there is no significant skewing of X inactivation in females with SLE.44,47 Conceivably, some X-linked gene plays a significant role in the pathway leading to manifestations of the disease, as a good number of them are needed for normal immune homeostasis. Yet, among possible candidates that affect B cells identified by microchip analysis of single nucleotide polymorphisms (SNPs),48 none so far can explain the sex difference in susceptibility. Possibly, a relevant gene is imprinted such that it has an effect only when inherited by a female. Lu et al.,49 suggest that chance de-methylation of genes on the inactive X that affect T lymphocytes can increase their transcriptional output and may contribute to the striking female predilection of this disease.

Conclusion

The single active X chromosome is responsible for sex differences in kidney diseases, as males are uniquely vulnerable to mutations in their only copy of the X-linked genome. The female response to similar mutations depends not only on the effect of the mutation, but also on the nature of her cellular mosaicism: that is, how many of her cells are normal and whether these are enough to provide the function of the gene. Cellular mosaicism is most often advantageous, mediating either transfer of essential gene products to the cells that need them or alternatively eliminating deleterious cells. Such dynamic interactions permit some women to completely avoid clinical disease and others to survive gestation, albeit at the cost of some clinical manifestation. Although relatively uncommon, there is also the possibility of metabolic interference when products from mutant cells interfere with the function of the normal cells.50 The disorders discussed here result from severe elimination of gene function. It is likely that more subtle differences in the expression of these and other genes will produce more nuanced differences in how males and females manifest their mutations.

X inactivation has provided unique insights into many aspects of cell biology. The ability to examine both the active and inactive chromosomes or genes within the same cell is priceless. It has revealed the importance of CpG islands in maintaining the silence of nonexpressed genes and the existence of a histone code. X inactivation also provides a tool to examine the clonal origin of tumor cells. Such studies provide the means to explore the complexity of renal development using females, heterozygous for X-linked mutations affecting the kidney as the probe.

DISCLOSURES

None.

REFERENCES

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